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A Community of Beautiful Minds (Summer 2007 Trust Magazine article)

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More than 200 Pew Biomedical Scholars were gathered in a hotel ballroom earlier this year for the 20th anniversary reunion of the Pew Scholars Program in the Biomedical Sciences. It's fair to say that they were excited. They were already veterans of annual meetings during their four-year Scholar period (attendance is expected), and many of them had attended previous alumni meetings. They looked forward to hearing their peers present work in progress, scientists outside the program give talks, and other speakers broaden their perspective by connecting the biomedical sciences to societal and policy issues.

And so it was a surprise to me to hear about some Scholars' lack of enthusiasm for the meetings—that is, before they attend their first one. When Roderick MacKinnon, M.D. (1992 Scholar), now at Rockefeller University, was preparing to go to his first, he had his doubts.

While he appreciated the Scholar's stipend, he also thought, "Gee, I'd much rather have the money it'll cost to go to the meeting to do more experiments."

He expressed this feeling when, as the first science presenter at the anniversary meeting, he began to describe his latest work. Then he added: "But I certainly have come to realize—and I think everybody here agrees—that, actually, these meetings are far more important even than the funding of the specific science that we could do at the time. They are much more important to our careers."

MacKinnon spoke from experience. His major achievement is elucidating the structure and mechanism of ion channels. The discovery helped open up the chemistry of the cell, and for this contribution MacKinnon was awarded the Nobel Prize in Chemistry in 2003. During his research, he made progress by using techniques from unrelated scientific disciplines—electrophysiology, biophysics and molecular biology— but the clincher turned out to be tools from X-ray crystallography, which he mastered with the help of William I. Weis, Ph.D. (1994 Scholar), a structural biologist at Stanford University. The two had met at a Pew Biomedical Scholars gathering.

MacKinnon continues to benefit from attending the meetings and talking to Scholars, an opportunity he is afforded as a current member of the program's National Advisory Committee. "The older I get," the 51-year-old said, "it's even more true."

Science can be a highly competitive enterprise, yet here I was hearing the opposite. Is this possible? Are the valuable science updates at the meetings actually upstaged by the contacts the participants make and the resulting sharing of ideas and methods? I thought I'd explore the

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extent to which this attitude pervades the Pew Scholars— who now number more than 400 from nearly 200 universities and research institutions—and the various ways their personal interactions turn them into a community.

After learning about the program's benefits, it is clear to me why the meetings would not, at first, strike the Scholars as the most valuable part of the experience. The Pew Scholars Program in the Biomedical Sciences, housed at the University of California at San Francisco, annually selects 20 early- to mid-career investigators in basic and clinical research based on a specific research proposal. For four years they receive annual stipends of $60,000 for equipment, supplies, travel or other needs—whatever will best advance the research and the Scholar's career. This flexibility has always been the hallmark of the award.

"It encourages them to take a long view of their work, and the program consistently emphasizes this approach," says Jim O'Hara, managing director of Pew's Health and Human Services Policy program. With four years of funding assured, he adds, they might be more venturesome in their research and future applications for support from other sources than would otherwise be likely.

The Pew Scholars are already well vetted for their scientific curiosity. Their selection is determined less by what their proposed project might produce (as they would have to specify on an application for most grants from the National Institutes of Health and disease-based research foundations) than by their own proven excellence, ability to set their own goals, innovativeness as researchers and willingness to try out new investigative directions as the research dictates. The history of Torsten N. Wiesel, M.D., sets the program's tone. He chairs the program's National Advisory Committee (as well as that of the Pew Latin American Fellows Program in the Biomedical Sciences; see sidebar below, "**La Comunidad**"), and, with David H. Hubel, Ph.D., won a Nobel Prize for discovering how the visual system processes information. The scientists worked together for 25 years, and Wiesel wryly says that the partnership "can be described as a 'massive fishing trip,' an expression commonly used by [NIH] study sections to disparage bad grant requests. Our research was seldom 'hypothesisdriven,' to use another term (this one always implying approval). So be it," he says. "But the lack of a hypothesis need not necessarily prevent one from catching big fish."

The National Advisory Committee as a whole leads by example. Like its two chairs (Nobel laureate Joshua Lederberg, Ph.D., preceded Wiesel; both are based at Rockefeller University), they have broad scientific interests, are interdisciplinary in their scientific approaches and methods, and are devoted to training younger scientists. Because they pick the Scholars, they must be seasoned judges of intellectual talent and have interests beyond science. And they must be willing to serve as mentors, inspiring and guiding the Scholars in relationships that often extend long after either's direct connection to the program. At the annual meetings they can be

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seen deep in discussion with their younger colleagues, asking tough questions and sharing their years of experience.

