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

Disease dissection & target discovery

Drug Development Phase 2b/3
Outline of presentation

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

- Basic Research
- Discovery
- Preclinical Development
- Clinical Development
  - Phase 1
  - Phase 2
  - Phase 3
- FDA filing
  - Approval & launch

- Discovery Target
- Lead candidate
- IND
- NDA filed
The beginning

- **Basic Research**
  - Target Identification
    - Understand disease mechanism
    - Identify target
    - Characterise target
  - Target validation
  - Lead Generation
    - Compound synthesis
    - Chemical starting point
    - Screening
    - Identify & optimise leads
    - Validate efficacy in biological models
  - Lead Optimisation
    - Examine tox & safety in animals
    - Formulate dosage & test stability
    - Test PK/PD properties
  - Testing before FTIM studies
How do you develop a new treatment for a skin disease?

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

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
Combinatorial chemistry and High throughput screening

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

- 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

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Physicochemical optimisation

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

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

GPCR/ion channel  Intracellular enzyme
Pharmacokinetic optimisation

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

![Graph showing drug concentration over time for oral and IV dosing](image-url)
Safety optimisation

Front loading to identify common safety issues with new drugs using predictive assays
What makes a development candidate drug?

<table>
<thead>
<tr>
<th>Clinical candidate profile</th>
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<tr>
<td><strong>Affinity for Target receptor and potency</strong></td>
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<tr>
<td>Binding assay (pK&lt;sub&gt;1&lt;/sub&gt;)</td>
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<tr>
<td>PD assay (pA)</td>
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<tr>
<td><strong>Selectivity</strong></td>
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<td>Secondary pharmacology screen</td>
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<table>
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<tr>
<th>Drug-like properties in vitro</th>
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<tr>
<td>Solubility (PBS/ 1%DMSO, µg/ml)</td>
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<tr>
<td>LogD&lt;sub&gt;7.4&lt;/sub&gt;</td>
</tr>
<tr>
<td>Pka</td>
</tr>
<tr>
<td>Mr</td>
</tr>
<tr>
<td>PPB (%) human, rat, dog</td>
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<tr>
<th>DMPK in vitro</th>
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<tr>
<td>Human hepatocytes</td>
</tr>
<tr>
<td>Clint (µl/min/10&lt;sup&gt;6&lt;/sup&gt; cells)</td>
</tr>
<tr>
<td>Papp in CACO2 (cm/second x10&lt;sup&gt;6&lt;/sup&gt;)</td>
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<tr>
<td>CYP inhibition IC&lt;sub&gt;50&lt;/sub&gt; (µM)</td>
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<table>
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<tr>
<th>DMPK Preclinical species</th>
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<tbody>
<tr>
<td>Hepatocytes Clint (µl/min/10&lt;sup&gt;6&lt;/sup&gt;)</td>
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<tr>
<td>Microsomes Clint (ml/min/kg)</td>
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<tr>
<td>Vss (l/kg)</td>
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<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
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<tr>
<td>F% (KA salt in CMC/tween)</td>
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Compounds with optimised balance of key properties.
The end of the beginning

**Target identification & validation**

**Discovery**

**Preclinical Development**

**Target Identification**
- Understand disease mechanism
- Identify target
- Characterise target

**Target validation**

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

**Lead Optimisation**

**Testing before FTIM studies**
- Examine tox & safety in animals
- Formulate dosage & test stability
- Test PK/PD properties
Studies and other activities before FTIM studies

- 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
  - Assessment of monitorability of toxic effects
  - Characterisation of dose response toxic effects
  - Setting of exposure margins

- Drug metabolism and distribution
  - Comparison 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
Single ascending and multiple ascending dose studies in man

- 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

Dose progression in SAD studies

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

Conflicting demands

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

Drug Concentration vs. Log Dose

Exposure limit based on preclinical toxicology

Maximum dose based on preclinical toxicology
Determining the safety & tolerability of single doses in man

- Cmax
- AUC\text{0-24}
Determining the safety & tolerability of repeated dosing in man

- Effects of repeat dosing examined in multiple ascending dose studies
- Usually 2-4 dose levels examined
- Dosing for 10-14 days
- Safety and tolerability profile of repeat dosing can be very different from single acute dosing
- Drug accumulation
- Repeated subclinical organ injury with no drug-free recovery time
- Essential to understand pharmacokinetics of repeat dosing

Graph:
- 1000 mg daily
- Plasma concentration (nM) vs. Time (h)
- Regular peaks and troughs indicating repeated dosing
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

Clinical Development

Phase 1  Phase 2a  Phase 2b  Phase 3

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

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**

![Graph](image-url)
Conclusions

- 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.