

# The NICHD Connection

## October 2013

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## Hot Off the Press: Guilty Until Proven Innocent

By Shana R. Spindler, PhD



Protein aggregates, or large clumps of unwanted protein, are a common feature of neurodegenerative diseases. Proteins are made of long chains of amino acid building blocks. Once assembled, the amino acid chain wiggles and folds to produce a working protein. But this folding doesn't always succeed, and sometimes it creates a misfolded, dysfunctional product. These faulty proteins are often rather sticky, and can bind to other proteins, causing protein aggregation and cell damage.

The cell must eliminate these renegade proteins before disease ensues. To do so, the cell employs elaborate "quality control" systems that constantly check proteins for misfolding and mark them for degradation. A specialized class of enzymes called E3-Ligases carries out the marking. If we are to fully understand and treat the disease processes involving protein misfolding, we need to understand how the E3-Ligase successfully discriminates between the good and the bad. One problem: misfolded proteins are prone to aggregation, and difficult to handle in a test-tube, making experiments nearly impossible.

In an interesting twist, NICHD researchers in collaboration with the MRC Laboratory of Molecular Biology in Cambridge, UK, used Human

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## Letter from the Editor

### *And we're back...*

Why are you here? Not the proverbial question of your existence, but the question of why you chose the NICHD for your research endeavors. We each have a different reason for coming to the NIH. For some, specific labs pique their interests. For others, the atmosphere of multidisciplinary collaboration is magnetic. And for many of these fellows, the NIH has far exceeded their expectations.

This month, NICHD fellows share their thoughts on working at the NIH. Dr. Parmit Singh, visiting fellow from India, describes his path to higher education and how the NIH has shaped his life ([page 4](#)). His sincere words offer thanks to all of the members of our community who have offered guidance and support in his pursuit of scientific progress and education.

Postbac Jeffery Head describes an unanticipated experience volunteering at the NIH Children's Inn, where he solidified his connection with the NICHD research mission ([page 6](#)). If you are a junior trainee who would like to learn

more about activities outside the lab, check out Amanda Krause's recap from last month's postbac orientation ([page 9](#)).

For our more senior fellows, Dr. Yvette Pittman presents an excellent guide on preparing for your K99/R00 grant application submission ([page 7](#)), complete with a tip sheet containing advice from previous K99/R00 NICHD applicants ([page 8](#)). If you plan to apply for a K99/R00 in the near future, print this guide and tape it above your computer monitor!

But wait, that's not all! In this issue, you will also find an elegant study from the Bonifacino and Hegde labs ([page 1](#)) in our "Hot Off the Press" column and some **very entertaining images** from [last month's NIH-wide relay race](#).

It's good to be back!

Your Editor in Chief,  
Shana R. Spindler, PhD

Questions, comments, ideas? Please contact me at [Shana.Spindler@gmail.com](mailto:Shana.Spindler@gmail.com).

## Hot Off the Press: Guilty Until Proven Innocent (continued from page 1)

Immunodeficiency Virus (HIV) membrane proteins to study this discrimination problem. Once HIV infects a cell, it hijacks one of the cell's E3-ligase enzymes to selectively mark a protein called CD4 for degradation. CD4 degradation is crucial for HIV to efficiently produce new mature HIV particles. Earlier work had shown that specific mutations in CD4 allow it to avoid destruction by HIV. The team realized that CD4, together with its mutant that escapes destruction, provides a model to explore how an E3-Ligase selects proteins for destruction. This model had the advantage of avoiding the complications of working with misfolded proteins. The disadvantage was that these proteins normally operate in a cellular membrane.

The team therefore inserted the proteins into an artificial membrane vesicle, called a liposome, to permit their analysis. With the major technical hurdle out of the way, they could use their simple model system to ask: "How does an E3-Ligase discriminate between the normal CD4 and mutated CD4 proteins?" The answer was surprising...it doesn't—to any significant degree at least.

The team found in their test-tube system that CD4 was marked for destruction regardless of the mutation. Scratching their heads, they returned their attention to the cell. In vivo, the mutated CD4 lacks the degradation label—a long string of the small protein ubiquitin. The team hypothesized that a protein that removes ubiquitin, called a deubiquitinase (DUB), may be at work. Indeed, when the group

introduced a DUB into the test-tube system, the number of ubiquitin labels on CD4 decreased. Importantly however, the decrease was much more dramatic on the mutated CD4.

