

The NIH CATALYST

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CLINICAL RESEARCH TURNS OVER A NEW LEAF



Following is a reprint of the Executive Summary of the report and recommendations of an NIH committee convened to review and electrify clinical research at NIH. The committee was headed by Stephen Strans, NIAID. An implementation plan is now being finalized and will be published along with the entire "Report of the NIH Committee on the Recruitment and Career Development of Clinical Investigators" in the months ahead. The implementation plan will be published in a future issue of *The NIH Catalyst*.

Rapid changes in academic medicine and science are "bedeviling" clinical investigators nationwide, as Dr. Joseph Goldstein described recently in the first Shannon Lecture¹. At the NIH, the morale of clinical investigators has waned in recent years, and clinical investigators have begun to feel undervalued and undersupported. Nonetheless, NIH, with its Clinical Center and large research portfolio, has the ability to transcend these problems and to remain a bastion of clinical research excellence. Revitalization of clinical research is now a major priority of the NIH leadership and the scientific community.

The Committee on the Recruitment and Career Development of Clinical Investigators was formed to review the current state of clinical research and to offer specific recommendations to the deputy director for intramural research and the NIH associate director for clinical research to improve the recruitment, training, development, and tenure process for NIH clinical investigators. A three-month study by more than 40 senior NIH scientists led to this report's key findings and specific recommendations.

The Committee found that NIH clinical researchers are disheartened by a perceived decline in numbers of patients, increased obstacles to studying patients, and diminished respect for patient-ori-

¹ The NIH Shannon Lecture, January 13, 1997, Bethesda, Maryland.

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SEND IN THE CLONES!

On March 13, Scottish researcher Ian Wilmut filled Masur Auditorium and several overflow rooms with scientists and others eager to learn of his comp defeating the dogmas of mammalian cell differentiation. On the same day, the National Bioethics Advisory Commission assembled for its first meeting in response to a presidential directive that it produce a report and recommendations on the state of the art and the legal and ethical ramifications of human cloning research—a directive inspired by Wilmut's cloning achievement with sheep.

The NIH Catalyst seized the moment, dispatching NIDCD Fellow David Ebreinstein to conduct a one-on-one interview with Wilmut after he'd addressed the NIH masses, Scientific Editor Celia Hooper to snap photos of Wilmut engaged in this dialogue, and Managing Editor Fran Pollner to cover the ethics panel deliberations, the results of which may well shape the types of cloning-related research NIH scientists will be allowed to pursue. Our reports—and a technical review by NICHD's Alan Wolfe, whose own research is connected to the issue at hand—follow.

WILMUT'S LUCKY LAMB SHEPHERDS IN NEW ERA OF DEVELOPMENTAL RESEARCH

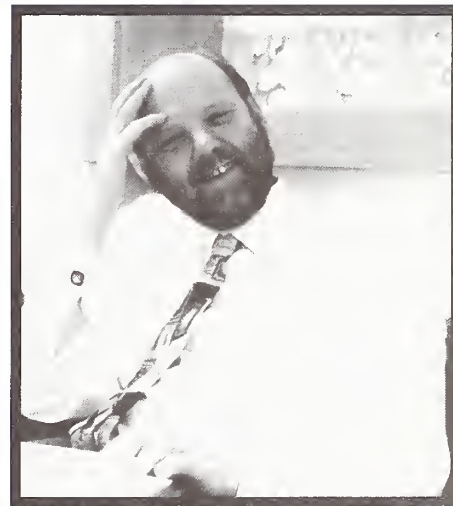
by David Ebreinstein

Ian Wilmut admits to some good fortune when he created the lamb named Dolly, the first mammal to be cloned from the DNA of an adult animal. He paraphrases the British scientist Peter Medawar on the definition of a good experiment: "You have to go far enough forward that it really does add to knowledge, but not attempt to go so far forward that it doesn't work, or you don't understand it. . . . I think we got lucky with this one, and it's gone a long way," he said in a recent interview with *The NIH Catalyst*.

But Wilmut was not trying to make history. Since the mid-1980s, his goal had been to manipulate the genes of farm animals as easily as other scientists modify mouse genes. With such techniques, drug companies could genetically manipulate livestock to generate large quantities of human drugs or hormones in the animals' milk, or perhaps create a scrapie-free strain of sheep. So it was actually attempts to manipulate the sheep genome, not clone it, that led Wilmut and his colleagues to produce Dolly.

A decade ago, Wilmut's lab and others had tried to culture the livestock equivalent of mouse embryonic stem (ES) cells—undifferentiated cells that are

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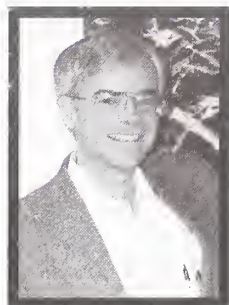
Celia Hooper

Ian Wilmut: A Man On the G₀

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'TIS BETTER TO GIVE AND RECEIVE: ON THE ART OF SHARING



Michael Gottesman

We often say that the large size of the intramural program provides a critical mass of scientific know-how and allows us to realize economies of scale because we can share expensive or unique services. Organizations such as the Division of Computer Research and Technology (DCRT), the Office of Research Services (ORS), and the intramural portion of the National Center for Research Resources (NCRR)—including the Bioengineering and Instrumentation Program (BEIP), the Veterinary Resources Program (VRP), the NIH Library, and the Medical Arts and Photography Branch—were established originally to provide high-quality services at reasonable cost and convenience. But now, as the growth of the intramural research budget has flattened, our research resources have become increasingly precious, prompting us to take a hard look at the functioning and cost of these shared services and to rethink how we will provide these services in the future.

Last fall, I established a shared resources subcommittee (SRS) of the Board of Scientific Directors, chaired by Edward Korn (scientific director, NHLBI) and Arthur Levine (scientific director, NICHD), to begin this effort. The SRS has given me a preliminary report, and we have begun to implement some of the recommendations. First, the committee strongly endorses the need for shared resources at NIH and points out the important role that support staff within these programs have played in the intramural program. However, in some cases, pooled money (management funds) intended to support shared resources was being used to support independent research programs. The committee has strongly advised that management funds intended to support shared services should not be used to hire and support fully independent scientists. NIH has endorsed this principle. Where such hiring has occurred, the independent staff should be transferred to institute intramural programs where appropriate funding and scientific oversight for their programs can be provided. This does not mean that someone hired to provide a support service cannot work collaboratively with other NIH scientists, or that the director of a shared facility cannot have some funds to carry on research activities, but that their independent research activities should be a small percentage of their effort.

Given this principle, the SRS has recommended that some investigators in DCRT be transferred to NICHD and that the In Vivo NMR Center, in which

a large amount of original, independent imaging research occurs, be transferred to NINDS. Currently, many different institutes use the NMR Center's equipment and services, and we will develop a charter that specifies NINDS' obligation to guarantee imaging access for users from all institutes. The SRS is also reviewing other central services and formulating recommendations about their organizational location and structure.

The need for new shared resources arises from time to time, and one of the subcommittee's tasks is figuring out how to provide them as needed—but not necessarily in perpetuity. The idea of using a lead institute to initiate a new program that can serve as a shared resource seems practical and has a history of success at NIH. The Pilot Plant (NIDDK) and the Protein Expression Lab (NIAMS) follow this model. This year, NHGRI offered to be the lead institute for a megabase sequencing facility for use by the intramural program: the NIH Intramural Sequencing Center (NISC; see box on page 14), will be established this summer and will provide high-throughput sequencing and informatics for intramural projects deemed of scientific merit. Almost all of our intramural programs have decided to provide start-up funds for NISC, and sequencing will be done on a fee-for-service basis beginning in late summer. No permanent personnel will staff NISC, so if the technology becomes outmoded, or the need no longer exists, the program can be discontinued with minimal financial loss. Some of the services provided by the NIH facility at Frederick and some of our transgenic animal facilities also use this concept of a lead institute with fee-for-service charges.

My office wants to encourage development of the best possible portfolio of shared resources at NIH, but I need to know what shared services you think we need—and don't need. I will use the SRS to vet the ideas, and together we will devise ways to make the services available as quickly as possible. One recent example was the suggestion by Mike Lenardo (NIAID) that we have an on-line, intranet-accessible database of sharable equipment and surplus materials. NCRR has created this database: <<http://www.ncrr.nih.gov/sharedbc/sharetop.htm>>.

Talk to your scientific directors about establishing lead agency status for existing services you think you can provide or that should be provided to the intramural community. If your scientific director cannot help you, let me know what you have in mind, and we will see what we can do.

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CATALYTIC REACTIONS

Below are comments we received in response to questions posed or issues raised in recent issues.

More on Daycare

1. You ask what burning questions or problems blocking the efficient conduct of research would (readers) like the *Catalyst* to dig into in future issues.

Sick-child care. Sick children have a significant impact on a laboratory as parents must take unscheduled leave for extended periods of time. Much of this time, children are not sick enough to actually need to stay home, but they are not well enough to return to school/daycare. I have colleagues at other institutions where sick-child care is available for this very same reason. It allows my colleagues to operate with a smaller (i.e., more efficient) staff and to avoid the uncertainties we face.

2. At the direction of HHS Secretary Donna Shalala, an NIH committee is now developing a strategy for improving NIH work life. You ask what *Catalyst* readers would recommend.

