Fostering Communication and Collaboration

The NIH Catalyst

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Supercomputing at Your Fingertips

Biowulf Turns 10; More Vital Than Ever

by Christopher Wanjek

Him the sturdy-in-war bespake with words,
proud earl of the Weders answer made,
hardy 'neath helmet:—"Hygelac's, we,
fellows at board; I am Beowulf named."

Many of the most challenging calculations contemplated by NIH researchers day in and day out—such as those needed for molecular dynamics, bioinformatics, or calculating the marginal odds of the Washington Nationals reaching the World Series within our lifetime—require supercomputing.

And for the last ten years, the NIH Center for Information Technology has met this supercomputing demand with Biowulf, a homegrown, high-performance parallel computing cluster—playful wordplay on what is elsewhere known as a Beowulf cluster system.

Now entering its second decade, Biowulf is more powerful and vital than ever. The facility is supported by the NIH Management Fund, which means that all NIH researchers can freely tap into this shared resource, one of the largest general-purpose biomedical computing clusters in the world.

The capacity is there for most biomedical and chemistry research tasks, says CIT's Steven Fellini, the architect of the Biowulf cluster since its origin in 1999. Fellini provided an overview of this facility at a daylong symposium on Biowulf on February 3, which brought together both seasoned and potentially new users from across the NIH intramural program.

Fellini's goal is to inspire NIH researchers to design projects that can take full advantage of this computing resource. "Physicists think big, but many biologists haven't thought like this in the past," he said.

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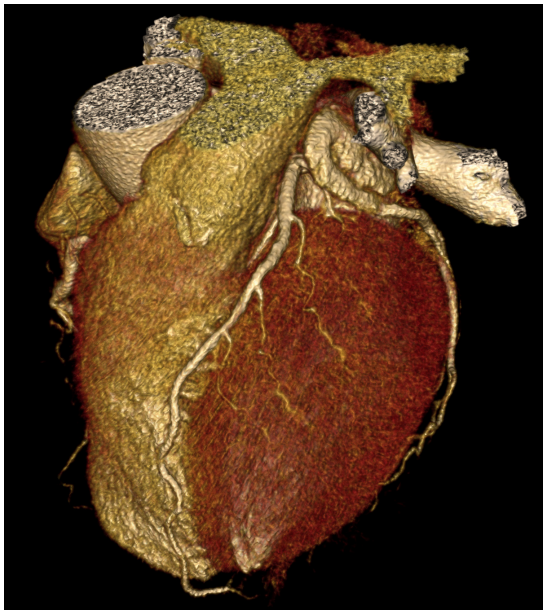
The Heart of NHLBI's New CT Scanner

by Christopher Wanjek

To see into someone's heart is to truly know that person, perhaps better than he knows himself, and to understand his potential. Andrew Arai of the National Heart, Lung, and Blood Institute is after such insight, only his end goal is to understand a patient's potential to drop dead of a heart attack as a result of blockages in his coronary arteries.



The diseased heart of a patient seen in the NIH Clinical Center. Although the heart is full of blood, only a few small arteries supply this muscle with the blood and oxygen needed to keep beating. Photo courtesy Andrew Arai et al., NHLBI.

Arai and fellow members of NHLBI's Laboratory of Cardiac Energetics have a new machine to guide them in this endeavor, Toshiba's Aquilion ONE CT scanner, which leaps from the previous generation's 64 detectors to 320, providing whole-organ scans in about a sixth of a second.

The speed reduces radiation and contrast dose, and the single-rotation scan eliminates the need to reconstruct slices from multiple points in time, providing the investigator a three-dimensional image with dynamic information such as blood flow.

Arai is part of two heart protocols using the CT scanner that could help revolutionize how coronary artery disease is detected and treated. This scanner, however, can be used to perform perfusion imaging of just about any organ, as well as tumor perfusion, pulmonary embolism, and bone and joint physiology studies, according to David Bluemke, director of the Clinical Center's Radiology and Imaging Sciences.

"This machine can do many things, and this is why we got it for the Clinical Center," said NHLBI Scientific Director Bob Balaban. "We hope all of the intramural programs will find a use."

For Arai, the charm of the new device—one of about 20 installed worldwide—is the ability to see signs of coronary heart disease not visible without invasive catheterization coupled with ultrasound.

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From the Deputy Director for Intramural Research

The NIH Intramural Program at the Crossroads

Michael Gottesman

The NIH intramural program is widely regarded as the most successful biomedical research program ever assembled in terms of the scope and impact of its basic research accomplishments and the impact of this science and training activities on the practice of medicine and improvements in public health. It has been, and remains, a model for other federal laboratories, for research foundations, and for other governments who seek to establish research laboratories.

By establishing a creative, stably funded environment that remains attractive to the most talented researchers and by providing research resources and opportunities for interaction that are unprecedented, the NIH intramural program has fostered an explosion of knowledge and its practical applications. Just a handful of the discoveries that have emerged from the NIH intramural program—such as the use of fluoride to prevent tooth decay, the use of lithium to manage bipolar mental illness, the development of blood tests to detect HIV and hepatitis, and vaccines against hepatitis, Hemophilus influenza, and human papillomavirus, among others—have repaid many times over in public health savings the total past investment, and any foreseeable future investment, in this program. Many other discoveries have improved the quality of health care in this country and the world.

But the very success of the NIH intramural program, both as a model for effective research activities copied elsewhere and as a training ground for hundreds of successful investigators who have gone on to establish outstanding extramural research programs, has raised questions about whether it continues to play a critical role in the overall research enterprise. Some believe that the best days of the intramural research program are past; others note that the difficulty in conducting truly innovative translational and clinical research in the extramural environment makes the NIH intramural program more critically important than ever before, which therefore provides opportunities for productive intramural-extramural interactions.

We believe the facts show that the NIH intramural research program continues to make critical contributions to the public health despite restricted budgets and that recent new approaches to research at the NIH have adapted to the changing research environment, indicating many more years of innovative and productive science. There are, however, some daunting challenges, mentioned below, that must be met to guarantee the future success of this distinctive research facility.

Despite four years of flat budgets, which represent a decrease in real buying power of approximately 16 percent, the intramural program continues to be highly productive, especially in areas of research that are difficult to pursue in most extramural environments. The establishment of several new trans-NIH initiatives to leverage the enormous talent and resources that exist across the NIH has enabled many new research initiatives in clinical immunology, new imaging modalities, systems biology, biodefense, HIV, stem cells, biomarkers, and epigenetic regulation of gene expression.

Individual intramural programs have collaborated to take the lead in new approaches to translational research, such as the NIH Chemical Genomics Center (NHGRI), the high-throughput RNAi screening program (NCI and NHGRI), the image probe development center (NHLBI), and a new cGMP PET facility (CC and NIBIB). The Clinical Center remains the foremost clinical research facility in the world, and through its online clinical research training program and coursework in managing a clinical research facility, it is a role model and potential resource for the aspiring Clinical and Translational Science Awards programs established by the NIH Roadmap. Enabling clinical research at the NIH is a major goal of the NIH leadership and a newly established Intramural Clinical Research Steering Committee.

The challenges that have developed in recent years to sustaining the research programs at the NIH are substantial, but not insurmountable. Declining budgets have led to new, more efficient ways to support research at the NIH and to a paring of less productive research personnel through outside expert review. But they have also made new recruitments and the development of new research programs more difficult.

Federal requirements such as very stringent rules restricting outside activities of research personnel, travel restrictions, salary caps, and other growing administrative requirements have affected the NIH's ability to recruit and retain top researchers. Maintaining the preeminence of the NIH Clinical Center in the face of rapidly rising costs of hospital management and pharmaceuticals is a unique challenge faced by the NIH.

The solutions to some of these problems lie within the control of the leadership and staff of the NIH; other obstacles to success are controlled by forces such as the economic health of the country and the regulatory environment in the United States, which affect all biomedical researchers. While all hospitals face budgetary constraints, the Clinical Center faces unique constraints, such as no reimbursement stream and no private philanthropy.

Yet the NIH intramural research program remains a vital, critical component of the overall U.S. biomedical research effort. With continued support from the American public and its representatives we will solve these problems and demonstrate, once again, that "the past is prologue."

—Michael Gottesman, DDIR

Commentary:

Dual-Use Research: Fostering a Culture of Responsibility

by Henry Metzger, Scientist Emeritus

A previous article in *The NIH Catalyst* reviewed the increasing concern about the deliberate misapplication of advances in biomedical research that would pose a threat to public health and safety (*NIH Catalyst*, May–June 2008). The Congressionally mandated Commission on the Prevention of Weapons of Mass Destruction Proliferation and Terrorism recognizes this public concern, stating in a report published in December: "To date, the U.S. government has invested most of its nonproliferation efforts and diplomatic capital in preventing nuclear terrorism. The Commission believes that it should make the more likely threat—bioterrorism—a higher priority." The report, "World at Risk," is available at http://www.preventwmd.gov/report.

