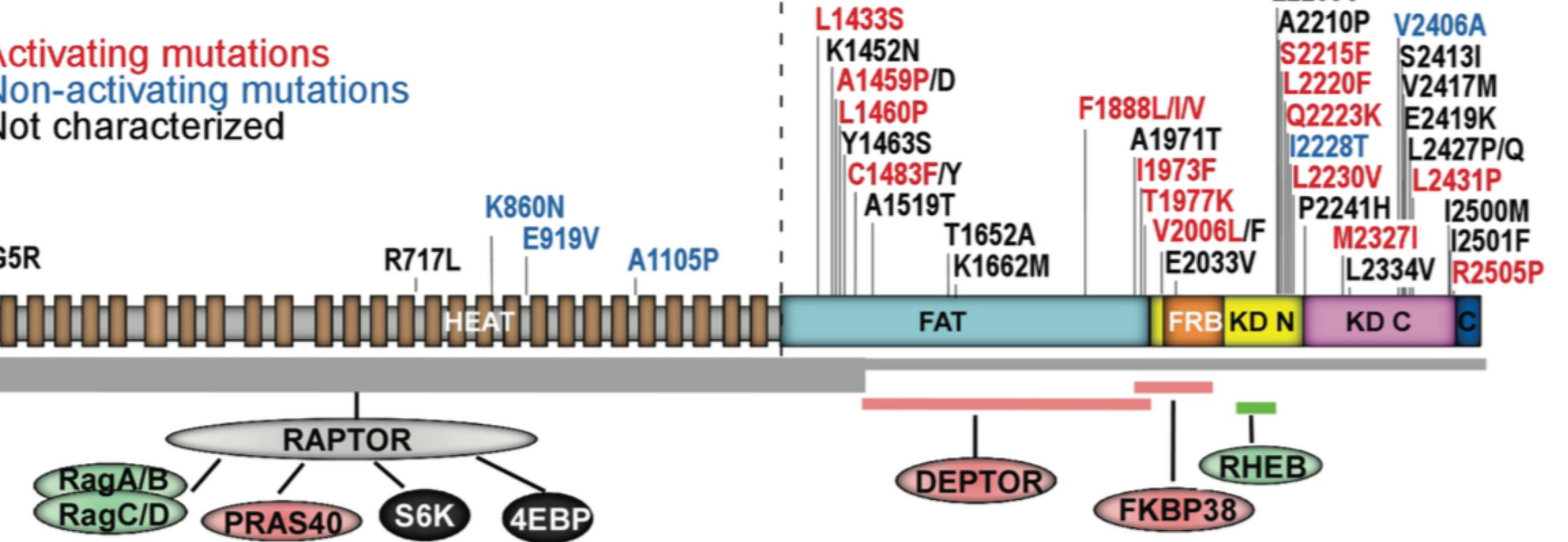
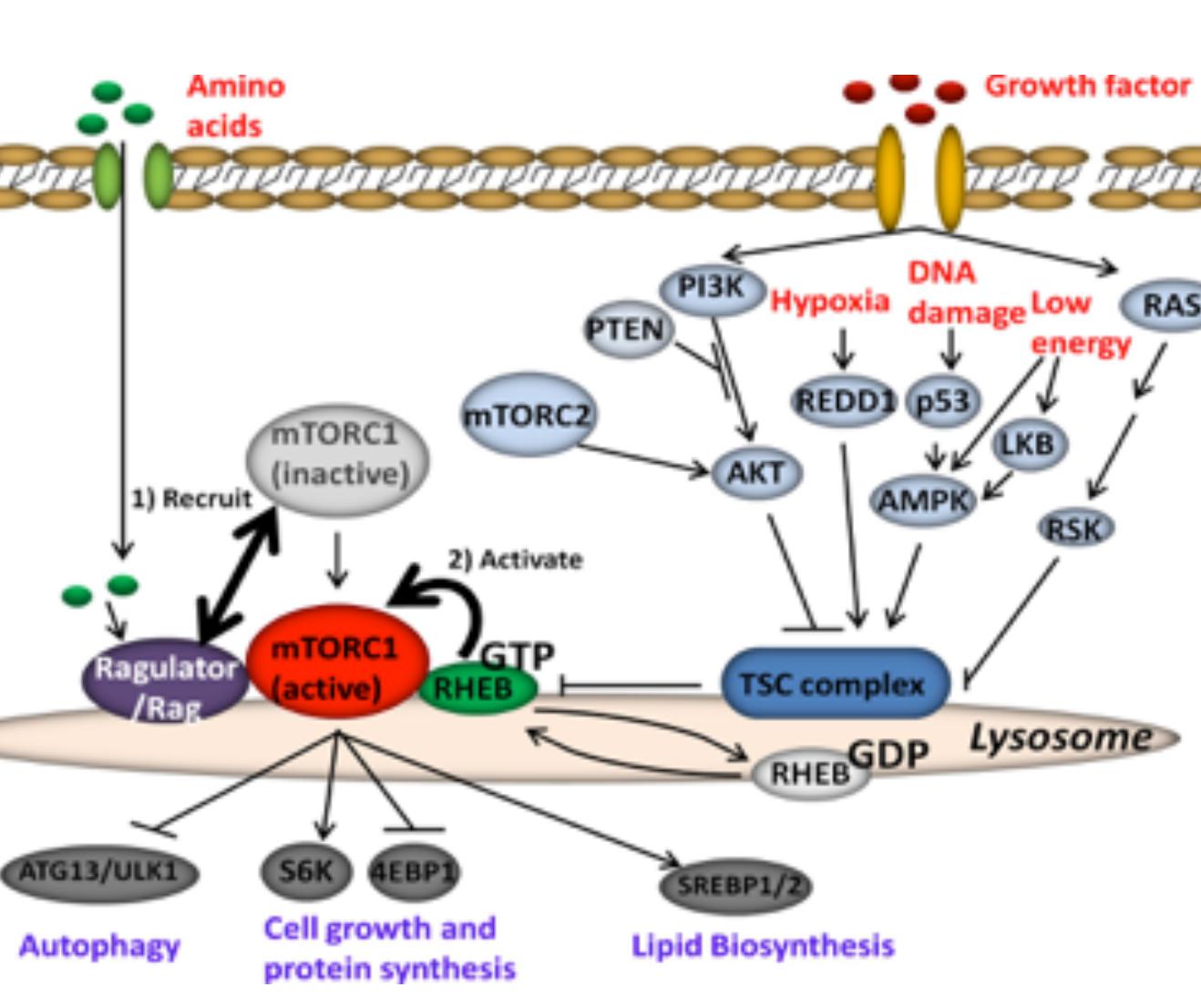
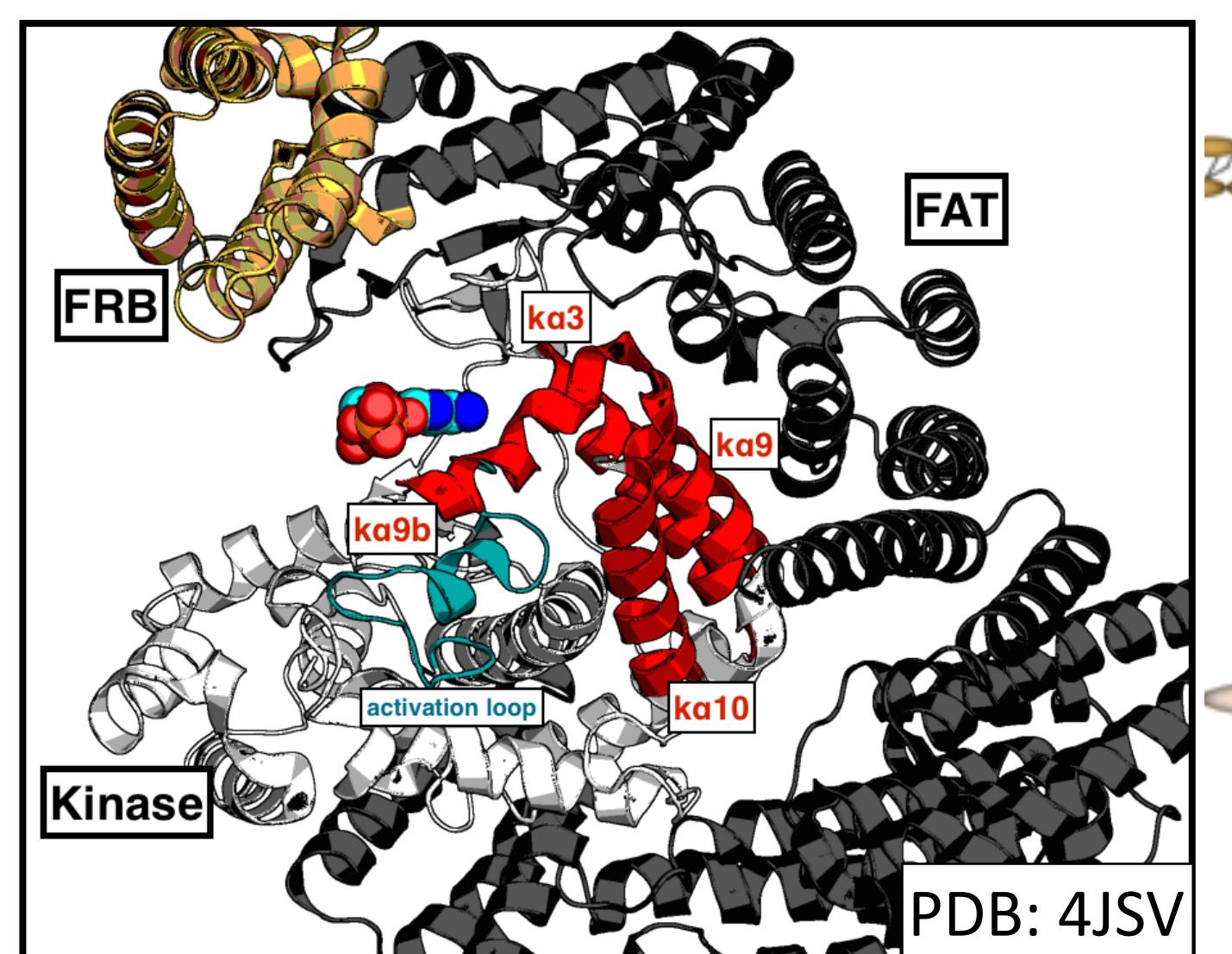


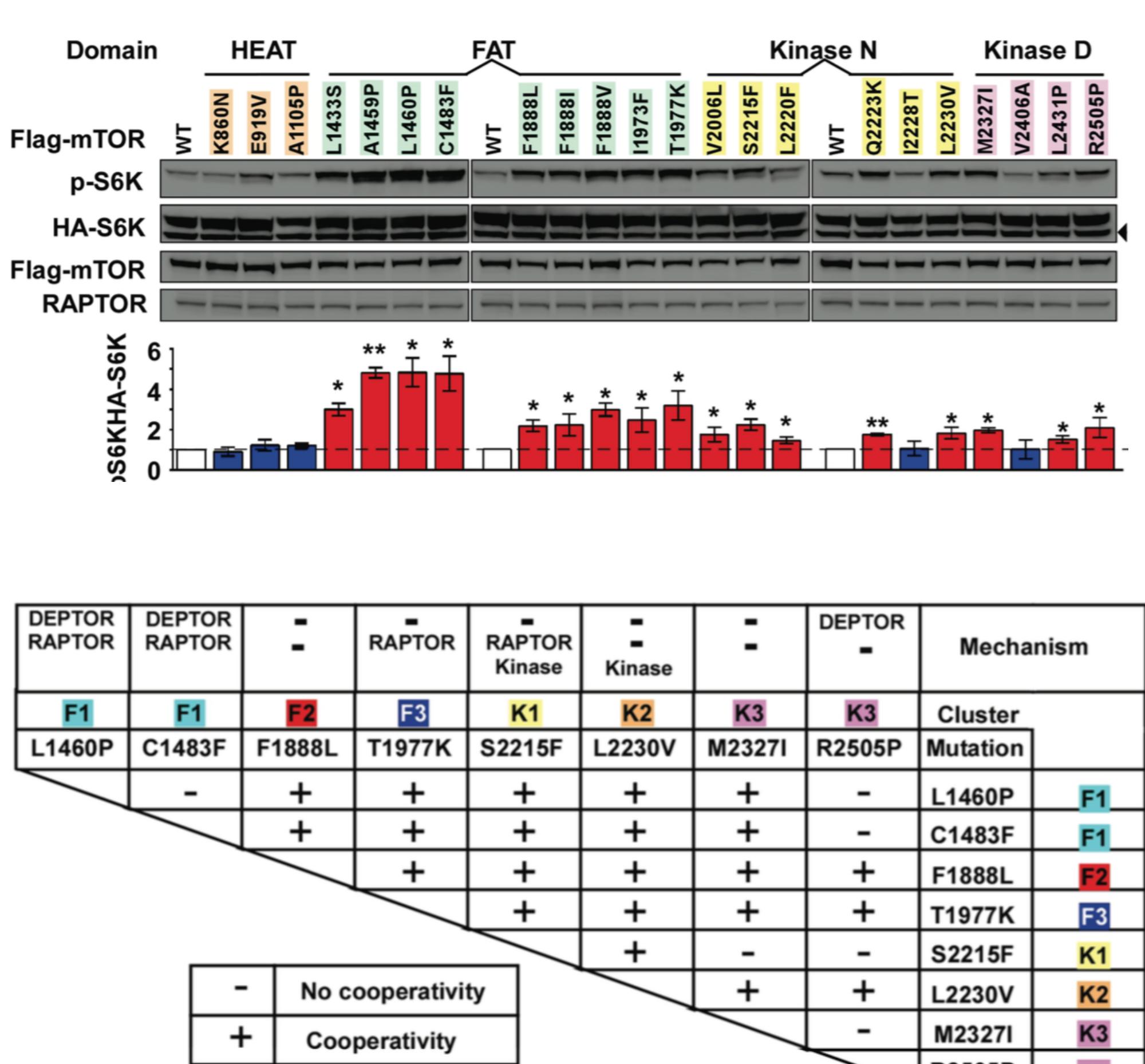
SIMULATING MTOR HYPERACTIVATING MUTATIONS TO UNDERSTAND FUNCTIONALLY