TRANSCRIPTOMIC ANALYSIS OF DESMOID TUMOR RESPONSE TO NIROGACESTAT: NOVEL MECHANISMS OF RESISTANCE?

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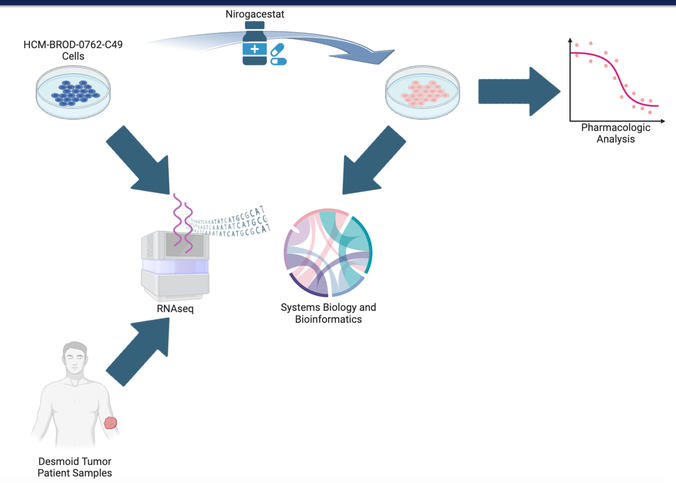
Background

- Desmoid tumors are rare benign fibromatous tumors that despite their benign nature can exhibit locally-aggressive biology, high recurrence rates, and poor outcomes
- Along with overexpression of **β-catenin**, desmoid tumors highly express **Notch1**, with cross-talk between these pathways putatively contributing to proliferation of desmoid tumors
- Traditionally, local therapies such as radiation and surgery were primarily used to treat desmoid tumors, but recently novel systemic agents are shifting this treatment paradigm
- Recently, the notch/γ-secretase inhibitor nirogacestat has been approved for the treatment of desmoid tumors, but the exact mechanism of action and cell biology underpinning response remain to be refined and represent the **knowledge gap** addressed in this study.

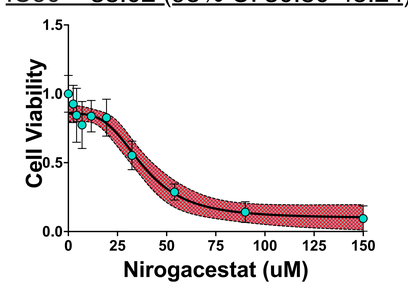
Experimental Design



Experimental design overview in which cells from the desmoid tumor cell line HCM-BROD-0762-C49 are treated with nirogacestat for pharmacologic and transcriptomic analysis. Furthermore, the cell transcriptomes were compared to a published cohort of desmoid tumor patient samples to validate their use as a desmoid tumor model system.

Nirogacestat Pharmacology in Desmoid Tumor Cells

IC50 = 38.02 (95% CI 30.80-45.24)



Dose response of nirogacestat in HCM-BROD-0762-C49 desmoid tumor cell line reveals a marked drop in viability at 72 hours upon treatment with the drug, with maximum effect at approximately 100 uM. Each datapoint (aquamarine dots) represents six biologic replicates. Dose response curve was interpolated (red cloud) using prism and an IC50 was calculated.

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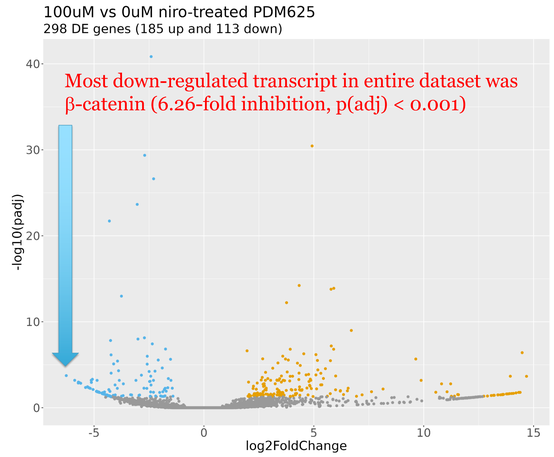
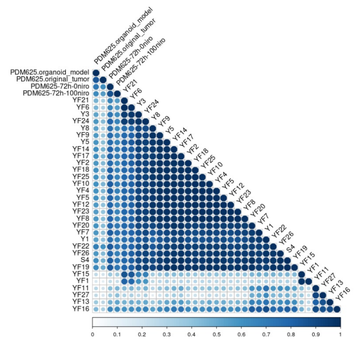
Transcriptomic Analysis

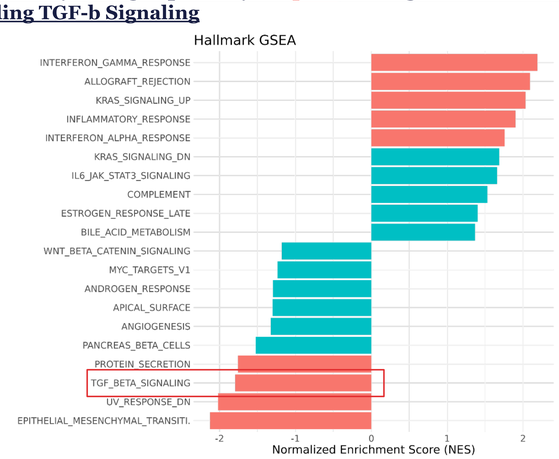
Transcriptomic Analysis of Nirogacestat-treated HCM-BROD-0762-C49 cells Yields ~300 Differentially Expressed Genes (upregulated genes in orange, downregulated genes in blue), including β-catenin Inhibition



Transcriptomic Correlation Analysis Demonstrates High Degrees of Similarity Between HCM-BROD-0762-C49 and Patient Tumor Samples, Underscoring the Clinical Translatability of the Model System



Bioinformatic Pathway Analysis Demonstrates Enrichment of Canonical Pathways Which Potentially Underpin Responses to Nirogacestat (Significantly-changed pathways in pink, nonsignificant trend in blue), Including TGF-b Signaling



Summary/Future Directions

- HCM-BROD-0762-C49 cells are a novel preclinical model system to study desmoid tumor biology and recapitulate clinical responses seen in patients
- HCM-BROD-0762-C49 cells demonstrated transcriptional similarities with actual desmoid tumor patient samples
- Nirogacestat demonstrated antitumor efficacy in desmoid tumors
- Nirogacestat was associated with down-regulation of b-catenin as well as novel transcriptomic signatures including TGF-b inhibition
- Future Directions
  - Validate HCM-BROD-0762-C49 cells to study other clinically-relevant scenarios including radiotherapy
  - Study the long-term effects and resistance mechanisms of nirogacestat in desmoid tumor cells
  - Expand preclinical mechanistic studies to include other clinically-relevant desmoid tumor treatments including sorafenib
  - Characterize synergy of nirogacestat with other systemic therapies

References/Acknowledgements

- Acknowledgements
  - Jefferson Sarcoma Research Group
- References
  - Gounder et al. Nirogacestat, a γ-Secretase Inhibitor for Desmoid Tumors. N Engl J Med. 2023.
  - Sakorafas et al. Abdominal desmoid tumors. Surg Oncol. 2007.
  - Escobar et al. Update on desmoid tumors. Ann Oncol. 2012.

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