Defining questions in the use of CTCs in a Cancer Prevention Setting

Emily Greenspan, Ph.D.

Program Manager

PQ Program Director, Center for Strategic Scientific Initiatives (CSSI)
Office of the Director, National Cancer Institute (NCI)
National Institutes of Health (NIH)

World CTC Summit, Boston MA

November 12, 2012

NCI Center for Strategic Scientific Initiatives (CSSI): Concept Shop

Director
Douglas Lowy, MD

CENTER for STRATEGIC SCIENTIFIC INITIATIVES

~$190M (FY12)

Deputy Director
Jerry S.H. Lee, PhD

Office of Cancer Clinical Proteomics Research

Director
Henry Rodriguez, PhD, MBA

Office of Physical Sciences-Oncology

Director
Larry A. Nagahara, PhD

Office of Cancer Nanotechnology Research

Director
Piotr Grodzinski, PhD

Office of Cancer Genomics

Director
Daniela S. Gerhard, PhD

The Cancer Genome Atlas Program Office

Director
Kenna M.Shaw, PhD

*Center for Cancer Genomics (CCG) shown in yellow

NCI Center for Strategic Scientific Initiatives (CSSI): Concept Shop

Director
Douglas R. Lowy, MD

CENTER for STRATEGIC SCIENTIFIC INITIATIVES

~$190M (FY12)

Deputy Director
Jerry S.H. Lee, PhD

Mission

"…to create and uniquely implement exploratory programs focused on the development and integration of advanced technologies, **trans-disciplinary approaches, infrastructures, and standards**, to accelerate the **creation and broad deployment** of **data, knowledge, and tools** to empower the **entire cancer research continuum** in better understanding and leveraging knowledge of the cancer biology space **for patient benefit**…"

IMAT Innovative Molecular Analysis Technologies — **2003, 2007, 2011**

CLINICAL PROTEOMIC TECHNOLOGIES FOR CANCER — **2005, 2010**

PHYSICAL SCIENCES in ONCOLOGY — **2008**

Provocative Questions Project — **2011**

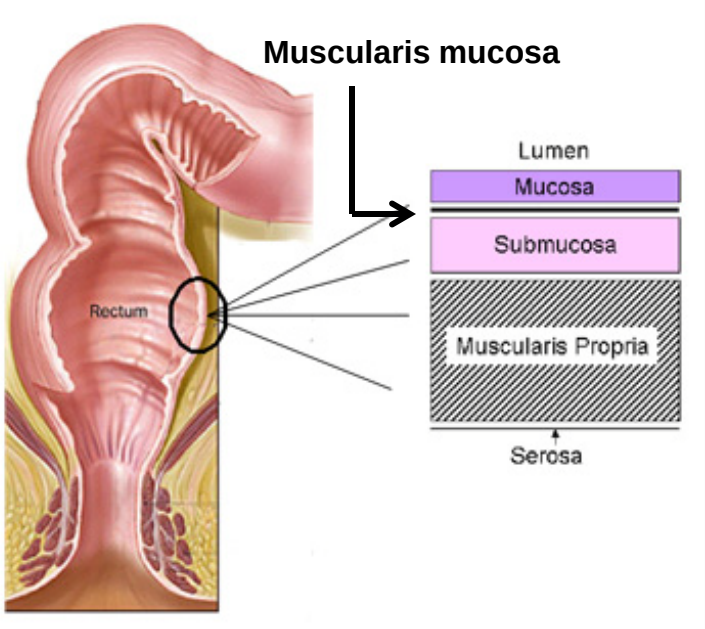
NCI Alliance for Nanotechnology in Cancer — **2004, 2008**

