Summary of VBL Research Project

Theme	Drug screening for controlling hedgehog signaling using Gorlin syndrome-derived iPS cells
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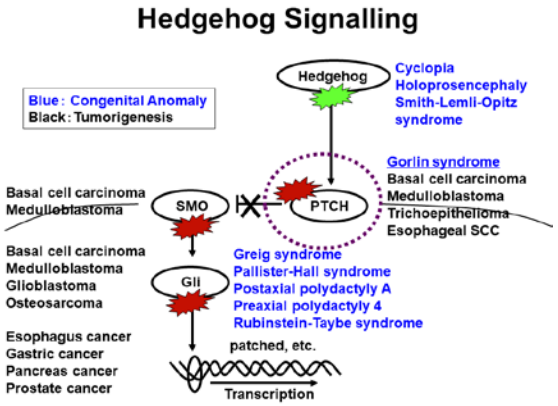
Gorlin syndrome, also called nevoid basal cell carcinoma syndrome, is an autosomal dominant neurocutaneous disease characterized by developmental anomalies such as palmar pits and rib anomaly, and tumorigenesis such as medulloblastoma, and basal cell carcinoma. This syndrome is mainly caused by a mutation of *PTCH1*, a human homologue of Drosophila *patched*, including frameshift, missense, or nonsense mutations. Genotype-phenotype correlation has not been established.



PTCH1 is a member of hedgehog signaling, which is a highly conserved pathway in vertebrates, composed of hedgehog, SMO, and GLI proteins as well as PTCH1. Given that hedgehog signaling regulates cell growth and development, disorder of this pathway gives rise to not only developmental anomalies but also diverse tumors such as those seen in Gorlin syndrome. We recently reported, for the first time, a nationwide survey of Gorlin syndrome in Japan, noting that the frequency was 1/235 800 in the Japanese population, and that the frequency of basal cell carcinomas was significantly lower in Japan than in the USA and Europe, suggesting that ethnicity and genetic background contribute to these differences.

SInce many clinical trials using newly discovered molecular inhibitors are still ongoing, these agents should be established as new therapeutic options for hedgehog pathway dependent tumors in patients with or without Gorlin syndrome. In this project, we will apply novel natural compounds library found by Prof. Ishibashi and Dr. Arai, to Gorlin syndrome-derived iPS cells to explore the effective hedgehog inhibitors.