INTRODUCTION TO DRUG DISCOVERY AND ITS FUNDING including the Alabama Drug Discovery Alliance

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Topics to Cover

The Drug Discovery and Development Pipeline
Funding Opportunities at NIH and Foundations
Funding Opportunities at UAB with the ADDA
Drug Discovery & Development

Source: http://dlab.cl/molecular-design/drug-discovery-phases/
The Drug Discovery Pipeline

1. Target ID
2. Target validation
3. Assay development
   - Primary screen
   - Secondary screen
   - Lead optimization
   - Preclinical development
   - Clinical development – phase I, II and III
   - Regulatory approval
Target ID and Validation

- Target ID
- Target validation
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How do you identify a target?

- Target: the naturally existing cellular or molecular structure involved in the disease that the drug-in-development is meant to act on

- So: you need to:
  - Understand the molecular mechanism of the disease of interest
  - Identify a therapeutic target in this mechanism (enzyme, gene, receptor, channel, etc)

- Comes out of basic research
How do you validate a target?

- Analysis in cell culture
  - For example using siRNA

- Analysis in mouse models
  - For example using knockout mice

- Clinical data (protein or gene expression)

- The best ‘validation’ is the existence of a drug that works in humans
  - ‘me too’ drugs
Target Evaluation Criteria

- Functional role played in tissue of Interest; KO phenotype
- **Novelty** (i.e. does it represent a therapeutic advance or is it an existing target for which, arguably, patentable new chemical entities need to be discovered?)
- **Druggability** of the target (enzymes, G-proteins, receptors are generally more “druggable”)
- Spectrum (for infectious disease targets)
- **Selectivity** (how selective is the target i.e. expressed exclusively in a particular tissue, such as a tumor?)
- Genetic essentiality (for infectious disease targets)
- Cellular location (60% of known targets are on the membrane)
- Amenable to HTS (can gene product be expressed & purified?)
- Amenable to rational drug design?
- **Intellectual property potential**, risk vs return, impact etc.

- Discussed in more detail on March 30
Assay development and HTS

1. Target ID
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4. Primary screen
5. Secondary screen
6. Lead optimization
7. Preclinical development
8. Clinical development – phase I, II and III
9. Regulatory approval

Preclinical development → Clinical development – phase I, II and III → Regulatory approval
What is HTS?

- It is a **system** that uses specialized automation equipment and high density microtiter plates to screen a large number of “wells” in a short period of time.

- Throughput of 30,000 to 100,000 compounds per day is common.
Key System Components

- Compound management
- Precision robotics for liquid and plate handling
- Informatics
  - Associating data with a particular compound
  - Analyzing data from a screen
- Cheminformatics
- People

- More info about HTS on March 23 in Bob Bostwick’s lecture (next week)
Using microtiter plates

96-well
100-200μl

384-well
25-50μl

1536-well
4-10 μl

3456-well
1-2 μl
General Approach HTS Campaign

- Develop an assay; test in duplicate with 10k compounds
- Typical HTS screen within the ADDA: 100,000 – 300,000 compounds
- Eg 2,000 ‘hits’ identified
- Cherry-picking; dose-response testing
- Counterscreens? Eg related enzyme, toxicity?
- Chemists look at the structure of active compounds and generate a shortlist.
  - Depends on # of hits what happens next
    - Still a large number? Another medium throughput screen needed (that is different than the original HTS)
    - Smaller number that the PI can do in the lab? What is the # of compounds the PI can handle?
- Compounds are re-ordered and tested
- Fine-tuning list of attractive compounds is an ongoing process
Types of HTS Assays

- **Cell-based assays**
  - **Pro:** more physiologically relevant
    - Membrane penetration
    - Metabolism
  - **Con:** exclude compounds that would work with some ‘tweaking’; expensive; higher variability

- **Biochemical assays**
  - **Pro:** you know your compound hits your target; cheaper than cell-based
  - **Con:** you won’t know whether your compounds have undesired ‘off-target’ effects
Assay Development

Why is this a bottleneck?

