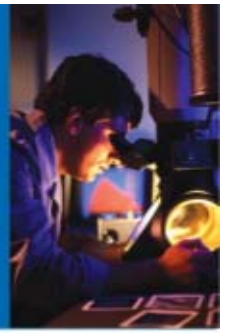
The Association of the British Pharmaceutical Industry



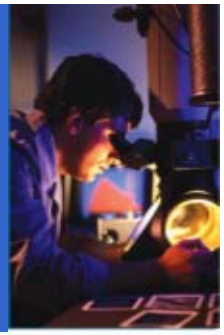
Calculation of the Minimum Anticipated Biological Effect Level (MABEL) and 1st dose in human

Jennifer Sims, PhD

AstraZeneca

Member of ABPI / BIA Early Stage Clinical Trials Taskforce

Acknowledgements



ABPI/ BIA Taskforce Members (Chaired by Dr David Chiswell and Professor Sir Colin Dollery)

Members of the Preclinical & Translation to the Clinic Working Group

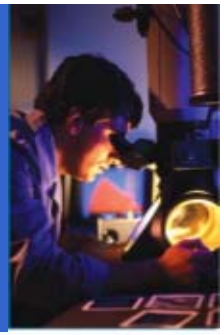
J. Sims, Syngenta
C. Springall, Covance
D. Austin, GSK*
P. Lloyd, Novartis*
M. Dempster, GSK*
P. Lowe, Novartis*
M. Owen, GSK
K. Chapman NC3Rs
S. Kennedy, GSK
J. Cavagnaro, Independent
D. Everitt, Johnson& Johnson
D. Glover, Independent
H Parmar, AstraZeneca
P. Round, CAT
N. Deschamps-Smith, ABPI

R. Peck, Lilly, Chair ABPI/BIA Clinical Trial Design Working Group*

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

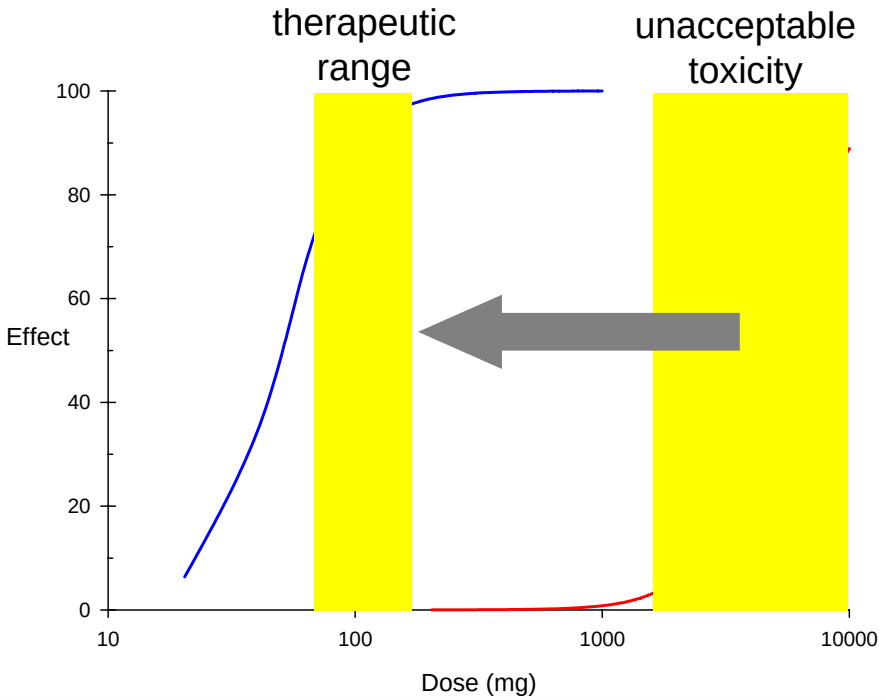
BIO's BioSafe Expert Nonclinical Safety Assessment Committee Members:

Drs. L. Andrews (Genzyme), J. Cavagnaro (Access Bio), M. Dempster (GSK), J. Green (BiogenIdec, Chair), S. Heidel (Lilly, Vice-chair), C. Horvath (Archemix Corp), A. Levin, M. Rogge (BiogenIdec, Sec.), J. Sims (AstraZeneca), R. Soltys (Genentech), J. Stoudemire (Ascenta), T. Terrell (Allergan), G. Treacy (Centocor), and G. Warner (Wyeth)



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."



