Fostering Communication and Collaboration

The NIH Catalyst

A Publication for NIH Intramural Scientists

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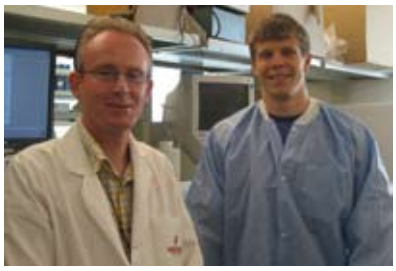
Therapeutic Drug Design

NIA is Sending TNF-α Inhibitors Where They are Needed the Most: the Brain

by Vanessa C. McMains (NIDDK), Special to The Catalyst

In today's highly specialized scientific community, usually one lab makes a therapeutic chemical, another lab analyzes whether it will bind to a specific target, still another lab tests the compound on cells for real effects.

The NIA Drug Design and Development Section does it all; and if the lab's recent research on TNF-α inhibitors continues to prove fruitful, researchers here are hoping for a breakthrough for the treatment of Alzheimer's, Parkinson's and other debilitating diseases of the central nervous system.



NIA's David Tweedie and summer student Ryan Short.

TNF-α, or tumor necrosis factor alpha, is implicated in a multitude of conditions, including rheumatoid arthritis and cancer, as well as many neurodegenerative diseases. And TNF-α lowering agents are being prescribed as therapeutic agents with somewhat mixed success.

What's new from NIA is the attempt to design drugs that can cross the blood-brain barrier to test the potential value of anti-TNF-α therapies for neurological diseases. Cell biologist and pharmacologist David Tweedie and medicinal chemist Weiming Luo lead this work under the guidance of Section Chief Nigel Greig.

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NIH must reinvent what it is best at

Translating Translational Research

by Eric Schaffer, Catalyst Writer-Intern

Translational research, with its mantra "bench to bedside and back," emerged as a top priority for the NIH intramural program in 2003, coupled with the new NIH Roadmap targeting the reemergence of clinical research as a major goal. The call was for focused communication between the laboratory and clinic to translate basic biomedical research into effective new therapies—and to bring clinical observations back to the lab.

The topic remains a hot one, featured on the cover of Nature on June 12, 2008, with an editorial and several news stories prominently featuring opinions about what the NIH is and isn't doing.

But the concept of "translational research" isn't so innovative or radical, says Alan Schechter, chief of NIDDK's Molecular Medicine Branch, one of NIH's most vocal proponents of translational research. The combination of basic and clinical research has been at the heart of the NIH mission since before the Clinical Center was in its blueprint phase.

What has happened along the way, Schechter said, is the vast success of basic research—spurred, in part, by the genetics revolution, bioinformatics and other lab techniques—which has lured many a promising scientist and physician to a life at the bench. The NIH has been a victim of its own success, too, now competing among the numerous research institutions that NIH helped to create for an ever-shrinking, highly qualified pool of scientists, especially physician-scientists, willing to undertake translational research.

As a result, despite the presence of the NIH Clinical Center—the largest hospital in the world dedicated to clinical research, purposefully placed at the geographic heart of the Bethesda campus—the NIH is having difficulty maintaining its prominence in the realm of translational research.

So what's a successful research institution to do? Essentially the NIH hopes to generate mechanisms to do more with what it has, to create ways to streamline the translation of benchwork into medical practice, all the while continuing efforts to recruit clinical investigators and to fill the Clinical Center to its capacity with patients.

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aerial photo by Duane Lempke

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From the Deputy Director for Intramural Research

Progress on New Trans-NIH Science


Michael Gottesman

A great deal of activity has taken place at the NIH over the past two years related to defining and developing grass-roots scientific projects that could draw resources and talent from all of the NIH Institutes and Centers. In the Office of Intramural Research, these activities have been facilitated by Paul Liu, Genetics and Molecular Biology Branch, NHGRI; Crystal Mackall, CCR NCI; and Charles Dearolf, Assistant Director, OIR. This is a progress report on some of these activities.

A one-day conference convened by Neal Young, Director of the Center for Human Immunology (CHI), and the CHI Executive Committee and Scientific Advisory Board, was held on June 23, 2008, to obtain input from outside experts on scientific themes and organizational structures for the CHI, to present the existing vision of the CHI to the general NIH intramural community, and to assess the level of interest among intramural investigators to participate. The major scientific theme that came out from the conference is a high-throughput and high-content description of the human immune system in health and disease. It is envisioned that an atlas of human immune system, or "immunome," will be generated, which can serve as the reference standard for basic and clinical studies of many diseases with immunologic components.

One important initial goal is to establish robust multidimensional platforms for large-scale data collection. Such platforms, once established, will serve as the basis for collaborations throughout the NIH campus on investigator-initiated projects relevant to human immunology. Space has been assigned to the CHI on the 7th floor of Building 10 and funding has been obtained from the OD and several ICs to establish the Center and fund it for at least the next five years.

A new trans-NIH project under development, the Bone Marrow Stromal Cell Transplantation Center (BMSCTC), would establish cell processing procedures to develop clinical-grade human bone marrow stem cells (BMSCs) for the treatment of patients with skeletal and non-skeletal diseases and disorders. Rapidly adherent BMSCs contain a subset of stem cells capable of regenerating bone, cartilage, myelosupportive stroma and adipocytes. BMSCs can be expanded *ex vivo* while maintaining their multi-potentiality and have been used in pre-clinical studies for bone regeneration. BMSCs have been proposed for treatment of non-skeletal conditions, as an immunosuppressive reagent, and as an adjuvant for hematopoietic stem cell transplantation. Thus, BMSCs are an easily accessible source of cells that can be used for a wide range of conditions.

A large number of investigators from 13 ICs have expressed interest in using BMSCs. The BMSCTC has been identified as one of the two "Manhattan Projects" by the IC Directors for further consideration. Establishment of this Center would entail the use of the NIH CC Department of Transfusion Medicine to expand BMSCs for clinical protocols initiated by investigators from all institutes. Look for an upcoming Catalyst article about the people involved and science planned at this Center.

The Systems Biology initiative sponsored two significant workshops. On May 12, six intramural scientists presented talks at a systems biology workshop designed to inform the community about ongoing research here at NIH. On June 26–27, the initiative sponsored a second workshop, "Computing the Future: Systems Biology and the NIH." A number of extramural scientists presented talks, then discussed with NIH leaders productive directions the NIH program could take. Afterwards, there was a recommendation that a Systems Biology Center should focus on the biological issue of mouse and human tissue-specific functional genomics and cellular reprogramming. This research will span the interests of a range of ICs, and will include studies into normal networks, disease networks, and cellular therapies.

The Systems Biology initiative, together with several intramural scientists and Scientific Directors, strongly endorsed the development of an RNA interference (RNAi) facility. RNAi is a powerful tool that allows investigators to determine the functions of genes systematically and in a relatively unbiased manner. The facility will provide intramural researchers with access to high quality, full genome RNAi screening in mammalian cells, as well as the necessary bioinformatics support. The facility will be housed at the NIH Chemical Genomics Center. NCI is taking the lead in funding the facility, with additional support from the OIR Director's Challenge Awards and from other ICs.

The NIH Director's Challenge Awards, previously described in The Catalyst, provided $500,000 to fund six investigator-initiated projects recommended by the Trans-NIH Imaging Initiative. Last November, the Imaging Initiative announced an NIH-wide call for proposals, requesting applications that would promote novel, interdisciplinary scientific collaborations that involve the development and application of new methodologies and approaches. The winning proposals include projects to develop a Cryo-PhotoActivation Localization Microscope, label-free imaging of biochemical processes in live cells and viruses using high-definition infrared micro-spectroscopy, and the development of a novel method for monitoring gene expression by magnetic resonance imaging.

I want to remind you that the OIR will expand the Director's Challenge Award program in FY2009. This fall, we will solicit ideas from senior and tenure-track investigators for exciting topics that deserve additional support. We will select several, then issue a call for proposals that both relate to one of the topics and bring together investigators from multiple ICs. Successful projects can receive two years of support for up to $250,000 per year.

—Michael Gottesman, DDIR
with Paul Liu and Charles Dearolf


Paul Liu


Charles Dearolf

COMMENTARY

Lessons Learned from a Stolen Laptop and Protected Health Information

Certain events have such impact that they qualify as life-changing. In my case, the theft of my government-issued laptop computer and the breach of personally identifiable information have made me understand the power and danger of computerized or digital information. I want to share with you lessons learned from this unfortunate experience.

Upon the theft of my computer in February, the NIH has renewed its commitment to computer security. However, many people at the NIH — from Bethesda to facilities across the nation and even those working in the field — are probably still at risk for compromising confidential information. Whether you are a scientist, administrator or member of the scientific and support staff, you might have access to private information. And even if your laptop is secure (i.e., encrypted), you might have other digital and paper records improperly protected.

Many pieces of personally identifiable information need to be protected beyond the obvious: names, addresses and social security numbers. For example, the first three digits of a ZIP code is considered protected health information as long as fewer than 20,000 people live within that region. Age "over 89" also is considered an identifier. Even a fax number without a name attached is covered by HIPAA (Health Insurance Portability and Accountability Act) Rules. The Privacy Rule, an extension of HIPAA, protects all individually identifiable health information held or transmitted by a covered entity or its business associate, in any form or media, whether electronic, paper or oral.

In talking with people over the past two months, I have come to realize that many have unintentionally violated these rules. To reemphasize: You must protect the scrap of paper reminding you to call a particular patient; you must protect the USB flash drive "stick" with digital information, such as contact lists or reminders to follow-up on an abnormal lab test; you must protect data on your laptop, PDA or BlackBerry.

The electronic age has created dangers with the incredible storage capacity on modern devices. A typical NIH laptop computer can easily contain the text contents of every U.S. phonebook and all associated personally identifiable information on those people. That computer would still have enough capacity to contain the Encyclopedia Britannica and multiple other references. A small USB stick can contain a single file with information on hundreds of thousands of patients. A PDA or BlackBerry further complicates the issue, for there is easy access to information through cashed Internet sites or saved e-mails messages.

Encryption of Windows-based laptops is now standard practice at the NIH. Macintosh laptops, PDAs and BlackBerrys currently cannot be encrypted to similar standards and thus can be riskier devices. The small size and portability of these devices make them easy targets for theft or misplacement and thus may compromise protected information.

Learning how to manage the information on portable electronic devices is difficult. Knowing when it is safe to delete information is not trivial. For example, an e-mail message received on a BlackBerry or laptop while away from the office may require action when the user gets back to the office. If it is important, one might be inclined to leave files on the BlackBerry or laptop for review until the issue is resolved. Will you remember to delete all files from the portable device a few days later when the task is completed? Synchronizing multiple copies of files is complicated when they are distributed on multiple devices. Also, do you have the most current version of the document? It can take hours to systematically delete data from USB drives while making sure you have copies of what should be saved.

Working with confidential information requires vigilance in other ways as well. Since the theft of my laptop, I have watched other people misusing electronic devices in public places. I have seen people reading confidential information on laptops in airplanes. I have met people asking for help to find lost PDAs or BlackBerrys. Even though none of these behaviors was done with malicious intent, it is much too easy to compromise the integrity of information stored on portable electronic devices.

For all of the above reasons, NIH may want to consider establishing a policy advisory group under the sponsorship of the NIH CIO and the three functional NIH Deputy Directors to better educate the NIH community on how to recognize sensitive information and how to manage and safeguard that information. Given the turnover of staff, this is — and will be — an ongoing need.

We must continue to improve our handling of protected health information and other confidential information. Achieving those goals depends on all of us, as individuals, working to support and implement privacy standards. I hope others can learn from my experience. I can guarantee that it is better to learn such lessons vicariously than through personal experience.

For more information, please review the following documents:

* www.hhs.gov/ocr/privacysummary.pdf
* www.hhs.gov/ocr/hipaa/guidelines/incidentalud.pdf
* www.hhs.gov/ocr/hipaa/guidelines/research.pdf

Andrew Arai
Senior Investigator
NHLBI Laboratory of Cardiac Energetics

Protecting Privacy: The Cost of Identity Theft

Privacy Awareness Training is mandatory for anyone working at the NIH. The online course takes approximately 30-60 minutes and must be completed by September 30. Refer to <http://irtsectraining.nih.gov>.

Protecting privacy is involved intricately in NIH achieving its mission, for if privacy is breached, the public may wish to discontinue their involvement in NIH clinical studies. The training course covers ways to protect your own privacy, as well as the privacy of your co-workers and the public.

