

# ERA-NET Neuron NEWSLETTER 20



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## News From NEURON II

**A special symposium on “Synaptopathies” will be held within the framework of NEURON II activities in Bonn, Germany in May 14, 2014, adjacent to NEURON’s meeting of the Network Steering Committee**

By the deadline of March 10th, 2014, 139 pre-applications were received in response to the JTC on “Neuroinflammation”. Following the review process, the coordinators of selected pre-applications will be invited to send their full application by June 24, 2014.

## From the desk of the coordinator | February 2014

Although the year 2014 races on at a rapid pace, a number of NEURON 2013 activities deserve reflection (and forecast)



Priv.-Doz. Dr.  
Marlies Dorlöchter

The annual January launch of a Joint Transnational Call (JTC) for proposals constitutes a major highlight. NEURON launched its latest JTC for ‘European Research Projects on Neuroinflammation’ on January 10th, 2014 (<http://www.neuron-eranet.eu/>). The aim of the call is to facilitate multi-national, collaborative research projects addressing key questions relating to inflammatory processes in the nervous system. Proposals ranging from understanding the basic mechanisms of disease development to proof-of-concept clinical studies in humans accepted. These include research on the role of inflammation in neurological and psychiatric disorders or associated with traumatic brain injury, pathogen infection or toxicity in the nervous system. The deadline for proposal submission was March 10th, 2014.

In the first months of 2014 the 12 best projects from the JTC2013 funding program, “European Research Projects on Mental Disorders”, will commence their research,

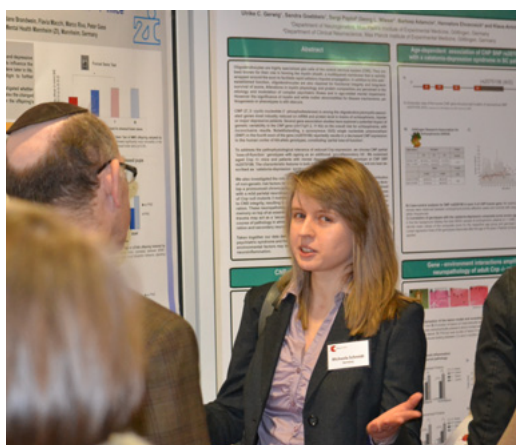


More information can be found in our web page  
<http://www.neuron-eranet.eu/index.php>  
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to which the funding organisations look forward with high expectations. In total, 48 research groups from 11 European countries, Canada and Israel are collaborating in these projects. The consortia address various neuropsychiatric disorders, ranging from autism spectrum disorders and other neurodevelopmental disorders, to depression, obsessive-compulsive disorders and addiction. State-of-the-art methodology, such as magnetic resonance imaging is employed to address important research questions and to find ways to translate the results into clinical application. The projects are listed on the NEURON website <http://www.neuron-eranet.eu/en/505.php>.



Dr. Michaela Schmidt, Germany (POSEIDON consortium)  
at the poster session, Lisbon symposium on Mental Health



Prof. Carlo Sala, Italy (AMRePACELL consortium) at the plenary  
session, Lisbon symposium on Mental Health

The area of mental disorders includes several diseases, which exact a heavy toll on patients, their families and friends and society as a whole. For this reason the NEURON partners initiated a funding program in this field already in 2010. The final Symposium of JTC 2010 'Mental Disorders' was held in Lisbon in January 2014. Two members of the original Peer Review Panel for this call attending the presentations were delighted with the results of the projects they selected for funding four years earlier. The high quality of the funded projects is evidenced in the large number of publications stemming from them, many in very high-profile journals such as Science or Nature.

In September 2013 the ERA-Net NEURON celebrated its 10th anniversary in Warsaw, Poland, with excellent presentations of projects funded within JTC2011 "Cerebrovascular Disorders". NEURON was launched in 2003 with a pilot collaboration between Poland, Israel, Luxemburg and Germany. NEURON's development is best characterized by its proliferation: within four years, 18 funding organizations from 13 countries joined the ERA-Net. In 2012 the number of funding organizations increased to 23 from 18 countries, and NEURON took on a global dimension with Canada's accession in 2009.


