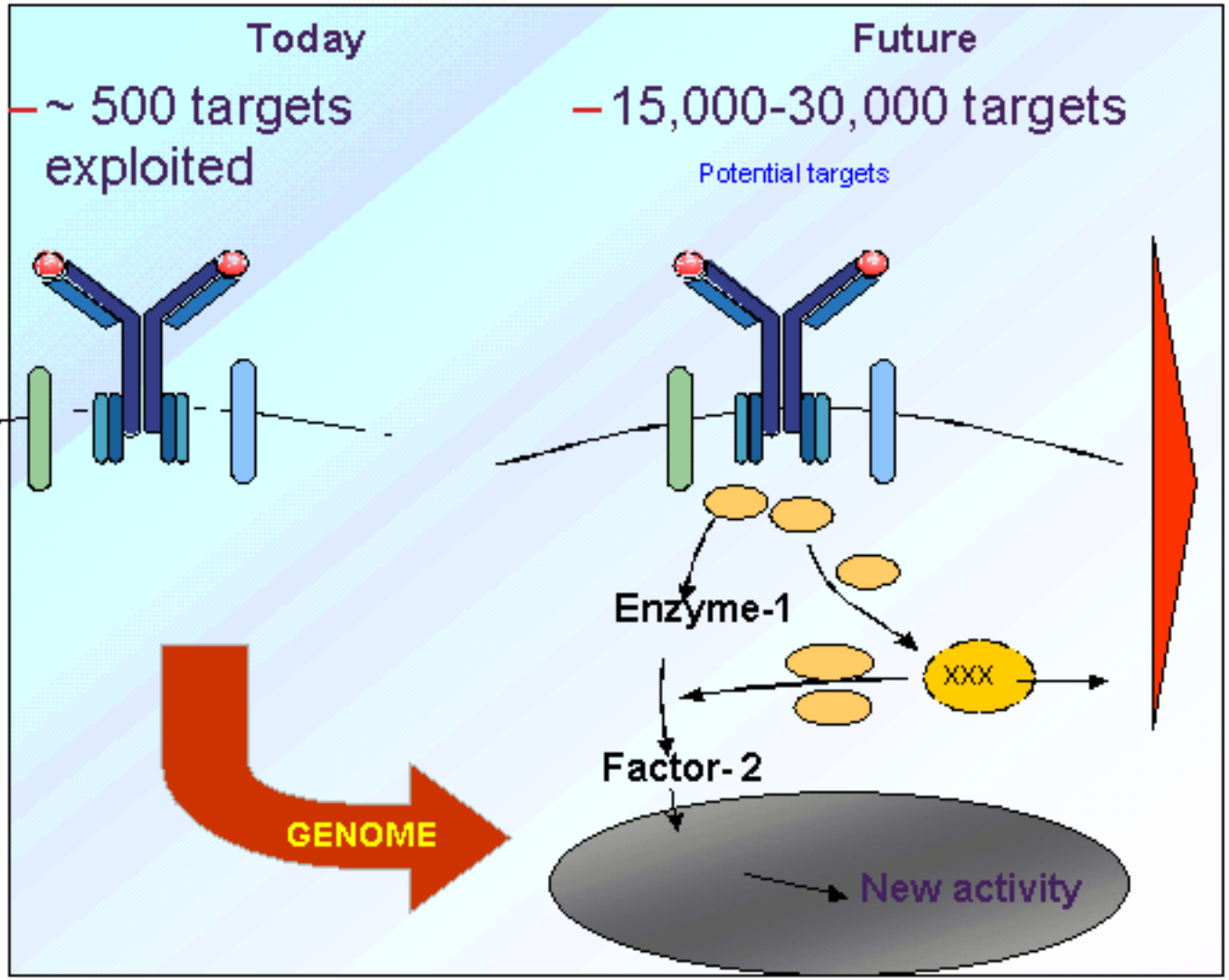
Humanising Drug Discovery to Make Earlier & Better Stop/Go Decisions in Pharma R&D

Dr Paul Newbold

Genomic Revolution:



- Exponential increase in potential targets
- Research geared towards speed / prioritisation
- Human Validation

Potential implications of new targetability: TGN1412

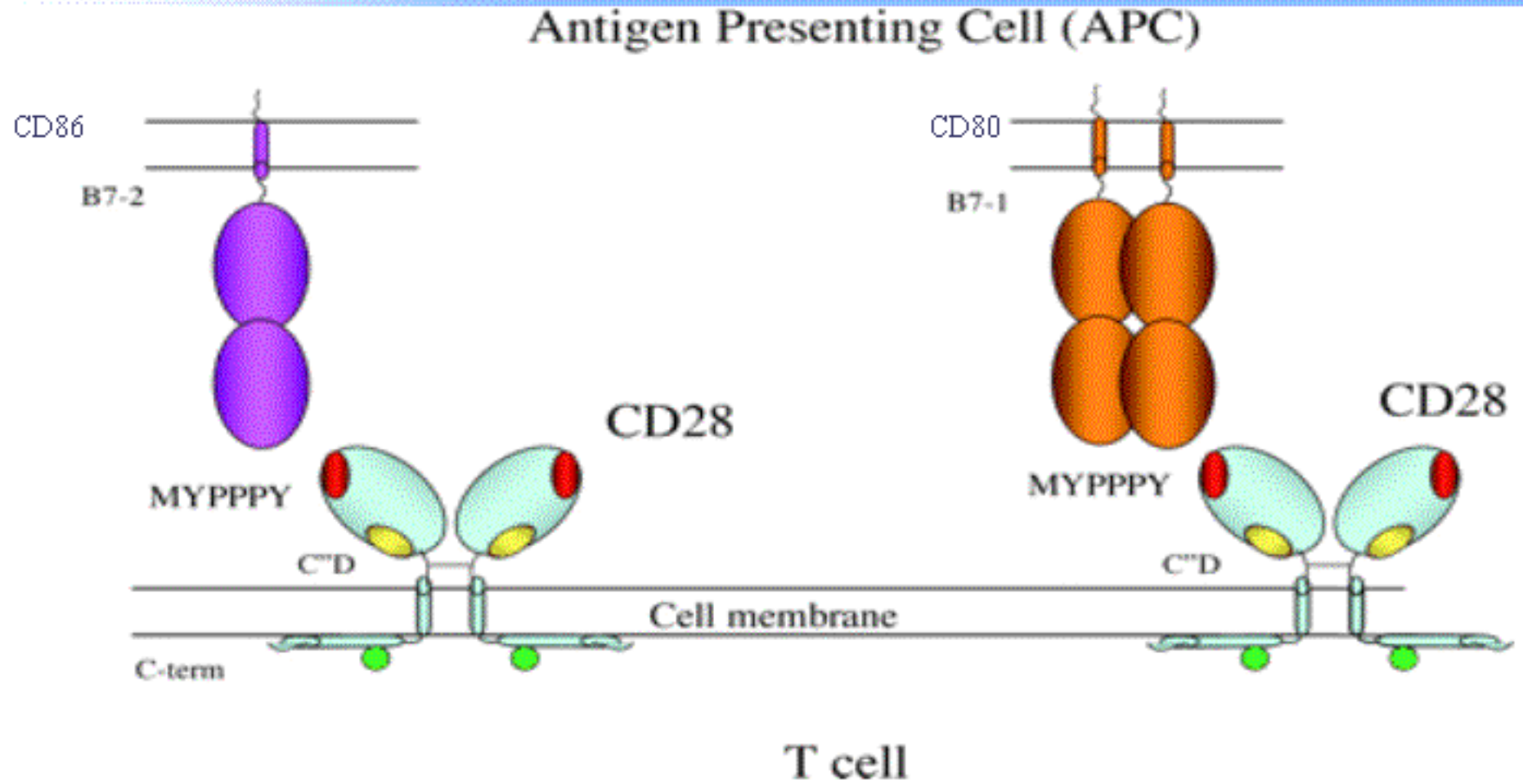


Figure 1. Location of sites of interaction of CD80 (B7-1) and CD86 (B7-2) and of superagonist mAbs mapped to the surface of CD28. The structure of CD28 as a disulfide-linked Ig-like homodimeric domain on the surface of the T cell is illustrated schematically, depicting interactions with either the monomeric B7-2 or the homodimeric B7-1. The surface exposure the MYPPPY loop that has been shown crystallographically to interact with both B7-2 and B7-1 is colored red and the C"D loop that interacts with the superagonistic antibodies is shown in yellow. The cytoplasmic carboxylterminus of CD28 is indicated and the potential phosphorylation site(s) is indicated as a green circle.

