



All participants of the NEURON conference, scientists, Ministry representatives and project managers of funding agencies.

FROM THE DESK OF THE COORDINATOR

In May 2012 the ERA-NET NEURON organized a midterm scientific symposium on mental disorders in Loven di Menaggio at Lake Como, Italy

We all know that as the average life span of human population gradually increases, the prevalence of diseases has significantly increased. And among the many diseases affecting health, disorders of the brain are major causes for impaired quality of life and increasing health care costs.

Consequently and along NEURON's mission to link ministries and funding agencies from European countries, Israel and Canada in the field of disease-related neurosciences, the agenda of the conference centered around past and coming joint activities for human brain research. Despite some progress in understanding the molecular mechanisms of various neurological and psychiatric disorders, research is still far from being able to offer solutions to conquer them. An important agenda item was the scientific symposium on 'Mental Disorders'.

Among the most important activities of NEURON are the

yet annually launched joint transnational calls for proposals for research groups operating in the NEURON partner countries. In each call we addressed different areas of research into brain diseases, and as a matter of routine NEURON established mid-term and final symposia of funded projects that serve the mutual comprehensive information exchange between scientists, ministry representatives and project managers of different funding organisations.

13 funding organizations participated in the 2010 NEURON joint call for proposals on "European Research Projects on Mental Disorders" providing grants for ten transnational research consortia. In the mid-term symposium at Lake Como the coordinators of these consortia presented their work and results. They had been assessed most excellent and selected for funding from a pool of more than 100 applications by a review panel composed of renowned international experts.



Participants of the scientific symposium on 'Mental Disorders' from left to right: Prof. Julia Stingl, Germany; Prof. Carlo Sala, Italy; Prof. Christine Winter, Germany; Prof. Christelle Baunez, France; Prof. Wolfgang Sommer, Germany; Prof. Michael Deuschle, Germany; PD Dr. Marlies Dörlöchter, NEURON coordinator; Prof. Alexander Sartorius, Germany; Prof. Rita Gerardy-Schahn, Germany. Dr. Christelle Depienne, France and Prof. Cecilia Gotti unfortunately had to leave early.

These projects are funded with over 10 million euros, and the number of high quality results and most interesting research findings in terms of high impact publications was valued as indeed positive and significant evidence for the success of the NEURON funding measure.

Such findings may provide a better scientific foundation for the development of curative treatments or prevention strategies of neurological and psychiatric disorders. All this in view of the concerted effort of ministries, funding agencies and research groups to reach the long term goal to cure patients, and help their relatives.

The conference took place at a most inspiring location in the Villa Vigoni at Lake Como, enabling fruitful discussions and new impulses for NEURON.

Depicted on the following pages are details of the eleven projects funded under the frame of the 2010 Joint Transnational Call and interviews with three Project's Coordinators.



The landscape, villa and well organised service produced an inspiring and relaxed atmosphere and an intellectual exchange at high level.

ERA-NET NEURON

Funded Projects
JTC 2010
"Mental Disorders"AMRePACELL

Development of new experimental models for mental retardation and autism by iPS technology: generation of human affected and animal model neurons by reprogramming skin fibroblasts and testing gene correction using in vitro and in vivo models

*Prof. Carlo Sala -
project coordinator*

AUSZ_EUCan

From autism to schizophrenia: Study of the genetic mechanisms underlying brain dysfunction and structural phenotypes in schizophrenia and autistic spectrum disorders / AUSZ

*Prof. Marie-Odile Krebs -
project coordinator*

DBS_F20rat

Describing pathophysiology to promote focal therapy in treatment of schizophrenia – an animal experimental study

*Prof. Christine Winter -
project coordinator*

EUHFAUTISM

European High-functioning Autism network: Translational research in a phenotypically well characterised sample

*Prof. Thomas Bourgeron -
project coordinator*

NeuConnect

Novel strategies for the treatment of schizophrenia based on genetic variation of the neural cell adhesion molecule NCAM and enzymes involved in its posttranslational modifications

*Prof. Rita Gerardy-Schahn -
project coordinator*

NICO-GENE

Modeling human polymorphisms for nicotine addiction in mice

*Prof. Uwe Maskos -
project coordinator*

TRANSALC

Translational neuroimaging in alcoholism: identification of altered brain connectivity and treatment efficacy predictors

*Prof. Wolfgang Sommer -
project coordinator*

POSEIDON

Pre-, peri- and postnatal Stress in human and non-human offspring: a translational approach to study Epigenetic Impact on Depression

*Prof. Michael Deuschle -
project coordinator*

STNDBS-ICD

Subthalamic Nucleus Deep Brain Stimulation for the treatment of Impulse Control Disorders

*Prof. Christelle Baunez -
project coordinator*

SuppHab

Improvement of treatment resistant depression by suppression of lateral habenula activity

*Prof. Alexander Sartorius -
project coordinator*

PADRE

Pharmacogenomics of Antidepressant Drug Response (PADRE): tentative drug response biomarkers from human lymphoblastoid cells.

