alamaya

Foundation for Research in Schizophrenia

NEWSLETTER NO 7 – MARCH 2010

In Andean Indian, alamaya means hope for a miracle

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NEWS FROM THE FOUNDATION

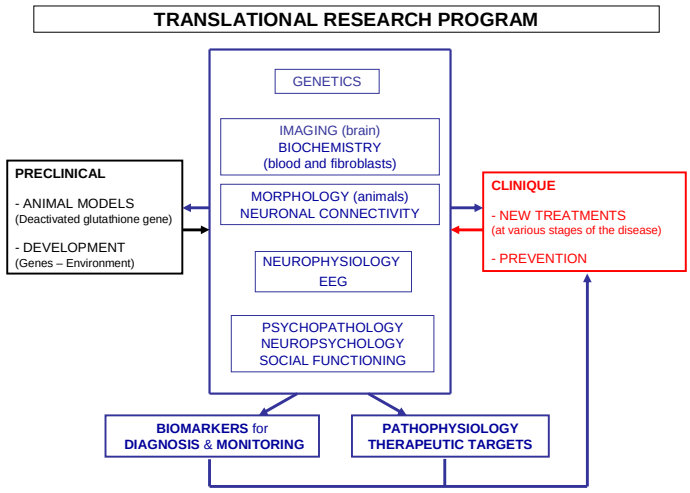
The launch of the **Friends of the Foundation**, a circle of people actively supporting Alamaya's mission, has taken a **positive start**. Over 300 mails were sent out between April 2009 and February 2010. They were addressed to the personal networks of the Friends' Committee members and to various contacts of the Foundation; the rate of positive returns (approx. 20%) represents an **encouraging result**.
The Friends of the Foundation is a circle open to all people and institutions interested in research in schizophrenia, and sensitive to the suffering caused by the disease. Members of the circle donate an **annual contribution** and are regularly informed of **research outcomes** (conferences, visits of the laboratory, etc.).
For further information, please contact the secretariat of the Foundation (see details overleaf).

Besides advocacy targeted at issues related to schizophrenia and psychiatric disorders in general, which are still too largely taboo in our society, **fundraising** among donors of the private sector represents the main objective of the Foundation. Thus Alamaya benefits since several years from the generous and ongoing support of the **Loterie Romande**, which is essential to uphold the activities of the Unit for Research in Schizophrenia (URS). It can also count on the precious support of the **Stanley Thomas Johnson Foundation**. Thanks to those two institutions, following positions could be financed between January and December 2009: 1 molecular biologist (100%), 1 doctoral student (100%), 1 technician (100%), 1 biologist (50%) – as well as some laboratory equipment. **Half of the financing** of the URS depends on **private donors** – the Alamaya Foundation is therefore constantly striving to secure new funding sources.

NEWS FROM RESEARCH

The scientific studies conducted at the URS and supported by the Alamaya Foundation are based on the observation of a **glutathione deficiency** (main protective agent of nervous cells against oxidative stress) in the brain of patients affected by schizophrenia. This deficiency is likely to inhibit the normal functioning of contacts between nervous cells, and, in the course of brain development, lead to the "malformation" of certain neurons. Presently, these disturbances are considered as a **risk factor** liable to explain the disorders which patients suffer from.
The work program of the URS is **translational** and focuses on the interaction between clinical and basic research.

Clinical research, in patients, is aimed at identifying the **causes** and **mechanisms** of the disease. **Basic research** focuses on the **consequences** of a reduced glutathione level; the artificial lowering of glutathione synthesis in neuron cultures, brain slices and / or animals allows to develop "models" that are intended to evaluate whether a reduced glutathione level, in particular during development, generates anomalies similar to those observed in patients. These models are also essential to examine the effectiveness of new medications.



The different research fields involved require the collaboration of various specialists, thus justifying a **multidisciplinary research group**.

Comparison chronic patients – young patients

Results achieved to this day show that the **anomalies of the glutathione system** identified in chronic patients are **already present at the outset of clinical symptoms of the disease** – and that they are much more pronounced with respect to the central functions of glutathione synthesis and its protective action.

This proves that they are **inherent to the pathology of schizophrenia** and do not result from the evolution of the disease nor from its treatment. Ideally, it should be explored whether they are already present during the first prodromic episodes (forerunners of the disease) in adolescents.

