Recent Research in Pancreatic Cancer

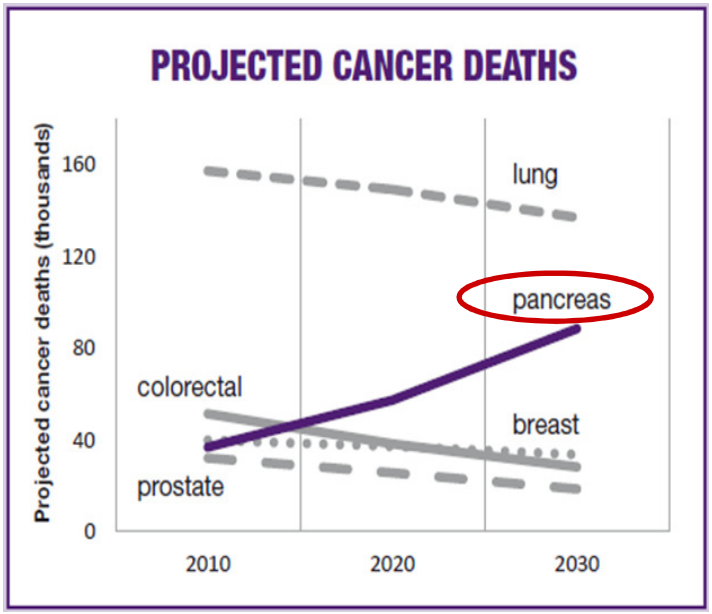
Robert Vonderheide, MD, DPhil
Associate Cancer Center Director for Translational Research
Abramson Cancer Center
University of Pennsylania
Philadelphia, PA

Abramson Cancer Center
Penn Medicine

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 Female		Male	
All Malignant Cancers	1,638,910	577,190	↓↓	-15.1	↓↓↓	-22.9
Oral Cavity & Pharynx	40,250	7,850	↓↓↓	-30.0	↓↓↓↓	-32.1
Esophagus	17,460	15,070	↓↓	-11.1	↑	5.6
Stomach	21,320	10,540	↓↓↓↓	-40.5	↓↓↓↓	-44.9
Colon and Rectum	143,460	51,690	↓↓↓↓	-33.0	↓↓↓↓	-36.0
Liver & Intrahepatic Bile Duct	28,720	20,550	↑↑↑↑	33.3	↑↑↑↑	58.5
Pancreas	43,920	37,390	↑	3.2	–	0.0
Larynx	12,360	3,650	–	0.0	↓↓↓	-30.0
Lung & Bronchus	226,160	160,340	↑	6.0	↓↓↓	-29.4
Melanoma of the skin	76,250	9,180	↓↓	-20.0	↑	7.9
Breast	229,060	39,920	↓↓↓	-32.0		
Cervix Uteri	12,710	4,220	↓↓↓↓	-35.1		
Corpus and Uterus, NOS	47,130	8,010	↓	-2.3		
Ovary	22,280	15,500	↓↓	-14.0		
Prostate	241,740	28,170			↓↓↓↓	-40.9
Urinary Bladder	73,510	14,880	↓	-8.3	↓	-5.0
Kidney & Renal Pelvis	64,770	13,570	↓	-10.7	↓	-6.5
Brain & Other Nervous System	22,910	13,700	↓↓	-12.5	↓↓	-11.7
Hodgkin Lymphoma	9,060	1,190	↓↓↓↓	-40.0	↓↓↓↓	-44.4
Non-Hodgkin Lymphoma	70,130	18,940	↓↓	-20.6	↓↓	-18.0
Myeloma	21,700	10,710	↓↓	-16.1	↓	-10.4
Leukemia	47,150	23,540	↓↓	-14.5	↓↓	-11.2

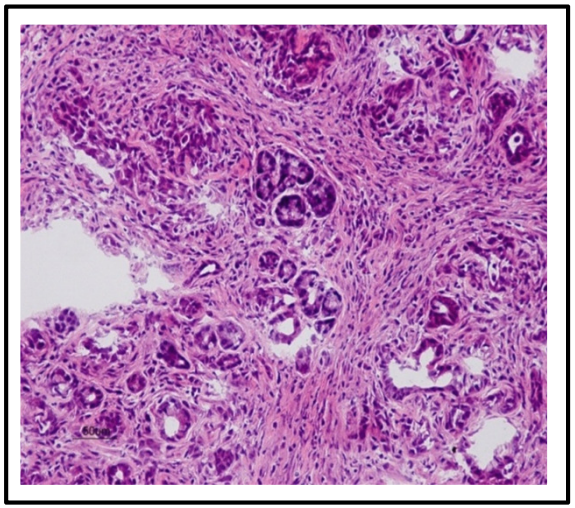
AACR Cancer Progress Report 2012



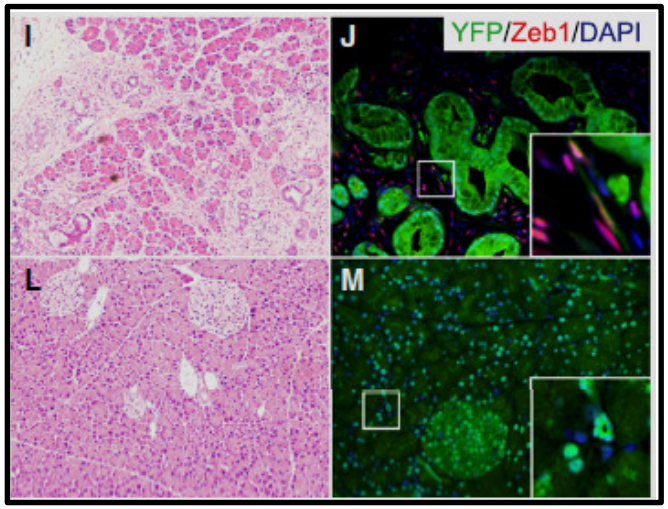
Pancreatic Cancer Action Network Report 2012

Biological challenge:
Hostile microenvironment in pancreatic cancer

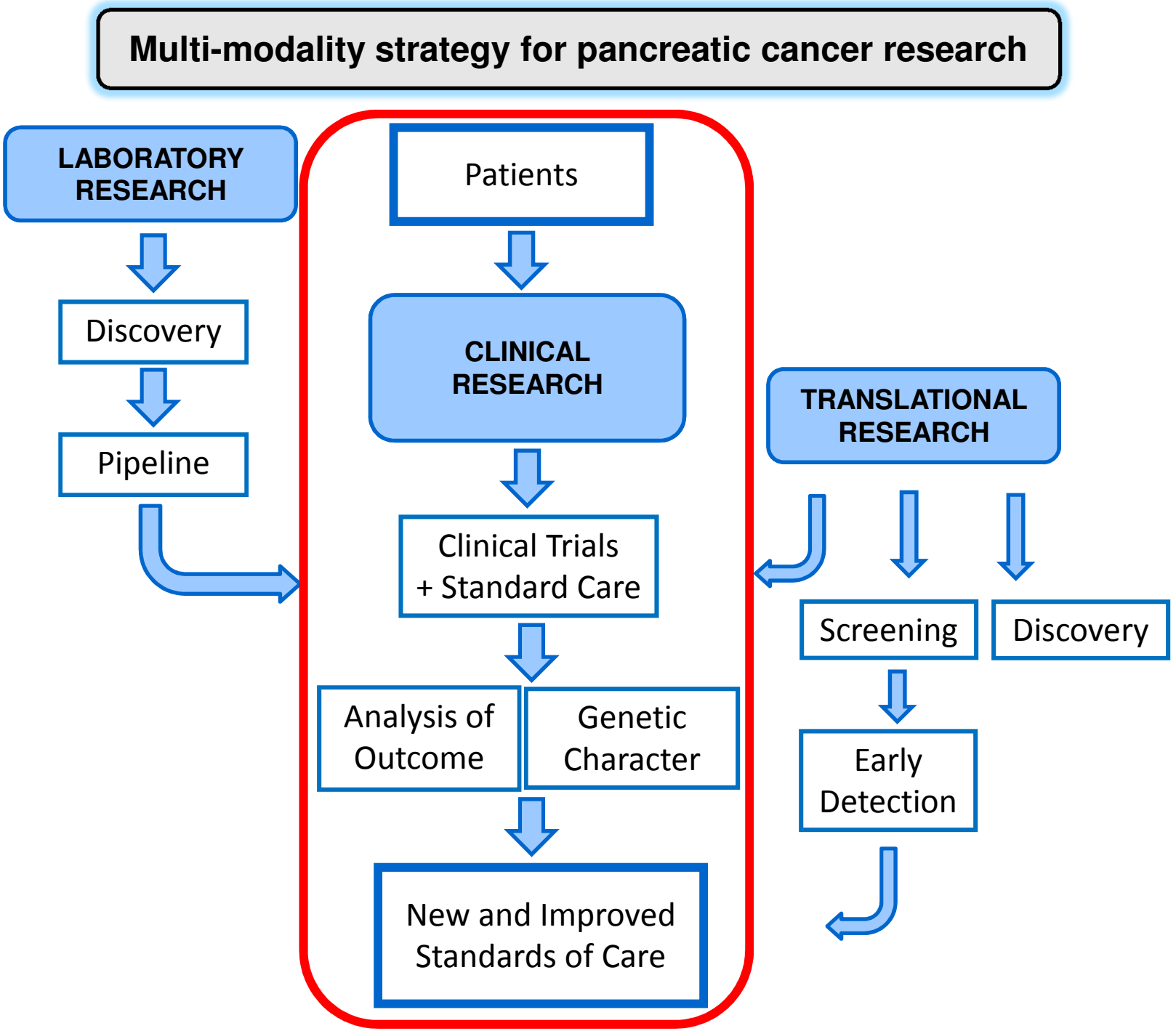
- Desmoplastic stroma and immune suppression is a pharmacological and biological barrier
- Inflammation drives oncogenesis, progression, and metastasis
- Novel genetically engineered mouse models provide a robust scientific foothold for discovery and translation