U.S. Food and Drug Administration

CENTER FOR DRUG EVALUATION AND RESEARCH

Guidance for Industry and Reviewers

Estimating the Ma… …tial Clinical Trials for Th… …Volunteers

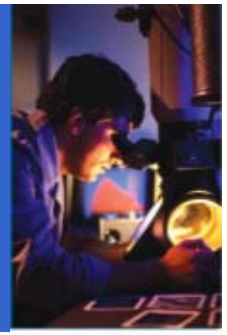
Step 1	**Determine… …fect Level" (NOAEL)**
Step 2	**Convert N… …nt Dose" (HED)** **- generally… …e area**
Step 3	**Select HE… …species** **- additiona… …tors, binding epitopes** **- default: … …st HED)**
Step 4	**Apply a sa… …a:** **"Maximu… …se" (MRSD)**
Step 5	***Adjus… …logically active dose***

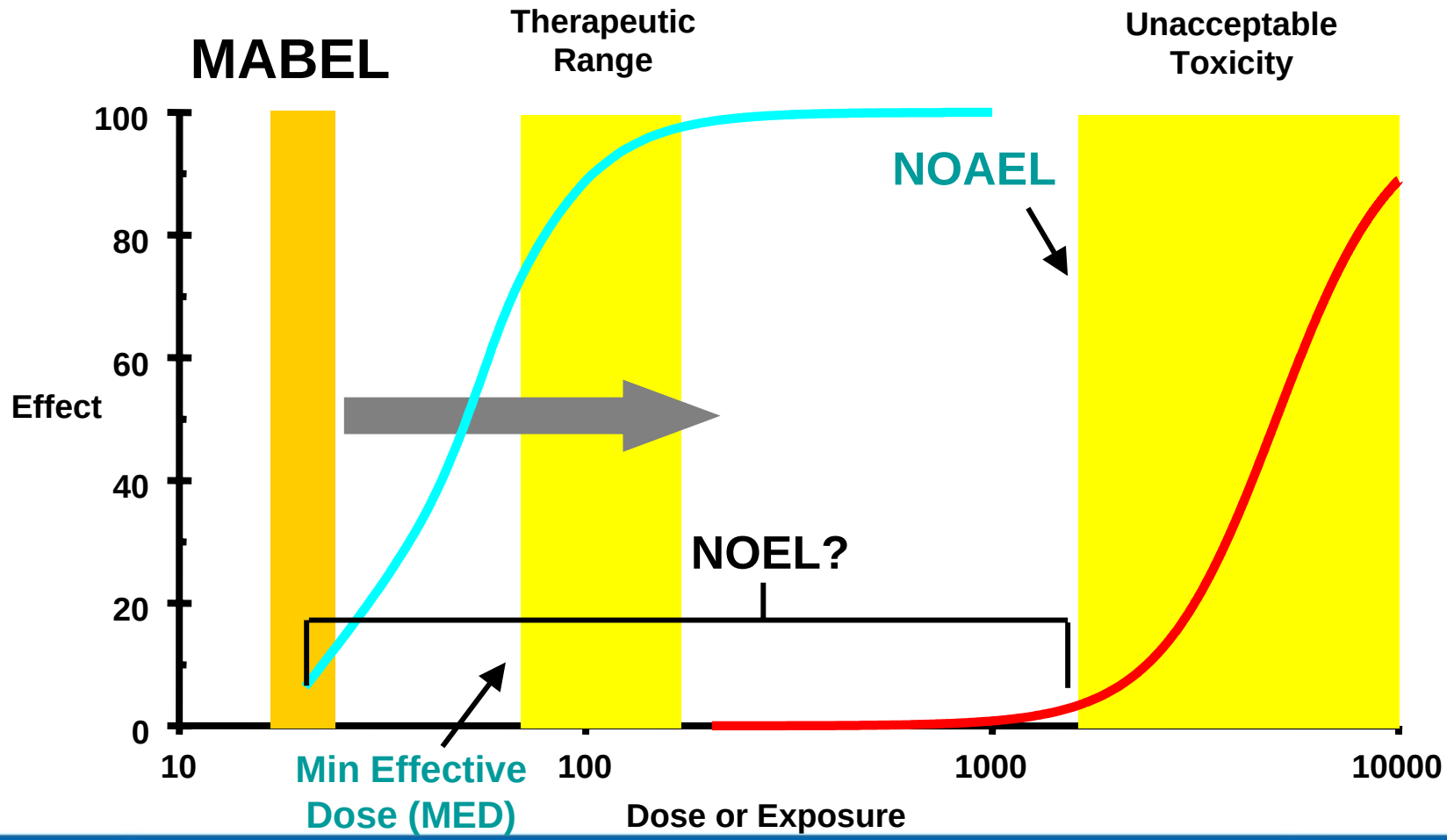
But…

Why start with the highest dose you think is safe?