More support for parents in the form of more extensive and less expensive daycare and sick-child care. We desperately need this, unless we are going to require our scientists not to become parents (or maybe the plan is to return to allowing only those fathers with stay-at-home wives to be scientists at NIH, or to require women to remain childless and men to limit fathering to a superficial level).

3. The physical condition of the outdated NIH daycare facilities on campus could cost \$250,000 to fix. You ask, is the investment worthwhile?

In the NIH budget, \$250,000 is a very small amount. It is shameful that repairs of such small magnitude have not been performed. NIH should make a much larger investment in on-site daycare. The increased productivity will be well worth it. This investment should be made based upon the benefit to the NIH mission alone. After all, this is the reason that private companies make this investment—it affects the bottom line.

—Maryalice Stetler-Stevenson, NCI

Alessandra Barelli, a former NIHer and mother of two children who have attended or are attending the POPI preschool in Building 35, also decries the problem of sick-child care. At the Catalyst's request, she called around to find out what commercial sick-child care is available. Barelli found that com-

mercial care is scarce, hard to find, expensive, and primarily headquartered in Virginia. After considerable effort, she turned up the following possibilities:

◆ *Mother's Aid Professional In-home Childcare provides temporary and emergency services for children and elderly people and posthospital care for people of all ages. In operation since 1979, they serve the entire metropolitan area. Charges are \$50 for the yearly registration fee, \$15 for an agency fee (\$25 for last-minute calls), and then \$7–\$10 per hour for caregivers.*

◆ *Doctor Care Nanny Services specializes in full- and part-time, in-home or drop-off care for sick children, including evening and weekend care, throughout the metropolitan area. They charge a one-time application fee of \$200, then \$10 per hour for the caregiver. Credit card prepayment is required.*

◆ *Tri-Cities Nursing offers emergency sick care for children and elderly people, as well as postsurgery care for people of all ages. Tri-Cities charges \$50 for an eight-hour day of care, but requires registration and other fees, bringing the one-day total to \$76. (This appears to be the best deal in town, Barelli says.)*

◆ *We Sitt provides emergency sick care for children in Metro-accessible areas of Maryland.*

Fortunately, neither Barelli nor the Catalyst staff have had to try out any of these services yet, so this information should not be considered an endorsement of any of the mentioned services, nor should omission of a service be considered a judgment against it.

—Celia Hooper

I enjoy reading the *Catalyst*. In the March-April 1997 issue, I read the Catalytic Reaction about the NIH preschool and was glad to know that NIH approved the \$250,000 upgrade for the daycare facilities; however, I was extremely disappointed by the picture of the preschool as portrayed in the Catalytic Reaction section by Rosaura Valle.

I have two children who went to the NIH preschool and they absolutely loved it. As parents, we enjoyed each and every day that our children spent at that school. We were grateful that we had the opportunity to enroll our children there, since we had looked at many

preschools and were very impressed by the setup, atmosphere, and curriculum of the NIH preschool. We chose to send our children to preschool to better learn the English language since we speak Chinese at home, and by the time they went to kindergarten, they spoke English very well. Not only did the preschool prepare them by developing their language skills, it did what a preschool should do, namely, it fostered their social skills and their muscle coordination.

As for the suggestion [the letter writer] made concerning the diversity of the preschool, I believe that the preschool already embraces internationality and diversity, since the children are of many different ethnicities and races. It teaches the children to be accepting of different people because the children interact naturally; it also exposes the children to many different holidays and the customs of those holidays. There are teachers who are of various ethnic backgrounds and do speak many languages fluently—Spanish, French, Chinese, Arabic, and Farsi.... If parents would like their children to learn about the heritage, traditions, and cooking of particular cultures in detail, that type of learning can be done at home. There are so many more fundamental aspects of development that children need to learn at school.

I hope that you print my letter. . . . I am also mailing a copy to the NIH preschool director and the teachers there. I would like them to know that . . . we, as parents, are still very much thankful to them in our hearts for giving our children the best start to life.

—Anonymous

On May 12, the POPI preschool director and staff received a "Quality of Work Life Award" for more than 20 years of excellence in providing "loving, child-centered care."

—C.H.

On Lower-Cost "Cool" Methods

As a follow-up to the article on Molecular Interaction Analysis Using Surface Plasmon Resonance (March-April 1997 issue), please note that Biacore, Inc., currently has four instruments, not just the stated two, on the market. The other two instruments, the Biacore X and the Biacore Probe, have a base price of \$101,000 and \$58,000, respectively. This should at least help with the cost concerns mentioned.

—Michael A. Robinson
BIA Account Specialist



CLINICAL RESEARCH TURNS A NEW LEAF *continued from page 1*

ented research as a rigorous and valuable discipline. The Committee concluded that these complaints need to be addressed if NIH is to mount and sustain a broad and vital patient-oriented research program. Rising national interest in the evolution and success of clinical research and substantive new commitments at NIH, such as the construction of a major new Clinical Research Center, make this a propitious time for the rejuvenation of patient-oriented research.

The Committee identified four focus areas and made recommendations for addressing problems in each:

- **Ongoing NIH clinical research efforts and projections of existing trends.**

- **The nature and adequacy of training and professional development for clinical researchers.**

- **The mechanisms by which clinical researchers are reviewed, tenured, and promoted.**

- **Recruitment of clinical researchers to NIH and how that process should be improved.**

Problem areas identified by the Committee led to 32 recommendations designed to forge a full career track for clinical researchers at NIH, to secure stable support for clinical research activities, and to ensure an optimal environment for conducting clinical research at NIH. The essence of these recommendations is summarized below.

Personnel Mechanisms and Funding

Despite the beneficial application of Title 38 at NIH, personnel, salary, and funding mechanisms continue to generate powerful disincentives to the recruitment and support of the best clinical investigators.

- ◆ Under newly clarified authorities, tenure-track clinicians are covered under Title 42 appointments with a pay cap of \$148,400. Despite this, ICDs have largely been restricting salaries to a noncompetitive \$77,000. ICDs should raise the general salary cap for Title 42 appointees to \$115,700 (Executive Level IV), with the possibility of exceptions to \$148,400 (Executive Level I) for scarce medical specialties.

- ◆ Because all clinicians, including those in training, must be protected under the Federal Tort Claims Act, they must occupy full-time-equivalent (FTE) positions. With shrinking FTE allocations, there is a disincentive to sustain clinical training. This disincentive does not hold for postdoctoral training in basic laboratory science, where non-FTE personnel mechanisms, such as the Visiting Fellow and IRTA Programs, are an option. NIH should develop alternatives to the use of a full FTE for each clinician or otherwise ensure that all can be readily supplied with malpractice insurance.

- ◆ The current method of funding the Clinical Center leads to progressively higher per

capita management fund costs as ICDs reduce their clinical efforts. This funding formula must be changed to eliminate this negative feedback spiral, either by providing a fixed allocation to the Clinical Center or taxing all institutes in proportion to the size of their intramural budgets.

- ◆ Staff clinician appointments are being used to circumvent the tenure process. More than half of staff clinicians surveyed spend less than the requisite 50% of their time on clinical service obligations; many of them control substantial independent budgets. Staff clinicians' appointments must be distinguished from tenured investigators', and both appointment mechanisms must be used properly.

Promotion and Tenure

- ◆ Patient care is a necessary but time-consuming part of clinical research. In addition, clinical investigators may have training and clinical service obligations. All of these activities must be weighed in performance and promotion reviews.

- ◆ Memberships of the Boards of Scientific Counselors and Institute Promotion and Tenure Committees must be supplemented by individuals who actively conduct clinical research to evaluate NIH clinical investigators fairly. Similarly, clinical researchers must be included among those whose opinions are solicited regarding an individual's potential for tenure or promotion. Letters soliciting this advice must summarize the candidate's clinical and teaching obligations.

- ◆ Because clinical research may take longer than basic research and may require more collaborative effort, the five-year/eight-year rule should routinely be relaxed to provide clinical researchers up to eight years of postdoctoral training prior to competition for tenure-track positions. Largely patient-oriented researchers should be permitted up to eight years in a tenure-track position, especially for outside recruits. The total length of stay in nonpermanent positions at NIH, however, should not exceed 14 years.

- ◆ To ensure the fairest tenure review of clinical investigators, a Committee on Clinical Investigation should be formed to advise the Central Tenure Committee, analogous to the role played by the ad hoc Epidemiology Committee and the Computer Science and Engineering Committee.

Research Support and Training

- ◆ The best clinical investigation occurs in an atmosphere in which high-quality medicine is practiced. The NIH associate director for clinical research must develop and employ measures for supplementing clinical consultative services where required and for ensuring high overall quality of clinical services. Clinical directors and chiefs of clinically oriented laboratories set the standards

for their junior colleagues. Unless senior staff exhibit and demand the highest standards, their junior colleagues may fail to do so as well.

- ◆ Bench research requires adequate space and budget and also the support of technicians and fellows. Clinical research likewise requires specific resources, not just clinical associates and nurses who manage inpatients. Many studies would profit by the availability of research coordinators and data managers. Some ICDs have appreciated this; many have not. NIH must develop more uniform support for both inpatient and outpatient clinical studies. The current transition to greater reliance on the outpatient clinic has not brought a commensurate shift in support services for that area.

- ◆ It takes years of practice and formal training to become adept at bench research. Clinical research is also complex, and proficiency in it requires training that is not available in medical schools and residency programs. NIH has developed a valuable Core Curriculum for Clinical Research that serves as an excellent introduction to the field. The NIH should now expand this program for selected M.D.s and Ph.D.s to provide in-depth training in ethics, trial design, epidemiology, informatics, etc. These programs could lead to advanced degrees in clinical investigation.

