



Immune Therapy for Pancreatic Cancer

December 16, 2014

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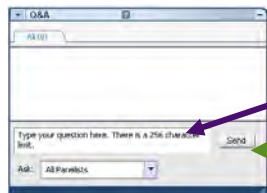
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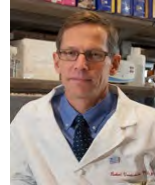
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Immune therapy for pancreatic cancer

Robert Vonderheide, MD, DPhil

**Abramson Cancer Center
University of Pennsylvania
Philadelphia, PA**



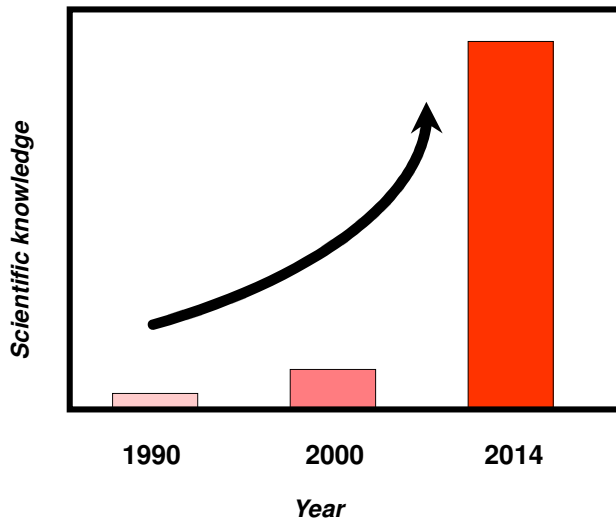
December 16, 2014

Abramson Cancer Center
 Penn Medicine

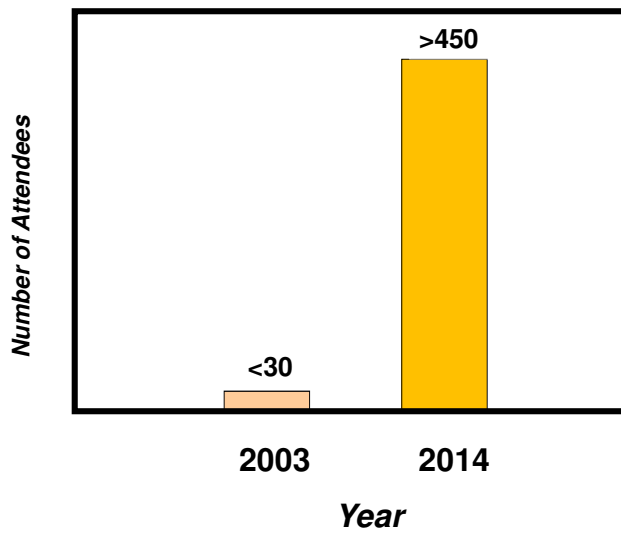
The clinical and biological challenges:

**Early detection is difficult
Suboptimal response to standard therapies
Main tumor mutation (Kras) is currently 'undruggable'
Hostile microenvironment in pancreatic cancer**

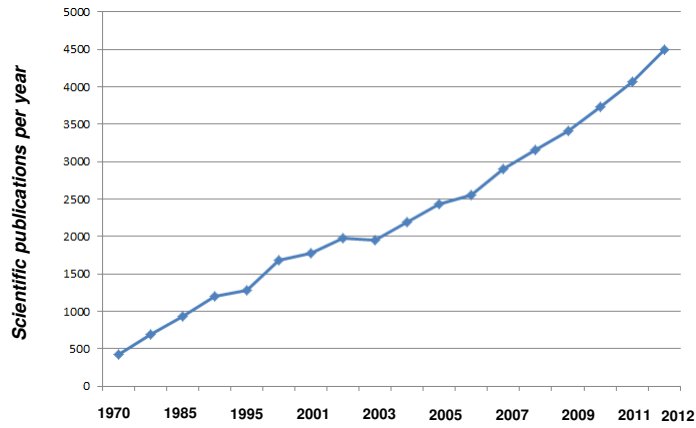
What we know about pancreatic cancer



Attendance at a national scientific meeting on pancreatic cancer

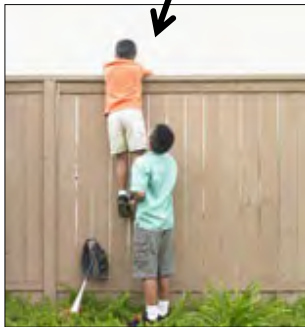


Massive increase in the depth and breadth of research activity in pancreatic cancer