Potential implications of new targetability: TGN1412

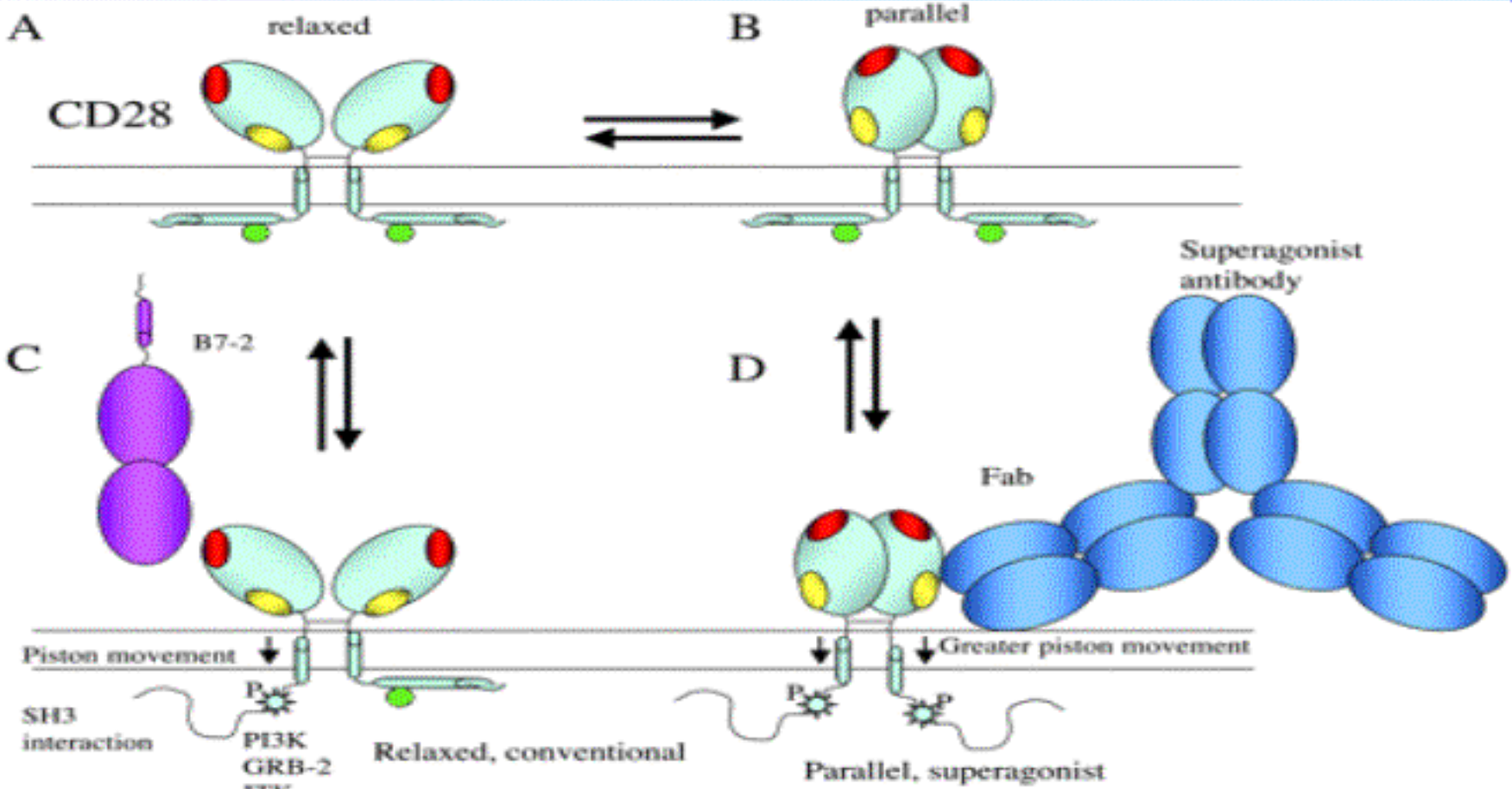


Figure 2. A differential conformation model for CD28-mediated conventional and superagonist signaling. The unliganded disposition of the hypothesized relaxed (A) and parallel (B) conformations of CD28 is indicated. Color coding of interacting sites is as in Fig. 1. The conventional or costimulatory binding of B7-2 to CD28 results in the liberation of the carboxylterminus of CD28, making this proline-rich domain available for SH3 domain interaction. This would result in the kinase-dependent phosphorylation of the potential PI3-kinase, GRB-2, and ITK binding site (C). Drawn approximately to scale, the binding of a full antibody to the C"D superagonist site promotes the more complete liberation of the cytoplasmic domains of CD28, making them more available for both SH3 and kinase and adaptor interaction (D).

From Primates Given TGN1412

Table 68: Mean peak serum concentrations in each dosing group after administration of TGN1412 in cynomologus monkeys

Cytokine	Mean peak cytokine level (range) pg/ml		
	Control group (0 mg/kg)	Low dose group (5 mg/kg)	High dose group (50 mg/kg)
IL-2	37 (20-60)	25 (0-84)	100 (25-211)
IL-4	12 (0-18)	13 (8-18)	17 (0-40)
IL-5	6 (3-7)	49 (6-139)	107 (11-458)
IL-6	7 (0-22)	68 (32-101)	128 (24-390)
TFN-alpha	20 (11-26)	20 (15-27)	22 (19-26)
IFN-gamma	18 (0-35)	23 (19-32)	33 (17-93)

These were not regarded as significant and a NOAEL from the primate toxicology studies was defined 500 fold higher than the starting dose in FTIM (0.1mg/kg).

From Volunteers Given TGN1412

Cytokine table:

	PREDOSE	1 HOUR	4 HOURS	DAY 2	DAY 3 00:10	DAY 4	DAY 5	DAY 6 am
Mean TNFalpha;	<2.8	1943	> 5000	836	107	<2.8	<2.8	3.00
Mean IFN g	<7.1	99	> 5000	4730	1366	89	43	27
MeanIL-10	<2.8	76	2158	1771	272	19	10	8
Mean-IL-6	< 3.0	29	1330	1204	96	466	95	43
Mean-IL4	<2.6	9	1205	13	24	3	3	3
Mean-IL2	4.70	57	3317	137	14.	4	3.	4

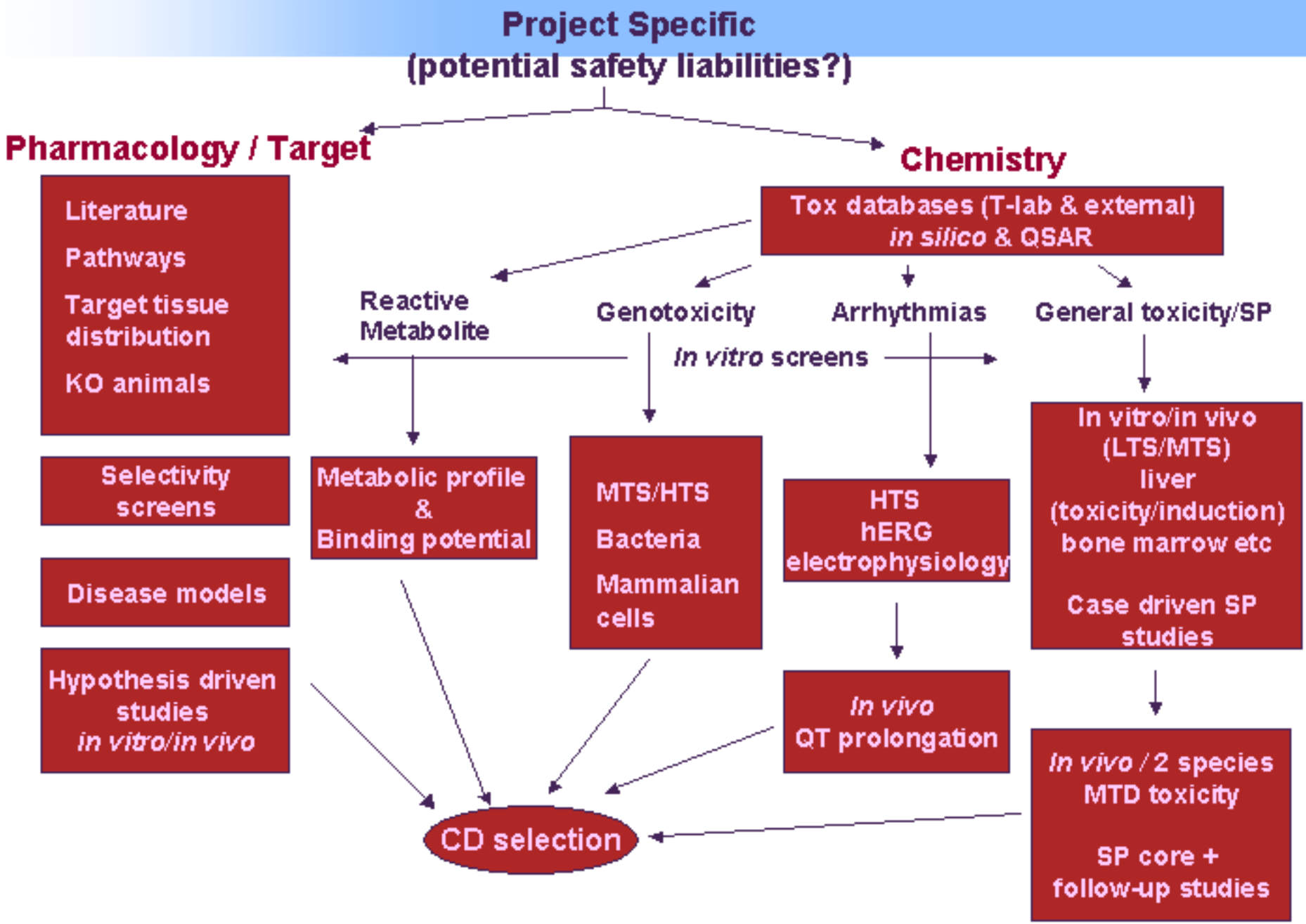
The table only shows mean values rounded to the closest integer. This is only to provide a schematic representation of changes in Cytokine values. The symbols (<) and (>) indicates values below and above the assay limits and hence are not exact values.