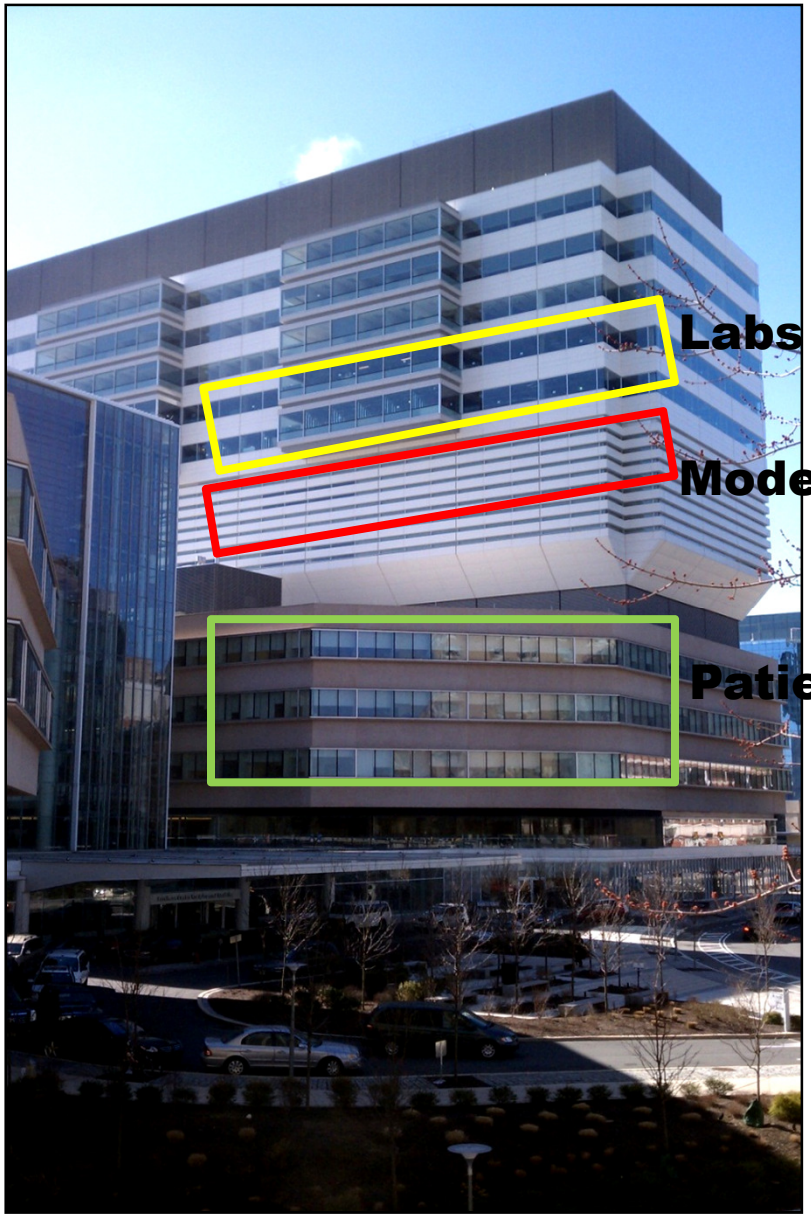
KPC mouse
Bayne et al, *Cancer Cell*, 2012

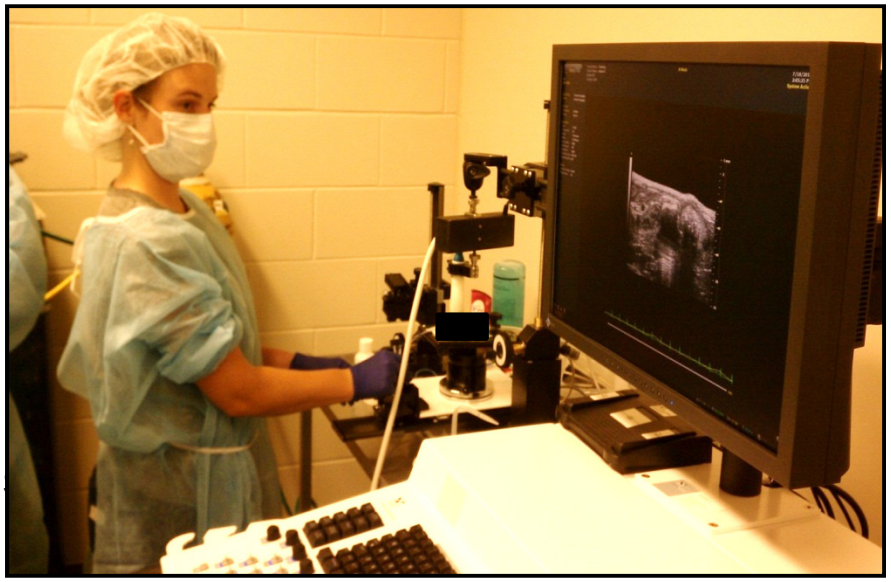


KPC-Y mouse
Rhim et al, *Cell*, 2012

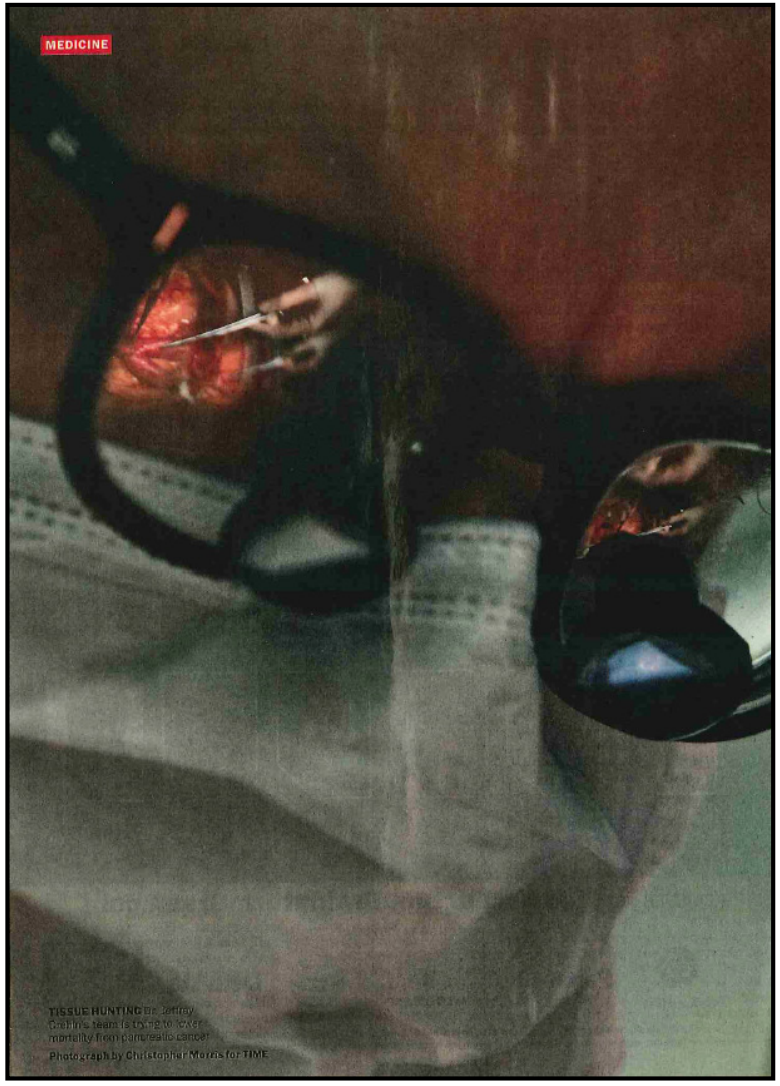

Multi-modality strategy for pancreatic cancer research
LABORATORY RESEARCH
Discovery
Pipeline
Patients
CLINICAL RESEARCH
Clinical Trials + Standard Care
Analysis of Outcome
Genetic Character
New and Improved Standards of Care
TRANSLATIONAL RESEARCH
Screening
Discovery
Early Detection

