Technology Brief: Small Molecule Inhibitors of Nuclear Export of Topoisomerase II Alpha for Multiple Myeloma Treatment

Docket Number: 08MB014

Summary	• Inhibitors of topoisomerase II, such as doxorubicin, are effective chemotherapy for multiple myeloma. • Resistance to these agents may arise when cancer cells export topoisomerase II alpha from the nucleus to the cytoplasm. • Scientists at Moffitt Cancer Center have identified small molecules that inhibit nuclear export of topoisomerase II alpha and sensitize human myeloma cells to topoisomerase II inhibitors such as doxorubicin. • These newly identified export inhibitors may be useful as agents for treating multiple myeloma and other hematologic cancers, either alone or in combination with topoisomerase II inhibitors.
Features and Benefits	• The two nuclear export signals in topoisomerase II alpha were targeted by in silico screening against a library of drug-like molecules. • The 20 top-scoring compounds were assayed for inducing cell death in human multiple myeloma cell lines NCI-H929 and RPMI 8226, both as single agents and in combination with topoisomerase II inhibitors. • Two inhibitors have IC_{50} values in the low micromolar range as single agents. • Nuclear export inhibitors are synergistic in combination with inhibitors of topoisomerase II in inducing death of human multiple myeloma cells. • These newly identified inhibitors may be useful as single agents in treatment of multiple myeloma, or in combinations to overcome resistance to topoisomerase II inhibitors.
Stage of Development	Proof of concept in human multiple myeloma cell lines. Testing planned in patient cell samples.
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Patent Status	PCT patent application filed.

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