NEURON's development entailed several steps, among which the building of common and mutual trust was not the least important. To this end, the 32 well-attended NEURON

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meetings since 2007 contributed a great deal to the programme's success. The number of 100 regular NEURON participants at these meetings also reveals that many represented their funding organization on a permanent basis. In other words, NEURON has a very high degree of staff continuity. The impact and success of NEURON can certainly be attributed in no small measure to this kind of personal engagement and involvement. In this regard, it is quite rewarding to see that NEURON has sparked interest among a wider audience and has been invited to present its work during the European Month of the Brain in May 2013 and in Global Scientia, a journal designed to create a portal for the transfer and sharing of new developments in scientific knowledge.

Looking forward to 2014, NEURON will undoubtedly confront challenges both known and new. We thank our partners for a very successful and high-spirited 2013 and wish us all great zeal in 2014. You are cordially invited to our webpage (<http://www.neuron-eranet.eu/index.php>) to browse the salient highlights and news and to subscribe to our newsletter.

Sincerely yours,



Marlies Dorlöchter

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The funding of research projects in a competitive environment is a process necessitating a highly professional approach from both a scientific and administrative standpoint. As before, following an extensive and thorough evaluation process in the 6th Joint Translational Call (JTC) on Mental Disorders, NEURON II announced that funding has been awarded to 12 research projects. Since transparency of the evaluation process is essential to building trust among the parties concerned, the details of this process are described here.

The 6<sup>th</sup> JTC attracted avid interest among the ERA partners: Seventeen funding organizations from 16 countries committed initially a total of €11.1 million to fund the best research projects. By the 11.3.2013 deadline, no less than 91 eligible pre-applications were submitted to DLR, Germany, the Joint Call Secretariat. The pre-proposals involved 369 researchers requesting a total of €82.6 million. A team of 48 experts reviewed the pre-applications and qualified 39 of them (42.9%) for the next stage of submitting full applications.

The full applications were evaluated by a peer review panel comprising 16 experts who offered their time and expertise to facilitate NEURON in the selection process. The experts recommended the funding of the 12 (30.8% success) most pertinent projects. The funding organizations ended up providing € 9.9 million to support these projects, backing a total of 48 researchers from the respective partner countries.

The abstracts of the 12 funded research projects are presented below.



Dr. Iiris Hovatta



## Novel molecular pathways and biomarkers of anxiety disorders (AnxBio)

**Project Coordinator:** Dr. Iiris Hovatta, University of Helsinki, University of Helsinki, Finland.

**Project Partners:** Prof. Christoph Turck, Max Planck Society, Munich, Germany,

Dr. Angelika Erhardt, Max Planck Society, Munich, Germany,

Dr. Alon Chen, Weizmann Institute of Science, Rehovot, Israel.

Anxiety and fear are normal responses to threatening situations. However, in anxiety disorders these responses are excessive and prolonged, disrupting daily life. Anxiety disorders are the most common mental disorders in the EU, affecting approximately one in seven people. The drugs currently used to treat anxiety disorders are only helping a subset of patients and are associated with adverse side effects. There is a need to develop more highly targeted therapies. The ability to develop such therapies is contingent on the understanding of the molecular mechanisms that regulate anxiety. The AnxBio project will use modern genomic and proteomic methods to reveal the biological pathways involved in the regulation of anxiety. Based on this data, we will formulate specific hypotheses and test them in anxiety models. This approach could lead to the establishment of biomarkers to more accurately diagnose anxiety disorders and to the identification of molecular targets towards the development of more effective treatments.



Prof. Julia Stingl



## Role of genetic polymorphisms in drug metabolizing cytochrome P450 enzymes expressed in the brain for affective disorders, (BrainCYP)

**Project Coordinator:** Prof. Julia Stingl, Federal institute for drugs and medical devices, Bonn, Germany.

**Project Partners:** Dr. Roberto Viviani, University Ulm, Ulm, Germany,

Prof. Magnus Ingelman-Sundberg, Karolinska Institute, Stockholm, Sweden,

Prof. Rachel Tyndale, University of Toronto and Centre for Addiction and Mental Health, Toronto, Canada.

