

Non-Clinical Drug Development:

With Examples from Oncology Therapeutics

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Drug Development

Drug discovery & screening

Non-clinical development

Animal scale up

Phase I studies

Phase II studies

Phase III studies

Specific examples from anticancer drug development

Overview of Anticancer Drug Development

Flow chart indicating the development of an anticancer drug from IND (chemical synthesis and formulation development to animal models for efficacy to assay development to animal PK and PD), through clinical development (Phase I, Phase II, Phase III) to NDA.

Goals of Non-Clinical Testing of Small Molecule Drugs and Biologicals

To characterize potential adverse drug effects

- Define end organ toxicities

- Define reversibility of toxicity

To characterize pharmacokinetic profile

To characterize beneficial pharmacodynamic effects

- Proof of principle

To guide safe use in human clinical studies

- To determine a safe & reasonable starting dose

- Provide monitoring guidelines for the clinical study

Provide sufficient data to conclude that patients are not exposed to unreasonable risks

Oncology drug development is changing in the new era of targeted cancer therapies

Targeted Therapies & Preclinical Development

(adapted from Paoletti 2005)

<u>Characteristic</u>	<u>Cytotoxic Agents</u>	<u>Targeted Agents</u>
Discovery	Cell based, empirical	Receptor based screen, rationale
Mechanism	Often unknown	Basis for screening
Pharmacological Effect	Cytotoxic	Cytostatic
Specificity	Non-selective	Selective
Dose and schedule	Pulsed, cyclical at MTD	Continuous, at tolerable dose

Targeted Therapies & Phase I Trials

(adapted from Paoletti 2005)

<u>Characteristic</u>	<u>Cytotoxic Agents</u>	<u>Targeted Agents</u>
Objectives	PK, MTD	Optimal biological dose (OBD), PK, PK-PD
Disease	All types	All types or target bearing
Dose	Toxicity-guided escalation	Biomarker-guided escalation
Endpoints	Toxicity, MTD, PK	Target inhibition, OBD, PK
Design	Dose escalation in small cohorts	Dose escalation to target inhibition

Components of Non-Clinical Drug Development

In vitro studies: Cell lines, cell-free systems (drug screening)

Drug formulation

Chemistry, Manufacturing, and Controls: Drug supply & quality

In vivo efficacy studies: Animal models and proof of principle

Non-clinical safety studies

In Vitro Study Goals: Define the Drug's Pharmacology

Molecular mechanism of action and specific drug targets

Molecular pharmacology

Determinants of response

Intracellular pharmacodynamics

Mechanisms of drug resistance

In Vitro Study Systems

Cell-free assay for specific molecular effects

Enzyme inhibition, receptor blockade, etc.

Yeast-based screening in genetically defined target

Mammalian cell lines: (murine, human, etc.)

Preclinical Pharmacology In Vitro Studies of Cancer Agents (1)

Define anticancer effects

Growth inhibition, differentiation, apoptosis, etc

Impact on defined biochemical and molecular pathways

RNA, DNA and protein biosynthesis, signaling kinases, etc

Spectrum of antitumor activity

Human tumor cell lines

Preclinical Pharmacology In Vitro Studies of Cancer Agents (2)

Cellular uptake and membrane transport
MDR, MRP, etc

Mechanisms of resistance

In vitro drug metabolism
P450 isoenzymes

Effects on hERG channels (prolonged QT interval risk)

Preliminary protein binding studies

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Drug Supply and Formulation

Drug supply: bulk chemical synthesis, natural product isolation, etc.

Good Manufacturing Practice (GMP) guidelines for pharmaceutical product manufacturing

Formulation for clinical delivery of drug: vehicles for intravenous or other routes of administration

Drug Supply Issues

Paclitaxel source from the bark and wood of the Pacific Yew tree

Early drug supply limited the amount available for initial clinical trials

Newer semisynthetic production from the needles of the Yew tree (renewable)

Drug Formulation Issues

Poor water solubility of natural products

Paclitaxel formulation in Cremophore EL™ (increased toxicity?)

