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The black box of drug discovery and development- what goes on between having an idea and getting a new drug approved.

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The Drug Discovery & Development Process

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Outline of presentation

- The drug discovery & development process
- Finding the right molecule
- Progressing a candidate drug from research into humans

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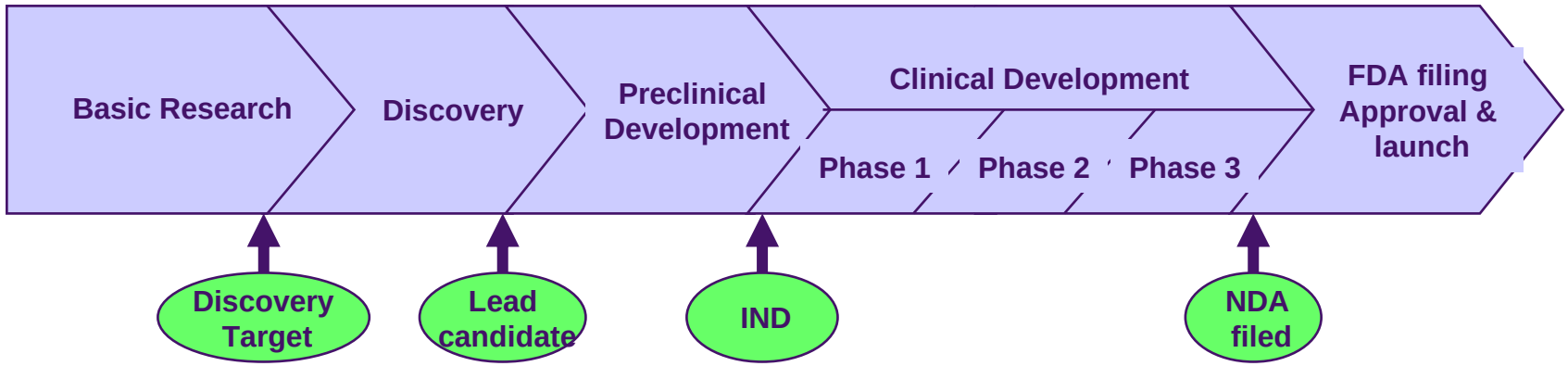
Overview of the drug discovery and development process



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The beginning

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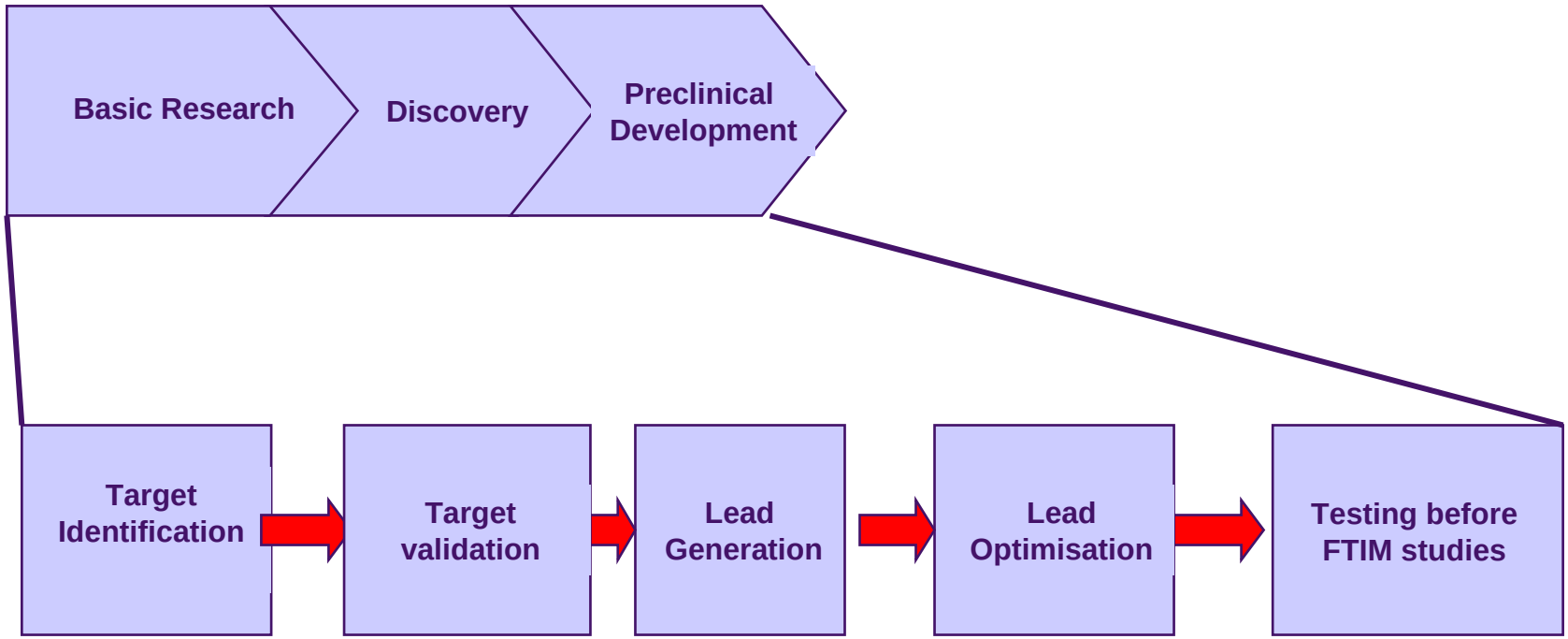

- Understand disease mechanism
- Identify target
- Characterise target

- Compound synthesis
- Chemical starting point
- Screening
- Identify & optimise leads
- Validate efficacy in biological models

- Examine tox & safety in animals
- Formulate dosage & test stability
- TestPK/PD properties

How do you develop a new treatment for a skin disease?

