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

June 16, 2015

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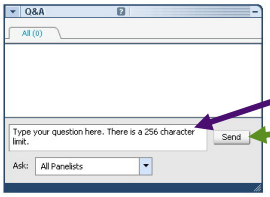

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PANCREATIC CANCER ACTION NETWORK

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

PANCREATIC CANCER ACTION NETWORK

Topics for today

WAGE HOPE

- 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

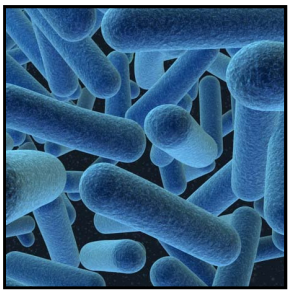
No magic or smart bullet drugs;
our normal cells are innocent bystanders

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.

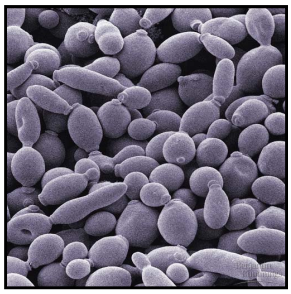
"Father of Chemotherapy"

Paul Ehrlich

We have "magic bullet" drugs for diseases caused by bacteria, yeast and viruses



Bacteria



Yeast

Viruses

Foreign invaders

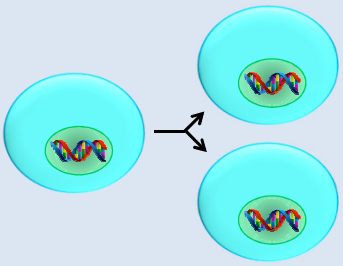
Genes going to the dark side

Cancer is a genetic disease: when good genes go bad

The enemy within

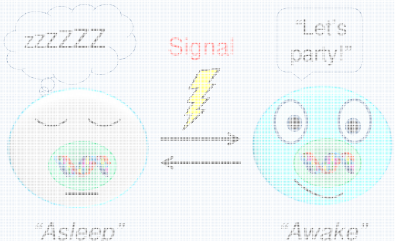
Cancer chemotherapy: two general classes of drugs

Conventional cytotoxic drugs



- Target DNA replication, cell division
- Gemcitabine, 5-FU, paclitaxel, oxaliplatin

Signal targeted drugs

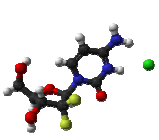


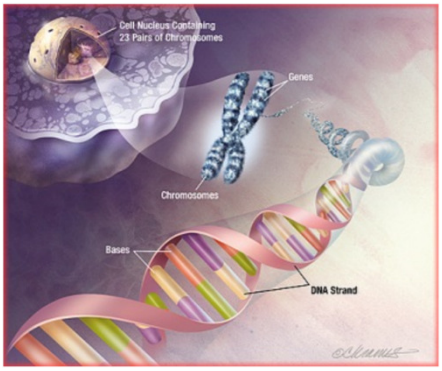
- Target "defective" proteins in cell signaling
- Herceptin, Gleevec, Tarceva, Zelboraf

Conventional anti-cancer drugs target rapidly growing cells

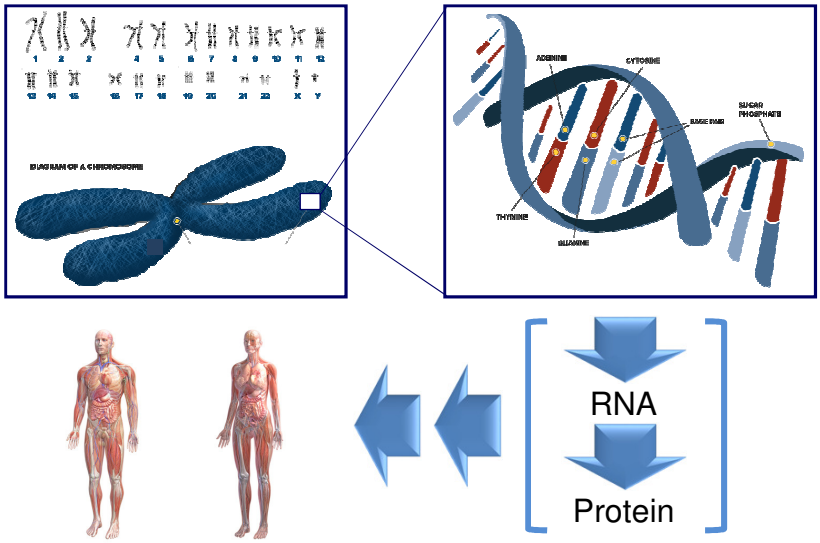
- Conventional cytotoxic anticancer drugs are NOT magic bullets. Ideally they should target only the cancer cells. However, they target proliferating cells whether normal or cancer.
- Normal cells of the hair follicles, bone marrow and intestinal epithelium are rapidly dividing and are especially sensitive 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



