ERA-NET Neuron

NEWSLETTER 33

Austria | Belgium | Canada | Finland | France | Germany | Israel | Italy | Latvia | Netherlands | Norway | Poland | Portugal | Romania | Slovakia | Spain | Switzerland | Turkey | United Kingdom

Announcements from ERA NET NEURON Cofund

2020 Call for proposals on "Sensory Disorders" now open!!

Preproposal Submission Deadline: March 10th, 2020

2020 Call for proposals on Ethical, Legal, and Social Aspects (ELSA) of Neuroscience now open!!

Proposal Submission Deadline: April 28th, 2020

From the desk of the coordinator | January 2020

Marlies Dorlöchter

This first issue of the ERA-NET NEURON newsletter for the year 2020 covers events and outcomes from the busy and exciting NEURON meeting that took place in Lisbon on September, 17-20th, 2019. The meeting was organized back-to-back with the 5th International Conference on Neuroethics (ICONE5) with the aim to increase the networking and discussion opportunities for the two communities of biomedical sciences and humanities. The ICONE conference that preceded the NEURON meeting was opened by A. Jacomo as organizer of the ICONE, J. M. Pereira de Almeida as Vice-Rector of the Catholic University of Portugal as host and M. Schindel as representative of the initiative under the umbrella of ERA-NET NEURON addressing Ethical, Legal, and Social Aspects (ELSA) of Neuroscience.

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Funded by the European Commission

More information can be found on our website
http://www.neuron-eranet.eu/index.php
era-net neuron
EraNeuron

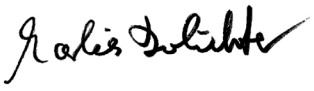
Produced by CSO-MOH, IL

A hundred and sixty participants attended the ERA-NET NEURON meeting in Lisbon, which comprised of several parts: a joint Midterm Symposium for 12 projects of the JTC 2017 'Synaptic Dysfunction in Disorders of the Central Nervous System' and three projects of the Ethical, Legal, and Social Aspects (ELSA) of Neuroscience' Call 2017, a joint poster session and two workshops dealing with ethics for Early Career Researchers (pg. 3), a young investigators satellite meeting (pg. 4), a Peer Review Panel (PRP) meeting of the Joint Transnational Call (JTC 2019) on Biomarkers, and a general NEURON meeting.

One of the main outcomes of the PRP meeting and following discussions were the results of the selection of the JTC 2019 on 'Translational Biomarkers in Brain Disorders'. In total 15 projects were chosen to be funded (see project details on pg. 5). A unique aspect of this specific review procedure was the participation of patient representatives in the meeting and in the evaluation process. Three patient reviewers were present at the PRP meeting and discussed the proposals together with the scientific reviewers. This is another step in the Responsible Research Innovation (RRI) efforts of ERA-NET NEURON to increase patient/patient representatives' involvement.

Last, but not least, we are happy to announce the **launch of two final Joint Transnational Calls for NEURON Cofund I – JTC 2020 on 'Sensory Disorders' and JTC 2020 on 'Neuroethics (ELSA)', as well as a NEW Partnering Tool** to assist potential applicants in finding suitable partners and networking opportunities in neuroscience!

Wishing you all a successful, fruitful and happy 2020!



ERA-NET NEURON Joint Midterm Symposium for 2017 Calls on Synaptic Dysfunction and Ethical, Legal and Social Aspects (ELSA) of Neuroscience

17-18 September, 2019, Lisbon, Portugal

Forty early career researchers, 59 principle investigators of JTC2017 projects, three organizers of workshops and representatives from several funding agencies gathered and participated in the exciting Midterm Symposium that brought together consortia from two separate JTC2017 calls, one on Synaptic Dysfunction and the second on Ethical, Legal, and Social Aspects (ELSA) of Neuroscience. Midterm Symposia, which occur approximately halfway into a project's runtime, are an opportunity for research groups from the NEURON-funded projects of a specific call to share their latest achievements.

Twelve transnational research consortia are funded under NEURON's JTC2017 on Synaptic Dysfunction. Defective synaptic communication is the origin of numerous neurological and mental disorders and these constitute a heavy burden for patients, their families and the society. Under the JTC2017 on ELSA of Neuroscience, three consortia are funded with the goal to form multinational collaborations that address research questions around the ethical, philosophical, legal and socio-cultural aspects related to neuroscientific research, thus assisting the process of promoting the adaption of neuroscientific methods and ensuring findings are utilized in ways which allow for the best possible benefit for our society. Both calls aim to facilitate multinational and interdisciplinary collaborative research projects, and the Midterm Symposium served as a platform and opportunity for discussion and exchange of ideas between all the engaged participants.

Poster Prize winner Maria Banqueri (middle) with Marlies Dorlöchter (right) and Erkki Raulo (left) from ERA-NET NEURON

In accordance with ERA-NET NEURON's longtime support and investment in Early Career Researchers (ECRs), and in the framework of this Midterm Symposium, ECRs from all participating consortia were invited to present posters on their work. Additionally, a dedicated young investigators satellite meeting was organized (see pg. 4) and two workshops devoted to ECRs were arranged on the topics of "How to write a good Ethics Self-Assessment" (moderated by T.M. Spranger, University of Bonn) and "Practical Ethics – practice examples of the Munich Graduate School for Ethics in Practice" (moderated by Alexander Bagattini, Munich Graduate School for Ethics in Practice). One of the highlights of the evening was the ceremony in which a poster prize was awarded to Maria Banqueri, from the MicroSynDep consortium that studies the involvement of microglia in major depressive disorder.

A brief review of the inaugural ERA-NET NEURON 'Young Investigator's Satellite Meeting 2019'

By Mila Mirceta[1] and Monika Schmidt[1]

Scientific collaboration is the cornerstone of many well-executed research studies but establishing a wide network of colleagues can be challenging as a young investigator, particularly at the doctoral or post-doctoral trainee stage. Towards fostering these skills, ERA-NET Neuron hosted a trainee-specific satellite meeting at the 2019 Midterm Symposium in Lisbon, Portugal.

The session was organized by Mila Mirceta and Monika Schmidt, under the guidance of Frank Kooy, Christopher Pearson (both consortium AUTISYN) and Anna Gossen (ERA-NET NEURON). This exciting and well-received satellite meeting was attended by 30 trainees from 21 different research groups (12 ERA-NET NEURON consortia) working on a variety of topics, ranging from basic research on synapses to ethical issues in neuroscience.

Mila Mirceta (left) and Frank Kooy (right)

Over the course of the session, one trainee from each consortium had the opportunity to present their work in a concise manner to fellow trainees from the various ERA-NET research groups/consortia. This valuable opportunity allowed trainees to practice and hone their presentation skills towards a broad audience. It was also a great introduction to the exciting projects from the diverse ERA-NET NEURON funded consortia. It provided a great foundation for the trainees before delving into the rest of the midterm symposium talks and poster sessions.

Following every short talk, many trainees actively participated in asking questions and suggesting new research avenues for their fellow trainees. Such opportunities to ask questions in less intimidating, and supportive environments are often lacking for trainees during international meetings, where the discussions and questions during sessions are dominated by more established scientists. As such, there is a great demand, and appreciation amongst trainees for such trainee-focused events.


Scientific Headbanz Game during the Young Investigators Satellite Meeting

An integral part of the session was a fun networking activity to engage and mobilize trainees. Through a scientific version of the "Headbanz" game, trainees asked "yes/no" questions to guess the neuroscience-related word tied around their forehead. The game generated many laughs and was positively talked about at future networking sessions in the evening, fostering a community amongst trainees at the meeting. Overall, feedback following the session was overwhelmingly positive, and trainees spent the rest of the conference strengthening relationships and sharing scientific ideas following this exciting session.

[1] Both authors are young investigators in the Pearson lab, The Hospital for Sick Children in Toronto, Canada, working on project AUTISYN funded under NEURON's JTC2015.