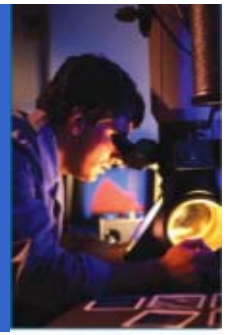
Better to start with the lowest dose you think is active

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)

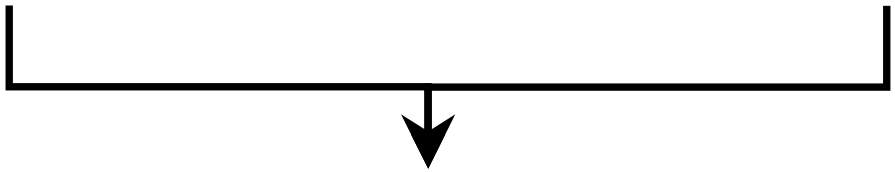
- adjust for anticipated **exposure** in man
- adjust for **inter-species differences in affinity / potency**

Apply ≥10-fold safety factor

Pharmacology

Estimate human “Minimal Anticipated Biological Effect Level” (MABEL)

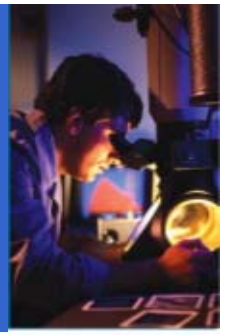
- **justify based on pharmacology**
- adjust for anticipated **exposure** in man
- include anticipated duration of effect
- adjust for **inter-species differences in affinity / potency**



“Maximum Recommended Starting Dose”

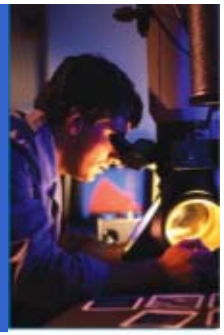
- define anticipated safety window based on NOAEL and MABEL
- appropriate safety factor, if necessary, based on potential risk

Pharmacology data



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

Receptor occupancy



TGN1412 + CD28 ⇄ mAb – ligand complex

K_d = 1.88 nM

Dose 0.1mg/kg = 7 mg
MW 150,000
plasma volume 2.5L

Tcell 1.9 x 10^6 mL^{-1}
CD28 / cell 150,000

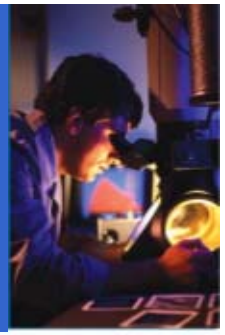
TGN1412 = 18.7 nM
(immediately post-dose)

