Multitarget hedgehog pathway inhibitors and uses thereof.

KEYWORDS

- ❑ CANCER
- ❑ CANCER STEM CELL (CSC)
- ❑ SMO INHIBITORS
- ❑ GLI INHIBITORS
- ❑ HEDGEHOG
- ❑ MEDULLO-BLASTOMA
- ❑ BASAL CELL CARCINOMA
- ❑ GLIOMA
- ❑ PANCREATIC CANCER

AREA

- ❑ PHARMACEUTICAL

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Co-Ownership
Sapienza University of Rome 90%, University of Siena 10%.

Inventors
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Industrial & Commercial Reference
Target therapy for the inhibition of Hedgehog-dependent tumors.

Time to Market
Preclinical phase is on the point of being completed.

Availability
Cession, Licensing, Research, Development and Experimentation.

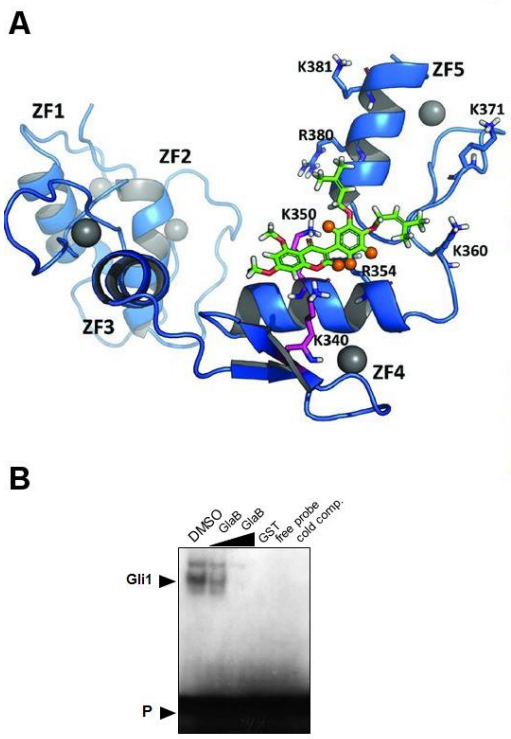

Fig. 1 Analysis of Gli1/GlaB interaction.
A) The predicted binding mode of GlaB (green sticks) to Gli1ZF (blue cartoons). Residues highlighted by the single-point mutation study to impact on Gli1 binding to DNA are shown as blue sticks; K340 and K350 of the GlaB binding site are colored magenta. GlaB protons highlighted by the NMR study are shown as orange spheres.
B) Inhibition of Gli1/DNA binding by GlaB. EMSA using recombinant GST-Gli1ZF-WT in the presence of different concentrations of GlaB or with DMSO only. The shifted complex is competed with a 50× excess of cold probe.

Abstract

Aberrant activation of Hedgehog signaling is the result of genetic mutations of pathway components or other Smo-dependent or independent mechanisms, all triggering the downstream effector Gli1.
We set up the docking-based virtual screening of a natural products library available *in house* (about 1000 compounds, both isolated from higher plants) with the aim to identify small molecules binding to Gli1 zinc finger domain and impairing Gli1 activity by interfering with its interaction with DNA.
Among selected compounds, one product, named Glabrescione B (GlaB) showed a robust inhibitory effect on Gli1 activity and tumor growth both *in vitro* and *in vivo*.

Publications

- ❖ AA.VV. Gli1/DNA interaction is a druggable target for Hedgehog-dependent tumors. EMBO Journal, 2015, 34(2), 200-217.
- ❖ AA.VV. Inhibition of Hedgehog-dependent tumors and cancer stem cells by a newly identified naturally occurring chemotype. Cell Death & Disease, 2016, 7, e2376.
- ❖ AA.VV. Polymeric glabrescione B nanocapsules for passive targeting of Hedgehog-dependent tumor therapy in vitro. Nanomedicine, 2017, 12(7), 711-728.