“If this group were constituted into the faculty of a single department,” said Eugene P. Kennedy, Ph.D., a biochemist at Harvard University who has evaluated the program, “that department would be one of the most distinguished in the nation.”

That Scholars representing every class since the program’s inception continue to attend anniversary meetings suggests that they feel part of an ongoing community, and the evaluations of the 20th anniversary meeting confirmed it.

Participants liked the series of three panels on science policy, whose speakers included Francis S. Collins, M.D., Ph.D., former director of the Human Genome Project and now of the NIH; former U.S. Representative John E. Porter, who championed significant increases in NIH funding while in Congress and who continues advocating for research funding as board chair of Research!America; and Sheryl G. Stolberg, an award-winning science writer and now the White House correspondent for The New York Times. In addition, Princeton University president and molecular biologist Shirley M. Tilghman, Ph.D. (and former advisory committee member), spoke on a scientist’s social responsibility. One participant wrote, “The more global perspective and broader issues are something we often don’t have a chance to hear and discuss.”

But more than anything, the Scholars praised the opportunity to see one another—as one scientist wrote, “It re-energizes us and gives the ‘Old Scholars’ and ‘New Scholars’ a chance to interact for the first time.”

They devoted many hours listening to the presentations of their colleagues. Sometimes they felt out of their element, but most relished the challenge to keep up, as I would hear directly.

Gary H. Gibbons, M.D. (1994 Scholar) is a cardiologist at the Morehouse School of Medicine, where his research group’s work on vascular biology and the pathogenesis of vascular diseases has resulted in several patents. “We’re experts in our field and at the top of our game,” he told me during the conference, “so it’s interesting to go to talks where we’re not only not the experts but have only average understanding.”

The participants dedicated even more hours to talking shop. Every day, I passed a pleasant 45 minutes during lunch, while, on the other side of the table, a couple of scholars, different ones each time, were deep into discussing science, with an occasional wave of the hands or a laugh to punctuate a point. They could have been sitting at a table for two and were not even disturbed by a photographer edging up to record the fact of their conversation.

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Seeing these exchanges is a common experience for a former member of the program's National Advisory Committee, Michael B. A. Oldstone, M.D. He is a virologist at the Scripps Research Institute, and his awards include membership in the Institute of Medicine of the National Academy of Sciences. "For me, the heart of the program is the dynamics of people meeting," he said. He regards the gatherings less as a conference and more as a retreat. "The informality is really what's terrific."

Nancy M. Hollingsworth, Ph.D. (1996 Scholar), a biochemist and cell biologist at Stony Brook University, has a list of exchanges with her fellow Scholars, and she recounted them in the oral history that is part of the program (see feature below, "**Making a Community with the Future**"). Her lab studies chromosome structure and function during meiosis in yeast. She pioneered a "mutant screen" through which she identified the gene Hop1, a component of the protein structure (known as synaptonemal complex) that mediates chromosomal pairing. At a meeting during her Scholar years, she met Carolyn F. Kisker, Ph.D. (2000 Scholar), now a structural biologist at the Rudolf Virchow Center for Experimental Biomedicine, in Germany, and the two collaborated on the structural crystallization of Hop1.

At another meeting, Hollingsworth met Kevan M. Shokat, Ph.D. (1996 Scholar), a cellular and molecular pharmacologist at the University of California at San Francisco; they began a collaboration that put her in touch with a company that supplies her with her radioactive analogs free, and that has led to several publications. She teaches with Maurice J. Kernan (1997 Scholar), a neurobiologist at Stony Brook, noting, as faculty colleagues, "we would have done that, anyway, but it helps that we have the bond."

"I always come away inspired to try something new," said Gregory J. Hannon, Ph.D. (1997 Scholar), professor at the Cold Spring Harbor Laboratory. He recalled a Scholars meeting when Craig C. Mello, Ph.D. (1995 Scholar), a molecular biologist at the University of Massachusetts School of Medicine, described his work on RNAi, a biological process that silences genes individually. As a research tool, RNAi can disable genes in laboratory animals, so that scientists can study the effects of the genes' absence. For patients, the technique has the potential to silence genes that cause diseases. Not long afterward, in February 1998, Mello, with Andrew Z. Fire, Ph.D., currently of Stanford University, would publish a paper on that discovery in the journal Nature. Eight years later, this discovery would earn the two a Nobel Prize. Mello's talk interested Hannon, and the two chatted, but because Mello is a worm biologist and Hannon works on fruit flies, Mello's idea "just sort of percolated for a year," said Hannon in the RNA Interviews series by the Ambion company.

