



Rational approach to selective inhibitor design using multitarget constraints



Gerstner Sloan Kettering
Graduate School of Biomedical Sciences

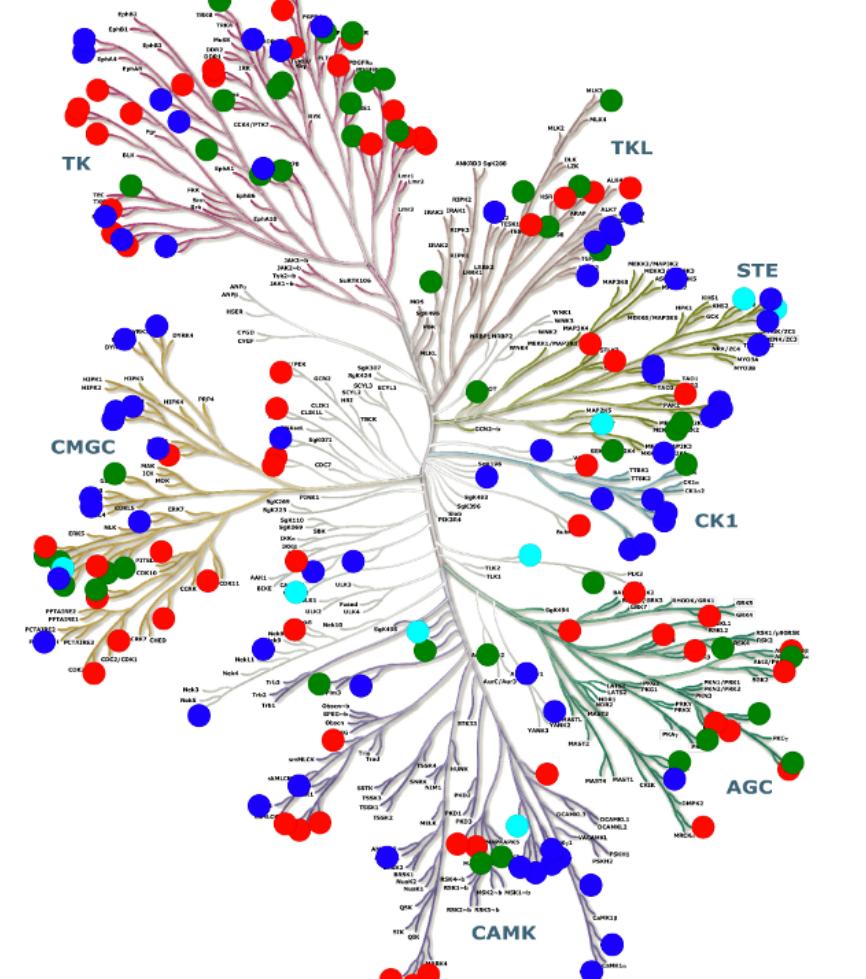
Steven K. Albanese, Patrick Grinaway, Sonya Hanson, Lucelenie Rodriguez, Zhiqiang Tan, John Chodera

Memorial Sloan Kettering
Cancer Center

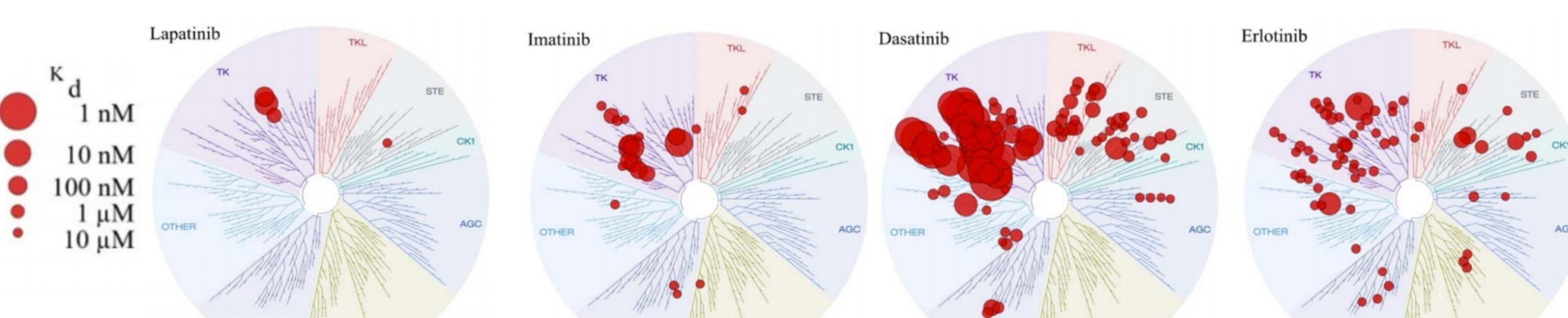
Kinase inhibitors have great potential for promiscuity

518 human kinases...