You're guilty until you're proven innocent, according to the E3-Ligase. The team's data, as well as mathematical modeling, suggests that the E3-Ligase may inspect and mark a broad range of proteins, while the DUB removes this mark. However, a slightly higher affinity of the E3-Ligase for "bad" proteins prevents them from being unmarked by the DUB for slightly longer. The researchers posit that the back-and-forth dance between the E3-Ligase and DUB amplifies the ubiquitin labeling process, slating only the "bad" proteins for the trash. To be sure, the researchers added a DUB inhibitor to the mix and found the mutated CD4 was once again marked for degradation.

The idea that E3-Ligases and DUBs work as a team for protein quality control is completely novel. "If we generalize this kind of idea, the same method may be applied to misfolded proteins," said Dr. Zairong Zhang, first author of the study. "This result provides a guiding principle: it may be feasible to develop a specific DUB inhibitor to treat diseases caused by protein aggregation."

### REFERENCE:

Zhang ZR, Bonifacino JS, Hegde RS. Deubiquitinases Sharpen Substrate Discrimination during Membrane Protein Degradation from the ER. *Cell* 154(3): 609-22.

Dr. Zhang, former NICHD fellow in the Cell Biology and Metabolism Program, is now an Associate Research Scientist at the Yale University School of Medicine.

## Reflections on getting to the NIH: One stop on my lifelong journey of learning

By Parmit Kumar Singh, PhD

Since my childhood, two people have inspired me to pursue higher studies. My first motivator was my grandfather, Shri Ramashray Singh, who was poorly educated due to a lack of formal education opportunities in his rural area of India. Regardless, he always encouraged everyone in our area to seek a higher education. My second source of inspiration is Dr. Rajendra Babu, the first president of India, who was not only from my home state of Bihar, but also from my home district, Siwan. He was known for his down-to-earth nature, sincerity, and honesty.

But my biggest motivation to pursue higher studies in scientific research came from my undergraduate training in agriculture. During a course, I read about India's "green revolution," in which scientists introduced high-yielding varieties of seeds to help increase the production of food grains, an important benefit to society. The day I received my doctoral degree from India's Center for Cellular and Molecular Biology, I was very happy. For me, a PhD is not just another degree, it is a way to follow my

role models, to fulfill the last dream of my grandfather, to serve my society, and to inspire people to become educated.

I chose postdoctoral work at the NIH because I thought I could serve society in a more efficient way after exposure to modern technology. At the NIH, a visiting fellow has many opportunities, like grant writing workshops, teaching workshops, and leadership training. The Foundation for Advanced Education in the Sciences (FAES) classes can help fellows gain new strengths or explore new fields of research. But, for me, the biggest strength of the NIH is that most of the institutes are in the same campus. This brings people from different fields under the same umbrella to discuss scientific views, experiments, and challenges.

My life is full at the NIH. I have met wonderful people who have contributed to my learning, including my mentor, people in the Program in Cellular Regulation and Metabolism (PCRM), FAES teachers, the Office of Education, the NIH library staff,

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## Reflections on getting to the NIH (continued from page 4)

and many others. For their mentorship and guidance, I am forever grateful.

After my postdoc, I want to be an independent scientist. I want to give back by encouraging others to participate in science to make our society a better place, free of disease, poverty, and hunger. I want to help start FAES-like programs where I go in the future, so that students can satisfy their hunger for knowledge and pursue their interests. But most important, I want to encourage more and more people to strive for higher education. This will give me the satisfaction of continuing to fulfill my grandfather's dream.

Education can unite society by limiting poverty and sources of discrimination. A beautiful example of this is the NIH, where people from different parts of the world work together for the betterment of humanity without regard for sex, caste, religion, or region. There are many ways to earn money and live life, but doing science for the betterment of society and encouraging others to pursue higher education is more meaningful, at least to me, than making money.

रोशनी जो मिली है मुझको यहाँ,  
उससे एक नया दिया जलाऊंगा,  
फिर न हो किसी के पथ में अंधियारा,  
ऐसी एक मशाल बनके जल जाऊंगा, परमीता।

I will light a new lamp (enlighten) with the light (knowledge) that I got here. There should not be darkness in anybody's life any further. Therefore, I will burn like a torch to light their path ~ Parmit.

