

ERA-NET Neuron

NEWSLETTER 31



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News From NEURON Cofund

NEURON 2019 Call for Proposals for Transnational Research Projects on "Biomarkers" is closed. 80 preproposals were submitted, involving 327 research groups.

JTC 2018 on "Mental Disorders" - 14 projects were chosen for funding out of 124 pre-proposals. Total grant volume for the 14 projects: 12.3 m€. Chosen research projects are hereby presented.


From the desk of the coordinator | March 2019




Marlies Dorlöchter

ERA-NET NEURON supports research across the spectrum of neurosciences and mental health, in universities and hospitals, in dedicated units, centres and institutes of partner countries. The annual Joint Transnational Calls specify topics and areas whereupon - following a selection process - interdisciplinary and international research consortia are funded for a three years period. In 2016, under the umbrella of NEURON, a joint transnational call (JTC 2016) was launched together with the European Commission using the ERA-NET Cofund mechanism in the field of 'External Insults to the Nervous System'. The aim of the call was to facilitate multinational, collaborative research projects that address important questions relating to external insults to the central nervous system. These insults often cause permanent disability and constitute a heavy burden for patients and their families. This includes, and



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<http://www.neuron-eranet.eu/index.php>
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is underpinned, by fundamental research into the basic mechanisms of disease through proof-of-concept clinical studies in humans to neurorehabilitation. The focus of the call was on primary physical insults to the central nervous system, i.e. Traumatic Brain Injury (TBI) and Spinal Cord Injury (SCI).

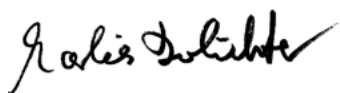
In January 2019 the 19 funded consortia of [JTC 2016](#), comprising 92 research groups, gathered at the NEURON midterm symposium 'Joint Transnational Call 2016 – External insults to the nervous system' in Bonn, Germany. At this, so far largest, NEURON midterm symposium 167 funders, researchers, clinicians and early career researchers discussed progress of the work, scientific findings, methodology and possible further inter-consortia collaborations.

NEURON's goals of monitoring and early career researcher support were fulfilled within the annual midterm symposia. The researchers of the funded research consortia (as well as the funders) met and presented their ongoing work. The program comprised five different scientific sessions, a [workshop on quality assurance](#), a poster session with award for the best poster, the [EPNA award](#) ceremony, and two satellite workshops organized by funded consortia. Cutting-edge science was presented with often promising applicability to the clinics, thereby increasing the hope to significantly improve diagnosis and therapy in such pathologies in the near future. Early career researchers of the participating research groups were invited by NEURON to attend and present their work with posters, and a poster prize was awarded.

We enjoyed this exciting symposium very much and look forward to our next midterm symposium in Lisbon, September 2019. In our next symposium, which will be back-to-back with the 5th ICONE (International Conference on Neuroethics), the NEURON consortia of the 2017 calls 'Synaptic Dysfunction' and 'Neuroethics' will present and discuss their work.

Sincerely yours,

Marlies Dorlöchter.



Bonn, January 2019



NEURON Joint Call 2018 "Mental Disorders"

14 transnational research consortia are funded under the umbrella of the NEURON JTC 2018 "Mental Disorders". In total, 62 research groups from 11 European countries, Canada and Israel collaborate in these projects. The total funding volume of the call amounts to about 12.3 M€.

In the following pages you can learn about the projects and their goals.

We wish them all much success!

The Pleiotropic Effects of ADNP in Mental Disorders (ADNPinMED)



Frank Kooy

Project Coordinator:

Frank Kooy, University of Antwerp, Belgium

Project Partners:

Illana Gozes, Tel Aviv University, Israel

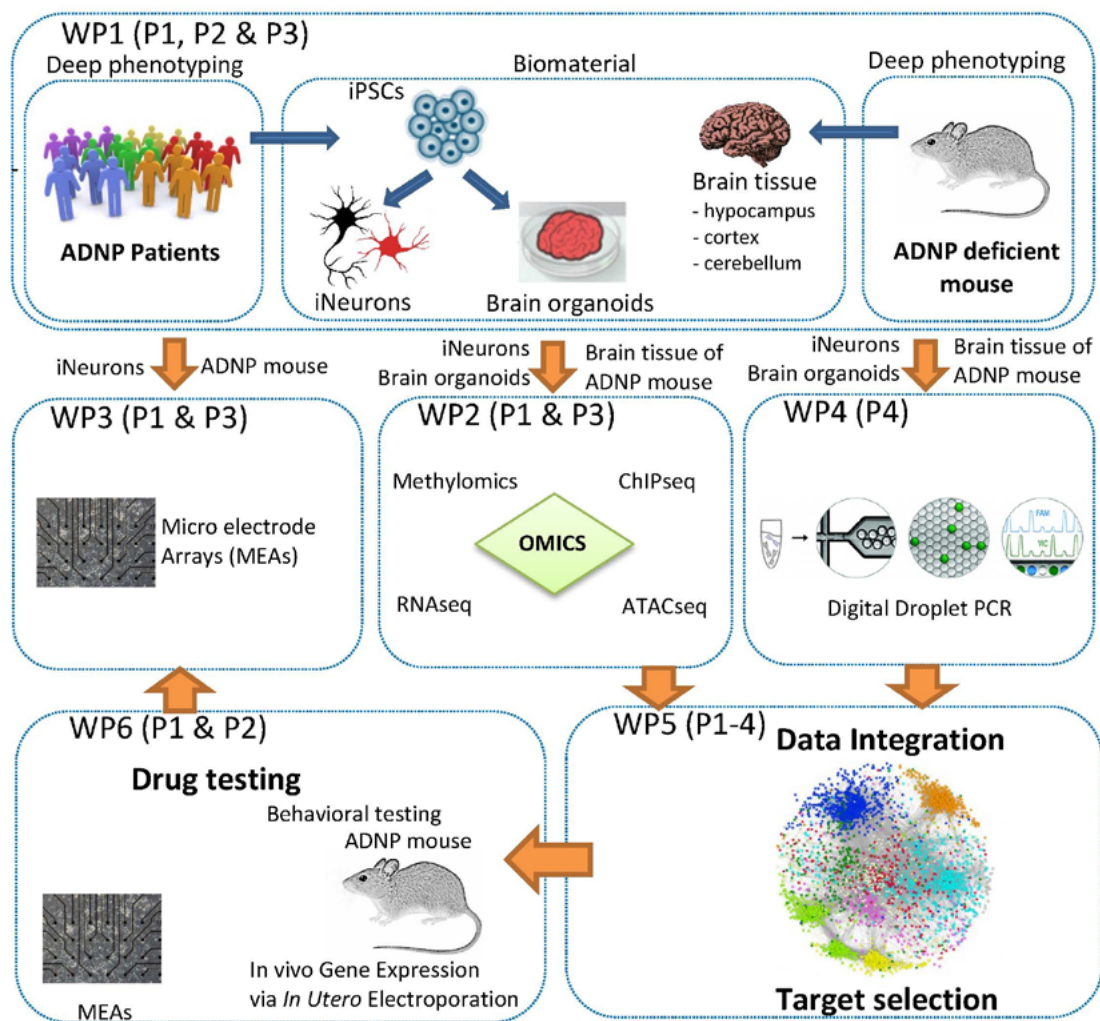
Patricio Fuentes, European Institute of Oncology, Italy

Christopher Pearson, University of Toronto, Canada



Recent technological breakthroughs in sequencing technologies led to the identification of an unprecedented number of novel disease genes involved in neurodevelopmental disorders such as intellectual disability, autism, or schizophrenia. Interestingly, many genes that were originally identified to result in for instance autism, have subsequently been demonstrated to play a role in other neurodevelopmental disorders as well. We are an existing, established and productive ERA-NET Neuron consortium. In our ongoing network, we studied mutations in ADNP, originally identified as a gene involved in syndromic autism, using a suite of cellular and animal models and tools developed. Our results indicated a much broader clinical phenotype than anticipated, suggesting that mutations in ADNP have many more consequences. Based on our preliminary results, we hypothesize that this is a consequence of the disturbances of the epigenetic regulation in patients. In the current project, we aim to use our current resources to investigate the involvement of the epigenome in the phenotypical presentation of mental disorders, using ADNP as a model. Our work will be based on the materials we generated in the ongoing application, including unique cellular and animal models of the disorder. Our project includes disease characterization in patients and animal models, transcriptomics and epigenomics, functional analysis, mosaicism analysis, data integration and preclinical drug testing. These results will enable a full

characterization of the consequences of the ADNP mutation that can be linked to the specific aspects of the diseases caused by ADNP mutations.



