Structural biology and drug design:

An overview

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The Long Road to a New Drug

Discovery
- Project Team and Plans
- Synthesis of Compounds
- Screening

Exploratory Development
- Studies in Healthy Volunteers Phase I

Full Development
- Studies in 100-300 Patients (Phase II)
- Clinical Data Analysis
- Candidate Medicine Tested in 3-10,000 Patients (Phase III)
- Large Amounts of Candidate Medicine Synthesized

Registration
- NDA/MAA
- EU/USA

Extensive Safety Studies
- Formulations Developed
- Candidate
- Early Safety Studies
Drug Development

• The average time it takes to bring a drug to market is ~15 years
• The average cost to bring a drug to market is ~$800 million
• New approaches and methods for drug discovery are being employed to reduce the time and expense of bringing a drug to market
• Classical vs. Rational
Drug discovery

![Diagram of drug discovery process]
Drug and drug design

- A drug is a key molecule involved in a particular metabolic or signaling pathway that is specific to a disease condition or pathology.

- Action of activation (agonist) or inhibition (antagonist) to a biological target (protein, receptor, enzymes, cells...).

- **Drug design** is the approach of finding drugs by design, based on their biological targets.

- An important part of drug design is the prediction of small molecules **binding** to a target protein (pharmacophore, docking, QSAR,...)
Virtual screening - Chemoinformatics

- Exploit any knowledge of target(s) and/or active ligand(s) and/or gene family.
- It involves computational technique for a rapid assessment of large libraries of chemical structures in order to guide the selection of likely drug candidates.

Structure based
Docking...

Ligand based
QSAR, similarity search

Pharmacophore based

knowledge based
Chemical-Biology network
Drug-likeness with a simple counting method, ‘rule of five’

- Octanol-water partition coefficient (logP) ≤ 5
- Molecular weight ≤ 500
- No. hydrogen bond acceptors (HBA) ≤ 10
- No. hydrogen bond donors (HBD) ≤ 5
- If two or more of these rules are violated, the compound might have problems with oral bioavailability.


Rules have always exception.
(antibiotics, antibacterials and antimicrobials,...)
What the chemist sees.

Aspirin

Sildenafil

Viagra !!!
1D structure, line notation

CC(=O)OC1=CC=CC=C1C(=O)O

CCCC1=NN(C2=C1NC(=NC2=O)C3=C(C=CC(=C3)S(=O)(=O)N4CCN(CC4)C)OCC)C

SMILES – Simplified Molecular Line Entry System
What a protein sees.

Aspirin
Sildenafil

Electrostatic fields (red are negative and blue positive)
What a protein sees.

Aspirin  Sildenafil

Green are hydrophilic area and red are hydrophobic areas
Ligand based- QSAR

- Based on a set of experimental data (biological activity, solubility, toxicity, permeability, ...) one tries to correlate these data with some structural descriptors.
- Method used are usually, PLS, SVM, NN, K-means.
Descriptors

1D descriptors:
MW, number of features,…

2D descriptors:
Topological, physicochemical, BCUT,…
Descriptors

QSAR based on 3D interaction energies (GRID, CoMFA...)

GRID: Determines a total interaction energy. \[ E_{\text{tot}} = E_{\text{vdw}} + E_{\text{elec}} + E_{\text{hb}} \]

Structural model

Molecular interaction field (GRID)  PCA and PLS model
Blue areas represent the favorable electronegative region and red the unfavorable electronegative regions (based on CoMFA).

Green areas represent the favorable steric region and yellow the unfavorable steric regions (based on CoMFA).
De novo design-Scaffold hopping

Concept for scaffold hopping

Protein-ligand complex
De novo design: Scaffold hopping

Scaffold removed
De novo design: Scaffold hopping

physicochemical description

Hydrophobic

H-bond donor

H-bond acceptor

De novo design: Scaffold hopping

physicochemical description
De novo design: Scaffold hopping
New scaffold insert
Scaffold hopping: Example with HIV protease

Bergmann R. et al., j. med. Chem. 2007. 50(11): 2708-2717
A pharmacophore is the ensemble of **steric and electronic features** that is necessary to ensure the optimal supramolecular **interactions** with a specific biological target structure and to trigger (or to block) its biological response. A pharmacophore does not represent a real molecule or a real association of functional groups, but a **purely abstract concept** that accounts for the common molecular interaction capacities of a group of compounds towards their target structure.
Pharmacophore: chemical features

- The chemical features can be hydrogen bonds acceptors, hydrogen bond donors, charge interactions, hydrophobic areas, aromatic rings, positive or negative ionizable group.) The shape or volume is also considered.

Pharmacophores represent chemical functions, valid not only for the currently bound, but also unknown molecules. The steric hindrance may explain lack of activity.
Atom is acceptor if it’s a nitrogen, oxygen or sulfur and not an amide nitrogen, aniline nitrogen and sulfonyl sulfur and nitro group nitrogen.

