Recent Research in Pancreatic Cancer

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Lineberger Comprehensive Cancer Center
Pre-lecture knowledge evaluation

1. What is the average time to develop a drug, from bench to bedside?
   a. One to five years
   b. Fifteen to 20 years

2. How many gene mutations cause pancreatic cancer?
   a. One
   b. Five
   c. Ten to 20

3. What is KRAS?
   a. A Croatian food company known for its chocolate products
   b. The holy grail of pancreatic cancer research

4. What are new directions for advancing pancreatic cancer treatment?
   a. Developing “smarter” drugs
   b. DNA sequencing and personalized medicine
   c. Methods for early detection
   d. Improving drug delivery
   e. Harnessing the immune system

Fighting pancreatic cancer: “a humbling disease”*

Pancreatic cancer treatment
Anti-cancer drug discovery – the long and winding road
The pancreatic cancer cell – a worthy opponent
KRAS – the four letter word in pancreatic cancer
Hope for the future?

*Dr. Anirban Maitra, MD Anderson Cancer Center
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The fundamental problem with all cancer therapy

No magic, or smart bullet drugs; our normal cells are innocent bystanders
We have “magic bullet” drugs for diseases caused by bacteria, yeast and viruses

Bacteria
Yeast
Viruses

Foreign invaders

Cancer is a genetic disease: when good genes go bad

The enemy within
Conventional anti-cancer drugs target rapidly growing cells

- Conventional cytotoxic anticancer drugs are NOT magic bullets. Ideally they should target only the cancer cells. However, they target proliferating cells whether normal or cancer.
- Normal cells of the hair follicles, bone marrow and intestinal epithelium are rapidly dividing and are especially sensitive to inhibition by anti-neoplastic drugs. This results in the toxic side effects common to most anticancer drugs.

Gemcitabine (Gemzar) blocks the production of DNA, needed for growth: not a magic bullet
DNA: the template for making proteins

Our conventional anti-cancer drugs are poisons
Is there a better way?
History of cancer chemotherapy: the era of targeted anti-cancer drugs begins in 1998

- Antibiotics shown to have anti-tumor activity
- FDA approves cyclophosphamide
- FDA shows that post-surgery chemotherapy improves cure rate
- FDA approves paclitaxel for ovarian cancer
- FDA approves imatinib for CML
- FDA approves cetuximab for colon cancer
- FDA approves trastuzumab for HER2 positive metastatic breast cancer

Conventional cytotoxic
Molecularly targeted

Farber uses antifolates to induce remission of ALL
FDA approves MTX
Heidelberger develops 5-FU
Combination therapy induces ALL remission
FDA approves cisplatin for ovarian cancer

