NEWSLETTER 2017

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On January 18th, 2017, the **friends and donors** of the Alamaya Foundation were invited to **visit the exhibition** entitled AUGUST STRINDBERG. DE LA MER AU COSMOS (From the Sea to the Cosmos), at the *Musée cantonal des Beaux-Arts* in Lausanne. The visit was brilliantly guided by Mr Camille Lévêque-Claudet, curator of the Museum and organizer of the exhibition, who very generously facilitated free entrance for the guests of the Foundation. Internationally renowned as a writer and author of plays like *The Father* and *Miss Julie*, August Strindberg (1849–1912) was also one of Sweden's greatest visual artists. He was a man of heightened sensibility, and suffered from psychological disorders. The event in Lausanne was a rare opportunity to see his main masterpieces brought together in a single exhibition.

The studies conducted at the Unit for Research in Schizophrenia (URS, Center for Psychiatric Neuroscience, Department of Psychiatry, Lausanne University Hospital), whose financing half depends on private donors, have led to **major progress** in the understanding of the causes and mechanisms resulting in psychosis. The research group supported by Alamaya is **widely renowned** on the international level, and their results have been published in the most influential scientific journals of biological psychiatry. The team of the URS includes several young PhD students, with a very promising scientific career ahead of them, who positively contribute to these achievements. Furthermore, Kim Do Cuénod, head of the URS, regularly receives highly interesting applications from young researches who wish to join her group. Unfortunately, the financial means to hire these candidates and maintain her team in the medium term are scarce.

Become A Sponsor!

The Alamaya Foundation has thus set up a SPONSORSHIP PROGRAM FOR PHD STUDENTS of the URS. A PhD student's contract last for a period of **4 to 5 years** until the completion of his/her thesis. The average annual cost of his/her salary, including social security contributions and part of the laboratory material needed for his/her work, amounts to **CHF 60'000**. Sponsors can choose to **ensure all or part of his/her annual salary**, and will receive regular updates on progress achieved.

Sponsorships thus have a twofold objective: they not only help to **advance a pioneering research program**, which meets crucial, urgent and too often unrecognized needs, but also serve to **further a high level academic community**.

Two donor foundations, the Brixham Foundation and the Juchum Foundation, have very generously subscribed to the sponsorhip program launched by the Alamaya Foundation, which is intended for any person or institution wishing to encourage research in the fields of schizophrenia, autism and bipolar disorders.

NEWS FROM RESEARCH

Brain anomalies identified in patients are related on one hand to a particular type of **inhibitory neurons, called parvalbumin interneurons** (PVI), which play a key role in the *microcircuits* of the cortex, and, on the other hand, to the **cells responsible for the formation of myelin** (called oligodendrocytes); myelin is the protective envelope of **nervous fibres**, which connect the different parts of the central nervous system, and make up the *macrocircuits* of the brain These anomalies are most probably **responsible for various manifestations of the disease**, including sensory, cognitive, affective and social disorders as well as hallucinations, whose variability depends on the neuronal circuits that are directly involved. Cognitive disorders involving memory, attention, concentration and the ability to plan actions are heavily disturbing for the private and professional life of patients.

The aim is to discover the origin of the anomalies mentioned above. We know that the convergence of genetic and environmental risk factors during the development of the brain influences the formation of parvalbumin interneurons and/or of myelin. A **deficient control of the balance between oxidations and reductions** (called "redox regulation") plays a crucial role in these phenomena. The redox state of cells has indeed important consequences: if it is slightly oxidized, it modifies the function of many enzymes and receptors, whereas massive oxidation leads to the destruction of proteins, lipids and DNA.

Several **genetic** anomalies involved in schizophrenia lead to redox dysregulation and oxidative stress or directly affect synaptic connections and disturbed neurons. Identified **environmental** risk factors such as infections, inflammations, and physical or psychological trauma lead to oxidative stress as well. Environmental risk factors are particularly harmful when they occur during the **development of the brain**, i.e. between pregnancy and puberty. Thanks to our experimental models, we were able to comprehensively validate these hypotheses.

