Killing KRAS: The Key to a Pancreatic Cancer Treatment Breakthrough?

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Killing KRAS: The Key to a Pancreatic Cancer Treatment Breakthrough?

Channing J. Der, PhD
University of North Carolina at Chapel Hill
Lineberger Comprehensive Cancer Center

Topics for today

- Cancer drug discovery – the long and winding road; not for the faint at heart
- KRAS – will this be the key to a breakthrough in pancreatic cancer treatment?
Cancer drug discovery – the long and winding road

The fundamental problem with all cancer therapy

No magic or smart bullet drugs; our normal cells are innocent bystanders
German scientist was a pioneer in modern chemotherapy (Nobel Prize in 1908). He spent years studying the effects of chemicals on tissue and in search of “magic bullets” that kill the microbe or cancer cell but not the person with the disease.

"Father of Chemotherapy"

Paul Ehrlich

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

Cancer chemotherapy: two general classes of drugs

- **Conventional cytotoxic drugs**
  - Target DNA replication, cell division
  - Gemcitabine, 5-FU, paclitaxel, oxaliplatin

- **Signal targeted drugs**
  - Target defective proteins in cell signaling
  - Herceptin, Gleevec, Tarceva, Zelboraf
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 blocks the production of DNA, needed for the growth of normal and cancerous cells: not a magic bullet
DNA: the template for making proteins

Our conventional anti-cancer drugs are poisons

Is there a better way?
Beginning in 1982, genes mutated in cancers were discovered

- **Boveri** proposes existence of tumor suppressor genes and oncogenes
- **Knudsen** proposes “2-hit” hypothesis to explain genetic basis of inherited and sporadic retinoblastomas
- The first human tumor suppressor gene (RBP) is cloned
- The first human tumor exomes are sequenced (breast and colon)
- 572 genes are listed in the Cancer Genome Census

1st human chromosome abnormality (Ph) identified

Viral src oncogene is derived from normal gene

The first mutated genes (HRAS and KRAS) identified in human cancer

More than 1% of all human genes are implicated via mutation in cancer

**Will these mutated genes provide the targets for the design of “magic bullet” cancer drugs?**

The era of targeted anti-cancer drugs begins in 1998

- **1942** Farber uses antifolates to induce remission of ALL
- **1948** FDA approves MTX
- **1951** Hitchings & Elion develop 6-MP & 6-TG
- **1953** FDA approves cyclophosphamide
- **1957** Fein shows that post-surgery chemotherapy improves cure rate
- **1959** FDA approves paclitaxel for ovarian cancer
- **1965** FDA approves imatinib for CML
- **1972** FDA approves trastuzumab for HER2 positive metastatic breast cancer
- **1998** FDA approves cetuximab for colon cancer
- **2001** FDA approves gefitinib for lung cancer
- **2003** FDA approves bevacizumab for ovarian cancer
- **2004** FDA approves erlotinib for non-small cell lung cancer

- **Conventional cytotoxic**
- **Molecularly targeted**

*COSMIC v72*
Cancer chemotherapy: two general classes of drugs

**Conventional cytotoxic drugs**
- Target DNA replication, cell division
- Gemcitabine, 5-FU, paclitaxel, oxaliplatin

**Signal targeted drugs**
- Target "defective" proteins in cell signaling
- Herceptin, Gleevec, Tarceva, Zelboraf

The cancer cell never "sleeps"

I have good news and I have bad news

First, the good news…
Herceptin targets HER2 overexpressing breast cancers

Normal breast cells with low levels of the HER2 protein

Breast cancer cells overexpress HER2, leading to uncontrolled growth

Herceptin antibody blocks HER2 function and blocks growth

Since Herceptin in 1998, 33 additional signaling targeted cancer drugs have reached the cancer patient

Progress has been significant
And now the bad news…

The cancer cell is a formidable enemy: built to survive
FDA approval of vemurafenib (Zelboraf) for the treatment of late-stage melanoma in 2011

