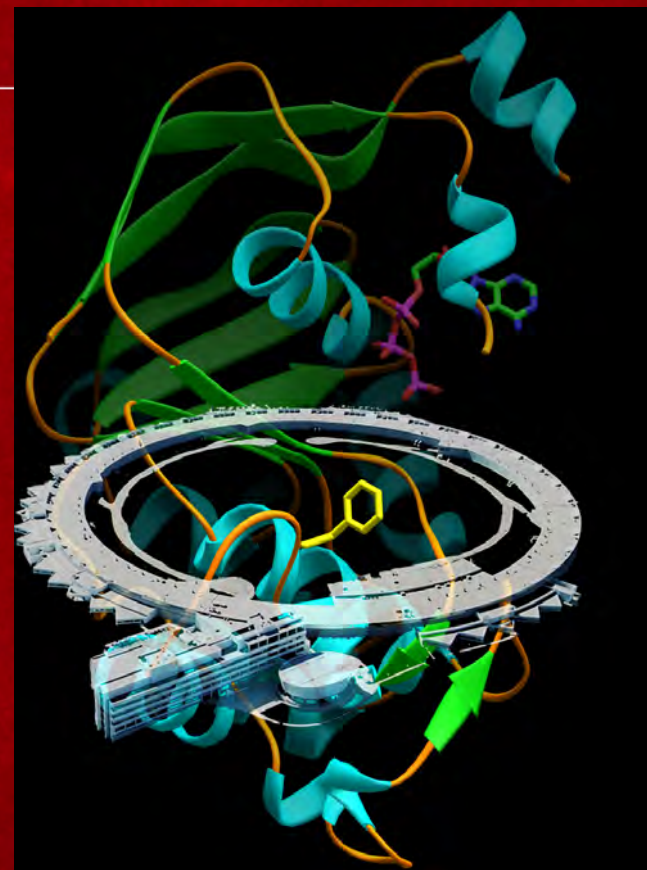


DOE X-ray Light Sources and Pharmaceutical Discovery

Stephen R. Wasserman

Eli Lilly and Company

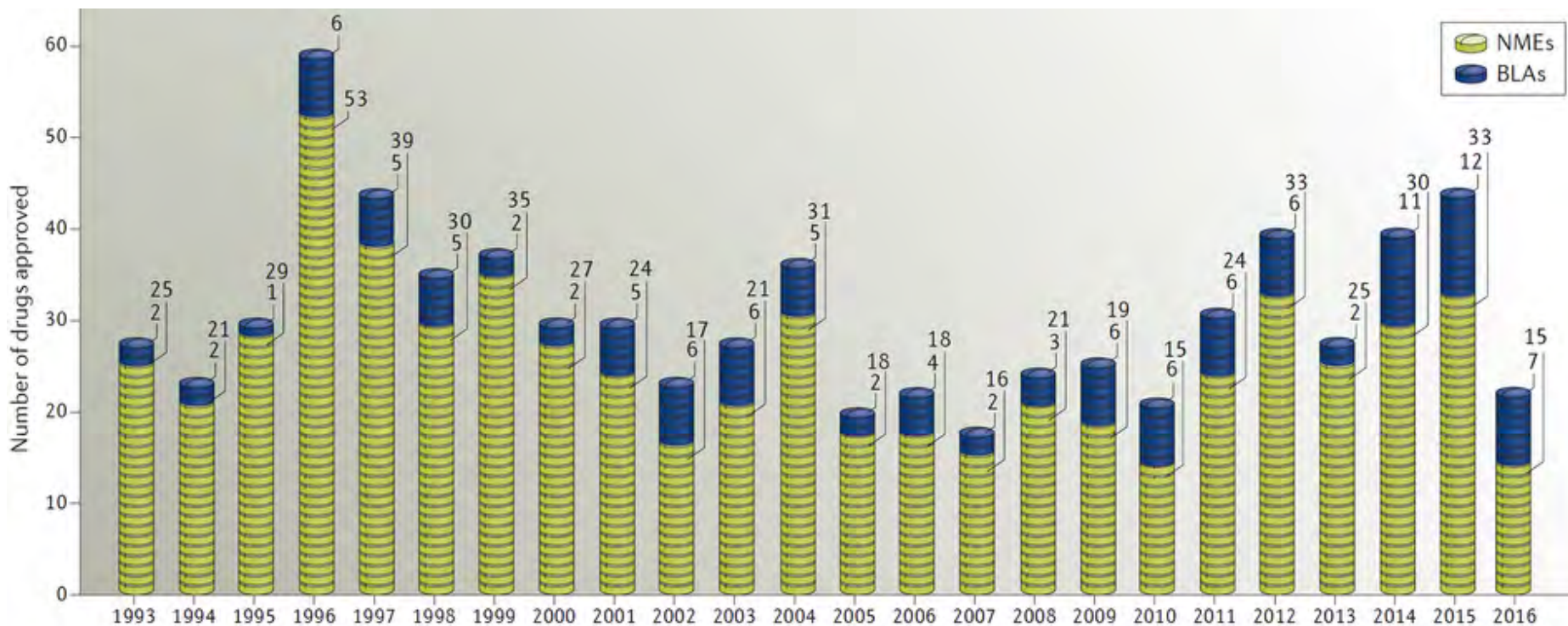
Basic Energy Sciences Advisory Committee
July 14, 2017



Non-Confidential Presentation July 14, 2017
Copyright© 2017 Eli Lilly and Company

Lilly
Answers That Matter.

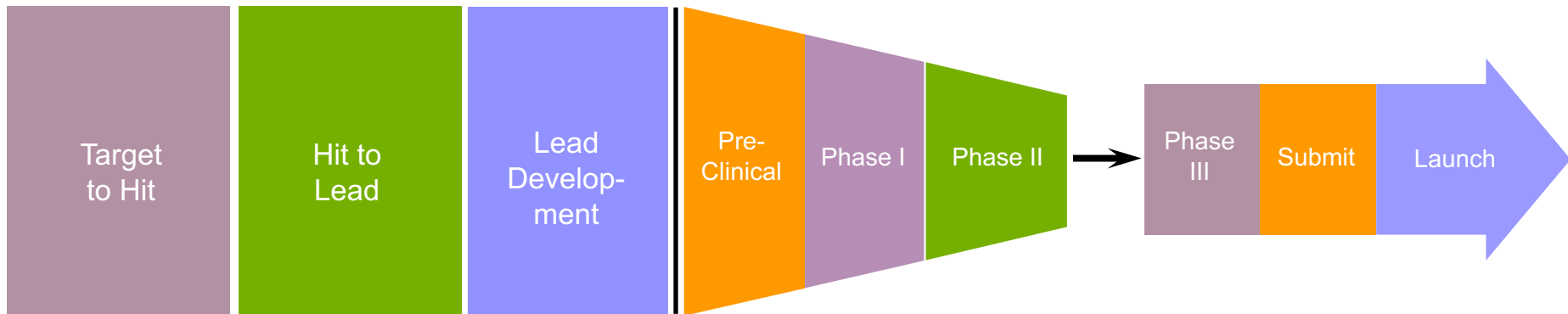
FDA Approvals



Nature Reviews | Drug Discovery

- A. Mullard, *Nature Reviews Drug Discovery*, 16, 73–76 (2017)

