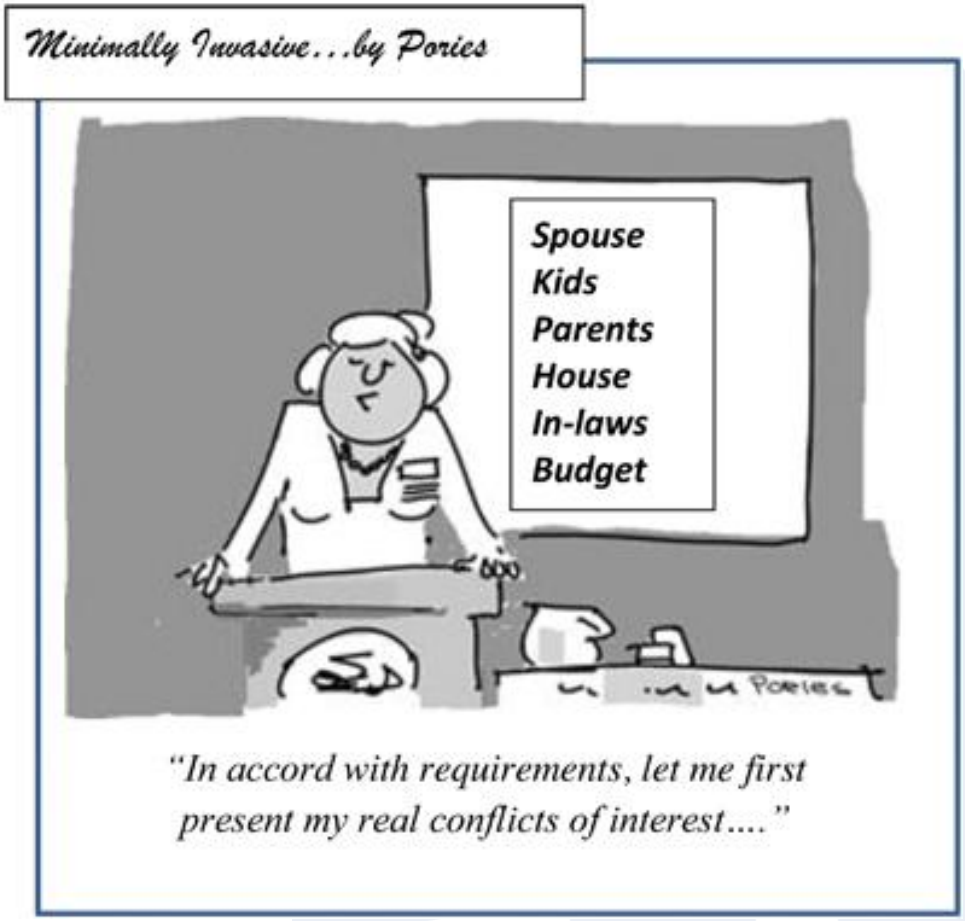
AAS
Association for Academic Surgery

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

Disclosures- None



My story and background

College/Medical School

Barnard College/Columbia University

1982--1990 (Basic Research)

Residency training

University of California, San Francisco

Boston Children's/MIT

Faculty Positions

Beth Israel Deaconess Medical Center

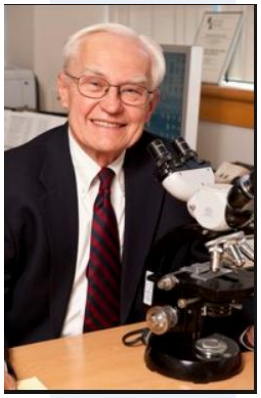
1998-2007

Massachusetts General Hospital

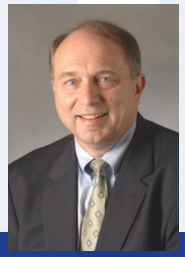
2008-present



Orlo Clark ,Judah Folkman, Doug Hanahan PhD



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

*New England Journal of Medicine, 285:1182-1186, **1971***

TUMOR ANGIOGENESIS: THERAPEUTIC IMPLICATIONS

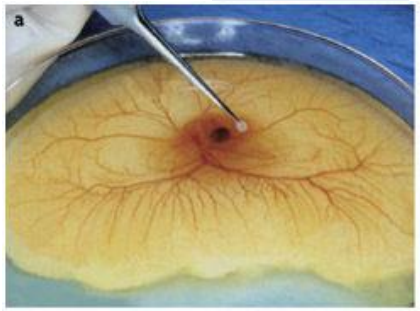
JUDAH FOLKMAN, M.D.

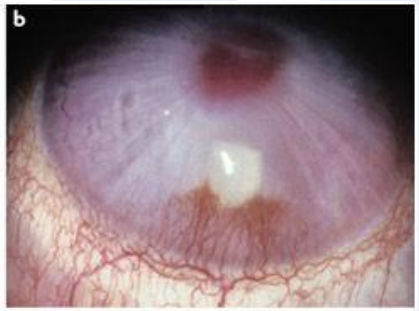
1. ". . . solid tumors are **dependent** upon **new** capillary sprouts. . ."

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."

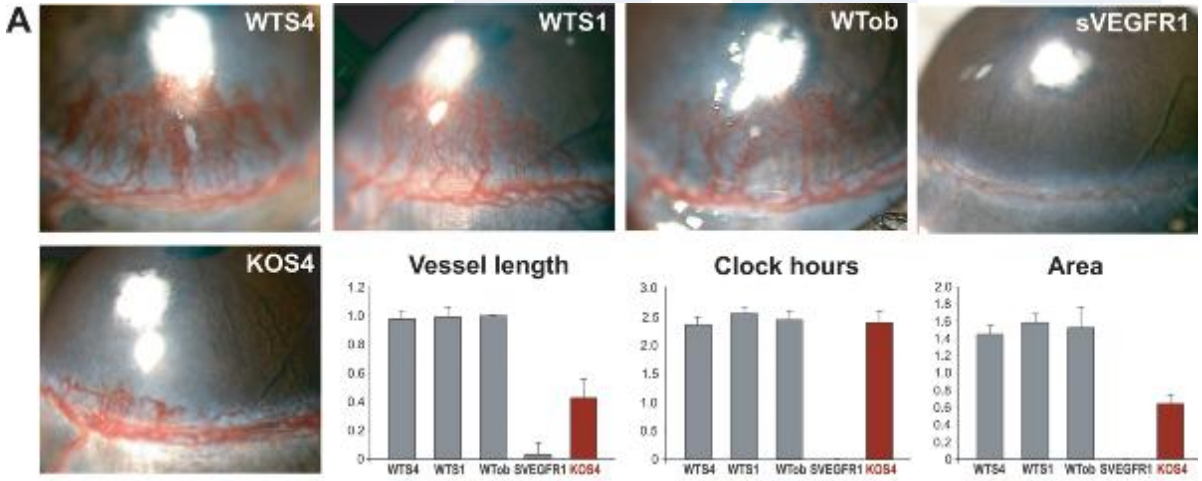




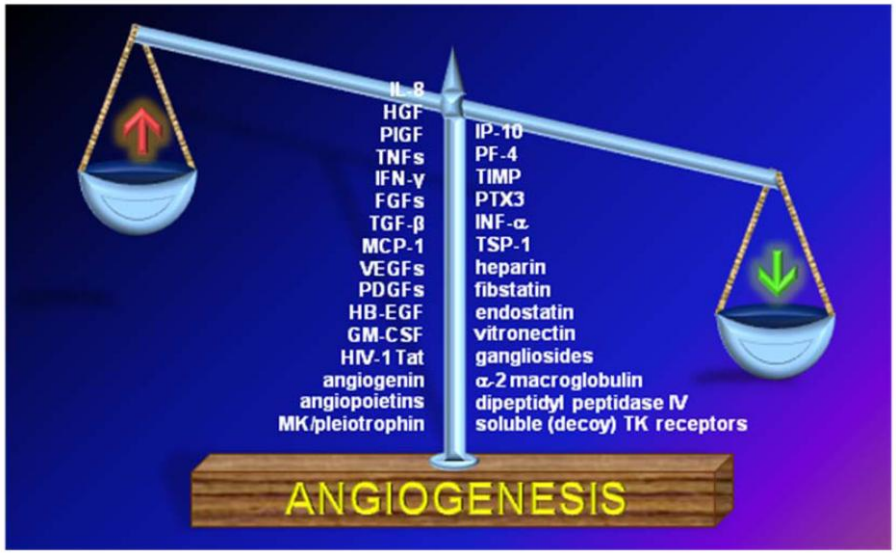
Rejection

- *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 4th modality for cancer treatment" (in addition to surgery, radiation and chemotherapy).

