Introduction to Drug Development in Commercializing Biomedical Technology

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Drug Discovery and Development

- What is a drug and how does it work?
- What is the drug development process?
- What are the inherent risks in drug discovery and development?
- How can we de-risk early drug development?
- How do we enable “Medicines for Many”?
What is a drug?

In pharmacology, a pharmaceutical drug, also called a medication or medicine, is a chemical substance used to treat, cure, prevent, or diagnose a disease or to promote well-being.
How does a drug work?

Pharmacokinetics and pharmacodynamics
(PK and PD)
Pharmacokinetics (PK) is a branch of pharmacology dedicated to determining the fate of substances administered to a living organism.
Pharmacodynamics (PD) is the branch of pharmacology concerned with the effects of drugs and the mechanism of their action.
PK and PD: Summary

- PK is what your body does to the drug
- PD is what the drug does to your body
PK and PD + Drug Metabolism

• PK is what your body does to the drug
• PD is what the drug does to your body

• Drug Metabolism can explain the disconnect between drug levels and observed PD effect
  – PK produces new metabolites
  – Metabolites can affect PD (and tolerability)
    • New metabolite(s) may have desired PD effect
    • New metabolite(s) may have altered PK and distribution
    • New metabolite(s) may not be well tolerated
    • New metabolite(s) may affect metabolism of other drugs
DM + PK/PD Examples

Terfenadine (antihistamine + hERG)

Fexofenadine (antihistamine)

Zomepirac - withdrawn (NSAID)

Reactive intermediate

Glutathione adduct
CNS Preclinical Drug Development

- Fragments*
- Crystallography
- Modeling

- HTS

- Med Chem

- Enzyme IC50
- Cell IC50
- In vitro BBB permeability (LLCPK1-MDR1)

- CYP inhibition, Microsomes
- Class Selectivity

- Protein Production
- Assay development

- Mouse PK (iv/po) & BBB penetration
- Protein / tissue binding

- PD species PK/PD

- Full Panel
- CNS Selectivity / hERG

- Hepatocyte Stability

- Efficacy model / Mouse PK/PD

- Second Species PK/PD
- Monkey or Dog (critical path)

- Multi-dose Tox
- Cardio Tox

- AMES / MNT, Reactive intermediate

- Hepatocyte Induction and Time Dep. Inhibition

- Business Development

- Project Management

- Intellectual Property Protection

- Chemistry and Formulation

- Regulatory

- Chemical and Manufacturing Controls

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Drug Development Stages to Approval

Drug discovery: targets and receptors, small-molecule drugs, large-molecule drugs

Drug development: methodologies following GLP – pharmacodynamics, pharmacokinetics, toxicology, drug delivery systems

Clinical trials in humans: protocols following GCP

Manufacturing: procedures following GMP

Marketing application

Compliance with regulatory requirements is necessary
Expense and Revenue for a Drug

1. Drugs take a long time to develop
   • Discovery and development molecules are most often deficits

2. Drugs can make money for a long time
1. Drug development requires ~15 years from target to approval
2. The large majority of ideas fail
1. New targets are essential
2. The bulk of the cost is developing the new target
Drug Development is High Risk

- Two highly selective HMG-CoA reductase inhibitors (statins)
- Both successfully brought to market in US and Europe
  - Which molecule earned > $125 billion?
  - Which molecule induced rhabdomyolysis leading to >50 deaths?

Lipitor (atorvastatin)  Baycol (cerivastatin)
Why Drugs “Fail”

- Pharmacokinetics ~ 10%
- Toxicology ~ 20%
- Pharmacodynamics (efficacy) ~ 40%
- CMC (Chemistry, Manufacturing and Controls) ~ 10%
- Economics / Market Decisions ~ 20%
Drug discovery often is organized in a step-wise fashion for practicality. Assays become more complex, with lower throughput, as compounds become closer to the desired drug profile...
Target Selection: UTSW Competitive Advantage

- Target selection in drug discovery is defined as the decision to focus on finding an agent with a particular biological action that is anticipated to have therapeutic utility — is influenced by a complex balance of scientific, medical and strategic considerations.
- Target identification: to identify molecular targets that are involved in disease progression (phenotypic or target-based)
- Target validation: to prove that manipulating the molecular target can provide therapeutic benefit for patients.
Pharma, Biotech, Investors are Dubious

Merck Wants Its Money Back if University Research Is Wrong

A drug company says economic sticks, not just carrots, are needed to fix the reproducibility crisis in science.

by Antonio Regalado  April 27, 2016

Believe it or not: how much can we rely on published data on potential drug targets?

Florian Prinz, Thomas Schlange and Khursu Asadullah

**GRAPHIC**

Biotech giant posts negative results

Amgen papers seed channel for discussing reproducibility.

