Integration of physiological and biochemical concepts into the development of biopharmaceuticals

Philip Lowe PhD

Modelling & Simulation, Novartis Pharma AG
Basel, Switzerland

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Abstract

- The goal of this talk is to give those who are based in a more laboratory based environment some examples of how the results of ligand binding assays are interpreted and used within the context of preclinical and clinical drug development. The majority of the talk will focus on pharmacokinetic-pharmacodynamic model based analyses, as there are serious interpretation issues if classical non-compartmental analyses are blindly applied to the nonlinear behaviours common with biopharmaceuticals

- By incorporating aspects of mechanism into PKPD models, one gains a deeper understanding of the basis of drug disposition and pharmacology, greater biological realism and thereby better extrapolatability, or prediction, of patient responses. For biopharmaceuticals especially, mechanistic aspects of physiology and biochemistry can be linked by explicitly describing drug distribution and elimination together with drug target production (expression) and turnover. Drug-target binding is modelled enabling target capture to be quantitated and correlated with clinical responses. Examples will include:
  - Omalizumab capturing IgE thereby alleviating the signs and symptoms of allergic asthma
  - Non-clinical to clinical translation of a monoclonal antibody with highly nonlinear pharmacokinetics characteristic of target mediated drug disposition (TMDD)
  - Canakinumab capturing interleukin-1β thereby alleviating the pain and inflammation experienced by patients with cryopyrin associated periodic syndromes

- The overall objective of a PKPD modelling and simulation process could be realised, to deliver physiologically and biochemically reasonable predictions of the effectiveness of the drugs. Through simulation from the models, suitable posologies – doses and regimens – for specific groups of patients were suggested

Biochemistry of binding
Drug and target related by an *equilibrium* reaction



Drug + Target ⇆ Drug-Target Complex

Add drug, mass balance "pushes" reaction to the right

Enzyme kinetics

Michalis-Menton $E + S \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_3} E + P$ (∝)

assumptions

① $e \lll S$ usually at least 100×

② $v = k_3[ES]$ v = overall rate

③ $k_2 \ggg k_3$ Michalis Menton assumption

so that $E + S \rightleftharpoons ES$ is in eqm.

Phil's 3rd year notes, 1977

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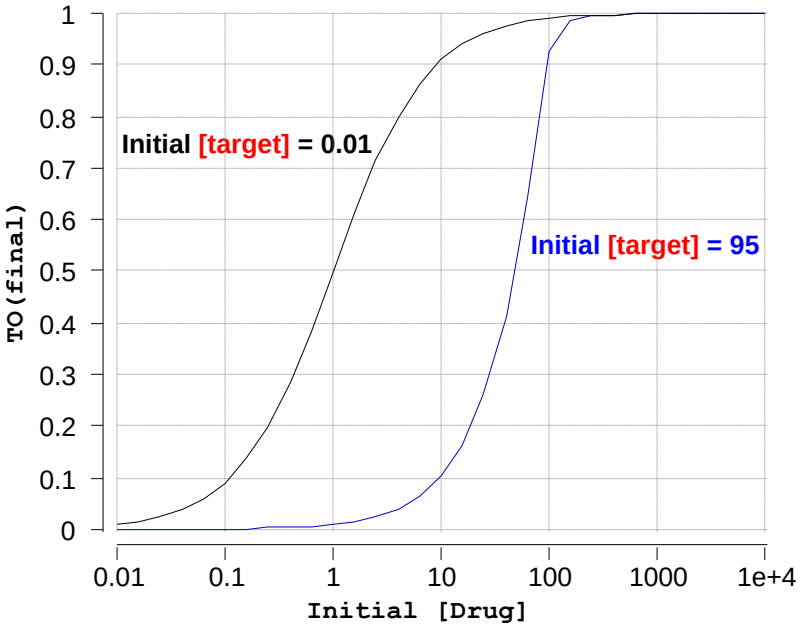
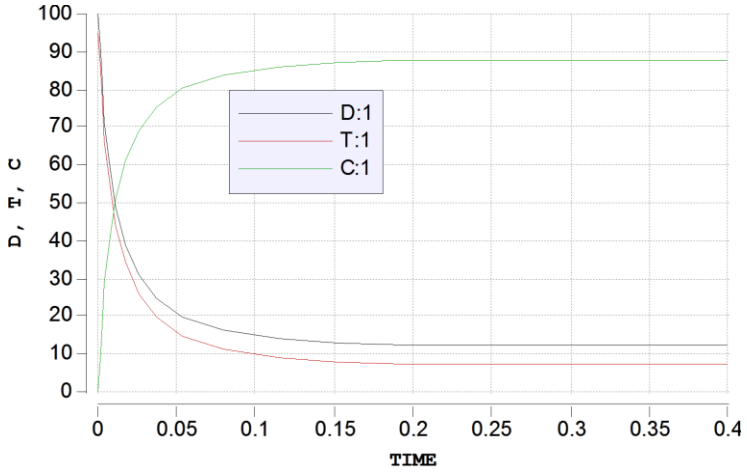
"Test-tube" scenario *Drug-target binding is a function of target loading or expression*

$$d/dt(D) = -k_{on}*D*T + k_{off}*C \quad ;Drug$$
$$d/dt(T) = -k_{on}*D*T + k_{off}*C \quad ;Target$$
$$d/dt(C) = +k_{on}*D*T - k_{off}*C \quad ;Complex$$

```
TO = C/(C+T)          ;Target occupancy

init(D) = 100         ;initial [drug]
init(T) = 95          ;initial [target]
init(C) = 0           ;initial [complex]
```





K_d is equal to $EC_{50,\ added\ drug}$ only when [target] << [drug]

Shift depends on amount of target in system, i.e. expression or load level

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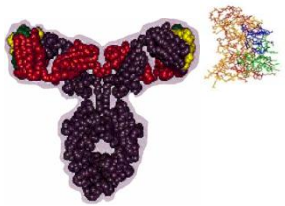
Target binding incorporated into a PKPD model

