Overview of the Drug Discovery and Development Process
Source: http://dlab.cl/molecular-design/drug-discovery-phases/
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. (lecture Holly Meadows March 4)

- Discussed in more detail next week, February 11
DRUG DISCOVERY & DEVELOPMENT

Source: http://dlab.cl/molecular-design/drug-discovery-phases/
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 1000s of compounds per day is common
Key System Components

- Compound management
- Precision robotics for liquid and plate handling
- Cheminformatics
- People
MICROTITER PLATES

- 96-well: 100-200µl
- 384-well: 25-50µl
- 1536-well: 4-10 µl
- 3456-well: 1-2 µl
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.

Compounds are re-ordered, confirmed (purity, structure) and tested

Fine-tuning list of attractive compounds is an ongoing process
ASSAY DEVELOPMENT

Why is this a bottleneck?
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

More info about HTS on February 25 in Bob Bostwick's lecture
From Hit to Lead

> 100,000 compounds

HTS

More information in lecture on March 18 by Dr. Corinne Augelli-Szafran

Few interesting ‘scaffolds’ (hits)

Medicinal Chemistry Program

Several ‘lead compounds’
Goal in Med Chem Program: 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
SAR: Effect on Many Parameters

- SAR for target potency
- SAR for target selectivity
- Receptor-drug interactions
- Modifications to modulate metabolism
- Modifications to reduce toxicity
- Modifications to allow patentability
- Physical properties and formulation
- Scaffold-hopping to allow patentability
Pharmacokinetic and ADME Studies

▶ PD: ‘What the Drug Does to the Body’
▶ PK: ‘What the Body Does to the Drug’
  ▶ Try to make it more water soluble to eliminate it out of the body asap!

▶ In vitro assay examples:
  ▶ Absorption: Caco-2 permeability assay
  ▶ Metabolic stability: liver microsomes or hepatocytes

▶ In vivo testing examples:
  ▶ Radiolabeled compound
  ▶ Various routes of administration

▶ More info on April 1 in lecture by Dr. Ed Acosta about PK/ADME
Candidates selected for in vivo efficacy testing

Most promising compound (plus backup compound) tested for toxicity in relevant animal species
  - Rodent and non-rodent
    - Mimic clinical use of the compound

More info in lecture on April 8 by Dr. Lutfiya Miller
Summary Pre-clinical Development

- Things to consider, among others:
  - Hits the target/organ of choice
  - Efficacy in animals
  - Not toxic/Therapeutic Window
  - Pharmacokinetic and ADME studies
  - 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: $$$!
DRUG DISCOVERY & DEVELOPMENT

Source: http://dlab.cl/molecular-design/drug-discovery-phases/
IND Application

- IND: Investigational New Drug

- The CCTS has an IND/IDE support office; Dunya Ritchey and myself are available for consultation

- I will present how to submit an IND on February 18
Focus: SAFETY!

20-100 healthy volunteers

Information learned:
- Absorption and metabolism
- (Side) Effects on organs and tissues as dose increases
Clinical Trials: Phase II

- Focus: EFFICACY!
  - ‘Proof of Concept’

- 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 22
NDA: New Drug Application

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

- Phase IV Clinical Trials
  - Safety monitoring
- Additional indications
- Marketing
Drug Discovery & Development

Source: http://dlab.cl/molecular-design/drug-discovery-phases/
Success Rate

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

Success Rate For Each Phase

Preclinical: 64%
Phase 1: 44%
Phase 2: 22%
Phase 3: 65%
Registration: 83%

Percent Calculated To Achieve 1 Approval
Preclinical: 3%
Phase 1: 5%
Phase 2: 12%
Phase 3: 54%
Registration: 83%
Cost for 1 compound: $263,5M
Who Funds What?

ADDA

Investigational New Drug (IND) Application

New Drug Application (NDA)

Clinical Trials

Phase 1
Phase 2
Phase 3

“Valley of Death”

Basic Research

Funding: Largely Public
Example: NIH, DoD

Translational Research

Funding: Mix of Government & Private
Underfunded Area

Clinical Development

Funding: Largely Industry & For-Profit
FDA Oversight

FDA Review & Approval

Variable

1-6 years

5-10 years

1-2 years

Source: Parkinson’s Action Network
ADDA: UAB + SR

Target Identification  High Throughput Screening  Medicinal Chemistry  Cell Culture Studies  Animal Studies  Clinical Trials

Outlicense
How Long?

Drug Discovery and Development Timeline

- **Drug Discovery**
  - ~ 5,000 – 10,000 compounds
  - 3 – 6 years

- **Pre-Clinical**
  - 250

- **Clinical Trials**
  - Phase 1
    - 20–100 volunteers
    - 6 – 7 years
  - Phase 2
    - 100–500 volunteers
    - 6 – 7 years
  - Phase 3
    - 1,000–5,000 volunteers
    - 6 – 7 years

- **FDA Review**
  - 0.5 – 2 years

- **Scale-Up to Mfg.**
  - INDEFINITE

- **Post-Marketing Surveillance**

Source: appliedclinicaltrialsonline.com
CCTS DRUG DISCOVERY
SEMINAR SERIES

WHEN: MONDAYS, 12 NOON - 1 PM
WHERE: PCAMS, 1924 7th Avenue South
A light lunch will be served.
This series is approved for 1 course credit (GBSC 701.VTE, pass/fail)

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You can attend in person or via Zoom: https://uasystem.zoom.us/j/367521813
You can also dial in by phone: 646-558-8656. Access Code: 367-521-813
Questions? Email adda@uab.edu