His scientific legacy

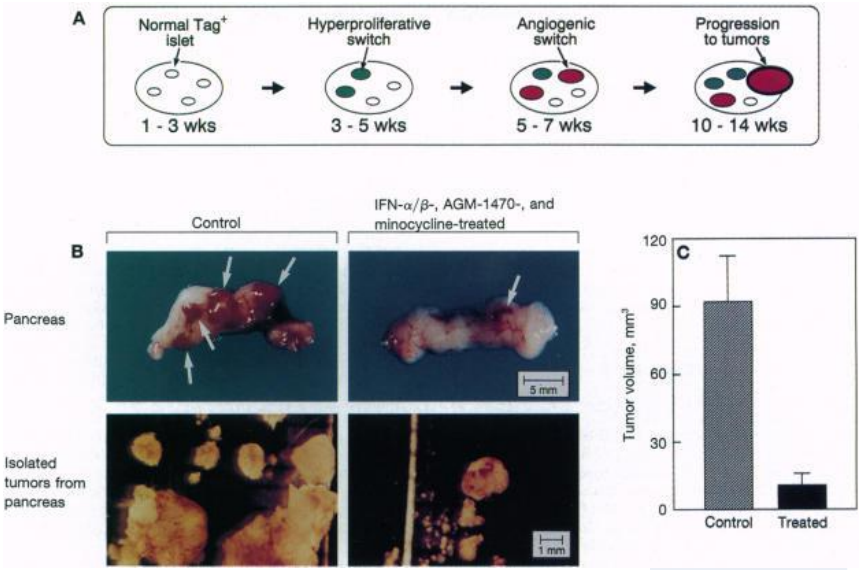
Publications	**447**
Book chapters and reviews	**116**
Trainees	**165**
Patents (issued and pending)	**477**

His scientific legacy

AAS Association for Academic Surgery

Drug/Company	Type of inhibitor	Targets	Use	Indication
Bevacizumab (Avastin) Genentech/Roche	Monoclonal Antibody	VEGF-A	First or second line First line First line First line Off-label	Metastatic colorectal cancer Nonsmall cell lung cancer Recurrent glioblastoma Metastatic renal cell carcinoma Wet age-related macular degeneration Macular edema following CRVO
Aflibercept (Zaltrap) Regeneron/Sanofi	Chimeric soluble receptor	VEGF-A, VEGF-B, PlGF	Second line	Metastatic colorectal cancer
Pegaptanib (Macugen) Eyetech 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 (Eleya) Regeneron/Bayer	Chimeric soluble receptor	VEGF-A, VEGF-B, PlGF	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

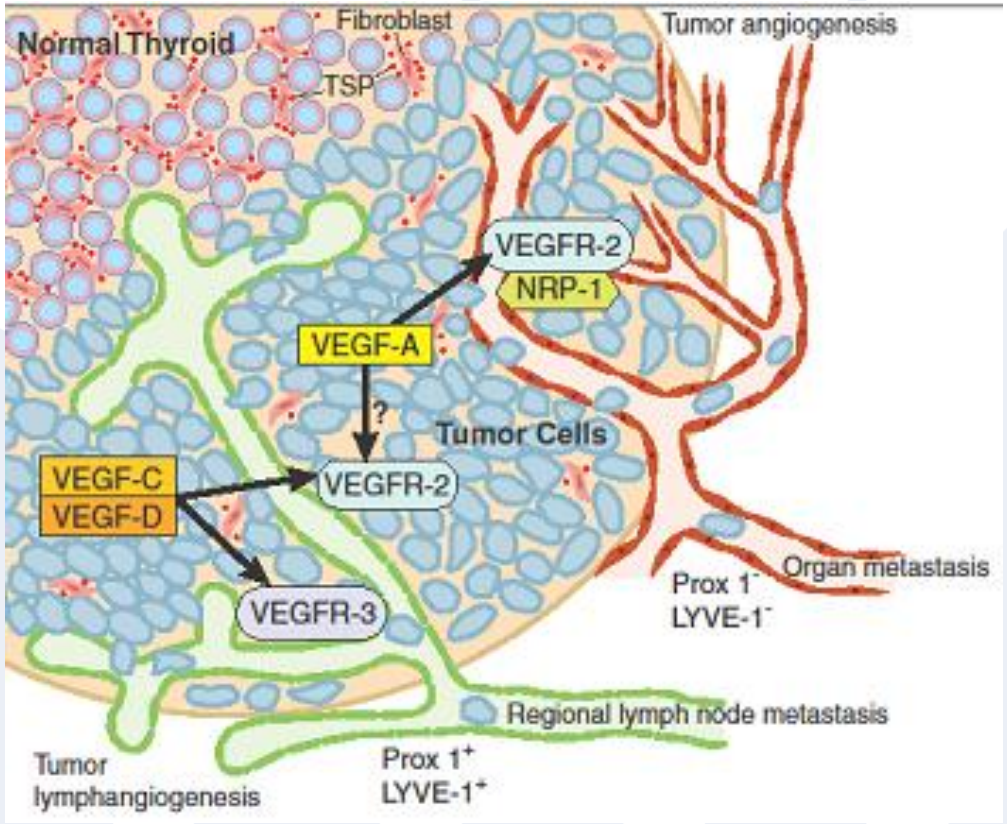
AAS
Association for
Academic Surgery


A
Normal Tag+ islet
Hyperproliferative switch
Angiogenic switch
Progression to tumors
1 - 3 wks
3 - 5 wks
5 - 7 wks
10 - 14 wks
B
Control
IFN-α/β-, AGM-1470-, and minocycline-treated
Pancreas
Isolated tumors from pancreas
5 mm
1 mm
C
Tumor volume, mm3
120
90
60
30
0
Control
Treated

