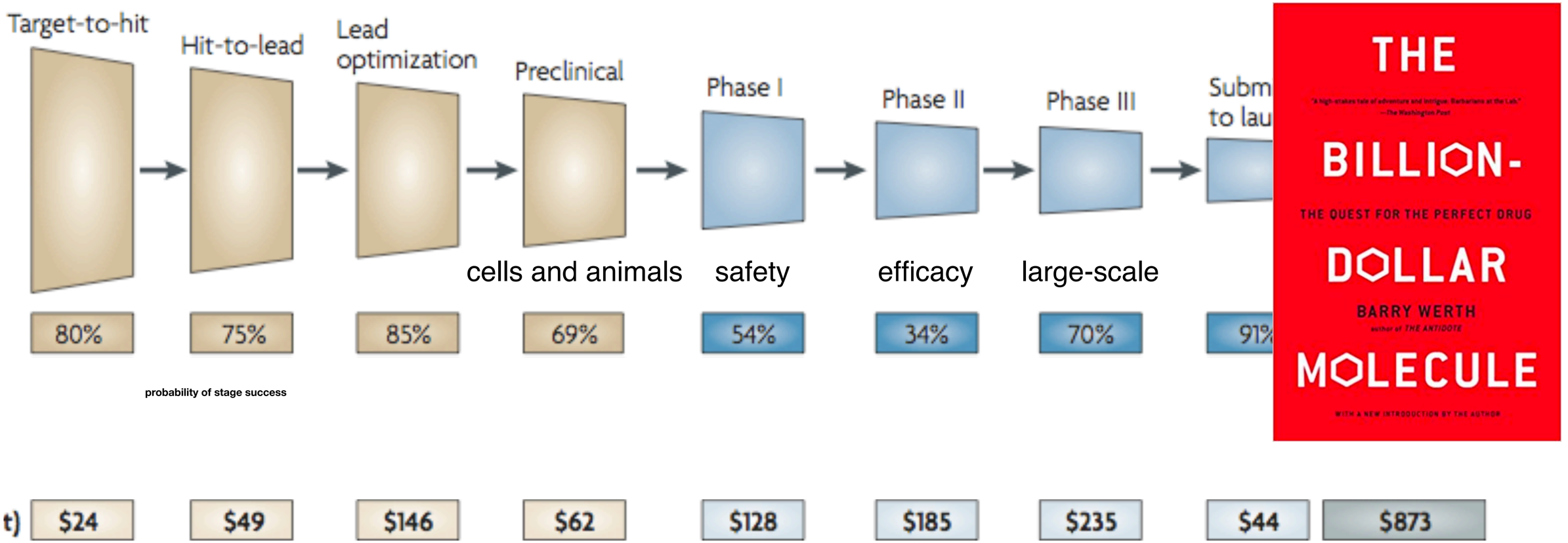
1/14/2020 Preliminaries

- You are in Chem 456 - Computational Biochemistry and Drug Design
- Your instructor is Dr. David Minh
- The course web page is at https://daveminh.github.io/Chem456/. Bookmark this on your computer and your phone
- If you care, code for the web page is at https://github.com/daveminh/Chem456

Week 1 Module 1
Principles of Structure-Based Drug Design

- This module will consist of a mini-lecture, an interactive structural visualization exercise, and a review
- At the end of this module, you should be able to, at least at a very basic level, answer the following questions:
  - Why is there interest in structure-based drug design?
  - What are the physiological functions of the biological macromolecules targeted by drugs?
  - What are biological macromolecules made of?
  - What does it mean for a biological macromolecule to be folded?
  - How do most drugs interact with their targets?

Drug discovery is expensive and often fails



Much drug design is still by trial-and-error.
Can we do better with a more rational approach?

Chodera et al. Curr. Op. Struct. Bio. 2011, 21 (2), 150–160.
for updated numbers see
Pammolli et al. bioRxiv 2019, 670471. https://doi.org/10.1101/670471.

