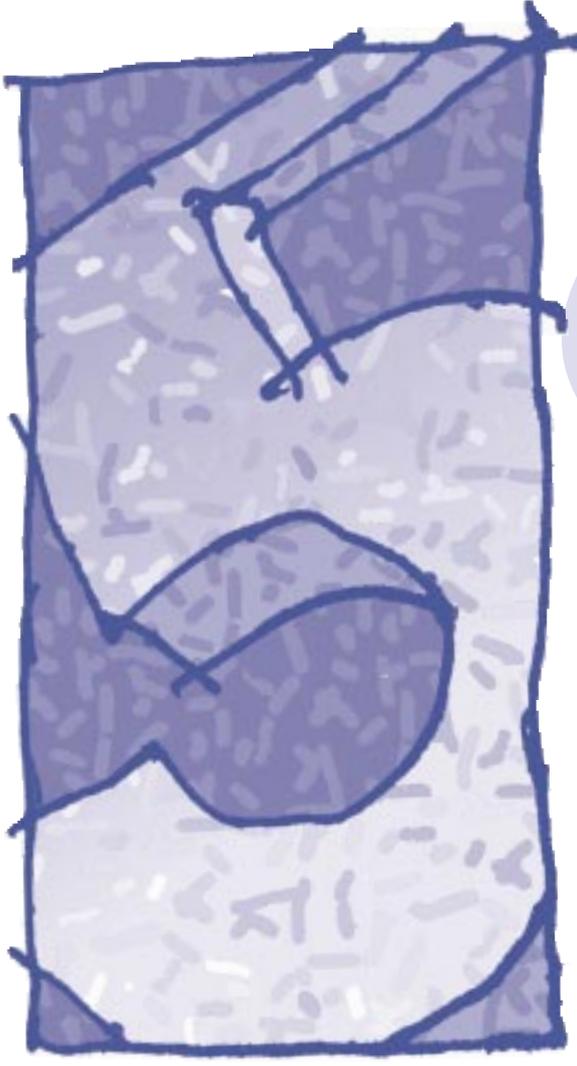


research NHGRI



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.

Microarray Technologies

The most exciting technology in genetics research? The DNA chip of course, featured in the pages of *The New York Times*, *Fortune*, and other media aimed at movers and shakers.

But the chip, a miniature marvel for analyzing DNA, is just one of a group of technologies known as microarrays. Microarrays are large numbers of parallel elements (often, but not always, DNA) grouped in a very small space for computer analysis.

Scientists at the DIR's Cancer Genetics Branch (CGB) have been refining one microarray method and using it to study cancer since 1996. Their arrayer robot positions functional gene fragments so precisely that today more than 10,000 can fit on a portion of an ordinary microscope slide. DNA probes labeled with fluorescence are then placed on the slide to hybridize with their complements among the fragments, each of which represents a particular human gene. The slide is put into a scanner that measures the brightness of each fluorescent dot, an indication of gene activity. Computer analysis of gene activity patterns allows scientists to compare the pattern of gene expression between normal and diseased cells.

Recently CGB researchers have used the system to study a frequently fatal childhood cancer called alveolar rhabdomyosarcoma (ARMS) and discovered that its cells have a characteristic gene-expression "finger-

print". The pattern distinguishes those tumor cells from other cancers, even when the samples come from different patients.

Such research studies are hoped ultimately to be useful for diagnosis or for explaining in detail what goes on in a tumor cell, according to Michael Bittner, who heads the Teleonomics Unit of the CGB. "However, to really get an insight into those questions, we're going to have to examine a very large number of samples. As it is, not having had any ability of this kind up until now, we have only the very dimmest sense of how the genes interact with each other and what genes are on what pathway," he points out.

The CGB is collaborating with other researchers in investigating the effects of disease viruses on gene expression in the host's cells. Viruses under study include HIV and the Ebola virus.

A major aim of this work is to answer controversial questions about the role of viruses in cancers and autoimmune diseases.

The lab intends to continue characterizing gene expression in different kinds of tumor tissues. Bittner wonders, for example, how many different cancers are hiding out under the single term "breast cancer?"

