We will start momentarily at 2pm ET

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Fan of the Week
Elizabeth Thompson, unemployed chemist

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Travel Award to Summer 2014 London Science Forum

April 25, 2014; 3:00pm EDT

Richard O’Kennedy, Ph.D.
Biochemist
President, London International Youth Science Forum

www.acs.org/ic_london

The London International Youth Science Forum (LIYSF) is a two-week scientific conference with attendees from all over the world. Learn about this summer’s upcoming forum, July 23-August 6, 2014, and how you can apply for a travel award to take you there.
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Primer in Drug Target Classes

ACS webinars - 2014 Drug Discovery Series
Session 2: March 27th 2014

John P. Overington
EMBL-EBI

email: jpo@ebi.ac.uk
twitter: @johnpoverington
linkedin: uk.linkedin.com/in/joverington/
Different Types of Drugs

Drugs Approved 2013

Assigned USANs 2013

ChEMBL
https://www.ebi.ac.uk/chembl

- The world’s largest primary public database of medicinal chemistry data
  - ~1.4 million compounds, ~9,000 targets, ~12 million bioactivities
- Truly Open Data - CC-BY-SA license
- ChEMBL data also loaded into BindingDB, PubChem BioAssay and BARD

Spreadsheet Views

Target Class Data
Affinity of Drugs for their ‘Targets’

$K_i$, $K_d$, $IC_{50}$, $EC_{50}$, & $pA_2$ endpoints for drugs against their ‘efficacy targets’


**SureChEMBL**

https://www.surechembl.org

- New Public chemistry patent resource
- ‘Acquired’ SureChem product from Digital Science
  - Automatically extracted chemical structures from full-text patent
  - ~15 million chemical structures
  - Updated daily
  - Plan to add molecular target, sequence, disease, animal model, cell-line indexing....
Antibacterial Drug Targets

<table>
<thead>
<tr>
<th>ATC Drug class</th>
<th>Target</th>
<th>Target type</th>
<th>Number of drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>J01A Tetracyclines, J01G Aminoglycosides, J01X Spectinomycins, J04AB Capreomycin</td>
<td>Ribosome 30S subunit</td>
<td>Riboprotein</td>
<td>24</td>
</tr>
<tr>
<td>J01B Amphenicols, J02F Macrolides, lincosamides, streptogramins, J01XX Linezolid</td>
<td>Ribosome 50S subunit</td>
<td>Riboprotein</td>
<td>22</td>
</tr>
<tr>
<td>J01C Penicillins, J01D Cephalosporins, monobactams &amp; carbapenems</td>
<td>Penicillin-binding proteins</td>
<td>Protein</td>
<td>85</td>
</tr>
<tr>
<td>J01D Bactams</td>
<td>Beta-lactamases</td>
<td>Protein</td>
<td>2</td>
</tr>
<tr>
<td>J01E Trimethoprim</td>
<td>Dihydrofolate reductase (DHFR)</td>
<td>Protein</td>
<td>3</td>
</tr>
<tr>
<td>J01E Sulphonamides, J04A Aminosalicylic acid, J04AB Dapsone, aldesulfone</td>
<td>Dihydropteroate synthase (DHFR)</td>
<td>Protein</td>
<td>23</td>
</tr>
<tr>
<td>J01M Quinolones</td>
<td>Topoisomerase II</td>
<td>Protein</td>
<td>27</td>
</tr>
<tr>
<td>J01XG Glycopeptides, J01XB Polypeptides, J01Y Dihydrostreptomycin, J01XX Nitrofurans, J01XX Rifamycins, J01XX Rifamycin, rifamycin, methenamine, mandelic acid, nitroxoline, daptomycin, bacitracin, J01NB Morinamide, J01NA Glycopeptides, J01LB Polypeptides</td>
<td>-</td>
<td>-</td>
<td>22</td>
</tr>
<tr>
<td>J01XX Spectinomycin, J04AB Capreomycin</td>
<td>-</td>
<td>-</td>
<td>22</td>
</tr>
</tbody>
</table>

n.b. includes all antibacterial active ingredients with assigned ATC code

Approved Tetracycline Structures

demeclocycline

doxycycline

chlorotetracycline

lymecycline

metacycline

oxytetracycline

tetracycline

minocycline

rolitetracycline

pipacycline

clomocycline

tigecycline
Tetracycline Binds 30S Ribosomal Subunit


Antibacterial Drug Targets (J01 & J04)

N=223 drugs, 13 molecular targets – March 2014 ATC list

Santos & Overington unpublished
**Audience Question**

- What percentage of the human genome is a drug target?
  - 53%
  - 35%
  - 8%
  - 1%

