

The NICHD Connection

February 2016

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The Surprising Role of Splicing in HIV-1 Integration

By Shana R. Spindler, PhD

Viruses are simple. Get in, replicate, get out. The human immunodeficiency virus (HIV)-1, on the other hand, prefers a more complex approach. HIV-1 genetic material hitches a ride into the nucleus. There, it inserts into the host genome, where it can lurk quietly in the unsuspecting cell until it's transcribed and sent off anew. But HIV-1 is picky—it prefers certain spots in the DNA. New research from the Levin laboratory at the NICHD shows just how discerning HIV-1 can be. According to their study, HIV-1 integrates preferentially into intron dense genes by taking advantage of the cell's own RNA splicing mechanisms.

The first work to map HIV-1 insertion occurred over a decade ago, with a few hundred sites mapped in 2002. When deep sequencing technology became available, researchers were quick to identify nearly 40,000 different HIV integration sites in the human genome. As large as the number seemed, it was only a tiny fraction of the possible sites, and therefore an incomplete sampling. Fast forward six or seven years. Deep sequencing technology became much more powerful. Dr. Henry Levin, of the NICHD Section on Eukaryotic Transposable Elements, saw this as an opportunity to generate the largest collection of HIV-1 integration data for humans to date.

With several ideas about how to approach the problem, a postdoctoral fellow in the lab, Dr. Parmit Kumar Singh, took the lead. Rather than using a single tube approach to sequencing, Singh ran a large number of ligation reactions with an even larger number of polymerase chain reactions. His approach worked. Singh amassed nearly one million HIV-1 integration sites, replicated over nine integration libraries. "We can now say it goes into this gene but not that gene," Levin said, referring to HIV-1 integration. About 4,000 genes contained most of the integration sites, with the top hits showing a high enrichment for cancer-associated genes.

The implications for cancer gene preference during HIV-1 insertion are

HOT
OFF THE
PRESS

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Letter from the Editor

I had the privilege last month to chat with Drs. Henry Levin and Parmit Singh about their work on Human Immunodeficiency Virus (HIV)-1. Their recent study, published in the November 2015 issue of *Genes & Development*, establishes a foundation for understanding where HIV-1 inserts into the genome, and why. It's one of those papers that makes you a little giddy as you read, because it's a piece of work that is—dare I say it—groundbreaking. Check it out in our first **“Hot Off the Press” article** of 2016.

Our next feature article, **a piece on the “Becoming an Effective Scientist” course for postbaccalaureates**, is a great read for NICHD fellows at all levels of training. Dr. Afrouz Anderson, course director for the 2015 series, expands upon the course benefits for both postbac students and postdoctoral instructors. In an environment with limited teaching opportunities (compared to a four-year University setting), the “Becoming an Effective Scientist” course is a unique opportunity within the NICHD to hone those pedagogical skills.

Both of these articles deserve your attention, so I won't steal any more of your time here. But before I go, a friendly reminder to take a look at the **February announcements** and **events**, including info about the 2016 fellows retreat (with a very cool key speaker reveal), several fellowship opportunities, and upcoming NICHD workshops—do take advantage!

Your Editor in Chief,
Shana R. Spindler, PhD

Please send your questions and comments to **Shana.Spindler@gmail.com**.

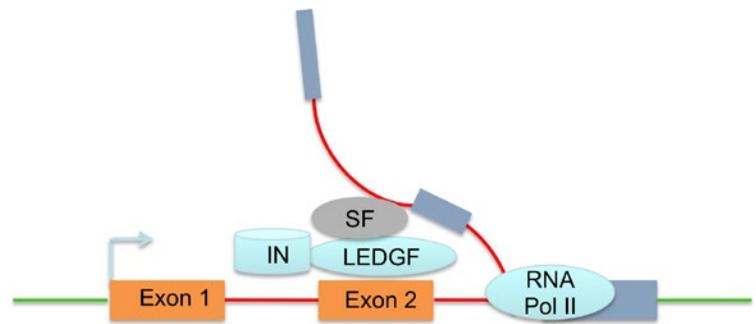
The Surprising Role of Splicing in HIV-1 Integration (continued from page 1)

large—and not only for those infected with HIV-1. During the first successful gene therapy trials in the 1990s, researchers used genetic information from gamma-viruses to introduce DNA into patients with Severe Combined Immunodeficiency (SCID), a genetic disorder that leaves the body unable to fight even the smallest infection. While the therapy was successful, some of the treated individuals developed a fatal leukemia, likely due to the gamma-virus propensity to activate proto-oncogenes. In an attempt to avoid this complication, researchers switched to lentivirus-based vectors.

