

The Alamaya Foundation pursues its relentless efforts to collect the private funds needed to advance the studies conducted by the team of the Unit for Research in Schizophrenia (URS), directed by Prof. Kim Do Cuénod. The URS work program is targeted at the dysfunctions linked not only to **SCHIZOPHRENIA** but also to **AUTISM**, **BIPOLAR DISORDERS** and **DEPRESSION**, which the URS has included in its research given the common mechanisms involved in these diseases. The **MISSION** of the Alamaya Foundation, which was set up in 2002, is therefore essential considering the great number of **CHILDREN** and **YOUNG ADULTS** affected by these psychiatric disorders, whose perspectives for the future are painfully and persistently threatened.

Public funds cover only half the costs of the research conducted at the URS, the other half has to be covered through the support of private donors. Despite the **IMPORTANT AND RECOGNIZED PREVALENCE** of psychiatric diseases, the financing of research in this field remains a **MAJOR CHALLENGE** and falls a long way behind the means invested for the benefit of somatic medicine.

To thank the friends and donors of the Foundation and bring them together, the Committee of the "Friends of the Foundation" invited them to a conference given by Mr **CLAUDE NICOLLIER**, entitled **"UNDERSTAND THE UNIVERSE"**. The conference took place on September 22<sup>nd</sup>, 2015, at the *Abbaye de l'Arc*, a historic place in Lausanne, which opened its doors for the very first time to an external organization: a great recognition of Alamaya's work and mission! Following Mr Nicollier's fascinating talk, Prof. Michel Cuénod, Chair of the Foundation, presented an overview of the latest progress achieved by the URS research team. The event ended with a cocktail and interesting discussions between members of the URS staff and the public.



Claude Nicollier, astrophysicist and astronaut, 1<sup>st</sup> Swiss citizen in space, participated in 4 missions with the space shuttles Atlantis, Endeavour, Columbia and Discovery.



From left to right.: Kim Do Cuénod (Director, URS) Françoise Muller (Chair, Friends of the Foundation Committee), Michel Cuénod (Chair, Alamaya Foundation), Cristina Marich (Secretary, Alamaya Foundation)

The Website of the Alamaya Foundation, which is now compatible with smart phones and tablets, features a **"NEWS"** page where you can access more photos of the conference as well as a great deal of additional information concerning events, articles and publications related to the research program sponsored by Alamaya.

## NEWS FROM RESEARCH

The studies conducted at the URS are carried out in close **collaboration** between researchers and clinicians of the **Service of General Psychiatry** (Department of Psychiatry, Lausanne University Hospital), headed by **Prof. Philippe Conus**.

Brain anomalies identified in patients affect on one hand a particular type of **inhibitory neurons, i.e. parvalbumin interneurons (PVI)**, and, on the other hand, **nervous fibres and their myelin** (protective envelope) which connect the different parts of the central nervous system. These anomalies are **responsible for the various manifestations** of the disease, in particular neuronal synchronization (EEG), cognitive, affective and social disorders as well as hallucinations, whose variability depends on the different neuronal circuits that are directly involved. Cognitive disorders concerning memory, attention, concentration and the ability to plan actions are heavily disturbing for the private and professional life of patients.

### IMMUNE INTERACTIONS AND REDOX



Evidence suggests 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 (dysregulation between oxidations and reductions in cells). We have explored the reverse possibility, i.e. that redox dysregulation may cause immune reactions. In the prefrontal cortex of glutathione deficient mice, which are thus vulnerable to oxidative stress (as we have shown previously), *Daniella Dwir* (PhD student, URS) has observed a strong increased action of "microglial" immune cells indicating a reciprocal effect of oxidative stress on inflammation in the brain. She has shown that a receptor called RAGE is the common denominator between oxidative stress and neuroinflammation. More interestingly, RAGE activation is triggered by an enzyme (MMP), which is itself stimulated by oxidative stress. **Through blocking this enzyme with an inhibitor, one can prevent the activation of RAGE and consequently the vicious circle initiated either by oxidative stress or inflammation. This observation opens up highly innovative and interesting perspectives for novel treatments.**

### TRAUMA IN YOUNG PSYCHOTIC PATIENTS

As shown by *Jan Cabungcal* and *Pascal Steullet* (senior researchers, URS) in the animal model, the combination of a genetic default (deficient production of glutathione) and stress has different consequences according to the age of the animal at the occurrence of stress: in very young or pubertal mice, it leads – in the medial prefrontal cortex – to a loss of inhibitory parvalbumin interneurons (PVI), which are essential for any cognitive, affective or social performance; the same cells are deficient in the same brain areas of patients. The loss of PVIs is permanent and persists in adults. However, when additional stress is applied in the adult animal, it has no effect on PVIs. Hence **it appears that there is a critical period during youth when the brain is particularly sensitive to environmental insults.**

Following these observations, we have investigated the occurrence of trauma in the past of early psychosis patients (TIPP cohort). *Luis Alameda* (clinician-scientist, URS & Service of General Psychiatry) has shown that **a fourth of patients had experienced physical or sexual violence.** Their social functioning is particularly affected, especially if abuse occurred before the age of 11 years. These results are in concordance with literature and highlight **childhood as a very sensitive and critical period to environmental insults/trauma.** They are an example of **translational research**, moving from experimental observations to clinical issues, and paving the way for a better

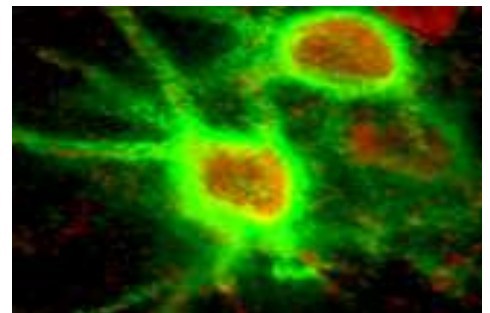
understanding of the consequences linked to abuse and trauma.

