Introduction to Drug Discovery and Development

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Introduction to Drug Discovery and Development

What is Drug Discovery?

- The Process by which new medicines are identified.
- Involves interdisciplinary approaches of
  - Biochemistry, molecular biology, organic chemistry, physical biochemistry, pharmacology, cell biology and physiology

Introduction to Drug Discovery and Development

Investigational New Drug (IND) Application

- *A request for authorization from FDA to administer an IND or biologic product to humans*
  - This is literally seeking permission to perform a clinical trial.
- The trial can proceed if the FDA does not file a hold with 30 days of receiving the application
- The application must contain information on:
  - Animal pharmacology and toxicology studies
  - Manufacturing processes and procedures for the drug or biologic

New Drug Application (NDA)

- *When the sponsor of a new drug has enough evidence of the drug's safety and effectiveness has been obtained to meet FDA's marketing approval an NDA.*
- If the NDA is approved by the FDA the product can be marketed in the U.S.
- The application must contain data from specific technical viewpoints including:
  - nonclinical pharmacology and toxicology
  - chemistry, manufacturing and controls
  - clinical pharmacology
  - Medical
  - Statistics

Drug Development Terminology

- Hit: Some positive result, usually with low specificity and low efficacy (mM range) of a drug screen, often times **via high throughput screen**

- Lead (compound): Suboptimal drug that needs modification to better fit the target for higher efficacy and less off--target effect

ADME: Lipinski's rules of five

ADME: Absorption, distribution, metabolism and excretion .

- Method to **determine potential biological activity in an oral drug**.
  –Also known as Pfizer's rule of five

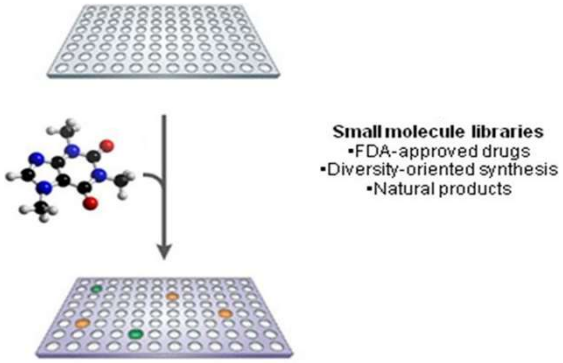
- Number of H--Bond donors no more than 5
- Number of H--bond acceptors, 10 or less
- Molecular Weight <500 da
- ClogP (partition coefficent between octanol/water) is a measure of lipophilicity. ClogP < 5

Screening Strategies

➢ High Throughput	Large # of compounds
➢ Focused Screen	Use identified classes of small molecules
➢ Fragment Screen	(portions of compounds)
➢ Virtual Screen	Docking and molecule dynamic approaches
➢ Physiological Screen	Tissue or animal impact

High Throughput Screening (HTS)

- Hundreds of small molecule libraries exists and are created
- Need way to evaluate each quickly and inexpensively.
- 96well (multiples of to 1,152!) wells holding compounds, plasmid DNA, and other reagents.
- Purified proteins and cell based assays allow for screening of "activity" to discover a "hit"



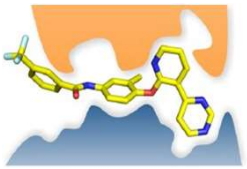
Fragment Based Drug Discovery - Why is there the need for new methodology?

- *While HTS generally works for most, enzyme classes in some cases this does not work*
- *The limitations of HTS was highlighted by researchers from GSK who examined success rates in antibiotic drug discovery.*
- ***This trend is also showing up with some protein-protein interaction targets***
- ***FBDD the way forward with these targets?***

New Approach FBDD

Fragment Based Drug Design – novel approach using smaller compounds…

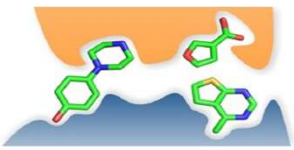
Typical compound hit from HTS screen



- Large molecule (MW between 250 – 600)
- Broad surface contact with no high quality interactions in key pockets
- May contain functional groups that contribute poorly to protein binding
- Emphasis on potency (30 µM – nM hit activity)

The idea that large molecules can be considered combinations of two or more individual fragments is a fundamental principle of fragment--based drug discovery

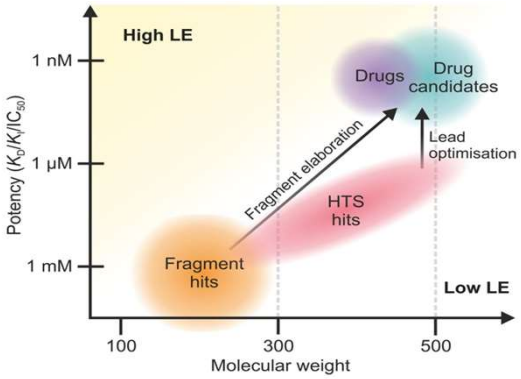
Typical compound hits from FBDD



- Smaller molecule MW between (150-300)
- High proportion of the functional groups involved in binding
- Clearly interacts with pockets
- Potency in the range of mM to 30 µM
- Emphasis on efficiency and design

HTS vs FBDD

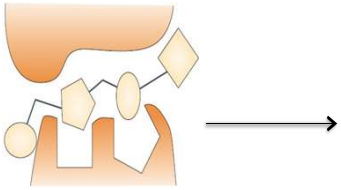
- lower HTS yield low µM – nM
- Fragments potent but can be "built"



