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

- **University**: 4y, 22
- **Residency**: 8y, 30
- **Clinical Fellowship**: 3y, 33
- **First faculty Appt**: 2y, 35
- **Post-tenure bliss**: 10y, 45
- **Mid Career**: 10y, 45
- **Late Career**: 10y, 55
- **Other end of stethoscope**: 10y, 65

**Characteristics**:
- **University**: Enthusiastic, talented but nervous
- **Residency**: Entitled and invincible
- **Clinical Fellowship**: Humble but quick learners
- **First faculty Appt**: Confident and Reflexive
- **Post-tenure bliss**: Top of game & Perplexed about Career

**Other End of Stethoscope**:
- Wise but few new tricks; Accelerate or wind down

**Business of running a research team**

**Wise but few new tricks**

**First faculty Appt**: 35

**Medical School**: 4y, 22

**Residency**: 8y, 30

**Clinical Fellowship**: 3y, 33

**First faculty Appt**: 2y, 35

**Post-tenure bliss**: 10y, 45

**Mid Career**: 10y, 45

**Late Career**: 10y, 55

**Other end of stethoscope**: 10y, 65
Overview

- 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 Physician-Scientist Career Pipeline in 2005
Build It, and They Will Come

Timothy J. Ley, MD
Leon E. Rosenberg, MD

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.

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-


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

MD-PhD program graduates

95% do residencies

- Medicine, 29%
- Surgery, 11%
- Pediatrics, 10%
- Pathology, 8%
- Neurology, 8%
- Radiology, 7%
- Psychiatry, 6%
- Dermatology, 5%
- Radiation oncology, 3%
- Ophthalmology, 4%
- Anesthesiology, 2%
- OB/Gyn, 1%
- Emergency Medicine, 1%
- Postdoc, 5%

Brass et al., Academic Medicine, April 2010
MD-PhD program graduates: residency

Trends in residency choices

Graduation year

Residency choice

- Medicine/Neurology/Pathology/Pediatrics
- Dermatology/Ophthalmology/RadiationOncology/Surgery
Academia, 68%
Research Institute, 5%
Industry, 8%
Private Practice, 16%
Other, 3%

Brass et al., Academic Medicine, April 2010
Research by MD-PhD program graduates

Are you doing research?

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>No data</th>
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<tbody>
<tr>
<td>Percentage</td>
<td>82%</td>
<td>13%</td>
<td>5%</td>
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Do you have research grants?

<table>
<thead>
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<th>Yes</th>
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<th>No data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage</td>
<td>61%</td>
<td>14%</td>
<td>25%</td>
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What kinds of research are you doing?

<table>
<thead>
<tr>
<th>Types of research</th>
<th>Basic</th>
<th>Translational</th>
<th>Clinical</th>
<th>Health Sys</th>
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<tr>
<td>Count</td>
<td>417</td>
<td>304</td>
<td>314</td>
<td>11</td>
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</table>

Brass et al., Academic Medicine, April 2010
An “Objective” Analysis of One Person’s Path — *Mine*
Career Path

Training & Leadership
- MGH Residency
- MSTP UNC Endo Fellowship
- Chief, Thyroid Unit MGH
- Chief, Endo Northwestern
- President Endo Soc
- Chair, DoM Northwestern
- HHMI ABIM
- Dean Northwestern

- Oppenheimer Van Meter Award Koch Award
- Endo Soc ATA Endo
- ASCI AAP AAAS IOM

Recognition

Editorial
- DeGroot PMM Harrison’s
- Editor Editor
Impact of Disruptive Technologies

- Cloning
- DNA Sequencing
- Human Mutation Analyses
- Automated DNA Sequencing
- ‘Omics

Key Technologies:
- Gel shift Assays
- Transfection
- CAT/Luc Assays
- In situ Assays
- Transgenic Assays
- ENU
- Gene Mutagenesis
- Knockout