Camptothecin derivatives formulated in a dimethylacetamide, polyethylene glycol and phosphoric acid vehicle

Later formulated as a lipid colloidal dispersion

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In Vivo Study Goals: Animal Models

Efficacy: Proof of therapeutic principle

Toxicology: Toxicity profile

Practical Issues:

- Animal pharmacokinetics and pharmacodynamics

- Starting dose and schedule for clinical trials

Animal Models

Proof of Principle

Animal screening is too expensive for routine use

Efficacy in animal models of specific disease states occurs after in vitro studies

Evaluation of therapeutic index

Toxicity versus efficacy

Ideal Animal Model

Validity

Selectivity

Predictability

Reproducibility

“There is no perfect tumor model”

Endostatin: An Endogenous Inhibitor of Angiogenesis and Tumor Growth

O'Reilly et al, Cell 88:277-285 (1997)

Photograph of a mouse with tumor growth that was treated with endostatin. Another photograph of a mouse with tumor growth that was treated with a saline solution. The tumor on the mouse treated with saline solution appears to be much larger than the tumor on the rat that was treated with endostatin.

Animal Models in Cancer

Spontaneous tumors

- Idiopathic

- Carcinogen-induced

- Transgenic/gene knockout animals: p53, RB, etc

Transplanted tumors

- Animal tumors: Lewis lung, S180 sarcoma, etc

- Human tumor xenografts: human tumor lines implanted in immunodeficient mice (current NCI standard in vivo efficacy testing system)

- Human tumors growing in vivo in implantable hollow fibers

Human Tumor Xenografts

Athymic “nude” mice developed in 1960’s

Mutation in nu gene on chromosome 11

Phenotype: retarded growth, low fertility, no fur, immunocompromised

Lack thymus gland, T-cell immunity

First human tumor xenograft of colon adenocarcinoma by Rygaard & Poulson, 1969

Athymic Nude Mice

Six photographs of athymic nude mice

Murine Xenograft Sites

Subcutaneous tumor (NCI method of choice) with IP drug administration

Intraperitoneal

Intracranial

Intrasplenic

Renal subcapsule

Site-specific (orthotopic) organ inoculation

Xenograft Study Endpoints

Toxicity Endpoints:

- Drug related death
- Net animal weight loss

Efficacy Endpoints

- Clonogenic assay
- Tumor growth assay (corrected for tumor doubling time)
- Treated/control survival ratio
- Tumor weight change

Xenograft Tumor Weight Change

Tumor weight change ratio (used by the NCI in xenograft evaluation)

Defined as: treated/control x 100%

Tumor weight in mg = $(a \times b^2)/2$

a = tumor length

b = tumor width

T/C < 40-50% is considered significant

Xenograft Advantages

Many different human tumor cell lines transplantable

Wide representation of most human solid tumors

Allows for evaluation of therapeutic index

Good correlation with drug regimens active in human lung, colon, breast, and melanoma cancers

Several decades of experience

Xenograft Disadvantages

Brain tumors difficult to model

Different biological behavior, metastases rare

Survival not an ideal endpoint: death from bulk of tumor, not invasion

Shorter doubling times than original growth in human

Less necrosis, better blood supply

Difficult to maintain animals due to infection risks

Host directed therapies (angiogenesis, immune modulation) may not be applicable

Human vs. murine effects

Ability to mimic the human tumor microenvironment is limited

Other Animal Models

Orthotopic animal models: Tumor cell implantation in target organ

- Metastatic disease models

Transgenic Animal Models

- P53 or other tumor suppressor gene knockout animals

- Endogenous tumor cell development

- May be of high value for mAb therapies

Low passage xenograft tumors

- Direct implantation from patients to animals

Non-Clinical Efficacy Testing The FDA Perspective

(J. Leighton, FDA ODAC Meeting, March 13, 2006)

Pharmacological activity assessed by models of disease are generally of low relevance to safety (IND) and efficacy (NDA) decisions

Efficacy in vivo and in vitro from non-clinical studies may not dependably predict clinical efficacy

- Heterogeneity of disease
- Interspecies differences in ADME
- Role of immune system

Pharmacology studies are useful for:

- Assessing an appropriate schedule (daily, weekly, q3wks)
- Justification for a drug combination
- Understanding effect at a molecular target
 - Examine receptor specificity
 - Identifying and evaluating biomarkers

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Non-Clinical Safety Studies

Safety pharmacology

Pharmacokinetic and toxicokinetics studies

Genotoxicity studies

Reproductive toxicity studies

Carcinogenicity studies

Formal toxicology studies

Single dose toxicity studies

Repeated dose toxicity studies

Excellent reference:

Anticancer Drug Development Guide, 2nd edition, BA Teicher and PA Andrews, editors,
Humana Press, Totowa, NJ, 2004