The scientists also plan to look at more general genetic questions such as which genes are expressed all the time at fairly

constant levels no matter what kind of cell they're from. Or conversely, which genes vary a lot depending on what the cell is doing currently in life.

The better-known gene chip—a piece of glass the size of a postage stamp enclosed in a black plastic case—is getting a workout at the DIR's Genetics and Molecular Biology Branch. In collaboration with the chip's maker Affymetrix, the lab has already used the chip experimentally to look for alterations in large genes like the breast cancer genes BRCA1 and BRCA2, both in humans and in our closest relatives, chimpanzees and gorillas.

The scientists have recently turned their attention to *Atm*, the gene for ataxia-telangiectasia (AT) that was discovered at the DIR in 1995. AT is a rare fatal disease. Children with AT are predisposed to cancer and exceptionally sensitive to radiation.

AT occurs when a child inherits two altered *Atm* genes, one from each parent. Although each possesses a single mutant gene, the parents (called carriers) do not have AT. But there is a strong suspicion that carriers also run a three- to four-fold increased risk of cancer.

"Because so many people carry alterations in the *Atm* gene, even if the risk associated with being a carrier turns out to be low, it could become a public health consideration because of the large number of people it would affect," says Joseph



Hacia, who supervises the chip project. Carrier frequency of the mutant gene has been roughly estimated at 1% of the population, more than 2.5 million people in the U.S. alone.

With the first chip containing the huge *Atm* gene, the scientists found they could detect about 91% of altered genes present. The chip's design has since been improved. "What we're hoping is that instead of being 91% accurate we're going to be closer to 95% accurate, or perhaps higher," Hacia reports.

That accuracy range, he points out, is still not optimal for clinical use. But it is accurate enough for population studies on historical tissue samples. Such retrospective surveys could make carrier estimates more accurate. And, if their risk of cancer turns out to be higher than in noncarriers, the studies could reveal just what that risk is. ●

http://www.nhgri.nih.gov/DIR/VIP/Learning_Tools/research_technique.html

June, 1994

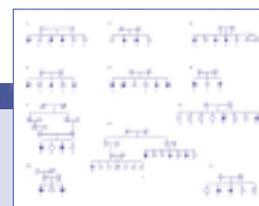
FUSION project to study the incidence of Type II diabetes in the Finnish population started.

September, 1994

Location of the gene for Wolfram syndrome determined.

September, 1994

Germline p16 mutations in familial melanoma reported.



Pendred syndrome

Research

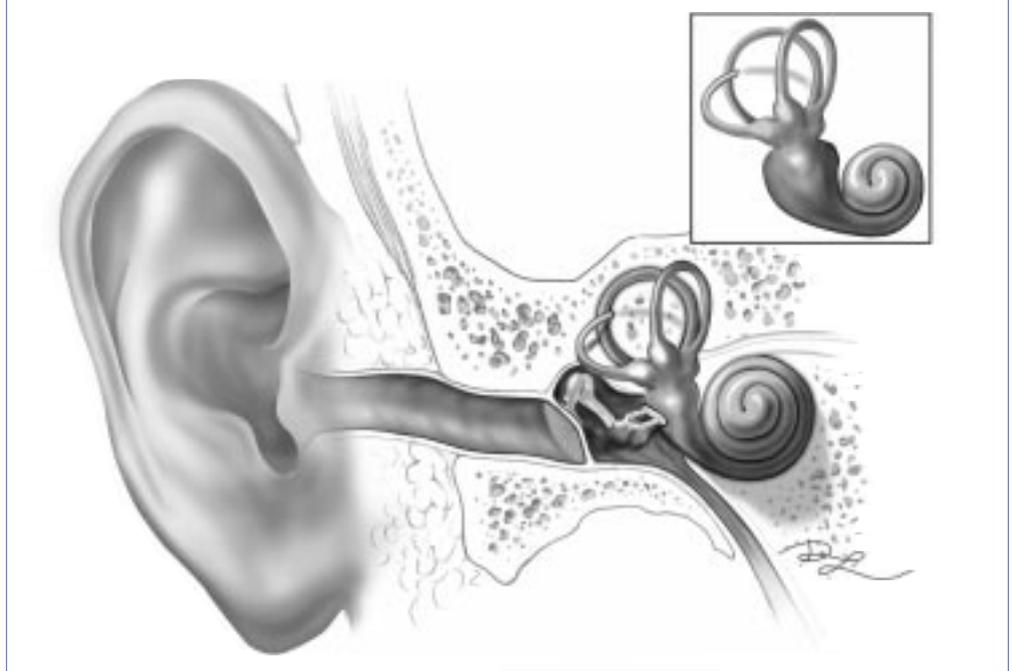
What's the point of mapping human chromosomes? A satisfying answer to that question can be found in the DIR's Genome Technology Branch.

