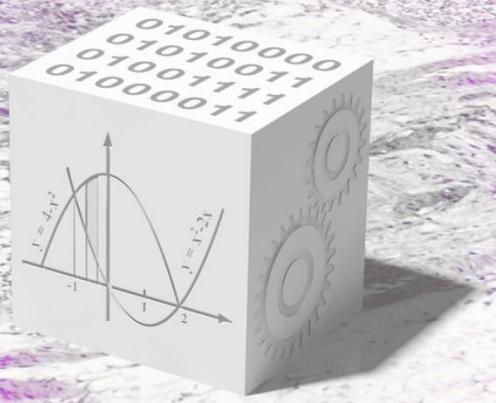
National Cancer Institute



Bringing a Different Mindset: NCI's Physical Sciences-Oncology Initiative

Larry A. Nagahara
Associate Director
Physical Sciences in Oncology Initiative
Division of Cancer Biology (DCB)
National Cancer Institute (NCI)
National Institutes of Health (NIH)

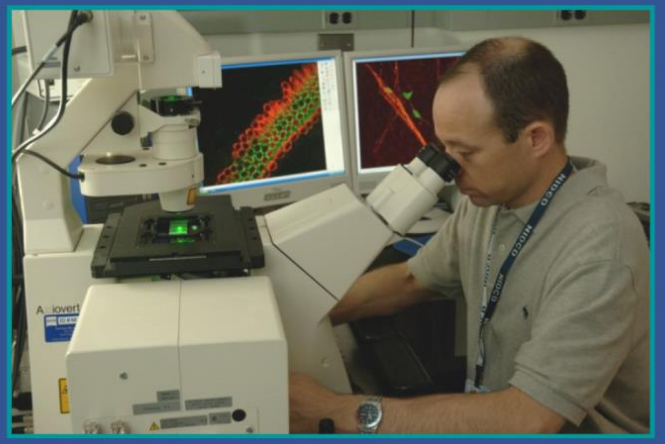
Aerospace Materials for Extreme Environments Review: May 18-21, 2015

PHYSICAL SCIENCES in ONCOLOGY

NIH National Institutes of Health

NIH: Steward of Medical and Behavioral Research for the Nation

"Science in pursuit of fundamental knowledge about the nature and behavior of living systems… and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability."



National Institutes of Health (NIH): 27 Institutes and Centers

PHYSICAL SCIENCES— in ONCOLOGY

NHGRI NIA NIDA

NEI NIAAA CIT

FIC CSR NIBIB

NINDS NIDCD NIMH

NINR NLM NIDDK

NIMHD NIDCR NIEHS

NIGMS NICHD CC

NIAMS NCCAM NIAID NCI NHLBI NCATS

NIH Budget ~ $30.8 Billion (FY12)

- ***~82% for extramural support***
- ***~63,000 grants and contracts***

NCI Budget ~ $ 5.07 Billion (FY12)

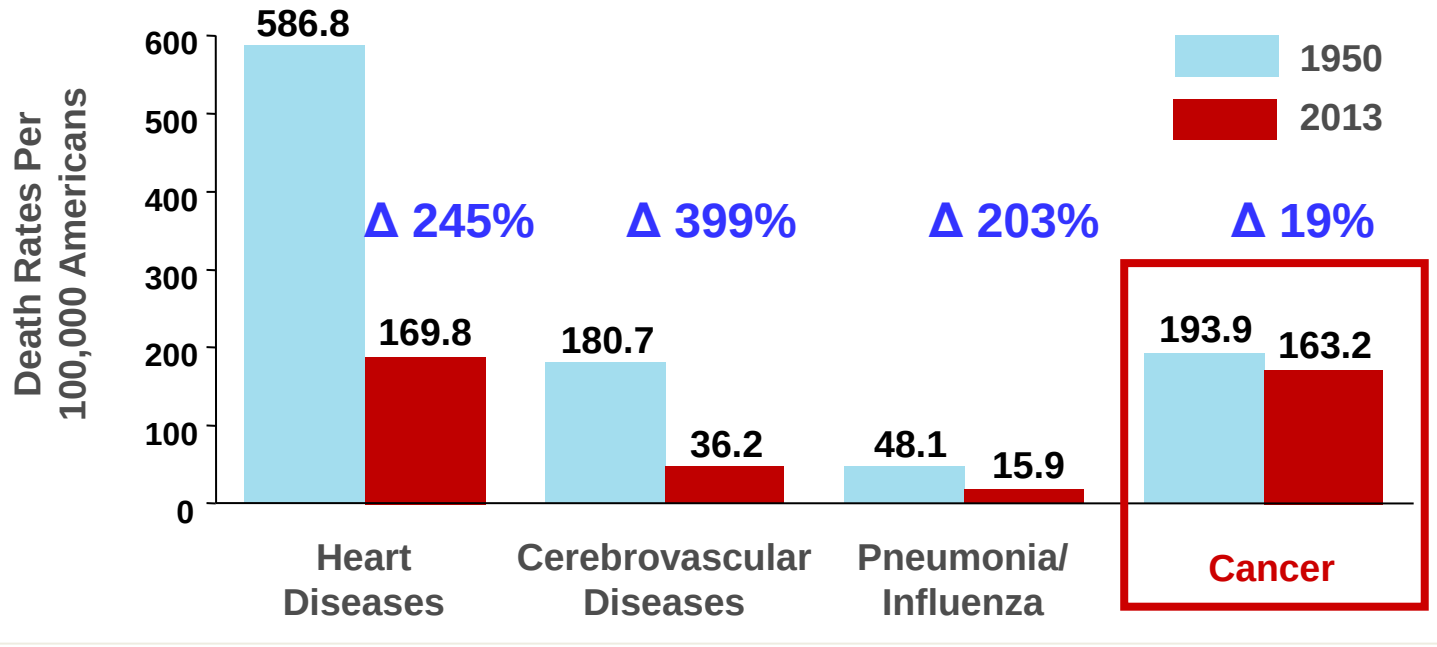
- ***~ 76% for extramural support***
- ***~7,800 grants and contracts***

In the US, Cancer Continues to be Represent an Enormous Burden

PHYSICAL SCIENCES— in ONCOLOGY

- **589,430** Americans died of cancer in 2015 (projection)
- **1,658,370** Americans will be diagnosed with cancer this year
- **$263.8 billion** in 2010 for cancer healthcare costs & lost productivity