Publications on breast cancer in 2012: 13,925 in 2002: 5,090

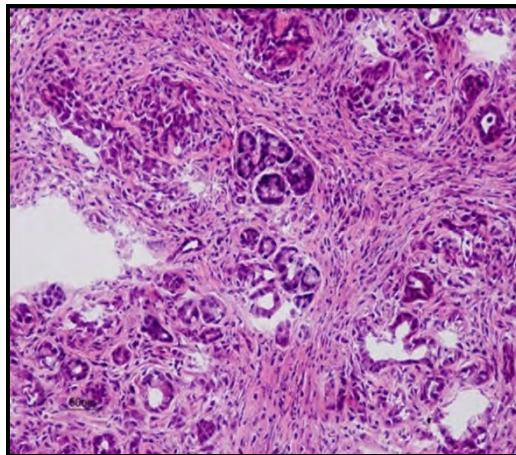
We are here



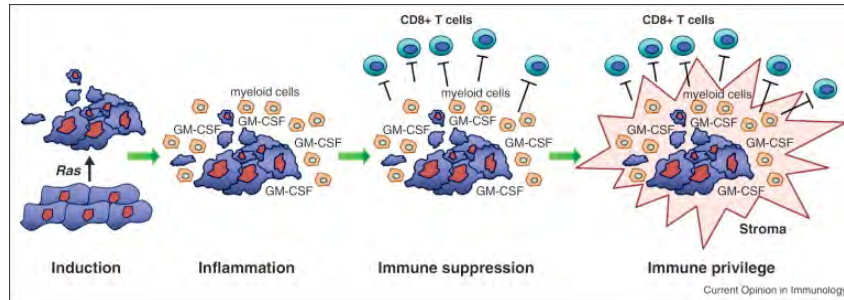
Redesigned chemotherapy for pancreatic cancer

- Two new combinations of drugs for patients with metastatic disease
 - FOLFIRINOX (Conway et al, NEJM, 2011)
 - Gemcitabine/Abraxane (Von Hoff et al, NEJM, 2013)
- Rates of major tumor regression to initial therapy for metastatic disease have gone from <5% to 25%-30%, with better 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, such as immune therapy, can be added
 - Chemotherapy does not 'ruin' the immune system

The challenge and opportunity of stroma



Immune biology of pancreatic cancer



Bayne and Vonderheide, *Curr Opin Immunol*, 2013

Cancer immunotherapy trials for patients with pancreatic cancer

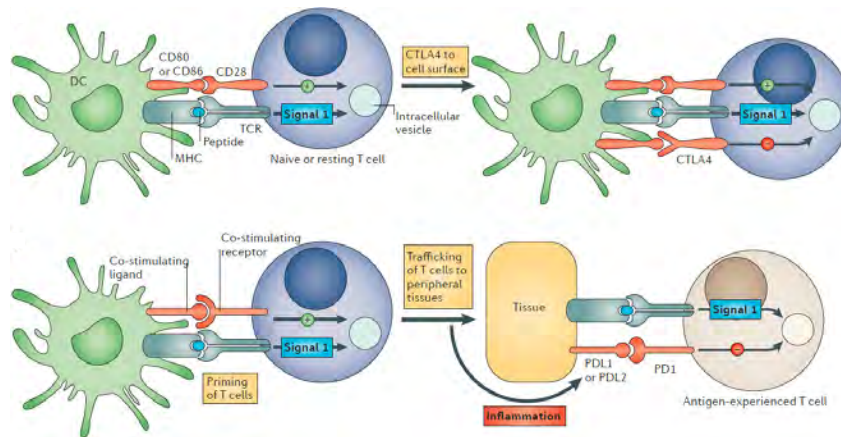
	2014	2013
Treatment clinical trials for PDA *		
• Open trials	372	385
• Immunotherapy trials	20	13
Percentage of all trials exploring immunotherapy for PDA	5.4%	3.0%
• Same calculation in melanoma:	22.1%	17.0%
• Same calculation in breast cancer:	3.9%	1.0%

