

## **Abstract**

The presented doctoral thesis is focused on the role of the Hedgehog (HH) signaling pathway in cancer pathogenesis. HH signaling pathway is an evolutionarily conserved signaling pathway that plays an essential role in embryonic development. Its activity is strictly limited to stem and progenitor cells for example in brain, lung, skin or prostate. HH pathway also plays a key role in tissue homeostasis and regeneration. Aberrantly activated HH pathway is essential in cancer progression.

The aim of the presented thesis was to elucidate new details about the HH signaling pathway. We identified a new target gene of the HH pathway – the anti-apoptotic protein survivin. Survivin is considered to be an important tumor marker associated with a poor prognosis of patients. We showed that the inhibitor of HH pathway effectors GLI1 and GLI2 GANT61 reduced the survivin level in cancer cells. Subsequently, we used GANT61 and the inhibitor of the anti-apoptotic BCL2 protein family obatoclax to inhibit melanoma cells growth. We showed that the combination of these inhibitors was very effective in the eradication of melanoma cells in vitro. We also proved that GANT61 triggers the process of apoptosis in melanoma cells.

We found out that the HH signaling pathway is canonically activated in many cell lines of various tumor origins. Next, we tested the so-called “rheostat model” of MITF transcription factor in melanoma. According to the model, a high-MITF level is associated with high differentiation and low invasion and a low-MITF level is connected with a low differentiation and proliferation rate and high invasion. We established cell lines with inducibly regulated MITF levels. We observed that cell characteristics did not reflect the reduction of MITF level – neither proliferation rate nor invasion decreased. But the expression of differentiation markers decreased. It implies that the role of MITF needs to be more researched and defined better.

The presented results highlight the role of HH signaling in tumor progression and point out the importance of combined therapy.