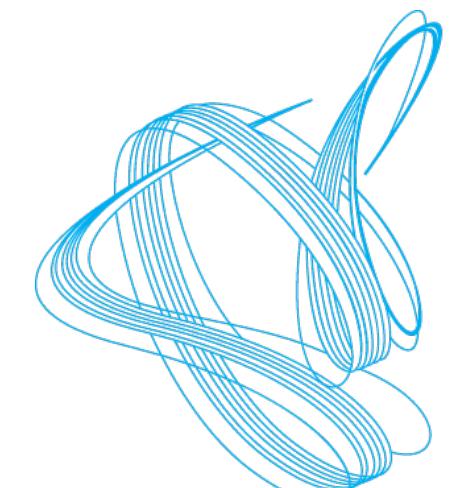


Using physical modeling to predict the



Gerstner Sloan Kettering Graduate School of Biomedical Sciences



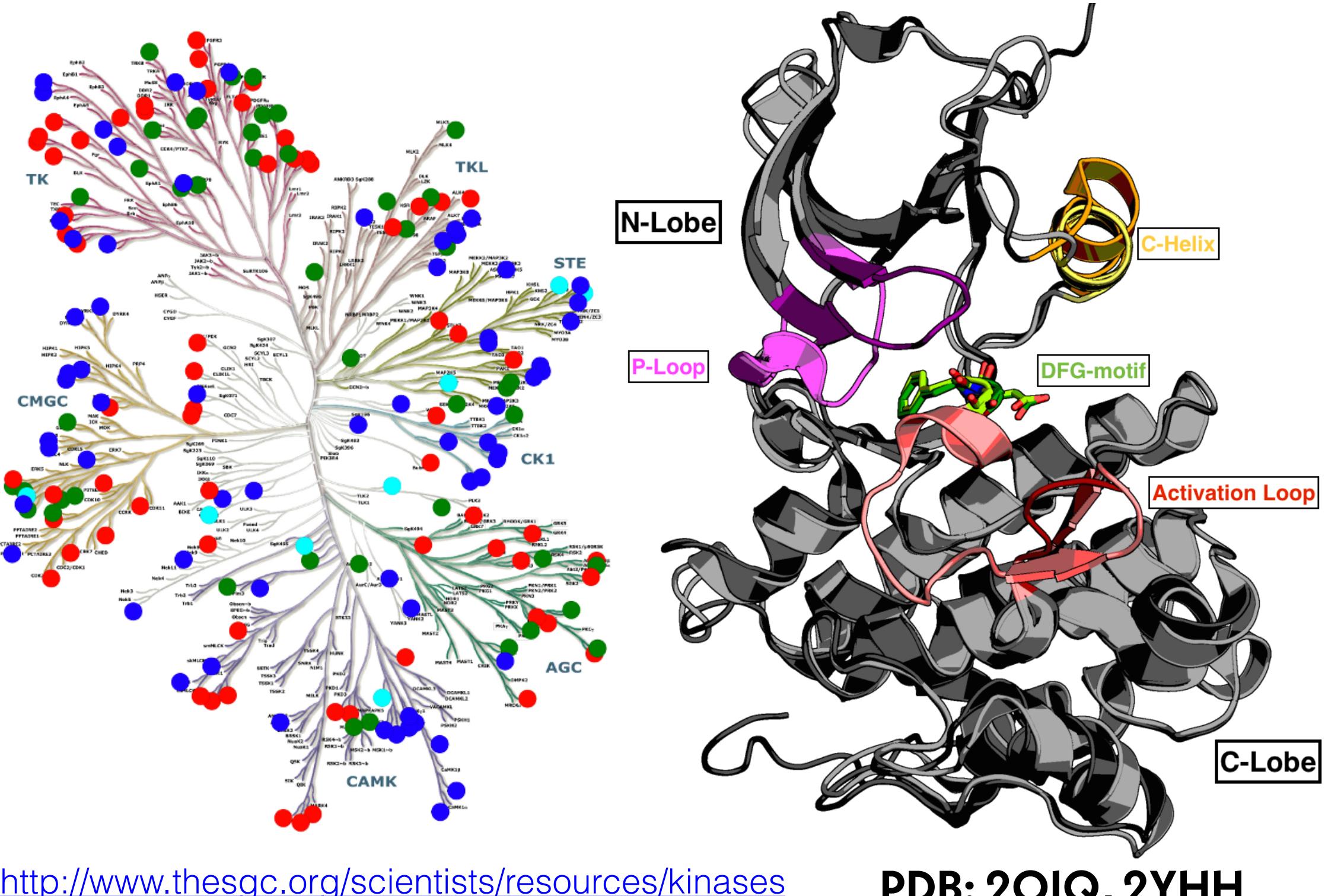
Memorial Sloan Kettering Cancer Center

kinases on drug susceptibility