There is general agreement that the scientific community itself must take responsibility for promoting the appropriate oversight of the disclosure, by publication or otherwise, of new findings that could readily be misapplied—so-called dual-use research findings. The importance of inculcating a "culture of responsibility" is the principal message in the draft reports on this subject by both the U.S. government's National Science Advisory Board on Biosecurity (2007) and the AAAS's Center for Science, Technology and Security Policy (2008), as well as the statement of the U.S. representative to the Biological Weapons Convention meeting that convened in early December.

The NIH Committee on Scientific Conduct and Ethics, consisting of a scientist from each intramural program, has decided that dual-use research will be the principal focus of the Research Ethics case discussions in 2009. The group has agreed on a common template that summarizes the issues, contains illustrative case studies on which the discussion can be focused, and describes the procedure to be used by investigators if they have questions related to this topic. A recently established Dual Use committee can be consulted about whether a particular research project might constitute dual-use research. Contact the committee at dualuse@mail.nih.gov. ■

Further reading

National Science Advisory Board on Biosecurity at http://oba.od.nih.gov/biosecurity/biosecurity_documents.html

- Strategic Plan for Outreach and Education on Dual Use Research Issues (Dec. 2008)
- Proposed Framework for the Oversight of Dual Use Life Sciences Research (2007)

AAAS Center for Science, Technology and Security Policy at http://cstsp.aaas.org/content.html?contentid=1899

- AAAS Workshop Report: Education of Dual Use Life Science Research (2008)

Faster Cures

by Mary Kay Floeter, NINDS

FasterCures recently issued a report with recommendations for revitalizing the clinical research in the NIH intramural research program. The report wrote: "Yet the Clinical Center is an underutilized resource. With only 1,400-1,500 active protocols per year, it rarely reaches 60 percent occupancy, and its potential as a national resource for the public health is not being met."

Let's look at that occupancy number a bit more carefully. The Clinical Center calculates bed occupancy each day from the midnight census. A patient electively admitted Monday morning and discharged Friday evening has occupied his bed at a rate of 57 percent, having been present at midnight four times during the week. Since much of our clinical research focuses on chronic conditions, many patients are admitted electively during the workweek. Unlike that of an acute-care hospital that provides emergency care, the Clinical Center census has a regular and predictable periodicity, waning on weekends and during the holidays. The staffing follows the census pattern. There are no doctors or nurses idly watching empty beds.

Achieving higher bed occupancy rates will require a change in the way we now conduct clinical research programs: Investigators and their staff will need to utilize the Clinical Center on weekends, and the Clinical Center departments will need to increase staffing to provide full coverage on weekends. Perhaps this is a good change, but we should enter it fully informed.

Editor's note: In 2003 the Milken Institute, an economic think tank, created a program called *FasterCures* with the goal of identifying and implementing solutions to accelerate the process of discovery and clinical development of new therapies for the treatment of deadly and debilitating diseases. In 2007, *FasterCures* turned its eye to the NIH to examine how to strengthen the mission and impact of our intramural research program. David Baltimore, the co-recipient of the 1975 Nobel Prize in Medicine and currently a professor of biology at Caltech, led a task force with other recognized leaders in biomedical research and research policy. This group reviewed previously published reports on the NIH intramural program and interviewed many NIH and non-NIH scientists.

In January, the *FasterCures* task force issued its report, available at http://www.fastercures.org. Many of the recommendations in the report are consistent with current trends and policies affecting intramural research. Mary Kay Floeter, acting clinical director at NINDS and chief of its electromyography section, submitted her commentary to *The NIH Catalyst* on one aspect of the report. Several higher-ranking NIH scientists disagree with the task force's calculation of Clinical Center occupancy, which in fact has been 60 percent or higher every year for the last seven years measured by a five- or seven-day census. Nevertheless, a two-thirds occupancy rate represents a significant underutilized capacity, according to Clinical Center Director John Gallin. ■

The Training Page

From the Fellows Committee: Funding Opportunity: FARE Time Again

by Catherine Jozwik, USUHS

We've all heard the adage, "It's not what you know, it's who you know." For scientists, however, both whom and what you know are critically important for a successful career. During the next few months, FelCom will sponsor two events to help you to meet other scientists and expand your knowledge.

One event is the Sixth International Opportunities Expo on April 2, which brings to the NIH valuable contacts from companies and governments from around the world. (*See announcement on page 9.*) The other event is the annual FARE travel award competition, which allows you to expand your scientific network and keep up with the most recent advances in your chosen field.

Applications for the 16th annual Fellows Award for Research Excellence (FARE 2010) competition are being accepted from February 23 through March 24. FARE, held annually since 1995, provides recognition for outstanding scientific research performed by intramural NIH postdoctoral fellows. FARE winners receive a $1,000 travel award to present their work at a scientific meeting. This is a great opportunity to showcase your achievements to influential scientists in your area of expertise.

FARE is organized by FelCom and sponsored and supported by OITE, the Office of Research on Women's Health and NIH scientific directors. Applicants submit a research abstract, which is evaluated anonymously on scientific merit, experimental design and overall quality by a panel of volunteer judges comprising NIH postdoctoral fellows, tenured and tenure-track investigators, and staff scientists.

The award is competitive, but the odds are encouraging, with about 25 percent of applicants receiving a travel award. FARE winners will present their work at the FARE 2010 awards ceremony during the NIH Research Festival and serve as judges for the FARE 2011 competition.

The competition is open to any NIH postdoctoral fellow with fewer than five years postdoctoral experience in the NIH intramural program. Pre-IRTAs performing doctoral dissertation research are eligible. Visiting fellows and scientists must not have been tenured at their home institute. Questions about eligibility should be addressed to your institute's scientific director.

Submit your application at http://felcom.od.nih.gov/subcommittee/fare.aspx. The 54 study sections have been revised and improved for FARE 2010; early submission increases the chances that an abstract will be assigned to the preferred study section. Winners will be announced by August 15. The travel award must be used between October 2009 and September 2010.

NIH fellows, staff scientists, and tenured and tenure-track investigators are encouraged to support FARE and the NIH fellows by volunteering to serve as study section judges.

For additional questions, contact your IC's FelCom representative, listed at http://felcom.od.nih.gov/members.aspx. ■

From the Office of Intramural Training & Education: Enhancing Research Efficacy, Focus on Communication Competence

by Julie Gold, OITE Leadership and Professional Development Coach

The NIH trainee population is truly international, with 70 percent of trainees representing 90 countries. As if acclimating to a new lab and a new research structure were not difficult enough, many international fellows face the additional challenge of adapting to a whole new culture, a new language, and a new style of communication.

OITE offers programming in spoken and written English and cultural coaching to help trainees gain the confidence and skills necessary to succeed as scientists. A large part of what we do is geared toward helping people feel more comfortable with American culture and the English language.

Specialized workshops offer a chance for practice with trained teachers and other international trainees, an opportunity that may not be available in the lab or at home. Increasing comfort levels with both English and American culture can lead to enhanced communication in the lab. This may mean not only better science but also a greater sense of well-being.

Here are examples of just a few of the practice opportunities offered by OITE:

- English practice, including large-group seminars and small-group workshops to practice skills taught in the seminars. Students learn tricks for speaking and understanding English usually left out of traditional English curricula that focus on vocabulary and grammar.
- Mock interviews, in which students and fellows can focus on effectively presenting their accomplishments, listening and responding well, and understanding how interviewers evaluate candidates.
- One-on-one meetings to discuss both specific challenges students and fellows have faced in understanding issues ranging from common practices in the U.S. to confusing interpersonal situations—whether in the lab or outside of work.
- Training to help understand how to be clear in making requests and in understanding what is culturally acceptable in situations such as requesting a modification to a protocol, asking for additional help, or requesting vacation days.
- Introductions to various management and personality styles that help students and fellows understand what is important to their PIs and colleagues.
- Brown bag lunches on American culture during which people ask questions about American interpersonal communication, etiquette, quirks of using frequent-shopper cards, or anything else on fellows' minds.

Sometimes our students and fellows feel that their science suffers because of difficulties in communication or interpersonal dynamics. Scientists who feel comfortable expressing themselves and listening are in a better position to move science forward. By offering programming to enhance communication competence, we are truly pleased to help our scientists further the NIH mission of extending "healthy life and reduc[ing] the burdens of illness and disability." ■

NHGRI Makes Mission Possible

by Ray MacDougall, NHGRI

The National Human Genome Research Institute Division of Intramural Research adopted a statement of vision, mission and values this past January that reflects the core, overarching principles for its more than 40 scientific investigators and 500 laboratory and administrative staff. The statement is the culmination of a 10-month process in which all NHGRI scientific investigators participated.

With the institute's intramural program's 15-year mark at hand, NHGRI Scientific Director Eric Green called for the new statement to be developed. He has been an eyewitness to the evolution of the NHGRI intramural program, launched just a year prior to his arrival at NIH in 1994.

NHGRI Scientific Director Eric Green initiated the plan to rearticulate his institute's vision, mission and values.

"I thought this was an opportune time to rearticulate a strategic vision for the research we conduct in light of significant advances in genomics and genetics," Green said.

