

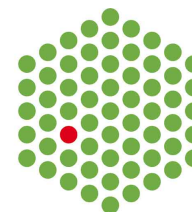
ChEMBL: The Organization of Drug Discovery Data

4th Summer School in Chemoinformatics
Strasbourg

John P. Overington
25th June 2014

wellcometrust

EMBL





DE QUOI T'OCCUPES TU EXACTEMENT ?

DE LA RÉIFICATION

NON, JE ME PROMÈNE. PRINCIPALEMENT JE ME PROMÈNE.

JE VOIS, C'EST UN TRAVAIL TRÈS SÉRIEUX, AVEC DE GROS LIVRES ET BEAUCOUP DE PAPIERS SUR UNE GRANDE TABLE.

ChEMBL – Data for Drug Discovery

1. Scientific facts

1102 | J. Med. Chem. 2003, 45, 3412-3423

Design of Selective Thrombin Inhibitors Based on the (R)-Phe-Pro-Arg Sequence

Rita C. Dalbó, Stuart M. Ashe,¹ Alan B. Smith,² Paul V. Filds,² Edward Hawthwood,¹ Stanley J. Lipkind,¹ Keith James,¹ Andrew B. McIntyre,¹ Zsolt Oroszlanyi,¹ Richard J. Peeling,¹ and David J. Kemp¹

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Abstract

Protein and selective inhibitors of thrombin were sought based on the (R)-Phe-Pro-Arg sequence. The objective was to generate similar binding interactions to those achieved by potent competitive inhibitors of the arginine type, by introducing the rigid and robust interaction with the catalytic serine function, as well as by stabilizing and forming acid type inhibitors. Improving the substrate interaction by substitution of arginine with a dihydrobenzamide residue provided potent lead 2 ($IC_{50} = 0.37 \text{ nM}$). Through an amide bond, which H-bonds to the active site, we identified a lead 3 ($IC_{50} = 0.17 \text{ nM}$), which is potentiated by the bulky hydrophobic allyl side chain. An iterative program of optimization was followed by 7-aminodipiperidine then gave compound 4, which provided a further gain in selectivity over arginine. However, previous work had shown that these compounds were likely to be hepatotoxic. Lead 3 ($IC_{50} = 0.17 \text{ nM}$ and $IC_{50} = 0.2$), respectively, and further rapid hepatic extraction, presumably by biliary conjugation. Accordingly, both proved short acting when administered intravenously in rats and showed poor activity when given intraduodenally. The aim was to reduce hepatotoxicity below a IC_{50} of 1 nM , which is a previously reported value that had been effectively preventing rapid clearance. It was anticipated that compounds of this type would rely on the active site, specifically the mode of absorption from the gastrointestinal tract. Recent oral absorption studies showed that lead 3 ($IC_{50} = 0.17 \text{ nM}$) was not orally bioavailable. However, it was shown by compound 12. However, in the final analysis, its oral bioavailability proved poor, relative to molecules with similar physicochemical properties derived from argapaptins, consistent with the hypothesis that molecular shape is an additional important determinant of peroral absorption.

Introduction

The search for potent selective and orally active thrombin inhibitors has gathered momentum in recent years. Thrombin is the last in a cascade of proteolytic plasma serine proteases, which by stabilizing the open conformation of fibrin, activates TPA and increasing fibrinolysis. Thrombin is also a key enzyme in the cascade, and in particular thrombin has been an attractive target for their crucial role in providing supraphysiological therapy by increasing fibrinolytic activity in acute myocardial infarction and stroke. Additionally, by keeping molecular weight small, the opportunity exists for obtaining oral activity.

Two small molecular weight inhibitor types are emerging as interesting alternatives to the larger thrombin inhibitors. The first is the peptide type, which is small and orally bioavailable. The second is the non-peptide type, which is small and orally bioavailable. The first is the peptide type, which is small and orally bioavailable. The second is the non-peptide type, which is small and orally bioavailable.

Correspondence should be addressed to Prof. David J. Kemp, Pfizer Global Research and Development, Sandwich, Kent CT11 9NA, United Kingdom. E-mail: david.j.kemp@pfizer.com

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3. Insight, tools and resources for translational drug discovery

ChEMBL - OPEN ACCESS MEDICAL CHEMISTRY DATA

ChEMBL is the largest public domain repository of small molecule bioactive compounds. It contains over 20 million structures and is continuously growing.

ChEMBL is a free, open access, online database of small molecule bioactive compounds. It contains over 20 million structures and is continuously growing.

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The molecular pharmacists

Discovering new drugs is a complex and costly process. It involves the identification of potential targets, the synthesis of compounds, and the testing of those compounds in cells and animals.

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nature SCHISTOSOME GENOMICS

Whole genome sequencing of the parasitic flatworm *Schistosoma mansoni* has revealed a wealth of new genes and pathways, providing insights into the biology of this major human pathogen.

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Rosetta

Rosetta is a protein structure prediction software package that uses a combination of physics-based and knowledge-based energy functions to predict the structure of a protein from its amino acid sequence.

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>Thrombin

MAIIVGQLPGCLALALCLVWVAVNTLEEVKGNLRECEVETCS
 TEAEALASLAIQVAVKVIYKIAKPELHPTVQVAGDGLKPLP
 YRYKPHKINSTINPFDADQKPKIIVYKPVQDQVYVAFVFN
 SGGVSLPKIPFLKPEKSIDHTYELDKETDKYQVFNFRNCR
 SSSDGGLRVYVYVAGVPPDFQVYKQKQKQYQVFNFRNCR
 SEAGDGLRFLPEKSIDHTYELDKETDKYQVFNFRNCR
 SEAWLFAANCLIPPKVRFVYVYVAGVPPDFQVYKQKQYQV
 LMLKLRVYVYVYVYVYVYVYVYVYVYVYVYVYVYVYVYV
 HVEVPKCKSTRIIRIDMFCRITFVYVYVYVYVYVYVYVYV
 RDGKIVYVYVYVYVYVYVYVYVYVYVYVYVYVYVYVYVY

NC1=CC=C(C=C1)N2C(=O)N(C2)C(=O)O

Compound

$K_i = 4.5 \text{ nM}$

Bioactivity data

APTT = 11 min.

Assay/Target

Design of Novel Thrombin Inhibitors

Journal of Medicinal Chemistry, 2003, Vol. 45, No. 10, 1895

Protein and selective inhibitors of thrombin were sought based on the (R)-Phe-Pro-Arg sequence. The objective was to generate similar binding interactions to those achieved by potent competitive inhibitors of the arginine type, by introducing the rigid and robust interaction with the catalytic serine function, as well as by stabilizing and forming acid type inhibitors. Improving the substrate interaction by substitution of arginine with a dihydrobenzamide residue provided potent lead 2 ($IC_{50} = 0.37 \text{ nM}$). Through an amide bond, which H-bonds to the active site, we identified a lead 3 ($IC_{50} = 0.17 \text{ nM}$), which is potentiated by the bulky hydrophobic allyl side chain. An iterative program of optimization was followed by 7-aminodipiperidine then gave compound 4, which provided a further gain in selectivity over arginine. However, previous work had shown that these compounds were likely to be hepatotoxic. Lead 3 ($IC_{50} = 0.17 \text{ nM}$ and $IC_{50} = 0.2$), respectively, and further rapid hepatic extraction, presumably by biliary conjugation. Accordingly, both proved short acting when administered intravenously in rats and showed poor activity when given intraduodenally. The aim was to reduce hepatotoxicity below a IC_{50} of 1 nM , which is a previously reported value that had been effectively preventing rapid clearance. It was anticipated that compounds of this type would rely on the active site, specifically the mode of absorption from the gastrointestinal tract. Recent oral absorption studies showed that lead 3 ($IC_{50} = 0.17 \text{ nM}$) was not orally bioavailable. However, it was shown by compound 12. However, in the final analysis, its oral bioavailability proved poor, relative to molecules with similar physicochemical properties derived from argapaptins, consistent with the hypothesis that molecular shape is an additional important determinant of peroral absorption.

Supporting Information Available: X-ray costructure of thrombin with compound 12 is available from the Cambridge Structural Database (CCDC 181143). Supporting Information is available on the WWW under <http://www.interscience.wiley.com/jpages/0893-2247/suppmat>.

2. Organization, curation and standardization of pharmacology data

The screenshot displays the ChEMBL website interface. The top navigation bar includes 'ChEMBL' and 'wellcome trust' logos. Below the navigation bar, there are search options for 'Compounds', 'Targets', 'Assays', and 'Documents'. The main content area is divided into 'Ligand Search', 'Target Search', 'Browse Targets', 'Browse Drugs', 'Browse Drug Targets', 'Drug Approvals', and 'About'. A 'List Search' section is visible on the right, with options for 'SMILES Search', 'ChEMBL ID Search', and 'Keyword Search'. Below this, there is a 'Biologicals Blast Search' section. The bottom part of the screenshot shows a table of drug targets with columns for Molecule, Molecule Type, First Approval, ATC Code, USAN Stem, Mechanism of Action, Target Name, Action Type, Organism, Target Type, Binding Site Name, and Mechanism Refs.

Molecule	Molecule Type	First Approval	ATC Code	USAN Stem	Mechanism of Action	Target Name	Action Type	Organism	Target Type	Binding Site Name	Mechanism Refs
	Small molecule	2013	A10BH04	-gliptin	Dipeptidyl peptidase IV inhibitor	Dipeptidyl peptidase IV	INHIBITOR	Homo sapiens	SINGLE PROTEIN		DailyMed
	Small molecule	2013		-rafenib	Serine/threonine-protein kinase B-raf inhibitor	Serine/threonine-protein kinase B-raf	INHIBITOR	Homo sapiens	SINGLE PROTEIN		DailyMed
	Small molecule	2013			Kelch-like ECH-associated protein 1 inhibitor	Kelch-like ECH-associated protein 1	INHIBITOR	Homo sapiens	SINGLE PROTEIN		DailyMed, PubMed, PubMed
	Small molecule	2013	A16AX09		Glutamine chelating agent	Glutamine	CHELATING AGENT	Homo sapiens	SMALL MOLECULE		DailyMed
	Oligonucleotide	2013	C10AX11	-rsen	Apo-B 100 mRNA antisense inhibitor	Apo-B 100 mRNA	ANTISENSE INHIBITOR	Homo sapiens	NUCLEIC-ACID		DailyMed

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

MyChEMBL - 8GB FOSS!



myChEMBL LaunchPad

Welcome to the myChEMBL LaunchPad, providing access to all resources distributed with the myChEMBL virtual machine.

Web Interface

This web interface provides quick access to the myChEMBL data without any prior knowledge of SQL or RDKit.

phpPgAdmin Console

Use the phpPgAdmin console to explore the myChEMBL PostgreSQL database and run SQL queries (**user:** mychembl, **password:** read).

Web Services

Access to a local version of the official ChEMBL Web Services, which connect to the myChEMBL PostgreSQL database.

IPython Notebooks

A selection of programmatic tutorials written in Python and presented using interactive IPython Notebooks.

KNIME Integration

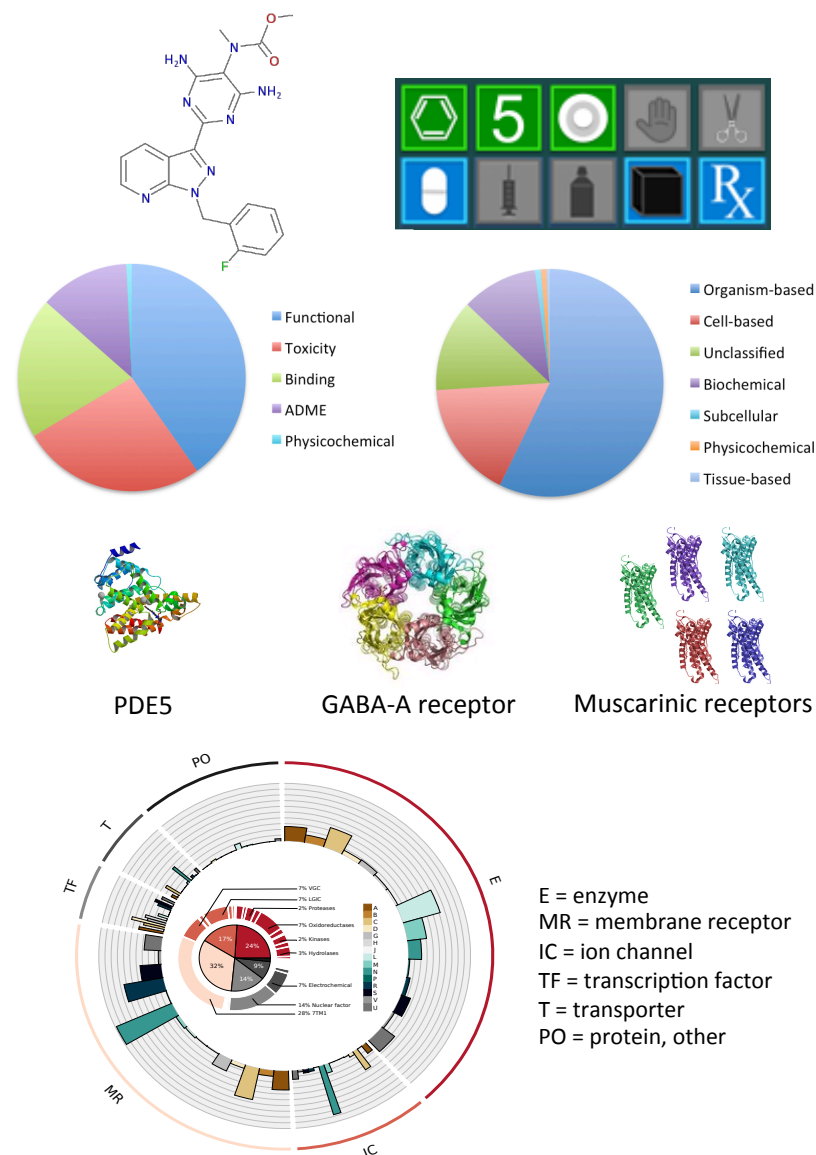
Learn how to connect the KNIME workbench to myChEMBL and also how to start processing ChEMBL data within a workflow environment.

More Information

For more details on the myChEMBL project, including background, acknowledgements and references.

ChEMBL - Added Value in Curation

- Annotation of approved drug and USAN information
 - Small molecules and biotherapeutics
 - Human and pathogen targets
 - Direct molecular targets
 - Mode of action assigned
- Standardization and correction of chemical structures
- Classification of assays
 - assay type, format, organisms, cell-lines
- Standardization and validation of assay endpoints
 - unit conversion, identification of errors, duplicates
- Detailed representation of molecular targets
 - single proteins vs. protein complexes, protein-protein interactions *etc.* and protein family classification



Spreadsheet Views

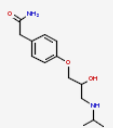
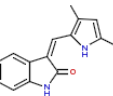
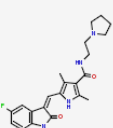
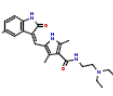
EMBL-EBI Services Research Training About us

ChEMBL wellcome trust

Search ChEMBL... Compounds Targets Assays Documents Activity Source Filter

ChEMBL Compound Search Results: 106 Hits Please select...