How is a Fragment Increased

❖ *Goal is to increase potency, to move from mM to ~10 nM*

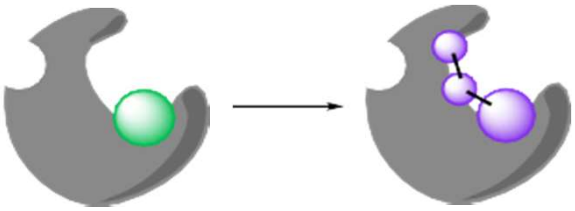
Elaboration of HTS hit



Modified compound with higher potency

Fragment Elaboration

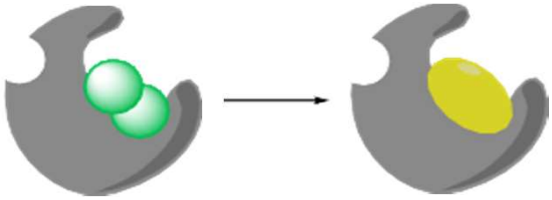
Fragment Growing



- Most successful and frequent method of increasing potency
- Typically a single fragment in a binding pocket is 'grown' using chemical synthesis to pick up further interactions with the protein.
- *This is the case that is the most likely to arise where a single fragment binds to protein or multiple fragments bind to a specific area of the binding pocket*
- *X-Ray information on how the ligand binds to the protein is key to guiding fragment development.*

Fragment Elaboration

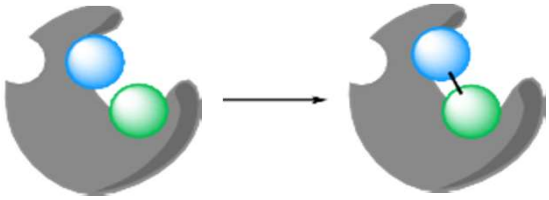
Fragment Merging



- *Find several fragments binding in close proximity*
- *Chemical synthesis uses overlap to design lead compound*
- *X-ray information on how the ligand binds to the protein is key to guiding fragment development, steps of merging overlapping compounds is "tricky" sometimes loss of binding occurs*

Fragment Elaboration

Fragment Linking

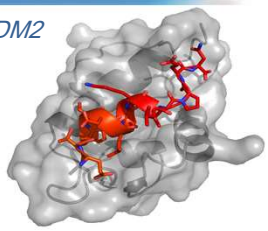


- Create flexible linkers between different binding pocket/ligands
- Considered best way to increase potency can be created similar to HTS lead development
- Linked compound should have higher binding afinity with correct linker
- Considered the most difficult

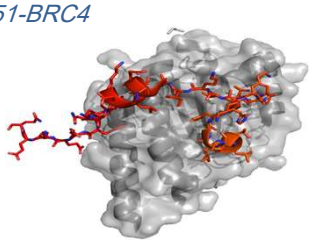
Few examples of this have been successfully produced – but often against protein-protein undruggable interactions

Why protein-protein interactions as targets?

p53-HDM2



RAD51-BRC4



❖ *Protein-Protein interactions (PPI's) are found throughout biological systems. Typically these are defined as difficult targets as success rates in targeting these has been low especially using HTS approaches.*

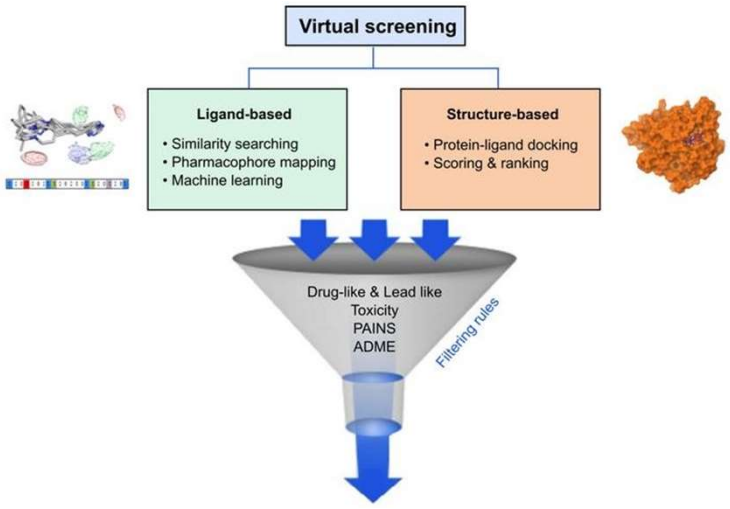
❖ *Unlike conventional targets they do not have distinct binding pockets however they have what is known as 'hot-spots' typically on the surface of the protein*

❖ *FBDD has been used successfully against a number of these targets however none to date have been approved as drugs although in a number of cases there are compounds in Phase I/II development.*

Virtual Screening (VS)

- The process of screening large databases on the computer for molecules having desired properties and biological activity and also to predict their binding to a target receptor.
- Use of high-performance computing to analyze large database of chemical compounds in order to identify possible drug candidates.
- It has evolved over the past decade as a well accepted strategy in the discovery of new lead compounds.

Virtual Screening (VS)



Significance of Virtual Screening ?

- VS is a computational filter:
  - Reduces the size of a chemical library to be screened experimentally– Saves time & money
- May improve likelihood of finding interesting compounds
  - As opposed to random screening, Enhance "hit rates"
- HTS versus VS:
  - Use VS to exclude compounds which are predicted not to bind, helping to "enrich" the library
  - VS can also help to identify false-negatives in HTS