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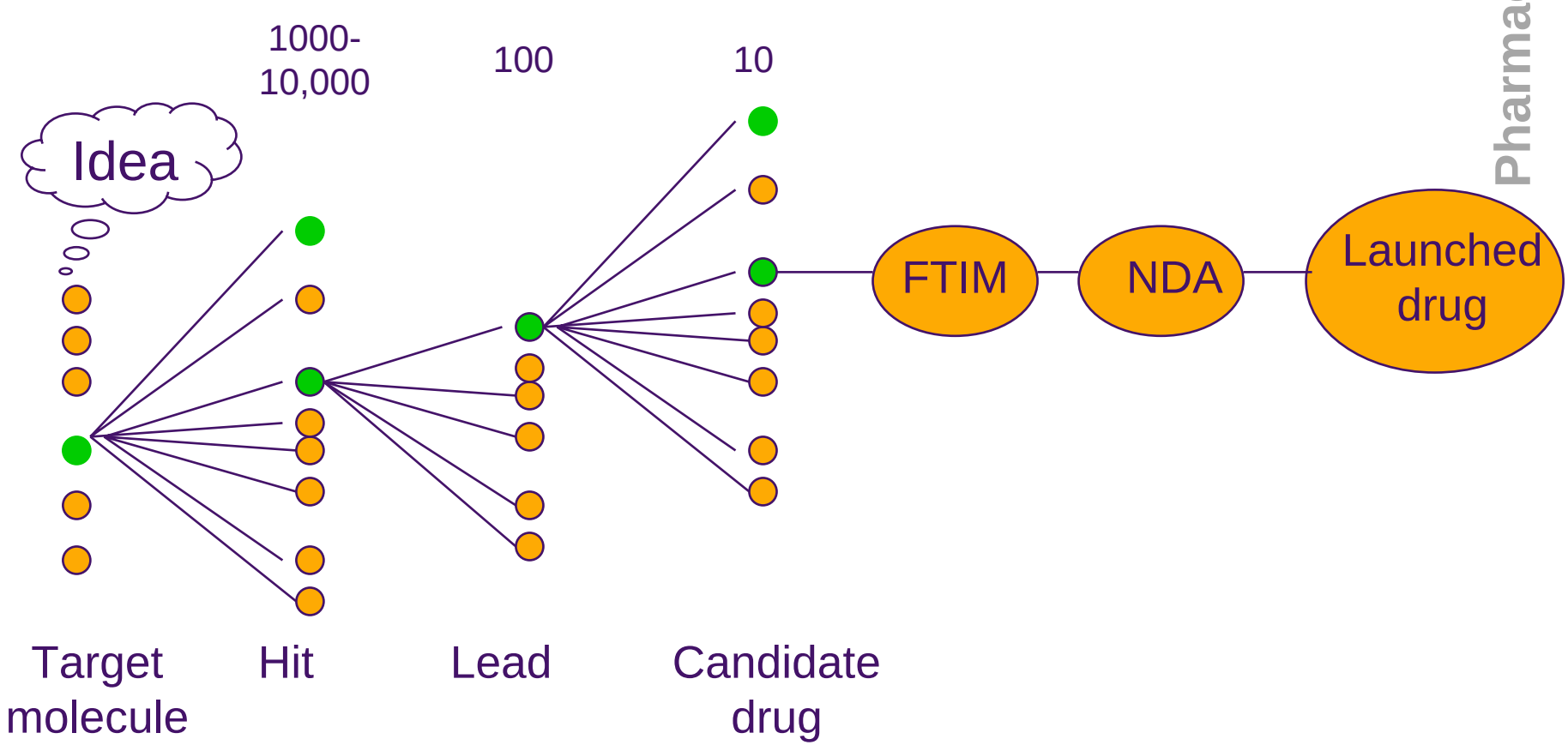

The permutations are enormous and the chance of success is low !!

The complexity of disease

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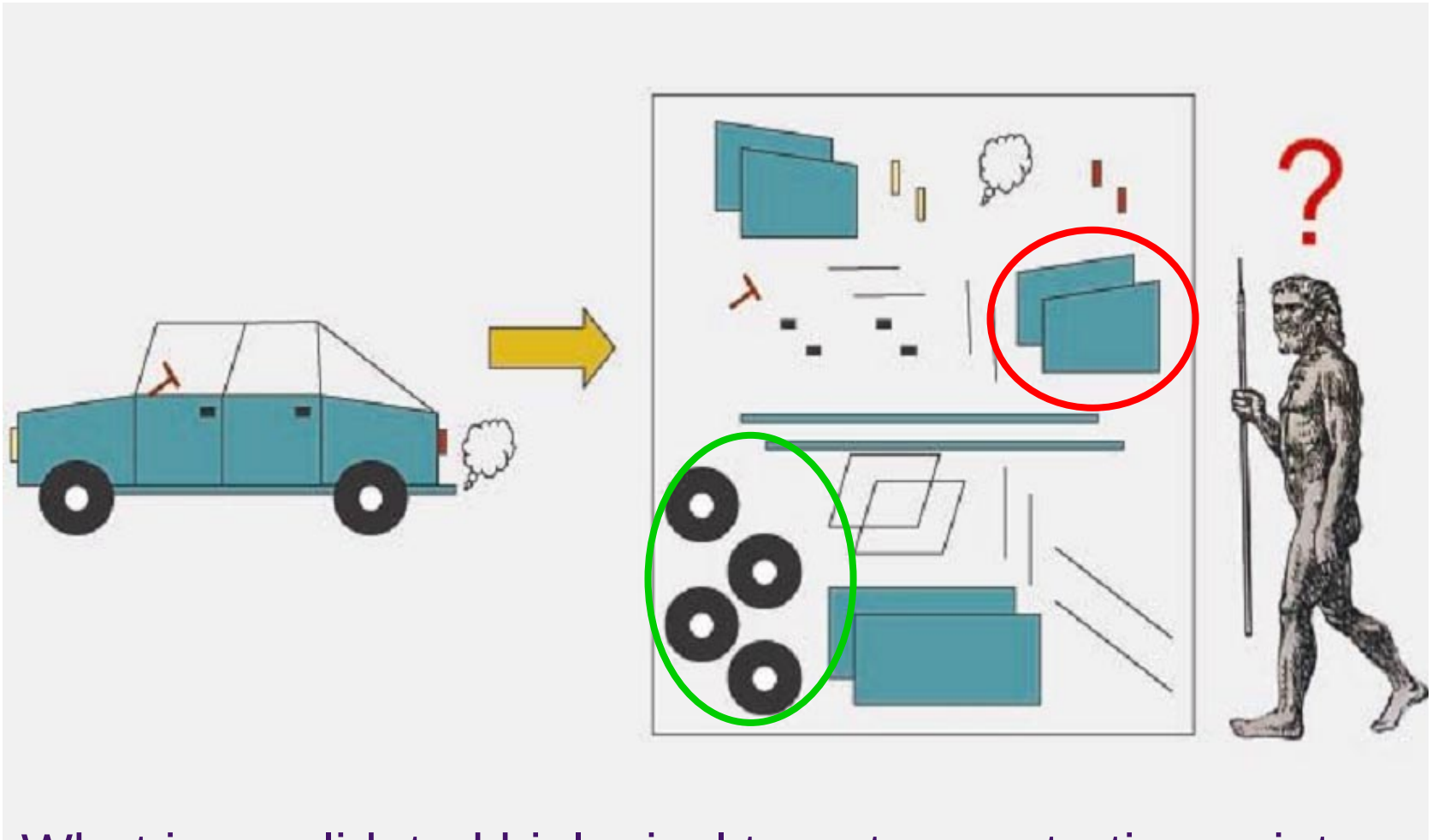
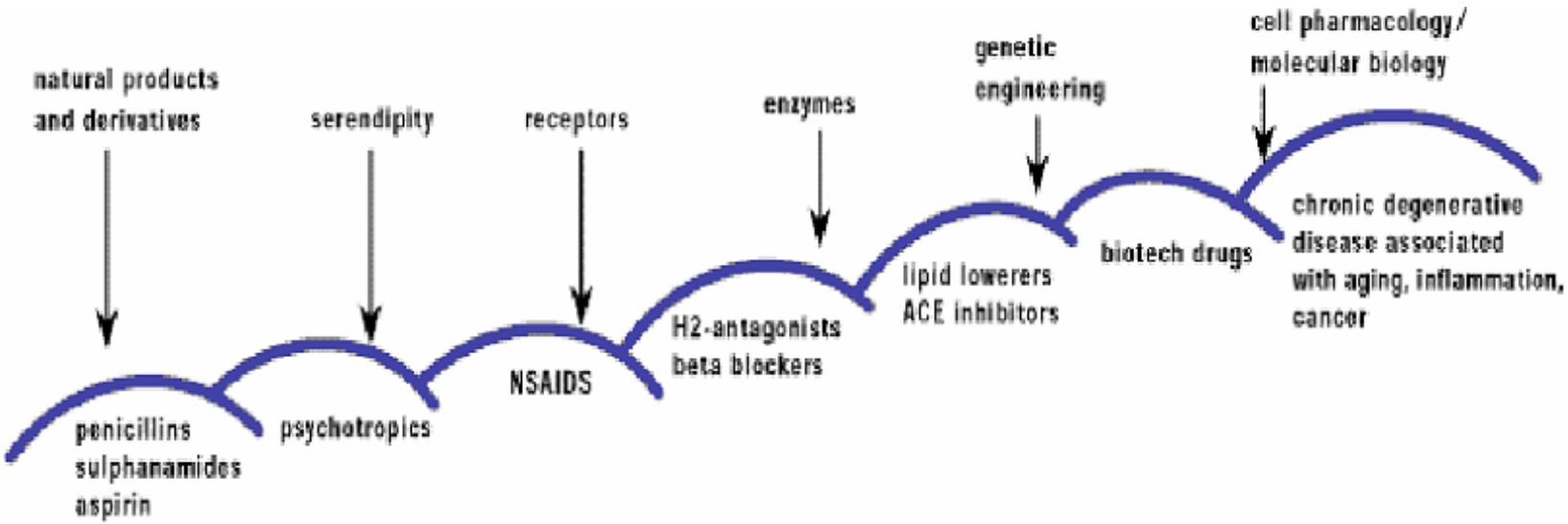