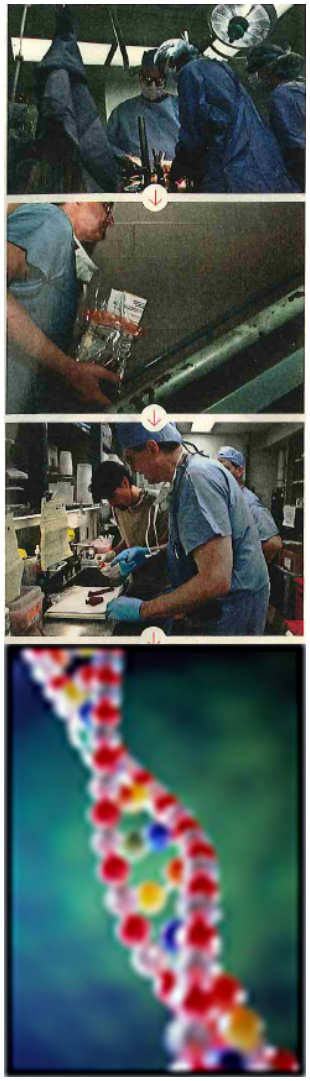
Multi-modality strategy for pancreatic cancer research

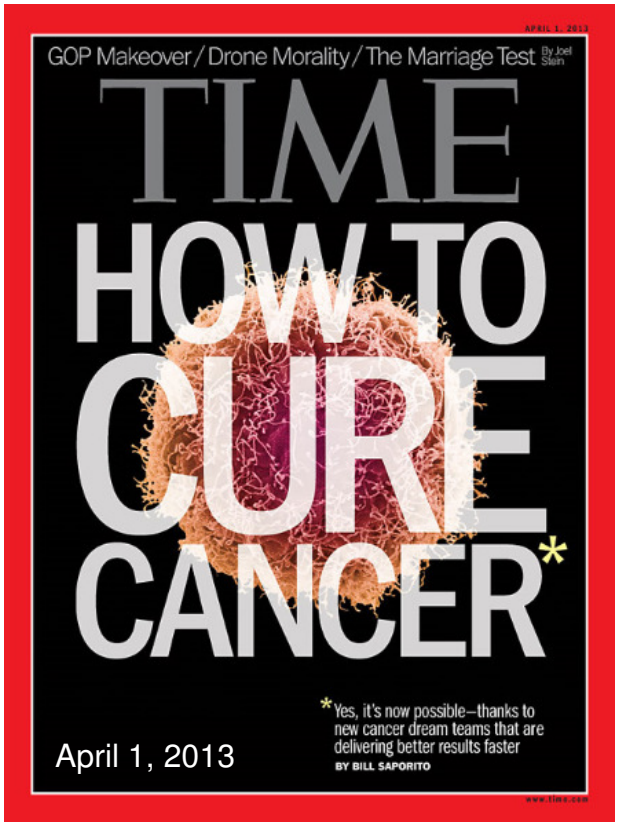




Next generation genetic sequencing of pancreatic cancer







STAND UP TO CANCER™
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Personalized diagnostics for pancreatic cancer

Expanding gene tests in cancer

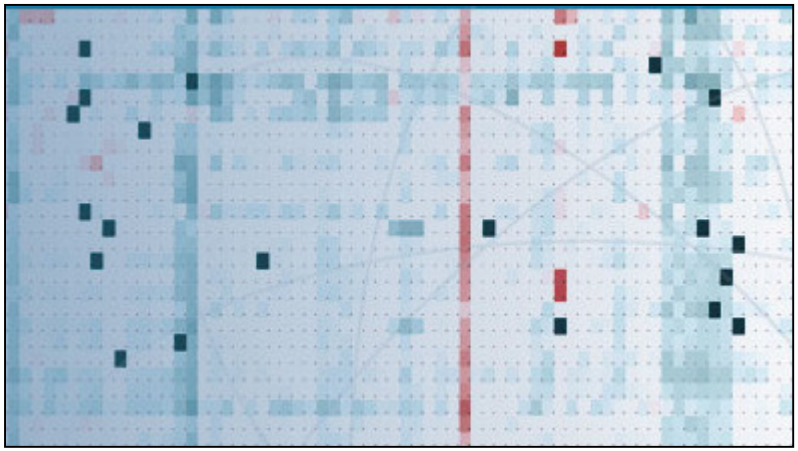
Penn's center is among those forging ahead aggressively, with an eye to tailored treatment.

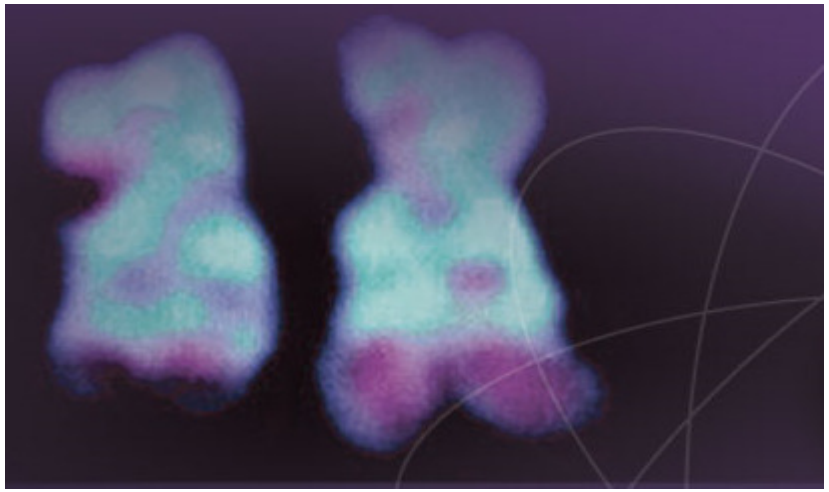
By Stacey Burling
INQUIRER STAFF WRITER

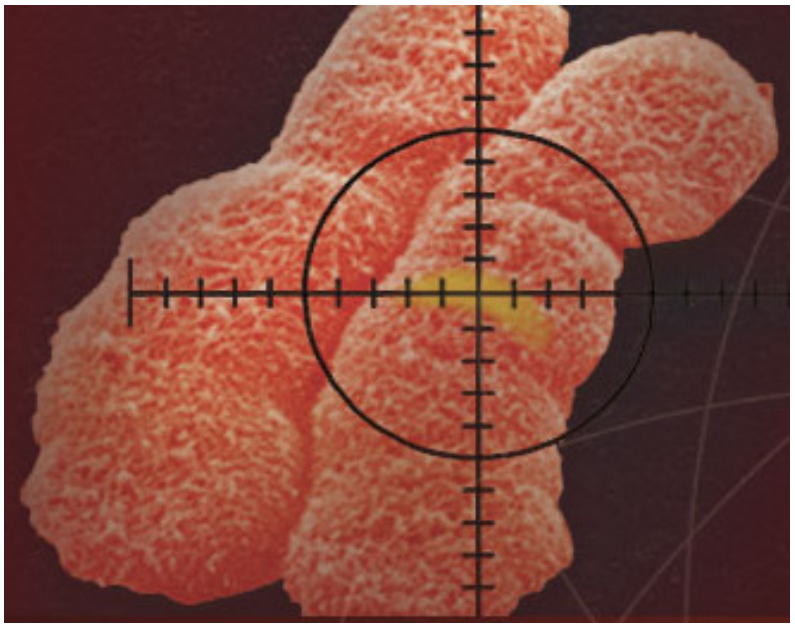
The University of Pennsylvania's Abramson Cancer Center has raised its bet that the future of cancer treatment lies in our genes.

