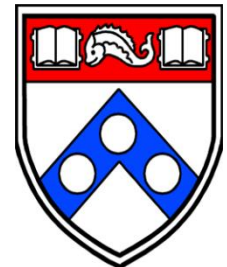


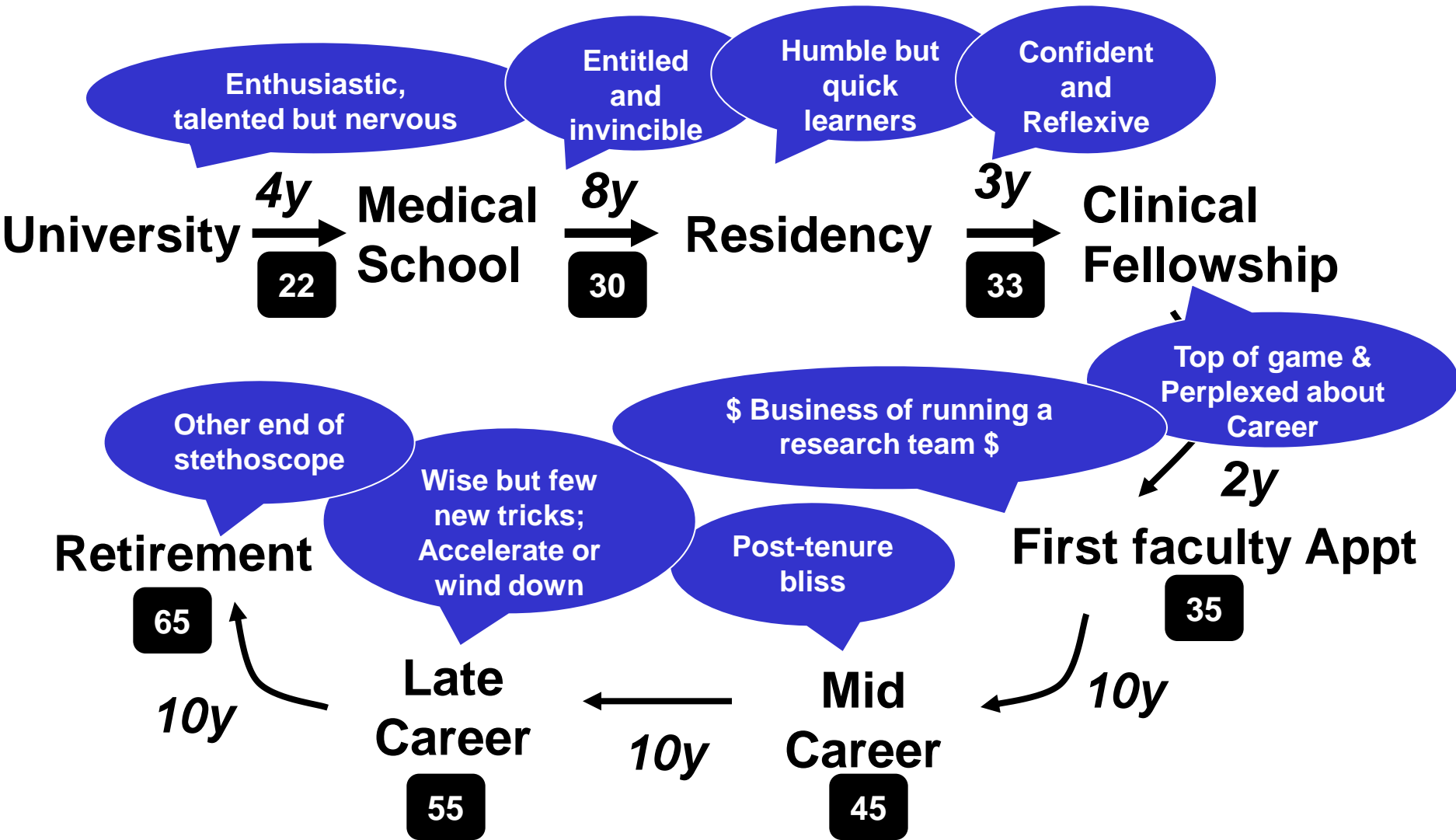
Career Pathways for Physician-Scientists

J. Larry Jameson, M.D., Ph.D.
Dean, Perelman School of Medicine

ITMAT
July 27, 2011



Life Cycle of a Physician Scientist



- Research context for physician-scientists
 - Nationally
 - At Penn
- An analysis of one person's career path
- A little science with a few pearls
- Discussion

The Pipeline Is Narrow

The Physician-Scientist Career Pipeline in 2005

Build It, and They Will Come

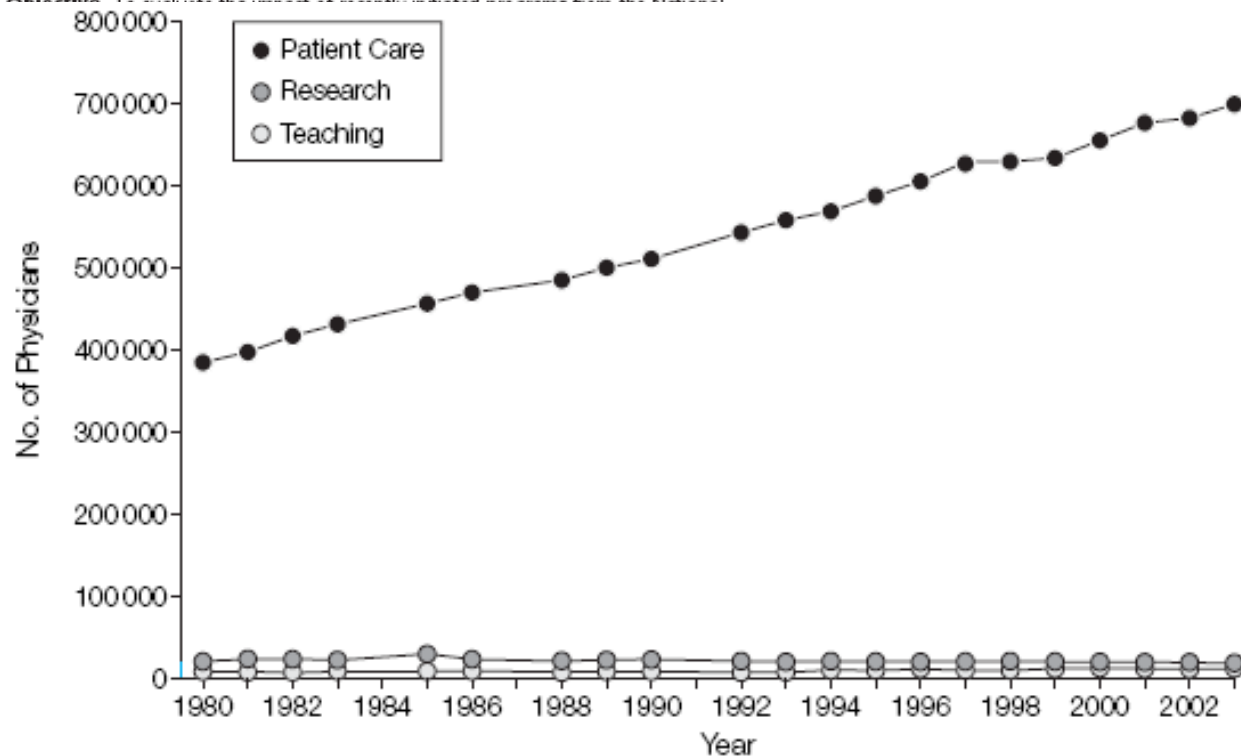
Timothy J. Ley, MD

Leon E. Rosenberg, MD

PHYSICIAN-SCIENTISTS ARE DEFINED as individuals with an MD degree who perform medical research as their primary professional activity. These investigators have contributed much to this nation's preeminent position in medical science. The majority of physician-scientists have only 1 professional de-

Context Physician-scientists play a unique and critical role in medical research. Nonetheless, a number of trends followed during the 1980s and 1990s revealed that this career pathway was in serious jeopardy. Physician-scientists were declining in number and were getting older. A variety of factors were thought to contribute to this problem, including increasing indebtedness of medical school graduates caused by rapidly rising medical school tuition costs.

Objective To evaluate the impact of research-related income from the National

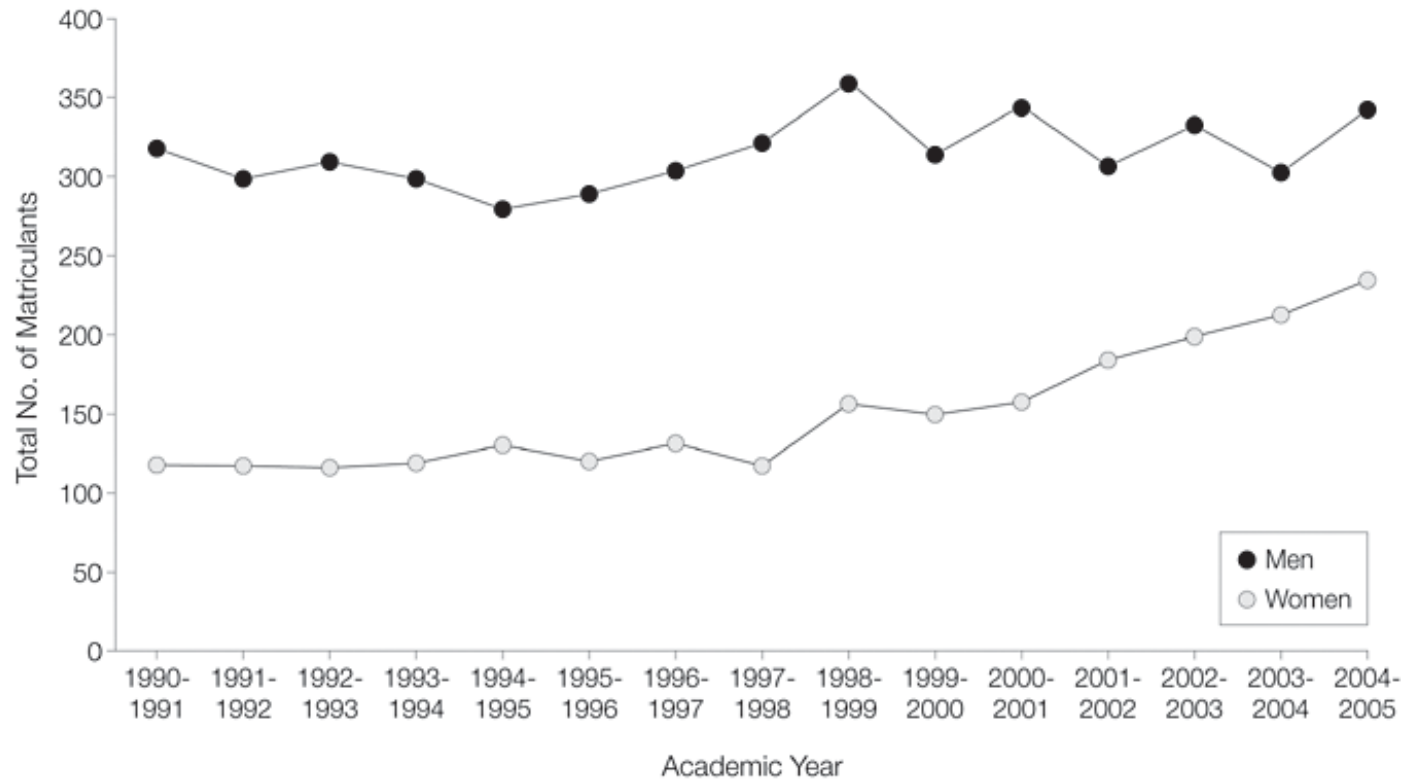


Ley, T. J. et al. JAMA 2005;294:1343-1351.