"Drafting such a document is important for future growth of our program and for defining our unique role in both the field of genomics and the broader NIH research enterprise."

Leadership transitions at NIH and in the country added to the value of examining the intramural program's mission at this time, according to Green, along with the fact that a comprehensive NHGRI strategic planning initiative stepped off in April 2008.

The 700-word NHGRI intramural strategic vision is available at http://www.genome.gov/27529600. The final product tells just part of the story; the rest occurred behind the scenes and offers lessons in crafting such a statement in terms that are inclusive, motivational and action oriented.

Green enlisted two NHGRI branch chiefs—senior investigators Leslie Biesecker (an M.D.) and Elaine Ostrander (a Ph.D.)—to spearhead the crafting of the document. Town hall-style gatherings, faculty retreat exercises and brainstorming circles, along with critiques from multiple levels of both the rank and file and the leadership, served to engage as many NHGRI minds as possible in the endeavor.

Biesecker and Ostrander met to plan the process a few weeks ahead of an April 2008 investigator retreat, agreeing that the mission statement should provide the answer to how NHGRI intramural researchers define themselves. "We knew we would want to be as inclusive as possible, expressing a set of core values," Ostrander said.

At the retreat, they introduced the process by first drawing inspiration from the missions of iconic government agencies such as NASA, successful private companies such as Starbucks and Microsoft, and even the science fiction of Gene Roddenberry: To boldly go where no man has gone before.

They worked through tepid enthusiasm early in the process by creative means, encouraging dialog under the warmth of springtime sun at the retreat and subsequently hosting town hall gatherings in their homes.

"There was a vast amount of eye rolling at first, in part because it was hard to articulate why we were doing this," Ostrander rememberd. The exercise required developing a big picture view. "It turns out to be a really important thing to do," she said. "We needed to have a document to use in response to those who ask us how NHGRI is unique."

At those early town hall meetings, in the absence of the top NHGRI leadership, small groups of investigators were challenged to come up with a set of core values and an overarching statement. "It was striking how similar individual statements were to each other," Ostrander said.

They were encouraged by the solidarity of purpose. Biesecker and Ostrander synthesized content from the town halls into a rough document presented at a meeting on campus for free-for-all discussion among all NHGRI investigators. Green and other institute leaders attended this meeting and chimed in with their views about the document for the first time.

"We received really great comments" from everyone, Ostrander said. "They were measured, but definitely were going to have their time to go at it."

Debate and discussion at this meeting focused on thematic thrusts, placing into sharper focus such tenets as genomic variation, evolution and clinical research. Green and NHGRI Deputy Scientific Director Andy Baxevanis subsequently forged further into the process of grooming the document.

"Eric had a lot of substantive comments, and Andy was able to come up with the right words," Ostrander said. "Our focus at this point was to be sure the words hadn't lost their meaning along the way. Reflecting back six months to the beginning of the process, we recalled that the memorable corporate missions we looked at used strong language and the ones we couldn't remember used long elaborate qualifiers to make sure no one was offended. We ended with a document that I think reflects the views of NHGRI investigators."

Elaine Ostrander and Leslie Biesecker spearheaded the crafting of the document. Photos courtesy of NHGRI and The NIH Record*, respectively.*

At the annual NHGRI intramural program retreat this past October, Biesecker and Ostrander presented the new strategic vision to NHGRI's Board of Scientific Counselors, who provided valuable additional feedback. Subsequently, the document went through a few final stages of evolution, capturing some elements of a research charge to "make it more of a living document," Ostrander said.

With satisfaction that the final strategic vision provides a resource for investigators to explain just what the NHGRI intramural program is and does, Ostrander added, "All of us have gone back to use these sound bites." ■

Editor's note: The NIH Intramural Research Program as a whole also embarked on the process of assessing and rearticulating its mission, vision, guiding principles and distinguishing features. This will be published later this year as part of a larger document describing NIH intramural research.

Revitalizing Clinical Research in the Intramural Research Program

by Dan Kastner, Deputy Director for Intramural Clinical Research

The following essay augments an editorial by Michael Gottesman and Dan Kastner in the November–December 2008 issue of The NIH Catalyst.

In this the first *Catalyst* of 2009, I have the distinct pleasure of introducing myself as the Deputy Director for Intramural Clinical Research (DDICR) and chair of the newly formed Intramural Clinical Research Steering Committee (ICRSC). The overarching goal of the DDICR and ICRSC is to help revitalize clinical and translational investigations in the NIH intramural research program (IRP).

At the beginning of this new year we find ourselves at a critical juncture, with the intramural clinical research enterprise having been eroded by a number of long-standing trends, some peculiar to the IRP and some common to the broader clinical research enterprise, exacerbated by five years of flat NIH budgets. Our challenge is to develop a visionary agenda and novel paradigms that will allow the IRP to take full advantage of its unique opportunities in clinical and translational research within the broader context of the NIH mission.

The IRP has been and should continue to be ideally suited to clinical and translational research, with the world's largest research hospital in close proximity to first-rate basic science, stable funding that permits patient cohorts to be followed over prolonged periods, a review system that encourages projects with substantial intellectual risk but the possibility of great benefit, and the ability to admit patients and perform studies without the permission of third-party payors.

Dan Kastner is an NIH Distinguished Investigator, the clinical director for NIAMS, and the newly appointed Deputy Director for Intramural Clinical Research.

"With increased outside scrutiny by patient advocacy groups crying out for cures, a new administration sympathetic to renewed growth in biomedical research, and a new NIH director yet to be chosen, change of some sort is imminent, and it is incumbent upon us to distill our own experience in formulating the best possible plan to maximize the clinical impact of the intramural research program."

With increased outside scrutiny by patient advocacy groups crying out for cures, a new administration sympathetic to renewed growth in biomedical research, and a new NIH director yet to be chosen, change of some sort is imminent, and it is incumbent upon us to distill our own experience in formulating the best possible plan to maximize the clinical impact of the IRP. In this essay I will outline my own perspective on intramural clinical research, summarize what I believe to be the critical challenges facing clinical research in the IRP, propose a dozen steps to reinvigorate our intramural clinical research enterprise, and summarize the role of the DDICR in clinical research and the current activities of the ICRSC.

Given the unique facilities and resources available on the Bethesda campus, it is my firm belief that clinical research should be a major focus of the IRP, with an emphasis in five specific areas of clinical investigation. First, the IRP is extremely well suited as a clinical laboratory to study human biology and pathophysiology, taking advantage of the freedom to perform tests based on scientific merit rather than insurance company approval and on the close physical and intellectual proximity of bench and bedside.

Second, continuing in the same vein, the IRP has a long reputation for studying rare diseases that may inform our understanding of normal human biology, both because of our long-recognized reputation as a quaternary referral center and our ability to subsidize patient travel from sites near and far. The new Rare and Undiagnosed Disease Program at once amplifies and capitalizes on these strengths.

Although the IRP can also play an important role in the study of common diseases, I think it is important particularly to define those areas in which the unique resources of the IRP can complement studies already underway extramurally. A third area in which the IRP can excel is in the conduct of high-risk interventional trials for life-threatening conditions for which no adequate treatment options currently exist. However, Phase III studies of new agents in common diseases may be less desirable for the IRP, because there are already mechanisms for such studies to be conducted in academic medical centers or even through networks of private physicians.

Fourth, the IRP presents opportunities for studies that rely on sophisticated or expensive technologies such as advanced imaging that may not be available in extramural settings. Fifth, as evidenced by the new Center for Human Immunology, the IRP can be the crucible for testing new models for trans-institute clinical investigation.

In all cases, we must never lose sight of the fact that no matter how much intellectual and personal satisfaction we may derive from our research careers, ultimately we are serving the public, who pays our salaries and rightly expects something in return.

Focused intramural clinical research can have an important impact on the diagnosis and treatment of human disease, catalyzed by all of the special opportunities noted above. In my own case, I've been very fortunate to be able to use these resources to study inherited disorders of inflammation. Over a 20-year period our group has found genes underlying known illnesses and stumbled upon genetic variants that define heretofore unrecognized diseases.

Each of these several projects has grown out of encounters with specific patients at the NIH Clinical Center and has led to further clinical and translational studies that have elucidated new pathways in innate immunity and established life-saving treatments. The patients have been the common threads that brought

M.D.s, Ph.D.s, and M.D./Ph.D.s together into multidisciplinary teams. Patient-centered research excites in a way that no cell line or animal model can, paying rich dividends to us, to our patients, and to the public at large.

During the past several years I have become increasingly aware of the overall status of clinical research at the NIH as a senior investigator, as a member of the Blue Ribbon Panel on the Future of Intramural Clinical Research (chaired by Ed Benz, President of the Dana-Farber Institute, and Nobel laureate Joe Goldstein of the University of Texas Southwestern Medical Center at Dallas), and for the last three years as Clinical Director of NIAMS. Over the 23 years that I have been in the IRP there has been a gradual decline in clinical research activity, which has been widely noted, with the Clinical Center inpatient census now hovering around 65 percent and the number of new tenure-track clinical investigators decreasing.

