



AAS

Association for  
Academic Surgery

**Sareh Parangi MD**  
**Professor of Surgery**  
Massachusetts General Hospital  
**Harvard Medical School**

# Disclosures- None

*Minimally Invasive...by Pories*



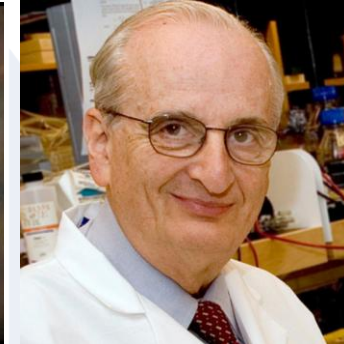
*"In accord with requirements, let me first present my real conflicts of interest...."*

# My story and background

## College/Medical School

Barnard College/Columbia University

1982--1990 ( Basic Research )



Orlo Clark ,Judah Folkman, Doug Hanahan PhD

## Residency training

University of California, San Francisco

Boston Children's/MIT

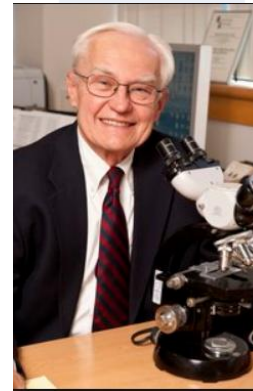
## Faculty Positions

Beth Israel Deaconess Medical Center

1998-2007

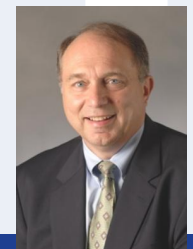
Massachusetts General Hospital

2008-present



Hal Dvorak MD/Jack Lawler PhD /Rich Hodin MD

Keith Lillemoe





Born in 1933

Father was a rabbi

Harvard Medical School at 19

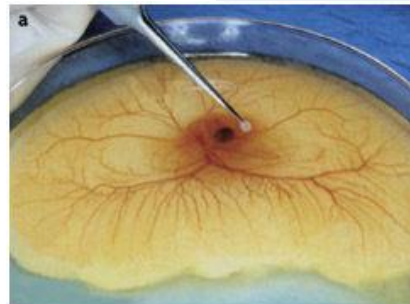
Professor at HMS- 34

Courtesy of Marsha Moses PhD  
Director of Harvard Vascular Biology Program

## **TUMOR ANGIOGENESIS: THERAPEUTIC IMPLICATIONS**

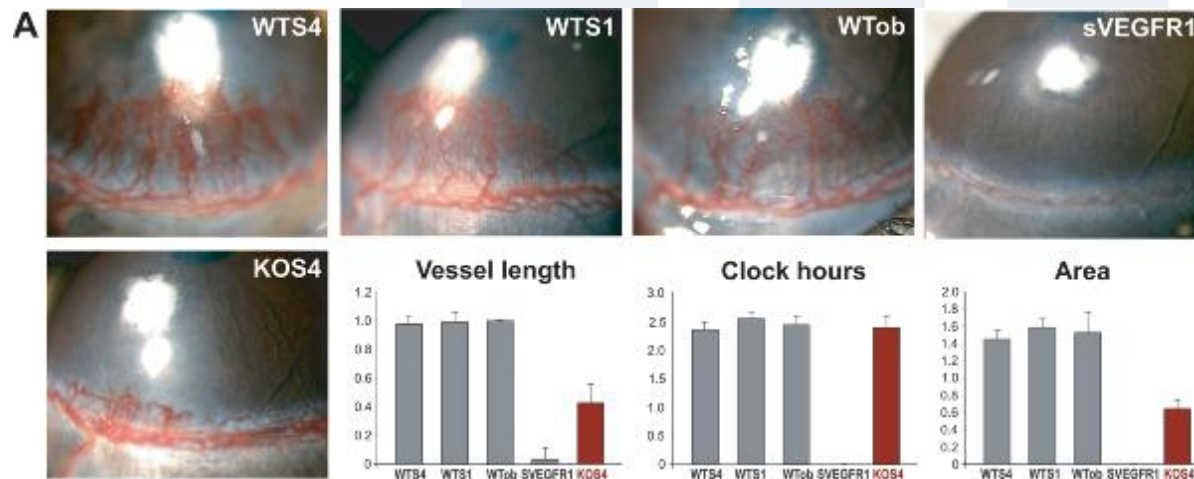
JUDAH FOLKMAN, M.D.

1. “. . . solid tumors are **dependent** upon **new** capillary sprouts. . .”
2. “. . . without neovascularization solid tumors might become completely **dormant**...”
3. “the term **anti-angiogenesis** is proposed to mean the prevention of new vessel sprouts from penetrating into an early tumor implant.”
4. “the necrotic center of a large tumor was at one time well vascularized, however, the **high pressures** which build up in a large tumor could **diminish blood flow** to the center.”

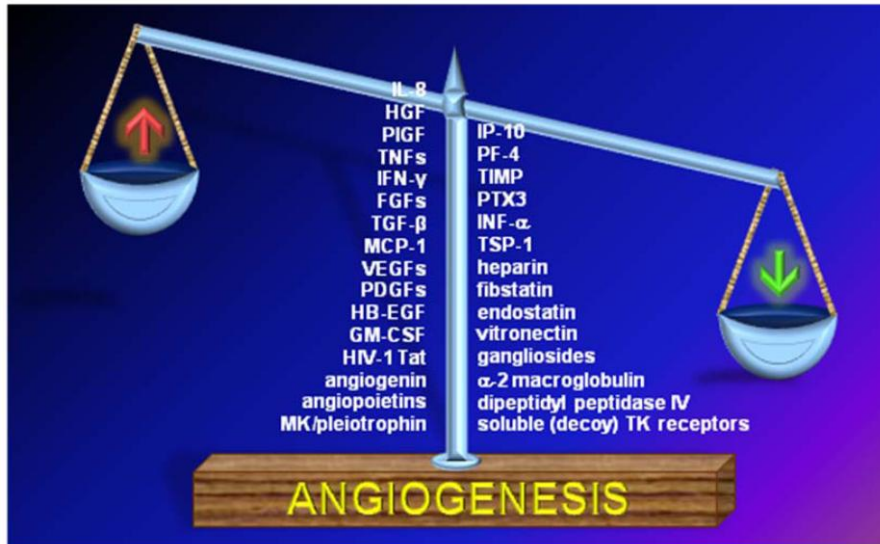


# Rejection

- 1970- Folkman sends in first NIH grant  
*Hypothesis: Tumor growth is dependent on blood supply*
- Review summary-pink sheet  
*“It is common knowledge that the hypervascularity associated with tumors is due to dilation of host vessels and not new vessels and that this dilation is probably caused by the side effects of dying tumor cells. Therefore, tumor growth cannot be dependent upon blood vessel growth any more than infection is dependent upon pus.”*



# Angiogenesis



1998-

**Judah Folkman-**

*"If you have a cancer and you are a mouse, we can take good care of you"*

2004-

**Mark McClellan, FDA commissioner**

*"Anti-angiogenic therapy can now be considered the 4<sup>th</sup> modality for cancer treatment" (in addition to surgery, radiation and chemotherapy).*

