Grants 101 Part III

NIH Structure & Behind the Scenes at a Study Section

Bill Parks

Center for Lung Biology

UW Medicine

Center for Lung Biology
University of Washington

What You Will Learn in This Last Session

- The NIH
- The grant review process
- Getting into the reviewer's head
- Tips on how to keep reviewers happy and supportive of your proposal

- *Focus on NIH F and K applications – but widely applicable to other mechanisms, including society/foundation grants*

National Institutes of Health

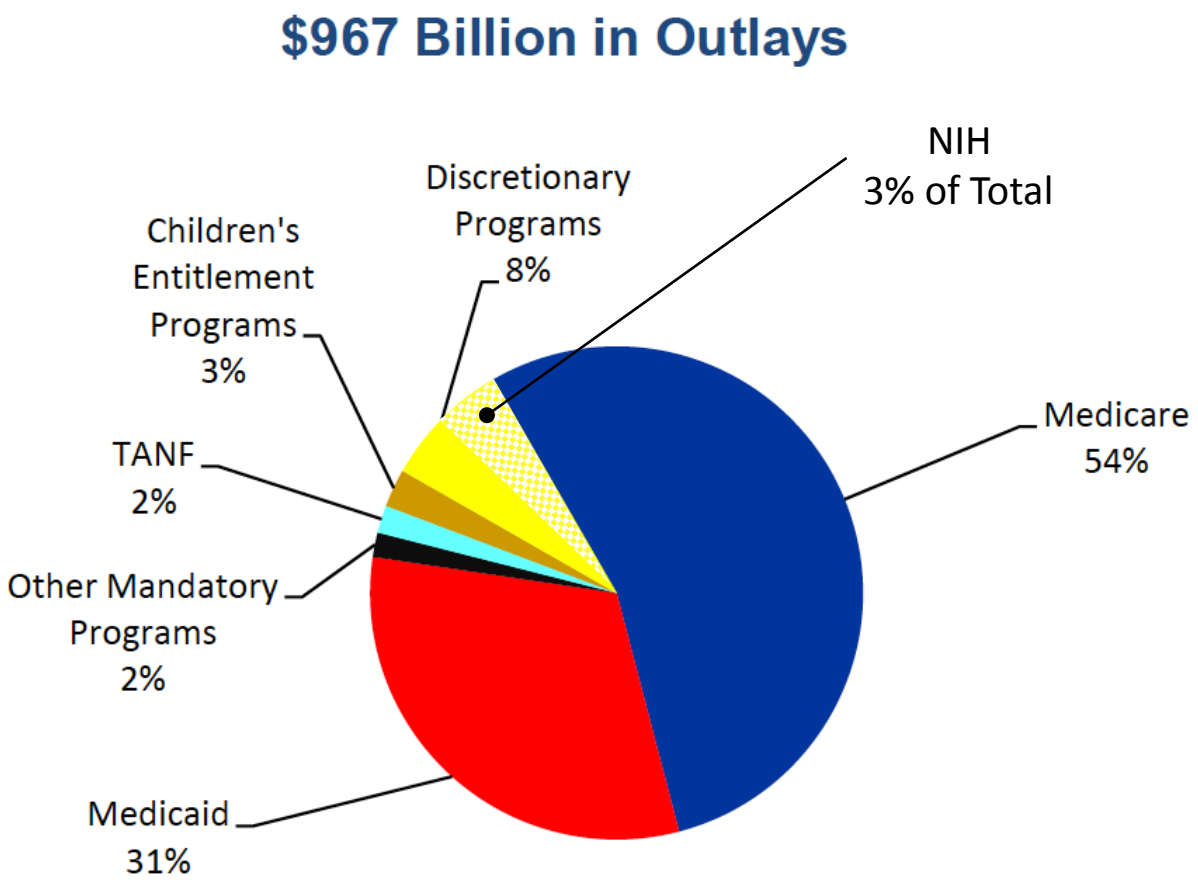
US Department of Health and Human Services

The Boss

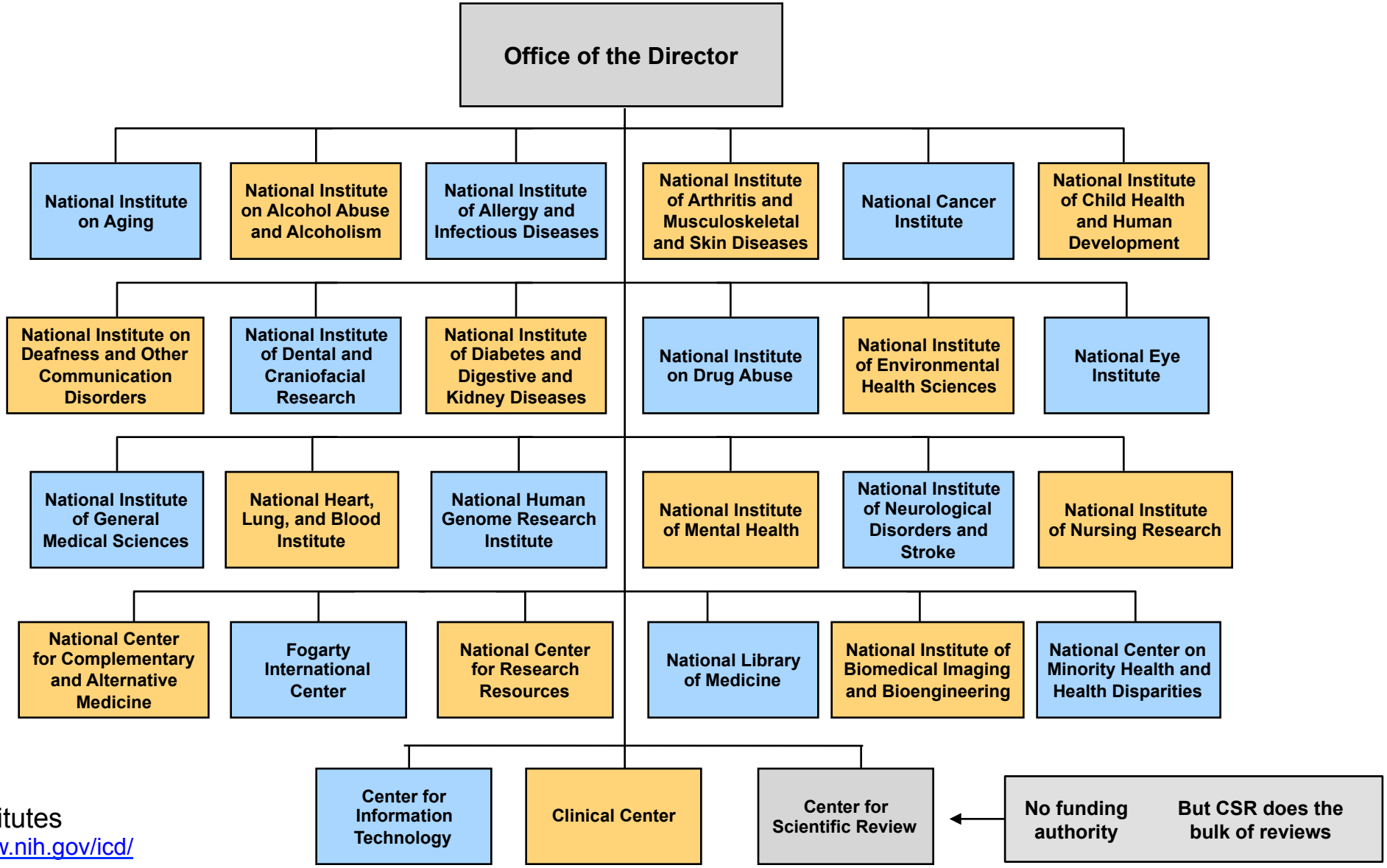
Kathleen Sabelius
H&HS

Francis Collins, MD PhD

H&HS Budget FY2013



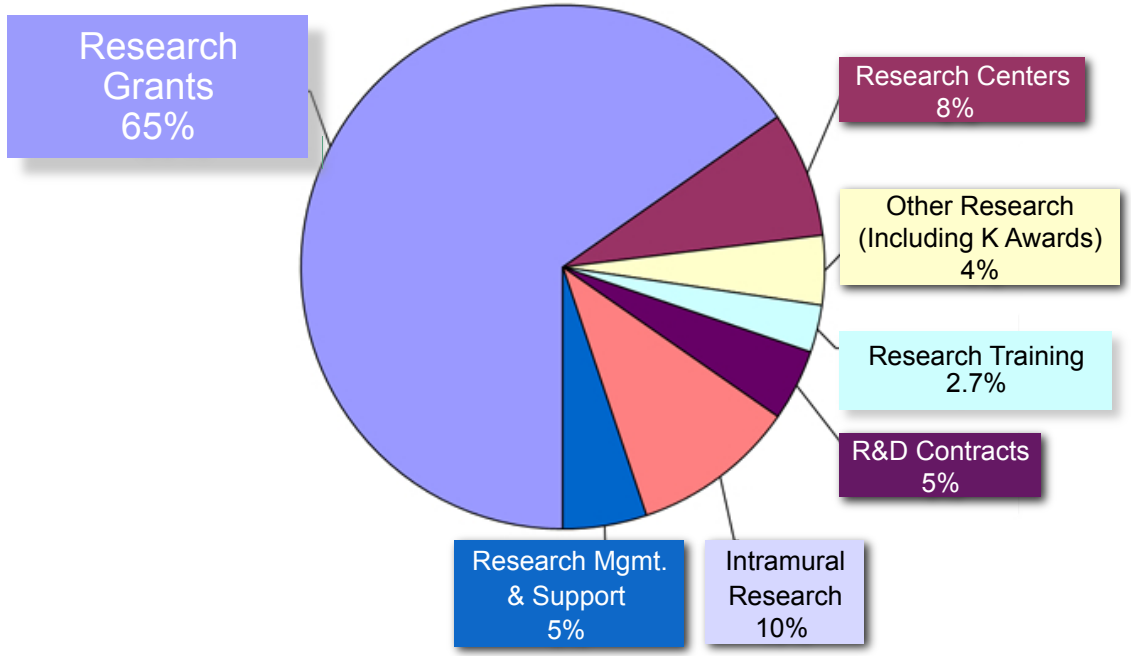
All NIH Institutes Review Grant Applications