Drug input/output and target production and turnover added to binding reaction

iv dose

target production or expression



mAb + target ⇌ mAb – target complex

elimination mAb

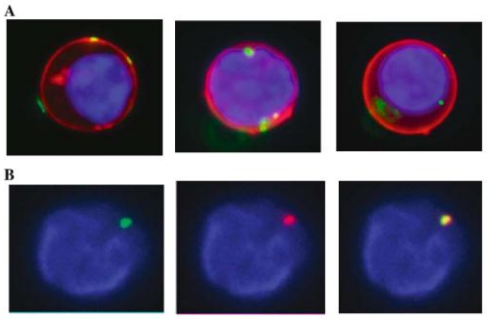
elimination target

elimination mAb – target complex

slow clearance
V ~ 3 L central, for 70 kg
$t_{1/2}$ ~ 3-4 w

general rule:
faster than a mAb for most (not all) proteins

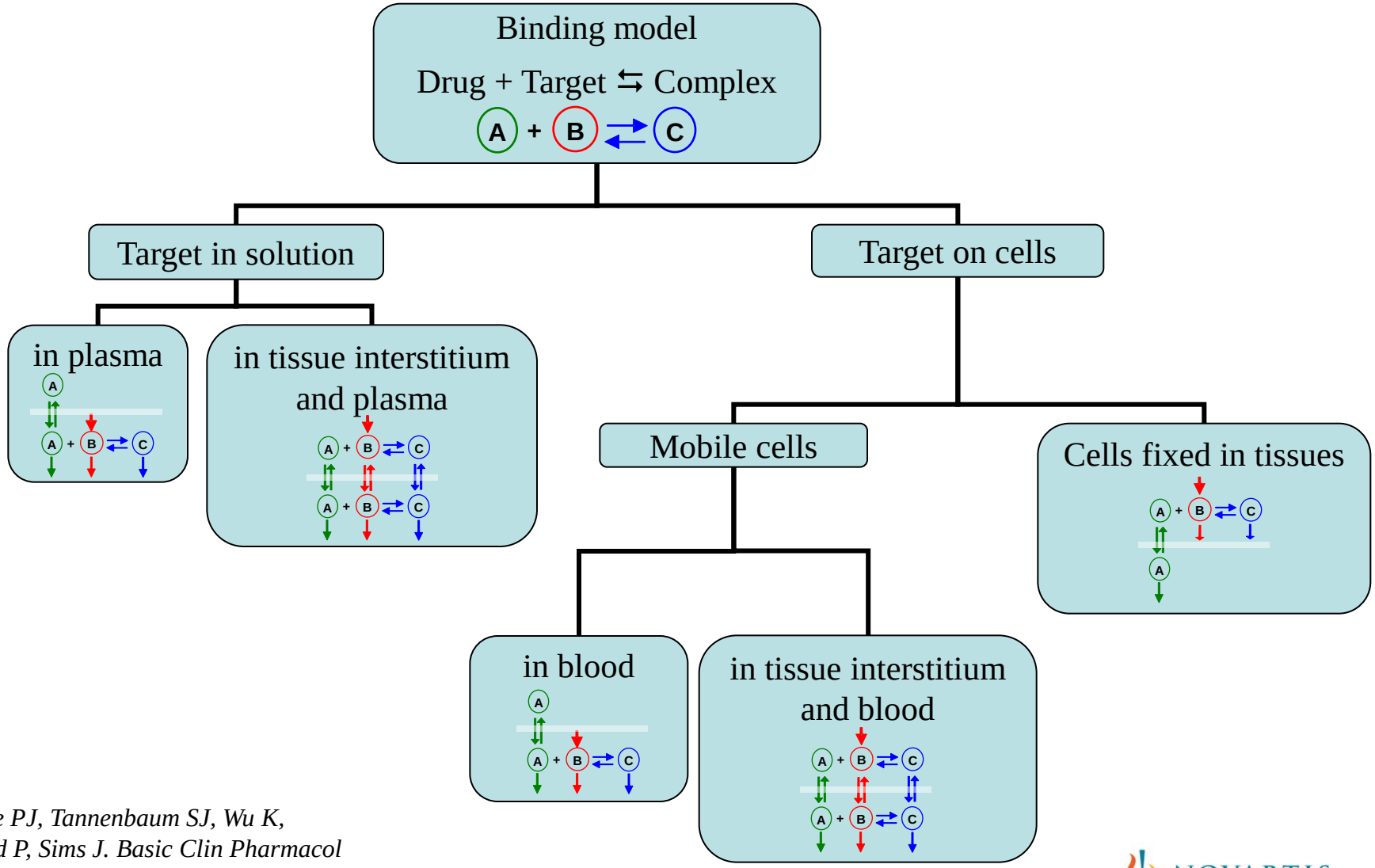
general rule:
soluble target – slow
cell surface target – faster



Mager DR, Jusko WJ. J PKPD 2001; 28: 507-532

Ng CM et al. Pharm Res 2006; 23:95-103

Taxonomy of drug-target binding physiological localisations



Lowe PJ, Tannenbaum SJ, Wu K, Lloyd P, Sims J. Basic Clin Pharmacol Toxicol 2009; 106:195-209

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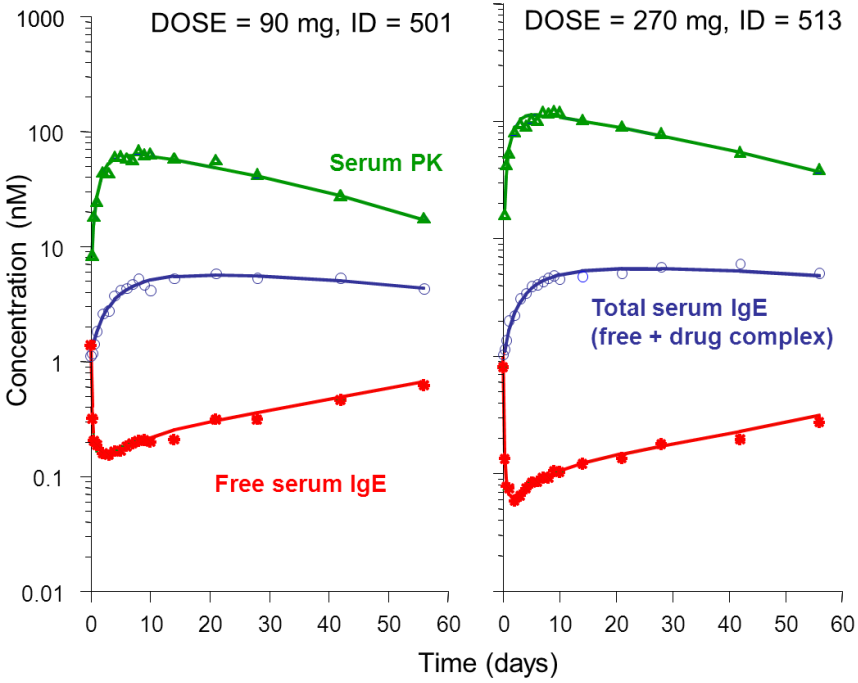
Components of the PKPD model

- Pharmacokinetics of the monoclonal antibody:
  - species differences often well understood and easily characterised
  - good prediction to man, either by scaling and/or by reference to prior similar antibodies
- Binding affinity to the target ligand:
  - species differences understood during *in vitro* characterisation
- Localisation, expression and turnover of target, clearance of drug-target complex
  - species differences often not well characterised
- Potentially, competition with other binding proteins
  - Such that observed *in vivo* binding not same as isolated *in vitro* system

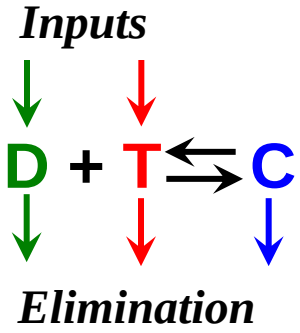
Example 1: Target turnover and binding model

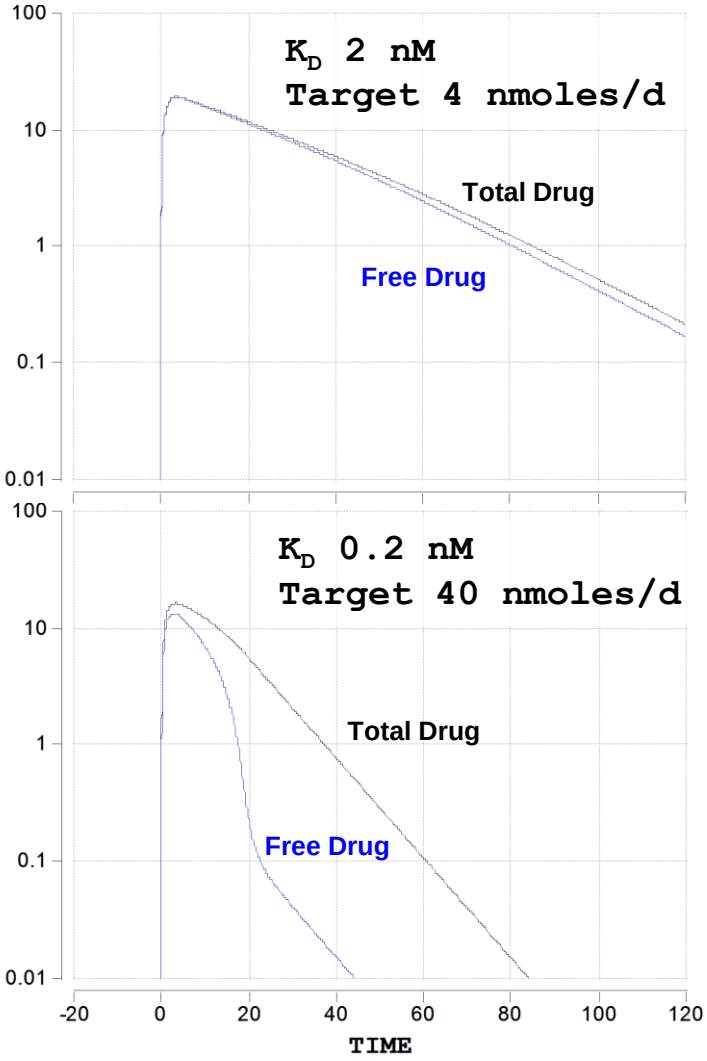
i) Model compares well with omalizumab, total and free IgE data

ii) What if assay measures free drug? iii) what if expression & K_D different?