But that was the problem: HIV-1 itself is a lentivirus. Singh's work suggested that patients undergoing gene therapy with lentivirus vectors could need long-term monitoring for clonal proliferation of cells. Singh needed to understand HIV-1 integration at the gene level. He became interested in the cellular factors that enabled HIV-1 attraction to specific genes. During a time in biomedical science when research questions are increasingly focused and narrow in scope, Singh's study was taking on complex elements of HIV-1 biology, gene therapy, and the beauty of developmental biology.

In a gene-level analysis, Singh identified a striking pattern: HIV-1 integration heavily

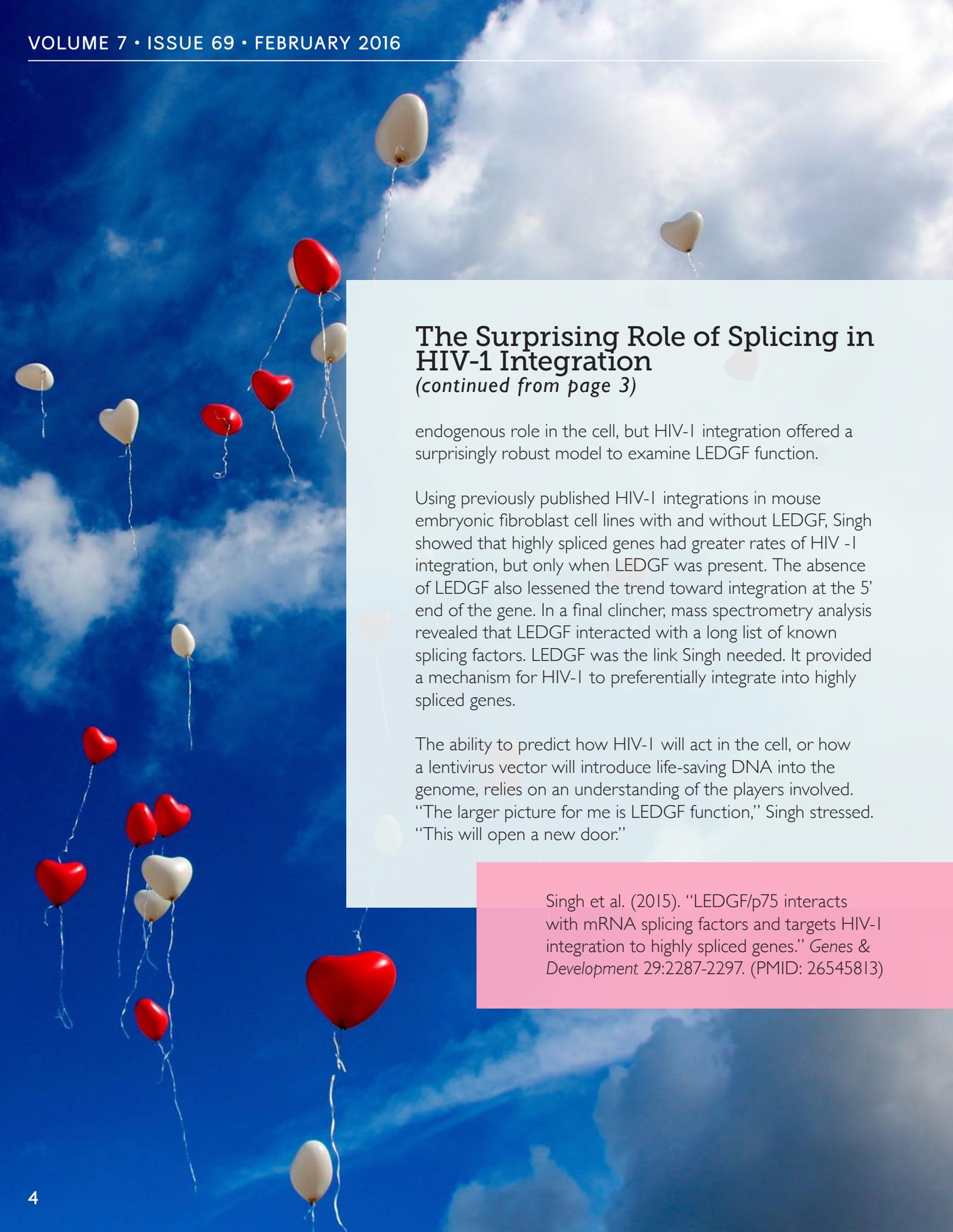
avored the five prime (5') end of the gene. On a wild hunch, he hypothesized that introns may be involved. In an elegant set of experiments, Singh showed that increased intron number led to greater likelihood for HIV integration into the gene—and it was not due to gene length. It was his "AHA!" moment. In collaboration with Dr. Brian T. Luke of NCI, NIH, Singh determined that intron number was the largest predictor for HIV-1 integration into a gene.



