Non-Clinical Drug Development:

With Examples from Oncology Therapeutics

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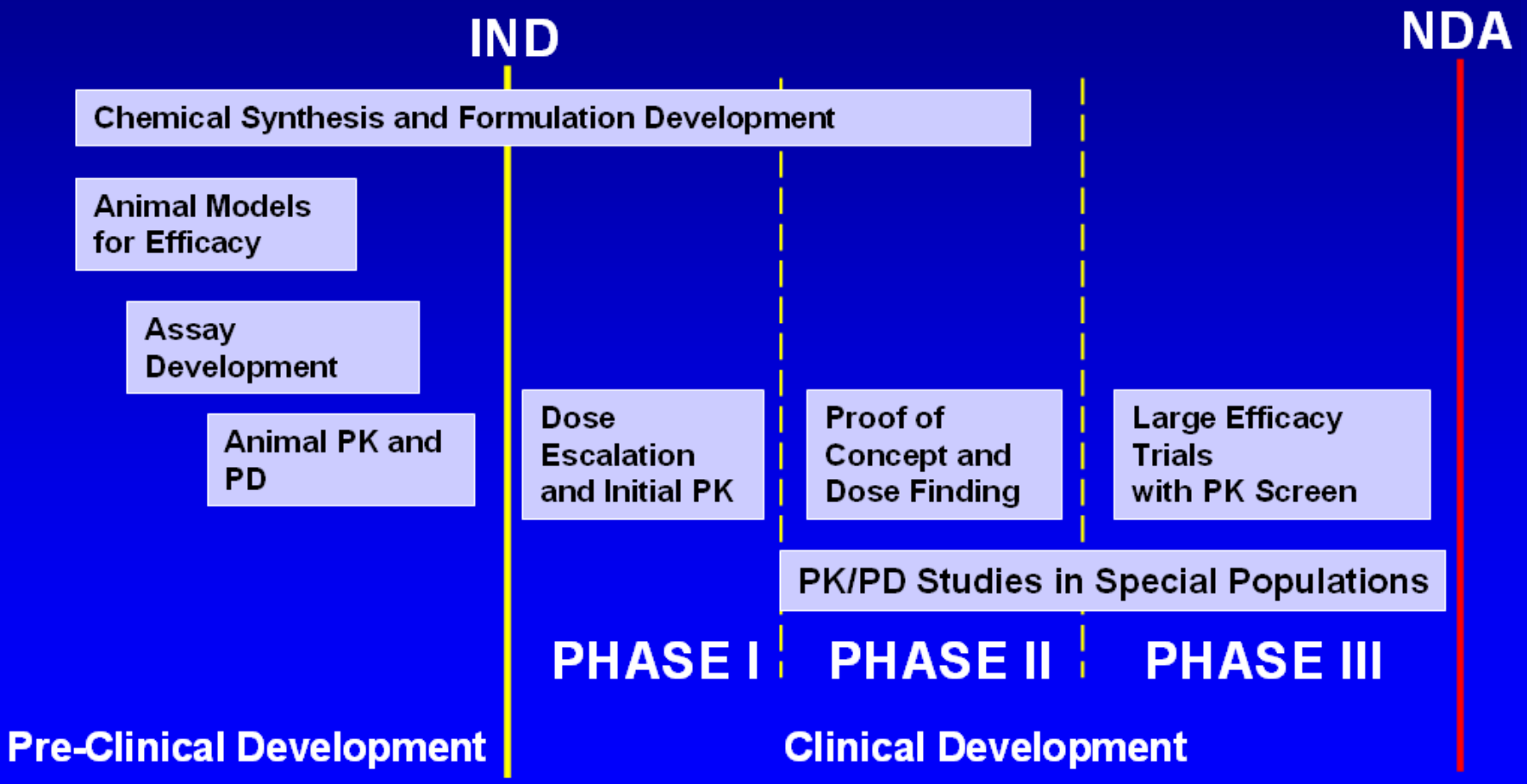
Drug Development

- 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



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)

Characteristic	Cytotoxic Agents	Targeted Agents
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)

Characteristic	Cytotoxic Agents	Targeted Agents
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
- 5. 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

