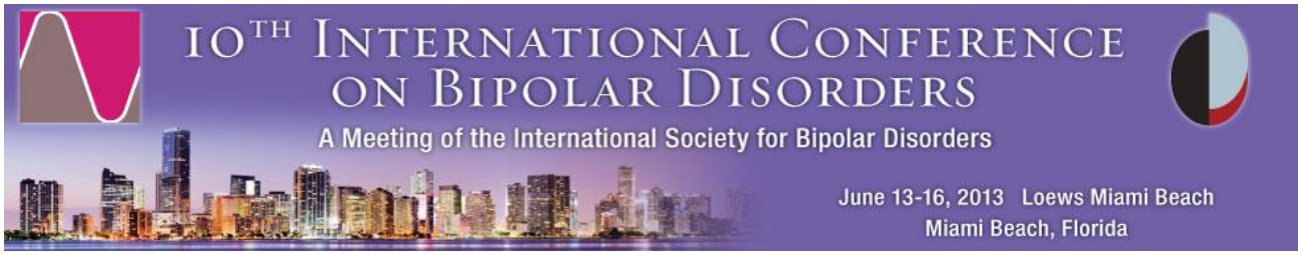

Keynote Presentation

Title: Genetic Analysis of Relevant Biological Pathways in Bipolar Disorder

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Abstract of the Presentation

As it has been the case with most complex genetic disorders such as bipolar disorder, progress in molecular biology has been slow and has identified a small number of common and rare risk genes contributing to the disorder. The genetic architecture of bipolar disorders seem to include a substantial polygenic component involving thousands of common alleles of very small effect, many of which increase susceptibility to different major psychiatric disorders. Confirming such small effects may not be feasible even with very large sample sizes (above 100,000 patients). It may thus be more informative to know if these small effects are concentrated in genes relating to a specific clinical subgroup or to a particular biological mechanism, or implicating specific biological pathways. Three examples of this strategy will be described:

1°) The first one involves the identification of "candidate symptoms," rendering diagnostic entities presumably more likely to have a similar and simpler genetic basis. The candidate symptom approach has led to the identification of early-onset bipolar disorder (Leboyer et al, 2005) resulting in the identification of two genes involved in the phosphoinositidyl signalling pathway and of the association with a SNA25 promoter variant, through a genome-wide-association study (GWAs) (Etain et al, 2010 ; Jamain et al, subm).

2°) The second one relies on the genetic exploration of the severely disrupted circadian rhythms observed among bipolar patients. Exploration of candidate biological system, such as melatonergic pathway revealed mutations correlated with a decreased activity of the protein encoded by the gene acetylserotonin methyltransferase (ASMT) which is the last enzyme of the melatonin synthesis. Haplotype analysis of the gene showed a significant association with bipolar disorder (Etain et al, 2012). While several analysis of circadian genes (RORA, TIMELESS) revealed associations with specific chronotypes observed in bipolar disorders. Our results and those reported in depression strongly suggest that the melatonin biosynthesis might play a significant role in susceptibility to bipolar disorders. Nevertheless, further studies are required to understand the impact of a melatonin/clock defect on human behaviour and to determine how this intermediate clock related phenotypes might orientate therapeutic strategies.

3°) The third one is based on the repeated demonstration of inflammation and immune dysfunctions in bipolar disorder. We have recently started to describe a pathway implicating Human Endogenous Retro-virus (HERVs) which are part of the human genome, and evolve differently from « classical genes », as part of the (retro) transposable elements. In case of reactivation, such endogenous retrovirus by producing a toxic retroviral envelope (Perron et al, 2012) induce an immuno-inflammatory cascade. This reactivation is possibly induced by environmental events such as early infections by toxoplasmosa Gondii known to be associated with bipolar disorder (Hamdani et al, 2012). The magnitude of this reactivation along with its immuno-inflammation consequences is possibly modulated by immuno-genetic background in a fine tuning interaction which will be described. Altogether, independent studies on immuno-inflammation, immuno-genetics, retro-viruses, and infectious diseases enable us to depict a new relationship between immuno-inflammation and bipolar disorder. If confirmed, this will enable the identification of pathophysiological mechanisms and biomarkers paving the way towards innovative therapies (Leboyer et al, 2012).