Cartoon model for interactions that help direct HIV-1 to transcription units with a large number of introns. Abbreviations: Splicing Factors (SF), HIV-1 Integrase (IN), RNA Polymerase II (RNA Pol II)

In search of a cellular factor that linked HIV-1 integration to intron number, Singh turned his attention to LEDGF, a chromatin binding factor previously associated with HIV-1 integration. In animal studies, knocking out LEDGF caused mice to die, which of course made it terribly difficult to study. Nothing had been known about LEDGF's

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The Surprising Role of Splicing in HIV-1 Integration

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endogenous role in the cell, but HIV-1 integration offered a surprisingly robust model to examine LEDGF function.

Using previously published HIV-1 integrations in mouse embryonic fibroblast cell lines with and without LEDGF, Singh showed that highly spliced genes had greater rates of HIV-1 integration, but only when LEDGF was present. The absence of LEDGF also lessened the trend toward integration at the 5' end of the gene. In a final clincher, mass spectrometry analysis revealed that LEDGF interacted with a long list of known splicing factors. LEDGF was the link Singh needed. It provided a mechanism for HIV-1 to preferentially integrate into highly spliced genes.

The ability to predict how HIV-1 will act in the cell, or how a lentivirus vector will introduce life-saving DNA into the genome, relies on an understanding of the players involved. "The larger picture for me is LEDGF function," Singh stressed. "This will open a new door."

Singh et al. (2015). "LEDGF/p75 interacts with mRNA splicing factors and targets HIV-1 integration to highly spliced genes." *Genes & Development* 29:2287-2297. (PMID: 26545813)

Rigor and a Love for Research: Becoming an Effective Scientist

By Afrouz Anderson, PhD

Among the many opportunities for eager students on the NIH campus, NICHD's "Becoming an Effective Scientist" is a course that continues to set itself apart year after year. The NICHD Office of Education launched the course in Fall 2005 with the mission to familiarize postbaccalaureates (postbacs) with the process of conducting research on a variety of biomedical topics. Each week offers a new research topic taught by a postdoctoral researcher within the field. By pairing curious, energetic postbacs with postdoctoral, clinical, and visiting fellows, the course provides breadth and rigor in a casual and entertaining setting. But postbacs aren't the only group to benefit from the course; the postdoctoral instructors gain valuable teaching experience too.



COURSE BASICS

The first session of the course focuses on effective communication and presentation of scientific research, which is vital for research progress and collaboration. Scott Morgan, communication coach at NICHD for over 10 years, leads the discussion.

For the following sessions, the students learn about cutting-edge research strategies in fields as diverse as imaging, molecular biology, gene therapy, cell biophysics, and many more. The core of every lesson focuses on each field's impact on children and human health, to emphasize the importance of everyday science experiments and to clarify the clinical relevance.

BENEFITS TO POSTBACS

The enthusiastic environment of the course has encouraged questions from postbacs, including how to find a suitable lab, how to understand expectations in the lab, and how to tackle the details of experimental and data analysis. The casual environment makes it possible for students to relax and openly interact with instructors. The students' eagerness has not been limited to learning about research topics, as postbacs have found personal experiences from each instructor's research career to be helpful.

In each session, students are exposed to different perspectives on what to expect from the research process and how to deal with scientific challenges.

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Becoming an Effective Scientist (continued from page 5)

To further the process of critical thinking, instructors ask open-ended questions, such as “How would you run this experiment?” or “What does this figure imply?” Posing questions to students not only encourages them to build upon their prior knowledge to resolve and understand various problems, but it also develops their curiosity. Group exercises provide an opportunity for students to learn how to understand hypotheses, experiments, and results as they review articles and interpret figures together.

