FOSTERING COMMUNICATION AND COLLABORATION

The NIH CATALYST

A PUBLICATION FOR NIH INTRAMURAL SCIENTISTS

NATIONAL INSTITUTES OF HEALTH ■ OFFICE OF THE DIRECTOR ■ VOLUME 14, ISSUE 1 ■ JANUARY–FEBRUARY 2006

Many Sizes To Fit All

THE WAYS AND MEANS OF NIH TECH TRANSFER

by Fran Pollner

It may sound like a variation on the sardonic "We're from the government, and we're here to help you," but when Rochelle Blaustein says, "Tell us what you need, and we'll figure out how to get it for you," she's telling it like it is to NIH scientists.

Fran Pollner

Lili Portilla, NHLBI tech transfer officer, at her Research Festival post

And to back that promise up, there's a track record of thousands of agreements forged by Blaustein and other NIH IC tech-transfer officers whereby NIH scientists and labs have secured needed resources—material, financial, intellectual—not within their immediate reach at NIH.

Blaustein heads the Office of Technology Transfer and Development at NIDDK and co-chairs the Technology Development Coordinators Committee (TDCC), an umbrella group for all IC tech-transfer officers that meets monthly to compare notes and problem solve.

In an interview with *The NIH Catalyst*, Blaustein and two of her colleagues—NIAID's Cindy Fuchs, TDCC chair, and NHLBI's Lili Portilla, immediate past TDCC chair—discussed the various mechanisms at their disposal to further the research objectives of NIH scientists while also meeting NIH's obligations to facilitate the transfer of new technology to the public arena.

"We're responsible," Fuchs said,

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A New 'Pathway to Discovery' on the NIH Roadmap

IMAGING PROBE DEVELOPMENT CENTER COMING SOON

by Robert Balaban

Fran Pollner

Good Chemistry: *Gary Griffiths, first director of the new Imaging Probe Development Center, NHLBI, says this NIH Roadmap–generated core resource offers a "unique and exciting opportunity" for brainstorming between chemists and biomedical scientists*

A new NIH core resource equipped to enable concurrent synthesis of multiple types of imaging and detection agents will open this June.

Gary Griffiths

The soon-to-be home of the IPDC

Its new director has been recruited, and the facility is taking shape to match the mission and services identified in early NIH Roadmap discussions of critical "Pathways to Discovery" initiatives.

The NHLBI-affiliated Imaging Probe Development Center (IPDC) will harness and combine the talents of chemists and biomedical scientists to produce known imaging probes that are not commercially available and to generate novel imaging probes for biomedical research and clinical applications.

It will serve the intramural community as well as extramural scientists who may be limited in their investigation of interesting probes by a lack of synthetic chemistry capabilities.

The IPDC will initially generate known imaging probes for targeting receptors, cells, and tissues and for preclinical in vivo evaluations. The center will solicit

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Finding Ways To Cast a Wider Net

Michael Gottesman

I have repeatedly underscored the fact that the NIH Intramural Program has had limited success in recruiting under-represented minority scientists to our tenure-track and tenured scientific positions. In hopes of improving our recruiting record, last year the NIH Diversity Council—a group of senior scientists and administrators with an interest in fostering diversity—in cooperation with the Office of Intramural Research, analyzed the search process used by 10 of our recent search committees.

They found clear signs that the intent of the original search process was to cast a wide net to find the most diverse and qualified applicants. Unfortunately, they also found that the process used by many of these search committees more closely resembled a *selection* process—in which candidates who responded to ads were evaluated and ranked—rather than a *search* process—in which special efforts were made to contact individuals and urge them to apply for our positions.

With this grasp of the central problem, the Diversity Council made a series of recommendations about how to improve the search process. After discussion with the scientific directors (SDs), the Office of Intramural Research recently released a new policy, effective January 1, 2006, governing searches at the NIH for principal investigator positions—tenure-track, tenured, senior scientist, and senior clinician positions.The policy can be found at:

<http://www1.od.nih.gov/oir/sourcebook/irp-policy/search.htm>.

Although the new process resembles the old one, there are certain critical differences:

Step 1: Establishment of a new position by the SD should reflect a long-term scientific need of the institute or center and involve the input of senior investigators and/or the Board of Scientific Counselors.

Step 2: The committee should consist of the same representation as in the past: a chair who is not the lab or branch chief but who is a subject matter expert; a representative of the Deputy Director for Intramural Research (DDIR); the woman scientist advisor (WSA) or her designee; an under-represented minority scientist; and an ex officio representative of the Office of Equal Opportunity and Diversity Management; plus other subject matter experts from within and outside the lab and the NIH.

Step 3: After the DDIR reviews the description of the position and a tentative ad sent by the SD, these are returned to the search committee. The search committee must review and approve both the ad and position description to be certain they are written to attract the widest possible range of qualified candidates.

Step 4: In the meeting in which the search committee reviews the ad, a representative of the DDIR will discuss a specific search plan with the search committee and answer questions about strategy.

Step 5: The ad must be nationally advertised in a broad range of publications and through minority scientific support organizations at the NIH and beyond. Each member of the search committee—not just the WSA and the under-represented minority scientist(s)—will be involved in reaching out to the scientific community to identify the most qualified applicants.

Step 6: The members of the search committee must review the applications of all minimally qualified applicants. Depending on the number of applications, all committee members may read all applications, or the work may be divided up among committee members. The short list of candidates (usually two or three) chosen by the search committee will be reviewed by the lab or branch chief, who will recommend a candidate to the SD. A letter from the search committee chair to the SD will describe the search process that led to its choices.

Step 7: The choice of the SD will be forwarded to the DDIR for review and approval (with a copy of a tenure-track agreement when applicable), along with the description of the search process, including a summary of the number of women and minority applicants.

Although many of these changes in the search process seem relatively small, we hope their cumulative effect will be to encourage more vigilance in our searches and, ultimately, improvement in the quality and diversity of our staff. I recognize the changes place even more burden on our search committee members, who have worked hard over the years to guarantee excellence at the NIH. I ask because I believe the Diversity Council is correct—the extra effort will be richly rewarded. We welcome your ideas about how to improve this process further.

—Michael Gottesman
Deputy Director for Intramural Research

Imaging Probe Development Center

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proposals from throughout the NIH scientific community for the preparation of these probes.

Although many such interesting agents have been described in the scientific literature, they are often not explored further due to lack of a reliable supply of reagent. The IPDC aims to rectify this situation.

The center will also seek to develop novel state-of-the-art imaging probes in collaboration with biological and biomedical scientists, both within NIH and extramurally, who can provide or suggest suitable targeting agent-receptor pairs.

As envisioned in the Roadmap, the IPDC will embrace and integrate under one roof three discrete advances:

- Exponential increases in knowledge of disease-related cellular substructures
- An ever-growing expertise in the design of target-specific probes
- Contemporaneous improvements in imaging modalities

The result will be a new generation of imaging and detection agents that boast both rational design and optimal contrast characteristics, says Gary Griffiths, IPDC director.

Irrespective of the imaging modality under consideration, the probes will need to exhibit high specific binding to their targets and rapid clearance from background, resulting in high target-to-background contrast ratios. The contrast ratio is the key characteristic of any good imaging agent, Griffiths notes.

Optimal ratios can be achieved in several different ways via various chemical modifications of the targeting probe either to achieve amplified target uptake and retention of probes and/or to lower binding to nontarget tissues or proteins.

Logistics

The IPDC will occupy approximately 10,000 square feet in new facilities at 9800 Shady Grove Road in the Rockville-Gaithersburg, Md., area. The facilities already contain the NIH Chemical Genomics Center, which is a NHGRI-affiliated component of the Molecular Libraries Screening Center Network, also an NIH Roadmap initiative.

Once fully staffed, in late 2006, the IPDC will house 15 to 20 scientists, mainly devoted to synthetic chemistry and related support functions. The chemistry staff will have a diverse skill set that encompasses expertise in developing probes based on optical, radionuclide, MRI, and other modalities.

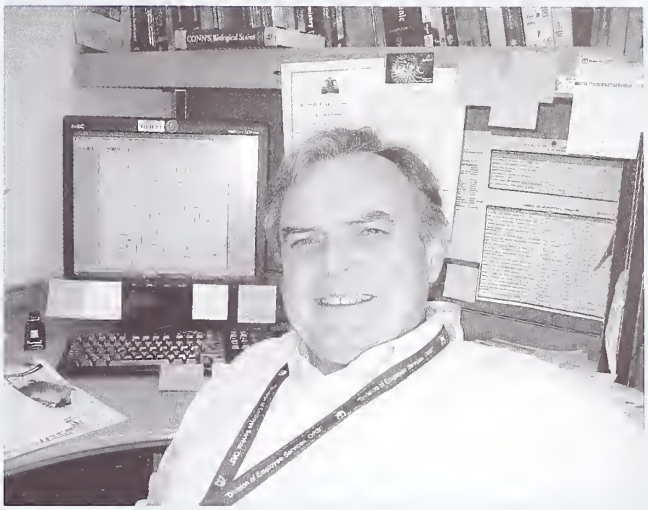
Initial funding for the IPDC came from each of the NIH institutes. It is anticipated that the center will become self-supporting through user fees applied on a cost-recovery basis.

The IPDC will operate under guidance from its steering committee, which has been drawn from multiple institutes and represents a wide range of expertise and interests across the spectrum of imaging technologies.

The steering committee meets monthly to discuss the progress and future directions of the IPDC and to advise the director on administrative matters and scientific operations.

