The Wnt Inhibitor VS-507 Reduces Cancer Stem Cell Function in vitro and Tumorigenicity in Mice


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ABSTRACT

VS-507 was previously identified as a selective inhibitor of cancer stem cell (Gupta et al., Cell, 2009) using a high throughput screen that capitalized on the cancer stem cell (CSC) phenotype of cells pushed through EMT (epithelial-mesenchymal transition). We have now characterized the mechanism, CSC selectivity and anti-tumor activity of VS-507. In Wnt3A-stimulated MDA-MB-231 breast cancer cells, VS-507 was found to preferentially inhibit β-catenin signaling in a dose-dependent manner as indicated by a TOP-Flash reporter assay. Inhibition of β-catenin signaling in VS-507-treated cells correlated with decreased protein expression of LRPS and LRP6, the common co-receptors of the Wnt signaling pathway. Since human mammary cells driven through EMT by stable overexpression of the transcription factor Twist have been shown to demonstrate the hallmarks of CSCs, we used HMLE-Twist cells to assess selectivity of VS-507 for CSC inhibition. In proliferation assays, VS-507 showed 10-fold greater potency against CSC-like mesenchymal HMLE-Twist cells as compared to non-CSC-like epithelial control HMLE cells. In addition, VS-507 induced dose-dependent inhibition of secondary tumour sphere formation by SUM159 cells, further indicating inhibition of the CSC phenotype. Furthermore, VS-507 eliminated Aldefluor-positive CSC sub-populations in SUM159 and HS578T triple negative breast cancer cell lines, while the cytotoxic chemotherapeutic agents paclitaxel and cisplatin induced an increase in Aldefluor-positive cells. Finally, efficacy of VS-507 was characterized upon systemic administration of the compound to mice. Inhibition of both primary tumor growth and experimental metastasis were observed. These observations suggest that VS-507 is a potent anti-tumor agent that attenuates Wnt/β-catenin signaling, cancer stem cell self-renewal, tumor growth and metastasis. These results support clinical development of VS-507 for the treatment of triple negative breast cancer.

INTRODUCTION

Fig 1: Critical to target cancer stem cells for a durable clinical response

Fig 2: Structure and target of VS-507. VS-507 reduces expression of the Wnt co-receptors LRPS & LRP6 and blocks β-catenin-mediated transcription

RESULTS

Fig 3: VS-507 blocks Wnt-stimulated β-catenin signaling

Fig 4: VS-507 selectively targets cancer stem cells

Fig 5: Opposing effects of VS-507 and Paclitaxel on secondary tumour sphere formation

Fig 6: Opposing effects of VS-507 and chemotherapy on Aldefluor-positive cancer stem cells

Fig 7: VS-507 Inhibits xenograft tumor growth and metastasis

SUMMARY

VS-507 inhibits Wnt/β-catenin signaling in breast cancer cells
• Reduction of LRPS & LRP6 expression
• Dose-dependent inhibition of β-catenin-mediated transcription

VS-507 selectively targets Cancer Stem Cells in triple negative breast cancer lines
• Greater potency in reducing viability of HMLE-Twist cells vs. HMLE control cells
• Blockade of secondary tumour sphere formation in contrast to paclitaxel
• Elimination of Aldefluor-positive CSCs in contrast to increased Aldefluor-positive cells following treatment with standard of care agents

VS-507 reduces tumor growth and experimental metastasis to the lungs