...with a shared fold

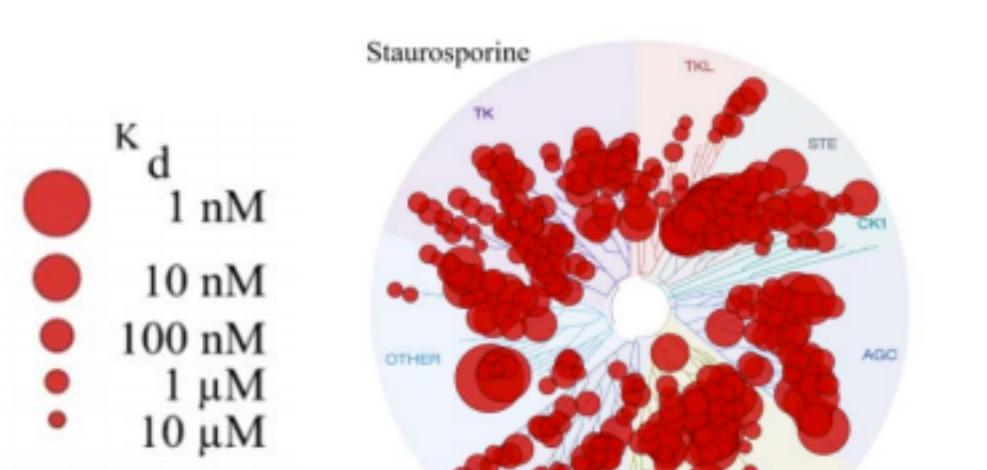


<http://www.thsgc.org/scientists/resources/kinases>



Davis et. al. Nat. Biotechnol. 29:11, 2011