Example 1:

Pharmacophore
Pharmacophore

Example 2 with 3 inhibitors

Agonist at D2 receptor

• Dopamine
  (2 rotations and 2 OH groups)

• Apomorphine (no rotations)

• 5-OH DPAT
  (one OH group and many rotation)
Example 2

Active agonists define important groups:

- Aromatic ring
- meta OH group
- N atom, right distance from aromatic ring
- Other molecular “scaffolding does NOT get in the way at the receptor
Pharmacophore

Effect of pH

pH = 7

pH = 1
Pharmacophore

Which conformation?

• Some drugs are rigid (e.g., strychnine, a Glycine receptor antagonist)

• But most drugs have some conformational flexibility, and can have different shapes (e.g., sildenafil)

Pharmacophore should be presented only by high energy conformation (Xray, NMR, minimisation, stochastic search)
Pharmacophore flexibility

A pharmacophore is usually obtained by connecting the average spatial positions of the pharmacophoric points of all the molecules. But sometime, several binding site or flexible binding site.
Pharmacophore

- Binding site activity can be flexible
Pharmacophore

Chemical structure diversity of hERG blockers

*potent blockers have basic N .... and aromatic rings
Pharmacophore

Pharmacophore model of hERG blockers

31 hERG blockers superimposed

N = Nitrogen atom
C0, C1, C2 = centroids (centers of mass)

Are features of the site unique to hERG?

Ala-scanning mutagenesis of residues near inner pore

KcsA
(Doyle et al., 1998)

MK-499
IC$_{50}$ = 34 nM

P

M2 / S6

KcsA
TYPRALWWSVETATTVGYGDLYPVT'LWRLVAVVV\text{MAGITSFGLVTAALATWFGRE}

hERG
KYVTALYFTFSSLTSVGFVN\text{PSNTEKIFCSICVMILGSILMY\text{ASIFGNVSAI}QRLY}

Ala substitution
Ala scan

Dofetilide (or MK-499)

E-4031

Bepridil

normalized current @ 0 mV (I_{drug}/I_{control})
What is a good pharmacophore?

- As many protein structures are described as sets of points, pharmacophore identification is commonly reduced directly to the problem of finding points common to all functional ligand conformations.

Pharmacophore identification

- From X-ray crystallography
  - measure X-ray structure with drug at the active site (can sometime be done) or infer binding by measuring distance between likely binding groups.

- From comparison of active compounds
  - The traditional way to identify binding groups.

- Automatic identification of pharmacophores (GALAHAD, Pharmacophore elucidation…).
Structural based design: Docking

- Active molecule
- Active site
- Similarity
- Fit to site
- Active
- Inactive

Cherry-picked for biological screening
Docking

- Individual with the best properties is the result
  - Highest rank
Structural based design: Docking

Comparison of some of the docking tools.

Structural based design: Docking

Induced fit docking

Substrate (ligand) + Enzyme (receptor) → Substrate (ligand) + Enzyme (receptor)

Lock and Key

Induced Fit
Structural based design: an example with antidepressant

Zhou, Sciences 2007
Chemogenomics and Pharmacogenomics

Chemogenomics: Studied the biological effect of a wide array of small molecules on a wide array of macromolecular targets.
Pharmacogenomics: Design drugs according of the genetic variation.
Chemical network: example with neurotransmitter transporters
Drug efficacy-mutation: an example with citalopram

**A441G**
- CIT: 2.5x gain of function
- CIT with “ears”: 2x gain of function

**V343S**
- CIT: 4.5x gain of function
- Des-CN: 4.9x gain of function
  - [Des-F: 7.4x gain of function]

**V343N**
- CIT: 3.5x gain of function
- Des-CN: 35.5x gain of function
  - [Des-F: 3.8x gain of function]

**S438T**
- CIT: 175x loss of function
- Monomethyl: 3.5x loss of function

**A173S**
- CIT: 4.5x gain of function
- Des-F: 16.5x gain of function
Chemogenomics and Pharmacogenomics: an example with citalopram

- **V343S**
  - CIT: 4.5x *gain* of function
  - Des-CN: 4.9x *gain* of function
  - [Des-F: 7.4x *gain* of function]

- **V343N**
  - CIT: 3.5x *gain* of function
  - Des-CN: 35.5x *gain* of function
  - [Des-F: 3.8x *gain* of function]

- **A173S**
  - CIT: 4.5x *gain* of function
  - Des-F: 16.5x *gain* of function

- **A441G**
  - CIT: 2.5x *gain* of function
  - CIT with “ears”: 2x *gain* of function

- **S438T**
  - CIT: 175x *loss* of function
  - Monomethyl: 3.5x *loss* of function
  - [Des-F: 3.8x *gain* of function]
Conclusion

- According of the information you have, different strategies can be used.

- If you can develop different strategies which come to the same conclusion, that will reinforce your hypothesis.

- The most information (experimental) you have, the better your validation will be.