- Assays must be correctly specified, free or total
- If higher affinity binding and higher target expression, major differences between free and total





Meno-Tetang GML, Lowe PJ. Clin Pharm Tox 2005; 96: 182-192

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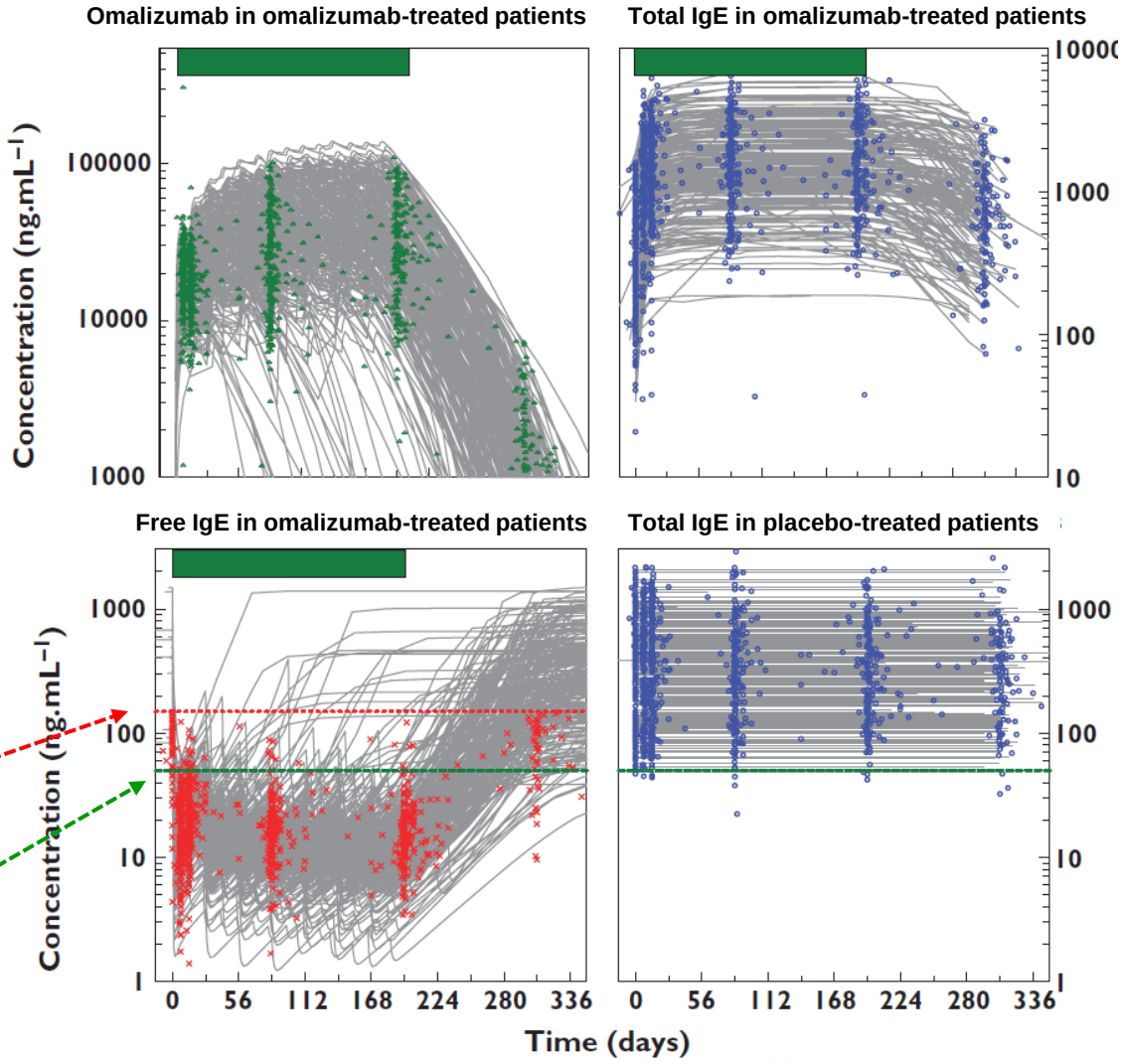
Xolair-IgE model allowed reconstruction of free IgE versus time profiles for individual patients

- Model applied to data from the INNOVATE study patients
- Randomised, double-blind, placebo-controlled study over 28 weeks
- Omalizumab: n=226
  Placebo: n=214
- Model-simulated omalizumab regimens derived through dosing table to achieve at least 0.016 mg.kg^{-1} per IU.mL^{-1} IgE at baseline



Upper limit of quantification for free IgE

Target level of free IgE (50 ng/mL)

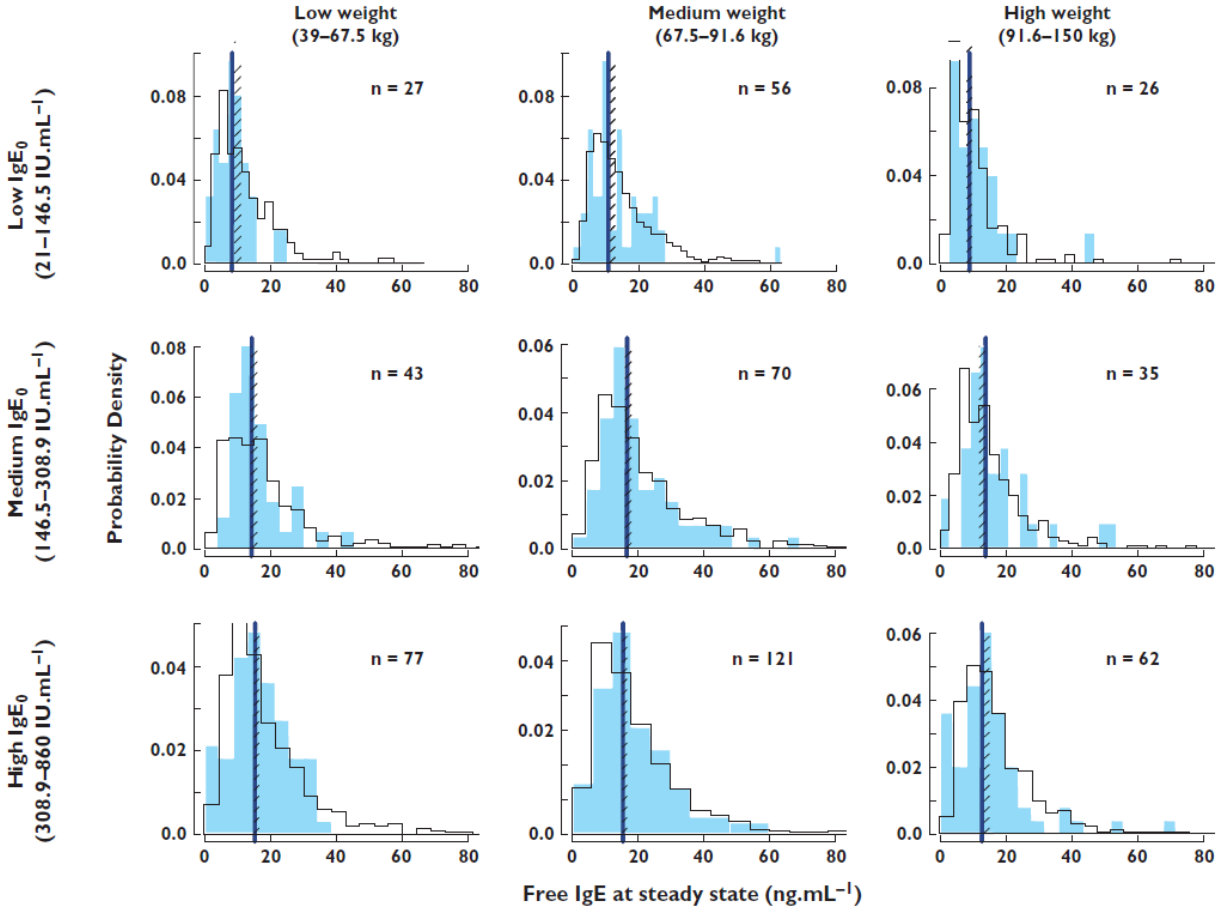
Total serum IgE (free + drug complex) o
Serum PK Δ Free serum IgE x

Lowe PJ, et al. Br J Clin Pharmacol 2009; 68(1):61-76.