Unlike Other Major Disease Killers, Cancer Continues to Take Nearly the Same Toll as it did in 1950



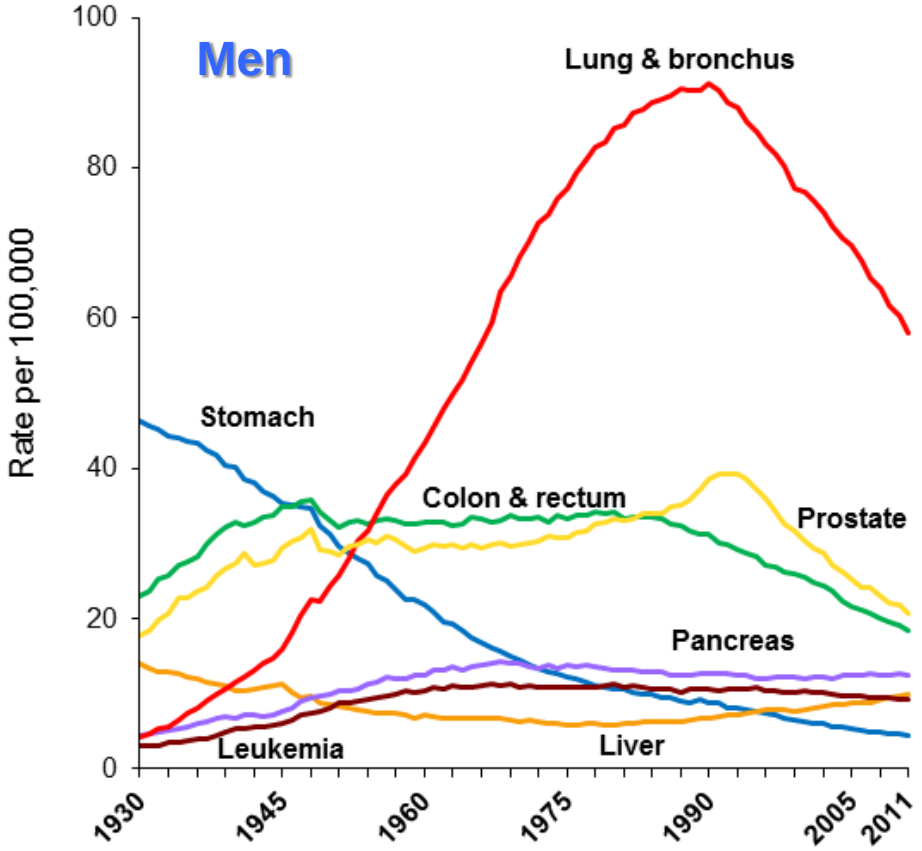
Source for 2012 deaths and diagnoses: American Cancer Society (ACS) 2012 Cancer Facts & Figures; Atlanta, Georgia
Source for 2010 age-adjusted death rate: National Center for Health Statistics, NCHS Public-use file for 2010 deaths.

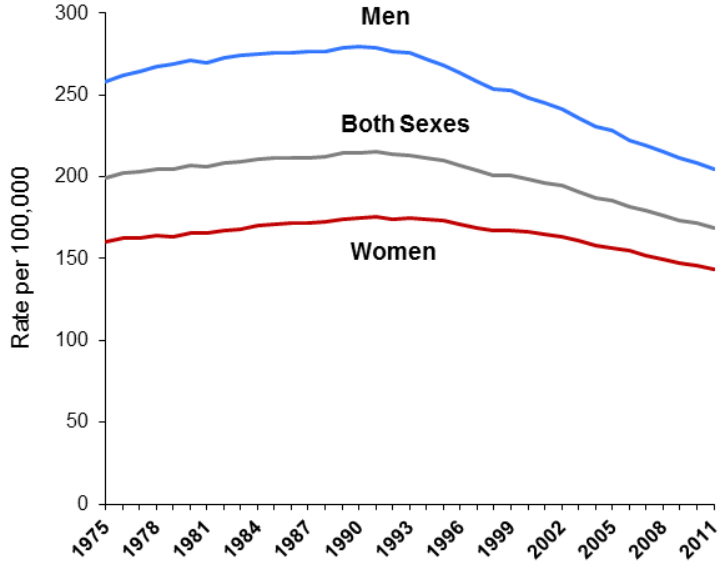
NATIONAL CANCER INSTITUTE

Trends in Cancer Death Rate in the US

PHYSICAL SCIENCES— in ONCOLOGY

Source: National Center for Health Statistics
Centers for Disease Control and Prevention





NCI's Physical Sciences-Oncology Initiative

PHYSICAL SCIENCES— in ONCOLOGY

12 Awards

PS-OC RFA

Sep

Phase I

2008 2009 2012 2013 2014 2015

Feb Jul Oct

Pre-Award Think Tanks

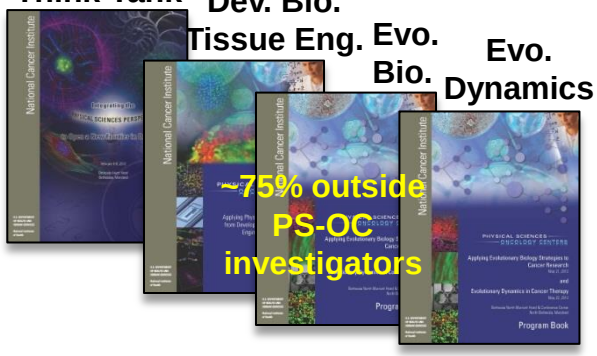
~300 extramural participants

Feb Think Tank

Apr Dev. Bio. Tissue Eng.

May Evo. Bio.