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

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

Components of Non-Clinical Drug Development

1. In vitro studies: Cell lines, cell-free systems (drug screening)
2. Drug formulation
3. Chemistry, Manufacturing, and Controls: Drug supply & quality
4. *In vivo efficacy studies: Animal models and proof of principle*
5. Non-clinical safety studies

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

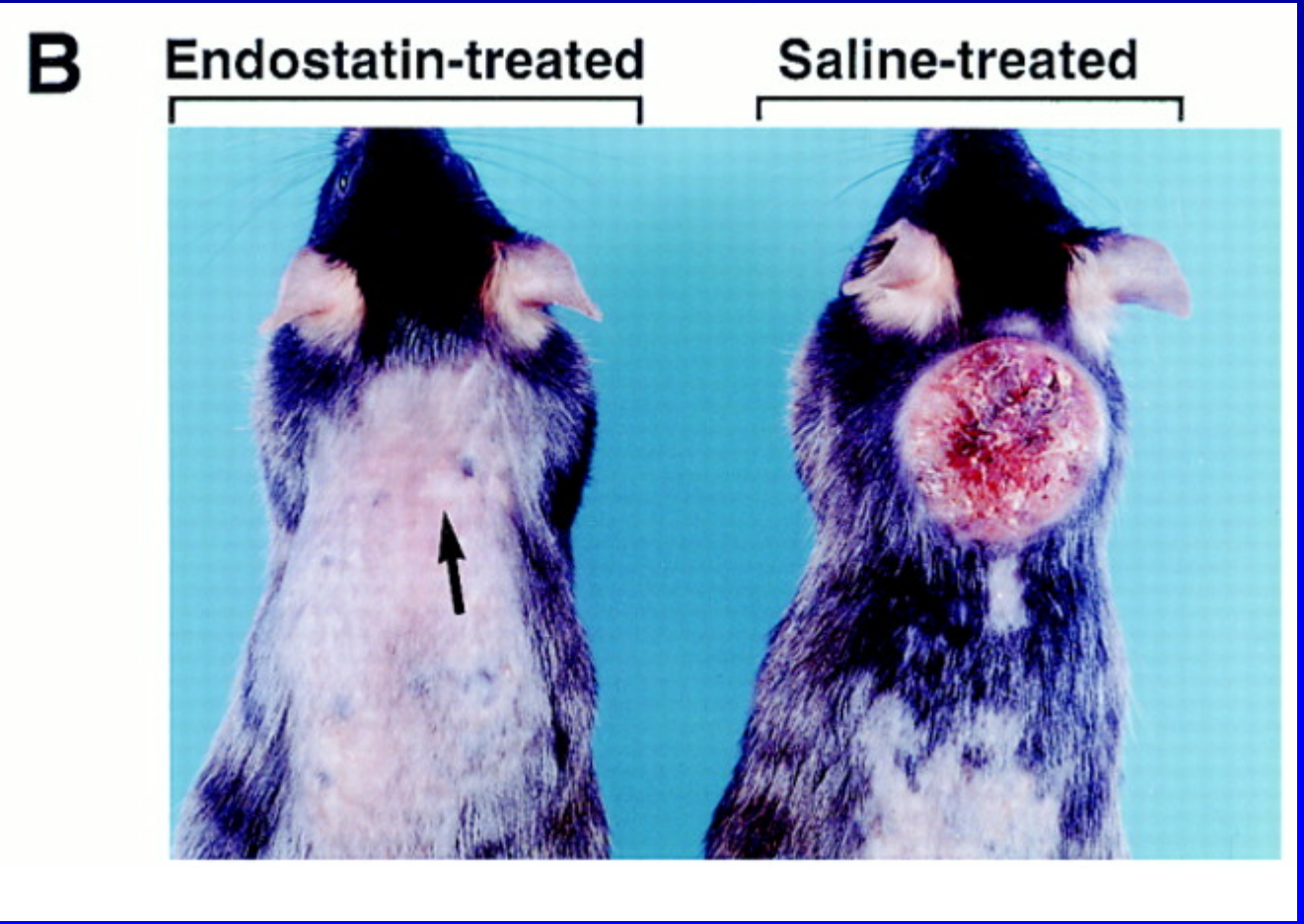
Ideal Animal Model

- 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)