Steven K. Albanese, Daniel L. Parton, Kevin Hauser, Christopher Negron, Sonya M. Hanson,
Lucelenie Rodriguez-Laureano, Mehtap Isik, Lingle Wang, Robert Abel, John D. Chodera

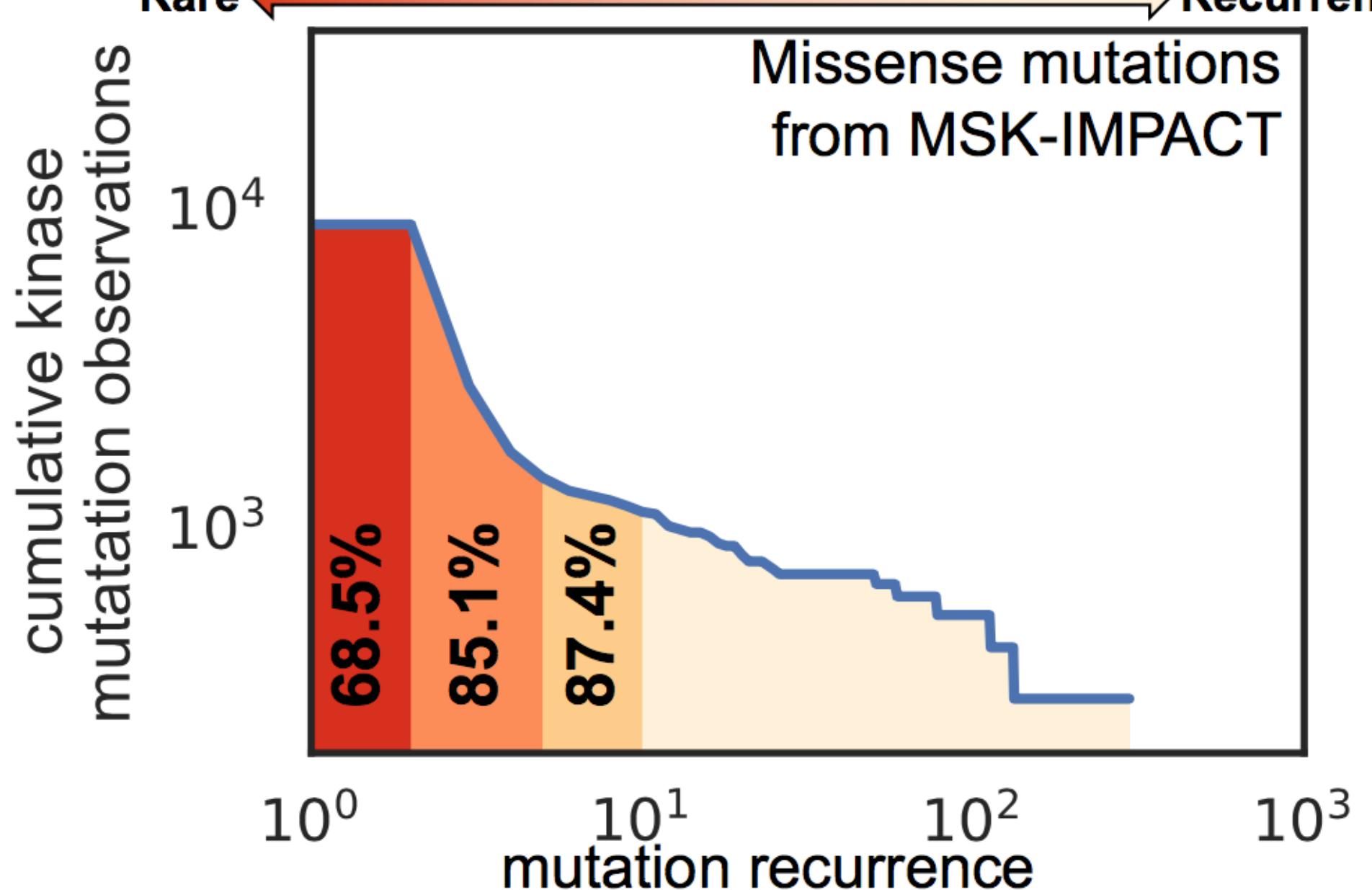
Kinases are a commonly mutated therapeutic target

