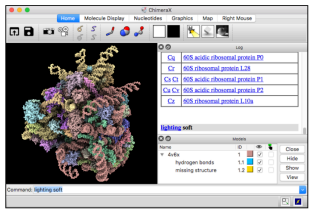
While we are waiting for other folks… Install ChimeraX:

https://www.cgl.ucsf.edu/chimerax/download.html

Download UCSF ChimeraX

UCSF ChimeraX is the next-generation visualization program from the Resource for Biocomputing, Visualization, and Informatics at UC San Francisco.

- Download is **free for academic, government, nonprofit, and personal use**; commercial users, please see commercial licensing.
- ChimeraX uses recent graphics features and **works best on a newer computer** (≤ 3 years old).
- Please **cite ChimeraX** in publications for which it was used.



Latest Production Release
Daily Builds
Change Log and Platform Notes
Older Releases
Download & Citation Counts

▸ **Features**
▸ **Missing Features**

https://www.nature.com/articles/s41587-020-00778-3

Latest Production Release

Production releases are stable platforms for ChimeraX Toolshed bundles to work with. You may need to use an older release if a bundle you wish to use has not been updated yet.

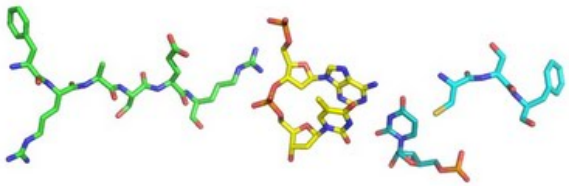
Operating System	Distribution	Notes
Windows 10 64-bit	ChimeraX-1.1.exe built: 2020-09-10 21:31:12 PDT committed: 2020-09-09 15:22:27 PDT size: 300.2 MiB md5: 0bbf1dee03bb33ee71c2d930ce454794 sha256: 7fed35e29f498466c7559b6f357531ce4f3ed15b1663783b014713b196441460	Download is a Windows installer. Tested on Windows 10. See Windows notes below.
macOS 10.13 64-bit	ChimeraX-1.1.1.dmg built: 2020-10-07 22:51:41 PDT committed: 2020-10-07 01:32:49 PDT size: 337.4 MiB md5: 32a908b72535aeeb4bcdbd8c9d3fff1a sha256: 2678efba1b11cd9400f2c432189e1b56ee73108f582c6427b13f7f0af5ed2cdb	Download is a disk image containing the application. Tested on macOS 10.13. Also works on 10.14, 10.15, and 11.0 (Big Sur).
Generic Linux 64-bit	ChimeraX-1.1.tar.gz built: 2020-09-10 21:42:44 PDT committed: 2020-09-09 15:22:27 PDT size: 390.9 MiB md5: a081f3b964aae69bf7e6f1b3bfc34e1d sha256: a5f8bc54e55bda7243d49953bf329731ffac173bcb8ca1ed0e55fbf917601bf5	Download is a tarball of the **chimerax** application directory. ChimeraX executable is **chimerax/bin/ChimeraX**. Tested on Ubuntu 16.10 and Fedora 25. See Linux notes below.

Why is it so hard to design new small molecule drugs?

Inquiry Immersion 20-21
James Fraser
(he/him)

Who am I?

- James (or Jaime, but not Jamie or Jim) Fraser - he/him pronouns
  - Background in Protein Biophysics and Evolutionary Biology
  - Ph.D. in Molecular and Cell Biology from UC Berkeley
  - I've run a lab at UCSF since 2011



- If you have additional questions:
  - email: **jfraser@fraserlab.com**
  - twitter: **@fraser_lab**

Class information

https://fraserlab.com/inquiry/

Schedule

Monday Jan 4 - 2:30-4PM

- James Fraser: Intro to class and contrasting kinase and phosphatase drug discovery
  - Structural Mechanism for STI-571 Inhibition of Abelson Tyrosine Kinase
  - Allosteric inhibition of SHP2 phosphatase inhibits cancers driven by receptor tyrosine kinases.
- install ChimeraX

Tuesday Jan 5 - 2:30-4PM

- John Irwin: Docking what works and what doesn't
  - What docking is, how it works, and why it is hard; a review of some notable success stories "what docking ca
    detailed look at 2 or 3 stories, focusing on how to run a docking campaign, and what to expect from the outc
  - resources DOCK Blaster, ZINC, DUDE, and how to use them.

Wednesday Jan 6 - 2:30-4PM

- Tom Goddard: ChimeraX demo
  - Elucidating the active delta-opioid receptor crystal structure with peptide and small-molecule agonists.
  - VR experience in Genentech Hall N453

Thursday Jan 7 - 2:30-4PM

- James Fraser: Fragment-based design and Crystallography 101
  - Discovery of a selective inhibitor of oncogenic B-Raf kinase with potent antimelanoma activity.
  - Discovery of a potent and selective Bcl-2 inhibitor using SAR by NMR
  - An expanded allosteric network in PTP1B by multitemperature crystallography, fragment screening, and coval
- Liam McKay: Tour of Crystallography facility
  - Crystalizing Lysozyme

Friday Jan 8 - 2:30-4PM

- Tanja Kortemme: Rosetta and Biologics
  - De novo design of potent and selective mimics of IL-2 and IL-15
  - Engineered ACE2 receptor traps potently neutralize SARS-CoV-2
  - De novo design of picomolar SARS-CoV-2 miniprotein inhibitors.

Monday Jan 11 - 2:30-4PM

- David Bulkley: CryoEM facility tour
- James Fraser: cryoEM in drug discovery and antibiotics talk Synthetic group A streptogramin antibiotics that overc

Tuesday Jan 12 - 2:30-4PM

- Class time to work on final presentation

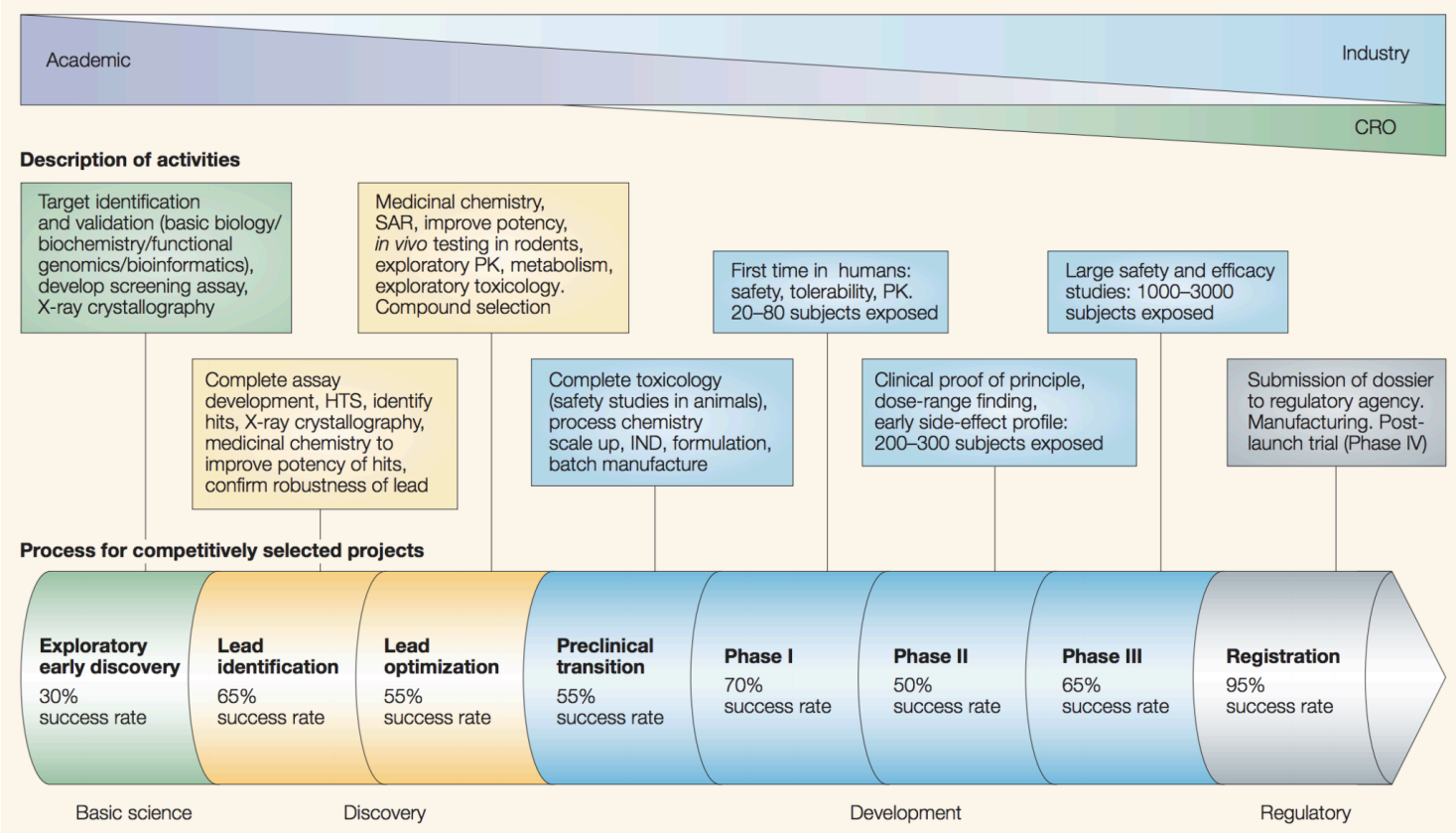
Thursday Jan 14 - 11AM-12PM

- final presentation!

Circle!

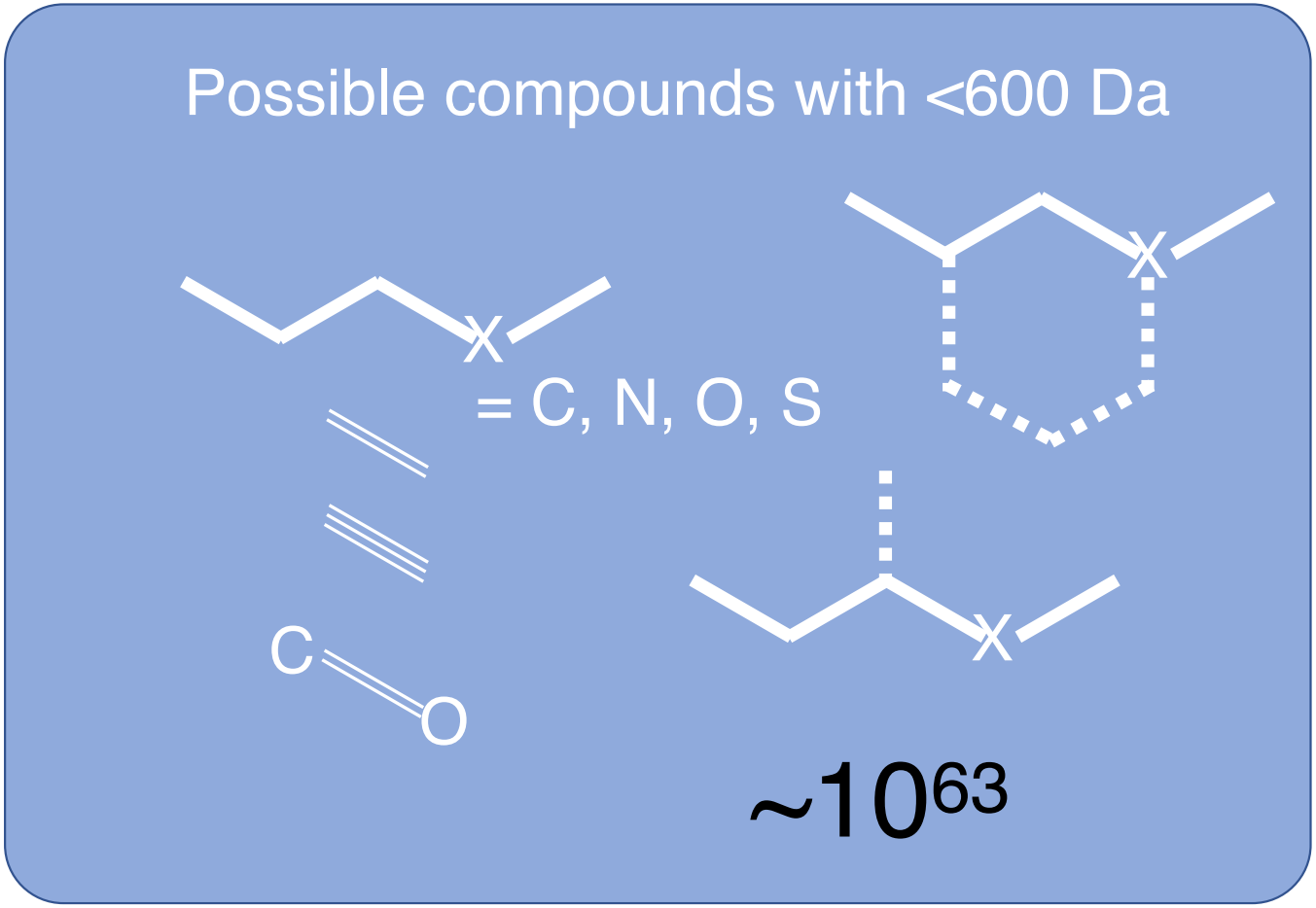
- Who are you?
- Did you make a new year’s resolution?
- What is one piece of pop culture you consumed over break?
- Why did you sign up for this class, what do you want to learn?
- Free for all questions?

Why is it so hard to design new small molecule drugs?



Nwaka S and Ridley RG *Nature Reviews Drug Discovery* 2, 919-928 (2003)

Chemical space

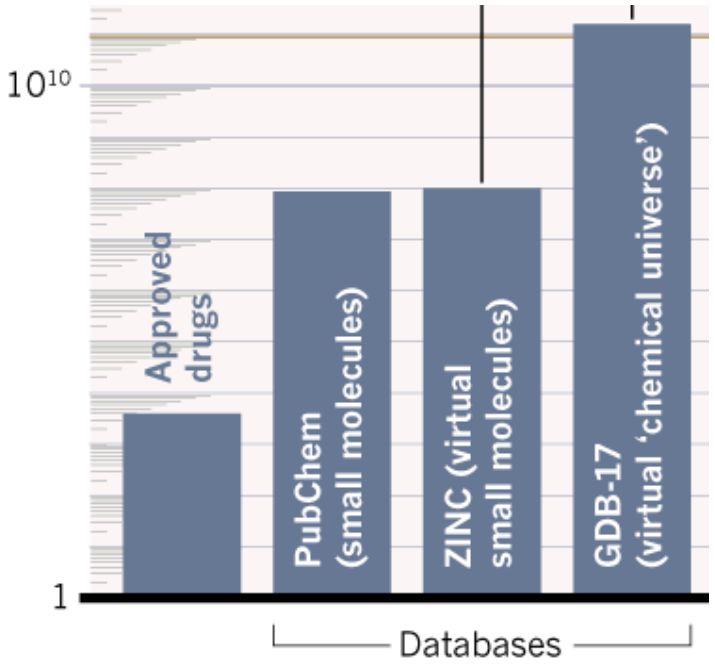


Bohacek RS *et al Molecular Research Reviews* 1,3-50 (1996)

Chemical space is huge!

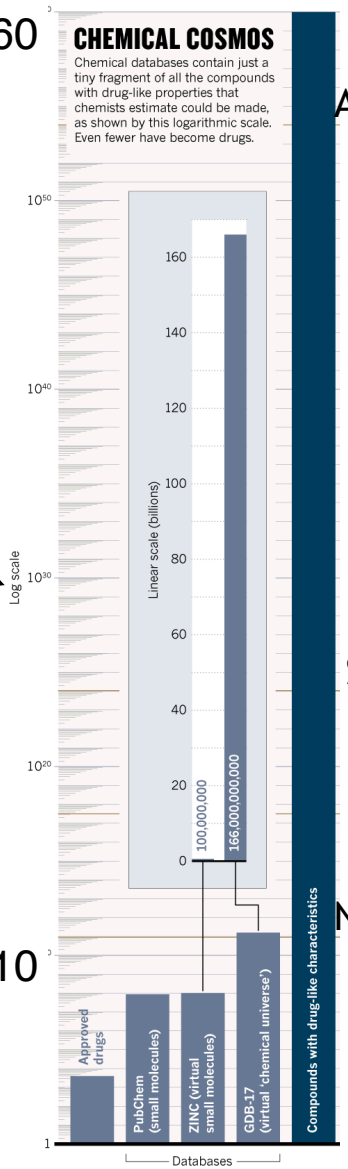
Mullard A *Nature* 549,445 (2017)

Chemical space is huge!



Mullard A *Nature* 549,445 (2017)

Log scale!



10^{60} Atoms in the solar system

Stars in the universe

Neurons in the human brain

10^{10}

Mullard A *Nature* 549,445 (2017)

- What are the molecular interactions between ligand and protein?
- What are they worth energetically?
- How does that relate to affinity?
- How many interactions in between a typical drug and protein?
- How do they scale with size?
- What happens to specificity?