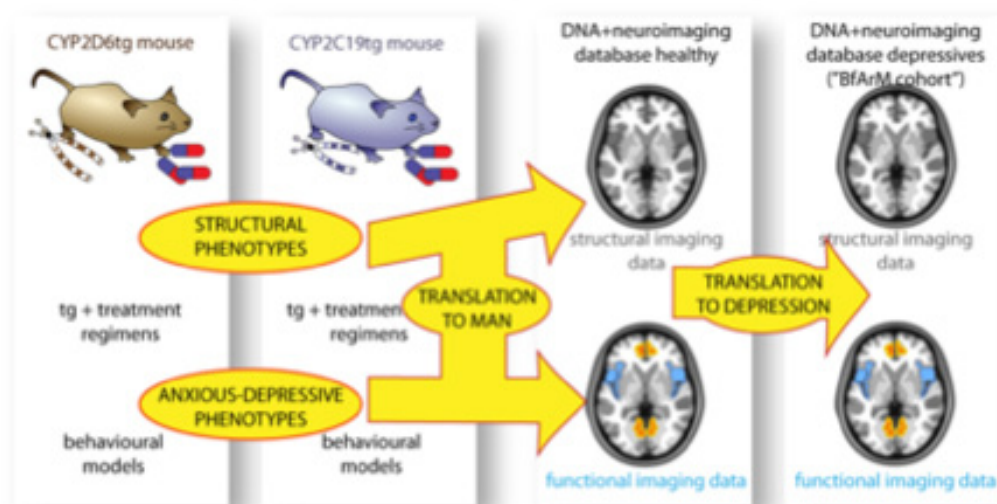
Cytochrome P450 (CYP) enzymes are proteins that help eliminate external substances such as drugs and toxins ingested or absorbed by an organism. Many drug-metabolising enzymes can also modify substances produced by the organism itself. The BrainCYP project focuses on two P450 enzymes, CYP2C19 and CYP2D6, which vary genetically in humans. These enzymes are expressed in the brain, and are able to metabolise CNS active substances such as antidepressants, antiepileptics, cannabinoids, and tryptamine derivatives. The genes coding these two enzymes occur in the population with variants that exhibit extreme effects on their activity. For example, some individuals have no



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functioning CYP2D6 protein in their organism, while others have so much CYP2D6 that its function is enhanced 10-15 times. Evidence pointing to the importance of these CYP variants to brain function is derived from studies showing differences in the susceptibility to affective disorders as well as differences in brain activity obtained with modern neuroimaging methods. Accordingly, this genetic variation may have practical implications for the treatment of mental disorders. BrainCPY brings together groups that work with laboratory animals carrying the two CYP genetic variants and groups that use neuroimaging to assess the impact of genetic variants on brain function..

Structure of the BrainCYP project:



Prof. Hannes Lohi



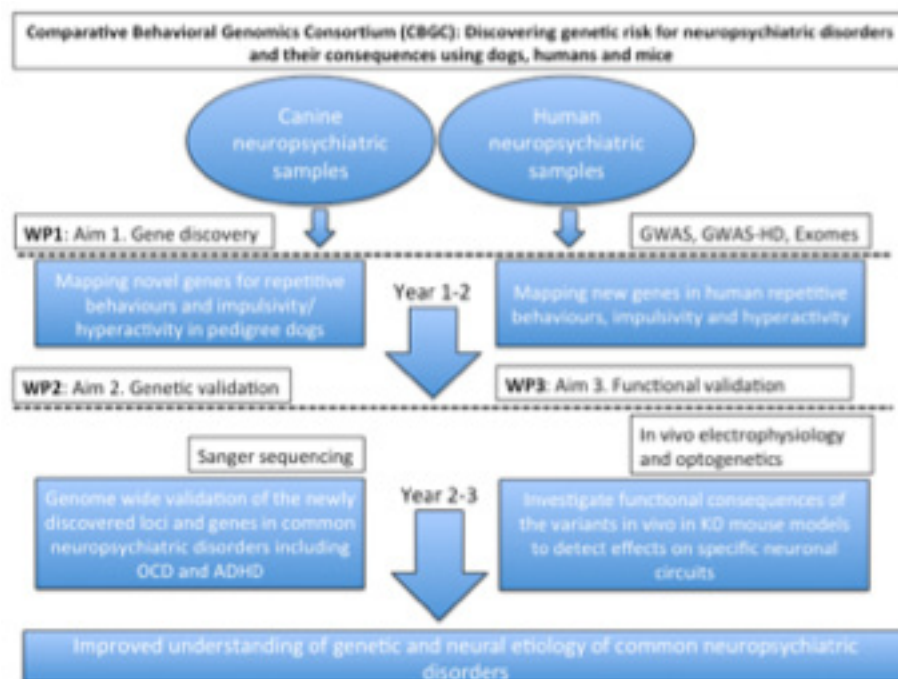
## Discovering genetic risk factors for neuropsychiatric disorders and their consequences using dogs, humans and mice, (CBGC)