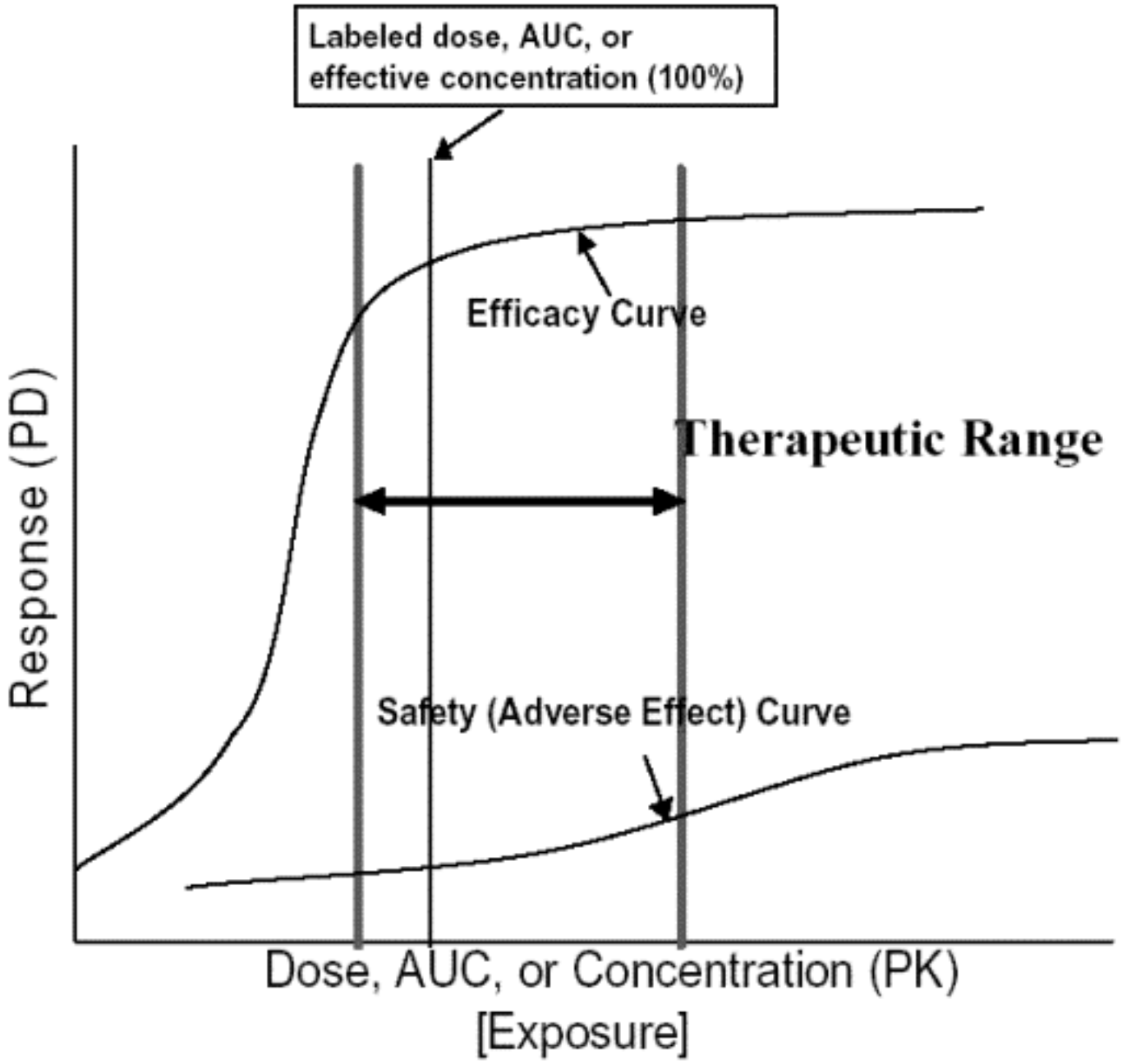
Table from Prof Duff Expert Committee Report, July 25th, 2006.

What can be done to model drug effects and safety?

- In Vitro data
- In Vivo animal data – translational data
- PK data for exposure
- Early human experiments
- Appropriate patient segments
- Toxicological data

