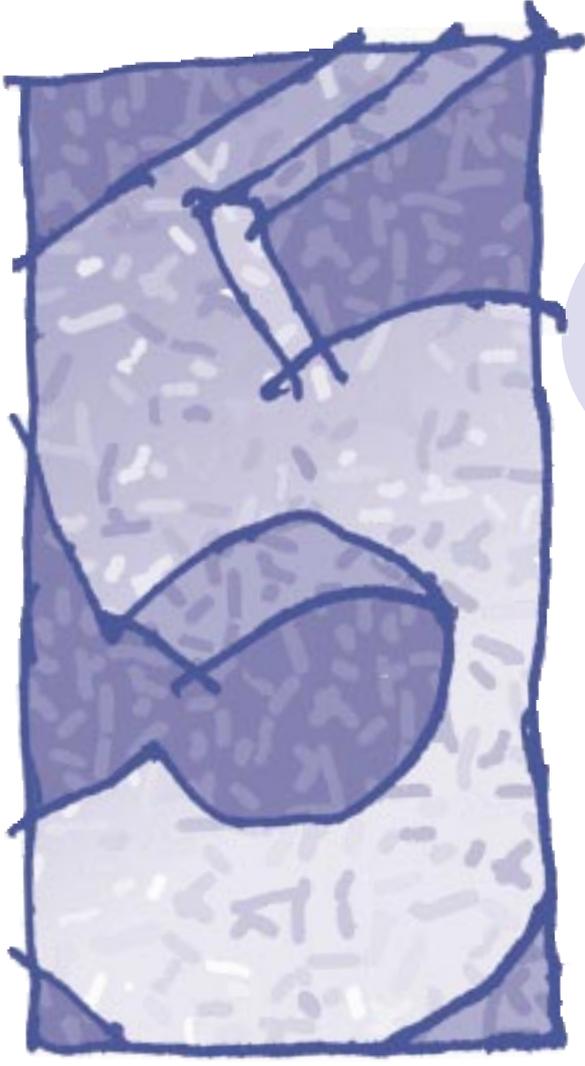


research NHGRI



National
Human
Genome
Research
Institute



Five Amazing Years of Research

IN HOLLYWOOD, THE STORY WOULD BEGIN WITH THE NAPKIN. BUT IN THE REAL WORLD, THE NAPKIN CAME LATER, AT THE END OF 1992. THE ORIGINS OF THE NATIONAL HUMAN GENOME RESEARCH INSTITUTE'S DIVISION OF INTRAMURAL RESEARCH—AFFECTIONATELY TERMED "WORLD-CLASS" BY NHGRI DIRECTOR FRANCIS COLLINS—BEGAN SOME TIME BEFORE THE NAPKIN ENTERED THE TALE.

At the start of this decade, human genetics was just about the hottest research topic around. The Human Genome Project, just getting underway, was expected to generate a torrent of information, clearly the basis for decades of fruitful additional investigation. The National Institutes of Health was supporting genetics labs everywhere. Several institutes at the NIH had intramural research programs in genetics. But NIH possessed no coordinated human genetics research effort on the Bethesda campus.

Serious talk about setting one up began during James Watson's tenure as head of what was then called the National Center for Human Genome Research. "After all, the intramural program of NIH is supposed to be a flagship endeavor that's on the cutting edge of high-risk but high-payoff biomedical research in all possible areas," says Collins, who was on NCHGR's external advisory council from its beginning. "Starting an intramural program out of the Genome Center seemed to make a lot of sense."

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5 YEARS AT NHGRI

April, 1993
Francis Collins named director of NCHGR.



August, 1993
DIR labs open, Jeffrey Trent named scientific director.

December, 1993
Hopkins/DIR team clones first hereditary colon cancer gene.

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In 1992 Watson departed, and Bernadine Healy, then NIH director, set about finding his successor. Collins was a natural choice. A creative, skillful advocate for genetics and a major figure in medical genetics, Collins led the research team at the University of Michigan that identified the cystic fibrosis gene and participated in the successful search for many others, including the gene that causes Huntington's disease.

