Informatics problems and solutions for phenotypic screenings, an AstraZeneca perspective

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AstraZeneca

Phenotypic screening at AZ

Important complement to target based approaches

Annotated set (20K) plus diversity set

Investment in in-house chemical proteomics facility

Collaborations for CRISPR technology just announced
Press release

Current data resources

Bioactivity data
- In-house
  - SAR screening
  - HTS
  - Panel screenings
- Commercial
  - GoStar (GVKBio)
  - BioPrint (Cerep)
- Public
  - ChEMBL
  - PubChem

Target Prediction
- Molecular fingerprints
- Bayesian Models (Collaboration with Dr Andreas Bender)

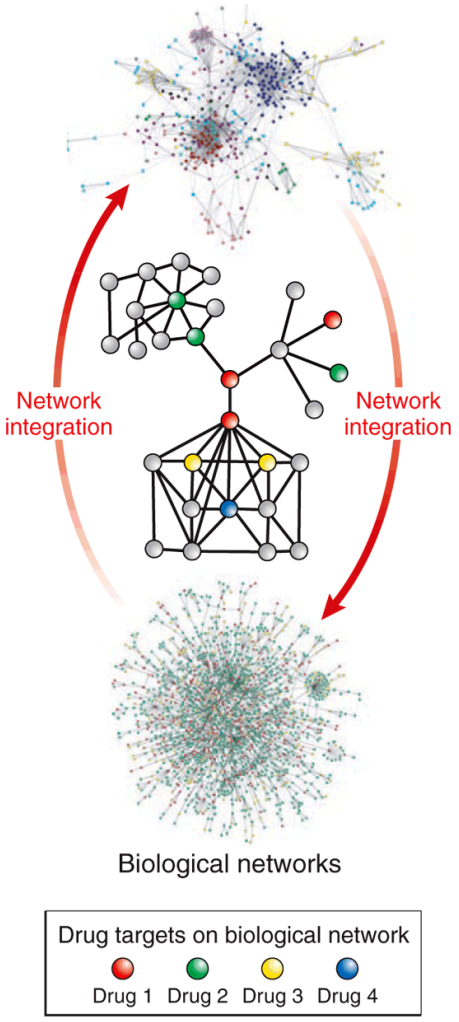
Target Enrichment Analysis
- Published in JBS

Pathway analysis
- GeneGo
- IPA

Textmining
- PubMed

Improvements
- Bio-Assay Ontology (Collaboration with Prof. Stephan Schürer)
- Cortelis Data Fusion

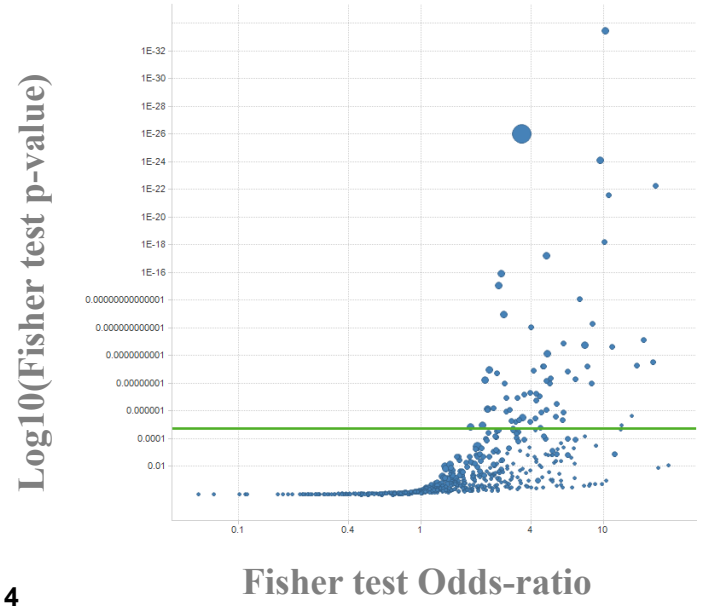
Sustainability
- IMI Open Phacts



Example: Target enrichment analysis

For each target a contingency matrix is generated with the number of compounds (Journal of Biomolecular Screening 2014):

Target X	Ph. Scr. Inactive	Ph. Scr. Active
Target X Inactive	596	17
Target X Active	87	26



Fisher's test:

P-value = 3.24e-12

Odds-ratio = 10.42

Bonferroni Correction for significance cut-off (2060 targets in analysis): 0.05/2060 = 2.43e-05

Enriched targets needs to be experimentally validated:

- **Pharmacological experiments**
- **RNAi**
- **Genome Editing**

Current bottleneck

How can in silico methods best support a target identification hypothesis generated from a chemical proteomics experiment?

- Which are the best known agonist tool compounds for a given target?
- In which cell types and tissues are a target expressed?
- Which is the subcellular location for a protein?
- Which other proteins is an identified protein known experimentally to interact with? Directionality?
- If there is no known small molecule modulators known for a target, which is the closest protein according to a protein classification with a known small molecule?