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



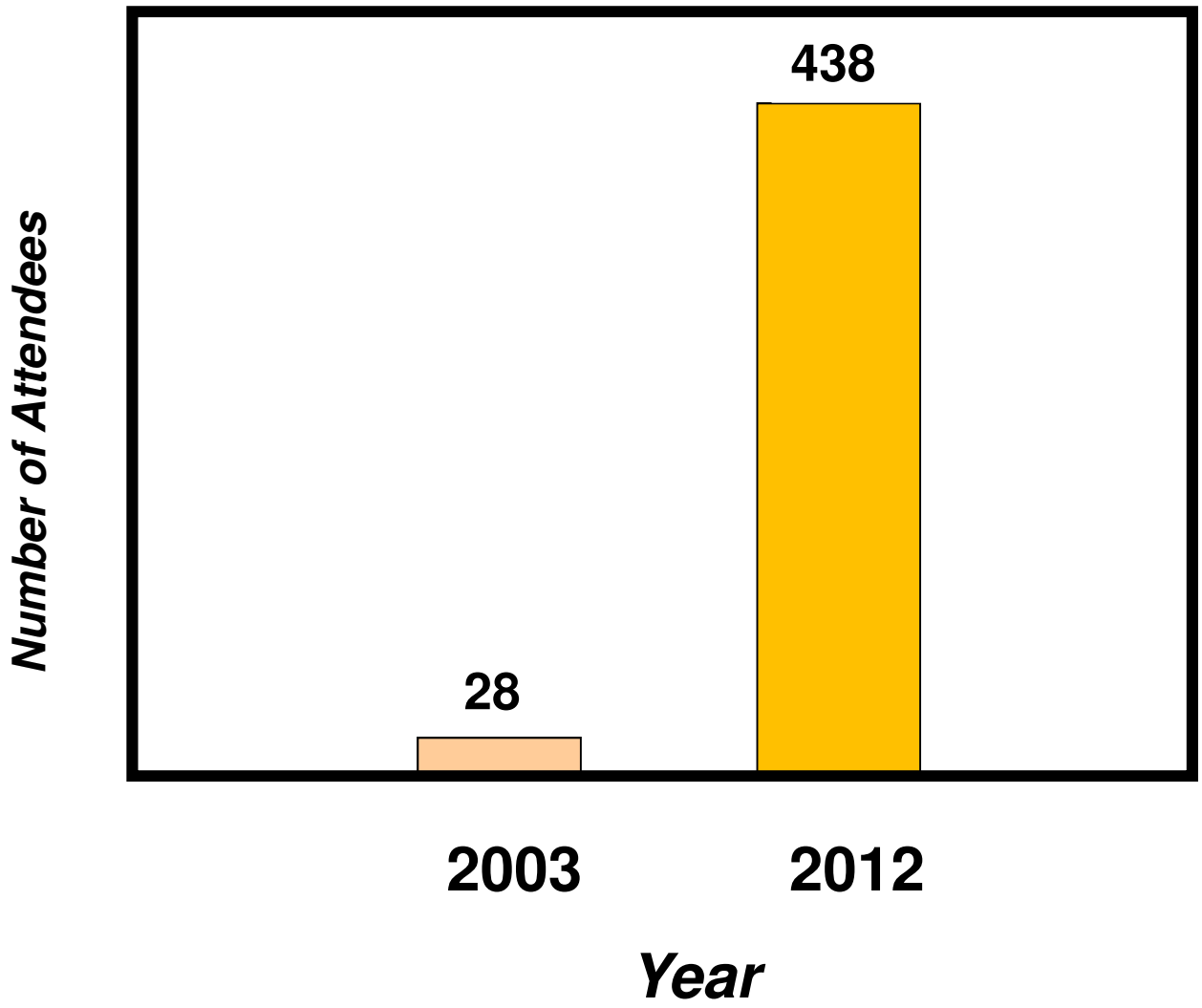




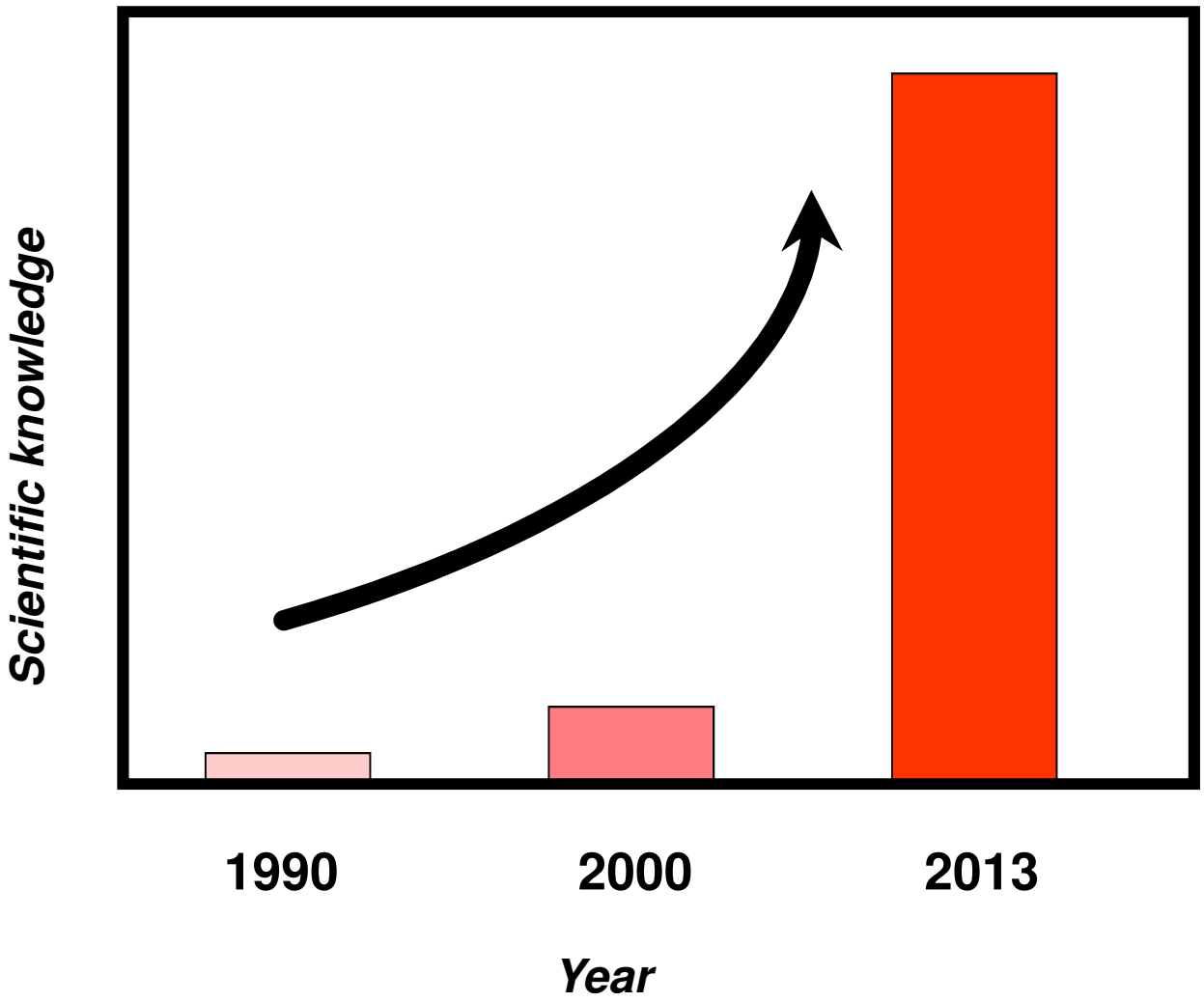
Personalized care in pancreatic cancer

Comprehensive molecular and clinical profile

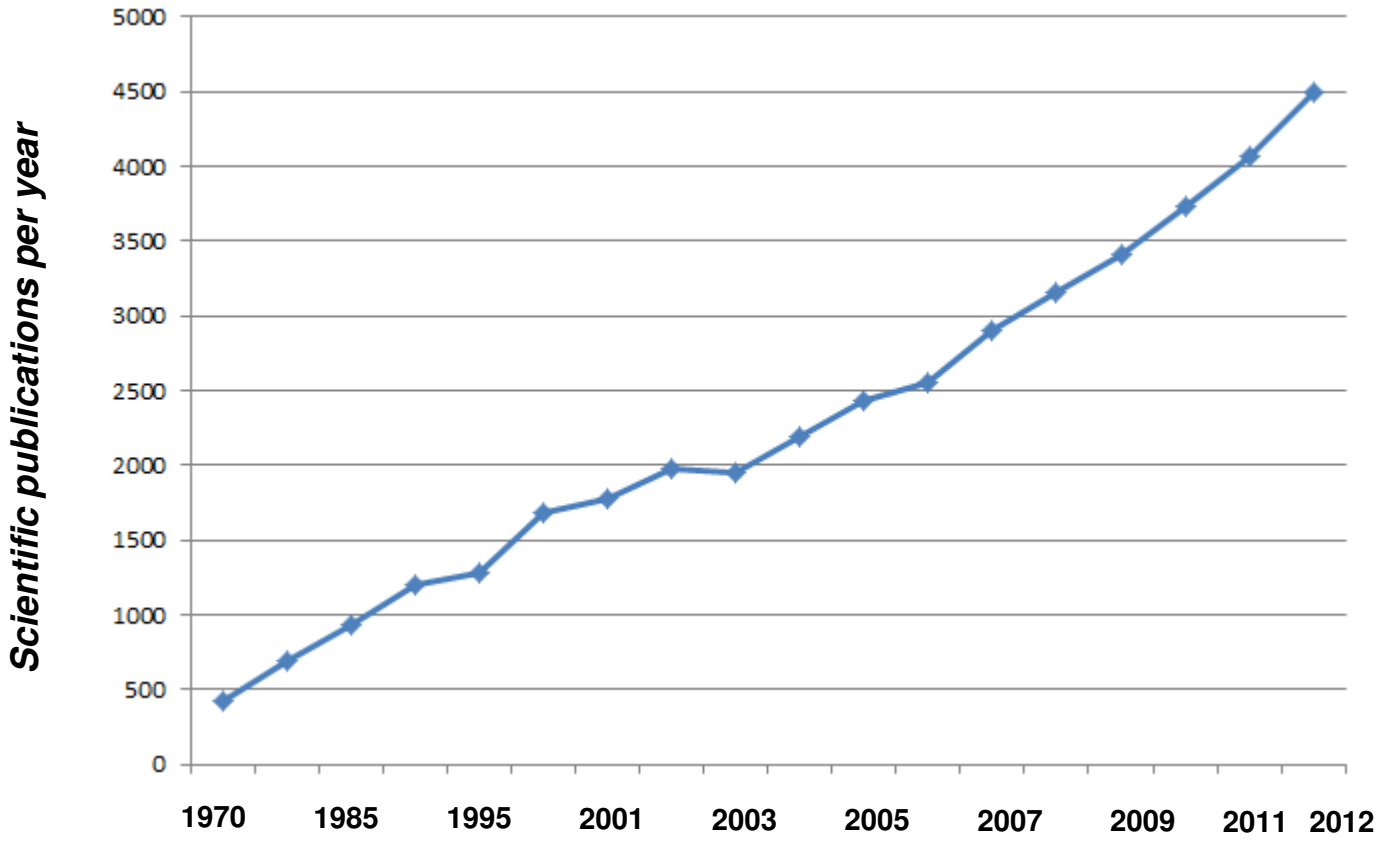
Attendance at a national scientific meeting on pancreatic cancer