# His scientific legacy

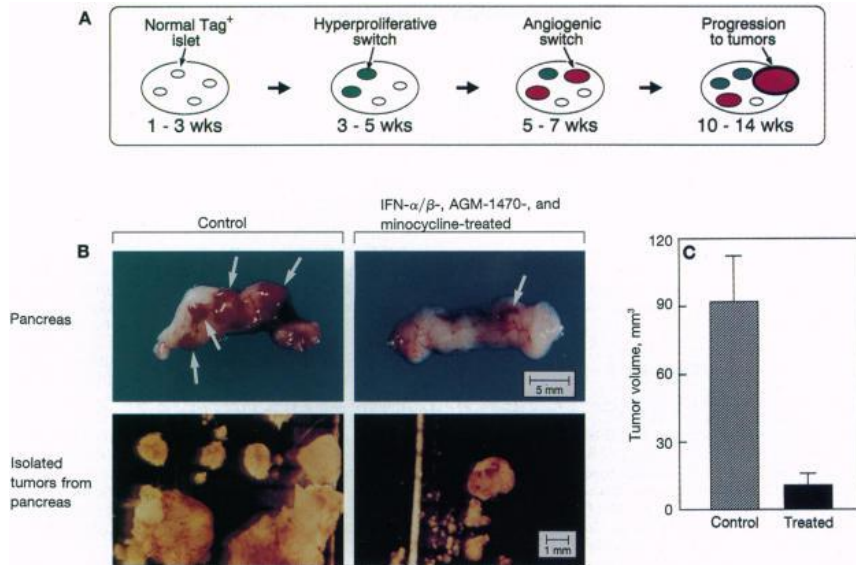
Publications	<b>447</b>
Book chapters and reviews	<b>116</b>
Trainees	<b>165</b>
Patents (issued and pending)	<b>477</b>



# His scientific legacy

Drug/Company	Type of inhibitor	Targets	Use	Indication
Bevacizumab (Avastin) Genentech/Roche	Monoclonal Antibody	VEGF-A	First or second line	Metastatic colorectal cancer
			First line	Nonsmall cell lung cancer
			First line	Recurrent glioblastoma
			First line	Metastatic renal cell carcinoma
			Off-label	Wet age-related macular degeneration Macular edema following CRVO
Aflibercept (Zaltrap) Regeneron/Sanofi	Chimeric soluble receptor	VEGF-A, VEGF-B, PIGF	Second line	Metastatic colorectal cancer
Pegaptanib (Macugen) Eyeteq Pharms	Pegylated aptamer	VEGF-A165	First line	Wet age-related macular degeneration
Ranibizumab (Lucentis) Genentech/Roche	Fab fragment of antibody	VEGF-A	First line	Wet age-related macular degeneration Macular edema following CRVO
Aflibercept (Eylea) Regeneron/Bayer	Chimeric soluble receptor	VEGF-A, VEGF-B, PIGF	First line	Wet age-related macular degeneration Macular edema following CRVO
Sorafenib (Nexavar) Bayer/Onyx	Tyrosine kinase inhibitor	VEGFR, PDGFRs, FGFR1, KIT, RAF	First line First line	Metastatic renal cell carcinoma Unresectable hepatocellular carcinoma
Sunitinib (Sutent) Pfizer	Tyrosine kinase inhibitor	VEGFRs, PDGFRs, KIT, FLT-3	First line Second line First line	Metastatic renal cell carcinoma Gastrointestinal stromal tumor Unresectable pancreatic neuroendocrine tumors
Pazopanib (Votrient) GlaxoSmithKline	Tyrosine kinase inhibitor	VEGFRs, PDGFRs, KIT	First line Second line	Metastatic renal cell carcinoma Advanced soft tissue sarcoma
Axitinib (Inlyta) Pfizer	Tyrosine kinase inhibitor	VEGFRs, PDGFRs, KIT	First line	Metastatic renal cell carcinoma
Vandetanib (Caprelsa) Astra Zeneca	Tyrosine kinase inhibitor	VEGFRs, EGFR, RET	First line	Late-stage medullary thyroid cancer
Cabozantinib (Cometriq) Exelixis	Tyrosine kinase inhibitor	VEGFR2, RET, MET	First line	Progressive medullary thyroid cancer
Regorafenib (Stivarga) Bayer/Onyx	Tyrosine kinase inhibitor	VEGFRs, TIE2, PDGFRs, RET, KIT, FGFRs	Second line Second line	Metastatic colorectal cancer Gastrointestinal stromal tumor

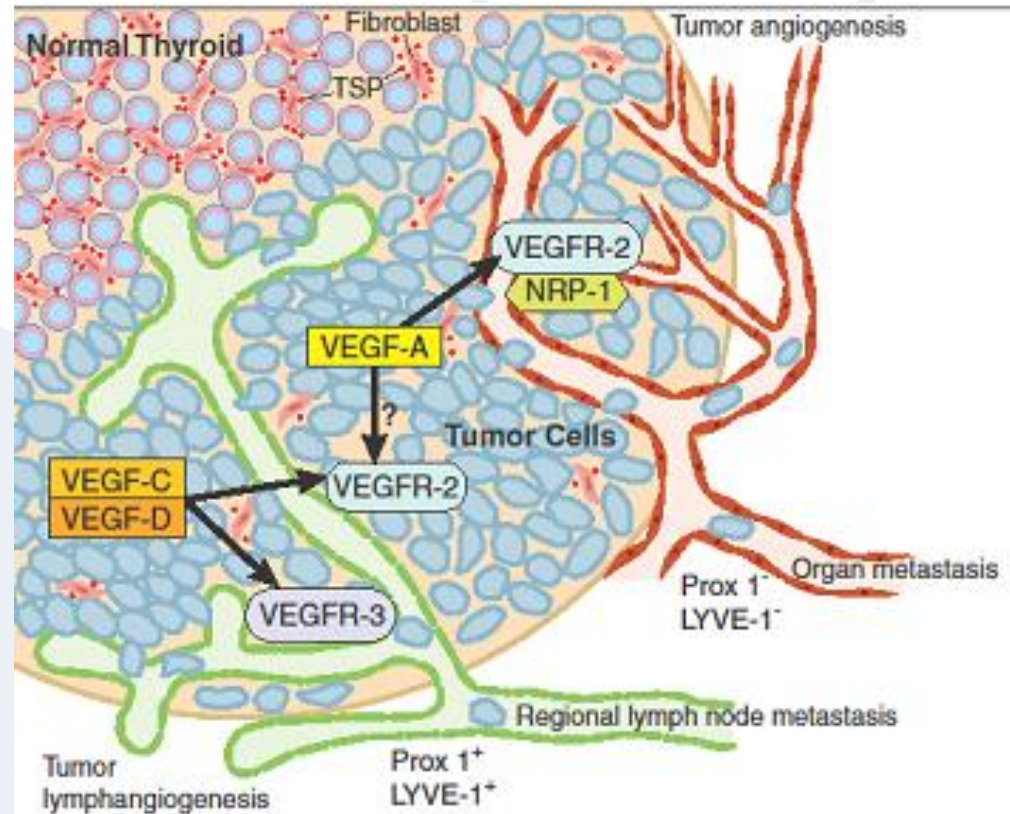




# Animal models of cancer

Complex interaction  
between different cell  
types:

- Tumor cells
- Endothelial cells
- Lymphatics
- Stromal cells
- Immune cells
- Inflammatory cells



# First phase....

- Smaller grants – 1998-2007
    - Institutional support
    - ACS
    - K08 grant
    - Foundation grants
  - ATA grant--- connection to my clinical practice
- Testing antiangiogenic therapies in pancreatic cancer

# 2007 - Making the jump to independence

- Demonstrate independence
- First and senior author publications
- Obtain independent “space”
- Obtain additional pilot grants

