ALTRE TIPOLOGIE DI RICERCA

Area di Ricerca Neuromotoria

PROGETTO CONTO CAPITALE MINISTERO DELLA SALUTE

Riabilitazione robot-assistita dell'arto superiore: nuove prospettive di trattamento e di ricerca

Nell'ambito del progetto sono state condotte delle ricerche bibliografiche e indagini di mercato per la scelta delle migliori apparecchiature per le attività previste. Si è proceduto dunque all' acquisto di due sistemi di realtà virtuale, un sistema di Elettromiografia di superficie wireless con accelerometro, un sistema di realtà virtuale per il controllo del tronco e degli arti, un sistema di EEG e un sistema robotico per la riabilitazione della mano. Nel corso del 2015 inizieranno le sperimentazioni per il setting e la validazione della nuova piattaforma integrata.

CENTRO NAZIONALE PER LA PREVENZIONE E IL CONTROLLO DELLE MALATTIE - BANDO CCM 2010

Unità Operativa del progetto: Nuove conoscenze e problematiche assistenziali nell'ictus cerebrale: un programma strategico di ricerca e sviluppo.
La presa in carico delle persone con ictus cerebrale: implementazione dei percorsi di cura integrati e degli strumenti di gestione.
Obiettivo 2 dal titolo: Il percorso riabilitativo dopo ictus cerebri: sperimentazione ragionata della continuità terapeutica
Progetto coordinato dalla Regione Emilia Romagna

Il progetto ha visto complessivamente la partecipazione di 178 strutture, di cui 28 ospedali, per acuti e 150 strutture di riabilitazione ospedaliera e/o territoriale.
Il progetto si è concluso ed aveva come obiettivi:
- La messa a punto di un sistema di raccolta dati clinici e demografici delle persone affette da ictus ricoverata nell'arco di tre mesi in alcuni ospedali dell'Emilia Romagna, Toscana, Umbria, Lazio, Campania, Calabria e Sicilia;
- La verifica dei percorsi garantiti per questa patologia;
- L'individuazione di anomalie nella rete assistenziale al fine di dare strumenti alle regioni per lo sua implementazione;
- Individuare indicatori precoci causa di disabilità e mortalità a distanza di tempo.

31 Ospedali in fase acuta hanno arruolato complessivamente 1331 pazienti ed il numero totale di decessi in fase acuta è pari a 75.
Le strutture di riabilitazione ospedaliera sono 43, il numero totale dei pazienti arruolati in fase di riabilitazione ospedaliera è di 359 ed il numero totale di decessi in fase di riabilitazione ospedaliera è di 15.
Le strutture di riabilitazione post-ospedaliera territoriale sono 21, il numero totale dei pazienti arruolati in fasedi riabilitazione post-ospedaliera è di 359.

La fase di raccolta dati relativa al follow up è stata completata per l'88,4 % sul totale dei pazienti. L'età media del campione è risultata pari a 68,2 anni in Campania ad un massimo di 76,6 in Umbria.
La distribuzione per sesso è di 694 maschi (52%) e 638 femmine (48%). La distribuzione per età e sesso è inlinea con altri studi sulla malattia cerebro-vascolare condotti in vari paesi europei.-
La verifica dei percorsi garantiti per questa patologia;

CENTRO NAZIONALE PER LA PREVENZIONE E IL CONTROLLO DELLE MALATTIE-BANDO CCM 2012

La presa in carico delle persone con mielolesione nelle regioni italiane: implementazione dei percorsi di cura integrati ospedale e degli strumenti di gestione.
Consulenza scientifica a cura di Marco Franceschini.

Il progetto, con la creazione di un network inter-regionale, intende stimare l'incidenza delle lesioni midollari traumatiche e descrivere le criticità nei percorsi assistenziali nelle fasi ospedaliera, territoriale e di integrazione socio-sanitaria, descrivere gli esiti di salute attraverso l'utilizzo di scale di misura della disabilità già validate quali l'ASIA e la SCIM all'ingresso ed alla dimissione dalle Unità Spinali in alcune regioni italiane. Si intende inoltre promuovere l'appropriatezza clinico-organizzativa nelle Unità Spinali delle regioni partecipanti attraverso la condivisione dei protocolli clinico-assistenziali (protocolli clinici- diagnostici – terapeutici – riabilitativi) e la definizione delle best practice in accordo alle evidenze della letteratura internazionale.
La popolazione in studio è rappresentata da tutti i nuovi casi di pazienti con diagnosi clinica di lesione del midollo spinale di origine traumatica, ricoverati nelle strutture di ricovero per acuti delle regioni partecipanti al progetto (Emilia Romagna, Friuli Venezia Giulia, Lazio, Lombardia, Marche, Piemonte, Toscana, Umbria, Veneto, Puglia e Sicilia) e la cui diagnosi clinica è effettuata nel periodo di studio: inizio della rilevazione dei dati per lo studio di incidenza - dal 1 Settembre 2013 al 31 Agosto 2014. A tal fine sono state messe a punto alcune schede di rilevazione dati (Scheda di segnalazione di nuovo caso di lesione midollare di origine traumatica; Questionario Rilevazione dati di Struttura delle US partecipanti; Scheda di rilevazione Dati della persona con Mielolesione in Ingresso ed in Uscita dalle US) e un data base di raccolta globale dei dati. Vengono registrati anche tutti casi in ingresso nelle strutture riabilitative (US e non) coinvolte, con lesione midollare di origine non traumatica ed in fase anche non post acuta (Cronici). E' in atto il follow-up dello studio.

PROGETTI UNIONE EUROPEA

eWall for Active Long Living - e-Wall: Electronic Wall to Improve Quality of Life for the Elderly

L'invecchiamento della popolazione costituisce una delle principali sfide del progetto europeo dal titolo "eWall for Active Long Living" (eWALL: Electronic Wall to Improve Quality of Life for the Elderly; FP7 grant agreement no 610658), presentato nel 7° Programma Quadro nel Programma specifico "Cooperation".
La sfida consiste nel dare agli anziani uno stile di vita autonomo, in quanto tale fattore ha un impatto importante oltre che sulla vita stessa dei soggetti, dei parenti e dei care givers, anche sui sistemi sanitari e assicurativi nazionali.
Il progetto eWall prevede la progettazione e realizzazione di un prodotto facile da installare che può essere montato su una parete a domicilio e comprende tutta la tecnologia dell'informazione e della comunicazione necessaria per consentire una serie di servizi per l'anziano. Il progetto multidisciplinare prevede una valutazione sull'impatto della qualità della vita dei soggetti tramite strumenti avanzati. Il sistema eWall estenderà le piattaforme di assistenza e renderà significativamente più autonoma la vita delle persone anziane.
I soggetti anziani possono manifestare una serie di fragilità, tra cui il calo delle condizioni cardiopolmonari, l'indebolimento delle funzioni muscolari, e un minore controllo neuromuscolare dei movimenti, che comportano un elevato rischio di cadute e una maggiore vulnerabilità alle malattie cardiovascolari e polmonari. Per quanto riguarda le funzioni cognitive, gli anziani possono manifestare un declino della funzione di memoria, una minore capacità di orientamento e l'incapacità di far fronte a situazioni complesse. La demenza lieve è un'altro disordine che colpisce questa parte della popolazione e che richiede il costante sostegno dei caregivers.
Il sistema eWall è costituito da un'ampia rete di sensori integrati nella casa o indossati dal paziente e verifica le attività quotidiane degli anziani tramite un complesso di servizi intelligenti, personalizzati ed auto-adattativi che permette il controllo di un corretto stile di vita. Tra le sue funzionalità, eWall suggerisce scelte appropriate (ad esempio ricordando l'assunzione di farmaci prescritti) e corregge eventuali comportamenti errati o rischiosi per la salute (ad esempio l'allontanamento inconsueto dalla casa). Inoltre, provvede alla diagnostica immediata delle criticità (come cadute, luci accese durante la notte, eccessiva inattività, complicazioni cardiache), sempre applicando gli standard più avanzati per il rispetto totale della dignità e la privacy. Il sistema è gestibile tramite una semplice interfaccia integrata nella parete di casa grazie a soluzioni tecnologiche di domotica evoluta sviluppate appositamente.
Il progetto è stato avviato nel novembre 2013. Tredici partner tra aziende e istituzioni, che rappresentano l'eccellenza europea della ricerca e dello sviluppo, collaborano per progettare, realizzare e validare questo prodotto che rappresenta il futuro dell'assistenza avanzata, integrata nella vita di tutti i giorni.
L'IRCCS San Raffaele Pisana mette a disposizione di questo impegnativo progetto uno staff di medici, ingegneri, epidemiologi, terapisti e tutta la specifica esperienza nella cura, la riabilitazione e la telemedicina su pazienti anziani, sia partecipando alla progettazione delle piattaforme standardizzandone le caratteristiche, sia valutando l'impatto di questo prodotto innovativo sulla qualità della vita dei pazienti.
Nel 2014 l'IRCCS San Raffaele Pisana ha contributo alla stesura delle linee guida, alla definizione degli "user requirements", alla valutazione dei prototipi e alla validazione delle specifiche tecniche (grazie all'intervento di professionisti altamente specializzati nella riabilitazione motoria e cognitiva, e la telemedicina).
Gli altri partner internazionali coinvolti sono:
- Aalborg Universitet (Danimarca);
- Hewlett Packard italiana srl (Italia);
- Ericsson Nikola Tesla D.D. (Croazia);
- Roessingh Research and Development bv (Olanda);
- Cure Centrum fur die Untersuchung und Realisierung Endbenutzerorientierter interaktiver systeme (Austria);
- Research and Education Laboratory in Information Technologies (Grecia);
- Universitatea Politehnica din Bucuresti (Romania);
- Ss. Cyril and Methodius University in Skopje (Macedonia);
- Javna Ustanova Univerzitet Crne Gore Podgorica (Montenegro);
- Technical University of Sofia (Bulgaria);
- Sveuciliste u Zagrebu Fakultet Elektrotehnike i Racunarstva (Croazia);
- Stelar Security Technology Law Research (Germania).

SCRIPT: Supervised Care & Rehabilitation Involving Personal Tele-robotics.

È stato dimostrato che la riabilitazione robot-assistita permette il recupero di soggetti affetti da ictus e il risparmio di risorse economiche, poiché riesce a fornire un allenamento costante e controllato al soggetto e inoltre permette la ripetizione di determinati esercizi ritenuti fondamentali al recupero funzionale del paziente. Sulla base di tale presupposto, il progetto europeo SCRIPT ha avuto come scopo quello di sviluppare due esoscheletri di mano e polso (uno passivo e uno attivo) e di eseguire con essi la riabilitazione di soggetti affetti da ictus in un ambiente videoludico. I soggetti arruolati per la sperimentazione seguono un percorso di riabilitazione robot-assistita autonomamente a domicilio, sotto la supervisione a distanza di clinici (tele-riabilitazione). La comunicazione paziente-clinico è possibile grazie a una interfaccia disponibile per entrambi e funzionante tramite internet.
Alla fine di tre anni di progetto, SCRIPT ha valutato l'efficacia della tele-riabilitazione robotica, della riabilitazione eseguita con gli esoscheletri sviluppati e ha valutato eventuali differenze tra i due approcci riabilitativi.
Sono stati sviluppati due esoscheletri. Presso il San Raffaele Pisana la fase di sperimentazione ha coinvolto 13 soggetti; su due soggetti sono state inoltre svolte misurazioni per uno studio di cross-section per confrontare esoscheletri attivi e passivi.
L'IRCCS San Raffaele Pisana ha inoltre offerto la propria conoscenza e struttura per il "fine tuning" e la valutazione funzionale dei nuovi prototipi robotici per migliorarne il design, la funzionalità e l'efficacia. Grazie alla creazione di focus group ai quali hanno partecipano medici, tecnici, terapisti, bioingegneri, pazienti e associazioni dei familiari di pazienti con particolari patologie, l'Istituto ha contribuito alla definizione e ottimizzazione dei prototipi passivi sensorizzati per la riabilitazione di mano e polso.
Gli altri partner internazionali coinvolti nel progetto sono stati:

- The University of Hertfordshire Higher Education Corporation;
- R. U. Robots Ltd;
- The University of Sheffield;
- Universiteit Twente;
- Roessingh Research and Development bv;
- Moog bv;
- User Interface Design GmBh.

FONDAZIONE GOSSWEILER

Does the Action Observation treatment improve the upper limb speed of movement and deftness of parkinsonian patients?

La malattia di Parkinson (MP) è una delle principali cause di disabilità motoria tra gli adulti costituisce un onere sociale ed economico per il nostro Paese.
La terapia fisica viene utilizzata insieme al trattamento farmacologico intensivo per migliorare le prestazioni motorie in pazienti con malattia di Parkinson.
I pazienti con carenti capacità motorie partecipano con difficoltà alla terapia fisica per cui fornire un contributo rilevante alla plasticità neurale legata all'esperienza, alla neuroriabilitazione, alla riparazione, e al recupero può costituire una sfida.
In questi casi, l'osservazione finalizzata di azioni può indirizzare sistemi fronto-parietali specializzati (sistemi dei neuroni-specchio) che consentono la comprensione delle azioni e delle intenzioni motorie degli altri e l'apprendimento osservazionale.
Il primo obiettivo specifico di questo progetto è quello di valutare l'efficacia dell'osservazione finalizzata di azioni come strumento per migliorare la funzione degli arti superiori in termini di bradicinesia e destrezza, e per indagare la stabilità degli effetti del trattamento a 4/6 mesi di follow-up in termini di miglioramento funzionale e qualità di vita (QoL) di pazienti in stadio II-IV di Hoehn e Yahr e di indagare la stabilità degli effetti del trattamento a 4/6 mesi di follow-up in termini di miglioramento funzionale e di qualità della vita (QoL).
Il secondo obiettivo intende valutare la fattibilità e l'efficacia di un protocollo di teleriabilitazione a casa sfruttando l'osservazione finalizzata di azioni per migliorare la destrezza nei pazienti con malattia di Parkinson.
Il progetto proposto si articola in due fasi: la prima parte prevede un trial randomizzato controllato in cieco per valutare l'efficacia della terapia dell'osservazione finalizzata di azioni rispetto al trattamento standard in pazienti con malattia di Parkinson. Vengono randomizzati 45 pazienti in 3 gruppi.
La seconda parte dello studio sfrutta i risultati forniti dalla prima fase e arruola successivamente 60 pazienti sottoposti a teleriabilitazione a domicilio attraverso un sistema basato su un dispositivo tablet.Viene effettuato un trial randomizzato controllato per valutare l'efficacia dell'azione della terapia di osservazione finalizzata al domicilio contro il trattamento standard a domicilio in pazienti con malattia di Parkinson.
A seguito dei risultati clinici derivati dal primo studio (la scelta migliore in termini di video e di esercizio) verrà definita una seconda parte basata sulla tele-riabilitazione al domicilio.
La tecnologia delle telecomunicazioni viene utilizzata per fornire supporto nella riabilitazione a lungo termine di persone con malattia di Parkinson.
Questa tecnologia offrirà possibilità interessanti alle tecnologie assistive.
Si tratta di un sistema a basso costo altamente accessibile basato sulla tecnologia per facilitare l'osservazione ed eseguire esercizi di movimento ripetitivo.
In questo progetto, vine applicato un programma di riabilitazione nuovo e non invasivo basato su video selezionati per l'osservazione finalizzata di azioni quotidiane per poter indurre neuroplasticità e migliorare le prestazioni cognitive-motorie nei pazienti con malattia di Parkinson.
Il presente progetto costituisce dunque un tentativo di attuare un'osservazione finalizza di azioni quotidiane dei pazienti al loro domicilio.
Se efficace, questa procedura è altamente applicabile al sistema sanitario nazionale.
I costi sono trascurabili sia a livello di personale (formazione degli operatori sanitari e di alcuni controlli nelle prime sessioni di formazione), sia per la semplice formazione dei pazienti al domicilio o presso le strutture sanitarie.
Con le nuove tecnologie di telecomunicazione e di informatica, facilmente disponibili, il personale medico è aggiornato sui risultati delle sessioni giornaliere tramite internet, migliorando quindi le decisioni cliniche.
Inoltre, l'esercizio quotidiano potrebbe prevenire il ricovero dei pazienti con malattia di Parkinson, riducendo così i costi per il servizio sanitario nazionale.
Questi vantaggi sembrano essere rilevanti per il sistema sanitario nazionale per la grande quantità di pazienti con malattia di Parkinson e per la necessità di interventi innovativi, a basso costo, e al domicilio.

Area di Ricerca Parkinson e disturbi del movimento

CINQUE PER MILLE

Ambiente e neuroriabilitazione nella eziopatogenesi e progressione delle malattie neurodegenerative con particolare interesse per il Morbo di Parkinson.

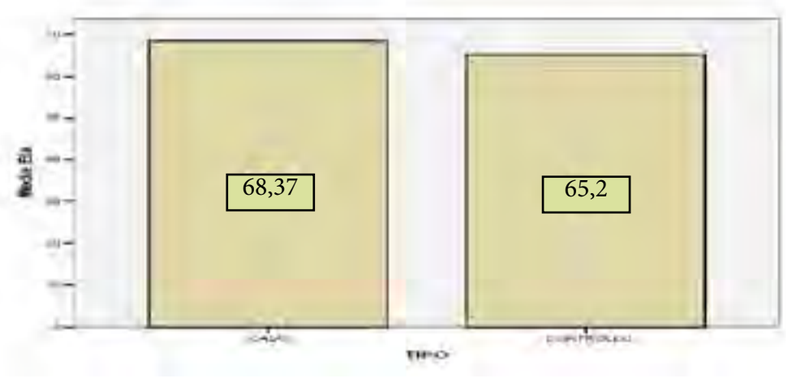
Il progetto di ricerca è composto da 2 sottoprogetti finalizzati rispettivamente:
1. allo studio dell'influenza dell'ambiente e familiarità sull'eziopatogenesi della malattia di Parkinson (MP);
2. alla sperimentazione di una rete assistenziale per l'ottimizzazione delle cure delle malattie neurodegenerative. Il progetto si svolge presso l'IRCCS San Raffaele di Roma.

STUDIO DELL'INFLUENZA DELL'AMBIENTE E FAMILIARITÀ SULL'EZIOPATOGENESI DELLA MALATTIA DI PARKINSON

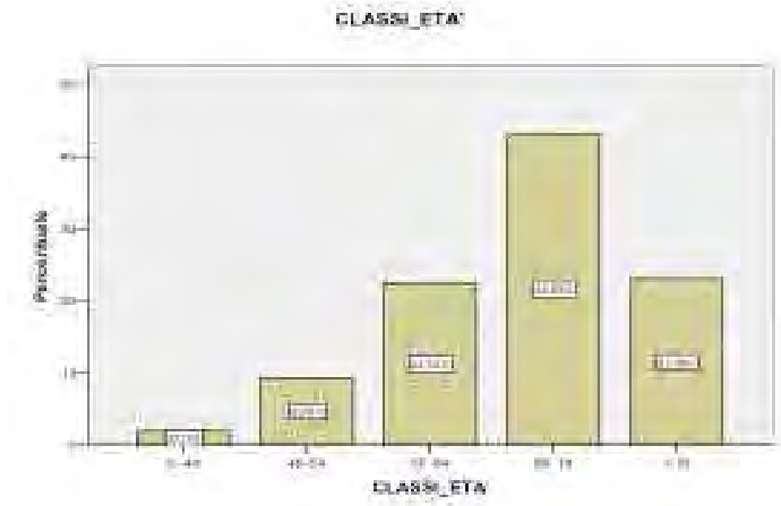
La malattia di Parkinson (MP) è una malattia neurodegenerativa che presenta, nelle varie popolazioni del mondo, un tasso di prevalenza estremamente variabile. In Italia sono riportati dati di prevalenza compresi tra 65,6 e 243/100.000 abitanti. I tassi di prevalenza sono risultati aumentare progressivamente con l'età. Si calcola che tra la popolazione generale compaia un nuovo caso ogni 4000 abitanti e al di sopra dei 50 anni di età, 1 ogni 1000.
E' essenziale considerare che la MP è una malattia cronica, progressivamente invalidante, non solo per quanto riguarda la sua storia naturale, ma anche successivamente all'introduzione della terapia farmacologica. La nosografia delle malattie neurodegenerative, compresi i parkinsonismi, basata sinora su criteri clinico-patologici, è in corso di ridefinizione alla luce delle recenti scoperte derivanti dagli studi di tipo genetico e di biologia molecolare. Nell'ultimo decennio studi sulla genetica della MP hanno portato all'identificazione di alcune mutazioni per le forme di tipo familiare.
Nella maggior parte dei casi però le cause della MP restano sconosciute, e modelli di tipo monogenico non sembrano molto verosimili. Probabilmente ci si trova di fronte a complesse interazioni di molti fattori di tipo genetico e non-genetico. La potenziale multifattorialità dell'eziologia della MP, combinata alla presenza di un quadro di debole suscettibilità genetica sostiene un modello di interazione gene-ambiente come modello eziologico preferenziale. A completamento delle variabili considerate nella definizione del modello ezio-patologico della MP una serie di variabili ambientali sono state investigate in studi di tipo clinico ed epidemiologico. Fra queste vari aspetti dello stile di vita, la dieta, l'occupazione, la residenza.
Una delle ipotesi accreditate è che la maggior parte dei casi di MP, in quanto malattia multifattoriale, sia originata da una interazione sfavorevole che si viene a creare tra le sostanze chimiche assorbite dall'organismo ed il metabolismo delle stesse. In condizioni di particolare suscettibilità individuale (predisposizione genetica), questa interazione può aumentare lo stress ossidativo a livello dei neuroni della sostanza nigra provocandone la perdita, e, quindi, favorire lo sviluppo della MP. Attualmente le sostanze chimiche studiate per un possibile ruolo neurotossico sono i solventi organici, i fumi di scarico, il monossido di carbonio, i metalli pesanti, gli erbicidi e pesticidi. È stato evidenziato un accumulo di pesticidi in reperti autoptici di soggetti affetti da MP, proprio a livello della sostanza nigra. E'possibile che questo meccanismo si possa attivare a livello della sostanza nigra, con produzione locale di radicali liberi. In soggetti non esposti l'età

di esordio della MP è intorno ai 61 anni, mentre nei soggetti che presentano una storia positiva di esposizione professionale a solventi e metalli è stato evidenziato un anticipo dell'esordio della malattia. Tra i metalli coinvolti vi sono: mercurio, rame e manganese, composti di piombo, ferro, rame, zinco ed alluminio.
Nonostante ciò, non esistono dati che indichino in modo certo il ruolo di parametri ambientali come concausa per l'insorgenza della MP. Infine, la MP inoltre tende a ricorrere nella stessa famiglia più frequentemente di quanto possa avvenire per effetto del caso. Questo fenomeno viene ormai confermato in modo molto consistente dagli studi epidemiologici. Circa il 15-25% dei pazienti riferisce infatti la presenza di familiarità positiva.
Il progetto si prefigge di studiare il ruolo dell'ambiente e della predisposizione genetica nell'eziologia e nella fisiopatologia della MP. Obiettivo è il calcolo dell'Odds Ratio per i singoli fattori di rischio, di tipo genetico (SNPs), ambientale (occupazione, life-style, etc.), clinici (stipsi, etc.). Ulteriori endpoints riguardano: i) la valutazione dell'interazione gene-ambiente fra le SNPs valutate nei gruppi in studio con i fattori di rischio della malattia; ii) la validazione dei principali meccanismi connessi con le fasi precoci della malattia; iii) la creazione di un biorepository per lo studio dei fattori di rischio della MdP.
La popolazione dei casi è rappresentata dai soggetti con diagnosi confermata di MP afferenti agli ambulatori del servizio di neuroriabilitazione dell'IRCCS San Raffaele Pisana. I controlli, appaiati per sesso ed età (± 5 anni) sono stati selezionati fra gli afferenti al centro riabilitativo San Raffaele Pisana per prestazioni non legate a patologie di tipo neurodegenerative.
A tutti i soggetti che finora hanno dato il consenso a partecipare allo studio è stato somministrato un questionario per la rilevazione semi-quantitativa dell'esposizione ad agenti ambientali-occupazionali da personale addestrato. L'intervista, proposta dopo gli accertamenti clinici di routine, ha una durata di circa 15 minuti. La dimensione dello studio è stata valutata con il software dedicato. I parametri inseriti sono stati scelti sulla base della prevalenza della familiarità con pazienti affetti dalla malattia di Parkinson nella popolazione generale.
Il questionario predisposto è stato somministrato a 746 soggetti ed ha rilevato la presenza per la maggior parte di pazienti classificati come CASI (67.2%) vs CONTROLLI (32.8%). La rilevazione dei soggetti intervistati mostra che il campione sia rispetto alla variabile sesso e sia rispetto al tipo paziente per età media è ugualmente rappresentato:

	Frequenza	Percentuale	Percentuale valida	Percentuale cumulata
FEMMINA	363	48,7	48,7	48,7
MASCHIO	383	51,3	51,3	100,0
Totale	746	100,0	100,0	



Il livello di istruzione è medio alto (i diplomati sono il 37.4% e i laureati 23.3%) con età media di 67 anni deviazione standard 9.62. I soggetti sono per lo più concentrati nella penultima classe (43.03%) nella quale ricadono tendenzialmente persone con età in cui si inizia ad andare in pensione. Altro aspetto da notare è la quasi uguaglianza delle due classi 55-64 (non ancora età del tutto pensionabile) e 75+ anni (sicuramente età pensionabile) infatti i soggetti sono per il 57.1% pensionati.



L'analisi eseguita distinguendo i gruppi per sesso mostra che nel sottogruppo femminile le differenze percentuali di CASO vs CONTROLLO rispetto al sottogruppo maschile sono minori: infatti CASO femminili è il 54.8% vs CONTROLLO 45.2% mentre CASO maschile è il 78.8% vs CONTROLLO 21.1%. In base alla significatività del Chi–quadrato di Pearson è possibile affermare che il sesso e la tipologia paziente sono effettivamente correlati (al livello del 5%).

		TIPO	
		CASO	CONTROLLO
		Conteggio	Conteggio
SEX	FEMMINA	199	164
	MASCHIO	302	81

Test Chi-quadrato di Pearson

		TIPO
SEX	Chi-quadrato	48,793
	df	1
	Sig.	,000(*)

I risultati sono basati sulle righe e colonne non vuote di tutte le tabelle più interne.
* La statistica Chi-quadrato è significativa al livello 0.05.

Essendo il progetto volto allo studio dell'incidenza dell'ambiente lavorativo all'origine della MP si nota che la variabile 'ultima attività lavorativa' rispetto al tipo paziente il 25.2% dei CASO ha ricoperto un ruolo di impiegato e a seguire con il 10.8% ha svolto attività in ambito scolastico.

SPERIMENTAZIONE DI UNA RETE ASSISTENZIALE PER L'OTTIMIZZAZIONE DELLE CURE DELLE MALATTIE NEURODEGENERATIVE

La MP rappresenta la seconda patologia neurologica che produce disabilità, ed evolve per decenni, con crescente degrado della qualità della vita. L'assistenza sanitaria è spesso inadeguata; si riscontra un notevole numero di ricoveri anche di pazienti che non necessitano di ricovero e i medici di medicina generale spesso non vengono coinvolti. Gli obiettivi di questa parte del progetto sono volti a verificare l'efficacia di protocolli di trattamenti fisioterapici standardizzati, specifici e multidisciplinari.
La valutazione del disturbo del movimento della deambulazione e della postura si è avvalsa di un sistema integrato di analisi computerizzata del movimento, cammino e della postura (gait analiysis 3D-GA). La 3D-GA consente, attraverso l'analisi computerizzata della deambulazione di monitorare il movimento del paziente e di misurare quantitativamente aspetti della deambulazione che diventano fondamentali nella valutazione della sua limitazione funzionale. Si è voluta verificare la validità dell'esame 3D-GA come valutazione clinica quantitativa dell'effetto della levodopa nella MP. Sono stati reclutati 20 pazienti che hanno effettuato valutazione clinica con scale UPDRS parte III da 2 operatori in cieco ed hanno effettuato esame di gait analysis (3D-GA) utilizzando un sistema optoelettronico. Tutti i pazienti hanno eseguito le valutazioni in fase OFF (dopo sospensione di 12 ore della terapia farmacologia) ed in fase ON dopo somministrazione di una dose sovramassimale di farmaco (250 mg di levodopa pronta). In tutti i pazienti studiati le percentuali di miglioramento motorio ottenute con scala clinica UPDRS parte III erano sovrapponibili alle percentuali di miglioramento ottenute con valutazione 3D GA. Si auspica pertanto un ruolo crescente dell'innovazione tecnologica e dell'uso di sistemi avanzati per la valutazione quantitativa degli interventi terapeutici sia di natura farmacologia, chirurgica che riabilitativa. Questi si stanno infatti dimostrando preziosi nell'arricchire ed integrare i tradizionali metodi di valutazione clinica e possono fornire informazioni ed indici di grande utilità nella scelta e nel controllo dei percorsi terapeutici.

Questi sistemi computerizzati di valutazione sono stati applicati anche allo studio dell'efficacia di nuove tecniche e dispositivi medici, come ad esempio GONDOLA®, che è un innovativo dispositivo personale portatile di riabilitazione che può consentire alle persone con Parkinson di recuperare parte delle capacità motorie e dell'autonomia in molte attività personali quotidiane, con conseguente miglioramento della qualità di vita. GONDOLA® è stato progettato per erogare individualmente la Foot Mechanical Stimulation (FMS), una terapia riabilitativa complementare rispetto alle cure farmacologiche. L'innovazione tecnologica di GONDOLA® si basa su stimolazioni del sistema nervoso periferico. Più precisamente, stimola specifiche aree dei piedi con impulsi meccanici controllati. I pazienti che rispondono positivamente alla Terapia FMS, erogata da GONDOLA®, possono acquisire maggiore sicurezza e maggiore velocità nella deambulazione e nel controllo del movimento e possono quindi riappropriarsi di parte della propria indipendenza. In questa direzione è stato intrapreso un'iniziale progetto pilota, randomizzato, controllato in singolo cieco, cross-over, in cui pazienti con PD vengono randomizzati in 2 gruppi: terapia GONDOLA o SHAM (placebo) GONDOLA, utilizzando la Gait Analysis all'inizio e alla fine di ogni ciclo di trattamento per una maggiore accuratezza della valutazione di efficacia.
La valutazione del disturbo della fonazione e della deglutizione è avvenuta tramite il metodo di trattamento della voce Lee Silverman Voice Treatment (LSVT), che è stato appositamente studiato e testato per adattarsi ai problemi delle persone con MP ed altre malattie neurologiche (PSP, MSA). LSVT® è un trattamento intensivo volto all'aumento dell'intensità vocale, mediante l'incremento della pressione dell'aria sottoglottica per una migliore vibrazione cordale. Il principio della tecnica è espresso dal motto "Think loud, think shout" (pensa ad alta voce pensa a un urlo!): lo sforzo fonatorio incrementa il tono dei muscoli laringei e la frequenza della voce. LSVT® migliora sia la voce che l'eloquio degli individui con malattie neurologiche attraverso il trattamento della patologia fisica sottostante associata al disturbo della voce. La terapia si concentra sull'aumento del volume immediatamente trasferito alla comunicazione quotidiana, permettendo ai pazienti di mantenere e/o migliorare la loro comunicazione orale. LSVT® è stato somministrato con un programma intensivo di 16 sedute individuali in un mese (sedute di un'ora quattro giorni consecutivi alla settimana per quattro settimane). Ogni seduta consiste nella ripetizione di compiti simili, come la produzione di "ah" sostenuta alla massima durata e alla massima estensione possibile. L'aumento dell'intensità vocale nell'eloquio spontaneo e il maggiore controllo della sonorità vengono mantenuti per un tempo gradualmente più lungo. L'alto sforzo delle funzioni vocali associato al feedback propriocettivo e all'automonitoraggio uditivo-vocale, aiuta i pazienti a rigraduare l'ampiezza dell'uscita motoria del proprio linguaggio e a mantenere il giusto livello durante la conversazione. Sono stati seguiti 20 pazienti affetti da MP sottoposti a 16 sedute secondo la metodica descritta, per impostare un miglioramento dell'efficacia respiratoria, con aumento della capacità inspiratoria ed espiratoria, dell'adduzione delle corde vocali, dell'attività e della sinergia dei muscoli laringei, dei movimenti articolatori laringei e sovralaringei. I risultati hanno mostrato in tutti i soggetti un aumento del volume della voce con miglioramento della raucedine, del tremore della voce, dell'ipernasalità, chiarezza dell'eloquio attraverso un aumento dell'ampiezza della voce e dell'intensità vocale. Quindi i disturbi della voce, scarsamente controllati dalla terapia farmacologica, possono realmente beneficiare di metodiche riabilitative intensive specifiche.
Lo scopo di questo studio randomizzato controllato è quello di analizzare se il training deambulatorio attraverso dispositivi elettromeccanici, come i treadmill e i Robot per la deambulazione, siano efficaci ad aumentare l'endurance in soggetti con malattia di Parkinson. Obiettivo secondario è quello di confrontare gli effetti indotti da questi trattamenti sia sui parametri dell'andatura e dell'equilibrio, nonché sulle misure specifiche per la malattia. Trenta partecipanti cognitivamente intatti con malattia di Parkinson e disturbi dell'andatura sono stati inclusi nello studio. I pazienti sono stati sottoposti ad un programma riabilitativo tramite robot o treadmill per 45 minuti, 5 volte alla settimana per 4 settimane. Dieci soggetti su 30 hanno raggiunto l'endpoint primario di un aumento minimo al 6MWT di 50 metri. La mediana del 6MWT è stata di 15,7 metri. Il punteggio totale dell'UPDRS ha mostrato un miglioramento significativo in tutto il gruppo, dopo l'allenamento del cammino senza differenze tra i gruppi di trattamento. La scala FOG -Q ha mostrato un significativo miglioramento dopo l'allenamento sia in tutto il campione che nel sottogruppo robot. La scala PDQ39 mostra un punteggio migliorato in tutto il campione così come nel gruppo robot.
Un addestramento intensivo del camminare è fattibile nelle persone con malattia di Parkinson con un aumento significativo della resistenza in almeno un terzo dei soggetti, indipendentemente dall'età, durata della malattia, dalla gravità della compromissione motoria e della disabilità del cammino.

ISTITUTO NAZIONALE PER L'ASSICURAZIONE CONTRO GLI INFORTUNI SUL LAVORO (INAIL)- BANDO 2010

Studio del ruolo dell'ambiente lavorativo nella patogenesi del Morbo di Parkinson

La Malattia di Parkinson (MP) è una malattia neurodegenerativa che presenta, nelle varie popolazioni del mondo, un tasso di prevalenza estremamente variabile. In Italia sono riportati dati di prevalenza compresi tra 65,6 e 243/100.000 abitanti. I tassi di prevalenza sono risultati aumentare progressivamente con l'aumentare dell'età. Tuttavia, pur essendo diffusa soprattutto tra la popolazione anziana, circa il 15% dei pazienti contrae la malattia prima dei 50 anni; si calcola che tra la popolazione generale compaia un nuovo caso ogni 4000 abitanti e, al di sopra dei 50 anni di età, 1 ogni 1000. In generale l'incidenza della malattia è di 3 soggetti su mille nella popolazione generale e 1% in quella sopra i 65 anni. La malattia di Parkinson è una malattia cronica, progressivamente invalidante, non solo per quanto riguarda la sua storia naturale, ma anche successivamente all'introduzione della terapia farmacologica.
A completamento delle variabili considerate nella definizione del modello ezio-patologico del Parkinson, una serie di variabili ambientali sono state investigate in studi di tipo clinico ed epidemiologico. Fra questi vari aspetti dello stile di vita, la dieta, l'occupazione, la residenza.
Una delle ipotesi accreditate è che la maggior parte dei casi di malattia di Parkinson, in quanto malattia multifattoriale, sia causata da una interazione sfavorevole che si viene a creare tra le sostanze chimiche assorbite dall'organismo ed il metabolismo delle stesse. In condizioni di particolare suscettibilità individuale (predisposizione genetica), questa interazione può condurre a situazioni di "stress ossidativi" a livello dei neuroni della sostanza nigra, provocandone la perdita e quindi favorire lo sviluppo della malattia di Parkinson. Attualmente le sostanze chimiche accreditate per un possibile ruolo neurotossico sono: solventi organici, fumi esausti, monossido di carbonio, metalli pesanti, erbicidi e pesticidi. In soggetti non esposti l'età di esordio della malattia di Parkinson è intorno ai 61 anni mentre nei soggetti invece che presentano una storia positiva di esposizione professionale a solventi e metalli è stato evidenziato un anticipo dell'esordio della malattia. Tra i metalli coinvolti vi sono: mercurio, rame e manganese, composti di piombo, ferro e rame zinco ed alluminio.
In questo progetto sono state indagate, attraverso uno studio caso-controllo, eventuali associazioni della malattia di Parkinson con determinate professioni, ambienti lavorativi, stili di vita.
A tutti i soggetti che hanno fornito il consenso a partecipare allo studio è stato somministrato da personale addestrato un questionario validato per la rilevazione dell'esposizione ad agenti ambientali-occupazionali e per l'analisi dello stile di vita.
Le aree indagate sono state:
– Zone di residenza attuale e pregressa (indirizzo, città, provincia con specifica se area rurale o urbana, data di residenza).
– Occupazione attuale e pregressa e (in caso di occupazione a rischio, indicazione della durata dell'esposizione e le eventuali sostanze implicate).
– Attività del tempo libero: se è svolta un'attività nel tempo libero che possa comportare il contatto con sostanze tossiche.
– Uso di sostanze d'abuso: eventuale utilizzo attuale o pregresso delle più comuni sostanze d'abuso.

– Fumo: eventuale esposizione a fumo di sigaretta, sigaro o pipa, attivo o passivo.
– Dieta: peso (attuale e pregresso), altezza, abitudini alimentari prima dell'isorgenza della malattia, uso di integratori, vino, birra, superalcolici.
– Familiarità: composizione della famiglia e eventuale presenza di familiarità per Parkinson Idiopatico, Tremore Essenziale, Alzheimer, Atrofia Multisistemica, Paralisi Sopranucleare Progressiva.
L'endpoint primario dello studio è il calcolo dell'Odds Ratio per i singoli fattori di rischio di tipo ambientale (in particolare Occupazione e Stile di vita).
Un ulteriore endpoint riguarda le correlazioni tra esposizioni professionali a composti chimici organofosforici, utilizzati come pesticidi e metalli e sviluppo della malattia.
In ogni caso, vista l'importanza di avere dati sul possibile ruolo degli SNPs nella modificazione dell'effetto dei fattori di rischio, viene effettuata una raccolta per un subset di 100 soggetti (50 MP e 50 controlli) per valutare tramite uno studio esplorativo la presenza di marcate differenze fra i due gruppi in merito alla frequenza allelica di alcune SNP candidate, riportate dalla letteratura come associate alla MP o ai pathways evidenziati dai risultati dello studio epidemiologico.
Nella seconda parte del progetto viene condotta una analisi particolare dell'esposoma dei soggetti inseriti nello studio di sensibilità per poter associare la presenza di gene-environment interaction con l'esposizione a sostanze specifiche tipiche dell'inquinamento urbano.
A completamento della raccolta, i controlli devono essere in numero almeno uguale a quello dei casi di MP per permettere il raggiungimento di una potenza statistica ottimale. Inoltre viene condotto lo studio di associazione fra danno genomico, esposizione ambientale e lavorativa e rischio Parkinson.
Le caratteristiche del campione sono state descritte mediante statistiche riassuntive (frequenze assolute e percentuali, media e deviazione standard). In una prima analisi di tipo esplorativo si sono confrontati i casi e i controlli relativamente alla distribuzione delle caratteristiche socio-demografiche, allo stile di vita, alla residenza corrente e pregressa, alle professioni correnti e pregresse, all'esposizione a sostanze tossiche. Per i dati di natura categoriale è stato applicato il test del Chi-Quadrato, mentre per i dati di natura continua è stato applicato il t-test di Student. Successivamente è stata effettuata un'analisi di regressione logistica semplice che ha permesso di stimare l'effetto puro dei potenziali fattori di rischio per il Morbo di Parkinson. Secondariamente è stata effettuata un'analisi di regressione multipla, e con l'ausilio del metodo di selezione del modello 'backward stepwise' (criterio per inclusione di una variabile: $p<0.10$) sono stati individuati alcuni fattori fortemente associati al Morbo di Parkinson. I risultati sono stati espressi mediante la stima degli odds ratio, e relativi intervalli di confidenza al 95% e p-value. La significatività statistica è stata verificata con $p<0.05$.
Ulteriori analisi verranno effettuate per approfondire le relazioni tra i diversi fattori di rischio per la malattia e per verificare il ruolo dell'esposizione ambientale, occupazionale e a sostanze tossiche, nonché il ruolo della familiarità e della genetica, nello sviluppo del Morbo di Parkinson. Il software utilizzato per le analisi statistiche è STATA/SE V12.
Il campione era composto da 520 casi affetti da Morbo di Parkinson e da 257 controlli non affetti da malattia. In tabella 1 sono riassunte le caratteristiche socio-demografiche, le abitudini al fumo e l'esposizione a sostanze tossiche per il gruppo dei casi e dei controlli.

Socio-Demographic Information, Smoking Habits and Exposure to Toxic Substances	CASES (N=520) N (%) / MEAN ± SD	CONTROLS (N=257) N (%) / MEAN ± SD	Comparison p-value
SEX			
Female (n=375)	208 (40%)	170 (66%)	<0.001*
Male (n=399)	312 (60%)	87 (34%)	
AGE (YRS)	68.28 ± 9.55	65.18 ± 9.60	<0.001*
<55 years old (n=90)	54 (10%)	36 (14%)	0.004*
55-59 years old (n=67)	36 (7%)	31 (12%)	
60-64 years old (n=120)	65 (12%)	55 (21%)	
65-69 years old (n=146)	96 (18%)	50 (19%)	
70-74 years old (n=186)	133 (26%)	53 (21%)	
75-79 years old (n=112)	88 (17%)	24 (11%)	
≥80 years old (n=62)	48 (9%)	14 (5 %)	
EDUCATION			
Primary School or Analphabet (n=119)	91 (18%)	28 (11%)	0.070
Secondary School (n=194)	119 (25%)	65 (26%)	
Diploma (n=285)	181 (35%)	104 (41%)	
University Degree (n=163)	126 (24%)	57 (22%)	
BMI (mean)	25.59 ± 3.77	25.52 ± 4.33	0.850
Underweight – BMI<18.50 (n=15)	10 (2%)	7 (3%)	0.880
Normal Range - BMI: 18.50-24.99 (n=371)	222 (43%)	105 (42%)	
Pre-Obese – BMI: 25-29.99 (n=288)	204 (40%)	100 (40%)	
Obese – BMI≥30 (n=94)	80 (15%)	40 (16%)	
BMI (strata)	25.78 ± 4.16	26.03 ± 4.31	0.450
Underweight – BMI<18.50 (n=17)	8 (2%)	7 (3%)	0.110
Normal Range - BMI: 18.50-24.99 (n=321)	240 (47%)	130 (52%)	
Pre-Obese – BMI: 25-29.99 (n=303)	208 (40%)	80 (32%)	
Obese – BMI≥30 (n=126)	59 (12%)	35 (14%)	
BMI change	-0.19 ± 2.39	-0.50 ± 1.88	0.070
Weight loss – shift down in BMI class (n=108)	75 (15%)	33 (13%)	0.001**
No weight change – no shift in BMI class (n=612)	397 (77%)	215 (85%)	
Weight increase – shift up in BMI class (n=47)	33 (8%)	4 (2%)	
SMOKING HABITS			
No (n=399)	271 (52%)	128 (50%)	0.660
Ex Smoker (n=269)	186 (36%)	82 (32%)	
Yes (n=116)	63 (12%)	47 (18%)	
Cigarettes Smokers (n=367)	240 (96%)	127 (98%)	0.260
Age at which started smoking (n=367)	19.49 ± 6.99	18.91 ± 6.37	0.440
Age at which stopped smoking (n=…)	57.30 ± 19.42	55.67 ± 7.50	0.880
Average no. of cigarettes (n=366)	14.72 ± 11.72	15.63 ± 10.51	0.470

Current Smokers (n=45)	15 (7%)	5 (3%)	0.096
Age at which started smoking (n=36)	32.87 ± 13.77	17.67 ± 10.76	0.616
Age at which stopped smoking (n=14)	51.29 ± 16.00	30 (one subject only)	not applicable
Average no. of cigars (n=13)	2.05 ± 3.54	1.83 ± 0.29	0.810
Pipe Smokers (n=18)	14 (6%)	2 (2%)	0.060
Age at which started smoking (n=16)	26.37 ± 9.64	43.00 ± 32.53	0.190
Age at which stopped smoking (n=9)	43.33 ± 25.73	48.50 ± 26.16	0.800
Average no. of pipes (n=16)	1.54 ± 0.86	1.50 ± 0.71	0.960
LIVES WITH SMOKERS			
No (n=336)	236 (44%)	120 (57%)	0.500
Yes (n=423)	289 (56%)	186 (53%)	
No. hours with smokers (n=424)	4.03 ± 3.73	4.66 ± 4.58	0.900
No. years with smokers (n=423)	27.00 ± 12.90	26.02 ± 14.65	0.480
WORKS WITH SMOKERS			
No (n=471)	318 (61%)	153 (69%)	0.710
Yes (n=302)	200 (39%)	102 (30%)	
No. hours with smokers (n=302)	6.81 ± 2.91	6.43 ± 3.37	0.310
No. years with smokers (n=301)	21.98 ± 10.83	20.55 ± 12.59	0.310
TOXIC SUBSTANCES			
No (n=694)	456 (88%)	243 (95%)	0.005*
Yes (n=78)	64 (12%)	14 (5%)	
List of Substances			
Pesticides and fertilizers (n=23)	19 (30%)	6 (43%)	not performed
Inhalant substances (n=3)	3 (5%)	0 (0%)	
Paint (n=9)	9 (14%)	0 (0%)	
Car Body Paint (n=2)	2 (3%)	0 (0%)	
Glue (n=4)	3 (5%)	1 (7%)	
Trichloroethylene (n=2)	1 (2%)	1 (7%)	
Lumber (n=1)	1 (2%)	0 (0%)	
Potassium cyanide (n=1)	0 (0%)	1 (7%)	
Pesticides and fertilizers; trichloroethylene (n=2)	2 (3%)	0 (0%)	
Paint; solvents (n=6)	4 (6%)	2 (14%)	
Paint, glue, solvents (n=2)	1 (2%)	1 (7%)	
Paint, inhalant substances (n=1)	1 (2%)	0 (0%)	
Other (n=3)	3 (5%)	0 (0%)	
Unspecified (n=17)	13 (25%)	2 (14%)	

Table 1. Sample Description.
Comparisons: Chi-squared test for categorical variables, Student's t-test for continuous variables. * statistical significance - p-value<0.05

E' emerso che nel primo gruppo vi era una maggiore numerosità di maschi (60%) mentre nel secondo gruppo erano prevalenti le femmine (66%), e tale differenza nella distribuzione per sesso è risultata statisticamente significativa (p<0.001).
I casi avevano un'età media di 68.28 ± 9.55 anni mentre i controlli di 65.18 ± 9.60. Benché questa differenza sia risultata statisticamente significativa (p<0.001), la probabilità che i tre anni di differenza – e quindi la possibilità che i controlli abbiano avuto tre anni di tempo in meno per sviluppare la malattia - possano avere distorto i risultati appare poco probabile.
Il campione è stato ulteriormente suddiviso in classi di età così definite: <55 anni, 55-59 anni, 60-64 anni, 65-69 anni, 70-74 anni, 75-79 anni, ≥80 anni; è apparso che una maggiore proporzione di controlli si distribuiva nelle classi di età inferiori ai 65 anni (p=0.004), tuttavia non è emersa una netta differenza.
Per lo studio del Body-Mass-Index (BMI) si è messo in relazione il peso attuale e il peso abituale di ciascun individuo e si sono classificati i soggetti in base alle seguenti classi di BMI: sottopeso BMI<18.50; normopeso BMI: 18.50-24.99; pre-obesità BMI: 25-29.99; obesità BMI≥30. E' emerso che una proporzione maggiore di casi rispetto ai controlli (8% vs 2%) ha subito un aumento di peso (attuale) tale da determinare un salto di classe di BMI, ed una proporzione maggiore di controlli rispetto ai casi è rimasta nello stessa classe (85% vs 77%) (p-value=0.001).
Nei pazienti inclusi sono stati indagati i seguenti possibili sintomi di esordio di malattia : tremore, stitichezza, depressione, iposmia, e disturbi del sonno. Il primo era presente in circa la metà del gruppo (54%), mentre gli altri sono risultati più rari, essendo presenti in circa il 30%-40% dei pazienti (stitichezza 42% ; depressione 40% ; iposmia 32% ; disturbi del sonno 39%).
La localizzazione iniziale di malattia era a destra nel 46% dei casi, a sinistra nel 49% e bilaterale nell'1%, non nota nel restante 4%.
Infine, la severità di malattia è classificata secondo la scala di Hoehn & Yahr, che copre un range da 1 a 5. In base a questa scala è risultato che la maggior parte dei casi aveva un punteggio tra 2 e 3 (28%), tuttavia lo stadio non è stato riportato nel 42% dei casi per cui si rende necessario il controllo delle cartelle cliniche dei pazienti inclusi, per risalire al dato mancante.
La tabella 2 riporta l'analisi descrittiva del campione.

Characteristics of Parkinson's Disease	CASES (N=520) N (%)
TREMOUR	
No	228 (44%)
Yes	281 (54%)
Unknown	11 (2%)
CONSTIPATION	
No	299 (56%)
Yes	216 (42%)
Unknown	11 (2%)
DEPRESSION	
No	301 (58%)
Yes	206 (40%)
Unknown	13 (2%)
HYPOSMIA	
No	343 (66%)
Yes	166 (32%)
Unknown	11 (2%)
SLEEP DISTURBANCES	
No	304 (58%)
Yes	202 (39%)
Unknown	14 (3%)
HOEN&YAHAR CLASSIFICATION	
Stage 1	18 (3%)
Stage 1.5	24 (5%)
Stage 2	115 (22%)
Stage 2.5	59 (11%)
Stage 3	78 (15%)
Stage 4	10 (2%)
Stage 5	1 (0.2%)
Unknown	217 (42%)
AFFECTED SIDE	
Bilateral	6 (1%)
Right	237 (46%)
Left	254 (49%)
Unknown	23 (4%)

Table 2. Case Cohort Description

Infine, un numero maggiore di casi (12% vs 5%) è risultato esposto a sostanze tossiche (quali pesticidi e concimi, vernici, colle, solventi e colori per pittura, vernici per carrozzeria, trielina, cianuro di potassio ecc) nelle attività di tempo libero (p=0.003).
Le abitudini alimentari sono state studiate approfondendo il quantitativo di frutta, verdura carne, pesce, salumi ed affettati, caffè, té, coca-cola/altre bibite, bibite energetiche, integratori alimentari, vino, birra e liquori assunto. E' emerso che i casi consumano meno verdura rispetto ai controlli (68% vs 78% di consumo giornaliero, p-value=0.023), mangiano più affettati e salumi (14% vs 6% di consumo giornaliero, p-value=0.016), e tendono a bere più frequentemente vino (41% vs 32% beve con regolarità, p=0.002). Non è emersa differenza statisticamente significativa tra casi e controlli rispetto ai restanti alimenti, bibite e integratori. La Tabella 3 riporta i risultati completi sulle abitudini alimentari.

Eating and Drinking Habits	CASES (N=520) N (%)	CONTROLS (N=257) N (%)	Comparison p-value
FRUIT			
Never (n=9)	1 (0.2%)	3 (1%)	0.130
Monthly (n=9)	6 (1%)	3 (1%)	
Weekly (n=121)	82 (16%)	29 (12%)	
Daily (n=644)	429 (83%)	215 (86%)	
VEGETABLES			
Never (n=3)	3 (1%)	0 (0%)	0.033*
Monthly (n=12)	9 (2%)	3 (1%)	
Weekly (n=204)	153 (30%)	51 (20%)	
Daily (n=546)	355 (68%)	196 (78%)	
MEAT			
Never (n=37)	21 (4%)	16 (6%)	0.088
Monthly (n=87)	55 (11%)	32 (13%)	
Weekly (n=377)	289 (75%)	188 (75%)	
Daily (n=67)	55 (10%)	12 (6%)	
FISH			
Never (n=24)	17 (3%)	7 (3%)	0.920
Monthly (n=166)	114 (22%)	52 (21%)	
Weekly (n=326)	278 (75%)	188 (75%)	
Daily (n=11)	8 (2%)	3 (1%)	
COLD CUTS-SALAME			
Never (n=49)	31 (6%)	18 (7%)	0.016*
Monthly (n=219)	92 (18%)	47 (19%)	
Weekly (n=493)	323 (62%)	170 (68%)	
Daily (n=58)	71 (14%)	15 (6%)	
COFFEE			
Never (n=80)	53 (10%)	27 (11%)	0.730
Monthly (n=22)	15 (3%)	7 (3%)	
Weekly (n=23)	18 (3%)	5 (2%)	
Daily (n=643)	432 (83%)	211 (84%)	
TEA			
Never (n=397)	293 (59%)	104 (42%)	0.860
Monthly (n=205)	139 (27%)	69 (28%)	
Weekly (n=101)	70 (14%)	33 (13%)	
Daily (n=150)	106 (20%)	44 (18%)	
COLA			
Non-drinker (n=407)	264 (51%)	143 (57%)	0.110
Drinker (n=361)	254 (49%)	107 (43%)	
ENERGY DRINKS			
Non-drinker (n=739)	506 (97%)	239 (96%)	0.420
Drinker (n=25)	15 (3%)	10 (4%)	
SUPPLEMENTS INTAKE			
No (n=636)	418 (82%)	198 (79%)	0.310
Yes (n=148)	94 (18%)	54 (21%)	
WINE			

Non-drinker (n=184)	105 (20%)	79 (31%)	0.007*
Occasional drinker (n=297)	169 (38%)	98 (37%)	
Drinker (n=296)	215 (41%)	82 (32%)	
BEER			
Non-drinker (n=313)	199 (38%)	114 (45%)	0.088
Occasional drinker-Drinker (n=464)	320 (62%)	141 (55%)	
LIQUEURS			
Non-drinker (n=616)	421 (80%)	215 (85%)	0.720
Drinker (n=180)	98 (19%)	32 (13%)	

Table 3. Eating and Drinking Habits.
Comparisons: Chi-squared test for categorical variables, Student's t-test for continuous variables. * statistical significance - p-value<0.05

Dall'analisi sulle aree di residenza degli individui è emersa una differenza statisticamente significativa soltanto relativamente alla residenza più recente; nello specifico, i casi hanno vissuto più a lungo in una zona urbana rispetto ai controlli (37.23 ± 20.39 anni vs 31.67 ± 18.40 anni, p<0.001), mentre non è emersa differenza per il numero medio di anni trascorsi in una zona rurale. Questo dato probabilmente è stato influenzato dall'ubicazione del nostro Centro, a cui afferiscono principalmente pazienti residenti in zone urbane.
I risultati su tutta la storia di residenza della popolazione campionaria sono riassunti in tabella 4.

Current and Previous Areas of Residence	CASES (N=329)	CONTROLS (N=257)	Comparison
	N (%)	N (%)	p-value
CURRENT AREA			
Rural (n=78)	53 (16%)	25 (10%)	0.350
Urban (n=696)	464 (80%)	230 (90%)	
Average years in rural area (n=78)	29.81 ± 19.01	30.44 ± 20.33	0.890
Average years in urban area (n=681)	37.23 ± 20.39	31.67 ± 18.40	<0.001*
PREVIOUS AREA 1			
Rural (n=58)	38 (9%)	20 (9%)	0.950
Urban (n=662)	395 (91%)	267 (91%)	
Average years in rural area (n=58)	22.34 ± 11.04	21.00 ± 10.25	0.670
Average years in urban area (n=662)	17.33 ± 13.54	15.57 ± 12.20	0.120
PREVIOUS AREA 2			
Rural (n=43)	28 (9%)	15 (9%)	0.870
Urban (n=648)	286 (91%)	162 (92%)	
Average years in rural area (n=43)	15.25 ± 8.44	18.40 ± 7.80	0.240
Average years in urban area (n=648)	13.32 ± 9.54	12.91 ± 9.04	0.510
PREVIOUS AREA 3			
Rural (n=24)	13 (7%)	11 (10%)	0.880
Urban (n=215)	174 (93%)	101 (90%)	
Average years in rural area (n=24)	19.85 ± 12.18	18.27 ± 14.20	0.810
Average years in urban area (n=275)	14.33 ± 10.41	13.47 ± 9.64	0.560
PREVIOUS AREA 4			
Rural (n=14)	8 (6%)	5 (5%)	0.770
Urban (n=126)	78 (95%)	58 (92%)	
Average years in rural area (n=14)	13.43 ± 6.00	10.40 ± 7.89	0.300
Average years in urban area (n=136)	10.58 ± 10.06	13.91 ± 9.31	0.140
PREVALENT AREA			
Rural (n=61)	40 (8%)	21 (8%)	0.610
Urban (n=711)	477 (92%)	234 (92%)	

Table 4. Description of Areas of Residence of the Sample Population.
Comparisons: Chi-squared test for categorical variables, Student's t-test for continuous variables. * statistical significance - p-value<0.05

Dall'analisi delle occupazioni professionali è emerso che, relativamente all'occupazione più recente, un gran numero di soggetti erano pensionati o non lavoravano (64% casi e 47% controlli); un numero maggiore di controlli erano casalinghe (22% vs 12%), oppure lavoravano in ufficio o negozio (24% vs 16%) (p=0.001). Questi risultati sono tuttavia da leggere in relazione all'età della campione che è mediamente di 67 anni, e alla distribuzione del sesso (66% di femmine fra i controlli).
Per tale ragione si sono studiate anche le professioni precedenti, per cui nel gruppo dei controlli è risultato prevalente il lavoro in ufficio o in negozio, mentre nel gruppo dei casi era più frequente il lavoro come artigiano o operaio. Infine per ciascun individuo si è considerato il lavoro eseguito per il maggior numero di anni ed è emerso che il 20% dei casi era stato artigiano o operaio, contro l'8% dei controlli; inoltre una proporzione maggiore di controlli aveva riportato come occupazione prevalente pensionato, nessuna attività lavorativa oppure casalinga (29% vs 11%) (p<0.001).

Current and Previous Job Occupation	CASES (N=520)	CONTROLS (N=257)	Comparison
	N (%)	N (%)	p-value
CURRENT OCCUPATION			0.001*
Farmer (n=6)	3 (0.6%)	3 (1%)	
Other (n=3)	2 (0.4%)	1 (0.4%)	
Social Worker/Sanitary Staff (n=16)	10 (2%)	6 (2%)	
House-keeper /House-wife (n=120)	63 (12%)	57 (22%)	
Soldier/Security (n=6)	5 (1%)	1 (0.4%)	
Artisan/Hand-Worker (n=20)	14 (3%)	6 (2%)	
Pension/Inactivity (n=432)	332 (64%)	120 (47%)	
Worker often on the Road (n=3)	2 (0%)	1 (0.4%)	
Clerk (n=147)	85 (16%)	62 (24%)	
PREVIOUS OCCUPATION 1			0.025*
Farmer (n=10)	8 (2%)	2 (1%)	
Other (n=7)	6 (1.5%)	1 (0.5%)	
Social Worker/Sanitary Staff (n=29)	19 (5%)	10 (5%)	
House-keeper /House-wife (n=17)	12 (3%)	5 (3%)	
Soldier/Security (n=14)	14 (4%)	0 (0%)	
Artisan/Hand-Worker (n=106)	82 (20%)	24 (13%)	
Pension/Inactivity (n=3)	2 (0.5%)	1 (0.5%)	
Worker often on the Road (n=16)	13 (3%)	3 (2%)	
Clerk (n=357)	246 (61%)	141 (75%)	
PREVIOUS OCCUPATION 2			0.120
Farmer (n=5)	2 (1%)	3 (5%)	
Other(n=6)	6 (4%)	0 (0%)	
Social Worker/Sanitary Staff (n=7)	5 (4%)	2 (3%)	
House-keeper /House-wife (n=2)	1 (1%)	1 (2%)	
Soldier/Security (n=7)	5 (4%)	2 (3%)	
Artisan/Hand-Worker (n=14)	11 (12%)	0 (0%)	
Pension/Inactivity (n=0)	0 (0%)	10 (16%)	
Worker often on the Road (n=7)	5 (4%)	2 (3%)	
Clerk (n=111)	69 (50%)	42 (68%)	
PREVALENT OCCUPATION			< 0.001*
Farmer (n=12)	9 (2%)	3 (1%)	
Other (n=12)	11 (2%)	1 (0.4%)	
Social Worker/Sanitary Staff (n=33)	24 (5%)	13 (4%)	
House-keeper /House-wife (n=105)	49 (10%)	56 (23%)	
Soldier/Security (n=18)	17 (3%)	1 (0.4%)	
Artisan/Hand-Worker (n=118)	99 (20%)	19 (8%)	
Pension/Inactivity (n=19)	5 (1%)	14 (6%)	
Worker often on the Road (n=13)	10 (2%)	5 (2%)	
Clerk (n=497)	271 (55%)	136 (56%)	

Table 5. Description of Job Occupation of the Sample Population.
Comparisons: Chi-squared test for categorical variables, Student's t-test for continuous variables. * statistical significance - p-value<0.05

Lo studio ha confermato i dati della letteratura che riportano un maggior rischio di malattia in soggetti che effettuano professioni che comportano il contatto con sostanze potenzialmente tossiche (ad es. artigiani, operai, agricoltori). Per meglio indagare questo interessante risultato, è in corso una classificazione delle esposizioni a tossici professionali mediante costruzione di job exposure matrixes.
Dall'analisi di regressione logistica semplice è stato stimato che i maschi hanno un odds di malattia quasi tre volte superiore rispetto alle femmine (p<0.001); tuttavia, come precedentemente accennato, questo risultato andrebbe verificato in un campione con ugual numero di casi e controlli e bilanciato per sesso. Inoltre, emerge un trend crescente per età, per cui soggetti con età compresa tra 75 e 80 anni hanno un odds di malattia di 2 volte superiore rispetto a soggetti di età < 55 anni (p=0.015), e i soggetti con 80 anni o più hanno un odds di 2.30 volte superiore (p=0.026). E' stato inoltre evidenziata un'associazione tra malattia e incremento di classe del BMI, per il quale è stato stimato un odds quasi 6 volte superiore rispetto ad una classe di BMI invariata (p=0.001). Si ritiene che quest'ultimo dato sia da confermare con un'analisi statistica su un campione meglio bilanciato. Il fumo attivo è risultato avere un effetto protettivo, con un odds ratio (OR) di 0.63 (p=0.038), e l'esposizione a sostanze tossiche nel tempo libero è risulta essere nociva (OR=3.52, p=0.001). E' inoltre emerso un trend per il consumo di carne e insaccati che raggiunge significatività statistica al consumo giornaliero (carne: OR=2.88, p=0.018; insaccati: OR=2.75, p=0.014). L'associazione con il consumo di vino è confermata, per cui risulta un odds di 1.97 (p-value=0.001) per un bevitore occasionale e un odds di 1.58 (p=0.019) per un bevitore regolare, rispetto ad un soggetto astemio. Infine, per l'analisi di regressione sono state considerate soltanto le professioni prevalenti. Rispetto ad un occupazione casalinga, ed escludendo il pensionamento o l'inattività, tutte le professioni sono risultate fortemente associate al Morbo di Parkinson.
Dall'analisi di regressione multipla mediante il metodo 'backward stepwise' è emerso che il sesso, l'età, la variazione di classe del BMI, il fumo attivo, il fumo passivo in casa, l'esposizione a sostanze tossiche nel tempo libero e il consumo di insaccati, il consumo di bevande energetiche e di liquori, e le professioni prevalenti nel campione sono tutti fattori associati al Morbo di Parkinson. L'assunzione di bevande energetiche, molte delle quali contenenti caffeina e taurina, è risultata come fattore protettivo anche se al limite della significatività (OR=0.40, p=0.065), così come l'assunzione di liquori (OR=0.56, p=0.038).
I risultati completi sono riassunti in tabella 6.

Potential Risk Factors	Unadjusted Odds Ratio	95% Confidence Interval	p-value	Adjusted Odds Ratio	95% Confidence Interval	p-value
SEX						
Female (n=479)	1.00			1.00		
Male (n=599)	2.93	2.14 - 4.01	<0.001*	2.23	1.48 - 3.34	<0.001*
AGE (YRS)						
<55 years old (n=90)	1.00			1.00		
55-59 years old (n=67)	0.77	0.41 - 1.47	0.433	0.75	0.34 - 1.65	0.478
60-64 years old (n=110)	0.96	0.55 - 1.70	0.896	0.97	0.48 - 1.97	0.937
65-69 years old (n=136)	1.28	0.74 - 2.20	0.373	1.32	0.67 - 2.6	0.426
70-74 years old (n=156)	1.67	0.99 - 2.84	0.056	1.74	0.9 - 3.35	0.098
75-79 years old (n=116)	2.09	1.15 - 3.81	0.015*	2.16	1.16 - 5.22	0.018*
≥80 years old (n=62)	2.29	1.10 - 4.74	0.026*	3.59	1.39 - 9.24	0.008**
EDUCATION						
Primary School or Analphabet (n=119)	1.47	0.87 - 2.49	0.151			
Secondary School (n=184)	0.83	0.54 - 1.28	0.396			
Diploma (n=253)	0.79	0.53 - 1.17	0.235			
University Degree (n=183)	1.00					
BMI (current)						
Underweight + BMI<18.50 (n=43)	0.62	0.22 - 1.75	0.365			
Normal Range - BMI: 18.50-24.99 (n=320)	1.00					
Pre-Obese - BMI: 25-29.99 (n=288)	1.41	1.01 - 1.97	0.045*			
Obese - BMI≥30 (n=94)	0.91	0.57 - 1.46	0.704			
BMI (usual)						
Underweight - BMI<18.50 (n=17)	0.68	0.23 - 1.82	0.439			
Normal Range - BMI: 18.50-24.99 (n=327)	1.00					
Pre-Obese - BMI: 25-29.99 (n=304)	0.96	0.69 - 1.35	0.833			
Obese - BMI≥30 (n=120)	0.95	0.61 - 1.48	0.807			
BMI change						
Weight loss - shift down in BMI class (n=103)	1.23	0.79 - 1.91	0.357	1.46	0.83 - 2.57	0.188
No weight change - no shift in BMI class (n=612)	1.00			1.00		
Weight increase - shift up in BMI class (n=47)	5.82	2.86 - 16.04	0.001**	4.84	1.81 - 14.58	0.012*
SMOKING HABITS						
No (n=399)	1.00			1.00		
Ex Smoker (n=268)	1.07	0.77 - 1.50	0.686	0.78	0.47 - 1.12	0.147
Yes (n=316)	0.63	0.41 - 0.98	0.038*	0.52	0.3 - 0.9	0.020*
LIVES WITH SMOKERS						
No (n=330)	1.00			1.00		
Yes (n=425)	1.11	0.82 - 1.50	0.501	1.84	1.11 - 2.41	0.013*
WORKS WITH SMOKERS						
No (n=471)	1.00					
Yes (n=302)	0.94	0.69 - 1.28	0.710			
TOXIC SUBSTANCES						
No (n=699)	1.00			1.00		
Yes (n=78)	3.52	1.65 - 7.52	0.001*	2.22	1.07 - 4.61	0.032*
FRUIT						
Never (n=6)	1.00					
Monthly (n=9)	6.00	0.42 - 85.25	0.186			

Potential Risk Factors	Unadjusted Odds Ratio	95% Confidence Interval	p-value	Adjusted Odds Ratio	95% Confidence Interval	p-value
Weekly (n=111)	8.48	0.85 - 84.81	0.069			
Daily (n=644)	5.99	0.62 - 57.89	0.122			
VEGETABLES						
Never/Monthly (n=15)	1.00					
Weekly (n=204)	0.75	0.20 - 2.76	0.666			
Daily (n=549)	0.45	0.13 - 1.61	0.221			
MEAT						
Never (n=37)	1.00					
Monthly (n=87)	1.31	0.60 - 2.86	0.500			
Weekly (n=577)	1.58	0.80 - 3.09	0.185			
Daily (n=67)	2.88	1.20 - 6.94	0.018*			
FISH						
Never (n=24)	1.00					
Monthly (n=166)	0.90	0.35 - 2.31	0.831			
Weekly (n=566)	0.83	0.34 - 2.03	0.680			
Daily (n=11)	1.10	0.22 - 5.40	0.908			
COLD CUTS-SALAME						
Never (n=49)	1.00			1.00		
Monthly (n=139)	1.14	0.58 - 2.24	0.712	1.22	0.54 - 2.73	0.634
Weekly (n=493)	1.10	0.60 - 2.03	0.752	0.98	0.48 - 1.98	0.946
Daily (n=86)	2.75	1.23 - 6.14	0.014*	3.88	1.41 - 10.67	0.009*
COFFEE						
Never (n=50)	1.00					
Monthly (n=22)	1.09	0.40 - 3.00	0.865			
Weekly (n=23)	1.83	0.61 - 5.48	0.277			
Daily (n=643)	1.04	0.64 - 1.71	0.867			
TEE						
Never (n=307)	1.00					
Monthly (n=205)	1.03	0.71 - 1.50	0.868			
Weekly (n=103)	1.09	0.67 - 1.75	0.732			
Daily (n=150)	1.23	0.81 - 1.88	0.330			
COLA						
Non-drinker (n=407)	1.00					
Drinker (n=361)	1.28	0.95 - 1.74	0.105			
ENERGY DRINKS						
Non-drinker (n=739)	1.00			1.00		
Drinker (n=25)	0.72	0.32 - 1.62	0.424	0.40	0.15 - 1.06	0.065
SUPPLEMENTS INTAKE						
No (n=616)	1.00					
Yes (n=145)	0.82	0.57 - 1.20	0.313			
WINE						
Non-drinker (n=184)	1.00					
Occasional drinker (n=297)	1.97	1.34 - 2.91	0.001*			
Drinker (n=294)	1.58	1.08 - 2.31	0.019*			
BEER						
Non-drinker (n=314)	1.00					
Occasional drinker-Drinker (n=461)	1.31	0.97 - 1.78	0.080			
LIQUORS						
Non-drinker (n=636)	1.00			1.00		
Drinker (n=100)	1.09	0.69 - 1.70	0.722	0.56	0.32 - 0.97	0.038*

PREVALENT RESIDENCE AREA						
Rural (n=61)	1.00					
Urban (n=711)	1.07	0.62 - 1.86	0.809			
PREVALENT OCCUPATION						
House-keeper /House-wife (n=105)	1.00			1.00		
Farmer(n=12)	3.43	0.88 - 13.38	0.076	4.73	0.87 - 25.79	0.073
Soldier/Security/Worker often on the Road/Other(n=45)	6.20	2.54 - 15.15	<0.001*	3.88	1.38 - 10.94	0.010*
Social Worker/Sanitary Staff (n=33)	2.49	1.11 - 5.61	0.027*	1.96	0.73 - 5.26	0.182
Artisan/Hand-Worker (n=118)	5.95	3.19 - 11.1	<0.001*	3.99	1.89 - 8.42	< 0.001*
Clerk (n=407)	2.28	1.47 - 3.52	<0.001*	1.83	1.06 - 3.13	0.029*

Table 6. Analysis of Risk Factors for Parkinson's Disease - Logistic Regression
Adjusting cofactors: Sex, Age, BMI Change, Smoking Habits and Living with Smokers, Toxic Substances, Cold Cuts-Salame, Energy Drinks, Liquors, Prevalent Occupation excl.Pension/Inactivity.
* statistical significance - p-value<0.05

Successivamente sarà necessaria un'attenta analisi delle relazioni di confondimento e interazione fra tutti i potenziali fattori di rischio, e dovrà essere eseguita una analisi di regressione multipla che tenga conto di tali relazioni per verificare i reali fattori di rischio per il Morbo di Parkinson.

Area di Ricerca Cefalea e Dolore Neuropatico

L'IMPATTO DELLA CEFALEA CRONICA PER LA SANITÀ PUBBLICA – CREAZIONE DI UN REGISTRO PER LA EMICRANIA CRONICA

Progetto in collaborazione con Istituto Superiore di Sanità e altri centri Cefalee Italiani

Secondo le recenti stime dell'Organizzazione Mondiale della Sanità i pazienti affetti da emicrania nel mondo sono 1.012.944.000 (Lim et al 2012). L'emicrania è quindi la terza malattia più frequente del genere umano e si conferma la malattia neurologica più disabilitante (2.6 volte più della Sclerosi Multipla, 3.3 volte più dell'Alzheimer, 40.6 volte più del Parkinson).
L'emicrania cronica (EC), cioè una cefalea presente >15 giorni al mese, deriva dall'evoluzione progressiva di un'emicrania in forma episodica (EE). Si calcola che ogni anno approssimativamente il 2.5% dei soggetti affetti da EE presenti una trasformazione in forma cronica (Manack AN et al 2011) e che tale percentuale può raggiungere il 14% se rilevata in centri specialistici (Katsarava et al 2004). La prevalenza della EC nella popolazione generale varia considerevolmente in rapporto all'area geografica ed anche in relazione ai diversi criteri classificativi. Essa oscilla dal 0.5% al 5.1%, con una prevalenza media del 1.4% - 2.2%, simile a quella della epilessia (Natoli JL et al 2010).
Esistono dei fattori di rischio riconosciuti per la trasformazione dell'emicrania episodica (EE) in EC: sesso femminile, età, basso livello socioeconomico, separazione o divorzio, eventi stressanti, obesità, russamento, patologie dolorose concomitanti, traumi cranici o cervicali, abuso di caffeine, iperuso di farmaci, ansia, depressione, presenza di allodinia durante l'attacco emicranico ed una frequenza degli attacchi emicranici > 6/mese (Lipton RB et al 2009).
E' dimostrato che i soggetti con EC, rispetto a quelli con EE, hanno maggiori comorbilità (psichiatriche, cardiocerebrovascolari, respiratorie, dolori cronici, osteoartrosi e obesità) (Buse et 2010; Bigal et al 2008) ed imponenti costi economici diretti (spese mediche, farmaci, ospedalizzazione) ed indiretti (mancata produttività, assenteismo); in Italia circa 3.5 miliardi di euro all'anno (Bloudek LM et al 2012).
L'EC è una patologia ad alto impatto economico sia per il soggetto sia per il sistema sanitario. Lo studio longitudinale americano AMPP (American Migraine Prevalence and Prevention) ha stimato una media di costi annuali per persona, includendo i costi diretti e quelli indiretti, circa 4.4 volte maggiori per i soggetti affetti da EC rispetto a quelli con EE (7.750$ vs 1.757$) (Munakata et al 2009). Le spese mediche, l'accesso al pronto soccorso, le visite mediche generali o specialistiche sono significativamente maggiori nei soggetti con EC rispetto a quelli con EE con costi totali diretti per individuo oltre 10 volte superiori e quasi 50 volte maggiori rispetto a soggetti con altre forme di cefalea episodica(Lantéri-Minet M et al 2003). I soggetti affetti da EC hanno maggiore disabilitá (scala MIDAS: 63.4 EC vs 10 EE) (Lipton 2010), significativa riduzione della qualità della vita (Lantéri-Minet M et al 2011), minore produttività, e minor probabilità di avere impieghi full time (37.8% EC vs EE 52,3%) e circa il doppio di probabilità di essere disoccupati (20% EC vs EE 11.1%) (Buse et al 2010; Blumfeld et al 2011). Più della metà dei pazienti con EC (57.4%) ha riportato una perdita di 5 giorni di lavoro o scuola in più nei precedenti 3 mesi rispetto a quelli affetti da EE (24.3%) ed il 58.1 % una ridotta produttività in confronto al 18.2% nella EE (Buse et al 2012).
Malgrado l'alta prevalenza e la disabilità della EC, solo il 6.6% dei soggetti con EC assume un farmaco preventivo antiemicranico, i restanti 84,6% solo farmaci analgesici per l'attacco, in prevalenza antinfiammatori, che per altro risultano efficaci solo nella metà dei casi (Lantéri-Minet M et al 2003). Non stupisce come la metà dei soggetti con EC vada incontro alla medication overuse headache (MOH) con un rischio globale che si aggira tra 31.1%-69.2% (Prencipe M et al 2001; Zwart et al 2004; Castillo et al 1999). Solo un quarto dei pazienti con EC ritorna a forma episodica

in un periodo di 2 anni, quelli che continuano ad essere cronici malgrado la profilassi hanno un aumento della disabilità correlato alla cefalea (Manack A et al 2010). L'utilizzo di esami diagnostici e strumentali nei soggetti con CDH è molto alto, nel lavoro di Lantéri-Minet M (Lantéri-Minet M et al 2003) si è stimato che il 53,8% dei soggetti avesse effettuato esami strumentali per la cefalea. Da queste osservazioni deriva la necessità di creare un registro per la emicrania cronica per meglio caratterizzare ed affrontare questa probabilità.

Gli obiettivi del registro sono di diverso tipo:
- Clinico-assistenziali: garantire identificazione, visibilità ed accesso alle cure per la popolazione affetta da EC.
. Economici:
Consentire la riduzione dell'enorme aggravio economico per il SSN e per la società rappresentato da tali pazienti in termini di costi diretti (visite mediche, procedure diagnostiche o terapeutiche inutili/inadeguate, accessi al PS o ospedalizzazioni) ed indiretti (riduzione della produttività, assenteismo) mediante il controllo del grado di appropriatezza diagnostico-terapeutica dei diversi centri/ospedali, promuovendo l'applicazione delle vigenti linee guida AGENAS (www.agenas.it/agenas_pdf/Cefalea%20nell'adulto%20.pdf).
- Regolamentare l'accesso dei pazienti alle moderne procedure terapeutiche ad alto costo (impianto di neurostimolatori, tossina botulinica ecc).
- Medico-legali: definire i criteri di farmacoresistenza nella EC allo scopo di ottenere l'estensione a tutto il territorio nazionale di quanto previsto dalla Circolare Regionale della Lombardia n° 30 del 14/12/06 pubblicata sul BUR regionale il 15/1/07 in tema di invalidità civile per le cefalee croniche farmacoresistenti.
- Scientifici: creare il primo database al mondo sulla EC. Al database clinico-epidemiologico sarà associato un database biologico che consentirà lo sviluppo di studi di correlazione fenotipo-biotipo (biobanca, system-medicine).
Il riferimento del registro sono i medici operanti nei centri cefalee ospedalieri, universitari e territoriali italiani selezionati.
Le figure professionali coinvolte sono: neuroepidemiologo (ISS), biostatistico (ISS), neurologi (3 dell'IRCCS San Raffaele Pisana) e i neurologi dei centri selezionati, data Manager (ISS), biologo (IRCCS San Raffaele Pisana).
I dati demografici, epidemiologici e clinici dei pazienti vengono raccolti mediante una apposita scheda su un portale web creato ad hoc.
Vengono identificati 2 neurologi di riferimento che saranno disponibili a fornire per via telefonica, web o fax informazioni dettagliate su procedure ecc.
Nel corso del 2014 con la collaborazione dei centri partecipanti, ad hoc è stato costruito un database informatizzato per la raccolta di tutti i dati e le variabili previste nel protocollo.