What we know about pancreatic cancer



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



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

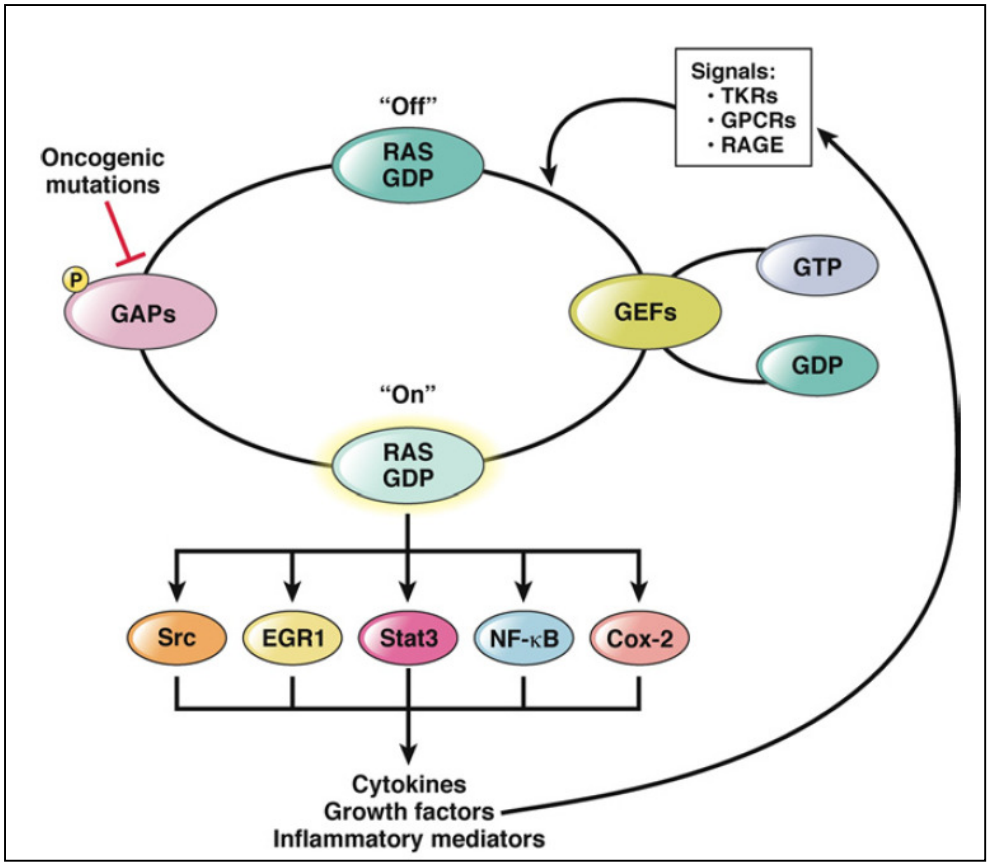
Ruxolitinib and chemotherapy for pancreatic cancer

- 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)

Mutant Kras oncogene

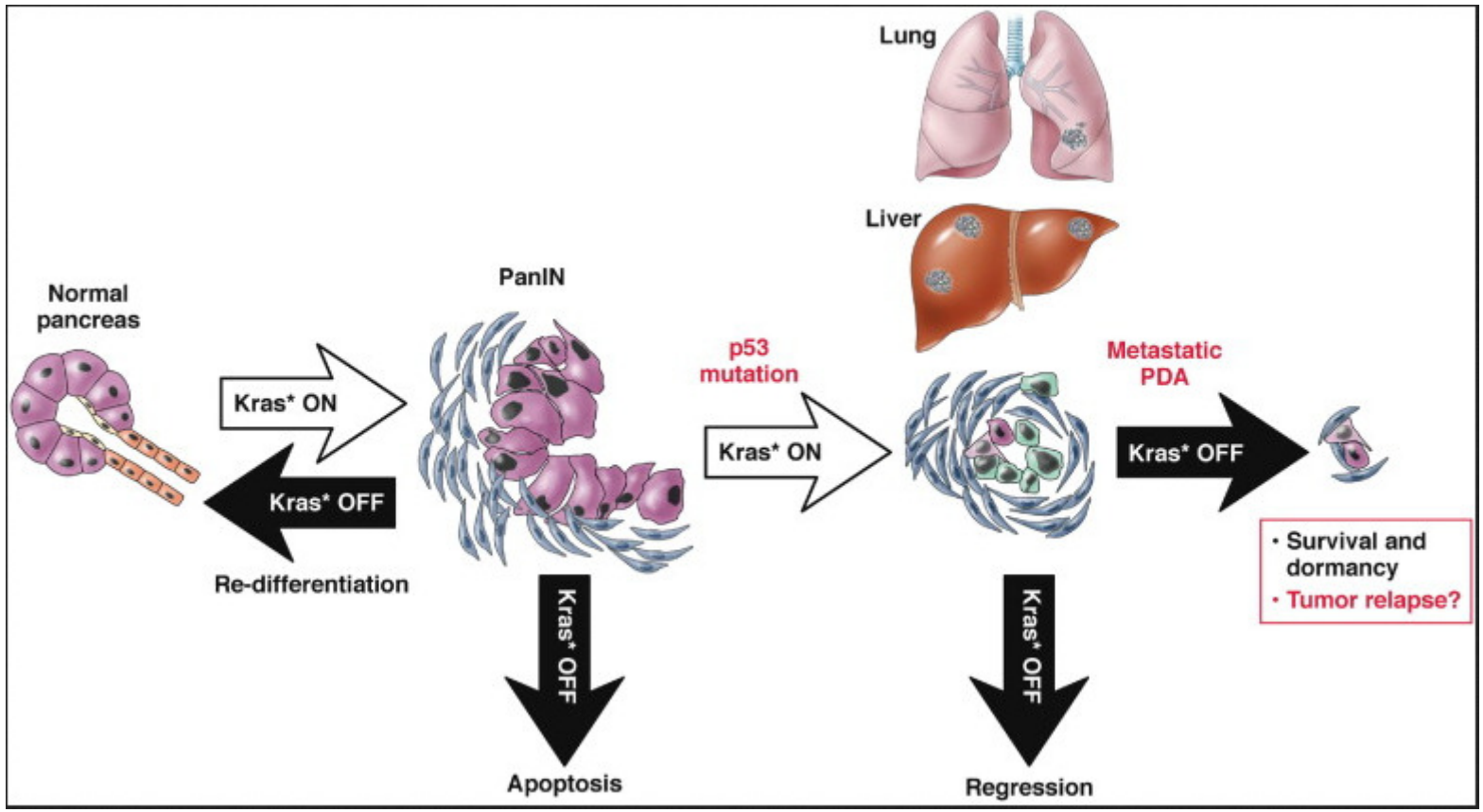
- More than 95% of all patients with pancreatic ductal adenocarcinoma have mutations in Kras in the tumor
- There are cooperating mutations but no other common ‘driver’ mutations