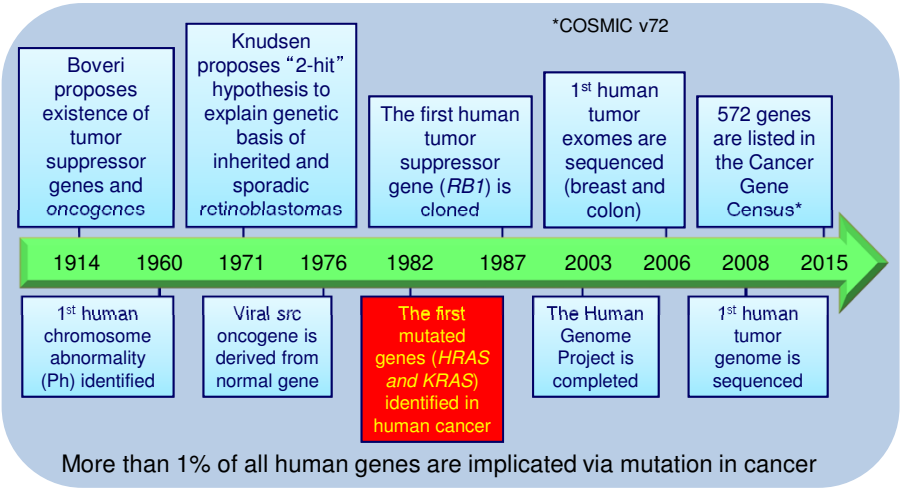
RNA

Protein

Our conventional anti-cancer drugs are poisons

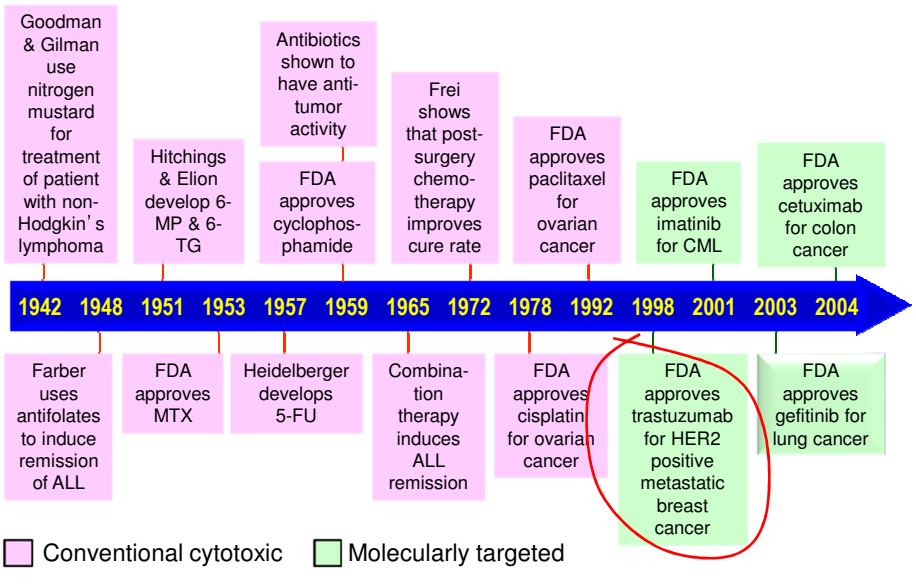
Is there a better way?