One of our best success stories in the development of targeted therapies for cancer treatment – but…

Initial rapid response to vemurafenib treatment of BRAF-mutant malignant melanoma is followed by rapid recurrence

38 year old male with metastatic melanoma, subcutaneous metastatic deposits

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)

Cancer sites

Pancreatic cancer chemotherapy

- 5-FU was superior to best supportive care
- Gemcitabine superior to 5-FU with a median survival of 5.65 months as compared to 4.41 months and 1-year survival of 18% versus 2%
- Gemcitabine plus erlotinib versus gemcitabine alone with improved median survival of 6.4 months versus 5.9 months and 1-year survival of 26% versus 20%
- FOLFIRINOX versus gemcitabine with improved median survival of 11.1 months versus 6.8 months and 1-year survival of 36% versus 17%; FOLFIRINOX with greater toxicity but significantly reduced quality of life impairment compared with gemcitabine
- Gemcitabine plus nab-paclitaxel versus gemcitabine alone with improved median survival of 8.5 months versus 6.7 months and rate of 1-year survival (35% versus 22%), but rates of peripheral neuropathy and myelosuppression were increased


Anti-cancer drug discovery

Not for the faint of heart
Fighting pancreatic cancer: “a humbling disease”*

*Dr. Anirban Maitra
MD Anderson Cancer Center
Chair of the Pancreatic Cancer Action Network’s Scientific Advisory Board

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
Drug discovery: 1 in 5,000 odds of success

- **Research & Preclinical Testing**: 6.5 years
  - Assess biological activity
  - 5,000 compounds evaluated

- **Clinical Trials Phases I - III**: 7 years
  - Anticancer activity & toxicity
  - 5 enter trials

- **FDA & Phase IV**: 1.5 years
  - Review & approval, evaluation of long term effects
  - 1 approved

Source: Regulatory and Scientific Affairs, PhRMA

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Development of 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 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 – FDA approves STI571/Gleevec for CML treatment
2001 – Larger study confirms earlier findings
2002 – FDA approves STI571/Gleevec for GIST treatment

19 years from target discovery to getting a drug approved

The fundamental problem with all cancer therapy

We have no magic or smart bullet drugs; our normal cells are innocent bystanders
Genetics of human diseases (NOT cancer): one gene, one disease

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td>Familial hypercholesterolemia</td>
<td>1 in 500</td>
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<tr>
<td>Polycystic kidney disease</td>
<td>1 in 1250</td>
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<tr>
<td>Neurofibromatosis type I</td>
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<td>Huntington's disease</td>
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<td>Sickle cell anaemia</td>
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<td>Cystic fibrosis</td>
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<td>lysosomal acid lipase deficiency</td>
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<td>Galactosemia</td>
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<td>Duchenne muscular dystrophy</td>
<td>1 in 7,000</td>
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<tr>
<td>Hemophilia</td>
<td>1 in 10,000</td>
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Over 4,000 human diseases are caused by single gene defects. Cancer is not so simple

Cancers arise through mutations in many genes: it’s complicated

KRAS – will this be the key to a breakthrough in pancreatic cancer treatment?

What is KRAS?

The KRAS protein: “The beating heart of cancer”
I have good news and I have bad news

First, the good news…

KRAS mutations are found in the major pancreatic cancer type

- Neuroendocrine tumors (<5%) – also called islet cell or endocrine tumors
- Exocrine tumors (>95%) – primarily adenocarcinomas

- KRAS mutations are found in adenocarcinomas
Mutation of the KRAS gene: the gatekeeper of pancreatic cancer development

KRAS mutations are found in nearly 100% of pancreatic cancers

Nearly every pancreatic cancer may benefit from a KRAS drug

Researchers have shown that if we can “Kill KRAS”, the pancreatic cancer will stop growing

K-Ras4B protein
And now the bad news…

What does KRAS do? Why is it broken in cancer cells?