The laboratory of Eric Green, Chief of the Branch, completed a physical map of chromosome 7, which accounts for about 5% of the human genome, in 1997. In the meantime, researchers studying a genetic disease known as Pendred syndrome, which is thought to account for 5–10% of hereditary deafness, discovered that the defective gene resided on chromosome 7, so they teamed up with Green's lab to isolate the gene.

Pendred syndrome is noteworthy because, in addition to deafness, its other hallmark feature is goiter, an enlargement of the thyroid gland. The question that fascinates researchers is: How can one defective gene cause these two dramatically different abnormalities?

At the end of last year, post-doctoral fellow Lorraine Everett, working in Green's lab, identified the Pendred syndrome gene. In the few months since, the lab's scientists and collaborators have already made progress toward understanding the mutant gene's disruptive effects.

All Pendred syndrome patients examined so far have a mutation in the identified gene. A couple of mutations seem to account for a significant portion of cases, but numerous other mutations have also been uncovered.



The human auditory system. Boxed is a cochlea of a Pendred syndrome patient with fewer turns in the "spiral" as well as other structural differences.

"As with many other genetic diseases, we are finding common mutations and very rare ones," says Green.

The scientists have also identified at least one mutation that causes deafness only, with no thyroid disease. "That implies certain defects in the gene can result in deafness alone," says Green. "This observation makes untangling the function of the gene even more interesting." Green expects that identifying additional mutations and correlating them to specific abnormalities in patients will provide insight about the function of the encoded protein in the ear and thyroid.

The Pendred syndrome studies involve collaborations with research groups around the world and at NIH itself. Green's laboratory is now working with the National Institute on Deafness and Other Communication

Disorders to study the deafness component of the disease and with the National Institute of Diabetes and Digestive and Kidney Diseases to examine the role of the encoded protein in the thyroid.

Green's lab is now enlisting the help of the laboratory mouse. The scientists have already sequenced the corresponding mouse gene and verified that it is very similar to the human Pendred syndrome gene. They have also studied where and when the gene is turned on, discovering that it is expressed in a very limited way within the mouse embryo—for example within certain cells of the developing cochlea in the inner ear. In humans, the syndrome's deafness is accompanied by a distinctive malformation of the cochlea.

"Right now we're in the process of making a knockout mouse, that will carry defective

copies of the Pendred syndrome gene," says Green. "Our prediction is that such a mouse will likely have an abnormally developed cochlea and perhaps goiter."

Green points out that in the past, his lab's strengths have been in genome mapping and sequencing, not in making mouse models of human disease, screening patients for mutations, characterizing proteins, or understanding ion transport across membranes. "But because we built a strong infrastructure for studying genes on chromosome 7, we were able to identify the Pendred syndrome gene in just over a year. And then in the past few months, thanks to the remarkable strengths which exist in a variety of disciplines at NHGRI, we have been able to launch ourselves into whole new areas of research." ●

<http://www.nhgri.nih.gov/NEWS/Pendred/>

May, 1995

Collaboration with Howard University to investigate susceptibility to non-insulin dependent diabetes mellitus and hereditary prostate cancer in African-Americans began.

June, 1995

Gene and its related mutations that cause ataxia-telangiectasia isolated.

June, 1995

Mutations in Fas gene found to cause ALPS.

July, 1995

Mutated gene that causes hypochondroplasia isolated.

July, 1995

Clinical genetics training program admits first student. Clinical genetics residency begins.

