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Anti-tumor and Immunostimulatory Properties of ST316, a Peptide Antagonist of β-Catenin for Treatment of Cancers with Aberrant Wnt Pathway Activity

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Abstract

ST316 represents a significant challenge as a therapeutic target due to its multifaceted role in tumor development as well as normal cellular homeostasis. Dysregulation of the Wnt/β-catenin signaling pathway is implicated in various cancers, including colorectal, hepatobiliary, breast, ovarian and pancreatic cancers. We developed ST316 as a potent antagonist of the interaction of β-catenin with BCMA, a receptor implicated in oncogenic Wnt signaling. ST316 is currently being evaluated in a Phase II clinical study (NCT03587674) in patients with selected advanced solid tumors.

Figure 4: (A) ST316 inhibits the Wnt/β-catenin pathway, as evidenced by the downregulation of Axin2 in ST316-dependent cell lines COLO320DM and HCT116. No impact on Axin2 expression was observed in ST316-independent cell lines HCT116, COLO320DM and MV4-11. Comparison of ST316 and vehicle control was performed on genes that were regulated in any of the three cell lines. (B) COLO320DM cells display a significant downregulation of Wnt target genes, oncogenic signature genes and inflammation-related genes in ST316 treatment. HCT116 and MV4-11 displayed a trend in terms of ST316-induced downregulation of their respective Wnt target genes, while COLO320DM cells were more resistant, indicating that the antitumor effects of ST316 are mediated by inhibition of the Wnt/β-catenin pathway. To further explore cancer-specific effects of ST316, qRT-PCR analysis was performed on two selected genes (TP53, ESR1). ST316 over eight-weeks suppressed expression of both target genes in colorectal and uterine in advanced solid tumors. ST316 is a potent, selective inhibitor of the Wnt/β-catenin signaling pathway, and it may be a potential therapeutic option in the treatment of advanced solid tumors.

Figure 5: In the +PD1/-ST316 group, tumor burden was significantly decreased compared to the -PD1/+ST316 group. These findings demonstrate the sustained anti-tumor immunostimulatory effects of ST316 and highlight its potential as a therapeutic agent in targeting cancers with clinically activated Wnt signaling.

Figure 2: Wnt/β-catenin pathway signaling impacts both oncogenic and the tumor immune microenvironment (TME) in cancer cells, this pathway is frequently activated as a result of oncogenic mutations leading to its stabilization. In the Wnt signaling pathway, canonical Wnt signaling is an oncoprogenic program in tumors with an activated Wnt/β-catenin pathway. In TME, Wnt signaling can act as an immunosuppressive program in Tumor Associated Macrophages (TAM) and Dendritic Cells (DC) leading to upregulation of M2 markers (IL10, IL4R, CD206). TAM, DC, and M2 macrophages are generally characterized by their pro-inflammatory activity and expression of immunosuppressive markers. In addition, Wnt can modulate surface expression of checkpoint molecules such as PD-1.

Figure 3: Wnt/β-catenin-dependent cell lines (DU4475, COLO320DM and MV4-11) exhibited a pronounced anti-proliferative activity in the presence of ST316. A significant decrease in the cell number was observed compared to control-treated cells. This anti-proliferative effect was confirmed by a significant reduction in cell viability (50% and 100% of control-treated cells) in DU4475 and MV4-11, respectively.

Table 1: Summary of cell proliferation experiments using different Wnt/β-catenin modulators. Tarembercept mice were administered a single dose of recombinant Tarembercept (3 mg/kg), a 1000-fold increase in recombinant Tarembercept (30 mg/kg), or vehicle on Day 13. Tumor volume was measured weekly until Day 24. Data are expressed as mean ± SEM (n = 6 mice per group). Comparison of control and treated groups were performed using ANOVA with Tukey’s post hoc test. **p < 0.01, ***p < 0.001, ****p < 0.0001.

Table 2: ST316 decreases CD4+ CD25+ Tregs in 3T3-L1 and in 3T3-L1 adipocytes. A single dose increase in CCL20+ T cells (20 ng/ml) was observed in 3T3-L1 adipocytes compared to control treated adipocytes. In the 3T3-L1 adipocytes, ST316 (1000-fold increase in ST316) was administered on Day 13. Data are expressed as mean ± SEM (n = 6 mice per group). Comparison of control and treated groups were performed using ANOVA with Tukey’s post hoc test. **p < 0.01, ***p < 0.001, ****p < 0.0001.

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Wnt/β-Catenin in Cancer and TME

Tumors

Promotion of Immune Escape and Resistance to Checkpoint Inhibitors

Conclusion

Sapience Therapeutics is developing the β-catenin antagonist peptide ST316 for Wnt pathway-dependent cancers such as colorectal cancer. ST316 effectively targets the transcriptional activity of oncogenic β-catenin resulting in reduction of Wnt target genes involved in angiogenesis, cell division, cell migration and immunosuppressive processes. Consequently, ST316 treatment results in reduced cell viability and tumor growth inhibition, marked by the reduced expression of Wnt target genes within tumor tissues.

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