Neuron Joint Transnational Call 2019: Translational Biomarkers in Brain Disorders

Fifteen transnational research consortia were selected to be funded under JTC2019 on 'Transnational Biomarkers in Brain Disorders'. In total, 60 research groups from 13 European countries and Canada collaborate in these projects. The total funding volume of the call amounts to about 12.1 M€. We wish them all remarkable achievements!

Altered Translation in Autism (ALTRUISM)

Marija Mihailovic

Project Coordinator:

Marija Mihailovic, Istituto Europeo di Oncologia, Dept of Experimental Oncology, Milan, Italy

Project Partners:

Thomas Bourgeron, Institut Pasteur, Neuroscience, Université de Paris, Paris, France

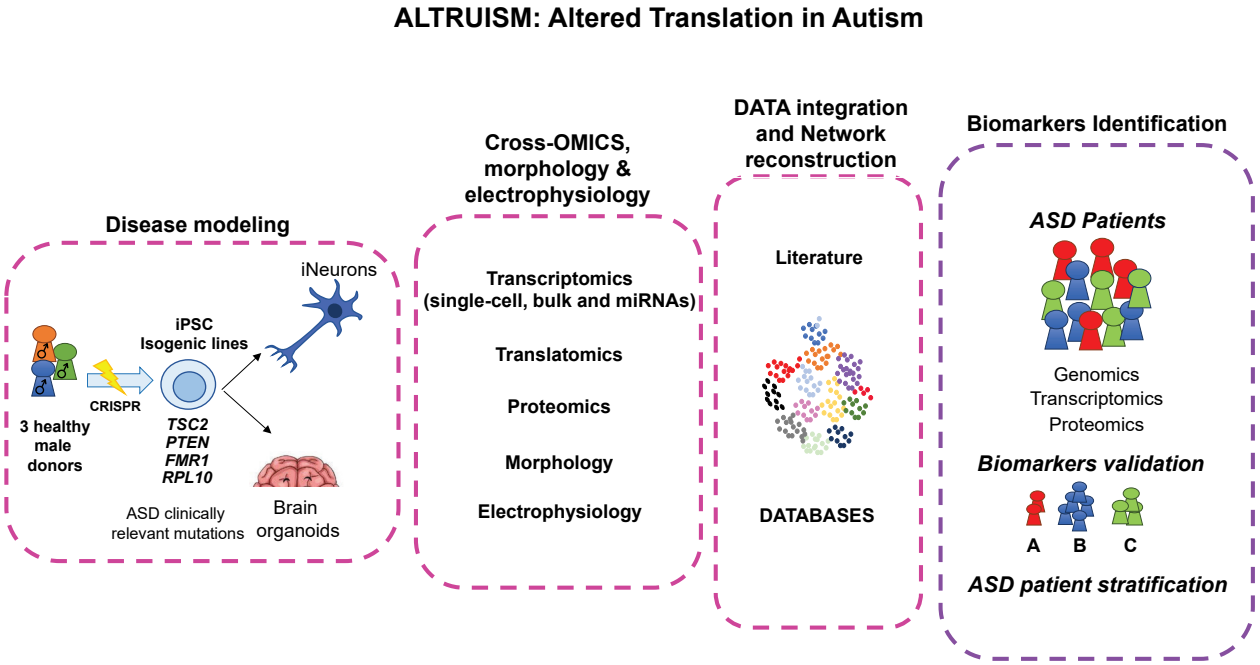
Matthias Selbach, Max-Delbrück-Centrum für Molekulare Medizin in der Helmholtz-Gemeinschaft, Berlin, Germany

Gerhard Schratt, ETH Zurich - Swiss Federal Institute of Technology, Institute for Neuroscience, Dept of Health, Science and Technology (D-HEST), Zurich, Switzerland

Ivan Topisirovic, CIUSSS du Centre-Ouest-de-l'Île-de-Montréal – Hôpital général juif - Lady Davis Institut, Dept of Oncology McGill University, Montreal, Canada

Autism spectrum disorder (ASD) is a complex lifelong neurodevelopmental condition of high prevalence with atypical social, behavioral and cognitive function, which creates a high economic burden for public health. The extraordinary complexity and heterogeneity of genotypes and phenotypes are major challenges when investigating ASD. In spite of elusive etiology, dysregulated protein synthesis has emerged as a point of convergence among mechanisms underlying ASD. This project aims to understand the pathophysiology of ASD downstream of mutations in FMR1, PTEN, TSC1/2 and RPL10, which directly impinge on protein synthesis. Molecular understanding of ASD will enable efficient patient stratification and identification of predictive biomarkers for a possible drug repurposing of already existing therapies targeting translational regulators. This will be achieved by using a combination of modern high-throughput technologies (-omics) for quantification of transcriptomes and proteomes along with morphological and functional studies in iPSC derived neurons and brain organoids harboring distinct mutations. As proof-of-principle, we will screen blood samples from deeply phenotyped patients for

newly identified biomarkers. The personalized medicine approach proposed here will pave the way for new ASD treatments, significantly ameliorating the life quality of patients and their families, with dramatic benefit for the health systems worldwide.



Biomarkers of ANTidepressant RESponse: early indicators and novel targets (ANTaRES)

Eleni Tzavara

Project Coordinator:

Eleni Tzavara, CNRS, INCC, Paris, France

Project Partners:

Raoul Belzeaux, AP-HM Assistance Publique Hopitaux de Marseille, Dept of Psychiatry, Marseille, France

Gustavo Turecki, McGill University, Douglas Hospital Research Centre, Dept Psychiatry, Montreal, QC, Canada

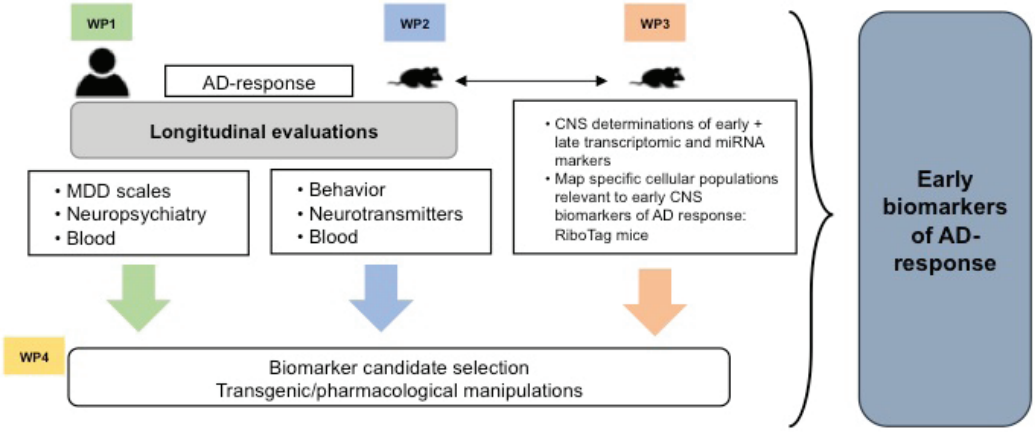
Miquel Martin Sanchez, UPF Universitat Pompeu Fabra, Dept of Health and Experimental Sciences, Barcelona, Spain

Patricia Robledo, IIS Institut Hospital del Mar d'Investigacions Mèdiques (IMIM), Integrative Pharmacology and Systems Neuroscience, Barcelona, Spain

ANTaRES aims to identify early biomarkers of antidepressant action, to distinguish future responders / non-responders. We have recently identified the transcription factor Elk-1, an ERK downstream partner as a specific module within the stress-response, a novel outcome biomarker of response to treatment, but also an ideal mediator of individual responses to antidepressant treatment at early stages. We capitalize on this novel framework to investigate early biomarkers of response to antidepressant treatments, a promising avenue for the development of predictive biomarkers of the drug response. We use hypothesis-based (Elk-1 and its regulators) but also large-scale analyses to identify yet unknown mRNA and miRNA early biomarker candidates. We propose a translational (in patients and mice) and multi-level (blood, CNS, individual CNS cell populations) approach with a longitudinal design. For this we build a strong collaboration between clinicians, translational investigators, molecular and cellular biologists to

- Identify peripheral "early post-treatment biomarkers" of antidepressant response in a novel prospective patient cohort
- Validate "early post-treatment biomarkers" in blood and link blood alterations with CNS alterations in cell specific populations in mouse models
- Select the best "hits" and validate plausibility and causality by targeted manipulations in the animal.