Drug Discovery and Development

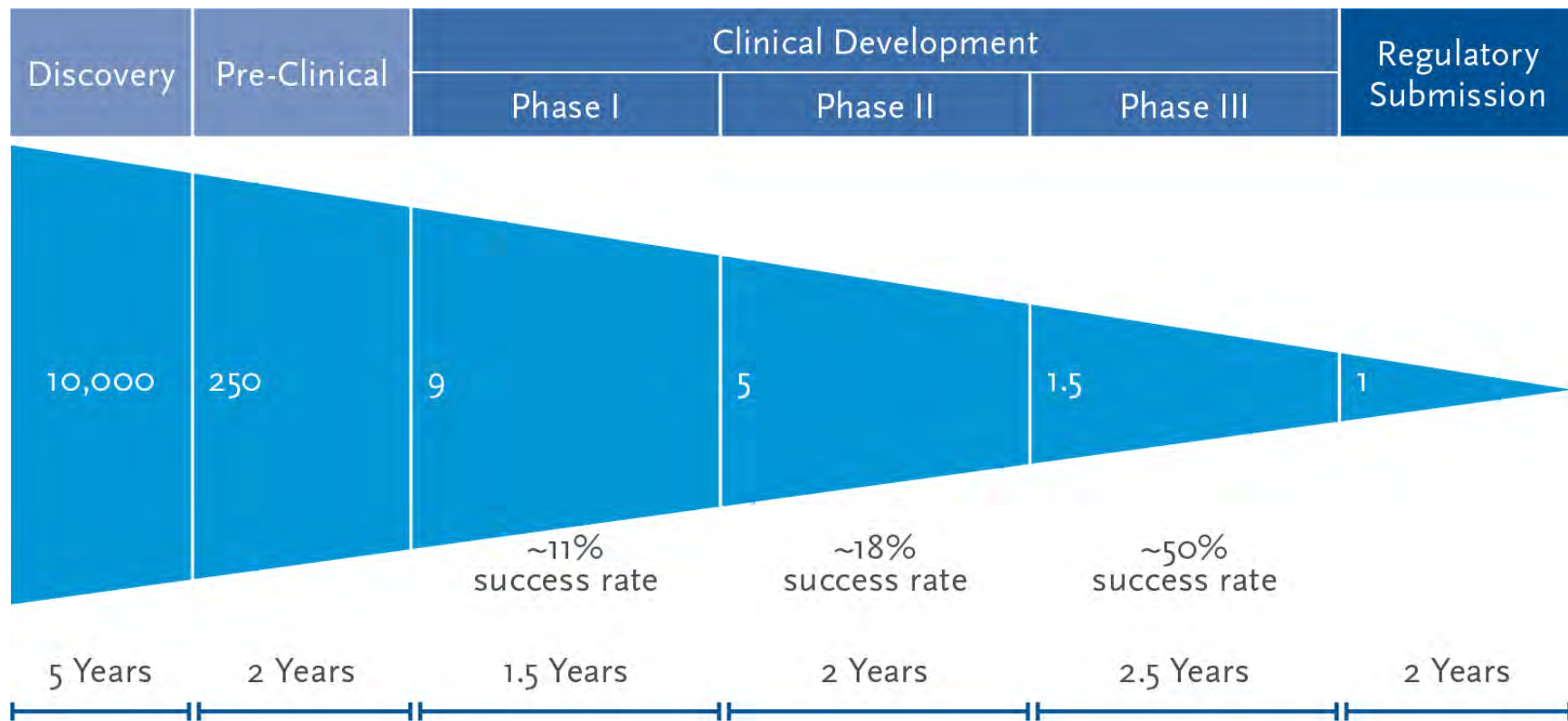


R&D Budgets – US Synchrotron Users

<ul style="list-style-type: none"> • Total (2016) \$69.4 B 	<ul style="list-style-type: none"> • Roche 		B\$ 10.3	(9.9B CHF)
	<ul style="list-style-type: none"> • Merck 		\$ 10.1	
<ul style="list-style-type: none"> • Pharma Worldwide \$157 B 	<ul style="list-style-type: none"> • Novartis 		\$ 9.0	
	<ul style="list-style-type: none"> • Pfizer 		\$ 7.9	
	<ul style="list-style-type: none"> • Lilly 		\$ 5.2	
	<ul style="list-style-type: none"> • Gilead 		\$ 5.1	
	<ul style="list-style-type: none"> • BMS 		\$ 4.9	
	<ul style="list-style-type: none"> • Glaxo SmithKline 		\$ 4.6	(£ 3.6B)
	<ul style="list-style-type: none"> • AbbVie 		\$ 4.4	
	<ul style="list-style-type: none"> • Amgen 		\$ 3.8	
	<ul style="list-style-type: none"> • Takeda 		\$ 3.1	(¥ 346M)
	<ul style="list-style-type: none"> • Vertex 		\$ 1.0	

Sources: 2016 Annual Reports, Statistica.com

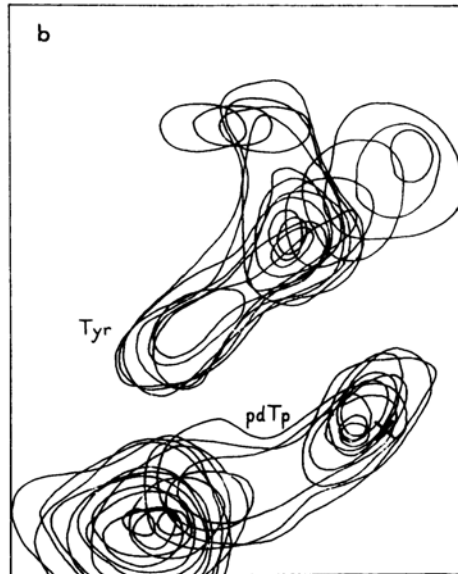
Attrition



- Strategic Portfolio Management & New Influencers in R&D Decision-Making
- <https://www.quintiles.com/assets/0/111/118/233/1336/313de5b8-3332-4bf5-a654-f2396c58e231.pdf>