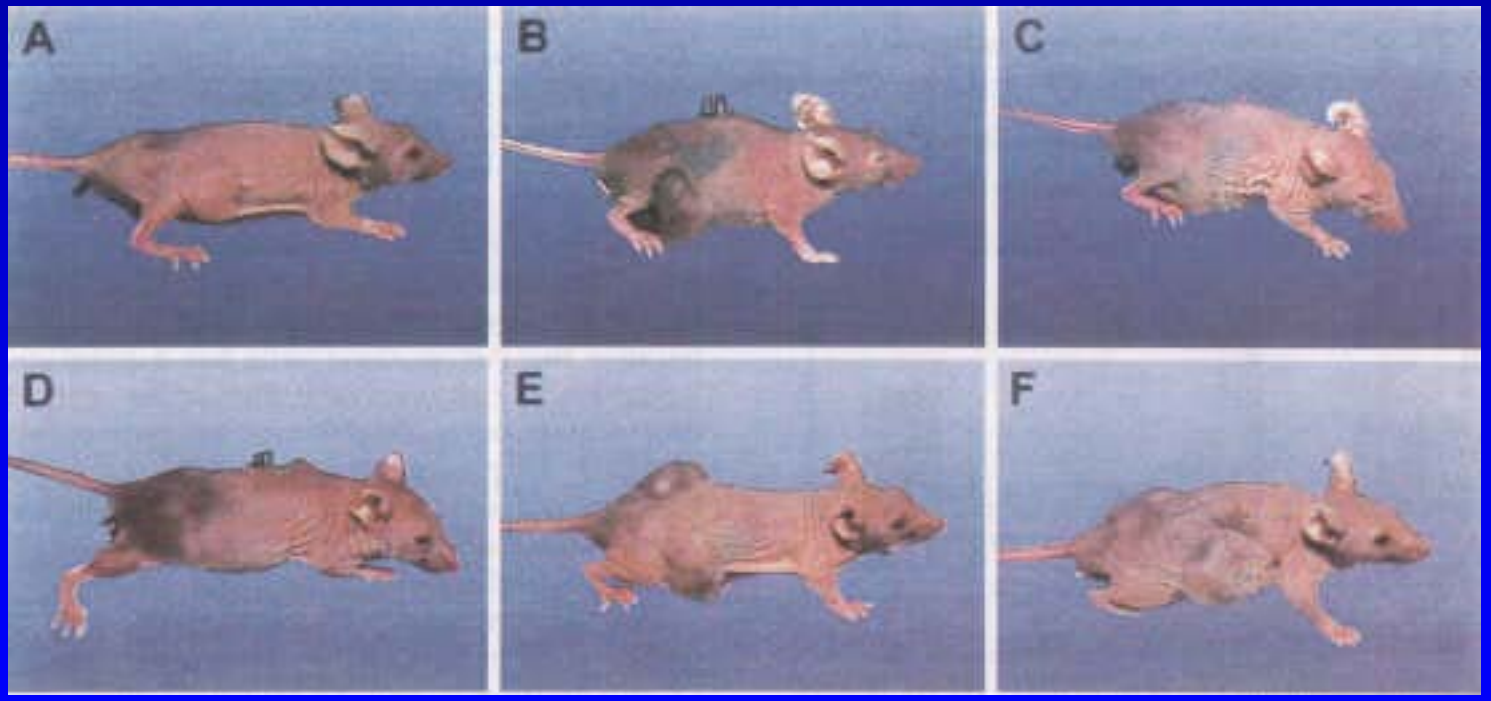
Animal Models in Cancer

- 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



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

Components of Non-Clinical Drug Development

1. In vitro studies: Cell lines, cell-free systems (drug screening)
2. Drug formulation
3. Chemistry, Manufacturing, and Controls: Drug supply & quality
4. In vivo efficacy studies: Animal models and proof of principle
5. *Non-clinical safety studies*

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 ≤ 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