Composition of the Physician Workforce in the United States, 1980-2003

MSTP Enrollment Is Growing... Slowly

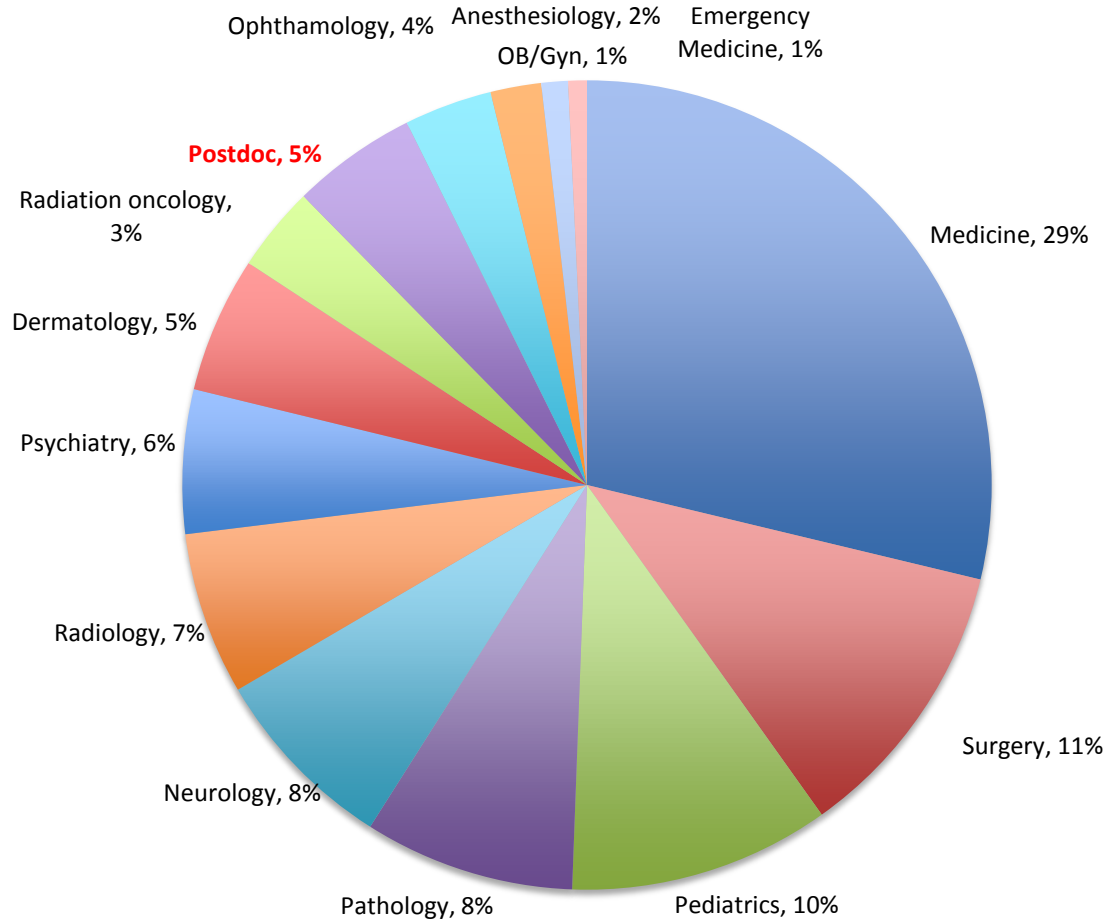
Numbers of Matriculating MD-PhD Students in the United States, 1990-2004



Ley, T. J. et al. JAMA 2005;294:1343-1351.

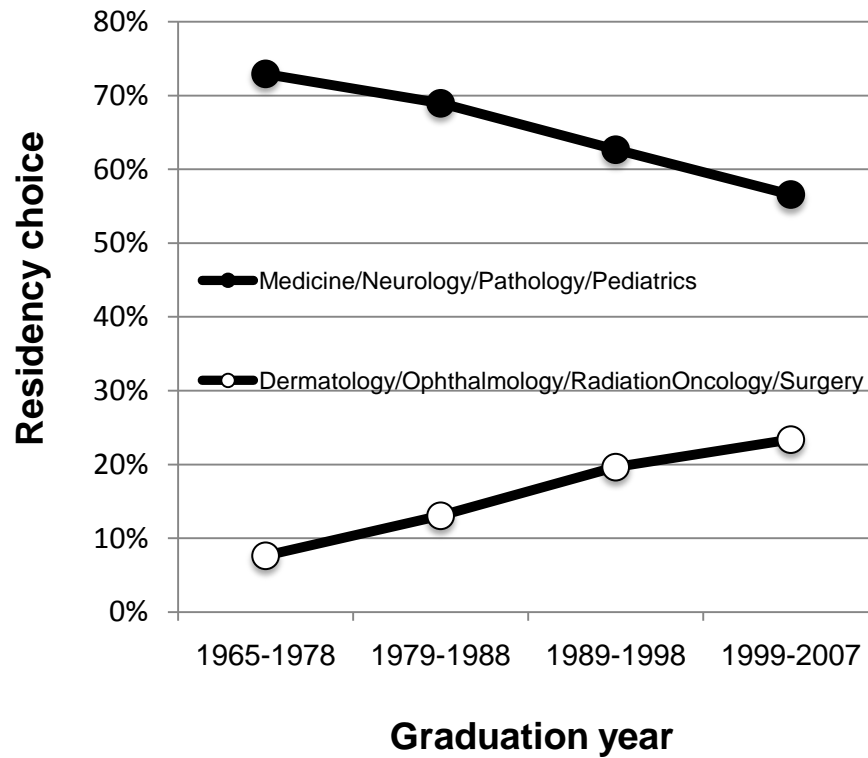
MD-PhD program graduates

95% do residencies

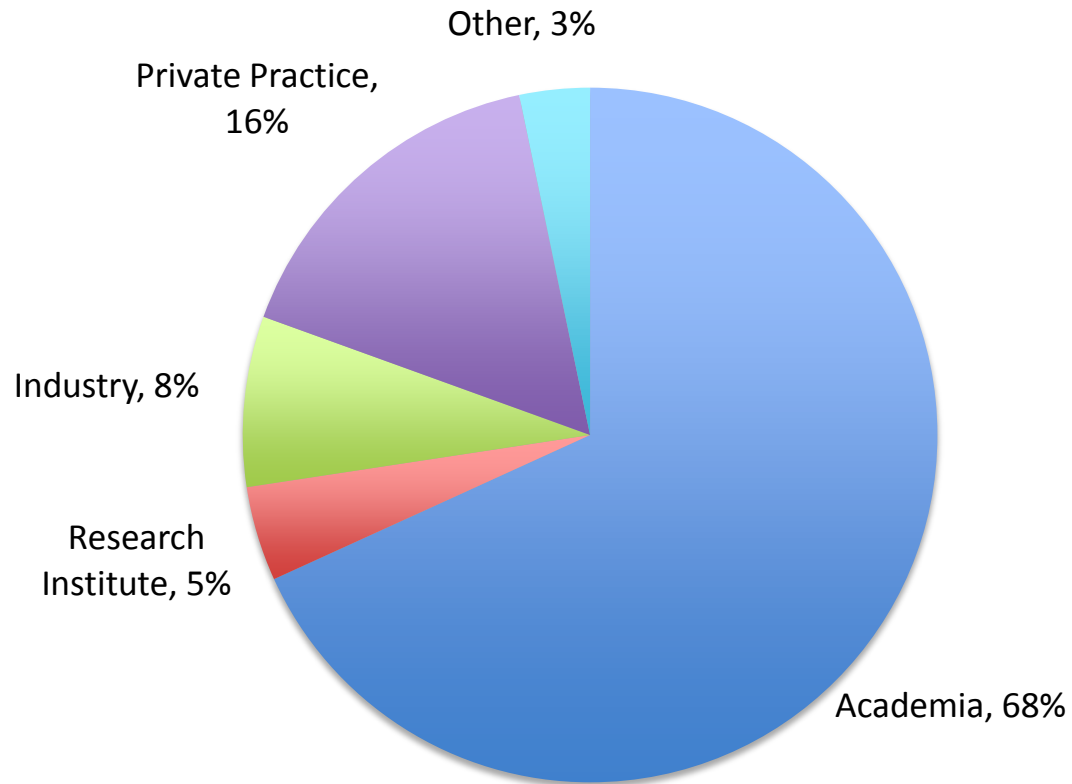


Brass et al., Academic Medicine, April 2010

Trends in residency choices



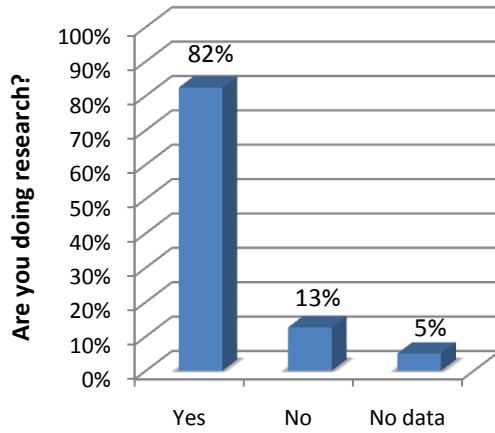
MD-PhD program graduates: Long term outcomes



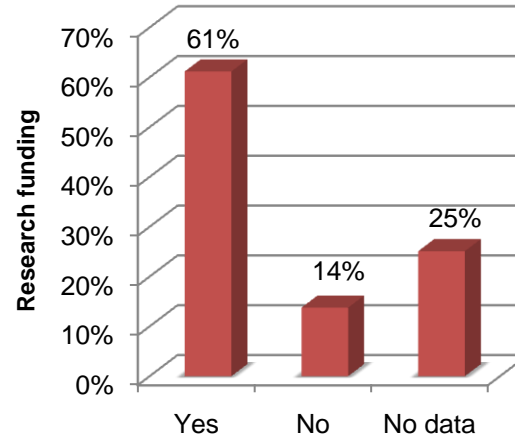
Brass et al., Academic Medicine, April 2010

Research by MD-PhD program graduates

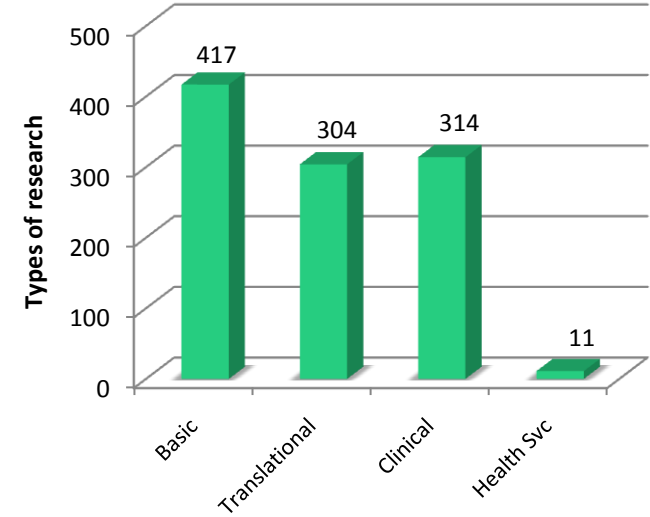
Are you doing research?



Do you have research grants?



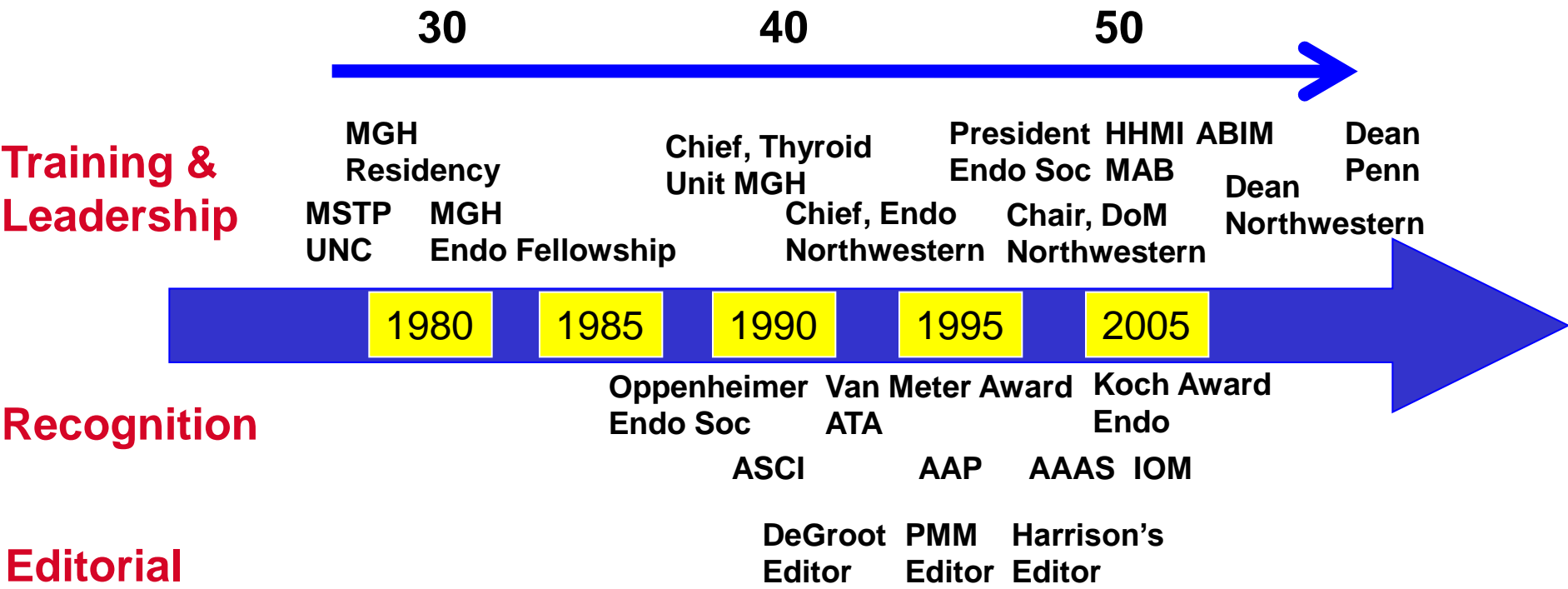
What kinds of research are you doing?