What is a validated biological target as a starting point for drug discovery?

Drug Target Classes



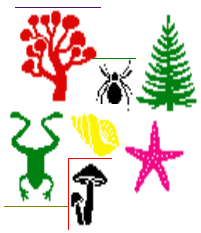
- GPCRs
- Nuclear hormone receptors
- Ion channels
- Enzymes (proteases kinases
- Targets outside these classes are technically challenging

Lead generation

What is a lead like molecule?

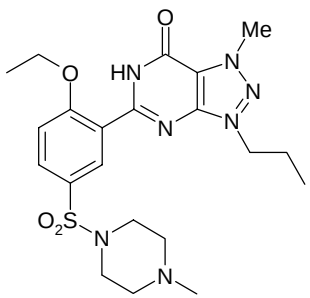
- MW <450
- logP <5 (lipophilic)
- Hydrogen bond donor < 5
- Hydrogen bond acceptor > 10 (sum of N's and O's)

How do you identify a chemical lead?

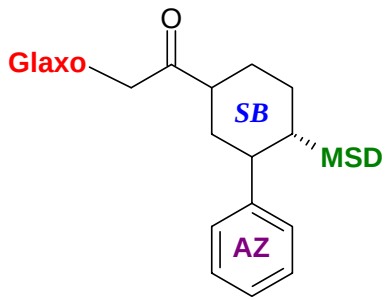


Natural Products

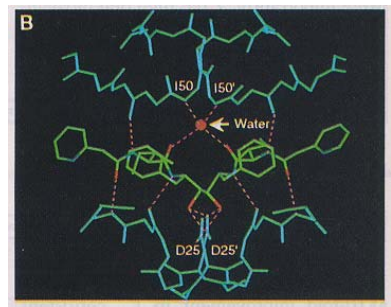
File Screening



From other drugs



Me-too



Target based design

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Combinatorial chemistry and High throughput screening

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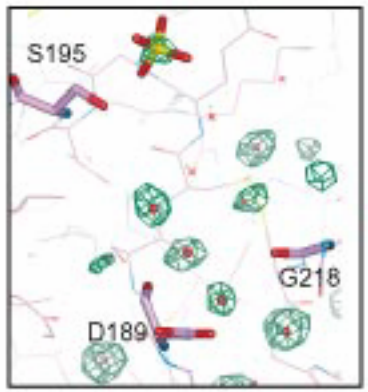
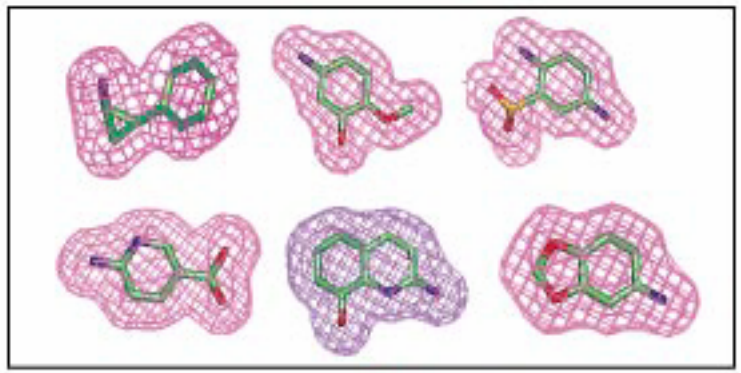
Combinatorial chemistry

- A synthetic strategy that produces large chemical libraries





High throughput screen

- An approach for identifying leads in the absence of a chemical starting point from a large compound bank (library)
- The best compound libraries contain compounds which cover a broad chemical conformational space
- New automation means possible to screen 0.2-1 million compounds per day