<table>
<thead>
<tr>
<th>In-house data in line with published results</th>
<th>Model reproduced 1:1</th>
<th>Model adapted to internal needs (cell line, assays)</th>
<th>Literature data transferred to another indication</th>
<th>Not applicable</th>
</tr>
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<tbody>
<tr>
<td>12 (66%)</td>
<td>12 (56%)</td>
<td>0</td>
<td>1 (7%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Inconsistencies that led to project termination</td>
<td>11 (26%)</td>
<td>28 (60%)</td>
<td>2 (5%)</td>
<td>4 (9%)</td>
</tr>
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</table>

**TABLE**

**LEGEND**

- Oncology
- Women’s health
- Cardiovascular
- Model adapted to internal needs
- Literature data transferred to another indication
- Not applicable
- Inconsistencies
- Literature data in line with in-house data
- Main dataset was reproducible
- Some results were reproducible
De-Risking Drug Development
Validation and Process

Process vs. Creativity over Time

1. Process is the partner of creativity - not the enemy
2. Validation is essential to de-risking new technologies
   - Too often a technology fails to recapitulate from academia to pharma
De-Risking Technology

1. Product exclusivity
   - Intellectual property protection
   - Patents
     - File Intellectual Property Questionnaires (IPQ)
     - Ensure collaboration agreements are in place
     - Never disclose without a CDA / NDA

2. Independent validation
   - Collaborator networks
   - Blinded coworkers
   - Contract Research Organization (CRO)

3. In vivo Proof of Concept (POC)
   - Blinded, randomized PK/PD experiments
   - Solid toxicokinetics (tolerability plus drug levels)
   - Preclinical therapeutic index (TI)

4. Chemistry and Manufacturing Plan

5. Competitive and Market Analyses

6. Transparency
Failing late is expensive (often >$300 Million)

Identifying liabilities early:
  • Decreases cost of failure
  • Shifts resources to more promising programs

Critical evaluation of preclinical drug discovery data decreases risk
  • Target relevance / redundancy
  • On-target toxicity
  • Target engagement
  • Reproducibility

In vitro – In vivo correlations (IVIVC) are critical to understanding how/where drugs work (or don’t work)
CNS Preclinical Drug Development

**Fragments**

- Crystallography
- Modeling

**HTS**

- Enzyme IC50
  - CYP inhibition, Microsomes
  - Cell IC50

**Med Chem**

- Full Panel
  - CNS Selectivity / hERG
  - In vitro BBB permeability (LLCPK1-MDR1)

**Intellectual Property Protection**

- Intellectual Property Protection

**Protein Production**

- Protein Production
- Assay development

**Assay development**

- Cell IC50

**Rodent PK (iv/po) & BBB penetration**

- Rodent PK (iv/po) & BBB penetration
- Protein / tissue binding

**PD species PK/PD**

- PD species PK/PD
- Full Panel
  - CNS Selectivity / hERG

**Hepatocyte Stability**

- Hepatocyte Stability
- AMES / MNT (critical path)

**Multi-dose Tox Cardio Tox**

- Multi-dose Tox
- Cardio Tox

**Regulatory**

- Regulatory

**Chemical and Manufacturing Controls**

- Chemical and Manufacturing Controls

**Chemistry and Formulation**

- Chemistry and Formulation

**Meet “go” criteria**

- Meet “go” criteria

**Control**

- Control

**Second Species PK/PD Monkey or Dog (critical path)**

- Second Species PK/PD Monkey or Dog (critical path)

**Regulatory**

- Regulatory

**CYP inhibition, Microsomes**

- CYP inhibition, Microsomes

**Class Selectivity**

- Class Selectivity

**In vitro BBB permeability (LLCPK1-MDR1)**

- In vitro BBB permeability (LLCPK1-MDR1)

**Solubility & logD**

- Solubility & logD

**Efficacy model / Rodent PK/PD**

- Efficacy model / Rodent PK/PD

**Multi-dose Tox Cardio Tox**

- Multi-dose Tox
- Cardio Tox

**Hepatocyte Induction and Time Dep. Inhibition**

- Hepatocyte Induction and Time Dep. Inhibition

**UT Southwestern Medical Center**

- UT Southwestern Medical Center
De-Risking Drug Development Programs Early

- Do not take short cuts in preclinical programs
  - Extreme economic pressure to deliver drug candidates
  - High political/career pressure to find success
  - This is the time to “fail”, yet it can be harmful to careers
  - This is the “cheap” time to fail!

- Good organizations utilize metrics that align professional success with good science
  - Separate “bad” decisions from “undesired” outcomes
  - Celebrate “good” decisions regardless of the desired outcome

- Never let relationships replace data (start with Research Tools)
  - “In God we trust, all others must bring data” – W. Edwards Deming
Validation of Research Tools - 1

- **In vitro assays**
  - Are they disease relevant?
  - Are redundancies addressed?
  - Do they assess anti-target selectivity?
  - **Do they work in other hands?**

- **Cellular systems**
  - Are the most disease relevant cells used?
  - Are similar results seen in other systems?
  - What is the effect of serum?
  - Is toxicity adequately measured?
  - **Do they work in other hands?**

- **Chemical matter**
  - Can you own it?
  - Is it drug like?
  - Is the SAR “flat”?
  - Can you make it?
Avoid PAIN