Bringing together information



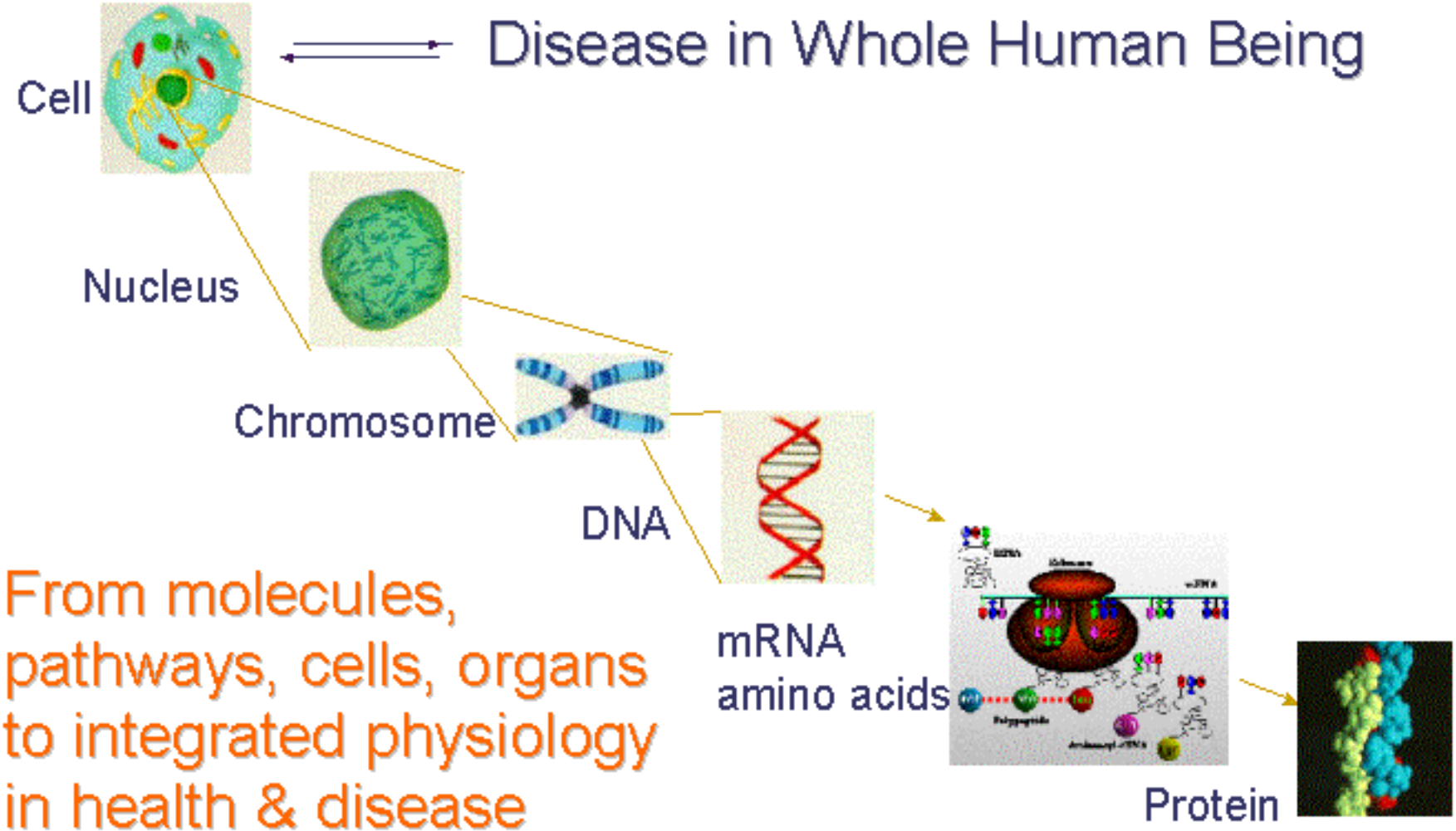


< Huang and Lesko, J Clin Pharmacol, 44: 559. June 2004>

Human tissue in Target Validation and Safety Evaluation

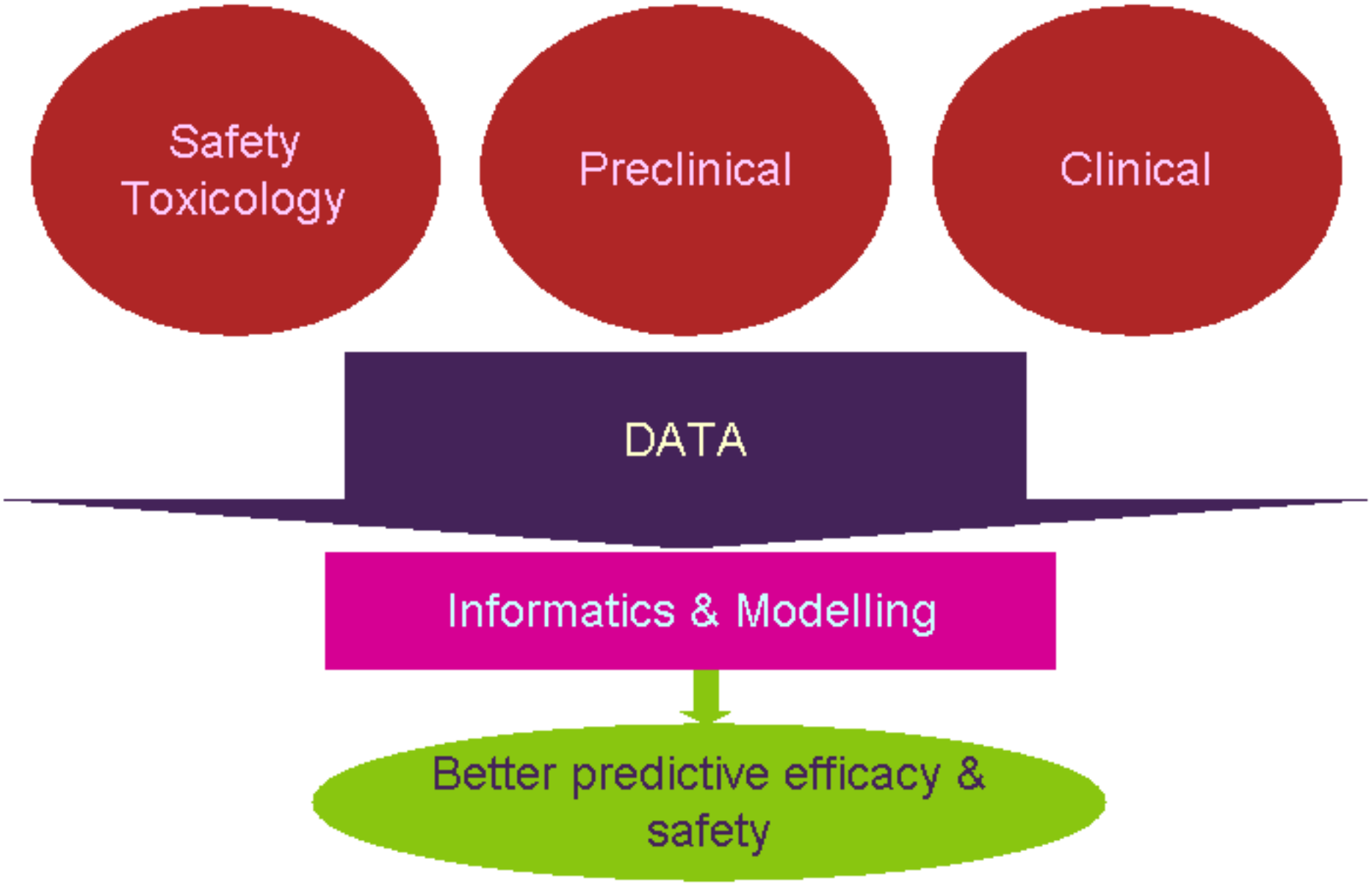
- Tissue from well characterised patients
  - Understanding the clinical phenotype
- Histopathological and Immunocytochemical Analysis
  - understanding the pathological phenotype
  - understanding receptor distribution
  - disease and normal tissue
  - holistic tissue distribution
- Bioanalysis
  - functional assays
  - in vitro pharmacology in human cells
  - organ of interest and other tissues
- Molecular biology
  - Affymetrix, Taqman
  - understanding genotype

Modelling of Human Disease



From molecules, pathways, cells, organs to integrated physiology in health & disease

It needs to be Multidisciplinary Approach



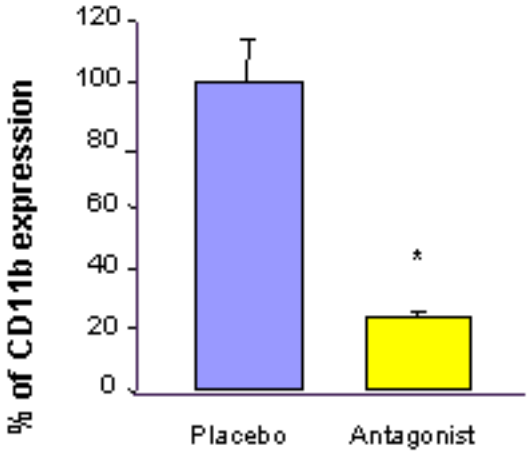
Developing Animal models of disease

- Models that reflect aspects human disease
- Models that can be used in a translational way:
  - Human —Model→ Animal —Predict→ Human
  - Understand target distribution differences
  - Understand target functional differences
    - For efficacy and safety implications