Optimising leads

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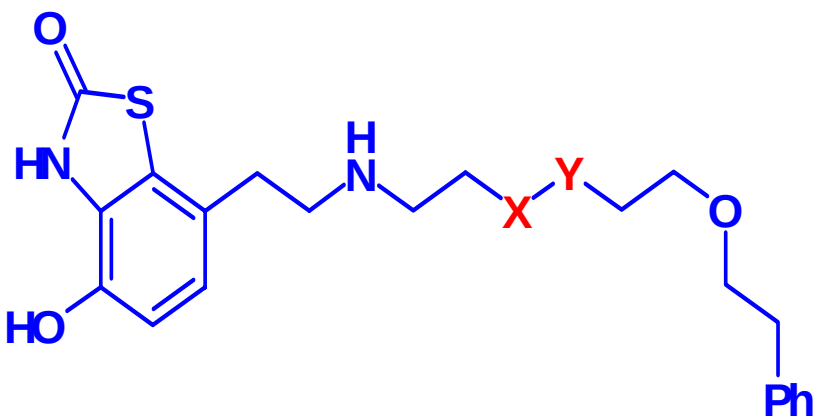
- Pharmacological Potency
- Physicochemical optimisation
  - Lipinski's rule of 5
- Cellular optimisation
  - Where is the target?
  - Do the drug properties allow efficient access to the target?
- Pharmacokinetic optimisation
  - Volume distribution
  - Clearance, Half-life
  - Bioavailability
- Safety optimisation
  - HERG/QT
  - P450
  - Hepatoxicity

Pharmacological Potency optimisation

- Determine the SAR for range compounds based on core leads



X	Y	D_2	β_2	α_1
O	CH_2	7.41 0.81	7.59 0.47	7.2 0.8
SO_2	CH_2	8.94 0.90	7.95 0.69	5.7 .06
NH	SO_2	8.76 0.74	7.39 0.43	6.7 .1
Salmeterol		-	7.52 0.61	-

Physicochemical optimisation

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Lipinski's 'rule of 5' based on review properties of marketed drugs

Poor absorption or permeation is likely if :

A. There are more than 5 H-bond donors (expressed as the sum of OHs and NHs);
B. The MW is over 500;
C. The Log*P* is over 5
D. 10 H-bond acceptors (expressed as the sum of Ns and Os).

Cellular optimisation

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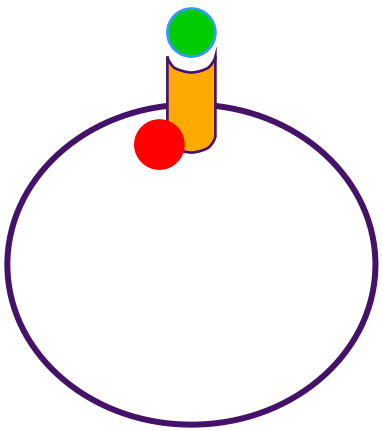
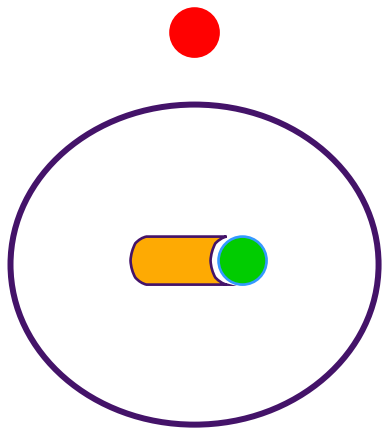
- Where is the target?
- Do the drug properties allow efficient access to the target?

GPCR/ion channel



Intracellular enzyme



Pharmacokinetic optimisation

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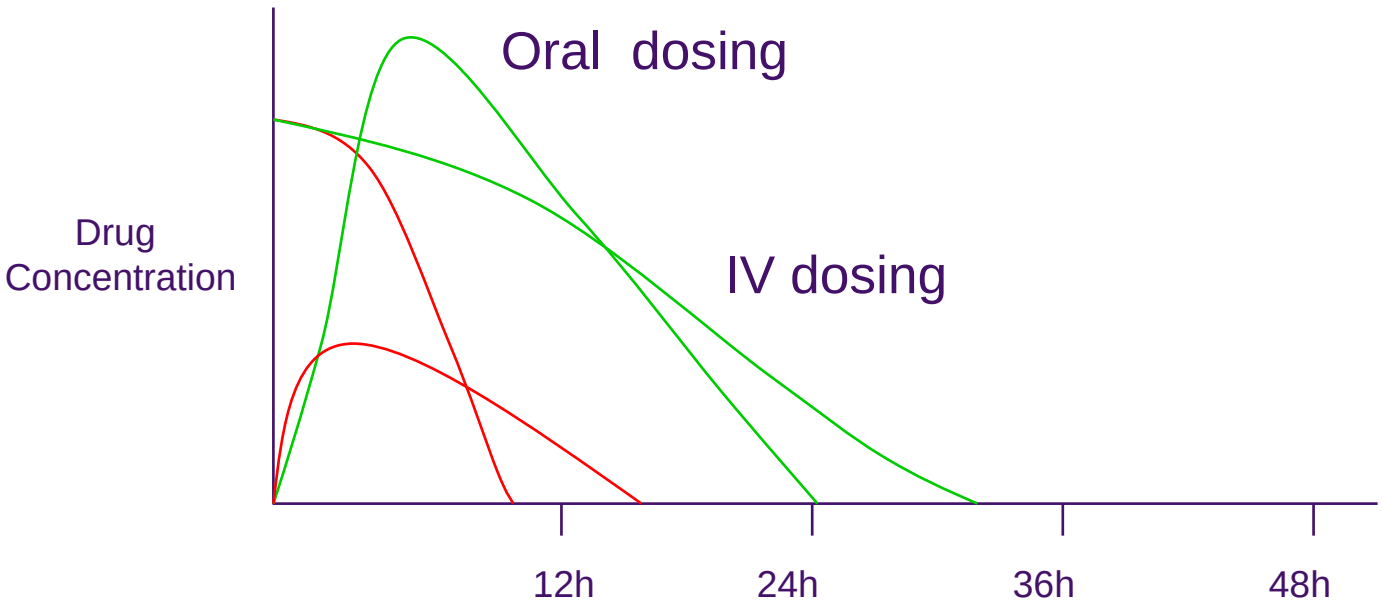
- Clearance- measure of drug elimination
- Half-life
- Volume distribution-
- Bioavailability