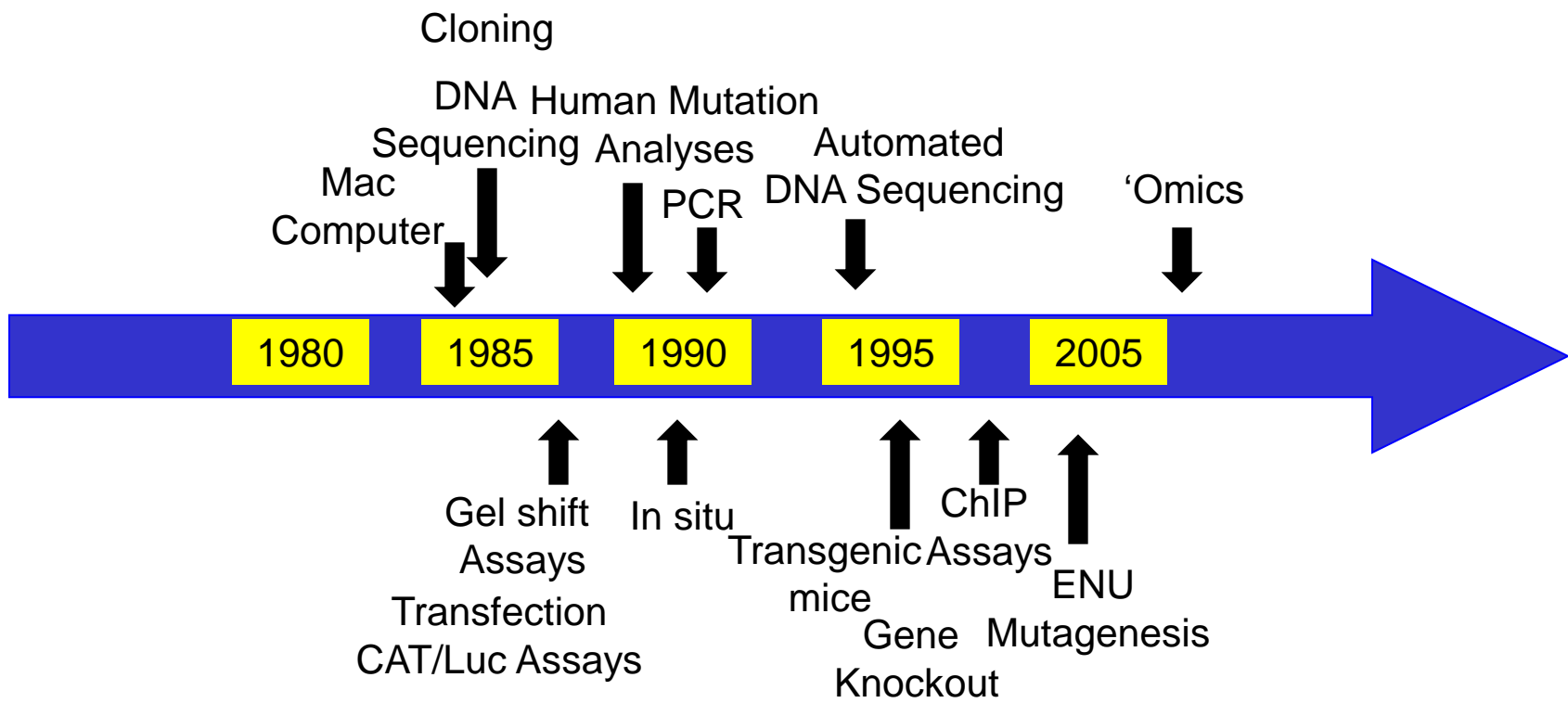
Brass et al., Academic Medicine, April 2010

An “Objective” Analysis of One
Person’s Path — *Mine*

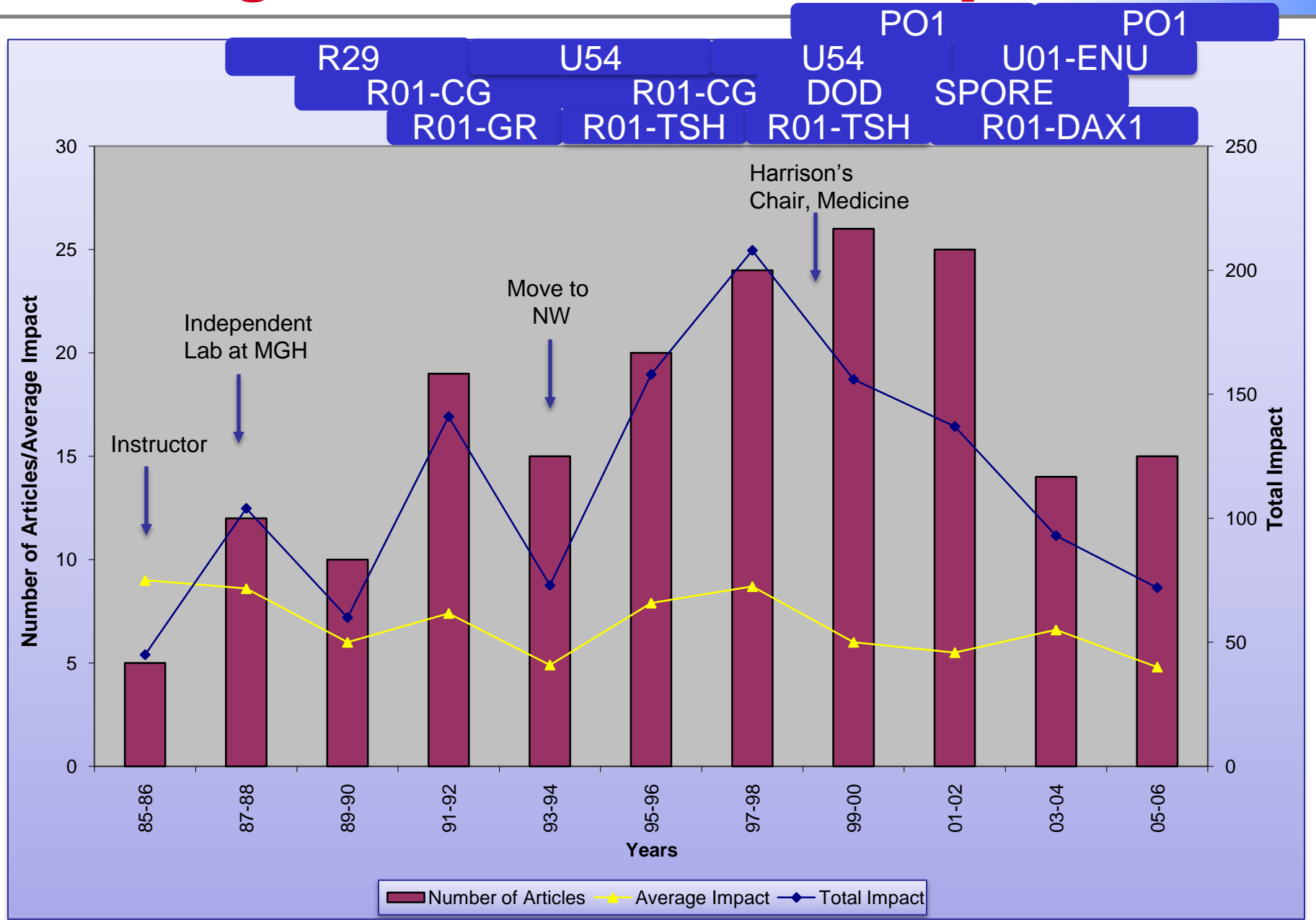
Career Path



Impact of Disruptive Technologies



Balancing Science and Leadership



Reflections on the Data

- Grants should be staggered
- Collaborative grants stimulate new research areas
- New technologies drive laboratory science
 - But, are not sufficient ... novel ideas are necessary*
- Clinical relevance engenders interest
- A high impact paper is usually no more work
- The quality of the team & its chemistry are key ingredients
- Build relationships with colleagues and mentors
- Leadership roles consume time & energy but have impact too

- Collaboration and collegiality are hallmarks of this institution
- Long standing tradition of scientific excellence
- Attract faculty of the highest caliber from across the country
- A rich environment for faculty professional development
- Institutional commitment to mentoring

Faculty

Administrative Tools

Professional Development

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Fax: 215-573-2592
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University of Pennsylvania

University of Pennsylvania Health System

FAPD » Professional Development » Career Management

Advance Mentoring Series Courses and Resources

Resources

'Shaping a Career in Academic Medicine: A Guide for Mentor/Mentee Conversations

Document with guidelines on conversations between mentor/mentee on the tenure and clinician educator tracks

Courses

Course Title	Description	Date/Time/Location	Instructor
Establishing a Productive Relationship with Your Mentor ENROLL NOW	This session is designed for junior faculty who are just starting to work with their assigned mentors or who are looking for additional mentors.	October 17, 2011 3:30 to 5:00 p.m. BRB 251	Dr. Marcia Brose
Getting the Most Out of Mentoring: Asbury Mentoring Award Winners Panel ENROLL NOW	Past winners of the Asbury Award for Mentoring will discuss the important ways mentors can help your career flourish. The Asbury winners will bring along one of their own mentees, who will add to the discussion. <i>PLEASE NOTE: Faculty registering for this session are <u>encouraged to attend this session with their mentor(s)</u>.</i>	November 14, 2011 3:30 to 5:00 p.m. BRB 251	Dr. Steven Albelda Dr. David Asch Dr. Charles O'Brien



Courses and Resources for:

- [Attaining Teaching Excellence](#)
- [Career Management](#)
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Advance Scientific Writing Courses and Resources

Resources

[All About Grants Tutorials -- NIAID](#)

Link to the NIAID (National Institute for Allergy and Infectious Diseases) website which provides on-line tutorials on preparing RO1 grant applications. Tutorials help biomedical investigators, especially new ones, plan, write, and apply for the basic NIH research project grant, the RO1. Advice comes from the experience of NIAID staff, including former NIH grantees.

[Authorship and Accountability](#)

PowerPoint presentation in which Harold "Hal" Sox, M.D., Editor, *Annals of Internal Medicine*, lists the qualifications to be listed as an author as well as the specific ways in which an author is accountable for a paper's content.

[Essentials of Writing Biomedical Research Papers](#)

This guide is used and recommended by both Dr. Judith Swan and Dr. Elizabeth Colston, who teach classes in *Advance's* Scientific Writing Series.