Area di Ricerca Cardiovascolare

CENTRO NAZIONALE PER LA PREVENZIONE E IL CONTROLLO DELLE MALATTIE (CCM)

Piattaforma Italiana per lo studio delle polimorbidità:scenario epidemiologico, aspetti clinici e farmacologici, prospettiva di genere e contesto farmaco-economico.

Ente coordinatore responsabile: Istituto Superiore di Sanità
Istituti coinvolti: IRCCS San Raffale Pisana e Agenzia Nazionale per i Servizi Sanitari (AGENAS).

L'Unità Operativa coinvolta dell'IRCCS San Raffaele, si è occupata di coordinare le attivita di analisi dei database del San Raffaele Roma Pisana, del gruppo CINECA di Bologna e dell'AGENAS di Roma, per la mappatura dell'impatto assistenziale delle polimorbidità in Italia. In questa prima fase, ogni singola Unità Operativa ha effettuato le analisi preliminari sui rispettivi database di pertinenza, relativamente a:
1. Valutazione della distribuzione delle prescrizioni farmacologiche;
2. Valutazione della distribuzione di alcune diagnosi principali: malattia coronarica (CAD), insufficienza cardiaca congestizia (ICC), ipertensione arteriosa (IA), dislipidemia, diabete mellito, broncopneumopatia cronica ostruttiva (BPCO).
L'Unità Operativa ha utilizzato il database delle RSA (progetto Atlante) di pertinenza dell'IRCCS San Raffaele Pisana.
Relativamente alla distribuzione delle prescrizioni farmacologiche e polifarmacoterapia si è osservato che, all'interno del campione (n=727), ogni paziente assume in media più di 5 farmaci (precisamente: 5.6, deviazione standard: 2.9).
La distribuzione dei farmaci a seconda delle diverse classi di appartenenza è riportata in Tabella 1.

Tabella 1. Distribuzione dei farmaci nel campione IRCCS Sar

Classi di farmaci	Frequenza (%) (n=727)
Farmacigastrointestinali	
Lassativi	61 (8.4%)
Antiulcera	502 (69.1%)
Farmacicardiovascolari	
Aspirinaedantitrombotici	394 (54.2%)
Diuretici	284 (39.1%)
Ace inibitori	130 (17.9%)
Beta bloccanti	102 (14.0%)
Calcioantagonisti	86 (11.8%)
Statine	69 (9.5%)
Antagonisti del recettore dell'angiotensina II	57 (7.8%)
Digitale	45 (6.2%)
Farmacineurologici	
Antipsicotici	263 (36.2%)
Benzodiazepine	198 (27.2%)
Antidepressivi	184 (25.3%)
Antidementigeni	20 (2.8%)
Antiparkinsoniani	89 (12.2%)
Altreclassi di farmaci	
Analgesici	58 (8.0%)
Antiosteoporosi (includevit. D)	76 (10.5%)
Ipoglicemiciorali	72 (9.9%)
Insulina	59 (8.1%)
Corticosteroidi	18 (2.5%)

Una volta ultimate le elaborazioni dei dati anche per genere ed età, ed effettuato un merge dei risultati derivanti dai database delle altre Unità Operative, si procederà allo sviluppo di un algoritmo basato sul web e struttuato per punti nodali, per la diagnosi di pazienti anziani affetti da polimorbidità cardiometaboliche e respiratorie. Lo sviluppo dell'algoritmo avverrà utilizzando Case Builder™ (www.case-builder.com), un software appositamente progettato per scopi educativi e di analisi di dati.
Case Builder™ permetterà infatti la costruzione di algoritmi per sviluppare percorsi di trattamento, disponibili su una piattaforma gratuita educativa accessibile previa registrazione. Il gruppo di ricerca è stato formato all'utilizzo del software ed ha già pubblicato alcuni algoritmi per la diagnosi ed il trattamento di patologie cardiovascolari, disponibili sul sito dell'International society of Cardiovascular Pharmacology (ISCP) (http://iscp02.3psmedia.net/Learning).
Dopo aver creato il suddetto algoritmo per la diagnosi dei pazienti anziani con polimorbidità e per l'uso terapeutico di farmaci che agiscono sui sistemi cardiometabolico e respiratorio, si prevede, la diffusione dello stesso a scopo educativo, in modo che sia disponibile ai medici sulla piattaforma interattiva online gratuita, previa registrazione.

CENTRO NAZIONALE PER LA PREVENZIONE E IL CONTROLLO DELLE MALATTIE – CCM 2011

Modelli innovativi di gestione integrata tele-gestita ospedale-territorio del malato cronico a fenotipo complesso: studio di implementazione, validazione ed impatto

Centro coordinatore: Fondazione Salvatore Maugeri Lumezzane IRCCS San Raffaele Pisana, Unità Operativa 2
Altre Unità Operative coinvolte: Regione Veneto, Università di Firenze.

La broncopneumopatia cronica ostruttiva (BPCO) è comune nei pazienti con scompenso cardiaco (SCC) ed è predittiva di mortalità in modo indipendente; la stessa cosa vale per lo SCC che è, a sua volta, comune nei soggetti affetti da BPCO, nei quali si riuniscono molteplici fattori di rischio cardiovascolare. Si tratta quindi di un malato complesso, multimorbido, spesso fragile che mostra un altissimo rischio di re-ospedalizzazioni e che necessita di una cura integrata con un approccio personalizzato e multidisciplinare.
Si tratta di uno studio randomizzato (1:1), controllato, prospettico della durata di 4 mesi più ulteriori 4 mesi di follow-up. Nei quattro centri coinvolti sono arruolati 120 pazienti con fenotipo complesso (SCC e BPCO accertate e documentate) con almeno una ospedalizzazione per una delle due cause nei 6 mesi precedenti. Nel gruppo di trattamento i pazienti sono seguiti al domicilio tramite un percorso di telesorveglianza e riallenamento domiciliare all'esercizio fisico. I pazienti del gruppo controllo sono seguiti tramite l'assistenza usuale fornita a questa tipologia di pazienti. Vengono eseguite visite di controllo a 4 mesi ed 8 mesi in cui verranno eseguiti esami clinici, questionari e scale di valutazione.
Obiettivo principale del programma è la valutazione della fattibilità ed efficacia di un modello organizzativo di gestione integrata di continuità di cure ospedale-territorio, basato su una piattaforma innovativa di tele-gestione, monitoraggio e teleriabilitazione nel paziente affetto da malattia cronica a fenotipo complesso (modellizzato sul cluster Scompenso Cardiaco/BPCO).
L'obiettivo primario dello studio consiste nella riduzione delle ospedalizzazioni per tutte le cause. Gli obiettivi secondari prevedono la riduzione delle ospedalizzazioni cardiovascolari e/o respiratorie, il miglioramento della tolleranza allo sforzo (test del cammino), il miglioramento della qualità della vita, la riduzione delle instabilizzazioni senza ricovero, la riduzione della disabilità, l'incremento della capacita funzionale, l'esecuzione di almeno il 70% delle sedute riabilitative

proposte e la valutazione economica organizzativa.
Il programma proposto vuole intervenire sui molteplici problemi medico-infermieristici e gestionali che il paziente con patologia cronica deve affrontare alla dimissione. L'equipe che dimette il paziente ha la funzione di coordinare e favorire l'apprendimento delle tecniche di autogestione della malattia, che permettono al paziente l'identificazione delle condizioni sub-critiche prevenendo il più possibile le riacutizzazioni. Il piano educazionale che coinvolge i familiari riveste un ruolo cruciale per la riuscita del programma e costituisce una componente preponderante nella fase ospedaliera preparatoria alla dimissione. L'infermiere ed il fisioterapista assumono un ruolo centrale in tutti gli interventi domiciliari di continuità di cura ed diventano una interfaccia essenziale nel dialogo tra paziente e specialista. L'infermiere e il fisioterapista, ognuno per le proprie competenze, hanno il compito di raccogliere informazioni riguardanti anamnesi e sintomi, svolgono attività di educazione sanitaria, di training, di verifica dell'aderenza alle prescrizioni, di valutazione del benessere generale, del grado di assistenza fornito dal caregiver, di aggiornamento della scheda clinica. Se necessario inoltre attivano l'intervento dello specialista per il consulto o la second-opinion telefonica.
Nel 2014 sono stati arruolati 40 pazienti (20 gruppo A e 20 gruppo B); terminato l'arruolamento il follow up terminerà a marzo 2015. Ogni paziente ha eseguito valutazione cardiologica, ECG, Ecocardiogramma, EGA, spirometria e valutazioni funzionali.

AGENZIA SPAZIALE ITALIANA (ASI)

Exerc/Orthostatic Tolerance (originariamente: "Different kinds of structured exercise training as countermeasure to space flight-induced orthostatic intolerance and muscolo-skeletal function impairment")

Gli astronauti si adattano bene alla microgravità dell'ambiente spaziale, ma quando ritornano sulla terra presentano segni di intolleranza ortostatica e decondizionamento fisico. Anche dopo voli brevi circa il 20% degli astronauti presenta sintomi sincopali o presincopali quando il soggetto assume la posizione eretta il giorno dell'atterraggio; e lo stesso vale per circa l'83% degli astronauti dopo voli spaziali di lunga durata. I meccanismi alla base di questa reazione non sono stati ancora del tutto definiti, probabilmente perché nel fenomeno sono coinvolti più fattori. Le alterazioni del sistema nervoso atonomo e delle funzioni neuromuscolari indotte dalla permanenza nello spazio sono considerate come le più probabili concause di questo problema. L'incapacità di elevare adeguatamente le resistenze periferiche (vasocostrizione) e la ipovolemia che si verifica durante i voli sono considerati i fattori principali dell'intolleranza ortostatica post volo.
Blaber et al hanno utilizzato la variabilità della frequenza caridaca (HRV) per determinare se la regolazione autonoma del cuore negli stessi 29 astronauti che hanno o non hanno avuto episodi di intolleranza ortostatica dopo il volo spaziale fosse differente prima di tale volo, e/o se fossero influenzate in modo differente da voli spaziali di minor durata (8-16 giorni). Coloro che hanno portato a termine il test senza sintomi e coloro che non lo hanno portato a termine hanno entrambi presentato un incremento dell'attività simpatica in risposta al test ortostatico prima del volo, ma solo i primi hanno mantenuto la medesima risposta dopo il volo, mentre i secondi hanno presentato un ridotto bilancio simpatico-vagale e una maggiore attività parasimpatica in posizine supina prima del volo.
Questi risultati suggeriscono che lo stato neurovegetativo nella fase pre-volo e l'alterazione del controllo del cuore e della vascolatura nella fase post-volo possano contribuire all'insorgere dell'intolleranza ortostatica.
Inoltre, anche una attenuata funzione baroriflessa cardiaca piuò compromettere la capacità di massimizzare l'aumento della frequenza cardiaca e, di conseguenza, la portata cardiaca in posizione eretta dopo il volo spaziale. L'attenuazione della risposta cronotropa cardiaca mediata dai baroriflessi arteriosi negli astronauti con pre-sincope in seguito all'esposizione all'ambiente microgravitazionale potrebbe quindi contribuire all'intolleranza ortostatica, limitando la risposta tachicardica in aggiunta agli effetti sulla vasocostrizione periferica. E' stato rilevato che durante Lower Body Negative Pressure (LBNP) l'attivazione simpatica muscolare (MSNA) era inferiore prima dell'esordio dei sintomi presincopali nei soggetti con intolleranza ortostatica mentre l'attivazione della MSNA era preservata nei soggetti tolleranti dopo BED rest di breve durata. Questi risultati supportano la tesi di una ridotta attività simpatica in soggetti con ipotensione ortostatica. Dai dati riportati si evince che le alterazioni nella regolazione autonomica cardiovascolare rappresentano uno dei principali meccanismi responsabili dell'intolleranza ortostatica.
Molte contromisure sono state testate per contrastare l'intolleranza ortostatica. Tra queste l'esercizio fisico è stato quello maggiormente utilizzato durante il volo spaziale a causa della sua prevedibile capacità di avere un effetto positivo sulla capacità fisica, sulla regolazione del sistema nervoso autonomo, sulla forza muscolare, la resistenza e la potenza che insieme sono indebolite dall'assenza di gravità. L'esercizio fisico è una importante componente della routine lavorativa durante i voli spaziali e potrebbe avere effetti salutari su vari disturbi causati dalla microgravità, incluso l'indebolimento muscolo-scheletrico e l'intolleranza ortostatica post-volo.
L'importanza di mantenere l'astronauta in forma durante i voli spaziali più lunghi è resa evidente dal fatto che la pratica routinaria dell'attività fisica è considerata obbligatoria dalle Autorità Responsabili delle missioni.
Ad oggi gli astronauti dedicano 2/3 ore al giorno all'attività fisica durante il volo. Nonostante ciò, l'esercizio fisico si è dimostrato solo parzialmente efficace nel contrastare il decondizionamento cardiovascolare e l'intolleranza ortostatica dopo i voli spaziali.
Secondo i dati esaminati, nessun programma di esercizio fisico strutturato è stato mai svolto dagli astronauti specificamente rivolto a valutare gli adattamenti neurovegetativi in risposta a uno specifico programma di allenamento quale definito dalla dose di attività fisica da svolgere al fine di prevenire o almeno ridurre l'intolleranza ortostatica che si verifica al rientro nello spazio gravitazionale terrestre dopo voli spaziali.
Non è stata ancora identificata la prescrizione ottimale di esercizio negli astronauti (in termini di modalità, frequenza, intensità e durata) per raggiungere questo scopo.
La dose di allenamento influenza fortemente la regolazione nervosa cardiovascolare.
Recentemente il gruppo di ricerca ha sviluppato un nuovo metodo, chiamato TRIMPi (individualized Training IMPulse), che rappresenta una misura integrata e individualmente detereminata, delle risposte biologiche al carico di allenamento. Questo metodo utilizza un unico parametro che tiene conto degli effetti sia del volume che dell'intensità del programma di allenamento; cioè la dose di esercizio, sulla regolazione nervosa cardiovascolare. Questo metodo è stato utilizzato sia in corridori di maratona che in pazienti affetti da insufficienza cardiaca.
E' stato riscontrato un rapporto dose-response curvilineo tra il carico di allenamento individualizzato (cioè il valore di TRIMPi) e i parametri che esprimono il funzionamento del sistema nervos autonomo con un incremento della variabilità del componente a bassa frequenza del battito cardiaco e della pressione arteriosa, marker di modulazione simpatica cardiaca e vascolare, al picco del carico di esercizio allenante.
L'aumento di attività simpatica diretta al cuore e ai vasi potrebbe essere fondamentale nel prevenire l'intolleranza ortostatica poiché una ridotta risposta simpatica vasocostrittrice rappresenta un meccanismo predominante dell'intolleranza ortostatica assieme al contributo di un incremento relativamente attenuato della frequenza cardiaca (FC). Pertanto, piani di allenamento di resistenza aerobica, di elevata intensità, programmati individualmente sulla base del TRIMPi, potrebbero dimostrarsi efficaci nel contrastare l'intolleranza ortostatica degli astronauti dopo voli spaziali.
Il progetto si prefigge di valutare l'efficacia di un programma di allenamento aerobico strutturato, personalizzato in base al TRIMPi, nel prevenire l'intolleranza ortostatica e i meccanismi che ne sono all'origine, legati principalmente alla regolazione nervosa cardiovascolare, in astronauti durante un volo spaziale. Come metodologia consolidata per la valutazione del controllo nervoso del sistema cardiovascolare durante lo stress ortostatico (ortostatismo attivo) pre e post volo

spaziale, vengono utilizzati l'analisi spettrale della variabilità FC e della pressione arteriosa e la sensibilità baroriflessa.
A tal fine gli astronauti utilizzano sistemi esistenti di esercizio e di monitoraggio cardiovascolare presenti a bordo della Stazione Spaziale Internazionale (ISS) come il tapis-roulant, e il modulo ARMS (un sistema di ricerca fornito dall'Agenzia Europea Spaziale che dovrebbe essere disponibile a terra e a bordo dello shuttle o dello European Physiological Module).
Durante i due mesi precedenti il lancio un membro dell'equipaggio esegue un test da sforzo incrementale al tredmill a esaurimento muscolare, registrante la FC e i livelli di acido lattico presenti nel sangue (campioni di 25ml di sangue capillare dal lobo dell'orecchio) per la determinazione del TRIMPi individualizzato.
Nello stesso periodo viene eseguito il test di tolleranza ortostatica che consiste in 10 minuti di riposo supino seguiti da 20 minuti di stazione eretta senza supporto (Ortostatismo attivo) mentre la pressione arteriosa, la FC e l'attività respiratoria sono registrate in maniera continua, battito a battito, in maniera non invasiva, con l'ausilio dei sistemi in dotazione alla NASA.
Durante l'intera missione gli astronauti compiono il programma di allenamento strutturato progettato prima del volo sulla base del metodo TRIMPi, secondo la programmazione prevista per la regolare attività fisica a bordo, che dovrebbe consistere approssimativamente di due ore al giorno (una la mattina e una nel pomeriggio). Durante la sessione di esercizio aerobico gli astronauti indossano un cardiotacografo in grado di memorizzare i dati di FC.
Entro 4 giorni dall'atterraggio (dal giorno 3 + 1) l'astronauta esegue un test di tolleranza ortostatica che consiste in 10 minuti di riposo supino seguiti da 20 minuti di stazione eretta senza supporto (Ortostatismo attivo) mentre la pressione arteriosa, la FC e l'attività respiratoria sono registrate in maniera continua, battito a battito, non invasiva con l'ausilio dei sistema in dotazione alla NASA, come fatto nel periodo pre-volo.
Il controllo nervoso del sistema cardiovascolare a riposo e in risposta allo stress ortostatico è valutato mediante analisi spettrale della variabilità della FC (HRV) e della pressione arteriosa, utilizzando un algoritmo auto regressivo su tutti i parametri registrati. In breve, dalle serie di variabilità battito per battito di lunghezza e stazionarietà adeguata (solitamente da 250 a 355 battiti) il software elabora semplici statistiche e la miglior stima auto regressiva della densità spettrale di potenza per la FC e la PA.
La potenza delle componenti spettrali a bassa e alta frequenza (rispettivamente LF e HF) della FC è espressa sia in unità assolute (msec 2) che normalizzate (n.u.); quelle della pressione arteriosa solo in unità assolute (mmHg2). Il controllo baroriflesso integrato della FC è calcolato mediante il metodo delle sequenze. Con questo metodo le serie temporali battito per battito della pressione arteriosa sistolica (SAP) e dell'intervallo RR vengono analizzate alla ricerca di sequenze di tre o più battiti consecutivi in cui la SAP e l'intervallo RR variano nella stessa direzione, sia in aumento che in diminuzione (cioè +RR/+SAP e –RR/-SAP). Queste sequenze sono state identificate come sequenze baroriflesse. Una regressione lineare viene applicata a ciscuna sequenza individuale e soltanto quelle sequenze in cui r2 è >0.85 vengono accettate e ne viene calcolata l'inclinazione (slope). Viene quindi calcolato lo slope medio ottenuto dalla media di tutti gli slope individuali rilevanti nel periodo di test, il quale è considerato una misura integrata della sensibilità baroriflessa (BRS) spontanea per quel periodo sperimentale. La componente LF nella variabilità dell'intervallo RR e della PA sono considerate espressione della regolazione simpatica efferente cardiaca e vascolare, rispettivamente mentre la componente HF nella variabilità dell'intervallo RR è considerata una espressione della modulazione vagale cardiaca, come lo è la BRS.
La metodologia globale è già stata impiegata con successo per valutare il controllo nervoso del sistema cardiovascolare non solo in studi di microgravità simulata (BED-REST) ma anche nello spazio, come durante la missione Shuttle STS 107 Columbia.
I dati ottenuti da questo studio potrebbero fornire una base per la progettazione efficace di programmi di addestramento all'esercio fisico che gli astronauti possono effettuare in future missioni di lunga durata sull'ISS, in cui protocoli di contromisure di attività fisica sono fortemente consigliate dall'Agenzia Spaziale Europea e dalla NASA.
Lo sviluppo di contromisure specifiche per accelerare la riabilitazione in missioni di esplorazione

potrebbe trovare delle applicazioni cliniche nel prevenire disturbi legati all'inattività o a problemi di gravitazione e alle persone con disabilità qui sulla terra. Queste misure consentono di prevenire disfunzioni autonomi che legate allo stress gravitazionale sono come quelle riscontrate nei soggetti allettati e con scompenso cardiaco come ipotensione ortostatica, l'atrofia o antigravità dei muscoli. Questo punto è particolarmente importante per una società che sta invecchiando con molte persone anziane costrette a letto. La conoscenza accumulata dagli studi sulle funzioni neurali autonomiche nello spazio dovrebbe essere di grande utilità per stabilire contromisure e metodi preventivi efficaci per diverse categorie di pazienti caratterizzati da segni e sintomi di disfunzioni autonomiche.

AGENZIA ITALIANA DEL FARMACO (AIFA) – BANDO 2009

Trattamento farmacologico nell'anziano con patologia cardiovascolare associata a malattie croniche: inappropriatezza prescrittiva e valutazione di esito nella popolazione istituzionalizzata e residente in comunità

Centro Coordinatore: Dipartimento di Farmacologia Clinica e Preclinica, Università di Firenze
Unità 1: IRCCS San Raffaele Pisana, in collaborazione con le Regioni Lazio e Puglia

Il presente studio è osservazionale, retrospettivo multicentrico e coinvolge tra le varie Unità Operative anche il Dipartimento di Scienze Internistiche dell'IRCSS San Raffaele Pisana.
Lo studio è volto a identificare, come obiettivi primari:
- i principali indicatori di prescrizione inappropriata (PI) tra pazienti anziani, istituzionalizzati e residenti in comunità, affetti da malattie cardiovascolari (insufficienza cardiaca, aritmia cardiaca, malattia coronarica, ictus ischemico ed emorragico) e altre comorbidità croniche;
- la relazione tra gli indicatori di PI identificati e end-point "difficili" nelle suddette coorti di pazienti anziani.
Nel progetto è prevista la valutazione delle cartelle cliniche/database di pazienti in tre differenti setting: ricoveri ospedalieri (setting A), database di medicina generale (setting B) e residenze comunitarie o case di cura (setting C).
Il Dipartimento di Scienze Internistiche dell'IRCSS San Raffaele Roma Pisana si occupa dell'analisi retrospettiva dei dati tratti dalle cartelle cliniche delle Residenze Sanitarie Assistenziali (RSA) relative alle regioni Lazio e Puglia.
Nell'anno 2013 è stato effettuato un emendamento sostanziale al progetto relativo alla modificazione del periodo di revisione dei dati clinici relativi al setting C (RSA). Tale emendamento è stato richiesto in seguito alla pubblicazione nel 2012 di nuovi criteri di PI che avrebbero potuto influenzare l'approccio prescrittivo da parte del personale medico. Per quanto riguarda la costruzione dei database delle RSA, poichè la numerosità campionaria della popolazione sarebbe potuta non essere sufficiente qualora si fossero identificati i soli soggetti con diagnosi "incidente" di patologia cardiovascolare al baseline, è stato deciso di utilizzare i soggetti con patologia cardiovascolare "prevalente" riservandosi di valutare la numerosità dei soggetti "incidenti" per eventuali analisi di sensibilità.
Per la costruzione del database dei dati amministrativi, le dimensioni hanno permesso di identificare una coorte di soggetti con patologia cardiovascolare incidente (data indice) al baseline.
Le patologie concomitanti in studio sono state identificate nel periodo precedente (o concomitante) la data indice. E'stato deciso di considerare ogni categoria farmacologica che, qualora

impiegata nel soggetto anziano con patologia cardiovascolare ed altre comorbidità, incrementi il rischio di eventi cardiovascolari acuti, ospedalizzazione e mortalità (esiti primari del protocollo). A tal scopo sono stati esaminati i criteri di inappropriatezza ad oggi noti (es.: Beers) integrati da una revisione della letteratura esistente incentrata sul paziente anziano con patologia cardiovascolare. Gli indicatori sono stati quindi esaminati, in questa fase, senza escludere i farmaci cardiovascolari (o altre categorie farmacoterapeutiche) che, per caratteristiche delle popolazioni in cui saranno "validati", avrebbero potuto comportare problematiche di interpretazione dei risultati (i.e., confondimento da indicazione).
E' stata creata una query "standard" che identifica ed estrae nei database amministrativi, attraverso il flusso delle dimissioni ospedaliere, i pazienti affetti da patologie cardiovascolari (SDO codificate tramite gli specifici ICD9CM indicati nel protocollo). Tale query verrà successivamente adattata alle strutture dati dei sistemi informativi delle varie unità.
E' attualmente in corso la definizione degli indicatori di PI, mediante due fasi:
1. revisione degli indicatori ad oggi noti (es.: criteri di Beers) assieme ad una valutazione sistematica sia delle linee guida di trattamento delle patologie per le quali i 'farmaci inappropriati' in studio vengono impiegati (i.e., approccio di definizione degli indicatori CRIME) che della letteratura medica;
2. valutazione degli indicatori selezionati effettuata in base ad un consenso di esperti tramite il metodo Delphi (i.e., scala "tipo Likert").
Sono stati presi in esame, assieme ai nuovi indicatori, anche i criteri selezionati dal GeriatricWorking Group AIFA.
Nel 2015 ci si propone di calcolare la densità di incidenza delle malattie cardiovascolari per i soggetti esposti al farmaco relativo all'indicatore di PI e per i non esposti.

NEURON JOINT CALL 2011: "EUROPEAN RESEARCH PROJECTS ON CEREBROVASCULAR DISEASES "

Role of danger signals in stroke and therapeutic targeting by nanobodies (NanoStroke) Partner del progetto

Il progetto europeo, coordinato dal dr. Tim Magnus, Germania è svolto da un team multidisciplinare composto da: Anna Planas, Barcelona (Spagna), Christoph Kleinschnitz and Guido Stoll, Würzburg (Germania) Carlos Matute, Bilbao, (Spagna), Andrea la Sala, Roma (Italia) and Friedrich Koch-Nolte.
L'attività del progetto "Nanostroke" si è concentrata prevalentemente nella selezione e allestimento di colture cellulari neuronali. Tali colture sono necessarie per lo studio del ruolo dei recettori purinergici nella regolazione di: a) resistenza delle cellule neuronali alla deprivazione di ossigeno e glucosio (oxygen glucose deprivation, OGD) che mimano le condizioni a cui sono esposte in seguito ad ictus; b) ruolo dei recettori purinergici con particolare attenzione al P2Y11 e P2X7 nella regolazione delle funzioni delle cellule infiammatorie esposte a sostanze rilasciate da cellule neuronali danneggiate da esposizione a condizioni di OGD prolungate. L'attività di allestimento delle colture cellulari ha compreso la selezione dei tipi cellulari più adatti all'approccio sperimentale scelto, l'acquisizione di strumentazione idonea a generare la condizione di OGD, la coltura e la raccolta di mezzi condizionati di cellule neuronali esposte a diverse intensità di OGD.

UNIONE EUROPEA - "7TH FRAMEWORK PROGRAMME"

SICA-HF: Studio della valutazione delle co-morbidità determinanti un peggioramento dello Scompenso Cardiaco

Il progetto prevede la collaborazione con i seguenti Istituti:
• Charité – Universitätsmedizin Berlin, Germany, Applied Cachexia Research, Department of Cardiology and Department of Pharmacology and Toxicology, Center for Cardiovascular Research
• University of Hull, United Kingdom
• Military Hospital Wroclaw, Poland
• Medizinische Hochschule Hannover, Germany
• GABO:mi Gesellschaft für Ablauforganisation :milliarium mbH & Co. KG, Germany
• Universität Rostock, Germany
• V.A. Almazov Federal Center for Heart, Blood & Endocrinology, Russian Federation
• M V Lomonosov Moscow State University, Russian Federation
• Institute of Cardiology, Siberian Branch, Russian Academy of Medical Sciences, Russian Federation
• Russian Cardiology Research and Production Complex, Russian Federation

Lo scompenso cardiaco cronico (CHF) rappresenta una delle principali cause di morbilità e mortalità. I pazienti affetti da CHF presentano numerose co-morbidità, quali diabete, obesità, ipertensione arteriosa, dislipidemia ed alterazioni del metabolismo glucidico. Inoltre, soprattutto negli stadi avanzati della malattia i pazienti con CHF possono sviluppare cachessia, che rappresenta un fattore prognostico infausto. Il progetto SICA-HF, articolato in 16 progetti di ricerca clinici e pre-clinici (WorkPackages [WPs]), intende valutare l'impatto che queste co-morbidità determinano nei pazienti con CHF, a livello clinico, vascolare, cellulare e molecolare.
Lo studio è parte di un più ampio progetto collaborativo che coinvolge la Comunità Europea e la Russia (per un totale di 11 centri più il coordinatore) ed ha ricevuto un finanziamento dalla Comunità Europea nell'ambito del Settimo Programma Quadro.
Lo studio, prospettico, multicentrico, multinazionale, longitudinale, ha come obiettivo di reclutare 1.600 pazienti con scompenso cardiaco a causa di varie eziologie comuni, indipendentemente dalla frazione di eiezione ventricolare sinistra, e con o senza comorbidità all'ingresso nello studio. Inoltre, 300 pazienti con diabete mellito tipo 2 senza CHF e 150 soggetti sani fungono da gruppo di controllo. Il progetto prevede che almeno il 50% dei pazienti arruolati sia di sesso femminile e che l'età media dei gruppi sia omogenea.
I partecipanti sono sistematicamente studiati ad intervalli annuali fino a 48 mesi. Tutti i soggetti vengono caratterizzati al basale, mentre i pazienti con CHF sono valutati ulteriormente dopo 4-6 mesi, 16-18 mesi e, ove applicabile, ogni anno, in base alla durata del progetto.
Ulteriori indagini sono focalizzate sui meccanismi cellulari e subcellulari e sulle cellule progenitrici endoteliali, in sottogruppi selezionati.
Lo scopo di questo progetto consiste nella descrizione dettagliata dei pazienti con CHF e le sopramenzionate co-morbidità al fine di identificare nuove strategie terapeutiche e migliorare gli outcome di morbidità e mortalità di questi pazienti.
La peculiarità di questo progetto consiste nella valutazione pre-clinica e clinica dei pazienti reclutati, dato che campioni ematici e tissutali dei pazienti verranno valutati sia dal punto di vista clinico che mediante analisi in vitro, su modelli cellulari ed animali presso i laboratori di ricerca coinvolti nello studio.
Nel corso dell'anno sono stati reclutati 20 pazienti, sono state effettuate 10 visite di controllo a 4-6 mesi dall'arruolamento e 5 visite di controllo a 16-18 mesi dall'arruolamento.
Si è proceduto alla stesura dei report per la Comunità Europea e per la Russia

Area di ricerca epidemiologia clinica e molecolare

PROGETTO RETE RSA

Studio sulla Complessità dell'Anziano in RSA: creazione di un data-BasE traslaziOnale.

Progetto Sc@rabeo

Sc@rabeo è l'acronimo di Studio sulla Complessità dell'Anziano in RSA: creazione di un dataBasE traslaziOnale. L'obiettivo del progetto è la creazione di una banca dati geriatrica volta a promuovere la ricerca e a migliorare le cure in una ampia popolazione di anziani residenti presso un gruppo di Residenze Sanitarie Assistenziali (RSA) distribuite sul territorio Nazionale. Il progetto di ricerca coinvolge le RSA del gruppo San Raffaele: Rocca di Papa, Flaminia, Trevignano, Montecompatri, Rosa dei Marganai, San Nicandro Garganico, Troia, Andria, Modugno, Alberobello, Locorotondo, Ostuni, Campi Salentina, Alessano, Crispiano, Torricella.
Tale progetto costituisce l'estensione a tutte le RSA del gruppo San Raffaele di un progetto pilota condotto presso le RSA di Rocca di Papa, Trevignano, Alberobello, Andria.
Lo studio prevede la compilazione della scheda di valutazione multidimensionale LTCF (Long Term Care Facility) e di una scheda di acuzie, riguardante tutti i pazienti con età > 65 anni, residenti in RSA, attraverso la suite web-based "Atl@nte web".
Il progetto è stato avviato in tutte le RSA del gruppo San Raffaele. E' stato acquistato il software Atl@nte e distribuito per consentire localmente l'input via web. Gli ospiti delle varie RSA ricevono una valutazione multidimensionale all'ingresso e mediamente ogni 6 mesi. Al 31 dicembre 2014 sono stati inseriti dati di circa 700 soggetti.
Nel corso del 2015 è previsto il raggiungimento della soglia dei 1000 soggetti con valutazioni ripetute. La disponibilità di tale database, che determinerà la fine della fase di avvio, permetterà l'avvio della produzione scientifica. E' prevista inoltre la pubblicazione congiunta dei dati con altre realtà (Umbria e Veneto) che utilizzano lo stesso software.

BANDO INAIL – ISTITUTO NAZIONALE PER L'ASSICURAZIONE CONTRO GLI INFORTUNI SUL LAVORO – ANNO 2010

Valutazione di biomarker di instabilità genetica, danno ossidativo e lesioni precoci in sangue, cellule esfoliate dalla mucosa boccale ed esalato bronchiale di lavoratori a rischio-amianto

Il progetto è stato disegnato per approfondire le conoscenze degli eventi precoci della cancerogenesi da amianto e per pianificare con i risultati ottenuti strategie di prevenzione e di management degli esposti. A tale scopo sono stati comparati una batteria di biomarcatori di instabilità genetica, di danno ossidativo e di lesioni precoci in personale addetto alla bonifica di amianto, in soggetti non esposti ad amianto e in soggetti sottoposti a esposizione intensa ad amianto nel passato.
Rispetto al progetto iniziale sono state apportate alcune modifiche al reclutamento dei soggetti esposti, provenienti dalla zona di Pisa e Genova e reclutati tramite l'Istituto di Medicina del Lavoro di Pisa e l'Istituto per la Ricerca sul Cancro di Genova. In tutti i soggetti sono stati misurati i seguenti biomarcatori di danno genomico e danno ossidativi: Micronuclei, Addotti DNA, Leukotriene-Isoprostano Citochine e SMRP.
Il progetto si è concluso a settembre 2014 con un reclutamento di 467 individui di cui 186 non esposti, 201 provenienti dalla coorte dei soggetti con pregressa esposizione e 80 correntemente occupati in lavorazioni che prevedono la possibile esposizione ad amianto. Le analisi di laboratorio e statistiche sono da completare e le pubblicazioni dei risultati sono previste per il 2015.

FONDAZIONE UMBERTO VERONESI

Micronucleus frequency in exfoliated buccal cells as a biomarker of DNA aging and risk for age-related diseases

Il test del Micronucleo è uno dei più popolari saggi di instabilità genomica. In considerazione dell'associazione fra la frequenza di MN e l'invecchiamento il progetto prevede la validazione di questo saggio come indicatore precoce di rischio per le patologie associate all'invecchiamento.
Lo studio prevede una parte prevalentemente statistica dedicata alla creazione di una curva di invecchiamento biologico basata sulla frequenza di micronuclei da comparare con una curva di inveechiamento cronologico. Inoltre, è previsto il completamento di uno studio di coorte storico basato su dati forniti dal progetto collaborativi HUMNxl.
Una prima versione della curva di invecchiamento biologica è stata disegnata basandosi sul modello delle radiazioni ionizzanti e pubblicata. Peraltro è stata realizzata una revisione sistematica con meta-analisi della letteratura, correlando la frequenza di micronucleo alle principali patologie legate all'invecchiamento.

FONDAZIONE PER LA RICERCA SCIENTIFICA TERMALE (FORST)

Effectiveness of thermal water nasal inhalation and irrigation in rhinopharyngitis and sinusitis

Rinofaringite e sinusite sono un problema di salute comune. Alcuni effetti benefici di cure inalatorie con acque termali sono stati dimostrati in termini di sintomi, funzionalità nasale, citologia e microbiologia. Tali effetti potrebbero dipendere dalla regolazione dell'espressione di diverse componenti del sistema immunitario innato nelle cellule dell'epitelio nasale.
La ricerca intende valutare l'efficacia di un ciclo standard di 2 settimane di cure inalatorie con acqua termale in 200 pazienti adulti con rinofaringite o sinusite, reclutati consecutivamente tra quanti vi si sottopongono presso le Terme di Genova srl, Acquasanta (Genova). Le misurazioni includono: scala dei sintomi, valutazione clinica, rinomanometria e livelli locali di un pannello di biomarker dell'infiammazione (High Throughput rt PCR analysis, western blotting). Nell'analisi dei dati si terrà conto di fattori quali fumo di tabacco, esposizioni lavorative, dieta.
Obiettivi secondari sono la valutazione dell'efficacia a 1 anno dalle inalazioni, in termini di sintomatologia e di eventi acuti; dei fattori clinici e socio-economici che influenzano la compliance dei pazienti e i cambiamenti nella sintomatologia a breve e a lungo termine; degli eventuali eventi avversi.
All'accettazione, il medico responsabile della ricerca intervista il paziente utilizzando un questionario strutturato per la raccolta delle informazioni su: lavoro, fumo, dieta, anamnesi patologica remota e a 1 anno (in particolare ORL), punteggio sulla scala dei sintomi. Viene effettuata una valutazione clinica comprendente una rinomanometria con lavaggio nasale e la raccolta di cellule della mucosa nasale.

Dopo 2 settimane, terminato il ciclo standard di cure inalatorie, si ripetono scala dei sintomi e valutazione clinica, e si valuta la tollerabilità della terapia.
Un anno dopo, il paziente viene intervistato telefonicamente su: anamnesi patologica a 1 anno, particolarmente ORL, scala dei sintomi ed eventuali cambi di abitazione, lavoro, fumo, dieta.
Questionari, schede cliniche e campioni biologici vengono contrassegnati con un codice alfanumerico, per assicurare la cecità dello studio e il rispetto della privacy. Un database dedicato con accesso ristretto raccoglie dati e informazioni relative ai pazienti.
Le cellule nasali sono analizzate con High Throughput (HT) real-time PCR utilizzando una card con 48 mini-pozzetti contenenti altrettanti geni implicati nel sistema immunitario innato e nell'infiammazione, per identificare in 25 pazienti un numero appropriato di geni candidati da testare in seguito in singoli saggi per real-time PCR negli altri camponi. Le proteine pro-infiammatorie corrispondenti vengono visualizzate nel lisato cellulare per western blot con gli anticorpi appropriati.
Dopo analisi statistica uni e multivariata, i risultati dello studio sono condivisi con la comunità scientifica internazionale.

Il progetto è iniziato ufficialmente alla fine dell'anno 2013. L'unità di Epidemiologia Clinica e Biostatistica dell'IRCCS San Raffaele Pisana ha l'incarico di garantire la gestione del progetto. In questo ruolo, ha curato gli adempimenti amministrativi e quelli relativi ai Comitati Etici, garantendo inoltre la comunicazione tra i partner e con l'ente finanziatore.
Sono stati messi a punto il questionario clinico-metodologico e il materiale per il consenso informato. Sono stati ottenuti il parere favorevole del Comitato Etico dell'IRCCS San Raffaele Pisana di Roma e quello del Comitato Etico Regionale della Liguria.
Sono stati realizzati un kick-off meeting e un midterm meeting.
Nel corso di alcuni incontri preliminari, sono stati sperimentati e perfezionati il questionario clinico-epidemiologico, il protocollo di reclutamento e il sistema di codifica dei pazienti e dei campioni.
In totale, a 60 pazienti eligibili è stato chiesto di partecipare allo studio e 40 hanno aderito. Il Principal Investigator incontra regolarmente il personale delle Terme per il monitoraggio e supporto al reclutamento e per la gestione dei campioni biologici.
Tali campioni, opportunamente codificati, vengono conservati presso la struttura in un congelatore dedicato e sono periodicamente inviati al laboratorio di Roma per le analisi.
I dati clinico-epidemiologici e i parametri rinomanometrici vengono inseriti in un database costruito appositamente.
Un primo set di campioni nasali è stato analizzato per espressione genica e proteine (Università "Sapienza" – Fisiopatologia Umana e IRCCS San Raffaele Pisana – Unità di Patologia Cellulare e Molecolare). L'attività di laboratorio si è focalizzata sul mettere a punto la tecnica per l'isolamento di mRNA e proteine. In particolare, è stata misurata l'espressione di geni della risposta infiammatoria-riparativa tramite l'uso di una card microfluida. Inoltre, è stata validata l'espressione genica, misurando l'espressione delle proteine codificate da quei geni che hanno mostrato un aumento o una diminuzione significativa nei pazienti sotto trattamento, paragonati a soggetti di controllo.
E' stata richiesta e ottenuta dall'ente finanziatore una proroga di 6 mesi, oltre la durata del progetto inizialmente prevista di due anni per portare a termine il follow-up telefonico a un anno (obiettivo secondario).
Nel corso del 2015 si prevede di concludere il reclutamento dei 200 pazienti previsti per la sperimentazione (T0 e T1), di procedere all'input dei dati nel database e di effettuare le analisi di laboratorio.
Nel 2015 e primi mesi del 2016, si procederà con le interviste telefoniche (T2) e verranno effettuate le analisi statistiche, per procedere alla pubblicazione dei risultati della sperimentazione.

AIRC – ASSOCIAZIONE ITALIANA PER LA RICERCA SUL CANCRO

Micronucleus assay in buccal exfoliated cells to measure DNA damage and predict cancer in healthy subjects

Lo studio del danno al DNA nelle cellule esfoliate della mucosa boccale è un metodo minimamente invasivo per lo studio di esposizioni genotossiche di origine ambientale o occupazionale, maanche di nutrizione, procedure mediche, stile di vita, fattori genetici, trattamenti farmacologici. Il progetto prevede l'identificazione dei principali gaps conoscitivi nell'uso di questo marker.
Lo studio prevede vari work packages che utilizzano metodi diversi, sia di tipo epidemiologico e statistico, nel disegno e analisi di studi di coorte storica e di round robin, sia di laboratorio citogentico.
Il progetto, concluso alla fine del 2014, ha prodotto vari risultati che sono stati prevalentemente disseminati utilizzando la rete di laboratori partecipanti al progetto internazionale HUMNxl.
Nel corso dei tre anni del progetto sono stati pubblicati differenti lavori.

7° PROGRAMMA QUADRO

FRAILOMIC Initiative: Utility of omic-based biomarkers in characterizing older individuals at risk for frailty, its progression to disability and general consequences to health and well-being - The FRAILOMIC Initiative

Il progetto è coordinato dall'Università di Madrid e prevede la collaborazione con:

- Servicio Madrileno de Salude
- World Health Organization
- Life Length SL
- YH TouHealth AB
- Evercyte GMBH
- Sistema Genomicos SL
- Mosauques Diagnostica GMBH
- Innovacion Desarrollo Y Transferenc de Tecnologia SA
- Nihce Science & Technology LTD
- University of Bedfordshire
- Universidad Autonoma de Madrid
- Centre Hospitalier Universitaire de Toulouse
- Institut Nazional de la Sante et de la Recherche Medicale (INSERM)
- Azienda Sanitaria di Firenze
- Azienda Ospedaliero-Universitaria di Parma
- Università di Innsbruck
- Cardiff Metropolitan University
- Friedrich Schiller University Jena
- Universitat de Valencia

Area di ricerca Biotecnologie Avanzate

POR FESR 2007-2013 – REGIONE SICILIA
Linea di Intervento 4.1.1.1

Sistema integrato per l'armonizzazione delle procedure e la gestione delle biobanche. SIASOPs BioBank

Il progetto ha visto quale obiettivo principale la strutturazione di una piattaforma di gestione informatica per l'accesso multiutente in remoto. La soluzione software sviluppata per la gestione dei dati clinici relativi agli utenti della banca dati Biologica è oloHEALTH-Biobim, realizzata con tecnologia "web based" pura utilizzabile (lato client) sui più recenti sistemi operativi Microsoft Windows, Apple e Linux e sui Sistemi Operativi dei tablet più diffusi, mentre la componente server è installabile su Sistema Operativo Linux (O.S. CENTOS a 64 bit) o Windows (Windows 2008 Server). oloHEALTH-Biobim è in linea con le raccomandazioni del nuovo Codice dell'Amministrazione Digitale, garantendo altresì piena e continua conformità alle normative nazionali e regionali. Il sistema è dotato di moduli che offrono la possibilità di elaborare statistiche ed estrapolare grafici sull'attività; in particolare l'architettura del software facilita l'estrazione di qualunque flusso dati e report che verrà espressamente richiesto dagli utenti. Per tali motivi, il sistema si è rivelato uno strumento essenziale per gestire e documentare processi di analisi dei campioni biologici e per la ricerca.
Il sistema oloHEALTH-Biobim può essere, a sua volta, integrato con altri strumenti IT in grado di fornire informazioni sul ciclo di vita del campione, in particolare per quanto riguarda le fasi di prelievo e processazione (codifica SPREC). I test di validazione delle metodiche e degli strumenti introdotti nel programma SPRECware sono stati condotti tra la BioBIM dell'IRCCS San Raffaele Pisana e il Laboratorio Campisi, partner del progetto SIASOPs BioBank. La validazione tecnica del programma è stata effettuata mediante prove di ricezione di campioni con etichettatura SPREC, decodifica estemporanea dello SPREC mediante smartphone a partire da QR-code e ricerca di campioni con determinate caratteristiche preanalitiche effettuata tramite portale SPRECware.
La disponibilità di un applicativo utilizzabile in diverse biobanche e la validazione tecnica del sistema hanno permesso l'esecuzione di alcuni studi di farmacogenetica e "biomarker discovery" su casistiche selezionate di pazienti. I risultati ottenuti sono stati oggetto di divulgazione scientifica in occasione del "9th International Conference of Anticancer Research", (in Ottobre 2014 a Porto Carras, in Grecia) nell'ambito del quale è stato organizzato uno "Special symposium" su "Biobanks: A research infrastructure for the future of translational and clinical research". In questa occasione, oltre ad aver divulgato i risultati scientifici alla comunità internazionale, è stata effettuata una condivisione di esperienze con biobanche internazionali (Biobanca del Lussemburgo, della Grecia e del Qatar) sotto l'egida della società scientifica di riferimento internazionale ISBER (International Society for Biological and Environmental Repositories).
Il progetto ha visto la costituzione di un Consorzio che coinvolge, oltre alla San Raffaele S.p.A., che gestiva l'IRCCS San Raffaele Pisana nel momento della presentazione del progetto complessivo, le seguenti strutture ed enti di ricerca:
- Ontario S.r.l.
- University Of Pittsburgh Medical Center Italy S.r.l. (UPMC)
- L.C. Laboratori Campisi S.r.l.
- Centro Nazionale Per Le Risorse Biologiche (CNRB) e
- Fondazione Ri.MED

PON 2007-2013

Biomarker, Biomateriali e Farmaci Innovativi per la Diagnosi e per la Terapia dell'ischemia Cerebrale e dei Tumori Plurifarmacoresistenti della Testa, del Collo e della Mammella Attraverso la Realizzazione di una Rete di Biobanche – BIBIOFAR

Il progetto ha preso avvio formale alla fine del 2013. Per quanto riguarda le attività previste dalla Unità, allo stato attuale è stato completato lo studio della distribuzione territoriale delle diverse tipologie di biobanche nelle aree di intervento. Le strutture censite sono state analizzate per definirne l'eleggibilità di aggregazione in una rete regionale di biobanche di ricerca traslazionale in campo medico, utilizzando criteri di classificazione e standard qualitativi derivanti dell'analisi delle esperienze di biobanche nazionali ed internazionali. In merito all'analisi delle linee guida, è stata posta particolare attenzione alla standardizzazione degli aspetti regolatori, infrastrutturali e bioinformatici che possano essere messi in comune per il coordinamento delle biorisorse. In particolare, sono state valutate la capacità delle biobanche afferenti al network di garantire la preservazione della sicurezza, qualità e integrità dei campioni conservati e dei dati ad esso associati, siano essi clinici che procedurali. Inoltre, sono state analizzate le soluzioni tecnologiche ed informatiche utilizzate per le operazioni di stoccaggio/recupero dei campioni biologici.
L'attività svolta nella prima fase ha, quindi, permesso l'identificazione di un potenziale protocollo di integrazione che rispetti le necessità delle singole istituzioni a cui le stesse fanno riferimento, unitamente ai pre-requisiti tecnici. Per uno studio approfondito del protocollo sono stati valutati numerosi sistemi di integrazione di biobanche utilizzati in network nazionali ed internazionali e sono state presentate le diverse possibili piattaforme di integrazione ai partners del progetto. A seguito di questa attività si è individuato come strumento ottimale un Portale delle biobanche chiamato BIOCAM TRN (Translational Research Network), in quanto dedicato alla ricerca traslazionale. Attraverso questo sistema, le biobanche che aderiscono al network potranno integrarsi nel portale a vari livelli. L'attività progettuale è in corso.
Il Consorzio realizzato per il progetto e coordinato dal Prof. L. Annunziato dell'Università Fedrico II di Napoli, in qualità di Presidente del Consorzio, prevede il coinvolgimento della San Raffaele S.p.A., in quanto gestore dell'IRCCS San Raffaele Pisana al momento della presentazione del progetto:
- Bio-Ker S.r.l.
- Neatec S.p.A.
- CEINGE- Biotecnologie Avanzate S.c.ar.l.
- Universita degli Studi di Salerno
- S.D.N. S.p.A.
- Merigen research S.r.l.
- NeaTech.It S.r.l.
- Angelantoni Life Science S.r.l.
- Biocam S.c.a.r.l.
- Universita degli Studi di Napoli Federico II
- CRdC Nuove Tecnologie per le Attivita Produttive S.c.a.r.l.

RICERCA SPONSORIZZATA DA PRIVATI

Cancer related-inflammation

Studio spontaneo no profit parzialmente sponsorizzato dalla ditta Merck KGaA.

Nel corso del 2014 è proseguita la collaborazione tra la BioBIM e la ImmunoOncology Platform della Merck Serono. Il progetto prevedeva l'analisi retrospettiva di numerosi marcatori infiammatori su campioni di tessuti tumorali umani, inclusi carcinomi del tratto gastrointestinale, della mammella e del polmone. Lo scopo del progetto è quello di definire alcune componenti specifiche della risposta infiammatoria associata alla progressione tumorale, al fine di identificare possibili nuovi target terapeutici. Nel complesso, è stata analizzata l'espressione immunoistochimica della legumaina, ILT2, ILT3, ILT4 e ILT5 in biopsie di tessuti di carcinoma colorettale, mammario e polmonare. Ulteriori valutazioni immunoistochimiche sono state eseguite in biopsie di tessuti normali corrispondenti, qualora disponibili. Per quanto riguarda la legumaina, gli studi di immunoistochimica sono stati estesi a lesioni infiammatorie ed adenomi con vari gradi di differenziazione, al fine di analizzare il pattern di espressione della legumaina nella progressione tumorale. Infine, è stata eseguita una caratterizzazione mediante analisi istologica e immunoistochimica delle cellule infiammatorie infiltranti il tumore.

ALTRE TIPOLOGIE DI RICERCA

LABORATORIO DI NEUROBIOLOGIA MOLECOLARE E CELLULARE

Bando ISS-Istituzioni USA

Innovative immunotherapeutic strategies in Alzheimer's disease by intracellular antibody technology

Le strategie immunoterapeutiche dirette a neutralizzare la neurotossicità e la sinaptotossicità delle forme oligomeriche del peptide beta amiloide (AβO) sono tra le più promettenti nella lotta contro la malattia di Alzheimer (AD). La generazione e l'accumulo cerebrale dell'AβO è considerato infatti uno degli eventi precoci e determinanti nella patogenesi dell'AD. La generazione e l'applicazione di anticorpi intracellulari diretti specificatamente contro l'AβO rappresenta uno strumento terapeutico importante perché unisce la specificità degli anticorpi ricombinanti diretti contro conformeri specifici neurotossici come l'AβO, con la capacità di veicolare tali forme anticorpali verso i siti di localizzazione cellulare coinvolti nella formazione, l'accumulo e l'azione patologica dell'AβO. Dopo aver generato, caratterizzato ed applicato in vitro anticorpi intracellulari anti-Aβ 1-42 oligomerica diretti verso diversi compartimenti cellulari tra cui quelli pre e post-sinaptico, ci si propone di valutare gli effetti in vivo di questi anticorpi anti-AβO diretti verso il compartimento post-sinaptico, un sito di azione dell'AβO molto rilevante nella patogenesi dell'AD.
In questo anno di progetto, al fine di valutare in vivo gli effetti neuroprotettivi e sinaptoprotettivi degli anticorpi intracellulari anti-Aβ1-42 oligomerica in un modello murino di AD, sono state inizialmente testate due differenti dosi di rAAV (1x109 e 3x109 unità di trasduzione virale) in topi wt mediante iniezione intracerebroventricolare (icv). Poiché nel modello murino utilizzato di AD si osservano deficit cognitivi e morte neuronale tra i 4 ed i 9 mesi di età, appropriati gruppi di topi wt sono stati iniettati a 2-3 di età. Una volta raggiunta l'età di 4 mesi, i topi sono stati sacrificati, i cervelli sono stati rimossi, ed è stata effettuata un'analisi della compartimentalizzazione cerebrale, dei livelli proteici, dell'efficienza di trasduzione e di eventuali sintomi citotossici associati all'espressione degli anticorpi intracellulari iniettati. A questo scopo sezioni coronali ed estratti proteici totali di cervello sono stati analizzati mediante immunofluorescenza e western blot con anticorpi anti-myc per il riconoscimento degli scFvs. La colorazione con Cresyl violet è stata effettuata per rilevare eventuali livelli di morte neuronale. Eventuali risposte immunitarie avverse dovute all'infezione con rAAV (serotipo 1/2) sono state valutate mediante immunocolorazione con anticorpi specifici anti-LN3 ed anti-GFAP. Le analisi effettuate hanno rivelato che, utilizzando dosi di rAAV pari a 1x109 e 3x109 unità di trasduzione virale, l'efficienza di trasduzione (data come percentuale di neuroni infettati) di tali vettori è sostanzialmente bassa. Inoltre, in queste condizioni sperimentali, i livelli di espressione proteica degli scFv anti-Aβ1-42 oligomerica si mantengono elevati fino a 1.5 mesi dopo l'iniezione. Probabilmente entrambi i risultati sono legati all'iniezione di dosi di rAAV non ottimali anche se non si può escludere che la vita media (t ½) degli anticorpi intracellulari sia breve una volta iniettati nel parenchima cerebrale rispetto a quanto invece osservato su colture neuronali primarie. Non sono stati osservati fenomeni di citotossicità né risposte immunitarie avverse. Dosi maggiori di rAAV ed eventuali iniezioni multiple dovranno essere quindi valutate su topi wt per trovare le condizioni ottimali di iniezione prima di testare l'efficacia neuroprotettiva e sinaptoprotettiva degli scFv anti-Aβ1-42 oligomerica sul modello murino di AD.

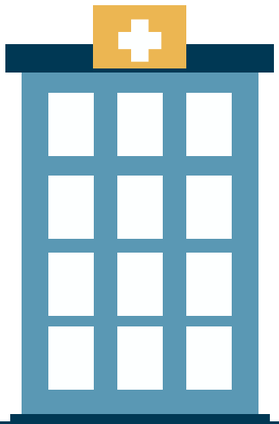
LABORATORIO DELLE PATOLOGIE CRONICO-DEGENERATIVE

Ministero della Salute – Dispositivi Medici
Anno 2012

Studio delle contaminazioni microbiche e polimicrobiche a carico dei dispositivi medici per la nutrizione enterale/parenterale

Il progetto si pone come obiettivo generale l'identificazione dei microrganismi (batteri o miceti) più frequentemente coinvolti nella formazione di biofilm a livello di dispositivi medici per la nutrizione enterale/parenterale (cateteri venosi centrali).
L'attenzione è rivolta all'individuazione di forme vitali non coltivabili dei batteri Stafilococcus aureus, Pseudomonas aeruginosa ed Escherichia coli, che sono le specie maggiormente responsabili di infezioni associate all'uso dei cateteri venosi centrali (CVC).
Lo studio prevede anche di investigare i ceppi resistenti ai disinfettanti comunemente utilizzati ed alle terapie antibiotiche convenzionali.
Le attività del suddetto progetto sono state articolate su tre fasi principali:
(1) definizione delle caratteristiche dei pazienti da arruolare nello studio;
(2) analisi dei CVC rimossi dai pazienti;
(3) valutazione dello sviluppo di possibili biofilm batterici e/o misti.
Sono state identificate e stabilite le caratteristiche dei pazienti da arruolare nello studio quali, ad esempio:
- ugual numero di maschi e femmine;
- con e senza febbre;
- in corso e non di terapia antibiotica.

Sono in fase di analisi i dispositivi rimossi dai pazienti con diverse metodiche di isolamento e di caratterizzazione biochimica.
Particolare attenzione è dedicata alla identificazione dei microrganismi selezionati e all'analisi l'eventuale resistenza nei confronti dei chemioterapici somministrati al paziente.
Come è noto le resistenza da parte dei batteri agli antibiotici maggiormente utilizzati in terapia ha assunto una dimensione globale coinvolgendo anche l'ambiente comunitario, per lungo tempo esente da queste problematiche, ma ove le segnalazioni di ceppi resistenti sono ormai purtroppo sempre più frequenti. Sul fenomeno della resistenza agli antibiotici sono emerse da più parti ipotesi che hanno chiamato in causa la grande adattabilità dei batteri ai più disparati ambienti, la loro rapida riproduzione, le possibilità che hanno di scambiarsi materiale genetico anche tra specie diverse e, soprattutto un uso intenso degli antibiotici per il trattamento delle infezioni. La resistenza ai farmaci è spesso correlata con fallimenti terapeutici se si utilizza l'antibiotico non efficace in vitro, anche se in realtà il successo di una terapia dipende da molti fattori che includono la gravità dell'infezione, l'età e le condizioni generali dell'ospite, il patogeno in causa, le caratteristiche farmacocinetiche delle molecole, la sede dell'infezione, ecc.
La scelta del farmaco da impiegare viene inoltre suggerita da considerazioni che tengono conto del patogeno più frequentemente coinvolto nella specifica infezione e della sua resistenza agli antibiotici.
I ceppi isolati dai cateteri venosi centrali sono stati identificati mediante le classiche tecniche di batteriologia e l'utilizzo di test biochimici (API System, bioMèrieux).
La valutazione della sensibilità agli antibiotici è stata effettuata con il metodo della diffusione da dischetto, Kirby- Bauer secondo le linee guida dell'NCCLS come di seguito descritto:
Oxacillino–resistenza in S. aureus. L'oxacillino/meticillino–resistenza in S. aureus è stata messa in evidenza utilizzando il saggio dell'agar screening su piastre di Mueller-Hinton agar con 6 mg/L di oxacillina in duplicato, con e senza il 2% di Na- Cl e un inoculo di 5x105 CFU per spot. La lettura è stata eseguita dopo 24 ore di incubazione. I ceppi sono stati mantenuti ad una temperatura non superiore ai 35,5°C. In queste condizioni il ceppo inducibile è risultato sensibile al farmaco sul terreno privo di sale, mentre lo stipite costitutivo ha manifestato resistenza all'oxacillina su entrambi i terreni. Gli stafilococchi coagulasi-negativi (CNS) sono stati valutati mediante Kirby-Bauer con dischetto di oxacillina (1 µg) su terreno MH non contenente NaCl.
È noto che gli stafilococchi sono i più comuni microrganismi patogeni delle infezioni associate a cateteri e/o a diversi corpi estranei usati nella pratica medica. Uno dei contributi maggiori al meccanismo etio-patogenetico di queste infezioni, risiede proprio nella capacità di questi microrganismi di formare biofilm su bio-superfici. Benché non del tutto delucidate, le basi molecolari del meccanismo di formazione del biofilm negli stafilococchi mettono in evidenza che questo è un fenomeno biologico complesso e multifattoriale. L'abilità di formare biofilm richiede che vengano esplicate almeno due proprietà: la prima risiede nell'adesione del microrganismo ad una superficie; la seconda, che sia in grado di accumulare strati multipli di una sostanza detta slime, costituita da un esopolisaccaride detto polisaccaride intracellulare di adesione (PIA), composto da N-acetylglucosamina, legata con legami □-1,6, parzialmente deacetilata e carica positivamente, nella quale le cellule vengono racchiuse e, in qualche modo, protette dall'attacco del sistema immunitario e dagli antibiotici.
I geni biosintetici responsabili della produzione del PIA sono localizzati in un operon detto icaADBC, presente in entrambe le specie maggiori, Staphylococcus aureus e Staphylococcus epidermidis. La produzione del PIA è correlata con la patogenesi di questi microrganismi, tuttavia la sua presenza da sola non è sufficiente per la formazione di un biofilm: sono stati messi in evidenza diversi fattori addizionali indipendenti dalla espressione del gene ica.
La complessa regolazione della formazione di biofilm, dipendente fortemente dalle condizioni ambientali e dalla concentrazione cellulare, dimostra quindi come esso abbia un ruolo importantissimo nella sopravvivenza del microrganismo conferendogli un vantaggio selettivo nell'eziologia delle successive infezioni.
La produzione di biofilm è stata controllata utilizzando il terreno Rosso Congo descritto da Freeman et al. e Cramton et al.



CLINICAL TRIAL CENTER

Nel corso del 2014 sono attivi i seguenti studi:

TRIALS CLINICI SPONSORIZZATI

- 110390 (ZOSTER-006). Studio clinico di fase III, randomizzato, con osservatore in cieco, controllato con placebo, multicentrico, per valutare l'efficacia profilattica, la sicurezza e l'immunogenicità del vaccino gE/AS01B di GlaxoSmithKline (GSK) Biologicals, somministrato per via intramuscolare con schedula a 0 e 2 mesi a soggetti adulti di 50 anni di età ed oltre.
- 113077 (ZOSTER-022). Studio clinico di fase III, randomizzato, con osservatore in cieco, controllato con placebo, multicentrico, per valutare l'efficacia profilattica, la sicurezza e l'immunogenicità del vaccino gE/AS01B di GlaxoSmithKline (GSK) Biologicals, somministrato per via intramuscolare con schedula a 0 e 2 mesi a soggetti adulti di 70 anni di età ed oltre.
- 14910A. Studio di coorte non interventistico, multinazionale, prospettico, per studiare i modelli d'uso di Selincro® e la frequenza delle reazioni avverse al farmaco nella pratica clinica di routine. ti di 70 anni di eta` ed oltre
- 15338A. Studio FORTE II. Studio non interventistico, prospettico, longitudinale per valutare l'impatto di una terapia di nuova introduzione sulla fatica in pazienti con Malattia di Parkinson in Italia - Studio FORTE II.
- 6002-014. Studio multicentrico randomizzato di fase 3, della durata di 12 settimane, condotto in doppio cieco, controllato con placebo, per valutare l'efficacia di 20 e 40 mg/die di istradefillina somministrata per via orale, come trattamento per soggetti affetti da malattia di Parkinson da moderata a grave.
- ARC207 SAVING. Le implicazioni del sotto o non ottimale trattamento della BPCO nella fase di stabilità clinica.
- B1481022. Studio di fase 3, multicentrico, in doppio cieco, randomizzato, controllato con placebo, a gruppi paralleli, per valutare l'efficacia, la sicurezza e la tollerabilità di PF-04950615 nel ridurre l'occorrenza di eventi cardiovascolari maggiori in soggetti ad alto rischio
- BAY94-8862/14564. Studio multicentrico, randomizzato, in doppio cieco, double-dummy, per valutare la sicurezza e l'efficacia di BAY 94-8862 rispetto all'eplerenone in soggetti giunti d'urgenza in ospedale a causa del peggioramento dell'insufficienza cardiaca cronica con disfunzione sistolica del ventricolo sinistro, con diabete mellito di tipo 2 con o senza nefropatia cronica o con sola nefropatia cronica moderata.
- BIA-91067-301. Efficacia e sicurezza di BIA 9-1067 nella malattia di Parkinson idiopatica con fenomeni di "wearing-off" trattati con Levo-Dopa e un inibitore di Dopa-Decarboxilase (DDCI): studio in doppio cieco, randomizzato, controllato col placebo e col farmaco di controllo, a gruppi paralleli, multicentrico.
- BUC-SI-11-001. Studio clinico sull'efficacia e la tollerabilità di un immunostimolante a base di batteri inattivati (BUCCALIN®) nella profilassi degli episodi infettivi delle vie aeree (rinotracheobronchiti, malattie da raffreddamento). Studio in doppio cieco vs placebo, randomizzato, multicentrico.
- CACZ885M2301. Studio randomizzato, in doppio cieco, controllato verso placebo, evento-dipendente, di canakinumab somministrato sottocute con frequenza trimestrale nella prevenzione di eventi cardiovascolari ricorrenti in pazienti con pregresso infarto miocardico clinicamente stabili e con elevati livelli di proteina C-reattiva ad alta sensibilità (hsCRP).
- CAFQ056A2299. Studio in aperto per valutare la sicurezza, la tollerabilità e l'efficacia di AFQ056 in pazienti affetti da malattia di Parkinson con discinesie indotte da L-dopa.
- CL2-16257-096. Effects of oral chronic administration of ivabradine (7.5 mg bid) in comparison to placebo (bid) on top of beta-blockers, on central aortic blood pressure. Randomized, cross-over, double blind, multicentre, study over 10 weeks in patients with stable coronary artery disease and a resting heart rate equal or superior to 70 bpm, already treated with beta-blockers.
- CL3-16257-097. Sicurezza della somministrazione orale cronica di una formulazione a rilascio modificato di ivabradina rispetto alla formulazione a rilascio immediato di ivabradina in pazienti

con cardiopatia coronarica stabile. Studio randomizzato, doppio cieco, a gruppi paralleli, multicentrico, della durata da 6 a 12 mesi.
- CLCZ696B2228. A multicenter, randomized, double-blind, parallel group study to assess the safety and tolerability of initiating LCZ696 in heart failure patients comparing two titration regimens.
- CLCZ696B2314. Studio multicentrico, randomizzato, in doppio cieco, a gruppi paralleli, con controllo attivo per valutare l'efficacia e la sicurezza di LCZ 696 in confronto a Enalapril su morbilità e mortalità in pazienti con insufficienza cardiaca cronica e ridotta frazione di eiezione
- CLCZ696D2301. Studio multicentrico, randomizzato, in doppio cieco, a gruppi paralleli, verso controllo attivo per valutare l'efficacia e la Sicurezza di LCZ696 rispetto a valsartan sulla morbilità e mortalità in pazienti con insufficienza cardiaca (NYHA Classe II-IV) con frazione di eiezione preservata.
- CLE-20098-068. Studio osservazionale di coorte per la valutazione della sicurezza dell'agomelatina nella pratica clinica standard in pazienti depressi.
- CQVA149A3401. Studio multicentrico, randomizzato, prospettico, in aperto, della durata di 12 settimane per valutare l'efficacia e la sicurezza di glicopirronio (50 microgrammi q.d.) o di indacaterolo maleato e glicopirronio bromuro in combinazione a dose fissa (110/50 microgrammi q.d.) relativamente ai sintomi e allo stato di salute in pazienti con broncopneumatia cronica ostruttiva (BPCO) moderata che passano a tali trattamenti dal trattamento con qualsiasi regime standard per la BPCO.
- FER-CARS-04. Studio multicentrico prospettico randomizzato a due bracci per valutare l'impatto del carbossimaltosio ferrico sulla capcità di esercizio fisico nei pazienti affetti da insufficienza cardiaca cronica con carenza di ferro.
- LAQ-MS-305 (CONCERTO). Studio multinazionale, multicentrico, randomizzato, in doppio cieco, a gruppi paralleli, controllato con placebo seguito da un periodo di trattamento attivo, per valutare l'efficacia, la sicurezza e la tollerabilità di due dosaggi di somministrazione orale di laquinimod (0,6 mg/die o 1,2 mg/die) in soggetti affetti da sclerosi multipla recidivante remittente (relapsing remitting multiple sclerosis, RRMS).
- LDCD-001. Studio di fase IIa per valutare la farmacocinetica, la sicurezza, l'efficacia e la tollerabilità della somministrazione orale intermittente di formulazioni standard di Levodopa/carbidopa verso somministrazione intra-orale semi-continua di LD di levodopa/carbidopa in pazienti con Malattia di Parkinson avanzata affetti da fluttuazioni motorie.
- LSH-10-001. Studio randomizzato, con controllo, per la valutazione della sicurezza e degli effetti cardiovascolari di Algisyl-LVR come metodo di contenimento della dilatazione ventricolare sinistra nei pazienti affetti da cardiomiopatia dilatativa (AUGMENT-HF).
- LSH-11-001. Studio in aperto di "Roll Over" per i pazienti randomizzati al gruppo di controllo nello studio LSH-10-001 (AUGMENT-HF).
- NOH401. PHOENIX: Uno studio clinico su pazienti con ipotensione ortostatica neurogena sintomatica per valutare gli effetti sostenibili della terapia con droxidopa.
- P0990. Studio prospettico, non interventistico sulla prevalenza Incidenza dei disturbi del Controllo degli impulsi e l'Associazione di sintomi neuRopsichiatrici, processi cognitivi e qUalità della vita nel Morbo di ParkinSon – ICARUS

SPERIMENTAZIONI CLINICHE SPONTANEE

- Saggio del micronucleo in cellule esfoliate della mucosa boccale per misurare il danno al DNA e predire lo sviluppo di tumori in soggetti sani.
- Structured exercise training as countermeasure to space flight-induced orthostatic intolerance.
- Genomic instability in the elderly as a marker of frailty. (Instabilità genetica come marcatore di fragilità negli anziani).
- Caratterizzazione fenotipica e sequenziamento genomico nella psicosi schizofrenica.
- La riabilitazione con una stimolazione audio-video a 10 Hz modula i ritmi cerebrali e migliora le prestazioni cognitive e motorie in pazienti neurologici? Verso un'applicazione clinica basata sull'utilizzo di Internet a casa da parte dei pazienti.
- Ricerca dei tratti personalità correlabili al complesso psico-fisiologico nella malattia di Parkinson e loro influenza nei processi di recupero.
- ACQUASANTA. Studio osservazionale sull'efficacia terapeutica di acqua termale nelle rinofaringiti e sinusiti.
- AOSTRO. Action observation treatment to improve cortical plasticity and upper limb functions in chronic stroke patients: a RCT study from basic neuroscience to traditional and home-based clinical rehabilitation.
- ASA-001. Studio clinico per valutare l'attività di aggregazione piastrinica ed il profilo di sicurezza di una nuova formulazione sublinguale di Acido Acetil-Salicilico in soggetti ad aumentato rischio cardiovascolare.
- AVIRR-PD. Fattori predittivi nello sviluppo della Malattia di Parkinson: analisi della variabilità dell'intervallo cardiaco R-R in familiari di pazienti affetti
- BIOMARKERS OF ASBESTOS EXPOSURE. Valutazione di biomarker di instabilità genetica, danno ossidativo e lesioni precoci in sangue, cellule esfoliate dalla mucosa boccale ed esalato bronchiale di lavoratori a rischio-amianto.
- COMBIRIAB. Studio osservazionale sul monitoraggio dei parametri funzionali di riabilitazione respiratoria, tolleranza allo sforzo fisico e qualità di vita in pazienti affetti da broncopneumatia cronica ostruttiva con recente riacutizzazione (COMBIRIAB).
- Database geriatrico. Database Geriatrico per lo Studio dell'Utilizzo della Valutazione Multidimensionale in una popolazione anziana ospitata in regime di Residenza Sanitaria Assistenziale (RSA) nella Regione Lazio.
- DEEP TMS PARK. Utilizzo della "Deep TMS" per il trattamento e la riabilitazione motoria di soggetti affetti da malattia di Parkinson e da paralisi sopranucleare progressiva.
- FARIF-PD. Studio caso-controllo sui fattori di rischio familiari e diagnosi precoce della malattia di Parkinson.
- FARM87SA2B. Effetto di un intervento integrato di e-learning, basato sulla valutazione geriatrica multidimensionale, nel migliorare la qualità della prescrizione farmacologica in pazienti anziani ospedalizzati.
- FARM9LBBBL. Trattamento farmacologico nell'anziano con patologia cardiovascolare associata a malattie croniche: inappropriatezza prescrittiva e valutazione di esito nella popolazione istituzionalizzata e residente in comunità (Pharmacological treatment in the elderly patient affected by cardiovascular disease and other chronic comorbidities: inappropriate prescribing and outcome evaluation among institutionalized and community-dwelling elders).
- FARM9X59Y4. Studio clinico e farmacocinetico per valutare l'equivalenza terapeutica e la bioequivalenza del generico Levodopa-Benserazide (TEVA ITALIA) verso l'originator (MADOPAR®).
- FRAILCLINIC. "Feasibility and effectiveness of frailty screening and management programs implemented in different clinical settings" "Attuabilità ed efficacia di programmi di screening e gestione della fragilità implementati in diversi contesti clinici".
- GONDOLA PILOTA. Studio pilota cross-over sull'utilizzo della "Gondola" per la riabilitazione motoria di soggetti affetti da malattia di Parkinson e da Paralisi Sopranucleare Progressiva.
- GONDOPARK. Studio multicentrico, doppio cieco randomizzato per gruppi paralleli sull'utilizzo

della “Gondola” per la riabilitazione motoria di soggetti affetti da malattia di Parkinson.
- ISMAR. Indagine SICOA AIMAR sulla epidemiologia ospedaliera e sulla gestione clinica delle comorbilità respiratorie e cardiache in pazienti ospedalizzati in unità cardiologiche e pneumologiche.
- ISPAF-2. Indagine Sicoa Paziente Atrial Fibrillation – 2.
- LAMP-PD. Modalità di somministrazione della levodopa e del pramipexolo nella malattia di Parkinson (studio LAMP-PD). Studio multicentrico, randomizzato, con controllo attivo, in aperto, a gruppi paralleli per valutare il rischio di discinesie in pazienti con malattia di Parkinson in fase iniziale.
- MARE. Progetto MARE (Metabolic syndrome and Artery REsearch) 2.
- MIRRORPARK. Does the Action Observation treatment improve the upper limb speed of movement and deftness of parkinsonian patients?
- OCK2. Studio clinico sulla somministrazione di Eparina sodica non frazionata nebulizzata in pazienti con BPCO.
- ORTITO. Protocollo clinico-strumentale per la valutazione della soluzione ortesica neurologica più appropriata in pazienti affetti da stroke in fase riabilitativa.
- PESO-PD. Studio osservazionale prospettico sulla perdita di peso nei pazienti con malattia di Parkinson - Progetto Pilota.
- Progetto Cadute. Studio multicentrico osservazionale di coorte sulla frequenza ed i fattori predittivi di caduta nei pazienti con Malattia di Parkinson.
- PRO-LIVER. Registro nazionale di pazienti con cirrosi epatica per la stima della prevalenza della trombosi venosa portale.
- RBNE08LN4P. Approccio integrato clinico e sperimentale allo studio dell’invecchiamento cerebrale e delle malattie neurodegenerative: basi molecolari, epidemiologia genetica, neuroimaging multimodale e farmaco genetica.
- RC 10/0804. Valutazione prospettica di parametri innovativi di rischio cardiovascolare in pazienti con aumentato rischio cardiovascolare.
- REG.I.RE. - Studio Osservazionale trasversale per la valutazione dei dati epidemiologici di prevalenza ed incidenza dell’insufficienza respiratoria finalizzati alla corretta programmazione sanitaria ed all’ottimizzazione dell’impiego delle risorse economiche per il trattamento della malattia.
- Registro TOSCA. Studio Osservazionale Multicentrico sulla prevalenza ed il significato prognostico dei difetti ormono-metabolici nei Pazienti con insufficienza cardiaca cronica.
- REPOSI 2014. Progetto Collaborativo REPOSI 2014: Registro dei Pazienti per lo Studio delle Polipatologie e Politerapie in Reparti della Rete SIMI. Progetto Collaborativo Istituto di Ricerche Farmacologiche “Mario Negri” e Società Italiana di Medicina Interna (SIMI).
- REVIS. Restoration of Vision after Stroke.
- RF-2009-1528677. Stimolazione transcranica per indurre il sonno: Efficacia delle tecniche tDCS e TMS.
- RF-2009-1546787. Adattamento del ventricolo destro nell’ipertensione arteriosa polmonare: iterazione tra forma e danno miocardico.
- RF-2010-2319113. Sistema a griglia per la valutazione degli effetti della riabilitazione cognitiva in pazienti con malattia di Alzheimer e malattia di Parkinson.
- ROBOPARK. Utilizzo di un robot per la riabilitazione del cammino in soggetti affetti da malattia di Parkinson.
- ROBOSTROKE. Utilizzo di un robot per la riabilitazione del cammino in soggetti affetti da Stroke.
- SCRIPT_mec_ORTHO. “Feasibility of Supervised Care & Rehabilitation Involving Personal Tele-Robotics for arm/hand function of chronic stroke patients” “SCRIPT: Supervised Care and Rehabilitation Involving Personal Tele-robotics”.
- SICA-HF. Studio di valutazione delle co-morbidità che determinano un peggioramento dello scompenso cardiaco.
- SIRT. Effetti del training fisico sui markers biologici di infiammazione/necrosi e stress ossidativo nel paziente con scompenso cardiaco.

- SR-NCDs. Applicazione di un approccio di Systems Medicine alla valutazione degli effetti della riabilitazione respiratoria in pazienti affetti da insufficienza respiratoria: implementazione di una piattaforma integrata di dati clinici, epidemiologici e biologici.
- TOQ-PD. Studio osservazionale per caratterizzare i problemi dell’OFF mattutino in pazienti affetti da malattia di Parkinson nella pratica clinica.
- Richiesta di parere per l’attivazione delle sedi decentrate di raccolta e/o processazione dei campioni della BioBanca, ridefinita come BioBIM ovvero BioBanca Interistituzionale Multidisciplinare.
- Utilizzo di un robot per la riabilitazione dell’arto superiore di pazienti con danno neurologico in fase sub-acuta.