- ◆ Clinical research is not a solitary venture. The advancement of medical understanding, as well as the advancement of one's career and reputation, may warrant participation in extramural or multicenter collaborations. Current regulations that limit such activities should be abandoned or interpreted as narrowly as possible.

In addition to these 12 major recommendations above, the Committee made 20 others, both general and specific. The thrust of all these recommendations is to reinforce the excitement, sense of discovery, and unbounded opportunity that clinical investigators once enjoyed at NIH. Restoring a creative clinical environment will require attention to many more issues than this Committee could consider. It will take resources, imagination, leadership, and courage: the imagination to create new ways of translating bench science into practical medicine, the leadership to recruit, unite and inspire talented people, and the courage to cast aside bureaucratic obstacles and old habits that stand in the way.

Therefore, the final recommendation of the Committee is to **establish a Clinical Research Revitalization Committee—consisting of scientific directors, clinical directors and other NIH clinical researchers—to provide advice to the deputy director for intramural research and the associate director for clinical research in implementing these recommendations and suggesting innovations to improve clinical research at NIH.** ■

WILMUT: 'WE GOT LUCKY. . .'
continued from page 1

the traditional starting point for transgenic work in lab animals. But the sheep cells wouldn't remain ES-like for more than three cell-division cycles, or "passages"; after that, their morphology changed, showing signs of differentiation. The traditional transgenic techniques require cells that remain undifferentiated much longer.

In 1987, however, Wilmut heard—in a now famous barroom conversation—that Steen Willadsen (now of the St. Barnabas Medical Center in West Orange, N.J.) had managed to produce calves with a new procedure: Willadsen took cells from the interior of many-celled embryos (blastocysts) and transferred their nuclei into eggs whose own nuclei had been removed (enucleated eggs). Although Willadsen had previously accomplished nuclear transfer from 16-cell embryos, it was generally believed that nuclei from older embryos, which have begun transcription and differentiation, could not be completely "deprogrammed" by the egg cytoplasm to restart normal development.

Wilmut realized that the sheep cell lines he had already made, which were also derived from interior blastocyst cells, might be useful for manipulating genes after all, if he used them as nuclear donors. He hoped to select donor cells that had been through several rounds of cell division, allowing enough time "to be able to do gene targeting to select the cells with the [desired] change . . . and then do nuclear transfer and therefore get your calf or lamb—or whatever it was—with the change," he says.

Research in large animals takes time; the gestation of a sheep is five months. And after two sheep seasons of testing, the longevity of the ES-like cells still appeared to be a limiting factor—only early-generation donor cells, through

passage 3, produced any lambs. But Wilmut and his colleagues were persistent. They decided to manipulate the cell cycles of the donor and recipient cells more carefully, and that turned out to be critical.

Normally, the cell cycle consists of four phases: M (mitosis), G₁, S (DNA replication phase), and G₂, although early embryonic cells and stem cells skip the "gap" phases, G₁ and G₂. If a cell is deprived of serum (which includes growth factors), it exits the cycle at G₁ and slips into a quiescent state, known as G₀, where it can remain for months

or years, until growth factors are added back to the medium. It was known that successful nuclear transfer required some coordination of the cell cycles of donor and recipient, and the later-passage cells allowed Wilmut's group to manipulate the more complex cycles of differentiated cells.

They decided to use recipient eggs at three different positions in their cycles—but to use donor cells only in G₀. In this case, convenience dictated the choice: cells could be held in G₀ as long as necessary, whereas G₁, another possibility, would require precise timing. It was during these experiments that Keith Campbell, the cell biologist in the group, pointed out that G₀ might be advantageous for another reason—the lack of transcriptional activity in the cells might allow such a nucleus to be reprogrammed more easily in the egg. At that point, the scientists realized the possible significance of G₀ and stopped discussing their work with others. "In our country, if you've gone public with information, you can't patent it. . . . If we had talked to anybody about that, we would've lost the patent."

In March of 1996, Wilmut's group published a paper in *Nature* showing their ground-breaking results: five lambs had been born, the first mammals ever generated from cells of an established cell line—passages 6 through 13. This achievement suggested that gene manipulation of farm animals would indeed

be possible. Putting the donor cells into G₀ appeared to be the critical new trick; the phase of the recipient egg turned out to be less important.

But not everyone was convinced. Some researchers credited the nuclear transfer and cell-cycle manipulation, while others thought he had simply used the right cells, Wilmut recalled. "And so what we were trying to do this year [in 1996] was to take another embryo population, a fetal population, and an adult population [of donor nuclei] and just see how powerful the nuclear transfer technique was. And the answer is yes, . . . it's the nuclear transfer that is powerful."

The result from the adult cell line was, of course, the most famous of the three, but Dolly was almost an afterthought. "We were having a lot of success with the new [donor] embryo cells and . . . fetal cells; then we thought, well, let's stick the adults on, as it were. But the original intention 18 months ago [was] to just do embryo and fetal cells." In fact, the adult mammary epithelium cells they used were in the lab's cold room only because another group was studying the manipulation of milk protein genes.

Wilmut is now eager to improve the efficiency of nuclear transfer, which yielded only one lamb out of 277 adult nuclei that were transplanted. One of his first steps will be to try adult cell types other than mammary epithelium. There are also many basic science questions remaining: How is the chromatin structure—long thought to be a key to the regulation of transcription and thus development—affected by the nuclear transfer? What specific proteins in the egg are involved in "reprogramming" nuclei derived from mature animal cells? What's special about the G₀ chromatin? But Wilmut probably won't investigate such basic questions in his lab. "I guess my primary focus would probably be to try and improve the method, whereas [basic scientists] would want to understand it, I suspect."

Wilmut's work has likely opened up a whole new realm of investigation for both basic and applied researchers. That can be exhilarating, but it can also be frustrating. So many unknowns surround these experiments, Wilmut acknowledged, that he often finds himself unable to answer questions. "I went into a lab meeting [at NIH] . . . and I almost wrote on the board 'we don't know'—I didn't have anything to say." ■



Celia Hooper

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THE ETHICS OF CLONING: A MODEL OF HETEROGENEITY

by Fran Pollner

Several humans in sheep's clothing disrupted the first meeting, March 13, of the National Bioethics Advisory Commission to plumb the legal and ethical depths of human cloning. They were animal rights activists, and their message, that "cloning is baaad," was unequivocal.

More ambivalence was expressed by most of the scientists, theologians, and ethicists hastily gathered to help the commissioners meet the request from President Bill Clinton delivered only weeks earlier: to produce a set of policy recommendations on the issue of research related to human cloning. They were given 90 days from the end of February to do the job.

Roman Catholic, Protestant, Judaic, and Islamic scholars interpreted the morality of cloning from their respective traditions, as did medical ethicists and legal experts. And a cell biologist laid out some of the scientific dilemmas that must necessarily inform the ethical considerations.

Distinguishing between cloning human beings and conducting cloning-related research that revolves around other pursuits, such as strategies to thwart cancer and genetic disease, would be among the tasks of the panel in arriving at policy recommendations. So would synthesizing the concerns of disparate schools of thought and beliefs in a pluralistic society and constructing safeguards against potential abuses.

Religion

Reflecting Roman Catholicism, Boston College theologian Lisa Cahill warned against "conscienceless science," the "irresistible attraction of research prestige," and profiteering from human beings as a commodity. Cloning, with its "biogenetic link to one lineage only" and the ability to produce offspring without the contribution of a male parent, is a "violation of the essential reality of the human family," she said, and is easily distinguished from genetic research into disease therapies.

Ironically, although the terror of cloning lies largely in a perceived loss of individuality, in truth, cloned individuals would be no more alike than identical twins—and even less so, several

speakers noted, since mitochondrial and intrauterine factors would be different, not to mention inputs and responses after birth.

In that sense, the ability to clone genetically equivalent human beings brings into sharp focus a fundamental theological tenet: that human beings are not reducible to their physical beings. Clearly, the same "body" does not equal the same person.

But human cloning, per se, is "intrinsically morally flawed," according to Albert Moraczewski, a scientist and a theologian with the National Conference of Catholic Bishops. Human procreation, he said, ought to be the result of the "sex act between two committed partners," not a "technology that eliminates the need for the male."

Along similar lines, Protestant theologian Gilbert Meilaender, of Valparaiso (Ind.) University, declared that "genesis takes a man and woman" and distinguished between "begetting" and "making" a child. Begetting, he said, frees the man and woman from self-absorption and confers genetic independence from the parents upon the child. He cautioned against using the pursuit of health as a knee-jerk justification. "Progress," he said, "is always an optional goal."

He suspected that cloning is different not only in degree but in kind from other reproductive technologies and that cloned individuals might be designated "another rational species," a concept that inspired a blanket rejection from another Protestant thinker. In the event that children ever result from cloning, admonished Nancy Duff, of the Princeton Theological Seminary, "it is imperative to assume they are the same human beings as the rest of us." She said she did not "rule out completely the morality of cloning



Fran Pollner

Bioethics Chair Harold Shapero

research," which she considered acceptable if the potential benefits are compelling. In her own inventory of potential uses, genetic disease research would be on the positive side of the ledger; cloning to replicate a dying child or to replicate soldiers and athletes would not.