Courses

Course Title	Description	Date/Time/Location	Instructor
Writing an Article for Publication Part 1: Writing the "Results" Section ENROLL NOW	This session will focus on relating the results text to the figures in a way that tells a compelling scientific story. <i>The Perelman School of Medicine at the University of Pennsylvania is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.</i> <i>These activities have been approved for AMA PRA Category 1 Credit(s)™.</i>	September 15, 2011 12 noon to 1:30 p.m. Stellar-Chance 104	Dr. Elizabeth Colston

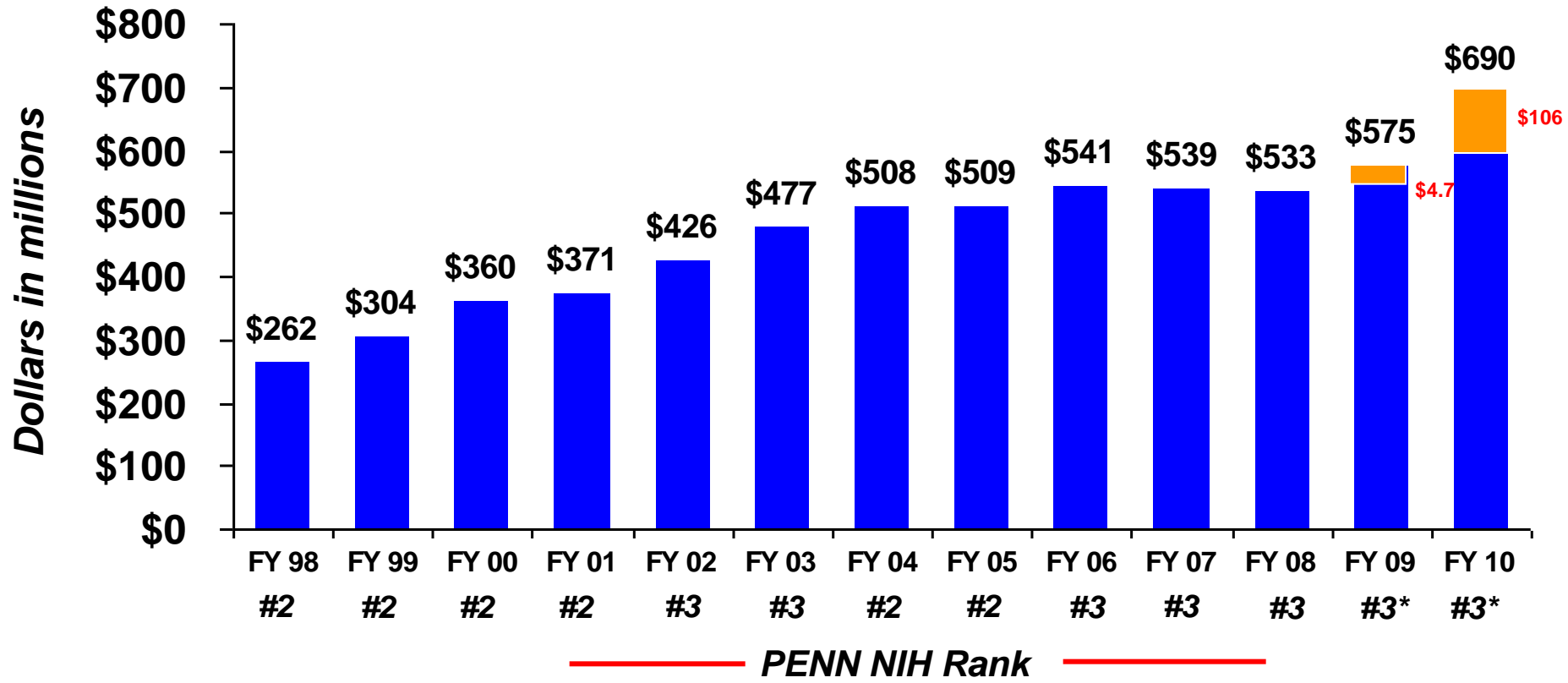


Courses and Resources for:

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- [Technology](#)

Growth in Total Research Funding

PENN PSOM Funding Trends: Total FY98 - FY10

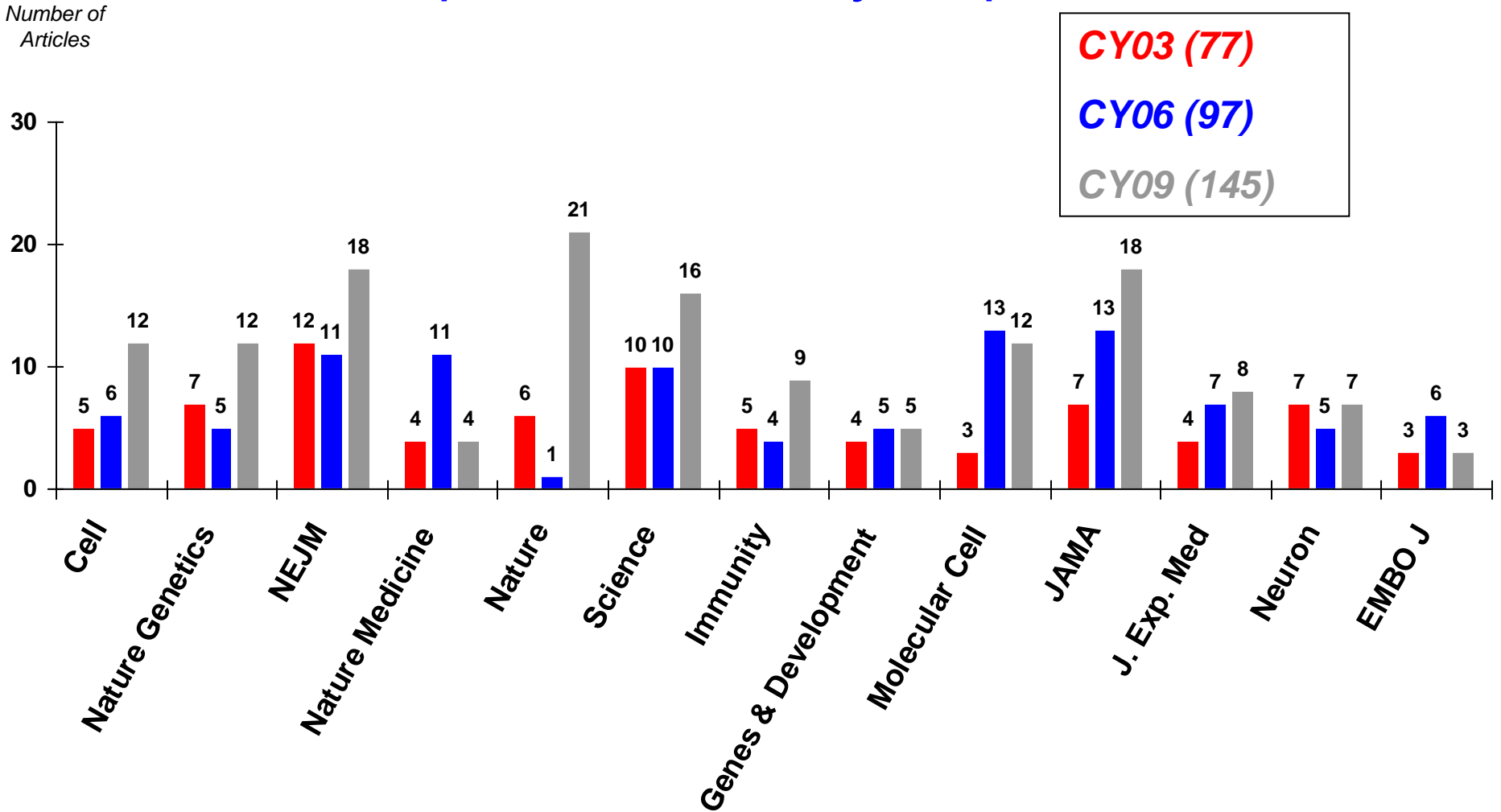


■ Total Research Funding
■ ARRA Funding

* Estimated based on preliminary data

Penn SOM Publications in Top Tier Journals

Number of Penn Articles per Journal *Top 13 Journals by "Impact"*



Source: PubMed Search Engine; CSC Analysis

Major SOM Facilities



**Clinical Research
Building**

204,211 GSF



**Biomedical
Research Building**

385,000 GSF



Blockley Hall

166,425 GSF

School of Medicine Facilities

Translational Research Center Dedication May 3, 2011



531,373 GSF (400k GSF SOM)

A Few Vignettes

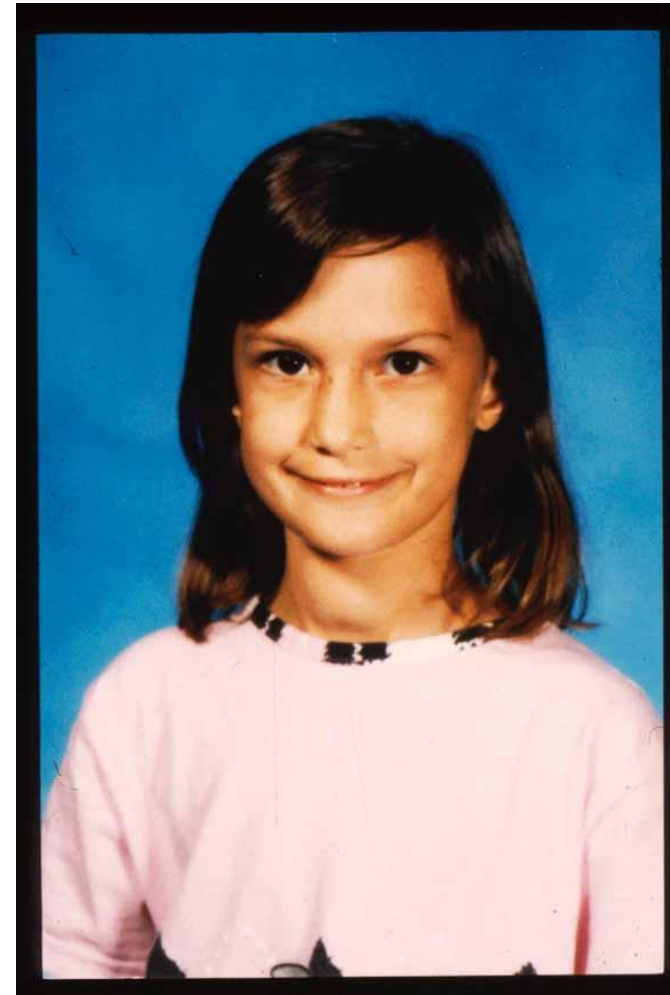
RTH: A Dominant Negative Mechanism

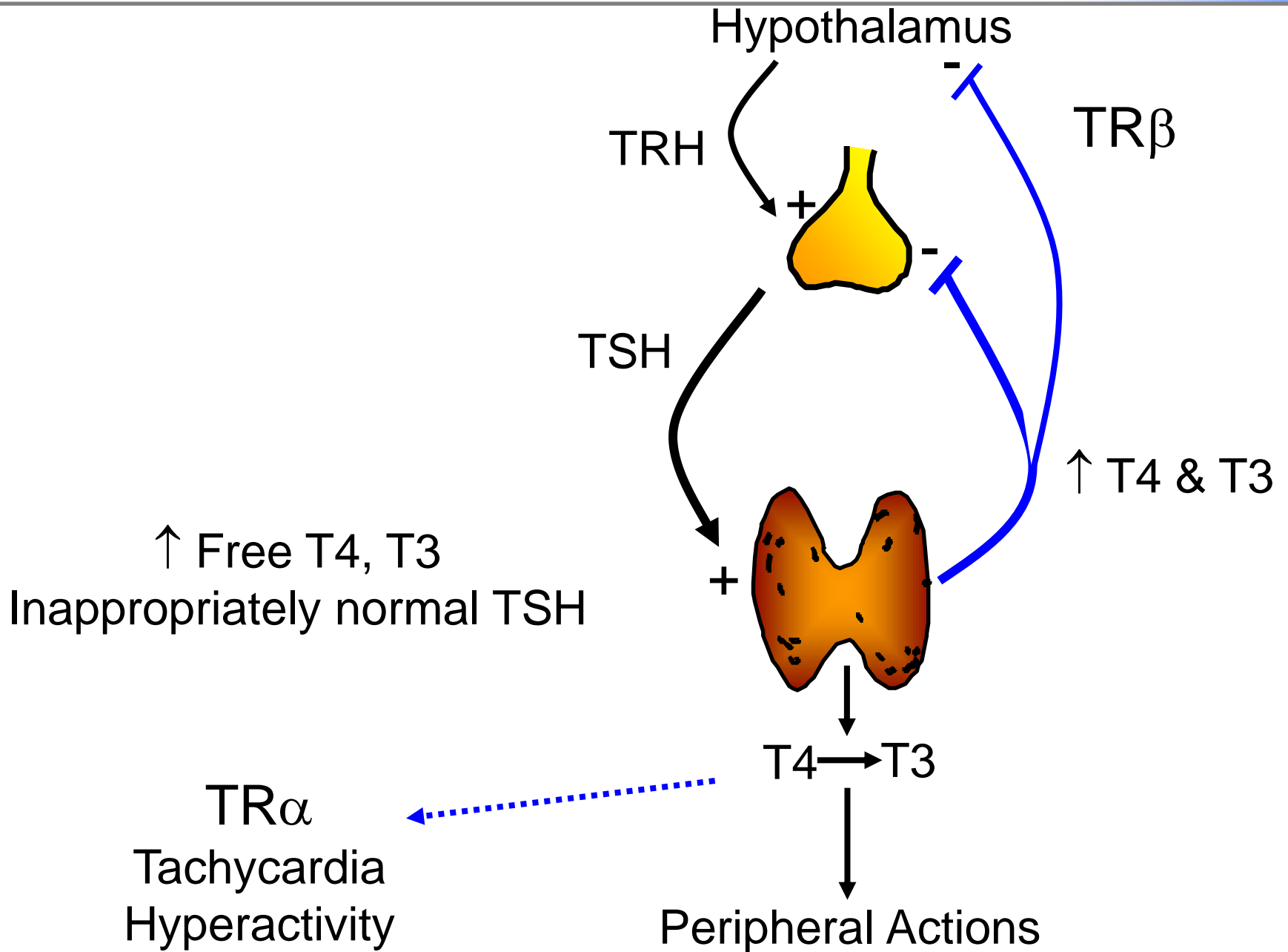
MW presented at age 15 months with developmental delay and growth retardation. Her pulse was 140 bpm.