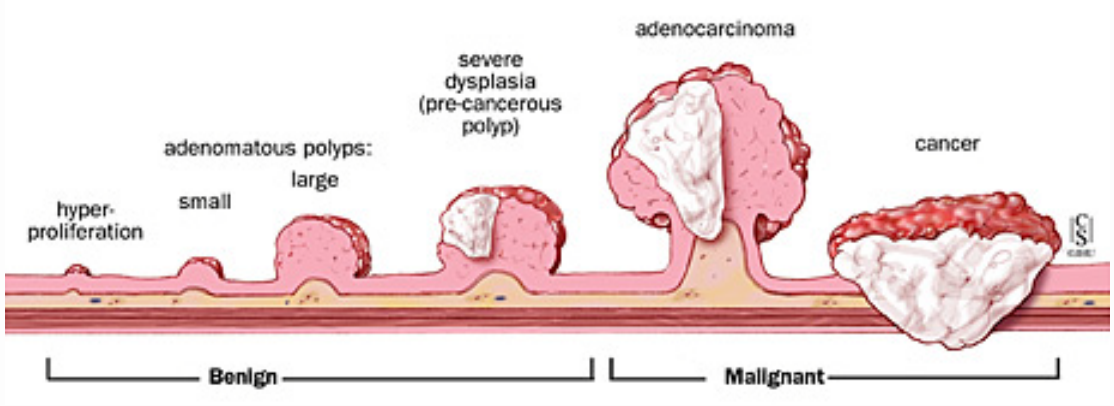
THE CANCER GENOME ATLAS — **2005, 2008**

Cancer Target Discovery & Development (CTD²) — **2010**

Integration of CTC enumeration/characterization into cancer prevention trials

Big question in cancer prevention field: **which premalignant lesions will progress to malignant and/or metastatic disease?**

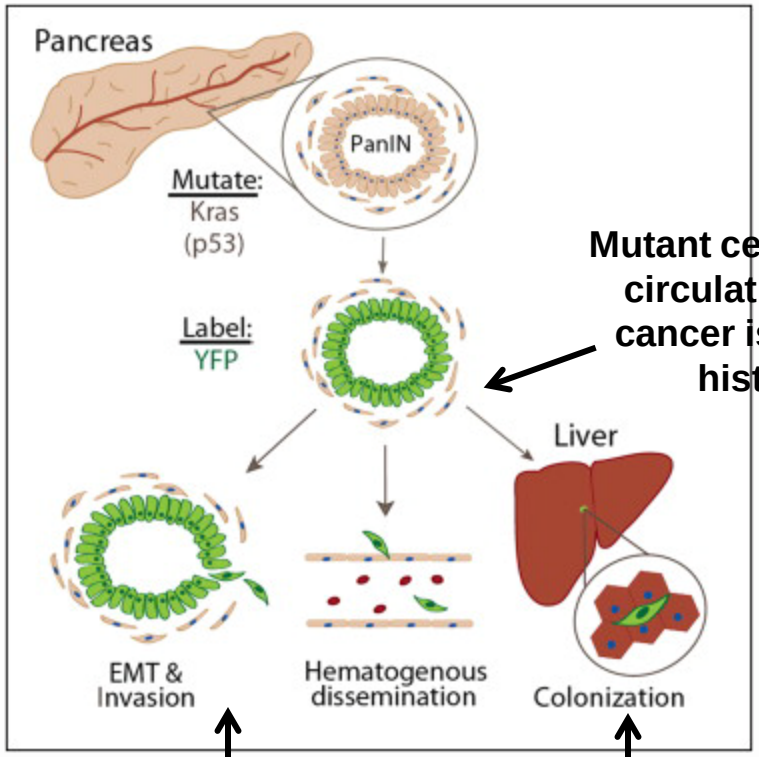




Is it be possible to measure CTCs at pre-malignant or at least pre-metastatic stages of the disease to help determine the likelihood for progression?

Is it possible to detect CTCs before the development of malignant disease?

In a mouse model of pancreatic cancer circulating pancreatic cells (CPCs) were detected at the stage of pancreatic intraepithelial neoplasias (PanINs), 8-10 weeks before the development of pancreatic ductal adenocarcinoma (PDAC)