518 human kinases... ...with a shared fold

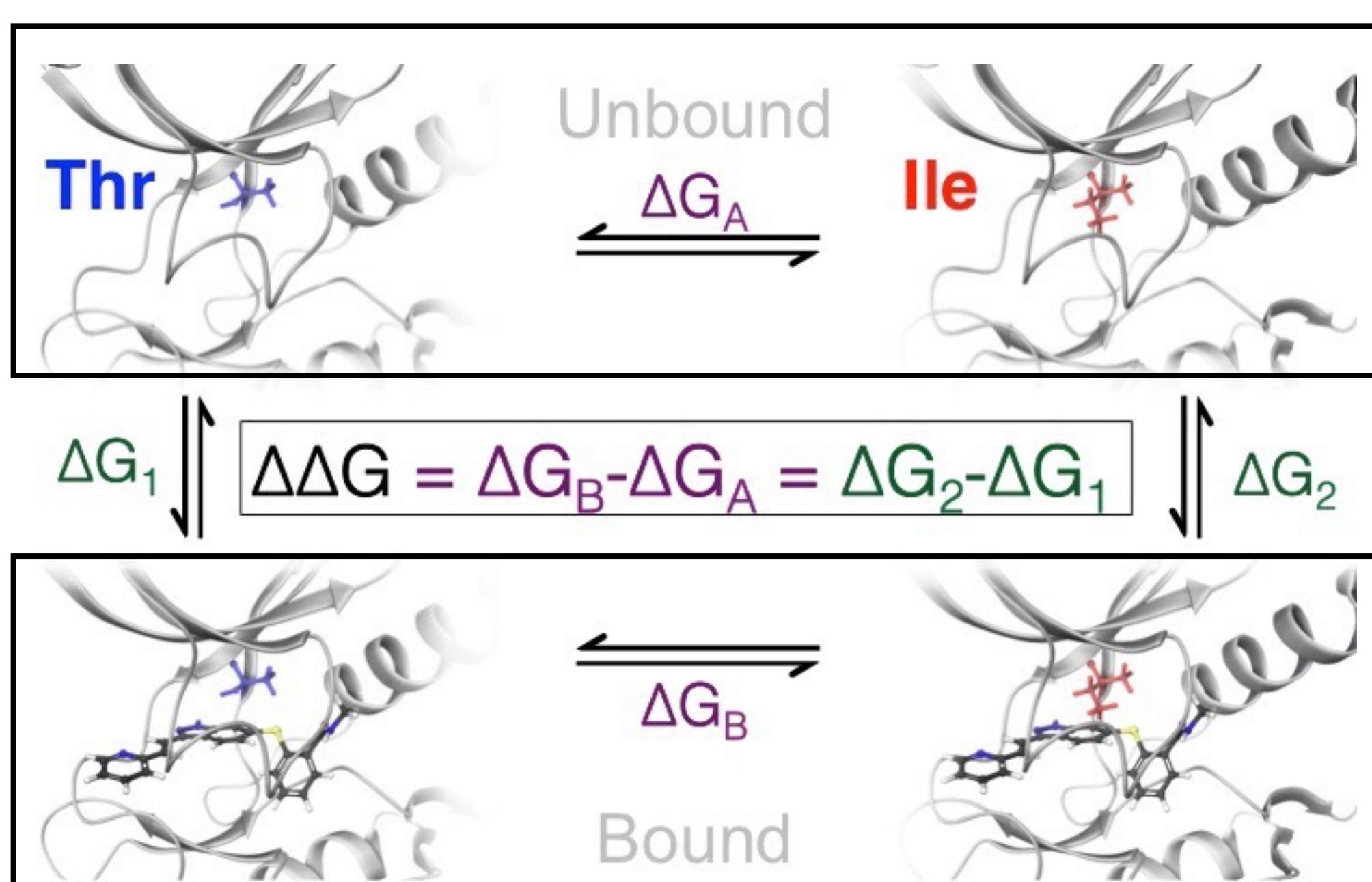


<http://www.thesgc.org/scientists/resources/kinases>