Safety optimisation

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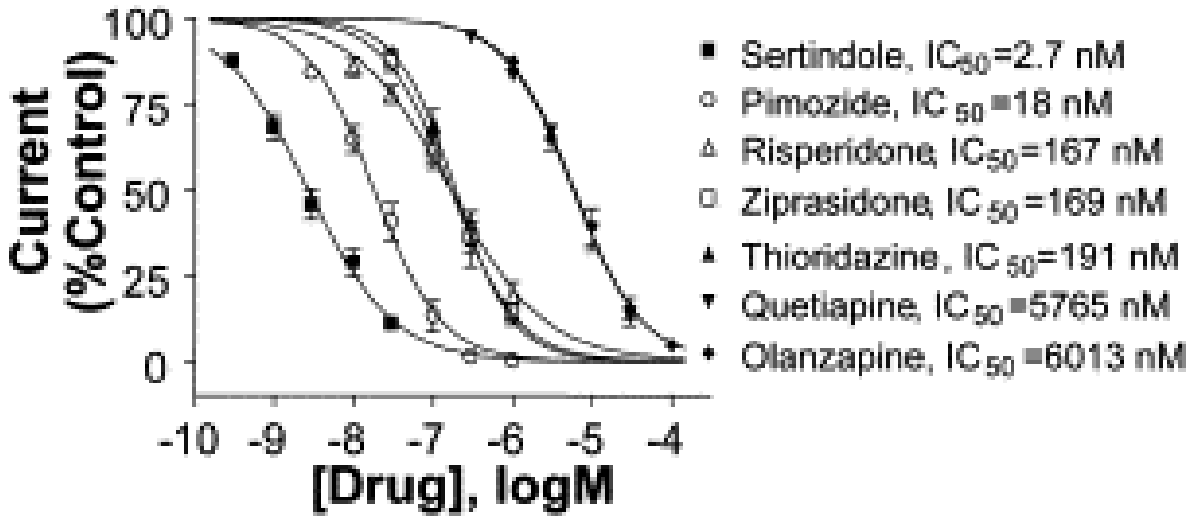
Front loading to identify common safety issues with new drugs using predictive assays



Drug	ΔQT_c (ms)[b]	HERG IC_{50} (nM)	[Total plasma] (nM)	[Total plasma]/HERG IC_{50}
Thioridazine	29.6	191	2064	10.8
Ziprasidone	15.5	169	414	2.4
Quetiapine	4.8	5765	3329	0.6
Risperidone	3.0	167	143	0.9
Olanzapine	1.1	6013	176	0.03

What makes a development candidate drug?

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Clinical candidate profile	
Affinity for Target receptor and potency	
Binding assay (pK_i)	>8
PD assay (pA)	>8
Selectivity	
Secondary pharmacology screen	>100-fold against significant targets
Drug-like properties in vitro	
Solubility (PBS/ 1%DMSO, μg/ml)	50
$LogD_{7.4}$	1-4
Pka	
Mr	200-500
PPB (%) human , rat, dog	<98%
DMPK in vitro	
Human hepatocytes Clint (μl/min/10^6 cells)	<5
Papp in CACO2 (cm/second x10^6)	
CYP inhibition IC_{50} (μM)	>10 μM
DMPK Preclinical species	
Hepatocytes Clint (μl/min/10^6)	<10
Microsomes Clint (ml/m in/kg)	<10
Vss (l/kg)	
$t_{1/2}$ (h)	
F% (KA salt in CMC/tween)	>30

Compounds with optimised balance of key properties.

The end of the beginning

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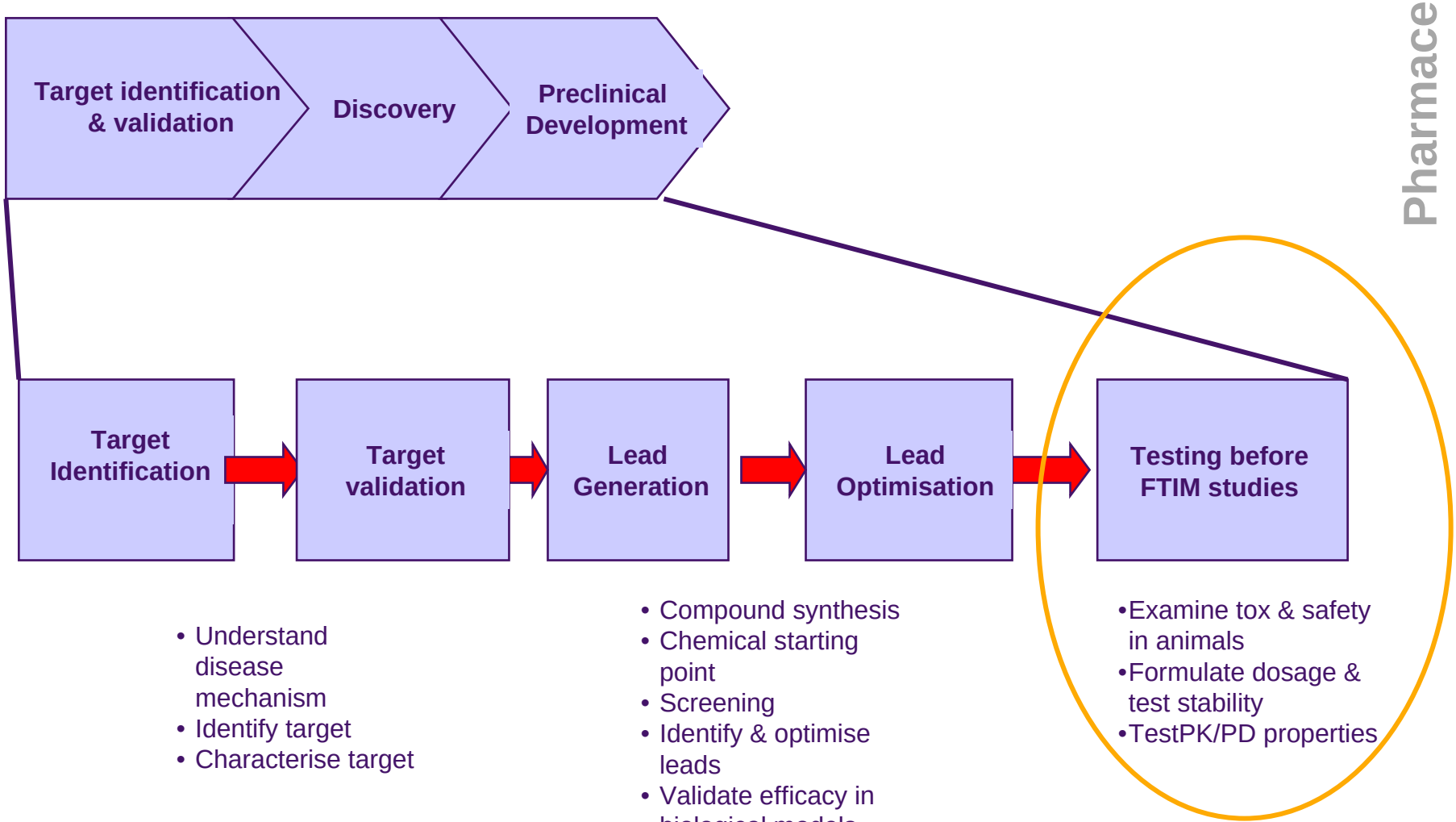