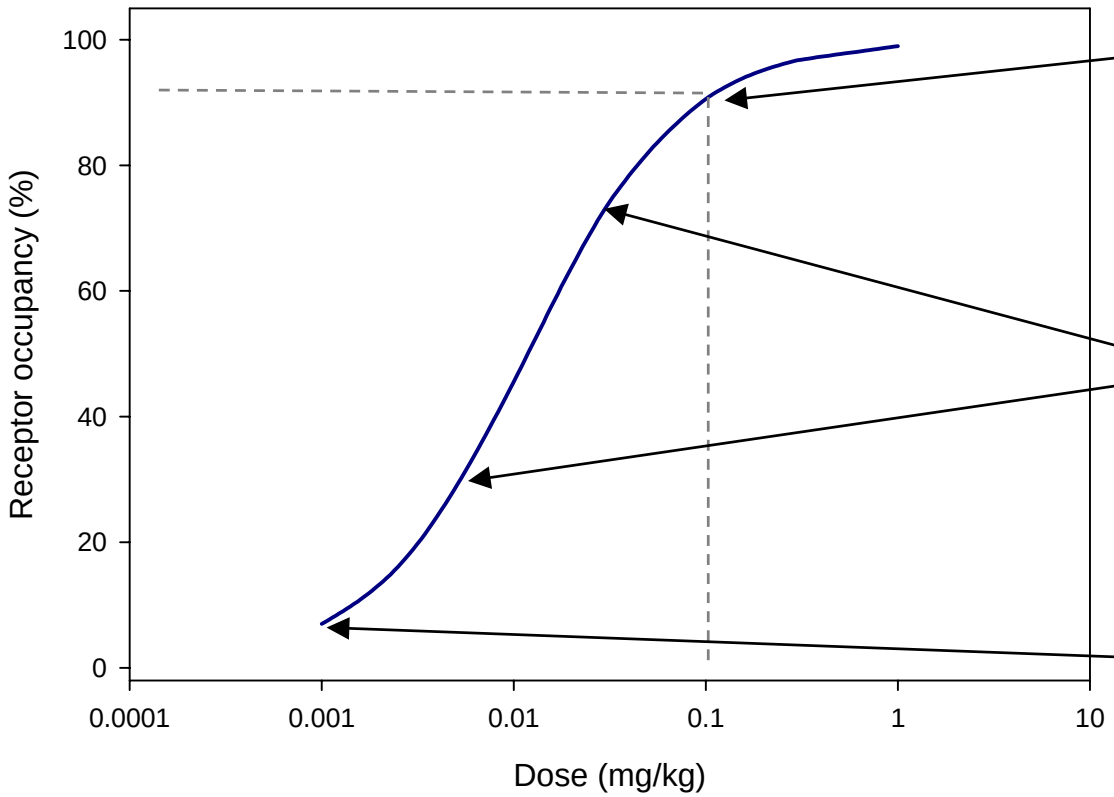
CD28 = 0.95 nM
at baseline

CD28-TGN1412 = 0.86 nM
at equilirium

90% receptor occupancy

Receptor occupancy



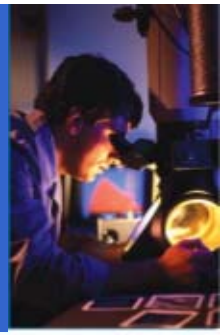


90% receptor occupancy may be appropriate for an antagonist

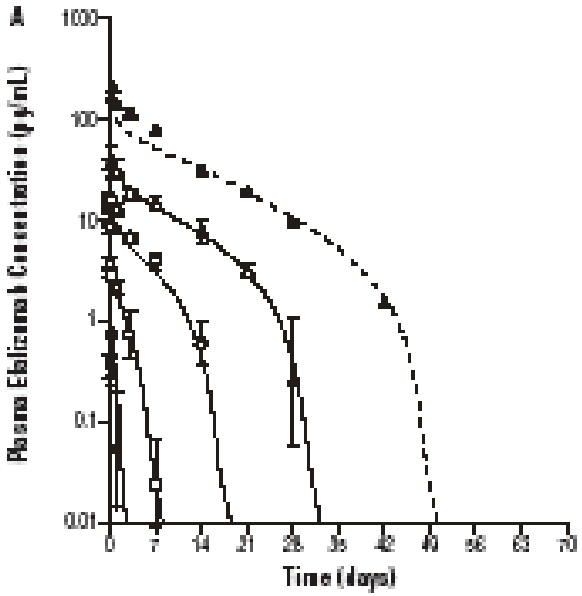
BUT, >10% may be acceptable even for an agonist: Known pharmacology, human experience, confidence in preclinical data

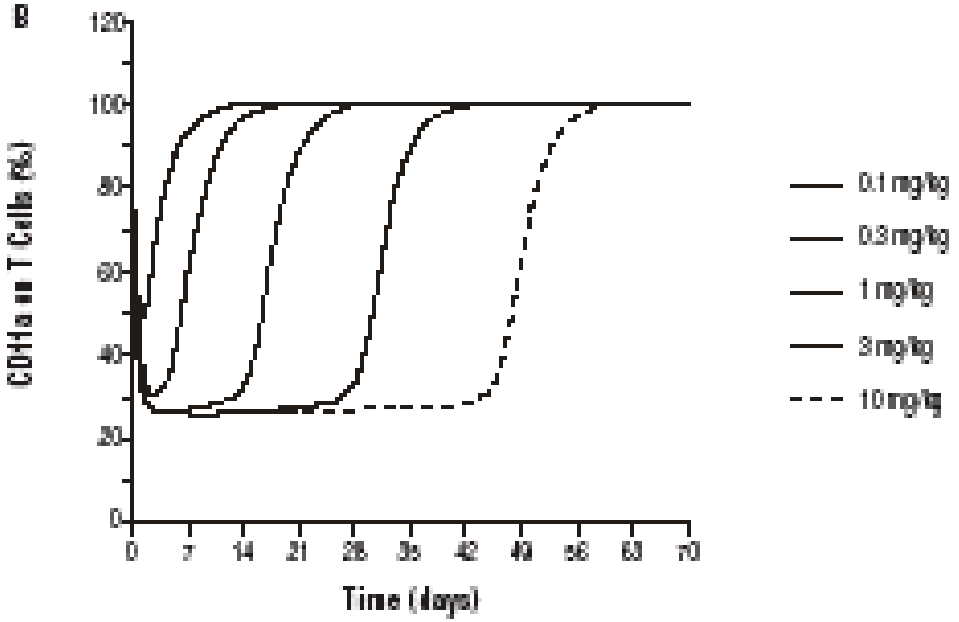
<10% receptor occupancy may be more appropriate for an agonist at CD28: -0.001mg/kg dose

High receptor occupancy may be appropriate for antagonist effect



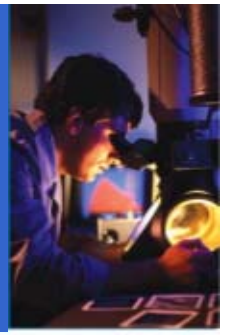
anti-CD11a mAb





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

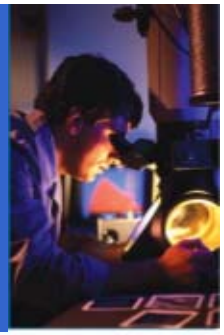
High receptor occupancy may be appropriate for antagonist effect