Translational models

LPS challenge model for airway neutrophilia

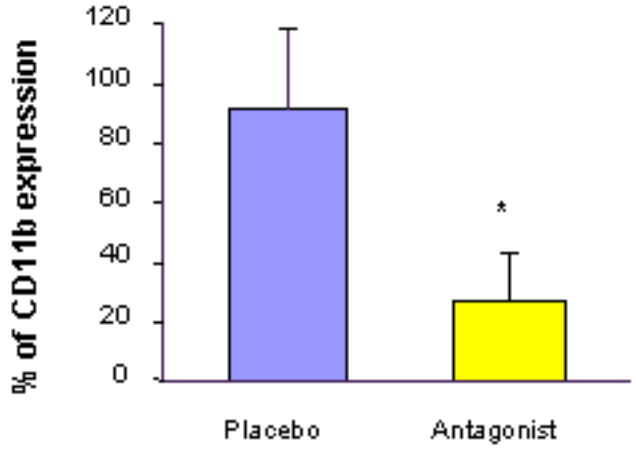
Animal



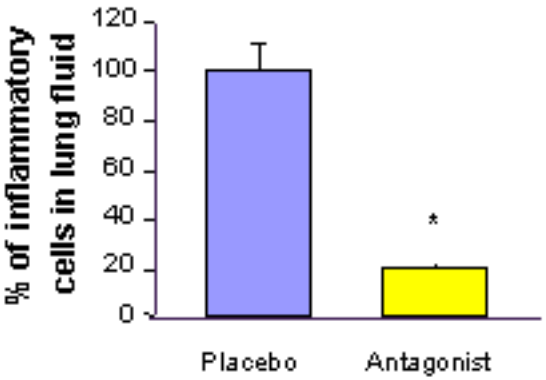
Blood biomarkers

Cell activation following treatment

Human



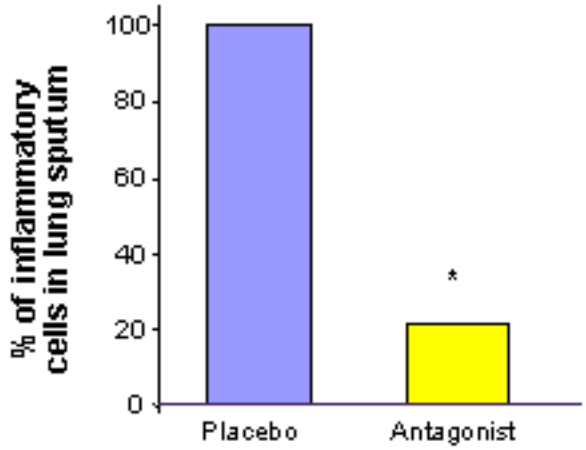
LPS Challenge to lung



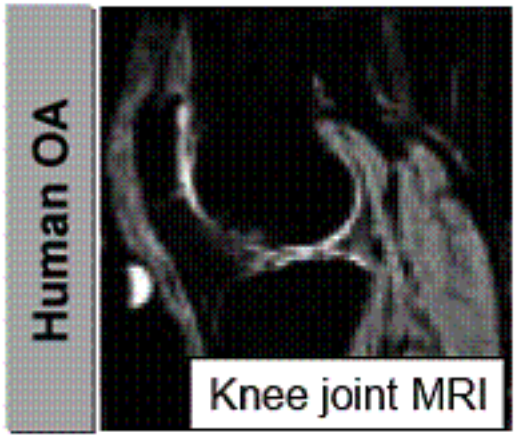
Inflammatory challenge

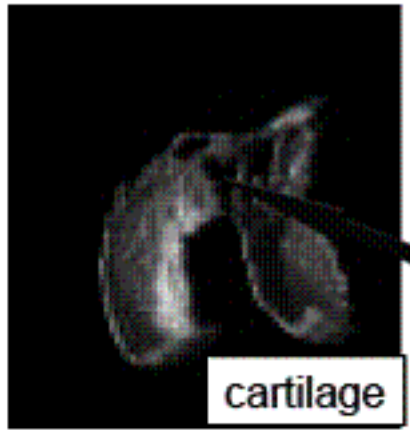
Inflammatory cells in lung following LPS- challenge

LPS challenge to lung

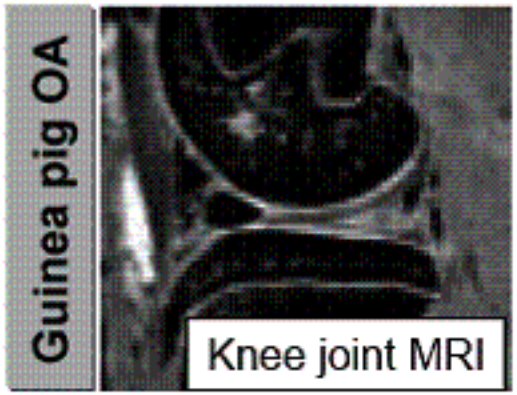


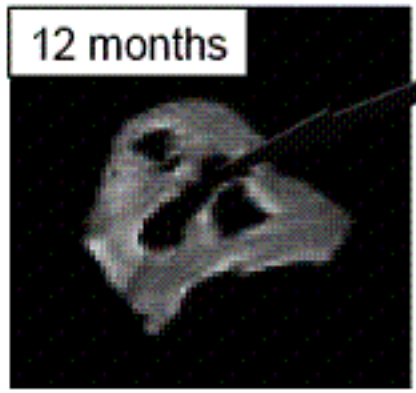
Animal models of aspects of disease





Focal loss of articular cartilage is a cardinal feature of OA





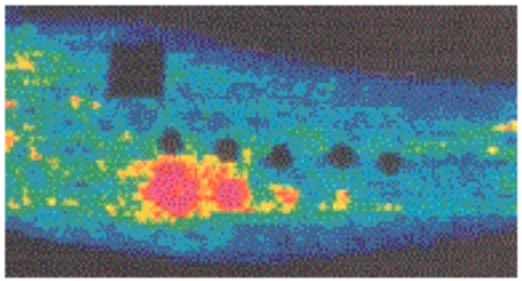
Linked in with this are
biological pathways in each system
Does the process in the animal
Reflect that in the human?

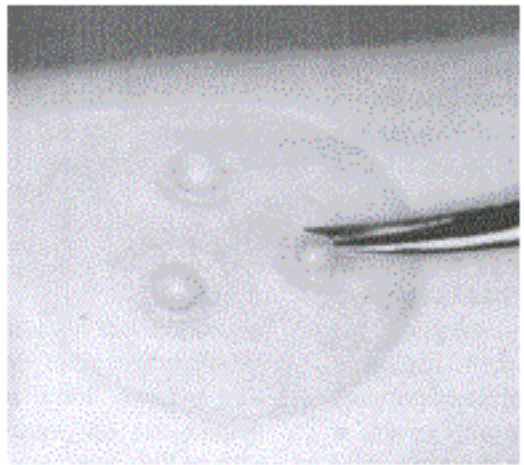
What can be done clinically for early concept testing?

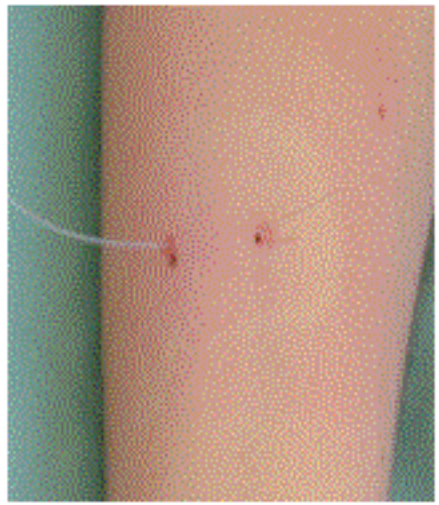
- We don't have to wait until candidate drug selection
- Potential to do studies in healthy volunteers/patients to get early efficacy understanding in simple models
- Exploratory IND approach
  - can help identify, **early in the process**, promising candidates for continued development
  - involve dosing a limited number of subjects with a limited range of doses for a limited period of time
  - studies involve administering either sub-pharmacologic doses of a product, or doses expected to produce a pharmacologic, but not a toxic, effect
  - the potential risk to human subjects is less than for a traditional phase 1 study
  - can use sub-optimal compounds

Human skin as a means to study inflammation

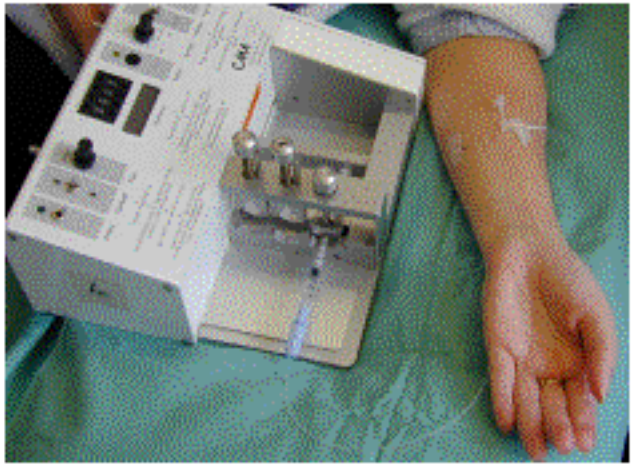
- Quantification of inflammatory reactions
- Investigation of inflammatory cell recruitment
- Mediator analysis and the development of microdosing approaches to investigate drug activity
- Allows local administration of target to study efficacy with reduced safety risks