SIGNIFICANT STRUCTURAL REARRANGEMENTS

Steven K. Albanese, Jianing Xu, Sonya M. Hanson, Josh Fass, James Hsieh, John Chodera

mTOR mutations are observed in cancer



Clinically observed mTOR mutations are hyperactivating through multiple mechanisms

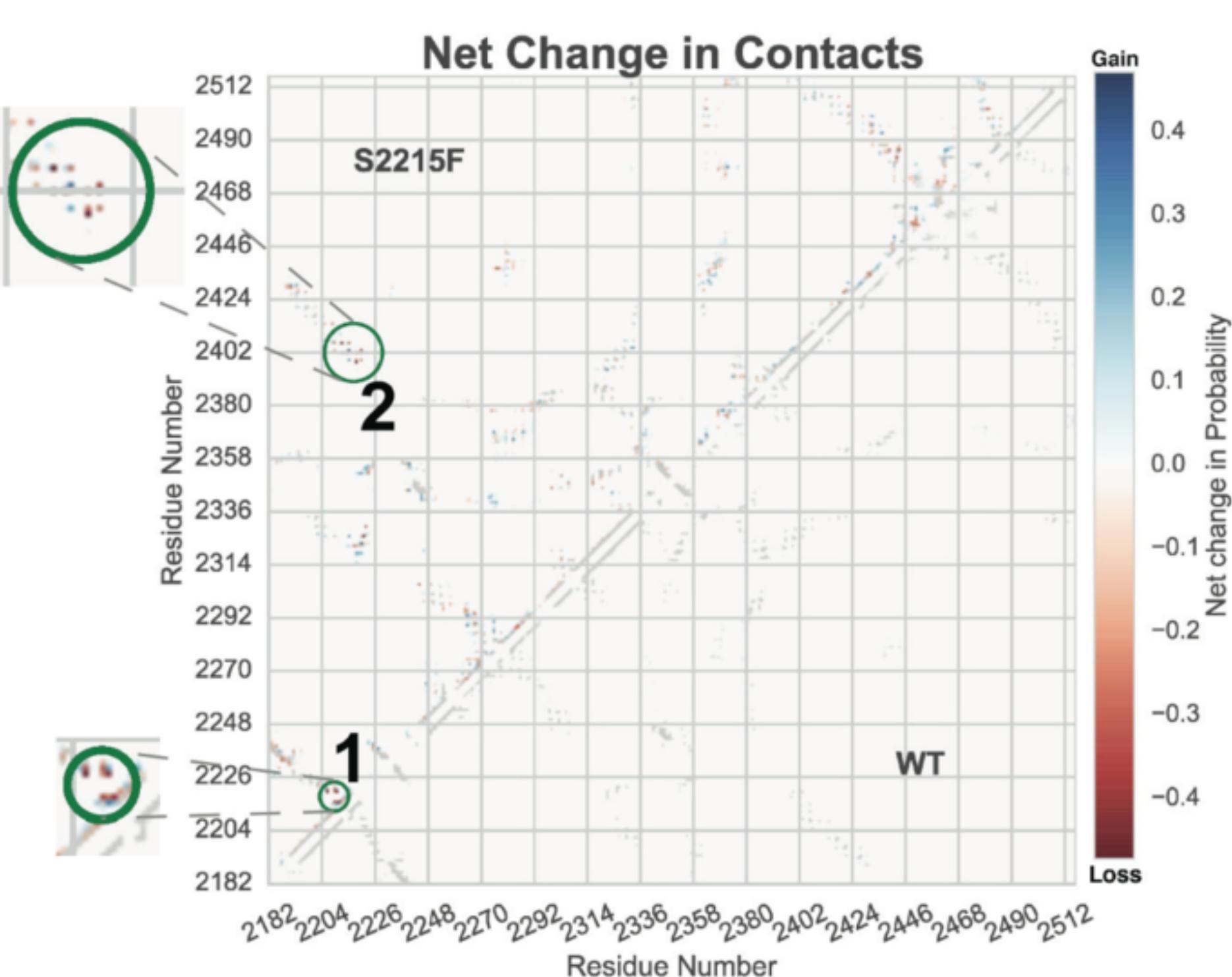


(Top) Mutations in the FAT and kinase domains induce higher phosphorylation of S6K. Shown is an immunoblot of whole cell lysate from 293T cells transfected with HA-tagged S6K and