NIH Institutes
http://www.nih.gov/icd/

The Bulk (~85%) of the NIH Budget Supports Extramural Research & Training

FY2013 President's Budget Request
Total NIH Budget Authority
$30.9 Billion*

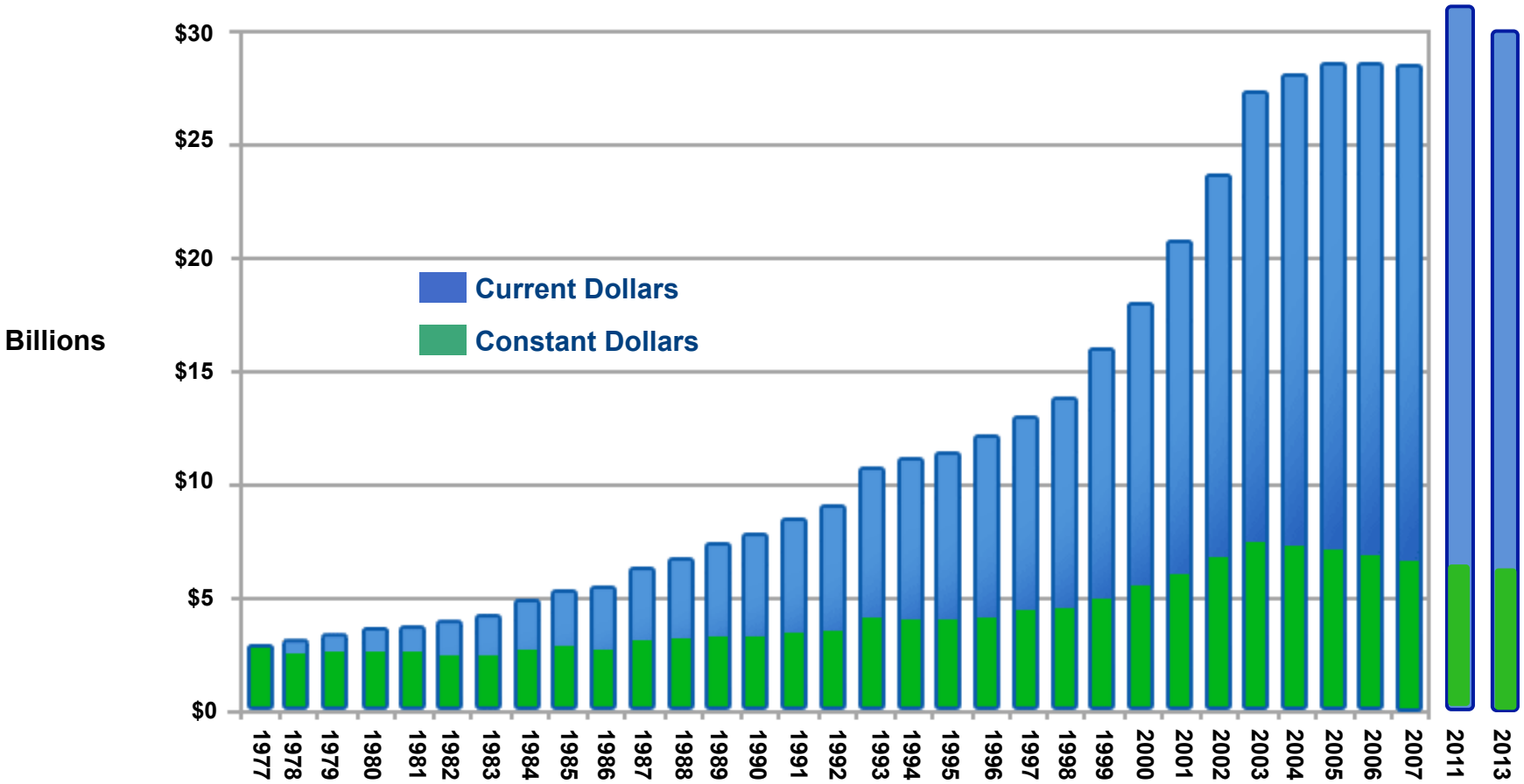


*~4% of DOD budget

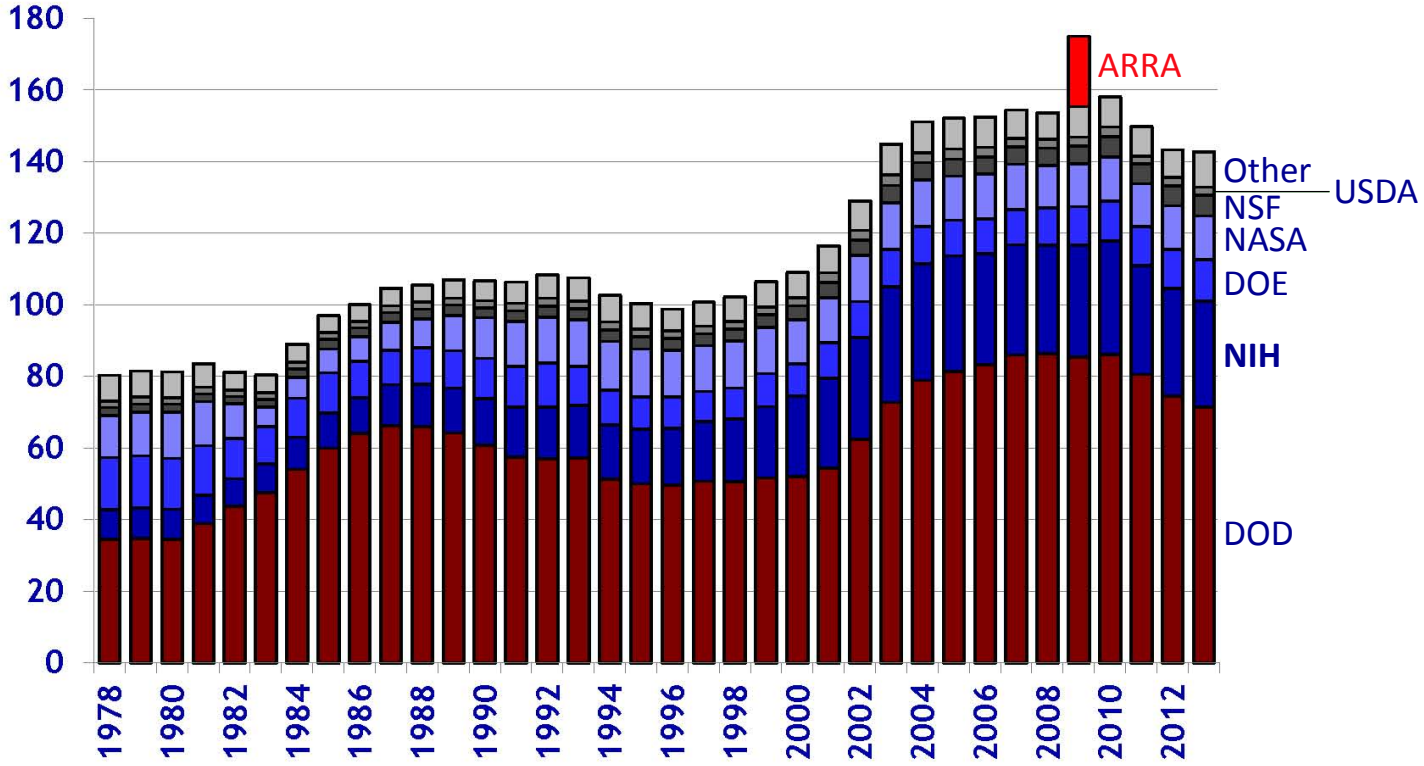
Appropriations Varies Among Institutes

	Appropriation	FY 2011 President's Budget
Cancer	NCI	5,264,643
Heart, Lung & Blood	NHLBI	3,187,516
	NIDCR	423,511
Diabetes, Digestive, Kidney	NIDDK 3/	2,007,589
Neurol. Disorders & Stroke	NINDS	1,681,333
Allergy & Infectious Dis.	NIAID 4/	4,977,070
General Med. Sci.	NIGMS	2,125,090
Child Hlth. & Human Dev.	NICHD	1,368,894
	NEI	724,360
	NIEHS	707,339
	NIA	1,142,337
	NIAMS	555,715
Deafness & Communication Disorders	NIDCD	429,007
	NIMH	1,540,345
	NIDA	1,094,078
	NIAAA	474,649
	NINR	150,198
	NHGRI	533,959
	NIBIB	325,925
Research Resources	NCRR	1,308,741
	NCCAM	132,004
	NCMHD	219,046
	FIC	73,027
	NLM	364,802
Office of the Director	OD	1,220,478
	B&F	125,581
	Type 1 Diabetes 3/	-150,000
	Subtotal, Labor/HHS	**32,007,237**
	Interior/Superfund Research Program	81,763
	Total, NIH Discretionary B.A.	**32,089,000**
	Type 1 Diabetes	150,000
	Total, NIH Budget Authority	**32,239,000**
	NLM Program Evaluation	8,200
	Total, Prog. Level	**32,247,200**