K-Award

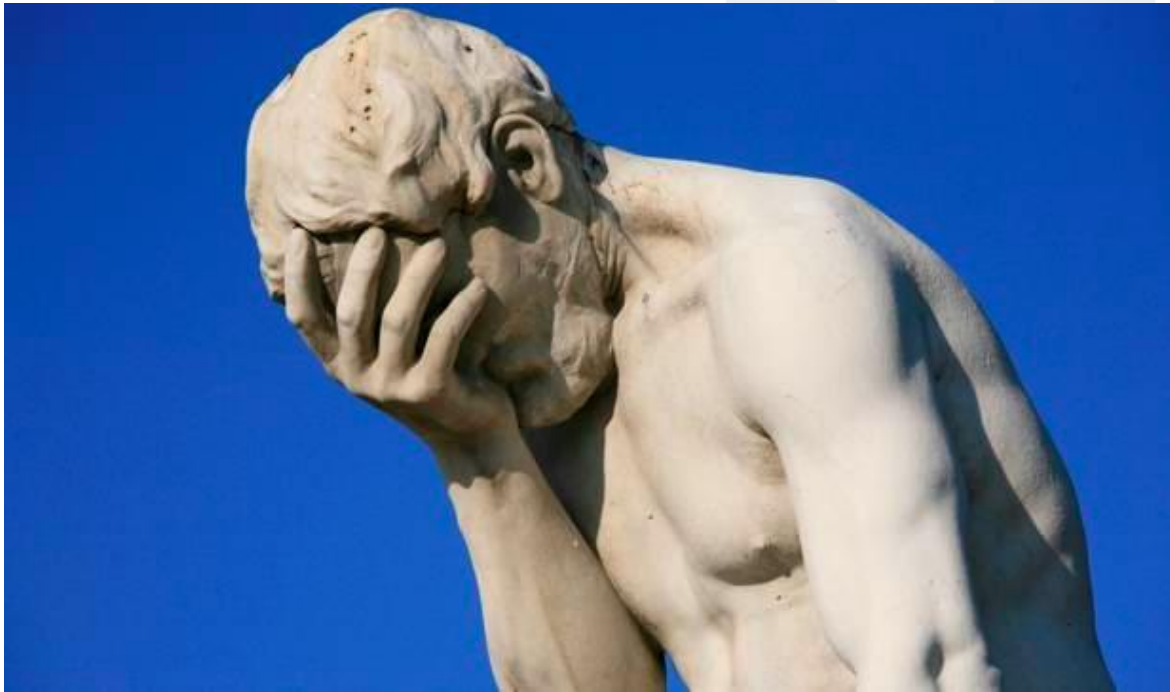


R01-Award



# Starting the process for R01 grant

- 2007 → started to write R01 grants



# Starting the process for R01 grant

- Preparation
  - 28 publications total
  - > 12 publications in my area of funded grants (Cancer Research, Clinical Cancer Research, etc...)
  - Meeting with various mentors
  - Understanding the study sections
- First R01's submitted NCI in 2007 → non fundable score



**SUMMARY STATEMENT**

**PROGRAM CONTACT:**  
Elizabeth Snyderwine  
301-435-1878  
elizabeth\_snyderwine@nih.gov

( Privileged Communication )

**Release Date:** 06/13/2010

**Application Number:** 1 R01 CA149738-01A1

**Principal Investigator**

**ARANGI, SAREH MD**

**Applicant Organization:** MASSACHUSETTS GENERAL HOSPITAL

**Review Group:** ICER  
Integrative and Clinical Endocrinology and Reproduction Study Section

**Meeting Date:** 06/07/2010  
**Council:** OCT 2010  
**Requested Start:** 12/01/2010

**RFA/PA:** PA10-067  
**PCC:** C  
**Dual PCC:** P  
**Dual IC(s):**

**Project Title:** The Role of BRAF Mutation in Thyroid Cancer Proliferation

**SRG Action:** Impact/Priority Score: 17 Percentile: 5

**Human Subjects:** 10-No human subjects involved

**Animal Subjects:** 30-Vertebrate animals involved - no SRG concerns noted

Project Year	Direct Costs Requested	Estimated Total Cost
1	225,000	385,986
2	225,000	385,986
3	225,000	385,986
4	225,000	385,986
5	225,000	385,986
<b>TOTAL</b>	<b>1,125,000</b>	<b>1,929,930</b>