Beginning in 1982, genes mutated in cancers were discovered



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



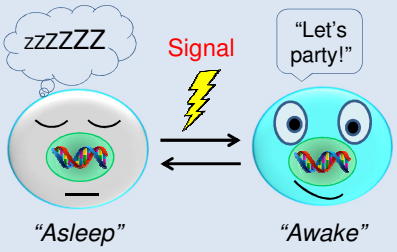
Cancer chemotherapy: two general classes of drugs

Conventional cytotoxic drugs

The cancer cell never "sleeps"

- Target DNA replication, cell division
- Gemcitabine, 5-FU, paclitaxel, oxaliplatin

Signal targeted drugs

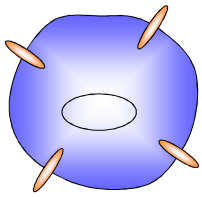


- Target "defective" proteins in cell signaling
- Herceptin, Gleevec, Tarceva, Zelboraf

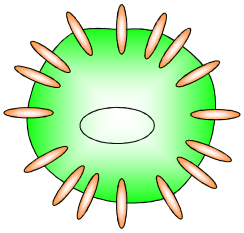
I have good news and I have bad news

First, the good news…

Herceptin targets HER2 overexpressing breast cancers

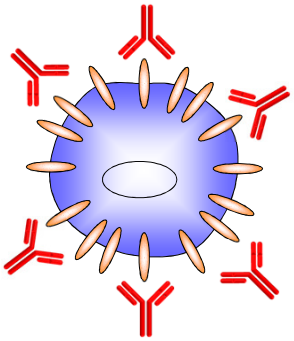


Normal breast cells with low levels of the HER2 protein



Breast cancer cells overexpress HER2, leading to uncontrolled growth

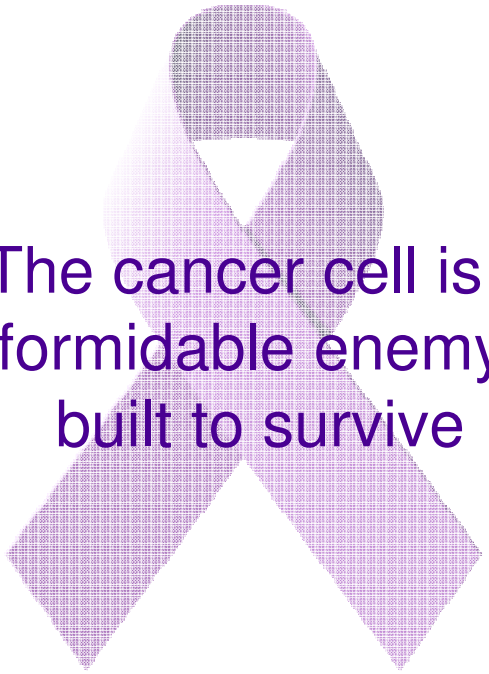
Herceptin antibody blocks HER2 function and blocks growth



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

Progress has been significant

And now the bad news…



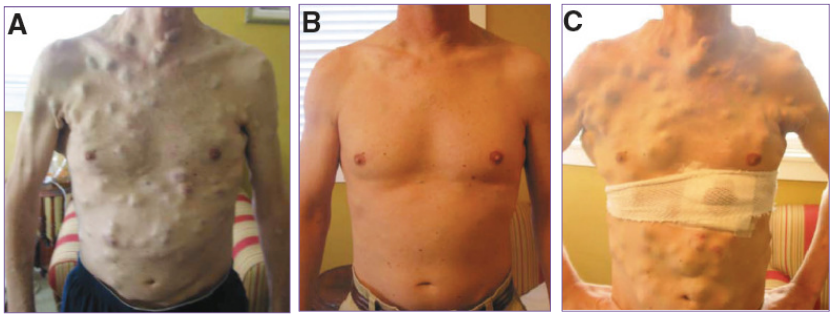
The cancer cell is a formidable enemy: built to survive

