DRUG DISCOVERY AND DEVELOPMENT-PRECLINICAL ASPECTS

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Biomedicine Masters Program,
Lund University

Wayne Russell, PhD.
TODAY'S TALK:

- INTRODUCTION TO DRUG DISCOVERY
- WHAT ARE DRUGS
- THE DISCOVERY PROCESS
- DISCOVERY METHODS
- ZEALAND PHARMA
MY RESEARCH BACKGROUND

1994-1998
PhD-Imperial College
Department of Biochemistry

1998-2004
Post-Doctoral Researcher-Lund University
Medical Faculty

2004-2010
Senior Scientist-AstraZeneca, Lund
Department of Integrative Pharmacology

2010-
Senior Scientist-Zealand Pharma
Department of Pharmacology
“Doctors are men who prescribe medicines of which they know little, to cure diseases of which they know less, in human beings of whom they know nothing”

Voltaire 1694-1778
INTRODUCTION TO DRUG DISCOVERY
DEVELOPING DRUGS IS EASY?!
HOW ARE DRUGS MADE?

- Filter process: takes 5-10,000 molecules to make 1 drug
  - Requires several "shots on goal" for success due to high attrition rate

- Process to market is long and costly
  - Approx 10-15 years from idea to market
COST OF MAKING DRUGS? (FIGURES FROM 2000-2001)

- Estimated cost for drug development approx $800- $900 million and increasing!
  - Equivalent to buying Forty F16 jet fighters!
- Divided between the different phases
  - approx $335 million in preclinical
  - approx $467 million in clinical
  - approx $100 million in post approval
- Huge attrition rate-for every 30,000 compounds designed
  - 0.67% (200) enter clinical phase
  - 0.027% (8) are approved!
THE EXPECTED LIFETIME OF A DRUG

● **Competition**
  - First (in class) to market - when is next in class?
  - Other class(es) for therapy - market share?
  - Accepted treatment algorithm - when is drug used?
  - Generics

● **'Patent Game’**
  - Period of patent protection is 20 years (from filing date)
  - Balance of risk and gain for early vs late filing
GLP-1 agonists for the treatment of diabetes

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Short-acting GLP-1 receptor agonists</th>
<th>Long-acting GLP-1 receptor agonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compounds</td>
<td>Exenatide, Lixisenatide</td>
<td>Albiglutide, Dulaglutide, Exenatide-LAR, Liraglutide</td>
</tr>
<tr>
<td>Half-life</td>
<td>2–5 h</td>
<td>12 h–several days</td>
</tr>
</tbody>
</table>

**Effects**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Short-acting GLP-1 receptor agonists</th>
<th>Long-acting GLP-1 receptor agonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting blood glucose levels</td>
<td>Modest reduction</td>
<td>Strong reduction</td>
</tr>
<tr>
<td>Postprandial hyperglycaemia</td>
<td>Strong reduction</td>
<td>Modest reduction</td>
</tr>
<tr>
<td>Fasting insulin secretion</td>
<td>Modest stimulation</td>
<td>Strong stimulation</td>
</tr>
<tr>
<td>Postprandial insulin secretion</td>
<td>Reduction</td>
<td>Modest stimulation</td>
</tr>
<tr>
<td>Glucagon secretion</td>
<td>Reduction</td>
<td>Reduction</td>
</tr>
<tr>
<td>Gastric emptying rate</td>
<td>Deceleration</td>
<td>No effect</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Reduction</td>
<td>Reduction</td>
</tr>
<tr>
<td>Heart rate</td>
<td>No effect or small increase (0–2 bpm)</td>
<td>Moderate increase (2–5 bpm)</td>
</tr>
<tr>
<td>Body weight reduction</td>
<td>1–5 kg</td>
<td>2–5 kg</td>
</tr>
<tr>
<td>Induction of nausea</td>
<td>20–50%, attenuates slowly (weeks to many months)</td>
<td>20–40%, attenuates quickly (~4–8 weeks)</td>
</tr>
</tbody>
</table>

Abbreviations: GLP-1, glucagon-like peptide 1; LAR, long-acting release.
What are the problems getting from bench to bedside?
Why drugs fail?

Drug companies are removing more compounds from the pipeline at all levels of testing than ever before.