FLAG-tagged mTOR and densitometry of phospho-S6K vs. HA-S6K (mean \pm SEM for 3 independent experiments). (Bottom) Mutations from different functional clusters exhibit complementary activation when combined as double mutants. Determined on the basis of S6K phosphorylation.

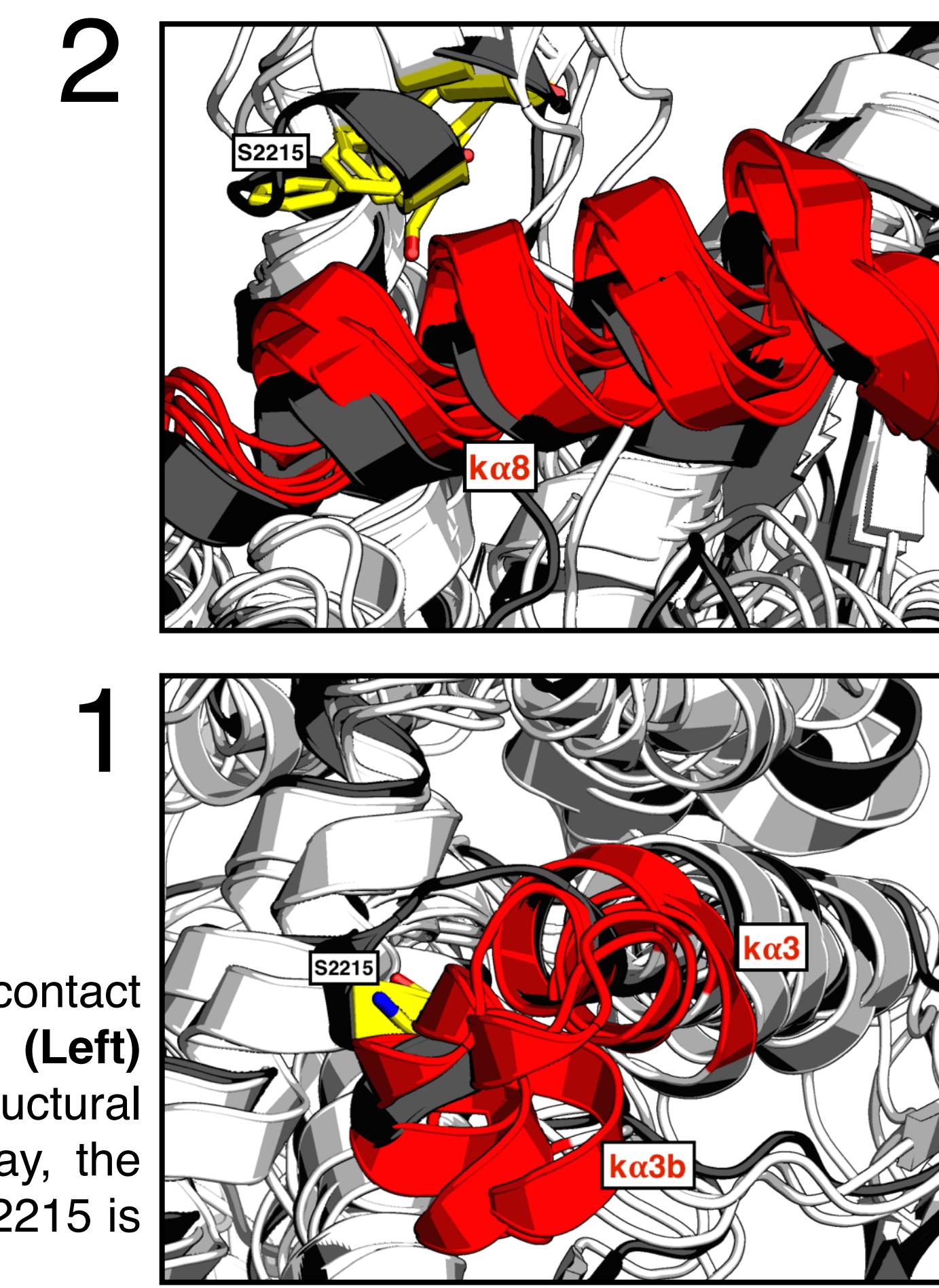
Contact:
steven.albanese@choderelab.org

Special thanks to the mdtraj team and Folding@home donors.

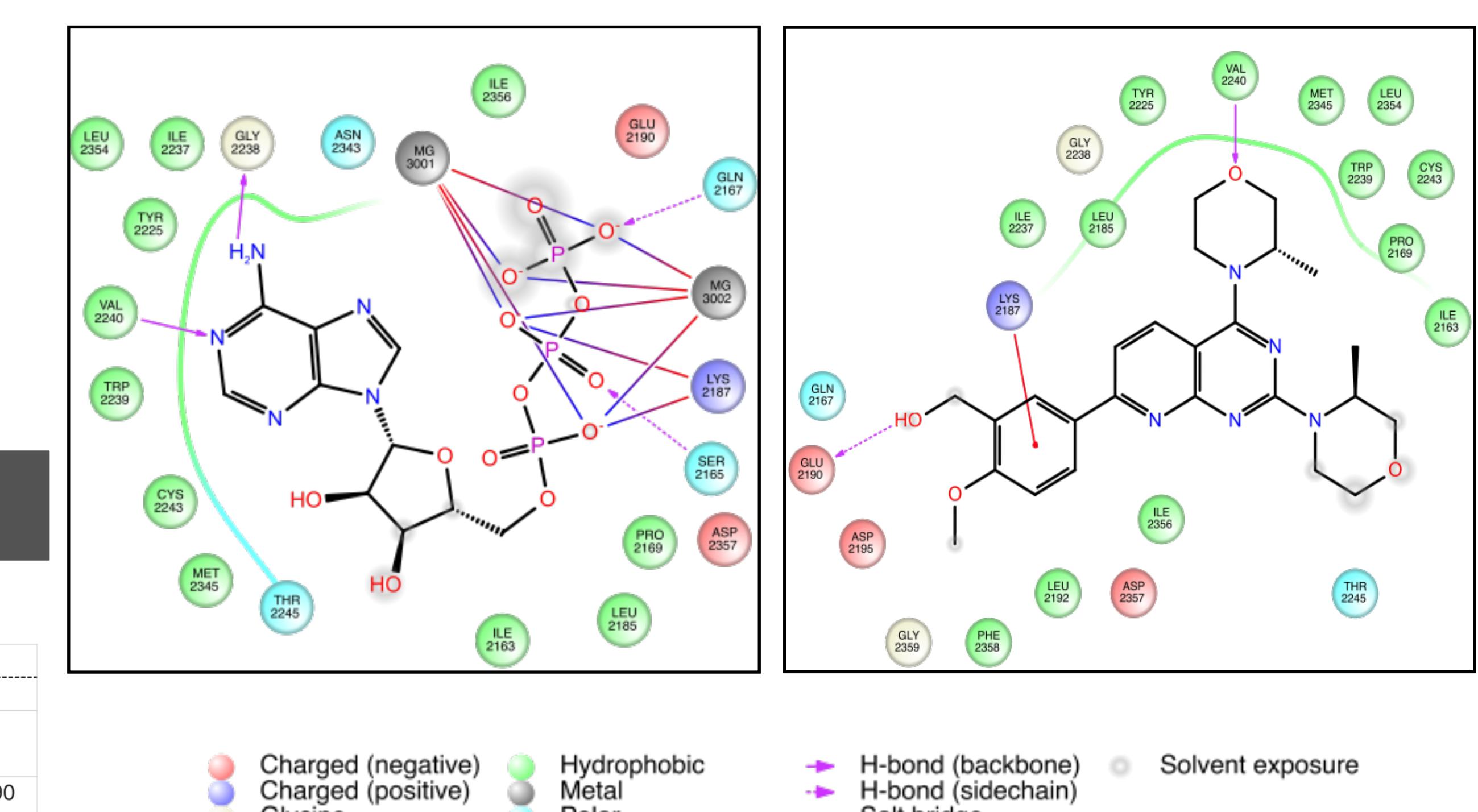