**Project Coordinator:** Prof. Hannes Lohi, University of Helsinki, Helsinki, Finland.

**Project Partners:** Prof. Paul Arnold, The Hospital for Sick Children, Toronto, Canada, Dr. Rui Costa, Champalimaud Center for the Unknown, Lisbon, Portugal.

Children with psychiatric disorders such as obsessive-compulsive disorder (OCD) and attention deficit hyperactivity disorder (ADHD) suffer from highly disabling symptoms which interfere with their ability to function in daily life. These disorders often persist into adulthood and potentially lead to the development of other problems later on in life, including depression and substance abuse. We know that OCD and ADHD affect specific brain circuits and that genetics apparently play an important role in their development. We still do not fully understand, however, which genes contribute to ADHD and OCD and how variation in these genes can lead to brain circuit dysfunction. One avenue of psychiatric genetic research involves the study of animals, such as dogs and mice, which exhibit

compulsive, impulsive or hyperactive traits similar to those associated with OCD and ADHD. Pedigree dogs are particularly helpful because their relative genomic homogeneity facilitates gene-mapping. Mice enable the testing of genetic variants on their brains in a very precise manner in a laboratory setting. The Comparative Behavioural Genomics Consortium (CBGC) will study OCD- and ADHD-related traits across humans, dogs and mice in order to gain novel insights regarding the role genetic variants play in childhood psychiatric disorders, leading ultimately to new avenues for early detection and treatment of these conditions.



*Figure 1. A schematic overview of the proposed novel and original research strategy to identify novel genes, pathways and related neural circuits in common neuropsychiatric disorders through cross-species phenomic and genomic analyses (human, dog, mouse). The CBGC will apply novel “phenomic” approaches including the use of related behavioural tasks in both dogs and humans for gene identification. The analyses of the function of identified gene variants in neural circuit activity and behavior will then be performed in mice. We propose that mapping genes conferring risk for behavioral traits in dogs and humans will facilitate the discovery of genetic risk factors for common and serious neuropsychiatric disorders including ADHD and OCD.*



Prof. Salah El Mestikawy



## VGLUT3 and vulnerability to addiction (COFACE)

**Project Coordinator:** Prof. Salah El Mestikawy, Douglas hospital, McGill University, Montréal, Canada.

**Project Partners:** Prof. Frank Bellivier, GH Saint-Louis Lariboisière, Paris, France, Dr. Stéphane Jamain, INSERM U 955, Créteil, France, Prof. Christian Rosenmund, Charité – Universitätsmedizin, Berlin, Germany, Prof. Åsa Mackenzie, Uppsala University, Uppsala, Sweden.