"Technology is morally neutral in Jewish tradition," Elliot Dorff, of the University of Judaism, Los Angeles, told the panel. Rather, the uses to which it is put determines its moral status. "Our tradi-

tion is not passive regarding the medical cards we are dealt. Illness and healing are ultimately in God's hands, but we are given permission—and the obligation—to heal, as individuals and as a community," he said. Cloning research could be a tool for healing—or for exploitation. "Can we get a hair from Michael Jordan's head, with or without his consent, and clone ten Michael Jordans—and be their agent?" he asked.

Dorff recalled an old cartoon depicting Satan rising from the steam of the then newly invented steam engine. In the minds of some, he reflected, "to go more than 20 miles per hour was to be in league with the devil." As with the steam wafting into the air, the cloning "genie is out of the bottle," he said. In practical terms, it is legislation and professional standards that will bend the technology to morally acceptable uses.

Like Dorff, Moshe Tendler, a rabbi, a professor of Talmudic law, and a teaching biologist at Yeshiva University, urged the panel not to recommend a ban on cloning research. "We have a duty to be constructive in this world," he asserted, noting that, historically, governments the world over have at times promulgated policies undermining this duty—either by issuing blanket bans in areas of biomedical research that could benefit humanity or, conversely, by promoting

physician participation in research activities that actually constitute atrocities against humanity.

Aziz Sachedina, of the University of Virginia, prefaced his remarks on the Islamic view of cloning with a "thank you" to the panel. "You have the gratitude of the entire Muslim tradition in North America. This marks the first time a representative of Islam appears in such a forum," he said. He noted that potential abuses of other technologies, such as in vitro fertilization, have been addressed by Muslim jurists, but possible human cloning, per se, has not. He presented the general backdrop against which such issues are viewed.

Although the Koran is silent on when humans first possess a soul, Suni Muslims (50% of U.S. Muslims and 80% of Muslims worldwide) place the event at 120 days gestation, before which burial is not required in the event of in utero death (and without bones, a conceptus may not be buried and has no funeral rites). After 120 days, the fetus is considered a biological and moral being who must be buried in the event of death. Shiite Muslims, however, place ensoulment at 21 days.

The report of the derivation of multiple viable human embryos through the extraction of cells from a blastocyst at George Washington University in 1993 raised fundamental moral/spiritual questions for Muslims about interpersonal spousal relationships. But cloning calls forth another category of dilemma. A child cloned into being "could not lead a normal life," he said. "In Islamic law," he explained, "the child belongs to the father. The father's identity must be clear. Lineage must be clear. Without proper lineage, there is no inheritance." A lesbian woman pregnant through artificial insemination by an anonymous donor or by implantation of an anonymously donated fertilized egg, for example, would be viewed as a serious problem in Islam, Sachedina indicated. "Female infertility, however, would not be a problem, since multiple wives and temporary marriage for the purpose of childbearing are legal. But a child who exists outside a legitimate spousal relationship would have no guarantee of natural inheritance."

Law

To John Robertson, a professor at the University of Texas Law School, however, the legal implications of human cloning are relatively minor. "It's not qualitatively different from current genetic selection practices. It's not that radical a step away from techniques now used to ensure healthy offspring, like prenatal screens."

In fact, he maintained, cloning, which "takes the genome as it is," is much less ominous than the ability to manipulate the genome.

In the in vitro fertilization setting, he said, cloning embryos by nuclear transfer or blastomere separation "falls within the fundamental freedom of married couples to have biological offspring, with the same legal protection as other noncoital means. If random, leftover embryo donation for the couple who lack gametes is allowed, a couple should also be able to decide to replicate DNA they know (from a consenting adult not involved in the child rearing), and this should have the same legal protections. It's cloning of self for rearing by self that poses more problems."

Since the intent of the procedure is to create life, it would necessarily be deemed a benefit to the child and, therefore, allowable experimentation, he reasoned. The bottom line, Robertson said, is that research must be permitted, as should cloning for infertility—if it proves safe and effective.

The scientific bottom line, however, is that clinical applications of cloning are at the other end of a tunnel lined with question marks. The unknowns

were addressed by Princeton University developmental biologist Shirley Tilghman, whose overall assessment was that the cloning experiment in which a newborn lamb was generated from an adult sheep mammary cell would contribute only "modestly" to answers she and other scientists have long been seeking regarding the process of gene reactivation and the selection of pathways that determine cell type.

Science

Tilghman recapped some of the telling statistics leading to the birth of Dolly: of 277 egg-cell fusions, 247 survived six days in oviduct culture, 29 developed appropriately enough to be implanted into foster mothers, and one of these saw the light of live birth. The report of the work, she said, provided no insight into why only 29 of 247 developed normally.

Embryogenesis, she said, entails the reactivation of silent genes, followed by a selective re-silencing that constitutes cell differentiation. This process takes 18 hours in mice but about three days in sheep and humans. "At least in one cell type—the mammary cell—it is possible to reverse the silencing," Tilghman said of the lessons learned from the experiment. "[Researcher Ian Wilmut] took a cell that was 90% silenced and fused it with an unfertilized egg from which the DNA had been removed. His source of cells—the mammary gland—had been allowed to go into a quiescent state and had not divided for three to four days; he used *resting* nuclei for this *one* successful experiment."

A Double-Edged Technology

Speaking at a Senate subcommittee hearing on cloning technology the day before the National Bioethics Advisory Commission met, NIH Director Harold Varmus characterized the "idea of generating human clones of mature individuals" as the stuff of "interesting movies, but poor science and poor ethics." He registered his agreement with the conclusion reached by an NIH advisory panel in 1994 that there is "no justification for federal funding of research involving nuclei transplantation for [the purpose of] cloning an existing human being or making carbon copies of an existing embryo."

However, he said, the technology could be put to beneficial uses, including developing animal models of disease more reflective of humans; developing ways to turn on, turn off, and redirect human genes; and generating cell therapies—such as marrow cells for cancer patients, skin cells for burn patients, and nerve cells for patients with brain diseases.

MAMMALIAN CLONING: DECONSTRUCTING DEVELOPMENT

Tilghman listed several "things that could go wrong" during the course of this and similar experiments.

✓ Physical disruption of the egg may occur during the large-needle enucleation.

✓ Gene reactivation may be inefficient.

✓ Mammary gene products may exert a negative impact on early development. "Perhaps these products are toxic to the egg. This," Tilghman said, "is a critical issue: success may be tissue-specific. Which cells would be poor donors?"

✓ Transplantation may be inefficient.

The first and last potential problems are inherent to all embryo manipulations, she noted, but the two in between "are unique to this experiment, and we know very little about these."

"As a scientist," she continued, "I worry about silent somatic mutations in the donor nucleus—which has existed in the sheep for six years, in this case. There could be a somatic mutation innocuous to the mammary gland that is now permanent in *every* cell of the new organism," she observed.

"We know almost nothing about inefficient reactivation of genes required *late* in development. That would be most troublesome, and there is precedent for it: 20 years ago in England in experiments in which frogs could not develop past the tadpole stage," she cautioned.

The 18-member panel, chaired by Harold Shapiro, president of Princeton University, anticipated meeting several more times in person and countless times over the wires before delivering its report to the President at the designated time at May's end. As this issue of *The NIH Catalyst* went to press, it was virtually certain the panel would recommend continuation of the moratorium on human cloning on safety grounds alone—and would attempt to construct a framework for addressing the larger social policy issues should scientific uncertainties be resolved in the future. ■

Ayes and Nays

Of 19 national scientific societies responding to a survey by the RAND Critical Technologies Institute, 14 felt adult donation of DNA for developmental research should be allowed; the same number felt adult donation of DNA to clone a human should be prohibited.

An industrial-strength scientific effort is now under way to understand the molecular events that make individuals and their cellular components different from each other. The mapping of individual genes and their mutations and activity states underpins the great advances of molecular medicine. Individual cells differ on the basis of the constellation of active and inactive genes they express, which is in turn determined by developmental history. Remarkably, under certain circumstances, this developmental history is reversible, and the clearest and most compelling demonstration of this reversibility is the recent cloning of the lamb named "Dolly" by Ian Wilmut and colleagues (1).

The advent of mammalian cloning extends key observations John Gurdon made more than 30 years ago regarding the frog *Xenopus laevis* (2). Gurdon used a strategy for nuclear transplantation developed earlier by Robert Briggs and Thomas King (3) to demonstrate unequivocally that nuclei from tadpole intestinal epithelial cells could direct the development of fertile adult frogs. Over the subsequent two decades, these experiments were repeated in ever-increasing detail by a dedicated group of investigators until the pluripotency of adult cell nuclei was definitively established in 1986 (4, 5).

This work laid a firm scientific foundation for mammalian cloning. Nevertheless, despite much effort, no single

transplanted adult frog nucleus has ever yielded a cell that grew into another adult frog. The work by Wilmut and colleagues shattered a barrier and revealed that cells of mature higher animals are not just pluripotent, but totipotent. Their use of an adult cell derived from sheep mammary epithelium as a donor in the nuclear transplantation experiment that gave rise to Dolly indicates that adult nuclei can also become totipotent.