Evo. Dynamics



~75% outside PS-OC investigators

Nov

Phase II PS-ON PAR Approved

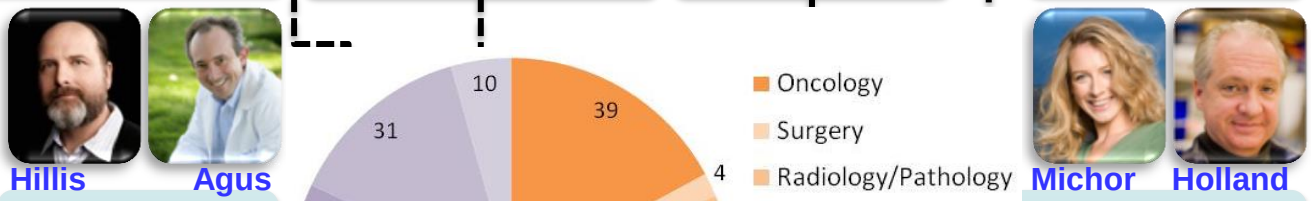
PAR-14-169
PAR-15-021

PS-OC Network (Phase I): Physical scientists & cancer researchers integrated at the start

PHYSICAL SCIENCES— in ONCOLOGY

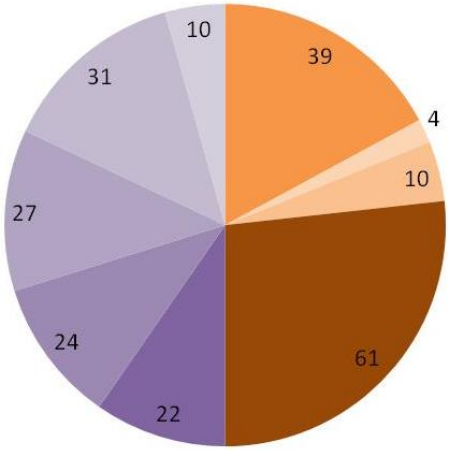
Liphardt Weaver O'Halloran Licht Shuler Hempstead Manalis Jacks

Stanford | **Northwestern** | **Cornell** | **MIT**

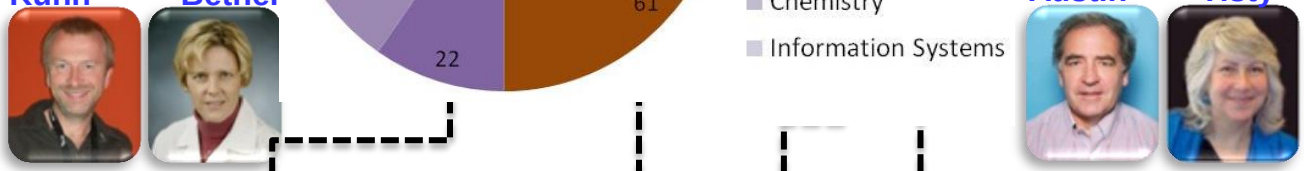


Hillis Agus Michor Holland

USC | **DFCI**



Scripps | **Princeton**



Kuhn Bethel Austin Tlsty

ASU | **TMHRI** | **Moffitt** | **Johns Hopkins**

Davies Grady Ferrari Curley Gatenby Gillies Wirtz Semenza

PI + SI

12 "Virtual" Centers

Over 110 Institutions:
- 83 Domestic
- 32 Foreign

corresponding to:
- 700+ investigators, collaborators, & advisors
- 550+ trainees (post-docs, graduate, & undergraduate)

participating in the PS-OC Network

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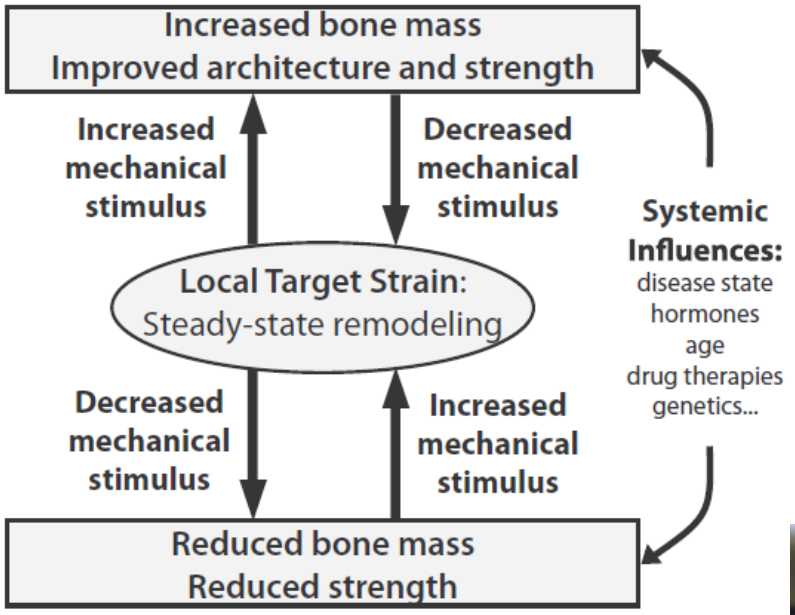
~~Aerospace~~ Materials under Extreme Environment: Bone Metastasis

PHYSICAL SCIENCES— in ONCOLOGY

Wolff's Law: "Mechanostat"