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

Testing antiangiogenic therapies in pancreatic cancer

  - ATA grant--- connection to my clinical practice

2007 – Making the jump to independence

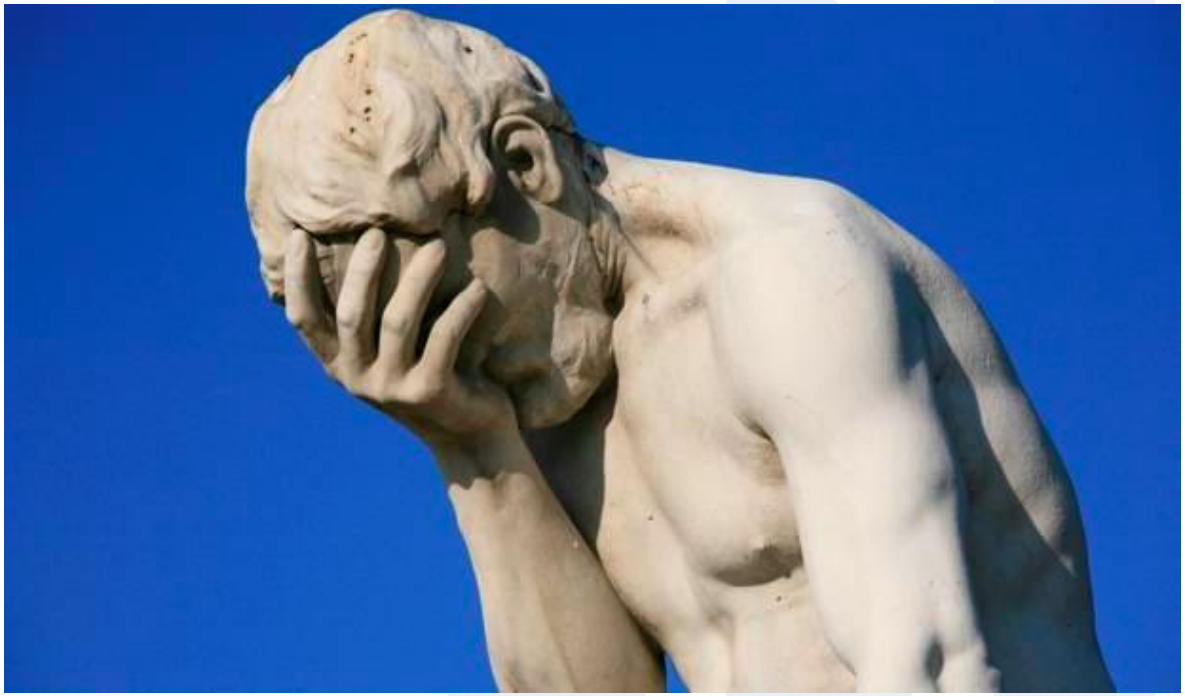
- Demonstrate independence
- First and senior author publications
- Obtain independent “space”
- Obtain additional pilot grants

K-Award

R01-Award

Starting the process for R01 grant

- 2007 → started to write R01grants



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
(Privileged Communication)

PROGRAM CONTACT:
Elizabeth Snyderwine
301-435-1878
elizabeth_snyderwine@nih.gov

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

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

rincipal Investigator

ARANGI, SAREH MD

pplicant 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:
Dual PCC:
Dual IC(s):

Project Title: The Role of BRAF Muta Thyroid Canc asion

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

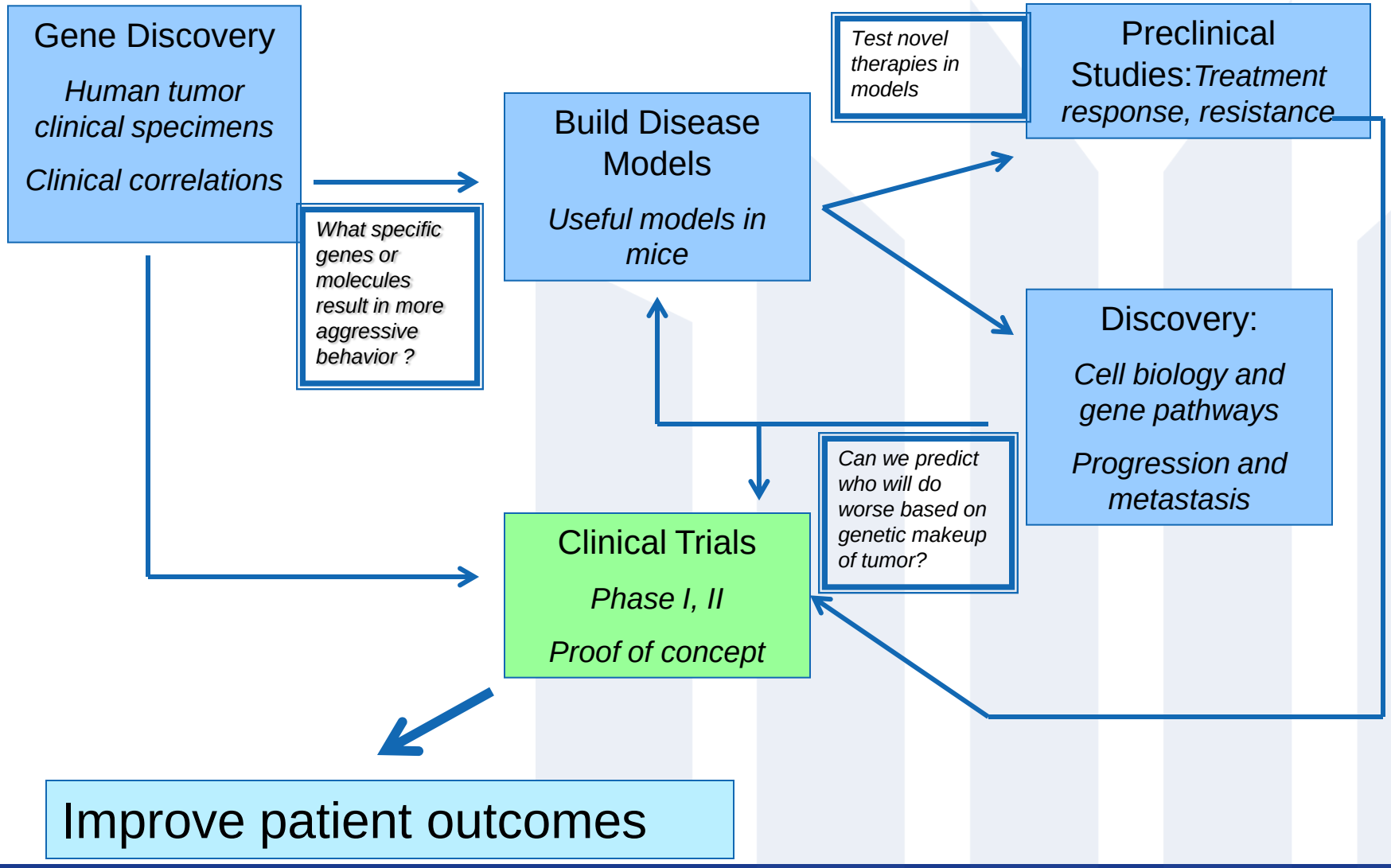
Project Year	Direct Costs Requested	Estimated Total Cost
1	225,000	385,986
2	225,000	385,986
3	225,000	385,986
4	225,000	385,986
5	225,000	385,986
TOTAL	1,125,000	1,929,930

AAS
Association for Academic Surgery

25 TS R01

66 grants/last 10 years = 6 grants/year

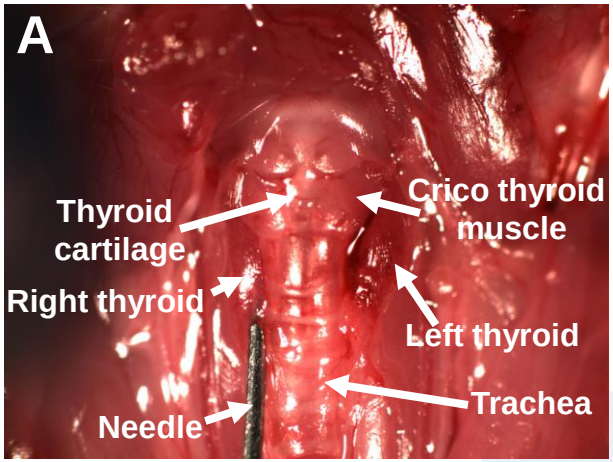
How to use the money?
Better define my lab effort

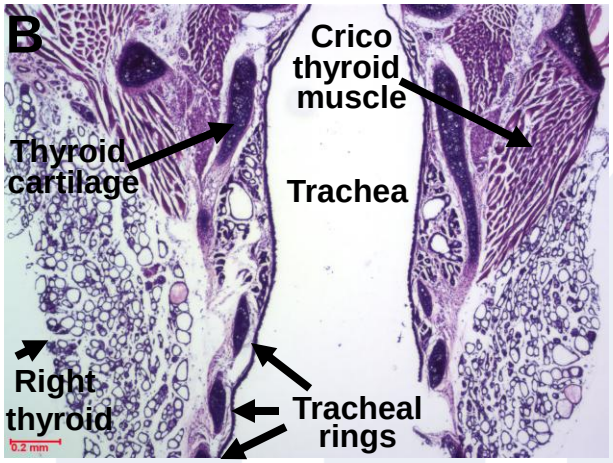


Development of a simple orthotopic mouse model using fluorescent human thyroid cancer cells