* Clinicaltrials.gov, assessed by RHV

Monoclonal antibodies can stimulate the immune system

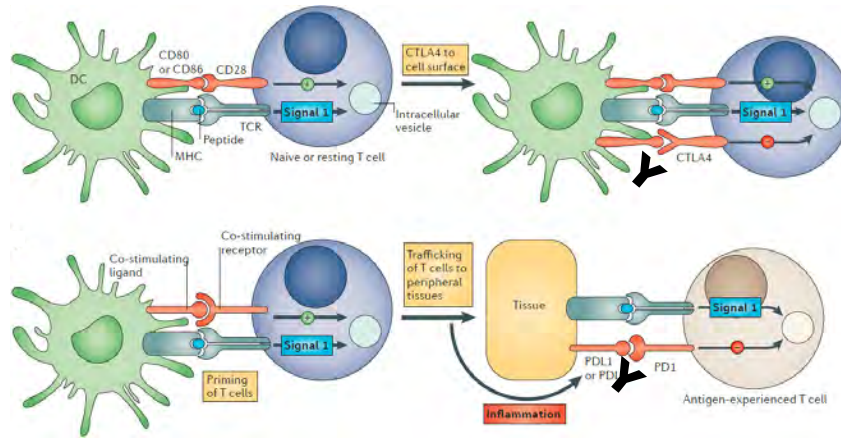


Negative immune checkpoints: the 'brakes'



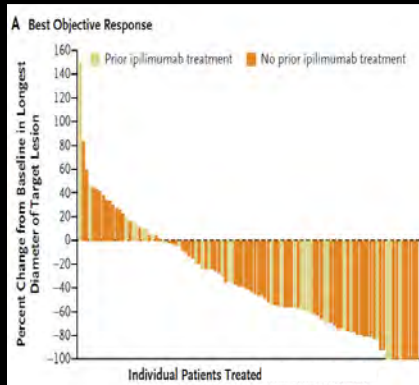
Pardoll, Nat Rev Can, 2012

Negative immune checkpoints: the 'brakes'



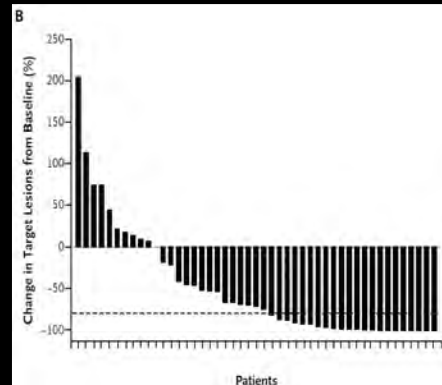
Pardoll, Nat Rev Can, 2012

PD-1 antibody with and without CTLA-4 antibody



Pembrolizumab for patients with metastatic melanoma

Hamid et al, NEJM, 2013



Nivolumab plus ipilimumab for patients with metastatic melanoma

Wolchok et al, NEJM, 2013

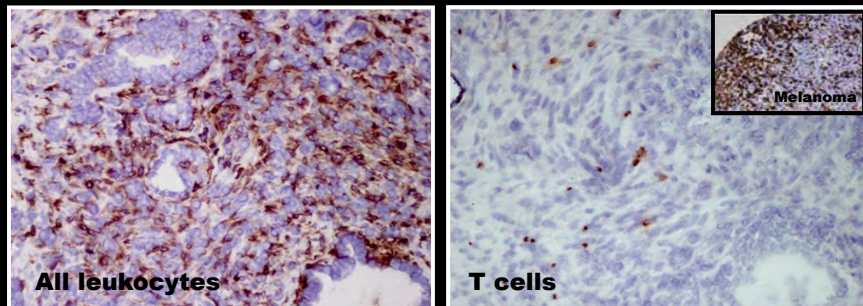
Checkpoint antibody clinical trials in patients with pancreatic cancer

Results so far using antibodies against negative immune checkpoints in patients with pancreatic cancer

- Single agent ipilimumab – no responses (Royal et al., *J Immunother*, 2010; Le et al., *J Immunother*, 2013)
- Single agent α PD-L1 – no responses (Brahmer et al., *NEJM*, 2012)