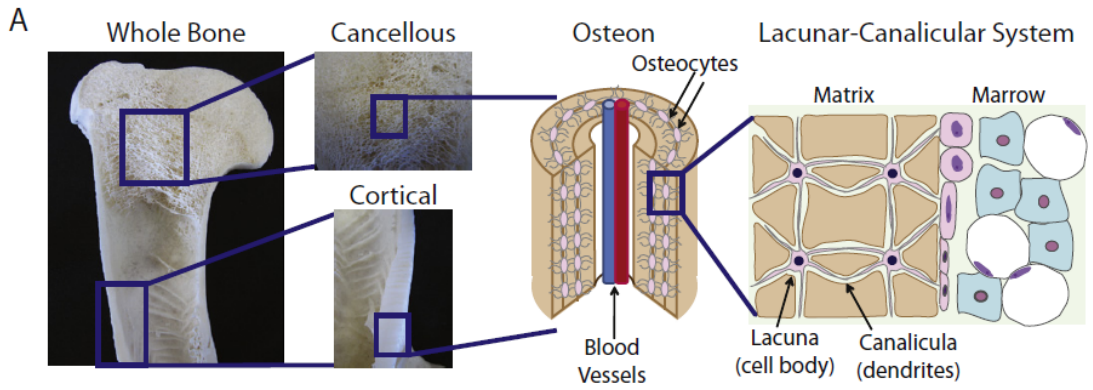


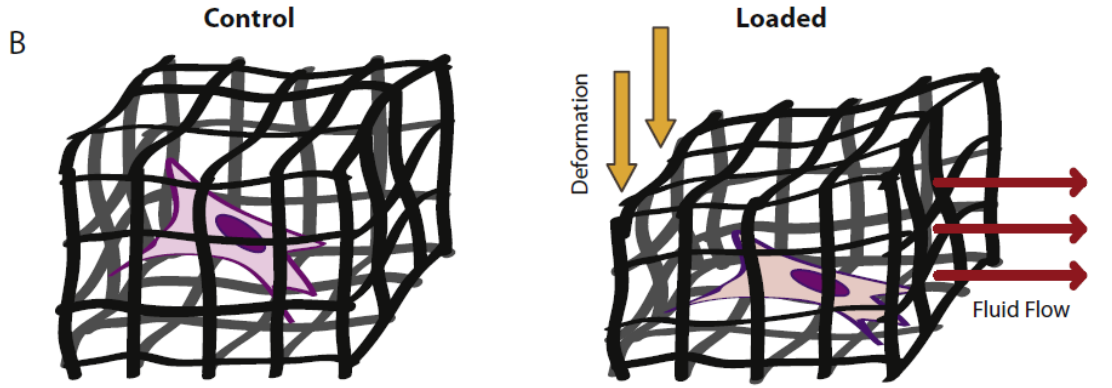
Claudia Fischbach-Teschl
Cornell University

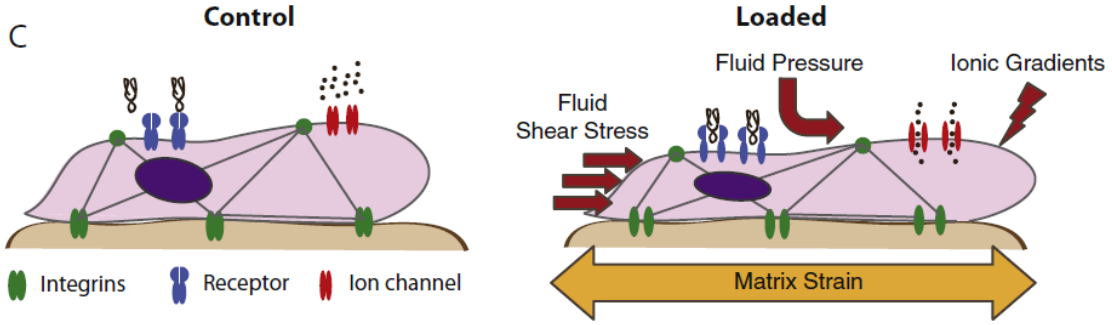
Biology and Engineering Considerations: Bone Metastasis

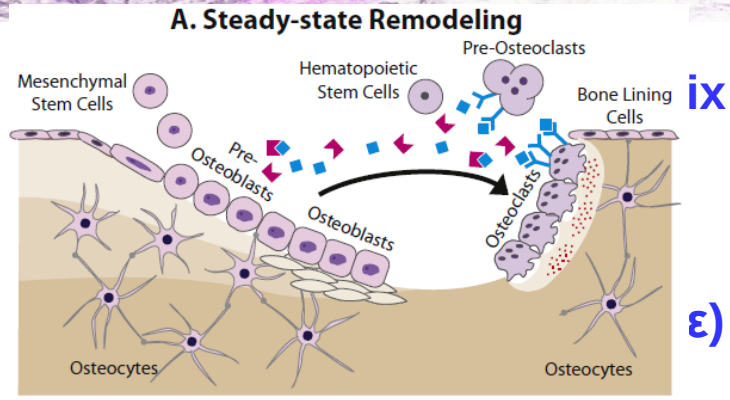
PHYSICAL SCIENCES— in ONCOLOGY

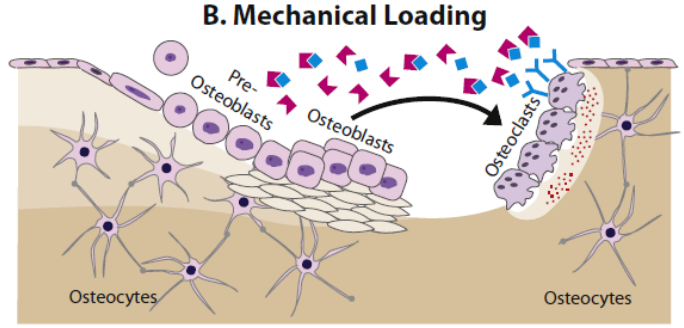
Advanced Drug Delivery Reviews 79–80 (2014) 119–134

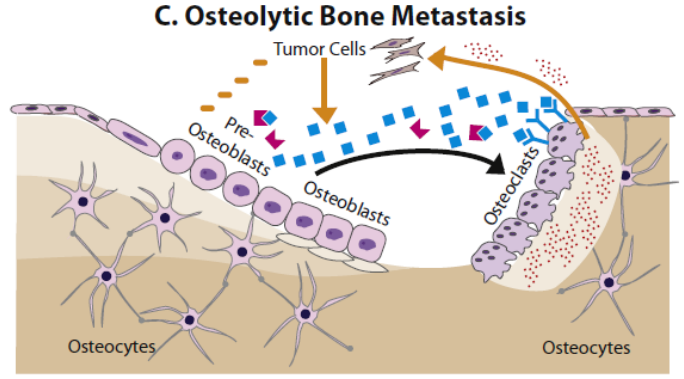












Physical Sciences-Oncology Network (PS-ON)
(PS-OC) Program: PAR-14-169
(PS-OP) Program: NOT-CA-14-039

PHYSICAL SCIENCES— in ONCOLOGY

FY09 **FY14** **FY16**

Pre-Award → RFA-CA09-009 → **PS-ON: PS-OC PAR-14-169/ PS-OP NOT-CA-14-039** → Future

Current PS-OC Program:

- **12 U54 PS-OCs ~$30M/year**
- **100+ institutions and 600+ investigators worldwide**
- **4 Themes:**
  - Physics (Physical Laws and Principles) of Cancer
  - Evolution and Evolutionary Theory of Cancer
  - Information Coding, Decoding, Transfer, and Translation in Cancer
  - De-convoluting Cancer's Complexity

Re-issuances of Physical Sciences-Oncology Initiative:

