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Zomepirac - withdrawn (NSAID)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
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 (7.4, measured)
- 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/profiling (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)

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

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
- $K_i$, $K_i$, 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
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
- Compliance with regulatory requirements is necessary
- Marketing application
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)
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

Business

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 Khusru Asadullah

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Validation and Process

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
Director of Biopharmaceutical Product Development

1. Aid investigators in drafting drug discovery and development plans
   • Compound progression plan
   • Minimize drug discovery cycle time

2. Identify and utilize CRO’s for “commodity” services
   • Free investigators to focus on creating
   • Leverage each organization for their strengths while extracting full value

3. Provide expert drug discovery advice
   • Intellectual property
   • Medicinal chemistry
   • Drug metabolism and pharmacokinetics (DMPK)
   • Target engagement
   • Selectivity profiling
   • Avoiding PAINS and toxicophores
   • CMC

4. Design of clinically relevant efficacy studies
   • Properly powered, blinded and randomized studies
   • PK / PD relationships

5. Funding
   • Active networking with local venture funds
   • POC fund
     ➢ UT System – decision by January 2017
     ➢ UT Southwestern – collecting input
CNS Preclinical Drug Development

Fragments* → Crystallography → Modeling

HTS → Med Chem

Enzyme IC50 → Cell IC50 → In vitro BBB permeability (LLCPK1-MDR1) → Solubility & logD

CYP inhibition, Microsomes → Class Selectivity

Rodent PK (iv/po) & BBB penetration, Protein / tissue binding → PD species PK/PD

CNS Selectivity / hERG → Full Panel

Hepatocyte Stability → AMES / MNT (critical path)

Efficacy model / Rodent PK/PD

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

Multi-dose Tox Cardio Tox

Hepatocyte Induction and Time Dep. Inhibition

Chemical and Manufacturing Controls

Regulatory

Intellectual Property Protection → Chemistry and Formulation
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
Milestones and Tranches:
A: Enter collaboration agreement to leverage novel biology
B: Positive SAR
C: Successful assay transfer and validation
D: Series expansion with focus on physical properties
E: Lead molecule with acceptable DMPK profile selected for in vivo POC
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.
Technology Development

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: kevin.hunt@utsouthwestern.edu
Drug Discovery and Development

• What is a drug and how does it work?
• What is the drug development process?
• What the inherent risks in drug discovery and development?
  ➢ Target relevance
  ➢ Reproducibility
  ➢ Competitive advantages
  ➢ Intellectual property
  ➢ Large capital requirements
• How can we de-risk early drug development?
  ➢ Robust intellectual property protection
  ➢ Validation
  ➢ Proof of concept (POC) studies
• How do we bring partners to the table?
  ➢ Model to