In the wake of this revelation, developmental biologists are asking: What does the re-acquisition of totipotency imply for the molecular mechanisms that establish cell fate? Early embryogenesis requires the totipotent egg nucleus to cleave during repeated cell division, generating daughter cells that progressively acquire all of the separate cellular identities that exist in the tissues of an organism. This requires the precisely staged association of transcription factors and specialized chromosomal proteins with the regulatory elements of genes. As development proceeds, an increasing number of cells exists in the embryo, and the regulatory nucleoprotein complexes that establish cell lineages or identities become more elaborate and resistant to physical and biochemical perturbation. This functional specialization of chromatin and chromosomes also becomes more difficult to reverse when an embryonic cell nucleus is transplanted into an enucleated egg. As a general rule, the more differenti-



Fran Pollner

National Bioethics Advisory Commission members, left to right: Rbetaugh Dumas, vice provost for health affairs, University of Michigan; Lawrence Milke, director, Honolulu State Department of Health; R. Alta Charo, professor of law, University of Wisconsin; Arturo Britto, assistant professor of clinical pediatrics, University of Miami; Carol Greider, senior staff scientist, Cold Spring Harbor Laboratory; Eric Cassell, professor of public health, Cornell Medical College. [Other members are Chairman Harold Shapiro, Patricia Backlar, Alexander Capron, James Childress, David Cox, Ezekiel Emanuel, Laurie Flynn, Steven Holtzman, Bette Kramer, Bernard Lo, Thomas Murray, and Diane Scott-Jones.

by Alan Wolffe, NICHD

ated the cell from which a donor nucleus is taken, the more unlikely it is that correct development will proceed.

Nevertheless, persistent attempts to break the rule have led to dividends in amphibia, where nuclei taken from adult keratinocytes or reticulocytes have, in a few notable instances, been shown to support the development of all the cell types found in a tadpole (4, 5). These findings demonstrate that the regulatory nucleoprotein complexes that control the specific patterns of gene activity in highly differentiated keratinocytes or reticulocytes can be disassembled.

The first experiments that examined specific gene activity within somatic nuclei that had been transplanted into an egg revealed that nucleoli disappeared and active ribosomal RNA genes were inactivated (6). The disappearance of the nucleoli—which represent the compartmentalization of rRNA synthesis to a specific chromosomal structure—and the inhibition of rRNA transcription clearly demonstrated that egg cytoplasm has the capacity to influence nuclear function. As development of the embryo containing the transplanted nucleus proceeds, the ribosomal genes are reactivated and nucleoli reappear.

Researchers were better able to understand the influence of cytoplasm on nuclear function after Merriam and Barry demonstrated that there is considerable movement of proteins from the egg cytoplasm to the somatic nucleus following transplantation (7, 8). This movement is concomitant with nuclear swelling and with a significant reduction in the amount of transcriptionally inactive heterochromatin within the nucleus. Subsequent work examined the association of specific components of the transcriptional machinery with individual genes. Both the regulatory nucleoprotein complexes that activated transcription and those that repressed transcription were found to be unstable in an egg environment (9, 10). This was in marked contrast to their stability in the nuclei of differentiated cells (11). Molecular chaperones that are stored in the egg have been shown to have a causal role in directing the loss of chromosomal proteins specific to somatic nuclei and thus the remodeling of somatic nuclei following exposure to egg cytoplasm

(12). However, this is only part of the process. The transplanted somatic nucleus progressively acquires the proteins and modifications normally associated with the embryonic chromosome. Many of these specialized modifications are also characteristic of the transformed cell nuclei found in many tumors.

The orchestrated exchange of somatic nuclear proteins for egg cytoplasmic components takes time, and it is the failure to effect the restructuring of chromatin, chromosomes, and nuclei before cell division that most probably leads to chromosomal damage and the developmental abnormalities apparent in many nuclear-transplant embryos. In this regard, the mammalian cloning experiments provide additional insight (1). These investigators made use of adult somatic cells that they synchronized in G_0 —a quiescent state within the cell cycle. This state of quiescence is normally achieved by starving cells for serum, causing cells in G_1 to leave the cell cycle. This exit can be reversed by adding back serum in culture or, evidently, by transplanting a G_0 cell nucleus into the egg. This might facilitate the remodeling of chromatin by attuning the nuclear and cytoplasmic cell cycles just before entry into S phase. DNA replication itself will further facilitate the disruption of regulatory nucleoprotein complexes (13). Therefore, using the strategy of Wilmut and colleagues (1), an embryonic chromosomal structure might be established in a transplanted nucleus before cell division occurs, thereby preventing chromosomal damage. If this hypothesis is true, then simple manipulations of somatic cell nuclei that would facilitate nuclear remodeling, such as pre-incubation with the molecular chaperone nucleoplamin, would greatly facilitate the efficiency of animal cloning.

The original interpretation of nuclear transplantation experiments in amphibia suggested that the genetic material is not irreversibly altered as development proceeds. This concept had a major impact on developmental science at the time.

However, we now know that this is not universally true, since cell-type-specific rearrangement of immunoglobulin genes and generalized loss of telomeric sequences occur in conjunction with differentiation and aging. Moreover, specific patterns of cytosine methylation and demethylation correlate with gene activity and repression in particular cells. The mammary epithelial cell nucleus used by Wilmut did not undergo VDJ recombination to define the antibody repertoire; however, loss of telomeric sequences presumably has occurred. Hence, the aging of mammalian clones may differ from that in animals derived from the fusion of gametes. As for DNA methylation, it must either be reversible or unimportant for the establishment of differential states of gene activity—the stuff for future studies.

A final technical point is that much of early embryonic development is driven through the activity of proteins and messenger RNAs stored in the egg. Masked maternal mRNA is translationally silent until fertilization (or nuclear transplantation). Recruitment to the translational machinery then initiates the determinative events that restrict the fates of embryonic cells. The same molecular chaperones that facilitate the remodeling of somatic nuclei following transplantation also facilitate the unmasking of maternal mRNA (14, 15). Importantly, the maternal determinants will differ from egg to egg. Thus, a true clone from a nuclear-transplant embryo is not achievable in the sense that monozygotic identical twins are clonal.

Recognition of the success of mammalian cloning will surely have a major impact on many aspects of basic developmental biology. The experiments are simple and powerful. They answer a crucial biological question regarding development by clearly demonstrating the reversibility of determinative mechanisms. Differential gene activation is what drives development, not the irreversible alteration of the genetic material itself. The dramatic affirmation of

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Just Ask!

this conclusion should stimulate experiments that seek to define the developmental ground state of totipotency. Molecular understanding of how specific patterns of gene activity can be reversed in the egg surely will have general relevance for human disease. ■

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Dear Just Ask:

How does one go about forming an interest group? We would like to start a Clinical Pharmacology Interest Group. In general, the individuals we are aware of who want to participate are oncology-focused, but it could be open to all clinical pharmacologists. Thanks.

—William D. Figg, NCI



Lorna Heartley

Celia Hooper

Dear WDF:

Thanks for asking a question that pops up several times a year. Here are the steps to take to establish a new interest group.

1. Talk to your colleagues interested in the subject area to assess enthusiasm for starting a new group. Be sure to identify people from other institutes (and possibly other area institutions, such as USUHS, FDA, EPA, Georgetown, Howard) and talk to them, too. Get e-mail and surface mail addresses and phone numbers for people interested in forming a group.

2. Check the list of existing interest groups to make sure there isn't one already in your area. Talk to the heads of related groups to see if a subset of their members have any interest in collaborating with you on the formation of the new group.

3. If there seems to be sufficient interest and energy to make a stab at it, call an organizational meeting. Notify the csarina of the interest groups (that's me) two or three weeks in advance, and I will publicize the meeting on the

DDIR's Bulletin Board. You should also contact the *Yellow Sheet* and maybe the *NIH Record* to get the word out.

4. If energy and participation at the organizational meeting are high, set a course for your group. Decide who will be the head or contact point. De-

cide when and where you will meet and how you will communicate with group members. Consider establishing a listserv list. Make arrangements for teleconferencing if there are folks at NIH facilities in North Carolina, Frederick, or Baltimore who are interested in participating. Decide what your group will do at its meetings (journal club? intramural speakers? outside speakers? networking? postdoc posters?) and whether or not you will be affiliated with one of the major faculties (Genetics, Neurobiology, Clinical Research, Molecular Biology, Structural Biology, Cell Biology, or Immunology). Send all *this* information to the csarina, and I will publish it on the DDIR's BB and in *The NIH Catalyst*. I'll also add the name of your group's contact person to my listserv of interest group heads and send you my boilerplate letter on interest groups. You may want to discuss creating a web page for your group, proposing a speaker for the Wednesday Afternoon Lectures, or applying for support for an outside speaker at an interest group symposium.

Good luck with your group, and keep in touch.

—C.H.

Can We Talk?

Having trouble being understood by members of the opposite sex?

The Office of Human Resource Management and the Division of Workforce Development are offering a course designed to improve the communication skills of women and men—"Speaking Across the Gender Gap." To register for the September 11 class, call Joyce LaPlante at 402-3380 by August 14.

Interest Group Gazette

The air is filled with the scent of spring and the anticipation of summer—and several new interest groups have sprouted since our Nov.-Dec. issue.

First, the Chemistry Interest Group is up and running with a home page at <http://chem.info.nih.gov/chemig>—which provides meeting time and place. Contacts are Ken Kirk, NIDDK (496-2619; e-mail: <kennethk@bdg8.niddk.nih.gov>); Ken Jacobson, NIDDK (496-9024; e-mail: <kajacobs@helix.nih.gov>); and John Schwab, NIGMS (594-5560; e-mail: <schwabj@gml.nigms.nih.gov>).

