Integrated Network Modeling for Novel Target Searches and Better Predictive Models

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Objective: Introduce the concept of using GENome scale Metabolic (GEM) modeling and Integrated Network (IN) modeling to support improved searches for novel drugs and markers. Specifically to show how such modeling approaches leverage a broad array of omics data to give insight and decision support. Specifically, to introduce the point that IN models may allow systems pharmacology models that have higher predictive validity.

Methods: GEM models are used alone and with Protein-Protein INteraction (PPIN) Network and Transcriptional Regulatory Network (TRN) models to allow evaluation of the full set of known pathways and metabolites in searching for novel targets and markers, and also to ensure that systems models contain a complete set of the most relevant pathways.

Results: Results are given for several cases in Non-Alcoholic Fatty Liver Disease (NAFLD) and Non-Alcoholic SteatoHepatitis (NASH) (Mardinoglu et al., 2014), as well as for Hepatocarcinoma (Agren et al., 2014). We will review published results and up-to-date (unpublished) results of a number of clinical and other studies in which IN models have been calibrated and validated (Lee et al., 2016).

Conclusions: GEM and IN modeling represent an advance in integrating a wide variety of heterogenous omics and other data to yield insights not available via traditional approaches. These techniques also highlight the key pathway differences in healthy and diseased tissues (for example, between normal germ-line and cancerous cells). This provides a good check on model completeness for traditional mass-balance models based upon differential equations. The approach highlights relevant pathways that might otherwise not be included. Predictive validity is critical for decision support with high impact (Scannell and Bosley, 2016). The analysis provides models with better predictive validity.

References: