NATIONAL HUMAN GENOME RESEARCH INSTITUTE Division of Intramural Research

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In 2003, the National Human Genome Research Institute (NHGRI) and scientists worldwide celebrated both the 50th anniversary of the discovery of the double-helical structure of DNA and the successful completion of the Human Genome Project. Having reached the pinnacle accomplishment of finishing the human genome sequence, we also unveiled an exciting and bold vision for the future of genomics research, which detailed myriad opportunities for using the fruits of the Human Genome Project to improve human health.

This foundational information — a high-quality, comprehensive human genome sequence and its ongoing interpretation — provided by the Human Genome Project makes the once Herculean task of identifying the molecular basis of simple genetic diseases now almost routine. Meanwhile, our ability to define the genetic determinants of more complex genetic disorders has been dramatically improved. Further, we have many opportunities to predict illnesses before symptoms occur, and to detect adverse drug responses based on genetic information. We also have unprecedented opportunities to design gene-based therapies. In addition, our ability to define the role of genetic factors in maintaining good health is greatly enhanced. Such developments have, appropriately, led to an increased emphasis on the study of the ethical, legal, and social implications of genetic and genomic discoveries.

At the forefront of efforts to capitalize on the opportunities created by the Human Genome Project is the NHGRI Division of Intramural Research. Since its inception in 1993, we have assembled a talented group of investigators with diverse expertise, all with a passion for genetics and genomics. By taking full advantage of the highly collegial nature of NIH and its remarkable infrastructure for performing cutting-edge basic and clinical research, our investigators have established internationally recognized research programs. These programs provide fertile training grounds for researchers and clinicians at all levels, and are helping to cultivate the next generation of geneticists and genome scientists.

The NHGRI Division of Intramural Research is dedicated to utilizing genomics to transform our understanding of biology and to use that information for improving human health. We invite you to learn more about our research and training programs by reading the following pages and visiting our Web site at genome.gov/DIR.

Sincerely,

Eric D. Green, M.D., Ph.D.
Scientific Director
National Human Genome Research Institute

Francis S. Collins, M.D., Ph.D.
Director
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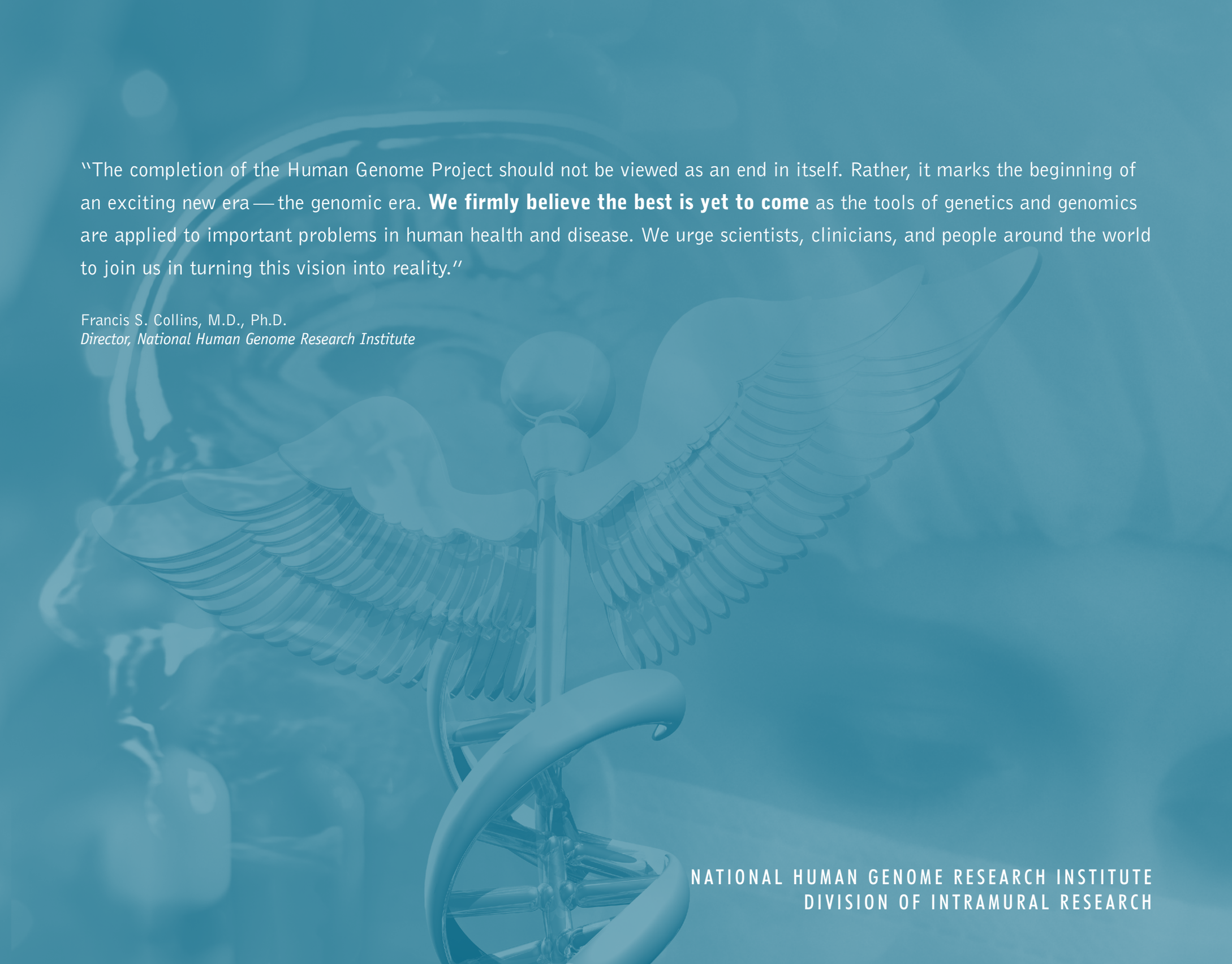