BENEFITS TO POSTDOCTORAL INSTRUCTORS

Another notable aspect of this course lies within the teaching opportunity that it creates for postdoctoral fellows. Dr. Mark Bayfield, a previous course director and one of the initiators of the course, says, “I found helping coordinate the course to be very helpful with my subsequent job search. In the absence of this course we felt that teaching opportunities at NIH were difficult to come by, but this course would help fill a gap for NICHD postdocs hoping to apply for academic positions.”

Dr. Aarthi Ashok, also one of the previous course directors, says, “Helping with the design and delivery of this course was a very important aspect of my teaching portfolio. I continue to use elements from this course now when I teach undergraduates at the University of Toronto to critically evaluate primary literature.” She adds, “I was able to demonstrate my ability to develop a course that was well structured, provoked critical thinking, and had concrete learning outcomes for postbaccalaureates interested in careers in science.”

The “Becoming and Effective Scientist” course has provided a valuable learning opportunity for postbacs and an important teaching opportunity for postdocs. Over the past 11 years, the unique platform of the program has broadened students’ research interests while helping them improve their research and communication skills.

To learn more about the next offering of “Becoming an Effective Scientist,” or to volunteer as a course instructor for future sessions, please contact Dr. Yvette Pittman (pittmanyv@mail.nih.gov) in the Office of Education.

Congratulations to Our 2015 NICHD Graduates

Two NICHD Graduate Partnership Program students received their doctoral degrees in 2015. Please join *The NICHD Connection* in wishing our graduates a bright future ahead!

AFROUZ ANDERSON, PHD

Dissertation title: "Application of Functional Near Infrared Spectroscopy in Neurodevelopmental Disorders"

NICHD mentor: Dr. Amir H. Gandjbakhche

Partner mentor and school: Dr. Dennis L. Matthews,
University of California, Davis

RUILIANG BAI, PHD

Dissertation title: "Quantitative Study of Water Dynamics in Biomimetic Models and Living Tissue by NMR and MRI: Perspectives on Direct Detection of Neuronal Activity"

NICHD mentor: Dr. Peter J. Basser

Partner mentor and school: Dr. Robert M. Briber, University of Maryland, College Park

