The Department of Neuroscience is formed by twelve Laboratories; the activities of research are dedicated to the study of neurological and psychiatric diseases, evaluated by the biological point of view, clinical and epidemiological aspects and the quality of care. In the Department, activities like drug information service, preparation of clinical trial protocols and epidemiological studies are developed not only in the neurological field. Traditionally, part of the Department is devoted to the development of experimental models for the pharmacological, neurochemical and pathogenetic studies in Alzheimer, Parkinson or prion's diseases, epilepsy, depression and cognitive impairment. More recently, consolidated expertise were established in the studies of amyotrophic lateral sclerosis (ALS) pathogenesis, cerebral stroke, Rett syndrome, trauma and drug abuse. Some of these disorders, like epilepsy, ALS and Alzheimer's disease, are investigated from the clinical and epidemiological points of view to evaluate drug and care efficacy. Genetic investigations and the use of biomaterial tools are the last acquired expertise. A specific sector is dedicated to the elderly with cohort studies in relation to the dementia, but also to the evaluation of quality of services and polytherapies in aging. The activities of the Department are aimed to the integration of the different expertise to develop multidisciplinary approaches. The purpose is to address at different levels, knowledge, therapy and clinical practice to the numerous questions, largely unresolved, proposed by the disorders of nervous system.

MAIN RESULTS (2016)

The studies developed in the Department during the 2016 are related to neurodegenerative disorders, epilepsy, cerebral stroke and spinal/brain trauma, however also the analysis of the appropriateness of the therapies in the elderly has been object of various studies.

Growing evidences show that inflammation is involved in the genesis and the progression of pathological events, acute and chronic. On these basis several laboratories are engaged to develop experimental models useful to identify therapeutic approaches based on the inflammatory components of the neurological disorders, in some cases the studies have achieved the appropriate evidence to support the clinical investigations. The use of biomaterials and nanoparticles...
to pass the blood brain barrier and to guarantee a slow release of the drugs is another aspect treated transversally in the Department. Other experimental projects are devoted to stimulate the regenerative response following the acute spinal/brain traumatic injury. In this contest and in neurodegenerative disorders models, it has been also investigated the use of staminal cells to favour the regenerative response. Another relevant aspect of the experimental research in Alzheimer and Parkinson disease, is focused on the pathogenetic role of the small soluble aggregates, named oligomers, responsible of the neuronal dysfunction associated to protein misfolding diseases, it has been coined the term “oligomeropathies” to underline the central role role of these forms. A relevant line of research that involves the Neurological Disorders Lab is the evaluation at the global level the frequency and the trend of the main disorders. The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD). The group associated to GBD project involved 1700 scientists 120 countries. GBD is coordinated by the Institute for Health Metrics and Evaluation (IHME, Washington University) and it is funded by Bill & Melinda Gates Foundation. The data collected and analyzed by the scientists documented the disabilities and mortality associated to 300 different disorders (including the pathologies associated to drug abuse) in 188 countries distint by sex age since 1990 up to 2015, allowing geographic and time comparisons. The instruments developed by HME to analyze the data can be utilized at global, national and local level, to understand the health trends during the time. The Italian scientists involved in the GBD at the moment are 15. Five of them belong to the IRCCS Mario Negri

SELECTED PUBLICATIONS (2016)


The lab studies evaluated the genetic and biological bases of neurodegenerative disorders associated to the aging, in particular Alzheimer’s disease (AD), spongiform encephalopathies (TSE) and Parkinson’s disease (PD), there is also a unit dedicated to spinal injury and regeneration. The genetic studies are focused to identification of causal factors in the familial forms or risk factors in sporadic ones. In both populations have been studied gene encoding proteins involved in the physiopathology of AD and PD. The role of proteic aggregates in the neurodegenerative pathogenesis has been investigated using in vitro and in vivo models. In the last years it has been shown the pathogenic role of oligomers, small soluble aggregates of β-amyloid and α-synuclein in AD and PD respectively, we coined the term oligomeropathies to indicate the relevance of these forms in the neuronal dysfunction that characterized these disorders. The development of experimental models based on the oligomers activity has demonstrated the role of inflammation in the neurodegenerative processes: The experimental evidence of the anti-amyloidogenic activity of doxycycline has been used to develop a protocol to test the preventive effect of the drug to avoid the development of fatal familial insomnia, a genetic form of prion disease in at risk subjects.

