Novel Activators of Apoptosis That Target XIAP for Cancer Therapy
RU 1034

Technology Summary
Essentially all human cells have the ability to activate an intrinsic cell suicide program when they are no longer needed or have become seriously damaged. The execution of this program leads to a morphologically distinct form of cell death termed apoptosis. Besides playing a critical role for shaping the developing organism, apoptosis plays an important role to prevent the survival and accumulation of cancer cells. However, cancerous cells can escape apoptosis by over-expressing prosurvival proteins, such as Inhibitor of Apoptosis Proteins (IAPs). IAPs block apoptosis by directly inhibiting caspases, the key enzymes responsible for executing apoptosis. Because inhibition of IAPs in cancer cells can lead to selective tumor cell killing, these proteins are attractive pharmacological targets for developing new anti-cancer drugs.

Our scientists have developed novel screening platforms to identify potent and specific small-molecule antagonists of the human XIAP protein, which is commonly over-expressed in a variety of human cancers. One class of newly developed compounds target XIAP at the mitochondrial outer membrane to promote selective cancer cell killing. Other compounds, termed Xaripin D and P, were identified in a high-throughput screen and cause potent and selective down-regulation of XIAP protein levels. Xaripins promote effective killing of certain melanoma cells, and they also sensitize glioma cells to death receptor (TRAIL) mediated apoptosis. These results provide proof-of-concept for developing these compounds as anti-cancer agents in the clinic.

Area of Application
Promotion of cell death to treat cancer and other neoplastic diseases

Stage of Development
Discovery – mitochondrial targeting of IAP-binding peptides is sufficient to inhibit IAPs and selectively kill cancer cells in vitro.

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Patent Information
U.S. patent application US 2013-0244325-A is pending.

References