Mutant cells enter the circulation before cancer is found on histology

CPCs express cancer stem cell-associated markers

Inflammation is necessary and sufficient for EMT, invasion and dissemination

Rhim AD, et al., Cell, 2012

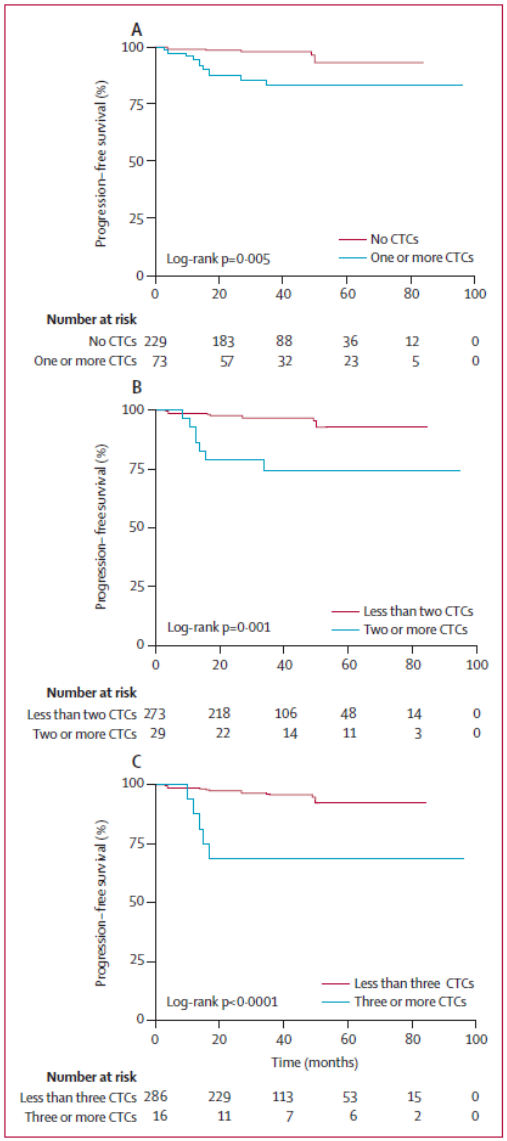
… and before metastatic disease?

Circulating tumour cells in non-metastatic breast cancer: a prospective study

Anthony Lucci, Carolyn S Hall, Ashutosh K Lodhi, Anirban Bhattacharyya, Amber E Anderson, Lianchun Xiao, Isabelle Bedrosian, Henry M Kuerer, Savitri Krishnamurthy

In a cohort of 703 chemonaive patients with non-metastatic breast cancer the presence of 1 or more CTC (assessed by Veridex CellSearch®) predicted early recurrence and decreased overall survival.

- If there is no intravasation how do the cells get into the bloodstream? Leaky tumor?



Lucci A, et al., Lancet Oncol, 2012

Complicating factors

Cells from benign diseases may gain entry into the bloodstream

- No healthy patients had any CTCs in either assay
- No patients in the study had CRC after 3 years of follow up
- CECs may be caused by **inflammation**
  - Morphology may reveal they are not CTCs

Circulating Epithelial Cells in Patients with Benign Colon Diseases

Klaus Pantel,[1] Eric Denève,[2] David Nocca,[2] Amandine Coffy,[3] Jean-Pierre Vendrell,[4] Thierry Maudelonde,[5] Sabine Riethdorf,[1] and Catherine Alix-Panabières[3,4,5*]

Table 1. Distribution of patients with benign colon diseases related to the presence of CTCs and counts of CTCs detected by the EPISPOT and CellSearch assays.

	EPISPOT assay	*P*	CellSearch assay	*P*
CTC+ patient age, years[a]	52.5	0.37	65.8	0.13
CTC+ patients, n/total (%)[b]	10/53 (18.9)		6/53 (11.3)	
Sex				
Female	3/20 (15)	0.72	2/20 (10)	1.0
Male	7/33 (21.2)		4/33 (12.1)	
Disease type		0.86		1.0
Diverticulosis	5/23 (21.7)		3/23 (13)	
Benign polyps	1/12 (8.3)		1/12 (8.3)	
Crohn disease	2/7 (28.6)		1/7 (14.3)	
Ulcerative rectocolitis	1/5 (20)		0/5 (0)	
Other	1/6 (18.7)		1/6 (18.7)	
CTC count[c]				
Total	2.4 (0–41), 0		1.1 (0–37), 0	
Per disease				
Diverticulosis	3.5 (0–41), 0		2 (0–37), 0	
Benign polyps	0.5 (0–6), 0		0.2 (0–3), 0	
Crohn disease	1 (0–6), 0		0.8 (0–5), 0	
Ulcerative rectocolitis	6.4 (0–32), 0		0	
Other	0.4 (0–2), 0		0.4 (0–3), 0	