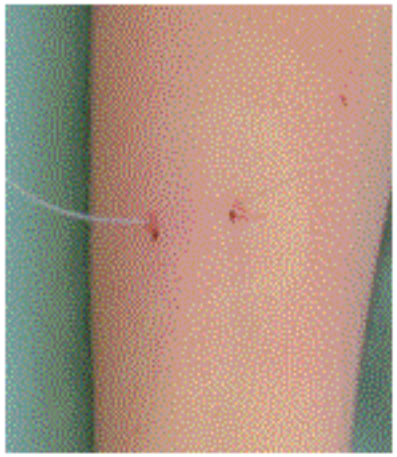


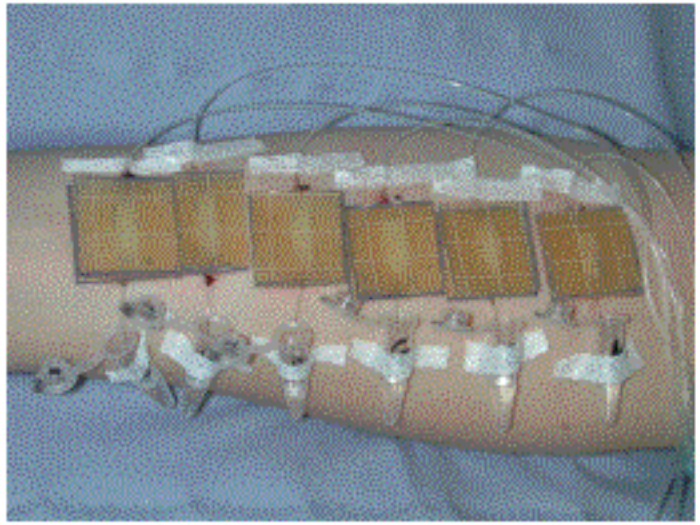




Dermal Microdialysis & Microdosing







- Single Dose and/or
- Mutiple Dose including Dose Ranging Possible

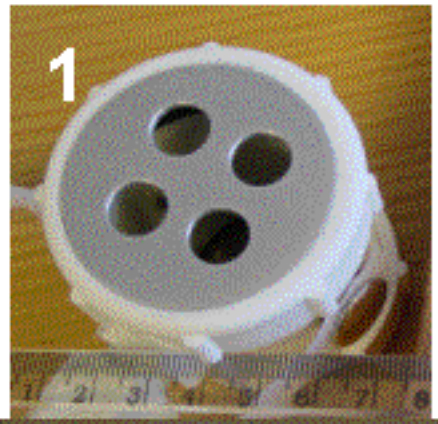
In the same subject

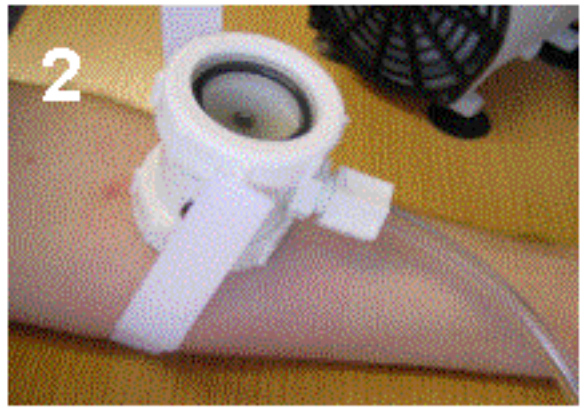
Could Be Applied to Some Small Molecule & Biologic Targets

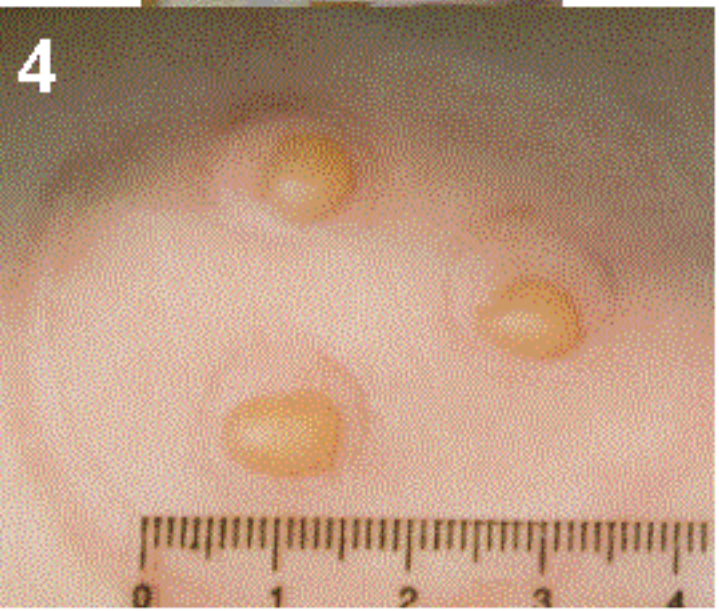
Microdialysis as a tool for micro dosing

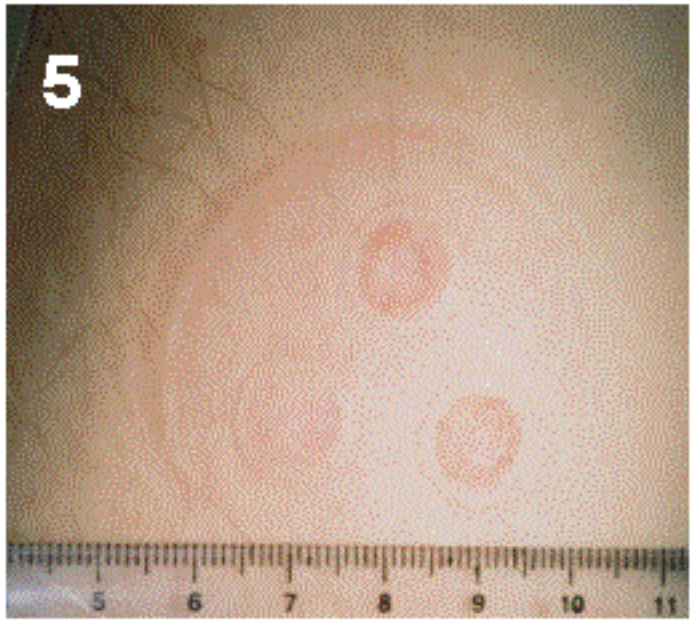
- Development of Microdialysis as a tool to investigate Inflammation (Asthma/Rhinitis, RA/OA, Skin etc)
  - Mechanisms (eg Chemokines, iNos etc)
  - Sub-optimal compounds
  - Model Compounds (eg Steroids, Cyclosporin, NSAID etc)
  - Target Validation
  - Cellular Changes
  - Biomarkers, Cytokines & Proteomics
  - Diagnostics & Mediators
  - PK/PD Relationships

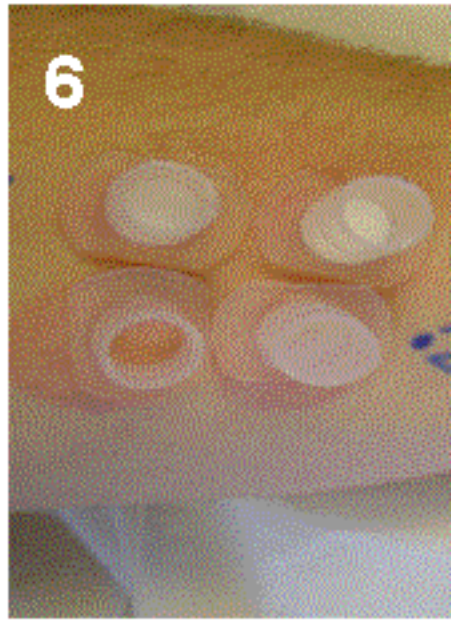
Vacuum skin chambers











Urate Crystal Skin Inflammation

- Need safe and malleable *in vivo* inflammation models for early PoP for novel inflammation targets
- Skin is visible and safely accessible
- Monosodium urate crystals are a potent inflammatory stimulus *(gout)*