Timeline:
- 1980
- 1985
- 1990
- 1995
- 2005
## Balancing Science and Leadership

### Years vs. Impact

<table>
<thead>
<tr>
<th>Years</th>
<th>Number of Articles</th>
<th>Average Impact</th>
<th>Total Impact</th>
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<tr>
<td>85-86</td>
<td>5</td>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td>87-88</td>
<td>10</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>89-90</td>
<td>10</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>91-92</td>
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<td>5</td>
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<tr>
<td>93-94</td>
<td>10</td>
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</tr>
<tr>
<td>95-96</td>
<td>10</td>
<td>5</td>
<td>50</td>
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<tr>
<td>97-98</td>
<td>10</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>99-00</td>
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<td>5</td>
<td>50</td>
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<td>01-02</td>
<td>10</td>
<td>5</td>
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</tr>
<tr>
<td>03-04</td>
<td>10</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>05-06</td>
<td>10</td>
<td>5</td>
<td>50</td>
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</table>

**Key Events:**
- Independent Lab at MGH
- Move to NW
- Harrison’s Chair, Medicine

**Programs & Grants:**
- R29
- R01-CG
- R01-GR
- U54
- R01-TSH
- DOD
- SPORE
- PO1

### Notes
- Balancing Science and Leadership.
Reflections on the Data

• Grants should be staggered
• Collaborative grants stimulate new research areas
• New technologies drive laboratory science
  
  \textit{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
Perelman School of Medicine

• 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
## 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

<table>
<thead>
<tr>
<th>Course Title</th>
<th>Description</th>
<th>Date/Time/Location</th>
<th>Instructor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Establishing a Productive Relationship with Your Mentor</td>
<td>This session is designed for junior faculty who are just starting to work with their assigned mentors or who are looking for additional mentors.</td>
<td>October 17, 2011 3:30 to 5:00 p.m., BRB 251</td>
<td>Dr. Marcia Brose</td>
</tr>
<tr>
<td>Getting the Most Out of Mentoring: Asbury Mentoring Award Winners Panel</td>
<td>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. PLEASE NOTE: Faculty registering for this session are encouraged to attend this session with their mentor(s).</td>
<td>November 14, 2011 3:30 to 5:00 p.m., BRB 251</td>
<td>Dr. Steven Albeida, Dr. David Asch, Dr. Charles O'Brien</td>
</tr>
</tbody>
</table>
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

<table>
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<tr>
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<th>Description</th>
<th>Date/Time/Location</th>
<th>Instructor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Writing on Article for Publication Part 1: Writing the “Results” Section</td>
<td>This session will focus on relating the results text to the figures in a way that tells a compelling scientific story.</td>
<td>September 15, 2011 12 noon to 1:30 p.m. Stellar-Chance 104</td>
<td>Dr. Elizabeth Colston</td>
</tr>
<tr>
<td>Enroll Now</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Courses and Resources for:
- Attaining Teaching Excellence
- Career Management
- Mentoring
- Research
- Scientific Writing
- Technology
Growth in Total Research Funding

PENN PSOM Funding Trends: Total
FY98 - FY10

Dollars in millions

FY 98 FY 99 FY 00 FY 01 FY 02 FY 03 FY 04 FY 05 FY 06 FY 07 FY 08 FY 09 FY 10
#2 #2 #2 #3 #3 #3 #2 #2 #3 #3 #3 #3
$262 $304 $360 $371 $426 $477 $508 $509 $541 $539 $533 $575 $690

Total Research Funding
ARRA Funding

* Estimated based on preliminary data
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
- Blockely Hall: 166,425 GSF
School of Medicine Facilities

Translational Research Center
Dedication May 3, 2011

531,373 GSF (400k GSF SOM)
A Few Vignettes
MW presented at age 15 months with developmental delay and growth retardation. Her pulse was 140 bpm.