Physical Sciences-Oncology Network (PS-ON)

- **Two Programs (PAR):**
  - Physical Sciences Oncology Centers (PS-OCs): PAR-14-169
  - Physical Sciences Oncology Projects (PS-OPs): NOT-CA-14-039
- **2 Themes (suggested):**
  - The Physical Dynamics of Cancer
  - Spatial Organization and Cancer
- **Competition under Type 1 (New)**
- **Funding Mechanism:**
  - PS-OCs – U54 – up to $1.5M (DC)/year (5 years max.)
  - PS-OPs – U01 – up to $0.5M (DC)/year (5 years max.) (Foreign Institutions are also welcome to apply)

PS-OC PAR Suggested Thematic Areas

PHYSICAL SCIENCES— in ONCOLOGY

Based on:

1) **Inputs from scientific workshops (75% external to PS-OC Program);**
2) **Scientific advances from program;**
3) **Portfolio analysis of NCI portfolio;**
4) **NCI program leaders**

The Physical Dynamics of Cancer

- ***Overview:*** ***Physical properties such as bioelectric signals, transport phenomena, mechanical cues, and thermal fluctuations*** **may regulate (+/-) the initiation and progression of cancer.**
- ***Relevant Physical Science Approaches:*** **Precision measurements on single-cells and bulk samples, high-dimensional analysis, computational physics**

Spatio-Temporal Organization and Information Transfer in Cancer

- ***Overview:*** ***Organization of structures across all length scales (e.g., subcellular, cell, tissue, organ) and time scales*** **is required for maintaining the transfer of information that is critical for controlled growth.**
- ***Relevant Physical Science Approaches:*** **Advanced imaging and measurements, tissue mimetic and engineering, computational physics**

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Announcement for Physical Sciences - Oncology Centers (PS-OC)

PHYSICAL SCIENCES— in ONCOLOGY

Funding Opportunity Title

Physical Sciences-Oncology Network (PS-ON): Physical Sciences-Oncology Centers (PS-OC) (U54)

Funding Opportunity Announcement (FOA) Number

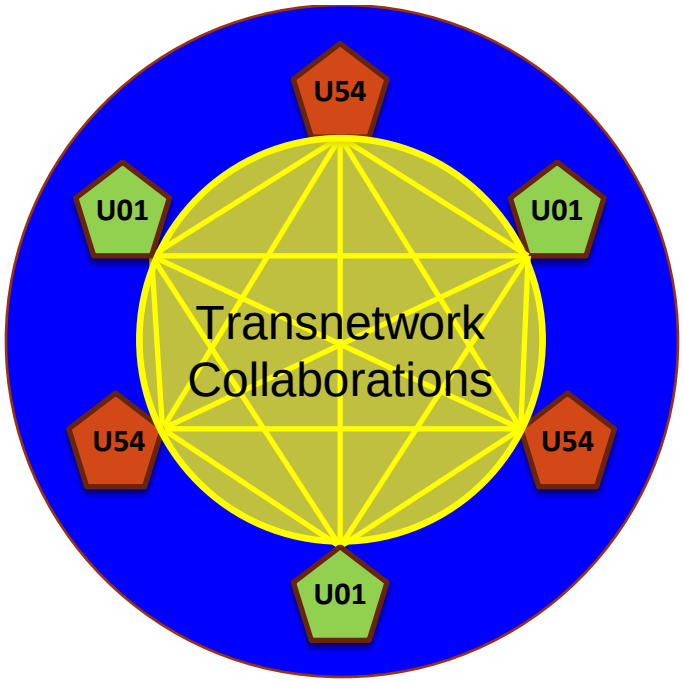
PAR-14-169

Application Due Date(s)

~~June 9, 2014~~

~~February 26, 2015~~

November 25, 2015



POC: Sean.Hanlon@nih.gov

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Announcement for Physical Sciences - Oncology Projects (PS-OP)

PHYSICAL SCIENCES— in ONCOLOGY

Funding Opportunity Title

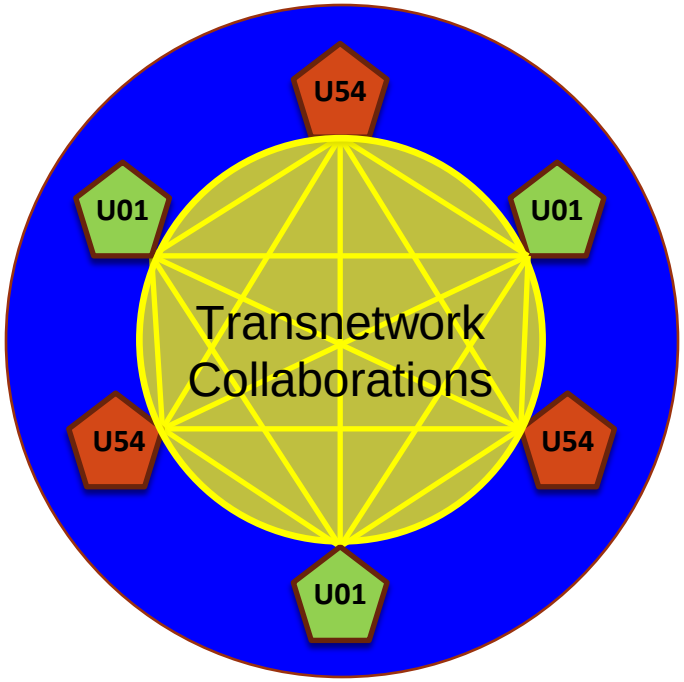
Physical Sciences-Oncology Network (PS-ON): Physical Sciences-Oncology Projects (PS-OP) (U01)

Funding Opportunity Announcement (FOA) Number

PAR-15-021

Application Due Date(s)

~~February 26, 2015~~
November 25, 2015
May 26, 2016
September 21, 2016
May 26, 2017
September 21, 2017



POC: Nas.Kuhn@nih.gov

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Reaching Across the "Other" Pond, Disciplines & Agencies: AFOSR Collaborations