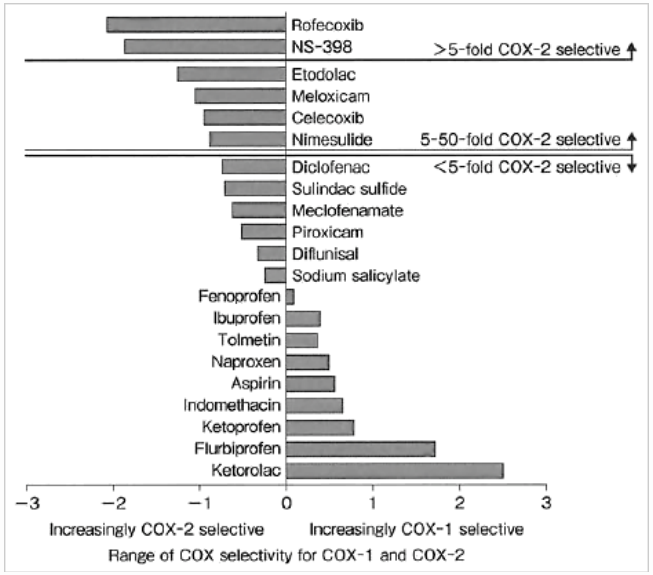
[a] Data are presented as the mean.
[b] Data are presented as the number of CTC+ patients/total number of patients in the group (percent).
[c] Data are presented as the mean (range), median.