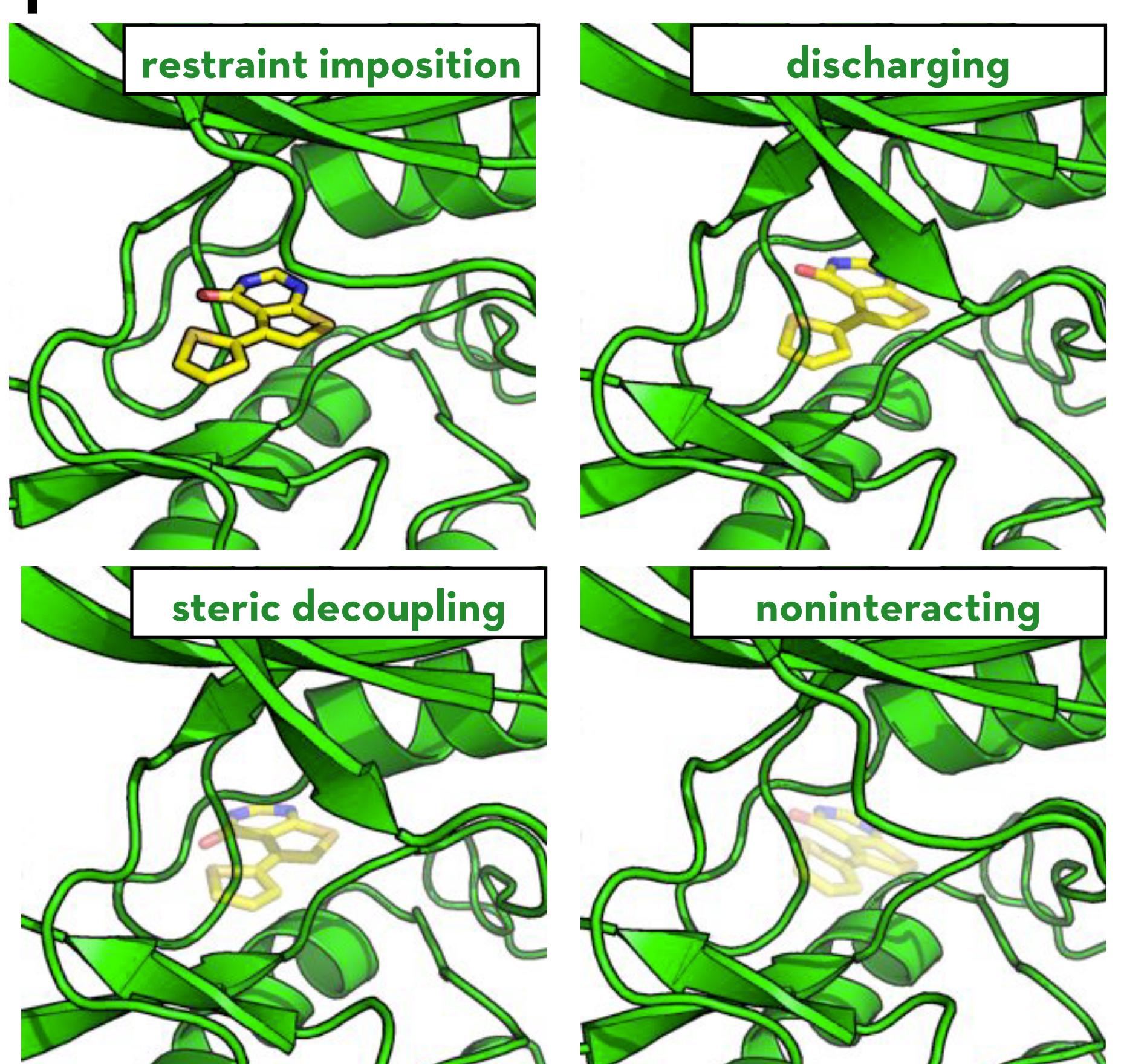
PDB: 2OIQ, 2YHH



Alchemical free energy calculations can predict impact of mutations on ligand binding