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Technical Description

Candidate inhibitors of the Hh signaling pathway have been first selected *in silico* among an *in house* library of natural products. Thanks to the available crystallographic structure of Gli1/DNA complex, Gli1 inhibitors have been identified by a structure-based approach relying on the shape and electrostatic complementarity between ligands and the binding site on Gli1. In contrast, based on the knowledge of a number of SMO antagonists in clinical trials, natural products targeting SMO receptor have been identified in a *ligand-based* pharmacophoric approach. By these models, a number of natural compounds has been selected for *in vitro* and *in vivo* analyses. Experimental studies highlighted Glabrescione B (GlaB) as potent Hedgehog inhibitor with antitumor efficacy *in vitro* and *in vivo* in models of medulloblastoma and basal cell carcinoma.

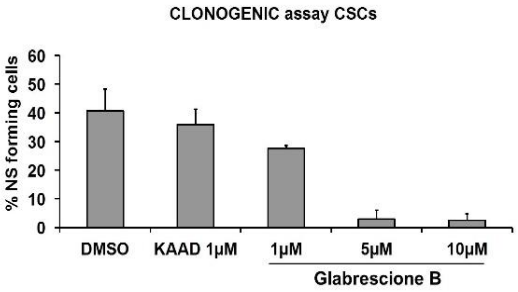

Fig. 2 Effect of GlaB on the self-renewal of CSCs.

Technologies & Advantages

Glabrescione B (GlaB) is a naturally occurring isoflavone that inhibits in a specific manner the Hedgehog signaling pathway through competing with DNA for the binding to the Gli1 protein. Different from FDA-approved Hedgehog inhibitors (Vismodegib and Sonidegib) or currently in clinical trials that act on the upstream effector SMO receptor, GlaB acts at a downstream level by directly blocking the last and most powerful effector of the Hedgehog signaling, namely Gli1.

This mechanism of action has been verified by EMSA, NMR spectroscopy and a number of cell-based assays. The competitive advantage of GlaB compared to SMO antagonists is twofold: i) GlaB is not affected by the drug-resistant mutations identified on the SMO receptor in patients treated with SMO antagonists; ii) GlaB is effective also in those tumors where aberrant activation of the Hedgehog signaling, and the hyperactivation of Gli1, does occur downstream – and independent by – the SMO receptor.
To date, this mechanism of action involving the direct inhibition of Gli1 is showed only by GlaB, which also proved to be safe *in vivo* up to high doses, as well as to be specific for Gli proteins.

Applications

Glabrescione B (GlaB) can be used as therapeutic agent in tumors whose growth and proliferation are dependent from the Hedgehog signaling pathway.
In this field, particular emphasis is given to brain tumors such as medulloblastoma, in which the role of the Hedgehog signaling has been largely investigated and for which no effective therapeutic agents are available to date.
Since aberrant activation of the Hedgehog signaling pathway has been found in other tumor types, including glioma, basal cell carcinoma, multiple myeloid leukemia, pancreatic, lung, stomach, prostate cancer, ovarian carcinoma, colon, liver, and breast cancer, GlaB can be used as specific anticancer agents also in these Hedgehog-dependent malignancies.
Moreover, GlaB could be used alone, or in combination with other anticancer agents.

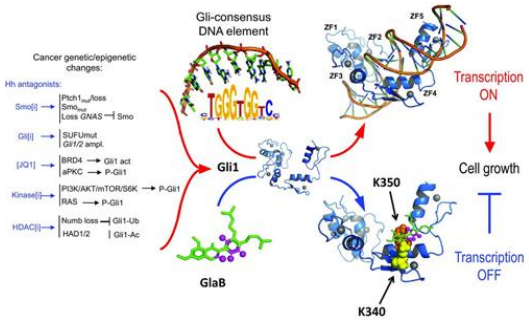

Fig. 3 Schematic model of GlaB mechanisms of action.

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