Identity theft now surpasses drug trafficking as the number one crime in America, according to the Bureau of Justice Statistics. The Bureau's 2005 report on identity theft found that approximately 1.6 million households experienced theft of an account other than a credit card (such as a banking account), and 1.1 million households discovered misuse of their personal information (such as social security number). The average amount lost in these households was $1,620. The Identity Theft Resource Center reports that it can take between 330 and 600 hours to recover from this crime, and many individuals spend up to one year struggling with their identity theft case.

The Exit Interview: Questions for (former!) NHGRI Director Francis Collins

Francis Collins, the director of the National Human Genome Research Institute, stepped down on August 1 to explore writing projects and other professional opportunities. Collins served as NHGRI's director since April 1993. Widely respected, he led the Human Genome Project to its successful conclusion in 2003, and subsequently initiated and managed a wide range of projects that built upon the foundation laid by the sequencing of the human genome.

Collins has appeared in over 20 issues of The NIH Catalyst (which also made its NIH debut in 1993) and agreed to an "exit" interview.

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What unique roles or opportunities do you see for the NHGRI and NIH intramural programs in the area of human genetics?

There are many terrific opportunities here. Many of them relate to individual research projects, but there are also some larger collaborations underway that could be quite groundbreaking. For example, Julie Segre and Eric Green are organizing a major program in the human skin microbiome, taking advantage of the combined resources of the Clinical Center and the NIH Intramural Sequencing Center (NISC). Colleen McBride and Larry Brody have organized a fascinating program called the Multiplex Project, which is studying how 1,000 people seen at Henry Ford Hospital in Detroit react to being given information about their risks for several common diseases—a real test of the personalized medicine approach to prevention. Les Biesecker and Eric Green of NHGRI are collaborating with investigators at NHLBI in a program called ClinSeq, which is applying high-throughput sequencing to discover new and interesting genetic contributions to cardiovascular disease. And I am particularly excited about the possibility that the NIH intramural program could formalize a powerful and integrated program in therapeutics for rare and neglected diseases.

Collins at a public symposium at the Smithsonian Institution celebrating completion of the Human Genome Project, 2003. Credit: Ernie Branson

Taking advantage of the remarkable facilities of the NIH Chemical Genomics Center (NCGC), investigators with an interest in a particular disease are already provided with the ability to develop small molecule research probes for almost any target. Recent exciting examples include Gaucher's disease and schistosomiasis. What is needed now is to expand the medicinal chemistry capabilities to turn these research probes into clinical candidates, and then the Roadmap-funded RAID program can pick up the most promising compounds and take them to the next step of toxicology testing and GMP synthesis.

[Also] the Clinical Center is the perfect place to conduct Phase 0, 1 and 2 trials for these new therapeutic approaches for rare and neglected diseases. The NIH Intramural program may be the only place in the world that can do all of this within one facility, and my hope is that NIH can now push that agenda forward with great intensity.

One of your many strengths as NHGRI Director has been your close attention to the ethical, legal and social implications of genome research. Perhaps as advice to the next director, what challenges remain, and what successes in these realms to you see possibly coming undone without vigilance?

Collins at a 2003 press conference announcing the discovery of genetic mutations that cause Hutchinson-Gilford progeria syndrome, one of his many areas of expertise. Credit: Maggie Bartlett

The ELSI [Ethical, Legal and Social Implications] program has been one of the most important experiments conducted by NHGRI, as the existence of such a program has led to the recruitment of a remarkable cohort of ethicists, lawyers, social scientists, theologians and others to focus on the potential challenges presented by the rapidly accelerating pace of genomic research. A major accomplishment has been the signing of the Genetic Information Nondiscrimination Act (GINA) by President Bush on May 21, 2008—the culmination of 13 years of legislative effort by many dedicated experts, fueled by a foundation based on ELSI research.

But there are many challenges still remaining: to name just a few, the regulation of genetic testing, the arrival of direct to consumer marketing of genome analysis, concerns about privacy and informed consent, the issue of human enhancement, and the optimum use of intellectual property claims.

What are some of the big questions that biomedical science needs to answer? Along these lines, what kinds of joint ventures or trans-NIH initiative do you envision among the NIH ICs?

Now that we have the genome sequence, we need to figure out how it functions and how that is affected in health and disease. I counted up the major projects that NHGRI is leading to address that question (many of those in collaboration with other ICs), and there are 19 of them! They range from very basic programs such as the Encyclopedia of DNA Elements

(ENCODE) to a very specific and intense approach to cancer, the Cancer Genome Atlas (joint with NCI).

Was there a big difference between starting an Institute and maintaining it?

Oh, yes. One of my biggest and most exciting tasks when I arrived in 1993 was to start the NHGRI intramural program. Many people at that time said that it would be impossible to recruit senior leaders from the outside to come to NIH and serve as Branch Chiefs. But because of the unique opportunity to start a flagship program in the rich environment of the intramural campus, it was possible to bring in phenomenal leaders like Jeff Trent, Bob Nussbaum, Jennifer Puck, Max Muenke and Eric Green. Getting strong leaders right from the beginning, and turning them loose to set up one of the most highly productive and competitive programs in human genetics in the world, has made the maintenance of the program much easier—though one can never be complacent!

Collins at a 2002 press conference to announce the analysis of the mouse genome. Credit: Maggie Bartlett

What do you rank as one of your (or your institute's) top achievements?

I'd have to point to the completion of all of the goals of the Human Genome Project, ahead of schedule and under budget, in April 2003. But since then, another major achievement has been the success of the HapMap project in defining the nature of human genetic variation, leading to the discovery of nearly 200 genetic variants associated with common diseases like diabetes and heart disease.

Is there anything you wanted for NIH but just couldn't quite pull off?

In order to really understand gene-environment interactions, a population-based prospective cohort study is badly needed in the U.S., with at least half a million people enrolled. With other experts, I tried to make the case for this, starting about four years ago. But other than some pilot work, this has not received the necessary momentum to get off the ground. Almost everyone agrees this project (sometimes known as the American Genes and Environment Study, or AGES) would be incredibly valuable, but the steep price tag has made it difficult to get it started.

What should NHGRI look for in your replacement? Perhaps a polar opposite, a tuneless hack afraid of engine grease?

Someone who is broadly familiar with the science of genomics, who is not afraid of taking risks, who likes working collaboratively with lots of different experts, and who has a passion for seeing basic science discoveries turned into major advances for human health.

You wrote that you may "need greater latitude than my current position allows to pursue other potential positions of service without encountering any possible conflicts of interest, whether real or perceived." Did the new conflict of interest rules play a role in your decision to leave? Is the NIH hurting itself with such rules?

As an NIH institute director, I believe it is very important not to participate in any activities that have even the slightest appearance of any conflict of interest, particularly given the current climate of Congressional scrutiny and public concern. I understand, therefore, why the current conflict of interest rules have to be quite strict for senior leaders. As I came to the decision that it was time for me to seek other opportunities to serve, I concluded that my search process would be best conducted as a private citizen. And so I will become unemployed on August 1, and will spend several months exploring other opportunities without the risk of jeopardizing myself, NHGRI or NIH.

Aside from book projects, what other adventures do you have planned? Over the years you have worked in Africa with your daughter. Will you be making more mission trips?

I will become an unpaid Special Volunteer at NIH, in order to keep my lab going and allow my talented research team in Building 50 to continue the superb work they are doing on diabetes, progeria, and asthma. Other adventures will depend on what the next calling turns out to be. And I honestly don't know the answer to that right now!

Can all the CDs from the skits at the NHGRI retreats go on eBay to the highest bidder now?

Uh, let's hope that those are hidden away somewhere, only to be revealed after I am REALLY retired. And that could be quite a while! ■

Collins at a NHGRI retreat, with his guitar and surrounded by children, a typical scenario. Credit: Maggie Bartlett

The Training Page

From the Office of Intramural Training and Education: Job Applications, Made Easy

by Caroline Small, OITE Communications Intern

If the thought of applying for a job makes you queasy, the Office of Intramural Training and Education (OITE) has a series of workshops for you. To help trainees jumpstart their job search, starting this fall the OITE will offer curriculum tracks focusing on industry jobs, academic jobs, and how to make career decisions. The aim is to provide the tools you need to take your next career steps.

Lori Conlan, director of the Office of Postdoctoral Services, says that industry careers are "a black box" to many people at the NIH. OITE's industry job search series is designed to shine a light into that box. Monthly workshops will help trainees with everything from understanding the difference between biotechnology and big pharmaceuticals, to writing a résumé and cover letter that will get attention, and to negotiating a salary offer.

The academic job track focuses on developing research and teaching statements, deciding where to apply, and navigating the interview process. Because applications for academic jobs are generally due in late fall, the initial sessions in this track will be concentrated during September, October and November. In the spring the series will address handling job offers, including evaluating and negotiating offers and setting up an academic lab.

A third, more general, track is in development. The Career 101 series is designed for trainees who are making career decisions. It will help them evaluate their skills and values and explore career options, and will continue with general job search tips, suggestions for improving CVs and résumés (yes, there's a difference), and a session on interviewing skills.

The OITE also runs workshops on improving communication skills, from writing a scientific manuscript to presenting a scientific talk or poster to improving spoken English. The goal of NIH training programs is not only to help trainees develop strong scientific credentials, but also to help them choose a career path that dovetails with their interests and skills and to provide them with professional skills that will ensure their success.

The new OITE workshop series will contribute to generating a confident trainee population that is comfortable with its career decisions and is highly sought after by employers in all sectors. For more information on programming in the OITE, visit www.training.nih.gov. ■

From the Fellows Committee: Essential Knowledge of Animal Research Policies for Fellows — An online resource, in plain English

by Sudha Chennasamudram (FDA CBER), FelCom Publicity Subcommittee

Many key questions in the biomedical sciences can be addressed only through studies involving a complete functional organism, making animal research an indispensable tool. Researchers conducting such studies are obligated to ensure the highest standards of animal care and use.

Not only do ethical and legal accountabilities demand proper and respectful handling of laboratory animals, but reliable results can be obtained only under adequate and standardized care, minimizing all potential distress. Thus, it is not surprising that there is a vast amount of information on standards and regulations concerning animal research. A new document now available on the NIH Fellows Committee (FelCom) website is designed to make NIH animal use policy more accessible to fellows who may be new either to NIH or to animal research. It provides both the basics of legal/technical issues and links to more in-depth information.

The document was drafted by Jan Gutermuth, the FelCom liaison to the Animal Research Advisory Committee (ARAC), which develops NIH animal care and use program policy. ARAC is administered by the Office of Animal Care and Use (OACU), which oversees the use of animals in the NIH intramural program and ensures compliance with federal laws and regulations, often setting national and international standards.

As a visiting fellow in the laboratory of Stephen Katz (Dermatology Branch, NCI) investigating mechanisms of immune tolerance in a mouse model of autoimmunity, Gutermuth recognized the need for easily accessible information on animal use and policies, especially for international fellows, who might find that the policies and regulations in the United States vary from those in their home countries. The language is unambiguous for researchers whose first language is not English. Gutermuth worked in collaboration with OACU Director Jim Taylor and OIR Deputy Director Richard Wyatt.

As the FelCom liaison on ARAC, Gutermuth serves as both a source of information and a voice for fellows with questions or concerns about animal research policies. Contact him at <gutermja@mail.nih.gov>.

"Essential Knowledge on Animal Research in the NIH Intramural Research Program" is available at <http://felcom.od.nih.gov/materials/Essentials%20of%20animal%20research%20at%20the%20NIH.pdf>.

In-depth information on animal care and use policies and regulations can be found at <http://oacu.od.nih.gov>. ■

AAALAC, the Association for Assessment and Accreditation of Laboratory Animal Care International, made an accreditation site visit from June 9 to 13. AAALAC's report was glowing, noting that we run a spectacular program. Congratulations to the Office of Animal Care and Use and all NIHers who take animal care and wellbeing seriously.

The Awards Page

Intel Science Winner Has NIH Roots

by Eric Schaffer, Catalyst Writer-Intern

Each year, the Intel Science Talent Search drives thousands of high school students from across the country to develop innovative research projects at cutting-edge laboratories in a quest to achieve the oldest and most prestigious award for young scientists in America.

This year's winner of the "baby Nobel" is Shivani Sud, an aspiring geneticist from Durham, N.C., whose lifelong interest in cancer research has led her to spend every summer since eighth grade at the bench: at Temple University in 2004 and 2005; at an NCI lab in 2006; and at Duke University in 2007.