Association for Academic Surgery

Anatomy
Normal
Mouse
Thyroid

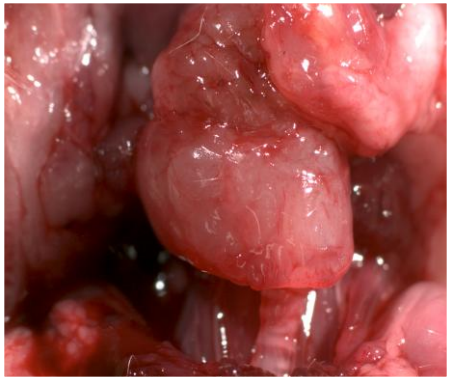


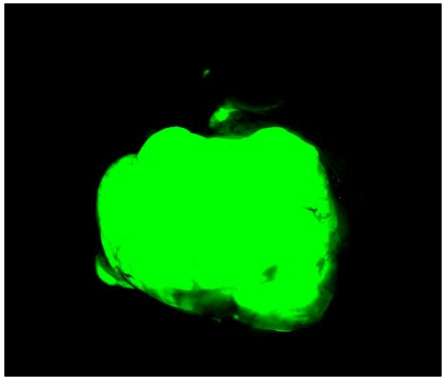


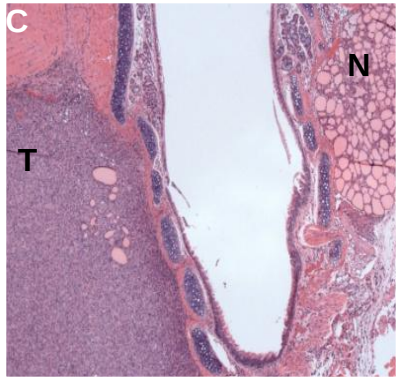
GFP

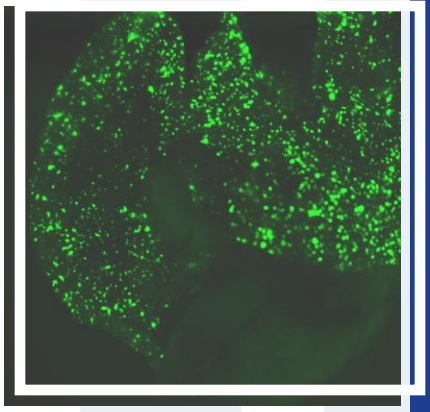
Histology

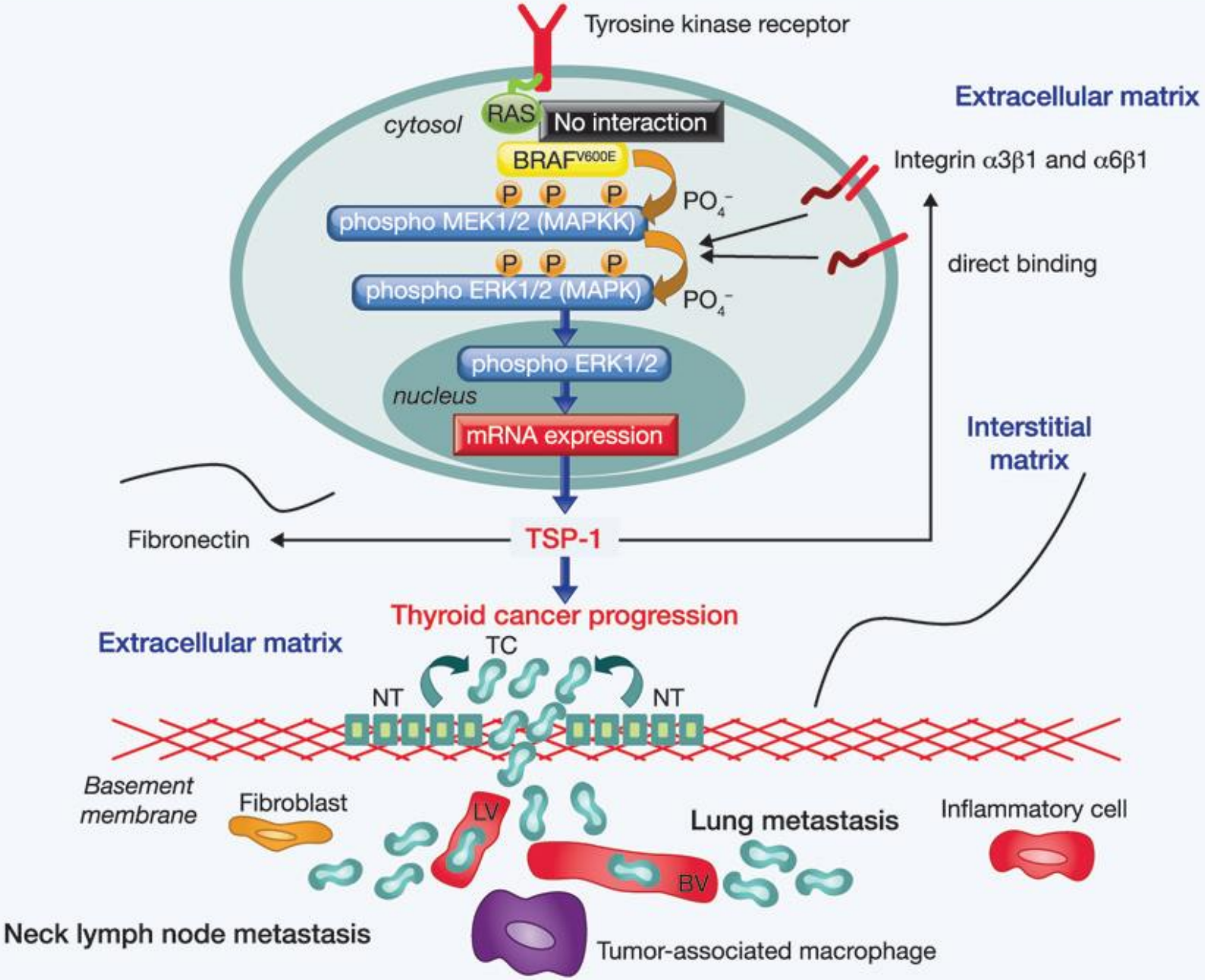
Lungs



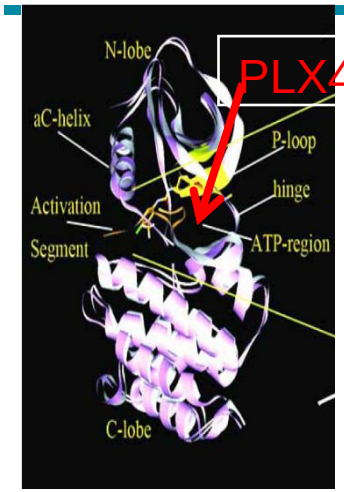


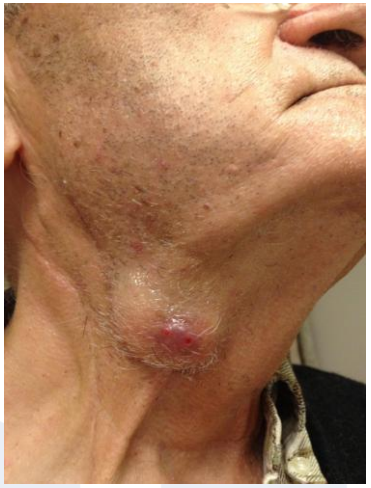


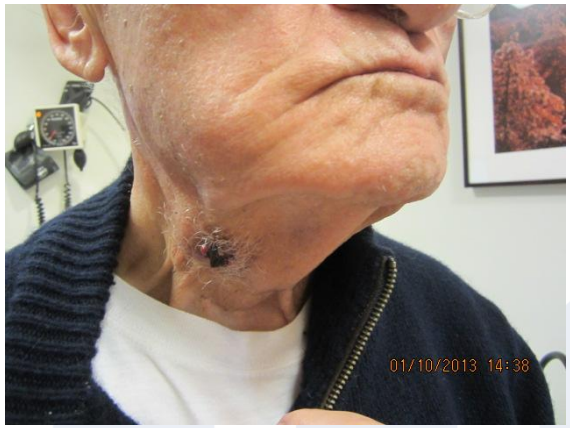


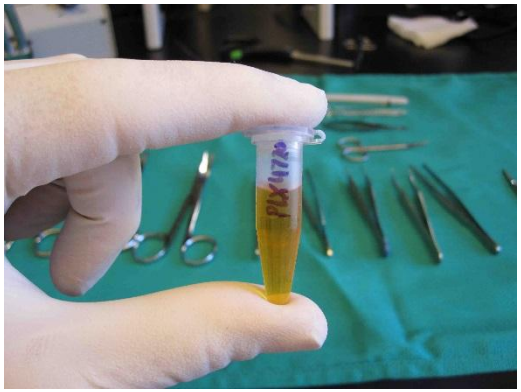


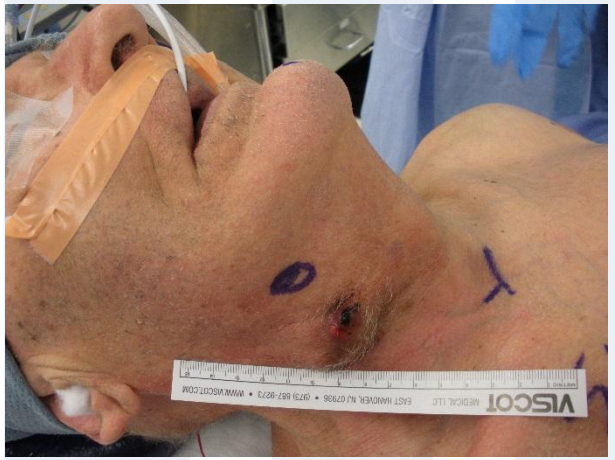
From mice to men





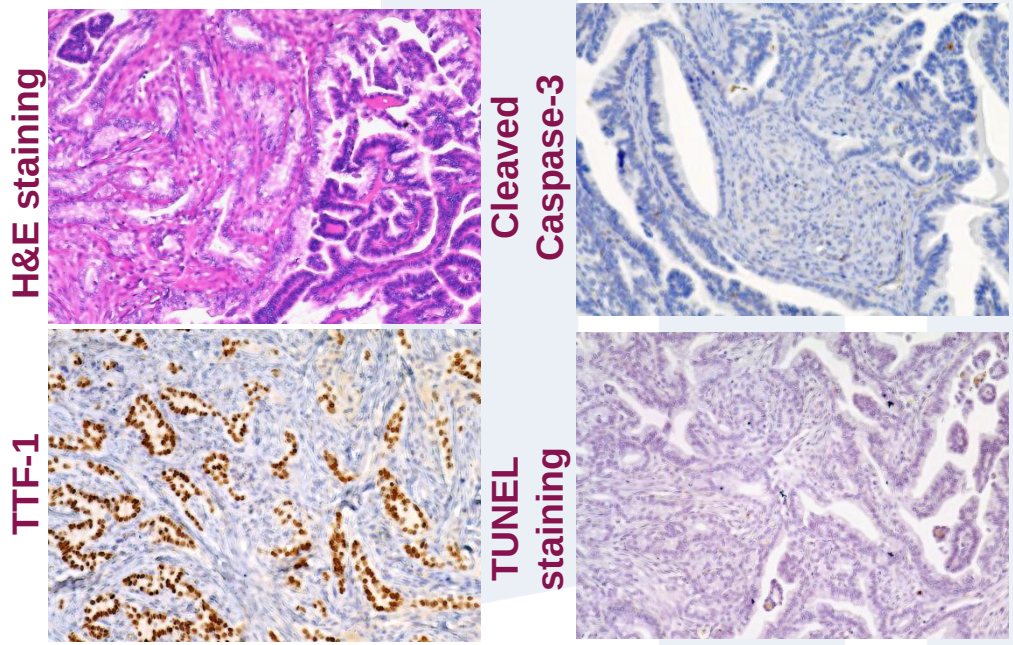




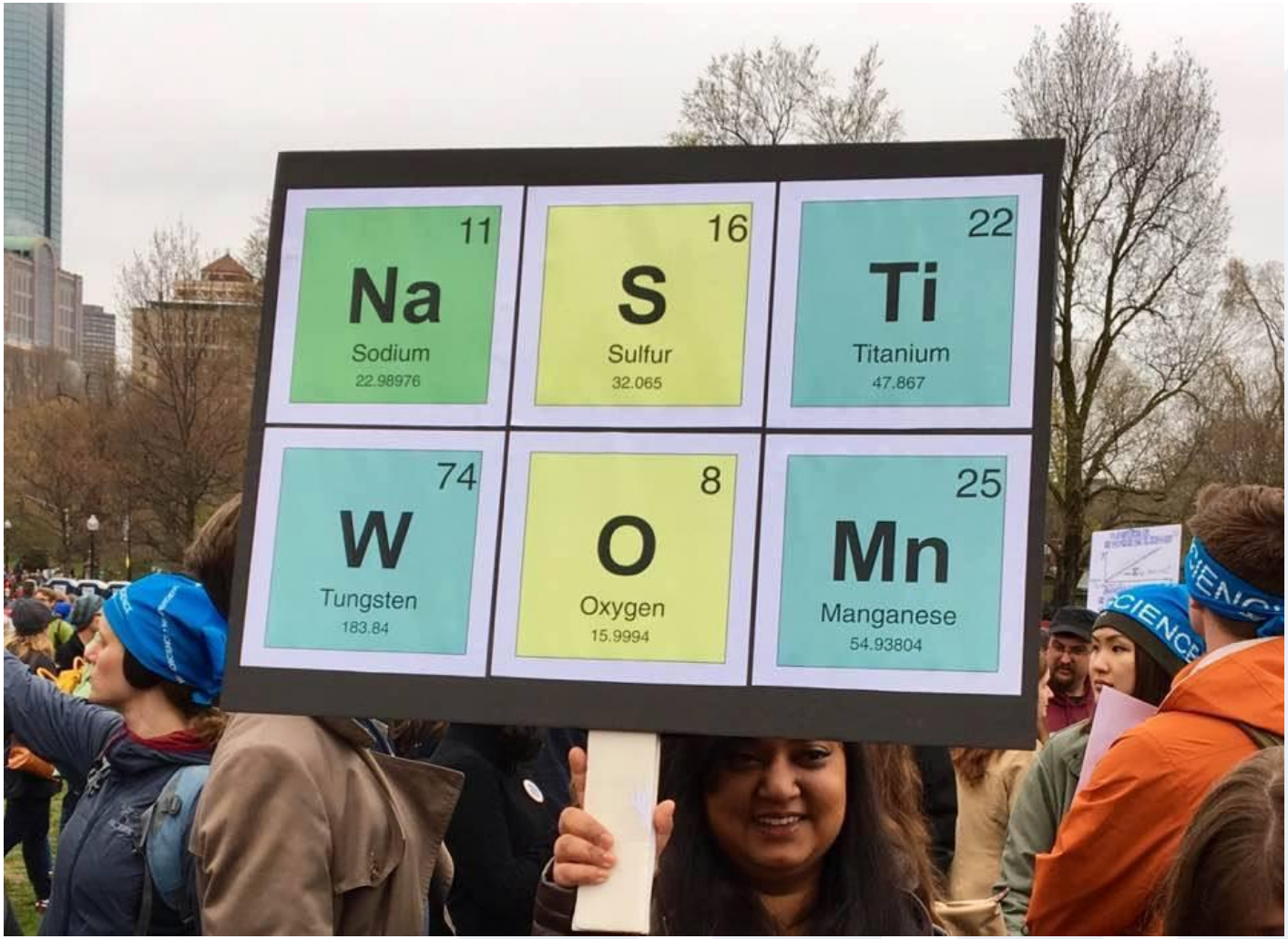


Lessons learned from treated patients
Pathway interactions are extremely complex