Collins believes strongly that scientific administrators should remain rooted in the real world of research, so he told her he didn't want the job unless a lab came with it. "But of course that didn't necessitate starting a new program in the Genome Center," he notes. "Potentially I could have had a lab in one of the other institutes."

Setting Up the DIR

Collins was elated about the opportunity of designing and launching a coordinated intramural program in genetics, even though at times he got more than he bargained for. "In fact, it was a heck of a lot of work. Setting up a program from scratch and recruiting a series of world-class leaders to head up the various labs and branches was a massively challenging undertaking."

Which brings us to the napkin. It was the usual paper napkin in the usual modest restaurant, the customary storytelling-device kind of napkin on which leading characters

sketch out The Map that will lead them into adventure and shape their futures.

In this case, the restaurant was Olga's in Ann Arbor, and the characters were Michigan colleagues Collins and Jeffrey Trent, a leader in cancer genetics who now heads the DIR. What they outlined on the napkin was a plan for organizing the DIR around elements of human genetics that are still the program's focus: gene identification, genetic diagnosis, mechanisms of genetic disease, clinical genetics, and gene therapy.

"We tried to come up with programs in the broadest sense and how we would structure them. Then we listed people to head those programs as well as some other key investigators that we might want to encourage to come," Trent recalls.

"In my opinion, the way you should develop an academic program is not to preassign a bunch of pigeonholes, but to recruit absolutely the most outstanding investigators you can, regardless of the specific area you're interested in. So on that napkin we defined by a series of broad brushstrokes areas where we wanted an emphasis. But our recruitment efforts focused on who the best people were. Whether they worked on animal models of genetic disease or on inserting genes into patients was really less critical to us," Trent says.

The Stone House Meeting

Early in 1993, Trent and Collins organized a small meeting at the Stone House on the NIH campus, bringing together a dozen or so leading genetics researchers. "We trotted out the napkin vision for them, the labs and branches we thought could make a nice interdigitated set of scientific units for this program, and asked them to give us advice about whether that was the right model, and also how we might actually get this set up and going," Collins says.

Robert Nussbaum, who heads the DIR's Laboratory of Genetic Disease Research, remembers it well. "That meeting really was a turning point, because the talk changed from idle speculation to a serious consideration of what this program might look like. The possibility of pulling it off, and bringing a group of really good people together from all over the country, started to feel like maybe it could actually happen."

"We intended to make the Stone House meeting an opportunity to get advice, but also to get other really wonderful scientists excited," Collins says. "And it worked! Several of those people ended up coming here. That was a stunning achievement."

It was stunning because Collins had been told repeatedly, by people inside and outside NIH, that he would never succeed in persuading competent scientists in mid-career to move from academia to the NIH; the

salaries were too low and the bureaucracy too infuriating. "I decided not to believe that. I really was convinced that we had a scientific vision compelling enough to override those other issues, that people would be willing to consider less lucrative financial circumstances, and be willing to deal with the bureaucracy, if they felt this was a unique opportunity to work on fascinating problems and with colleagues that they had always wanted to work with. It was a bit of a gamble, but it worked."

A Matter of Space

So the DIR got its formal start the following summer. For Lance Liotta, now at the NCI but at that time head of the NIH intramural programs, the big problem was finding space and resources for the new program. When it was decided to locate many of the researchers and labs in Building 49, then brand-new, he remembers spending a lot of time soothing other scientists who had been promised the space. "We were trying to make sure that nobody lost anything by it," he says.

With two and three DIR people shoehorned into offices designed to hold one, the space crunch—and the grumbling about it—still persists. "That has been our greatest challenge, not having sufficient space to completely flesh out our vision. I was worried about that from the beginning," Collins says. "That's the one slightly frustrating aspect of all this. Because the

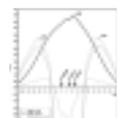


July, 1996
Spectral karyotyping used to visualize the complete set of human chromosomes in color and to identify abnormalities.

September, 1996
Members of the first class of the Johns Hopkins University/NHGRI Genetic Counseling Program matriculated.

October, 1996
Gene map of human genome published.

October, 1996
Improved method of retroviral transfer for insertion of genes into stem cells.



November, 1996
First localization of a gene that predisposes men to hereditary prostate cancer determined.

