Calculation of the Minimum Anticipated Biological Effect Level (MABEL) and 1st dose in human

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Acknowledgements

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* For input into MABEL and PK/PD modelling aspects in particular

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Paracelsus 1493 – 1541

Alle Ding' sind Gift und nichts ohn' Gift; allein die Dosis macht, das ein Ding kein Gift ist.
"All things are poison and nothing is without poison, only the dose makes a thing be poison."
Guidance for Industry and Reviewers

Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers

Step 1 Determine \textit{No Observable Adverse Effect Level} (NOAEL)

Step 2 Convert NOAEL to a \textit{Human Equivalent Dose} (HED)
- generally normalised to body surface area

Step 3 Select HED from the most appropriate species
- additional factors: metabolism, receptors, binding epitopes
- default: most sensitive species (lowest HED)

Step 4 Apply a safety factor (>10-fold) to give a:
\textit{“Maximum Recommended Starting Dose” (MRSD)}

Step 5 Adjust based on pharmacologically active dose

But…

\textbf{Why start with the highest dose you think is safe?}

\textbf{Better to start with the lowest dose you think is active}
A safe starting dose in man should be driven by pharmacology & toxicology.

MABEL  Therapeutic Range  Unacceptable Toxicity

Effect

Dose or Exposure

Min Effective Dose (MED)  NOAEL  NOEL?

10 100 1000 10000

A safe starting dose in man should be driven by pharmacology & toxicology.
Summary: MABEL approach

**Toxicology**

Determine “No Observable Adverse Effect Level” (NOAEL)

Convert NOAEL to a “Human Equivalent Dose” (HED)
  - adjust for anticipated exposure in man
  - adjust for inter-species differences in affinity / potency

Apply >10-fold safety factor

**Pharmacology**

Estimate human “Minimal Anticipated Biological Effect Level” (MABEL)
  - justify based on pharmacology
  - adjust for anticipated exposure in man
  - include anticipated duration of effect
  - adjust for inter-species differences in affinity / potency

“Maximum Recommended Starting Dose”
  - define anticipated safety window based on NOAEL and MABEL
  - appropriate safety factor, if necessary, based on potential risk
Pharmacology data

- Understanding of mechanism of action
- Receptor occupancy estimates
- In vitro, ex vivo and/or in vivo concentration-response data
Receptor occupancy

$$K_d = 1.88 \text{ nM}$$

- **TGN1412** + **CD28** → **mAb – ligand complex**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>0.1mg/kg = 7 mg</td>
</tr>
<tr>
<td>MW</td>
<td>150,000</td>
</tr>
<tr>
<td>Plasma volume</td>
<td>2.5 L</td>
</tr>
<tr>
<td><strong>TGN1412</strong> = 18.7 nM</td>
<td>(immediately post-dose)</td>
</tr>
<tr>
<td><strong>Tcell</strong> = 1.9 x 10^6 mL^-1</td>
<td>CD28 / cell 150,000</td>
</tr>
<tr>
<td><strong>CD28</strong> = 0.95 nM</td>
<td>at baseline</td>
</tr>
<tr>
<td><strong>CD28-TGN1412</strong> = 0.86 nM</td>
<td>at equilibrium</td>
</tr>
</tbody>
</table>

90% receptor occupancy
Receptor occupancy

Dose (mg/kg)

Receptor occupancy (%)

0.0001 0.001 0.01 0.1 1 10

0 20 40 60 80 100

<10% receptor occupancy may be more appropriate for an agonist at CD28: -0.001mg/kg dose

90% receptor occupancy may be appropriate for an antagonist

BUT, >10% may be acceptable even for an agonist:
Known pharmacology, human experience, confidence in preclinical data
High receptor occupancy may be appropriate for antagonist effect

anti-CD11a mAb

Joshi et al An overview of the pharmacokinetics and pharmacodynamics of efalizumab: a monoclonal antibody approved for use in psoriasis
J Clin Pharmacol 2006; 46: 10-20
High receptor occupancy may be appropriate for antagonist effect

- Initial dose may result in short duration of suppression of ligand
- Increasing doses have minimal impact on extent of suppression but increase the duration of suppression

- Duration of effect is governed by:
  - binding affinity to the target
  - ligand concentration and ligand turnover
  - and not only by the kinetics of mAb
In-vitro concentration-response data

In vitro human T cell proliferation

5.11A1 – murine parent to TGN1412
minimally effective conc: 0.1 µg/mL
initial concentration (immediately post dose)
plasma volume (man) = 2.5 L
dose (man) = 0.25 mg
~0.003 mg/kg #

# - 70 kg subject
NB difference in potency between 5.11A1 and TGN1412 not known

Figure 4. Stimulation of human T cells by superagonistic anti-CD28 mAb

Luhder F et al. Topological requirements and signalling properties of T cell-activating, anti-CD28 antibody superagonists
J. Exp. Med. 2003; 197(8): 955-966
TGN1412: MABEL dose calculation

**Toxicology**

- NOAEL: 50.0 mg/kg
- HED: 16.0 mg/kg
  - adjust for anticipated exposure in man (not done)
  - adjust for inter-species differences in affinity / potency (not done)

Apply ≥10-fold safety factor: 1.6 mg/kg
increased to 160-fold: 0.1 mg/kg

**Pharmacology**

- MABEL
  - justify based on pharmacology
  - adjust for anticipated exposure in man
  - include anticipated duration of effect
  - adjust for inter-species differences in affinity / potency

**in-vitro T-cell proliferation (0.1 µg/mL) murine parent to TGN1412 (5.11A1)**

ref 3 = ~0.003 mg/Kg in man

initial 10% receptor occupancy ~0.001 mg/kg in man

“Maximum Recommended Starting Dose”

- define anticipated safety window based on NOAEL and MABEL
- appropriate safety factor based on potential risk

0.001 mg/kg
Why did pharmacology approach and MRSD approach give such different outcome?
Selection of relevant species for safety assessment

What are the criteria for the selection of a pharmacologically relevant species?