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



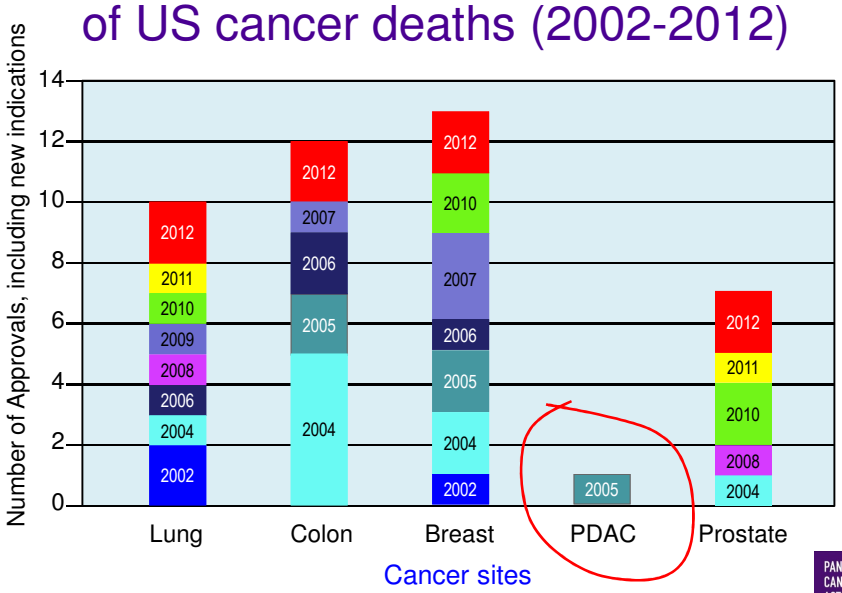
0 weeks 15 weeks 23 weeks

Wagle et al (2012) JCO 29:3085

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)



Sources: www.fda.gov , www.cancer.gov, www.pancan.org

PANCREATIC CANCER ACTION NETWORK

Pancreatic cancer chemotherapy

1970	5-FU was superior to best supportive care
1997	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%
2005	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%
2011	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
2013	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

Wolfgang et al (2013) CA Cancer J Clin 63:318

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

PhRMA 2014

Drug discovery: 1 in 5,000 odds of success

Research & Preclinical Testing	Clinical Trials Phases I - III	FDA & Phase IV
6.5 years	7 years	1.5 years
Assess biological activity	Anticancer activity & toxicity	Review & approval, evaluation of long term effects
5,000 compounds evaluated	5 enter trials	1 approved

Source: Regulatory and Scientific Affairs, PhRMA

Development of Herceptin for breast cancer treatment

1980

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

1990

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

2000

17 years from target discovery to drug approval

Development of Gleevec for leukemia treatment

1960 – Abnormal chromosome 22 (Ph) identified in CML patients

1970

1973 – Ph chromosome due to 9 and 22 translocation

1980

1982 – Abl oncogene rearrangement identified in Ph chromosome

1984 – Bcr-Abl identified as possible cause of CML

1990

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

2000

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

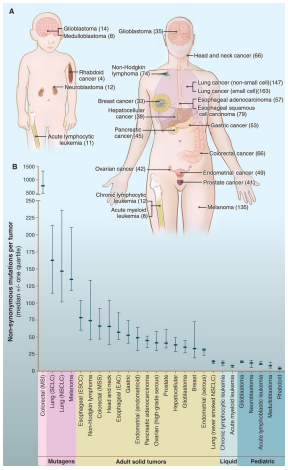
Genetics of human diseases (NOT cancer): one gene, one disease

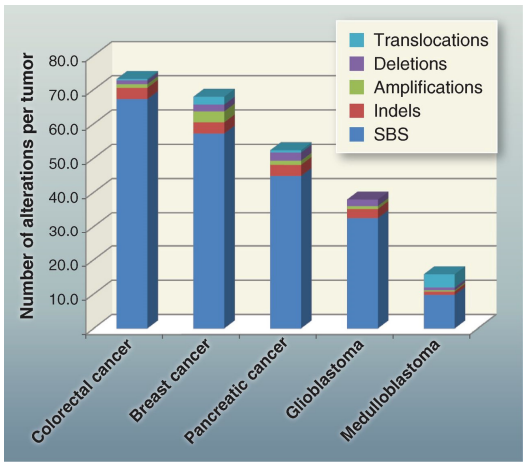
http://en.wikipedia.org/wiki/Genetic_disorder