Targeting Adolescent Neurocognitive Processes In Depression To Promote Intervention Response (ADORE)



Jean-Luc Martinot

Project Coordinator:

Jean-Luc Martinot, French Institute of Health and Medical Research (INSERM), France

Project Partners:

Patricia Conrod, University of Montreal, Canada

Catherine Belzung, Institute of Health and Medical Research (INSERM), University of Tours, France

Igor Branchi, National Institute of Health, Italy

Florin Tibu, Universitatea Stefan cel Mare din Suceava, Romania



The World Health Organization “Health for the world’s adolescents” report revealed that depression is the predominant cause of illness and disability and among the top three causes of mortality for adolescent boys and girls. Recent studies point to lasting effects of adolescent onset depression, including risk for treatment-resistance in adulthood.

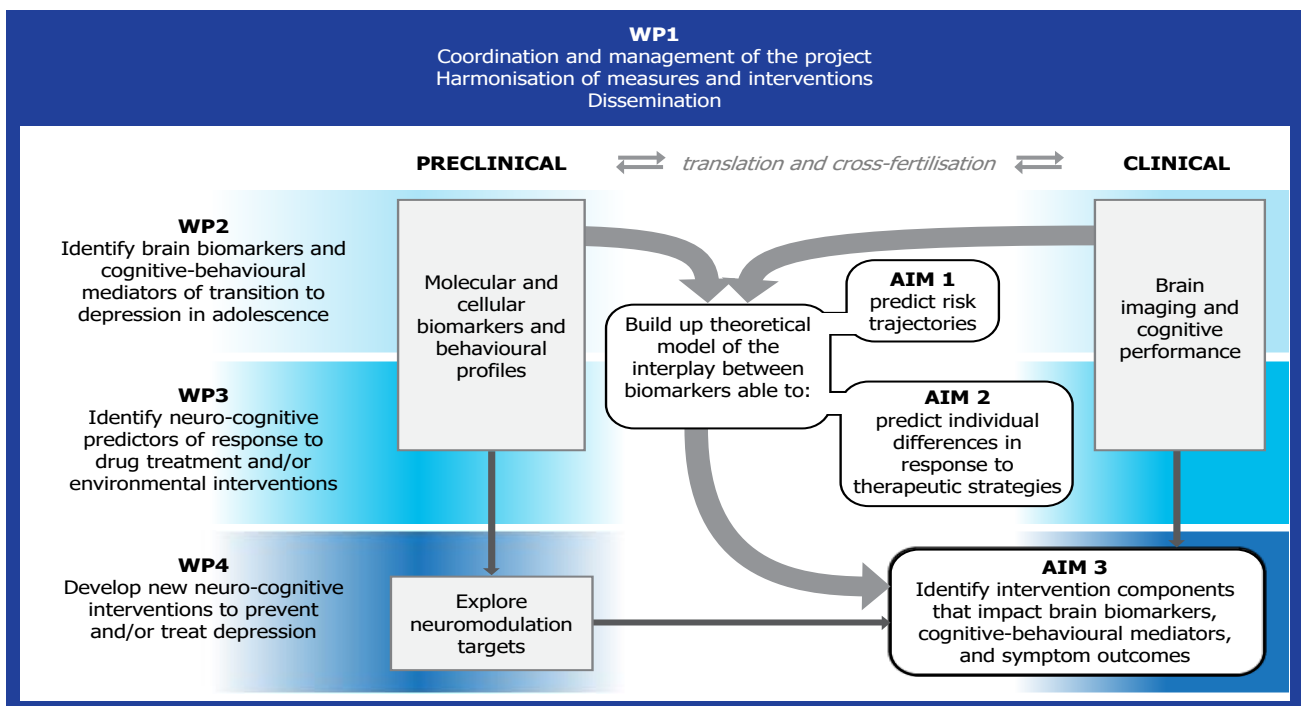
There is a need for better prevention, particularly targeted approaches that address the needs of those most vulnerable to depression.

The proposed consortium will conduct researches on humans and animals, aiming to provide novel intervention components for at-risk individuals during the critical adolescent period. The researches will be focused on core brain regions and cognitive functions (reward, memory, stress response, and self-referent thinking) developing in adolescence, and relevant to depression risk.

Using three exceptional cohorts which have recently completed long-term follow-up of adolescents at varying risk for depression, we will search for deviations of brain and cognitive functions involved in the transition to early-onset depression and subsequent to early onset depression; and we will recruit new samples to determine the role of these deviations in treatment response.

Measures will be highly harmonized across experiments in animals and analyses in humans, including complementary intervention approaches. The causal role of cerebral or environmental factors on the deviations of cognitive functions and behaviors, and on intervention response, will be tested in animal studies and using existing databases from at risk youth.

The third year of this project, new brain targets for prevention of depression will be tested in animals. Novel cognitive targets for intervention will be applied in new at-risk adolescent samples: Canadian adolescents who did not respond to previous prevention for depression, and Romanian adolescents exposed to early childhood adversity.



Multiscale Analysis Of Anti-Nmda Receptor Auto-antibody In Psychosis (AutoScale)

Project Coordinator:

Laurent Groc, University of Bordeaux, France

Project Partners:

Marion Leboyer, Mondor Institute for Biomedical Research, Fondation FondaMental – INSERM, France

Christian Geis, Jena University Hospital, Germany

Josep Dalmau, Hospital Clinic de Barcelona (HCB), Spain

Pierre Marquet, Laval University, Canada

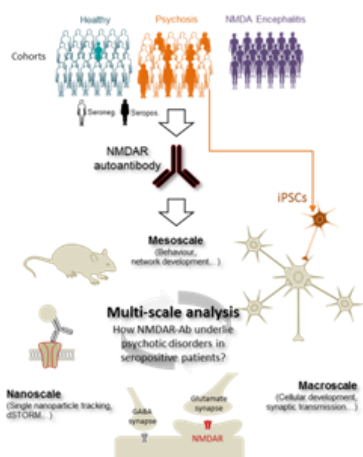


Laurent Groc



Psychotic disorders, encompassing schizophrenia and bipolar disorders, are major health problems worldwide. Growing evidence suggest that these major psychoses have a neurodevelopmental component involving synaptic imbalance, mostly between glutamatergic and dopaminergic neurotransmitter systems. However, the complexity of psychotic disorders limits our understanding of them. Of the numerous converging factors involved in these psychiatric disorders, immune status, including autoimmunity, is particularly relevant. A role for autoimmune dysfunction in psychiatric disorders, reported in schizophrenia almost a century ago, is supported by specific autoimmune responses to self-antigens identified in psychotic disorder. A number of syndromes characterized by global encephalopathy and focal psychiatric symptoms were found to result from autoimmune dysfunction, caused by anti-neuronal antibodies that alter synaptic transmission, such as NMDAR-Ab in encephalitis, thus reinforcing the role of autoimmunity in major psychosis. The role of autoimmunity against neuronal receptor targets in the pathogenesis of psychotic disorders has gained tremendous support over the last years and urgently requires multidisciplinary in-depth investigations to unravel the molecular mechanisms underlying psychosis and to offer new therapeutic strategies. We found that almost 20% of patients diagnosed with schizophrenia are

seropositive for these auto-antibodies, opening therapeutical options for these patients. We plan to tackle this major challenge with a complementary and synergistic consortium of clinical and basic research experts, who contributed greatly to the current understanding of autoimmunity in brain disorders. Our objective is to uncover how NMDAR-Ab underlie psychotic disorders in seropositive NMDAR-Ab patients, using a unique and multi-scale combination of experimental approaches, from pre-clinical experiments to clinical exploration.