At the next Scholars meeting, he heard a talk by Richard W. Carthew, Ph.D. (1995 Scholar). A molecular biologist now at Northwestern University, Carthew, last year, contributed to research proving that RNA silencing is the fly's immune response to infection by viruses. At the session

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Hannon attended, Carthew described how he used embryo injections to show that RNAi worked in the fly. “That’s what really pulled me in,” Hannon said. “The notion that this phenomenon was going to be universal really captivated me.”

He shifted the entire emphasis of his lab to RNAi, although, instead of gene function, he studies the mechanism of RNAi. He and his team identified the activity called RNA Induced Silencing Complex and one of the complex’s protein components. They identified the enzyme Dicer, which begins the RNAi process by cutting long RNA molecules into shorter ones. They showed the gene-silencing effectiveness of “short hairpin” RNAs, thus extending the possibilities for functional studies.

And in June, Hannon’s lab and others published a finding that a family of microRNAs enables a crucial tumor suppressor network, called the p53 pathway, to arrest cancer growth and even eradicate cancers.

Mello’s talk set Hannon thinking, and then Carthew’s changed his career, Hannon acknowledged: “I actually called the lab from that Pew meeting and said, ‘You know what? Get out those Drosophila cells and see if they do RNAi.’ And they did.”

The reality of a Scholars’ community became fully clear to me when I witnessed the start of a potential collaboration. Susan K. McConnell, Ph.D. (1989 Scholar), a neuroscientist at Stanford University, had just given a talk on the development of the central nervous system, her laboratory’s focus. In her conclusion, she had said, “This program is very dear to my heart” (she now serves on the National Advisory Committee). I wanted to follow up and saw her at one of the science fairs. “My first Pew meeting transformed the way I do science,” she said. “I have neurobiology training, and after my first meeting, I viewed my own research as primitive compared to others. It was like a bucket of ice water.”

Just then, Michael Lagunoff, Ph.D. (2002 Scholar), approached her. He is a microbiologist at the University of Washington School of Medicine and on a normal day does not cross paths with a neurobiologist. He had attended McConnell’s talk and was riveted by her movies of living slices of the developing ferret brain, with neurons imaged by a technique called time-lapse confocal microscopy.

Their work, he felt, might have something in common. “I have movies that we’ve taken from infected cells that change the way they move,” he said, “and I think it might be related to something neurons do, because it looks a lot like the neuron movement rather than a different cell type in the body’s movement.”

They agreed to chat together, but first he answered my request to elaborate on his aims: “What I’m interested in talking to her about is this: Can we understand what the virus is doing in the

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cell by understanding whether it activates something that is happening in neurons already? Could a virus activate, in a different cell type, something that looks similar to that?

“The molecular mechanism could actually be similar, and we could get ideas from that,” he concluded, “so we’re taking ideas from one field to a completely different one.”

They retreated to a table and chairs by the side of the room. “See?” McConnell called back to me. “It’s taking place right in front of your eyes.”

Science evokes conflicting feelings. On the one hand, it offers “a seemingly inexhaustible sense of wonder,” as Torsten Wiesel says. But he also remembers hitting the wall, enduring “the frustration that is the daily bread of so much scientific research.” At the anniversary meeting, the Scholars often compressed both of these opposing moods into one sentence.

Francis M. Brodsky, D.Phil. (1988 Scholar), a microbiologist and immunologist at the University of California at San Francisco, described her work on the cell’s mechanism for accepting macromolecules, work that could help explain how the immune system works, which is basic to vaccination and certain therapies. She brought the Scholars up to date on her lab’s progress, ending with this comment: “That’s what we knew in 1988. We’re getting closer—we’re not there yet.”

Brodsky has also written science-based detective novels—“biomysteries”— under the name of B. B. Jordan. They’re easier: The loose ends are tied up and the murders solved by the last page.

Susan McConnell expressed the wonder and frustration in another way. Summing up her talk on neuronal development, she put a slide on the screen and said, “I don’t know if it’s really wonderful or totally pathetic that 15 years of work is summarized on this one slide.”

Then she added, “Science gives us more questions than answers.” She had widespread agreement from 200 knowing, and sympathetic, colleagues.

How important is this? It can make a difference when “things are a little hard,” Jan Erikson, Ph.D. (1993 Scholar), an immunologist at The Wistar Institute, said in her oral history. Then she mused: “I must say, one of the sources of friendship in science has come from the Pew [program], because it has gotten us together in such wonderful ways.”

