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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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“Detecting Human Exposure to Environmental Toxins”
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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

dr. Molly Schmid
Tech Coast Angels

Dr. John P. Overington
EMBL-EBI

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Different Types of Drugs

Santos et al, unpublished

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
Assay Organism Data

Drug Approvals
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, J01XX 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>J01X Steroid antibiotics</td>
<td>Ribosome 70S ribosome- EF-G complex</td>
<td>Riboprotein</td>
<td>1</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>J01C Bactams</td>
<td>Beta-lactamases</td>
<td>Protein</td>
<td>2</td>
</tr>
<tr>
<td>J01E Trimethoprim</td>
<td>DHFR</td>
<td>Protein</td>
<td>3</td>
</tr>
<tr>
<td>J01F Sulphonamides, J04A Aminosalicylic acid, J04AB Dapsone, aldesulfone</td>
<td>Dihydropteraate synthase</td>
<td>Protein</td>
<td>23</td>
</tr>
<tr>
<td>J01I Quinolones</td>
<td>Topoisomerase II</td>
<td>Protein</td>
<td>27</td>
</tr>
<tr>
<td>J01A Glycopeptides, J01B Polyoxins, J01D Imidazole derivatives, J01E Nitrofuran derivatives, J01XX Rifmoins, chloroform, methenamine, mandelic acid, nimodipine, diapenepin, bacinaxin, J04AB Minomamide, delamanid, J01X Chloramphenicol</td>
<td>-</td>
<td>-</td>
<td>22</td>
</tr>
<tr>
<td>J01X Fosfomycin</td>
<td>UDP-N-acetylmuramoyl peptidoglycan transferase</td>
<td>Protein</td>
<td>1</td>
</tr>
<tr>
<td>J04AB Cylclosine, J04AK Terizidone</td>
<td>Alanine racemase + D-Ala- D-Ala ligase</td>
<td>Protein</td>
<td>2</td>
</tr>
<tr>
<td>J04AB Rifampicin derivatives</td>
<td>DNA-dependent RNA polymerase</td>
<td>Protein</td>
<td>4</td>
</tr>
<tr>
<td>J04AC Isoniazid, J04AD Thiocarbamide derivatives</td>
<td>Enoyl-acyl carrier protein reductase</td>
<td>Protein</td>
<td>4</td>
</tr>
<tr>
<td>J04AE Ethambutol</td>
<td>Arabosyltransferase</td>
<td>Protein</td>
<td>1</td>
</tr>
<tr>
<td>J04AE Pyrazinamide</td>
<td>Fatty Acid Synthase I</td>
<td>Protein</td>
<td>1</td>
</tr>
<tr>
<td>J04AE Bedaquiline</td>
<td>ATP Synthase</td>
<td>Protein</td>
<td>1</td>
</tr>
</tbody>
</table>

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

Approved Tetracycline Structures

demeclocycline
doxycycline
chlortetracycline
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>Total targets</th>
<th>Small-molecule drug targets</th>
<th>Biotherapeutic drug target</th>
<th>Total drugs</th>
<th>Small molecules</th>
<th>Biotherapeutics</th>
</tr>
</thead>
<tbody>
<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
22% of drug targets
33% of small mol drugs

Ion channels
PDBe: 4kfm
12% of drug targets
18% of small mol drugs

Nuclear receptors
PDBe: 3e00
6% of drug targets
17% of small mol drugs

Protein kinases
PDBe: 4foc
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

<table>
<thead>
<tr>
<th>Kinase Inhibitor</th>
<th>US Launched</th>
<th>Off-label Indication</th>
<th>ATC Code</th>
<th>Market Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tofacitinib</td>
<td>Yes</td>
<td>Arthritis</td>
<td>M7000C</td>
<td>Xeljanz</td>
</tr>
<tr>
<td>Tozasertib</td>
<td>No</td>
<td>Arthritis</td>
<td>M7000C</td>
<td></td>
</tr>
<tr>
<td>Lapatinib</td>
<td>Yes</td>
<td>Breast cancer</td>
<td>M0170E</td>
<td>Perjeta</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>Yes</td>
<td>Non-small cell lung cancer</td>
<td>M0170E</td>
<td>Iressa</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>Yes</td>
<td>Non-small cell lung cancer</td>
<td>M0170E</td>
<td>Tarceva</td>
</tr>
<tr>
<td>Staurosporine</td>
<td>No</td>
<td>No trials</td>
<td>N0180D</td>
<td></td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Yes</td>
<td>Renal cell cancer</td>
<td>N0180D</td>
<td>Sutent</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Yes</td>
<td>Hepatocellular cancer</td>
<td>N0180D</td>
<td>Sorafenib</td>
</tr>
<tr>
<td>Imatinib</td>
<td>Yes</td>
<td>Chronic myelogenous leukemia</td>
<td>N0180D</td>
<td>Gleevec</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>Yes</td>
<td>Non-small cell lung cancer</td>
<td>N0180D</td>
<td>Sprycel</td>
</tr>
</tbody>
</table>


---

## Kinase Inhibitor Polypharmacology

- Staurosporine (no trials)
- Sunitinib
- Sorafenib
- Imatinib
- Dasatinib

- Erlotinib
- Gefitinib
- Lapatinib
- Tofacitinib
- Tozasertib (Ph. II)

US launched

Kinase Inhibitor Attrition

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
115 are ‘targeted’ (67 protein targets)
166 act through protein targets

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

Cancer Genome Landscapes

Review
Nature Reviews Cancer 4, 177-183 (March 2004) | doi:10.1038/nrc1299
A census of human cancer genes
P. Andrew Futreal, Lachlan Coin, Mhairi Marshall, Thomas Down, Timothy Hubbard, Richard Wooster, Nazneen Rahman & Michael R. Stratton

Discovery and saturation analysis of cancer genes across 21 tumour types
Michael S. Lawrence, Peter Stojanov, Craig H. Mermel, James T. Robinson, Lev A. Garney, Todd R. Golub, Matthew Meyerson, Stacey B. Gabriel, Eric S. Lander & Gad Getz

Cancer Genomics and Targets

Genome sequencing → Identifying cancer driver genes

Mountains

Hills

\[ \begin{align*}
58 & 127 \\
138 & \\
513 & \\
60 & 10 \\
9 & 11 \\
385 & \\
1 & \\
27 & \\
60 & 127 \\
385 & 513 \\
138 & \\
60 & 58 & 50 & 10 \\
127 & TCGA
\end{align*} \]

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

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
Acknowledgements

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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

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