Report Targeted Expert Meeting Basic and Clinical Neuroscience
11-12 September 2009, Istanbul, Turkey

Coordinator: Martien Kas, The Netherlands
Co-chair: Eero Castrén, Finland

I. Summary of main lectures

Topic 1
Translational research for psychiatric disorders; 'of mice and men'

Main lecturer: David Collier, United Kingdom
Discussants: Klaus-Peter Lesch, Germany
Wolfgang Wurst, Germany

Molecular genetic analysis of complex neuropsychiatric disorders such as schizophrenia and depression has been criticized for failing to provide benefits to patients. One means of achieving translational benefit is to produce genetic animal models of a disease which can be used to develop new therapeutic approaches and better understand pathology. Because of this, animal models are highly relevant to the functional testing of neurobiological mechanisms underlying psychiatric disorders. There are two main means to achieve this, the use of phenotypically-based animal models in which specific lines of inbred mice are selected as genetic models for the disease, by cross-species alignment of disease-related traits or endophenotypes, and the reverse approach, in which mice are engineered to possess a parallel genetic disease risk factor to humans, such as a genetic knockout or duplication. However, the complexity and heterogeneity of these disorders makes it very difficult to develop animal models based on the criteria of face, predictive and construct validity. The first approach is based on the notion that in different species, the same genes may independently give rise to alleles with similar functional and phenotypic effects, either under similar selection or through similar genomic mechanisms, which may not always be true. The second approach is hampered by limited knowledge of the underlying genetics of complex disorders. Genome-wide association studies have revealed novel susceptibility genes for a wide variety of neuropsychiatric disorders and are opening novel opportunities for the development of animal models based on both high risk (e.g. CNVs) and low risk (e.g. common SNP variation) alleles. For example, the discovery of the role of copy number variants in disorders such as schizophrenia, epilepsy and autism provide the opportunity for the rapid development of mouse models with equivalent deletion or duplication of the same set of genes, which have immediate face value. This session addresses the opportunities and pitfalls for translational animal models of psychiatric disorders.

Topic 2
Drug target discovery and validation using animal models for psychiatry

Main lecturer: Todd Gould, USA
Discussants: Enrico Domenici, Italy
Berend Olivier, The Netherlands

Bipolar disorder afflicts approximately 1–3% of both men and women, and is coincident with major economic, societal, medical, and interpersonal consequences. Current mediations used for its treatment are associated with variable rates of efficacy and often intolerable side effects. While preclinical and clinical knowledge in the neurosciences has expanded at a tremendous rate, recent years have seen no major breakthroughs in the development of novel types of treatment for bipolar disorder. Approaches to develop novel treatments for

psychiatric disorders generally, and bipolar disorder specifically, was discussed. Deliberate (i.e. not by serendipity) treatments may come from one of two general mechanisms: (1) Understanding the mechanism of action of current medications and thereafter designing novel drugs that mimics these mechanism(s); (2) basing medication development upon the hypothetical or proven underlying pathophysiology of the disease. In regards to the first approach, data from preclinical studies in rodents indicate that lithium may exert some of its antidepressant and antimanic effects through inhibition of the enzyme glycogen synthase kinase-3 (GSK- 3). Additionally, there is also extensive clinical evidence indicating that lithium is effective in reducing the risk of both attempted and completed suicide. While suicide can not be modelled in rodents, approaches that assess mouse behaviour in tests relevant to well validated endophenotypes (deconstructed components of complex behavioural phenotypes) associated with suicide including aggression and impulsivity may be useful. These endophenotypes can be used in combination with human genetic, biochemical, and pharmacological findings in suicide research. In regards to the second approach, recent genome-wide association studies have implicated polymorphisms in a small number of genes with a mood disorder diagnosis. Behavioural characterization of mice that harbour mutations in these genes may reveal their roles in mood disorder pathophysiology, leading eventually to therapeutics that target the underlying disease pathophysiology, rather than symptoms.

Topic 3
Gene x Environment interactions; novel mechanisms underlying behavioural regulation

Main lecturer: Cornelius Gross, Italy
Discussants: Eberhard Fuchs, Germany
Vaishnav Krishnan, USA

Recent studies have shown that gene by environment (GxE) interactions are relevant for the development of psychiatric disorders. Mice can be used to model GxE risk factors for psychiatric traits (to test novel candidate genes, to better define the behavioral and neural traits involved, and to identify molecular mechanisms as a way to find new drug targets). In this seminar, several procedures and genes were discussed that have been used to model psychosocial stress in humans carrying common polymorphisms. For example, mice have been used to model the 5-HTTLPR x stress risk factor for depression-related traits. This will encompass two environmental manipulations applied to heterozygous 5-HTT knockout mice (which has been used to approximate the 5-HTTLPR S allele). The use of high and low maternal care as a model for adverse early life experiences was introduced. Furthermore, other models, such as adult psychosocial stress as a model for adult life stress events were discussed. It was shown that these different forms of environmental events interact with the 5-HTT deletion in mice. However, these two GxE interactions highlighted how despite sharing the same genetic predisposing factor, they are likely to involve different molecular mechanisms. The hope is that these examples will help to highlight some of the potential and problems of using rodent models to track down the molecular mechanisms of human GxE risk factors for psychopathology.