10 records per page Show / hide columns

Compound	Synonyms	Max Phase	Parent Mol Weight	ALogP	PSA	HBA	HBD	#RO5 Vio.	Med Chem Friendly	QED Weighted	
 CHEMBL24	Atenolol Tenormin ICI-86082 SID855957 Esatenolol SID90340978	4	266.34	67	84.58	4	3	0	Y	.65	<input checked="" type="checkbox"/>
 CHEMBL276711	SU-5416 SID50107014 SID49674962 Semaxinib Semaxanib	0	238.28	2.75	44.89	1	2	0	Y	.74	<input checked="" type="checkbox"/>
 CHEMBL13608	Toceranib PHA-291639 PHA-291639E Toceranib Phosphate	0	396.46	2.76	77.23	3	3	0	Y	.68	<input checked="" type="checkbox"/>
 CHEMBL535	SU-11248 Sutent Sunitinib SID26758053 SID50100120 Sunitinib Malate	4	398.47	3	77.23	3	3	0	Y	.63	<input checked="" type="checkbox"/>

ChEMBL Statistics

- DB: ChEMBL_18
- Targets: 9,414
- Compound records: 1,566,998
- Distinct compounds: 1,359,508
- Activities: 12,419,715
- Publications: 53,298
- [Release Notes](#)

ChEMBL Blog

- [New Drug Approvals 2014 - Pt. III - Droxidopa \(Northern™\)](#)
- [New Drug Approvals 2013 - Pt. XXX - Umeclidinium bromide and Vilanterol \(Anoro Ellipta™\)](#)

Target Class Data

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EBI > Databases > Small Molecules > ChEMBL Database > Target Search > Target Classification Hierarchy

Search ChEMBL... Compounds Targets Assays Documents Activity Source Filter

Ligand Search Target Search **Browse Targets** Browse Drugs Browse Drug Targets Drug Approvals About

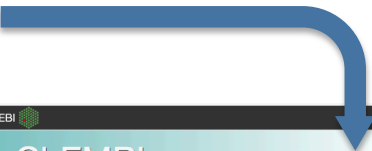
Protein Target Tree Taxonomy Tree

* Click arrows or use keyboard arrows (on selected items) to navigate tree

Clear Selections Select All Collapse All Open All Fetch selected targets Search Tree: Search

[Protein Kinases](#) [GPCRs \(Family A\)](#) [Ligand Gated Ion Channels](#) [Voltage Gated Ion Channels](#) [Nuclear Hormone Receptors](#)

- Enzyme (3779)
 - Kinase (670)
 - Protein Kinase (648)
 - Protein kinase regulatory subunit (35)
 - Protease (446)
 - Serine protease (187)
 - Metallo protease (128)
 - Cysteine protease (77)
 - Aspartic protease (37)
 - Threonine protease (9)
 - Protease unclassified (1)
 - Protease inhibitor (1)
 - Oxidoreductase (70)
 - Phosphodiesterase (76)
 - Hydrolase (66)
 - Phosphatase (70)
 - Protein Phosphatase (70)
 - Cytochrome P450 (57)
 - Lyase (29)
 - Transferase (28)
 - Isomerase (21)
 - Ligase (5)
 - Aminoacyltransferase (1)
- Membrane receptor (866)
- Ion channel (548)
- Transporter (240)
- Transcription factor (146)
- Adhesion (16)
- Auxiliary transport protein (36)
- Epigenetic regulator (104)
- Secreted protein (62)
- Structural protein (38)
- Surface antigen (28)
- Other cytosolic protein (231)
- Other membrane protein (20)
- Other nuclear protein (16)
- Unclassified protein (1381)



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ChEMBL wellcome trust

Search ChEMBL... Compounds Targets Assays Documents Activity Source Filter

ChEMBL Target Search Results: 835 Please select...

10 records per page Show / hide columns

ChEMBL ID	Preferred Name	UniProt Accession	Target Type	Organism	Compounds	Bioactivities	
ChEMBL6191	SPS1/STE20-related protein kinase YSK4	Q66JN5	SINGLE PROTEIN	Homo sapiens	89	96	<input checked="" type="checkbox"/>
ChEMBL6186	Serine/threonine-protein kinase Sgk3	Q86B51	SINGLE PROTEIN	Homo sapiens	640	1181	<input checked="" type="checkbox"/>
ChEMBL6167	Serine/threonine-protein kinase LATS1	Q95835	SINGLE PROTEIN	Homo sapiens	95	133	<input checked="" type="checkbox"/>
ChEMBL6166	Mitogen-activated protein kinase kinase kinase kinase 4	Q95819	SINGLE PROTEIN	Homo sapiens	1556	2018	<input checked="" type="checkbox"/>
ChEMBL6182	Serine/threonine-protein kinase PPTAIRE-1	Q94921	SINGLE PROTEIN	Homo sapiens	110	148	<input checked="" type="checkbox"/>
ChEMBL6156	Tripeptidyl-peptidase 2	P29144	SINGLE PROTEIN	Homo sapiens	1	1	<input checked="" type="checkbox"/>
ChEMBL6151	Serine/threonine-protein kinase 31	Q98XU1	SINGLE PROTEIN	Homo sapiens	1	1	<input checked="" type="checkbox"/>
ChEMBL6150	Serine/threonine-protein kinase 32A	Q8WU08	SINGLE PROTEIN	Homo sapiens	76	76	<input checked="" type="checkbox"/>
ChEMBL6149	Serine/threonine-protein kinase SIK3	Q9Y2K2	SINGLE PROTEIN	Homo sapiens	84	92	<input checked="" type="checkbox"/>
ChEMBL6144	G protein-coupled receptor kinase 6	P43250	SINGLE PROTEIN	Homo sapiens	548	1087	<input checked="" type="checkbox"/>

Showing 1 to 10 of 835 entries

-- Previous 1 2 3 4 5 Next --

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- [New Drug Approvals 2013 - Pt. XXX - Umeclidinium bromide and Vilanterol \(Anoro Ellipta™\)](#)

Assay Organism Data

The image displays two screenshots of the ChEMBL website. The top screenshot shows the 'Target Classification Hierarchy' page, where the 'Taxonomy Tree' is selected. A blue arrow points from the 'Plasmodium' node in the tree to the 'ChEMBL Target Search Results' page shown in the bottom screenshot. The bottom screenshot shows the search results for 'ChEMBL Target Search Results: 4649', displaying a table of target data.

ChEMBL Target Classification Hierarchy (Taxonomy Tree):



- Eukaryotes (8126)
 - Mammalia (7314)
 - Primates (4550)
 - Rodentia (2258)
 - Other (506)
 - Viridiplantae (168)
 - Apicomplexa (131)
 - Plasmodium (99)
 - Other (15)
 - Eimeria (9)
 - Cryptosporidium (8)
 - Arthropoda (131)
 - Kinetoplastida (101)
 - Eukaryotes (other) (71)
 - Aves (51)
 - Nematoda (48)
 - Lepidosauria (23)
 - Teleostei (22)
 - Amphibia (20)
 - Echinodermata (15)
 - Platyhelminthes (15)
 - Mollusca (15)
 - other (1)
 - Bacteria (1517)
 - Fungi (503)
 - Viruses (372)
 - Archaea (8)
 - Unclassified (2)

ChEMBL Target Search Results: 4649

CHEMBL ID	Preferred Name	UniProt Accession	Target Type	Organism	Compounds	Bioactivities	
CHEMBL6198	Aspartic protease PM4	Q60989	SINGLE PROTEIN	Plasmodium vivax	10	12	✓
CHEMBL6197	Transporter	Q7JHP9	SINGLE PROTEIN	Macaca mulatta	67	67	✓
CHEMBL6196	UDP-glucuronosyltransferase 2B4	P06133	SINGLE PROTEIN	Homo sapiens	81	117	✓
CHEMBL6195	Ubiquitin carboxyl-terminal hydrolase isozyme L3	P15374	SINGLE PROTEIN	Homo sapiens	19	23	✓
CHEMBL6191	SPS1/STE20-related protein kinase YSK4	Q56JN5	SINGLE PROTEIN	Homo sapiens	89	96	✓
CHEMBL6190	Voltage-dependent anion-selective channel protein 2	P45880	SINGLE PROTEIN	Homo sapiens	1	1	✓
CHEMBL6189	UDP-glucuronosyltransferase 2B28	Q8BY84	SINGLE PROTEIN	Homo sapiens	8	9	✓
CHEMBL6186	Serine/threonine-protein kinase Sgk3	Q96BR1	SINGLE PROTEIN	Homo sapiens	640	1181	✓
CHEMBL6182	NADP-dependent malic enzyme, mitochondrial	Q16728	SINGLE PROTEIN	Homo sapiens	6	10	✓
CHEMBL6177	NAD kinase	Q95544	SINGLE PROTEIN	Homo sapiens	15	25	✓

Drug Approvals

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Malaria Data

ChEMBL-NTD

Kinase SARfari

GPCR SARfari

DrugEBILITY

Web Services

FAQ

ChEMBL Statistics

- DB: ChEMBL_17
- Targets: 9,356
- Compound records: 1,520,172
- Distinct compounds: 1,324,941
- Activities: 12,077,491
- Publications: 51,277
- [Release Notes](#)

ChEMBL Blog

- [New Drug Approvals 2014 - Pt. III - Droxidopa \(Nothera™\)](#)
- [New Drug Approvals 2013 - Pt. XXX - Umeclidinium bromide and Vilanterol \(Anoro Ellipta™\)](#)

EBI > Databases > Small Molecules > ChEMBL Database > Home

Compounds Targets Assays Documents [Activity Source Filter](#)

Ligand Search
Target Search
Browse Targets
Browse Drugs
Browse Drug Targets
Drug Approvals
About

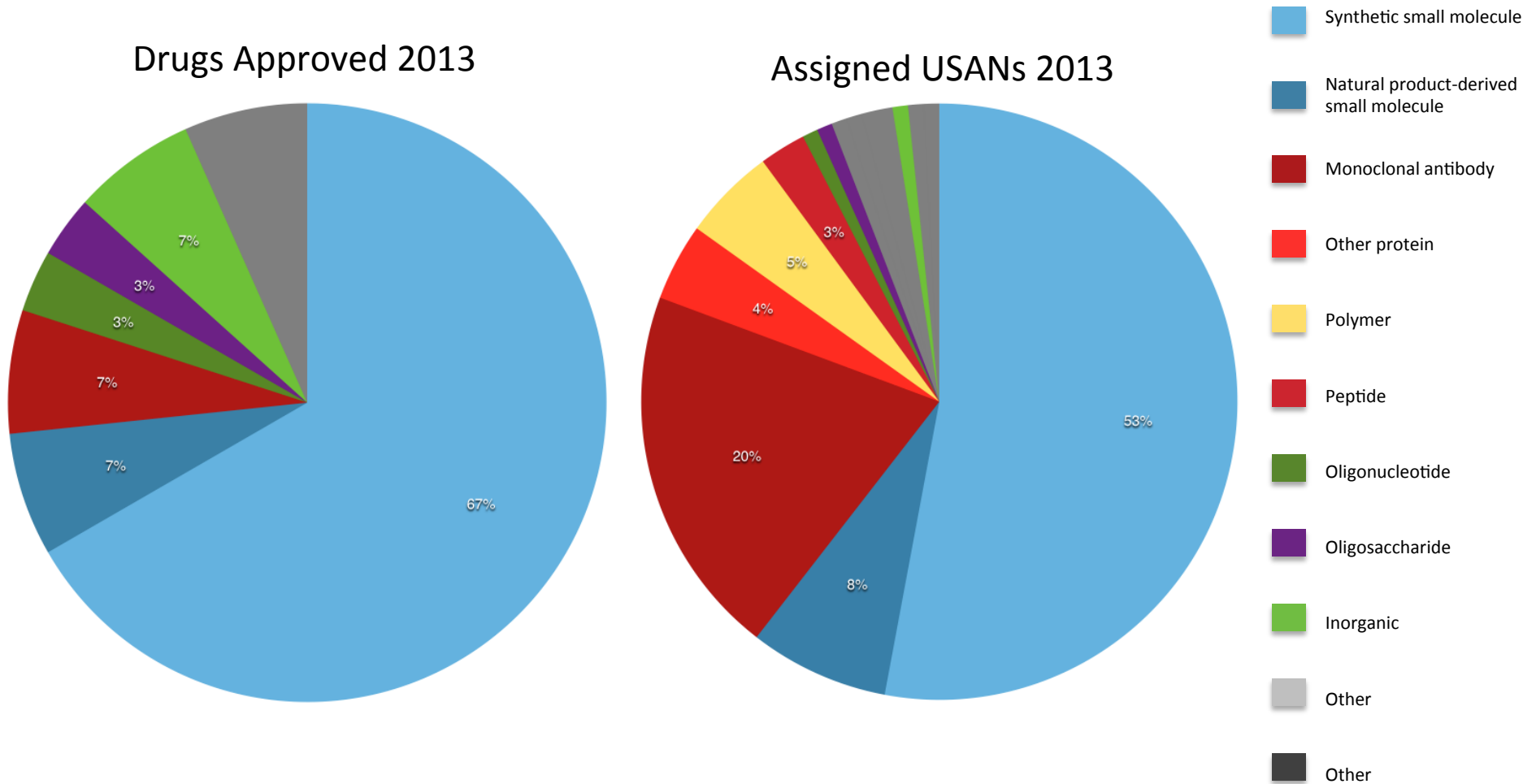
The following table lists US Food and Drug Administration (FDA) drug approvals for New Molecular Entities (NMEs) from 2009 onwards. Links are to the corresponding Drug Approval Monographs on the ChEMBL-og.

Subscribe to the RSS feed to receive new drug approvals [RSS](#)