*Prof. Julia Stingl -
project coordinator*

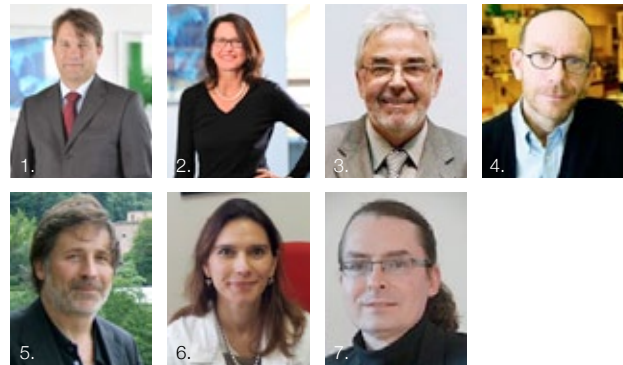


Interview with Prof. Michael Deuschle **Central Institute of Mental Health,** **Mannheim, Germany**

Michael Deuschle is the coordinator of the project titled: "Pre-, Peri- and Postnatal Stress in Human & Non-Human Offspring: a Translational Approach to Study Epigenetic Impact on Depression". This project is funded under the 3rd ERA-NET NEURON joint transnational call.

How were the partners chosen and the consortium assembled?

In Mannheim, experts in epigenetics, child psychology, longitudinal studies and stress wanted to study ELS effects' on epigenetic regulation in humans. A translational approach seemed imperative. We started the cooperation with Moshe Szyf, who is a leading expert in epigenetics and had a cooperation with scientists using rhesus ELS models. We included rodent models being available in the labs of Peter Gass, Marco Riva and Francesca Cirulli. A translational approach with various species, various stressors allowing the examination of various tissues from brain to cord blood is most appropriate to study effects of ELS on epigenetic regulation.



The participants in the research are:

(1) Michael Deuschle **(2) Marcella Rietschel** **(3) Manfred Laucht** Central Institute of Mental Health, Mannheim, Germany
(4) Moshe Szyf from McGill University in Montreal **(5) Marco Riva** **(6) Francesca Cirulli** from University of Milan **(7) Peter Gass** Central Institute of Mental Health, Mannheim, Germany

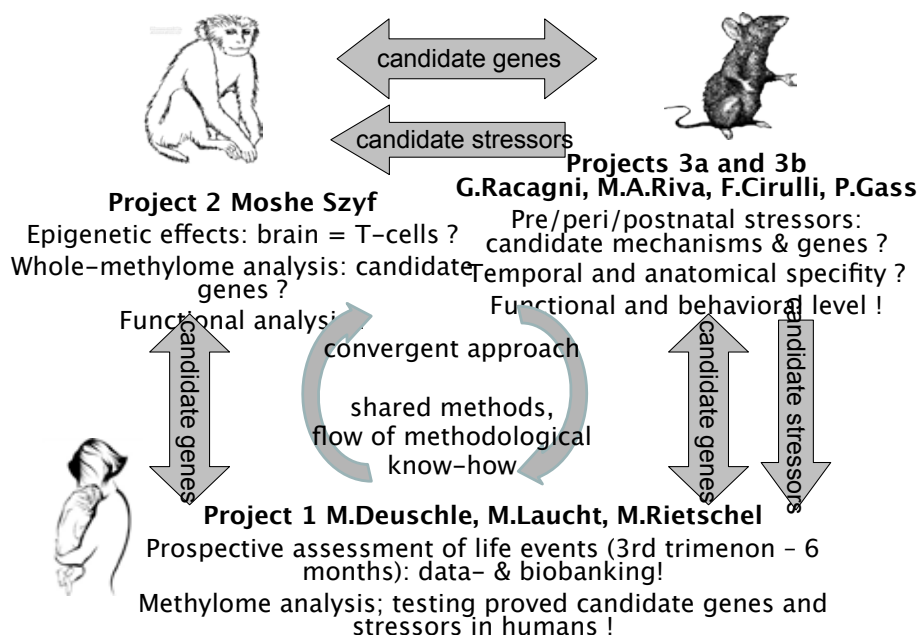
Please describe the aims of your project and its focus

Early life stress or ELS increases the risk for common diseases including depression. POSEIDON will clarify whether ELS leads to differential methylation and programming of gene expression that may increase the risk for adult diseases.

