Early detection of psychotic disorders has recently become a major focus for research and service development, leading to a considerable conceptual shift in psychiatry and to the development of a preventive approach to main psychiatric disorders. Based on the evidence that treatment delay has a negative impact on outcome, specialized programs to reduce duration of untreated psychosis and set up specifically adapted treatment have developed around the World; the TIPP (Treatment and early Intervention in Psychosis Program) was launched in Lausanne in 2004. Since then, over 400 early psychosis patients (EP) have been treated at this specialized clinical and research center. Since March 2013, TIPP widened its focus to take care of ultra high risk (UHR) patients who present with prodromal manifestations of psychosis. In the frame of such programs, the approach to mental disorders is changing in a major and promising way as the concept of clinical staging is gaining momentum, with the aim to develop stage specific treatments where earlier phases of illnesses are treated with more benign and more efficient approaches. However, improvement has so far been hampered by a major lack of evidence based knowledge of the mechanisms involved in the development and progression of psychotic disorders. Stages are currently defined almost exclusively on the basis of imprecise clinical dimensions with established but unfortunately limited validity. Therefore there is an important need for basic neurobiological research in this domain, in order to uncover neurobiological mechanisms which may lead to the identification of reliable biomarkers of such disorders.
In this context, a translational research program, implemented in 2009 at the Department of Psychiatry CHUV between TIPP (P Conus) and the CNP (Centre de Neurosciences Psychiatriques; K Do), has gained considerable momentum thanks to the first phase of NCCR Synapsy. The research program is based on three axes: (1) Cross sectional multimodal (clinical assessment, brain imaging, EEG, neurobiological) assessment of patients in the various stages of the disorder (prodrome, first episode, early relapse and chronic phase); (2) Longitudinal multimodal assessment of patients throughout the successive stages of the illness starting from the prodrome and (3) Bi-directional translation between human and animal models with experiments leading to similar endpoint assessments being conducted in both.

WHERE WE WANT TO GO

The main aims of the project are: (a) To create stage specific biomarker profiles in order to allow early detection and monitoring of the efficacy of new drugs, both in animal models and humans; (b) To identify potential new treatments and preventive targets based on new critical pathophysiological molecular signaling pathways. In order to do so, biological correlates have been assessed by using non-invasive technologies such as EEG (M Muray, CIBM) and brain imaging (MRS, MRI, DTI; R Guerette, CIBM; P Haggman, Radiologie-CHUV; J-P Thiran, LSS-SFBL) as well as blood and fibroblasts transcriptomics and metabolomics (OMICS), both in humans and animal models where ever possible. The tight partnership between preclinical and clinical components which are both based on a precise hypothesis will ensure effective translation from bench to bedside and vice versa.

ONGOING PROJECTS

A CORE NEUROBIOLOGICAL MECHANISM IMPACTING LOCAL MICROCIRCUITS AND LONG RANGE CONNECTIONS.

Based on converging evidence pointing at redox imbalance and oxidative stress in blood, fibroblasts, CSF and brain of patients suffering of schizophrenia1 (including association with the disease of common variants and CNV in genes involved in GSH metabolism), the project proposed that redox imbalance represents one hub on which converge various causal genetic and environmental risk factors during neurodevelopment, leading to a failure to properly optimize and regulate connectivity improvements1.

The genetic vulnerability factors involve either redox regulation genes directly affecting glutathione (GSH) metabolism, or genes which indirectly lead to oxidative stress, including DISC1, PROD, G72, NRG, DTNB1. Environmental factors known to favor major psychiatric disorders generate oxidative stress which, if the redox regulation is impaired, could perturb the developing nervous system in a time and region specific manner. As a consequence, two key systems, essential for cognitive and affective functioning, will be particularly affected: local microcircuits and long range connections. The critical role of oxidative stress has been validated in a GSH deficient animal model (GCLM-KO mouse model) reproducing numerous schizophrenia phenotypes including NMDA receptor hypofunction, impaired parvalbu min fast-spiking GABA interneurons (Pv)1.1 neural synchronization1,2 and behavioral anomalies.