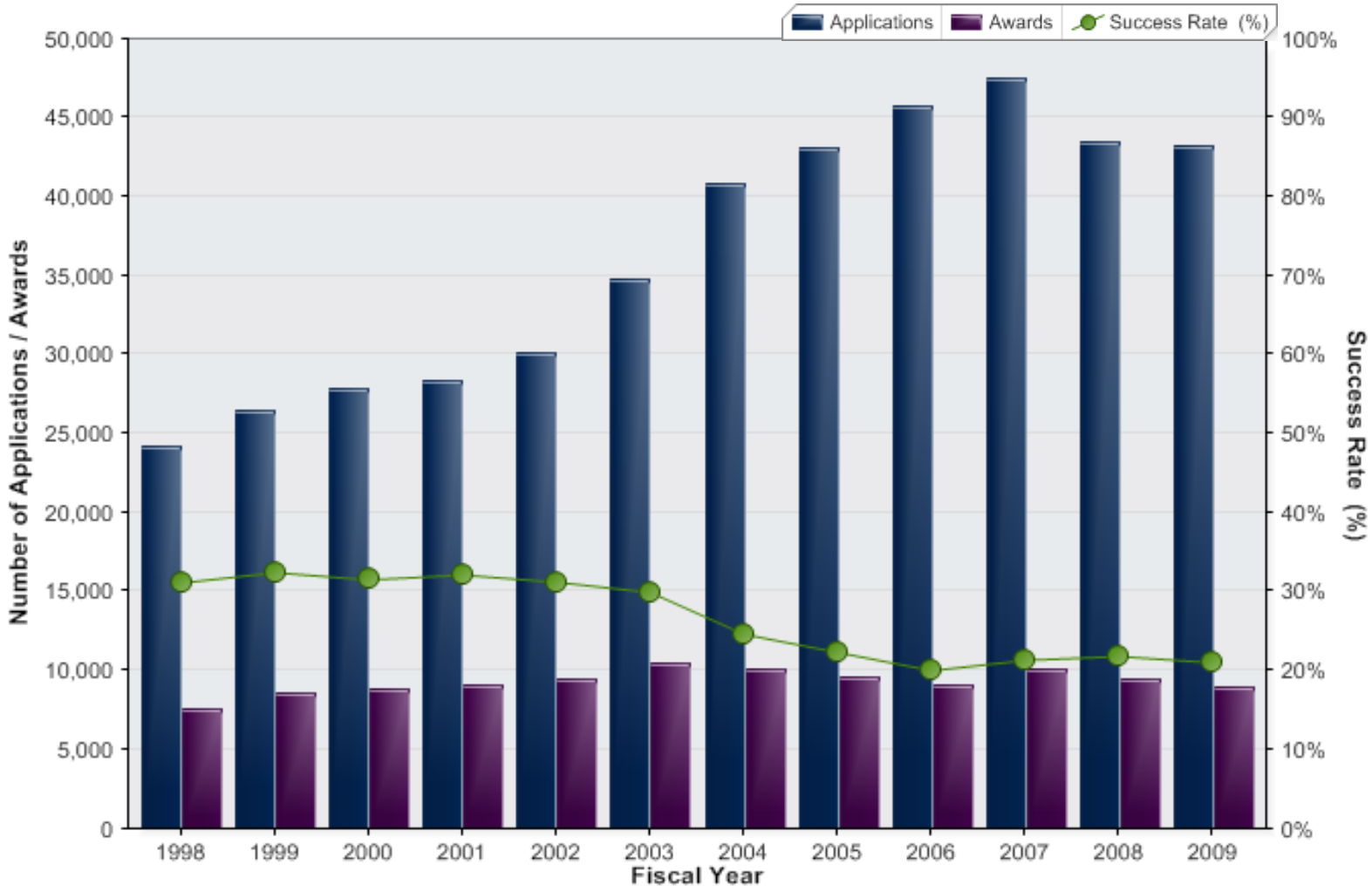
Growth in NIH Budget has been Stagnant



…but Compared to Other Federal Funded Research Programs

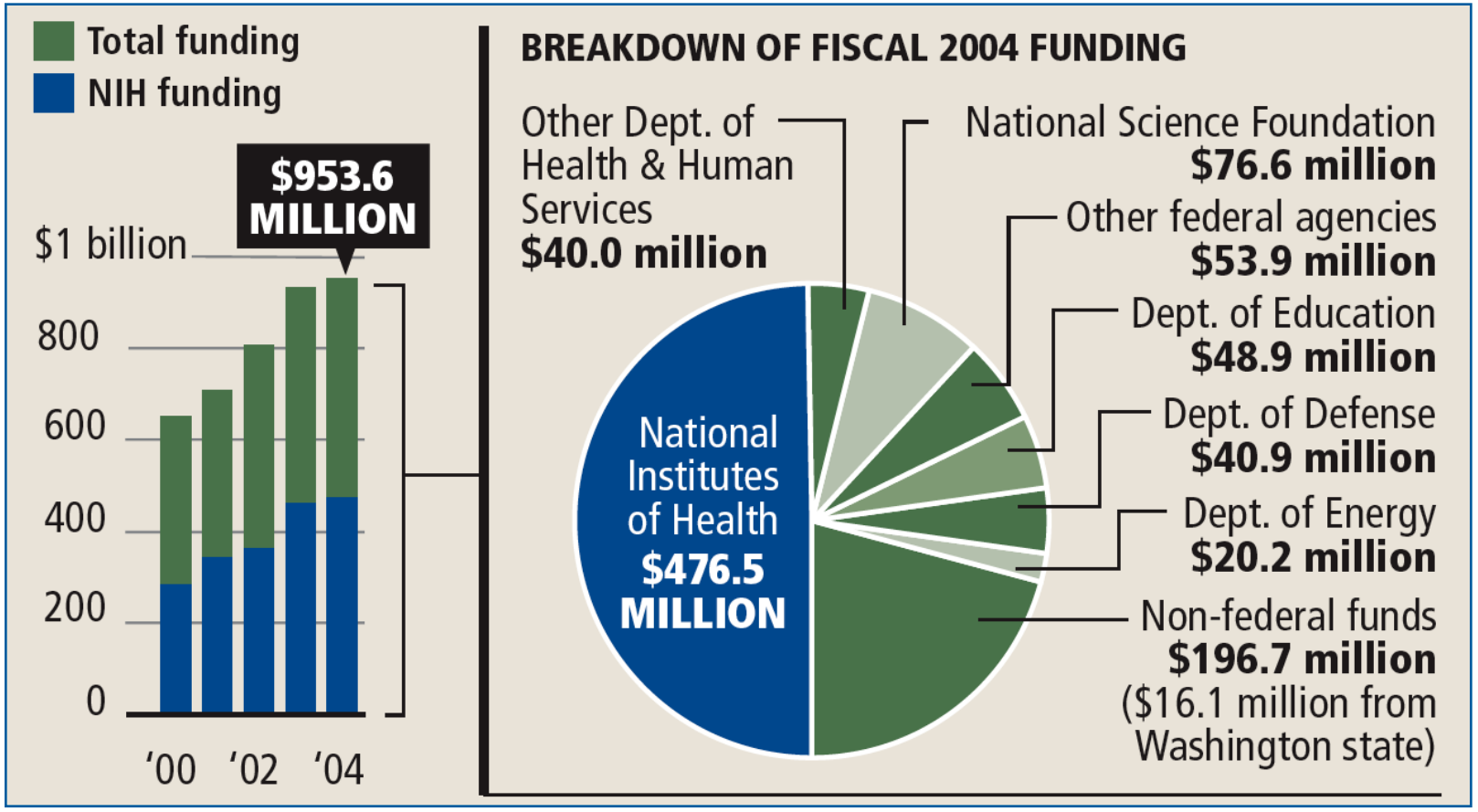


More Applications + Flat Budget = Reduced Paylines



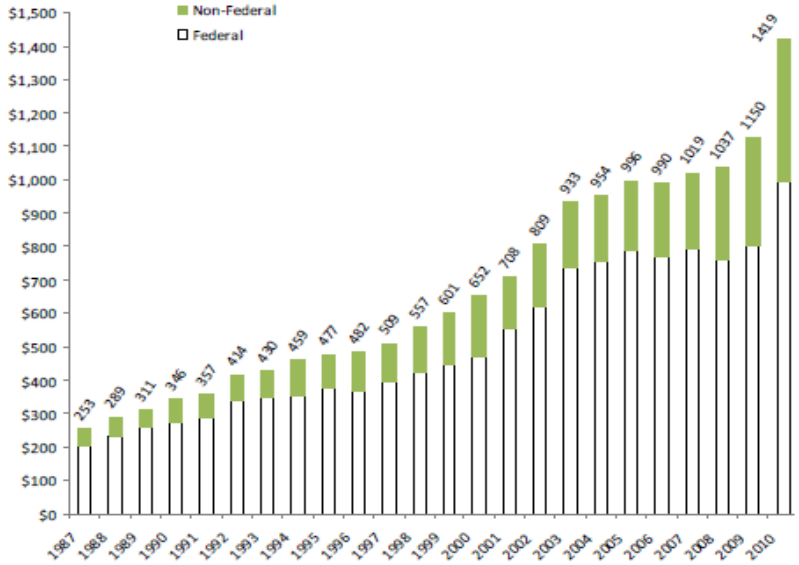
NIH Funds at UW

50% of Research Funds at UW Come from the NIH

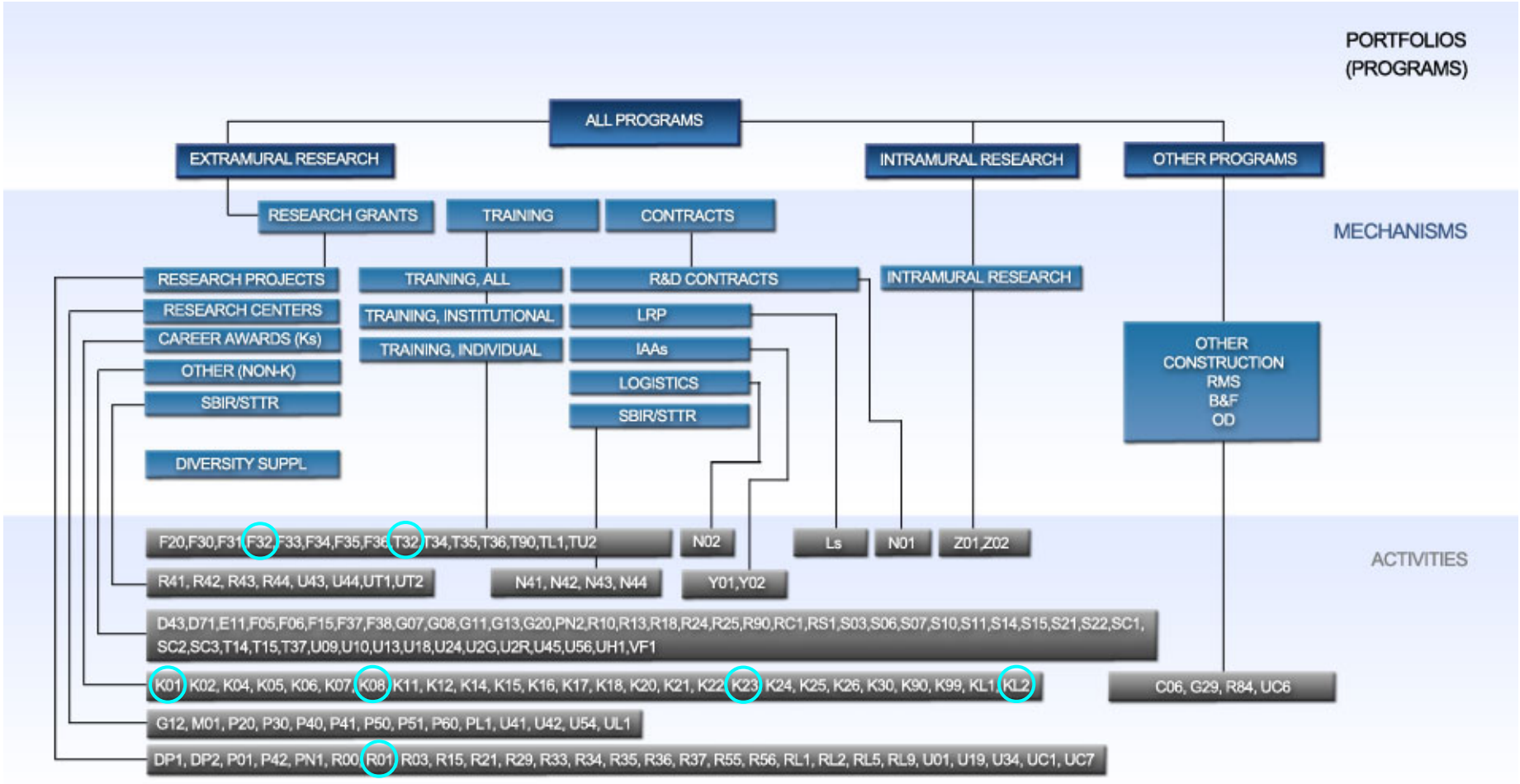


Importance of Having NIH Funding

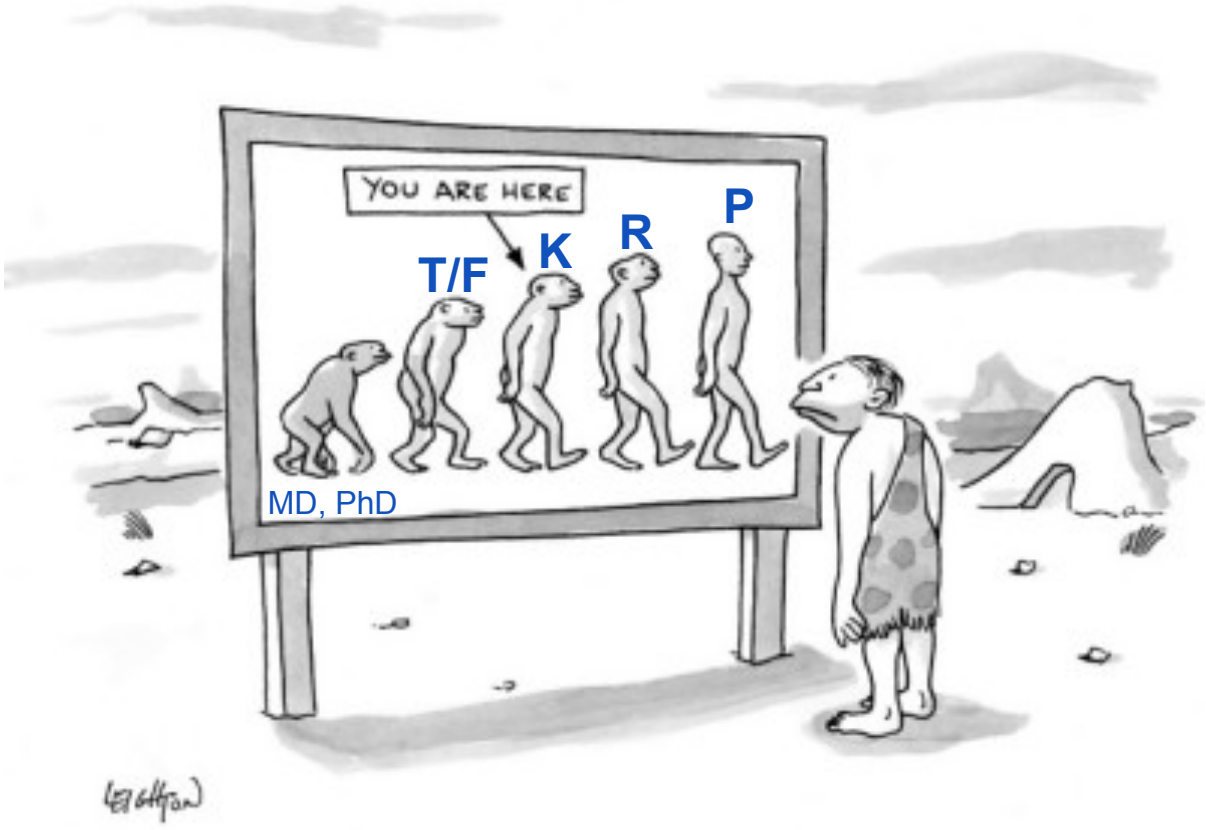
- NIH grants are gold standard of UW funding (and just about anywhere else)
  - Rigorous peer-review
  - NIH funding = High quality, relevant research
- Essential for advancement and promotion
  - Your salary support
- Most important:
  - Indirect Costs
    - *Main UW Campus: $1 = $0.54*
    - *SLU Campus: $1 = $0.74*



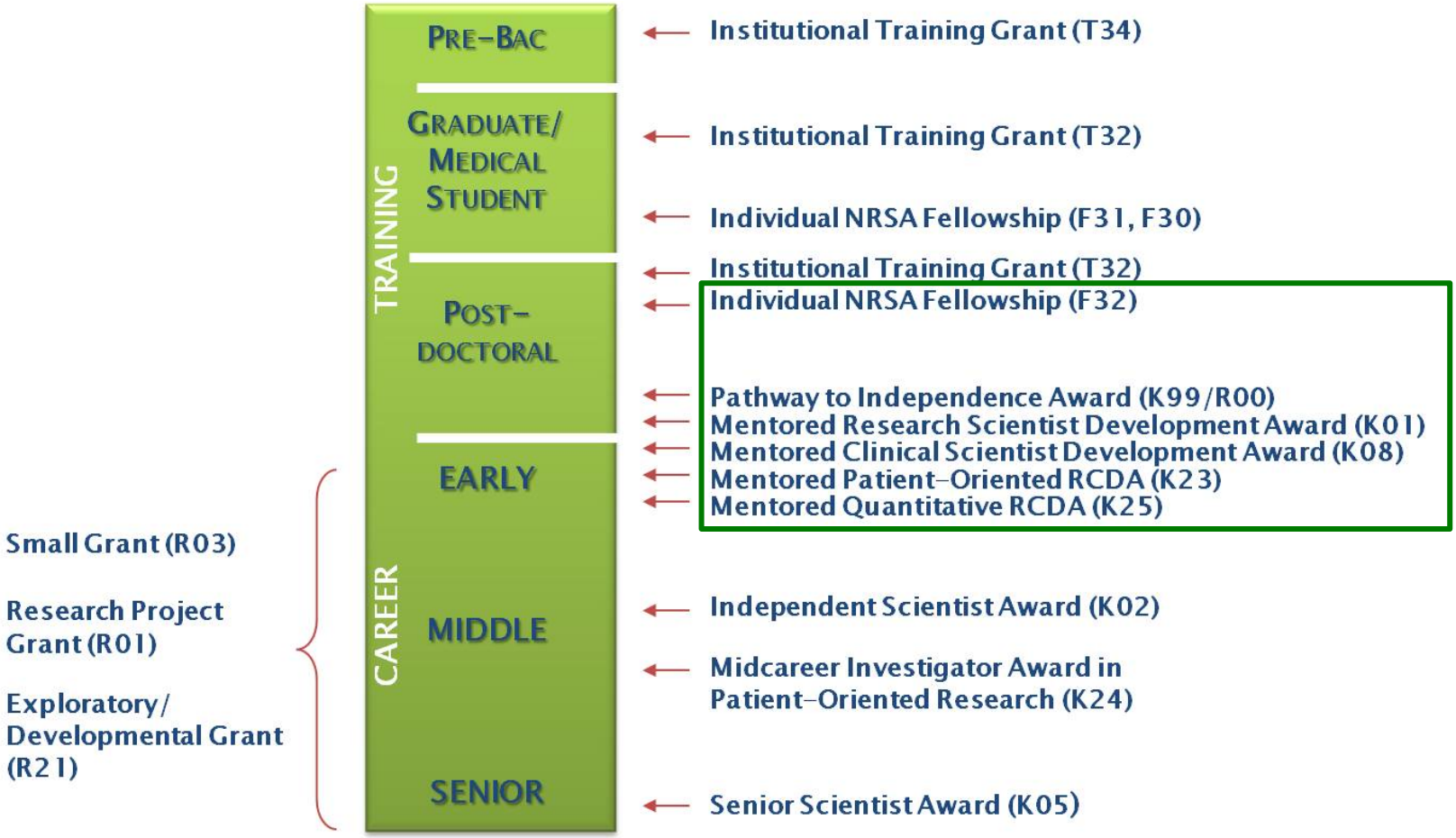
NIH Award Mechanisms



What is the Right Grant Mechanism for You?



Grant Mechanisms with Career Stage



Award Mechanisms for You

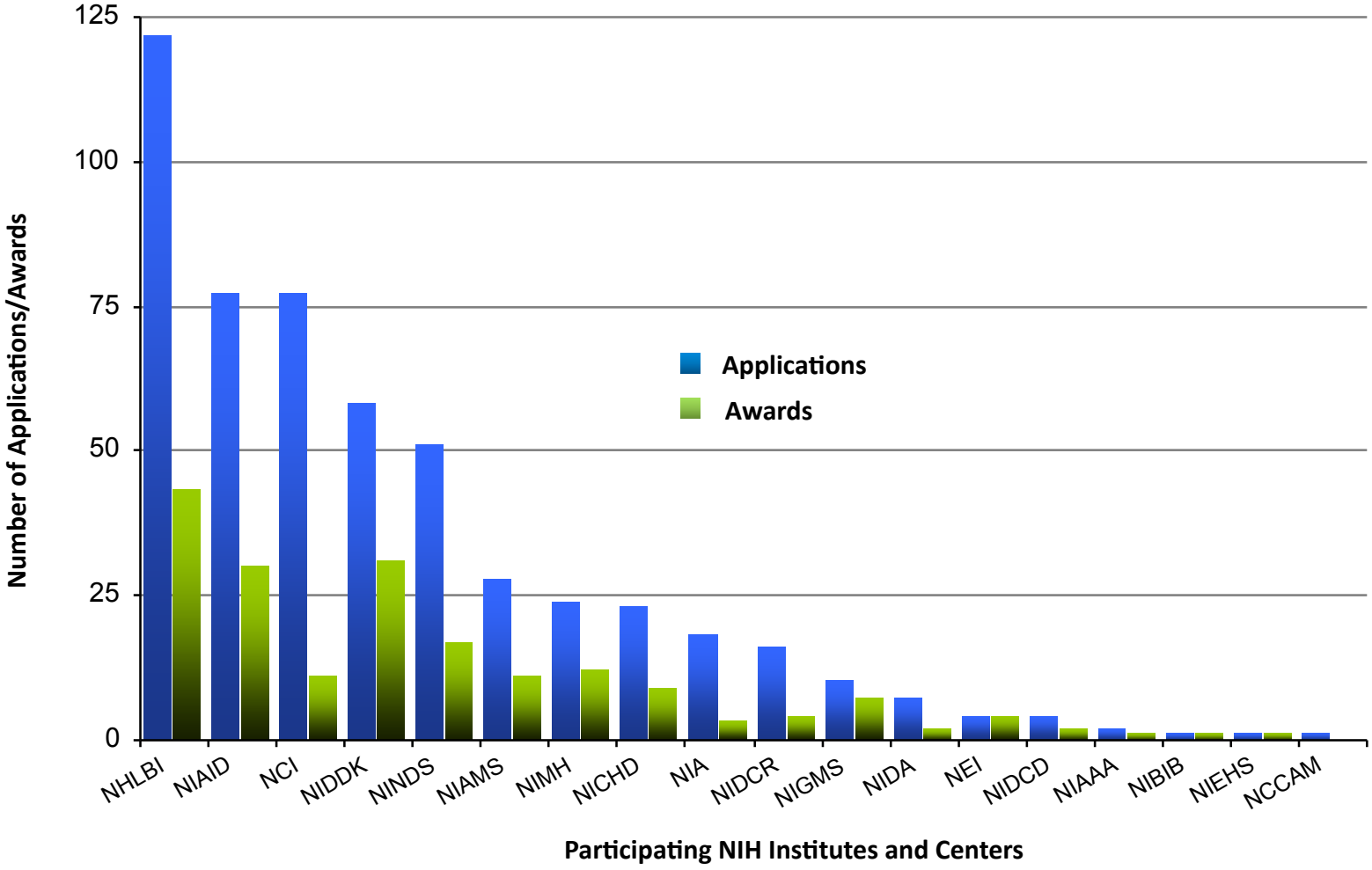
Types

- F: Training Awards (8th of Apr, Aug, Dec)
  - F32 (NRSA) Several others
  - Salary support + ~$5K (which UW keeps)
  - 3 yrs
  - Funds for tuition, off-site training, others
  - http://grants.nih.gov/training/F_files_nrsa.htm
- K: Career Development Awards (12th of Mar, Jul, Nov)
  - K01: Mentored Research Scientist
  - K08: Mentored Clinical Scientist
  - K23: Mentored Patient-Oriented Research
  - 75% effort ($75K cap on salary) + $25K supplies
  - K99/R00: Pathway to Independence
    - K: 2 yr, $90K/yr
    - R: 3 yr, $249K/yr
    - Info: http://grants1.nih.gov/grants/guide/pa-files/PA-06-133.html
  - Several others
- Loan Repayment
  - *You do the research. NIH will repay your student loans.*
  - Up to $35000/yr
  - http://www.lrp.nih.gov/