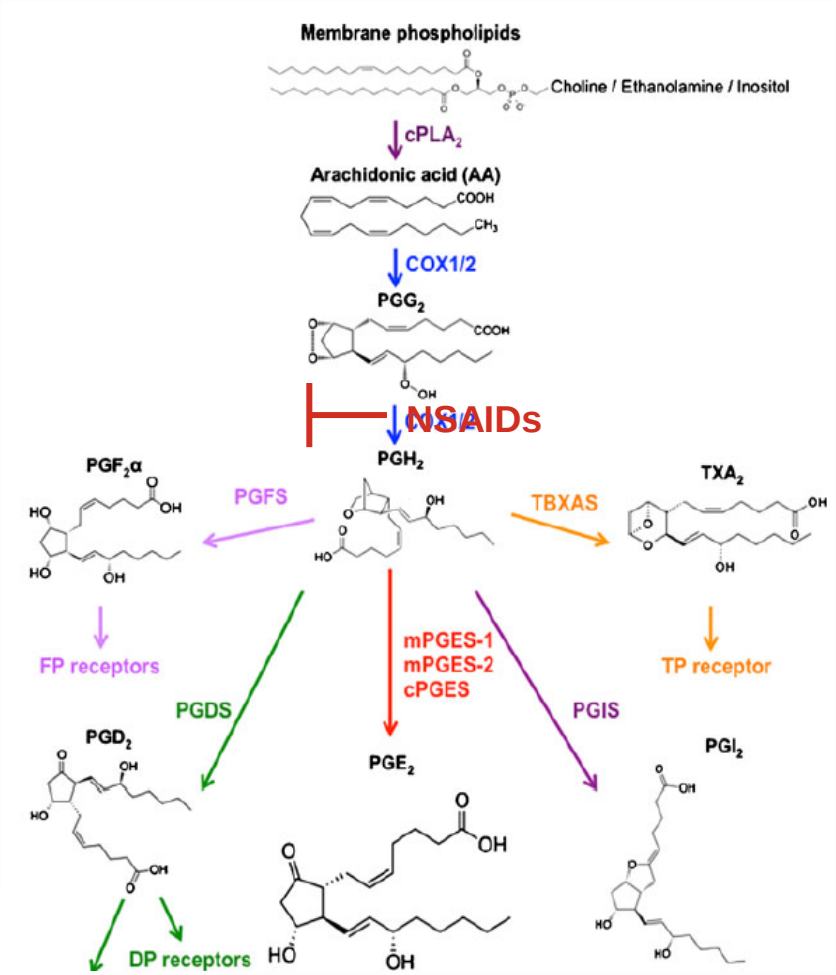
Pantel K, et al., Clin Chem, 2012

Complicating factors #2

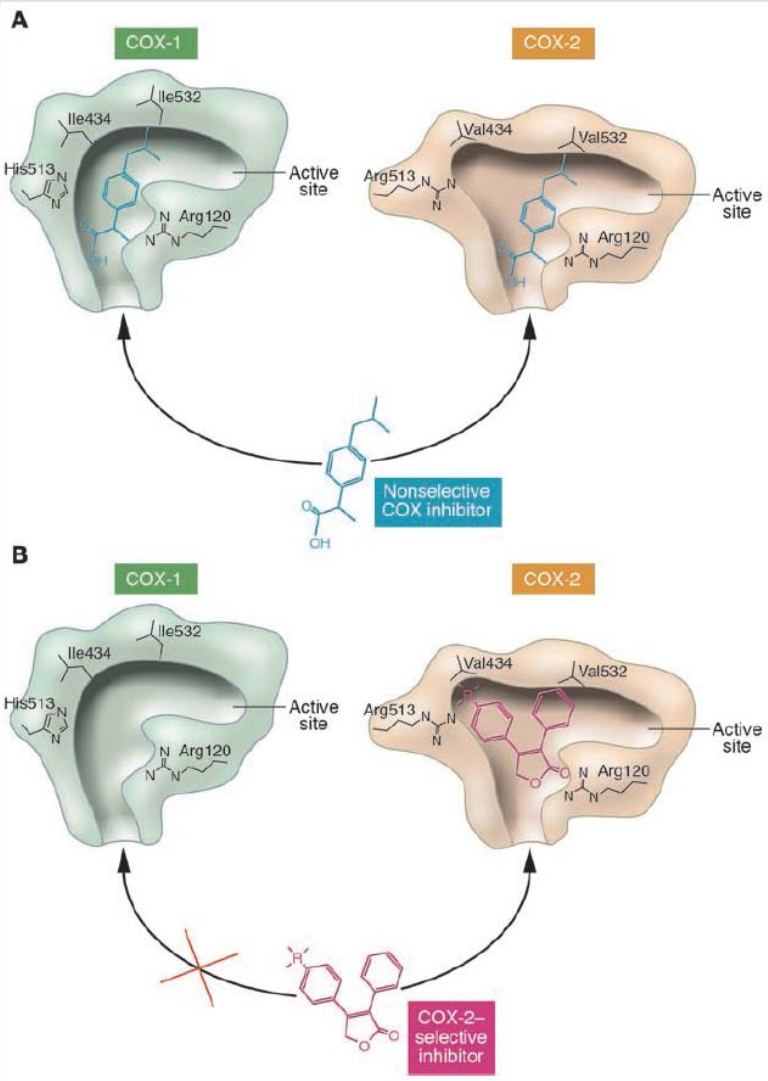
Patients enrolled in prevention trials often have long term use of chemopreventive agents, e.g. Non-steroidal anti-inflammatory drugs (NSAIDs)

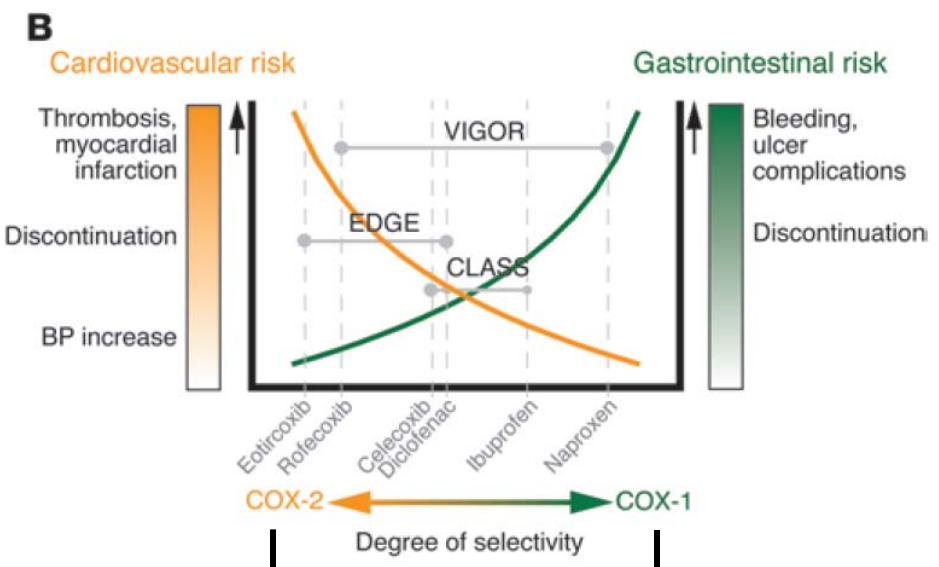
- NSAIDs have a long history of being effective chemopreventive agents for colorectal cancer (CRC) and other cancers
- Cardiovascular toxicity associated with long term use of COX-2 specific inhibitors has led to renewed interest in COX-1 inhibitors (aspirin, ibuprofen) as chemopreventive agents