The specific objectives of the current research:
- Creation of translational models to develop potential therapeutic approaches
- Identification of genetic and biological markers of AD and PD
- Clarify the therapeutic role of doxycycline in TSE and AD
- Development of appropriate techniques to release the drug by nanoparticles and biomaterials
- Development of cellular model iPSC and potential cell therapy protocols

**MAIN RESULTS (2016)**

The activation of sirtuin 2, an enzymatic protein with deacetylasic activity, reduced the amyloidogenic metabolism and improve the cognition in two Alzheimer murine models.

The microglial modulation by minocycline induced a long lasting protective effect in an experimental model of spinal traumatic injury.
The cognitive decline induced by the cerebral application of small soluble aggregates (oligomers) of \( \beta \)-amyloid 1-40 and 1-42 is partially dependent on the inflammatory reaction involving non neuronal cells and it is antagonized by anti-inflammatory drugs. The oligomers of \( \alpha \)-synuclein, essential component of the Lewy bodies, intracellular aggregates that characterize Parkinson’s disease and other neurodegenerative disorders, injected in the cerebral ventricle have different features from the effect induced by \( \beta \)-oligomers, i.e. is not dependent from the activation of Toll-like 4 receptors.

Doxycycline, a tetracycline with a good passage of the blood brain barrier, reduced the formation of \( \beta \)-amyloid aggregates and antagonized the inflammatory component induced by the in vivo intracerebral application of \( \beta \)-oligomers.

**SELECTED PUBLICATIONS (2016)**


LABORATORY OF NEUROLOGICAL DISORDERS

HEAD OF LABORATORY

Ettore Beghi, M.D.
Neurology specialist. Research Fellow in Medical Statistics and Epidemiology, Mayo Clinic, Rochester, MN.
Past chair of the Epilepsy Center and the Neuropathology Unit, University of Milano-Bicocca.
Associate Editor of Neuroepidemiology and Epilepsia Open. Member of the Editorial Board of Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration, Clinical Neurology & Neurosurgery, Clinical Drug Investigation. Reference of 50 journals.
Chair of the European ALS registries. Co-chair of the Epidemiology Panel, European Academy of Neurology.
Author of more than 500 scientific publications (350 in indexed journals).

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RESEARCH ACTIVITIES

- Incidence, prevalence, risk factors, prognosis and treatment of epilepsy and seizures
- Incidence, risk factors, prognosis and treatment of amyotrophic lateral sclerosis
- Incidence, prevalence, treatments and rehabilitation of Parkinson disease
- Prevalence and treatment of headache
- Incidence, course and treatment of acute and chronic inflammatory polyradiculoneuropathy

The members of the Laboratory of Neurological Disorders have background and experience in the planning and conduction of descriptive, analytic, and experimental studies in the field of epilepsy, ALS and other acute and chronic neurological disorders. The head of the laboratory has long-lasting clinical experience maturated during pluriennial hospital activities. The clinical background and the need to perform studies in in- and outpatients with neurological disorders fueled collaborations with several Italian and foreign institutes which led to the implementation of collaborative groups and consortia with neurologists, child neurologists and general practitioners in the entire country. The staff of the laboratory has also gained experience in the assessment of administrative records, a valuable source of epidemiological data in large strata of the Italian population, and in the implementation and conduction of randomized clinical trials. Collaborations are also in act between the laboratory and other groups involved in basic science located in the Mario Negri Institute and occasionally also in external institutions.

MAIN RESULTS (2016)

Epilepsy diagnosis: In about one third of cases a confident diagnosis of epileptic seizures vs. psychogenic non-epileptic seizures can be established on clinical ground based on video data alone. This finding benefits all affected patients, particularly those with no access to video-EEG monitoring units. Epilepsy prognosis: The long-term prognosis of epilepsy is favorable in up to 80% of cases. Early seizure remission is not invariably followed by terminal remission and seizure outcome varies according to well-defined patterns. Prolonged seizure remission and terminal remission can be observed in patients with drug-resistant epilepsy.
suggesting that drug resistance is a dynamic process. Epilepsy treatment: Treatment of the first unprovoked seizure reduces the risk of a subsequent seizure but does not affect long-term seizure control. Antiepileptic drugs are associated with adverse events, but do not seem to affect the mortality rate. The decision to start antiepileptic drug treatment following a first unprovoked seizure should be individualized and based on patient preference, clinical, legal, and socio-cultural factors. ALS diagnosis: 5% of patients previously diagnosed with ALS are later found to have other diseases. Thus, at the time of a first diagnosis of ALS, the possibility still exists that another, less severe clinical condition, is present.