The human project covers the "stress history" of mothers-to-be and infants from pregnancy to 6 months after birth. Prenatal stress effects' are studied cross-sectionally comparing DNA methylation in cord blood. Postnatal stress effects will be studied by analyzing postnatal changes of methylation in saliva cells. The rhesus project validates our human findings, allows access to primate brain and give a longitudinal perspective by studying the offspring in adult age. The rodent studies analyze specific perinatal stressors and their longitudinal effects on DNA methylation, gene expression and behavior.

Looking back on the first two years of funding, what are its main achievements?

We did whole methylome studies in extreme groups of offspring of mothers being stressed versus nonstressed during pregnancy and found a set of differentially methylated genes. We learned that in monkeys differential methylation in brain and T-cells is reasonably similar. The rodent studies showed strong behavioral effects of ELS



and longitudinal effects at the level of growth factors and stress regulation, which underlines the significance for adult physiology.

What advantages do you see in carrying out your research as part of the ERA-Net NEURON? What is the added value achieved?

It is impossible to gain insights in complex mechanisms of early life origins of adult disease without gathering the expertise from areas ranging from biochemistry, animal models to humans. An international coordinated approach is imperative for findings being validated with different models in different species.

What do you think was the main challenge of this research consortium?

The time frames in longitudinal studies within restricted funding periods are challenging.

What would be the next stages of research in your project?

We will fulfill our recruitment aims of the human cohort, will complete respective animal studies and want to broaden our approach to other tissues, like placenta.

Considering your subject, what are your expectations about impact on diagnostic and understanding of the pathomechanisms of the disease?

Our research will contribute to give the ELS-adult disease association a pathophysiological underpinning. We intend to provide an algorithm based on identified risk factors, like a set of differentially methylated genes and clinical risks that could be used as a diagnostic tool to give families information whether experienced ELS led to biochemical traces. Then, the kids may be somewhat more vulnerable for future diseases. We consider that information an important step forward towards preventive medicine.

Do you have plans to continue the collaboration between the consortium partners? If yes, what are they?

The infant cohort is precious for future studies. We will continue with our collaboration and study persistence and behavioral significance of stress-induced differential methylation for behavior and phenotype. ELS is relevant for future psychiatric, but also metabolic disorders and we intend to study the relevance of early life programming for physical disorders.



Interview with Prof. Carlo Sala **National Neurological Institute Carlo Besta,** **Milano, Italy**

Carlo Sala is the coordinator of the project titled: "Development of New Experimental Models for Mental Retardation and Autism by IPS Technology: Generation of Human Affected and Animal Model Neurons by Reprogramming Skin Fibroblasts and Testing Gene Correction Using IN VITRO and IN VIVO Models". This project is funded under the 3rd ERA-NET NEURON joint transnational call.

How were the partners chosen and the consortium assembled?

The consortium was formed because each partner has the complementary scientific and technical expertise necessary for carrying out the project efficiently. In addition the fact that among some of us there were established collaborations and faithful friendships.

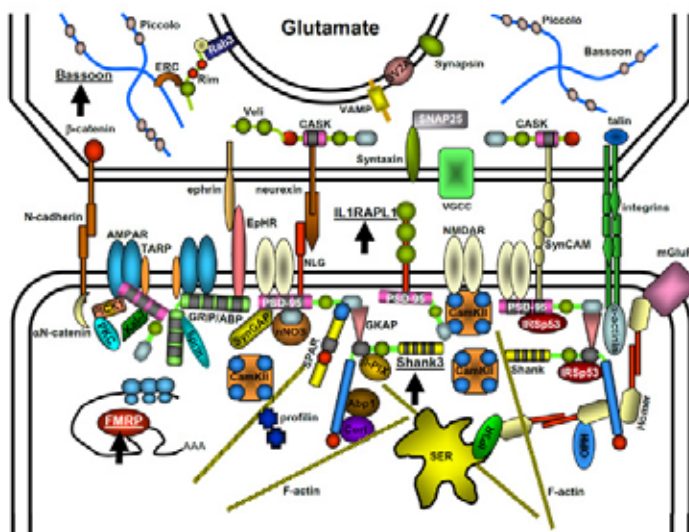
Please describe the aims of your project and its focus.