Needles in enormous haystacks

Finding that rare needle…

High throughput screening

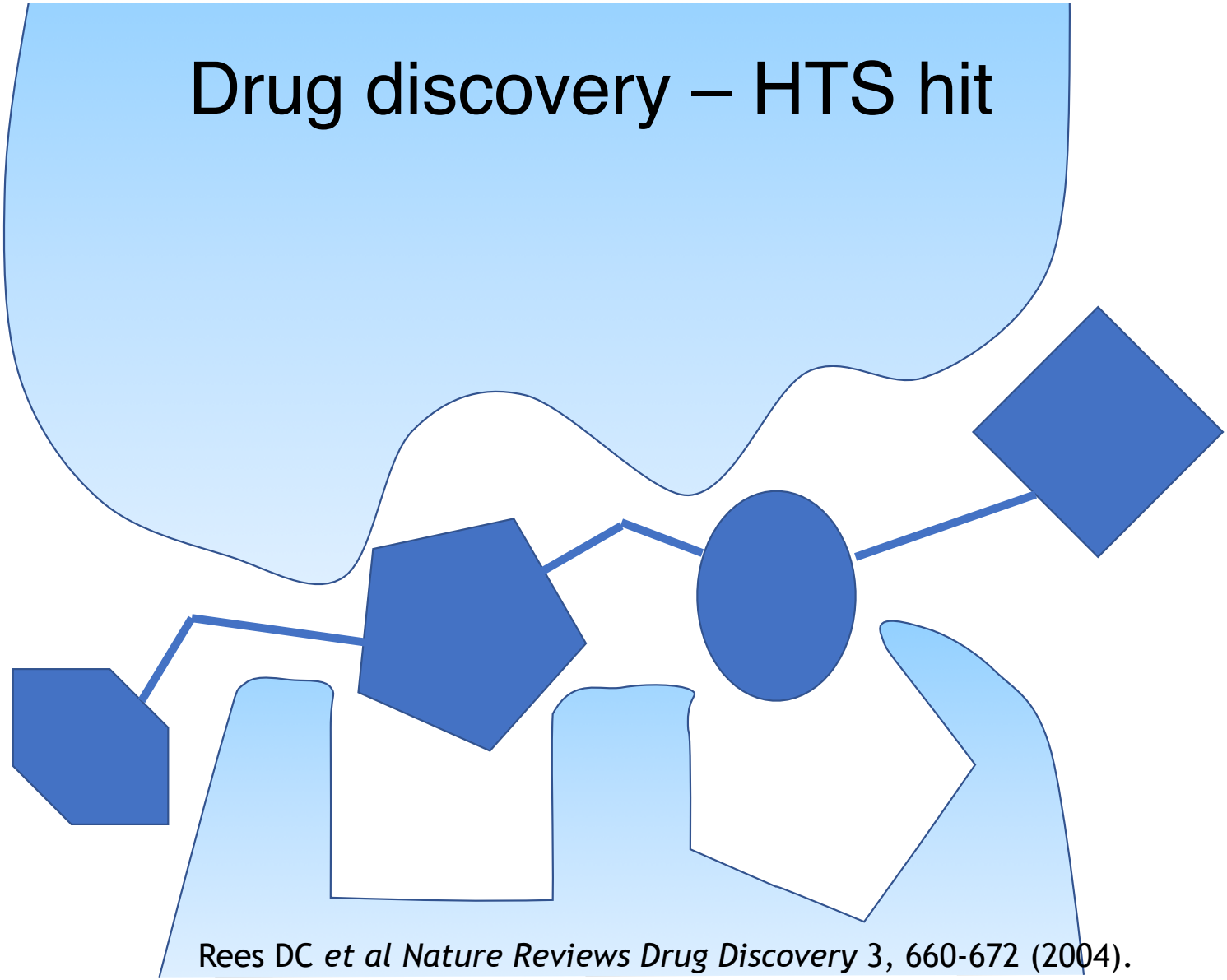
Library
30 heavy atoms
~10^6

Hit

Lead

Candidate

Drug discovery – HTS hit



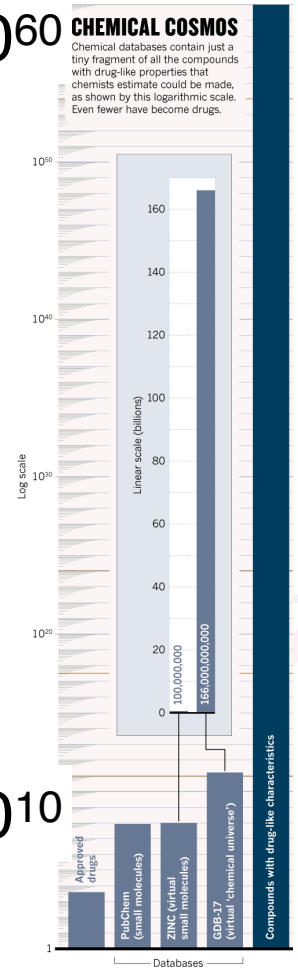
Rees DC *et al Nature Reviews Drug Discovery* 3, 660-672 (2004).

High throughput screening

Library
30 heavy atoms
~10^6

10^{60}

Vast undersampling!

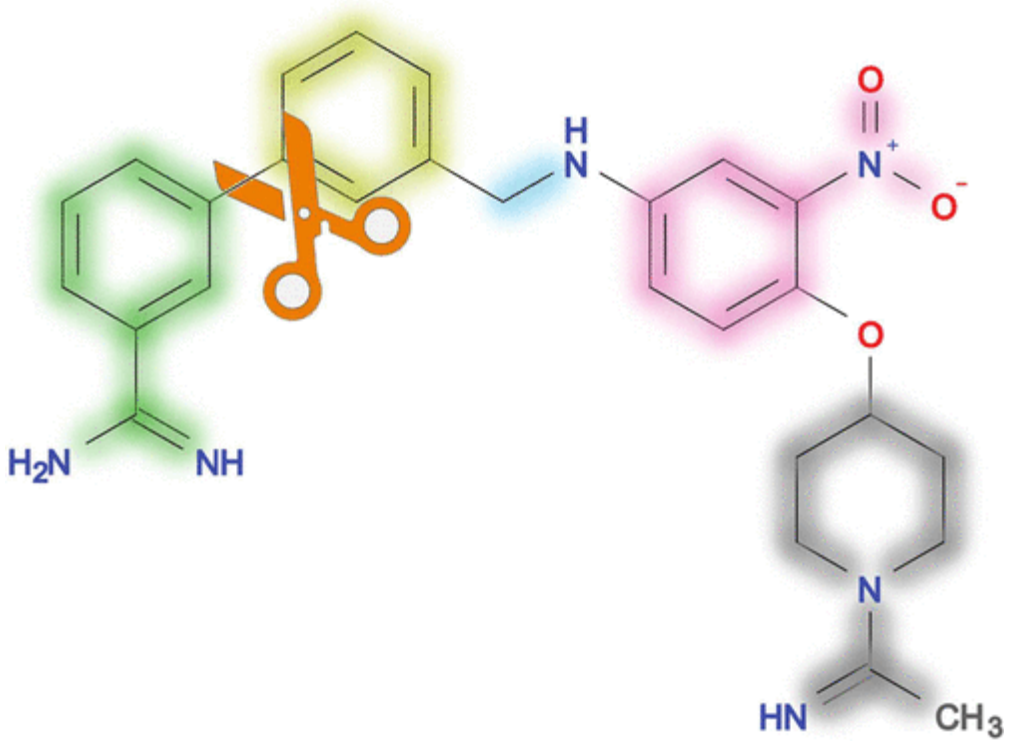


10^{10}

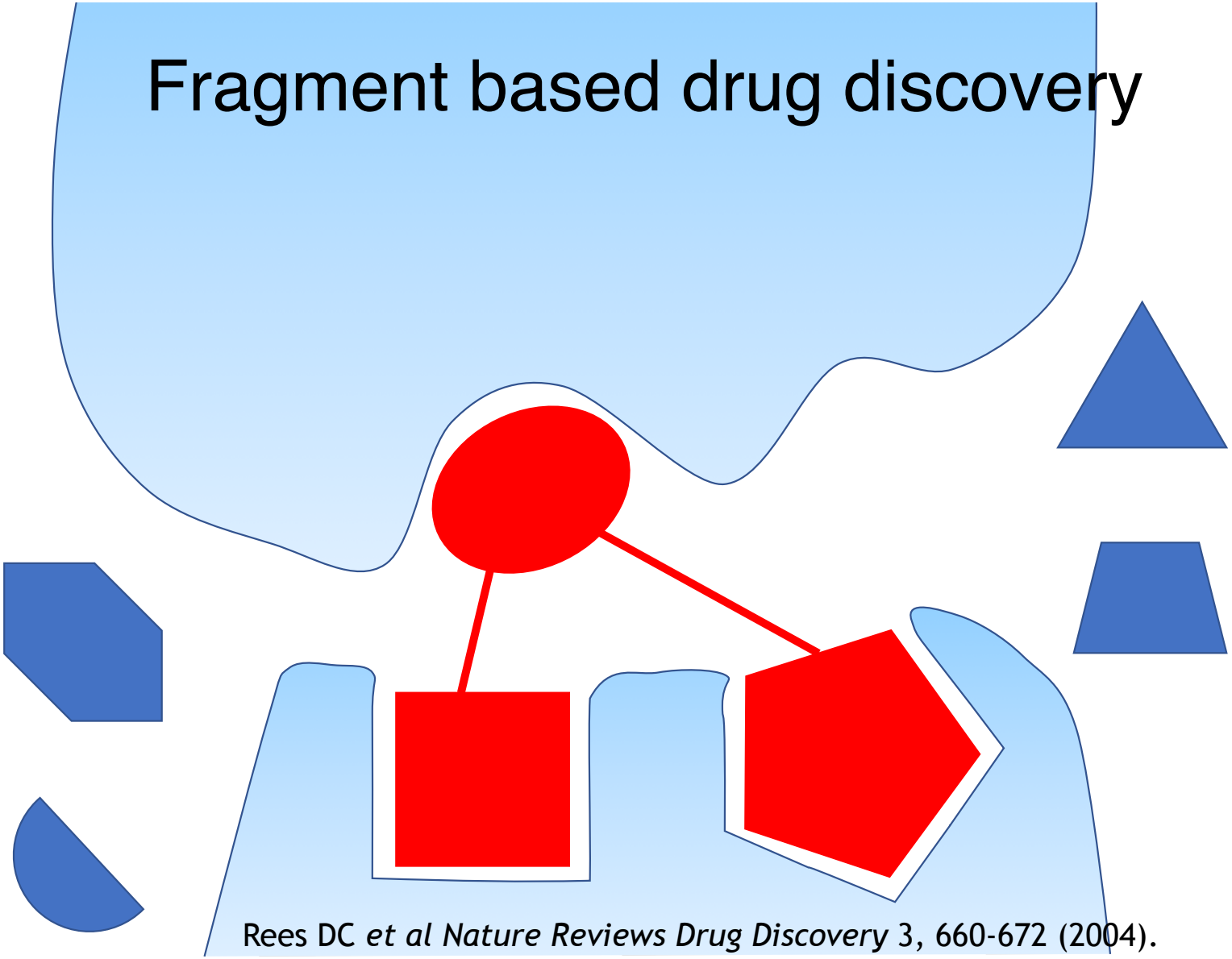
Candidate

Lead

What is a **fragment**?

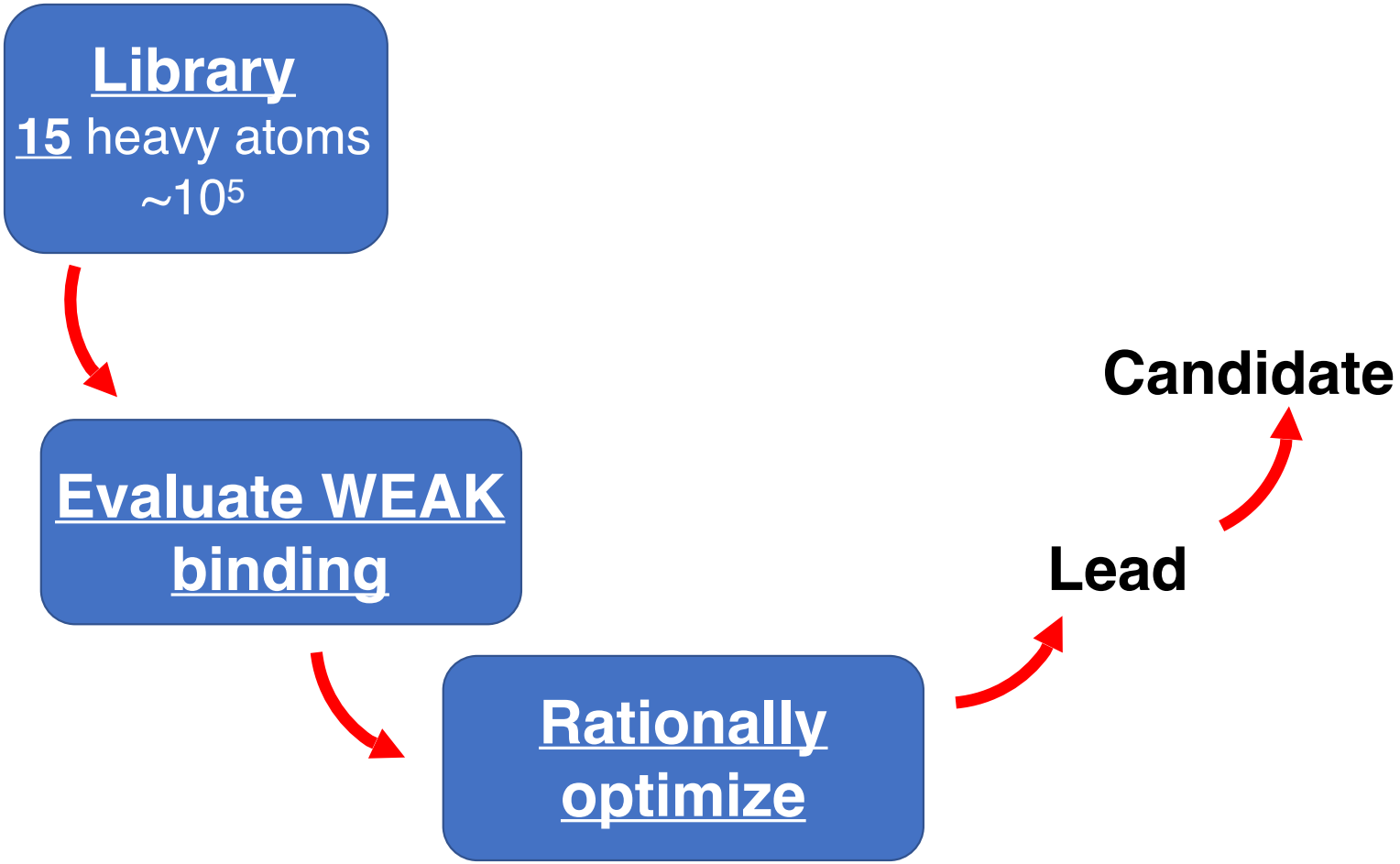


Fragment based drug discovery



Rees DC *et al Nature Reviews Drug Discovery* 3, 660-672 (2004).

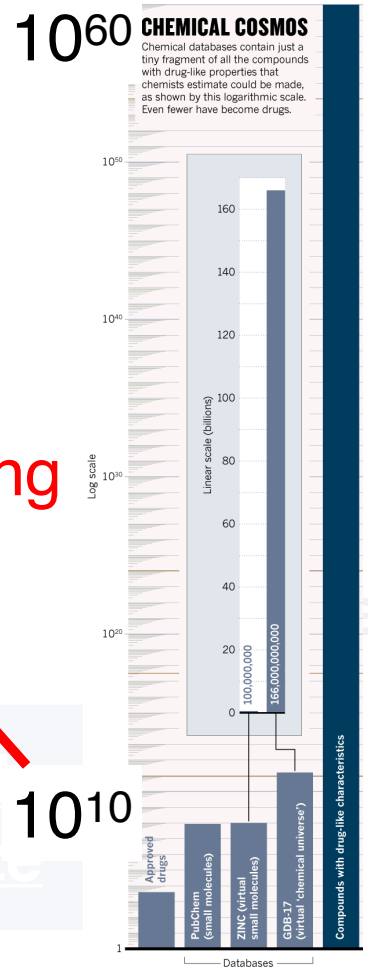
Fragment based drug discovery



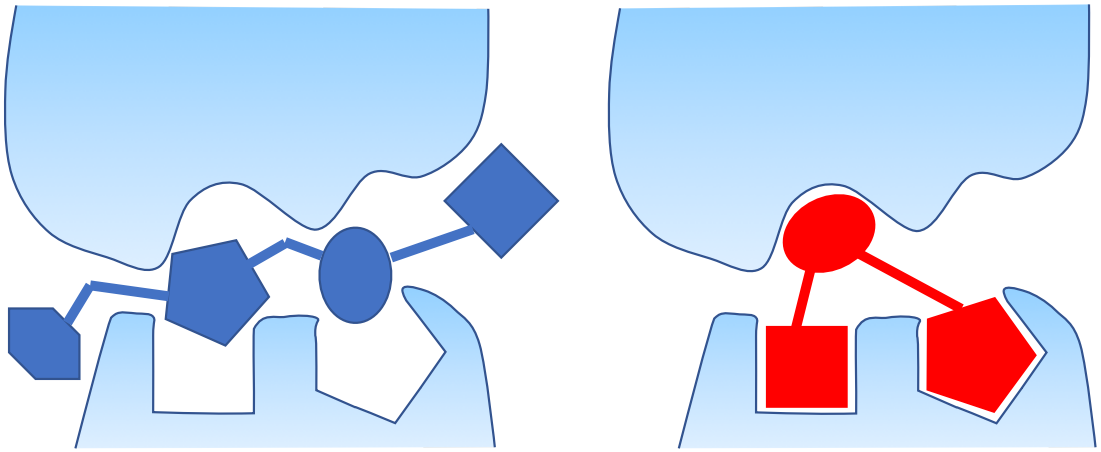
Fragment based drug discovery

Library
15 heavy atoms
~10^5

Less undersampling



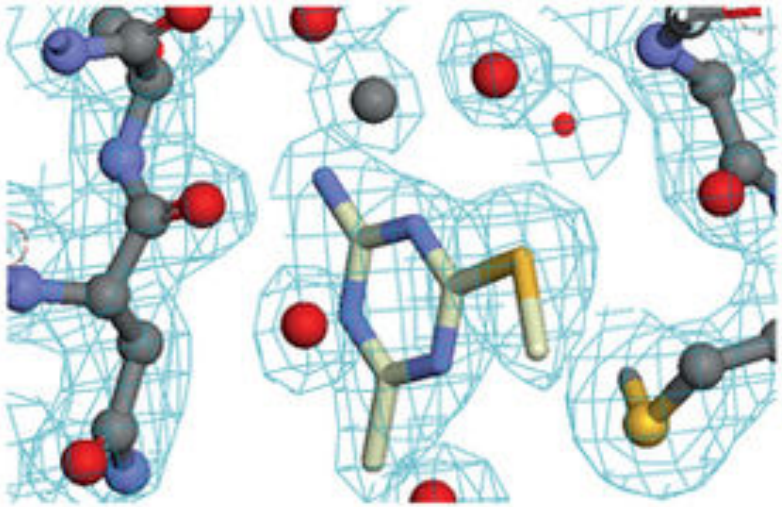
HTS vs Fragment based



	High-throughput screening	Fragment-based
Library size	1,000,000 – 10,000,000	<10,000
Molecular weight	>300 kDa	<300 kDa
Screening	More flexible	Well characterized targets
Affinities	µM	mM
Optimization	Fixing problems, improving affinity	Iterative improvement
Main downside	Attrition, can't solve " challenging" targets	Biophysical methods are hard!

