NATIONAL CANCER INSTITUTE
Technology Transfer Center

Small Molecule Ephrin (Eph) Tyrosine Kinase Inhibitors for the Treatment of Colorectal Cancer and Other Eph Growth-dependent Solid Tumors

Summary

The National Cancer Institute (NCI) seeks research co-development partners and/or licensees for the development and commercialization of small molecule inhibitors of the Eph receptor tyrosine kinase for Eph growth-dependent solid tumors such as colorectal cancer.

NIH Reference Number

E-182-2019

Product Type

- Therapeutics

Keywords

- NVP-BHG712, Regioisomer NVP-Iso, Ephrin, Eph Kinase Inhibitors, Colorectal Cancer, Eph-related cancers, Solid Tumors, Small Molecule, Tyrosine kinase inhibitors, Tosato

Collaboration Opportunity

This invention is available for licensing and co-development.

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Description of Technology

Advanced colorectal carcinoma is currently incurable, and new therapies are urgently needed. Ephrin (Eph) receptors are a clinically relevant class of receptor tyrosine kinases. Related signaling pathways are associated with oncogenesis of a number of cancers. NCI investigators found that phosphotyrosine-dependent Eph receptor signaling sustains colorectal carcinoma cell survival, thereby uncovering a survival pathway active in colorectal carcinoma cells. Furthermore, colorectal cancers express the EphrinB2 ligand and its Eph receptors at significantly higher levels than numerous other cancer types. Colorectal cancer patients with the highest levels of EphrinB2 expression in their tumor have a lower probability of survival than those with the lowest levels.

The NCI investigators found that a small-molecule inhibitor of the Eph kinase, NVP-BHG712 and its regioisomer NVP-Iso, reduce human colorectal cancer cell growth *in vitro* and tumor growth in mice. Proof-of-concept data demonstrate inhibition of the Eph tyrosine kinase inhibits the growth of human colorectal carcinomas. Eph signaling sustains colorectal carcinoma cell survival and growth and that inhibition of the phosphotyrosine-dependent Eph signaling is effective at blocking this prosurvival function. Several derivatives of these prototype compounds have been synthesized and tested for inhibition of the Eph tyrosine kinase activity. Two of these new derivatives have promising biochemical and functional profiles. These small molecule inhibitors have the potential to be developed as a therapeutic for colorectal cancers, other types of Eph-growth dependent tumors, and diseases where the Eph kinase plays a pathogenic role.

Potential Commercial Applications

- Therapeutics for colorectal cancer
- Therapeutics for other Eph growth-dependent cancers, including breast, lung, prostate, and brain

Competitive Advantages

- Differs in targeting selectivity from many other tyrosine kinase inhibitors
- Distinct mechanism of action from Regorafenib, the only existing receptor tyrosine inhibitor approved to treat metastatic colorectal cancer; Regorafenib is a multi-targeted tyrosine kinase inhibitor developed to inhibit VEGF-dependent tumor angiogenesis
- Promising combination therapy when used with other tyrosine kinase inhibitors and antibodies – such as Cetuximab (approved for metastatic colorectal cancer)
- Overcome resistance to EGFR or BRAF treatment in various tumor types; attributed to EphA2 kinase activity

Inventor(s)

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Development Stage

- Pre-clinical (in vivo)

Publications

Diprima M, et al. Identification of Eph receptor signaling as a regulator of autophagy and a therapeutic target in colorectal carcinoma. [(PMID 31545551)]

Patent Status

- **PCT:** PCT Application Number PCT/US2020/050439 , Filed 11 Sep 2020

Therapeutic Area

- Cancer/Neoplasm

Updated

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