Biakin et al, Nature, 2012



Pasca di Magliano and Logsdon, Gastroenterology, 2013

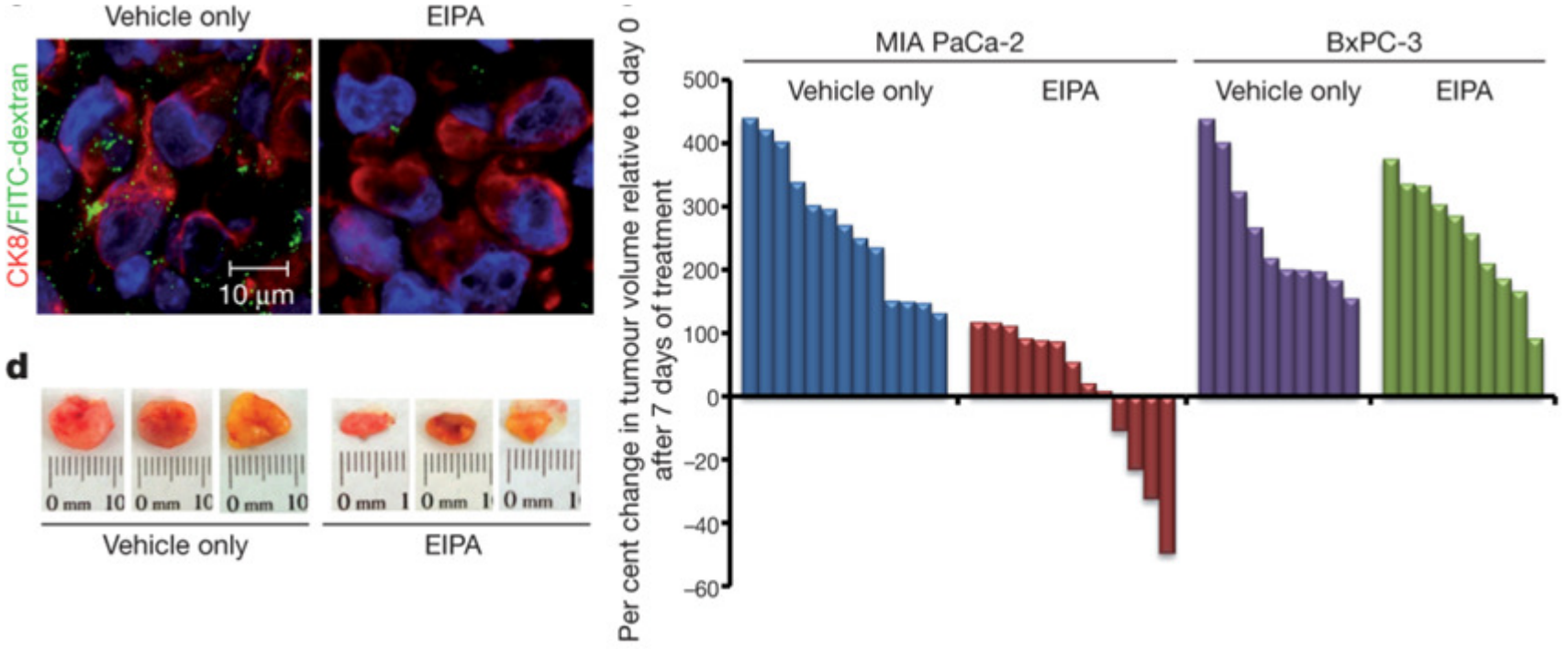
Tumor growth depends on mutant Kras ‘oncogene’



Pasca di Magliano and Logsdon, Gastroenterology, 2013
See also,
Collins et al, J Clin Invest, 2011
Ying et al, Cell, 2012

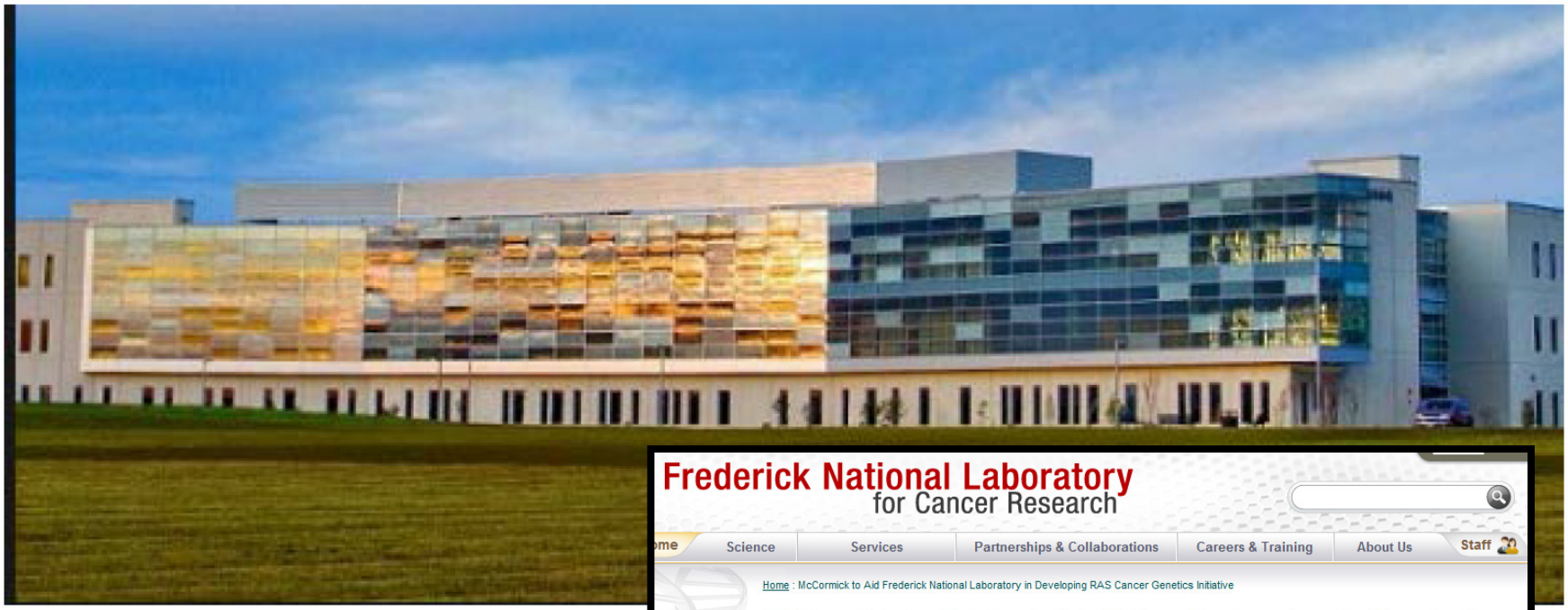
Mutant Kras also drives tumor cell ‘appetite’

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



Commisso et al, Nature, 2013

‘Project Ras’



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

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 SAIC-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 SAIC-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 derail this stubborn and long-known driver of many cancers, including those of the pancreas, colon, and lung.

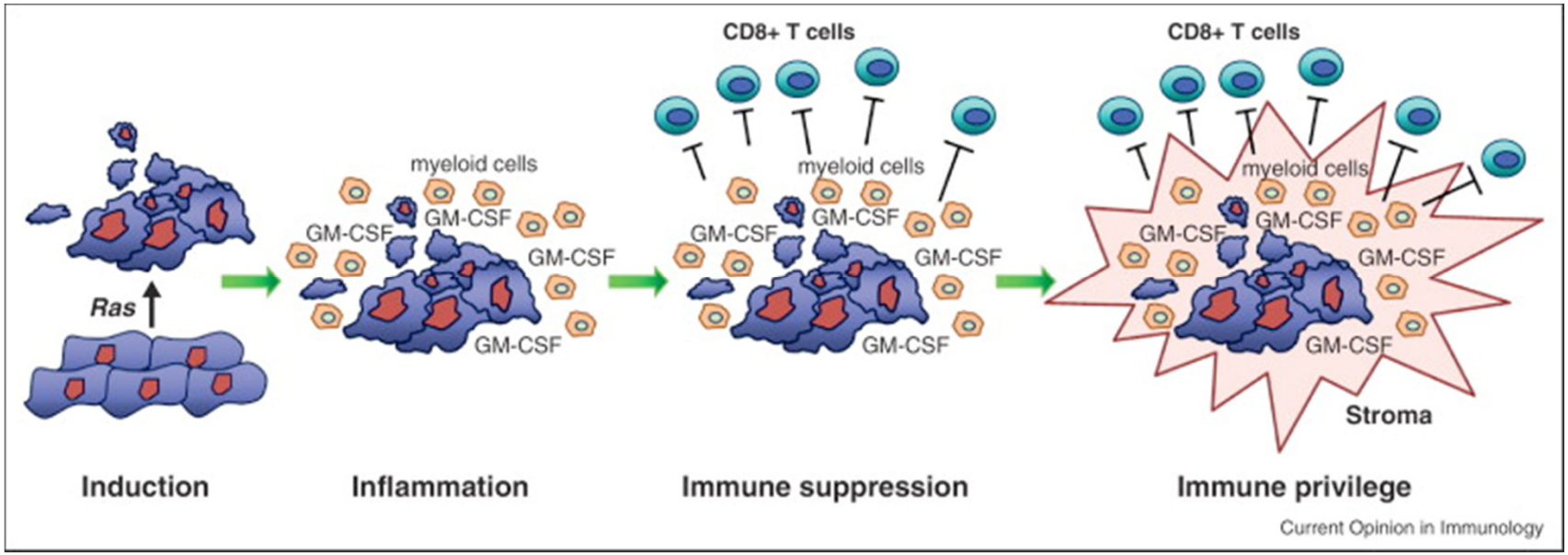
In an April 8 address to a plenary session of AACR’s annual meeting in Washington, D.C., NCI Director Harold Varmus, M.D., said his vision is to “finally after 30 years learn how to target the cancer cells that exist in somewhere around a quarter of all human tumors that are driven by mutations in RAS”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

Photo courtesy of Frank McCormick

http://deainfo.nci.nih.gov/advisory/ncab/165_0613/McCormick.pdf

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)

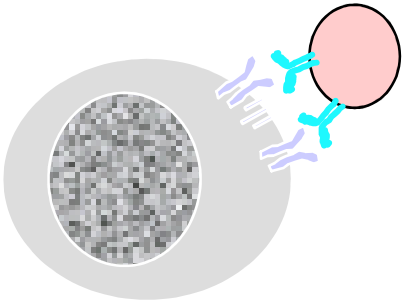


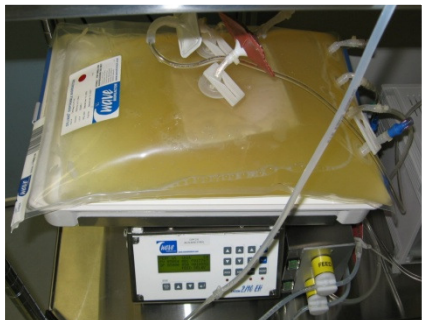
Bayne and Vonderheide, Curr Opin Immunol, 2013