Massachusetts YEAR

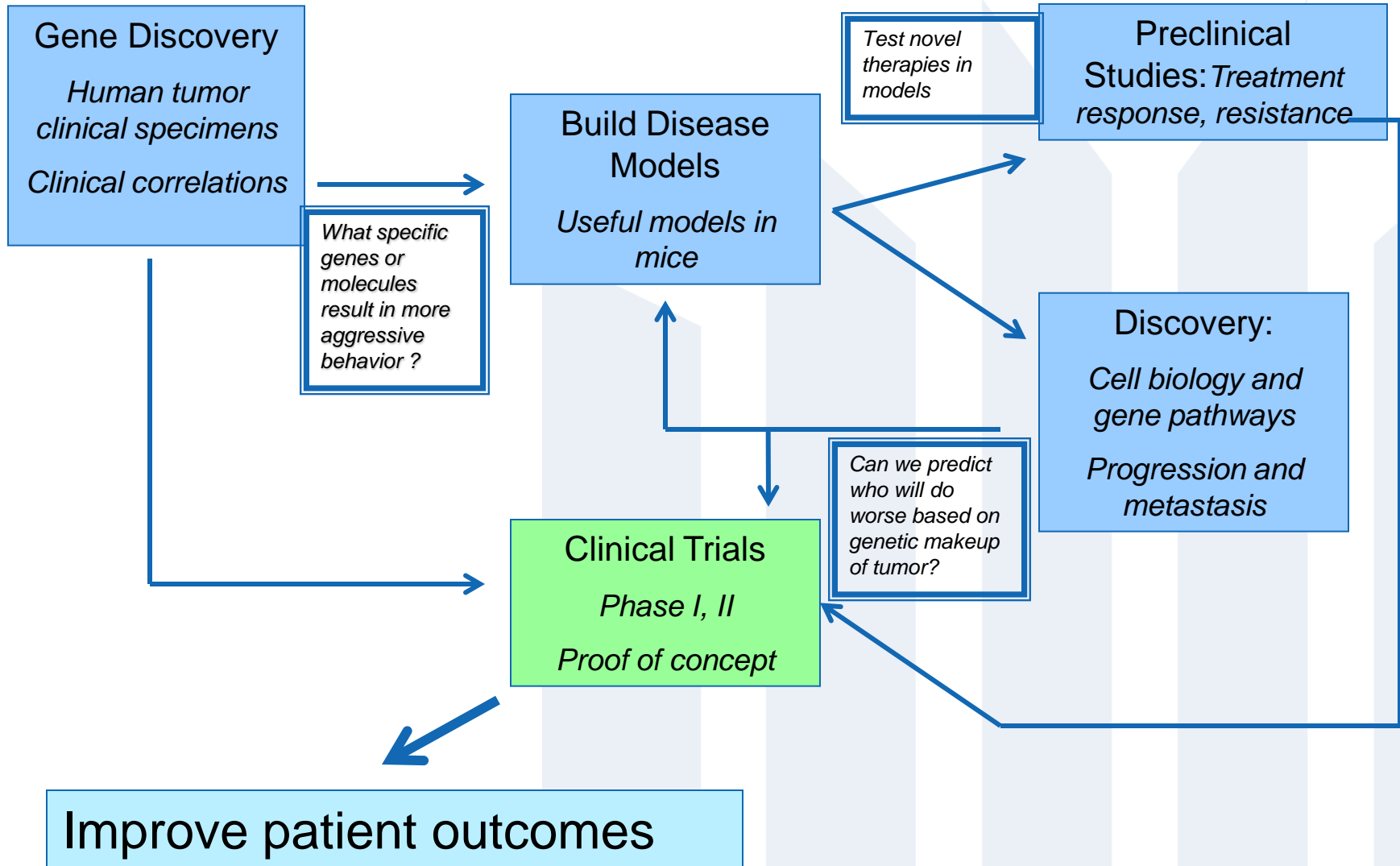
# 25 TS R01

The Spirit of America



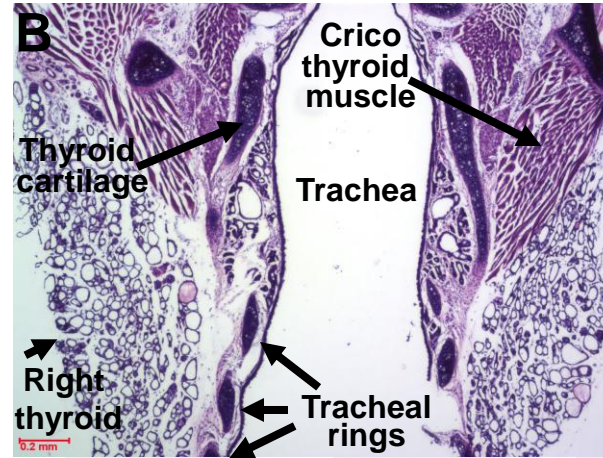
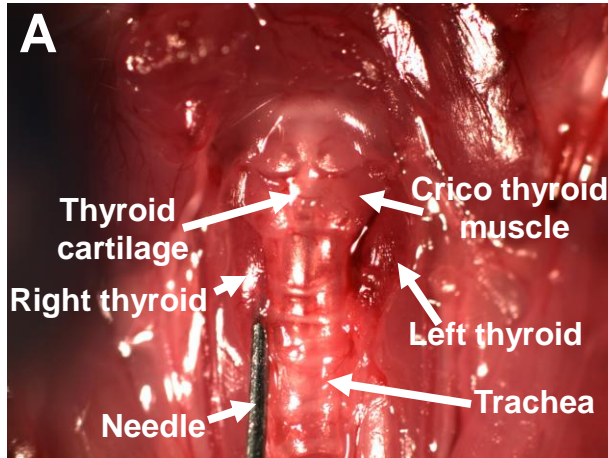
66 grants/last 10 years = 6 grants/year

# How to use the money? Better define my lab effort

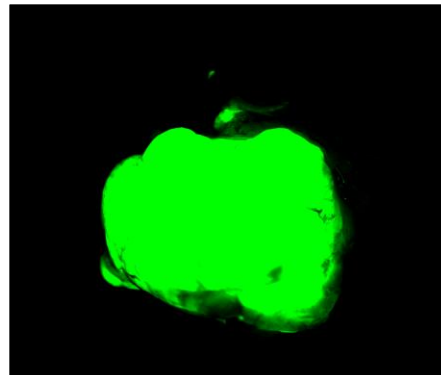
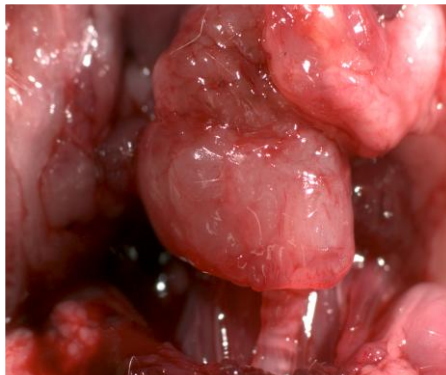