ANTARES: Biomarkers of ANTidepressant RESponse : early indicators and novel targets.



A multidisciplinary approach to the identification of BIOmarkers of MIGraine: a proof of concept study based on the stratification of responders CGRP monoclonal Antibodies (BIOMIGA)

Cristina Tassorelli

Project Coordinator:

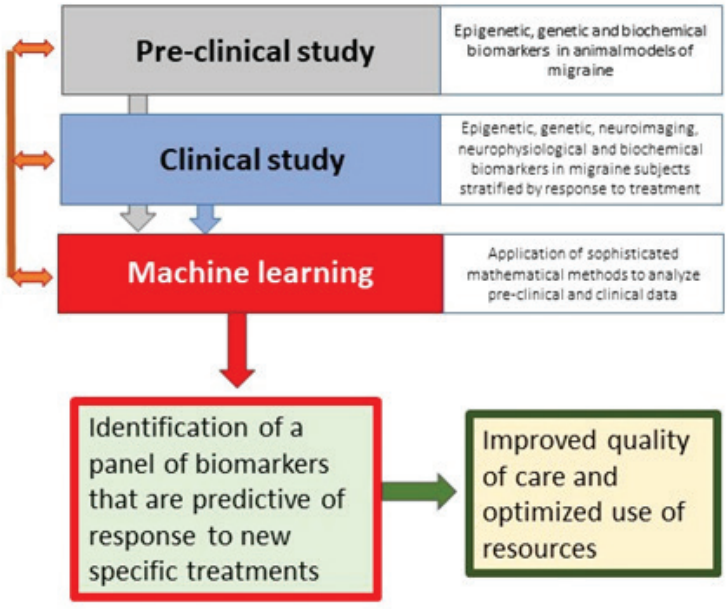
Cristina Tassorelli, IRCCS C. Mondino Foundation, Headache Science Center, Pavia, Italy

Project Partners:

Patricia Pozo Rosich, Vall d'Hebron Institute of Research, Headache Research Group, Barcelona, Spain

Arne May, Universitätsklinikum Hamburg-Eppendorf, Institut für Systemische Neurowissenschaften, Hamburg, Germany

Migraine is a common neurological disorder and a major source of disability. Though curable in principle, migraine generally improves poorly with available treatments, due to their limited efficacy and scarce tolerability. In 2018, monoclonal antibodies (mABs) against calcitonin gene-related peptide (CGRP) receptor have been approved. These mABs are the first specific preventive treatment for migraine ever developed. They are highly effective in a subgroup of patients, well tolerated, but costly. The main objective of this project is the identification of predictive biomarkers of response to CGRP-targeted mAbs in patients with migraine. To this end, we will use a hypothesis-driven, multidisciplinary approach that combines fundamental research in a validated animal model of migraine with a variegated and integrated 'omics' approach on a carefully characterized population of migraine sufferers. Three partners with an established long-standing and complementary expertise in animal modeling and epigenetics, neuroimaging and biochemical profiling in humans will collaborate to achieve the project's objective. We expect important spin-offs to the improved management of migraine, but also to the understanding of CGRP-based mechanisms underlying migraine pathophysiology. Healthcare providers and the pharmaceutical industry will be engaged once the biomarker(s) have been identified to optimize access to care, reduce disability and socio-economic impact of migraine.



Translational biomarkers of traumatic stress (BioStress)

Raul Andero

Project Coordinator:

Raul Andero, Universitat Autònoma de Barcelona, Institute of Neuroscience, Bellaterra, Spain

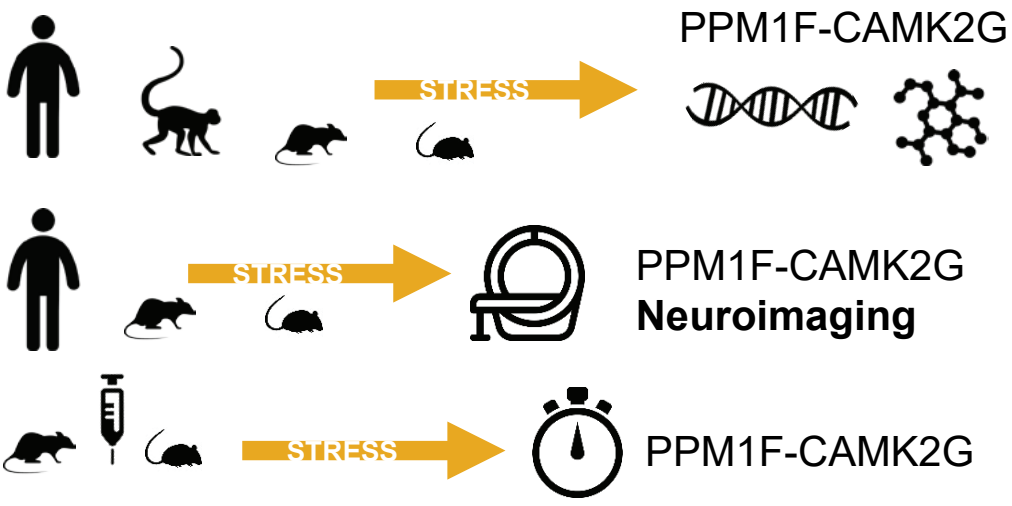
Project Partners:

Torsten Klengel, University Medical Center Göttingen, Dept of Psychiatry and Psychotherapy, Göttingen, Germany

Narcis Cardoner, University Hospital Parc Tauli, Psychiatry and Legal Medicine, Sabadell, Spain

Carmen Sandi, EPFL, Brain Mind Institute, Lausanne, Switzerland

Two in 3 people will be exposed to traumatic stress such childhood trauma, interpersonal violence, accidents or sexual violation during their lifetime. This number is highly affected by cultural, political and regional factors across the world. From those, around 5-10% percent will develop Posttraumatic stress disorder (PTSD) which is often comorbid with major depressive disorder and a host of medical conditions. The goal of this grant is to combine relevant biological and psychological biomarkers of trauma with algorithms to predict and prevent the negative consequences of developing disorders after exposure to traumatic stress. This translational proposal has a multidisciplinary and complementary team that includes two psychiatrists with notable experience in neuroscience research - Dr Klengel and Dr Cardoner - and two neuroscientists that combine research in human and rodent studies - Dr Sandi and Dr Andero -. Thus, the strong point of this proposal is the ideal team we have built that will help us to be successful in the study of biomarkers of stress and psychopathology. The results of the studies derived from this grant will likely improve how patients are treated after exposure to traumatic stress.