Sud won the top prize for a screening procedure that could change the way early-stage colon cancer is diagnosed and treated. Colon cancer, the second leading cause of cancer-related death, has a tendency to recur after surgery, and varying chemotherapies for the recurring cancer can have different success rates. Sud analyzed a publicly available data set that included RNA fingerprints of colon cancer samples and recurrence rates after surgery and chemotherapy, and came up with a 50-gene predictor for patient response to an array of chemical agents.

Testing this predictor on cell lines, she was able to ascertain that the assay could improve success rates of treatment and spare patients the burden of chemotherapy in cases where it wouldn't be useful.

At NIH, Sud worked with Maria Tsokos, a senior investigator in NCI's Laboratory of Pathology, whom she credits for helping her to focus her interests on gene signatures. This, she said, led to her award-winning research at Duke under the guidance of Anil Potti, an assistant professor in the Department of Medicine and Institute for Genome Sciences and Policy.

Sud and her Duke lab hope to soon publish her research and move it into phase-one clinical trials. Sud herself wishes to expand her work: Concerned that her method relies on microarray technology, which is hard to perform without advanced equipment, she wants to develop a similar assay that relies on simpler PCR technology.

The Intel Science Talent Search, sponsored by Westinghouse from its creation in 1942 until 1998, singles out amazing young people who show incredible promise for scientific research. Shivani Sud is no exception. She attended a public high school whose science program, she said, "could use a little help." So on her own, she sought opportunities in cancer research labs.

Driven by her fascination with the enigma of cancer and her personal experience of a family member's struggle with cancer in her childhood, Sud would spend late nights at the lab trying to perfect her screening method. She didn't think to submit her research to Intel, she said, until a lab mate suggested giving it a shot.

Shivani Sud with Craig Barrett, Intel Chairman of the Board

For her first-place prize, Sud has a received a $100,000 scholarship. She will attend Princeton this fall and intends to pursue a career in biological research. She aims to earn a PhD/MD because it would offer her more opportunities for clinical research.

A list of the ten Intel science winners is at <http://www.societyforscience.org/sts/67sts/winners.asp>. ■

NIH Director's Pioneer Award Symposium Expands:

Two-Day Event Will Showcase Variety of Highly Innovative Research, Promote Interaction

The fourth annual NIH Director's Pioneer Award Symposium is on September 22–23 at Natcher Conference Center (Building 45), extended to two days this year to ensure ample opportunity for interaction with Pioneer and New Innovator award recipients. The agenda, posted at <http://nihroadmap.nih.gov/pioneer/symposium2008>.

NIH Director Elias Zerhouni will open the symposium and announce the fifth cohort of Pioneer Award recipients, scientists taking bold and imaginative approaches to important biomedical problems, and the second group of New Innovator Award recipients, similarly innovative new investigators who have not yet received R01 or comparable NIH grants.

Speakers and their topics are:

* Emery Brown, Mass General Hospital/MIT, "Imaging Loss of Consciousness Under Anesthesia"
* Frances Jensen, Children's Hospital Boston/Harvard Medical School, "Understanding Cognitive Consequences of Early Life Epilepsy"
* Takao Hensch, Children's Hospital Boston/Harvard Medical School. "Epigenetic Control of Critical Period Plasticity"
* Thomas Clandinin, Stanford University, "Toward a Genetic Dissection of Visual Computation"
* Mark Schnitzer, Stanford University, "New Paradigms for in vivo Microscopy in Live Subjects"
* Gina Turrigiano, Brandeis University, "Mapping the Location of Synaptic Proteins Using Super-Resolution Fluorescence Microscopy"
* Lisa Feldman Barrett, Boston College/Harvard Medical School/Massachusetts General Hospital – "What Is an Emotion?"
* Peter Bearman, Columbia University, "Social Dynamics and Autism Prevalence"
* Marshall Horwitz, University of Washington School of Medicine, "Inferring Cell Lineage from Somatic Mutations"
* James Collins, Boston University, "A Network Biology Approach to Antibiotic Action and Bacterial Defense Mechanisms"
* Rustem Ismagilov, University of Chicago, "Space – The Final Frontier"
* Margaret Gardel, University of Chicago, "Emergent Behaviors of the Cellular Cytoskeleton"

Attendance is free; registration is not required. Activities of the symposium are supported in part by the Foundation for the National Institutes of Health through grants from Booz Allen Hamilton and the Ewing Marion Kauffman Foundation. ■

TNF-α Inhibitors

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Nigel Greig and David Tweedie

Double-edged sword

TNF-α is a cytokine released by immune cells that induces inflammation. TNF-α is needed to provide a protective action to fight infections and to induce repair mechanisms to heal damaged tissues. TNF-α is released by microglial cells, which are brain-resident macrophage-like cells and the main line of immune defense in the central nervous system.

But TNF-α can be a double-edged sword. Although needed for proper immune responses, too much TNF-α for too long can exacerbate conditions such as Alzheimer's and Parkinson's diseases, Tweedie said. Once TNF-α is released in the brain, it can activate surrounding microglial cells, which causes them to unleash more TNF-α, creating a perpetuating cycle.

Whether too much TNF-α is the cause or the effect of various diseases remains to be determined. What is known, Tweedie said, is that "too much TNF-α makes the environment in the brain much more hostile for the neurons."

State of TNF-α therapy

Other researchers have already demonstrated that reducing the biological effects of TNF-α has beneficial effects in the clinical setting of Alzheimer's disease. TNF-α can be captured by biological therapeutic approaches before it promotes inflammation; one such example is the biological agent Enbrel® (Etanercept). Alzheimer's patients treated with the drug demonstrate measurable improvements in cognitive abilities within a matter of hours. These treatments are a strong indicator that TNF-α is a real effecter in the progression of Alzheimer's disease, Greig said.

But there's a downside: This type of drug therapy cannot cross the blood-brain barrier and must be injected into the spine at regular intervals. This kind of invasive treatment can be painful for the patient, not to mention costly. (One treatment involves injecting patients and then placing them upside-down.)

Tweedie's approach uses analogues of the small molecule thalidomide to inhibit TNF-α. Specifically, he adds sulfur groups to the rings of thalidomide to generate thiothalidomides in order to assess potential increases in the drug's effectiveness. Unlike current biological treatments in clinical trials, a major advantage of thalidomide is its ability to cross the blood-brain barrier.

Thalidomide and its analogues appear to work by destabilizing the messenger-RNA levels of TNF-α instead of binding to the secreted protein. "Rather than capturing TNF-α before it hits its target, we are essentially turning off the faucet at the source," said Greig.

Nevertheless, some TNF-α is needed for normal function in the body. "Just enough is a good thing," said Tweedie. "Also if we switch off the synthesis of TNF-α too soon, it may cause more harm than good to the organism. We need to understand the therapeutic window for a given situation to be able to minimize those potential dilemmas."

The purpose of the inhibitors is to down-regulate the over production of TNF-α, not prevent its action in the body entirely. Tweedie's group has shown that their inhibitors do not completely prevent all TNF-α from being synthesized and secreted. This fact could mean less potential side effects from the drugs if used in a clinical setting.

Thalidomides' infamy... and legacy

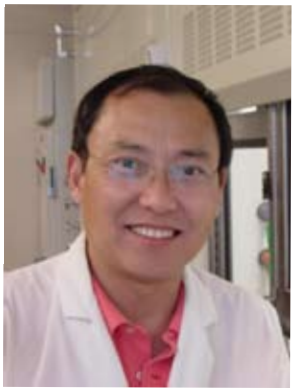
Thiothalidomides seem like the perfect candidates for therapeutics, but their parent compound has a tarnished reputation. Over 10,000 children were born with severe birth defects during the late 1950s and early 1960s from thalidomide prescribed to their mothers to relieve morning sickness during pregnancy. The drug was banned shortly afterwards.

Researchers from Israel discovered in the early 1960s that thalidomide reduced inflammation, but it was not until the 1990s that TNF-α was discovered as the target. Later the drug was approved as a treatment for certain types of cancer and an inflammatory condition caused by leprosy, yet tight regulations remain on who can get access to these meds.

These regulations seem less worrisome to Tweedie's cause, for the NIA is looking to use thiothalidomides to treat people with diseases associated with aging, at a time when women are past child-bearing age.

Greig's lab has found so far that the analogues with most promise for use as therapeutics are 3'6'-dithiothalidomide, which has two sulfur groups, and 3,2',6'-trithiothalidomide, which has three added sulfur groups to the thalidomide backbone. These compounds work to lower TNF-α levels 20 to 30 times better than thalido-

The new Biomedical Research Center in Baltimore, home to Greig's lab and many other NIA and NIDA labs.



NIA Chemist Weiming Luo

mide, without any toxicity.

Thalidomide shows no anti-TNF-α activity at the low concentrations that are effective for the analogues. Direct measures of the analogues effectiveness show reductions in the TNF-α RNA and secreted protein levels in a range from 28 to 92 percent, depending of the concentration of drug used. Strong supportive results like these indicate great potential for these candidates.

Drug discovery, one-stop shopping

The creation of new drug compounds requires many levels of interaction between the scientists. Luo and Tweedie discuss which analogues they will make based on the success of the previous compounds. Luo synthesizes the compounds in the chemistry lab and verifies their structure with techniques such as chromatography, mass spectrometry and nuclear magnetic resonance. Once the verification is complete, he passes the drugs onto Tweedie.

Tweedie initially tests his thiothalidomides for toxicity in vitro using mouse macrophage-like cells. He uses various assays to judge for cellular stress and viability based on the presence of cytoplasmic proteins detected in the culture media in which the cells are grown.

Once he finds inhibitors that cause minimal cell stress, he tests the effectiveness *in vivo*. Tweedie gives the TNF-α inhibitors to rodents, then he exposes the animals to LPS, which is a component found in bacteria cell walls that cause a large activation of the immune system. He checks for reduced levels of TNF-α RNA and secreted protein in the circulating blood plasma and in the central nervous system of rats treated with the inhibitors, for these markers indicate the effectiveness of the inhibitor.

Through a whole series of experiments, Tweedie determines the most effective concentration of each thiothalidomide for inhibition of TNF-α. By combining the toxicity data with the biological activity data, Tweedie "is the filtering system and [the one] who decides which drugs will go on to the next step," Greig said.

Candidate inhibitors are then sent to NIA collaborators who study various aspects of Alzheimer's disease in either *in vivo* or *in vitro* models systems. They test the drugs for positive effects in the animals on a cellular level and on a cognitive level, acting essentially as "rodent psychologists."

Based on the success of the disease models, Tweedie and his collaborators will choose one of the drugs that act on a specific central nervous system disease to submit a package for patent rights. Although the thiothalidomides are disease non-specific in their action, Greig hopes they will target Alzheimer's or Parkinson's disease, for there is a portion of the population in real need of treatments.

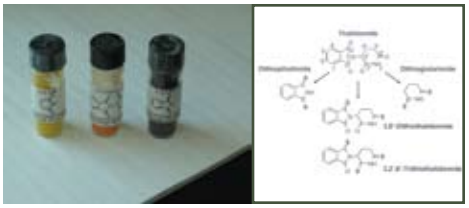
Greig describes his lab as "an integrated assembly line because of the daily interactions and constant feedback." This type of interaction is what makes the lab so successful, he said, and is also responsible for the quick turn-around time between designing a chemical to determining whether it will be potentially useful as a therapeutic.

In addition to the sulfur-modified thalidomide, other TNF-α inhibitor analogues are in the works. But perhaps only Tweedie decides if they make the cut. ■

Further reading:

"TNF-α Inhibition as a treatment strategy for neurodegenerative disorders: new drug candidates and targets," Tweedie et al., Current Alzhheimer Research, 4: 378-385 (2007).

"Thiothalidomides: Novel isosteric analogues of thalidomide with enhanced TNF-α inhibitory activity," Zhu et al., Journal of Medicinal Chemistry, 46:5222-5229 (2003).



Tweaking thalidomide.

Photographs by Vanessa McMains.

Letter to the Editor: 508 Compliance

Dear Catalyst:

With regard to the article on 508 Compliance in the May-June issue of the Catalyst, there is little question that images generate the greatest challenge to making online information accessible to the visually impaired. As a microscopist, I feel that some images may be well described by a few sentences or short paragraph of text, while others — for example, micrographs or MRIs — would require many pages of text to describe in the graphic sense.