Decrypting Cadherin-13 function in cortico-cerebellar circuitry underlying neurodevelopmental disorders! (DECODE!)



Nael Nadif Kasri



Project Coordinator:

Nael Nadif Kasri, Stichting Katholieke Universiteit Nijmegen, The Netherlands

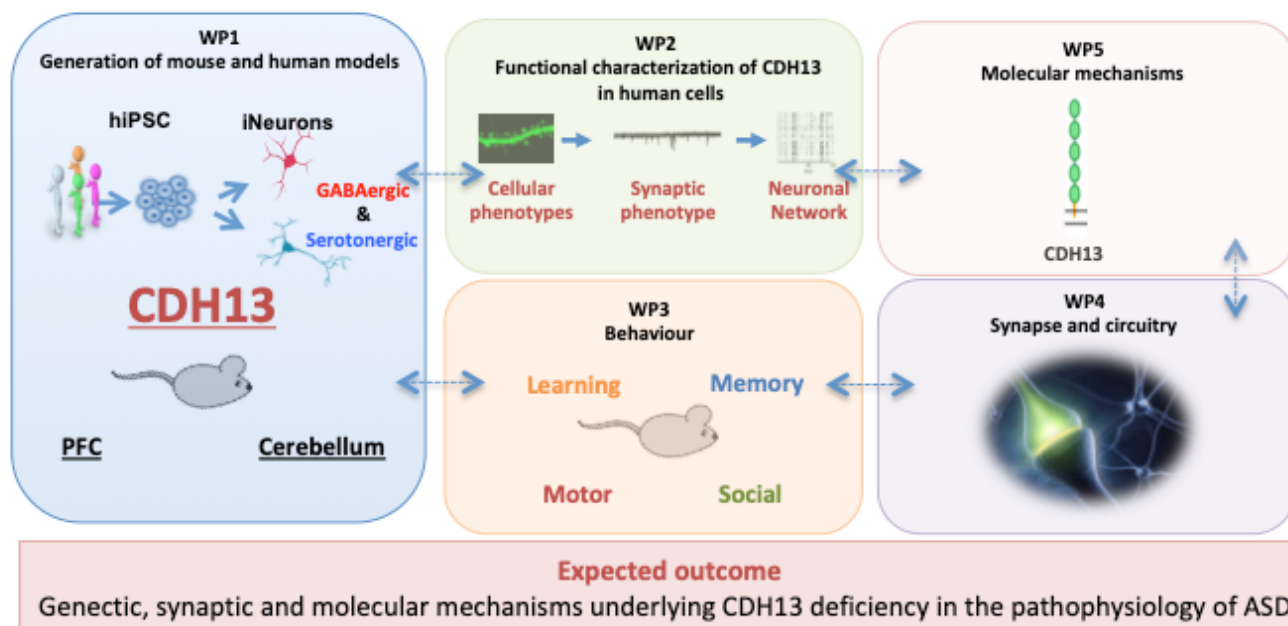
Project Partners:

Klaus-Peter Lesch, University of Wuerzburg, Germany

Graziella Di Cristo, University of Montreal, Canada

Fabrice Ango, Institute for Functional Genomics (IGF), France

Autism spectrum disorder (ASD) is a heterogeneous group of neurodevelopmental disorders, characterized by early-onset deficits in social behaviour and communication across multiple contexts, together with restricted, repetitive patterns of behaviour, interests, or activities. Neurodevelopmental disorders are the single largest contributors to disease burden in Europe and they constitute the leading source of years lost to disability from all medical causes. Maladaptive cognition and behavior increase the risk for these disorders, especially ADHD, ASD, alcohol/drug use disorders and (comorbid) depression. Direct and indirect costs associated with these disorders strongly burden society, but although considerable research efforts go into specific disorders, there is relatively little work studying the underlying traits of attention, impulsivity, emotion regulation and social cognition implicated in a wide range of disorders. The recent progress in human genetics have led to the identification of hundreds of genes associated with autistic-like behaviors, including a growing number of genes encoding synaptic proteins. In particular, genetic variations in Cadherin-13 (CDH13) have been associated with several neurodevelopmental and psychiatric disorders. Recently, rare de novo and inherited deletions at the CDH13 locus have been linked to ASD, indicating the clinical relevance for loss-of-function mutations in CDH13. Previous work from members of DECODE! has shown that CDH13 is predominantly expressed at the intersection of where neurons communicate with each other, the synapse. In DECODE! we will develop mouse models to study the function of CDH13 in specific types of neurons that are thought to be involved in the behaviour associated with ASD. In addition we will harness the potential of human induced pluripotent stem cells (iPSCs) to characterize CDH13 dysfunction in patient iPS-derived cultured neurons. Understanding specific alterations caused by CDH13 deficiency in mouse and human models will ultimately help us designing targeted treatment of specific ASD symptoms for precision medicine.



Examining the synergistic effects of a cognitive control videogame and a home-based, self-administered non-invasive brain stimulation on alleviating depression (DiSCoVeR)



Mor Nahum



Project Coordinator:

Mor Nahum, Hebrew University of Jerusalem, Israel

Project Partners:

Daphne Bavelier, University of Geneva, Switzerland

Friedhelm Hummel, Clinical Neuroengineering, EPFL, Switzerland

Frank Padberg, University Hospital, Ludwig Maximilian University (LMU) Munich, Germany

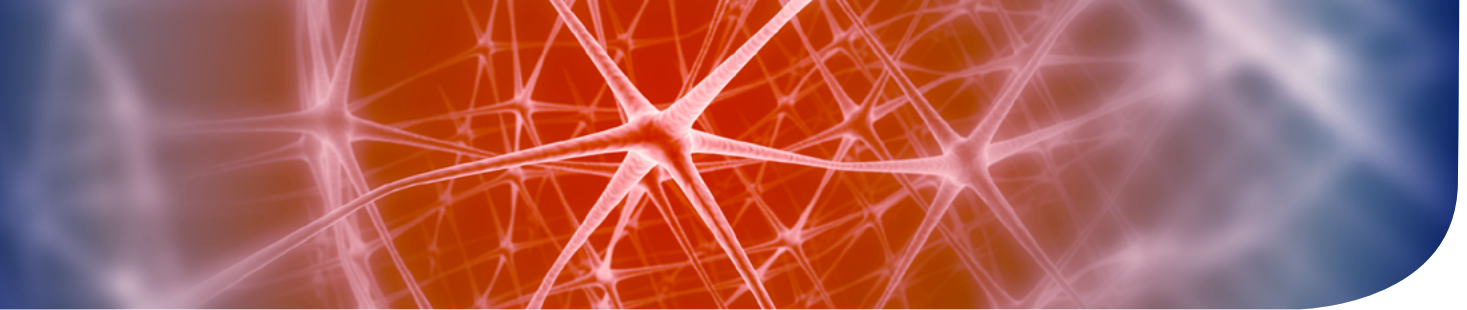
Omer Bonne, Hadassah Medical Center, Israel

