Modelling and simulation support for design of First-in-Man studies: the MABEL approach

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30th November – 1st December, 2011

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M&S in early development (to support FTiM)

- M&S to support design of First-in-Man studies – the MABEL approach
- Utilising prior information (*in-vitro*, pre-clinical and literature)
- Biomarker role in chain of causal evidence
- Animal (*in-vitro & in-vivo*) studies
- Defining PK-PD strategy

M&S should

- design safe studies to achieve, efficiently, desired goal, whether it be
  - healthy volunteer safety and tolerability
  - PK and PD
  - safety assessment plus clinical benefit
- highlight uncertainties in whatever model(s) is (are) chosen
  - may not always be popular with our project teams, but a key point in design-test cycle

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Abstract for examples

- As with clinical drug development, preclinical development also has phases:
  - "I" initial *in vivo* pharmacology
  - "II" non-GLP dose range finding
  - "III" GLP toxicology
- Together with an array of *in vitro* experiments comparing species, these enable an integrated safety assessment prior to entry into man, documenting to investigators and authorities the minimum ***acceptable*** biological effect level (MABEL) for a first dose in man
- A pharmacokinetic-pharmacodynamically drug-target binding guided process to ascertain the MABEL will be exemplified.

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European Medicines Agency

effective 01-Sep-07

GUIDELINE ON STRATEGIES TO IDENTIFY AND MITIGATE RISKS FOR FIRST-IN-HUMAN CLINICAL TRIALS WITH INVESTIGATIONAL MEDICINAL PRODUCTS

For investigational medicinal products for which factors influencing risk according to section 4.1 have been identified, an additional approach to dose calculation should be taken. Information about pharmacodynamics can give further guidance for dose selection. The 'Minimal Anticipated Biological Effect Level' (MABEL) approach is recommended. The MABEL is the anticipated dose level leading to a minimal biological effect level in humans. When using this approach, potential differences of sensitivity for the mode of action of the investigational medicinal product between humans and animals, need to be taken into consideration e.g. derived from *in-vitro* studies. A safety factor may be applied for the calculation of the first dose in human from MABEL as discussed below.

The calculation of MABEL should utilise all *in vitro* and *in vivo* information available from pharmacokinetic/pharmacodynamic (PK/PD) data such as:

i) target binding and receptor occupancy studies *in vitro* in target cells from human and the relevant animal species;
ii) concentration-response curves *in vitro* in target cells from human and the relevant animal species and dose/exposure-response *in vivo* in the relevant animal species.
iii) exposures at pharmacological doses in the relevant animal species.

Wherever possible, the above data should be integrated in a PK/PD modelling approach for the determination of the MABEL.

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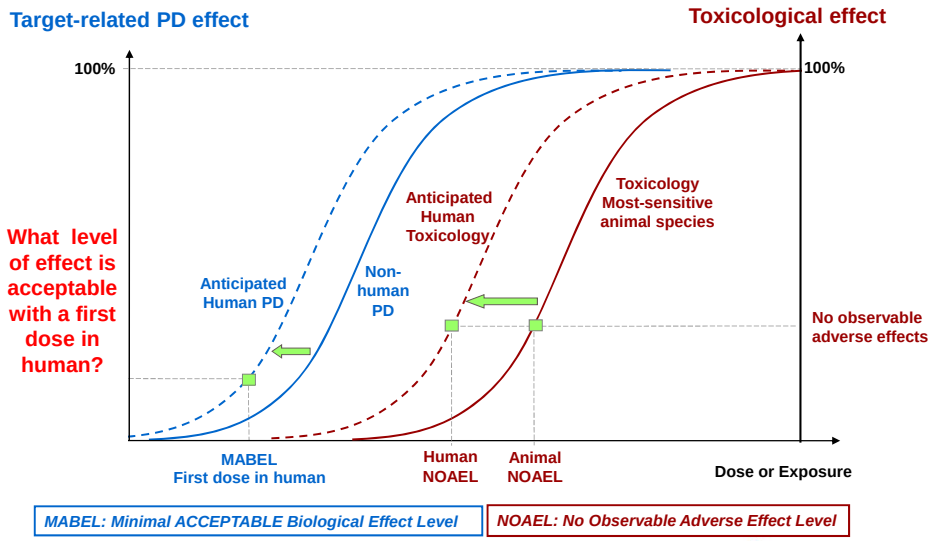
Beyond the "safety factor approach" *From NOAEL to MABEL, minimal ACCEPTABLE biological effect level for a first dose in a human*