Non-Clinical Toxicology Studies

GLP Toxicology is expected

Use the clinical schedule, route, and formulation

Single dose acute toxicity studies required in 2 mammalian species prior to FIH studies

Classically rat and dog for small molecules

Non-human primates for biologicals

Repeat dose toxicology required for anticipated duration of clinical use for most non-oncology agents

3 mo. toxicology for \leq 3 mo. clinical study

Recommendations for anticancer agents may differ from other therapeutic areas

Expected Toxicology Testing for Phase I Oncology Drug Studies

(J. Leighton, FDA ODAC Meeting, March 13, 2006)

Clinical Schedule	Preclinical study schedule *
Every 21 d	Single dose study
Every 14 d	2 doses, 14 d apart
Weekly x 3, week off	Weekly x 3
Daily x 5, break	Daily x 5
Continuous daily	Daily for 28 days

* Study schedule does not include a recovery period

28 day toxicology is generally sufficient for DRUG trials extending beyond 28 days

Non-Clinical Toxicology Studies For Oncology Drug Combinations

May not be necessary for testing in advanced cancer patients

May exclude if:

No PK, PD, or metabolic interactions anticipated

Drugs are not packaged as a combination

All components well studied individually

Single Dose Toxicity Studies

Dose escalation study may be an alternative to a single dose design

Dose range should include maximally tolerated dose (MTD) and no adverse effect level (NOAEL)

Standard design

Early sacrifice at 24 to 48 hr and after 14 days

Repeated Dose Toxicity Studies

Duration of repeated dose studies related to duration of anticipated clinical use

Use same schedule and duration

Typically 14-28 days

Should include recovery group

Use can support repeat dose clinical studies

Non-Clinical Toxicology Endpoints

Ongoing Endpoints

- Clinical signs, behavior

- Body weights and food consumption

- Clinical pathology (in larger species)

 - Hematology

 - Chemistry panels

- Toxicokinetics

End of Study Endpoints

- Macroscopic changes at necropsy

- Organ weights

- Histopathology of all organs

Maximum Recommended Starting Dose (MRSD) for FIH Trials

Determination of the No Observed Adverse Effect Level (NOAEL)

Conversion of NOAEL to Human Equivalent Dose (HED)

Selection of the most appropriate animal species

Application of a safety factor to determine MRSD

Compare MRSD with pharmacologically active dose (PAD)

FDA Guidance for Industry July 2005

Selection of MRSD

(FDA Guidance 2005)

Flow chart showing the following steps in the selection of MRSD.

1. Determine NOAELs (mg/kg) in toxicity studies
2. Is there justification for extrapolating animal NOAELs to HED based on mg/kg (or other appropriate normalization?)

↓
NO

Convert each animal
NOAEL to HED based
on BSA

Select HED from most ←
appropriate species

Choose safety factor and
divide HED by that factor

↓
YES

HED (mg/kg) =
NOAEL (mg/kg)
(or other appropriate
normalization)

Maximum Recommended
→ Starting Dose (MRSD)

Consider lowering dose based
on a variety of factors, e.g., PAD

Step 1: Determination of No Observed Adverse Effect Level (NOAEL)

NOAEL Definition

The highest dose level that does not produce a significant increase in adverse effects in comparison to the control group

Not the same as the no observed effect level

Review all available data in all species tested

Adverse events can be overt toxicities, surrogate laboratory markers, or exaggerated PD effects

Adverse effects defined as events that are considered unacceptable if produced by the initial dose in a Phase I clinical trial

FDA Guidance for Industry July 2005

Step 2: Convert Animal Dose to Human Equivalent Dose (HED)

Normalization of toxic dose levels across species often based upon body surface area
Deviations from BSA normalization must be justified

Animal dose in mg/kg is converted to mg/m² and reconverted to mg/kg
Many cancer treatments are dosed based on BSA (mg/m²)

FDA Guidance for Industry July 2005

HED Calculation

$$\text{HED (mg/kg)} = \frac{\text{Animal Km}}{\text{Human Km}} \times \text{Animal Dose (mg/kg)}$$

Km: mg/kg to mg/m² conversion factor

Adult human = 37

Child (20 kg) = 25

Mouse = 3

Rat = 6

Cynomolgus, rhesus or stumptail monkey = 12

FDA Guidance for Industry July 2005

Exceptions to BSA Scaling

Weight based (mg/kg) scaling

- Oral therapies limited by local toxicities

- Exposure parameters that scale by weight predict toxicity

 - Example C_{max} for antisense molecules

- Proteins administered IV with $M_r > 100,000$

Other scaling factors

- Alternate routes of administration (e.g. topical, intranasal, subcutaneous, intramuscular)

 - Normalize to area of application or to mg

- Administration into anatomical compartments with limited outside distribution (e.g. intrathecal, intravesical, intraocular, or intrapleural)

 - Normalize to compartmental volumes

Step 3: Most Appropriate Species Selection

After the NOAEL from all toxicology studies are converted to HED, then the MRSD must be derived from the most appropriate species

By default, use the most sensitive species, but must also consider...