- 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

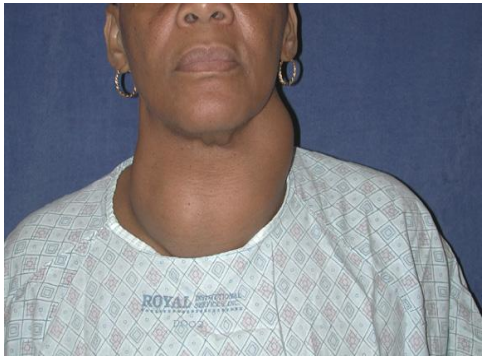


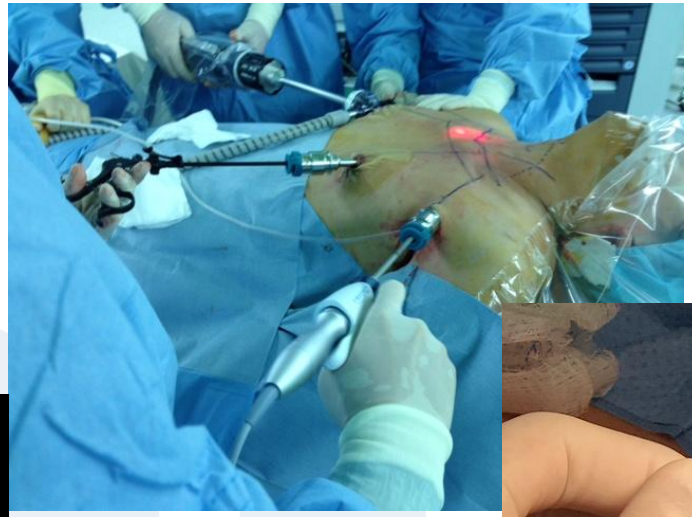
8 P's for Success in Research

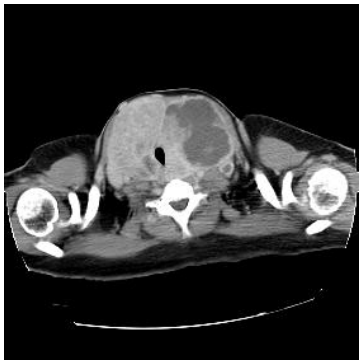
Association for Academic Surgery

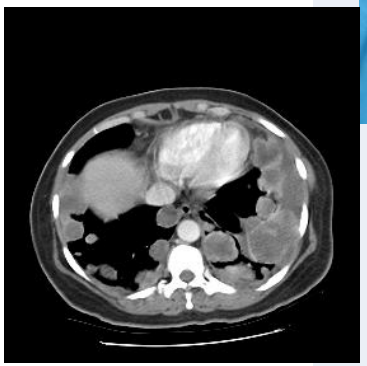
- **Passion**
  - Choose areas of research that you are interested in
  - Clinically relevant
- **Push yourself**- Don't wait to be pulled
- **Protect** your time
- **Plan:**
  - Plot a path- might not be a straight path
  - Careers are full of twists and turns
- **Partner** (Mentor/Collaborator/Chair/Colleagues)
- **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