### FORNIX

Another example illustrating the significance of our translational approach consists in the evidence we obtained in glutathione deficient mice showing an impairment of the integrity of the nervous pathway called "fornix", a neuronal circuit which is important for memory. This observation has prompted the investigation of the same structure in early psychosis patients and revealed the same deficit. These results have already been mentioned last year in a preliminary way, and have afterwards been confirmed and refined in order to be published. **They could potentially be considered as "non-invasive" markers of the disease, paving the way for early detection and intervention measures.**

### METALLOPROTEASES IN PARVALBUMIN INTERNEURONS (PVI)

As we have shown repeatedly, PVIs play a crucial role in all cognitive functions of the brain and are deficient in patients suffering from schizophrenia. They are enwrapped in a specific envelope, called perineuronal net, which protects them and stabilizes synaptic contacts. To allow the development of new synapses, the perineuronal net must be partly degraded. This opening requires the intervention of molecules which are specialized in the degradation of proteins, called metalloproteases.



Thanks to a collaboration with *Prof. Jean Rossier* (University of Paris Descartes), *Jan Cabungcal* showed that PVIs selectively produce certain metalloproteases, only those which are effective on the perineuronal net. **This important discovery paves the way for assays aimed at influencing these specific PVI metalloproteases in order to avoid the degradation of the perineuronal net when it is not required.**

### EFFECTS OF DOPAMINE ON NEURONAL SYNCHRONIZATION



Dopamine plays an essential role in cognitive performances such as working memory, attention or the planning of actions, which are all disturbed in patients affected by schizophrenia. Dopamine produces its effects by modulating oscillations of cortical microcircuits, as *Pascal Steullet* showed in mice: dopamine favours high frequency oscillations in the anterior cingulate cortex, the increase being even stronger after the degradation of the perineuronal net. **This result contributes to a better understanding of the role of dopamine in the pathophysiology of schizophrenia.**

### DEVELOPMENT OF NOVEL REDOX MODULATORS

The search for new molecules is ongoing and aimed at identifying redox modulators, which efficiently cross the blood-brain barrier and have little or no side effects. *In vitro* tests have been developed with a view to discovering, among a great number of molecules and by means of a process called "screening assay for high throughput" (collaboration with EPFL), those molecules which have a strong antioxidant power. The selected molecules will be tested *in vivo* in our animal models and ultimately in patients. This project is carried out by *David Ramonet* (post-doc, URS) and *Radek Skupiński* (PhD student, URS). **They have obtained highly promising preliminary results with one of the molecules tested in vitro.**

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## COLLABORATIONS

Scientists and researchers from all over the world are interested in collaborating with Prof. Kim Do Cuénod and her group. In Switzerland, present collaborations include in particular several departments of the Lausanne University Hospital (CHUV), the Federal Schools of Technology of Lausanne (EPFL) and Zurich (EPFZ), and the School of Engineering & Architecture of Fribourg. At the international level, they include among others the Universities of Harvard, Maryland, Johns Hopkins, Emory, Pittsburgh and George Washington in the USA as well as two research institutes in Denmark and Israel.

## PUBLICATIONS

Recent results achieved by the URS team have been published in scientific journals with very high impact factors such as *Neuron*, *Molecular Psychiatry*, *Proceedings of the National Academy of Sciences USA*, *Biological Psychiatry* and *Schizophrenia Bulletin*. Specific advancements have also prompted wide coverage in the local press (24heures, Le Matin, Tribune de Genève, RTS Info) and in specialized magazines (EPFL, University of Lausanne, Psychomédia) in Switzerland (see Media page of our Website).

## CONFERENCES

Kim Do Cuénod is regularly invited to present the results and perspectives of her research program at major international meetings, research centres and universities. She was notably invited to give a special lecture at the annual meeting of the *Society for Neuroscience* in the USA, the most important meeting worldwide in the field of neuroscience with over 30'000 participants each year. She was also invited to give an online "virtual" conference in the context of a webinar organized by *LabRoots*, a leading scientific social networking website based in California (see News page of our Website). Furthermore, she also gives conferences at the request of service clubs, schools and various associations, thus contributing to inform the general public and vulgarize scientific issues.

## HONORS



Corroborating the excellence of the studies conducted at the URS, two members of the group have been rewarded for their projects. Dr Jan-Harry Cabungcal received the *Young Investigator Award*

2015 of the Swiss Society of Biological Psychiatry and Aline Monin received an *Award of the Faculty of Biology and Medicine of Lausanne University* for her doctoral thesis (see News page of our Website).

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