Specificity of COX enzymes





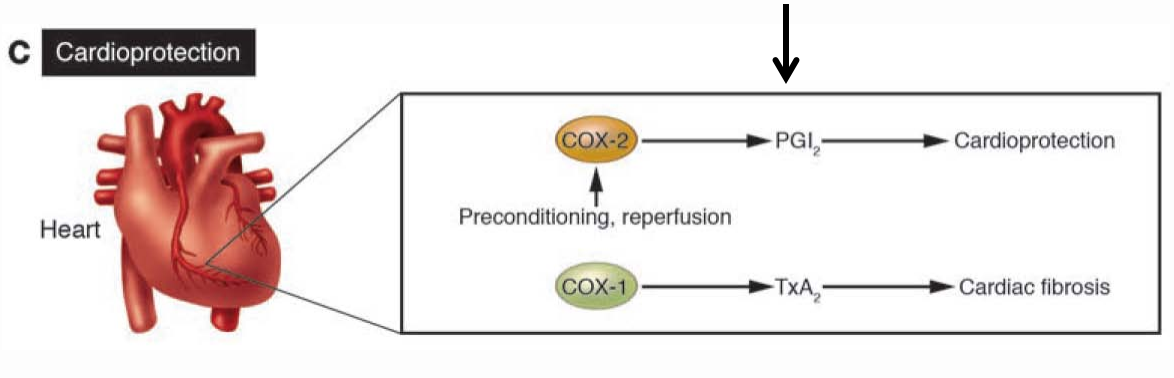
Attributed to inhibition of PGI_2 in endothelial cells, stimulating thrombomodulin and removing the natural suppression to thrombin activation; Coxibs usually don't inhibit TxA_2

Attributed to inhibition of protective PGE_2 and PGI_2 by gastroduodenal epithelium and platelet TxA_2

Grosser T, et al., J Clin Invest, 2006

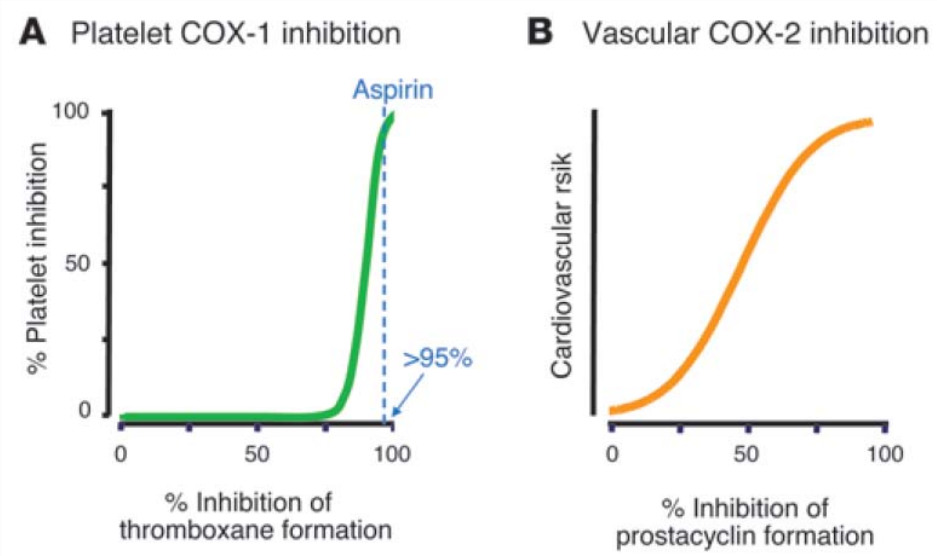
NSAIDs disrupt the balance COX derived eicosanoids