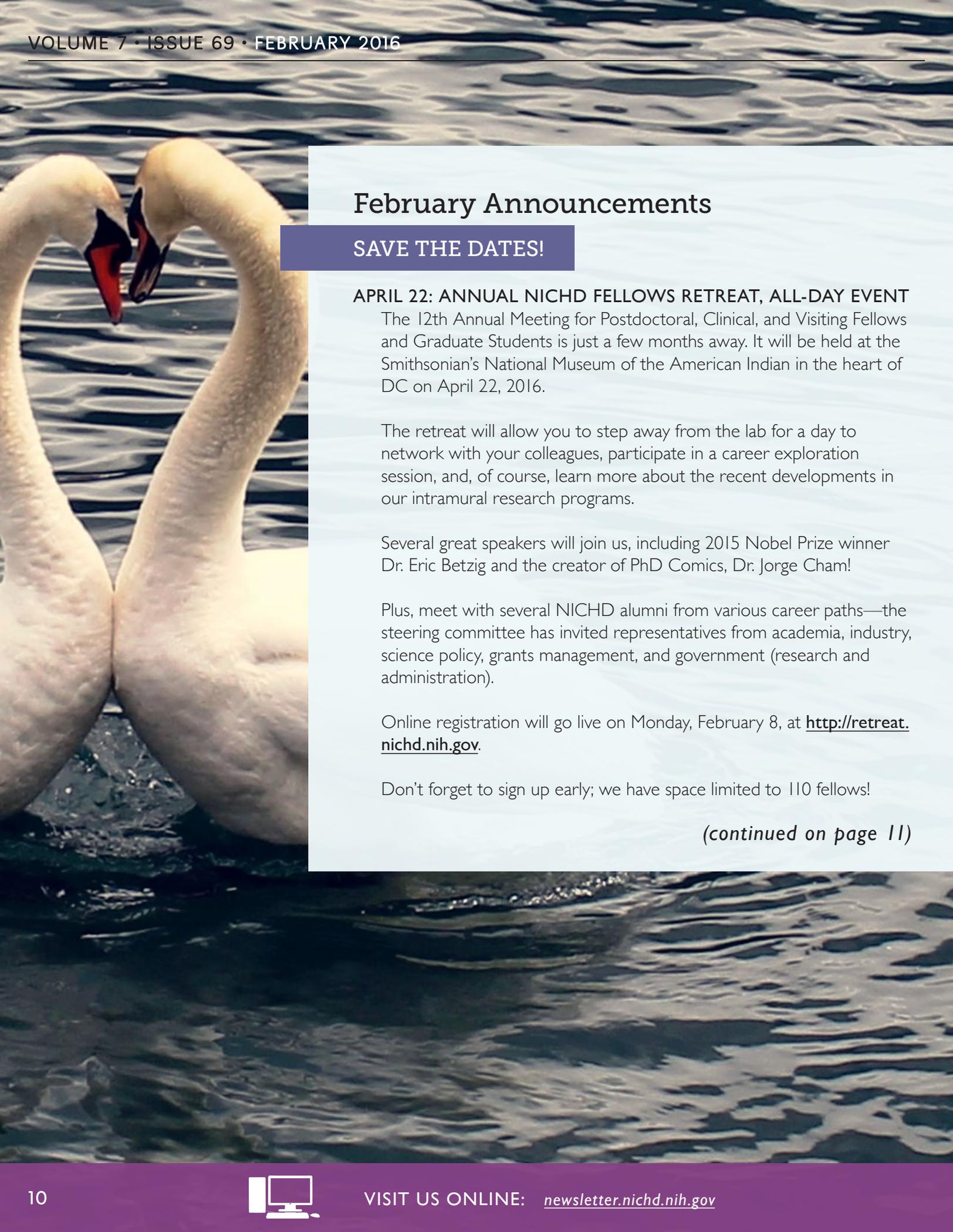
Life Outside Lab

"8,000 feet above sea level"

By Dr. Sudhir Rai, visiting postdoctoral fellow in the Levin lab

Location: Katra, Jammu and Kashmir, India
December 15, 2015

Dr. Rai took this photo on his way to the historic Hindu temple Shri Mata Vaishno Devi. On December 7, 2015, about one week before he took the picture, Dr. Rai married Dr. Shilpi Yadav (a geologist) in Mumbai, India. Upon marriage, they visited the popular temple. This photo is from their journey there together.



February Announcements

SAVE THE DATES!

APRIL 22: ANNUAL NICHD FELLOWS RETREAT, ALL-DAY EVENT

The 12th Annual Meeting for Postdoctoral, Clinical, and Visiting Fellows and Graduate Students is just a few months away. It will be held at the Smithsonian's National Museum of the American Indian in the heart of DC on April 22, 2016.

The retreat will allow you to step away from the lab for a day to network with your colleagues, participate in a career exploration session, and, of course, learn more about the recent developments in our intramural research programs.

Several great speakers will join us, including 2015 Nobel Prize winner Dr. Eric Betzig and the creator of PhD Comics, Dr. Jorge Cham!

Plus, meet with several NICHD alumni from various career paths—the steering committee has invited representatives from academia, industry, science policy, grants management, and government (research and administration).

Online registration will go live on Monday, February 8, at <http://retreat.nichd.nih.gov>.

Don't forget to sign up early; we have space limited to 110 fellows!

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February Announcements

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SAVE THE DATES!

MARCH 11: NICHD POSTDOC AND GRADUATE STUDENT ORIENTATION

(For new postdocs and graduate students)

Friday, March 11, 10 a.m. – 11:30 a.m.

Building 31, room 2A48

Led by the NICHD Office of Education, the orientation will highlight both NICHD and NIH-wide intramural resources for postdoc fellows and graduate students. Topics will include:

- » Career-planning tools
- » Grant opportunities for fellows
- » Ideas for presenting your science locally
- » Core facilities available to you

We will share information about key programs to support your professional development, complementing the mentored experience you will have at the bench. Don't miss this opportunity to meet fellows from other research areas and different buildings on campus.

To register, please contact Yvette Pittman (pittmanyv@mail.nih.gov).

MARCH 8: “HELPFUL HINTS, TIPS, AND LESSONS LEARNED FROM APPLYING TO THE NIH K AND PRAT FELLOWSHIP AWARDS”

Tuesday, March 8, 12:00 noon- 1:00 p.m.

Bldg. 10, Room 6N204

Offered by the NIAMS, NICHD, and NIDCR Intramural Training Offices

A panel of intramural postdocs who were each awarded a NIH grant (K99/R00, K22, and PRAT) will share their application process experiences—from why and when they applied for the fellowship to grant-writing techniques and how much time was dedicated to completing the application. Learn about grantsmanship training, guidance materials, and how a mentor's contributions and referee support can make the process easier.