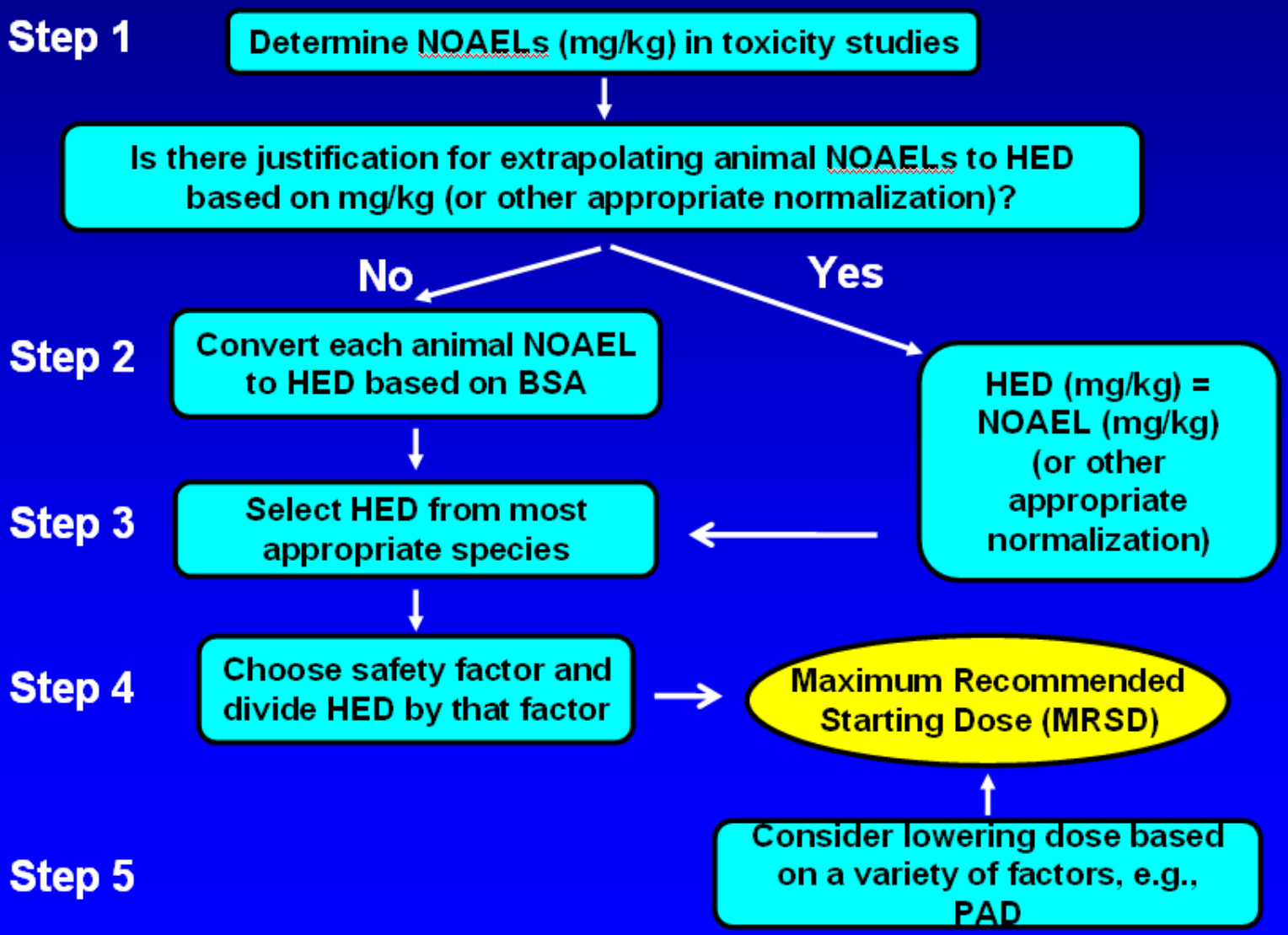
Maximum Recommended Starting Dose (MRSD) for FIH Trials

1. Determination of the No Observed Adverse Effect Level (NOAEL)
2. Conversion of NOAEL to Human Equivalent Dose (HED)
3. Selection of the most appropriate animal species
4. Application of a safety factor to determine MRSD
5. Compare MRSD with pharmacologically active dose (PAD)

-- FDA Guidance for Industry July 2005

Selection of MRSD

(FDA Guidance 2005)



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/m^2 and reconverted to mg/kg
  - Many cancer treatments are dosed based on BSA (mg/m^2)

-- FDA Guidance for Industry July 2005

HED Calculation

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

- Km: mg/kg to mg/m^2 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 Cmax for antisense molecules
  - Proteins administered IV with Mr > 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 data
  - 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