Elmars Rancans, Riga Stradins University, Latvia

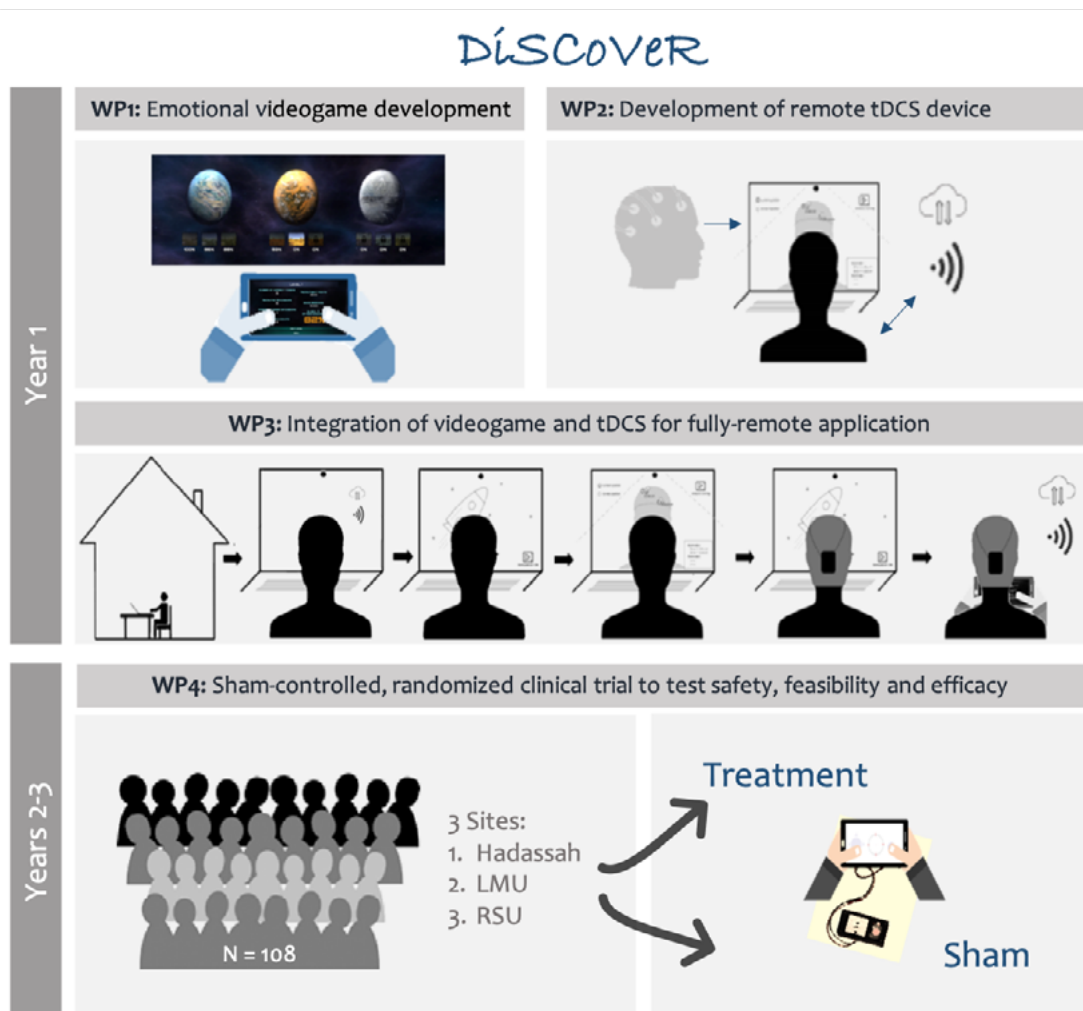
Depression is a chronic and debilitating illness, estimated to become the first ranked disease in terms of global health burden by the year 2030. Although anti-depressant medications and supportive psychological interventions are effective, long-term prognoses remain poor as depression often recurs and the probability of other depressive episodes increases with each recurrence. Furthermore, properly trained providers, access to care, drug acceptability and stigma remain major barriers to treatment. Hence there is a pressing need for providing novel and effective treatment options that address these limitations.

The DiSCoVeR project team will develop and test a novel treatment approach, self-administered in the comfort of one's home. The approach combines two novel, yet promising, treatments for depression: a videogame training and non-invasive brain stimulation (NIBS). The videogame will target emotional and cognitive control, shown to improve mood and emotion regulation in depression. NIBS targets brain mechanisms underlying cognitive control that were found abnormal in depression. Their combination should have a synergistic effect leading to increased learning and to higher compliance rates.

Our interdisciplinary team will develop an action videogame that trains key emotional and cognitive control processes, such as inhibition, working memory and task switching, as each of these processes may facilitate recovery from depression. We will further develop a portable, remotely-monitored NIBS set-up to allow self-administered stimulation safely in the comfort of one's home. An integrated platform will support patient's self-delivering the videogame and NIBS at home, along with online monitoring by clinicians. Finally, we will carry out a randomized control trial in 108 chronically



depressed patients to evaluate the impact of our combined treatment approach, comparing it to a placebo treatment. The multi-center trial will allow us to evaluate the efficacy of our combined treatment approach on reducing depression symptoms. If successful, the DiSCoVeR project can ultimately lead to a novel, cost-effective and useful treatment option for depression.



Impact of Early life MetaBolic and psychosocial stress on susceptibility to mental Disorders; from converging epigenetic signatures to novel targets for therapeutic intervention (EMBED)



Francesca Cirulli

Project Coordinator:

Francesca Cirulli, National Institute of Health, Italy

Project Partners:

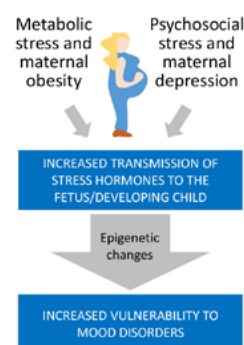
Marcella Rietschel, Central Institute of Mental Health, Germany

Moshe Szyf, McGill University, Canada

Robi Tacutu, Romanian Academy, Romania



Nearly 40% of the EU population each year suffers from a mental disorder. Extensive research on the biology of stress now shows that healthy development can be derailed by excessive or prolonged activation of stress response systems in the body and brain during fetal life. Such toxic stress exposure can have damaging effects on cognition, emotionality and mental health across the lifespan. The consortium has been built to integrate basic researchers and clinicians to work on two very relevant cohorts (offspring of obese or stressed mothers) that will be here combined in a very innovative way to address specific questions on mental health risk factors and their potential prevention. One main concept is that maternal obesity during prenatal life can trigger similar responses to maternal stress, altering developmental trajectories and increasing the risk for mental health at adulthood. It is hypothesized that maternal stress might be accompanied by inappropriate nutrition patterns which could synergize in activating stress-response systems in the developing organism. These adverse experiences can increase the likelihood of developmental delays and later health problems, including heart disease, diabetes, and depression. This consortium will assess whether common biological signals characterise early exposure to metabolic and psychological stress, affecting the long-term expression of genes involved in brain as well as in immune-metabolic function, triggering mental disorders. A special emphasis will be given to long-lasting epigenetic modifications, which could alter context- and time-dependent expression of genes relevant for brain function as well as peripheral hormones, cytokines or adipokines, indices of immune-metabolic function, that might be used in the clinic for disease prevention and health promotion during pregnancy.



The concept of EMBED stems from evidence, collected also by the collaborators, indicating that maternal stress and maternal obesity might share some mechanisms that will ultimately lead to unique epigenetic signatures of risk for mental disorders.

