“Kinase Chemical Genetics and Cancer Drug Discovery”

Abstract: The kinase domain is found in ~2% of human genes, and an estimated 30% of the human proteome is phosphorylated or involved in kinase mediated signal transduction. Kinases can play dual roles as both enzymes and as conformational switches, and this is thought to contribute to their broad utility in biology. Recent advances in genome analyses have led to increased sensitivity for identifying genetic variations across the protein kinase superfamily (‘kinome’), with defects in kinase regulation or signaling linked to an extensive range of diseases including diabetes, neurodegeneration, and cancer.

Kinases belong to one of the most successfully drugged classes of therapeutic targets. Indeed, kinase inhibitors (KIs) have emerged as an important therapeutic modality for cancer treatment. Since the approval of Imatinib in 2001, over 30 new KIs have been granted approval for clinical use. Many of the clinical KIs have become transformative therapies, altering the course of disease progression. Remarkably, even with the explosive growth of clinical KIs, some estimates suggest that we are currently only exploiting less than 5% of the full therapeutic potential of kinases.

In my talk, I will present our work on two areas of kinase inhibitor development: (a) targeting the non-catalytic functions of kinases/pseudokinases and (b) targeting kinase networks through rational polypharmacology. In both approaches I will present the integrated use of genetics and chemistry to guide the development of tool compounds that have provided insights into the structural and mechanistic properties of cancer signaling pathways, and also new leads for therapeutic development.

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