**"Inhibition of Hedgehog-dependent tumors by isoflavonoids: Synthesisand preclinical studies"**

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**Abstract**

Hedgehog signaling is essential for tissue development and stemness and its deregulation has been observed in many tumors. 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. For this reason, understanding the poorly elucidated mechanism of Gli1-mediated transcription allows to identify novel molecules blocking the pathway at a downstream level, representing a critical goal in tumor biology. Here, we clarify the structural requirements of the pathway effector Gli1 for binding to DNA and identify Glabrescione B as the first small molecule binding to Gli1 zinc-finger and impairing Gli1 activity by interfering with its interaction with DNA. Remarkably, as a consequence of its robust inhibitory effect on Gli1 activity, Glabrescione B 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. The identification of the structural requirements of Gli1/DNA interaction highlights their relevance for pharmacologic interference of Gli signaling.