CONVENZIONI E COLLABORAZIONI ISTITUZIONALI

SCUOLE DI SPECIALIZZAZIONE E TIROCINI

Sono attive le seguenti Scuole di Specializzazione:

Università degli Studi di Roma "Sapienza"
- Scuola di Specializzazione in Medicina Fisica e Riabilitazione
- Scuola di Specializzazione Medicina e Psicologia
- Tirocinio terapisti occupazionali

Università degli Studi di Roma "Tor Vergata"
- Scuola di Specializzazione in Medicina Fisica e Riabilitazione
- Scuola di Specializzazione in Geriatria
- Convenzione per il tirocinio pratico per gli studenti che frequentano il Corso di Laurea Magistrale Biotecnologie Industriali della Facoltà di scienze MM FF NN della Scuola Istruzione a Distanza-IaD al fine di completare il percorso formativo accademico dei tirocinanti e di agevolarne la scelta professionale
- Tirocini curriculari Corso di Laurea in Biologia Cellulare e Molecolare

Università Campus Biomedico
- Scuola di Specializzazione in Neurologia
- Scuola di Specializzazione in Radiodiagnostica

Università LUMSA
- Master in Neuropsicologia

Libera Università degli Studi di Scienza Umane e Tecnologiche (LUDES)
- Tirocinio di Formazione per i Fisioterapisti

Seconda Università degli Studi di Napoli
- Dipartimento di Biologia e Patologia Cellulare e Molecolare
- Facoltà di Psicologia

Università degli Studi di Urbino "Carlo Bo"
- Centro Interuniversitario IRIDE, per lo svolgimento di Tirocinio in Psicologia Clinica.

Università degli Studi di Modena e Reggio Emilia
- Facoltà di Scienze della Formazione

Università di Salerno
- Tirocinio di formazione e orientamento con il Dipartimento di Farmacia

Altri Istituti
- Istituto di Formazione in Analisi Transazionale, Istituto Auximon
- Istituto Walden Associazione Italiana di Psicologia e Terapia Cognitivo Comportamentale
- Scuola Internazionale di Ricerca e Formazione in Psicologia Clinica e Psicoterapia Psicoanalitica
- S.I.R.P.I.D.I.
- Centro Italiano di Psicologia Analitica - C.I.P.A
- Scuola di Psicoterapia Strategica Integrata Seraphicum (SCUPSIS)
- Istituto di Terapia Relazionale Integrata (ITRI)

- Centro Studi Martha Harris (Psicoterapia Psicoanalitica, Modello Tavistock)
- Istituto Italiano Psicoterapia Relazionale (I.I.P.R.)

- Scuola Italiana di Ipnosi e Psicoterapia Ericksoniana (S.I.I.P.E.)
- Scuola di Analisi Transazionale (SIFP)
- Lo spazio psicoanalitico
- Scuola Superiore di Specializzazione in Psicologia Clinica _SSSPC Università Pontifica Salesiana
- Engim San Paolo
- IDI – Istituto Dermopatico dell'Immacolata

COLLABORAZIONI NAZIONALI

Istituto Superiore di Sanità – Collaborazione Scientifica per Progetti di ricerca nell'ambito di:
- riabilitazione
- patologie cardiovascolari
- malattie respiratorie
- neuroscienze
- malattie infettive
- tabagismo
- neoplasie
- medicina di genere.

Università degli Studi di Roma "Sapienza":
- I Facoltà di Medicina e Chirurgia
- Dipartimento di Neurologia e Psichiatria per una collaborazione scientifica nell'ambito del trattamento del dolore acuto e cronico.

Università Cattolica del Sacro Cuore:
- Istituto di fisiologia umana

Università degli Studi di Roma "Tor Vergata":
- Dipartimento di Medicina Interna nei settori della:
o Cardiologia, con particolare riguardo alla diagnosi e cura dell'ipertensione arteriosa e allo studio del valore predittivo e diagnostico dei marker di funzione cardiovascolare
o Diagnosi e terapia delle dislipedemie
o Prevenzione, primaria e secondaria, e cura della malattia aterosclerotica mediante la gestione informatizzata dei pazienti sul territorio
o Diabetologia, endocrinologia, andrologia
o Biochimica clinica
o Medicina interna, oncologia
o Attuazione di strategie innovative in ricerca traslazionale nel campo della broncopneumopatia cronica ostruttiva
o Ricerca specifica sul tema degli effetti metabolici ed autonomici del training fisico in pazienti cardiopatici anziani e con ridotta tolleranza allo sforzo.
- Dipartimento di Biologia, Accordo di collaborazione scientifica sui meccanismi molecolari dell'invecchiamento.
- Dipartimento di Neuroscienze.

Università Telematica San Raffaele Roma
- Attivazione laboratori nell'ambito della Biologia applicata ed in particolare nei settori della fisiologia, della microbiologia e della microbiologia clinica

Casa di Cura del Policlinico Milano, settore delle neuroscienze

COLLABORAZIONI INTERNAZIONALI

Imperial College of Science, Technology and Medicine, Londra, UK - Laboratorio di Fisiologia Vascolare comune e progetti di ricerca sugli effetti cardiovascolari degli ormoni.

Division of Cardiology, Department of Internal Medicine, Jikei University Tokio, Giappone - Collaborazione studi su recettori mineralocorticoidi.

Musashino Medical Center, University Tokio, Giappone - Collaborazione scientifica in ambito cardiovascolare.

Molecular Cardiovascular Research Institute-Tufts Medical Center, Boston, USA - Collaborazione per ricerca cardiovascolare

Applied Cachexia Research, Charite Universitätsmedizin, Campus Virchow-Klinikum, Berlin-Germany - Collaborazione per ricerca cardiovascolare

Instrumentation Laboratories, Delaware, USA - Clinical Evaluation Program Agreement

Diabetes Research Institute, University of MIAMI - Accordo di collaborazione scientifica per la ricerca e cura del diabete

Plant Product and Human Nutrition Group, Institute of Biomedical and Life Sciences, University of Glasgow

Institute for Molecular and Translational Therapeutic Strategies (IMTTS), Hannover Medical School, Germany

University of Barcellona, Cooperation in collaborative research in the field of home care assistance and services (through tele-assistance and tele-rehabilitation) and systems biology of COPD.

Merck KGaA Agreement PD-L1 expressione in human lung, gastric, and breast cancer tissue

Center for Human Nutrition Washington University School- RF 2011-2012

Laboratory del Department of Psichiatry and Human Behaviour University of California, Irvine, CA-USA

Aalborg Universitet, Coordinator Consortium for project e-WALL

University of Hertfordshire Higher Education Corporation, Coordinator Consortium for project SCRIPT

Servicio Madrileno De Salud Hospital Universitario de Getafe, Coordinator Consortium for project FRAILOMIC

Fundacion de Investigacion Biomedica del Hospital Universitario de Getafe, Coordinator Consortium for project FRAILCLINIC

SERVIZI BIBLIOTECARI

La biblioteca collabora attivamente con tutte le biblioteche dello proprio ambito disciplinare sul territorio nazionale. Partecipa all'Organizzazione delle biblioteche scientifiche promossa e finanziata dal Ministero dalla Salute (Bibliosan), al Catalogo Nazionale dei Periodici (ACNP), al sistema per lo scambio di documenti (NILDE) e al Gruppo Italiano Documentalisti dell'Industria Farmaceutica e degli Istituti di Ricerca Biomedica (Gidif-Rbm). Rappresenta l'Istituto ed il gruppo Bibliosan all'interno di gruppi di lavoro d'ambito biblioteconomico.
I servizi bibliotecari si concretizzano nella consulenza, guida all'uso, consultazione e riproduzione delle risorse nonché nella consultazione e la riproduzione di copie della produzione scientifica dell'Istituto dal 1999 ad oggi.
A disposizione degli utenti si trovano anche i seguenti strumenti, materiali e risorse:
- banche dati: PubMed + LinkSource, Cinahl, Journal Citation Reports, Web of Science, Scopus, Banche Dati EBSCO, BMJ BestPractice, Cochrane Library, ProQolid, Faculty of 1000, OECD;
- più di 7.000 periodici scientifici di editori quali Elsevier ScienceDirect, Wiley, Nature, Springer ma anche New England Journal of Medicine, Stroke, Blood, Science e i più importanti periodici italiani d'ambito medico-sanitario: Assistenza Infermieristica e Ricerca, Educazione Sanitaria & Promozione della Salute, Sole 24 Ore Sanità, Mecosan, Medicina e Morale, Organizzazione Sanitaria, Panorama della Sanità, Psicoterapia cognitiva e comportamentale, Sanità Pubblica e Privata, Tecnica Ospedaliera etc.
- tutti gli anni di periodici cartacei correnti e interrotti sono esposti a scaffale aperto e liberamente consultabili unitamente ad enciclopedie, dizionari, repertori;
- strumenti per la gestione delle bibliografie (RefWorks);
- oltre 1.000 testi di ambito clinico, sanitario e scientifico.
La biblioteca si occupa anche dell'organizzazione di corsi volti all'approfondimento e alla formazione all'uso delle risorse disponibili.
Le risorse sono accessibili a distanza, dall'interno dei computer della rete aziendale e da remoto. Sul portale istituzionale www.sanraffaele.it, è presente una area dedicata ai servizi e alle risorse della biblioteca: http://www.sanraffaele.it/contenuti/37/biblioteca.
L'andamento positivo dello sviluppo dei servizi bibliotecari è illustrato nel grafico che segue.

SERVIZI BIBLIOTECARI

SCUOLE UNIVERSITARIE E UNIVERSITÀ TELEMATICA

SCUOLE UNIVERSITARIE

Nell'Anno Accademico 2013/2014 in collaborazione con l'Università degli studi di Roma "Sapienza", si sono svolti i seguenti corsi:

Corso di Laurea in Scienze Infermieristiche
Presidente Prof. Elisa Petrangeli
Vicepresidente Luca Poli
Direttore didattico Vittorio Filonardi
N° di studenti I anno: 74
N° di studenti II anno: 70
N° di studenti III anno: 37

Corso di Laurea in Fisioterapia
Presidente: Vittorio Di Piero
Vice Presidente: Prof. Giuseppe Bruno
Direttore didattico: Maria Rita Bartolucci
N° di studenti I anno: 12
N° di studenti II anno: 10
N° di studenti III anno: 10

UNIVERSITÀ TELEMATICA SAN RAFFAELE ROMA

L'Università Telematica San Raffaele Roma, istituita con decreto del Ministro dell'Istruzione, dell'Università e della Ricerca 8 Maggio 2006, è un Ateneo non statale, legalmente riconosciuto, che rilascia titoli di studio con valore legale in Italia e nell'Unione Europea.
La sede legale dell'Ateneo è sita in Roma, Via Val Cannuta, 247. Gli spazi complessivamente disponibili hanno una superficie totale di circa 1.800 metri quadrati divisi tra spazi per la didattica per gli studenti, per i laboratori, per la ricerca e per gli uffici amministrativi.
La sede periferica di Milano, sita in Via Daverio 7, e la sede di Acireale (CT), sita in Corso Umberto 188, entrambe sedi d'esame, dispongono di aule, laboratori ed uffici amministrativi.
L'offerta didattica è erogata in modalità e-learning, attraverso l'utilizzo di internet e delle nuove tecnologie digitali. Gli studenti possono pertanto accedere alla piattaforma didattica in qualsiasi momento ed in qualsiasi luogo; anche coloro che per ragioni fisiche, geografiche o lavorative ne sarebbero esclusi. La lezione ex cathedra viene in sostanza sostituita da lezioni registrate e disponibili on line 24 ore su 24 e integrate con specifico materiale didattico: slide, materiale illustrativo, problemi e discussioni in linea. Le lezioni online sono integrate da attività seminariali e di laboratorio. Le prove finali relative ad ogni insegnamento sono da sostenersi in modalità frontale.
Il corpo accademico, altamente qualificato, è composto da docenti ed esperti di chiara fama nazionale e internazionale, garantendo un alto livello qualitativo dell'insegnamento.
L'efficacia del percorso didattico è garantita dalla presenza di tutor, figure adeguatamente formate per assicurare il proprio sostegno e supporto dal punto di vista della didattica, del metodo di studio, della tecnologia, dell'orientamento universitario e professionale e della spinta motivazionale. Grazie agli strumenti telematici i docenti e i tutor sono a disposizione degli studenti in qualsiasi momento per rispondere a domande e fornire chiarimenti.
I corsi di laurea dell'Università Telematica San Raffaele Roma sono legati ai settori in cui il primato dell'industria italiana è testimoniato dall'alto livello qualitativo raggiunto dal "Made in Italy" e riconosciuto a livello internazionale: il design e la moda, l'alimentazione e lo sport.

Il rapporto vitale con i settori industriali e sportivi di riferimento garantisce agli studenti una relazione proficua con il mondo produttivo e il mercato del lavoro, anche attraverso la possibilità di accedere a stage professionalizzanti nelle realtà più qualificate. Esperti e professionisti del mondo dell'industria e dello sport assicurano un percorso di studio che valorizza l'apprendimento teorico e la formazione pratica.
L'offerta didattica dell'Università Telematica San Raffaele Roma si articola in tre Facoltà per cinque corsi di laurea. In particolare:

1. Facoltà di Scienze Motorie
- Corso di Laurea in Scienze delle attività motorie e sportive
Il corso ha l'obiettivo di fornire competenze specifiche relative alla comprensione, conduzione e gestione di attività motorie a carattere educativo, adattativo, ludico o sportivo, finalizzandole allo sviluppo, al mantenimento e al recupero delle capacità motorie e del benessere psicofisico a esse correlato. I settori scientifici attivati all'interno della laurea di primo livello tendono a dare una preparazione bilanciata dei tre aspetti professionali preminenti: educativo e rieducativo, sportivo e organizzativo-gestionale.
- Corso di Laurea Magistrale in Scienze e Tecniche delle Attività Motorie Preventive e Adattate
Il corso è finalizzato a fornire competenze scientifiche avanzate nel campo dell'esercizio fisico, con particolare riguardo alle aree preventiva e adattativa. Si propone di formare laureati magistrali in possesso di solide conoscenze inerenti il mantenimento della migliore efficienza fisica lungo l' arco dell'intera vita, sia in soggetti normali che predisposti o affetti da patologie correlate a sedentarietà e stili di vita scorretti. I professionisti formati saranno in grado di adattare le attività motorie alle esigenze di soggetti con disabilità motorie o patologie che possano trarre beneficio dall'esercizio fisico e possiederanno competenze mirate alla prevenzione e al recupero, mediante l'attività motoria, di situazioni di disagio infantile e adolescenziale.

2. Facoltà di Agraria
- Corso di Laurea in Scienze dell'Alimentazione e della Gastronomia
Il corso si propone di formare una nuova figura professionale in grado di gestire tutti gli aspetti che riguardano la produzione ed il consumo del cibo, da quelli igienico-sanitari a quelli giornalistici e culturali; una figura poliedrica che sappia coniugare le conoscenze tecniche e scientifiche con quelle umanistiche, economiche e giuridiche; un professionista in grado di affrontare con competenza e creatività le sfide del settore alimentare del XXI secolo.
- Corso di Laurea Magistrale Scienze della Nutrizione Umana
Il corso offre una formazione specifica per diventare professionisti nel campo della nutrizione e affronta tutti gli aspetti della Nutrizione Umana in un'ottica fortemente multidisciplinare che integra diversi ambiti conoscitivi - da quello biomedico a quello della nutrizione, dalla caratterizzazione degli alimenti alla gestione agroalimentare - al fine di rispondere in maniera esauriente alle crescenti necessità del settore.

3. Facoltà di Architettura e Design Industriale
- Corso di Laurea in Moda e design industriale.
Il corso intende rispondere alle nuove competenze richieste dal mercato nei ruoli progettuali e di management creativo. Il percorso formativo predilige un approccio multidisciplinare che combina pragmatismo e immaginazione, managerialità e progettualità fornendo concrete esperienze di progetto e conoscenza e "case history" specifiche.
L'offerta formativa post lauream, invece, si articola attualmente in Master di primo e secondo livello e Corsi di Perfezionamento.
L'infrastruttura telematica ad uso degli studenti e del personale di Ateneo, si articola in quattro strumenti principali: le piattaforme didattiche, la segreteria didattica on-line, il servizio di posta elettronica e il sito internet d'Ateneo.
La piattaforma utilizzata per la quasi totalità delle attività didattiche di Unisanraffaele è una personalizzazione di Moodle (Modular Object-Oriented Dynamic Learning Environment, www.moodle.org), un sistema in grado di recepire contenuti didattici che prevede il tracciamento delle attività per garantire il rispetto di quanto prescritto dalla normativa universitaria in merito all'obbligo della frequenza.
Le principali tipologie di contenuto didattico utilizzate dall'Università sono:
a) le videolezioni, nella forma di lezioni frontali in cui è presente sia l'immagine del docente che la presentazione PowerPoint. Il video della lezione è sincronizzato con le diapositive le quali sono titolate e permettono di spostarsi da un punto all'altro della lezione;
b) le audio-lezioni nella forma di slide commentate da audio (rapid learning). In questo caso il docente dovrà inviare l'audio all'Università, la quale si occuperà di sincronizzare l'audio alle diapositive. Le tracce audio registrate dovranno essere una per ogni slide della presentazione. Al termine di una lezione costituita da 20 diapositive il docente dovrà produrre 20 piccole tracce audio autonome;
c) (c) materiale testuale, file e directory: i docenti possono pubblicare file di diverso formato, singolarmente oppure organizzati in cartelle;
d) link – possono essere utilizzati link a siti o video di particolare interesse, sia interni che esterni alla piattaforma.
Le principali metodologie di comunicazione con gli studenti sono:
- il forum di discussione - consente lo scambio di messaggi tra tutti gli utenti del corso o all'interno di opportuni sottogruppi;
- i quiz - che consentono l'utilizzo di domande di diverso tipo (risposta chiusa, risposta aperta, di tipo numerico, a corrispondenza;
- il glossario - consente di archiviare informazioni in modo strutturato: si può quindi utilizzare sia come glossario vero e proprio, sia come ambiente in cui inserire contributi. E' possibile assegnare valutazioni e commenti ai "termini" inseriti e creare alcuni link in modo automatico all'interno del corso;
- il compito - tramite il compito è possibile predisporre un'area in cui lo studente può inviare documenti al docente (eventualmente vincolato da scadenze). I docenti possono essere avvisati via e-mail dell' avvenuta consegna e far avere allo studente una valutazione e commenti sul lavoro consegnato;
- la chat - consente uno scambio sincrono di messaggi. Le chat possono essere lasciate sempre aperte, ad uso degli studenti, oppure aperte e chiuse a discrezione dei docenti. Ad esempio è possibile utilizzare la chat per il ricevimento studenti, oppure per una lezione on-line in cui ognuno porta i suoi contributi. E' possibile salvare le sessioni passate della chat in modo da rivederle in momenti successivi.

La Segreteria Didattica on-line ha il compito di fornire sia le funzionalità rivolte all'amministrazione universitaria (segreteria studenti) per la gestione del percorso dello studente dall'immatricolazione al conseguimento del titolo, sia i servizi web a valore aggiunto rivolti al singolo studente.
L'attività scientifica e di ricerca dell'Ateneo comprende i seguenti prodotti della ricerca:
- Pubblicazioni scientifiche nazionali ed internazionali che abbiamo rilevanza accademica e diffusione nella comunità scientifica, carattere di scientificità.
- Tutte le pubblicazioni non accademiche con International Standard Book Number (ISBN)/International Standard Serial Number (ISNN), che si rivolgono ad un pubblico più eterogeneo rispetto a quello accademico.
- Convegni scientifici, organizzati da una comunità scientifica di riferimento o da enti/istituzioni/associazione di professionisti, nonché network universitari e associazioni accademiche che abbiano ad oggetto tematiche scientifiche e la cui discussione avvenga tramite presentazioni di paper (su invito o submission), nonché esposizione di poster paper o relazioni su invito.
- Partecipazioni a convegni in qualità di relatore e/o di redattore del contributo a convegni nazionali o internazionali organizzati all'interno del proprio ambito scientifico di riferimento, nonché da associazioni di categoria o ordini professionali. Lo scopo di tali convegni è l'aggiornamento

continuo e la partecipazione del ricercatore per permettere, attraverso una condivisione del proprio know how, il miglioramento delle conoscenze globali in relazione a determinati ambiti di riferimento.
- Convegni/Seminari/Corsi, a cui il ricercatore partecipa in qualità di partecipante, ai fini di un aggiornamento professionale/scientifico per il miglioramento della propria attività di ricerca/didattica attinente all'Ateneo.
- Partecipazione a varie attività nel campo della ricerca, quali ad esempio partecipazione a: editorial board di riviste nazionali/internazionali; scientific board nell'ambito di book series promosse da editoriinternazionali e per prodotti editoriali; attività di coordinamento nell'ambito di special issues di riviste o book series; attività di referaggio per riviste accademiche e/o per convegni scientifici.

NOMINE INCARICHI E RICONOSCIMENTI

Giorgio Albertini

- International Association for the Scientific Study of Intellectual and Developmental Disabilities – Responsabile per l'Italia dello Special Interest Research Group sulla Sindrome di Down
- Componente della International Society on Early Intervention (ISEI)

Piero Barbanti

- Tesoriere della Società Italiana di Neurogeriatria
- Consigliere dell'Associazione Neurologica Italiana per la Ricerca sulle Cefalee (ANIRCEF)
- Membro del Comitato Scientifico dell'Associazione per una Scuola delle Cefalee (ASC)
- Presidente dell'Associazione Italiana per la lotta contro le Cefalee

Massimiliano Caprio

- Working Group Leader and Management Committee Member – COST(European Cooperation in Science and Technology) Action BM 1301 "Aldosterone and Mineralocorticoid Receptor"
- Associate Editor – Journal of Endocrinology
- Membro della Commissione Scientifica Società Italiana di Andrologia e Medicina della Sessualità (SIAMS)

Marco Franceschini

- Chairman Comitato Permanente per la Ricerca, International Society of Physical and Rehabilitation Medicine (ISPRM)
- Assistant Editor of European Journal of Physical Rehabilitation Medicine
- Componente Comitato Scientifico della Fondazione Louvain Bionics

Patrizia Ferroni

- Best Abstract Award "VEGF A gene promoter polymorphisms and risk of venous thromboembolism in ambulatory cancer patients" Congress on Controversies in Thrombosis and Hemostasis (CiTH) Berlin, Germany - October 30 - November 1, 2014

Fiorella Guadagni

- Componente Comitato Scientifico Health Data Consulting S.r.l. (HDC S.r.l)
- Invited reviewer of the call "Method and Tools for Individualized Medicine German Federal Mi-

nistry if Educatione and Research (BMBF)

Ferdinando Iellamo

- Componente Editorial Board Chest
- Componente Editorial Board European Jpurnal of Applied Physiology
- Componente Editorial Board Frontiers in Physiology: Exercise Physiology
- Review Editor nella rivista Frontiers in Cardiovascular Medicine: General Cardiology Sect

Vincenzo Marzolla

- Travel Grant: ESH-ISH Satellite: Putting the A back into RAAS, Santorini, Grecia
- Travel Grant: International Society of Endocrinology, Chicago, USA
- First Prize as Young Investigator, 2nd Meeting on New Trends in Cardiovascular Drug Therapy, Roma

Anna Teresa Palamara

- Presidente Sezione III Consiglio Superiore di Sanità
- Componente Comitato scientifico dell' Istituto superiore di sanità
- Componente Direzione Scientifica della Fondazione "Istituto Pasteur-Cenci Bolognetti " della "Sapienza" Università di Roma
- Presidente della Società Italiana di Microbiologia (SIM)

Eleonora Palma

- Coordinatore nazionale Commissione di Epilettologia Sperimentale della Lega Italiana Contro l'Epilessia

Cristina Roseti

- Vincitrice Morris-Coole Prize 2013 (miglior lavoro sull'epilessia)

Matteo Antonio Russo

- Componente di Editorial Board delle seguenti riviste scientifiche:
- Immunity and Aging
- Functional Neurology

- Neuroscience and Medicine
. Journal of Carcinogenesis and Mutagenesis
. Journal of Cancer Science and Terapy
. Prevention and Research
. The Scientific World Journal
. Open Journal of Pathology
. Pathology Discovery
. European Medical Journal

- Referee per le seguenti riviste scientifiche:
. ARS
. Cancer Research
. Oncogene
. Biomedicine & Pharmacotherapy
. Frontiers in Biosciences Histopthology
. Journal of Molecular Medicine
. Journal of Biological Regulators and Homeostatic Agents

Patrizio Sale

- Componente Direttivo Nazionale Società di Riabilitazione Neurologica (SIRN)

Maurizio Volterrani

- Componente Consiglio Direttivo Società Italiana Cardiologia Ospedaliera Accreditata (SICOA)
- Direttore Centro Studi Società Italiana Cardiologia Ospedaliera Accreditata (SICOA)
- Governor per l'Italia della International Society of Cardiovascular Pharmacotherapy (ISCP)
- Componente Steering Committee dello studio paneuropeo RELAX-AHF EU
- Componente Editorial Board Cardiac Failure Review
- Componente Editorial Board European Journal of Heart Failure
- Componente Comitato Etico dell'IRCCS San Raffaele Pisana
- Componente Comitato Tecnico-Scientifico dell'IRCCS San Raffaele Pisana

ATTIVITA' DI FORMAZIONE

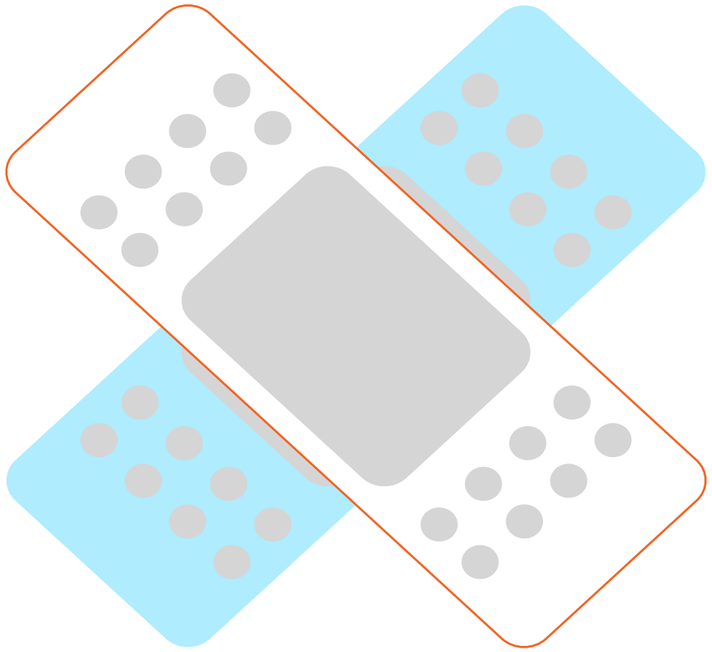
Nel 2014 il Provider San Raffaele ha organizzato ed è stato sede di 14 corsi ECM che hanno visto coinvolto il network San Raffaele, per un totale di 154 crediti circa.

DATA		TITOLO	LUOGO	NUMERO DI CREDITI ECM
Febbraio	15	Introduzione alla lettura critica di un lavoro scientifico	San Raffaele	9
Aprile	18	Le cadute in età geriatrica: la necessità dell'approccio multidisciplinare	San Raffaele Modugno	11.5
Maggio	19	"Ora riesco a mangiare" dallo svezzamento alla indipendenza	IRCCS San Raffaele Pisana	7.5
Giugno	27	Plasticità del sistema neroso e riabilitazione: meccanismi di recupero e strategie di intervento	IRCCS San Raffaele Pisana	5.4
Settembre	23	Le scale di valutazione nella pratica clinica del trattamento della Malattia di Parkinson	IRCCS San Raffaele Pisana	5
Ottobre	10	La riabilitazione respiratoria: un percorso possibile in RSA	San Raffaela Ostuni	9.1
	20	Elettrocardiografia – esecuione ed interpretazione basilare dell'ecg – Ed.i	San Raffaele Rocca di Papa	28.8
	27	Elettrocardiografia – esecuione ed interpretazione basilare dell'ECG– Ed.1	San Raffaele Rocca di Papa	28.8
	31	Progetto Ulisse: viaggio tra i vari profili di pazienti ipertesi	Formazione a Distanza Corso FAD	5
Novembre	11	Corso base di riabilitazione cardiologica	IRCCS San Raffaele Pisana	4.7
	13	La prevenzione delle cadute in ambito ospedaliero	IRCCS San Raffaele Pisana	5
Dicembre	5	La valutazione del paziente in riabilitazione	San Raffaele Montecompatri	14
	10	Formulazione della diagnosi infermieristica in riabilitazione	IRCCS San Raffaele Pisana	14
	17	La gestione del paziente psichiatrico: problematiche mediche, psicologiche, sociali e riabilitative	San Raffaele Montecompatri	6

ATTIVITA' ASSISTENZIALE

L'attività assistenziale dell'IRCCS San Raffaele Pisana si inserisce nell'ambito di una organizzazione che comprende un totale di 298 posti letto, con le seguenti Unità Operative (UU.OO.):
- Riabilitazione Neuromotoria
- Riabilitazione Pediatrica
- Cardiologia Riabilitativa
- Riabilitazione Respiratoria
- Medicina Interna

All'interno dell'IRCCS sono attivi i seguenti Laboratori e Servizi specialistici che offrono un fondamentale supporto alla clinica ed alla ricerca svolgendo un'attività trasversale agli obiettivi delle differenti UU.OO.:
- Laboratorio di Neurofisiopatologia
- Laboratorio per lo Studio delle Posture e del Movimento (Gait Analysis)
- Laboratorio per lo Studio della Funzionalità Cardiaca
- Laboratorio per lo Studio della Funzionalità Respiratoria
- Laboratorio di Patologia Clinica e Biotecnologie Avanzate
- Laboratorio di Robotica Riabilitativa
- Servizio di Otorinolaringoiatria con Laboratorio di Audiologia/Audiologia Infantile, Foniatria con sistema di videoendoscopia per lo studio delle prime vie aeree e Deglutologia
- Servizio di Diagnostica per Immagini
- Servizio di Idrokinesiterapia
- Terapia Occupazionale
- Rieducazione Funzionale



DATI DI ATTIVITÀ

Nel corso dell'anno 2014 il numero totale dei pazienti dimessi in regime di ricovero ordinario è stato di 4370, di cui 2795 pazienti per la Riabilitazione e 1575 pazienti per l'U.O. di Medicina (tab. n. 1).

Tab. n. 1 - Dimessi IRCCS San Raffaele Pisana - anno 2014

Discipline	N° Dimessi regione	N° Dimessi fuori regione	Totale	Degenza Media
Medicina interna	1533	42	1575	6,80
Riabilitazione	2524	271	2795	28,71
Riabilitazione dh	545	29	574	25,99
	4602	342	4944	21,42

RICOVERI ORDINARI

Analizzando i dati per ciascuna U.O. (tab. n. 2), si osserva che la maggior parte dei ricoveri è attribuibile all'U.O. di Riabilitazione Neuromotoria (1165 pazienti sul totale dei dimessi pari al 41,7%, di cui il 92,3% residenti nella Regione Lazio) ed all'U.O. di Riabilitazione Cardiologica (831 pazienti sul totale dei dimessi pari al 29,7%, di cui il 92,4% residenti nella Regione Lazio). Per le UU.OO. di Riabilitazione Respiratoria e di Riabilitazione Pediatrica l'ammontare dei pazienti dimessi è in termini percentuali rispettivamente del 23,4% (653 di cui il 96,5% residenti nella Regione Lazio) e del 5,2% (146 di cui il 34,9% residenti nella Regione Lazio).
La degenza media dei pazienti dimessi dalle UU.OO. va da un minimo di 21,54 giorni per la Riabilitazione Respiratoria ad un massimo di 38,17 giorni per la Riabilitazione Neuromotoria, con una media totale di 28,71 giorni.

Tab. n. 2 - Ricoveri U.O. di Riabilitazione Anno 2014 – Degenza ordinaria

U.O. RIABILITAZIONE RICOVERI ORDINARI	Dimessi		Totale dimessi	Totale gg. Degenza	Degenza Media fuori regione	Degenza Media residenti	Degenza Media totale
	Fuori regione	Residenti					
R. Pediatrica	95	51	146	3608	21,17	31,31	24,71
R. Respiratoria	23	630	653	14066	22,00	21,52	21,54
R. Neuromotoria	90	1075	1165	44473	39,64	38,05	38,17
R. Cardiologica	63	768	831	18101	22,33	21,74	21,78
Totale	271	2524	2795	80248	27,65	28,83	28,71

RICOVERI IN DAY HOSPITAL

Per quanto concerne l'attività di Day Hospital, ci sono stati 14918 accessi, per un totale di 574 pazienti (tab. n. 3). Dei pazienti ricoverati in regime di day hospital il 5,1% proviene da regioni diverse dalla Regione Lazio.

Tab. n. 3 – Attività di DH - anno 2014

	N° Dimessi regione	N° Dimessi fuori regione	Totale	Totale accessi	Numero medio accessi/pz
Riabilitazione dh	545	29	574	14918	25,99

Esaminando i dati più nel dettaglio (tab. n .4), si evidenzia che, su un totale di 574 pazienti, 100 sono stati dimessi dal DH di Riabilitazione Pediatrica (il 18,0% dei quali provenienti da regioni diverse dalla Regione Lazio), 230 dal DH di R. Neuromotoria e 244 dal DH di Riabilitazione Cardiologica.
Il numero medio di accessi per paziente è di circa 25,99 giorni, andando da un minimo di 22,30 accessi per la Riabilitazione Cardiologica ad un massimo di 28,93 accessi per la Riabilitazione Pediatrica.

Tab. n. 4 – Attività di DH per disciplina – anno 2014

Riabilitazione DH	DIMESSI		Totale dimessi	ACCESSI		Totale accessi	Accessi Medi fuori regione	Accessi Medi residenti	Accessi Medi totale
	Fuori regione	Residenti		Fuori regione	Residenti				
R. Pediatrica	18	82	100	216	2677	2893	12,00	32,65	28,93
R. Neuromotoria	8	222	230	182	6403	6585	22,75	28,84	28,63
R. Cardiologica	3	241	244	73	5367	5440	24,33	22,27	22,30
Totale	29	545	574	471	14447	14918	16,24	26,51	25,99

Dall'analisi dei dati SIO relativi alle MDC attribuite ai pazienti dimessi per l'anno 2014, sia di riabilitazione che di medicina, (tab. 5), emerge che il 39,3% sono attribuibili alla MDC5, pertanto diagnosi legate a malattie e disturbi del Sistema Cardiocircolatorio, il 24,8% attribuibili alla MDC 1, ovvero diagnosi legate a Malattie e disturbi del Sistema Nervoso ed il 28,8% attribuibili alla MDC 4, ovvero diagnosi legate a Malattie dell'apparato Respiratorio.

Tab. 5 Classificazione dei dimessi per MDC (Riabilitazione e Medicina).

Major Diagnostic Categories	ORD.	D.H.	TOT.	%
MDC 1 Malattie e disturbi del sistema nervoso	1013	213	1226	24,80
MDC 4 Malattie e disturbi dell' apparato respiratorio	930		930	18,81
MDC 5 Malattie e disturbi dell'app. cardiocircolatorio	1699	244	1943	39,30
MDC 8 Malattie e disturbi del sistema muscolo-scheletrico e del tessuto connettivo	478	87	565	11,43
MDC 19 Malattie e disturbi mentali	35	29	64	1,29
ALTRI	215	1	216	4,37
TOTALE	4370	574	4944	100,00

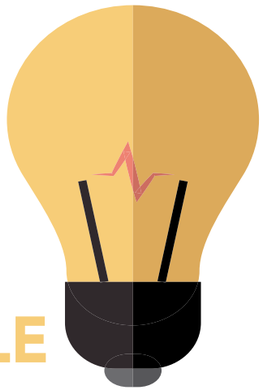
PROVENIENZA DEI PAZIENTI

L'IRCCS San Raffaele Pisana conferma la propria capacità attrattiva con ricoveri provenienti da tutte le regioni italiane. Considerando la totalità dei ricoveri, ordinari e diurni, il 6,9% dei pazienti provengono da regioni diverse dalla regione Lazio (342 su un totale di 4944 pazienti).

Attività Ambulatoriale

Complessivamente, nell'anno 2014 presso l'IRCCS San Raffaele Pisana sono state erogate 60.489 prestazioni di carattere ambulatoriale.

INNOVAZIONE E ECCELLENZA ASSISTENZIALE



AREA DI RICERCA NEUROMOTORIA

Nell'ambito della medicina riabilitativa moderna ed attuale un ruolo significativo è svolto dalla tecnologia e dallo sviluppo di dispositivi robotici per la riabilitazione. L'esperienza dell'ultimo decennio ha messo in evidenza l'importanza delle tecnologie robotiche in riabilitazione, sia in termini di risultati clinici, sia in termini di effetti positivi sui costi sanitari e sull'incremento della produttività. Negli ultimi anni, la tecnologia ha offerto al mondo della riabilitazione alcuni strumenti robotizzati per la rieducazione dell'arto superiore e del cammino.
La cura del paziente in riabilitazione neuromotoria all'IRCCS San Raffaele Pisana, è incentrata sull'eccellenza dei trattamenti anche mediante l'utilizzo di protocolli riabilitativi nuovi e all'avanguardia. A tal fine sono stati acquisiti alcuni robot, quali:

Mit Manus

E' un robot prodotto presso il Massachusetts Institute of Technology (M.I.T. Institute) all'avanguardia nella riabilitazione dell'arto superiore. Tale robot è stato sviluppato e testato sia per l'utilizzo in ambito riabilitativo, che come dispositivo di ricerca nel movimento della spalla e del gomito. Sono stati effettuati numerosi studi su prestigiose riviste internazionali per dimostrare l'efficacia dell'utilizzo del robot per la riabilitazione di pazienti affetti da stroke, paralisi cerebrale infantile e cerebro lesioni. In alternativa il dispositivo è stato utilizzato nel controllo del movimento psicofisico e nella ricerca nei disturbi del movimento.
Il robot InMotion 2.0 costituisce quindi uno strumento avanzato sia per la ricerca sia per la pratica clinica in ambito riabilitativo. Il dispositivo, dotato di tutti i sistemi di sicurezza previsti e di marchio CE, è costituito da un braccio meccanico in grado di muoversi su due piani. Il soggetto, in posizione seduta, posizionando il braccio paretico su di uno specifico supporto e, partendo dal centro, deve raggiungere dei bersagli posizionati in forma circolare, come in un orologio. Il sistema, dotato di un braccio meccanico a bassissima inerzia, controllato da un sistema di controllo computerizzato, permette movimenti attivi e passivi sui due piani. Esso registra in contemporanea il comportamento del braccio umano durante l'esecuzione dei movimenti, che possono essere attivi (guidati dalla macchina), passivi (completamente gestiti dal braccio umano) oppure misti. Il sistema è in grado di riconoscere la componente volontaria del movimento del paziente e, se questa non fosse sufficiente a raggiungere il target, il braccio meccanico "accompagna" il soggetto fino al raggiungimento dell'obiettivo, vincolandone la traiettoria. Si realizza cioè la migliore condizione possibile per l'apprendimento motorio. Il Comitato Etico dell'Istituto ha autorizzato ed approvato una sperimentazione clinica sull'uso del robot nel primo mese dall'evento acuto dell'Ictus per confermare l'efficacia di un trattamento intensivo e precoce nel recupero funzionale dell'arto superiore. La ricerca, condotta in collaborazione con l'Istituto Sant'Anna di Pisa e il centro di riabilitazione "Auxilium Vitae" di Volterra si è conclusa recentemente e sono in corso le analisi dei dati finali.

G-EO

Il secondo sistema robotico di cui è dotato l'Istituto è il G-EO della Reha Technologies. Si tratta di uno strumento motorizzato, dotato di sei motori. Il robot segue il principio dell' effettore finale. Il paziente imbracato e fissato su un sistema di scarico del peso corporeo sta in piedi su di due piattaforme, le cui traiettorie sono liberamente programmabili nel piano sagittale. Attualmente il dispositivo è in grado di simulare l'allenamento ripetitivo di tre situazioni rilevanti per la locomozione nella vita quotidiana: il cammino nel piano, l' ascesa e la discesa delle scale. I piedi del paziente vengono fissati alle piattaforme attraverso degli attacchi, i quali, per ragioni di sicurezza del paziente, si aprono quando nella caviglia viene raggiunta una posizione prestabilita.
Le piattaforme sono mosse in alto e in basso, in avanti e indietro ed inclinate attraverso sei motori. Grazie ad una rampa, il paziente può essere spinto sulla sua sedia a rotelle da dietro fino alla

posizione di fissaggio, oppure può salire da solo, il tutto con l' aiuto di un solo terapista.
La macchina può essere impostata in base alle capacità individuali del paziente, grazie a ciò vengono soddisfatti i moderni concetti di riabilitazione che prediligono allenamenti ripetitivi e mirati.
Lo scopo della terapia su questo nuovo dispositivo è il ripristino della funzione locomotoria e del controllo dell' equilibrio.
Il GEO assiste i movimenti dei pazienti con deambulazione compromessa a causa di danni per lo più conseguenti a danno neurologico a livello corticale. Si ritiene che questi movimenti possano fornire dei "suggerimenti" sensoriali molto importanti per il miglioramento e mantenimento delle abilità locomotorie. L'esoscheletro è dotato di sensori elettronici a livello del piede che consentono di controllare costantemente il carico del peso corporeo sulle varie parti della pianta del piede.
Presso l'IRCCS San Raffaele Pisana è stato approvato dal Comitato Etico e attivato uno studio sperimentale all'avanguardia sulla validazione e sull'utilizzo di tale metodologia, volto al miglioramento del cammino nelle persone con esiti di stroke e con malattia di Parkinson.
In queste prime esperienze cliniche il robot ha dimostrato di essere uno strumento valido per il recupero del cammino in fase precoce. Soprattutto nel trattamento dei pazienti con Parkinson, con disabilità medio gravi, si sono evidenziati dei promettenti successi. I dati preliminari mostrano come l'utilizzo nei pazienti con Parkinson renda possibile un recupero della velocità e della simmetria del cammino.
Nel mese di Aprile: si è aggiunto un sistema avanzato, un modulo che permette un riapprendimento ed un controllo motorio più efficace nella disabilità di tipo neuromotoria. Il robot è controllato dal paziente e supporta l'attività del cammino qualora il paziente non sia in grado di camminare attivamente. Inoltre è presente la possibilità di immergere il paziente in una realtà virtuale portando idealmente la persona all'interno di paesaggi montani, di città o di piccoli villaggi.

AMADEO

L'Amadeo è un dispositivo robotico di tipo end-effector creato per la riabilitazione della porzione distale dell'arto superiore ed è prodotto in Austria, a Graz.
Il robot consente alle falangi distali delle cinque dita di essere collegate, bloccandole, a delle slitte scorrevoli, che permettono movimenti di flessione ed estensione delle dita e di apertura e chiusura del palmo della mano. L'avambraccio ed il polso sono fissati ad un supporto: viene così favorito il movimento selettivo della mano e l'abbandono delle sinergie con i distretti più prossimali dell'arto superiore. Così posizionato, il paziente può compiere gesti di presa globale e di precisione o sequenze motorie delle singole dita in un numero molto alto di ripetizioni.
Il movimento viene effettuato dal paziente in modo interattivo: gli esercizi, simili a videogames, consentono di impostare il grado di difficoltà e di mettere alla prova abilità cognitive quali attenzione e memoria. Il software fornisce feedback visivi sull'andamento e la riuscita della performance, curando anche l'aspetto motivazionale della terapia.
Il robot ha inoltre una ottima capacità di personalizzazione del trattamento. Infatti, se lo scopo generale degli esercizi è il recupero di forza muscolare e controllo del movimento, all'interno di ogni esercizio è possibile variare diversi parametri, adattandoli al paziente anche nel corso della stessa seduta:
• il movimento può essere passivo, gestito quindi completamente dal robot;
• il movimento può essere solo attivo nel caso in cui il paziente sia in grado di effettuare tutto il movimento; in questo caso il robot serve solo da guida e controllo col feedback del movimento e registra l'attività fatta.
Il robot consente di selezionare le sole dita da coinvolgere nell'esercizio e l'escursione articolare (0- 180°), consentire il movimento globale o delle singole dita, variare la sequenza di reclutamento delle dita e la velocità richiesta, la resistenza opposta dalle slitte al movimento, il numero e la frequenza delle ripetizioni, fino a 60 al minuto.
Il dispositivo può trovare applicazione in tutte le limitazioni funzionali della mano dipendenti da cause neurologiche (ictus cerebrale, cerebropatie di varia origine, sclerosi multipla, lesioni midollari a livello cervicale, lesioni del plesso brachiale e delle vie nervose periferiche dell'arto superiore, probabilmente anche nel Parkinson). Potrebbe trovare indicazioni anche in alcune limitazioni funzionali della mano da causa reumatico/ortopedica.

SCRIPT

(Supervised Care and Rehabilitation Involving Personal Tele-robotics)

Progetto Europeo ICT

In collaborazione con l'Università londinese dell'Hertfordshire, UK

È stato dimostrato che la riabilitazione robot-assistita permette il recupero di soggetti affetti da ictus e il risparmio di risorse economiche poiché riesce a fornire un allenamento al soggetto costante e controllato e inoltre permette la ripetizione di determinati esercizi ritenuti fondamentali al recupero funzionale del paziente. Sulla base di tale presupposto il progetto europeo SCRIPT ha avuto come scopo quello di sviluppare due esoscheletri di mano e polso (uno passivo e uno attivo) e di eseguire con essi la riabilitazione di soggetti affetti da ictus in un ambiente videoludico.
I soggetti arruolati per la sperimentazione hanno seguito un percorso di riabilitazione robot-assistita autonomamente a domicilio, sotto la supervisione a distanza di clinici (tele-riabilitazione). La comunicazione paziente-clinico sarà possibile grazie a una interfaccia disponibile a entrambe le parti e funzionante tramite internet.
I partner internazionali coinvolti nel progetto sono:

- The University of Hertfordshire Higher Education Corporation, coordinatore del progetto
- R. U. Robots Ltd
- The University of Sheffield
- Universiteit Twente
- Roessingh Research and Development bv
- Moog bv
- User Interface Design gmbh

Il sistema per la riabilitazione robotica SCRIPT, costituisce l'evoluzione del sistema SCRIPT (Supervised Care & Rehabilitation Involving Personal Tele-Robotics), che, è composto da una nuova raccolta di sei videogiochi interattivi sviluppati per lo svolgimento di serie di esercizi ripetuti che si traducono in un processo di riabilitazione ma in un ambiente pseudo-ludico. La novità fondamentale nel disegno di questa macchina risiede nella possibilità di controllare attivamente il movimento dell'arto del paziente per correggerne o assisterne l'evoluzione del movimento all'interno dell'esercizio richiesto.
Nell'ambito delle attività previste dal progetto di ricerca europeo SCRIPT, sono stati trattati 13 pazienti a domicilio che hanno effettuato un training riabilitativo per il polso e per la mano mediante l'utilizzo del guanto robotico Script, con un follow-up a tre mesi dal termine del trattamento. Sono state somministrate scale cliniche quali FM, Action Research Arm Test (ARAT), Ashwort e Box and Block test e sale funzionali sulla qualità della vita, sulla percezione del trattamento robotico e sulla soddisfazione personale rispetto al trattamento proposto e ai risultati ottenuti.
I dati preliminari ottenuti dai nostri pazienti mostrano come vi sia una correlazione tra tempo di trattamento effettuato e risultati ottenuti in termini di miglioramento della funzionalità della mano. La maggioranza dei pazienti ha mostrato una grande soddisfazione a livello di fattibilità del trattamento, facilità di uso e risultati attesi e ottenuti.

AREA DI RICERCA CEFALEA E DOLORE NEUROPATICO

Uso della neurostimolazione vagale transcutanea mediante GammaCore per la terapia acuta dell'emicrania
In collaborazione con l'IRCCS Carlo Besta di Milano

Il trattamento di neuromodulazione mirato alle cefalee, impiegato per la prima volta al mondo nel trattamento della cefalea a grappolo cronica farmacoresistente, sta cambiando grazie alla messa a punto dello stimolatore nVNS, acronimo di noninvasive vagal nerve stimulation (gammacore).
Questo tipo di stimolazione può essere utilizzata sia nel trattamento sintomatico e sia in quello di profilassi.
I nuovi strumenti di stimolazione, tipo il gammacore, offrono una gestione esclusivamente clinica del paziente cefalalgico in trattamento di neuromodulazione, senza richiedere il posizionamento neurochirurgico di un microcatetere di collegamento con il generatore di impulsi posizionato in sede extracranica. Questo tipo di stimolazione può essere utilizzata sia nel trattamento sintomatico e sia in quello di profilassi dell'emicrania.
Il device, delle dimensioni di un cellulare, va collocato sul lato destro del collo ed emette treni rettangolari di stimoli della durata di circa 90 secondi la cui intensità può essere variata tramite un'apposita rotella, fino a che il paziente non percepisce lievi contrazioni muscolari sottocutanee.
Presso l'IRCCS San Raffaele, in collaborazione con l'IRCCS Carlo Besta Milano, è in corso uno studio osservazionale per il trattamento acuto dell'attacco in pazienti con emicrania senz'aura. I soggetti reclutati, di età compresa tra 18 e 65 anni, utilizzano il gammacore per il trattamento di 3 attacchi consecutivi mediante una doppia stimolazione del nervo vago di destra, della durata di 60 secondi ciascuna, per ogni singolo attacco. L'efficacia del tratamento sul dolore (misurata mediante VAS) e sui sintomi associati, viene valutata dopo 30, 60 e 120 minuti e successivamente dopo 12 e 24 ore. E' prevista la possibilità di ricorrere a una rescue medication nei pazienti non responsivi a 2 ore dal trattamento.
Sono stati arruolati complessivamente 20 pazienti (14 F, 6M), con un'età media di 39 ± 11 ed una durata di malattia in anni di 25 ± 9. Il 40% aveva una diagnosi di emicrania senza aura, il 55% emicrania senza aura e il 45% di emicrania cronica. In totale sono stati trattati 49 attacchi ed il 43% ha avuto una risposta positiva entro 60 minuti. E' in corso l'arruolamento di altri pazienti.

AREA DI RICERCA CARDIOVASCOLARE

E' in atto uno studio su un dispositivo medico Algisyl-LVR. Si tratta di un dispositivo nuovo e di una nuova procedura volta a prevenire o invertire il progresso di rimodellamento del LV nella cardiomiopatia dilatativa. L'alginato è un polisaccaride idrocolloide presente come componente strutturale nell'alga bruna marina. Il prodotto è altamente biocompatibile (citotossicità, mutageneticità, emolisi, irritazione o sensibilizzazione) e la cinetica dell'alginato è stata adattata in modo che l'Algisyl-LVR risulti simile per proprietà funzionali al tessuto miocardico: un materiale deformabile e poroso. I due differenti componenti dell'alginato formano un idrogel di calcio reticolato pochi minuti dopo la miscelazione, rendendolo così subito pronto da iniettare. I polimeri di alginato non si degradano biochimicamente nei tessuti degli organismi superiori.
I principi di ingegneria tessutale impiegati con Algisyl-LVR mirano all'aspetto più importante del ventricolo compromesso, riducendo direttamente la tensione della parete (migliorando le prestazioni dei miociti) grazie a una riduzione strategica e mirata del raggio della camera interna. Questo approccio è unico ed evita le conseguenze negative, potenzialmente involontarie, di altre terapie quali l'alterazione delle prestazioni diastoliche, dell'emodinamica periferica o l'aumento del carico di lavoro del miocita.
Algisyl-LVR viene impiantato (iniettato) direttamente nel tessuto miocardico durante una singola procedura chirurgica (cardiotoracica). Gli impianti sono permanenti e servono ad aumentare lo spessore della parete del LV e ridurre la tensione della parete del LV, con la conseguente riduzione delle dimensioni della camera del LV e una migliorata efficienza di pompaggio. I posizionamenti degli impianti fungono inoltre da struttura protesica, con la funzione di prevenire l'accrescimento ventricolare progressivo e ripristinare una forma più vantaggiosa per il ventricolo sinistro dilatato.
I dati sperimentali dimostrano che il dispositivo produce un miglioramento immediato e sostenuto della funzione cardiaca.
Si prevede che Algisyl-LVR migliori la struttura e il funzionamento del cuore malato con un progresso associato dello stato clinico del paziente e della sua qualità della vita.

Patients' Empowerment Partecipazione attiva dei pazienti e dei loro caregiver

Adesione alla "QUARTA GIORNATA NAZIONALE DELLA MALATTIA DI PARKINSON" – Evento Nazionale in cui il Clinical Trial Center ha aderito alla Quarta Giornata Nazionale di Parkinson Promossa dalla Lega Italiana per la lotto contro la Malattia di Parkinson, le sindromi extrapiramidali e le demenze (LIMPE), con la collaborazione delle associazione dei Pazienti, al fine di offrire informazioni personalizzate e divulgazione scientifica a tutte le persone interessate. Con l'obiettivi di diffondere la conoscenza della malattia e sensibilizzare l'importanza di una diagnosi precoce. Il CTC il giorno 24/11/2014, insieme ad altri 50 Centri Parkinson distribuiti in tutto il territorio Nazionale, ha fornito assistenza e informazione a tutte le persone interessate.

ABSTRACT DELLE PUBBLICAZIONI

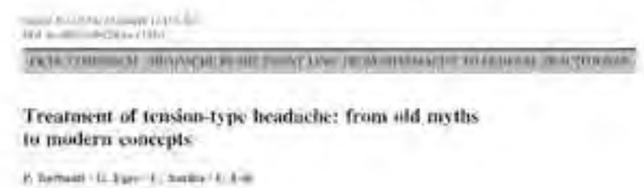
ABSTRACT DELLE PUBBLICAZIONI

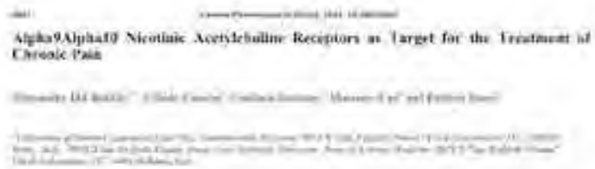

Frontiers in HUMAN NEUROSCIENCE

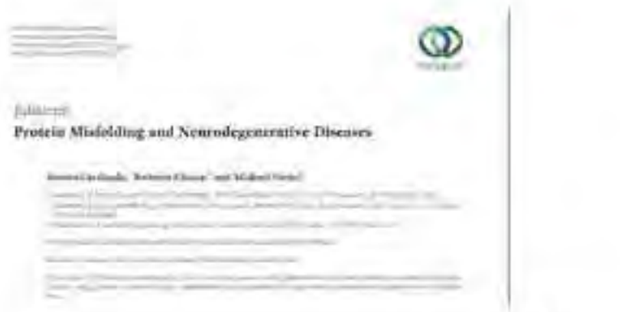
Effects of robot-assisted gait training in progressive supranuclear palsy (PSP): a preliminary report

Clinical Study

Action Observation Therapy in the Subacute Phase Promotes Dexterity Recovery in Right-Hemisphere Stroke Patients


Treatment of tension-type headache: from old myths to modern concepts


Alpha9Alpha10 Nicotinic Acetylcholine Receptors as Target for the Treatment of Chronic Pain


Protein Misfolding and Neurodegenerative Diseases

BRIEF REPORT

Right Ventricular Systolic Dysfunction Is Related to Exercise Intolerance in Patients With Chronic Obstructive Pulmonary Disease

Estimated Glomerular Filtration Rate Is an Easy Predictor of Venous Thromboembolism in Cancer Patients Undergoing Platinum-Based Chemotherapy

PLOS

Hsp90 Blockers Inhibit Adipocyte Differentiation and Fat Mass Accumulation

High Prevalence of Poor Quality Drug Prescribing in Older Individuals: A Nationwide Report From the Italian Medicines Agency (AIFA)

Glutathione: new roles in redox signaling for an old antioxidant

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6814 Current Pharmaceutical Design, 2014, Vol. 20, No. 41

Beyond Acetylcholinesterase Inhibitors for Treating Alzheimer's Disease: α7-nAChR Agonists in Human Clinical Trials

Patrizia Russo[1,*], Alessandra Del Bufalo[1], Alessandra Fiorucci[2], Massimo Fini[3] and Alfredo Cesario[3]

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Franceschini M, Iocco M, Molteni F, Santamato A, Smania N.
Management of stroke patients submitted to botulinum toxin type A therapy: a Delphi survey of an Italian expert panel of specialist injectors.
Eur J Phys Rehabil Med. 2014 Oct;50(5):525-532.

Spasticity is a common disabling symptom of several neurological conditions including stroke. Botulinum toxin type A (BTX-A) injection represents the gold standard therapy for focal spasticity. Post-stroke management of patients receiving BTX-A therapy has been variously investigated, but general agreement on how and when to implement rehabilitation is lacking. To perform a national survey of experts on the most appropriate rehabilitation procedures after BTX-A therapy for the focal treatment of spasticity.
The study employed the Delphi technique through the COSMO project (Consensus on Post-Injection Management in Post-stroke Spasticity).
Italian neurologists and physiatrists with experience in BTX-A therapy were selected to participate in the survey. Their anonymous opinions on key issues in treatment strategies in post-stroke spasticity were collected in three sequential rounds facilitated by a web platform. Consensus on a given issue was defined as agreed opinion by at least 66% of the survey participants.
In all, 44 Italian experts were involved. Positive consensus was reached on the need to start rehabilitation during the first week after BTX-A injection therapy, with a rehabilitation program comprising both stretching combined with electrical stimulation and exercise therapy. Functional surgery may be considered only after 12-24 months in cases of BTX-A therapy failure. The use of commercial or custom-made orthoses in selected cases was recommended. The appropriate time interval between two BTX-A injections is 3-6 months, and clinical assessment should be performed 1 month after injection.
The results of this national survey confirm that clinical experts on the use of BTX-A therapy for spasticity after stroke agree on the need to initiate rehabilitation treatment immediately after BTX-A injection: muscle stretching exercises, eventually combined with neuromuscular electrical stimulation, may enhance the effect of BTX-A therapy. Outcome after BTX-A therapy should be assessed at repeated follow-up visits.
This expert panel survey can provide guidance for clinicians in the assessment of patients treated with BTX-A therapy.

Gison A, Dall'Armi V, Donati V, Rizza F, Giaquinto S.
Dispositional optimism, depression, disability and quality of life in Parkinson's disease.
Funct Neurol. 2014 Apr-Jun;29(2):113-119.

Very little research on dispositional optimism (DO) has been carried out in the field of Parkinson's disease (PD). The present cross-sectional study, focusing on this personality trait, was performed with two main aims: i) to compare DO between patients with PD and a control group (CG); ii) to perform, in the PD group, a regression analysis including health-related variables, such as depression, anxiety, quality of life (QoL) and activities of daily living. Seventy PD participants and 70 healthy volunteers were enrolled in the study. The Mann-Whitney test was used to compare life orientation between the PD and CG groups. In the PD group, Pearson's correlation analysis was used to investigate the relationship between the measures of DO and the other variables. Means of log-linear regression were also used. Mean ratios adjusted for sex, age, education, and severity of disease were estimated, with relative 95% confidence intervals and p-values. The main results were as follows: i) no significant difference in DO was found between the PD participants and the CG; ii) DO was positively associated with QoL and emotional distress and inversely correlated with the Unified Parkinson's Disease Rating Scale; iii) DO was not correlated with disability. In conclusion, high DO predicts a satisfactory quality of life, low emotional distress and reduced disease severity in PD.

Gison A, Rizza F, Bonassi S, Dall Armi V, Lisi S, Giaquinto S.
The sense-of-coherence predicts health-related quality of life and emotional distress but not disability in Parkinson's disease.
BMC Neurol. 2014 Oct 10;14(1):193.

Personality traits are deemed important in many fields of Medicine. The present study aimed at evaluating i) the presence of Sense-of-Coherence (SOC) in patients suffering from Parkinson¿s Disease (PD) in comparison with an age-matched general control population, ii) the influence of SOC on health-related variables, such as depression and anxiety, quality of life (Qol), and activities of daily living (ADL). SOC was measured in 50 PD patients and in 50 matched controls enrolled in cross-sectional study. The other clinical measures included: Mini Mental State Examination (MMSE), Movement Disorder Society revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Well-being Index (WHO-5), Hospital Anxiety and Depression Scale (HADS) and the Barthel Index of ADL (BI). Data were analysed with univariate statistics and loglinear adjusted regression models. No difference emerged between PD and controls on socio-demographic and SOC. A statistically significant positive correlation was found between SOC and Qol (0.40, p<0.004) and a negative significant correlation between SOC and emotional distress (-0.37,p<0.008). The multivariate regression analysis confirmed the negative effect of SOC on total emotional distress (-3%, p=0.01) and positive effect on Qol (2%, p=0.01).SOC and BI were uncorrelated. SOC is predictive of QoL and emotional distress in PD, whereas no evidence of a predictive effect for disability could be found. These results support only partially, the Salutogenic Theory in PD, i. e. a strong SOC positively influences psychosocial health, but does not influence physical health.

Giustini A, Varela E, Franceschini M, Votava J, Zampolini M, Berteanu M, Christodoulou N.
UEMS Position Paper. New technologies designed to improve functioning: the role of the physical and rehabilitation medicine physician.
Eur J Phys Rehabil Med. 2014 Oct;50(5):579-583.

Paoloni M, Tavernese E, Fini M, Sale P, Franceschini M, Santilli V, Mangone M.
Segmental muscle vibration modifies muscle activation during reaching in chronic stroke: A pilot study.
NeuroRehabilitation. 2014 Jan 1;35(3):405-414.
Segmental muscle vibration (SMV) improves motor performances in neurological conditions, including stroke. The objective of the study is to determine if SMV modifies upper limb muscular activity in chronic stroke patients performing a reaching movement. We randomized 22 chronic stroke patients to an experimental group (EG; n = 12), receiving 10 sessions of exercise + 120 Hz SMV over the biceps brachii (BB) and the flexor carpi ulnaris (FCU) muscles, or to a control group (CG; n = 10) receiving exercise only. All subjects performed a reaching movement with the affected side before and 4 weeks after therapy ended. We recorded surface EMG activity of the anterior deltoid (AD), posterior deltoid (PD), BB, triceps brachii (TB), FCU and extensor carpi radialis (ECR) muscles. We calculated muscular onset times, modulation ratio, co-contractions and degree of contraction. After SMV, onset times of the PD (p = 0.03), BB (p = 0.02) and ECR (p = 0.04) in the EG were less anticipated than at baseline; the modulation ratio increased in AD (p = 0.003) and BB (p = 0.01); co-contractions decreased in the pairs BB/TB (p = 0.007), PD/BB (p = 0.004) and AD/BB (p = 0.01); and the degree of contraction decreased in BB (p = 0.01). The modulation of muscular function induced by SMV may aid to explain its action on smoothness and coordination of movements.
Pistoia F, Sacco S, Franceschini M, Sarà M, Pistarini C, Cazzulani B, Simonelli I, Pasqualetti P, Carolei A.
Comorbidities: a key issue in patients with disorders of consciousness.
J Neurotrauma. 2014 Oct 21. [Epub ahead of print]

The objective of this study was to identify the impact of comorbidities on outcomes of patients with vegetative state (VS) or minimally conscious state (MCS). All patients in VS or MCS consecutively admitted to two Post-Acute Care Units within a 1- year period were evaluated at baseline and at 6 months through the Coma Recovery Scale – Revised Version (CRS-R) and the Disability Rating Scale (DRS). Comorbidities were also recorded for each patient along the same period. Six-month outcomes included death, full recovery of consciousness, and functional improvement. One hundred and thirty-nine patients (88 men and 51 women, median age 59 years) were included. Ninety-seven patients were in VS (70%) and 42 in MCS (30%). At 6 months, 33 patients were dead (24%), 39 had a full recovery of consciousness (28%) and 67 remained in VS or MCS (48%). According to DRS scores, 40% of patients (n=55) showed a functional improvement in the level of disability. One hundred and thirty patients (94%) showed at least one comorbidity. Severity of comorbidities (HR=2.8, 95% CI 1.71-4.68; p<0.001) and the presence of ischemic or organic heart diseases (HR 2.6, 95% CI 1.21-5.43; p=0.014) were the strongest predictors of death together with increasing age (HR=1.0, 95% CI 1.0-1.06; p=0.033). Respiratory diseases and arrhythmias without organic heart diseases were negative predictors of full recovery of consciousness (OR=0.3, 95% CI 0.12-0.7, p=0.006; OR=0.2, 95% CI 0.07-0.43, p<0.001) and functional improvement (OR=0.4, 95% CI 0.15-0.85, p=0.020; OR=0.2, CI 0.08-0.45, p<0.001). Our data show urnal that comorbidities are common in these patients and some of them influence recovery of consciousness and outcomes.

Pistoia F, Sarà M, Sacco S, Franceschini M, Carolei A.
Silencing the brain may be better than stimulating it. The GABA Effect.
Curr Pharm Des. 2014;20(26):4154-4166.

Cases of recovery from vegetative and minimally conscious state after the administration of various pharmacological agents have been recently reported. These agents include CNS depressants (zolpidem, baclofen, lamotrigine) and CNS stimulants (tricyclic antidepressants, selective serotonin reuptake inhibitors, dopaminergic agents, methylphenidate). The action of CNS depressants as awakening agents sounds paradoxical, as they are commonly prescribed to slow down brain activity in the management of anxiety, muscle tension, pain, insomnia and seizures. How these drugs may improve the level of consciousness in some brain-injured patients is the subject of intense debate. Here we hypothesize that CNS depressants may promote consciousness recovery by reversing a condition of GABA impairment in the injured brain, restoring the normal ratio between synaptic excitation and inhibition, which is the prerequisite for any transition from a resting state to goal-oriented activities (GABA impairment hypothesis). Alternative or complementary mechanisms underlying the improvement of consciousness may include the reversal of a neurodormant state within areas affected by diaschisis (diaschisis hypothesis) and the modulation of an informative overload to the cortex as a consequence of filter failure in the injured brain (informative overload hypothesis). A better understanding of how single agents act on neural networks, whose functioning is critical for recovery, may help to advance a tailored pharmacological approach in the treatment of severely brain injured patients.

Sale P, Franceschini M, Mazzoleni S, Palma E, Agosti M, Posteraro F.
Effects of upper limb robot-assisted therapy on motor recovery in subacute stroke patients.
J Neuroeng Rehabil. 2014 Jun 19;11:104.

There is little evidence available on the use of robot-assisted therapy in subacute stroke patients. A randomized controlled trial was carried out to evaluate the short-time efficacy of intensive robot-assisted therapy compared to usual physical therapy performed in the early phase after stroke onset.
Fifty-three subacute stroke patients at their first-ever stroke were enrolled 30±7 days after the acute event and randomized into two groups, both exposed to standard therapy. Additional 30

sessions of robot-assisted therapy were provided to the Experimental Group. Additional 30 sessions of usual therapy were provided to the Control Group.
The following impairment evaluations were performed at the beginning (T0), after 15 sessions (T1), and at the end of the treatment (T2): Fugl-Meyer Assessment Scale (FM), Modified Ashworth Scale-Shoulder (MAS-S), Modified Ashworth Scale-Elbow (MAS-E), Total Passive Range of Motion-Shoulder/Elbow (pROM), and Motricity Index (MI).
Evidence of significant improvements in MAS-S ($p=0.004$), MAS-E ($p=0.018$) and pROM ($p<0.0001$) was found in the Experimental Group. Significant improvement was demonstrated in both Experimental and Control Group in FM (EG: $p<0.0001$, CG: $p<0.0001$) and MI (EG: $p<0.0001$, CG: $p<0.0001$), with an higher improvement in the Experimental Group.
Robot-assisted upper limb rehabilitation treatment can contribute to increasing motor recovery in subacute stroke patients. Focusing on the early phase of stroke recovery has a high potential impact in clinical practice.

Amirabdollahian F, Ates S, Basteris A, Cesario A, Buurke J, Hermens H, Hofs D, Johansson E, Mountain G Nasr N, Nijenhuis S, Prange G, Rahman N, Sale P, Schätzlein F, Van Schooten B, Stienen A.
Design, development and deployment of a hand/wrist exoskeleton for home-based rehabilitation after stroke - SCRIPT project.
Robotica, Volume 32, Special Issue 08, December 2014,1331–1346.

Changes in world-wide population trends have provided new demands for new technologies in areas such as care and rehabilitation. Recent developments in the field of robotics for neurorehabilitation have shown a range of evidence regarding usefulness of these technologies as a tool to augment traditional physiotherapy. Part of the appeal for these technologies is the possibility to place a rehabilitative tool in one's home, providing a chance for more frequent and accessible technologies for empowering individuals to be in charge of their therapy.
This manuscript introduces the Supervised Care and Rehabilitation Involving Personal Tele-robotics (SCRIPT) project. The main goal is to demonstrate design and development steps involved in a complex intervention, while examining feasibility of using an instrumented orthotic device for home-based rehabilitation after stroke.
The project uses a user-centred design methodology to develop a hand/wrist rehabilitation device for home-based therapy after stroke. The patient benefits from a dedicated user interface that allows them to receive feedback on exercise as well as communicating with the health-care professional. The health-care professional is able to use a dedicated interface to send/receive communications and remote-manage patient's exercise routine using provided performance benchmarks. Patients were involved in a feasibility study (n=23) and were instructed to use the device and its interactive games for 180 min per week, around 30 min per day, for a period of 6 weeks, with a 2-months follow up. At the time of this study, only 12 of these patients have finished their 6 weeks trial plus 2 months follow up evaluation.
With the "use feasibility" as objective, our results indicate 2 patients dropping out due to technical difficulty or lack of personal interests to continue. Our frequency of use results indicate that on average, patients used the SCRIPT1 device around 14 min of self-administered therapy a day. The group average for the system usability scale was around 69% supporting system usability.
Based on the preliminary results, it is evident that stroke patients were able to use the system in their homes. An average of 14 min a day engagement mediated via three interactive games is promising, given the chronic stage of stroke. During the 2nd year of the project, 6 additional games with more functional relevance in their interaction have been designed to allow for a more variant context for interaction with the system, thus hoping to positively influence the exercise duration. The system usability was tested and provided supporting evidence for this parameter. Additional improvements to the system are planned based on formative feedback throughout the project and during the evaluations. These include a new orthosis that allows a more active control of the amount of assistance and resistance provided, thus aiming to provide a more challenging interaction.

Basteris A, Johansson E, Klein P, Nasr N, Nijenhuis S, Sale P, Schätzlein F, Stienen A.
Creating gesture controlled games for robot-assisted stroke rehabilitation.
Biomedizinische Technik 2014; 59.

Regular training exercises are fundamental to regain functional use of arm and hand control after a stroke. With the SCRIPT system, the patient can practice hand excercising independently at home by playing gesture controlled games using a robotic glove (orthosis). The system could offer prolonged rehabilitation out of the clinic, with low cost treatment.
In the first version of the system (Script 1), a set of therapeutic games were developed within the project and tested in formative and summative evaluations. The main findings indicate that motivational aspects play a major role. The main issues detected concerns the challenge for the patients to understand and remember the correct gestures. Following a User Centered Design process, these findings helped to improve the new version of the system (Script 2).

Ates S, Leon B, Basteris A, Nijenhuis S, Nasr N, Sale P, Cesario A, Amirabdollahian F, Stienen AHA.
Technical evaluation of and clinical experiences with the SCRIPT passive wrist and hand orthosis.
Procs 7th Int Conf on Human System Interactions, HSI 2014; Jun 2014, 188-193.

Rehabilitation robots are useful tools to objectively quantify and treat post-stroke impairments. The SCRIPT Passive Orthosis (SPO) is an passively actuated hand orthosis that can be used for interactive therapy at home. In the last year the SPO was used independently by 24 patients in three EU countries. In this paper we report on the technical challenges this has presented and the feedback we were given by therapists and patients. This includes the range-of-motion of the device, the assistive characteristics, the potential for grasp detection, and the user acceptance.

Borgohain R, Szasz J, Stanzione P, Meshram C, Bhatt M, Chirilineau D, Stocchi F, Lucini V, Giuliani R, Forrest E, Rice P, Anand R; Study 016 Investigators.
Randomized trial of safinamide add-on to levodopa in Parkinson's disease with motor fluctuations.
Mov Disord. 2014 Feb;29 (2): 229-237.

Levodopa is effective for the motor symptoms of Parkinson's disease (PD), but is associated with motor fluctuations and dyskinesia. Many patients require add-on therapy to improve motor fluctuations without exacerbating dyskinesia. The objective of this Phase III, multicenter, double-blind, placebo-controlled, parallel-group study was to evaluate the efficacy and safety of safinamide, an □-aminoamide with dopaminergic and nondopaminergic mechanisms, as add-on to l-dopa in the treatment of patients with PD and motor fluctuations. Patients were randomized to oral safinamide 100 mg/day (n = 224), 50 mg/day (n = 223), or placebo (n = 222) for 24 weeks. The primary endpoint was total on time with no or nontroublesome dyskinesia (assessed using the Hauser patient diaries). Secondary endpoints included off time, Unified Parkinson's Disease Rating Scale (UPDRS) Part III (motor) scores, and Clinical Global Impression-Change (CGI-C). At week 24, mean ± SD increases in total on time with no or nontroublesome dyskinesia were 1.36 ± 2.625 hours for safinamide 100 mg/day, 1.37 ± 2.745 hours for safinamide 50 mg/day, and 0.97 ± 2.375 hours for placebo. Least squares means differences in both safinamide groups were significantly higher versus placebo. Improvements in off time, UPDRS Part III, and CGI-C were significantly greater in both safinamide groups versus placebo. There were no significant between-group differences for incidences of treatment-emergent adverse events (TEAEs) or TEAEs leading to discontinuation. The addition of safinamide 50 mg/day or 100 mg/day to l-dopa in patients with PD and motor fluctuations significantly increased total on time with no or nontroublesome dyskinesia, decreased off time, and improved parkinsonism, indicating that safinamide

improves motor symptoms and parkinsonism without worsening dyskinesia.

Stocchi F; ADAGIO investigators.
Benefits of treatment with rasagiline for fatigue symptoms in patients with early Parkinson's disease.
Eur J Neurol. 2014 Feb;21(2):357-360.

Fatigue is a common symptom of Parkinson's disease (PD), often considered by patients as one of the most disabling PD symptoms with significant impact on quality of life. Our aim was to assess the benefits of rasagiline treatment on fatigue in early PD patients.
In this sub-study of ADAGIO (N Engl J Med 2009; 361: 1268), 1105 untreated PD patients were randomized to receive rasagiline 1 mg/day (n = 270) or 2 mg/day (n = 277) or placebo (n = 558) for 36 weeks. The 16-item Parkinson Fatigue Scale (PFS) was assessed at baseline and at week 36/early withdrawal visit. Changes from baseline to last observed visit for each rasagiline group were compared with placebo using ancova.
Mean baseline PFS score was 2.2 ± 0.9 units. At 36 weeks, patients receiving placebo showed greater progression of symptoms (0.17 units) from baseline in PFS scores compared with the 1 mg/day (0.03 units) and 2 mg/day rasagiline groups (-0.02 units); the difference versus placebo was significant for both rasagiline groups ($P < 0.01$).
Symptoms of fatigue can be detected in patients with early PD and progressively worsen over time. Rasagiline was associated with significantly less progression of fatigue compared with placebo over a 9-month period.

Stocchi F, Antonini A, Barone P, Tinazzi M, Zappia M, Onofrj M, Ruggieri S, Morgante L, Bonuccelli U, Lopiano L, Pramstaller P, Albanese A, Attar M, Posocco V, Colombo D, Abbruzzese G; DEEP study group.
Early DEtection of wEaring off in Parkinson disease: the DEEP study.
Parkinsonism Relat Disord. 2014 Feb;20(2):204-211.

Assessing the frequency of Wearing-Off (WO) in Parkinson's disease (PD) patients, and its impact on Quality of Life (QoL).
Consecutive ambulatory patients, who were on dopaminergic treatment for ≥ 1 year, were included in this multicentre, observational cross-sectional study. In a single visit, WO was diagnosed based on neurologist assessment as well as using the validated Italian version of a patient self-rated 19-question Wearing-Off Questionnaire (WOQ-19); WO was defined for scores ≥ 2. QoL was evaluated by the 8-item Parkinson's Disease Questionnaire (PDQ-8).
617 subjects were included, with a mean anti-Parkinson treatment duration of 6.6 ± 4.6 years, 87.2% were on levodopa treatment. Neurologists identified presence of WO in 351 subjects (56.9%), whereas 415 subjects (67.3%) were identified by the self-administered WOQ-19. In patients with a <2.5 years disease duration, WO was diagnosed in 12 subjects (21.8%) by neurologists and in 23 subjects (41.8%) by the WOQ-19. The most frequent WO symptoms, as identified by WOQ-19, were "slowness of movements" (55.8%) and "reduced dexterity" (48.8%). Younger age, female gender, Unified Parkinson's Disease Rating Scale (UPDRS) part II score and duration of anti-Parkinson treatment were found significantly associated with WO. The number of motor ($p < 0.0001$) and non-motor ($p < 0.0001$) WO symptoms correlated with PDQ-8 total score.
WO is common already at the early stages of PD and is underestimated by routine neurological clinical evaluation. The number of WO symptoms, both motor and non motor, increases along with disease duration and has a negative impact on patients QoL.

Barbanti P, Egeo G.
Pharmacological trials in migraine: it's time to reappraise where the headache is and what the pain is like.

Headache. [Epub ahead of print] 2014 Dec 19.

Most pharmacological trials deal with migraine as if it were a clinically homogeneous disease, and when detailing its characteristics, they usually report only the presence, or absence, of aura and attack frequency but provide no information on pain location, a non-trivial clinical detail. The past decade has witnessed growing emerging evidence suggesting that individuals with unilateral pain, especially those with associated unilateral cranial autonomic symptoms, are more responsive than others to trigeminal-targeted symptomatic and preventive therapy with drugs such as triptans or botulinum toxin. A simple way for migraine research treatment to take a step forward might be to step back, reappraise, and critically evaluate easily obtainable patient-reported clinical findings along with current knowledge on pain features.

Tullo V, Valguarnera F, Barbanti P, Cortelli P, Sette G, Allais G, d'Onofrio F, Curone M, Zava D, Pezzola D, Benedetto C, Frediani F, Bussone G.
Comparison of frovatriptan plus dexketoprotein (25 mg or 37.5 mg) with frovatriptan alone in the treatment of migrain attacks with or without aura: a randomized study.
Cephalalgia 2014 May;34(6):434-445.