SELECTED PUBLICATIONS (2016)


IRFMN

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LABORATORY OF MOLECULAR NEUROBIOLOGY

Caterina Bendotti, Pharm.D.

She got her degree in Pharmacy at the University of Milano in 1984; Research assistant in Neuropharmacology I of the Mario Negri Institute (IRFMN) until 1986. From 1986 to 1988 post doc at the Genetic developmental Lab, Dept. of Physiology of the Johns Hopkins University, Baltimore, USA. 1988 -1992 research fellow in the laboratory of Neuropharmacology and in the 1992, she became head of the Unit and from 1998 of the Lab of Molecular Neurobiology at the IRFMN. Member of scientific advisory boards (SINS, MND, TLFAISLA), editorial board (J.N.C.; CNS & ND-DT), international meetings (MND, ENCALLS), co-organizer of scientific meetings (2007, 2010, 2014, 2016), Co-author of 160 articles (H index=42)

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RESEARCH ACTIVITIES

The laboratory is mainly engaged in the study of Amyotrophic Lateral Sclerosis (ALS), a rare disease caused by the degeneration of motor neurons that control muscles for movement and breathing causing total paralysis and death within 2-5 years of diagnosis. There is no cure for ALS. Our main interest is to understand, through the study of transgenic mice carrying the human SOD1 gene mutation, responsible for about 20% of familial ALS, how this disease develops and progresses and how to hinder its evolution. The main laboratory research projects are:

- Comparative analysis of two ALS mouse models (transgenic mice for human mutant SOD1 G93A) that despite they carry the same transgene number, show a different onset and duration of the disease. The variability in the onset and course of the disease is also a characteristic of ALS patients. The purpose is to investigate the mechanisms at the basis of this difference in order to identify drug targets for potential therapies that may slow the disease in early stages and for the identification of prognostic biomarkers useful for monitoring the efficacy of experimental treatments.

- Investigation of the molecular mechanisms of motor neuron degeneration in primary cultures of motor neurons, astrocytes and microglia.

- Evaluation of pharmacological therapeutic interventions, cell or gene therapy in mouse model of ALS in the context of various collaborations.

MAIN RESULTS (2016)

Characterization of the neuropathological and biochemical profile of the two murine models of ALS and demonstration that the accelerated progression of the disease does not depend on the rapid loss of motor neurons but rather to their dysfunction especially at the level of the axon and neuromuscular junction. This happens through a deficiency of the immune response in the peripheral nerve level that would prevent axon regeneration. Thus, the rapid course of the disease in mice, and possibly humans, with ALS might be slowed by restoring proper immune response. Among the potential therapeutic targets we identified MHC1 and CCL2. In vivo studies are currently underway to validate this hypothesis. The earlier onset and rapid progression of the disease also seems to depend on
the early accumulation of protein aggregates in motor neurons due to low levels of chaperones and proteasome subunits. This observation was recently confirmed from the comparative analysis of the blood cells of patients with early versus late onset. In fact, in the first group it was observed a reduction of factors involved in the protein quality control as foldase and chaperones putting forward to the development of therapeutic approaches to strengthening the control system of protein quality.

SELECTED PUBLICATIONS (2016)


Nardo G, Trolese MC, Bendotti C. Major Histocompatibility Complex I Expression by Motor Neurons and its Implication in Amyotrophic Lateral Sclerosis. Front Neurol. 2016 7:89


RESEARCH ACTIVITIES

The aim of our laboratory is to identify the mechanisms and the key proteins that regulate the intracellular pathways of in both chronic and acute neurodegenerative diseases as well as neurodevelopment syndromes. To better identify the protein signaling, we inhibit the action of these proteins with the use of cell penetrating peptides to prevent neurodegeneration. As a strategy against AD synaptic dysfunction, we designed a peptide able to interact with amyloid-β (Aβ) protein reducing its aggregation and toxicity, in fact this small peptide Tat-Aβ1-6A2V(D) prevents the synaptopathy both in vitro and in vivo. We also characterized the synaptic injury in P301L mouse model of tauopathy proving a strong interaction between sex and tau: females are affected more severely than males, showing an increase of agglomerates of P-Tau correlated to a proportional decrease in postsynaptic marker levels (Buccarello et al. 2016). In the same model of tauopathy, we also demonstrated how a low fat protein diet induces a neuroprotective effect against synaptopathology and cognitive-locomotor impairments. In Rett syndrome, we demonstrated, for the first time, that JNK is a key molecule that play a pivotal role in this pathology, regulating general wellbeing conditions as well as the biochemical alterations of dendritic spine and the related behavioral impairments (i.e., locomotor and exploratory performances) in MeCP2 mice models. The D-JNKI1 treatment induced an improvement of wellbeing and a reduction of behavioral impairment and synaptic injury.

