NEWSLETTER 2018

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On 15 February 2018, Kim Do Cuénod gave her **INAUGURAL LESSON** as Full Professor at the Faculty of Biology and Medicine of Lausanne University. The lesson was entitled: *Psychiatrie et neurobiologie: ensemble pour mieux traiter et prévenir la schizophrénie*. It took place at Lausanne University Hospital in the presence of a large audience. The video of the lesson can be seen on our Website www.alamay.net (under "Research").

Kim Do Cuénod was named winner of the **2018 SIRS OUTSTANDING BASIC SCIENCE AWARD**. The award is granted biennially by the *Schizophrenia International Research Society* (SIRS) in recognition of an outstanding basic research contribution to schizophrenia research. The contribution may be preclinical or work which emphasizes the interface between basic and clinical research. The selection of the award recipient is based on the quality of the contribution and its impact on advancing schizophrenia research. It is a great honour for award recipients to be held in such high consideration by their peers. The award ceremony took place during the SIRS Conference in Florence (4-8 April 2018).

At the same Conference, Kim Do Cuénod was also presented with the **2018 ELSEVIER SENIOR *SCHIZOPHRENIA RESEARCH* AWARD**, which acknowledges her outstanding contributions to the field of schizophrenia research and the significant impact her article entitled "*Redox dysregulation, neuroinflammation and NMDA receptor hypofunction: a "central hub" in schizophrenia pathophysiology*?" generated among journal readers, based on the citations this article received during the past year. The award is granted by *Elsevier*, publisher of *Schizophrenia Research.*

In the framework of events organized for the friends and donors of the Alamaya Foundation, a guided tour of the exhibition entitled **AI WEIWEI – D'AILLEURS C'EST TOUJOURS LES AUTRES** took place on 18 January 2018 at the *Musée cantonal des Beaux-Arts* in Lausanne (mcb-a).

Ai Weiwei is one of the most important and influent artists of the last ten years. More than forty of his works produced since 1995 have been shown in Lausanne, a striking evidence of the wealth of his art and his deep knowledge of the cultural tradition of his country. The exhibition proved Ai Weiwei to be an allround artist: outstanding craftsman, encyclopedic mind, impressive communicator, and a man committed to the big issues of this world.

It was the last exhibition of the mcb-a at the *Palais de Rumine*, its historic location in Lausanne. Ai Weiwei thus included the various institutions hosted at the *Palais de Rumine* since its opening in the design of this exhibition, i.e. the museums of fine arts, of archeology and history, zoology, geology, the currency museum, and the university library.

The Foundation is deeply grateful to **Mr Camille Lévêque-Claudet**, curator at the *Musée Cantonal des Beaux-Arts*, for the organization of the visit and his fascinating comments – as well as to **Mr Bernard Fibicher**, director of the Museum, for his support.

The event ended with a cocktail, generously sponsored by Ms Françoise Muller – Chair of the Friends of the Foundation, during which Ms Cristina Marich, secretary of the Foundation, delivered a short speech to summarize some of the recent and most significant breakthroughs achieved by the Unit for Research in Schizophrenia (URS), directed by Prof. Kim Do Cuénod.

She also outlined that psychiatric disorders are diseases like many others; as in the case of diabetes, epilepsy or cancer, cells which don't operate properly are at the origin of the problem. Psychiatric diseases are due to biological dysfunctions; they are in no way "mystical", and we may all be faced with them one day or another.

To raise broader awareness and increased commitment from sponsors, donors, and the general public, we must popularize the human and social issues at stake in psychiatric disorders, and promote the importance of research, which may – in the long run – allow to spare future generations the devastation caused by these disorders; they not only very painfully affect patients and their families but also generate significant costs for society.

NEWS FROM RESEARCH

N-ACETYL-CYSTEINE (NAC) IMPROVES CONNECTIVITY

The NAC study in patients with a first psychotic episode has already been presented in a previous newsletter. In short, it showed that:

- NAC improves positive symptoms but only in subgroup of patients, who have a high oxidation blood marker; this finding emphasizes the key role of redox dysregulation (imbalance between free radicals and antioxidants leading to oxidative stress, a central phenomenon in several psychiatric disorders).
- Treatment with NAC allows to improve an important cognitive function, the speed of information processing, which positively influences other aspects of cognition.
- NAC also increases the level of brain glutathione, another significant finding since it involves the mechanism of glutathione (major antioxidant of the human organism) deficiency, which leads to oxidative stress.

These results have been published in the journal *Schizophrenia Bulletin*.

