Kinase Inhibitors

Src Inhibitors

Src kinase activity is elevated in some human tumors, including breast and colon cancer. The activity of src plays a role in cell proliferation and transformation. We are studying the activities of a kinase inhibitor, which shows selectivity toward the src family protein kinases. We are using this inhibitor to study the biological activities of src family kinases. Furthermore, work is in progress to identify functional targets of src kinases at the G2-M phase of the cell cycle.

EGFR/HER2 Inhibitors

Amplification of the HER family of tyrosine kinases occurs in a subset of tumors. EGFR and HER2 are transforming in cell culture models, and are tumorigenic in transgenic mice. Therapeutic antibodies targeting the extracellular domains of these receptors have been successful in the treatment of cancer. Pharmalogical advances have led to the development of small molecule inhibitors of these receptors. For example, ZD1839 (Iressa) is a synthetic tyrosine kinase inhibitor selective for EGFR. We are studying the basis for the sensitivity of some tumors to these inhibitors. Although the 4 members of the HER family share many structural and functional characteristics differences in mouse models, and tissue expression patterns reveal that each member has unique characteristics. Using selective inhibitors we can gain a better understanding of the roles of these receptors.

Rapamycin

Rapamycin is a natural product that inhibits mTOR, causing inhibition of translation initiation factors. The drug inhibits cell proliferation and causes G1 cell cycle arrest. We are currently assessing the mechanism of its antiproliferative activity and effects on cell cycle. Additionally, the potential synergy between ansamycins and rapamycin is being evaluated.

MEK Inhibitors

MEK inhibitors prevent the Ras-Raf dependent activation of MAP kinase. We have shown that ansamycins affect both the PI3k/Akt and Ras/MAPK signaling pathways. Using these inhibitors along with commercially available inhibitors of the PI3k pathway, we are delineating which cellular phenotypes of ansamycins are attributive to which pathway. Additionally, we are interested in understanding the role of the Ras-MAPK pathway in breast and colon cancer.

Androgen Antagonists

Androgen antagonists prevent the growth of prostate cancer cells and induce a G1 cell cycle arrest. The mechanism of this growth arrest is being determined. We are studying the effect of these antagonists on p27, cyclin E, and cyclin D/cdk complexes. We are also interested in studying downstream targets of androgen receptor.