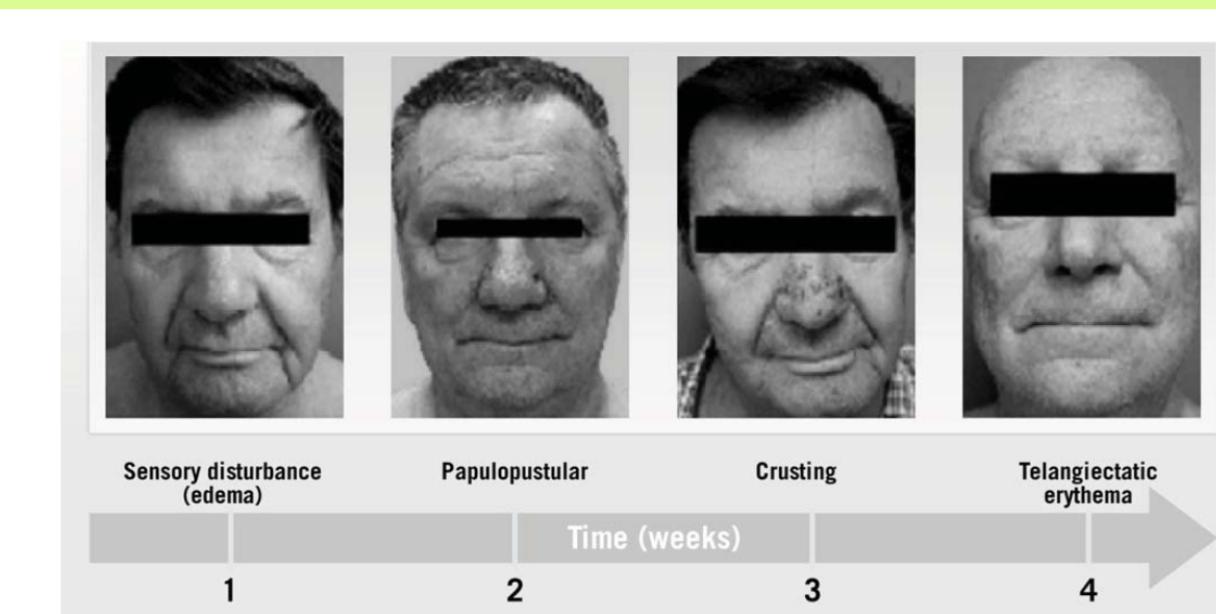
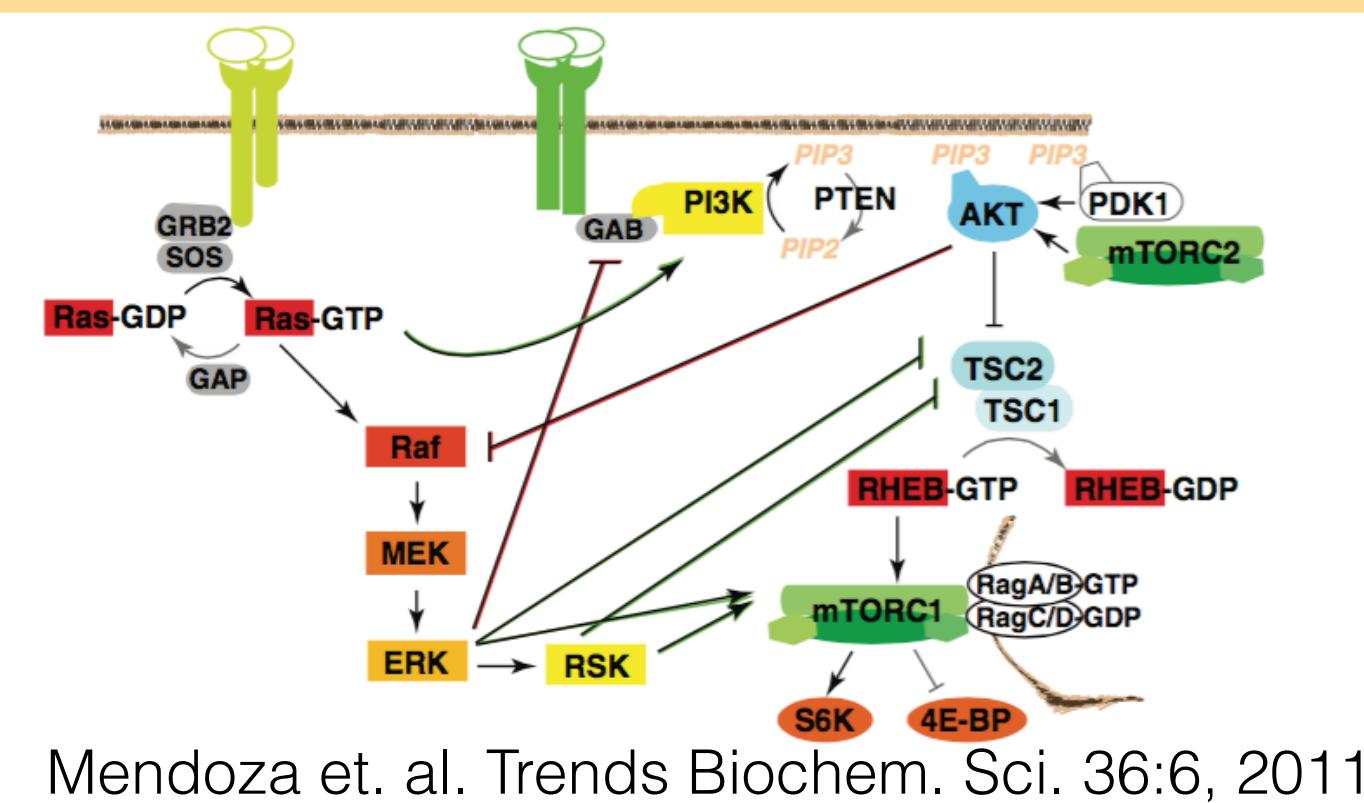
How can multitarget constraints address problems in SMKI design?