Studies and other activities before FTIM studies

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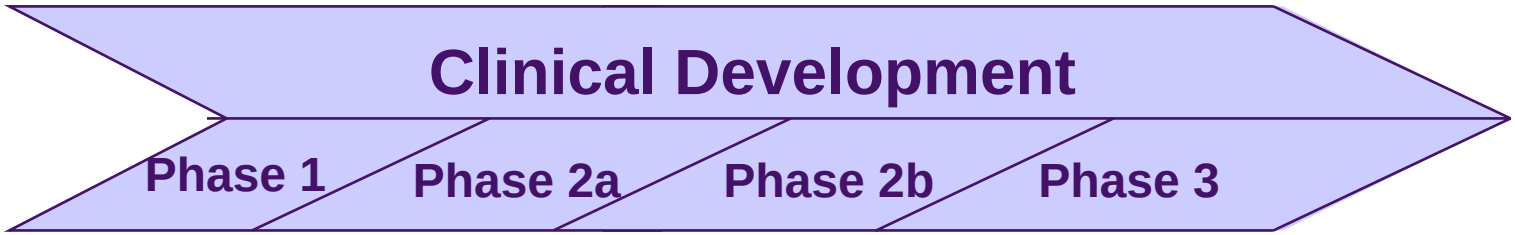
- Pharmaceutical and analytical studies
  - Large scale compound synthesis
  - Drug substance characterisation-impurities
  - Formulation for preclinical safety and initial human studies
- Safety Pharmacology, Toxicology and toxicokinetic studies in two preclinical species
  - Identification of effects major organ function
  - Identification of target organs for toxicity
  - Asssment of monitorability of toxic effects
  - Characterisation of dose response toxic effects
  - Setting of exposure margins
- Drug metabolism and distribution
  - Comparison of of metabolite profiles in man to preclinical species
  - Characterisation of drug distribution

First into man studies and the early clinical testing of new drugs



Phase 1 and 2 of drug development are hypotheses generating activities which underpin the hypotheses that are tested in pivotal trials in Phase 3

A failure to understand the properties and effects of a new drug in Phase 1 and 2 is a recipe for disaster in Phase 3

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Single ascending and multiple ascending dose studies in man

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- Essential for the development of new drugs
- Usually performed in healthy volunteers
  - Excellent safety record but not risk free
  - Sensitive subject as no health benefits to volunteers
- Requires experienced staff and access to specialised methodologies for safety monitoring
  - Telemetry and Bedside Monitoring
  - Digital ECG
  - Experience in interpretation of frequent serial measurements
  - Specialised biochemical monitoring
- Iterative process with review of data by safety review committee before recommendation on proceeding to next dose level

Determining the safety & tolerability of single doses in man

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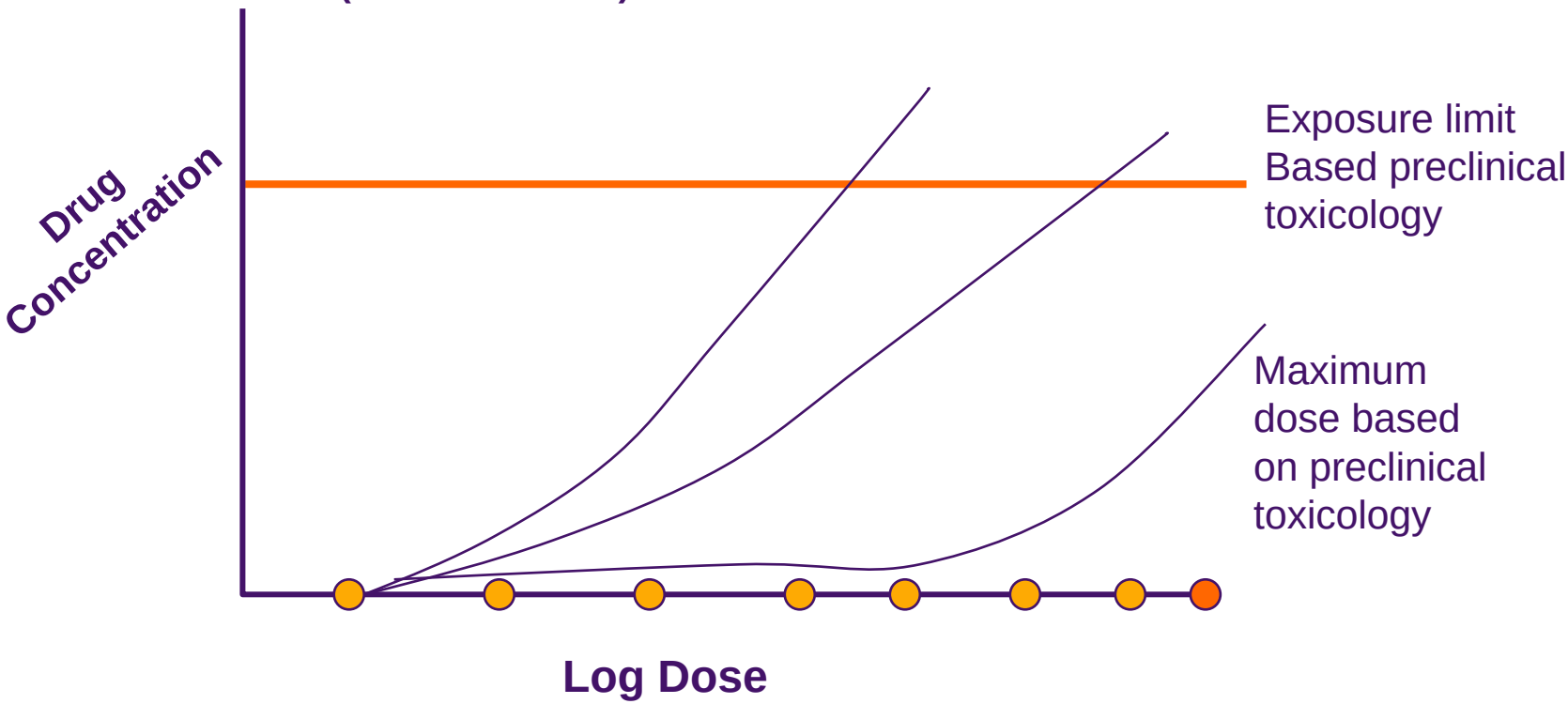
Dose progression in SAD studies

- **Starting dose 10mg (Cmax 7nM)**
- **Anticipated ‘therapeutic’ exposure 286nM**
- **Maximum exposure C max 8790nM**
- **9 dose levels (3 in each cohort)**