The current members of the IPDC steering committee and their institutional affiliations are Christopher Austin (NHGRI), Robert Balaban (NHLBI), Allen Braun (NIDCD), Martin Brechbiel (NCI/NIAID), Henry Bryant (CC/DRD), Peter Choyke (NCI), Amir Gandjbakhche (NICHD), Daniel Hommer (NIAAA), Robert Innis (NIMH), Peter Jahrling (NIAID), Yong Sok Lee (CIT), King Li (CC/DRD), Roderic Pettigrew (NIBIB), Kenner Rice (NIDDK/NIDA), James Sellers (NHLBI), Richard Siegel (NIAMS), and Afonso Silva (NINDS). ■

The Shoe Fits



Fran Pollner

Gary Griffiths

With more than 25 years experience in synthetic chemistry, much of it related to biological imaging and the application of chemistry to biological systems within interdisciplinary environments, Gary Griffiths expects to feel comfortably at home at the Imaging Probe Development Center. He's on board now at NHLBI as the first director of the IPDC and preparing for the opening of facilities in June.

Griffiths' most recent research relates to targeted approaches to cancer diagnosis and therapy. He has designed, prepared, and tested numerous monoclonal antibody conjugates of chemotherapeutic drugs, polymers, enzymes, toxins, and radionuclides and has developed several agents for human clinical trials.

Griffiths has also worked extensively on binary targeting systems involving bispecific antibodies and low- molecular-weight diagnostic and therapeutic agents. Designed for high in vivo target-specific uptake coupled with rapid background tissue clearance, binary targeting systems achieve the high target-to-background needed for high therapeutic indices and high-contrast diagnostics. They offer flexibility in synthetic design of the imaging or therapy agent.

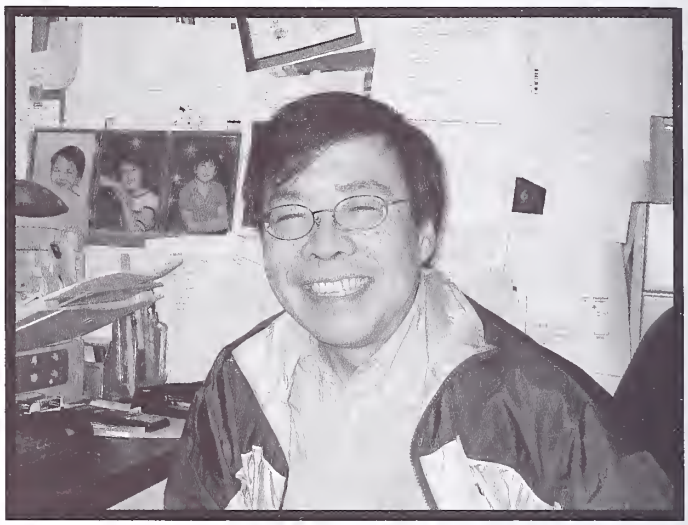
Along with an extensive bibiography, Griffiths has a patent portfolio that includes 35 U.S. patents, a similar number of foreign counterparts, and additional patent applications in progress.

Griffiths earned his B.Sc. in chemistry from the University of Liverpool, England, in 1975 and his Ph.D. in organic chemistry from the University of Nottingham, England, in 1980. He held postdoctoral appointments at University College, Dublin, and the University of California, Berkeley, and in 1985 became a senior scientist for a biopharmaceutical company, where he served also as assistant director of chemistry and immunochemistry and then as director of chemistry and radioimmunology. Starting in 1994, he served as the executive director of chemistry research and as an adjunct member of the Garden State Cancer Center, the translational and clinical research arm of the Center for Molecular Medicine and Immunology, Belleville, N.J.

—Robert Balaban

Open Access and Public Archiving: The Future of Scientific Publishing?

by Kuan-Teh Jeang, NIAID



Fran Pollner

Kuan-Teh-Jeang

The other day while driving, I heard an intriguing statistic on National Public Radio. The *Baltimore Sun*, a major newspaper, had announced that print circulation was 8 percent lower in 2005 than 2004. In newspaper circles, 8 percent is a big drop. Was this mismanagement by the *Sun*? The answer appears to be "no." Rather, the *Sun* appears to be reflecting a trend. Most major newspapers reported comparable drops in print-subscription–based distribution. By contrast, free Internet news sites, like those at CNN, the *New York Times*, and even the *Sun*, are experiencing explosive growth in daily traffic.

How are the ups and downs of newspapers relevant to scientific publishing? Fundamentally, scientific and news publishing are similar. Both strive to share information widely and in a timely and efficient way. Both want their contents preserved accurately for posterity. Hence, the closely monitored trend in mass journalism presages a corresponding looming contest in scientific publishing.

Choices

At issue now is the choice between two different ways of publishing research: the traditional journal (for which subscribers and sometimes authors pay) and the nascent "open-access" (authors pay) counterpart. Inherent in the open-access model is the idea that authors (or the funders of their research) pay for the submission and publication of papers; once published, the paper is free in full text to all interested readers.

Traditional journals, like print journalism, remain the dominant force at the moment. However, slowly but surely, the open-access web and electronically based upstarts are gaining traction. Indeed, a senior science writer at the *New York Times* recently told me—when asked how the *Times* sees its free web-based competitors—"We're running scared!"

As we move into the 21st century, the physical landscape of scientific publishing is being reshaped by the rise of web and digital technology. In the not-too-distant past, subscription-based scholarly communication was the primary way to disseminate information within academia in developed economies. Now, the pervasiveness of the Internet offers the potential for numerous additional communities—within or outside academia, in rich and in poor nations—to access previously guarded knowledge. Such access is in keeping not only with the concept that publicly funded science should be shared without charge, but also with the tradition long embraced by scientists that access to large databases such as the genomes of animals and plants and archives like PubMed should be free and public.

Open-Access Positives

Nonetheless, broad acceptance of open-access publishing is at a tipping point. Several factors may yet influence

Logo representing the open-access online journal Retrovirology, *edited by the author*

its success or failure. The first is the economics of publishing for a wide audience. The web promises to be a low-cost venue that can reach, with unparalleled rapidity, large numbers of geographically dispersed and economically disparate parties.

Contrast this availability with the rising cost of the traditional print model, which threatens affordability by even the best-funded libraries in wealthy nations. For example, United Kingdom statistics show that between 1998 and 2003, the average subscription price of academic journals rose by 58 percent while retail prices increased by only 11 percent[1].

A second factor is public demand in developed and developing worlds. The view that at-large access to scientific data is not needed because of lack of public interest is incongruent with empirical experience. Existing numbers indicate that only one-third of the users of PubMed are academicians and researchers, whereas two-thirds are the "public"—clearly not indifferent. As science moves increasingly toward globalization, access models that transcend professional classifications, national boundaries, and accidents of birth are timely and necessary.

Open-Access Unknowns

What of the long-term viability of the open-access model? Traditional journals have withstood the test of time for 340 years. If this tried-and-trusted approach is to be supplanted, the evidence must firmly support the survivability of the alternative. To date, the author-pays financial model is not fully tested in sustainability. Moreover, because most open-access publications are relatively young and have yet to garner prestige, it remains to be seen whether authors and reviewers will flock to these forums in numbers sufficient to drive and sustain quality exchange of scientific knowledge.

A second challenge is the permanent archiving of published knowledge. Printed journals have been stored and curated for centuries. Would digital media be similarly durable, and at what long-term cost to maintain appropriate repositories? One solution to the permanent archiving of electronic data comes from the NIH Library of Medicine's PubMed Central initiative[2].

Currently, NIH, the Howard Hughes Medical Institute, the United Kingdom's Wellcome Trust, Germany's Max-Planck

Society and Deutsche Forschungsgemeinschaft, and France's CNRS and INSERM[3] have all encouraged their funded researchers to deposit peer-reviewed articles into publicly accessible repositories. The two major publishers of open-access journals—Public Library of Science (PLoS) and Biomed Central—have also adopted policies of directly and immediately depositing their published works into PubMed Central.

A final important consideration of open-access publishing is its impact on learned societies. At least one-third of all subscription journals are published by not-for-profit organizations. The income surplus generated from publishing is used by societies to support research grants, meetings and conferences, fellowships for students and postdocs, and other worthwhile activities. Learned societies and their publishing endeavors are integral to the fabric of science, and it is crucial that accommodations be reached for societies' publishing to adapt to or co-exist with open-access alternatives.

Emerging evidence suggests that a balanced co-existence could happen. Data released by the American Society for Cell Biology show that when its flagship journal, *Molecular Biology of the Cell*, migrated to complete open access within two months after an issue has been published, author submissions increased by 14 percent and overall subscriptions increased by 16 percent. There is no inherent barrier to the profitability of an author-pays open-access model. Learned societies with their vast experience in publishing and their loyal membership may yet prosper with open-access publishing, as they have with traditional journals.

Personal Take

I have an interest in the evolution of scientific publishing. Twelve years ago I helped start a traditional journal, the *Journal of Biomedical Science*, which I edited for more than 10 years.

Two years ago, I left that project to found *Retrovirology*, an exclusively web-based open-access journal—found at <**www.retrovirology.com**>.

Although I have an abiding loyalty to my scientific societies and feel that they deserve continuing revenue streams, my personal read of the winds of change is that open-access publishing and publicly accessible digital repositories like PubMed Central may well be the dominant future players. For the near term the print format of scientific communication is likely to continue. However, just as music, television, and movies are moving to full digitalization, it is inescapable that scientific publishing and archiving must do the same.

Based on the acceptance that *Retrovirology* has gained within my scientific community, it seems to me that scientists do look beyond the cover of a journal to recognize the value of open accessibility to their work. Our journal caters to a relatively small cohort of retrovirologists, but it is accessed steadily 1,000 times each day, 30,000 times each month. These numbers are disproportionate to our known academic audience and suggest that a significant percentage of our readers are members of the public who value and trust our content.

Public access, public trust, and public archives—are these not the wave of the future of scientific publishing?

References

1. "Economic Analysis of Scientific Publishing: A Report Commissioned by the Wellcome Trust," The Wellcome Trust, October 2003.
2. NIH policy statement:
<**http://grants.nih.gov/grants/guide/notice-files/NOT-OD-05-022.html**>.
3. The Berlin Declaration:
<**http://www.zim.mpg.de/openaccess-berlin/berlindeclaration.html**>.

Nanotechnology Seminar Series

The NCI Nanotechnology Seminar Series on nanotechnology in cancer diagnosis, treatment, and prevention resumed **January 24, 2006,** 3:00–4:00 p.m. in the Natcher Conference Center (Balcony B) on the NIH campus.

Michael Hawkins, chief medical officer, American Bioscience, Inc., developers of a nanoparticle albumin-bound (nab™) delivery platform most recently applied with paclitaxel (Abraxane), was the featured speaker.

Sign-language interpreters provided on request; individuals needing reasonable accommodations should contact Travis Earles at 301-496-1550 or the Federal Relay 1-800-877-8339.

The talk will be webcast:
<**http://videocast.nih.gov/**>

For more information on the lecture series, visit:
<**http://nano.cancer.gov/**>.

'Real Solutions To Real Problems'

The NCI Cancer Biomedical Informatics Grid (caBIG) annual meeting will be held **April 9–11, 2006**, at the Hyatt Regency Crystal City in Arlington, Va.

"Delivering Real Solutions to Real Problems" is this year's theme at the conference, designed to foster networking through informational presentations, interactive breakout sessions, exhibit displays, and technology demonstrations.

For registration information, visit the caBIG website:
<**https://caBIG.nci.nih.gov**>.

Logistical questions can be directed to Nikeisha Henry at 240-744-7047 or
<**cabig2006@esi-dc.com**>.

Data, Anyone?

Checked out the NIH Intramural Database lately?
<**http://intramural.nih.gov/search/**>

Women's Health SIG: X Marks Coronary Risk

Carolyn Bondy, chief of the Women's Health Research section and chief of the Developmental Endocrinology Branch, NICHD, speaks on "Disparity in X-chromosome Gene Dosage and the Risk for Coronary Disease." Friday, **February 24, 2006**, 11:30 a.m–12:30 p.m., Wilson Hall, 3rd floor, Building 1.

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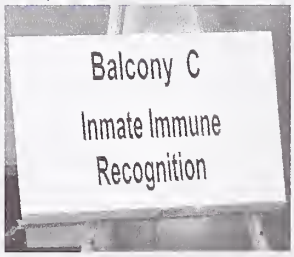


Aarthi Ashok

We hear that attendees at this Research Festival workshop (covered in the November-December 2005 issue of The NIH Catalyst*) reacted to one another with alacrity.—Ed.*

What Is So Fair as a Day in October?

Statistics compiled by Shirley Forehand
Photos by Cherie Butts

The 2005 Research Festival Job Fair got a good review from both prospective employers and fellows, the latter of whom attended in record numbers—992. Exhibitors registered their highest overall satisfaction level since the Job Fair's inception in the year 2000—4.49 on a scale of 1 to 5—on the evaluation forms (33 of 43 responded), and nearly all expressed an interest in returning next year.

The exhibitors were more satisfied with the quality and quantity of fellows who visited their booths than with the level of preparedness of these job seekers to discuss employment options. (In preparation for the fair, the NIH Fellows Committee [FelCom] offers workshops on résumé preparation and on interviewing skills; career development activities added this year included a seminar—by a representative from ScienceCareers.org and *Science* magazine's Next Wave—on how to make a good impression in just two minutes.)

At this year's fair, FASEB offered an individual résumé review service, which was deemed the most valuable aspect of the fair by the fellows. But the heavy demand for the service overwhelmed it, and FelCom is currently discussing how to manage it better next year. Fellows also noted that too few representatives of academia were in the mix of prospective employers, which included biotech and pharmaceutical companies, hospitals, foundations, and government agencies (including NIH).

Job Fair coordinator Shirley Forehand at her post directing attendees to tables of interest.

A light at the top of the Job Fair tunnel

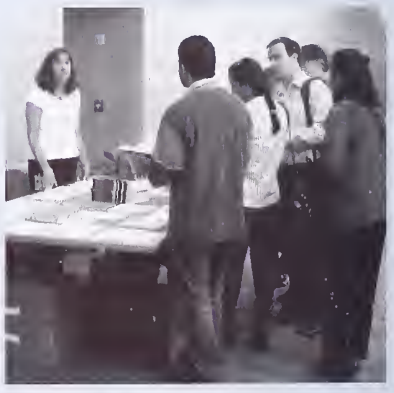
Milling around the Johnson & Johnson table

Heidi Erickson, NCI, talking shop with a prospective employer

Science *magazine representative giving fellows interview tips*

The Federation of American Societies for Experimental Biology provided much-in-demand résumé-critiquing services . . . .

. . . for which the lines were l-o-o-o-n-g



Susan Olivo-Marston, NICI cancer prevention fellow, provides career development information at the NIH Fellows Committee booth

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"for helping the ICs achieve their programmatic missions." The impetus for collaboration may originate in a company that is, for instance, exploring the commercial potential of a proprietary compound on which an NIH scientist has published related research. Or it could arise from within an institute that could use the services of an enterprise with certain high-throughput technology, screening assays, or preclinical models.

In each case, the IC tech-transfer office is the brainstorming center to craft the type of agreement that best serves both science and the public interest. It also assists the institute in the process of finding the right partner.

Since 1986, when the CRADA mechanism (see below) was established by Congress, NIH has executed 1,400 such joint research agreements with outside partners. In a brochure, NIAID cites the development and/or testing of hepatitis and pneumococcal vaccines and of humanized monoclonal antibody to prevent respiratory syncytial virus as examples of the many public health advances gained through CRADAs the institute has undertaken with industry.

In 2004, 87 CRADAs were approved NIH-wide; they ran the gamut from very early stage basic research through phase II clinical trials, Blaustein said.

But, she added, CRADAs account for "fewer than half of our major agreements. They are just one tool in our arsenal."

M-CRADAs, MTAs, and CTAs are others. NIAID has acquired proprietary cytokines and other biological materials through the M-CRADA mechanism for the purpose of exploring biological properties, Fuchs noted.

M-CRADAs typically arise from the interest of an NIH scientist in a proprietary material. If the involved company foresees a potential patent or product strategy, it will opt for the licensing option of an M-CRADA. Otherwise, the MTA may suffice, with such rewards as acknowledgment in any published paper or simply new knowledge.

Similarly, if a proprietary compound that is already on the market is needed for a clinical trial for a different indication, either a CRADA or a CTA could be an appropriate transfer mechanism. In each of their three institutes, dozens of CTAs are executed annually, Portilla, Fuchs, and Blaustein said. Often, they observed, the company values exchanging use of their drug or device solely for the resulting data it needs for regulatory purposes.

A key to executing the appropriate agreement is specificity, Portilla emphasized, noting that NIH tech-transfer officers are "a lot more savvy now than when we started out in 1989."

For instance, she said, "early on, NHLBI had very broad research plans" in conjunction with CRADA agreements. "Now they are much more focused, so that an investigator working on a CRADA can work on other lab research without its being implicated in the CRADA."

Instead of describing research material as a cardiovascular agent, its use would be targeted to a more specific indication, such as hypercardiomyopathy. In that way, the researcher could work on a different compound applied to the same disease and in collaboration with other companies.

Blaustein offered the example of a firm's wanting to collaborate on a treatment for "inflammatory diseases," which, in her office, was narrowed down to "autoimmune inflammatory disease."

Fuchs cited the need for flexibility at the VRC, whose mandate to develop vaccines is often best met by being able to partner with different companies that have different delivery technologies. "We create the carveout language" to allow, for example, one HIV vaccine candidate to be tested in multiple contexts, she said. ■

Fran Pollner

Tech Transfer Material Witnesses: (left) Rochelle Blaustein, NIDDK, and Lili Portilla, NHLBI

Ernie Branson

Cindy Fuchs, NIAID

For a list of IC technology development coordinators, see **<http://ott.od.nih.gov/nih_staff/tdc.html>**.

Tools of the Tech-Transfer Trade

The NIH Office of Technology Transfer is responsible for securing patents for NIH inventions and negotiating licenses for the commercialization of products that arise from those inventions (see "From Bench to Tech Transfer and Back to the NIH Scientist," *The NIH Catalyst*, May-June 2005, page 8).

The other arm of tech transfer at NIH resides within the institutes and centers, where collaborative research and material transfer agreements between NIH labs and scientists and outside entities—industry, academia, other U.S. government agencies, and even foreign governments—are negotiated. These arrangements vary in complexity, are usually mutually beneficial, and invariably culminate in expedited scientific advances and public health benefit.

Among the most used and useful tech-transfer mechanisms are:

■ **CRADA: Cooperative Research and Development Agreement,** a mechanism created by Congress in the Federal Technology Transfer Act of 1986, under which NIH scientists and outside collaborators, typically industry or academia, contribute research know-how and materials, intellectual acumen, personnel, and, in the case of the outside partner, occasionally funds to a joint research effort that will benefit the industry partner with an exclusive option to license inventions arising from the collaboration.