Davis et. al. Nat. Biotechnol. 29:11, 2011

Improve **selectivity** by targeting (+) kinase of interest and antitargeting (-) related kinases

Handle **complex networks of kinase signaling** by targeting (+) multiple kinases

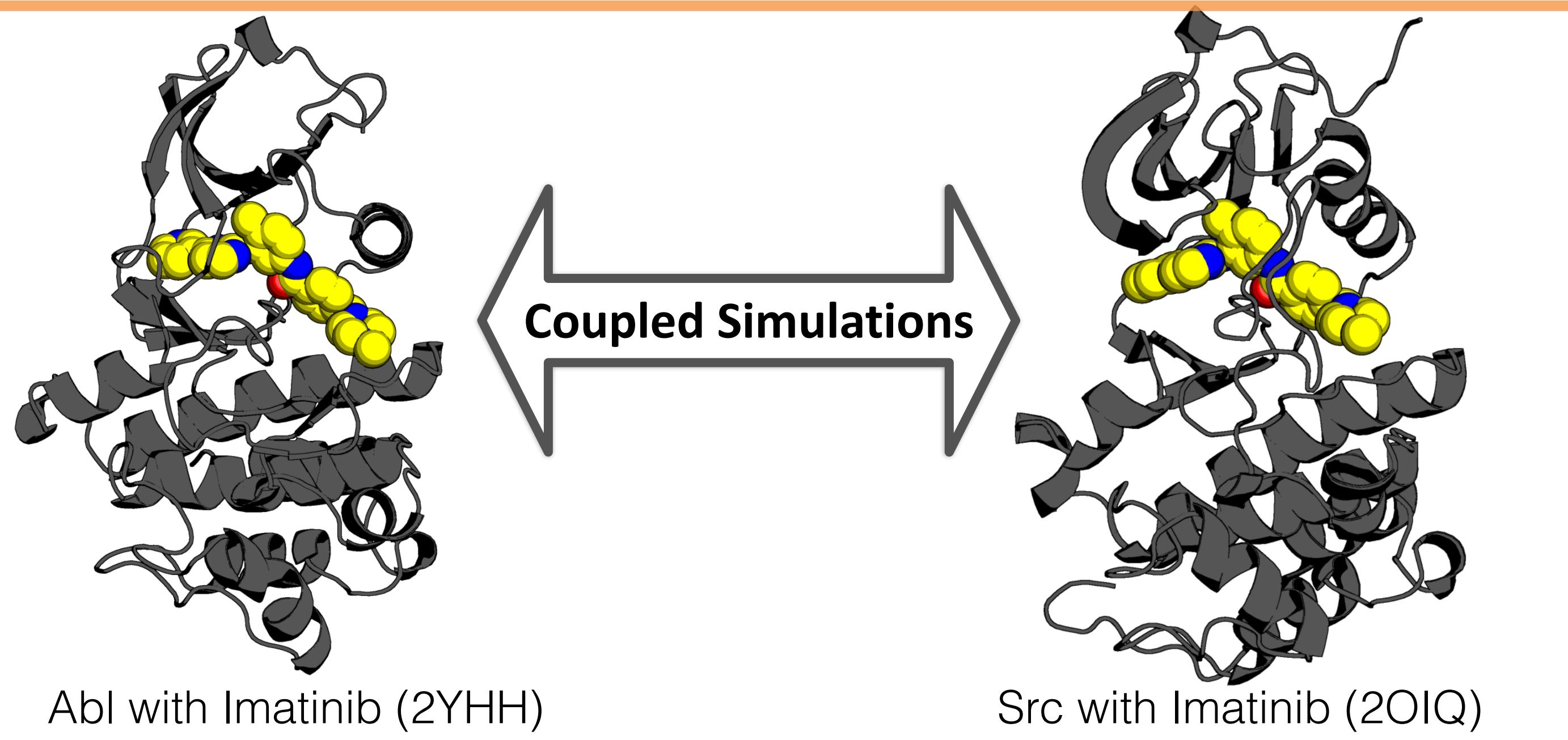


Huillard et. al. Eur J. Cancer 50:3, 2014

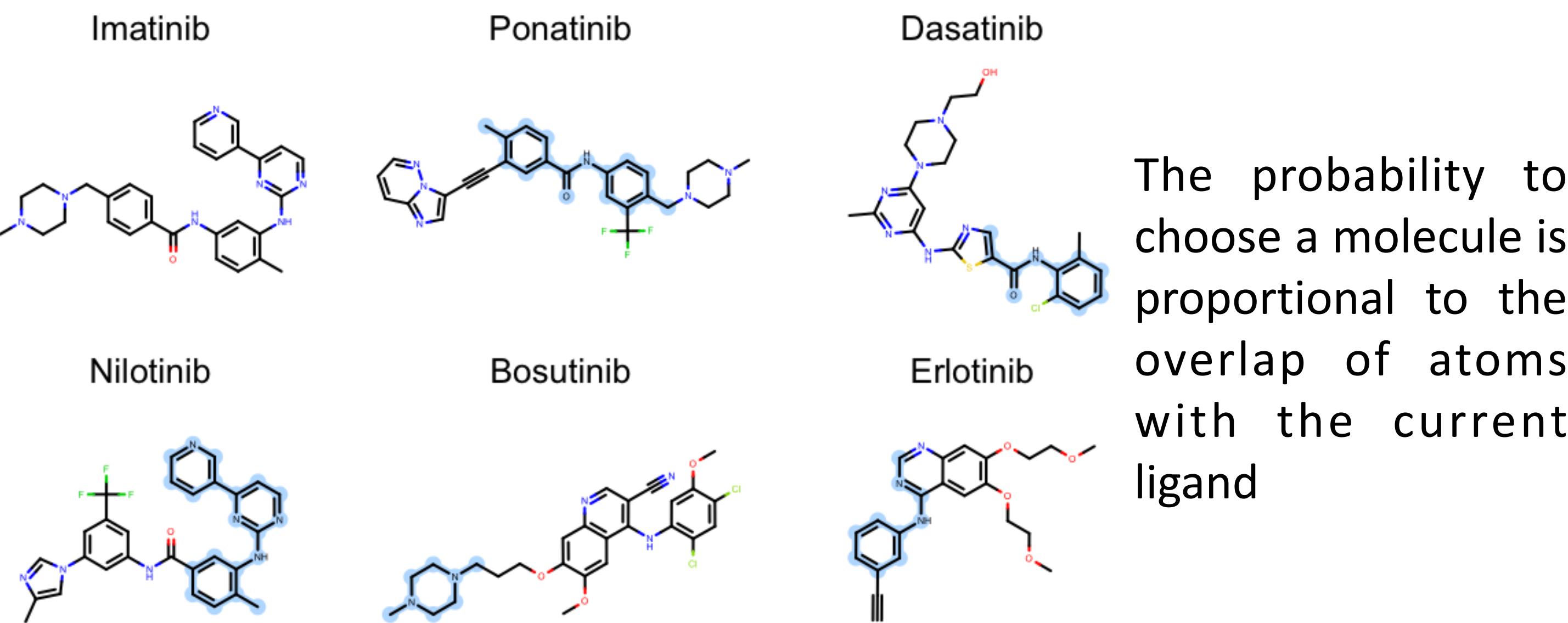
Minimize **on-target toxicity** by targeting (+) oncogenic mutant and antitargeting (-) wild type kinase