Drug targets are biological macromolecules

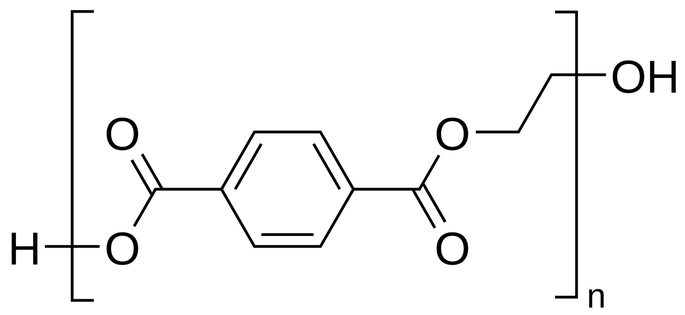
- Most are proteins, including
  - Enzymes - catalysts that speed up a chemical reaction
  - Receptors - take a signal and pass it along
    - G protein coupled receptors - pass information across a cell membrane
    - Transcription factors - signal to print out instructions to make a certain protein
  - Membrane transporters - transport molecules across a membrane
  - Ion channels - allow ions to pass through a membrane
- Others include
  - Deoxyribonucleic acid (DNA)
    - stores genetic information
    - cancer drug target
  - The ribosome
    - makes proteins
    - common antibiotic drug target

see Landry, Y.; Gies, J.-P. Drugs and Their Molecular Targets: An Updated Overview. *Fundam Clin Pharmacol* **2008**, *22* (1), 1–18. https://doi.org/10.1111/j.1472-8206.2007.00548.x.
also see Therapeutic Target Database: http://idrblab.net/ttd/

Discuss: how can modulating these functions treat disease?

Biological macromolecules are heteropolymers

- Polymers - made of smaller building blocks - monomers - that are covalently joined together
  - Homopolymers - monomers repeat, e.g. in a plastic
  - Heteropolymers - monomers do not exactly repeat
- Different types of macromolecules are made of different types of building blocks