■ **M-CRADA: Materials-CRADA**, generally used by NIH to gain access to otherwise unavailable proprietary material, in exchange for which the company can receive an exclusive license to inventions that arise from the defined research

■ **MTA: Material Transfer Agreement,** under which material is exchanged but no research collaboration is contemplated.

■ **CTA: Clinical Trial Agreement**, establishing ground rules for the conduct of NIH clinical studies involving proprietary materials and the respective roles of NIH investigators and collaborators ■

Selected NIH Intramural Research Accomplishments 2005

Discoveries that add to the body of knowledge about normal and abnormal biological functions and behavior:

Identification of disease genes

- Identification of genes implicated in overall susceptibility to prostate cancer and of multiple loci that distinguish between more- and less-aggressive and life-threatening disease (NHGRI)
- Identification of the gene—*PIP5K3*—that, when mutated, causes Francois-Neetens mouchetée fleck corneal dystrophy, providing new inroads into corneal biochemistry and physiology and the role of endosome-to–trans-Golgi network transport in cellular metabolism (NEI)
- Delineation of the clinical, physiological, and pathological effects of a motor neuron disease caused by mutations in the $p150^{Glued}$ subunit of dynactin, a protein essential for axonal transport, reinforcing the suspicion that axonal transport is impaired in many neurodegenerative disorders (NINDS)
- Identification (in studies involving Caucasians in Tennessee) of a functionally relevant polymorphism in the regulatory region of the *CYP2J2* gene that confers a lower risk of hypertension (NIEHS)
- Variants of the melanocortin-1 receptor (*MC1R*) gene were found to be associated with a two- to fourfold increased risk of sporadic and familial melanoma, particularly among individuals with multiple variant alleles and those with fewer additional risk factors (NCI)
- Data from the International Lymphoma Epidemiology Consortium link genetic variation in TNF and IL-10 with increased risk of non-Hodgkin's lymphoma, particularly diffuse large B-cell lymphoma, suggesting that common polymorphisms in TNF and IL-10—key cytokines for the inflammatory response and Th1-Th2 balance—could be susceptibility loci for non-Hodgkin's lymphoma; the findings underscore the importance of using consortia for investigating the genetic basis of chronic diseases such as cancer (NCI)
- Results from the Spanish Bladder Cancer Study and meta-analyses show that the *GSTM1* null genotype increases the overall risk of bladder cancer and the *NAT2* slow-acetylator genotype increases risk particularly among cigarette smokers, providing compelling evidence for the role of common polymorphisms in cancer etiology; these polymorphisms could account for up to 31 percent of bladder cancers (NCI)
- Continuing studies of specific mutations in the *LRRK2* gene establish that a significant number of Parkinson's disease patients have a genetic predisposition, raising the possibility of genetic testing for this disease and facilitating the development of cell-based and animal-based models to explore etiology and related therapies (NIA, NHGRI, NIMH, NCBI)
- Discovery of a new gene, *FANCM*, which is mutated in one subgroup of patients with Fanconi anemia (FA), provides evidence for direct enzymatic movement of the complex of FA proteins along DNA and suggests drugs that enhance the FA DNA damage response as a potential therapeutic option; the discovery also sheds light on how DNA damage signals are transmitted in the FA pathway—and in repair pathways involved in certain cancers and aging (NIA)
- Identification of a common variant of plasma membrane calcium pump PMCA2 that modifies the severity of age-related hearing loss caused by a mutation in the gene encoding cadherin 23, raising the possibility that this or other variants of PMCA2 may underlie individual variability of hearing loss associated with more common causes such as noise or aging (NIDCD, NHLBI)
- Evidence that mutations in a gene located on chromosome 12 cause stuttering, a disorder of unknown origins (NIDCD)
- Haplotype linkage of *TPH2* (the gene for tryptophan hydroxylase 2) to depression and suicide attempt in three of four ethnically diverse populations, moving the field closer to identifying specific genetic loci that contribute to this vulnerability (NIAAA)
- Evidence that the short variant of the gene that codes for the serotonin transporter protein in the brain is associated with poorly regulated amygdala response and impaired emotional reactivity, thus increasing vulnerability to persistent bad moods and stress-induced depression (NIMH)

Important new animal models

- A low-calorie diet was found to lessen the severity of dopamine nerve cell damage and motor dysfunction in a monkey model of Parkinson's disease, possibly by inducing increased production of two different nerve cell growth factors in the brain (NIA, CC, NIMH)
- Demonstration that the *Drosophila melanogaster* homolog of a gene (*DSCR1*) in the chromosomal region involved in human Down syndrome is crucial for maintaining the function and integrity of mitochondria, suggesting that the increased level of DSCR1 may contribute to the mitochondrial dysfunction in Down syndrome (NINDS)
- Demonstration that the Stat family transcription factors Stat5a and Stat5b are essential for normal lymphoid development: The development of T cells, B cells, and NK cells was severely impaired in mice in which these transcription factors were deleted using Cre-lox technology (NIAMS, NIDDK)
- Demonstration in a rat model of craving and relapse that cocaine craving induced by exposure to cocaine cues was higher 30 days after withdrawal than one day after, reflecting time-dependent increases in the responsiveness of the central amygdala ERK pathway to cocaine cues, with implications for neuroadaptations related to other responses such as food craving or fear (NIDA)
- A double-mutant mouse model—loss of brain-derived neurotrophic factor (BDNF) gene allele in addition to serotonin transporter (SERT) knockout—displays exacerbated brain monoamine deficiencies and increased stress; the model serves to elucidate the role of serotonin in the actions of antianxiety and antidepressant drugs and the mechanism underlying epistatic interactions between SERT and BDNF polymorphisms in human psychiatric disorders (NIMH, NICHD, NIAAA)
- Demonstration of the first replication of the BK virus, a human pathogen, in an animal model (squirrel) (NIDDK, CC, NCI, CBER)
- Discovery that the cytokine thymic stromal lymphopoietin (TSLP) is critical in mediating the development of asthma in a murine model and that a TSLP receptor fusion protein can block development of lung inflammation, with therapeutic implications (NHLBI, NIAID)

Basic discoveries in cell, molecular, and structural biology with implications for the treatment of human disease

- Discovery that abnormal prion protein lacking a GPI anchor into the cell membrane may be unable to signal cells to start the lethal disease process associated with transmissible spongiform encephalopathies; this anchorless prion protein promoted the formation of amyloid plaques in brain tissue but did not cause clinical disease, which may have implications for the treatment of Alzheimer's disease (NIAID)
- Discovery that CCR5, the receptor exploited by HIV for initial infection and subsequent disease progression, also functions in West Nile virus (WNV) pathogenesis, but in a beneficial way: to clear virus from the brain and to limit mortality, raising the possibility that HIV inhibitors that act by blocking CCR5 may render patients more susceptible to WNV (NIAID)
- Discovery that hemoglobin C protects against malaria by disturbing the expression of a key parasite protein, PfEMP-1,

that promotes adherence of infected red blood cells to the lining of blood vessels in the brain and other critical tissues, causing inflammation and circulatory obstruction (NIAID)

