K Awards: the Next Step

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NIH and Career Development Awards

- Types of training awards
- Getting information about K's
- Components of a K application
- Tips on writing a great application

Overview of Relevant K Awards–Early Career

- **K08 Mentored Clinical Scientist Research Career Development Award**
  - Laboratory focused research
  - May use human samples

- **K23 Mentored Patient-Oriented Research Career Development Award**
  - Patient-oriented research
  - Must be directly involved in interacting with subjects

Clinical doctoral degree: MD, DVM, PharmD
US citizen, permanent resident

Overview of Relevant K Awards–Early Career

- **K01 Mentored Research Scientist Development Award**
  - Used differently by different institutes. e.g., NIAID limits to epidemiology, modeling techniques, and outcomes research
- **K02 NIH Independent Scientist Award**
  - Provides 3-5 years of salary support and "protected time" for newly independent scientists who can demonstrate the need for a period of intensive research focus as a means of enhancing their research careers.
- **K25 Mentored Quantitative Research Career Development Award**
  - Quantitative or engineering degree moving to health-related topics

PhD or MD (or other health-related doctorate)
US citizen, permanent resident

Overview of Relevant K Awards–Early Career

- **K22 Career Transition Award**
  - Move from a postdoctoral research position to an independent research position—not mentored
- **K99/R00 Pathway to Independence Award**
  - Transition from a mentored postdoctoral research position to a stable independent research position with independent NIH or other independent research support

PhD or MD (or other health-related doctorate)
US citizen, permanent resident (except K99/R00)

K08 and K23- Mentored Research Career Development Awards

- K08- for basic or lab-based research project
- K23- for clinical/patient-oriented project
- 3 - 5 yr award
  - 3 yrs for more senior individual (e.g. MD MPH)
  - 5 yrs for more junior individual, but must justify a didactic 2 yr phase
- Salary: $90,000/yr* + Fringe Benefits
- Research Support:
  - $50,000/yr*
  - At least 75% effort committed to research

Health professional doctorate
US citizen, permanent resident
***Varies by institute**

K01 Mentored Research Scientist Development Award

- Focus varies by institute
- MDs or PhDs
- 3 - 5 years
- Salary: $75,000/ yr + Fringe Benefits
- Research Support: $25,000/yr
- ≥75% effort on health-related research

US citizen or permanent resident

Details vary by institute—be sure to look at the information for your own institute

K22 Career Transition Award

- Available in some institutes, not others
- Focus varies by institute
- MDs or PhDs
- Provides support (~$250K total) for the first ~2 years of research as an independent faculty member
- Not mentored

US citizen or permanent resident

Details vary by institute—be sure to look at the information for your own institute

K99/R00 Pathway to Independence Award

- Facilitates transition from postdoc to independence
- Mentored period/Independent period
- MDs or PhDs
- 3 - 5 years
  - 1-2 yrs Mentored
  - 2-3 yrs Independent
- Details vary by institute

US citizen or permanent resident

Details vary by institute—be sure to look at the information for your own institute

NIH Career Development Awards

- K Kiosk

http://grants.nih.gov/training/careerdevelopmentawards.htm

- NIAID

http://www.niaid.nih.gov/researchfunding/traincareer/pages/mentorK.aspx

Finding information and contacts at NIH

- **Go to K Kiosk and click on the desired award**

Grants & Funding

Funding Opportunities
- Funding Opportunities (RFAs, PAs) & Notices
- Unsolicited Applications (Parent Announcements)
- Research Training & Career Development
  - Extramural Training Mechanisms
  - Intramural
  - News
  - Career Resources
  - Q&A and FAQs
- Small Business (SBIR/STTR)
- Contract Opportunities

NIH-Wide Initiatives
- New and Early Stage Investigators
- Stem Cell Information
- NIH Common Fund
- OppNet (Behavioral & Social Sciences)

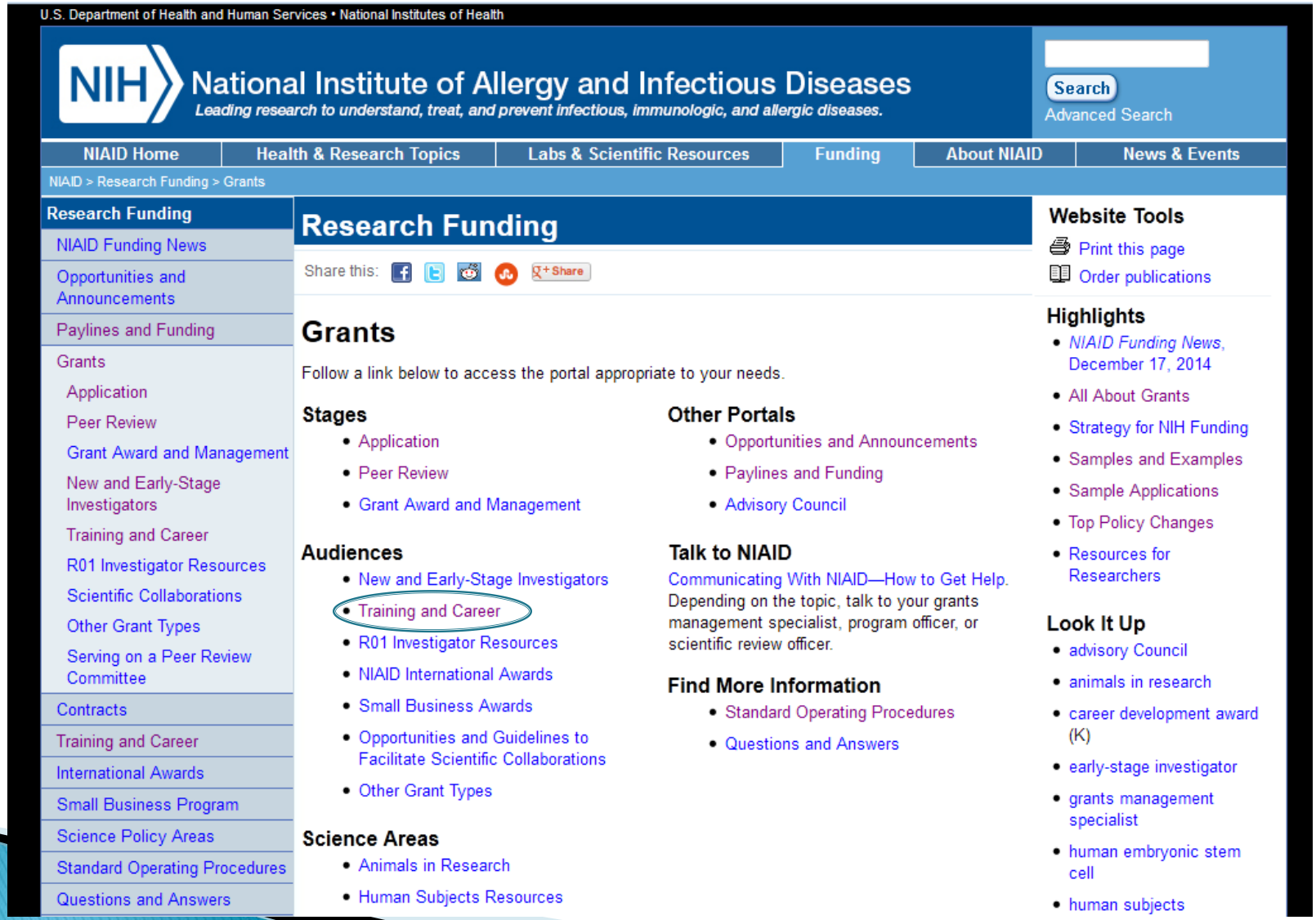
Award Data
- NIH Reports (RePORT)