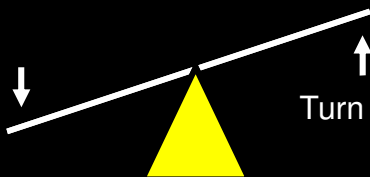
Clinicaltrials.gov

Immune cells in pancreatic cancer



Strategies to tip the balance of immunity

Turn on T cells



Turn off negative factors

Immunity

No immunity

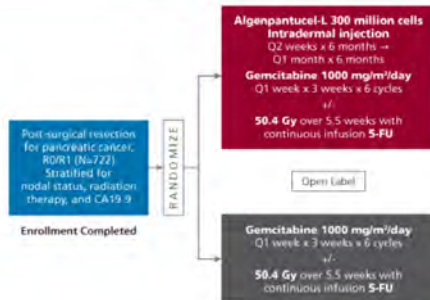
IMPRESS Trial: Algenpantucel-L vaccine with chemoradiation therapy for patients with resectable PDA

IMPRESS: Immunotherapy for Pancreatic Resectable Cancer Survival Study¹

Study Status¹

ENROLLMENT COMPLETED¹ (722 Patients)

IMPRESS Phase 3 Study Schema¹



Tumor-specific cancer cell lines modified to express the carbohydrate alpha-gal

Study Details¹

Study Design

- Randomized phase 3 study of standard adjuvant therapy alone or in combination with algenpantucel-L in patients who have undergone surgical resection for pancreatic cancer

Key Inclusion Criteria

- Surgical resection for adenocarcinoma of the pancreas; extent of resection must be R0 or R1
- ECOG PS ≤ 2
- First vaccination within 10 weeks of surgery

Key Exclusion Criteria

- Active metastases
- Current immunosuppressive therapy
- Chronic systemic corticosteroid therapy

Key Endpoints

- Primary:** Overall survival (OS)
- Secondary:** Disease-free survival (DFS)

R0=complete resection with grossly and microscopically negative margins of resection; R1=grossly negative but microscopically positive margins of resection; 5-FU=5-Fluorouracil; CA19-9=cancer antigen 19-9.

PILLAR trial open for patients with locally advanced non resectable disease NCT01836432

Combining vaccines with checkpoint antibody for patients with pancreatic cancer

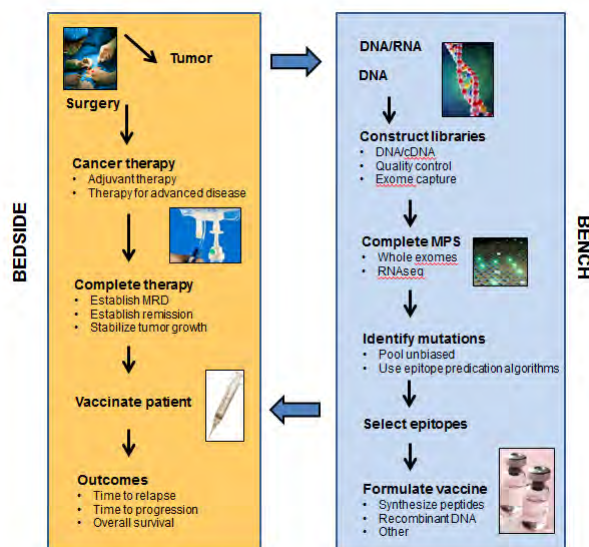
Dual component gene therapy vaccine

- GVAX pancreas – irradiated, whole cell tumor vaccine, secretes GM-CSF
- LADD Listeria – live, attenuated *Listeria monocytogenes* expressing mesothelin
- Survival benefit in patients given both components rather than GVAX alone, now a randomized study nationwide, NCT02004262
- Next step is to add anti-PD-1 antibody (trial at Johns Hopkins to open soon, NCT02243371)

GVAX plus ipilimumab

- Patients who receive FOLFIRINOX then go on to receive GVAX pancreas plus anti-CTLA-4 antibody (trial at Johns Hopkins, NCT01896869)

The road to personalized cancer vaccines



Vonderheide and Nathanson, *Nature Medicine*, 2013

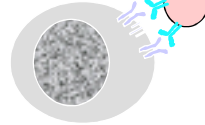
Engineered T cell therapy for pancreatic cancer