Parkinson's disease research

Update

It was international news when scientists in the DIR's Genetic Disease Research Branch found a gene that causes Parkinson's disease. Until that 1997 report, most experts believed the disease—which eventually strikes about one in a 100 people—was probably due to unknown factors in the environment. Now the discovery is helping scientists puzzle out the causes of a number of other serious brain diseases.

The causes of most cases of Parkinson's disease—whose symptoms include trembling of a limb, rigidity, a slow, shuffling walk, and stooped posture—are still a mystery. In the original report, the gene mutation was found in families of Italian and Greek origin, and subsequently a different mutation in the same gene has been linked to the disease in a German family.

The Parkinson's research was led by Dr. Mihael Polymeropoulos' and Dr. Robert Nussbaum's laboratories at NHGRI, in collaboration with researchers outside of NHGRI.

The normal gene produces a protein called alpha synuclein. The finding of an alteration in this protein not only hints at why Parkinson's develops, but suggests that it may be one of several forms of frightful degenerative diseases of the brain that all share a common mechanism.

Polymeropoulos' hypothesis is that in these diseases, the normal cellular apparatus for

protein breakdown goes awry, leading to an accumulation of debris in the brain that is eventually severely disabling and ultimately deadly. One of the other disorders is the extremely common affliction of aging: Alzheimer's disease. The others are rare but also well-known: Huntington's disease, Amyotrophic Lateral Sclerosis (ALS or Lou Gehrig's disease), and the so-called prion diseases, such as Creutzfeldt-Jakob, a human disease, and its livestock analog commonly called Mad Cow disease.

Brains of Parkinson's disease patients examined after death contain microscopic brain structures called Lewy bodies. Lewy bodies appear to be tombs for proteins the body has failed to recycle, including alpha synuclein.

“Although the alpha synuclein mutations are a rare cause of Parkinson's, we have shown that in all Parkinson's—even in patients who don't have any alterations in the gene—alpha synuclein is a major constituent of the Lewy bodies. So finding the altered gene has identified a rare direct genetic way of recruiting alpha synuclein into Lewy bodies. But there must be many other ways that this can happen, genetic and non-genetic. Alpha synuclein may be a final common pathway for developing intracellular accumulations such as Lewy bodies,” note Polymeropoulos and Nussbaum.

According to Polymeropoulos, there is a growing consensus among people studying

There is a growing consensus among people studying Parkinson's, Alzheimer's, and Huntington's that they may all be looking at the same process.

Parkinson's, Alzheimer's, and Huntington's that they may all be looking at the same process. In each disease, the inclusions that infest the brain are different from each other and accumulate in different regions, and the constituent proteins are different (beta amyloid in Alzheimer's and huntingtin in Huntington's disease). “But there may be a common theme being that cellular proteins fail to undergo normal repair and eventually degradation which is primarily conducted by the protein garbage grinders known as proteasomes.”

“Proteasomes are cellular subunits responsible for degrading the bulk of cellular proteins. These macromolecular machines act like garbage grinders inside the cell. They're cylinders; abnormal



August, 1995
President Clinton experiments with chromosome microdissection during a tour of NIH.

October, 1995
High-frequency alteration in the BRCA1 gene found in several discrete population groups, including Eastern Europeans and Ashkenazi Jews.



Dr. Mihael Polymeropoulos



Dr. Robert Nussbaum

proteins are fed into one end and out the other end come small peptide fragments. But in these diseases, something goes terribly wrong with the garbage-grinding process. Either the proteins are abnormal, perhaps folded abnormally, and they clog the proteasome, or perhaps components of the proteasomes themselves are dysfunctional," Polymeropoulos explains.

And how do Mad Cow and the other prion diseases fit into this grand unified theory of neurodegenerative disease? Prions are peculiar proteins that can persuade other proteins to fold abnormally, thus helping to gum up the works. The Parkinson's protein, abnormally folded alpha synuclein, apparently shares the prion protein's persuasive powers. It, too, is

believed to induce abnormal folding in other proteins, further challenging the brain's ability to dispose of rubbish and eventually overwhelming it.