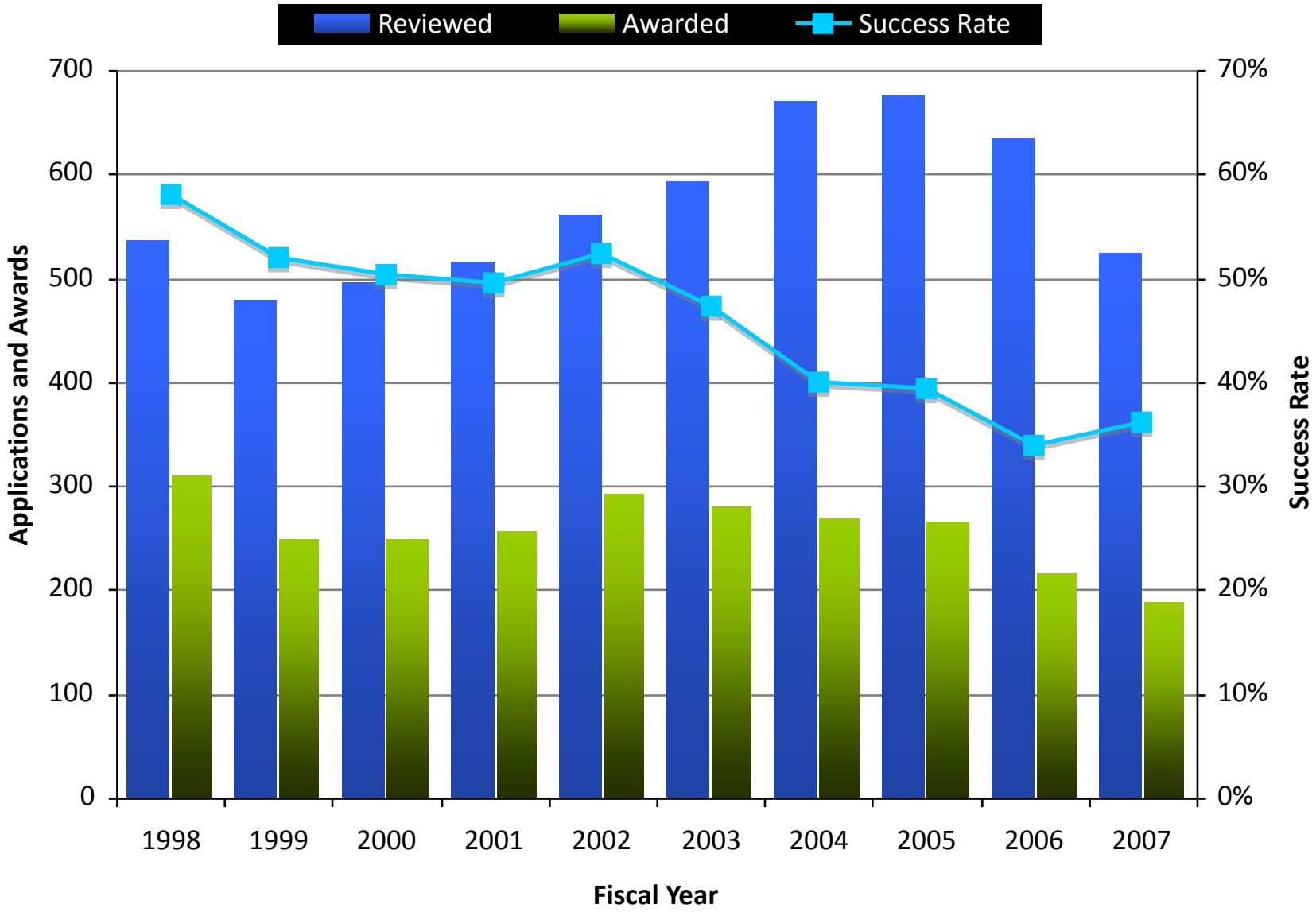
Eligibility and Restrictions

- F: Training Awards
  - 0-7 yrs post degree (MD, PhD, DDS, etc.)
  - US citizens, non-citizen nationals, permanent residents
  - Not renewable
  - Foreign training OK - with clear advantages & justification
- K: Career Development Awards
  - US citizens, non-citizen nationals, permanent residents
  - K01: PhD typically (differs markedly among institutes)
  - K08: Clinical degree: MD, MD/PhD, DO, DDS, PharmD, etc.
  - http://grants.nih.gov/grants/guide/pa-files/PA-10-059.html
  - Strong evidence of institutional comment and training
  - Institute-specific mechanisms, rules and restrictions
  - K99/R00: no more than 5 yrs of postdoc training
  - K99/R00: no citizen restrictions
- Loan Repayment
  - US citizens, non-citizen nationals, permanent residents
  - Doctoral degree
  - Educational debt ≥ 20% base salary
  - Conducting government-sponsored research
  - Several exclusions

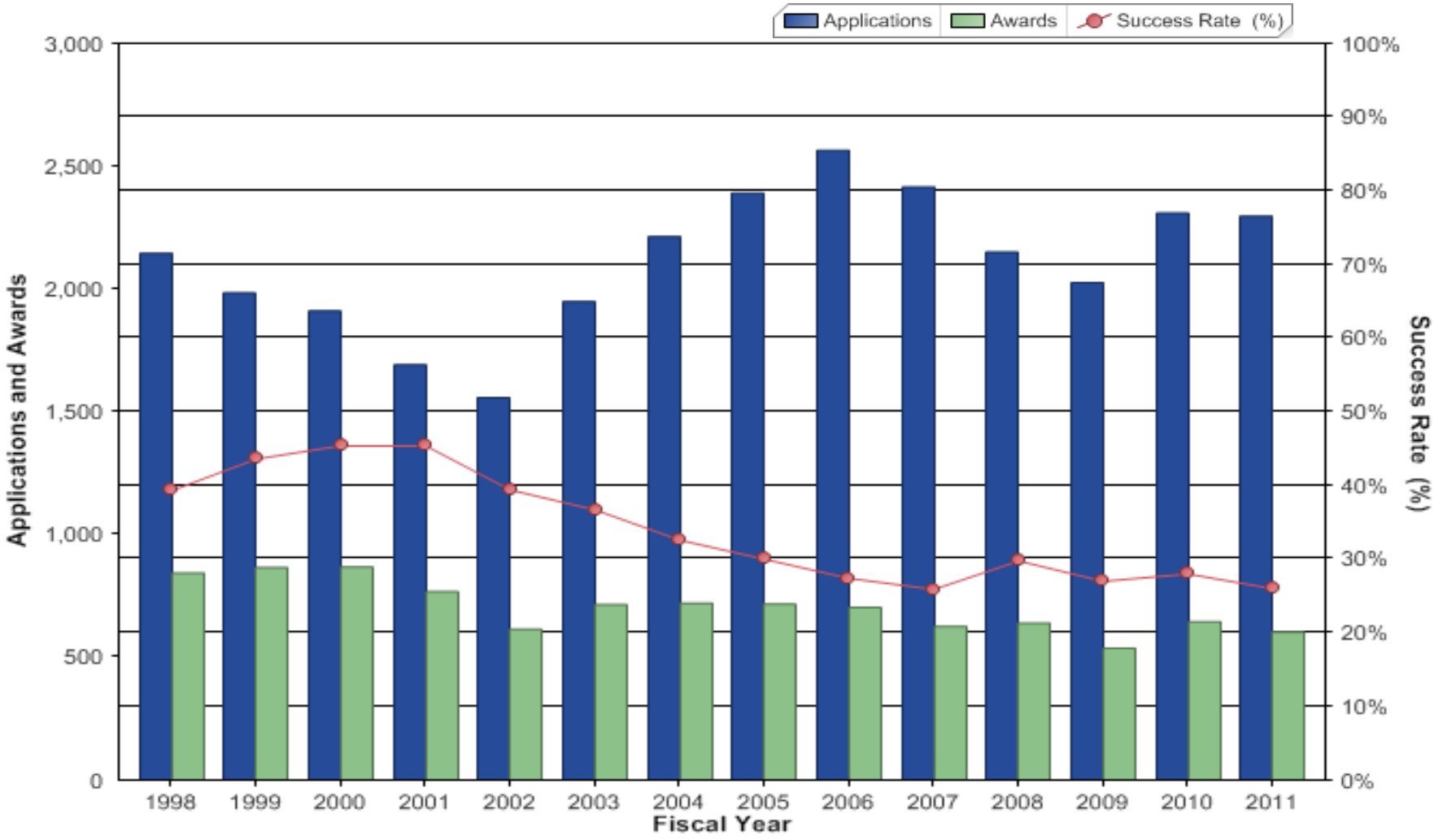
K08 Awards by Institute - 2007



Success Rates - K08s

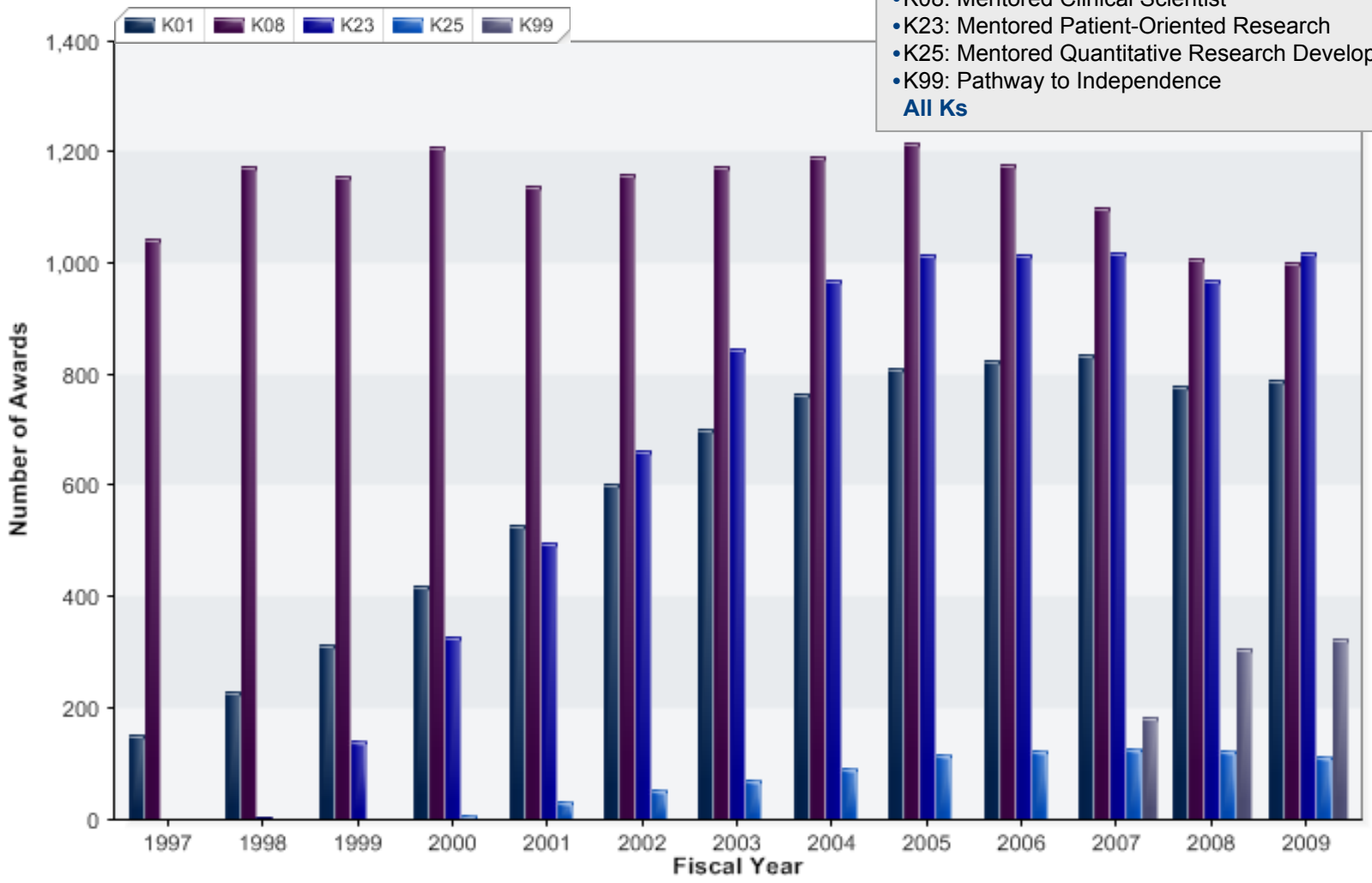


F32 Success Rates



Good Odds with Entry Level Career Awards

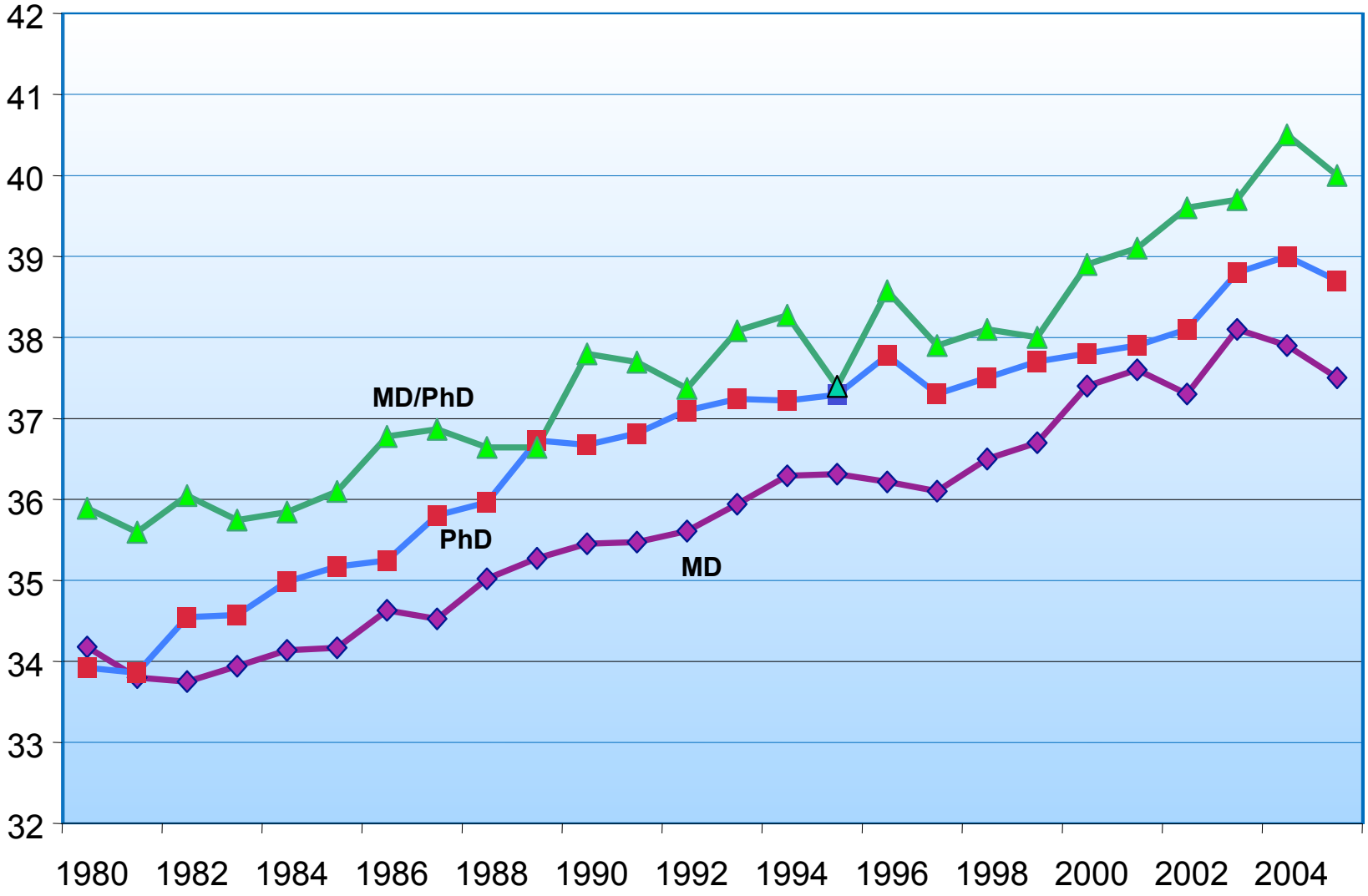
	2009 Success Rates
•K01: Mentored Research Scientist	38%
•K08: Mentored Clinical Scientist	47%
•K23: Mentored Patient-Oriented Research	44%
•K25: Mentored Quantitative Research Development	22%
•K99: Pathway to Independence	29%
All Ks	**38%**