Biopsies

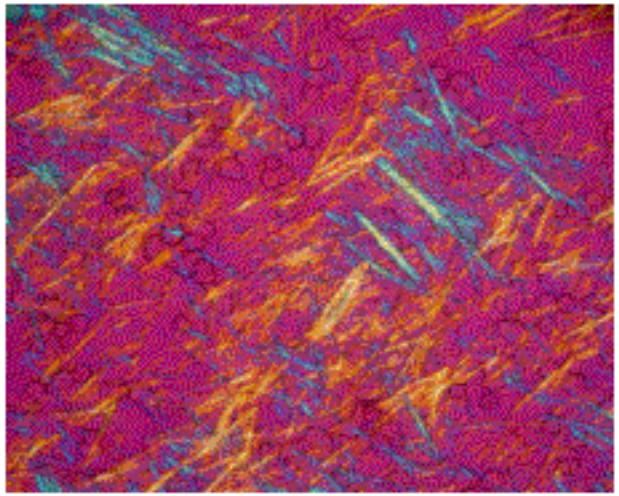
- Histology
- ICC

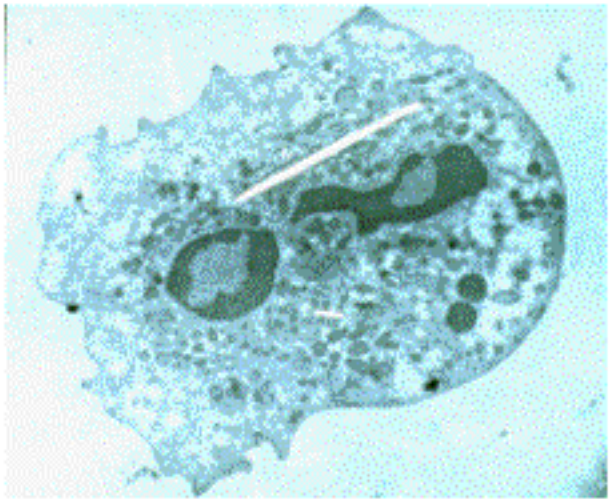
Skin Chamber fluid

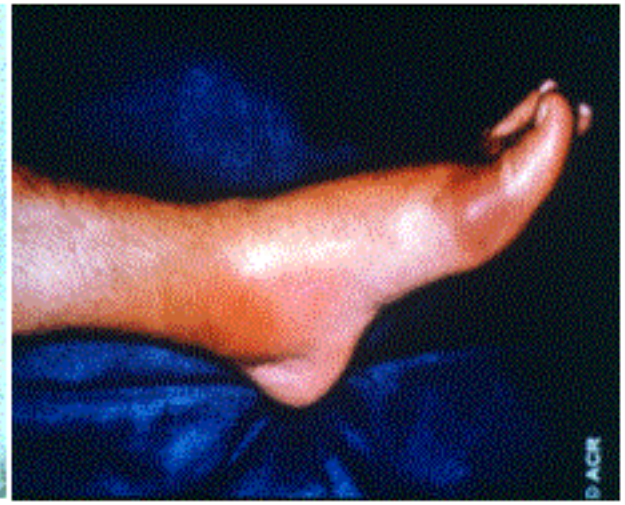
- Cell counts
- Cell characterisation
- Soluble mediators

Clinical

- Laser doppler
- Systemic inflammatory markers (blood)
- Subjects assessment of discomfort
- Investigators assessment of inflammation
- Safety

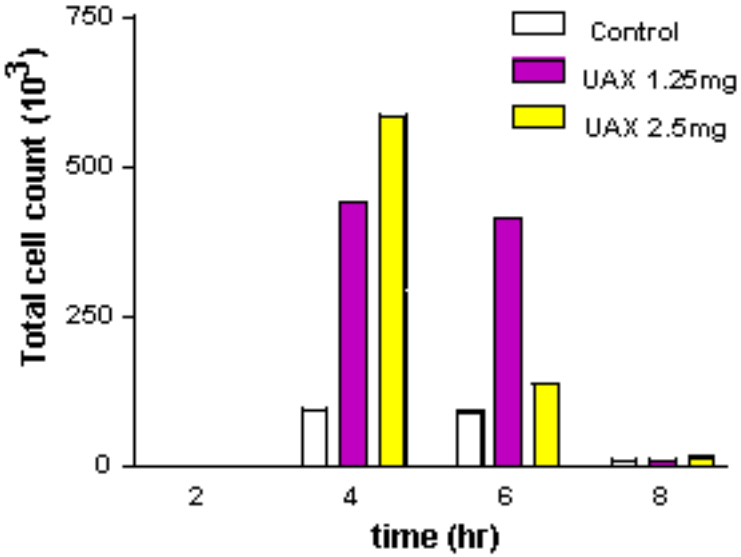




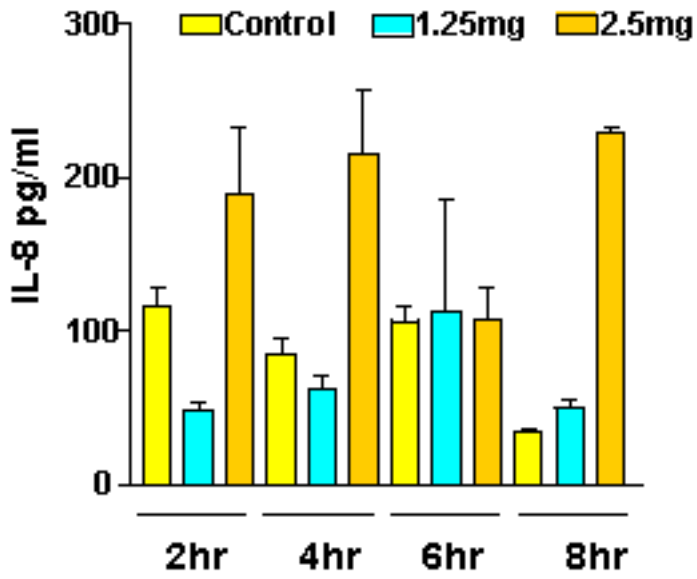


Urate crystals in skin chambers

- Chamber applied to de-roofed vacuum blister
- GMP crystals applied 2 hours
- Fluid for cells and mediators (20-plex Luminex)
- Neutrophils, IL-8 and other chemokines



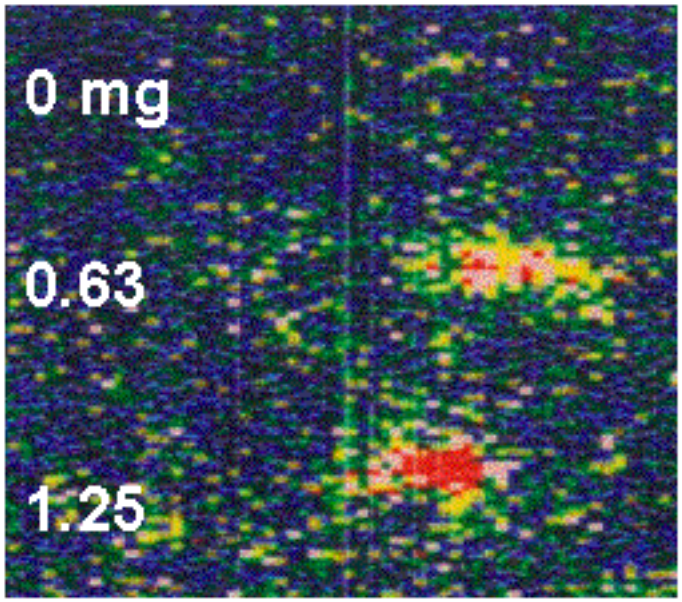
Neutrophil exudate, #7

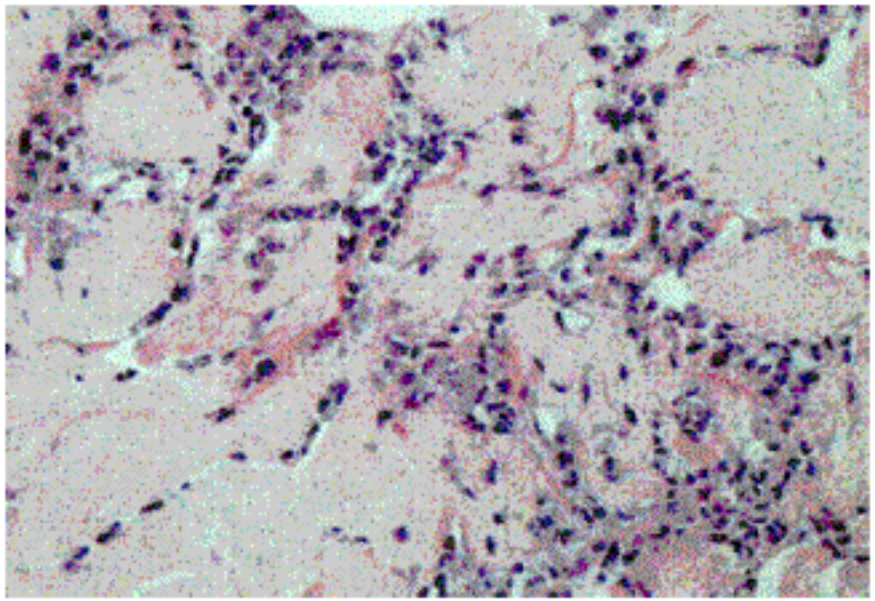


Luminex (IL-8), #7

Intradermal urate crystals

- Graded doses 0- 2.5mg injected
- Quantitate inflammation with laser doppler
- Biopsy shows neutrophil, then macrophage infiltrate
- Safe, well tolerated, and with no lab changes
- Some inter-patient subject variability (timecourse, intensity)

