Bench to Bedside:
The Drug Development Pipeline

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Outline for this session

Introduction
- The goal
- The pathway
- The players
- The challenges

Illustration
- Multiple Sclerosis
- Natalizumab

Innovations
- Tissue on chip
What is a drug?

A product that alleviates, cures or prevents disease, or is intended to affect the structure or function of the body.

Antibiotics

Chemotherapeutic agents

Tricyclic antidepressants

Insulin (~100x bigger than antibiotic)

Antibody (600x bigger than antibiotic)
What qualities do we want in a new drug?

- Efficacy
- Safety
- Affordability
- Convenience
What is the path to get there?

- Study of Disease
- Pre-Clinical Research
- Clinical Research
- Drug Sponsor
- FDA Approval

Efficacy
Safety
Affordability
Convenience
What are the challenges?

14 years
Average length of time from target discovery to approval of a new drug.

85% Failure rate
From Phase I to FDA approval, during clinical trials.

$2.6 Billion
Cost per successful drug, when all failures are factored in.

Why do these challenges exist?

Dr. Francis Collins, “Tackling the bottlenecks in the drug development pipeline”, NIH Director’s Blog, January 2014
Hay et al, Nature Biotechnology, January 2014
PR, Tufts CSDD 2014 Cost Study, November 2014
Questions?
Example:
Multiple Sclerosis (MS) and *natalizumab*

**Multiple Sclerosis (MS)**
- Affects 90 per 100,000 people in the US
- Due to damage to myelin, the insulation for nerves
- Thought to be caused by immune cells

**Natalizumab**
- Prevents immune cells from entering the brain

*Image credit: ADAM, Inc.*

Carrie Hersh, “Multiple Sclerosis,” Cleveland Clinic Continuing Education
Multiple sclerosis:
Identified as disease in 1868
Pre-clinical research: Is there a way to cure multiple sclerosis?
How do immune cells enter inflamed brain tissue?

Receptors that *might* be involved

Test antibodies that block each one

Result
Features of clinical trials

- Randomization
- Placebo
- Blinded
- Study size
Clinical trials are run in phases

- **Phase 1**: Safety
  - 50 Healthy participants

- **Phase 2**: Efficacy
  - 100’s Patients

- **Phase 3**: Efficacy
  - 1000’s Patients

Drug Approval Process, fda.gov
At each phase, many drugs fail

**Phase 1:**
- 50 Healthy participants
- Safety
- 33% Not safe

**Phase 2:**
- 100’s Patients
- Efficacy
- 42% Not effective

**Phase 3:**
- 1000’s Patients
- Efficacy

Drug Approval Process, fda.gov
Data from Hay et al, Nature Biotechnology, January 2014
60% of trials in Phase 3 are suspended

1000’s Patients
Efficacy in specific populations

Reason for suspension
- Efficacy: 54%
- Safety: 9%
- Commercial: 18%
- Unknown: 19%

Drug Approval Process, fda.gov
Data from Hay et al, Nature Biotechnology, January 2014
Why are safety and efficacy hard to predict?

- Research models of disease are not the same as humans
- Studies of humans are limited by available materials
- A new drug needs to be better than current drugs

Data from Hay et al, Nature Biotechnology, January 2014
Questions?
Natalizumab had very promising results

1997 - 1999

1999 - 2003

2003 -

Drug Approval Process, fda.gov
Natalizumab suspended 3 months later:
Two cases of fatal brain inflammation
(PML: Progressive multifocal leukoencephalopathy)

During multiple sclerosis:
Immune cells enter brain, cause damage

Natalizumab prevents immune cells from entering the brain

During infection with JC virus:
Immune cells enter the brain, stop the spread of virus, and protect brain tissue

A.D.A.M. Inc, Medline, National Library of Medicine
Key points from the natalizumab story

Discoveries in different fields led to the development of natalizumab

Pre-clinical studies could not predict complications due to JC virus infection

The FDA wants to make SAFE drugs available to patients
The Drug Approval Process

FDA's Center for Drug Evaluation and Research (CDER) evaluates new drugs before they can be sold.

Drug sponsor develops a plan for testing the drug on animals for toxicity. Multiple species are used to gather basic information on the safety and effectiveness of the drug.

Animals Tested

The typical number of healthy volunteers used in Phase 1; this phase emphasizes safety.

The typical number of patients used in Phase 2; this phase emphasizes the drug's composition and effectiveness.

The typical number of patients used in Phase 3.

At the end of Phase 2, FDA and sponsors discuss how large-scale studies in Phase 3 will be done.

FDA reviews the IND to assure there are adequate informed consent and human subject protection.

At the end of Phase 3, FDA and sponsors discuss how small-scale studies in Phase 4 will be done.

FDA approves the drug on humans.

Sponsor must test new drugs on animals for metabolism and excretion.

The FDA seeks to have it approved investigated/researched.

Brand-name and generic, are effective and their health benefits outweigh their known risks.

Provides doctors and patients the information they need to use medicines wisely. CDER ensures that drugs, both new and existing, provide the benefits that outweigh their known risks.

The center's evaluation not only prevents quackery, but also provides doctors and patients the information they need to decide whether to use medicines wisely.
To address the challenges

**Repurposing of approved drugs**
- Use drugs already approved for safety
- Test in other candidate diseases

**Improve laboratory models of disease**
- Better understand the current models
- New models

**New technology: do more with less**
- More data from small clinical samples
- Allows better study of human biopsies, blood
Innovative approach:
Tissue chip for drug screening

Tissue chips
- Mimic human tissues
- Screen drugs before testing in humans

Pre-Clinical
Tissue Chips
Clinical

Dr. Francis Collins, “Tackling the bottlenecks in the drug development pipeline”, NIH Director’s Blog, January 2014
Summary
The drug development pipeline

• The goals
  – Safety, Efficacy, Affordability

• The pathway
  – Long, expensive, challenging

• The players
  – Scientists…Pharma…FDA…Patients

• The challenges
  – Difficult to understand how the body works
  – Difficult to predict how a drug will act in humans

• Innovations
  – Facilitated by growing scientific knowledge
  – Facilitated by new technology
Thank you!

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addgene

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