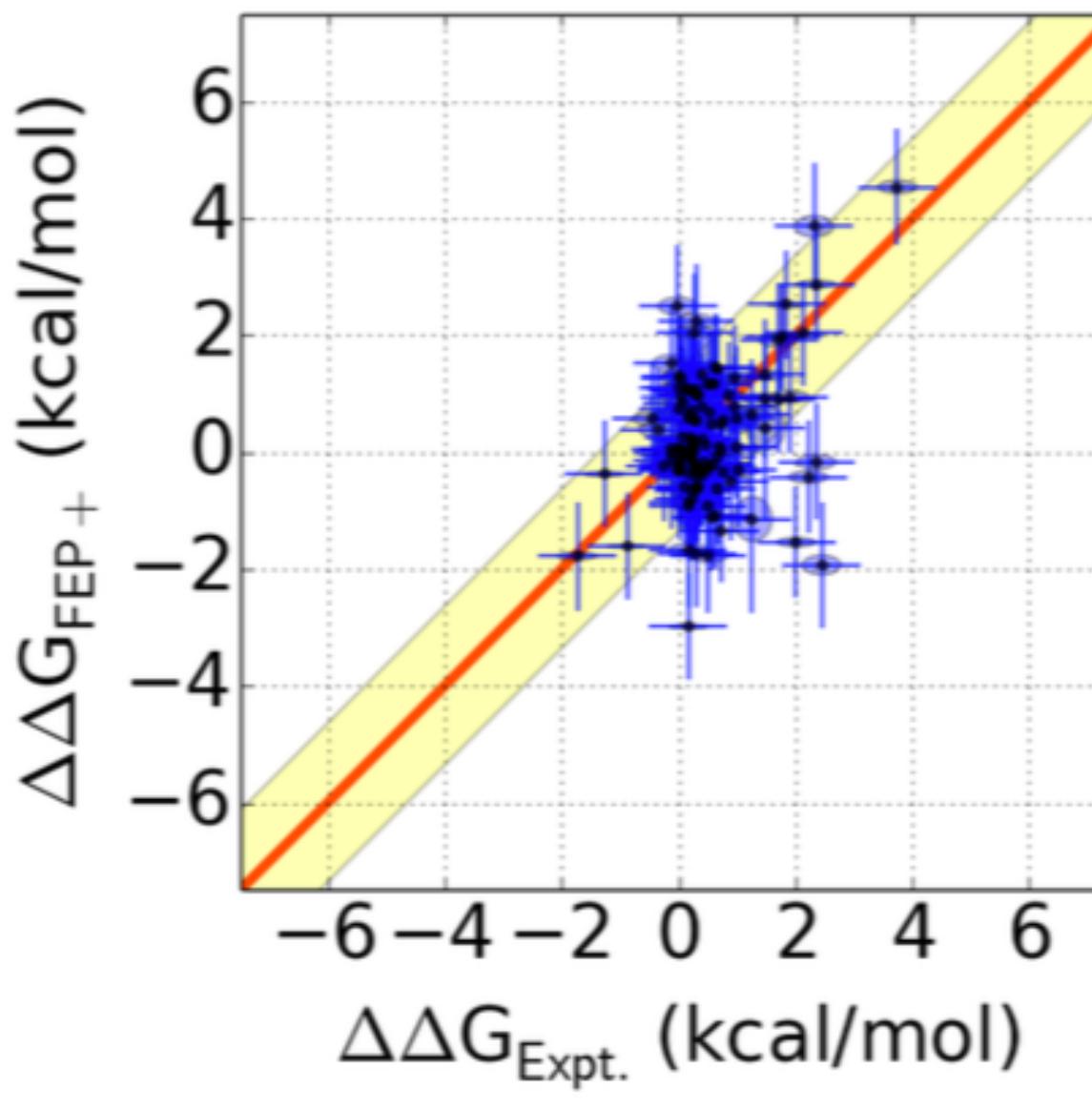
multiple simulations of alchemical intermediates



Retrospective study suggests free energy calculations are capable of predicting resistance

Relative free energy calculations performed on 131 mutation-inhibitor pairs for Abl and compared to publicly available IC₅₀ and K_d data