Microglial activation in Complement C4-stratified schizophrenic patients and in a mouse model of C4 overexpression (microSCHIZ)



Ryad Tamouza



Project Coordinator:

Ryad Tamouza, University Hospital Henri Mondor, INSERM, France

Project Partners:

Corentin Le Magueresse, Institut du Fer à Moulin, INSERM, France

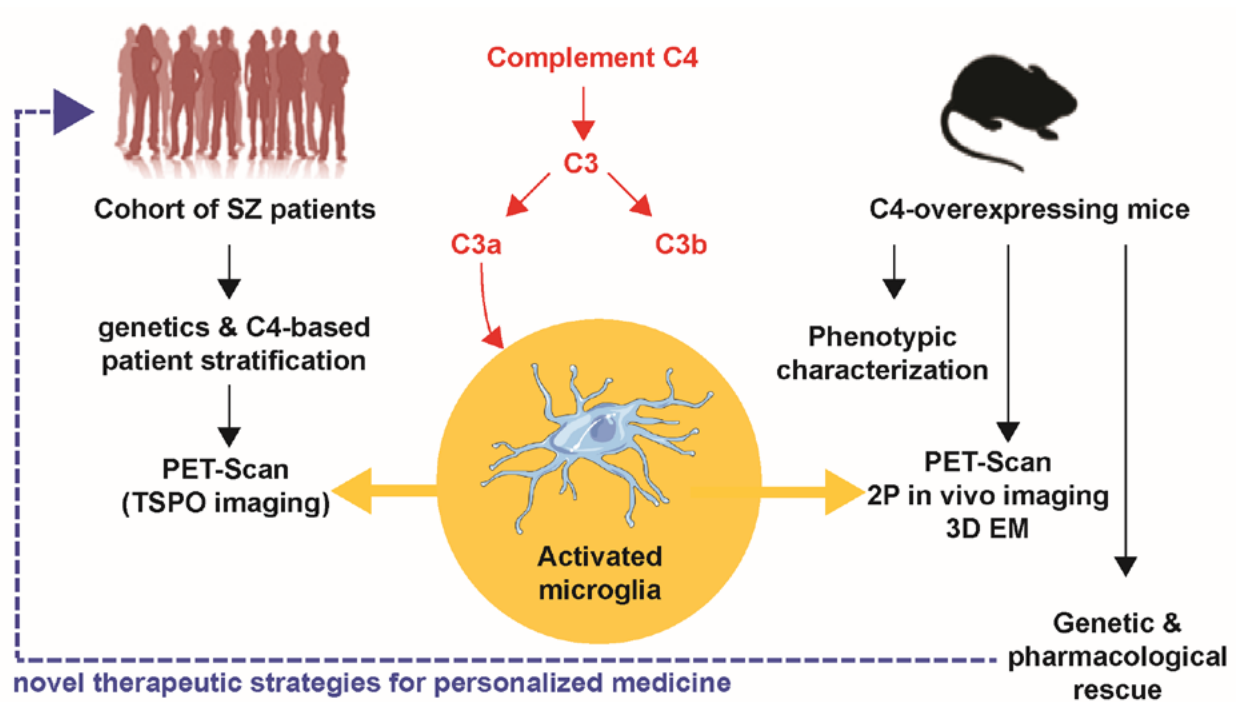
Martin Fuhrmann, DZNE, Germany

Benoît Zuber, University of Bern, Switzerland

Baiba Jansone, University of Latvia, Latvia

Schizophrenia (SZ) is a frequent and severe psychiatric disorder suffering from lack of progress in terms of treatments. Recent genetic association studies identified SZ-associated genomic regions mapping to the major histocompatibility complex (MHC). In particular, genetic variants conferring high expression of C4, a member of the classical complement cascade, were demonstrated to be strongly associated with SZ risk. Microglial cells are part of the brain innate immune system and can be activated by immune challenges, in particular by C3a, downstream of C4 in the complement cascade. Microglial activation has been found in subsets of SZ patients. We also observed microglial activation in a novel mouse model of elevated C4 expression in the prefrontal cortex, along with neuronal alterations consistent with those observed in the brain of SZ patients. Accordingly, we hypothesized that high C4 expression activates microglia, thereby giving rise to SZ-associated neural endophenotypes. To test this hypothesis, we propose a multidisciplinary approach involving clinicians and fundamental scientists. In humans, we will analyse the correlations between C4 genetics/expression and disease severity further allowing the analysis of microglial activation using PET-Scan imaging in C4-stratified patients. In parallel we will investigate, in a mouse model of high C4 expression, the interactions between neurons and activated microglial cells using PET-Scan, electrophysiology, in vivo 2 photon imaging, 3D electron microscopy and behavioral studies.

By combining human studies and a new mouse model of schizophrenia, we expect to be able to identify schizophrenia-causing neurobiological mechanisms paving the way towards innovative therapeutic options.



Microbiome Gut-Brain interaction in Anorexia Nervosa (MiGBAN)



Beate Herpertz-Dahlmann



Project Coordinator:

Beate Herpertz-Dahlmann, University Hospital Aachen, Germany

Project Partners:

John F Baines, Christian-Albrechts-University of Kiel, Germany

Andreas Karwautz, Medical University Vienna, Austria

Sergueï O. Fetissov, INSERM, University of Normandie, France

Roger Adan, University Medical Center Utrecht, The Netherlands

Anorexia nervosa (AN) is one of the most serious chronic disorders of youth. Up to now we only know moderately effective treatment strategies; less than 50% of affected patients fully recover. Recently, there has been an emerging evidence of an association between the bacteria living in the human gut (gut microbiome) and the brain; several studies demonstrated that the composition of the microbiome and its metabolism have an important influence on the development of mental disorders and on weight regulation disorders such as obesity. In AN, fasting ("starvation") induces severe perturbations of the gut microbiome, which do not alleviate with weight gain. Thus, our aim is to improve the course of this disabling disorder by manipulating the patients' gut bacteria. Our work plan comprises an observational study by which we want to compare the microbiome of patients with a short duration of illness with the microbiome of those who are chronically ill. We hypothesize that changes of the microbiome of chronically ill patients are more profound than those of patients with a short duration of AN. In addition, we want to administer polyunsaturated fatty acids (PUFA) and psychobiotics ("live bacteria, which when applied in adequate amounts, confer mental health benefits") to patients with AN, which have been shown to improve weight, mood and the course of many mental disorders. Moreover, there is a well-known animal model for AN: access to a running wheel and reduction of food induce similar symptoms as observed in AN, such as physical hyperactivity and amenorrhea. We plan to parallel our studies in humans with very similar investigations in rodents to better understand the underlying mechanisms of the disorder. We hope that by intensively studying the microbiome in patients and animals we will have the chance to find new effective therapeutic tools for these difficult to treat adolescents.

