Thermally triggered theranostics for pancreatic cancer


Document Version:
Publisher’s PDF, also known as Version of record

Queen's University Belfast - Research Portal:
Link to publication record in Queen's University Belfast Research Portal

Publisher rights
Copyright 2016 The Author.

General rights
Copyright for the publications made accessible via the Queen's University Belfast Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The Research Portal is Queen's institutional repository that provides access to Queen's research output. Every effort has been made to ensure that content in the Research Portal does not infringe any person's rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact openaccess@qub.ac.uk.

Open Access
This research has been made openly available by Queen's academics and its Open Research team. We would love to hear how access to this research benefits you. – Share your feedback with us: http://go.qub.ac.uk/oa-feedback

Download date:28. Feb. 2024
Gli1/DNA interaction is a druggable target for Hedgehog-dependent tumors

P. Infante1, M. Moriz, R. Alfonsi2, C. Ingalina2, B. Botta2, L. Di Marcellino2
1Istituto Italiano di Tecnologia, CNLS@Sapienza, Rome, Italy, 2Sapienza University, Molecular Medicine, Rome, Italy

Background: Hedgehog (Hh) pathway is essential for tissue development and stemness, and when deregulated leads to tumorigenesis. Although many Hedgehog-driven human cancers involve upstream pathway activation (i.e., either loss-of-function of the receptor Ptc1 or gain-of-function mutations of the transmembrane transducer Smo), Smo-independent hyperactivation of the downstream Gli transcription factor is responsible for the development of several tumors and resistance to therapy. This raises the need to identify novel Gli1 inhibitors, a challenging issue mostly due to the lack of information on the structural requirements of Gli1/DNA interaction.

Material and Methods: Molecular characterization of Gli1/DNA binding was performed by a mix of computational and experimental structure-based in vitro studies. Molecular dynamics simulations were carried out to identify the residues involved in DNA binding. The data obtained were then used to set up the docking-based virtual screening of a natural product library available in house, with the aim to discover pharmacological agents able to interfere with Gli1/DNA interaction. The molecules identified as potential Gli inhibitors were investigated for their functional activity through a Gli-dependent luciferase reporter screening assay. The assay was most active for its effectiveness to counteract Hh-dependent tumor growth by medulloblastoma and basal cell carcinoma allograft model from Ptch1+/− mice and orhtotopic medulloblastoma xenografts.

Results: We identified a small molecule, Glabrescione B (GlaB), an isoflavone naturally found in the seeds of Derris glabrescens (Leguminosae), able to impair Gli1/DNA binding as revealed by Chip and EMSA assays. In agreement with these molecular results, GlaB revealed great antitumor efficacy. Indeed, we observed that GlaB strongly inhibited the growth of Hedgehog-dependent tumor cells in vitro and in vivo as well as the self-renewal ability and clonogenicity of tumor-derived stem cells.

Conclusions: Our study highlighted the relevance of structural details of Gli1/DNA interaction as a promising tool to discover small molecules able to inhibit Hh pathway by directly targeting Gli1. Here we identified GlaB as a potent and specific Gli1 inhibitor able to interfere with Gli1/DNA binding, resulting in the inhibition of Hh-dependent tumor cells and cancer stem cells growth, thus becoming a profitable pre-clinical candidate.

No conflict of interest.