Drugs for migraine attacks include triptans and NSAIDs; their combination could provide greater symptom relief.
A total of 314 subjects with history of migraine, with or without aura, were randomized to frovatriptan 2.5 mg alone (Frova), frovatriptan 2.5 mg+ dexketoprofen 25 mg (FroDex25) or frovatriptan 2.5 mg + dexketoprofen 37.5 mg (FroDex37.5) and treated at least one migraine attack. This was a multicenter, randomized, double-blind, parallel-group study. The primary end point was the proportion of pain free (PF) at two hours. Secondary end points were PF at one and four hours, pain relief (PR) at one, two, four hours, sustained PF (SPF) at 24 and 48 hours, recurrence at 48 hours, resolution of nausea, photophobia and phonophobia at two and four hours, the use of rescue medication and the judgment of the treatment.
The results were assessed in the full analysis set (FAS) population, which included all subjects randomized and treated for whom at least one post-dose intensity of headache was recorded. The proportions of subjects PF at two hours (primary end point) were 29% (27/93) with Frova compared with 51% (48/95 FroDex25 and 46/91 FroDex37.5) with each combination therapies ($P < 0.05$). Proportions of SPF at 24 hours were 24% (22/93) for Frova, 43% (41/95) for FroDex25 ($P < 0.001$) and 42% (38/91) for FroDex37.5 ($P < 0.05$). SPF at 48 hours was 23% (21/93) with Frova, 36% (34/95) with FroDex25 and 33% (30/91) with FroDex37.5 (P = NS). Recurrence was similar for Frova (22%, 6/27), FroDex25 (29%, 14/48) and FroDex37.5 (28%, 13/46) (P = NS), meaning a lack of improvement with the combination therapy. Statistical adjustment for multiple comparisons was not performed. No statistically significant differences were reported in the occurrence of total and drug-related adverse events. FroDex25 and FroDex37.5 showed a similar efficacy both for primary and secondary end points. There did not seem to be a dose response curve for the addition of dexketoprofen.
FroDex improved initial efficacy at two hours compared to Frova whilst maintaining efficacy at 48 hours in this study. Tolerability profiles were comparable. Intrinsic pharmacokinetic properties of the two single drugs contribute to this improved efficacy profile.

Roseti C.
Interview with Cristina Roseti, 2013 Morris-Coole/Epilepsia prize winner.
Epilepsia. 2014 May;55(5):638-639.

Cogliati Dezza I, Zito G, Tomasevic L, Filippi MM, Ghazaryan A, Porcaro C, Squitti R, Ventriglia M, Lupoi D, Tecchio F.
Functional and structural balances of homologous sensorimotor regions in multiple sclerosis fa-

tigue.
J Neurol. 2014 Dec 19. [Epub ahead of print]

Fatigue in multiple sclerosis (MS) is a highly disabling symptom. Among the central mechanisms behind it, an involvement of sensorimotor networks is clearly evident from structural and functional studies. We aimed at assessing whether functional/structural balances of homologous sensorimotor regions-known to be crucial for sensorimotor networks effectiveness-decrease with MS fatigue increase. Functional connectivity measures at rest and during a simple motor task (weak handgrip of either the right or left hand) were derived from primary sensorimotor areas electroencephalographic recordings in 27 mildly disabled MS patients. Structural MRI-derived inter-hemispheric asymmetries included the cortical thickness of Rolandic regions and the volume of thalami. Fatigue symptoms increased together with the functional inter-hemispheric imbalance of sensorimotor homologous areas activities at rest and during movement, in absence of any appreciable parenchymal asymmetries. This finding supports the development of compensative interventions that may revert these neuronal activity imbalances to relieve fatigue in MS.

Ferreri F, Vecchio F, Ponzo D, Pasqualetti P, Rossini PM.
Time-varying coupling of EEG oscillations predicts excitability fluctuations in the primary motor cortex as reflected by motor evoked potentials amplitude: an EEG-TMS study.
Hum Brain Mapp. 2014 May;35(5):1969-1980.

Motor evoked potentials (MEPs) elicited by a train of consecutive, individual transcranial magnetic stimuli demonstrate fluctuations in amplitude with respect to time when recorded from a relaxed muscle. The influence of time-varying, instantaneous modifications of the electroencephalography (EEG) properties immediately preceding the transcranial magnetic stimulation (TMS) has rarely been explored. The aim of this study was to investigate the influence of the pre-TMS motor cortex and related areas EEG profile on time variants of the MEPs amplitude.
MRI-navigated TMS and multichannel TMS-compatible EEG devices were used. For each experimental subject, post-hoc analysis of the MEPs amplitude that was based on the 50th percentile of the MEPs amplitude distribution provided two subgroups corresponding to "high" (large amplitude) and "low" (small amplitude). The pre-stimulus EEG characteristics (coherence and spectral profile) from the motor cortex and related areas were analyzed separately for the "high" and "low" MEPs and were then compared.
On the stimulated hemisphere, EEG coupling was observed more often in the high compared to the low MEP trials. Moreover, a paradigmatic pattern in which TMS was able to lead to significantly larger MEPs was found when the EEG of the stimulated motor cortex was coupled in the beta 2 band with the ipsilateral prefrontal cortex and in the delta band with the bilateral centro-parietal-occipital cortices.
This data provide evidence for a statistically significant influence of time-varying and spatially patterned synchronization of EEG rhythms in determining cortical excitability, namely motor cortex excitability in response to TMS.

Babiloni C, Del Percio C, Lizio R, Infarinato F, Blin O, Bartres-Faz D, Dix SL, Bentivoglio M, Soricelli A, Bordet R, Rossini PM, Richardson JC.
A review of the effects of hypoxia, sleep deprivation and transcranial magnetic stimulation on EEG activity in humans: challenges for drug discovery for Alzheimer's disease.
Curr Alzheimer Res. 2014;11(5):501-518.

Different kinds of challenge can alter cognitive process and electroencephalographic (EEG) rhythms in humans. This can provide an alternative paradigms to evaluate treatment effects in drug discovery. Here, we report recent findings on the effects of challenges represented by sleep deprivation (SD), transient hypoxia, and transcranial magnetic stimulation (TMS) in healthy volunteers on cognitive processes and EEG rhythms to build a knowledge platform for novel research for drug discovery in AD Alzheimer's disease (AD). Sleep pressure enhanced frontal delta rhythms (< 4 Hz) during the night, while SD increased slow rhythms in the theta range (4-7 Hz), and reduced resting state alpha rhythms (8-12 Hz) after the following day. Furthermore, SD transiently affected cognitive performance. In contrast, transient experimental hypoxia induced abnormal posterior resting state delta and alpha rhythms in healthy volunteers that resemble the abnormal EEG rhythms typically recorded in AD patients. However, the relationship between the cognitive and EEG effects of such challenges is poorly understood. TMS reversibly interfered with higher brain functions during EEG recordings, but few studies have investigated the relationship between the cognitive and EEG effects of TMS. In conclusion, SD is the most mature challenge model for testing new drugs for AD. Future investigation is needed to better understand the opportunities offered by TMS and hypoxia challenges.

Babiloni C, Del Percio C, Lizio R, Marzano N, Infarinato F, Soricelli A, Salvatore E, Ferri R, Bonforte C, Tedeschi G, Montella P, Baglieri A, Rodriguez G, Famà F, Nobili F, Vernieri F, Ursini F, Mundi C, Frisoni GB, Rossini PM.
Cortical sources of resting state electroencephalographic alpha rhythms deteriorate across time in subjects with amnesic mild cognitive impairment.
Neurobiol Aging. 2014 Jan;35(1):130-142.

Here we test the hypothesis that cortical source mapping of resting state electroencephalographic (EEG) rhythms could characterize neurodegenerative disorders inducing cognitive impairment such as Parkinson's disease related dementia (PDD) and Alzheimer's disease (AD).
To address this issue, eyes-closed resting state EEG rhythms were recorded in 13 PDD, 20 AD, and 20 normal elderly (Nold) subjects. Age, gender, and education were carefully matched across the three groups. Mini Mental State Evaluation (MMSE) score probed subjects' global cognitive status, and was matched between the PDD and AD groups. EEG rhythms of interest were delta (2-4 Hz), theta (4-8 Hz), alpha1 (8-10.5 Hz), alpha2 (10.5-13 Hz), beta1 (13-20 Hz), and beta2 (20-30 Hz). EEG cortical sources were estimated by low resolution brain electromagnetic source tomography (LORETA).
With respect to the Nold and AD groups, the PPD group was characterized by peculiar abnormalities of central delta sources and posterior cortical sources of theta and beta1 rhythms. With respect to the Nold group, the PDD and AD groups mainly pointed to lower posterior cortical sources of alpha1 rhythms, which were positively correlated to MMSE score across all PDD and AD subjects as a whole (the lower the alpha sources, the lower the MMSE score). This alpha decrease was greater in the AD than PPD patients.
The results suggest that topography and frequency of eyes-closed resting state cortical EEG rhythms distinguished PDD and AD groups.
SIGNIFICANCE: We report the existence of different effects of neurodegeneration on the cortical neural synchronization mechanisms generating resting state EEG rhythms in PDD and AD patients.

Sale P, Mazzoleni S, Lombardi V, Galafate D, Massimiani MP, Posteraro F, Damiani C, Franceschini M. Recovery of hand function with robot-assisted therapy in acute stroke patients: a randomized-controlled trial.
Int J Rehabil Res. 2014 Sep;37(3):236-242.

In the last few years, not many studies on the use of robot-assisted therapy to recover hand function in acute stroke patients have been carried out. This randomized-controlled observer trial is aimed at evaluating the effects of intensive robot-assisted hand therapy compared with intensive occupational therapy in the early recovery phases after stroke with a 3-month follow-up. Twenty acute stroke patients at their first-ever stroke were enrolled and randomized into two groups. The

experimental treatment was performed using the Amadeo Robotic System. Control treatment, instead, was carried out using occupational therapy executed by a trained physiotherapist. All participants received 20 sessions of treatment for 4 consecutive weeks (5 days/week). The following clinical scales, Fugl-Meyer Scale (FM), Medical Research Council Scale for Muscle Strength (hand flexor and extensor muscles) (MRC), Motricity Index (MI) and modified Ashworth Scale for wrist and hand muscles (MAS), were performed at baseline (T0), after 20 sessions (end of treatment) (T1) and at the 3-month follow-up (T2). The Barthel Index was assessed only at T0 and T1. Evidence of a significant improvement was shown by the Friedman test for the FM [experimental group (EG): P=0.0039, control group (CG): P<0.0001], Box and Block Test (EG: P=0.0185, CG: P=0.0086), MI (EG: P<0.0001, CG: P=0.0303) and MRC (EG: P<0.0001, CG: P=0.001) scales. These results provide further support to the generalized therapeutic impact of intensive robot-assisted treatment on hand recovery functions in individuals with acute stroke. The robotic rehabilitation treatment may contribute toward the recovery of hand motor function in acute stroke patients. The positive results obtained through the safe and reliable robotic rehabilitation treatment reinforce the recommendation to extend it to a larger clinical practice.

Sale P, Stocchi F, Galafate D, De Pandis MF, Le Pera D, Sova I, Galli M, Foti C, Franceschini M.
Effects of robot assisted gait training in progressive supranuclear palsy (PSP): a preliminary report.
Front Hum Neurosci. 2014 Apr 17;8:207.

Progressive supranuclear palsy (PSP) is a rare neurodegenerative disease clinically characterized by prominent axial extrapyramidal motor symptoms with frequent falls. Over the last years the introduction of robotic technologies to recover lower limb function has been greatly employed in the rehabilitative practice. This observational trial is aimed at investigating the changes in the main spatiotemporal following end-effector robot training in people with PSP.
Five cognitively intact participants with PSP and gait disorders were enrolled.
Patients were submitted to a rehabilitative program of robot-assisted walking sessions for 45 min, 5 times a week for 4 weeks.
The spatiotemporal parameters at the beginning (T0) and at the end of treatment (T1) were recorded by a gait analysis laboratory.
Robot training was feasible, acceptable and safe and all participants completed the prescribed training sessions. All patients showed an improvement in the gait spatiotemporal index (Mean velocity, Cadence, Step length, and Step width) (T0 vs. T1).
Robot training is a feasible and safe form of rehabilitation for cognitively intact people with PSP. The lack of side effects and the positive results in the gait parameter index in all patients support the recommendation to extend the trials of this treatment. Further investigation regarding the effectiveness of robot training in time is necessary.

Bloem BR, Stocchi F.
Move for Change Part III: a European survey evaluating the impact of the EPDA Charter for People with Parkinson's Disease.
Eur J Neurol. Mar 2013; 20(3): 461–472.

The Move for Change campaign is a three-part series of pan-European surveys designed by the European Parkinson's Disease Association (EPDA) to assess the impact that the EPDA Charter for People with Parkinson's disease (PD) has had since its launch in 1997. Here, we report results from the second survey, focusing on the third right of the Charter; that is, 'all patients have the right to have access to support services'. Although the level of evidence for different support services varies, it is important to ensure that patients can access services with clinically proven benefits.
This survey comprised nine questions administered online via the EPDA and PD organization Web sites. Accessibility of support services was defined as 'services/medication/multidisciplinary healthcare professionals, etc. being available and on hand to patients when required'.
Neurologists and general practitioners (GPs) received highest accessibility results (90.0 and 87.0% of respondents, respectively), with moderate results for physiotherapists (68.0%) and PD organizations (72.0%) and lower results for PD specialist nurses (26.0%), occupational therapists (23.0%), and counselors (27.0%). Support provided by neurologists and PD specialists was considered to be 'very helpful' by 59.0 and 55.7%, respectively, whilst only 31.8% of respondents gave such favorable ratings to GPs. Funding of services was variable across Europe.
These data demonstrate the challenges faced by PD patients in accessing the adequate care and support required throughout the course of their disease. These findings can assist healthcare professionals and policymakers in improving access to support services for patients and their families across Europe.

Borgohain R, Szasz J, Stanzione P, Meshram C, Bhatt MH, Chirilineau D, Stocchi F, Lucini V, Giuliani R, Forrest E, Rice P, Anand R; Study 018 Investigators.
Two-year, randomized, controlled study of safinamide as add-on to levodopa in mid to late Parkinson's disease.
Mov Disord. 2014 Sep;29(10):1273-1280.

In a 6-month double-blind, placebo-controlled study of Parkinson's disease patients with motor fluctuations, safinamide 50 and 100 mg/d significantly increased ON-time without increasing dyskinesia. Further long-term safinamide use in these patients was evaluated over an additional 18 months. Patients continued on their randomized placebo, 50, or 100 mg/d safinamide. The primary endpoint was change in Dyskinesia Rating Scale total score during ON-time over 24 months. Other efficacy endpoints included change in ON-time without troublesome dyskinesia, changes in individual diary categories, depressive symptoms, and quality of life measures. Change in Dyskinesia Rating Scale was not significantly different in safinamide versus placebo groups, despite decreased mean total Dyskinesia Rating Scale with safinamide compared with an almost unchanged score in placebo. Ad hoc subgroup analysis of moderate to severe dyskinetic patients at baseline (36% of patients) showed a decrease with safinamide 100 mg/d compared with placebo (P = 0.0317). Improvements in motor function, activities of daily living, depressive symptoms, clinical status, and quality of life at 6 months remained significant at 24 months. Adverse events and discontinuation rates were similar with safinamide and placebo. This 2-year, controlled study of add-on safinamide in mid-to-late Parkinson's disease with motor fluctuations, although not demonstrating an overall difference in dyskinesias between patients and controls, showed improvement in dyskinesia in patients at least moderately dyskinetic at baseline. The study additionally demonstrated significant clinical benefits in ON-time (without troublesome dyskinesia), OFF-time, activities of daily living, motor symptoms, quality of life, and symptoms of depression.

Cesario A, Auffray C, Agusti A, Apolone G, Balling R, Barbanti P, Bellia A, Boccia S, Bousquet J, Cardaci V, Cazzola M, Dall'Armi V, Daraselia N, Ros LD, Del Bufalo A, Ducci G, Ferri L, Fini M, Fossati C, Gensini G, Granone PM, Kinross J, Lauro D, Lo Cascio G, Lococo F, Lococo A, Maier D, Marcus F, Margaritora S, Marra C, Minati G, Neri M, Pasqua F, Pison C, Pristipino C, Roca J, Rosano G, Rossini PM, Russo P, Salinaro G, Shenhar S, Soreq H, Sterk PJ, Stocchi F, Torti M, Volterrani M, Wouters EF, Frustaci A, Bonassi S.
A systems medicine clinical platform for understanding and managing non- communicable diseases.
Curr Pharm Des. 2014;20(38):5945-5956.

Non-Communicable Diseases (NCDs) are among the most pressing global health problems of the twenty-first century. Their rising incidence and prevalence is linked to severe morbidity and mortality, and they are putting economic and managerial pressure on healthcare systems around the world. Moreover, NCDs are impeding healthy aging by negatively affecting the quality of life of a growing number of the global population. NCDs result from the interaction of various genetic, environmental and habitual factors, and cluster in complex ways, making the complex identi-

fication of resulting phenotypes not only difficult, but also a top research priority. The degree of complexity required to interpret large patient datasets generated by advanced high-throughput functional genomics assays has now increased to the point that novel computational biology approaches are essential to extract information that is relevant to the clinical decision-making process. Consequently, system-level models that interpret the interactions between extensive tissues, cellular and molecular measurements and clinical features are also being created to identify new disease phenotypes, so that disease definition and treatment are optimized, and novel therapeutic targets discovered. Likewise, Systems Medicine (SM) platforms applied to extensively-characterized patients provide a basis for more targeted clinical trials, and represent a promising tool to achieve better prevention and patient care, thereby promoting healthy aging globally. The present paper: (1) reviews the novel systems approaches to NCDs; (2) discusses how to move efficiently from Systems Biology to Systems Medicine; and (3) presents the scientific and clinical background of the San Raffaele Systems Medicine Platform.

Italiano D, Bianchini E, Ilardi M, Cilia R, Pezzoli G, Zanettini R, Vacca L, Stocchi F, Bramanti P, Ciurleo R, Di Lorenzo G, Polimeni G, de Luise C, Ross D, Rijnbeek P, Sturkenboom M, Trifirò G.
Effectiveness of risk minimization measures for cabergoline-induced cardiac valve fibrosis in clinical practice in Italy.
J Neural Transm. 2014 Sep 18. [Epub ahead of print]

On June 2008, the European Medicines Agency (EMA) introduced changes to the Summary of Product Characteristics (SPC) for cabergoline and pergolide, to reduce the risk of cardiac valvulopathy in users of these drugs. To assess the effectiveness of EMA recommendations in Italian clinical practice, we retrospectively reviewed medical charts of patients with degenerative Parkinsonism treated with cabergoline in three large Italian clinics between January 2006 and June 2012. The prevalence and the severity of cardiac valve regurgitation were assessed in patients who stopped cabergoline therapy prior to June 2008 or continued therapy after that date. In addition, the proportion of patients undergoing echocardiographic examination in each cohort was evaluated. A total of 61 patients were available for evaluation. The proportion of patients who underwent a baseline echocardiographic examination increased from 64 % in the period before the 2008 SPC changes to 71 % among those who continued treatment after that date. However, only 18 and 29 % of patients underwent at least two echocardiographic examinations during the pre-SPC and cross-SPC change period, respectively. No severe cardiac valve regurgitation was documented in any of the study patients using cabergoline either prior or after 26th June 2008. Our findings show that the 2008 changes to the SPC resulted in an increase in physicians' awareness of cabergoline-induced valvulopathy risk in Italy. However, only a small percentage of patients underwent serial echocardiography.
Further efforts are needed to achieve better compliance with the prescribing guidelines for cabergoline treated patients in clinical practice.

Rizos A, Martinez-Martin P, Odin P, Antonini A, Kessel B, Kozul TK, Todorova A, Douiri A, Martin A, Stocchi F, Dietrichs E, Chaudhuri KR; EUROPAR and the IPDMDS non-Motor PD Study Group.
Characterizing motor and non-motor aspects of early-morning off periods in Parkinson's disease: An international multicenter study.
Parkinsonism Relat Disord. 2014 Nov;20(11):1231-1235.

The characteristic off periods that develop over time in subjects with Parkinson's disease (PD) on chronic levodopa therapy are usually considered to be motor complications but more recently the important contribution of non-motor off and non-motor fluctuations has also been acknowledged. Early-morning off (EMO) periods in PD patients are known to be a cause of significant disability, in addition to having a negative impact on quality of life. Yet EMOs are poorly defined, particularly in relation to non-motor symptoms (NMS).

This European, multicentre, observational study was undertaken to characterize the range and patterns of NMS that occur during EMO periods in a consecutive series of PD patients.
The results demonstrate that EMO periods are common and occur in 59.7% of subjects across all disease stages in line with other reports. However, importantly, in 88.0% of those, EMOs were found to be associated with NMS. The predominant NMS associated with EMO were urinary urgency, anxiety, dribbling of saliva, pain, low mood, limb paresthesia and dizziness. The patterns of dopaminergic treatment being taken by patients in this study suggested that a prolonged-release or continuous drug delivery strategy can alleviate some NMS associated with EMO.
In light of these findings it is suggested that greater awareness, recognition and appropriate treatment of EMO and NMS could improve the overall 24-h management of PD. An EMO-specific scale/questionnaire which captures both motor and NMS associated with EMO over the off time period is warranted.

Sale P, Stocchi F, Galafate D, De Pandis MF, Le Pera D, Sova I, Galli M, Foti C, Franceschini M.
Effects of robot assisted gait training in progressive supranuclear palsy (PSP): a preliminary report.
Front Hum Neurosci. 2014 Apr 17;8:207. Published online Apr 17, 2014.

Background and Purpose: Progressive supranuclear palsy (PSP) is a rare neurodegenerative disease clinically characterized by prominent axial extrapyramidal motor symptoms with frequent falls. Over the last years the introduction of robotic technologies to recover lower limb function has been greatly employed in the rehabilitative practice. This observational trial is aimed at investigating the changes in the main spatiotemporal following end-effector robot training in people with PSP. It was a pilot observational trial. Five cognitively intact participants with PSP and gait disorders were enrolled.Patients were submitted to a rehabilitative program of robot-assisted walking sessions for 45 min, 5 times a week for 4 weeks. The spatiotemporal parameters at the beginning (T0) and at the end of treatment (T1) were recorded by a gait analysis laboratory. Robot training was feasible, acceptable and safe and all participants completed the prescribed training sessions. All patients showed an improvement in the gait spatiotemporal index (Mean velocity, Cadence, Step length, and Step width) (T0 vs. T1). Robot training is a feasible and safe form of rehabilitation for cognitively intact people with PSP. The lack of side effects and the positive results in the gait parameter index in all patients support the recommendation to extend the trials of this treatment. Further investigation regarding the effectiveness of robot training in time is necessary.

Stocchi F.
Therapy for Parkinson's Disease: what is in the pipeline?
Neurotherapeutics. 2014 Jan;11(1):24-33.

Despite advances in the treatment of Parkinson's disease there are still many unmet needs, including neuroprotection, treatment of motor complications, treatment of dyskinesia, treatment of psychosis, and treatment of nondopaminergic symptoms. In this review, I highlight the obstacles to develop a neuroprotective drug and some of the treatment strategies recently approved or still in clinical trials designed to meet these unmet needs.

Stocchi F, Abbruzzese G, Ceravolo R, Cortelli P, D'Amelio M, De Pandis MF, Fabbrini G, Pacchetti C, Pezzoli G, Tessitore A, Canesi M, Iannacone C, Zappia M; FORTE Study Group.
Prevalence of fatigue in Parkinson disease and its clinical correlates.
Neurology. 2014 Jul 15;83(3):215-220.

The aim of the study was to assess in a noninterventional setting the prevalence and severity of fatigue in patients with Parkinson disease (PD).
This was a cross-sectional study conducted in Italian patients with PD. Objectives included the evaluation of the current prevalence and severity of fatigue in patients with PD measured using

the 16-item Parkinson Fatigue Scale (PFS-16), distressing fatigue (defined as a PFS-16 mean score ≥3.3), and assessment of its clinical correlates.
A total of 402 patients were enrolled and 394 patients completed the PFS-16 questionnaire with a PFS-16 mean (±SD) score of 2.87 ± 0.99. Of these, 136 patients (33.8%) reported distressing fatigue (PFS-16 mean score ≥3.3). Patients with distressing fatigue were older ($p = 0.044$) and had a longer duration of PD ($p < 0.0001$) than those without distressing fatigue. The presence of distressing fatigue was associated with higher total Unified Parkinson's Disease Rating Scale (UPDRS) scores, poorer quality of life (39-item Parkinson's Disease Questionnaire [PDQ-39]), worse social and psychological behaviors, a higher severity of depressive symptoms, and a higher prevalence of sleep disorders (all $p < 0.001$). Logistic regression analyses revealed that higher total UPDRS scores, female sex, depression, sleep disorders, as well as higher UPDRS activities of daily living scores and PDQ-39 mobility scores increase the likelihood of distressing fatigue in patients with PD.
Approximately one-third of patients with PD have distressing fatigue, which is significantly associated with depression and sleep disorders. The fact that the presence of fatigue worsens patient quality of life supports the need to better diagnose and treat this debilitating symptom.

Stocchi F, Hsu A, Khanna S, Ellenbogen A, Mahler A, Liang G, Dillmann U, Rubens R, Kell S, Gupta S. Comparison of IPX066 with carbidopa-levodopa plus entacapone in advanced PD patients.
Parkinsonism Relat Disord. 2014 Dec;20(12):1335-1340.

IPX066, an investigational extended-release carbidopa-levodopa (CD-LD) preparation, has demonstrated a rapid attainment and prolonged maintenance of therapeutic LD plasma concentrations in advanced Parkinson's disease (PD). This phase-3 crossover study assessed its efficacy and safety vs. CD-LD plus entacapone (CL + E).
At baseline, all patients had motor fluctuations despite a stable regimen of CL + E or CD-LD-entacapone combination tablets (CLE). The study included a 6-week conversion from CL + E or CLE to IPX066, followed by two 2-week, double-blind crossover treatment periods in randomized order, one on IPX066 (and placebo CL + E), the other on CL + E (and placebo IPX066), separated by 1-week open-label IPX066 treatment. The primary efficacy measure was mean percent daily "off" time during waking hours (from patient diaries).
Of 91 randomized patients, 84 completed the study. Their median daily LD dosage was 1495 mg from IPX066 and 600 mg from CL + E, corresponding, after correction for bioavailability, to an approximately 22% higher LD exposure on IPX066. Compared with CL + E, IPX066 demonstrated a lower percent "off" time (24.0% vs. 32.5%; $p < 0.0001$), lower "off" time (3.8 vs. 5.2 h/day; $p < 0.0001$), and higher "on" time without troublesome dyskinesia (11.4 vs. 10.0 h/day; $p < 0.0001$). Other endpoints, including patient-reported treatment preference, also favored IPX066 ($p < 0.05$). During double-blind treatment, 20.2% and 13.6% of patients reported adverse events on IPX066 and CL + E, respectively. The most common were dyskinesia (4 patients), insomnia (3), and confusional state (3) for IPX066, and fall (2) for CL +
In advanced PD, IPX066 showed improved efficacy, compared with CL + E, and appeared to be well tolerated.

Stocchi F, Radicati FG, Torti M.
Drug safety evaluation of ropinirole prolonged release.
Expert Opin Drug Saf. 2014 Mar;13(3):383-389.

The need for multiple administrations and a difficult titration schedule has always represented a limit in the use of dopamine agonists in the treatment of early Parkinson's disease. To avoid these problems, Ropinirole prolonged release (RPR), a non-ergoline dopamine receptor agonist that can be taken once a day, has been formulated. The prolonged release formulation has higher patient compliance due to a simpler and fastest titration schedule; the once-a-day administration makes this molecule especially suitable for young Parkinsonian patients who are still working and having an active lifestyle.
In this paper, we will review ropinirole's mechanism of action including pharmacokinetics and pharmacodynamic data and the results of the main clinical studies in early and advanced PD patients. We will also discuss safety data shown during the experimental phase and after RPR commercialization. This article reviews the use of RPR in early and advanced Parkinsonian patients. Medical literature on the use of RPR in Parkinson's disease was identified using MEDLINE and the reference lists of published articles.
RPR is effective in the treatment of patients with early Parkinson's disease; in advanced Parkinsonian patients, the amount of daily off-time significantly decreases, improving the mean on time. RPR has also demonstrated to be effective in ameliorating the quality of sleep without increasing the occurrence of daily sleepiness and nocturnal psychosis. RPR was generally well tolerated in both early and advanced Parkinsonian patients.

Stocchi F, Stirpe P.
The relevance of dopaminergic level in nocturnal disability in Parkinson's disease: implications of continuous dopaminergic stimulation at night to treat the symptoms.
J Neural Transm. 2014 Aug;121 Suppl 1:S79-83. Epub 2014 Jul 3.

Sleep problems are an under-emphasized cause of disability in Parkinson's disease (PD). Difficult sleep maintenance (light and fragmented sleep) and difficulties in initiating sleep are often the earliest and the most frequent symptoms observed in PD patients. In fluctuating patients, nocturnal akinesia, dystonia, painful cramps, and parasomnias may aggravate nocturnal problems. Treatment of sleep problems can be complex and challenging for the physicians. Dopaminergic treatment may improve some of the nocturnal symptoms in PD. In this paper, the effect of drugs and technique that ensure a more continuous delivery of dopaminergic drugs on sleep problems in PD is reviewed.

Olanow CW, Kieburtz K, Stocchi F.
Initiating levodopa therapy for Parkinson's disease.
Mov Disord. 2014 Mar;29(3):430.

Wong TH, Chiu WZ, Breedveld GJ, Li KW, Verkerk AJ, Hondius D, Hukema RK, Seelaar H, Frick P, Severijnen LA, Lammers GJ, Lebbink JH, van Duinen SG, Kamphorst W, Rozemuller AJ; Netherlands Brain Bank, Bakker EB; International Parkinsonism Genetics Network (Stocchi F, Vacca L collaborators), Neumann M, Willemsen R, Bonifati V, Smit AB, van Swieten J.
PRKAR1B mutation associated with a new neurodegenerative disorder with unique pathology.
Brain. 2014 May;137(Pt 5):1361-1373.

Pathological accumulation of intermediate filaments can be observed in neurodegenerative disorders, such as Alzheimer's disease, frontotemporal dementia and Parkinson's disease, and is also characteristic of neuronal intermediate filament inclusion disease. Intermediate filaments type IV include three neurofilament proteins (light, medium and heavy molecular weight neurofilament subunits) and □-internexin. The phosphorylation of intermediate filament proteins contributes to axonal growth, and is regulated by protein kinase A. Here we describe a family with a novel late-onset neurodegenerative disorder presenting with dementia and/or parkinsonism in 12 affected individuals. The disorder is characterized by a unique neuropathological phenotype displaying abundant neuronal inclusions by haematoxylin and eosin staining throughout the brain with immunoreactivity for intermediate filaments. Combining linkage analysis, exome sequencing and proteomics analysis, we identified a heterozygous c.149T>G (p.Leu50Arg) missense mutation in the gene encoding the protein kinase A type I-beta regulatory subunit (PRKAR1B). The pathogenicity of the mutation is supported by segregation in the family, absence in variant databases,

and the specific accumulation of PRKAR1B in the inclusions in our cases associated with a specific biochemical pattern of PRKAR1B. Screening of PRKAR1B in 138 patients with Parkinson's disease and 56 patients with frontotemporal dementia did not identify additional novel pathogenic mutations. Our findings link a pathogenic PRKAR1B mutation to a novel hereditary neurodegenerative disorder and suggest an altered protein kinase A function through a reduced binding of the regulatory subunit to the A-kinase anchoring protein and the catalytic subunit of protein kinase A, which might result in subcellular dislocalization of the catalytic subunit and hyperphosphorylation of intermediate filaments.

Allais G, Bussone G, Tullo V, Cortelli P, Valguarnera F, Barbanti P, Sette G, D'Onofrio F, Curone M, Benedetto C.
Frovatriptan 2.5 mg plus dexketoprofen (25mg or 37.5mg) in menstrually related migraine. Subanalysis from a double-blind, randomized trial.
Cephalalgia. 2014 Jul 22. pii: 0333102414542290. [Epub ahead of print]

The purpose of this article is to investigate the efficacy and safety of frovatriptan plus dexketoprofen 25 or 37.5 mg (FroDex25 or FroDex37.5, respectively) compared to that of frovatriptan 2.5 mg (Frova) in menstrually related migraine (MRM).
The aim of this article is to analyze a subgroup of 76 women who treated an MRM attack in this multicenter, randomized, double-blind, parallel-group study.
The primary end-point was the proportion of patients who were pain free (PF) at two hours. Secondary end-points included pain-relief (PR) at two hours and 48 hours sustained pain free (SPF). PF rates at two hours were 29% under Frova, 48% under FroDex25 and 64% under FroDex37.5 ($p < 0.05$). PR at two hours was Frova 52%, FroDex25 81% and FroDex37.5 88%, while 48 hours SPF was 18% under Frova, 30% under FroDex25 and 44% under FroDex37.5.
Combining frovatriptan+dexketoprofen produced higher PF rates at two hours compared to Frova while maintaining efficacy at 48 hours. Tolerability profiles were comparable.

Allais G, Tullo V, Cortelli P, Barbanti P, Valguarnera F, Sette G, D'Onofrio F, Curone M, Zava D, Pezzola D, Reggiardo G, Omboni S, Frediani F, Bussone G, Benedetto C.
Efficacy of early vs. late use of frovatriptan combined with dexketoprofen vs. frovatriptan alone in the acute treatment of migraine attacks with or without aura.
Neurol Sci. 2014 May;35 Suppl 1:107-113.

Early triptan use after headache onset may help improve the efficacy of acute migraine treatment. This may be particularly the case when triptan therapy is combined with a nonsteroidal anti-inflammatory drug (NSAID). The objective of this is to assess whether the combination of frovatriptan 2.5 mg + dexketoprofen 25 or 37.5 mg (FroDex25 and FroDex37.5) is superior to frovatriptan 2.5 mg alone (Frova) in the acute treatment of migraine attacks in patients who took the drug within 30 min from the onset of pain (early use) or after (late use). A total of 314 subjects with a history of migraine with or without aura were randomized into a double-blind, multicenter, parallel group, pilot study to Frova, FroDex25 or FroDex37.5 and were required to treat at least one migraine attack. In the present post hoc analysis, traditional migraine endpoints were compared across study drugs for subgroups of the 279 patients of the full analysis set according to early (n = 172) or late (n = 107) drug use. The proportion of patients pain free at 2 h in the early drug use subgroup was 33 % with Frova, 50 % with FroDex25 and 51 % with FroDex37.5 mg (p = NS combinations vs. monotherapy), while in the late drug use subgroup was 22, 51 and 50 % ($p < 0.05$ FroDex25 and FroDex37.5 vs. Frova), respectively. Pain-free episodes at 4 h were 54 % for early and 34 % for late use of Frova, 71 and 57 % with FroDex25 and 74 and 68 % with FroDex37.5 ($p < 0.05$ for early and $p < 0.01$ for late use vs. Frova). The proportion of sustained pain free at 24 h was 26 % under Frova, 43 % under FroDex25 mg and 40 % under FroDex37.5 mg (p = NS FroDex25 or 37.5 vs. Frova) in the early drug intake subgroup, while it was 19 % under Frova, 43 % under FroDex25 mg and 45 % under FroDex37.5 mg ($p < 0.05$ FroDex25 and FroDex37.5 vs. Frova) in the late drug intake subgroup. Risk of relapse at 48 h was similar (p = NS) among study drug groups (Frova: 25 %, FroDex25: 21 %, and FroDex37.5: 37 %) for the early as well as for the late drug use subgroup (14, 42 and 32 %). FroDex was found to be more effective than Frova taken either early or late. The intrinsic pharmacokinetic properties of the two single drug components made FroDex combination particularly effective within the 2-48-h window from the onset of the acute migraine attack. The efficacy does not seem to be influenced by the time of drug use relative to the onset of headache.

Barbanti P, Egeo G, Aurilia C, Fofi L.
Treatment of tension-type headache: from old myths to modern concepts.
Neurol Sci. 2014 May;35 Suppl 1:17-21.

Tension-type headache (TTH) is the second most common human disease, accounting for intense disability, high costs and numerous workdays lost. Tension-type headache is less simple and easy-to-treat than commonly thought. Antidepressants, despite their poor tolerability, are still the first-choice drugs for preventing TTH. The most widely studied non-pharmacological approach to TTH, cognitive-behavioral techniques, effectively relieve pain only in selected patients. The most frequently used and recommended treatments for acute TTH, NSAIDs and paracetamol have scarce efficacy as documented by their low therapeutic gain over placebo in the 2-h pain-free response. Their effectiveness may be increased by a more proper use and by the adjunction of caffeine, antiemetics, myorelaxants or tranquillizers but the risk of medication-overuse headache must be considered. Hence, the need for more effective and tailored treatments in TTH remains.

Barbanti P, Egeo G, Aurilia C, Fofi L, Della-Morte D.
Drugs targeting nitric oxide synthase for migraine treatment.
Expert Opin Investig Drugs. 2014 Aug;23(8):1141-1148.

Ample evidence that nitric oxide (NO) is a causative molecule in migraine has encouraged research to develop drugs that target the NO-cGMP cascade for migraine treatment. NO synthase (NOS) inhibition is an innovative therapeutic principle.
This paper reviews the rationale underlying NOS inhibition in migraine treatment. It also provides a review on the efficacy and safety data for NOS inhibitors (nonselective NOS inhibitor L-N(G)-methyl-arginine hydrochloride [L-NMMA], selective inducible NOS [iNOS] inhibitors GW273629 and GW274150, combined neuronal NOS [nNOS] inhibitor and 5-HT1B/1D receptor agonist NXN-188) in acute or preventive migraine treatment.
The data highlighted herein, from four placebo-controlled trials and 1 open-labeled clinical trial using 4 different NOS inhibitors on a total of 705 patients, provide convincing efficacy data only for the nonselective NOS inhibitor L-NMMA. Unfortunately, this NOS inhibitor raises cardiovascular safety concerns and has an unfavorable pharmacokinetic profile. As experimental studies predicted, iNOS inhibitors are ineffective in migraine. Still, upcoming selective nNOS inhibitors are a hope for migraine treatment, with the nNOS isoform being most clearly involved in trigeminovascular transmission and central sensitization. Future studies should help to clarify whether NOS inhibition is equally fruitful in acute and preventive treatment. It should also clarify if nNOS inhibition holds promise as a therapeutic tool for the treatment of chronic migraine and other forms of headache.

Fofi L, Allais G, Quirico PE, Rolando S, Borgogno P, Barbanti P, Benedetto C.
Acupuncture in cluster headache: four cases and review of the literature.
Neurol Sci. 2014 May;35 Suppl 1:195-198.

Although cluster headache (CH) is the most disabling form of primary headache, little evidences regarding alternative and complementary therapies are available. Only few dated studies and some isolated cases are described. We describe four patients with CH treated with acupuncture as a preventive treatment, combined with verapamil or alone. All patients received acupuncture treatment twice/week for 2 weeks, then once/week for 8 weeks, and then once/alternate weeks for 2 weeks. According to Traditional Chinese Medicine the acupoints selected were: Ex HN-5 Taiyang, GB 14 Yangbai (both only on the affected side), GB 20 Fengchi (on both sides), LI 4 Hegu, LR 2 Xingjiang, SP 6 Sanyinjiao, ST 36 Zusanli (all on both sides). At each point, after the insertion of the needle, the feeling of "De Qi" was evoked; after obtaining this sensation the acupoints were not further stimulated for a period of 20 min, until their extraction. In all patients an interruption of cluster attacks was obtained. To our knowledge, this is the first report concerning acupuncture in CH patients which details the protocol approach, acupoints and duration of the treatment. Our results offer the opportunity to discuss the emerging role of acupuncture in the therapy of CH, assuming a possible influence on opioid system.

Palmirotta R, Barbanti P, De Marchis ML, Egeo G, Aurilia C, Fofi L, Ialongo C, Valente MG, Ferroni P, Della-Morte D, Guadagni F.
Is SOD2 Ala16Val Polymorphism associated with Migraine with Aura phenotype?
Antioxid Redox Signal. 2014 Oct 8. [Epub ahead of print]

Several studies suggest a role of oxidative stress in the physiopathology of migraine, particularly in the form with aura. In a case-control study, we investigated the association between migraine and superoxide dismutase 1 (SOD1) and superoxide dismutase 2 (SOD2) genes in a cohort of 490 consecutive unrelated Caucasian migraineurs (migraine with aura [MwA], n=107; migraine without aura [MwoA], n=246; chronic migraine [CM], n=137) and 246 healthy controls recruited at our Headache and Pain Unit and stored in the Interinstitutional Multidisciplinary BioBank (BioBIM). Migraine phenotype was carefully detailed using face-to-face interviews. We examined polymorphisms of SOD1 gene (A/C substitution-rs2234694) and SOD2 gene (C/T transition-rs4880-Ala-16Val). The rs4880 TT (Val/Val) genotype was associated (p=0.042) with the presence of unilateral cranial autonomic symptoms (UAs) in MwA patients. We also found a mild correlation between SOD2 rs4880 genotype and the type of acute migraine treatment (p=0.048) in MwA patients. Our findings suggest that SOD2 is a disease-modifier gene influencing oxidative mechanisms in MwA. These observations lead to the hypothesis that SOD2 polymorphism may cause a defective control of the oxidative phenomena linked to cortical spreading depression, the neurophysiological hallmark of migraine aura, causing an overstimulation of trigeminal neurons and UAs triggering.

Palmirotta R, Barbanti P, Ludovici G, De Marchis ML, Ialongo C, Egeo G, Aurilia C, Fofi L, Abete P, Spila A, Ferroni P, Della-Morte D, Guadagni F.
Association between migraine and ACE gene(insertion/deletion) polymorphism: the BioBIM study.
Pharmacogenomics. 2014 Feb;15(2):147-155.

In the present case-control study, we investigated the correlation between the common ACE insertion/deletion (I/D) polymorphism and migraine.
Genotyping of the ACE I/D variant was performed in 502 Caucasian patients with migraine and 323 age-, sex- and race/ethnicity-matched healthy controls. We investigated associations between ACE genetic variants and sociodemographic and/or clinical features of migraineurs.
We found a significant association between ACE insertion/insertion (I/I) polymorphism and lower use of pharmacological prophylaxis in migraine patients with aura and in those with chronic migraine. Moreover, ACE I/I polymorphism was significantly more common in migraine patients with aura who had a negative family history of migraine.
Our data suggest that although the ACE I/D polymorphism is not a direct risk factor for migraine, the ACE I/I genotype may influence the clinical feature of this disease being associated with reduced use of prophylactic agents in patients with migraine with aura and in those with chronic migraine.

Allais G, Tullo V, Cortelli P, Barbanti P, Valguarnera F, Sette G, D'Onofrio F, Curone M, Reggiardo G, Omboni S, Frediani F, Bussone G, Benedetto C.
EHMTI-0052. efficacy of early vs. late use of frovatriptan combined with dexketoprofen vs. frovatriptan alone in the acute treatment of migraine attacks with or without aura.
The Journal of Headache and Pain. 2014;15:G3. doi:10.1186/1129-2377-15-S1-G3

Barbanti P, Palmirotta R, De Marchis M, Ludovici G, Ialongo C, Egeo G, Aurilia C, Fofi L, Ferroni P, Morte D, Guadagni F.
EHMTI-0241. association between migraine and sod1 and sod2 genes polymorphisms: The biobim study.
The Journal of Headache and Pain. 2014;15:B4. doi:10.1186/1129-2377-15-S1-B4

Cardinale A, Chiesa R, Sierks M.
Protein misfolding and neurodegenerative diseases.
Int J Cell Biol. 2014;2014:217371. doi: 10.1155/2014/217371. Epub 2014 Mar 31.

Cardinale A, de Stefano MC, Mollinari C, Racaniello M, Garaci E, Merlo D.
Biochemical characterization of Sirtuin 6 in the brain and its involvement in oxidative stress response.
Neurochem Res. 2014 Nov 1. [Epub ahead of print]

Sirtuin 6 (SIRT6) is a member of nicotinamide adenine dinucleotide-dependent deacetylase protein family and has been implicated in the control of glucose and lipid metabolism, cancer, genomic stability and DNA repair. Moreover, SIRT6 regulates the expression of a large number of genes involved in stress response and aging. The role of SIRT6 in brain function and neuronal survival is largely unknown. Here, we biochemically characterized SIRT6 in brain tissues and primary neuronal cultures and found that it is highly expressed in cortical and hippocampal regions and enriched in the synaptosomal membrane fraction. Immunoblotting analysis on cortical and hippocampal neurons showed that SIRT6 is downregulated during maturation in vitro, reaching the lowest expression at 11 days in vitro. In addition, SIRT6 overexpression in terminally differentiated cortical and hippocampal neurons, mediated by a neuron-specific recombinant adeno-associated virus, downregulated cell viability under oxidative stress condition. By contrast, under control condition, SIRT6 overexpression had no detrimental effect. Overall these results suggest that SIRT6 may play a role in synaptic function and neuronal maturation and it may be implicated in the regulation of neuronal survival.

Cardinale A, Merlo D, Giunchedi P, Biocca S.
Therapeutic application of intrabodies against age-related neurodegenerative disorders.
Curr Pharm Des. 2014;20(38):6028-6036.

Many neurodegenerative diseases, referred to as misfolding diseases, are characterized by the formation and accumulation of pathological extracellular and intracellular misfolded aggregates. Ageing is considered the major risk factor for neurodegenerative disorders and, due to increase of mean lifespan, the clinical relevance is growing dramatically with a urgent need to find new effective therapeutic approaches. The intracellular antibody technology is a gene-based strategy which exploits the specificity of recombinant antibodies to neutralize or modify the function of intracellular and extracellular target antigens. Intrabodies can potentially recognize all the pathological conformers of a misfolding-prone protein, and therefore they are emerging as therapeutic

agents for the treatment of misfolding diseases as well as molecular tools for the understanding of their pathogenesis. Here we focus on the application of intrabodies against two major age-related neurodegenerative disorders, Alzheimer's disease (AD) and Parkinson's disease (PD) and the description of in vivo gene delivery systems available for their potential entering in the clinical setting.

Soukupová M, Binaschi A, Falcicchia C, Zucchini S, Roncon P, Palma E, Magri E, Grandi E, Simonato M.
Impairment of GABA release in the hippocampus at the time of the first spontaneous seizure in the pilocarpine model of temporal lobe epilepsy.
Exp Neurol. 2014 Jul;257:39-49.

The alterations in GABA release have not yet been systematically measured along the natural course of temporal lobe epilepsy. In this work, we analyzed GABA extracellular concentrations (using in vivo microdialysis under basal and high K(+)-evoked conditions) and loss of two GABA interneuron populations (parvalbumin and somatostatin neurons) in the ventral hippocampus at different time-points after pilocarpine-induced status epilepticus in the rat, i.e. during development and progression of epilepsy. We found that (i) during the latent period between the epileptogenic insult, status epilepticus, and the first spontaneous seizure, basal GABA outflow was reduced to about one third of control values while the number of parvalbumin-positive cells was reduced by about 50% and that of somatostatin-positive cells by about 25%; nonetheless, high K(+) stimulation increased extracellular GABA in a proportionally greater manner during latency than under control conditions; (ii) at the time of the first spontaneous seizure (i.e., when the diagnosis of epilepsy is made in humans) this increased responsiveness to stimulation disappeared, i.e. there was no longer any compensation for GABA cell loss; (iii) thereafter, this dysfunction remained constant until a late phase of the disease. These data suggest that a GABAergic hyper-responsiveness can compensate for GABA cell loss and protect from occurrence of seizures during latency, whereas impaired extracellular GABA levels can favor the occurrence of spontaneous recurrent seizures and the maintenance of an epileptic state.

Apuzzo D, Giotti C, Pasqualetti P, Ferrazza P, Soldati P, Zucco GM.
An observational retrospective/horizontal study to compare oxygen-ozone therapy and/or global postural re-education in complicated chronic low back pain.
Funct Neurol. 2014 Jan-Mar;29(1):31-39.

Acute low back pain (LBP) is the fifth most common reason for physician visits and about nine out of ten adults experience back pain at some point in their life. In a large number of patients LBP is associated with disc herniation (DH). Recently, oxygen-ozone (O2O3) therapy has been used successfully in the treatment of LBP, reducing pain after the failure of other conservative treatments. The aim of this study was to assess the effects of O2O3 therapy in back pain rehabilitation, comparing three groups of patients suffering from chronic back pain associated with DH submitted to three different treatments: intramuscular O2O3 infiltrations, global postural An observational retrospective/horizontal study to compare oxygen-ozone therapy and/or global postural re-education in complicated chronic low back pain re-education (GPR), or a combination of the two (O2O3+GPR). The data show that pain severity before treatment was significantly lower in the patients treated with GPR alone (VAS score 7.4) than in the O2O3+GPR patients (VAS score 8.5) and the O2O3 patients (VAS score 8.6). At the end of treatment, pain severity was lower in the O2O3 patients than in the GPR-alone patients. After some years of follow-up only the difference between O2O3+GPR and GPR-alone remained significant.

Vernieri F, Altamura C, Palazzo P, Altavilla R, Fabrizio E, Fini R, Melgari JM, Paolucci M, Pasqualetti P, Maggio P.

1-Hz repetitive transcranial magnetic stimulation increases cerebral vasomotor reactivity: a possible autonomic nervous system modulation.
Brain Stimul. 2014 Mar-Apr;7(2):281-286.

Neuromodulation techniques, i.e. repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), can modify cerebral hemodynamics. High frequency rTMS appeared to decrease cerebral vasomotor reactivity (VMR), while there is still poor evidence about the effect of low frequency (LF) rTMS on cerebral blood flow (CBF) and VMR.
The present study aimed to test if LF rTMS decreases CBF and increases cerebral VMR. Monolateral or bilateral hemispheric involvement and duration of the effect were considered. A possible role of autonomic nervous system in CBF and VMR modulation was also investigated.
Twenty-four right-handed healthy subjects underwent randomly real (12) or sham (12) 20-min 1-Hz rTMS on left primary motor cortex. Mean flow velocity and VMR of middle cerebral arteries were evaluated by means of transcranial Doppler before (T0), after 10 min (T1) and after 2 (T2), 5 (T3) and 24 h (T4) from rTMS. Heart rate variability (HRV) was studied within the same timing interval, assessing low frequency/high frequency (LF/HF) ratio as index of autonomic balance.
After real rTMS compared with sham stimulation, MFV decreased bilaterally at T1 ($F = 3.240$, $P = .030$) while VMR increased bilaterally ($F = 5.116$, $P = .002$) for at least 5 h (T3). LF/HF ratio decreased early after real rTMS ($F = 2.881$, $P = .040$).
1-Hz rTMS may induce a bilateral long-lasting increase of VMR, while its effect on MFV is short-lasting. Moreover, HRV changes induced by rTMS suggest a possible autonomic nervous system modulation.

Cavedo E, Redolfi A, Angeloni F, Babiloni C, Lizio R, Chiapparini L, Bruzzone MG, Aquino D, Sabatini U, Alesiani M, Cherubini A, Salvatore E, Soricelli A,Vernieri F, Scrascia F, Sinforiani E, Chiarati P, Bastianello S, Montella P, Corbo D, Tedeschi G, Marino S, Baglieri A, De Salvo S, Carducci F, Quattrocchi CC, Cobelli M, Frisoni GB.
The Italian Alzheimer's Disease Neuroimaging Initiative (I-ADNI): validation of structural MR imaging.
J Alzheimers Dis. 2014;40(4):941-952.

The North American Alzheimer's Disease Neuroimaging Initiative (NA-ADNI) was the first program to develop standardized procedures for Alzheimer's disease (AD) imaging biomarker collection. We describe the validation of acquisition and processing of structural magnetic resonance imaging (MRI) in different Italian academic AD clinics following NA-ADNI procedures.
373 patients with subjective memory impairment (n = 12), mild cognitive impairment (n = 92), Alzheimer's dementia (n = 253), and frontotemporal dementia (n = 16) were enrolled in 9 Italian centers. 22 cognitively healthy elderly controls were also included. MRI site qualification and MP-RAGE quality assessment was applied following the NA-ADNI procedures. Indices of validity were: (i) NA-ADNI phantom's signal-to-noise and contrast-to-noise ratio, (ii) proportion of images passing quality control, (iii) comparability of automated intracranial volume (ICV) estimates across scanners, and (iv) known-group validity of manual hippocampal volumetry.
Results on Phantom and Volunteers scans showed that I-ADNI acquisition parameters were comparable with those one of the ranked-A ADNI scans. Eighty-seven percent of I-ADNI MPRAGE images were ranked of high quality in comparison of 69% of NA-ADNI. ICV showed homogeneous variances across scanners except for Siemens scanners at 3.0 Tesla ($p = 0.039$). A significant difference in hippocampal volume was found between AD and controls on 1.5 Tesla scans ($p < 0.001$), confirming known group validity test.
This study has provided standardization of MRI acquisition and imaging marker collection across different Italian clinical units and equipment. This is a mandatory step to the implementation of imaging biomarkers in clinical routine for early and differential diagnosis.

Mallio CA, Sarà M, Pistoia ML, Occhicone F, Errante Y, Giona A, Zobel BB, Quattrocchi CC.
Bilateral remote cerebellar haemorrhage after spinal surgery: a case study and review of the literature.
Brain Inj. 2014;28(9):1216-1222.

Remote cerebellar haemorrhage is a rare and unpredictable complication after intracranial and spinal surgery, although less frequently found in the latter. The physiopathology of this phenomenon has not been definitely explained.
To describe and discuss the potential implications and pathomechanism of a bilateral remote cerebellar haemorrhage case after spinal surgery and review the literature related to this rare phenomenon.
A 75 year-old man developed bilateral remote cerebellar haemorrhage after a lumbar laminectomy. Brain CT and MRI examinations showed chronic bilateral remote cerebellar haemorrhage, right haemoventricle and bilateral supratentorial subarachnoid haemorrhage. Subsequently, the patient underwent rehabilitation therapy with improvement of symptoms.
When large cerebrospinal fluid loss is observed during spinal surgery, brain imaging study should be carried out. The pathogenetic hypothesis of microcirculation vessels tearing, the role of previous spinal surgery and of cerebellar atrophy should be considered and validated with further investigation.

Marcotulli C, Leonardi L, Tessa A, De Negris AM, Cornia R, Pierallini A, Haggiag S, Pierelli F, Santorelli FM, Casali C.
Early-onset optic neuropathy as initial clinical presentation in SPG7.
J Neurol. 2014 Sep;261(9):1820-1821.

Minniti G, Scaringi C, Lanzetta G, Bozzao A, Romano A, De Sanctis V, Valeriani M, Osti M, Enrici RM.
Whole brain reirradiation and concurrent temozolomide in patients with brain metastases.
J Neurooncol. 2014 Jun;118(2):329-334.

A second course of whole brain radiation therapy (WBRT) has been employed in selected patients with progressive brain metastases providing favorable symptomatic palliation with acceptable toxicity, although its efficacy and safety remain matter of debate. In the present study we have evaluated the outcomes in patients with progressive intracranial disease treated with WBRT reirradiation and concurrent temozolomide between October 2010 and May 2013. Data were obtained from a prospectively maintained database including patients with brain tumors treated with radiotherapy at Sant'Andrea Hospital. We identified 27 patients (10 males and 17 females) with a median age of 54 years who received WBRT reirradiation at a dose of 25 Gy in ten fractions plus concomitant daily temozolomide administered orally at a dose of 75 mg/m(2). At the time of repeat WBRT all patients had a KPS ≥ 60. The primary disease sites were lung (n = 18) and breast (n = 9). The median overall survival after the second course of WBRT was 6.2 months and the median time to progression was 5.5 months. Eight patients experienced complete resolution of symptoms, 9 patients had a significant improvement, and 6 patients had no change in their neurologic function. Four patients had further deterioration after reirradiation. Overall, 85 % of patients improved or maintained their neurologic status. No severe acute toxicity during or after the second course of WBRT reirradiation was observed. On multivariate analysis with the Cox proportional hazards model, stable or absent extracranial metastases (p = 0.005) and response to treatment (p = 0.01) were independent favorable prognostic factors for survival. The median and 12-month survival rates were 12 months and 50 % in patients with stable or absent extracranial disease and 4.6 months and 7 % in those with progressive extracranial disease (p = 0.001). In conclusion, in the respect to the small number of treated patients, repeat WBRT plus concomitant temozolomide may be a treatment option in selected patients with multiple brain metastases to improve or maintain neurological conditions and quality of life with acceptable toxicity. The favorable effects of concomitant temozolomide on survival remain unclear.

Romano A, Albertini G, Guida D, Cornia R, Settecasi C, Condoluci C, Moraschi M, Fantozzi LM, Bozzao A, Pierallini A.
A Cervical Flexion-Extension MRI Study in Down Syndrome.
Indian J Pediatr. 2014 Sep 2. [Epub ahead of print]

The aim of the study is to assess what kind of information MR examination in flexed and extended positions provides in Down syndrome (DS) subjects with suspected cranio-cervical instability.
Between 2005 and 2008, 35 subjects with DS were recruited in the study. Ethics committee approval was granted and a signed informed consent was obtained from the parents. All the subjects were affected by hypotonic status and ligament laxity established by clinical evaluation, but were asymptomatic about focal neurological symptoms due to medullar damage caused by cranio-cervical instability. Each patient underwent lateral supine radiographs and MR imaging in the neutral, active flexed and extended positions. For evaluating the atlanto-axial and atlanto-occipital joint stability, multiple measurements were calculated.
A significant reduction of anterior subarachnoid space in flexed position was evident in DS subjects compared to healthy controls in neutral and flexed positions. Both, space available for cord and ligamentous thickness showed significant differences between DS subjects and healthy controls.
In DS subjects with occipito-cervical instability, the anterior subarachnoidal space reduction was significantly reduced in flexed position.
In DS subjects with asymptomatic cranio-cervical instability, anterior subarachnoidal evaluation and ligamentous status could add new information about the risk of spinal cord damage.

Romano A, Biraschi F, Tavanti F, Beccia M, Dilisi F, Castrignanò A, Giuliani G, Pierallini A, Fantozzi LM, Rasura M, Bozzao A.
Role of multidetector CT in the recognition of hyperdense middle cerebral artery sign (HMCAS) in patients with acute cerebral ischaemia: correlation with DWI-MRI sequences and clinical data.
Radiol Med. 2014 Aug 21. [Epub ahead of print]

The aim of this study was to verify the sensitivity and specificity of the hyperdense middle cerebral artery sign (HMCAS) obtained by multidetector computed tomography (CT) in predicting acute stroke, using diffusion-weighted (DW) magnetic resonance imaging (MRI) as a reference. The location of the HMCAS, the extension of the ischaemic lesion and its prognostic value were also assessed.
The CT examinations of 654 patients with symptoms related to acute cerebral stroke were retrospectively reviewed. DW-MRI confirmed recent stroke in 175 patients. Two expert neuroradiologists analysed the CT examinations of these patients in four phases. Sensitivity, specificity and interobserver reliability was evaluated. Patients were divided into three groups according to the HMCAS site (M1-M2-M3) and the Alberta Stroke Program Early CT Score (ASPECTS) on DW-MRI was calculated. The ASPECTS average score was correlated with the National Institutes of Health Stroke Scale (NIHSS) and modified Rankin scale (mRS) at 3 months.
In 41 patients, the presence of HMCAS was confirmed (71 % sensitivity; 100 % specificity; Interobserver reliability k, 84 %). An inverse correlation was found by comparing the ASPECTS and NIHSS scores (Rsq = -0.206). After logistic regression analysis, HMCAS was found to be independently associated with a poor outcome (mRS >2) at 3 months after adjusting for age, NIHSS on admission, risk factors and aetiology of stroke.
Our study demonstrated that HMCAS obtained with multidetector CT can be detected in more than 70 % of patients with large acute ischaemic lesion and it is an unfavourable prognostic sign.

Romano A, Tavanti F, Rossi Espagnet MC, Terenzi V, Cassoni A, Suma G, Boellis A, Pierallini A,

Valentini V, Bozzao A.
The role of time-resolved imaging of contrast kinetics (TRICKS) magnetic resonance angiography (MRA) in the evaluation of head-neck vascular anomalies. A preliminary Experience.
Dentomaxillofac Radiol. 2014 Nov 20:20140302. [Epub ahead of print]

In this preliminary report, we describe our experience with time-resolved imaging of contrast kinetics-MR angiography (TRICKS-MRA) in the assessment of head-neck vascular anomalies (HNVAs). We prospectively studied six consecutive patients with clinically suspected or diagnosed HNVAs. All of them underwent TRICKS-MRA of the head and neck as part of the routine for treatment planning. A digital subtraction angiography (DSA) was also performed. TRICKS-MRA could be achieved in all cases. Three subjects were treated based on TRICKS-MRA imaging findings and subsequent DSA examination. In all of them, DSA confirmed the vascular architecture of HNVAs shown by TRICKS-MRA. In the other three patients, a close follow up to assess the evolution of the suspected haemangioma was preferred. TRICKS sequences add important diagnostic information in cases of HNVAs, helpful for therapeutic decisions and post-treatment follow up. We recommend TRICKS-MRA use (if technically possible) as part of routine MRI protocol for HNVAs, representing a possible alternative imaging tool to conventional DSA.

Tavanti F, Coppola V, Romano A, Beccia M, Giuliani G, Pierallini A, Bozzao A.
Diffuse axonal injury with selective involvement of the corticospinal tract. A diffusion tensor imaging case study.
Neuroradiol J. 2014 Sep;27(4):397-399.

The identification of diffuse axonal injury (DAI) can be difficult, especially using conventional imaging (CT or MRI), which usually appears normal. Diffusion tensor imaging (DTI) is useful in identifying white matter abnormalities in patients with DAI. We describe the case of a 17-year-old female with severe closed head injury and right-side hemiparesis, studied with DTI and MR-tractography. In this case, DTI was useful to detect focal and diffuse signs of DAI.

Babiloni C, Buffo P, Vecchio F, Onorati P, Muratori C, Ferracuti S, Roma P, Battuello M, Donato N, Noce G, Di Campli F, Gianserra L, Teti E, Aceti A, Soricelli A, Viscione M, Andreoni M, Rossini PM, Pennica A.
Cortical sources of resting-state EEG rhythms in "experienced" HIV subjects under antiretroviral therapy.
Clin Neurophysiol. 2014 Sep;125(9):1792-1802.

Treatment-naïve patients with human immunodeficiency virus (HIV) are characterized by diffuse abnormalities of resting-state cortical electroencephalographic (EEG) rhythms (Babiloni et al., 2012a). Here, we tested the hypothesis that these EEG rhythms vary as a function of the systemic immune activity and antiretroviral therapy (ART) in HIV patients.
Resting-state eyes-closed EEG data were recorded in 68 ART-HIV patients (mini mental state evaluation (MMSE) of 27.5 ± 0.3 SEM), in 60 treatment-naïve HIV subjects (MMSE of 27.5 ± 0.4 SEM) and in 75 age-matched cognitively normal subjects (MMSE of 29.3 ± 0.1 SEM). Based on the CD4 lymphocytes' count, we divided ART-HIV subjects into two subgroups: those with CD4>500 cells/μl (ART-HIV+) and those with CD4<500 cells/μl (ART-HIV-). EEG rhythms of interest were delta (2-4 Hz), theta (4-8 Hz), alpha 1 (8-10.5 Hz), alpha 2 (10.5-12 Hz), beta 1 (13-20 Hz), and beta 2 (20-30 Hz). Cortical EEG sources were estimated by LORETA software.
Widespread theta, alpha, and beta sources were lower in ART-HIV subjects than in control subjects. Furthermore, occipital and temporal alpha 1 sources were lower in treatment-naïve HIV than in ART-HIV subjects. Moreover, the opposite was true for widespread pathological delta sources. Finally, parietal, occipital, and temporal alpha 1 sources were lower in ART-HIV- than in ART-HIV+ subjects.

In ART-HIV subjects, cortical sources of resting-state alpha rhythms are related to systemic immune activity and cART.
This EEG procedure may produce biomarkers of treatment response in patients' brain compartments for longitudinal clinical studies.

Babiloni C, Pennica A, Vecchio F, Onorati P, Muratori C, Ferracuti S, Roma P, Donato N, Noce G, Del Percio C, Bonacci C, Di Campli F, Gianserra L, Teti E, Aceti A, Soricelli A, Viscione M, Rossini PM, Andreoni M.
Antiretroviral therapy effects on sources of cortical rhythms in HIV subjects: Responders vs. mild responders.
Clinical Neurophysiology 2014 [Epub ahead of print] doi: 10.1016/j.clinph.2014.03.036

We tested the hypothesis that 5 months of combined anti-retroviral therapy (cART) affect cortical sources of resting state cortical electroencephalographic (EEG) rhythms in naïve HIV subjects. Eyes-closed resting state EEG data were recorded at baseline (i.e. pre-treatment; T0), T1 (after 4weeks of cART), T2 (after 8weeks of cART), and T5 (after 5months of cART) in 38 naïve HIV subjects. EEG data were also recorded in 40 age-matched cognitively normal subjects for control purposes. EEG rhythms of interest were delta (2-4Hz), theta (4-8Hz), alpha 1 (8-10.5Hz), alpha 2 (10.5-13Hz), beta 1 (13-20Hz), and beta 2 (20-30Hz). Cortical EEG sources were estimated by LORETA software. Compared to the control group, the HIV group at T0 showed greater delta sources and lower widespread alpha sources. cART induced a global improvement of biological (viral load, CD4 count) and EEG (delta, alpha) markers, remarkable even after 4weeks. Compared to HIV Responders (>100cells/μl at 5-month follow up), the HIV Mild Responders (<100cells/μl) showed greater parietal delta sources at baseline and lower occipital alpha sources at 5-month follow up. In naïve HIV subjects, 5months of successful cART affect brain synchronization mechanisms at the basis of the generation of delta and alpha rhythms.
The present EEG markers may be useful secondary neurophysiological end points for pharmacological clinical trials in naïve HIV subjects.

Babiloni C, Del Percio C, Arendt-Nielsen L, Soricelli A, Romani GL, Rossini PM, Capotosto P.
Cortical EEG alpha rhythms reflect task-specific somatosensory and motor interactions in humans.
Clin Neurophysiol. 2014 Oct;125(10):1936-1945.

Anticipating sensorimotor events allows adaptive reactions to environment with crucial implications for self-protection and survival. Here we review several studies of our group that aimed to test the hypothesis that the cortical processes preparing the elaboration of sensorimotor interaction is reflected by the reduction of anticipatory electroencephalographic alpha power (about 8-12Hz; event-related desynchronization, ERD), as an index that regulate task-specific sensorimotor processes, accounted by high-alpha sub-band (10-12Hz), rather than a general tonic alertness, accounted by low-alpha sub-band (8-10Hz). In this line, we propose a model for human cortical processes anticipating warned sensorimotor interactions. Overall, we reported a stronger high-alpha ERD before painful than non-painful somatosensory stimuli that is also predictive of the subjective evaluation of pain intensity. Furthermore, we showed that anticipatory high-alpha ERD increased before sensorimotor interactions between non-painful or painful stimuli and motor demands involving opposite hands. In contrast, sensorimotor interactions between painful somatosensory and sensorimotor demands involving the same hand decreased anticipatory high-alpha ERD, due to a sort of sensorimotor "gating" effect. In conclusion, we suggest that anticipatory cortical high-alpha rhythms reflect the central interference and/or integration of ascending (sensory) and descending (motor) signals relative to one or two hands before non-painful and painful sensorimotor interactions.

Babiloni C, Del Percio C, Boccardi M, Lizio R, Lopez S, Carducci F, Marzano N, Soricelli A, Ferri R, Triggiani AI, Prestia A, Salinari S, Rasser PE, Basar E, Famà F, Nobili F, Yener G, Emek-Savaş DD, Loreto G, Mundi C, Thompson PM, Rossini PM&, Frisoni GB.
Occipital sources of resting state alpha rhythms are related to local gray matter density in subjects with amnesic mild cognitive impairment and alzheimer's disease.
Neurobiol Aging 2014 [Epub ahead of print] DOI: 10.1016/j.neurobiolaging.2014.09.011

Occipital sources of resting-state electroencephalographic (EEG) alpha rhythms are abnormal, at the group level, in patients with amnesic mild cognitive impairment (MCI) and Alzheimer's disease (AD). Here, we evaluated the hypothesis that amplitude of these occipital sources is related to neurodegeneration in occipital lobe as measured by magnetic resonance imaging. Resting-state eyes-closed EEG rhythms were recorded in 45 healthy elderly (Nold), 100 MCI, and 90 AD subjects. Neurodegeneration of occipital lobe was indexed by weighted averages of gray matter density, estimated from structural MRIs. EEG rhythms of interest were alpha 1 (8-10.5 Hz) and alpha 2 (10.5-13 Hz). EEG cortical sources were estimated by low-resolution brain electromagnetic tomography. Results showed a positive correlation between occipital gray matter density and amplitude of occipital alpha 1 sources in Nold, MCI, and AD subjects as a whole group ($r = 0.3$, $p = 0.000004$, $n = 235$). Furthermore, there was a positive correlation between the amplitude of occipital alpha 1 sources and cognitive status as revealed by Mini Mental State Examination score across all subjects ($r = 0.38$, $p = 0.000001$, $n = 235$). Finally, amplitude of occipital alpha 1 sources allowed a moderate classification of individual Nold and AD subjects (sensitivity: 87.8%; specificity: 66.7%; area under the receiver operating characteristic curve: 0.81). These results suggest that the amplitude of occipital sources of resting-state alpha rhythms is related to AD neurodegeneration in occipital lobe along pathologic aging.

Babiloni C, Vecchio F, Buffo P, Iacoboni M, Pistoia F, Sacco S, Sara M, Rossini PM.
Mechanisms of cortical neural synchronization related to healthy and impaired consciousness: evidence by quantitative electroencephalographic studies.
Curr Pharm Des. 2014;20(26):4225-4238.

In this paper, we review the contribution of our research group to the study of human consciousness by quantitative electroencephalographic (EEG) techniques. We posit that EEG techniques can be extremely useful for a direct measurement of brain electrophysiological activity related to human consciousness for their unsurpassable high temporal resolution (milliseconds). This activity can be expressed in terms of event-related potentials as well as changes of EEG rhythms of interest, for example the dominant alpha rhythms (about 8-12 Hz). The results of our studies, and those of several independent groups, lead support to the hypothesis that these techniques provide important insights about the neurophysiologic mechanisms underlying cortical neural synchronization/desynchronization and the regulation of neuromodulatory systems (e.g. dopaminergic, noradrenergic, cholinergic, etc.) at the basis of brain arousal and consciousness in healthy subjects and in patients with impairment of the consciousness. A possible interaction of these mechanisms and the drugs administered to patients with consciousness disorders is discussed.

Barnard ND, Bush AI, Ceccarelli A, Cooper J, de Jager CA, Erickson KI, Fraser G, Kesler S, Levin SM, Lucey B, Morris MC, Squitti R.
Dietary and lifestyle guidelines for the prevention of Alzheimer's disease.
Neurobiol Aging. 2014 Sep;35 Suppl 2:S74-8.

Risk of developing Alzheimer's disease is increased by older age, genetic factors, and several medical risk factors. Studies have also suggested that dietary and lifestyle factors may influence risk, raising the possibility that preventive strategies may be effective. This body of research is incomplete. However, because the most scientifically supported lifestyle factors for Alzheimer's disease are known factors for cardiovascular diseases and diabetes, it is reasonable to provide preliminary guidance to help individuals who wish to reduce their risk. At the International Conference on Nutrition and the Brain, Washington, DC, July 19-20, 2013, speakers were asked to comment on possible guidelines for Alzheimer's disease prevention, with an aim of developing a set of practical, albeit preliminary, steps to be recommended to members of the public. From this discussion, 7 guidelines emerged related to healthful diet and exercise habits.

Abete P, Della-Morte D, Gargiulo G, Basile C, Langellotto A, Galizia G, Testa G, Canonico V, Bonaduce D, Cacciatore F.
Cognitive impairment and cardiovascular diseases in the elderly. A heart-brain continuum hypothesis.
Ageing Res Rev. 2014 Nov;18:41-52.

The aging population is increasing and, therefore, a higher prevalence of cardiac disease is emerging; including hypertension, coronary artery disease, atrial fibrillation and chronic heart failure. Large cohort studies have revealed a relationship among increased risk for cognitive impairment and dementia in cardiovascular diseases probably due to embolic stroke or chronic cerebral hypoperfusion. Thus, the aim of the present review is to overview the studies that investigate the presence and/or the development of cognitive impairments and dementia in patients with varied types of cardiovascular disease. Finally, a continuum among hypertension, coronary artery disease, atrial fibrillation and chronic heart failure with to the development of cognitive impairment and progression to dementia has been hypothesized.

Debette S, Goeggel Simonetti B, Schilling S, Martin JJ, Kloss M, Sarikaya H, Hausser I, Engelter S, Metso TM, Pezzini A, Thijs V, Touzé E, Paolucci S, Costa P, Sessa M, Samson Y, Béjot Y, Altintas A, Metso AJ, Hervé D, Lichy C, Jung S, Fischer U, Lamy C, Grau A, Chabriat H, Caso V, Lyrer PA, Stapf C, Tatlisumak T, Brandt T, Tournier-Lasserve E, Germain DP, Frank M, Baumgartner RW, Grond-Ginsbach C, Bousser MG, Leys D, Dallongeville J, Bersano A, Arnold M; CADISP-plus consortium. (Palmirotta R. collaborator)
Familial occurrence and heritable connective tissue disorders in cervical artery dissection. Neurology. 2014 Nov 25;83(22):2023-2031.

In a large series of patients with cervical artery dissection (CeAD), a major cause of ischemic stroke in young and middle-aged adults, we aimed to examine frequencies and correlates of family history of CeAD and of inherited connective tissue disorders.
We combined data from 2 large international multicenter cohorts of consecutive patients with CeAD in 23 neurologic departments participating in the CADISP-plus consortium, following a standardized protocol. Frequency of reported family history of CeAD and of inherited connective tissue disorders was assessed. Putative risk factors, baseline features, and 3-month outcome were compared between groups.
Among 1,934 consecutive patients with CeAD, 20 patients (1.0%, 95% confidence interval: 0.6%-1.5%) from 17 families (0.9%, 0.5%-1.3%) had a family history of CeAD. Family history of CeAD was significantly more frequent in patients with carotid location of the dissection and elevated cholesterol levels. Two patients without a family history of CeAD had vascular Ehlers-Danlos syndrome with a mutation in COL3A1. This diagnosis was suspected in 2 additional patients, but COL3A1 sequencing was negative. Two patients were diagnosed with classic and hypermobile Ehlers-Danlos syndrome, one patient with Marfan syndrome, and one with osteogenesis imperfecta, based on clinical criteria only.
In this largest series of patients with CeAD to date, family history of symptomatic CeAD was rare and inherited connective tissue disorders seemed exceptional. This finding supports the notion that CeAD is a multifactorial disease in the vast majority of cases.

Della-Morte D, Palmirotta R, Rehni AK, Pastore D, Capuani B, Pacifici F, De Marchis ML, Dave KR, Bellia A, Fogliame G, Ferroni P, Donadel G, Cacciatore F, Abete P, Dong C, Pileggi A, Roselli M, Ricordi C, Sbraccia P, Guadagni F, Rundek T, Lauro D.
Pharmacogenomics and pharmacogenetics of thiazolidinediones: role in diabetes and cardiovascular risk factors.
Pharmacogenomics. 2014 Dec;15(16):2063-2082.

The most important goal in the treatment of patients with diabetes is to prevent the risk of cardiovascular disease (CVD), the first cause of mortality in these subjects. Thiazolidinediones (TZDs), a class of antidiabetic drugs, act as insulin sensitizers increasing insulin-dependent glucose disposal and reducing hepatic glucose output. TZDs including pioglitazone, rosiglitazone and troglitazone, by activating PPAR-? have shown pleiotropic effects in reducing vascular risk factors and atherosclerosis. However, troglitazone was removed from the market due to its hepatoxicity, and rosiglitazone and pioglitazone both have particular warnings due to being associated with heart diseases. Specific genetic variations in genes involved in the pathways regulated by TDZs have demonstrated to modify the variability in treatment with these drugs, especially in their side effects. Therefore, pharmacogenomics and pharmacogenetics are an important tool in further understand intersubject variability per se but also to assess the therapeutic potential of such variability in drug individualization and therapeutic optimization.

Palmirotta R, Barbanti P, Ialongo C, De Marchis ML, Ludovici G, Egeo G, Aurilia C, Fofi L, Valente MG, Ferroni P, Della-Morte D, Guadagni F.
Progesterone receptor gene PROGINS polymorphism correlates with late onset of migraine.
DNA Cell Biol. 2014 Dec 10. [Epub ahead of print]

Progesterone influences central neuronal excitability, a key event in migraine pathophysiology. Progesterone receptor gene (PGR) rs1042838 (G/T - Val660Leu) variant is indicative of PROGINS haplotype and associated to a reduced PGR activity. With the aim of investigating whether any type of association existed between this genetic variant and migraine pathophysiology, genotyping was performed in 380 consecutive migraine patients and 185 age-, sex-, and race-ethnicity-matched healthy controls from Interinstitutional Multidisciplinary BioBank (BioBIM) of IRCCS San Raffaele Pisana, Rome, Italy. rs1042838 genotypes did not correlate with demographics or clinical migraine features. However, TT (Leu) genotype was significantly associated with a later age of migraine onset: Patients affected by migraine with aura showed a linear relationship between copy number of the T allele carried by the individual and the age of migraine onset. Our data suggest that the PROGINS PGR polymorphism does not directly predispose to migraine but significantly delays migraine onset probably via a reduction in brain neuronal excitability.

Gheorghiade M, Vaduganathan M, Greene SJ, Mentz RJ, Adams KF Jr, Anker SD, Arnold M, Baschiera F, Cleland JG, Cotter G, Fonarow GC, Giordano C, Metra M, Misselwitz F, Mühlhofer E, Nodari S, Frank Peacock W, Pieske BM, Sabbah HN, Sato N, Shah MR, Stockbridge NL, Teerlink JR, van Veldhuisen DJ, Zalewski A, Zannad F, Butler J.
Site selection in global clinical trials in patients hospitalized for heart failure: perceived problems and potential solutions.
Heart Fail Rev. 2014 Mar;19(2):135-152.

There are over 1 million hospitalizations for heart failure (HF) annually in the United States alone, and a similar number has been reported in Europe. Recent clinical trials investigating novel therapies in patients with hospitalized HF (HHF) have been negative, and the post-discharge event rate remains unacceptably high. The lack of success with HHF trials stem from problems with understanding the study drug, matching the drug to the appropriate HF subgroup, and study execution. Related to the concept of study execution is the importance of including appropriate study sites in HHF trials. Often overlooked issues include consideration of the geographic region and the number of patients enrolled at each study center. Marked differences in baseline patient co-morbidities, serum biomarkers, treatment utilization and outcomes have been demonstrated across geographic regions. Furthermore, patients from sites with low recruitment may have worse outcomes compared to sites with higher enrollment patterns. Consequently, sites with poor trial enrollment may influence key patient end points and likely do not justify the costs of site training and maintenance. Accordingly, there is an unmet need to develop strategies to identify the right study sites that have acceptable patient quantity and quality. Potential approaches include, but are not limited to, establishing a pre-trial registry, developing site performance metrics, identifying a local regionally involved leader and bolstering recruitment incentives. This manuscript summarizes the roundtable discussion hosted by the Food and Drug Administration between members of academia, the National Institutes of Health, industry partners, contract research organizations and academic research organizations on the importance of selecting optimal sites for successful trials in HHF.

