

Novel mutation-resistant smoothened inhibitors for cancer therapy

Value Proposition

The hedgehog signaling pathway is an important mediator of developmental and cellular differentiation processes in both embryonic and adult tissues, but can also promote tumor growth and progression if dysregulated. Two forms of cancer, basal cell carcinoma (BCC; the most common form of skin cancer) and medulloblastoma (MB; a common pediatric brain tumor), are known to be driven by hedgehog signaling. Drugs targeting the hedgehog pathway component smoothened (SMO) have proven to be effective anti-cancer therapeutics in BCC and MB. However, like most cancer therapies, tumors eventually develop resistance, compromising efficacy. This technology provides for a SMO inhibitor which maintains antagonist activity against both normal and mutant forms of SMO, which may be useful as a novel therapeutic agent for anti-cancer therapy in BCC or MB patients who have developed resistance to existing therapies.

Technology

This invention is a novel small molecule inhibitor of SMO, which has been developed to be mutation-resistant. Using an *in vitro* cell culture system, this compound was shown to inhibit both normal and the D473H-mutant form of SMO which has been observed in human medulloblastoma treated with an existing FDA-approved SMO antagonist. Importantly, in a side-by-side comparison, this compound was as effective as two separate marketed SMO antagonists at suppressing hedgehog signaling, and retained full inhibitory activity against D473H-mutant SMO, whereas both marketed therapies were ineffective. Additionally, *in vivo* efficacy has been demonstrated in a mouse model of hedgehog-dependent hair regrowth.

Other applications

Although the role of hedgehog signaling in the progression of cancers other than BCC or MB is less clear, several clinical trials are ongoing using SMO inhibitors in numerous cancers including pancreatic, gastrointestinal, and lung. This invention may be applicable as a therapy to these types of cancers in addition to BCC and MB.

Advantages

Existing therapies targeting SMO in cancer are rendered

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ineffective by specific mutations in SMO. Compared to marketed therapies, this invention shows similar inhibition of normal SMO but dramatically improved activity against a clinically-relevant SMO mutation. This may be useful as a therapy to treat patients with BCC or MB who have developed resistance to current therapies.

Publications

- [Identification of a novel Smoothened antagonist that potently suppresses Hedgehog signaling \(Bioorganic & Medicinal Chemistry, 2012\)](#)

Patents

Patent Number: 9,512,106

Title: SMOOTHENED MODULATORS AND METHODS OF USE THEREOF

Country: United States of America

Patent Number: 2895474

Title: Novel Smoothened Modulators as a base for treatment

Country: United Kingdom