Pancreatic cancer
A deadly disease with a highly unmet medical need
The many faces of Pancreatic Cancer
Cancer related deaths

Ten leading cancer types for deaths 2007

<table>
<thead>
<tr>
<th>Estimated Deaths</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung and Bronchus</td>
<td>90,330</td>
<td>72,130</td>
</tr>
<tr>
<td>Colon and Rectum</td>
<td>27,870</td>
<td>40,970</td>
</tr>
<tr>
<td>Prostate</td>
<td>27,350</td>
<td>27,300</td>
</tr>
<tr>
<td>Leukemia</td>
<td>12,470</td>
<td>9,810</td>
</tr>
<tr>
<td>Liver and Intrahepatic Bile Duct</td>
<td>10,840</td>
<td>8,840</td>
</tr>
<tr>
<td>Esophagus</td>
<td>10,730</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>10,000</td>
<td></td>
</tr>
<tr>
<td>Urinary Bladder</td>
<td>8,990</td>
<td></td>
</tr>
<tr>
<td>Kidney and Renal Pelvis</td>
<td>8,130</td>
<td></td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td>291,270</td>
<td>273,560</td>
</tr>
</tbody>
</table>

4. Pancreas 16,090 6%

| 1997 | #4 | 5% | #4 | 5% |
| 1987 | #5 | 5% | #5 | 5% |
| 1977 | #4 | 5% | #5 | 5% |

Jemal et al., CA Cancer J Clin 2007, 57: 43-66
Incidence of PDAC

Geographical variation
reasons widely unknown
• speculative ...
Incidence of PDAC

Diagnosis at late stage
- site of the organ
- no early symptoms
- no screening
- no tumor marker

Jemal et al., CA Cancer Statistics 2005, 55: 10-22
To be honest with yourself

„from the analysts couch“*

Few cytotoxic drugs work convincingly
  • ≥ 30% difference
  • VERY few work in pancreatic cancer
  • Severe side effects in the elderly

• NO marker on diagnosis, potential response or resistance

Therefore, it is not possible to survive pancreatic cancer the way you can survive breast or colorectal cancer°
but if you are ...

We have to face the facts. Chemotherapy has a totally questionable track record. If you’re not killed by the side effects first time round, you’re basically a goner when the cancer returns owing to the damage done to the immune system. I mean, in view of that, what’s your opinion on doctors’ huge salaries on oncology wards? Also, the medical establishment’s massive investment in smear campaigns to destroy the credibility of effective and side effect-free alternative cancer therapies. What do you have to say about that?

You’re Fired.
# Research Funding

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>2007 Spending (in millions)</th>
<th>2008 Spending (in millions)</th>
<th>2009 Spending (in millions)</th>
<th>2009 ARRA Spending (in millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>$226.9</td>
<td>$247.6</td>
<td>$246.9</td>
<td>$48.0</td>
</tr>
<tr>
<td>Prostate</td>
<td>296.1</td>
<td>285.4</td>
<td>293.9</td>
<td>47.0</td>
</tr>
<tr>
<td>Breast</td>
<td>572.4</td>
<td>572.6</td>
<td>599.5</td>
<td>85.5</td>
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<tr>
<td>Colorectal</td>
<td>258.4</td>
<td>273.7</td>
<td>264.2</td>
<td>44.5</td>
</tr>
<tr>
<td>Bladder</td>
<td>19.8</td>
<td>24.1</td>
<td>25.9</td>
<td>2.8</td>
</tr>
<tr>
<td>Melanoma</td>
<td>97.7</td>
<td>110.8</td>
<td>103.7</td>
<td>17.6</td>
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<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>113.0</td>
<td>122.6</td>
<td>130.9</td>
<td>14.0</td>
</tr>
<tr>
<td>Kidney</td>
<td>35.2</td>
<td>43.4</td>
<td>45.2</td>
<td>7.2</td>
</tr>
<tr>
<td>Leukemia</td>
<td>205.5</td>
<td>216.4</td>
<td>220.6</td>
<td>33.9</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>73.3</td>
<td>87.3</td>
<td>89.7</td>
<td>10.7</td>
</tr>
</tbody>
</table>
Moral support – patient organisations

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Foundations</th>
<th>Patient Org</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>&gt; 20</td>
<td>&gt; 50</td>
</tr>
<tr>
<td>Breast</td>
<td>&gt; 20 (10)</td>
<td>&gt; 50</td>
</tr>
<tr>
<td>Kidney</td>
<td>15 (4)</td>
<td>&gt;20</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>3 (1)</td>
<td>3</td>
</tr>
<tr>
<td>Childhood leucemia</td>
<td>&gt;20 (10)</td>
<td>&gt; 50</td>
</tr>
</tbody>
</table>
The American Congress shall pass a bill

AD-VŌ-CATE, verb:
TO TELL CONGRESS TO KNOW IT. FIGHT IT. END IT.

Urgent Action Alerts!

1. Letters Sent to Key Committees. On July 18, the authors of the Pancreatic Cancer Research & Education Act (S. 362/H.R. 733) sent letters to the leaders of the Senate Health, Education, Labor & Pensions (HELP) and House Energy & Commerce Committees urging them to move the bill out of their committees so that the full Senate and House can vote on it. Click here for a list of all members of Congress who signed onto those letters. If any of your members signed on, please click on one or both of the buttons below to send them a thank you note for their leadership on this issue. If your members did not sign onto the letter, please see below for other ways to reach out to them.