Fragment based drug discovery

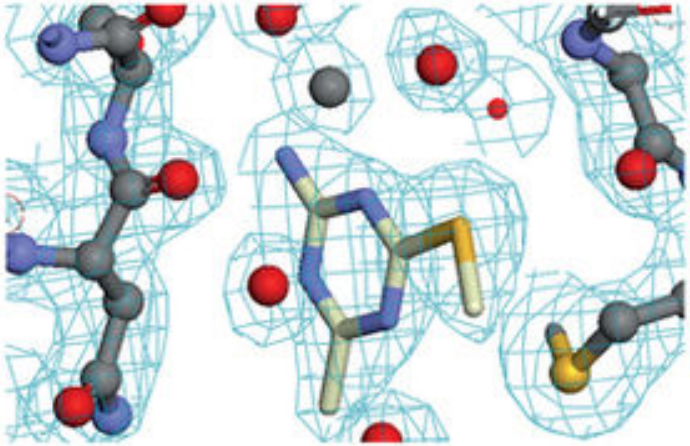
Assessing drug-target interaction



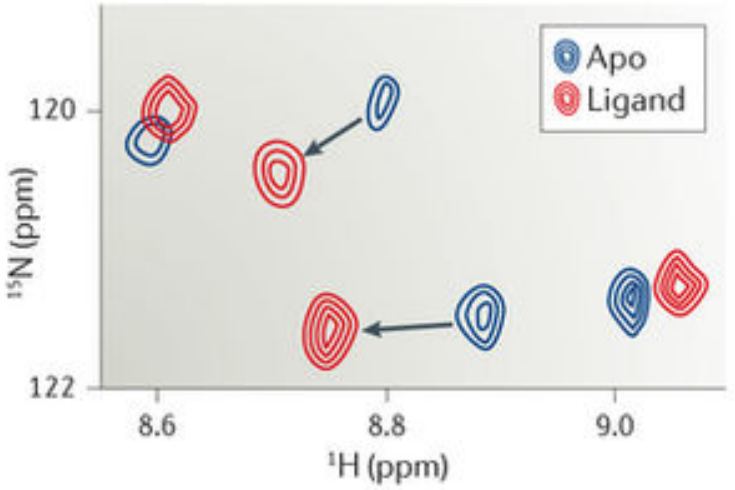
High resolution X-ray (or Cryo-EM) structure

Renaud JP *et al*. *Nature Reviews Drug Discovery* 15,679-698 (2016)

Assessing drug-target interaction



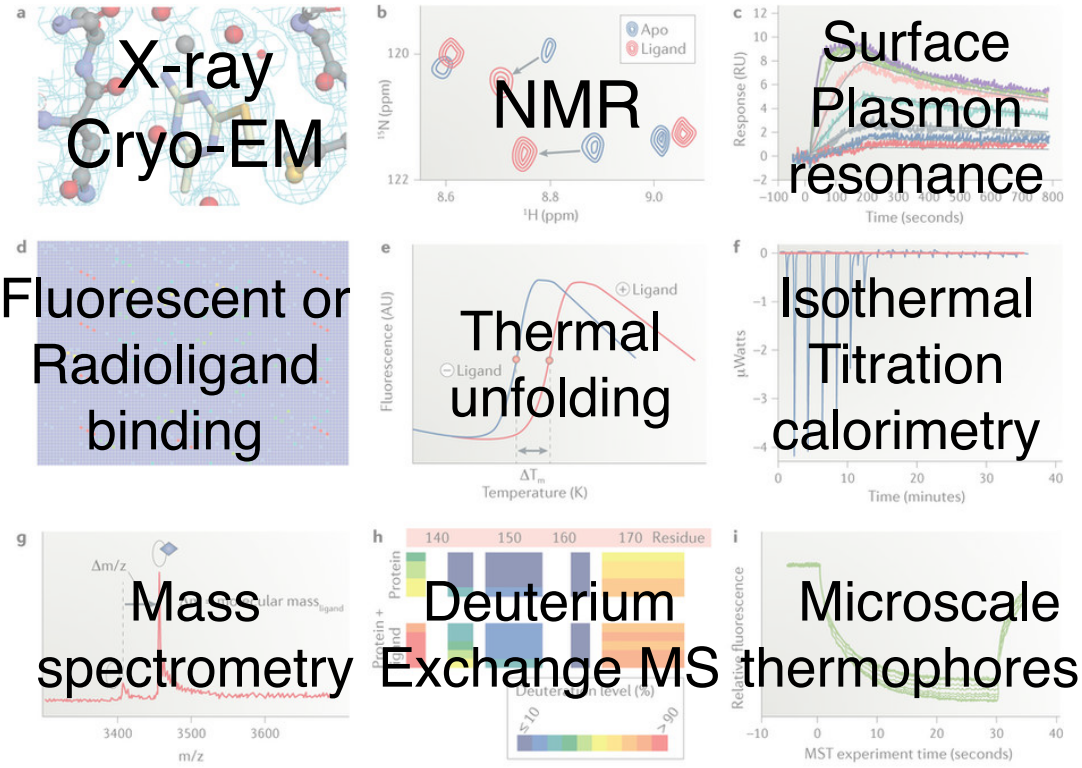
X-ray
Cryo-EM



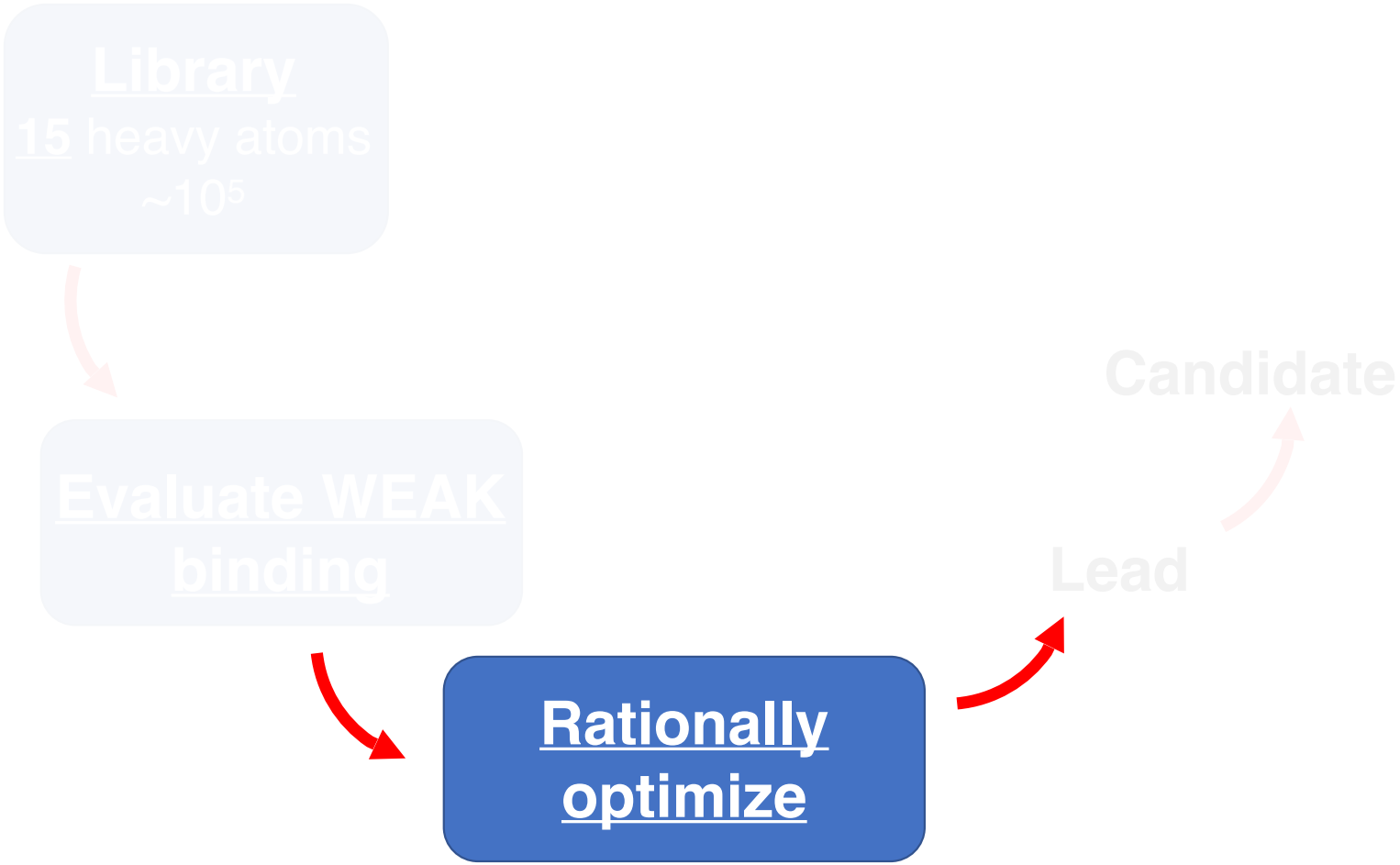
NMR

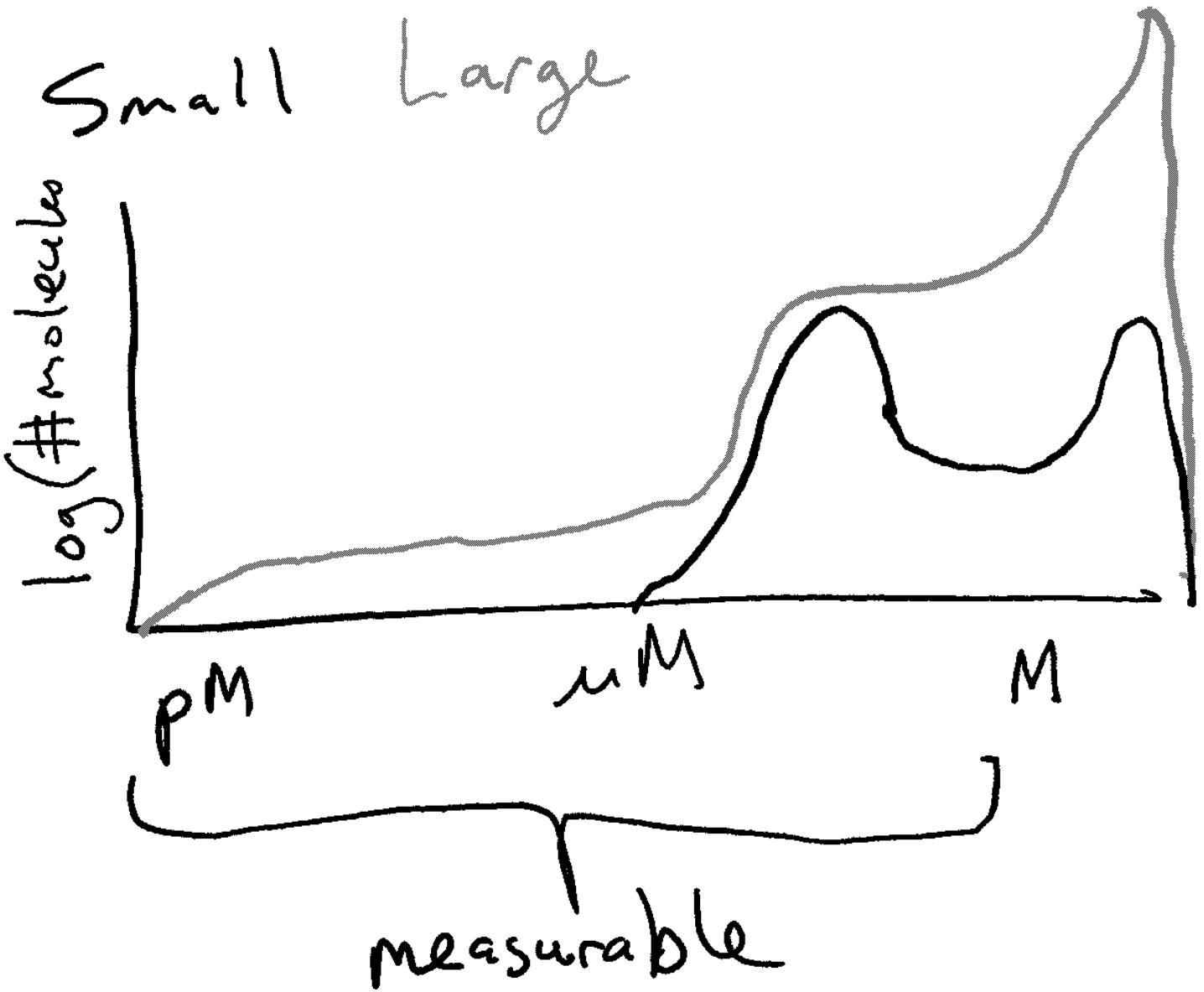
Renaud JP *et al*. *Nature Reviews Drug Discovery* 15,679-698 (2016)

Assessing drug-target interaction

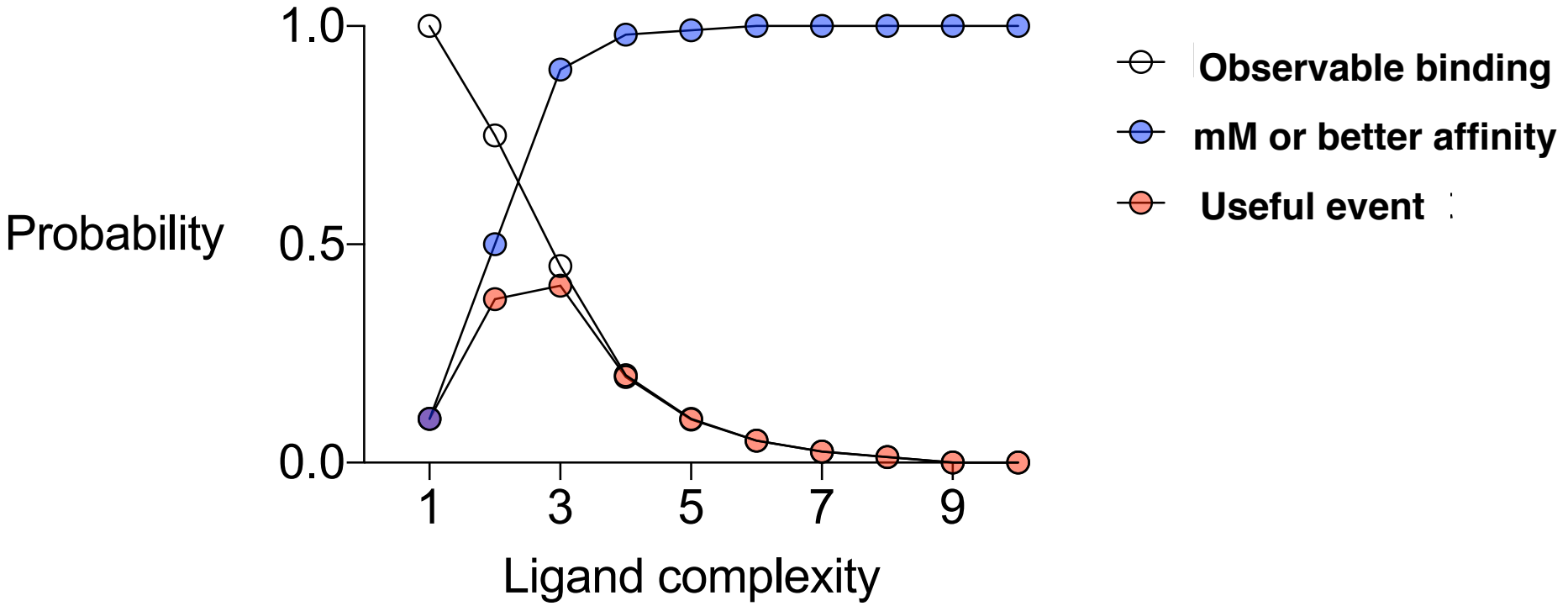


Fragment based drug discovery




Small
Large
log(#molecules)
pM
μM
M
measurable

Why Fragments? Observability x Affinity = Usefulness

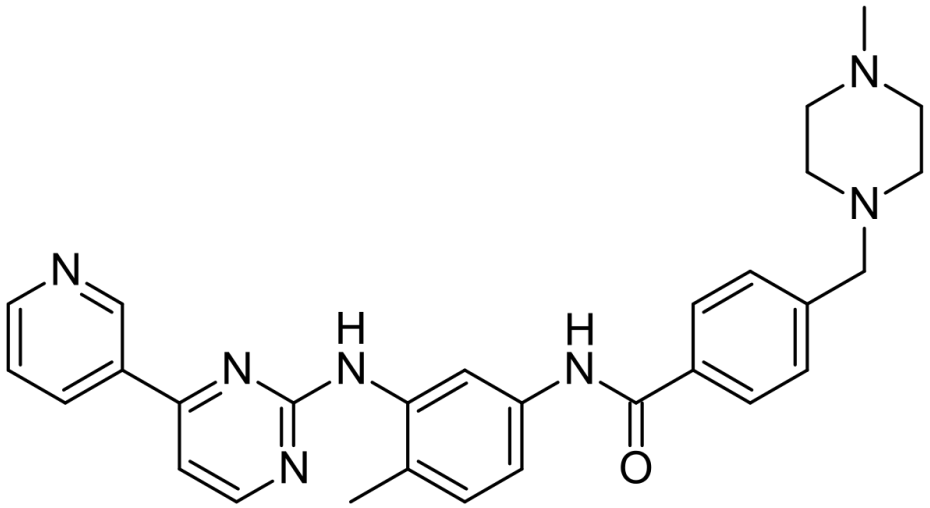


J Med Chem. 2016 Sep 22;59(18):8189-206. doi: 10.1021/acs.jmedchem.6b00197. Epub 2016 May 16.

