Overview

1. What is pancreatic cancer?
2. How do we study pancreatic cancer?
3. Recent concepts in pancreatic cancer research
4. Q & A Forum
Part 1: What is pancreatic cancer?

- cells have to “work together” for the sake of the whole
- your DNA encodes a series of rules for cells
- cancer occurs when one cell stops following the rules, and grows when it should not
- this is usually caused by mutations in the parts of your DNA that encode the rules
Where do mutations come from?

A segment of DNA that encodes the information to carry out a function is called a “gene”

There are many genes in a row on one piece of DNA

One full piece of DNA is a chromosome 23 pairs of chromosomes make up the human genome
Where do mutations come from?

3.2 Billion letters in a genome

\[
\times
\]

10 Trillion cells in an adult’s body

= 

\(~3 \times 10^{21}\) letters of DNA in you body!

(and lots of opportunities for mistakes)

Where do mutations come from?

<table>
<thead>
<tr>
<th>Things you can’t control</th>
<th>Things you can control</th>
</tr>
</thead>
<tbody>
<tr>
<td>• copying errors</td>
<td>• cigarette smoke</td>
</tr>
<tr>
<td>• oxygen</td>
<td>• sunlight &amp; other radiation</td>
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<tr>
<td>• byproducts of metabolism</td>
<td>• chemical carcinogens</td>
</tr>
<tr>
<td></td>
<td>• viruses (rarely)</td>
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<td>• chronic inflammation</td>
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</table>
What do the mutations do?

Oncogenes

Tumor suppressors

What is pancreatic cancer?

“Where the hell is the pancreas, anyway? I don’t even know what the damn thing does beside give you cancer.”

-Hawk Hawkins (Tommy Lee Jones), Space Cowboys
What is the pancreas?

What is the pancreatic cancer?

95% exocrine

5% endocrine
Types of pancreatic cancer

Pancreatic Carcinoma

Exocrine Pancreatic Tumors

Solid

- Acinar adenocarcinoma
- Medullary Carcinoma
- Colloid Carcinoma
- Pancreatoblastoma
- Solid Pseudopapillary Neoplasm
  - Classical
  - Adenosquamous
  - Mixed ductal endocrine
  - Signet ring carcinoma
  - Pleomorphic large cell carcinoma
- Undifferentiated carcinoma
  - with osteoclast-like features
  - with anaplastic features
  - with sarcomatoid features

Cystic

- Serous cystadenocarcinoma
- Mucinous cystadenocarcinoma

Pancreatic Neuroendocrine Tumors (PNETs)

Functional (usually benign)

- Insulinoma
- Gastrinoma
- Glucagonoma
- Somatostatinoma
- VIPoma

Non-functional (90% malignant)

- Ductal Adenocarcinoma
  - Classical
  - Adenosquamous
  - Mixed ductal endocrine
  - Signet ring carcinoma
  - Pleomorphic large cell carcinoma
  - Undifferentiated carcinoma
  - with osteoclast-like features
  - with anaplastic features
  - with sarcomatoid features

Precursor lesions of exocrine pancreatic cancer

Exocrine precursors

Pancreatic Intraepithelial Neoplasia (PanINs)

- PanIN 1a
- PanIN 1b
- PanIN 2
- PanIN 3 (carcinoma in situ)

Mucinous Cystic Neoplasms (MCNs)

- MCN with low-grade dysplasia
- MCN with moderate dysplasia
- MCN with high-grade dysplasia
- MCN with invasive carcinoma

Intraductal Papillary Mucinous Neoplasms (IPMNs)

- IPMN with low-grade dysplasia
- IPMN with moderate dysplasia
- IPMN with high-grade dysplasia
- IPMN with invasive carcinoma
How PDA Develops

- PanINs can progress to ductal adenocarcinoma
- More advanced PanINs accumulate more mutations

The genetics of pancreatic cancer

Ductal pancreatic tumors have an average 63 mutations per tumor
(Jones et al., 2008 Science)

But just four genes are mutated in MOST pancreatic tumors...

K-ras: “turned on” in 95-100% of pancreatic tumors; tells cells to grow

cdkn2a: “turned off” in 95-100% of pancreatic tumors; stops cell growth

p53: “turned off” in 75-95% of pancreatic tumors; stops cell growth

dpc4: “turned off” in ~55% of pancreatic tumors; stops cell growth/spreading
Part 2: How do we study pancreatic cancer?

