From Big Data to Smart Data. How Quantitative Systems Pharmacology Can Support CNS Pharmaceutical R&D

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Objectives: Traditional bio-informatics tools are very powerful in elucidating correlations or associations between data and certain clinical endophenotypes from large sets of data. However correlation is not identical to causation and many clinical development programs have failed to support the one gene-one protein-one disease hypothesis.

Mental Health issues, including Alzheimer’s disease (AD) are rapidly becoming a major burden with only symptomatic treatments available and many more clinical trial failures. At the same time, extensive and longitudinal information of thousands of patients is currently being collected at a substantial cost.

Methods: In order to optimize the use of this information for developing successful therapeutic interventions, identifying protective lifestyles or defining subpopulations of patients that will respond to specific therapies, we need to convert this information into actionable knowledge. Quantitative Systems Pharmacology is a set of mechanism-based computer models of human brain circuits (i.e. virtual human patients) with relevant and actionable predictive outcome for CNS R&D, especially in terms of clinical trial development in Neurology and Psychiatry. The model includes formalized representations of domain expertise in CNS (neurobiologists, neuropharmacologists, imagers and clinicians), has over 30 targets in addition to 5 common human genotypes (such as COMTVal158Met, the s/l 5-HTT, the D2DRTaq1A1 allele and CACNA1C genotype derived from human imaging studies) and has the complete pharmacology of all CNS active drugs, including PK profile and metabolites. It is essentially a form of Physiology-Based Pharmacodynamic Modeling.

Results: We will show examples where we correctly and blindly prospectively predicted an unexpected clinical outcome suggesting that our QSP platform captures better the human clinical environment than preclinical animal models. In addition, we will explore possible hypotheses why some clinical trials in AD and schizophrenia failed.

Conclusions: Running virtual patient trials in silico, i.e. identifying which comediations or genotypes influence the dose-response of a new investigative drug can improve clinical trial success.