Protein-Protein Interactions and Inhibitors

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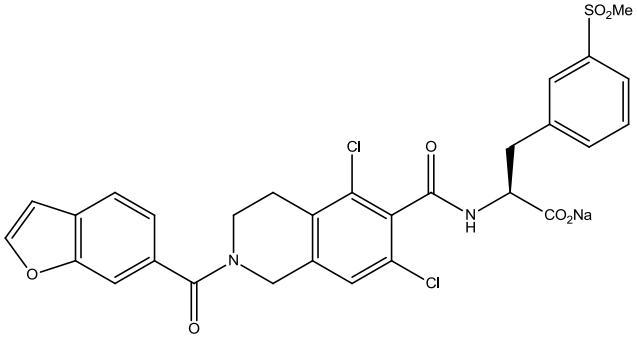
Why PPI inhibitors?

- PPIs are involved in many biological / disease processes
  - Estimated ca 300K relevant PPIs in man
- Huge potential – relatively unexplored
  - Previously considered intractable targets but now significant interest
  - Driven by need to find new therapeutic targets
  - Traditional targets eg GPCRs , kinases etc have intense competition

Current Industry Activity

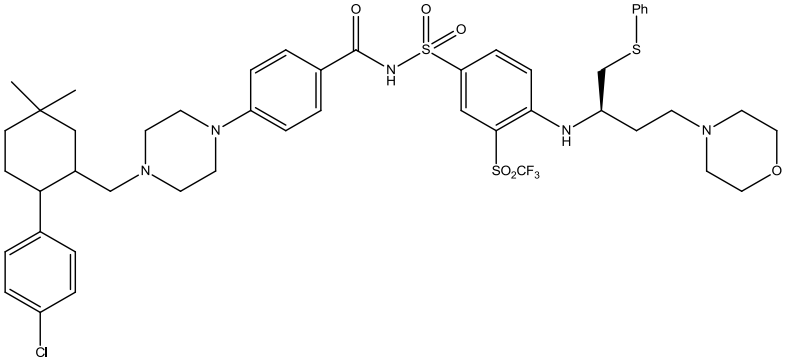
- **Compounds in Clinical Development**
  - SARcode: SAR1118-023 (ICAM-1/ LFA-1 inhib.)– Phase III for ‘dry-eye’ (intraocular)
  - Abbott / Genentech: Navitoclax (Bcl2 inhib.) – Phase II CLL
  - Teva : Obatoclax (Bcl2 inhib.) – Phase II non-Hodgkins Lymphoma (parenteral)
  - Roche: RO5503781 (MDM2 / p53 inhib.) – cancer (oral)
- **PPI Alliances**
  - Boehringer-Ingelheim / Forma – access to PPI inhibs for cancer therapy
  - BMS / Ensemble - 8 PPI targets
  - Shionogi / Evotec – fragment-based discovery for PPIs
  - Many companies have efforts in the PPI area
- **Academic Engagement**
  - Several academic groups engaged in PPI inhibitor discovery

PPI Inhibitors in Clinical Development



SAR 1118-23
MW 637.5

ICAM-1 / LFA-1 inhibitor



Navitoclax
MW 974.6

Bcl-2 inhibitor

Target Tractability

- Perceived difficulties with PPIs
  - Protein surfaces large and featureless?
    - Protein contact surface generally 750 – 1500A^2
    - Binding energy predominantly hydrophobic
  - Large lipophilic molecules required to inhibit PPI?
    - ‘hot spots’ present on some proteins
    - Binding cavities
    - Small subset of residues may contribute most of free energy of binding – protein partner / small molecule
- How can we identify which PPIs are tractable?
  - Structural biology
  - Computational methodologies
    - Molecular dynamics simulation – identify binding cavities

Source of Hits (1)

- **Is each PPI different?**
  - Are there (will there be) privileged scaffolds cf GPCRs , kinases etc?
    - α-helix, β-sheet mimics, others?
    - Need for library expansion?
      - **More 3D structures?**
      - **'Lipinski' compliance?**
- **Where to look?**
  - Forma
    - 150K compounds with 2-5 stereocentres derived from 'diversity-oriented synthesis' approach to identify novel chemical space
    - Additional library based on protein mapping and interface analysis
  - Ensemble
    - Library of >4m macrocycles prepared via 'DNA-programmed chemistry'
    - MW 500-1000Da
    - Large – 'can reach further across the protein interaction and access whatever features might be there' – Nick Terrett

Source of Hits (2)

- **Peptidomimetics?**
  - Dale Boger – α-helix , β-sheet short peptides – 40K library
- **Fragments?**
  - Screening technologies – low affinity detection
- **HTS?**
  - Suitability of current collections?
- **Rational design?**
  - is current structural biology developed sufficiently?

Druggability of Hits / Leads

- Current optimised inhibitors tend (not all) to have high MWt and high logP
  - Eg navitoclax violates 3 Lipinski ‘rules’; MWt 975Da; clogP 12; HBA 12

- Ligand efficiencies tend to be slightly lower than ‘traditional’ targets
  - LE PPI inhibitors 0.24 - 0.27
  - LE Protease inhibitors 0.25 - 0.35
  - LE Kinase inhibitors 0.30 – 0.40
- Is it inevitable that we will need to operate outside currently accepted guidelines for drug-likeness?

- Do we need to re-evaluate ‘drug-likeness’ for this class?

- One school of thought suggests that reducing PSA, rotatable bond count and H-bonding groups should predict good oral bioavailability and may off-set high MWt and clogP?

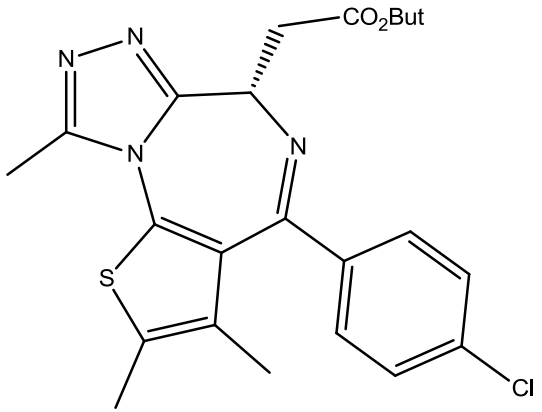
- What about target promiscuity (tox.)? – will greater molecular complexity (3D mols) off-set increase in logP?

Screening Methodologies

- Examples of common screening platforms;
  - Fluorescence polarisation (FP)
  - Fluorescence Energy Transfer (FRET)
  - ALPHA- screen (cf FRET)
  - ELISA
  - SPR
  - ITC
  - NMR
- Binding affinities of hits may be low esp fragment-based hits (10-100μM or greater)
  - Quality of data?
  - False hits?
  - Requirement for orthogonal assays?
  - Limitations of computational methods for early PPI discovery?

A recent ‘drug-like’ inhibitor!

Structural Genomics Consortium : Panagis Filippakopoulos et al ; Nature 2010



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Bromodomain - BRD4 inhibitor
Kd ca 50nM
F= 49%!