How we usually think about the “progress” of science:

1. **Basic science**
   - How does it work?

2. **Translational science**
   - Applying basic science to find new therapies

3. **Preclinical screening**
   - Should this drug be tested in humans

4. **Clinical research**
   - Does it work?
How it actually works

Basic science
How does it work?

Translational science
Applying basic science to find new therapies, and study how they affect tumors

Clinical research
Does it work?

Preclinical screening
Should this drug be tested in humans?

Model Systems for Studying Cancer Models

<table>
<thead>
<tr>
<th>Model</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria</td>
<td>Extremely fast growth (30 minutes)</td>
<td>Haploid, unicellular</td>
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<tr>
<td></td>
<td>Powerful genetic tools</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Powerful biochemical techniques</td>
<td></td>
</tr>
<tr>
<td>Yeast</td>
<td>Very fast growth (100 minutes)</td>
<td>Unicellular</td>
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<tr>
<td></td>
<td>Eukaryotic cells</td>
<td>Significant evolutionary divergence</td>
</tr>
<tr>
<td></td>
<td>Powerful genetic and biochemical techniques</td>
<td>Not useful for efficacy screens</td>
</tr>
<tr>
<td>Mammalian Cell Culture</td>
<td>Fast growth (18 - 24 hours)</td>
<td>2D growth is different than 3D growth</td>
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<td></td>
<td>Accurate genetics (especially in human cells)</td>
<td>Only one or a few cell types (no stroma)</td>
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<tr>
<td></td>
<td>Powerful genetic and biochemical techniques</td>
<td>No immune system</td>
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<tr>
<td></td>
<td></td>
<td>Often inaccurate in predicting response to therapy</td>
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<tr>
<td>Drosophila (Fruit flies)</td>
<td>Multicellular</td>
<td>Significant evolutionary divergence</td>
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<tr>
<td></td>
<td>Reasonably fast growth (7 days)</td>
<td>Differences in organ composition/structure</td>
</tr>
<tr>
<td></td>
<td>Powerful genetic tools</td>
<td>Not useful for efficacy screens</td>
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<tr>
<td>Zebrafish</td>
<td>Vertebrate</td>
<td>Few antibodies available</td>
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<tr>
<td></td>
<td>Optically clear for longitudinal studies</td>
<td>Difficult to interpret histopathology</td>
</tr>
<tr>
<td></td>
<td>Powerful genetic techniques</td>
<td>Very slow generation time (3-4 months)</td>
</tr>
<tr>
<td>Mice</td>
<td>Mammal</td>
<td>Slow generation time (9 weeks)</td>
</tr>
<tr>
<td></td>
<td>Fairly accurate genetics</td>
<td>Mice are not small, furry people</td>
</tr>
<tr>
<td></td>
<td>Powerful genetic tools</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Accurate histopathology of diseases</td>
<td></td>
</tr>
<tr>
<td>Humans</td>
<td>Most accurate</td>
<td>Least manipulable</td>
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<tr>
<td></td>
<td></td>
<td>Extremely slow generation time (16 – 40 years)</td>
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<tr>
<td></td>
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<td>Genetically outbred</td>
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**Systems for studying cancer**

- **Humans**
- **Tumor Cells**
- **Xenografts**

- **Patient Derived Xenografts**
- **Genetically Engineered Mouse Models**

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This video has been kindly provided by Johannes Wilbertz, from the Karolinska Institute, in Stockholm (Sweden) and belongs to a large collection of educational videos available from the International Society for Transgenic Technologies (ISTT) web site.

https://www.youtube.com/watch?v=1m9kQuIXzEA
Mice can be engineered to get pancreatic cancer

1. **Study human tumors** to learn what mutations occur most frequently

2. **Engineer the same mutations** into mice, restricting them to just pancreas cells

3. **Evaluate the model** to confirm that it looks like human pancreatic cancer

4. **Confirm** that the mouse pancreatic tumors **respond to drugs** in a manner similar to human patients
Uses of Mouse Models of Cancer

• Studies of cancer gene function
  (Mouse +/- Gene X)
• A source of genetically defined cells of many types
  (Isolate cell lines from different tissues)
• Understand the biology of specific diseases
  (Engineer mice with a type of cancer, and study how it works)
• Understand the role of environment in disease and its interaction with genetics
• Understand the interactions of drugs with cancer
  (Pharmacology and molecular biology of tumors treated with drugs)
• As final efficacy screens before clinical trials (pre-clinical trials)
• Better interpret the results of clinical trials (co-clinical and post-clinical trials)