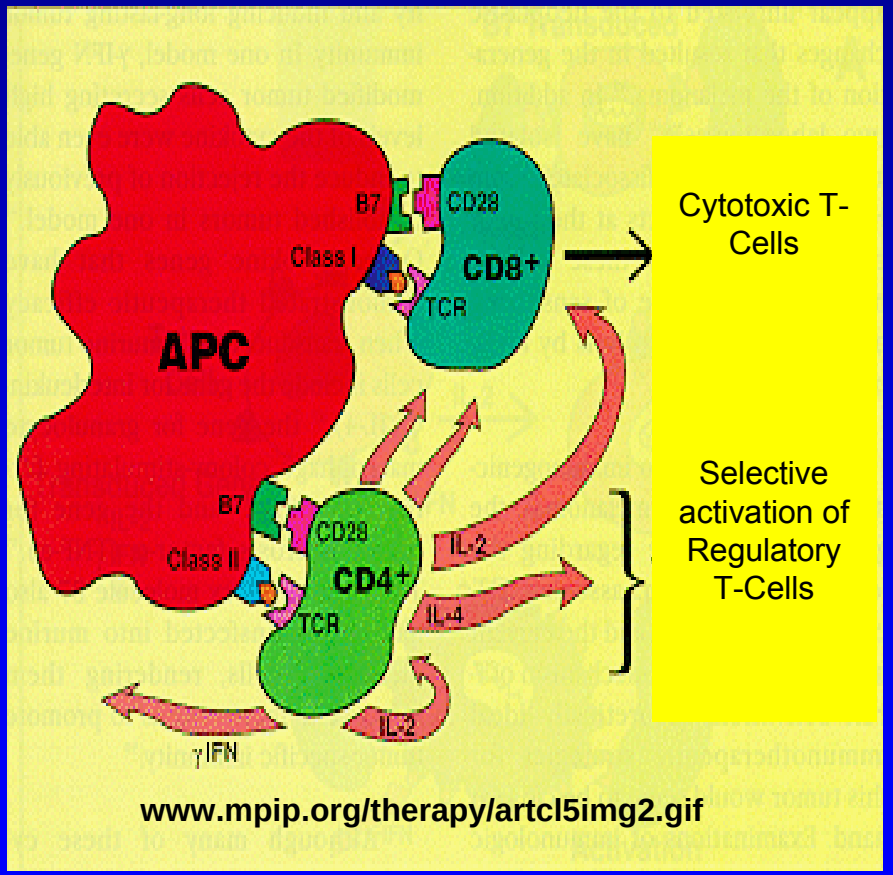
- If a robust estimate of the pharmacologically active dose (PAD) is available from preclinical studies
- Convert to HED and compare to the MRSD
- If PAD < MRSD consider decreasing the starting dose

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

A Failure of Preclinical Safety Testing?

