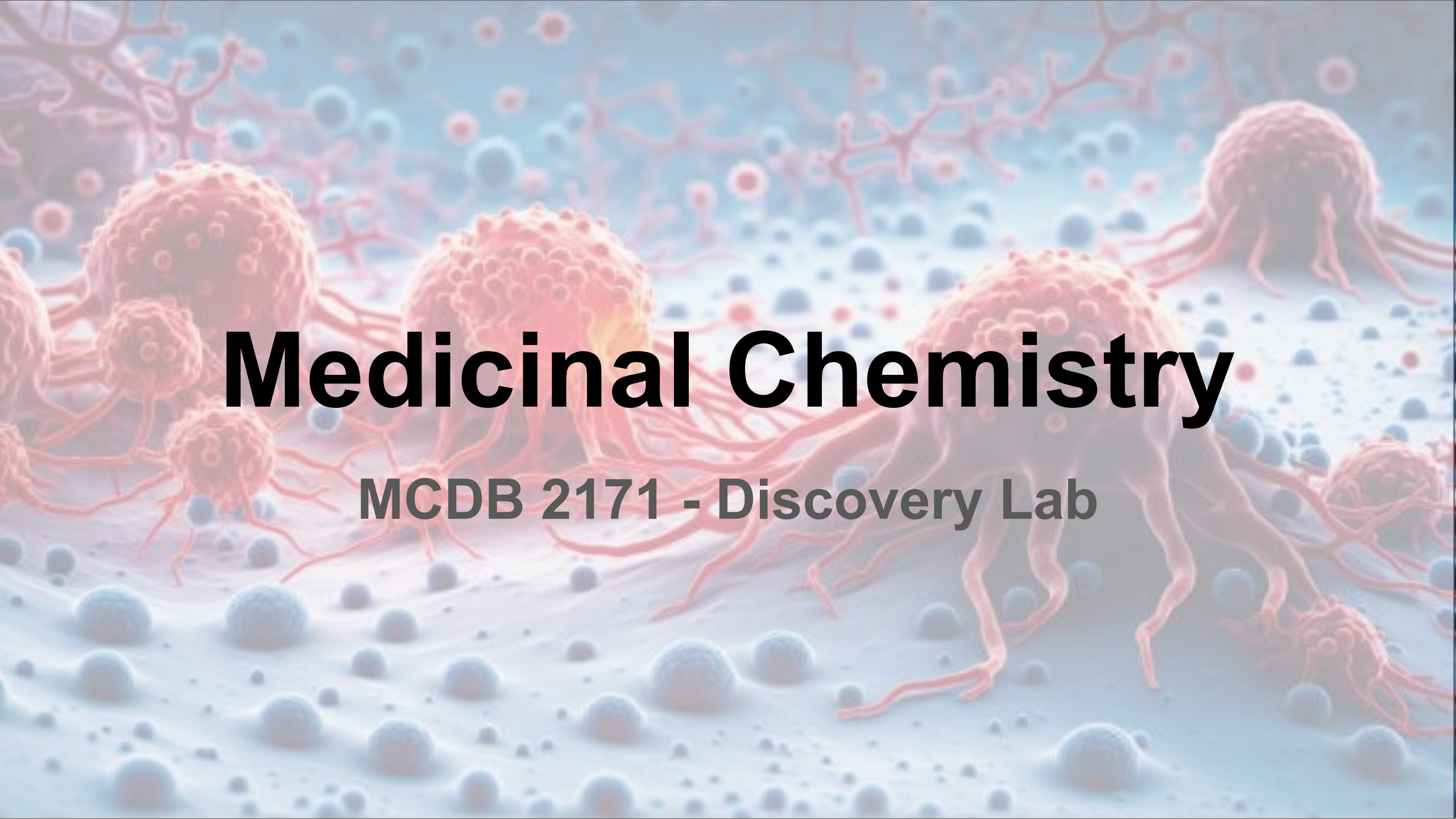


Medicinal Chemistry

MCDB 2171 - Discovery Lab

Agenda

- What’s going on in labs
- New content
  - Medicinal chemistry

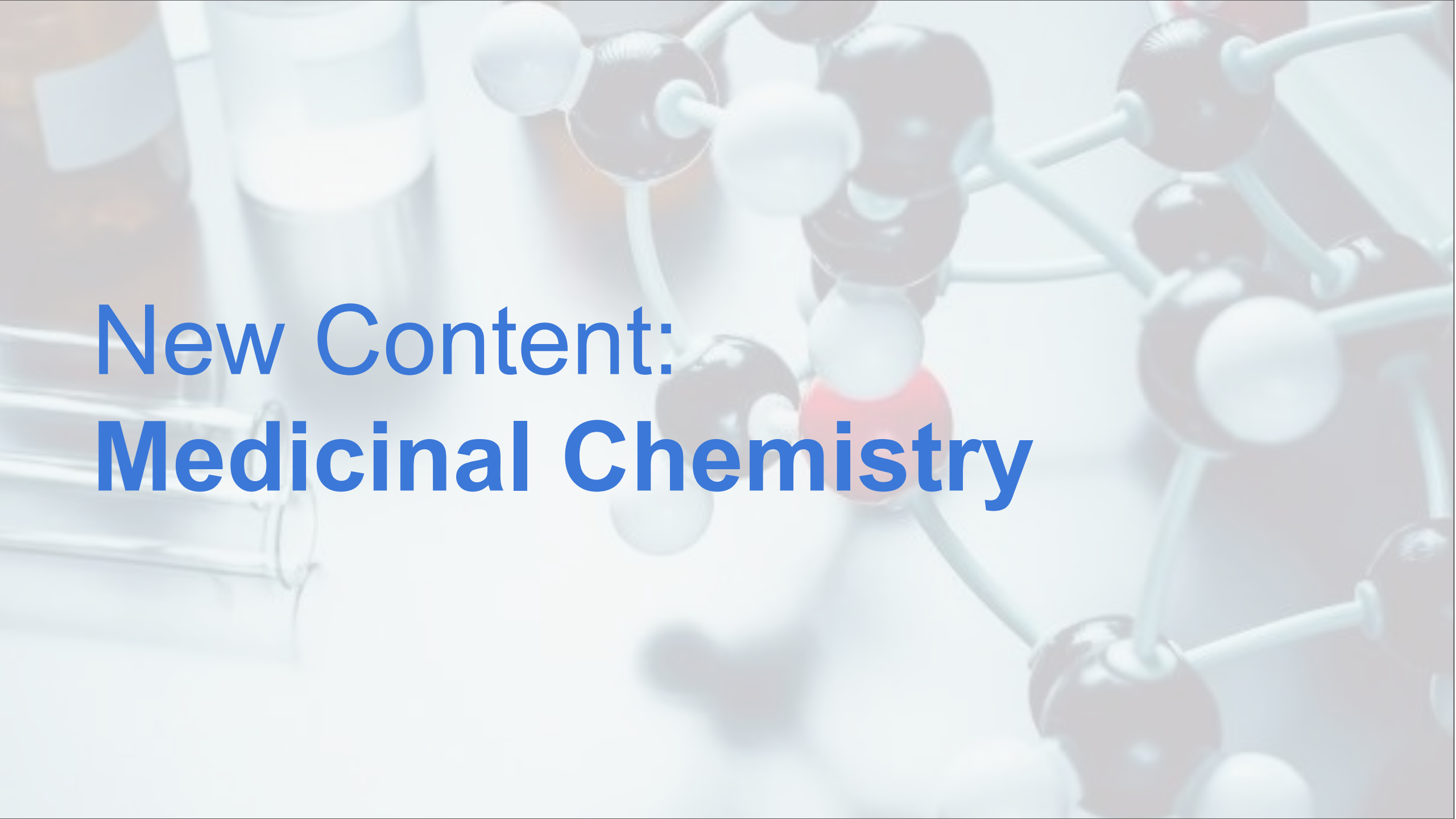
Labs

This Week

- Finish re-running compounds as needed and entering **ALL** data
- Do project proposal with your groups and submit by Friday at 5PM
- Submit your individual lab notebooks by Friday / per TA policies

Next Week

- Peer review project proposals
- Create group lab notebooks
- Plan your research project and make stock solutions



New Content:
Medicinal Chemistry

Learning Objectives

- Explain the desirable and undesirable qualities of a drug
- Compare the ways that drugs can be classified
- Describe the purpose of chemically altering a compound's structure
- Identify the importance of functional groups in drug design and development
- Describe the mechanism of action of a chemotherapy or immunotherapy

Defining “Drug”

- Something that meets the following criteria:
  - Is a specific chemical compound
    - NOT a mixture
  - Has a physiological effect on the body
  - Does not include food or water