At the heart of the National Institutes of Health lies the Clinical Center, where bench meets bedside. The Clinical Center is the largest facility in the world devoted purely to clinical research. But maintaining an appropriate clinical research portfolio at the NIH is threatened by the rising costs of patient care and operating hospital facilities, by the numbers and quality of physicians entering the field, and by a focus on exciting progress in laboratory research. (Aerial photography by Duane Lempke, Sisson Studios, Inc.)

At least part of the problem is budgetary. With the institution of a formula that passed the unit costs of clinical research on to the NIH institutes in the late 1980s, Clinical Center admissions dropped, unit costs increased, and there was a significant exodus of talented clinical investigators. These trends were partially reversed by the institution of the "school tax" model proposed early in Harold Varmus' tenure as NIH director to stabilize IC contributions to the CC budget, whereby the Clinical Center budget is apportioned to the institutes according to the size of the institute's intramural program and not the level of hospital utilization, a formula that tends to encourage clinical activity.

In the present era of prolonged flat budgets, however, the funds raised by this mechanism have not kept up with the cost of running a state-of-the-art clinical research hospital, leading to "cost sharing" that threatens to undercut the rationale for the school tax, incrementally. To be fair, if the Clinical Center budget were to keep pace with medical inflation, in the current budgetary environment it would be necessary to make different, but perhaps equally painful, choices.

Although financial relief would alleviate some of the problems of the intramural clinical research program, substantial challenges would remain. Some of the problems are generic, having been noted in many academic medical centers across the country. These include the prolonged length of time that it takes to obtain training in both clinical medicine and one's chosen area of research; the perception that laboratory research provides a more sure path for physician-scientists to advance; the unavoidable reality that research involving patients is by its very nature time-consuming and unpredictable; the length of time that it takes to obtain scientific and ethical approval for human-subjects protocols; and the problem of receiving appropriate credit for contributions to translational projects that include collaborators from multiple institutions and disciplines.

There are also a number of challenges that are unique to or accentuated in the IRP. Recruitment of outstanding clinical fellows can be difficult because academic medical centers try to hold on to their best medical residents; because the clinical-training environment in specific disciplines in the IRP may be weighted toward unique subsets of patients; and because of the perception, right or wrong, that clinical fellows at the NIH get insufficient exposure to the grant-writing process that most probably will be their future.

At the level of senior investigators, salary differentials remain in some specialties that make it difficult to recruit or retain highly qualified individuals. On the Benz-Goldstein Committee we also noted that, as evidenced by the status of the clinical leadership in some of the NIH institutes, clinical research is sometimes not given appropriate priority within the IRP, despite its visibility and importance to the public.

More recently, a subcommittee of the Medical Executive Committee (MEC) chartered by the Intramural Working Group and chaired by NIAID Clinical Director Cliff Lane found that intramural investigators regard the protocol development and approval process as a the largest logistical hurdle for conducting clinical research in the IRP. Perhaps such regulatory issues are compounded by the risk-averse culture of a government institution, which may be at odds with the (intellectual) risk-taking on which the IRP prides itself.

Finally, I would note that the number of intramural clinical investigators who serve as physician-scientist role models has gradually decreased. Seeing Tony Fauci, a busy institute director, rounding with the NIAID team on Wednesday mornings speaks volumes about his own priorities and the priorities of his institute. With the graying of the NIH and a shift towards a more basic-oriented faculty and leadership, the number of such physician-scientist role models has markedly declined since I first joined the IRP in 1985.

In response to a recommendation of the Benz-Goldstein Blue Ribbon Panel, the position of DDICR was created to strengthen support and planning for clinical research in the office of the Deputy Director for Intramural Research (DDIR). Since I assumed this position in early November, I've spent considerable time thinking about the challenges before us and the opportuni-

Revitalizing Clinical Research

continued from page 7

ties for change. In relatively broad conceptual terms, I list 12 ways in which we can work to reinvigorate the intramural clinical research enterprise:

1. With the appointment of the new NIH director, it will be essential that a vision and list of priorities for intramural clinical research be firmly established at the top, with involvement of the leadership of the various ICs and intramural programs.

2. We should strive for broader participation in the ongoing clinical governance structure, with involvement of IC directors, scientific directors, clinical directors, and active clinical investigators. Although the MEC and Board of Scientific Directors should clearly maintain important roles in this area, the role of the IRP should be coordinated with institute-wide initiatives in order to maximize intramural leadership in projects that it is likely to do best.

3. With the involvement of the new NIH director and the clinical and scientific leadership of the NIH, we must settle on a way of funding the Clinical Center that is fiscally responsible, allowing for updating of capital equipment, but that does not unduly discourage hospital use by intramural investigators.

A patient room in the Mark O. Hatfield Clinical Research Center, which opened in 2005. In 2008 there were 1,450 clinical protocols under way in the Clinical Center that operated at an approximate 64-percent capacity. Approximately 24 percent of NIH principal investigators conduct these research protocols, or 202 tenured principal investigators among 857 tenured scientists. Photo courtesy of the Clinical Center.

4. Consistent with the previous point, we must find ways of funding clinical trials of drugs and biologicals that do not penalize the investigator. The IRP has a long and proud history of doing comparative efficacy studies of competing therapies that no pharmaceutical company would fund. Assessing drug costs to an NIH laboratory or branch, as is currently being debated, would have the predictable effect of discouraging trials of all but the least expensive agents. Relying upon the largesse of the pharmaceutical companies is a risky proposition in these troubled economic times. It also invites the conflicts of interest that are commonplace in the extramural world, thus robbing the IRP of one of its most distinctive features and robbing the public of an important type of unbiased clinical research that regrettably is not done almost anywhere else.

5. We must develop imaginative new career paths for recruiting the best and brightest young investigators to the NIH clinical program. One such possibility, championed by Bob Balaban, the NHLBI scientific director, would entail a highly competitive 10-year program whereby young clinical investigators could participate in the NIH tenure track and eventually choose either to stay with the IRP or to have transitional funds to return to the extramural world.

6. In the tenuring process, we should give appropriate credit to team scientists, whether they be clinical investigators, epidemiologists, or basic scientists participating in multidisciplinary projects, so long as these individuals make identifiably important contributions to their respective projects.

7. In the area of IC leadership, we must enhance the role of the clinical directors by providing defined resources and access to the IC directors and by ensuring that adequate emphasis be placed on new recruitments to the clinical director positions as they open.

8. We must encourage clinical research activity at all levels, perhaps by offering pay incentives to clinical investigators for substantial initiation of clinical protocols.

9. We should develop new models for the scientific review of clinical programs, including standardized and streamlined scientific review of clinical protocols and engagement of the Boards of Scientific Counselors to encourage and reward intramural clinical research initiatives that take advantage of the unique clinical and translational resources of the IRP.

"In all cases, we must never lose sight of the fact that no matter how much intellectual and personal satisfaction we may derive from our research careers, ultimately we are serving the public, who pays our salaries and rightly expects something in return."

10. We should make the overall human-subjects protocol review process more user-friendly by developing new resources, whether within NIH institutes or collaboratively between or among institutes, in order to assist investigators in the preparation and implementation of protocols and to accelerate the process.

11. We must provide incentives for and broaden investigator participation in the human-subjects review process. Members and chairs of the Institutional Review Boards (IRBs) should include seasoned clinical investigators who can bring both experience and wisdom to bear to balance human-subjects protections with the urgency to advance medical science, commanding the respect of their clinical research communities. Membership on other busy committees often appears much more desirable than IRB participation, despite the centrality of IRBs to our mission. We need to be both imaginative and generous in defining "carrots" that will change this perception, while staying clear of "sticks" unless absolutely necessary.

12. We should initiate a voluntary program whereby each IC would attempt to recruit at least one new tenured or tenure-track clinical investigator, who actually sees patients and writes protocols, within the next two years.

I should point out that these proposals are intended to stimulate discussion while introducing the broader NIH community to my vision for clinical research in the IRP. However strongly I believe in them, they are not mandates. In fact, my formal role is relatively modest. As spelled out in the ICRSC Charter, the DDICR chairs the ICRSC, approves appointments for

"Recruitment of outstanding clinical fellows can be difficult because academic medical centers try to hold on to their best medical residents; because the clinical-training environment in specific disciplines in the intramural program may be weighted toward unique subsets of patients; and because of the perception, right or wrong, that clinical fellows at the NIH get insufficient exposure to the grant-writing process that most probably will be their future."

tenure-track clinical investigators, reviews the career pathways of staff clinicians, and serves on the NIH Clinical Compensation Panel, the NIH Compensation Committee, the Central Tenure Committee (ad hoc), and the Board of Scientific Directors (ex officio). The DDICR also advises the DDIR and the NIH director on issues related to intramural clinical research. With all of these committee memberships the DDICR has some voice in the issues outlined above, but, to paraphrase our new president, this has more to do with the power of ideas (I hope!) than the idea of power.