Predictive check of the omalizumab–IgE model on to the distribution of free IgE at steady state for different regions of the dosing table

Comparison of:

- model simulation of a total of 19,330 virtual patients, split into nine subsets of the dosing table
- observed data from the Phase III studies for the numbers of patients indicated



observed results

predicted results from model simulation

Lines = medians of the observed data

Cross-hatched areas = 95% confidence interval for the median from the simulations

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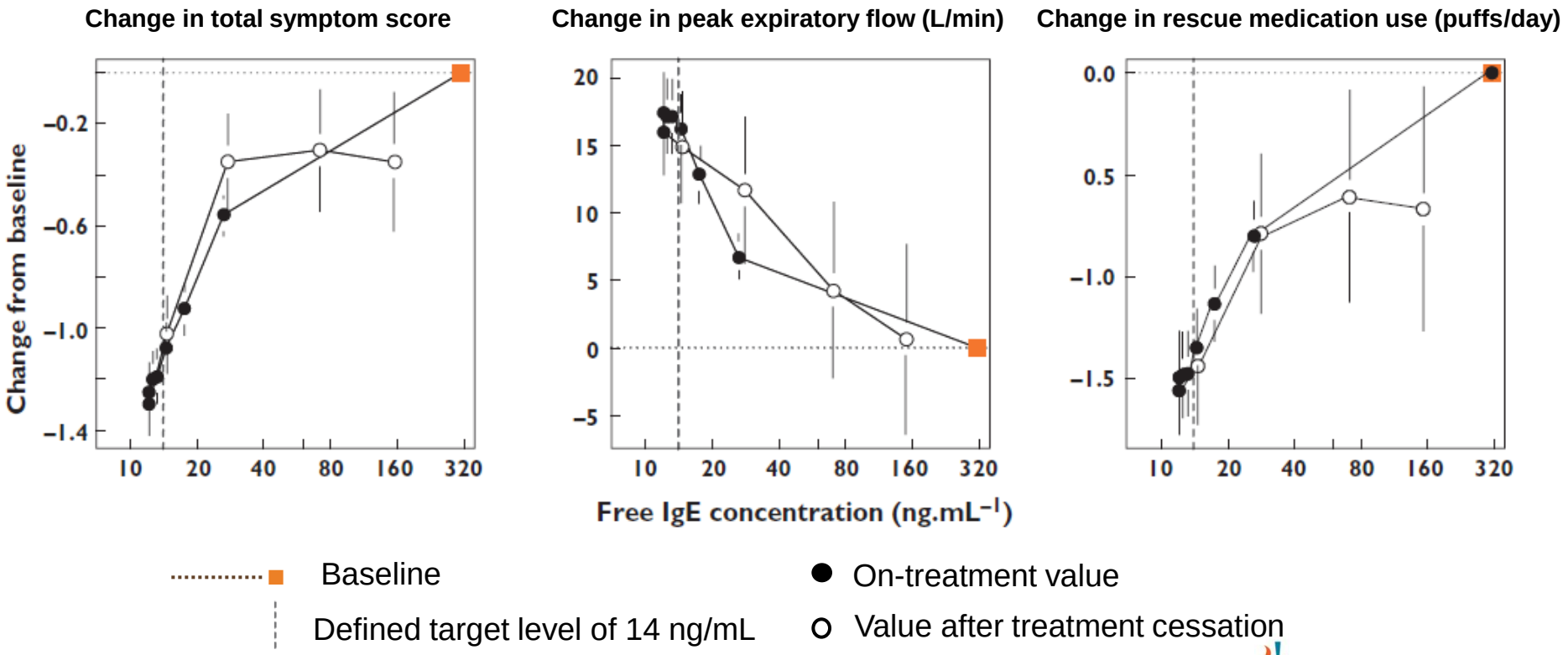
Lowe PJ, et al. Br J Clin Pharmacol 2009; 68(1):61-76.

Direct correlation between mean free IgE and change from baseline in signs and symptoms of asthma

- Combined data from four Phase III trials (n=898 omalizumab-treated patients)
- As free IgE suppressed by binding with omalizumab, mean total asthma symptom scores and rescue medication use decreased and morning peak expiratory flow increased



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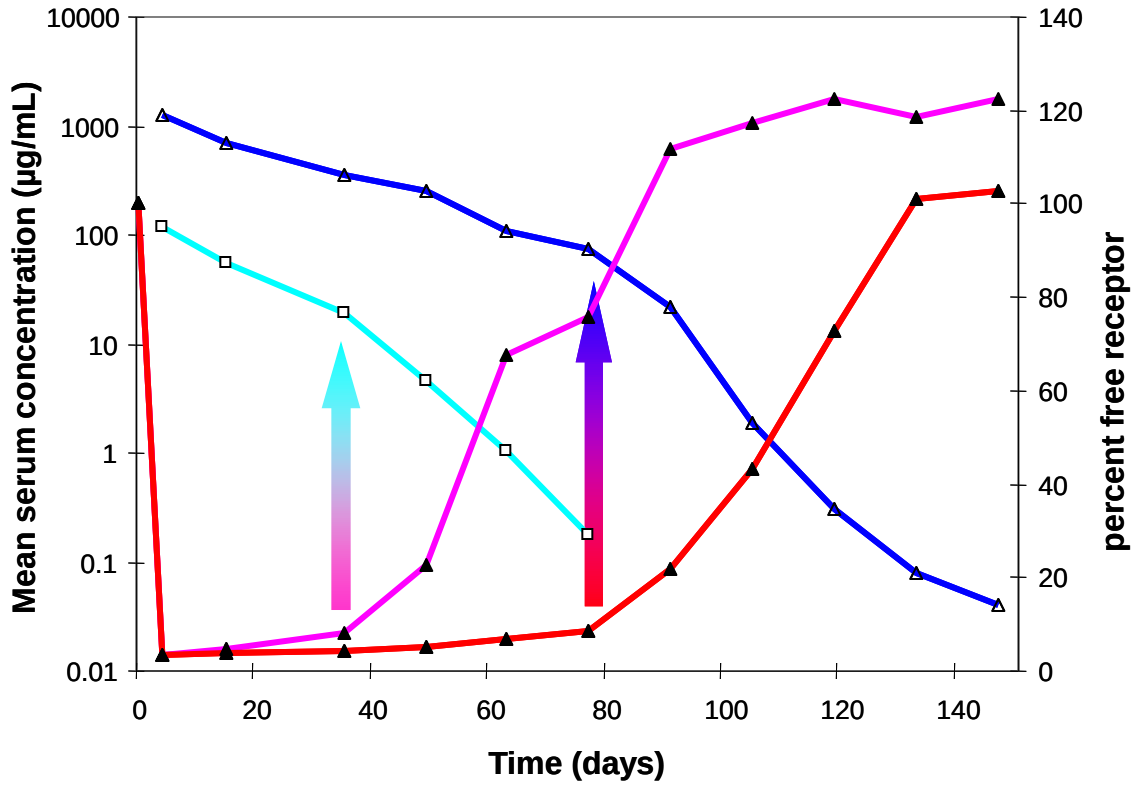
Lowe PJ, et al. Br J Clin Pharmacol 2009; 68(1):61-76.

Example 2: Nonclinical to clinical translation:

An antibody against a cell surface target in cynomolgus monkey



- Faster elimination when saturation less then 90%
- Independent saturation assay correlates with break points in PK

