THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center®

IMPACT REPORT

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Stupid Strong Charitable Foundation

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HOW YOUR GIFT IS MAKING CANCER HISTORY®

I am incredibly grateful for the generous funding of Stupid Strong Charitable Foundation, which has helped my team perform cutting-edge research at The University of Texas MD Anderson Cancer Center. Our goal is to perform in-depth analyses of gastric adenocarcinoma and particularly, peritoneal carcinoma, to discover new targets for clinical trials and, thus, improve the lives of gastric adenocarcinoma patients everywhere.

Gastric adenocarcinoma is a major health burden globally, with more than one million new cases per year. It is the leading cause of cancer mortality in ten countries. In the United States, more than 26,000 new cases are expected in 2020. The scientific community's efforts into studying gastric adenocarcinoma at a detailed molecular level have lagged behind many cancers (e.g., colorectal, breast, lung and prostate cancers). A recent report suggests that profiling results can be different in patients with primary cancer vs. metastatic cancer. This detail is important because of our emphasis on studying peritoneal carcinoma, which has been incredibly aggressive in patients.

We have not initiated early detection efforts for gastric adenocarcinoma in most parts of the world, so patients are diagnosed in late stages and have an overall survival rate of less than 12 months. Clearly, we have much work to do to improve outcomes for these patients.

There are two major phenotypes, or observable characteristics, of gastric adenocarcinoma: diffuse (dGAC) and intestinal (iGAC). dGACs are poorly differentiated tumors with poor survival outcomes and no specific therapy available, whereas iGACs are more differentiated and more likely to overexpress HER2, thus improving overall survival because we have therapies to treat it. Nevertheless, once the cancer is metastatic, it is an incurable condition in most patients. Our research is particularly focused on dGACs that are often associated with Peritoneal carcinoma, which is a difficult clinical condition requiring specific treatment. Patients with peritoneal carcinoma often have rapid declines in their clinical conditions, and we have few or no options for such patients. We must confront this challenge.

One particular type of cell — signet ring cell — seems to have a unique significance in gastric adenocarcinoma, particularly dGAC. The presence of signet ring cells portends a poor prognosis. The frequency of dGAC with signet ring cells in patients has been rising since 1973, particularly in the black population. This understanding imposes a unique challenge, as well as a huge opportunity.

We currently know very little about signet ring cells and their molecular makeup. Several investigators have reported on gastric adenocarcinoma and signet ring cells, but overall the effort is quite limited and does not provide the kind of insight we need to develop a novel treatment strategy. This is where our studies, so generously supported by Stupid Strong, are filling a major unmet need.

The following are some of our accomplishments:

Identification of potential peritoneal carcinoma therapeutic targets
We are lucky to be collaborating with Wa Xian, Ph.D., and Frank McKeon, Ph.D., both at the University of Houston, who have developed a specialized cancer stem cell culture system to isolate various species of cancer stem cells (published in *Cell* and *Nature Protocol*). **We are excited to have identified three genes as potential therapeutic targets for peritoneal cancer, since this is a disease with virtually no current treatment options.** We believe that further experimentation involving these genes will demonstrate therapeutic benefit for this vulnerable patient population.

Single-cell sequencing
As mentioned, there exists very little scientific investigation of gastric adenocarcinoma at a molecular level. Thanks to your support, we have sequenced 20 unique cases (the manuscript is in second revision for *Nature Medicine*). **In yet another example of the resilience of cancer, we have discovered that cancer cells switch their lineage and that there is considerable heterogeneity in gastric adenocarcinoma that can resist treatment.**

We have also discovered that a 12-gene signature can determine the aggressiveness of gastric adenocarcinoma, and we have validated this signature in publicly available data on nearly 1,400 patients.

Discovered GRK3 as new target for peritoneal carcinoma
The gene, GRK3, was over-expressed in primary GACs compared with adjacent normal tissues. Testing in 393 paired normal samples and primary tumors revealed that higher GRK3 expression was significantly associated with more advanced disease state, metastases and shorter survival. Importantly, GRK3 inhibitor, LD2, demonstrated strong anti-tumor activity in vivo in patient-derived xenografts (PDXs, cancer cell lines grown in animals for the sake of testing) with high GRK3 and YAP1 expression. **Your generous support has helped us understand what to look for in this disease, and how to treat it!**

Established new mouse models and cell lines
In order to replicate expected therapeutic response in humans, thanks in part to your generous funding, we established three new peritoneal carcinoma cell lines and molecularly characterized them in vitro. **This gave us the ability to further test this disease so that we can anticipate how humans will respond to certain therapies.**

The expression of oncogenes (genes associated with cancer) and cancer stem cell markers varied among the cell lines. All three peritoneal carcinoma cell lines successfully formed PDXs. **Finally, these cell lines were suitable for preclinical testing of chemotherapy and target agents in vitro and in vivo. This is a major accomplishment!**

We are incredibly grateful for the support of Stupid Strong and look forward to updating you on our progress in the future. This type of philanthropic funding is giving hope to patients suffering from malignancies with few therapeutic options.
Thank you.