Brain/Behavior:

- Microbes interact with brain („Gut-Brain Axis“)
- Microbes influence cell neogenesis, learning, mood, anxiety
- Microbial diversity reduced in AN and linked to depression and ED symptoms

Intestinal tract:

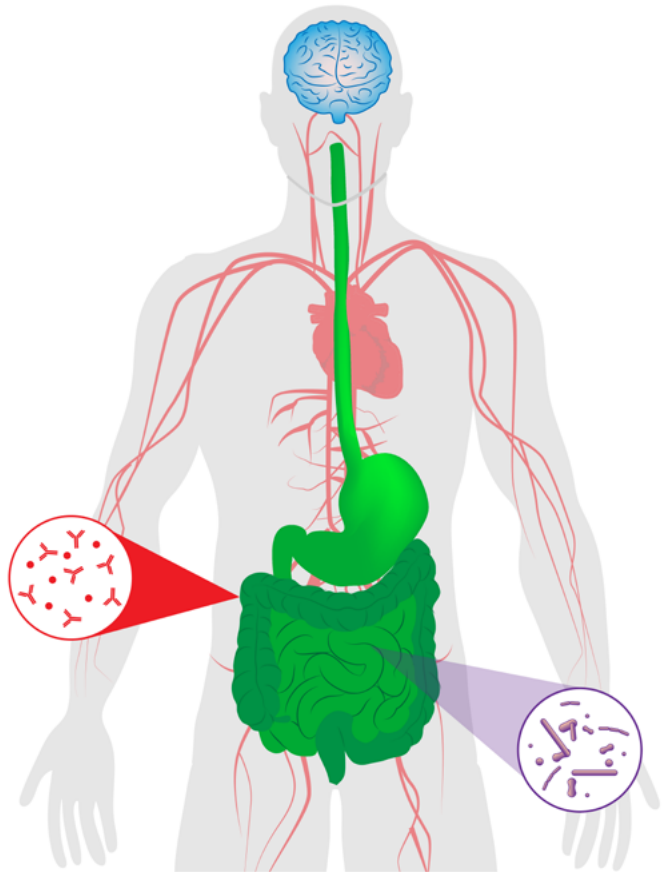
- Microbes degrade nutrients and regulate gut permeability
- Production of increased fecal branched-chain fatty acid in AN
- Increased gut permeability in AN animal model

Immunology:

- Bacterial antigens traverse intestinal wall
- Low grade inflammation in AN
- Antibodies against hunger/satiety hormones in AN

Gut microbiome:

- Microbe diversity reduced
- Altered bacterial community-structures
- More protein-fermenting and less butyrate-producing taxa (probably feed on mucin and aggravate gut permeability/inflammation)



Disruption of the spatio-temporal dialogue between migrating cortical neurons as underlying factor in Autism Spectrum Disorder (nEUrotalk)



Olga Penagarikano

Project Coordinator:

Olga Penagarikano, University of the Basque Country, Spain

Project Partners:

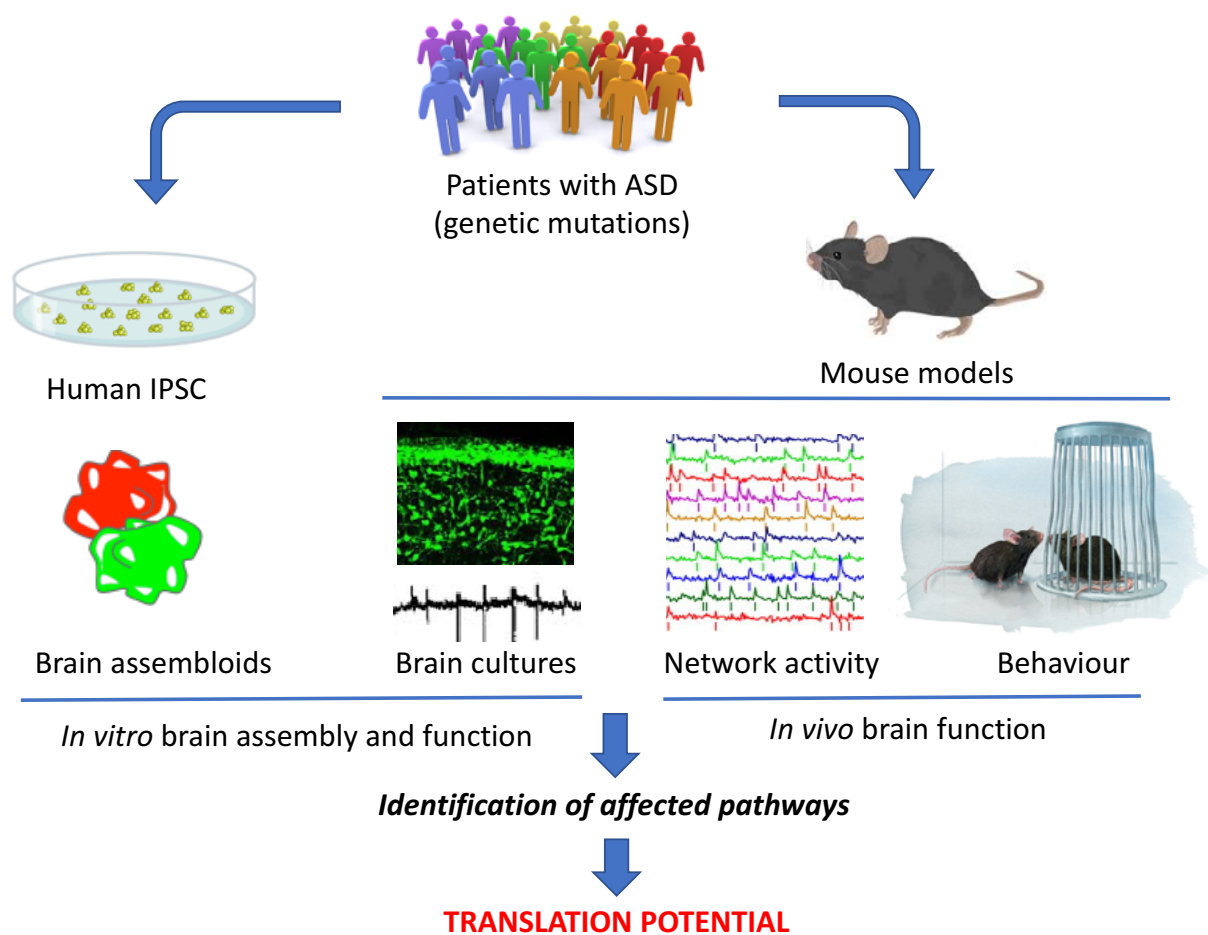
Laurent Nguyen, University of Liege, Belgium

Jean Bernard Manent, INMED INSERM, France

Silvia Cappello, Max Planck Institute, Germany



Autism is characterized by impaired social communication and repetitive behaviors and affects 1 in 59 children. Although several brain alterations have been found in patients, to date, no unifying neurobiological mechanism responsible for the disorder has been reported, which has made the development of pharmacological treatments challenging. Although many different genes have been associated with autism, these can be subdivided by their similar function, and it is currently accepted that common affected biological pathways for subsets of patients could be identified. The identification of these shared affected biological pathways is critical, as it will help develop pharmacotherapies and stratify patients for specific treatments. One of the most common neurobiological abnormalities found in autistic brains is an altered proportion of the two major classes of neurons that compose the cerebral cortex, a part of the brain involved in higher order cognitive functions, such as social behavior: excitatory and inhibitory neurons. During brain development, these two classes of neurons co-interact to coordinate their final number and location in the cortex, as they are born and migrate from separate distal sites within the brain. The precise proportion and location of these neurons is critical for proper brain function. Several studies have shown that if the migration of either of these two major classes of neurons is altered, the numbers and location of the other class is in turn affected. Many of the genes that are associated with ASD are known to be involved in migration of either class of neurons. In the present project, we propose that alterations in the communication between excitatory and inhibitory neurons during cerebral cortex development lead to the final observed abnormal numbers and location of these cells in a subset of patients with ASD. In short, we aim to better understand the mechanisms that impair brain development in ASD with the goal of identifying targets that could be pharmacologically tackled.