K Kiosk – Information about NIH Career Development Awards

Program	Description
Policies and Notices	Career Award Policy Issues
K01	**NIH:** Mentored Research Scientist Development Award (Parent K01) (PA-14-044) (see NOT-OD-14-036) **NCI:** NCI Mentored Research Scientist Development Award to Promote Diversity (K01) (PAR-12-050) **NIH/BD2K:** Mentored Career Development Award in Biomedical Big Data Science for Clinicians and Doctorally Prepared Scientists (K01) (RFA-HG-14-007) **NIDDK:** NIDDK Mentored Research Scientist Development Award (K01) (PAR-12-020) **NINDS:** NINDS Faculty Development Award to Promote Diversity in Neuroscience Research (K01) (PAR-12-152) **NLM:** NLM Career Development Award in Biomedical Informatics (K01) (PAR 13-284) **FIC:** International Research Scientist Development Award (IRSDA) (K01) (PAR-13-072)
K02	**NIH:** Independent Scientist Award (Parent K02) (PA-14-045) (see NOT-OD-14-036)
K05	**NCI:** Established Investigator Award in Cancer Prevention & Control (PAR-12-065)
K07	**NIH:** Academic Career Award (Parent K07) (PA-11-192) (See NOT-OD-11-063)

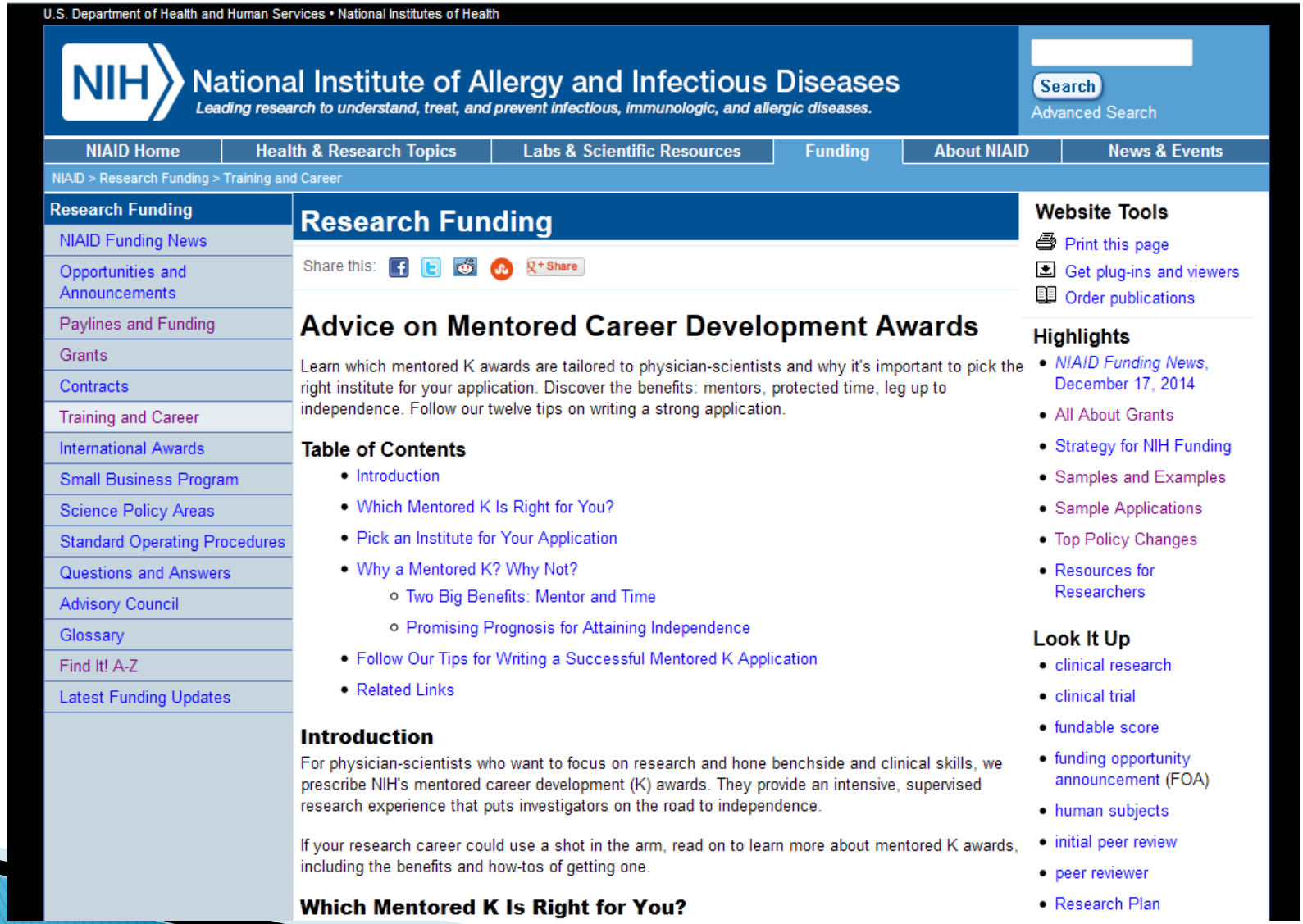
NIAID Training Advice Website

http://www.niaid.nih.gov/researchfunding/grant/pages/default.aspx



NIAID Training Advice Website

http://www.niaid.nih.gov/researchfunding/traincareer/pages/mentorK.aspx



U.S. Department of Health and Human Services • National Institutes of Health

NIH National Institute of Allergy and Infectious Diseases

Leading research to understand, treat, and prevent infectious, immunologic, and allergic diseases.

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NIAID > Research Funding > Training and Career

Research Funding

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Research Funding

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Advice on Mentored Career Development Awards

Learn which mentored K awards are tailored to physician-scientists and why it's important to pick the right institute for your application. Discover the benefits: mentors, protected time, leg up to independence. Follow our twelve tips on writing a strong application.

Table of Contents

- Introduction
- Which Mentored K Is Right for You?
- Pick an Institute for Your Application
- Why a Mentored K? Why Not?
  - Two Big Benefits: Mentor and Time
  - Promising Prognosis for Attaining Independence
- Follow Our Tips for Writing a Successful Mentored K Application
- Related Links

Introduction

For physician-scientists who want to focus on research and hone benchside and clinical skills, we prescribe NIH's mentored career development (K) awards. They provide an intensive, supervised research experience that puts investigators on the road to independence.

If your research career could use a shot in the arm, read on to learn more about mentored K awards, including the benefits and how-tos of getting one.

Which Mentored K Is Right for You?

Website Tools

- Print this page
- Get plug-ins and viewers
- Order publications

Highlights

- *NIAID Funding News*, December 17, 2014
- All About Grants
- Strategy for NIH Funding
- Samples and Examples
- Sample Applications
- Top Policy Changes
- Resources for Researchers

Look It Up

- clinical research
- clinical trial
- fundable score
- funding opportunity announcement (FOA)
- human subjects
- initial peer review
- peer reviewer
- Research Plan

Program Announcement

READ THIS CAREFULLY!!

- Purpose
- Eligibility
- Deadlines
- Page limits
- Links to forms
- Required sections
- Review criteria