Early mechanistic BIOmarkers for late Epilepsy and long-term Brain Injury Outcome (EBio2)

Jens Dreier

Project Coordinator:

Jens Dreier, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Center for Stroke Research Berlin, Berlin, Germany

Project Partners:

Alon Friedman, Dalhousie University, Dept of Medical Neuroscience, Halifax, Nova Scotia, Canada

Annamaria Vezzani, Mario Negri Institute for Pharmacological Research IRCCS, Dept of Neuroscience, Milano, Italy

Ischemic and hemorrhagic stroke and traumatic brain injury (TBI) are leading causes of death and disability, imposing a burden on patients, their families, and society. Through a combinatorial approach based on improved and novel analyses of electrocorticography (ECoG), brain magnetic resonance imaging (MRI) and selected blood molecules, we will search for common fingerprints of neuro-vascular-astrocytic network dysfunction reflecting early lesion progression and late epilepsy. Retrospectively, we will identify the most promising biomarker combination exploiting our prospectively collected database of 200 patients with aneurysmal subarachnoid hemorrhage (SAH) who underwent 14-day neuromonitoring, had MRIs at 4 different time points, and were evaluated for outcome at 6 months and for epilepsy at 3 years. In a lateral translation approach, we will test the predictive value of the proposed biomarkers for neurological outcomes with a focus on epilepsy in 3 animal models of brain injuries. We envision a revolution in real-time monitoring of post-injury brain dynamics that will allow novel personalized treatments.

Genomic, epigenetic and proteomic biomarkers in psychosis: a translational approach including high-risk individuals, patients with schizophrenia and animal models (GEPI-BIOPSY)

Javier Labad

Project Coordinator:

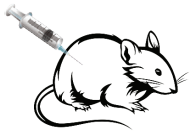
Javier Labad, Fundació Parc Taulí, Neuroscience Translational Unit I3PT - UAB, Sabadell, Spain

Project Partners:

Marie-Odile Krebs, Institute of Psychiatry and Neuroscience of Paris, Physiopathologie des Maladies Psychiatriques, Paris, France

Thomas Schulze, Ludwig Maximilian University, Institute of Psychiatric Phenomics and Genomics (IPPG), Munich, Germany

Our project aims to identify prognostic biomarkers associated with the psychotic phenotype using an integrative dataset and a machine-learning approach. We will study genetic (polygenic risk scores for schizophrenia), epigenetic (genome-wide DNA methylation) and proteomic (quantitative high-throughput information of 100s to 1000s of proteins) biomarkers in the blood of individuals with and without psychotic experiences and in patients with schizophrenia at different stages of the illness in order to assess the progression of these biomarkers. We will also use an animal model of schizophrenia (prenatal maternal immune activation [MIA] with the viral mimic polyinosinic-polycytidylic acid) in order to determine the pathological value of the same biomarkers (epigenetic and proteomic signatures) in blood and brain tissue as well as the relationship between DNA methylation and proteomic patterns in peripheral vs brain tissue. Similar behavioural measures (pre-pulse inhibition, cognitive function, social interaction, and anhedonia) will be also studied under a translational approach in both, adolescents (with and without psychotic experiences) and rats (MIA vs controls), in order to correlate them with genomic, epigenetic or proteomic signatures in blood. Machine learning methods will be used for identifying potential clusters or subtypes in terms of behavioural data and complimentary biomarkers at the genomic, epigenetic and proteomic level.



Pregnant rats administered vehicle (n= 5), or Poly (n= 15) x 2 experiments: 40 total

Randomization of pups (N=20 C,60 Poly x 2 experiments: 160 total; 50% of each sex)

ADOLESCENTS *CAPE-P15 & CAARMS. Recruitment until reaching N=150 in 3 groups*:

SCHIZOPHRENIA N= 100 *Comparative group for 'omics'*

BEHAVIORAL MEASURES

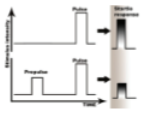
ADOLESCENT-ADULT GROUP

Behavior assessment at adolescence (PND 30-40) and adulthood (PND 70-80)

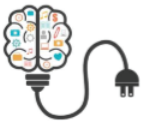
ADOLESCENT—BIOCHEMISTRY GROUP

Behavior assessment at adolescence (PND 30-40) Sacrificed for obtaining blood and brain samples

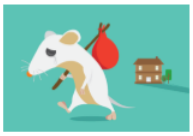
Non-affected and most affected (behaviorally) will be compared with 'omic' data



PPI



W.MEMORY



ANHEDONIA

SOCIAL

50 HC (Healthy controls)

50 PE (psychotic experiences; UHR-)

50 UHR +

EPIGENETICS IN BRAIN & BLOOD

PROTEOMICS IN BRAIN & BLOOD

GENOMICS (PRS for SCZ)

EPIGENETICS IN BLOOD

PROTEOMICS IN BLOOD

Metabolic profiling of the gut-brain axis as a new stratification process to improve behavioural disorders: proof of concept in alcohol dependence (GUT2BEHAVE)

Nathalie Delzenne

Project Coordinator:

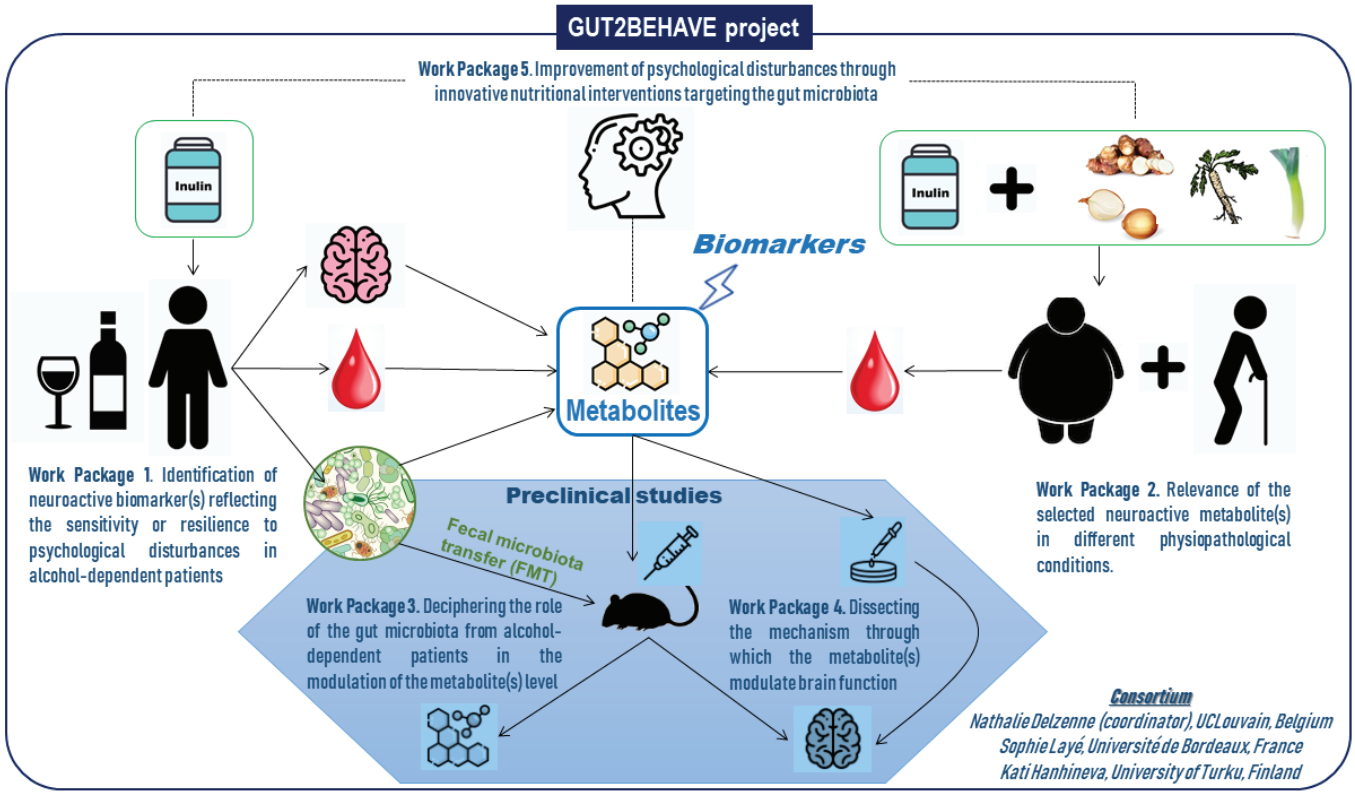
Nathalie Delzenne, Université catholique de Louvain / Louvain Drug Research Institute, Metabolism & Nutrition research group – UCLouvain/LDRI/MNUT, Brussels, Belgium

