Biotechnology and the Emergence of New Therapeutics

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
Outline

1. Small molecule drugs
   - High-throughput screening
   - Rational drug design

2. Protein drugs (“biologics”)
   - Recombinant DNA technology
Outline

1. Small molecule drugs
   - High-throughput screening
   - Rational drug design

2. Protein drugs ("biologics")
   - Recombinant DNA technology
Small molecules as drugs

• “Small molecule” drugs bind to proteins to change their function
Small molecules are stored in chemical libraries

“Libraries” of small molecules can include up to 0.5 - 3 million molecules

- Pharmaceutical companies
- National Institutes of Health (NIH)
- Academic labs

Image Credit: Wikimedia Commons, User: Zanimum
Small molecule libraries are the starting point for finding new drugs in high-throughput screening.

Begin with large numbers of small molecules (10,000-1 million)

End up with 2 drugs
High-throughput screening

Testing large libraries of small molecules for their ability to exert a **desired effect** on a cell, protein, or organism.
A desired effect is any biological or chemical change with relevance to a disease.

Examples:

• Tumor cell death
• Blocking viral replication
Measuring a desired effect

Looking for a change in:

- Appearance
- Chemical reaction
- Biologic process
Measuring a desired effect

Looking for a change in:
- Appearance
- Chemical reaction
- Biologic process

Example from lab:

Tumor cells → Small molecule drug → Wait a few days → Determined cell #
Measuring a desired effect
Measuring a desired effect
High-throughput screening: overview

1. Add cells to a microplate
2. Add small molecules from library (10,000-1 million)
3. Measure desired effect
4. Identify “hits”
Robots help with high-throughput screening
High-throughput screening results in hits

1. Add cells to a microplate
2. Add small molecules from library (10,000-1 million)
3. Measure desired effect
4. Identify “hits”
High-throughput screening results in hits

Identify “hits”

Confirm & refine hits

3-6 of the best small molecules are selected for further drug development
Drug Development

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

1. Drug Discovery
2. Drug Development
3. Animal Studies
4. Human Studies
5. FDA Approval
Examples of recently approved drugs with origins in high throughput screening

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Review of high-throughput screening

- Small molecule libraries are the starting points of high-throughput screens
- Test libraries for small molecules that give a desired effect
- Result in hits that can be further developed before animal/clinical testing
Questions?
Outline

1. Small molecule drugs
   - High-throughput screening
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2. Protein drugs ("biologics")
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Outline

1. Small molecule drugs
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Traditionally…

Trial-and-error testing of small molecules for a desired effect
Rational drug design

Predict that modulation of a specific protein target will have therapeutic value.
Rational drug design

Predict that modulation of a specific protein target will have therapeutic value.

Goal: Identify small molecules that bind to the protein target to give a therapeutic effect.
Rational drug design

Predict that modulation of a specific protein target will have therapeutic value.

Goal: Identify small molecules that bind to the protein target to give a therapeutic effect.

Image Credit: Wikimedia Commons, User: A2-33
A method of determining protein 3-D structure

X-ray beam → Protein crystal

Beam deflection patterns analyzed computationally

Protein model

Image Credit: Wikimedia Commons, User: Splette
Proteins are made of building blocks

Building blocks = amino acids

DNA instructs the linear order of amino acids

Amino acid properties instruct the 3D shape of the protein
3-D protein modeling

Human hemoglobin protein

Image Credit: Wikimedia Commons, User: Gabby8228
Rational Drug Design: HIV-1 protease inhibitors

- Block the action of a key viral protein in HIV-1
- Prevent formation of functional virus

Image Credit: Wikimedia Commons, User: BetacommandBot
To replicate HIV-1 first makes non-functional proteins.

Non-functional protein chain.

Virus CANNOT replicate.
HIV-1 protease makes functional viral proteins
HIV-1 protease makes functional viral proteins

Viral protease

Non-functional protein chain

Functional viral proteins. Virus can replicate.
Viral protease

Drug

Protease doesn’t work!
HIV-1 protease makes functional viral proteins

Viral protease cannot chew the protein chain.

Functional viral proteins are not formed. Virus CANNOT replicate.
HIV-1 protease and drug
Review of rational drug design

• Begin with a protein target

• Look for a small molecule that binds to the protein target

• Protein structure can help us design a drug that binds to the protein
Questions?
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2. Protein drugs ("biologics")
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Outline

1. Small molecule drugs
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2. Protein drugs ("biologics")
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Insulin signaling

- Ingest food

- Insulin is released by cells in the pancreas

- Causes tissues to take up glucose (sugar)
Type I diabetics cannot produce insulin

- Insulin-producing cells in the pancreas are destroyed
- Results in insulin deficiency
Type I diabetics cannot produce insulin

- Insulin-producing cells in the pancreas are destroyed
- Results in insulin deficiency
- Treat by giving insulin
Central Dogma

DNA

RNA

Protein (insulin)

“Stored information”

“Messenger”

“Performs a Function”
Making human protein for biologics

Gene (segment of DNA) for human insulin
Making human protein for biologics

Gene (segment of DNA) for human insulin

Add DNA to a cell
Making human protein for biologics

Cell makes human insulin from DNA instructions
Making human protein for biologics
Making human protein for biologics

Recombinant DNA technology: Inserting human genes into cells that can rapidly produce large amounts of the protein
Biologics are costly

- A difficult and costly production process
- Requires strict cell-growing conditions
- Contamination is a threat

http://benchmarks.cancer.gov/nci-b-roll-collection/lab-research/
Summary

1. High-throughput screens
   - Identifying drugs from large chemical libraries

2. Rational drug design
   - Starting with a protein target to design drugs

3. Biologics
   - Synthesizing proteins to help treat...
Thank You!

Questions?