Addiction is a compulsive pattern behavior that takes place at the expense of most other activities. It leads to a loss of control and reoccurring episodic abstinence and relapse. The economic and societal costs of addiction are tremendous. The secret of addiction lies in the nervous system, more particularly in the dysfunction of brain communications in the reward system. To communicate with each other, brain cells (or neurons) use a combination of electrical and chemical signals. These messengers, called neurotransmitters, are released by specific neurons. The neurotransmitters, dopamine (DA), acetylcholine (ACh) and glutamate, are key players in addiction. The role of dopamine release in reward prediction and the use of addictive drugs is well documented. The role of acetylcholine neurons, however, is still poorly understood. Acetylcholine neurons have long been believed to communicate solely with ACh. We recently made the surprising discovery that acetylcholine neurons from the nucleus accumbens (a particularly important area of the reward system) use two transmitters: glutamate and acetylcholine. In the COFACE project we investigate the implications of this neuronal “bilingualism” on addiction. Our findings could lead to the establishment of alternative medications for the treatment of addiction.



Dr. Véronique Deroche-Gamonet



## Cocaine addiction: a translational study to identify and characterize dysfunctional neural networks (COCADDICT)

**Project Coordinator:** Dr. Véronique Deroche-Gamonet, INSERM, Bordeaux, France.

**Project Partners:** Prof. Rainer Spanagel, Central Institute for Mental Health, MANNHEIM, Germany, Prof. Marco Leyton, McGill University, Montreal, Canada, Dr. Cyril Herry, INSERM, Bordeaux, France.

Only approximately 15-20% of the people who try cocaine become severely addicted, continuing to use the drug despite accumulating adverse consequences. Unfortunately, we know little about why some people lose control of cocaine use, and medications to treat cocaine addiction have yet to be discovered. To address these issues, COCADDICT will examine sequential stages of the addiction process in individuals with varying addiction

risk. The studies will benefit from coordinated research streams in both cocaine users and animals in a high face validity model. By exploiting new brain imaging methods in both humans and animals, we will dissociate alterations that are related to addiction from those that are related to prolonged drug use without loss of control. By using novel brain activation techniques, we will identify the relevant neurochemistry within these circuits, and determine whether addiction-related neural changes can be reversed in experimental animals. Together, the studies will help to identify neurobiological trajectories of addictive behaviour as well as potential treatment targets.



Prof. Kristina  
Leuner



## HYPerforin analogues, zinc and TRPC6 channels – a new antidepressant concept? (HYPZITRP)

**Project Coordinator:** Prof. Kristina Leuner, Friedrich-Alexander-University Erlangen/Nuremberg, Erlangen, Germany

**Project Partners:** Dr. Alexandre Bouron, CEA, Grenoble, France,  
Prof. Gabriel Nowak, Jagiellonian University Krakow, Krakow, Poland.

Depression is a widespread illness characterized by low mood, pleasure, motivation and reward. The treatment of major depressive disorders is confounded by high rates of treatment resistance and low rates of lasting remission. These clinical realities, paired with the high economic burden of treating depression necessitate a better understanding of the pathophysiology of depression and the development of alternative therapeutic approaches to treating this disease. Current treatment strategies are based primarily on the monoamine hypothesis of depression. Recent work, however, suggests that the neuropathology of depression is stratified across the reduction of synaptic plasticity. Evidence suggests that the canonical transient receptor potential channel 6 (TRPC6) regulates synaptic plasticity, most likely via the influx of calcium and zinc ions. TRPC6 channels are the molecular target of hyperforin, the active antidepressant constituent of St. John's wort extracts, which have been used since Paracelsus to treat mild to moderate depression. Hyperforin is chemically unstable and is only modestly potent in TRPC6 channels. These qualities limit its use as a lead compound for a new class of antidepressants. The HYPZITRP project will focus on the synthesis and detailed pharmacological and behavioural characterization of new derivatives of hyperforin. It will also examine the interplay of zinc and TRPC6 channels in the pathophysiology of depression.