Project Partners:

Kati Johanna Hanhineva, University of Turku, Dept of Biochemistry, Turku, Finland

Sophie Layé, Université de Bordeaux-Bordeaux INP, Laboratoire NutriNeuro, UMR 1286 INRAe, Bordeaux, France

Alcohol dependence (AD) affects 5-10% of the population in industrialized countries and is a major cause of premature death. AD patients are prone to develop emotional and cognitive symptoms that increase the risk of relapse, and the current treatments have limited efficacy. Our previous data show that AD patients display alterations of gut microbiota and emphasize the possible causal role of altered gut microbiota in emotional disturbances and brain inflammation. The aim of the project is to propose biomarkers involved in gut-brain axis to control emotional and cognitive functions to better stratify patients and to design innovative treatment of AD. By taking advantage of biological samples in existing cohorts of AD patients (feces, blood, brain), we will search for relevant metabolites (untargeted metabolomics) reflecting psychological and metabolic alterations related to gut microbiota. The relevance of the selected biomarkers in other pathophysiological contexts and the influence of confounding factors will be evaluated in existing cohorts of obese and elderly patients. Original preclinical studies will dissect the mechanisms through which the selected metabolite(s) influence brain function and behaviour. Finally, we will examine whether a prebiotic strategy is able to modulate these metabolites and therefore improve mood and cognition. The GUT2BEHAVE project innovates in the scientific rationale and health care for psychiatric diseases that require personalized approach.


GUT2BEHAVE project
Work Package 5. Improvement of psychological disturbances through innovative nutritional interventions targeting the gut microbiota
Inulin
Inulin
Biomarkers
Metabolites
Work Package 1. Identification of neuroactive biomarker(s) reflecting the sensitivity or resilience to psychological disturbances in alcohol-dependent patients
Work Package 2. Relevance of the selected neuroactive metabolite(s) in different physiopathological conditions.
Preclinical studies
Fecal microbiota transfer (FMT)
Work Package 3. Deciphering the role of the gut microbiota from alcohol-dependent patients in the modulation of the metabolite(s) level
Work Package 4. Dissecting the mechanism through which the metabolite(s) modulate brain function
Consortium
Nathalie Delzenne (coordinator), UCLouvain, Belgium
Sophie Layé, Université de Bordeaux, France
Kati Hanhineva, University of Turku, Finland

Identification and clinical validation of biomarkers for long-term outcome after cerebral ischemia (iBioStroke)

Aurel Popa-Wagner

Project Coordinator:

Aurel Popa-Wagner, University of Medicine and Pharmacy, Functional Sciences, Craiova, Romania

Project Partners:

Nikolaus Plesnila, University of Munich, Institute for Stroke and Dementia Research, Munich, Germany

Tarja Malm, University of Eastern Finland, University of Eastern Finland, Kuopio, Finland

Israel Fernández Cadenas, Fundació Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau, Sant Pau Hospital, Barcelona, Spain

Agnieszka Slowik, Jagiellonian University, Medical College, Neurology, Krakow, Poland

Ischemic stroke is an acute disease which often results in severe long-term consequences such as physical disability, depression, cognitive decline or even dementia. To date, patients at risk for these late consequences of stroke are not duly diagnosed and treated due to the lack of reliable biomarkers. The main hypothesis of the current consortium is that a combination of extracellular vesicles EV- and genetic polymorphism-based biomarkers present in blood and CSF predict favorable or unfavorable long-term outcome after ischemic stroke. Based on this hypothesis, the current consortium of leading clinical and experimental European stroke researchers will address the following two specific aims: 1) carry out proteomic and miRNA analysis of ND-EVs and performing a Genome-Wide Association Study on ED-EVs isolated from blood and CSF of acute and chronic stroke patients (on admission and three months after the insult) and 2) carry out longitudinal proteomic and miRNA analysis of ND-EVs isolated from from blood and CSF of young and aged rats and mice subjected to transient focal cerebral ischemia (1, 3, 6, and 12 month after stroke). Results from these screenings will be correlated with clinical and functional sequels of stroke (neuroimaging, sensory-motor dysfunction, cognitive decline, and depression). The results have the potential to immediately improve current clinical practice and to provide scientific knowledge on how the young and aged brain respond to acute injury.

INPUT

Human/Mouse/Rat miRNA blood-derived ND-NV profile after stroke

Data processing and miRNA selection by correlative analysis with indices of stroke recovery

OUTPUT

miRNA signature of stroke recovery

Clustering on Human datasets

Clustering on rodents datasets

Select 3 up- and 3 down regulated miRNA Biomarkers

Select 3 up- and 3 down regulated miRNA Biomarkers

Screen human samples by PCR

Screen rodent samples by PCR

Cross-Validation for translational purpose

A neurocomputational biomarker assay for schizophrenia based on E/I-balance (IMBALANCE)

Philipp Sterzer

Project Coordinator:

Philipp Sterzer, Charité - Universitätsmedizin Berlin, Dept of Psychiatry and Psychotherapy, Berlin, Germany

Project Partners:

Tobias Donner, University Medical Center Hamburg-Eppendorf (UKE), Dept of Neurophysiology and Pathophysiology, Hamburg, Germany

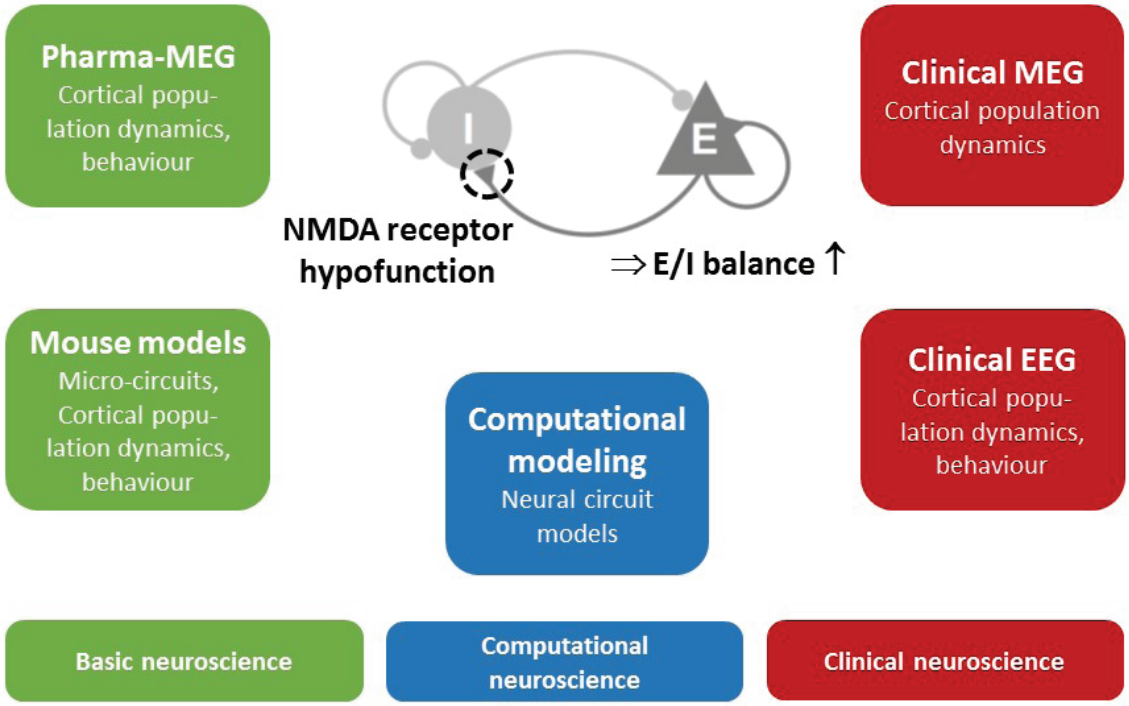
Jaime de la Rocha, Universitat de Barcelona, Institute for Biomedical Research August Pi i Sunyer, Barcelona, Spain