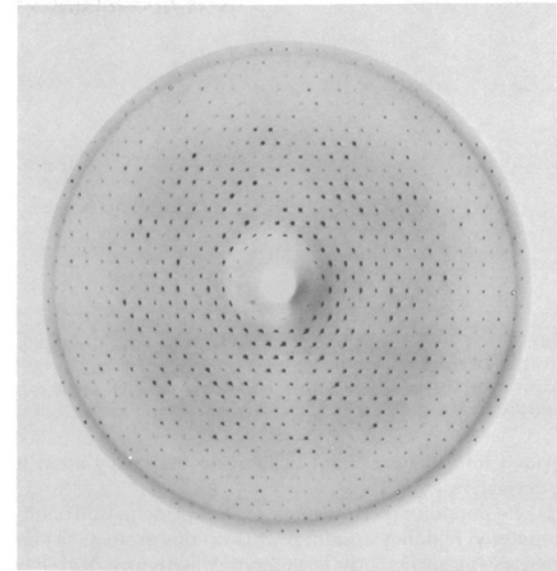
Early Experiments

- Protein/Inhibitor
 - *S. aureus* nuclease



A. Arnone et al., *PNAS*, 1969,
64, 420-427

- Synchrotron Diffraction
 - Rubredoxin
 - Exposure: 5 hours

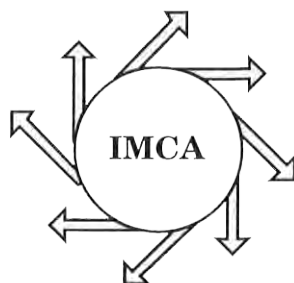


J.C. Philips et al., *PNAS*, 1976,
73, 128-132

Pharmaceutical Industry and Synchrotrons



Noel Jones, Eli Lilly (1993)

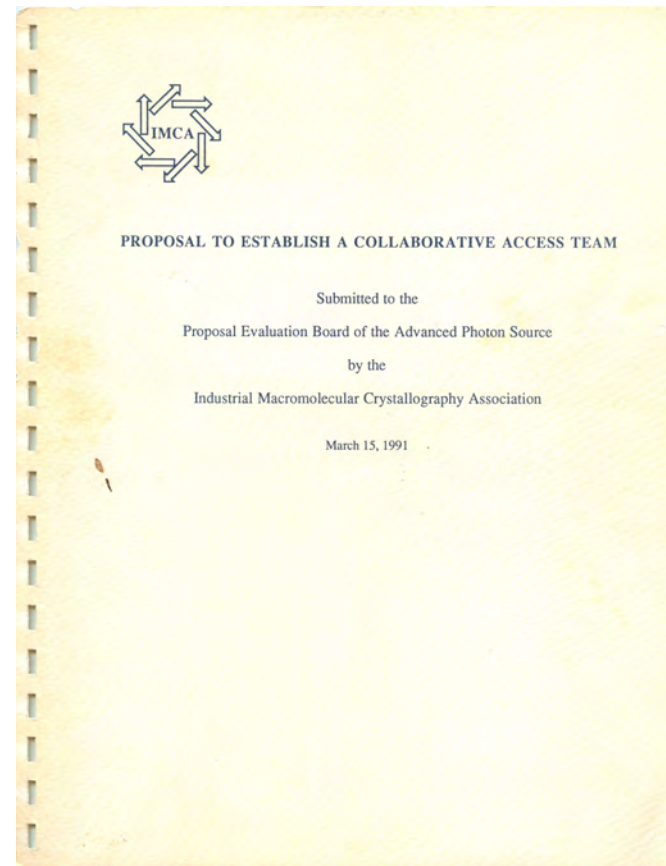


IMCA founded 1991



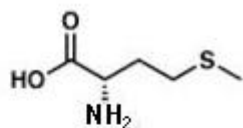
Keith Watenpaugh, Upjohn (1986)

A. J. Howard, *Nature Structural Biology, Synchrotron Supplement*, 1998, 623-626



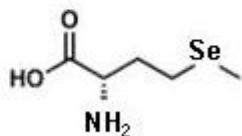
Selenomethionine

- “seleno-methionyl proteins appear to be essentially isostructural with their natural methionyl counterparts”