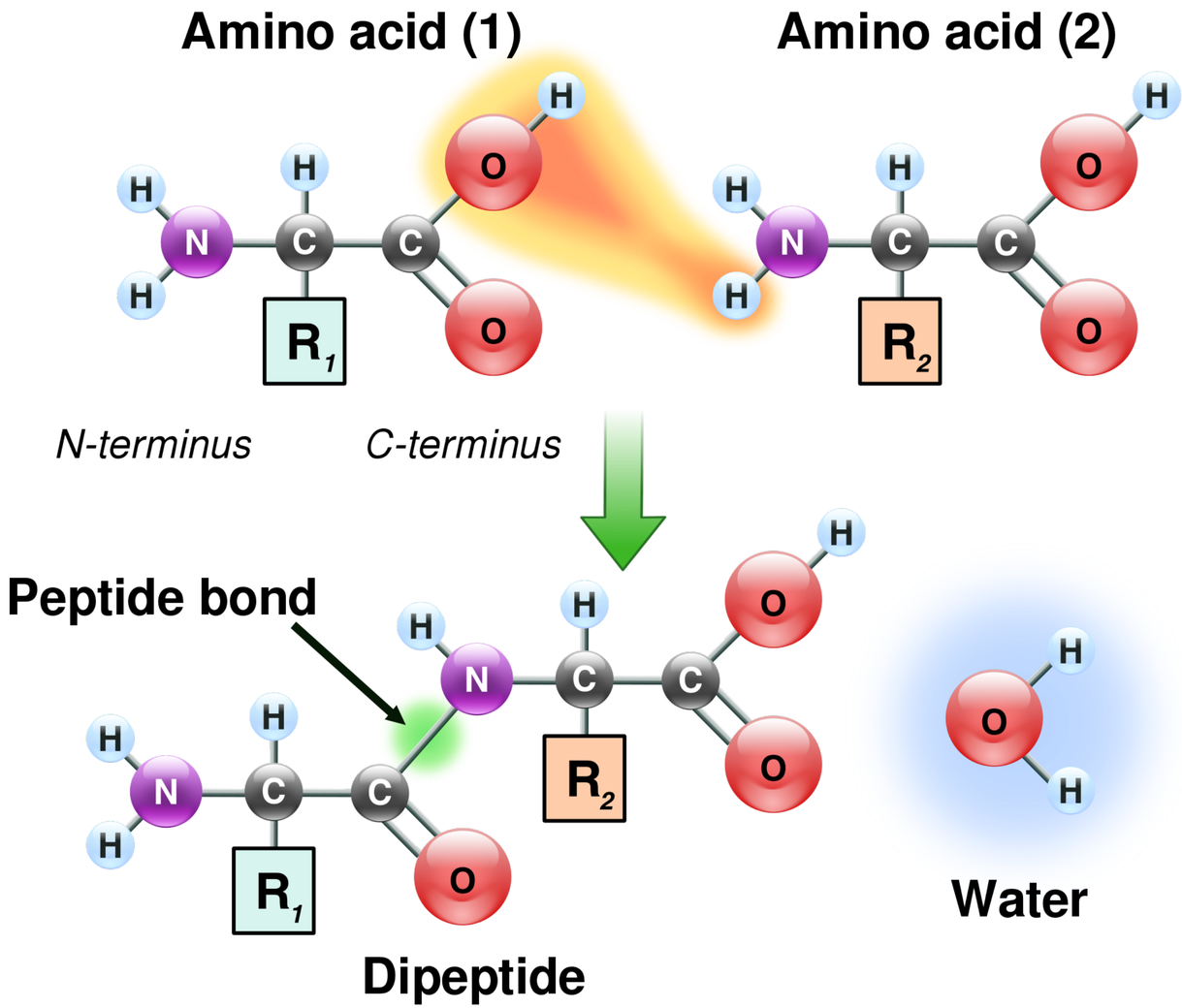


Polyethylene terephthalate, a homopolymer

https://commons.wikimedia.org/wiki/File:Polyethyleneterephthalate.svg

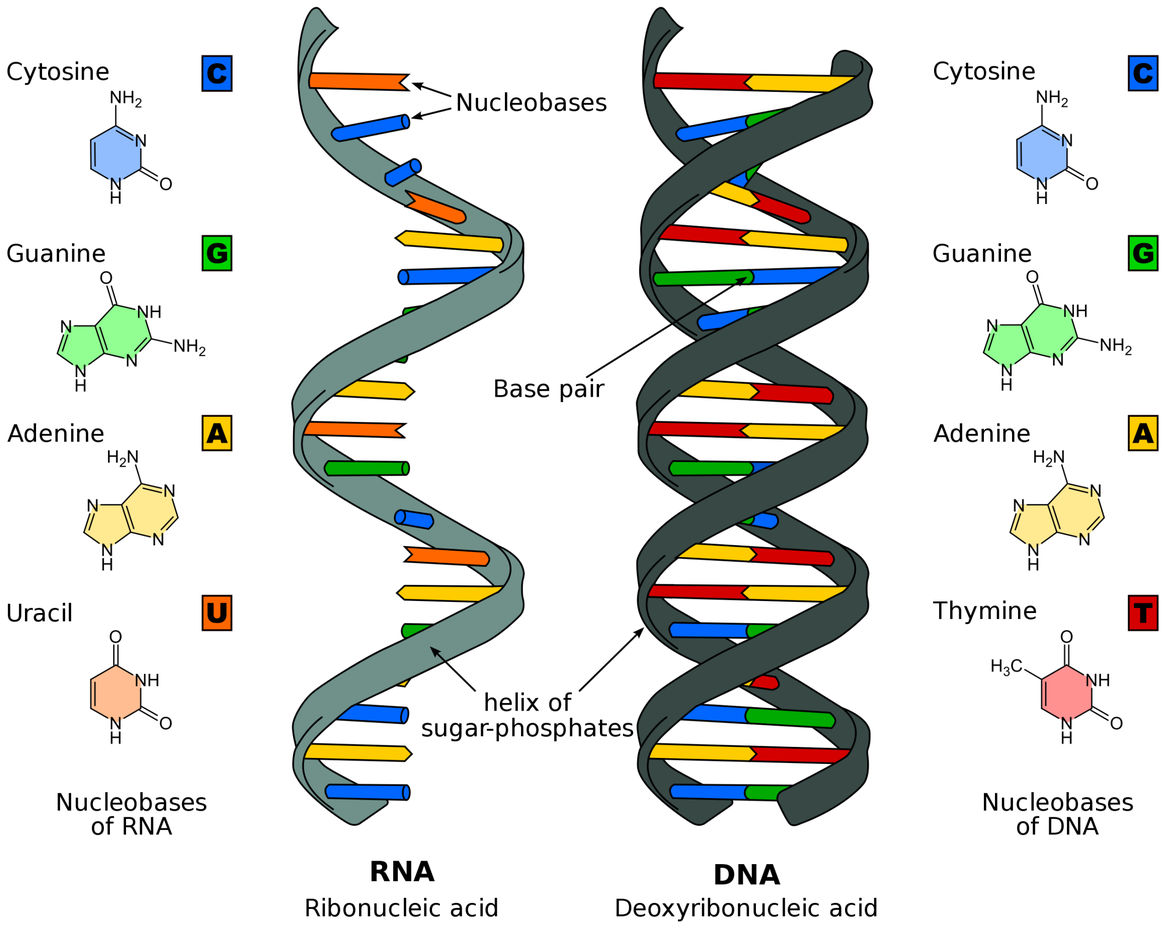
The monomers are small organic molecules