The ICRSC was established by the DDIR as a forum for trans-NIH governance and policy development in the area of human-subjects research. The current membership includes two institute directors (Betsy Nabel of NHLBI and Griff Rodgers of NIDDK), two scientific directors (Lee Helman of NCI and Richard Nakamura of NIMH), four clinical directors (Richard Cannon of NHLBI, Bill Gahl of NHGRI, Markus Heilig of NIAAA, and Carter Van Waes of NIDCD), two active clinical investigators (Steve Holland of NIAID and Shelia Zahm of NCI), an IRB Chair (Howard Austin of NIDDK), and an IRB Administrator (Jean Radcliffe of Neurosciences Combined IRB). Ex officio members include John Gallin, director of the Clinical Center; Cliff Lane, chair of the Medical Executive Committee; Charlotte Holden, director of the Office of Human Subjects Research; and the head of Bioethics in the Clinical Center.

The current ICRSC Charter lists two specific areas of initial focus:

- Standards and strategies for the development, review, and implementation of human-subjects protocols, including IRB operations, support, and accountability, and ethical interactions with the pharmaceutical industry (including technology transfer);
- Standards and strategies for the development, review, and implementation of human-subjects research more broadly, including the scientific review of protocols, and the BSC review of clinical programs.

In a future issue of *The NIH Catalyst* I will give a detailed account of the progress that the ICRSC has made in formulating a bold new approach to the development and review of clinical protocols.

The front entrance to the Mark O. Hatfield Clinical Research Center shortly before its opening in 2005, as evidenced by the presence of a contruction worker and lack of the ever present patients, buses and taxis seen today. Since the Clinical Center opened in 1953, clinical research has been a key feature of the NIH intramural research program. Photo courtesy of the Clinical Center.

Clearly, we stand at the threshold of a new adventure in the life of the NIH IRP. Although the clinical program is not the only unique aspect of the IRP, it is certainly an important one. As stewards of this precious public resource, we must keep in mind that it is not an entitlement that we are here, but rather our privilege to have a role in reinvigorating clinical and translational research in the NIH IRP. ■

Sixth International Opportunities Expo

The NIH Visiting Fellows Committee (VFC) invites all NIH fellows and graduate students to participate in the Sixth International Opportunities Expo on Thursday, April 2, at the Natcher Conference Center from 12:30 p.m. to 4:00 p.m.

The Expo provides a great opportunity for fellows to obtain information on research, grants, and job opportunities available overseas and in their home countries. (Nearly 70 percent of NIH fellows are visiting scientists.) Fellows will be able to network with science and technology representatives and establish valuable contacts for the next step forward in their scientific career. Last year, the International Opportunities Expo featured science and technology representatives from government and the private sector.

For this year the VFC is excited to announce that the keynote speaker will be Jeffrey Boutwell, executive director of Pugwash Conferences on Science and World Affairs. The Pugwash Conferences bring together influential scholars from the international community to discuss key issues concerning science and technology such as agricultural biotech, HIV/AIDS, and the security of nuclear weapons.

This year's attendees will include Nature Publishing Group, Howard Hughes Medical Institute, Henry Jackson Foundation, Canadian Institutes of Health, Embassy of Switzerland, Fundación Progreso y Salud, Embassy of Austria, French National Center for Scientific Research (CNRS), and EURAXES. A list of all speakers and exhibitors will be posted on the VFC website, http://felcom.od.nih.gov/subCommittee/vfc/index.aspx, and disseminated via email. Special thanks to Fogarty International Center and OITE for sponsoring this event.

Supercomputing at Your Fingertips

continued from page 1

But that's changing, he added. More than 300 researchers from 19 institutes and centers used Biowulf last year, leading to at least 75 published research papers primarily dependent on Biowulf data-crunching. Slowly, his group, the Helix Systems Staff, led by Steven Bailey, is alerting intramural researchers to projects they never thought they could do.

"Research that would not otherwise have been possible is getting done," said Susan Chacko, a computational biologist, co-organizer of the symposium with Fellini, and a member of CIT's Helix Systems team who teaches users how to approach and use Biowulf.

Think Big

A Beowulf cluster emulates a supercomputer by networking dozens or even thousands of inexpensive computer processors—now numbering 6,300 in Biowulf, up from 80 a decade ago—running Free and Open Source Software (FOSS) such as Linux. The technology was created at NASA Goddard Space Flight Center in Greenbelt, Md., in 1994.

The technology was enabled by the dawn of cheap and relatively fast microprocessors, faster networking, and FOSS. For example, InfiniBand networking can transfer data between CPUs at 16 gigabytes per second, compared with about a gigabyte per second via Ethernet, with a latency as low as a few hundred nanoseconds.

Although "real" supercomputers are needed for singular, massive tasks, such as solving equations of general relativity for the crushing gravity near a black hole, a Beowulf cluster can handle parallel tasks nearly equally as well, tasks such as processing thousands of BLAST commands for amino-acid sequences. Some 3,000 jobs might be running on the Biowulf system at any given time, using at least 4,000 processors.

Susan Chacko

Yet Beowulf computing comes at a fraction of the price. The larger supercomputers today cost in the range of $30 million up front plus another $30 million to run for four years, Fellini said. In contrast, Biowulf was incrementally built with yearly hardware purchases of less than a million dollars.

Credit: CIT

The Biowulf cluster is housed in Building 12, occupying 3,000 square feet of space. Visitors might feel they are descending into Grendel's lair, as the heat and hum of the computers grow more intense as one approaches the system through double doors secured by a retinal scanning device. A sophisticated cooling system was installed three years ago to handle the growth.

Era of Monsters upon Us Once More

Many routine research projects these days require serious computation, Chacko said. At the NIH these include large-scale distributed memory tasks such as molecular dynamics and de novo protein structure generation, multijob calculations common in bioinformatics, anything GWAS, mass spectroscopy, biostatistics, proteomics, and computational chemistry such as calculations on PubChem.

Some molecular dynamics calculations on Biowulf take a thousand days for a millisecond's length of simulation and are thus running on the system for months to accumulate precious nanoseconds. Biowulf can handle these monster calculations or whatever your Grendel be.

Biowulf has grown with the anticipated needs of the community, Fellini said. In 2008 his group expanded the InfiniBand network and added 1,700 processors primarily to meet the demand of molecular dynamics jobs. This year CIT will increase storage capacity to accommodate terabytes of data—and that's per user, said Fellini, laughing in disbelief over how far computing has come in the past decade.

"Some users are getting the idea of scale," Fellini said. Storage will increase from 25 terabytes total to perhaps 400 terabytes for a start.

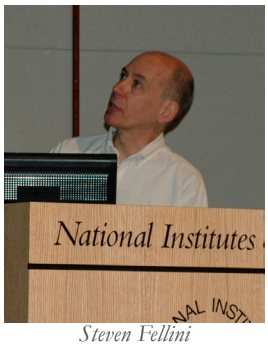
Biowulf Today

About half of the jobs on Biowulf are "swarms" of single-threaded tasks such as those required by bioinformatics or BLAST, where each BLAST search is independent of the next. Other jobs are memory-intensive tasks that take weeks or months to perform. In terms of CPU cycles consumed, molecular dynamics is the most common task. In terms of sheer job numbers, then bioinformatics tops the list.

The beauty of the system, Chacko said, is the flexibility to accommodate special projects, such as data processing needed for an upcoming conference, and the ability to halt most jobs at any point to collect data partly through a long calculation.

Researchers also have a great deal of freedom in the applications they want to run, Chacko said. The Helix team regularly installs applications it thinks the community will use, and users come with applications they've found. Some, like members of Sriram Subramaniam's lab in the biophysics section of NCI's Laboratory of Cell Biology, write their own imaging-analysis software.

At the February 3 Biowulf symposium celebrating the system's tenth anniversary, presentations covered protein-structure generation, protein-binding simulations, amyloid ion-channel modeling, GWAS, genomic variance projects, virtual colonoscopies, statistical significance assignment in mass spectrometry, and PubChem calculations. Subramaniam, a regular Biowulf user, presented a talk titled "Computing the Molecular Structures of Cells and Viruses Using 3D Electron Microscopy." Video archives of all of the talks are available at http://biowulf.nih.gov/symposium.



Steven Fellini

The legend goes that NASA's Thomas Sterling and Donald Becker named their computer cluster Beowulf after the hero of the same name in the Old English epic poem, who had "thirty men's heft of grasp in the gripe of his hand." Biowulf takes that power a bit further.

But when considering the specs—GNU/Linux parallel processing system with eight-processor configurations comprising 2.8 GHz Intel EMT64, 2.8 GHz AMD Opteron, 2.8 GHz Xeon and 1.4 GHz Itanium processors—Biowulf and Beowulf perhaps are similar in their impenetrable language.■

Heart of NHLBI's New CT Scanner

continued from page 1

Credit: C Wanick

Andrew Arai of NHLBI is involved with several clinical protocols using the new Toshiba Aquilion ONE CT scanner.