10 records per page Search: Show / hide columns

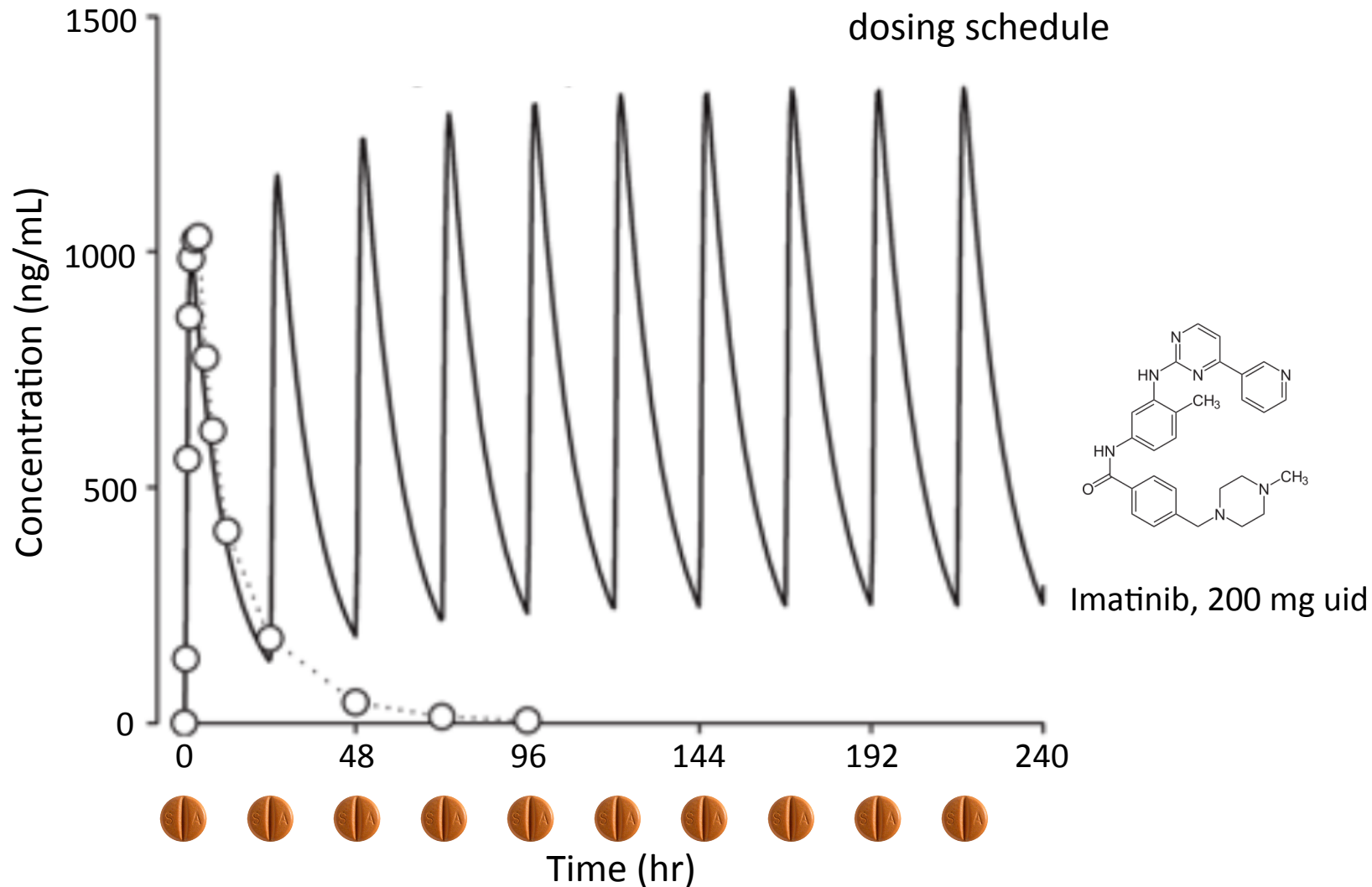
Generic Name	Trade Names	ATC Code	Date of Approval	Drug Monograph	Icon
Afatinib Dimaleate	Gilotrif	L01XE13	2013-07-12	http://chembl.blogspot.co.uk/2013/07/new-drug-approvals-2013-pt-xi-afatinib.html	
Dabrafenib Mesylate	Tafinlar	L01XE23	2013-05-29	http://chembl.blogspot.co.uk/2013/06/new-drug-approvals-2013-pt-ix.html	
Trametinib Dimethyl Sulfoxide	Mekinist	L01XE25	2013-05-29	http://chembl.blogspot.co.uk/2013/06/new-drug-approvals-2013-pt-x-trametinib.html	
Radium Ra 223 Dichloride	Xofigo	V10XX03	2013-05-15	http://chembl.blogspot.co.uk/2013/05/new-drug-approvals-2013-pt-vii-radium.html	
Vilanterol Trifenatate	Breo Ellipta	R03AK10	2013-05-10	http://chembl.blogspot.co.uk/2013/05/new-drug-approvals-2013-pt-viii.html	
Canagliflozin	Invokana	A10BX11	2013-03-29	http://chembl.blogspot.co.uk/2013/04/new-drug-approvals-2013-pt-v.html	
Gadoterate Meglumine	Dotarem	V08CA02	2013-03-20	http://chembl.blogspot.co.uk/2013/05/new-drug-approvals-2013-pt-vi.html	

Different Types of Drugs



Filling The Gaps – Exposure Data

- Large 'tides' of target exposure during dosing schedule



Filling the Gaps – Exposure Data

Citation: Jawhari D, Alzawi M, Ghannam M (2011) Bioequivalence of a New Generic Formulation of Imatinib Mesylate 400mg Tablets Versus Glivec in Healthy Male Adult Volunteers. *J Bioequiv Availab* 3: 161-164. doi:10.4172/jb.100077

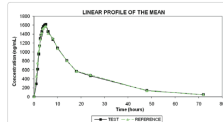


Figure 2: Plasma concentrations of imatinib mesylate 400mg tablets (Test) and glivec (Reference).

within 80% to 125% FDA acceptance range for generic drugs which indicated that Imatinib tablets 400mg and Glivec tablets 400mg are bioequivalent under fed conditions. The pharmacokinetics of the formulations tested was the same and healthy subjects were well tolerated to Imatinib and no major side effects were observed.

Conclusion

Based on statistical results, it can be concluded that both products tested in this study comply with regulatory requirements to be claimed bioequivalent. According to the above, the test product can be considered interchangeable with the reference based on their biopharmaceutical performance. Both products were well tolerated of imatinib included in this study are bioequivalent, and that both products can be considered equally effective and interchangeable in medical practice based on the pharmacokinetic effect.

Acknowledgment

All authors are employees of Hikma Pharmaceuticals PLC, which is the sponsor of the Bioequivalence study for imatinib 400 mg tablets. The authors wish to acknowledge the support of Hikma pharmaceuticals Research and development Department/Oncology section. The authors thank Dr Francisco Centeno Technical Director at Center for Clinical Pharmacology, Hikma S.A., Hospital Basilio Latorre Pinar, Havana, Cuba, Santiago, Chile, 11000, Santiago, Chile, for critical review. Many thanks to Dr. Ayman Abbas for his review.

References

1. Robinson DR, Wu YM, Liu SF (2003) The protein tyrosine kinase family of the human genome. *Oncogene* 19: 5548-57.
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ISSN 0709-0851, an open access journal
Volume 3(7): 161-164 (2011) - 164

Bioequivalence & Research Article

Bioavailability of a New C Tablets Versus Glivec in M Dalia Jawhari, Mahmoud Alzawi and Mahmoud BS: Pharmacy, Jordan

Abstract

Imatinib is a highly selective cost of the drug is prohibitively expensive. The aim of this study was to evaluate the bioequivalence of a new generic formulation of imatinib mesylate 400mg tablets (Test) versus Glivec (Reference) in healthy male volunteers. In a 2-period, 2-sequence, crossover study in accordance with Good Clinical Practice (GCP) guidelines, 12 healthy male volunteers, aged 18 to 45 years, of at least 70 kg or equal to 18.5 and below 30 kg period, a single 400 mg dose of a 12-hour overnight fast. They (3) were separated by at least 14 days period of the study. Hematology of the study. Safety was evaluated. Samples were analyzed employing the analytical range with appropriate adverse events, safety results are parameters of interest for this study. t_{max} were provided for after AUC_{0-80} was used for all statistical tests. t_{max} (20.0%), 3.87 hrs (25.8%), 3.87 hrs (20.0%), 3.10 (10.5%) respectively. The ratio imatinib-400 mg were 90%, 90% and 90% respectively with low RSECV 12.9% for C_{max} , and 8.3% for AUC_{0-80} , and 8.0% for AUC_{0-80} . The results indicated that the products are equivalent and interchangeable according to FDA rulings.

Keywords: Imatinib, Bioequivalence, Glivec, Tyrosine kinase inhibitor

Introduction

Imatinib is the 4-[[4-methyl-1-piperazinyl] methyl]-N-[4-methyl-3-[[[3-(3-pyridinyl)-2-pyrimidinyl] amino] phenyl] benzamide, which is represented by the following structure (Figure 1).

Protein tyrosine kinases participate in signal transduction pathways which regulate cellular processes such as growth, metabolism,

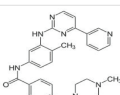


Figure 1:

differentiation, adhesion and apoptosis [1]. Deregulation of protein tyrosine kinase activity has been associated with the pathogenesis of various cancers, including chronic myeloid leukemia (CML) and gastrointestinal stromal tumor (GIST), as well as other proliferative diseases [1].

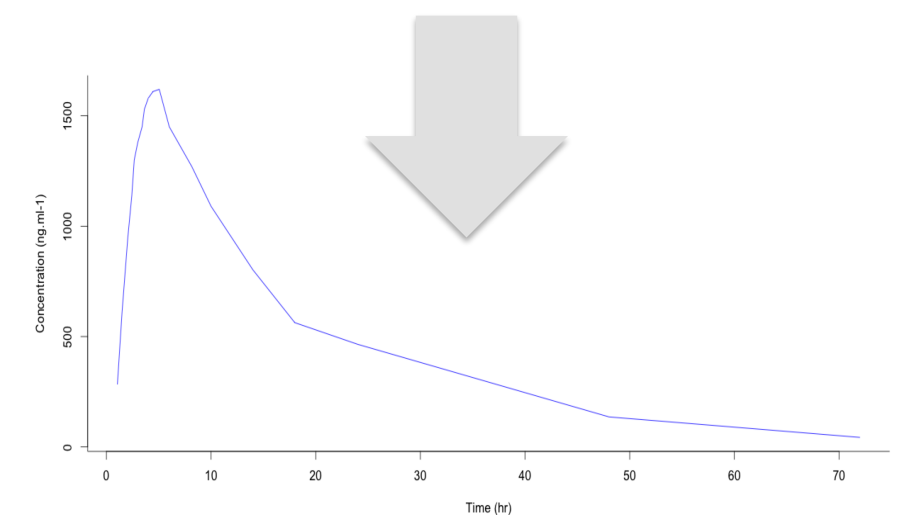
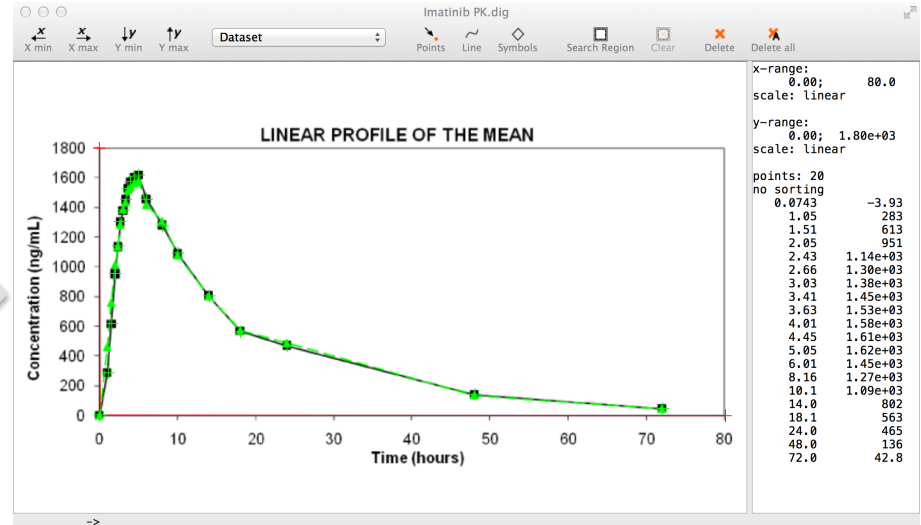
CML is a hematologic stem-cell disorder associated with a specific chromosomal translocation known as the Philadelphia Chromosome (Ph⁺). Ph⁺ is detected in 95% of patients with CML, from which 20% of them have acute lymphocytic leukemia [1]. The molecular consequences of the Ph⁺ translocation is the fusion of the ABL (Abelson leukemia virus) proto-oncogen on chromosome 9 to the Bcr (breakpoint cluster

Corresponding author: Mahmoud Ghannam, Jordan, E-mail: mghannam@em.ordj

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Citation: Jawhari D, Alzawi M, Ghannam M (2011) Bioequivalence of a New Generic Formulation of Imatinib Mesylate 400mg Tablets Versus Glivec in Healthy Male Adult Volunteers. *J Bioequiv Availab* 3: 161-164. doi:10.4172/jb.100077

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Only ~1% of Genome is a Drug Target