Desirability of Drugs

Desired

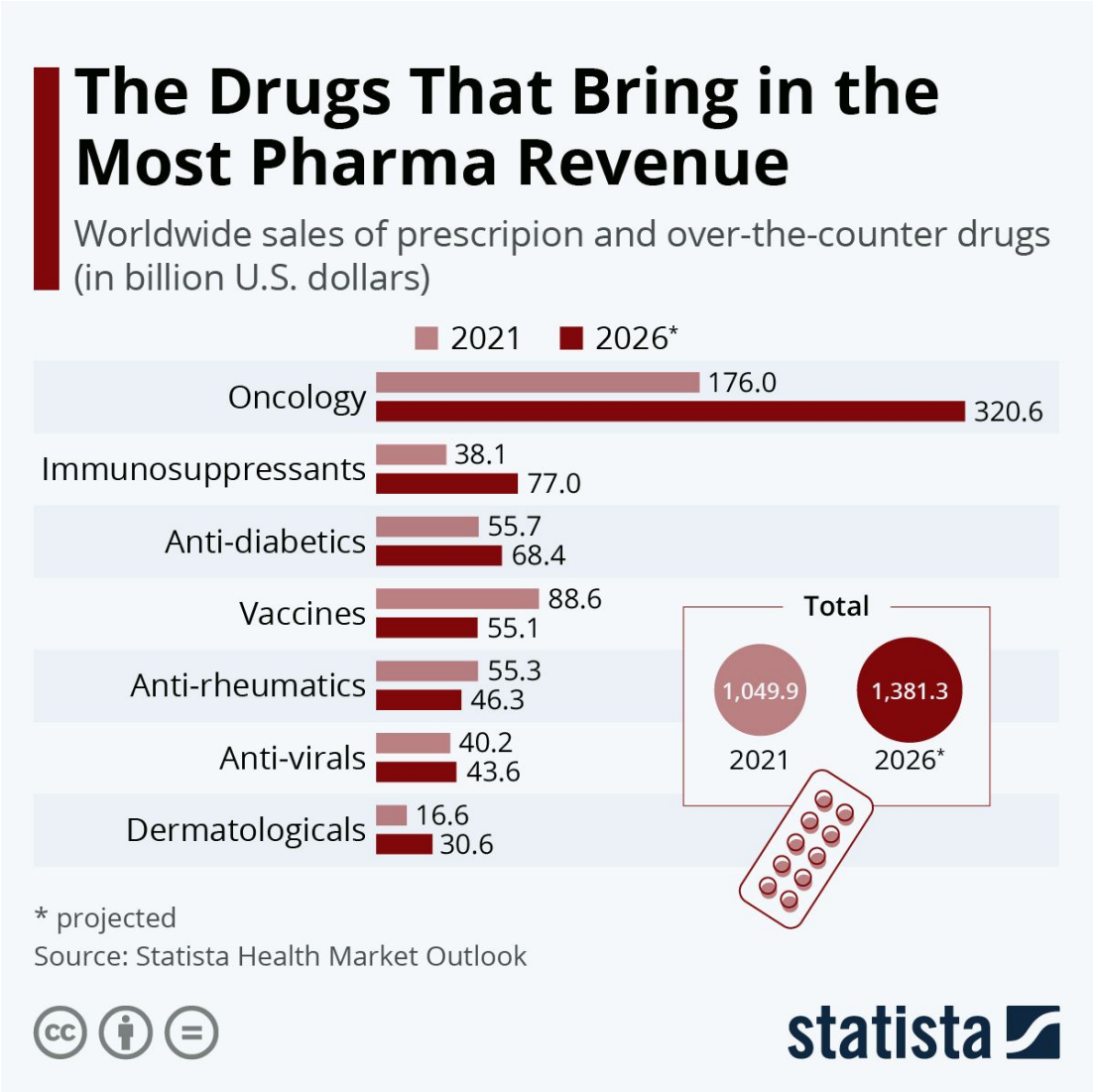
- Cures or treats condition
- Kills infectious pathogens
- Relieves pain / swelling
- Economical

Undesired

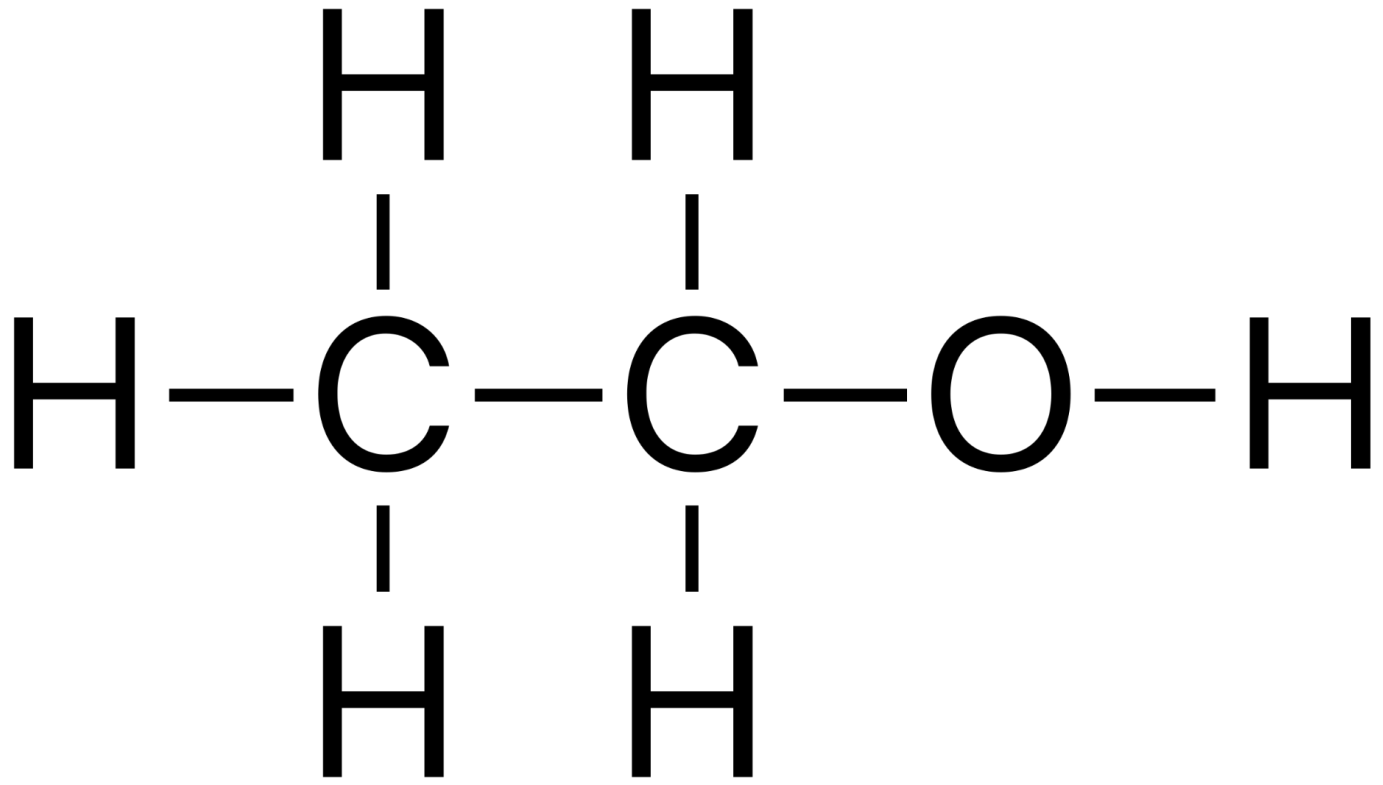
- Toxic to human cells
- Addictive
- Side effects
- Uneconomical