- Target – sequence homology, expression of receptor or epitope
- In vitro binding affinity, receptor occupancy, on/off rate – compared to human
- In vitro bioactivity / potency – compared to human
- Pharmacologic activity (in vivo)
Relative potency in humans and species used for safety assessment: Relevance of cynomolgus monkey?

Expert Scientific Group on Phase 1 Clinical Trials Final Report, November 2006

Summary of *in vitro* activation and proliferation responses of human and Cynomolgus macaque lymphocytes to immobilised TGN1412

<table>
<thead>
<tr>
<th></th>
<th>TGN1412 evoked activation</th>
<th>TGN1412 evoked proliferation</th>
<th>IL-2 evoked activation</th>
<th>IL-2 evoked proliferation</th>
<th>TGN1412+IL-2 evoked activation</th>
<th>TGN1412+IL-2 evoked proliferation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human PBMC</td>
<td>+++</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>Could not be tested*</td>
<td>Could not be tested*</td>
</tr>
<tr>
<td>Macaque PBMC</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>

*: TGN1412 stimulates activation, IL-2 secretion and proliferation when given alone.

In initial *in vitro* assays, in which PBMC from Cynomolgus macaques were stimulated with immobilised TGN1412, cells did not undergo a proliferative response. Early indications are that Cynomolgus macaque PBMC are activated by TGN1412 but do not undergo proliferation. However, when exogenous human IL-2 was added to cultures of Cynomolgus macaque PBMC stimulated with immobilised TGN1412 then a strong proliferative response was observed. No proliferative response was observed following the addition of human IL-2 alone to Cynomolgus macaque PBMC cultures.
Consider all available preclinical data

• In vitro data

• Effects of candidate drug in animal species / models
  • Understand the limitations of animal species for predicting human safety
  • Information on relative potency in animal species versus humans

• Effects of surrogate / related products in animals models
  • Understand the limitations of animal species for predicting human safety
  • Information on relative potency in animal species versus humans
Peripheral T cell depletion observed with 5.11A1 (murine parent to TGN1412) in humanised mouse model

- Dose: 0.3 mg per mouse I.P
- Establish dose-response for T-cell depletion in this model?
- Account for relative potency of 5.11A1 and TGN1412

Ref: Legrand N et al.
Transient accumulation of human mature thymocytes and regulatory T cells with CD28 superagonist in “human immune system” Rag2-/-γc-/- mice
Blood 2006; 108: 238-245
Splenomegaly and lymphadenopathy observed in rats given JJ316 (mouse anti-rat CD28 antibody)

- Dose: 1mg per rat I.P
- Establish dose-response for lymphocytosis in this model?
- Account for relative potency of JJ316 and TGN1412

Figure 5. JJ316 treatment in vivo induces splenomegaly and lymphadenopathy. LEW rats received a single i.p. dose of 1 mg anti-CD28 mAb JJ319 (left), JJ316 (right) or PBS (as JJ319, not shown) and were killed 3 days later.
Consider all available preclinical data

- **In vitro data**
- **Effects of candidate drug in animal species / models**
  - Understand the limitations of animal species for predicting human safety
  - Information on relative potency in animal species versus humans
- **Effects of surrogate / related products in animals models**
  - Understand the limitations of animal species for predicting human safety
  - Information on relative potency in animal species versus humans

No dose-response data
Starting dose for FTIH study

- Therapeutic Range
- Unacceptable Toxicity
- NOEL
- NOAEL
- Min Effective Dose (MED)
- Starting dose?

Dose or Exposure

Effect
But, even if one is able to calculate MABEL and estimate a safe starting dose…

…What next?

Even if the starting dose is safe and set at a fraction of the MABEL at some stage the dose escalations will enter the pharmacological dose range
Remember the dose-response curve
Dose escalation

Make use of preclinical data & PK/PD models developed to identify starting doses

- Build preclinical dose/concentration/response into model
- Refine model with initial human PK and PD data
- Adapt subsequent doses appropriately

Consider “split” dose approach to dosing

- e.g. 10% on day 1, 30% on day 2 and 60% on day 3
Summary

- Understand the target mechanism and pharmacology
- Understand the limitations of the preclinical data for predicting human safety
- Translate the science to humans and account for differences in relative potency
- Estimate the clinical starting dose for FTIH study using both toxicology AND pharmacology
  - No simple algorithm for use of MABEL – case by case!
- Use PK/PD data from initial and subsequent dose cohorts to aid dose escalation in FTIH study
- Consider stopping rules, exposure limitations based on the pharmacology and toxicology
- Design the right clinical study to mitigate risk