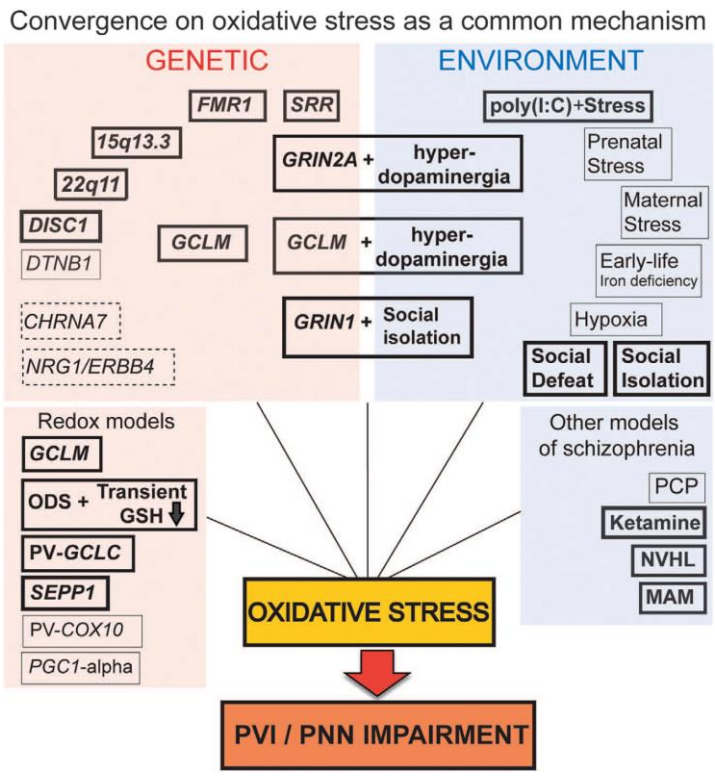
CONVERGENCE ON OXIDATIVE STRESS AND DEFICIENT PARVALBUMIN NEURONS

A **significant breakthrough** concerning the role of oxidative stress in schizophrenia has been achieved. Formerly, the URS had put forward that oxidative stress is a mechanism among several others leading to the disease. This hypothesis was based on the observation that an anomaly in the gene of the synthetizing enzyme of the major antioxidant in the human body, called glutathione, causes its decrease, and is associated to the disease in certain patients. This genetic anomaly has been reproduced in the animal model, thus leading to redox dysregulation, decreased glutathione, and consequently to permanent oxidative stress in the animal. The model has allowed to replicate several biological anomalies related to the disease, such as deficiencies in parvalbumin interneurons and nervous fibres as well as their physiological and behavioural consequences. These observations thus reinforced the hypothesis that oxidative stress during the development of the brain could cause deficits similar to those identified in patients.

Now there are many animal models based on other genetic or environmental anomalies, which are used in different laboratories, and which all replicate certain aspects of schizophrenia or autism. The URS has studied these other models, and has reached the conclusion that nearly all of them are subject to oxidative stress, in particular if they are exposed to environmental stress during the development of the brain.

This oxidative stress is linked to anomalies of parvalbumin interneurons, and is most probably responsible for these anomalies. Indeed, in cases in which it has been tested, it was shown that the administration of an antioxidant not only reduces oxidative stress but also restores parvalbumin interneurons and their function.

Thus it seems that **various mechanisms, either of genetic, environmental or combined origin, finally lead to oxidative stress, which disturbs the normal functioning of parvalbumin interneurons (PVI, see figure); these interneurons are highly important for all cognitive functions**.



It is clearly too early to extrapolate from animal models to patients, but **these results suggest that a great number of causal agents converge on oxidative stress, which therefore takes on a more general importance than initially proposed by the URS**. These pioneering results have been published in *Molecular Psychiatry*, a scientific journal with a very high impact factor in the field of biological psychiatry.

COLLABORATIONS AVEC DES GROUPES DE RECHERCHE INTERNATIONAUX

A collaboration with Dr Christel Becker (INSERM, Paris) has led to another publication in *Molecular Psychiatry*. This joint project focused on the role of oxidative stress in animal model of depression. Adult mice exposed to severe stress develop symptoms of depression following a second episode of less intense stress in 40% of cases. The URS laboratory demonstrated that these vulnerable animals show an increase of the brain oxidative stress marker and a deficit of parvalbumin interneurons; these effects can be reversed through the administration of antioxidants.

The INSERM team consequently asked itself the following question: what allows part of the mice to avoid depression? It showed that resistant animals have a high level of BDNF, which is an important protective agent of neurons, and that BDNF activates another agent, called Nrf2, which stimulates the antioxidant defences of the organism. Vulnerable mice produce not enough BDNF, and are thus no longer protected by the action of Nrf2. If Nrf2 is genetically blocked, all stressed mice develop depression, which can be reversed by antioxidants.

In this model, redox dysregulation thus plays a crucial role in the outbreak of depression, involving parvalbumin interneurons, a mechanism similar to the one that the URS demonstrated in models of schizophrenia. These observations contribute to the theory proposing that the couple "oxidative stress/parvalbumin interneurons" plays a predominant role in the pathophysiology of psychiatric disorders.

In addition to the many collaborations established by Kim Do Cuénod with colleagues working at universities and research institutes in Switzerland, several European countries and the USA, it has to be noted that several **international consortia** have resorted to the expertise and skills of the URS in the framework of their projects. These include among others:

Collaborations	Projects
GENETICS	
James MacCabe King's College, London, UK	**STRATA consortium: GWAS;** Predicting Response to Antipsychotic medication; Discover genetic, clinical, demographic predictors of treatment resistant schizophrenia (TRS); Elucidate mechanism(s) underlying TRS; Delineate subtypes of TRS; Develop predictive algorithms; sample size ≅ 7000
BIOMARKERS	
Philip McGuire EU consortium	**EU-GEI consortium: Oxidative stress in people at high risk for psychosis** peripheral markers of oxidative stress/ inflammation
Philip McGuire King's College, London, UK	**OPTIMISE: Redox & glutamate in first episode psychosis** relationship between peripheral markers of oxidative stress/ inflammation and a) the response to treatment. b) neuroimaging measures of brain glutamate function in patients.
Alan Brown Columbia University, New York, USA	**Prenatal biomarkers and risk of schizophrenia and bipolar disorders in Finnish birth cohort**
Diana Perkins North Carolina University, Chapel Hill, USA	**The North American Prodrome Longitudinal Study (NAPLS) 3,4** relationship between peripheral markers of oxidative stress/ inflammation and a) clinical outcomes in people at high risk b) MRI and EEG measures c) environmental risks during development (early trauma, cannabis consumption)
BIOMARKER GUIDED TREATMENT	
Andreas Meyer-Lindenberg Central Institute of Mental Health, Mannheim, D	**Enhancing Schizophrenia Prevention and Recovery through Innovative Treatments (ESPRIT) (NAC) :** advisor
Stephan Marder Yvonne Yang UCLA, USA	**NAC treatment in chronic schizophrenia, negative and cognitive symptoms :** collaboration for markers analysis
Dost Ongur McLean Hospital, Harvard, USA	**Redox markers guided treatment in FEP :** project in progress

Kim Do Cuénod is also invited to give **plenary conferences** at many international meetings; visit the **News/Events** page of our Website to learn more.

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