Design Principles for Fragment Libraries: Maximizing the Value of Learnings from Pharma Fragment-Based Drug Discovery (FBDD) Programs for Use in Academia.

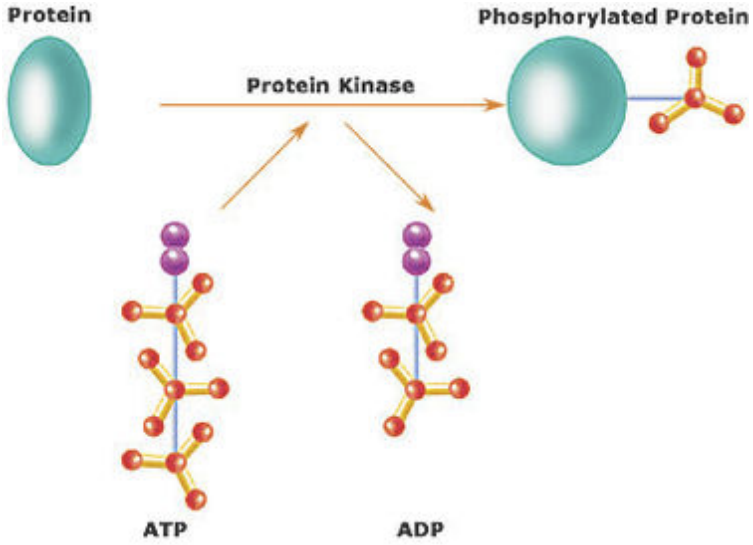
Keserű GM[1], Erlanson DA[2], Ferenczy GG[1], Hann MM[3], Murray CW[4], Pickett SD[3].

Kinases have become one of the major drug target classes over the past 20 years

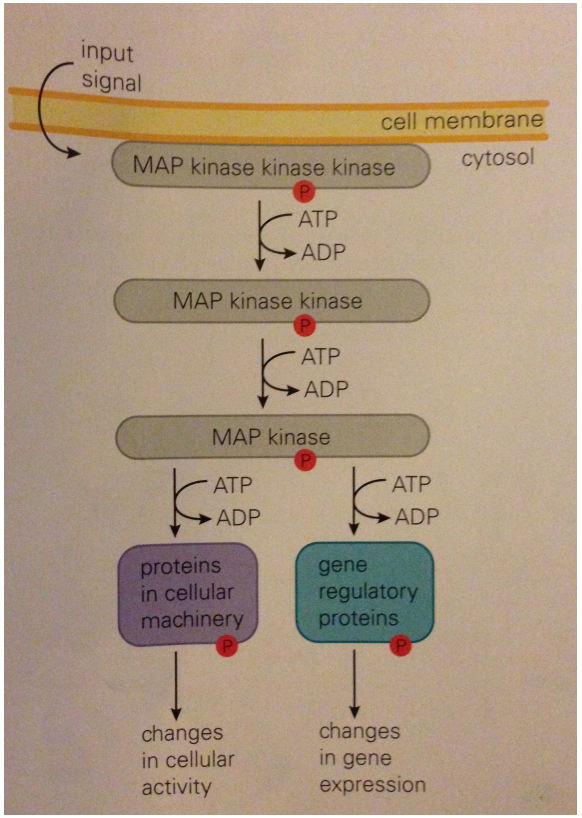


Break!

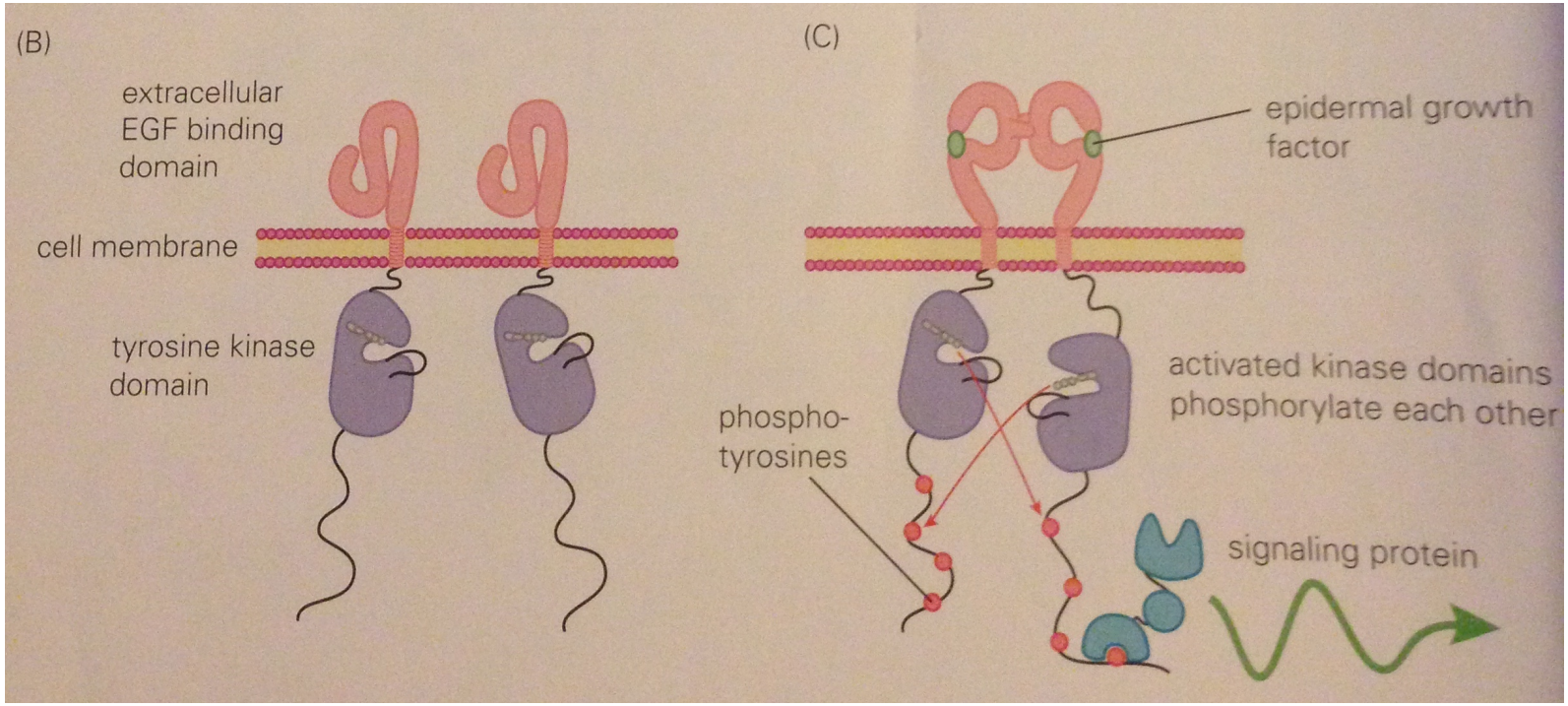
Kinases are enzymes that control cellular information flow



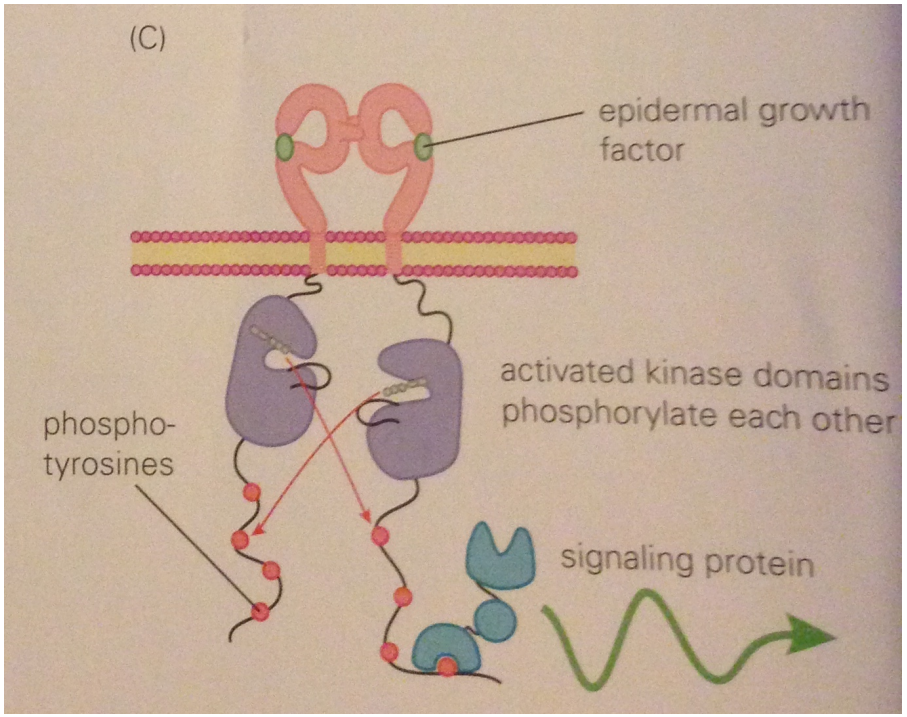
Control many **growth**/cell cycle signals
Antagonized by **phosphatases**
(to which there are no inhibitors in the clinic)

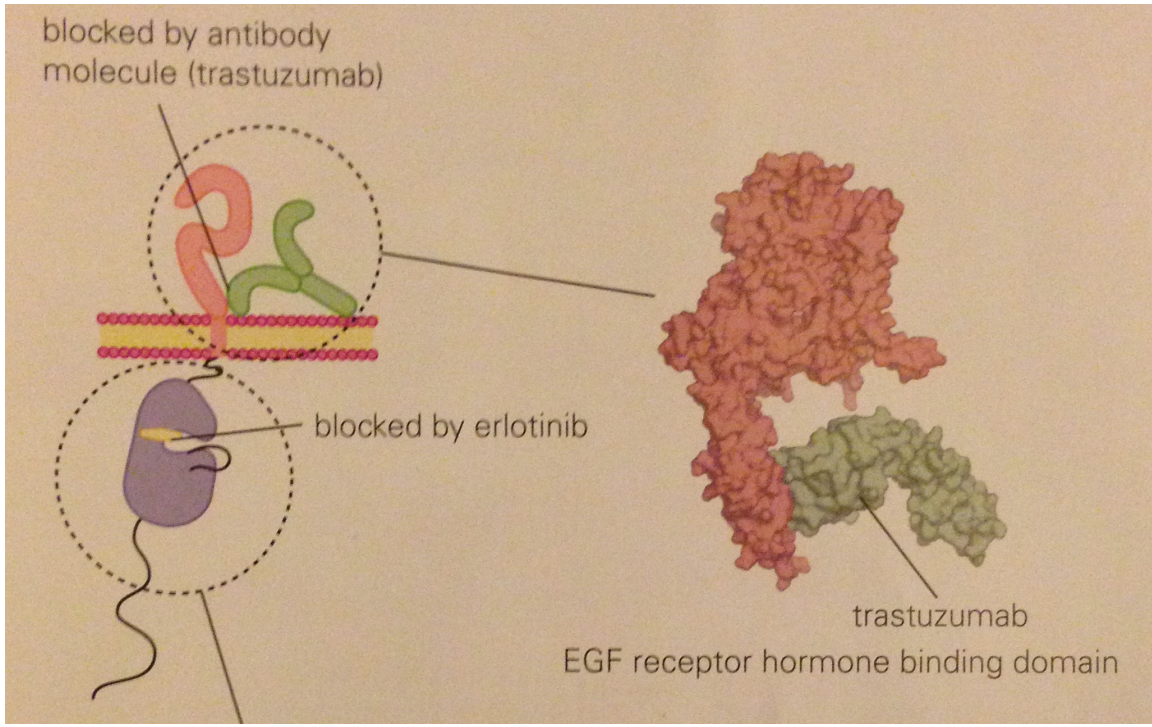


Receptor Kinases transmit signals from outside the cell, often through ligand-induced dimerization



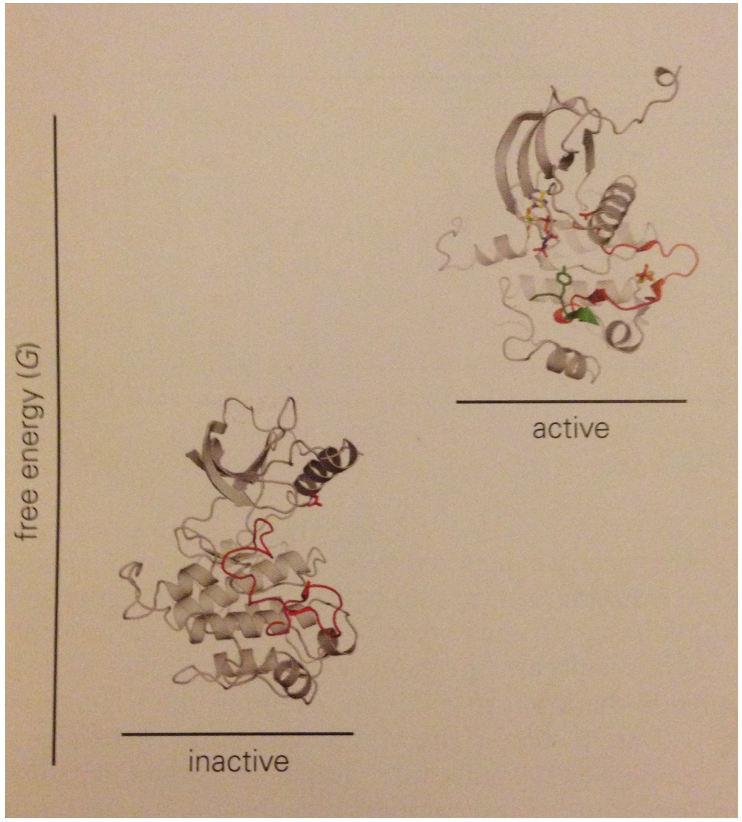
Therapeutic antibodies block extracellular dimerization, often using a distinct set of interactions

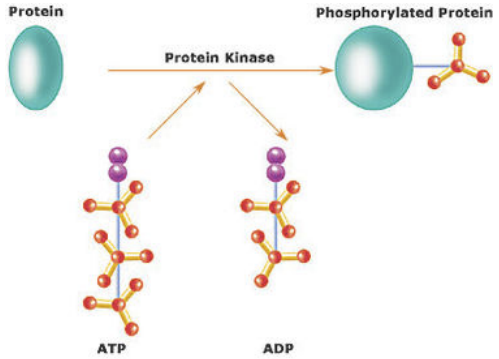




More on antibodies from Prof. Kortemme (next Tuesday)

Kinases switch between active and inactive conformations

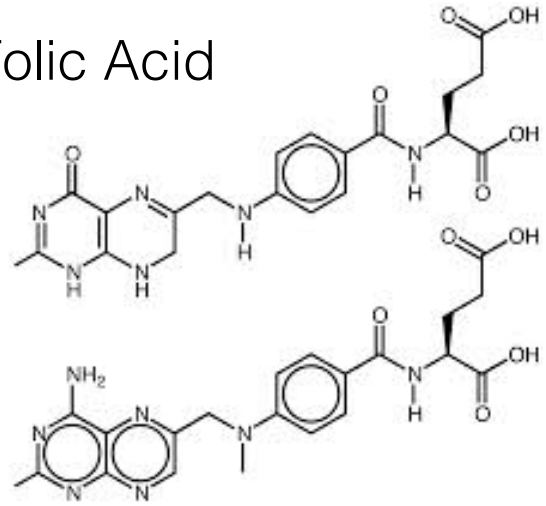




Hyperactive kinases are a common cause of cancer

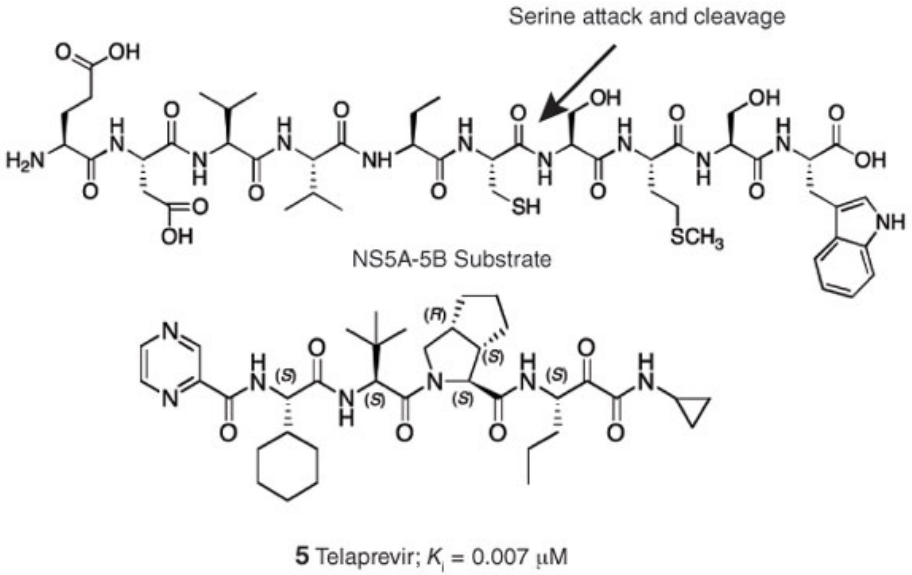
Drugs targeting enzymes (like kinase intracellular domain) tend to look like natural substrates (like ATP)

