INTRODUCTION

- Pancreatic ductal adenocarcinoma (PDAC) is a deadly, invasive pancreatic cancer with 5-year survival for patients close to 7.1%.
- The difficulty of researching PDAC comes from a variety of factors that lead to its development, its genetic and epigenetic heterogeneity, the complicated tumor microenvironment, the human immune system’s role, and extensive fibrosis.
- Similarly, chromosomal alterations, ubiquitin proteases, and transcription factor alterations play a role in PDAC progression.

PDAC INVESTIGATION MODELS

There are currently five types of models being used to investigate PDAC.

HUMAN PDAC CELL LINE
Cancerous cells were grown in a petri dish.

CELL LINE-BASED XENOGRAFT
Transplanting cell lines into a severe combined immunodeficient mouse model.

PATIENT DERIVED TUMOR XENOGRAFT (PDX)
Transplanting a piece of a patient’s tumor rather than a cell line into a mouse model.

GENETICALLY ENGINEERED MOUSE MODELS (GEMMS)
Takes specific gene mutations in oncogenes or tumor suppressor genes involved in PDAC and expresses them in a mouse model.

ORGANOID
Cells from a tissue arrange themselves in resemblance to that in the human body in a 3D culture.

PDAC MODEL COMPARISON

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human PDAC Cell Line</td>
<td>Good for screening essential genes Identifying biomarkers Can’t show tumor progression Homogeneous</td>
</tr>
<tr>
<td>Cell Line-Based Xenograft</td>
<td>Tumor development is quick Environment allows for some genetic variety Less genetic diversity and phenotypically than in human PDAC</td>
</tr>
<tr>
<td>Patient Derived Tumor Xenograft (PDX)</td>
<td>Stroma is included in the transplant Most closely resembling human PDAC Low eligibility rates for tumor removal Lower transplantation success rate</td>
</tr>
<tr>
<td>Genetically Engineered Mouse Models (GEMMs)</td>
<td>Confirm causative roles for genes in PDAC Exhibit many symptoms seen in human PDAC Expensive and time consuming Still wide range of differences.</td>
</tr>
<tr>
<td>Organoid</td>
<td>Developed from a small amount of tissue Contains significant of genetic variety Newly developed Still under investigation</td>
</tr>
</tbody>
</table>

GEMM MODELS IN PDAC

We chose to use GEMMs when investigating PDAC due to the wide variety of specific pathways and genes including KRAS that are being examined with this model, and the causative roles that can be determined from the results.

PATHWAYS IDENTIFIED FROM GEMM MODELS

Preliminary research identified the following:
- KRAS gene associated with RAS/MAPK pathway plays a pivotal role in cancer, including PDAC. It is involved with tumor suppressor genes and starting oncogenic events.
- Trp53 is a gene used for encoding tumor protein p53. Mutation of TP53 is widely associated with PDAC following the mutation of KRAS.
- p38 Alpha MAPK or mitogen-activated protein kinase 1 is a pathway activated with protein kinases. This pathway is involved in an array of biological processes including apoptotic process, cellular response, regulation, and development.
- p38y promotes PDAC tumorigenesis. Figure 1 shows three common MAPK pathways in mammals.

FUTURE WORK

- Investigate KRAS and its interaction with other genes both in humans and mice to understand its relation to PDAC progression. Figure 2 highlights this interaction.
- Explore pathways with genes that include PIK3CA, RAF1, GRB2, and ERBB2. These areas of research show promise in finding the next step in building therapies.

ACKNOWLEDGEMENTS

The research has been made possible through funding from the Mayo Biomedical Innovator Program, student-faculty collaborative research by the Office of Research and Sponsored Programs at UW-Eau Claire, and National Institute of General Medical Sciences of the National Institutes of Health, under NDSU COBRE Award Number 1P20GM109024.