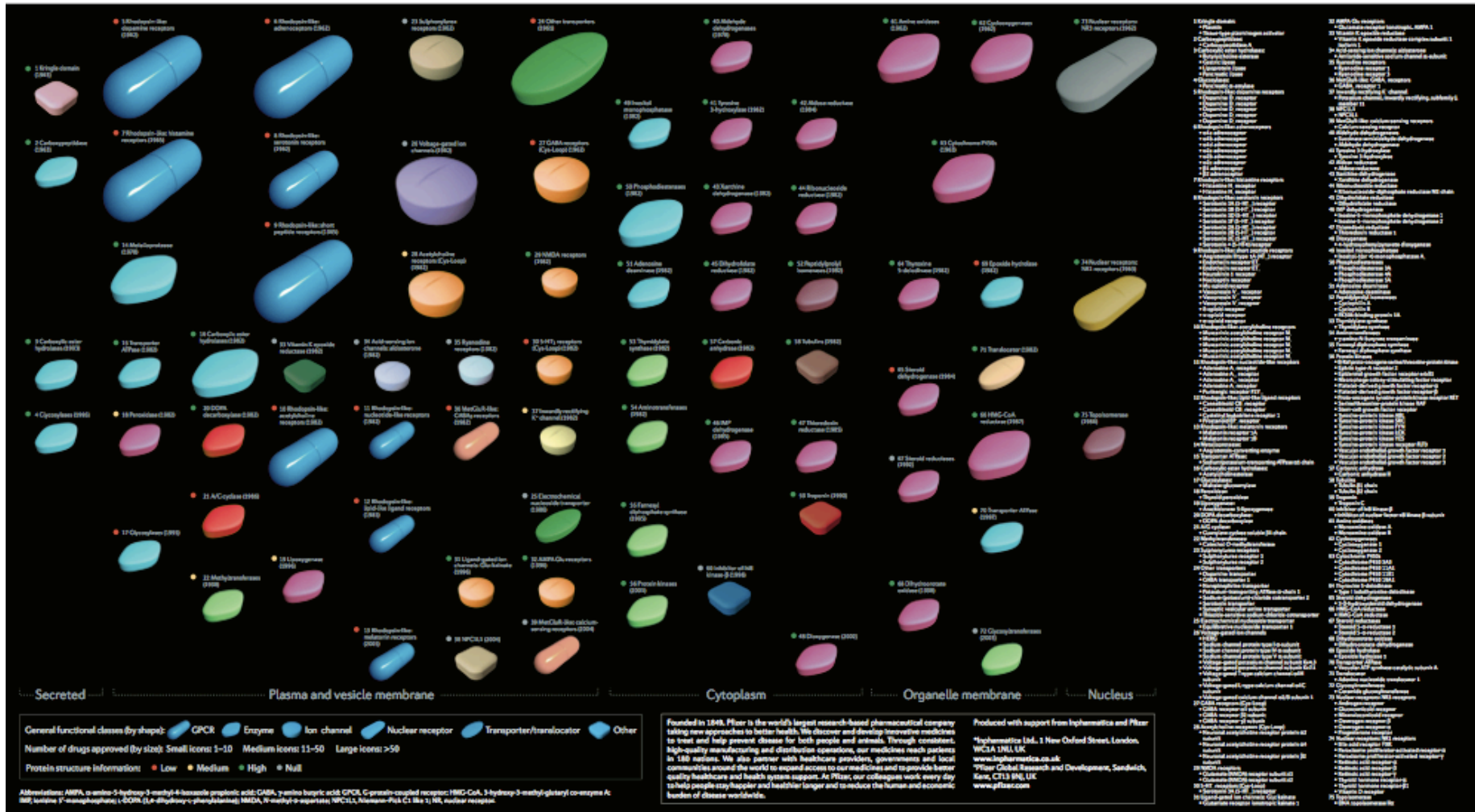
The molecular pharmacopoeia

The human targets of FDA-approved oral drugs

John P. Overington*, Bissan Al Lazikani* and Andrew L. Hopkins†



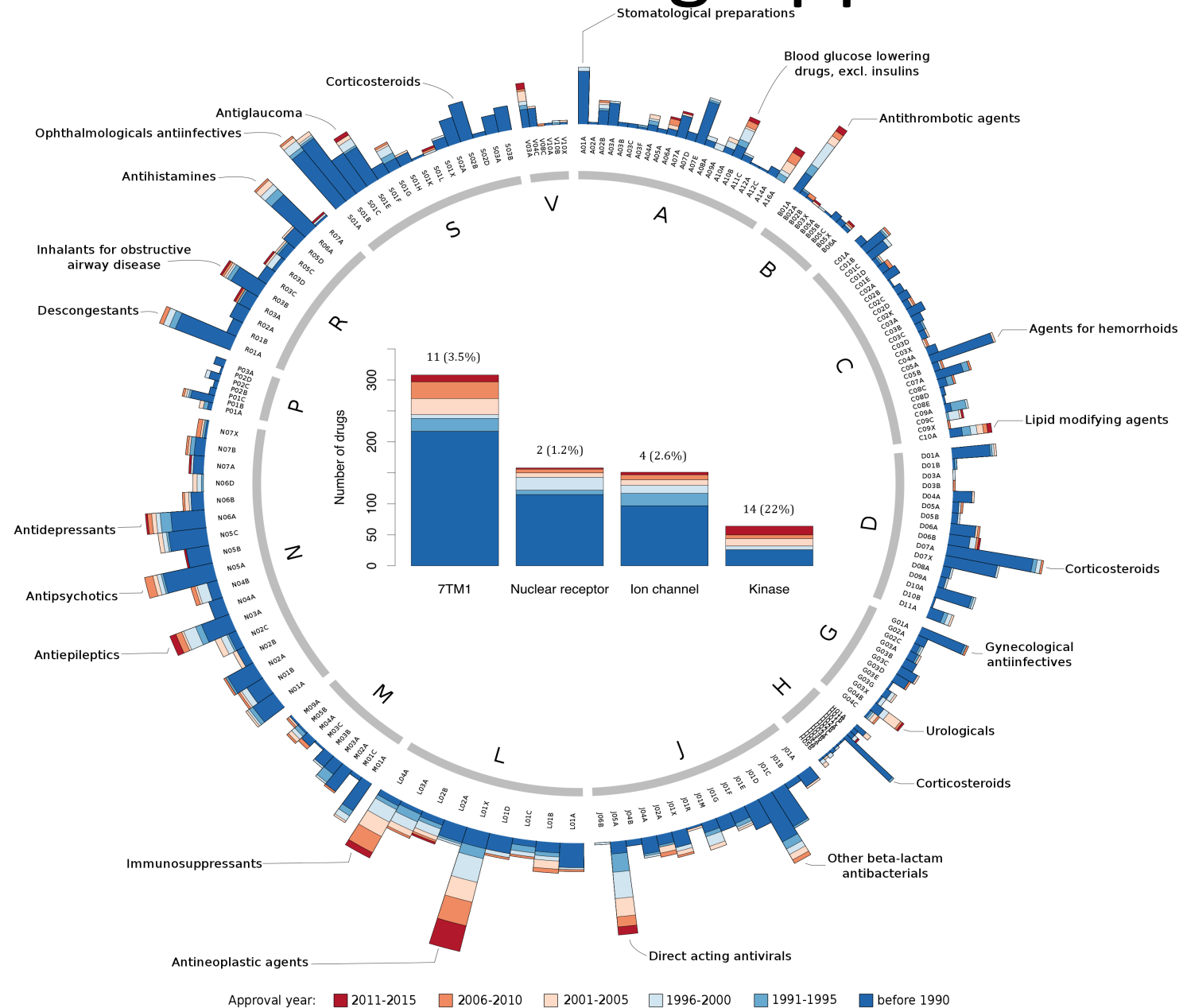
The molecular pharmacopoeia of 186 human protein drug targets for FDA-approved oral drugs. The drug targets are grouped into target subfamilies where there are multiple related drug targets. The size of the icons represents the number of drugs approved for that target or target subfamily. The horizontal axis illustrates the cellular location of a drug target. The vertical axis illustrates an approximate timeline depicting when the first drug for a target or target subfamily was approved (older drug targets are at the top of the chart). The dates next to the targets illustrate the year in which the first USAN (United States Adopted Name) was assigned for the first drug against that target or any target in the subfamily (which usually occurs in the late stages of clinical development). The availability of protein structural information for the target or target subfamily is illustrated by the coloured dot next to the target name. The shapes of the icons represent the general functional classes of drug targets and related groups within a functional class are coloured the same.



Drug Targets and Drugs

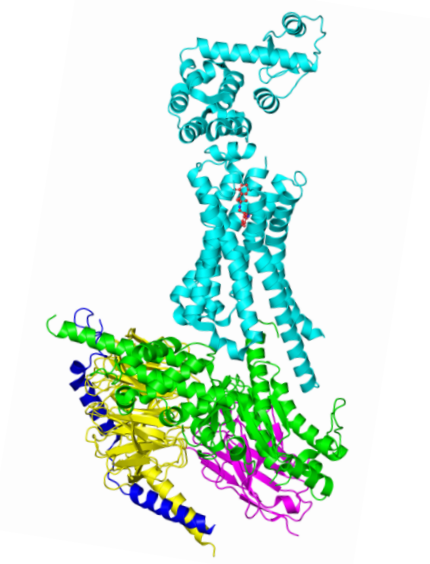
Drug target Class	Targets			Drugs		
	Total targets	Small-molecule drug targets	Biotherapeutic drug target	Total drugs	Small molecules	Biotherapeutics
Human Protein	315	243	86	1133	951	182
Pathogen Protein	52	49	4	205	200	5
Other human biomolecules	15	3	13	75	50	25
Other pathogen biomolecules	8	7	2	102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

Innovation in Drug Approvals



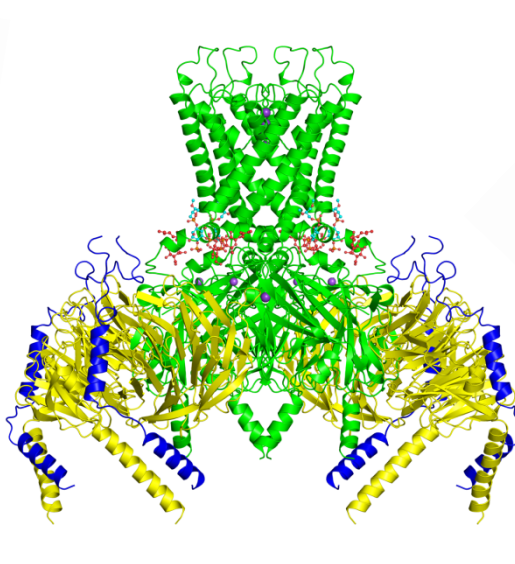
Privileged Target Families

Rhodopsin-like GPCR
PDBe: 3sn6



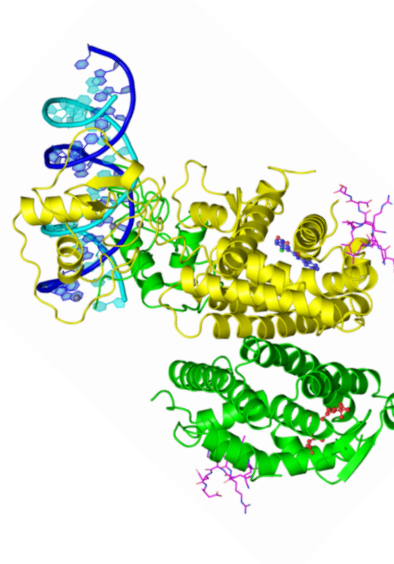
22% of drug targets
33% of small mol drugs

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

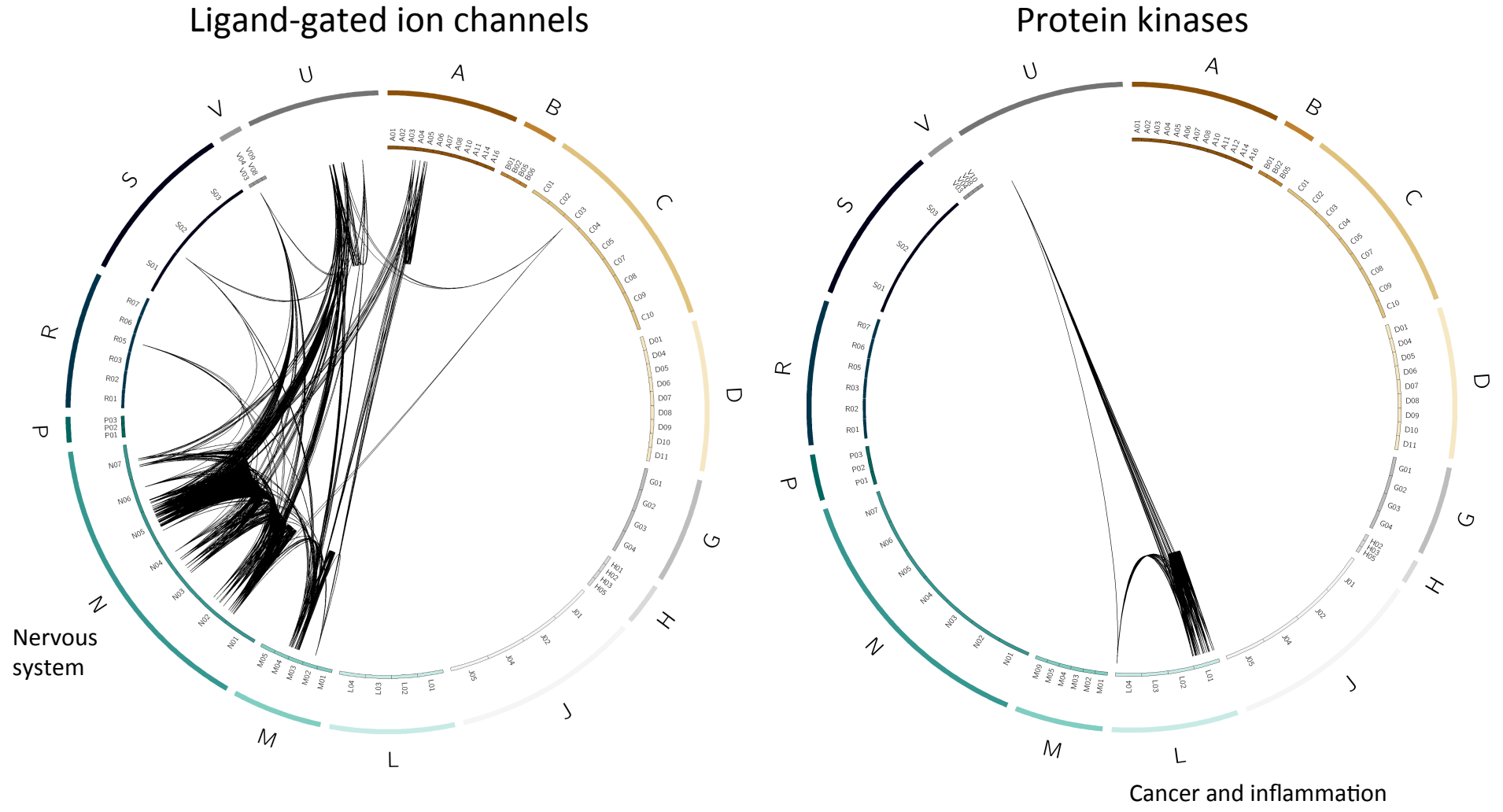
Protein kinases
PDBe: 4foc



13% of drug targets
2.4% of small mol drugs

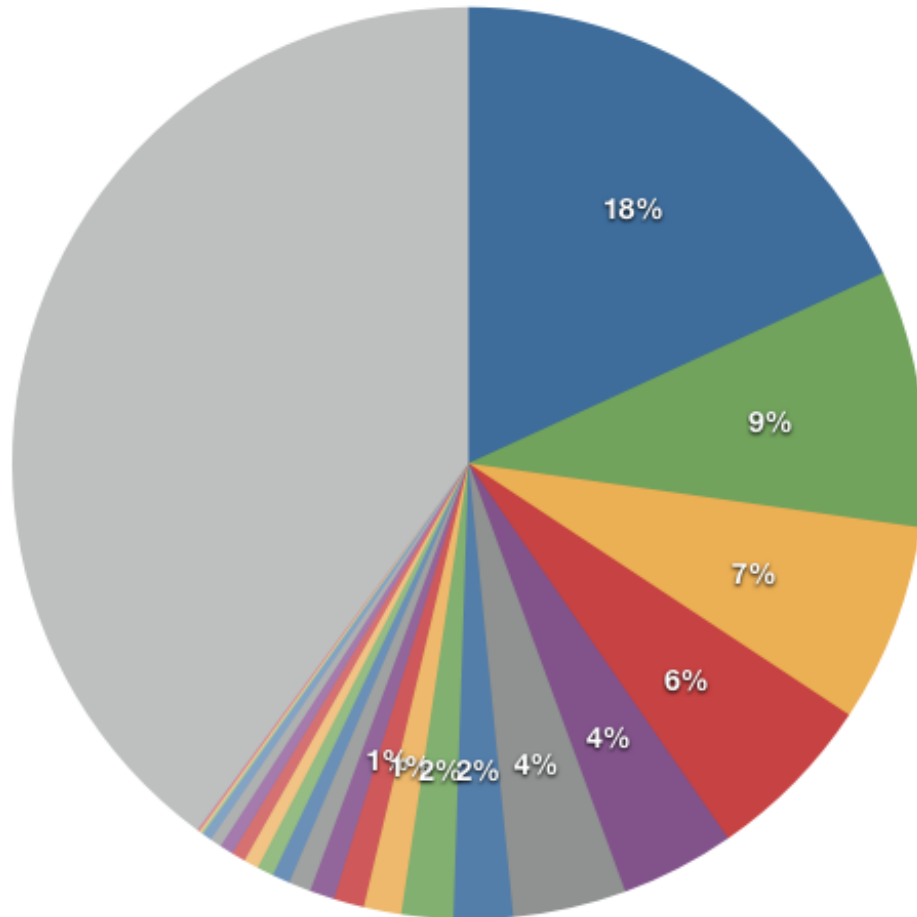
Over 53% of all targets and 70% of drugs modulate these four target classes