- Pharmacokinetic ADME differences

- Class pharmacodynamic effects

- Agent pharmacology, receptor cross reactivity, etc

Example

- Phosphorothioate antisense DLT in humans and monkeys is complement activation

- Does not occur in rodents

FDA Guidance for Industry July 2005

Step 4: Application of a Safety Factor

Applied to the HED derived from the NOAEL from the most appropriate species

Divide the HED by the safety factor to determine the MRSD

By default, a safety factor = 10 is recommended
May raise or lower with justification

Altering the Safety Factor

Increasing the safety factor

- Steep dose response curve
- Severe toxicities anticipated
- Non-monitorable toxicity
- Toxicities without premonitory signs
- Variable bioavailability
- Irreversible toxicity
- Unexplained mortality
- Large PK variability
- Non-linear PK
- Inadequate dose-response
- Novel therapeutic target
- Animal models with limited utility

Decreasing the safety factor

- Requires highest quality toxicology data
- Well characterized class of drugs
- If NOAEL is based on toxicity studies of longer duration than the proposed clinical trial

Step 5: Adjustments Based on the Pharmacologically Active Dose

If a robust estimate of the pharmacologically active dose (PAD) is available from preclinical studies

Convert to HED and compare to the MRSD

If $PAD < MRSD$ consider decreasing the starting dose

A Phase I Study of TGN1412: A Critical Dissection of Clinical Disaster

A Failure of Preclinical Safety Testing?

CD28 and T Cell Activation

CD28 is a co-stimulatory receptor found on all CD4 regulatory T-cells and about 50% of CD8 cytotoxic T-cells

CD28 signaling activated by endogenous membrane bound ligands, B7-1 (CD80) and B7-2 (CD86)

Normal activation of T-lymphocytes requires two signals

First Signal: Specific antigen complex presented to the T-Cell receptor (TCR) by the antigen presenting cell (APC)

Second Signal: Co-stimulatory activation of CD28 on the T-cell by B7 molecules

Graphic illustration

www.mpip.org/therapy/artcl5img2.gif

“Super Agonist” Anti-CD28 Antibodies Activate T-Lymphocytes

Directly activate T-cells via CD28 WITHOUT requiring TCR activation

Binds CD28 specifically in a linear conformation

T-cells activated independent of the T-cell receptor

Preferential activation of regulatory (CD4+) T-cell subsets

TH1: activate WBC mediated immunity, and self vs. graft response

TH2: stimulate B cells and antibody production

Graphic illustration of superagonistic → T-cell-activation

Therapeutic Rationale

Autoimmune diseases

Enhance regulatory T cells to block autoimmunity

Efficacy in preclinical models of rheumatoid arthritis, autoimmune neuritis, autoimmune encephalomyelitis

Hematological malignancies

Capacity to reconstitute collapsed T cell compartment in diseases such as B-CLL

Ex vivo evidence of activation of T cells independent of TCR specificity

Improve antigen presentation by B-CLL cells

Expansion of regulatory T lymphocytes and induction of anti-inflammatory cytokines

No detectable adverse side effects other than lymphocytosis

TGN1412: An Anti-CD28 “Super Agonist” Antibody

Recombinant, humanized IgG4-kappa antibody, MW 24 kDa
Developed by TeGenero, a European biotechnology company