Bootstrap	
MUE (kcal/mol)	0.79 0.92 0.66
RMSE (kcal/mol)	1.08 1.29 0.89
Bayesian	
MUE (kcal/mol)	0.77 0.89 0.66
RMSE (kcal/mol)	0.96 1.11 0.83



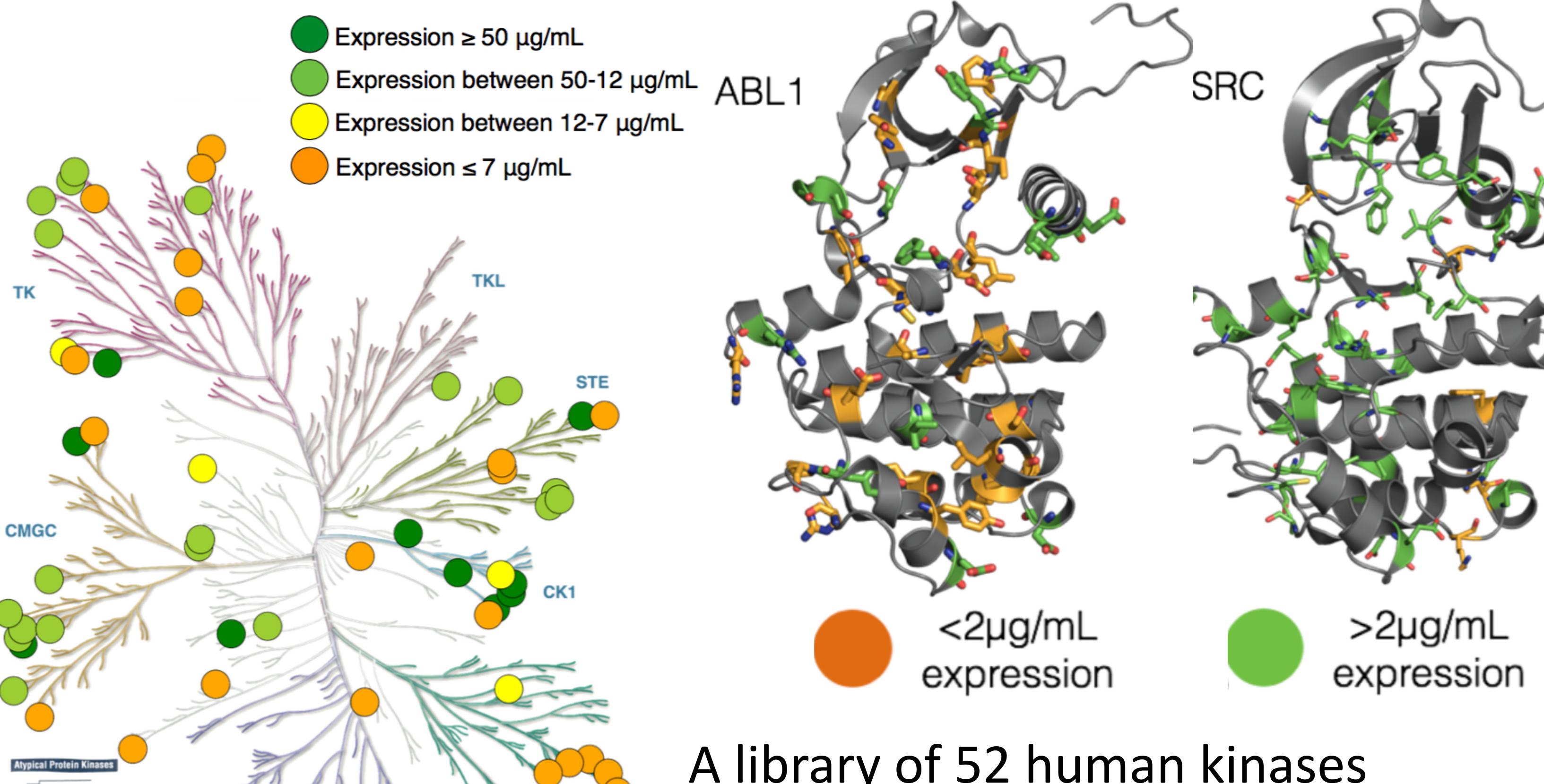
Bootstrap	
Accuracy	0.89 ^{0.93} 0.83
Specificity	0.95 ^{0.98} 0.90
Sensitivity	0.50 ^{0.71} 0.25
Bayesian	
Accuracy	0.91 ^{0.94} 0.86
Specificity	0.93 ^{0.95} 0.90
Sensitivity	0.70 ^{1.00} 0.47