Disorder	Prevalence
	Autosomal dominant
Familial hypercholesterolemia	1 in 500
Polycystic kidney disease	1 in 1250
Neurofibromatosis type I	1 in 2,500
Hereditary spherocytosis	1 in 5,000
Marfan syndrome	1 in 4,000
Huntington's disease	1 in 15,000
	Autosomal recessive
Sickle cell anaemia	1 in 625
Cystic fibrosis	1 in 2,000
Tay-Sachs disease	1 in 3,000
Phenylketonuria	1 in 12,000
Mucopolysaccharidoses	1 in 25,000
Lysosomal acid lipase deficiency	1 in 40,000
Glycogen storage diseases	1 in 50,000
Galactosemia	1 in 57,000
	X-linked
Duchenne muscular dystrophy	1 in 7,000
Hemophilia	1 in 10,000

Over 4,000 human diseases are caused by single gene defects.
Cancer is not so simple

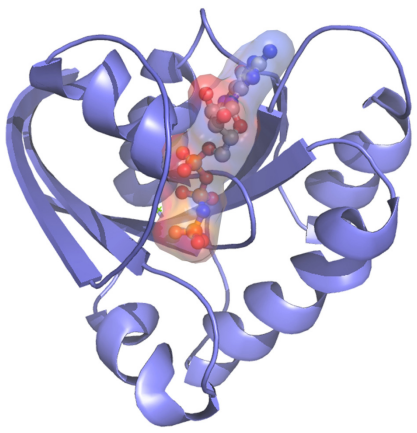
Cancers arise through mutations in many genes: it's complicated





Vogelstein et al (2013) Science 339:1546

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



What is KRAS?

The KRAS protein: “The beating heart of cancer”