Footprint of Target Classes Across Disease

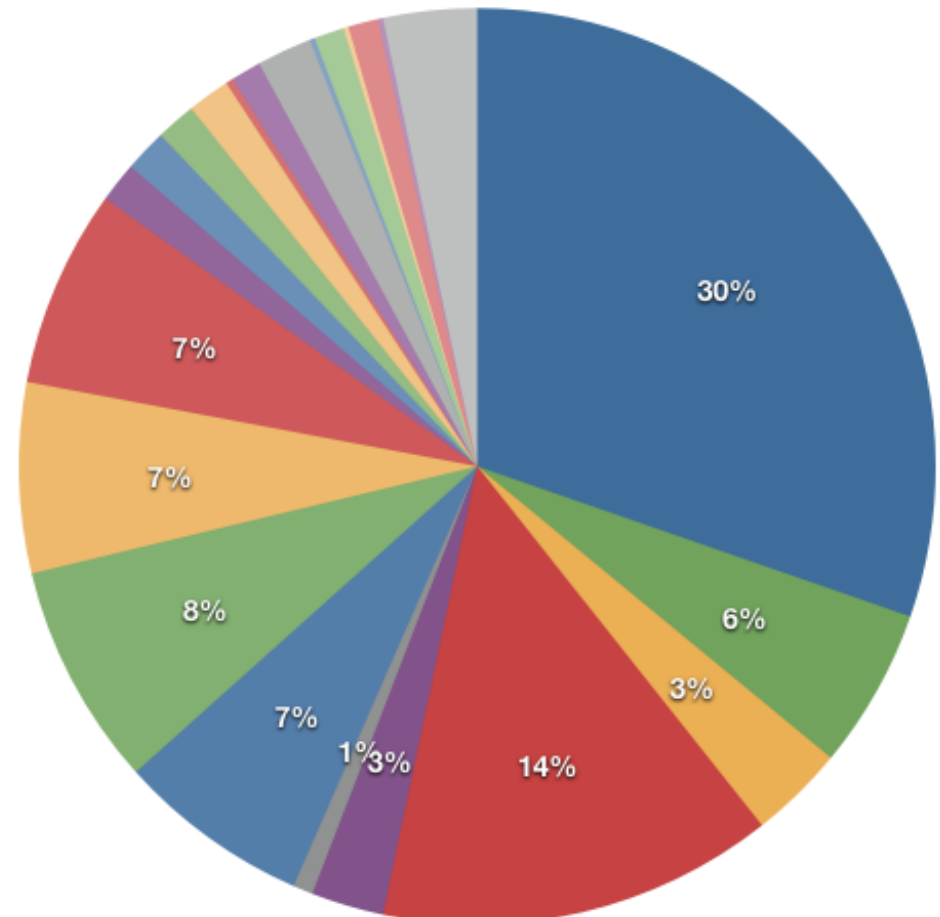


Privileged Target Families

ChEMBL17

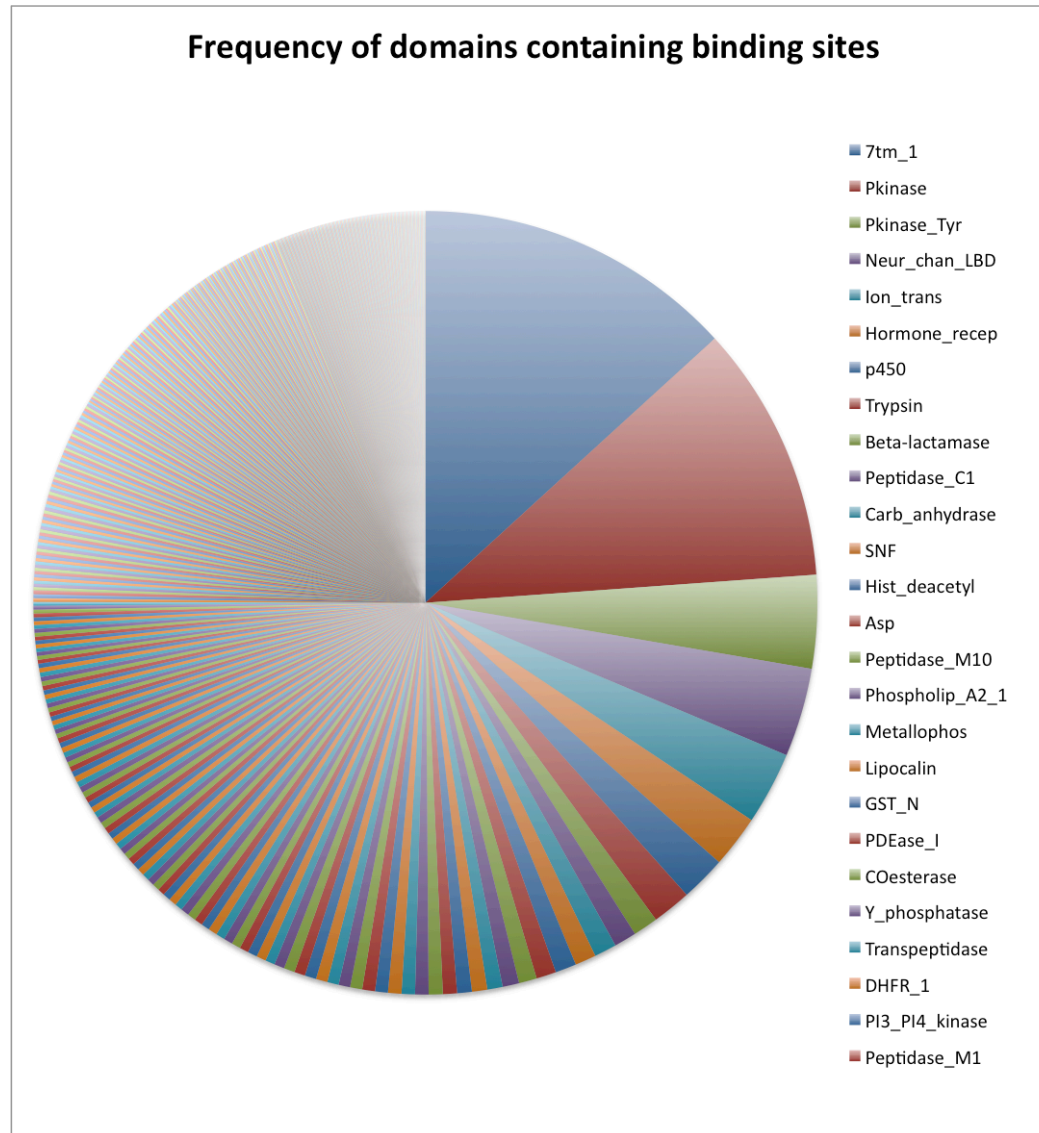


Drugs



- 7TM1
- kinase
- protease
- nuclear receptor
- hydrolase
- CYP450
- VGIC
- redutase
- transporter electrochem
- LGIC
- PDE
- phosphatase
- lyase
- isomerase
- 7TM2
- 7TM3
- NTPase
- transferase
- TRP
- KIR
- TLR
- SUR
- ligase
- other

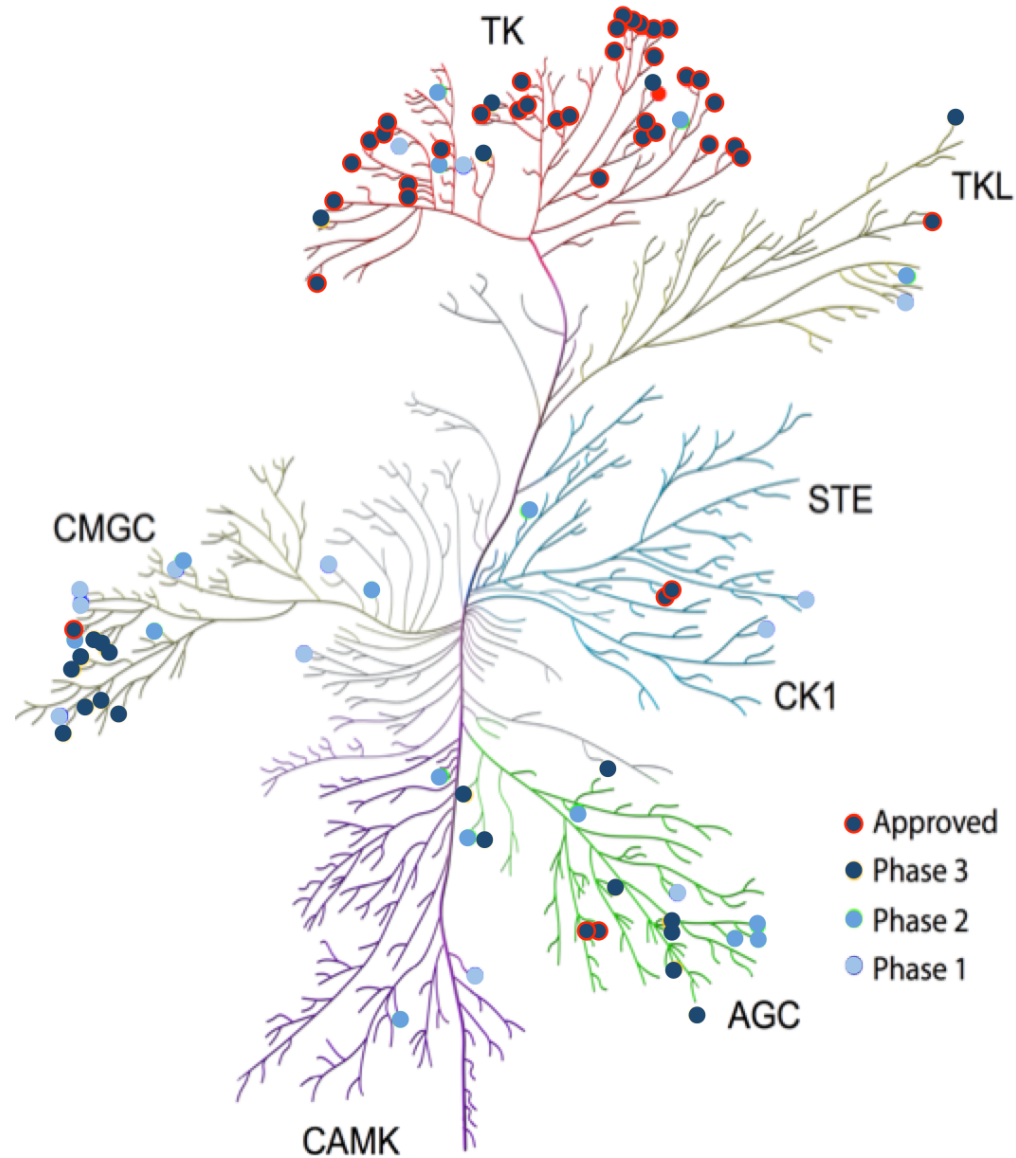
Domain-level Binding Site Annotation



Depleted and Enriched Pfam Domains

Neur_chan_memb	-1.63
zf-C4	-0.94
ANF_receptor	-0.88
SH2	-0.83
Pkinase_C	-0.70
fn3	-0.53
SH3_1	-0.51
Lig_chan	-0.50
C2	-0.50
C1_1	-0.50
Guanylate_cyc	-0.46
HATPase_c	-0.46
I-set	-0.44
adh_short	-0.39
PH	-0.39
Ank	-0.39
.....	
Metallophos	0.35
Phospholip_A2_1	0.38
Peptidase_M10	0.41
Asp	0.45
SNF	0.48
Hist_deacetyl	0.48
Carb_anhydrase	0.50
Peptidase_C1	0.51
Trypsin	0.51
Beta-lactamase	0.57
p450	1.00
Hormone_recep	1.19
Ion_trans	1.66
Neur_chan_LBD	2.02
Pkinase_Tyr	2.12
Pkinase	5.87
7tm_1	7.30

Clinical Kinome



Clinical Kinome

- 399 Clinical stage human kinase inhibitors
 - 31 Approved small molecule kinase inhibitors
 - 17 -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

Kinase inhibitors — Edited

View Zoom 125%

Function Table Chart Text Shape Media Comment

Share Tips

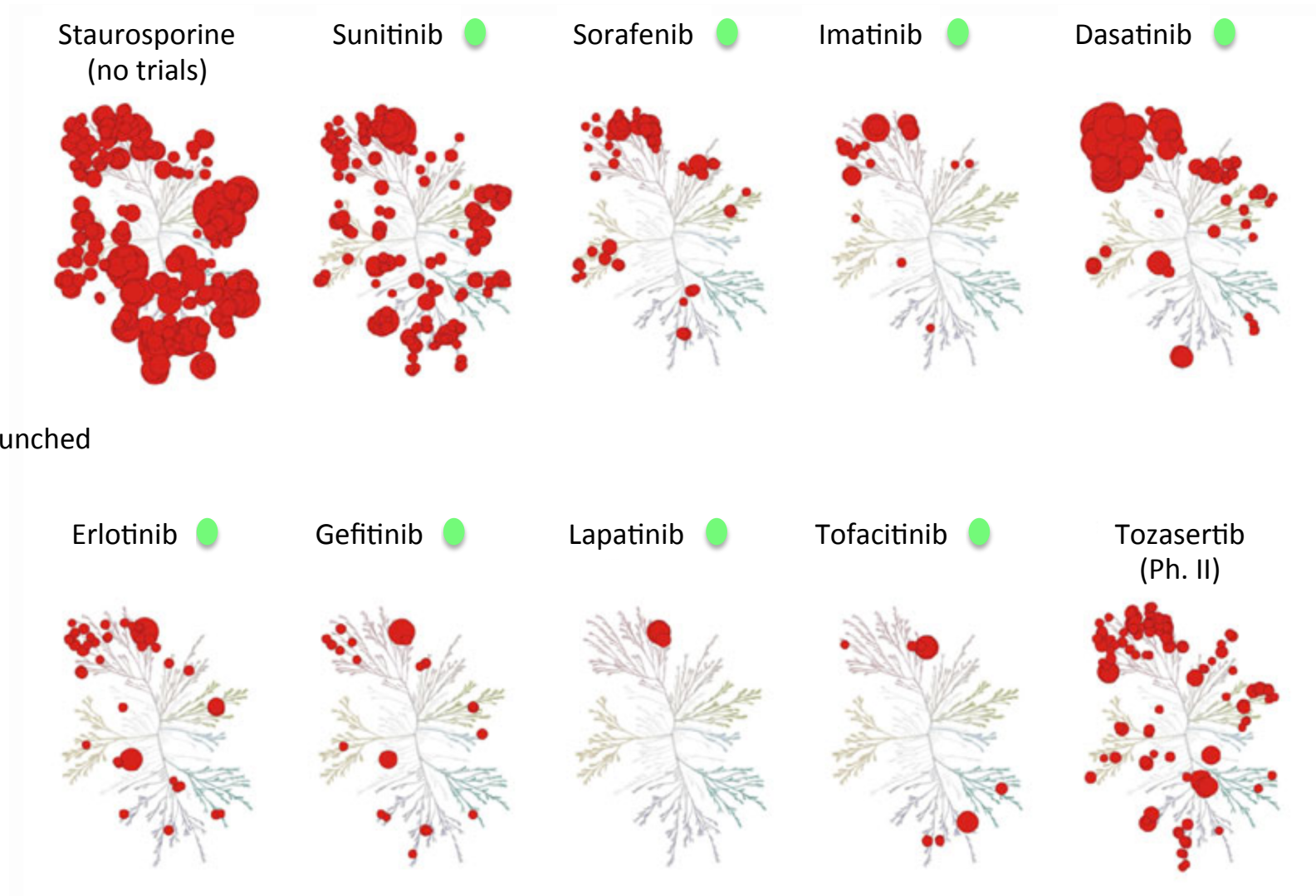
Comounds by phase (small molecules) Approval Time Course Companies