Chromatin and Chromosomes Interest Group

Meeting time: 11:00 a.m.
Meeting place: Bldg. 32 Conf. Rm.
Contact: David Clark, NIDDK, 496-6966
fax: 496-5239
e-mail: <djclark@helix.nih.gov>

The group meets every other Thursday, with two speakers, usually from different groups on campus, each time. Its scope now includes nuclear structure and transport. May meetings featured Misha Grigoriev, speaking on "A Histone Octamer Acts as a Reflective Barrier for Spontaneous DNA Branch Migration," and Vasily Studitsky, speaking on "Transcription Through the Nucleosome: Eukaryotic Polymerases," followed by Adam Bell, speaking on "Identification of the Minimal Sequences of the Chicken β -globin Insulator," and Toshi Tsukiyama: "Characterization of Yeast NURF-like Factors"

Head and Neck Biology Interest Group

Meeting time: 3:30 p.m.
Meeting place: Bldg. 10, Rm. 9C401
Contact: Frank Ondrey, 435-2072
fax: 402-1140
e-mail: <fondrey@pop.nidcd.nih.gov>

This group meets on the second Monday of every other month and will have presentations by members and local guests aimed at both clinical research and basic science. On April's agenda were talks on gene therapy to increase salivary gland saliva production and on the use of vegetable oil preparations as atomized topical agents for the same purpose.

Viral Hepatitis Interest Group

The group held its first monthly meeting April 21 and was scheduled to meet May 19, June 16, and July 14 (the third Monday of the month, generally, except for July). The group anticipates hearing informal presentations from member labs on current research.
Meeting time: 3:30 p.m.
Meeting place: Bldg. 10, Rm. 1C726 (Transfusion Medicine Conference Room)
Contact: T. Jake Liang, 496-1721
fax: 402-0491
e-mail: <jliang@nih.gov>

Interinstitute Bioethics Interest Group

An organizational meeting is scheduled for Tuesday, June 10, 3:00 - 5:00 p.m. in Building 45 (Natcher), G 1 and 2. Contact Miriam Keltz, NIA, at 496-9322 for more information (e-mail at <mk46u@nih.gov>).

Biotechnology Interest Group

The newly formed BTIG held an organizational meeting in late April. Its purpose is to disseminate information to aid scientists in their interactions with the biotechnology industry. Areas to be addressed include but are not limited to technology transfer, biotechnology start-ups, financing/funding, industry collaborations, the relationships among biotechnology and academics, career options, patents and licensing, and emerging technologies. All interested parties are encouraged to participate. Contact Dan Sullivan at <dsul@helix.nih.gov>.

Breast Biology Interest Group (BBIG)

Due to the May holiday, the June breast conference, and vacation schedules in July and August, the next BBIG meeting will be in September.

What's in a Name?

It was once called Youth and Family Development, but now it's the **Human Development Across the Life-Span Group**. Members' interests include such topics as behavioral problems in children, fatherhood, child sexual abuse, and teenage pregnancy. Contact Kim Roberts at <roberts@ssed.nichd.nih.gov> or Kim Kendziora, e-mail coordinator, at <kimk@helix.nih.gov>.

—Bev Stuart

Electronic Etceteras and Essentials...

Thanks to *The Catalyst's* visiting postdoc, David Ehrenstein (on a detail from NIDCD), Wednesday Afternoon Lectures (WALs) now has a home on the web. The site includes links to some speakers' lab home pages so audience members can preview the research of this spring's speakers. Coming soon to the page: an exciting lineup of speakers for the fall WALs. The URL for the page is: <<http://www1.od.nih.gov/wals/index.html>>

Recycle that Research Equipment! Staff at NCRR have now made a new, improved, web version of Mike Lenardo's listing of available equipment, reagents, and other sundry items that are either sought by scientists or being made available by scientists. We'll have more on this in our next issue, but you might want to beta-test the page now by pointing your browser to <<http://www.ncrr.nih.gov/sharedbc/sharetop.htm>>

Looking for back issues of *The NIH Catalyst*? The electronic version of this newsletter is quite a bit behind the print version, but old issues can be obtained at the Catalyst web site: <<http://www.nih.gov/news/irnews/catalyst/>>. If you are having trouble getting your print version of this newsletter, send an e-mail message to Beverly Stuart at <bs48k@nih.gov> requesting an address fix.

Guidelines for the Conduct of Research, NIH's slim and popular brochure on the *dos* and *don'ts* of appropriate behavior and collegiality, has been revised and is now being reprinted. Hard copies will be available from Audrey Boyle (Bldg. 1, room 114) by June. For now, turn to the recently posted web version of the revised document: <<http://www.nih.gov/news/irnews/guidelines.htm>>.

FOR BIOLOGY BUFFS

Interested in the Biologists Forum? Call Klara Post, NICHD, at 496-5538.

RECENTLY TENURED

Alisa Goldstein received her Ph.D. in genetic epidemiology from the University of California at Los Angeles in 1988 and came to NIH that summer as an IRTA fellow in the Environmental Epidemiology Branch of the NCI Division of Cancer Epidemiology and Genetics. She is now a senior investigator in the Genetic Epidemiology Branch and section chief of the newly formed Population and Statistical Genetics Section.

My interests are the genetic and environmental determinants of cancer. My research at NCI has focused on family and genetic epidemiologic studies of several cancers, including cutaneous malignant melanoma/dysplastic nevi (CMM/DN) and the nevoid basal cell carcinoma syndrome (NBCCS), and on the development and assessment of genetic epidemiologic methods. My studies emphasize the integration of epidemiologic, clinical, and molecular approaches.

The Genetic Epidemiology Branch has a long-standing interest in the study of familial melanoma. I have taken the lead role in the genetic epidemiologic analyses of familial melanoma since 1990. My laboratory colleagues and I have identified and evaluated two melanoma-susceptibility genes (*p16/CDKN2A* and *CDK4*). *CDKN2A* appears to account for one-third of familial melanoma kindreds, whereas *CDK4* mutations have been detected in only two kindreds to date. Although the tumor suppressor *p16* and proto-oncogene *CDK4* are hypothesized to have different functions, we have shown that there are no differences in the ages at CMM diagnosis, number of CMM tumors, or clinical course of disease between kindreds with *p16* mutations and those with *CDK4* mutations.

Recently, we incorporated genetic data on *p16* into clinical and epidemiologic analyses of the CMM kindreds previously screened for *CDKN2A* mutations, comparing kindreds with and without mutations that impair the function of *p16*. We showed that the risk of pancreatic cancer was significantly increased only in kindreds with *p16* mutations. Genetic factors, such as the kind of mutations found in *p16*, may explain the inconsistent occurrence of other cancers in melanoma-prone kindreds. To follow up on these findings, we are currently examining the relationship between factors such as sun exposure, clinical features, and *p16* and/or *CDK4* mutations. My current and future work involves searching for additional melanoma genes, assessing risks of different tumors associated with the various genes, evaluating environmental and clinical risk factors, and examining gene-gene and gene-environment interactions in this complex, heterogeneous, and potentially fatal form of skin cancer that

will claim an estimated 7,300 lives this year in the United States.

Another major focus of my research has been on NBCCS, a multisystem disorder with variable expression. My colleagues and I helped localize the NBCCS gene to a small region on chromosome 9q and, last year, identified a candidate gene, *PTCH*, the human homologue of the drosophila patched gene. We previously examined the relationship between sun exposure and the development of basal cell carcinomas (BCCs) in patients with NBCCS; although sun exposure did not appear necessary for the development of BCCs, it exacerbated BCC development. Also, clinical evaluation of African-American families with NBCCS (in whom the development of BCCs was rare) provided cor-

roborating evidence that sun exposure and skin pigmentation contribute to the expression of BCCs in NBCCS gene carriers. My future work will include examining genotype-phenotype correlations, assessing the interaction of sun exposure, X-irradiation, and skin type, and searching for modifying genes and environmental risk factors. We have recently started a study of patients with medulloblastoma in collaboration with other researchers from NIH and the Children's National Medical Center. We are clinically evaluating patients with medulloblastoma, assessing risks of cancer in family members, examining tumors for mutations in the *PTCH*, *APC*, (adenomatous polyposis coli), or other candidate genes and evaluating the relationship between molecular genetic alterations, tumor characteristics, response to treatment, and survival in this cohort.

I am also involved in two new studies. First, colleagues from NCI, NIDR, and Taiwan have started a genetic epidemiologic study of nasopharyngeal carcinoma (NPC) in Taiwan. The goals of the study are to map gene(s) that predispose individuals to NPC, to examine gene-environment interactions, and to evaluate risk-factor differences between multiple-case and single-case families. Second, collaborating researchers from NCI, NHGRI, and Shanxi Province, China, have recently started a genetic epidemiologic study to examine the role and interaction of genetic and environmental factors in the etiology and prevention of cancers of the esophagus and stomach.

James Hurley received his Ph.D. in biophysics from the University of California in San Francisco in 1990 and was a research associate at the University of Oregon Institute of

Molecular Biology in Eugene before joining the NIDDK Laboratory of Molecular biology in 1992, where he is now a senior investigator.

My group is interested in the fundamental mechanisms cells use to transmit signals across membranes. Our approach is to use X-ray crystallography and other structural methods to understand in atomic detail how signaling proteins work as miniature machines. We choose projects we hope will provide information relevant to large families of homologous proteins, and we always aim for structural data in the presence of activators or substrates in order to learn as much as possible about mechanism. In particular, we are focusing on the regulated production and mode of action of the second messengers diacylglycerol, calcium, and cyclic AMP. My work concerns three of the key protein players in these second-messenger pathways: phospholipase C, protein kinase C, and adenylyl cyclase.