"The completion of the Human Genome Project should not be viewed as an end in itself. Rather, it marks the beginning of an exciting new era — the genomic era. **We firmly believe the best is yet to come** as the tools of genetics and genomics are applied to important problems in human health and disease. We urge scientists, clinicians, and people around the world to join us in turning this vision into reality."

Francis S. Collins, M.D., Ph.D.
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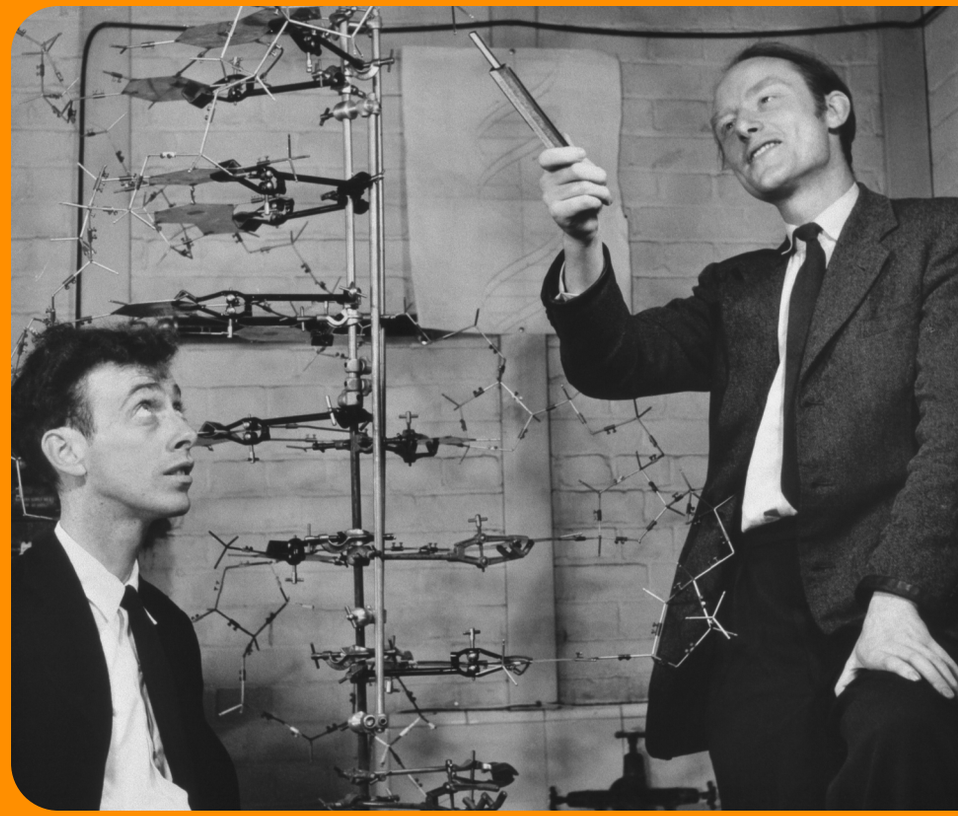
NATIONAL HUMAN GENOME RESEARCH INSTITUTE
DIVISION OF INTRAMURAL RESEARCH



James Watson, Ph.D. and Francis Crick, Ph.D., 1953

We have known for most of the past century that rogue genes are responsible for many, if not most, human diseases. However, for much of this time, it was extremely difficult to bridge the chasm between understanding the principles of human genetics and medicine's ultimate aim — easing human suffering.

The discovery of the double-helical structure of DNA by James Watson and Francis Crick in **1953** created great hope that this situation would change. Although they received the Nobel Prize for their discovery in **1962**, it was not until the **1970s** that researchers had sufficient tools in their molecular biology "arsenal" to begin even rudimentary manipulations of DNA and to start zeroing in on the candidate genes responsible for genetic illnesses. In **1983** — 30 years after Watson and Crick's seminal paper in *Nature* — a genetic marker linked to Huntington's disease was found on human chromosome 4.

Following the breakthrough in Huntington's disease, the pace of genetic discoveries began to quicken. A few years later, in **1986**, researchers identified the gene for chronic granulomatous disease on the X chromosome, and the genes for Duchenne muscular dystrophy and retinoblastoma were discovered shortly thereafter. Then, in **1989**, an international team of investigators identified the genetic defect responsible for cystic fibrosis, the most common genetic disorder among Caucasians.

These landmark accomplishments convinced many in the worldwide scientific community that there was an urgent and compelling need to obtain the complete sequence of all 24 human chromosomes — roughly three billion bases in total. In **1988**, the U.S. Congress funded both the National Institutes of Health (NIH) and the Department of Energy (DOE) to "coordinate research and technical activities related to the human genome." NIH established the Office of Human Genome Research in **1989**, appointing James Watson as its first Director. Together, the NIH and DOE programs joined forces with international partners and launched the Human Genome Project.

The Office of Human Genome Research soon evolved into the National Center for Human Genome Research (NCHGR), with Francis Collins, the co-discoverer of the cystic fibrosis gene, as its new Director. In recognition of its accomplishments and key role in advancing the mission of NIH, NCHGR was granted Institute status in **1997**, becoming the National Human Genome Research Institute (NHGRI).

In April **2003**, a mere 13 years after the Human Genome Project's launch, NHGRI and its partners completed the human genome sequence, and the world celebrated the generation of the full genetic blueprint of a human being. In an effort to interpret the human genome sequence by detailed comparisons with evolutionary relatives, NHGRI and others in the genomics community then set out to sequence the genomes of many other members of the animal kingdom. The availability of these additional genome sequences, coupled with ever-improving experimental and computational methods for inferring function from genomic data, has provided researchers powerful new ways to study the role of genetics in human health and disease.

THE DIVISION OF INTRAMURAL RESEARCH
From Base Pairs to Bedside

Although the completion of the Human Genome Project was a magnificent achievement, it was actually just the first step toward fulfilling the goal of improving human health through genetics-based studies. With this goal in mind, in 1993, the Director of NIH established a dynamic, cutting-edge Intramural Program within the then-named National Center for Human Genome Research to serve as the focal point for genetics and genomics research at NIH and worldwide. It was envisioned that this program would develop novel genomic expertise, technologies, and approaches that other research institutions, including other NIH Institutes, could then use for studying the various hereditary disorders afflicting humankind.

