Recent Research in Pancreatic Cancer

Robert Vonderheide, MD, DPhil
Associate Cancer Center Director for Translational Research
Abramson Cancer Center
University of Pennsylvania
Philadelphia, PA
Clinical challenge:
High and growing number of deaths from pancreatic cancer

| Cancer                      | Total est 2012 Incidence | Total est 2012 deaths | Change in Death Rates 1990-2008
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All Malignant Cancers</td>
<td>1,639,510</td>
<td>577,150</td>
<td>Male: -22.9</td>
</tr>
<tr>
<td>Oral Cavity &amp; Pharynx</td>
<td>80,250</td>
<td>7,050</td>
<td>Female: -15.1</td>
</tr>
<tr>
<td>Esophagus</td>
<td>17,460</td>
<td>15,070</td>
<td>Male: -21.1</td>
</tr>
<tr>
<td>Stomach</td>
<td>21,320</td>
<td>10,540</td>
<td>Female: -40.5</td>
</tr>
<tr>
<td>Colon and Rectum</td>
<td>143,460</td>
<td>51,690</td>
<td>Female: -32.1</td>
</tr>
<tr>
<td>Liver &amp; Intrahepatic Bile Duct</td>
<td>28,720</td>
<td>20,550</td>
<td>Female: -33.3</td>
</tr>
<tr>
<td>Pancreas</td>
<td>43,920</td>
<td>37,390</td>
<td>Male: -30.0</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>12,360</td>
<td>3,650</td>
<td>Male: -32.0</td>
</tr>
<tr>
<td>Lung &amp; Bronchus</td>
<td>226,160</td>
<td>160,340</td>
<td>Male: -29.4</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>76,250</td>
<td>5,180</td>
<td>Male: -7.9</td>
</tr>
<tr>
<td>Breast</td>
<td>228,000</td>
<td>29,500</td>
<td>Male: -26.0</td>
</tr>
<tr>
<td>Cervix Uteri</td>
<td>12,710</td>
<td>4,220</td>
<td>Female: -35.1</td>
</tr>
<tr>
<td>Corpus and Uterus, NOS</td>
<td>47,130</td>
<td>8,010</td>
<td>Female: -2.3</td>
</tr>
<tr>
<td>Ovary</td>
<td>22,200</td>
<td>15,000</td>
<td>Male: -14.0</td>
</tr>
<tr>
<td>Prostate</td>
<td>241,740</td>
<td>28,170</td>
<td>Male: -40.9</td>
</tr>
<tr>
<td>Urinary Bladder</td>
<td>73,510</td>
<td>14,880</td>
<td>Male: -5.0</td>
</tr>
<tr>
<td>Kidney &amp; Renal Pelvis</td>
<td>64,770</td>
<td>13,570</td>
<td>Male: -6.5</td>
</tr>
<tr>
<td>Brain &amp; Other Nervous System</td>
<td>22,910</td>
<td>13,700</td>
<td>Male: -11.7</td>
</tr>
<tr>
<td>Hodgkin Lymphoma</td>
<td>5,000</td>
<td>1,100</td>
<td>Male: -44.4</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>70,130</td>
<td>18,940</td>
<td>Male: -18.0</td>
</tr>
<tr>
<td>Myeloma</td>
<td>21,700</td>
<td>10,710</td>
<td>Male: -10.4</td>
</tr>
<tr>
<td>Leukemia</td>
<td>47,150</td>
<td>23,640</td>
<td>Male: -11.2</td>
</tr>
</tbody>
</table>

AACR Cancer Progress Report 2012  
Pancreatic Cancer Action Network Report 2012
Biological challenge: Hostile microenvironment in pancreatic cancer

- Desmoplastic stroma and immune suppression is a pharmacological and biological barrier
- Inflammation drives oncogenesis, progression, and metastasis
- Novel genetically engineered mouse models provide a robust scientific foothold for discovery and translation

KPC mouse  

KPC-Y mouse  
Rhim et al, *Cell*, 2012
Multi-modality strategy for pancreatic cancer research

LABORATORY RESEARCH
- Discovery
- Pipeline

CLINICAL RESEARCH
- Patients
  - Clinical Trials + Standard Care
    - Analysis of Outcome
    - Genetic Character
- New and Improved Standards of Care

TRANSLATIONAL RESEARCH
- Screening
  - Discovery
- Early Detection
Multi-modality strategy for pancreatic cancer research
Next generation genetic sequencing of pancreatic cancer
Personalized diagnostics for pancreatic cancer

Expanding gene tests in cancer

Penn’s center is among those forging ahead aggressively, with an eye to tailored treatment.