Conflicting demands

- **Need to get to high exposures**
- **Need to minimise risk to subjects**



Determining the safety & tolerability of single doses in man

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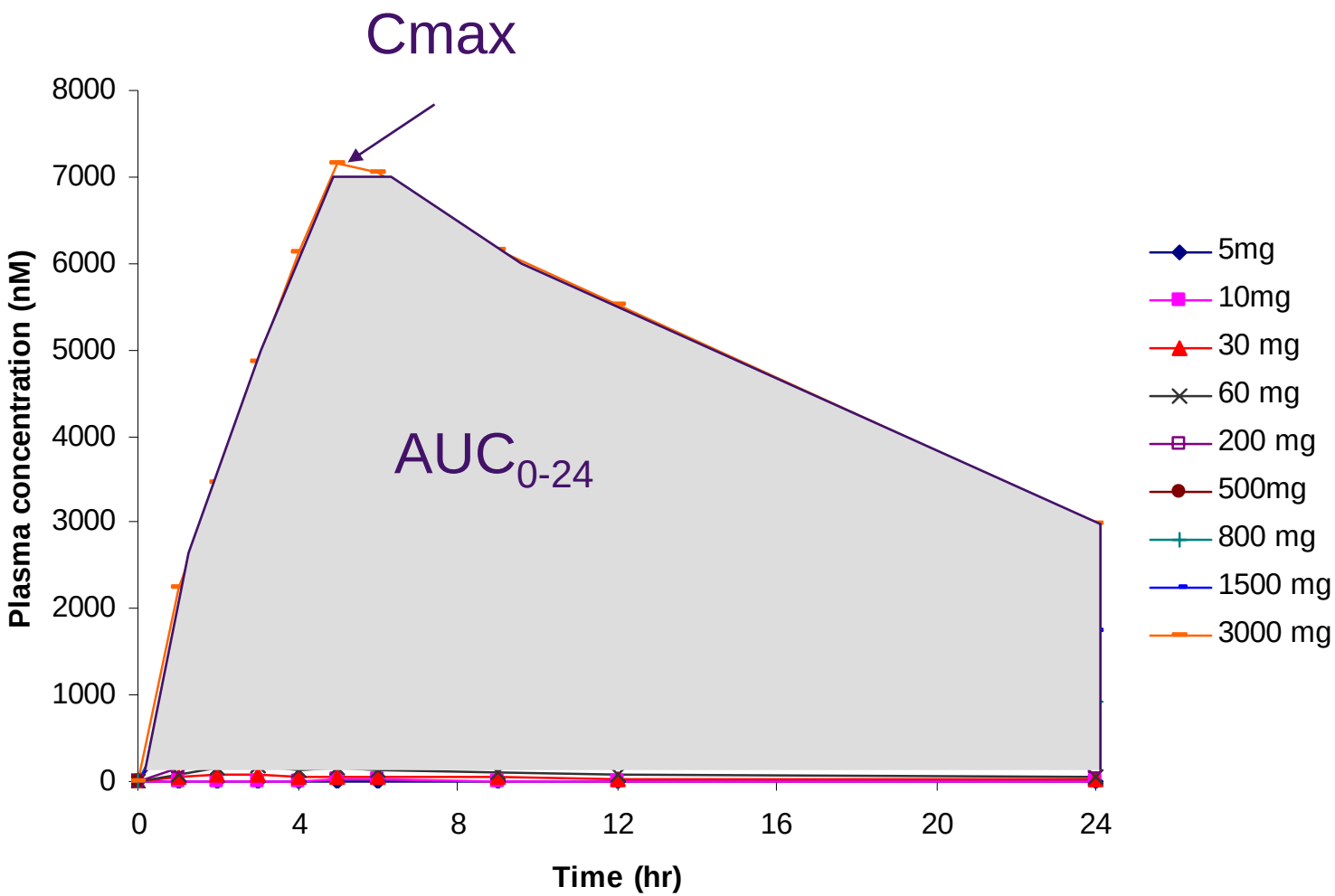

Determining the safety & tolerability of repeated dosing in man

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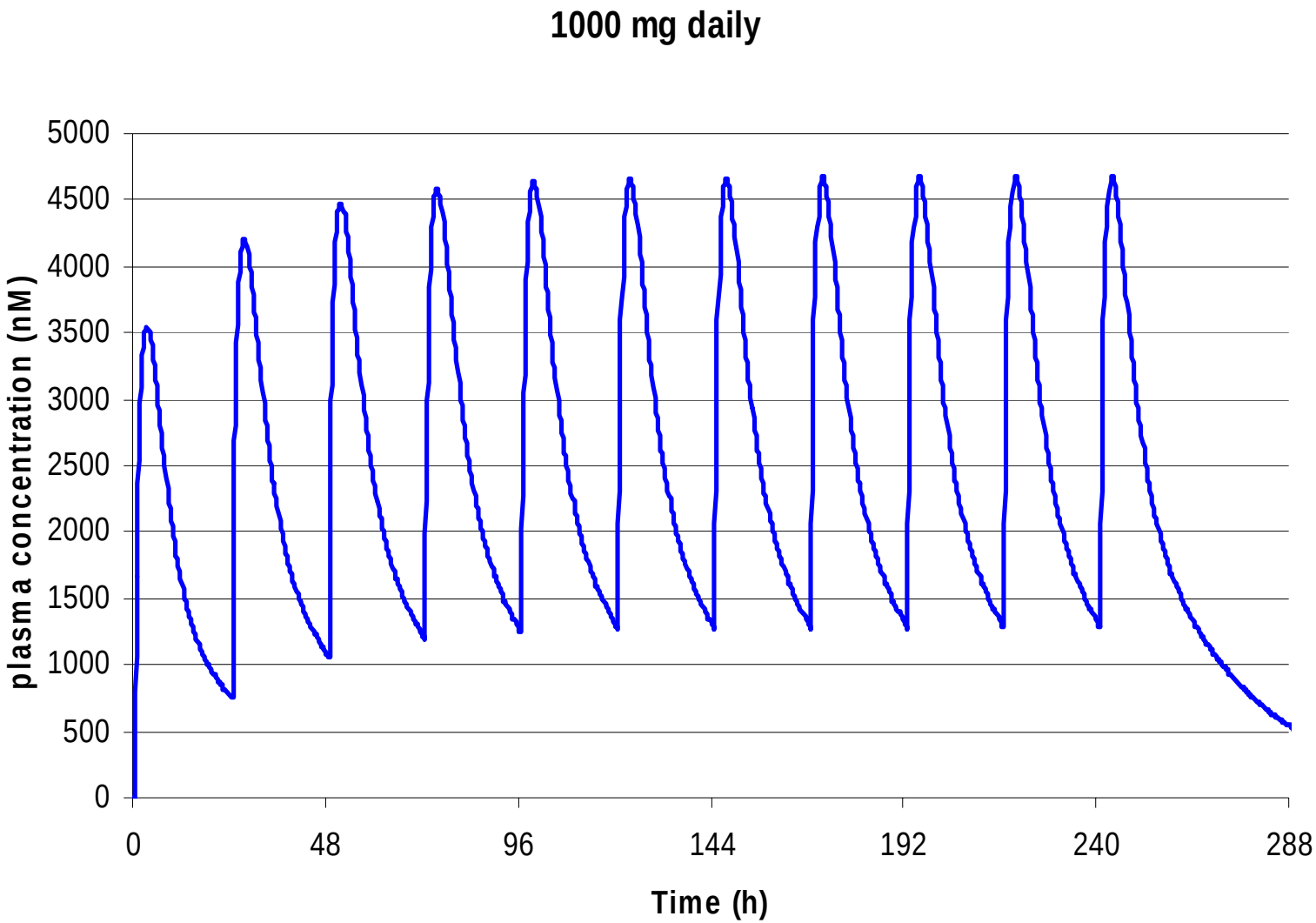