FDA approved signal transduction inhibitors

<table>
<thead>
<tr>
<th>FDA Approved Drug</th>
<th>Indications</th>
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<tbody>
<tr>
<td>Trastuzumab (HER2)</td>
<td>HER2 positive metastatic breast cancer (1998) and gastric cancer (2010)</td>
</tr>
<tr>
<td>Imatinib (BCR-ABL)</td>
<td>CML (2001) and GIST (2002)</td>
</tr>
<tr>
<td>Gefitinib (EGFR)</td>
<td>for NSCLC (2003)</td>
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<tr>
<td>Cetuximab (EGFR)</td>
<td>for metastatic CRC (2004) and SCCHN (2006)</td>
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<tr>
<td>Erlotinib (EGFR)</td>
<td>for NSCLC (2004) and PDMG (2005)</td>
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<tr>
<td>Sorafenib (RAf, VEGFR, PDGFR)</td>
<td>for RCC (2005)</td>
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<tr>
<td>Sunitinib (Flt3, VEGFR, PDGFR)</td>
<td>for GIST and RCC (2006), and pancreatic neuroendocrine tumors (2011)</td>
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<tr>
<td>Dasatinib (BCR-Ab1, Src, Lyn, Yes, Fyn, Kit, EphA2 and PDGFR)</td>
<td>for imatinib-resistant CML and Ph-positive ALL (2006) and Ph-positive CML (2010)</td>
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<tr>
<td>Panitumumab (EGFR)</td>
<td>for CRC (2006)</td>
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<tr>
<td>Lapatinib (EGFR, HER2)</td>
<td>for metastatic breast cancer (2007)</td>
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<tr>
<td>Temsirolimus (mTOR)</td>
<td>for RCC (2007)</td>
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<tr>
<td>Nitotinib (BCR-ABL, Kit, PDGFR)</td>
<td>for CML (2007)</td>
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<tr>
<td>Everolimus (mTOR)</td>
<td>for RCC (2009), pancreatic neuroendocrine tumors (2011), HER2-negative breast cancer (2012) and renal angiomyolipoma associated with TSC (2012)</td>
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<tr>
<td>Pazopanib (VEGFR)</td>
<td>for RCC (2009)</td>
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<tr>
<td>Vemurafenib (B-Raf)</td>
<td>for B-Raf(V600E) metastatic melanoma (2011)</td>
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<tr>
<td>Vandetanib (VEGFR, EGFR, Ret)</td>
<td>for thyroid cancer (2011)</td>
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<tr>
<td>Crizotinib (ALK, Met)</td>
<td>for ALK rearranged NSCLC (2011)</td>
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<tr>
<td>Axitinib (VEGFR, PDGFR, Kit)</td>
<td>for RCC (2012)</td>
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<td>Vemurafenib (B-Raf)</td>
<td>for B-Raf(V600E) metastatic melanoma (2010)</td>
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<tr>
<td>Regorafenib (VEGFR1-3, TIE-2, PDGFR, PDGFR, RET, Kit, Raf)</td>
<td>for metastatic CRC (2012) and GIST (2013)</td>
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<tr>
<td>Pertuzumab (HER2)</td>
<td>for HER2 positive metastatic breast cancer (2012)</td>
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<td>Axitinib (VEGFR1-3)</td>
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<td>Ponatinib (AT1, Src)</td>
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<td>Cabozantinib (MET, VEGFR2)</td>
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<td>Bosutinib (A, Src)</td>
<td>for Ph positive CML (2012)</td>
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<td>Dabrafenib (B-Raf)</td>
<td>for B-Raf(V600E) melanoma (2013)</td>
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<tr>
<td>Regorafenib (VEGFR2, TIE2, etc)</td>
<td>GIST (2013)</td>
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<tr>
<td>Trametinib (MEK1/2)</td>
<td>for B-Raf V600E/K metastatic melanoma (2013)</td>
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<tr>
<td>Aftatinib (EGFR, HER2/4)</td>
<td>for EGFR mutant NSCLC (2013)</td>
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Compiled from http://www.centerwatch.com

30 approved, many more in the pipeline
How has the new wave of anti-cancer drugs impacted pancreatic cancer?

Well...

**FDA drug approvals for top 5 causes of US cancer deaths (2002-2012)**

<table>
<thead>
<tr>
<th>Year</th>
<th>Lung</th>
<th>Colon</th>
<th>Breast</th>
<th>PDAC</th>
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<td>2012</td>
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Sources: [www.fda.gov](http://www.fda.gov), [www.cancer.gov](http://www.cancer.gov), [www.pancan.org](http://www.pancan.org)
Why has there been less progress in pancreatic cancer treatment?

Is there hope for better targeted anti-cancer drugs for pancreatic cancer?

Fighting pancreatic cancer: “a humbling disease”

- Pancreatic cancer treatment
- Anti-cancer drug discovery – the long and winding road
- The pancreatic cancer cell – a worthy opponent
- KRAS – the four letter word in pancreatic cancer
- Hope for the future?
Drug discovery: the long and winding road

- **It’s expensive** - the average cost of bringing a drug to market is $1.2 billion to $1.3 billion dollars
- **It’s risky** - there is roughly a 1 in 5-10,000 chance of a compound’s achieving the arduous trek from the laboratory to the marketplace
- **It takes time** - the developmental time frame can be 15-20 years

PhRMA 2010

Drug discovery – 1:5,000 odds of success

<table>
<thead>
<tr>
<th>Research &amp; Preclinical Testing</th>
<th>Clinical Trials Phases I - III</th>
<th>FDA &amp; Phase IV</th>
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</thead>
<tbody>
<tr>
<td>6.5 years</td>
<td>7 years</td>
<td>1.5 years</td>
</tr>
<tr>
<td>Assess biological activity</td>
<td>Anticancer activity &amp; toxicity</td>
<td>Review &amp; approval, evaluation of long term effects</td>
</tr>
<tr>
<td>5,000 compounds evaluated</td>
<td>5 enter trials</td>
<td>1 approved</td>
</tr>
</tbody>
</table>

Source: Regulatory and Scientific Affairs, PhRMA
Development of trastuzumab (Herceptin) for breast cancer treatment