Bottlenecks in drug discovery
Non-problematic steps in drug discovery
When you go from this:
What are you aiming for in an HTS assay:
To have a reasonable chance to believe the results of a single determination, i.e. one well

For that you need:
Reproducibility from well to well
Reproducibility from assay plate to assay plate
Reproducibility from day to day
Lead optimization and preclinical development

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From hit to lead

> 100,000 compounds

More information in lecture on May 4 by Dr. Corinne Augelli-Szafran

Few interesting ‘scaffolds’ (hits)

Several ‘lead compounds’
Establish SAR

- Structure-Activity-Relationship
  - Analogues purchased or synthesized

- All analogues need to be tested for efficacy, selectivity, etc
  - Using one or more in vitro assays

- Data used for feedback to generate more analogues

- Promising compounds tested for
  - ADME (in vitro)
  - Initial PK (in vivo) – BEFORE TESTING FOR EFFICACY!!
SAR: effect on many parameters

Examples of ADME studies

- **In vitro:**
  - Absorption: Caco-2 permeability assay
  - Metabolic stability: liver microsomes or hepatocytes
  - CYP profiling
    - Which isoforms metabolize the compound
    - Which isoforms are inhibited by the compound
    - Which isoforms are induced by the compound

- **In vivo:**
  - Radiolabeled compound
  - Various routes of administration

- More info on April 6 in lecture by Dr. Ed Acosta about PK/ADME
Candidate selection

- Candidates selected for in vivo efficacy testing
- Most promising compound (plus backup compound) tested for toxicity in relevant animal species
  - Acute tox in 2 mammalian species
  - Repeat tox in rodent and non-rodent
    - Mimic clinical use of the compound
- More info in lecture on April 20 by Dr. Paul Bushdid
Summary Pre-clinical Development

- Things to consider, among others:
  - Hits the target/organ of choice
  - Efficacy in animals
  - Not toxic
    - Multiple species
  - Pharmacokinetic studies
  - ADME (Absorption, Distribution, Metabolism, Elimination)
  - Formulation studies

- Depends on the indication what tests need to be done, and how to do them

- Everything according to GLP before you can submit an IND: $$$!
The goal: an IND application

(Investigational New Drug)

The CCTS has an IND/IDE support office; Penny Jester and myself are available for consultation.

I will present regulatory issues and how to submit an IND on May 18.
Clinical development/Approval

Target ID → Target validation → Assay development

Primary screen → Secondary screen → Lead optimization

Preclinical development → Clinical development – phase I, II and III → Regulatory approval
Clinical Trials: Phase I

- 20-100 healthy volunteers
- Information learned
  - Absorption and metabolism
  - Effects on organs and tissues
  - Side effects as dose increases
Clinical Trials: Phase II

- Several 100 patients
- Information learned
  - Effectiveness in treating disease
  - Short-term side effects
  - Dose range
Clinical Trials: Phase III

- Several 1000 patients
- Information learned
  - Benefit vs risk
  - Less common and longer-term side effects
  - Labeling information

Lecture about clinical trials by Dr. Rich Whitley on April 13
NDA: New Drug Application

- Submit for approval to regulatory agencies
  - US: Food & Drug Administration (FDA)
  - Europe: European Medicines Agency (EMEA)
  - Others
- Approval
Drug Discovery Pipeline

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   - **Clinical development – phase I, II and III**
   - **Regulatory approval**
After approval

- Phase IV Clinical Trials
  - Safety monitoring
- Additional indications
- Marketing
Success Rate in Clinic

NME Success Rates By Phase And Overall 2007-2011 Industry Portrait, Pure

Success Rate For Each Phase:
- Preclinical: 30.4% (64%)
- Phase 1: 19.4% (44%)
- Phase 2: 8.6% (22%)
- Phase 3: 1.9% (65%)
- Registration: 1.2% (83%)

Percent Calculated To Achieve 1 Approval:
- Preclinical: 3%
- Phase 1: 5%
- Phase 2: 12%
- Phase 3: 54%
- Registration: 83%
Cost to Develop a Drug

Cost for 1 compound: $263,5M
Who funds what?

