Recent Research in Pancreatic Cancer

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Why is pancreatic cancer so hard to treat?

1. No effective early detection tests
2. Biologically very aggressive (high level of genetic instability)
3. Rich stromal infiltration which contributes to poor response to therapeutic agents
4. Resistant to standard DNA damaging agents (i.e. chemotherapy and radiation) with previously unrecognized contribution of tumor cell heterogeneity

More research is needed!!
Pancreas anatomy and physiology

Pancreatic Cancer
Non-neoplastic Pancreas

Adenocarcinoma

“Desmoplasia”

Adenocarcinoma
Pancreatic Cancer Metastasizes at Early Stages

70% of stage I patients who undergo resection develop recurrent disease

Pancreatic epithelial cells invade into bloodstream and can be found in liver during the pre-malignant PanIN stage

Rhim et al. Cell, 2012
The Multidisciplinary Approach to Pancreatic Cancer Care (est. 2002)

- Open, rapid access
- Comprehensive, single day evaluation and treatment plan
- Surgeons/Medical and Radiation Oncologists/
  Gastroenterologists/
  Radiologists/Pathologist/
  Endocrinologist
- Same day pancreatic protocol CT scans
- Mid-day Pancreatic Tumor Board
- On-site Social Worker
- Biosample collection

Michigan Pancreatic Cancer Research Center

1) Cancer Database
   - optimize patient care, improve outcomes
   - provide a link between basic lab research and patient data

2) Pancreatic Cancer Tissue Bank (collection and tracking of samples)
   - blood
   - operative tissue samples (frozen/fresh/paraffin)
   - endoscopic samples (pancreatic juice, FNA)

3) Provide the infrastructure for basic, translational and clinical studies
Establish Research Network

Monthly meetings of basic scientists and clinicians involved in pancreatic cancer research or in the care of pancreatic cancer patients

Building Collaborations

Multidisciplinary Clinics

Research Laboratories
Have We Made Any Advancements in the Treatment of Pancreatic Cancer?

Yes
- operations done more safely
- advances in imaging have taken a lot of the guesswork out of operative decision making
- Able to resect some pts previously considered unresectable (combo of chemo/rad/surg)
- Median survival has increased with systemic chemotherapy

Lots of exciting work being done in the lab, but needs to be advanced to the clinical setting
Chemotherapy for Pancreatic Cancer: a Timeline of Very Slow Progress

Pre-1996: Many drugs tested, nothing worked
1996: Gemcitabine is better than 5FU. Gem is FDA approved
1996-2005: Many tested, no drug or combo is better than Gem
2005: Erlotinib + Gem is better than Gem.
   Erlotinib is FDA approved for pancreatic cancer
2005: Capecitabine + Gem is better than Gem?
2006: Oxaliplatin + Gem is not better than Gem
2006: Bevacizumab + Gem is not better than Gem
2007: Cetuximab + Gem is not better than Gem
2008: Bev + Gem-Erlotinib is not better than Gem-Erlotinib
2009: Cisplatin + Gem is not better than Gem
2009: Axitinib + Gem is not better than Gem
2009: Capecitabine + Gem is better than Gem?
2010: FOLFIRINOX is better than Gem!!
2013: Abraxane + Gem is better than Gem

What else is needed to improve outcomes for pancreatic cancer patients?

A better understanding of the molecular mechanisms of pancreatic cancer development and progression

-Identify early detection biomarkers
-Identify novel targets for therapeutics
Advances in the Basic/Translational Research Front

1) Modeling Pancreatic Cancer
2) Genomic Sequencing
3) Cancer Stem Cells and Intratumoral Heterogeneity
4) Metastasis
5) Targeting the Tumor Microenvironment
6) Early Detection

1) Modeling Pancreatic Cancer

Established commercially obtained cell lines
Genetically engineered mouse models of pancreatic cancer
Primary human pancreatic cancer xenografts
3-D primary cultures of pancreatic cancer
Oncogenic Kras is required for both the initiation and maintenance of pancreatic cancer in mice

J Clin Invest 2012

- Can turn Kras on and off in the adult mouse
- Kras critical for the initiation and maintenance of pancreatic cancer
- Serves as a more advanced genetically engineered mouse model to study pancreatic cancer
Primary Human Pancreatic Cancer Xenografts

Patient Research Platform

- Outcomes Database
- Tissue Bank
  - Tissue (paraffin & frozen: tumors and uninvolved pancreas)
  - Blood
  - Serum
  - CTCs
- Biopsy or resection
- Tumor Xenograft Program
  - Partner with our drug discovery team and Pharma
- Molecular Analysis
  - Gene expression
  - Mutational status
  - Pathways analysis
3-D Primary Cultures

- Tumor derived cancer associated fibroblasts
- 3-D Biomatrix
  - allows for individual patient, high-throughput drug screening

2) Genomic Sequencing
Molecular Genetics

Series of genetic events involving activating oncogenes and loss of tumor suppressor genes

- K-ras 90-95%
- p16 80%
- p53 60%
- DPC4 50%

Next Gen sequencing

- Applied Biosystems ABI 3730XL 1 Mb/day
- Roche / 454 Genome Sequencer FLX 100 Mb/run
- Illumina / Solexa Genetic Analyzer 2000 Mb/run

Reference Genome
Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes
A. Blankin, et al. (ICGC Consortium)
Nature 14 Nov 2012

- Next generation sequencing of 99 primary PDAs
- Defined mutational profile
- Begins to help us try to subtype PDAs

Much work needs to be done to better understand how this information can be used to more effectively treat patients
Mutation-driven Clinical Trials for Targeted Therapies

- AKT inhibitor
- BRAF inhibitor
- C-MET inhibitor
- EGFR inhibitor
- JAK inhibitor
- MEK inhibitor
- PI3K inhibitor
- Umbrella Study Personalized Access

Molecular Eligibility?