Srdjan Ostojic, Ecole Normale Supérieure Paris, Laboratoire de Neurosciences Cognitives et Computationelles, Inserm U960, Paris, France

Peter Uhlhaas, University of Glasgow, Institute of Neuroscience and Psychology, Glasgow, United Kingdom

Schizophrenia is a severe mental disorder that remains poorly understood. The accuracy of the clinical diagnosis is poor and the search for biomarkers that could aid diagnosis and individualized treatment has remained elusive. The present project aims to develop and validate a novel biomarker assay that is firmly grounded in a recent mechanistic theory regarding higher brain function and the pathophysiology of schizophrenia: The balance between excitatory and inhibitory neurons in the cerebral cortex ('E/I balance'), which is key for brain function, is fundamentally disturbed in schizophrenia. We will assess several candidate biomarkers of E/I balance, in an interdisciplinary translational neuroscience approach that will bridge across levels of brain organization via an integrated computational framework. Pharmacological interventions in healthy humans will target the key neurotransmitter systems involved in E/I balance to establish a set of non-invasive electrophysiological and behavioural biomarkers. Neural recordings in a mouse model of the disease with selective circuit perturbations and multi-scale computational modeling will bridge the gap between large-scale neural signals and microcircuits. Candidate neurocomputational biomarkers will be translated to patient data, probing the utility of neural and behavioural readouts of E/I balance in clinical diagnosis. This integrated approach holds promise to establish a novel mechanism-based biomarker assay for schizophrenia.

IMBALANCE – developing a neurocomputational biomarker assay for schizophrenia based on E/I balance



E/I balance = excitatory-inhibitory balance; E = excitatory cortical neuron (pyramidal cell); I = inhibitory interneuron; NMDA = N-methyl-D-aspartate; MEG = magnetoencephalography; EEG = electroencephalography

Discovery, verification and validation of a biomarker profile for depression (MOODMARKER)

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This project aims at identifying a biomarker profile for major depressive disorders (MDD). We will use an iterative strategy of biomarker profile discovery, verification and validation. Discovery: To identify a biomarker profile, proteomics will be conducted for CSF and CSF extracellular vesicles (CSF-EVs; WP1) and post-mortem limbic brain tissue from MDD patients having died by suicide and matched controls (WP2; with in situ validations in WP3), as well as for limbic brain tissue from chronic social stress (CSS) and control mice (WP4). Verification: The CSF/CSF-EVs biomarker profile will be verified in a new, larger cohort of MDD patients (WP5). Proteomic findings will be verified in human brain samples at the mRNA (transcriptomics) and epigenetic (genome-wide methylation & miRNome) (WP6, WP8). In limbic brain from CSS/control mice, for a specific cell type implicated by the biomarker profile, RNA will be extracted for the study of the transcriptome (WP7) and the miRNome (WP8). Validation: Blood plasma-EVs will be obtained from MDD patients before and during antidepressant treatment and proteomics will be applied (WP9). CSS/control mice will receive an antidepressant drug or vehicle, and plasma-EVs and limbic brain tissue will be collected for proteomics (WP10). Data from most WPs will be investigated using deep bioinformatics pathway analyses (WP11). The establishment of this MDD biomarker profile is expected to be diagnostic, prognostic and treatment responsive.

Multi-level integrative 'omics to identify biomarkers in Schizophrenia and other major psychoses (Muliobio)

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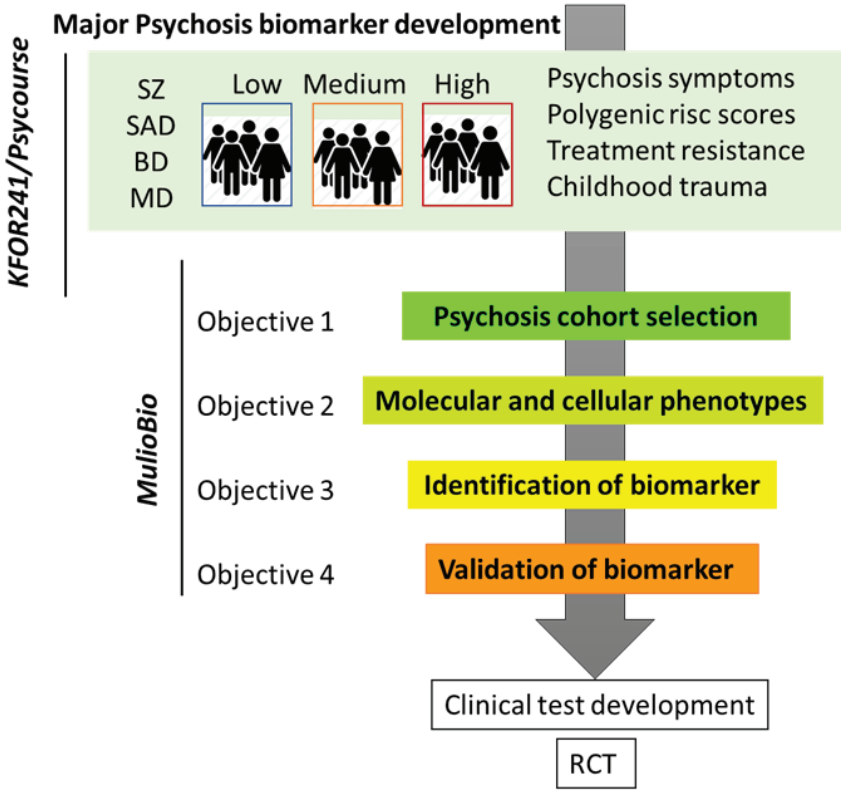
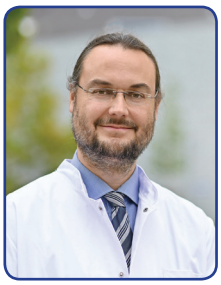
The principal goal of MulioBio is to discover and validate molecular correlates of major psychosis symptoms enabling disease state diagnosis independently of subjective psychometric evaluations. We define molecular correlates as molecular pathways which are significantly associated with psychosis symptoms and therefore predictive of disease state. Workplan: We aim to address several issues of prior BM research in psychiatric diseases. These issues are addressed as 4 major objectives: Objective 1: Selecting a unique patient cohort suffering from major psychosis, stratified based on phenomics and genomics. Objective 2: Multi-omics immuno-profiling of the patient cohort covering molecular and cellular phenotypes. Objective 3: Integrating multi-omic profiles with patient disease course using computational biology and machine learning analysis for biomarker discovery. Objective 4: Validating the predictive BM discovered in an independent patient cohort Exploitation of results: At the end of MulioBio we will have achieved the discovery and validation of a new biomarker. The next step will be to technically validate the discovered biomarkers. After the technical validation TGS Schulze and colleagues will test the clinical utility via an european-wide RCT and depending on the results the biomarkers will then be labelled CE IVD, with the support of future partners with expertise in health technology assessment and medical devices regulation.



Neuroimaging and Blood Biomarkers as Indicators of Ketamine Efficacy in Treatment Resistent Depression (NeuroMarKet)



Martin Walter

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Major Depressive Disorder (MDD) is highly chronic with treatment resistance in 30% of patients (TRD). Increasing use of the NMDA antagonist ketamine, an efficient antidepressant (AD), needs to be balanced by side effects particularly in the target group of severe depression. Here, clinical decisions lack estimation on patients' individual benefit.