"The CT scanner may turn out to be the most sensitive tool for detecting coronary artery disease," Arai said. "Significant heart disease starts somewhere between a 50- and 70-percent blockage. If you're talking about a three-millimeter [artery], you're looking for something that's one and a half or two millimeters across… . This is the first technology that can routinely do that kind of resolution" quickly and noninvasively, he said.

His screening protocol, with patients referred to him by area hospitals, aims to determine the onset of coronary heart disease at an earlier stage, before, as is often the case, the patient learns of the disease after suffering from a disabling heart attack. Arai also is characterizing patients to see whether they fit in other heart-study protocols.

Marcus Chen, a staff clinician in the Laboratory of Cardiac Energetics, has become expert in processing images from the Aquilion ONE scanner and the point person for advice. Other CT scans, he explained, need to take five or six slabs of images to cover the entire heart, resulting in a loss of temporal uniformity. Also, the images don't always join smoothly, leaving a blurring or "Venetian blind" artifact from one image to the next that could be misread as coronary artery disease.

Although cardiac catheterization is the gold standard of coronary artery imaging, Arai said, it cannot readily identify noncalcified plaque such as cholesterol and fibrous scar tissue, major contributors to blockage and early markers of disease.

"All you would see in the cath lab would be the bright lumen [of the blood vessel] and white specks of calcium," said Arai. "One thing we are interested in from a research standpoint is the noncalcified plaque, which would just disappear in the cath lab."

But who gets tested and when? Although noninvasive, the machine does present a significant X-ray radiation dose. Arai's group is trying to assess the risk of heart disease, particularly with a second protocol he is involved in with NHGRI, and to determine who would best benefit from such a scan.

"No one right now is 100 percent sure how this will fit with medical care," Arai said. "This is one of the hot research items to try to understand the importance of calcified plaque and noncalcified plaque versus the blockages."

Researchers over the past 40 years have identified many risk factors for coronary artery disease, but these are far from perfect predictors. The CT scan might identify the earliest onset of blockage, which might be remedied by aggressive cholesterol management as opposed to treating greater blockage later with angioplasty and bypass surgery.

The new CT scanner should complement and extend other highly advanced CT scanners in the Clinical Center, including both single- and dual-source 64-slice scanners and an upcoming 256-slice CT scanner. These devices were implemented with Rod Pettigrew, director of the National Institute of Biomedical Imaging and Bioengineering, a collaborator with Arai.

"This full complement of advanced cardiovascular CT imaging devices at the Clinical Center continues the NIH tradition of being a leading center in imaging of cardiovascular disease," Pettigrew said.

The Aquilion ONE CT scanner debuted in 2007, although Johns Hopkins University in Baltimore had a prototype with 200-plus detectors in 2006. Bluemke, the formal clinical director of the MRI division at Johns Hopkins during that time, helped guide NHLBI in its purchase of the machine last year.

Jumping from 64 to 320 detectors was no simple feat, Chen explained. Rotating the internal components so fast results in a g-force of about 20 times the earth's gravity. Remarkable engineering was needed to build a scanner capable of rotating the precise medical imaging equipment in such a way. The manufacturers aimed for 320 detectors to replace the five images typically needed from a 64-detector machine.

Credit: C Wanick

Marcus Chen and the Toshiba Aquilion ONE CT scanner. Chen is a medical doctor and staff clinician in the NHLBI Laboratory of Cardiac Energetics.

The new CT scanner is operated in a collaboration between the Department of Radiology and NHLBI and is now available for patients within the Clinical Center. Bluemke and Arai encourage other clinical and research uses of the new machine and can offer expert advice. ■

Colleagues

Office of Technology Transfer, Bringing Home the Bacon

by Christopher Wanjek

What totals 449,890,024 and rhymes with holler? No, it's not the number of peptides studied by any NIH scholar or the bacteria count on desktops with the worse squalor.

This handsome sum of nearly a half billion refers to the numbers of dollars collected from NIH royalties since 2003 and managed by the NIH Office of Technology Transfer (OTT).

The NIH has few peers when it comes to biomedical patents and licenses, commercialized products resulting from these activities, or the amount of royalties collected. The NIH intramural research program accounts for most of the royalties collected by all U.S. federal government agencies.

There is a misperception held by some, from the "outside" as well as from within the NIH, that government scientists cannot profit from their inventions or, at a minimum, not profit well. The roughly $10 million handed out each year to scores of NIH inventors suggests otherwise.

The OTT wants to set the record straight and, at the same time, highlight its services to the NIH intramural community. Doing so can help recruitment and also increase morale. The first step in this endeavor has been the creation of a website, called the Product Showcase, at http://www.ott.nih.gov/productshowcase/.

Gardasil®, Kepivance®, Velcade®, Thyrogen®—the site reads like a glossy annual report from a proud pharmaceutical company. Yet while these drugs have been further developed and marketed by various companies, they are all homegrown. Products showcased on the site are used every day to detect, treat, or prevent disease or to assist researchers as they continue to explore ways to develop newer and more effective health care products and procedures.

The OTT is responsible for facilitating the transfer of NIH inventions to the commercial sector for further research and commercial development into products that benefit the public health. The OTT evaluates, patents, markets, licenses and monitors NIH intramural inventions and administers the resulting royalties. The OTT also has the lead responsibility for NIH intramural and extramural technology-transfer policy matters.

Since 2003, the NIH has had 572 U.S. patents issued and entered into 1,575 licenses. There were 88 U.S. patents issued and 259 licenses in fiscal year 2008 alone.

A most recent example of OTT's handiwork in helping NIH scientists with their handiwork is the NIAID's "Mast Cell Line for Research on Allergies and Inflammatory Diseases," which has won the 2009 Excellence in Technology Transfer Award from the Federal Laboratory Consortium for Technology Transfer (FLC).

This technology, also called the "LAD2 cell line," is a research tool that has been transferred to scientists worldwide, enabling research on a variety of allergic and autoimmune diseases. This national-level FLC award recognizes the significant impact that the technology and its successful transfer to others for research and commercial use has enjoyed.

Look for an expansion of the Product Showcase and OTT's section on success stories in the months to come. ■

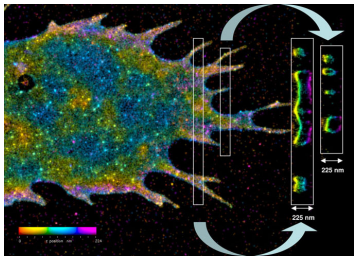
PALM Gets a Hand: a first-person report on imaging breakthroughs

by Catherine Galbraith, NIDCR

Super-resolution microscopy was voted Method of the Year by *Nature Methods*, and several labs at NIH have had significant roles in developing one of the techniques, photoactivated localization microscopy (PALM).

PALM uses photoactivatible fluorophores to illuminate a small subset of spatially non-overlapping proteins. The location of these tagged proteins can then be determined with nanometer precision. The process is repeated many times, and all of the single-molecule positions are merged to create a super-resolution image that overcomes the resolution barrier of 200–250 nm imposed by Abbe's Law, which governs the diffraction limit of light.

The story of PALM is as colorful as the images it generates, with a then-jobless physicist named Eric Betzig developing the concept in his cottage in rural Michigan. Betzig and former Bell Labs colleague Harald Hess further developed the technique, first in Hess' living room and then in Jennifer Lippincott-Schwartz's lab in the NICHD Cell Biology and Metabolism Branch. At this time, Sam Hess, a former postdoc in Josh Zimmerberg's NICHD lab and now at the University of Maine, published the conceptually similar fPALM technique.



iPALM pinpoints 3D distribution of fluorescently tagged membrane proteins. Cross-sections of small regions of the image are shown in the boxes on the right and reveal two layers of the labeled membrane proteins, at the top and bottom of the cell. Courtesy of Hess et al.

Betzig and Hess have moved to HHMI's Janelia Farms, yet PALM continues to grow at NIH through a trans-NIH imaging initiative guided by Zimmerberg. PALM originally required two to eight hours to collect a single color super-resolution image of a fixed specimen. New versions of PALM and fPALM provide ways of actually visualizing the dynamic molecular interaction between multiple proteins in living cells.

For example, James Galbraith of NINDS and I have collaborated with the Betzig lab to develop multicolor PALM and live-cell PALM. With live-cell PALM we can collect a super-resolution image in 20 seconds and look at the molecular assembly of the adhesive structures that cells use to migrate. Lippincott-Schwartz's group worked with the Betzig lab to create sptPALM, short for single-particle-tracking PALM. Their version of sptPALM can simultaneously highlight spatial and temporal heterogeneities of multiple proteins in the membranes of living cells. These techniques can be used to elucidate new levels of molecular protein assembly mechanisms.

More recently, James Galbraith and I, Lippincott-Schwartz's lab and Clare-Waterman's group in NHLBI, have been developing the interferometric or iPALM technique invented by Harald Hess and Gleb Shtengel at Janelia Farms. With iPALM, we can pinpoint fluorescent labels in their specimens to within 10–20 nm in three dimensions, accurate enough to image subcellular ultrastructure. iPALM provides a way of closing the gap between electron tomography and light microscopy, enabling both molecular specification and resolution of cellular nanoarchitecture.