NHGRI researchers were first to find a gene that causes Parkinson's disease and, recently, Dr. Polymeropoulos' team discovered a second PD gene. Researchers elsewhere have followed suit in the search for PD genes as well. One group has recently mapped another PD locus and cloned a gene for juvenile Parkinson's. ●

http://www.nhgri.nih.gov/DIR/LGDR/PARK/park_home.html

October, 1995

After four years, patients who had undergone gene therapy for treatment of adenosine deaminase deficiency still showed improved immune activity.

June, 1996

Anti-HIV genes successfully introduced into human lymphocytes.

June, 1996

Atm mouse model developed.

continued from page 1

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

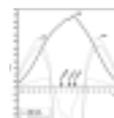


July, 1996
Spectral karyotyping used to visualize the complete set of human chromosomes in color and to identify abnormalities.

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.

This fall, DIR researchers will team up with the Smithsonian Institution to give Washingtonians an inside look at cutting-edge genetic research and a chance to learn about diagnostic and therapeutic techniques still on the scientific horizon.

As part of the Smithsonian's *Campus on the Mall* lecture series, leaders in the field of

genetics from the Washington area will conduct a series of eight evening seminars designed to shed light on some of the public's most intriguing genetic concerns, as well as to pique their curiosity about some of the latest developments in genetics.

The weekly series will open on October 13 with a discussion of the Human Genome

Project, followed by a primer on the basic concepts or "the ABC's of genetics". Later topics will include the genetics and treatment of cancer, issues associated with genetic testing, mapping the human genome, and gene therapy techniques. The series is part of the DIR's Science Education and Outreach effort and will run through December 1.

Eight of the nine speakers are DIR investigators: Barbara Bowles Biesecker, Michael Blaese, Lawrence Brody, Francis Collins, Claire Francomano, Eric Green, Robert Nussbaum, and Jeffrey Trent. The ninth speaker is Dean Hamer, of the National Cancer Institute's Laboratory of Biochemistry. ●

For more information:
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A SUMMER OF SCIENCE

The summer of '98 will be a memorable one for the 44 high school, college, and graduate students selected to intern in nearly every DIR laboratory. For many, it's their first real exposure to the biomedical sciences—and what better place to learn than at NHGRI and NIH. The 23 females and 21 males, chosen competitively from nearly 1,000 applicants from across the U.S., applied to the DIR under NIH's Summer Internship Program in Biomedical Research. The interns, many planning careers in science and medicine, work side-by-side with Genome scientists on projects ranging from the genetics of cancer to monitoring behavioral changes in a colony of mice that are models for Huntington's disease.

Now in its fifth year, the internship program has helped hundreds of students from around the country develop and hone skills for scientific investigation. The students spend at least eight

weeks working in state-of-the-art biomedical research and training facilities with guidance from DIR scientists.

In addition to laboratory experience, students attend a regular series of lectures by NIH investigators and learn about the latest discoveries in NIH Institutes. At the end of the summer, students present their work during "Poster Day," where they get a chance to share their research experience with their peers and scientists from across the NIH campus. A number of students are fortunate enough to have the results from their summer research published in leading scientific journals.

The internship program has reinforced career choices for a number of summer students, many who have gone on to complete graduate degrees and begin basic or clinical research careers in the biomedical sciences.

"The students really get an excellent introduction to bio-



medical research," says DIR scientific director, Jeffrey Trent. "In addition to participating in research, they receive a sampling of research happening at other institutes at NIH. That is what makes the internship program unique. No where else can students get access to so many experts in biomedical research on one campus." ●

http://www.nhgri.nih.gov/DIR/VIP/summer_intern.html

Mona Jabbour, a University of Virginia student, with her mentor Leslie Biesecker. Jabbour was one of over 40 students who studied in DIR labs this summer.



April, 1997
Tumor suppressor gene *MEN1* identified.

June, 1997
Mutation in the alpha-synuclein gene identified in families with Parkinson's disease.

July, 1997
Physical map of human chromosome 7 completed.



July, 1997
Gene responsible for Niemann-Pick disease type C identified.

July, 1997
Mouse model of NPC developed.