- Proteins are made of
  - 20 standard amino acids
  - linked by peptide bonds
  - modifications, e.g.
    - post-translational modification
    - disulfide bonds
    - cofactors and prosthetic groups



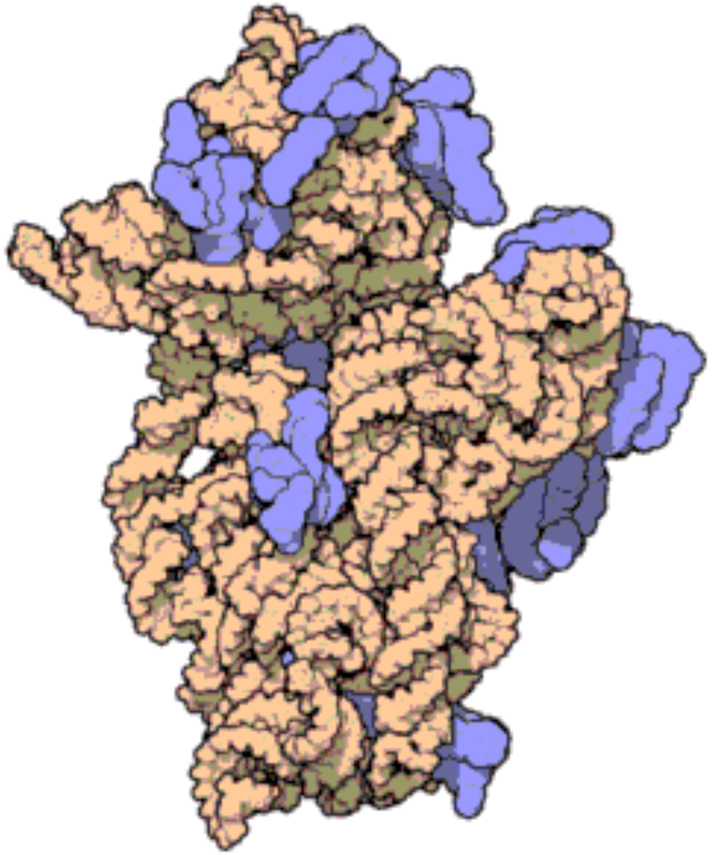
The monomers are small organic molecules

- DNA and RNA are made of nucleic acids
- DNA usually forms a double helix
- RNA is more flexible and can have complex structure



