NEWSLETTER 2020

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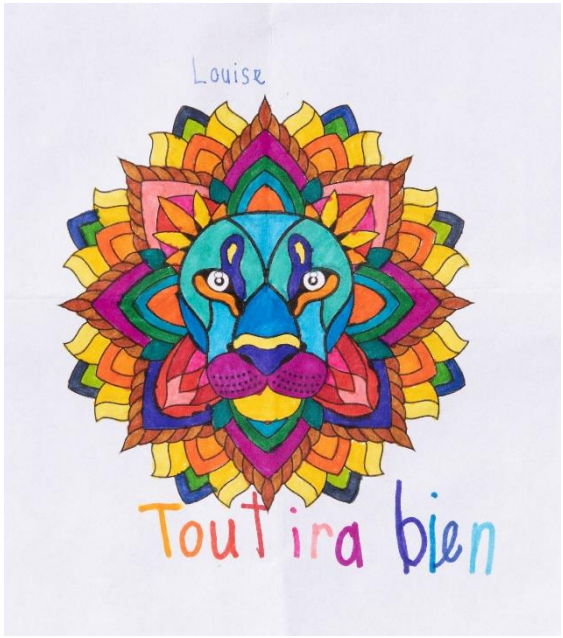
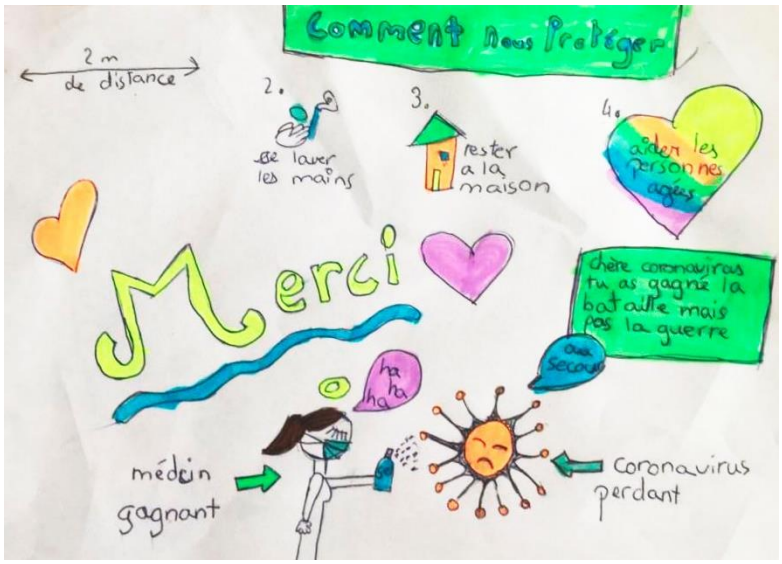
It is hardly possible to consider the year 2020 without addressing the subject of the **Covid-19** pandemic, which has deeply affected a wide range of activities, including those linked to scientific research.

The laboratories at the Centre for Psychiatric Neuroscience were closed during several weeks and the studies under way had to be interrupted. Most of the people with administrative jobs had to work from home. Furthermore, many members of the Unit for Research in Schizophrenia (URS) and of other research groups mobilized to lend a hand to the staff of the CHUV (Lausanne University Hospital) that was struggling with the influx of patients and the reorganization of many services, which had to be urgently undertaken to face the situation.

A great number of grateful and encouraging messages sent by the public reached CHUV staff; among these, there were many children's drawings which deeply moved their recipients. A few of them are featured below.

