Neuroscience Applied 3 (2024) 104083

Contents lists available at ScienceDirect

Neuroscience Applied

journal homepage: www.journals.elsevier.com/neuroscience-applied

Addressing pitfalls in translation

Translational failures in neuropsychiatry have been widely discussed for quite some time now, prompting the development of several suggestions for solutions. Prominent solution suggestions include enhancement of preclinical study design and data quality, preregistration of preclinical studies, and improved back-translation of clinical diagnoses for preclinical usage based on the RDoC framework.

This Special Section attempts to highlight what can be learnt from less well-known solution suggestions that have been developed by PREMOS (Predictive Model Systems), a cluster supported by the European Brain Research Area (EBRA) (Hölter, 2022). While taking methodological issues into account, these suggestions focus more on advancing translation by facilitating mechanistic insights and improving our understanding of disease etiologies. This will require broadening our perspective, and also our approach in disease-related investigations using animal and other model systems in preclinical neuropsychiatry.

Many of these suggestions were developed by interdisciplinary teams working together in the field of mouse genetics, because these scientists also took seriously the seminal work of Crabbe, Wahlsten and Dudek in 1999 that demonstrated the limits of reproducibility in a cross-laboratory study (Crabbe et al., 1999). As a consequence, robustness of readouts as well as their clinical relevance became key criteria for the choice of tests used by this community. They were applied for the comprehensive characterization of all organ systems in knockout mouse models that were systematically generated to elucidate mammalian gene function in an international effort. In successive European (Hrabe et al., 2015; Mandillo et al., 2008) and international (Groza et al., 2023) consortial efforts this community worked on questions of experimental design, harmonization of experimental protocols and other differences in laboratory conditions and animal facilities (and the limits thereof), the development of standard operating procedures and their cross-laboratory validation, as well as on data and metadata documentation, quality control, analysis, and public availability.

But beyond all of these very important methodological aspects that need to be considered to ensure good data quality in preclinical model systems, biological relevance was naturally always a key concern. One example of this is the fact that both sexes were included from the beginning in 2003 in this large-scale phenotyping endeavour. As a result, the IMPC database constitutes an unmatched publicly available resource of not only male, but also female mouse phenotypic data. This is noteworthy, since an educational session during the 35th ECNP congress in Vienna in 2022 highlighted that sex is still not systematically considered as a biological variable in basic neuroscience and preclinical studies, with potentially detrimental consequences for the translational success of the insights gained. Maybe the development and validation of test readouts for female mice that are clinically relevant in neuropsychiatry require more efforts, but it should be feasible.

Broadening our perspective and approach does not only mean (i) consistently including the female sex at all stages of the translational process, but also (ii) embracing the naturally occurring diversity of disease symptoms that might be due to genomic or environmental factors, or their interactions, and (iii) considering brain-body interactions. In spite of decades of calls for more interdisciplinary research, most studies published today are still very focused instead of a broader consideration of multiple body systems that might be clinically relevant in the context of disease comorbidities. Similarly, preclinical studies including environmental factors like diets or considering genetic factors are still rare, although they could enhance our mechanistic understanding as well as target identification.

One of the main conclusions of the EBRA PREMOS cluster was that preclinical evidence for clinical trials should be based on a broad range of evidence, for example on a tiered use of multiple models and doses. Model validity, i.e. ensuring the similarity of biological mechanisms and functions of the model used to humans, is the prerequisite for enhancing the chances of translational success of any findings obtained in model systems. Genetic, genomic and phenotypic cross-species comparisons would be helpful for ensuring model validity.

The different contributions to this Special Section are individual examples for the inclusion of potential translationally relevant aspects that have so far largely been ignored as outlined above. “GPR101 loss promotes insulin resistance and diet-induced obesity risk” (Garrett et al., 2023) is an original article investigating the therapeutic potential of a receptor predominantly expressed in the hypothalamus. It looks at multiple body systems and employs a dietary challenge. The original article “Co-expression of prepulse inhibition and schizophrenia genes in the mouse and human brain” (Garrett et al., 2024) leverages the large-scale genotype-phenotype information gathered in the IMPC resource and Allen Brain Atlas gene expression data for a cross-species comparison of a schizophrenia endophenotype considering both sexes. And last, but not least, the review article “Assessment of quality of life and wellbeing in mouse preclinical research – A scoping review” (Sanz et al., 2024) identifies the most used quality of life and wellbeing measures and outcomes assessed in recent mouse research. It proposes approaches to develop a composite of measures in mice which could improve the translational potential of these particularly relevant outcome measures in human clinical trials.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

https://doi.org/10.1016/j.nsa.2024.104083
Received 30 January 2024; Received in revised form 3 July 2024; Accepted 4 July 2024
Available online 4 July 2024

the work reported in this paper.

Acknowledgement

This work has been supported by the German Federal Ministry of Education and Research during the initial phase of the German Center for Mental Health (DZPG), grant 01EE2303E.

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Handling Editor: Prof. A. Meyer-Lindenberg