Drug Economics

- A drug is “economic” if it is cheap and easy to produce
  - This makes the drug cheaper on consumers and producers alike
- Chemotherapies are notoriously good investments
  - This incentivizes companies to invest in their research



Activity - Question 1

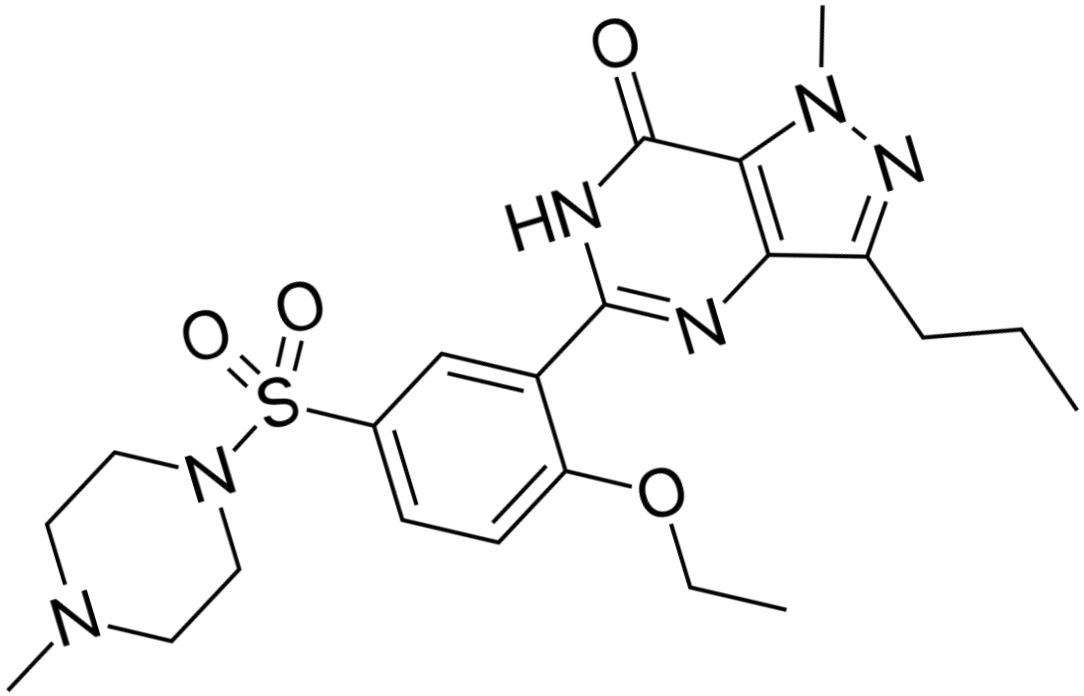


Classifying Drugs

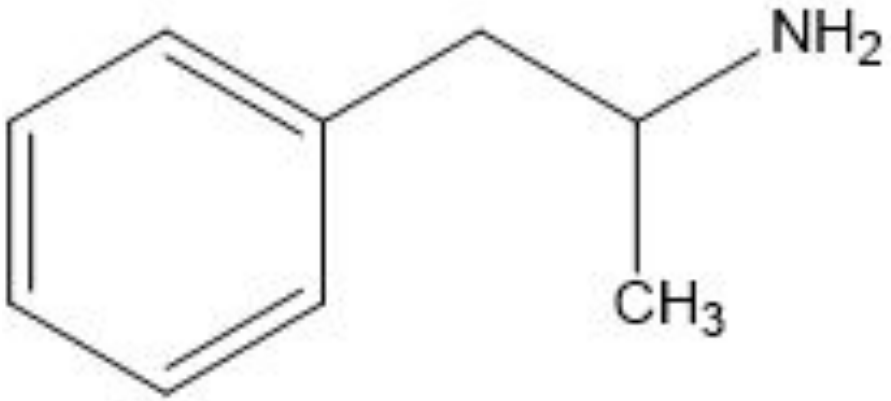
- How have you heard drugs classified? There are three
  - Physiological effect (e.g., antibiotics that kill bacteria)
  - Chemical structure (e.g., penicillin family drugs that disrupt bacterial membranes)
  - Physiological target (e.g., opioid pain meds that bind to opioid receptors in the brain)

By Physiological Effect

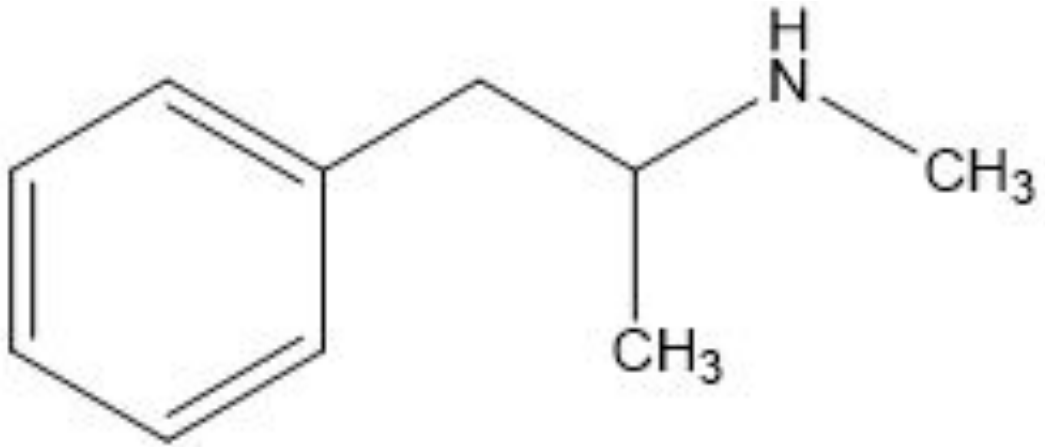