To register, please contact Yvette Pittman (pittmanyv@mail.nih.gov).

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February Announcements

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SAVE THE DATES!

THREE-WEEK GRANT WRITING WORKSHOP— RESERVE YOUR SPOT NOW

Are you planning to apply for the K99/R00 Pathway to Independence Award in 2016? The upcoming deadlines are **June 12** and **October 12**, and we have an NIH grant-writing course that's just for you!

In collaboration with three other institutes, we are offering an NIH Grant Writing Course for fellows in May 2016. Led by Dr. Paula Gregory, this three-week course will help students prepare a successful NIH grant proposal, with special emphasis on the career transition “K” grant series. With high reviews from past participants, NHGRI has offered this course for several years, and as a result, many of their fellows have been awarded NIH grants!

In a small-group setting, classes will combine didactic presentations with group discussions, assignments, and proposal writing. A distance learning component will allow students to submit their writing between the in-person meetings, and they will receive edits and feedback.

Please contact Yvette Pittman at pittmanyv@mail.nih.gov, if you are interested.

NICHD only has four slots reserved. Below is the schedule for this on-campus workshop:

May 4 (1-4 pm) and May 5 (9-12noon)
May 12 (1-4 pm) and May 13 (9-12noon)
May 18 (1-4 pm) and May 19 (9-12noon)

MARK YOUR CALENDARS FOR THE “WRITE WINNING GRANT PROPOSALS” ANNUAL WORKSHOP

Thursday, July 14, 2016
9:00 a.m. – 1:30 p.m.

This workshop will address both practical and conceptual aspects that are important to the proposal writing process. Attendees will receive the “Grant Writer’s Workbook”—an invaluable, up-to-date reference tool for those who intend to write NIH grant proposals. It includes topics from how to prepare a compelling Specific Aims page to insights into which review criteria are most important.

For more information, please contact Yvette Pittman (pittmanyv@mail.nih.gov).

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JOIN US FOR THE NICHD EXCHANGE QUARTERLY MEETING: PERIVIALE BIRTH: CAUSES, CONSEQUENCES, COUNSELING, AND MANAGEMENT

Friday, February 12
6100 Executive Blvd., Room 5A01
3:00–5:00 p.m.



The causes, consequences, counseling, and management of women at risk for delivering at gestations of near the limits of viability remain some of the most challenging issues faced by obstetricians, neonatologists, and perinatal and neonatal nursing staff. Complex, ethically challenging decisions need to be made quickly. These are often carried out in an emotionally charged environment, in the face of limited or no evidence-based data, and in clinical settings that may be rapidly changing. The speakers will present some of these challenges and describe how the healthcare team and parents handle these complexities every day, starting from the obstetric wards and continuing through the hospital course of newborn infants in neonatal intensive care units and beyond.

- » Dr. Roberto Romero
Causes: Intrauterine infection/inflammation as a cause of delivery at periviable gestations
- » Dr. Rose Higgins
Consequences: Short and long-term outcomes at 22-26 weeks gestation—what is the evidence?
- » Dr. Tonse Raju
Compassionate counseling and evidence-based management—it takes a team!

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NHGRI & ASHG FELLOWSHIP OPPORTUNITIES

The National Human Genome Research Institute (NHGRI) and the American Society of Human Genetics (ASHG) are now accepting applications for the 2016 **Genetics and Public Policy** Fellowship and 2016 **Genetics and Education** Fellowship.

NHGRI & ASHG Fellowship Opportunities:

The Genetics and Public Policy Fellowship is designed as a bridge for genetics professionals wishing to transition to a policy career. This unique fellowship provides three separate types of policy experience: within NHGRI's Policy and Program Analysis Branch; on Capitol Hill serving elected officials in the Legislative Branch; and at ASHG in the non-profit science advocacy sector.

Please visit <http://www.genome.gov/10003979> to learn about the fellowship and how to apply.

2016 Genetics and Education Fellowship:

The Genetics and Education Fellowship is designed for genetics professionals with an advanced degree who are early in their careers and interested in the developing their expertise in national genomic literacy efforts, science education policy and program development. This fellowship provides professional experiences within NHGRI, ASHG and federal or not-for-profit educational agencies.

