Drug discovery and development and how I ended up working in Pharma

Chad Elmore, PhD
AstraZeneca Pharmaceuticals
Outline

- Astrazeneca
- Drug Discovery and Development
- A bit about me
- My role at AstraZeneca
AstraZeneca

• One of the World’s Largest Pharmaceutical Companies, formed through merger in 1999

• >10,000 staff in Research and Development (60,000 total)

• Major research locations in UK, Sweden and USA

• Annual R&D Expenditure ~$5 billion
Global R&D Sites

- Gaithersburg, MD
- Boston, MA
- Cambridge, UK
- Macclesfield, UK
- Göteborg, Sweden
Some established drugs and key current research areas:

- **Tagrisso**: metastatic non-small cell lung cancer
- **Brilinta**: cardiovascular
- **Faslodex**: breast CANCER treatment
- **Symbicort**: asthma RESPIRATORY
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From discovery to patients...

Including the cost of failure this can cost $5 billion/drug

>80% of drugs tested in people don’t make it
Phases of work – target selection

academia

Internal Work

Competitors

$$$
### Phases of work – target selection

<table>
<thead>
<tr>
<th>Target Selection (TS)</th>
<th>Before screening can start, the project needs to develop the science and technology for the screening approach. Key reagents produced and assays are developed.</th>
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</table>

- **Target selection**
- **Hit ID**
- **Lead ID**
- **Lead Optim**
- **Preclinic Develop**
- **Phase I**
- **Phase IIa**
- **Phase IIb**
- **Phase III**
- **Product Maint**
Phases of work – Hit ID

**Hit Identification**

High Throughput Screening assay development, screening and Active-to-hit evaluation.
Phases of work – Hit ID

Automation is the name of the game!!!
Phases of work – Lead generation

- Lead generation: The process of identifying a series of compounds that have the potential to be developed into drugs.

Diagram:
- Target selection
- Hit ID
- Lead ID
- Lead Optim
- Preclinical Develop
- Phase I
- Phase Ia
- Phase Iib
- Phase II
- Phase III
- Product Maint
Lead Identification – Finding a drug

- High Throughput Screening
- Rational Drug Design
- Improving Known Drugs

Structure activity relationship → Hit to Lead Processes → Lead Compound
Phases of work – Lead Optimization

Lead Optimization: The process of identifying a series of compounds that have the potential to be developed into drugs.
Medicinal Chemists and Lead Optimization

**Physical properties**
pKa, H-bonding, solubility, lipophilicity

**Biological properties**
in vitro affinity & efficacy
selectivity & toxicity
in vivo models

**Computational chemistry**
3-D molecular properties
receptor & enzyme models
QSAR, cheminformatics

**Metabolism & Pharmacokinetics**
clearance, metabolism, oral bioavailability, duration

**Lead generation**
targeted libraries ‘lead-like’ & ‘drug-like’ molecules

**Synthesis**

**Structure Activity Relationship**

Which compounds to make next?
Phases of work – Lead Optimization

Drug Core

Biological properties
-- potency
-- selectivity
-- side effects
-- low dose

Metabolism
-- once a day dosing
-- safety
Phases of work – Lead Optimization

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Phases of work – Lead Optimization

Drug Core

- Biological properties
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  - selectivity
  - side effects
  - low dose

- Metabolism
  - once a day dosing
  - safety
Lead Optimisation – Making a drug better

- Lead Optimization… taking our lead series and delivering a candidate drug, which needs to be……

- Potent
  - active at receptor at concentrations < $1 \times 10^{-8}$ M so it can be administered in a reasonably sized tablet!

- Selective
  - no unwanted pharmacological activities, side effects

- Bioavailable – ideally a tablet taken once or twice daily
  - must be absorbed, retained and stable to metabolism in the body
Lead Optimization – Finding a drug
Phases of work – Preclinical development

Preclinical development

PK/PD/pivotal toxicology to support Phase 1 completed as appropriate. Efficacy demonstrated in vitro and in vivo as appropriate, IP filed and preparation for first time in human (FTIH) progressing.
Preclinical work

• To understand pharmacokinetics of the drug
  – ADME - Absorption, Distribution, Metabolism, Excretion
  – (what the body does to the drug)

• To test the impact a drug has on an enzyme / receptor / biomarker in vivo

• To test the efficacy of a drug in a disease model
  – In oncology, typically a tumour xenograft

• To test different treatment regimens in a disease model
  – Combinations of drugs, dosing schedules etc.

