In recent years, the focus of cancer research has shifted from agents that act on rapidly dividing cells to molecules that target specific proteins and pathways that are dysregulated in tumors. Molecules with such specificity are potentially less toxic to normal cells, while maintaining or improving efficacy. One subset of these oncology targets includes genes ordinarily active during embryonic development while abnormally reactivated in adults through sporadic mutation that can lead to tumor growth. In the case of the Hedgehog (Hh) pathway, receptor smoothened (SMO) is inhibited by the Hh receptor Patched (PTCH). This inhibition is normally released when Hh binds to PTCH, but inappropriate activation of this pathway occurs in presence of mutations. Once activated, SMO initiates activation of transcription factors and expression of Hh target genes essential for cellular growth, differentiation, and survival. The discovery of the mechanism of action of cyclopamine, a steroidal alkaloid that blocks Hh signaling with an EC$_{50}$ of approximately 300 nM, indicated that small molecules could block the Hh pathway. However, cyclopamine has limitations as a viable therapeutic agent; for instance its structural complexity, scarcity, poor aqueous solubility, and poor chemical stability in acid. Two high-throughput cell-based assays in Hh responsive cell lines, hit-to-lead optimization of the screening hits, robust in vitro assay and two in vivo models, the Calu6 PK/PD and medulloblastoma allograft model, were critical to the successful discovery of vismodegib. Vismodegib (GDC-0449, (2-chloro-N-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide) is a small-molecule selective Hh pathway inhibitor (HPI) that targets SMO with an IC$_{50}$ of 13 nM in Gli luciferase assay. Furthermore, it produced complete tumor regression at doses as low as 12.5 mg/kg BID in a medulloblastoma allograft mouse model. Vismodegib was discovered by Genentech, Inc., under a collaboration agreement with Curis, Inc., and was the first HPI approved in the US for the treatment of adults with metastatic or locally advanced basal cell carcinoma. Since the initiation of Vismodegib clinical trials, other HPI have entered early stage clinical testing and several more discovered over the last decade are in pre-clinical development.

References