Protein kinase Cs are a family of about a dozen calcium and lipid-activated enzymes with a ubiquitous role in signaling. In what was a technically innovative strategy—entirely determining structure by using phase information from zinc ions—we determined the first crystal structure of a protein kinase C C1 domain bound to its potent activator, the tumor promoter phorbol ester. The structure explains how phorbol ester activates protein kinase C by stabilizing the membrane-inserted form of the C1 domain.

Phorbol ester caps a polar groove on the otherwise highly hydrophobic tip of the C1 domain, creating a nearly ideal membrane interaction surface. The structure is a template for understanding more than 50 other C1 domains from protein kinase Cs and many other signaling proteins.

Phospholipase Cs are a family of enzymes that play a key role in signaling downstream of many receptors by generating the second messengers IP3 and diacylglycerol. We determined a structure of phospholipase C-delta 1 that showed how the catalytic and C2 domains work together to dock phospholipase C onto membranes. C2 domains are of great interest because they occur in over 60 proteins besides phospholipase Cs. By analyzing the structure bound to a calcium analogue, we directly characterized a calcium-induced conformational change in a C2 domain for the first time.

Taken together, our findings on protein kinase C and phospholipase C show how two ubiquitous lipid-activator binding domains, C1 and C2, interact with phospholipid bilayers in strikingly different ways. We propose that C1 inserts deeply into the bilayer in pursuit of its hydrophobic ligand and probably serves as a high-affinity mem-



David Ehrenstein

Alisa Goldstein



David Ehrenstein

James Hurley

brane anchor. In contrast, we think that C2 binds polar anionic headgroups at the bilayer surface. The rigidity of C2's interactions with other protein domains suggests that C2 could have an important role in governing the stereochemistry of multidomain protein-membrane complexes.

Adenylyl cyclases are the classic effector of receptor-mediated signal transduction, producing cyclic AMP in response to hormone stimulation. Mammalian adenylyl cyclases are complex integral membrane proteins, but their catalytic domains are soluble. We solved the first structure of a soluble catalytic domain from adenylyl cyclase and showed that it is a dimer that looks like a Christmas wreath. The structure was solved in the presence of a potent small molecule activator, forskolin, which binds at the dimer interface and helps "glue" the wreath together. The active site is in the center of the wreath, while regulatory sites that bind proteins are on the outside of the wreath. This permits many different regulatory mechanisms to operate at the same time and allows "mix-and-match" regulation of different adenylyl cyclase isoforms.

Using site-directed mutagenesis and biophysical techniques, my lab is currently exploring the role of the C2 domain in phospholipase C activation; we're using computer modeling to understand the array of different adenylyl and guanylyl cyclases based on the structure we've solved. We are also working on structures of several other proteins in phosphoinositide and cyclic nucleotide signaling—and I'm always interested to hear from NIH colleagues who work on signaling proteins that present new structural questions.

Klaus Strebel received his Ph.D. in microbiology from the University of Heidelberg, Germany, in 1985. He joined the NIAID Laboratory of Molecular Microbiology in 1986 and is currently a microbiologist in that lab.

From a molecular virologist's point of view, viruses represent comparatively simple model systems in which to study fundamental biological and biochemical mechanisms. Despite the relative simplicity of their genomes, virus replication is a complex process that depends heavily on the activity of host cellular factors. Using HIV as a model system, my group is interested in studying the function of viral proteins and their interaction with host cell machinery. My work to date has focused on two HIV accessory proteins, Vif and Vpu, which function in early and late stages of virus replication. The experiments in my lab involve a wide variety of biochemical, virological, and im-



Klaus Strebel

munocytochemical techniques, and we hope our studies will not only contribute to the general understanding of retrovirus function, but also provide a basis for the assessment of viral proteins as potential antiviral targets.

When I joined the LMM in 1986, my initial work involved the functional characterization of the HIV-1 Vif protein. I was one of the first to show that Vif has a crucial function in regulating viral infectivity. However, despite the dramatic impact of Vif on virus replication in human lymphocytes and macrophages, the precise biochemical function of Vif is still unclear. One of our main efforts is aimed at the identification of viral or cellular targets for Vif. We recently demonstrated the stable association of Vif with the core of HIV particles, a finding that suggests a role for Vif as a virion component. In addition, we observed a striking association of Vif with intermediate filaments, in particular vimentin, in virus-producing cells. The association of Vif with vimentin results in a reversible, microtubule-dependent perinuclear aggregation of intermediate filament networks. We are currently investigating the possible role of vimentin association of Vif with its role in regulating viral infectivity. In particular, we are investigating the possibility that the interaction of core-associated Vif with the intermediate filament network assists in nuclear targeting of preintegration complexes following virus entry into a target cell.

In a separate line of research, we have recently identified a phenotypically dominant (transdominant) Vif mutant that interferes with HIV replication in permissive cells. Permissive cells normally do not require Vif function, most likely because of the presence of a cellular Vif-like factor. We postulate that transdominant Vif is capable of interfering not only with the function of wild-type Vif but, in addition, with the activity of a putative cellular Vif-like factor in permissive cells as well.

Interestingly, transdominant Vif protein has a reduced affinity for vimentin but is incorporated into virions at increased levels. We are currently investigating the molecular basis of the transdominant effect of the mutant Vif protein and its potential as an antiviral compound.

In 1987, I identified a novel protein, Vpu, encoded exclusively by HIV-1. Since then, we have been characterizing this protein to understand its function. We now know that Vpu is an integral membrane protein that regulates the release of virus from the cell membrane and, independently, causes degradation of the HIV receptor, CD4. While HIV-2 lacks a Vpu gene, we recently

found that this virus nonetheless expresses a similar Vpu-like activity, encoded by its Env glycoprotein, to regulate virus release. The ability to induce CD4 degradation, however, is unique to Vpu. CD4 degradation is a multistep process that occurs in the endoplasmic reticulum (ER), is energy-dependent, and involves the physical interaction between Vpu and CD4. Amino acids critical for this function of Vpu are located in its cytoplasmic domain. In contrast, regulation of virus release by Vpu requires the Vpu transmembrane domain, is regulated from a post-ER compartment, and correlates with an ion-channel activity of Vpu. No such information is currently available for HIV-2 Env; however, because Vpu and HIV-2 Env can functionally complement each other, it is likely that regulation of virus release is based on similar mechanisms for both viruses.

Future efforts will focus on the detailed characterization of both the mechanisms of CD4 degradation and the regulation of virus release. From those studies, we expect to gain insights into general principles of protein degradation in the ER and the mechanisms involved in the late stages of virus production.

Robert Tycko received his Ph.D. in chemistry from the University of California at Berkeley in 1984. After postdoctoral research at the University of Pennsylvania, he became a member of the technical staff at AT&T Bell Laboratories in 1986. He joined the Laboratory of Chemical Physics of NIDDK as an investigator in 1994.



David Ehrenstein

Robert Tycko

I have worked in the area of solid-state nuclear magnetic resonance (NMR) spectroscopy since 1980. Before I moved to NIH in 1994, my research was primarily in physical chemistry and condensed-matter physics.

Among other things, my group at AT&T Bell Laboratories discovered and studied unusual molecular rotational motions in the molecular forms of carbon called "buckyballs" (*Science* magazine's Molecule of the Year in 1991), measured electronic properties of superconductors derived from buckyballs that are important to our understanding of the physical basis of superconductivity, and used a novel technique called "optically pumped NMR" to obtain the first experimental evidence for peculiar states of electrons, called "skyrmions," in thin films of semiconductors at very low temperatures. We also developed a method, based on complicated radio-frequency pulse sequences, for obtaining high-field NMR spectra of solid samples that look as if the spectra were taken in zero magnetic field. Such "zero-field" spectra exhibit much higher resolution than do ordinary

solid-state NMR spectra and permit the direct measurement of interatomic distances in disordered solids.

When I moved to NIH, I changed the focus of my research to problems in biophysics and structural biology. Biomolecular NMR spectroscopy is a huge and mature field, in part due to many important contributions from my colleagues in the Laboratory of Chemical Physics. However, most activity in this field is liquid-state NMR, meaning that it is restricted to biopolymers in isotropic solutions. Biomolecular solid-state NMR is currently a small field at a relatively early stage of development, with less than 20 active groups worldwide. Current solid-state NMR techniques yield local structural information, such as interatomic distances or bond angles at specific isotopically labeled sites in a biopolymer, rather than complete, global-structure information. But solid-state NMR measurements can be carried out on biopolymers in noncrystalline solid or fibrous form, in frozen solutions, in membrane-bound form, and in disordered or unfolded states. These measurements can therefore provide atomic-level structural information about systems that cannot be characterized by existing liquid-state NMR or diffraction techniques.

In recent work, we developed a new approach to the determination of peptide and protein backbone conformations, or local secondary structure, that uses two-dimensional (2D) spectroscopy in combination with a solid-state NMR technique called "magic-angle spinning" (MAS). Our 2D MAS methods provide structural information in the form of the relative orientations of isotopically labeled chemical groups, for example ^{13}C -labeled carbonyl groups in a peptide backbone, rather than in the more traditional form of internuclear distances. In general, these

methods will be useful as a means of testing models for protein structures and as a means of characterizing the conformations of partially structured proteins and protein-folding intermediates. We are currently pursuing several specific applications. One is in a structural study of a peptide derived from the V3 loop of the HIV-1 envelope glycoprotein gp120, bound to an anti-gp120 antibody. Our 2D MAS measurements so far indicate that the conserved GPGR motif in the middle of the V3 loop does not adopt a type II β -turn conformation that had been predicted by other researchers.