The major aim of this project is to develop new experimental models to study intellectual disabilities and autism using neurons derived from the differentiation of induced pluripotent stem (iPS) cells obtained from human



The participants in the research are:

(1) **Carlo Sala** from National Neurological Institute Carlo Besta, Milano, Italy (2) **Eckart Gundelfinger** from Leibniz Institute for Neurobiology in Magdeburg (3) **Pierre Billuart** from Institut Cochin in Paris (4) **Jacek Jaworski** from International Institute of Molecular and Cell Biology in Warsaw.

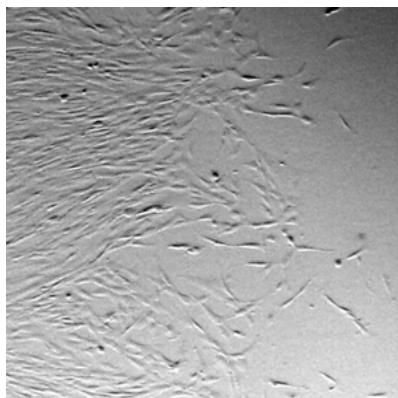


The Synapse

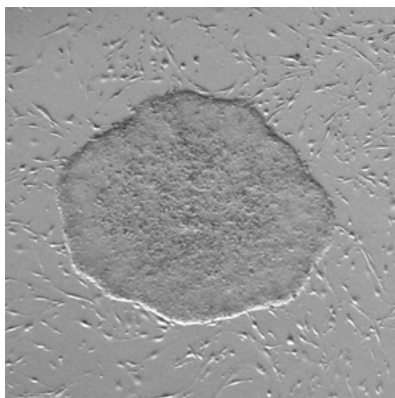
patients as well as disease mouse models. Ultimately, this project will deliver a rational basis for genetic and pharmacological therapies to patients affected by intellectual disability syndromes.

Looking back on the first two years of funding, what are its main achievements?

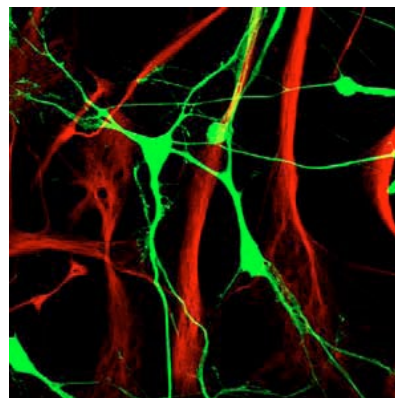
We were able to collect fibroblasts from patients affected by different intellectual disabilities syndromes and autism and to reprogram these fibroblasts in pluripotent stem



From fibroblasts



to hiPS



to neurons

(iPS) cells. To date we have developed a reliable protocol to induce neuronal differentiation in vitro and in vivo of these iPS cells.

What advantages do you see in carrying out your research as part of the ERA-Net NEURON? What is the added value achieved?

The ERA-Net NEURON allows us to perform very competitive and cutting edge projects with a perfect consortium size. This allows a very strong and efficient collaboration among partners. The chance to develop a new project with other laboratories with similar interests and complementary expertise is a very important added value that could be only achieved in the ERA-Net consortium.

What do you think was the main challenge of this research consortium?

Our main challenge is to develop novel therapeutic approaches and perspectives for treatment of intellectual disabilities and autism syndromes – devastating neurodevelopmental disorders orphan of a cure.

What would be the next stages of research in your project?

We are now characterizing the neuronal and synaptic defects in the iPS cells-derived neurons of patients affected from different intellectual disabilities syndromes, this will help to develop and test genetic and pharmacological rescue of neuronal functional alterations.

Considering your subject, what are your expectations about impact on diagnostic, therapy and understanding of the pathomechanisms of the disease?

We think that the scientific and technical approach that we are using in our project will help to better understand the cellular and molecular pathogenesis mechanisms of some intellectual disabilities and autism syndromes and will contribute to develop the rationale for genetic and pharmacological therapies.

Do you have plans to continue the collaboration between the consortium partners? If yes, what are they?

Absolutely yes! We would like to continue the collaboration because each partner has overlapping competences and the only way to achieve our main goals is to continue fruitful scientific and technical collaboration.



Interview with Prof. Christine Winter from the University Hospital Carl Gustav Carus, Technical University Dresden, Germany

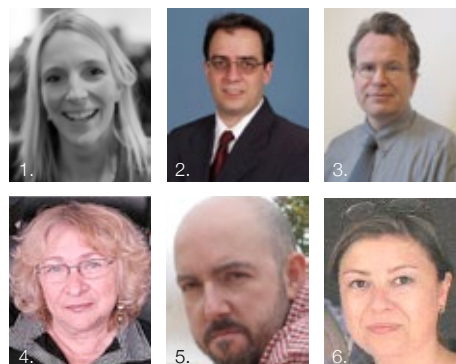
Christine Winter is the coordinator of the project titled: "Describing Pathophysiology to Promote Focal Therapy in Treatment of Schizophrenia – an Animal Experimental Study". This project is funded under the 3rd ERA-NET NEURON joint transnational call.