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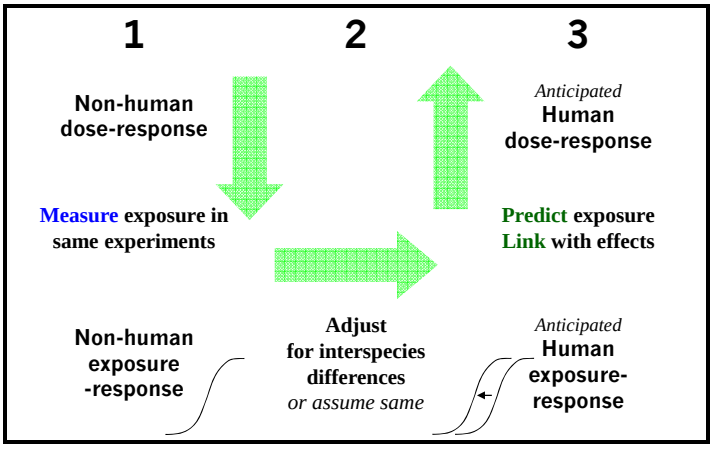
How? A process for scaling drug effects from non-human species to man

Xenobiotica, 2007; 37(10–11): 1331–1354
P. J. LOWE[1], Y. HIJAZI[1], O. LUTTRINGER[1], H. YIN[2], R. SARANGAPANI[2], & D. HOWARD[2]



... rather than assuming that a mg/kg bodyweight dose in pharmacology or toxicology species will give equivalent effects in man

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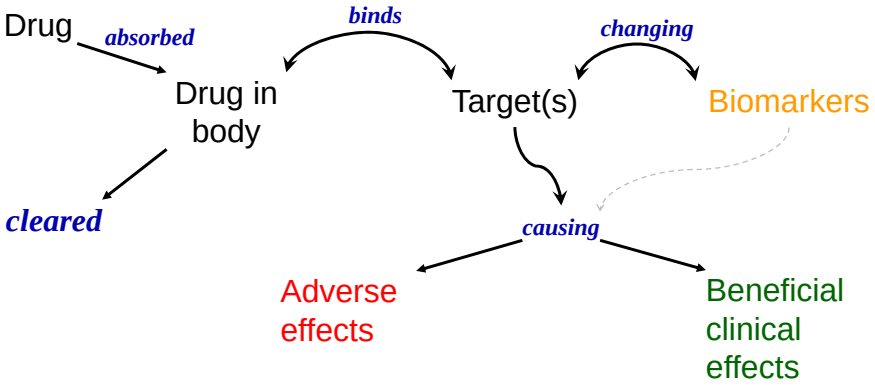
How? A concept – document causal chain from drug exposure to clinically measureable effects



Investigate, for each step in the causal chain

- interspecies differences
- *(and, note, different departments often provide the data!)*

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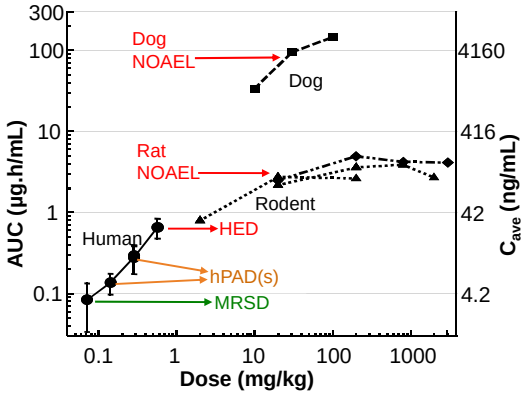
Example of correlative review of non-human and human (predicted) exposure and toxicity



- Extended pharmacology studies provide initial exploration of NOAEL
- Correlate exposure (AUC, C_{ave}) with NOAEL or LOAEL through simple exposure-response graphics or function
- Account and correct for interspecies differences such as unbound fraction, receptor potency, etc.

