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EDITORIAL

Translational medicine: from disease- and patient-specific stem cell research to clinical trials and back again

Matthias Jung[1] · **Dan Rujescu**[1]

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Psychiatric diseases such as Alzheimer's disease (AD) are among the major causes of suffering and death in the USA, in Europe, and in other industrialized countries as well. The number of patients is growing in correlation with the number of elderly people in our society. Particularly, the risk for Alzheimer's disease is strongly elevated with the age of people. Accordingly, there is a growing interest in our aging society. The United States National Institute of Health provides a database (clinicaltrials.gov), which currently lists many clinical trials analyzing a variety of chemical compounds for the treatment of AD. There are promising results in preclinical studies and early clinical trials for therapeutic drugs or antibodies, but the most of the studies have been withdrawn or failed to work in patients. The high number of failed clinical trials highlights the fact that drug development is predominantly affected by the difficult translation of animal models into the human system. Psychiatric diseases most often are multifactorial. Research in the field of human genetics revealed that DNA variations including copy number variations (CNVs), single-nucleotide polymorphisms (SNPs), and functional homozygous mutations confer a risk for psychiatric diseases. DNA variations influence their onset, progression, and their treatment. Genome-wide association studies (GWAS) recently described by a variety of genetic loci in European and American cohorts. The technological advance in the field of RNA and DNA sequencing will further accelerate and enlarge the execution of such studies. Additionally, meta-analysis projects and epidemiological research provide strongly growing scientific fields for psychiatric diseases. Currently, many studies are carried out focusing on DNA variations as risk factors, which may provide a target for drug development. Even the analysis of risk loci with unknown function provides a target for drug development by the application of phenotype-based approaches. New promising approaches for drug development arise from the analysis of the disease- and patient-specific genetic background. The complex and multigenic mechanisms, which confer a risk for certain diseases, are poorly understood, but DNA variations as well as mutations found in psychiatric patients are suggested to provide potential targets for drug development. Cellular two-dimensional and organotypic three-dimensional stem cell-based in vitro models hold a great promise for the functional characterization of DNA variations necessary for further advance in the field of translational medicine aiming at the transfer of neuroscience research from bench to bedside. Rodents are broadly and increasingly applied for disease modeling, but notably these animals poorly mimic complex human diseases. Even though at a first glance organ development in rodents and humans is roughly comparable, there are many significant differences in molecular and cellular mechanisms regulating development and function of human organs, especially of the human brain. Accordingly, the analysis of disease mechanisms is limited by these species-specific differences. One can conclude that species-specific differences most probably represent a major road block during drug development. The same holds true for toxicological testings. Many tests in rodents or other animals did not faithfully represent the human response.

Stem cell-based in vitro models are very different from cell lines-based in vitro models. The majority of cell lines lost their natural characteristics due to their

✉ Dan Rujescu
dan.rujescu@uk-halle.de

[1] Department of Psychiatry, Psychotherapy, and Psychosomatics, Martin-Luther-University Halle, Julius-Kühn-Str. 7, 06112 Halle, Germany

immortalization. Accordingly, the analysis of mature and functional properties in cell lines is often restricted to a certain aspect or basic cellular signaling pathways. More advanced disease-specific stem cell models combine basic cell models with disease-specific aspects. Disease-specific aspects may be reflected by mimicking the (1) differentiation and maturation status of certain cells, (2) the specific cell composition of a certain tissue, (3) physical impulses necessary for maturation, and (4) the 3D structure of certain tissues. Disease- and patient-specific stem cell-based in vitro models require the application of a certain stem cell type, which has been termed induced-pluripotent stem cells (iPS cells). Likewise human embryonic stem cells, iPS cells show an unlimited proliferation and the capability to differentiate into every cell type of the human body. In 2012, the Nobel Committee awarded Shinya Yamanaka and Sir John Gurdon the Nobel Prize in Physiology or Medicine "for the discovery that mature cells can be reprogrammed to become pluripotent." Today, many laboratories have successfully generated iPS cells from different cell types using different innovative methods. The scientific field of disease-specific stem cell models recently revealed different approaches focusing different tissue-related aspects of diseases. Tissue-engineered nerve grafts have been described for peripheral nerve regeneration. Modeling the blood brain barrier (BBB) was described as a model for studying Alzheimer's disease, but BBB models offer the opportunity to study many other diseases affecting proper BBB functionality such as epilepsy and multiple sclerosis. There is also the promising opportunity to study pharmacological aspects of drugs in BBB models. Brain models for neurodevelopmental psychiatric disorders and traumatic brain injury have been established with the focus on developmental patterning of cells and cell populations. Recent approaches in the field of stem cell research focus on the establishment of high-throughput screening (HTS) techniques, which requires standardization and miniaturization of stem cell-based in vitro models. Promising technical advance has been described for the application of microfluidic systems enabling various chemical and physical stimuli suitable for HTS. In conclusion, it is not surprising that disease- and patient-specific stem cell research is one of the fastest-growing scientific fields because it provides great potential to revolutionize the field of drug development and disease modeling, especially in the case of psychiatric diseases.