Investigational New Drug (IND) Application

New Drug Application (NDA)

Clinical Trials
  Phase 1
  Phase 2
  Phase 3

Basic Research
  Funding: Largely Public
  Example: NIH, DoD
  Variable

Translational Research
  Funding: Mix of Government & Private
  Underfunded Area
  1-6 years

Clinical Development
  Funding: Largely Industry & For-Profit
  FDA Oversight
  5-10 years

FDA Review & Approval
  1-2 years

Source: Parkinson's Action Network
Topics to Cover

- The Drug Discovery and Development Pipeline
- Funding Opportunities at NIH and Foundations
- Funding Opportunities at UAB with the ADDA
Funding Opportunities at NIH

- NCATS initiatives: [https://ncats.nih.gov/funding/open](https://ncats.nih.gov/funding/open)
  - NCATS is accepting proposals on an ongoing basis to collaborate with scientists supporting the Bridging Interventional Development Gaps (BrIDGs) and Therapeutics for Rare and Neglected Diseases (TRND) programs

- NCI: Chemical Biology Consortium
  - NExT library
  - Development Therapeutics Program

- Other institutes sometimes have drug discovery programs or opportunities
Foundations

- Examples
  - CF Foundation funding screening of FDA-approved drugs library
  - Michael J Fox Foundation Therapeutic Pipeline Program
  - Alzheimer’s Drug Discovery Foundation
  - Children’s Tumor Foundation Drug Discovery Initiative
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Funding Opportunities at UAB:

The Alabama Drug Discovery Alliance

a Collaboration between UAB and Southern Research
What is the ADDA?

A partnership between:

• Southern Research (SR): not for profit research institute
• UAB School of Medicine
• UAB CCC
• UAB CCTS

With the goal to:

• Harness UAB’s large and productive research base towards discovery of new therapeutic agents
  • Generate new Intellectual Property (IP)
  • License IP to pharmaceutical companies
The Drug Discovery Pipeline

Pipeline:  
- Basic Research  
- Drug Discovery  
- Drug Development  
- Clinical Trials

UAB:  
- Basic Research  
- Drug Discovery  
- Drug Development  
- Clinical Trials

SR:  
- Basic Research  
- Drug Discovery  
- Drug Development  
- Clinical Trials

ADDA:  
- Basic Research  
- Drug Discovery  
- Drug Development  
- Clinical Trials
Who funds what?

ADDAG

Investigational New Drug (IND) Application

New Drug Application (NDA)

Clinical Trials

Phase 1

Phase 2

Phase 3

Basic Research

Funding: Largely Public
Example: NIH, DoD

Variable

1-6 years

Translational Research

Funding: Mix of Government & Private
Underfunded Area

1-6 years

Clinical Development

Funding: Largely Industry & For-Profit
FDA Oversight

5-10 years

FDA Review & Approval

1-2 years

Source: Parkinson’s Action Network
The Pilot Grant Process

Request for Applications:  
- Scientific rationale  
- IP aspects  
- (Commercialization potential)

Identify scientific reviewers  
- Three reviewers per application  
- UAB and SR scientists

Review applications for IP and commercialization aspects  
- UAB IIE and SR

Determine awardees  
- ADDA Advisory Board

With PI, identify project team members  
- Scientific input (UAB and SR faculty)  
- IP and commercialization input (UAB IIE and SR)  
- Meet quarterly; develop Compound Progression Pathway

2-stage process:  
1) Pre-application (2 pages)  
2) Full application (9 pages)
Organizational Aspects Projects

- All projects have teams built around them with expertise in:
  - Basic cell biology
  - Pathology
  - High Throughput Screening and Assay Development
  - Medicinal Chemistry
  - Preclinical Animal Models
  - Clinical Applications
  - Intellectual Property

- Project teams meet on a quarterly basis
  - Discuss what has been done in the last quarter
  - Discuss what will be done in the coming months
  - Develop a Compound Progression Pathway
Compound Progression Pathway

1. Target Identification and Validation (PI)
2. HTS Assay Development (PI in close contact with SR personnel)
3. Screen and Confirm Hits in 2° and 3° Assays (SR/PI’s lab)
4. Lead Optimization – Iterative Med Chem; Prelim PK (SR)
5. Preclinical Development – POC In Vivo; ADME/Tox
6. Clinical Development - Phase I, II, III
Pilot grants are for $50,000 per year (direct costs) for 2 years, with funding of year 2 depending on progress in year 1.

For assay development projects, these funds cover costs incurred at UAB; SR funds the actual screen and potentially downstream medicinal chemistry efforts.

An agreement between UAB (IIE) and SR is in place to facilitate easy transfer of materials and ideas/IP.

If sufficiently attractive, additional funds can be invested past 2 years.
Next Lecture’s Topic: High Throughput Screening

*Bob Bostwick – March 23 (next week)*