Engineered from monoclonal mouse anti-human CD28
Expressed in CHO cells

Binds to human CD28 with $K_d = 1.88 \text{ nM}$

Prepared in a buffered solution for IV infusion

TGN1412 Non-Clinical Safety Studies

Cross species amino acid homology of binding epitope on CD28

Cynomolgus monkey (*Macaca fascicularis*) vs. human

Identical binding epitope

Rhesus monkey (*Macaca mulatta*) vs. human

1 AA difference

Marmoset monkey (*Callitrix jacchus*) vs. human

2 to 6 AA differ

Rodent vs. human

Very low homology

Anti-rat CD28 orthologue mAb also developed and tested

No substantial safety signals

In vitro treatment of human PBMC with soluble TGN1421

Some polyclonal T cell proliferation

Some T cell specific cytokine secretion

TGN1412 Primate Toxicology

TGN1412 long-term administration to *Macaca mulatta*

- No change in systemic cytokine serum concentrations

- No long term (5 months) side effects

TGN1412 in cynomolgus monkeys expanded CD4+ and CD8+ T cells

- Activation of T cells peaked at day 15

- Mild lymphocytosis

Moderate elevation of IL-2, IL-5, IL-6 but no evidence of severe acute release of cytokines

- No evidence for cytokine storm

TGN1412 Regulatory Oversight

Initial first in human, first in class TGN1412 study proposed by sponsor

Approved by two European Regulatory Agencies (in UK and in Germany) and by local research ethics committee

TGN1412 starting dose calculation of 0.1 mg/kg met current regulatory requirements

TGN1412 Clinical Study Design

Sponsor

TeGenero

Contract Research Organization

Parexel International

TGN1412 Supplier/Manufacturer

Boehringer Ingelheim

Location

Parexel Clinical Pharmacology Unit housed in leased space at Northwick Park and St. Mark's Hospital (UK NHS Hospital) in London

Suntharalingam et al NEJM 2006

TGN1412 Clinical Study Design

Research Subjects

Normal healthy paid volunteers

First cohort of 8 Subjects: 6 treatment and 2 controls

All males, median age 29.5 yr (19 to 34 yr) in good health

Randomized, double-blind, placebo-controlled

Planned admission on day 1 and to remain inpatient until day 3

Single 3-6 minute intravenous infusion within minutes of all subjects

All subjected treated 10 minutes apart

Dose: 0.1 mg/kg of TGN1412 infused at 2 mg/min

Other planned doses: 0.5, 2, 5.0 mg/kg

Suntharalingam et al NEJM 2006

TGN1412 Acute Reactions

Study initiated at 0800 hr on 13 March 2006

Reactions started within 90 min

Rapid onset of clinical symptoms

Headache, myalgias, nausea, diarrhea, erythema, vasodilatation, and hypotension

Rapid induction of pro-inflammatory cytokines (cytokine storm)

At 12-16 hr became critically ill

Pulmonary infiltrates, lung injury, renal failure, disseminated intravascular coagulation

Suntharalingam et al NEJM 2006

TGN1412 Immunological Changes

Profound lymphopenia and monocytopenia noted at 24 hours

Extreme elevations of

TNF-alpha

IL-2, IL-6, and IL-10

Interferon-gamma

Prolonged (2 days) cytokine release in 2 most ill pts

Suntharalingam et al NEJM 2006

TGN1412 Critical Care

All 6 treated patients transferred to ICU at adjacent public hospital within hours
Two controls allowed to leave prior to breaking double blinded code

Critical care support initiated

Hemodialysis, vasopressors, respiratory support, high dose steroids, anti-IL2
receptor antagonist antibodies

Two patients developed cardiovascular shock and acute respiratory distress syndrome
requiring mechanical ventilation

Suntharalingam et al NEJM 2006

TGN1412 Patient Outcomes

All patients survived (miraculously)

Long-term neurological, psychological, and immunological sequelae to be defined

Suntharalingam et al NEJM 2006

What Went Wrong?

Extensive review by healthcare agencies and committees

EMEA

UK Medical and Healthcare Products Regulatory Agency (MHRA)

Expert Scientific Group on Phase One Clinical Trials

Clinical trial findings published in the NEJM

Suntharalingam et al NEJM 2006

Lessons are still being debated

TGN1421 Protocol Violations

Minor protocol violations found during retrospective scrutiny

Documentation of full medical history for 1 subject was incomplete

Minor employment procedural error

Sponsor's insurance policy not reviewed

Placebo treated volunteers not formally unblinded before discharge

TeGenero/Parexel contract not in place prior to study initiation

TGN1412 Aftermath

No errors in manufacture, formulation or administration

No contamination with bacterial endotoxin

Conclude that unpredicted biological effects of the test substance caused the dramatic clinical effects

TeGenero files for bankruptcy in June 2006

Failure of Non-clinical Safety Studies?