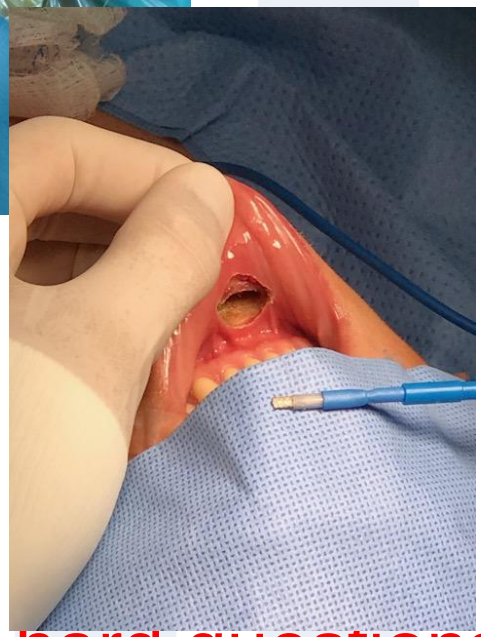
Why go into academic surgery





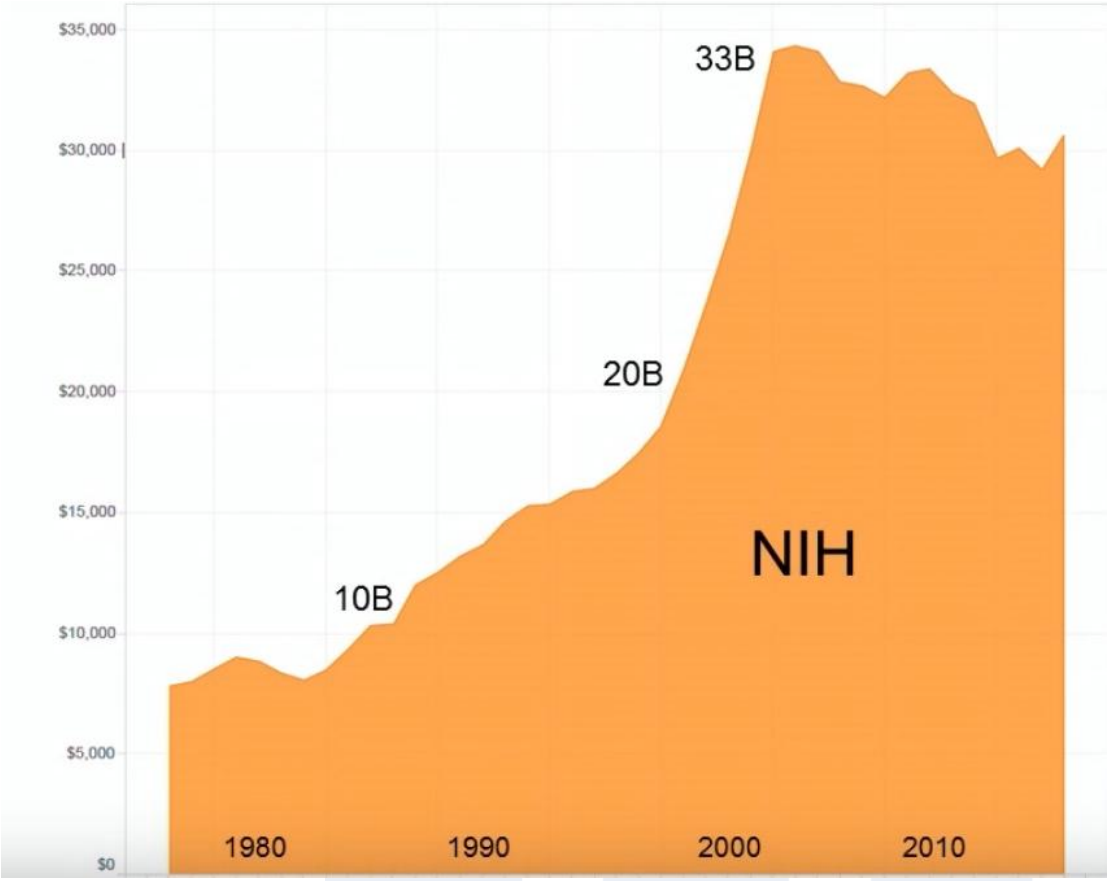






Your patients need you to ask the hard questions and they need your innovation

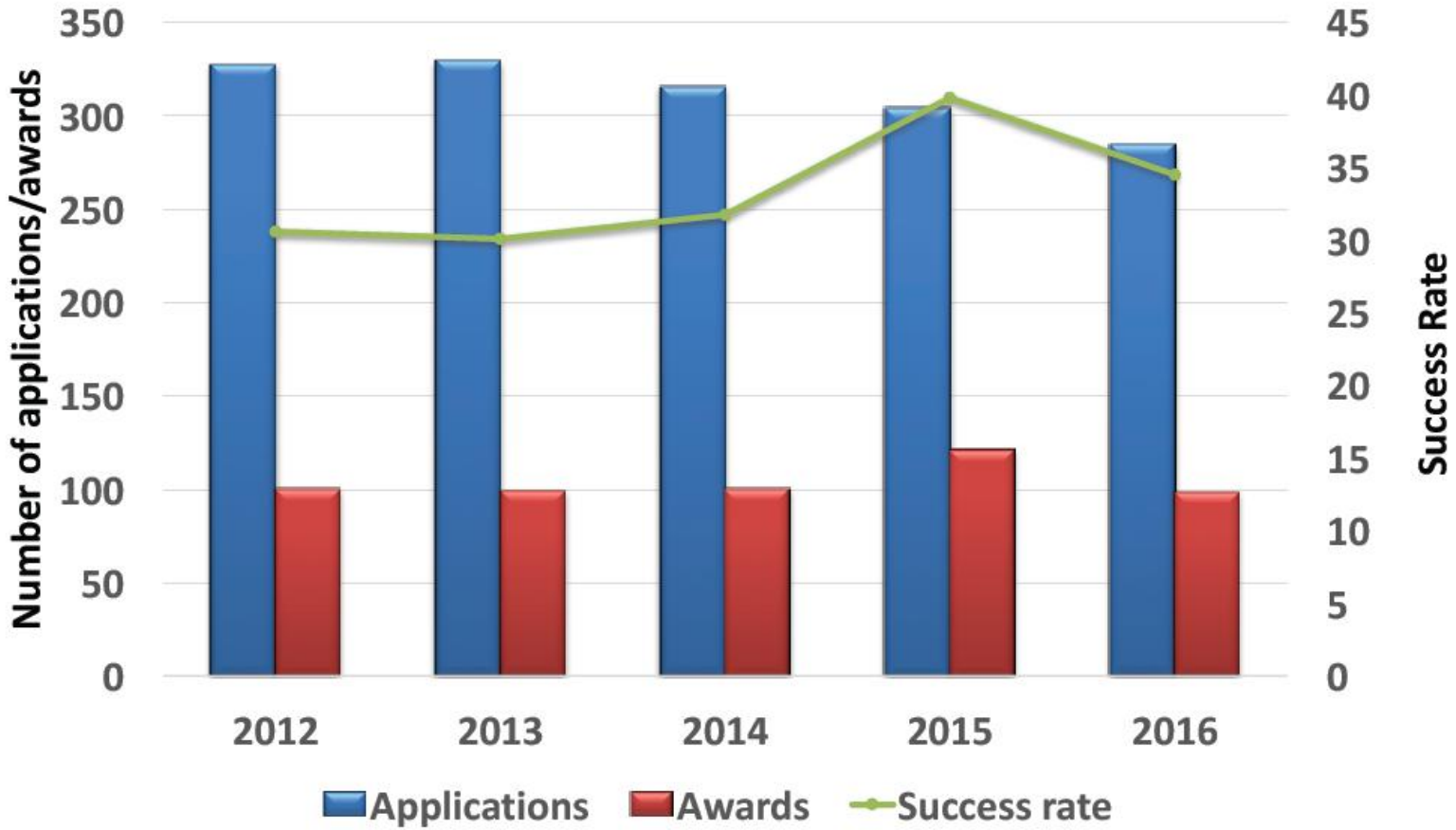
Why go into academic surgery