Folic Acid



Methotrexate

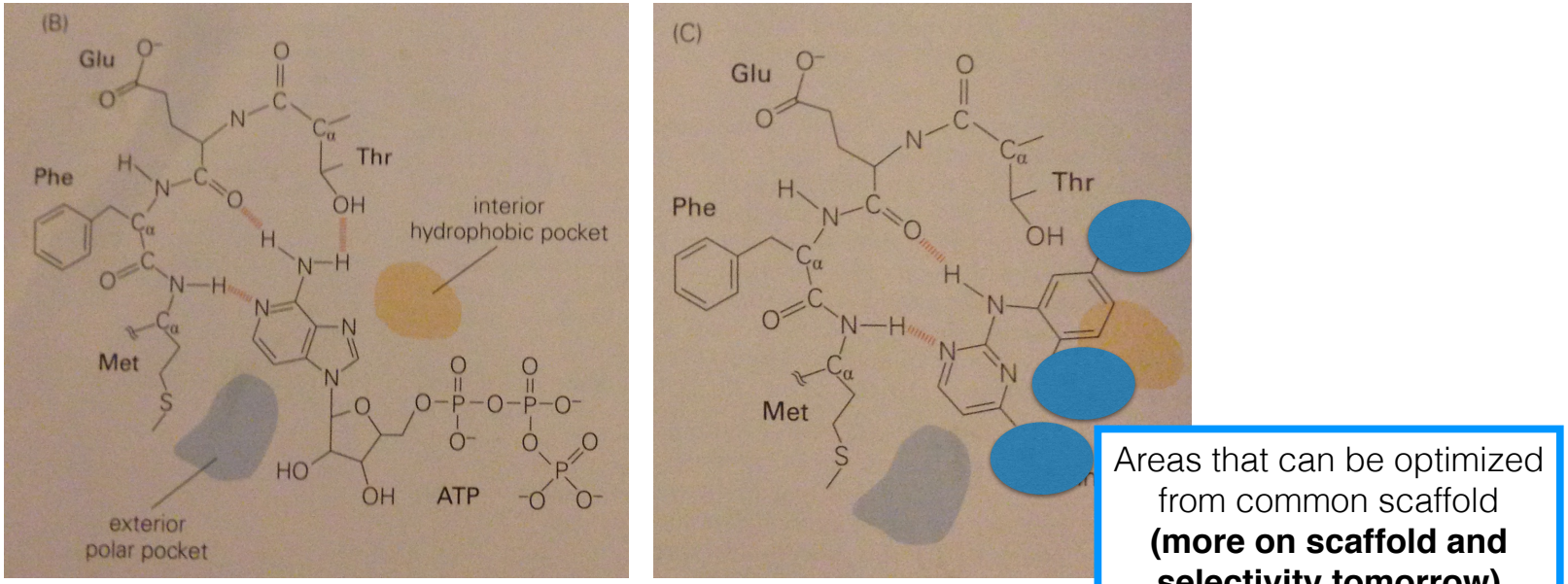
Target: DHFR



5 Telaprevir; K_i = 0.007 μM

Target: HCV Protease

Kinase inhibitors mimic ATP and compete for the same binding site



Areas that can be optimized from common scaffold **(more on scaffold and selectivity tomorrow)**

Large medicinal chemistry efforts to "tune" selectivity for an individual kinases' ATP binding site

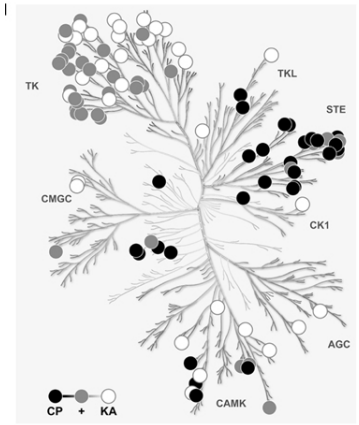
Keep in mind - nucleosides (base and ribose) are relatively hydrophobic

The kinase active site is highly conserved and optimized for ATP binding

Description	CHK1	CDK2	SRC	ABL	EGFR	RAF	MEK
Ribose/hydrophobic pocket	L15 G16	I10 G11	L273 G274	L248 G249	L718 G719	I463 G464	L74 G75
"Roof" of adenine pocket	V23	V18	V281	V256	V726	V471	V82
Glu-Lys ion pair	K38 E55	K33 E51	K295 E310	K271 E286	K745 E762	K483 E501	K97 E114
Gatekeeper residue	L84	F80	T338	T315	T790	T529	M143

Only the "gatekeeper" residue is variable

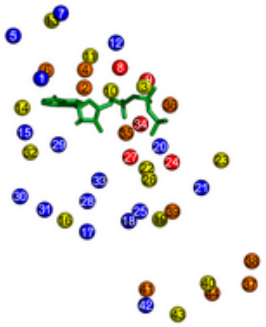
Catalytic aspartate	D130	D127	D386	D363	D837	D576	D190
Phosphate binding region	N135	N132	N391	N368	N842	N581	N195
"Floor" of adenine pocket	L137	L134	L393	L370	L844	F583	L197



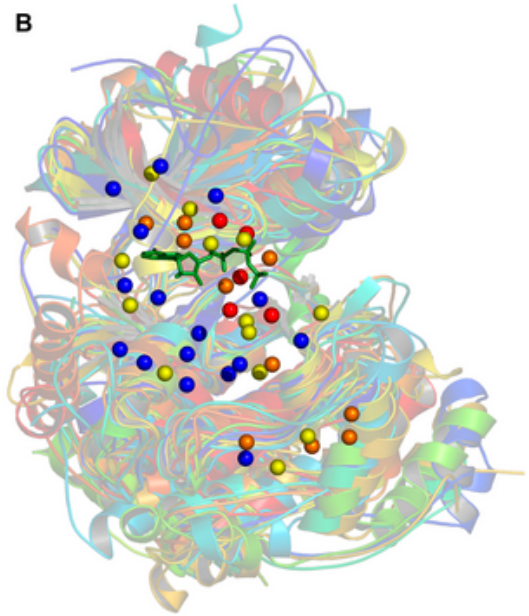
…because of this kinases were considered "undruggable"

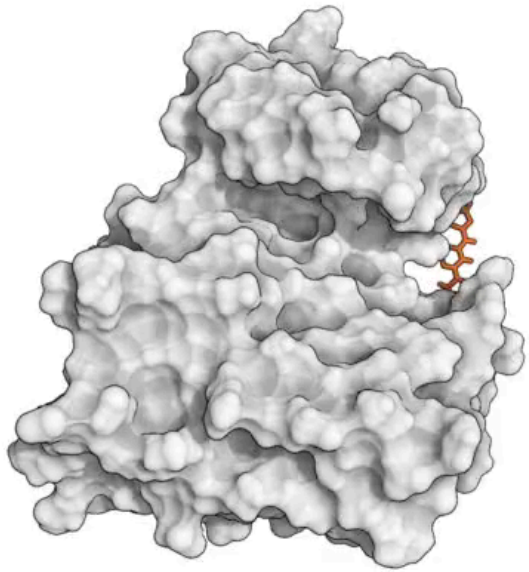
Fortunately two things help : 1) conservation is reduced away from the binding site, 2) kinases are structurally plastic

A



B





Conservation, Variability and the Modeling of Active Protein Kinases

James D. R. Knight, Bin Qian, David Baker, Rashmi Kothary

Published: October 3, 2007 • https://doi.org/10.1371/journal.pone.0000982

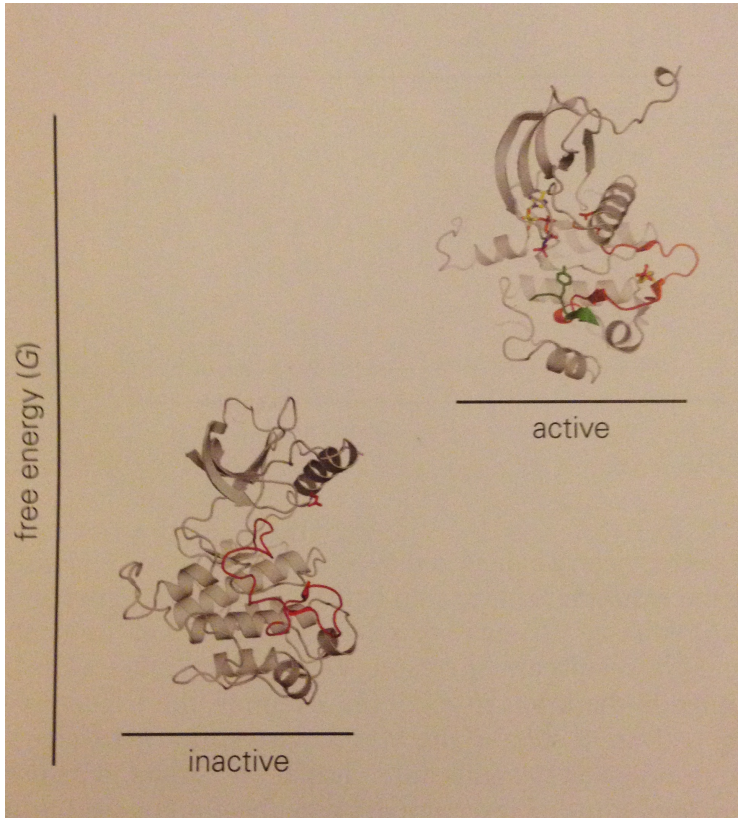
How Does a Drug Molecule Find Its Target Binding Site?

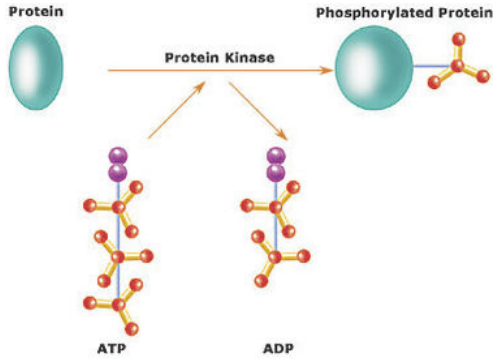
Yibing Shan[†], Eric T. Kim[†], Michael P. Eastwood[†], Ron O. Dror[†], Markus A. Seeliger[§] and David E. Shaw[*†‡]

View Author Information

Cite this: *J. Am. Chem. Soc.* 2011, 133, 24, 9181-9183

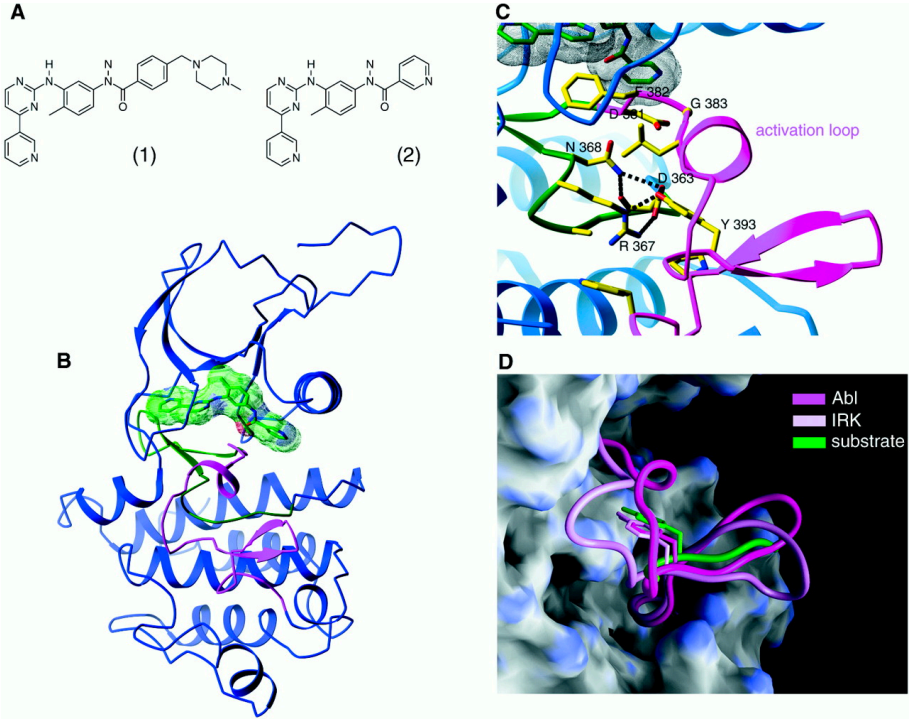
Kinases switch between active and inactive conformations





Hyperactive kinases are a common cause of cancer

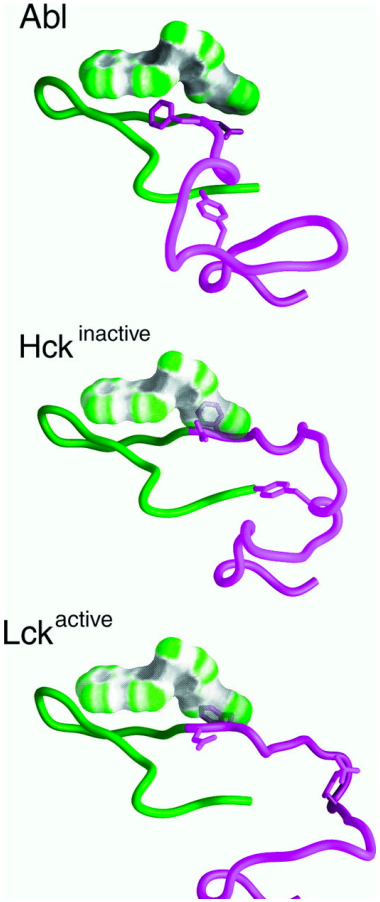
Binding of Gleevec to Abl exploits the active-inactive equilibrium



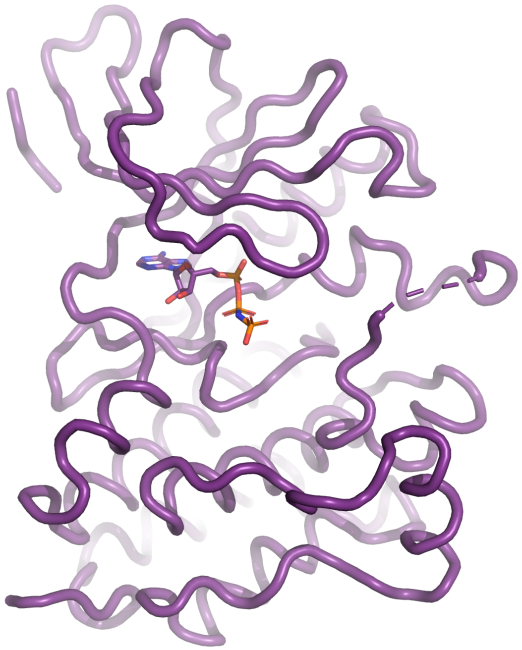
Structural Mechanism for STI-571 Inhibition of Abelson Tyrosine Kinase

Thomas Schindler[1], William Bornmann[3], Patricia Pellicena[4], W. Todd Miller[4], Bayard Clarkson[3], John Kuriyan[1,2,*]
+ See all authors and affiliations

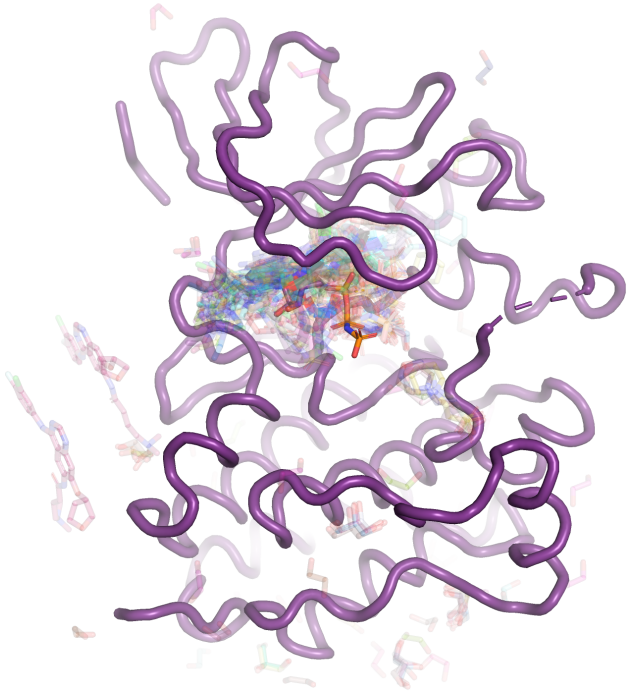
Science 15 Sep 2000:
Vol. 289, Issue 5486, pp. 1938-1942
DOI: 10.1126/science.289.5486.1938



While kinase inhibitors maintain overlap with the adenine ring of ATP, the search for specificity goes elsewhere