- Elucidation of the travels of glucose transporter 4 between the adipose cell interior and the plasma membrane in response to insulin (NICHD, NIDDK)
- Finding that ocular-specific antigens are typically expressed in human thymic tissue but in widely varying degrees, suggesting that differences in susceptibility to autoimmune uveitis are at least partly the result of different levels of thymic expression of uveitogenic antigens (NEI, NIAID)
- Use of a toxin from tarantulas to characterize the molecular mechanism by which voltage-activated potassium channels detect and react to changes in membrane voltage, a key but poorly understood aspect of how voltage-dependent channels carry out their essential signaling functions throughout the brain and other body systems (NINDS)
- Determination that the clearance of the neurotransmitter glutamate is slower in the hippocampus of younger animals, which permits glutamate to travel longer distances and increases the importance of glutamate receptors that are located beyond the synapse in the developing brain (NINDS)
- Discovery of a novel physiological mechanism for the production of tissue-specific glucocorticoid receptors, providing insights into the anti-inflammatory action of glucocorticoids, one of the worlds most prescribed class of drugs (NIEHS)
- Elucidation of the regulation of genes that control cellular senescence, immortalization, tumor suppression, and organismal aging in studies of the expression of tumor suppressor p16 during replicative senescence (NIA)
- Manipulating the growth conditions and thus the structure and toxic properties of amyloid-β peptide fibrils, which accumulate in the brains of patients with Alzheimer's disease, with implications for the development of treatments for Alzheimer's disease (NIDDK, NIA, DBEPS)
- Identification of a novel mechanism controlling directional cell migration that is distinct from chemotaxis and depends on Rac protein activity, a finding relevant to the field of tissue bioengineering (NIDCR)
- The uncovering of a novel mechanism explaining how dietary deficiency of docosahexaenoic acid (DHA), an ω-3 polyunsaturated fatty acid highly enriched in neuronal membranes, can upset the interaction between the Akt signaling pathway and membrane phospholipid levels, thereby compromising neuronal survival; these findings underscore the neurological deficits associated with ω-3 fatty acid deficiency and support protective effects of DHA in pathological models such as brain ischemia or Alzheimer's disease (NIAAA)
- Elucidation of the pathway by which stress may induce reinstatement of cocaine-seeking behavior in detoxified cocaine addicts and underlie the co-morbidity between addiction and other stress-related psychiatric disorders: Foot-shock stress caused the release of corticotropin-releasing factor in rats, which, in the cocaine-experienced cohort, induced glutamate release and dopamine activation, triggering relapse (NIDA)
- Demonstration that the mNotch1 intracellular domain can functionally replace that of mNotch2 in vivo, suggesting that these key signaling molecules are functionally redundant (CBER)
- The finding that loss of memory CD4+ T cells during acute SIV infection is considerably more marked than previously thought—rapid and throughout the body, not just in mucosal tissue—with critical implications for vaccine development and interventional therapies (VRC, NIAID)
- The finding that CCR5-tropic HIV virus infection of immature dendritic cells (DC) allows the development of a reservoir of infected DCs that infect T cells efficiently upon maturation (VRC, NIAID)
- Identification of the superior colliculus as the region of the brain that not only generates saccadic eye movements but also contributes to directing attention to specific features in the visual field, providing a first step towards understanding the circuits in the brain that underlie visual attention and how perception is affected when there are deficits in shifts of attention (NEI)
- Discovery that myosin-XVa, a protein found to be defective in some forms of deafness, delivers whirlin to the tips of stereocilia of auditory sensory cells and is a key event in hair-bundle morphogenesis (NIDCD, NHLBI)
- Identification of a protein complex involved in the trafficking of NMDA receptors, contributing to the understanding of this process in normal and disease states (NIDCD)
- Identification of the genes that encode receptors for bitter tastants and demonstration that bitter taste is hard-wired in dedicated cells at the periphery (NIDCR)
- Elucidation of the structure of amyloid fibrils of human amylin, present in 90 percent of patients with Type 2 diabetes (NIAMS)
- Awakening of the mobile somatic "Sleeping Beauty" transposon system (jumping genes) to expose the weak points in cancer genes and gain insights into better treatment approaches (NCI)
- Identification of cross-talk between nitric oxide (NO) and thrombospondin-1 in NO-mediated regulation of angiogenesis, with implications for therapeutic approaches to angiogenic aspects of cancer progression (NCI)
- Elucidation of the underlying mechanisms of hemolysis-associated pulmonary hypertension—which occurs in 30 percent of patients with sickle cell disease and is a major cause of mortality in this population—and its strong association with high hemolytic rate, arginase release from red cells, iron overload, and kidney disease (NHLBI, CC, NIDDK)
- Discovery of cannabinoid receptors (CB1) in hepatocytes whose activation by endocannabinoids stimulates fatty acid synthesis, suggesting that the endocannabinoid anandamide contributes to diet-induced obesity and that the fatty acid synthase pathway may be a common molecular target for central and peripheral metabolic regulation (NIAAA)
- Brain scan evidence that sniffing oxytocin (compared with placebo) dampens amygdala response to threatening scenes, especially to threatening faces, as well as communication between the amygdala and upper brainstem fear-response sites, suggesting a pivotal role for oxytocin in regulating social fear and its possible value in treating autism, which has been linked to overactivation in the amygdala when looking at faces (NIMH)
- Clarification of the neural mechanism underlying the risk for schizophrenia conferred by *COMT* gene variants (NIMH)
- Demonstration by fMRI that the amygdala of patients with Williams syndrome—who have 21 missing genes on chromosome 7 and atypical responses to people and events expected to induce fear and anxiety—undergoes less activation than that of healthy volunteers when confronted with pictures of threatening people and more activation when confronted with threatening scenes with no social component; three areas of the prefrontal cortex were implicated in this atypical amygdala response (NIMH)
- Elucidation of the "yin-yang" regulation of synaptic plasticity by proneurotrophins and mature neurotrophins through activation of two different receptors, with implications for understanding a wide range of cellular processes (NICHD)
- Study of the locust olfactory system to elucidate the manner in which neural circuits process sensory information (NICHD)
- Elucidation of the antiviral protein kinase PKR (and other stress-responsive protein kinases) activation pathway (NICHD)
- Elucidation of the role of Notch signaling in neural development (NICHD)

Selected NIH Intramural Research Accomplishments 2005

Development of new or improved instruments and technologies for use in research and medicine

Advances in imaging

- The use of real-time MRI to treat congenital aortic coarctation in an animal model demonstrated the clinical potential of this single modality to diagnose, treat, and promptly identify complications—without exposing children and staff to ionizing radiation (NHLBI)
- Development of an automated system—virtual colonoscopy computer-aided polyp detection—that can locate precancerous polyps on CT scans with high sensitivity comparable with that of optical colonoscopy, a minimally invasive procedure that may increase the use of asymptomatic screening (CC)
- Application of a comprehensive image reconstruction methodology to the first human positron emission tomography data acquired from the NIH High Resolution Research Tomograph (CC, CIT, NIMH, NINDS)
- Development of a registration, segmentation, and three-dimensional fusion tool to support radiofrequency ablation treatment planning (CC, CIT)
- Demonstration that disparate NMR and X-ray crystallography measurements yield quantitatively consistent information about the motion of a small, rigid protein (NIDDK, CIT)
- Design of an electron paramagnetic resonance imaging system that allows for noninvasive in vivo functional imaging in small animal models for the investigation of tissue oxygen concentrations and the development of tumor treatment strategies (NCI, CIT)
- Development of novel diagnostic methods using new kinds of spectroscopic imaging: high-throughput Fourier transform infrared spectroscopic imaging of tissue microarrays, coupled with the statistical pattern recognition of spectra indicative of endogenous molecular composition, enabling histopathologic characterizations of, for example, prostatic tissue without need for dyes or molecular probes and differentiating between benign and malignant prostatic epithelium (NIDDK, NCI)
- Localization of the minor capsid protein L2 of the human papillomavirus, a possible vaccine antigen, by cryoelectron microscopy and three-dimensional image reconstruction (CIT, NCI, NIAMS)

Advances in bioinformatics

- Development of a computer search tool that rapidly compares DNA sequences among animal species and identifies those sequences that have remained essentially unchanged during evolution, a strong indication that the DNA segment is essential to gene function (NINDS, NIMH))
- Complete sequencing of the canine genome, opening the door to comparative studies of cancer susceptibility genes in dogs and humans—species whose malignancies resemble one another in clinical presentation, histology, and biology (NHGRI)

Advances in biotechnology

- Replication and production of infectious hepatitis C virus (HCV) from a cloned viral genome in tissue culture, providing an in vitro means to better study the biology of HCV and to screen a wider range of potential therapeutic compounds (NIDDK)
- Development of a method for circulating endothelial cell isolation and validation, used to probe vascular disease, which includes multiple marker verification, high-sensitivity mRNA amplification, and confirmation of endothelial-specific genes by microarrays and real-time PCR (CC, NHLBI, CIT)
- Creation of a model to improve understanding of the molecular mechanisms for optimal transport of metabolites through large channels (NICHD, CIT)
- Synthesis of a compound that blocks the effects of anthrax lethal toxin at the protective antigen channel in cell and animal studies, paving the way for rational design of new drugs to treat inhalational anthrax (NICHD, NIAID)
- Development and characterization of monoclonal antibodies that can neutralize the protective antigen toxin of *Bacillus anthracis* (NIAID, DBEPS)

Development of new or improved approaches for preventing or delaying the onset or progression of disease and disability

- Discovery that farnesyltransferase inhibitors, a class of experimental anticancer drugs, prevent a crucial event in the development of progeria, raising the hope that these agents may be used to treat children with this otherwise-fatal genetic disorder (NHGRI)
- Characterization of heart lesions in rats associated with ingestion of ephedrine and caffeine, the active ingredients in ephedra-based dietary supplements, contributing to the FDA's ability to evaluate the heart toxicity of ephedra-containing herbal medicines and the banning of such dietary supplements (NIEHS)
- Findings from the ongoing Agricultural Health Study that farmers who use agricultural insecticides experience lasting neurological symptoms—including headaches, fatigue, insomnia, dizziness, cognitive problems, poor balance, hand tremors, and numbness—even when they are no longer using the products, exposing the health effects of everyday agricultural chemical use, in contrast to previous studies that focused on pesticide poisoning or high-dose exposures (NIEHS, NCI)
- Development of a clinical protocol to evaluate the efficacy of erythropoietin in reducing infarct size and left ventricular remodeling in patients with large myocardial infarctions, with the aim of preventing such common clinical complications as congestive heart failure and arrhythmia (NIA)
- Continuing studies of of monoclonal antibody for IL-2 receptor blockade in patients with uveitis suggest that treatment-related induction of $CD^{56bright}$ is responsible for the therapeutic lessening of inflammation and that $CD^{56bright}$ may be the body's natural agent in calming uveitis and other autoimmune conditions such as multiple sclerosis; a Phase III study of the IL-2 receptor blocker daclizumab to treat uveitis is in preparation (NEI)
- Identification of a novel mechanism by which inflammatory mediators (prostaglandin E_2) activate growth-promoting pathways, shedding light on the relationship between inflammatory processes and tumor progression and the observed association between the use of anti-inflammatory agents and a reduced incidence of colon cancer; the findings may provide a molecular framework to evaluate new anticancer chemopreventive strategies (NIDCR, NIAID)
- Data gathered from studies involving more than 70,000 individuals show that minorities participate in clinical research at the same rate as non-Hispanic whites when they are made aware of the study and meet the medical requirements, countering the widely held notion that minorities are less willing to participate and suggesting that minority involvement in clinical research is more a matter of access than attitude (CC, OBSSR)
- Demonstration that infused nitrite solutions prevent hepatic and cardiac ischemia-reperfusion injury and infarction in mice (NHLBI, CC, NIDDK)
- Results from a nested study within the Childhood Cancer Survivor Study show that the risk of subsequent primary thyroid cancer among survivors who received upper-body or head and neck radiotherapy increases with rising therapeutic radiation doses up to 20 to 29 grays, with declines at higher doses consistent with a cell-killing effect; these findings support long-term follow-up of childhood survivors of any cancer treated with radiotherapy, not just Hodgkin's lymphoma (NCI)