Novartis, ancient data on file

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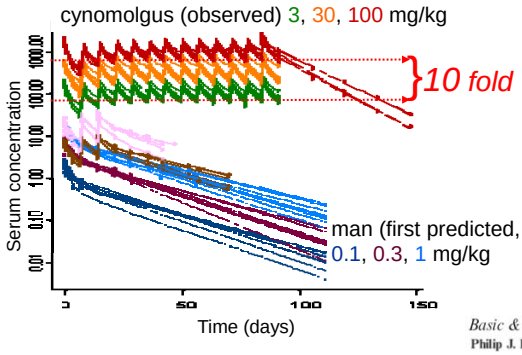
Exposure safety envelope over time *and start to consider occupancy or free target suppression in safety assessment*

Pharmacokinetics – generate large exposure safety margin for potential "off target" effects

Limit exposure through study design



Pharmacodynamics – target ligand suppression "on target"

- Cell surface target: Biological response, receptor occupancy and/or PK nonlinearity
- Soluble target: measure total ligand or mAb-ligand complex
- mAb-ligand binding model used to predict suppression of free ligand

Basic & Clinical Pharmacology & Toxicology, **106**, 195–209
Philip J. Lowe[1], Stacey Tannenbaum[2], Kai Wu[3], Peter Lloyd[4] and Jennifer Sims[4]

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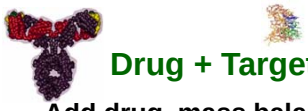
Binding characteristics. Biotherapeutic and target related by simple *equilibrium* reaction



Drug + Target ⇆ Drug-Target Complex

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

Phil's 3rd year notes, 1977

Enzyme kinetics

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

assumptions

① $e \ll S$ usually at least 100×

② $v = k_3[ES]$ v = overall rate

③ $k_2 \gg k_3$ Michalis Menton assumption

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

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Dose for first clinical study? MABEL? What is occupancy at early times, before significant distribution and clearance?

Quick method

- If [*mAb*] >> [*target*], 1:1 binding, use

$$Occupancy = \frac{[mAb]}{K_D + [mAb]}$$

- Binding affinity 1.88 nM (TGN1412)
- 0.1 mg/kg (7 mg) in 2.5 L plasma
- Peak Occupancy 90.9%

With Expression

- 150000 CD28 receptors per T cell
- 1.3×10^9 T lymphocytes/litre blood
- Assume 1:1 binding & fast equilibrium
- Peak Occupancy 90.6% @ 0.1 mg/kg
- or 10% @ 1.5 µg/kg *(1.1µg/kg quick method)*

Microsoft Excel Worksheet

mAb + Target ⇆ *Target-mAb Complex*

$$K_D = \frac{[mAb][Target]}{[Complex]}$$

$$TD = mAb + Complex \qquad \therefore mAb = TD - Complex$$

$$TT = Target + Complex \qquad \therefore Target = TT - Complex$$

$$Complex = \frac{(K_d + TD + TT) - \sqrt{(K_d + TD + TT)^2 - 4.TD.TT}}{2}$$

$$Occupancy = \frac{Complex}{TT}$$

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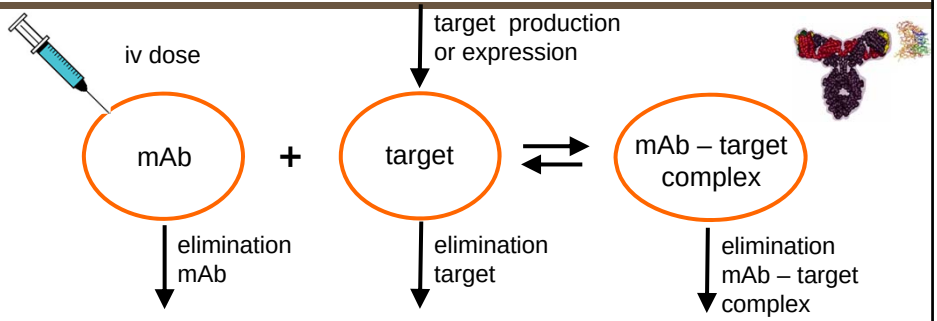
Incorporating dynamics of drug distribution and elimination plus target turnover – a PKPD binding model