- Group drugs by what medicinal benefit they provide the patient
- Kill bacteria, relieve fever, reduce blood pressure, etc…
- Limitation to this characterization-
  - Exemplified by sildenafil
  - Originally treated high blood pressure



By Chemical Structure



Adderall



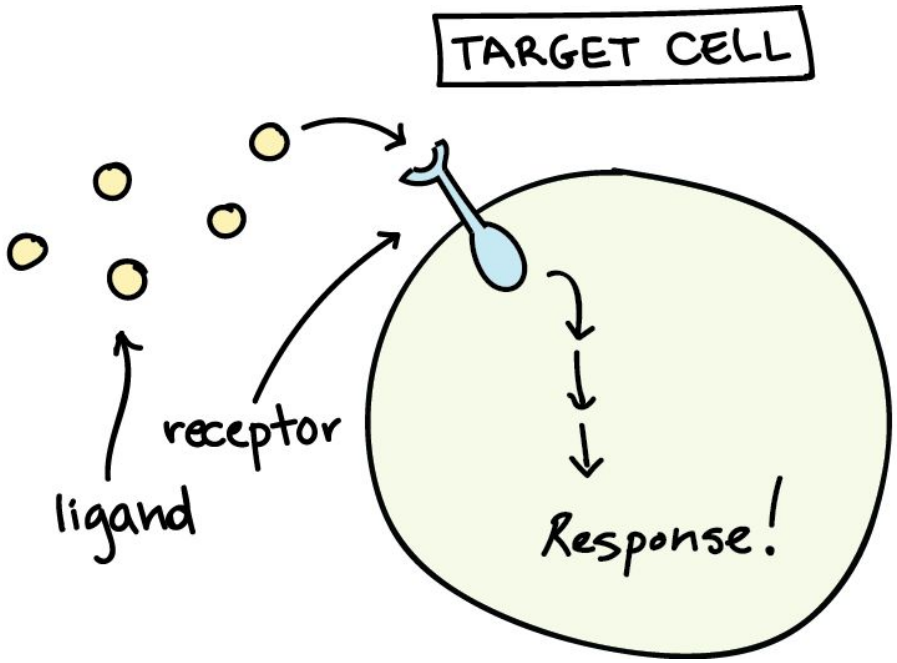
Methamphetamine

By Physiological Target

- Drugs can be classified by how they actually operate in the body
- Often, there is some target they will attempt to bind to
- These targets are called **receptors** and are specifically shaped
- Drugs act as something called a **ligand**
  - Ligands are compounds that can fit into complementary receptors
  - Ligand has another meaning in chemistry; they aren't the same
- We can categorize drugs by the type of receptor they act on