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Prof. Martin Schaefer

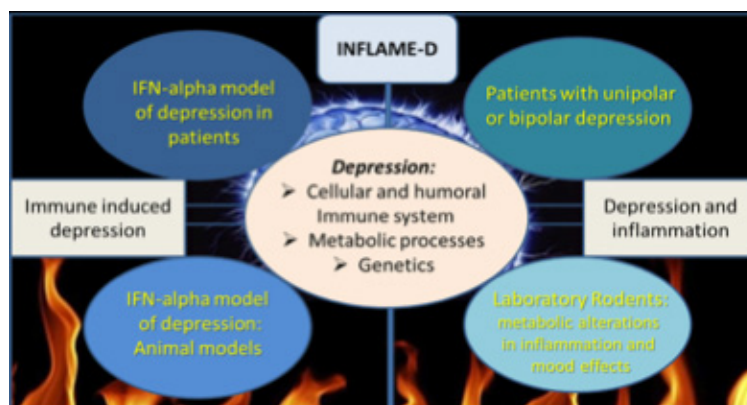


## Role of inflammation and related processes in the development, phenomenology and treatment of depression (INFLAME-D)

**Project Coordinator:** Prof. Martin Schaefer, Kliniken Essen-Mitte, Essen, Germany.

**Project Partners:** Dr. Lucile Capuron, Université Bordeaux, Bordeaux, France,  
Dr. Annamaria Cattaneo, IRCCS Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy,  
Dr. Astrid Friebe, Ruhr University Bochum, Bochum, Germany,  
Prof. Marion Leboyer, Mondor Institute for Biomedical Research, Paris-Est-Créteil, France.

Depression is currently the most common psychiatric disease with an overall prevalence in Europe of 6-10%. Current pharmacological treatments elicit a clinical response in 50-60% of patients, while only 30-40% achieves full recovery. There is still limited knowledge on the pathophysiology of mood disorders. The possible impact of the immune system has been discussed in recent years. Depressive symptoms have been found to be associated with chronic autoimmune diseases and cytokine treatment. Thus brain-immune interactions may constitute a new field of interest in which alternative treatment strategies to address mood disorders can be developed. The INFLAME-D project adopts a multi-disciplinary and translational approach to decipher the psycho-immunological mechanisms involved in the pathophysiology of depression and bipolar disorders. Basic and clinical research will endeavour to detect immune changes in patients and animals suffering from primary psychiatric mood disorders or from depression induced by immune therapy. The impact of these changes on the development of depression will be assessed. This project will enable the identification of biomarkers for the diagnosis and prognosis of depression and will facilitate the development of innovative treatment strategies.



*The INFLAME-D project combines results from clinical trials and animal models of immune related depression and results from immune changes in patients with primary mood disorders and animal models of depression like behaviour to investigate the role of inflammation in the phenomenology (occurrence, phenotypic expression, treatment responsiveness) of depression in vulnerable populations.*

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Prof. Claudia Buss



## Biological mechanisms of transgenerational transmission of early life stress (MecTranGen)

**Project Coordinator:** Prof. Claudia Buss, Charité Universitätsmedizin Berlin, Berlin, Germany.

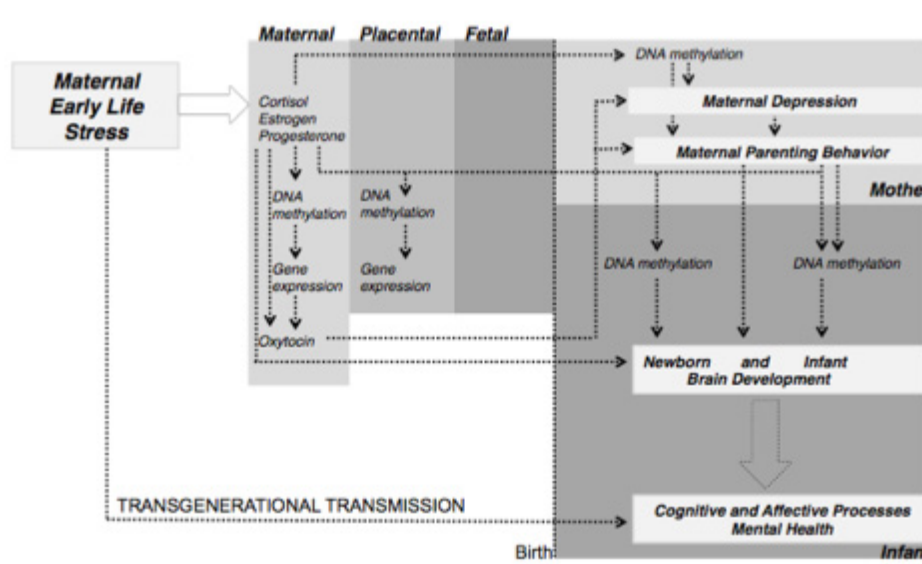
**Project Partners:** Prof. Elisabeth Binder, Max-Planck Institute of Psychiatry, Munich, Germany,

Prof. Katri Räikkönen, University of Helsinki, Helsinki, Finland,

Prof. Michael Meaney, McGill University, Montreal, Canada,

Prof. Pathik Wadhwa University of California, Irvine, USA.