Highlights of some translational aspects of the project

A metabolic profiling performed in fibroblasts (baseline and oxidative stress) of 30 EP and 20 control subjects revealed an abnormal reactivity to oxidative stress. Indeed, besides abnormalities in the regulation of redox/anti-oxidant system and in the phosphorylating metabolism, we found alterations in the regulation of arginine and extracellular matrix related metabolism which should be further investigated as potential early markers in SZ (Fourier et al, SNF 2013).

In the years to come we will have to keep up to this very positive assessment and continue to work hard towards the goals defined in the initial project. The NCCR Synapsys focuses on specific projects for which a better integration with the rest of the NCCR is suggested. We will work in the coming months to address these issues.

On behalf of the Steering Committee, I would like to take this opportunity to thank all of the members of the NCCR Synapsy for their efforts towards the success of the NCCR. We still have considerable work ahead of us to prepare the second phase: we will have to prepare a final proposal by June 2014. But all these efforts are worthwhile given the impact that the NCCR will have, and is already having, on Swiss neuroscience and psychiatry.

PIM

REFERENCE

“I HOPE I NEVER HAVE TO CHOOSE BETWEEN RESEARCH AND CLINICS”

Camille Piguet is supported by a grant for clinician researchers from Synapsy. She works part-time (50%) in the laboratory of Neurology and Imaging of Cognition headed by Prof. Vuillemier at the University of Geneva (UNIGE) and dedicates the other 50% of her time to working in the Mood Disorder program directed by Prof. Aubry in the Department of Psychiatric Specialties at the University Hospital, Geneva.

In the middle of October, Camille Piguet gave birth to two babies: a little sister for her 3 year old and a rather big research project to investigate susceptibility to bipolar disorder, to be carried out with the NCCR Synapsy. While the first baby rounded her tummy, the second was launched with a serious push …… and then she left on maternity leave. Camille Piguet doesn’t want to give up anything; and so, she lives three lives: that of a clinician, a researcher and a mother.

‘I always wanted to study medicine. But then, I also wanted to know how things work.’ In the sixth year of medical school, Camille started an internship in the Neurology and Imaging of Cognition laboratory, run by Prof. Patrik Vuilleumier at the University of Geneva. It was here that she discovered the reality of imaging research: ‘8 hours a day in front of a computer’. Even so, she became enthusiastic about this exciting field of research, close to human beings and how they function. From this moment, the relationship between psychiatry and cognitive neuro-imaging gels, and the doctor becomes a researcher, carrying out her MD-PhD on correlating neuronal function in thought disorders in mood disorders in the same laboratory, thanks to a grant from the Swiss National Science Foundation.

Four and a half years later, Camille is both a Ph.D and a mother. She obtains a clinician-researcher laboratory grant from Synapsy that enables her to continue in her research theme and embark on two professional careers: half-time in the laboratory and half time in the Mood Disorder program in the Department of Psychiatric Specialties, directed by Prof. Jean-Michel Aubry. ‘Being able to work in this clinical department allows me to carry on in the same vein as my thesis work, while bringing new, exciting perspectives to my research, states the clinician-researcher.

Right before going on maternity leave Camille feels unruffled. ‘A deep-rooted collaboration has been set up between the clinical department and the researchers and I feel happy that the project will carry on while I’m away’. Things could get more complicated later. Although very organised, Camille Piguet, doesn’t want to play superwoman. ‘With my three lives, it’s often difficult to find a good balance’.

Conducting two careers in parallel means specialising in psychiatry on the one hand (6 years full-time), and an academic career on the other, which inevitably involves work experience in a laboratory abroad. This may not be easy with two small children and a husband who is already established as a doctor. ‘For the moment I haven’t had to choose between doing one career or the other and I really hope I never have to make that choice as I am so passionate about them both’ maintains Camille Piguet. ‘I think it will be rather a question of how much time I can spend on each’.

Anyway, what drives Camille is to contribute one way or another to the understanding of psychiatric disorders. ‘I’m really happy that I could take advantage of the opportunities that arose and feel so lucky to have such a stimulating and interesting career, and I must say I never hesitated for a moment to have my wonderful children’.

Anne-Muriel Brouet, NCCR SYNAPSY media officer