Small Molecules that Inhibit Mutant KRAS

KRAS is one of the most commonly mutated oncogenes in all human cancers. The frequently occurring G12D mutation had proved undruggable, until this discovery of a modified imidazothiazole compound which prevents GDP displacement by GTP, thus inhibiting KRAS's ability to bind to (and activate) downstream effectors. A compound library was screened in two assays and #87 (with an imidazothiazole scaffold) showed the most promise in preventing GDP displacement (by GTP) and inhibiting KRAS-Raf binding with an IC50 of 61μM.

COMMERCIAL OPPORTUNITY

- Oncogenic mutations in KRAS lead to it being permanently bound by GTP (as opposed to GDP) rendering KRAS constitutively active. The mutated KRAS oncogene is found in approximately 90% of pancreatic cancers (pancreatic adenocarcinoma), 40% of colorectal cancer, 30% of lung cancers, and generally in about 20-30% of all human cancers, with the G12D mutation being the most frequent at approximately 43%, representing nearly 50,000 US patients annually. These cancers are particularly difficult to treat—with a tendency to poor outcomes, due to an association between *KRAS* mutations and lack of response to EGFR tyrosine kinase inhibitors and chemotherapy.
- Scientists and physicians have long deemed KRAS "undruggable." This has created numerous attempts to treat KRAS mutated cancers by inhibiting KRAS's immediate downstream targets, including AstraZeneca's Selumetinib (a MEK inhibitor), Merck's MK-2206 (AKT inhibitor), Bayer's Sorafenib (a pan-RAF inhibitor). Attempts to block Ras signalling by altering its cellular location via inhibitors of post-translational lipid modifications, such as palmitylation, garenylgarenylation and farnesylation, have also failed in clinical trials.
- None of these agents against downstream targets address the driving mutation of the tumor, and most patients develop resistance by upregulating compensatory pathways. However, by focusing directly on inhibiting KRAS activation, this small molecule can prevent KRAS signaling through all of its downstream pathways, thereby offering targeted therapy to a patient population where there is a great unmet need.

TECHNOLOGY

The Mant-GDP assay was used to identify targets that could inhibit GTP from replacing fluorescently labeled GDP that was bound to mutant G12D KRAS. The GST-RBD ELISA was used to identify compounds that could prevent the binding of activated KRAS to its downstream effector Raf-1. The Torrey Pines Institute for Molecular Studies (TPIMS) library (over 6 million compounds comprised in 62 mixtures based on similarity of chemical scaffold) was screened in these two assays. The most promising mixture was the 2239 sample which contained 1008 compounds all having the imidazothiazole scaffold. 20-50 individual compounds were selected, synthesized, and evaluated. Of these, only number 87 was able to inhibit the displacement of GDP with an IC50 of 61μM.

PUBLICATION/PATENT

- Provisional patent applications filed on March 18, 2015 and April 24, 2015 for Dr. Sebti.

CONTACT

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

LICENSING OPPORTUNITY

MOFFITT CANCER CENTER