Engineered T cell therapy for cancer

1. Remove the immune cells from blood

2. Engineer killer lymphocytes in our clinical laboratory



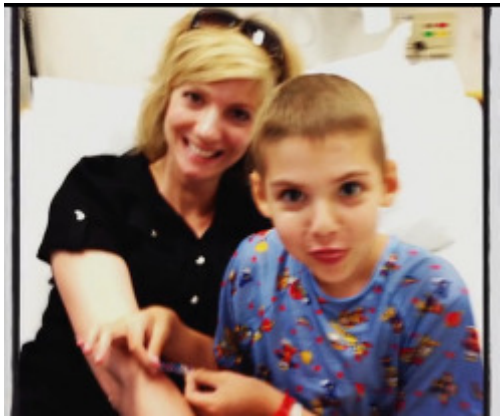


3. Prepare cells for re-infusion

+ chemotherapy

4. Give patient engineered T cells

Porter et al, NEJM, 2011



SHARE YOUR STORY

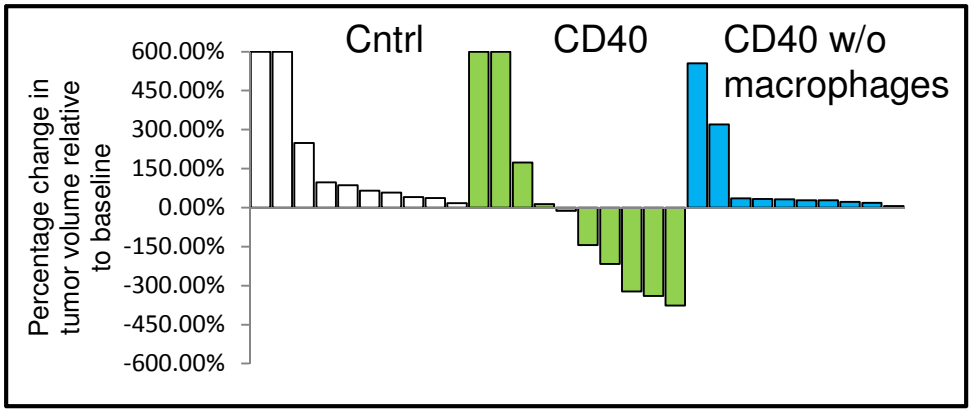
Curing Cancer: The Philadelphia Award and Dr. Carl June

from **Rich Tolsma Productions** PRO 3 months ago NOT YET RATED

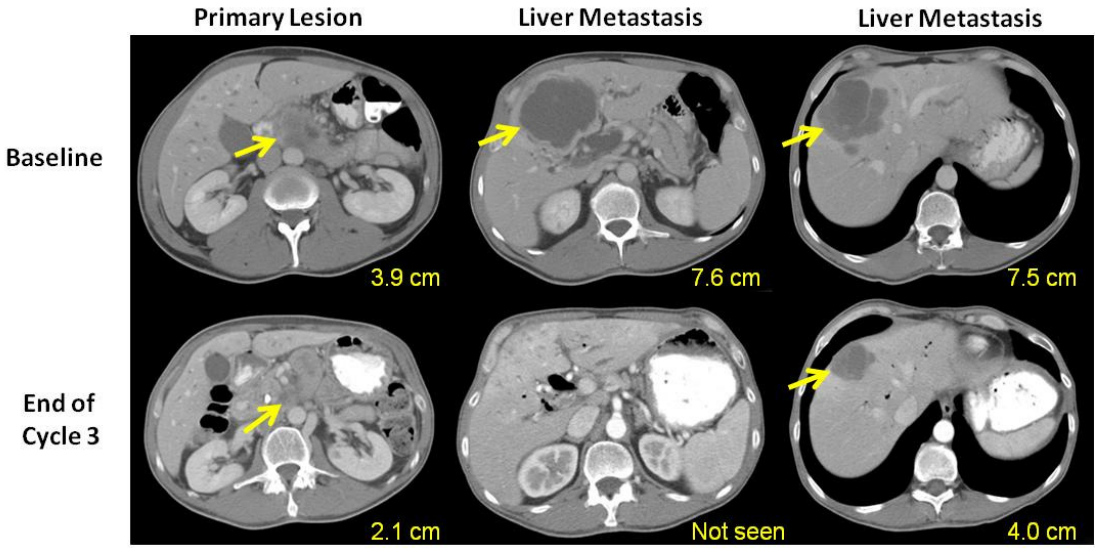
This year the prestigious Philadelphia Award honored Penn Medicine's Dr. Carl June for his breakthrough work in curing leukemia in a number of patients. He and his team have developed a process that involves genetically engineering the patient's immune system that holds promise for curing many types 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



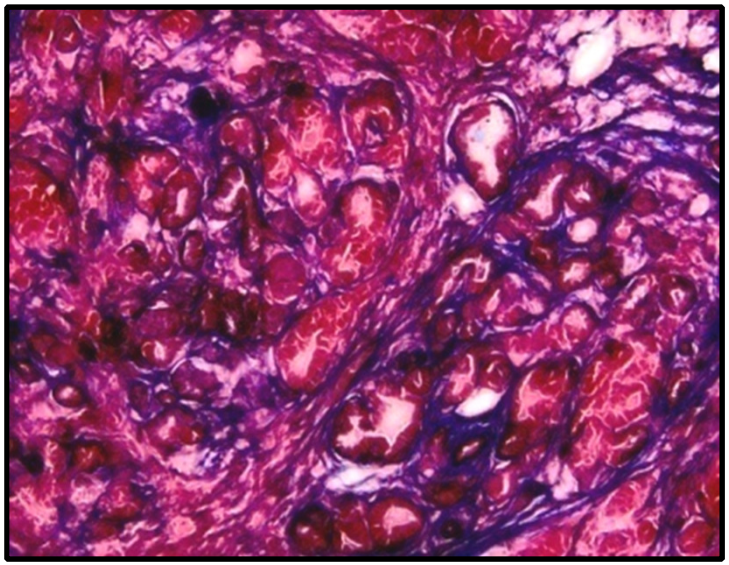
Major and durable tumor regressions in metastatic patients receiving CD40 mAb and gemcitabine

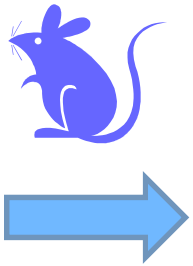


Beatty GL et al, Science, 2011

CD40 antibody as immune therapy for pancreatic cancer

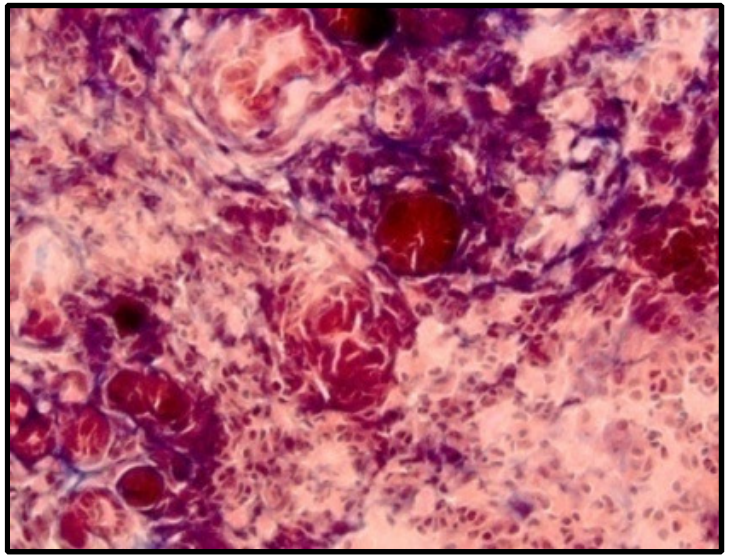
Before treatment





CD40 immune activation

After treatment



Beatty et al, Science, 2011

Research
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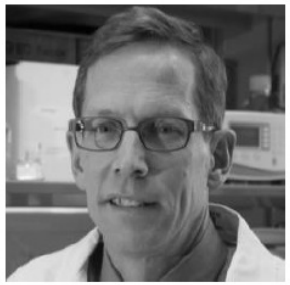
GRANT SNAPSHOT

