

# Stapled Peptides as Inhibitors of Mutant KRAS



***Oncogenic KRAS, predominately the G12D mutation, is believed to be the driver mutation in 20 – 30% of all human cancers, and scientists and physicians have long deemed this molecule “undruggable.” This has led researchers to target KRAS’s downstream effectors, an example of which is the protein Raf. Stapled peptides that inhibit RAS from activating Raf by blocking Raf’s RAS Binding Domain (RBD) have been created. In vitro assays have revealed FY-A-100-1 to inhibit the binding of Raf to the G12D mutant KRAS by 95%.***

## 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 cancers, 30% of lung cancers, and generally in about 20 – 30% of all human cancers, with the G12D mutation being the most frequent. These cancers are particularly difficult to treat – with a tendency to poor outcome, 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 administering inhibitors of KRAS’s immediate downstream targets, with drugs such as AstraZeneca’s Selumetinib (a MEK inhibitor), Merck’s MK-2206 (AKT inhibitor) and Bayer’s Sorafenib (a pan-RAF inhibitor). Sorafenib has been particularly effective, and is FDA approved, for the treatment of liver, kidney, and thyroid cancer, and clinical trials look promising in colorectal cancer.
- As Raf has proved a viable target, Dr. Sebti’s work is focused on targeting Raf’s RAS Binding Domain (RBD) with the use of stapled peptides, thus inhibiting KRAS’s ability to bind and activate Raf. FY-A-100-1 has proved to be the most potent at inhibiting this interaction. As shown by *in vitro* pull down assays, where this compound blocked Raf-KRAS binding by approximately 95%.

## TECHNOLOGY

In collaboration with Dr. Cai (University of South Florida), Dr. Sebti has made several stapled peptides such as FY-A-100-1 and FY-A-100-2 designed against the helical domain (78-92, LHDCLMKALKV RGLQ) Raf’s RAS Binding Domain (RBD). The synthesis was conducted in solid phase. In pulldown assays, FY-A-100-1 showed a 95% inhibition of GST-tagged RBD binding to the G12D KRAS mutant from lysates of NIH-3T3 cells that ectopically expressed mutant G12D KRAS. The FY-A-100-2 was a much less potent inhibitor, which demonstrates the importance of lysine 85. Furthermore, FY-A-90-1A, which is identical to FY-A-100-1 except for having a “CH<sub>2</sub>” shorter side chain of residue 82, which forms the staple in FY-A-100-1, was not active. FY-A-90-1B (non-stapled peptide of 1A) and FY-A-90-2A and 2B (stapled and non-stapled derivatives of FY-A-90-1A and 1B with an alanine at position 85) also had little activity compared to DMSO control.

## PUBLICATION/PATENT

- Provisional patent application filed on April 20, 2015 for Dr. Sebti.

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### LICENSING OPPORTUNITY