- Animal, human subjects info
- Contacts

Department of Health and Human Services

Part 1. Overview Information

Participating Organization(s)	National Institutes of Health (NIH)
Components of Participating Organizations	National Heart, Lung, and Blood Institute (NHLBI) National Human Genome Research Institute (NHGRI) National Institute on Aging (NIA) National Institute on Alcohol Abuse and Alcoholism (NIAAA) National Institute of Allergy and Infectious Diseases (NIAID) National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) National Institute of Biomedical Imaging and Bioengineering (NIBIB) *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) National Institute on Deafness and Other Communication Disorders (NIDCD) National Institute on Drug Abuse (NIDA) National Institute of Mental Health (NIMH) National Institute of Nursing Research (NINR) National Center for Complementary and Alternative Medicine (NCCAM) Division of Program Coordination, Planning and Strategic Initiatives, Office of Research Infrastructure Programs (ORIP) Office of Behavioral and Social Sciences Research (OBSSR) Office of Dietary Supplements (ODS) **Special Note**: Because of the differences in individual Institute and Center (IC) program requirements for this FOA, prospective applicants strongly encouraged to the Table of IC-Specific Information, Requirements and Staff Contacts, to make sure that their application is responsive to the requirements of one of the partici NIH ICs.
Funding Opportunity Title	**Mentored Research Scientist Development Award (Parent K01)**
Activity Code	K01 Research Scientist Development Award - Research & Training
Announcement Type	Reissue of PA-11-190
Related Notices	• June 4, 2014 - Notice NOT-14-074 supersedes instructions in Section III.3 regarding applications that are essentially the same. • May 2, 2014 - See Notice NOT-OD-14-088. Notice of Clarification of Career (K) Award Eligibility. • February 27, 2014 - See Notice NOT-EB-14-003. Notice of Change to the Duration of Career Development Awards Supported by the NIBIB. • February 3, 2014 - See Notice NOT-HG-14-018. Notice of NHGRI Participation.
Funding Opportunity Announcement (FOA) Number	**PA-14-044**
Companion Funding Opportunity	None
Number of Applications	See Section III. 3. Additional Information on Eligibility.
Catalog of Federal Domestic Assistance (CFDA) Number(s)	93.242; 93.856; 93.855; 93.846; 93.213; 93.279; 93.839; 93.838; 93.837; 93.233; 93.361; 93.273; 93.286; 93.866; 93.351; 93.173; 93.865
Funding Opportunity Purpose	The purpose of the NIH Mentored Research Scientist Development Award (K01) is to provide support and "protected time" (three, four, or five years) for an intensiv supervised career development experience in the biomedical, behavioral, or clinical sciences leading to research independence. Although all of the participatin Institutes and Centers (ICs) use this support mechanism to support career development experiences that lead to research independence, some ICs use the K01 aw individuals who propose to train in a new field or for individuals who have had a hiatus in their research career because of illness or pressing family circumstance ICs utilize the K01 award to increase research workforce diversity by providing enhanced research career development opportunities. Prospective candidates are encouraged to contact the relevant NIH staff for IC-specific programmatic and budgetary information: Table of IC-Specific Information, Requirements and Staff Contacts.