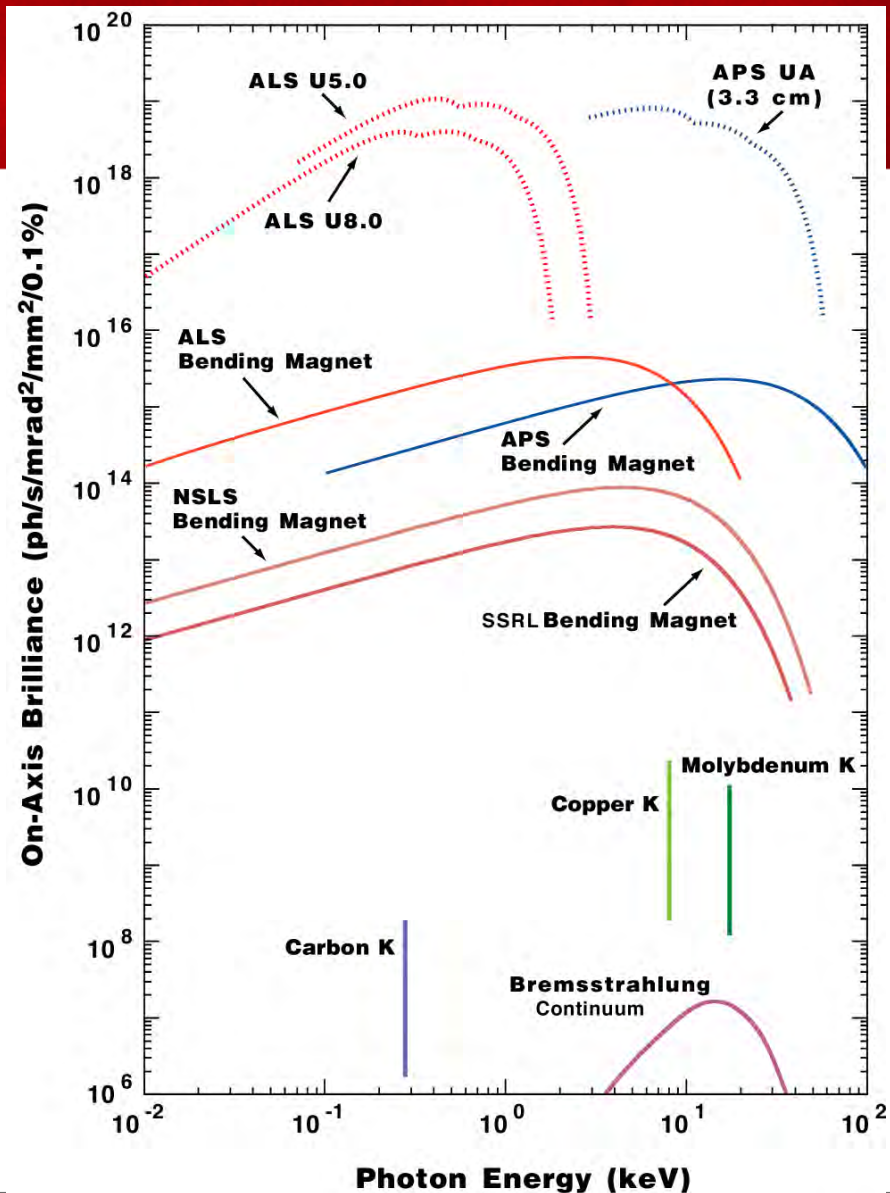


Methionine

W. A. Hendrickson, J. R. Horton,
D. M. LeMaster, *EMBO Journal*,
9,1665 – 1672 (1990)



Se-methionine



Beamlines

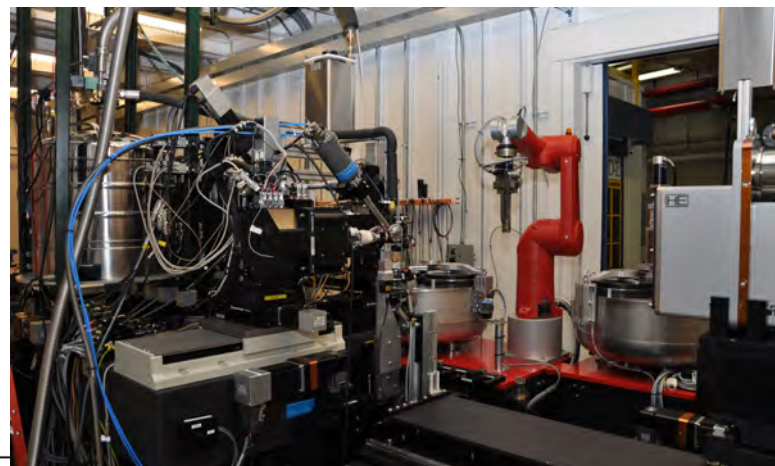
APS: Industrial Macromolecular
Crystallography Association