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

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



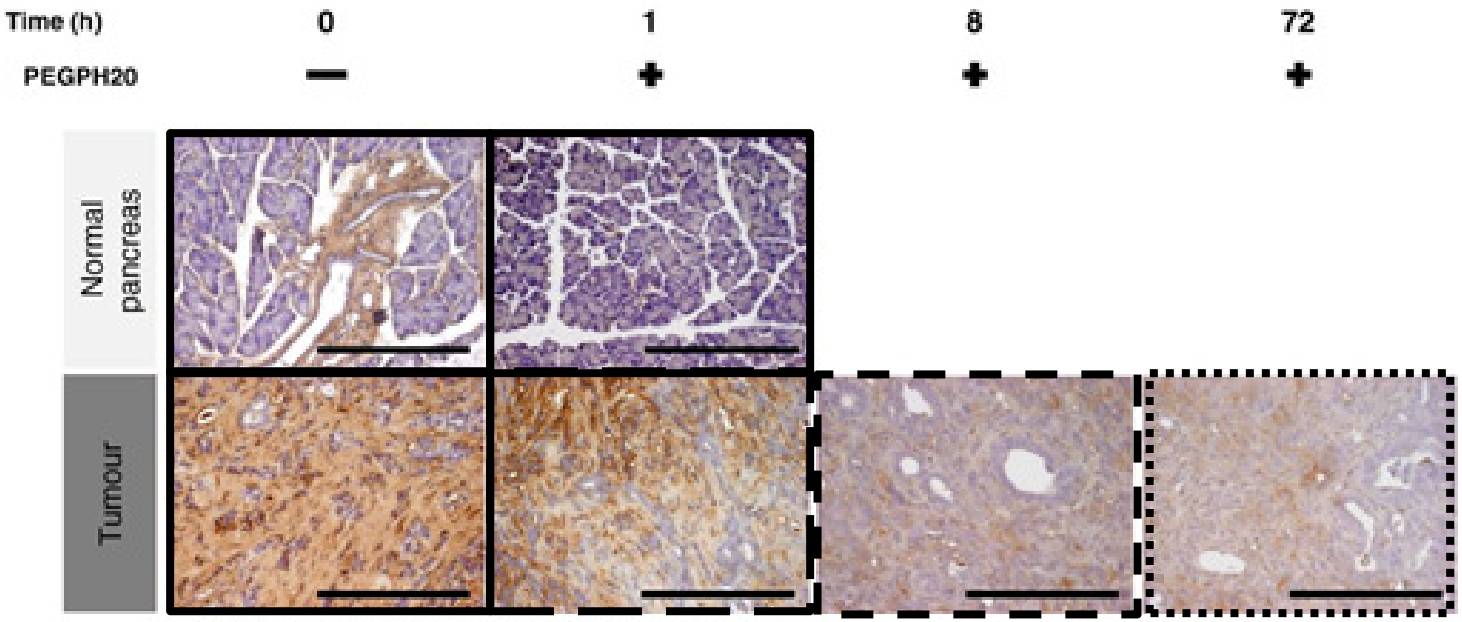
Research Project:	*Accelerating Development of CD40 Therapy for Pancreatic Cancer*
Award Period:	July 1, 2013 – June 30, 2016
Amount:	$1,000,000

The Tempur-Pedic – Inaugural RAN Grant in Memory of Tim Miller was awarded to Robert Vonderheide, MD, DPhil and Dafna Bar-Sagi, PhD.

The challenge and opportunity of stroma

Dense stroma surrounding pancreatic cancer

After treatment with hyaluronidase



Chemotherapy cannot penetrate the surrounding stroma

Chemotherapy can now penetrate and cause tumor regression

Olive et al, Science, 2009
Provenzano et al, Cancer Cell, 2012
Jacobetz et al, Gut, 2013

The challenge and opportunity of autophagy

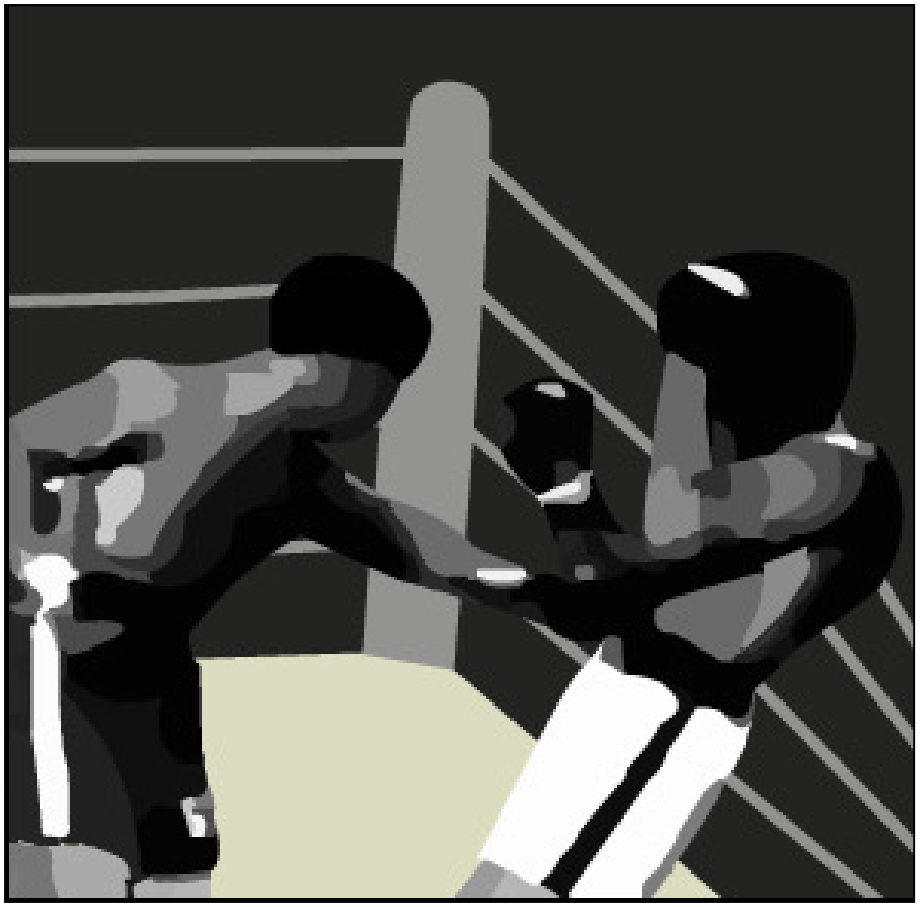
Autophagy is a 'rope-a-dope' mechanism for pancreatic cancer to go into hiding

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
Selvakumaran et al, Clin Can Res, 2013

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

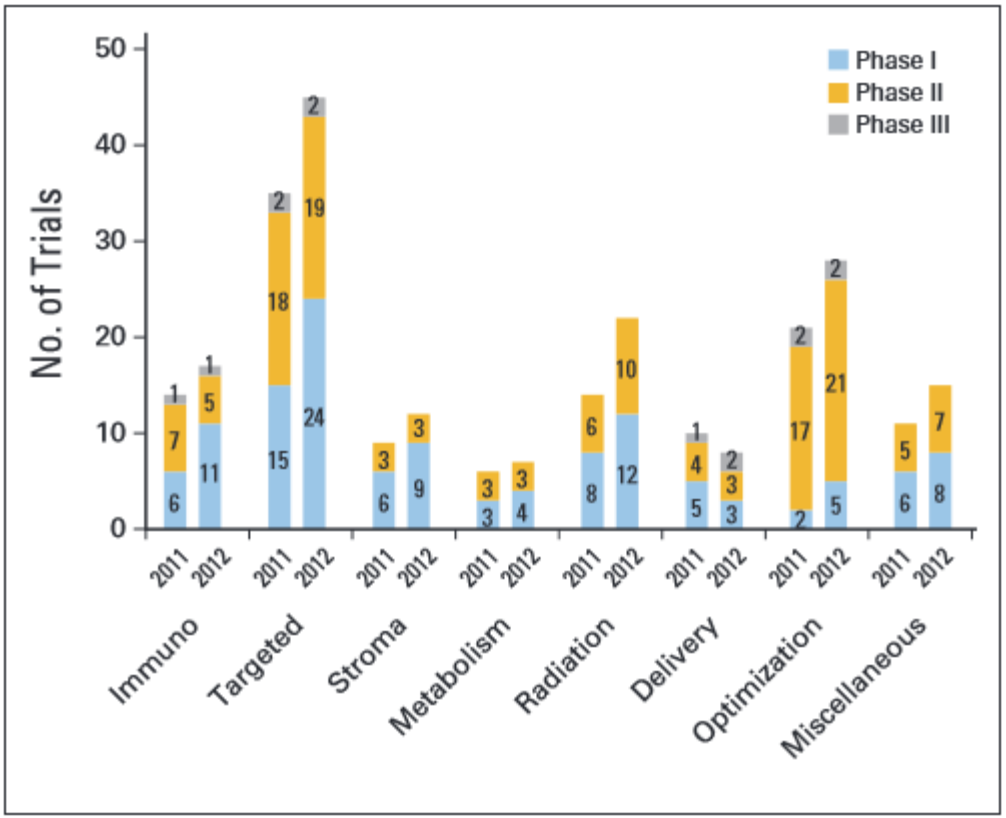


Fig 3. Pancreatic ductal adenocarcinoma clinical trials open in United States in 2011 and 2012 by treatment type. Targeted indicates those targeted to signal

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**

Information

To make an appoint at Penn:
1-800-789-PENN

Abramson Cancer Center
Penn Medicine

Clinical trial information:
www.oncolink.org

OncoLink
Abramson Cancer Center of the University of Pennsylvania

Pancreatic Cancer Action Network:
www.pancan.org

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