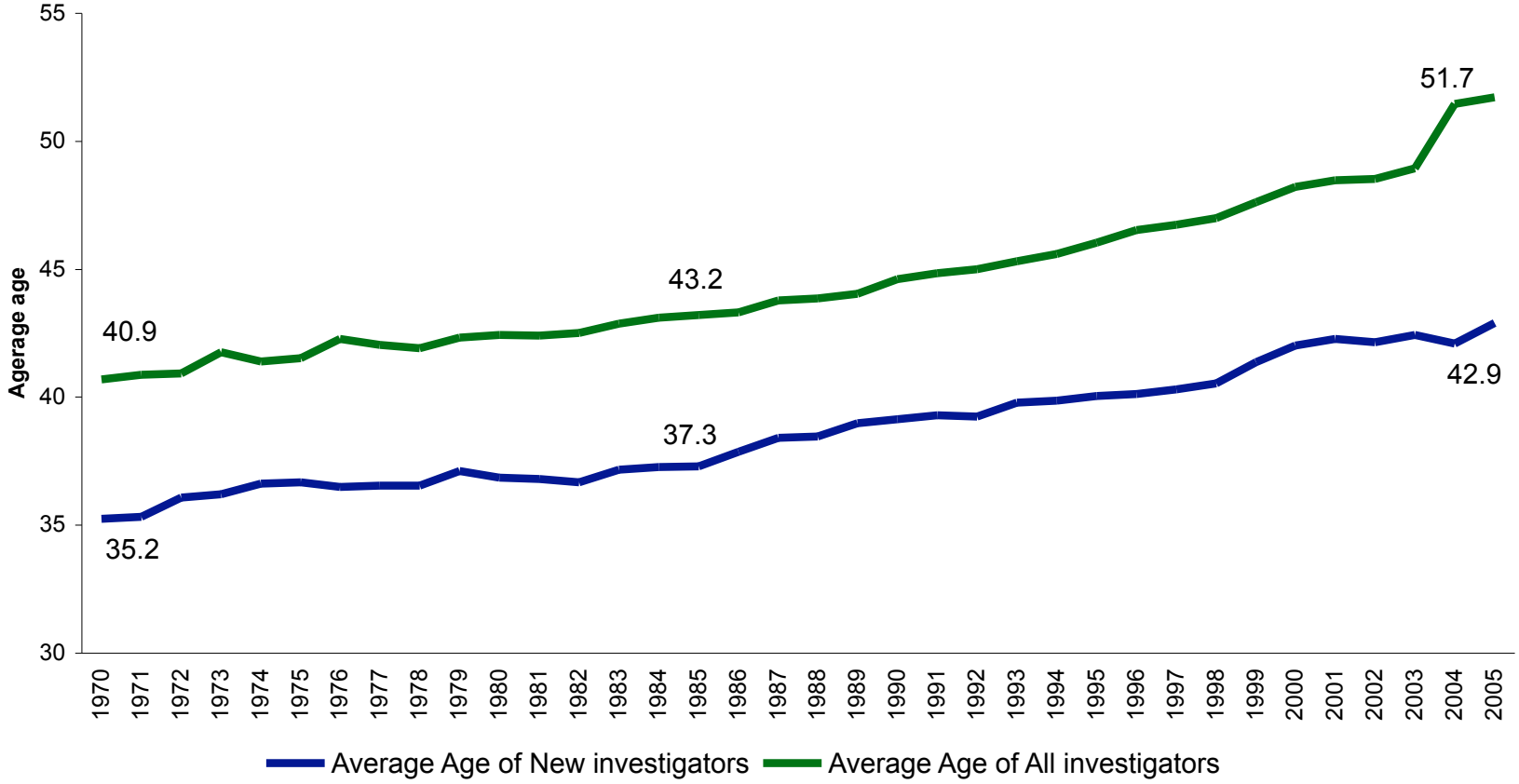
Life Beyond Training and Career Development?

RPGs (e.g., R01s)

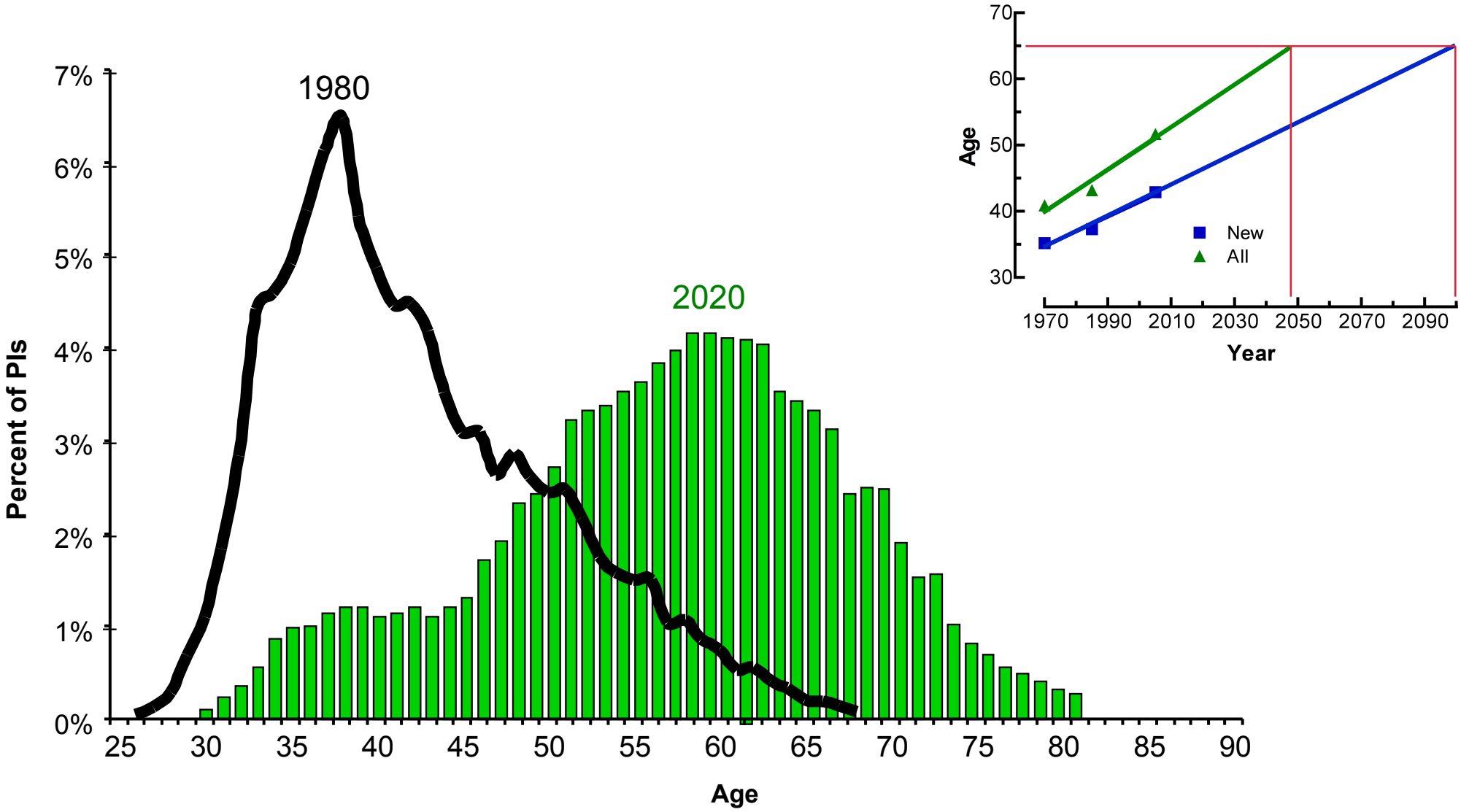
Average Age at Time of Appointment to Assistant Professor at US Medical Schools



Average Age of R-series Awardees

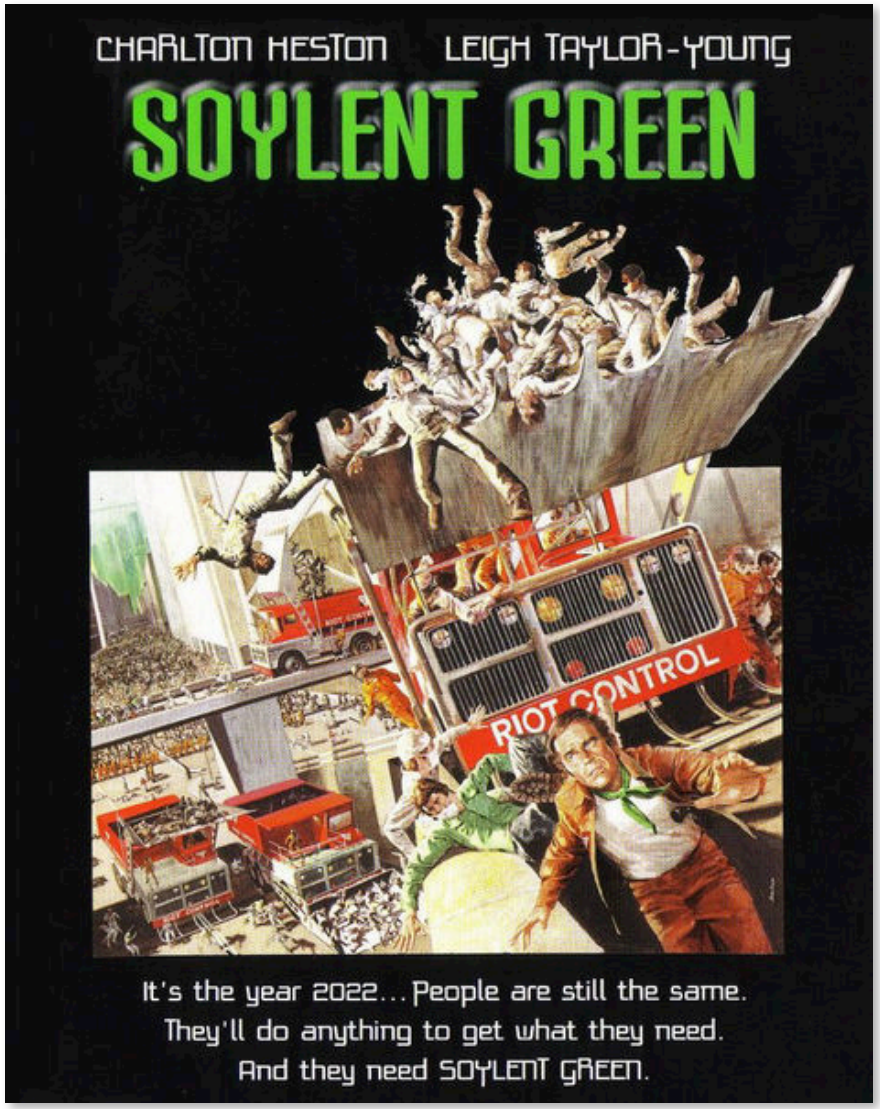


Get a Grant and Retire



Need to Fund More Young Investigators

…and the Old Ones Need to Move On



Early Stage Investigators

- Not previously a PI on any PHS-supported research project

  Exceptions

  - Small R-series (R03, R15, R21)
  - Mentored and nonmentored K awards
  - Details at: http://grants.nih.gov/grants/new_investigators/

- Early Stage Investigators (ESI)
  - Within 10 years of completing terminal research degree
  - Within 10 years of completing medical residency (or the equivalent)
  - Extensions: injury, birth

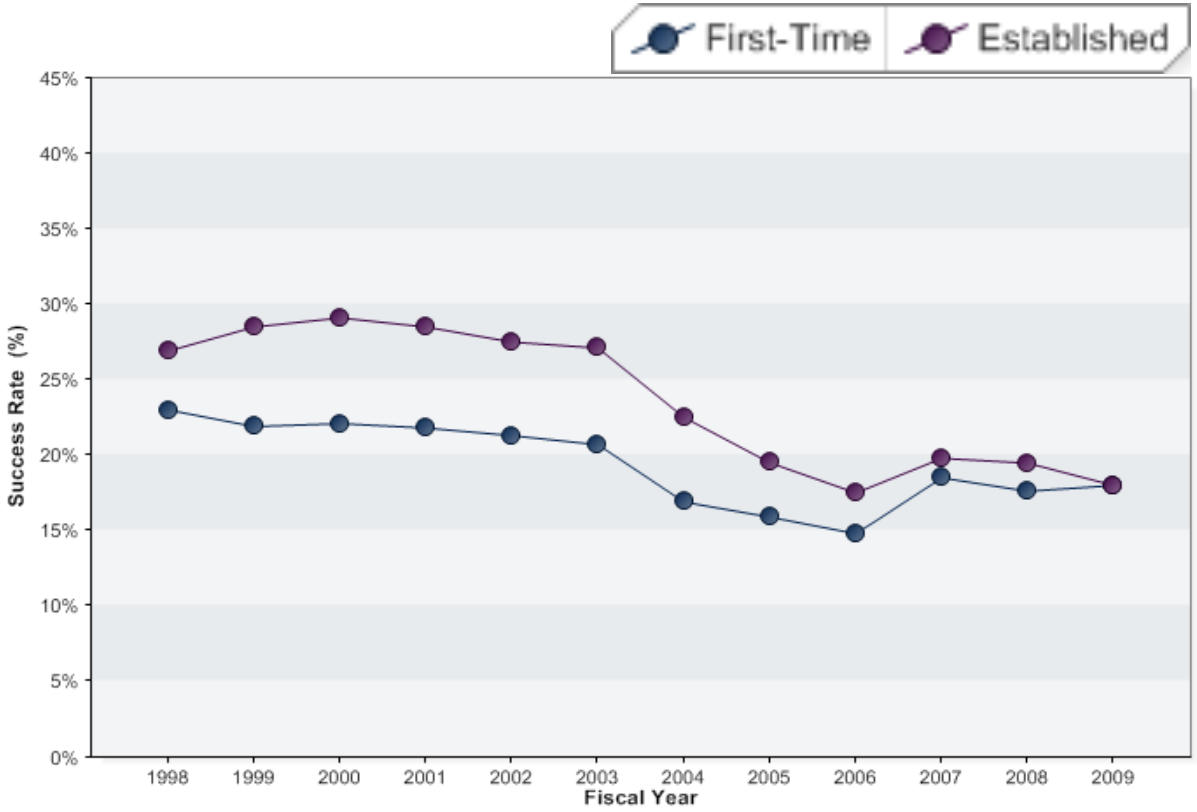
- Breaks for ESIs
  - Separate payline 5-10 points higher
  - Fund all years requested
  - Expedited review for revision (if within 5-10% of payline): http://grants.nih.gov/grants/guide/notice-files/NOT-OD-06-013.html
  - 1st competitive renewal: payline 5 points higher

