University of Nebraska Medical Center
BREAKTHROUGHS FOR LIFE

University of Nebraska Medical Center
DigitalCommons@UNMC

Posters: 2022 Summer Undergraduate Research Program

Summer Undergraduate Research Program

Summer 8-10-2022

Effect of MUC16 Blockade using the Humanized AR9.6 Antibody in Patient Derived Organoid Models of PDAC

Jordan N. Muirhead
University of Nebraska Medical Center

Satish Sagar
University of Nebraska Medical Center

Christabelle Rajesh
University of Nebraska Medical Center

Adrian Black
University of Nebraska Medical Center

Prakash Radhakrishnan
University of Nebraska Medical Center

Follow this and additional works at: https://digitalcommons.unmc.edu/surp2022

Recommended Citation

Muirhead, Jordan N.; Sagar, Satish; Rajesh, Christabelle; Black, Adrian; and Radhakrishnan, Prakash, "Effect of MUC16 Blockade using the Humanized AR9.6 Antibody in Patient Derived Organoid Models of PDAC" (2022). *Posters: 2022 Summer Undergraduate Research Program*. 37.
https://digitalcommons.unmc.edu/surp2022/37

This Poster is brought to you for free and open access by the Summer Undergraduate Research Program at DigitalCommons@UNMC. It has been accepted for inclusion in Posters: 2022 Summer Undergraduate Research Program by an authorized administrator of DigitalCommons@UNMC. For more information, please contact digitalcommons@unmc.edu.

Effect of MUC16 Blockade Using the Humanized AR9.6 Antibody in Patient-Derived Organoid Models of PDAC

Jordan Muirhead, Satish Sagar, Christabelle Rajesh, Adrian Black, Prakash Radhakrishnan

Eppley Institute for Research in Cancer and Allied Diseases, Fred & Pamela Buffett Cancer Center, University of Nebraska Medical Center, Omaha, NE 68198

Background

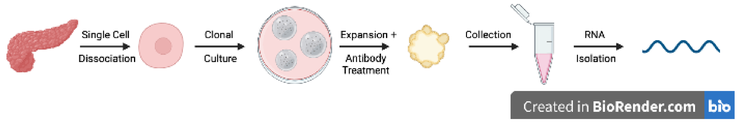
Pancreatic cancer is an aggressive malignancy, 90% of which is accounted for by Pancreatic ductal adenocarcinoma (PDAC). As of 2022, PDAC accounts for 3.2% of new cancer cases and 8.2% of all cancer related deaths, owing to its poor overall survival of a mere 11.5% [1]. Patients with PDAC often present at a late-stage of disease progression, thereby increasing the need for effective standard of care, which is met with issues of therapeutic resistance. Mutations in the *KRAS* oncogene is a salient feature of PDAC that acts partly by increasing the expression of pro-tumoral proteins such as Mucin-16 (MUC-16) [2]. MUC16, a heavily glycosylated transmembrane protein is overexpressed in more than 65% of PDAC cases and is absent in the normal pancreas, making it a suitable biomarker for PDAC [3]. Our research focusses on the development of the humanized, monoclonal antibody AR9.6 (HuAR9.6) [4] that targets MUC16 and its application in clinically relevant patient-derived PDAC organoids.

Objective

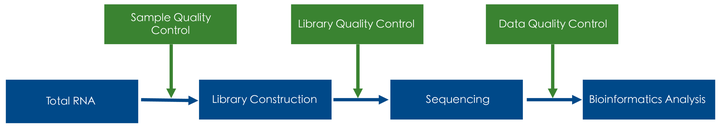
Evaluate the MUC16 mediated transcriptomic changes by using the humanized AR9.6 antibody in patient-derived organoid models of PDAC.

Methods

Development of Primary PDAC Organoids from RAP #142 [5]



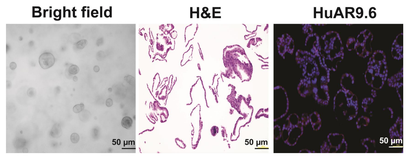
RNA Sequencing and Bioinformatic Analysis by Novogene



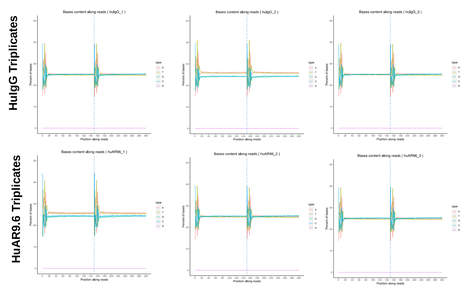
Adapted from Novogene Corporation Inc.

