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EDITORIAL

Re-engineering CNS drug discovery and development using computer aided modeling

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Translating biological knowledge into useful therapeutic interventions for patients is a steep challenge. Of all the indications, Neurology and Psychiatry rank among the lowest in success rate for clinical development likely because the brain is an extremely complex organ with many non-linear feedback circuits. In addition, the brain is not accessible to the same extent as other organs and biomarkers are limited.

Many experimental drugs can successfully "treat" preclinical transgene animal models of "CNS disorders", only to find out later that they fail in clinical trials. Possible reasons for this translational disconnect include incomplete pathology, different PK and metabolism of experimental drugs, different pharmacology on human vs rodent targets, absence of important common genotype variants and important differences in neuronal circuits (Geerts 2009). Also, most importantly many of the genetic constructs for developing preclinical models affect only a tiny minority of patients leading to a substantial disconnect between mouse and human pathology.

At the same time, a large amount of longitudinal and cross-sectional clinical data in psychiatry and neurology with deep phenotyping are being collected and made freely available to the scientific community. These can be used to train artificial intelligence networks in machine learning approaches.

However, the number of possible combinations of "confounding" factors, such as age, underlying comorbidities, genotypes, comedications, disease state far exceeds the number of available patients, casting some doubt on the generalizability of predictions made using AI or ML.

Previous studies have suggested that therapeutic programs informed by genetic risk factors in patient populations have a higher probability of success (Nelson, Tipney et al. 2015). However, the development of these new therapeutics for which by definition there are no or limited clinical data available, relies on limited biological knowledge from these genetic risk factors often derived from preclinical animal models. In addition, the time-dependent level of target engagement with different therapeutic modalities (now including also biologics, gene therapy and antisense nucleotides) adds additional complexity to the drug development process.

Combining Physiology-Based Pharmacokinetic (PBPK) modeling (what does the body do with the drug?) with Quantitative Systems Pharmacology modeling (what does the drug do the body?) is a powerful combination of modeling technologies to address the challenges of CNS R&D.

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

Such a platform need to be developed step-by-step with integration of various modeling modules through a multiscale approach where intracellular processes in different brain cell types (for instance, formation and degradation of misfolded tau protein) need to be combined with impact on system variables (in this example. the impact of tau oligomers on voltage-gated ion channels, action potential firing and synchronization of neuronal networks. This will allow to bridge molecular processes often described by biomarkers to functional outcomes that are proxy to clinical scales, useful for patients.

The development of such models necessitates a number of soft skills, such as cross-disciplinary interactions with domain experts, correct conversion of the scientific assumptions into equations, extensive literature search for finding quantitative parameters and mining of existing databases with a focus on the human patient.

Applications of such a platform in CNS R&D include (1) target validation using sensitivity analysis, (2) optimization

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of the pharmacological profile of candidate therapeutics, (3) 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.

Another exciting development is related to the concept of "synthetic virtual placebo patients" where the clinical trajectory of individual patients that are enrolled in the active treatment arm would be simulated as if they were allocated to the placebo arm. This would allow to reduce the number of patients in a clinical trial by limiting the intrinsic variability which in turn would accelerate enrollment and the availability of successful therapeutics.

Further applications of this approach could improve rational polypharmacy guidance in clinical practice – where Pk-PK interactions are well documented—but many currently prescribed drug combinations have negative pharmacodynamic interactions. Acceptance of this strategy could optimize the prescription landscape and improve patient response while reducing costs of healthcare.

I hope that the development of complex computerized models of human biology and pathology as pertaining to In Silico Pharmacology can become a catalyst for these many exciting and useful applications in R&D, not only in the particularly difficult area of CNS but for many other diseases as well.

References

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