Please visit <http://www.genome.gov/27556152> for more details.

NHGRI and ASHG will accept applications for either fellowship submitted by **April 25, 2016**.

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CALL FOR APPLICATIONS: INTRAMURAL AIDS RESEARCH FELLOWSHIPS 2016

A major mission of the NIH Intramural Research Program and the Office of AIDS Research (OAR), in the Office of the Director, is to train the next generation of researchers to continue the battle to halt the AIDS pandemic. To expand our efforts to build this workforce, the Office of AIDS Research, the Office of Intramural Research, and the Office of Intramural Training & Education will provide competitive fellowships to encourage the recruitment of new researchers from other scientific disciplines to the broad field of AIDS research.

Postdoctoral trainees and graduate students in the NIH Intramural Research Program, both U.S. citizens and visiting fellows, whose work is directly applicable to HIV/AIDS research, will be eligible for support.

The application deadline for 2016 AIDS Research Fellowships is **February 26, 2016 at 5:00 pm (EST)**. Decisions will be announced in early April. Applications will be accepted from current or new graduate students and postdoctoral fellows (only IRTAs, CRTAs, and Visiting Fellows may apply). There are no citizenship restrictions. Individuals from underrepresented populations are particularly encouraged to apply.

The OITE will host an online information session on the fellowship on Tuesday, February 9, 2016 at 11:00 AM. This is a Q&A session to answer any questions you have about putting together the best application possible. Dr. Phil Ryan will be online to answer questions regarding the research plan, career development plan, and other application materials. Please register for the session here: <https://attendee.gotowebinar.com/register/5753777705546804737>.

For additional information and a list of required application documents, please visit: https://www.training.nih.gov/assets/2016_IARF_Call_for_Applications_508.pdf

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February Announcements

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VOLUNTEERS NEEDED FOR TAKE YOUR CHILD TO WORK DAY

On Thursday, April 28, NIH will celebrate its 22nd Take Your Child to Work Day. Last year we hosted over 3,600 students and had 150 different events. In the past, NICHD has put on many wonderful activities for the students, made possible by volunteers from the NICHD community. **We are currently recruiting volunteers to host new activities.** We are looking for activities such as lab tours, demos, or hands-on projects between 30 and 45 minutes long. The more interactive, the better!

If you are interested in participating, please contact Theresa Cruz cruzth@mail.nih.gov by February 19th.

February Events

WEDNESDAY, FEBRUARY 10

Three-minute-Talks (TmT) Workshop #2: Improvisation for Scientists

Led by the Alan Alda Center for Communicating Science, this workshop will teach you how to prepare a talk for a general scientific audience and explain the significance of your research as it relates to human health.

Restricted to TmT participants. To learn more about the TmT competition, please contact Yvette Pittman (pittmanyv@mail.nih.gov).

FRIDAY, FEBRUARY 12, 3 – 5 PM

NICHD Exchange Quarterly Meeting
Perivable Birth: Causes, Consequences, Counseling, and Management
6100 Executive Blvd., Room 5A01

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February Events

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MONDAY, FEBRUARY 22, 12 – 1:30 PM

“The Application and Interviewing Process for Medical and Graduate Schools”

(For postbacs)

Building 31, room 2A48

During this lunchtime session, NICHD postbacs will hear firsthand about applying and interviewing for graduate or medical school and life for the first two years as a student. Several panelists at various academic levels will answer questions about transitioning to professional school.

Topics may include qualities of a strong application, survival tips for the intense course load, key factors when choosing a program, a typical day in professional school, how to handle being wait-listed, and what panelists wish they had known or done differently before entering an MD or PhD program.

Pizza will be served.

To register, please contact Yvette Pittman (pittmanyv@mail.nih.gov).

FRIDAY, FEBRUARY 26, 10 AM – 12 PM

“21st Century Networking: LinkedIn and Beyond”

(For all fellows)

Led by Scott Morgan

As you are preparing for job searches, presenting yourself as professionally and effectively as possible is essential. Having a carefully thought-out LinkedIn profile is an important step to introducing yourself with clarity and skill. Always remember, the first thing a committee or hiring manager does after receiving your application is Google you!

This workshop will cover the necessary marketing and networking tools for a modern day scientist. With in-class exercises, topics will include resume building, creating an online presence with LinkedIn, professional speed dating, and negotiating with employees.

Please contact Yvette Pittman (pittmanyv@mail.nih.gov) to register.