Welcome to 4 researchers

FALL 1998

10

Childhood disorders, the role genes play in activating the immune system, and how faulty cell transmission can lead to osteoporosis are some of the research interests of four new investigators at the NHGRI. The findings from their research could lead to results as diverse as discovering the gene that causes attention-deficit disorder to using gene therapy to treat immune deficiency diseases such as AIDS, cancer, and lysosomal storage disorders.

Maximilian Muenke, MD

Medical Genetics Branch



Dr. Muenke seeks the genes that direct brain, face, and skull formation. To find these genes, he evaluates people with abnormal craniofacial development. He has studied extensively holoprosencephaly (HPE), the most common structural problem of the forebrain that, in turn, influences the face. The condition appears in one in every 16,000 live births with varying severity. Some forms of HPE are inherited; others arise when the fetus is exposed to certain chemicals. The disease causes mental retardation, cleft lip, missing or improper placement of noses or eyes, and incorrect formation of the front teeth. Muenke and his colleagues found the first gene, known as Sonic Hedgehog, which causes HPE. He suspects that some of the alterations in this gene interfere with the ability to bind cholesterol, an important component for normal brain development. Low cholesterol has been found in some patients to cause HPE. The genetics of attention-deficit hyperactivity

disorder (ADHD) also interest Muenke, who is hunting for ADHD genes in large families where several members are affected.

http://www.nhgri.nih.gov/Intramural_research/People/muenke.html

Fabio Candotti, MD

Clinical Gene Therapy Branch



A different gene controls each of the many steps involved in activating the immune system, the body's warrior against invaders. Detrimental alterations in certain genes cause several different—and often fatal—immune deficiency diseases. Dr. Candotti investigates ways to create gene therapy for severe combined immunodeficiencies. Patients with these disorders can have problems with either their B cells (the ones that make antibodies) or T cells (the ones that kill foreign organisms or that stimulate other cells involved in immune responses). These white blood cells, like other blood components, are all formed from the same kind of ancestral cells. Candotti is especially interested in a gene called JAK3 that, when faulty, restricts cell development. He suspects that a well-ordered JAK3 is critical in the molecular signaling that tells the progenitor cell to become a T cell instead of some other blood component. By understanding the mechanism at the root of immune system diseases, Candotti believes that eventually it will be possible to develop ways to correct a faulty genetic code directly.

http://www.nhgri.nih.gov/Intramural_research/People/candotti.html

Pamela Schwartzberg, MD, PhD

Genetics Disease Research Branch



Dr. Schwartzberg studies how cells communicate with each other. Cells receive external signals that tell them to divide or change their properties in other ways. Before any changes can occur, however, those signals must be transmitted to the nucleus. This process, known as signal transduction, is governed by various molecules. If problems occur in the molecules or how they transmit signals, cells can continue dividing, leading to cancer. Or, in other cases, cells could fail to divide and produce key molecules required for normal growth and development. Schwartzberg studies tyrosine kinases, a group of signal-transducing molecules, and their genes. In her work with mouse Src genes, she evaluates how various alterations influence the cell signals that direct bone formation. Certain mutations, for instance, give mice osteopetrosis, a disorder where bones thicken and become brittle. This area of research may lead to new treatments for other bone diseases, including osteoporosis. Schwartzberg's laboratory also investigates failures in other tyrosine kinases that cause immune system disorders.

http://www.nhgri.nih.gov/Intramural_research/People/schwartz.html

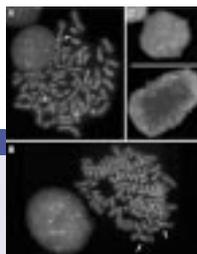
Donna Krasnewich, MD, PhD

Medical Genetics Branch



Dr. Krasnewich studies a rare inherited childhood disorder known as carbohydrate-deficient glycoprotein syndrome (CDGS). Affected children have severe developmental delays, abnormal fat distribution and sexual maturation, along with heart, blood, nerve, vision, and bone problems. Approximately 200 CDGS cases exist world-wide, but Krasnewich expects to see more as doctors learn to properly diagnose the disease. The syndrome got its name in 1986 when researchers realized that several medical problems were caused by faults in the making of certain complex sugars. These N-linked oligosaccharides (or glycans) work in enzymes, blood-clotting agents, cell communication, proteins that hold cells together, embryonic development, and organ functioning. Krasnewich studies the final products of N-glycan synthesis, a production process that may involve 200 steps or more, to learn what can go wrong upstream. Understanding the process and the roles N-linked glycans play in the body may lead not only to treatments for CDGS patients, but to better blood-clotting products as well. ●

http://www.nhgri.nih.gov/Intramural_research/People/krasnewich.html



August, 1997

Gene associated with familial Mediterranean fever identified.