- 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 Tcell proliferation

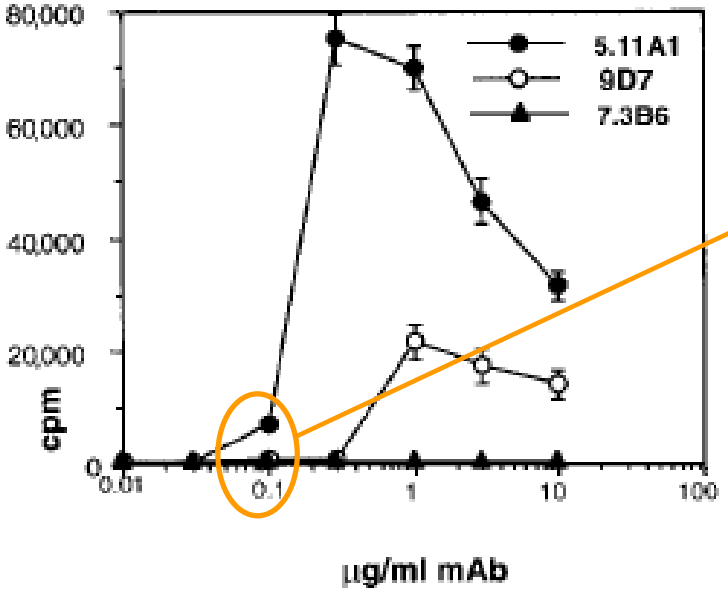


Figure 4. Stimulation of human T cells by superagonistic anti-CD28 mAb

5.11A1 – murine parent to TGN1412

minimally effective conc: 0.1 μg/mL

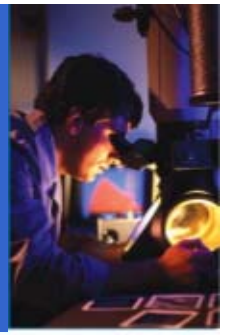
initial concentration (immediately post dose)
plasma volume (man) = 2.5 L
dose (man) = 0.25 mg
~0.003 mg/kg #

- 70 kg subject

NB difference in potency between 5.11A1 and TGN1412 not known

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**

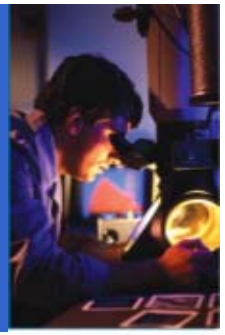
in-vitro T-cell proliferation (0.1 µg/mL) murine parent to TGN1412 (5.11A1) [ref 3] = ~0.003 mg/Kg in man

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

"Maximum Recommended Starting Dose"

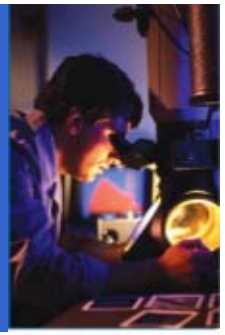
- define anticipated safety window based on NOAEL and MABEL
- appropriate safety factor based on potential risk

0.001 mg/kg



Why did pharmacology approach and MRSD approach give such different outcome?

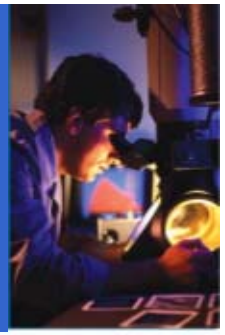
Selection of relevant species for safety assessment



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

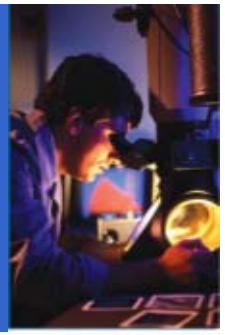
Summary of *in vitro* activation and proliferation responses of human and Cynomolgus macaque lymphocytes to immobilised TGN1412

	TGN1412 evoked activation	TGN1412 evoked proliferation	IL-2 evoked activation	IL-2 evoked proliferation	TGN1412+IL-2 evoked activation	TGN1412+IL-2 evoked proliferation
Human PBMC	++++	++++	–	–	Could not be tested*	Could not be tested*
Macaque PBMC	++	–	–	–	+++	+++

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

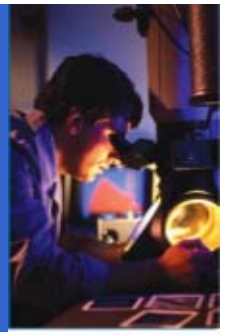
In initial *in vitro* assays, in which PBMC from Cynomolgus macaques were stimulated with immobilised TGN1412, cells did not undergo a proliferative response. Early indications are that Cynomolgus macaque PBMC are activated by TGN1412 but do not undergo proliferation. However, when exogenous human IL-2 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