https://en.wikipedia.org/wiki/Nucleic_acid#/media/File:Difference_DNA_RNA-EN.svg

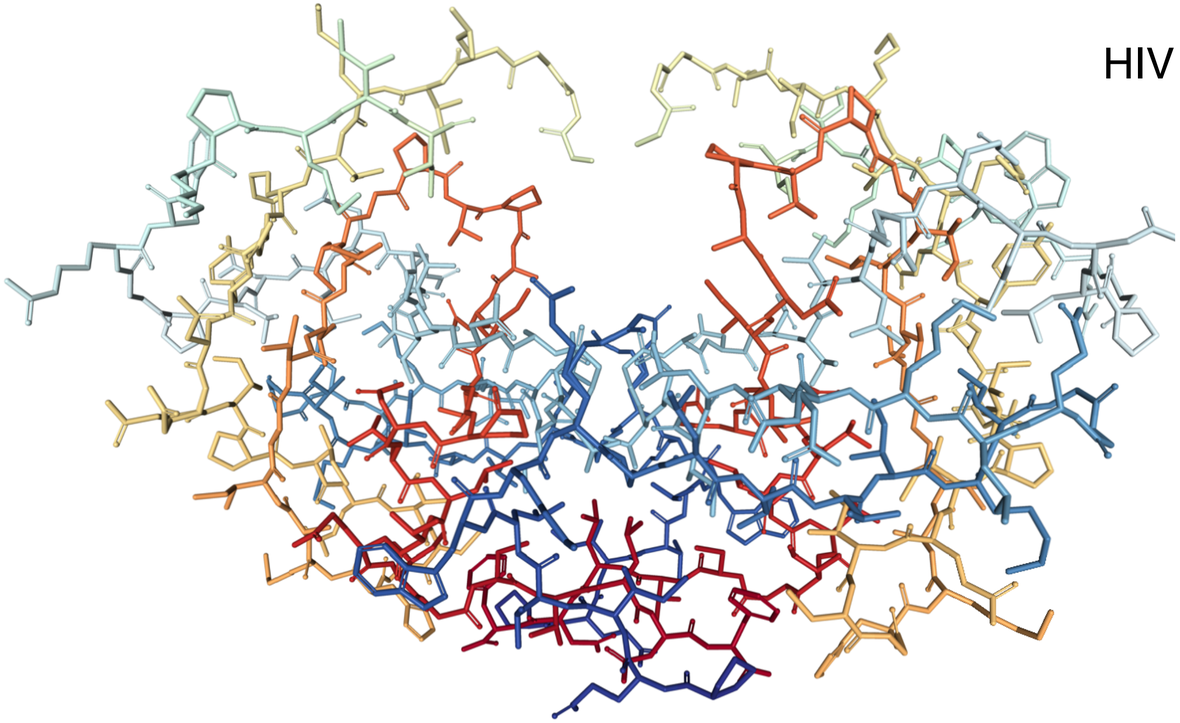
Macromolecules can be tightly complexed



30S subunit from a bacterial ribosome,
which is made of both protein and RNA

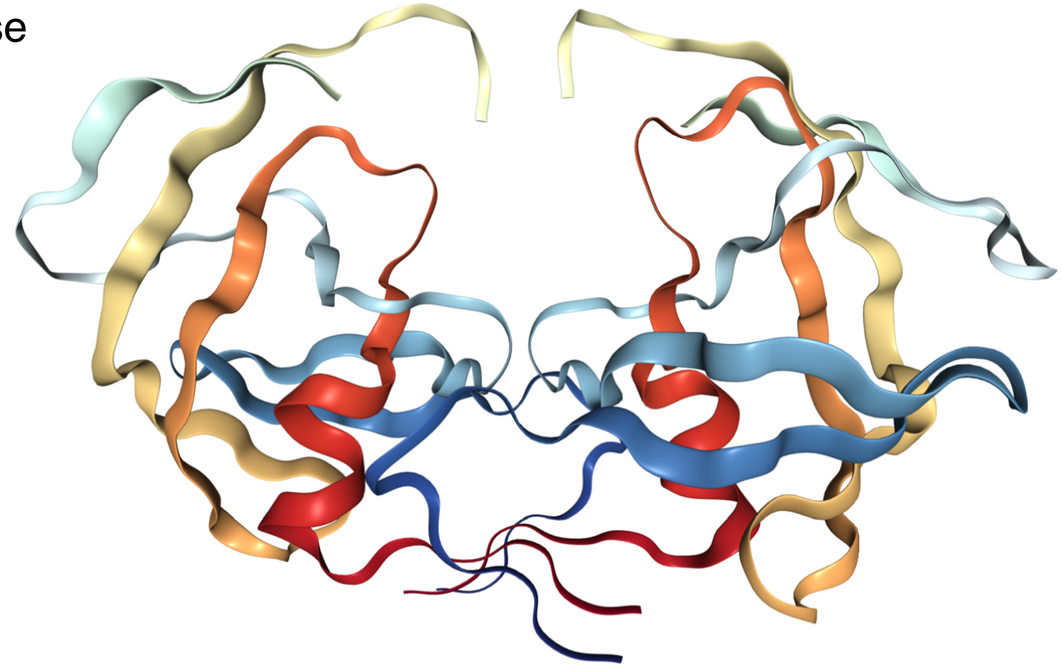
Many drug targets have folded structures