Malara NM, Givigliano F, Trunzo V, Macrina L, Raso C, Amodio N, Aprigliano S, Minniti AM, Russo V, Roveda L, Coluccio ML, Fini M, Voci P, Prati U, Di Fabrizio E, Mollace V.
In vitro expansion of tumour cells derived from blood and tumour tissue is useful to redefine personalized treatment in non-small cell lung cancer patients.
J Biol Regul Homeost Agents. 2014 Oct-Dec;28(4):717-731.

The clinical development of locally and advanced non-small cell lung cancer (NSCLC) suffers from a lack of biomarkers as a guide in the selection of optimal prognostic prediction. Circulating Tumour Cells (CTCs) are correlated to prognosis and show efficacy in cancer monitoring in patients. However, their enumeration alone might be inadequate; it might also be critical to understand the viability, the apoptotic state and the kinetics of these cells. Here, we report what we believe to be a new and selective approach to visually detect tumour specific CTCs. Firstly, using labelled human lung cancer cells, we detected a specific density interval in which NSCL-CTCs were concentrated. Secondly, to better characterize CTCs in respect to their heterogeneous composition and tumour reference, blood and tumour biopsy were performed on specimens taken from the same patient. The approach consisted in comparing phenotype profile of CTCs, and their progenitor Tumour Stem Cells, (TSCs). Moreover, NSCL-CTCs were cultivated in short-time human cultures to provide response to drug sensitivity. Our bimodal approach allowed to reveal two items. Firstly, that one part of a tumour, proximal to the bronchial structure, displays a predominance of CD133+. Secondly, specific NSCL-CTCs Epithelial Cell Adhesion Molecule (EpCAM)+CD29+ can be used as a negative prognostic factor as well the high expression of CTCs EpCAM+. These data were confirmed by drug-sensitivity tests, in vitro, and by the survival curves, in vivo.

McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR; PARADIGM-HF Investigators and Committees.
Angiotensin-neprilysin inhibition versus enalapril in heart failure.
N Engl J Med. 2014 Sep 11;371(11):993-1004.

We compared the angiotensin receptor-neprilysin inhibitor LCZ696 with enalapril in patients who had heart failure with a reduced ejection fraction. In previous studies, enalapril improved survival in such patients.
In this double-blind trial, we randomly assigned 8442 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either LCZ696 (at a dose of 200 mg twice daily) or enalapril (at a dose of 10 mg twice daily), in addition to recommended therapy. The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure, but the trial was designed to detect a difference in the rates of death from cardiovascular causes. The trial was stopped early, according to prespecified rules, after a median follow-up of 27 months,

because the boundary for an overwhelming benefit with LCZ696 had been crossed. At the time of study closure, the primary outcome had occurred in 914 patients (21.8%) in the LCZ696 group and 1117 patients (26.5%) in the enalapril group (hazard ratio in the LCZ696 group, 0.80; 95% confidence interval [CI], 0.73 to 0.87; P<0.001). A total of 711 patients (17.0%) receiving LCZ696 and 835 patients (19.8%) receiving enalapril died (hazard ratio for death from any cause, 0.84; 95% CI, 0.76 to 0.93; P<0.001); of these patients, 558 (13.3%) and 693 (16.5%), respectively, died from cardiovascular causes (hazard ratio, 0.80; 95% CI, 0.71 to 0.89; P<0.001). As compared with enalapril, LCZ696 also reduced the risk of hospitalization for heart failure by 21% (P<0.001) and decreased the symptoms and physical limitations of heart failure (P=0.001). The LCZ696 group had higher proportions of patients with hypotension and nonserious angioedema but lower proportions with renal impairment, hyperkalemia, and cough than the enalapril group.
LCZ696 was superior to enalapril in reducing the risks of death and of hospitalization for heart failure.

Pezzuto B, Badagliacca R, Poscia R, Ghio S, D'Alto M, Vitulo P, Mulè M, Albera C, Volterrani M, Fedele F, Vizza CD.
Circulating biomarkers in pulmonary arterial hypertension: Update and future direction.
The Journal of Heart and Lung Transplantation 2014 [Epub ahead of print]

Pulmonary arterial hypertension (PAH) is a complex disease with a poor prognosis. In recent years, great advances have occurred in our understanding of the pathophysiologic mechanisms underlying the characteristic vascular proliferative lesions, thus allowing the development of several specific drugs. Nevertheless, PAH still presents a high mortality; therefore, early diagnosis and prognostic stratification seem to be of paramount importance in order to choose the best therapeutic strategies. Circulating biomarkers have been proposed as potentially noninvasive and objective parameters for diagnosis, prognosis, and response to therapy. The molecules evaluated to date, including markers of dysfunction and neurohormonal activation, myocardial injury, inflammation and oxidative stress, vascular damage and remodelling, end-organ failure, and gene expression, reflect the complex pathophysiology of PAH. However, not one of these shows all the characteristics of the ideal biomarker; thus, a multiparameter approach is probably desirable. Moreover, future direction could be research of structural proteins specifically expressed in the pathologic tissue that act as disease-specific markers. This report presents an extensive review of circulating biomarkers in PAH and some consideration about potential future direction in this area.

Savarese G, Perrone-Filardi P, D'Amore C, Vitale C, Trimarco B, Pani L, Rosano GMC.
Cardiovascular effects of dipeptidyl peptidase-4 inhibitors in diabetic patients: A meta-analysis.
Int J Cardiol 2014 Dec 3 [Epub ahead of print]

Dipeptidyl peptidase-4 inhibitors (DPP-4is) improve glucose control in patients with type 2 diabetes mellitus (DM); however, only few studies were properly designed to evaluate their cardiovascular (CV) effects. The purpose of this study was to assess the impact of DPP-4i treatment on CV morbidity and mortality.
Randomized clinical trials enrolling more than 200 patients, comparing DPP-4 versus placebo or active treatments in patients with DM and reporting at least one event among all-cause and CV mortality, myocardial infarction (MI), stroke and new onset of heart failure (HF) were included in the analysis.
Ninety-four trials enrolling 85,224 patients (median follow-up=29weeks) were included in the analysis. Compared to control, treatment with DPP-4i did not affect all-cause and CV mortality, as well as stroke, in the short and long terms (< and >29weeks, respectively). DPP-4i reduced the risk of MI in the short (RR: 0.584 [95% CI: 0.361 to 0.943]; p=0.028), but not in the long term. Additionally, long-term treatment with DPP-4 was associated with a 15.8% increased risk of HF (RR: 1.158 [CI: 1.011 to 1.326]; p=0.034). No heterogeneity among studies or publication bias was detected. DPP4is do not affect all cause- and CV-mortality and stroke in diabetic patients; the reduction in MI observed with short-term treatment does not persist in the long term. Long-term use of DPP-4i in diabetic patients is associated with increased risk of HF.

Sgarbanti R, Amatore D, Celestino I, Marcocci ME, Fraternale A, Ciriolo MR, Magnani M, Saladino R, Garaci E, Palamara AT, Nencioni L.
Intracellular redox state as target for anti-influenza therapy: are antioxidants always effective?
Curr Top Med Chem. 2014;14(22):2529-2541.

Influenza virus infections represent a big issue for public health since effective treatments are still lacking. In particular, the emergence of strains resistant to drugs limits the effectiveness of anti-influenza agents. For this reason, many efforts have been dedicated to the identification of new therapeutic strategies aimed at targeting the virus-host cell interactions. Oxidative stress is a characteristic of some viral infections including influenza. Because antioxidants defend cells from damage caused by reactive oxygen species induced by different stimuli including pathogens, they represent interesting molecules to fight infectious diseases. However, most of the available studies have found that these would-be panaceas could actually exacerbate the diseases they claim to prevent, and have thus revealed "the dark side" of these molecules. This review article discusses the latest opportunities and drawbacks of the antioxidants used in anti-influenza therapy and new perspectives.

Aquilano K, Baldelli S, Ciriolo MR.
Glutathione: New roles in redox signalling for an old antioxidant.
Frontiers in Pharmacology. 2014;5(196).

The physiological roles played by the tripeptide glutathione have greatly advanced over the past decades superimposing the research on free radicals, oxidative stress and, more recently, redox signaling. In particular, GSH is involved in nutrient metabolism, antioxidant defense, and regulation of cellular metabolic functions ranging from gene expression, DNA and protein synthesis to signal transduction, cell proliferation and apoptosis. This review will be focused on the role of GSH in cell signaling by analysing the more recent advancements about its capability to modulate nitroxidative stress, autophagy, and viral infection.

Ravenna L, Cardillo I, Curzio G, Baldi A, Mattioni M, Vincenzi B, Russo MA, Soddu S, Verdina A.
Mesothelioma and hypoxia: Modulation of the inflammation-related phenotype and identification of prognostic markers.
J Cancer Sci Ther. 2014;6(9):378-387.

Bianco A, Patanella AK, Nociti V, Marti A, Frisullo G, Plantone D, De Fino C, Fetta A, Batocchi AP, Rossini PM, Mirabella M.
Second-Line Therapy with Fingolimod for Relapsing-Remitting Multiple Sclerosis in Clinical Practice: The Effect of Previous Exposure to Natalizumab.
Eur Neurol. 2014 Nov 7;73(1-2):57-65.

To evaluate efficacy and safety of fingolimod for relapsing-remitting multiple sclerosis, particularly in patients previously exposed to natalizumab. Method: Prospective observational single-centre second-line cohort study. Among 71 patients treated with fingolimod 0.5 mg/day for a mean duration of 21.75 ± 12.60 months, the annualized relapse rate was 0.66 (C.I. 95% 0.27-1.05) with a significant difference between 26 patients with prior natalizumab exposure (1.15; C.I. 95% 0.12-2.17) and 45 not exposed (0.38; C.I. 95% 0.18-0.57; p = 0.002). In a multivariate negative regression model, only previous exposure to natalizumab (p = 0.049) and duration of fingolimod treatment

($p < 0.001$) significantly correlated with the annualized relapse rate. Previous exposure to natalizumab ($p = 0.028$) and duration of treatment with fingolimod ($p < 0.001$) were confirmed by restricting the analysis to the first 12 months of treatment with fingolimod, but were no longer statistically significant by analysing only patients (n = 51) with at least 12 months of treatment with fingolimod (0.32; C.I. 95% 0.08-0.55 vs. 0.22; C.I. 95% 0.11-0.32; p = NS). No differences were observed in neuroradiological outcomes and disability progression in patients exposed to natalizumab and not exposed. The rate of discontinuation due to adverse events was 11.3%, with no differences between the two groups. Our study confirms efficacy and side effects of fingolimod in a second-line clinical practice cohort. Prior natalizumab exposure and duration of treatment with fingolimod are independent predictors of annualized relapse rate during the first 12 months of treatment with fingolimod, but not in the long-term, and may be influenced by the 3 months washout period between the two drugs.

Caliandro P, Mirabella M, Padua L, Simbolotti C, De Fino C, Iacovelli C, Sancricca C, Rossini PM.
Idiopathic inflammatory myopathies evaluated by near infrared spectroscopy.
Muscle Nerve. 2014 Oct 7. doi: 10.1002/mus.24476. [Epub ahead of print]

We evaluated whether near infrared spectroscopy (NIRS) can determine the metabolic patterns of dermatomyositis (DM), polymyositis (PM), and inclusion body myositis (IBM). We enrolled 10 consecutive patients affected by DM, 11 by PM, 9 by IBM, and 3 groups of healthy controls. We measured changes in oxygenated and deoxygenated hemoglobin/myoglobin in the extensor digitorum communis during venous and arterial occlusion testing (VOT) and post-occlusion hyperemia. DM showed lower oxygen consumption (P=0.04) during VOT and reduced oxygen supply after VOT (P=0.04) versus controls. IBM showed higher oxygen consumption (P=0.04) during VOT and higher oxygen supply after VOT (P=0.03) than controls. DM showed reduced oxidative metabolism compared with IBM (P=0.001) and impaired ability to supply oxygen compared with PM (P= 0.03) and IBM (P= 0.001). NIRS differentiates samples of DM and IBM patients from controls, but it cannot distinguish PM patients from a sample of healthy subjects.

Caliandro P, Padua L, Rossi A, Rossini PMR, Stalberg E, Feurra M, Ulivelli M, Bartalini S, Giannini F, Rossi S.
Jitter of corticospinal neurons during repetitive transcranial magnetic stimulation. Method and possible clinical implications.
Brain Stimul. 2014 Jul-Aug;7(4):580-586.

Repetitive transcranial magnetic stimulation (rTMS) of the motor cortex activates corticospinal neurons mainly through the depolarization of cortico-cortical axons belonging to interneurons of superficial layers.
We used single-fiber electromyography (SFEMG) to estimate the "central jitter" of activation latency of interneural pools from one pulse of TMS to another.
We evaluated 10 healthy subjects and one patient with multiple sclerosis. By recording SFEMG evoked activity from the left first dorsal interosseous (FDI), we first used a standard repetitive electrical 3 Hz stimulation of the ulnar nerve at the wrist to calculate the mean consecutive difference from at least 10 different potentials. The same procedure was applied during 3 Hz repetitive TMS of the contralateral motor cortex. The corticospinal monosynaptic connection of the FDI and the selectivity of SFEMG recording physiologically justified the subtraction of the "peripheral jitter" from the whole cortico-muscular jitter, obtaining an estimation of the actual "central jitter."
All subjects completed the study. The peripheral jitter was 28 μs ± 6 and the cortico-muscular jitter was 344 μs ± 97. The estimated central jitter was 343 ± 97 μs. In the patient the central jitter was 846 μs, a value more than twice the central jitter in healthy subjects.
Current results demonstrate that the evaluation of the central component of the cumulative cortico-muscular latency variability in healthy subjects is feasible with a minimally invasive approach.

We present and discuss this methodology and provide a "proof of concept" of its potential clinical applicability in a patient with multiple sclerosis.

Curcio G, Mazzucchi E, Marca GD, Vollono C, Rossini PM.
Electromagnetic fields and EEG spiking rate in patients with focal epilepsy.
Clin Neurophysiol. 2014 Aug 11. doi: 10.1016/j.clinph.2014.07.013. [Epub ahead of print]

Despite the increase in mobile telephone technology use and possible effects on brain excitability, no studies have investigated the impact of GSM like (Global System for Mobile Communications) signal on the ongoing spiking activity in human epileptic patients.
Brain electrical (electroencephalogram, EEG) activity of 12 patients with focal epilepsy has been recorded under both Real and Sham exposure following a double-blind, crossover, counterbalanced design: before the exposure (pre-exposure/baseline session), during the Real or Sham 45min exposure (during-exposure session), and after the exposure (post-exposure session). As dependent variables both spiking activity (spikes count) and EEG quantitative indices (spectral power and coherence data) have been considered.
Spiking activity tended to be lower under Real than under Sham exposure. EEG spectral content analysis indicated a significant increase of Gamma band under Real exposure, mainly evident in Parieto-occipital and Temporal areas. Connectivity data indicated increased interhemispheric (left temporal to right frontal Regions of Interest, ROIs) instantaneous coherence, in the Beta frequency band during-exposure with respect to baseline session. No significant modification of lagged coherence was observed.
Acute GSM exposure in epileptic patients slightly influences their EEG properties, without reaching any clinical relevance.
No signs were found of an increased risk of incoming seizures for these patients as a consequence of using mobile phones.

Gorgoni M, Ferlazzo F, Ferrara M, Moroni F, D'Atri A, Fanelli S, Gizzi Torriglia I, Lauri G, Marzano C, Rossini PM, De Gennaro L.
Topographic electroencephalogram changes associated with psychomotor vigilance task performance after sleep deprivation.
Sleep Med. 2014 Sep;15(9):1132-1139.

The psychomotor vigilance task (PVT) is a widely used method for the assessment of vigilance after sleep deprivation (SDEP). However, the neural basis of PVT performance during SDEP has not been fully understood. In particular, no studies have investigated the possible relation between EEG topographical changes after sleep loss and PVT performance. The aim of the present study is to assess the EEG topographic correlates of PVT performance after SDEP.
During 40 h of SDEP, 16 healthy male subjects were evaluated in four sessions performed at the same time (11:00 a.m. and 11:00 p.m.) of the first and second day with: (a) subjective sleepiness recordings by means of the Karolinska Sleepiness Scale (KSS); (b) EEG recordings (5 min eyes-open condition); and (c) PVT.
SDEP induced a slowing of PVT reaction times (RTs), higher level of subjective sleepiness and an increase of delta, theta, alpha and beta 1 EEG activity. Only slowest PVT RTs were influenced by circadian factors, with longer RTs in the morning. Both fastest PVT RTs and KSS scores were positively correlated with post-SDEP changes in EEG theta activity, mainly in centro-posterior areas, but not with other EEG frequencies. KSS scores and PVT measures were also positively correlated. These findings suggest that SDEP differently affects PVT variables, and that an increase in theta activity may be the principal EEG basis of the post-SDEP slowing of fastest PVT RTs. Similar neural mechanisms seem to underlie both performance deterioration to PVT and the increase of subjective sleepiness.

Gorgoni M, Ferlazzo F, Moroni F, D'Atri A, Donarelli S, Fanelli S, Gizzi Torriglia I, Lauri G, Ferrara M, Marzano C, Rossini PM, Bramanti P, De Gennaro L.
Sleep deprivation affects somatosensory cortex excitability as tested through median nerve stimulation.
Brain Stimul. 2014 Sep-Oct;7(5):732-739.

Changes of cortical excitability after sleep deprivation (SD) in humans have been investigated mostly in motor cortex, while there is little empirical evidence concerning somatosensory cortex, and its plastic changes across SD.
To assess excitability of primary somatosensory cortex (S1) and EEG voltage topographical characteristics associated with somatosensory evoked potentials (SEPs) during SD.
Across 41 h of SD, 16 healthy subjects participated in 4 experimental sessions (11.00 a.m. and 11.00 p.m. of the 1st and 2nd day) with: a) subjective sleepiness ratings; b) EEG recordings; c) SEPs recordings; d) behavioral vigilance responses.
A clear enhancement of cortical excitability after SD was indexed by: (a) an amplitude increase of different SEPs component in S1; (b) higher voltage in occipital (around 35-43 ms) and fronto-central areas (around 47-62 ms). Circadian fluctuations did not affect cortical excitability. Voltage changes in S1 were strongly related with post-SD fluctuations of subjective and behavioral sleepiness.
Sleep may have a role in keeping cortical excitability at optimal (namely below potentially dangerous) levels for the human brain, rebalancing progressive changes in cortical responsiveness to incoming inputs occurred during time spent awake. On the other hand, higher level of cortical responsiveness after sleep loss may be one of the mechanisms accounting for post-SD alterations in vigilance and behavior.

Granata G, Luigetti M, Coraci D, Del Grande A, Romano A, Bisogni G, Bramanti P, Rossini PM, Sabatelli M, Padua L.
Ultrasound evaluation in transthyretin-related amyloid neuropathy.
Muscle Nerve. 2014 Sep;50(3):372-376.

Familial amyloid polyneuropathy is a rare condition caused by mutations of the transthyretin gene (TTR). We assessed the pattern of nerve ultrasound (US) abnormalities in patients with TTR-related neuropathy.
Seven patients with TTR-related neuropathy (TTR-N) and 5 asymptomatic TTR-mutation carriers (TTR-C) underwent neurological examination, nerve conduction studies, and US evaluation.
Multifocal US abnormalities were identified in 6 of 7 TTR-N patients. A single patient with only a mild sensory polyneuropathy had normal nerves on US evaluation. In the TTR-C, we only detected an enlarged ulnar nerve at the elbow. Interestingly, disease severity correlated with number of nerves affected on US evaluation.
No specific pattern of US abnormalities was identified in this cohort. However, in TTR-related amyloid neuropathy, US may be a helpful tool in monitoring disease progression, and/or clinical response to pharmacological treatment.

Guerra A, Petrichella S, Vollero L, Ponzo D, Pasqualetti P, Määttä S, Mervaala E, Könönen M, Bressi F, Iannello G, Rossini PM, Ferreri F.
Neurophysiological features of motor cortex excitability and plasticity in Subcortical Ischemic Vascular Dementia: A TMS mapping study.
Clin Neurophysiol. 2014 Sep 16. doi: 10.1016/j.clinph.2014.07.036. [Epub ahead of print]

To evaluate neurophysiological features of M1 excitability and plasticity in Subcortical Ischemic Vascular Dementia (SIVD), by means of a TMS mapping study.
Seven SIVD and nine AD patients, along with nine control subjects were tested. The M1 excitability was studied by resting thresholds, area and volume of active cortical sites for forearm and hand's examined muscles. For M1 plasticity, coordinates of the hot-spot and the center of gravity (CoG) were evaluated. The correlation between the degree of hyperexcitability and the amount of M1 plastic rearrangement was also calculated.
Multivariate analysis of excitability measures demonstrated similarly enhanced cortical excitability in AD and SIVD patients with respect to controls. SIVD patients showed a medial and frontal shift of CoG from the hot-spot, not statistically different from that observed in AD. A significant direct correlation was seen between parameters related to cortical excitability and those related to cortical plasticity.
The results suggest the existence of common compensatory mechanisms in different kind of dementing diseases supporting the idea that cortical hyperexcitability can promote cortical plasticity.
This study characterizes neurophysiological features of motor cortex excitability and plasticity in SIVD, providing new insights on the correlation between cortical excitability and plasticity.

Iorio R, Sabatelli M, Del Grande A, Bisogni G, Damato V, Plantone D, Marti A, Frisullo G, Romano A, Rossini PM, Luigetti M.
Distinct lymphocytes subsets in IgM-related neuropathy: clinical-immunological correlations.
Neurol Sci. 2014 Sep 6. [Epub ahead of print]

IgM-related neuropathy generally presents as a late-onset demyelinating polyneuropathy with predominant sensory loss and ataxia. However, we recently reported the clinical, neurophysiological and pathological findings from our cohort and identified in about a third of patients an atypical phenotype. We analyzed by flow cytometry the different lymphocytes subsets in the peripheral blood of patients affected by IgM-related neuropathy, chronic inflammatory demyelinating polyneuropathy (CIDP), monoclonal gammopathy of undetermined significance and healthy subjects, to investigate whether different immunological patterns may differentiate the classical phenotype from atypical forms. IFN-gamma producing CD4+ and CD8+ T lymphocytes, as well as CD4+ and CD8+ T cells expressing T-bet (T-helper type 1, Th1) were increased in CIDP patients. The percentage of circulating CD4+ and CD8+ T cells producing IL-10 as well as the percentage of CD19+ cells expressing Blimp-1 were higher in patients with IgM-neuropathy. We did not find any significant differences in the different lymphocytes subsets in the IgM-related neuropathy between patients with classical and atypical phenotype. Th1 cells are increased in CIDP patients while a T helper type 2-phenotype seems to prevail in patients with IgM-neuropathy. Further studies involving a larger patient population are needed to evaluate if different lymphocytes subset may be involved in different clinical phenotypes of IgM-related neuropathy.

Lefaucheur JP, André-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, Cantello RM, Cincotta M, de Carvalho M, De Ridder D, Devanne H, Di Lazzaro V, Filipović SR, Hummel FC, Jääskeläinen SK, Kimiskidis VK, Koch G, Langguth B, Nyffeler T, Oliviero A, Padberg F, Poulet E, Rossi S, Rossini PM, Rothwell JC, Schönfeldt-Lecuona C, Siebner HR, Slotema CW, Stagg CJ, Valls-Sole J, Ziemann U, Paulus W, Garcia-Larrea L.
Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS).
Clin Neurophysiol. 2014 Nov;125(11):2150-2206.

A group of European experts was commissioned to establish guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS) from evidence published up until March 2014, regarding pain, movement disorders, stroke, amyotrophic lateral sclerosis, multiple sclerosis, epilepsy, consciousness disorders, tinnitus, depression, anxiety disorders, obsessive-compulsive disorder, schizophrenia, craving/addiction, and conversion. Despite unavoidable inhomogeneities, there is a sufficient body of evidence to accept with level A (definite efficacy) the analgesic effect

of high-frequency (HF) rTMS of the primary motor cortex (M1) contralateral to the pain and the antidepressant effect of HF-rTMS of the left dorsolateral prefrontal cortex (DLPFC). A Level B recommendation (probable efficacy) is proposed for the antidepressant effect of low-frequency (LF) rTMS of the right DLPFC, HF-rTMS of the left DLPFC for the negative symptoms of schizophrenia, and LF-rTMS of contralesional M1 in chronic motor stroke. The effects of rTMS in a number of indications reach level C (possible efficacy), including LF-rTMS of the left temporoparietal cortex in tinnitus and auditory hallucinations. It remains to determine how to optimize rTMS protocols and techniques to give them relevance in routine clinical practice. In addition, professionals carrying out rTMS protocols should undergo rigorous training to ensure the quality of the technical realization, guarantee the proper care of patients, and maximize the chances of success. Under these conditions, the therapeutic use of rTMS should be able to develop in the coming years.

Luigetti M, Del Grande A, Conte A, Lo Monaco M, Bisogni G, Romano A, Zollino M, Rossini PM, Sabatelli M.
Clinical, neurophysiological and pathological findings of HNPP patients with 17p12 deletion: a single-centre experience.
J Neurol Sci. 2014 Jun 15;341(1-2):46-50.

Classic clinical manifestations of HNPP are characterized by recurrent painless mononeuropathies, but a minority of patients present with an atypical clinical pattern, including CMT-like neuropathy, acute or chronic inflammatory demyelinating neuropathy-like polyneuropathy, and carpal tunnel syndrome. Electrophysiological examination plays a central role in the diagnosis of HNPP, disclosing a non-uniform conduction slowing, more pronounced at entrapment sites.
We report clinical, electrophysiological and pathological findings from 73 patients with HNPP, coming from 53 unrelated families, followed at our Institute of Neurology over a 20-year period.
Typical presentation with recurrent multiple mononeuropathies was observed in 28/64 (44%) patients. In the remaining 36/64 (56%), we observed an atypical clinical presentation, characterized by generalized weakness and cramps, chronic ulnar neuropathy, carpal tunnel syndrome, chronic sensory polyneuropathy, Guillain-Barrè-like presentation, and CMT-like presentation. Nine patients were asymptomatic for neuropathic symptoms. Nerve conduction studies showed in all cases a sensori-motor demyelinating polyneuropathy with conduction abnormalities preferentially localized at common entrapment sites. When performed, sural nerve biopsy disclosed the focal thickening of the myelin sheath in all patients.
About half of the patients with HNPP from our cohort showed an atypical clinical presentation. Neurophysiological examination represents the main tool for a proper diagnosis.

Mariani S, Ventriglia M, Simonelli I, Bucossi S, Siotto M, Squitti R.
Meta-analysis study on the role of BDNF Val66Met polymorphism in Parkinson's disease.
Rejuvenation Res. 2014 Nov 28. [Epub ahead of print]

To evaluate a possible involvement of Brain-derived neurotrophic factor (BDNF) Val66Met polymorphism in the susceptibility to Parkinson's disease (PD), we performed a meta-analysis of all studies on the topic published from 2002 to 2014. This contribution reviews and compares the data from two previous meta-analyses including two studies not previously considered.
We selected studies referring a genetic comparison between PD patients and healthy controls, so 15 studies involving 3754 cases and 4026 controls were included in our meta-analysis
We found no association between Val66Met polymorphism and the risk of developing PD in overall analysis. The ethnicity specific meta-analysis produced no significant association too.
Our data do not support a major role for the BDNF Val66Met polymorphism in the pathogenesis of PD.

Pal A, Siotto M, Prasad R, Squitti R.

Towards a unified vision of Copper involvement in Alzheimer's Disease: a Review Connecting basic, experimental, and clinical research.
J Alzheimers Dis. 2014 Sep 26. [Epub ahead of print]

Copper is an essential micronutrient for physiological cell functioning and central nervous system (CNS) development. Indeed, it is a cofactor of many proteins and enzymes in a number of molecular pathways, including energy generation, oxygen transportation, hematopoiesis, cellular growth and metabolism, and signal transduction. This is because it serves as a catalyst of reduction-oxidation (redox) reactions in these processes. When copper is kept under control, bound to special proteins, it yields key properties. However, when it spirals out of control, it is exchanged among small compounds (it is loosely bound to them), and its redox activity makes it dangerous for cell viability, promoting oxidative stress. Copper homeostasis in the CNS is securely synchronized, and perturbations in brain copper levels are known to underlie the pathoetiology of wide a spectrum of common neurodegenerative disorders, including Alzheimer's disease. The main objective of this review is to provide some of the most relevant evidence gleaned from recent studies conducted on animal models and humans, and to discuss the evidence as it pertains to a new concept: Aberrant copper metabolism, which appears to have a genetic basis, is a modifiable risk factor accelerating Alzheimer's disease and initiation/progression of cognitive deficits in a percentage of susceptible persons.

Porcaro C, Medaglia MT, Thai NJ, Seri S, Rotshtein P, Tecchio F.
Contradictory reasoning network: an EEG and FMRI study.
PLoS One. 2014 Mar 25;9(3):e92835. doi: 10.1371/journal.pone.0092835. eCollection 2014.

Contradiction is a cornerstone of human rationality, essential for everyday life and communication. We investigated electroencephalographic (EEG) and functional magnetic resonance imaging (fMRI) in separate recording sessions during contradictory judgments, using a logical structure based on categorical propositions of the Aristotelian Square of Opposition (ASoO). The use of ASoO propositions, while controlling for potential linguistic or semantic confounds, enabled us to observe the spatial temporal unfolding of this contradictory reasoning. The processing started with the inversion of the logical operators corresponding to right middle frontal gyrus (rMFG-BA11) activation, followed by identification of contradictory statement associated with in the right inferior frontal gyrus (rIFG-BA47) activation. Right medial frontal gyrus (rMeFG, BA10) and anterior cingulate cortex (ACC, BA32) contributed to the later stages of process. We observed a correlation between the delayed latency of rBA11 response and the reaction time delay during inductive vs. deductive reasoning. This supports the notion that rBA11 is crucial for manipulating the logical operators. Slower processing time and stronger brain responses for inductive logic suggested that examples are easier to process than general principles and are more likely to simplify communication.

Aleksovska K, Leoncini E, Bonassi S, Cesario A, Boccia S, Frustaci A.
Systematic Review and Meta-Analysis of Circulating S100B Blood Levels in Schizophrenia.
PLoS One. 2014 Sep 9;9(9):e106342. eCollection 2014.

S100B is a calcium-binding protein secreted in central nervous system from astrocytes and other glia cells. High blood S100B levels have been linked to brain damage and psychiatric disorders. S100B levels have been reported to be higher in schizophrenics than healthy controls. To quantify the relationship between S100B blood levels and schizophrenia a systematic literature review of case-control studies published on this topic within July 3rd 2014 was carried out using three bibliographic databases: Medline, Scopus and Web of Science. Studies reporting mean and standard deviation of S100B blood levels both in cases and controls were included in the meta-analysis. The meta-Mean Ratio (mMR) of S100B blood levels in cases compared to controls was

used as a measure of effect along with its 95% Confidence Intervals (CI). 20 studies were included totaling for 994 cases and 785 controls. Schizophrenia patients showed 76% higher S100B blood levels than controls with mMR= 1.76 95% CI: 1.44-2.15. No difference could be found between drug-free patients with mMR= 1.84 95%CI: 1.24-2.74 and patients on antipsychotic medication with mMR= 1.75 95% CI: 1.41-2.16). Similarly, ethnicity and stage of disease didn't affect results. Although S100B could be regarded as a possible biomarker of schizophrenia, limitations should be accounted when interpreting results, especially because of the high heterogeneity that remained >70%, even after carrying out subgroups analyses. These results point out that approaches based on traditional categorical diagnoses may be too restrictive and new approaches based on the characterization of new complex phenotypes should be considered.

Altavista MC, Cassetta E, Brusa L, Viselli F, Denaro A, Ventriglia M, Pasqualetti P, Peppe A. Wearing-off detection in clinical practice: The wearing off real practice key (WORK-PD) study in Parkinson's disease.
Parkinsonism Relat Disord 2014 [Epub ahead of print]

Verifying the validity and feasibility of the WOQ-19 as a useful tool in routine clinical practice and in management of patients.
532 consecutive Parkinson's disease (PD) patients were recruited from 6 different neurological outpatient units, specialized in movement disorders, of central Italy. Inclusion criteria were diagnosis of PD and any current pharmacological treatment of PD while exclusion criteria were evident cognitive or depressive impairment, infusion with dopamine agonists or Duodopa, or Deep Brain Stimulation therapy. Patients were asked to complete the Italian version of WOQ-19 before the neurological visit. A medical form for the collection of demographic and clinical data of patients and for the evaluation of comprehensibility and usability the WOQ-19 was filled by the neurologist during the visit.
Our data confirmed that WOQ-19 was able to identify WO in 69% of patients, a percentage similar to the recently reported in the Italian WOQ-19 validation study. Motor symptoms were more frequent than non-motor symptoms (80% vs. 20%). Patients who experienced WO had a higher age of PD onset, more severe disease, longer disease duration and were more likely to be female. The WOQ-19 was understandable for the patient, easily administered and suitable for routine outpatient use. It could be also particularly useful in clinical practice in the early identification of non-motor symptoms, often under reported by patients and revealed only with clinical support.

Boccardi M, Bocchetta M, Apostolova LG, Barnes J, Bartzokis G, Corbetta G, DeCarli C, deToledo-Morrell L, Firbank M, Ganzola R, Gerritsen L, Henneman W, Killiany RJ, Malykhin N, Pasqualetti P, Pruessner JC, Redolfi A, Robitaille N, Soininen H, Tolomeo D, Wang L, Watson C, Wolf H, Duvernoy H, Duchesne S, Jack CR Jr, Frisoni GB; for the EADC-ADNI Working Group on the Harmonized Protocol for Manual Hippocampal Segmentation.
Delphi definition of the EADC-ADNI Harmonized Protocol for hippocampal segmentation on magnetic resonance.
Alzheimers Dement. 2014 Aug 14.[Epub ahead of print]

This study aimed to have international experts converge on a harmonized definition of whole hippocampus boundaries and segmentation procedures, to define standard operating procedures for magnetic resonance (MR)-based manual hippocampal segmentation.
The panel received a questionnaire regarding whole hippocampus boundaries and segmentation procedures. Quantitative information was supplied to allow evidence-based answers. A recursive and anonymous Delphi procedure was used to achieve convergence. Significance of agreement among panelists was assessed by exact probability on Fisher's and binomial tests.
Agreement was significant on the inclusion of alveus/fimbria (P = .021), whole hippocampal tail (P = .013), medial border of the body according to visible morphology (P = .0006), and on this

combined set of features (P = .001). This definition captures 100% of hippocampal tissue, 100% of Alzheimer's disease-related atrophy, and demonstrated good reliability on preliminary intrarater (0.98) and inter-rater (0.94) estimates.
Consensus was achieved among international experts with respect to hippocampal segmentation using MR resulting in a harmonized segmentation protocol.

Bocchetta M, Boccardi M, Ganzola R, Apostolova LG, Preboske G, Wolf D, Ferrari C, Pasqualetti P, Robitaille N, Duchesne S, Jack CR Jr, Frisoni GB; EADC-ADNI Working Group on The Harmonized Protocol for Manual Hippocampal Segmentation and the Alzheimer's Disease Neuroimaging Initiative; EADC-ADNI Working Group on The Harmonized Protocol for Manual Hippocampal Segmentation and the Alzheimer's Disease Neuroimaging Initiative.
Harmonized benchmark labels of the hippocampus on magnetic resonance: The EADC-ADNI project.
Alzheimers Dement. 2014 Sep 12. [Epub ahead of print]

A globally harmonized protocol (HarP) for manual hippocampal segmentation based on magnetic resonance has been recently developed by a task force from European Alzheimer's Disease Consortium (EADC) and Alzheimer's Disease Neuroimaging Initiative (ADNI). Our aim was to produce benchmark labels based on the HarP for manual segmentation.
Five experts of manual hippocampal segmentation underwent specific training on the HarP and segmented 40 right and left hippocampi from 10 ADNI subjects on both 1.5 T and 3 T scans. An independent expert visually checked segmentations for compliance with the HarP. Descriptive measures of agreement between tracers were intraclass correlation coefficients (ICCs) of crude volumes and similarity coefficients of three-dimensional volumes.
Two hundred labels have been provided for the 20 magnetic resonance images. Intra- and inter-rater ICCs were >0.94, and mean similarity coefficients were 1.5 T, 0.73 (95% confidence interval [CI], 0.71-0.75); 3 T, 0.75 (95% CI, 0.74-0.76).
Certified benchmark labels have been produced based on the HarP to be used for tracers' training and qualification.

Boccia S, Mc Kee M, Adany R, Boffetta P, Burton H, Cambon-Thomsen A, Cornel MC, Gray M, Jani A, Maria Knoppers B, Khoury MJ, Meslin EM, Van Duijn CM, Villari P, Zimmern R, Cesario A, Puggina A, Colotto M, Ricciardi W.
Beyond public health genomics: proposals from an international working group.
Eur J Public Health. 2014 Dec;24(6):876-878. Epub 2014 Aug 27.

European Innovation Partnership on Active and Healthy Ageing, Action Plan B3; Mechanisms of the Development of Allergy, WP 10; Global Alliance against Chronic Respiratory Diseases, Bousquet J, Addis A, Adcock I, Agache I, Agusti A, Alonso A, Annesi-Maesano I, Anto JM, Bachert C, Baena-Cagnani CE, Bai C, Baigenzhin A, Barbara C, Barnes PJ, Bateman ED, Beck L, Bedbrook A, Bel EH, Benezet O, Bennoor KS, Benson M, Bernabeu-Wittel M, Bewick M, Bindslev-Jensen C, Blain H, Blasi F, Bonini M, Bonini S, Boulet LP, Bourdin A, Bourret R, Bousquet PJ, Brightling CE, Briggs A, Brozek J, Buhl R, Bush A, Caimmi D, Calderon M, Calverley P, Camargos PA, Camuzat T, Canonica GW, Carlsen KH, Casale TB, Cazzola M, Cepeda Sarabia AM, Cesario A, Chen YZ, Chkhartishvili E, Chavannes NH, Chiron R, Chuchalin A, Chung KF, Cox L, Crooks G, Crooks MG, Cruz AA, Custovic A, Dahl R, Dahlen SE, De Blay
F, Dedeu T, Deleanu D, Demoly P, Devillier P, Didier A, Dinh-Xuan AT, Djukanovic R, Dokic D, Douagui H, Dubakiene R, Eglin S, Elliot F, Emuzyte R, Fabbri L, Fink Wagner A, Fletcher M, Fokkens WJ, Fonseca J, Franco A, Frith P, Furber A, Gaga M, Garcés J, Garcia-Aymerich J, Gamkrelidze A, Gonzales-Diaz S, Gouzi F, Guzmán MA, Haahtela T, Harrison D, Hayot M, Heaney LG, Heinrich J, Hellings PW, Hooper J, Humbert M, Hyland M, Iaccarino G, Jakovenko D, Jardim JR, Jeandel C, Jenkins C, Johnston SL, Jonquet O, Joos G, Jung KS, Kalayci O, Karunanithi S, Keil T, Khaltaev

N, Kolek V, Kowalski ML, Kull I, Kuna P, Kvedariene V, Le LT, Lodrup Carlsen KC, Louis R, MacNee W, Mair A, Majer I, Manning P, de Manuel Keenoy E, Masjedi MR, Melen E, Melo-Gomes E, Menzies-Gow A, Mercier G, Mercier J, Michel JP, Miculinic N, Mihaltan F, Milenkovic B, Molimard M, Momas I, Montilla-Santana A, Morais-Almeida M, Morgan M, N'Diaye M, Nafti S, Nekam K, Neou A, Nicod L, O'Hehir R, Ohta K, Paggiaro P, Palkonen S, Palmer S, Papadopoulos NG, Papi A, Passalacqua G, Pavord I, Pigearias B, Plavec D, Postma DS, Price D, Rabe KF, Radier Pontal F, Redon J, Rennard S, Roberts J, Robine JM, Roca J, Roche N, Rodenas F, Roggeri A, Rolland C, Rosado-Pinto J, Ryan D, Samolinski B, Sanchez-Borges M, Schünemann HJ, Sheikh A, Shields M, Siafakas N, Sibille Y, Similowski T, Small I, Sola-Morales O, Sooronbaev T, Stelmach R, Sterk PJ, Stiris T, Sud P, Tellier V, To T, Todo-Bom A, Triggiani M, Valenta R, Valero AL, Valiulis A, Valovirta E, Van Ganse E, Vandenplas O, Vasankari T, Vestbo J, Vezzani G, Viegi G, Visier L, Vogelmeier C, Vontetsianos T, Wagstaff R, Wahn U, Wallaert B, Whalley B, Wickman M, Williams DM, Wilson N, Yawn BP, Yiallouros PK, Yorgancioglu A, Yusuf OM, Zar HJ, Zhong N, Zidarn M, Zuberbier T.
Integrated care pathways for airway diseases (AIRWAYS-ICPs).
Eur Respir J. 2014 Aug;44(2):304-323.

The objective of Integrated Care Pathways for Airway Diseases (AIRWAYS-ICPs) is to launch a collaboration to develop multi-sectoral care pathways for chronic respiratory diseases in European countries and regions. AIRWAYS-ICPs has strategic relevance to the European Union Health Strategy and will add value to existing public health knowledge by: 1) proposing a common framework of care pathways for chronic respiratory diseases, which will facilitate comparability and trans-national initiatives; 2) informing cost-effective policy development, strengthening in particular those on smoking and environmental exposure; 3) aiding risk stratification in chronic disease patients, using a common strategy; 4) having a significant impact on the health of citizens in the short term (reduction of morbidity, improvement of education in children and of work in adults) and in the long-term (healthy ageing); 5) proposing a common simulation tool to assist physicians; and 6) ultimately reducing the healthcare burden (emergency visits, avoidable hospitalisations, disability and costs) while improving quality of life. In the longer term, the incidence of disease may be reduced by innovative prevention strategies. AIRWAYSICPs was initiated by Area 5 of the Action Plan B3 of the European Innovation Partnership on Active and Healthy Ageing. All stakeholders are involved (health and social care, patients, and policy makers).

Bousquet J, Jorgensen C, Dauzat M, Cesario A, Camuzat T, Bourret R, Best N, Anto JM, Abecassis F, Aubas P, Avignon A, Badin M, Bedbrook A, Blain H, Bourdin A, Bringer J, Camu W, Cayla G, Costa DJ, Courtet P, Cristol JP, Demoly P, de la Coussaye JE, Fesler P, Gouzi F, Gris JC, Guillot B, Hayot M, Jeandel C, Jonquet O, Journot L, Lehmann S, Mathieu G, Morel J, Ninot G, Pelissier J, Picot MC, Radier-Pontal F, Robine JM, Rodier M, Roubille F, Sultan A, Wojtusciszyn A, Auffray C, Balling R, Barbara C, Cambon-Thomsen A, Chavannes NH, Chuchalin A, Crooks G, Dedeu A, Fabbri LM, Garcia-Aymerich J, Hajjam J, Gomes EM, Palkonen S, Piette F, Pison C, Price D, Samolinski B, Schunemann HJ, Sterk PJ, Yiallouros P, Roca J, Perre PV, Mercier J.
Systems medicine approaches for the definition of complex phenotypes in chronic diseases and ageing. From concept to implementation and policies.
Curr Pharm Des. 2014;20(38):5928-5944.

Chronic diseases are diseases of long duration and slow progression. Major NCDs (cardiovascular diseases, cancer, chronic respiratory diseases, diabetes, rheumatologic diseases and mental health) represent the predominant health problem of the Century. The prevention and control of NCDs are the priority of the World Health Organization 2008 Action Plan, the United Nations 2010 Resolution and the European Union 2010 Council. The novel trend for the management of NCDs is evolving towards integrative, holistic approaches. NCDs are intertwined with ageing. The European Innovation Partnership on Active and Healthy Ageing (EIP on AHA) has prioritised NCDs. To tackle them in their totality in order to reduce their burden and societal impact, it is proposed that NCDs should be considered as a single expression of disease with different risk factors and entities. An innovative integrated health system built around systems medicine and strategic partnerships is proposed to combat NCDs. It includes (i) understanding the social, economic, environmental, genetic determinants, as well as the molecular and cellular mechanisms underlying NCDs; (ii) primary care and practice-based interprofessional collaboration; (iii) carefully phenotyped patients; (iv) development of unbiased and accurate biomarkers for comorbidities, severity and follow up of patients; (v) socio-economic science; (vi) development of guidelines; (vii) training; and (viii) policy decisions. The results could be applicable to all countries and adapted to local needs, economy and health systems. This paper reviews the complexity of NCDs intertwined with ageing. It gives an overview of the problem and proposes two practical examples of systems medicine (MeDALL) applied to allergy and to NCD co-morbidities (MACVIA-LR, Reference Site of the European Innovation Partnership on Active and Healthy Ageing).

Calzetta L, Passeri D, Kanabar V, Rogliani P, Page C, Cazzola M, Matera MG, Orlandi A.
Brain natriuretic peptide protects against hyperresponsiveness of human asthmatic airway smooth muscle via an epithelial cell-dependent mechanism.
Am J Respir Cell Mol Biol. 2014 Mar;50(3):493-501.

Brain natriuretic peptide (BNP) relaxes airways by activating natriuretic peptide receptor-A and elevating cyclic guanosine monophosphate. BNP is more effective in passively sensitized human bronchi compared with control airways. The molecular and cellular patterns involved in this signaling are unknown. The aim of this study was to investigate the influence of BNP on airway smooth muscle (ASM) cells obtained from donors with asthma and healthy donors and to identify the mechanisms involved in BNP-mediated relaxation. The contractile response of ASM cells was microscopically assessed in vitro in the presence of 1 μM BNP or with supernatant from human bronchial epithelial (BEAS-2B) cells pretreated with 1 μM BNP. We investigated the role of muscarinic M2 receptors and inducible nitric oxide synthase (iNOS), quantified the release of acetylcholine and nitric oxide (NO), and assessed the gene/protein expression of iNOS and myosin phosphatase target subunit 1 (MYPT1). Supernatant from BEAS-2B cells treated with BNP reduced the hyperreactivity of asthmatic ASM cells by shifting the potency of histamine by 1.19-fold but had no effect in healthy ASM cells. BNP was not effective directly on ASM cells. Blocking muscarinic M2-receptors and iNOS abolished the protective role of supernatant from BEAS-2B treated with BNP. BNP stimulated the release of acetylcholine (210.7 ± 11.1%) from BEAS-2B cells that in turn increased MYPT1 and iNOS gene/protein expression and enhanced NO levels in asthmatic ASM supernatant (35.0 ± 13.0%). This study provides evidence that BNP protects against bronchial hyperresponsiveness via an interaction between respiratory epithelium and ASM in subjects with asthma.

Calzetta L, Rogliani P, Cazzola M, Matera MG.
Advances in asthma drug discovery: evaluating the potential of nasal cell sampling and beyond.
Expert Opin Drug Discov. 2014 Jun;9(6):595-607.

Inhaled corticosteroid anti-inflammatory therapy is effective at controlling disease symptoms of asthma, but a subset of patients remains symptomatic despite optimal treatment, creating a clear unmet medical need. Moreover, none of the currently available drugs for asthma are really disease-modifying or curative. Although murine models of asthma, based on transgenic and knockout animals, may offer an integrated pathophysiological system for studying the characteristics of airway inflammation and hyperresponsiveness, these alterations are noteworthily different compared with those observed in asthmatic patients. Since a clear functional and inflammatory relationship between the nasal mucosa and bronchial tissue in patients suffering from asthma and allergic rhinitis has been recognized, using preclinical models based on human nasal cells sampling might support a prompt and effective anti-inflammatory drug discovery in asthma.

The authors provide a review, which discusses the potential role of nasal cell sampling and its application in advanced drug discovery for asthma. The contents range from the similarities and differences between asthma and allergic rhinitis up to artificial airway models based on sophisticated human lung-on-a-chip devices.
Nasal cell sampling and processing have reached a great potential in asthma drug discovery. The authors believe that models of asthma, which are based on human nasal cells, can provide valuable indications of proof of pharmacological and potential therapeutic efficacy in both preclinical and early clinical settings.

Calzetta L, Rossi P, Bove P, Alfonsi P, Bonizzi L, Roncada P, Bernardini R, Ricciardi E, Montuori M, Pistocchini E, Mauti P, Mattei M.
A novel and effective balanced intravenous-inhalant anaesthetic protocol in Swine by using unrestricted drugs.
Exp Anim. 2014 Oct 30;63(4):423-433.

Nowadays, because of increasing employment of swine for experimental studies and medical training, it is hopeful to investigate novel and effective anaesthetic protocols for preserving the animal welfare in medical investigation and concurrently improving the quality of research. Therefore, the aim of this study was to investigate a novel and effective anaesthetic protocol in swine undergoing major surgery, by translating know-how of combined anaesthesia from human protocols. Seven landrace swine were anaesthetized for three hours by a combined trial anaesthetic protocol (sedation: medetomidine, acepromazine, atropine and tramadol; induction: propofol, medetomidine and acepromazine; anaesthesia: isofluorane, propofol, medetomidine and acepromazine) and both clinical and haemodynamic parameters were compared with those of five swine anaesthetized with a control protocol (sedation: diazepam, ketamine and atropina; induction: diazepam and ketamine; anaesthesia: isofluorane). Both cardiac frequency (CF) and mean blood pressure (MBP) were significantly ($P<0.05$) more stable in trial protocol (CF: 78.3 ± 4.6-81.1 ± 5, MBP: 63.9 ± 10.7-96.4 ± 13.0) compared to control protocol (CF: 93.7 ± 5.5-102.5 ± 8.5, MBP: 71.0 ± 6.6-108.7 ± 7.2). The body temperature remained stable in trial protocol (°C: 36.9 ± 0.7-37.2 ± 0.3) compared to control anaesthesia (°C: 36.4 ± 0.3-37.3 ± 0.2, $P<0.05$). Haematosis improved undergoing combined anaesthesia (+2%, $P<0.05$) whereas did not change in control animals. There were no differences in respiratory rate between trial and control protocols. This study demonstrates that the proposed balanced intravenous-inhalant protocol permits to carry out a very effective, stable and safe anaesthesia in swine undergoing deep anaesthesia.

Cazzola M, Calzetta L, Page CP, Matera MG.
Use of indacaterol for the treatment of COPD: a pharmacokinetic evaluation.
Expert Opin Drug Metab Toxicol. 2014 Jan;10(1):129-137.

Indacaterol is a β2-agonist with a rapid onset of action and a bronchodilating effect that lasts for 24 h.
This review considers indacaterol in chronic obstructive pulmonary disease patients, in whom it is rapidly absorbed into the systemic circulation with serum levels measurable after 5 min and Cmax being reached approximately 15 min post-dose. Its disposition kinetics are characterized by at least two phases, a relatively fast decline of the concentrations within the first 12 h, followed by a terminal elimination phase. The increase in systemic exposure is dose-proportional, but systemic concentrations are low at the recommended doses. Indacaterol is relatively highly bound to plasma proteins regardless of concentration. Metabolic clearance and/or biliary clearance account for the majority of its systemic excretion. Weight, age, gender and ethnicity significantly influence its pharmacokinetic profile, but it is not necessary to adjust the dose based on these covariates. Substrates, inhibitors or inducers of UGT1A1 and CYP3A may also affect the pharmacokinetic profile of indacaterol.
Blood concentrations of indacaterol are unable to predict its bronchodilator effects. Furthermore, at the recommended doses, systemic concentrations of indacaterol are low and this is the likely reason for its safe profile.

Cazzola M, Calzetta L, Page CP, Rogliani P, Facciolo F, Gavaldà A, Matera MG.
Pharmacological characterization of the interaction between aclidinium bromide and formoterol fumarate on human isolated bronchi.
Eur J Pharmacol. 2014 Dec 15;745:135-143.

Long-acting muscarinic receptor antagonists (LAMAs) and long-acting β2-adrenoceptor agonists (LABAs) cause airway smooth muscle (ASM) relaxation via different signal transduction pathways, but there are limited data concerning the interaction between these two drug classes on human bronchi. The aim of this study was to investigate the potential synergistic interaction between aclidinium bromide and formoterol fumarate on the relaxation of human ASM. We evaluated the influence of aclidinium bromide and formoterol fumarate on the contractile response induced by acetylcholine or electrical field stimulation (EFS) on human isolated airways (segmental bronchi and bronchioles). We analyzed the potential synergistic interaction between the compounds when administered in combination by using Bliss independence (BI) theory. Both aclidinium bromide and formoterol fumarate completely relaxed segmental bronchi pre-contracted with acetylcholine (Emax: 97.5±2.6% and 96.4±1.1%; pEC50 8.5±0.1 and 8.8±0.1; respectively). Formoterol fumarate, but not aclidinium bromide, abolished the contraction induced by acetylcholine in bronchioles (Emax: 68.1±4.5% and 99.0±5.6%; pEC50 7.9±0.3 and 8.4±0.3; respectively). The BI analysis indicated synergistic interaction at low concentrations in segmental bronchi (+18.4±2.7%; $P<0.05$ versus expected effect) and from low to high concentrations in bronchioles (+19.7±0.9%; $P<0.05$ versus expected effect). Low concentrations of both drugs produced a synergistic relaxant interaction on isolated bronchi stimulated with EFS that was sustained for 6h post-treatment (+55.1±9.4%; $P<0.05$ versus expected effect). These results suggest that combining aclidinium bromide plus formoterol fumarate provides synergistic benefit on ASM relaxation of both medium and small human airways, which may have major implications for the use of this combination in the clinic.

Cazzola M, Calzetta L, Segreti A, Facciolo F, Rogliani P, Matera MG.
Translational Study Searching for Synergy between Glycopyrronium and Indacaterol.
COPD. 2014 Sep 15. [Epub ahead of print]

We aimed to explore whether the acute bronchodilation induced by indacaterol 150 µg and glycopyrronium bromide 50 µg is additive or synergistic with respect to monocomponents by testing the type of effect ex vivo on isolated human bronchi and then in vivo in COPD patients. Both indacaterol and glycopyrronium caused a concentration-dependent relaxation of human isolated bronchial tissues sub-maximally pre-contracted with acetylcholine; glycopyrronium was significantly more potent than indacaterol. The analysis of data using the Bliss Independence (BI) criterion indicated that glycopyrronium plus indacaterol produced an additive interaction at the isoeffective concentrations inducing EC20 and a significant synergistic relaxant effect at isoeffective concentrations inducing EC30. In COPD patients, the inhalation of indacaterol and glycopyrronium in combination significantly anticipated at 15 min post-administration the mean peak of bronchodilatory effect compared to the two drugs administered alone. The study of interaction between indacaterol and glycopyrronium by BI analysis evidenced an additive effect for FEV1 between 5 min and 180 min post-inhalation, with synergistic interaction at 15 min post-administration, compared to the bronchodilation induced by these drugs administered alone. This study suggests that the combination ensures a broncholytic effect that is greater than that induced by the single monocomponents.

Coelho P, García-Lestón J, Costa S, Costa C, Silva S, Fuchs D, Geisler S, Dall'Armi V, Zoffoli R, Bonassi S, Pásaro E, Laffon B, Teixeira JP.
Immunological alterations in individuals exposed to metal(loid)s in the Panasqueira mining area, Central Portugal.
Sci Total Environ. 2014 Mar 15;475:1-7. Epub 2014 Jan 11.

Environmental studies performed in Panasqueira mine area (central Portugal) identified high concentrations of several metal(loid)s in environmental media, and individuals environmentally and occupationally exposed showed higher levels of As, Cr, Mg, Mn, Mo, Pb and Zn in blood, urine, hair and nails when compared to unexposed controls. To evaluate the presence of immunological alterations attributable to environmental contamination, we quantified neopterin, kynurenine, tryptophan, and nitrite concentrations in plasma, and analysed the percentage of several lymphocytes subsets, namely CD3(+), CD4(+) and CD8(+) T-cells, CD19(+) B-cells, and CD16(+)56(+) natural killer (NK) cells in a group of individuals previously tested for metal(loid) levels in different biological matrices. The environmentally exposed group had significantly lower levels of %CD8(+) and higher CD4(+)/CD8(+) ratios, whereas the occupationally exposed individuals showed significant decreases in %CD3(+) and %CD4(+), and significant increases in %CD16(+)56(+), when compared to controls. Analysed biomarkers were found to be influenced by age, particularly neopterin, kynurenine and kynurenine to tryptophan ratio (Kyn/Trp) with significantly higher levels in older individuals, and %CD3(+), %CD8(+) and % CD19(+) with significantly lower values in older individuals. Males environmentally exposed showed significantly lower values of %CD19(+) when compared to control females. The concentration of Pb in toenails was associated to the level of neopterin, kynurenine and Kyn/Trp ratio (all direct), and the concentration of Mn in blood to the level of %CD8(+), %CD19(+) (both inverse) and CD4(+)/CD8(+) ratio (direct). Overall our results show that the metal(loid) contamination in Panasqueira mine area induced immunotoxic effects in exposed populations, possibly increasing susceptibility to diseases.

Collins A, Koppen G, Valdiglesias V, Dusinska M, Kruszewski M, Møller P, Rojas E, Dhawan A, Benzie I, Coskun E, Moretti M, Speit G, Bonassi S for the ComNet project.
The comet assay as a tool for human biomonitoring studies: the ComNet project.
Mutat Res Rev Mutat Res. 2014 Jan-Mar;759:27-39.

The comet assay is widely used in human biomonitoring to measure DNA damage as a marker of exposure to genotoxic agents or to investigate genoprotective effects. Studies often involve small numbers of subjects, and design may be sub-optimal in other respects. In addition, comet assay protocols in use in different laboratories vary significantly. In spite of these difficulties, it is appropriate to carry out a pooled analysis of all available comet assay biomonitoring data, in order to establish baseline parameters of DNA damage, and to investigate associations between comet assay measurements and factors such as sex, age, smoking status, nutrition, lifestyle, etc. With this as its major objective, the ComNet project has recruited almost 100 research groups willing to share datasets. Here we provide a background to this project, discussing the history of the comet assay and practical issues that can critically affect its performance. We survey its diverse applications in biomonitoring studies, including environmental and occupational exposure to genotoxic agents, genoprotection by dietary and other factors, DNA damage associated with various diseases, and intrinsic factors that affect DNA damage levels in humans. We examine in depth the quality of data from a random selection of studies, from an epidemiological and statistical point of view.

Costa C, García-Lestón J, Costa S, Coelho P, Silva S, Pingarilho M, Valdiglesias V, Mattei F, Dall'Armi V, Bonassi S, Laffon B, Snawder J, Teixeira JP.
Is organic farming safer to farmers' health? A comparison between organic and traditional farming.
Toxicol Lett. 2014 Oct 15;230(2):166-176.

Exposure to pesticides is a major public health concern, because of the widespread distribution of these compounds and their possible long term effects. Recently, organic farming has been introduced as a consumer and environmental friendly agricultural system, although little is known about the effects on workers' health. The aim of this work was to evaluate genetic damage and immunological alterations in workers of both traditional and organic farming. Eighty-five farmers exposed to several pesticides, thirty-six organic farmers and sixty-one controls took part in the study. Biomarkers of exposure (pyrethroids, organophosphates, carbamates, and thioethers in urine and butyrylcholinesterase activity in plasma), early effect (micronuclei in lymphocytes and reticulocytes, T-cell receptor mutation assay, chromosomal aberrations, comet assay and lymphocytes subpopulations) and susceptibility (genetic polymorphisms related to metabolism - EPHX1, GSTM1, GSTT1 and GSTP1 - and DNA repair-XRCC1 and XRCC2) were evaluated. When compared to controls and organic farmers, pesticide farmers presented a significant increase of micronuclei in lymphocytes (frequency ratio, FR=2.80) and reticulocytes (FR=1.89), chromosomal aberrations (FR=2.19), DNA damage assessed by comet assay (mean ratio, MR=1.71), and a significant decrease in the proportion of B lymphocytes (MR=0.88). Results were not consistent for organic farmers when compared to controls, with a 48% increase of micronuclei in lumphocytes frequency (p=0.016) contrasted by the significant decreases of TCR-Mf (p=0.001) and %T (p=0.001). Our data confirm the increased presence of DNA damage in farmers exposed to pesticides, and show as exposure conditions may influence observed effects. These results must be interpreted with caution due to the small size of the sample and the unbalanced distribution of individuals in the three study groups.

Del Bufalo A, Cesario A, Salinaro G, Fini M, Russo P.
Alpha9 alpha10 nicotinic acetylcholine receptors as target for the treatment of chronic pain.
Curr Pharm Des. 2014;20(38):6042-6047.

Chronic pain is a widespread healthcare problem affecting not only the patient but in many ways all the society. Chronic pain is a disease itself that endures for a long period of time and it is resistant to the majority of medical treatments that provide modest improvements in pain and minimum improvements in physical and emotional functioning. More co-existing chronic pain conditions may be present in the same individual (patient). The α9α10 nicotinic acetylcholine receptor (nAChR) may be a potential target in the pathophysiology of chronic pain, as well in the development of breast and lung cancers. α-conotoxins (α-CNT) are small peptides used offensively by carnivorous marine snails known as Conus that target nAChR. Among α-CNT there are potent and selective antagonists of α9α10 nAChR such as RgIA and Vc1.1 that produces both acute and long lasting analgesia. Moreover, these peptides accelerate the recovery of nerve function after injury, likely through immune/inflammatory-mediated mechanisms. We review the background, findings, implications and problems in using compounds that act on α9α10 nAChR.

Filippini P, Rutella S.
Recent advances on cellular therapies and immune modulators for graft-versus-host disease.
Expert Rev Clin Immunol. 2014 Oct;10(10):1357-1374.

The efficacy of allogeneic hematopoietic stem cell transplantation is counterbalanced by the occurrence of life-threatening immune-mediated complications, such as graft-versus-host disease (GVHD), a multistep disease which is reportedly fatal to approximately 15% of transplant recipients. It is now established that T-cell-dendritic cell interactions, T-cell activation, release of proinflammatory cytokines and T-cell trafficking partake in GVHD pathogenesis. This article will focus on the most recent strategies aimed at preventing/treating GVHD by manipulating components

of the innate and adaptive immune response from both the donor and the host.

Frisoni GB, Jack CR, Bocchetta M, Bauer C, Frederiksen KS, Liu Y, Preboske G, Swihart T, Blair M, Cavedo E, Grothe MJ, Lanfredi M, Martinez O, Nishikawa M, Portegies M, Stoub T, Ward C, Apostolova LG, Ganzola R, Wolf D, Barkhof F, Bartzokis G, DeCarli C, Csernansky JG, deToledo-Morrell L, Geerlings MI, Kaye J, Killiany RJ, Lehéricy S, Matsuda H, O'Brien J, Silbert LC, Scheltens P, Soininen H, Teipel S, Waldemar G, Fellgiebel A, Barnes J, Firbank M, Gerritsen L, Henneman W, Malykhin N, Pruessner JC, Wang L, Watson C, Wolf H, deLeon M, Pantel J, Ferrari C, Bosco P, Pasqualetti P, Duchesne S, Duvernoy H, Boccardi M; EADC -European Alzheimer's Disease Consortium and the ADNI - Alzheimer's Disease Neuroimaging Initiative.
The EADC-ADNI Harmonized Protocol for manual hippocampal segmentation on magnetic resonance: Evidence of validity.
Alzheimers Dement. 2014 Sep 27.

An international Delphi panel has defined a harmonized protocol (HarP) for the manual segmentation of the hippocampus on MR. The aim of this study is to study the concurrent validity of the HarP toward local protocols, and its major sources of variance.
Fourteen tracers segmented 10 Alzheimer's Disease Neuroimaging Initiative (ADNI) cases scanned at 1.5 T and 3T following local protocols, qualified for segmentation based on the HarP through a standard web-platform and resegmented following the HarP. The five most accurate tracers followed the HarP to segment 15 ADNI cases acquired at three time points on both 1.5 T and 3T. The agreement among tracers was relatively low with the local protocols (absolute left/right ICC 0.44/0.43) and much higher with the HarP (absolute left/right ICC 0.88/0.89). On the larger set of 15 cases, the HarP agreement within (left/right ICC range: 0.94/0.95 to 0.99/0.99) and among tracers (left/right ICC range: 0.89/0.90) was very high. The volume variance due to different tracers was 0.9% of the total, comparing favorably to variance due to scanner manufacturer (1.2), atrophy rates (3.5), hemispheric asymmetry (3.7), field strength (4.4), and significantly smaller than the variance due to atrophy (33.5%, $P < .001$), and physiological variability (49.2%, $P < .001$).
The HarP has high measurement stability compared with local segmentation protocols, and good reproducibility within and among human tracers. Hippocampi segmented with the HarP can be used as a reference for the qualification of human tracers and automated segmentation algorithms.

Galeone C, Edefonti V, Parpinel M, Leoncini E, Matsuo K, Talamini R, Olshan AF, Zevallos JP, Winn DM, Jayaprakash V, Moysich K, Zhang ZF, Morgenstern H, Levi F, Bosetti C, Kelsey K, McClean M, Schantz S, Yu GP, Boffetta P, Amy Lee YC, Hashibe M, La Vecchia C, Boccia S.
Folate intake and the risk of oral cavity and pharyngeal cancer: A pooled analysis within the INHANCE Consortium.
Int J Cancer. 2014 Jun 26. [Epub ahead of print]

There are suggestions of an inverse association between folate intake and serum folate levels and the risk of oral cavity and pharyngeal cancers (OPCs), but most studies are limited in sample size, with only few reporting information on the source of dietary folate. Our study aims to investigate the association between folate intake and the risk of OPC within the International Head and Neck Cancer Epidemiology (INHANCE) Consortium. We analyzed pooled individual-level data from ten case-control studies participating in the INHANCE consortium, including 5,127 cases and 13,249 controls. Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were estimated for the associations between total folate intake (natural, fortification and supplementation) and natural folate only, and OPC risk. We found an inverse association between total folate intake and overall OPC risk (the adjusted OR for the highest vs. the lowest quintile was 0.65, 95% CI: 0.43-0.99), with a stronger association for oral cavity (OR = 0.57, 95% CI: 0.43-0.75). A similar inverse association, though somewhat weaker, was observed for folate intake from natural sources only in oral cavity cancer (OR = 0.64, 95% CI: 0.45-0.91). The highest OPC risk was observed in heavy alcohol drinkers with low folate intake as compared to never/light drinkers with high folate (OR = 4.05, 95% CI: 3.43-4.79); the attributable proportion (AP) owing to interaction was 11.1% (95% CI: 1.4-20.8%). Lastly, we reported an OR of 2.73 (95% CI:2.34-3.19) for those ever tobacco users with low folate intake, compared with nevere tobacco users and high folate intake (AP of interaction =10.6%, 95% CI: 0.41-20.8%). Our project of a large pool of case-control studies supports a protective effect of total folate intake on OPC risk.

Giannetta E, Feola T, Gianfrilli D, Pofi R, Dall'Armi V, Badagliacca R, Barbagallo F, Lenzi A, Isidori AM.
Is chronic inhibition of phosphodiesterase type 5 cardioprotective and safe? A meta-analysis of randomized controlled trials.
BMC Med. 2014 Oct 20;12(1):185.

The myocardial effects of phosphodiesterase type 5 inhibitors (PDE5i) have recently received consideration in several preclinical studies. The risk/benefit ratio in humans remains unclear.
We performed a meta-analysis of randomized, placebo-controlled trials (RCTs) to evaluate the efficacy and safety of PDE5i on cardiac morphology and function. From March 2012 to December 2013 (update: May 2014), we searched English-language studies from MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and SCOPUS-selecting RCTs of continuous PDE5i administration that reported cardiovascular outcomes: cardiac geometry and performance, afterload, endothelial function and safety. The pooled estimate of a weighted mean difference between treatment and placebo was obtained for all outcomes using a random effects model. A test for heterogeneity was performed and the I(2) statistic calculated.
Overall, 1,622 subjects were treated, with 954 randomized to PDE5i and 772 to placebo in 24 RCTs. According to our analysis, sustained PDE5 inhibition produced: (1) an anti-remodeling effect by reducing cardiac mass (-12.21 g/m(2), 95% confidence interval (CI): -18.85; -5.57) in subjects with left ventricular hypertrophy (LVH) and by increasing end-diastolic volume (5.00 mL/m(2); 95% CI: 3.29; 6.71) in non-LVH patients; (2) an improvement in cardiac performance by increasing cardiac index (0.30 L/min/m(2), 95% CI: 0.202; 0.406) and ejection fraction (3.56%, 95% CI: 1.79; 5.33). These effects are parallel to a decline of N-terminal-pro brain natriuretic peptide (NT-proBNP) in subjects with severe LVH (-486.7 pg/ml, 95% CI: -712; -261). PDE5i administration also produced: (3) no changes in afterload parameters and (4) an improvement in flow-mediated vasodilation (3.31%, 95% CI: 0.53; 6.08). Flushing, headache, epistaxis and gastric symptoms were the commonest side effects.
This meta-analysis suggests for the first time that PDE5i have anti-remodeling properties and improve cardiac inotropism, independently of afterload changes, with a good safety profile. Given the reproducibility of the findings and tolerability across different populations, PDE5i could be reasonably offered to men with cardiac hypertrophy and early stage heart failure. Given the limited gender data, a larger trial on the sex-specific response to long-term PDE5i treatment is required.

Kim CH, Lee YC, Hung RJ, McNallan SR, Cote ML, Lim WY, Chang SC, Kim JH, Ugolini D, Chen Y, Liloglou T, Andrew AS, Onega T, Duell EJ, Field JK, Lazarus P, Le Marchand L, Neri M, Vineis P, Kiyohara C, Hong YC, Morgenstern H, Matsuo K, Tajima K, Christiani DC, McLaughlin JR, Bencko V, Holcatova I, Boffetta P, Brennan P, Fabianova E, Foretova L, Janout V, Lissowska J, Mates D, Rudnai P, Szeszenia-Dabrowska N, Mukeria A, Zaridze D, Seow A, Schwartz AG, Yang P, Zhang ZF.
Exposure to secondhand tobacco smoke and lung cancer by histological type: a pooled analysis of the International Lung Cancer Consortium (ILCCO).
Int J Cancer. 2014 Oct 15;135(8):1918-1930.

While the association between exposure to secondhand smoke and lung cancer risk is well established, few studies with sufficient power have examined the association by histological type. In this

study, we evaluated the secondhand smoke-lung cancer relationship by histological type based on pooled data from 18 case-control studies in the International Lung Cancer Consortium (ILCCO), including 2,504 cases and 7,276 control who were never smokers and 10,184 cases and 7,176 controls who were ever smokers. We used multivariable logistic regression, adjusting for age, sex, race/ethnicity, smoking status, pack-years of smoking, and study. Among never smokers, the odds ratios (OR) comparing those ever exposed to secondhand smoke with those never exposed were 1.31 (95% CI: 1.17-1.45) for all histological types combined, 1.26 (95% CI: 1.10-1.44) for adenocarcinoma, 1.41 (95% CI: 0.99-1.99) for squamous cell carcinoma, 1.48 (95% CI: 0.89-2.45) for large cell lung cancer, and 3.09 (95% CI: 1.62-5.89) for small cell lung cancer. The estimated association with secondhand smoke exposure was greater for small cell lung cancer than for nonsmall cell lung cancers (OR=2.11, 95% CI: 1.11-4.04). This analysis is the largest to date investigating the relation between exposure to secondhand smoke and lung cancer. Our study provides more precise estimates of the impact of secondhand smoke on the major histological types of lung cancer, indicates the association with secondhand smoke is stronger for small cell lung cancer than for the other histological types, and suggests the importance of intervention against exposure to secondhand smoke in lung cancer prevention.

Kirsch-Volders M, Bonassi S, Knasmueller S, Holland N, Bolognesi C, Fenech MF.
Commentary: critical questions, misconceptions and a road map for improving the use of the lymphocyte cytokinesis-block micronucleus assay for in vivo biomonitoring of human exposure to genotoxic chemicals-a HUMN project perspective.
Mutat Res Rev Mutat Res. 2014 Jan-Mar;759:49-58.

The lymphocyte cytokinesis-block micronucleus (CBMN) assay has been applied in hundreds of in vivo biomonitoring studies of humans exposed to genotoxic chemicals because it allows the measurement of both structural and numerical chromosome aberrations. The CBMN cytome assay version which, apart from measuring micronuclei (MN) already present in cells in vivo or expressed ex vivo, also includes measurement of nucleoplasmic bridges (NPB), nuclear buds (NBUD), necrosis and apoptosis, is also increasingly being used in such studies. Because of the numerous published studies there is now a need to re-evaluate the use of MN and other biomarkers within the lymphocyte CBMN cytome assay as quantitative indicators of exposure to chemical genotoxins and the genetic hazard this may cause. This review has identified some important misconceptions as well as knowledge gaps that need to be addressed to make further progress in the proper application of this promising technique and enable its full potential to be realised. The HUMN project consortium recommends a three pronged approach to further improve the knowledge base and application of the lymphocyte CBMN cytome assay to measure DNA damage in humans exposed to chemical genotoxins: (i) a series of systematic reviews, one for each class of chemical genotoxins, of studies which have investigated the association of in vivo exposure in humans with MN, NPB and NBUD induction in lymphocytes; (ii) a comprehensive analysis of the literature to obtain new insights on the potential mechanisms by which different classes of chemicals may induce MN, NPB and NBUD in vitro and in vivo and (iii) investigation of the potential advantages of using the lymphocyte CBMN cytome assay in conjunction with other promising complementary DNA damage diagnostics to obtain an even more complete assessment of the DNA damage profile induced by in vivo exposure to chemical genotoxins in humans.

Landi D, Maggio P, Lupoi D, Palazzo P, Altamura C, Falato E, Altavilla R, Vollaro S, Coniglio AD, Tibuzzi F, Passarelli F, Silvestrini M, Pasqualetti P, Vernieri F.
Cortical ischemic lesion burden measured by DIR is related to carotid artery disease severity.
Cerebrovasc Dis. 2014 Dec 24;39(1):23-30.

Over time, exposure to cerebrovascular risk factors and carotid artery disease may cause multiple asymptomatic brain cortical and subcortical microinfarcts, which are commonly found at brain autopsy. So far, lack of convenient neuroimaging tools limited the investigation of grey matter ischemic damage in vivo. We applied the Double Inversion Recovery (DIR) sequence to explore the impact of carotid artery disease on intracortical ischemic lesion load in vivo, taking into account the impact of demographic characteristics and vascular risk factors.
DIR was acquired in 62 patients with common cerebrovascular risk factors stratified in three groups according to carotid artery disease severity. Intracortical lesions scored on DIR (DIRIns) were classified by vascular territory, lobe and hemisphere. White matter hyperintensities (WMHs) volume was also quantified on Fluid Attenuated Inversion Recovery sequence (FLAIR).
Among demographic characteristics and cerebrovascular risk variables explored, General Linear Model indicated that age and carotid artery disease were significantly associated to DIRIns. After correcting for age, DIRIns load was found to be significantly dependent on carotid artery stenosis severity ($F(2, 58) = 5.56$, $p = 0.006$). A linear positive correlation between DIRIns and WMHs was found after correcting for age ($p = 0.003$).
Carotid disease severity is associated with DIRIns accrual. Microembolism and impaired cerebral hemodynamics may act as physiopathological mechanisms underlying cortical ischemic damage. The role of other factors, such as small vessel disease and the possible interaction with carotid disease, remains to be further explored.

Larghi A, Lococo F, Mainenti S, Petrone G, Cesario A, Granone P, Scambia G, Costamagna G.
EUS-guided fine needle tissue acquisition for the diagnosis of pleural metastases from endometrial cancer.
Eur Rev Med Pharmacol Sci. 2014 May;18(9):1379-1382.

Transesophageal EUS-FNA have become a useful tool in the evaluation of the mediastinum, especially during the staging work-up examination of patients with non-small-cell lung cancer (NSCLC) or other malignancies. We report a challenging case of a 53 years-old woman with an endometrial adenocarcinoma who subsequently presented with right pleural effusion, diffuse pleural thickening with few pleural lesions. The patient referred a long history of exposure to amiantum, this posing a differential diagnosis between primary pleural tumour (mesothelioma) and neoplastic pleural localization of the endometrial cancer. The cytological examination of the pleural effusion (sampled via thoracenthesis) was not adequate to reach a diagnosis. Although a right-video-assisted thoracoscopy was considered the gold standard in this clinical setting to achieve a tissue acquisition of the pleura, an EUS (as the least invasive procedure) was attempted to reach a definitive diagnosis. EUS-FNTA of the pleura was done using a 19-Gauge needle and the pathological and immunophenotypic features were diagnostic for a pleural metastasis of high-grade endometrial serous carcinoma. The patient received adjuvant chemotherapy with a complete regression of the pleural lesions. We take the opportunity of this challenging case to discuss the efficacy and safety of EUS-FNAT to sample the pleural lesions with the use of a large calibre needle if the lesion lies just under the EUS cursor. We may assume that, in selected patients, this technique could be presented as a viable option to the more invasive surgical procedure, which has been previously the gold standard for the pleural tissue acquisition.

Leoncini E, Ricciardi W, Cadoni G, Arzani D, Petrelli L, Paludetti G, Brennan P, Luce D, Stucker I, Matsuo K, Talamini R, La Vecchia C, Olshan AF, Winn DM, Herrero R, Franceschi S, Castellsague X, Muscat J, Morgenstern H, Zhang ZF, Levi F, Dal Maso L, Kelsey K, McClean M, Vaughan TL, Lazarus P, Purdue MP, Hayes RB, Chen C, Schwartz SM, Shangina O, Koifman S, Ahrens W, Matos E, Lagiou P, Lissowska J, Szeszenia-Dabrowska N, Fernandez L, Menezes A, Agudo A, Daudt AW, Richiardi L, Kjaerheim K, Mates D, Betka J, Yu GP, Schantz S, Simonato L, Brenner H, Conway DI, Macfarlane TV, Thomson P, Fabianova E, Znaor A, Rudnai P, Healy C, Boffetta P, Chuang SC, Lee YC, Hashibe M, Boccia S.
Adult height and head and neck cancer: a pooled analysis within the INHANCE Consortium.
Eur J Epidemiol. 2014 Jan;29(1):35-48.