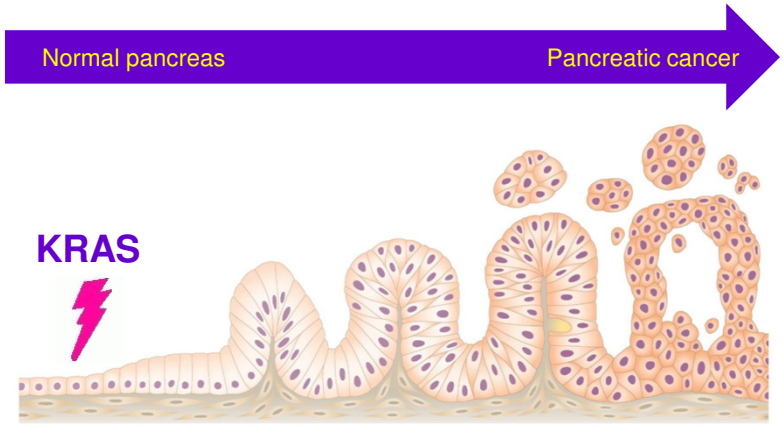
I have good news and I have bad news

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

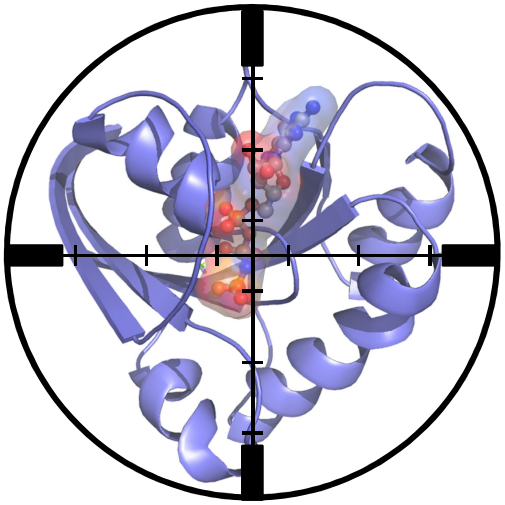


KRAS mutations are found in nearly 100% of pancreatic cancers

Biankin et al (2012) Nature 491:399

Nearly every pancreatic cancer may benefit from a KRAS drug

KRAS normal KRAS mutation

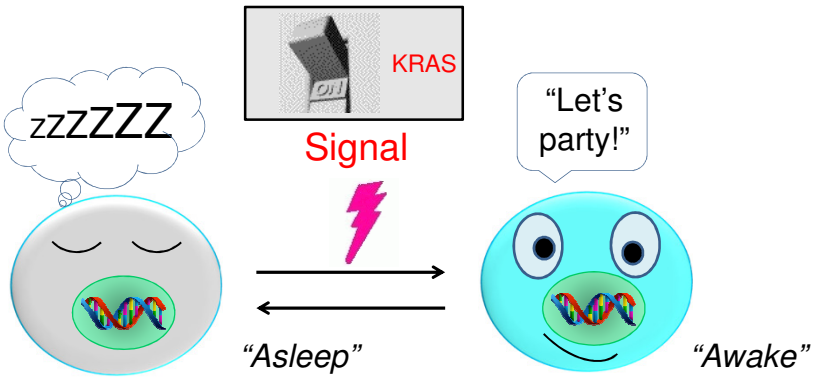


K-Ras4B protein

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

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

Cell, Vol. 53, 549–554, May 20, 1988, Copyright © 1988 by Cell Press

Most Human Carcinomas of the Exocrine Pancreas Contain Mutant c-K-*ras* Genes

Concepcion Almoguera,* Darryl Shibata,† Kathleen Forrester,* John Martin,† Norman Arnheim,‡ and Manuel Perucho*

"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?

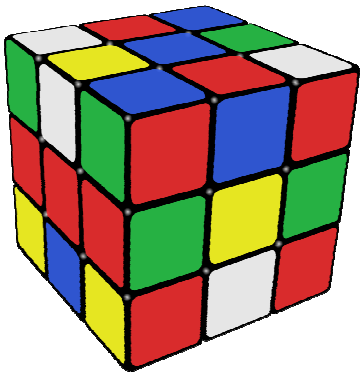
"Know your enemy" - Sun Tzu

The Art of War - a treatise on military tactics

Chinese military general, strategist, and philosopher

"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

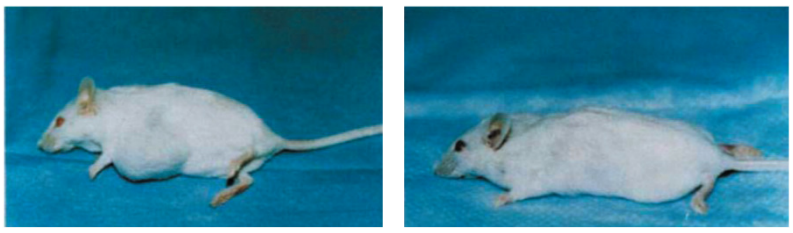
FTIs cause H-Ras mammary tumor regression in mice
1995

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



ARTICLES

Inhibition of farnesyltransferase induces regression of mammary and salivary carcinomas in *ras* transgenic mice

Nancy E. Kohl[1], Charles A. Omer[1], Michael W. Conner[2], Neville J. Anthony[3], Joseph P. Davide[1], S. Jane deSolms[3], Elizabeth A. Giuliani[3], Robert P. Gomez[1], Samuel L. Graham[3], Kelly Hamilton[1], Laurence K. Handt[4], George D. Hartman[3], Kenneth S. Koblan[1], Astrid M. Kral[1], Patricia J. Miller[1], Scott D. Mosser[1], Timothy J. O'Neill[1], Elaine Rands[1], Michael D. Schaber[1],

FTIs are not effective against *KRAS*-mutant pancreatic cancers

A phase II study of farnesyl transferase inhibitor R115777 in pancreatic cancer: a Southwest Oncology Group (SWOG 9924) study.
Macdonald et al (2005) Invest New Drugs 23:485