For projects started between 1990 and 2004, the United States, Europe and Japan have seen sharp rises in the attrition of drugs tested in trials.

Most of the product failures in phase II and III trials are because researchers are unable to demonstrate efficacy or sufficient safety.

- **Phase II 2008–10**
  - Efficacy
  - Safety
  - Strategic
  - Pharmacokinetics/bioavailability
  - Commercial/financial
  - Not disclosed

- **Phase III 2007–10**
  - Efficacy
  - Safety
  - Strategic
  - Pharmacokinetics/bioavailability
  - Commercial/financial
  - Not disclosed
How reproducible are data?

Bayer Healthcare:

Amgen: Only 47 of 53 (11%) landmark cancer publications could be replicated. Nature 2012
THE PATENT CLIFF

What happens when patents expire?

The Patent Cliff: the drop in blockbuster drug sales 2011-2012

- Worldwide sales Q2 2012: LIPITOR $1.22bn, PLAVIX $741m, Worldwide sales Q2 2011: LIPITOR $2.59bn, PLAVIX $1.865bn
- Worldwide sales Q2 2012: ZYPREXA $1.408bn, SEROQUEL IR $1.129bn, Worldwide sales Q2 2011: ZYPREXA $379.5m, SEROQUEL IR $277m

Pfizer
LIPITOR Patent expired: November 2011
Worldwide sales Q2:
- 2011: $2.59bn
- 2012: $1.22bn

Lilly
ZYPREXA Patent expired: October 2011
Worldwide sales Q2:
- 2011: $1.408bn
- 2012: $379.5m

Bristol-Myers Squibb
PLAVIX Patent expired: May 2012
Worldwide sales Q2:
- 2011: $1.865bn
- 2012: $741m

AstraZeneca
SEROQUEL IR Patent expired: March 2012
Worldwide sales Q2:
- 2011: $1.129bn
- 2012: $277m

pharmaceutical-technology.com
WHAT ARE DRUGS
What is a drug?

- Food and Drug Administration (USA) defines drugs, in part, by their intended use, as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" and "articles (other than food) intended to affect the structure or any function of the body of man or other animals" [FD&C Act, sec. 201(g)(1)].

- Drugs must be generally recognized as safe and effective

- Benefits of use must always outweigh potential risk
WHAT TYPES OF DRUG ARE THERE?

- Small Molecules
- Antibodies
- Peptides
- Proteins
- Gene Therapies
- Stem Cell Therapies
- siRNA Therapies
- Traditional Therapies
- New Therapies

ZEALAND PHARMA
**PRODRUGS**

- Are ‘inactive’ analogues of the drug that are activated in the body by metabolism

- Are used when active compound has poor:
  - bioavailability
  - solubility or taste
  - chemical stability
  - does not cross BBB

- **Plavix (Sanofi-Avantis)**
  - blood clot inhibitor
  - 2nd most prescribed drug WW
  - $9 billion in sales 2010
  - liver metabolism to active drug
**SOFT DRUGS**

- Are biologically active compounds that are specifically designed to be deactivated in a controlled and predictable manner.

- Can be used when parent compound has poor:
  - target selectivity
  - therapeutic index (efficacy vs safety)
  - metabolic degradation

- **Ultiva (GSK/Abbott)**
  - analgesic/anaesthetic
  - μ opioid receptor agonist
  - rapid onset
  - fast offset due to metabolism (T1/2 = 4 min)
TARGETED DRUGS

- Are biologically active at site of interest (can be soft/hard or prodrug!)

- Can be used when compound has poor therapeutic index:
  OR

- When ‘target’ has unique metabolism:

- Valaciclovir (GSK)
  - anti-viral (prodrug of aciclovir)
  - utilizes viral thymidine kinase for primary activation
  - utilizes host cell kinases for final activation
WHAT IS A DRUG TARGET?