By Stacey Barth

Inquirer Staff Writer

The University of Pennsylvania’s Abramson Cancer Center has raised its bet that the future of cancer treatment lies in our genes.

At Penn Medicine, Robert Daber (left) and David B. Roth check for flaws in a flow cells, which hold tumor DNA

Philadelphia Inquirer, Aug 9, 2013
Personalized care in pancreatic cancer

Comprehensive molecular and clinical profile
Attendance at a national scientific meeting on pancreatic cancer

Number of Attendees

Year

2003 2012

28 438
What we know about pancreatic cancer

Scientific knowledge

Year

1990  2000  2013
Massive increase in the depth and breadth of research activity in pancreatic cancer

Scientific publications per year

Publications on breast cancer in 2012: 13,925
in 2002: 5,090
We are here
Recent research findings for today’s discussion

- Chemotherapy combinations
- Kras, the oncogene
- Immunology and immune therapies
- Stroma
- Autophagy
Redesigned chemotherapy for pancreatic cancer

• Two new combinations of drugs for patients with metastatic disease
  – FOLFIRINOX (Conway et al, New England Journal of Medicine, 2011)
  – Gemcitabine/Abraxane (Von Hoff et al, ASCO, 2013)

• Rates of major tumor regression to initial therapy have gone from <5% to 25%-30%, with an improvement in patient survival
  – But still not a ‘cure’

• Implications and next steps
  – It’s not just gemcitabine alone anymore
  – Provides a better initial approach to stabilize our patients so additional therapies can be added
  – We also need to test these new therapies in patients after surgery
Randomized phase II study of ruxolitinib/capecitabine vs capecitabine alone for patients with recurrent metastatic pancreatic cancer
  – Interim analysis announced August 21, 2013
Six-month survival of patients marked improved in combination arm
  – No major toxicity issue reported
Ruxolitinib is a “JAK1/JAK2 inhibitor”, already FDA-approved for a blood disorder (MF)
More than 95% of all patients with pancreatic ductal adenocarcinoma have mutations in Kras in the tumor

There are cooperating mutations but no other common ‘driver’ mutations


Pasca di Magliano and Logsdon, Gastroenterology, 2013
Tumor growth depends on mutant Kras ‘oncogene’

Pasca di Magliano and Logsdon, Gastroenterology, 2013
See also,
Collins et al, J Clin Invest, 2011
Ying et al, Cell, 2012
Mutant Kras also drives tumor cell ‘appetite’


- Kras mutation
- Specialized uptake of albumin
- Altered amino acid metabolism
- Tumor growth

![Image of cellular uptake and tumor growth graphs]

McCormick to Aid Frederick National Laboratory in Developing RAS Cancer Genetics Initiative

(FREDERICK, Md., May 9, 2013)—Frank McCormick, Ph.D., director of the Helen Diller Family Comprehensive Cancer Center at the University of California, San Francisco, and associate dean of the UCSF School of Medicine, has signed a consulting agreement with SAGE-Frederick Inc. to work with the Frederick National Laboratory for Cancer Research (FNLCR), on behalf of the National Cancer Institute (NCI), to develop a proposal for intensive study of cancer cells driven by mutations of the RAS gene.

McCormick, who recently completed his term as president of the American Association for Cancer Research (AACR), will help SAGE-Frederick develop a proposal — to be submitted to NCI and its advisory boards and committees for their review and approval — of a potential, Frederick-based initiative to deal with the stubborn and long-known driver of many cancers, including those of the pancreas, colon, and lung.