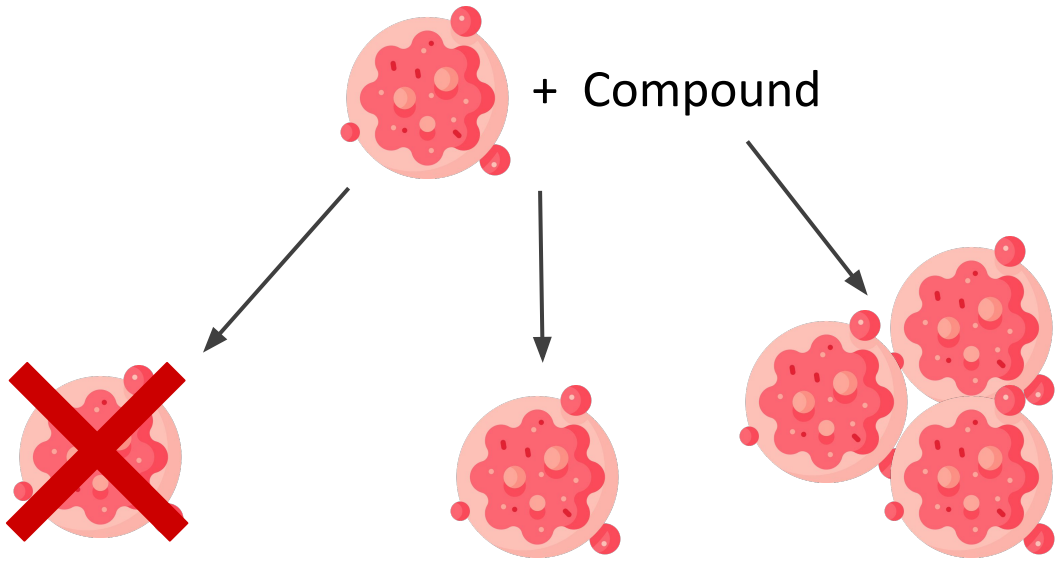
Reviewing Receptors

- Something in a living organism that can “dock” ligands
- Shaped a certain way; only fits specifically-shaped ligands
- When a ligand “docks”:
  - The receptor sends a signal
  - Some biological response is triggered