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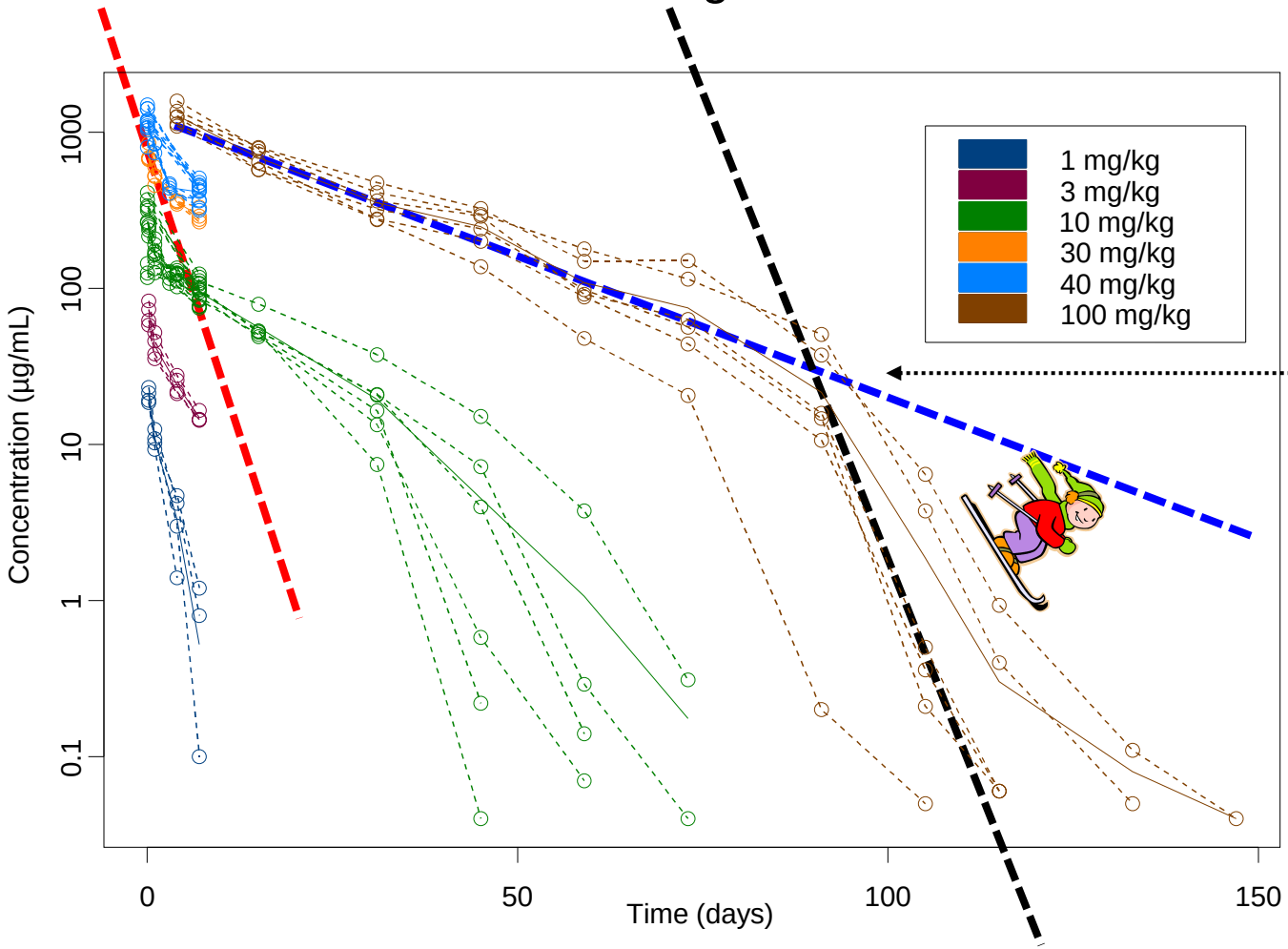
Clear target mediated disposition with dose and time

Cynomolgus monkey pharmacokinetics of free monoclonal

- Rapid elimination at lower doses and concentrations
- Slower elimination when target saturated



Which half-life?

- Alpha half-life, distribution to tissues
- Beta half-life, when target saturated
- Gamma or TMDD half-life, when not saturated

Saturation level

"Over the cliff"

Varies from subject to subject

Same data as in Lowe PJ, et al. Basic Clin Pharmacol Toxicol 2009; 106: 195-209

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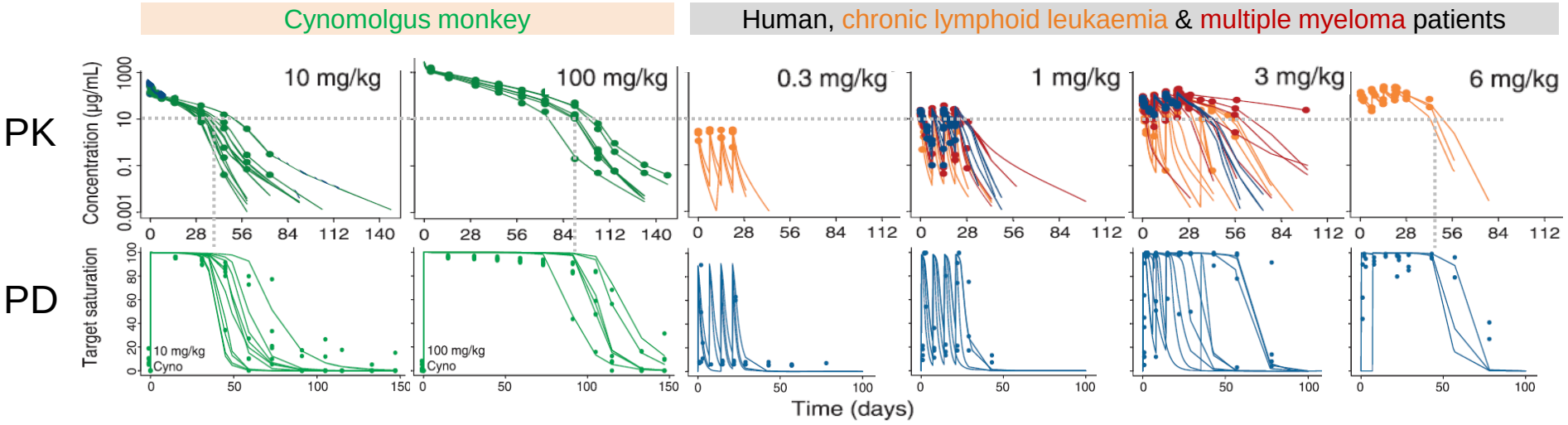
Monoclonal antibody binds and occupies cell surface target

Nonlinear PK correlates with target saturation; need to assess target expression and replenishment; level of receptor or target can vary between species and between diseases



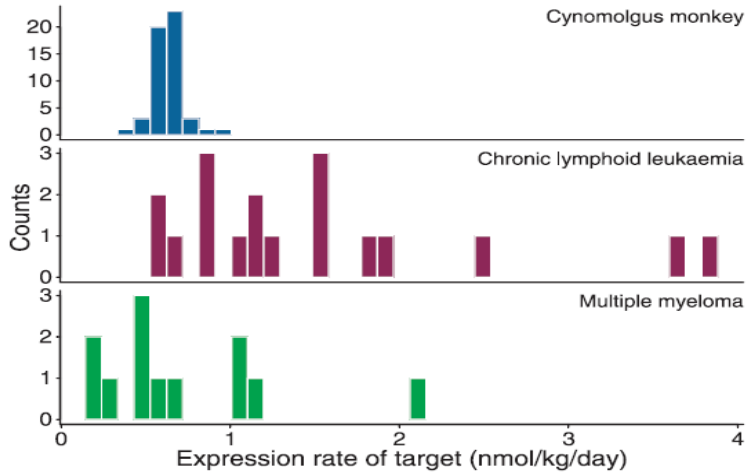


Fig. 6. Distribution of individual cynomolgus monkey and patient values for the turnover or expression rate of the target.

- Target expression consistent between cynomolgus monkeys
- Humans vary by more than order of magnitude
- More target → higher dose to achieve saturation
- Model used to advise on dose and regimen for next cancer indication

Lowe PJ, et al. Basic Clin Pharmacol Toxicol 2009; 106: 195-209

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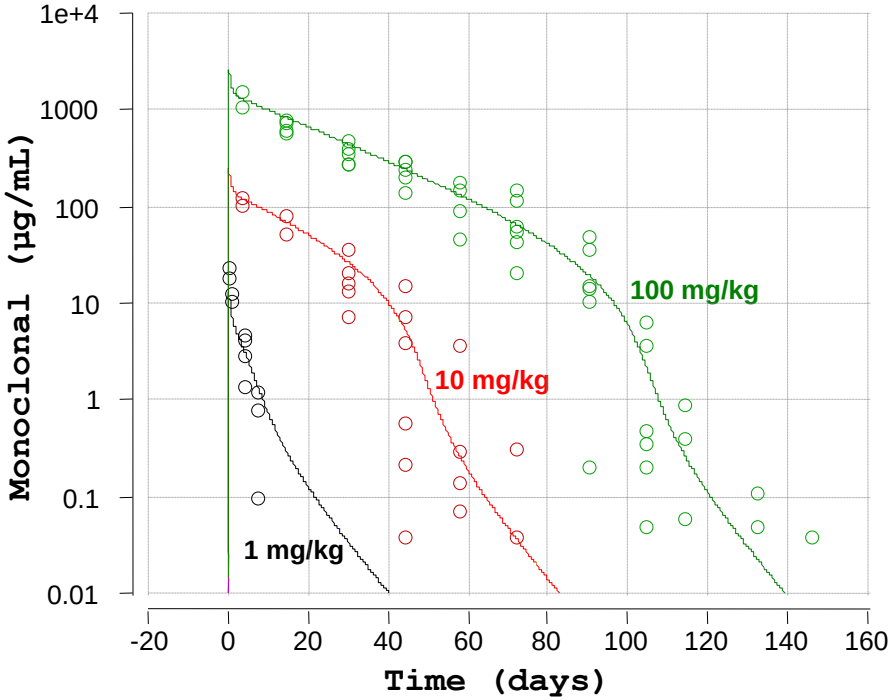
Target binding model enables direct display of occupancy