   THANK YOUR SENATORS
   THANK YOUR REPRESENTATIVE

2. Support Continues to Build for Pancreatic Cancer Legislation. Well over half of both the U.S. Senate and the U.S. House are now co-sponsoring the Pancreatic Cancer Research & Education Act. In fact, the bill has more support than the majority of bills currently under consideration in Congress and continues to have more co-sponsors and bi-partisan support than any other bill referred to the Senate HELP and House Energy & Commerce Committees. Tell your members of Congress that you want them to move this legislation forward and send it to the president’s desk this year!

SEND A MESSAGE TO YOUR SENATORS
SEND A MESSAGE TO YOUR REPRESENTATIVE
The lost organ

Comment From the Editor

Pancreatologists: An Endangered Species?

The pancreas was identified and named by the Greeks. Herophilus (335–280 BC), an anatomist and surgeon, first described it. Ruphos, an anatomist, gave the pancreas its name. The significance of the main duct was already recognized in the 17th century. In 1889, Fitz established the concept of “transgenic mice” carrying cloned genes integrated into the mouse genome was demonstrated to be a tractable and reproducible method. In 1984, Palmiter and Brinster began using the elastase gene promoter to control expression of SV40 T-antigen in pancreatic acinar cells. Those mice reliably developed acinar cell (exocrine pancreatic) tumors in a heritable manner being one of the first “oncomice” generated.

The history of Schmid's organ...
Pancreatic Cancer

Reasons for Failure

• Late diagnosis
  • Location in the body
  • No tumour markers

• Therapeutic catastrophe
  • 20% operable (median survival time 24 months!)
  • 80% inoperable (median survival time 6 months!!!)
    • No chemotherapy with significant impact

• In consequence
  • 20% operable (median survival time 24 months!)
  • 80% inoperable (median survival time 6 months!!!)
Pancreatic Cancer

- **What is special?**
  - The histological make-up of the tumor
    - Connective tissue (desmoplasia)
    - No hormones involved
  - Immune surveillance
  - Immunosuppression

Hanahan & Weinberg, Cell, 2000
The AIM is to have a goal
The goal is to have a target

Modern tumor therapy *per definitionem* requires an identifiable molecule or pathway that can be addressed
Signal transduction pathways

Mutations /deletions
Increased / disturbed function / concentration
Targeted Therapies

Phase I

FTIM

EOP1

Phase I Multiple Ascending Dose Patients

Tumour 160 choices

Dose 3 choices

Schedule 6 choices

Combination 20 choices

Patient Selection 2 choices

~120,000 opportunities to get it wrong

Courtesy of Prof. Andrew Hughes, AstraZeneca

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What we have

✔ Understanding of the molecular biology & genetics

✔ Preclinical models
  • Consisting of both tumor cells and connective tissue cells

✔ Preclinical animal models
  ✔ Mimicking the development of pancreatic cancer in man

✔ High-throughput analysis
  ✔ “omics”
What we should do different

- Concentrate on the UNIQUE features of pancreatic cancer
- Treat not only the tumour cells but the entire tumour and the entire patient
What needs to be done?!

Proposal & action plan

This is a wake-up call
Summary

Pancreatic cancer is a deadly disease with highly unmet medical need, craving more **attention**
- lobbying with politicians
- discussion with grant agencies
- Action plan with professional societies

Pancreatic cancer is a deadly disease with highly unmet medical need, craving more **action**
- Translational research at the Pancreas Centers taking a holistic approach
  - Population-based studies with biological samples
- Large combined genomic/proteomic studies
- Whole cancer genome sequencing during clinical studies
Gene-Enviroment-Continuum

<table>
<thead>
<tr>
<th>GENE</th>
<th>GENE</th>
<th>GENE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENVIROMENT</td>
<td>ENVIROMENT</td>
<td>ENVIROMENT</td>
</tr>
</tbody>
</table>

- **Tumor Suppressor Genes**
  - PRSS1
  - SPINK1
  - CFTR
- **Low penetrance genes**
Figure 1.1. Development of the pancreatic adenocarcinoma following a stepwise, canonically progression of pancreatic intraepithelial neoplasias, as evident on the histological level.

Pathophysiology of pancreatic cancer

- Normal
- PanIN-1A
- PanIN-1B
- PanIN-2
- PanIN-3

- Telomere shortening
- K-ras
- p16
- p53
- DPC4
- BRCA2
- LOH 9p
- LOH 18q, 17p, 6q
The smoking cancers

Epidemiology of Early Onset Pancreatic Cancer

Weighted $R^2 = 0.53$

$p < 0.0001$
Is it possible to diagnose early?

PanIN acknowledged early neoplastic lesions withdraw from routine imaging

High resolution MRI or direct pancreaticoscopy

Venu et al., Gastrointest. Endosc. 2002;55:82-89
Yamaguchi et al., Gastrointest. Endosc. 2000;55:67
Diagnostic Requirements

What are the **IMPORTANT** questions?

**Establishment of proper diagnosis**

Differential diagnosis

- Chronic pancreatitis
- Autoimmune pancreatitis
- Other pancreatic tumors

**Precise and reliable evaluation of resectability**

**Staging**