Several epidemiological studies have shown a positive association between adult height and cancer incidence. The only study conducted among women on mouth and pharynx cancer risk, however, reported an inverse association. This study aims to investigate the association between height and the risk of head and neck cancer (HNC) within a large international consortium of HNC. We analyzed pooled individual-level data from 24 case-control studies participating in the International Head and Neck Cancer Epidemiology Consortium. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated separately for men and women for associations between height and HNC risk. Educational level, tobacco smoking, and alcohol consumption were included in all regression models. Stratified analyses by HNC subsites were performed. This project included 17,666 cases and 28,198 controls. We found an inverse association between height and HNC (adjusted OR per 10 cm height = 0.91, 95% CI 0.86-0.95 for men; adjusted OR = 0.86, 95% CI 0.79-0.93 for women). In men, the estimated OR did vary by educational level, smoking status, geographic area, and control source. No differences by subsites were detected. Adult height is inversely associated with HNC risk. As height can be considered a marker of childhood illness and low energy intake, the inverse association is consistent with prior studies showing that HNC occur more frequently among deprived individuals. Further studies designed to elucidate the mechanism of such association would be warranted.

Leuzzi G, Cesario A, Cafarotti S, Lococo F, Dall'Armi V, Novellis P, Romano R, Siciliani A, Meacci E, Granone P, Margaritora S.
Surgical treatment in patient with non-small-cell lung cancer with fissure involvement: anatomical versus nonanatomical resection.
J Thorac Oncol. 2014 Jan;9(1):97-108.

Despite the intense debate concerning the prognostic impact of fissure involvement (FI) in patients with non-small-cell lung cancer, no specific surgical strategies have been yet recommended when this condition occurs. In this setting, we report our monocentric 10-years experience to investigate this issue.
From January 2000 to January 2010, the clinical data of 40 non-small-cell lung cancer patients with FI undergoing curative resection were retrospectively reviewed. The sample was stratified according to the type of resection: group A (28 patients): anatomical resection (bilobectomy [21 patients], pneumonectomy [7 patients]); group B (12 patients): nonanatomical resection (lobectomy plus wedge resection [LWR]). The end-points were (1) impact of different surgical approach on the pulmonary function (measured before surgery and 1 month after discharge); (2) disease-specific survival; and (3) tumor recurrence.The t test, [illegible], and log-rank tests, Kaplan-Meier method, and Cox and logistic regression analyses were used for the statistical analysis.
No differences between the two groups were found when comparing the clinical characteristics, histology, pN or pT status, p-stage, residual (R1) disease, tumor grading, or tumor size. Similarly, the baseline preoperative function (tested as forced expiratory volume in 1 second-%-predicted, FEV1%) was likewise comparable (92.5% ± 21.0% in group A versus 85.2% ± 20.0% in group B; p = not significant). The decline of FEV1% after surgery was slightly higher in group A (-24.9% ± 13.5%) when compared with that in group B (-19.5% ± 13.3%), but this difference was not statistically significant (p = ns). Nevertheless, the 5-year disease-specific survival was 56% for group A and 47% for group B (p = ns). The recurrence rate did not differ between the patients undergoing a LWR (3 of 12 patients) and those undergoing a bilobectomy or pneumonectomy (9 of 28 patients) (p = ns). The presence of FI extended for more than 3 cm was found to be the most significant prognostic factor when analyzing survival (p = 0.002) and recurrence rate (p< 0.001).
Our results suggest that nonanatomical resection (LWR) could be considered as a feasible surgical option (especially in "frail" patients with an extent of FI less than 3 cm) in the light of the similar oncological and functional outcome compared with anatomical resection. Further studies based on larger series are needed to confirm these preliminary data and also to investigate the impact on the postoperative quality of life.

Leuzzi G, Meacci E, Cusumano G, Cesario A§, Chiappetta M, Dall'armi V, Evoli A, Costa R, Lococo F, Primieri P, Margaritora S, Granone P.
Thymectomy in myasthenia gravis: proposal for a predictive score of postoperative myasthenic crisis.
Eur J Cardiothorac Surg. 2014 Apr;45(4):e76-88.

Thymectomy plays an important role in patients with myasthenia gravis (MG). This study aimed to explore predictors of postoperative myasthenic crisis (POMC) after thymectomy and to define a predictive score of respiratory failure.
The clinical data of 177 patients with MG undergoing thymectomy from January 1995 to December 2011 were retrospectively reviewed. The following factors were analysed in relation to the occurrence of myasthenic crisis: gender, age, body mass index (BMI), anti-acetylcholine receptor-antibody level, bulbar symptoms, comorbidities, duration of symptoms, Osserman-stage, Myasthenia Gravis Foundation of America (MGFA) stage, history of myasthenic crisis, use of immoglobulins or plasmapheresis, kind of therapy, spirometric and blood gas parameters, histology, kind of surgery, non-myasthenic complications and duration of intubation.
Twenty-two patients experienced postoperative respiratory failure after thymectomy. Univariate analysis revealed a correlation with age >60 years (odds ratio (OR) = 1.79, 95% confidence interval (CI) = 1.04-6.78; P = 0.040); Osserman-stage (IIB- OR = 5.16, 95% CI = 1.10-24.18; P = 0.037, III-IV- OR = 8.75, 95% CI = 1.53-50.05; P = 0.015); bulbar symptoms (OR = 7.42, 95% CI = 1.67-32.84; P = 0.008); BMI >28 (OR = 3.99, 95% CI = 1.58-10.03; P = 0.003); preoperative plasmapheresis (OR = 2.97, 95% CI = 1.18-14.04; P = 0.021); duration of symptoms >2 years (OR = 4.00, 95% CI = 1.09-14.762; P = 0.036); extended surgery (OR = 2.52, 95% CI = 1.02-6.22; P = 0.045); lung (OR = 4.05, 95% CI = 1.44-11.42; P = 0.008), pericardial (OR = 3.78, 95% CI = 1.45-9.82; P = 0.006) or pleural resection (OR = 3.23, 95% CI = 1.30-8.03; P = 0.012); Vital Capacity % <80% (OR = 0.20, 95% CI = 0.05-0.82; P = 0.025) and PaCO2 >40 mmHg (OR = 3.76, 95% CI = 1.12-12.68; P = 0.032). Multivariate logistic regression analysis showed that Osserman-stage (IIB- OR = 5.69, 95% CI = 1.09-29.69; P = 0.039 (III-IV- OR = 11.33, 95% CI = 1.67-76.72; P = 0.013), BMI >28 (OR = 3.65, 95% CI = 1.10-12.15; P = 0.035), history of myasthenic crisis (OR = 24.10, 95% CI = 2.34-248.04; P = 0.007), duration of symptoms >2 years (OR = 5.94, 95% CI = 1.12-31.48; P = 0.036) and lung resection (OR = 8.48, 95% CI = 2.18-32.97; P = 0.002) independently predict POMC. Excluding history of preoperative myasthenic crisis (statistically associated with Osserman-stage), we built a scoring system according to the OR of Osserman-stage (I-IIA, IIB, III-IV), BMI (<28, ≥ 28), duration of symptoms (<1, 1-2, >2 years) and association with a pulmonary resection. This model helped in creating four classes with increasing risk of respiratory failure (Group I, 6%; Group II, 10%; Group III, 25%; Group IV, 50%).
Our model facilitates the stratification of patient risk and prediction of the occurrence of POMC. Moreover, it could help to guide the anaesthesiologist's decision on the duration of intubation. Further studies based on larger series are needed to confirm these preliminary data.

Leuzzi G, Nachira D, Cesario A, Novellis P, Petracca Ciavarella L, Lococo F, Facciolo F, Granone P, Margaritora S.
Chest wall tumors and prosthetic reconstruction: A comparative analysis on functional outcome.
Thoracic Cancer. 2014 [Epub ahead of print]

Lipsi R, Rogliani P, Calzetta L, Segreti A, Cazzola M.
The clinical use of regenerative therapy in COPD.
Int J Chron Obstruct Pulmon Dis. 2014 Dec 12;9:1389-1396.

Regenerative or stem cell therapy is an emerging field of treatment based on stimulation of en-

dogenous resident stem cells or administration of exogenous stem cells to treat diseases or injury and to replace malfunctioning or damaged tissues. Current evidence suggests that in the lung, these cells may participate in tissue homeostasis and regeneration after injury. Animal and human studies have demonstrated that tissue-specific stem cells and bone marrow-derived cells contribute to lung tissue regeneration and protection, and thus administration of exogenous stem/progenitor cells or humoral factors responsible for the activation of endogenous stem/progenitor cells may be a potent next-generation therapy for chronic obstructive pulmonary disease. The use of bone marrow-derived stem cells could allow repairing and regenerate the damaged tissue present in chronic obstructive pulmonary disease by means of their engraftment into the lung. Another approach could be the stimulation of resident stem cells by means of humoral factors or photobiostimulation.

Lococo F, Cesario A, Leuzzi G, Apolone G.
Second primary non-small-cell lung cancer: implications of the new adenocarcinoma classification in the challenging decision of the best surgical strategy.
Eur J Cardiothorac Surg. 2014 Jun;45(6):1115-1116.

Lococo F, Cesario A, Paci M, Filice A, Versari A, Rapicetta C, Ricchetti T, Sgarbi G, Alifano M, Cavazza A, Treglia G.
PET/CT assessment of neuroendocrine tumors of the lung with special emphasis on bronchial carcinoids.
Tumour Biol. 2014 Sep;35(9):8369-8377.

Pulmonary neuroendocrine tumors (pNETs) arise from bronchial mucosal cells known as enterochromaffin cells which are part of the diffuse neuroendocrine system. The pathological spectrum of pNETs ranges from low-/intermediate-grade neoplasms such as bronchial carcinoids (BCs), also known as typical or atypical carcinoids, to high-grade neoplasms as large-cell neuroendocrine carcinoma and small-cell lung cancer. The tumor biology of pNETs still represents a matter of open debate. The distinct features among the different pNETs include not only their pathologic characteristics but also their clinical behavior, epidemiology, treatment, and prognosis. In this sense, a correct pathological identification in the preoperative setting is a key element for planning the best strategy of care in pNETs and especially in BCs. Controversial results have been reported on the diagnostic accuracy of fluorine-18-fluorodeoxyglucose positron emission tomography or positron emission tomography/computed tomography (F-18-FDG PET or PET/CT) in BCs. On the other hand, there is increasing evidence supporting the use of PET with somatostatin analogues (DOTA-TOC, DOTA-NOC, or DOTA-TATE) labeled with gallium-68 (Ga-68) in pNETs. Herein, we review the pertinent literature aiming to better define the current state of art of PET/CT in the detection and histological differentiation of pNETs with special emphasis on BCs.

Lococo F, Bobbio A, Villard M, Cesario A, Magdeleinat P, Alifano M, Regnard JF.
Is a surgical procedure really contraindicated in spontaneous pneumothorax patients who have undergone prior contralateral pneumonectomy?
Ann Thorac Surg. 2014 May;97(5):1855-1856.

Lococo F, Cesario A, de Franco S, Ricchetti T, Sgarbi G, Treglia G.
Is 18FDG PET/CT evaluation really useful in the diagnosis of elastofibroma dorsi?
Rev Esp Med Nucl Imagen Mol. 2014 Jan-Feb;33(1):62.

Lococo F, Cesario A, Margaritora S, Apolone G, Cavuto S, Leuzzi G, Pasqua F, Cardaci V, Ciavarella LP, Granone P.
Time-trend analysis of the pulmonary function after surgical treatment for esophageal cancer.
Eur

Rev Med Pharmacol Sci. 2014;18(21): 3189-3198.

The aim of the study is to evaluate, in function of time, the modification of pulmonary function after radical esophagectomy with the aim of identifying clinical and/or surgical predictors of functional worsening.
Data of 57 patients operated from 01/06 to 06/11 were retrospectively reviewed. Thirty-eight patients (67%) underwent transhiatal cervico-laparotomic (CL-Group) and 19 (33%) a Mc-Keown cervico-thoraco-laparotomic esophagectomy (CTL-Group). The pulmonary function has been evaluated before and one month after surgery. The outcome has been benchmarked with demographic/clinical characteristics, the type of operation and the presence of post-operative pulmonary complications (POPCs).
Mean age and male/female distribution were 66.6±10.6 yrs and 39/18, respectively. A total of 14 (24% of total sample) POPCs occurred with a significantly higher occurrence in the CTL-Group (71% vs 28%, $p < 0.001$) and in those patients with a pre-operative concurrent pathological condition (64% in COPD patients vs 36% in patients without COPD, $p = 0.021$). A global worsening of the spirometric parameters (expressed as the baseline percentage change, Δ) emerged, but this decrease was significantly higher in the CTL-Group in terms of Δ-FVC ($p = 0.005$) and Δ-FEV1 ($p = 0.005$). Similarly, those patients who have experienced a POPC, showed a higher reduction of the pulmonary function regardless of the surgical approach when compared with those who did not (Δ-FVC: $p = 0.053$ and Δ-FEV1%: $p = 0.015$).
In the context of a global reduction of pulmonary function, patients who underwent trans-thoracic esophagectomy or experienced a POPC showed a significantly worse pattern. These patients could be the "best target" for therapeutic rehabilitative strategies in the pre-operative and/or post-operative setting. This assumption is to be proven through prospective clinical trials.

Lococo F, Treglia G, Cesario A, Paci M, Filice A, Versari A, Filosso PL.
Functional imaging evaluation in the detection, diagnosis, and histologic differentiation of pulmonary neuroendocrine tumors.
Thorac Surg Clin. 2014 Aug;24(3):285-292.

Pulmonary neuroendocrine tumors (pNETs) have distinct pathologic characteristics. Typical carcinoids are indolent neoplasms with a good prognosis, whereas atypical carcinoids have a less indolent behavior. Both are optimally treated with complete surgical excision. More aggressive pNETs often present with local invasion, thoracic lymph nodal metastases, and distant spread. Patients may not be candidates for surgical resection and are treated with chemotherapy and/or radiation therapy. This article examines the potential role of functional imaging evaluation using (18)F FDG and somatostatin analogues labeled with (68) Ga DOTA-peptides in well-differentiated pNETs with particular attention to clinical and surgical implications.

Marzetti E, Lorenzi M, Antocicco M, Bonassi S, Celi M, Mastropaolo S, Settanni S, Valdiglesias V, Landi F, Bernabei R, Onder G.
Shorter telomeres in peripheral blood mononuclear cells from older persons with sarcopenia: Results from an exploratory study.
Frontiers in Aging Neuroscience. 2014;6(233)

Telomere shortening in peripheral blood mononuclear cells (PBMCs) has been associated with biological age and several chronic degenerative diseases. However, the relationship between telomere length and sarcopenia, a hallmark of the aging process, is unknown. The aim of the present study was therefore to determine whether PBMC telomeres obtained from sarcopenic older persons were shorter relative to non-sarcopenic peers. We further explored if PBMC telomere length was associated with frailty, a major clinical correlate of sarcopenia.
Analyses were conducted in 142 persons aged ≥65 years referred to a geriatric outpatient clinic

(University Hospital). The presence of sarcopenia was established according to the European Working Group on Sarcopenia in Older People criteria, with bioelectrical impedance analysis used for muscle mass estimation. The frailty status was determined by both the Fried's criteria (physical frailty, PF) and a modified Rockwood's frailty index (FI). Telomere length was measured in PBMCs by quantitative real-time polymerase chain reaction according to the telomere/single-copy gene ratio (T/S) method.
Among 142 outpatients (mean age 75.0 ± 6.5 years, 59.2% women), sarcopenia was diagnosed in 23 individuals (19.3%). The PF phenotype was detected in 74 participants (52.1%). The average FI score was 0.46 ± 0.17. PBMC telomeres were shorter in sarcopenic subjects (T/S = 0.21; 95% CI: 0.18-0.24) relative to non-sarcopenic individuals (T/S = 0.26; 95% CI: 0.24-0.28; p = 0.01), independent of age, gender, smoking habit, or comorbidity. No significant associations were determined between telomere length and either PF or the FI.
PBMC telomere length, expressed as T/S values, is shorter in older outpatients with sarcopenia. The cross-sectional assessment of PBMC telomere length is not sufficient at capturing the complex, multidimensional syndrome of frailty.

Matera MG, Calzetta L, Rogliani P, Cesario A, Cazzola M.
New Treatments for COPD in the elderly.
Curr Pharm Des. 2014;20(38):5968-5982.

Matera MG, Rogliani P, Calzetta L, Cazzola M.
Phosphodiesterase inhibitors for Chronic Obstructive Pulmonary Disease: what does the future hold?
Drugs. 2014 Oct 10. [Epub ahead of print] PubMed

Phosphodiesterase-4 (PDE4) inhibitors have broad anti-inflammatory activity, inhibiting the airway inflammation associated with chronic obstructive pulmonary disease (COPD), especially by reducing airway neutrophils that are key cells in COPD. A careful evaluation of the results of several meta-analyses allows us to consider the use of PDE4 inhibitors as very important in those patients with COPD who are particularly susceptible to exacerbations, the so-called 'frequent exacerbators'. Consequently, PDE4 inhibitors should be used earlier and more frequently than is the case today, but they are prescribed sporadically because of side effects. Several strategies are conceivable to avoid side effects, but, unfortunately, many of these approaches are yet to be successfully translated into clinical effectiveness after several decades of research. A novel alternative approach is to administer multiple drugs simultaneously or drugs capable of two distinct primary pharmacological actions based on distinct pharmacophores (bifunctional drugs) in order to produce additive or synergistic effects and, consequently, to dispense these drugs at lower doses, inducing fewer side effects. The fact that we have realized that there is a need to target simultaneously more PDEs unquestionably represents an advance in the possible use of PDE inhibitors. Actually, the possibility that multivalent (multifunctional) ligands, which feature two or more pharmacophores, may deliver superior efficacy is an approach that is being explored. Recognizing the role of specific targeted therapy aimed at subcellular domains has changed our understanding of the use of PDE inhibitors, and offers an opportunity to improve both the therapeutic tolerability and efficacy of these drugs.

Mazzucco W, Rossi M, Cusimano R, Franchi M, Bonifazi M, Mistretta A, Vitale F, Ricciardi W, Negri E, Boccia S, La Vecchia C.
Use of trastuzumab for breast cancer: the role of age.
Curr Pharm Des. 2014;20(38):5957-5962.

Indication for the use of trastuzumab was given in Italy in 2000 for the treatment of HER-2 metastatic breast cancer and in 2006 for early stage breast cancer. Information on trastuzumab use and on its possible variation with age in Italy is however limited. Using health care administrative databases, we evaluated the prevalence of the use of trastuzumab, and the probability for administration since the first hospitalization for breast cancer in various age groups, in two series of Italian women diagnosed with breast cancer in the Lombardy region (2004-2009) and in the Palermo district. The ratio between trastuzumab users and patients with a hospitalization for breast cancer increased from 2.9% in 2004 up to 17.2% in 2009 in Lombardy. Patients aged <65 years were more frequent users (9.6%) compared to those aged ≥ 75 years (1.3%). Similarly, in the Palermo district the ratio increased from 10.6% in 2006 to 28.5% in 2008, with subjects aged <65 years more frequently using trastuzumab (19.1%), than subjects aged ≥ 75 years (6.2%). The age ratio between younger and older patients decreased over time in both settings (from 15 in 2004 to 10.2 in 2006, and 5.2 in 2009 in Lombardy, and from 4.0 in 2006 to 2.3 in 2009 in the Palermo district). The proportion of breast cancer patients using trastuzumab increased over time both in Lombardy and in Palermo district, though geographical differences persisted. Younger breast cancers patients were more likely to receive a trastuzumab treatment than elderly ones, but the difference declined over calendar period.

Miele L, Dall'Armi V, Cefalo C, Nedovic B, Arzani D, Amore R, Rapaccini G, Gasbarrini A, Ricciardi W, Grieco A, Boccia S.
A case-control study on the effect of metabolic gene polymorphisms, nutrition, and their interaction on the risk of non-alcoholic fatty liver disease.
Genes Nutr. 2014 Mar;9(2):383.

The oxidative stress is a key issue in the etiology of non-alcoholic fatty liver disease (NAFLD). The aim of our study was to evaluate the effect of metabolic gene polymorphisms involved in the oxidative stress (GSTT1, GSTM1, SULT1A1, CYP2E1, and 1A1), lifestyle and nutrition aspects, and their interaction, on the risk of NAFLD. We enrolled 294 cases and 359 controls, and collected demographics, anthropometric, lifestyle, and nutrition data. A subgroup of NAFLD provided additional data on nutrients and on physical activity engagement. Each patient provided a blood sample for DNA extraction and genotyping. Clinical and laboratory data were collected from cases. Multivariable analysis shows a significant protective effect of age, gender, and moderate drinking habits on the risk of NAFLD, while an increased risk for greater consumption of fruit and grilled meat or fish. Significant interactions were reported between alcohol consumption, fruit intake, grilled meat and fish, and selected genetic variants. From the subgroup analysis, a moderate/high consumption of fat and/or grilled meat/fish, and a high consumption of white meat increase the risk of NAFLD. Engaging any physical activity at least 1 time/week halves the risk of NAFLD. Besides confirming the beneficial effect of moderate alcohol intake and regular physical activity, and the increased risk associated with high fruit and fat intake, for the first time, we report a detrimental effect of grilled food on NAFLD risk. An effect modification by selected gene variants increases the risk in combination with fruit and grilled food intake.

Panic N, Mastrostefano E, Leoncini E, Persiani R, Arzani D, Amore R, Ricci R, Sicoli F, Sioletic S, Bulajic M, Ugo DD, Ricciardi W, Boccia S.
Susceptibility to Helicobacter pylori infection: results of an epidemiological investigation among gastric cancer patients.
Mol Biol Rep. 2014 Jun;41(6):3637-3650.

The aim of this study was to identify the clinical, demographic, lifestyle factors and selected genetic polymorphisms that affect the susceptibility towards Helicobacter pylori (H. pylori) infection in gastric cancer patients. Histological confirmed gastric adenocarcinoma cases that underwent curative gastrectomy between 2002 and 2012 were included. Gastric biopsy samples were obtained to determine the H. pylori status, and further cagA status and vacA m and s genotypes by polymerase chain reaction. Patients were interviewed with structured questionnaires, and blood

samples were collected for EPHX1, GSTM1, GSTT1, IL1B, IL1-RN, MTHFR and p53 genotyping. Proportions were compared in univariate analysis, while the relation between putative risk factors and H. pylori status and genotype were measured using logistic regression analysis. One hundred forty-nine gastric cancer patients were included, of which 78.5% were H. pylori positive. Among positive patients 50% were cagA+, 72.5% vacA m1 and 80.7% vacA s1. The presence of cagA was less frequent among vacA m1 (p = 0.031) and vacA s1 (p = 0.052) subtypes. The presence of father history for any cancer was a significant risk factor for H. pylori infection [adjusted odds ratio (OR) = 8.18, 95% confidence interval (CI) 1.04-64.55]. EPHX1 exon 3 T > C (OR = 0.35, CI 95% 0.13-0.94), IL1B-511 T > C (OR = 0.38, CI 95% 0.15-0.97) and IL1-RN VNTR (OR = 0.19, CI 95% 0.06-0.58) polymorphisms were protective towards H. pylori infection in the univariate analysis. Wine consumption was associated with higher risk of carrying the H. pylori vacA m1 virulent subtype (p = 0.034). Lastly, cardiovascular diseases were less common among cagA positive subjects (p = 0.023). Father history of any cancer is a risk factor for H. pylori infection. Polymorphisms in IL1B-511, IL1-RN and EPHX1 exon 3 genes might be protective towards H. pylori infection.

Paone G, Conti V, Biondi-Zoccai G, De Falco E, Chimenti I, Peruzzi M, Mollica C, Monaco G, Giannunzio G, Brunetti G, Schmid G, Ranieri VM, Frati G.
Long-term home noninvasive mechanical ventilation increases systemic inflammatory response in chronic obstructive pulmonary disease: a prospective observational study.
Mediators Inflamm. 2014. ID503145, 11 pages.

Long-term home noninvasive mechanical ventilation (NIV) is beneficial in COPD but its impact on inflammation is unknown. We assessed the hypothesis that NIV modulates systemic and pulmonary inflammatory biomarkers in stable COPD.
Among 610 patients referred for NIV, we shortlisted those undergoing NIV versus oxygen therapy alone, excluding subjects with comorbidities or non-COPD conditions. Sputum and blood samples were collected after 3 months of clinical stability and analyzed for levels of human neutrophil peptides (HNP), interleukin-6 (IL-6), interleukin-10 (IL-10), and tumor necrosis factor-alpha (TNF-alpha). Patients underwent a two-year follow-up. Unadjusted, propensity-matched, and pH-stratified analyses were performed.
Ninety-three patients were included (48 NIV, 45 oxygen), with analogous baseline features. Sputum analysis showed similar HNP, IL-6, IL-10, and TNF-alpha levels (P > 0.5). Conversely, NIV group exhibited higher HNP and IL-6 systemic levels (P < 0.001) and lower IL-10 concentrations (P < 0.001). Subjects undergoing NIV had a significant reduction of rehospitalizations during follow-up compared to oxygen group (P = 0.005). These findings were confirmed after propensity matching and pH stratification.
These findings challenge prior paradigms based on the assumption that pulmonary inflammation is per se detrimental. NIV beneficial impact on lung mechanics may overcome the potential unfavorable effects of an increased inflammatory state.

Pelucchi C, Lunet N, Boccia S, Zhang ZF, Praud D, Boffetta P, Levi F, Matsuo K, Ito H, Hu J, Johnson KC, Ferraroni M, Yu GP, Peleteiro B, Malekzadeh R, Derakhshan MH, Ye W, Zaridze D, Maximovitch D, Aragonés N, Martín V, Pakseresht M, Pourfarzi F, Bellavia A, Orsini N, Wolk A, Mu L, Arzani D, Kurtz RC, Lagiou P, Trichopoulos D, Muscat J, La Vecchia C, Negri E.
The stomach cancer pooling (StoP) project: study design and presentation.
Eur J Cancer Prev. 2014 Feb 20. [Epub ahead of print]

Gastric cancer affects about one million people per year worldwide, being the second leading cause of cancer mortality. The study of its etiology remains therefore a global issue as it may allow the identification of major targets, besides eradication of Helicobacter pylori infection, for primary prevention. It has however received little attention, given its comparatively low incidence in most high-income countries. We introduce a consortium of epidemiological investigations named the

'Stomach cancer Pooling (StoP) Project'. Twenty-two studies agreed to participate, for a total of over 9000 cases and 23 000 controls. Twenty studies have already shared the original data set. Of the patients, 40% are from Asia, 43% from Europe, and 17% from North America; 34% are women and 66% men; the median age is 61 years; 56% are from population-based case-control studies, 41% from hospital-based ones, and 3% from nested case-control studies derived from cohort investigations. Biological samples are available from 12 studies. The aim of the StoP Project is to analyze the role of lifestyle and genetic determinants in the etiology of gastric cancer through pooled analyses of individual-level data. The uniquely large data set will allow us to define and quantify the main effects of each risk factor of interest, including a number of infrequent habits, and to adequately address associations in subgroups of the population, as well as interaction within and between environmental and genetic factors. Further, we will carry out separate analyses according to different histotypes and subsites of gastric cancer, to identify potential different risk patterns and etiological characteristics.

Posteraro B, Persiani R, Dall'Armi V, Biondi A, Arzani D, Sicoli F, Bonassi S, D'Ugo D, Ricciardi W, Boccia S.
Prognostic factors and outcomes in italian patients undergoing curative gastric cancer surgery.
Eur J Surg Oncol. 2014 Mar;40(3):345-351.

Survival of patients after curative surgical resection for gastric cancer (GC) remains poor, thus emphasizing the need for better definition of prognostic factors to improve the long-term course of disease. From 1999 to 2009, 110 patients had curative-intent gastrectomy for adenocarcinoma. Clinicopathological features, Helicobacter pylori infection, dietary habits and lifestyle, and the presence of proinflammatory gene polymorphisms were evaluated.At the end of follow-up, 55 deaths had occurred, 48 of them due to GC, whereas the median overall survival (OS) and disease-free survival (DFS) were 62 and 51 months, respectively. From the Kaplan-Meier analysis and log-rank test, statistically significant differences in OS and DFS were found for tumor site (only for DFS), tumor size, lymph node metastasis ratio (NR), and tumor-node-metastasis stage, but not for age, comorbidity, H. pylori infection, cigarette smoking, and IL1B or TNFA polymorphisms. Multivariable Cox regression analysis revealed NR was an independent prognostic factor for OS and DFS. Cardia tumor and patient age 65 years or older were also independent prognostic factors for OS and DFS.
Tumor-related factors remain strongest predictors of survival in GC patients after surgery. Particularly, NR was an effective feature in identifying patients at high risk for adverse outcome.

Rogliani P, Calzetta L, Segreti A, Barrile A, Cazzola M.
Diabetes mellitus among outpatients with COPD attending a university hospital.
Acta Diabetol. 2014 Dec;51(6):933-940.

Type 2 diabetes mellitus is a common comorbidity of COPD, but there are still many doubts about the relation among diabetes and COPD. We retrospectively collected data from patients afferent to our Respiratory Diseases outpatient clinic at the Tor Vergata University Hospital between 2010 and 2012. The study population was analyzed by clusters of age, gender, body mass index (BMI), smoking status, lung function, concomitant pharmacologic therapies and comorbidities. The values of the association between variables were expressed as odds ratio. Data were adjusted for gender, age and possible confounding variables by Mantel-Haenszel method. We identified 493 patients with COPD. Ninety-two (18.7 %) patients were affected by type 2 diabetes mellitus, with no significant gender differences. The prevalence distribution was similar among the different age clusters, but the association was stronger in patients younger than 65 years. The association was present only in obese subjects in whom it was significant only in patients with moderate-to-severe COPD, but not mild COPD. The presence of cardiovascular diseases was significantly associated

with diabetes mellitus in patients with COPD. There was a slight association of inhaled corticosteroid (ICS) use with the presence of diabetes mellitus in COPD, but the combination of an ICS with a 2-agonist apparently reduced this association. The association with type 2 diabetes mellitus was greater in patients with COPD respect to general population, and correlated with the increase in BMI and the presence of other comorbidities, suggesting that both diseases may be targets of systemic inflammation.

Rossi A, Guerriero M, Corrado A; OPTIMO/AIPO Study Group (Pasqua F collaboratore).
Withdrawal of inhaled corticosteroids can be safe in COPD patients at low risk of exacerbation: a real-life study on the appropriateness of treatment in moderate COPD patients (OPTIMO).
Respir Res. 2014 Jul 8;15:77.

It has been suggested that withdrawal of inhaled corticosteroids (ICS) in COPD patients on maintenance treatment results in deterioration of symptoms, lung function and exacerbations. The aim of this real-life, prospective, multicentric study was to investigate whether withdrawal of ICS in COPD patients at low risk of exacerbation is linked to a deterioration in lung function and symptoms and to a higher frequency of exacerbations.
914 COPD patients, on maintenance therapy with bronchodilators and ICS, FEV1>50% predicted, and <2 exacerbations/year were recruited. Upon decision of the primary physicians, 59% of patients continued their ICS treatment whereas in 41% of patients ICS were withdrawn and regular therapy was continued with long-acting bronchodilators mostly (91% of patients). FEV1, CAT (COPD Assessment Test), and occurrence of exacerbations were measured at the beginning (T0) and at the end (T6) of the 6 months observational period.
816 patients (89.3%) concluded the study. FEV1, CAT and exacerbations history were similar in the two groups (ICS and no ICS) at T0 and at T6. We did not observe any deterioration of lung function symptoms, and exacerbation rate between the two groups at T0 and T6.
We conclude that the withdrawal of ICS, in COPD patients at low risk of exacerbation, can be safe provided that patients are left on maintenance treatment with long-acting bronchodilators.

Rossi P, Bove P, Montuori M, De Majo A, Ricciardi E, Mattei M, Bernardini R, Calzetta L, Mauti P, Intini L, Quattrini V, Chiaramonte C, Vespasiani G.
Partial nephrectomy using radiofrequency incremental bipolar generator with multi electrode probe: experimental study in bench pig kidneys.
BMC Urol. 2014 Jan 10;14:7.

The aim of this research project was the realization of an incremental bipolar radiofrequency generator with inline 4-electrode probe for partial renal resection without clamping of the vessels.
The experimentation was carried out across two phases: the preliminary realization of a specific generator and an inline multielectrode probe for open surgery (Phase 1); system testing on 27 bench kidneys for a total of 47 partial resection (Phase 2). The parameters evaluated were: power level, generator automatisms, parenchymal coagulation times, needle caliber, thickness of the coagulated tissue "slice", charring, ergonomy, feasibility of the application of "bolster" stitches.
The analysis of the results referred to the homogeneity and thickness of coagulation, energy supply times with reference to the power level and caliber of the needles. The optimal results were obtained by using needles of 1.5 mm caliber at power level 5, and with coagulation times of 54 seconds for the first insertion and 30 seconds for the second.
The experimentation demonstrated that the apparatus, consisting of a generator named "LaparoNewPro" and fitted with a dedicated probe for open surgery, is able to carry out a coagulation of the line of resection of the renal parenchyma in a homogeneous manner, in short times, without tissue charring, and with the possibility of stitching both on coagulated tissue and the caliceal system. The generator automatism based on the flow of the current supplied by each electrode is reliable, and the cessation of energy supply coincides with optimal coagulation.

Rota M, Bosetti C, Boccia S, Boffetta P, La Vecchia C.
Occupational exposures to polycyclic aromatic hydrocarbons and respiratory and urinary tract cancers: an updated systematic review and a meta-analysis to 2014.
Arch Toxicol. 2014 Aug;88(8):1479-1490.

Exposure to polycyclic aromatic hydrocarbons (PAHs) has been associated with an excess risk of respiratory tract and bladder cancers in several industries, but the issue requires further quantification. We updated a previous systematic review by reviewing in details cohort studies on workers employed in selected industries with potential PAH exposure published between 2006 and 2014, and we summarized through a meta-analytic approach the main results of all available cohort studies published between 1958 and 2014 investigating cancers of the respiratory and urinary tracts. Thirteen papers on cohort studies investigating cancer risk in workers exposed to PAHs were retrieved through the literature search. These included workers from aluminum production industries (seven studies), iron and steel foundries (two studies), asphalt workers (two studies), and carbon black production (two studies). In the meta-analysis, an excess risk of respiratory tract cancers (mainly lung cancer) was found in iron and steel foundries [pooled relative risk (RR) 1.31, 95 % confidence interval (CI) 1.08-1.59 from 14 studies], while a weak excess risk (pooled RR 1.08, 95 % CI 0.95-1.23 from 11 studies) emerged for aluminum production. A borderline increase risk was also observed for cancer of the bladder in the aluminum production (pooled RR 1.28, 95 % CI 0.98-1.68 from 10 studies) and in iron and steel foundries (pooled RR 1.38, 95 % CI 1.00-1.91 from 9 studies). This updated review and meta-analysis confirm the increased risk from respiratory tract and bladder cancers in selected PAH-related occupations. It cannot be ruled out whether such excesses are due, at least in part, to possible bias or residual confounding.

Russo P, Del Bufalo A, Frustaci A, Fini M, Cesario A.
Beyond Acetylcholinesterase Inhibitors for Treating Alzheimer's Disease: α7-nAChR Agonists in Human Clinical Trials.
Curr Pharm Des. 2014;20(38):6014-6021.

The neuronal nicotinic alpha7-acetylcholine receptor (α7-nAChR) is a promising and attractive drug target for improving cognitive deficits in neuropsychiatric and neurological disorders such as Alzheimer's disease (AD). α7-nAChR belongs to the family of ligand gated ion channels. α7-nAChR is expressed in key brain regions (e.g. pre- and frontal cortex, hippocampus). It is involved in essential cognitive functions such as memory, thinking, comprehension, learning capacity, calculation, orientation, language, and judgment. α7-nAChR binds to amyloid peptide (Aβ) inducing either receptor activation or inhibition in an Aβ concentration-dependent mode. Aβ oligomers induce τ phosphorylation via α7-nAChR activation. α7-nAChR agonists and/or α7-nAChR positive allosteric modulators may be useful in AD therapy. The current review enlightens: (i) α7-nAChR neurobiology, (ii) α7-nAChR role in cognition and (iii) in AD, and (iv) the clinical status of the most promising molecules for the treatment of cognitive dysfunction in AD.

Russo P, Del Bufalo A, Milic M, Salinaro G, Fini M, Cesario A.
Cholinergic receptors as target for cancer therapy in a systems medicine perspective.
Curr Mol Med. 2014;14(9):1126-1138.

Epithelial cells not innervated by cholinergic neurons express nicotinic and muscarinic acetylcholine (ACh) receptors (nAChR, mAChR). nAChR and mAChR are components of the auto-/paracrine-regulatory loop of non-neuronal ACh release. The cholinergic control of non-neuronal cells may be mediated by different effects (synergistic, additive, or reciprocal) triggered by these receptors. The ionic events (Ca(+2) influx) are generated by the ACh-opening of nAChR channels,

while the metabolic events by ACh-binding to G-proteincoupled mAChR. Effective inter- and intracellular signaling is crucial for valuable cancer cells proliferation and survival. Depending on cancer cell type, different AChR have been identified. The proliferation of airways epithelial cancer cells and pancreatic cancer cells may be under the control of α7-nAChR and M3-mAChR, while breast cancer cells and colon cancer cells are regulated by α9-nAChR, and M3-mAChR, respectively. In turn, these receptors may activate different pathways (Ras-Raf-1-Erk-AKT) as well as other receptors (β- adrenergicR). nAChR or mAChR antagonists may inhibit cancer growth. Inhibition of M3 by antisense or antagonists (Darifenacin, Tiotropium) reduces lung or colon cancer proliferation, as well as inhibition of α9- nAChR [polyphenol (-)-epigallocatechin-3-gallate] diminishes breast cancer cells growth. α7-nAChR silencing inhibits lung cancer proliferation. Moreover, inhibition of the nAChR-β-adrenergicR pathway (β-blockers) could be also useful. This review will describe the future translational perspectives of cholinergic receptors druginhibition in a complex disease such as cancer that poses compelling treatment challenges. Cancer happens as consequence of disease-perturbed molecular networks in relevant organ cells that change during progression. The framework for approaching these challenges is a systems approach.

Russo P, Fini M, Cesario A.
Editorial: disease control and active and healthy ageing: new paradigms of therapeutic strategy.
Curr Pharm Des. 2014;20(38):5919-5920.

Segreti A, Calzetta L, Rogliani P, Cazzola M.
Umeclidinium for the treatment of chronic obstructive pulmonary disease.
Expert Rev Respir Med. 2014 Dec;8(6):665-671.

Umeclidinium is a novel inhaled long-acting muscarinic receptor antagonist (LAMA) approved for treatment of chronic obstructive pulmonary disease (COPD). It provides a bronchodilation of at least 24 h, is well tolerated and has a safe profile. In this article, we describe its pharmacokinetic and pharmacodynamic characteristics. Moreover, we present a meta-analysis of randomized clinical trials carried out in COPD patients, in which the change of forced expiratory volume in 1 s (FEV1) induced by umeclidinium has been compared with that elicited by placebo or the active compound tiotropium. The data generated by the pivotal trials indicate that umeclidinium bromide delivered once-daily via the Ellipta™ inhaler is an effective and well-tolerated treatment for COPD. Therefore, it could to be used as an alternative to LAMAs already in the market, although substantial information is still lacking. It is likely that in the future, umeclidinium will be used frequently, mainly in combination with vilanterol, which is a new once-daily long-acting β2-agonist (LABA).

Tufegdzic M, Panic N, Boccia S, Malerba S, Bulajic M, La Vecchia C, Sljivic A, Trbojevic-Stankovic J, Krstic M.
The weekend effect in patients hospitalized for upper gastrointestinal bleeding: a single-center 10-year experience.
Eur J Gastroenterol Hepatol. 2014 Jul;26(7):715-720.

This study was conducted to assess the possible weekend effect in patients with upper gastrointestinal bleeding (UGIB) on the basis of a 10-year single-center experience in Serbia.
A retrospective analysis of hospital records in the University Clinic 'Dr Dragisa Misovic-Dedinje', Belgrade, Serbia, from 2002 to 2012 was conducted. Patients admitted for UGIB were identified, and data on demographic characteristics, symptoms, drug use, alcohol abuse, diagnosis and treatment were collected. Univariate and multivariate logistic regression were used to assess the association between weekend admission and the occurrence of rebleeding and in-hospital mortality.

Analyses included 493 patients. Rebleeding occurred significantly more frequently on weekends (45.7 vs. 32.7%, P=0.004). Weekend admission [odds ratio (OR)=1.78; 95% confidence interval (CI): 1.15-2.74], older age (OR=1.02; 95% CI: 1.00-1.03), and the presence of both melaena and hematemesis (OR=2.29; 95% CI: 1.29-4.07) were associated with the occurrence of rebleeding. No difference between weekend and weekday admissions was observed for the in-hospital mortality rate (6.9% vs. 6.0%, P=0.70). Older age (OR=1.14; 95% CI: 1.08-1.20), presentation with melaena and hematemesis (OR=4.12; 95% CI: 1.56-10.90) and need for surgical treatment (OR=5.16; 95% CI: 1.61-16.53) were significant predictors of all-cause mortality. Patients with nonvariceal bleeding had significantly higher rebleeding rates on weekends (44 vs. 32.3%, P=0.013).
There was no significant weekend effect in the mortality of patients admitted for UGIB, irrespective of the source of bleeding. Increased attention to older patients presenting with a more severe clinical picture is needed to prolong survival and prevent rebleeding.

Ugolini D, Bonassi S, Cristaudo A, Leoncini G, Ratto GB, Neri M.
Temporal trend, geographic distribution, and publication quality in asbestos research.
Environ Sci Pollut Res Int. 2014 Dec 6. [Epub ahead of print]

Asbestos is a well-known cause of cancer and respiratory diseases. The aim of the current study was to investigate the scientific production in asbestos research evaluating temporal trend, geographic distribution, impact factor (IF) of published literature, and taking into account socioeconomic variables. The PubMed database was searched starting from 1970. Publication numbers and IF were evaluated as absolute values and after standardization by population and gross domestic product (GDP). Six thousand nine hundred seven articles related to asbestos were retrieved. Publications grew steeply in the 1970s, leveled off in the 1980s, decreased in the 1990s, and then increased again. Mesothelioma, lung neoplasms, and occupational diseases are the most commonly used keywords. In the period of 1988-2011, 4220 citations were retrieved, 3187 of whom had an impact factor. The US, Italy, and the UK were the most productive countries. European countries published about 20 % more asbestos-related articles than the US, although the latter reached a higher mean IF, ranking second after Australia. When the national scientific production (sum of IF) was compared taking into account socioeconomic variables, Australia and Scandinavian countries performed very well, opposite to all main asbestos producers like Russia, China, and Brazil (except for Canada). The American Journal of Industrial Medicine and the Italian La Medicina del Lavoro published the highest numbers of articles. This study provides the first bibliometric analysis of scientific production in asbestos research. Interest appears to be higher in selected countries, with strong national features, and is growing again in the new millennium.

Ugolini D, Casanova G, Ceppi M, Mattei F, Neri M.
Familiarity of physicians, translational researchers, nurses, and other health professionals with evidence-based medicine terms and resources.
J Cancer Educ. 2014 Sep;29(3):514-521.

Evidence-based medicine (EBM) is a central theme in health practice and training. The understanding of EBM technical terms and the familiarity with EBM resources were surveyed in four different health professional categories. A self-administered questionnaire on the familiarity with EBM terminology and resources was proposed to 218 health professionals (physicians, translational researchers, nurses, and others) working in the oncology field. Relationships between variable and familiarity were examined: Pearson ?(2) or exact Fisher test was used for the categorical variables and one-way ANOVA for the continuous ones. The odds of familiarity for subjects, who had followed or not at least one EBM course, were estimated fitting a multiple logistic regression model adjusted for age, gender, and profession. All subjects completed the questionnaire. The majority of health personnel seemed to lack a sound knowledge of key EBM terms and sources. Physicians showed the highest knowledge of terms, nurses the lowest. Physicians also declared

the largest familiarity with the widest variety of resources, followed by others and the researchers. The most popular resource was PLNG, the Italian Guideline System. People who attended at least one EBM course showed consistently higher percentages of knowledge, but the association was irrelevant for nurses. The main perceived barrier to implement EBM in practice was a lack of personal time. Familiarity of health professionals with EBM terminology and resources is still limited to the medical field and needs to be improved. Increasing education may be pivotal, even if different approaches should be developed for different professional categories.

Calzetta L, Bonassi S, Dall'Armi V, Pasqua F, Cesario A.
A dutch research protocol on advance care planning in COPD patients: A critical revision.
BMJ Open. 2014 20 March 2014

Evidence-based medicine (EBM) is a central theme in health practice and training. The understanding of EBM technical terms and the familiarity with EBM resources were surveyed in four different health professional categories. A self-administered questionnaire on the familiarity with EBM terminology and resources was proposed to 218 health professionals (physicians, translational researchers, nurses, and others) working in the oncology field. Relationships between variable and familiarity were examined: Pearson X(2) or exact Fisher test was used for the categorical variables and one-way ANOVA for the continuous ones. The odds of familiarity for subjects, who had followed or not at least one EBM course, were estimated fitting a multiple logistic regression model adjusted for age, gender, and profession. All subjects completed the questionnaire. The majority of health personnel seemed to lack a sound knowledge of key EBM terms and sources. Physicians showed the highest knowledge of terms, nurses the lowest. Physicians also declared the largest familiarity with the widest variety of resources, followed by others and the researchers. The most popular resource was PLNG, the Italian Guideline System. People who attended at least one EBM course showed consistently higher percentages of knowledge, but the association was irrelevant for nurses. The main perceived barrier to implement EBM in practice was a lack of personal time. Familiarity of health professionals with EBM terminology and resources is still limited to the medical field and needs to be improved. Increasing education may be pivotal, even if different approaches should be developed for different professional categories.

Raspopovic S, Capogrosso M, Petrini FM, Bonizzato M, Rigosa J, Di Pino G, Carpaneto J, Controzzi M, Boretius T, Fernandez E, Granata G, Oddo CM, Citi L, Ciancio AL, Cipriani C, Carrozza MC, Jensen W, Guglielmelli E, Stieglitz T, Rossini PM, Micera S.
Restoring natural sensory feedback in real-time bidirectional hand prostheses.
Sci Transl Med. 2014 Feb 5;6(222):222ra19.

Hand loss is a highly disabling event that markedly affects the quality of life. To achieve a close to natural replacement for the lost hand, the user should be provided with the rich sensations that we naturally perceive when grasping or manipulating an object. Ideal bidirectional hand prostheses should involve both a reliable decoding of the user's intentions and the delivery of nearly "natural" sensory feedback through remnant afferent pathways, simultaneously and in real time. However, current hand prostheses fail to achieve these requirements, particularly because they lack any sensory feedback. We show that by stimulating the median and ulnar nerve fascicles using transversal multichannel intrafascicular electrodes, according to the information provided by the artificial sensors from a hand prosthesis, physiologically appropriate (near-natural) sensory information can be provided to an amputee during the real-time decoding of different grasping tasks to control a dexterous hand prosthesis. This feedback enabled the participant to effectively modulate the grasping force of the prosthesis with no visual or auditory feedback. Three different force levels were distinguished and consistently used by the subject. The results also demonstrate that a high complexity of perception can be obtained, allowing the subject to identify the stiffness and shape of three different objects by exploiting different characteristics of the elicited sensations. This approach could improve the efficacy and "life-like" quality of hand prostheses, resulting in a keystone strategy for the near-natural replacement of missing hands.

Cimolin V, Galli M, Celletti C, Pau M, Castori M, Morico G, Albertini G, Camerota F.
Foot type analysis based on electronic pedobarography data in individuals with joint hypermobility syndrome/ehlers-danlos syndrome hypermobility type during upright standing.
J Am Podiatr Med Assoc. 2014 Nov;104(6):588-593.

Joint hypermobility syndrome/Ehlers-Danlos syndrome hypermobility type (JHS/EDS-HT) is a rheumatologic condition characterized by generalized joint hypermobility and musculoskeletal and nonmusculoskeletal findings related to congenital laxity of connective tissue. Because foot pain and other foot problems are reported to make daily life problematic to manage for individuals with JHS/EDS-HT, and thanks to the availability of modern technology, the aim of the present study was to quantitatively characterize foot type in individuals with JHS/EDS-HT during upright standing.
Forty feet of 20 women with JHS/EDS-HT (mean ± SD age, 36.03 ± 14.01 years) were assessed clinically and with a pressure-sensitive mat during upright standing.
Forty-five percent of feet had a high arch (pes cavus), 27.5% had a normal arch, and 27.5% had a low arch (pes planus or flatfoot).
From a clinical perspective, the characterization of foot type in JHS/EDS-HT is important to identify, develop, and enhance the rehabilitative options. An understanding of the relationship between pes cavus and foot pain in these patients could, in fact, improve the clinical management of these patients.

Cimolin V, Galli M, Vismara L, Albertini G, Sartorio A, Capodaglio P.
Gait pattern in lean and obese adolescents.
Int J Rehabil Res. 2014 Oct 16. [Epub ahead of print]

Obesity is the most common chronic disorder in children and adolescents. As walking is the most common daily task and is recommended for weight management, quantifying how obesity affects the biomechanics of gait provides important insight into the relationship between metabolic and mechanical energetics, mechanical loading and associated risk for musculoskeletal injury. This study quantitatively compared gait in 12 obese and 10 lean adolescents. Obese adolescents showed longer stance duration, excessive hip flexion during the whole gait cycle and an increased hip movement in the frontal plane compared with lean participants. In the obese, the knee was slightly extended in stance phase and the ankle was in a plantar flexed position at initial contact and at toe-off, with a greater ankle range of motion. Kinetic data showed higher values of maximum power generated at hip level during the stance phase; ankle power displayed a higher absorption at initial stance and higher values of power generation in the terminal stance. Because obese adolescents are encouraged to walk to increase their physical activity and energy expenditure level, injury prevention and rehabilitative programmes should take our findings into consideration and include specific strengthening of the lower limb proximal and distal muscles, together with weight loss and reconditioning interventions.

Siotto M, Pasqualetti P, Marano M, Squitti R.
Automation of o-dianisidine assay for ceruloplasmin activity analyses: usefulness of investigation in Wilson's disease and in hepatic encephalopathy.
J Neural Transm. 2014 Oct;121(10):1281-1286.

Ceruloplasmin (Cp) is a serum ferroxidase that plays an essential role in iron metabolism. It is routinely tested by immunoturbidimetric assays that quantify the concentration of the protein both in its active and inactive forms. Cp activity is generally analyzed manually; the process is

time-consuming, has a limited repeatability, and is not suitable for a clinical setting. To overcome these inconveniences, we have set the automation of the o-dianisidine Cp activity assay on a Cobas Mira Plus apparatus. The automation was rapid and repeatable, and the data were provided in terms of IU/L. The assay was adapted for human sera and showed a good precision [coefficient of variation (CV) 3.7 %] and low limit of detection (LoD 11.58 IU/L). The simultaneous analysis of Cp concentration and activity in the same run allowed us to calculate the Cp-specific activity that provides a better index of the overall Cp status. To test the usefulness of this automation, we tested this assay on 104 healthy volunteers and 36 patients with Wilson's disease, hepatic encephalopathy, and chronic liver disease. Cp activity and specific activity distinguished better patients between groups with respect to Cp concentration alone, and providing support for the clinical investigation of neurological diseases in which liver failure is one of the clinical hallmarks.

Squitti R.
Copper subtype of Alzheimer's disease (AD): Meta-analyses, genetic studies and predictive value of non-ceruloplasmim copper in mild cognitive impairment conversion to full AD.
J Trace Elem Med Biol. 2014 Oct;28(4):482-485.

Alzheimer's disease (AD) is the most common form of dementia. A myriad of complex factors contribute to AD, promoting the deposition in plaques of amyloid-beta (Aβ), which is the main constituent of this pathognomonic sign of AD at autopsy brain inspection. Aβ toxicity is related to oxidative stress, which results in synaptic loss in specific brain areas, eventually leading to cognitive decline. Metal, and especially copper, dyshomeostasis is a key factor in these processes. Recent studies have demonstrated that the serum fraction of copper that is not bound to ceruloplasmin (Non-Cp copper, also known as 'free' or labile copper) increases in a percentage of AD patients and mild cognitive impairment (MCI) subjects; this is considered a precursor of AD. Non-Cp copper is the exchangeable fraction of low molecular weight copper in serum. It is distinguished from the copper structurally bound to the ceruloplasmin protein, a master protein of iron metabolism. Non-Cp copper levels are higher than normal reference values (range 0-1.6μmol/L) in about 50% of amnestic MCI subjects and 60% of AD patients, typifying them in a subset of AD. Meta-analyses, genetic studies and a prognostic study evaluating the predictive value of Non-Cp copper in MCI conversion to full AD demonstrate the existence of this copper phenotype of AD.

Squitti R, Ghidoni R, Siotto M, Ventriglia M, Benussi L, Paterlini A, Magri M, Binetti G, Cassetta E, Caprara D, Vernieri F, Rossini PM, Pasqualetti P.
Value of serum nonceruloplasmin copper for prediction of mild cognitive impairment conversion to Alzheimer disease.
Ann Neurol. 2014 Apr;75(4):574-580.

Meta-analyses show that nonbound ceruloplasmin (non-Cp) copper (also known as free or labile copper) in serum is higher in patients with Alzheimer disease (AD). It differentiates subjects with mild cognitive impairment (MCI) from healthy controls. However, a longitudinal study on an MCI cohort has not yet been performed to assess the accuracy of non-Cp copper for the prediction of conversion from MCI to AD during a long-term follow-up.
The study included 42 MCI converters and 99 stable MCI subjects. We assessed levels of copper, ceruloplasmin, non-Cp copper, iron, transferrin, ferritin, and APOE genotype. A multiple Cox regression analysis-with age, sex, baseline Mini-Mental State Examination, APOE4, iron, non-Cp copper, transferrin, ferritin, hypercholesterolemia, and hypertension as covariates-was applied to predict the conversion from MCI to AD.
Among the evaluated parameters, the only significant predictor of conversion to AD was non-Cp copper (hazard ratio = 1.23, 95% confidence interval = 1.03-1.47, p = 0.022); for each additional micromole per liter unit (μmol/l) of non-Cp copper, the hazard increased by ~20%. Subjects with non-Cp copper levels >1.6 μmol/l had a hazard conversion rate (50% of conversion in 4 years) that was ~3× higher than those with values ≤1.6 μmol/l (<20% in 4 years). The rate of conversion was similar between APOE4 carriers and noncarriers (p = 0.321), indicating that the non-Cp copper association was independent of APOE4.
Non-Cp copper appears to predict conversion from MCI to AD. These results encourage healthy life style choices and dietary intervention to modify this risk.

Squitti R, Siotto M, Polimanti R.
Low-copper diet as a preventive strategy for Alzheimer's disease.
Neurobiol Aging. 2014 Sep;35 Suppl 2:S40-50. Epub 2014 May 15.

Copper is an essential element, and either a copper deficiency or excess can be life threatening. Recent studies have indicated that alteration of copper metabolism is one of the pathogenetic mechanisms of Alzheimer's disease (AD). In light of these findings, many researchers have proposed preventive strategies to reduce AD risk. Because the general population comes in contact with copper mainly through dietary intake, that is, food 75% and drinking water 25%, a low-copper diet can reduce the risk of AD in individuals with an altered copper metabolism. We suggest that a diet-gene interplay is at the basis of the "copper phenotype" of sporadic AD. Herein, we describe the pathways regulating copper homeostasis, the adverse sequelae related to its derangements, the pathogenic mechanism of the AD copper phenotype, indications for a low-copper diet, and future perspectives to improve this preventive strategy.

Qiu YQ, Hua XY, Zuo CT, Li T, Zheng MX, Shen YD, Xu JG, Gu YD, Rossini PM, Xu WD.
Deactivation of distant pain-related regions induced by 20-day rTMS: a case study of one-week pain relief for long-term intractable deafferentation pain.
Pain Physician. 2014 Jan-Feb;17(1):E99-E105.

Deafferentation pain secondary to brachial plexus avulsion, spinal cord injury, and other peripheral nerve injuries is often refractory to conventional treatments. Stimulation of the primary motor cortex (M1) has been proven to be an effective treatment for intractable deafferentation pain. The mechanisms underlying the attenuation of deafferentation pain by motor cortex stimulation remain hypothetical.
The purpose of this case report is to: (1) summarize a case in which a patient suffering chronic intractable deafferentation pain for 25 years underwent rTMS treatment over M1, (2) describe the evidence from PET imaging, and (3) reveal a possible relief mechanism with cortical plasticity. Study design: Case report. Setting: University hospital. This patient had successful pain control with no transient or lasting side effects. The pain relief remained stable for at least one week. At the end of the 20-day procedure, pain relief was obtained according to the Visual Analog Scale (VAS) (-34.6%) and the McGill Pain Questionnaire (MPQ) (-31.6%). In the PET/CT scans, the glucose metabolism was significantly reduced contralaterally to the pain side in the anterior cingulate cortex (ACC), insula, and caudate nucleus. There was no statistically significant difference in any other cortical area.
Limitations: Single case of a patient with long-term intractable deafferentation pain having a PET study.
This study implies that a single session of 20 Hz rTMS over the motor cortex could reduce the pain level in patients suffering from long-term, intractable deafferentation pain. The stimulation of the M1 induces deactivation in the ACC, insula, and caudate nucleus. The changes in these pain-related regions may mirror an adaptive mechanism to pain relief after rTMS treatment.

Serra L, Silvestri G, Petrucci A, Basile B, Masciullo M, Makovac E, Torso M, Spanò B, Mastropasqua C, Harrison NA, Bianchi ML, Giacanelli M, Caltagirone C, Cercignani M, Bozzali M.
Abnormal functional brain connectivity and personality traits in myotonic dystrophy type 1.
JAMA Neurol. 2014 May 1;71(5):603-611.

Myotonic dystrophy type 1 (DM1), the most common muscular dystrophy observed in adults, is a genetic multisystem disorder affecting several other organs besides skeletal muscle, including the brain. Cognitive and personality abnormalities have been reported; however, no studies have investigated brain functional networks and their relationship with personality traits/disorders in patients with DM1.
To use resting-state functional magnetic resonance imaging to assess the potential relationship between personality traits/disorders and changes to functional connectivity within the default mode network (DMN) in patients with DM1.
We enrolled 27 patients with genetically confirmed DM1 and 16 matched healthy control individuals. Patients underwent personality assessment using clinical interview and Minnesota Multiphasic Personality Inventory-2 administration; all participants underwent resting-state functional magnetic resonance imaging. Investigations were conducted at the Istituto di Ricovero e Cura a Carattere Scientifico Santa Lucia Foundation, Catholic University of Sacred Heart, and Azienda Ospedaliera San Camillo Forlanini.
Intervention: Resting-state functional magnetic resonance imaging.
Main outcomes and measures: measures of personality traits in patients and changes in functional connectivity within the DMN in patients and controls. Changes in functional connectivity and atypical personality traits in patients were correlated.
We combined results obtained from the Minnesota Multiphasic Personality Inventory-2 and clinical interview to identify a continuum of atypical personality profiles ranging from schizotypal personality traits to paranoid personality disorder within our DM1 patients. We also demonstrated an increase in functional connectivity in the bilateral posterior cingulate and left parietal DMN nodes in DM1 patients compared with controls. Moreover, patients with DM1 showed strong associations between DMN functional connectivity and schizotypal-paranoid traits.
Our findings provide novel biological evidence that DM1 is a clinical condition that also involves an alteration of functional connectivity of the brain. We speculate that these functional brain abnormalities, similarly to frank psychiatric disorders, may account for the atypical personality traits observed in patients with DM1.

Tecchio F, Cancelli A, Cottone C, Zito G, Pasqualetti P, Ghazaryan A, Rossini PM, Filippi MM.
Multiple sclerosis fatigue relief by bilateral somatosensory cortex neuromodulation.
J Neurol. 2014 Aug;261(8):1552-1558.

Multiple sclerosis-related fatigue is highly common and often refractory to medical therapy. Ten fatigued multiple sclerosis patients received two blocks of 5-day anodal bilateral primary somatosensory areas transcranial direct current stimulation in a randomized, double-blind sham-controlled, cross-over study. The real neuromodulation by a personalized electrode, shaped on the MR-derived primary somatosensory cortical strip, reduced fatigue in all patients, by 26 % in average ($p = 0.002$), which did not change after sham ($p = 0.901$). Anodal tDCS over bilateral somatosensory areas was able to relief fatigue in mildly disabled MS patients, when the fatigue-related symptoms severely hamper their quality of life. These small-scale study results support the concept that interventions modifying the sensorimotor network activity balances could be a suitable non-pharmacological treatment for multiple sclerosis fatigue.

Tezenas du Montcel S, Durr A, Rakowicz M, Nanetti L, Charles P, Sulek A, Mariotti C, Rola R, Schols L, Bauer P, Dufaure-Garé I, Jacobi H, Forlani S, Schmitz-Hübsch T, Filla A, Timmann D, van de Warrenburg BP, Marelli C, Kang JS, Giunti P, Cook A, Baliko L, Bela M, Boesch S, Szymanski S, Berciano J, Infante J, Buerk K, Masciullo M, Di Fabio R, Depondt C, Ratka S, Stevanin G, Klockgether T, Brice A, Golmard JL.
Prediction of the age at onset in spinocerebellar ataxia type 1, 2, 3 and 6.
J Med Genet. 2014 Jul;51(7):479-486.

The most common spinocerebellar ataxias (SCA)--SCA1, SCA2, SCA3, and SCA6--are caused by (CAG)n repeat expansion. While the number of repeats of the coding (CAG)n expansions is correlated with the age at onset, there are no appropriate models that include both affected and preclinical carriers allowing for the prediction of age at onset.
We combined data from two major European cohorts of SCA1, SCA2, SCA3, and SCA6 mutation carriers: 1187 affected individuals from the EUROSCA registry and 123 preclinical individuals from the RISCA cohort. For each SCA genotype, a regression model was fitted using a log-normal distribution for age at onset with the repeat length of the alleles as covariates. From these models, we calculated expected age at onset from birth and conditionally that this age is greater than the current age.
For SCA2 and SCA3 genotypes, the expanded allele was a significant predictor of age at onset (-0.105±0.005 and -0.056±0.003) while for SCA1 and SCA6 genotypes both the size of the expanded and normal alleles were significant (expanded: -0.049±0.002 and -0.090±0.009, respectively; normal: +0.013±0.005 and -0.029±0.010, respectively). According to the model, we indicated the median values (90% critical region) and the expectancy (SD) of the predicted age at onset for each SCA genotype according to the CAG repeat size and current age.
These estimations can be valuable in clinical and research. However, results need to be confirmed in other independent cohorts and in future longitudinal studies.

Vecchio F, Lacidogna G, Miraglia F, Bramanti P, Ferreri F, Rossini PM.
Prestimulus interhemispheric coupling of brain rhythms predicts cognitive-motor performance in healthy humans.
J Cogn Neurosci. 2014 Sep;26(9):1883-1890.

Physiological and neuroimaging studies suggest that human actions are characterized by time-varying engagement of functional distributed networks within the brain. In this study, we investigated whether specific prestimulus interhemispheric connectivity, as a measure of synchronized network between the two hemispheres, could lead to a better performance (as revealed by RT) in a simple visuomotor task. Eighteen healthy adults underwent EEG recording during a visual go/no-go task. In the go/no-go task, a central fixation stimulus was followed by a green (50% of probability) or red visual stimulus. Participants had to press the mouse button after the green stimuli (go trials). Interhemispheric coupling was evaluated by the spectral coherence among all the electrodes covering one hemisphere and matched with those on the other. The frequency bands of interest were delta (2-4 Hz), theta (4-8 Hz), alpha 1 (8-10.5 Hz), alpha 2 (10.5-13 Hz), beta 1 (13-20 Hz), beta 2 (20-30 Hz), and gamma (30-40 Hz). The task-related results showed that interhemispheric connectivity decreased in delta and increased in alpha band. Furthermore, we observed positive delta and negative alpha correlations with the RT; namely, the faster the RT, the lower delta and the higher alpha connection between the two hemispheres. These results suggested that the best performance is anticipated by the better functional coupling of cortical circuits involved during the processing of the sensorimotor information, occurring between the two hemispheres pending cognitive go/no-go task.

Vecchio F, Miraglia F, Bramanti P, Rossini PM.
Human brain networks in physiological aging: a graph theoretical analysis of cortical connectivity from EEG data.
J Alzheimers Dis. 2014;41(4):1239-1249.

Modern analysis of electroencephalographic (EEG) rhythms provides information on dynamic brain connectivity. To test the hypothesis that aging processes modulate the brain connectivity network, EEG recording was conducted on 113 healthy volunteers. They were divided into three groups in accordance with their ages: 36 Young (15-45 years), 46 Adult (50-70 years), and 31 Elder-

ly (>70 years). To evaluate the stability of the investigated parameters, a subgroup of 10 subjects underwent a second EEG recording two weeks later. Graph theory functions were applied to the undirected and weighted networks obtained by the lagged linear coherence evaluated by eLORETA on cortical sources. EEG frequency bands of interest were: delta (2-4 Hz), theta (4-8 Hz), alpha1 (8-10.5 Hz), alpha2 (10.5-13 Hz), beta1 (13-20 Hz), beta2 (20-30 Hz), and gamma (30-40 Hz). The spectral connectivity analysis of cortical sources showed that the normalized Characteristic Path Length (λ) presented the pattern Young > Adult>Elderly in the higher alpha band. Elderly also showed a greater increase in delta and theta bands than Young. The correlation between age and λ showed that higher ages corresponded to higher λ in delta and theta and lower in the alpha2 band; this pattern reflects the age-related modulation of higher (alpha) and decreased (delta) connectivity. The Normalized Clustering coefficient (λ) and small-world network modeling (σ) showed non-significant age-modulation. Evidence from the present study suggests that graph theory can aid in the analysis of connectivity patterns estimated from EEG and can facilitate the study of the physiological and pathological brain aging features of functional connectivity networks.

Vecchio F, Miraglia F, Curcio G, Della Marca G, Vollono C, Mazzucchi E, Bramanti P, Rossini PM.
Cortical connectivity in fronto-temporal focal epilepsy from EEG analysis: A study via graph theory.
Clin Neurophysiol. 2014 Oct 2. [Epub ahead of print]

It is believed that effective connectivity and optimal network structure are essential for proper information processing in the brain. Indeed, functional abnormalities of the brain are found to be associated with pathological changes in connectivity and network structures. The aim of the present study was to explore the interictal network properties of EEG signals from temporal lobe structures in the context of fronto-temporal lobe epilepsy.
To complete this aim, the graph characteristics of the EEG data of 17 patients suffering from focal epilepsy of the fronto-temporal type, recorded during interictal periods, were examined and compared in terms of the affected versus the unaffected hemispheres. EEG connectivity analysis was performed using eLORETA software in 15 fronto-temporal regions (Brodmann Areas BAs 8, 9, 10, 11, 20, 21, 22, 37, 38, 41, 42, 44, 45, 46, 47) on both affected and unaffected hemispheres.
The evaluation of the graph analysis parameters, such as 'global' (characteristic path length) and 'local' connectivity (clustering coefficient) showed a statistically significant interaction among side (affected and unaffected hemisphere) and Band (delta, theta, alpha, beta, gamma). Duncan post hoc testing showed an increase of the path length in the alpha band in the affected hemisphere with respect to the unaffected one, as evaluated by an inter-hemispheric marker. The affected hemisphere also showed higher values of local connectivity in the alpha band. In general, an increase of local and global graph theory parameters in the alpha band was found in the affected hemisphere. It was also demonstrated that these effects were more evident in drug-free patients than in those undergoing pharmacological therapy.
The increased measures in the affected hemisphere of both functional local segregation and global integration could result from the combination of overlapping mechanisms, including reactive neuroplastic changes seeking to maintain constant integration and segregation properties.
This reactive neuroplastic mechanism seeking to maintain constant integration and segregation properties seems to be more evident in the absence of antiepileptic treatment.

Vecchio F, Miraglia F, Marra C, Quaranta D, Vita MG, Bramanti P, Rossini PM.
Human brain networks in cognitive decline: a graph theoretical analysis of cortical connectivity from EEG data.
J Alzheimers Dis. 2014;41(1):113-127.

The aim of this study was to investigate the neuronal network characteristics in physiological and pathological brain aging. A database of 378 participants divided in three groups was analyzed: Alzheimer's disease (AD), mild cognitive impairment (MCI), and normal elderly (Nold) subjects. Through EEG recordings, cortical sources were evaluated by sLORETA software, while graph theory parameters (Characteristic Path Length λ, Clustering coefficient λ, and small-world network λ) were computed to the undirected and weighted networks, obtained by the lagged linear coherence evaluated by eLORETA software. EEG cortical sources from spectral analysis showed significant differences in delta, theta, and alpha 1 bands. Furthermore, the analysis of eLORETA cortical connectivity suggested that for the normalized Characteristic Path Length λ) the pattern differences between normal cognition and dementia were observed in the theta band (MCI subjects are find similar to healthy subjects), while for the normalized Clustering coefficient (λ) a significant increment was found for AD group in delta, theta, and alpha 1 bands; finally, the small world λ) parameter presented a significant interaction between AD and MCI groups showing a theta increase in MCI. The fact that AD patients respect the MCI subjects were significantly impaired in theta but not in alpha bands connectivity are in line with the hypothesis of an intermediate status of MCI between normal condition and overt dementia.

Vecchio F, Miraglia F, Valeriani L, Scarpellini MG, Bramanti P, Mecarelli O, Rossini PM.
Cortical Brain Connectivity and B-Type Natriuretic Peptide in Patients With Congestive Heart Failure.
Clin EEG Neurosci. 2014 Jul 3. [Epub ahead of print]

The brain has a high level of complexity and needs continuous oxygen supply. So it is clear that any pathological condition, or physiological (aging) change, in the cardiovascular system affects functioning of the central nervous system. We evaluated linear aspects of the relationship between the slowness of cortical rhythms, as revealed by the modulation of a graph connectivity parameter, and congestive heart failure (CHF), as a reflection of neurodegenerative processes. Eyes-closed resting electroencephalographic (EEG) data of 10 patients with CHF were recorded by 19 electrodes positioned according the international 10-20 system. Graph theory function (normalized characteristic path length λ was applied to the undirected and weighted networks obtained by lagged linear coherence evaluated by eLORETA software, therefore getting rid of volumetric propagation influences. The EEG frequency bands of interest were: delta (2-4 Hz), theta (4-8 Hz), alpha 1 (8-10.5 Hz), alpha 2 (10.5-13 Hz), beta 1 (13-20 Hz), beta 2 (20-30 Hz), and gamma (30-40 Hz). The analysis between B-type natriuretic peptide (BNP) values and λ showed positive correlation in delta, associated with a negative correlation in alpha 2 band. Namely, the higher the severity of the disease (as revealed by the BNP vales), the higher the λ in delta, and lower in alpha 2 band. Results suggest that delta and alpha λ indices are good markers of the severity of CHF.

Zappasodi F, Olejarczyk E, Marzetti L, Assenza G, Pizzella V, Tecchio F.
Fractal Dimension of EEG Activity Senses Neuronal Impairment in Acute Stroke.
PLoS One. 2014 Jun 26;9(6):e100199. doi: 10.1371/journal.pone.0100199. eCollection 2014.

The brain is a self-organizing system which displays self-similarities at different spatial and temporal scales. Thus, the complexity of its dynamics, associated to efficient processing and functional advantages, is expected to be captured by a measure of its scale-free (fractal) properties. Under the hypothesis that the fractal dimension (FD) of the electroencephalographic signal (EEG) is optimally sensitive to the neuronal dysfunction secondary to a brain lesion, we tested the FD's ability in assessing two key processes in acute stroke: the clinical impairment and the recovery prognosis. Resting EEG was collected in 36 patients 4-10 days after a unilateral ischemic stroke in the middle cerebral artery territory and 19 healthy controls. National Health Institute Stroke Scale (NIHss) was collected at T0 and 6 months later. Highuchi FD, its inter-hemispheric asymmetry (FDasy) and spectral band powers were calculated for EEG signals. FD was smaller in patients

than in controls (1.447±0.092 vs 1.525±0.105) and its reduction was paired to a worse acute clinical status. FD decrease was associated to alpha increase and beta decrease of oscillatory activity power. Larger FDasy in acute phase was paired to a worse clinical recovery at six months. FD in our patients captured the loss of complexity reflecting the global system dysfunction resulting from the structural damage. This decrease seems to reveal the intimate nature of structure-function unity, where the regional neural multi-scale self-similar activity is impaired by the anatomical lesion. This picture is coherent with neuronal activity complexity decrease paired to a reduced repertoire of functional abilities. FDasy result highlights the functional relevance of the balance between homologous brain structures' activities in stroke recovery.

Zito G, Luders E, Tomasevic L, Lupoi D, Toga AW, Thompson PM, Rossini PM, Filippi MM, Tecchio F.
Inter-hemispheric functional connectivity changes with corpus callosum morphology in multiple sclerosis.
Neuroscience. 2014 Apr 25;266: 47-55.

Multiple sclerosis (MS) affects myelin sheaths within the central nervous system, concurring to cause brain atrophy and neurodegeneration as well as gradual functional disconnections. To explore early signs of altered connectivity in MS from a structural and functional perspective, the morphology of corpus callosum (CC) was correlated with a dynamic inter-hemispheric connectivity index. Twenty mildly disabled patients affected by a relapsing-remitting (RR) form of MS (EDSS≤3.5) and 15 healthy subjects underwent structural MRI to measure CC thickness over 100 sections and electroencephalography to assess a spectral coherence index between primary regions devoted to hand control, at rest and during an isometric handgrip. In patients, an overall CC atrophy was associated with increased lesion load. A less efficacious inter-hemispheric coherence (IHCoh) during movement was associated with CC atrophy in sections interconnecting homologous primary motor areas (anterior mid-body). In healthy controls, less efficacious IHCoh at rest was associated with a thinner CC splenium. Our data suggest that in mildly disabled RR-MS patients a covert impairment may be detected in the correlation between the structural (CC thickness) and functional (IHCoh) measures of homologous networks, whereas these two counterparts do not yet differ individually from controls.

Alzetta R, Cesario A, Fini M.
Hyper-Longevity, A Late-Modern Paradigm for Understanding Longevity, Ageing and their Complexities in Western Developed Globalised Countries.
Curr Pharm Des. 2014;20(38):5921-5927.

If longevity is a biological and demographic indicator to determine human lifetime extension, hyper-longevity notion can represent a heuristic tool to better disentangle the complex bio-psycho-social implications of ageing and elderly in Western developed globalised countries. Departing from the assumption of a holistic approach to human condition understanding, it is possible to reveal the grounds and patterns of a multilayered and multidimensional structuring of longevity and ageing in our societies that would lead to a form of hyper-longevity. Socio-cultural processes, underlying hyper-longevity notion, rise the question of transition from modern/ late-modern societies to post-modern ones and it offers room for a cultural analysis of concepts, such as space time compression, digital capitalism, knowledge and mass information society. These are relevant ideas that can contribute to reshape and rethink the boundaries and traits of ageing experience in 21(st) century societies. To better catch the point emerging social category of Baby Boomers is presented and used to provide a concrete context related example on how hyper-longevity can better explain complex social evidences in many cultural respects and social domains. As a conclusive step some preliminary reflections, largely centered on the relation between Baby Boomers, hyper-longevity and bio-medical sciences are presented and discussed to provide a starting point for further future analyses within a trans and inter-disciplinary framework.

Anker SD, Coats AJ, Morley JE, Rosano G, Bernabei R, von Haehling S, Kalantar-Zadeh K.
Muscle wasting disease: a proposal for a new disease classification.
J Cachexia Sarcopenia Muscle. 2014 Mar;5(1):1-3.

Muscle wasting and cachexia are the ultimate consequence of aging and a variety of acute and chronic illnesses. Significant efforts are made by many stakeholders to develop effective therapies. An important aspect of successful therapeutic development research is a common nomenclature for effective communication between researchers and clinicians, to the public, and also with regulatory bodies. Despite several efforts to develop consensus definitions for cachexia and sarcopenia, including such new terms for muscle wasting as myopenia, a common conceptual approach and acceptable vocabulary and classification system are yet to be established. Notwithstanding the potential need to translate such disease definitions and terminologies into different languages, we advocate the use of the term "muscle wasting" as the unifying entity that represents the single most common disease process across a large spectrum of cachexia and in sarcopenia-associated disorders. In this paper, we outline a first proposal for the disease nomenclature and classification of "Muscle Wasting Diseases." This concept can be applied in acute and chronic disease settings. It is pertinent for wasting diseases, cachexia, and sarcopenia of any severity and due to any underlying illness. The concept of muscle wasting disease underscores the most common denominator of the underlying wasting processes, i.e., muscle wasting, without ignoring the advanced disease states that are also accompanied by fat tissue wasting. The term muscle wasting disease is easily understood by both the scientific community and the lay public. This may promote its general use and efforts to heighten education and awareness in the field.

Armani A, Cinti F, Marzolla V, Morgan J, Cranston GA, Antelmi A, Carpinelli G, Canese R, Pagotto U, Quarta C, Malorni W, Matarrese P, Marconi M, Fabbri A, Rosano G, Cinti S, Young MJ, Caprio M.
Mineralocorticoid receptor antagonism induces browning of white adipose tissue through impairment of autophagy and prevents adipocyte dysfunction in high-fat-diet-fed mice.
FASEB J. 2014 Aug;28(8):3745-3757.

The mineralocorticoid receptor (MR) controls adipocyte function, but its role in the conversion of white adipose tissue (WAT) into thermogenic fat has not been elucidated. We investigated responses to the MR antagonists spironolactone (spiro; 20 mg/kg/d) and drospirenone (DRSP; 6 mg/kg/d) in C57BL/6 mice fed a high-fat (HF) diet for 90 d. DRSP and spiro curbed HF diet-induced impairment in glucose tolerance, and prevented body weight gain and white fat expansion. Notably, either MR antagonist induced up-regulation of brown adipocyte-specific transcripts and markedly increased protein levels of uncoupling protein 1 (UCP1) in visceral and inguinal fat depots when compared with the HF diet group. Positron emission tomography and magnetic resonance spectroscopy confirmed acquisition of brown fat features in WAT. Interestingly, MR antagonists markedly reduced the autophagic rate both in murine preadipocytes in vitro (10(-5) M) and in WAT depots in vivo, with a concomitant increase in UCP1 protein expression. Moreover, the autophagy repressor bafilomycin A1 (10(-8) M) mimicked the effect of MR antagonists, increasing UCP1 protein expression in primary preadipocytes. Hence, we showed that adipocyte MR regulates brown remodeling of WAT through a modulation of autophagy. These results provide a rationale for the use of MR antagonists to prevent the adverse metabolic consequences of adipocyte dysfunction.

Armani A, Marzolla V, Rosano G, Caprio M.
Mineralocorticoid vs glucocorticoid receptors: solo players or team mates in the control of adi-

pogenesis?
Int J Obes (Lond). 2014 Dec;38(12):1580-1581.

