The Discovery of Novel Kinase Inhibitors as Anti-Cancer Agents

A number of therapeutic agents used in the treatment of cancers target mitosis; these successes have encouraged research into mitotic kinases such as the Polo-like kinase (PLK) family. At the Campbell Family Institute, PLK4, a less well studied member, was identified as a potential anti-cancer target. We initiated a search for potent and selective inhibitors of this kinase to better understand its function and, ultimately, to identify a therapeutic agent. The presentation will include a brief narrative of our target identification and will key on the lead generation and optimization work that resulted in the clinical candidate (CFI-400945). This work includes a stereoselective synthesis developed to obtain CFI-400945 with high enantiomeric excess and concludes with preclinical data that supports the clinical development of this new anticancer agent.

TTK is a second mitotic kinase of interest and several laboratories have recently disclosed drug discovery programs against this anticancer target. Our approach to TTK inhibition built on our work with PLK4 and was part of collaboration with Professor Dennis Slamon at UCLA. This part of the talk will describe the structure guided lead optimization work which yielded nanomolar TTK inhibitors with potent anti-proliferative activity. Regular in-house ADME studies provided key feedback for driving the synthetic optimization of the pharmacokinetic properties of the molecules. Selected compounds were moved forward into mice xenograft studies; a potent TTK inhibitor (CFI-401870) with high selectivity and oral bioavailability was chosen for IND enabling studies.

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