## Thoughts of a Postbac: Volunteering at the Children's Inn

By Jeffery Head

Considering that my lab is tucked neatly away in building 6B, it is somewhat unsurprising that prior to November of last year I had never even heard of the Children's Inn. As far as I was concerned, the NIH campus consisted only of the monolithic Clinical Research Center, the cafeteria in building 31, and a whole bunch of other buildings that could all be completely empty as far as I knew. That is why I am thankful a fellow postbac convinced me to stray from the comfort of the building 6 complex and head over to the Children's Inn to teach science experiments to some of the kids staying there.

The first time we went I was nervous and couldn't stop wondering if all of the experiments we had planned would just fall flat on their face. Our participation was not compulsory—we were only going to be doing a few basic and fun experiments—and yet I was still afraid of disappointing a group of five- to ten-year-olds. What I thought was sure to be an hour of my partner and I obviously faltering in our attempts to get these kids excited about science (as I had seen far too many a substitute teacher do in middle school) turned out to be one of the best experiences I've had at the NIH to date.

The kids were eager to participate and seemed genuinely interested in understanding why the reactions they were seeing were happening. They especially never got tired of hearing (or seeing) why dry ice combined with



water produced so much “fog” (pictured above). Although it would be a stretch to say that these experiments sparked the children's lifelong love of science, I can't help but hope that some of what they learned will stick with them.

As idealistic as this hope may be, one thing is certain—the kids are always amazed with what you show them and love the attention of every volunteer. Seeing firsthand how I could personally bring even a little joy to kids faced with unimaginable difficulty has made me feel a stronger connection with the mission of our research here at the NICHD, and I would highly recommend that everyone try leading a session.

If you have any questions or would like more information you can email me anytime at [headjr@mail.nih.gov](mailto:headjr@mail.nih.gov).

## Preparing for Your K99/R00 Grant Application Submission

By Yvette Pittman, PhD

Have you considered writing an application for the NIH Pathway to Independence (K99/R00) Award? At the initial thought of applying for this prestigious career transition award, you may feel a bit overwhelmed, pondering where to start. The Office of Education is here to guide you and offer our support as you go through the application process.

The K99/R00 award provides up to five years of research support consisting of two phases. The first mentored phase (K99) allows you to obtain additional training, complete research projects, publish results during the remaining time of your intramural postdoctoral training, and bridge the accomplished work to your independent research program. The second phase provides up to three years of research support when the awardee has obtained a full-time, tenure-track, faculty position. Both domestic and international fellows are eligible to apply. However, applications—and resubmissions—may now be submitted ONLY up to the end of your fourth year. Throughout the year, there are three application deadlines: February 12, June 12, and October 12.

After you have met with your mentor to discuss your interest in applying, and have secured his or her support to pursue your research ideas, we highly recommend that you set up a meeting with the Office of Education. At the beginning of your grant-writing experience, we will provide you with a detailed checklist of items that you will need to complete—starting from five to six months before the deadline to the in-person electronic submission date. In addition to the newly organized checklist we have in place,

we have summarized the documentation required for a completed application. We can provide you with a document full of advice for fellows applying for career development awards.

To maximize the competitiveness of our fellows, the Division of Intramural Research has established a review committee of senior PIs who read through fellows' applications and offer editorial and scientific guidance to the applicants. We also offer you guidance for writing the career development and mentoring components of the grant. This will all strengthen your K99/R00 application!

For fellows applying for the K99 award, you should plan to participate in our annual summer grantsmanship workshop with other Institutes and Centers (ICs). It includes individualized coaching sessions on specific aims for those with grants in preparation. This workshop includes a workbook that has received high praise from fellows. Another helpful tool is the recently released eRA Commons video tutorials on YouTube; here is the web link: <http://www.youtube.com/playlist?list=PLOEUwSnjvqBLbEX3RInwT4g3uMIuF0xct>.

For example, one of tutorials guides you and your referees on how to submit a reference letter through eRA Commons to support career development award applications.

Be sure to check out the K99/R00 tip sheet, which several NICHD fellows who previously applied for the K99/R00 award created, on the following page.