Preclinical in vitro studies failed to predict toxicity in vivo
mAb was not presented to lymphocytes in a manner that mimicked its
presentation in vivo

Binding of TGN1412 to cell surfaces is a requirement for activation of lymphocytes
and triggering of the cytokine storm

In vivo primate studies failed to predict human toxicity
Lymphocytes from Cynomolgus monkeys do not respond to TGN1412
binding in the same way as human cells
TGN1412 is not superagonistic in this species (a pharmacodynamic
difference)

Stebbins et al, J Immunol 2007;179:3325

In Vitro Lymphocyte TGN1412 Studies (*Stebbins et al, J Immunol 2007;179:3325*)

- Graphic illustration of Human PBMC + Aqueous TGN1412 }
and Primate PBMC + Air-dried TGN1412 } → No proliferation or
release of TNF- α ,
IL-6 or IL-8
- Graphic illustration of human PBMC + Air-dried TGN1412 } → Proliferation and
release of TNF- α ,
IL-6 or IL-8
CYTOKINE STORM!

TGN1421 Trial Learning Points

(modified from Dayan et al, Br J Immunol 151:231)

TGN1421 Study Problem	Detail	Learning Point
Interpretation of preclinical studies	Low level cytokine release in primates should have prompted more caution	Minor but potentially important effects in preclinical studies should raise caution across species
Use of human in vitro studies	Insufficient in vitro human studies on PBL were performed	In vitro studies on human material as close as possible to the target tissue can be important
Location of study unit	Located in a tertiary care hospital	Rapid access to an intensive care unit was important as events unfolded rapidly

TGN1421 Trial Learning Points

(modified from Dayan et al, *Br J Immunol* 151:231)

TGN1421 Study Problem	Detail	Learning Point
Choice of starting dose	Subtle difference between primate and human target may explain marked difference in potency. Calculation of initial dose based on NOAEL proved to be dangerously wrong	Prediction of risk and dose range from animal studies may prove unreliable: extra caution with wider margins of safety are required with potentially risky modes of action. Use of MABEL?
Dosing interval between subjects	No proper interval allowing for the observation of possible side effects between subjects	In FIH studies, investigators should expect the unexpected
Preparation for adverse events	Preparation for possible adverse events (cytokine storm) was inadequate. Investigators did not expect it, recognize it, or treat it early	Where there is a known theoretical risk, investigators should plan for its potential occurrence

MABEL Instead of NOAEL, MAYBE ?

Re-evaluation of the TGN1412 trial has led to new recommendations for starting dose selection in Europe

EMEA Guidelines, 2007

Consider factors that may add to potential risk

Mode of action

Nature of target

Relevance of animal models

MABEL: minimal anticipated biological effect level

The anticipated dose level leading to a minimal biological effect level in humans

Consider differences in sensitivity for the mode of action across species

Consider selection of starting doses based upon reduction from the MABEL, not NOAEL dose

Calculation of MABEL *(EMA Guidelines, 2007)*

MABEL calculations should utilize all in vitro and in vivo information from PK/PD experiments, including...

- Target binding and receptor occupancy data in target cells in vitro in human and animals

- Concentration-response curves in vitro in target human cells and dose/exposure-response in vivo in relevant animals

- Exposures at pharmacological doses in relevant animals

Wherever possible an integrated PK/PD modeling approach should be used

Apply a safety factor to the MABEL for the recommended starting dose

If NOAEL method gives a different estimation, use the lowest value unless otherwise justified

Problems with the MABEL (or any approach)

Estimation of MABEL may prove difficult with some agents, such as those that target the immune system

In vivo immune response are much greater than in vitro

Agents such as TGN1421 may act via a trigger or threshold effect

Immunological cascade may amplify any biological action

MABEL may not exist

For other agents, overestimation of MABEL may lead to extremely low starting doses resulting in a conclusion of no biological activity

Dayan et al, Br J Immunol 151:231

Issues Raised by TGN1412

Ethics of FIH trials in volunteers/patients

Species-specific pharmacology & toxicology of targeted agents

Immunologics/biologics offer special problems in evaluation

Greater transparency and input in early therapeutic development

Inherent risks in developing novel agents with new mechanisms of action

The Clinical Pharmacology Challenge!

**Preclinical
Pharmacology**

**Early Clinical
Trials**

→ **Clinical
Pharmacologist** → **Translational dose
And toxicity endpoints**

**Traditional
animal studies
PK/PD
Toxicology**

**Traditional PK/PD
Biomarkers &
Molecular endpoints
Patient selection**

**Biomarkers &
Molecular targets**

TRANSLATIONAL MEDICINE