TFT’s included: T4 = 33 µg/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 TRβ gene revealed an Leu 454 Ser mutation.
Free T4, T3
Inappropriately normal TSH

↑ Free T4, T3
Inappropriately normal TSH

TRα
Tachycardia
Hyperactivity

Peripheral Actions

T4 → T3

Hypothalamus

TRH

TSH

TRβ

↑ T4 & T3
RTH Mutants: Dominant Negative Effects

Positive Regulation: TREtk

Negative Regulation: TSHα

Chatterjee VKK et al., J Clin Invest 1991; 87:1977
RTH Mutants Cluster

Cluster 3
Cluster 1
Cluster 2

Dimerization

TR β

DBD
Mechanism: 2nd Site Mutations

TRβ

DBD

C127S

DBD-
P214R

NCoR-

L428R

Dimer-
P453H

RTH

Luciferase Activity

WT

DBD

WT + RTH

DBD

WT + RTH / DBD-

WT + RTH / NCoR-

WT + RTH / Dimer-

Nagaya T et al., J Biol Chem 1993; 268:15766
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

GnRH pulses

LH pulses

GnRH

LH

FSH

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 $\rightarrow$ ? 1° gonadal failure

Testicular biopsy: Leydig cell hypoplasia
- Arrest of spermatogenesis
- LH stimulation $\rightarrow$ normal testosterone !!

Serum LH bioactivity reduced when tested in vitro

Family history: Consanguinity
- Infertility in 3 maternal uncles

Hypothesis: Mutation in LHβ gene
1st Gonadotropin Gene Mutation

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

LHβ Gene Mutation Eliminates Bioactivity

Gln 54 Arg

Wild type

Gln 54 Arg

RIA

Bioactivity

LH IU/L

0 10 20 30 40 50

0 10 20
Nuclear Receptors SF-1 and DAX-1

SF-1: Steroidogenic Factor-1

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

Abnormal VMH
GnRH deficiency
Gonadotropin deficiency
Adrenal agenesis
Gonadal agenesis
XY sex reversal
Mullerian structures present
Decreased Dax-1

Luo X et al: Cell 77:481, 1994
Heterozygous G35E Mutation in SF-1

### Human SF-1 Mutations

<table>
<thead>
<tr>
<th>SF1 Mutation</th>
<th>Genotype</th>
<th>Karyotype-Phenotypic sex</th>
<th>Adrenal Function</th>
<th>Gonad</th>
<th>Uterus</th>
<th>Year Published</th>
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</thead>
<tbody>
<tr>
<td>G35E</td>
<td>heterozygous</td>
<td>XY-female</td>
<td>Failure</td>
<td>Dysgenetic</td>
<td>Present</td>
<td>1999</td>
</tr>
<tr>
<td>R255L</td>
<td>heterozygous</td>
<td>XX-female</td>
<td>Failure</td>
<td>Ovary</td>
<td>Present</td>
<td>2000</td>
</tr>
<tr>
<td>R92Q</td>
<td>homozygous</td>
<td>XY-female</td>
<td>Failure</td>
<td>Dysgenetic</td>
<td>Present</td>
<td>2002</td>
</tr>
<tr>
<td>Deletion</td>
<td>heterozygous</td>
<td>XY-female</td>
<td>Normal</td>
<td>Agenesis</td>
<td>Absent</td>
<td>2004</td>
</tr>
<tr>
<td>C19X</td>
<td>heterozygous</td>
<td>XY-female</td>
<td>Normal</td>
<td>Dysgenetic</td>
<td>Present</td>
<td>2004</td>
</tr>
<tr>
<td>18delC</td>
<td>heterozygous</td>
<td>XY-female</td>
<td>Normal</td>
<td>Dysgenetic</td>
<td>Absent</td>
<td>2004</td>
</tr>
</tbody>
</table>

SF1 mutations account for ~10% of XY gonadal dysgenesis
Steroidogenic Pathways

- Cholesterol → Pregnenolone → Progesterone
- Progesterone → 17α-OH P5 → Δ4-Androstenedione → Testosterone
- Progesterone → 17α-OH P4 → Deoxycorticosterone → 11-Deoxycortisol
- Deoxycorticosterone → Corticosterone → Cortisol
- Corticosterone → Aldosterone
- 3β-HSD
- CYP11A1
- CYP17
- 17β-HSD
- CYP21A1
- CYP19
SF-1 Drives Differentiation of ES Cells

LIF removal from media → Cell Death → ~ Day 4 (cell proliferation) → Day 7-8 → cAMP → Steroidogenesis ~ Day 10

Graphs showing:
- Progesterone: ES vs. SF-1-ES
- Testosterone: ES vs. SF-1-ES
- Estradiol: ES vs. SF-1-ES
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
"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.-