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	
1	Research Code	Research Code Alternate 1	Research Code Alternate 2	Research Code Alternate 3	Research Code Alternate 4	Research Code Alternate 5	USAN/INN	USAN stem	USAN/INN Year	Tradenname US	Tradenname EUR	Tradenname JAP	Tradenname CHN	ATCC	Vet ATCC	High Phase	Company	
2	BIBW-2992						Afatinib	-tinib	2010	Gilotrif	Tovok Tomtovok Giotrif	Giotrif		L01XE13	QL01XE13	4	Boehringer Ingelheim	EGFR ERBB2
3	AG-13736						Axitinib	-tinib	2005	Inlyta	Inlyta	Inlyta		L01XE17	QL01XE17	4	Pfizer	KIT PDGFRB
4	PF-05208763	SKI-606					Bosutinib	-tinib	2005	Bosulif	Bosulif			L01XE14	QL01XE14	4	Pfizer	ABL1 SRC
5	BMS-907351	XL-184					Cabozantinib	-tinib	2011	Cometriq	Cometriq			L01XE26		4	Bristol-Myers Squib	MET VEGFR2
6	LDK-378	NVP-LDK378					Ceritinib	-tinib	2013	Zykadia				L01XE28		4	Novartis	ALK
7	PF-02341066						Crizotinib	-tinib	2009	Xalkori	Xalkori	Xalkori		L01XE16	QL01XE16	4	Pfizer	ALK MET RON
8	GSK-2118436						Dabrafenib	-rafenib	2011	Tafinlar	Tafinlar			L01XE23	QL01XE23	4	GlaxoSmithKline	BRAF
9	BMS-354825						Dasatinib	-tinib	2005	Sprycel	Sprycel			L01XE06	QL01XE06	4	Bristol-Myers Squib	ABL1 SRC TE
10	OSI-774	CP-358774	R-1415	Ro-508231	RG-1415		Erlotinib	-tinib	2001	Tarceva	Tarceva	Tarceva		L01XE03	QL01XE03	4	Astellas	EGFR ERBB2
11	RAD-001	NVP-RAD001					Everolimus	-rolimus	2003	Zortress Zortican Afinitor Xience V	Afinitor Votubia Certican	Afinitor Certican		L01XE10 L04AA18	QL01XE10 QL04AA18	4	Novartis	FKBP-12/MTO
12	HA-1077	AT-877					Fasudil	-dil	1997			Eril		C04AX32		4	Asahi Kasei Pharma	(ROCK)
13	AZD-1839	ZD-1839					Gefitinib	-tinib	2002	Iressa	Iressa			L01XE02	QL01XE02	4	AstraZeneca	EGFR ERBB2
14	PCI-32765	JNJ-54179060					Ibrutinib	-brutinib	2012	Imbruvica				L01XE27		4	Pharmacyclics	BTK
15	BPI-2009H						Icotinib	-tinib					Conmana			4	Beta Pharma	EGFR
16	STI-571	NVP-STI571	CGP-57148				Imatinib	-tinib	2002	Glivec	Gleevec	Glivec		L01XE01	QL01XE01	4	Novartis	ABL1 DDR1 K
17	GW-572016	GW-2016					Lapatinib	-tinib	2003	Tykerb	Tyverb	Tykerb		L01XE07	QL01XE07	4	GlaxoSmithKline	EGFR ERBB2
18	AMN-107	NVP-AMN107					Nilotinib	-tinib	2006	Tasigna	Tasigna	Tasigna		L01XE08	QL01XE08	4	Novartis	ABL1 DDR1 K
19	GW-786034						Pazopanib	-anib	2005	Votrient	Votrient	Votrient		L01XE11	QL01XE11	4	GlaxoSmithKline	KIT (PDGFR)
20	AP-24534						Ponatinib	-tinib	2010	Iclusig	Iclusig			L01XE24	QL01XE24	4	Ariad	ABL1 FLT3 (V)
21	BAY-73-4506						Regorafenib	-rafenib	2008	Stivarga	Stivarga	Stivarga		L01XE21	QL01XE21	4	Bayer Health Care	ABL BRAF DD RAF1 RET SA
22	INCB-18424	INC-424					Ruxolitinib	-tinib	2010	Jakafi	Jakavi			L01XE18	QL01XE18	4	Incyte	JAK1 JAK2
23	AY-22989					Rapamycin	Sirolimus	-rolimus	1993	Rapamune Cypher	Rapamune Cypher	Cypher		L04AA10	QL01AA10	4	Pfizer	FKBP-12/MTO
24	BAY-43-9006						Sorafenib	-rafenib	2007	Nexavar	Nexavar	Nexavar		L01XE05	QL01XE05	4	Bayer Health Care	KIT (PDGFR)
25	SU-11248						Sunitinib	-tinib	2006	Sutent	Sutent	Sutent		L01XE04	QL01XE04	4	Pfizer	FLT3 KIT (PDGFR)
26	CCI-779						Temsirolimus	-rolimus	2004	Torisel	Torisel			L01XE09	QL01XE09	4	Pfizer	FKBP-12/MTO
27	CP-690550					Tasocitinib	Tofacitinib	-citinib	2010	Xeljanz	Xeljanz			L04AA29	QL04AA29	4	Pfizer	(JAK)
28	GSK-1120212	JTP-74057					Trametinib	-metinib	2011	Mekinist				L01XE25	QL01XE25	4	GlaxoSmithKline	MEK1 MEK2
29	TRM-986	Ba-9	A-9			Biolimus A9	Umirolimus	-rolimus	2009			Nobori				4	Biosensors International	FKBP-12/MTO
30	AZD-6474	ZD-6474					Vandetanib	-anib	2006	Zactima	Caprelsa			L01XE12	QL01XE12	4	AstraZeneca	EGFR (EPhR)
31	RG-7204	PLX-4032	Ro-5185426				Vemurafenib	-rafenib	2010	Zelboraf	Zelboraf			L01XE15	QL01XE15	4	Roche	BRAF MEK1 M
32	ABT-578						Zotarolimus	-rolimus	2005	Endeavor Resolute		Endeavour				4	Abbott	FKBP-12/MTO
33	MLN-8237						Alisertib	-sertib	2010							3	Takeda	AURa

Text Brigatinib

Overington, Bellis, Al-Lazikani & Wennerberg, unpublished

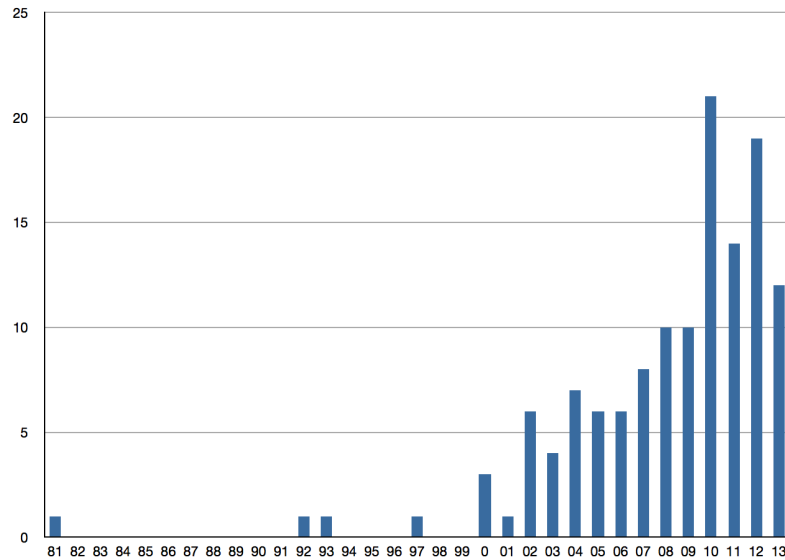
Kinase Inhibitor Polypharmacology



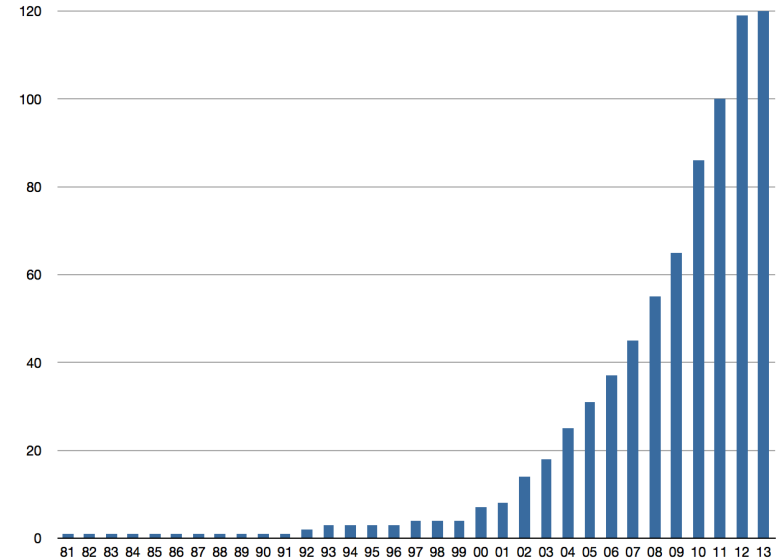
Adapted from Ghoreschi *et al*, *Nature Immunology* **10**, 356 - 360 (2009)