August, 1997

AIB1 gene found to be expressed at abnormally high levels in the tumor cells of breast cancer patients.



September, 1997

Removal of the Dvl1 gene from mice found to disrupt their normal social behavior.

December, 1997

Mutated gene that causes Pendred syndrome identified using the recently completed physical map of human chromosome 7.

Visiting Investigators Strengthen Research Efforts While at DIR

Each year, the DIR hosts visiting scientists from across the US and around the world through its Visiting Investigator Program (VIP). The VIP allows tenured or tenure-track professionals to spend up to a year in DIR laboratories learning research technologies, developing research collaborations, or pursuing a sabbatical research project.

The 1998 awardees hope that their research efforts will lead to better treatment of Parkinson's disease, Batten disease, and breast cancer.

Georg Auburger, MD

Germany's Georg Auburger is pursuing genetic leads on Parkinson's disease. Auburger, a neurology professor researching inherited ataxias and dystonias in his homeland, arrived in the U.S. after having collected blood samples from over 200 patients in Germany, Spain, Portugal, and Yugoslavia with

familial Parkinson's disease. Collaborating with Robert Nussbaum's lab, he is screening these DNA samples seeking alterations for Parkinson's disease. Auburger is convinced the treatment of Parkinson's will benefit greatly from looking into the genetic basis of the disease.

Hannah Mitchison, PhD

Hannah Mitchison, University College, London, is focusing on Batten Disease, a rare and fatal inherited neurodegenerative disease that strikes seemingly normal children and infants; symptoms include blindness, seizures, mental impairment, and the loss of motor skills. Although researchers discovered a gene that causes Batten disease, they still know little about its evolution. Mitchison is spending her time here designing a mouse model for Batten's. The long-term goal is to test new kinds of therapies to more effectively treat the disease.



Carolyn Whitfield-Broome, Ph.D.

Carolyn Whitfield-Broome, PhD

Howard University's Carolyn Whitfield-Broome is focusing her efforts on studying the BRCA 1 and BRCA 2 genes in African-Americans. The two BRCA genes account for approximately three to eight percent of breast cancer cases. Whitfield-Broome is analyzing DNA samples for alterations

that may be specific to African-Americans. She is searching for a change in a particular protein, investigating whether it's truncated or shorter. Her research goal is to make it easier to pinpoint African-Americans who are at heightened risk for breast cancer. ●

<http://www.nhgri.nih.gov/DIR/VIP/vip.html>

DIR HONORS FIRST RETIREE

On May 1, Genome employees gathered to celebrate the Institute's first retiree: Patsy Frye. She was an NHGRI employee since early 1995, but her NIH career spanned 36 years.

"Patsy exemplified commitment and competence," says NHGRI scientific director, Jeffrey Trent. "As the Institute's first retiree, she has indeed set a standard for others to emulate."

Frye joined the DIR in 1995 as deputy administrative officer and played a major role in recruiting personnel for the DIR.

"Patsy and I worked as a team at Genome for several years," says Frye's supervisor, Linda Adams. "As I look back it's easy to see that our overall challenges and successes wouldn't have been possible without a person of her caliber, her professionalism, and her constant diligence."



Frye joined NIH in June, 1962. She worked at several institutes over the ensuing 36 years, assuming progressively more responsible positions—an effort that was recognized with the NIH Director's Award.

A jubilant Frye said she enjoyed working at NHGRI. "I took pleasure in helping build up the DIR. It's a young institute, full of dynamic, energetic and wonderful people."

She now looks forward to not rising at 4:00 a.m. or making the 100 mile round-trip commute between NIH and her home in Lovettsville, Virginia.