After a quick Google search, I learned that devices have been developed to allow the blind to feel 2D graphics or hear colors. One such device, described at <http://www.nist.gov/public_affairs/releases/visual_display.htm>, was developed by NIST, and was briefly mentioned in a 508 Compliance training session I recently attended. It seems to me that even a complex image could be processed to simplify it sufficiently so that it could be read by such a device and still convey a great deal of information.

I hope that devices such as the one developed by NIST will soon be made widely available at reasonable cost to the visually impaired. By all means, they should be made available to the visually impaired at the NIH and all other federal government agencies. Are any readers aware of movement in this direction?

Mathew P. Daniels, Ph.D.
danielsm2@nhlbi.nih.gov
Director, Electron Microscopy Core Facility, NHLBI

Editor's note: DHHS has posted a Section 508 checklist for PowerPoint documents, at <http://www.hhs.gov/web/policies/checklistppt.html>.

Translational Research

continued from page 1

Key to this will be removing the barriers to *clinical* research, both at an institutional and investigator level. And in the process of self-analysis, even the wording of "bench to bedside" is under scrutiny, for clinical research starts with patients, which feeds bench work. There's no hierarchy; all researchers are equal players in the endeavor to make patients well. This concept must be inherent in any translational research program to recruit researchers, said those interviewed for this article.

The effort may serve as a model for other biomedical research facilities also faced with a changing landscape of clinical research.

Translational roadblocks

The loss of focus on translational research is no trivial matter. "Many in Congress and the public believe that NIH is not delivering new therapies to a degree consistent with the money going in," Schechter said. Whether that's true or not, he added, an effective way to produce new therapies is through translational research, which, when you get right down to it, "is a synonym for clinical research," he said.

On the surface, translational research is straightforward: Scientists work on a treatment at the bench; clinicians test it at the patient's bedside; and observations of patients go back to the lab to inform further research. But the devil's in the details.

Alan Schechter, chief of NIDDK's Molecular Medicine Branch, one of NIH's most vocal proponents of translational research.

Cliff Lane, NIAID's clinical director, is leading an Intramural Working Group subcommittee, comprising the entire Medical Executive Committee, investigating these details. The initial findings from the group are expected by summer's end. Lane said there is a "sentiment... [among NIH researchers] that it is increasingly difficult to do clinical studies," and that his group was identifying elements that "provide less 'value-added' than desired."

In meeting with patients and doctors in recent months, the subcommittee has focused on four elements for initial study: issues concerning the availability of resources, the scientific review process, the institutional review board, and technology transfer. The subcommittee's initial recommendations will focus on improvement to the IRB process.

Clinical Center Director John Gallin added two more elements that PIs often relay to him: conflict-of-interest issues and a comparatively low salary cap for "hot shot" physicians expert in medical subspecialties.

But turning basic research into applicable therapies is very much feasible, said Minkyung Song, program director at NCI's Developmental Therapeutics Program and co-founder of NIH's Translational Research Interest Group (TRIG). Strategies for addressing clinical relevance of model systems are becoming available, and high-quality human specimens are easier to attain.

Transition, by the numbers

Faced with obstacles, and enticed by advances in basic research, scientists have gravitated to the bench. Since the 1970s, the number of clinical investigators at NIH and across the country has steadily dwindled while the total number of researchers has grown.

There is a "sentiment... that it is increasingly difficult to do clinical studies," said Cliff Lane, NIAID Clinical Director, who leads a group identifying elements that "provide less 'value-added' than desired."

There were 14,479 U.S.-based physician-scientists in 1998, down from 18,535 in 1983, a 22-percent decline, according to a 2002 article in Nature by Ajit Varki and Leon Rosenberg, "Emerging opportunities and career paths for the young physician-scientist." Also, the percentage of physicians engaged in research shrank from 4.6 percent in 1985 to 1.8 percent in 2003, according to a 2005 article in JAMA by Timothy Ley and Rosenberg, "The Physician-Scientist Career Pipeline in 2005."

Rosenberg, of Princeton University, documented that the number of NIH research project grants awarded to PhDs, to MDs and to MD/PhDs in 1970 were somewhat comparable: 2,000 (53% of the total) and 1,200 (43%), respectively. This changed markedly by 1997: 5,200 (~70%) and 2,100 (25%), respectively. These figures are from a 1999 article in the Journal of Clinical Investigation, "The physician-scientist: An essential—and fragile—link in the medical research chain."

Closer to home, since 2001, as the number of tenured investigators at the NIH climbed from 907 to 943, the number of tenured PIs on clinical protocols decreased from 192 to 156, according to data compiled by the Clinical Center's Office of Protocol Services. Similarly, the number of tenure track PIs listed on clinical protocols has fallen from 48 to 18. One highlight, however, is the increase in individual principal investigators writing clinical protocols: 461 investigators in 2001, and 547 in 2007, reflecting an increase in the number of staff clinicians writing protocols.

No lab is an island

In order to make more effective use of the successes of basic research, NIH has to encourage scientists to move laboratory discoveries into the clinic more quickly, and to translate clinical research data back to the laboratory, said Song.

To accommodate this, Song helped create the TRIG in 2007. The TRIG fosters communication between basic and clinical scientists across disciplines and guides the training of a new generation of translational researchers. This scientist-run group aims to accelerate application of research discoveries towards proof-of-concept clinical studies and the development of personalized treatments, predictive or monitoring tools, improved models, and safer and more effective therapeutics through the strengthening of communication networks within NIH.

Working in a lab shouldn't feel like living on an island, said Song. The establishment of forums for sharing resources, tools and information is the most important thing NIH can do to promote translational research. "It's timely to integrate and coordinate efforts in both the intramural and extramural programs," Song said. "As early

Min Song of NCI is a co-founder of the NIH Translational Research Interest Group.

as possible, we need to confirm laboratory results in real human specimens."

New and ongoing efforts

The TRIG's first major event was in May and exceeded expectations with a large turnout of about 100 researchers at Natcher for what was a two-hour huddle on the status and necessary future course of translational research at NIH. Cutting to the chase, OIR Deputy Director Richard Wyatt opened the meeting with a talk provocatively titled "Challenges of Translational Research at the NIH."

A "fund of knowledge" has been accumulating since the 1970s. Programs such as the Human Genome Project, which have accumulated enormous bodies of knowledge but have seen little clinical application, are an investment that will soon pay off, said OIR Deputy Director Richard Wyatt.

A top challenge is to fill the Clinical Research Center with outstanding science projects; it is now running at about two-thirds its capacity, Wyatt said. Steering clear of mandates—just two additional physician-scientists for each IC with an intramural program would likely fill the CRC and then some, according to NIAMS Director Stephen Katz, who gave a report on the Six IC Directors' Working Groups on the CRC at a meeting of Scientific Directors in June—Wyatt said the NIH must foster an environment that makes translational research more enticing.

A step in that direction is the new professional designation, Assistant Clinical Investigator, to mentor and enable clinical research careers. Other ongoing and evolving programs are:

* **ProtoType**, an automated protocol-authoring tool now ready for primetime, to be utilized by several "brain" IRBs;
* **Clinical and Translational Science Awards Program**, once predominantly extramural but now with more linkages to the Clinical Center and the intramural program;
* **Bench-to Bedside-Awards**, an intramural funding mechanism opened to extramural researchers in FY2006;
* **NIH-RAID** (Rapid Access to Interventional Development) Pilot Program, modeled after NCI's RAID program, to speed to movement of therapeutic agents from bench to bedside;
* **NIH Chemical Genomics Center** (NCGC), established as part of the Molecular Libraries Screening Center Network, an NIH Roadmap initiative, to develop and optimize biochemical and cellular assays, perform quantitative high-throughput screening of diverse small molecules, and perform chemistry optimization to produce chemical probes.

Although you might think you know these programs, it may be worth to re-examine them, for they have undergone changes, said Gallin.

The Clinical Center is also reexamining its vision and mission to find the intersection of what it is passionate about (e.g. cutting-edge clinical research, rare diseases), what it is best in the world at (phenotyping, high-risk studies, bench-to-bedside), and what drives the resource engine (patients, drugs, equipment). By doing so, Gallin said, the Clinical Center hopes to solve concurrent problems such as underutilized capacity, the lower-than-desired number of PIs, priority setting, budget constraints and other barriers to conducting clinical research.

Translational Tools: BTRIS

Another promising step for translational research is the Biomedical Translational Research Information System (BTRIS), led by James Cimino, who came to NIH from Columbia University after developing a similar program there. Cimino is now chief of the new CC Laboratory for Informatics Development.

BTRIS functions as a repository for clinical research data collected from NIH research protocols, intramural as well as extramural. By aggregating and organizing enormous amounts of information, the system will be able to provide researchers with easy access to clinical and non-clinical data from all different fields of study, facilitating cooperation between researchers in disparate institutes and centers.

"The underlying thing we're talking about here is the reuse of biomedical data," Cimino told an audience at the February town hall meeting on BTRIS at the Lipsett Amphitheater. "Reuse can happen for a number of reasons: We can do patient care with those data; we can do research with those data; we can do administrative processes with those data." When you add together these uses, "that now has a fancy name, called translational research."

BTRIS is accessible only to a small group of volunteers who are participating in its planning and testing. A demo will be available to all researchers in September, and the first real version of BTRIS should be available in July 2009. Cimino said he hesitated to call the system CRIS-II, a follow-up to the Clinical Research Information System that it will complement, because he wanted the name to reflect the focus on translational research.

Clinical Center Director John Gallin

Five Years Onward

With the nascent TRIG and BTRIS, the NIH may be on the verge of an enormous change in research efficiency and productivity, said Wyatt. The establishment of a forum for communication between labs and across institutes and centers should increase collaborative efforts, and a renewed focus on the recruitment of physician-scientists should strengthen the connection between the clinic and the lab.

A "fund of knowledge" has been accumulating since the 1970s, Wyatt said, when clinical research began to slow down at NIH and basic research began to pick up. Programs such as the Human Genome Project, which have accumulated enormous bodies of knowledge but have seen little clinical application, are an investment that will soon pay off when translated into new treatments.

Song is equally optimistic, noting NIH's strengths in the ability to tackle rare diseases and conduct research in tailored medicine that pharmaceutical companies are unwilling to take on, as well as high-risk research that is economically unfeasible for drug companies.

"Thanks to enormous advances in protocols for handling and storing high-quality human specimens, molecular analysis technologies and bioinformatics, it's now feasible to carry out translational research by arranging team work," Song added.

"If the enthusiasm continues, there is hope for translational research," said Schechter. ■

The TRIG will host a mini-symposium on the first day of the 2008 NIH Research Festival, October 14, from 2:00 p.m. to 4:00 p.m at the Natcher Conference Center Conference Room F1/F2. This will feature five speakers culled from over 40 abstract submissions. The title is "Bridging the Gap between Research Discoveries and Clinical Evaluation," chaired by Min Song.

Annual Update

Scientific Interest Group Directory

Scientific Interest Groups (SIGs), a.k.a. NIH Inter-institute Interest Groups, are assemblies of scientists with common research interests. These groups are divided into seven broad, process-oriented parent groups, or faculties, and more than 100 smaller, more focused groups centered on particular research models, subjects or techniques. The latter groups are initiated and run by scientists in the Intramural and Extramural Research Programs at NIH. The interest groups sponsor symposia, poster sessions and lectures; offer mentoring and career guidance for junior scientists; help researchers share the latest techniques and information; act as informal advisors to the Deputy Director of Intramural Research; provide advice for the annual NIH Research Festival; and serve as hosts for the Wednesday Afternoon Lecture Series.