MAIN RESULTS (2016)

Alzheimer disease (AD): the cell permeable peptide Aβ1-6A2V(TAT)(D), which counteracts the Aβ oligomers toxic effect, showed a neuroprotective effect preventing the synaptopathy both in vitro and in vivo AD model (Cimini et al. 2016). Tauopathy: The P301L model showed a spine injury similar to that detected in AD, with P-tau accumulation in the postsynaptic terminal most marked in females than in males (Buccarello et al. 2016). We found also a neuroprotective effect of a low fat protein diet on synaptopathy, cognitive and locomotor damage in the same mouse model. JNK in the presynaptic compartment: with the Super Resolution and biochemical methods we localized JNK in the presynaptic region and its interaction with the
t-SNARE proteins, in particular with Syntaxin-1/2 and SNAP25. Electrophysiological studies proved the JNK’s action on the modulation of vesicle release in the presynaptic compartment.

Rett Syndrome (RTT): we demonstrated for the first time, a role of JNK in this pathology. Treatment with D-JNKI1 in MeCP2y/- mouse model with severe phenotype leads to: 1) an improvement of wellbeing, 2) a recovery of locomotor impairment, 3) a recovery of synaptic function and 4) a protection of inflammatory state.

Angelman syndrome (AS): we detected the JNK activation in AS mouse model that leading to an alteration of dendritic spines; by analogy to RTT we will evaluate the effect of D-JNKI1 peptide in this model.

SELECTED PUBLICATIONS (2016)


RESEARCH ACTIVITIES

Research interests span the areas of Behavioural Neuroscience and Psychopharmacology.
Research projects mainly focus on experimental animal models and their translational application to complex human disorders such as drug abuse, anxiety and depression.
Effects of recreational drug use in adolescent. This pattern of drug use is growing in number and is becoming an international problem, even without leading to drug addiction and dependence.
Behavioural and pharmacological characterization of the so called “New Psychoactive Substances” to establish how they work to produce changes in brain chemistry and how these changes may reinforce behaviour to induce drug taking and possibly abuse.
The transition from initial recreational drug use to addiction, in adolescents and adults may occur through the progressive engagement of different pavlovian and instrumental learning systems in the brain.
Investigation of the neural basis of these learning mechanisms underlying addiction as well as the molecular and neurochemical basis of drug conditioned cues inducing seeking behaviour.
Preclinical efficacy of pharmacological agents in controlling drug seeking and relapse.

MAIN RESULTS (2016)

Experimental approaches include behavioural and cognitive testing in rodents, intravenous drug self-administration (cocaine, amphetamine, nicotine, GHB) operant conditioning maintained by sucrose and saccharine, oral drug self-administration (alcohol, alcoholic-beer, near-beer, saccharine solution), unbiased conditioned place preference (to evaluate mechanisms underlying the acquisition as well as the expression of drug-induced place conditioning, extinction and reinstatement; cocaine, d-amphetamine, morphine, GHB, New Psychoactive Drugs), intra-cerebral and systemic pharmacology, targeted neural and neurochemical brain lesions, immuno-histochemistry, pre-clinical magnetic resonance imaging (MRI).
SELECTED PUBLICATIONS (2016)


RESEARCH ACTIVITIES

Prion diseases, also known as transmissible spongiform encephalopathies, are progressive and invariably fatal degenerative disorders of the central nervous system that affect humans and other animals. They result from the conformational change of a cellular protein of unclear function (denominated prion protein, PrP) into a self-propagating pathogenic isoform (prion) that accumulates in the brain of the patients. Three different manifestations of prion diseases are recognized: sporadic, infectious and genetic. Genetic prion diseases display autosomal dominant inheritance and are linked to mutations in the PrP gene, on chromosome 20. Different PrP mutations are associated with different disease phenotypes.