- Drugable protein targets can be (approx.) subdivided into 3 classes:
  - Receptors: 47%
  - Channels: 5%
  - Enzymes: 38%
DRUG TARGETING METHODS

● Clinical Observation
  - Can suggest routes for improvement of known drugs or new uses of existing drugs (drug re-profiling)

● Physiological Approach
  - Design of compounds based on thorough understanding of biochemical and physiological processes in disease.
  - Exact mechanism of action unknown-developed at later timepoint
  - No target ID/validation

● Target-Based Approach
  - Comparing expression of target in health vs disease and linking to disease pathology
  - Define function of target
  - Target validation
APPROACHES TO LEAD DISCOVERY

● Serendipity
  - ’Chance’ favours the brave!

● Screening biological activity of natural products

● Chemical modification of known molecules

● Rational drug design
  - Establish link between biological properties and molecular structure
    Pharmacophore-based
    Receptor-based
DRUG DEVELOPMENT BY SERENDIPITY?

- A. Flemming 1928
  - Bacterial cultures contaminated with mould = Antibiotics

- Pfizer Research 1989
  - Hypertension drug fails clinical endpoints, but unexpected side effects = Viagra

- "Chance" discovery leads to success!
  - Place in modern drug discovery?
  - Drug ‘re-profiling’
Investigate structural components using active and inactive ligands

Determine important chemical groups required for biological function

Generate new ligands which have 'active' chemical groups in same 3D location
RATIONAL DRUG DESIGN-RECEPTOR

- Investigate 3D structure of biological target (x-ray structure or 3D modelling using homologous structures)
- Determine important chemical groups required for chemical interaction
- Generate new ligands which have optimal/improved chemical interactions
THE DISCOVERY PROCESS
SO HOW DOES THE DISCOVERY PROCESS WORK?

"I think you should be more explicit here in Step Two."
WHO DISCOVERS NEW DRUGS/DRUG TARGETS?

- Pharma and Academia have complementary skill sets
  - Basic research and Drug Development
  - Pharma develop high throughput screening and financial ’critical mass’
  - Academia unravel disease mechanisms/generate new target ideas
THE DRUG DISCOVERY PROCESS

Target Identification and Validation → Hit Identification → Lead Identification → Lead Optimisation

**Chemistry**
- Combinatorial chemistry
- Medicinal chemistry
- Focused libraries
- Structure-based medicinal chemistry

**Biology**
- Genomics
- Proteomics
- Bioinformatics
- Ultra HTS
- Hit confirmation
- Hit confirmation
- Further screening
- Affinity/Selectivity assays
- Affinity/Selectivity assays
- Efficacy assays
- Disease models

**ADME/Tox**
- 
- In silico ADME/Tox (empirical models)
- In vitro ADME/Tox (primary assays)
- In silico ADME/Tox (empirical/mechanistic models)
- In vitro ADME/Tox (secondary/in-depth assays)
- In vivo ADME/Tox
**Target Identification:**
- Is this a molecule/pathway that is important in disease pathophysiology?
- Will modification of the molecule/pathway produce a beneficial effect on a disease process?

**Target Validation:**
- Is a form of risk assessment. The better the validation, the lower the risk in advancing a project.
- Hunch<anecdotal findings<literature precedent<cell model<animal model<pharmacology in animal model<pharmacology in human disease
HIT IDENTIFICATION

- Molecules identified at this stage have an affinity for the target, but little else is known about them (e.g., antagonist, agonist, partial agonist profile).

- Need to develop a test system that will allow you to determine compounds that interact with your target
  - Traditionally, this was often achieved by using whole animal systems
  - With the advent of molecular biology, however, it is common to test for interactions using recombinant proteins expressed in cell lines, HTS
LEAD IDENTIFICATION

- Identify hits that have good ‘drug’ properties
- Validated hits would be tested to determine factors such as:
  - Selectivity versus a panel of closely related targets
  - Physicochemical characteristics
  - Drug-like properties
  - Pharmacokinetic/Metabolic properties (half life etc.)
- Those molecules with acceptable potency, physical and ADME properties can be advanced through lead optimisation
LEAD OPTIMISATION

- Molecules fulfilling the lead identification criteria can go to “finishing school”
  - At this stage, medicinal chemists conduct further SAR to improve potency and selectivity.
  - This is also the opportunity to improve physicochemical and drug-like properties

- When the field has been narrowed down, the best molecules are advanced to animal models and preliminary toxicology
At this stage, optimised leads are scrutinised for drug properties:

- Potency
- Selectivity
- Bioavailability
- IP position
- Safety

Scale up potential (can you make enough of it cheaply enough?)