However, complex multifactorial neuropsychiatric diseases such as bipolar disorders cannot be reduced to either predominantly synaptic, circadian or immuno-inflammatory defect since interplays between several components are likely to be dynamically impacted and retroact on each other both in time and in space across several levels (from metabolic to structural aspects). The rapid accumulation of considerable amounts of biological information makes it possible to investigate biological pathways associated with complex diseases at a systems level, the ultimate of personalized medicine. But this requires the production of biologically relevant dynamics data feeding into biological modelling approaches capable of predicting molecular and physiological consequences that can then be experimentally verified (Turck and Iris, 2011, Bio-Modeling Systems).

About the Foundation FondaMental.

FondaMental is a foundation for scientific cooperation created in June 2007 by decree from the Ministry of Higher Education and Research, within the context of the "Thematic Research and Treatments Networks" (RTRS). The Foundation has for ambition to defeat psychiatric diseases and the hardships they generate. To this end, the foundation harnesses a scientific and medical network of excellence that most particularly addresses those pathologies regarded as amongst the most invalidating: schizophrenia, bipolar disorders, severe autism (Asperger's syndrome), resistant depression, suicidal behaviors and post-traumatic stress. The Foundation's strength lies in its unique ability to merge research and clinical care to better understand better treat and prevent psychiatric diseases.

To meet the challenges imposed by these pathologies, the Foundation FondaMental attached itself to four missions:

- Favor early diagnosis through the inception of a national network of Expert Centers;
- Accelerate research in psychiatry at the national level;
- Educate and train health professionals and all actors implicated;
- Better inform the public in order to change the perception of mental diseases.

For more information, please visit www.fondation-fondamental.org

About Bio-Modeling Systems (BMSystems):

Bio-Modeling Systems, an innovative company founded in 2004, is the first and, to date, only company to successfully create in-silico heuristic models validated in-vivo. BMSystems' heuristic models, built by its biologists using an integrated IT solution called CADI ™ (Computer Assisted Deductive Integration) have led to discoveries, patents, and operational businesses in the fields of infectious diseases, immunology, neurology, psychiatry, oncology, dermatology and innovative bioprocesses for industrial biotech. BMSystems' models describe the biological phenomena involved in pathological states and provide new mechanisms to explain the cause of certain diseases, identify and select predictive biomarkers, offer new combinations of molecules and new therapeutic strategies, thereby contributing to the development of Mechanism-Based Medicine.

This i) results in a significant reduction of short-term risks in therapeutic developments, ii) provides a new life to clinically well characterized molecules while iii) concurrently preserving the medium term potential for new drugs development.

Bio-Modeling Systems has made central and peripheral neurological diseases its primary axis of research, embodied by on-going programs and filed patents:

- DECIUS: On-going European collaborative research program addressing the identification of biomarkers attached to chronic anxiety. The first scientific results have been obtained and will be formally presented in May, at the 9th International Workshop on Computational Neuropsychiatry in Munich.
- IDUNN: Successfully completed research program that led to a novel combinatorial treatment addressing age-related degenerative disorders, such as Parkinson's disease; Patent pending.
- WO/2010/029131. Combinatorial treatment for psychiatric disorders; Patent ownership shared with the CEA and exclusively licensed to a start-up created at the CEA in 2013.
- PSY-LYCO: On-going research program with the FondaMental Foundation to decipher the immuno-inflammatory mechanisms that could give rise to psychiatric diseases, such as bipolar disorders and schizophrenia, and thus open novel therapeutic strategies.
- FIBROMYLAGIA. Identification of the mechanisms leading to the disease; program initiated.

BMSystems has successfully completed programs in infectious diseases, oncology, neurology, psychiatry, dermatology, immunology and metabolic disorders which led to patents and the creation of new companies exploiting these patents.

For more information and access to presentations & publications, please visit http://www.bmsystems.net.

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