We will validate a combination of AD response biomarkers focusing on peripheral and central mechanisms associated with glutamatergic plasticity. Ketamine was shown to rectify altered glutamate levels, dampened mTOR pathway, decreased BDNF and increased acetylated alpha-tubulin. Markers will thus assess these sources of disturbed brain networks which show a plastic modification early after successful treatment. Pretreatment biomarkers are monitored after ketamine to assess changes and their potential as active probes for individual improvement. Efficacy of the combination of peripheral BDNF, Tubulin and mTOR

regulated proteome with non-invasive MRI markers of glutamate and brain connectivity is compared to a newly established blood biomarker. Markers correspondence is tested across existing datasets and within a prospective trial. Animal and human studies align in timepoints, models and modalities. Focusing on a fundamental pathophysiological signature we will contribute to validated stratification and response monitoring and rely on established collaborations combining latest technological advances on proteomics and neuroimaging.

Neurovascular damage determines disease pathophysiology in pediatric mild traumatic brain injury: source of new biomarkers (Neu-vasc)

Jerome Badaut

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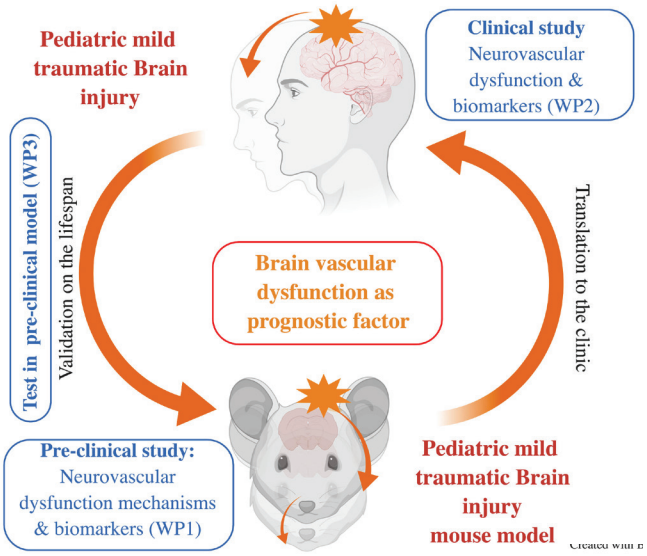
Roger Thompson, University of Calgary, Hotchkiss Brain Institute, Calgary, Canada

Peter Filipcik, Slovak Academy of Science, Institute of Neuroimmunology, Bratislava, Slovakia

Mild traumatic brain injury (mTBI) is a major pediatric clinical problem caused by primary mechanical trauma followed by disruption of brain functions that manifests with or without loss of consciousness and neurological symptoms. Importantly, part of mTBI patients (30%) can develop long-term sequels on the developing brain with to date no good tools for prognostic and classification of subjects within mTBI pathophysiology. Strategies to stratify mTBI in children are urgently needed for diagnostic and predictive value applicable to long-term outcomes.

Our main hypothesis is that, in pediatric mTBI (pmTBI), neurovascular damage determines disease pathophysiology, with early blood-flow alteration and promotes the presentation of blood biomarkers for early and long-term outcomes.

With the combination of experts in clinical and preclinical brain injury research fields, we proposed a translational project to: 1) validate the early loss of cerebral blood flow (CBF) as diagnostic for pmTBI along blood miRNA changes; 2) the molecular and cellular mechanisms linking vascular dysfunction and neuronal activity; 3) and assess the usefulness of these biomarkers for lifetime prognostic from experimental models and at the same time studying the mechanisms behind acceleration of brain aging after pmTBI.



This project could benefit directly patients with the use of laser flow Doppler at the emergency room to classify pmTBI in parallel with new blood biomarker development.

Novel biomarkers in neurological and psychiatric disorders: autoantibodies to neuronal nicotinic acetylcholine receptors (NicAb)


Socrares Tzartos

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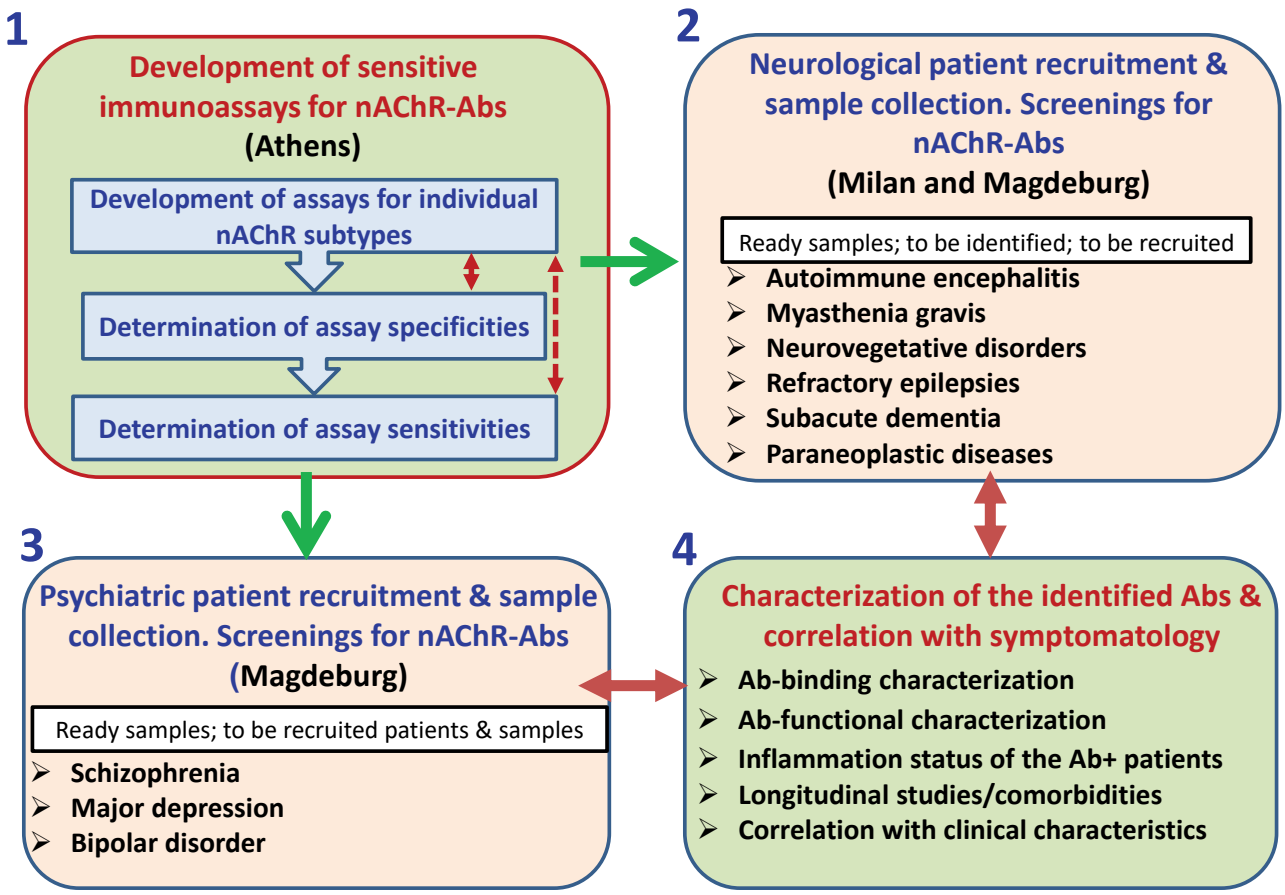
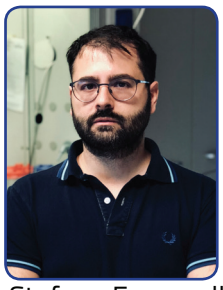
Johann Steiner, University of Magdeburg, Dept of Psychiatry and Psychotherapy, Magdeburg, Germany

Nicotinic acetylcholine receptors (nAChRs) are pentameric subunit complexes of two major subtypes, muscle and neuronal, which mediate neurotransmission for muscle contraction or regulate neuronal excitability and neurotransmitter release in the CNS, respectively. Neuronal nAChRs are drug targets for neuropsychiatric diseases. Neuronal nAChR reduced expression and/or impairment may be involved in neuropsychiatric diseases including Alzheimer's, Parkinson's, autism, schizophrenia, affective disorders and drug addiction. Antibodies (Abs) against nAChRs could cause nAChR loss and dysfunction, likely resulting in serious diseases. Abs to muscle nAChRs cause myasthenia gravis while Abs to neuronal nAChRs have been reported in patients with schizophrenia, bipolar disorder and autoimmune dysautonomia. However, systematic state-of-the-art studies with cell based assays are still lacking. We aim to develop immunoassays (Athens) to detect new Abs to neuronal nAChRs in patients with neurological (Milan) and psychiatric (Magdeburg) diseases of suspected autoimmune etiology. Two large biobanks of sera/CSF from patients with well-characterized neuroimmunological disorders (autoimmune encephalitis and related disorders, myasthenia gravis), and schizophrenia, major depression and bipolar disorder, will be tested. Study of Ab binding and function and their correlation with particular symptoms will lead to new biomarker tests for disease diagnosis, monitoring and therapy selection.