• To understand the safety and toxicities of the drug
Phases of work – Phase I

Phase 1 Small studies, normally conducted in healthy subjects, aiming to establish PK, tolerability and potentially evidence of clinical target engagement.
Phases of work – Phase 2

Phase 2a
Trials with efficacy as primary endpoints to reach Proof of Principle (PoP). PoP shows that the candidate drug results in a biological and/or clinical change associated with the disease and mechanism of action.

Phase 2b
Randomised controlled trials, dose-range finding studies to select the dose(s) for Phase 3, producing a data package to support Proof of Concept (PoC)...PoC indicates that the treatment with the candidate drug results in a clinical change on an accepted endpoint or surrogate in patients with the disease plus evidence of a high degree of confidence of success in Phase 3.
Phases of work – Phase 3

Confirmatory study with registrational intent
Large expensive studies in large patient population
Phases of work – Product Maintenance

Product Maintenance

maximise the product value throughout the product life-cycle.
Phases of work – Product Maintenance

Environmental Fate

New Indications

Comparison vs. Other therapies
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My pathway to a career in the Pharmaceutical industry

High school in Louisiana (1987) – Thibodaux and Natchitoches
   Investigated the pH dependence of lakes on the types of trees surrounding them.

BS in Chemistry (1991) – Rose-Hulman Institute of Technology in Terre Haute, IN
   Conducted research on the ene reaction.

PhD in Organic Chemistry (1997) – U of Illinois – Urbana, Champaign
   Investigated the mechanism that enzymes use to produce natural products.

Interviewing…

>200 jobs applications (mailed) over 1.5 years. Two hits at end: a contract lab and Merck.

1997 – 2004 (NJ)

2004 – 2011 (DE)
2011 – present (Sweden)
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  • I manage a team that incorporates radioactivity into drug molecules.
What is Radioactivity?

• Every element has a unique number of protons
  Carbon has 6, oxygen has 8, Uranium has 92

• The number of neutrons can vary creating isotopes

• An isotope has the same number of protons but different number of neutrons
  • Carbon-14 (8 neutrons, 6 protons)
  • Tritium (H-3, 2 neutrons, 1 proton)
  • Deuterium (H-2, 1 neutron, 1 proton) – not radioactive

  > 1500 isotopes are known to exist.

• 280 isotopes are stable, >1250 unstable (radioactive).
What is Radioactivity?

Number of neutrons

Band of stability

1:1 proton: neutron

> lead

Atomic number Z, protons
What is Radioactivity?

- Radioactive decay can take place by:
  - $\beta^-$ emission -- neutron excess
    - Neutron to proton and $\beta^-$
  - $\beta^+$ emission -- proton excess
    - Proton to neutron and $\beta^+$
  - Electron capture
    - $14^6\text{C} \rightarrow 14^7\text{N} + ^0\beta^- + \nu$
  - Fission -- Large nuclides
    - $236^{\text{U}} \rightarrow 90^{\text{Sr}} + ^{141}_{54}\text{Xe} + 3\text{n}$
  - Alpha particle
    - $241^{\text{Am}} \rightarrow 237^{\text{Np}} + ^4\text{He}$
How is radioactivity useful?

- HPLC (High-Pressure Liquid Chromatography)
- UPLC (Ultra Performance Liquid Chromatography)
- SFC (Supercritical fluid chromatography)

Separates by polarity
Detects by UV (and others Including Radioactivity)
UTILITY OF RADIOACTIVITY
ULTRAVIOLET VS RADIOMETRIC

More polar

less polar

Abs @ 210 nm

Radioactivity

Time, min

Polar Metabolites

Drug X

Non-polar Metabolites
Tritium Manifold
Tritium Gas Reaction
Basic Research
Development of a PET (positron emission tomography) ligand for the CCR2 receptor

Markus Artlesmair

Many compounds

[18F]FDG whole body image.

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PET radioligand for imaging brain 5-HT$_{1B}$ receptors

Anton Lindberg

Sangram Nag, Magnus Schou, Akihiro Takano, Junya Matsumoto, Nahid Amini, Lars Farde, Victor W. Pike, Christer Halldin
Light Catalyzed Aminocarbonylation of Alkyl Iodides

Malvika Sardana

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This project has received funding from the European Union’s Horizon 2020 research and innovation programme under the Marie Sklodowska–Curie grant agreement No 675071 and 675417.
[\textsuperscript{11}C]AZ10419096 – a full antagonist PET radioligand for imaging brain 5-HT\textsubscript{1B} receptors

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Isolated area for preparation of samples for humans
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