		Prediction	
		s	r
Experiment	S	107	6
	R	9	9

FEP+ was capable of correctly classifying most of the mutants as either sensitive or resistant to inhibition

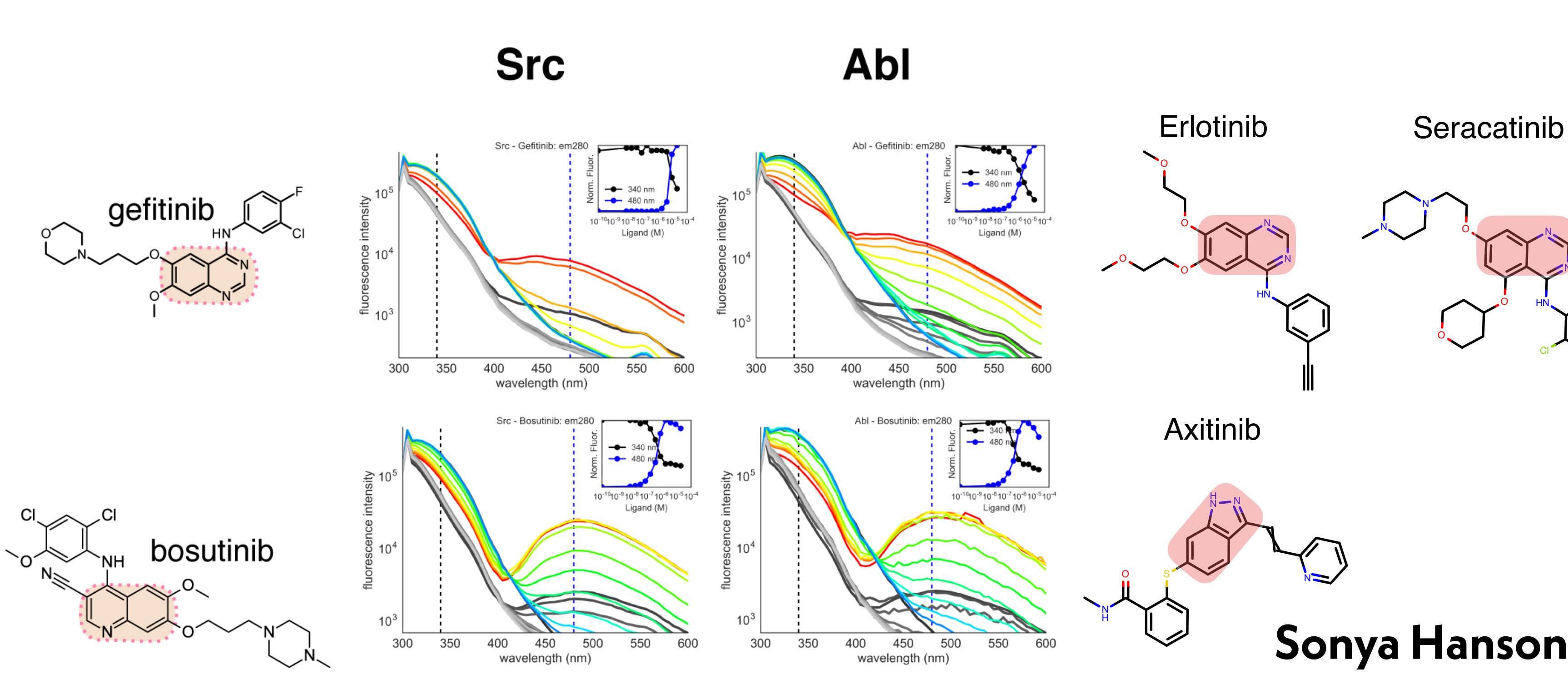
Kevin Hauser, Post-Doc Schrödinger

Which kinases are experimentally tractable?



A library of 52 human kinases
expressible in *E. coli* using an
automated protocol, with the ability
to quickly engineer clinical mutations

A fluorescence assay allows for the direct measurement of binding affinities *in vitro*



References:

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<http://doi.org/10.1110/ps.051750805>