Understanding Pancreatic Cancer

Advances in Pancreatic Cancer Research
Michael VanSaun, PhD

Wage Hope
Pancreas Adenocarcinoma: Advances and Opportunities

- Progression of disease
- Use of human tumor models in research
- Use of mouse models in research
- Advancements in early detection
- Tumor microenvironment
- Reprogramming the tumor immune response
- Advancements in clinical research
Pancreatic Ductal AdenoCarcinoma Model of Genetic Progression

- 24 pancreas cancers
- Investigated over 21,000 protein-encoding genes
- Found over 20,000 mutations/changes/alterations (avg 63)
- Able to group them into 12 core signaling pathways with mutations in 67-100% of the pancreas cancers

Different Patients Have Different Genetic Mutations

Potential Therapeutic Targets that Warrant Investigation in Pancreatic Cancer


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Patient Derived Xenograft Model


Assessment of Therapeutic Response

Jimeno A et al. Mol Cancer Ther 2009;8:310-314
Recurrent Pancreas Cancer – A case with PDX success

- Patient with resected pancreatic cancer, on adjuvant gemcitabine
- Progresses on 1st line therapy and develops supraclavicular LN met, local recurrence and lung mets
- CA19-9 >100,000 U

Manuel Hidalgo and Anirban Maitra

Patient enrolled in individualized therapy of pancreatic cancer trial (NCI00276744)

STUDY DESIGN

Whipple Resection

First passage xenograft

5 – 6 mice

F2 Xenograft

F3 xenograft

5 mice/group

CONTROL

TREATMENTS

Treat Recurrent Tumor Based on Best In Vivo Response

Hidalgo, Maitra
An argument for targeting low-frequency mutations “Making a Mountain out of a (Genetic) Molehill”

Bi-allelic mutation of PALB2 (Partner and localizer of BRCA2)

Germline “Inheritable”

Somatic “non-inheritable”

172-175 del TTGT

JVS10 + 2 T>C

Deficient BRCA1, BRCA2 or PALB2 is associated with:

• Defective repair of DNA double-strand breaks

• Hypersensitivity to mitomycin C (DNA interstand cross-linkers)

Zhang et al, Mol Cancer Res 2009
Dramatic Response of the Patients’ Xenograft to Mitomycin C

Patient lived five years after progressing on 1st line gemcitabine

High-Throughput Screening of PDX to Predict Response

- PDX tumors were treated with twenty different combinations of therapeutic compounds to determine reproducibility.

Guo 2015 NatMed N=42 PDXs
Production of Organoid Cultures from Human Tumors

- Pancreatic ductal organoid cultures can be made for normal and tumor tissue.
- Provides personalized high throughput analysis.

Pancreatic Organoids Offer High Throughput Screening

- Pancreatic organoids exhibit ductal and disease stage specific characteristics

Boj et al. 2015
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Genetically Engineered Mouse Models (GEM) of Pancreas Cancer

- Unprecedented opportunity to explore preclinical diagnostic and therapeutic strategies
  - Cancers recapitulate the clinical, histopathological and molecular features of the human disease
  - Allow study of specific alterations in oncogenic signaling pathways
    - EGFR, Notch and Hedgehog
  - Small molecule inhibitors targeted against these pathways can be tested in these transgenic models prior to clinical trials

Modeling Pancreatic Cancer in Mice to Mimic Human PDAC

Four commonly used mouse models that recapitulate human PDAC

1. Kras
2. Kras and TP53
3. Kras and CDKN2A
4. Kras and TGFBR2

GEM of Pancreas Neoplasms

<table>
<thead>
<tr>
<th>Submitter</th>
<th>Background</th>
<th>Model</th>
</tr>
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<tbody>
<tr>
<td>Grippo</td>
<td>FVB</td>
<td>Ela-KRAS^{G12D}</td>
</tr>
<tr>
<td>Sandgren and Schmid</td>
<td>B6, B6/129SvJae</td>
<td>Ela-TGF, Ela-TGF; p53^{−/−}</td>
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<tr>
<td>Konieczny</td>
<td>B6/129SvJae</td>
<td>Mist1-Kras^{G12D}</td>
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<tr>
<td>Guerra</td>
<td>B6/129SvJ/FVB</td>
<td>Ela-tTA; tet-o-cre; LSL-Kras^{G12V}, Ink4a/Arf</td>
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<tr>
<td>Bardeesy</td>
<td>FVB/B6</td>
<td>Pdx1-cre; LSL-Kras^{G12D}, Ink4a/Arf</td>
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<td>B6/129SvJae</td>
<td>Pdx1-cre; LSL-Kras^{G12D}</td>
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<tr>
<td>Hingorani</td>
<td>B6/129SvJae</td>
<td>Pdx1-cre; LSL-Kras^{G12D}, LSL-p53^{R172H}</td>
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<tr>
<td>Lewis</td>
<td>FVB/129SvB6</td>
<td>TVA-RCAS-PyMT</td>
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<tr>
<td>Rustgi</td>
<td>B6/SJL</td>
<td>Kras–KRASt^G12V</td>
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<tr>
<td>Means</td>
<td>B6/DBA2</td>
<td>Pdx1-HB-EGF</td>
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<tr>
<td>Thayer</td>
<td>B6/C3F1</td>
<td>Pdx1-SHH</td>
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<tr>
<td>Bar-Sagi</td>
<td>B6</td>
<td>Ela-PRSS1^{R122H}</td>
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</table>