# Development of a simple orthotopic mouse model using fluorescent human thyroid cancer cells

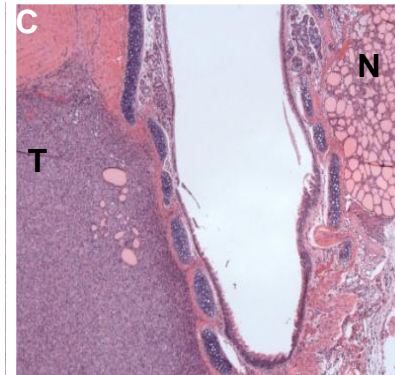
Anatomy  
Normal  
Mouse  
Thyroid



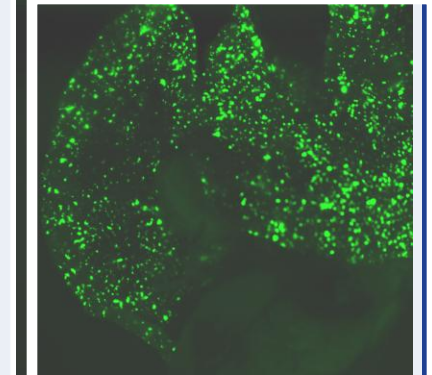
GFP

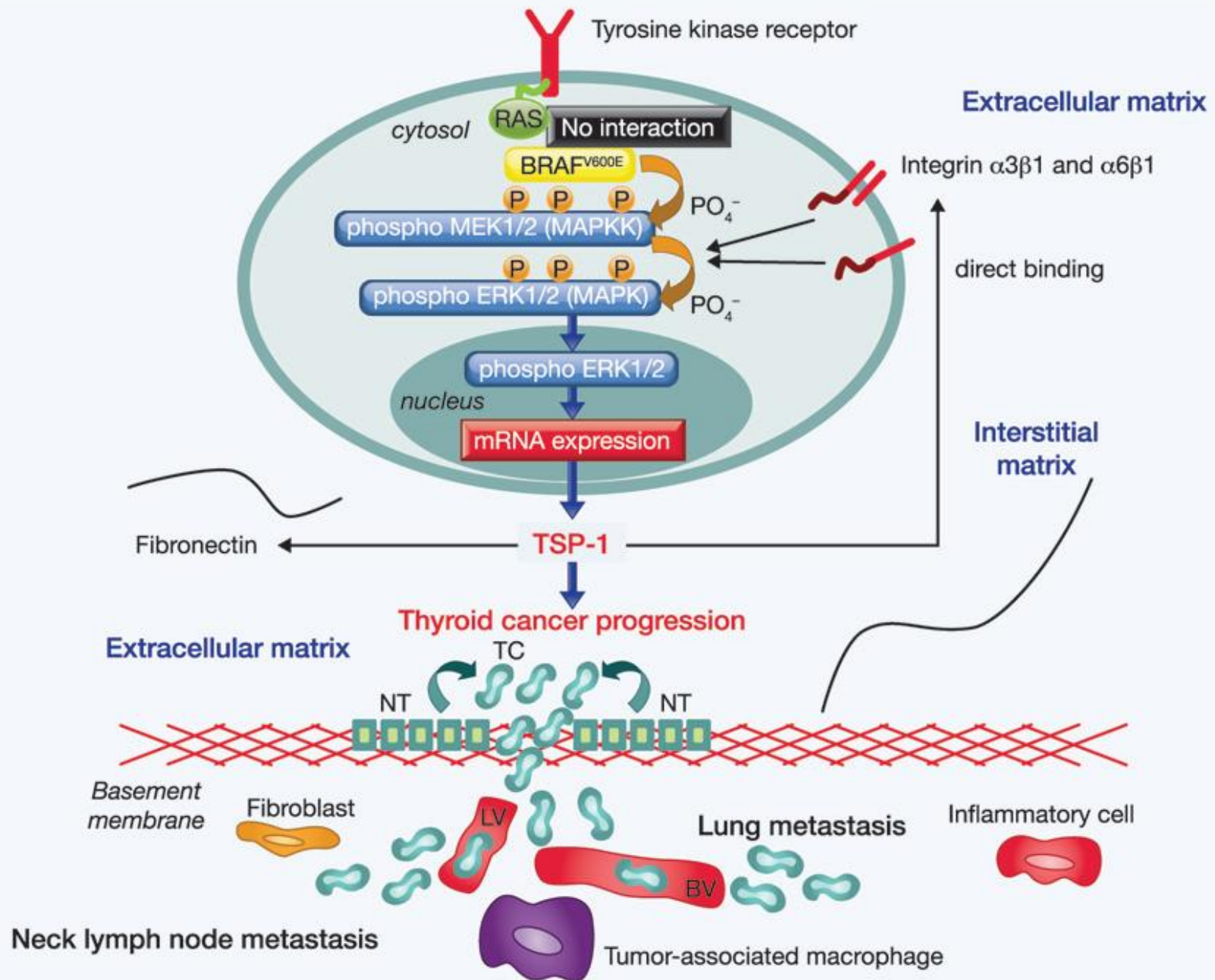


Histology

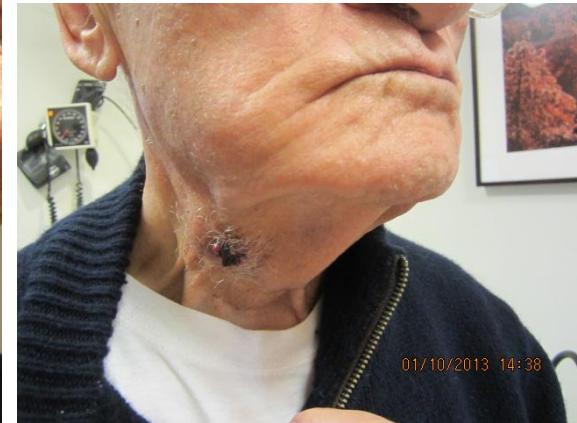
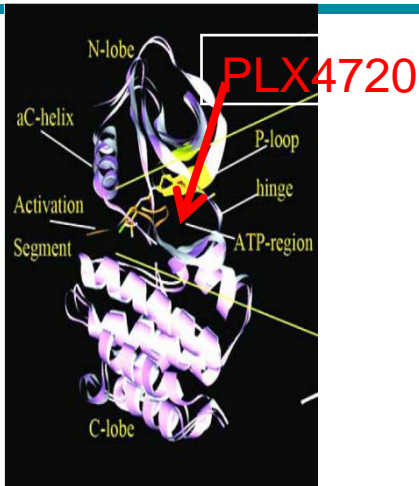


Lungs





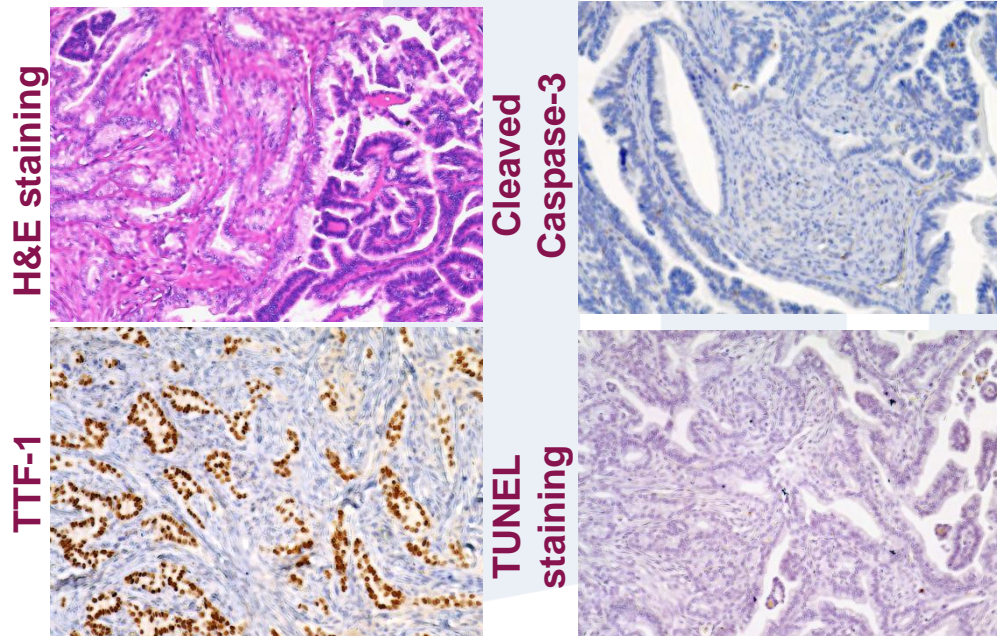
# From mice to men



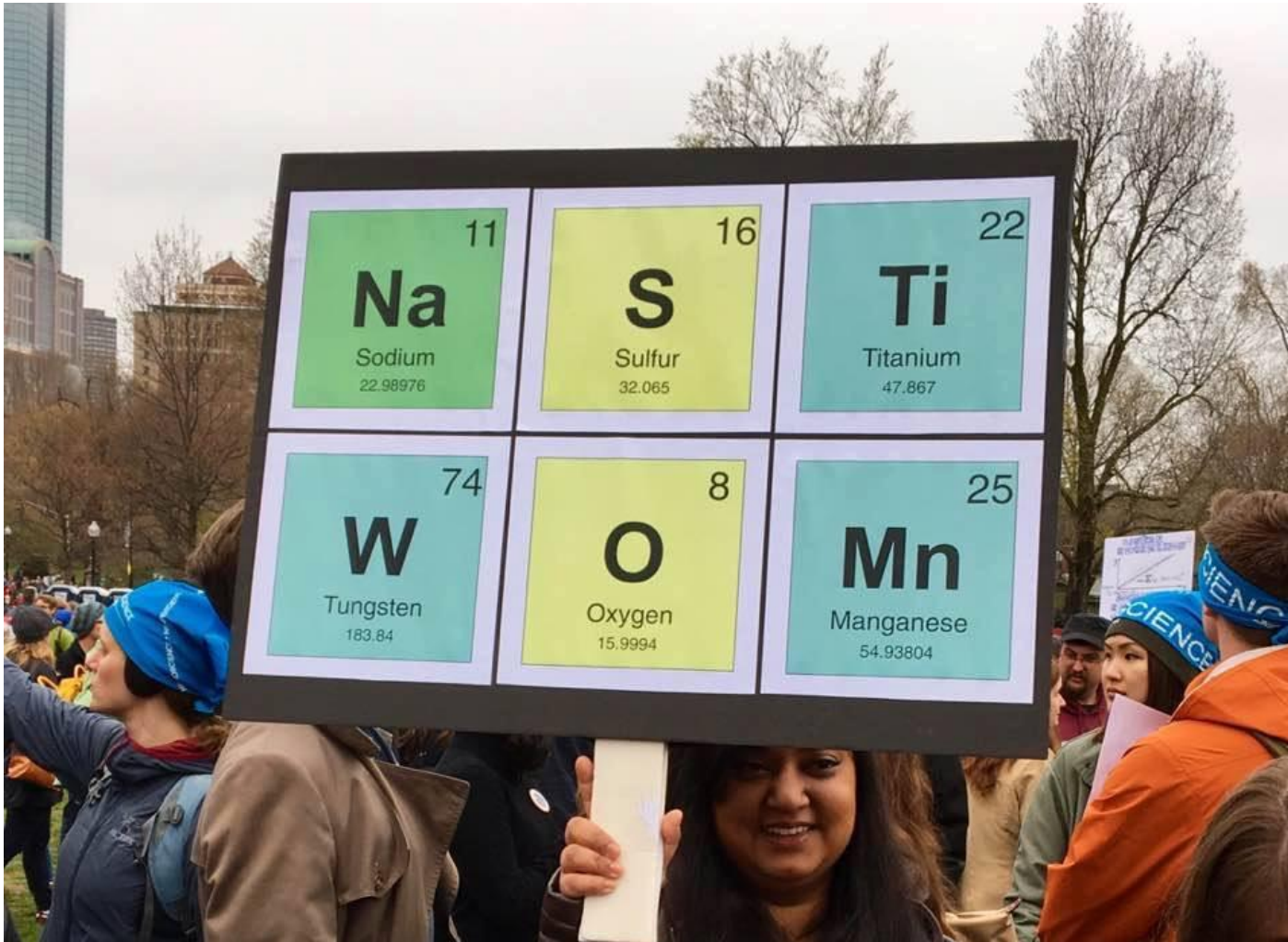
# Lessons learned from treated patients

## Pathway interactions are extremely complex

- Activation of upstream signaling pathways
  - Resistance to therapy
  - Development of cutaneous squamous cell carcinomas
  - Marked resistance to apoptosis
- Effects of BRAF and BRAF inhibitors on immune system
  - Need improved models