PGI_2 mainly from endothelial cells



Selective inhibition of COX-2 alters the balance of PGI_2 and TxA_2 synthesis

Discordant dose-response relationships for inhibition of platelet COX-1 and vascular COX-2



Grosser T, et al., J Clin Invest, 2006

Aspirin may also have a therapeutic effect on preexisting cancer

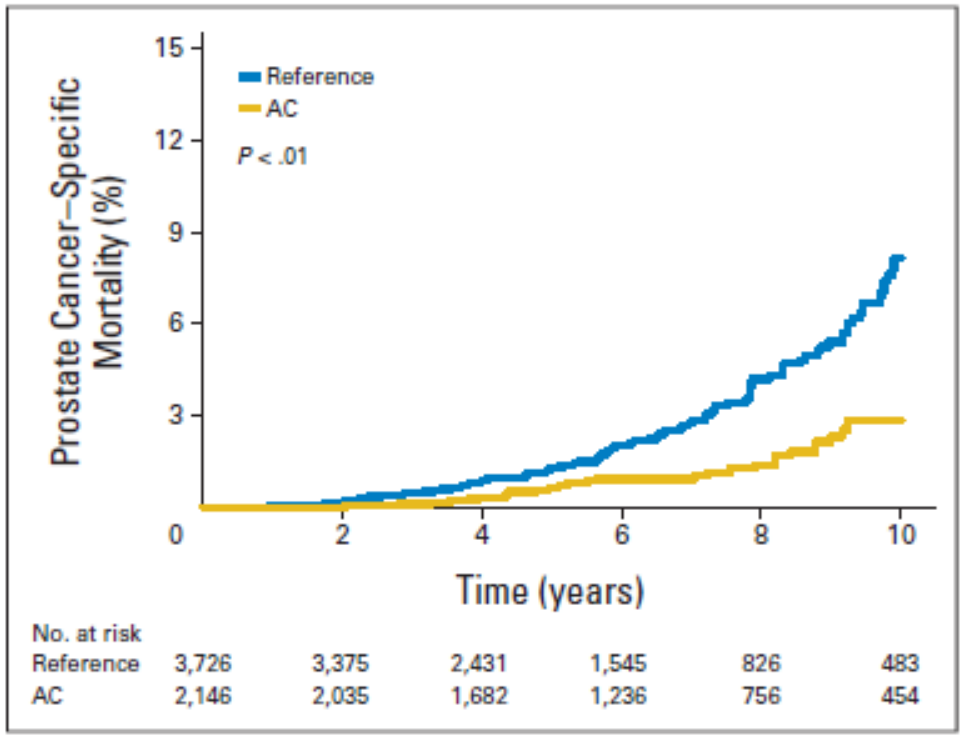
Center for Strategic Scientific Initiatives

Aspirin Use and the Risk of Prostate Cancer Mortality in Men Treated With Prostatectomy or Radiotherapy

Kevin S. Choe, Janet E. Cowan, June M. Chan, Peter R. Carroll, Anthony V. D'Amico, and Stanley L. Liauw

Study comprised ~6000 men with adenocarcinoma of the prostate treated with radical prostatectomy or radiotherapy

- ~37% were receiving ACs (warfarin, clopidogrel, enoxaparin, and/or aspirin)
- The risk of prostate cancer specific mortality was significantly decreased in the AC (especially aspirin) group from ~8 to 3%



National Cancer Institute

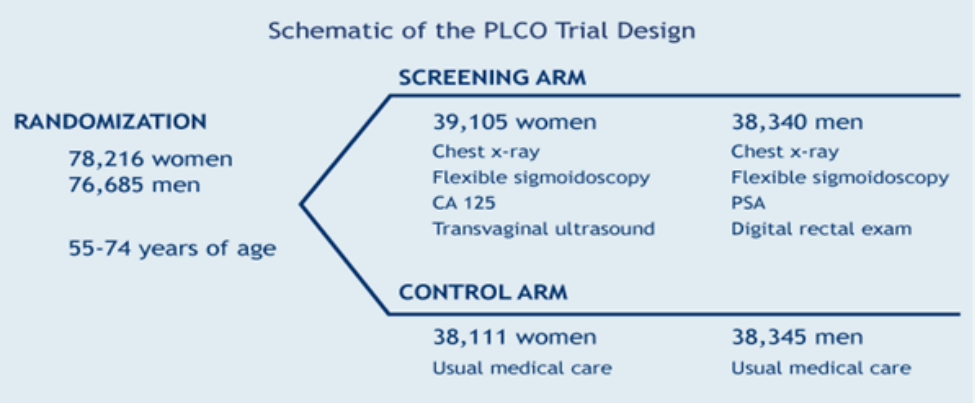
Choe KS, et al., J Clin Oncol, 2012

How can CTC enumeration/characterization be incorporated into huge, long prevention trials?

