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Transgenic animal models in translational biomedicine*

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Recent revolutionary transgenic approaches have significantly increased the power of translational biomedical research. For instance, genetic animal models of brain disorders such as schizophrenia, bipolar disorder, depression, Parkinson's disease and attention deficit hyperactivity disorder have been created. Such animal models are the valuable tools for the study of aetiology and pathogenesis of human disorders, as well as for the early pre-clinical drug development in pharmacology. In this article the advantages of transgenic mouse and rat models for studying and modeling human disease are reviewed. At the Saint Petersburg University there is a library of the most relevant animal models of neuropsychiatric disorders, including mice lacking the dopamine transporter (DAT-KO mice) and rats without brain serotonin (tryptophan hydroxylase 2 knockout, TPH2-KO). This collection of psychopharmacology-relevant mutant models is planned to be routinely used in future collaborative studies with Russian and international drug development institutions and companies.

Keywords: disease modeling, knockout animals, knock-in animals, transgene techniques, mice, rats, Psychopharmacology, dopamine, trace amines.

While numerous discoveries in various fields of Medicine have been made by means of using normal animals in the past, recent revolutionary transgenic approaches have significantly increased the power of translational biomedical research. In coming years, the use of genetically modified mice as models of human disorders will remain the frontier of research in Pathology and in pre-clinical Pharmacology of human disorders. Very recent opportunity to develop genetically-modified rats is an additional factor that significantly enhances scientific novelty and value of this trend of research. Genetic animal models of brain disorders such as schizophrenia, bipolar disorder, depression, Parkinson's disease and attention deficit hyperactivity disorder (ADHD) — are the valuable tools for the study of aetiology and pathogenesis of such disorders. They are also critical in studies aimed at the search for new methods of pharmacological correction of these conditions (*in vivo* screening for novel antipsychotics, mood stabilizers, cognitive enhancers, anti-parkinsonian, antidepressant and anxiolytic drugs), and helpful in increasing our knowledge about the development, structure and function of various neurotransmitter systems of the central nervous system. Similarly, studies involving genetic animal models of other human disorders (such as cancer, cardiovascular diseases, sugar diabetes and obesity) are of high

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demand in modern pre-clinical Pharmacology. With the costs of drug development rising sharply, drug companies are exploring new *in vivo* animal models to guide early pre-clinical drug development. Despite a plethora of available technologies to discern biological mechanisms *in vitro*, the relevance of such technologies is only as good as the physiological models to which they are applied. A complete picture of the biological interactions occurring in drug action and toxicity requires the examination of intact multicellular organisms. Animal models have physical characteristics or suffer from illnesses similar to those seen in humans. They allow comparisons to be drawn between animal and human organism, in order to deepen the understanding of human body functions and dysfunctions. Mice, rats and humans share about 99 % of genes making rodents good model organisms for studying human gene function in health and disease. Both mice and rats are relatively small, easily handled, have a short generation time, and are genetically inbred. Transgenic mouse models have become powerful tools for gene-based drug discovery and development. Their reproductive and nervous systems resemble those of humans, and they suffer from many similar diseases and syndromes, such as cancer, diabetes mellitus and even anxiety. Manipulating their genes can lead them to develop other diseases that do not naturally affect them, and as a result research on mice has helped understanding of both mechanisms of human health and the causes of disease. Furthermore, many human diseases including major mental disorders can be modeled in the mouse, making it an ideal platform to accelerate the validation process of drugs in the discovery pipeline. These models are invaluable during the early stages of drug discovery and development, particularly for the identification and validation of novel drug targets, optimization of lead compounds, and assessment of risk and toxicity. It is not surprising therefore, that Drs. Martin Evans, Mario Capecchi and Oliver Smithies won the 2007 Nobel Prize in Physiology and Medicine for work that made "knockout" (loss of function) and "knock-in" (gene replacement or addition) in mice possible.

However, while mice have proven to be as extremely useful rodent model and techniques have been developed for routine disruption of their genes, in many circumstances, rats are considered a superior laboratory animal for studying and modeling human disease. Rats are physiologically more similar to humans than are mice. It is widely believed that the rat is a better model than the mouse for many human diseases, and particularly for neurological, behavioral, and addiction disorders. In addition, rat models are superior to mouse models for testing the pharmacodynamics and toxicity of potential therapeutic compounds, partially because the number and type of many of their detoxifying enzymes are very similar to those in humans. Their larger size makes rats more conductive to study by instrumentation, and also facilitates manipulation such as blood sampling, catheter implantation, and performing brain surgeries. Because of their larger size it is also much easier to perform surgical procedures and monitor physiological states in rats than in mice.

In our laboratory at the Saint Petersburg University we have a collection of the most relevant animal models of neuropsychiatric disorders. Particularly, we have several mouse and rat models with specific alterations in different components of the frontal cortex-basal ganglia circuitry. By using these models, we are able to better understand the contribution of various neurotransmitter systems in manifestation of mental pathology- related processes. Studies involving mice lacking the dopamine transporter (DAT-KO mice) provided numerous advances on the role of dopamine in various physiological and pathologi-

cal processes and effects of clinically used drugs [1]. Recently we significantly extended these studies by developing DAT-KO rats [2]. Rats without brain serotonin (tryptophan hydroxylase 2 knockout, TPH2-KO) represent another exciting model for psychopharmacological research. Several intriguing observations have been made on mice and rats lacking trace amine-associated receptors (TAAR1, TAAR2, TAAR5, TAAR6, TAAR8, TAAR9) highlighting important physiological roles of trace amines and their receptors that are emerging as novel targets for Pharmacology of several disorders [3]. This library of Psychopharmacology-relevant mutant models at the Saint Petersburg State University will be routinely used in future collaborative studies with Russian and international drug development institutions and companies.

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