The Mouse Hospital is a preclinical therapeutics infrastructure

Surgery  Drugs  Imaging

People  Model  Pathology

Database
Ultrasound is a non-invasive imaging technique

cm scale

High resolution ultrasound can be used to image mice
3D ultrasound allows quantitative measurement of tumor volume over time.
Part 3: Recent concepts in pancreatic cancer research

- Genome sequencing and tumor development
- Imaging
- Stroma
- Immunotherapy
- Cachexia
- NIH Ras initiative
- Cancer Metabolism
- Biomarkers (BCAAs)
- Personalized medicine

DNA sequencing to learn about pancreatic tumor development

- A genome sequence is the complete list of letters that make up a person's DNA.
  - By comparing the genome of a patient's tumor to the rest of their body, it is possible to identify a complete list of mutations in the tumor.

- In 2008, the first whole-genome sequences from pancreatic tumors were reported by a team of scientists at Johns Hopkins (Jones et. al, 2008)
  - K-ras, p53, CDKN2A, and DPC4 are important genes in PDA
  - There are NO OTHER frequently altered genes in PDA
  - Yet most tumors have several dozen other mutations, each of which is rare

- In 2012, a more comprehensive survey of genetic alterations was completed by Andrew Biankin and colleagues (Australian Pancreatic Cancer Genome Initiative), largely reaffirming the previous findings.
Sequencing to learn about pancreatic tumor development

- In 2011, Christine Iacobuzio-Donohue published a paper where multiple metastases were sequenced from a single patient (Yachida et. al, 2011)
  - the very first cell that forms a tumor probably originates 17 years prior to death!!!
  - metastases to other organs occur only very late in the disease process
  - there is an exceptional amount of heterogeneity between metastases and within different parts of the tumor

Development of new imaging markers to diagnose PDA

Kimberly Kelly, U. Virginia

- used a specially engineered virus to identify a new imaging probe that could light up early pancreatic tumors in mice
- learned that the probe binds to a protein called plectin-1 that is altered in PanIN3
- currently adapting this technology for use in humans
Tumor “Stroma” plays a significant role in pancreatic cancer

- Tumors recruit normal cells from the rest of the body
- These cells, and the materials they secrete, are called STROMA
- Ductal pancreatic tumors have more stroma than any other cancer
- For a long time, it was thought the stroma was the body’s way of fighting the tumor
- Then the field believed that all stroma was supporting tumor growth
- The current understanding reflects a blend between these two extremes

New drugs in clinical trials, targeting the stroma:

- PEGPH20 (Halozyme)
- TH302 (Threshold pharmaceuticals)
The role of the immune system in pancreatic cancer

- The immune system recognizes proteins that are not “normally” found in the body
- Because of all the mutations in tumor cells, they make many mutant proteins that are not normally found in the body
- Why doesn’t the immune system attack pancreatic tumors?

Some of the cell types in the tumor STROMA are specialized cells that locally repress the immune system!

Doug Fearon, U. Cambridge  
- developing new drug combinations to reverse the immunosuppressive environment of the stroma

Bob Vonderheide, UPenn  
- using an antibody to stimulate the immune system to overcome this “immune-suppressive” environment

Cachexia

Wasting syndrome that is often found in pancreatic cancer patients

- Doug Fearon (Cold Spring Harbor Labs) – found that there are stromal cells that play a role in cachexia. (2013)
- Olive Lab- mouse model that develops cancer associate cachexia (2014)
- Brian Wolpin (Harvard) – cachexia begins in patients years prior to diagnosis with pancreatic cancer
- search for the “cachexia factor”
In 2013, the National Cancer Institute launched the “Ras Initiative”.

Cancer Metabolism
Cancer and metabolism or fundamentally linked

- Otto Warburg (Nobel Laureate)- 1924 put forth the “Warburg Hypothesis” suggesting that the metabolism of cancer cells is dramatically altered to support growth.
Glutamine supports pancreatic cancer growth through a KRAS–regulated metabolic pathway

Biomarkers

Elevation of circulating branched-chain amino acids is an early event in human pancreatic adenocarcinoma development
Personalized Medicine

Using genetic information from a specific patient to guide their treatment

- “Targetable mutations”
- “Non-oncogene dependencies”
- Systems biology