Incorporating complex drug PK with multiple binding targets into a QSP model to predict combined PD effects

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Objectives: More antibody drugs are being made in di- and trimer forms to bind multiple targets in a pathway or to bridge cell types. These antibodies, antibody fragments, and nanobodies range in size from 12-15 kDa, have very different pharmacokinetic properties and tissue access, and can be more efficient at blocking a pathway or targeting a tumor [1, 2, 3]. With potential drugs having multiple binding sites with differing affinities, understanding the multiplex binding and subsequent effects is more complex than simply evaluating multiple monoclonal antibodies. Incorporating the pharmacokinetics and pharmacodynamics (PK and PD) of these types of drugs into a quantitative systems pharmacology (QSP) model can be complicated. The functional pharmacodynamics of a multimeric antibody may include single targets as well as combinations of soluble and cellular targets. When evaluating the PD of a multimeric-antibody using a QSP model, it may be necessary to assess each monomeric binding separately and all different combinations of the di- and trimeric binding.

Methods: We developed a model structure to evaluate the binding of multiple di- and trimer drugs to soluble targets or cell receptors. The model was designed to be flexible, permitting the evaluation of alternative targets. The model can simulate mono-, di-, or trimer drug binding combinations with different affinities. This structure can distinguish the ligand binding order and allow binding to one target to have the same or differing affinity for binding subsequent targets. The model quantifies unbound, partially-bound, and fully-bound drugs to allow for evaluation efficacy based on both limited target and drug concentrations. This model allows the clearance rates to be different for each possible combination of complexes, incorporating an additional layer of detail to better predict PK and PD and the potential impact of target-mediated drug disposition.

Results: The model was set up to have drug binding of 1, 2, or 3 targets with the ability to have an additional target for a potential tetrameric binding. It was used to simulate different combinations of targets with overlap between drug targets. The model was used to evaluate the possible pharmacodynamic effects by simultaneously targeting multiple ligands of the same, separate, or combinations of pathways. The model was calibrated to and replicated the published results of the single target antibodies. Data from antibodies that bind a single soluble or cellular target were compared to hypothetical di- and trimer antibodies and nanobodies to evaluate potential new target

combinations. The amount of bound and free targets was used to measure the effect of each hypothetical drug.

Conclusion: This model allows for explicit comparison of target binding for different drugs with competitive binding and enables accurate accounting of all possible receptor and target bound combinations. Simulating binding to multiple targets helps determine synergistic or anti-synergistic effects when targeting a particular set of pathways. This functionality can drive the identification of the ideal combination of targets to increase drug efficacy. In addition, the model can be used to evaluate optimal dosing regimens for multimeric antibodies based on toxicity and efficacy.

References

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