These promising results pave the way for the development of a **biomarker profile** required for the early diagnosis of the disease.

Clinical trial in early psychosis

N-acetyl-cysteine (NAC) has proved beneficial in chronic patients; we have therefore set up a clinical trial with NAC involving **young patients** in the early phase of psychosis. After a long period of preparation, the trial started at the beginning of 2009. Within the space of one year, 44 patients (among the cases treated in the framework of the early intervention program of the Department of Psychiatry at the Lausanne University Hospital) turned out to be eligible for the trial; 34 were well enough to be asked to participate, 16 agreed and 18 refused. The number of patients who accepted to take part in the trial represents a great **success** given the complexity of the study and of the interaction with psychotic individuals. At this stage, it is still too early to draw any conclusions regarding the effect of NAC in young patients.

Cortical synchronization

Recordings by means of electroencephalography (EEG) performed during the first NAC study in chronic patients revealed that NAC led to a **spectacular improvement of auditory evoked potentials**; these findings were published in 2008 in the scientific journal ***Neuropsychopharmacology***, the official publication of the *American College of Neuropsychopharmacology*. Through re-examining the recordings and analyzing them with another method, we found that **NAC also improves the neuronal synchronization at rest**, thus adding a further argument to the positive objective effects of the treatment. This improvement corresponds in particular to the **amelioration of certain disorganization symptoms in patients**.

Animal model with a glutathione deficit

In mice with a strongly lowered glutathione level since conception, we found that **only some parts of the brain are particularly sensitive to the dysfunction of the glutathione system** and show signs of oxidative stress. We were able to monitor the phenomenon in two areas, the anterior cingular cortex and part of the hippocampus. It is very interesting to note that **the human equivalents of these two brain areas are directly affected in patients suffering from schizophrenia**.
Oxidative stress causes **specific defects** of a class of inhibitory neurons that are essential to the synchronization of large neuron populations directly involved in **cognitive functions**. Through these observations, we are coming onto one of the central problems linked to the pathology of schizophrenia.

The part of the study of this experimental model concerning the hippocampus led to an important publication at the end of 2009 in the ***Journal of Neuroscience***, one of the world's most important journals in the field of neuroscience.

Measure of cerebral metabolites

To achieve a better understanding of the disease, it is important to identify the consequences of a glutathione deficit of genetic origin on other key substances of the nervous system. To this effect, patients are examined by means of **magnetic resonance spectroscopy** (MRS), the only method that presently allows the non-invasive measure of cerebral metabolites; this method can now be applied to small laboratory animals by using a high magnetic intensity. Thus it becomes possible to **compare the values measured in humans and in animals**.

This approach should allow to identify **biological markers** of the disease and to evaluate which substances are likely to compensate for the metabolic alterations in mice before testing them in humans.

Indicating the regional and international relevance of our research, numerous **collaborations** have been developed, in particular with: the Brain and Mind Institute and the Center for BioMedical Imaging of the **EPFL**, the Service of Radiology of the **CHUV** (Lausanne University Hospital), colleagues in **Oslo** (N), **Copenhagen** (DK), **Harvard-Boston** and **Stanford** (USA), and **Riken-Tokyo** (J). In 2009, the results achieved by the URS have been presented at **conferences** – of **scientific** nature on the one hand and to the purpose of **vulgarization** on the other hand – in **Switzerland** (Bern, Lausanne, Montreux, Sion, Vevey, Zurich), **Germany** (Berlin), **Canada** (Vancouver) and the **United States** (Bethesda, San Diego, Stanford).

WE THANK ALL THE FRIENDS AND DONORS OF THE FOUNDATION
THEIR SUPPORT IS ESSENTIAL TO ADVANCING RESEARCH

Avec le soutien de la Loterie Romande

Registered office: Chemin de la Becque 42, CH – 1814 La Tour-de-Peilz
Secretariat: Ms Cristina Marich – c/o MMC SA, Grand Chemin 63, CH – 1066 Epalinges
Phone +41 (0)21 341 41 03 – Fax +41 (0)21 341 41 01 –
Email cmarich@alamaya.net
Bank details: Banque Julius Baer & Cie SA, Rue du Grand-Chêne 7-9, CH – 1002 Lausanne
IBAN: CH 65 0851 5026 0026 6200 3 – BIC: BAERCHZZ – CLEARING: 8515
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