TFT's included: T4 = 33 $\mu\text{g/dL}$
TSH = 3.2 mIU/mL

RTH was diagnosed. By age 7, she developed chest pain, shortness of breath, and experienced tachycardia (>200 bpm) with exertion. ADHD was severe. She was treated with β -blockers and methimazole, resulting in clinical improvement but worsening goiter.

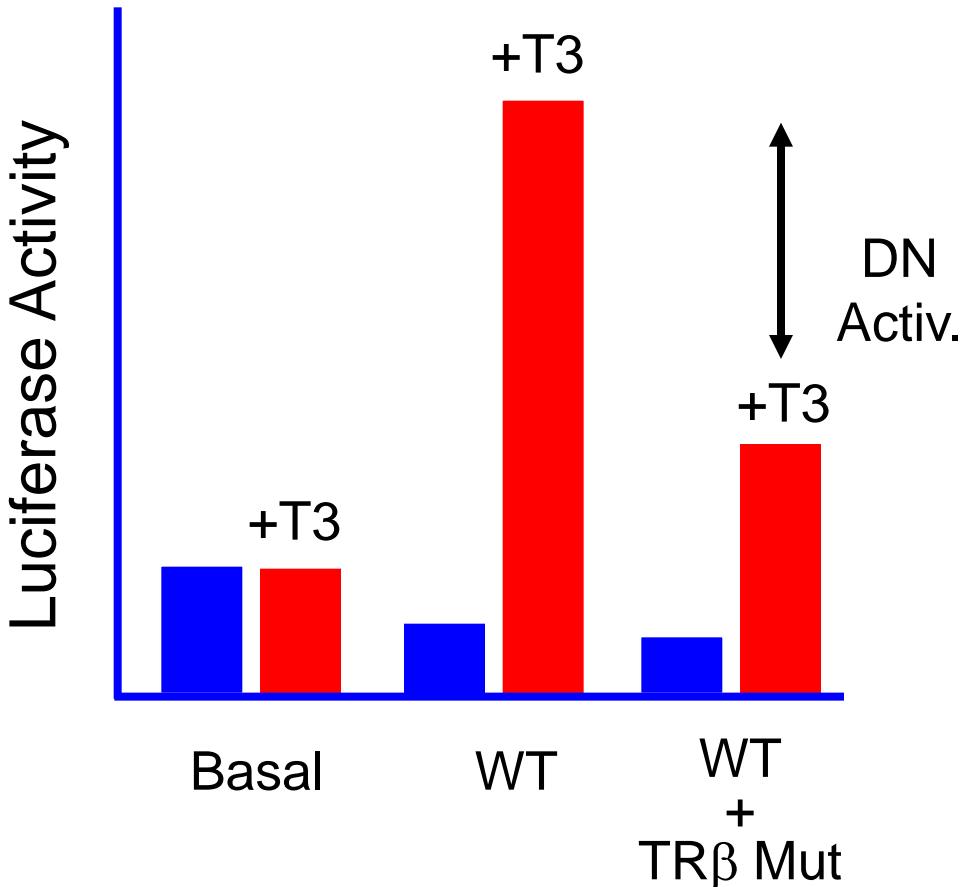
Analysis of the TR β gene revealed an Leu 454 Ser mutation.



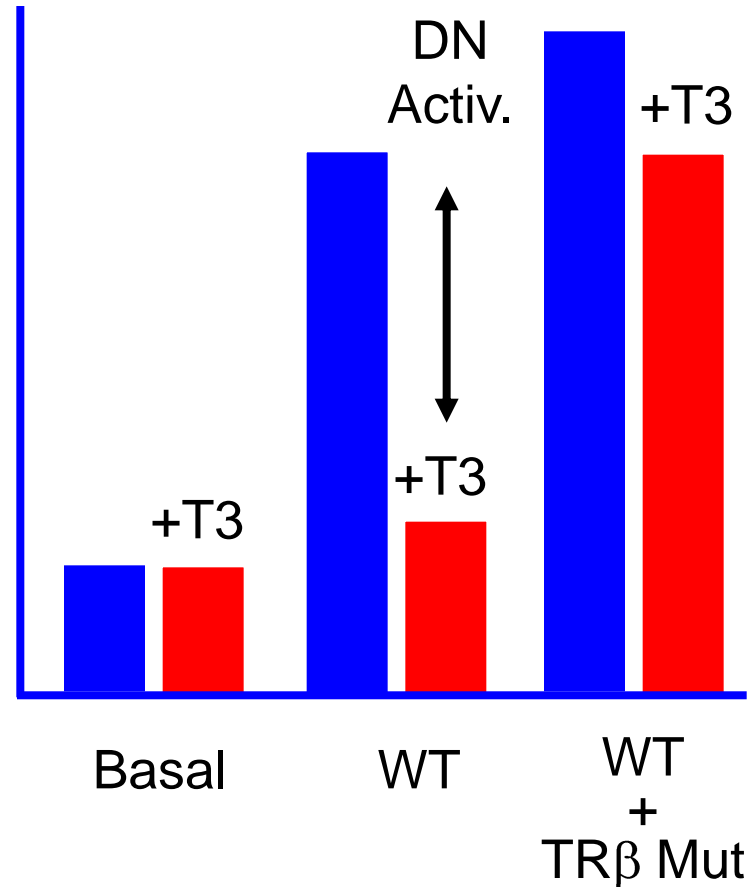


RTH Mutants: Dominant Negative Effects

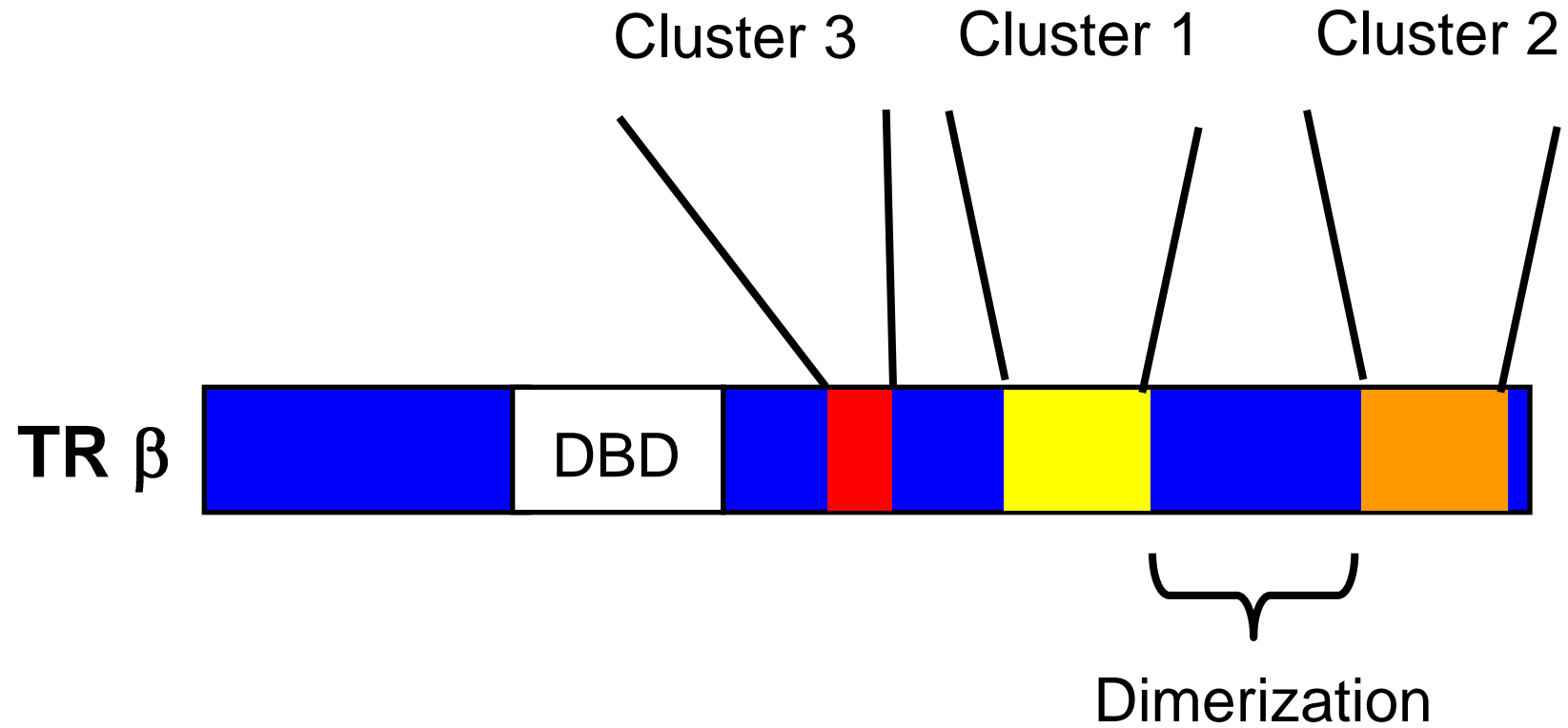
Positive Regulation: TREtk



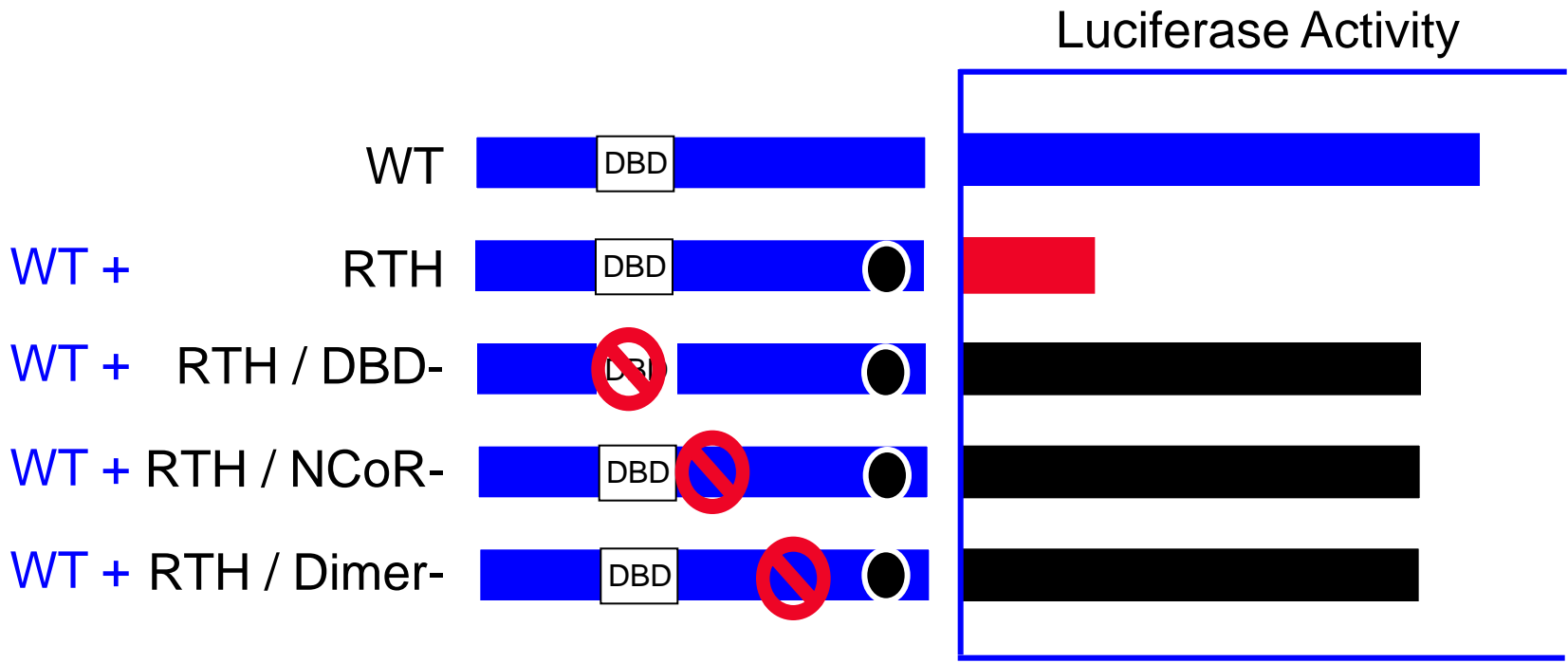
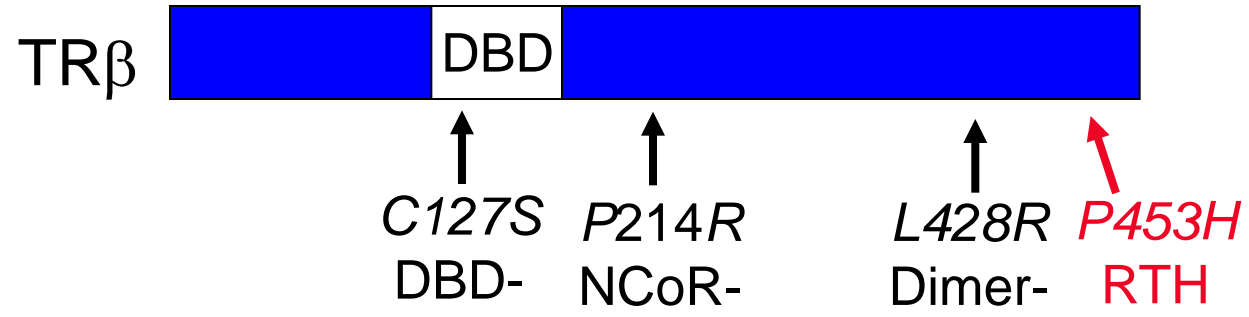
Negative Regulation: TSHα