Oligodendrocyte precursor cell dysfunction linked to schizophrenia: from mechanisms towards new therapeutic strategies (OPCphrenia)



Maria Cecilia Angulo



Project Coordinator:

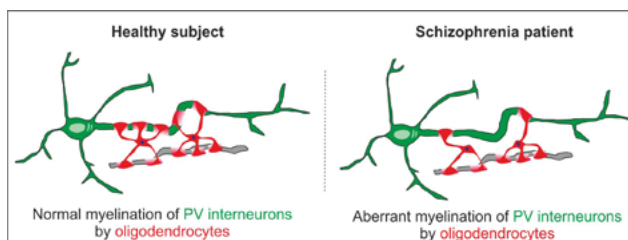
Maria Cecilia Angulo, Center of Psychiatry and Neuroscience, INSERM, France

Project Partners:

Steven Kushner, Erasmus MC Rotterdam, The Netherlands

Anastassia Voronova, Governors of the University of Alberta, Canada

Schizophrenia is a heritable neurodevelopmental disorder affecting ~0.5% of the world population. Primary symptoms include hallucinations, delusions as well as impaired cognition, attention and social function. Previous studies of the brain from people with schizophrenia have identified a specific class of neurons, known as fast-spiking inhibitory interneurons, which function critically in coordinating brain activity. Moreover, recent findings also implicate abnormal integrity of myelin, a fatty substance that coats nerve cell projections and is essential for efficient neuronal signal propagation. Myelin is produced solely by oligodendrocytes, a non-neuronal cell type in the brain. Schizophrenia patient studies have suggested that myelination impairments could be a critical determinant of the disease. Yet, the mechanisms linking oligodendrocyte lineage cell dysfunction to schizophrenia are unknown. Our team has discovered critical forms of communication between interneurons and oligodendrocyte precursor cells (OPCs), as well as unique properties of interneuron myelination. Given their intrinsic regenerative capacity as the cell type responsible for generating oligodendrocytes and the most actively dividing cell type in the adult brain, OPCs represent a novel potential therapeutic target for enhancing the repair of myelin deficiencies in schizophrenia. Notably, we recently discovered that OPCs derived from genetically-identified familial schizophrenia patients have impaired function and defective myelination potential. Thus, we propose that schizophrenia is likely to be, at least in part, an OPC disease ("OPCphrenia"), arising from aberrant interneuron-OPC communication. In this proposal, we aim to discover the detailed mechanisms of interneuron-OPC communication and investigate potential therapeutic strategies for aberrant schizophrenia-related OPC dysfunction by re-balancing the levels of interneuron-secreted factors. We will leverage novel methodological advances, mouse genetics, and human patient samples to



advance the understanding of schizophrenia pathophysiology and identify new molecular targets for future therapeutic intervention.

Preclinical Phase II Testing of Psilocybin in Alcohol Addiction and Epigenetic and Neuroimaging Studies on the Mode of Action (Psi-Alc)



Rainer Spanagel



Project Coordinator:

Rainer Spanagel, Central Institute of Mental Health (CIMH), Germany

Project Partners:

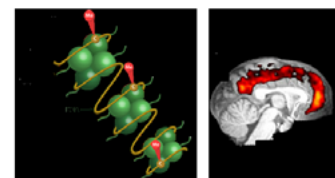
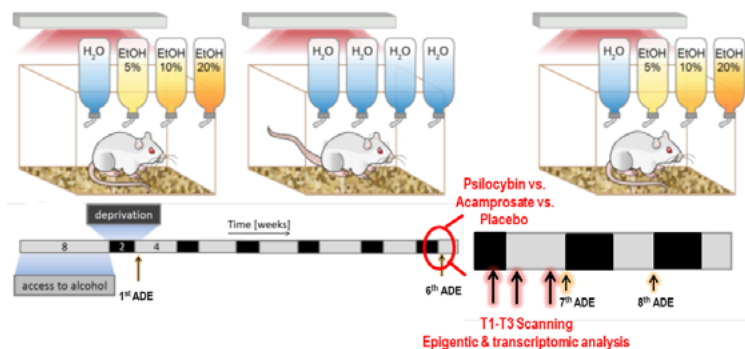
Roberto Ciccocioppo, University of Camerino, Italy

Mickaël Naassila, University of Picardie Jules Verne, France

Franz X. Vollenweider, Psychiatric Hospital, University of Zurich, Switzerland

Worldwide more than 2 billion people consume alcohol. Nearly 60 million EU citizens engage in harmful drinking and 23 million Europeans are suffering from alcohol addiction. Approved pharmacological treatments for alcoholism are limited in their effectiveness, and new drugs that can be translated into the clinic are warranted. In the last decade there was considerable enthusiasm that advances in the neuroscience of alcohol addiction would soon translate into mechanistically novel alcoholism therapies. However, several novel mechanisms that appeared to hold great promise based on preclinical data failed to translate to the human condition. In our Psi-Alc proposal we will attempt to improve the reliability of preclinical academic research as well as enhance the chance of clinical translatability of our findings. Our consortium is interested in the neurobiological underpinnings of alcohol addiction and the development of new treatment possibilities. By using a unique DSM-5 based rat model for alcohol addiction and implementing the novel concept of randomized multi-center preclinical phase II testing in laboratory animals we will be able to produce meaningful and translatable results for subsequent cost-intensive Phase II/III testing in alcohol addicted patients.

With this approach and integrating experimental human studies we will test the efficacy of psilocybin for treating alcohol addiction and will translationally study the underlying neurobiological mechanism.



A novel paradigm for effective and safer treatment of schizophrenia: biased (ANT) agonists with a characterized polypharmacological profile (PSYBIAS)



Jana Selent



Project Coordinator:

Jana Selent, Hospital del Mar Research Institute (IMIM), Spain

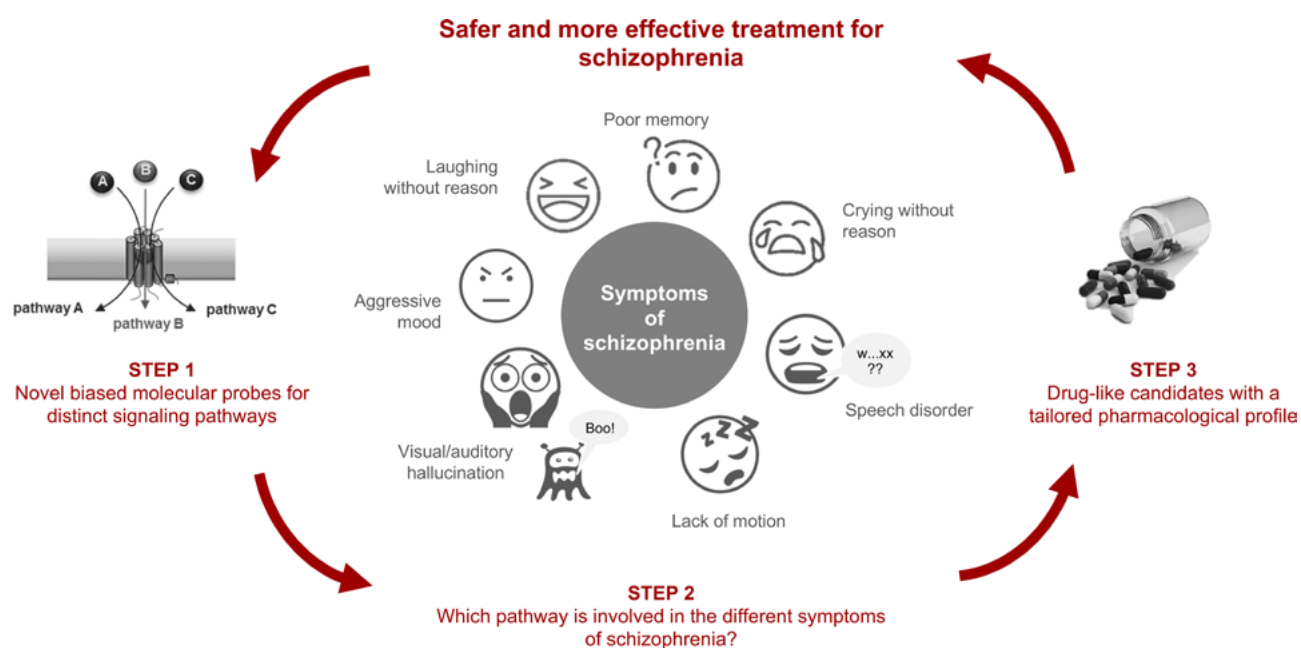
Project Partners:

