Method of Using Selective Inhibitors of Nuclear Export to Overcome Resistance to Chemotherapy Using Topoisomerase II Inhibitors

Topoisomerase (topo) II alpha is an enzyme that induces small breaks in the DNA necessary for replication, which are later resealed. Therapeutic administration of Topo II inhibitors (doxorubicin, etoposide) traps the enzyme on the DNA strain, thus preventing resealing and causing cell death. However, cancer cells can export the topo II from the nucleus to cytoplasm (away from the DNA), becoming resistant to topo II inhibitors. Our technology is a novel compound that inhibits the topoisomerase (topo) II alpha cytoplasmic export, thereby offering a promising novel approach to circumvent drug resistance in malignancies such as leukemias, lymphomas, myeloma, breast, testicular, thyroid etc.

COMMERCIAL OPPORTUNITY

- Topo II inhibitors (Etoposide, Doxorubicin, Mitoxantrone and Amsacrine) are used as 1st, 2nd or 3rd line therapy in multiple cancers, including hematologic malignancies (multiple myeloma, lymphomas and leukemias), solid tumors (breast, prostate, lung, ovarian, thyroid, bladder , gastric and sarcomas), as well as rare or unusually aggressive tumors (Merkel carcinoma, carcinomas of unknown origin, neuroblastoma, aggressive endocrine tumors), and childhood neurological malignancies.
- Despite the fast and dramatic initial control of the tumor, resistance to topo II inhibitors is inevitable. While multiple mechanisms of resistance have been proposed, we have identified inhibitors of the nuclear export signal (NES) transport of topo II that resensitize resistant cancer cells to topo II inhibitors.
- Our novel NES compounds can be administered when patients become resistant to topo II inhibitors, thus helping to prolong its therapeutic action. In 2013, worldwide sales of Doxil (doxorubicin) were estimated to be approximately $600M, with $250M coming from the US market alone. We anticipate that the market for our compounds could be comparable.
- Doxorubicin (one of the most widely used topo II inhibitors) was granted an orphan drug exclusivity by the FDA, so that when the patent expired in October 2009, it was protected against generic competition until May 2014. Hence, if a therapeutic drug is developed using our compound(s), then it may also qualify for an orphan drug status.

TECHNOLOGY

139,735 small molecules at the NCI Developmental Therapeutics Program repository were screened on the ability to inhibit the nuclear export NES of the topo II. The 40 highest scoring compounds were assayed *in vitro*. Multiple myeloma and acute myeloid leukemia cell lines initially resistant to doxorubicin were resensitized to the drug after treatment with four of our NES-compounds (NCI-35847; NCI-80640; NCI-9138; NCI-155877). These CRM1-selective inhibitors of nuclear export molecules had IC_{50}s of 7.2 $\pm$ 1.7 μM, 8.8 $\pm$ 3.0 μM, 9.5 $\pm$ 1.1 μM, and 18.3 $\pm$ 2.3 μM, respectively, with most showing a 2 to 4-fold increase in nuclear localization of topo II alpha in plateau density cells treated with NES inhibitors at 25 μM versus control cells.

PUBLICATION/PATENT

- Presented at ASH 2010: Blood (ASH Annual Meeting Abstracts) 2010;116: Abstract 3012.
- US Non-Provisional patent application filed on 6/3/2013 for Drs. Sullivan and Ostrov

CONTACT

Haskell Adler PhD MBA
Senior Licensing Manager
Haskell.Adler@Moffitt.org
(813) 745-6596

LICENSING OPPORTUNITY

MOFFITT CANCER CENTER