Inhibitors of Extracellular Signal-Regulated Kinase (ERK) regulated signaling pathways

Summary

This technology is a set of novel ATP-independent, extracellular signal-regulated kinase (ERK) inhibitors that have the potenital to provide specific targeting compared to existing ERK1/2 inhibitors. The lead ATP-independent ERK inhibitor candidates, interact with specific ERK substrate docking sites inhibiting substrate interactions and phosphate transfer. This precise targeting of key substrates in turn is predicted to reduce off target side effects and overcome the development of drug-resistance.

Key Investigator
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Field
oncology

Technology
Small molecule inhibitor
ERK

Advantages
Novel targeting
Reduced side effects
Reduced drug resistance

Status
Available for licensing and for sponsored research

Patent Status
US Patent 9,115,122 issued 8/25/2015

UMB Docket Reference
PS-2013-025
PS-2013-054

External Reference
1. BioChem J. 2015 May 1;467(3):425-38.
2. Org Biomol Chem 2013 Jun 1414;11(22): 3706-32.
3. Nat Commun. 2011 Jul 19;2:402.

Market

There is considerable interest in the development of inhibitors for the MAPK/ERK pathway members, which are estimated to be mutated in 30% of all cancers. Currently no FDA approved ERK inhibitors are available on the market though several are under clinical investigation (LY3214996; Eli Lilly, LTT462; Novartis, BVD-523; BioMed Discoveries). Available drugs that target the MAPK/ERK pathway are directed towards the upstream BRAF protein. The FDA has approved the BRAF inhibitors Vemurafenib (Zelboraf, Daiichi Sankyo, Genentech) and Dabrafenib (Tafinlar, GSK), with early results showing reduction in lesions of the bone, liver, and lungs. However, the majority of tumor regressions relapsed within 2-20 months after treatment with BRAF inhibitors. The majority of relapses resulted from acquired resistance associated with reactivation of the ERK signaling. These studies come in light of data that indicate a strong correlation with phospho-ERK expression in combination with Ras mutations in some late stage cancers (e.g. colorectal, pancreatic) and poor patient prognosis.

Technology

The novel ATP-independent ERK inhibitors were developed using computational and experimental methods to target ERK-substrate docking domains to selectively interfering with ERK1/2 regulation of substrate proteins. Currently available inhibitors of ERK1/2 are non-specific due to ATP competition, limiting their potential use as a therapeutic agents. The lead ATP-independent ERK inhibitors have been used to target ERK2 and has identify key structural groups that impart activity toward melanoma cancer cells containing mutant B-Raf and activated ERK1/2 signaling. Mutations in upstream regulators of the ERK1/2 proteins result in the constitutive activation of ERK1/2 that is characteristic to many drug resistant cancers. These compounds have the potential to prevent or overcome drug resistance associated with clinically relevant kinase inhibitors and may be used as a tool to elucidate the complex biological roles of ERK1/2 to develop novel anti-cancer therapeutics. These compounds have also been shown to enhance the antitumour activity of CHK2 inhibition in both a human diffuse large B-cell lymphoma (DLBCL) xenograft model as well as primary human DLBCL cells, suggesting inhibition of both ERK and CHK2 as a combinatorial therapy for human lympomas.

Technology Status

The results are supported by experimental evidence that includes interference of ERK substrate phosphorylation and inhibition of downstream ERK signaling functions.

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