Specific aims of the program:

• To understand the mechanisms of synaptic dysfunction and phenotypic heterogeneity in genetic prion diseases.
• To develop anti-prion molecules.
• To study prion-like protein spreading in neurodegenerative diseases.

MAIN RESULTS (2016)

How different mutant PrPs cause different genetic prion diseases is not known. We found that different mutant PrPs accumulate in different compartments of the neuronal secretory pathway, impairing the membrane delivery of ion channels essential for neuronal function.

Our results suggest that the phenotypic variability of genetic prion diseases may be due to different effects of mutant PrP on intracellular transport (Chiesa et al., 2016). We have characterized the neuroprotective properties of a cationic tetrapyrole with anti-prion activity (Massignan et al., 2016), and discovered new anti-prion molecules which are being tested in cell and mouse models of acquired and genetic prion disease.

We found that the prion protein family member Shadoo induces ionic currents and makes cells hypersensitive to the same antibiotics as some mutant PrPs. These results suggest that the channel activity that is characteristic to some pathogenic PrP mutants may be linked to a physiological function of Shadoo (Nyste et al., 2016).

We have found that monoclonal antibody 15B3 that selectively detects patholo-
Biological aggregates of PrP also recognizes oligomeric but not monomeric forms of amyloid-β, an aggregating peptide implicated in the pathogenesis of Alzheimer’s disease. Thus the 15B3 antibody offers a potential research, diagnostic and therapeutic tool for Alzheimer’s disease.

**SELECTED PUBLICATIONS (2016)**


Three-dimensional tomography reconstruction of an abnormal Golgi in a thalamic neuron of fatal familial insomnia transgenic mice.
RESEARCH ACTIVITIES

The Laboratory main scientific interests include the pathogenesis of stroke and of traumatic brain injury and the development of protective strategies. The laboratory has significantly contributed to the knowledge of the role of inflammation in brain injury and to the identification of novel therapeutic strategies through manipulation of the inflammatory response. Clinically relevant experimental models of cerebral ischemia and brain trauma, and cellular cultures to reproduce selected aspects of the conditions are available in the lab. Clinical research studies in patients are also performed.

Research lines:
• The complement system in acute brain injury: early work of the lab has established that complement inhibition by C1-inhibitor or by targeting the lectin pathway of complement activation (LP) provide neuroprotection with a wide therapeutic window; present efforts aim at elucidating the neuroprotective mechanisms.
• Brain endothelium and thromboinflammation: investigations on the vascular events, focusing on hemodynamics by two-photon microscopy and phenotype profiling of activated endothelium in experimental models of stroke and traumatic brain injury; endothelial activation in cell cultures following exposure to hypoxic or inflammatory stimuli. The lab research includes also analysis of atherosclerotic plaques in patients, vascular events associated to cardiovascular pathology.

MAIN RESULTS (2016)
• Pharmacological targeting of the lectin pathway of complement activation (LP) is protective in experimental traumatic brain injury. This result was achieved thanks to the synthesis of a novel glycomimetic mannose-binding lectin (MBL) antagonist and the characterization of its binding properties (De Blasio et al., 2016; Stravalaci et al. 2016; Goli et al, 2016).
• The LP appears to be at a crossroad between complement, coagulation and kinin cascades, making it a hub in several pathogenic vascular events. We have reviewed available clinical evidence that implicate the LP in the progression...
of brain damage in stroke, with LP circulating recognition molecules acting as prognostic markers in ischemic stroke patients (Fumagalli et al, 2016; Zangari et al, 2016).

- Macrophages recruited in the ischemic lesion provide selective protective functions and support the idea that they act as a key anti-inflammatory subpopulation, limiting the detrimental phase of acute brain ischemia. We found that depletion of macrophages worsens the ischemic lesion and increases the M1/M2 polarization ratio in a mouse model of stroke, highlighting a critical role of macrophages at the early stage of lesion evolution (Perego et al., 2016).

- Pharmacological manipulations or mesenchymal stem cells induce morphological and phenotypical switch of microglia and/or recruited macrophages thus driving protective polarization in vitro and in vivo injury (Pasetto et al, in press, Pischitta et al, 2016).

SELECTED PUBLICATIONS (2016)


LABORATORY OF NEUROCHEMISTRY AND BEHAVIOR

HEAD OF LABORATORY

Roberto William Invernizzi, Biol.Sci.D.