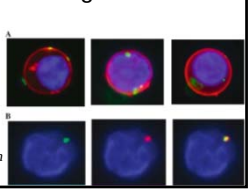
slow clearance
V ~ 3 L central, for 70 kg
$t_{½}$ ~ 3-4 w

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

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

Mager DR, Jusko WJ. General Pharmacokinetic Model for Drugs Exhibiting Target-Mediated Drug Disposition. J PKPD 2001; 28: 507-532

Ng CM, Stefanich E, Anand BS, Fielder PJ, Vaickus L. Pharmacokinetics/pharmacodynamics of nondepleting anti-CD4 monoclonal antibody (TRX1) in healthy human volunteers. Pharm Res 2006; 23:95-103



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Three 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 &/or by reference to prior similar antibodies
- Binding affinity to the target ligand:
  - species differences understood during *in vitro* characterisation of the drug
- **Localisation, expression and turnover of target, clearance of drug-target complex**
  - species differences sometimes not well understood

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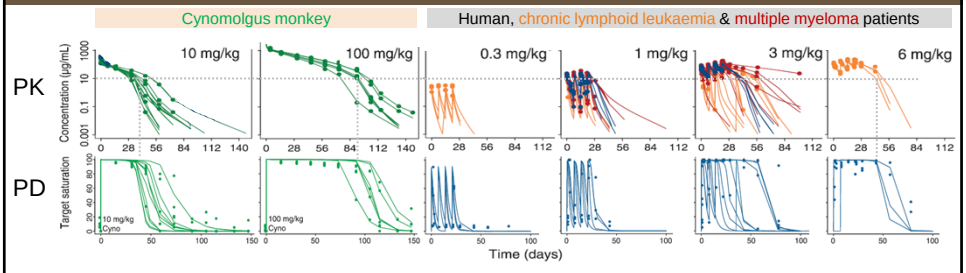
Monoclonal antibody binds and occupies cell surface target

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



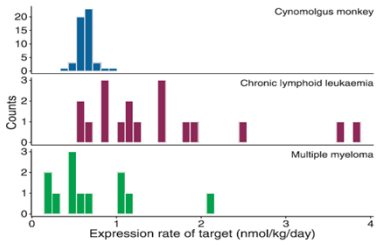


Fig. 6. Distribution of individual cynomolgus monkey and patient values for the turnover or expression rate of the target.

- 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

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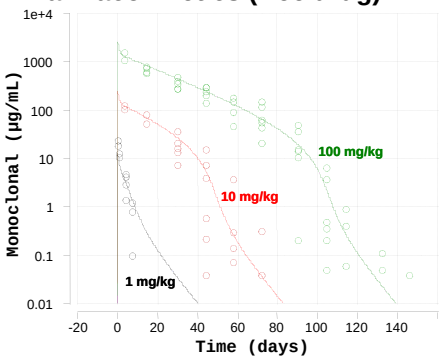
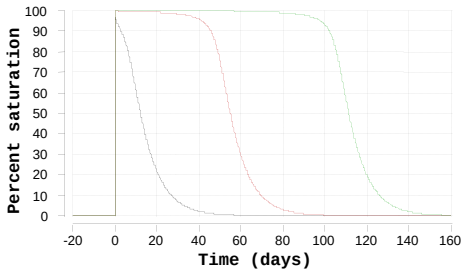
Target binding model enables direct display of occupancy

Calculated from quantities of mAb-target complex and total target
Adjust parameters to selected species using in vitro and in vivo data

Pharmacokinetics (free drug)



Saturation, or target occupancy




```
DADT(TA) =      -FA*CLA/V -CPLX*CLC/V -PS*(FA/V+AP/VP)
DADT(TB) = RINB -FB*CLB/V -CPLX*CLC/V
DADT(AP) =                          PS*(FA/V-AP/VP)
CPLX=((KD*V+TA+TB)-((KD*V+TA+TB)**2-4*TA*TB)**0.5)/2
FA  = TA-CPLX            ;FREE A = TOTAL A - COMPLEX
FB  = TB-CPLX            ;FREE B = TOTAL B - COMPLEX
SAT = 100*CPLX/TB
```

