1. Protein Design
2. ADME and Toxicity

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Protein Design

- Determine amino acid sequence that will **fold** into a given three dimensional structure
- Maybe even that will have given chemical properties (function)
- Like small molecule design, a huge search problem (there are 20^n possible sequences of length n), but key differences…

Comparison to Ligand Design

	Proteins	Ligands
Discrete search space?	Based on residue identity	No inherent partitioning
Libraries	Rotamer libraries	Small molecule libraries, fragment libraries
Rigidity approximations	Rigid backbone commonly assumed	No, very flexible
Potential sets	Many mature ones	Charges a problem
Size, energy computation speed	Larger, especially bad if non-pairwise	Smaller, so fast energy computations
Experimental screening infrastructure	Automated and manual	Highly developed high throughput techniques
Synthesis	Not a big problem	Can be impossible for some structures

ADMET

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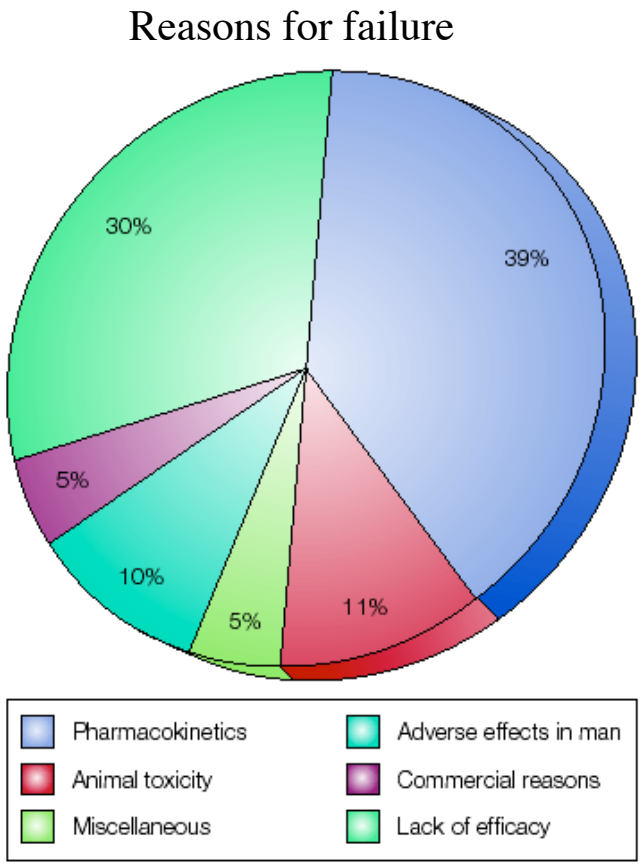
In Vivo Issues

- Absorption
  - Has to get into bloodstream, like through intestinal wall
- Distribution
  - Move to target tissue/organ
- Metabolism
  - Enzymes break down the drug (especially in the liver, by cytochrome P450 enzymes)—the metabolite might be inactive or more active
- Excretion
  - Have to get out, shouldn't build up
- Toxicity
  - Don't poison us, interactions, etc.

Big Problem

- Historically, develop compound, then test ADMET (in vivo)
  - Often fails and then have to go start all over
- Want to consider ADMET as early in the development process as possible, to avoid bad directions



Waterbeemd and Gifford, 2003

Specific Challenges

- Properties like
  - Lipophilicity
  - Solubility
  - Etc.
- Affect issues like
  - Can the drug be taken orally?
  - Will it cross the blood-brain barrier?
  - How will cytochrome P450 affect it?
  - Is is hepatotoxic?
- Answers to these types of questions give information on feasibility and also on dose size and frequency

Lipinski's Rule of Five

- Seminal result from 1997, widely utilized
- Rule of thumb for oral bioavailability
- Based on characteristics of existing drugs
- Name comes because "5" appears in most of the guidelines
  - Molecular weight <500 Da
  - Number of H bond donors ≤5
  - Number of H bond acceptors ≤10
  - Octanol/water partition coefficient (LogP) <5

Techniques

- For ADME
  - QSAR
    - Most widely used and effective today
    - Depends on existing drugs
  - Docking
    - As for checking cytochrome P450 binding
  - Simulation
    - Use physiologic models
    - As Gastroplus or IDEA for absorption
- For Toxicity
  - Rule based system
    - Built up based on expert knowledge (see DEREK)
  - QSAR and other such statistical techniques

Readings

- Predicting Blood-Brain Barrier Permeation from Three-Dimensional Molecular Structure (Crivori, et. al.)
- Validation of Model of Cytochrome P450 2D6: An in Silico Tool for Predicting Metabolism and Inhibition (Kemp, et. al.)
- Characteristic Physical Properties and Structural Fragments of Marketed Oral Drugs (Vieth, et. al.)