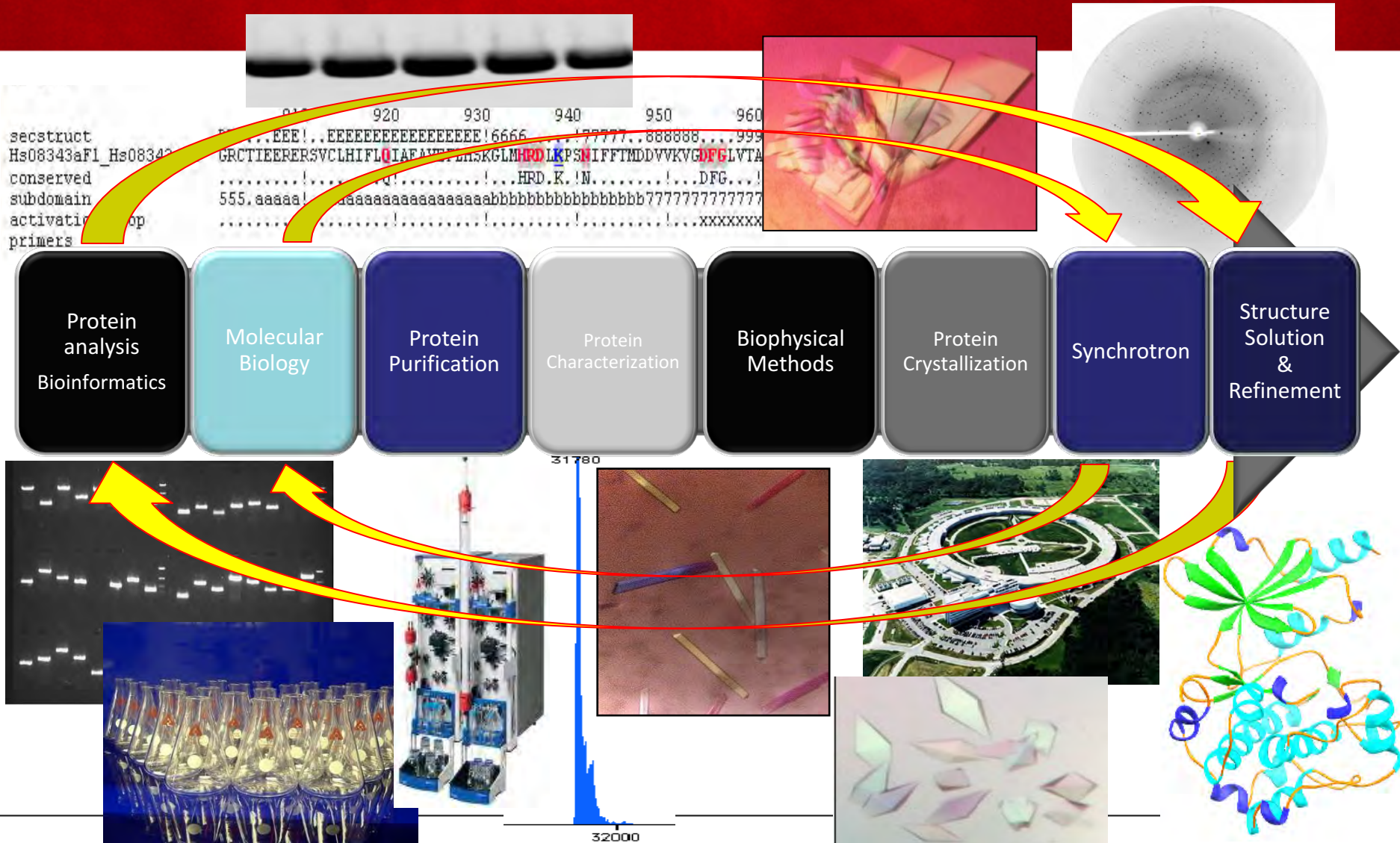
APS: Lilly Research Laboratories



ALS: Berkeley Center for Structural
Biology, Beamline 5.0

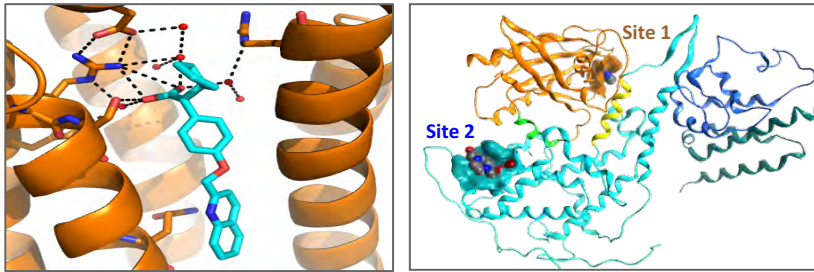


Structural Biology: Genes to Structures

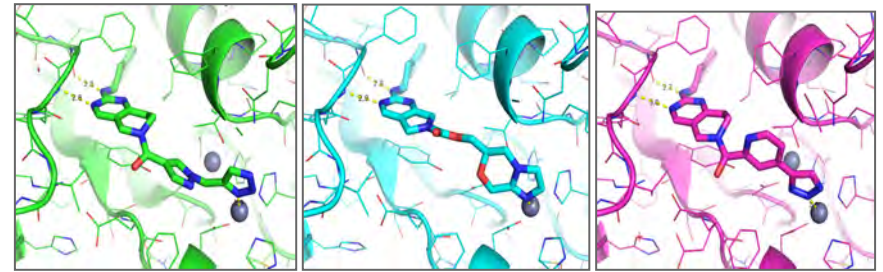


The Power of Protein Structures

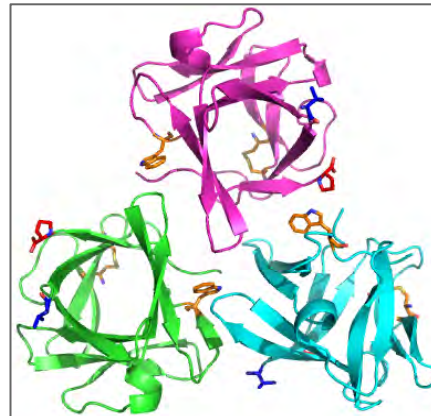
Identify ligand pockets and binding modes