Checklist of requirements prior to phase 2a program

- Safe and well tolerated with single dosing
- Safe and well tolerated with repeat dosing
- Characterisation of effects food
  - Early studies conducted fasting state
  - Food ingestion can produce marked increases in Cmax and AUC which can lead to unexpected toxicity if low Therapeutic index
- Characterisation of magnitude potential drug interactions
  - Pharmacokinetic eg P450 inhibitors
  - Pharmacodynamic

First into man studies and the clinical testing of new drugs

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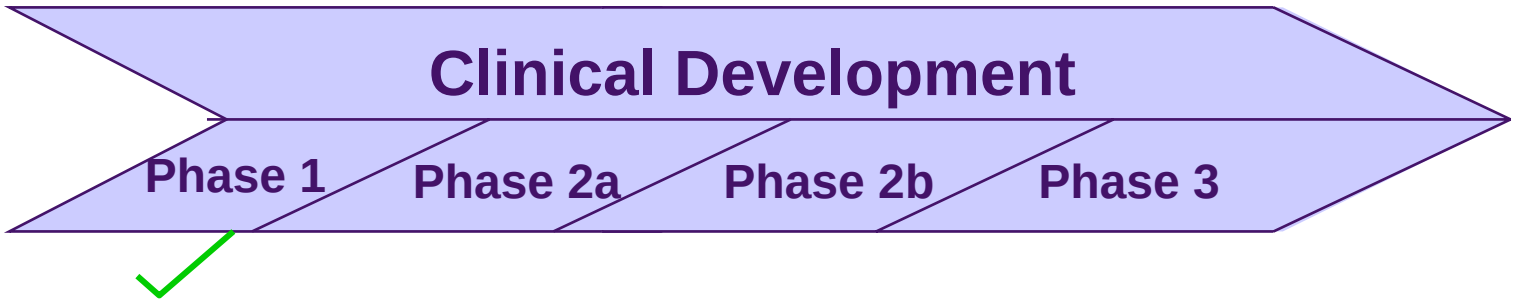

Phase 2a studies

- Usually but not always the first opportunity to collect information on the effects of a drug on a disease
- For novel therapeutic approaches important to design efficient studies which provide confidence in approach using small numbers of patients
- Safety and tolerability assessment important as differences not uncommon between normal volunteers and patients

Phase 2a studies in Dermatology

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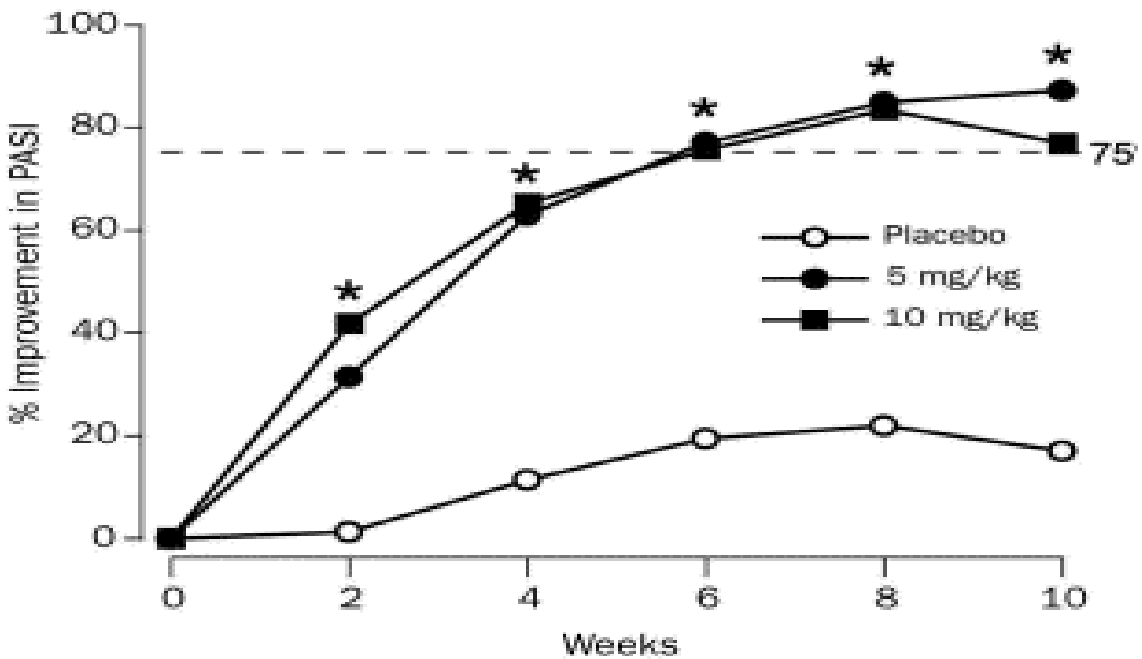
The accessibility of the skin:

- **facilitates assessment of clinical effect**
  - Less requirement for inclusion of patients using subjective criteria needed for other diseases eg morning stiffness in RA
- **Allows samples to be easily collected to investigate cellular and other effects of specific therapeutic interventions**

Infliximab

CTLA4-Ig



Conclusions

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- Drug discovery and development is an exciting, stimulating constantly changing process in a multidisciplinary environment
- Understanding of the process is difficult from a perspective outside of the pharmaceutical industry
- Successful translation of research advances in our speciality into meaningful new medicines will require different expertises and different ways of working than we are familiar with.