*Only ~1% of Genome is a Drug Target*
Drug Targets and Drugs

<table>
<thead>
<tr>
<th>Drug target Class</th>
<th>Targets</th>
<th></th>
<th></th>
<th>Drugs</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total targets</td>
<td>Small-molecule drug targets</td>
<td>Biotherapeutic drug target</td>
<td>Total drugs</td>
<td>Small molecules</td>
<td>Biotherapeutics</td>
</tr>
<tr>
<td>Human Protein</td>
<td>315</td>
<td>243</td>
<td>86</td>
<td>1133</td>
<td>951</td>
<td>182</td>
</tr>
<tr>
<td>Pathogen Protein</td>
<td>52</td>
<td>49</td>
<td>4</td>
<td>205</td>
<td>200</td>
<td>5</td>
</tr>
<tr>
<td>Other human biomolecules</td>
<td>15</td>
<td>3</td>
<td>13</td>
<td>75</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>Other pathogen biomolecules</td>
<td>8</td>
<td>7</td>
<td>2</td>
<td>102</td>
<td>99</td>
<td>3</td>
</tr>
</tbody>
</table>

Santos et al, unpublished

Drug Targets Present in Model Organisms

Santos et al, unpublished
Drug Target Classes and Therapeutic Areas

Privileged Target Families

Rhodopsin-like GPCR  
PDBe: 3sn6

Ion channels  
PDBe: 4km

Nuclear receptors  
PDBe: 3e00

Protein kinases  
PDBe: 4foc

22% of drug targets  
33% of small mol drugs

12% of drug targets  
18% of small mol drugs

6% of drug targets  
17% of small mol drugs

13% of drug targets  
2.4% of small mol drugs

Over 53% of all targets and 70% of drugs modulate these four target classes
Molecular Targets of Current Drugs

- Frequency distribution of drug target families follows a log Normal/power law distribution
  - Likely outcome of
    - Building on previous drug prototypes, exploiting subtype selectivity
    - Importance of lead matter
    - Challenging to ‘drug’ new families

Domains within human genome

- Frequency of drugged domains is very skewed from underlying ‘natural’ distribution in human genome
  - Clear empirical evidence of ‘privileged’/druggable domains
Footprint of Target Classes Across Disease

Ligand-gated ion channels

Protein kinases

Nervous system

Cancer and inflammation

Santos *et al*, unpublished

Privileged Target Families

ChEMBL17

Drugs

Santos, unpublished
Clinical Kinome

- 399 Clinical stage human kinase inhibitors
  - 29 Approved small molecule kinase inhibitors
    - 15 -tinib – tyrosine kinase inhibitors
    - 5 -rolimus – mTor inhibitors
    - 4 -rafenib – Raf inhibitors
    - 2 -anib – angiogenesis inhibitors
    - 1 -metinib – met inhibitor
    - 1 -brutinib – Bruton tyrosine kinase inhibitors
    - 1 -dil – Rho kinase inhibitor (Japan only)
  - 38 Phase 3
  - 143 Phase 2
  - 189 Phase 1
    - Phase 1:2 ratio is atypical due to many kinase inhibitor trials being phase 1/2 oncology trials
Kinase Inhibitors in Clinical Development

Overington, Bellis, Al-Lazikani & Wennerberg, unpublished

Kinase Inhibitor Polypharmacology

Adapted from Ghoreschi et al, Nature Immunology 10, 356 - 360 (2009)
Kinase Inhibitor Attrition

Overington, unpublished

USAN to approved fraction! – ~0.2 is long term mean for all drugs across all classes

Overington, unpublished
Kinase Inhibitor Productivity

Overington, unpublished

Cancer Drugs and Targets

~250 FDA approved cancer drugs

166 act through protein targets

115 are ‘targeted’ (67 protein targets)

Updated in canSAR: Bulusu et al, Nucleic Acids Res. 42 D1040-7 (2014)
Cancer Genes

Cancer Genomics and Targets

Genome sequencing

Identifying cancer driver genes

'Mountains'

'Hills'

Genes

Different studies

Cancer Targets

583 cancer genes

564

19

48

67 cancer drug targets

Al-Lazikani et al, unpublished

Genomic Data Integration

http://cansar.icr.ac.uk

Drug annotated target networks

Network environment profiles

Mutation profiles

Drug activities

Audience Question

What will the future of drug targets be focused on?
• GPCRs
• Nuclear Receptors
• Ion Channels
• Enzymes
• Non-Enzymes

Centre for Therapeutic Target Validation

• Collaboration to pinpoint processes in the human body that impact on disease.
• Public-private initiative:
  – **GSK**: expertise in disease biology and translational medicine
  – **EMBL-EBI**: expertise in life science data integration and analysis
  – Wellcome Trust Sanger Institute: expertise in the role of genetics in disease
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Institute of Cancer Research
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Paul Workman

FiMM, Helsinki
Krister Wennerberg

University of Dundee
Andrew Hopkins

http://chembl.blogspot.com

2014 Drug Discovery Series:
Session 2: Primer in Drug Target Classes

Dr. Molly Schmid
Tech Coast Angels

Dr. John P. Overington
EMBL-EBI

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