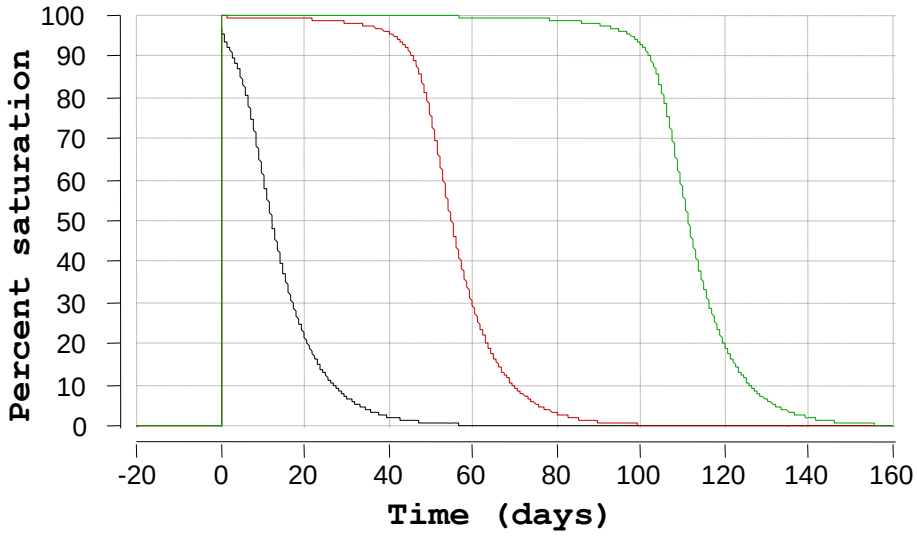
Calculated from quantities of mAb-target complex & total target

To scale adjust parameters to selected species using in vitro & in vivo data

Pharmacokinetics (free drug)



Saturation, or target occupancy




```
D/DT(TD) =       -FD*CLD/V -CPLX*CLC/V -Q*(FD/V+DP/VP)
D/DT(TT) = RINB -FT*CLT/V -CPLX*CLC/V
D/DT(DP) =                                Q*(FD/V-DP/VP)
CPLX=((KD*V+TD+TT)-((KD*V+TD+TT)**2-4*TD*TT)**0.5)/2
FD  = TD-CPLX              ;FREE D = TOTAL D - COMPLEX
FT  = TT-CPLX              ;FREE T = TOTAL T - COMPLEX
SAT = 100*CPLX/TT
```

- Clearances (drug D, target T, complex C)
- Volumes (central, peripheral)
- Rate of target production or expression
- Binding constant (or K_M, IC_{50}, EC_{50})

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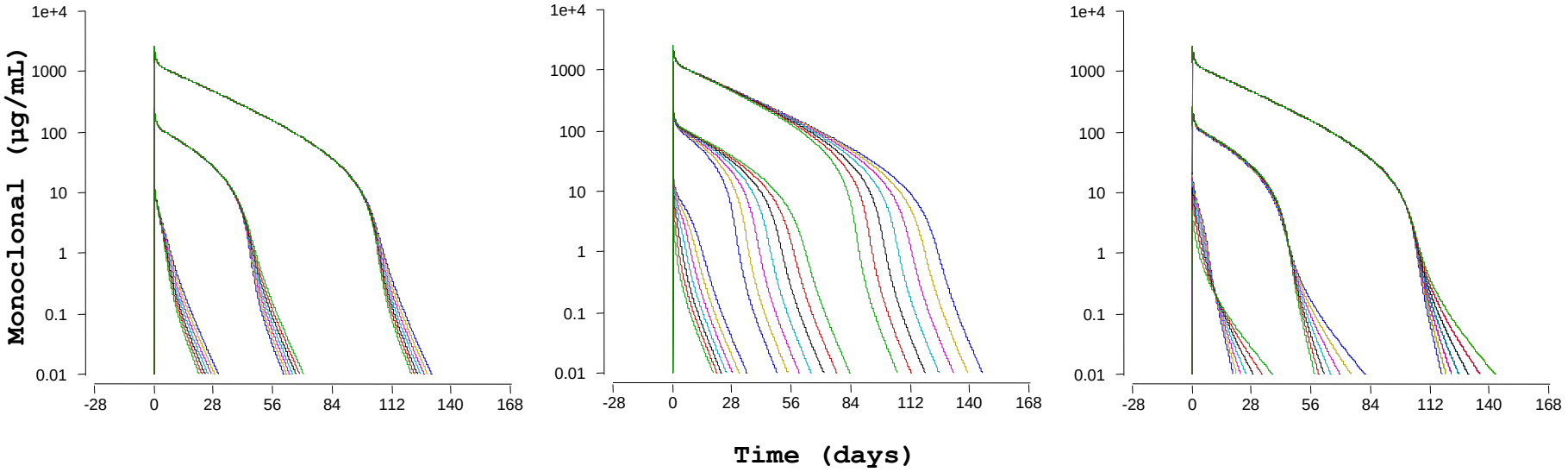
Lowe PJ, et al. Basic Clin Pharmacol Toxicol 2009; 106: 195-209

Sensitivity to target turnover and binding

Knowledge of synthesis rate of target (i.e. expression level) most important factor for predicting dose required for duration of target saturation

Binding constant, K_D | Synthesis rate of target | Clearance of target

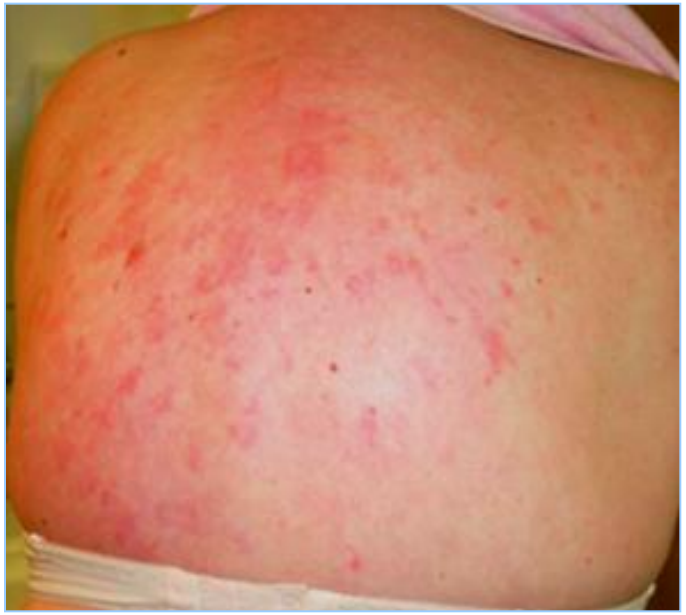


- 4 fold range from highest to lowest in each batch of simulations
- 1, 10 and 100 mg/kg doses
- All other parameters as in prior slide

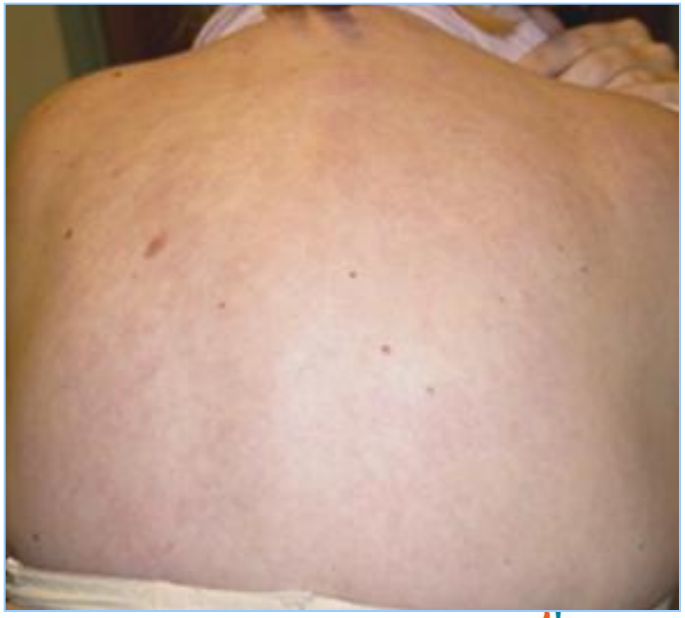
Example 3: Ilaris™, canakinumab, ACZ885, a fully human mono-clonal anti-interleukin-1β antibody for inflammatory disorders