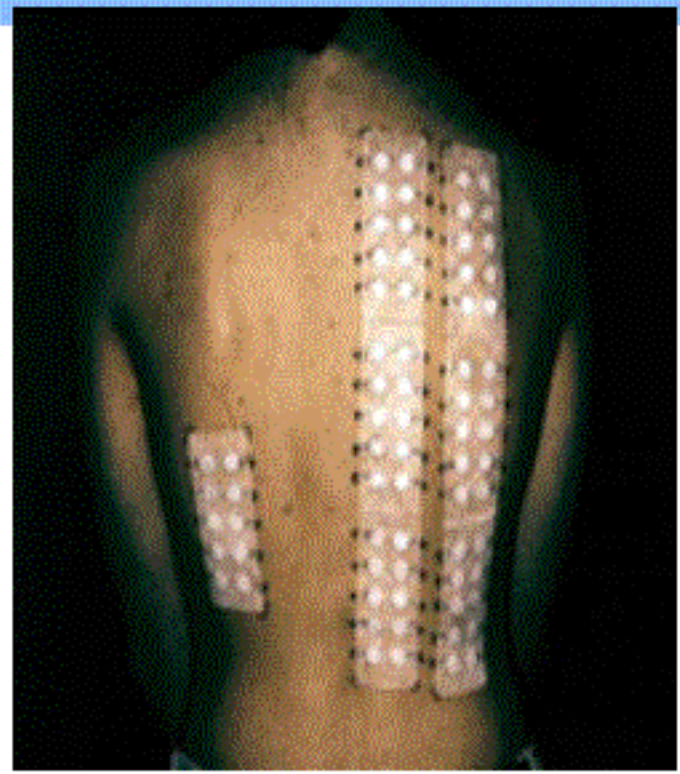


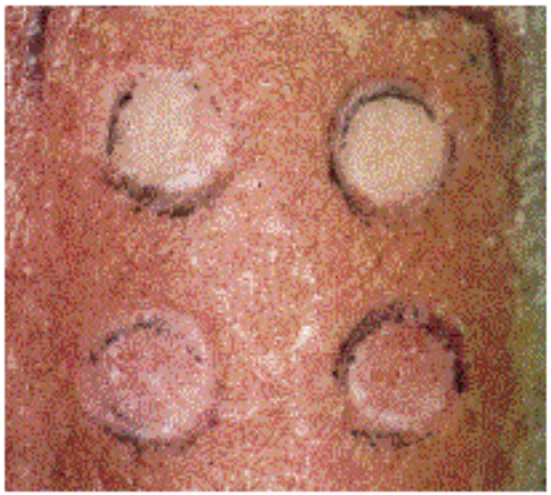


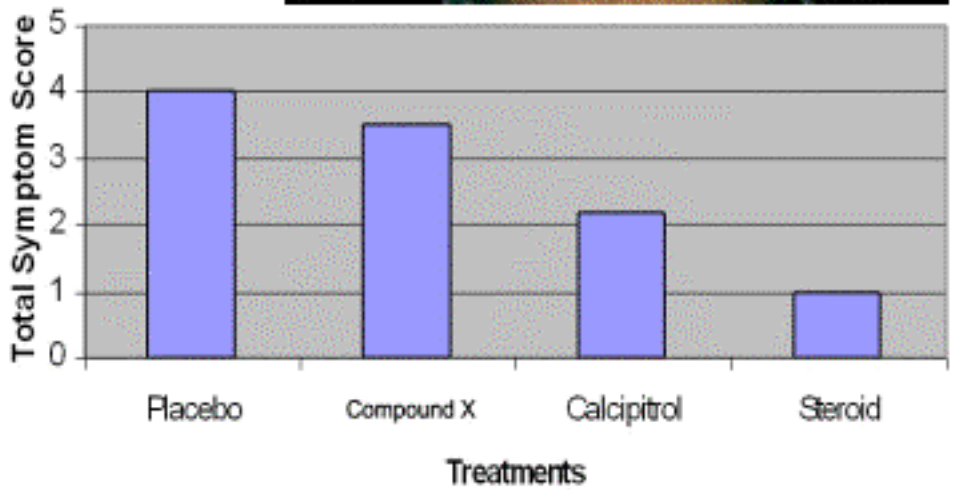
Same model has been created in animals for translational models

Testing mechanisms in Patients

- Only 75 gms of GMP material for Tox, PARD, DMPK and Clinical PoC Patients
- Limited toxicology program
- 26 patients with psoriasis treated. Highly significant result
- Steroid>>Calcipitrol>>NCE=Placebo



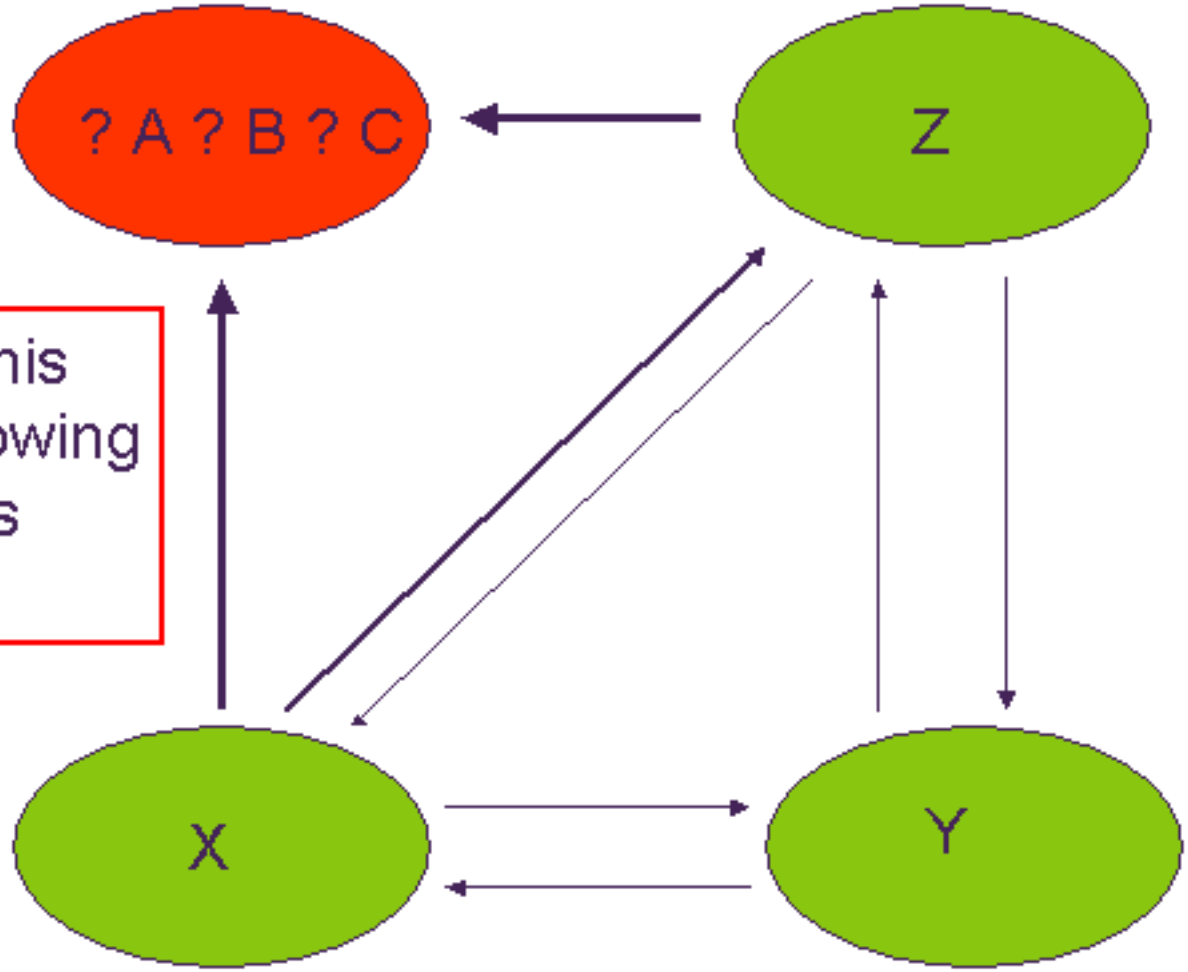




Human Animal

In Vivo

In Vitro



The solution to this equation lies in knowing the initial values for X, Y and Z

Summary

- It is important to understand target biology in humans (disease and healthy) from the start of the drug identification process
- The holistic distribution of the target and its biology needs to be understood
- Newer technologies can give a better insight into disease and target biology
- Appropriate animal models based on disease understanding and target biology may be developed
- Early human studies should be considered where possible
  - eIND type approaches
- Data from multiple sources can be modelled to provide better predictions for safety and efficacy