To create a SIG, contact OIR Communications Director Christopher Wanjek. The following list contains active SIGs, to the best of our knowledge, although the asterisk indicates the SIG did not confirm meeting and contact information. A current list is always posted at <http://www.nih.gov/sigs>. *Websites listed below should be active by September 2008.*

MAJOR INTEREST GROUPS

Cell Biology Interest Group
Meeting time/place: time varies; Bldg 32 library
Contact: Jennifer Lippincott-Schwartz, 301-402-1010 or 301-402-1009, jlippin@helix.nih.gov
LISTSERV: CELBIO-L

Clinical Research Interest Group*
Meeting time/place: CC Grand Rounds once every other month
Contact: Cliff Lane, 301-496-7196, clane@nih.gov

Genetics Interest Group*
Meeting time/place: two all-day symposia a year, tba
Contact: Dan Kastner, 301-496-8364, kastnerd@mail.nih.gov
LISTSERV: GIG-L

Immunology Interest Group
Meeting time/place: seminars 4:15 p.m. Wed.; Bldg 10, Lipsett
Contact: Juan Rivera, 301-496-7592, riveraj@mail.nih.gov
LISTSERV: IMMUNI-L
http://sigs.nih.gov/immunology

Molecular Biology/Biochemistry Interest Group
Meeting time/place: No regular meetings
Contact: Christopher Wanjek, interim lead

Neurobiology Interest Group
Meeting time/place: Fridays at 4 p.m.; 35/BB-1000
Contact 1: Mark Stopfer, 301-451-4534, stopferm@mail.nih.gov
Contact 2: Jeff Diamond, 301-435-1896, diamondj@ninds.nih.gov
http://sigs.nih.gov/neuro

Structural Biology Interest Group
Meeting time/place: 3rd Thursdays, 4 p.m.; Bldg 50, 1st-floor conf. room
Contact: Alasdair Steven, 301-496-0132, stevena@mail.nih.gov
http://sigs.nih.gov/sbig

OTHER INTEREST GROUPS

14-3-3 Protein Interest Group
Meeting time/place: 3rd Wednesdays, 4 p.m.; Bldg 40, 1st-floor conf. room
Contact: David Klein, 301-496-6915, kleind@mail.nih.gov

Acetyltransferase Interest Group
Meeting time/place: varies
Contact 1: David Klein, 301-496-6915, kleind@mail.nih.gov

AIDS Interest Group
Meeting time/place: varies
Contact: Leonid Margolis, 301-594-2476, margolis@helix.nih.gov
LISTSERV: AIDSINTG-L
http://sigs.nih.gov/AIDS

Animal Well-Being Interest Group
Meeting time/place: quarterly; Bldg 14G
Contact: Jim Weed, 301-435-7257, weedj@mail.nih.gov
http://sigs.nih.gov/AWIG

Apoptosis Interest Group
Meeting time/place: 1st Mondays, 4 p.m.; Bldg 49, Room 1 50/59AB
Contact: Richard Youle, 301-496-6628, youler@ninds.nih.gov
http://sigs.nih.gov/cell-death

Behavioral & Social Sciences Interest Group
Meeting time/place: lecture series, varies
Contact: Ronald Abeles, 301-496-7859, abeles@nih.gov
LISTSERV: BSSRIG-L

Bioethics Interest Group
Meeting time/place: usually 1st Mondays, 3 p.m.; place varies
Contact: Miriam Kelty, 301-229-5639, keltym@mail.nih.gov
http://sigs.nih.gov/bioethics

Bioinstrumentation Interest Group*
Meeting time/place: varies
Contact: Paul Smith, smithpa@ors.od.nih.gov, 301-435-1945

Biomedical Computing Interest Group
Meeting time/place: Thursdays, 3 or 5:30 p.m.; Bldg 10, 2C116
Contact 1: Jim DeLeo, 301-496-3848, jdeleo@nih.gov
Contact 2: Carl Leonard, cleonard@cc.nih.gov
LISTSERV: BCIG-L

Biomedical Research History Interest Group
Meeting time/place: varies
LISTSERV: BRHIG-L
Contact: Joseph November, 301-594-5485, novemberj@mail.nih.gov

Biophysics Interest Group
Meeting time/place: seminars, varies
Contact: Peter Basser, 301-435-1949, pjbasser@helix.nih.gov
http://sigs.nih.gov/biophysics

Biosciences Business Interest Group
Meeting time/place: monthly, noon; Bldg 37, 4th-floor conf. room
Contact: Val Bliskovsky, 301-435-7249, bliskovv@mail.nih.gov
LISTSERV: BIOSCIBUS-L
http://www3.cancer.gov/bbig/

Calcium Interest Group
Meeting time/place: varies
Contact 1: Arthur Sherman, 301-496-4325, asherman@nih.gov
Contact 2: Indu Ambudkar , 301-496-1478, iambudkar@dir.nidcr.nih.gov
LISTSERV: CALCIUM-L
http://sigs.nih.gov/cig

Chemistry Interest Group
Meeting time/place: Fridays, 10 a.m.
Contact: Dan Appella, 301-451-1052, appellad@niddk.nih.gov
LISTSERV: CHEMIG
http://sigs.nih.gov/chemistry

Carcinogenesis Interest Group*
Meeting time/place: varies
Contact: Umberto Saffiotti, 301-402-2971, saffiotu@mail.nih.gov

Cell & Molecular Neuroscience Interest Group*
Meeting time/place: varies
Contact: Ron McKay, 301-496-6574, mckayr@ninds.nih.gov

Chromatin & Chromosomes IG
Contact: David Clark, clarkda@mail.nih.gov

Chronobiology Interest Group
Meeting time/place: 1st Wednesdays, 4 p.m.; Bldg 49, Rm 6A46
Contact: Steven Coon, 301-451-6622, coons@mail.nih.gov
LISTSERV: CHRONIG-L
http://sigs.nih.gov/chronobiology

Clinical Applications of Stem Cells IG
Contact: Manfred Boehm, boehmm@nhlbi.nih.gov

Clinical Pharmacology Interest Group*
Meeting time/place: course and meeting on Thursdays Sep-Apl, 6:30 p.m.; Bldg 10, Lipsett
Contact: Donna L. Shields, 301-435-6618, dshields@mail.cc.nih.gov
LISTSERV: CLINPHARMACOL-L
http://sigs.nih.gov/clinicalpharmacology

Cognitive Neuroscience Consortium
Meeting time/place: bimonthly, last Wednesdays, 4:15 p.m.; NSC Bldg., Rm 2172, plus forums
Contact: Emmeline Edwards, 301-496-9248, ee48r@nih.gov
http://sigs.nih.gov/cnc

Critical Illness & Injury Interest Group
Meeting time/place: varies
Contact 1: Anthony Suffredini, 301-402-3485, asuffredini@cc.nih.gov
Contact 2: Scott Somers, 301-594-3827, somerss@nigms.nih.gov
http://sigs.nih.gov/criticalillness

Culture & Qualitative Research Interest Group
Meeting time/place: varies
Contact 1: Martha Hare, 301-594-1908, harem@mail.nih.gov
Contact 2: Rhonda Moore, 301-451-9385, moorerh@mail.nih.gov
http://sigs.nih.gov/culture

Cytokine Interest Group
Meeting time/place: varies, symposium
Contact: Daniela Verthelyi , 301-827-1702, daniela.verthelyi@fda.hhs.gov
LISTSERV: CYTOKN-L
http://sigs.nih.gov/cytokines

Data & Research Resources Sharing Interest Group
Meeting time/place: 4th Wednesdays, 3-4:30 p.m.; Rockledge 1, Rm 5147
Contact 1: J.P. Kim, 301-435-0679, jpkim@nih.gov
Contact 2: Marilyn Miller, 301-496-9350, millerm@nia.nih.gov
http://sigs.nih.gov/DARES

Domestic Violence Research Interest Group*
Contact: John Umhau, umhau@nih.gov

DNA Repair Interest Group
Meeting time/place: 3rd Tuesdays; Natcher Room J, videoconference at 14 remote sites
Contact 1: Kenneth Kraemer, 301-496-9033, kraemerk@nih.gov
Contact 2: Vilhelm Bohr, 410-558-8162, vbohr@nih.gov
LISTSERV: DNAREPAIR-L
http://sigs.nih.gov/DNA-repair

Drosophila Interest Group
Meeting time/place: 3rd Tuesdays, 1:15 p.m.; Bldg 6B, Rm. 4B429
Contact: Jim Kennison, 301-496-8399, Jim_Kennison@nih.gov
LISTSERV: DROSOPHILA
http://sigs.nih.gov/Drosophila

Drosophila Neurobiology Interest Group
Meeting time/place: every other Friday, noon; Bldg 35, Rm BB-1000
Contact: Ward Odenwald, 301-496-5940, OdenwaldW@mail.nih.gov
http://sigs.nih.gov/DNIG

Economics Interest Group
Meeting time/place: varies
Contact: James A. Schuttinga, 301-496-2229, js41z@nih.gov
http://sigs.nih.gov/Econ

Emergency Preparedness and Biodefense Interest Group
Meeting time/place: 1st Thursdays, 3 p.m.; Bldg 50, 1st-floor conf. room
Contact: Mike Bray, 301-451-5123, mbray@niaid.nih.gov
SIG URL: http://sigs.nih.gov/EPB

End of Life Interest Group*
Meeting time/place: 3rd Thursdays, 3 p.m.; NINR Conference Room, 6701 Democracy Blvd., Suite 710
Contact: Josephine Boyington, 301-594-2542, boyingtonje@mail.nih.gov

Endocrinology Interest Group
Meeting time/place: varies
Contact 1: Karel Pacak, 301-402-4594, karel@mail.nih.gov
Contact 2: Tomoshige Kino, 301-496-5800, kinot@mail.nih.gov

Engineering & Physical Sciences Interest Group*
Meeting time/place: varies
Contact: Richard Leapman, 301-496-2599, leapmanr@mail.nih.gov

Epidemiology & Clinical Trials Interest Group
Meeting time/place: Varies
Contact: Martina Vogel-Taylor, 301-496-6614, martinav@nih.gov
LISTSERV: Epidem-L
http://sigs.nih.gov/epidemiology

Epigenetics Interest Group
Meeting time/place: final Thursdays, 3 p.m.; EPN (6130 Executive Blvd.) conf. room G
Contact: Mukesh Verma, 301-594-7344, Vermam@mail.nih.gov
http://sigs.nih.gov/epigenetics

Epilepsy Interest Group
Meeting time/place: varies; seminars and Data Blitz session
Contact: William Theodore, 301-496-1505, theodorw@ninds.nih.gov
http://sigs.nih.gov/epilepsy

Epithelial Transport Biology Interest Group
Meeting time/place: varies (new SIG)
contact: Viswanathan Raghuram, 301-402-1311, raghuramv@mail.nih.gov
http://sigs.nih.gov/epithelia

Flow Cytometry Interest Group
Meeting time/place: two all-day meetings per year; next meeting Sept. 5 at 9 a.m. in Lipsett
Contact 1: Bill Telford, 301-435-6379, telfordw@mail.nih.gov
Contact 2: Jim Simone, 301-594-6191, simonej@mail.nih.gov
LISTSERV: FCIG-L
http://sigs.nih.gov/FCIG

Fluorescence Interest Group
Meeting time/place: 2nd and 4th Fridays, 4 p.m.; Bldg 10, Rm 5N264
Contact 1: Jay Knutson, 301-496-2557, jaysan@helix.nih.gov
Contact 2: Dan Sackett, 301-594-0358, sackettd@mail.nih.gov
http://sigs.nih.gov/Fluorescence

Free Radical Interest Group
Meeting time/place: monthly on Friday, 3 p.m.; Bldg.10, Radiation Biology conf. room
Contact: Michael Graham Espey, 301-496-7511, SP@nih.gov
http://sigs.nih.gov/radical

Glycobiology Interest Group
Meeting time/place: varies, special events
Contact: Pamela Marino, 301 594-3827, marinop@nigms.nih.gov
LISTSERV: GLYCO-L
http://sigs.nih.gov/glyco

GTP Binding Proteins Interest Group*
Meeting time/place: varies
Contact: R. Victor Rebois, 301-496-9168, reboisv@nidcd.nih.gov

Handheld Users Group
Meeting time/place: varies
Contact: Ben Hope, 301-594-6473, tallguy@nih.gov
http://sigs.nih.gov/HUG

Hard Tissue Disorders Interest Group*
Meeting time/place: 9:30 a.m., day varies; Bldg 30, Rm 117
Contact 1: Pamela Robey, 301-496-4563, probey@dir.nidcr.nih.gov

Head & Neck Cancer Interest Group*
Meeting time/place: varies
Contact 1: Wendy Weinberg, 301-827-0709, wendy.weinberg@fda.hhs.gov
Contact 2: Carter Van Waes, 301-402-4216, vanwaesc@nidcd.nih.gov

HTS Assay Development Interest Group*
Meeting time/place: varies
Contact 1: Ingrid Li, 301-443-1421, ili1@mail.nih.gov
Contact 2: James Inglese, 301-496-7029, jinglese@mail.nih.gov

Hypoxia Inducible Factor (HIF) Interest Group*
Contact: Tawnya McKee, mckee@ncifcrf.gov

Annual Update

Scientific Interest Group Directory (cont.)

