Discovery of the Smoothened Inhibitors LEQ506 and LDE225 for the Treatment of Hedgehog-Dependent Tumors

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Research in recent years showed that the Hedgehog (Hh) signaling pathway can have a crucial role in tumorigenesis when reactivated in adult tissues. Genetic activation of the Hh pathway is implicated in cancers such as basal call carcinoma, (a common skin cancer) and medulloblastoma (a rare brain tumor).
Cell-based phenotypic screens performed in our laboratories identified multiple classes of Smoothened antagonists inhibiting Hh signaling. Structure-activity relationship studies led to the discovery of potent and selective inhibitors from two chemotypes which were optimized towards clinical candidates. During this work we applied a new method developed in house for predicting phototoxicity to mitigate a phototoxicity risk associated with one of our chemotypes. The selected inhibitors LEQ506 and LDE225 displayed good pharmacokinetic properties in preclinical species and showed efficacy in genetic mouse models of medulloblastoma. One of them, LDE225, is currently in registration for the treatment of advanced basal cell carcinoma.