- *Applies to R01 applications only*

Tip: *Apply for an R01 as soon as you can.*

Success Rates

New vs. Established

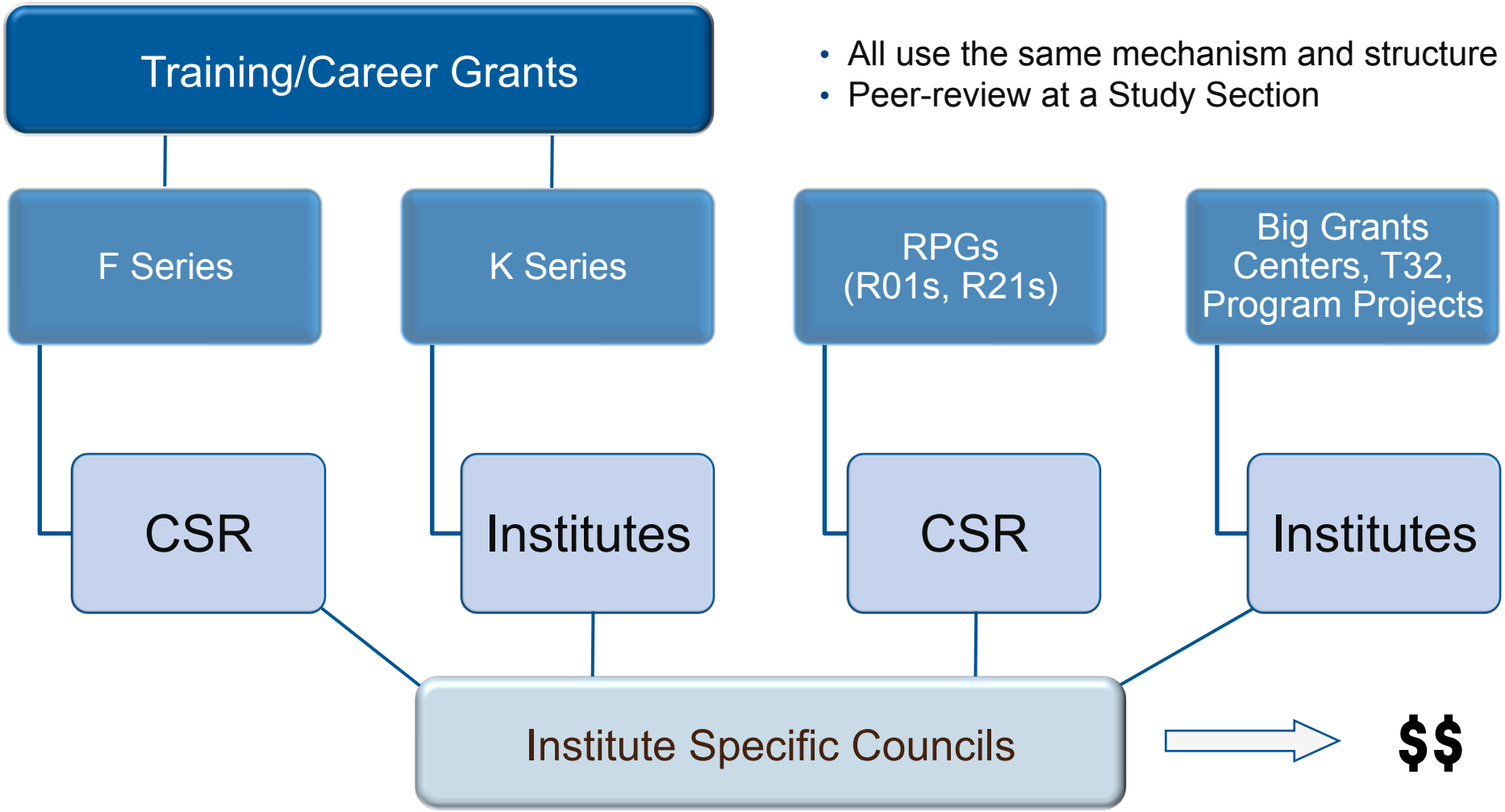


Grant Review Process

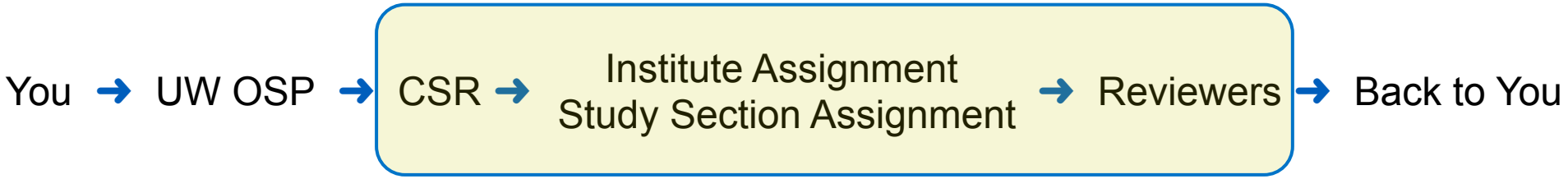
How Your Application is Evaluated

What Matters to the Reviewers

Who's Responsible for Review of Application Types?



The Fate and Evaluation of Your Proposal



Division of Receipt and Referral

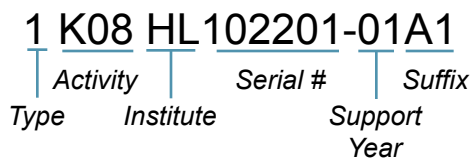
Your can influence this process

Cover Letter:

- Suggest Institute assignment
- Suggest Study Section
- Identify conflicts
- Identify areas of needed expertise
- Special situations
- *Do not recommend specific reviewers*

Pretty dull and needlessly long video of this topic
http://www.youtube.com/watch?v=DuuAGROm_1Q&feature=relmfu

NIH Grant Numbers



- Type Code
  - Indicates whether the application is new, a renewal, noncompeting, or other type
- Activity Code
  - Lists the type of grant
- Institute Code
  - Two-letter code for the name of the funding NIH Institute or Center
- Serial Number
  - Unique 5-6 digit number that identifies the specific application
  - Assigned by the CSR
- Support Year
  - Indicates the current year of support
  - E.g., 01 is a new grant
- Suffix Code (Optional)
  - Used for supplements, amendments, or fellowship institutional allowances

NIH Grant Numbers

K08 HL102201

- All you need for CV, Bios, Other Support

Who Do You Call?

Program Officer

- Institute based
- Before submission
- After initial (study section) review
- Has influence on funding
- Tracks progress

Scientific Review Officer (SRO)

- CSR based
- During initial review stage
- Has no influence on funding

CSR: Center for Scientific Review

- CSR: Center for Scientific Review
  http://public.csr.nih.gov/Pages/default.aspx
- Receives, assigns, and reviews
- ~70-80,000/yr
- 240 SRO (Scientific Review Officer)
- ~16,000 reviewers per year
- >220 Study Sections
- 1,600 grant review meetings/yr

Before Electronic Submission

Now

Study Sections

- Study Sections: Organ-, disease-, scientific-based expertise
  - 25 Integrated Review Groups (IRG)
  - >180 different Study Section committees
- ~80,000 applications/year
- 12-24 members per study section, essentially all from academia
  - Plus about another 12+ ad hoc reviewers
- 60-100+ applications per Study Section meeting
  - ~12 per member
  - 3 reviewers per applications
- Information from CSR web site
  - Study section scope and policies
  - Roster of reviewers
  - Schedules
- Study sections are advisory - they do not fund applications.

Beginnings of Peer Review of Grants

- **1879:** Response to Yellow Fever
  - $30,000 bid from the US Army for universities
- **1940:** Need for Penicillin
  - President Roosevelt set up the National Defense Research Committee.
  - Awarded contracts for rapid production projects
  - Identified 700 universities for future contracts
  - 21 penicillin production plants
  - Led to a 97% survival rate for wounded soldiers
- **1942:** Medical Research funding grew from $2.3 million to $7.5 million
  - Rating applications with an “A”, “B”, or “C”

1946: The Fundamental Tenets for NIH

1. The only possible source for adequate support of our medical research is the taxing power of the federal government.

2. The federal government and politicians must assure complete freedom for individual scientists in developing and conducting their research work.

3. Reviews should be conducted by outside experts essentially without compensation.

4. Program management and review functions should be separated.

Evolution of Study Sections

1946
The First NIH Study Section

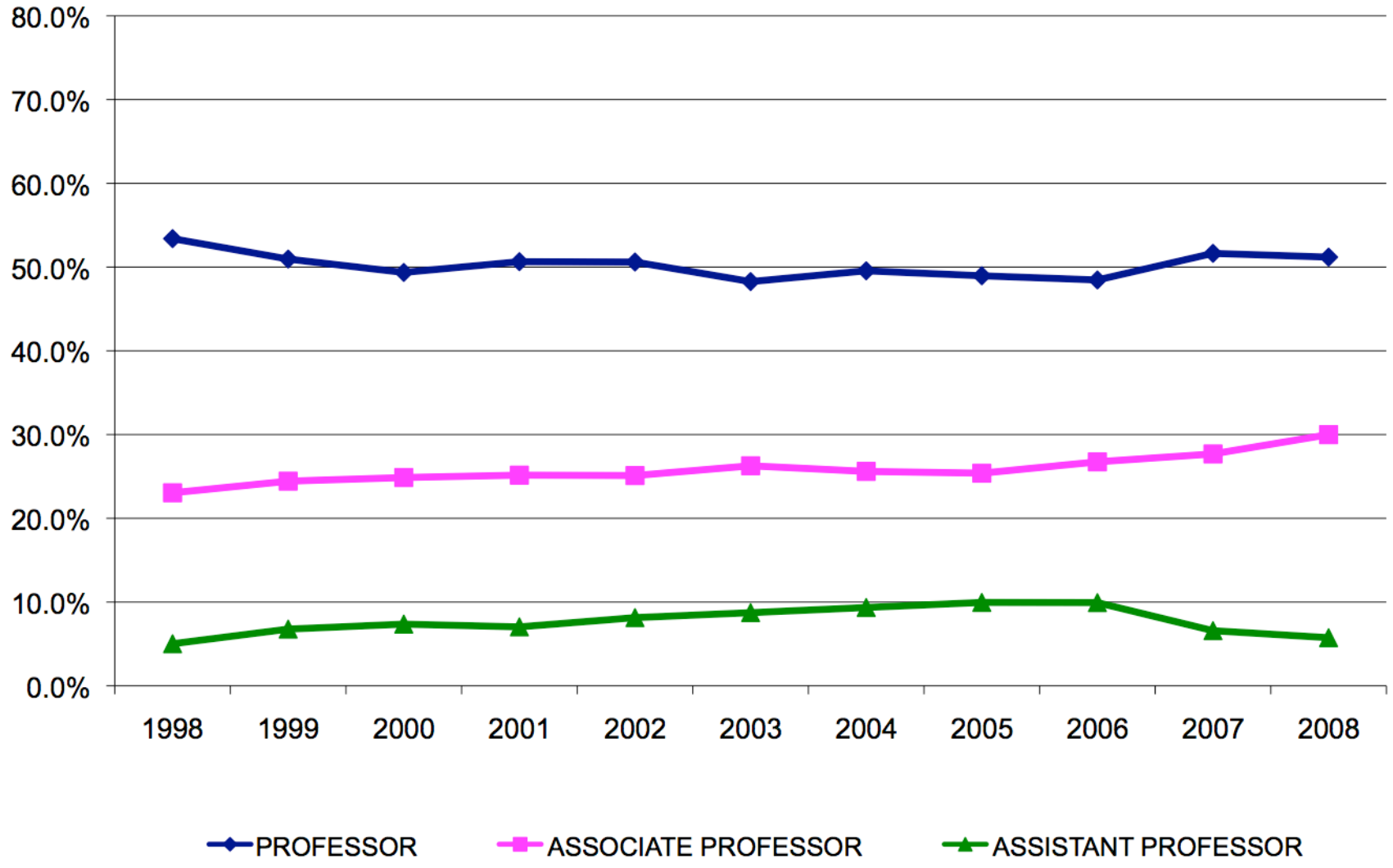
An NIH Study Section Today

Evolution of Study Sections

An NIH Study Section in the Near Future

Telepresencing

Most Reviewers are Established Investigators



Reviewers and Review Criteria

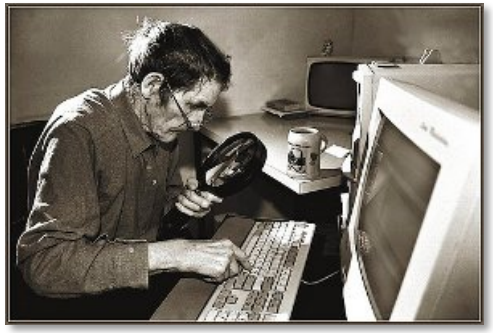
Review Process - Before the Meeting

- All via the internet

- Applications made available to reviewer 6-8 weeks before the meeting (eCD)
  - 3 reviewers/application
  - 1˚, 2˚, and 3˚
  - Occasion input from others

- Training grants (Fs, Ks)
  - Reviewers typically review applications on a wide range of topics
  - Unlikely to be an expert in all applications assigned

NIH to Reviewer



Review Process - Before the Meeting

- Scores and critiques are uploaded 1 week before study section
- Each criterion is given a score: 1, 2, 3…9 (best to really bad)
  - These are not discussed at the Study Section
  - But they are included in the Summary Statement you will get
- Each reviewer gives each application an overall Impact Score
  - Impact Score is not the mean of the criteria scores
  - Impact score is key and the only score discussed
- Initial scores and critiques become available to all committee members
- Applications are ranked in order of initial mean Impact Scores
- Lower 40-60% are not discussed (Impact Score of 4.5 – 5.0 and above)
  - Any “triaged” application can be resurrected at the meeting for discussion for any reason
  - Applicants receive the critiques and individual criteria scores
  - Impact Score is not given

Scored Review Criteria

Individual Training F-series Grants

- Overall Impact

Review Criteria

- Candidate
- Sponsor & training environment
- Research training proposal/plan
- Training potential

Career Development K-series Grants

- Overall Impact

Review Criteria

- Candidate
- Career development plan
  Career goals and objectives
  Plan to provide mentoring
- Research Plan
- Mentor(s), consultants, collaborators
- Environment &
  Institutional commitment

Investigator Initiated R-series Grants

- Overall Impact

Review Criteria

- Significance
- Approach
- Innovation
- Investigator
- Environment

NIH Scoring System

Overall Impact	Score	Descriptor	Scored Criteria
High Impact	1	Exceptional	Strengths
	2	Outstanding	
	3	Excellent	
Moderate Impact	4	Very Good	
	5	Good	
	6	Satisfactory	
Low Impact	7	Fair	
	8	Marginal	
	9	Poor	Weaknesses

Where and When Do Reviewers Review Grant Applications?