Image Processing Interest Group*
Meeting time/place: varies
Contact 1: Benes Trus, 301-402-7676, Benes_Trus@nih.gov
Contact 2: Matt McAuliffe, 301-594-2432, matthew.mcauliffe@nih.gov

Image-Guided Interventions Group*
Meeting time/place: 4th Mondays; 6707 Democracy Blvd, Ste 200, Rm 223
Contact: John W. Haller, 301-451-4780, hallerj@mail.nih.gov

Infectious Disease Imaging Interest Group*
Meeting time/place: 3 p.m., Tuesday or Thursday; Bldg 50, 1st-floor conf. room
Contact: Mike Bray; 301-451-5123; mbray@niaid.nih.gov

Integrative Neural-Immune Interest Group
Meeting time/place: varies
Contact: Socorro Vigil-Scott, 301-496-9255, vigilscs@mail.nih.gov
LISTSERV: neuralimmune
http://neuralimmune.nih.gov

Integrative Neuroscience Interest Group*
Meeting time: alt. Thursdays, 4 p.m.; Bldg 49, Rm 1A51
Contact: Bruce Cumming, 301-496-9375, bgc@lsr.nei.nih.gov

In Vivo NMR Interest Group*
Contact: Jeff Duyn; jhd@helix.nih.gov

Knowledge Management Interest Group*
Meeting time/place: varies
Contact 1: Geoffrey Marsh, 301-594-9683, geoff@mail.nih.gov
Contact 2: Paul Beatty, 301-594-9502, pbeatty@mail.nih.gov

Lab Managers Interest Group*
Contact: Dawn Walker, walkerd@exchange.nih.gov

Lambda Lunch (Bacterial and Phage Genetics)
Meeting time/place: Thursdays, 11 a.m.; Bldg. 37 Rm 6107/6041
Contact 1: Susan Gottesman, 301-496-3524, susang@helix.nih.gov
Contact 2: Robert Weisberg, 301-496-3555, rweisberg@nih.gov
LISTSERV: LAMBDA_LUNCH-L
http://sigs.nih.gov/Lambda_Lunch

Light Microscopy Interest Group
Meeting time/place: varies
Contact 1: James McNally, 301-402-0209, mcnallyj@mail.nih.gov
Contact 2: Christian Combs, 301-496-0014, combsc@nhlbi.nih.gov
http://sigs.nih.gov/LMIG

Liver Biology Interest Group
Meeting time/place: varies
Contact: Bin Gao, 301-443-3998, bgao@mail.nih.gov
http://sigs.nih.gov/Liver

Magnetic Resonance Imaging and Spectroscopy Interest Group
Meeting time/place: TBA
Contact: Doug Morris, MorrisD@ninds.nih.gov, 301-402-1613
http://sigs.nih.gov/mris

Mass Spectrometry Interest Group
Meeting time/place: 1st Thursdays, 10:30 a.m.; Bldg 10 Rm 7S235
Contact: Dawn Maynard, 301-402-6622, maynardd@mail.nih.gov
http://sigs.nih.gov/MS-IG

Membrane Protein Interest Group
Meeting time/place: varies on Tuesdays, monthly, 1 p.m.; Bldg 35 Room BB1000
Contact: Reinhard Grisshammer, 301-594-9223, rkgriss@helix.nih.gov
LISTSERV: MPIG-L
http://sigs.nih.gov/mpig

Microarray Users Group
Meeting time/place: first Wednesdays at 10 a.m., Journal Club meets 3rd Thursdays at 4 p.m.; place varies
Contact: Katherine Peterson, 301-402-5678, petersonk@nei.nih.gov
LISTSERV: MICROARRAY-USER-L

Mitochondria Interest Group
Meeting time/place: 1st Mondays, 3 p.m.; webcast
Contact 1: Steve Zullo, 301-435-2810, zullo@helix.nih.gov
Contact 2: Nadja Souza-Pinto, 410-558-8596, souzan@mail.nih.gov
LISTSERV: MITOCHONDRIA-L
http://sigs.nih.gov/mito

Molecular & Functional Biophotonics Interest Group
Meeting time/place: varies
Contact: Amir Gandjbakhche, 301-435-9235, amir@helix.nih.gov
http://sigs.nih.gov/BioPhotonics

Molecular Modeling Interest Group
Meeting time/place: varies; Bldg 12 conf. rm
Contact: Peter Steinbach, 301-496-1100, steinbac@helix.nih.gov
http://mmignet.nih.gov

Mood & Anxiety Disorders Interest Group
Meeting time/place: TBA
Contact: Holly Giesen, giesenh@mail.nih.gov

Motility Interest Group*
Meeting time/place: varies
Contact: Jim Sellers, 301-496-6887, sellersj@nhlbi.nih.gov

Mouse Club
Meeting time/place: 1st Tuesdays, 4 p.m.; Bldg 6A Rm 4A05
Contact: Heiner Westphal, 301-402-0545, hw@mail.nih.gov

Mucosal Immunology Interest Group
Meeting time/place: last Fridays, noon; Bldg 40 VRC Rm 1201
Contact 1: Brian Kelsall, 301-496-7473, bkelsall@niaid.nih.gov
Contact 2: Yasmine Belkaid, 301-451-8686, ybelkaid@niaid.nih.gov
LISTSERV: MIIG
http://sigs.nih.gov/MIIG

Muscle Interest Group
Meeting time/place: varies; usually Bldg 40 Rm 1203 or 1205
Contact: Andres Buonanno, 301-496-0170, buonanno@mail.nih.gov
LISTSERV: Muscle-IGL
http://sigs.nih.gov/muscle

Nanotech/Nanomedicine Interest Group*
Meeting time/place: varies
Contact 1: Kuan Wang, 301-496-4097, wangk@mail.nih.gov
Contact 2: Jeffrey Forbes, 301-451-9535, forbesj@mail.nih.gov

Neural Cell Function Interest Group
Meeting time/place: usually 3rd Fridays, 2:30-5 p.m.; Bldg 49 Rm 1A-51
Contact: Lee Eiden, 301-496-4110, eidenl@mail.nih.gov
http://sigs.nih.gov/NCFig

Neurodevelopmental Disorders Interest Group
Meeting time/place: 2nd Thursdays, 12:30-1:30 p.m.; Bldg 10 Rm 2-3330
Contact: Teresa Huggins, 301-435-3781, TeresaHuggins@mail.nih.gov
LISTSERV: NEURO_DEV_DIS-L
http://sigs.nih.gov/ndd

Neuroinformatics Special Interest Group
Meeting time/place: TBA
Contact: Kathryn Bognovitz, kbognovi@mail.nih.gov

Nonhuman Primate Neurobiology Research Interest Group
Meeting time/place: 12:30-2:00 p.m., day and place varies,
Contact: Matthew Novak, 301-435-9278, novakm@mail.nih.gov
http://sigs.nih.gov/monkeys

Pain Interest Group
Meeting time/place: 2nd Tuesdays, 3:30 p.m.; Bldg 49 Rm 1A51
Contact: Michael Iadarola, 301-496-2758, miadarola@dir.nidcr.nih.gov
http://sigs.nih.gov/pain

Patent Law & Technology Transfer Interest Group
Meeting time/place: varies (new SIG)
Contact 1: Cameron Good, goodc@mail.nih.gov, 410-550-6565
Contact 2: Thomas Paul, paulth@mail.nih.gov, 301-435-5571
LISTSERV: PATENT_SIG_L
http://sigs.nih.gov/patent

Pediatric Clinical Research & Outcomes Interest Group*
Meeting time/place: varies (new SIG)
Contact: Steven Hirschfeld, 301-496-0044, hirschfs@mail.nih.gov

Pediatric Neuroimaging Interest Group*
Meeting time/place: varies (new SIG)
Contact: Lisa Freud, 301-435-6879, freundl@mail.nih.gov

PET Interest Group
Meeting time/place: Fridays 2 p.m.; Bldg 10 Rm 1-5674
Contact: Peter Herscovitch, 301-451-4248, herscovitch@nih.gov
LISTSERV: PETINT-L
http://sigs.nih.gov/PET

Phage-Tech Interest Group
Meeting time/place: varies
Contact: Rotem Edgar, 301-451-8820, edgarr@mail.nih.gov
http://sigs.nih.gov/Phage

Pharmacogenetics Interest Group
Meeting time/place: last Thursdays, 3:30-5:00 p.m.; Rockledge 2
Contact: Pothur Srinivas, 301-435-0550, srinivap@mail.nih.gov
LISTSERV: PHIG-L
http://sigs.nih.gov/PhIG

Pigment Cell Research Interest Group
Meeting time/place: 3rd Thursdays, 12:30-2:00 p.m.; Bldg 49 Rm 1A51; yearly daylong meeting
Contact: Tom Hornyak, 301-451-1926, hornyakt@mail.nih.gov
LISTSERV: PIGINTGRP
http://sigs.nih.gov/pigment

Polyunsaturated Lipid Function IG
Meeting time/place: TBA
Contact: John Paul SanGiovanni, 301-496-6583, jpsangio@nei.nih.gov

Prostate Cancer Interest Group*
Meeting time/place: monthly on Fridays, 4 p.m.; Bldg 10 CRC Rm 2-3750
Contact: Marston Linehan, 301-496-6353, linehanm@mail.nih.gov

Protein Trafficking Interest Group
Meeting time/place: 2nd Tuesdays, 3:30 p.m.; Bldg 50 Rm 2328
Contact 1: Manu Hegde, 301-496-4855, hegder@mail.nih.gov
Contact 2: Peng Loh, 301-496-3239, lohp@mail.nih.gov
LISTSERV: ProtTRAF-L
http://sigs.nih.gov/PTIG

Proteomics Interest Group
Meeting time/place: 1st Fridays, seminars; Bldg 50 1st-floor conf. room
Contact: Sanford Markey, 301-496-4022, markeys@mail.nih.gov
LISTSERV: PROTIG
http://proteome.nih.gov/

Retinal Disease Interest Group
Meeting time/place: 2nd Tuesdays; Bldg 10 Rm 10N202
Contact: James Friedman, 301-443 6758, friedmanja@mail.nih.gov
http://sigs.nih.gov/RDIG

RNA Club
Meeting time/place: 1st Tuesdays, 4 p.m.; Bldg 31 Rm 2A48
Contact: Rich Maraia, 301-402-3567, maraiar@mail.nih.gov
LISTSERV: RNACLUB-L
http://sigs.nih.gov/NIH_RNA_Club

Stem Cell Interest Group
Meeting time/place: monthly seminars
Contact 1: Nadya Lumelsky, 301-451-9834, nadyal@nidcr.nih.gov
Contact 2: Manfred Boehm, 301-435-7211, boehmm@nhlbi.nih.gov
LISTSERV: STEMCELL_IG-L
http://sigs.nih.gov/SCIG

Stroke Branch Interest Group
Meeting time/place: varies at Suburban Hospital and Washington Hospital
Contact 1: Jose Merino, 301-435-9321, merinoj@ninds.nih.gov
Contact 2: John Kylan Lynch, 301-451-7968, LynchJ@ninds.nih.gov

Synaptic and Developmental Plasticity Interest Group*
Meeting time/place: bimonthly on a Tuesday, 11 a.m.; Bldg 35 Rm BB1000
Contact: Bai Lu, 301-435-2970, bailu@mail.nih.gov

Systems Biology Interest Group
Meeting time/place: 1st Thursdays, 2 p.m., monthly seminars; Bldg 10 Rm 7S235 (Berliner Rm)
Contact 1: Eric Billings, 301-496-6520, billinge@nhlbi.nih.gov
Contact 2: David Balshaw, 919-541-2448, balshaw@niehs.nih.gov
LISTSERV: SYSBIOSIG-L

Tobacco & Nicotine Research Interest Group
Meeting time/place: 4th Thursdays bimonthly, 2 p.m.; place varies yearly
Contact: Allison Hoffman, 301-402-5088, HoffmanAL@mail.nih.gov
http://sigs.nih.gov/tobacco

Transcription Factor Interest Group
Meeting time/place: 1st Thursdays, 2 p.m.; Bldg 50, 1st-floor conf. room
Contact 1: Stoney Simons, 301-496-6796, steroids@helix.nih.gov
Contact 2: Uli Siebenlist, 301-496-8917, USiebenlist@niaid.nih.gov
LISTSERV: TFACTORS
http://sigs.nih.gov/TFACTORS

Trans-Institute Angiogenesis Research Program (Tumor Angiogenesis & Invasion Working Group)
Meeting time/place: varies
Contact 1: William Figg, 301-402-3622, wdfigg@helix.nih.gov
Contact 2: Steven Libutti, 301-496-5049, slibutti@nih.gov
http://www.tarp.nih.gov

