"Optimizing Hits: Stuctural, Computational, and MedChem Approaches"

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Overview

- Once a library has been screened by high-throughput screening (HTS), 'hits' are optimized in a variety of manners:
  - The target can be crystallized in the presence of the hit, and the three-dimensional structure of the complex solved
  - A comparison of the chemical structures with activity can lead to a structural-activity relationship (SAR)
  - Analogizing of various side chains on a hit can identify positions that improve affinity and selectivity
- Once a hit has been improved, it can becomes a 'lead' for additional biological testing, and, if lucky, transitions into a 'drug candidate'

Structural Approaches

- Provide experimental data on how a small molecule ‘hit’ interacts with the target protein and suggest likely modifications to improve affinity and selectivity.
  - NMR and/or crystallographic methods can be used to determine the structures of protein-small molecule complexes
  - Crystalline complexes can be formed either by co-crystallization or crystal soaking
  - Initial hits can be low affinity 'fragments'
  - Compounds with very low solubility in water can be a problem
- Chicago area institutions provide access to many resources and facilities for carrying out structure based optimization
  - The most important resource is the Advanced Photon Source (APS) at Argonne National Laboratory, where synchrotron beamlines focused on macromolecular crystallography make it possible to tackle difficult problems and apply high throughput methods.

Computational Approaches

- Computational analysis of the HTS hits
  - Typical scenarios – too many hits, too few hits, no hits
  - Typical false positives
  - Mining for other types of activities in Pubmed/PubChem
  - Similarity, dissimilarity, mining for common scaffolds
  - Pharmacophore modeling
  - Searching for analogs
  - Choice of libraries for follow-up
- Methods for lead refinement and lead optimization
  - 2D and 3D QSAR
  - Docking, scoring
  - Computational fragment-based approach
  - 'Hot spots' in the binding sites
  - Receptor binding surface based compound searches
- Binding surface calculation and evolutionary substitution calcuation for promiscuity and specificty of enzyme functions.
  - Signature binding pockets for enzyme-class activities
  - Imprint of binding pocket generation and compound search
  - Model binding surface and perform large scale multiplex compound-receptor matching

MedChem Approaches

- Hit is from HTS, "Sigma", or "Merck" = non-proprietary
  - Database searches for structural IP space; SAR from literature
  - Synthesis of novel analogs including negative controls: screen for activity: NO-GO
  - Design of virtual library with MedChem groups to develop analogs using newer synthetic methodologies suitable for scale-up
  - *In silico* screening using docking or ligand-based approaches for triage
  - Iterative synthesis of analogs and testing on target protein and cell lines
  - Monitor absorption, distribution, metabolism, and excretion (ADME) and toxicity in animals