Vaccine development

■ Development of a recombinant, live, attenuated respiratory syncytial virus vaccine for intranasal administration that proved to be well-tolerated, immunogenic, and protective against a second vaccine dose in infants one to two months old (NIAID)

■ Testing of the VRC's HIV preventive prime-boost vaccine strategy in three Phase I/II clinical trials conducted by three international networks—the HIV Vaccine Trials Network, the International AIDS Vaccine Initiative, and the United States Military HIV Research Program (VRC)

■ Development of a recombinant DNA vaccine candidate against West Nile Virus, developed under a CRADA with Vical, Inc., now in Phase I clinical trial (VRC)

■ A DNA prime-recombinant adenoviral boost vaccine targeted at one of the influenza viral proteins, nucleoprotein (NP), induced strong antibody and T-cell responses in mice and protected against lethal challenge with highly pathogenic H5N1 virus, demonstrating that gene-based vaccination with NP may contribute to protective immunity against diverse influenza viruses (VRC, CBER)

■ Identification of a gene in *Moraxell catarrhalis* responsible for the biosynthesis of endotoxin, enabling the creation of a highly immunogenic, endotoxin-free knockout mutant without endotoxin with promise as a vaccine candidate or vaccine vehicle (NIDCD)

Development of new or improved ways to diagnose disease and disability

■ Women who tested positive for human papillomavirus (HPV) type 16 or 18 were at higher risk of developing cervical cancer over the next 10 years than were women who tested positive on a general screen for oncogenic HPV types but negative for those two specific types, suggesting that HPV screening that distinguishes HPV16 and HPV18 from other oncogenic HPV types may be useful clinically in deciding how best to manage women with these HPV infections (NCI)

Gene expression patterns

■ Development of a novel genetic model to identify genes that interact in head development in a dosage-specific manner, including BMP, hedgehog pathway members, and Zic gene family members (CBER)

■ Gene expression profiling of human bone and soft tissue sarcomas to delineate tumor classes and identify associated genes of potential biological and therapeutic interest (NHGRI, NCI)

■ The use of gene expression profiling and artificial neural networks to predict survival in neuroblastoma patients, including the identification of 19 predictor genes to distinguish between lower and higher survival potential in already stratified high-risk patients (NCI)

Development of new or improved ways to treat disease and disability

■ Demonstration that intermittent administration of IL-2 prolongs the lifespan of naïve and central memory CD4 T cells in HIV-infected patients (CC, NIAID, NCI)

■ Combination chemotherapy and infusion of autologous stimulated lymphocytes—adoptive cell-transfer therapy after nonmyeloablative but lymphodepleting chemotherapy—achieved tumor regression in patients with refractory metastatic melanoma (NCI, NEI)

■ A pilot study of nitisinone in patients with alkaptonuria, an inborn error of metabolism, achieved a 95 percent reduction of homogentisic acid, the accumulation of which causes the destruction of large joints and cardiac valves characteristic of the condition; a larger clinical trial with clinical outcome measures is now ongoing (NHGRI, CC, NEI)

■ Development of nucleoside analogs that block DNA synthesis beyond the point of HIV-1 incorporation—delayed chain termination—and should therefore be relatively resistant to excision and effective against drug-resistant HIV-1 reverse transcriptases, suggesting a research direction to complement already approved HIV-1 therapies (NCI)

■ Development of drug-device combination therapy—heat-activated chemotherapy encapsulated in a liposomal vector and delivered intravenously—to enhance effectiveness of local thermal ablation in the treatment of unresectable liver cancer (CC, NCI)

■ Identification of the enzyme that regenerates the 11-cis vitamin A required for light sensitivity of the retina, with implications for gene therapy for treating inherited blindness caused by *RPE65* mutations; clinical trials are planned (NEI)

■ Determination in primate studies that intravenous infusion of sodium nitrite, a drug designed to increase levels of the regulatory molecule nitric oxide, can prevent the cerebral vasospasm that may follow surgery for intracranial aneurysm (NINDS, NIDDK, CC, NHLBI)

■ Demonstration that inhaled nitrite reverses hypoxic neonatal pulmonary hypertension in sheep (NHLBI, CC, NIDDK)

■ Demonstration that neonatal multisystem inflammatory disorder is highly responsive to agents that inhibit IL-1, a significant advance in the treatment of autoinflammatory disorders (NIAMS) ■

Milestones in *Nature*

Two NCI investigators were cited for their historic discoveries in the December 2005 *Nature* supplement on "Milestones in Gene Expression" over the past 50 years:

Carl Wu

■ Carl Wu, chief of the Laboratory of Molecular Cell Biology and head of the Chromosome Structure and Gene Regulation Section (three papers related to work done in the NCI intramural program)

Shiv Grewal

■ Shiv Grewal, senior principal investigator and head of the Chromosome Biology Section, Laboratory of Molecular Cell Biology (three papers related to work done while at Cold Spring Harbor Laboratories) ■

3 Bioethics Honors

The CC Department of Clinical Bioethics and individual members have garnered these awards:

■ An Award for Excellence in Human Research Protection by the Bethesda-based Health Improvement Institute went to the department for its innovative "Framework and Benchmarks for Evaluation of Research."

Christine Grady

■ Christine Grady, head of the Section on Human Subjects Research and a fellow of the Hastings Center, was elected to a two-year term on the Hastings Center Fellows Council.

Zeke Emanuel

■ Department chair Ezekiel Emanuel coauthored, with Victor Fuchs of Stanford University, one of the 25 most frequently viewed articles published in *Health Affairs* for the year December 2004–December 2005: "Health Care Reform: Why? What? When?" *Health Affairs* **24**:1399–1414, 2005. ■

People

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Carole Bewley *received her Ph.D. in 1995 in a joint program in chemistry and oceanography from Scripps Institution of Oceanography, University of California, San Diego. She did postdoctoral work in protein NMR in the Laboratory of Chemical Physics, NIDDK, on a Cancer Research Institute fellowship and in 1999 joined the Laboratory of Bioorganic Chemistry, NIDDK, as a tenure-track investigator. She is currently a senior investigator and chief of the Section on Natural Products Chemistry.*

Fran Pollner

Carole Bewley

My research focuses on three main areas: the discovery and study of biologically active natural products, the design and synthesis of peptide and protein inhibitors of HIV-1 entry, and the discovery and characterization of novel carbohydrate-binding proteins.

Why natural products? Natural products are usually, but not limited to, small organic molecules produced by plants, bacteria, fungi, and lower eukaryotes such as invertebrates, to name a few. Natural products can also include peptides, proteins, and other larger-molecular-weight toxins.

There is abundant evidence that natural products bestow an increased level of fitness on the organism that produce them by providing a means of chemical defense, a primitive equivalent of higher organisms' immune systems.

Having evolved over millions of years to fit into specific receptors and thereby effect biological processes, natural products are endowed with chemical and three-dimensional properties that synthetic molecules may lack.

Natural products therefore represent ideal starting points for identifying inhibitors for, arguably, any biological process.

Thus, in the broadest sense, my laboratory is interested in identifying new natural product structures, especially those found in marine invertebrates and cyanobacteria, that exhibit interesting biological activities; we are also interested in determining the mechanism of action by which they inhibit the system of interest, and, ultimately, in pinpointing the structural basis for their activity.

Two systems that we study intensely and try to inhibit are HIV-1 entry into cells and mycothiol biosynthesis and detoxification in *Mycobacterium tuberculosis* (MTB), a pathway essential to MTB viability. As chemists, our efforts are divided between discovery-driven and hypothesis-driven research.

We use a variety of techniques to answer questions, including natural products chemistry, synthetic organic chemistry, and NMR spectroscopy for solving chemical and three-dimensional structures and mapping binding sites; biophysical techniques to describe modes and affinities of binding; and, of course, biological assays to provide lead molecules.

Several years ago, we identified a class of natural products originating from a marine sponge extract in NCI's Natural Products Open Repository, that effect mycothiol biosynthesis and detoxification in MTB. Mycothiol is a small-molecular-weight thiol unique to actinomycetes that replaces glutathione in this group of bacteria.

These compounds feature an unusual oxygen- and nitrogen-containing spiroring system that is key for competitive inhibition of the mycothiol biosynthetic and detoxification enzymes MshB and MCA, respectively.

Using these natural products as structural leads and inspiration, we recently completed the synthesis of a small natural product–like synthetic library whose structures combine important chemical features from the natural products with those important to the substrates. Within these second-generation inhibitors are two compounds that are lethal to MTB at low microgram doses.

In addition to having created a new class of MTB inhibitor, we also have in hand synthetic compounds that can readily be manipulated for further biological studies and can be used as probes for mycothiol metabolism in MTB.

A second example includes our work on novel carbohydrate-binding proteins isolated from marine cyanobacteria, also known as blue-green algae. It is becoming apparent that all cells and most viruses display on their surfaces specific carbohydrate structures or carbohydrate-binding proteins, or both, that are used for attachment, adhesion, and cell-to-cell recognition—especially noteworthy in the interactions between pathogens and their target cells. Protein-carbohydrate interactions govern or have been implicated in myriad recognition and binding events, such as sperm-egg interactions leading to fertilization, leukocyte homing during the course of inflammation, and trafficking of tumor cells during metastasis.