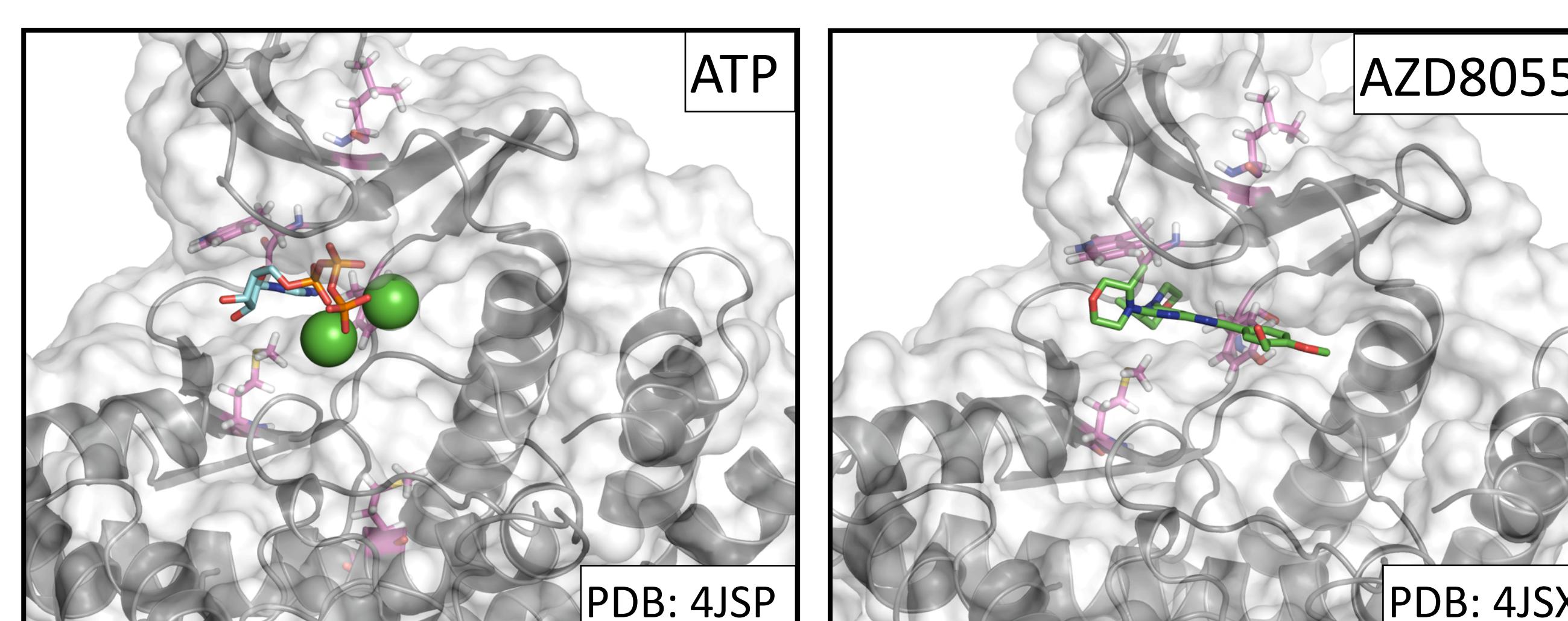
Mutations can perturb local structure



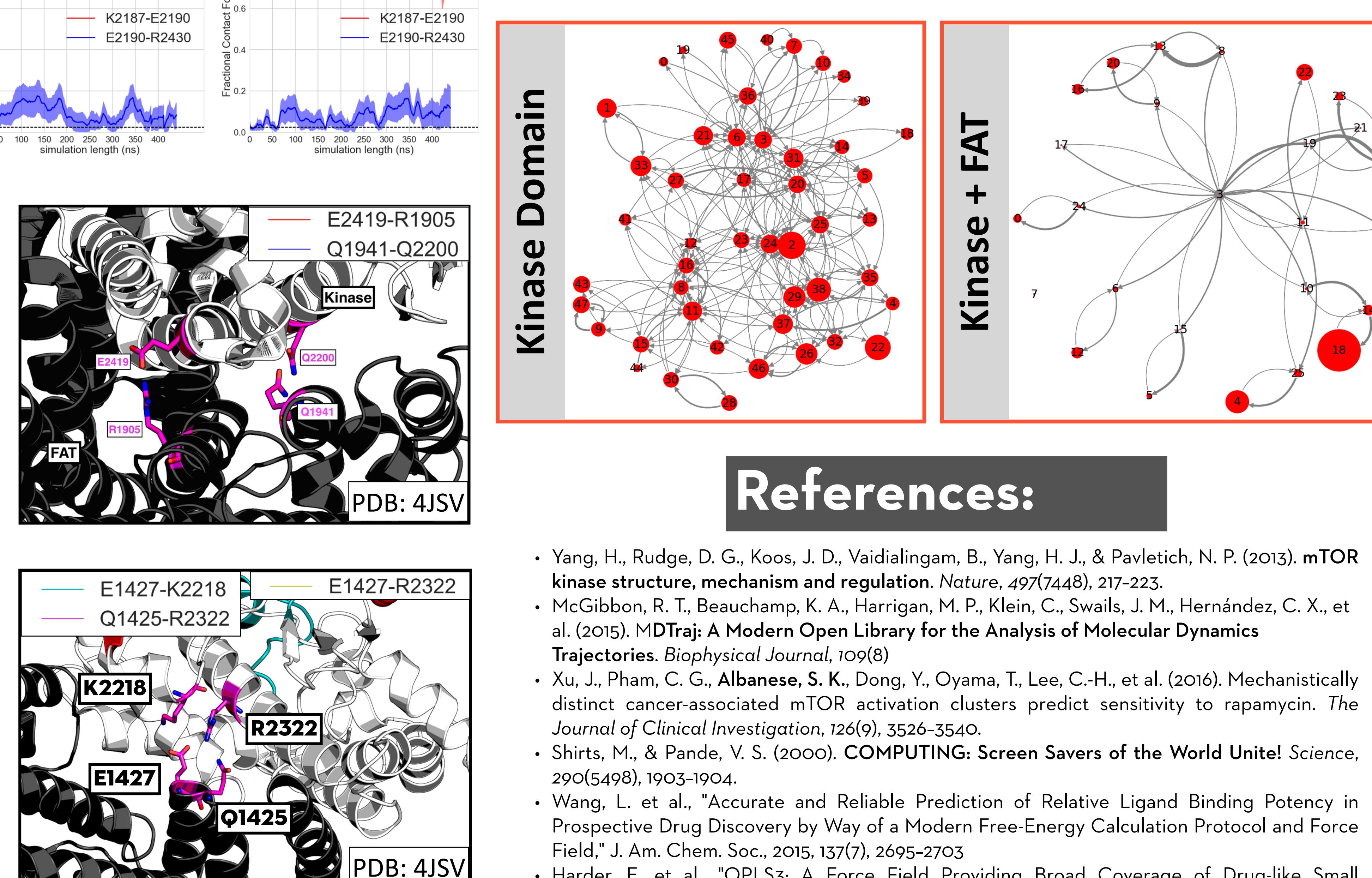
(Top) Contact map showing the difference in probability of forming a contact between WT and mutant S2215F for Kinase Domain residues (Left). Regions one and two highlighted in contact map, showing a structural perturbation in indicated helices. Starting structure is shown in gray, the residues indicated in the contact map are shown in red and residue 2215 is shown in yellow. All trajectories started from PDB: 4JSV



Predicting the effect of mutations on ATP and inhibitor affinity



Using Markov State Models to build a structural atlas of mTOR



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