The successful candidate will then be submitted to the health authorities to get permission to conduct clinical investigations.
DISCOVERY METHODS
SO HOW DOES IT WORK IN REALITY?
IDENTIFYING TARGETS IN COMPLEX DISEASES?

- Comparison of gene/protein expression in patients vs healthy controls
  - Describes up and down regulation of genes in disease
  - Highlights potentially important physiological pathways
- Comparison of phenotype in patients vs healthy controls
- Clinical observations
Technological advances have led to the development of HTS:

- Large chemical series synthesized in small scale
- Biological and chemical assays miniaturized and developed in multiwell formats
- Improvements in robotics

Large chemical libraries can be synthesized and screened in weeks rather than months/years (ca 10,000/day)
IN VITRO PHARMACOLOGY

- Identification & validation of target(s)
- Screening & selection of compounds
  - biochemical/transformed cell/primary cell/explant
  - potency, efficacy, agonist/partial agonist/antagonist
- Translational research
  - Patient blood or biopsy material

Increasing complexity
IN VIVO PHARMACOLOGY

- Identification & validation of target(s)
- Screening & selection of compounds
  - Naive animals
  - Mechanistic/‘Disease’ models
  - Pharmacodynamic/Pharmacokinetic studies
- Translational research
How the drug affects the body

How the body affects the drug

PHARMACODYNAMICS AND PHARMACOKINETICS?

Pharmacodynamics
Concentration vs. Effect

PK/PD
Effect vs. Time

Pharmacokinetics
Concentration vs. Time
SAFETY PHARMACOLOGY

- Approximately 20% of drugs fail due to toxicity (Kennedy 1997)
  - 11% in animal toxicity studies
  - 10% in clinical studies

- In vitro screening
  - Receptor, enzyme, ion channel panels-selectivity
  - hERG- cardiotoxicology

- In vivo screening
  - Cardiovascular, respiratory & CNS studies
  - Chronic dosing studies to support clinical program
ZEALAND PHARMA
100 employees
80 % of Zealand employees work in R&D
(Academics-46%; Technicians-48%; Students-6%)
Even distribution of women and men
Approximately 17% of employees have other nationality than Danish
Our corporate language is English.
ZEALAND PHARMA CONCEPT

Discovery

Pre-clinical development

Clinical studies

Identification of therapeutic targets and synthesis of peptide libraries

Innovation and design of therapeutically optimised peptides

Clinical studies to proof-of-concept
At Zealand Pharma...

... we generate ideas

... we innovate peptides into drugs

... we advance clinical development towards partnering and commercialization

Value Creation

Time span of 8-12 years
THE ZEALAND APPROACH TO PEPTIDE DRUG R&D

Mol Pharm
Pharm

Bioanalysis
Pharm

Med Chem
Pharm Dev

Target Product Profile
Generate ZP peptide drugs with defined qualities

IP protection and business case
Strengthen partner attraction and value potential
WORKING IN PHARMA INDUSTRY

A typical day/week?

20% Innovation

70% Project work

10% Administration
SÖKER NI KVALIFICERAD OCH KOMPETENT PERSONAL INOM LIFE SCIENCE?
MISSA DÅ INTE DETTA EVENEMANG!


Vilka deltagare finns året:
- 43 företag, bl.a Novo Nordisk, Camurus, Saromics och Apoteket AB
- 750 besökare
- 20% var studenter, doktorander eller postdocs från LTH, Medicinska och naturvetenskapliga fakulteten på Lund Universitet
- 50% hade mer än 10 års arbetsupplevelserhet från Life Science branschen

Annonsen senast 20 oktober på scienceskills.se
Kontakt: Annika Antius, 0770-53 05 80
annika.antius@scienceskills.se

SCIENCE SKILLS

Science Skills, Örebroutbildaren ekonomisk företag är en ny lagg i kompetensmiljön. Med nya moduler och tänkande hjälper vi det skänska näringslivet att ha rätt kompetens vid rätt tidpunkt.

Sponsor:

i samarbete med:
THANK YOU FOR YOUR ATTENTION!

Google picture search “confused”-1st out of 270 Million hits! (2011)

ANY QUESTIONS?