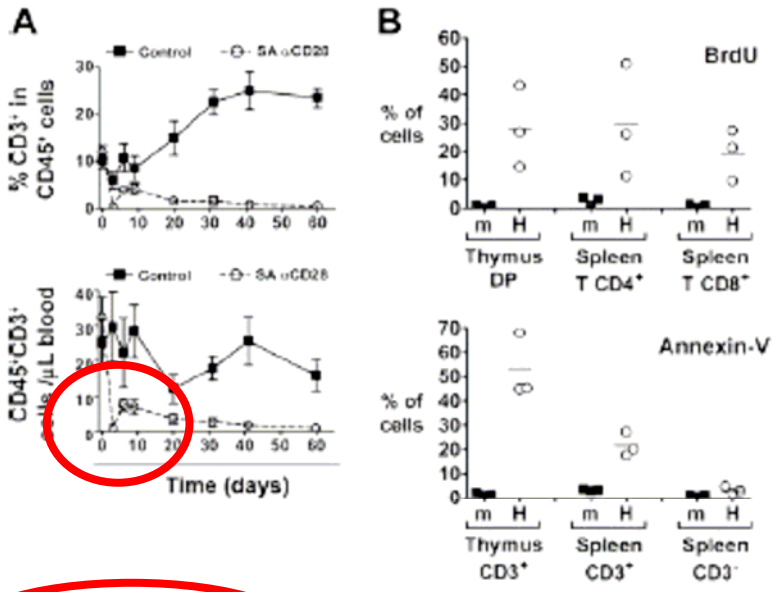


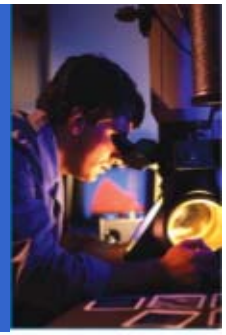
Figure 4. SA anti-CD28 treatment induces increased human thymic output despite T-cell depletion and high T-cell turnover in the periphery of HIS (BALB-Rag/γ) mice. (A) The percentage of CD3+ T cells among CD45+ cells (top) and the absolute number of human T cells (bottom) was monitored in the blood of IgG1 control (■) and SA anti-CD28–treated mice (○) over a 2-month period (mean ± SEM). Representative results from 1 experiment out of 3 are shown. (B) Control wild-type BALB/c mice (m) and HIS (BALB-Rag/γ) mice (H) were treated for 1 day with BrdU and incorporation by cells of the indicated subsets was analyzed (top panel). Proportion of Annexin-V+ cells was also determined in the indicated populations (bottom panel). Representative results from 1 experiment out of 2 are shown. Horizontal bars indicate mean values.

- **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 oberved In rats given JJ316 (mouse anti-rat CD28 antibody)



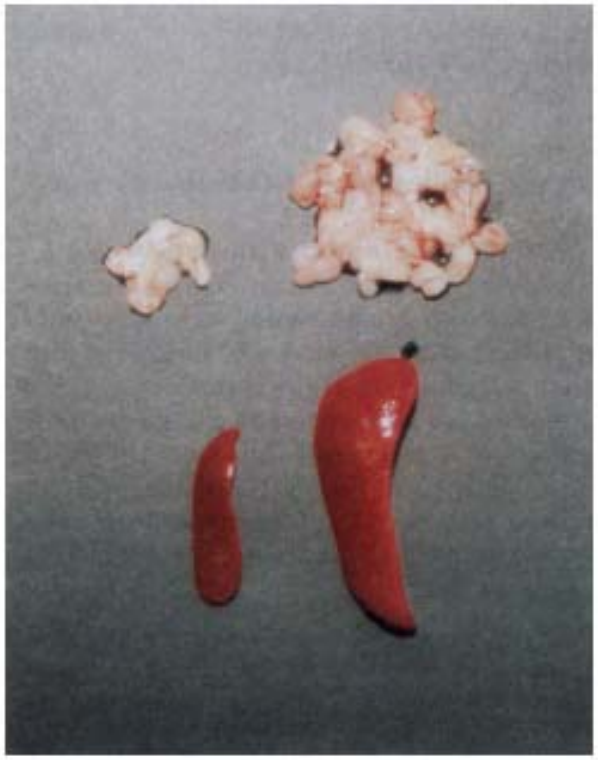


Figure 5. JJ316 treatment *in vivo* induces splenomegaly and lymphadenopathy. LEW rats received a single i.p. dose of 1 mg anti-CD28 mAb JJ319 (left), JJ316 (right) or PBS (as JJ319, not shown) and were killed 3 days later.