A second application involves an investigation of the conformational distributions of a 17-residue helix-forming peptide, originally designed by the group of R.L. Baldwin at Stanford, with the goal of addressing a current controversy regarding the precise nature of the helical structures that such peptides adopt. Our solid-state NMR measurements on frozen solutions show that when the helix content is high (i.e., when helical conformations predominate over random-coil conformations), α -helical conformations are strongly preferred over 3_{10} helical conformations but that 3_{10} helical conformations may become more common when the helix content is reduced by the addition of a denaturant. These results contradict suggestions in the literature that were based on electron-spin resonance measurements by others, but they are generally in line with recent theoretical work.

Our recent work has begun to demonstrate and exploit the potential of solid-state NMR in biophysics and structural biology. I plan to continue our research in these areas, and I look forward to developing new collaborations and interactions with other intramural scientists in the months and years to come. ■

DNA-SEQUENCING CENTER SOON TO MATERIALIZE

Plans for a shared intramural DNA-sequencing center have gotten the go-ahead from the Board of Scientific Directors and the co-sponsorship thus far of 14 institutes with NHGRI as the lead institute. The center will use automated equipment and specially trained staff for large-scale sequencing. It's designed to meet acute needs for significant sequencing throughput.

NHGRI will shoulder the largest share of the costs of building the center. Participating institutes will contribute to the center's start-up over the next two years and will be charged on a fee-for-service basis for sequencing projects. Only investigators in participating ICDs will have access. NCI will be constructing an adjacent sequencing facility for its research.

In addition to sequencing services, the new center will provide informatics expertise for exploiting the data that come pouring out, including state-of-the-art computational tools for DNA-sequence analysis. The fee for service—for both sequencing and informatics—should fall below that for commercial sequencing alone. The new center will not be responsible for small or routine sequencing projects that can be handled by individual labs or contractors. A governing board of scientific directors or their designates will oversee the center, and a panel of working intramural scientists will prioritize project proposals. Eric Green (<egreen@nhgri.nih.gov>) will direct the facility, which should be operational by late summer or early fall. ■

FARE GAME BECKONS ANEW

Another FARE (Fellows Award for Research Excellence) competition—FARE '98—is just around the corner. Abstracts will be accepted from July 1 through August 15, and winners will be announced by October 15, 1997.

To recap the results of the highly competitive FARE '97: 639 abstracts were submitted and 120 received awards, for an overall success rate of 18.8%.

The competition is sponsored by the Office of Education, the Office of Research on Women's Health, and the scientific directors; the award includes a \$1,000 travel fellowship to attend a meeting within the United States during the fiscal year.

Authors assign abstracts to one of 38 different study sections, designating also a second and third choice. Typically, the vast majority of abstracts remain in first-choice study sections. Second- or third-choice study section selections are used only when the first choice lacks a sufficient number of abstracts and has to be closed. The number of awards assigned to each study section depends on the number of abstracts submitted. For example, if 14.3% of the abstracts are assigned to developmental biology, then 14.3% of the awards are drawn from this section.

Each study section's review committee typically consists of a Fellows Committee member, a postdoctoral fellow, and a tenure-track or tenured scientist recommended by the scientific directors. The abstracts are judged without identifiers (names and institutes). If an abstract is recognized by a reviewer as originating from a specific laboratory or there is a perceived conflict of interest, that individual is excused from conducting the review and asked to find a replacement. All abstracts are read by at least three reviewers, each providing an independent ranking. Scores are tabulated and awards assigned in a final meeting.

The pool of applicants and successful candidates for FARE '97 awards can be accessed from the NIH Fellow's web site at <ftp://helix.nih.gov/felcom/index.html> under the section on Felcom Programs. Also at that site, there will soon be more details on how to submit abstracts, as well as samples of some winners. For information on FARE '98, contact the FARE '98 Committee by e-mail at <fellows@box-f.nih.gov>. ■

RESEARCH FEST '97: A CURE FOR THE SUMMERTIME BLUES

POSTER APPLICATION DEADLINE

Friday, June 13, 1997

5:00 p.m.

Ever wonder what that lab down the hall is really working on? Maybe you overheard fragments of conversation or noticed some unintelligible doodles on the corridor blackboard, but never got to ask. Now's your chance: the 11th annual NIH Research Festival comes to life during the week of October 6 through 10, featuring more than 20 workshops, more than 300 posters, and several symposia, all showcasing intramural research. "The NIH Research Festival is an annual opportunity to find out what your neighbors are up to and to be impressed anew by the extraordinary range and quality of research done in the NIH intramural program," according to Michael Gottesman, NIH deputy director for intramural research. Up-to-date details are available on the web at <http://pubnet-mac.nih.gov/festival97/>.

Most of the scientific sessions will be on Monday and Tuesday in the Natcher Center, including two major symposia hosted by the Structural Biology and Immunology Interest Groups. The symposia are aimed at NIH scientists and clinicians from a broad range of interests, not simply those familiar with the fields. Monday's immunology symposium will discuss activation of the T-lymphocyte response, from basic cell biology to clinical applications, and Tuesday's symposium will address the structural biology of viral diseases, including antiviral drug design. On the evenings following these symposia, the Technical Sales Association will sponsor picnic dinners.

Wednesday's program includes a job fair for postdocs, organized by the Office of Education and co-sponsored by National Foundation for Biomedical Research, and a special symposium honoring 60 years of intramural NIH research in Bethesda, co-sponsored by the DeWitt Stetten, Jr., Museum of Medical Research. Several distinguished current and former NIH investigators, including Martin Rodbell, Elizabeth Neufeld, and Eugene Braunwald, will speak at the Wednesday event, along with some of NIH's top brass. On Thursday and Friday, the Festival will conclude with the Technical Sales Association's Exhibit, featuring two large tents filled with the scientific equivalent of the massive boat/auto/RV shows at the D.C. Convention Center.

Alan Spiegel, scientific director of NIDDK and chair of the festival's organizing committee, is proud of this year's program, which he characterizes as "broadly representative of intramural science, and capturing some of the excitement of doing research at NIH." For more information, contact Greg Roa: phone 496-1776, fax 402-0601, e-mail gr25v@nih.gov. Researchers may submit poster applications electronically at the Research Fest web site at

<http://pubnet-mac.nih.gov/festival97/>

OH, WHAT A LOVELY WEB WE'LL WEAVE, MAY 28

New web tools, intranets, and useful biomedical sites are among the many sessions being offered in this all-day, DCRT-sponsored program focusing on effective use of the World Wide Web by information gatherers as well as information providers. Web Information Day, Wednesday, May 28, kicks off at the Natcher Conference Center at 9 a.m. with a keynote address by Vinton Cerf, the father of the Internet, who co-developed the computer networking protocol, TCP/IP, for the Defense Department's Advanced Research Projects Agency. Now senior vice president for data architecture at MCI Communications Corporation, Cerf is coordinating efforts to develop a high-speed network to carry the enormous growth of Internet traffic.

Web Day topics will focus on search engines, web site and page design, internet access from home and travel, hot new technologies, demonstrations of valuable NIH web sites, the creation of web documents, and other topics—and the nascent NIH Intramural Scientists Database is expected to make its debut at Web Day. For further information about this event, which is free to all NIH staff, visit <http://wid.dcrf.nih.gov> or call 4-DCRT. ■

National Institutes of Help! I've fallen and I can't get up!

TOP SIGNS YOU MAY BE DISSATISFIED WITH SCIENCE

Becoming a full-time parent becomes an increasingly attractive career alternative



Every article in CELL, SCIENCE, and NATURE evokes a yawn

BIG DEAL. I could have done that



You become increasingly fascinated with web sites that pertain to UFOs, government conspiracies, and 70s sit-coms



You name all your mice, and have long conversations with them

So, Zippy, have you had any new thoughts about our last discussion?



Dent

You begin to think that life can have meaning even if you don't work 60 hrs a week



CALL FOR CATALYTIC REACTIONS

In this issue, we are asking for your reactions in four areas: cloning research ramifications, resource sharing, hot methods, and NIH efforts in the realm of clinical investigation.

Send your responses on these topics or your comments on other intramural research concerns to us via e-mail:

**<catalyst@nih.gov>;
fax:402-4303; or mail:
Building 1, Room 209.**

In Future Issues...

- Summertime Escapades
- Frederick's Fields
- The Return of Seminar Highlights

1) Give us your thoughts on the charged scientific and political climate surrounding cloning research. What regulations in this area would best serve humanity?

2) Are you satisfied with the extent and quality of shared resources and services for intramural scientists? What should be added, deleted or changed?

3) We're still in the market for those invaluable hot and cool methods. Got any?

4) Is clinical research now getting the attention it deserves? What recommendations in the Straus Report would have the greatest impact on improving clinical research? Did the report miss any key areas?

The NIH Catalyst is published bi-monthly for and by the intramural scientists at NIH. Address correspondence to Building 1, Room 209, NIH, Bethesda, MD 20892. Ph: (301) 402-1449; fax: (301) 402-4303; e-mail: <catalyst@nih.gov>

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