PERSES: a relative free energy calculation for molecular design using multiple targets

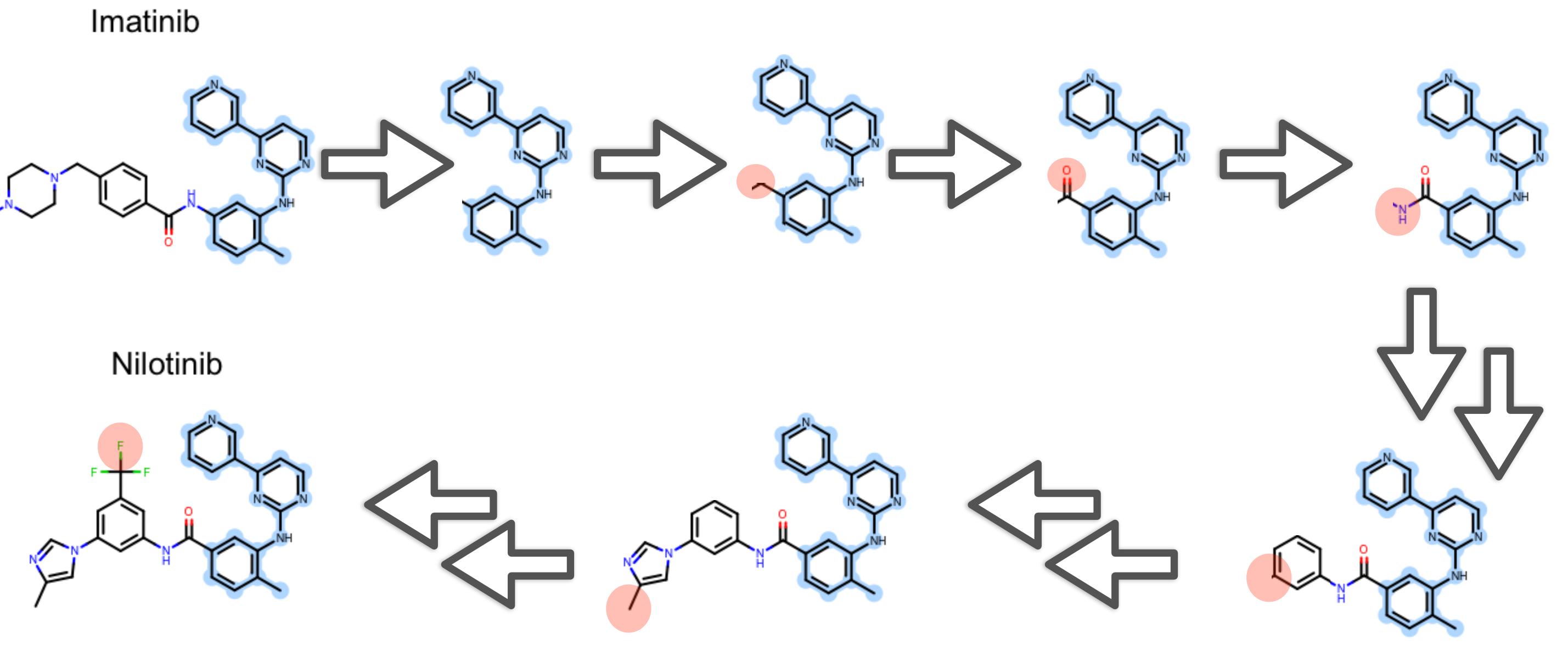
Start coupled simulations for each target