Started his career in the laboratory of Neuropharmacology of the Istituto di Ricerche Farmacologiche “Mario Negri” in 1976, where, at present, he heads the Laboratory of Neurochemistry and Behavior.

In 1986 he got his degree in Biological Sciences at the Milan State University.

He spent short periods as visiting scientist at the Karolinska Institutet in Stockholm (1988) and Nihon University in Tokyo (1995) and in 1996 he was nominated head of the Intracerebral Microdialysis Unit

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RESEARCH ACTIVITIES

- Neurobiological basis of psychotropic drug’s action
- Neurobiological basis of animal behaviour
- Role of brain serotonergic and glutamatergic systems in the effects of psychotropic drugs and in mechanisms controlling cognitive processes
- Development of novel pharmacological approaches for the treatment of Rett syndrome in an experimental model of the pathology, the Mecp2 knockout mice.

MAIN RESULTS (2016)

- The brain neurotransmitter serotonin (5-HT) is involved in the regulation of many brain functions and in the mechanism of action of various psychotropic drugs, including psychostimulants. We found that amphetamine-induced motor activity is strongly enhanced in mice lacking tryptophan hydroxylase-2 gene coding for the rate limiting enzyme in 5-HT synthesis. This finding suggests a significant role of 5-HT in the individual response to amphetamine’s effects.
- We investigated the role of cholesterol and the potential therapeutic effect of lovastatin in Mecp2 knockout mice, and found that the genetic background likely plays a major role in determining the effectiveness of lovastatin in rescuing motor deficits caused by Mecp2 deletion. In collaboration with the Analytical Instrumentation Unit of the “Mario Negri” Institute, we found that 24S-hydroxycholesterol (24S-OHC), a cholesterol metabolite mainly produced in the mammalian brain, was reduced in Mecp2 mutant mice. This suggests the occurrence of changes in brain cholesterol metabolism in RTT and the potential utility of using plasma levels of this metabolite as a biomarker of brain cholesterol homeostasis in RTT.
- In collaboration with other research teams, we contributed to establish the role of 5-HT in diurnal rhythms of aldehyde oxidase mutant mice and the role of glutamate reuptake in the potential therapeutic effect of stem cells in stroke.
SELECTED PUBLICATIONS (2016)


**STAFF**

Roberto William Invernizzi, Biol.Sci.D., Head of Laboratory

Mirjana Carli, Ph.D., Head of Pharmacology of Cognitive Behavior Unit

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**Serotonin and psychostimulants**

[Diagram showing serotonin and psychostimulants, with labels and data points indicating differences between WT and Tph2 ko mice in response to amphetamine.]
RESEARCH ACTIVITIES

Over the last thirty years the investigations of the Laboratory of Geriatric Neuropsychiatry have been mainly centered on the study of epidemiology and pharmacology (phase I, II, III trials and observational studies) of dementia and on the assessment of the quality of care and drug use in the elderly population. A large population-based survey has been conducted to investigate the prevalence, incidence and risk factors of dementia in the oldest old residing in the Varese province (Monzino 80-plus Study). Our research also includes the investigation of the relationship between various pathologies, particularly anemia, and the clinical, cognitive and functional condition of elderly subjects using data collected in another large population-based survey in Biella (Anemia and Health Study), and the evaluation of the quality of care of terminally ill patients in hospices (in collaboration with the Hospice “Via di Natale Franco Gallini”). In collaboration with the Geriatric Division of the Ospedali Regionali of Lugano and Mendrisio, Switzerland, we evaluate the impact of neuropsychological, functional and mobility variables on health-related outcomes and disease progression in hospitalized and ambulatory patients (Canton Ticino Study). Our laboratory has always been involved in developing and validating instruments able to reliably assess the different aspects characterising the clinical expression of dementia and Alzheimer’s disease: cognitive deficits, functional disability and behavioural disturbances, as well as global outcomes.

MAIN RESULTS (2016)

In the Monzino 80-plus prospective population-based study, the risk of dementia among the oldest-old was not significantly associated with a history of headache or with marital status at first visit. During 2016 the 510 patients with mild-to-moderate Alzheimer’s disease randomized all over Europe to the EU-FP7 NILVAD Study completed the 18-month follow-up period. The daily diet of 90% of the centenarians in the Centenarians at Trieste study consisted of milk, fruit and vegetables (both cooked or raw) throughout their lives, while red meat was eaten in 35% of the subjects and processed meat only in 21% of the centenarians. In the same population we saw a high percentage of emergency room use (30%), almost twice the specialist visits (16%); this could suggest a tendency to react to...
emergency situations rather than act preventively. In collaboration with the hospice “Via di Natale” of Aviano, in 2016 we initiated two research projects on patients with advanced cancer. The aim of the first study is to investigate whether the use of a set of clinical variables combined with the clinician’s judgement would improve the accuracy in estimating the life expectancy of these patients. In the second study, the nursing staff was involved to monitor the quality of death in the last hours of life of oncological terminal patients in hospice.