- KRAS is a signaling “on-off” switch
- The switch is stuck in the on position in cancer
In search of drugs to turn off KRAS

We have known since 1988 that essentially every exocrine pancreatic cancer has a KRAS gene mutation

“Twenty-one out of 22 carcinomas of the exocrine pancreas contained c-K-ras genes with mutations. We conclude…that c-K-ras…is a critical event …in most, if not all, human cancers of the exocrine pancreas.”

Why hasn’t anything been done about this?
The problem – is KRAS is undruggable?

Despite more than three decades of intense effort by academic and pharmaceutical research labs, we have failed to develop an effective KRAS drug – Why?

“Know your enemy” - Sun Tzu

“If you do not know your enemies nor yourself, you will be imperiled in every single battle”
We have underestimated the complexities of KRAS

We have had misconceptions, we have had missteps

An example of the heartbreak of KRAS drug discovery
Development of farnesyltransferase inhibitors as anti-Ras inhibitors

Identification of mutated Ras in human tumors
1982
FTase identified as a target for anti-Ras development
1990
FTIs block H-Ras-transformed cells in culture
1993
FTIs cause H-Ras mammary tumor regression in mice
1995
Phase I clinical trials
1999
Phase II clinical trials
2000
Phase III clinical trials
2002

Farnesyltransferase inhibitor causes tumor regression in HRAS-driven mouse model of breast cancer
FTIs are not effective against KRAS-mutant pancreatic cancers


Mistake? We studied the “wrong” RAS protein

- We made an HRAS drug that did not work on KRAS
- Researchers are now focused on KRAS
Many reached an erroneous conclusion from this failure, that KRAS is not a good target.
“I’ll be back”

2013 – Ras is back!

NCI Ras “Megaproject” is announced in 2013

Frederick National Laboratory for Cancer Research

NCI Ras Initiative
National Advisor: Frank McCormick, PhD
CEO: David C. Heimbrook, PhD
Leidos Biomedical Research

Scientific Framework for Pancreatic Ductal Adenocarcinoma (PDAC)
February 2014

High Level Recommendations
1. PDAC and diabetes mellitus
2. Biomarkers for early detection of PDAC
3. KRAS-specific therapies
4. Immunotherapy


A Ras research frenzy has begun

Do we know the “enemy” now?

Are we ready to go into battle?

Will we succeed in making an effective anti-KRAS drug for pancreatic cancer?

“The future ain't what it used to be.”
– Yogi Berra

“There are far, far better things ahead than any we leave behind.”
– C.S. Lewis

“Do not dwell in the past, do not dream of the future, concentrate the mind on the present moment.”
– Buddha
Nearly 100% of pancreatic cancers have a KRAS gene mutation

Pancreatic cancer is a very heterogeneous genetic disease

Multiple anti-KRAS therapies for different patient populations

KRAS normal

“One size [KRAS drug] will not fit all”

Pancreatic cancer researchers are cautiously optimistic that the time is now for a breakthrough, that KRAS will be defeated

The incredible dedication, passion and effort by advocates has made a significant impact on research and progress
Pancreatic cancer: better awareness is needed

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
Sarcoidosis
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
40 purple causes!


Raising awareness with our legislators
An increase in the number of NCI-funded pancreatic cancer investigators

More researchers, more talent, will translate to faster progress
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<tr>
<th>Lab</th>
<th>Collaborators</th>
<th>Support</th>
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<tr>
<td>Nicole Baker</td>
<td>Adrienne Cox, PhD</td>
<td>Pancreatic Cancer Action Network</td>
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<td>Devon Blake</td>
<td>Jen Jen Yeh, MD</td>
<td>CURE - Pancreatic Cancer Research Foundation</td>
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<td>Kirsten Bryant</td>
<td>Chris Counter, PhD</td>
<td>National Cancer Institute</td>
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<td>Daniel Zeitouni</td>
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Thank you for your participation.

If you have questions, please contact Patient Central at (877) 272-6226 or e-mail patientcentral@pancan.org.

www.pancan.org or wagehope.org