Things to do ahead of time

- Preliminary data to support hypotheses
- Publish papers
- Develop a good mentoring team
- Courses and Compliance
  - Human subjects training
  - Animal training
  - EH&S training

Preparing to write the application

- Read the instructions!
  - Program Announcement
  - SF424 Instructions

  http://grants.nih.gov/grants/funding/424/index.htm

  Note Section 7: Specific instructions for K applications
- Be aware of page limits
- Look at grant tutorials online
- Read a successful application (or two!)

How to Get Started

- Administrative Issues: Their Rules and Yours
- Timeline for preparing the application
- Mechanics: Putting Your Best Foot Forward
- Business pages
- Components of K Applications
- Review

Administrative Issues: Their Rules and Yours

- Figure out what kind of grant you will be writing
- Read the Program Announcement and Instructions—and read them again!
- Talk with a Training Officer
- Talk with your dept'l or division administrator

Timeline: Writing the application

- Start planning and writing very early (at least 4 months before due date)
- Talk with the administrator who will assist with application
- Talk with your mentor
- Have your mentor and others read the full application **early** (4-6 weeks before due date)

Timeline for Writing a Grant Application

>4 months ahead	Read NIH website about grants Talk with NIH official Decide on grant mechanism Meet with your grants administrator
Week -12-14	Think, read, cogitate about career development and research plans
Week -10	Draft Specific Aims, give to mentor, meet to discuss, revise
Week -6	Give full draft of to mentor; request letters

Timeline for Writing a Grant Application

Week -6	Work on business pages (biosketch, equipment, facilities, etc)
Week -5	Revise draft
Week -3	“Final” draft to mentor Begin to route business pages
Week -2	Finished text sent to Institutional Grants Office
Week -1	Submit to agency
Due Date	It’s there on time!!!

Mechanics: Writing the application

- Use formal language—no slang or jargon
- Use correct grammar, punctuation
- No typos!
- Leave white space on the pages-not solid text

Boring—and causes tired eyes……

these two lipoproteins as adhesins. The strain expressing both DbpA and DbpB acquired the ability to bind epithelial cells while only DbpB showed specificity for glioma cells *in vitro* (5). Later studies with the neuroborreliosis patients validated our results since antibodies mainly against DbpB were present in CSF after colonization by Lyme spirochetes (4, 12). Therefore, we anticipate that our *in vitro* experiments in the initial screen using non-infectious *B. burgdorferi* will identify surface localized *T. pallidum* adhesins. This non-adherent strain offers a cleaner background to study binding mechanisms since it does not express *B. burgdorferi* adhesins. Candidate adhesins identified from this experiment will help us select 3-4 surface proteins to express in the infectious, bioluminescent *B. burgdorferi* strain. ¶

We will first select the best luciferase reporter system and most useful promoter to express this reporter for *in vivo* imaging in the small animal model. Then, we will express and characterize the promising *T. pallidum* proteins, identified from the initial screen, in the infectious, sequenced *B. burgdorferi* strain to assess adherence to placental and neuronal cell lines *in vitro*. These results will form a foundation for our *in vivo* assessment of *T. pallidum* proteins in colonization of placenta and neuronal tissues. Hence, using the gain of function approach *in vitro* will allow us to test its validity also in the mouse model of infection. ¶

1A. Identification and characterization of *T. pallidum* adhesins with affinity for placental and/or neuronal tissues and other virulence factors. We have selected several genes of *T. pallidum* for the initial screen to determine them as candidate adhesins in this study. We will obtain clones containing these genes from Drs. Sheila Lukehart and Arturo Centurion at University of Washington at Seattle (please see their letters of support). We will also produce respective recombinant tagged proteins in *E. coli* and generate polyclonal antibodies against the proteins for which antisera are not available from our collaborators. ¶

We considered different features in selection of these proteins, such as; they (i) are known to be expressed during congenital syphilis or neurosyphilis on the basis of serological analysis, (ii) show specificity to a particular host receptor expressed in placenta and/or neuronal tissues, (iii) exhibit other potential activities important for pathogenesis, and (iv) were previously described membrane proteins with unknown function. Selected eight *T. pallidum* proteins, TP0171, TP0319, TP0435, TP0574, TP0954, TP0957, TP0971, and TP1037 have potential to contribute to neurosyphilis or congenital syphilitic manifestation. We will clone the genes along with their promoters in *B. burgdorferi* shuttle vector and transform the non-infectious *B. burgdorferi* B314 strain, which was also used to examine role of DbpA-DbpB, as described above (rationale). We will first assess the function of *T. pallidum* proteins expressed in *B. burgdorferi* as a surrogate system *in vitro*. Expression of *T. pallidum* genes in *B. burgdorferi* will be confirmed by Western blotting. Some of the selection criteria for candidate proteins are described here. ¶

(i) Several immunogenic proteins are identified but their functions not yet determined. TP0171 is a 15kD lipoprotein, which shows homology to proteins of *Listeria monocytogenes* and *L. innocua*, two pathogens causing adverse outcomes in pregnant women. TP0171 is a major membrane immunogen in *T. pallidum*. TP0435 (17kD) lipoprotein and TP0574 (previously known as TpN47) are two highly immunogenic proteins used in diagnosis of syphilis. However, their localization on the spirochete surface remains questionable and their roles have not been examined. This study will unequivocally determine their subcellular localization in the spirochete and will help us evaluate their roles. If one or more of these proteins are present on the spirochete's surface in our initial screen, they will be selected for further experiments. ¶