- **Interleukin-1-β, a major player in inflammation, can cause**
  - ***Urticaria, malaise, joint pain, conjunctivitis, fatigue, frequent migraines, cold sensitivity, deafness***
- **Canakinumab binds IL-1β to form inactive complexes: D+T⇆C**
  - **So driving these cryopyrin associated periodic syndrome symptoms into remission**

Baseline



24 hours



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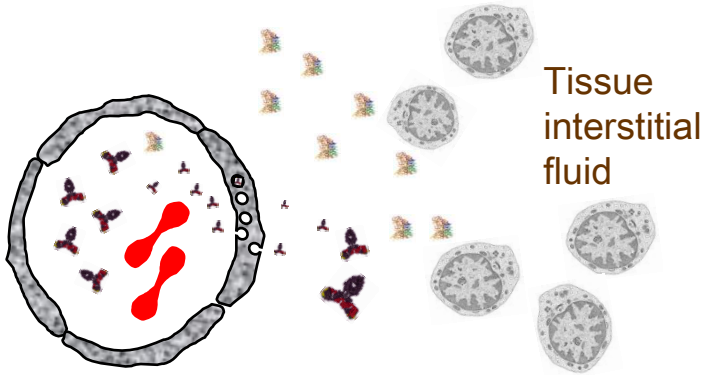
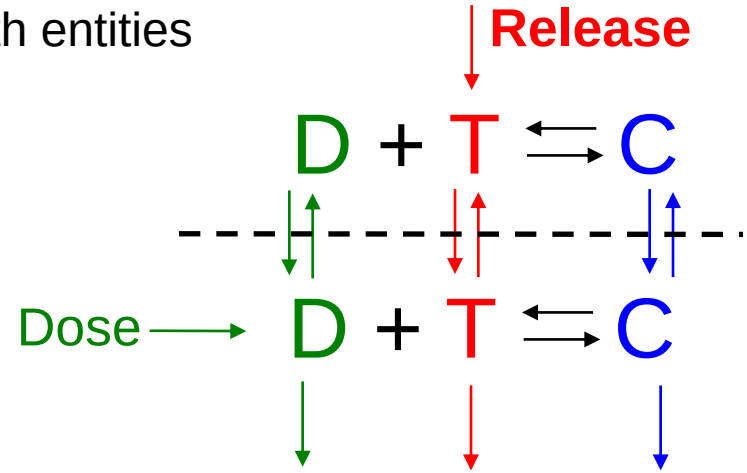
Binding model starts to link to an underlying multi-compartmental distributional physiology for the target

- IL-1β released into tissue interstitial fluids at sites of inflammation
- Canakinumab, as a protein, distributes between plasma and tissue interstitial fluid (lymph)
- Vascular endothelial permeation of both entities

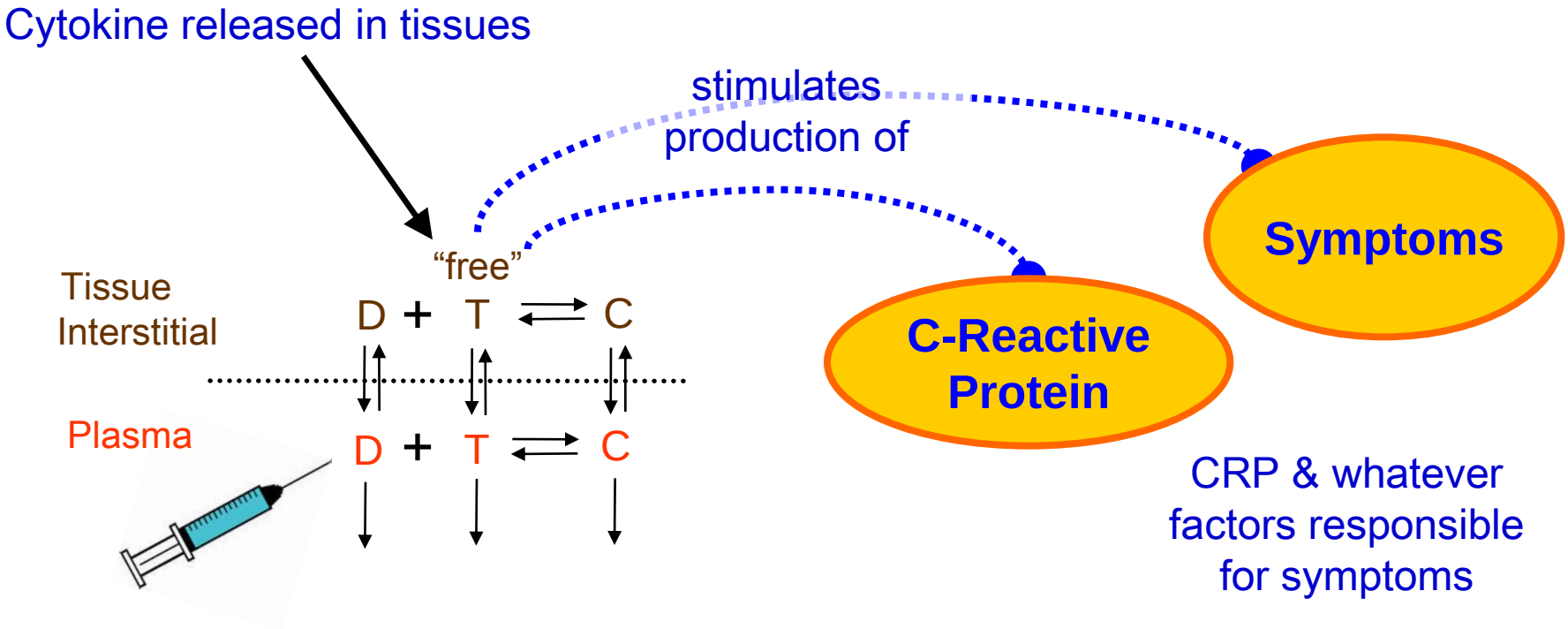




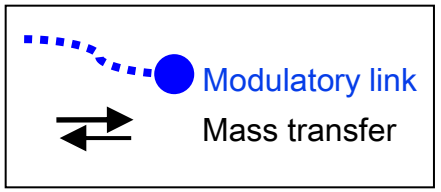
		Control subjects (n=20)		Rheumatoid Arthritis patients (n=20)	
	Protein	Lymph	Serum	Lymph	Serum
	IgG (mg/dL)	238 ± 32	890 ± 53	384 ± 45	1708 ± 104
Cytokine (pg/mL)	IL-1β	1.50 ± 0.25	3.4 ± 1.0	**14.8 ± 3.9**	0.8 ± 0.3
	TNFα	4.4 ± 1.1	2.0 ± 0.1	9.9 ± 1.1	4.7 ± 0.64

From
Olszewski et al (2001)
Arthritis & Rheumatism
44(3) 541-549

Free IL-1β linked to clinical measurements of inflammation and symptoms of disease



- All captured in a drug and disease model
- Parameters estimated from patients
- Simulations for prediction of dose and regimen
- Then test...