Peter Kolb, Philipps-Universität Marburg (UM), Germany

Michel Bouvier, University of Montreal (UdeM), Canada

Schizophrenia is a severe disease which affects about 1-2% of the global population. Treatment of this complex disease is far from being perfect. One of the main drawbacks of current treatments is associated to diverse side effects such as moving problems or shakiness similar to Parkinson's disease, a feeling like your mind has slowed down, increased appetite, abnormal electrical activity in the brain, or an altered heart rhythm among many others. Furthermore, there is a high percentage of patients who do not respond to available drugs. Hence, there is a clear need for improving current therapies. Unfortunately, the development of novel therapeutic agents has been hampered by some major obstacles. For instance, the main target of antipsychotic drugs, the serotonin 2A receptor, mediates multiple responses in the cell. An ideal drug should only inhibit responses linked to schizophrenia-like symptoms. However, current antipsychotic drugs broadly inhibit different signaling routes which is likely counterproductive and provokes diverse side effects. In addition, drugs that target the serotonin 2A receptor bind other numerous receptors of this class. Such complexity seems to contribute to both the therapeutic effects but also side effects of current drugs.

Our project will address these obstacles at the molecular, cellular and behavioral levels, and will provide a framework to improve the treatment of schizophrenia. In a first step, we apply state-of-the-art molecular and cellular technology to deliver novel molecular probes able to engage only one specific cellular response. In a second step, we use these probes in complex animal models to disclose pathways that are linked to schizophrenia-like behavior. Guided by the outcome, in a third step we design a small number of molecules that can mark a breakthrough for the development of a new class of antipsychotic drugs.



Targeting TAO2 and its downstream pathway as critical effectors of Autism spectrum disorders in 16p11.2 microdeletion patients (TAO2PATHY)



Froylan

Calderon de Anda



Project Coordinator:

Froylan Calderon de Anda, University Medical Center Hamburg-Eppendorf, Germany

Project Partners:

Peter Soba, University Medical Center Hamburg-Eppendorf, Germany

Joris de Wit, VIB Center for Brain & Disease Research/KU Leuven, Belgium

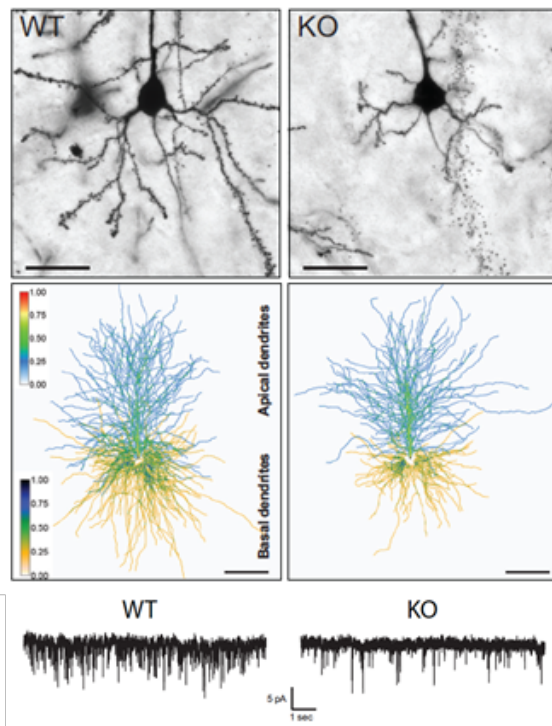
Karun Singh, McMaster University, Canada

Stephen Scherer, Hospital for Sick Children, Canada

Atypical brain connectivity is a major contributor to the pathophysiology of neurodevelopmental disorders (NDDs) including Autism spectrum disorders (ASD). TAO2 is one of several genes in the 16p11.2 microdeletion region, which is affected in about 1% of all ASD patients. Whether and how TAO2 contributes to NDDs/ASDs was until recently unknown. Using whole genome and exome sequencing of ASD families we identified three de novo mutations in TAO2. Moreover, we performed behavioral analysis in a Taok2 knockout (KO) mouse model and found impairments in cognition, anxiety and social interaction. These mice display hallmarks of 16p11.2 microdeletion patients including increased brain size, deficits in neuronal morphology, aberrant neural connectivity in multiple brain regions and reduced neurotransmission. Moreover, TAO2 is functionally linked to several additional ASD risk genes including MYO1A and Shank3 suggesting it is a central player regulating neuronal development and function.

Together, these data provide strong evidence that TAO2 is a novel ASD risk gene, which consequently led to the assignment as such by the Simons Foundation Autism Research Initiative (SFARI Category 2; strong ASD risk gene). Based on the critical role TAO2 might play in 16p11.2 patients and its function as a major hub for ASD linked genes it is an excellent candidate to identify novel treatment strategies that target this pathway.

Our proposal aims to test the hypothesis that TAO2 is a critical gene within the 16p11.2 locus and a molecular hub that regulates neuronal function relevant for ASDs. Our overall goal is to identify novel therapeutical approaches targeting the TAO2 pathway, which could potentially overcome 16p11.2- associated abnormalities in brain development and function and lead the way to develop treatment strategies for other ASDs affecting related genetic pathways within the TAO2 network.



TAOK2 KO mice have reduced dendrite growth and synaptic connectivity in the prefrontal cortex (PFC).

Top: Golgi-stained PFC neurons from P21 WT, *Taok2* Het and KO mice. Scale bars represent 20 μm. Bottom: Dendritic heat maps of superimposed neuron tracings for each condition. Blue to red (apical) and yellow to blue (basal) indicates increased probability of dendrite presence. Scale bars represent 30 μm

Lower panel: Representative traces of mEPSC spikes from WT and *Taok2* KO PFC neurons. Scale: 5 pA vs 1 sec.

UNveiling the MEchanism(s) underlying the switch to mania during antidepressant treatment: The role of glutamate (UNMET)



Judith Homberg

Project Coordinator:

Judith Homberg, Stichting Katholieke Universiteit, The Netherlands

Project Partners:

Laurence Ris, University of Mons, Belgium

Peter Gass, Central Institute of Mental Health Mannheim, Germany

Paolo Brambilla, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Italy

Daniela Jezova, Institute of Experimental Endocrinology, Slovakia

Bipolar Disorder (BD) is a severe psychiatric disorder characterized by the alternation of different behaviours such as mania and depression. The lifetime prevalence of BD type I, the type of BD associated with severe mood elevation, is around 0.6% in the general population. The treatment of BD is difficult because of the opposite nature of its symptoms (i.e. depression and mania). Furthermore, the available treatments treat symptoms but not the core mechanisms in the brain that are malfunctioning, and can cause severe side effects. Hence, there is an unmet need for novel approaches that target the primary malfunctioning mechanisms underlying BD, specifically mania. A well-known clinical feature of BD involves the switch from depression to mania during antidepressant treatment. The mechanisms underlying this switch are still elusive. Accordingly, our project will address in both animal and humans the neurobiological mechanisms underlying the switch to mania, taking advantage of the availability of two animal models, the serotonin transporter knockout (KO) rat and the dopamine transporter KO rat model. We hypothesize that the neurotransmitters serotonin and dopamine increase levels of the neurotransmitter glutamate in a brain circuitry that deals with mood states. In the end, UNMET will, by integrating behavioural, molecular, electrophysiological and metabolic approaches in rats together with neuroimaging techniques in rats and humans, provide a proof-of-principle of the glutamatergic mechanisms underlying mania. Furthermore, UNMET will test whether a drug approved for human use decreasing glutamate levels prevents the switch to mania during antidepressant treatment, with potential relevance for treatment of BD more general.