Results

Organoids generated from RAP #142 primary PDAC. Bright-field image , H&E staining, immunofluorescent staining with HuAR9.6

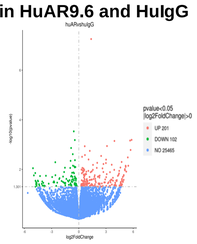


ATGC profiling validating quality of RNA yield



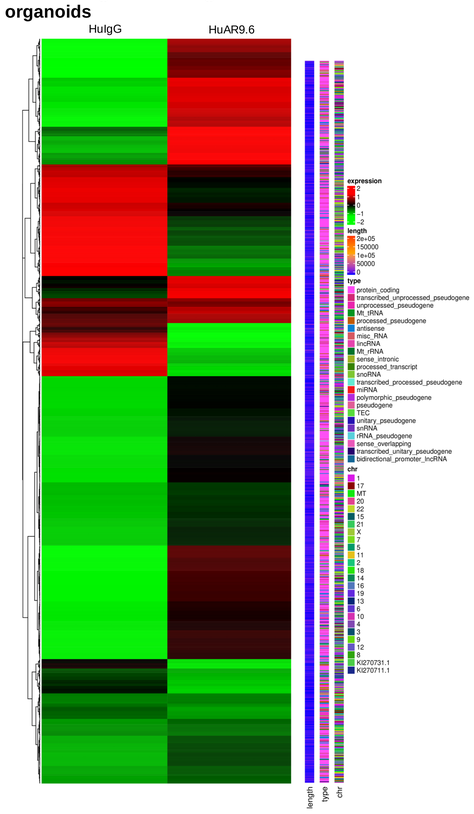
Differentially expressed genes in HuAR9.6 and HuIgG treated PDAC organoids

HuAR9.6 v HuIgG Gene Expression Venn Diagram

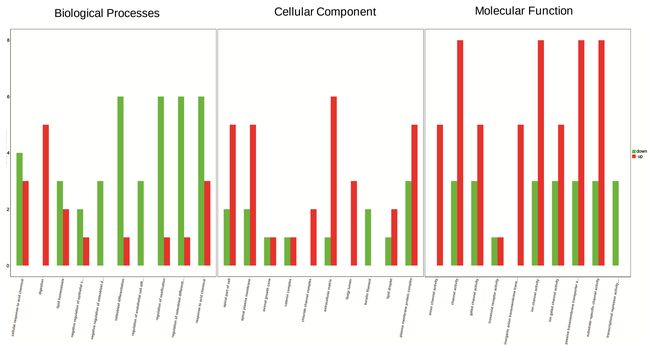


HuAR9.6 v. HuIgG Gene Expression Volcano Plot

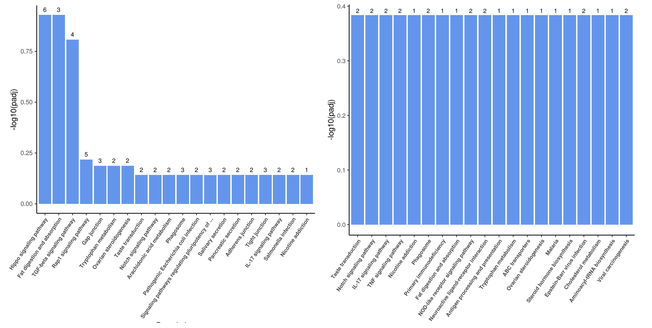
Heat map depicting clustering of differentially expressed genes in HuIgG vs HuAR9.6 treated PDAC organoids



Gene Ontology Analysis showing Biological Processes, Cellular Location and Molecular Function influenced by HuAR9.6 treatment in PDAC organoids



KEGG Enrichment Analysis stratifying the pathways influenced by HuAR9.6 treatment in PDAC organoids



Downregulated pathways

Upregulated pathways

Conclusions

- Tumor cells isolated from primary PDAC of RAP #142 successfully formed organoids *in vitro* that had a MUC16^{high} profile.
- RNA quality was determined to be proficient.
- About, 413 genes were uniquely expressed – of which 201 were upregulated and 102 were downregulated.
- Gene Ontology and KEGG Enrichment analyses revealed pathways like Hippo signaling were altered by blocking MUC16 in PDAC organoids.

References

1. Pancreatic Cancer — Cancer Stat Facts. https://seer.cancer.gov/statfacts/html/pancreas.html. Accessed 2 Aug. 2022
2. Liang, Chen et al. “Oncogenic KRAS Targets MUC16/CA125 in Pancreatic Ductal Adenocarcinoma.” Molecular cancer research : MCR vol. 15,2 (2017): 201-212. doi:10.1158/1541-7786.MCR-16-0296
3. Thomas, Divya et al. “Isoforms of MUC16 activate oncogenic signaling through EGF receptors to enhance the progression of pancreatic cancer.” *Molecular therapy : the journal of the American Society of Gene Therapy* vol. 29,4 (2021): 1557-1571. doi:10.1016/j.ymthe.2020.12.029
4. Sharma, Sai Kiran et al. “ImmunoPET of Ovarian and Pancreatic Cancer with AR9.6, a Novel MUC16-Targeted Therapeutic Antibody.” Clinical cancer research : an official journal of the American Association for Cancer Research vol. 28,5 (2022): 948-959. doi:10.1158/1078-0432.CCR-21-1798
5. Broutier, Laura et al. “Culture and establishment of self-renewing human and mouse adult liver and pancreas 3D organoids and their genetic manipulation.” *Nature protocols* vol. 11,9 (2016): 1724-43. doi:10.1038/nprot.2016.097