Numerous models generated that have mutations in common with the human disease
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Early Detection – Liquid Biopsy

- Blood Based Analysis
  - Serum Proteins
  - Cell Free DNA
  - Exosomes


Willem Stoorvogel Blood 2012;119:646-648
Detection of Metastasis: Finding Circulating Tumor Cells (CTCs)

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Components of Pancreas Cancer

- Contribution of host microenvironment:
  - Stromal (stellate) cells
  - Vasculature
  - Immune cells
  - "Stem cells"
  - Autocrine and paracrine signaling


Stromal Desmoplasia in Pancreatic Cancer

- Desmoplastic reaction
  - Pancreatic stellate cells (myofibroblasts) play a critical role
  - Poor vascularization/perfusion
    - leaky immature vessels, increased interstitial fluid pressure
    - impedes the delivery of oxygen and delivery of chemotherapeutic drugs to the tumor cells
  - Mostly at primary pancreatic tumor, rather than metastatic sites
  - Dynamic compartment critically involved in tumor formation, progression, invasion and metastasis
Stat3 Inhibition Enhances Drug Delivery to the Tumor

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Cancer Immunotherapy

- Multiple studies have demonstrated that inflammation is directly associated with cancer.

Immune Killing of Cancer Cells

- Immune cells in cancers exist in a suppressed state.
- "Taking off the brakes"
- Successful intervention leads to activation of cytotoxic (tumor killing) T cells.
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Clinical Trials: Time and Cost

<table>
<thead>
<tr>
<th>Time</th>
<th>Phase 1 (Checking for Safety)</th>
<th>Phase 2 (Checking for Efficacy)</th>
<th>Phase 3 (Confirm results)</th>
<th>FDA Review / Phase 4 trials</th>
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<tbody>
<tr>
<td>1-2 years</td>
<td>20-100 volunteers</td>
<td>100 - 500 patients</td>
<td>1,000 - 5,000 patients</td>
<td>Safety surveillance in ‘Real-life’ patients</td>
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<tr>
<td></td>
<td>1st state of testing in humans</td>
<td>How well does the drug work?</td>
<td>- Drug MUST be safe</td>
<td>- Comparison with current ‘gold standard’ treatment</td>
</tr>
<tr>
<td></td>
<td>$30 mill</td>
<td>$40 mill</td>
<td>$95 mill</td>
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</table>

Cost
• ICGC formed 2008
• Sequence 500 tumors from each of 50 cancers types
• $1 billion (US)
• To date: 14 countries, 28 cancer types, 25,000 tumors
Novel Clinical Trial Designs

- **Umbrella Trial**
  - Biomarker status obtained
  - Pt assigned to the drug that is most likely to respond based on biomarker status

- **Basket Trial**
  - Examine effect of an agent on a particular genetic mutation regardless of cancer type
  -Pts with different types of cancer grouped into separate study arms (“baskets”)
Pancreatic Cancer Genetics

- **Whole Exome Capture and Sequencing + CNV (n=142)**
- 1456 novel genes mutated

- **KRAS (93%)**
- **TP53 (42%)**
- **SMAD4 (20%)**
- **MLL3 (8%)**
- **PCDH15 (7%)**
- **TGFBR2 (6%)**
- **SF3B1 (5%)**
- **ARID1A (5%)**
- **ATM (5%)**
- **CDKN2A (4%)**

<table>
<thead>
<tr>
<th>Mutation class:</th>
<th>Total:</th>
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<tbody>
<tr>
<td>Missense</td>
<td>1684</td>
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<tr>
<td>Nonsense</td>
<td>99</td>
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<tr>
<td>Splice site</td>
<td>89</td>
</tr>
<tr>
<td>Indel:</td>
<td>144</td>
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<tr>
<td><strong>NonSilent:</strong></td>
<td><strong>2016</strong></td>
</tr>
<tr>
<td>Silent:</td>
<td>611</td>
</tr>
</tbody>
</table>

Biankin et al. 2012

Pancreatic Cancer Genome Report: APGI-1992

**Somatic simple mutations**
- ABC9
- ADAMTS20
- AMAC1L2
- B3GALT4
- BLID
- BRCC3
- C3orf62
- C11orf94
- CACNA1C
- CAPN11
- CENPE
- COLEC11
- CTGF
- FRMD6
- GPR137B
- IQCH
- KIR3DL1
- KLKB1
- LEMD2
- PIK3CD
- PXDN
- RPA1
- SIGLECP3

**Genes affected by inter-chromosomal translocations**
- FGFR1 (bi-allelic)
- LYPD6B
- NRK3
- SFTP8
- TNPO21
- TPS3BP2
- ZNF468

**Genes affected by intra-chromosomal breakpoint**
- 133 genes

**Expressed Fusion transcript**
- ATE1 – KLRAQ1

**Differential Methylation & Expression**
- 1800 genes
Response to Platinum-based Therapy

Pathway Inhibitors
Longer-term Clinical Vision

Identifying 100 trial patients with biomarker requires 1000 patients

Molecular Phenotyping for all candidate targets
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