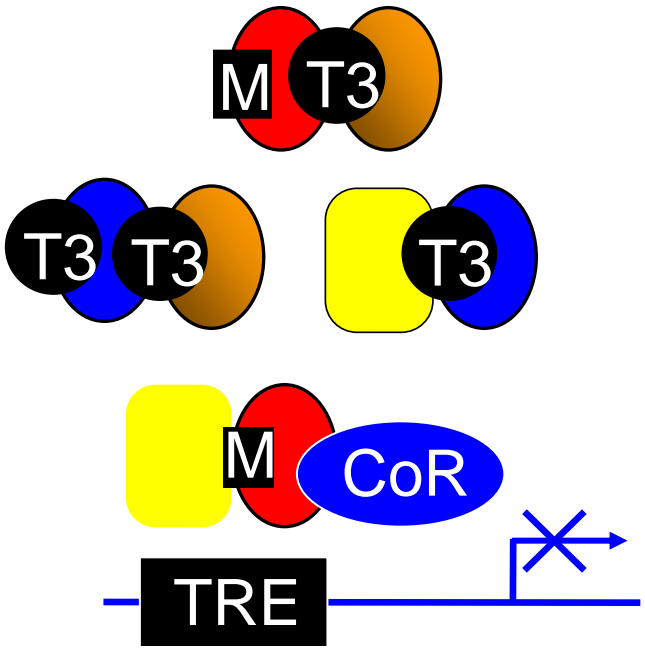
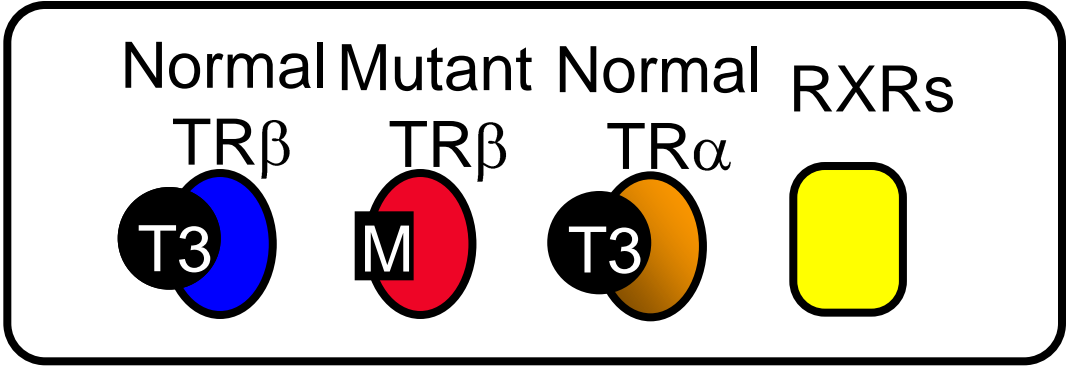
RTH Mutants Cluster



Mechanism: 2nd Site Mutations



Role of Mutant Receptors in RTH



Mutant Thyroid Hormone Receptors:

- Retain DNA binding
- Retain dimerization
- Retain transcriptional repression
- Lack transactivation
- Block wild type receptor action

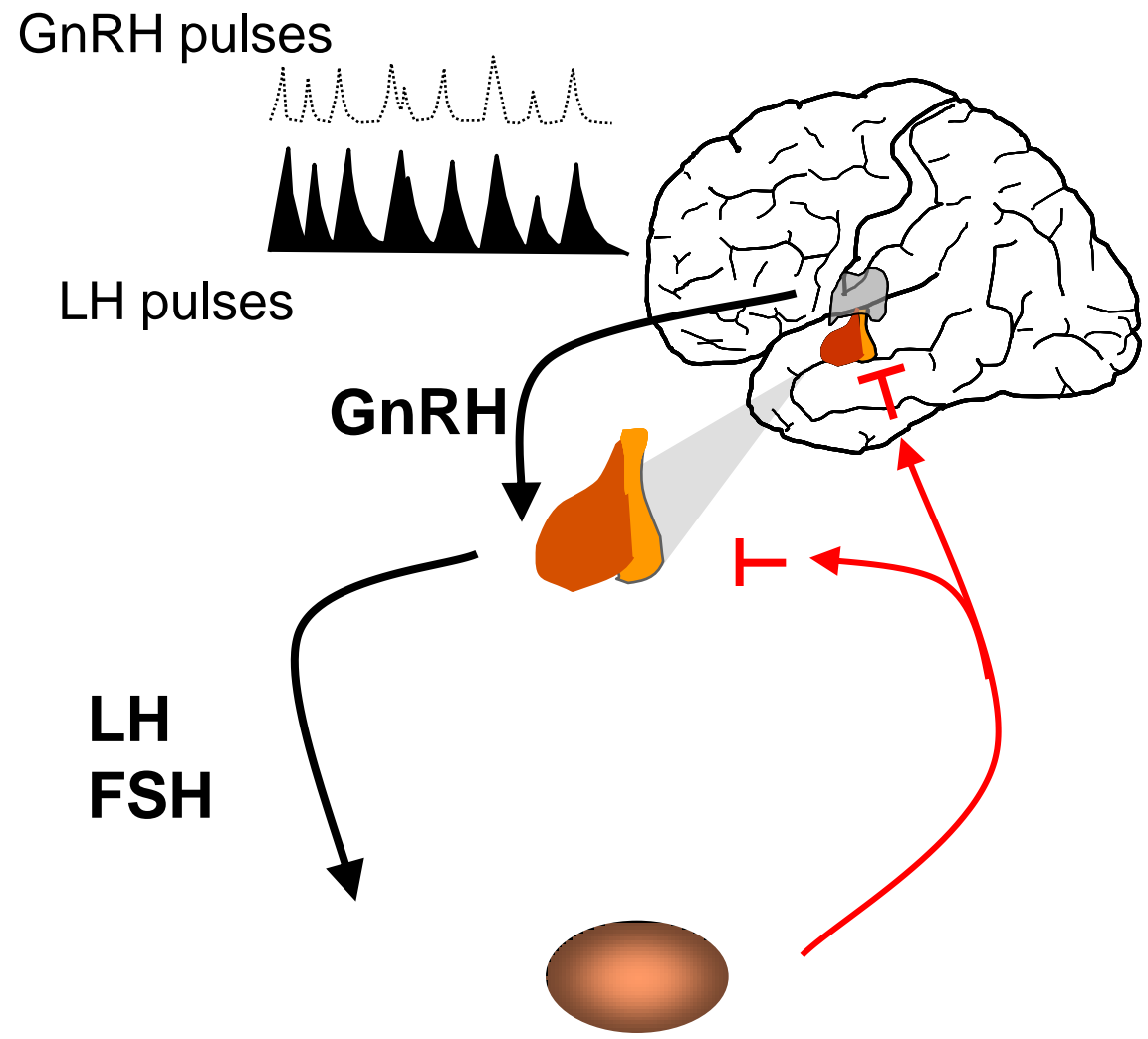
Genetic Disorders of HPG Axis

KAL1
 FGFR1
 GPR54
 SF1**
 DAX1**
 LEP
 LEPR

GNRHR
 SF1
 DAX1
 LHB
 FSHB

WT1
 SF1
 SRY
 SOX9
 DAX1
 FOXL2
 RSPO1
 ATRX
 DHH

FSHR
 LHR
 AMH
 AMHR
 WNT4
 INSL3
 AR
 ER



An Exception to a Venerable Rule

17 year old presents with pubertal delay. Treated with testosterone for 2 years; no evidence of spontaneous puberty after hormone withdrawal.

Karyotype XY

FSH normal

LH increased, low testosterone → ? 1° gonadal failure

Testicular biopsy: Leydig cell hypoplasia

Arrest of spermatogenesis

LH stimulation → normal testosterone !!

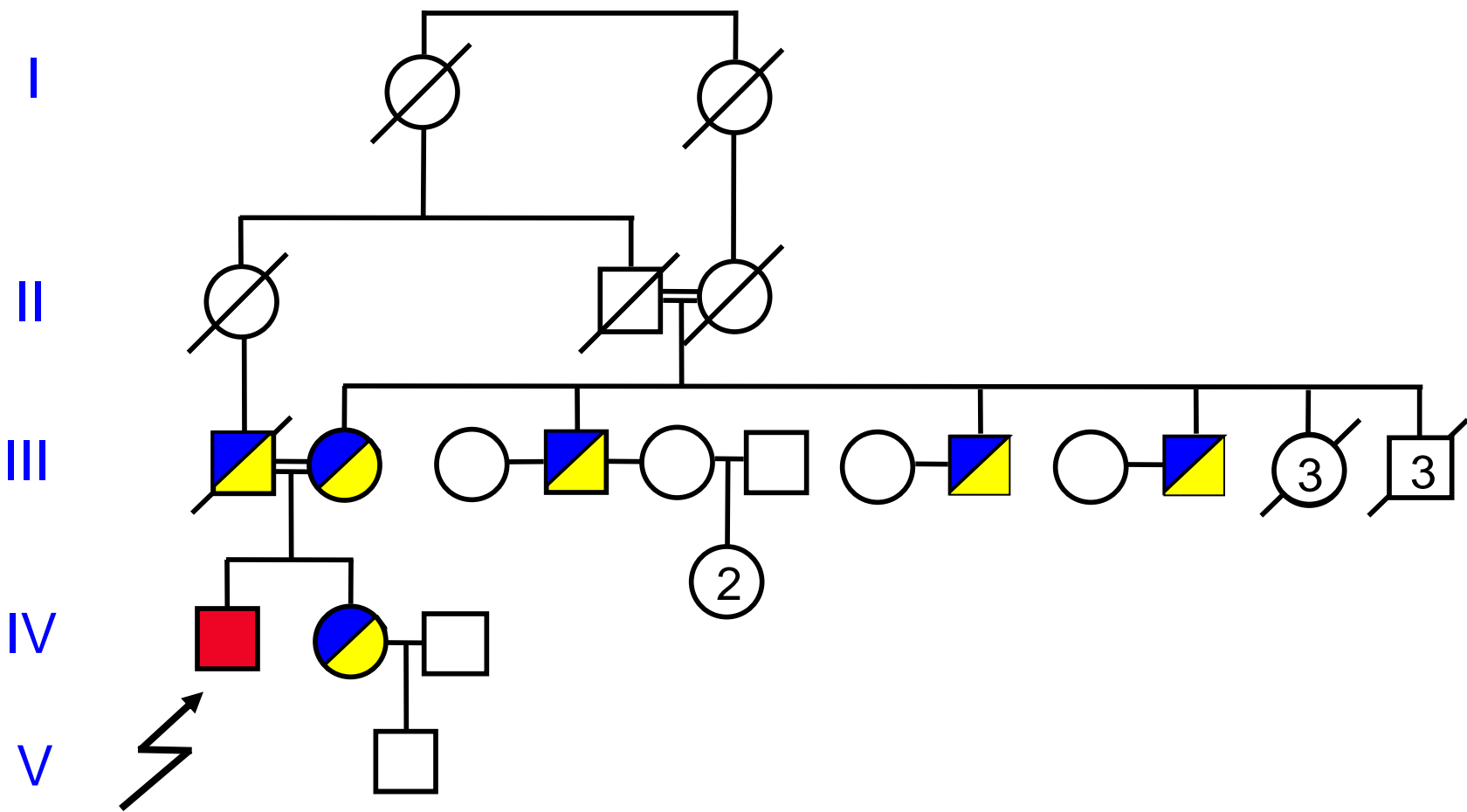
Serum LH bioactivity reduced when tested in vitro