Nature Methods provides an overview of PALM at http://www.nature.com/nmeth/journal/v6/n1/full/nmeth.f.244.html, with commentary by Lippincott-Schwartz and her colleague Suliana Manley. ■

Colleagues

On Tenure Track

Yamini Dalal, head of NCI's Chromatin Structure and Epigenetic Mechanisms lab, uses patient-derived tumor cells and nanoscale imaging to answer a question ancient to modern biology and key to understanding molecular mechanisms of cancer: How are centromeres regulated?

All cellular DNA in an organism is identical, but epigenetic regulation provides a second organization level allowing otherwise indistinguishable cells to attain different phenotypes, and hence different functions, throughout the body. Intimately related to DNA-packaging proteins called histones, epigenetic regulation is inheritable, with each cell lineage tightly controlled from birth to fate.

Yamini Dalal

Dalal's research focuses on centromeres, which attach to microtubules allowing cell division every cell cycle. Normally, each chromosome contains just one attachment site maintained for generations in the absence of a unique DNA signature. This is a fundamental example of epigenetic regulation. Regulation of the centromere is poorly understood, but consequences of dysregulation are apparent in cancer cells where centromeric proteins becomes spatio-temporally misplaced across the chromosomes. In Dalal's postdoctoral work at the Fred Hutchinson Cancer Research Institute in Seattle, she discovered an unusual molecular structure driven by the centromeric protein CenH3, which specifically marks a genomic region as the centromere. CenH3 overexpression by severalfold in many tumor cells creates multiple centromeric regions rather than just one per chromosome.

Human primary tumor cells from Thomas Reid's laboratory in the Cancer Genetics Branch provide Dalal an excellent model for epigenetic dysregulation and CenH3 overexpression. In collaboration with Paul Smith's laboratory in Biomedical Imaging, she uses atomic force microscopy (AFM) to analyze macrobiological chromatin samples from these cancer cells placed on tiny square substrate grids. The amplified deflections off the molecules render three-dimensional images, allowing real-time protein interaction observation at the single molecule level. Essentially, Dalal can take native cancer cell chromatin out one day to image with AFM the next. Understanding CenH3 dysregulation mechanisms will provide insight into cancer cell biology and perhaps other diseases by addressing basic biological questions such as "Where do centromeres come from?" and "How is epigenetic memory regulated?"

Access to experimental techniques from nanoscale to human tissue is where the strength of her work lies, an advantage found only at NIH. "I can't imagine doing [this type of work] in another place; the possibilities are endless. It's like being a kid in a candy shop; you have to restrain yourself and realize you can't do it all."

In such a rich environment with "the best people in the world, the quality of science is spectacular and the energy is really unbeatable," she said. Dalal takes the NIH and NCI missions seriously, having resources to actually do cancer research and not just draw parallels. Dalal is eager to recruit two postdocs and foster collaborations with those interested in epigenetics, mitosis, and centromeres. "LRBGE is a close-knit unit with great people doing superb science all in one building."

Rick Fairhurst, chief of the Malaria Pathogenesis and Human Immunity Unit, combines clinical fieldwork in Cambodia and Mali with research at NIH to understand mechanisms of natural resistance to malaria. Epidemiological observations of 2,000 malaria patients annually and laboratory research into parasitic disease mechanisms aim to reveal why "only" one to two percent of African children infected with malaria parasites die. Fairhurst hopes to learn a "lesson from Mother Nature and how she protects her kids" for vaccine and therapy development against malaria.

Approximately 300 million children suffer annually from malaria, and three million die from the disease. Chances of survival are greater due to genetic abnormalities, such as sickle cell trait and alpha-thalassemia, naturally selected to high prevalence because they afford malaria resistance. Resistance lies in the ability to handle parasitic burden, as opposed to lessening the burden. A resistant child, for example, could have parasites infecting five percent of red blood cells, or 200,000 circulating parasites per microliter of blood, and be completely healthy.

These genetic abnormalities weaken the parasites' strength by impairing the function of PfEMP1, now considered the real molecular killer, essentially by destabilizing the parasite's binding affinity to small blood vessels. Fairhurst believes that a better understanding of PfEMP1 and its role in causing disease is key to developing effective new malaria therapies.

Rick Fairhurst with unidentified papayas

Fairhurst credits excellent clinical M.D./Ph.D. training from University of California, Los Angeles, as crucial to success as an investigator. "Any results I obtain in the laboratory have to be consistent with epidemiological observations in the field to continue studying it seriously," he said. Three months spent overseas each year and his 25 trips to Africa and 12 to Cambodia are testimony to his involvement in the fight against malaria at ground level.

Observing real patients and parasites in the field have led to several questions to address in the laboratory: How do sickle-trait red blood cells impair PfEMP1 interactions with host cells? Which molecules mediate parasite-induced inflammatory reactions? If these genetic abnormalities are means to the same end via reduced PfEMP1 function, which molecular variation has the greatest protective effect? The answers will uncover how only a small percentage of parasite-infected children die from malaria and lead to effective vaccinations or therapies to save three million annually.

Expensive and labor-intensive, Fairhurst's ambitious research program relies on a supportive environment and continuous funding. For example, he and co-principal investigators recently enrolled 1,300 children in Mali and treateed approximately 775 episodes of malaria over the first five months of the study. Much time and energy goes into obtaining blood samples from these children. Hoping to forge collaborations locally, Fairhurst said that these samples are available to anyone interested in exploring hypotheses related to red cell pathology or inflammation.

—text by Katherine Jakubs

Colleagues

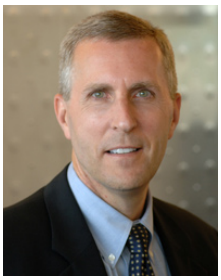
Recently Tenured

David A. Bluemke *is the director of the Clinical Center's Department of Radiology and Imaging Sciences. He received his bachelor's degree in chemical engineering from the University of Wisconsin-Madison and holds an M.S. in business from Johns Hopkins University (Baltimore). As a graduate of the University of Chicago, Bluemke earned his medical degree as part of the Medical Scientist Training Program and earned a Ph.D. in Biophysics and Theoretical Biology. His clinical training led him to residency at Johns Hopkins Hospital (Baltimore), followed by a fellowship in cross-sectional imaging in diagnostic radiology. Expanding his career at Hopkins, Bluemke served as clinical director of the MRI division before coming to NIH. His recent awards include the Outstanding Teacher Award from the Internal Society of Magnetic Resonance in Medicine and the Elite Reviewer award from the* Journal of the American College of Cardiology.

My research focuses on cardiovascular disease and its complications and seeks to better understand how subclinical disease can be detected, described, and tracked over time with newly developed imaging technologies. We applied these new methods to study a rare genetic disease called arrhythmogenic right ventricular dysplasia (ARVD). Through both single-center and multicenter trials, we evaluated the relationship between myocardial dysfunction and myocardial fibrosis in this condition. We are evaluating the relationship between genetic mutations and subclinical disease expression using advanced imaging as the outcome measure.

I am currently applying state-of-the-art cardiovascular imaging technologies in large cross-sectional and longitudinal population-based studies. An example of this is the Multi-Ethnic Study of Atherosclerosis (MESA), a study of 7,000 adults in six centers in the United States, sponsored by NHLBI. The MESA study has revealed the importance of myocardial size as well as structure and function in relationship to increased risk for cardiovascular events. The most common cardiovascular event in the MESA trial has been heart failure. MRI of the heart has revealed the importance of myocardial mass and remodeling above and beyond traditional risk factors for predicting heart events. Our future studies will allow us to study individual regions of the heart using highly sensitive methods to assess myocardial strain as an early indicator of myocardial dysfunction.

Whereas MESA is a general, population-based study, my lab is also studying the role of myocardial mechanics in type 1 diabetes in a 28-site multicenter study (EDIC study) sponsored by NIDDK. This study will allow us to assess the effect of diabetes care on myocardial dysfunction and compare the impact of the abnormal glycemic state in the type 1 and type 2 diabetes cohorts.


David A. Bluemke

Besides diabetes, metabolic derangement can be the result of dyslipidemia. We have recently identified sex differences in myocardial fat content. To further assess these effects, we are developing new MRI techniques to rapidly measure myocardial steatosis in relation to myocardial function. We plan on validation of these methods in animal studies with subsequent trials in patients at multiple sites who have received multiple medical therapies.

Advancement of technology is critical in a dynamic field such as medical imaging. We will be partnering with industry to develop novel imaging tools using MRI that have not previously existed in a clinical setting for simultaneous, multimodality imaging signal acquisition. These approaches should yield advances that allow us to create new opportunity that has not previously existed for early disease diagnosis and therapeutic targeting. ■

Meetings

Program Expanded for 2009 Biospecimen Symposium

The NCI Office of Biorepositories and Biospecimen Research is hosting its 2nd Annual Biospecimen Research Network Symposium from March 16 to 18, expanded from one day to three days this year to meet the growing demand for guidance on the proper storage and usage of biospecimens.