- 1981 – Detected as a transforming gene from a rat neuroblastoma (Neu)
- 1985 – Neu determined to be related to the EGF receptor tyrosine kinase and designated ErbB2/HER2
- 1987 – HER2 overexpressed in 25-30% breast cancer and correlates with poor prognosis
- 1989 – 4D5 mouse anti-HER2 monoclonal antibody made against HER2-overexpressing NIH 3T3 cells blocks growth of HER2-overexpressing cells
- 1992 – Humanized version of the 4D5 mouse anti-HER2 monoclonal antibody (trastuzumab; Herceptin) is made.
- 1998 – Approved by FDA for treatment of advanced breast cancers

17 years from target discovery to drug approval

Development of imatinib (Gleevec) for leukemia treatment

- 1960 – Abnormal chromosome 22 (Ph) identified in CML patients
- 1973 – Ph chromosome due to 9 and 22 translocation
- 1982 – Abl oncogene rearrangement identified in Ph chromosome
- 1984 – Bcr-Abl identified as possible cause of CML
- 1990 – Bcr-Abl causes leukemia in mice
- 1993 – Preclinical analyses of STI571 begins
- 1998 – STI571 clinical trials begin
- 1999 – STI571 reported to have strong efficacy in CML patients
- 2001 – Larger study confirms earlier findings
- 2001 – FDA approves STI571/Gleevec for CML treatment
- 2002 – FDA approves STI571/Gleevec for GIST treatment

19 years from target discovery to getting a drug approved
### Pre-lecture knowledge evaluation

1. What is the average time to develop a drug, from bench to bedside?
   - a. One to five years
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2. How many gene mutations cause pancreatic cancer?
   - a. One
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   - a. A Croatian food company known for chocolate
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4. What are new directions for advancing pancreatic cancer treatment?
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### Fighting pancreatic cancer: “a humbling disease”

- Pancreatic cancer treatment
- Anti-cancer drug discovery – the long and winding road
- The pancreatic cancer cell – a worthy opponent
- KRAS – the four letter word in pancreatic cancer
- Hope for the future?
There are skeptics about our progress

“Avastin, Erbitux, Gleevec... The new wonder drugs might make you think we’re finally beating this dreaded scourge. We’re not.”

- Scientists often cannot secure funding for risky research
- Urges patients to become better advocates for progressive change

He has been critical of cancer researchers; deserved?

“Know your enemy” - Sun Tzu

孙子兵法

The Art of War - a treatise on military tactics

Chinese military general, strategist, and philosopher
How well do we know the cancer cell?

The cancer cell is “smarter” than the cancer researcher

Our understanding of the cancer cell:
a work in progress

Herceptin approved for breast cancer (1998) 2013

Evolution of our understanding of the complexities of the cancer cell
The cancer cell is a much more resilient beast than we gave it credit for. It can overcome our best efforts; we need to get smarter, more creative.

The initial rapid response to vemurafenib treatment of malignant melanoma is followed by rapid recurrence.

38 year old male with metastatic melanoma, subcutaneous metastatic deposits

A 0 weeks  B 15 weeks  C 23 weeks

The cancer cell is much more complex than we had imagined

A genetic mess

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial hypercholesterolemia</td>
<td>1 in 500</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>1 in 1250</td>
</tr>
<tr>
<td>Neurofibromatosis type I</td>
<td>1 in 2,500</td>
</tr>
<tr>
<td>Hereditary spherocytosis</td>
<td>1 in 5,000</td>
</tr>
<tr>
<td>Marfan syndrome</td>
<td>1 in 4,000</td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>1 in 15,000</td>
</tr>
<tr>
<td>X-linked</td>
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</tbody>
</table>

Over 4,000 human diseases are caused by single gene defects. Cancer is not so simple
DNA sequencing: deciphering the genetic basis of cancer

- Sequencing of the 1st human genome began in 1990.
- Completed on April 14, 2003, at a cost of ~ $1 billion and 13 years to complete (April 14, 2003)

We are making amazing progress in our ability to sequence DNA

- Today it costs between $1,000 - 4,000 and takes just one to two days.
- Companies are working to get this down to $100 per genome
With the advances in DNA technology, we now have a very detailed picture of the genes that cause pancreatic cancer.

It is not simple.

There are ~60 genetic defects per pancreatic cancer.

