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The landscape of EPHA2 inhibition

EPH receptors belong to the largest family of receptor tyrosine kinases. They are involved in various developmental and cell-cell communication events. EPHA2, a member of this family, has emerged as an interesting therapeutic target, because malfunctioning is correlated with various diseases (disorders of cardiovascular and nervous system, cancer or pathogen infections). So far, investigation of EPHA2 function and therapeutic targeting of EPHA2 driven pathologies are hampered by the lack of appropriate and selective inhibitors. We established selectivity profiles of 235 clinical kinase inhibitors using a chemical proteomics screen and identified various EPHA2 inhibitors. The binding properties of these off-target inhibitors were investigated by different methods. Protein crystallography was used to delineate the structural determinants of EPHA2 inhibition by numerous clinically approved kinase inhibitors and tool compounds. The identified interaction sites were categorized according to their localization, kinome-wide conservation and their impact on drug target selection. Furthermore, we analyzed the effects on structural plasticity and kinase activity upon inhibitor binding. This combined approach provides a detailed analysis at the interface between structure and drug selectivity profiling. The landscape of EPHA2 inhibition that we have established enables drug repurposing studies and initiated medicinal chemistry programs focusing on the development of novel EPH inhibitors.

References:

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Gande SL, Saxena K, Sreeramulu S, Linhard V, Kudlinzki D, Heinzlmeir S, Reichert AJ, Skerra A, Kuster B, Schwalbe H. *Chembiochem.* 2016, 17:2257-2263.

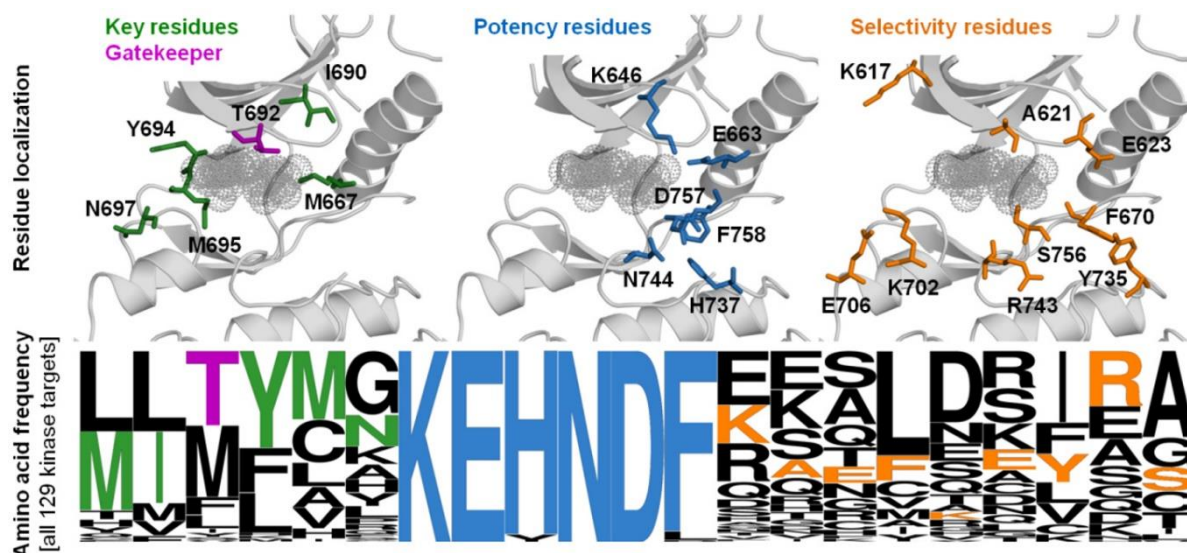


Fig 1:

Spatial positioning of key, potency and selectivity residues within the EPHA2 drug binding pocket. Key residues: found in inhibitor target proteins, not conserved in kinome; potency residues: highly conserved, add selectivity; selectivity residues: low conserved in binding pocket.

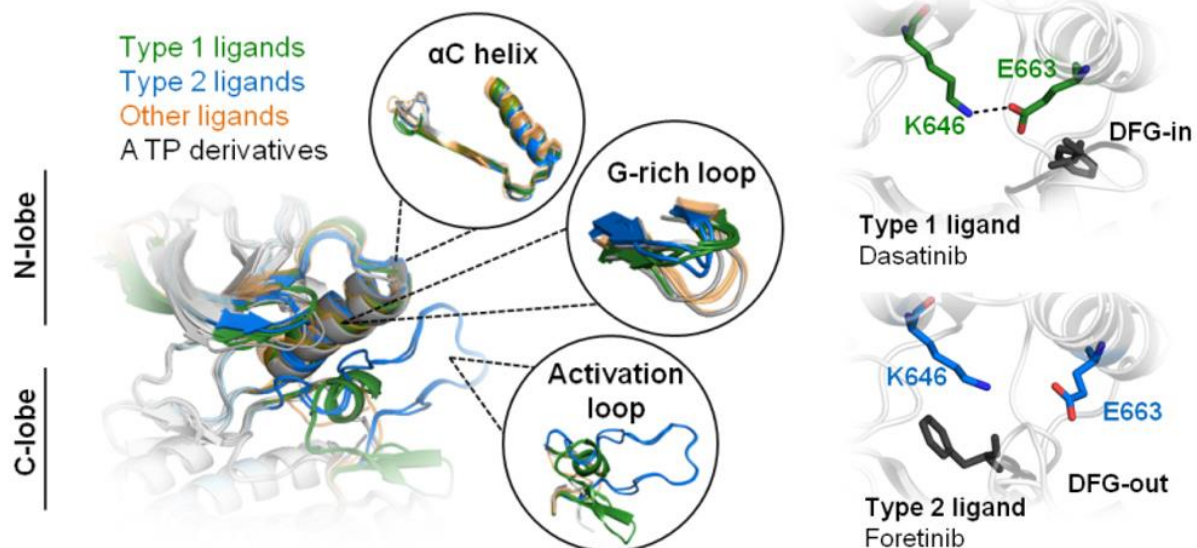


Fig 2:

Increased dynamics of kinase key motifs induced by the inhibitor binding. DFG-in inhibitors support the active K646/E663 salt bridge formation, whereas DFG-out ligands do not (inactive).