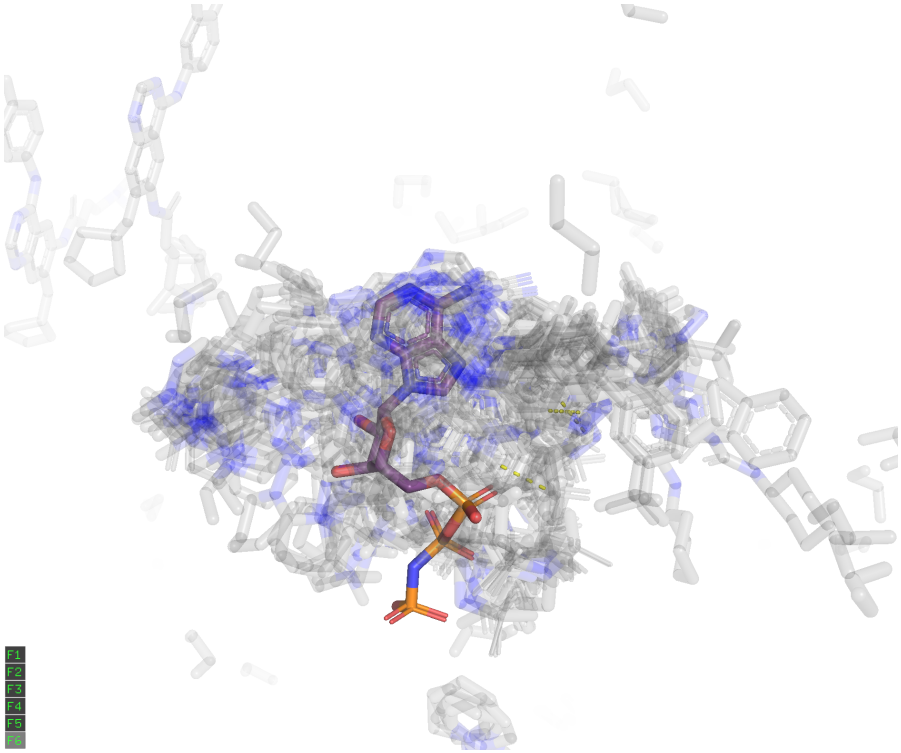


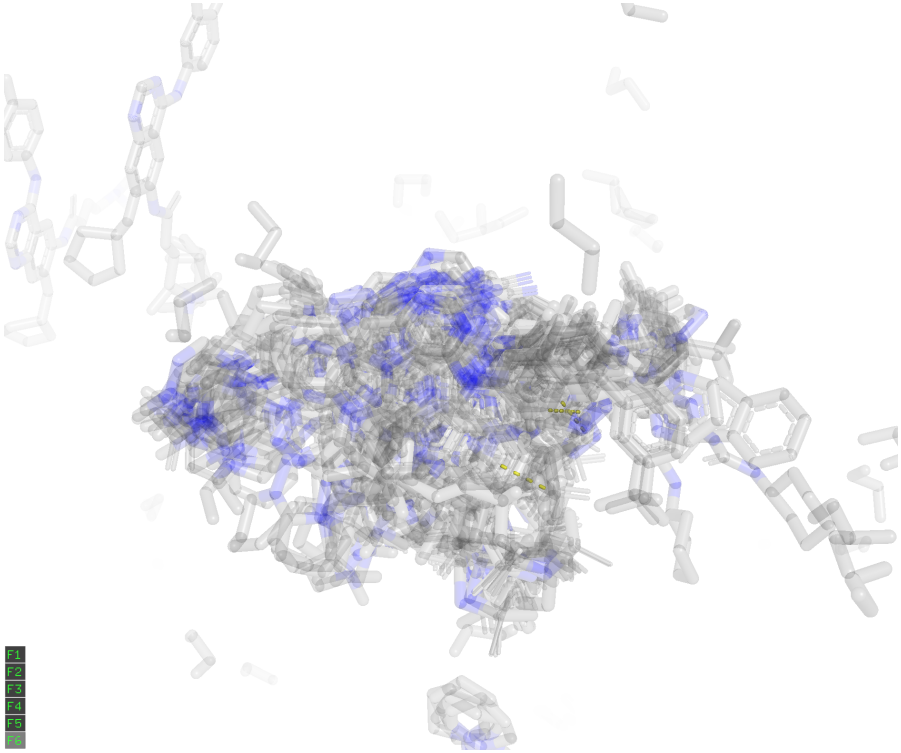
2GS7



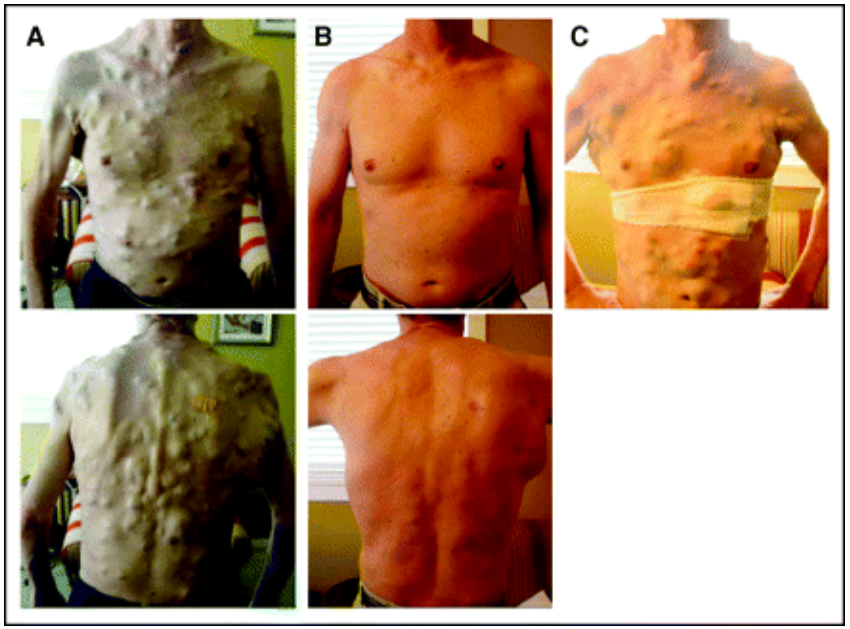
All EGFR ligands

Key “hinge” hydrogen bonds are a major design element in kinase inhibitors, but other areas provide specificity



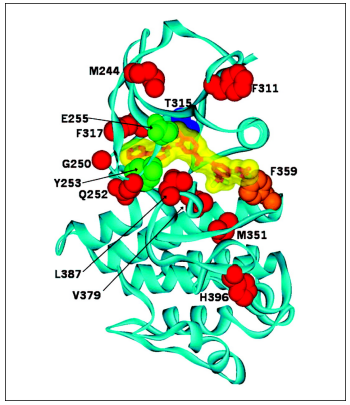


Clinical introduction of potent kinase inhibitors is closely followed by resistance

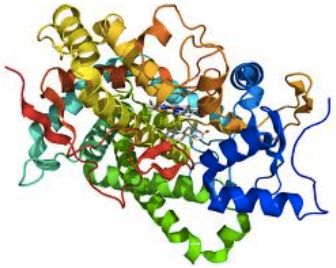


A 38-year-old man with BRAF-mutant melanoma and subcutaneous metastatic deposits. Photographs were taken (A) before initiation of PLX4032, (B) after 15 weeks of therapy with PLX4032, and (C) after relapse, after 23 weeks of therapy.

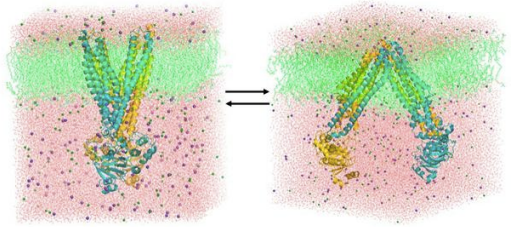
The common resistance mechanisms for small molecules



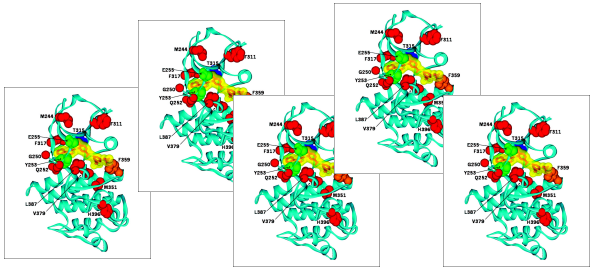
active site mutations



degradation of inhibitor

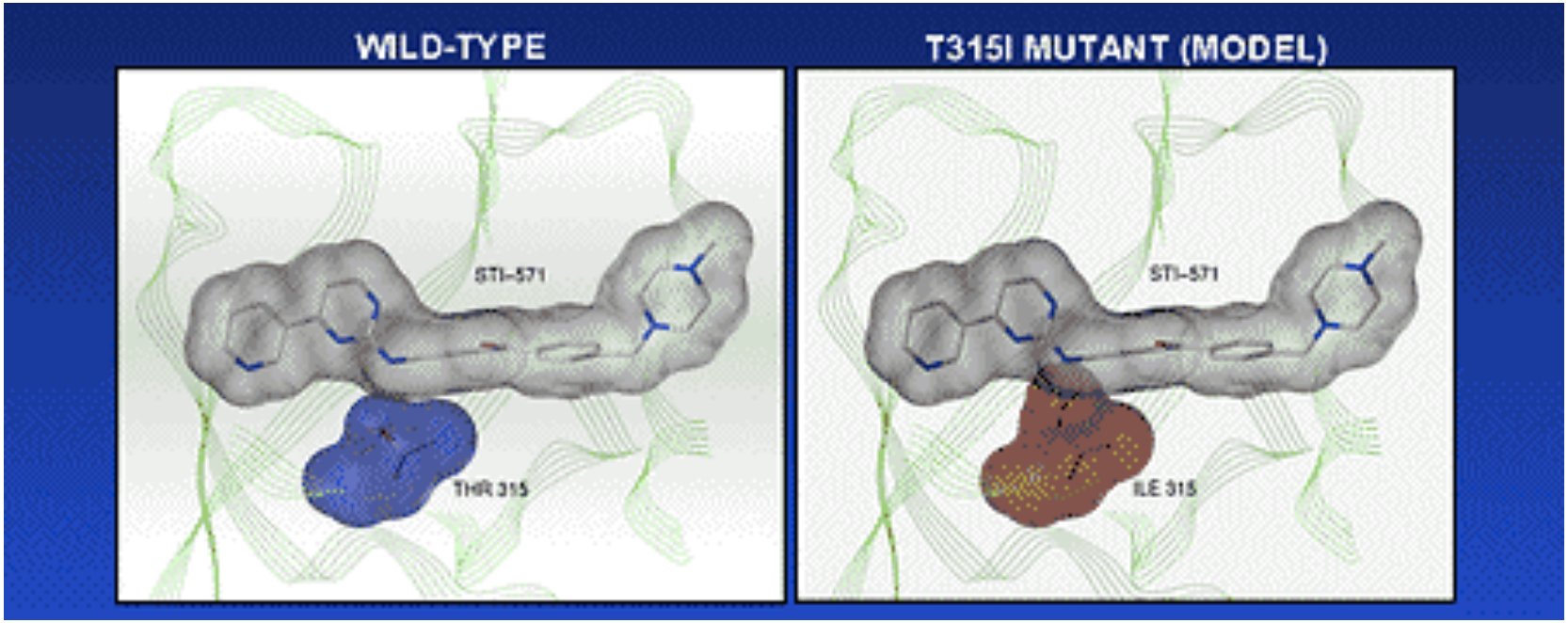


efflux



over-expression+other signaling

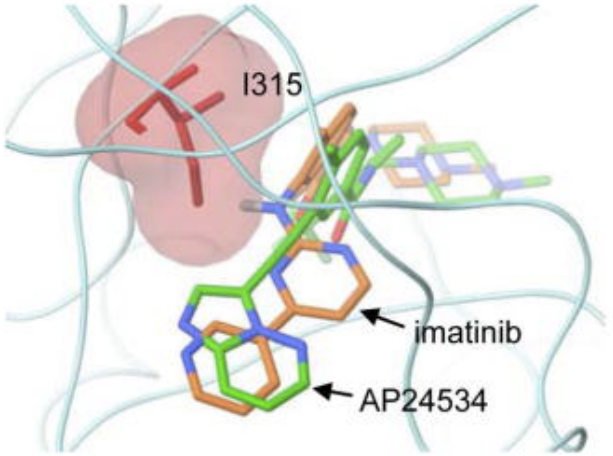
Active site mutations directly alter interactions with drugs



Mutation at variable "gatekeeper" residue

Protein modeling and structural biology play a large role in combating resistance

- X-ray crystallography of mutant proteins
- Trimming the molecule to avoid clashes caused by Small-to-Large mutations
- Conformational changes are difficult to predict (molecular dynamics simulations can help)



O'Hare…Clackson
Cancer Cell, 2009

VOLUME 29 · NUMBER 22 · AUGUST 1 2011

JOURNAL OF CLINICAL ONCOLOGY

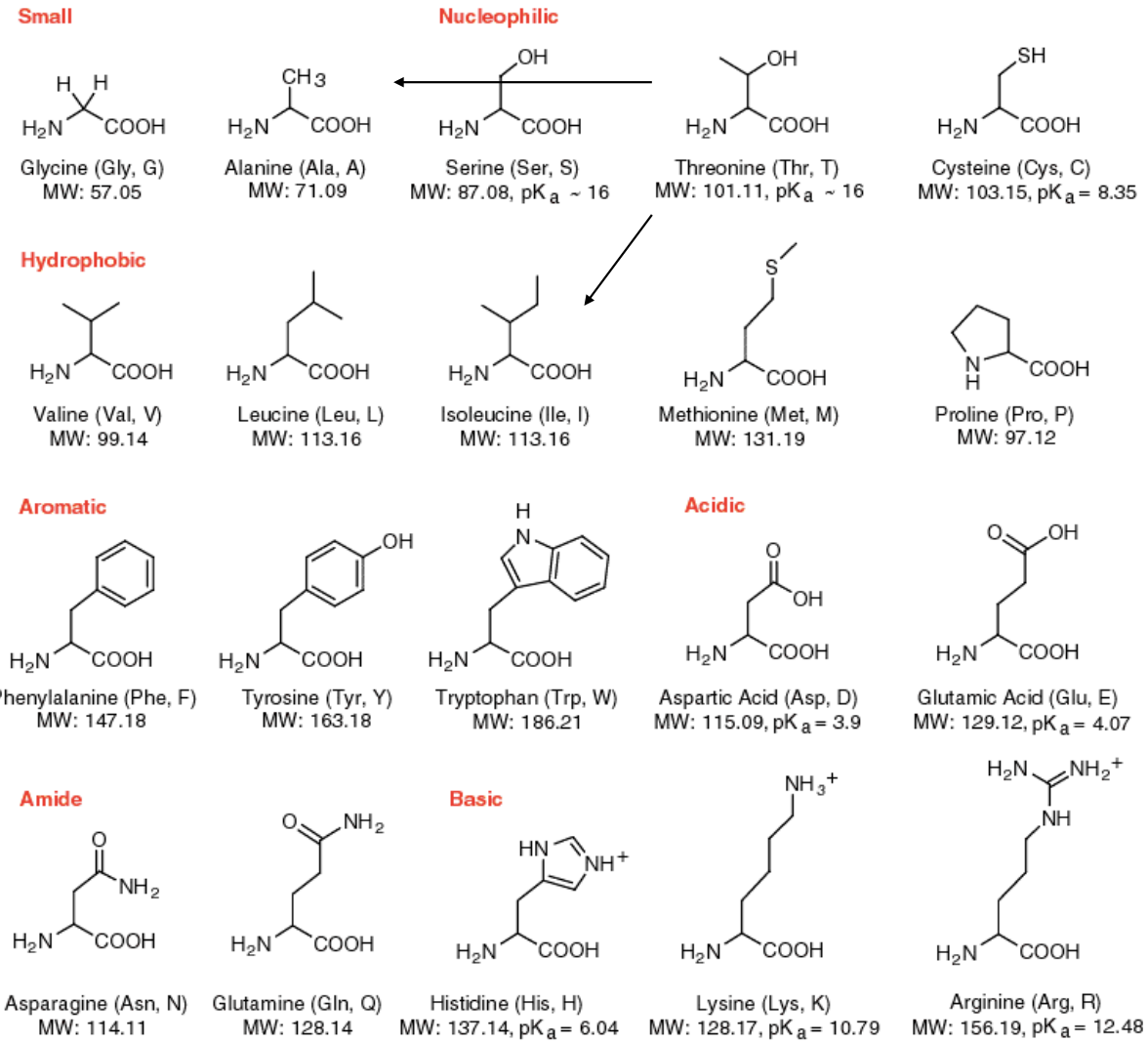
Table 2. Exemplary Mechanisms of Acquired Resistance to Kinase Inhibitors

Targeted Agent	Target Gene	Acquired Resistance via Secondary Mutation, Amplification, or Activation of Target	Acquired Resistance via Bypass	Acquired Resistance via Downstream Mutation
Imatinib				
	ABL	T315I	*IGF1R* amplification	
		Y253F/H	AXL overexpression*†	
		E255K/V		
		ABL amplification		
		T670I		
		V654A		
		D816A/G/H/V		
		D820A/E/G/Y		
	KIT	Y823D		
		KIT amplification		
	PDGFRA	T674I		
Gefitinib or erlotinib	*EGFR*	T790M	*MET* amplification	
		D761Y	HGF overexpression*†	
		L747S	IGFBP3 loss*†	
		T854A		
		EGFR amplification*		
Trastuzumab	*HER2*			
Lapatinib	*HER2/EGFR*			
PKC412	*FLT3*	N676K		
	FGFR			
AZD6044	*MEK1*	MEK1 P124L		
		BRAF amplification*		
PLX4032	*BRAF*	NRAS Q61K	COT overexpression†	MEK1 C121S
			PDGFRβ overexpression†	
			CRAF overexpression*†	
			AXL overexpression*†	
			HER2 overexpression*†	
Crizotinib	*ALK/MET*	L1196M		
		C1156Y		
		F1174L		

Abbreviations: IGF1R, insulin-like growth factor 1 receptor; HGF, hepatocyte growth factor; IGFBP3, insulin-like growth factor receptor binding protein-3; PDGFRβ, platelet-derived growth factor β; HER2, human epidermal growth factor receptor 2.

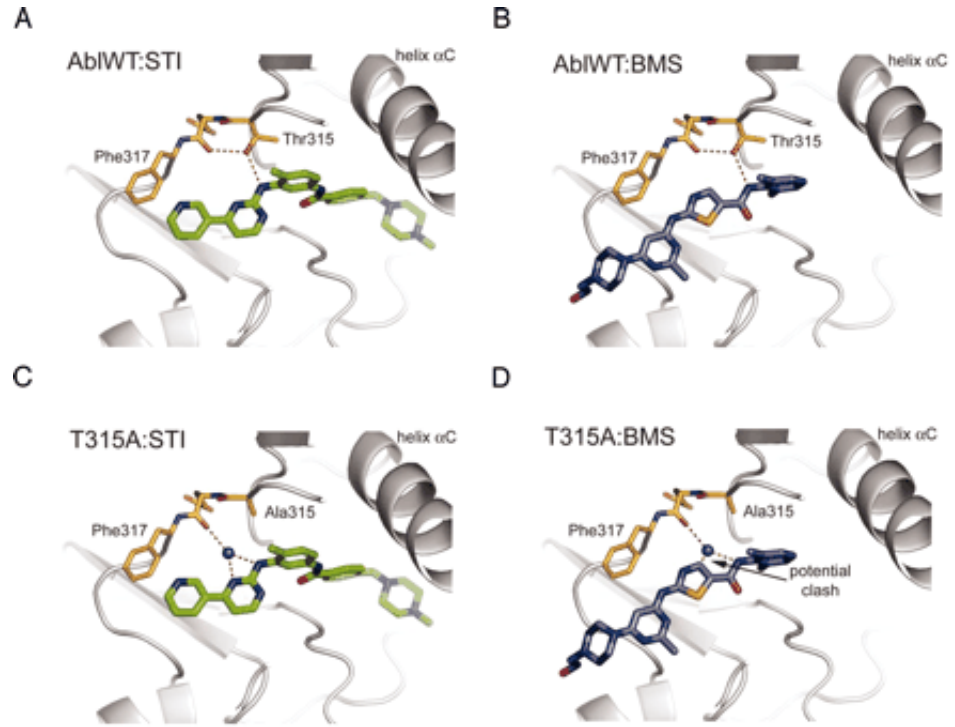
*Mechanisms that have been described in vitro.