NicAb


1
Development of sensitive immunoassays for nAChR-Abs
(Athens)
Development of assays for individual nAChR subtypes
Determination of assay specificities
Determination of assay sensitivities
2
Neurological patient recruitment & sample collection. Screenings for nAChR-Abs
(Milan and Magdeburg)
Ready samples; to be identified; to be recruited
Autoimmune encephalitis
Myasthenia gravis
Neurovegetative disorders
Refractory epilepsies
Subacute dementia
Paraneoplastic diseases
3
Psychiatric patient recruitment & sample collection. Screenings for nAChR-Abs
(Magdeburg)
Ready samples; to be recruited patients & samples
Schizophrenia
Major depression
Bipolar disorder
4
Characterization of the identified Abs & correlation with symptomatology
Ab-binding characterization
Ab-functional characterization
Inflammation status of the Ab+ patients
Longitudinal studies/comorbidities
Correlation with clinical characteristics

STROKE RISK PREDICTION IN ATHEROSCLEROSIS MEASURING CIRCULATING COMPLEMENT SYSTEM PROTEINS (STATEMENT)


Stefano Fumagalli

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Tom Eirik Mollnes, Institute of Clinical Medicine University of Oslo, Dept of Immunology, Oslo, Norway

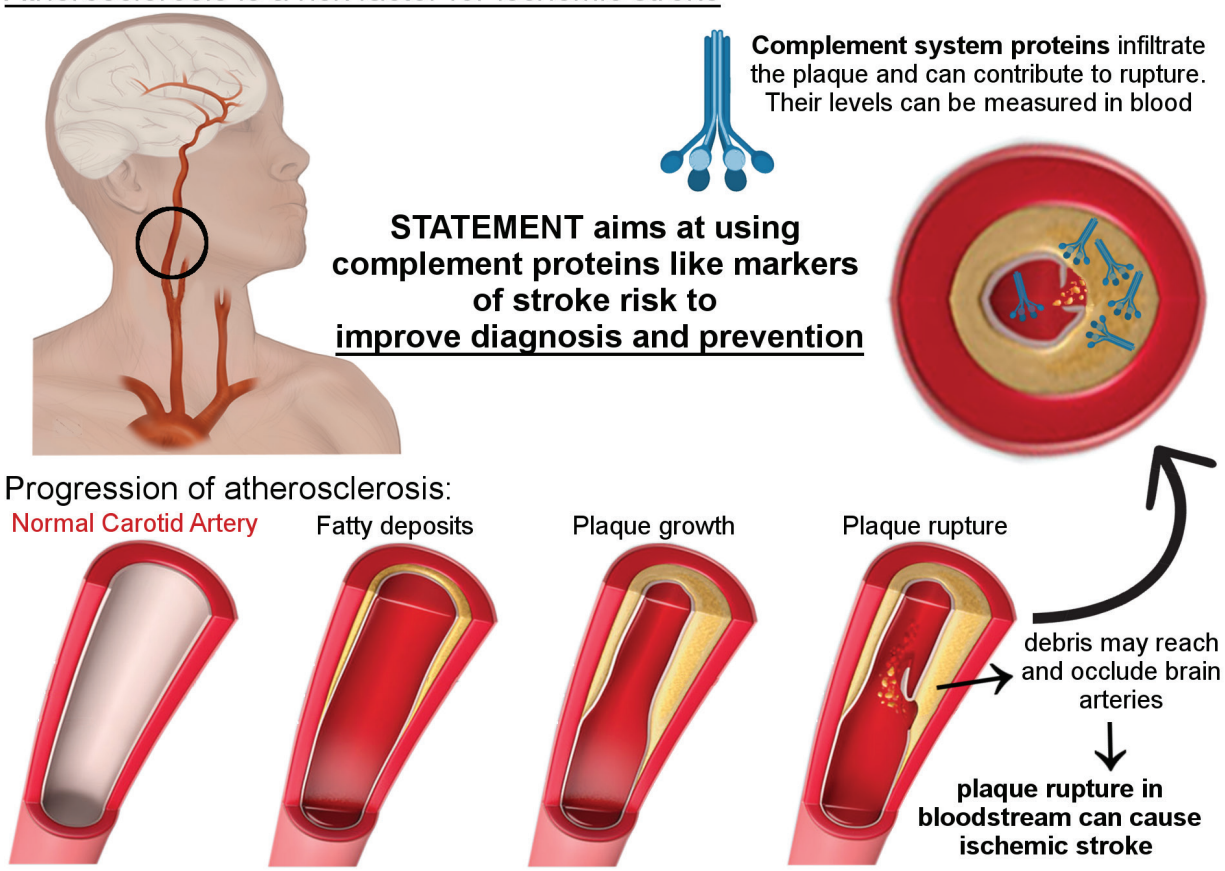
Emmanuelle Canet Soulas, INSERM U.1060/Université Lyon1, Laboratoire CarMeN, Bron, France

Ileana Manduteanu, Institute of Cellular Biology and Pathology"Nicolae Simionescu", Dept of Biopathology and Therapy of Inflammation, Bucharest, Romania

Stroke is the third cause of death and the first cause of long-term disability. Ischemic stroke accounts for 87% of all strokes. A major cause for ischemic stroke is represented by atherosclerotic vulnerable plaques, whose clinical detection is an unmet priority. The complement system is an inflammatory process involved in plaque's morphological evolution. STATEMENT aims at using the complement proteins as circulating bio sensors of plaque instability and stroke occurrence.

STATEMENT will focus on the pre-identified circulating complement biomarkers for plaque vulnerability, namely ficolins, initiators of the complement lectin pathway (LP). We will also analyze LP's downstream active products and other complement pathway proteins seeking markers with enhanced sensitivity. We will retrospectively analyze available cohorts of atherosclerotic patients undergone endarterectomy. The identified biomarkers will be analyzed in vitro to define their functional interactions with cellular plaque components, like macrophages, platelets, neutrophils and smooth muscle cells. The candidate biomarkers, selected on the basis of the retrospective patient study and on the in vitro study, will be finally tested in patients in a multicentric study (Italy, Norway and France).

STATEMENT will help advance prevention of neurologic complications and improve therapy by providing a marker for the early detection of rupture-prone atherosclerotic carotid plaques, bearing a risk for stroke.


Atherosclerosis is a risk factor for ischemic stroke
Complement system proteins infiltrate the plaque and can contribute to rupture. Their levels can be measured in blood
STATEMENT aims at using complement proteins like markers of stroke risk to improve diagnosis and prevention
Progression of atherosclerosis:
Normal Carotid Artery
Fatty deposits
Plaque growth
Plaque rupture
debris may reach and occlude brain arteries
plaque rupture in bloodstream can cause ischemic stroke