Badagliacca R, Poscia R, Pezzuto B, Nocioni M, Mezzapesa M, Francone M, Giannetta E, Papa S, Gambardella C, Sciomer S, Volterrani M, Fedele F, Vizza CD.
Right ventricular remodeling in idiopathic pulmonary arterial hypertension: Adaptive versus maladaptive morphology.
J Heart Lung Transplant. 2014 Nov 8. [Epub ahead of print]

Although increased pulmonary pressure is caused by changes in the pulmonary vasculature, prognosis in idiopathic pulmonary arterial hypertension (IPAH) is strongly associated with right ventricular (RV) function. The aim of this study was to describe the best RV adaptive remodeling pattern to increased afterload in IPAH.
In 60 consecutive patients with IPAH, RV morphologic and functional features were evaluated by echocardiography and cardiac magnetic resonance imaging. To address the question of the best RV adaptation pattern, we divided the study population into two groups by the median value of RV mass/volume ratio (0.46) because this parameter allows the distinction between RV eccentric (≤0.46) and concentric hypertrophy (>0.46). The two groups were compared for RV remodeling and systolic function parameters, World Health Organization class, pulmonary hemodynamics, and 6-minute walk test.
Despite similar pulmonary vascular resistance, mean pulmonary pressure, and compliance, patients with eccentric hypertrophy had advanced World Health Organization class and worse 6-minute walk test, hemodynamics, RV remodeling, and systolic function parameters compared with patients with concentric hypertrophy. The group with concentric hypertrophy had higher RV to pulmonary arterial coupling compared with the group with eccentric hypertrophy (1.24 ± 0.26 vs 0.83 ± 0.33, p = 0.0001), indicating higher RV efficiency. A significant correlation was found between pulmonary vascular resistance and RV to pulmonary arterial coupling (r = -0.55, r2 = 0.31, p = 0.0001), with patients with RV mass/volume ratio > 0.46 at the higher part of the scatterplot, confirming more adequate RV function.
Concentric hypertrophy might represent a more favorable RV adaptive remodeling pattern to increased afterload in IPAH because it is associated with more suitable systolic function and mechanical efficiency.

Butler J, Fonarow GC, Zile MR, Lam CS, Roessig L, Schelbert EB, Shah SJ, Ahmed A, Bonow RO, Cleland JG, Cody RJ, Chioncel O, Collins SP, Dunnmon P, Filippatos G, Lefkowitz MP, Marti CN, McMurray JJ, Misselwitz F, Nodari S, O'Connor C, Pfeffer MA, Pieske B, Pitt B, Rosano G, Sabbah HN, Senni M, Solomon SD,
Stockbridge N, Teerlink JR, Georgiopoulou VV, Gheorghiade M.
Developing therapies for heart failure with preserved Ejection Fraction: current state and future directions.
JACC Heart Fail. 2014 Apr;2(2):97-112.

The burden of heart failure with preserved ejection fraction (HFpEF) is considerable and is projected to worsen. To date, there are no approved therapies available for reducing mortality or hospitalizations for these patients. The pathophysiology of HFpEF is complex and includes alterations in cardiac structure and function, systemic and pulmonary vascular abnormalities, end-organ involvement, and comorbidities. There remain major gaps in our understanding of HFpEF pathophysiology. To facilitate a discussion of how to proceed effectively in future with development of therapies for HFpEF, a meeting was facilitated by the Food and Drug Administration and included representatives from academia, industry, and regulatory agencies. This document summarizes the proceedings from this meeting.

Caminiti G, Cardaci V, Conti V, D'Antoni V, Murugesan J, Battaglia D, Volterrani M.

Right ventricular systolic dysfunction is related to exercise intolerance in patients with chronic obstructive pulmonary disease.
J Cardiopulm Rehabil Prev. 2014 Oct 30. [Epub ahead of print]

To evaluate the impact of right ventricular dysfunction on exercise tolerance and potential changes resulting from exercise training in patients with chronic obstructive pulmonary disease (COPD) undergoing pulmonary rehabilitation.
Subjects were 44 patients with a history of symptomatic (Global Initiative for Chronic Obstructive Lung Disease classes 2-4) COPD attending a 4-week aerobic exercise training program. Right ventricle dysfunction was evaluated by echocardiography at admission using tricuspid annular plane systolic excursion (TAPSE). Exercise tolerance was evaluated at admission and discharge using the 6-minute walk test (6MWT). Change in distance walked (Δ6MWT) was defined as the difference between 6MWT distance at discharge minus distance at admission. Patients were divided into 2 groups according to the presence of right ventricle dysfunction (TAPSE ≤16 mm).
Median age and left ventricular ejection fraction was 70.2 ± 5.2 years and 54.4 ± 9.1%, respectively. Of the 44 patients, 14 (31.8%) had TAPSE ≤16 mm. Baseline 6MWT distance was less in the group with TAPSE ≤16 mm compared with TAPSE >16 mm (110.2 ± 34 vs 185.7 ± 41, respectively; P = .02). After the training program, 6MWT distance increased in both groups, but there was less increase in the group with TAPSE ≤16 mm compared with TAPSE >16 mm (+24.3% vs +32.8%, respectively; P < .001). Tricuspid annular plane systolic excursion was significantly correlated to distance walked at the baseline 6MWT (r = 0.44; P = .002) and to Δ6MWT (r = .36; P = .006).
Tricuspid annular plane systolic excursion ≤16 mm was an indicator of decreased 6MWT distance at baseline and 6MWT distance change in COPD patients undergoing pulmonary rehabilitation. This relationship seems to be independent of pulmonary function.

Caminiti G, Iellamo F, Manzi V, Fossati C, Cioffi V, Punzo N, Murugesan J, Volterrani M, Rosano G.
Anabolic hormonal response to different exercise training intensities in men with chronic heart failure.
Int J Cardiol. 2014 Oct 20;176(3):1433-1434.

Caminiti G, Fossati C, Battaglia D, Volterrani M.
Effects of hormonal therapy in patients with heart failure.
Journal of Cardiology and Therapy. 2014;1(8):168-174.

Castagna C, Iellamo F, Impellizzeri FM, Manzi V.
Validity and reliability of the 45-15 test for aerobic fitness in young soccer players.
Int J Sports Physiol Perform. 2014 May;9(3):525-531.

The aim of this study was to examine the reliability and validity of a popular field test for aerobic fitness used in soccer (45-15) in Italy. Alternating progressive 45-s runs with 15 s passive recovery until exhaustion, the test considers peak speed (PS) as a reflection of maximal aerobic speed (MAS). The validity and reliability of the 45-15 was assessed in 18 young male soccer players (age 16.7 ± 1.8 y, body mass 70 ± 7.45 kg, height 177 ± 0.5 cm, 55.62 ± 5.56 mL · kg-1 ·min-1) submitted to laboratory testing for aerobic fitness and repeatedly to the 45-15. Results showed that 45-15 PS was significantly related to VO2max (r = .80, P < .001, 95%CI .47-.93) and MAS (r = .78, P = .001, 95%CI .43-.93). No significant bias between MAS 45-15 PS (P = .11) was found during the measurement-consistency study. Receiver-operating-characteristic (ROC) analysis showed that 45-15 PS was sensitive in detecting VO2max changes in subjects as revealed by area under the curve (.97; 95%CI .73-1). Players with peak 45-15 speed equal to or above 16.5 km/h (ie, ROC cutoff) may be considered to have good aerobic fitness. In light of this study's findings, the 45-15 test may be considered a reliable and valid test to evaluate meaningful information to direct generic aerobic training in soccer.

Colasanti T, Vomero M, Alessandri C, Barbati C, Maselli A, Camperio C, Conti F, Tinari A, Carlo-Stella C, Tuosto L, Benincasa D, Valesini G, Malorni W, Pierdominici M, Ortona E.
Role of alpha-synuclein in autophagy modulation of primary human T lymphocytes.
Cell Death Dis. 2014 May 29;5:e1265.

It has been demonstrated that α-synuclein can aggregate and contribute to the pathogenesis of some neurodegenerative diseases and it is capable of hindering autophagy in neuronal cells. Here, we investigated the implication of α-synuclein in the autophagy process in primary human T lymphocytes. We provide evidence that: (i) knocking down of the α-synuclein gene resulted in increased autophagy, (ii) autophagy induction by energy deprivation was associated with a significant decrease of α-synuclein levels, (iii) autophagy inhibition by 3-methyladenine or by ATG5 knocking down led to a significant increase of α-synuclein levels, and (iv) autophagy impairment, constitutive in T lymphocytes from patients with systemic lupus erythematosus, was associated with abnormal accumulation of α-synuclein aggregates. These results suggest that α-synuclein could be considered as an autophagy-related marker of peripheral blood lymphocytes, potentially suitable for use in the clinical practice.

de Boer RA, van der Velde AR, Mueller C, van Veldhuisen DJ, Anker SD, Peacock WF, Adams KF, Maisel A.
Galectin-3: a modifiable risk factor in heart failure.
Cardiovasc Drugs Ther. 2014 Jun;28(3):237-246.

Myocardial galectin-3 is upregulated upon cardiac stressors such as angiotensin II and pressure overload leading to cardiac remodeling and heart failure. The expression level of galectin-3 mirrors the progression and severity of heart failure and therefore, galectin-3 is being used as a biomarker for heart failure. However, as galectin-3 is causally involved in pathological myocardial fibrosis it has been suggested that galectin-3 also actively contributes to heart failure development. In this review we discuss how galectin-3 could be a target for therapy in heart failure. Currently, attempts are being made to target or inhibit galectin-3 using natural or pharmaceutical inhibitors with the aim to ameliorate heart failure. Available experimental evidence suggests that galectin-3 inhibition indeed may represent a novel tool to treat heart failure. A strong interaction with aldosterone, another strong pro-fibrotic factor, has been described. Clinical studies are needed to prove if galectin-3 may be used to install specific treatment regimens.

Del Bufalo A, Russo P, Milic M, Pristipino C, Fini M, Cesario A.
Systems biology and systems medicine: the technological tools of the system approaches to complexity.
Med chem. 2014;4:473-480.

Desarzens S, Liao WH, Mammi C, Caprio M, Faresse N.
Hsp90 blockers inhibit adipocyte differentiation and fat mass accumulation.
PLoS One. 2014 Apr 4;9(4):e94127.

Geldanamycin derivatives are benzoquinone ansamycin antibiotics that bind to Hsp90 and alter its function. The alteration of Hsp90 activity limits some cellular hormonal responses by inhibiting nuclear receptors activation. The nuclear receptors activity, such as PPARγ, the mineralocorticoid and glucocorticoid receptors (MR and GR) play a critical role in the conversion of preadipocytes to mature adipocytes. Given the importance of these nuclear receptors for adipogenesis, we investigated the effects of geldanamycin analogues (GA) on adipocyte differentiation and function. We found that early exposure of preadipocyte cells to GA inhibited their conversion into mature adipocytes by inhibiting the adipogenic transcriptional program and lipid droplets accumulation.

Furthermore, GA altered the adipokines secretion profile of mature adipocyte. The anti-adipogenic effect of GA was also confirmed in mice fed a high fat diet. Biochemical analysis revealed that anti-adipogenic effects of geldanamycin analogues may result from the simultaneous inhibition of MR, GR and PPARγ activity. Taken together, our observations lead us to propose Hsp90 as a potent target for drug development in the control of obesity and its related metabolic complications.

Di Cola G, Jacoangeli F, Jacoangeli F, Lombardo M, Iellamo F.
Cardiovascular disorders in anorexia nervosa and potential therapeutic targets.
Intern Emerg Med. 2014 Oct;9(7):717-721.

Anorexia nervosa (AN) is an eating disorder in which a distorted self-perception of body image and an excessive fear of gaining weight result in extreme restrictions in eating habits. AN may be divided into two types: a "binge-eating/purging type" during which the individual regularly engages in overeating and then purging behavior, and a "restricting type", in which she does not. AN is a serious medical problem in young people in Western societies. It is widely reported that patients with AN exhibit an enhanced mortality rate as compared with age-matched healthy subjects, which has been mainly ascribed to cardiac complications. At least one-third of all deaths in patients with anorexia nervosa are estimated to be due to cardiac causes, mainly sudden death. Cardiovascular complications of AN can be present in up to 80% of cases, and among them alterations in cardiac electrical activity, structure and hemodynamics have been reported as causes of morbidity and mortality. The objective of this brief review is to summarize current knowledge on the main cardiovascular complications of AN, their underlying mechanisms and the possible therapeutic approaches.

Ferraro E, Giammarioli AM, Chiandotto S, Spoletini I, Rosano G.
Exercise-induced skeletal muscle remodeling and metabolic adaptation: redox signaling and role of autophagy.
Antioxid Redox Signal. 2014 Jul 1;21(1):154-176.

Skeletal muscle is a highly plastic tissue. Exercise evokes signaling pathways that strongly modify myofiber metabolism and physiological and contractile properties of skeletal muscle. Regular physical activity is beneficial for health and is highly recommended for the prevention of several chronic conditions. In this review, we have focused our attention on the pathways that are known to mediate physical training-induced plasticity.
An important role for redox signaling has recently been proposed in exercise-mediated muscle remodeling and peroxisome proliferator-activated receptor γ (PPARγ) coactivator-1α (PGC-1α) activation. Still more currently, autophagy has also been found to be involved in metabolic adaptation to exercise.
Both redox signaling and autophagy are processes with ambivalent effects; they can be detrimental and beneficial, depending on their delicate balance. As such, understanding their role in the chain of events induced by exercise and leading to skeletal muscle remodeling is a very complicated matter. Moreover, the study of the signaling induced by exercise is made even more difficult by the fact that exercise can be performed with several different modalities, with this having different repercussions on adaptation.
Unraveling the complexity of the molecular signaling triggered by exercise on skeletal muscle is crucial in order to define the therapeutic potentiality of physical training and to identify new pharmacological compounds that are able to reproduce some beneficial effects of exercise. In evaluating the effect of new "exercise mimetics," it will also be necessary to take into account the involvement of reactive oxygen species, reactive nitrogen species, and autophagy and their controversial effects.

Fox K, Ford I, Steg PG, Tardif JC, Tendera M, Ferrari R; SIGNIFY Investigators (Vitale C).
Ivabradine in stable coronary artery disease without clinical heart failure.
N Engl J Med. 2014 Sep 18;371(12):1091-1099.

An elevated heart rate is an established marker of cardiovascular risk. Previous analyses have suggested that ivabradine, a heart-rate-reducing agent, may improve outcomes in patients with stable coronary artery disease, left ventricular dysfunction, and a heart rate of 70 beats per minute or more.
We conducted a randomized, double-blind, placebo-controlled trial of ivabradine, added to standard background therapy, in 19,102 patients who had both stable coronary artery disease without clinical heart failure and a heart rate of 70 beats per minute or more (including 12,049 patients with activity-limiting angina [class ≥II on the Canadian Cardiovascular Society scale, which ranges from I to IV, with higher classes indicating greater limitations on physical activity owing to angina]). We randomly assigned patients to placebo or ivabradine, at a dose of up to 10 mg twice daily, with the dose adjusted to achieve a target heart rate of 55 to 60 beats per minute. The primary end point was a composite of death from cardiovascular causes or nonfatal myocardial infarction. At 3 months, the mean (±SD) heart rate of the patients was 60.7±9.0 beats per minute in the ivabradine group versus 70.6±10.1 beats per minute in the placebo group. After a median follow-up of 27.8 months, there was no significant difference between the ivabradine group and the placebo group in the incidence of the primary end point (6.8% and 6.4%, respectively; hazard ratio, 1.08; 95% confidence interval, 0.96 to 1.20; P=0.20), nor were there significant differences in the incidences of death from cardiovascular causes and nonfatal myocardial infarction. Ivabradine was associated with an increase in the incidence of the primary end point among patients with activity-limiting angina but not among those without activity-limiting angina (P=0.02 for interaction). The incidence of bradycardia was higher with ivabradine than with placebo (18.0% vs. 2.3%, P<0.001).
Among patients who had stable coronary artery disease without clinical heart failure, the addition of ivabradine to standard background therapy to reduce the heart rate did not improve outcomes. (Funded by Servier; SIGNIFY Current Controlled Trials number, ISRCTN61576291.).

Francone M, Chimenti C, Galea N, Scopelliti F, Verardo R, Galea R, Carbone I, Catalano C, Fedele F, Frustaci A.
CMR sensitivity varies with clinical presentation and extent of cell necrosis in biopsy-proven acute myocarditis.
JACC Cardiovasc Imaging. 2014 Mar;7(3):254-263.

The aim of this study was to determine whether clinical presentation and type of cell death in acute myocarditis might contribute to cardiac magnetic resonance (CMR) sensitivity.
Growing evidence indicates CMR is the reference noninvasive tool for the diagnosis of acute myocarditis. However, factors affecting CMR sensitivity are still unclear.
We retrospectively evaluated 57 consecutive patients with a diagnosis of acute myocarditis made on the basis of clinical history (≤3 months) and endomyocardial biopsy evidence of lymphocytic infiltrates (≥14 infiltrating leukocytes/mm(2) at immunohistochemistry) in association with damage of the adjacent myocytes and absence or minimal evidence of myocardial fibrosis. CMR acquisition protocol included T2-weighted (edema), early (hyperemia), and late (fibrosis/necrosis) gadolinium enhancement sequences. Presence of ≥2 CMR criteria denoted myocarditis. Type of cell death was evaluated by using in situ ligation with hairpin probes.
Three clinical myocarditis patterns were recognized: infarct-like (pattern 1, n = 21), cardiomyopathic (pattern 2, n = 21), and arrhythmic (pattern 3, n = 15). Tissue edema was observed in 81% of pattern 1, 28% of pattern 2, and 27% of pattern 3. Early enhancement was evident in 71% of pattern 1, 67% of pattern 2, and 40% of pattern 3. Late gadolinium enhancement was documented in 71% of pattern 1, 57% of pattern 2, and 47% of pattern 3. CMR sensitivity was significantly higher in pattern 1 (80%) compared with pattern 2 (57%) and pattern 3 (40%) ($p < 0.05$). Cell necrosis was the prevalent mechanism of death in pattern 1 compared with pattern 2 ($p < 0.001$) and pattern 3 ($p < 0.05$), whereas apoptosis prevailed in pattern 2 ($p < 0.001$ vs. pattern 1 and $p < 0.05$ vs. pattern 3).
In acute myocarditis, CMR sensitivity is high for infarct-like, low for cardiomyopathic, and very low for arrhythmic clinical presentation; it correlates with the extent of cell necrosis-promoting expansion of interstitial space.

Ganesh SK, Chasman DI, Larson MG, Guo X, Verwoert G, Bis JC, Gu X, Smith AV, Yang ML, Zhang Y, Ehret G, Rose LM, Hwang SJ, Papanicolau GJ, Sijbrands EJ, Rice K, Eiriksdottir G, Pihur V, Ridker PM, Vasan RS, Newton-Cheh C; Global Blood Pressure Genetics Consortium, Raffel LJ, Amin N, Rotter JI, Liu K, Launer LJ, Xu M, Caulfield M, Morrison AC, Johnson AD, Vaidya D, Dehghan A, Li G, Bouchard C, Harris TB, Zhang H, Boerwinkle E, Siscovick DS, Gao W, Uitterlinden AG, Rivadeneira F, Hofman A, Willer CJ, Franco OH, Huo Y, Witteman JC, Munroe PB, Gudnason V, Palmas W, van Duijn C, Fornage M, Levy D, Psaty BM, Chakravarti A.
Effects of long-term averaging of quantitative blood pressure traits on the detection of genetic associations.
Am J Hum Genet. 2014 Jul 3;95(1):49-65.

Blood pressure (BP) is a heritable, quantitative trait with intraindividual variability and susceptibility to measurement error. Genetic studies of BP generally use single-visit measurements and thus cannot remove variability occurring over months or years. We leveraged the idea that averaging BP measured across time would improve phenotypic accuracy and thereby increase statistical power to detect genetic associations. We studied systolic BP (SBP), diastolic BP (DBP), mean arterial pressure (MAP), and pulse pressure (PP) averaged over multiple years in 46,629 individuals of European ancestry. We identified 39 trait-variant associations across 19 independent loci ($p < 5 \times 10(-8)$); five associations (in four loci) uniquely identified by our LTA analyses included those of SBP and MAP at 2p23 (rs1275988, near KCNK3), DBP at 2q11.2 (rs7599598, in FER1L5), and PP at 6p21 (rs10948071, near CRIP3) and 7p13 (rs2949837, near IGFBP3). Replication analyses conducted in cohorts with single-visit BP data showed positive replication of associations and a nominal association ($p < 0.05$). We estimated a 20% gain in statistical power with long-term average (LTA) as compared to single-visit BP association studies. Using LTA analysis, we identified genetic loci influencing BP. LTA might be one way of increasing the power of genetic associations for continuous traits in extant samples for other phenotypes that are measured serially over time.

Greene SJ, Shah AN, Butler J, Ambrosy AP, Anker SD, Chioncel O, Collins SP, Dinh W, Dunnmon PM, Fonarow GC, Lam CS, Mentz RJ, Pieske B, Roessig L, Rosano GM, Sato N, Vaduganathan M, Gheorghiade M.
Designing effective drug and device development programs for hospitalized heart failure: a proposal for pretrial registries.
Am Heart J. 2014 Aug;168(2):142-149.

Recent international phase III clinical trials of novel therapies for hospitalized heart failure (HHF) have failed to improve the unacceptably high postdischarge event rate. These large studies have demonstrated notable geographic and site-specific variation in patient profiles and enrollment. Possible contributors to the lack of success in HHF outcome trials include challenges in selecting clinical sites capable of (1) providing adequate numbers of appropriately selected patients and (2) properly executing the study protocol. We propose a "pretrial registry" as a novel tool for improving the efficiency and quality of international HHF trials by focusing on the selection and cultivation of high-quality sites. A pretrial registry may help assess a site's ability to achieve adequate enrollment of the target patient population, integrate protocol requirements into clinical workflow, and accomplish appropriate follow-up. Although such a process would be associated

with additional upfront resource investment, this appropriation may be modest in comparison with the downstream costs associated with maintenance of poorly performing sites, failed clinical trials, and the global health and economic burden of HHF. This review is based on discussions between scientists, clinical trialists, and regulatory representatives regarding methods for improving international HHF trials that took place at the United States Food and Drug Administration on January 12th, 2012.

Iellamo F, Manzi V, Caminiti G, Vitale C, Massaro M, Cerrito A, Rosano G, Volterrani M.
Validation of rate of perceived exertion-based exercise training in patients with heart failure: Insights from autonomic nervous system adaptations.
Int J Cardiol. 2014 Sep 20;176(2):394-398.

Exercise prescription in cardiac patients is based on heart rate (HR) response to exercise. How to prescribe long-term exercise training outside medically-supervised settings also considering changes in individual physical capacity over time is unknown. In this study we hypothesized that in patients with chronic heart failure (CHF) the session-rate of perceived exertion (RPE), a subjective-based training methodology,
provides autonomic and functional capacity changes superimposable to those observed with HR-based Training Impulses (TRIMPi) method.
Twenty patients with stable CHF were randomized to either aerobic continuous training (ACT) or aerobic interval training (AIT) for 12 weeks. For each TRIMPi-guided exercise session, the session-RPE was recorded. By this method, internal training load (TL) is quantified by multiplying the RPE of the whole training session, using the Borg CR10-scale, by its duration. Heart rate variability (HRV), and baroreflex sensitivity (BRS) were assessed at baseline and at 3 weeks intervals.
Significant correlations were found between TRIMPi and individual session-RPE, for both ACT and AIT (r=0.63 to 0.81), (P<0.05). The same occurred when ACT and AIT groups were pooled together (r=0.72; P<0.01). R-R interval, HRV and BRS were significantly and very highly correlated with weekly RPE-session (r(2) ranged from 0.77 to 0.97; P<0.001). A significant relationship between session-RPE and performance at the 6MWT was also found.
Session-RPE is an easy-to-use, inexpensive and valid method for exercise prescription and health maintenance, consistent with objective physiological indices of training, that could be used for long-term physical activity in patients with CHF.

Isidori AM, Corona G, Aversa A, Gianfrilli D, Jannini EA, Foresta C, Maggi M, Lenzi A; SIAMS-ED Study Group (Caprio M).
The SIAMS-ED Trial: A National, Independent, Multicentre Study on Cardiometabolic and Hormonal Impairment of Men with Erectile Dysfunction Treated with Vardenafil.
Int J Endocrinol. 2014;2014:858715. Epub 2014 May 15.

Increased cardiovascular risk has been associated with reduced response to proerectile drugs. The Italian Society of Andrology and Sexual Medicine (SIAMS) promoted an independent, multicenter study performed in 604 men (55 ± 12 yrs) suffering from erectile dysfunction (ED) to assess multiple health outcomes and response to 6-month vardenafil challenge in a real-life setting. Overall, 30.8% men had metabolic syndrome. Cardiovascular risk stratification revealed a greater number of ED subjects with moderate risk of a major adverse cardiovascular event than the general population (P < 0.01). Age-adjusted pulse pressure was positively correlated with ED severity and negatively with androgens and waist circumference (P < 0.01). A decline in total testosterone was observed with increasing arterial pulse pressure (P < 0.05), which was not accompanied by compensatory LH rise. Follow-up on 185 men treated with vardenafil in an nonrandomized, open, single-arm trial documented a significant rise in IIEF-5 (delta = 6.1 ± 4.8) that was maintained in men with high cardiovascular risk. Mild adverse events occurred in <5%, with no differences between cardiovascular risk classes. In summary, ED is a frequent symptom in patients with an elevated, but often unknown, risk of future cardiovascular events. Androgens predict vascular resistance in ED patients. Vardenafil's response and safety profile were preserved in subjects with higher cardiovascular risk.

Kotecha D, Holmes J, Krum H, Altman DG, Manzano L, Cleland JG, Lip GY, Coats AJ, Andersson B, Kirchhof P, von Lueder TG, Wedel H, Rosano G, Shibata MC, Rigby A, Flather MD; on behalf of the Beta-Blockers in Heart Failure Collaborative Group.
Efficacy of β blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis.
Lancet. 2014 Sep 2. [Epub ahead of print]

Atrial fibrillation and heart failure often coexist, causing substantial cardiovascular morbidity and mortality. β–blockers are indicated in patients with symptomatic heart failure with reduced ejection fraction; however, the efficacy of these drugs in patients with concomitant atrial fibrillation is uncertain. We therefore meta-analysed individual-patient data to assess the efficacy of β blockers in patients with heart failure and sinus rhythm compared with atrial fibrillation.
We extracted individual-patient data from ten randomised controlled trials of the comparison of β–blockers versus placebo in heart failure. The presence of sinus rhythm or atrial fibrillation was ascertained from the baseline electrocardiograph. The primary outcome was all-cause mortality. Analysis was by intention to treat. Outcome data were meta-analysed with an adjusted Cox proportional hazards regression. The study is registered with Clinicaltrials.gov, number NCT0083244, and PROSPERO, number CRD42014010012.
18,254 patients were assessed, and of these 13,946 (76%) had sinus rhythm and 3066 (17%) had atrial fibrillation at baseline. Crude death rates over a mean follow-up of 1·5 years (SD 1·1) were 16% (2237 of 13,945) in patients with sinus rhythm and 21% (633 of 3064) in patients with atrial fibrillation. β-blocker therapy led to a significant reduction in all-cause mortality in patients with sinus rhythm (hazard ratio 0·73, 0·67-0·80; p<0·001), but not in patients with atrial fibrillation (0·97, 0·83-1·14; p=0·73), with a significant p value for interaction of baseline rhythm (p=0·002). The lack of efficacy for the primary outcome was noted in all subgroups of atrial fibrillation, including age, sex, left ventricular ejection fraction, New York Heart Association class, heart rate, and baseline medical therapy.
Based on our findings, β–blockers should not be used preferentially over other rate-control medications and not regarded as standard therapy to improve prognosis in patients with concomitant heart failure and atrial fibrillation.
Funding: Menarini Farmaceutica Internazionale (administrative support grant).

Marzolla V, Armani A, Feraco A, De Martino MU, Fabbri A, Rosano G, Caprio M.
Mineralocorticoid receptor in adipocytes and macrophages: A promising target to fight metabolic syndrome.
Steroids. 2014 Dec;91:46-53.

Aldosterone is the primary ligand for the mineralocorticoid receptor (MR) and has been considered long time a "renal" hormone, acting at this site as a key regulator of plasma volume, electrolyte homeostasis and blood pressure. A new exciting era of MR biology began with the identification of MR in different non-epithelial tissues such as brain, heart, vessels, macrophages/monocytes, and adipose tissue. The distribution of MR in such a wide range of tissues has suggested novel and unexpected roles for MR, for example in energy metabolism and inflammation. An increasing body of evidence suggests a detrimental effect of aldosterone excess on the development of metabolic alterations. Disturbances in glucose metabolism due to inappropriate activation of MR are frequently observed in patients with primary aldosteronism as well as in obese subjects. MR antagonists have beneficial effects on glucose tolerance and metabolic parameters in experimental animals, whereas their role in humans remains unclear. The aim of this review is

to discuss the pathophysiology of MR activation in experimental models, particularly at the level of adipocytes and macrophages, to discuss novel and sometimes contrasting insights from emerging studies, and to highlight deficiencies in the field.

Mazzone P, Paoloni M, Mangone M, Santilli V, Insola A, Fini M, Scarnati E.
Unilateral deep brain stimulation of the pedunculopontine tegmental nucleus in idiopathic Parkinson's disease: effects on gait initiation and performance.
Gait Posture. 2014 Jul;40(3):357-362.

The pedunculopontine tegmental nucleus (PPTg) is a component of the locomotor mesencephalic area. In recent years it has been considered a new surgical site for deep brain stimulation (DBS) in movement disorders. Here, using objective kinematic and spatio-temporal gait analysis, we report the impact of low frequency (40 Hz) unilateral PPTg DBS in ten patients suffering from idiopathic Parkinson's disease with drug-resistant gait and axial disabilities. Patients were studied for gait initiation (GI) and steady-state level walking (LW) under residual drug therapy. In the LW study, a straight walking task was employed. Patients were compared with healthy age-matched controls. The analysis revealed that GI, cadence, stride length and left pelvic tilt range of motion (ROM) improved under stimulation. The duration of the S1 and S2 sub-phases of the anticipatory postural adjustment phase of GI was not affected by stimulation, however a significant improvement was observed in the S1 sub-phase in both the backward shift of centre of pressure and peak velocity. Speed during the swing phase, step width, stance duration, right pelvic tilt ROM phase, right and left hip flexion-extension ROM, and right and left knee ROM were not modified. Overall, the results show that unilateral PPTg DBS may affect GI and specific spatio-temporal and kinematic parameters during unconstrained walking on a straight trajectory, thus providing further support to the importance of the PPTg in the modulation of gait in neurodegenerative disorders.

Mentz RJ, Greene SJ, Ambrosy AP, Vaduganathan M, Subacius HP, Swedberg K, Maggioni AP, Nodari S, Ponikowski P, Anker SD, Butler J, Gheorghiade M.
Clinical profile and prognostic value of anemia at the time of admission and discharge among patients hospitalized for heart failure with reduced ejection fraction: findings from the EVEREST trial.
Circ Heart Fail. 2014 May;7(3):401-408.

Anemia has been associated with worse outcomes in patients with chronic heart failure (HF). We aimed to characterize the clinical profile and postdischarge outcomes of hospitalized HF patients with anemia at admission or discharge.
An analysis was performed on 3731 (90%) of 4133 hospitalized HF patients with ejection fraction ≤40% enrolled in the Efficacy of Vasopressin Antagonist in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial with baseline hemoglobin data, comparing the clinical characteristics and outcomes (all-cause mortality and cardiovascular mortality or HF hospitalization) of patients with and without anemia (hemoglobin <12 g/dL for women and <13 g/dL for men) on admission or discharge/day 7. Overall, 1277 patients (34%) were anemic at baseline, which persisted through discharge in 73% and resolved in 27%; 6% of patients without baseline anemia developed anemia by discharge or day 7. Patients with anemia were older, with lower blood pressure, and higher creatinine and natriuretic peptide levels compared with those without anemia (all P<0.05). After risk adjustment, anemia at discharge, but not admission, was independently associated with increased all-cause mortality (hazard ratio, 1.30; 95% confidence interval, 1.05-1.60; P=0.015; and hazard ratio, 0.94; 95% confidence interval, 0.76-1.15; P=0.53, respectively) and cardiovascular mortality plus HF hospitalization early postdischarge (≤100 days; hazard ratio 1.73; 95% confidence interval, 1.37-2.18; P<0.001; and hazard ratio, 0.92; 95% confidence interval, 0.73-1.16; P=0.47, respectively). Neither baseline nor discharge anemia was associated with long-term cardiovascular mortality plus HF hospitalization (>100 days) on adjusted analysis (both P>0.1).

Among hospitalized HF patients with reduced ejection fraction, modest anemia at discharge but not baseline was associated with increased all-cause mortality and short-term cardiovascular mortality plus HF hospitalization.

Mollace V, Muscoli C, Dagostino C, Giancotti LA, Gliozzi M, Sacco I, Visalli V, Gratteri S, Palma E, Malara N, Musolino V, Carresi C, Muscoli S, Vitale C, Salvemini D, Romeo F.
The effect of peroxynitrite decomposition catalyst MnTBAP on aldehyde dehydrogenase-2 nitration by organic nitrates: role in nitrate tolerance.
Pharmacol Res. 2014 Nov;89:29-35.

Bioconversion of glyceryl trinitrate (GTN) into nitric oxide (NO) by aldehyde dehydrogenase-2 (ALDH-2) is a crucial mechanism which drives vasodilatory and antiplatelet effect of organic nitrates in vitro and in vivo. Oxidative stress generated by overproduction of free radical species, mostly superoxide anions and NO-derived peroxynitrite, has been suggested to play a pivotal role in the development of nitrate tolerance, though the mechanism still remains unclear. Here we studied the free radical-dependent impairment of ALDH-2 in platelets as well as vascular tissues undergoing organic nitrate ester tolerance and potential benefit when using the selective peroxynitrite decomposition catalyst Mn(III) tetrakis (4-Benzoic acid) porphyrin (MnTBAP). Washed human platelets were made tolerant to nitrates via incubation with GTN for 4h. This was expressed by attenuation of platelet aggregation induced by thrombin (40U/mL), an effect accompanied by GTN-related induction of cGMP levels in platelets undergoing thrombin-induced aggregation. Both effects were associated to attenuated GTN-induced nitrite formation in platelets supernatants and to prominent nitration of ALDH-2, the GTN to NO metabolizing enzyme, suggesting that GTN tolerance was associated to reduced NO formation via impairment of ALDH-2. These effects were all antagonized by co-incubation of platelets with MnTBAP, which restored GTN-induced responses in tolerant platelets. Comparable effect was found under in in vivo settings. Indeed, MnTBAP (10mg/kg, i.p.) significantly restored the hypotensive effect of bolus injection of GTN in rats made tolerants to organic nitrates via chronic administration of isosorbide-5-mononitrate (IS-5-MN), thus confirming the role of peroxynitrite overproduction in the development of tolerance to vascular responses induced by organic nitrates. In conclusion, oxidative stress subsequent to prolonged use of organic nitrates, which occurs via nitration of ALDH-2, represents a key event in GTN tolerance, an effect counteracted both in vitro and in vivo by novel peroxynitrite decomposition catalyst.

Montagna C, Di Giacomo G, Rizza S, Cardaci S, Ferraro E, Grumati P, De Zio D, Maiani E, Muscoli C, Lauro F, Ilari S, Bernardini S, Cannata S, Gargioli C, Ciriolo MR, Cecconi F, Bonaldo P, Filomeni G.
S-nitrosoglutathione reductase deficiency-induced S-nitrosylation results in neuromuscular dysfunction.
Antioxid Redox Signal. 2014 Aug 1;21(4):570-587.

Nitric oxide (NO) production is implicated in muscle contraction, growth and atrophy, and in the onset of neuropathy. However, many aspects of the mechanism of action of NO are not yet clarified, mainly regarding its role in muscle wasting. Notably, whether NO production-associated neuromuscular atrophy depends on tyrosine nitration or S-nitrosothiols (SNOs) formation is still a matter of debate. Here, we aim at assessing this issue by characterizing the neuromuscular phenotype of S-nitrosoglutathione reductase-null (GSNOR-KO) mice that maintain the capability to produce NO, but are unable to reduce SNOs.
We demonstrate that, without any sign of protein nitration, young GSNOR-KO mice show neuromuscular atrophy due to loss of muscle mass, reduced fiber size, and neuropathic behavior. In particular, GSNOR-KO mice show a significant decrease in nerve axon number, with the myelin sheath appearing disorganized and reduced, leading to a dramatic development of a neuropa-

thic phenotype. Mitochondria appear fragmented and depolarized in GSNOR-KO myofibers and myotubes, conditions that are reverted by N-acetylcysteine treatment. Nevertheless, although atrogene transcription is induced, and bulk autophagy activated, no removal of damaged mitochondria is observed. These events, alongside basal increase of apoptotic markers, contribute to persistence of a neuropathic and myopathic state.
Our study provides the first evidence that GSNOR deficiency, which affects exclusively SNOs reduction without altering nitrotyrosine levels, results in a clinically relevant neuromuscular phenotype.
These findings provide novel insights into the involvement of GSNOR and S-nitrosylation in neuromuscular atrophy and neuropathic pain that are associated with pathological states; for example, diabetes and cancer.

McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR; PARADIGM-HF Investigators and Committees (Volterrani M)
Angiotensin-neprilysin inhibition versus enalapril in heart failure.
N Engl J Med. 2014 Sep 11;371(11):993-1004.

Clinical trials in heart failure have focused on the improvement in symptoms or decreases in the risk of death and other cardiovascular events. Little is known about the effect of drugs on the risk of clinical deterioration in surviving patients.
We compared the angiotensin-neprilysin inhibitor LCZ696 (400 mg daily) with the angiotensin-converting enzyme inhibitor enalapril (20 mg daily) in 8399 patients with heart failure and reduced ejection fraction in a double-blind trial. The analyses focused on prespecified measures of nonfatal clinical deterioration. In comparison with the enalapril group, fewer LCZ696-treated patients required intensification of medical treatment for heart failure (520 versus 604; hazard ratio, 0.84; 95% confidence interval, 0.74-0.94; P=0.003) or an emergency department visit for worsening heart failure (hazard ratio, 0.66; 95% confidence interval, 0.52-0.85; P=0.001). The patients in the LCZ696 group had 23% fewer hospitalizations for worsening heart failure (851 versus 1079; P<0.001) and were less likely to require intensive care (768 versus 879; 18% rate reduction, P=0.005), to receive intravenous positive inotropic agents (31% risk reduction, P<0.001), and to have implantation of a heart failure device or cardiac transplantation (22% risk reduction, P=0.07). The reduction in heart failure hospitalization with LCZ696 was evident within the first 30 days after randomization. Worsening of symptom scores in surviving patients was consistently more common in the enalapril group. LCZ696 led to an early and sustained reduction in biomarkers of myocardial wall stress and injury (N-terminal pro-B-type natriuretic peptide and troponin) versus enalapril.
Angiotensin-neprilysin inhibition prevents the clinical progression of surviving patients with heart failure more effectively than angiotensin-converting enzyme inhibition.

Muscoli C, Lauro F, D'Agostino C, Ilari S, Giancotti LA, Gliozzi M, Costa N, Carresi C, Musolino V, Casale F, Ventrice D, Oliverio E, Palma E, Nistico' S, Procopio A, Mollace V.
Olea Europea-derived phenolic products attenuate antinociceptive morphine tolerance: an innovative strategic approach to treat cancer pain.
J Biol Regul Homeost Agents. 2014 Jan-Mar;28(1):105-116.

Morphine and related opioid drugs are currently the major drugs for severe pain. Their clinical utility is limited in the management of severe cancer pain due to the rapid development of tolerance. Restoring opioid efficacy is therefore of great clinical importance. A great body of evidence suggests the key role of free radicals and posttranslational modulation in the development of tolerance to the analgesic activity of morphine. Epidemiological studies have shown a relationship between the Mediterranean diet and a reduced incidence of pathologies such as coronary heart disease and cancer. A central hallmark of this diet is the high consumption of virgin olive oil as the main source of fat which contains antioxidant components in the non-saponifiable fraction, including phenolic compounds absent in seed oils. Here, we show that in a rodent model of opiate tolerance, removal of the free radicals with phenolic compounds of olive oil such as hydroxytyrosol and oleuropein reinstates the analgesic action of morphine. Chronic injection of morphine in mice led to the development of tolerance and this was associated with increased nitrotyrosin and malondialdehyde (MDA) formation together with nitration and deactivation of MnSOD in the spinal cord. Removal of free radicals by hydroxytyrosol and oleuropein blocked morphine tolerance by inhibiting nitration and MDA formation and replacing the MnSOD activity. The phenolic fraction of virgin olive oil exerts antioxidant activities in vivo and free radicals generation occurring during chronic morphine administration play a crucial role in the development of opioid tolerance. Our data suggest novel therapeutic approach in the management of chronic cancer pain, in particular for those patients who require long-term opioid treatment for pain relief without development of tolerance.

Nasso G, Bonifazi R, Romano V, Bartolomucci F, Rosano G, Massari F, Fattouch K, Del Prete G, Riccioni G, Del Giglio M, Speziale G.
Three-year results of repaired barlow mitral valves via right minithoracotomy versus median sternotomy in a randomized trial.
Cardiology. 2014 Apr 5;128(2):97-105.

The aim of the study is to clarify whether the results of repair of a complex mitral lesion (Barlow valve) at the intermediate-term follow-up are independent of the mode of surgical access [minithoracotomy vs. median sternotomy (MS)].
In a prospective randomized study of mitral repair for Barlow disease using either a minimally invasive (MI) approach or MS, we achieved an average follow-up of 3 years (echocardiography, physical examination and quality of life). Mitral repair was achieved with polytetrafluoroethylene chordal implantation for both leaflets.
Both groups included 80 patients. Mechanical ventilation time and intensive care unit and hospital stay were shorter in the MI group (p = 0.01, p = 0.013 and p = 0.02, respectively). During the follow-up, 5 patients in each group (6.25%) displayed mild mitral regurgitation, while 2 patients in each group (2.5%) developed recurrent regurgitation graded as at least moderate/severe. The rate of mitral reoperation was 2.5% in the MI group and 1.25% in the MS group (p = 0.9). The overall follow-up mortality was 3.75% in both the MI and the MS groups.
The 3-year results of repair of Barlow valves were satisfactory irrespective of the approach used to repair the valve. The advantages of MI surgery can be achieved in patients with mitral Barlow disease without concerns over the durability of repair.

Onder G, Bonassi S, Abbatecola AM, Folino-Gallo P, Lapi F, Marchionni N, Pani L, Pecorelli S, Sancarlo D, Scuteri A, Trifirò G, Vitale C, Zuccaro SM, Bernabei R, Fini M; Geriatrics Working Group of the Italian Medicines Agency.
High prevalence of poor quality drug prescribing in older individuals: a nationwide report from the Italian Medicines Agency (AIFA).
J Gerontol A Biol Sci Med Sci. 2014 Apr;69(4):430-437.

Poor quality of drug prescribing in older persons is often associated with increased drug-related adverse events, hospitalization, and mortality. The present study describes a set of prescribing quality indicators developed by the Geriatrics Working Group of the Italian Medicines Agency (AIFA) and estimates their prevalence in the entire elderly (≥ 65 years) population in Italy.
We performed a cross-sectional study using 2011 data from the OsMed (Osservatorio dei Medicinali) database, which comprises all prescribed drugs that are reimbursed by the Italian National Healthcare System. Yearly prevalence of drug prescribing quality indicators in the Italian older population (n = 12,301,537) was determined.

Overall, 13 quality indicators addressing polypharmacy, adherence to treatment of chronic diseases, prescribing cascade, undertreatment, drug-drug interactions, and drugs to be avoided were identified. Polypharmacy was common, with more than 1.3 million individuals taking greater than or equal to 10 drugs (11.3% of the study population). The prevalence of low adherence and undertreatment was also elevated and increased with advancing age, with highest prevalence occurring in individuals aged 85 years and older. Prevalence was less than 3% for quality indicators assessing the prescribing cascade, drug-drug interactions, and drugs to be avoided.
These results confirm the high frequency of suboptimal drug prescribing in older adults, using a database that covers the whole Italian population. In general, this descriptive study may help in prioritizing strategies aimed at improving the quality of prescribing in elderly population.

Onder G, Vetrano DL, Cherubini A, Fini M, Mannucci PM, Marengoni A, Monaco A, Nobili A, Pecorelli S, Russo P, Vitale C, Bernabei R.
Prescription drug use among older adults in Italy: a country-wide perspective.
J Am Med Dir Assoc. 2014 Jul;15(7):531.e11-5.

In Italy, prescription drug costs represent approximately 17% of total public health expenditures. Older adults commonly use multiple drugs and, for this reason, this population is responsible for a large portion of drug-related costs. In 2012, public expenditure for pharmaceuticals in primary care exceeded 11 billion Euros (approximately 15.2 billion US $), and older adults aged 65 or older accounted for more than 60% of these costs. Recently, increased attention has been focused on studies aimed at monitoring drug use and evaluating the appropriateness of drug prescribing in older adults. In this article, we examined studies that assessed these issues in different settings at a national level. Specifically, results of surveys of prescription drug use in primary care (OsMED), hospital (GIFA, CRIME, and REPOSI) and long-term care (ULISSE and SHELTER) settings are reviewed. Overall, these studies showed that the quality of drug prescribing in older patients is far from optimal. This leads to an increased risk of negative health outcomes and increased health care costs. Data from these studies are valuable, not only to monitor drug use, but also to target interventions aimed at improving the quality of prescribing. Translating the findings of clinical research and monitoring programs will be challenging, but it will lead to quantifiable improvements in the quality of drug prescribing at a national level.

Pelliccia F, Greco C, Vitale C, Rosano G, Gaudio C, Kaski JC.
Takotsubo syndrome (stress cardiomyopathy): an intriguing clinical condition in search of its identity.
Am J Med. 2014 Aug;127(8):699-704.

Takotsubo syndrome is a relatively frequent clinical entity presenting typically as an acute coronary syndrome in the absence of obstructive coronary artery disease and characterized angiographically by transient left ventricular systolic dysfunction, sparing the basal segments of the left ventricle ("apical ballooning"). Takotsubo syndrome characteristically affects peri- or postmenopausal women, albeit recent series show that men also are at risk. Takotsubo syndrome is characteristically triggered by severe emotional or physical stress, which suggests a pathogenic role for increased sympathetic activity leading to myocardial perfusion abnormalities and ventricular dysfunction. The reasons why severe emotional and physical stress result in the development of takotsubo syndrome in certain individuals but not others is still a matter of speculation, but strongly suggests the existence of predisposing factors/mechanisms in certain subjects. The present article reviews the different factors that can play a role in the development of takotsubo syndrome in different patients. We propose that triggers (ie, emotional stressors, physical stressors, iatrogenic stressors, and neurologic triggers), pathogenic mechanisms (ie, increased catecholamine levels, coronary vasomotor abnormalities leading to myocardial ischemia), and predisposing factors (ie, cardiovascular risk factors, endothelial dysfunction, comorbidities) all interact in a complex fashion and possibly differently in different patients to cause takotsubo syndrome. Identifying these factors may help in preventing and managing the condition more effectively.

Pelliccia F, Patti G, Rosano G, Greco C, Gaudio C.
Efficacy and safety of eplerenone in the management of mild to moderate arterial hypertension: Systematic review and meta-analysis.
Int J Cardiol. 2014 11/15;177(1):219-228.

The role of eplerenone in arterial hypertension has been investigated only in small studies. To systematically assess the efficacy and tolerability of eplerenone in patients with mild to moderate arterial hypertension, we did a meta-analysis of controlled randomized trials.
We performed an electronic literature search of Medline, Pubmed, Scopus and Cochrane databases for studies published up to March 31, 2014. Randomized studies comparing eplerenone with placebo or other antihypertensive drugs for net reduction of systolic and diastolic blood pressures (SBP; DBP) from baseline and for incidence of adverse events were considered. Weighted mean differences (WMD) and odds ratios with 95% confidence interval were calculated for continuous and dichotomous data, respectively.
A total of 11 trials and 3566 patients were overall included. Compared to placebo, eplerenone significantly reduced either SBP [WMD -8.07, 95% CI -8.17 to -7.96 mm Hg, $p < 0.00001$] and DBP [WMD -4.08, -4.15 to -4.01 mm Hg, $p < 0.00001$]. In the overall comparison, reduction of both SBP and DBP with eplerenone was greater than other antihypertensive agents (WMD for SBP -1.50 mm Hg, $p < 0.0001$; WMD for DBP -0.54 mm Hg, $p < 0.00001$); this was essentially driven by a greater anti-hypertensive action vs enalapril and losartan for SBP and vs losartan for DBP. Rates of any adverse event were significantly higher with eplerenone than placebo (odds ratio 1.37, 95% CI 1.1 to 1.71; $p = 0.005$), whereas the occurrence of serious adverse events and hyperkalemia was similar. There was no difference between eplerenone and other antihypertensives in the frequency of any or serious adverse events, whereas hyperkalemia was more common with eplerenone (odds ratio 2.36, 95% CI 1.00 to 5.57; $p = 0.05$).
This study-level meta-analysis provides a robust evidence that eplerenone has a reassuring safety profile and is effective in lowering blood pressure in patients with mild-to-moderate hypertension; this effect is at least comparable to that of other anti-hypertensive agents.

Pelliccia F, Rosano GM.
Medical research could soon be jeopardized by new European Union data protection regulations.
Eur Heart J. 2014 Jun 14;35(23):1503-1504.

Pelliccia F, Rosano G, Marazzi G, Vitale C, Spoletini I, Franzoni F, Speziale G, Polacco M, Greco C, Gaudio C.
Pharmacodynamic effects of atorvastatin versus rosuvastatin in coronary artery disease patients with normal platelet reactivity while on dual antiplatelet therapy--the PEARL randomized cross-over study.
Eur J Pharmacol. 2014 Feb 15;725:18-22.

High platelet reactivity during co-administration of clopidogrel and a CYP3A4-metabolized statin (i.e. atorvastatin) can be lowered by switching to a non-CYP3A4-metabolized statin (i.e rosuvastatin). Aim of this study was to verify if atorvastatin and rosuvastatin have different pharmacodynamic effects also when platelet reactivity while on dual antiplatelet therapy (DAPT) is normal at baseline. A total of 122 stable coronary artery disease patients receiving DAPT (clopidogrel 75 mg plus aspirin 100mg) who had evidence of normal platelet reactivity after a 1-week statin wash-out entered the trial. Patients were randomly assigned to atorvastatin (40 mg day, n=61) or rosuvastatin (20mg day, n=61) for 30 days. After another 1-week wash-out to avoid any carryover effect, cross-over was performed, and patients were switched to the other drug which was con-

tinued for 30 days. Platelet reactivity (expressed as P2Y(12) reaction units (PRU) by the VerifyNow assay [Accumetrics, San Diego, California]) was measured after 1-week statin wash-out and at the end of each treatment period. High platelet reactivity was defined as a PRU value >235. After 30-day atorvastatin, platelet reactivity did not significantly change as compared with pre-treatment evaluation (119 ± 66 vs. 136 ± 59 PRU, NS), with 2 patients only showing a PRU>235. Similarly, after 30-day rosuvastatin, platelet reactivity was unchanged vs. baseline (135 ± 46 vs. 128 ± 62 PRU, NS), with PRU>235 occurring in 3 patients. Atorvastatin does not negatively affect DAPT as compared with rosuvastatin when is given to stable coronary artery disease patients with normal platelet reactivity while in statin wash-out.

Pelliccia F, Rosano G, Patti G, Volterrani M, Greco C, Gaudio C.
Efficacy and safety of mineralocorticoid receptors in mild to moderate arterial hypertension.
Int J Cardiol. 2014 Oct 24. [Epub ahead of print]

The mineralocorticoid receptor antagonists have been shown to have favourable safety and cost-effectiveness profiles across a broad range of clinical indications, including heart failure, primary aldosteronism and resistant hypertension. The clinical biology of the first aldosterone blocker, i.e. spironolactone, and its effects in several organ systems has been well elucidated from multiple studies. The range of adverse effects experienced with spironolactone has led to its modification and the consequent synthesis of eplerenone. Scientific evidence accumulated so far supports the role of eplerenone as first-choice drug in heart failure, with lower prevalence rates of sex-related adverse effects associated with eplerenone as compared to spironolactone. In Europe, eplerenone is currently marketed only in some countries and only with the indication of heart failure, whereas its clinical efficacy and safety in mild to moderate hypertension is said to be uncertain. A review of available scientific evidence, however, discloses that 11 randomized clinical trials assessing eplerenone in >3500 hypertensives have been reported so far. The results of these studies clearly show that eplerenone is an effective antihypertensive agent when used alone or in combination with other medications. In doses ranging from 25 to 100mg daily, eplerenone monotherapy results in a dose-dependent reduction in clinic blood pressure. As compared to placebo, eplerenone reduces significantly blood pressure from baseline. In general, 100mg daily eplerenone has a blood pressure lowering that is 50 to 75% that of spironolactone. Eplerenone results in a greater reduction in blood pressure as compared with losartan, and comparison between eplerenone and amlodipine shows that both treatments decrease systolic blood pressure to a similar extent but eplerenone is better tolerated. In conclusion, there is now evidence that eplerenone can play an important role in the treatment of mild to moderate arterial hypertension and therefore scientific experts and regulatory authorities should support its wider use in clinical practice worldwide.

Radke RM, Diller GP, Duck M, Orwat S, Hartmann D, Thum T, Baumgartner H.
Endothelial function in contemporary patients with repaired coarctation of aorta.
Heart. 2014 Nov 1;100(21):1696-1701.

Previous studies have suggested endothelial dysfunction in adult patients after repair of aortic coarctation (CoA). It has been proposed to play a key role in the pathogenesis of arterial hypertension in the absence of re-coarctation. We aimed to assess the presence of endothelial dysfunction, the number of endothelial progenitor cells (EPC), and the levels of proinflammatory cytokines associated with endothelial injury in contemporary patients after CoA repair.
For this prospective observational study, 20 CoA patients and 22 healthy controls were recruited. Digital reactive hyperaemia was measured by peripheral arterial tonometry. Flow cytometry was used to quantify EPCs, and a comprehensive panel of laboratory markers of endothelial dysfunction was measured.
Half the patients had known arterial hypertension requiring medical treatment. Indices of reactive hyperaemia showed no significant difference between CoA patients (1.96±0.32) and controlss (1.765±0.48) (p=0.82). Circulating EPCs, defined by the number of CD34(+), CD34(+)/KDR(+), CD34(+)/AC133(+), CD34(+)/AC133(+)/KDR(+) or CD34(+)/CD45(-) labelled cells were equally not significantly different between the groups. Furthermore, plasma levels of inflammatory mediators and markers of endothelial function (IL-6, IL-8, ICAM1 and VCAM1) were not significantly different between the groups, as were vascular endothelial growth factor levels (p>0.05, for all).
By contrast with earlier reports, no clinically significant difference in endothelial function between adult patients with coarctation repair and healthy controls could be demonstrated. Therefore, endothelial dysfunction may not necessarily be present in this population. Further studies are required to identify mechanisms and to develop strategies to avoid arterial hypertension in these patients.

Rosano G, Pelliccia F, Gaudio C, Coats AJ.
The challenge of performing effective medical research in the era of healthcare data protection.
Int J Cardiol. 2014 Dec 15;177(2):510-511.

Sancho M, Gortat A, Herrera AE, Andreu-Fernández V, Ferraro E, Cecconi F, Orzáez M, Pérez-Payá E.
Altered mitochondria morphology and cell metabolism in apaf1-deficient cells.
PLoS One. 2014 Jan 9;9(1):e84666.

Apaf1 (apoptotic protease activating factor 1) is the central component of the apoptosome, a multiprotein complex that activates procaspase-9 after cytochrome c release from the mitochondria in the intrinsic pathway of apoptosis. Other cellular roles, including a pro-survival role, have also been described for Apaf1, while the relative contribution of each function to cell death, but also to cell homeostatic conditions, remain to be clarified.
Here we examined the response to apoptosis induction of available embryonic fibroblasts from Apaf1 knockout mice (MEFS KO Apaf1). In the absence of Apaf1, cells showed mitochondria with an altered morphology that affects cytochrome c release and basal metabolic status.
We analysed mitochondrial features and cell death response to etoposide and ABT-737 in two different Apaf1-deficient MEFS, which differ in the immortalisation protocol. Unexpectedly, MEFS KO Apaf1 immortalised with the SV40 antigen (SV40IM-MEFS Apaf1) and those which spontaneously immortalised (SIM-MEFS Apaf1) respond differently to apoptotic stimuli, but both presented relevant differences at the mitochondria when compared to MEFS WT, indicating a role for Apaf1 at the mitochondria.

Santi D, Giannetta E, Isidori AM, Vitale C, Aversa A, Simoni M.
Therapy of endocrine disease: effects of chronic use of phosphodiesterase inhibitors on endothelial markers in type 2 diabetes mellitus: a meta-analysis.
Eur J Endocrinol. 2014 Oct 2. [Epub ahead of print]

Diabetes mellitus (DM) is associated to endothelial dysfunction, reducing nitric oxide (NO)-dependent vasodilation and increasing production of pro-inflammatory factors, leading to increased long-term cardiovascular risk. Since the effects of phosphodiesterase-5 inhibitors (PDE5i) on endothelial function have not been systematically investigated, we conducted a meta-analysis of available randomised clinical trials (RCTs).
A thorough search of the literature was carried out. Relevant studies were considered according to RCT study design, enrolment of men with Type 2 DM, chronic administration of PDE5i and evaluation of endothelial function through both hemodynamic and endothelial inflammation-related parameters.
15 studies fulfilled the eligibility criteria but only 6 RCTs met the inclusion criteria and were analysed for 476 diabetic men, 239 randomized to Sildenafil and 237 to placebo, respectively. Four

RCTs evaluated flow-mediated dilation (FMD), demonstrating a weighted mean increase of 2.19% (CI95%: 0.48-3.90). This result showed a high heterogeneity (I2:98%). Thus, a further sub-group meta-analysis was performed, excluding one study through funnel plot. This analysis confirmed a significant, Sildenafil-related FMD improvement. Sildenafil improved endothelin(ET)-1 and high sensitivity C-reactive protein of about -0.94pg/mL and -0.36mg/L, respectively, not reaching statistical significance (p=0.69 and p=0.22, respectively). Finally, Sildenafil administration significantly reduced interleukin-6 (IL-6) serum levels (-0.82 pg/mL; CI95%:-1.58 to -0.07).
This meta-analysis suggests a beneficial effect of chronic PDE5i administration on endothelial function. Chronic Sildenafil administration seems to improve hemodynamic (FMD), and serum pro-inflammatory makers (IL-6) in diabetic men. Larger studies are needed to confirm the effects of chronic PDE5i on endothelial function.

Savarese G, Dei Cas A, Rosano G, D'Amore C, Musella F, Mosca S, Reiner MF, Marchioli R, Trimarco B, Perrone-Filardi P.
Reduction of albumin urinary excretion is associated with reduced cardiovascular events in hypertensive and/or diabetic patients. A meta-regression analysis of 32 randomized trials.
Int J Cardiol. 2014 Mar 15;172(2):403-410.

The association between renal dysfunction and risk of cardiovascular (CV) events and mortality has been reported in several studies. However, it is unclear whether reduction in urinary albumin excretion (UAE) is associated with reduced risk of clinical events. Therefore, we sought to investigate, in a meta-regression analysis of randomized studies enrolling hypertensive and/or diabetic patients, whether changes in UAE are associated with changes in CV outcomes and all-cause mortality.
MEDLINE, ISI Web of Science, Cochrane Database and Scopus were searched for randomized trials enrolling more than 200 diabetic and/or hypertensive patients, reporting UAE at baseline and at end of follow-up and CV events [CV death, myocardial infarction (MI), and stroke], as well all-cause mortality.
Thirty-two trials enrolling 80,812 participants were included in analyses. Meta-regression analysis showed that each 10% reduction of UAE was significantly associated with 13% reduction of MI (Regression Coefficient [RC]:0.0055; 95% Confidence Interval [CI]:0.0014 to 0.0095; p=0.010), with 29% reduction of stroke (RC:0.0124; CI:0.0030 to 0.0218; p=0.013) and with 14% reduction of the composite outcome (CV death, MI, stroke)(RC:0.0059; CI:0.0027 to 0.0090; p=0.001), whereas not significantly associated with all-cause (RC:0.0028; CI:-0.0047 to 0.0103; p=0.486) and CV mortality (RC:0.0028; CI:-0.0047 to 0.0103; p=0.447). Results were mostly confirmed by sensitivity analysis. No heterogeneity or publication bias was detected.
Reduction in UAE is associated with reduced risk of MI and stroke in diabetic and/or hypertensive patients. These findings suggest that UAE changes may represent a valuable intermediate endpoint for CV risk evaluation in clinical practice.

Savarese G, Rosano GMC, Parente A, D'Amore C, Reiner MF, Camici GG, Trimarco B, Perrone-Filardi P.
Reduction of C-reactive protein is not associated with reduced cardiovascular risk and mortality in patients treated with statins. A meta-analysis of 22 randomized trials.
Int J Cardiol. 2014 11/15;177(1):152-160.

The association between C-reactive protein (CRP) levels and risk of cardiovascular (CV) events has been reported in several studies. However, it is unclear whether a reduction in CRP is associated with a reduction in risk of clinical events. Therefore we sought to investigate, in a meta-regression analysis of randomized studies enrolling patients treated by statins, whether changes in CRP are associated with changes in risk of CV events or overall survival.
Randomized trials enrolling patients treated by statins, reporting CRP at baseline and at end of follow-up, CV events [myocardial infarction (MI) and stroke], CV and all-cause mortality were selected.
Twenty-two trials enrolling 54,213 participants were included in the analysis. Meta-analysis showed that active treatment significantly reduced risk of all-cause death by 8%, myocardial infarction by 11%, stroke by 10.3% and the composite outcome (including CV death, MI and stroke) by 8%, whereas risks of CV mortality was not significantly reduced. Meta-regression analysis revealed that reduction in CRP levels was significantly associated only with the reduction of MI, whereas no relationship was identified between changes in CRP and risk of stroke, CV and all-cause mortality, and the composite outcome.
These findings demonstrate that statin-induced changes in CRP do not correlate with major CV events apart from the risk of MI nor with overall survival in high-risk patients. These data suggest that although CRP may be a surrogate marker for coronary risk, it should not be used for predicting the effectiveness of statin therapy.

Scuteri A, Cunha PG, Rosei EA, Badariere J, Bekaert S, Cockcroft JR, Cotter J, Cucca F, De Buyzere ML, De Mayer T, Ferrucci L, Franco O, Gale N, Gillebert TC, Langlois M, Laucevicius A, Laurent S, Mattace Raso FU, Morrell CH, Muiesan ML, Munnery MM, Navickas R, Oliveira P, Orru' M, Pilia MG, Rietzschel ER, Ryliskyte L, Salvetti M, Schlessinger D, Sousa N, Stefanadis C, Strait J, Van Daele CL, Villa I, Vlachopoulos C, Witteman J, Xaplanteris P, Nilsson P, Lakatta EG; For the MARE Consortium.
Arterial stiffness and influences of the metabolic syndrome: a cross-countries study.
Atherosclerosis. 2014 Jan 30;233(2):654-660.

Specific clusters of metabolic syndrome (MetS) components impact differentially on arterial stiffness, indexed as pulse wave velocity (PWV). Of note, in several population-based studies participating in the MARE (Metabolic syndrome and Arteries REsearch) Consortium the occurrence of specific clusters of MetS differed markedly across Europe and the US. The aim of the present study was to investigate whether specific clusters of MetS are consistently associated with stiffer arteries in different populations. We studied 20,570 subjects from 9 cohorts representing 8 different European countries and the US participating in the MARE Consortium. MetS was defined in accordance with NCEP ATPIII criteria as the simultaneous alteration in ≥3 of the 5 components: abdominal obesity (W), high triglycerides (T), low HDL cholesterol (H), elevated blood pressure (B), and elevated fasting glucose (G). PWV measured in each cohort was "normalized" to account for different acquisition methods. MetS had an overall prevalence of 24.2% (4985 subjects). MetS accelerated the age-associated increase in PWV levels at any age, and similarly in men and women. MetS clusters TBW, GBW, and GTBW are consistently associated with significantly stiffer arteries to an extent similar or greater than observed in subjects with alteration in all the five MetS components--even after controlling for age, sex, smoking, cholesterol levels, and diabetes mellitus--in all the MARE cohorts. In conclusion, different component clusters of MetS showed varying associations with arterial stiffness (PWV).

Scuteri A, Laurent S, Cucca F, Cockcroft J, Cunha PG, Mañas LR, Raso FU, Muiesan ML, Ryliškyte L, Rietzschel E, Strait J, Vlachopoulos C, Völzke H, Lakatta EG, Nilsson PM; for the Metabolic Syndrome and Arteries Research (MARE) Consortium.
Metabolic syndrome across Europe: different clusters of risk factors.
Eur J Prev Cardiol. 2014 Mar 19. [Epub ahead of print]

Metabolic syndrome (MetS) remains a controversial entity. Specific clusters of MetS components - rather than MetS per se - are associated with accelerated arterial ageing and with cardiovascular (CV) events. To investigate whether the distribution of clusters of MetS components differed cross-culturally, we studied 34,821 subjects from 12 cohorts from 10 European countries and one cohort from the USA in the MARE (Metabolic syndrome and Arteries REsearch) Consortium.

In accordance with the ATP III criteria, MetS was defined as an alteration three or more of the following five components: elevated glucose (G), fasting glucose ≥110 mg/dl; low HDL cholesterol, <40mg/dl for men or <50 mg/dl for women; high triglycerides (T), ≥150 mg/dl; elevated blood pressure (B), ≥130/≥85 mmHg; abdominal obesity (W), waist circumference >102 cm for men or >88 cm for women.
MetS had a 24.3% prevalence (8468 subjects: 23.9% in men vs. 24.6% in women, $p < 0.001$) with an age-associated increase in its prevalence in all the cohorts. The age-adjusted prevalence of the clusters of MetS components previously associated with greater arterial and CV burden differed across countries ($p < 0.0001$) and in men and women ($p < 0.0001$). In details, the cluster TBW was observed in 12% of the subjects with MetS, but was far more common in the cohorts from the UK (32.3%), Sardinia in Italy (19.6%), and Germany (18.5%) and less prevalent in the cohorts from Sweden (1.2%), Spain (2.6%), and the USA (2.5%). The cluster GBW accounted for 12.7% of subjects with MetS with higher occurrence in Southern Europe (Italy, Spain, and Portugal: 31.4, 18.4, and 17.1% respectively) and in Belgium (20.4%), than in Northern Europe (Germany, Sweden, and Lithuania: 7.6, 9.4, and 9.6% respectively).
The analysis of the distribution of MetS suggested that what follows under the common definition of MetS is not a unique entity rather a constellation of cluster of MetS components, likely selectively risky for CV disease, whose occurrence differs across countries.

Scuteri A, Morrell CH, Orrù M, Strait JB, Tarasov KV, Ferreli LA, Loi F, Pilia MG, Delitala A, Spurgeon H, Najjar SS, AlGhatrif M, Lakatta EG.
Longitudinal perspective on the conundrum of central arterial stiffness, blood pressure, and aging.
Hypertension. 2014 Dec;64(6):1219-1227.

The age-associated increase in arterial stiffness has long been considered to parallel or to cause the age-associated increase in blood pressure (BP). Yet, the rates at which pulse wave velocity (PWV), a measure of arterial stiffness, and BP trajectories change over time within individuals who differ by age and sex have not been assessed and compared. This study determined the evolution of BP and aortic PWV trajectories during a 9.4-year follow-up in >4000 community-dwelling men and women of 20 to 100 years of age at entry into the SardiNIA Study. Linear mixed effects model analyses revealed that PWV accelerates with time during the observation period, at about the same rate over the entire age range in both men and women. In men, the longitudinal rate at which BP changed over time, however, did not generally parallel that of PWV acceleration: at ages>40 years the rates of change in systolic BP (SBP) and pulse pressure (PP) increase plateaued and then declined so that SBP, itself, also declined at older ages, whereas PP plateaued. In women, SBP, diastolic BP, and mean BP increased at constant rates across all ages, producing an increasing rate of increase in PP. Therefore, increased aortic stiffness is implicated in the age-associated increase in SBP and PP. These findings indicate that PWV is not a surrogate for BP and that arterial properties other than arterial wall stiffness that vary by age and sex also modulate the BP trajectories during aging and lead to the dissociation of PWV, PP, and SBP trajectories in men.

Scuteri A, Wang H.
Pulse wave velocity as a marker of cognitive impairment in the elderly.
J Alzheimers Dis. 2014 Jan 1;42(0):S401-10.

Carotid-femoral pulse wave velocity (PWV), an index of large artery stiffness, is a good proxy of arterial aging and also an independent marker of cardiovascular disease. A consistently growing number of studies has shown a significant inverse association of arterial aging and cognitive function: the greater the PWV, the lower the cognitive performance (and the greater its decline over time)-regardless of heterogeneity in study populations, sample size, and measure of cognitive functions adopted in each study. Therefore the epidemiological evidence and the biological plausibility require adoption of strategies to foster the routine measurement of PWV and cognitive function measurements in each and every older subject, particularly those at higher cardiovascular risk. Consistently, limited available healthcare resources should be progressively shifted from a sterile differential diagnosis between Alzheimer-type and vascular dementia to interventions aimed to reduce PWV and, thus, to prevent dementia before its onset or to decrease its rate of progression.

Shewan LG, Rosano G, Henein M, Coats AJS.
A statement on ethical standards in publishing scientific articles in the international journal of cardiology family of journals.
Int J Cardiol. 2014 1/1;170(3):253-254.

Spoletini I, Vitale C, Pelliccia F, Fossati C, Rosano GM.
Androgens and cardiovascular disease in postmenopausal women: a systematic review.
Climacteric. 2014 Dec;17(6):625-634.

Androgens play a pivotal role in cardiovascular function and their effects differ between men and women. In postmenopausal women, testosterone replacement within physiological levels is associated with overall well-being. However, a definitive explanation as to how androgens have an impact on cardiovascular health in postmenopausal women and whether they may be used for cardiovascular treatment has yet to be established. With these aims, a systematic review of the existing studies on the link between androgens and cardiovascular disease and the effects of testosterone therapy on cardiovascular outcomes in postmenopausal women has been conducted. The few existing studies on cardiovascular outcomes in postmenopausal women indicate no effect or a deleterious effect of increasing androgens and increased cardiovascular risk. However, there is evidence of a favorable effect of androgens on surrogate cardiovascular markers in postmenopausal women, such as high density lipoprotein cholesterol, total cholesterol, body fat mass and triglycerides. Further studies are therefore needed to clarify the impact of therapy with androgens on cardiovascular health in postmenopausal women. The cardiovascular effect of testosterone or methyltestosterone with or without concomitant estrogens needs to be elucidated.

Tassone EJ, Perticone M, Sciacqua A, Mafrici SF, Settino C, Malara N, Mollace V, Sesti G, Perticone F.
Low dose of acetylsalicylic acid and oxidative stress-mediated endothelial dysfunction in diabetes: a short-term evaluation.
Acta Diabetol. 2014 Aug 6. [Epub ahead of print]

Current guidelines suggest the use of low doses of acetylsalicylic acid (ASA) for patients with diabetes mellitus (DM) in primary prevention. However, the evidences demonstrating the beneficial effect of ASA in primary prevention are conflicting. In this pilot study, we evaluated in a group of diabetic patients, in primary prevention, the impact of ASA treatment on oxidative stress and vascular function. We enrolled 22 newly diagnosed diabetic patients, without any previous clinical evidence of cardiovascular disease, to receive, in primary prevention, ASA (100 mg/daily). We tested, in basal condition, after 4 weeks of ASA administration and after 4 weeks of pharmacological washout, the impact of ASA treatment on endothelial function, assessed by a semipletysmographic method, measuring the main oxidative stress parameters related to it. As expected, after 4 weeks of treatment, ASA induced a significant reduction of plasma thromboxane-A2, as a consequence of cyclooxygenase-1 inhibition. By contrast, ASA significantly increased the plasma and urine 8-iso-PGF2, a well-known prothrombotic molecule, parallel to an increase of plasma NOX2 levels. The enhancement of this oxidative pathway is associated with a significant impairment of endothelial vasodilation, assessed by reactive hyperemia index (RHI). The pharmacological washout reverted all parameters to basal condition. Our findings suggest that ASA utilization

for primary prevention in diabetic patients causes a significant increase of oxidative stress burden impairing the vascular function. Present data, if confirmed on a larger population, could permanently discourage the use of the ASA for the primary prevention in patients with DM.

Terracciano A, Scuteri A, Strait J, Sutin AR, Meirelles O, Marongiu M, Orru M, Pilia MG, Ferrucci L, Cucca F, Schlessinger D, Lakatta E.
Are personality traits associated with white-coat and masked hypertension?
J Hypertens. 2014 Oct;32(10):1987-1992.

Anxiety and other psychological dispositions are thought to be associated with blood pressure. This study tests whether personality traits have long-term associations with masked and white-coat effects.
A community-based sample of 2838 adults from Sardinia (Italy) completed the Revised NEO Personality Inventory, and 7 years later, blood pressure was assessed in the clinic and with ambulatory monitoring. Logistic regressions were used to test whether anxiety, neuroticism, extraversion, openness, agreeableness, and conscientiousness predicted the white-coat and masked hypertension phenomena. Age, sex, and antihypertensive medication use were tested as moderators.
Significant interactions were found between personality traits and antihypertensive medications in predicting masked and white-coat effects. Only among those taking antihypertensive medication, higher anxiety was associated with a higher risk of pseudo-resistant hypertension due to white-coat effect (odds ratio 1.39, 95% confidence interval 1.01-1.91) and higher conscientiousness was associated with a lower risk of masked uncontrolled hypertension (odds ratio 0.70, 95% confidence interval 0.49-0.99). There were no significant interactions with age or sex.
Among those on antihypertensive medications, anxious individuals were more likely to have pseudo-resistant hypertension due to white-coat effect and less conscientious individuals were at increased risk of masked uncontrolled hypertension. Particularly among anxious and less conscientious individuals, ambulatory monitoring may improve the tailoring of pharmacological treatments.

Terracciano A, Strait J, Scuteri A, Meirelles O, Sutin AR, Tarasov K, Ding J, Marongiu M, Orru M, Pilia MG, Cucca F, Lakatta E, Schlessinger D.
Personality traits and circadian blood pressure patterns: a 7-year prospective study.
Psychosom Med. 2014 Apr;76(3):237-243.

A nighttime dip in blood pressure is associated with decreased risk of cardiovascular morbidity and mortality. We examined whether personality traits predict nighttime dipping blood pressure. A community-based sample of 2848 adults from Sardinia (Italy) completed the Revised NEO Personality Inventory and 7 years later were examined with 24-hour ambulatory blood pressure monitoring. The primary analyses examined the associations of personality traits with continuous and categorical measures of mean arterial, systolic, and diastolic blood pressure nighttime dipping.
Agreeableness and conscientiousness were associated with more nocturnal blood pressure dipping (β= .05 [p = .025] and β= .07 [p < .001], respectively) and lower systolic blood pressure at night (β= -.05 [p = .018] and β= -.03 [p = .072], respectively). Nondippers were particularly more impulsive (p = .009), less trusting (p = .004), and less self-disciplined (p = .001), but there was no significant association between nocturnal dipping blood pressure and trait anxiety (p = .78) or depression (p = .59). The associations were stronger when comparing extreme dippers (nighttime drop ≥ 20%) to reverse dippers (nighttime increase in blood pressure). Indeed, scoring 1 standard deviation higher on conscientiousness was associated with approximately 40% reduced risk of reverse dipping (odds ratio = 1.43, confidence interval = 1.08-1.91).
We found evidence that reduced nighttime blood pressure dipping is associated with antagonism and impulsivity-related traits but not with measures of emotional vulnerability. The strongest associations were found with conscientiousness, a trait that may have a broad impact on cardiovascular health.

Amatore D, Sgarbanti R, Aquilano K, Baldelli S, Limongi D, Civitelli L, Nencioni L, Garaci E, Ciriolo MR, Palamara AT.
Influenza virus replication in lung epithelial cells depends on redox-sensitive pathways activated by NOX4-derived ROS.
Cell Microbiol. 2014 Aug 26 [Epubahead of print]

An overproduction of reactive oxygen species (ROS) mediated by NADPH oxidase 2 (NOX2) has been related to airway inflammation typical of influenza infection. Virus-induced oxidative stress may also control viral replication, but the mechanisms underlying ROS production, as well as their role in activating intracellular pathways and specific steps of viral life cycle under redox control have to be fully elucidated. In this study, we demonstrate that influenza A virus infection of lung epithelial cells causes a significant ROS increase that depends mainly on NOX4, which is upregulated at both mRNA and protein levels, while the expression of NOX2, the primary source of ROS in inflammatory cells, is downregulated. Inhibition of NOX4 activity through chemical inhibitors or RNA silencing blocks the ROS increase, prevents MAPK phosphorylation, and inhibits viral ribonucleoprotein (vRNP) nuclear export and viral release. Overall these data, obtained in cell lines and primary culture, describe a so far unrecognized role for NOX4-derived ROS in activating redox-regulated intracellular pathways during influenza virus infection and highlight their relevance in controlling specific steps of viral replication in epithelial cells. Pharmacological modulation of NOX4-mediated ROS production may open the way for new therapeutic approaches to fighting influenza by targeting cell and not the virus.

Aquilano K, Baldelli S, Ciriolo MR.
Nuclear recruitment of neuronal nitric-oxide synthase by β-syntrophin is crucial for the induction of mitochondrial biogenesis.
J Biol Chem. 2014 Jan 3;289(1):365-378.

Neuronal nitric-oxide synthase (nNOS) has various splicing variants and different subcellular localizations. nNOS can be found also in the nucleus; however, its exact role in this compartment is still not completely defined. In this report, we demonstrate that the PDZ domain allows the recruitment of nNOS to nuclei, thus favoring local NO production, nuclear protein S-nitrosylation, and induction of mitochondrial biogenesis. In particular, overexpression of PDZ-containing nNOS (nNOSα) increases S-nitrosylated CREB with consequent augmented binding on cAMP response element consensus sequence on peroxisome proliferator-activated receptor γ co-activator (PGC)-1 promoter. The resulting PGC-1α induction is accompanied by the expression of mitochondrial genes (e.g., TFAM, MtCO1) and increased mitochondrial mass. Importantly, full active nNOS lacking PDZ domain (nNOSβ) does not localize in nuclei and fails in inducing the expression of PGC-1α. Moreover, we substantiate that the mitochondrial biogenesis normally accompanying myogenesis is associated with nuclear translocation of nNOS. We demonstrate that α-Syntrophin, which resides in nuclei of myocytes, functions as the upstream mediator of nuclear nNOS translocation and nNOS-dependent mitochondrial biogenesis. Overall, our results indicate that altered nNOS splicing and nuclear localization could be contributing factors in human muscular diseases associated with mitochondrial impairment.