- At home or on a plane
- At the last minute - and thus a bunch in one sitting
- Hence, reviewers can be stressed, anxious, and not terribly sympathetic
- *Do not make the reviewer read papers or go to the internet*
- *Do not make the reviewer think!*
- *Do not tick off the reviewers!*

Don't let the reviewer become…

Baffled,

Bitter,

or Bored

The Review Process - at the Meeting

- Begin at 8 am EST (i.e., 5 am PST)
- Cramped room full of lap tops and several jet-lagged reviewers
- Review Grants in order - best to less best
  - Reviewed in groups
  - R01s from ESIs
  - R01s from Established Investigators
  - R21s, etc.
- 15-20 min per application (shorter is best)
- Lower 50% are not discussed
- Go to 6-7 pm
- Bar, eat, bar, sleep
- Repeat next day

The Review Process - at the Meeting

What happens?

- Application is announced and conflicts identified
- Chair asks the 3 reviewers to state their scores
- Primary reviewer discusses strengths and weaknesses using the scored criteria as a guide (but without stating criterion scores)
- Other reviewers concur or discuss differences
- Additional Review Criteria
  - Animals, Human Subjects, Resubmission
- Discussion opens to the committee
- Reviewers restate their scores (e.g., 2-4-5, 3-3-3)
- A range is established (e.g., 2-5, 3-3)
- Chair asks if anyone plans to vote outside of the range
- Committee posts scores online
- Additional Review Considerations: Budget, Resource Sharing, Bioethics training
- Repeat with the next application in order

Vagaries of Peer Review

- Reviewers are humans; humans err
- Assigned reviewers have the most influence on scoring
- A passionate reviewer (pro or con) can influence the group
- Any committee member can vote outside of the "range"
- Final Impact Score is usually (~85% of the time) close to the initial impact score
  - Scores change >1 point on only 15% of grants
  - Rarely for ESI applications (less than 1%)

Good video of a mock Study Section
http://www.youtube.com/watch?v=HMO3HoLJuJY

Score, Percentiles, Paylines

- Criterion Score
  - Whole numbers: 1-9
  - 1 (exceptional); 9 (um, well let's just hope you never get a 9)
  - Given by reviewers but not discussed at study section
  - Provided in Summary Statement of all applications (discussed and not discussed)

- Overall Impact Score
  - Not the mean of the criteria scores
  - Different criteria are weighted by each reviewer

- Final Impact Score, Percentile
  - Mean of all scores x 10 ➤ 10 – 90
  - Percentiled against similar applications across 3 meetings (not so for F's and K's)
  - Unknown to the committee (except the chair)

- Payline
  - Varies among institutes, ~10%
  - http://www.aecom.yu.edu/ogs/NIHInfo/paylines.htm

Scored Review Criteria

Individual Training F-series Grants

- Overall Impact

Review Criteria

- Candidate
- Sponsor & training environment
- Research training proposal/plan
- Training potential

Career Development K-series Grants

- Overall Impact

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- Candidate
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- Environment &
  Institutional commitment

Investigator Initiated R-series Grants

- Overall Impact

Review Criteria

- Significance
- Approach
- Innovation
- Investigator
- Environment

Focus on training potential

Focus on the science and you

Scored Review Criteria

Individual Training F-series Grants

- Overall Impact

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F32 Grant Sections

- Face Page
- Table of Contents
- Performance Site
- Project Description (i.e., Abstract)
- Public Health Relevance Statement
- References Cited
- Facilities
- Equipment
- Attachments
- Key Personnel
- Biosketches
- Clinical Trial
- PHS Fellowship Supplemental Form
- Introduction (revised only)
- Specific Aims
- Research Strategy
  - Significance
  - Preliminary Data
  - Approach
- Protection of Human Subjects
- Women & Minorities
- Planned Enrollment Table
- Children
- Vertebrate Animals
- Respective Contributions
- Selection of Sponsor and Institution
- Responsible Conduct of Research
- Applications for Concurrent Support
- Goals for Fellowship Training and Career
- Activities Planned under this Award
- Doctoral Dissertation and other Research Experience
- Sponsor(s)/Co-sponsor(s) Information

F32 Grant Sections That Reviewers Care About

- Face Page
- Table of Contents
- Performance Site
- Project Description (i.e., Abstract)
- Public Health Relevance Statement
- References Cited
- Facilities
- Equipment
- Attachments
- Key Personnel
- Biosketches
- Clinical Trial
- PHS Fellowship Supplemental Form

- Introduction (revised only)
- Specific Aims
- Research Strategy
  - Significance
  - Preliminary Data
  - Approach

- Protection of Human Subjects
- Women & Minorities
- Planned Enrollment Table
- Children
- Vertebrate Animals

- Respective Contributions
- Selection of Sponsor and Institution
- Responsible Conduct of Research
- Applications for Concurrent Support
- Goals for Fellowship Training and Career
- Activities Planned under this Award
- Doctoral Dissertation and other Research Experience
- Sponsor(s)/Co-sponsor(s) Information

K08 Grant Sections

- Face Page
- Table of Contents
- Performance Site
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- Public Health Relevance Statement
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- Budget
- Budget Justification
- Clinical Trial
- PHS Fellowship Supplemental Form
- Candidate's Background
- Career Goals and Objectives
- Developmental Activities during Award Period
- Training in Responsible Conduct of Research
- Statements by Mentor, Co-mentor
- Institutional Environment
- Institutional Commitment to Career Development
- Introduction (revised only)
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  - Significance
  - Innovation
  - Approach
- Human Subjects
- Women & Minorities
- Planned Enrollment Table
- Children
- Vertebrate Animals
- Select Agents
- Resource Sharing Plan

K08 Grant Sections That Reviewers Care About

- Face Page
- Table of Contents
- Performance Site
- Other Information
- Project Description
- Public Health Relevance Statement
- References Cited
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  - Approach
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Scored Review Criteria

Individual Training F-series Grants

- Overall Impact

Review Criteria

- Candidate
- Sponsor & training environment
- Research training proposal/plan
- Training potential

Career Development K-series Grants

- Overall Impact

Review Criteria

- Candidate
- Career development plan
  Career goals and objectives
  Plan to provide mentoring
- Research Plan
- Mentor(s), consultants, collaborators
- Environment &
  Institutional commitment

Overall Impact

Considering the candidate's (and sponsor's) qualifications and previous research experience, evaluate the proposed training experience as it relates to preparation for an independent research career.

Candidate

- *"Assess the candidate's potential to become an important contributor to biomedical or behavioral science"*

- Many factors are weighed:
  - Extent and level of education:
    - Undergraduate or graduate degree(s)
    - Fields
    - Academic performance
    - Mentors and institutions
  - Postdoctoral research or clinical experience:
    - Mentors and institutions
    - Fields
    - Productivity (very important)
  - Awards and honors
  - Other relevant research experience and professional training
  - Reference letters
    - Very important
    - Relative ranking: top 1-2%, top 25%
  - Evidence of commitment to a career in research

- Clinical degreed candidates (MD, DVM, DDS, etc.) vs. PhDs

Candidate

- Better to change fields or stay put?
  - *"Candidates may choose to remain in a scientific area related to their previous work or shift to an entirely new area of research…*
  - *…[regardless] the proposed training plan must augment the candidate's conceptual and/or experimental skills."*
  - Should be driven by your interests and career goals
  - Good proposals tend to do well.

- Better to move to another institution or stay put?
  - Moving is always considered to be better than staying in the same environment
  - But some environments (like UW) are BIG
  - Diversity in training and experience is viewed as a big plus

Biosketch

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
eRA COMMONS USER NAME	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training)*

INSTITUTION AND LOCATION	DEGREE	MM/YY	FIELD OF STUDY
College			
Graduate			
Postgraduate			
Postgraduate			

A. PERSONAL STATEMENT

Summarize your training, skills, desires, motivation. Do not ramble on. Do not discuss data.
MDs: Clarify the duration of your clinical training and how long you have been in the lab.
Explain any gaps in education/training.

B. POSITIONS AND HONORS

Positions and Employment

Past to current. Do not duplicate what's above.

Other Experience and Profession Memberships

Societies, committees, etc.

Honors

And nothing from High School - please!

C. PEER-REVIEWED PUBLICATIONS (selected from xx peer-reviewed publications)

Most relevant to the current application
List 5 only

Or list all publications

Additional publications of importance to the field
10 max

D. RESEARCH SUPPORT

Ongoing Research Support

Granting Agency (PI Name - if not you) Beginning-End Date (mo/yr)
Grant Title
The goals of this project are to…
Role: PI

Complete Research Support
Limit to last 3 years

Tips

- Important to show what you have done
- Keep the Personal Statement succinct
  - Experience, training and career goals
  - Gaps in training
- *DO NOT* include abstracts as Publications
- Up-to-date (no "*In press…since 2009"*)
- Full citations: all authors, accepted journal abbreviations
- Consistent format
- Name changed? Let us know
- Must match what we see at PubMed
- Some leeway is OK for ESIs
  - OK to list all publications
  - OK to include manuscripts submitted and in preparation
  - OK to add a section for abstracts (e.g., *Presentations*)

Biosketch

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
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Limit to last 3 years

Tips

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- Keep the Personal Statement succinct
  - Experience, training and career goals
  - Gaps in training

C. Peer-Reviewed Publications
1.
2.
etc.

Submitted/In Preparation/In Revision

Reviews, Chapters, Case Reports

Abstracts & Presentations

Sponsor and Training Potential

- *"Assess the qualifications of the sponsor…"*
  - Research expertise
  - Track record as a mentor
  - Reputation and standing
  - Overall productivity and impact of published work
  - Funding

- *"Evaluate the proposed training program…"*
  - Individually tailored to the applicant
  - More than just techniques
  - Didactic and career-enhancing activities
    - Courses, seminars, lab meetings, journal clubs, and scientific conferences
    - Research integrity
    - Opportunities to present and publish - with feedback
    - Opportunities and encouragement to write grants - with feedback
    - Opportunities to interact with other scientists
  - Advisory committee
    - Role of each member
    - Dates and agenda

- *"Evaluate the environment of the host laboratory and the institution as to be conducive to successful postdoctoral training"*

Sponsor and Training Potential

Co-mentor(s)?

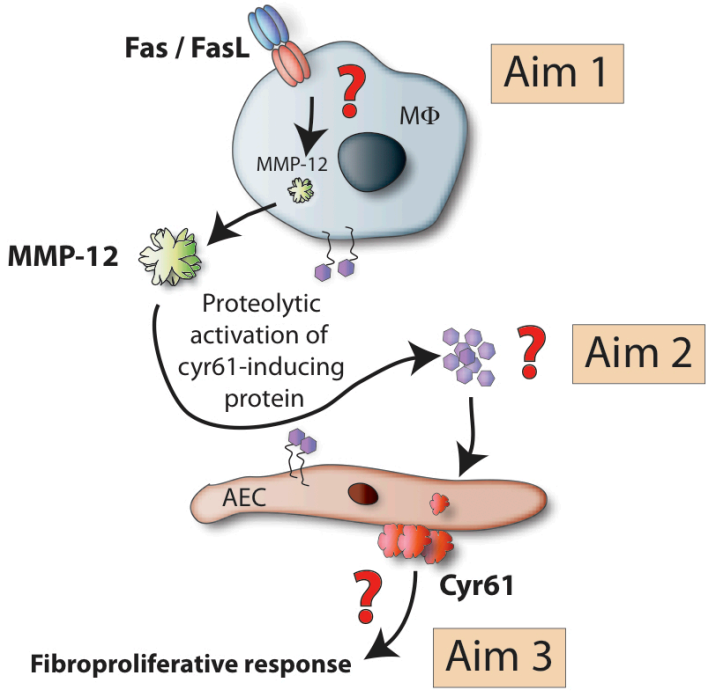
- Primary mentor is junior
- Primary mentor lacks training history
- New or specialized techniques, access to specimens, etc.

Research Proposal

- General approach
- Respective contributions of the applicant and the sponsor
- Must have scientific merit, but emphasis is on training
- "*Check for flaws so severe that they cast doubt on the applicant's or the sponsor's scientific judgment and qualifications or on whether such flawed research can serve as an appropriate vehicle for the candidate's development.*"
- Quite different from an R01

Specific Aims

- A dedicated page *(not included in 12-page limit for Research Strategy)*
- Introductory paragraphs
  - State purpose and importance
  - Concise summary of key findings
  - A clearly stated, mechanistic hypothesis
    "We (I) hypothesize that…"
  - Relate how aims will address the big picture (long-term goals) and advance the field
  - List of aims (2 or 3, maybe 4 – *but never 5 or more*)
- Good idea: diagram or cartoon summarizing ideas and aims
- Many Reviewers say this is the most important section



Background & Significance

- ~1 page
- Critically review the literature
  - No limit on number of citations
  - *Original, timely papers over reviews*
  - Do not be afraid to say you disagree with something (but explain why and how you will correct this travesty)
  - *Limit discussion to things (pathways, diseases, molecules, etc.) you will study*
  - Provide graphics (cartoon, model, pathways, etc.)
- Show (tempered) enthusiasm
- Know your audience
  - CSR database
  - Not a bad idea to cite work of study section members

Pet Peeves

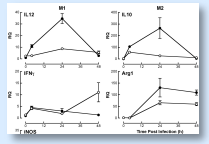
- Needlessly long
- Strays from focus
- Not timely or scholarly
- Reliance on reviews
- Unfettered enthusiasm
- Uses the word “exciting” more than once

Preliminary Data

- Summarize relevant experience and contributions
- Demonstrate your ability to do things
- Demonstrate feasibility of doing new things
- Critically interpret your data - say what it means
  - *Thus, these data indicate…*
  - Do not expect your reviewers to make your conclusions!
- Make figures clear
- Number the figures
- Embed figures near text
- Include legends (but not overly detailed)
- Do not rely on materials in the appendix or elsewhere

Pet Peeves

- Not crediting data you did not generate to its rightful source
- No figure numbers or legends
- Figures too small to see
- Figures a page or two away from the text
- No conclusions
- No link to the Aims
- Critical data not included in the proposal



Some simple advice: if you cannot see the details in a figure, then neither can the reviewers.