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

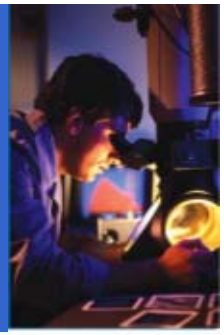
Eur. J. Immunol. 1997. 27: 239–247

Michael Tacke, Gabriele Hanke, Thomas Hanke and Thomas Hünig

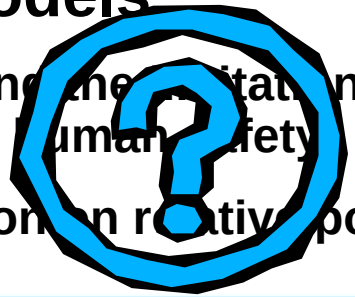
Institute for Virology and Immunobiology, University of Würzburg, Würzburg, Germany

CD28-mediated induction of proliferation in resting T cells *in vitro* and *in vivo* without engagement of the T cell receptor: evidence for functionally distinct forms of CD28

Consider all available preclinical data

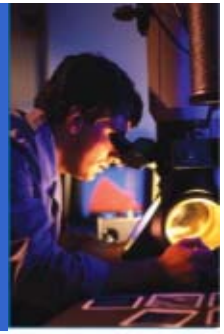


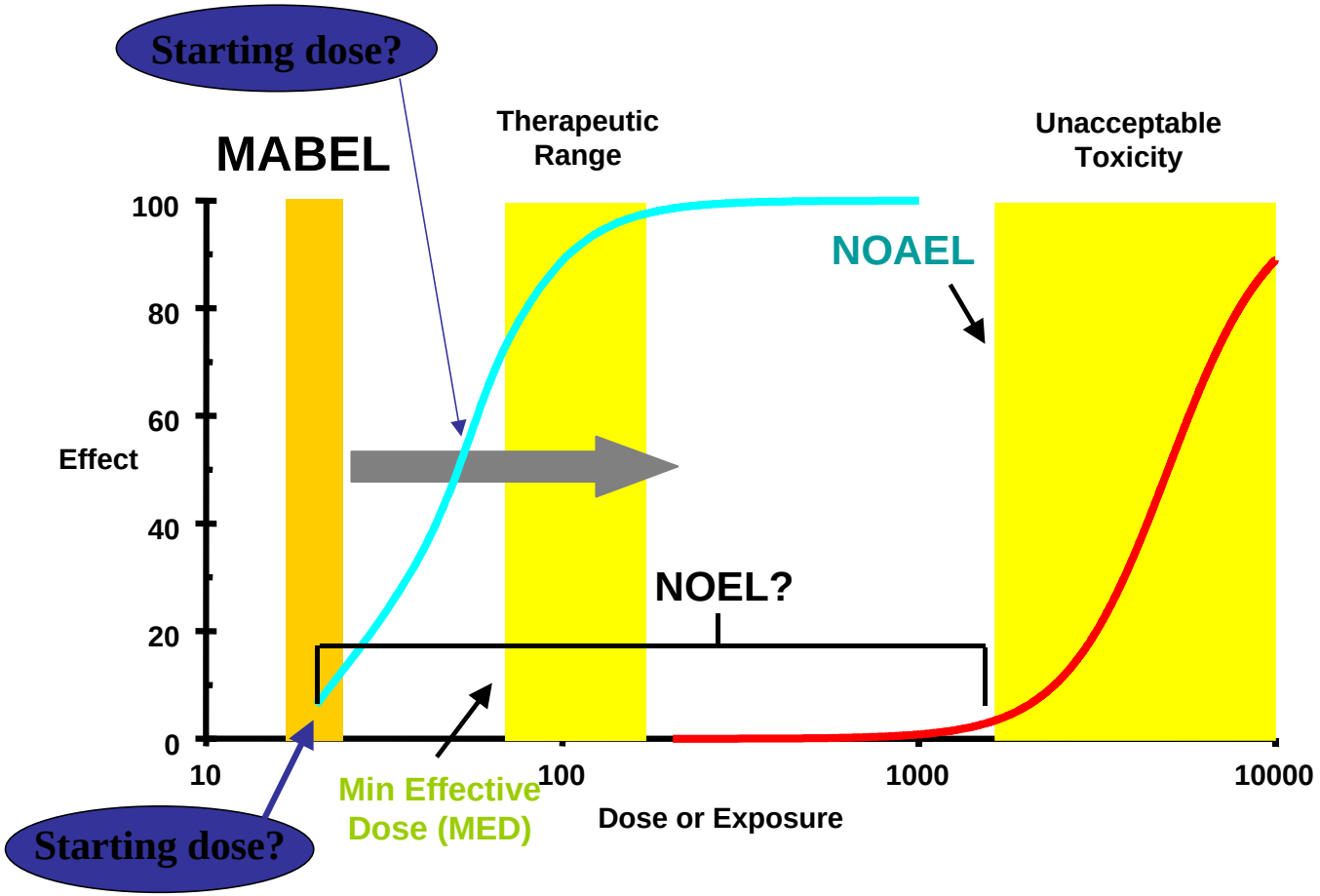
- **In vitro data**
- **Effects of candidate drug in animal species / models**
  - **Understand the limitations of animal species for predicting human safety**
  - **Information on relative potency in animal species versus humans**
- **Effects of surrogate / related products in animals models**
  - **Understand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



