Title: Drug Delivery in Pancreatic Cancer

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Background

- The 5-year survival rate for pancreatic adenocarcinoma has not changed.
- Many bright ideas in the laboratory look promising but end up failing in the phase II and III setting.
- There have been a multitude of negative phase II and III trials comparing gemcitabine to combination treatment.
    - Gemcitabine + erlotinib is the only new approved treatment regimen that has been approved for pancreatic cancer in the past 12 years.

Why all the Clinical Failures?

- Dr. Tuveson explained when you look at tissue from patients and compare it to tissue taken from the patient and immediately implanted it under the skin of an immunodeficient animal, the samples look vastly different.
- Cancer cells in the patient are surrounded by a lot of stroma; the stroma is rapidly replaced after engraftment in an animal.
- Animal xenografts are vastly different from primary tumor systems of patients. The reason for this is that patient tumor is polyclonal meaning there are multiple genetic programs present that you cannot grow in a lab or replicate in a lab setting.

Pancreatic Intraepithelial Neoplasia - **Where does Pancreas Cancer Come From?**

- Normal pancreas ductal epithelial cells and pancreas ductal adenocarcinoma are potentially related to each other and thought to share many gene products and have hallmark genetic mutations that occur in the preneoplastic progression called Pancreatic Intraepithelial Neoplasia (PanIN). To learn about this process in an invivo setting, Dr. Tuveson and colleagues set out to replicate this in a mouse model studying PanIN and pancreatic ductal adenocarcinoma in mice.
- Found when you express $Kras^{G12D}$ oncogene in the mouse pancreas, it induces PanIN1a and progresses to PanIN1b, 2 and 3 and the mice die of invasive pancreatic ductal adenocarcinoma.
- If they include tumor suppressor gene mutations $Kras^{G12D}$ + $Trp53^{R172H}$ the animals have the syndrome of pancreas cancer with cachexia, ascites, and >70% gross metastases.
- The animal experiences the same wasting syndrome as humans with pancreatic cancer experience. Pathologist report the disease in mice now has the histological and molecular heterogeneity seen in humans.
- Researchers are used to seeing heterogeneity in humans but not in a mouse model; now this can be replicated in an animal model.

Why do Pancreatic Cancer Drugs Fail?

- Dr. Tuveson shared some of the research conducted by Dr. Ken Olive, Assistant Professor at Columbia University and a post-doc in his laboratory.

<u>Sensitivity of Pancreatic Ductal Adenocarcinoma to Gemcitabine</u>

- Conducted the same experiment that was used to license gemcitabine years ago.
- Compared all transplantation models (xenografts and syngeneic models).

  - Cancer implanted under the skin or in the pancreas and compared the effects of treating the cancer with sodium chloride or gemcitabine. In the mice treated with sodium chloride, all the tumors grew.
  - Animals given gemcitabine had stable tumor growth.
- When Dr. Olive compared this result to Dr. Tuvenson's model (autochthonous/primary), he showed that both sodium chloride and gemcitabine had the same lack of effect.
- The question is why is gemcitabine not working any better than saltwater?
  - What are the possible mechanisms to explain this? Is this a difference in response to the drug or a difference in exposures to the drug?
  - Research showed it did not seem to be a pharmacodynamic issue so Dr. Olive looked at the pharmacokinetic parameters.

<u>Transplant Models versus Primary Cancer – Differences in Perfusion</u>

- Used contrast ultrasound bubbles which approximate the size of red blood cells and showed that the transplant model had a lot of vasculature perfusion compared to the primary cancer.
- The tumor under skin showed perfusion but the transplanted tumor in the pancreas showed a great lack of perfusion.
- Tumors transplanted under the skin had very little stroma. Stroma-rich primary mouse and human pancreatic ductal adenocarcinoma is hypovascular.
- They looked at the mean vessel density of pancreas cancer in the mouse versus human and found the mouse pancreatic cancer had one-fourth the vasculature density of normal pancreas tissue. Same result in human specimens.
- Sought validation that pancreatic adenocarcinoma is unusually hypovascular. They collaborated with Drs. Alex Chang, Mousumi Dhara and Christine Iacobuzio-Donahue and showed that in comparing normal pancreas, chronic pancreatitis and pancreatic adenocarcinoma, that pancreatic adenocarcinoma had only 10% of the vasculature in the core of that seen on the periphery. In comparing pancreatic adenocarcinoma to colon cancer, colon cancer has a 10-fold increase in vascular density than adenocarcinoma.

Proposed Mechanism of Drug Resistance in Pancreatic Ductal Adenocarcinoma (Dr. Olive's work):

- The mechanism may involve poor drug penetration as a primary problem.
- Employing methods to alter tumor perfusion are needed. Inhibiting the hedgehog pathway is one way to accomplish this.
- The hedgehog pathway in cancer is purported to be an important pathway in pancreatic cancer. Poor vasculature plays role in poor drug delivery and correlates with stromal abundance.

Mouse Pancreatic Ductal Adenocarcinoma Cytotoxic Trial Summary

- The mouse model resembles the human model of pancreatic ductal adenocarcinoma.
- It is not a drug responsive issue as most models propose. Cytotoxics (gemcitabine, adriamycin) are poorly delivered to primary pancreatic ductal adenocarcinoma in mice. Poor vasculature contributes to poor delivery and correlates with stromal abundance.
- Methods that modify the stroma, is a way to enhance drug delivery and should be evaluated clinically. Drug scheduling, researching additional modalities to target stroma and improve delivery, and improved methods to measure drugs in tumors are being studied.