1. Don’t believe your target is the exception
2. There is only one kind of luck in drug discovery – and it ain’t the good kind
Establish IVIVC in multiple species for pharmacokinetics
• In vitro ADME (Absorption, Distribution, Metabolism, Excretion) assays are critical
  • Clearance (CL)
    • P450 mediated? Aldehyde Oxidase? Xanthine Oxidase? Monoamine oxidase?
    • Extrahepatic CL? Whole blood stability?
  • Absorption (solubility and permeability)
  • Drug-drug interactions**
  • Distribution / Efflux / Basicity
    • Phospholipidosis / Lysosomotropism
    • CNS penetration ($B_u/P_u$ ratio)

Establish IVIVC in multiple species for pharmacodynamics
• Determine the $C_u$ that drives efficacy in each compartment
• Compare EC50 for PD effect vs. in vitro / cellular assays
  • Protein and tissue binding are critical data
  • Evidence of target engagement
Drug Metabolism and PK (DMPK)

Absorption (In vitro)
- Solubility (thermodynamic)
  - Buffer pH 7.4, FaSSIF pH 6.5; FeSSIF pH 5.0
- Phy-chem properties
  - MW, pKa (measured), logD, CLogP
- Permeability
  - PAMPA or MDCK permeability

Distribution (In vitro)
- $F_u_{\text{plasma}}$ (Human and PK species)
- Blood to plasma ratio (human and PK species)

Metabolism (In vitro)
- Liver microsomal stability (human and PK species)
- Hepatocytes stability (human and PK species)
- Plasma or blood stability, rhCYP stability, and MetID
- Cold MetID-LM, Blood/plasma, rCYPs, or other matrix
- Hepatocytes MetID/profiling (five species, preferably $^3$H or $^{14}$C)
- LM MetID/profileing (five species, preferably $^3$H or $^{14}$C)
- Bioactivation screening (human)

In vivo ADME
- Mass balance and tissue distribution in rat ($^3$H or $^{14}$C)
  - Renal or biliary clearance (cold)
- Blood/plasma metabolite profile in rat ($^3$H or $^{14}$C)
- MetID and profile in excreta in rat ($^3$H or $^{14}$C)
- Plasma metabolite profile in preclinical species (cold)

Transporter
- Hepatic uptake transporter substrate assessment
- Renal transporter substrate assessment
- P-gp and BCRP IC$_{50}$ determination
- Efflux transporter substrate assessment
- P-gp and BCRP substrate screen
- OATP-1B1, 1B3, OCT-1,2, OAT-1,3 2-point inhibition
  - IC$_{50}$ determinations
- MATE1/2K-2-point inhibition

Drug-Drug Interaction
- Direct and time-dependent CYP inhibition (LC/MS based)
  - IC$_{50}$ for CYP3A4 (two substrates), 1A2, 2D6, 2C9, 2C19, 2B6, and 2C8
- TDI screening for CYP3A4, 1A2, 2B6, 2C8, 2C9, 2C19, and 2D6
  - $K_i$, $K_{i,n}$ and $k_{inact}$ determination
- DME reaction phenotyping
  - rhCYP1A2, 2D6, 2C9, 2C19, 3A4; UGTs (cold)
  - CYPs, FMOs, UGTs (3H or 14C); Enzyme kinetics
- Induction
  - HepaRG CYP3A4 induction
  - CYP3A4, 1A2, 2B6 mRNA induction (human, 4 conc.)
  - EC$_{50}$ or Ind$_{max}$ for CYP3A4, 1A2, 2B6 mRNA (human)
- DDI predictions

Preclinical PK
- PK IV/PO profiles: at least two species
- Single dose escalation for rodent and non rodent (PK analysis)
- TK for 5-d rat tox
- Formulation studies
- Human PK prediction & PK/PD modeling
- Active/toxic metabolite(s) exposure
Preclinical Proof of Concept

PK/PD experiments
• Does the PD marker relate to disease outcome?
• Are data available from multiple labs?
• Is the PK/PD response dose proportional?

Efficacy models
• Discuss all caveats of models*
• Randomize and blind
  o Blinding is not sufficient
  o Address inherent bias
• Is efficacy dose responsive / proportional?
  o Does drug exposure change with time?
  o Does response change with time?

Tolerability studies
• Single ascending dose (SAD) and multiple ascending dose (MAD) studies
• Access drug levels at all time points vs. adverse events
• Full blinding
• Define TI (Therapeutic Index)
Proof of Concept (POC) Fund

Provide seed funding to catapult promising early-stage university-developed research – research that most often would not be funded by any other conventional source – to the point where private investment can be attracted.
Objective:
Cultivate collaborative relationships with the public and private sector to develop, protect, transfer, and commercialize research results for the public benefit

How we do it:
• Relationships
  – Faculty and administration
  – Collaborating institutions
  – Venture groups
  – Pharma and biotech
  – Community
• Know How
  – Patent law
  – Licensing
  – Science and technology analysis
  – Drug discovery and development
• Addressing Challenges
  – Funding gaps
  – Validating programs
Thank you

• Questions?

• Ask now or email: kwhuntinco@gmail.com