Discovery of a potent and selective inhibitor of DAPK1 and ZIPK

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Value Proposition

The **DAPK** family, including Zipper-interacting protein kinase (**ZIPK**), mediates cell death through the transmission of apoptotic and autophagic signals. This family of kinases also regulates both non-muscle and smooth muscle myosin phosphorylation. Another set of kinases called PIM kinases (**PIMKs**) prevent apoptosis and promote the proliferation of cancerous cells. **Compounds that selectively inhibit these kinases may therefore be useful in treating a variety of cancers, cardiovascular disorders, and ischemia-reperfusion injuries**. This novel therapeutic compound would enter a U.S. kinase inhibitor market that reached over $10B in 2016 with an addressable market of over 100 million individuals.

Technology

The current technology encompasses a pharmaceutical compound and related derivatives that selectively inhibit DAPKs and PIMKs to treat various disorders, including cancer. The inventors used a chemoproteomic drug discovery platform to identify a highly selective compound (**HS38**) that targets ZIPK in an ATP-competitive manner. The invention claims a multitude of pharmaceutical compound embodiments of and methods of treatment using HS38. This compound is shown to have remarkable selectivity towards the DAPK and PIMK families when evaluated against a diverse panel of purified protein kinases. *Ex vivo*, the inventors show that HS38 decreases the contractile force generated in both mouse aorta and rabbit ileum by putatively inhibiting the mechanisms by which ZIPK acts to increase calcium. HS38 is also shown to suppress intrinsic myogenic tone and enhanced tone associated with hypertension development in rodent cerebral arteries. In isolated human cerebral arterioles, HS38 suppresses myogenic tone development.

Advantages

- *Ex vivo* data highlighting feasibility of HS38 as a kinase inhibitor.
- HS38 can potentially treat various forms of cancer, cardiovascular disorders, and ischemia-reperfusion injuries.
- Technology would enter a strong U.S. kinase inhibitor market with an extensive addressable market.

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Publications

- Carlson D., et al (2013). Fluorescence lined enzyme chemoproteomic strategy for discovery of a potent and selective DAPK1 and ZIPK inhibitor. ACS Chem Biol. 8(12):2715-23.

Patents

Patent Number: 10,934,291

Title: KINASE INHIBITORS AND RELATED METHODS OF USE

Country: United States of America