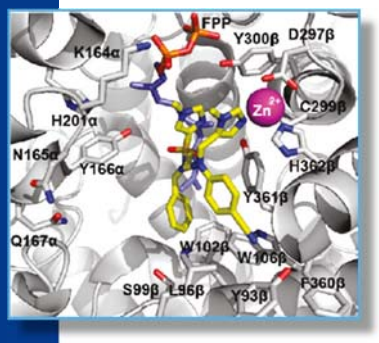
Novel Dual Inhibitors of Farnesyltransferase and Geranylgeranyltransferase-1 as Anti-Cancer Agents



This technology is a small molecule dual inhibitor of two enzymes necessary for localization and activation of the K-RAS protein, farnesyltransferase and gernaylgeranyltransferase-1. Mutant overactive K-RAS is found in about 25% of all human cancers, making it an attractive target for the development of first-in-class anti-cancer therapeutics. A novel inhibitor of RAS protein localization was recently acquired by Kadmon Corporation and is currently in Phase II clinical trials. Our lead compound in early preclinical development shows promising results for killing pancreatic, lung, breast, and prostate cancer cell lines.

COMMERCIAL OP PORTUNITY

- K-RAS is an elusive, yet attractive target for anticancer therapy since on average its overactive mutant forms are present in almost one-quarter of all cancer patients. Mutant K-RAS is found in about 80% of pancreatic cancers, up to 50% each of non-small cell lung and thyroid cancers, over 40% of colorectal cancers, and 30% of rhabdomyosarcomas.
- Blocking all methods of K-RAS localization to the cell membranes is thought to be crucial for inhibiting K-RAS activity and has been pursued by a number of pharmaceutical companies.
- Our lead compound is a dual inhibitor of two enzymes necessary for K-RAS targeting to cell membranes exhibits promising efficacy in killing several pancreatic and lung cancer cell lines, as well as breast and prostate cancer cell lines.
- Serious adverse events associated with high doses of another dual inhibitor of farnesyltransferase and geranylgeranyltransferase-1 developed by Merck were thought to explain its lack of efficacy in Phase II clinical trials.
- Kadmon Corporation has a K-RAS inhibitor (KD032) in Phase II trials that competes with all forms of activated K-RAS for docking sites within the cell membrane, creating the same desired end result as a dual farnesyltransferase and geranylgeranyltransferase-1 inhibitor.

TECHNOLOGY

Our lead compound is an ethylenediamine-based compound that inhibits farnesyltransferase (FT) with an IC_{50} value of 250±190nM and geranylgeranyltransferase-1 (GGT-1) with an IC_{50} value of 520±90nM *in vitro*. The compound inhibits the growth of many human cancer cell lines tested: ten pancreatic, two breast, two lung, and one prostate with IC_{50} values ranging from 2.6μM to 26μM. Two cell lines were tested to determine if the lead compound was capable of inhibiting activation of mutant oncogenic K-Ras by FT and GGT-1 (mouse NIH-3T3 fibroblasts and human MDA-MB-231breast cancer cells), and the compound was able to reduce activated K-Ras in the mouse fibroblasts by 100% at 10μM and by >50% in the human breast cancer cells at 30μM.

PUBLICATION/PATENT

- PCT application filed on 9/9/2011 for Drs. Said Sebti and Andrew Hamilton
- Fletcher, S. et al. *J. Med. Chem.* (2010) 53(19):6867-88.

CONTACT

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

LICENSING OPPORTUNITY

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