# Don't be afraid

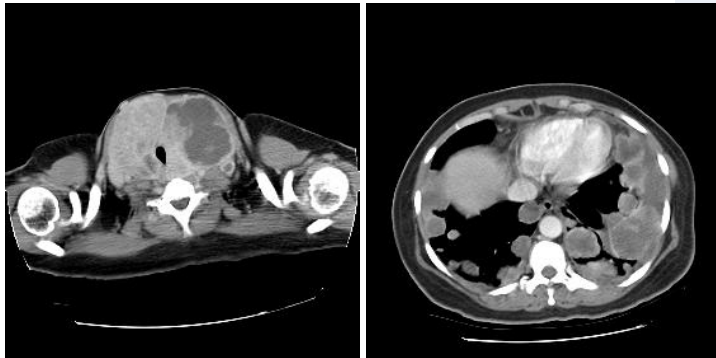
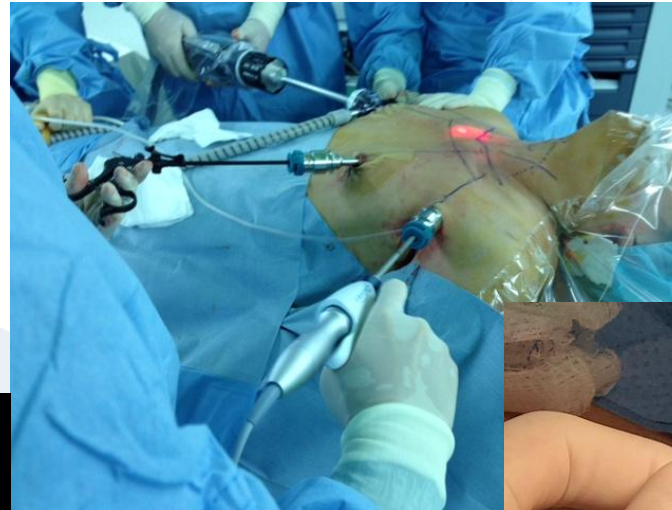
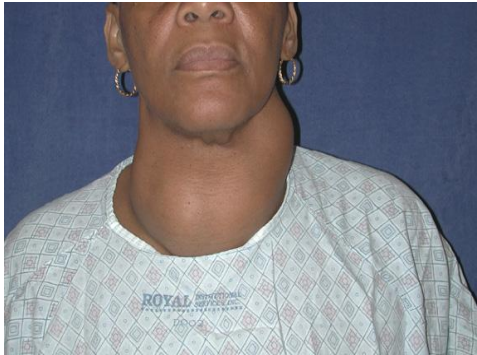




# 8 P's for Success in Research

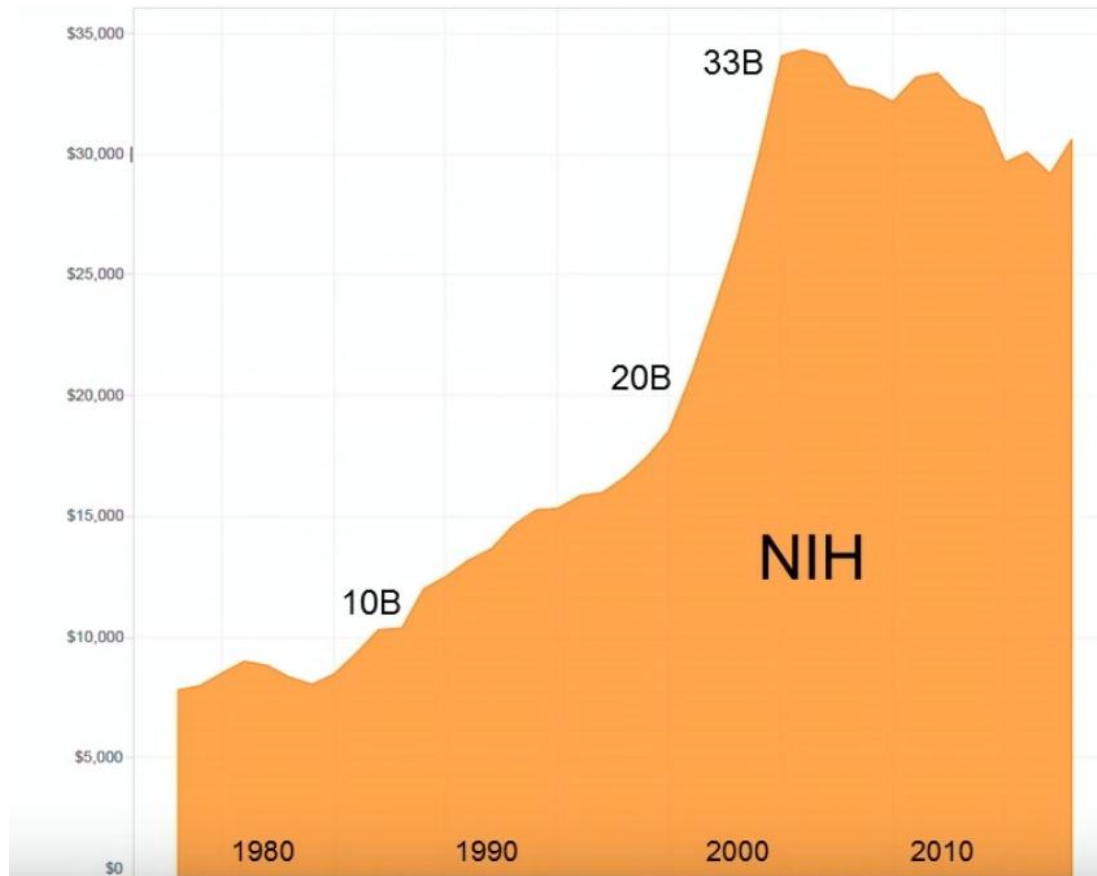
- **Passion**
  - Choose areas of research that you are interested in
  - Clinically relevant
- **Push yourself-** Don't wait to be pulled
- **Protect** your time
- **Plan:**
  - Plot a path- might not be a straight path
  - Careers are full of twists and turns
- **Partner** (Mentor/Collaborator/Chair/Colleagues)
- **Place** (Environment/Infrastructure)
- **Prove yourself-** metrics and data
- **Persistence**
  - Rejection and disappointment are ok but don't let them be deterrents
  - Don't sell yourself short