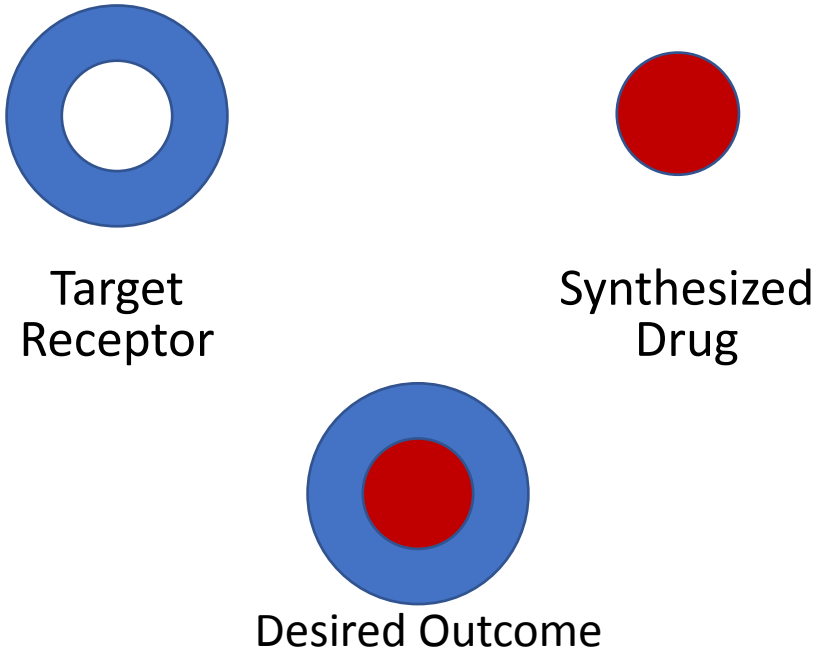


Types of Drug Development

Phenotypic Screens

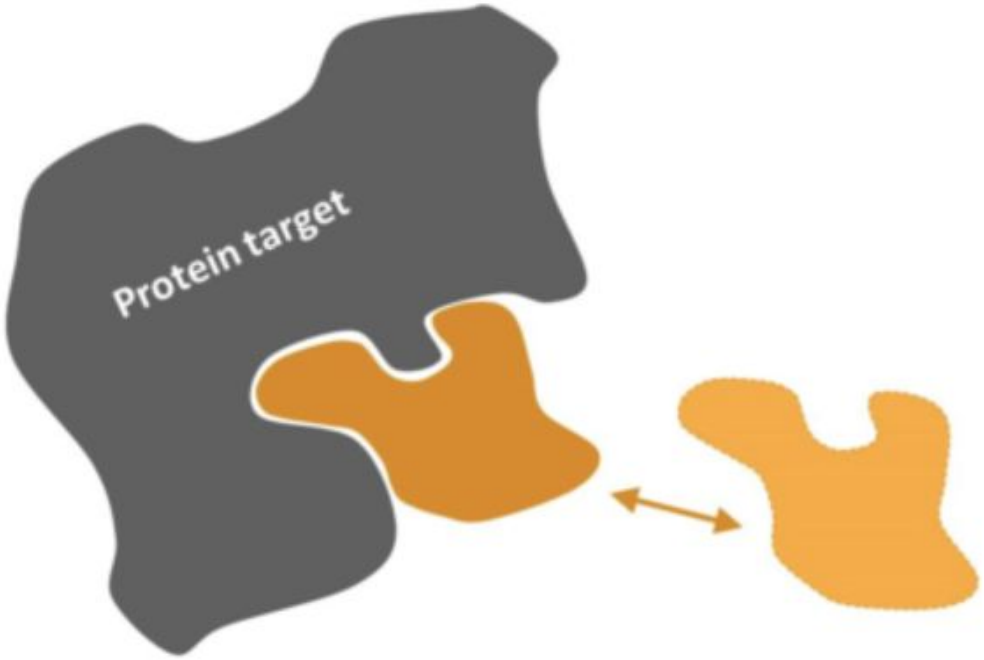


Target Approach



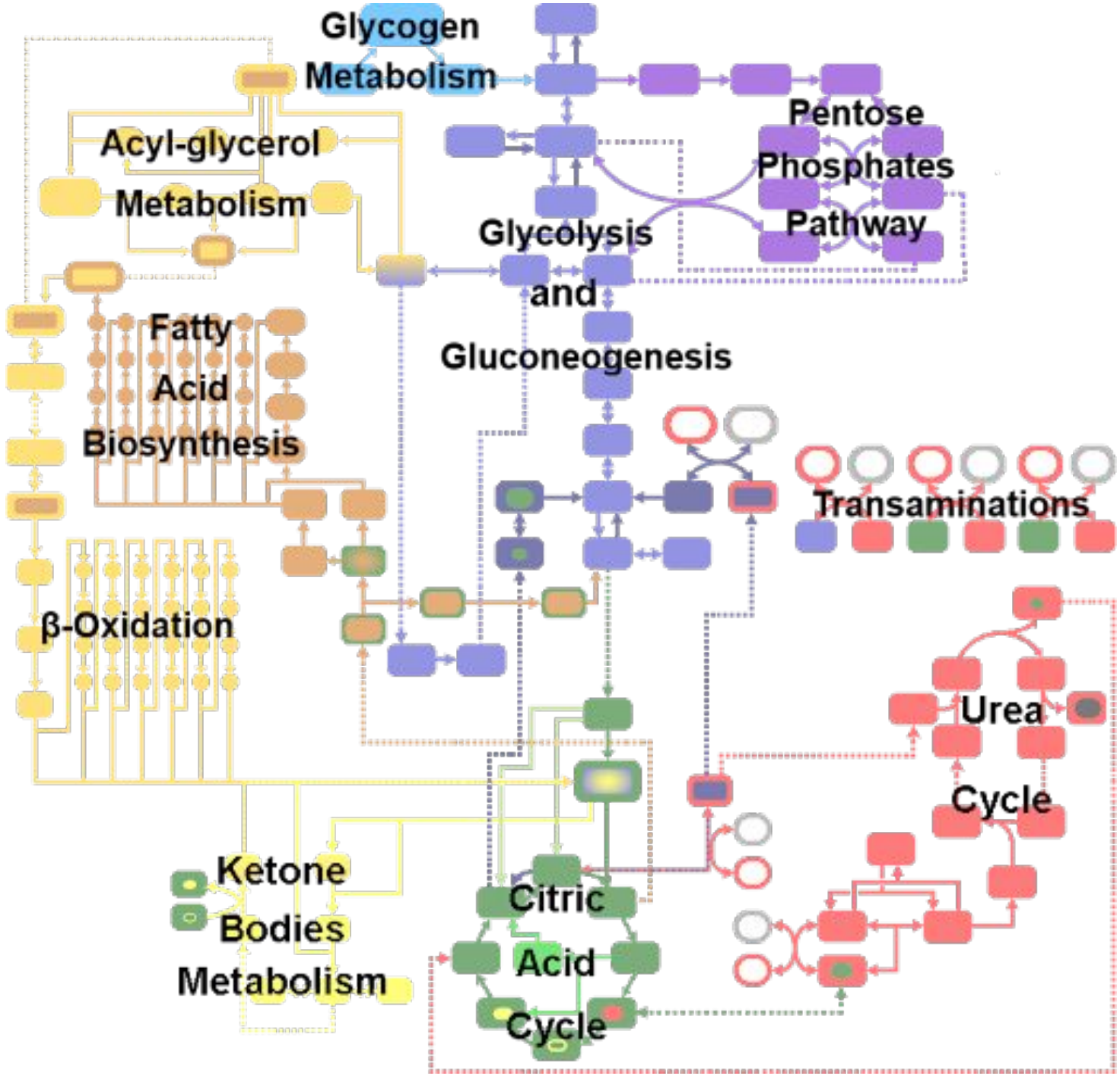
Target Approach

- Choose a molecular target
- Make a compound fit the receptor
  - Modifications to the chemistry
  - Get lucky, find something natural
    - Could use computational biology!
- Interacts and does something



The Problem: Metabolic Pathways

- Series of chemical reactions
  - From consumption to use
- Compound is transported through various body systems
  - Each with several processes
  - Can chemically alter the compound before it reaches target

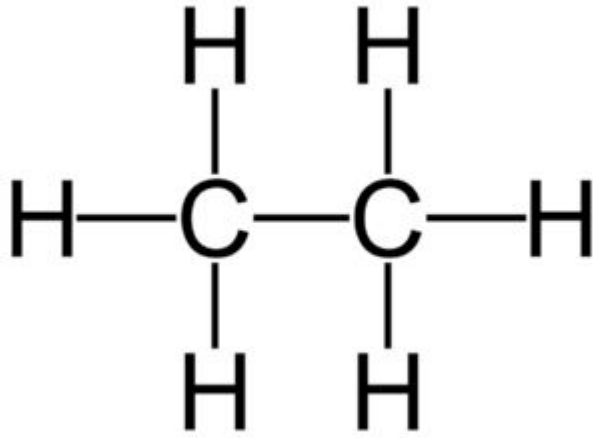

Glycogen
Metabolism
Pentose
Phosphates
Pathway
Acyl-glycerol
Metabolism
Glycolysis
and
Gluconeogenesis
Fatty
Acid
Biosynthesis
Transaminations
β-Oxidation
Urea
Cycle
Ketone
Bodies
Metabolism
Citric
Acid
Cycle

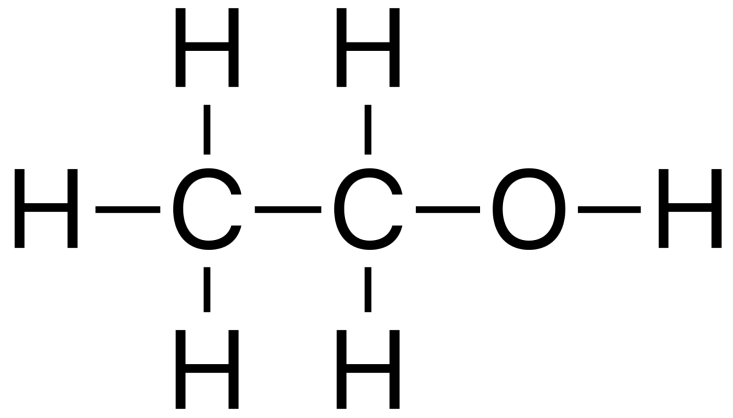
The Solution

- **Medicinal Chemistry**: Field of chemistry that modifies drugs
  - Changes the formula of the drug
  - Makes it survive metabolism
  - Ensures it can still bind to the target
- Compound is transported through various body systems
  - Each with several processes

Functional Groups

- **Functional Groups**: Atoms that affect function of a molecule
  - -OH is an alcohol group, for example