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

Grab our share of the money

NIDDK Career Development Awards



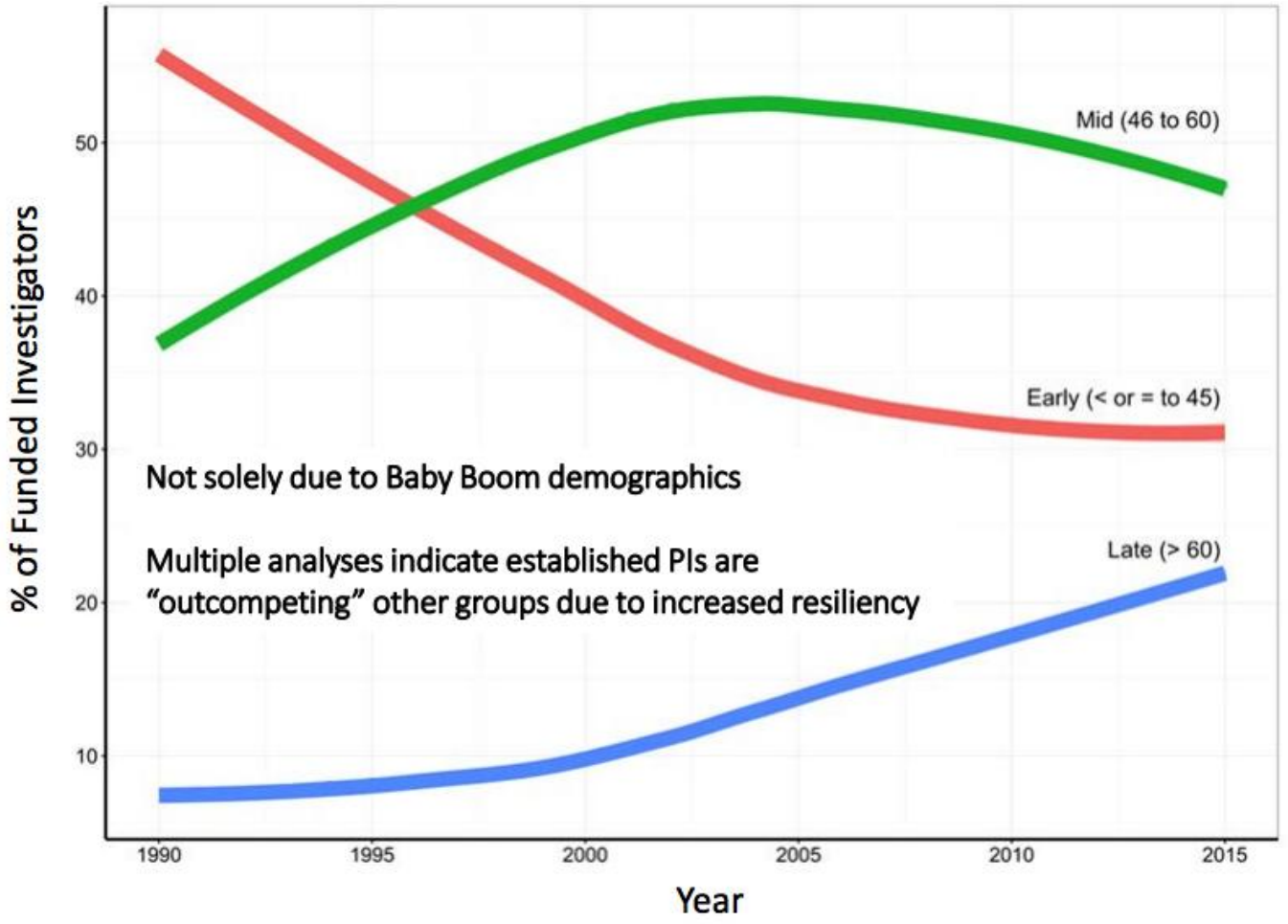
*includes K01, K08, K23, K99

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%
TOTAL (573)	87%	66%	79%	49%