II. Recommendations for further research

Following these main lectures and subsequent discussions, we agreed on a set of guidelines/statements that we think might help guide further research in this area and are particularly promising or worthy of mention.

- Animal models should be focused on clearly defined intermediate phenotypes and/or endophenotypes rather than on anthropomorphised psychiatric symptoms or complex syndromes. Endophenotypes are trait phenotypes with a strong genetic basis, whereas intermediate phenotypes may not be strongly influenced by genetics, but nonetheless are still associated with disease and useful because they are considered directly causative of more complex behavioural phenotypes.

- Studying different animal' species should be encouraged, since they will contribute to research of different aspects of disorders (e.g. Drosophila for neuronal networks and zebra fish for neurodevelopment). Certain species will be preferred in view of possibilities to interfere in the genome, manipulation of the environment, application of pharmacology, and comparable neuro-anatomy. For example, for some applications higher mammals are preferred for studies on translatable endophenotypes.

- Molecular and cellular biological markers of psychiatric disorders can be studied in human stem cells differentiated into neurons; in particular, the induced pluripotent stem cell technology is important, since it allows the examination of differentiated neurons directly derived from the patient with a diagnosed disorder.

- Given good quantitative data in certain fields of neuroscience computational modelling is gaining traction and should be encouraged.

- Better insights in human pathophysiology will provide a basis for translational research of psychiatric disorders. This will require better characterized disease endophenotypes and/or intermediate phenotypes in humans, and improved understanding of the relationship of these endophenotypes and/or intermediate phenotypes to specific genetic variations. Bidirectional translation (humans to preclinical models; preclinical models to humans) will be necessary.

- The creation of mouse models of rare human genetic variants of relatively high effect size for specific disease-relevant intermediate phenotypes and/or endophenotypes may be a promising avenue to do translational studies. New whole genome sequencing tools are predicted to lead to the discovery of such mutations. Common, low effect size variants coming out of genome-wide association studies (GWAs) are also good candidates but were considered less promising; because it is less likely they will show a phenotypic effect in mice. However, GWAs studies may be valuable in identifying biological pathways which can be manipulated rather than individual genes.

- Integrative analysis of endophenotypes and/or intermediate phenotypes (e.g., anatomical, physiological, molecular, behavioural) is recommended, since it will contribute to the definition of phenotypic specificity in relation to, for example, genetic variations. This integrated analysis should go hand-in-hand with psychiatric assessment of these phenotypes.

- The development of reverse translational paradigms (Perry et al., Arch. Gen. Psychiatry, 2009) that can be used in both humans and animals will contribute to further study the neurobiological mechanisms underlying psychiatric disorders.

- Sex effects are a highly promising and neglected area of research to help unravel the mechanisms of mental illness. More resources should be put into studies that include female and male subjects, both in human and animal models.

- Age has received too little attention in the mental illness field and could be a powerful variable to better understand anatomical, physiological, and molecular risk factors. Particularly important were considered brain changes associated with early postnatal development, adolescence, and old age. For example, there will be certain time windows during which relevant epigenetic mechanism may alter normal brain development and functioning.

Furthermore, based on these recommendations we have generated a symposium proposal for the next ECNP congress entitled 'From gene to phenotype: using genetics to define intermediate phenotypes in humans and animal models'.

In addition, we have identified that sex differences are an important factor that should receive more attention in the field of psychopathology; for that reason, we would highly suggest a next TEM on this topic.

Participants of the TEM Basic and Clinical Neuroscience 2009:

Name	Friday 11 September	Saturday 12 September
Martien Kas	Yes	Yes
Eero Castrén	Yes	Yes
Todd D. Gould	Yes	Yes
Enrico Domenici	Yes	Yes
Berend Olivier	Yes	Yes
David Collier	Yes	No
Klaus-Peter Lesch	Yes	Yes
Wolfgang Wurst	Yes	part time
Cornelius Gross	Yes	Yes
Eberhard Fuchs	Yes	Yes
Vaishnav Krishnan	Yes	Yes
Stefan Borgwardt	No	Yes
Andreas Heinz	No	Yes
Björn Johansson	Yes	Yes
Nina Karpova	Yes	Yes
Sulev Köks	Yes	Yes
Jean-Luc Martinot	Yes	Yes
Jonathan Mill	Yes	Yes
Kevin Mitchell	Yes	Yes
Nick F. Ramsey	Yes	Yes
Zoltan Sarnyai	Yes	Yes
Oliver Stiedl	Yes	Yes
Ron Stoop	Yes	Yes
Valter Tucci	Yes	Yes