Erikson knew there was something special at her first meeting. She studies the interplay among the various immune cells that activate or suppress the immune system, and at that meeting she gave a talk on the lymphocytes known as B cells, which are essential to the immune system when it encounters diseases. The thoughtfulness and acuity of the questions startled her. “I

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talked about this work at immunology meetings," she recalled, "and had never gotten the kinds of questions that required me to stand back and look at the whole picture."

In particular, she recalled, she was describing the use of gene segments when a Scholar asked simply, "Why did you do that?" As Erikson told the oral historian, "It wasn't a question I had ever answered," because at the time everybody studying B cells looked at gene-segment use. "I answered his question. It just made me think about the work in a new way."

She continued: "The gift there was the different people I was around, from diverse backgrounds, a group I was privileged to be among, a high level not just of science but of generosity— people happy to listen to someone else's work and comment on it.

"It's personal," she added. "I even get a birthday card from Pew every year." Then she mused once more: "The truth is I like that. That's nice. They humanize."

La Comunidad

"After all, science is essentially international, and it is only through lack of the historical sense that national qualities have been attributed to it." Marie Curie, D.Sc., twice a Nobel laureate

A sister initiative of the Pew Scholars program is the Pew Latin American Fellows Program in the Biomedical Sciences, now in its 17th year. The program, administered by the University of California at San Francisco, identifies talented early career Latin American scientists, helps place them in top scientists' laboratories in the United States so that they can absorb the latest research ideas and methods (they receive $30,000 for each of two years), and then provides $35,000 in support for them to establish their own labs when they return home. The Fellows are encouraged to use their postdoctoral training opportunity either to increase knowledge of their current area of research or to explore a new area relevant to their interests.

There are now more than 150 Fellows. Many have published in top ranking journals, often as first author, and several former Fellows have obtained prestigious awards, such as being named Howard Hughes Medical Institute investigators, for their continuing research. Virtually all of them play key roles in their institutions' research and development by participating in teaching, research training and supervision activities that draw directly on their experiences in the United States.

They have also proven to be a cohesive group. The Fellows' 15th anniversary meeting occurred in 2005, and more than 80 percent of the alumni attended—a sign of the esteem in which the program is held, observes Jim O'Hara, managing director of Pew's Health and Human Services Policy program. In addition to science presentations by their peers and a talk on competing for grants from the National Institutes of Health, the scientists networked with each other and the

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advisory committee, sowing the seeds for new collaborations. In their post-meeting evaluations, many praised not only the research but the progress of the presenters since their postdoctoral U.S. training. They appreciated the attention of the advisory committee members. And they enjoyed being able to reconnect with each other after many years and to establish new scientific partnerships—some describing specific collaborations that were set in motion during the meeting.

Making a Community with the Future

"If I could be king of the forest, we would be talking about science all day long." Bill Nye, the Science Guy

Joshua Lederberg, Ph.D., once agreed to sit for an oral history. In recounting his work on bacterial recombination of DNA, which led to a Nobel Prize, he said, "Look, the purpose of the experiment was to bring bacteria into the mainstream. Behind that was to bring DNA into genetics. Yes, this was the master molecule that was going to be available for further experimentation. I can say that without qualm."

Arthur Daemmrich, Ph.D., told this anecdote to participants attending the 20th anniversary meeting of the Pew Biomedical Scholars. Daemmrich, of the Chemical Heritage Foundation at the time, was discussing the value of oral history, an expertise of the foundation. "Here we have a huge turning point for molecular biology in the 20th century," he said. "Here we have a scientist with an intentional research agenda, developing the framework and then the particular molecule and method. That's an exciting moment to capture."

The Pew Scholars program is already familiar with oral histories— Lederberg, when he served as chair of its National Advisory Committee, recommended that the program cull the Scholars' own accounts of their careers, because he knew the firsthand perspective would be invaluable. The program adopted his idea, and now scores of Scholar histories constitute a unique story of recent biomedical science.

The Chemical Heritage Foundation, where the program's oral-history project is housed, is not only continuing the project but also enhancing it, Daemmrich said. It is reaching out to Scholars who have not been interviewed (involvement is voluntary) and plans to re-interview some of the scientists who participated previously.

It will establish a Web presence for the series, with a précis of each Scholar's biography as well as a table of contents; the full text, with the Scholar's agreement, will be available to historians and others through interlibrary loan. The foundation is found at www.chemheritage.org.

Marshall Ledger is the editor of Trust.