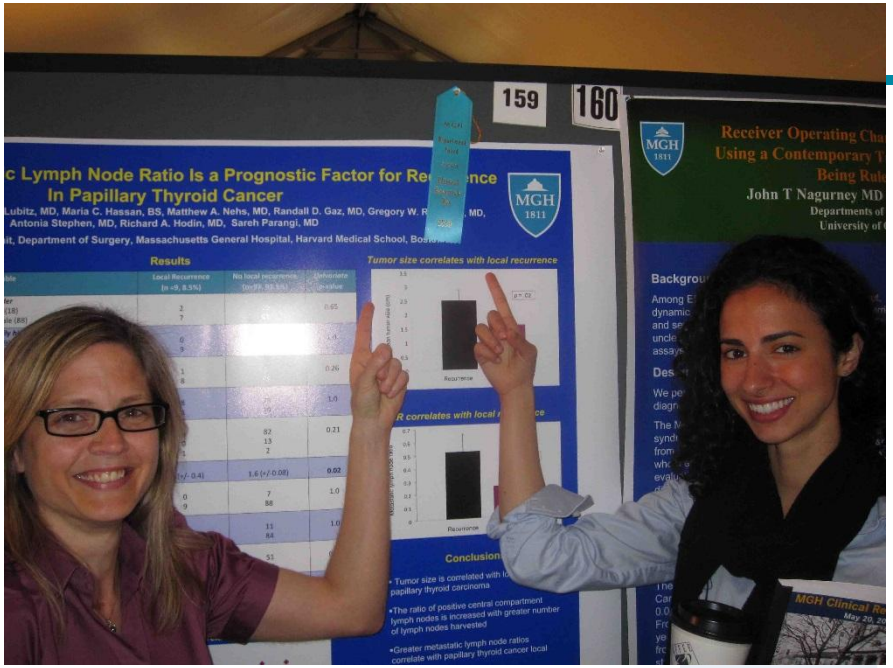
*all K01/K08/K23/K99 awardees whose K grants ended between 2005-2010

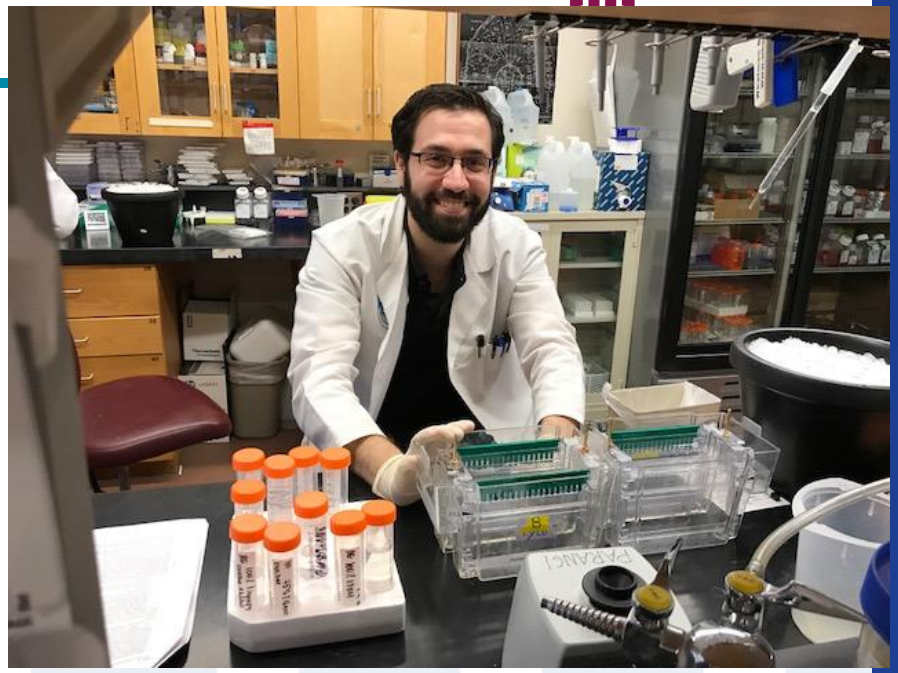
Established PI's outcompeting other groups



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

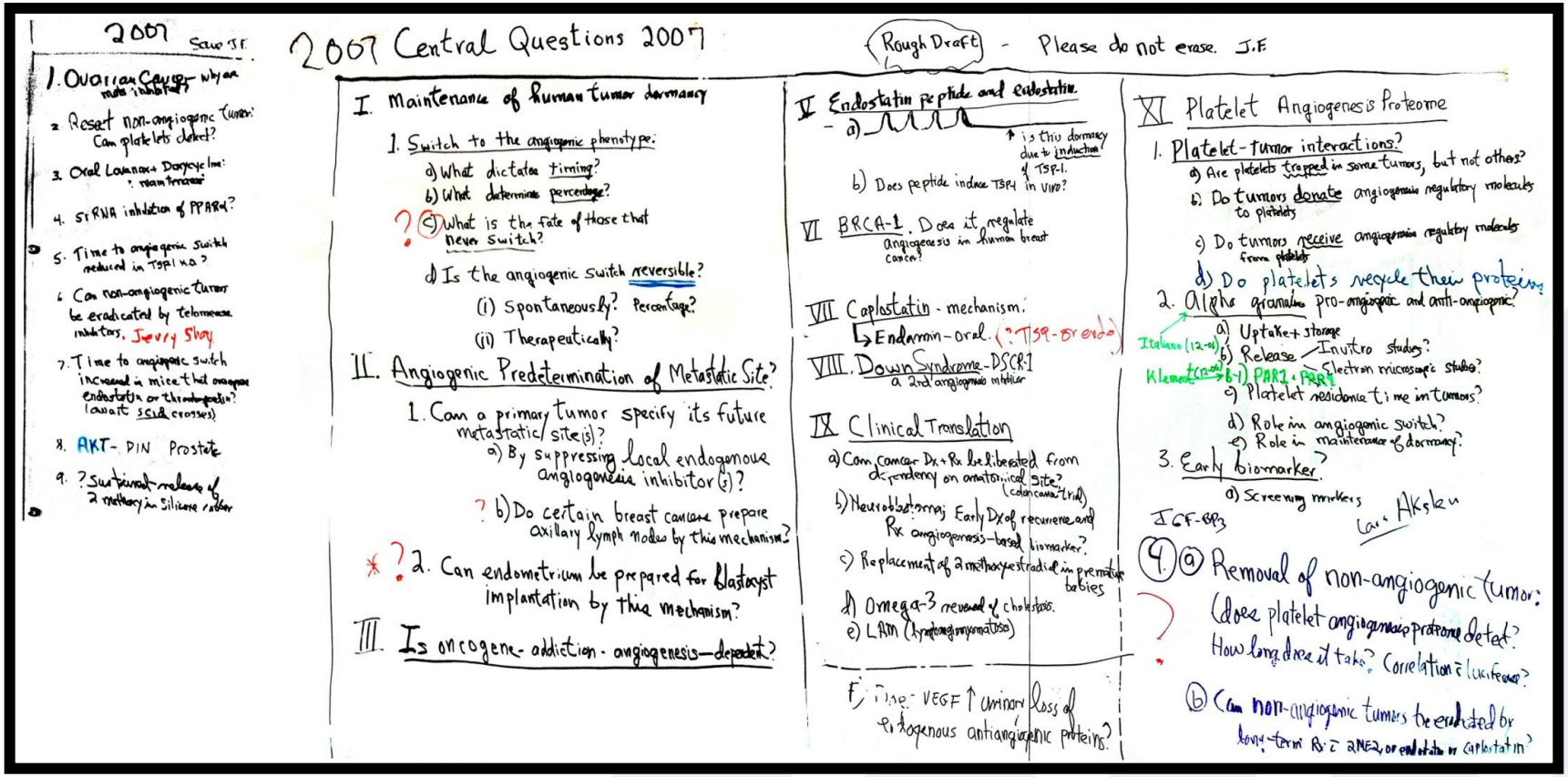
Your paycheck will be HUGE

Remember that life happens

AAS
Association for Academic Surgery

"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."



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