HIV protease



“Licorice” view showing all heavy atoms

http://www.rcsb.org/3d-view/2HB2

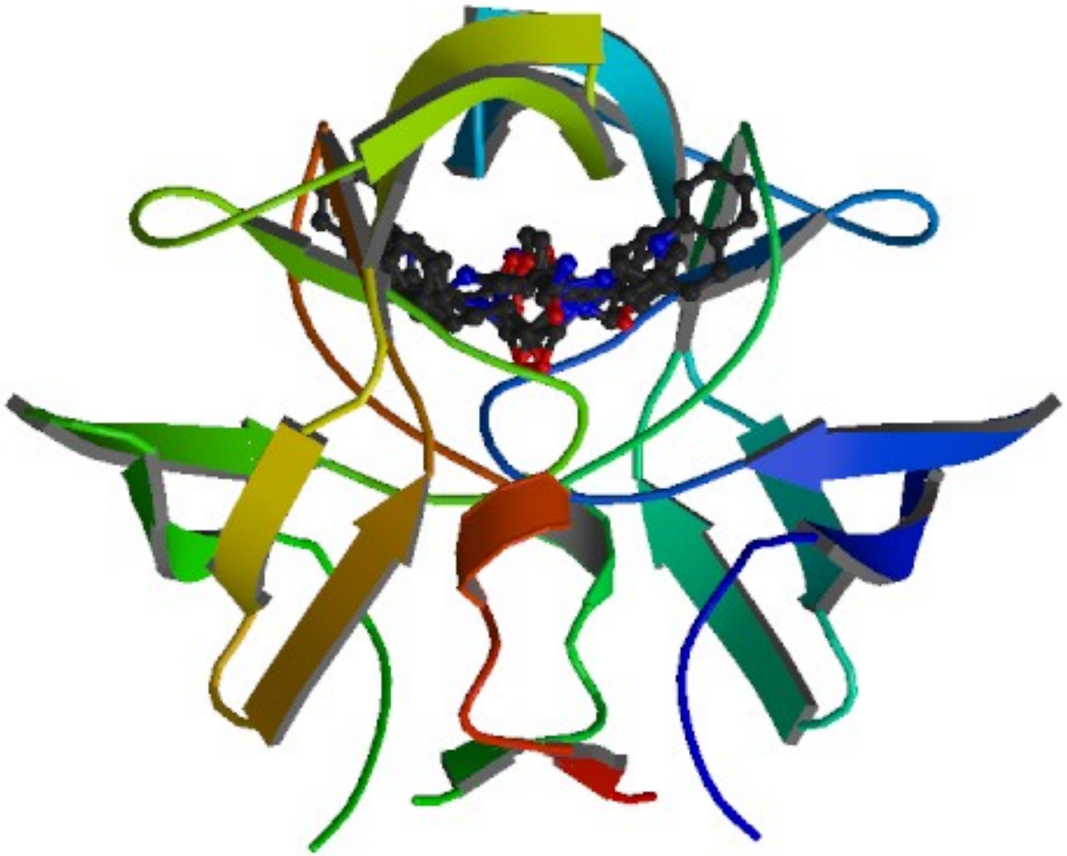


“Ribbon” view showing backbone, emphasizing α helices and β sheets

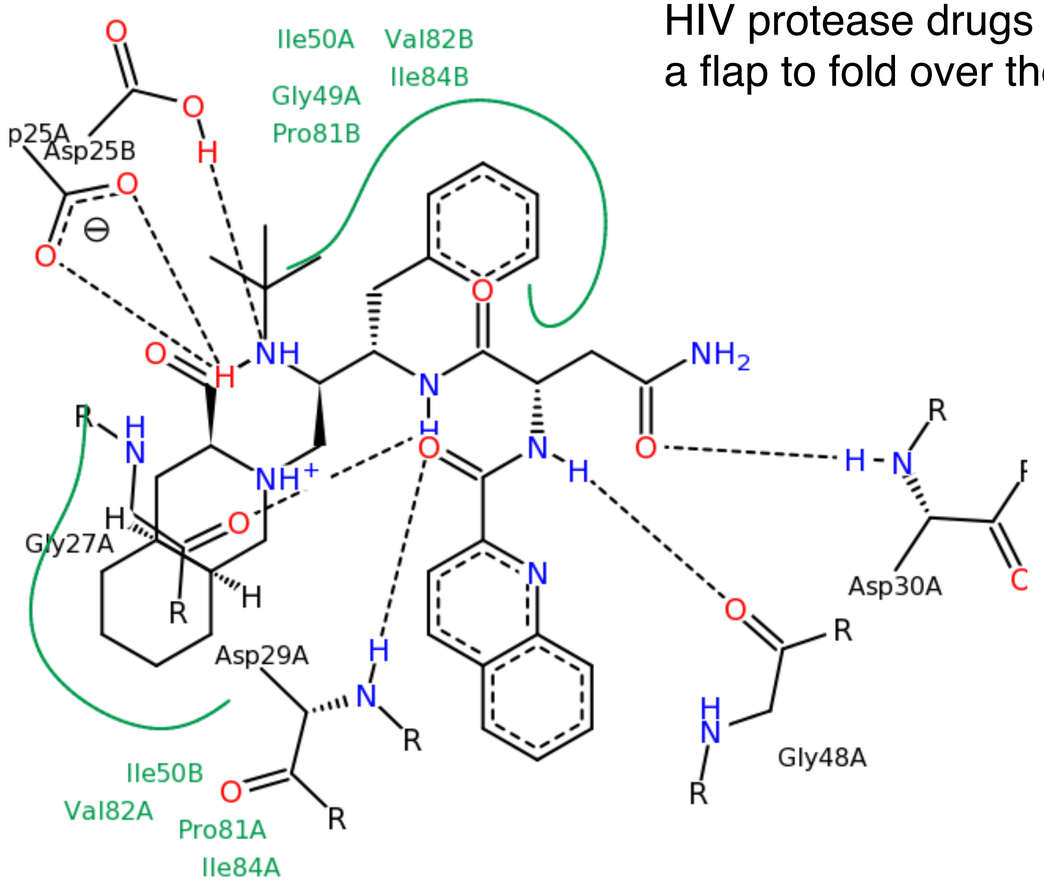
“Folded” does not mean that they are completely rigid, but they are *fairly* well-defined.