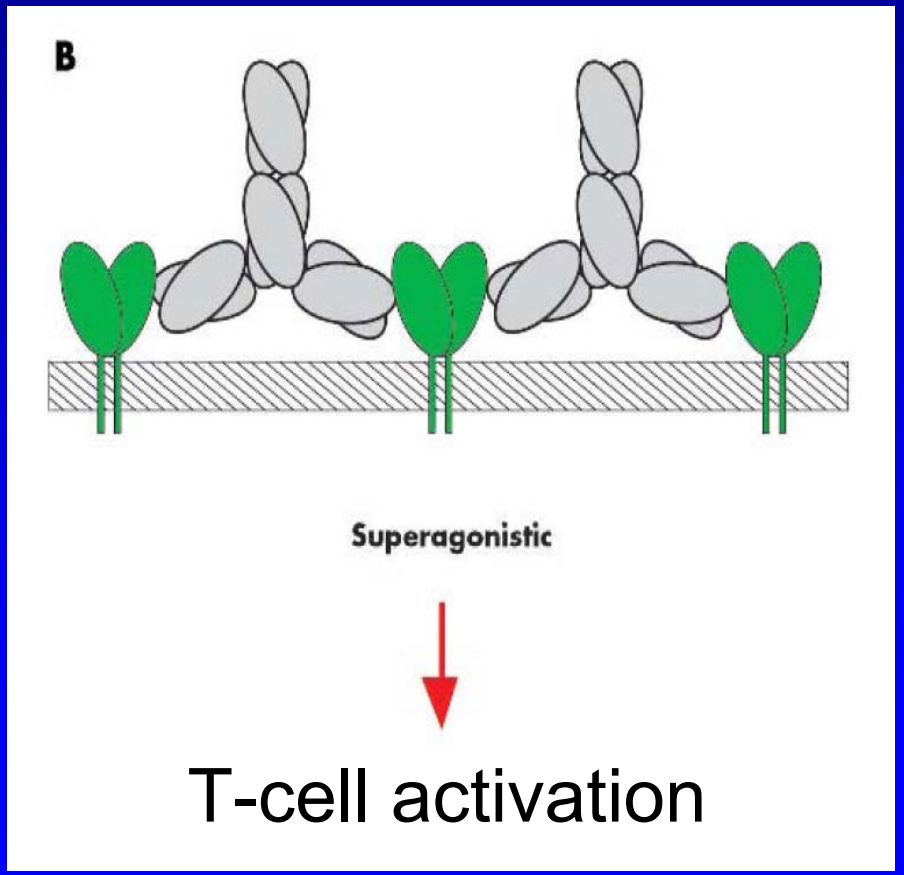
CD28 and T Cell Activation

- 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



“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



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 Kd = 1.88 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 conventions
  - 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
  - Boehnringer 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

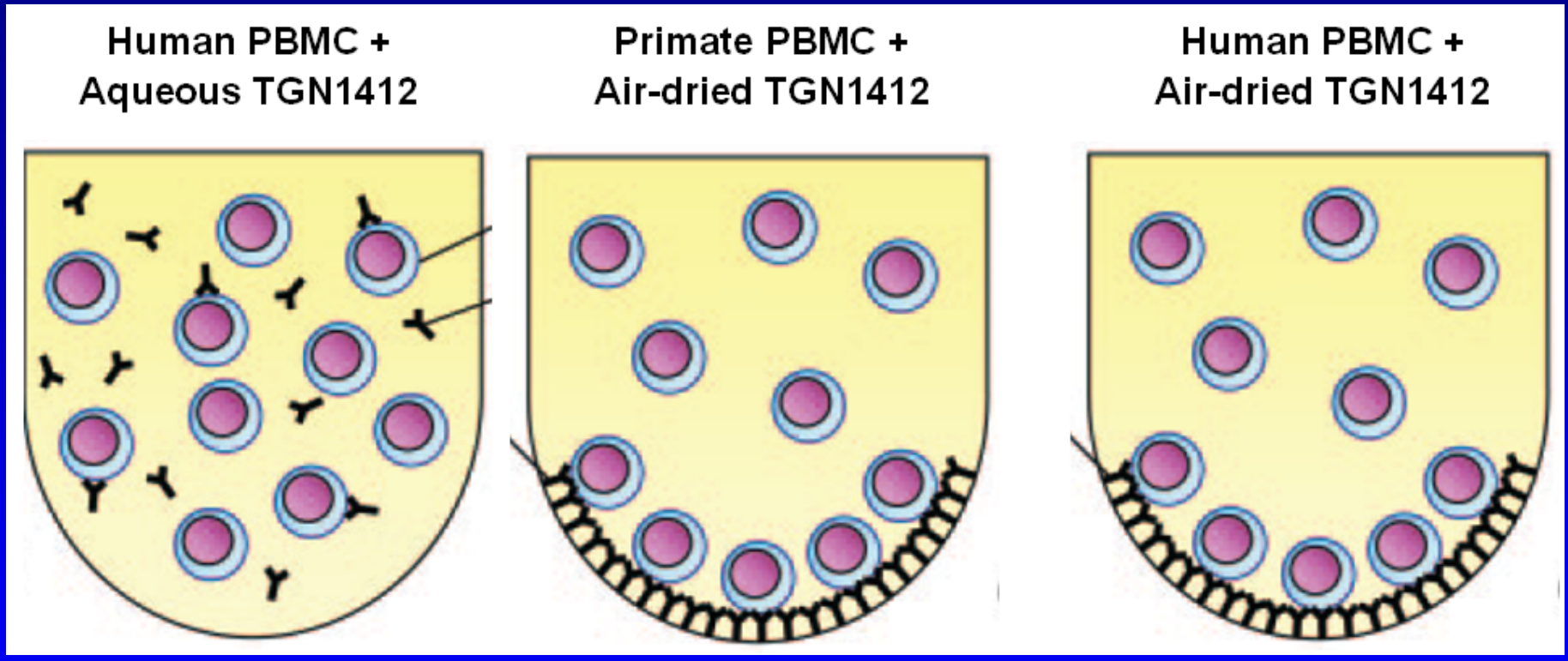
Failure of Non-clinical Safety Studies?