Translational Research Interest Group
Meeting time/place: varies (new SIG)
Contact: Min Song, 301-496-8783, songm@mail.nih.gov
LISTSERV: TRIG-L
http://sigs.nih.gov/trig

Viral Hepatitis Interest Group
Meeting time/place: monthly on Tuesdays, 4:15 p.m.; Bldg 10 Rm 9S235 (Bunim Rm)
Contact: Barbara Rehermann, 301-402-7144, Rehermann@nih.gov
LISTSERV: VHIG-L
http://sigs.nih.gov/vhig

Virology Interest Group
Meeting time/place: 1st Thursdays, noon plus November minisymposium; Bldg 4 Rm 433
Contact: Alison McBride, 301-496-1370, amcbride@nih.gov
LISTSERV: NIHVIG-L
http://sigs.nih.gov/vig

Washington Area NMR Interest Group
Meeting time/place: three mini-symposia per year
Contact: Daron Freedberg, 301-496-0837, daron_freedberg@nih.gov
http://www.nih.gov/sig/WANG

Washington Area Yeast Club
Meeting time/place: 2nd Wednesdays, 4:30 p.m.; Bldg 6A Rm 4A05
Contact: Henry Levin, 301-402-4281, levinh@mail.nih.gov

Women's Health Special Interest Group*
Meeting time/place: bimonthly on Fridays, 11:30 a.m.; Bldg 1 Wilson Hall
Contact: Vicki Malick, 301-496-7989, malickv@mail.nih.gov
LISTSERV: WHSIG

X-ray Diffraction Interest Group
Meeting time/place: varies, see http://mcl1.ncifcrf.gov/nihxray
Contact: Fred Dyda, 301-402-4496, fred.dyda@nih.gov
LISTSERV: NIHXRAY-L
http://sigs.nih.gov/xray

Zebrafish-Frog Interest Group
Meeting time/place: monthly, rotates through participating labs
Contact: Tom Sargent, 301-496-0369, sargentt@mail.nih.gov
http://sigs.nih.gov/zebrafrog

Colleagues

Recently Tenured

Susan Buchanan *received her Ph.D. from the Johann-Wolfgang-Goethe Universität in Frankfurt, Germany, in 1990. She completed postdoctoral fellowships at the MRC Laboratory of Molecular Biology, Cambridge, U.K., and at the University of Texas Southwestern Medical School Southwestern Medical Center, Dallas, before returning to the U.K. to establish a research group at Birkbeck College, London, in 1998. She joined NIDDK as an investigator in 2001 and is currently a senior investigator in the Laboratory of Molecular Biology, NIDDK.*

My group uses X-ray crystallography to study the structures of integral membrane proteins. About 30 percent of the human genome codes for membrane proteins, and a similar distribution is found in lower organisms. Membrane proteins are difficult to work with, however, due to their low abundance in cells and to their preference to reside in a lipid bilayer. Although a large number of pharmaceutical targets are membrane proteins, they currently represent less than 1 percent of all solved protein structures.

We study transporters embedded in the outer membranes of Gram-negative bacteria, which are surface accessible and therefore have the potential to be good vaccine or drug targets against infectious diseases.

One area of particular interest is the transport of small molecules and large proteins across the outer membrane by a single family of membrane proteins. We focus on iron transporters from several bacterial pathogens. Iron is essential for bacterial proliferation: If iron uptake could be blocked, an infection could be eradicated.

So far, our structures have shown how iron transporters specifically recognize Fe^{3+} bound to small molecules such as enterobactin (a siderophore synthesized by *Escherichia coli*) and citrate. Each transporter has a unique binding pocket for its preferred small molecule. When the correct substrate binds, the transporter undergoes conformational changes that send a signal across the outer membrane and prepare the system for transport.

However, transport into the periplasm is complicated and involves another protein complex and energy in the form of protonmotive force. We are still working to understand the actual transport process.

Even without knowing exactly how they function, we believe that these iron transporters may make good vaccine or drug targets because they are surface exposed and often antigenic. We are currently testing this idea using an iron transporter from *Yersinia pestis*. *Y. pestis* causes plague, and deletion of the gene encoding an iron transporter abolishes virulence in a mouse model of bubonic plague. We recently solved the structure of the *Y. pestis* iron transporter in two states, alone and in complex with its cognate Fe^{3+}-siderophore.

These structures allowed us to precisely define the binding pocket for the substrate. The next step is to use computational methods to screen for small molecules that effectively compete with the natural substrate for binding. This could lead to the design of novel antibiotics.

We also are collaborating with Joe Hinnebusch (NIAID), who is evaluating this protein and several others for a protective immune response in rat and mouse models of bubonic plague. We hope that this work will identify new vaccine targets.

Recently, we extended our work on small-molecule transporters to ask how proteins are ferried across the outer membrane. Some of the iron transporters that we study also facilitate the uptake of large protein toxins called colicins. Whether the transport mechanism is the same as found for small molecules or entirely different, we hope that our crystal structures will suggest answers.

We also have begun to study protein export through collaboration with Harris Bernstein (NIDDK). Together we have solved the structure of the transporter domain of an autotransporter from O157:H7 *E. coli*. This protein forms a transport channel similar to those found in iron transporters, but the secreted protein domain is very large. Exactly how it gets to the bacterial cell surface is still a mystery.

Our next major goal is to solve outer membrane protein structures from mitochondria. Most proteins residing in mitochondria are nuclear encoded and must be imported through a general protein-import channel. We aim to solve structures of this channel and others to see how similar these proteins are to bacterial outer membrane proteins, and how the passage of proteins across membranes varies between these systems. §

Ramanujan S. Hegde *received his M.D. and Ph.D. in 1999 from the University of California, San Francisco. After three years at the National Cancer Institute as an NCI Scholar, he joined the Cell Biology and Metabolism Program of NICHD in 2002, where he is currently a Senior Investigator heading the Protein Biogenesis Section.*

Cells have many thousands to millions of individual proteins that must be folded, processed, assembled and localized correctly to maintain normal organismal physiology. Conversely, defective protein maturation and trafficking cause a wide range of diseases ranging from cystic fibrosis to neurodegenerative disorders. Our laboratory is interested in the basic problem of how protein maturation normally occurs, how these events are regulated, and how misregulation leads to cellular dysfunction and disease. We are focused on four intertwined aspects of secretory and membrane protein metabolism.

Translocational regulation. A decisive step in the maturation of secretory and membrane proteins is their entry, or translocation, into the endoplasmic reticulum (ER). We have discovered that protein translocation is under regulatory control for at least two important reasons. In some cases, regulating translocation allows a single protein to have multiple locations—for example, the ER and cytosol—where it can serve independent functions. In other cases, translocation is regulated to limit the entry of certain proteins into the ER, for example, during ER stress when maturation capacity is limited. We are currently studying both mechanistic and physiologic aspects of this newly emerged field of translocational regulation.

Quality control. Our discovery of translocational regulation has raised a previously unappreciated question: What happens to secretory and membrane proteins that fail to be segregated into the ER? Because these proteins are often quite hydrophobic, they represent a high risk for aggregation and inappropriate interactions. Indeed, we have discovered that they can contribute to the propagation of cytosolic protein aggregates that typify various neurodegenerative diseases. Thus, the pathway for the selective recognition and degradation of non-translocated secretory and

membrane proteins is critical for normal cellular homeostasis. We are now identifying the machinery for selective recognition and degradation of these non-translocated proteins, and anticipate their important role in diseases of protein misfolding and aggregation.

Membrane protein insertion. Insertion of proteins into biological membranes is vital to all organisms. Although most membrane proteins utilize a highly conserved insertion pathway discovered over 25 years ago, others are inserted by yet unknown pathways. We have recently identified a novel ATPase that functions in insertion of "tail-anchored" membrane proteins. Tail-anchored proteins are found on essentially all cellular membranes in every organism and have diverse functional roles ranging from intracellular trafficking to regulation of cell death. Thus, this novel membrane insertion pathway is of broad biological importance for the cell. We are now taking various approaches to identify additional factors in this pathway and to define their mechanistic and physiologic roles in membrane protein insertion.

Neurodegeneration mechanisms. Neurodegeneration is the most common pathologic consequence of aberrant protein folding and metabolism. However, the pathways leading from misregulated protein metabolism to neuronal dysfunction are very poorly understood. We are applying insights from our mechanistic studies on secretory and membrane protein biogenesis to neurodegenerative diseases caused by the prion protein. We discovered that some of these diseases are a direct consequence of altered prion protein translocation into the ER. We are finding that exposure of what is normally a cell surface protein to the cytosol may cause disease via inappropriate interactions with cytosolic proteins involved in regulating lysosomal trafficking. In parallel studies, we showed that other disease-causing mutations in the prion protein may cause lysosomal dysfunction directly by its inappropriate intracellular trafficking. We are now identifying the specific pathways of mutant prion protein trafficking, and the cellular consequences of its mislocalization.

We anticipate that our laboratory's efforts will help elucidate the machinery and mechanisms for several basic cellular pathways of secretory and membrane protein metabolism. These insights will have direct implications for our understanding of various protein misfolding diseases, eventually leading to new therapeutic strategies. §

Paolo Lusso *received his medical degree from the University of Turin, Italy, and his Ph.D. from the Ministry of Scientific and Technologic Research, Rome. He came to NIH for the first time in 1986 to work at the NCI Laboratory of Tumor Cell Biology. He returned to Italy in 1994, where he became Chief of the Laboratory of Human Virology at the San Raffaele Scientific Institute in Milan and Associate Professor of Infectious Diseases at the University of Cagliari. In 2004, he was elected Member of the European Molecular Biology Organization (EMBO). In March 2008, he was appointed Senior Investigator at the NIAID Laboratory of Immunoregulation, where he heads the Unit of Viral Pathogenesis.*

My research focuses on understanding the mechanisms of viral pathogenesis, with the aim of developing novel strategies for the control and prevention of viral infections. Specifically, my interest has been concentrated on herpesviruses, in particular human herpesvirus 6 (HHV-6) and HIV.

In 1995, my research group was the first to establish a connection between the fields of HIV and the chemokine system with the discovery that three chemokines of the CC family (RANTES, MIP-1α and MIP-1β) act as specific endogenous inhibitors of HIV-1. This discovery, along with the subsequent identification of specific chemokine receptors as critical components of the HIV receptor complex, has led to the elucidation of several aspects of AIDS pathogenesis and opened new perspectives for the development of effective therapies and vaccines.

The identification of host factors that control HIV infection *in vivo* and thereby influence the natural course of HIV infection remains one of the major goals of my research. In fact, although RANTES, MIP-1α and MIP-1β represent major components of the anti-HIV activity produced by different cells of the immune system, several lines of evidence point to the existence of additional, still unrecognized, suppressive factors, which may play an important role in the *in vivo* control of HIV replication, particularly in subjects with long-term non-progressive infection.

I am currently using an integrated approach, combining classic protein purification methods with state-of-the-art transcriptomics and proteomics analyses, to identify the nature of novel HIV-suppressive factors produced *ex vivo* by stimulated immune cells.

A further step following the identification of new suppressive factors will be the characterization of their mechanism of action and their potential clinical relevance in HIV transmission and disease progression. This will involve extensive analysis of clinical samples to establish a correlation between the *in vivo* levels of the factors and the pace of disease progression, as well as the search for genetic polymorphisms linked to the variable clinical course of the disease in different individuals.

Endogenous suppressive factors such as CCR5-binding chemokines are believed to play a role also in determining the *in vivo* evolution of HIV-1, with the so-called "phenotypic switch" from the prevalent CCR5-tropic viral variants to the less frequent CXCR4-using variants, which typically emerge during the late stages of disease and are insensitive to inhibition by RANTES. I plan to continue investigating the mechanisms that restrict the early *in vivo* emergence of CXCR4-using HIV-1 strains, as well as those that eventually promote or allow their emergence, albeit belated.

Another major goal of my research is to develop novel strategies for the therapy and prevention of HIV infection. Over the past decade, with my collaborators in Italy, I have attempted to design specific HIV-1 inhibitors targeting CCR5, the chemokine receptor used for entry by the vast majority of wild-type HIV-1 isolates. Based on our previous identification of the primary determinants of CCR5 recognition and HIV-1 blockade in RANTES, we have rationally designed short synthetic peptides that block HIV-1 entry at low nanomolar concentrations while exerting no agonistic effects on CCR5.

I plan to continue investigation of the structure-function relationships in RANTES and related chemokines, with the aim of defining more precisely the receptor-ligand interface. While further molecular refinement of our biologically active peptides is in progress, we are currently exploring potential strategies for their *in vivo* delivery both as systemic therapeutics and as topical microbicides. §

Colleagues

Recently Tenured (cont.)