(ii) Based upon a comprehensive analysis of the available information, we anticipate that TP0954 protein may located on the outer membrane and may facilitate colonization of placenta and neuronal tissues by *T. pallidum*. If so proved, it will provide a model molecule to study molecular basis of congenital spirochete transmission and neurosyphilis. We anticipate that TP0954 encoded protein will be located on the surface of the *T. pallidum* since it possesses a potential signal peptide. In addition, the predicted 3D-structure of this protein using the Hiden Marko models (HMM) program with Protein Data Bank (PDB) shows similarity with several surface proteins in other organisms. These similar proteins include the PilF outer membrane lipoprotein of *Pseudomonas aeruginosa*, peroxisomal targeting signal 1 binding domain of *Trypanosoma brucei* Peroxin 5 protein, and yeast mitochondrial outer membrane translocon protein Tom70p. All possess tetratricopeptide repeats. Finally, one peptide of TP0954 showed 54% similarity with defined chondroitin sulfate A-binding variable domain of PfEMP1 *Plasmodium falciparum*. Furthermore, PfEMP1 of malaria parasite displayed on infected red blood cells (RBCs) promotes adherence of the RBC to placenta. Interestingly, we have previously shown that DbpB lipoprotein of *B. burgdorferi* shows affinity to chondroitin sulfates and mediates binding to the glial cells. Later analyses of cerebrospinal fluid from neuroborreliosis patients confirmed intrathecal (in situ) expression of DbpB by Lyme spirochetes (4, 12). This collective information strongly supports inclusion of this protein in this proposal. ¶

(iii) TP1037 encoded protein is designated as hemolysin III in the genome. Any organ can be affected due to *T. pallidum* dissemination after infection of the fetus by this spirochete. Anemia is common in congenital syphilis and non-hemolytic anemia can persist for weeks even after treatment (21). It will be useful to determine if hemolysinIII of *T. pallidum* is involved in this manifestation. Hemolysis on blood agar plates stimulated by *T. pallidum* hemolysin III will determine its enzymatic activity *in vitro*. These experiments will functionally establish its current predicted role on the basis of sequence homology with proteins of other pathogens. In addition, we will determine in our later experiments whether the expression of this hemolysin results in anemia in mice, similar to that seen in some syphilis patients and in congenital syphilis. ¶

(iv) We have selected three more proteins, which are known membrane proteins with unknown functions. First, Treponema-specific membrane lipoprotein (*tmpC* or TP0319) is an ABC-type nucleoside transport system that may transport purine nucleosides, which are essential for the survival of *T. pallidum* within its obligate human host. If it is not exposed to the surface of the spirochete in the initial analysis, it will serve as a negative control for all following experiments in the specific aim 2. Second, Dr. Norgard's group recently crystallized the membrane antigen (*tpd* or TP0971) of *T. pallidum*. It shows high affinity for human lactoferrin, suggesting its role as iron scavenger. These two proteins, TmpC and Tpd, are expressed at high levels in *T. pallidum* during infection (19) but their contribution to *T. pallidum* pathogenesis remains to be established. The current study will determine if they are located on the surface and potentially play a role in survival of the spirochetes in specific tissues during infection. Third, TP0957 encoded protein belongs to the extracellular solute-binding transporter superfamily that also includes sialic acid-binding protein in other bacteria. Sialic acids are found widely distributed in mammalian tissues. They are also components of gangliosides and are found attached to the glycosphingolipid (ceramide and oligosaccharide). Since gangliosides are predominantly found in the nervous system, TP0957 could be a potential adhesin for neuronal tissues. ¶

Although some of these selected proteins were initially predicted to be periplasmic proteins, Hazlett and coworkers (2005) showed that several periplasmic proteins of *T. pallidum* can get exposed due to outer membrane destablization facilitated by outer membrane protein encoded by TP0453 (7). Therefore, it is useful to determine exact location of these proteins and assess their roles in colonization of neuronal and/or placental tissues. ¶

1B. Evaluation of *T. pallidum* proteins in adherence to cell lines derived from human placenta and neuronal tissue. Colonization of specific tissues *in vivo* often can be predicted on the basis of *in vitro* binding experiments conducted with relevant cell lines and the pathogen. The focus of this study is to identify proteins important in colonization of placental and/or neuronal tissues. Therefore, we will use the human epithelial cell line obtained from placental choriocarcinoma, CCL-98, and fibroblast cell line, CRL7464 as model for placental colonization, while neuronal cell line, PC12, and C6 glioma cell lines will be used to depict colonization of the central nervous system (CNS) during infection. Radiolabeled *B. burgdorferi* will be used in the binding experiments to assess the contribution of *T. pallidum* proteins in adherence with the gain-of-function approach. The wells without the cell line monolayers, and *B. burgdorferi* strain transformed with the shuttle vector alone will provide negative controls for specific mammalian cells and expressed *T. pallidum* protein, respectively. A significantly higher level of adherence by *B. burgdorferi* expressing specific *T. pallidum* protein(s) on their surface to these cell lines, as compared to *B. burgdorferi* control will identify them as adhesin(s). In addition, these results will suggest potential role of these proteins in colonization of specific tissues by *T. pallidum* during infection of humans. We have extensive experience in conducting these experiments with *B. burgdorferi* and found them to be very useful in identifying the bacterial adhesins and host receptors, and predicting their contribution in specific tissue colonization *in vivo*. ¶

Visual Appeal

- Open space
- Clear organization
- Use of **Bold**, CAPITALS, underlining to define sections
- Figures and flow charts to explain experimental design

EXPECTED RESULTS AND INTERPRETATION Based upon our experience with TprK,[62] we expect that antibody specificity will be detected among different sequences for a given DR, and that the number of AA changes necessary to abrogate antibody binding will be few. We expect that antibodies will bind to sequences in the predicted loops, but these loops also contain conserved sequence in addition to the DR, so we cannot predict now whether there will be cross-reactive antibodies that bind the conserved regions of these loops. If so, this may have implications for the specificity of opsonization and neutralization, and may argue against a major role for TprC and D subspecies- and strain-specific immunity. The role of the conserved regions (within loops and separate from loops) in functional immunity, including cross-protection, will be explored formally using a complementary approach in Aim 4. Those results, along with results from Aims 2 and 3, will be evaluated together to reach conclusions or to develop further hypotheses.