Through further analysing the results of the NAC study, new aspects came to light: Philipp Baumann and Paul Klauser, clinician scientists at the URS, had observed anomalies of two important brain connections in patients, the cingulum and the fornix, which link the hippocampus – responsible for the functioning of memory – with other areas of the brain. They now could show that **NAC also improves the structure of the fornix and the functional connectivity of the cingulum**, in collaboration with the group of Prof. Patric Hagmann (Service of diagnostic radiology and interventional radiology, Lausanne University Hospital). **To this day, no treatment had allowed to influence connectivity**.

LINK BETWEEN OXIDATIVE STRESS AND NEUROINFLAMMATION

Several data suggest that the brain of patients is subject to immune reactions leading to neuroinflammation, which in turn is likely to induce oxidative stress. The URS thus wondered whether oxidative stress could conversely initiate neuroinflammation, and through which mechanisms.

Daniella Dwir, post-doctoral student at the URS, has worked 5 years on this issue during her PhD thesis, and was able to answer these questions. She saw that in the animal model, which is affected by oxidative stress and a deficit in parvalbumin interneurons (essential for cognitive functions) in the median prefrontal cortex, this same area reveals an important activation of microglial cells, responsible for immune defences, particularly during the pubertal period. She showed that this response involves a signalling pathway called MMP9 – RAGE, which activates a series of factors involved in immune defences. These in turn stimulate the development of oxidative molecules and thus permanently increase oxidative stress. Indeed, after it started in the young animal, the stress persists through adulthood. **It is thus a vicious circle, oxidative stress inducing neuroinflammation, which in turn increases oxidative stress, and so on**. Daniella subsequently showed that **this vicious circle can be interrupted through applying a substance that blocks the MMP9 enzyme**: the oxidative stress disappears and the parvalbumin neurons are normalized in the adult.

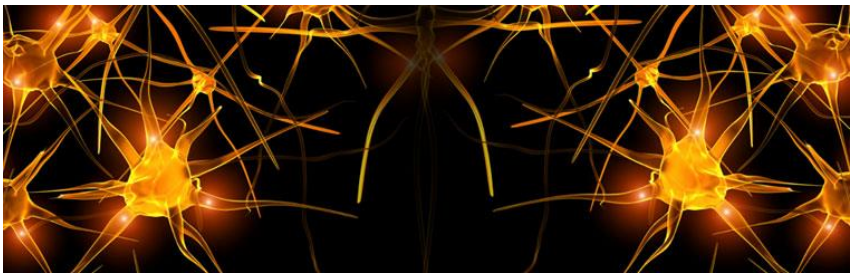
Unfortunately, it is unlikely that MMP9 can be blocked in patients for therapeutic purposes since it is involved in many other essential functions, which shouldn't be inhibited. A possible solution would be to find a way to alter it only in parvalbumin neurons.

OBJECTIVES

The exploration of **neurobiological markers** represents a key axis of the program conducted at the URS; it is aimed at the following objectives:

- the early identification of at risk individuals;
- the definition of the various stages of the disease;
- the assessment of illness progression;
- the development of new therapeutic tools;
- the development of preventive measures.

In parallel, innovative means of intervention have to be found to treat and protect individuals affected by the risks identified thanks to the markers; the URS strives in particular to identify **new molecules** with a direct impact on the neurons disturbed by oxidative stress, and more efficient than N-acetyl-cysteine (NAC), which insufficiently crosses the blood brain barrier. The efficiency of these molecules will be tested in the animal model, and subsequently in **clinical trials**.



The URS research program aims at ensuring the **translation of basic and clinical research to concrete solutions** in order to optimize the diagnosis, treatment and prevention of psychiatric diseases such as schizophrenia. It has to be noted that the initial hypothesis of the URS concerning the role and causes of oxidative stress has been largely confirmed and enriched with new findings, which are of crucial significance not only in the field of schizophrenia but also in those of autism, depression and bipolar disorders. **The scope and field of intervention of the URS have thus become much wider**; progress achieved in the understanding of a great number of mechanisms involved in these diseases represents a decisive asset for the identification of new therapeutic targets, and the development of preventive measures.

Furthermore, this program also allows to train **high level academic personnel**. On one hand, researchers gain knowledge in issues and interdisciplinary methods related to basic and clinical neuroscience, in an environment of scientific excellence and fruitful collaboration. On the other hand, doctors participating in the program learn about the neurobiological bases of psychiatric disorders, and gain an experimental knowledge of doctoral level.

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