Drug Design and Discovery

“…the most fruitful basis for the discovery of a new drug is to start with an old drug.”

James Black (Nobel Prize for Medicine, 1988)
Big Pharma

- Pharma spends > $50 billion/yr on R&D
- Mergers & acquisitions
- Licensing deals with biotech and small pharmaceutical companies
- Targeting chronic conditions, not acute
- Drug pipeline
Blockbuster Drugs

• Drugs with expected sales of over $1 billion
  – ~50% of new drugs => vulnerability when patent protection expires
• ~ $1 billion to develop, test, and obtain approval for new drug
• 99.9% of compounds wash out
• R&D expenditures not matched to NCE
Overview of Drug Discovery

- >21,000 drug products
- Only 1,357 unique drugs
  - 1204 small-molecule drugs
  - 166 biological drugs

Approaches to Drug Discovery

• Combinatorial chemistry
• High throughput screening - but high affinity compounds not necessarily better (often high MW)
• Genomics & proteomics (but target validation challenging)
• Computational approaches
  – Structure-based, “rational” drug design
  – Virtual screening
  – QSAR
  – *etc.*
Combi Chem and HTS

• “Proteins are inherently ‘sticky’ molecules. There may well be a danger that the binding reactions used in HTS … in conjunction with combinatorial chemistry will select-in nonspecific molecules.”

Steps in Drug Discovery

- Identify target (usually a protein)
- Target validation
- Identify initial “hits”
- Improve potency (hit -> lead)
- Optimize lead to candidate drug
- Large-scale production and preclinical animal safety studies
- Clinical trials
  - Phase I - small study on healthy subjects to confirm safety
  - Phase II - slightly larger study to confirm efficacy
  - Phase III - large study for safety and efficacy
Target Identification

• Targets of current drugs
• Compete for binding site of endogenous small molecule
• Druggability
  – Presence of protein folds that favor interaction with drug-like compounds
  – Ability of protein binding pocket to bind lead molecules with high affinity
How Many Drug Targets are There?

- Drew & Reiser (1996) - 483
- Golden (2003) - 273
- Wishart (2006) - 6,000 to 14,000
- Zheng et al. (2006) - 268
- Overington et al. (2006) - 324
  - (266 human); remainder bacterial, viral, etc.

Lower numbers usually obtained by requiring clear identification of target and assays to demonstrate interaction with target and efficacy.

How extrapolate to total number of targets?
Based on close homologs of 324 known targets => 1048 genes (3.5% of genome)
Privileged Druggable Domains

- Domains for which significant number of family members are drug targets

Promiscuity

• Polypharmacology - promiscuous modulation of several targets by a small molecule drug
  – e.g., protein kinase inhibitors not as selective as initially thought

• Also have promiscuous proteins that bind diverse range of ligands
  – Nuclear hormone receptors
  – Cytochrome P450s (CYP3A4)
Target Validation

• Proving that target is directly involved in disease process
• Knock-out gene of interest
  – Use RNA antisense technology to inactivate the gene
  – Use known small molecule inhibitor
Hit Identification

• High-throughput screening
• Virtual screening
• Lipinski’s Rule of 5
  – $\text{MW} \leq 500$
  – $\text{ClogP} \leq 5$
  – H-bond donors $\leq 5$
  – H-bond acceptors $\leq 10$
• Extensions
  – Polar surface area $\leq 140 \, \text{Å}^2$
  – Rotatable bonds $\leq 10$
Lead Identification

- Structural similarity to other compounds (e.g., QSAR) => ligand-based design
- Pharmacophore identification
- Docking and scoring => structure-based design
Lead Optimization

- Structure-based refinement
- ADMET experiment and modeling
  - Cytochrome P450 can affect half-life and cause drug-related side effects and toxicity
- Modification of compound as needed
- Anti-targeting
  - Identify proteins to which you do not want drug to bind
  - Human serum albumin can prevent drug from reaching target site
ADMET

- Absorption, distribution, metabolism, excretion, toxicity
- ~50% of drugs in development fail due to ADMET deficiencies and ~50% of drugs that make it to market have some ADMET problem
  - e.g., calcium-channel blocker, mibefradil (Posicor)
    - user to treat hypertension and angina
  - But potent inhibitor of liver metabolism
  - Withdrawn within year of launch (1997-98)
- Efforts to develop computational predictive models of ADMET
Why Drug Candidates Fail