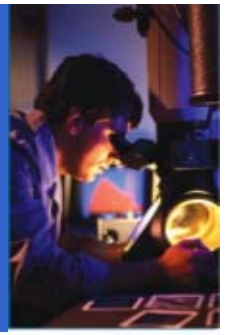
No dose-response data

Starting dose for FTIH study





Dose escalation

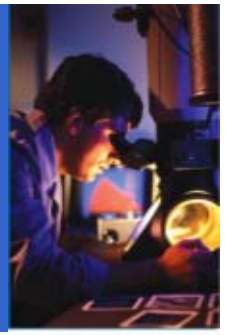


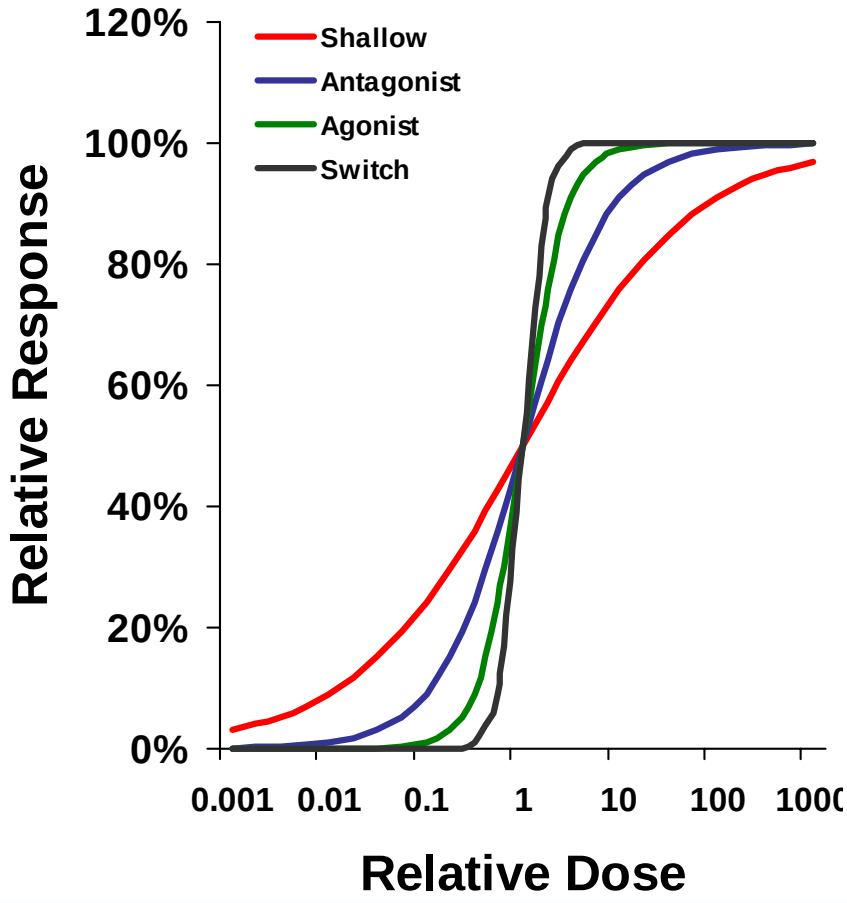
- **But, even if one is able to calculate MABEL and estimate a safe starting dose…**

…What next?

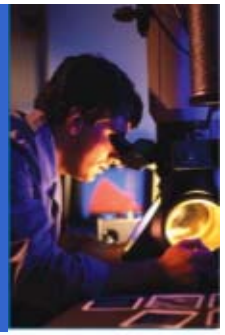
- **Even if the starting dose is safe and set at a fraction of the MABEL at some stage the dose escalations will enter the pharmacological dose range**

Remember the dose-response curve





Dose escalation



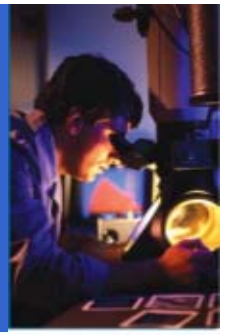
Make use of preclinical data & PK/PD models developed to identify starting doses

- 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**