alamaya
foundation for research in schizophrenia

# NEWSLETTER 2014

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## NEWS FROM THE FOUNDATION

As each year since 2011, the Alamaya Foundation participated in the **BRAIN WEEK** (10-13 March 2014) and in the **JOURNÉES DE LA SCHIZOPHRÉNIE** ("Days of Schizophrenia", 17-23 March 2014), two important annual events during which the general public can be approached and informed of the Foundation's mission.

Alamaya also benefitted from increased visibility abroad on two major occasions:

**SYMPOSIUM IN NEW YORK:** the Foundation featured among the sponsors of a scientific symposium, which took place on 7 May 2014, in New York (USA). The symposium was advertised as a Satellite Meeting of the 2014 Annual Meeting of the *Society of Biological Psychiatry (SOBP)*, an important American organization founded in l945 to encourage the study of the biological causes of and treatments for psychiatric disorders.


This event, entitled *Schizophrenia: could it be prevented?*, was organized in honour of Prof. Michel Cuénod's (Chair of the Alamaya Foundation) 80th birthday, and brought together several distinguished researchers from highly renowned American universities, as well as from Canada, Australia and Switzerland. The results and perspectives presented by these researchers underscored the relevance of the translational approach developed by Prof. Kim Do Cuénod's group, and corroborated the hypothesis of a possible prevention of schizophrenia. The symposium achieved a great success among participants.

**VIDEO CLIP:** a video clip on the translational research program supported by the Alamaya Foundation was produced at the request of the *American Psychiatric Association (APA)*, and broadcasted during its Annual Meeting, which took place at the beginning of May 2014, in New York. APA had chosen 5 research centers outside the United States for such a presentation: 1 in Japan, 1 in Shanghai and 3 in Europe, among which the Unit for Research in Schizophrenia (URS) in Lausanne. APA's choice represents a great honor and a first-rate acknowledgment of the work carried out at the URS. The clip can be accessed on our Website www.alamaya.net

Furthermore, Prof. Kim Do Cuénod, Director of the URS, is regularly invited to give **CONFERENCES** and to participate in **SEMINARS** in Switzerland, Europe and the United States in order to present the results achieved by her research group. She never fails to underline the importance of Alamaya's support during each of her talks.

## NEWS FROM RESEARCH

The present evolution of clinical psychiatry in the field of schizophrenia is aimed at an early detection of individuals who are at risk of the disease since experience shows that the prognosis is all the more favorable if the treatment begins early. It is therefore essential (a) to identify "biological markers", which are presently lacking, in order to be able to detect vulnerable persons; (b) to develop preventive treatments devoid of serious side effects. These are the objectives of the Unit for Research in Schizophrenia (URS), which strives to bridging clinical aspects with experimental research. The URS develops the following main working lines:

- Data collection in patients;
- Investigation of the disease mechanisms in experimental models;
- Exploration of biological markers and new potentially preventive treatments.

The translational approach of the URS has led to new discoveries in patients; among these are the following:

**MYELIN**: *Aline Monin* (doctoral student, URS) has studied the role of redox regulation in oligodendrocyte cultures; these are the cells responsible for the formation of myelin, which is essential to the proper functioning of nervous fibers. She has demonstrated that a glutathione deficit causes a delay in the maturation of oligodendrocytes, and that myelin is deficient in the prefrontal cortex of young mice with a low level of glutathione. She has also shown that this delay in the formation of myelin is linked to the excess of a particular enzyme, called "FYN kinase", probably due to the oxidation of regulatory proteins.
Following this observation, *Margot Fournier* (post-doc, URS) has shown that FYN is also increased in the cells of patients with a genetic anomaly hindering the formation of glutathione. The FYN factor could thus be developed as a potential marker for the disease.
The results of this study have been published in *Molecular Psychiatry*, the journal with the highest impact factor in the field of psychiatry and neuroscience.

**FORNIX**: *Alberto Corcoba* (doctoral student, URS, in collaboration with Prof. R. Gruetter, CIBM-EPFL) has developed a new method (MRI) allowing the observation of the integrity of nervous fibers in the brain of glutathione deficient mice; he recorded a reduced integrity in a nervous pathway originating in the hippocampus, called the fornix, which is linked to the inception of memory.

This observation in the animal model has prompted *Philipp Baumann* (clinician and researcher, URS & Service of General Psychiatry) and *Alessandra Griffa* (collaboration with Dr P. Hagmann, CHUV, and Dr J.-P. Thiran, EPFL) to analyze – with the same method – the integrity of the fornix in patients during their

first psychotic episode; as a result and for the first time, they have revealed a deficiency of this integrity (decreased gFA) in young patients. As explained below, the investigations concerning a structure which is central to the functioning of memory are of particular interest.