# Why go into academic surgery



**Your patients need you to ask the hard questions  
and they need your innovation**

# Why go into academic surgery

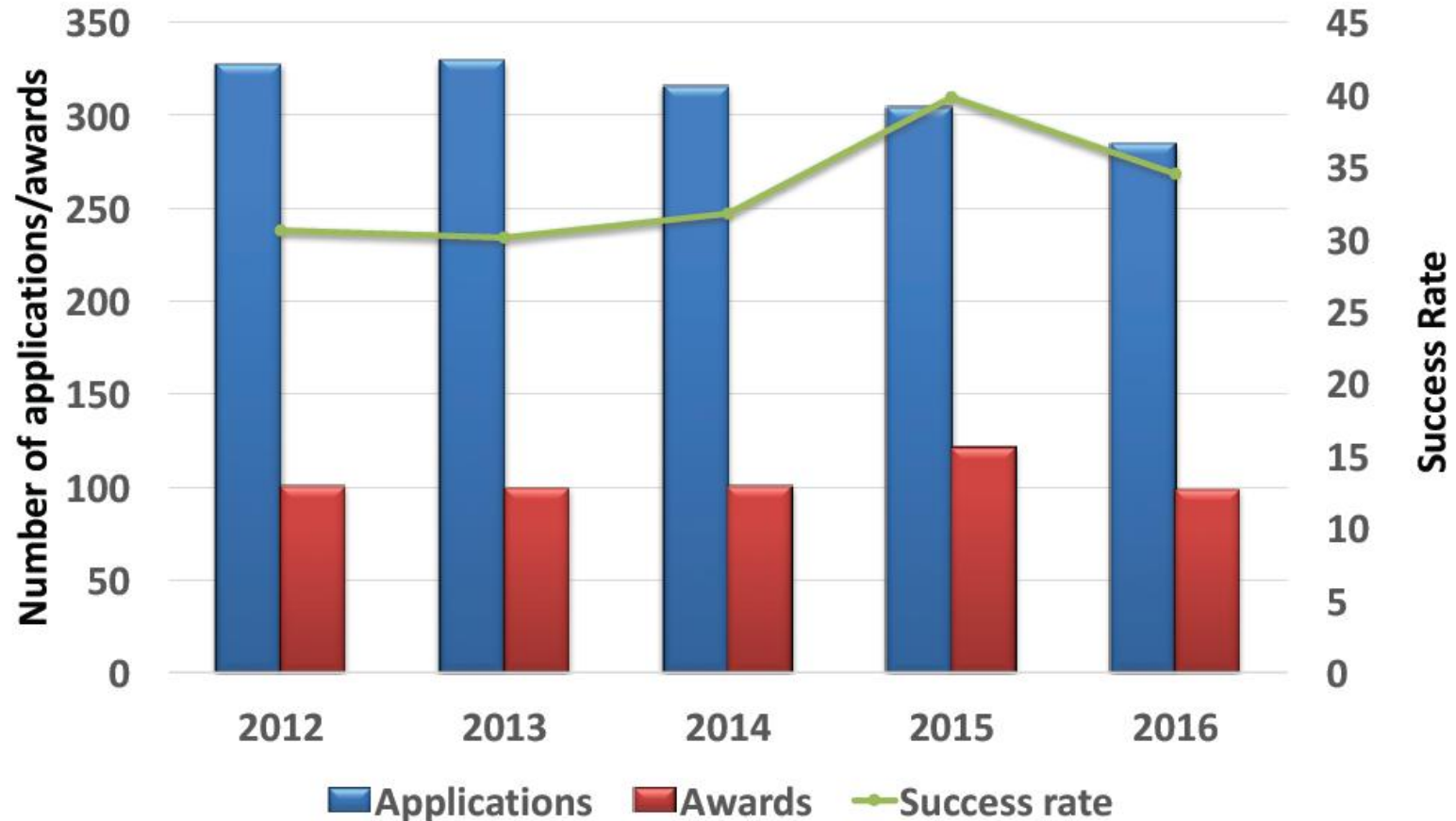


Federal R&D Funding (budget authority, millions of dollars)

Grab our share of the money



# NIDDK Career Development Awards



\*includes K01, K08, K23, K99

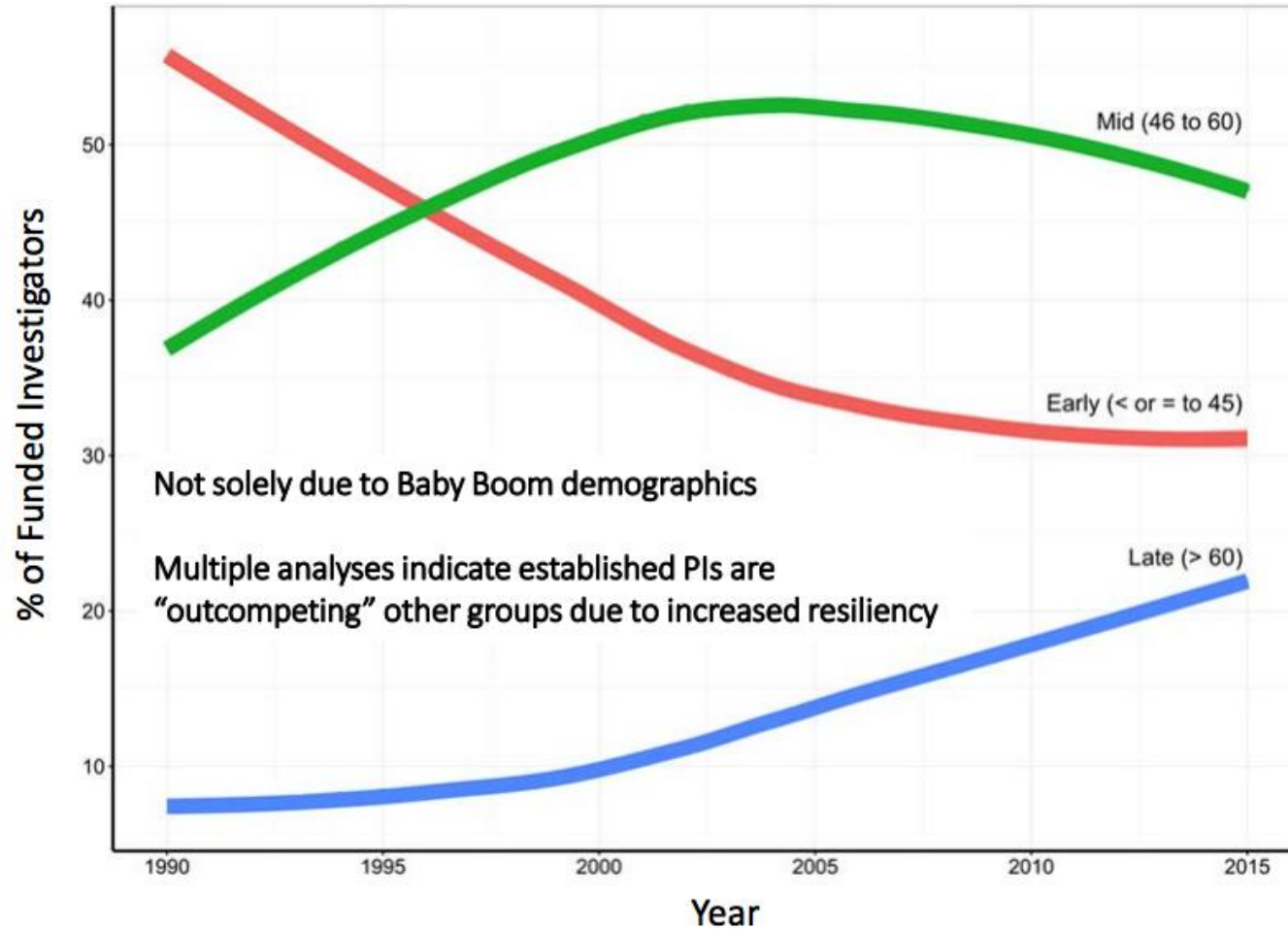
# Career Development Award: subsequent grant activity by degree -- 2005-2010 cohort\*



Degree (n)	% follow up any application	% follow up any award	% R01 application	% R01 award
MD (245)	87%	68%	78%	46%
MD/PhD (115)	90%	72%	83%	53%
PhD (206)	85%	61%	78%	51%
Other (7)	86%	71%	86%	71%
<b>TOTAL (573)</b>	<b>87%</b>	<b>66%</b>	<b>79%</b>	<b>49%</b>