1. Remove the immune cells from blood

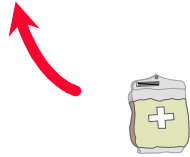


2. Engineer killer lymphocytes in a clinical laboratory

Anti-mesothelin[™]
NCT01897415

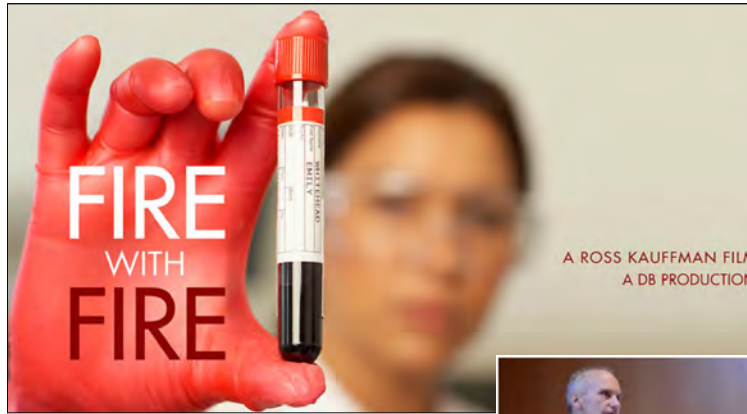


4. Give patient engineered T cells



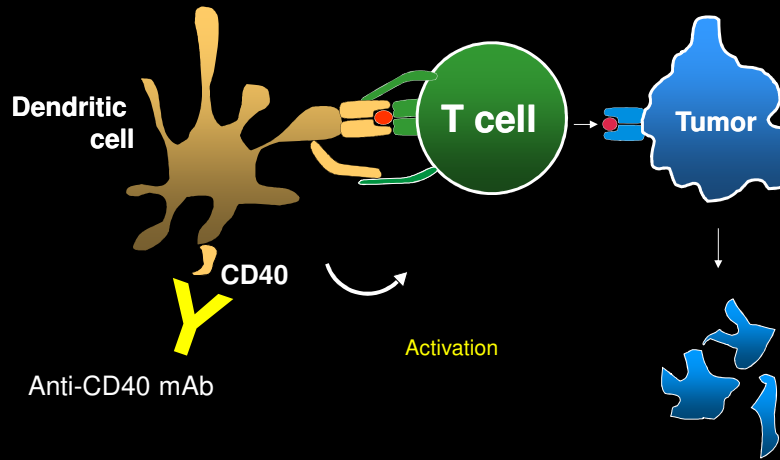
3. Prepare cells for re-infusion

Porter et al, NEJM, 2011
Grupp et al, NEJM, 2013
Maude et al, NEJM, 2014
Beatty et al, Can Immunol Res, 2014

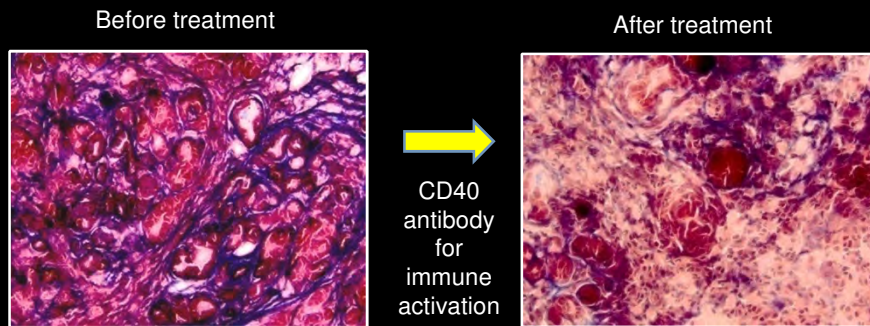


Curing Cancer: The Philadelphia Award and Dr. Carl June
By Matt Tennen Productions 2014
 The year the prestigious Philadelphia Award honored Penn Medicine's Dr. Carl June for his trailblazing work in curing leukemia is a handful of patients. He and his team have developed a process that involves genetically 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 the video for The Philadelphia Award and to meet Dr. June and his colleagues.

Testing CD40 antibodies as immune therapy for pancreatic cancer in the laboratory

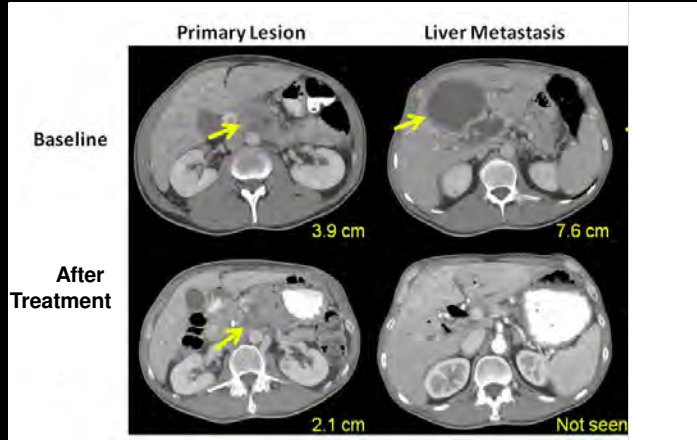


Testing CD40 antibodies as immune therapy for pancreatic cancer in the laboratory