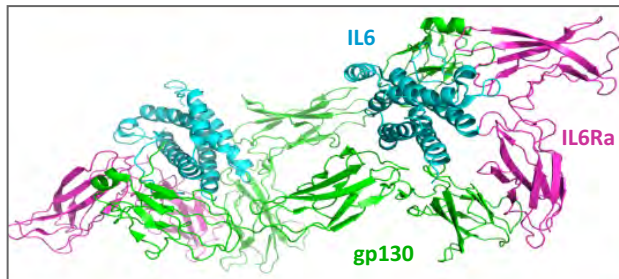
Structure Based Drug Design



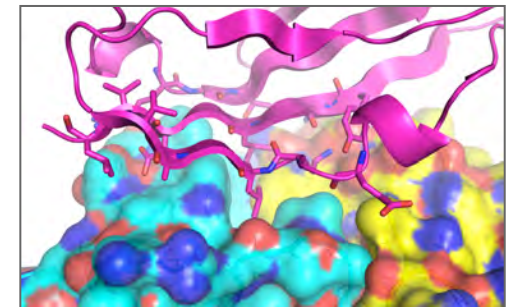
Visualization of protein engineering



Provide answers to biological questions

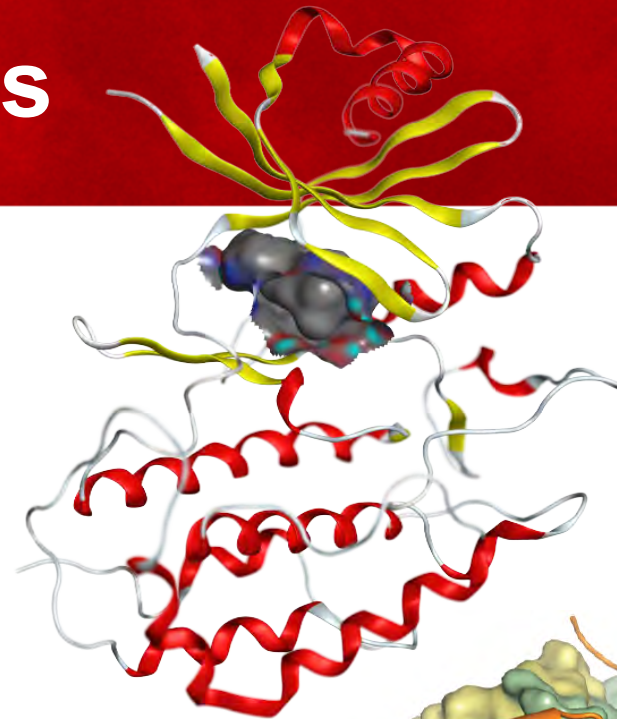


Identify antibody binding site epitopes

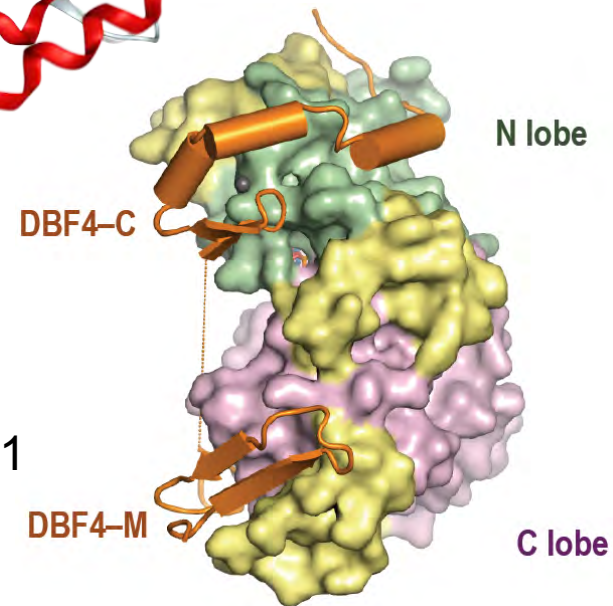


Engineered Structures

- Lilly CDC7 structure
 - 45 DNA constructs
 - 574 -> 330 amino acids



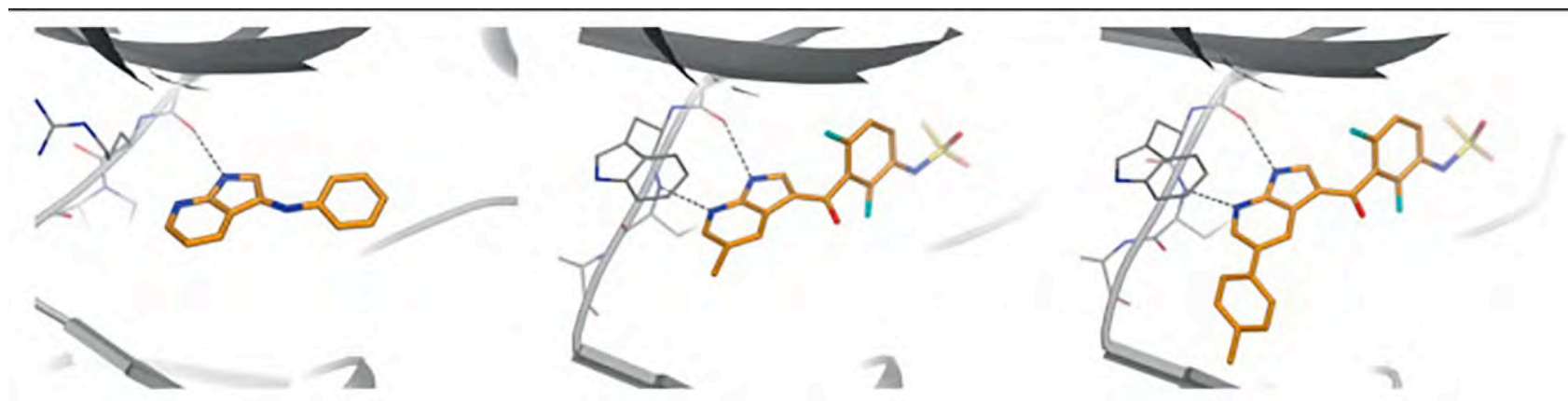
- CDC7+DBF4 structure
 - Hughes et al., *Nat. Struct. Mol. Biol.*, 2012, **19**, 1101



Design from Fragments



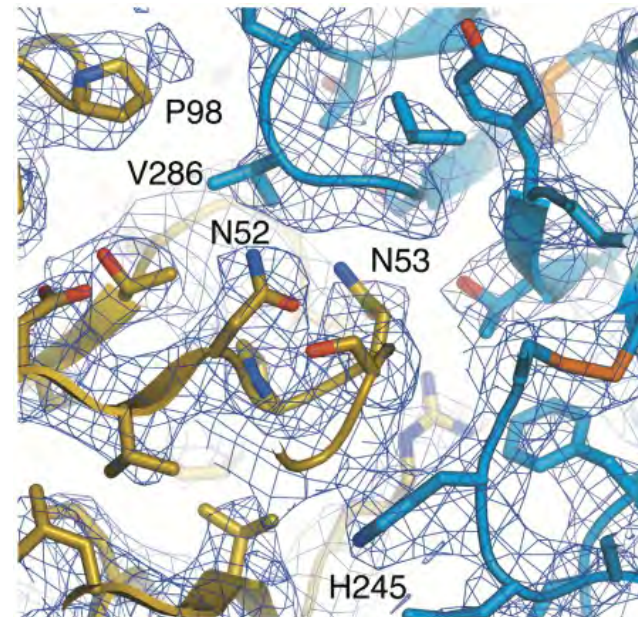
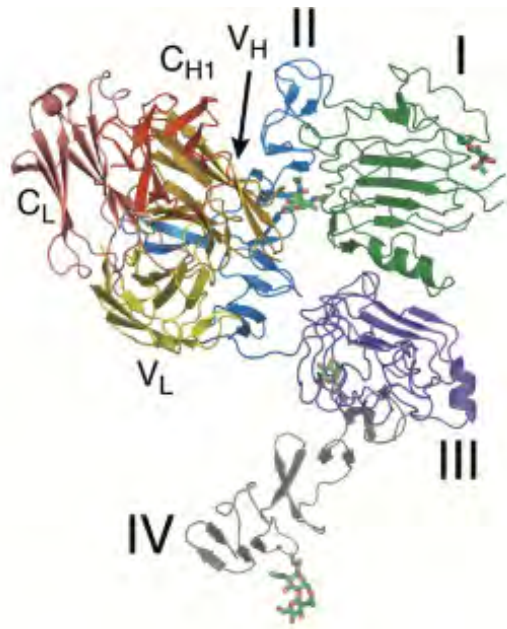
Vemurafenib, PLX4032
Late-stage melanoma



R.A.E. Carr et al., *Drug Discovery Today*, 2005, **10**, 987

C.W. Murray et al., *Trends in Pharmacological Sciences*, 2012, **33**, 224

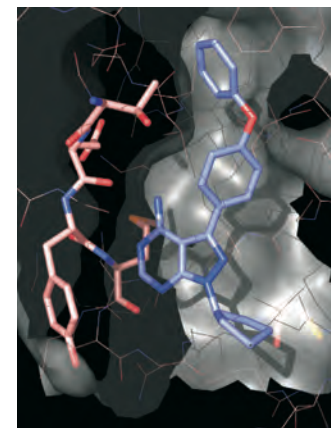
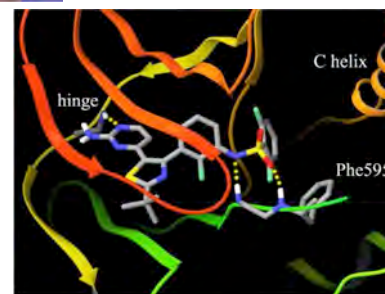
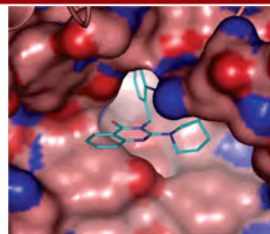
Biologics



- Pertuzumab – Metastatic breast cancer
- Human epidermal growth factor receptor 2 (ErbB2 or HER2)
- Approved 2012
- M.C. Franklin et al., *Cancer Cell*, 2004, **5**, 317

2013 US FDA Approvals

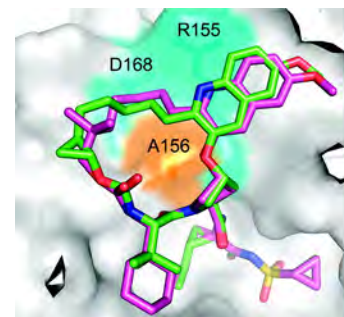
- Algoliptin - Type 2 diabetes (ALS)
 - J. Feng et al., *J. Med. Chem.*, 2007, **50**, 2297-2300
- Trametinib - Melanoma (APS, in-house)
 - Modeled into structure from another company
 - J. G. Gregar et al., *Mol. Cancer Ther.*, 2013, **11**, 909
- Dabrafenib - Melanoma (ALS, SSRL)
 - Modeled into structure from another company (ALS, SSRL)
 - T. R. Rheault et al., *ACS Med. Chem. Lett.*, 2013, **4**, 358-362
- Ibrutinib-mantle cell lymphoma (CHESS, NSLS)
 - Homology model from structure of Bruton's tyrosine kinase (BTK) and Lck
 - Z. Pan et al., *ChemMedChem.*, 2007, **2**, 58-61



