Biotechnology and the Emergence of New Therapeutics

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What we will discuss today

Part 1: What does it take to make a drug?
Vini Mani

Part II: Current methods in drug discovery
Kat Pak

Part III: Emerging classes of therapeutics
Dima Ter-Ovanesyan
What is a therapeutic/drug?

**Chemical or Biological substance** used in the treatment, cure or prevention of disease.
Examples of Therapeutics

Azithromycin
Albuterol
Aspirin

Chemical

Insulin
Stem Cells

Biological

Source: Wikimedia Commons, Contributed by: Mugwump12, Jurema Oliveira, Mendel, Magnus Manske, Giorgiogp2
A Historical Perspective

1874
Willow Bark
Salicylic Acid

Source: Wikimedia Commons, Contributed by: Magnus Manske
A Historical Perspective

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1922
First successful insulin treatment

Source: Wikimedia Commons, Contributed by: Magnus Manske, Raul654
A Historical Perspective

1874
Willow Bark
Salicylic Acid

1922
First successful insulin treatment

1959
First bone marrow transplant (cell therapy)

Source: Wikimedia Commons, Contributed by: Magnus Manske, Raul654, Chad McNeely
Central Dogma

DNA -> RNA -> Protein

"Stored information"

"Messenger"

"Performs a Function"
Proteins

• Many functions in the body
  – Catalyze reactions
  – Cell metabolism
  – Cell structure
  ... and many more!
Proteins: Examples

Collagen
• Structural protein
• “Holds” things together

HMG Co-A Reductase
• Enzyme
• Makes Cholesterol

Source: Wikimedia Commons, Contributed by: Nevit Dilmen, Emw
What happens when things go wrong?

- A lack of protein or defects in protein structure or function can cause disease

- To remedy this, replace the defective protein or find a way to change the function
Replacing a Defective Protein

• We sometimes see “deficiency” in a protein
• To combat this, we can inject a protein into a patient as a therapeutic

Ex. collagen
Changing a Protein’s Function

• “Small molecule” drugs bind to proteins to change their function
Sources of Small Molecule Drugs

• Derived originally from natural sources → ex. willow bark for aspirin
• Can be made in a laboratory setting → “chemical synthesis”
Questions?
How does a drug get to the market?

1. Drug Discovery
2. Drug Development
3. Animal Studies
4. Human Studies
5. FDA Approval
Who are the key players?

- Biotech
- Food and Drug Administration
- Academia
- Medicine

Therapeutics to Market
Example: Lipitor®

• Created by Bruce Roth in 1985
• Marketed by Pfizer after approval in 1996
• Best-selling drug in history → $125 billion in sales since 1996
• Lowers cholesterol and heart-attack risk
Drug Discovery

The process of finding a relevant protein and a way to change its function

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Discovery of Lipitor®

• Protein was identified in academia $\rightarrow$ HMG Co-A reductase (HMGCR) that makes cholesterol

• Statin discovered in industry: small molecule binding to HMGCR that causes loss of function $\rightarrow$ prevents production of cholesterol

Source: Wikimedia Commons, Contributed by: Emw
Drug Development

The process of finding the optimum drug and ensuring that it can work safely in the body

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Drug Development: Considerations

• Modify molecules to make sure they meet certain basic criteria:
  
  (1) Dissolves when put into the body
  (2) Is effective for function
  (3) Fast enough to work before it is excreted
  (4) Minimal toxicity
  (5) Chemically stable
Drug Development

- Found that statins inhibit HMGCR
- Tweak the drug to make sure it not only inhibits HMGCR effectively but also make sure that it does not adversely affect other basic functions

Source: Wikimedia Commons, Contributed by: Roadnottaken, Mykhal, Edgar181, Ju
Questions?
Animal Studies

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2. Drug Development
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Animal Studies

- **Purpose:** to test if drug gives *desired effect* and is *safe*
- Conducted in labs in sets of multiple animals per experimental “trial”, different types of animals used
- Also helpful in narrowing down options in drug development
- Takes *3-6 years*

Examine effects and levels of cholesterol

Lipitor
In-Human Studies

1. Drug Discovery
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Phases of Human Clinical Trials

Phase I: Safety
Phase II: Dosage and Efficacy
Phase III: Long-term efficacy
Basics: Clinical Trials

• Conducted in a hospital setting with the assistance of physicians

• **Placebo**: treatment with no medical effect → used to control for psychological effects

• “**Double-Blind**”: neither patient nor physician knows if it is therapy or placebo
How Trials Work

“Box” with drug or placebo

Randomize

Give to patients
How Trials Work

Patients monitored, full results are recorded and revealed after trial.

Patient experiences nausea.

Patient has healthy weight loss.

Patients monitored, full results are recorded and revealed after trial.
How Trials Work: Results

Patient experiences nausea

Patient has healthy weight loss

Last step: reveal which patients were on the placebo to analyze results further
Phase I

- **Purpose:** Make sure therapeutic is safe in humans
- **20-100 healthy, normal patients selected**

Normal cholesterol
Healthy subjects

OR

2 years

?
Phase II

• **Purpose:** Establishing dosage and efficacy

• 100-500 patients

 Patients with High cholesterol

OR

2 years ➔ ?
Phase III

- **Purpose**: Establish long-term efficacy and monitor side effects, **most crucial phase**

- **1000-5000 patients**

[Diagram showing patients with high cholesterol and a chemical structure with a question mark after 3 years]
Phases of Human Clinical Trials

- Phase I: 75% to Phase II
- Phase II: 48% to Phase III
- Phase III: 64% to approval
FDA Approval

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Approval and Market Survey

- FDA approval after trials takes about 1 year
- After approval, FDA surveys the drug on the market → sometimes referred to as Phase IV
- Lipitor® side effects have expanded since 1996

Possible side effects:
Memory loss
Confusion
FDA Market Survey: Thalidomide

- Drug used for prevention of morning sickness approved by FDA in the 60s
- After some time on the market, birth defects were seen and drug was pulled by FDA

Source: Wikimedia Commons, Contributed by: Otis Archives
Food for Thought

• No therapeutic is perfect $\rightarrow$ side effects
• Balance between safety and efficacy
• More conservative policies $\rightarrow$ less chance of high-risk therapeutics on market
By the Numbers

• Costs about $1 billion over 12-20 years to bring a therapeutic from bench to bedside
• About 8% overall success rate in approval
• 35 new drugs approved in 2011 → Relatively high
• Global spending for therapeutics → $1.1 trillion by 2015
• Up to 20% of revenue is filtered back into R&D
Summary

• Therapeutics are medically relevant chemical and biological agents
• Goal of drug discovery and development is to identify a desired function and design a therapeutic that meets all criteria
• FDA trial and approval process is designed to ensure safety of the therapeutic on the market
Thank You!

Questions?