In an April 8 address to a plenary session of AACR’s annual meeting in Washington, D.C., NCI Director Harold Varmus, M.D., said his vision is to “finally after 30 years learn how to target the cancer cells that exist in somewhere around a quarter of all human tumors that are driven by mutations in RAS and related genes.”
Immune therapy for cancer

- “The Future in Now” (AACR meeting, 2012)
- “A development as exciting as The Beatles were to music” (AACR Special Conference on Pancreatic Cancer, 2012)

Bayne and Vonderheide, Curr Opin Immunol, 2013
Engineered T cell therapy for cancer

1. Remove the immune cells from blood
2. Engineer killer lymphocytes in our clinical laboratory
3. Prepare cells for re-infusion
4. Give patient engineered T cells + chemotherapy

Porter et al, NEJM, 2011
Curing Cancer: The Philadelphia Award and Dr. Carl June

This year the prestigious Philadelphia Award honored Penn Medicine’s Dr. Carl June for his breakthrough work in curing leukemia in a number of patients. He and his team have developed a process that involves genetically engineering the patient’s immune system that holds promise for curing many types of cancer. We are happy to have had the opportunity to produce this video for The Philadelphia Award and to meet Dr. June and his colleagues.
CD40 antibody as immune therapy for pancreatic cancer

Tumor regressions after agonist CD40 mAb in laboratory experiments

Major and durable tumor regressions in metastatic patients receiving CD40 mAb and gemcitabine

Beatty GL et al, Science, 2011
CD40 antibody as immune therapy for pancreatic cancer

Before treatment

After treatment

CD40 immune activation

Beatty et al, Science, 2011
GRANT SNAPSHOT

2013 Tempur-Pedic – Pancreatic Cancer Action Network – AACR Inaugural Research Acceleration Network Grant in Memory of Tim Miller

Grantees: PI: Robert Vonderheide, MD, DPhil
Institutions: University of Pennsylvania
Co-PI: Dafna Bar-Sagi, PhD
New York University

Research Project: Accelerating Development of CD40 Therapy for Pancreatic Cancer

Award Period: July 1, 2013 – June 30, 2016

Amount: $1,000,000
The challenge and opportunity of stroma

Dense stroma surrounding pancreatic cancer

Chemotherapy cannot penetrate the surrounding stroma

After treatment with hyaluronidase

Chemotherapy can now penetrate and cause tumor regression

Olive et al, Science, 2009
Provenzano et al, Cancer Cell, 2012
Jacobetz et al, Gut, 2013
Autophagy is a ‘rope-a-dope’ mechanism for pancreatic cancer to go into hiding

Mediates resistance to chemotherapy and radiation therapy

Hydroxychloroquine inhibits autophagy and enhances effect of chemotherapy

Clinical trials underway with gemcitabine/abraxane

NCT01506973

Better inhibitors being designed

Yang et al, Genes Dev, 2011
McAfee et al, Proc Natl Acad Sciences, 2012
Pancreatic cancer can hide but it cannot run

Joe Louis on the 1946 Heavyweight match with Billy Conn:

“He can run, but he can't hide.”
Pancreatic cancer can hide but it cannot run
Research in clinical trials are critical

Fig 3. Pancreatic ductal adenocarcinoma clinical trials open in United States in 2011 and 2012 by treatment type. Targeted indicates those targeted to signal

Hoos et al, J Clin Oncology, 2013
Pancreatic cancer is a clinical EMERGENCY
Conclusions

- Research efforts in pancreatic cancer are accelerating
- New discoveries are driving novel therapies, and new means of early detection
  - “Inhibit Kras”
  - “Arm the immune system”
  - “Destroy the stroma”
- Clinical trials are critical
To make an appoint at Penn: 1-800-789-PENN

Clinical trial information: www.oncolink.org

Pancreatic Cancer Action Network: www.pancan.org

Patient and Liaison Services (PALS) program
Mon-Fri 7a.m.-5p.m. Pacific Time, Toll Free 877-272-6226; pals@pancan.org