2016 US FDA Approvals

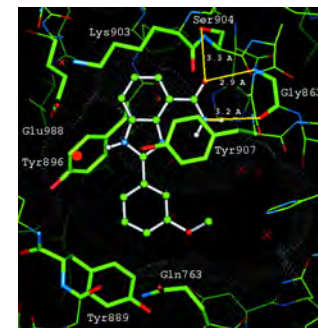
- Grazoprevir - Hepatitis C (APS)

- S. Harper et al., *ACS Medicinal Chemistry Letters.*, 2012, 3, 332-336
- Molecular modeling using previous structure from IMCA
 - N. Yao et al., *Structure*, 1999, 7, 1353-1363



- Rucaparib – Ovarian Cancer (SSRL)

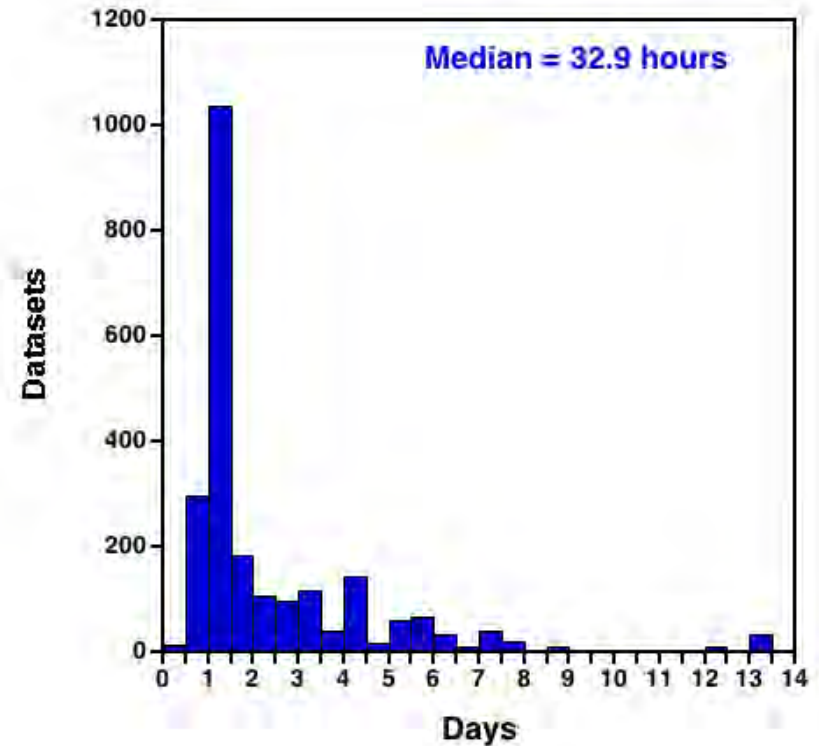
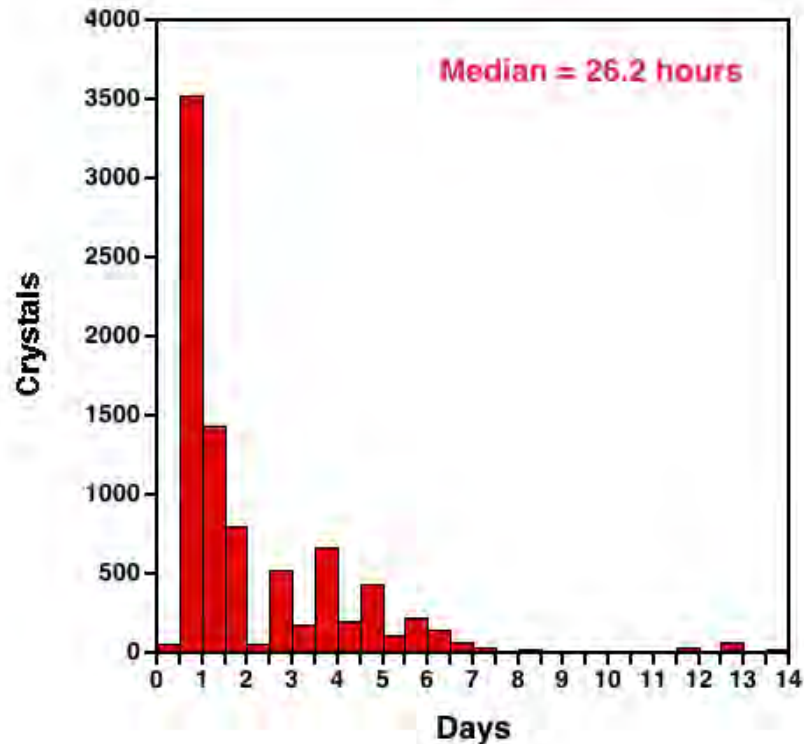
- A. W. White et al., *J. Med. Chem.*, 2000, 43, 4084-4097



Advantages for Drug Discovery

- Methods that see how ligands interact with protein
 - Diffraction: Xray and electron
 - NMR
 - Cryo-Electron Microscopy
- Before analysis at synchrotron
 - Smaller crystals
 - Laboratory source
 - Savings in crystallization time
- At synchrotron
 - Intense source
 - Tunable – anomalous experiments
 - High data rate
- After the synchrotron
 - Data quality
 - Automatic data analysis