Phase III trial of gemcitabine plus tipifarnib compared with gemcitabine plus placebo in advanced pancreatic cancer.
Van Cutsem et al (2004) J Clin Oncol 22:1430

Phase II and pharmacodynamic study of the farnesyltransferase inhibitor R115777 as initial therapy in patients with metastatic pancreatic adenocarcinoma.
Cohen et al (2003) J Clin Oncol 21:1301

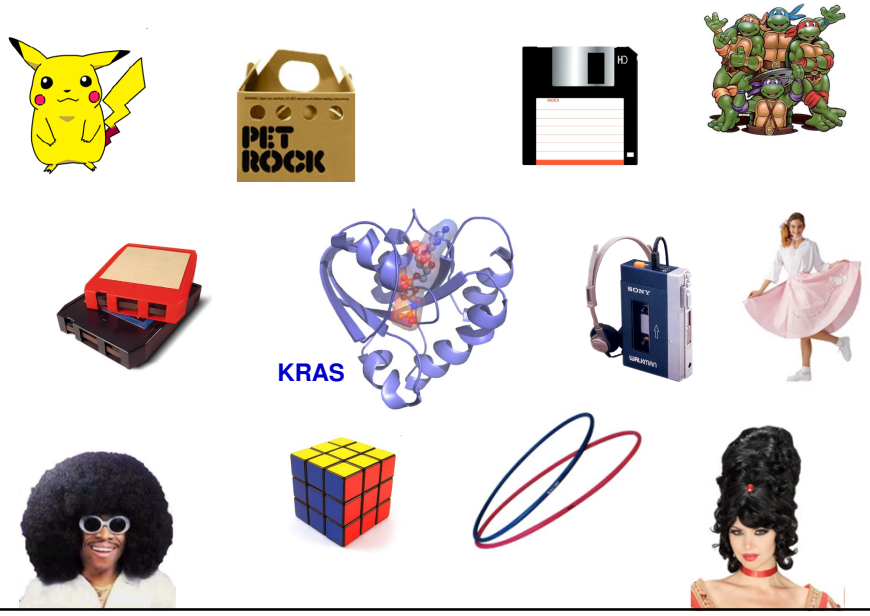
Mistake? We studied the "wrong" RAS protein

HRAS KRAS

- 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

KRAS: just another passing fad?



NCI Ras "Megaproject" is announced in 2013

http://www.cancer.gov/research/key-initiatives/ras

Thompson (2013) Nat Med 19:949

NATIONAL CANCER INSTITUTE

Scientific Framework for Pancreatic Ductal Adenocarcinoma (PDAC)

February 2014

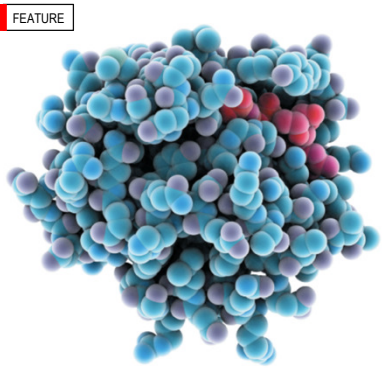
High Level Recommendations

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

http://deainfo.nci.nih.gov/advisory/ctac/workgroup/pc/pdacframework.pdf

A Ras research frenzy has begun

NEWS FEATURE



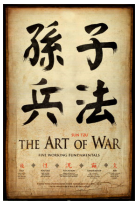
THE RAS RENAISSANCE

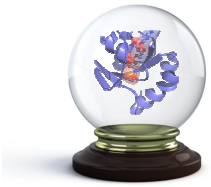
Thirty years of pursuit have failed to yield a drug to take on one of the deadliest families of cancer-causing proteins. Now some researchers are taking another shot.