MecTranGen deals with early life stress (ELS) in children. ELS represent a major social problem because of its unacceptably high prevalence and its harsh impact on mental and physical health. Growing evidence suggests that the consequences of exposure to abuse or neglect in childhood may be transmitted to a woman's offspring later on in life. Children of mothers exposed to ELS have a significantly higher risk of developing neurodevelopmental and psychiatric disorders. We do not adequately understand the pathways of the trans-generational transmission of ELS at this time. MecTranGen is comprised of studies critical for identifying targets for intervention(s) which can break the cycle of trans-generational transmission. The focus will be on ELS-associated alterations in stress biology during pregnancy, changes in maternal, placental and infant genes (i.e., epigenetic changes) and their association with maternal postpartum mental health, maternal parenting behavior and fetal and infant brain development. An understanding of these underlying biological pathways is critical for elucidating the cause of mental health problems in children of mothers exposed to ELS. It constitutes the first step in risk identification and in developing timely interventions, prior to the biological embedding of the adverse maternal experience in the child.





Dr. Vera  
Kalscheuer



## Molecular mechanisms of brain function in mtor-deficient intellectual disability syndromes (mTOR-DIDS)

**Project Coordinator:** Dr. Vera Kalscheuer, Max Planck Society, Berlin, Germany.

**Project Partners:** Dr. Vania Broccoli, Ospedale San Raffaele s.r.l., Milan, Italy,  
Prof. Susann Schweiger, Universitätsmedizin Mainz, Mainz, Germany,  
Prof. Rainer Schneider, Leopold Franzens Universität Innsbruck, Innsbruck, Austria.

Intellectual disability (ID) is characterized by significant limitations on both intellectual functioning and adaptive behaviour, which covers many everyday social and practical skills. It affects 1–3% of the general population and can be caused by a broad spectrum of factors, including birth complications and gene mutations. The number of novel genes linked to cognitive impairment is rapidly increasing, but our current understanding of their function and the underlying pathophysiologic mechanisms lags far behind. One common pathway in the pathogenesis of ID is the mammalian target of rapamycin (mTOR), which has been shown to play an important role in the uptake and processing of nerve cell stimulation.

In mTOR-DIDS, a collaborative study between four groups from three countries, we investigate the relationship between mTOR deficiency and cognitive dysfunction in Rett syndrome (RTT), CDKL5 disorder (CD) and Oritz/BBB/G syndrome (OS) using in vitro and in vivo model systems. All three syndromes are characterized by ID to varying degrees. A clear knowledge of cellular processes and molecules that are involved in ID could pave the way towards the identification of novel targets that can be used for the development of drug therapies for genetically caused ID.



Prof. Christine  
Winter



## Development of feedback-controlled neuromodulation strategies for the treatment of intractable repetitive hyperkinetic movement disorders (RD\_aDBS).

**Project Coordinator:** Prof. Christine Winter, Technical University Dresden, Dresden, Germany.

**Project Partners:** Dr. Samuel Ewing, Universitätsklinikum Freiburg, Freiburg, Germany,  
Prof. Konstantinos Meletis, Karolinska Institutet, Stockholm, Sweden,  
Prof. Alberto Priori, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.