LIMITATIONS AND ALTERNATIVE APPROACHES Completion of Aim 2 will require successful production and purification of a large number of recombinant proteins and peptides. OM proteins can be quite difficult to express in *E. coli*. We have been expressing Tpr proteins and other putative OM proteins from *T. pallidum* for ~15 years. The laboratory has used a number of different vectors, host strains, and growing conditions in order to optimize expression for individual molecules. We routinely express such proteins without the signal sequence to avoid toxicity to *E. coli*. Even so, the protein is often found in inclusions, which requires solubilization in urea or other agents before it can be purified (we typically use 6XHIS-tags for purification). Depending upon its intended use, the quality of the antibody that is produced following immunization with recombinant proteins is dependent upon the correct folding of the immunizing protein: if one wants an antibody simply to identify a protein in an immunoblot, correct folding is not necessary; if one wants antibody to recognize a 3-dimensional structure on an intact bacterium, however, correct folding may be critical. Lack of appropriate attention to this issue may be the reason that functional assay results obtained in one laboratory may not be successfully reproduced in another lab. For the proteins that are produced in this project, conditions for optimal folding will be determined, and the degree of correct folding will be evaluated by circular dichroism. Figure 5 shows an example of purified recombinant TprK (predicted to have a structure very similar to TprC and D) that has been optimally refolded in our lab; the spectrum is typical of a molecule rich in β-sheets, consistent with β-barrel structure. Purity of our recombinant proteins and peptides will be assessed by SDS-PAGE and immunoblotting (using anti-6xHIS and infection-immune rabbit serum). If further purification is needed, size exclusion chromatography will be used. Synthetic linear and cyclic peptides will be obtained commercially. We have considerable experience with performing ELISA and lymphocyte proliferation assays using whole recombinant proteins and synthetic peptides as antigens; we don't anticipate any problems with these assays.[56, 57, 59-61]

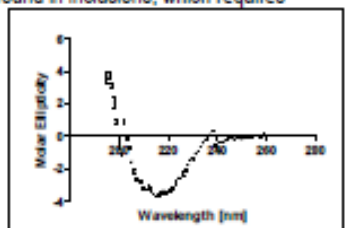


Figure 5. CD spectrum for purified refolded recombinant TprK, another likely OM protein of *T. pallidum*. The spectrum indicates abundant β-sheet composition.

Aim 3. Determine the role of the distinct regions of TprC and D in functional immunity, using homologous and heterologous *T. pallidum* strains as the targets of the functional assays.

RATIONALE AND PRELIMINARY DATA
Antibody can facilitate the killing of *T. pallidum* in two ways: opsonization for phagocytosis by macrophages,[63] and complement-mediated neutralization.[64] It is now widely believed that the major mechanism of clearance of *T. pallidum* from early lesions is by opsonophagocytosis, so the identification of the targets of opsonic antibody has been long-sought. Such targets are also surface-exposed antigens, so opsonization of *T. pallidum* has been used as a functional assay for surface-exposure of an antigen of interest. Several proteins have been reported to be opsonic targets in *T. pallidum*, including TprK,[44] although acceptance of these results has not been universal.[65] Data presented above indicate that several of the Tpr proteins, including TprC and TprD are also targets of opsonic antibody, and 3D

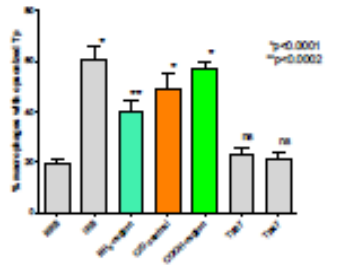


Fig. 6. Opsonization of *T. pallidum* Nichols strain by antisera directed to recombinant peptides of TprC/D.

Visual Appeal

- Open space
- Clear organization
- Use of **Bold**, CAPITALS, <u>underlining</u> to define sections
- Figures and flow charts to explain experimental design

immunosuppressive treatment, compared to the untreated group. We will compare the specific V region titer versus rate of variation in that V region to determine whether there is a positive correlation between measurable immunity and variant acquisition.

LIMITATIONS AND ALTERNATIVE PROCEDURES: As discussed in Aim 1, we do not anticipate having difficulty in obtaining enough *T. pallidum* DNA from the biopsies to complete the proposed experiments. The same limitations, with regard to the sensitivity of detecting variants that are present in low frequency, will apply to these studies. Again, however, this will make it more difficult for us to demonstrate accumulation of variant sequences and will make any positive findings even more meaningful.

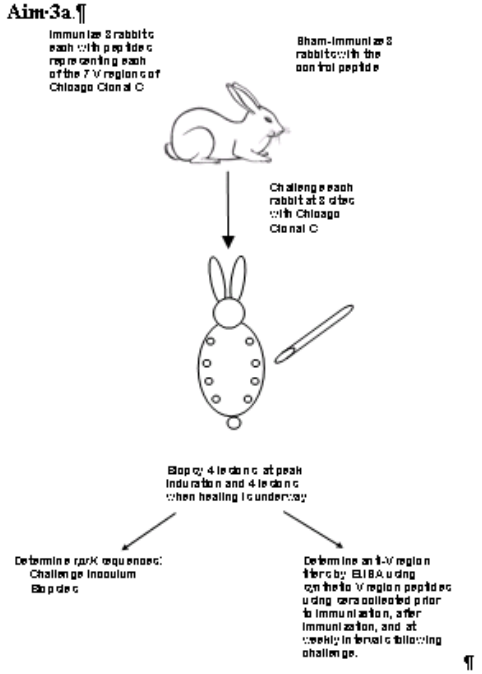
Specific Aim 3. Determine whether immune pressure selects for organisms with variant *tprK* sequences [02-04].