Ledford (2015) Cancer: The Ras renaissance. Nature 520:278

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

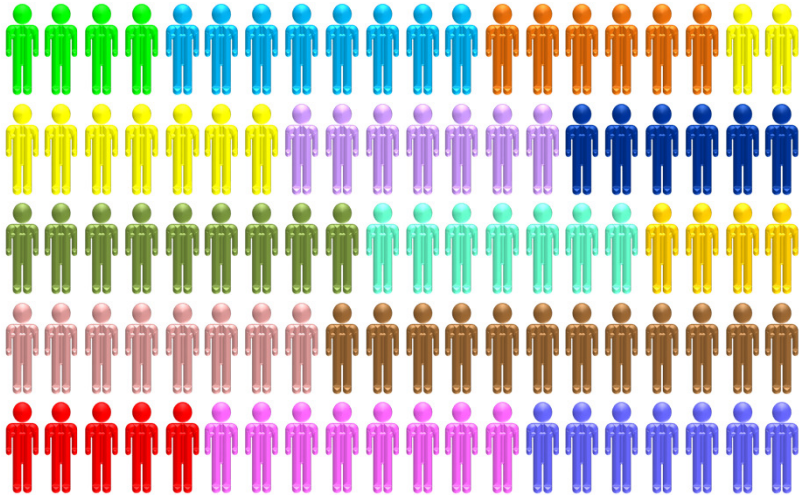
Nearly 100% of pancreatic cancers have a KRAS gene mutation

KRAS normal KRAS mutation

Pancreatic cancer is a very heterogeneous genetic disease

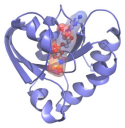
Biankin et al (2012) Nature 491:399

Multiple anti-KRAS therapies for different patient populations

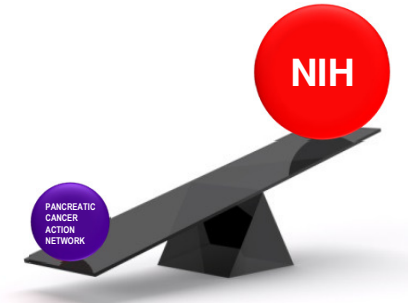


KRAS normal

"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



WAGE HOPE

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
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

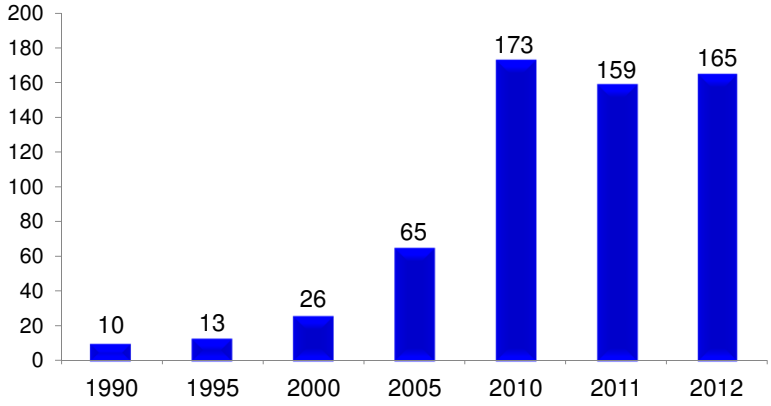
40 purple causes!

http://en.wikipedia.org/wiki/List_of_awareness_ribbons

WIKIPEDIA
The Free Encyclopedia

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

PANCREATIC CANCER ACTION NETWORK

PURPLESTRIDE
RALEIGH-DURHAM 2015

Ras researchers raise $8,954 for pancreatic cancer research

Lab

Nicole Baker
Devon Blake
Kirsten Bryant
Irem Dagliyan
Jeanne Dinh
Minh Huynh
Leanna Gentry
Tiki Hayes
Aaron Hobbs
Campbell Lawson
Swapnil Kher
Kent Rossman
Meagan Ryan
Angelina Vaseva
Kelsey Winchester
Daniel Zeitouni

Collaborators


Adrienne Cox, PhD


Jen Jen Yeh, MD


Sharon Campbell, PhD


Chris Counter, PhD


Kris Wood, PhD

Support

PANCREATIC CANCER ACTION NETWORK

CURE PANCREATIC CANCER LUSTGARTEN FOUNDATION

American Cancer Society

NATIONAL CANCER INSTITUTE

WAGE HOPE

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

PANCREATIC CANCER ACTION NETWORK