- These small differences in atoms cause LARGE changes:





Tying Chemistry to Biology

- Similar compounds can all act on the same class of receptor
  - With vastly different affinities
- **Affinity:** The ability of a chemical to react with something else
  - Gibbs free energy of docking can describe this
  - Negative ΔG = higher affinity

Chemotherapies: Doxorubicin

- **Topoisomerase II Inhibitor:**
  - Human DNA is incredibly large and can get tangled
  - Topoisomerase II cuts and reshapes DNA to prevent tangles in replication
- Doxorubicin stabilizes this enzyme, leaving the DNA tangled up
  - The tangled DNA cannot properly replicate
  - Mitosis therefore cannot occur properly
  - The tangles sometimes induce harmful (to the cell) DNA breaks too

Immunotherapies: Rituximab

- **CD20 Monoclonal Antibody:**
  - CD20 is a protein found on the surface of B cells (white blood cells that produce antibodies to fight infection)
  - The binding of rituximab and CD20 proteins activate other immune cells
  - These immune cells then kill the CD20-positive B cells
- Useful for certain cancers such as lymphoma as well as certain autoimmune diseases

Lecture Wrap-Up

- I hope you enjoyed this lecture and learned a thing or two
- I would like to be a science educator as a career
- That being said, your feedback on my teaching is super valuable
- Please please provide it in this short, anonymous survey: