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Treating Cancer Using Synthetic Peptide Inhibitors Derived from BRAF Protein

Lead Inventors

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Unmet Need

Lung cancer is the leading type of cancer across the world with over 1.55 million cases annually . In the United States, the annual incidence of lung cancer is approximately 191,646. It is the leading cause of cancer death for both men and women. The standard 5-year survival rate is 56 percent when the disease is localized and only 18 percent if metastasized. The rates for lung cancer survival are lower than other common cancers like prostate, breast, and colorectal. Chemotherapy, the standard treatment of this disease, often wreaks havoc on the entire body and has a low efficacy rate when used in lung cancer.

A need exists for cancer treatments that are safer, more effective, and cause fewer overall adverse effects to the patient. Therapeutic peptides are a promising and a novel approach to treat cancer. They have several advantages over proteins or antibodies: as they are (i) easy to synthesize, (ii) have a high target specificity and selectivity, and (iii) have low toxicity. There are few peptide treatments for non-small cell lung cancer, which comprise 85 to 90 percent of all lung cancers.

Opportunity

Braftide is a synthetic peptide inhibitor that works via a novel dual mechanism of action to inhibit BRAF, a protein that is responsible for cell proliferation, differentiation, and migration.

This protein is an integral part of the MAP kinase / ERK signaling pathway. Mutations in BRAF have been identified in melanoma, colorectal cancer, non-Hodgkins lymphoma, thyroid carcinoma, hairy cell leukemia, and non-small cell lung cancer.

The most common mutation in the BRAF gene is the V600E mutation, which is found to be promoting a multitude of cancers including non-small cell lung cancer.

Dr. Wang and the University of the Sciences investigators believe a reduction in BRAF kinase activity could be used as an adjunct therapy in treating certain types of cancer.

There are currently no peptide treatments for non-small cell lung cancer and only 12 recruiting or not yet recruiting clinical trials. The small number of studies taking place indicates a good opportunity for Braftide.

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Unique Attributes

- Braftide has demonstrated good permeability of the cellular membrane when conjugated with HIV-TAT. The HIV-TAT conjugation method of delivery has shown great promise and is currently being tested in phase three clinical trials for a protein therapeutic to treat stroke.

- Braftide binds to its target, BRAF, and functions by disrupting the MAPK signaling pathway thereby reducing total level of MEK protein by degradation of homo and heterodimers by proteolytic action. It causes allosteric inhibition of BRAF kinase activity and endogenous proteolytic degradation by disruption of the MAPK signaling cascade which generates monomeric BRAF. This unique action allows for further degradation of monomers of BRAF which are more susceptible to Braftide's action than the dimerized form.

- Braftide effectively inhibits BRAF kinase activity in *in vitro* settings. Normal BRAF and mutant BRAF (lung cancer mutant) are differentially inhibited at 364 nM.and 172 nM, providing an opportunity for selectivity that can be optimized.

Clinical Applications

Inventors envision Braftide being used as a combination therapy with current FDA-approved ATP-competitive inhibitors like Dabrafenib and Vemurafenib. These drugs can paradoxically activate the MAPK pathway at lower concentration, which remains a primary drawback. Braftide can help in mitigating this activation and in improving the potency of Dabrafenib/ Vemurafenib.

Stage of Development

In preclinical studies, with further *in vitro* research and an *in vivo* study required to validate efficacy.

Intellectual Property

US Provisional Patent filed May 2019.

Collaboration Opportunity

The University of the Sciences is seeking a collaborator or other sources of funding to support the next phases of research.

References and Publications

- Zhihong Wang* and Christine Candelora. *In Vitro* Enzyme Kinetics Analysis of Full-Length EGFR Purified from HEK293 Cells. Methods in Molecular Biology. 1487, 23-33. (2016) (* Corresponding author.)
- Zhihong Wang and Philip A. Cole. Catalytic Mechanisms and Regulation of Protein Kinases. Methods in Enzymology. 548, 1-21. (2014). (PMCID: PMC4373616)

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