A new ligand is proposed



New ligand is built in atom by atom



Select ligands that optimize an objective

$$[1] \quad K_d = \frac{[P][L]}{[PL]}$$

$$[2] \quad K_d \propto \left(\frac{Z_p Z_L}{Z_{PL}} \right)$$

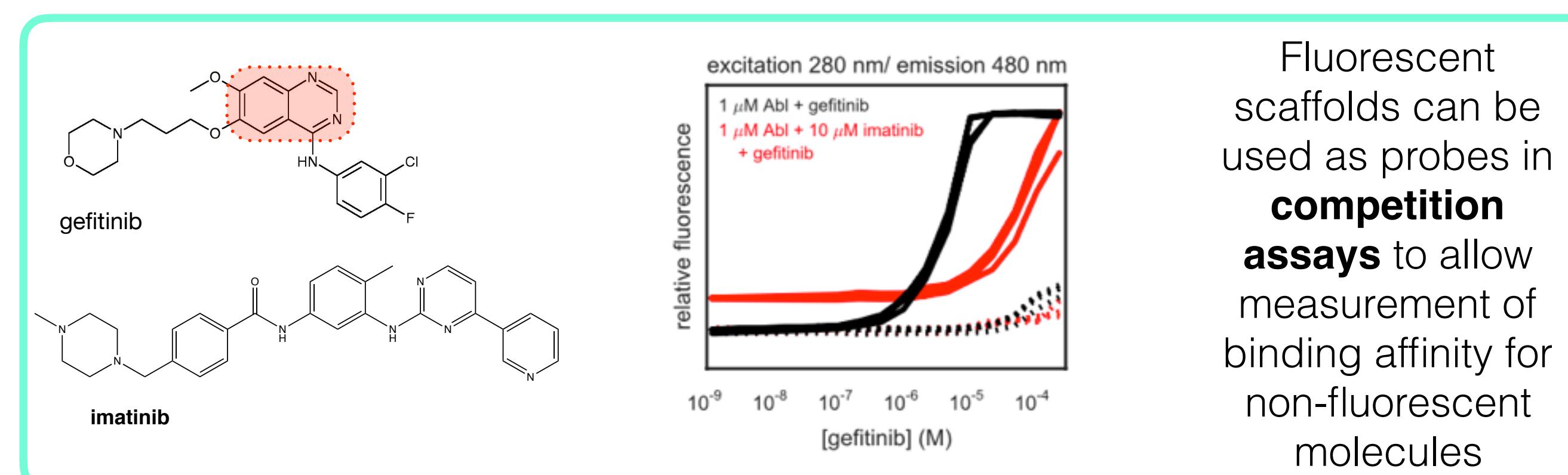
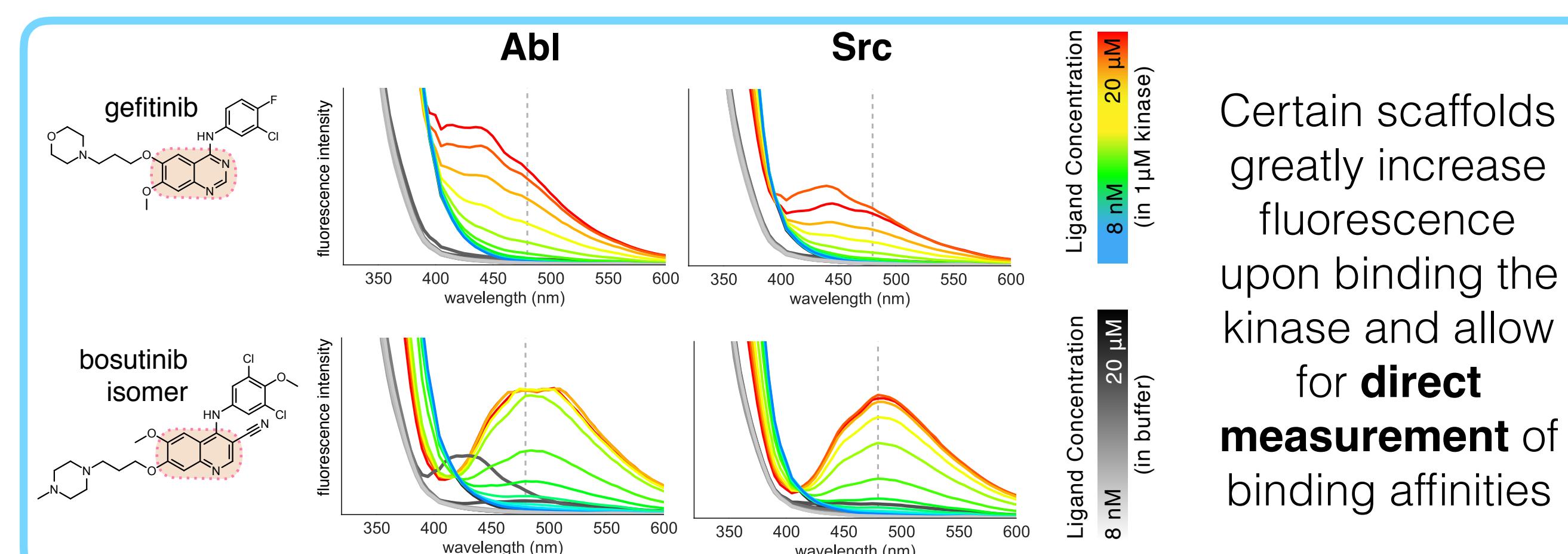
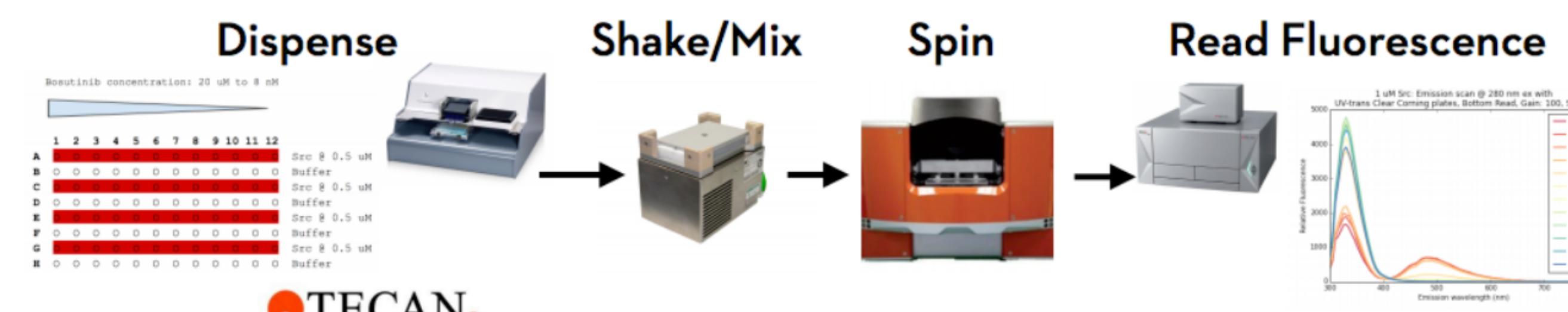
$$[3] \quad K_{d1,k} K_{d2,k} \propto \left(\frac{Z_{p1} Z_L}{Z_{P1L}} \right) \left(\frac{Z_{p2} Z_L}{Z_{P2L}} \right)$$