I became interested in these types of molecules from earlier high-resolution structural and mechanistic studies of cyanovirin-N, a potent HIV-1 fusion-blocking cyanobacterial protein originally discovered by NCI scientists and coincidentally also originating from NCI's Natural Products Repository.

Using a combination of multidimensional heteronuclear NMR techniques, isothermal titration calorimetry, and an HIV-1 fusion assay, we showed that cyanovirin-N contains two novel carbohydrate-binding motifs encoded into a single polypeptide chain that can bind with nanomolar affinities a small disaccharide ligand identical to the terminal arms of branched *N*-linked oligomannose structures.

This result was unheard of at the time: Carbohydrate-binding proteins almost universally bind their saccharide ligands with very weak affinities (high micromolar to millimolar) and typically oligomerize to augment avidity and selectivity. Not only was the demonstrated specificity and affinity unprecedented, the studies also demonstrated that cyanovirin-N exerts its potent antiviral activity through high-affinity interactions with high-mannose structures that are abundant on the HIV surface envelope glycoprotein gp120. Furthermore, cyanovirin-N exhibited a novel three-dimensional fold that to date cannot be placed into other known protein families.

A logical extension of these findings has led to a second large component of our research that is devoted to the discovery of other novel carbohydrate-binding proteins. These molecules are fascinating because they greatly expand our knowledge and understanding of protein-carbohydrate recognition and the structural and dynamic features that are necessary for high-affinity carbohydrate recognition. They also provide potentially valuable reagents for inhibiting or probing virus-cell or pathogen-cell interactions.

We have recently published structural

and biological studies on MVL, another cyanobacterial protein that potently blocks HIV-1 entry, albeit through carbohydrate-mediated interactions that are entirely distinct from those of cyanovirin-N.

Identification of a second protein with novel, high-affinity carbohydrate-binding properties and antiviral activity ensures that these organisms and the natural products they produce will continue to hold our interest.

Kirk Druey received *his M.D. degree from Rush Medical College in Chicago in 1987. After completing a residency in internal medicine at The New York Hospital/Weill Cornell Medical Center in New York in 1990, he joined NIH in 1991 as a clinical associate in the Allergy and Immunology Training Program in NIAID and went on to complete his postdoctoral training in the B-cell Molecular Immunology Section of the Laboratory of Immunoregulation. In 1997, he became acting head of the Molecular Signal Transduction Section of the Laboratory of Allergic Diseases (LAD), NIAID.*

Kirk Druey

As a kid with asthma, I wanted to understand how ordinary things that other people seemed to have no problem with—my dog, the horses I rode, the dusty barn, lawn mowing—made it so difficult for me to breathe. Initially, I pursued a career path—medicine—to help others with this disease. But the more I counseled and treated patients with asthma, the more I felt compelled to understand what caused it on a molecular level.

Asthma is a collection of symptoms including wheezing and shortness of breath. And although there are characteristic lung abnormalities such as hypercontractility of bronchial smooth muscle and extensive lung inflammation induced by allergen exposure, there is no single known etiology of asthma.

After my clinical training in allergy and immunology at the NIH Clinical Center and during postdoctoral training with John Kehrl in the Laboratory of Immunoregulation, NIAID, I investigated signal transduction pathways in the immune system.

In particular, I became interested in G protein–coupled receptors (GPCRs), which are by far the most common cell-surface receptors in the mammalian genome. These receptors rely on a molecular switch—the heterotrimeric G protein, which cycles between GDP- and GTP-bound forms—to transmit their signals. In asthma, GPCRs control not only the contractility of bronchial smooth muscle but also entry of inflammatory cells into the lung.

During the course of this postdoctoral work, I was instrumental in the discovery of a new family of regulators of G protein–mediated signal transduction. These regulators of G protein signaling, or RGS proteins, help determine the amplitude and timing of GPCR signaling in response to extracellular ligands. They bind to the α subunit of the G protein and accelerate its rate of GTP hydrolysis.

This large family of proteins (more than 25 members in mammalian cells) exhibits some promiscuity. That is, most RGS proteins bind similar G protein substrates although several RGS proteins are expressed in the same cell. Therefore, we asked how individual RGS proteins regulate specific GPCR pathways and what functions these proteins might have in the pathogenesis of asthma.

During my time as a tenure-track investigator in the LAD, I tried to address some of these issues, starting with straightforward biochemical questions. For example, how is the activity of certain RGS proteins regulated? We found key residues shared by many of these proteins that were sites of phosphorylation or palmitoylation.

These modifications directly affected the activity of a prototypical RGS protein, RGS16, by altering its subcellular localization or stability. Using genetic screening and assessment of various signaling pathways, we identified new binding partners for this and other RGS proteins that may also regulate RGS activity or implicate them in unique functions outside of the G protein realm.

The basic structure-function studies have set the foundation for us now to ask how certain RGS proteins control GPCR activity in individual cell types from normal and asthmatic lung. For example, mast cells are crucial initiators of the allergic process in the lung. Mast cells bind allergens, which then cross-link membrane-bound IgE antibody and cause the mast cells to degranulate and release inflammatory mediators. These compounds set off an allergic cascade culminating in bronchial hyperreactivity.

Surprisingly, we have found that mouse mast cells deficient in RGS13 exhibit markedly enhanced degranulation to IgE-allergen stimulation in vitro and dramatically increased anaphylaxis responses in vivo. Thus, RGS13 may normally suppress IgE-mediated allergic reactions, which are not known to be G-protein dependent. These results suggest that RGS proteins may control multiple intracellular signaling networks.

I believe these research efforts address critical problems in understanding allergic diseases generally and asthma specifically. In the near future, we plan to focus on understanding how RGS proteins control contractility of bronchial smooth muscle and the activation and migration of immune cells—both integral to the development of pathological abnormalities found in asthma.

Alexander Pletnev *earned his Ph.D. in chemistry in 1983 from the Institute of Molecular Biology and Genetics, USSR Academy of Sciences in Novosibirsk. In 1990, he received his Doctorate of Sciences Degree in biochemistry and molecular biology from the Institute of Molecular Biology, USSR Academy of Sciences. He joined NIAID in 1991 as a visiting scientist and initiated a successful research program to develop vaccines against diseases caused by flaviviruses. In 1997, he became a tenure-track investigator in the Laboratory of Infectious Diseases, NIAID, and is currently a senior investigator.*

My long-term interest in tickborne encephalitis stemmed from the high prevalence of this disease in Europe and Asia due to the highly neurovirulent tickborne encephalitis viruses (TBEV). This illness is rare in North America. TBEV is transmitted to various mammal species and causes human disease of varying severity, with up to 30 percent mortality. Most of these viruses are "select agents" (assigned to biosafety level 3 or 4), based on their high lethality and their potential for human infection by the oral or aerosol route.

Currently, a vaccine produced by formalin inactivation of TBEV is available in Europe, but multiple inoculations are

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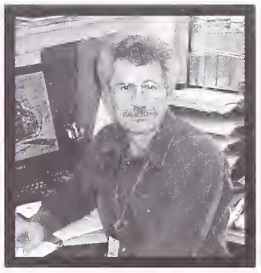
needed for effective immunity, and the breadth of its protective effect has been questioned. The goal of my research program is to develop a safe live attenuated virus vaccine that provides durable immunity after a single inoculation against the most neurovirulent members of the TBEV complex.



Alexander Pletnev

We developed a novel approach—chimerization—for the construction of live attenuated flavivirus vaccines. This pioneering strategy was based on conservation among flaviviruses of genome organization, number of viral proteins, replicative strategy, gene expression, virion structure, and morphogenesis. Specifically, this strategy involves the construction of a viable antigenic chimera from two heterologous flaviviruses—the structural protein genes of a full-length cDNA clone of a non-neuroinvasive partner (mosquito-borne dengue type 4 virus; DEN4) are replaced by the corresponding structural protein genes of another flavivirus that is neuroinvasive and against which protective immunity is sought. Because the structural proteins induced neutralizing protective antibodies, chimeric virus can be used as vaccine against the donor of the structural proteins.

I found that chimerization of TBEV or Langat virus (LGT; a member of the TBEV complex) with DEN4 completely ablated detectable neuroinvasiveness (the ability of virus to spread from peripheral tissues to the central nervous system, where it produces fatal encephalitis). Chimeras were immunogenic in mice and able to induce resistance against challenge with TBEV or LGT. Chimeric viruses were also attenuated, immunogenic, and efficacious in rhesus monkeys.

To determine the safety, infectivity, and immunogenicity of the LGT/DEN4 vaccine, a Phase I clinical trial in healthy adults was initiated at the Johns Hopkins School of Public Health Center for Immunization Research in Baltimore.

As a logical extension of our strategy for the development flavivirus vaccines, I have added West Nile virus (WN), a mosquito-borne flavivirus, to my research agenda. WN was chosen for study because this agent recently entered the United States for the first time and spread rapidly throughout North America, where it has produced severe neurological disease in humans, domestic animals, and birds. A high degree of attenuation for mice, geese, horses, and monkeys was achieved by chimerization of WN with DEN4. Despite the high level of attenuation in mice and monkeys, both the WN/DEN4 chimera and its deletion mutant WN/DEN4D30 induced a high titer of neutralizing antibodies and provided complete protection of animals against lethal WN challenge.

Currently, the WN/DEN4D30 vaccine is under evaluation for safety and immunogenicity in a clinical trial in healthy volunteers. In order to prevent sporadic or epidemic encephalitis caused by the other neurotropic flaviviruses such as St. Louis encephalitis, Powassan, or Japanese encephalitis virus, I plan to develop vaccines using the chimerization approach that has been successful for WN and TBEV viruses.

