Networks of Drugs & Drug Targets

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Imatinib (Gleevec) reduces the risk of breast cancer, ovarian cancers, colorectal cancer, and reduces inflammation, fever, and pain. It has a direct relation with diseases and an indirect relation with COX2 and 30 other inhibitors.

Gastrointestinal Stromal Tumor

C-KIT

PDGFRα

Chronic Myelogenous Leukaemia

BCR-ABL

C-KIT

PDGFRα

Direct relation with diseases

Indirect relation with diseases
Motivation

Many drugs target more than one protein
For many targets, there are more than one drug
What is intentional and what is accidental?

What have been the trends in the drug industry?

Different drug targets have distinctive relations to disease genes, i.e. different mechanisms

How do drug targets relate to disease-causing genes?
DRUGBANK Database

1179 FDA-approved small molecule & biotech drugs (different chemical entities)

890 / 1179 has human protein targets

390 Human Drug Target Proteins for Approved Drugs.

Wishart DS et al., *Nucleic Acids Res.* 2006 1;34

http://redpoll.pharmacy.ualberta.ca/drugbank/
Drug Target Network
A global measure of local clustering.

Randomized: $1090 \pm 17$

Observed: 588
Majority of the new drugs target already targeted proteins (me too drugs) - slow rate of target innovation.

3200 Experimental drugs

1014 Human Drug target Proteins with addition of Experimental Drugs.

We can probe the new trends of drug development by looking at changes in the Drug Target Network with addition of Experimental drugs.
### Topological Changes: Giant Component Size

<table>
<thead>
<tr>
<th></th>
<th>FDA Approved</th>
<th>All</th>
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<tbody>
<tr>
<td>Randomized:</td>
<td>1090 ± 17</td>
<td>2213 ± 25</td>
</tr>
<tr>
<td>Observed:</td>
<td>588</td>
<td>2001</td>
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**Experimental**

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<tbody>
<tr>
<td>Randomized:</td>
<td>1034 ± 22</td>
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<tr>
<td>Observed:</td>
<td>1197</td>
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Experimental drugs are more diverse, and promiscuity of the drugs are closer to random.
Cellular Location Profiles

Disease Proteins
- Membrane: 38%
- Exterior: 19%
- Cytoplasm: 15%
- Organelles: 10%
- Nucleus: 9%
- Unknown: 8%

Target Proteins (TP)
- Membrane: 62%
- Exterior: 15%
- Cytoplasm: 6%
- Organelles: 6%
- Nucleus: 8%
- Unknown: 4%

Experimental Targets
- Membrane: 42%
- Exterior: 21%
- Cytoplasm: 12%
- Organelles: 7%
- Nucleus: 9%
- Unknown: 7%

TP – Last 10 years
- Membrane: 69%
- Exterior: 9%
- Cytoplasm: 8%
- Organelles: 5%
- Nucleus: 2%
- Unknown: 7%
Motivation

What have been the trends in the drug industry?
- Mostly “me too” drugs
- But becoming more diverse

How do drug targets relate to disease-causing genes?
Total number of diseases 1,286

Total number of disease genes 1,777

Goh, K.I. et al, PNAS 2007
Drug Targets in Diseasome

1st Neighbors: \( \frac{1}{3} \)

2nd Neighbors: \( \frac{2}{5} \)

3rd Neighbors: \( \frac{1}{6} \)
Drug Targets in Diseasome

Approved Targets in the Diseasome

All Targets in the Diseasome
Drug Targets and Disease Genes

Many drugs do not target disease-causing genes.

Protein-protein interaction information to quantify the relations of drug targets to disease genes.
The particular drug is indicated for the disease

Random control: Keep disease genes constant, randomly select same number of drug targets
Drug targets vs Disease Genes on the PPI Network

Distance on the x-axis represents the number of steps away from a drug target in the PPI network. The y-axis shows the fraction of disease genes at each distance. The blue and red lines represent different methods or datasets comparing drug targets to disease genes. The green circle highlights an area of interest, possibly indicating a region of significant overlap or difference.
Average Distance for Different Disease Categories

- **Cancer**
- **Respiratory**
- **Psychiatric**
- **Endocrine**

**Average Shortest Distance**

- **Disease Genes vs Drug Targets**
- **Random Control**

![Bar chart showing the average shortest distance for different disease categories.](chart.png)
## Cancer Drugs vs Cancer Genes

### Distance vs # of Drug - Cancer Pairs

<table>
<thead>
<tr>
<th>Distance</th>
<th># of Drug - Cancer Pairs</th>
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<tbody>
<tr>
<td>0</td>
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<tr>
<td>1</td>
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<tr>
<td>4</td>
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<td>5</td>
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### Cancer Drugs

- **Imatinib**
  - Gastrointestinal stromal tumor
  - Leukemia
- **Abarelix**
  - Prostate cancer
- **Carmustine**
  - Non-Hodgkin lymphoma
- **Leuprolide**
  - Prostate cancer
- **Zoledronate**
  - Multiple myeloma
Conclusions

Abundance of “me too drugs”

Evolution towards more diverse set of targets

Targeting clustered regions in the Human Disease Network

Drugs mostly act palliatively
Acknowledgements

Kwang-Il Goh
Michael Cusick
Albert-László Barabási
Marc Vidal

CCSB / Vidal / Barabasi labs