SELECTED PUBLICATIONS (2016)


LABORATORY OF QUALITY ASSESSMENT OF GERIATRIC THERAPIES AND SERVICES

RESEARCH ACTIVITIES

The Laboratory and the Units promote and coordinate:
• projects on appropriate prescribing in the frail elderly people with multimorbidity and polypharmacy, with particular attention to the iatrogenic risk, deprescribing and pharmacovigilance;
• projects in the field of public health for the study of the quality of assistance and the right advocacy and promotion in mental health;
• pharmacoepidemiological investigations based on administrative database, record-linkage and network analysis models for the study of the complexity, frailty and polypharmacy in the elderly;
• the REPOSI Registry, a clinical network of more than 80 internal medicine and geriatric wards for the study of multimorbidity and polypharmacy in hospitalized elderly patients;
• assessment of the impact of service organization on mental health, frailty and quality of life in different settings of care conducted with Policy makers and caregiver and patient associations;
• training and educational intervention on the rational use of drugs and mental health services for health and social workers and citizens.

Moreover, they developed INTERCheck-WEB® a computerized support system to optimize drug prescription in older adults that is used in many studies and in many hospitals and long-term care.

Finally, the laboratory provide to clinicians and citizens a drug information service.

MAIN RESULTS (2016)

Non-adherence to guidelines is highly prevalent among elderly AF patients, despite adherence is independently associated with lower risk of all-cause and CV deaths. The association between AF and dementia was no longer statistically significant when death was considered a competing risk.

Comparing patients exposed to polypharmacy to those without, no difference was found in the dosage of imatinib, cytogenetic and molecular responses and hematological and extra-hematological toxicity.

Using multiple correspondence analysis among hospitalized elderly, four frailty phenotypes differently associated with adverse events were found. They can help defining the best care.

HEAD OF LABORATORY

Alessandro Nobili, M.D.
Doctor in Medicine and Master in Biotechnological and Pharmacoepidemiological Research.
Expert in pharmacoepidemiology, methodology of clinical research and geriatric pharmacology.
Promoter and coordinator of many research projects in the field of evaluation of appropriateness of drug prescribing and assessment of quality of care and services for the elderly.
Author of many scientific publications in international and national journals.

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Male sex, age >85 years, polypharmacy, ED visits and hospital admissions in the previous year and the location of an ED within 10 km from the patient’s place were associated with a higher risk to have more ED visits. People with bipolar disorder have access to psychosocial interventions of proven efficacy only sporadically. The combination of an educational intervention and the CPSS achieved a reduction in inappropriate psychotropic drug use, psychotropic duplicates, and potentially severe DDIs in nursing homes. The use of a specific tool and training for the identification of patients at risk of psychosis, in the framework of the integration of child and adolescent mental health and adult mental health services, allowed to intercept a significant number of young people with mental states at risk of psychosis. Chronic polypharmacy is an independent predictor of adverse outcomes among community-dwelling elderly people.

**SELECTED PUBLICATIONS (2016)**


Pasina L, et al. Therapeutic Duplicates in a Cohort of Hospitalized Elderly Patients: Results from the REPOSI Study. Drugs Aging 2016;33:647-54


RESEARCH ACTIVITIES

The current research relates to the neurobiology of CNS diseases by covering neuroscience, neuropharmacology and neuroimmunology. More specifically, the laboratory studies with multidisciplinary approaches the molecular, structural, epigenetic and functional modifications in the brain potentially involved in the etiopathogenesis of seizures and the associated neurological co-morbidities.

The research is focused on neuroactive inflammatory mediators, a hallmark of human epileptogenic brain tissue, and molecules apt to resolve neuroinflammation using adult and developmental models of epilepsy. We especially address acquired or genetic forms of epilepsy using in vivo and in vitro experimental models. Our research programme includes the preclinical discovery and clinical validation of novel predictive and prognostic biomarkers of epilepsy using noninvasive measures such as detection of blood molecules, MRI-based imaging and electrophysiological signatures. Using animal models we are developing novel target-specific disease-modifying drugs with the ultimate scope of translating the laboratory findings to the clinical applications.