RATIONALE: If variation of the TprK V regions has significance for persistence, <u>one must hypothesize that those organisms displaying new variant TprK antigens will have a selective advantage in the face of an ongoing immune response</u>. We will test this hypothesis, using information gathered in Aim 1 concerning the relative rates of variation of individual regions, and will first test whether immunity to the most diverse V region (e.g. V6) is more effective against organisms expressing that V6 region than is immunity against the least diverse V region, V1. Again, these experiments will take advantage of our ability to derive clonal isolates with defined V regions.

EXPERIMENTAL APPROACH: Two experimental approaches will be used to examine our hypothesis that anti-TprK V region immune pressure will select against treponemes expressing those V regions: 1) the effects of immunization with specific V regions, followed by infectious challenge with treponemes homologous for that V region on loss of founder V region sequences and rate of acquisition of variants; and 2) in vitro/in vivo selection using antisera raised against specific V region sequences. The experiments proposed in this aim will focus initially on the Chicago Clonal isolates that we already have in hand; additional experiments will be conducted using clones from Sea 81-4 and the Nichols strains to test the generalizability of our findings.

<u>a. Immunization with V regions</u>. Groups of 3 rabbits each will be immunized with synthetic peptides representing each of the 7 V regions of Chicago Clonal C. These rabbits and a sham-immunized control group will be challenged

Aim 3a.



Business Pages

- Cover letter
- Abstract, Project Narrative
- Face page
- Budget
- Budget Justification
- Biosketch
- Resources, Equipment, Facilities

Extra Required Components for K's

- Biographical Sketch for Candidate
- Biographical Sketches for Mentor,Co-mentors
- Current & Pending Support for Mentor
- Letters of Reference
  - 3-5 letters from well-established scientists familiar with the candidate
  - May not be directly involved with the application

Biosketch—Note New Format 5/15

OMB No. 0925-0001/0002 (Rev. 08/12 Approved Through 8/31/2015)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME:

eRA COMMONS USER NAME (credential, e.g., agency login):

POSITION TITLE:

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY

NOTE: The Biographical Sketch may not exceed five pages. Follow the formats and instructions below.

A. Personal Statement

Briefly describe why you are well-suited for your role in the project described in this application. The relevant factors may include aspects of your training, your previous experimental work on this specific topic or related topics, your technical expertise, your collaborators or scientific environment, and your past performance in this or related fields (you may mention specific contributions to science that are not included in Section C). Also, you may identify up to four peer reviewed publications that specifically highlight your experience and qualifications for this project. If you wish to explain impediments to your past productivity, you may include a description of factors such as family care responsibilities, illness, disability, and active duty military service.

B. Positions and Honors

List in chronological order previous positions, concluding with the present position. List any honors. Include present membership on any Federal Government public advisory committee.

C. Contribution to Science

Briefly describe up to five of your most significant contributions to science. For each contribution, indicate the historical background that frames the scientific problem; the central finding(s); the influence of the finding(s) on the progress of science or the application of those finding(s) to health or technology; and your specific role in the described work. For each of these contributions, reference up to four peer-reviewed publications or other non-publication research products (can include audio or video products; patents; data and research materials; databases; educational aids or curricula; instruments or equipment; models; protocols; and software or netware) that are relevant to the described contribution. The description of each contribution should be no

Tips and Pet Peeves

- **Keep the Personal Statement succinct**
  - **Make clear when you started your time in the lab**
  - **Do not follow the NIH example**
- **Honors—nothing from high school!!**
- **Contributions to Science—include publications**
  - **Up to 5 contributions, with supporting publications**
  - **Complete citations, all authors**
  - **Name changed? Let us know.**
  - **List link to My Bibliography**
- **Some leeway is OK for new investigators**
  - **OK to include manuscripts submitted and in preparation (separate section?)**
  - **OK to add another heading for abstracts (e.g., Presentations)**

Required Components for K's

- Specific Aims (1 page)
- Candidate Section*
- Mentor's statement, Co-Mentors (6 pages)
- Environment & Institutional Commitment to Candidate (1 page each)
- Research Plan*
- Human Subjects
- Vertebrate Animals

***12 page limit**

Required Components for K's

- Select Agents
- Consortium/Contractual Arrangements
- Letters of Support (Collaborators)
- Resource Sharing Plan
- Appendix (optional—read the rules)

Page limits—12 pages!!

- Specific Aims* (1 page)
- Candidate Information
  - Background
  - Career Goals and Objectives
  - Career Development/ Training Activities
  - Training in Resp. Conduct of Research* (1 page)
- Research Strategy
  - Significance
  - Innovation
  - Approach

*** NOT included in the 12 page limit!!!**

Candidate Section

- Candidate's Background
  - How did you get where you are?
  - Let the reviewers get to know you
- Career Goals and Objectives
  - Where do you want to be in 5, 10, 20 years?
  - Assess your own strengths & weaknesses

Candidate Section

- Career Development/Training Activities
  - How will this award fill your training gaps?
  - Time plan
  - Didactic coursework (req'd for 5 years)
  - Technical training
  - What will you be able to take with you to write an R01?