- 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 response 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)



No proliferation or release of TNF- α, IL-6 or IL-8

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)

TGN1412 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)

TGN1412 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 let 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

(EMEA 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)

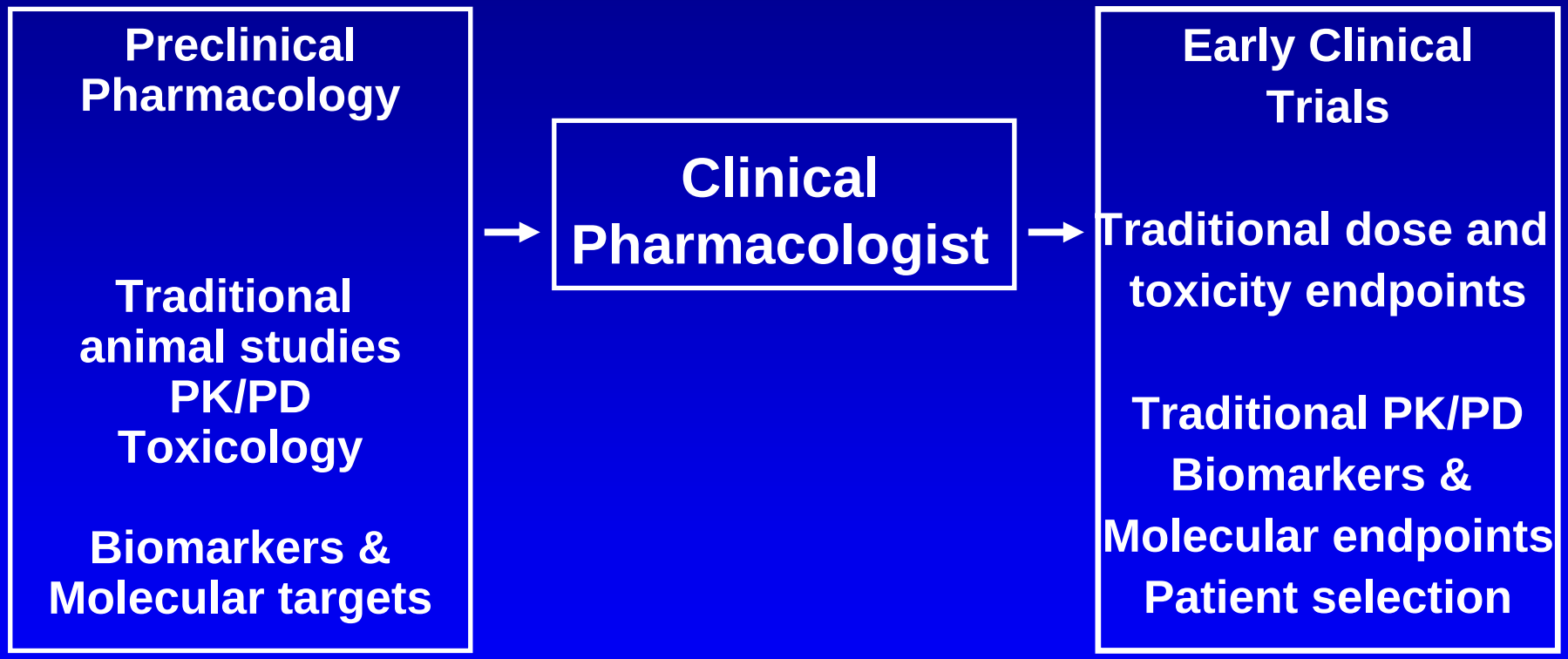
- Estimation of MABEL my prove difficult with some agents, such as those that target the immune system
  - In vivo immune response are much greater than in vitro
- Agents such as TGN1421 may act via a trigger or threshold effect
  - Immunological cascade may amplify any biological action
  - MABEL may 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!



Translational Medicine