CENTER for STRATEGIC SCIENTIFIC INITIATIVES

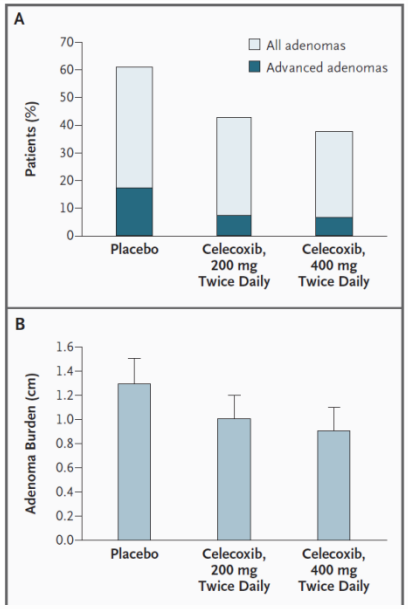
Prostate, Lung, Colorectal and Ovarian (PLCO) Screening Trial

- Overall goal is to determine if various early detection screening methods can reduce mortality from PLCO cancers
- Patients recruited to the study over 8 years and followed for a minimum of 13 years (screening at 3-5 year intervals)
- ~160 publications to date associated with the PLCO trial



Adenoma Prevention with Celecoxib (APC) Trial

- Overall goal is to determine if long term use of celecoxib can reduce the number adenomas in high-risk patients
- ~2000 patients recruited to the study over 4 years and had follow up colonoscopies at 1 year and 3 years
- Trial stopped early at 3 years – celecoxib associated with adverse cardiovascular events and not recommended for prevention of adenomas



NATIONAL CANCER INSTITUTE

Prorok PC, et al., Control Clin Trials, 2000; Bertagnolli MM, et al., NEJM, 2006

Potential Discussion Topics

- What are the best ways to determine if CTCs detected in early stage or non-metastatic cancers can predict the likelihood for progression to malignant or metastatic disease?

- Given NSAIDs multiple effects on cardiovascular biology, how could long-term use of NSAIDs impact CTC enumeration, characterization and/or clustering?

- How can CTC enumeration or characterization be incorporated into ongoing or future cancer prevention trials?

Relevant CSSI Funding Opportunities

Provocative Questions ($30M)

Due Date 12/04/12

- **Research Answers to NCIs Provocative Questions**
  - **Group A:** RFA-CA-12-015 (R01) [$5-$7M] & RFA-CA-12-016 (R21) [$2-$3M]
  - **Group B:** RFA-CA-12-017 (R01) [$5-$7M] & RFA-CA-12-018 (R21) [$2-$3M]
  - **Group C:** RFA-CA-12-019 (R01) [$5-$7M] & RFA-CA-12-020 (R21) [$2-$3M]
  - **Group D:** RFA-CA-12-021 (R01) [$5-$7M] & RFA-CA-12-022 (R21) [$2-$3M]

Innovative Molecular Analysis Technologies Program ($10.5M)

Reissue winter 2012

- Early-Stage Innovative Technology Development for Cancer Research (R21) [$5M]
- Validation and Advanced Development of Emerging Technologies for Cancer Research (R33) [$3.5M]
- Innovative and Early-Stage Development of Emerging Technologies in Biospecimen Science (R21) [$0.8M]
- Validation and Advanced Development of Emerging Technologies in Biospecimen Science (R33) [$0.7M]

http://cssi.cancer.gov/resources-current_funding.asp

Learn More About CSSI/CCG…

http://cssi.cancer.gov

PQ Program Manager

Emily J. Greenspan, PhD

IMAT Program Director

Tony Dickherber, PhD

Emily Greenspan, PhD, greenspanej@mail.nih.gov