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## Preparing for Your K99/R00 Grant Application Submission

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### A K99/R00 TIP SHEET—ADVICE FROM PREVIOUS NICHD APPLICANTS

1. Beside the K99/R00 program announcement, be sure to thoroughly read the **SF424 Application Guide**. Part 7 of this guide contains Supplemental Instructions for Preparing an Individual Research Career Development Award (CDA) Application (“K” Series). For example, part 7.4 is titled K-Specific Instructions for K Applications.
2. **Be mindful of your page limits.** The total number of pages for the following must not exceed 12 pages: candidate’s background, career goals and objectives, career development/training activities during award period, training in the responsible conduct of research, and research strategy. The specific aims section is limited to one page.
3. There are many **format specifications** for your text documents, such as file names, fonts, and page margins. Detailed instructions are included in the SF424 Application Guide.
4. In addition to the statement(s) of support from your mentor or co-mentor(s), **letters of reference** from at least three well-established scientists are required (electronic submission using eRA Commons).
5. Don’t forget the **required documents** that may not be your main focus while writing, such as project summary/abstract, project narrative, and facilities and other resources.
6. You should allow a sufficient amount of time to thoroughly think about your **career development plan** and how it complements your research strategy. You should discuss the outline with your mentor(s) before writing.
7. You should **consider the period of time** between submission, receiving your impact score, and the opportunity to resubmit, if applicable. This may affect your choice of your initial submission date.
8. **Time allowances** for the final stages of application preparation are crucial, such as getting feedback from other scientists and completing the electronic application for submission.
9. Based on discussions with academic researchers and review panelists, you are a more competitive applicant if you have **at least one first author paper** from your current postdoc at the time of review.
10. If you are including a mentoring committee, the **plan for mentoring** needs to be well tailored and the roles for each mentor should be explained.
11. Each of the sections takes much longer to complete than you anticipate; have a **detailed timeline** for each section before you begin writing.
12. **You can only use the following characters** when naming your attachment files: A-Z, a-z, 0-9, underscore (\_), hyphen (-), space, and period. The file name must be 50 or fewer characters. Attachments that do not follow this rule may cause the entire application to be rejected or cause issues during processing.

## Postbac Orientation Recap

By Amanda Krause

The postbac orientation on September 19 was very successful. About 15 NICHD postbacs turned out for the event, which lasted an hour and a half. We discussed current activities that postbacs can become involved in at the NIH.

NICHD postbacs can shadow in Tuesday Genetics Clinics where they are able to learn from the Genetics team. They can attend Intensive Care Unit (ICU) Rounds or ICU Simulator Rounds where they observe fellows and members of a healthcare team react to patient scenarios using the “Sim Man,” or patient simulator. Another wonderful activity is Explore INN volunteering, where postbacs can perform age-appropriate science experiments with children staying at the NIH, and thereby stimulate their interest in science (see [page 6](#)).

We also discussed career development opportunities through OITE and the NICHD Office of Education. Another great experience is writing for *The NICHD Connection*

newsletter (this newsletter). During the meeting we talked about possible opportunities to interview outstanding scientists working at the NIH about their research or careers and then write an article about the experience in this newsletter. Finally, postbacs can volunteer on the NIH campus through Learning Ally by creating recordings of medical textbooks for the blind, dyslexic, or individuals with learning challenges.

One opportunity that many of the NICHD postbacs are taking advantage of is the Becoming an Effective Scientist Class where postbacs can learn how to analyze scientific articles over free pizza lunch, every Monday at noon throughout the fall (you can still sign up!). Jeff and I will have career development events in the future to help IRTAs prepare for graduate or professional school. If you are interested in becoming involved in any of these opportunities, please email Jeff ([jeffrey.head@nih.gov](mailto:jeffrey.head@nih.gov)) or me ([amanda.krause@nih.gov](mailto:amanda.krause@nih.gov)).

## Life Outside Lab



McBain lab "Pinky and the Brainslicers" running team for the NIH relay race, September 19, 2013. From left to right: April Johnston (grad student), Mick Craig (postdoc), Chris McBain, Libby Barksdale (postdoc), David Collins (postbac). More photos from the relay can be found on [page 15](#).

## October Announcements

### GRAD STUDENTS GIVING A TALK TO THE MONTHLY PI MEETING!

The objective of the NICHD Graduate Students Talks is to provide our graduate students with practical experience for presenting their thesis research to a non-specialist audience in a formal setting. This will give graduate students an opportunity to enhance their oral presentation skills before their thesis defense, presenting at a scientific conference, or giving a job talk.