Most drugs are small molecules that specifically interact with the folded structures

HIV protease with saquinavir



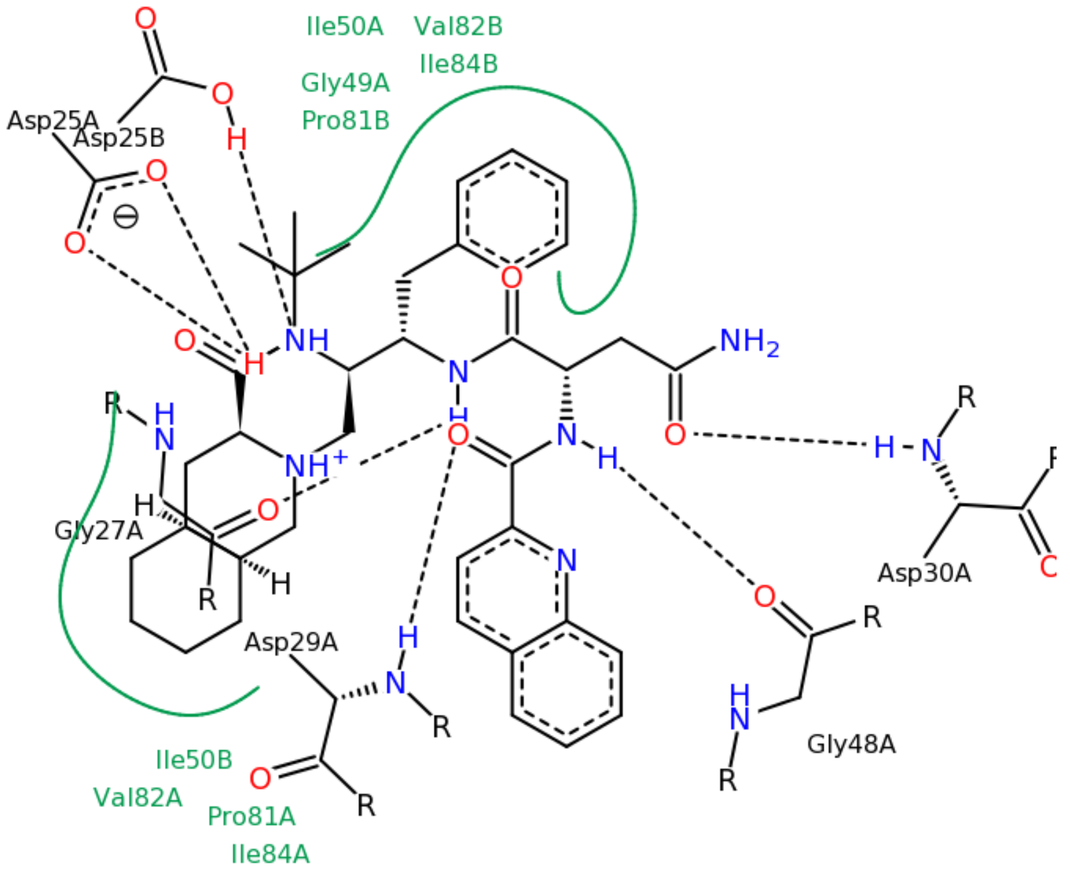
HIV protease drugs often cause a flap to fold over the active site



