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Discovery and development of dual inhibitors of MDM2 and XIAP

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MDM2 and XIAP promote cancer cell survival by inhibiting p53 and caspase activation to prevent apoptosis, respectively. Further, the RING domain of MDM2 can bind to the internal ribosome entry site (IRES) of *XIAP* mRNA transcripts to promote *XIAP* translation, increase MDM2 protein expression, and enhance resistance to apoptosis. We hypothesized that disrupting the interaction between MDM2 and *XIAP* would decrease expression of both proteins and enhance cancer cell apoptosis. A fluorescence polarization assay was developed for high-throughput screening of small-molecule inhibitors of *XIAP* IRES binding to the MDM2 RING domain. Of 141,394 small molecule compounds tested, 8 candidates disrupted MDM2–*XIAP* binding, and 3 compounds selected for further study (MX3, MX11, and MX69) reduced protein expression of both MDM2 and XIAP when added to cancer cells. MX11 and MX69, which bound to the MDM2 RING, and MX3, which bound to the *XIAP* IRES, induced the self-ubiquitination and degradation of MDM2, which not only led to the stabilization and activation of p53 but also inhibited XIAP, resulting in activation of caspases 3, 7, and 9. In a panel of acute lymphoblastic leukemia (ALL) and neuroblastoma cell lines, MX3 and MX69 induced apoptosis in an MDM2-, p53-, and XIAP-dependent manner. MX69 had little effect on normal hematopoiesis, and was thus tested in vivo in mice bearing ALL xenografts. Treatment with MX69 reduced disease burden, increased survival, and was well tolerated in mice. Altogether, these findings support further investigation of MX69 and its analogs as therapies to induce apoptosis in cancer cells.

Speaker Biography

Muxiang Zhou research is in the field of signaling pathway identification and molecular targeting of pediatric cancers. He have a broad background in molecular biology of childhood cancer and longstanding interest in understanding the role of several oncoproteins such as MDM2 and XIAP in mediating cancer cell promotion and resistance to anticancer treatment. His current research programs build logically on my previous work, translating basic studies on MDM2 and XIAP-mediated signaling into first preclinical and later a clinical investigation of small molecule inhibitors targeting MDM2 and XIAP for use as novel cancer treatments.

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