**Eligibility:** NICHD graduate students who have completed at least two years of thesis research at NIH

**Timing:** The seminar will be on a quarterly basis at the DIR Principal Investigator monthly meetings, which are held on Thursday afternoons.

**Nominations:** GST presenters are nominated by their PI, and the nominations should be forwarded to the Deputy Director, Liaison & Training, Brenda Hanning, at [hanningb@mail.nih.gov](mailto:hanningb@mail.nih.gov), including the student's name, years of NIH research training, and a title of their thesis project or proposed talk. The final selections will be made by the Office of the Scientific Director; and eight weeks prior to the seminar dates, the students and their mentors will be notified by the OSD. Note that speakers for October '13 to summer '14 have been selected.

## October Events and Save the Dates!

**TUESDAY, NOVEMBER 5, 3–5 PM, BLDG 31, RM 6C6**

NICHD Exchange: "Contraception: Or Baby Makes 3?"

### **Speakers:**

- » *Alicia Armstrong, MD*, Gynecologic Health and Disease Branch:  
"The Unintended Consequences of Unintended Pregnancy"
- » *Susan Newcomer, PhD*, Population Dynamics Branch:  
"The 37%: Understanding Why So Many Pregnancies In The U.S. Are Mistimed, Unintended, Unplanned, And/Or Unwanted"
- » *Lisa Kaeser, JD*, Office of Legislation and Public Policy (OLPP):  
"Perfectly Legal...Except When It's Not"
- » *Diana Blithe, PhD*, Contraceptive Discovery and Development Branch:  
"Contraceptive Development: Successes from the Past and Challenges for the Future"

**FRIDAY, NOVEMBER 8, 10 AM–12 NOON**

Job Interviewing Skills Workshop, for senior fellows  
(previously scheduled for October 23)

Will you be actively searching for employment this fall? Gain a competitive edge!

This workshop is designed to help scientists make a strong impression during a job interview. It focuses on identifying singular examples to help answer questions, and expected questions, themes, dilemmas and comportment will be analyzed through interactive exercises and peer review. Limited to 10 people and can include a one-one-one session with the instructor, Scott Morgan.

Please register with Yvette Pittman at [yvette.pittman@nih.gov](mailto:yvette.pittman@nih.gov).

**WEDNESDAY, NOVEMBER 13**

"Lunch and Chat Session: Preparing for Consulting Careers"

Are you thinking of a career in consulting after you complete your NIH fellowship?

The Office of Education is offering a brown bag lunch session with Diane Epperson, PhD, a lead associate at Booz Allen Hamilton. This is a great opportunity, in an informational group discussion, for you to learn about the application process, tips for resume and cover letter writing, and job search strategies related to consulting careers. Also, you can get a sense of what fellows could do throughout their training to prepare for the competitive job market, and of course, hear firsthand how her scientific experiences and skills led to a career in consulting.

If you would like to attend, please send Yvette Pittman ([yvette.pittman@nih.gov](mailto:yvette.pittman@nih.gov)) an email.

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## October Events and Save the Dates! (continued from page 12)

### TUESDAY, DECEMBER 3, 5:30 TO 7:00

NICHD Fellows Fall Social Event  
at the Bethesda Naval Bowling Center (directly across from  
the NIH campus)

\$3.25 per person per game & \$2.50 for Shoe Rentals

Food and Beverages available at the café

If you are up for a challenge, create your bowling team of  
four intramural fellows! Sign up with Stephanie Cologna at  
[stephanie.cologna@nih.gov](mailto:stephanie.cologna@nih.gov) by November 1<sup>st</sup>. You'll need  
your NIH ID to enter the Walter Reed National Military  
Medical Center.

### POSTPONED:

Graphics Workshop: creating  
and editing graphics for figures,  
diagrams, and cartoons

Due to a lapse in government  
funding, the Graphics Workshop  
previously scheduled for October  
1<sup>st</sup> was cancelled. Now that NIH  
is able to resume activities, we will  
reschedule the class and announce  
it in this space.

**Due to the U.S. Government Shutdown,  
this comic is currently unavailable.**

**(Comics have nothing to do with politics, but  
neither should Science or Research!)**



**www.phdcomics.com**

<http://www.phdcomics.com/comics/archive.php?comicid=1627>





# NTH Relay

SEPTEMBER 19, 2013