Baldelli S, Aquilano K, Ciriolo MR.
PGC-1α buffers ROS-mediated removal of mitochondria during myogenesis.
Cell Death Dis. 2014 Nov 6;5:e1515.

Mitochondrial biogenesis and mitophagy are recognized as critical processes underlying mitochondrial homeostasis. However, the molecular pathway(s) coordinating the balance between

these cellular programs is still poorly investigated. Here, we show an induction of the nuclear and mitochondrial peroxisome proliferator-activated receptor gamma, coactivator 1 alpha (PGC-1α) during myogenesis, which in turn co-activates the transcription of nuclear and mtDNA-encoded mitochondrial genes. We demonstrate that PGC-1α also buffers oxidative stress occurring during differentiation by promoting the expression of antioxidant enzymes. Indeed, by downregulating PGC-1α, we observed an impairment of antioxidants expression, which was accompanied by a significant reactive oxygen species (ROS) burst and increase of oxidative damage to proteins. In parallel, we detected a decrease of mitochondrial mass and function as well as increased mitophagy through the ROS/FOXO1 pathway. Upon PGC-1α downregulation, we found ROS-dependent nuclear translocation of FOXO1 and transcription of its downstream targets including mitophagic genes such as LC3 and PINK1. Such events were significantly reverted after treatment with the antioxidant Trolox, suggesting that PGC-1α assures mitochondrial integrity by indirectly buffering ROS. Finally, the lack of PGC-1α gave rise to a decrease in MYOG and a strong induction of atrophy-related ubiquitin ligases FBXO32 (FBXO32), indicative of a degenerative process. Overall, our results reveal that in myotubes, PGC-1α takes center place in mitochondrial homeostasis during differentiation because of its ability to avoid ROS-mediated removal of mitochondria.

Baldelli S, Lettieri Barbato D, Tatulli G, Aquilano K, Ciriolo MR.
The role of nNOS and PGC-1α in skeletal muscle cells.
J Cell Sci. 2014 Nov 15;127(22):4813-4820.

Neuronal nitric oxide synthase (nNOS) and peroxisome proliferator activated receptor γ co-activator 1α (PGC-1α) are two fundamental factors involved in the regulation of skeletal muscle cell metabolism. nNOS exists as several alternatively spliced variants, each having a specific pattern of subcellular localisation. Nitric oxide (NO) functions as a second messenger in signal transduction pathways that lead to the expression of metabolic genes involved in oxidative metabolism, vasodilatation and skeletal muscle contraction. PGC-1α is a transcriptional coactivator and represents a master regulator of mitochondrial biogenesis by promoting the transcription of mitochondrial genes. PGC-1α can be induced during physical exercise, and it plays a key role in coordinating the oxidation of intracellular fatty acids with mitochondrial remodelling. Several lines of evidence demonstrate that NO could act as a key regulator of PGC-1α expression; however, the link between nNOS and PGC-1α in skeletal muscle remains only poorly understood. In this Commentary, we review important metabolic pathways that are governed by nNOS and PGC-1α, and aim to highlight how they might intersect and cooperatively regulate skeletal muscle mitochondrial and lipid energetic metabolism and contraction.

Civitelli L, Panella S, Marcocci ME, De Petris A, Garzoli S, Pepi F, Vavala E, Ragno R, Nencioni L, Palamara AT, Angiolella L.
In vitro inhibition of herpes simplex virus type 1 replication by Mentha suaveolens essential oil and its main component piperitenone oxide.
Phytomedicine. 2014 May 15;21(6):857-865.

Several essential oils exert in vitro activity against bacteria and viruses and, among these latter, herpes simplex virus type 1 (HSV-1) is known to develop resistance to commonly used antiviral agents. Thus, the effects of the essential oil derived from Mentha suaveolens (EOMS) and its active principle piperitenone oxide (PEO) were tested in in vitro experimental model of infection with HSV-1. The 50% inhibitory concentration (IC50) was determined at 5.1μg/ml and 1.4μg/ml for EOMS and PEO, respectively. Australian tea tree oil (TTO) was used as control, revealing an IC50 of 13.2μg/ml. Moreover, a synergistic action against HSV-1 was observed when each oil was added in combination with acyclovir. In order to find out the mechanism of action, EOMS, PEO and TTO were added to the cells at different times during the virus life-cycle. Results obtained by yield reduction assay indicated that the antiviral activity of both compounds was principally due to an effect after viral adsorption. Indeed, no reduction of virus yield was observed when cells were treated during viral adsorption or pre-treated before viral infection. In particular, PEO exerted a strong inhibitory effect by interfering with a late step of HSV-1 life-cycle. HSV-1 infection is known to induce a pro-oxidative state with depletion of the main intracellular antioxidant glutathione and this redox change in the cell is important for viral replication. Interestingly, the treatment with PEO corrected this deficit, thus suggesting that the compound could interfere with some redox-sensitive cellular pathways exploited for viral replication. Overall our data suggest that both EOMS and PEO could be considered good candidates for novel anti-HSV-1 strategies, and need further exploration to better characterize the targets underlying their inhibition.

Desideri E, Vegliante R, Cardaci S, Nepravishta R, Paci M, Ciriolo MR.
MAPK14/p38α-dependent modulation of glucose metabolism affects ROS levels and autophagy during starvation.
Autophagy. 2014 Sep 1;10(9):1652-1665.

Increased glycolytic flux is a common feature of many cancer cells, which have adapted their metabolism to maximize glucose incorporation and catabolism to generate ATP and substrates for biosynthetic reactions. Indeed, glycolysis allows a rapid production of ATP and provides metabolic intermediates required for cancer cells growth. Moreover, it makes cancer cells less sensitive to fluctuations of oxygen tension, a condition usually occurring in a newly established tumor environment. Here, we provide evidence for a dual role of MAPK14 in driving a rearrangement of glucose metabolism that contributes to limiting reactive oxygen species (ROS) production and autophagy activation in condition of nutrient deprivation. We demonstrate that MAPK14 is phosphoactivated during nutrient deprivation and affects glucose metabolism at 2 different levels: on the one hand, it increases SLC2A3 mRNA and protein levels, resulting in a higher incorporation of glucose within the cell. This event involves the MAPK14-mediated enhancement of HIF1A protein stability. On the other hand, MAPK14 mediates a metabolic shift from glycolysis to the pentose phosphate pathway (PPP) through the modulation of PFKFB3 (6-phosphofructo-2-kinase/fructose 2,6-bisphosphatase 3) degradation by the proteasome. This event requires the presence of 2 distinct degradation sequences, KEN box and DSG motif Ser273, which are recognized by 2 different E3 ligase complexes. The mutation of either motif increases PFKFB3 resistance to starvation-induced degradation. The MAPK14-driven metabolic reprogramming sustains the production of NADPH, an important cofactor for many reduction reactions and for the maintenance of the proper intracellular redox environment, resulting in reduced levels of ROS. The final effect is a reduced activation of autophagy and an increased resistance to nutrient deprivation.

Desideri E, Vegliante R, Ciriolo MR.
Mitochondrial dysfunctions in cancer: genetic defects and oncogenic signaling impinging on TCA cycle activity.
Cancer Lett. 2014 Mar 7 [Epub ahead of print].

The tricarboxylic acid (TCA) cycle is a central route for oxidative metabolism. Besides being responsible for the production of NADH and FADH2, which fuel the mitochondrial electron transport chain to generate ATP, the TCA cycle is also a robust source of metabolic intermediates required for anabolic reactions. This is particularly important for highly proliferating cells, like tumour cells, which require a continuous supply of precursors for the synthesis of lipids, proteins and nucleic acids. A number of mutations among the TCA cycle enzymes have been discovered and their association with some tumour types has been established. In this review we summarise the current knowledge regarding alterations of the TCA cycle in tumours, with particular attention to the three germline mutations of the enzymes succinate dehydrogenase, fumarate hydratase and isocitrate dehydrogenase, which are involved in the pathogenesis of tumours, and to the aberrant regulation of TCA cycle components that are under the control of oncogenes and tu-

mour suppressors.

Lettieri Barbato D, Tatulli G, Aquilano K, Ciriolo MR.
Inhibition of age-related cytokines production by ATGL: A mechanism linked to the anti-inflammatory effect of resveratrol.
Mediators Inflamm. 2014; 2014: Article ID 917698. Epub 2014 Apr 8.

Ageing is characterized by the expansion and the decreased vascularization of visceral adipose tissue (vAT), disruption of metabolic activities, and decline of the function of the immune system, leading to chronic inflammatory states. We previously demonstrated that, in vAT of mice at early state of ageing, adipocytes mount a stress resistance response consisting in the upregulation of ATGL, which is functional in restraining the production of inflammatory cytokines. Here, we found that, in the late phase of ageing, such an adaptive response is impaired. In particular, 24-months-old mice and aged 3T3-L1 adipocytes display affected expression of ATGL and its downstream PPARα-mediated lipid signalling pathway, leading to upregulation of TNFα and IL-6 production. We show that the natural polyphenol compound resveratrol (RSV) efficiently suppresses the expression of TNFα and IL-6 in an ATGL/PPARα dependent manner. Actually, adipocytes downregulating ATGL do not show a restored PPARα expression and display elevated cytokines production. Overall the results obtained highlight a crucial function of ATGL in inhibiting age-related inflammation and reinforce the idea that RSV could represent a valid natural compound to limit the onset and/or the exacerbation of the age-related inflammatory states.

Lettieri Barbato D, Vegliante R, Desideri E, Ciriolo MR.
Managing lipid metabolism in proliferating cells: New perspective for metformin usage in cancer therapy.
Biochim Biophys Acta. 2014 Apr;1845(2):317-324.

Cancer cells metabolically adapt to undergo cellular proliferation. Lipids, besides their well-known role as energy storage, represent the major building blocks for the synthesis of neo-generated membranes. There is increasing evidence that cancer cells show specific alterations in different aspects of lipid metabolism. The changes of expression and activity of lipid metabolising enzymes are directly regulated by the activity of oncogenic signals. The dependence of tumour cells on the deregulated lipid metabolism suggests that proteins involved in this process could be excellent chemotherapeutic targets for cancer treatment. Due to its rare side effects in non-cancerous cells, metformin has been recently revaluated as a potential anti-tumourigenic drug, which negatively affects lipid biosynthetic pathways. In this review we summarised the emerging molecular events linking the anti-proliferative effect of metformin with lipid metabolism in cancer cells.

Montagna C, Di Giacomo G, Rizza S, Cardaci S, Ferraro E, Grumati P, De Zio D, Maiani E, Muscoli C, Lauro F, Ilari S, Bernardini S, Cannata S, Gargioli C, Ciriolo MR, Cecconi F, Bonaldo P, Filomeni G.
S-nitrosoglutathione reductase deficiency-induced S-nitrosylation results in neuromuscular dysfunction.
Antioxid Redox Signal. 2014 Aug 1;21(4):570-587.

Nitric oxide (NO) production is implicated in muscle contraction, growth and atrophy, and in the onset of neuropathy. However, many aspects of the mechanism of action of NO are not yet clarified, mainly regarding its role in muscle wasting. Notably, whether NO production-associated neuromuscular atrophy depends on tyrosine nitration or S-nitrosothiols (SNOs) formation is still a matter of debate. Here, we aim at assessing this issue by characterizing the neuromuscular phenotype of S-nitrosoglutathione reductase-null (GSNOR-KO) mice that maintain the capability to produce NO, but are unable to reduce SNOs.

We demonstrate that, without any sign of protein nitration, young GSNOR-KO mice show neuromuscular atrophy due to loss of muscle mass, reduced fiber size, and neuropathic behavior. In particular, GSNOR-KO mice show a significant decrease in nerve axon number, with the myelin sheath appearing disorganized and reduced, leading to a dramatic development of a neuropathic phenotype. Mitochondria appear fragmented and depolarized in GSNOR-KO myofibers and myotubes, conditions that are reverted by N-acetylcysteine treatment. Nevertheless, although atrogene transcription is induced, and bulk autophagy activated, no removal of damaged mitochondria is observed. These events, alongside basal increase of apoptotic markers, contribute to persistence of a neuropathic and myopathic state.
Our study provides the first evidence that GSNOR deficiency, which affects exclusively SNOs reduction without altering nitrotyrosine levels, results in a clinically relevant neuromuscular phenotype.
These findings provide novel insights into the involvement of GSNOR and S-nitrosylation in neuromuscular atrophy and neuropathic pain that are associated with pathological states; for example, diabetes and cancer.

Peluso I, Villano DV, Roberts SA, Cesqui E, Raguzzini A, Borges G, Crozier A, Catasta G, Toti E, Serafini M.
Consumption of mixed fruit-juice drink and vitamin C reduces postprandial stress induced by a high fat meal in healthy overweight subjects.
Curr Pharm Des. 2014;20(6):1020-1024.

Postprandial stress induced by acute consumption of meals with a high fat content results in an increase of markers of cardiometabolic risk. Repeated acute dietary stress may induce a persistent low-grade inflammation, playing a role in the pathogenesis of functional gut diseases. This may cause an impairment of the complex immune response of the gastrointestinal mucosa, which results in a breakdown of oral tolerance. We investigated the effect of ingestion of a fruit-juice drink (FJD) composed by multiple fruit juice and extracts, green tea extracts and vitamin C on postprandial stress induced by a High Fat Meal (HFM) in healthy overweight subjects. Following a double blind, placebo controlled, cross-over design, 15 healthy overweight subjects were randomized to a HFM providing 1334 Kcal (55% fat, 30% carbohydrates and 15% proteins) in combination with 500 mL of a placebo drink (HFM-P) or a fruit-juice drink (HFM-FJD). Ingestion of HFM-P led to an increase in circulating levels of cholesterol, triglycerides, glucose, insulin, TNF-□ and IL-6. Ingestion of HFM-FJD significantly reduced plasma levels of cholesterol and triglycerides, decreasing inflammatory response mediated by TNF-□ and IL-6. Ingestion of a fruit-juice drink reduce markers of postprandial stress induced by a HFM.

LABORATORIO DI PATOLOGIA MOLECOLARE E CELLULARE

Frustaci A, Russo MA, Francone M, Chimenti C.
Microvascular angina as prehypertrophic presentation of fabry disease cardiomyopathy.
Circulation. 2014 Oct 21;130(17):1530-1531.

Ravenna L, Principessa L, Verdina A, Salvatori L, Russo MA, Petrangeli E.
Distinct phenotypes of human prostate cancer cells associate with different adaptation to hypoxia and pro-inflammatory gene expression.
PLoS One. 2014 May 6;9(5):e96250.

Hypoxia and inflammation are strictly interconnected both concurring to prostate cancer progression. Numerous reports highlight the role of tumor cells in the synthesis of pro-inflammatory molecules and show that hypoxia can modulate a number of these genes contributing substantially to the increase of cancer aggressiveness. However, little is known about the importance of

the tumor phenotype in this process. The present study explores how different features, including differentiation and aggressiveness, of prostate tumor cell lines impact on the hypoxic remodeling of pro-inflammatory gene expression and malignancy. We performed our studies on three cell lines with increasing metastatic potential: the well differentiated androgen-dependent LNCaP and the less differentiated and androgen-independent DU145 and PC3. We analyzed the effect that hypoxic treatment has on modulating pro-inflammatory gene expression and evaluated the role HIF isoforms and NF-kB play in sustaining this process. DU145 and PC3 cells evidenced a higher normoxic expression and a more complete hypoxic induction of pro-inflammatory molecules compared to the well differentiated LNCaP cell line. The role of HIF1 and NF-kB, the master regulators of hypoxia and inflammation respectively, in sustaining the hypoxic pro-inflammatory phenotype was different according to cell type. NF-kB was observed to play a main role in DU145 and PC3 cells in which treatment with the NF-kB inhibitor parthenolide was able to counteract both the hypoxic pro-inflammatory shift and HIF1 activation but not in LNCaP cells. Our data highlight that tumor prostate cell phenotype contributes at a different degree and with different mechanisms to the hypoxic pro-inflammatory gene expression related to tumor progression.

Tafani M, Perrone GA, Pucci B, Russo A, Bizzarri M, Mechanick JI, Carpi A, Russo MA.
Reprogramming cancer cells in endocrine-related tumors: open issues.
Curr Med Chem. 2014;21(9):1146-1151.

Reprogramming technologies have been developed to revert somatic differentiated cells into pluripotent stem cells that can be differentiated into different lineages potentially useful in stem cell therapy. Reprogramming methods have been progressively refined to increase their efficiency, to obtain a cell population suitable for differentiation, and to eliminate viral plasmid which could be responsible for many unwanted side-effects when used in personalized medicine. All these methods are aimed to introduce into the cell genes or mRNAs encoding a set of four transcription factors (OCT- 4, SOX-2, KLF-4 and c-MYC) or a set of three lincRNAs (large intragenic non-coding RNAs) acting downstream of the reprogramming transcription factors OCT-4, SOX-2 and NANOG. Translational clinical applications in human pathologies and in developmental, repair and cancer biology have been numerous. Cancer cells can be, at least in principle, reprogrammed into a normal phenotype. This is a recently raised issue, rapidly advancing in many human tumors, especially endocrine-related cancers, such as breast, prostate and ovarian ca. The present review aims to describe basic phenomena observed in reprogramming tumor cells and solid tumors and to discuss their meaning in human hormone-related cancers. We will also discuss the fact that some of the targeted transcription factors are “normally” activated in a number of physiological processes, such as morphogenesis, hypoxia and wound healing, suggesting an in vivo role of reprogramming for development and homeostasis. Finally, we will review concerns and warnings raised for in vivo reprogramming of human tumors and for the use of induced pluripotent stem cells (iPSCs) in human therapy.

Basile C, Della-Morte D, Cacciatore F, Gargiulo G, Galizia G, Roselli M, Curcio F, Bonaduce D, Abete P.
Phase angle as bioelectrical marker to identify elderly patients at risk of sarcopenia.
Exp Gerontol. 2014 Jul 15;58C:43-46.

Several markers have been associated with sarcopenia in the elderly, including bioelectrical indices. Phase angle (PhA) is an impedance parameter and it has been suggested as an indicator of cellular death. Thus, the relationship between PhA and muscle mass and strength was investigated in 207 consecutively elderly participants (mean age 76.2±6.7years) admitted for multidimensional geriatric evaluation. Muscle strength by grip strength using a hand-held dynamometer and muscle mass was measured by bioimpedentiometer. PhA was calculated directly with its arctangent (resistance/reactance×180°/π). Linear relationship among muscular mass and strength and with clinical and biochemical parameters, including PhA at uni- and multivariate analysis were performed. Linear regression analysis demonstrated that lower level of PhA is associated with reduction in grip strength (y=3.16+0.08x; r=0.49; p<0.001), and even more, with muscle mass (y=3.04+0.25x; r=0.60; p<0001). Multivariate analysis confirms these relationships (grip strength =0.245, p=0.031; muscular mass =0.623, p<0.01). Thus, PhA is inversely related to muscle mass and strength in elderly subjects and it may be considered a good bioelectrical marker to identify elderly patients at risk of sarcopenia.

Cacciatore F, Della-Morte D, Basile C, Mazzella F, Mastrobuoni C, Salsano E, Gargiulo G, Galizia G, Rengo F, Bonaduce D, Abete P.
Long-term mortality in frail elderly subjects with osteoarthritis.
Rheumatology (Oxford). 2014 Feb;53(2):293-299.

Elderly subjects are characterized by a high prevalence of OA and clinical frailty. This study aimed to examine the predictive role of clinical frailty on long-term mortality in elderly subjects with and without OA.
Mortality was evaluated after a 12-year follow-up in 698 subjects with and 590 subjects without OA recruited in 1992. Clinical frailty was assessed according to the Frailty Staging System and stratified in tertiles.
After a 12-year follow-up, mortality was 42.2% in subjects without and 55.8% in subjects with OA (P = 0.256). With increasing frailty, mortality increased by 30.5% (P for trend < 0.001) in subjects without and by 45.6% in subjects with OA (P for trend < 0.001). Multivariate analysis showed that frailty [hazard ratio (HR) = 1.49 for each unit of increase, 95% CI 1.32, 1.94, P < 0.001) but not OA (HR = 1.28, 95% CI 0.987, 1.39, P = 0.412) was predictive of long-term mortality. Moreover, when Cox regression analysis was performed, frailty enhanced the risk of long-term mortality for each unit of increase by 32% (HR = 1.32, 95% CI 1.06, 1.65, P = 0.03) in the absence of OA and by 98% in the presence (HR = 1.98, 95% CI 1.63, 2.95, P < 0.01) of OA.
Clinical frailty significantly predicts mortality in subjects without OA and even more in those with OA. Thus clinical frailty may be considered a new prognostic factor to identify subjects with OA at high risk of mortality.

D’Ambrosio D, Tomaselli V, Gargiulo G, Roselli M, Della-Morte D, Abete P.
Evans syndrome presented with marginal zone lymphoma and duodenal neuroendocrine tumor in an elderly woman.
International Journal of Gerontology (in press)

Evans syndrome (ES) is an autoimmune disorder characterized by simultaneous or sequential development of autoimmune hemolytic anemia, immune thrombocytopenia, and/or neutropenia. ES can be classified as a primary (idiopathic) or secondary (associated with an underlying disease) syndrome. We report a case of ES in an elderly patient in the presence of multiple trigger factors such as recent influenza vaccine, marginal zone lymphoma, and neuroendocrine tumor G1. Whether this association is casual or causal remains a matter of speculation. It is however necessary to have a thorough work-up in a newly diagnosed ES and a more accurate search of miscellaneous factors especially in elderly patients.

Della-Morte D, Dong C, Beecham A, Wang L, Cabral D, Markert MS, Blanton SH, Sacco RL, Rundek T. Relationship between sirtuin and mitochondrial uncoupling protein genes and carotid artery stiffness.
Transl Res. 2014 Sep 6. [Epub ahead of print]

Smoking greatly increases the risk of atherosclerotic plaque and the effect may vary from individual to individual. A genome-wide scan was performed for smoking×single nucleotide poly-

morphism (SNP) interactions on carotid plaque burden (CPB) to identify the potential genetic moderators in Hispanics.
Carotid B-mode ultrasonography and genotyping by the Affymetrix 6.0 chip were performed in a discovery sample of 665 Caribbean Hispanics, followed by replication analyses in 264 Caribbean Hispanics. CPB was expressed as the sum of plaque areas over the segments in common and internal carotid arteries and bifurcation. Smoking was classified as 0, <20, and ≥20 cigarette pack-years. Assuming an additive genetic model, regression analysis was conducted to test for smoking×SNP interaction on the cube root transformed CPB while controlling for age, sex, and the top 3 principal components of ancestry.
Two SNPs showed a significant interaction with smoking on CPB with the similar effects in both discovery (P<1.0E-5) and replication (P<0.05) populations. Specifically, for SNP rs10205487 within MXD1, more smoking was significantly associated with greater CPB in A allele carriers (beta±SE: 0.24±0.08, P=0.005 in AG carriers; beta±SE: 0.48±0.12, P=0.0002 in AA carriers) but not in GG (P=0.06). For SNP rs7001413 within LY96 and JPH1, more smoking was significantly associated with greater CPB in GG carriers (beta±SE: 0.24±0.06, P=6.8E-5) but not in T carriers (P=0.06).
Our study suggests that genetic variants may modulate the effect of smoking on CPB and highlights several genes for further investigation of their role in atherosclerosis, especially in smoking population.

Della-Morte D, Wang L, Beecham A, Blanton SH, Zhao H, Sacco RL, Rundek T, Dong C.
Novel genetic variants modify the effect of smoking on carotid plaque burden in Hispanics.
J Neurol Sci. 2014 Sep 15;344(1-2):27-31.

Smoking greatly increases the risk of atherosclerotic plaque and the effect may vary from individual to individual. A genome-wide scan was performed for smoking×single nucleotide polymorphism (SNP) interactions on carotid plaque burden (CPB) to identify the potential genetic moderators in Hispanics.
Carotid B-mode ultrasonography and genotyping by the Affymetrix 6.0 chip were performed in a discovery sample of 665 Caribbean Hispanics, followed by replication analyses in 264 Caribbean Hispanics. CPB was expressed as the sum of plaque areas over the segments in common and internal carotid arteries and bifurcation. Smoking was classified as 0, <20, and ≥20 cigarette pack-years. Assuming an additive genetic model, regression analysis was conducted to test for smoking×SNP interaction on the cube root transformed CPB while controlling for age, sex, and the top 3 principal components of ancestry.
Two SNPs showed a significant interaction with smoking on CPB with the similar effects in both discovery (P<1.0E-5) and replication (P<0.05) populations. Specifically, for SNP rs10205487 within MXD1, more smoking was significantly associated with greater CPB in A allele carriers (beta±SE: 0.24±0.08, P=0.005 in AG carriers; beta±SE: 0.48±0.12, P=0.0002 in AA carriers) but not in GG (P=0.06). For SNP rs7001413 within LY96 and JPH1, more smoking was significantly associated with greater CPB in GG carriers (beta±SE: 0.24±0.06, P=6.8E-5) but not in T carriers (P=0.06).
Our study suggests that genetic variants may modulate the effect of smoking on CPB and highlights several genes for further investigation of their role in atherosclerosis, especially in smoking population.

Ferrelli F, Pastore D, Capuani B, Lombardo MF, Blot-Chabaud M, Coppola A, Basello K, Galli A, Donadel G, Romano M, Caratelli S, Pacifici F, Arriga R, Di Daniele N, Sbraccia P, Sconocchia G, Bellia A, Tesauro M, Federici M, Della-Morte D, Lauro D.
Serum glucocorticoid inducible kinase (SGK)-1 protects endothelial cells against oxidative stress and apoptosis induced by hyperglycaemia.
Acta Diabetol. 2014 Jun 25. [Epub ahead of print]

Diabetic hyperglycaemia causes endothelial dysfunction mainly by impairing endothelial nitric oxide (NO) production. Moreover, hyperglycaemia activates several noxious cellular pathways including apoptosis, increase in reactive oxygen species (ROS) levels and diminishing Na+-K+ ATPase activity which exacerbate vascular damage. Serum glucocorticoid kinase (SGK)-1, a member of the serine/threonine kinases, plays a pivotal role in regulating NO production through inducible NO synthase activation and other cellular mechanisms. Therefore, in this study, we aimed to investigate the protective role of SGK-1 against hyperglycaemia in human umbilical endothelial cells (HUVECs). We used retrovirus to infect HUVECs with either SGK-1, SGK-1Δ60 (lacking of the N-60 amino acids-increase SGK-1 activity) or SGK-1Δ60KD (kinase-dead constructs). We tested our hypothesis in vitro after high glucose and glucosamine incubation. Increase in SGK-1 expression and activity (SGK-1Δ60) resulted in higher production of NO, inhibition of ROS synthesis and lower apoptosis in endothelial cell after either hyperglycaemia or glucosamine treatments. Moreover, in this study, we showed increased GLUT-1 membrane translocation and Na+-K+ ATPase activity in cell infected with SGK-1Δ60 construct. These results suggest that as in endothelial cells, an increased SGK-1 activity and expression reduces oxidative stress, improves cell survival and restores insulin-mediated NO production after different noxae stimuli. Therefore, SGK-1 may represent a specific target to further develop novel therapeutic options against diabetic vascular disease.

Ferroni P, Guadagni F, Laudisi A, Vergati M, Riondino S, Russo A, Davì G, Roselli M.
Estimated glomerular filtration rate is an easy predictor of venous thromboembolism in cancer patients undergoing platinum-based chemotherapy.
Oncologist. 2014;19(5):562-567.

Reduced estimated glomerular filtration rate (eGFR) has been associated with increased venous thromboembolism (VTE) risk in the general population. VTE incidence significantly increases in cancer patients, especially those undergoing chemotherapy. Despite the evidence that a substantial number of cancer patients have unrecognized renal impairment, as indicated by reduced eGFR in the presence of serum creatinine levels within the reference value, chemotherapy dosage is routinely adjusted for serum creatinine values. Among chemotherapies, platinum-based regimens are associated with the highest rates of VTE. A cohort study was designed to assess the value of pretreatment eGFR in the risk prediction of a first VTE episode in cancer outpatients without previous history of VTE who were scheduled for platinum-based chemotherapy. Methods. Serum creatinine and eGFR were evaluated before the start of standard platinum-based chemotherapy in a cohort of 322 consecutive patients with primary or relapsing/recurrent solid cancers, representative of a general practice population. Results. Patients who experienced a first VTE episode in the course of chemotherapy had lower mean eGFR values compared with patients who remained VTE free. Multivariate Cox analysis demonstrated that eGFR had an independent value for risk prediction of a first VTE episode during treatment, with a 3.15 hazard ratio. Indeed, 14% of patients with reduced eGFR had VTE over 1-year follow-up compared with 6% of patients with normal eGFR values. Conclusion. The results suggest that reductions in eGFR, even in the presence of normal serum creatinine, are associated with an increased VTE risk in cancer outpatients undergoing platinum-based chemotherapy regimens. Determining eGFR before chemotherapy could represent a simple predictor of VTE, at no additional cost to health care systems.

Ferroni P, Guadagni F, Riondino S, Portarena I, Mariotti S, La Farina F, Davì G, Roselli M.
Evaluation of mean platelet volume as a predictive marker for cancer-associated venous thromboembolism during chemotherapy.
Haematologica. 2014 Oct;99(10):1638-1644.

Mean platelet volume has been proposed as a predictor for venous thromboembolism in cancer. We, therefore, investigated the effects of different anti-cancer drugs on mean platelet volume in order to assess its possible value in the risk prediction of a first thromboembolic episode in can-

cer outpatients during treatment. Pre-treatment mean platelet volumes were retrospectively evaluated in 589 ambulatory patients at the beginning of a new chemotherapy regimen. Moreover, serial changes were evaluated at baseline and before each chemotherapy cycle on 385 of the 589 patients who consented to have additional blood withdrawals during treatment. Cox proportional hazards survival analysis demonstrated a 2.7 hazard ratio (P=0.01) of developing a first venous thromboembolic episode during chemotherapy for patients with baseline mean platelet volumes below the 10(th) percentile (<7.3 fL). This index significantly declined during the first three months of chemotherapy (-6%; P<0.0001) reverting to baseline at the end of treatment. Multivariate regression analysis showed that normal baseline volumes (P=0.012) and platinum-based regimens (P=0.017) were both independent predictors of mean platelet volume decline during chemotherapy which, in turn, was associated with a 2.4 hazard ratio (P=0.044) of venous thromboembolism. In conclusion, low pre-chemotherapy mean platelet volume might be regarded as a predictor of increased venous thromboembolism risk in cancer patients and chemotherapy further decreases platelet volumes, possibly due to drug-induced platelet activation and destruction. Changes in mean platelet volumes during chemotherapy might provide additional information on thromboembolic risk of patients treated with anti-cancer drugs, particularly platinum compounds.

Ferroni P, Riondino S S, Formica V, Cereda V, Tosetto L, La Farina F, Valente MG, Vergati M, Guadagni F, Roselli M.
Venous thromboembolism risk prediction in ambulatory cancer patients. Clinical significance of neutrophil/lymphocyte ratio and platelet/lymphocyte ratio.
Int J Cancer. 2014 Jul 15. [Epub ahead of print]

Neutrophil/lymphocyte (NLR) and platelet/lymphocyte (PLR) ratios might represent a yet unrecognized risk factor for venous thromboembolism (VTE) in cancer out-patients receiving chemotherapy. Accordingly, this study was aimed at analyzing the significance of these novel markers in the risk prediction of a first VTE episode in a population representative of a general practice cohort. To this purpose, a mono-institutional cohort study was conducted to retrospectively analyze NLR and PLR in 810 consecutive cancer out-patients with primary or relapsing solid cancer at the start of a new chemotherapy regimen. Over a median follow-up of 9.2 months, VTE occurred in 6.7% of patients. Incidental VTE was diagnosed at time of restaging in 47% of cases. Median pre-chemotherapy NLR (p = 0.015) and PLR (p = 0.040) were significantly higher in patients with intermediate risk class who developed symptomatic VTE with a twofold increased VTE risk for both inflammation-based markers (NLR: p = 0.022; PLR: p = 0.037) and a worst 1-year VTE-free survival for patients with high NLR or PLR. However, only PLR (HR = 2.4, p = 0.027) confirmed to be an independent predictor of future VTE in patients in the intermediate risk class in multivariate analysis, together with ECOG performance status (HR = 3.4, p = 0.0002) and bevacizumab use (HR = 4.7, p = 0.012). We may, thus, conclude that PLR, but to a lesser extent NLR, could represent useful clinical predictors of VTE, especially in selected categories of patients such as those in the intermediate risk class in whom the assessment of PLR could allow a better risk stratification of VTE without additional costs to the national health systems.

Ferroni P, Roselli M, Portarena I, Formica V, Riondino S, LA Farina F, Costarelli L, Melino A, Massimiani G, Cavaliere F, Palmirotta R, Guadagni F.
Plasma plasminogen activator inhibitor-1 (PAI-1) levels in breast cancer - relationship with clinical outcome.
Anticancer Res. 2014 Mar;34(3):1153-1161.

Signaling pathways triggered by increased thrombin or plasminogen activator inhibitor-1 (PAI-1) expression drastically alter the tumor microenvironment, contributing to an adverse outcome. This study aimed to evaluate the prognostic value of coagulation/fibrinolytic activities in breast cancer (BC).

Coagulation/fibrinolytic activities were investigated in 187 patients with breast cancer, with respect to possible associations with clinicopathological features and survival outcomes.
Levels of plasma PAI-1 (p<0.001), D-dimer (p=0.037) and activated protein C-dependent thrombin generation (p=0.003) were higher in women with breast cancer compared to 187 healthy women. PAI-1 directly correlated with D-dimer levels (p=0.009) and Ki67 expression (p=0.027), which were both predictors of elevated PAI-1 levels at multivariate regression analysis. Cox analysis demonstrated that an elevated plasma PAI-1 level had a negative prognostic impact in terms of relapse-free (hazard ratio=2.5, p=0.021) and overall survival (hazard ratio=2.7, p=0.002).
Determination of plasma PAI-1 levels might provide important prognostic information in risk stratification and survival outcomes for patients with breast cancer.

Ferroni P, Roselli M, Riondino S, Guadagni F.
Predictive value of HDL cholesterol for cancer-associated venous thromboembolism during chemotherapy.
J Thromb Haemost. 2014 Dec;12(12):2049-2053.

Dyslipidemia is a well-known risk factor for the development of atherothrombosis; however, its involvement in venous thromboembolism (VTE) is still debated. Low levels of HDL cholesterol (HDL-C) have been found to be associated with VTE, which is a common complication of cancer and its treatment. VTE incidence is increased in cancer patients, especially those undergoing chemotherapy.
We sought to investigate the value of pretreatment HDL-C in the risk prediction of future VTE in a population of ambulatory cancer patients undergoing chemotherapy.
Blood lipid composition was retrospectively evaluated in 592 consecutive patients with primary (n = 373) or relapsing/recurrent (n = 219) solid cancers at the start of a new chemotherapy regimen (12% neoadjuvant, 31% adjuvant, 57% metastatic).
VTE occurred during chemotherapy in 38 patients (median time-to-event: 3 months). Mean HDL-C levels were lower in patients who developed VTE during chemotherapy (41 mg dL(-1) ; standard deviation [SD] 13 mg dL(-1)) than in those who did not (48 mg dL(-1) ; SD 14 mg dL(-1)). Cox proportional hazard survival analysis showed that HDL-C levels ≤ 43 mg dL(-1) were able to significantly predict a first VTE episode, with a hazard ratio of 2.87 (95% confidence interval 1.45-5.68). Moreover, patients with HDL-C levels ≤ 43 mg dL(-1) had worse 1-year VTE-free survival (86%) than those with HDL-C levels > 43 mg dL(-1) (96%; log rank test, 3.14).
Patients with low HDL-C levels have a three-fold higher risk of developing a first VTE episode during chemotherapy. Baseline analysis of HDL-C levels might be of clinical value in predicting VTE in cancer outpatients treated with anticancer drugs.

Formica V, Luccchetti J, Cunningham D, Smyth EC, Ferroni P, Nardecchia A, Tesauro M, Cereda V, Guadagni F, Roselli M.
Systemic inflammation, as measured by the neutrophil/lymphocyte ratio, may have differential prognostic impact before and during treatment with fluorouracil, irinotecan and bevacizumab in metastatic colorectal cancer patients.
Med Oncol. 2014 Sep;31(9):166.

The inflammatory index neutrophil/lymphocyte ratio (NLR) has an adverse prognostic value in patients with localized colorectal cancer (CRC). We aimed at evaluating its role in metastatic CRC (mCRC) patients treated with standard first-line chemotherapy. Among consecutive CRC patients referred to our Unit, those with metastatic disease eligible for treatment with fluorouracil, irinotecan and bevacizumab (FOLFIRI-Bev) were included in the study. NLR was routinely assessed before each treatment cycle and correlated with outcome together with common clinical, biochemical and histological variables. A sub-analysis focused on patients with stable disease (SD) was also performed to test the net influence of NLR changes independently of tumor shrinkage.

At multivariate Cox regression analysis, baseline NLR, taken as continuous variable, was the most powerful prognosticator for survival (HR 1.80, p 0.0019). Surprisingly, among SD patients, the prognostic effect of NLR changes after two cycles of therapy was of opposite sign, and those in whom NLR increased or was maintained had a 67 % reduction in the risk of death as compared with patients with significant NLR decrease: mOS 56 versus 23 months, respectively, p 0.02. In conclusion, we were able to confirm the adverse prognostic value of high baseline NLR for mCRC patients treated with FOLFIRI-Bev. However, FOLFIRI-Bev-induced NLR changes in SD patients seem to differently affect survival. The specific molecular pathways involved in NLR modulation by FOLFIRI-Bev warrant further investigation.

Koch S, Della-Morte D, Dave KR, Sacco RL, Perez-Pinzon MA.
Biomarkers for ischemic preconditioning: finding the responders.
J Cereb Blood Flow Metab. 2014 Jun;34(6):933-941.

Ischemic preconditioning is emerging as an innovative and novel cytoprotective strategy to counter ischemic vascular disease. At the root of the preconditioning response is the upregulation of endogenous defense systems to achieve ischemic tolerance. Identifying suitable biomarkers to show that a preconditioning response has been induced remains a translational research priority. Preconditioning leads to a widespread genomic and proteonomic response with important effects on hemostatic, endothelial, and inflammatory systems. The present article summarizes the relevant preclinical studies defining the mechanisms of preconditioning, reviews how the human preconditioning response has been investigated, and which of these bioresponses could serve as a suitable biomarker. Human preconditioning studies have investigated the effects of preconditioning on coagulation, endothelial factors, and inflammatory mediators as well as on genetic expression and tissue blood flow imaging. A biomarker for preconditioning would significantly contribute to define the optimal preconditioning stimulus and the extent to which such a response can be elicited in humans and greatly aid in dose selection in the design of phase II trials. Given the manifold biologic effects of preconditioning a panel of multiple serum biomarkers or genomic assessments of upstream regulators may most accurately reflect the full spectrum of a preconditioning response.

Pacifici F, Arriga R, Sorice GP, Capuani B, Scioli MG, Pastore D, Donadel G, Bellia A, Caratelli S, Coppola A, Ferrelli F, Federici M, Sconocchia G, Tesauro M, Sbraccia P, Della-Morte D, Giaccari A, Orlandi A, Lauro D.
Peroxiredoxin 6, a novel player in the pathogenesis of diabetes.
Diabetes. 2014 Oct;63(10):3210-3220.

Enhanced oxidative stress contributes to the pathogenesis of diabetes and its complications. Peroxiredoxin 6 (PRDX6) is a key regulator of cellular redox balance, with the peculiar ability to neutralize peroxides, peroxynitrite, and phospholipid hydroperoxides. In the current study, we aimed to define the role of PRDX6 in the pathophysiology of type 2 diabetes (T2D) using PRDX6 knockout (-/-) mice. Glucose and insulin responses were evaluated respectively by intraperitoneal glucose and insulin tolerance tests. Peripheral insulin sensitivity was analyzed by euglycemic-hyperinsulinemic clamp, and molecular tools were used to investigate insulin signaling. Moreover, inflammatory and lipid parameters were evaluated. We demonstrated that PRDX6(-/-) mice developed a phenotype similar to early-stage T2D caused by both reduced glucose-dependent insulin secretion and increased insulin resistance. Impaired insulin signaling was present in PRDX6(-/-) mice, leading to reduction of muscle glucose uptake. Morphological and ultrastructural changes were observed in islets of Langerhans and livers of mutant animals, as well as altered plasma lipid profiles and inflammatory parameters. In conclusion, we demonstrated that PRDX6 is a key mediator of overt hyperglycemia in T2D glucose metabolism, opening new perspectives for targeted therapeutic strategies in diabetes care.

Palena C, Roselli M, Litzinger MT, Ferroni P, Costarelli L, Spila A, Cavaliere F, Huang B, Fernando RI, Hamilton DH, Jochems C, Tsang KY, Cheng Q, Kim Lyerly H, Schlom J, Guadagni F.
Overexpression of the EMT driver brachyury in breast carcinomas: association with poor prognosis.
J Natl Cancer Inst. 2014 May 9;106(5).

The epithelial-mesenchymal transition (EMT) has been implicated as an important process in tumor cell invasion, metastasis, and drug resistance. The transcription factor brachyury has recently been described as a driver of EMT of human carcinoma cells.
Brachyury mRNA and protein expression was analyzed in human breast carcinomas and benign tissues. The role of brachyury in breast tumor prognosis and drug resistance and the ability of brachyury-specific T cells to lyse human breast carcinoma cells were also evaluated. Kaplan-Meier analyses were used to evaluate the association between brachyury expression and survival. All statistical tests were two-sided.
The level of brachyury expression in breast cancer cells was positively associated with their ability to invade the extracellular matrix, efficiently form mammospheres in vitro, and resist the cytotoxic effect of docetaxel. A comparison of survival among breast cancer patients treated with tamoxifen in the adjuvant setting who had tumors with high vs low brachyury mRNA expression demonstrated that high expression of brachyury is associated as an independent variable with higher risk of recurrence (hazard ratio [HR] = 7.5; 95% confidence interval [CI] = 2.4 to 23.5; P = 5.14×10(-4)) and distant metastasis (HR = 15.2; 95% CI = 3.5 to 66.3; P = 3.01×10(-4)). We also demonstrated that brachyury-specific T cells can lyse human breast carcinoma cells.
The studies reported here provide the rationale for the use of a vaccine targeting brachyury for the therapy of human breast cancer, either as a monotherapy or in combination therapies.

Palmirotta R, Barbanti P, Ludovici G, De Marchis ML, Ialongo C, Egeo G, Aurilia C, Fofi L, Abete P, Spila A, Ferroni P, Della-Morte D, Guadagni F.
Association between migraine and ACE gene(insertion/deletion) polymorphism: the BioBIM study.
Pharmacogenomics. 2014 Feb;15(2):147-155.

In the present case-control study, we investigated the correlation between the common ACE insertion/deletion (I/D) polymorphism and migraine.
Genotyping of the ACE I/D variant was performed in 502 Caucasian patients with migraine and 323 age-, sex- and race/ethnicity-matched healthy controls. We investigated associations between ACE genetic variants and sociodemographic and/or clinical features of migraineurs.
We found a significant association between ACE insertion/insertion (I/I) polymorphism and lower use of pharmacological prophylaxis in migraine patients with aura and in those with chronic migraine. Moreover, ACE I/I polymorphism was significantly more common in migraine patients with aura who had a negative family history of migraine.
Our data suggest that although the ACE I/D polymorphism is not a direct risk factor for migraine, the ACE I/I genotype may influence the clinical feature of this disease being associated with reduced use of prophylactic agents in patients with migraine with aura and in those with chronic migraine.

Riondino S, Roselli M, Palmirotta R, Della-Morte D, Ferroni P, Guadagni F.
Obesity and colorectal cancer: Role of adipokines in tumor initiation and progression.
World J Gastroenterol. 2014 May 14;20(18):5177-5190.

Obesity-associated diseases account for a large portion of public health challenges. Among obe-

sity-related disorders, a direct and independent relationship has been ascertained for colorectal cancer (CRC). The evidence that adipocyte hypertrophy and excessive adipose tissue accumulation (mainly visceral) can promote pathogenic adipocyte and adipose tissue-related diseases, has led to formulate the concept of "adiposopathy", defined as adipocyte and adipose tissue dysfunction that contributes to metabolic syndrome. Adipose tissue can, indeed, be regarded as an important and highly active player of the innate immune response, in which cytokine/adipokine secretion is responsible for a paracrine loop between adipocytes and macrophages, thus contributing to the systemic chronic low-grade inflammation associated with visceral obesity, which represents a favorable niche for tumor development. The adipocyte itself participates as a central mediator of this inflammatory response in obese individuals by secreting hormones, growth factors and proinflammatory cytokines, which are of particular relevance for the pathogenesis of CRC. Among adipocyte-secreted hormones, the most relevant to colorectal tumorigenesis are adiponectin, leptin, resistin and ghrelin. All these molecules have been involved in cell growth and proliferation, as well as tumor angiogenesis and it has been demonstrated that their expression changes from normal colonic mucosa to adenoma and adenocarcinoma, suggesting their involvement in multistep colorectal carcinogenesis. These findings have led to the hypothesis that an unfavorable adipokine profile, with a reduction of those with an anti-inflammatory and anti-cancerous activity, might serve as a prognostic factor in CRC patients and that adipokines or their analogues/antagonists might become useful agents in the management or chemoprevention of CRC.

Roselli M, Riondino S, Mariotti S, La Farina F, Ferroni P, Guadagni F.
Clinical models and biochemical predictors of VTE in lung cancer.
Cancer Metastasis Rev. 2014 Sep;33(2-3):771-789.

Venous thromboembolism (VTE) is a frequent complication of lung cancer and its treatment, especially in the advanced stages of disease. The risk of a pro-thrombotic state might increase through the activation of hemostasis, occurring both via the induction of a pro-coagulant activity and with platelet involvement, ultimately leading to the development of metastases. Despite the acknowledgement of an increased thrombophilic condition in cancer patients, and the experimental evidence that heparin compounds may have direct anticancer benefits, there is no univocal consent regarding VTE prevention in cancer outpatients receiving therapy. Thus, many authors highlighted the need for the development of stratification techniques to identify at-risk patients who might benefit from thromboprophylaxis. Clinical risk models were developed and validated, in order to assign high-risk patients to a proper thromboprophylaxis regimen that, however, might not be justified in all clusters. Besides, efforts have been devoted to identify candidate biomarkers that may be used in VTE risk assessment, although none has been recognized, so far, as a predictor for VTE in lung cancer patients. In this review, we will summarize the latest information concerning this very controversial topic, with focus on some of the proposed strategies to select the appropriate patients for prophylaxis.

Testa G, Cacciatore F, Della-Morte D, Mazzella F, Mastrobuoni C, Galizia G, Gargiulo G, Rengo F, Bonaduce D, Abete P.
Atenolol use is associated with long-term mortality in community-dwelling older adults with hypertension.
Geriatr Gerontol Int. 204 Jan;14(1):153-158.

The role of atenolol, a non-vasodilating beta-blocker drug, on long-term mortality in hypertensive older adults is still unclear. The aim of the present study was to evaluate long-term mortality in community-dwelling hypertensive older adults taking atenolol.
Long-term mortality after 12-year follow up in isolated hypertensive older adults (n = 972) was analyzed. The patients were stratified in the presence and absence of atenolol use. Systolic, diastolic and pulse arterial pressure were measured.
Older adults taking atenolol showed a greater mortality and higher pulse arterial pressure values than those not taking atenolol (73.9% vs 55.0%; P = 0.047 and 74.7 ± 14.1 vs 63.0 ± 14.2 mmHg, P < 0.001, respectively). Cox regression analysis showed that atenolol use (hazard risk 1.91; 95% confidence interval 1.04-4.31; P = 0.04) and pulse arterial pressure (hazard risk 1.02; 95% confidence interval 1.01-1.03; P = 0.032) were predictive of long-term mortality.
Atenolol use was related to increased mortality in community-dwelling hypertensive Older adults. This increase in mortality risk seems to be related to an increase of pulse arterial pressure.

Tiozzo E, Gardener H, Hudson BI, Dong C, Della-Morte D, Crisby M, Goldberg RB, Elkind MS, Cheung YK, Wright CB, Sacco RL, Rundek T.
High-density lipoprotein subfractions and carotid plaque: The Northern Manhattan Study.
Atherosclerosis. 2014 Sep 9;237(1):163-168.

The objective of this cross-sectional analysis was to investigate the relation between two major high-density lipoprotein cholesterol (HDL-C) subfractions (HDL2-C and HDL3-C) and carotid plaque in a population based cohort.
We evaluated 988 stroke-free participants (mean age 66 ± 8 years; 40% men; 66% Hispanic and 34% Non-Hispanic) with available data on HDL subfractions using precipitation method and carotid plaque area and thickness assessed by a high-resolution 2D ultrasound. The associations between HDL-C subfractions and plaque measurements were analyzed by quantile regression.
Plaque was present in 56% of the study population. Among those with plaque, the mean ± SD plaque area was 19.40 ± 20.46 mm^2 and thickness 2.30 ± 4.45 mm. The mean ± SD total HDL-C was 46 ± 14 mg/dl, HDL2-C 14 ± 8 mg/dl, and HDL3-C 32 ± 8 mg/dl. After adjusting for demographics and vascular risk factors, there was an inverse association between HDL3-C and plaque area (per mg/dl: beta = -0.26 at the 75th percentile, p = 0.001 and beta = -0.32 at the 90th percentile, p = 0.02). A positive association was observed between HDL2-C and plaque thickness (per mg/dl; beta = 0.02 at the 90% percentile, p = 0.003). HDL-C was associated with plaque area (per mg/dl: beta = -0.18 at the 90th percentile, p = 0.01), but only among Hispanics.
In our cohort we observed an inverse association between HDL3-C and plaque area and a positive association between HDL2-C and plaque thickness. HDL-C subfractions may have different contributions to the risk of vascular disease. More studies are needed to fully elucidate HDL-C anti-atherosclerotic functions in order to improve HDL-based treatments in prevention of vascular disease and stroke.

Barbanti P, Palmirotta R, De Marchis M, Ludovici G, Ialongo C, Egeo G, Aurilia C, Fofi L, Ferroni P, Morte D, Guadagni F.
Association between migraine and sod1 and sod2 genes polymorphisms: The biobim study.
The Journal of Headache and Pain. 2014;15:B4.

Formica V, Morelli C, Ferroni P, Nardecchia A, Tesauro M, Cereda V, Guadagni F, Roselli M.
Ppredictive role of neutrophil/lymphocyte ratio (nlr) for oxaliplatin efficacy in metastatic pancreatic cancer patients (pts).
Annals of Oncology. 2014 September 01;25(suppl 4):iv243-.

Albani G, Cimolin V, Fasano A, Trotti C, Galli M, Mauro A.
"Masters and servants" in parkinsonian gait: a three-dimensional analysis of biomechanical changes sensitive to disease progression.
Funct Neurol. 2014; 29(2): 99-105.

Gait disorder is a very frequent and disabling symptom in Parkinson's disease (PD). The aim of this study was to identify the main kinetic and kinematic features of PD gait according to different di-

sease stages: early (Early Group), intermediate without freezing (Non-Freezers) and intermediate with freezing (Freezers). Kinematic data showed a distal to proximal progression of impairment from the early to the intermediate with freezing stage. The Early Group showed more accentuated ankle dorsiflexion during stance than the other PD subgroups; the Freezers showed a more flexed hip position at initial contact and a reduced range of motion (ROM) during stance compared with the other patients. The individuals in the intermediate stage (with or without freezing) displayed limited knee ROM. Distal to proximal progression of lower limb impairment in PD might be an expression of a rostral to caudal degeneration of locomotor control centers. Evaluation of the relationship between gait features "Masters and servants" in parkinsonian gait: a three-dimensional analysis of biomechanical changes sensitive to disease progression and disease progression may promote the development of tailored rehabilitation programs.

Ancillao A, Galli M, Rigoldi C, Albertini G.
Linear correlation between fractal dimension of surface EMG signal from rectus femoris and height of vertical jump.
Chaos, Solitons & Fractals. 2014 9;66(0):120-126.

Fractal dimension was demonstrated to be able to characterize the complexity of biological signals. The EMG time series are well known to have a complex behavior and some other studies already tried to characterize these signals by their fractal dimension.
This paper is aimed at studying the correlation between the fractal dimension of surface EMG signal recorded over Rectus Femoris muscles during a vertical jump and the height reached in that jump.
Healthy subjects performed vertical jumps at different heights. Surface EMG from Rectus Femoris was recorded and the height of each jump was measured by an optoelectronic motion capture system.
Fractal dimension of sEMG was computed and the correlation between fractal dimension and eight of the jump was studied. Linear regression analysis showed a very high correlation coefficient between the fractal dimension and the height of the jump for all the subjects. The results of this study show that the fractal dimension is able to characterize the EMG signal and it can be related to the performance of the jump. Fractal dimension is therefore an useful tool for EMG interpretation.

Cau N, Cimolin V, Galli M, Precilios H, Tacchini E, Santovito C, Capodaglio P.
Center of pressure displacements during gait initiation in individuals with obesity.
Journal of NeuroEngineering and Rehabilitation. 2014;11(1):82.

Obesity is known to affect balance and gait pattern increasing the risk of fall and injury as compared to the lean population. Such risk is particularly high during postural transitions. Gait initiation (GI) is a transient procedure between static upright posture and steady-state locomotion, which includes anticipatory antero-posterior and lateral movements. GI requires propulsion and balance control. The aim of this study was to characterise quantitatively the strategy of obese subjects during GI using parameters obtained by the Center of Pressure (CoP) track.
20 obese individuals and 15 age-matched healthy subjects were tested using a force platform during the initiation trials. CoP plots were divided in different phases, which identified the anticipatory postural adjustments (APA1, APA2) and a movement phase (LOC). Duration, length and velocity of the CoP trace in these phases were calculated and compared.
The results show that the main characteristic of GI in obese participants is represented by a higher excursion in medio-lateral direction. This condition lead to longer APA length and duration, which are statistical significant during APA2 when compared to control subjects. We also found longer duration of APA1 and LOC phases. In terms of velocity, most of the phases were characterised by a reduced CoP velocity in antero-posterior direction and faster movement in medio-lateral direction as compared to the control group.
Our findings provide novel evidence in GI in obese subjects that may serve for developing exercise programs aimed at specifically improving balance in both the antero-posterior and lateral directions. Such programs together with weight management may be beneficial for improving stability during postural transitions and reducing risk of fall in this population.

Cimolin V, Galli M.
Summary measures for clinical gait analysis: a literature review.
Gait Posture. 2014 Apr;39(4):1005-1010.

Instrumented 3D-gait analysis (3D-GA) is an importantmethod used to obtain information that is crucial for establishing the level of functional limitation due to pathology, observing its evolution over time and evaluating rehabilitative intervention effects. However, a typical 3D-GA evaluation produces a vast amount of data, and despite its objectivity, its use is complicated, and the data interpretation is difficult. It is even more difficult to obtain an overview on patient cohorts for a comparison. Moreover, there is a growing awareness of the need for a concise index, specifically, a single measure of the 'quality' of a particular gait pattern. Several gait summary measures, which have been used in conjunction with 3DGA, have been proposed to objectify clinical impression, quantify the degree of gait deviation from normal, stratify the severity of pathology, document the changes in gait patterns over time and evaluate interventions.

Cimolin V, Vismara L, Galli M, Grugni G, Cau N, Capodaglio P.
Gait strategy in genetically obese patients: A 7-year follow up.
Res Dev Disabil. 2014 Apr 21;35(7):1501-1506.

The aim of this study was to quantitatively evaluate the change in gait and body weight in the long term in patients with Prader-Willi Syndrome (PWS). Eight adults with PWS were evaluated at baseline and after 7 years. During this period patient participated an in- and out-patient rehabilitation programs including nutritional and adapted physical activity interventions. Two different control groups were included: the first group included 14 non-genetically obese patients (OCG: obese control group) and the second group included 10 age-matched healthy individuals (HCG: healthy control group). All groups were quantitatively assessed during walking with 3D-GA. The results at the 7-year follow-up revealed significant weight loss in the PWS group and spatial-temporal changes in gait parameters (velocity, step length and cadence). With regard to the hip joint, there were significant changes in terms of hip position, which is less flexed. Knee flexion-extension showed a reduction of flexion in swing phase and of its excursion. No changes of the ankle position were evident. As for ankle kinetics, we observed in the second session higher values for the peak of ankle power in terminal stance in comparison to the first session. No changes were found in terms of ankle kinetics. The findings demonstrated improvements associated to long-term weight loss, especially in terms of spatial-temporal parameters and at hip level. Our results back the call for early weight loss interventions during childhood, which would allow the development of motor patterns under normal body weight conditions.

Duarte Nde A, Grecco LA, Galli M, Fregni F, Oliveira CS.
Effect of transcranial direct-current stimulation combined with treadmill training on balance and functional performance in children with cerebral palsy: a double-blind randomized controlled trial.
PLoS One. 2014 Aug 29;9(8):e105777.

Cerebral palsy refers to permanent, mutable motor development disorders stemming from a primary brain lesion, causing secondary musculoskeletal problems and limitations in activities of daily living. The aim of the present study was to determine the effects of gait training combined

with transcranial direct-current stimulation over the primary motor cortex on balance and functional performance in children with cerebral palsy.
A double-blind randomized controlled study was carried out with 24 children aged five to 12 years with cerebral palsy randomly allocated to two intervention groups (blocks of six and stratified based on GMFCS level (levels I-II or level III).The experimental group (12 children) was submitted to treadmill training and anodal stimulation of the primary motor cortex. The control group (12 children) was submitted to treadmill training and placebo transcranial direct-current stimulation. Training was performed in five weekly sessions for 2 weeks. Evaluations consisted of stabilometric analysis as well as the administration of the Pediatric Balance Scale and Pediatric Evaluation of Disability Inventory one week before the intervention, one week after the completion of the intervention and one month after the completion of the intervention. All patients and two examiners were blinded to the allocation of the children to the different groups.The experimental group exhibited better results in comparison to the control group with regard to anteroposterior sway (eyes open and closed; $p<0.05$), mediolateral sway (eyes closed; $p<0.05$) and the Pediatric Balance Scale both one week and one month after the completion of the protocol.
Gait training on a treadmill combined with anodal stimulation of the primary motor cortex led to improvements in static balance and functional performance in children with cerebral palsy.

Ferreira LA, Cimolin V, Costici PF, Albertini G, Oliveira CS, Galli M.
Effects of gastrocnemius fascia lengthening on gait pattern in children with cerebral palsy using the Gait Profile Score.
Res Dev Disabil. 2014 May;35(5):1137-1143.

The aim of the present study was to investigate the efficacy of the GPS regarding the quantification of changes in gait following the gastrocnemius fascia lengthening in children with CP. Nineteen children with CP were selected and evaluated in the preoperative period (PRE session) and approximately one year postoperatively (POST session; mean 13.1 ± 5.1 months) using 3D gait analysis and computing the GPS and GVSs. As the GPS represents the difference between the patient's data and the average from the reference dataset, the higher the value of GPS is, more compromised gait of the subject. A statistically significant improvement in mean GPS was found in the POST session (PRE: 13.38 ± 5°; POST: 10.26 ± 2.41°; $p<0.05$), with an improvement close to 23%. Moreover, the GVSs demonstrated statistically significant improvements in ankle dorsi-plantarflexion (PRE: 22.20 ± 16.36°; POST: 11.50 ± 6.57°; $p<0.05$) and pelvic rotation (PRE: 9.53 ± 3.87°; POST: 6.47 ± 2.98°; $p<0.05$). A strong correlation ($r=0.75$; $p<0.05$) was found between the preoperative GPS and the percentage of GPS improvement. The results demonstrated that the gastrocnemius fascia lengthening produced a global gait pattern improvement, as showed by the GPS value, which decreased after surgery. Besides this, the GVS permitted to better evidence the joints more compromised by the pathology and their improvement due to the surgery, in this case not only the GVS of the ankle joint but also of the pelvis were characterized by higher GVS values.

Galli M, Cimolin V, Rigoldi C, Condoluci C, Albertini G.
Effects of obesity on gait pattern in young individuals with Down syndrome.
Int J Rehabil Res. 2014 Nov 21. [Epub ahead of print]

In individuals with Down syndrome (DS), the prevalence of obesity is widespread; despite this, there are no experimental studies on the effect of obesity on gait strategy in DS individuals. The aim of this study is to assess the clinical gait analysis of a group of obese individuals with DS and a group of nonobese individuals with DS to determine whether obesity produces a different gait pattern in these participants. In addition, although females and males share a similar mass, they are characterized by different fat distribution and/or accumulation; thus, the presence of differences between females and males within the two DS groups was investigated. Gait analysis data of a group of 78 young individuals with DS and 20 normal-weight participants in the 5-18-year age range were considered. Among DS individuals, 40 were classified as obese (obese DS group), whereas 38 were classified as normal weight (nonobese groups). A three-dimensional gait analysis was carried out using an optoelectronic system, force platforms and video recording. Spatiotemporal, kinematic and kinetic parameters were identified and calculated for each participant. Our results show that most of the parameters were similar in the two groups of DS participants; the only differences were in terms of stance duration, longer in the obese DS group and dorsiflexion ability during the swing phase, which was limited in the obese DS group. The two DS groups were significantly different in terms of ankle stiffness (Ka index): both groups were characterized by reduced values compared with the control group, but the obese group presented lower values with respect to nonobese participants. The data showed that females were characterized by significant modifications of gait pattern compared with males in both groups, in particular, at proximal levels, such as the hip and the pelvis. Our findings indicate that the presence of obesity exerts effects on gait pattern in DS individuals and in particular on ankle joint stiffness. These results may have special clinical relevance; the biomechanical comparison of gait in young obese and nonobese DS individuals may provide a basis for developing either specific or common rehabilitative strategies.

Galli M, Cimolin V, Rigoldi C, Pau M, Costici P, Albertini G.
The effects of low arched feet on foot rotation during gait in children with Down syndrome.
J Intellect Disabil Res. 2014 Aug;58(8):758-764.

In children with Down syndrome (DS) hypotonia and ligament laxity are characteristic features which cause a number of orthopaedic issues, such as flat foot. The aim of this study was to determine if children with flat foot are characterised by an accentuated external foot rotation during walking.
Fifty-five children with DS and 15 typically developing children recruited as control group were assessed using three-dimensional gait analysis, using an optoelectronic system, force platforms and video recording. Parameters related to foot rotation were identified and calculated and the participants' foot morphology was assessed using the arch index.
Data obtained in this study showed that while DS children without flat foot displayed the foot position on the transverse plane globally close to controls during the whole gait cycle, the DS children with flat foot were characterised by higher extra-rotation of the foot in comparison with those without flat foot and controls.
Our results suggest that the presence of flatfoot lead the children with DS to extra-rotate their feet more than the children without flat foot. From a clinical point of view, these results could enhance the rehabilitative programmes in DS.

Grecco LA, Duarte Nde A, Mendonça ME, Cimolin V, Galli M, Fregni F, Oliveira CS.
Transcranial direct current stimulation during treadmill training in children with cerebral palsy: A randomized controlled double-blind clinical trial.
Res Dev Disabil. 2014 Nov;35(11):2840-2848.

Impaired gait constitutes an important functional limitation in children with cerebral palsy (CP). Treadmill training has achieved encouraging results regarding improvements in the gait pattern of this population. Moreover, transcranial direct current stimulation (tDCS) is believed to potentiate the results achieved during the motor rehabilitation process. The aim of the present study was to determine the effect of the administration of tDCS during treadmill training on the gait pattern of children with spastic diparetic CP. A double-blind randomized controlled trial was carried out involving 24 children with CP allocated to either an experimental group (active anodal tDCS [1mA] over the primary motor cortex of the dominant hemisphere) or control group (placebo tDCS) during ten 20-min sessions of treadmill training. The experimental group exhibited improvements in temporal functional mobility, gait variables (spatiotemporal and kinematics variables). The results

were maintained one month after the end of the intervention. There was a significant change in corticospinal excitability as compared to control group. In the present study, the administration of tDCS during treadmill training potentiated the effects of motor training in children with spastic diparetic CP.

Pau M, Coghe G, Atzeni C, Corona F, Pilloni G, Marrosu MG, Cocco E, Galli M.
Novel characterization of gait impairments in people with multiple sclerosis by means of the gait profile score.
J Neurol Sci. 2014 Oct 15;345(1-2):159-163.

The assessment of gait abnormalities in individuals with multiple sclerosis (MS) represents a key factor in evaluating the effectiveness of rehabilitation treatments. Despite the availability of sophisticated equipment to objectively evaluate the kinematic aspects of gait, there are still some difficulties in processing the large and complex amount of data they produce in the daily clinical routine. On the basis of the above-mentioned considerations we propose a novel characterization of gait kinematics in individuals with MS, based on a single measure (gait profile score, GPS) obtained from a quantitative three-dimensional analysis of gait performed using an opto-electronic system. We also investigated the correlation between GPS and the Expanded Disability Status Scale (EDSS) values. Thirty-four patients suffering from relapsing-remitting MS (13 female, 21 male, mean age 46.7 years) with an EDSS score of ≤6 underwent a gait analysis from which the GPS index was calculated. Their results were compared with those of a control group of healthy age- and gender-matched subjects. The GPS of individuals with MS was found significantly higher with respect to controls (9.12° vs. 5.67°, $p<0.001$) as the result of kinematic differences in gait patterns referring to pelvic tilt and rotation, hip flexion-extension and rotation, knee flexion-extension and ankle dorsi- and plantar-flexion. A moderate correlation was also found between the EDSS score of the participants and their GPS values ($r = 0.63$, $p < 0.001$). The GPS index thus appears suitable to represent gait deviations from physiological patterns in individuals affected by MS and potentially useful in assessing the outcomes related both to rehabilitation programs and pharmacologic/physical therapies.

Rigoldi C, Galli M, Mainardi L, Albertini G.
Evaluation of posture signal using entropy analysis and fractal dimension in adults with Down syndrome.
Comput Methods Biomech Biomed Engin. 2014 Apr;17(5):474-479.

The aim of this study was to explore new techniques in analysing postural control using nonlinear time-series analysis and to relate these results with the clinical knowledge on the postural system in Down syndrome (DS) subjects. In order to achieve the goal, we analysed the time domain and the frequency domain behaviour, the fractal dimension and the entropy of the centre of pressure signal in both directions during quiet standing in 35 participants with DS, comparing the results with a control population. DS patients evidenced a lack in postural control in anterior-posterior direction due to the impairment both in the high organisation and synergies and in the impairments due to ligament laxity and hypotonia. Maintaining posture is a task achieved by the integration of visual, vestibular and somatosensory receptors and the dynamical nature of this signal gives fundamental data about the lack of postural control in specific pathological condition.

Romano A, Albertini G, Guida D, Cornia R, Settecasi C, Condoluci C, Moraschi M, Fantozzi LM, Bozzao A, Pierallini A.
A Cervical Flexion-Extension MRI Study in Down Syndrome.
Indian J Pediatr. 2014 Sep 2. [Epub ahead of print]

To assess what kind of information MR examination in flexed and extended positions provides in Down syndrome subjects with suspected cranio-cervical instability.
Between 2005 and 2008, 35 subjects with DS were recruited in the study. Ethics committee approval was granted and a signed informed consent was obtained from the parents. All the subjects were affected by hypotonic status and ligament laxity established by clinical evaluation, but were asymptomatic about focal neurological symptoms due to medullar damage caused by cranio-cervical instability. Each patient underwent lateral supine radiographs and MR imaging in the neutral, active flexed and extended positions. For evaluating the atlanto-axial and atlanto-occipital joint stability, multiple measurements were calculated.
A significant reduction of anterior subarachnoid space in flexed position was evident in DS subjects compared to healthy controls in neutral and flexed positions. Both, space available for cord and ligamentous thickness showed significant differences between DS subjects and healthy controls. In DS subjects with occipito-cervical instability, the anterior subarachnoidal space reduction was significantly reduced in flexed position.
In DS subjects with asymptomatic cranio-cervical instability, anterior subarachnoidal evaluation and ligamentous status could add new information about the risk of spinal cord damage.

Salami F, Vimercati SL, Rigoldi C, Taebi A, Albertini G, Galli M.
Mechanical energy assessment of adult with Down syndrome during walking with obstacle avoidance.
Res Dev Disabil. 2014 Aug;35(8):1856-1862.

The aim of this study is analyzing the differences between plane walking and stepping over an obstacle for two groups of healthy people and people with Down syndrome and then, evaluating the movement efficiency between the groups by comprising of their mechanical energy exchanges. 39 adults including two groups of 21 people with Down syndrome (age: 21.6 ± 7 years) and 18 healthy people (age: 25.1 ± 2.4 years) participated in this research. The test has been done in two conditions, first in plane walking and second in walking with an obstacle (10% of the subject's height). The gait data were acquired using quantitative movement analysis, composed of an optoelectronic system (Elite2002, BTS) with eight infrared cameras. Mechanical energy exchanges are computed by dedicated software and finally the data including spatiotemporal parameters, mechanical energy parameters and energy recovery of gait cycle are analyzed by statistical software to find significant differences. Regards to spatiotemporal parameters velocity and step length are lower in people with Down syndrome. Mechanical energy parameters particularly energy recovery does not change from healthy people to people with Down syndrome. However, there are some differences in inter-group through plane walking to obstacle avoidance and it means people with Down syndrome probably use their residual abilities in the most efficient way to achieve the main goal of an efficient energy recovery.

Sale P, Stocchi F, Galafate D, De Pandis MF, Le Pera D, Sova I, Galli M, Foti C, Franceschini M.
Effects of robot assisted gait training in progressive supranuclear palsy (PSP): a preliminary report.
Front Hum Neurosci. 2014 Apr 17;8:207.

Progressive supranuclear palsy (PSP) is a rare neurodegenerative disease clinically characterized by prominent axial extrapyramidal motor symptoms with frequent falls. Over the last years the introduction of robotic technologies to recover lower limb function has been greatly employed in the rehabilitative practice. This observational trial is aimed at investigating the changes in the main spatiotemporal following end-effector robot training in people with PSP.
It is a pilot observational trial.
Five cognitively intact participants with PSP and gait disorders were enrolled.
Patients were submitted to a rehabilitative program of robot-assisted walking sessions for 45 min, 5 times a week for 4 weeks.

The spatiotemporal parameters at the beginning (T0) and at the end of treatment (T1) were recorded by a gait analysis laboratory.
Robot training was feasible, acceptable and safe and all participants completed the prescribed training sessions. All patients showed an improvement in the gait spatiotemporal index (Mean velocity, Cadence, Step length, and Step width) (T0 vs. T1).
Robot training is a feasible and safe form of rehabilitation for cognitively intact people with PSP. The lack of side effects and the positive results in the gait parameter index in all patients support the recommendation to extend the trials of this treatment. Further investigation regarding the effectiveness of robot training in time is necessary.

Siniscalchi A, Scaglione F, Sanzaro E, Iemolo F, Albertini G, Quirino G, Manes MT, Gratteri S, Mercuri NB, De Sarro G, Gallelli L.
Effects of phenobarbital and levetiracetam on PR and QTc Intervals in patients with post-stroke seizure.
Clin Drug Investig. 2014 Dec;34(12):879-886.

Sudden unexplained/unexpected death (SUDEP) is related to high mortality in patients with epilepsy. The prolongation of QT interval, involved in cardiac arrhythmia-related SUDEP, may be precipitated by antiepileptic drugs (AEDs). In this study, we evaluated the effects of phenobarbital and levetiracetam on PR-QTc intervals in patients with post-stroke seizures.
We performed an open-label, parallel group, prospective, multicenter study between June 2009 and December 2013 in patients older than 18 years of age with a clinical diagnosis of post-stroke seizure and treated with phenobarbital or levetiracetam. In order to exclude a role of cerebral post-stroke injury on modulation of PR and QTc intervals, patients with cerebral post-stroke injury and without seizures were also enrolled as controls.
Interictal electrocardiography analysis revealed no significant difference in PR interval between patients treated with an AED (n = 49) and control patients (n = 50) (181.25 ± 12.05 vs. 182.4 ± 10.3 ms; $p > 0.05$). In contrast, a significantly longer QTc interval was recorded in patients treated with an AED compared with control patients (441.2 ± 56.6 vs. 396.8 ± 49.3 ms; $p < 0.01$). Patients treated with phenobarbital showed a significantly longer QTc interval than patients treated with levetiracetam (460.0 ± 57.2 vs. 421.5 ± 50.1 ms; $p < 0.05$).
The study reported that in patients with late post-stroke seizures, phenobarbital prolonged QTc interval more so than levetiracetam.

Vimercati SL, Galli M, Stella G, Caiazzo G, Ancillao A, Albertini G.
Clumsiness in fine motor tasks: evidence from the quantitative drawing evaluation of children with Down Syndrome.
J Intellect Disabil Res. 2014 Apr 28. [Epub ahead of print]

Drawing tests are commonly used for the clinical evaluation of cognitive capabilities in children with learning disabilities. We analysed quantitatively the drawings of children with Down Syndrome (DS) and of healthy, mental age-matched controls to characterise the features of fine motor skills in DS during a drawing task, with particular attention to clumsiness, a well-known feature of DS gross movements.
Twenty-three children with DS and 13 controls hand-copied the figures of a circle, a cross and a square on a sheet. An optoelectronic system allowed the acquisition of the three-dimensional track of the drawing. The participants' posture and upper limb movements were analysed as well. Results showed that the participants with DS tended to draw faster but with less accuracy than controls.
While clumsiness in gross movements manifests mainly as slow, less efficient movements, it manifests as high velocity and inaccurate movements in fine motor tasks such as drawing.

Franchi C, Mari D, Tettamanti M, Pasina L, Djade CD, Mannucci PM, Onder G, Bernabei R, Gussoni G, Bonassi S, Nobili A; ELICADHE Investigators.
E-learning to improve the drug prescribing in the hospitalized elderly patients: the ELICADHE feasibility pilot study.
Aging Clin Exp Res. 2014 Aug;26(4):435-443.

E-learning is an efficient and cost-effective educational method.
This study aimed at evaluating the feasibility of an educational e-learning intervention, focused on teaching geriatric pharmacology and notions of comprehensive geriatric assessment, to improve drug prescribing to hospitalized elderly patients.
Eight geriatric and internal medicine wards were randomized to intervention (e-learning educational program) or control. Clinicians of the two groups had to complete a specific per group e-learning program in 30 days. Then, ten patients (aged ≥75 years) had to be consecutively enrolled collecting clinical data at hospital admission, discharge, and 3 months later. The quality of prescription was evaluated comparing the prevalence of potentially inappropriate medications through Beer's criteria and of potential drug-drug interactions through a specific computerized database.
The study feasibility was confirmed by the high percentage (90 %) of clinicians who completed the e-learning program, the recruitment, and follow-up of all planned patients. The intervention was well accepted by all participating clinicians who judged positively (a mean score of >3 points on a scale of 5 points: 0 = useless; 5 = most useful) the specific contents, the methodology applied, the clinical relevance and utility of e-learning contents and tools for the evaluation of the appropriateness of drug prescribing.
The pilot study met all the requested goals. The main study is currently ongoing and is planned to finish on July 2015.

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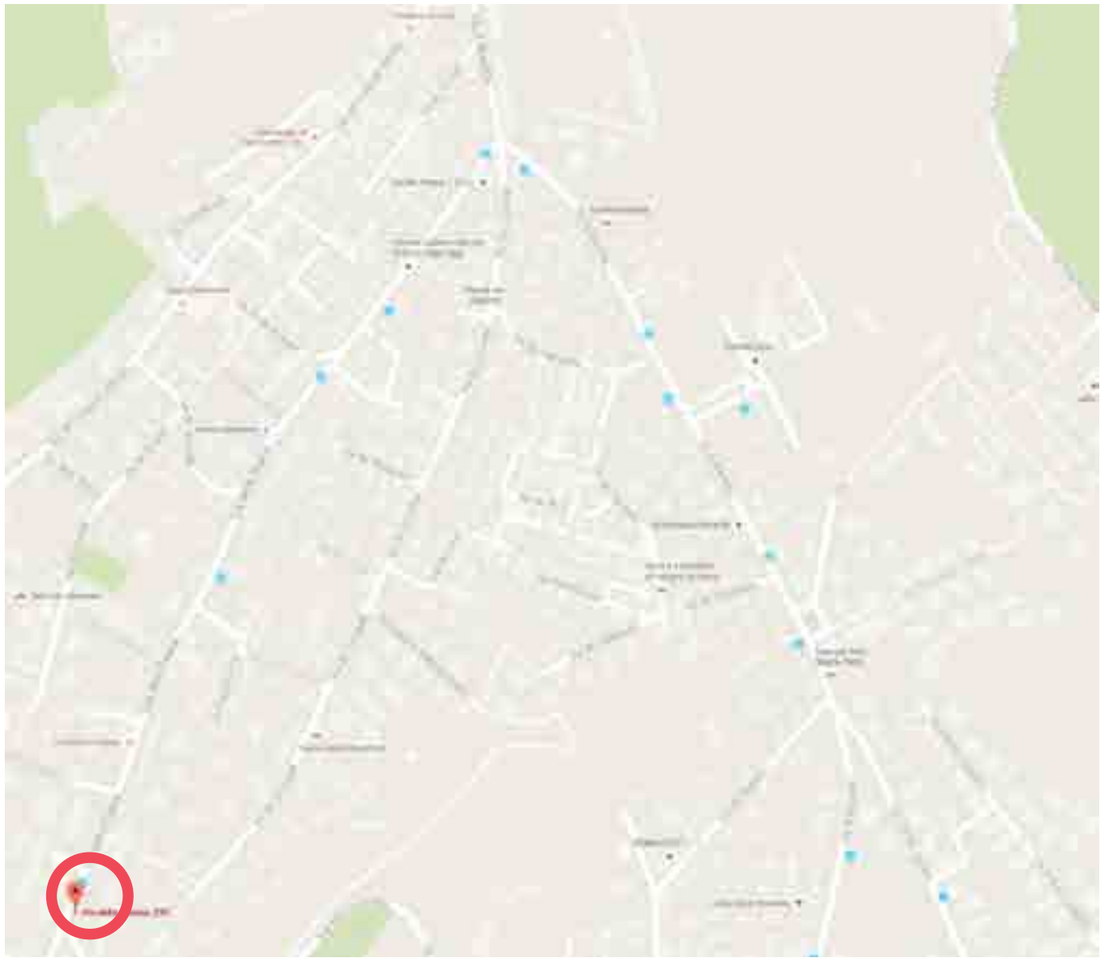

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