MAJOR GENE DISCOVERIES

Discoveries at the DIR involving the role of genes in disease include high-profile research with potentially immense social impact. Among them:

- **ATM**, the gene for ataxia-telangiectasia, a disease with many symptoms including a striking predisposition to cancer.
- **HPC1**, the first major gene for prostate cancer was mapped to Chromosome 1 by DIR investigators. The gene itself is being intensely pursued.
- **AIB1**, a gene that is part of the engine that drives growth of some cancer cells; for example, the gene appears to be expressed at abnormally high levels in tumor cells of most breast cancer patients.
- **MEN1**, a tumor suppressor gene which turns out to be involved in a large number of tumors in endocrine glands.
- A mutation in the gene for alpha-synuclein, found in some families with Parkinson's disease.
- **Dvl1**, the first mutant gene known to disrupt normal social behavior in mice, which may figure in human mental illness.
- **PDS**, a mutant gene involved in Pendred syndrome, which causes as many as one in 10 cases of hereditary deafness.
- **NP-C**, the gene responsible for Niemann-Pick disease type C, a rare disease that is well known because it afflicts the grandchildren of the prominent retired Notre Dame football coach Ara Parseghian.

intramural program at NIH is so tightly constrained, our space requirements have never been fully realized. They will be, finally, when Building 50 is finished in another two years.”

Procurement 101

Nussbaum had not been as hesitant about moving out of academic research as some. He knew NIH would give him access to experts in a variety of fields unmatched by any single university. “Also, there’s a long-standing tradition here of scientists being helpful to each other, collaborating and providing each other with research tools and reagents. I had the impression that, although the institutes are separate, scientists in the institutes have always interacted well. And it’s been borne out.”

But even he was astounded by the relentless regulations and paperwork. “We completely underestimated the amount of administrative infrastructure we needed. It was a shock. Procurement, getting supplies, was a major shock.”

Then something like a miracle occurred: the DIR was selected to pilot-test the new government credit card ordering system, “It sounds trivial, but instead of waiting weeks for a reagent or equipment, you could get it overnight,” recalls Kate Berg, who heads the DIR’s Office of Genome Ethics and Special Populations Research. “You can speed up research a lot that way, and it actually costs less.”

“I’m literally not sure I’d still be here if it weren’t for the NIH credit card system. It made an enormous difference, because 95% of our purchases—maybe even 99%—are below the cap on the credit card,” Nussbaum confirms. “Instead of everything you wanted to buy being a major headache, all of a sudden only a tiny percentage of what you wanted to buy was a major headache. That was just wonderful.”

Academic Modus Operandi

Bert Vogelstein, the renowned expert in cancer genetics at Johns Hopkins who heads the

DIR’s Board of Scientific Counselors, suggests that part of the DIR’s achievement is the role it has played in helping change the research culture of NIH. “One of the keys to their success has been their translation of what I might call the academic modus operandi from the university setting to the NIH. It’s been the only institute at NIH, at least recently, that has been totally staffed by people whose background is in the university, rather than in the government. That’s injected some good things into their program.”

Scientists at the DIR, he says, were already accustomed to the rigorous peer review, accountability, and competitive process for promotion that is part of the university environment and is being encouraged at NIH by director Harold Varmus and other NIH leaders. He says the DIR has been able to meld those with the different kinds of advantages of the NIH system, chiefly significant research resources and unsurpassed intellectual freedom. “When you combine the advantages of both systems, I think

you really have a dynamite organization.”

And the science produced by this dynamite organization? “I think they have far exceeded expectations,” Vogelstein says. “They’ve been able to develop new technologies, integrate technologies, do things on scales that would have been virtually impossible in university settings. They’ve generated an enormous number of high-quality publications. Their record now speaks for itself.”

Collins is even less restrained: “I would be completely unhesitant to stack our intramural program up against any program in human genetics at any institution in the world, and predict it would come out equal—or better.”

Today, the DIR is an elaboration of the napkin blueprint: a basic research limb with individual branches concentrating on molecular biology, genetic disease, and genome technology; and a clinical limb with branches investigating cancer genetics, medical genetics, and gene therapy. Also in place

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December, 1996
DNA microchip used to accurately identify mutations in BRCA1.



