

Oral Contributions [MS8]

[MS8] Cell signalling - interactions and allostery

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[MS8 - 02] Cooperative assemblies of oncogenic receptor tyrosine kinases

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We have been employing creative combinations of X-ray crystallography, Small-angle X-ray Scattering (SAXS) and electron microscopy in conjunction with molecular interaction studies and cellular interrogation of the systems under study to elucidate the structural and mechanistic principles underlying extracellular complexes of oncogenic class III receptor tyrosine kinases (RTK-III). Focusing on human Flt3 and CSF-1R and their complexes with their cognate cytokines, our studies have revealed the unexpected structural diversity of such assemblies, and have established that structural plasticity and molecular cooperativity both at the level of the cytokines and their receptors play critical roles in the assembly of signaling complexes.

In addition, our studies of how signaling mediated by CSF-1 can be abrogated by a viral decoy receptor from the Epstein-Barr Virus, have uncovered an unprecedented allosteric competitive inactivation mechanism that exploits the cooperativity of the target cytokine-receptor signaling complex.