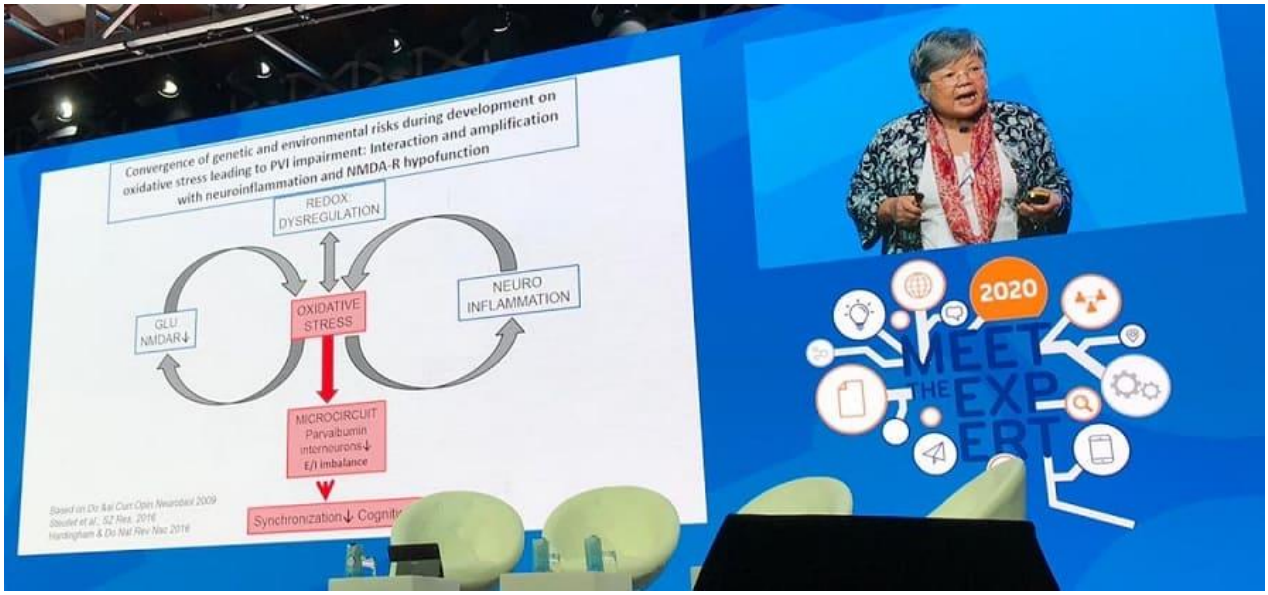




Many international meetings have been either cancelled or reorganized into virtual editions.
Among them, the Annual Meetings of the *Schizophrenia International Research Society* (SIRS) in Florence, of the *Society of Biological Psychiatry* (SOBP) in New York and of the *Federation of European Neuroscience Societies* (FENS) in Glasgow; Prof. Kim Do Cuénod had planned symposium presentations during all of these meetings.

However, shortly before the restrictions due to the pandemic, Kim Do Cuénod gave a keynote lecture at the 5th edition of the **"Meet the Expert"** Meeting, during which 400 experts gathered to discuss various aspects related to patient care, early intervention, and the latest technological advances in the field of mental health. The meeting took place in Madrid, on January 31st and February 1st, 2020, and was a great success. Psychiatrists from all over Spain attended it.

Following this meeting, Kim Do Cuénod was invited by Prof. Benedicto Crespo-Facorro, Head of the Department of Psychiatry of the University Hospital of Sevilla, to join the editorial board of the journal entitled *Revista Salud Psiquiatria y Salud Mental* / *Journal of Psychiatry and Mental Health*, of which he is editor-in-chief. This journal is the official scientific publication of the Spanish Society of Psychiatry and the Spanish Society of Biological Psychiatry.



NEWS FROM RESEARCH

Research in the field of schizophrenia faces many challenges due to the complexity of the disease, and to the fact that its diagnosis is only based on clinical, and therefore not entirely objective, observation. As in most other diseases, it requires markers related to well documented biological mechanisms allowing to stratify patients into sub-categories, to monitor the evolution of their pathology, and to objectively analyse treatment efficiency. These markers could for example be alterations of the concentration of specific molecules in the blood, of the electroencephalogram (EEG) or of brain imaging. The research program developed by Prof. Kim Do helps to meet these requirements: its objectives are to (a) understand the physiopathology of schizophrenia, (b) identify early biological markers, and (c) develop more rational, mechanistic and potentially preventive treatments.

EFFECTS OF OXIDATIVE STRESS ON THE MITOCHONDRIA OF PARVALBUMIN NEURONS: IMPLICATION OF MIR-137 AND COX6 THAT MAY LEAD TO A THERAPEUTIC APPLICATION

As we stated several times in past years, parvalbumin interneurons (PVI) of the prefrontal cortex play a key role in the performance of cognitive, affective and social activities, and their alterations in the brain of patients suffering from schizophrenia are directly linked to their symptoms.

These PVIs are inhibitory, which means that their activity blocks the activity of the main excitatory neurons. This very rapid sequence of excitation and inhibition can be detected in the form of high frequency electrical oscillations (40 Hz) during electroencephalo-graphic recordings (EEG), oscillations which are altered in patients. One of the specificities of PVIs is that, in order to generate these oscillations, they produce discharges at very high rates, requiring a significant consumption of energy, which is provided by the presence of abundant mitochondria.

Ines Khadimallah (research fellow at the URS) showed that, in the animal model, oxidative stress leads to an increase of a specific factor, called miR-137, which causes a dysfunction of mitochondria. As she also showed that the COX6 molecule is a specific marker of PVI mitochondria, and that this marker is lowered, we thus know that the mitochondria of PVIs are altered.
Furthermore, through adopting a "translational" approach, she observed that, in the blood of a group of patients, tiny vesicles from the brain, called exosomes, contain an excess of miR-137 that increases in parallel to the diminution of COX6, as in the animal model exposed to oxidative stress. We had previously demonstrated that a great number of animal models, representing the various known causes of the disease, are nearly all affected by oxidative stress, suggesting that oxidative stress could be present in a large number of patients.