How were the partners chosen and the consortium assembled?

Partners were chosen based on previous collaborations, research profile and focus as well as the affiliation and country.

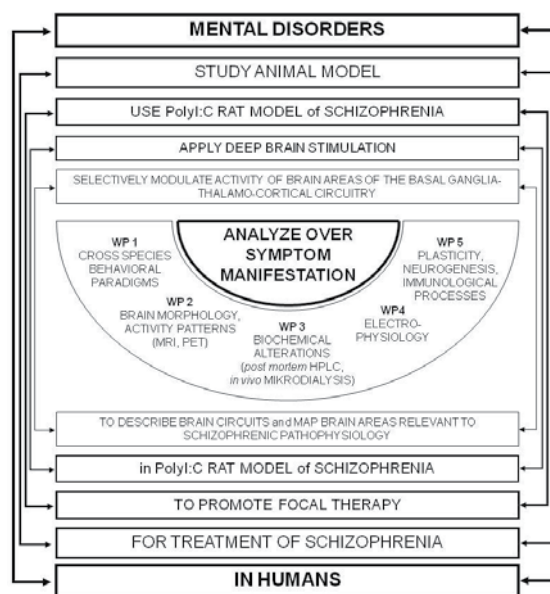
Please describe the aims of your project and its focus

The overall aim of the project is to foster our understanding of dysfunctional neural circuitries in schizophrenia and set a strong interdisciplinary foundation for the translational application and advancement of deep brain stimulation as a novel focal and causative strategy in the treatment of therapy-resistant schizophrenia. For that, in a tripartite animal experimental project we correlate the emergence of schizophrenia-like behavior in rats with the development



The participants in the research are:

(1) **Christine Winter** from the University Hospital Carl Gustav Carus, Technical University Dresden, Germany (2) **Clement Hamani** from University of Toronto (3) **Georg Juckel** from University of Bochum (4) **Ina Weiner** from Tel Aviv University (5) **Javier Pascau** and (6) **Marisa Soto** from Hospital General Universitario "Gregorio Marañon", Madrid



Summarizing structure of the project

of specific brain dysfunctions. We then study the preventative and curative potential of deep brain stimulation on schizophrenia-like behavior as well as the previously described associated brain dysfunctions.

Looking back on the first two years of funding, what are its main achievements?

Certainly, our major achievement so far was to prove acute deep brain stimulation effective in reducing behavioral deficits phenotypic of schizophrenia in two well es-

established rat models of this disorder. The ameliorating effects of deep brain stimulation were stimulation-parameter and stimulation-brain site specific.

What advantages do you see in carrying out your research as part of the ERA-Net NEURON? What is the added value achieved?

The straight forward thematic and project frame allows for scientific exchange beyond own projects and international collaborations

What do you think was the main challenge of this research consortium?

Most challenging was/is the future-oriented establishment of shared methodology allowing for prolonged co-operations and the establishment of scientific networks within the field of research.

What would be the next stages of research in your project?

Temporarily, we study the effects of prolonged deep brain stimulation applied continuously via an implantable micro-stimulator in a period when behavioral abnormalities are absent on the emergence of behavioral and neurobiological abnormalities phenotypic of schizophrenia in the adult rat. This approach will corroborate the specific findings of acute deep brain stimulation and allow testing the hypothesis that schizophrenia is the clinical representation of a progressive dysfunction of specific neuronal networks and that the preventive manipulation of these dysfunctional networks may halt the emergence of neurobiological abnormalities and associated behavioral deficits.

Considering your subject, what are your expectations about impact on diagnostic, therapy and understanding of the pathomechanisms of the disease?

Obviously, equivalent studies cannot be performed in humans. Though ethical concerns have to be carefully considered, we hope that results from our experiments drive the field and influence clinical work. It is unquestionable that tremendous effort will still be required by multidisciplinary teams to ascertain the symptoms most likely to respond to DBS and the most suitable target for each symptom. Though we are obviously far from applying the technique in humans, we think that experiments in this proposal may set a ground for the potential future application of DBS in patients with schizophrenia.

Do you have plans to continue the collaboration between the consortium partners? If yes, what are they?

Yes. One idea among others is to extend and directly combine the methodological approaches used by the respective partners, i.e. imaging, electrophysiology, biochemistry within behaving rats treated with deep brain stimulation to get a more refined insight into (patho)physiological brain network function and activity.