†Nongenetic mechanisms.

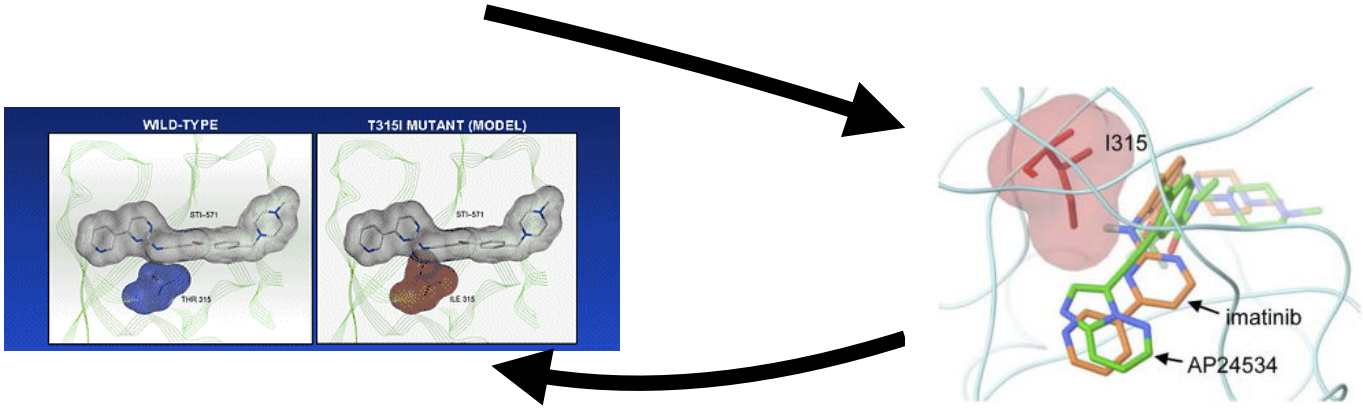

Small
Nucleophilic
Glycine (Gly, G)
MW: 57.05
Alanine (Ala, A)
MW: 71.09
Serine (Ser, S)
MW: 87.08, pKa ~ 16
Threonine (Thr, T)
MW: 101.11, pKa ~ 16
Cysteine (Cys, C)
MW: 103.15, pKa = 8.35
Hydrophobic
Valine (Val, V)
MW: 99.14
Leucine (Leu, L)
MW: 113.16
Isoleucine (Ile, I)
MW: 113.16
Methionine (Met, M)
MW: 131.19
Proline (Pro, P)
MW: 97.12
Aromatic
Acidic
Phenylalanine (Phe, F)
MW: 147.18
Tyrosine (Tyr, Y)
MW: 163.18
Tryptophan (Trp, W)
MW: 186.21
Aspartic Acid (Asp, D)
MW: 115.09, pKa = 3.9
Glutamic Acid (Glu, E)
MW: 129.12, pKa = 4.07
Amide
Basic
Asparagine (Asn, N)
MW: 114.11
Glutamine (Gln, Q)
MW: 128.14
Histidine (His, H)
MW: 137.14, pKa = 6.04
Lysine (Lys, K)
MW: 128.17, pKa = 10.79
Arginine (Arg, R)
MW: 156.19, pKa = 12.48

Compensatory chemical changes in drugs can target resistance mutations

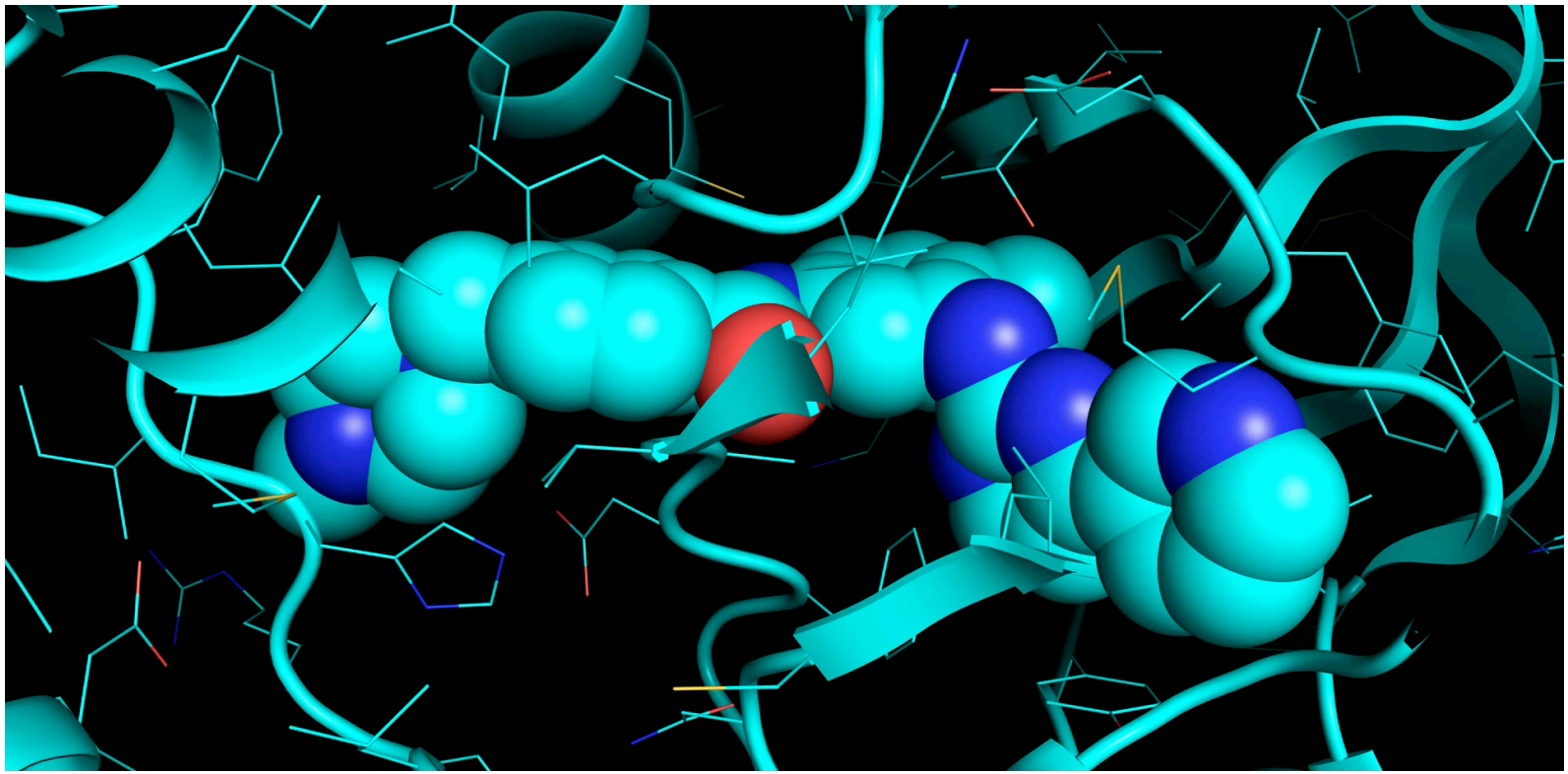
- Filling the new holes created by Large-to-Small mutations
- or exploiting solvent interactions



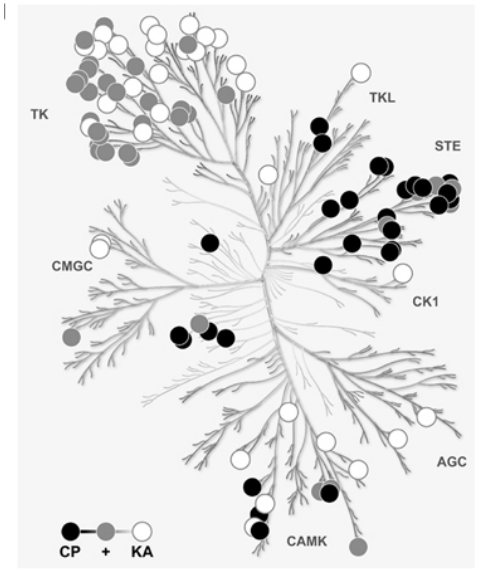
The cycle of compensatory changes - an evolutionary arms race!



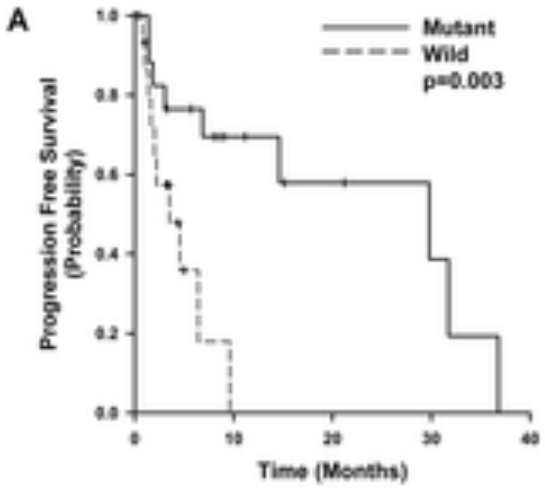
More common to have many cycles of this race for anti-virals and anti-bacterials than anti-cancer



Mutant kinase profiling and sequencing studies will enable rapid feedback between drugs



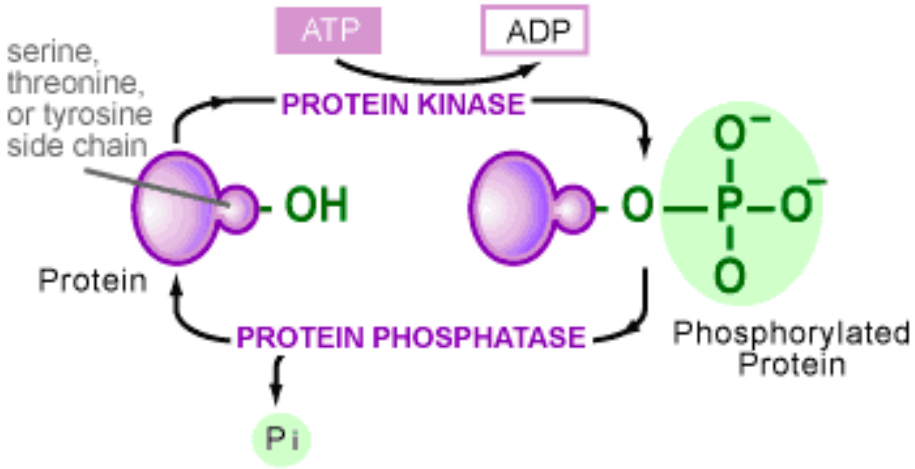
Kinase profiling to expand from WT to include mutants



Drugs targeting emerging resistance will be more effective

Keep in mind - nucleosides (base and ribose) are relatively hydrophobic

>200 small molecules tested in humans
>30 approved inhibitors



…but none against phosphatases
(a phosphopeptide is very charged!)

The disease biology of **phosphatases** is, perhaps, no less compelling than kinases

Table 3. Disease-related protein phosphatases. Each row shows a human protein phosphatase gene, its classification, disease(s), and whether it is a cancer gene.

Gene symbol	Fold	Family	Subfamily	Disease(s)	Cancer gene
CDKN3	CC1	DSP	CDKN3	Hepatocellular carcinoma	Yes
DUSP6	CC1	DSP	DSP6	Hypogonadotropic hypogonadism	
DUSP16	CC1	DSP	DSP8	Tumor suppressor	Yes
Laforin	CC1	DSP	Laforin	Lafora disease	
MTM1	CC1	Myotubularin	MTMR1	Cancer driver, severe X-linked myotubular myopathy	Yes
MTMR2	CC1	Myotubularin	MTMR1	Charcot-Marie-Tooth disease	
MTMR14	CC1	Myotubularin	MTMR14	Myopathy	
SBF1	CC1	Myotubularin	MTMR5	Charcot-Marie-Tooth disease	
SBF2	CC1	Myotubularin	MTMR5	Charcot-Marie-Tooth disease	
DNAJC6	CC1	PTEN	Auxilin	Parkinson's disease	
PTEN	CC1	PTEN	PTEN	Tumor suppressor	Yes
PTPN1	CC1	PTP	PTPN1	Diabetes mellitus type 2	
PTPN22	CC1	PTP	PTPN12	Diabetes mellitus type 1, rheumatoid arthritis, lupus	
PTPN13	CC1	PTP	PTPN13	Cancer driver	Yes
PTPN14	CC1	PTP	PTPN14	Choanal atresia and lymphedema	
PTPN11	CC1	PTP	PTPN6	Oncogene, LEOPARD syndrome 1, metachondromatosis, Noonan syndrome 1, Juvenile myelomonocytic leukemia	Yes
PTPRB	CC1	PTP	PTPRB	Tumor suppressor	Yes
PTPRO	CC1	PTP	PTPRB	Nephrotic syndrome	
PTPRQ	CC1	PTP	PTPRB	Deafness	
PTPRC	CC1	PTP	PTPRC	Tumor suppressor, severe combined immunodeficiency	Yes
PTPRF	CC1	PTP	PTPRD	Breasts and/or nipples, aplasia or hypoplasia	
PTPRZ1	CC1	PTP	PTPRG	Susceptibility to *Helicobacter pylori* infection	
PTPRK	CC1	PTP	PTPRK	Cancer gene	Yes
FIG4	CC1	Sac	FIG4	Yunis-Varon syndrome, Charcot-Marie-Tooth disease, amyotrophic lateral sclerosis, polymicrogyria	
SYNJ1	CC1	Sac	Synaptojanin	Parkinson disease	
EYA1	HAD	EYA	EYA	Melnick-Fraser syndrome, otofaciocervical syndrome, branchiootic syndrome	
EYA4	HAD	EYA	EYA	Deafness, dilated cardiomyopathy	
Dullard	HAD	FCP	DULLARD	Cancer gene	Yes
FCP1	HAD	FCP	FCP1	Congenital cataracts, facial dysmorphism, and neuropathy	
CECR5	HAD	NagD	CUT	Cancer gene	Yes
BPGM	HP	HP1	PGAM	Bisphosphoglycerate mutase deficiency	
PGAM2	HP	HP1	PGAM	Glycogen storage disease	
ACP2	HP	HP2	ACP2	Acid phosphatase deficiency	
MINPP1	HP	HP2	MINPP1	Thyroid cancer	Yes
PDP1	PPM	PPM	PDPc	Pyruvate dehydrogenase phosphatase deficiency	
PPM1D	PPM	PPM	PPM1D	Cancer gene, familial breast cancer	Yes
PPM1K	PPM	PPM	PPM1K	Maple syrup urine disease	
ACP5	PPPL	PAP	ACP5	Spondyloenchondrodysplasia	
PPP6C	PPPL	PPP	PPP6C	Oncogene	Yes
ALPL	AP	AP	AP	Hypophosphatasia	

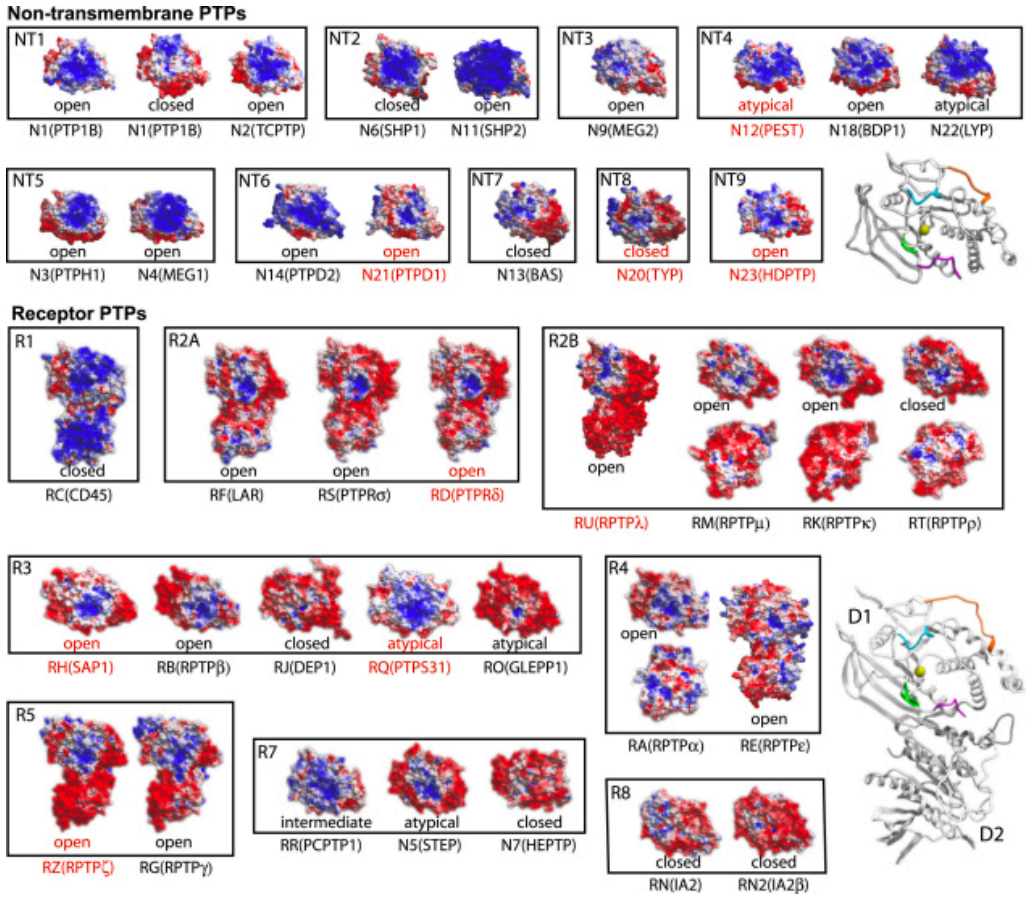
Chen, Dixon, Manning
Science Signalling, 2017