MAIN RESULTS (2016)

We discovered a potential novel molecular and mechanistic biomarker of epilepsy, namely the inflammatory mediator High Mobility group Box 1 (HMGB1), that predicts the therapeutic response to drugs and the development of epilepsy, or seizure relapse, both in in vivo rodent models of acquired epilepsy, and in patients.

We discovered noninvasive imaging (magnetic resonance spectroscopy) and behavioral cognitive deficit features which are predictive of epilepsy development after experience of an epileptogenic risk factor in animal models.

We identified combinations of antiinflammatory and antioxidant treatments, some of which in medical use, and microRNA-based epigenetic interventions that mediate clinically significant disease-modification effects in animal models of acquired epilepsy. These treatments when transiently applied either before or after disease onset greatly reduced the frequency and blocked the progression of spontaneous drug-resistant seizures, afforded neuroprotection and rescued the cognitive deficits in the animals.
We discovered that Monoacyl-glycerol-lipase (MAGL) is a new target for controlling benzodiazepine-resistant status epilepticus, a clinical emergence that can be reproduced in animal models. We also found that the therapeutic effect of MAGL inhibition is synergistic with the ketogenic diet, therefore providing a proof-of-concept evidence for the clinical translation of these findings.

SELECTED PUBLICATIONS (2016)


Oxidative stress and neuroinflammation: new therapeutic targets and biomarkers for epilepsy. Oxidative stress is ignited in the brain by epileptogenic injuries both in animal models of epilepsy and in humans affected by the disease. It represents a key mechanism for the development of seizures and the cognitive deficits. Our investigations have shown that oxidative stress occurs during epileptogenesis and induces the generation of a molecule named disulfide-HMG1 which is implicated in the generation of epileptic seizures. Moreover, this molecule is formed in the brain but can also be detected in blood before the animals develop epilepsy and acts as a biomarker which predicts the disease development and the therapeutic response to drugs.
LABORATORY OF ACUTE BRAIN INJURY AND THERAPEUTIC STRATEGIES

RESEARCH ACTIVITIES

Acute brain injury can have severe and long-lasting consequences. Pharmacological neuro-protection, both for traumatic brain injury (TBI) or hemorrhagic lesions, is not available, with repeated failures of several international trials. There is a gap from successful experimental interventions in animal models and failures in clinical applications. Essential for our research, therefore, is a lively connection/interplay between the laboratory and the clinical work. Parallel exploration of mechanisms in the clinical setting (through invasive monitoring and neuro-imaging, for instance) and in the lab could refine experimental models and develop neurorestorative treatments.

Specific aims of the program:
- To understand the mechanisms transforming an initial acute biomechanical injury into a chronic and progressive pathology.
- To understand the heterogeneity of TBI and identify biomarkers for acute brain injury.
- To interfere with injury evolution by reducing toxic events and fostering the endogenous reparative response.

MAIN RESULTS (2016)

Survivors of traumatic brain injury (TBI), are at risk of late neurodegeneration. The cellular drivers and molecular mechanisms of such progressive cognitive deterioration syndromes are unclear. In the experimental setting we have shown that a focal traumatic injury spreads to remote regions in the brain over time and is associated with neurodegeneration. We will use models of mild and severe TBI to understand the mechanisms transforming an initial biomechanical injury into a chronic and progressive pathology (Stocchetti, Zanier 2016).

We lack methods to track tissue biochemistry and hence select appropriate interventions for patients. We hypothesized that detailed label-free vibrational chemical analysis of focal TBI could provide such information. We demonstrated that Raman spectroscopy is able to capture early spatial and temporal changes in tissue biochemistry that are associated with brain injury in mice. Raman spectroscopy therefore shows promise as a probe that is sensitive to important pathological processes in TBI (Surmacki et al., 2016).
We aim at assessing neurorestorative strategies with a specific focus on mesenchymal stem cells (MSC) and their derivatives. We have shown that MSC improve outcome fostering protective and restorative processes after experimental TBI. Moreover, we have evidence that MSC released bioactive factors (secretome) mediate protective and restorative events, indicating the potential for a cell free approach (Pischiutta et al., 2016).

SELECTED PUBLICATIONS (2016)