PHYSICAL SCIENCES— in ONCOLOGY

UNSW AUSTRALIA

Peter Gunning

Expertise: Cancer Biology

Perelman School of Medicine University of Pennsylvania

Paul Janmey

Expertise: Mechano-biology

Elizabeth Gardiner

Expertise: Hematology

Laura Healy
PhD student
McCarty Lab

Owen McCarty

Expertise: Biomedical Engineering

ACBD
Australian Centre for Blood Diseases

OHSU OREGON HEALTH & SCIENCE UNIVERSITY

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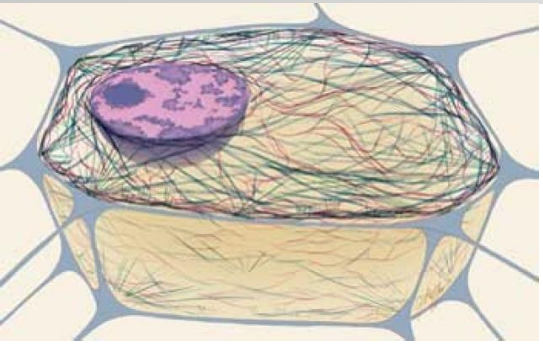
Collaboration between Peter Gunning, UNSW and Paul Janmey, UPenn



- Cytoskeleton is filamentous network of polymers that controls a cell's shape, stiffness and ability to move. The cytoskeleton responds to the stiffness of the surface to which cells adhere, and this response is often altered in cancer cells.

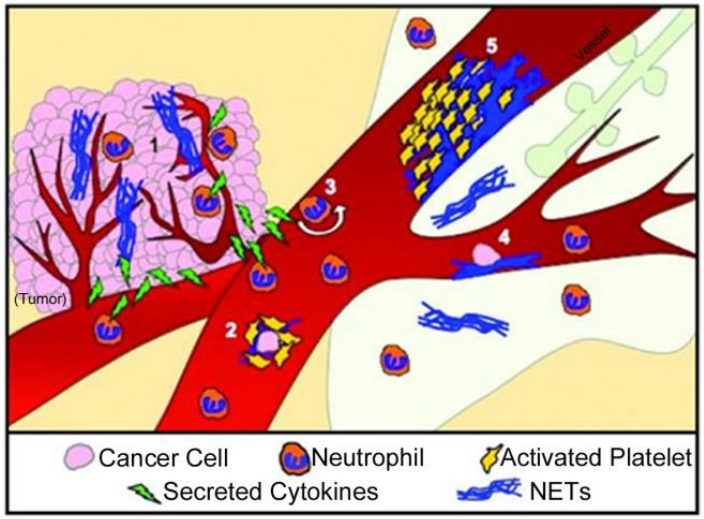
- The Janmey lab has found that prostate cancer cells, in contrast, do not respond to substrate stiffness. They appear to maintain their stiff, spread phenotype even on very soft substrates.

- The Gunning lab has found that a specific cytoskeletal protein, tropomyosin 4 (TPM4), is abnormally highly expressed in prostate cancer cells, and its expression is sufficient to make these cells stiffer than normal.
- Their collaboration seeks to establish a causal link between TPM expression and altered prostate cancer cell mechanobiology, and to test small molecule reagents developed by Gunning that inhibit the deleterious effects of TPM4.

Collaboration between Elizabeth Gardiner, Monash and Owen McCarty, OHSU

PHYSICAL SCIENCES— in ONCOLOGY

Regulation of Tumor Biology by the Blood Microenvironment



- **Netosis is a form of cell death in which neutrophils secrete their DNA to bind pathogen in extracellar traps (NETs)**
- **Blood platelets have been shown to induce NETs formation and promote thrombosis**
- ***In vitro* and *in vivo* work suggests that NETs may play a role in cancer-associated thrombosis**
- **The platelet secretome – the proinflammatory milieu secreted upon platelet activation, has been shown to promote cancer metastasis.**

Goal: Define the role of the platelet secretome in the cross-talk between platelets, neutrophils and tumor cells underlying metastasis and cancer-associated thrombosis.

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Figure adapted from: Demers M, Wagner DD. (Oncoimmunology) 2014

Learn More about NCI Physical Sciences in Oncology Initiative

PHYSICAL SCIENCES— in ONCOLOGY

http://physics.cancer.gov

Larry.Nagahara@nih.gov

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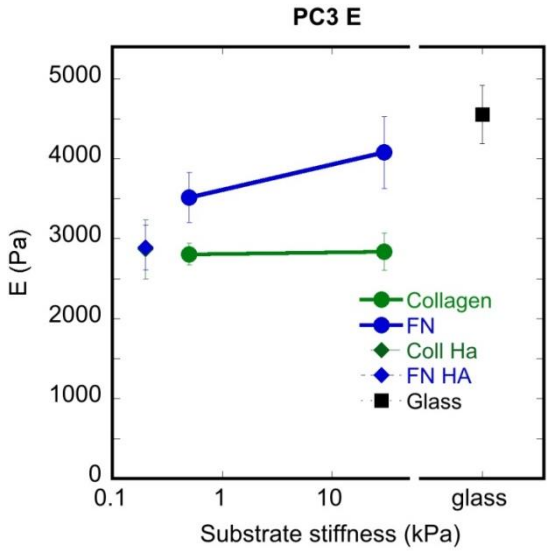
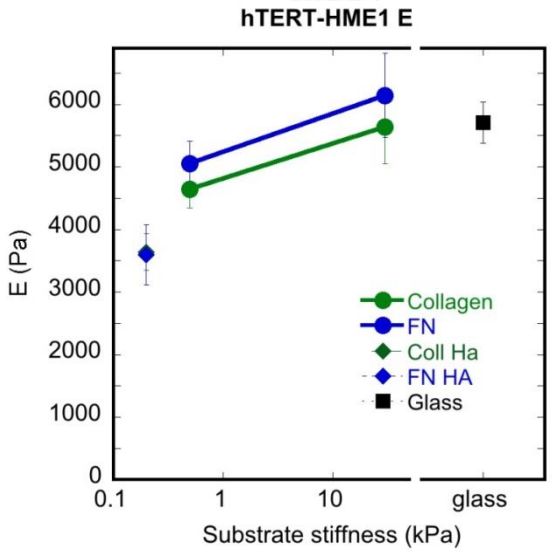
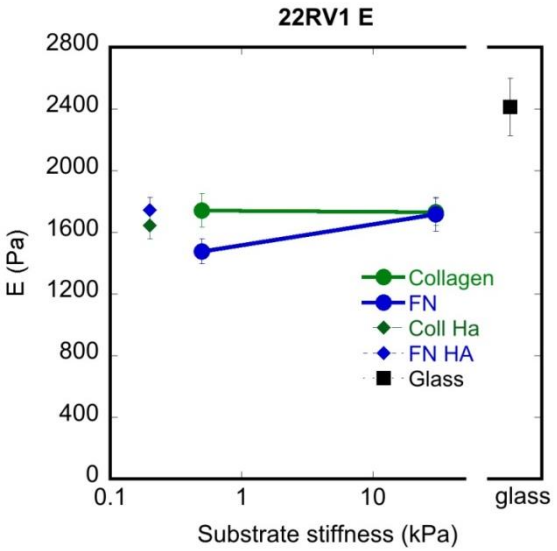
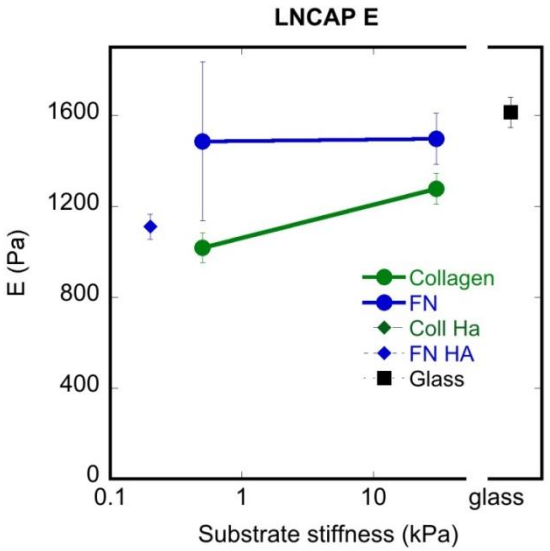
Additional Slides