December, 1996
Microarray technology used to analyze gene expression patterns in human cancer.

November, 1996
Spectral karyotyping used to visualize mouse chromosomes.

November, 1996
Gene that causes a subset of Parkinson's disease mapped.

December, 1996
Cloning and mapping of the human methionine synthase gene.

are essential resources: physical mapping, chromosome study, vector development, gene transfer expertise, bioinformatics, and lab animals.

The record, Vogelstein points out, includes the fact that DIR scientists have been involved in a significant portion of the total positional cloning efforts published to date. "That's really a remarkable achievement."

"You can have all the plans on paper, either napkins or much more elaborate documents, and if you don't have talented leadership, it isn't going to happen," Collins says. "We've collected a remarkable group of talented investigators, and they have

developed a fantastic sense of collegiality and interactivity, both within the NHGRI and with intramural programs of other institutes. That has sparked a wide variety of truly remarkable advances in our very short lifetime."

"Neither Francis nor I had any clue that it would be as much of a struggle, or as much of a joy, as it's been," Trent says. "We tremendously underestimated the amount of effort it would take to get the DIR going. But we also underestimated the amount of resources, and the intellectual climate, that we could call on here, and we would be able to bring to people. It's been a really rewarding five years." ● <http://www.nhgri.nih.gov/celebrate>

"The notion that in only five years, from being basically a diagram on the back of a napkin to the point where I can brag about this as a premier program—perhaps even the premier program in human genetics—it's pretty amazing."

—FRANCIS COLLINS, NHGRI DIRECTOR

BEYOND GENE DISCOVERY

For DIR scientists, gene discovery is only the first step toward explaining what genes do and how they do it. For example:

- DIR scientists try to find ways of using genes to treat disease. They have reported on the first successful trial of clinical gene therapy, treating two children who suffered from immune deficiency because they lacked the enzyme adenosine deaminase (ADA). Severe combined immunodeficiency has also been treated via gene therapy.
- DIR researchers develop technology. They created spectral karyotyping (SKY), an easy-to-use way of finding changes in chromosomes so small that they are invisible to the eye. SKY has been used to discover new chromosome abnormalities in leukemias and many solid tumors such as breast and brain cancer. They are devising techniques for gene transfer and techniques for disabling genes in order to create mouse models of human disease for study. They are also working on the frontiers of microarray technology for DNA analysis.
- DIR programs offer extensive training opportunities. In the fall of 1996, the first students entered a rigorous new program for training genetic counselors, unique in its focus on research, and situated jointly at NIH and the Johns Hopkins School of Hygiene and Public Health. Visiting investigators are encouraged to study at NHGRI through an innovative program. NHGRI has reached out to West African scientists inviting their active participation in a study of non-insulin dependent diabetes in Africans and African-Americans.
- NHGRI collaborates, both with scientists at the other NIH institutes, and at academic institutions like Johns Hopkins and many others, here and abroad. Its collaboration with Howard University in Washington has expanded beyond the African diabetes study to a large new multi-center study of familial patterns of prostate cancer in African-Americans, where the disease is unusually common.
- NHGRI fashions ways to assist other scientists. It is lead agency and manager for the new Center for Inherited Disease Research, a high-volume genotyping facility that helps researchers identify the genes (and their variants) that play important roles in complex diseases. These include the most common causes of human illness and death: high blood pressure and other familial diseases of the heart and circulatory system, diabetes, obesity, cancer, mental illness, asthma, arthritis—and also susceptibility to most kinds of infectious disease.
- Continuing investigations of the breast cancer genes BRCA1 and BRCA2, for example, have disclosed mutations at higher-than-usual frequency in a number of defined populations, including Ashkenazi Jews. These investigators have also uncovered three specific mutations associated with increased risk of breast, ovarian, and prostate cancers in the general population.



December, 1996
Collaboration with researchers at Wayne State University Medical School leads to successful antenatal treatment of XSCID with in utero bone marrow transplantation.

February, 1997
Center for Inherited Disease Research (CIDR) established to help scientists understand the genetic and environmental causes of common disorders.

February, 1997
NCHGR becomes Institute. NHGRI is born.

March, 1997
Mutations that cause Pallister-Hall syndrome identified.