Harnessing clinical knowledge to inform pre-clinical development of biologics

Karcher H, Lowe P

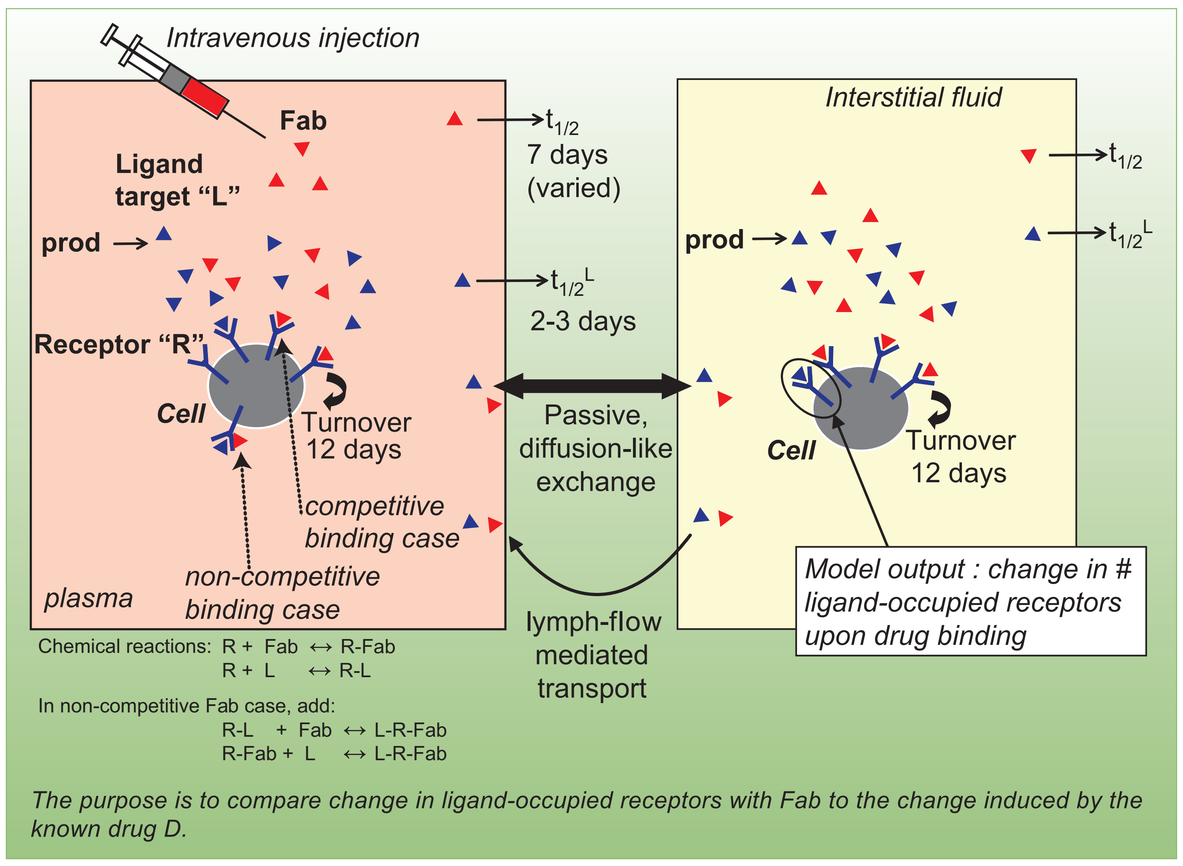
Modeling & Simulation, Novartis Pharma AG, Basel, Switzerland.

Background

- Well-characterized ligand-binding antibody drug D inhibits natural binding of the excess ligand "L" to a receptor "R", and downregulates it from 250,000 receptors/cell (disease) to 10,000 receptors/cell (healthy levels).
- Targeting the receptor could be a way to treat non-responders to drug D, or patients with very high ligand levels who cannot be treated with reasonable doses of drug D.
- Cross-linking the receptor yield to potentially dangerous clinical side-effects: monovalent biologics need to be used to block the receptor.

Modeling approach

Figure 1. *Model schematic. New biologics (Fab) is injected and distributed to the interstitial fluid. It binds to the target receptor "R" in plasma and interstitial fluid, thereby preventing binding of the natural ligand (blue triangle). The bound receptor undergoes endocytosis and is recycled.*



The purpose is to compare change in ligand-occupied receptors with Fab to the change induced by the known drug D.

- **Model structure :** set of ODE's written in Matlab to describe (i) chemical reactions, (ii) receptor/cell turnover, (iii) production, transport, and elimination.
- **Model output:** amounts of Fab, receptors, ligand, and bound species as a function of time.
- Clearance from the plasma compartment is adjusted to correspond to different possible half-lives of the Fab.
- Production rates optimized to achieve given, measured ligand concentration before drug treatment.