December, 1997

Alagille syndrome gene discovered.

January, 1998

Mutated gene that causes Hirschsprung's disease identified.

February, 1998

DNA chip technology used to analyze a region of the BRCA1 gene in chimpanzees, gorillas, and orangutans.



July, 1998

Microarray tissue chip developed to illuminate process of cancer development.

August, 1998

Publication of data management and analysis tools for gene expression arrays.

glossary of genetic terms

NEW AUDIO GLOSSARY OF GENETICS MAKES GENETICS EASIER TO UNDERSTAND FOR NON-SCIENTISTS

Today, genetic terms and concepts such as positional cloning, tumor suppressor genes, alleles, and markers have become common in major news events, high school biology classes, popular movies, and even conversations around the water cooler in the workplace.

Until recently, however, there have been few places for the public to turn for help in understanding the science behind these seemingly complicated and often confusing genetic terms. But now all of that is changing: Enter the Glossary of Genetic Terms from NHGRI.

The DIR Office of Science Education and Outreach has created a new multimedia “talking” glossary of genetic terms on the internet. The Glossary provides definitions in clear, non-technical language for nearly 200 terms commonly used when describing research in human genetics.

Now, with only the click of a mouse button, people can hear an NHGRI researcher demystify the meanings of some of the most daunting terms associated with genetics. Terms in the glossary range from more common ones like *DNA*, *gene*, and *chromosome* to less familiar ones such as *linkage*, *phenotype*, and *fluorescence in situ hybridization* (FISH).

Geared toward people with non-scientific backgrounds who want to develop a better understanding of the concepts of modern genetics, the glossary is a powerful resource for people around the globe. Since it is a web-based tool, it is available 24-hours a day from any internet connected computer. The glossary is also designed for use in classrooms and libraries and is available to these users in a CD-ROM version.

“We expect the audio glossary will be used by parents helping their children with their homework, people trying to better understand news stories, families coping with inherited disorders, journalists reading medical literature. The list goes on and on,” said Jeff Witherly, director of the Office of Science Education and Outreach.

For each genetic term, the glossary provides a brief written definition and an audio file in which an NHGRI researcher—a leader in the field of molecular biology, genetics, or medicine—explains the term in less than two minutes. Many of the terms also contain professionally designed illustrations that support the written and audio definitions, and most have a phonetic pronunciation guide. Each term also includes a list of other “related” definitions in the glossary that might be valuable in understanding the overall context of the definition.

“The entire glossary is exciting, but the audio definitions are truly the hallmark of the project,” said Witherly. “The audio provides an opportunity for some of today’s leading scientists to come out of their labs and share their knowledge with the public. We asked each scientist to explain the term as if they were talking with a neighbor or a relative, and the result is a really powerful way to learn more about this very special language of genetic research.”

Twenty-four investigators and advisors from within the DIR provided the audio definitions. Links from the glossary connect users to pages where they can view pictures of the contributors, read about their research interests or area of expertise, and peruse a list of their recent publications.

In keeping with NHGRI’s mission to educate the public about the research conducted within the institute, each contributor discusses terms that are relevant to his or her specific area of study. For example, investigators studying gene therapy explain terms concerning gene therapy techniques, while researchers studying cancer genetics explain terms like *melanoma* or the *BRCA1* and *BRCA2* genes.

“For a lot of people, science can seem like a bunch of meaningless technical terms, but here people can see the real person behind those terms. They can hear the

researcher and really get a feel for what drives the science.” said William Pavan, of the Genetic Disease Research Branch, who defines a number of terms related to his studies of the process by which unspecialized cells develop into cells with a specific function—cells of the nervous system, for example.

The glossary is a feature of the DIR’s revamped web site which debuted in July 1998. The new web pages offer links to the various labs and offices within the DIR, as well as to other on-line genetics resources and press releases for recent DIR findings.

The glossary is available on-line at: www.nhgri.nih.gov/glossary/. A limited number of copies on CD-ROM are available, free of charge, to schools and libraries through the Office of Science Education and Outreach. ●

www.nhgri.nih.gov/glossary/

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