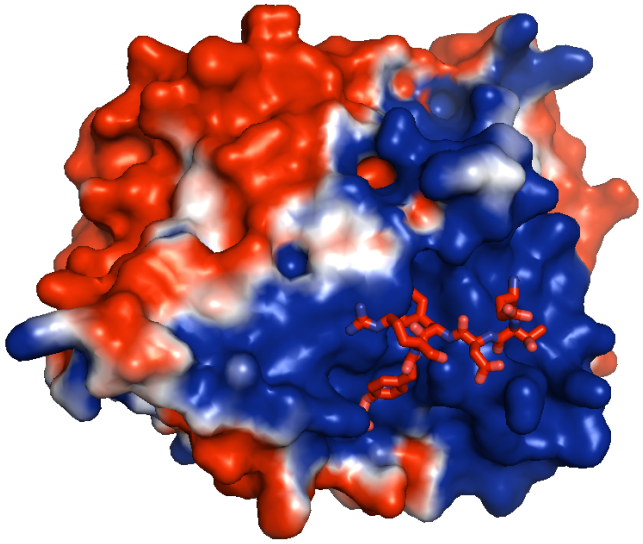
nature cell biology

PTP1B controls non-mitochondrial oxygen consumption by regulating RNF213 to promote tumour survival during hypoxia

Robert S. Banh[1,2,3], Caterina Iorio[2,11], Richard Marcotte[2,11], Yang Xu[1,2,3,11], Dan Cojocari[1,2], Anas Abdel Rahman[4,5], Judy Pawling[4], Wei Zhang[6], Ankit Sinha[1,2], Christopher M. Rose[7], Marta Isasa[7], Shuang Zhang[3], Ronald Wu[1,2], Carl Virtanen[2], Toshiaki Hitomi[8], Toshiyuki Habu[9], Sachdev S. Sidhu[6], Akio Koizumi[8], Sarah E. Wilkins[10], Thomas Kislinger[1,2], Steven P. Gygi[7], Christopher J. Schofield[10], James W. Dennis[4], Bradly G. Wouters[1,2] and Benjamin G. Neel[2,3,12]

The highly charged active sites of protein tyrosine **phosphatases** exemplify the difficulties of active site drug discovery

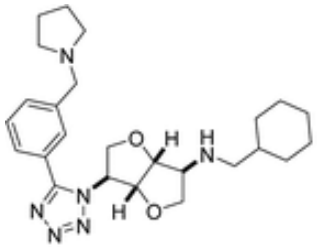




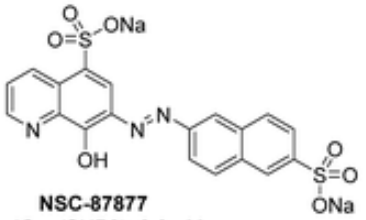
peptide with negatively charged pTyr substrate

Barr…Knapp, *Cell*, 2009

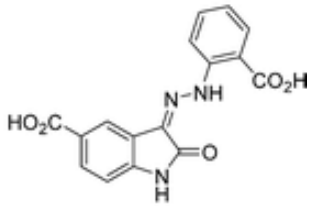
Phosphatase inhibitors with good potency had been developed, but none were bioavailable



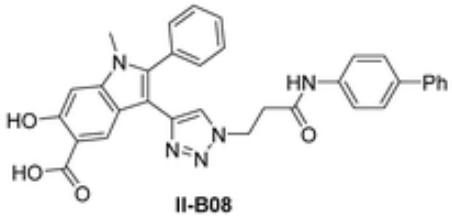
NAT6-297775
IC_{50} (SHP2): 2.5 μM



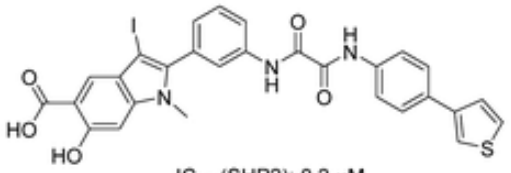
NSC-87877
IC_{50} (SHP2): 0.3 μM



IC_{50} (SHP2): 0.8 μM

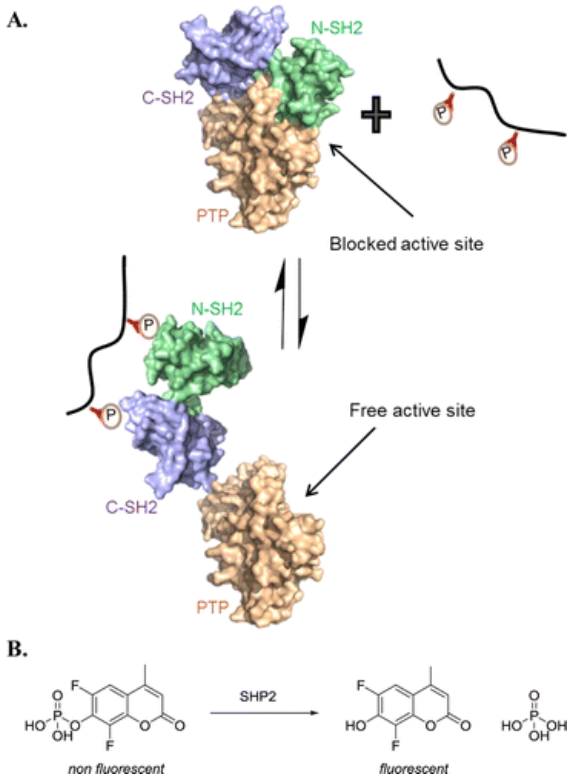


II-B08
IC_{50} (SHP2): 5.5 μM

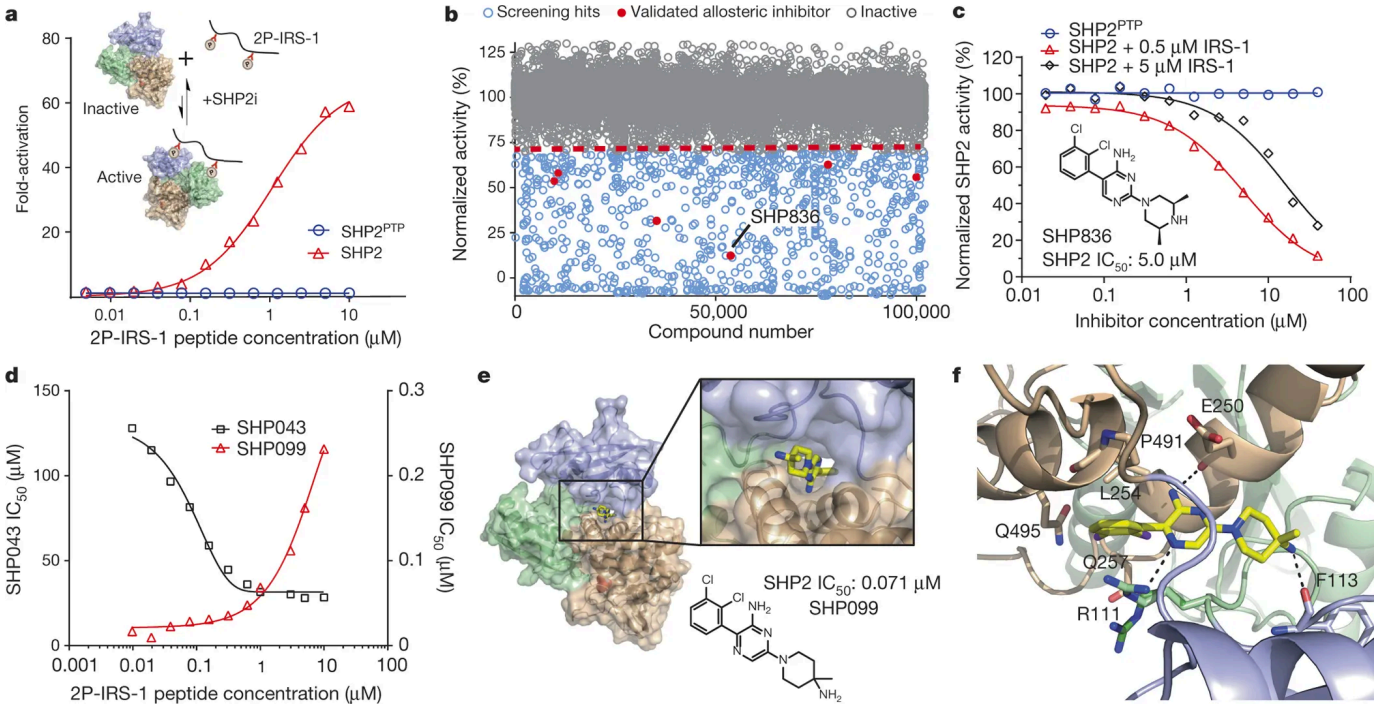


IC_{50} (SHP2): 0.2 μM

A new screening strategy for SHP2



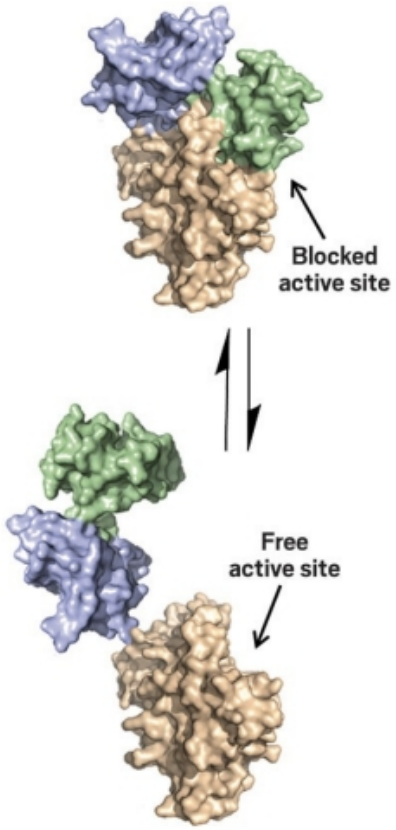
100,000 molecules screened **3 followup assays**

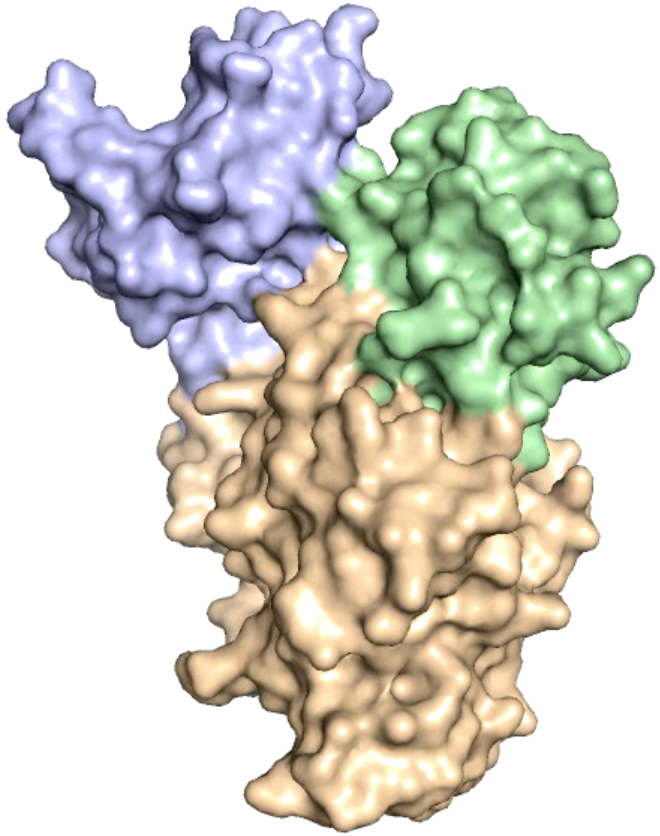


Contrast with active site inhibitor

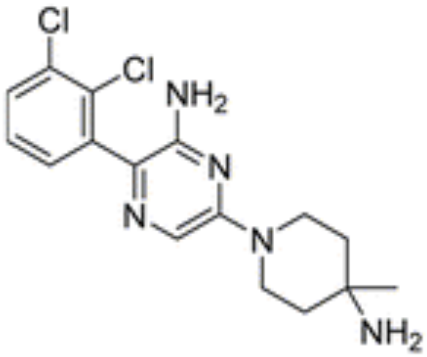
SHP836 - is a published ion channel inhibitor!

SHP2 brings new optimism for allosterically targeting **phosphatases**



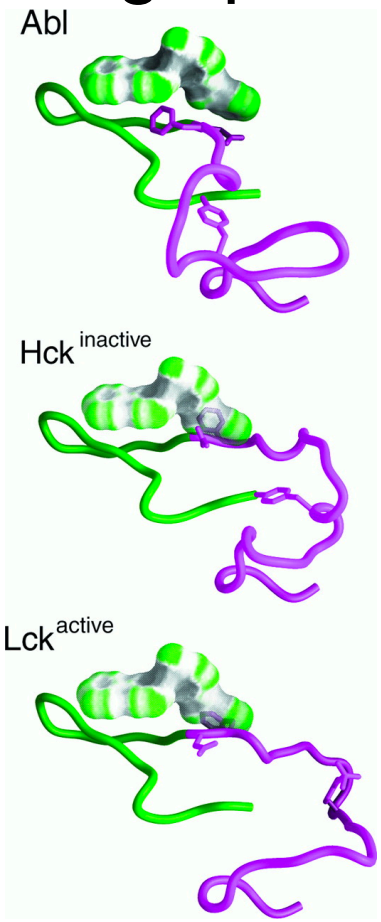


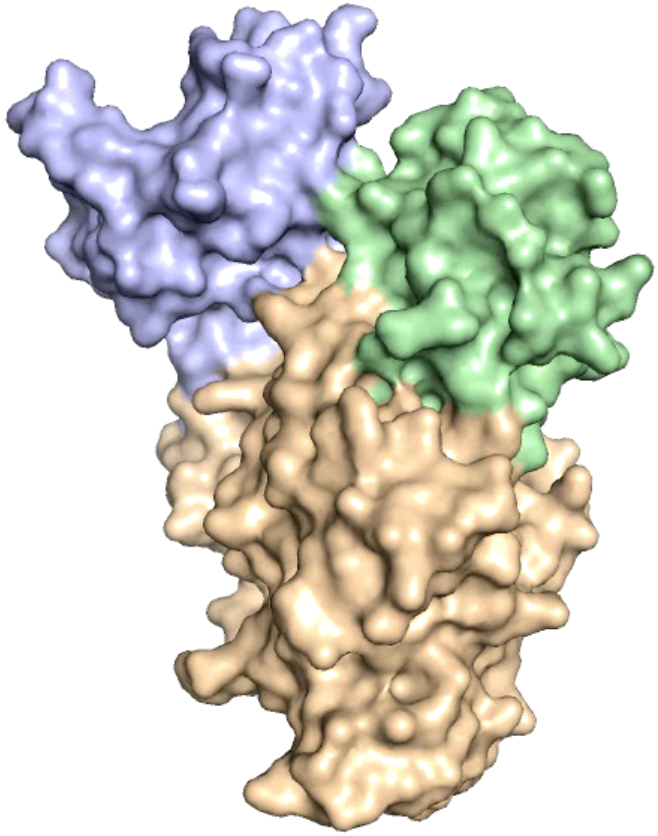
Novartis: SHP099



Chen…Fortin
Nature, 2016

Both kinases and phosphates can be inhibited by targeting specific inactive conformations





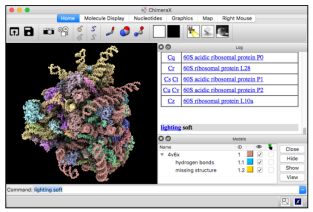
Install ChimeraX:

https://www.cgl.ucsf.edu/chimerax/download.html

Download UCSF ChimeraX

UCSF ChimeraX is the next-generation visualization program from the Resource for Biocomputing, Visualization, and Informatics at UC San Francisco.

- Download is **free for academic, government, nonprofit, and personal use**; commercial users, please see commercial licensing.
- ChimeraX uses recent graphics features and **works best on a newer computer** (≤ 3 years old).
- Please **cite ChimeraX** in publications for which it was used.



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Daily Builds
Change Log and Platform Notes
Older Releases
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▸ **Features**
▸ **Missing Features**

https://www.nature.com/articles/s41587-020-00778-3

Latest Production Release

Production releases are stable platforms for ChimeraX Toolshed bundles to work with. You may need to use an older release if a bundle you wish to use has not been updated yet.

Operating System	Distribution	Notes
Windows 10 64-bit	ChimeraX-1.1.exe built: 2020-09-10 21:31:12 PDT committed: 2020-09-09 15:22:27 PDT size: 300.2 MiB md5: 0bbf1dee03bb33ee71c2d930ce454794 sha256: 7fed35e29f498466c7559b6f357531ce4f3ed15b1663783b014713b196441460	Download is a Windows installer. Tested on Windows 10. See Windows notes below.
macOS 10.13 64-bit	ChimeraX-1.1.1.dmg built: 2020-10-07 22:51:41 PDT committed: 2020-10-07 01:32:49 PDT size: 337.4 MiB md5: 32a908b72535aeeb4bcdbd8c9d3fff1a sha256: 2678efba1b11cd9400f2c432189e1b56ee73108f582c6427b13f7f0af5ed2cdb	Download is a disk image containing the application. Tested on macOS 10.13. Also works on 10.14, 10.15, and 11.0 (Big Sur).
Generic Linux 64-bit	ChimeraX-1.1.tar.gz built: 2020-09-10 21:42:44 PDT committed: 2020-09-09 15:22:27 PDT size: 390.9 MiB md5: a081f3b964aae69bf7e6f1b3bfc34e1d sha256: a5f8bc54e55bda7243d49953bf329731ffac173bcb8ca1ed0e55fbf917601bf5	Download is a tarball of the **chimerax** application directory. ChimeraX executable is **chimerax/bin/ChimeraX**. Tested on Ubuntu 16.10 and Fedora 25. See Linux notes below.

Breakout room quiz

- Why is it easier to develop a kinase inhibitor than a phosphatase inhibitor?
- What does specificity mean in drug discovery? Which is more likely to be specific, a kinase inhibitor or a fragment?
- Did I install ChimeraX correctly?

Next class

Starting with a scaffold
(development of PLX4032/Vemurafenib)
and how crystallography is useful for fragment based discovery using a SARS CoV 2 example