$$[4] \quad K_{d1,k} \propto \left(\frac{Z_{p1} Z_L}{Z_{P1,L}} \right) \left(\frac{Z_{p2,L}}{Z_{21} Z_L} \right)$$

Multitarget relative alchemical free energy calculations allow for ranking molecules based on a flexible objective function that can be adjusted to accommodate multiple targets and antitargets (Equations 3 and 4)

P = protein c_o = standard concentration
L = ligand Z = partition function
 g_s = log bias
 $K_{d1,k}$ = dissociation constant for target 1 at ligand k

We can use fluorescence measurements to test our predictions

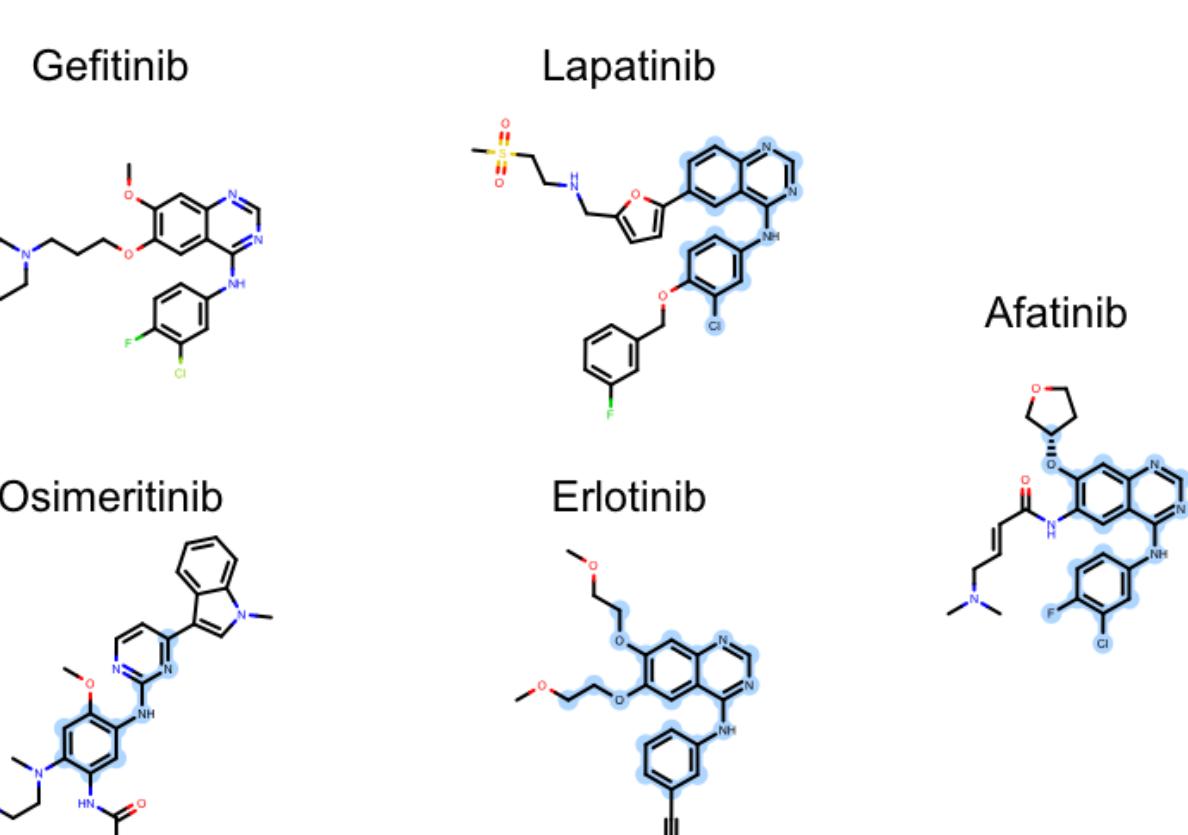
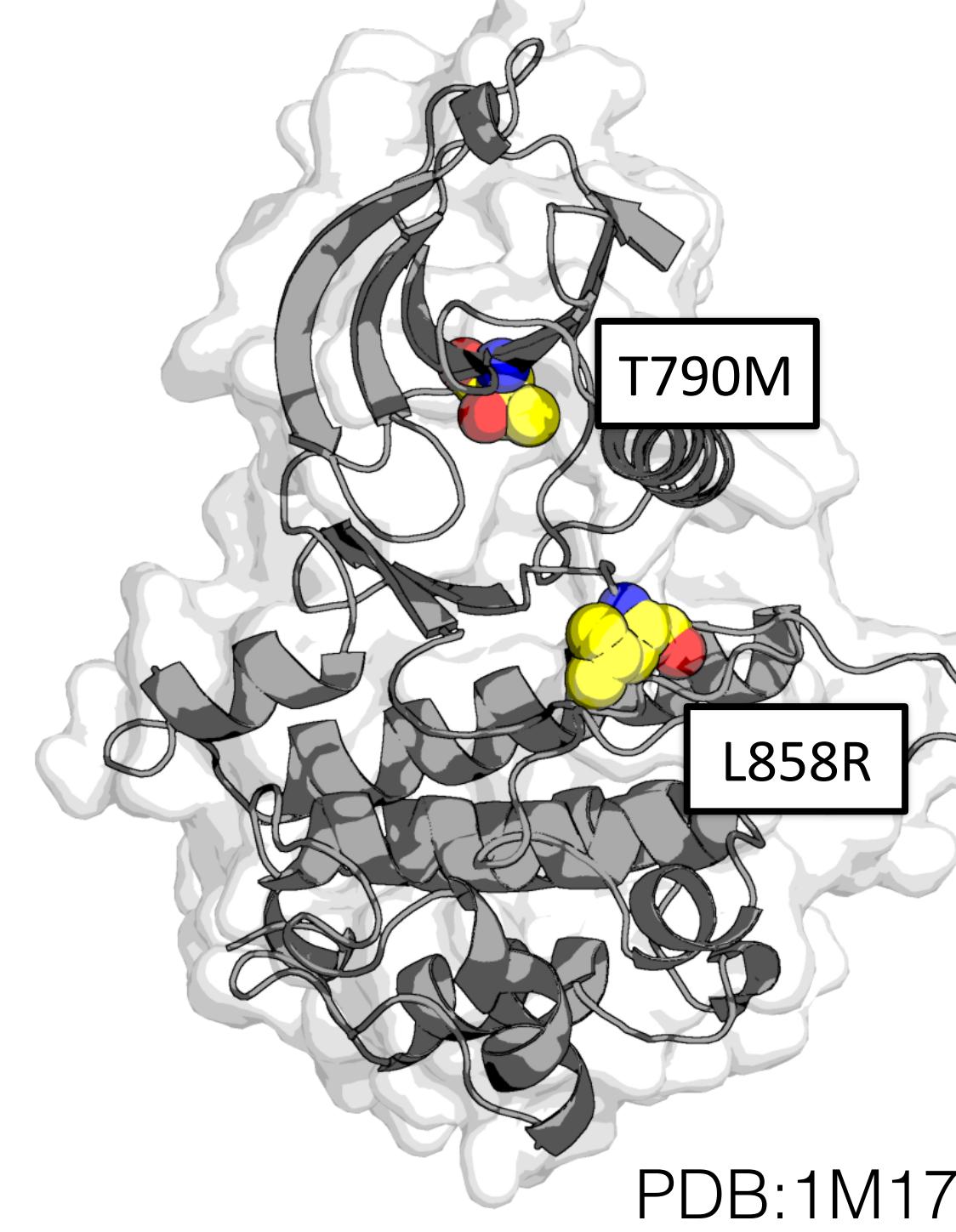


Sonya Hanson and Lucelenie Rodriguez

EGFR is a clinically interesting test case

Oncogenic and Resistance mutants

Mutant selective and dual targeted inhibitors as proof of principle



Contact:
steven.albanese@choderelab.org