Jun "Jim" Zhang *obtained his medical degree from the Shanghai Medical University, China, in 1988, followed by an internship at the International Peace Maternity and Child Hospital in Shanghai. He was later certified by the U.S. Educational Commission for Foreign Medical Graduates (ECFMG). He received his Ph.D. degree in epidemiology from the University of North Carolina at Chapel Hill in 1994. He conducted research with both Family Health International in North Carolina and the World Health Organization in Geneva, Switzerland. He was an assistant professor at the Mount Sinai School of Medicine in New York before joining the Epidemiology Branch at NICHD in 1997 as a tenure-track investigator. He is currently a senior investigator.*

My research focus has been on obstetric and perinatal issues that affect a large number of pregnant women and address the safe and efficacious clinical management of women in labor. Highlights of my research include the following studies:

Jun "Jim" Zhang

■ Empirical evaluation of the effect of epidural analgesia for labor pain on labor progress and the need for operative interventions such as Caesarean or forceps delivery. We found that epidural analgesia use does not result in an increased risk of prolonged labor, Caesarean delivery, or other unfavorable events during labor and delivery compared with intravenous analgesia.

■ Empirical evaluation of the existing labor curve currently used by clinicians with regard to labor progression or failure and the need for clinical intervention. Our study showed that the current diagnostic criteria of labor protraction and arrest were too stringent for contemporary obstetric populations, leading to excessive use of Caesarean delivery.

■ Empirical evaluation of labor progression and risk of Cesarean delivery in electively induced labor. We found that nulliparous women with an unfavorable cervix whose labor was induced had a high rate of labor arrest and a threefold increased risk of Caesarean delivery compared with nulliparous women with spontaneous onset of labor. Our study called for judicious use of labor induction in women delivering their first babies.

■ Randomized clinical trial on medical management with misoprostol for early pregnancy failure (or miscarriage). Our trial demonstrated that misoprostol is a safe, effective, well-tolerated, and inexpensive alternative to surgical management for early pregnancy failure.

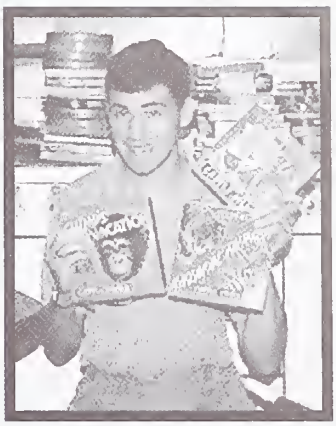
Today, more than one in four pregnant women in the United States deliver by Caesarean section, and the rate continues to rise. I am launching a large observational study to describe labor patterns in contemporary obstetric U.S. populations, with the aim of combating this rising Caesarean rate and identifying appropriate times to perform Caesarean delivery warranted by labor arrest. Findings from this study are anticipated to have a direct impact on obstetric practice.

In addition, identifying and diagnosing fetal growth restriction has been a longstanding challenge in modern obstetric and perinatal research.

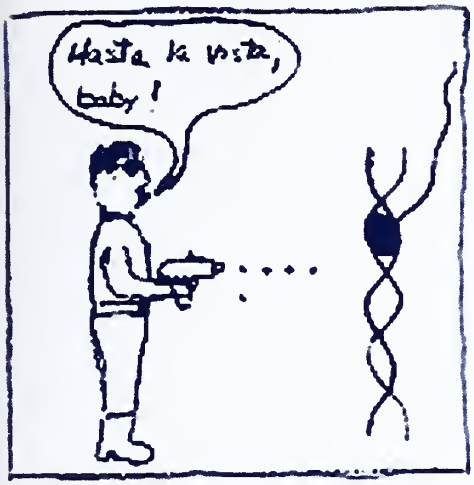
Pivotal to understanding the dynamics of human fetal growth and defining normal and abnormal fetal growth is the development of standards for fetal anthropometric parameters measured longitudinally throughout gestation. These parameters can be used to develop interval velocity curves and can be customized for physiological and genetic factors.

I am developing a prenatal ultrasound study to establish a U.S. national standard for normal fetal size and growth velocity at various gestational ages; the study will also provide a basis for an individualized standard for optimal fetal growth to improve the precision with which fetal growth restriction or excessive growth is diagnosed. As part of the study, I will also develop a new formula to improve fetal weight estimation by ultrasound and collect biological samples to study the causes of idiopathic fetal growth restriction. ■

Levity for the New Year: Science Meets Pop Culture

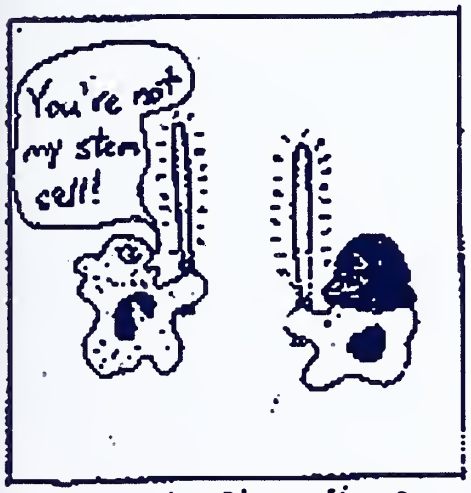


Cartoonist Ken Frauwirth (as seen on his website) is an assistant professor in the Department of Cell Biology and Molecular Genetics at the University of Maryland, College Park. A brief bio and links to his pages of cartoons appears when you click on: **<http://www.wam.umd.edu/~kfrauwir/index.html>.**

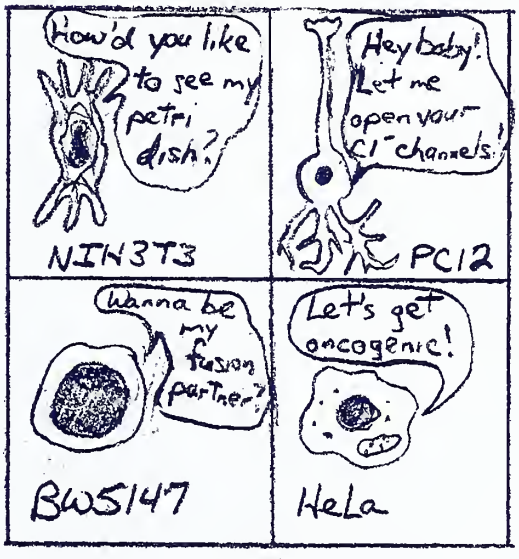


RNA Chain Termination

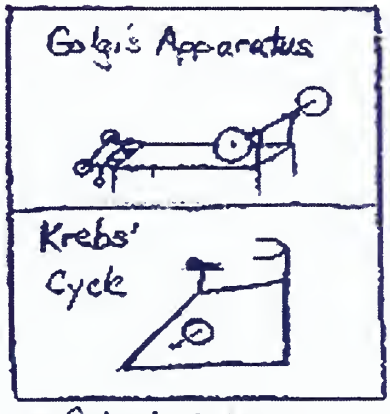
Scid Raw Mice



Leukocyte Skywalker



Popular Cell Lines



If biologists ran health clubs

Cell Cycle Arrest

If Ian Fleming had been a biochemist

Zinc finger

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: 402-4303; or mail: Building 2, Room 2E26.**

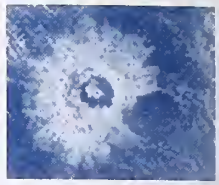
Also, we welcome "letters to the editor" for publication and your reactions to anything on the *Catalyst* pages.

In Future Issues...

- Inflammatory Statements
- Bench to Bedside
- Obesity Research

Kids' Catalyst

Exact Impact: Making Craters



NASAJ/PL

We're going to travel to the stars again . . . or just to the kitchen . . . to see how those big holes in moons and planets (including our own) are created.

When you look at the moon, you can tell that it's had more than a few interstellar encounters over the millennia that were strong enough to leave their mark: craters. Some large, some (relatively) small, these craters reveal hints about their origin that scientists analyze to figure out the shape of what hit the crater (asteroid), at what angle it was going when it hit, and how big it was.

So let's go to the surface of our own planet. What we'll need for this experiment is:

1. Flour, at least five cups, but you may end up using a five-pound bag. Expect to be covered in flour before we're done, so wear your jeans!

2. A shallow, long tray or box and a plastic bag to line it with. Something like a litter box would be perfect, but don't use it if it's not new! Yuck!

3. A rolling pin.

4. Marbles, beans, or just about any small object you wouldn't mind being covered in flour. No siblings allowed.

5. Contrasting powders. I used the strawberry and chocolate flavors of milk drinks, but you can certainly use colored sugar or any other nontoxic powder you wish.

6. A chart (that we'll make).

Now we're going to make a powder layer cake. Just as the surface of planets have different layers, so will our cake. Pour in enough flour to line the bottom of the tray and even out with the rolling pin. Sprinkle a thin layer of chocolate powder, then another thick layer of flour (evening out again), and finally some strawberry.

Take a bean and drop it into the powder from waist level and see what happens. Did you get all the way down to the bottom layer? Do you see chocolate on the surface now? Does it help with sound effects (just kidding).

Move to another section and drop another bean from over your head, and see the difference. Try this with different heights, different objects, and different angles, writing down your observations as you go. You can even vary how tightly packed the flour is. You can clearly see that the pattern in the flour is different for a bean dropped straight down from waist-high from one flung from the side. How do the other variables affect the pattern in the flour?

Scientists use a very similar experiment to reproduce craters, and they can predict what impact an asteroid can make. The actual crater itself may smooth over time—which helps us predict its age—but the mark will always be there, proving an encounter in the stars.

—Jennifer White

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