Maria I. Morasso *received her Ph.D. from the Instituto Venezolano de Investigaciones Cientificas (IVIC) in Caracas, Venezuela, in 1991. She was a postdoctoral fellow in the NICHD Laboratory of Molecular Genetics, led by Thomas Sargent, where she developed an interest in developmental skin biology. In 2000, she joined NIAMS as a tenure-track investigator. She is currently a senior investigator and head of the NIAMS Developmental Skin Biology Section.*

My lab explores how epidermal cells differentiate and ectodermal appendages (hair, teeth) form during embryonic development. My research has focused in characterizing the regulation and function of the Dlx homeobox transcription factor, a member of the murine Dlx family, with essential roles in epidermal, osteogenic and placental development.

The importance of Dlx3 in the patterning and development of ectodermal structures derived from epithelial-mesenchymal interactions during embryogenesis (i.e. tooth, hair) is corroborated by the effects of DLX3 mutations in patients with the autosomal dominant Tricho-Dento-Osseous (TDO) syndrome.

Anomalies in epithelial-mesenchymal-derived organs are characteristics of a group of human heritable pathological disorders defined as ectodermal dysplasias (EDs). DLX3 is among the few genes for which mutations have been linked directly with EDs.

We have developed inducible and knockin mouse models to pursue studies on the effects of the mutant protein in hair, bone (intramembraneous and endochondral) and tooth development. We are also performing analysis of conditional knockout lines to elucidate the signaling and regulatory pathways requiring normal morphogenesis of these tissues during embryogenesis. §

David M. Wilson, III, *received his Ph.D. from Loyola University of Chicago in 1993 and performed his postdoctoral training at the Harvard School of Public Health. In 1997, he became a Senior Biomedical Scientist at Lawrence Livermore National Laboratory in the Biology and Biotechnology Research Program. He started at NIA as a tenure-track investigator in the Laboratory of Molecular Gerontology (LMG) in 2002.*

My laboratory focuses on elucidating the molecular mechanisms of the base excision DNA repair (BER) pathway and delineating the contribution of core and auxiliary BER proteins to disease manifestation, therapeutic agent responsiveness and aging.

The free radical theory of aging proposes that the gradual accumulation of macromolecular oxidative damage over the lifespan of an organism leads to a gradual decline in cellular function and eventual death. It is our hypothesis that deficits or a decrease in the repair of oxidative DNA damage will translate into premature aging phenotypes and age-related disease. Evidence supporting the idea that genome surveillance systems are a major factor in adetermining longevity and cell functionality comes from studies of model organisms and human segmental progerias (e.g. Werner and Cockayne syndrome). In addition, defects in DNA damage responses have been causally linked to the age-associated diseases, cancer and neurodegeneration.

Many types of lesions are formed via attack of reactive oxygen species of DNA, with the most prominent being base modifications (e.g. 8-oxoguanine), abasic sites and single-strand breaks harboring non-conventional 3' or 5' termini. If unrepaired, these damages can promote cellular dysfunction or genetic instability. BER is the primary pathway for coping with spontaneous, oxidative and alkylative DNA damage. Using basic molecular and biochemical approaches, we have determined how specific human, core BER proteins recognize and process target lesions and/or coordinate with other components of the pathway. This research has centered largely on apurinic/apyrimidinic endonuclease 1 (APE1), the major mammalian repair protein for abasic sites

in DNA, and x-ray cross-complementing 1 (XRCC1), a key non-enzymatic scaffold protein for the efficient operation of single-strand break processing.

Current efforts on APE1 revolve around (i) determining which of its many identified biochemical activities are biologically important using strategic knockdown and complementation strategies, (ii) evaluating the role of APE1 (and BER more broadly) in clinical DNA-damaging agent resistance, and (iii) assessing the potential relationship of reduced BER capacity to disease development using established and in-development biochemical repair assays and defined population sets.

Studies centered on XRCC1 involve (i) elucidating the role of XRCC1 (and more broadly single-strand break repair) in oxidative stress resistance in non-dividing, neuronal cells, given the recent linkage of defects in single-strand break processing to inherited spinocerebellar ataxias, (ii) evaluating the involvement of XRCC1 deficiency on age-related pathologies using a heterozygous mouse model, and (iii) determining the contribution of XRCC1 to DNA damage responses, genome stability and telomere maintenance.

Finally, Cockayne syndrome (CS) is a rare, autosomal recessive disorder characterized by growth failure, impaired development of the nervous system, cutaneous photosensitivity and premature aging. Recent studies indicate that the pathophysiology of CS might arise, at least in part, due to a defect in the repair of endogenous DNA damage. My group, in collaboration with Dr. Vilhelm Bohr in LMG, recently identified a novel interaction with the CS complementation group B (CSB) protein and APE1. Efforts are now underway to delineate the biochemical roles of CSB and its precise molecular involvement in the BER response as an auxiliary factor. §

Colleagues

On Tenure Track

Rafael Casellas joined the NIAMS Molecular Immunology and Inflammation Branch in 2004. His laboratory focuses especially on the molecular mechanisms that maintain genomic integrity and stability in the B-cell genome as antibody genes undergo extensive mutation and recombination.

Casellas uses class-switch recombination—a mechanism that B cells use to express the various immunoglobulin classes of antibodies—as a model to study basic cellular processes. Class-switch recombination requires coordination of the transcriptional machinery, of DNA repair factors, and of chromatin-remodeling enzymes to induce a specific double-stranded break in the DNA and then to rejoin the appropriate DNA segments of the immunoglobulin region.

A "Renaissance man" in his youth, immersed largely in the humanities, Casellas turned to science when he realized that biology and genetics were also powerful at explaining the human experience—from the "taste of food to the mechanism of disease to the complexities of human behavior," he said. Genetics and molecular biology also represented the current edge to him, and Casellas has tried to maintain a position throughout his career at the forefront of that edge.

Casellas earned his doctorate at Rockefeller University in New York, working with Michel Nussenzweig on mechanisms of antibody diversification such as immunoglobulin-receptor editing and class-switch recombination. He then completed a postdoctoral stint with David Baltimore at the California Institute of Technology in Los Angeles, where he furthered his studies of B-lymphocytes.

Recent work from Casellas' laboratory has shown how repair enzymes recruited to DNA breaks inhibit RNA polymerase activity, illustrating that repair and transcription can be coordinated within the cell (Nature 447, 2007). Casellas not only demonstrated that these processes are linked, but also identified the signaling pathway, or ATM repair pathway, required to inhibit the action of the polymerase. In pursuing this research, Casellas has drawn upon the expertise of Tom Misteli and André Nussenzweig of NCI, whose labs had developed technologies that fostered his experiments.

"I really feel this is one of the best places to explore science," Casellas said, citing not only the quality of intramural collaborators but also the investigative freedom afforded by an environment not limited by the traditional grants mechanism. Casellas is now interested in mapping chromatin changes at the immunoglobulin locus during mutation and recombination, studying the mechanisms that underlie chromosomal translocations and the driving of B-cell development by small RNAs, and examining how the B-cell genome can be reprogrammed—and more. The list is long and diverse but in keeping with the kaleidoscopic inclinations of a Renaissance man.

– by Julie Wallace, NIDDK

NIH Research a Strong Presence at 2008 APA Meeting

by Stephanie Cooperstein, special to The Catalyst

The National Institute of Mental Health took advantage of the proximity of this year's annual American Psychiatric Association, held in May at the D.C. Convention Center, to offer an outpouring of both intramural and extramural research in a series of presentations, panel discussions, clinical briefings and press conference.

Highlights included new studies for clinically diagnosing and treating depression, schizophrenia, attention deficit hyperactive disorder (ADHD), autism and post-traumatic stress syndrome (PTSD).

One NIMH-sponsored symposium, "Treatments for Schizophrenia, Mood Disorders, Anxiety Disorders and Substance Abuse," drew an overflowing room of attendees. Featured here was Carlos Zarate, Chief of Experimental Therapeutics in NIHM's Mood and Anxiety Disorders Program, who presented a talk titled, "Developing Improved Therapeutics for Refractory Mood Disorders."

Zarate summarized ongoing research on targets for the development of novel therapeutics to assist in deterring recurrent mood episodes that current pharmacotherapy may not always effectively control. These findings include explanations of AMPA throughput enhancers or synaptic plasticity enhancing strategies, AMPA potentiators and glutamate reuptake enhancers.

"The NIH focus is on *true* translational research," said Zarate. "What we can do here [at NIH] is incredible: Our staff and resources allow for more high-risk and innovative studies that are difficult to do in other areas. We try to make major breakthroughs. Then, the concepts learned in our research are extended outward to show that plasticity applies in the medical field, across disorders and beyond medical disciplines."

Additional NIMH research findings included talks on how neuroimaging has increased our understanding of risks for disorder development. Presentations covered summaries of a 20-year ongoing longitudinal neuroimaging project of healthy children and adolescents to identify dynamic brain changes during adolescence.

Jay Giedd, Chief of NIMH's Unit on Brain Imaging in the Child Psychiatry Branch, discussed MRI studies showing increasing frontal lobe involvement in mental development from childhood to adulthood. And Joseph Piven of the University of North Carolina presented NIH-supported imaging data that identified brain enlargement in autistic patients.

Explaining how advanced imaging research can clearly redirect scientists to the usefulness of additional and newer research tactics, NIMH Psychiatry Fellow Philip Shaw introduced results of a group study for delayed brain maturation. This imaging study compared the brain scans of over 450 ADHD and non-ADHD children and found that the cortex matured about three years later in ADHD patients. Despite the delay, the order or sequence in which the different parts of the brain matured was similar between affected and unaffected children. "The study suggests we should look further into factors, such as genes, which might be responsible for this delay, especially as this delay can persist well into adulthood," said Shaw.

Not unlike the mice in early NIMH studies, the thousands of meeting attendees found themselves scurrying through the maze of the D.C. Convention Center from presentation to presentation. "These APA meetings are a great forum for us to present our work and disseminate knowledge — to both medical and press attendees," Zarate said. "They support a dialogue over current limitations on therapeutics, and we get avenues to further address the public's evolving mental health needs." ■

Catalytic Reactions?

If you have a photo or other graphic that reflects an aspect of life at NIH (including laboratory life) or a quotation that scientists might appreciate that would be fit to print in the space to the right, why not **send it to us via e-mail: catalyst@nih.gov>; fax:301-402-4303; or mail: Building 2, Room 2E26.**

Also, we welcome "letters to the editor" for publication and your reactions to anything on the Catalyst pages.

In Future Issues...

- Collaborations and the Ombudsman
- Update of Trans-NIH Initiatives
- What's going on in Building 33?

Demystifying Medicine

The NIH's novel and popular course "Demystifying Medicine," now in its seventh year, will be held every Tuesday from 4:00-6:00 p.m. in the Building 50 auditorium from January 13 to May 19. Although primarily for Ph.D. scientists and students, the course is widely attended by other students, physicians and administrative staff. The course involves patients, clinicians and basic scientists; and it concerns major human diseases. Refer to <http://www1.od.nih.gov/oir/DemystifyingMed/> for 2008 course contents for an overview. Those seeking academic credit should register through FAES. If not seeking credit, register by sending e-mail Listserv@list.nih.gov and subscribe DeMystifyingMed.your name. For further information, contact Win Arias, course director, ariasi@mail.nih.gov.

Assessing the Impact of Your Web Sites

The NIH Web Metrics Work Group is developing ways to assess and improve the performance of individual NIH Web sites. The group, led by Ann Poritzky, is based in the Office of Communications and Public Liaison and is open to NIH employees and contractors.

During monthly meetings, speakers present details on Web site evaluation strategies and practical suggestions for implementing them. One goal is to provide Web teams with options for obtaining reliable data as they develop or improve their sites. Another goal is to help Web teams clearly communicate evaluation results to support ongoing site improvements.

Recent meetings featured an introduction to Web analytics by Phil Kemelor, vice president of the Web consultancy Semphonic, and a presentation by Pew Internet Project researchers. Future programs will focus on developing evidence-based Web site evaluations, selecting tools and obtaining "actionable" results. Plans also include user group meetings for commonly used tools, such as Web Trends and the American Customer Satisfaction Index survey.

To join the Web Metrics Work Group e-mail list or if you have questions, contact Ann Poritzky, Web Analytics Specialist, at poritzkya@mail.nih.gov.

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