http://www.rcsb.org/pdb/101/motm_disscussed_entry.do?id=1hxb

Most drug-target interactions are noncovalent

- The interactions driving drug binding are primarily
  - steric - van der Waals. atoms like to be close but not *too* close.
  - electrostatic - like charges repel and opposite charges attract. H bonding often treated as electrostatic.
- Water can play an important role.
- Some drugs (like penicillin) bind to their targets covalently.



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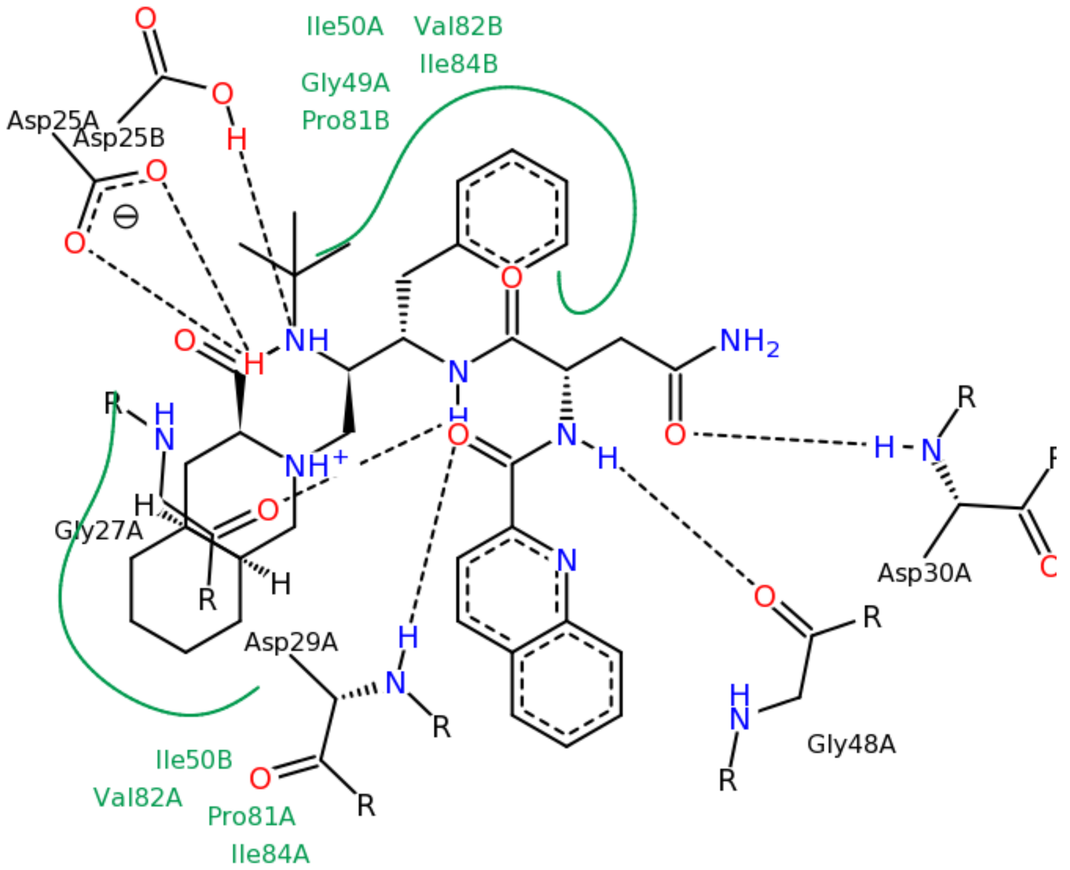
Drugs can be designed to optimize interactions

- There is a combinatorial explosion of ways to modify a small organic molecule to make it bind better
- Structure-based drug design (SBDD) uses the target's structure to
  - maximize interactions that favor binding
  - minimize interactions that disfavor binding



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Interactive Structural Visualization Exercise

Review Questions

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Misc

- A beautiful short video on “A basic introduction to drugs, drug targets, and molecular interactions”: https://www.youtube.com/watch?v=u49k72rUdyc