

Small-Molecule Inhibitors of Gli Function

Researchers in Dr. James Chen's lab at Stanford have discovered novel Hedgehog (Hh) pathway inhibitors that may serve as anti-cancer therapeutics. The Hh pathway plays a critical role in patterning, homeostasis, and oncogenic transformation of multiple tissues. The pathway controls the functions of the Gli transcription factors. Gli activity has been shown to promote the onset and/or progression of several cancers including basal cell carcinoma, medulloblastoma, pancreatic adenocarcinoma and prostate cancer. Inhibitors of the Hh pathway have been developed and show efficacy as anti-cancer agents. However, the emergence of tumors resistant to these drugs has presented a major challenge. In addition, the existing inhibitors are not appropriate for treatment of pediatric cancer as they will likely cause bone growth arrest and may interfere with cerebellar development. To help overcome these challenges, the inventors have developed a new class of Hh pathway inhibitors that selectively inhibit Gli1, a downstream pathway component. As such the inhibitors overcome the problem of drug resistance and may be used for treatment of pediatric cancer patients.

Stage of Research

The inventors have identified a lead compound. Compound testing in a murine medulloblastoma allograft model and in vitro cultures of basal cell carcinoma and small-cell lung cancer cells have been conducted, and the results are promising.

Applications

- Anti-cancer therapeutic
- Research tool for studying Hh pathway signaling mechanisms

Advantages

- New structural class of Hh pathway inhibitors
- Selective for Gli1
- **New mechanism for Hh pathway inhibition:**
 - May overcome drug-resistance issues
 - Potential for pediatric use
 - Potential to avoid side effects associated with inhibitors of upstream pathway components

Publications

- Ardecky R, Magnuson GK, Zou J, Ganji SR, Brown B, Ngo T, Lee J, Zeng FY, Sun Q, Stonich D, Salaniwal S, Sakata T, Rack PG, Casabar JKT, Mangravita-Novo A, Smith LH, Sergienko E, Chung TDY, Pinkerton AB, Pass I, Chen JK. [Small-molecule antagonists of Gli function](#). Probe Reports from the NIH Molecular Libraries Program [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2012 Dec 17 [updated 2014 May 13].

Patents

- Published Application: [WO2013192301](#)
- Published Application: [20150191489](#)
- Issued: [9,611,276 \(USA\)](#)

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