Research Plan

- This is the meat
- More narrative than technical
- For each aim, provide:
  - Rationale
  - Approach (brief summary of strategy)
  - Experiments
  - Expected results and interpretation
  - Potential pitfalls and alternative strategies & ideas
  - Future directions (short)
- Quantification and statistics
- Methods
  - Justify selection of techniques
  - Give priority to new or difficult methods
  - *Why* you are doing something, not *how*

Pet Peeves

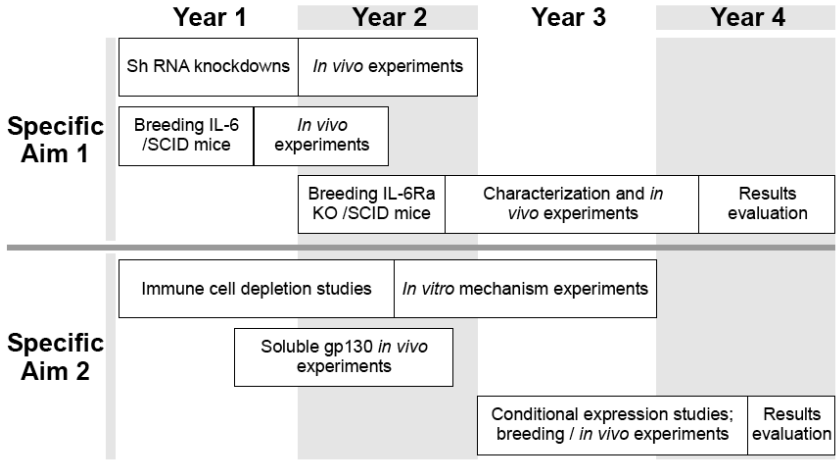
- No logical flow from aim to aim
- Aims dependent on preceding aim
- Overly detailed methods
- Overly ambitious
- Not focused
- No discussion on expected findings, interpretation, pitfalls, etc.
- Potential problem limited to mundane technical issues
- No letters from collaborators and consultants

Research Plan

- Priorities and time line
  - For some reason, reviewers like these

Aim	Description	YR 1	YR 2	YR 3	YR 4	YR 5
1A	Role of matrilysin in ischemia-reperfusion repair					
1B	Neutrophil activation *in vivo*					
2A	Neutrophil binding to KC/syndecan-1 complexes					
2B	Requirement of syndecan-1 shedding					
2C	Syndecan-1 association with integrins					
3A	Binding sites of KC:syndecan-1 interaction					
3B	Neutrophil activation with disrupted KC/syndecan-1.					
3C	Inhibit KC/syndecan-1 interaction *in vivo*					

Table IV. Timetable



Other Sections

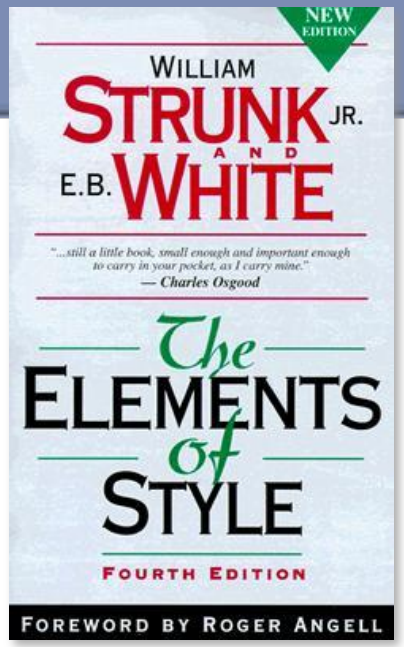
- Bibliography and References
- Human Subjects
- Vertebrate Animals
- Letters of Support
- Resource Sharing Plan
  - Generating new mice, datasets, others

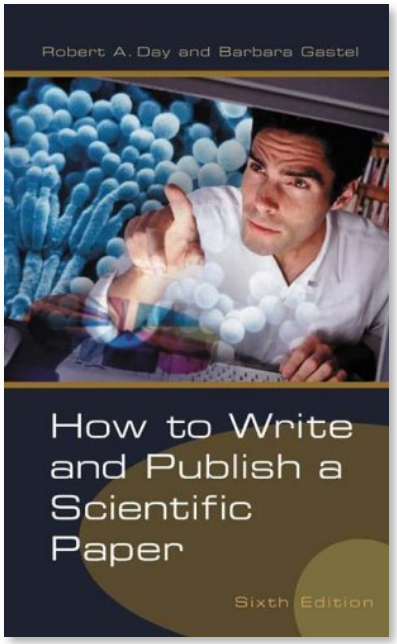
Pet Peeves

- All required sections are not addressed
- Incomplete references
  - List all authors and title
- References do not match citations
- Animal numbers are poorly or not justified

Presentation and Style

- Zero tolerance for tpyos
- Avoid excessive use of abbreviations
- Avoid vague terms: e.g., ‘affects’, ‘influences’
- Clean, concise English
  - Active voice is better than the passive voice
- Paragraphs and spaces
  - Don’t make it look dense or cluttered
- Flow
  - Logical transitions from sentence to sentence, paragraph to paragraph
  - Do the work for your reader
- Use some system (bold, numbers) to indicate sections and subsections
- *Again, read successful applications*





Which Would You Rather Read?

Aim 3. Define the Role of MMP10 in Governing Macrophage Transcriptional Responses.

Rationale and Approach. We predict that the phenotypes (i.e., excess inflammation and reduced alveolar damage) seen in smoke-exposed *Mmp10*$^{-/-}$ mice are due to the lack of this proteinase in macrophages. We hypothesize that MMP10 functions to control the activation state of macrophages. In support of this idea, we found that M1 markers are generally upregulated in *Mmp10*$^{-/-}$ macrophages, whereas M2 markers–particularly *in vivo*–are downregulated. With respect to mechanism, we predict that MMP10 acts on an endogenous macrophage protein that, in turn, sets off specific signaling events in these cells controlling their activation status. In support of this hypothesis, we have found that MMP10 selectively affects the expression of immune and remodeling pathways in cigarette smoke-exposed lungs (Table 3).

To test this idea and to focus specifically on gene expression in macrophages, we plan to undertake a systematic, computationally intensive search for MMP10-dependent pathways in specific subsets of macrophages. From these studies, we will build predictive maps to identify potential regulatory gene-product hubs, and the functional role of these proteins will be validated by various approaches to manipulate their production or activity.

Preliminary Data. We performed gene expression studies on total RNA isolated from flushed lungs of smoke-exposed (6 mo) and air-breathing wildtype and *Mmp10*$^{-/-}$ mice (n = 4/genotype/condition). RNA integrity was confirmed with Agilent Bioanalyzer 2100, and 500 ng/sample was amplified, labeled, and hybridized to MouseRef-8 BeadChip whole-genome expression arrays (Illumina). Image analysis, background subtraction, and normalization (quantile method) were performed using BeadStudio software (Illumina).

Differential Expression of Immune Genes is Seen Only in Wildtype Mice. Using whole lung RNA, we identified 92 genes that were differentially expressed in wildtype mice (smoke-exposed vs. control, FDR <0.05) but not in *Mmp10*$^{-/-}$ animals (smoke-exposed vs. control, FDR <0.05). GO analysis (Table 3) of these 92 genes showed enrichment of several immune-mediated pathways in the lungs of smoke-exposed wildtype mice–pathways that were not affected in null mice. These findings indicate that MMP10 plays an important role in regulating inflammation.

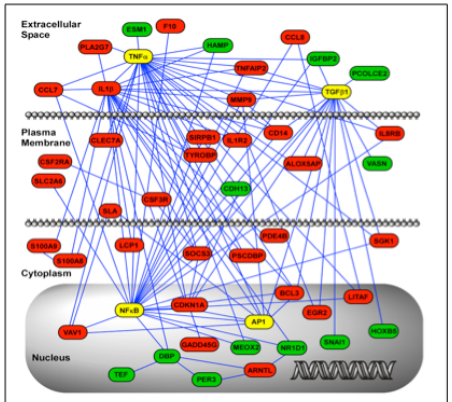


Fig. 10. Interactome of Differentially Expressed MMP10-dependent Genes.

Genetic Network Map of Activated Pathways. Using published gene product relationships among the differentially expressed genes in smoke-exposed wildtype mice, we created a genetic interaction network (Fig. 10). It is important to note that while the existence of this relational network in our smoking model is theoretical, each depicted gene product interaction has been experimentally confirmed. Furthermore, we and others have demonstrated that the functional stability of such networks is critically dependent on highly connected nodes or "hubs".[139,148] An example of one such hub that is upregulated during smoking is IL1β. Over-expression of IL1β has been demonstrated to cause inflammation and emphysema in adult mice[149] and pulmonary dysplasia and impaired alveolar septation in infant mice.[150] Another upregulated node in the interactome is CD14 (LPS receptor), a key component of TLR4 signaling, and a pathway that also mediates inflammatory responses to cigarette smoke exposure.[151] We confirmed the differential

Table 3. Enriched Biological Modules during Smoking

Functional Category	Fold Enrichment	P-Value	FDR
Response to Stimulus	8.4	6.4×10^{-11}	3.3×10^{-7}
Chemotaxis	21.7	6.2×10^{-10}	1.6×10^{-6}
Response to Wounding	8.5	4.8×10^{-7}	4.9×10^{-4}
Inflammatory Response	9.7	3.2×10^{-6}	2.1×10^{-3}
Immune System Process	4.3	5.5×10^{-6}	3.2×10^{-3}
Response to Stress	4.1	2.2×10^{-5}	1.1×10^{-2}
Defense Response	4.4	2.6×10^{-5}	1.2×10^{-2}
Cytokine	9.4	8.9×10^{-5}	1.5×10^{-2}
Leukocyte Chemotaxis	42.7	1.0×10^{-4}	4.0×10^{-2}

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Proposed Studies. Alveolar and tissue macrophages will be isolated from smoke-exposed and control wildtype and *Mmp10*$^{-/-}$ mice at different times, and subpopulations of activated macrophages will be sorted. We will also compare M1 and M2 macrophages differentiated from wildtype and *Mmp10*$^{-/-}$ BMDMs. Total RNA will be amplified, labeled, and hybridized to Illumina arrays. Because each BeadChip contains 8 identical arrays, the samples will be randomized to each platform to eliminate bias. For each time point/condition, 6 microarray experiments will be performed.

Summary Statement

SUMMARY STATEMENT
(Privileged Communication)

PROGRAM CONTACT:
Ricardo Cibotti
301-496-0569
cibottirr@mail.nih.gov

Release Date: 04/20/2011

Application Number: 1 K08 [redacted]

Principal Investigator

[redacted]

Applicant Organization: UNIVERSITY OF WASHINGTON

Review Group: AMS
Arthritis and Musculoskeletal and Skin Diseases Special Grants Review Committee

Meeting Date: 02/28/2011
Council: MAY 2011
Requested Start: 07/01/2011

RFA/PA: PA10-059
PCC: 4 B

Dual IC(s): AI

Project Title: [redacted]

SRG Action: Impact/Priority Score: 40
Human Subjects: 10-No human subjects involved
Animal Subjects: 44-Vertebrate animals involved - SRG concerns

Project Year	Direct Costs Requested	Estimated Total Cost
1	114,350	123,498
2	114,350	123,498
3	114,350	123,498
4	114,350	123,498
5	114,350	123,498
TOTAL	571,750	617,490

Summary Statement – Summary of Discussion

RESUME AND SUMMARY OF DISCUSSION: This is a new application for a K08 Mentored Clinical Scientist Development Investigator Award submitted by [redacted] from the University of Washington. Dr. [redacted] goal is to become an independent physician- scientist studying cutaneous immunology, with a focus on how T cell responses in the skin are regulated. The mentor, Dr. [redacted], is a senior investigator with a strong training record and significant experience in mouse immunology, mouse genetic, and specifically the biology of matrix-cell interaction, which is relevant to this proposal. Dr. [redacted], co-mentor, has expertise in bioinformatics to provide support for completion of Aim 3. Dr [redacted] is considered a very strong candidate; however, the lack of recent productivity was considered a minor weakness. The career development plan is appropriate but there is no inclusion of bioinformatics training. The environment is outstanding. The committee identified some minor weaknesses. There are concerns regarding the research plan which include the quality of the preliminary data, support for the proposed research plan, interpretation, degree of participation in aim 3, feasibility, and technical issues. The committee also pointed out that the deficiencies in the research plan reflect a lack of adequate mentoring. The committee views the application as very good with some minor weaknesses the career development and research plans.

- Not provided for applications not discussed
- Concerns raised here must be addressed in revised application

Criterion Scores and Overall Impact

CRITIQUE 1:

Candidate: 3
Career Development Plan/Career Goals /Plan to Provide Mentoring: 3
Research Plan: 4
Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s): 2
Environment and Institutional Commitment to the Candidate: 1

Overall Impact: This is a new K08 Mentored Clinical Scientist Research Career Development Award application from [redacted] proposes a five year plan with the goal of obtaining independent investigator status by focusing on investigating the role of CD103 and E-cadherin in maintaining the tolerant state of skin and further investigation of how E-cadherin may regulate Treg gene expression. She has received a strong background in basic immunology (six years total) and has published one first author basic science paper in a high impact journal. She has assembled an excellent team of formal and informal mentors and collaborators and will work in a very good environment with a plan of formal coursework, seminars, meetings and presentations. Minor issues

CRITIQUE 2:

Candidate: 2
Career Development Plan/Career Goals /Plan to Provide Mentoring: 2
Research Plan: 4
Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s): 2
Environment and Institutional Commitment to the Candidate: 2

CRITIQUE 3:

Candidate: 3
Career Development Plan/Career Goals /Plan to Provide Mentoring: 2
Research Plan: 4
Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s): 2
Environment and Institutional Commitment to the Candidate: 2

Some Top Reasons Why Grants Don't Get Funded

- Lack of new or original ideas.
- Diffuse, superficial, or unfocused research plan.
- Lack of knowledge of published, relevant work.
- Lack of preliminary data and/or experience with essential methodologies.
- Uncertainty concerning future directions (where will it lead?).
- Questionable reasoning in experimental approach.
- Absence of a sound hypothesis and clear scientific rationale.
- Unrealistically large amount of work.
- Poor training potential.
- Poor productivity.
- Mentor is not qualified, poorly funded, and/or not productive.

Didn't Make It

- Revised Application (A1)
  - One chance only
- Consider the critique (without emotion)
- Address concerns in an Introduction
  - 1 page before Specific Aims
  - Be agreeable but not obsequious
  - Be firm but not confrontational
- Do not re-submit until all is in order
- Seek advice

Review of a Revised Application

- Treated as new application
- Reviewers will likely not be the same
  - Maybe 1 or 2
  - But almost always at least 1-2 new reviewers
- Reviewers see the original critique (which includes your Abstract)
- Reviewers do not see the original (A0) application

Good Luck!