Editorial

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Use of Computer-Aided Modelling To Re-Engineer CNS Medication Research and Development

Erica Melena*

Editorial Office, Journal of In Silico & In Vitro Pharmacology, London, UK

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Corresponding author: Erica Melena

publisher@imedpub.com

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Editorial

It's difficult to turn biological knowledge into helpful treatment actions for patients. Because the brain is such a complicated organ with so many non-linear feedback pathways, neurology and psychiatry have one of the lowest success rates for clinical development of any indication. Furthermore, the brain is not as accessible as other organs, therefore biomarkers are limited.

Many experimental medications "treat" preclinical transgenic animal models of "CNS diseases" satisfactorily, only to fail in clinical trials later. Incomplete pathology, variable PK and metabolism of experimental medicines, distinct pharmacology on human vs rat targets, absence of critical shared genetic polymorphisms, and significant differences in neural circuits are all possible reasons for this translational mismatch.

Psychiatry and neurology longitudinal and cross-sectional clinical data with deep phenotyping are being collected and made publicly available to the scholarly community at the same time. These can be utilized in machine learning methodologies to train artificial intelligence networks.

However, the number of conceivable combinations of "confounding" factors, such as age, underlying comorbidities, genetics, Comedications, and disease stage, significantly outnumbers the number of accessible patients, raising questions about the generalizability of AI or ML predictions.

Previous research has found that therapy programmes based on genetic risk factors in patient groups are more likely to succeed. However, the development of these new treatments, for which no or restricted clinical evidence is accessible by definition, is based on limited biological knowledge acquired from genetic risk factors, which is frequently derived from preclinical animal models. Furthermore, the time-dependent level of target engagement with various therapeutic modalities (which now includes biologics, gene therapy, and antisense nucleotides) adds to the drug development process's complexity.

A useful combination of modelling methods to address the issues of CNS R&D is combining Physiology-Based Pharmacokinetic (PB-PK) modelling (what does the body do with the drug?) with Quantitative Systems Pharmacology modelling (what does the drug do to the body?)

We propose to re-engineer the R&D process by building advanced and complex computer models based on current understanding of biology and informed by various clinical databases, similar to the use of Computer-Aided Design in Engineering, where a prototype is fully developed and tested in silico before being physically implemented.

Such a platform must be built step by step, with the integration of various modelling modules using a multi-scale approach, in which intracellular processes in different brain cell types (for example, the formation and degradation of misfolded tau protein) must be combined with the impact on system variables (for example, the impact of tau oligomers on voltage-gated ion channels, action potential firing, and neuronal network synchronisation). This will allow researchers to connect biological processes commonly defined by biomarkers to functional results that can be used as a proxy for clinical measures.

The creation of such models necessitates a variety of soft skills, including cross-disciplinary interactions with domain experts, accurate conversion of scientific assumptions into equations, extensive literature searches for quantitative parameters, and database mining with a focus on the human patient.

Target validation using sensitivity analysis, optimization of the pharmacological profile of candidate therapeutics, identification of optimal dose and scheduling, (4) effect on biomarkers for target engagement, and (5) support clinical trial design by simulating both PK-PK and PD–PD interactions with comedications and relevant genotypes are some of the applications of such a platform in CNS R&D.

Another fascinating breakthrough is the concept of "synthetic virtual placebo patients," in which individual patients in the active

treatment arm's clinical trajectory is reproduced as if they were assigned to the placebo arm. This would allow for a reduction in the number of patients in a clinical trial by decreasing intrinsic variability, resulting in faster enrolment and availability of effective treatments.

In clinical practise, where Pk-PK interactions are well documented, but many currently recommended medication combinations have negative pharmacodynamic interactions, further implementations of this technique could improve rational polypharmacy counselling. Acceptance of this method could enhance the prescription landscape and patient responsiveness while lowering healthcare expenses.