Candidate Section

- Career Development/Training Activities
  - Training in manuscript & grant writing, manuscript reviewing, budget and lab management, directing staff/students
  - Attending scientific meetings, journal clubs
  - Presenting work orally, posters

Candidate Section

- Training in the Responsible Conduct of Research
  - Provide details per new requirements: format, topics, faculty participation, duration, frequency
  - Future plans for RCR training
  - 1 page (not counted in limit)

Statements of Support (6 pages total)

- Mentor's statement should include
  - Evidence of successful training history
  - Evidence of active productive research
  - Evidence of support for proposed research
  - Details about mentoring—frequency of meetings
  - Topic areas in which mentoring will occur
  - Plan for transitioning candidate to independence
- Co-Mentors' statements should be specific about the expertise that they bring to the mentoring team
- Co-mentors are different from collaborators

Environment & Institutional Commitment to the Candidate

- Description of Institutional Environment (1 page)
  - Intellectual environment
  - Available facilities, resources
- Institutional Commitment to Candidate's Research Career Development (1 page)
  - Usually letter from Chair/ Division Head
  - Guarantees >75% protected time for research training
  - Lab space, office, academic appointment

The Science: Last But Certainly Not Least!

- Schedule uninterrupted time to sit and think—days of time
- Keep a notepad handy to jot down your thoughts and ideas
- Think about the unknowns in the topic that you are studying
- Read the latest papers in your field as well as some well-written review articles

The Science: It comes together….

- Think in the shower
- Think as you walk around Green Lake
- Think as you are on the elliptical trainer at the gym
- Begin to see connections and patterns among your ideas
- Follow your heart as well as your mind

The Science: It comes together….

- Explore the most intriguing lines of research further—read related literature from other fields
- Synthesize the information
- Put “your disease” in the context of others
- Forest and trees……

Research Plan

- Specific Aims—1 page (not in 12-page limit)
- Research Strategy
  - Significance
  - Innovation
  - Approach

Specific Aims

- The most critical page in the application
- It is a one page summary of the application
  - Why is this problem significant?
  - What is the hypothesis(es), and what data support it?
  - What are the exciting new preliminary data that support your aims?
  - What are you going to do?
  - What will your results mean for the field?

Specific Aims—1 page!!

- List your aims simply
  - Be somewhat general
  - Avoid long (laundry) list of things you are going to do
  - 2-4 Specific Aims is sufficient
- Everything should not be dependent upon Aim 1
- Aims serve as the backbone of your Research Plan

Significance (Background)

- Assume you are not writing for an expert
- Emphasize general medical importance and then specific importance of your topic
- Identify gaps in knowledge; state how you will fill those gaps
- Tie the background to each Specific Aim
- Discuss relevant controversies in the field
- Avoid selective citation of the literature
- No limit on number of citations

Innovation

- What is new about your idea?
- Will it change the way people think about the topic?
- How will your results affect the future of research in your field?
- Will it affect research in other fields?
- Simply using a new method is not innovative

Approach: Research Design and Methods

- Organize by Specific Aim
  - Rationale and Hypothesis
  - Preliminary data
  - Experimental Approach
  - Expected Results & Interpretation
    - Statistical analysis
    - Relate expected results to the question
  - Potential Pitfalls and Alternative Approaches
- Other Important Sections
  - Future Directions
  - Timeline
  - Biohazards (Now included in Facilities section)

Approach: Preliminary Studies

- Show preliminary data relevant to each aim and clearly tie the data to the aim (highlight your data)
- Show data for critical methods
- Include control data
- About 3-4 readable figures or tables
- Convince reviewer that you can do (or will learn) what you propose
- Critically analyze the data and state how your proposal will clarify questions about it

Approach: Preliminary Studies

- Put figures on relevant pages
- Number figures; refer to figure number in the text in bold (**Fig.1**)
- Figures should be self-explanatory—legends, labeled axes, etc.

Approach: Research Design & Methods

- Justify choice of methods
- Details of methods are unimportant (boring)
  - But make sure the reviewers know *you* know the methods
- Get collaborators and consultants- strong letters
- Timeline
- Biohazards

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*					

Other Considerations

- Be thorough in addressing all questions
  - Humans subjects
  - Vertebrate Animals
- Address or state “Not applicable” to all categories
  - Select Agents, Resource Sharing, etc
- Bibliography
  - Correct format—list all authors

Scored Review Criteria

- Overall Impact
- Candidate
- Career Development Plan
- Research Plan
- Mentor(s), Consultants, Collaborators
- Environment & Institutional Commitment

Additional Review Criteria*

- Training in Responsible Conduct of Research
- Protection for Human Subjects
- Inclusion of Women, Minorities & Children
- Vertebrate Animals
- Biohazards

* These criteria DO affect the score

How do you know whether your application will be funded?

- Priority score posted on NIH Commons a few days after review
- Summary Statement 3-6 weeks later
- Paylines are posted by Institutes
- Paylines shift during the FY

What if you are not funded the first time?

- Read the comments carefully and put them away
- Read the comments again 3-5 days later
- Don’t get discouraged
- Discuss options with your mentor
- Revision-one revised application can be submitted
- Listen to what the reviewers said!!!

Don’t give up!!

- Initial failure is common
- Learn from a failed submission & succeed next time
  - Study criticisms in Summary Statement
  - Decide if problems are reparable
  - Attend diligently to each criticism
  - Keep a positive tone and attitude
- “Good” amended applications tend to do well

Response to Critiques- When you submit a revised application

- Restate each criticism and explain how you revised the application in response—make it easy for reviewer to find your “answers”
- Misunderstandings are *your* fault—if the reviewer missed a key fact in a figure or table, maybe it wasn’t clear enough

Response to Critiques- When you submit a revised application

- Be diplomatic and positive (most reviewers' comments are useful)
- Don't argue with reviewers
- Avoid tone that says "The reviewer didn't know anything about this area"
- Avoid overstating your data

The Rewards!

- Discovery!
- Help to understand, control, prevent or cure a disease
- Opportunity to develop the next generation of outstanding scientists

http://www.nesc.nhs.uk/images/biomedical%20scientists.jpg