- Clearances (drug A, target B, complex C)
- Volumes (central, peripheral)
- Rate of target production or expression ($R_{IN,B}$)
- Binding constant, K_D (or K_M, IC_{50}, EC_{50})

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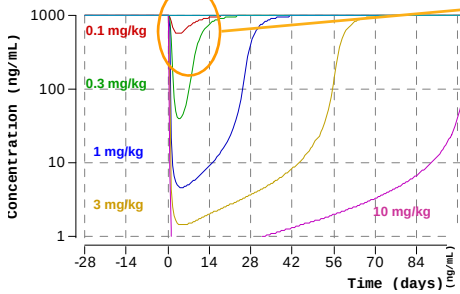
Scaled suppression of target free ligand to man

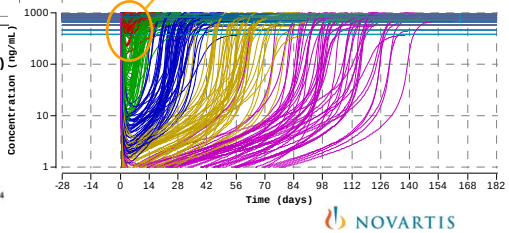
assuming in vitro binding affinity

- Prior model for mAb in human used for human simulations, only adjusting K_d to new value
- Specifies both monoclonal antibody clearance and distribution and target production and turnover
- Indicate uncertainty in predictions through e.g. Monte-Carlo simulation

MABEL



Monte-Carlo simulation



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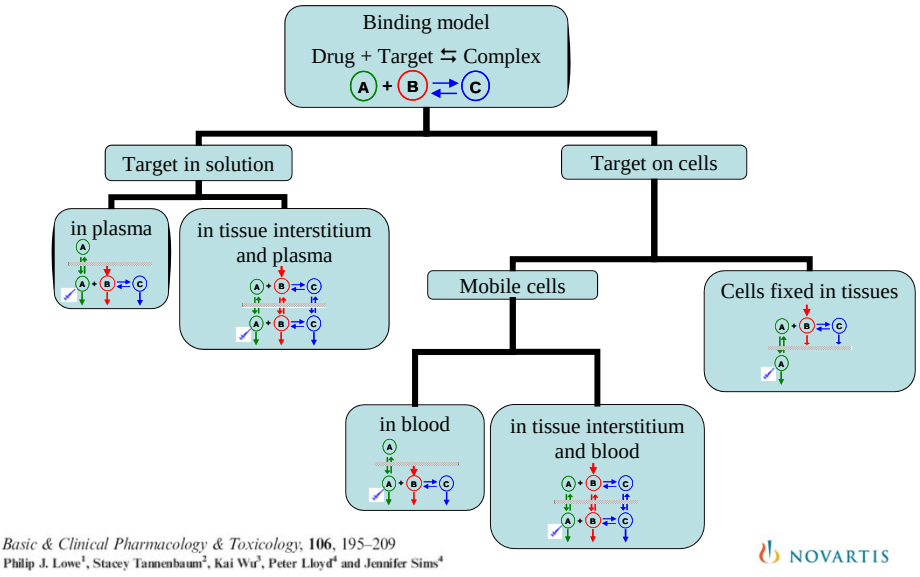
Taxonomy of drug-target binding physiological localisations



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Summary – to scale doses of biologics for man

- Understand mechanism of action and pharmacology, the location, expression and turnover of the target
- Delve into limitations of preclinical data for predicting human safety
- Translate the science to humans; account for differences in relative binding potency, expression and turnover
- Estimate the clinical starting dose for first time in human study using all pertinent studies, toxicology AND pharmacology – not just tox!
  - ➢No simple algorithm for use of MABEL – case by case – think and justify!

If necessary

- use PK/PD data from initial and subsequent dose cohorts to aid dose escalation within first human study
- Consider stopping rules, exposure limitations
- Design the right clinical study to mitigate risk

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