Immuno-modulation in Chronic Inflammation: Clinical Candidate Selection

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BACKGROUND

- In this case study, we look at an example of targeting a membrane bound protein for the treatment of Immune thrombocytopenic purpura and Rheumatoid Arthritis, using a monoclonal antibody.
- Our customer's candidate appears equipotent in a whole blood assay (Figure 1, right) but significantly less potent than a competitor molecule in a target cell proliferation assay (Figure 1, left). The competitor molecule was two years ahead and a tighter binder.
- Our goal was to provide quantitative decision-making guidance using a systems pharmacology model to help the team answer scientific and strategic questions
    - Scientific Questions
        - How do we reconcile the discrepancy in assay results?
        - Is assay performance inadequate to reflect the different molecules' target potency?
        - Which of these assays more closely reflect the human patient situation?
        - How do we derive dose and regimen (major Go/No-go criteria) from these divergent data sets?
    - Strategic Questions
        - Should the project be terminated given the competitor's head start?
        - Should a new lead generation campaign be started to find a tighter binder?
        - Should there be additional assay development or assay optimization?

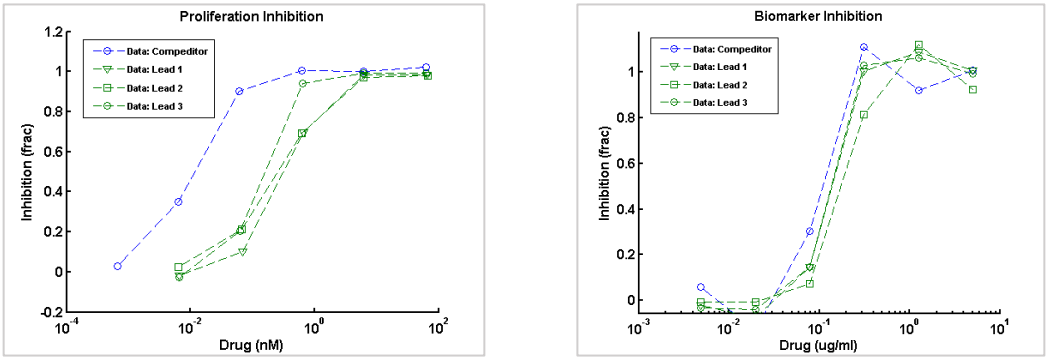

Figure 1. Discrepancy in Assay results

THE MODEL

The systems pharmacology model was based on first principles as a system of elementary mass-action, mechanistic PK/PD, ordinary differential equations. The model parameters and reactions include compartment volumes, ligand concentration and turnover rates, cell numbers and turnover rates, drug administration, target-mediated drug disposition on two cell types, and endogenous drug elimination. (Figure 2). Cell type 1 (C1) is the on-target cell whose binding to the antibody leads to disease amelioration whereas cell type 2 (C2) is the off-target cell expressing the target the antibody is against but does not lead to disease amelioration.

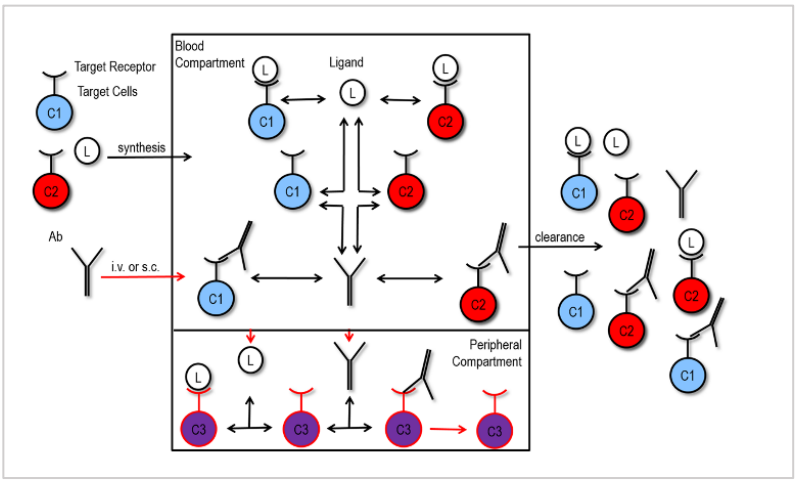

Figure 2. Systems Pharmacology Schematic

Immuno-modulation in Chronic Inflammation: Clinical Candidate Selection (cont'd)