Prostate cancer cell lines do not change stiffness in response to substrate stiffness

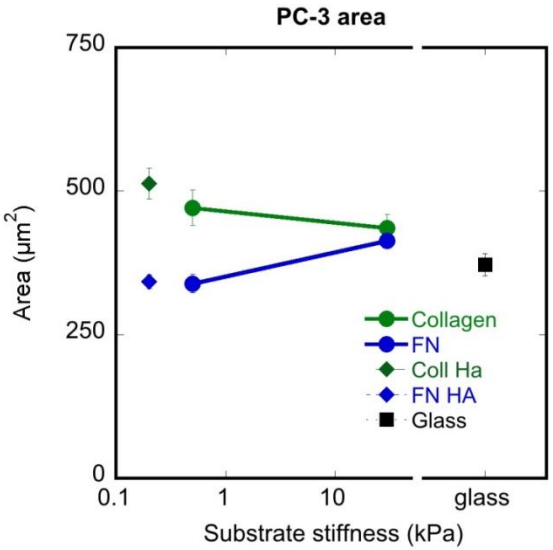


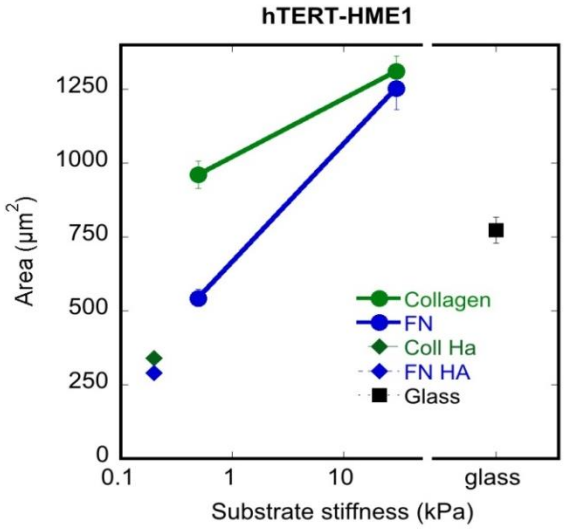


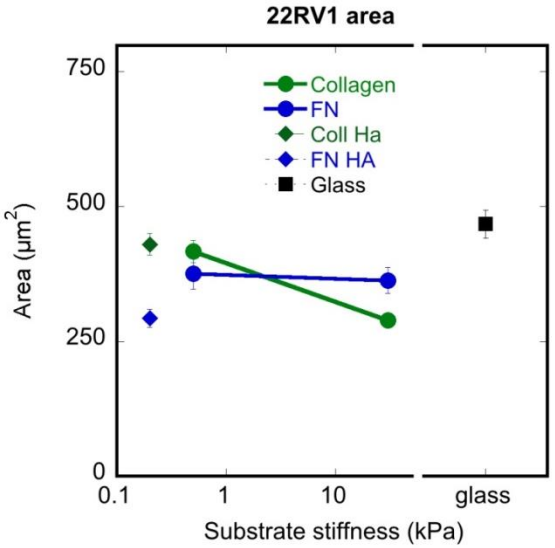


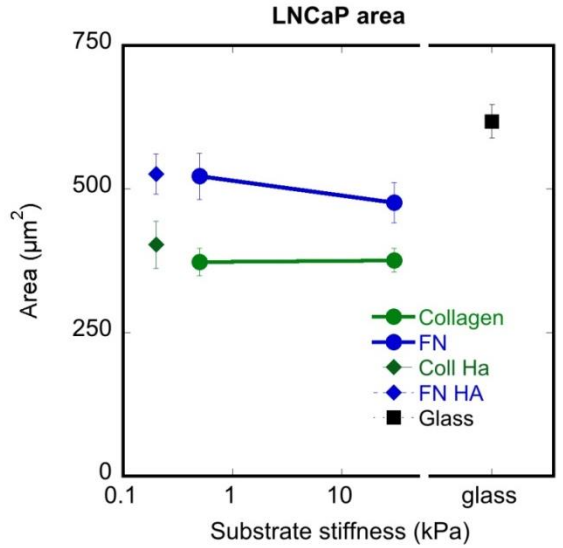


Prostate cancer cell lines do not change area in response to substrate stiffness

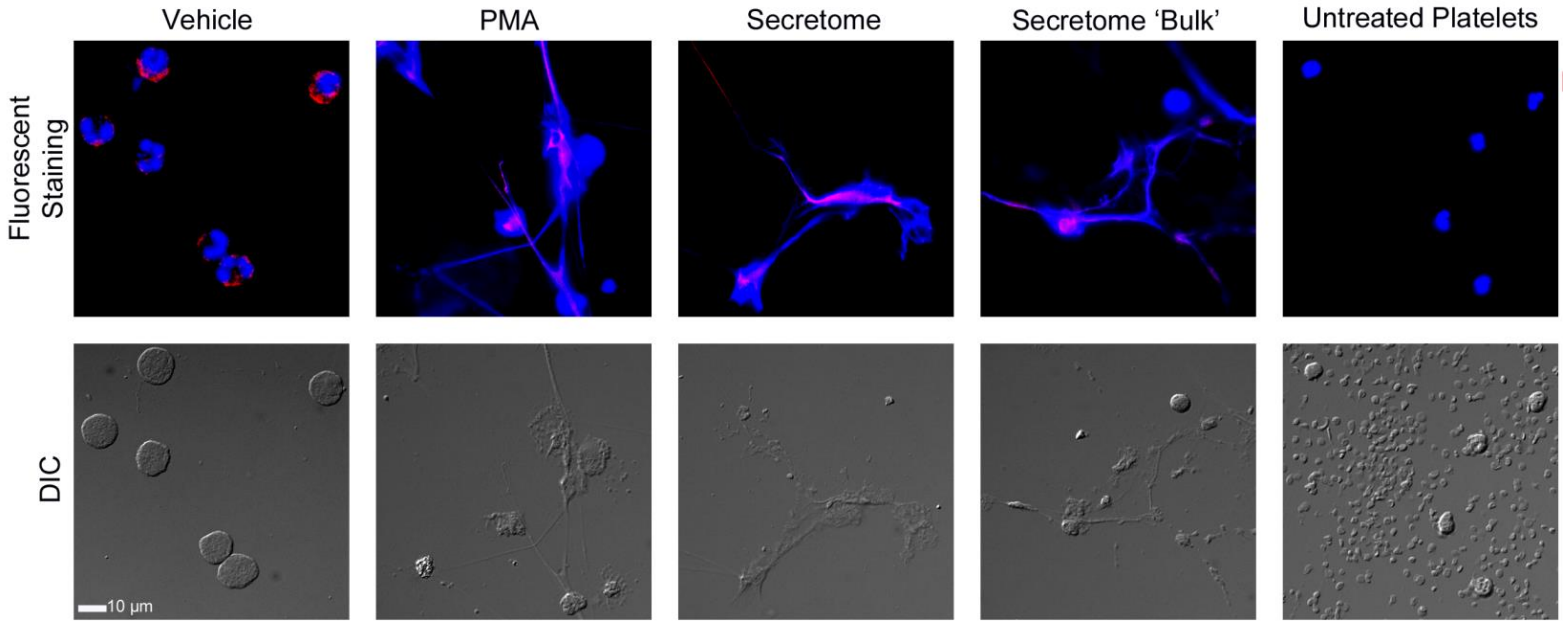


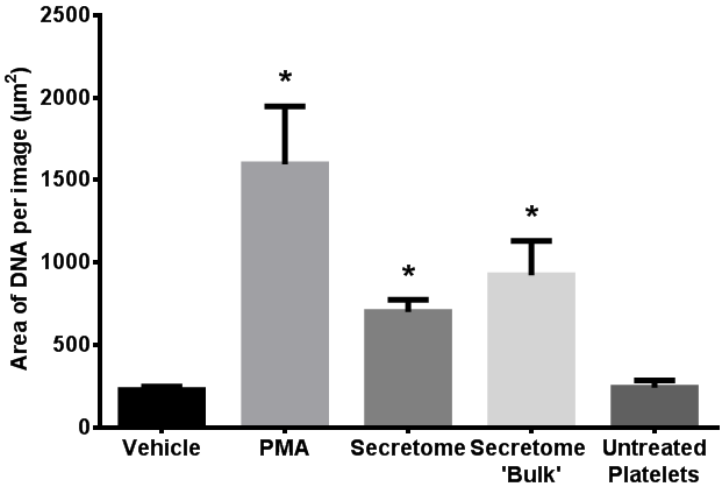


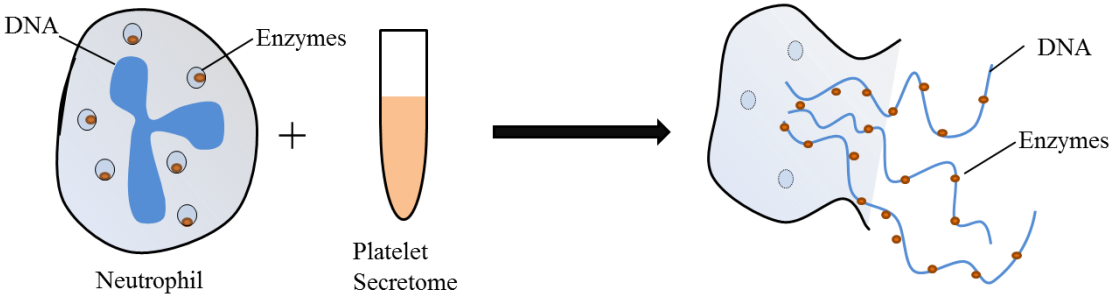




Visualization of NETs







- ***Results: First demonstration of platelet secretome inducing NETs formation***

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Outcomes

PHYSICAL SCIENCES— in ONCOLOGY

- Transferred the knowledge of platelet secretome assay from the Gardiner lab (Australia) to the McCarty lab (US)
- Transferred the knowledge of NETs formation assay to the Gardiner lab (Australia) from the McCarty lab (US)
- Planned future experiments to combine these approaches to determine the role of cross-talk between platelets and neutrophils in metastasis & cancer-associated thrombosis
- Opportunity: funding to support Laura Healy to spend a year in the Gardiner lab
- Drs. McCarty and Gardiner organized and spoke in a special session on the Physical Biology of Thrombus Formation at the 2015 Experimental Biology Meeting (Boston, MA, Apr 2015)
- Laura Healy and Drs. Gardiner and McCarty will generate an abstract for submission to the 2015 Society of Leukocyte Biology meeting (Chapel Hill, NC, Sep 2015)

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