European brain research: Addressing translational gaps

Sabine Hölter, Coordinator of the European Brain Research Area cluster PREMOS, calls attention to the translational value of animal models in brain research

More than one out of two Europeans are currently living with a brain disorder, causing tremendous societal and financial costs that call for effective investment in European brain research. This must involve the use of animal models to better understand disease etiologies and develop strategies for prevention and therapy.

The European Brain Council (EBC) has worked for two decades to promote brain research with the ultimate goal of improving the lives of Europeans living with brain conditions. To streamline and better co-ordinate brain research across Europe, while fostering global initiatives, EBC brought together the Human Brain Project, which is now transitioning to EBRAINS, the EU Joint Programme on Neurodegenerative Diseases and the ERA-Net NEURON under the EU-funded project the European Brain Research Area (EBRA).

To promote cooperation and exchange in all areas of brain research, EBRA has launched six "clusters", (1) including the Predictive Model Systems or PREMOS cluster. Our ambition is to build a broad coalition, ensuring the translational value of animal models in brain research wherever they cannot be replaced by alternative methods.

We need to join forces

The use of animals for scientific purposes is a longstanding practice in brain research. Nowadays, many brain research questions can be studied using alternative methods addressing the micro level of the brain (i.e., cells and synapses), but cellular systems or organoids cannot model complex behaviors or the complex physiology of a living organism. On the macro level, in-vivo studies in animal models necessary to develop/investigate medical treatments are still needed in brain research.

But how can we ensure that the models used are relevant?

The main gaps preventing the translation from laboratory research to the clinic are:

(i) That the majority of psychiatric and neurodegenerative disorders are complex and their origins unclear.

(ii) Clinical diagnoses are usually not based on neurobiology thus hampering the transfer of human clinical findings to the usage in preclinical studies.

(iii) The models used are often not sufficiently described and validated.

The PREMOS cluster has developed several ideas to address these gaps.

To better understand the origin of brain disorders, we need to improve the transfer of human clinical findings to the usage in preclinical studies on a larger scale and better involve patients in preclinical research discussions, as patients and clinicians do not always concur on what is a priority focus. It should be mandatory that human studies provide quantitative and biological data to optimize this transfer.

Genetic and environmental contributions to brain disease etiologies

We also need to better understand the genetic and environmental contributions to brain disease etiologies, and to better understand the early life period, including adolescence, both from a biological neurodevelopmental point of view and from a clinical perspective as this widens the scope for preventive measures against brain health problems in adulthood.

One way to make use of already existing resources and to prevent unnecessary duplication (and use of animals) would be to reinforce access to already existing animal models and their detailed information, including negative results, for example, available for IMPC models, through national, European and global repositories. Genetic and phenotypic cross-species comparison of such comprehensive data sets could, for example, help to better understand disease etiologies of neurodevelopmental disorders, because NDD patients do not only suffer from mental health disturbances, but they are also at high risk for medical comorbidities that interfere with quality of life and life expectancy. Trying to understand the shared genetic basis for such medical comorbidities in appropriate animal models could be impactful with respect to diagnosis, early disease detection and patient management and treatment.

Cross-species comparisons must be carried out more widely

To ensure that basic neuroscience discoveries in animal models are relevant for translation, the biological mechanisms and functions studied in a model must be similar to humans. Thus, to validate a model, cross-species comparisons must be carried out more widely, including brain function, symptom, target and drug response similarity. Often animal models display only a subset of the features observed in humans as they are limited to a controlled environment and specific genetic background. Additional experiments or different study designs are needed to overcome these limitations.

Preclinical evidence justifying clinical trials should be based on the tiered use of multiple models from different species to increase the predictive value of the preclinical evidence for translational success. Multiple doses should be investigated for the preclinical assessment of treatment effects, ideally over longer time periods. Authors, Reviewers and Editors should enforce clear statements about study limitations and the scope of conclusions, as well as the use of official nomenclature and detailed model descriptions.

To enhance the quality of preclinical data, training, quality control and quality management need to be improved. Further automation of assessments can also improve reproducibility, as it can reduce variability and allows the provision of long-term data, for example, on the effects of therapeutic interventions, which, in turn, enables the development of translational digital biomarkers and identification of early intervention time points.

Researchers with different expertise from basic and clinical neuroscience, animal and human genetics, bioinformatics and data science need to work together and closer interactions between preclinical scientists, clinicians and patients need to be fostered to ensure the translational value of animal models in brain research. Let's join forces across disciplines for the benefit of patients and to further reduce the number of animals needed!

References

(1) A cluster is understood as an association of research projects that can be directed towards basic research, clinical research and/or methodological approaches under a common topic and disease area.

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