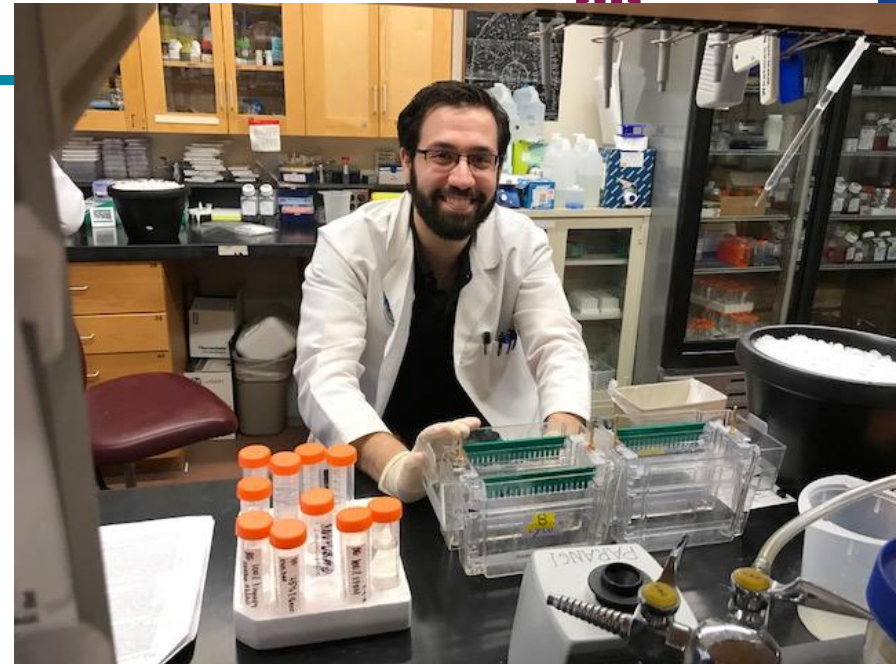
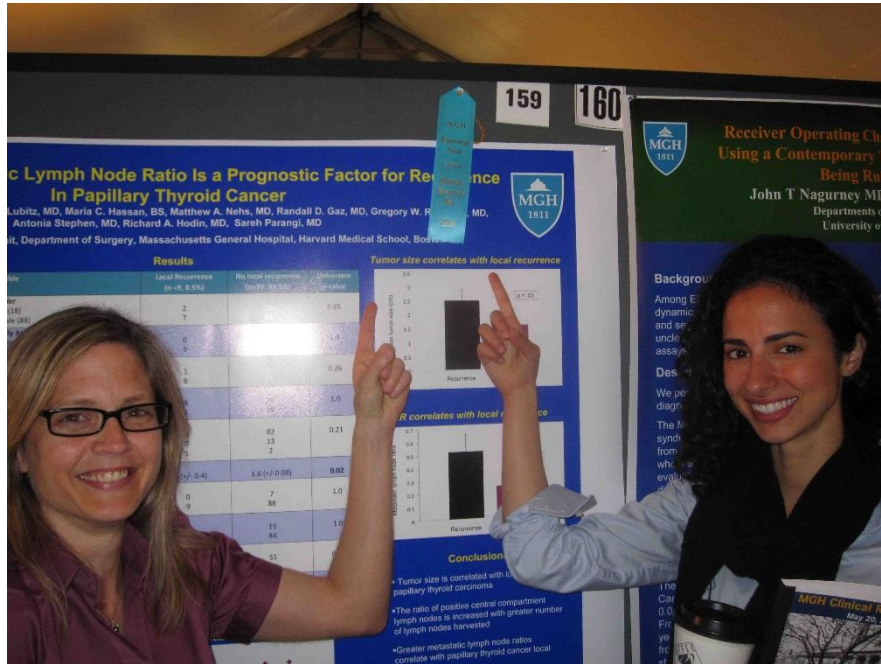
\*all K01/K08/K23/K99 awardees whose K grants ended between 2005-2010

# Established PI's outcompeting other groups



Age of Investigators Funded by NIH

# Why go into academic surgery



You get to play in the lab and people present your work

# Why go into academic surgery



Somebody needs to train the next generation-  
be a role model



# Why go into academic surgery



Get to go to meetings and meet up with old friends



Travel to fun places

# Why go into academic surgery



Your paycheck will be HUGE

# Remember that life happens



*“The problem of understanding the phenomenon of angiogenesis, of working out its biology, of connecting it to a large family of clinical diseases once thought to be totally separate entities, seems to have been tackled in somewhat the same way that the author E.L. Doctorow describes what it is like to write a novel. **‘Writing is like driving at night,’ he said, ‘You cannot see beyond the headlights, but you can make the whole trip that way.’”***

*“—Judah Folkman, M.D.”*

2007 *same yr.*

2007 Central Questions 2007

(Rough Draft) - Please do not erase. J.F

1. Ovarian Cancer - why are most inactivating?
2. Reset non-angiogenic tumor: Can platelets detect?
3. Oral Loxanox-Doxycycline: main process?
4. siRNA inhibition of PPAR $\alpha$ ?
5. Time to angiogenic switch reduced in Tsp1 KO?
6. Can non-angiogenic tumors be eradicated by telomerase inhibitors, *Very shy*
7. Time to angiogenic switch increased in mice that overexpress endothelin or thrombospondin? (await scid crosses)
8. AKT - PIN Prostate
9. ? Survival release of 2 methyl in Silicone rubber

### I. Maintenance of human tumor dormancy

#### 1. Switch to the angiogenic phenotype:

- a) What dictates timing?
- b) What determines percentage?

? ③ What is the fate of those that never switch?

d) Is the angiogenic switch reversible?

- (i) Spontaneously? Percentage?
- (ii) Therapeutically?

### II. Angiogenic Predetermination of Metastatic Site?

1. Can a primary tumor specify its future metastatic site(s)?

a) By suppressing local endogenous angiogenesis inhibitor(s)?

? b) Do certain breast cancers prepare axillary lymph nodes by this mechanism?

\* ? 2. Can endometrium be prepared for blastocyst implantation by this mechanism?

### III. Is oncogene-addiction-angiogenesis-dependent?

### IV. Endostatin peptide and Endostatin

- a) *is this dormancy due to induction of TSP-1?*
- b) Does peptide induce TSP1 in vivo?

### V. BRCA-1. Does it regulate angiogenesis in human breast cancer?

### VII. Coplastatin - mechanism.

↳ Endostatin-oral (? TSP-1 or endo)

### VIII. Down Syndrome - DSCR1 a 2nd angiogenesis inhibitor

### IX. Clinical Translation

- a) Can cancer Dx + Rx be liberated from dependency on anatomical site? (cancer trials)
- b) Neuroblastoma: Early Dx of recurrence and Rx angiogenesis-based biomarker?
- c) Replacement of a methoxyestradiol in premature babies
- d) Omega-3 removal of cholesterol
- e) LAM (hypertension)

F. Time: VEGF ↑ urinary loss of endogenous antiangiogenic proteins?

### XI. Platelet Angiogenesis Proteome

#### 1. Platelet-tumor interactions?

- a) Are platelets trapped in some tumors, but not others?
- b) Do tumors donate angiogenesis regulatory molecules to platelets?
- c) Do tumors receive angiogenesis regulatory molecules from platelets?
- d) Do platelets recycle their proteins?

#### 2. Alpha granules pro-angiogenic and anti-angiogenic?

- a) Uptake + storage *Itakura (12-14)*
- b) Release *Electron microscope studies*
- c) Platelet residence time in tumors? *Klemke (2007) PARI + PARI2*
- d) Role in angiogenic switch?
- e) Role in maintenance of dormancy?

#### 3. Early biomarker?

- a) Screening markers *Loi + AKSku*

④ ② Removal of non-angiogenic tumor:

Does platelet angiogenesis proteome detect? How long does it take? Correlation + luciferase?

⑤ Can non-angiogenic tumors be eradicated by long-term Rx of ANG2 or endostatin or coplastatin?

Vascular Biology Program Conference Room  
Karp 12, Children's Hospital Boston  
Courtesy of Marsha Moses, PhD  
Director of Vascular Biology Program

# Thank you



# Thank you

