Model Aided Drug Invention Case Studies in Research: In silico differentiation for dual targeting PD-1 and Tim-3 in I/O, and predicting optimal drug properties of a bispecific biologic to maximize tissue targeting in OA

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Objectives: Two studies will be shown, in collaboration with a biotech and large pharma, respectively, that highlight examples of Model Aided Drug Invention (MADI) efforts, which include mechanistic PK/PD and QSP approaches, that have accelerated the discovery and development of best-in-class therapeutics, and impacted critical decisions. Examples include: (1) predicting optimal drug properties and differentiation for bispecific biologics vs. fixed dose combinations (FDC) in targeting PD-1 and Tim-3; and (2) predicting optimal drug properties for a bispecific approach maximizing target coverage in the joint for Osteoarthritis. The results in the first study have been previously presented in part at 2016 AACR Annual Meeting, New Orleans, April 2016 and published in the conference proceedings as abstract 5001.

Methods: MADI is a mathematical modeling and engineering approach to translational medicine that aims to quantitatively integrate therapeutic mechanism of action knowledge in the context of human disease mechanisms.

Results: In the first study, optimal bispecific formats and affinities are identified, and the FDC approach is essentially equivalent to the optimal bispecific options targeting PD-1 and Tim-3. As part of the model benchmarking, a hypothesis is generated explaining as to why the dosing regimens for the marketed anti-PD-1s are so similar, even though their potencies differ by two orders of magnitude. Moreover, experiments to increase model certainty are prioritized and optimal experiments are designed using MADI. In the second study, optimal drug properties (e.g., affinity, avidity, and half-life) as well as dose regimen (administration, dose, and frequency) are identified, which appear to be counter intuitive, that helps prioritize targets, enable lead generation, and inform candidate selection.

Conclusions: MADI approaches de-risk projects, accelerate the development of best in class therapeutics, and reduce late stage attrition rates. This results is helping industry save money, accelerate timelines, and make better therapeutics, ultimately improving patients’ lives.