Kinase Inhibitor Attrition

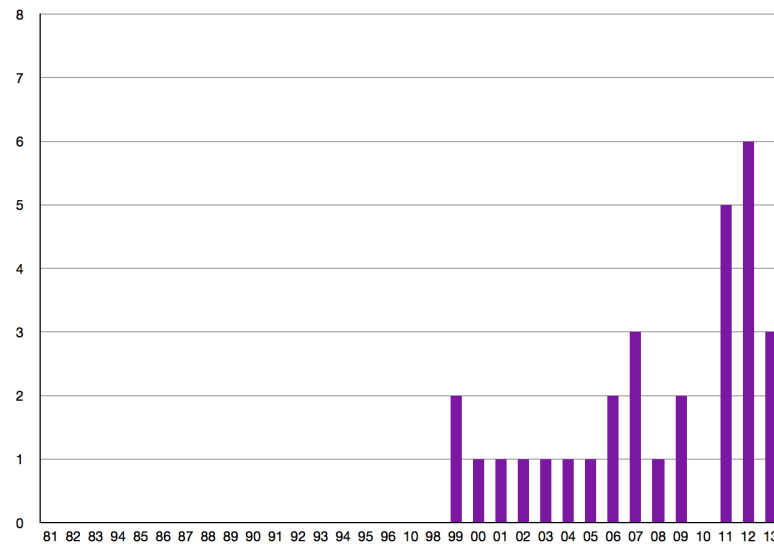
Kinase USANs



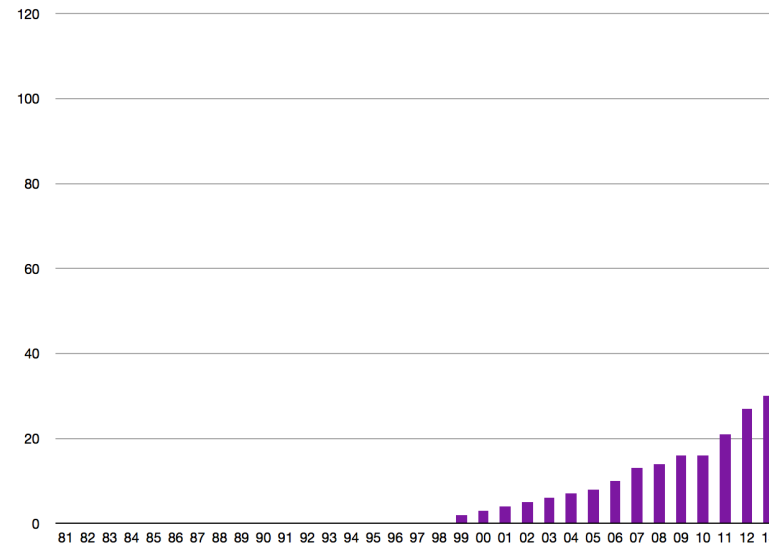
Cumulative Kinase USANs



Kinase Drugs



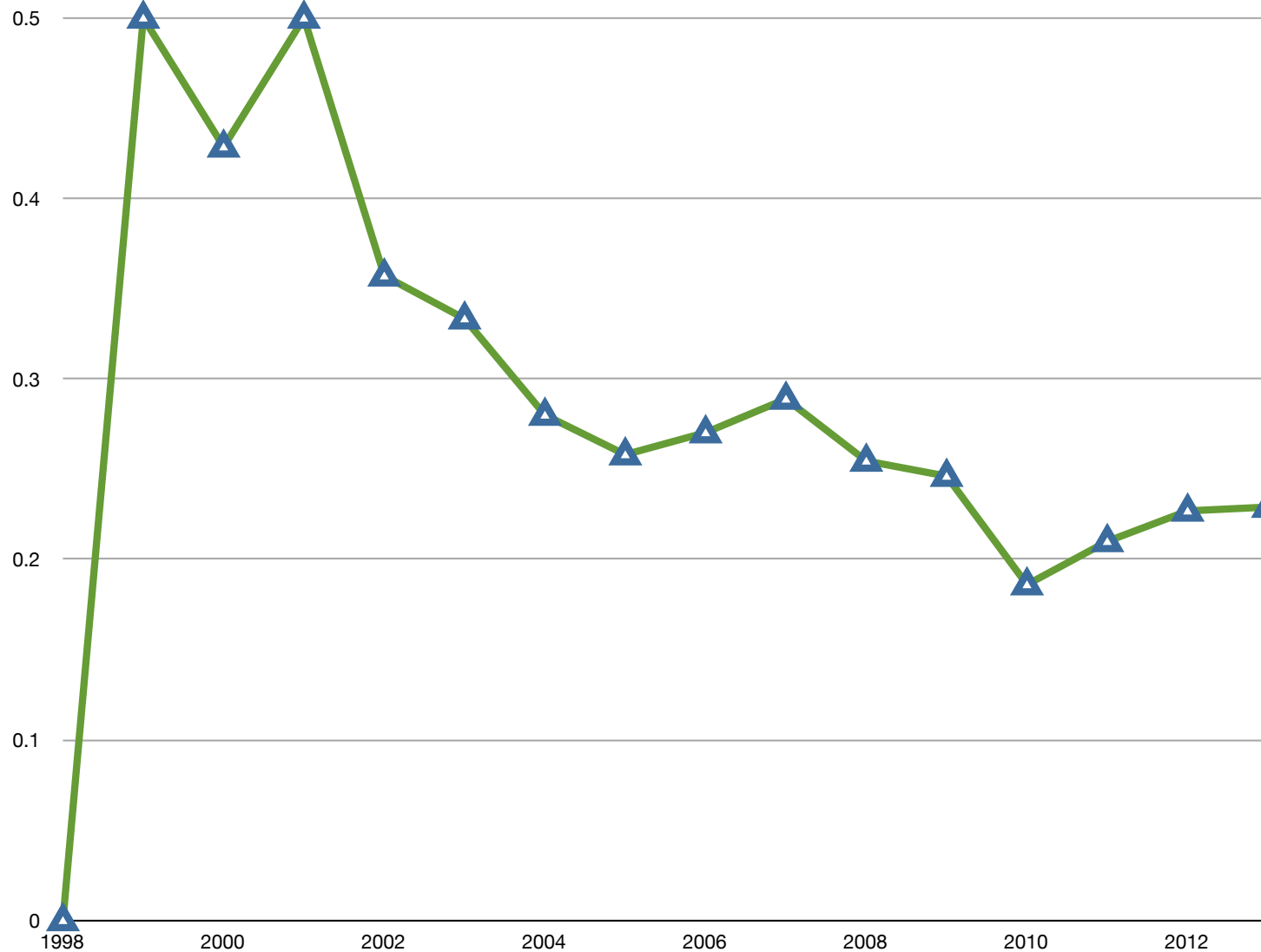
Cumulative Kinase Drugs



Overington, unpublished

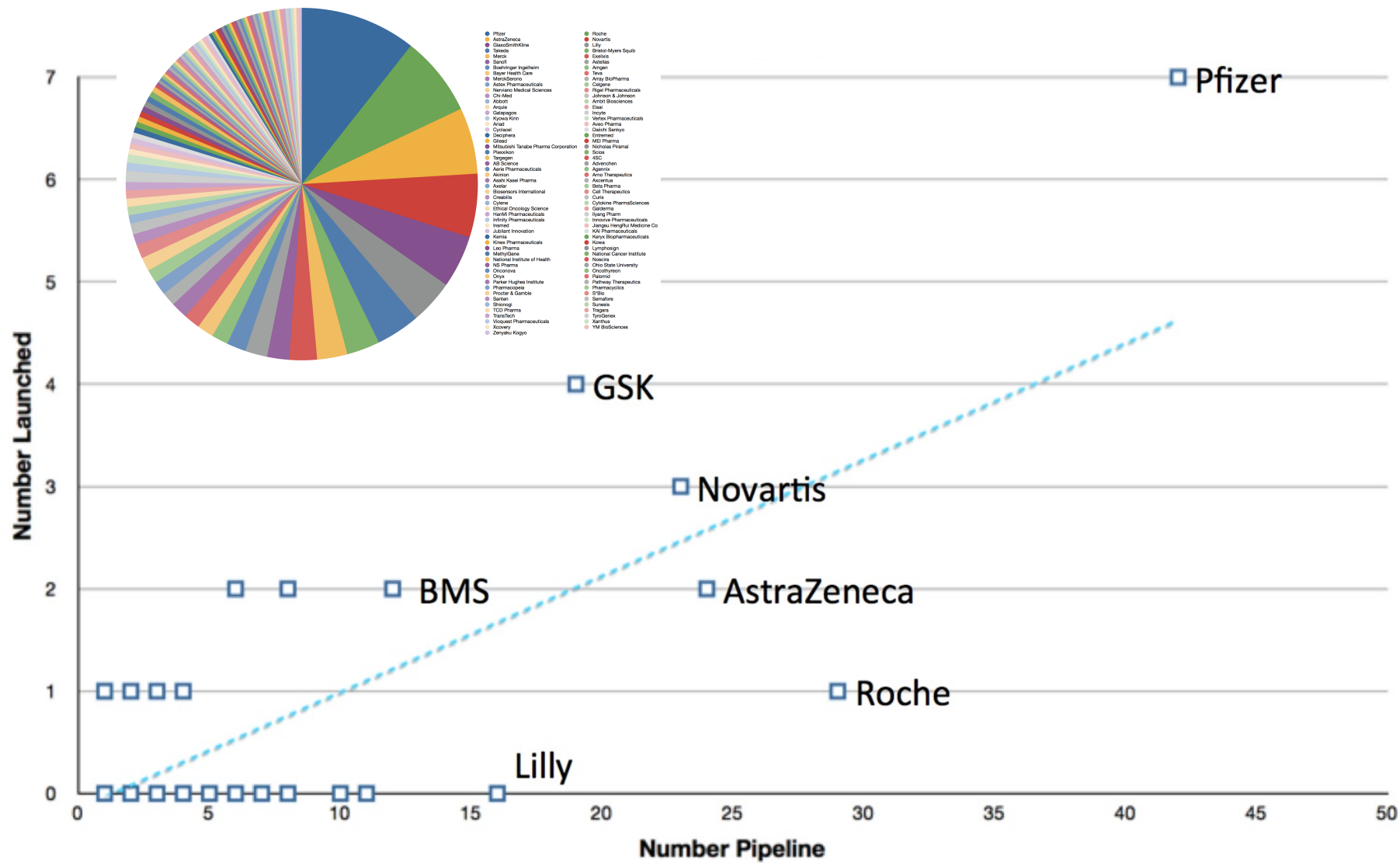
Kinase Inhibitor Attrition

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



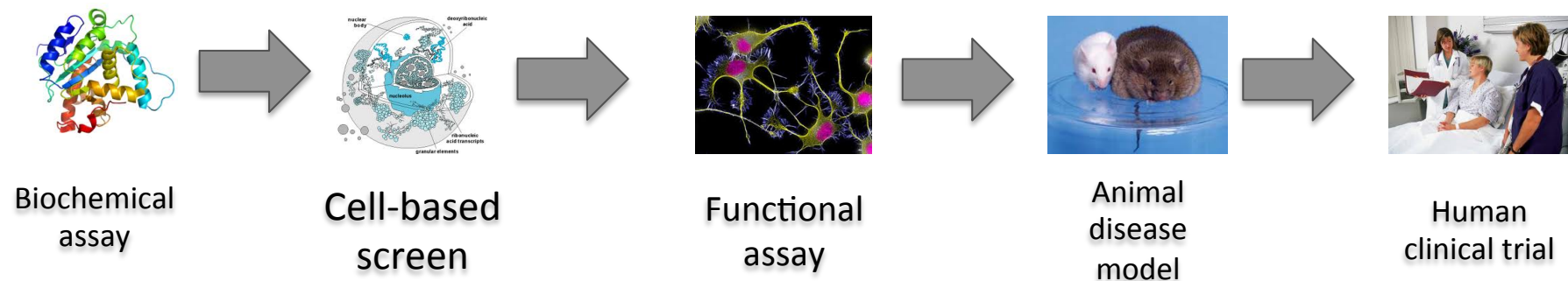
Overington, unpublished

Kinase Inhibitor Productivity



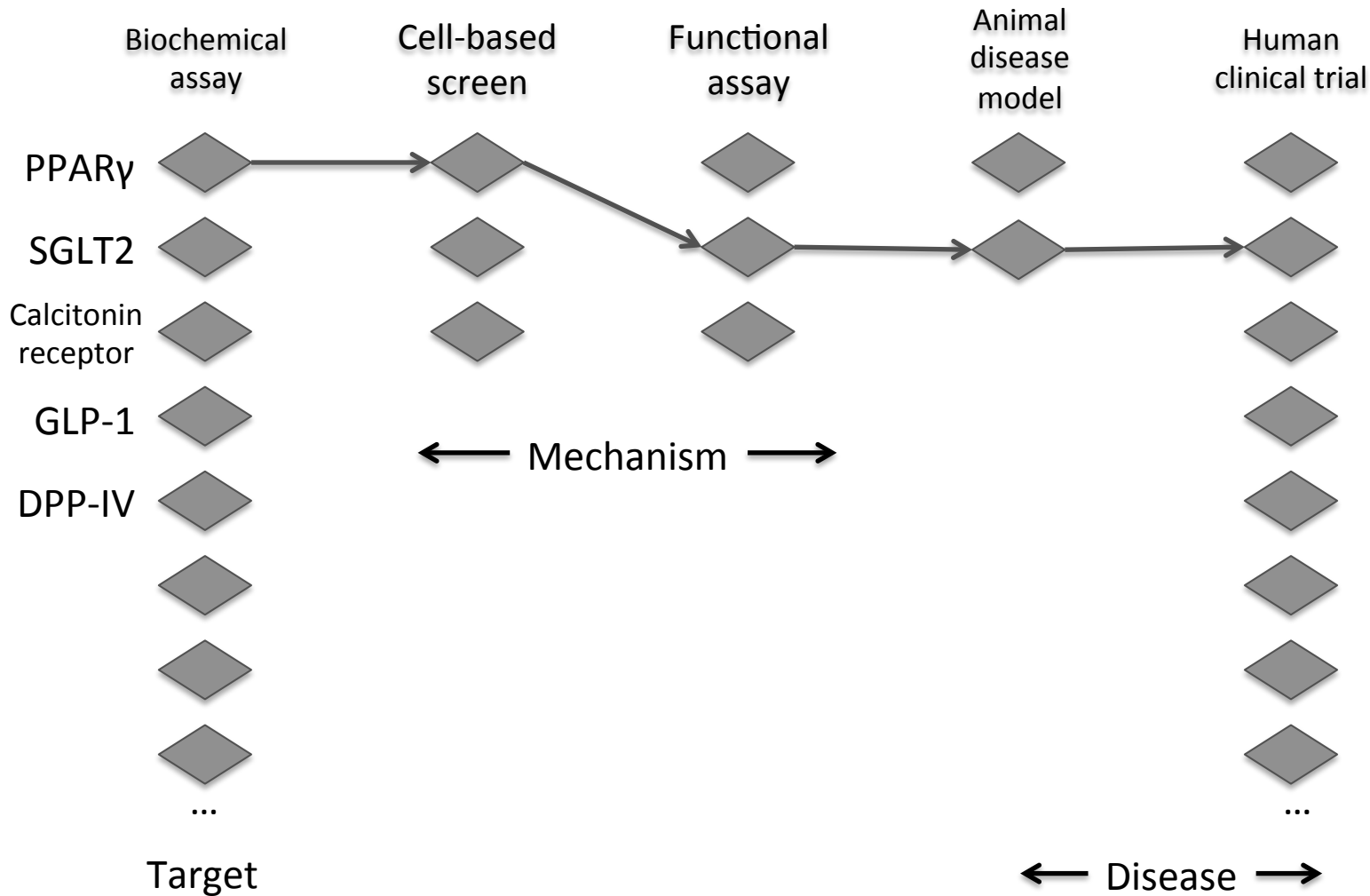
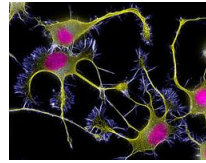
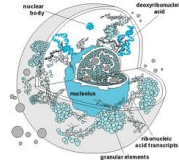
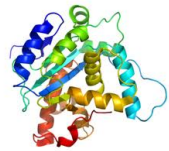
Overington, *unpublished*

Modern Drug Discovery Assay Cascade

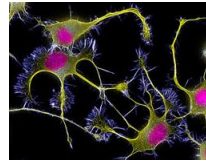
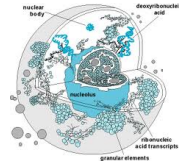


- Move from *'quick, low-cost, less predictive'* assays to *'slow, high-cost, more predictive'* assays
- Make selections on which compounds to progress to later assays on basis of positive activity in earlier screens
 - Early, cheap assays are used a lot of times, later expensive assays rarely
 - Attrition – failure of compounds in that pipeline