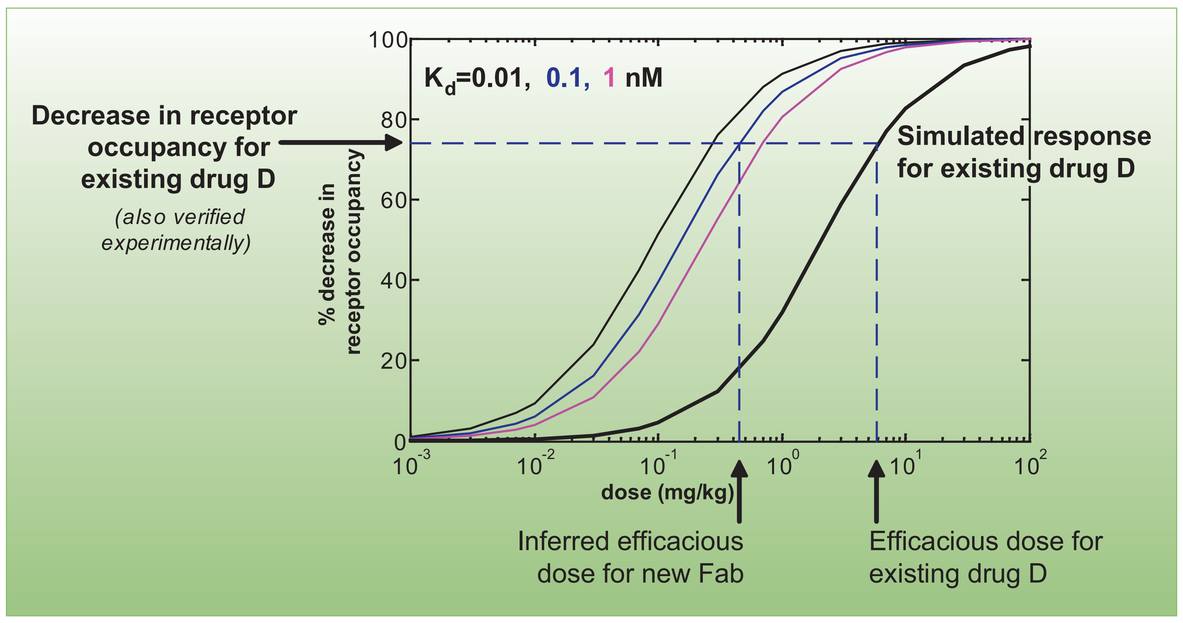
```
Matlab function for optimization of ligand production:
function steady_state_deviation = steady_state_L_prod (x, tspan,
p, y0, L_plasma_steady_state, system_options, iy)
p.L.plasma_synt = x;
p.L.skin_synt = x * p.int_v.skin / p.vol.plasma; %nmoles/
day. Ligand production is proportional to compartment size
[T,Y] = ode45 (@model_ODE, [0 tspan], y0, system_options,
p, iy);
% measurement refers to plasma ligand amount
steady_state_deviation = L_plasma_steady_state - Y (end,iy.L_
plasma;
```

- Different Fab affinities and competitive/non-competitive cases are simulated.

Results

- Model applied to well-characterized ligand-binding antibody drug predicted same receptor occupancy at steady-state as measured in patients.
- Obtained time-course of Fab, free and bound ligand, receptor, and their distribution for doses injected every two weeks.
- Focus on trough levels at steady-state to evaluate efficacy and choose Fab design accordingly.

Figure 2. *Predicted dose-response curve for receptor-targeting Fab (thin lines) and for well-characterized drug D (thick line).*



- From the known efficacious dose for drug D, corresponding receptor occupancy is derived.
- Necessary Fab dose inferred from required receptor occupancy for a variety of Fabs (different half-lives and affinities).

Table 1. *Summary of dose predictions that yield desired receptor occupancy, to be used to guide new biologics design*

Affinity of the Fab being developed	Dose necessary to achieve same receptor occupancy at steady-state as well-characterized drug D		
	Non-competitive binding	Competitive binding	
	No receptor downregulation	No receptor downregulation	Receptor downregulation
K_d = 0.01 nM	0.5 mg/kg	0.7 mg/kg	0.2 mg/kg
K_d = 0.1 nM	2 mg/kg	3 mg/kg	0.5 mg/kg
K_d = 1 nM	3 mg/kg	4 mg/kg	0.7 mg/kg

Assumptions: Fab half-life is 14 days, ligand levels fixed to disease levels.

Impact

- Given current knowledge on the target and associated ligand, team selects the best design for clinical efficacy of an anti-receptor Fab biologics:
  - Non competitive Fab, with an affinity <1 nM and a 40 kDa-PEG carrier to yield a 7-day half-life.

Future directions

- Incorporate animal and clinical data as they become available.
- Support first-in-man dose selection.

This study was supported by Novartis Pharma AG, Basel, Switzerland.

Note: all values on graphs and tables are fictitious. They intentionally do not correspond to results from the developed Fab.

Poster presented at the Population Approach Group Europe (PAGE), June 23-26, 2009, St. Petersburg, Russia. Support for poster preparation provided by MSCD India, Novartis Healthcare Private Limited.