Family history: Consanguinity

Infertility in 3 maternal uncles

Hypothesis: Mutation in LH β gene

1st Gonadotropin Gene Mutation

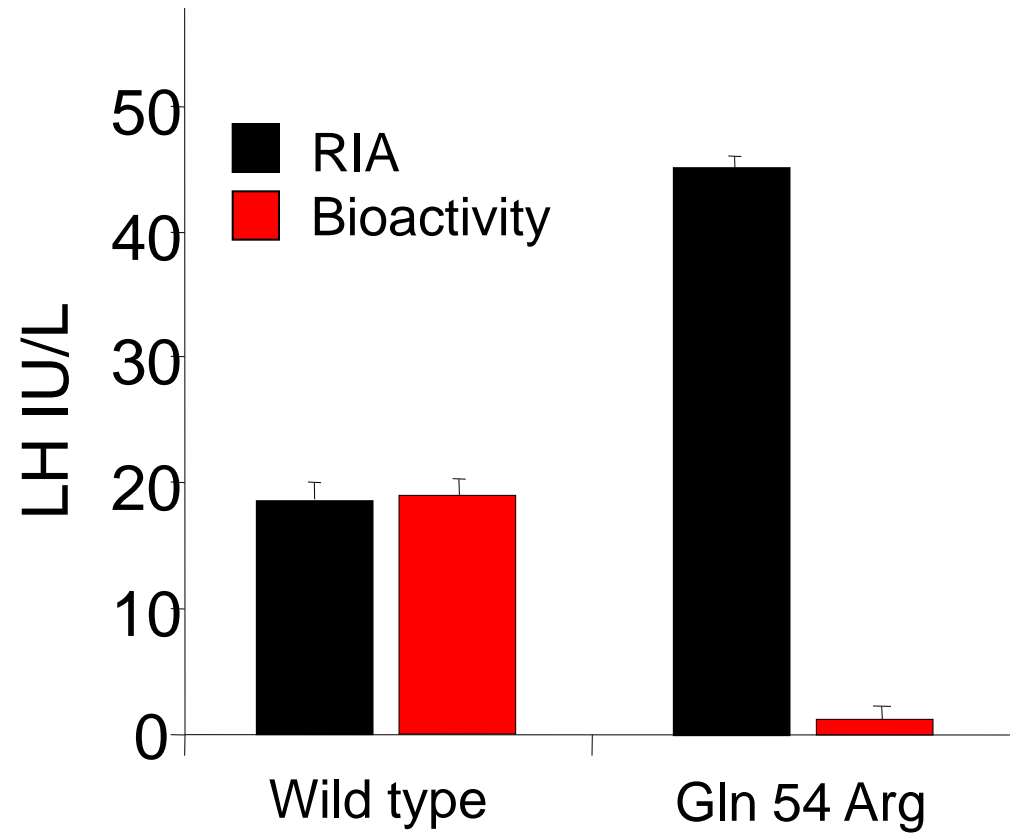
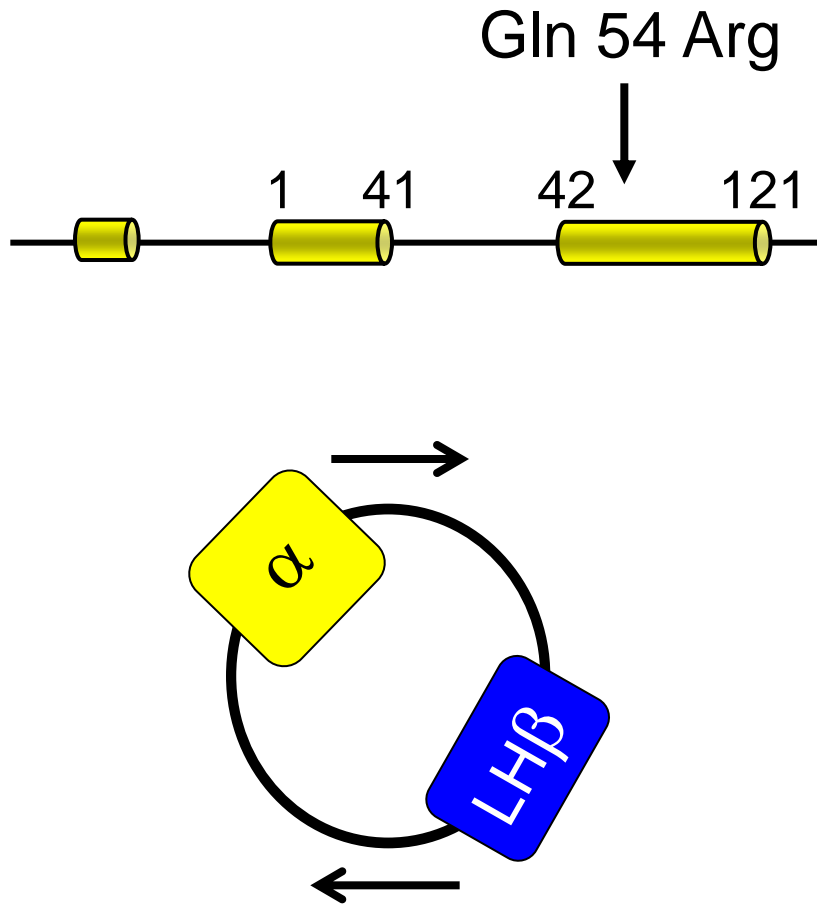