Efficacy Assay Cascade



Efficacy Assay Cascade



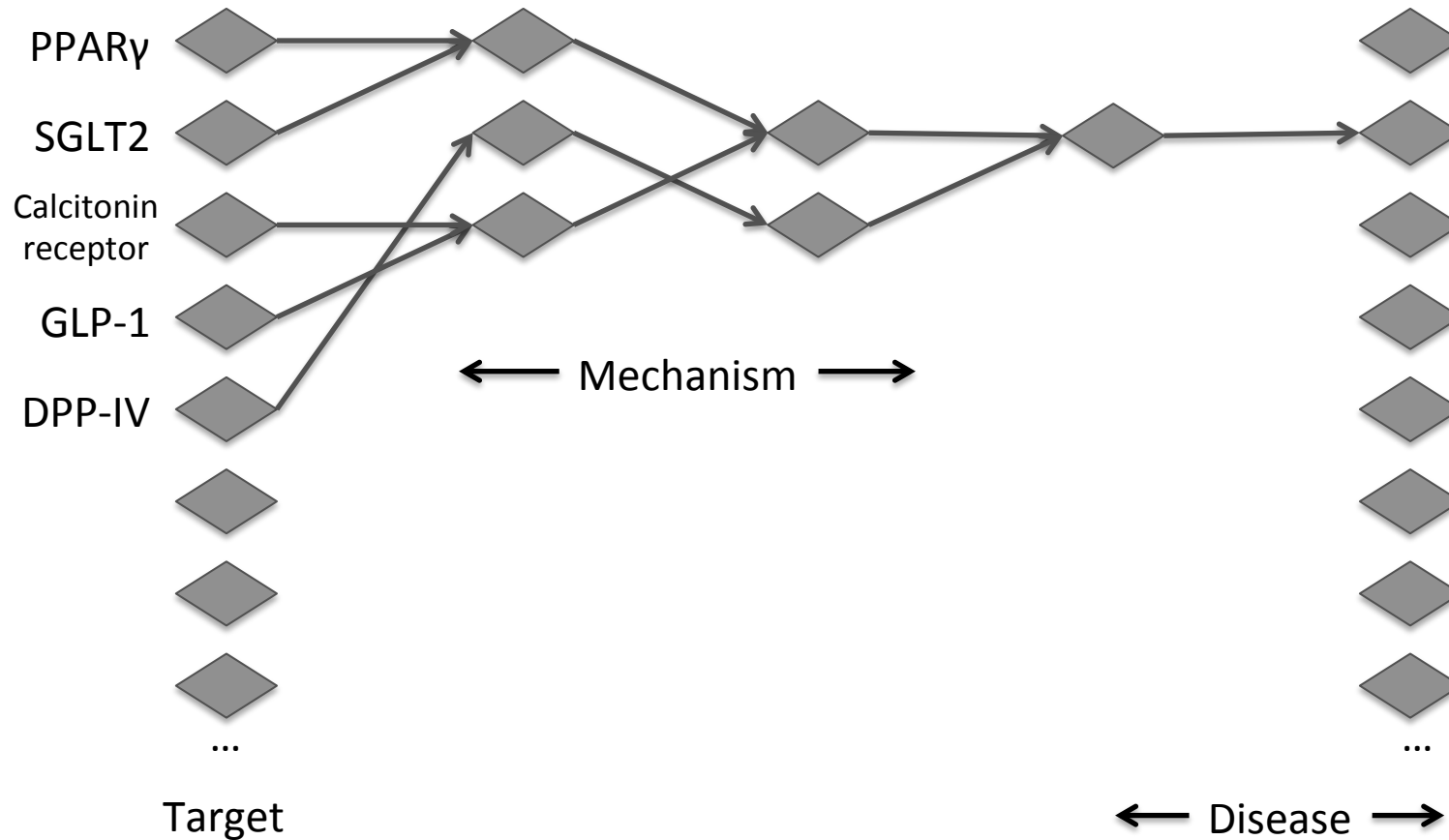
Biochemical
assay

Cell-based
screen

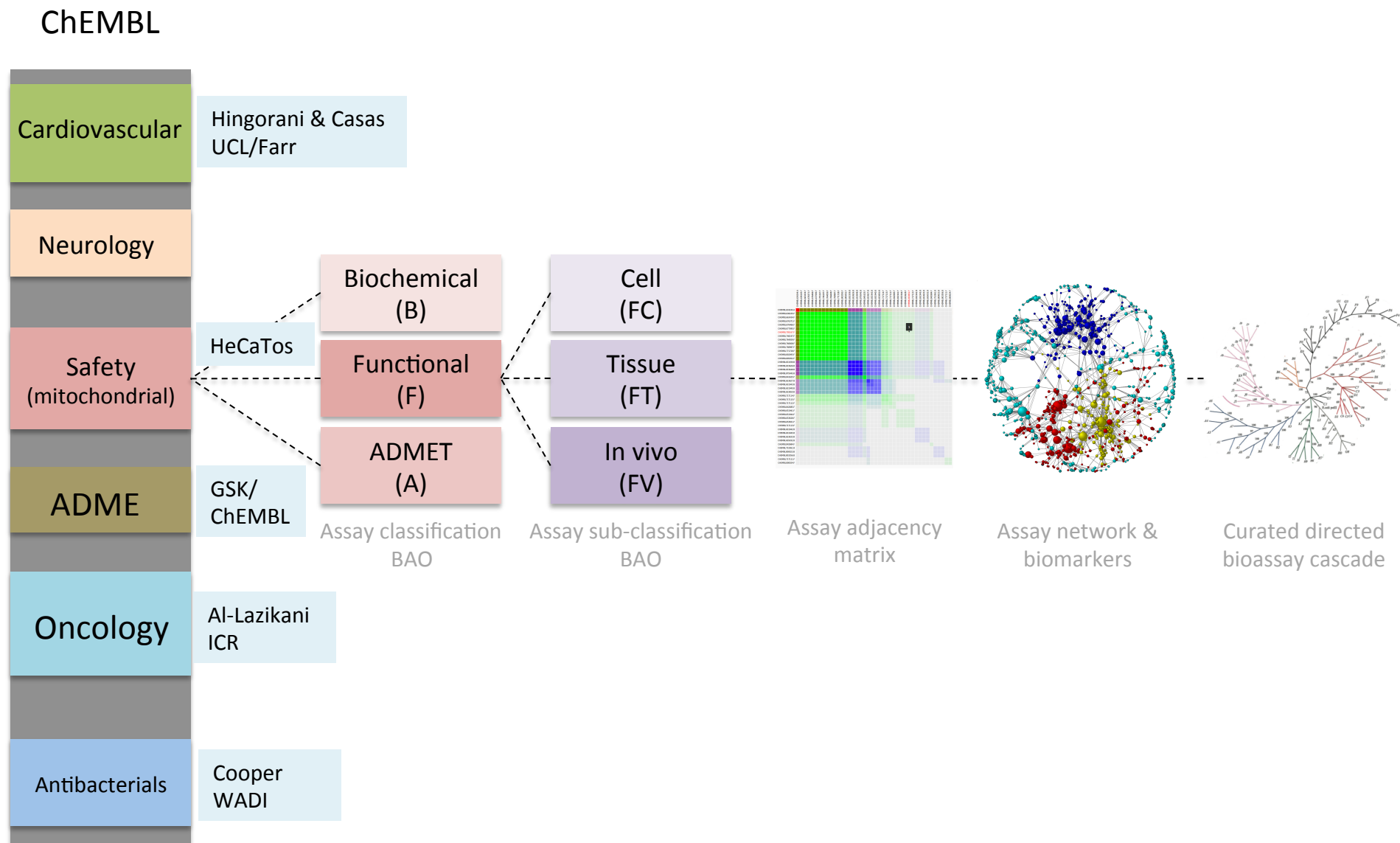
Functional
assay

Animal
disease
model

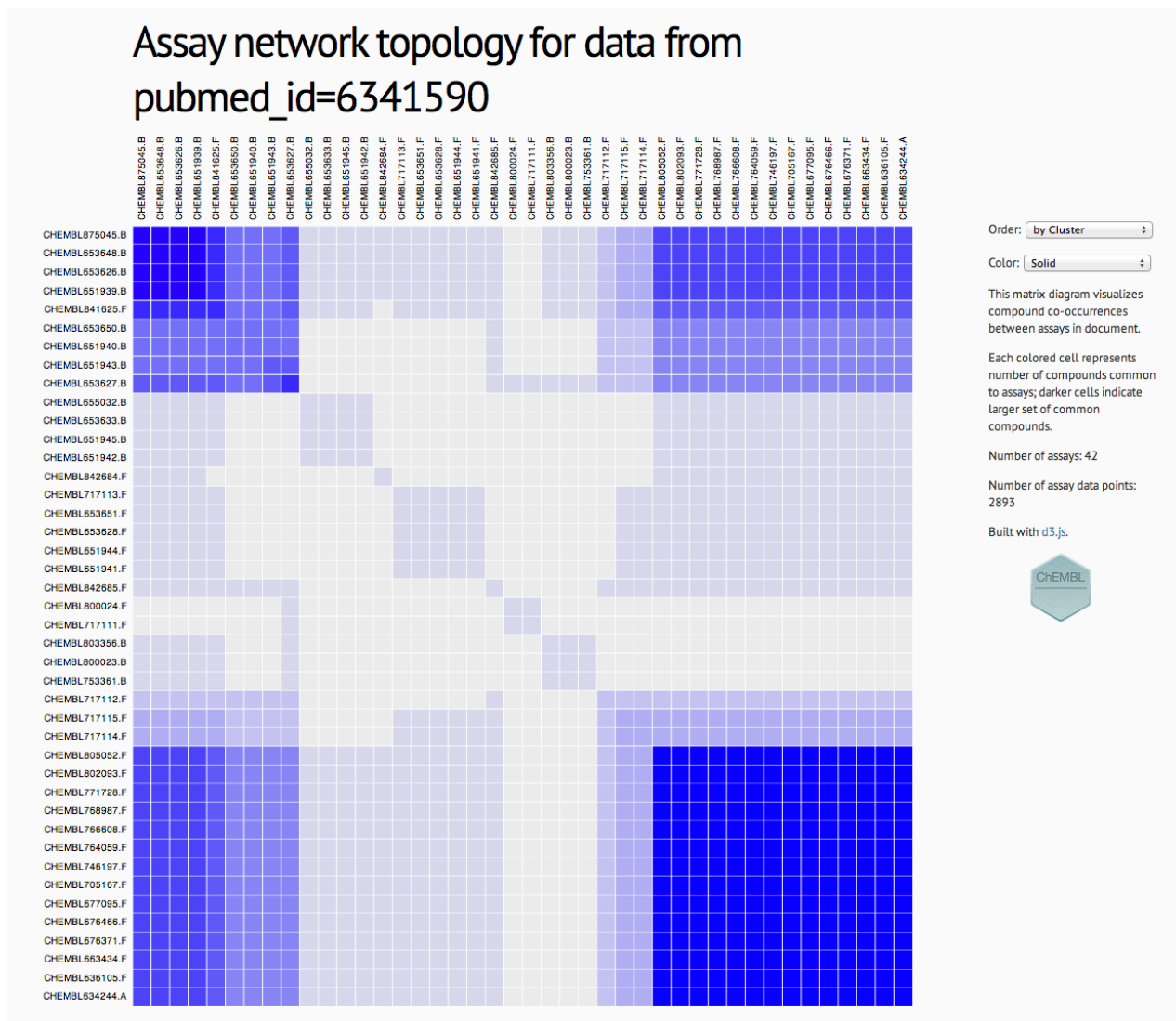
Human
clinical trial



ChEMBL Bioassay Annotation Strategy

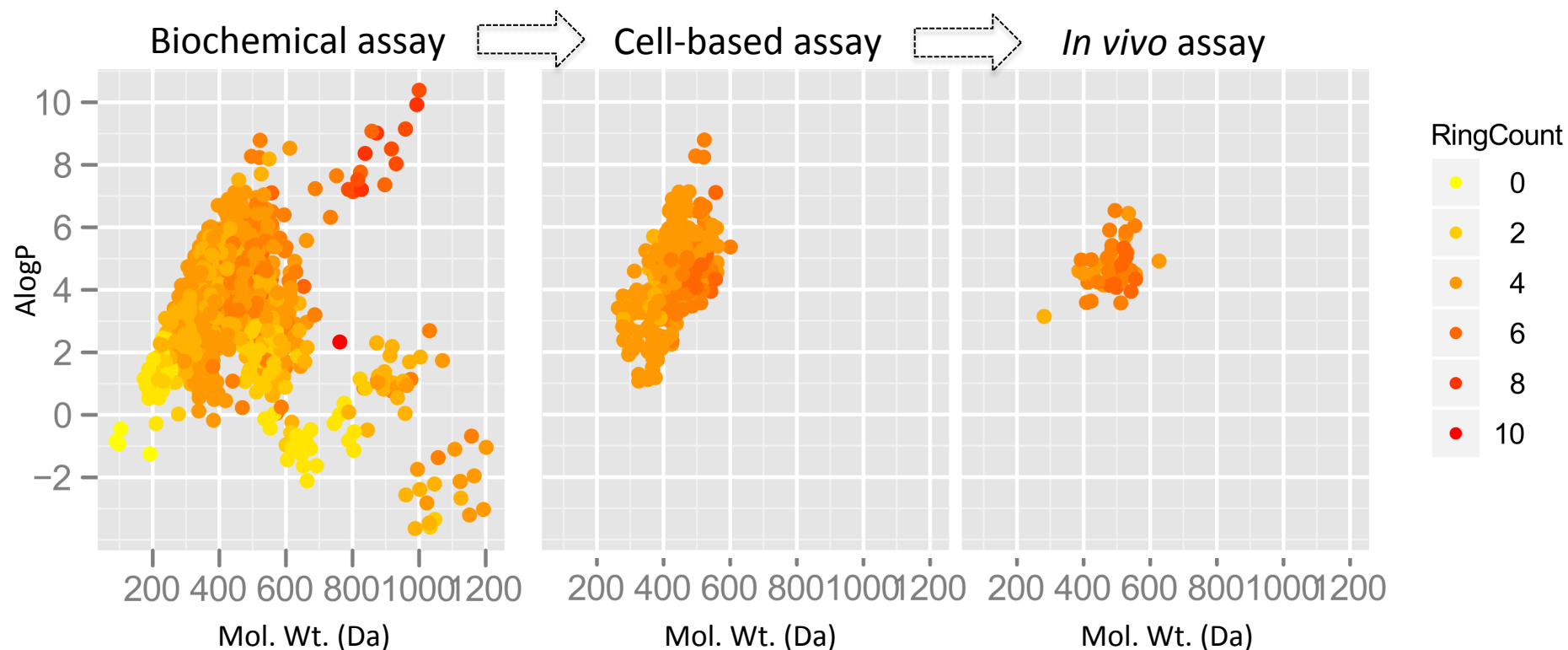


Assay Networks – Adjacency Matrix



EGFR Assay Cascades from ChEMBL

Physicochemical properties for cSrc EGFR pathway inhibitors



SureChEMBL

The screenshot shows the SureChem website interface. At the top, it says "Patent chemistry made easy and accessible" and "We're integrating patent chemistry into the scientific community and giving customers control over data." There are buttons for "SIGN UP FREE" and "TAKE THE TOUR". Below this is a search results page for a query. The results are displayed as a grid of chemical structures. The first structure is a complex polycyclic molecule with multiple hydroxyl groups and a methyl group. Below the structures, there are options to "View chemical page" and "View results as: Mark | Table".

Search

Draw or paste in a chemical structure to perform exact, similarity and substructure searches. Search by keyword, patent bibliographic field, command line, and combine all of them with structure search.

SIGN UP FREE
It takes just 30 seconds

Search [View more](#) | View [View more](#) | Link [View more](#)

This screenshot shows the search interface with a search box labeled "Enter your SureChem search". To the right, there are radio buttons for "Substructure", "Duplicate", "Exact", and "Similarity". Below the search box, there are several search results displayed as chemical structures.

The footer of the website contains a green button that says "See our products, sign up or get in touch". Below this, there are several columns of links: "LINKS" (Products, Contact), "HELP AND SUPPORT" (Get Support, Terms and Conditions, Privacy Policy, Legal Notice, Cookie Policy), "NEWS AND EVENTS" (Blog, Events), and "SIGN UP FOR THE SURECHEM MAILING LIST" (Enter your email and hit Enter). A small text block below the mailing list sign-up says: "You can sign up to the SureChem mailing list to receive updates on our coverage, features or products. We will never spam you."

11th December 2015 - The SureChem patent website has been acquired by the European Bioinformatics Institute (EMBL-EBI) and is being rebranded as SureChEMBL. During the transition phase a number of changes are made to the website's name and contents of some of our links and options (see [contactus](#)).

- EMBL-EBI acquired the SureChem product from Digital Science
 - 15 million chemical structures
 - Automatically extracted chemical structures from full-text patent
- Research community wants open access to patent data
 - Patent literature 2-3 years ahead of published literature
 - Better competitive position
- Plan to provide ongoing free, Open resource to entire community

SureChEMBL Data Coverage

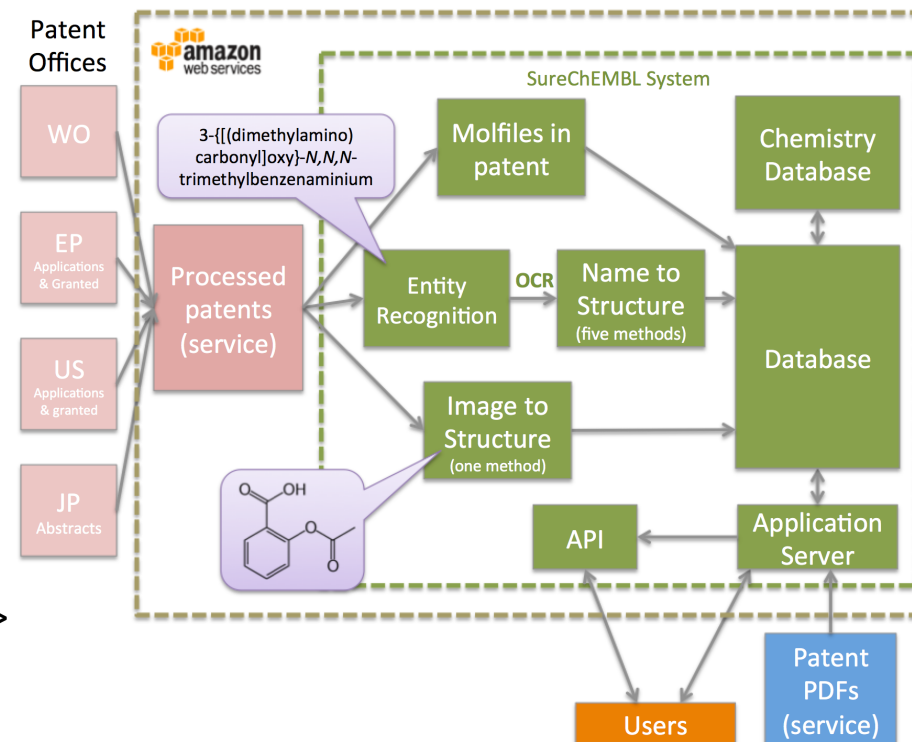
	Data	Description & Languages	Years
EP applications	Bib. data Full text	DocDB + Original Original (EN, DE, FR)	from 1978
EP granted	Bib. data Full text	DocDB + Original Original (EN, DE, FR)	From 1980
WO applications	Bib. data Full text	DocDB + Original Original (EN, DE, FR, ES, RU)	From 1978 From 1978
US applications	Bib. data Full text	DocDB + Original Original (EN)	From 2001 From 2001
US granted	Bib. data Full text	DocDB + Original Original (EN)	From 1920 From 1976
JP applications	Bib. data Full text	DocDB PAJ - English abstracts/titles	From 1973 From 1976
JP granted	Bib. data	DocDB	From 1994
90+ countries	Bib. data	DocDB	From 1920

SureChEMBL Chemistry Data Coverage

- Exemplified structures from patent title, description, abstract and claims
- Structures from text 1976 onwards
- Structures from images 2007 onwards
- USPTO have provided 'Complex Work Units' since 2001
 - CWU file types include MOL and CDX
 - CWUs processed as part of pipeline

SureChEMBL Plans

- UniChem/ChEMBL integration
- Enhanced entity extraction
 - Tag commonly used identifiers UniProt, ChEMBL, ChEBI, PubChem, PDB, Research codes
 - Proteins, diseases, animal models, cell lines, assays
- New search methods
 - Protein sequence-based searching, including biotherapeutics
- IMI Open PHACTS funding
 - refactor SureChEMBL API
 - RDF Conversion and semantic tagging -> *EBI RDF Platform*
- Status
 - Database running and updated
 - Legacy API running
 - Front-end running
 - Legacy user account system removed



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ChEMBL Database

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The ChEMBL-og

The Organization of Drug Discovery Data

Resources: [ChEMBL](#) | [SureChEMBL](#) | [ChEMBL-NTD](#) | [ChEMBL-Malaria](#) | [SARfaris](#) | [GPCR](#) | [Kinase](#) | [ADME](#) | [UniChem](#) | [DrugEBility](#)

Monday, 13 January 2014

ADME SARfari: A tool for predicting and comparing cross-species ADME targets



ADME studies are focused on understanding the disposition of a compound within an organism and the results of such studies play a critical role in the drug development process. ADME studies (more commonly referred to as pharmacokinetic or PK studies) are focused on 4 main areas: Absorption, Distribution, Metabolism and Excretion. More information on the PK measurement types can be found [here](#).

Comparisons of PK data across species is a potential problem drug researchers need to deal with, as model organism studies are the primary source of such data. For example, in an animal model study, which may be carried out on a compound as it passes through the drug development pipeline, is it meaningful to compare clearance or bioavailability data from a mouse or rat to human? Clearly there are many differences (physical, metabolic, genetic,...), which make answering these types of questions difficult. Building tools which guide researchers to potential answers or provide a better understanding of the inter-species differences are of great value - leading us nicely to the focus of this blog post.

<http://chembl.blogspot.com>