In collaboration with Raoul Jenni (psychologist and researcher at the URS), Ines Khadimallah noted that high frequency oscillations (40 Hz) are reduced in patients proportionally to the increase of miR-137; in parallel, their symptoms are aggravated and their cognitive performances are reduced. Very interestingly, in the animal model, the application of an antioxidant specifically targeted at mitochondria, called MitoQ, allows to normalize miR-137, COX6, and PVIs. Since this substance is used in humans, it is tempting to speculate that it might be effective in some patients.

These results will therefore prompt the URS to conduct a CLINICAL TRIAL to test whether the adjunction of MitoQ improves certain symptoms of the disease, and to monitor its efficiency thanks to the miR-137 and COX6 markers.

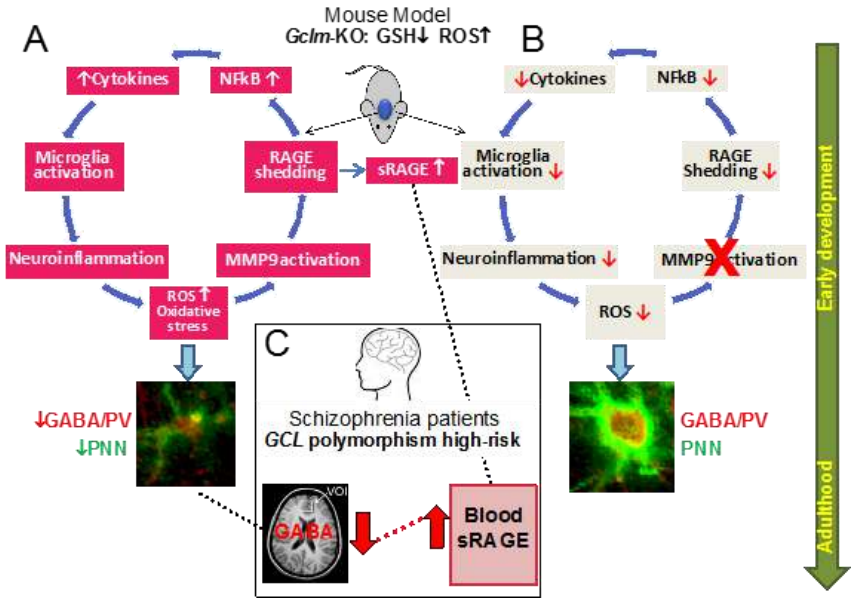
If successful, the treatment of patients suffering from schizophrenia with MitoQ will improve their symptoms and cognitive functions that are not well cured by present antipsychotics. Better cognition is essential to improved social and professional functioning, and quality of life. The asset of this treatment is to be based on pathophysiological mechanisms, and to be biomarker guided regarding both patient selection and efficacy assessment. It is therefore an **individualized treatment** of psychosis, a major innovation in the field of psychiatry. Thanks to a pioneering approach based on cutting-edge expertise, this study will thus potentially pave the way for a breakthrough in the treatment of psychiatric disorders, bringing highly significant benefits on the human, social and economic levels.

OXIDATIVE STRESS AND INFLAMMATION

As we reported two years ago, a variety of data suggest that the brain of patients is subject to immune reactions leading to neuroinflammation, which can induce oxidative stress. We then wondered if, conversely, oxidative stress in the brain could initiate neuroinflammation and by what mechanism.

Daniella Dwir (research fellow at the URS) had shown in our animal model, which is affected by oxidative stress and a deficit of parvalbumin neurons (PVIs) in the median prefrontal cortex, that this brain area presents – in particular during the puberty period – an important activation of *microglial* cells, which are responsible for immune reactions. She had also demonstrated that this response involves a signalling pathway called MMP9 – RAGE, which activates several factors related to immune defences. These will in turn stimulate the formation of oxidizing molecules, and permanently increase the level of oxidative stress. Indeed, once it broke out in the young animal, the stress persists until adulthood.

We are thus dealing with a vicious circle, oxidative stress inducing neuroinflammation, which in turn increases oxidative stress, and so on. This vicious circle can be interrupted by applying a substance that blocks the MMP9 enzyme: oxidative stress disappears and parvalbumin neurons are normalized in the adult.



Dwir & al., 2019

These observations in the animal led to a translation in humans: the soluble RAGE molecule, which increases in the brain during oxidative stress, can be measured in the blood of patients: its level is higher in patients than in control subjects, which probably indicates an inflammatory reaction in the brain. Furthermore, RAGE increases in parallel to the diminution of the GABA transmitter in the prefrontal cortex, mainly in patients who have a redox regulation problem. Since this inhibitory transmitter is used by parvalbumin neurons, it is tempting to speculate that these alterations reflect the deficiency of these neurons in the prefrontal cortex of patients. What we have shown recently is that **the adjunction of N-acetyl-cysteine to the treatment of patients leads to a decrease in blood RAGE values**, presumably reflecting an **improvement in parvalbumin neurons,** which is in turn reflected in an **improvement of cognitive functions**.

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