Most DNA mutations in cancer cells are “harmless” passengers

~10-20 mutations “drive” cancer

Genetic landscape of pancreatic cancer

A few mountains, many hills”

Provided by Dr. Anirban Maitra

Tumors from the same patient varied widely in their set of mutated genes

A single tumor biopsy sample (55%) underestimated genetic complexity of tumor


- Not all the cancer cells in one patient will respond to a particular treatment
- Accounts for why the cancer responds initially and then comes back

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KRAS is the biggest “mountain”

“The Big Four”

Pancreatic Cancer
Scanning the Horizon for Focused Interventions
A Report to the Director of the National Cancer Institute
The Pancreatic Cancer Working Group
Clinical Trials and Translational Research Advisory Committee (March 13, 2013)

1. PDAC and diabetes mellitus
2. Biomarkers for early detection of PDAC
3. Immunotherapy
4. RAS-specific therapies

NCI announces the Ras “Megaproject”
June 24, 2013

Headed by Dr. Frank McCormick (UCSF), a Pancreatic Cancer Action Network funded researchers

http://news.sciencemag.org/scienceinsider/2013/06/us-cancer-institute-megaproject-.html
The Mt. Everest of pancreatic cancer research

“Because it’s there”
- George Mallory*, 1924

*British mountaineer, died in 1924 on Mt. Everest climb

Kill KRAS, kill pancreatic cancer?
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Partial credit: KRAS chocolates!
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Increasing awareness of pancreatic cancer

By the pancreatic cancer patient and by cancer researchers
Pancreatic cancer: better awareness?

Breast cancer

ADD And ADHD
Adoption
Alzheimer’s Disease
Anti-gay Bullying
Arnold-chiari Malformation
Victims of 9/11
Child Abuse
Crohn's Disease
Animal Abuse
Cystic Fibrosis
Domestic Violence
Dyscalculia
Eating Disorder Awareness
Epilepsy
Father's Rights & Parental Rights
Fibromyalgia
Gastrointestinal Cancer
Gynecologic Cancers
Hidradenitis Suppurativa
Homelessness
Huntington's Disease
Loss
Lupus
Macular Degeneration
Migraine
Overdose Prevention
Pagan Pride Day
Pancreatic Cancer
Porphyria
Hemiplegia Hemiparesis or Pediatric Stroke
Pulmonary Hypertension
Religious Tolerance
Rett Syndrome
Suicide Prevention
Sarcoidosis
Thyroid Cancer
Ulcerative Colitis
Wildland Firefighters
Workers' Memorial Day
Xenophobia


Less than 5% of pancreatic cancer patients participate in clinical trials (2011)

Increasing patient involvement in clinical trials will accelerate the progress in finding better treatments
An increase in the number of NCI-funded pancreatic cancer investigators

More researchers, more talent, will translate to faster progress

The era of personalized medicine is here
Pancreatic cancers are not all the same; why should the treatments all be the same?

One treatment will not be the best for all patients

Pancreatic cancer is genetically very heterogeneous

Provided by Dr. Andrew Biankin (Garvan Institute)
Pancreatic cancers are not all the same: the era of personalized medicine is here

One treatment will not be the best for all patients

In search of early detection markers for early stage pancreatic cancer

- No early detection tests - most patients with localized disease have no recognizable symptoms or signs
- Most patients are not diagnosed until late in their disease, after their cancer has metastasized to other organs
- Researchers are looking for ways to detect early pancreatic cancer
In search of markers to detect early stage pancreatic cancer

Boy Wonder: Jack Andraka

Meet Jack Andraka, a high school student who at age 15 developed a test that might save countless lives by detecting early pancreatic cancer. Morley Safer reports.

Early detection of pancreatic cancer

- Visualizing the early stage cancer
  - Dr. Kimberly Kelly (UVA)

- Blood tests for markers of early stage cancer
  - Dr. Bert Vogelstein (JHMI)
Recent research has identified unexpected complexities of pancreatic cancer

Finding ways to overcome these complexities for improved therapy

Breaking down the barrier for improved drug delivery

• Researchers* discovered in 2009 that pancreatic cancers have built a “wall” around the tumor that prevents drugs from reaching the tumor.
• This exciting finding has prompted researchers to discover ways to break down this barrier so that drugs can reach the cancer and more effectively kill cancer cells.

*Drs. Ken Olive (Columbia) and David Tuveson (Cold Spring Harbor Laboratory)
Waking up our immune system

• Researchers* recently discovered that pancreatic cancers send out a signal that fools our T cells, tells them not to come.
• Clinical trials are now exploring ways to block that signal, to recruit the T cells to attack the cancer.

*Pancreatic Cancer Action Network-funded researchers (Drs. Dafna Bar-Sagi, NYU, and Robert Vonderheide, UPENN)

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Connecting the researchers with the families, the survivors