Integrative Sequencing Results
3) Cancer Stem Cells and Intratumoral Heterogeneity

Cancer Stem Cell Hypothesis:

• Cancers are driven by cells with stem cell properties

• Cancer stem cells are critical in the process of metastasis and tumor resistance

• This hypothesis doesn’t imply that all cancers arise from stem cells

Cancers are “driven” by cells with stem cell properties

Some studies suggest that tumors arise from a small subset of cells within a tumor termed cancer stem cells.

![Diagram](image)
Cancer stem cells are resistant to standard therapies

Several clinical trials underway to test therapies targeting cancer stem cells
Identification of Pancreatic CSCs from Primary Patient Tumors

Single markers
CD44 2-9%
CD24 3-28%
ESA 11-70%

Double Markers
CD44+ESA+ 1-16.9%
CD44+ESA+ 1.8-23%
CD44+CD24+ 0.5-2%

Triple Markers
CD44+CD24+ESA+ .2-.8%

Highly tumorigenic population with stem cell-like features
8 primary tumors and 2 mets evaluated

Cancer Res, 2007
Increased Pancreatic CSC in a Neoadjuvant-Therapy Treated Human Pancreatic Cancers

Pancreatic CSC Targets Currently Under Evaluation

- Hedgehog Pathway: GDC-0449, CUR199691 (Smoothened antagonists)
- Notch Pathway: GSI (Gamma secretase inhibitors), Anti-DLL4 antibody
- Wnt/β-catenin Pathway: Anti-Fzd antibody OMP-18R5
- Nodal/Activin Signaling: Alk4/7 inhibitor
- MET Pathway: XL184
- Chemokine receptor (CXCR4)
- Apoptosis-inducing pathway: Death receptor 5 (DR5) targeting antibody
4) New Understanding of the Process of Metastasis in Pancreatic Cancer

Complementary Evidence that CSCs are Important in the Process of Metastasis

*Rhim et al Cell 2012*

- Created a pancreas-specific Kras/p53 mutant/YFP mouse

- Found CD44^+CD24^+ YFP cells were present in PanIN lesions and enriched >100 fold in circulating YFP cells which lodged in the liver

- Paper suggests that metastasis occurs very early in the process of pancreatic tumorigenesis

- Supports notion that CSCs play a critical role in metastasis, and provides a model system to further interrogate this concept
5) Targeting the Tumor Microenvironment

Components:
Cancer cells
Stromal cells
Immune cells (T cells, macrophages)
Extracellular matrix

Preclinical and Clinical Work Underway

Stromal Targeting

SHH clinical trial

Hyaluronidase (active clinical trial of a PEGylated version- PEGH20 + gemcitabine)

Immune Cell Targeting

CD40 targeting antibody- targets this molecule on macrophages

Several approaches to upregulate T cell responses

6) Early Detection
CTC Labyrinth Microfluidics Device

<table>
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<th>CTC Recovery</th>
<th>WBC Removal</th>
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<tr>
<td>2nd</td>
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Isolation of Zeb1⁺ CTCs in Pancreatic Cancer Blood Samples
Ex-vivo Expansion of CTCs

Critical Path Forward

Improve our knowledge of disease biology to better select therapeutic targets (cellular heterogeneity, desmoplasia, resistance)

Early Detection: blood based assays, molecular imaging

Gain insights on individual molecular information to properly select patients for clinical trials

Increased focus on developing predictive biomarkers

More nimble clinical trial design

*Achieving these goals is only possible with collaborative efforts between clinicians and scientists*
How Does the Pancreatic Cancer Action Network Contribute to this Research Effort?

Award research grants - $5.1 million in 2014

Leaders in passage of the Recalcitrant Cancer Research Act

Key in developing an interactive network of scientists and clinicians across many institutions working together in a collaborative way

U. of Michigan Multidisciplinary Pancreatic Group Effort

Surgery
Diane Simeone
Rebecca Minter
Kevin Nguyen
Mike Mulholland
David Lubman
David Misek
Marina Pasca di Magliano

Internal Medicine
Michelle Anderson (GI)
Richard Kwon (GI)
Mark Zalupski (Med Onc)
Jim Scheiman (GI)
Vaibhav Sahai (Med Onc)
Chuck Burant (Endocrine)
Elena Stoffel (Genetics)
Andy Rhim (GI)

Radiology
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Radiation Oncology
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Chemistry
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Nursing/PA Support
Jan Hampton
Cindy Chinavere
Cindy DePetro
Andrea Ozog
Colleen Debeauclair
Thank you!!