Tourette syndrome is characterized by a combination of motor and vocal tics. Many Tourette-patients are or become refractory to current treatments or suffer side-effects severe enough to necessitate discontinuation of treatment. Deep brain stimulation (DBS) has shown promise in the treatment of some challenging patients. "Conventional"

continuous DBS, however, poorly matches the temporal presentation of symptoms and accordingly it may be ineffective and associated with stimulation-induced side effects. The future of DBS entails targeted modulation of only those brain regions implicated in the disease at only those times the symptoms are imminent or manifest. The RD\_aDBS project seeks to unravel the underlying pathology of Tourette to facilitate the development of a more effective, targeted DBS. It is designed to identify electrical brain signals which indicate or predict the onset of tics. As such, the project studies electrical and behavioral phenomena arising in animals with the specific brain abnormalities implicated in Tourette syndrome and compares them with the electrophysiological measurements of the nearest equivalent data recorded from human patients undergoing DBS treatment. The resulting translational database will be used to detect the onset of tics, enabling the development of a DBS device that interfaces directly with the brain region in which symptoms originate in order to suppress tics in a timely manner.



Dr. Froylan  
Calderon de  
Anda

## The role of TAO2 in brain connectivity and autism spectrum disorders (TAO2).

**Project Coordinator:** Dr. Froylan Calderon de Anda, University Medical Center Hamburg-Eppendorf (UKE), Hamburg, Germany.

**Project Partners:** Prof. Claudia Bagni, VIB Center for the Biology of Disease/KULeuven, Leuven, Belgium,

Prof. Karun Singh, McMaster University, Hamilton, Canada,

Dr. Stephen Scherer, The Center for Applied Genomics, Toronto, Canada.



Autism spectrum disorders (ASDs) are neurodevelopmental disorders characterized by the disruption of an individual's capacity for social communication. Approximately 1% of individuals in Asia, North America and in Europe are afflicted with an ASD. Recent research has found that genetics play a very important role in ASD risk. The TAO2 project studies the TAO2 gene, which is either missing or duplicated in individuals afflicted with ASD. Collaborating with the Autism Sequencing Consortium, the project seeks to discover new mutations in the TAO2 gene which may cause ASD, in the hope of aiding the development of more accurate genetic ASD diagnoses. In addition, we will conduct cellular and molecular studies to better understand the normal functioning of TAO2 in the development of brain connections and will determine how the TAO2 mutations detected in ASD patients potentially contribute to abnormal brain connectivity. Specifically, the project examines the possibility that FMRI, another ASD-linked gene, controls TAO2 function. This could lead to the identification of a new genetic pathway in the brain and ultimately facilitate the discovery of pharmaceuticals that could ameliorate deficits observed in ASD patients.





Prof. Luc Mallet



## Uncertainty monitoring vs. inhibition of action in obsessive-compulsive disorder: role of the subthalamic nucleus and effects of stimulation in humans and rodents (TYMON)

**Project Coordinator:** Prof. Luc Mallet, Institut national de la santé et de la recherche médicale (INSERM), Paris, France

**Project Partners:** Dr. Lars Wojtecki, Heinrich-Heine-University Duesseldorf, Düsseldorf, Germany,  
Dr. Rui Costa, Champalimaud Foundation, LISBON, Portugal.

Obsessive-Compulsive Disorder (OCD) is among the most common anxiety disorders. Its most severe forms exact a high cost on the affected individuals and society. 20–30% of OCD patients do not respond to the pharmacological and psycho-therapeutical interventions currently in use. Recent clinical trials have demonstrated the clinical efficacy of deep-brain stimulation of several subcortical nuclei or fibers in patients with severe treatment-resistant OCD. The TYMON Project focuses on the subthalamic nucleus (STN), which has proven to be a potent target. Current knowledge regarding the role of the STN in the psychopathological processes underlying OCD and the therapeutic mechanisms triggered by high-frequency stimulation of this area, however, is very limited. TYMON will assess the role of the STN in OCD, focusing on two specific cognitive processes that, when dysfunctional, could lead to compulsive checking: (i) uncertainty-monitoring – repetitive checking to reduce uncertainty before making a choice and (ii) inhibitory control – the inability to put a sequence of checking actions to an end. The project partners will experiment with mice models of OCD as well as with human OCD patients in order to: (a) analyse the role of the STN in these cognitive processes; (b) identify circuitry dysfunction in OCD; and (c) assess the mechanisms of deep brain stimulation that may revert compulsive checking.

