Application of Artificial Neural Networks to Infer Pharmacological Molecular-Level Mechanisms of Drug Evoked Clinical Responses

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The Roche Clinical Pharmacology Disease Modelling Group (CPDMG) aims to better understand the biological basis of observed inter-patient variability of the clinical responses to drugs administered both as monotherapies and in combination. Administration of drugs to human subjects drives widespread and diverse changes in their biology. However, the majority of these changes are NOT clinically relevant, generate noise and are a common source of false positive predictors of clinical response.

Clinically relevant drug evoked changes are those that mechanistically link direct drug effects on pharmacological targets to the downstream biological effects/effectors that actually drive clinically relevant patient-level responses, e.g., efficacy and/or adverse events. Roche has been using artificial neural networks to elucidate these molecular mechanisms. The predicted mechanisms are biologically explicit, directly inform design of experimental studies, and, strategies to adjust/modify responses. The methodology is systematic, knowledge constrained & data-driven (see Figure 1 for an overview of the approach) with the resulting mechanistic insights informing & synergising with other quantitative approaches such as exposure-response modelling.

Improved understanding of how our drugs drive clinical responses informs which combination dosing regimens (“right drugs”) specific patient populations (“right patients”) are most likely to benefit from. Drug evoked responses are driven by drug-molecular-target interactions that perturb target functions. These direct, "proximal effects" (typically activation and/or inhibition of protein function) propagate across the biological processes these targets participate in via “distal effects” to drive clinical responses. Artificial neural network based approaches are used by CPDMG to predict the mechanisms by which drug combinations evoke observed clinical responses. Over the last 5 years, CPDMG has successfully applied these approaches to inform key decisions across clinical development programs. Implementation of these approaches requires: (i) integration of prior relevant biological/clinical knowledge with large clinical and “omics” datasets; (ii) application of supervised machine learning (specifically, Artificial Neural Networks (ANNs)) to transform this knowledge/data into actionable, clinically relevant, mechanistic insights. In this presentation, key features of these approaches will be discussed by way of clinical examples taken from the field of oncology and cancer immunotherapy. This will provide a framework for outlining the current limitations of these approaches and how they may be addressed in the future.

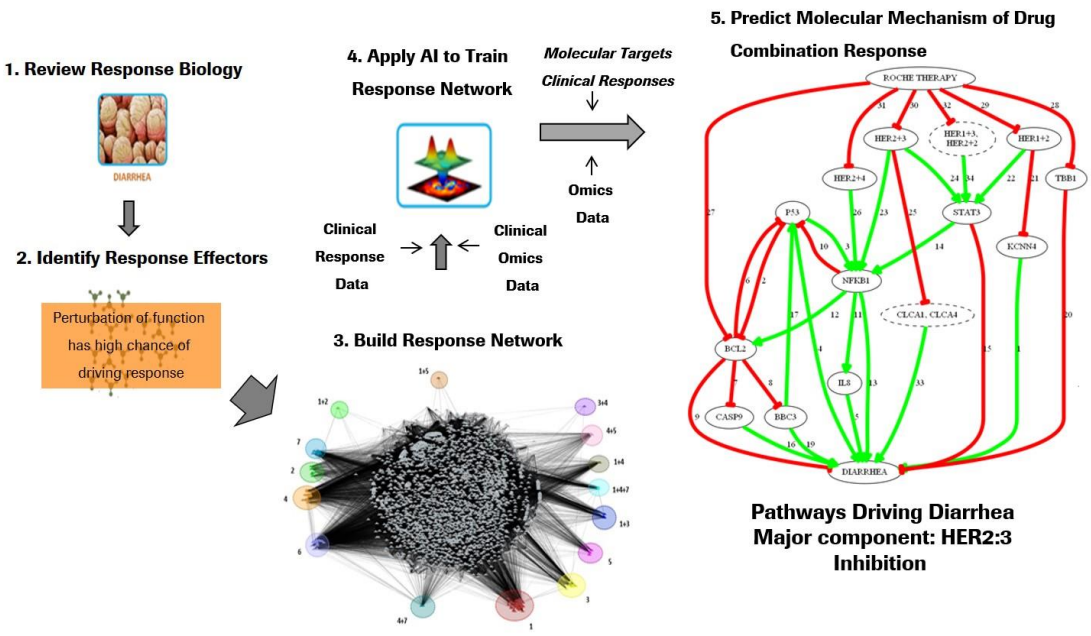

Figure 1 *Overview of Knowledge Constrained, Data Driven Methodology that leverages artificial neural networks (ANN)*