Human biospecimens are the foundation of the translational research that will transform patient care. The focus of the March symposium, called "Advancing Cancer Research through Biospecimen Science," is on the significant impact of preanalytical biospecimen variables on cancer research and molecular medicine.

The meeting will be held at the Bethesda North Marriott Hotel and Conference Center. Registration is free but required; visit http://www.brnsymposium.com for more details.

For more than 100 years, physicians have been collecting biospecimens (blood and other tissue samples) to detect and study disease. In the post-genomics era of biomedical science, biospecimens (blood and tissue samples) are assuming an even more prominent role in efforts to identify the key genes, RNAs, proteins, and signaling networks involved in cancer and then use that information to detect cancer at its earliest stages and develop a personalized therapeutic regimen to treat it.

The future of personalized medicine depends on the ability of researchers to compare the molecular workings from hundreds of malignant and normal tissues and tease out the differences that have diagnostic and therapeutic value.

Unfortunately, most of the millions of biospecimens in collections around the world are not suitable for making the type of comparisons that modern research demands. No standard protocol has governed how surgeons collect, pathologists prepare, and tissue banks store biospecimens. And, given the sensitivity of today's analytical techniques, it can be difficult to distinguish between molecular fingerprints related to cancer and those arising from the way a given biospecimen was handled.

The National Cancer Institute initiated the Biospecimen Research Network (BRN) in early 2006 to coordinate and support systematic investigation into how collection, processing, and storage of human biospecimens affect subsequent molecular analysis. The BRN sponsors, conducts, and collaborates on studies to evaluate the effects of biospecimen preanalytical variables on the outcomes of molecular assays for cancer diagnosis and research.

The BRN Symposium aims to help the cancer community develop comprehensive solutions addressing preanalytical biospecimen variability in cancer research; encourages participation from all stakeholders to improve the quality of biospecimen-based research; and fuels advances in personalized medicine. The symposium also will provide a forum to explore many important issues relevant to biospecimen science. ■

Meetings

Using the Past to Doctor the Future

by Vanessa C. McMains, NIDDK

The Office of NIH History is organizing a conference to examine the role of the physician researcher over the past 50 years and specifically address the trend of the declining number of research physicians. Senior administrators, physicians, historians, and social scientists will share their perspectives on the trends observed in the past, the challenges we now face, and suggestions to deal with the mounting problem.

The conference, "Research Physicians: From Golden Past to Threatened Future," is March 26 and 27 at The Cloisters, Building 60 on the main NIH campus.

Traditionally, medical doctors have contributed significantly to biomedical research with the benefit of being able to translate experiments from the bench to their use in patients. We are moving, however, toward an age in which major biomedical research is being conducted less and less by medical doctors and more and more by Ph.D. researchers. Although medical breakthroughs are not declining, there seems to be a pattern of disconnect between patients and their treatment that conventionally was bridged by physician researchers.

Many factors contribute to the decrease in medical students going into research, but one of the most significant is that medical students accrue massive debt through their medical training, said Robert Martensen, the history office director. Careers in research might not be financially rewarding for quick returns to pay off mounting bills. Also, research training is a difficult path, there is strong competition for research grants, and incentives are low.

Furthermore, there has been a change in how medical research operates, according to Martensen. Medical research today involves significantly less patient interaction than in the past. "Changes in American medicine rely heavily on tests and imaging studies and less on direct perceptual knowledge of the patient and their history," Martensen said.

Various types of research organizations have developed different techniques and models for keeping physicians in biomedical research. The two-day March conference will examine these methods , along with their successes and failures.

The meeting will bring together a multidisciplinary team to examine the policies and initiatives used by foundations, universities, government agencies. and pharmaceutical companies to retain physician researchers. "The idea is that by bringing organizational leaders, administrators, and social scientists together, we can actually use history to illuminate past and present policy," Martensen said.

The conference proceedings will be posted on the Office of NIH History website at http://history.nih.gov, which will include an active discussion forum and web links to related sites and resources. The organizers hope to come up with a list of suggestions or guidelines as a reference for research organizations in dealing with physician researchers. ■

Lecture Series and Symposium Honor NIH Greats

In the past two years, the NIH intramural community witnessed the passing of some of its finest researchers. Ed Rall, Jack Robbins, John Daly, Earl Stadtman, and Stephen Straus are among those who have died recently.

The NIH has celebrated these researchers' lives and careers with various types of tributes and services. This year, Rall and Straus are being honored with a lecture series bearing their names, and Stadtman will be honored with a symposium.

Rall was a consummate scientist, a charismatic mentor and recruiter and an engaging Renaissance man who profoundly influenced the style and substance of the intramural program. He died in February 2008. Rall recommended the addition of a cultural lecture to the Wednesday Afternoon Lecture Series in 1984 while he was the deputy director for intramural research, and so it is fitting that this lecture now bears his name.

The first J. Edward Rall Cultural Lecture was held on February 11. Speaker Atul Gawande, a Harvard-trained surgeon at Brigham and Women's Hospital in Boston and staff writer for the *New Yorker* magazine, spoke of the global problem of surgical complications. This lecture series reflects what was Rall's own broad cultural interests beyond science and his desire to enrich the NIH scientific community

Straus was the first director of the National Center for Complementary and Alternative Medicine, stepping into this position in 1999 as a highly productive and respected researcher in the NIAID Laboratory of Clinical Investigation. His expertise was in basic and clinical research related to conditions including chronic fatigue syndrome, Lyme disease, HIV, chronic hepatitis B virus and genital herpes infections, and chronic post-herpetic pain. Straus published more than 400 original research articles and edited several books before dying from brain cancer in May 2007 at the age of 60.

On March 10, NCCAM will hold the inaugural Stephen E. Straus Distinguished Lecture in the Science of Complementary and Alternative Medicine. Sherwin Nuland, Clinical Professor of Surgery at Yale University, will present a lecture titled "Chinese Medicine, Western Science, and Acupuncture" in the Masur Auditorium at 2:30 p.m. with a reception and poster session to follow at 4 p.m. Nuland is author of *How We Die*, a New York Times bestseller and National Book Award winner, among other books.

Stadtman was among the best-known NIH researchers and a pioneer in the study of fatty acids, amino acids, and free-radical production. During his 50-plus-year career at NIH, Stadtman represented the best the intramural program has to offer: an unwavering dedication to research as well as to the training of others, which in fact included two Nobel prize winners, ten members of the National Academy of Sciences, and several leaders of industry. His own long list of awards includes the National Medal of Science, the highest honor for achievement in science bestowed by the president of the United States.

On April 29 the National Heart, Lung, and Blood Institute will host a symposium to honor Stadtman, based on the Stadtman tradition with emphasis on science but also with his trainees brought together to pay tribute. Speakers include Nobel laureates Michael S. Brown and Stanley B. Prusiner, former Merck CEO P. Roy Vagelos, and NHLBI Director Elizabeth Nabel. More information is available at http://dir.nhlbi.nih.gov/stadtmansymposium. ■

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 (temporarily out of service); or mail: Building 1, Room 160.

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

In Future Issues...

- The Study of History to Improve the Future
- Biospecimens
- Laser Dissection

Call for Suggestions for Nobel Prize

The Nobel Prize for Physiology or Medicine (your choice) seems to grow more competitive each year. Most of the easy advancements to alleviate human suffering, such as ear plugs for spouses dragged to Yanni concerts or the invention of no-tears shampoo—what the Johnson brothers conceded to be low-hanging fruit in their acceptance speech in Stockholm—have already been recognized.

Today scientists are turning to fields and topics that are difficult to spell and usually must be abbreviated with hopes of winning the prize. Consider the 2006 Nobel laureates, Andrew Z. Fire and Craig C. Mello, who won for interfering RNA, a secret code for something long and cumbersome, to be sure.

There remains, however, one basic advance that hasn't been rewarded. I think a Nobel prize should be bestowed upon the person or team that made amoxicillin taste good. My two-year-old daughter had an ear infection, and she needed to take this twice daily. Unlike most medicines we have dropped, stuffed or injected into her, she loves amoxicillin. In perfect Japanese (her mother is from Japan), she would squeal "oishii," or delicious. She slurped down the pink goo from a little cup and begged us for more. There was no need to hide the medicine in a rolled-up slice of cheese; no need to use euphemisms, like tinky winky pinky juice; no wailing to the point that our neighbors would start thinking we were torturing the kid. No, in fact we told her straight up that this was ear medicine with the hope that she would learn to like all medicine. And it worked. She now yields to the eye drops, albeit with the euphemism "eye lotion."

Cancer is a serious disease. I believe there's an entire institute dedicated to its eradication. That's noble. Cures for malaria and HIV seem equally important. Yet if the medicines we create in NIH labs don't taste good, what are the chances that anyone will want to swallow them?

The NIH Catalyst seeks your help in identifying the inventors of tasty amoxicillin. A PubMed search for keywords "amoxicillin" and "yummy" surprisingly yielded no hits. We also welcome your suggestions for other noteworthy medical advances, which we will pass along to the Nobel committee.

-cw

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