Beatty et al, Science, 2011

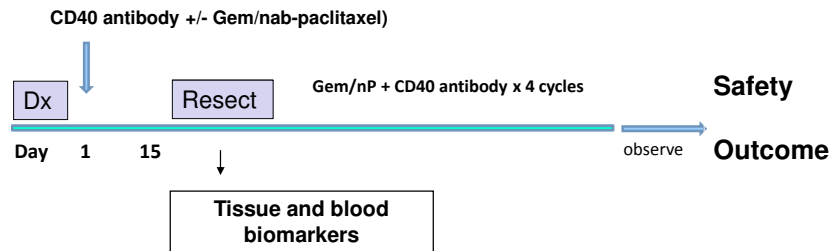
CD40 antibody immune therapy for pancreatic cancer



Beatty et al, Science, 2011

CD40 antibody for patients undergoing surgery

To open soon at Penn: Phase I study of preoperative CD40 antibody +/- chemo for patients with newly diagnosed resectable pancreatic carcinoma



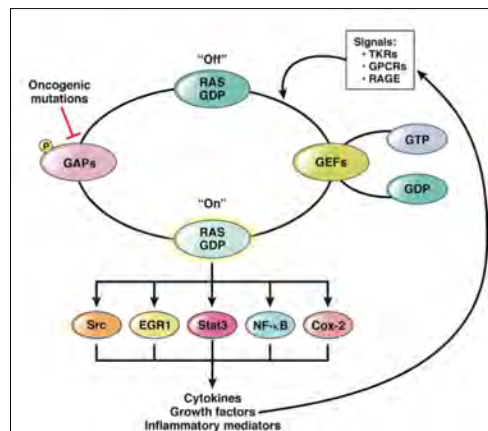
Recalcitriol with chemotherapy for patients with resectable pancreatic cancer

- Expression profiling of tumor stellate cells revealed Vitamin D receptor as a potential regulator of function *Sherman et al, Cell, 2014*
- Vitamin D agonists alter tumor stroma and facilitate tumor death in combination with chemotherapy in laboratory studies
- Phase I study of paricalcitol and chemotherapy delivered prior to, and again after, surgical resection of primary tumor
 - At Penn, NCT02030860



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
- Does mutant Kras cause such immune suppression?



Pasca di Magliano and Logsdon, Gastroenterology, 2013
Biakin et al, Nature, 2012

The Ras Initiative

<http://www.cancer.gov/researchandfunding/priorities/ras>



Frederick National Laboratory for Cancer Research

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

(FREDERICK, Md., May 9, 2012)—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 (FNLRC), 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 deal with the 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."

Pancreatic cancer is a clinical EMERGENCY



Research in clinical trials are critical

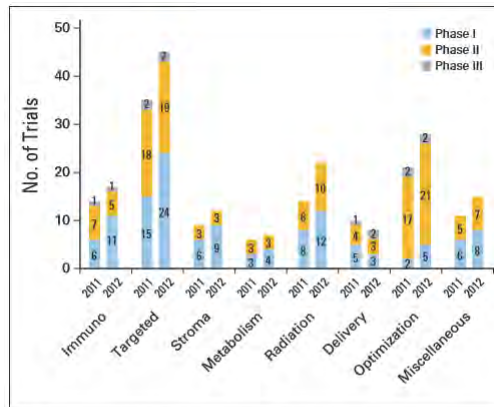


Fig 3. Pancreatic ductal adenocarcinoma clinical trials open in United States in 2011 and 2012 by treatment type. Targeted indicates those targeted to signal

Hoos et al, J Clin Oncology, 2013

Still, only 4% of patients with pancreatic cancer ever go on a clinical trial

Conclusions

- Research efforts in pancreatic cancer are accelerating
- New discoveries are driving novel therapies, especially immune therapies
- Clinical trials are critical





Thank you for your participation.

If you have questions, please contact our Patient and Liaison Services
(PALS) program at
(877) 272-6226 or e-mail pals@pancan.org.

www.pancan.org or wagehope.org