**HIPPOCAMPUS**: this brain structure plays an important role in the recording of memory; people in whom this structure is defective have difficulties in anchoring their memories. In the hippocampus of glutathione deficient mice, *Pascal Steullet* and *Jan Cabungcal* (senior researchers, URS) have shown that PV cells and oscillations are deficient.
In patients, the volume of the hippocampus is diminished, and *Philipp Baumann* has demonstrated that its decrease is proportionate to the decrease of gFA in the fornix (measure of the integrity of nervous fibers). Furthermore, the volume of the hippocampus is linked to a blood marker of redox dysregulation: the higher the state of oxidation, the smaller the hippocampus. This represents a direct evidence of the impact of redox balance, measured in the periphery, on a brain structure.
Finally and in parallel to these findings, recent data established by *Luis Alameda* (clinician and researcher, URS & Service of General Psychiatry) show that patients who were subject to traumatisms during adolescence have a smaller hippocampus. These observations have to be correlated with those made in mice by *Jan Cabungcal*, indicating that an additional stress in the young animal, and only in the young one, causes persistent anomalies of PV cells in the frontal cortex.
This combination of results confirms the important role of redox balance in the development of the brain and of the corresponding functions.

**OTHER ANIMAL MODELS**: *Jan Cabungcal* has studied the markers of oxidative stress in other animal models of schizophrenia and other diseases, such as autism.
In collaboration with *Patricio O'Donnell* (University of Maryland, USA), he showed that a neonatal lesion of the ventral hippocampus, a classical model of schizophrenia in rats, also causes an oxidative stress in the prefrontal cortex.
As in mice with a genetically induced low level of glutathione, the multiple morphological, physiological and behavioral effects of this intervention can be prevented by a treatment with N-acetyl-cysteine. This is all the more interesting since the intervention does not involve a manipulation of the redox system and clearly shows that diverse impacts can converge on a redox disturbance. Moreover, a model of autism displays the same oxidation characteristics as the glutathione deficient model of the URS. It could thus be possible that different pathological factors lead to oxidative stress, suggesting to selectively attempt to interfere with this redox pathway.

**IMMUNE REACTIONS**: several data suggest that immune reactions and inflammation can play a role in the development of schizophrenia. It is well-known that immune phenomena lead to oxidative stress. We have explored the reverse possibility that redox dysregulation could initiate immune reactions. *Daniella Dwir* (doctoral student, URS) has observed – in the prefrontal cortex of glutathione deficient mice, thus exposed to oxidative stress – a significant increase of immune "microglia" cells, which demonstrates the redox influence on immune reactions. It is also established that blocking the NMDAR receptor interacts with the immune and redox systems.

The multiple interactions described above suggest the existence of a scheme with several entries, involving retroactive and combined effects of NMDAR hypofunction, inflammation and redox dysregulation. It is probably by focusing on these three elements that preventive measures could be envisioned.

The work carried out with a long-term vision by the URS team is highly fruitful. The translational research program that has been developed step by step over the last 15 years is presently recognized as a **SCIENTIFIC APPROACH UNIQUE IN ITS KIND**. The interactions between clinicians and researchers, as well as between patients and experimental models, lead to essential developments in the exploration and knowledge of schizophrenia, and more generally of psychosis. Such an approach represents a **PIONEER ACHIEVEMENT** in the field of psychiatry.

Given her exceptional scientific accomplishments, Prof. **KIM DO CUÉNOD** was elected **INDIVIDUAL MEMBER** of the **SWISS ACADEMY OF MEDICAL SCIENCES (SAMS)** at the session held by the SAMS Senate on 20 May 2014. This election represents a great honor and a highly valuable acknowledgment of Kim Do Cuénod's career in the field of biological psychiatry.

**MANY HEARTFELT THANKS TO ALL OF YOU WHO SUPPORT US!**


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| **Registered Office**: | Chemin de la Becque 42, CH – 1814 La Tour-de-Peilz |
| **Secretariat**: | Ms Cristina Marich, Le Grand Chemin 63, CH – 1066 Epalinges – Phone +41 (0)21 341 41 03 – Email cmarich@alamaya.net |
| **Bank Details**: | Banque Julius Baer & Cie SA, Avenue de la Gare 39, CH – 1001 Lausanne |
| | IBAN: CH 65 0851 5026 0026 6200 3 – BIC: BAERCHZZ – CLEARING: 8515 |
| **PostFinance**: | Account n° 80-3244-6 |