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MODEL SIMULATION & ANALYSIS

- The model predictions were in agreement with the target cell proliferation assay and whole blood assay (Fig 3)
  - The competitor molecule (pM binder) is more potent than the customer's leads (nM binders)
  - Model predicts that the competitor's pM binder and our customer's nM binder are functionally equipotent in the presence of cell type 2 (off-target cell C2 in Figure 2)

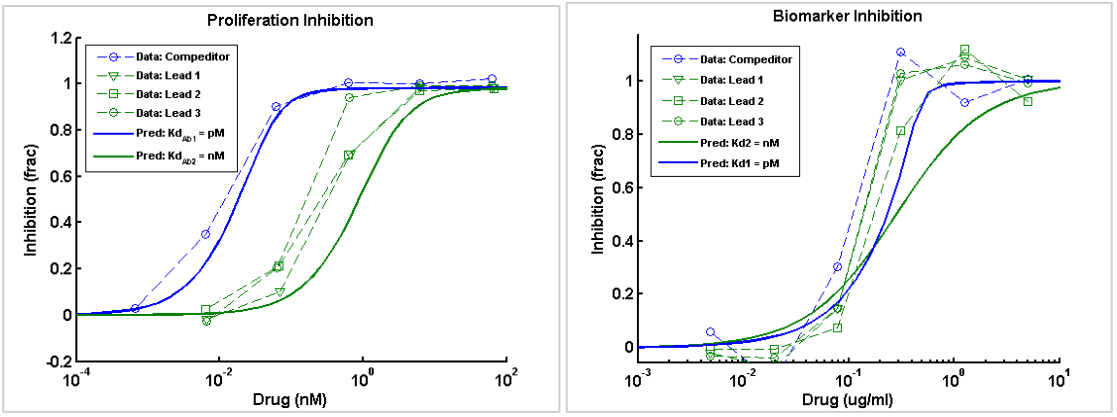

Figure 3. Model prediction agrees with assay data.

- Model simulations of thousands of different combinations of binding affinity and half-life showed that a weaker binder has a dosing advantage, with the competitor's pM binder requiring more frequent dosing than the customer's nM binder (Fig 4).

CONCLUSION

- We determined that affinity was the major parameter driving dosing advantage
- The total target burden on-target cells (C1) and off-target cells (C2) with different turnover rates drove 'apparent' data discrepancy.
- Our model analysis demonstrated that a weaker binder has a dosing advantage (Figure 4) which resulted in the decision to accelerate clinical development, and perform no additional assay development or additional lead generation.
- Modeling decreased the project R&D by 6 months to 1 year and saved a potential best-in-class drug.

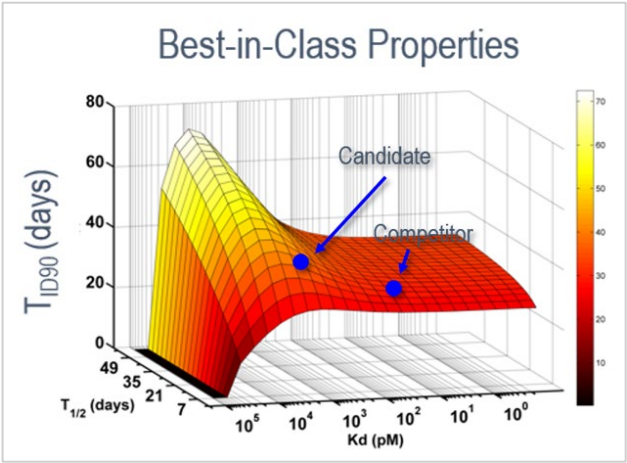

Figure 4. Model predicts that a weaker binder is a better molecule

EPILOGUE

- Upon entering the clinic, Phase 1 study results showed high non-linear PK for intravenous and subcutaneous dosing as well as high PK variability for subcutaneous dosing.
- The systems pharmacology model was updated with clinical data and predicted non-linear PK and target occupancy as well as variability in SC dosing.
- The model results were used to amend Phase 1 protocol, to prepare Medicine and Marketing for counterintuitive Phase 1 results and to obtain regulatory approval to change Phase 2 trial design.
- Customer's best-in-class molecule is now positioned to be first-in-class (competitor postponed clinical trials).
- More details on this Phase-1 interim analysis are available in the Applied BioMath Case Study titled "Immuno-modulation in Chronic Inflammation: Phase 1 Interim Analysis".