Proband

- LH = 64.2 IU/L
- FSH = 113 IU/L
- Testosterone = 51 ng/dL

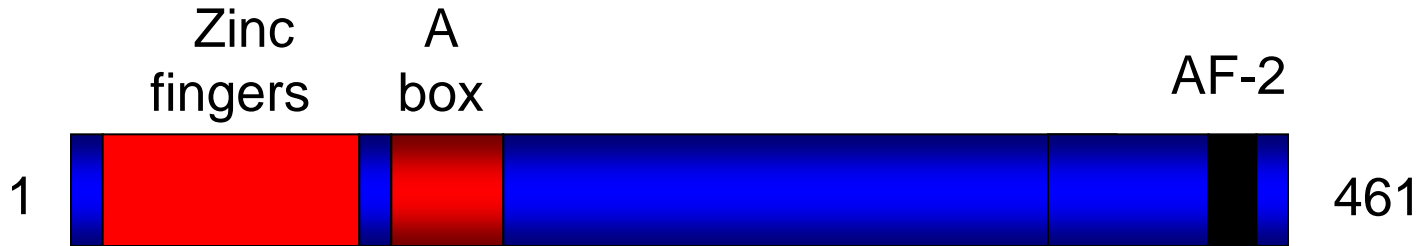
Weiss et al; N Engl J Med 1992; 326:179

LH β Gene Mutation Eliminates Bioactivity

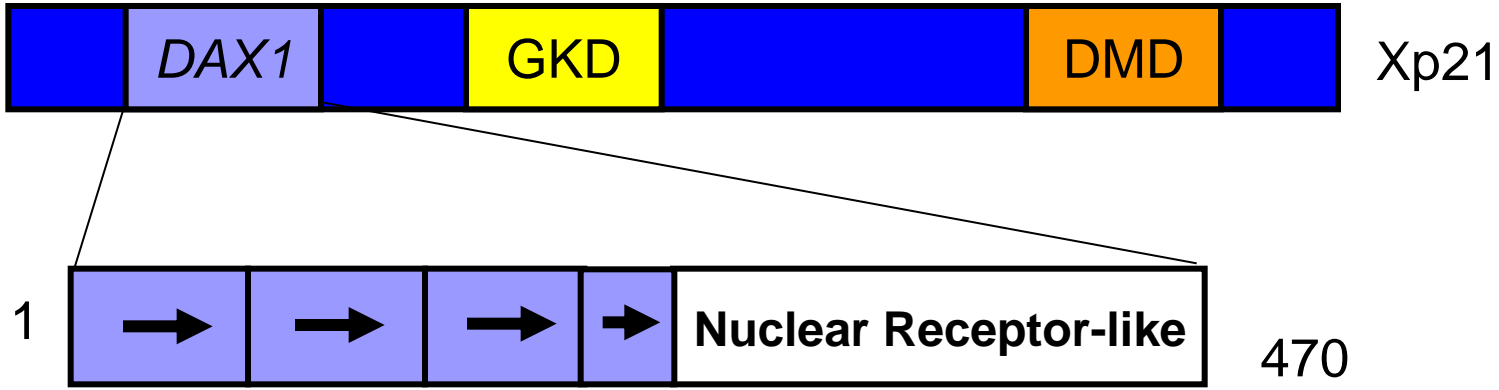


Nuclear Receptors SF-1 and DAX-1

SF-1: Steroidogenic Factor-1



DAX-1: Dosage sensitive sex-reversal,
Adrenal hypoplasia congenita, X-chromosome



Honda S et al: J Biol Chem 268:7494, 1993
Zanaria E et al: Nature 372:635, 1994

SF-1 Knockout Mouse

Abnormal VMH

GnRH deficiency

Gonadotropin deficiency

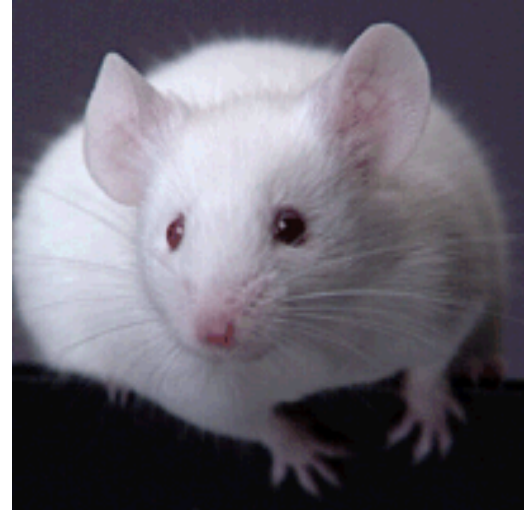
Adrenal agenesis

Gonadal agenesis

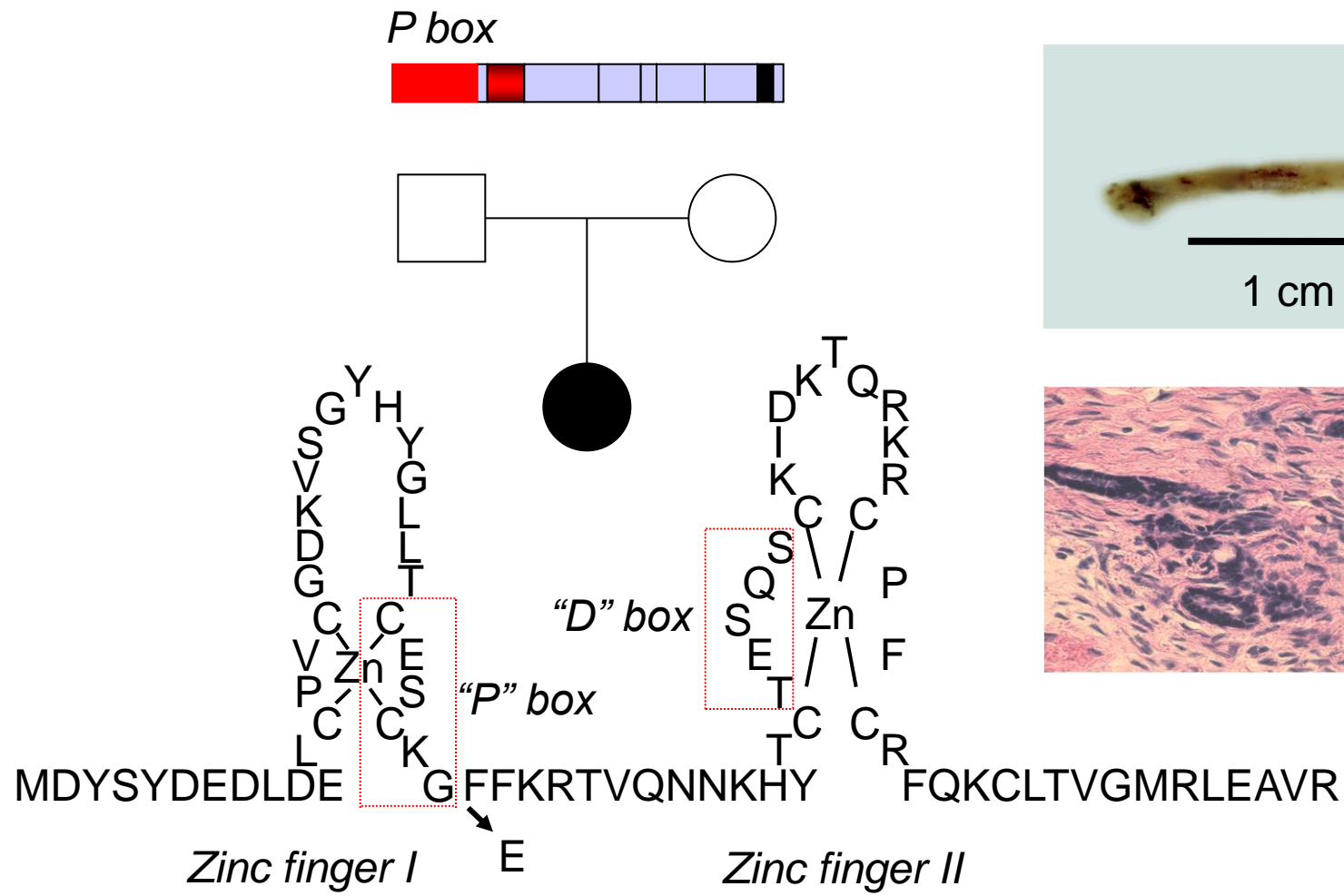
XY sex reversal

Mullerian structures present

Decreased Dax-1



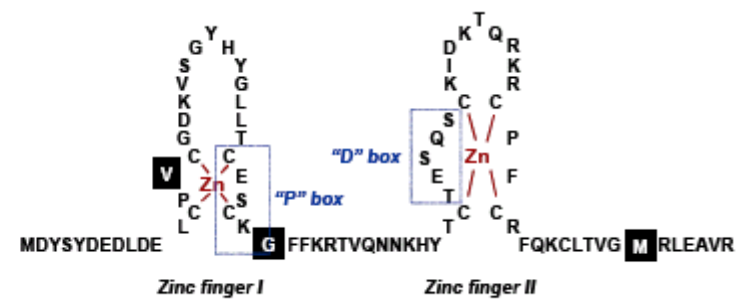
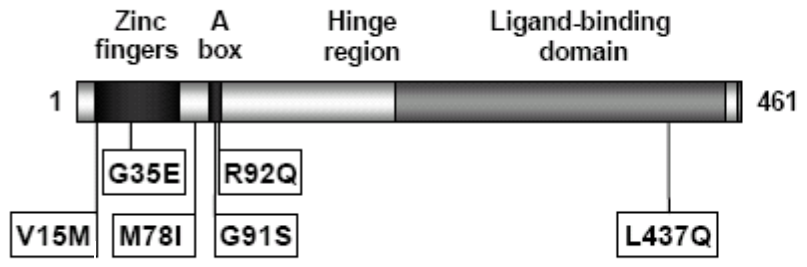
Heterozygous G35E Mutation in SF-1



Achermann JC et al. Nat Genet 22:125, 1999

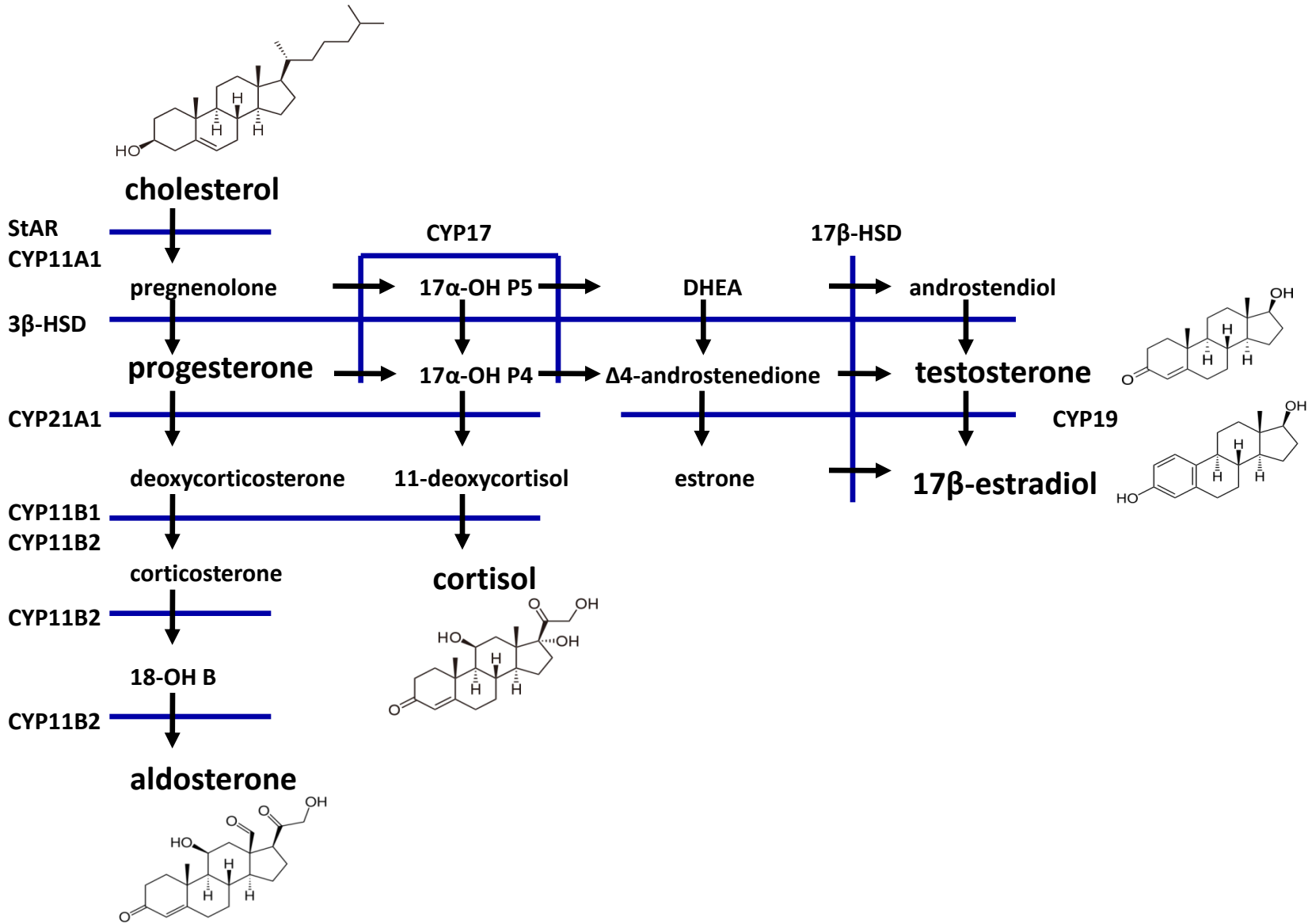
Human SF-1 Mutations

SF1 Mutation	Genotype	Karyotype-Phenotypic sex	Adrenal Function	Gonad	Uterus	Year Published
G35E	heterozygous	XY-female	Failure	Dysgenetic	Present	1999
R255L	heterozygous	XX-female	Failure	Ovary	Present	2000
R92Q	homozygous	XY-female	Failure	Dysgenetic	Present	2002
Deletion	heterozygous	XY-female	Normal	Agensis	Absent	2004
C19X	heterozygous	XY-female	Normal	Dysgenetic	Present	2004
18delC	heterozygous	XY-female	Normal	Dysgenetic	Absent	2004

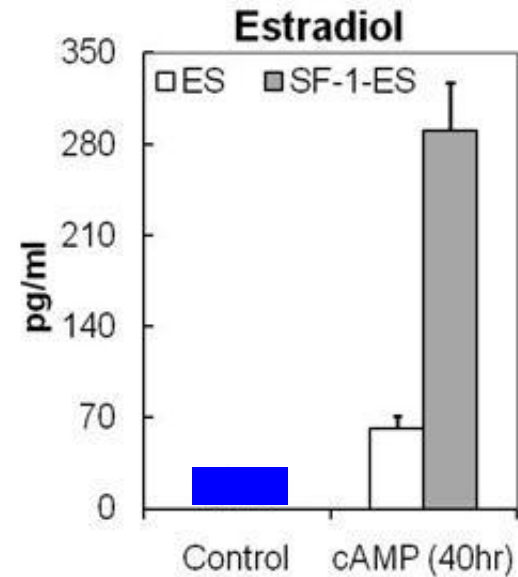
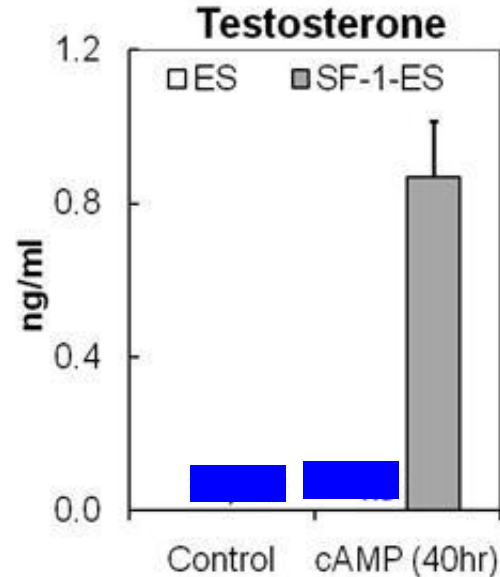
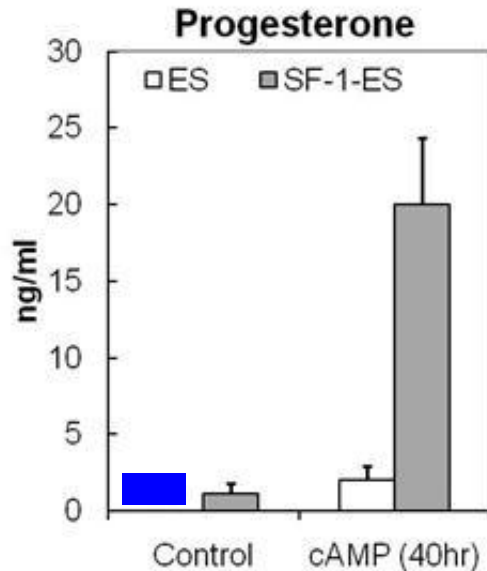
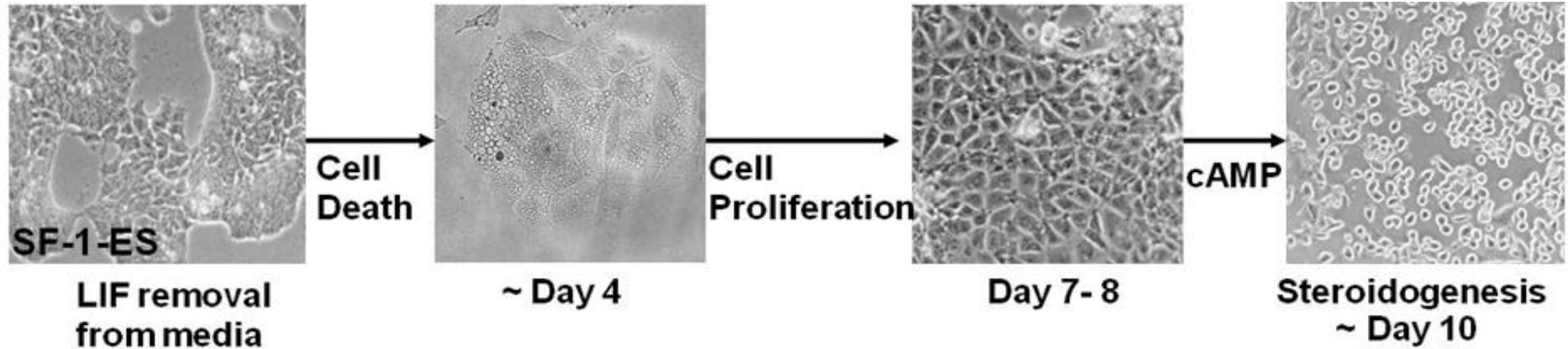


SF1 mutations account for ~10% of XY gonadal dysgenesis

Steroidogenic Pathways



SF-1 Drives Differentiation of ES Cells



Summary Points

- Identify and leverage your unique strengths
- Recognize and adopt disruptive technologies
- Surround yourself with high quality people
- Aspire to high impact research
- When in doubt....adapt to changes
- Make your research clinically relevant

Science Evolves Continuously

"Be inspired by the knowledge that exists at the time you train, but be irreverent toward this knowledge...for this is the road to true understanding" *-Charles Janeway, M.D.-*



Eaton's Portrait of Agnew