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Lachmann HJ et al J Exp Med 2009; 206(5):1029-36

Causal chain is modelled allowing prediction beyond data to simulate and propose posology for canakinumab in patients

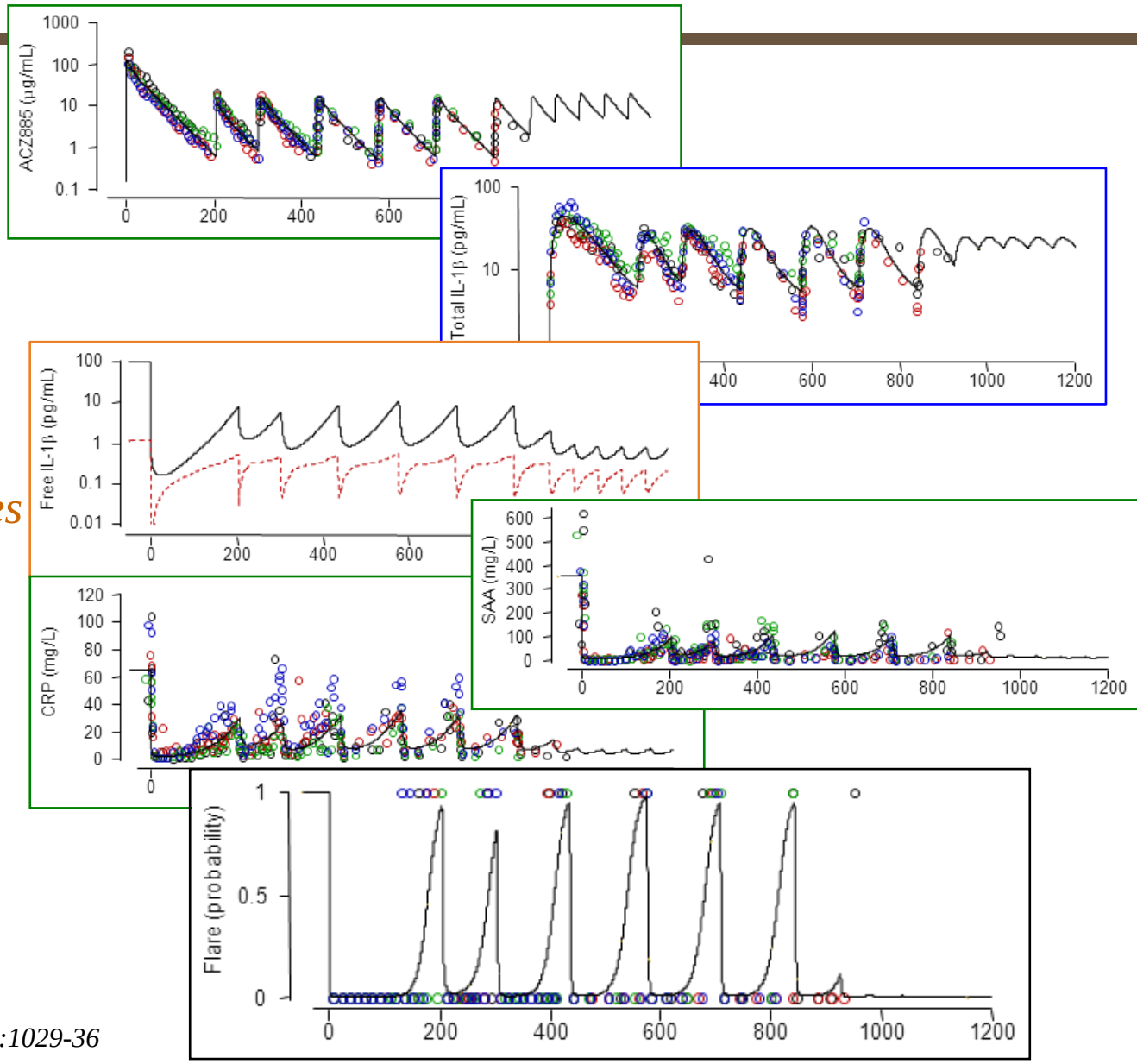
Canakinumab ↑ *(dosed)*

Total IL-1β ↑
formation of slowly eliminated DL complexes

Free IL-1β must ↓
mass action, available IL-1β taken into complexes

C-reactive protein ↓
Serum Amyloid A ↓
Inflammatory biomarkers respond to ↓ IL-1β

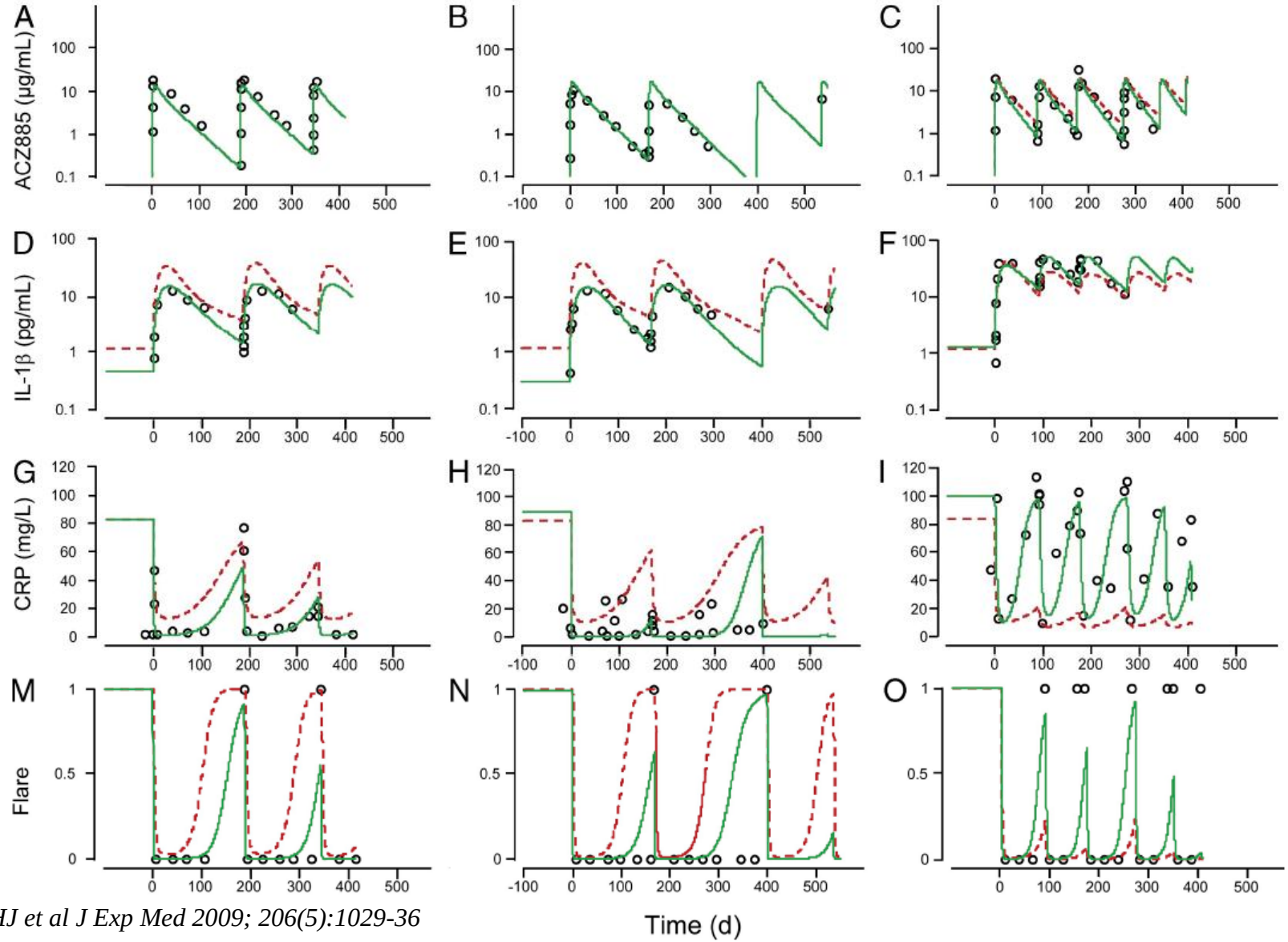
Symptoms ↓
due to less stimulation by IL-1β receptor in tissues



Lachmann HJ et al J Exp Med 2009; 206(5):1029-36

Allowing prediction to the subsequent three patients

Green is fitted, red predicted from prior 4 patients



Lachmann HJ et al J Exp Med 2009; 206(5):1029-36

Summary – drug-target binding models to quantitate capture or occupancy of ligands or receptors

- There is a hierarchy of drug-target binding and turnover models which describe physiologic location and nature of targets
- Closed, non-turning over (test-tube) models help understand differences between true binding constants (K_D) and observable half-max effect concentrations (EC_{50})
- Even simplest one compartment binding and turnover models useful for understanding capture of soluble targets located primarily in the central circulation
- Soluble targets primarily located in tissues require two or more compartments; increase in captured target in plasma enables whole body production estimate
- Binding of drug to target can, if molar dose in same range as molar amount target in body, give rise to dose, concentration and even time dependent nonlinear PK
- Such nonlinear or target mediated drug disposition can be used to estimate target occupancy without need for independent receptor occupancy assays
- Quantitation of nonlinear PK or capture of soluble targets can, if related to clinically relevant responses, be used to help set doses and regimens