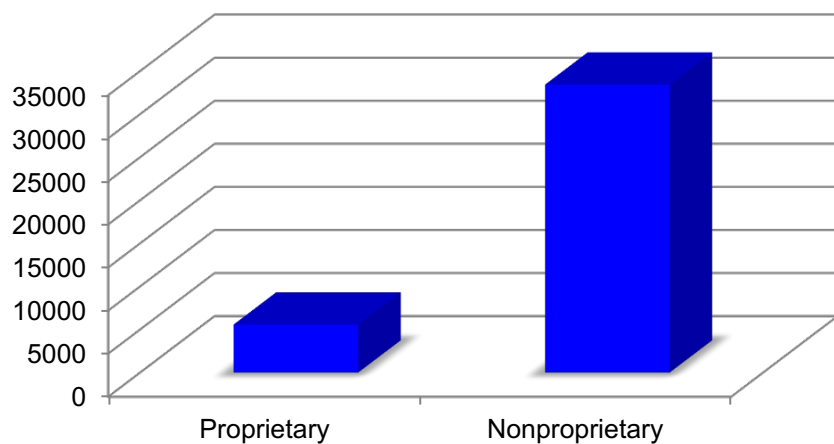
LRL-CAT Sample Turnaround



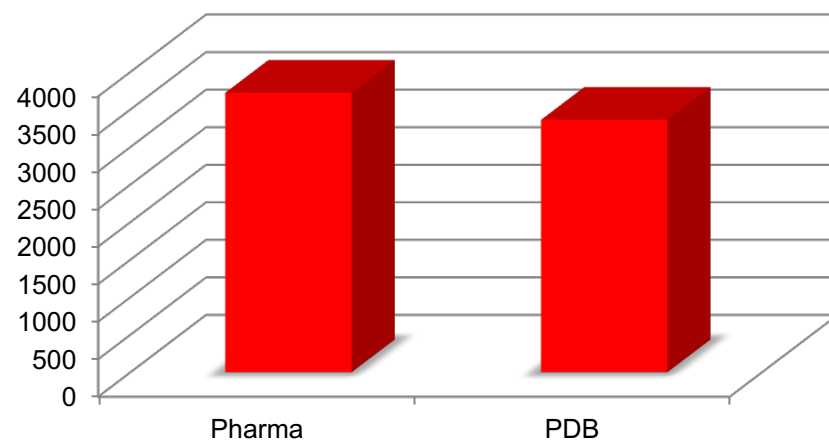
- ~16 hours to ship samples
- Lilly internal crystals, 2016

Productivity at US Light Sources

APS Hours (FY2013)



Structures (2012)

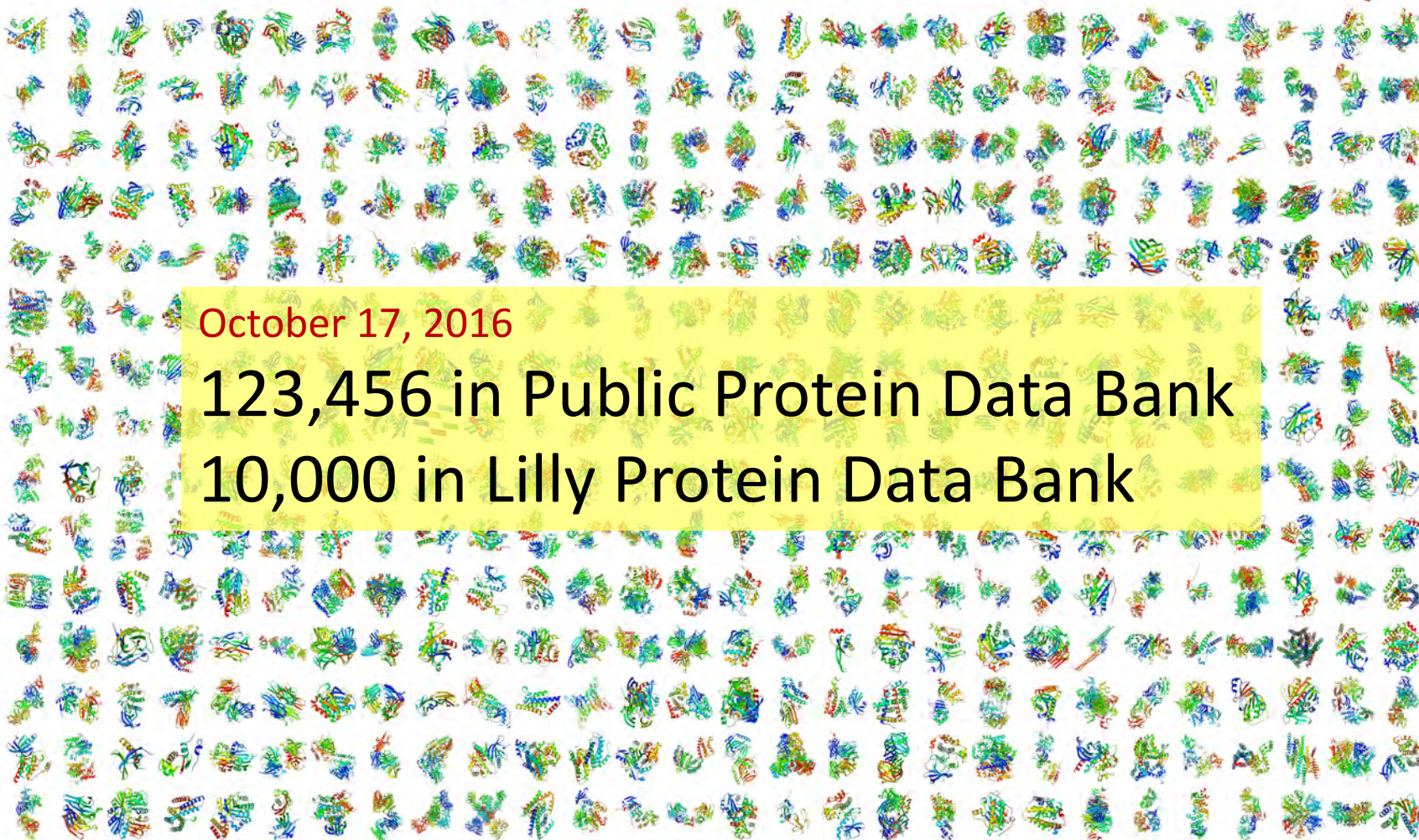


- Structures from survey of US pharmaceutical research (10 companies)
- Hours for Macromolecular Crystallography (MX) at the APS

Lilly Global Structural Biology - Impacting Drug Discovery



First 10,000 protein structures - nonredundant set, October 2016



October 17, 2016

123,456 in Public Protein Data Bank

10,000 in Lilly Protein Data Bank

Acknowledgments

- Lilly Global Structural Biology, Michael Sauder, K. Schwinn, D. Thompson
- Noel Jones (Lilly, ret.)
- User Office, Advanced Photon Source
- Industrial Macromolecular Crystallography Association (IMCA)
- Charles Eigenbrot, Genentech
- Glaxo SmithKline (US)
- Amgen
- Use of the Advanced Photon Source, an Office of Science User Facility operated for the U.S. Department of Energy (DOE) Office of Science by Argonne National Laboratory, was supported by the U.S. DOE under Contract No. DE-AC02-06CH11357.