Today, the NHGRI Division of Intramural Research is one of the premier research programs working to unravel the genetic basis of human disease. During its short existence, the NHGRI Intramural Program has made many seminal contributions to the fields of genetics and genomics. Highlights of NHGRI investigators' accomplishments in recent years include:

- Identification of the genes responsible for numerous human genetic diseases
- Development of new paradigms for mapping, sequencing, and interpreting the human and other vertebrate genomes
- Development and application of DNA microarray technologies for large-scale analyses of gene expression
- Creation of innovative computational tools for analyzing large quantities of genomic data
- Generation of animal models critical to the study of human inherited disorders
- Design of novel approaches for diagnosing and treating genetic diseases

NHGRI investigators, along with their collaborators at other NIH Institutes and various research institutions worldwide, have embarked on a number of high-risk efforts to unearth clues about the complex genetic pathways involved in human diseases. These efforts have used genomic sequence data from human and other species to pinpoint numerous disease genes, including those implicated in cancer, diabetes, premature aging, hereditary deafness, various neurological, developmental, metabolic, and immunological disorders, and others. These studies have brought together NHGRI basic scientists and clinicians in collaborations aimed at developing better approaches for detecting, diagnosing, and managing these often-debilitating genetic diseases.

"The NHGRI Division of Intramural Research consists of an amazing group of investigators leading productive programs, making seminal contributions in genetics and genomics, and blazing new paths for scientific and clinical discoveries — all while maintaining a spirited and highly collegial environment that fosters excellence."

Eric Green, M.D., Ph.D.

Scientific Director
National Human Genome Research Institute

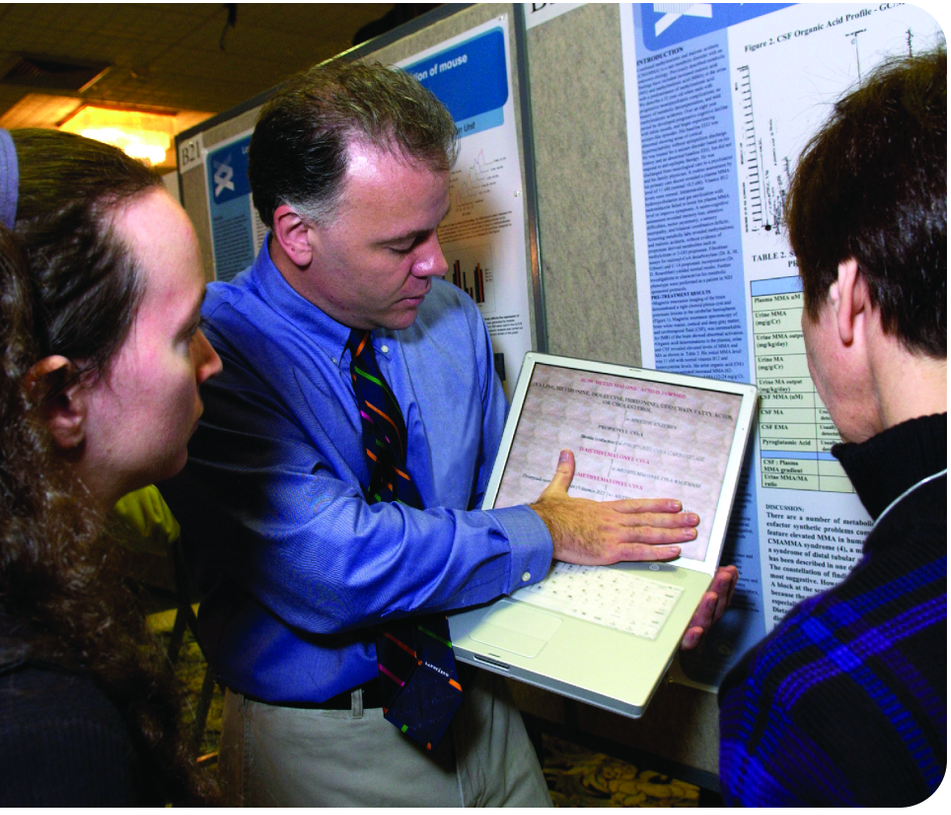
Organization and Structure

The NHGRI Division of Intramural Research plans and conducts a broad program of laboratory and clinical research on the main NIH campus in Bethesda, Maryland, as well as at other sites such as the Bayview campus in Baltimore, Maryland and the Twinbrook complex in Rockville, Maryland. The Division is led by the Scientific Director, with input from its Board of Scientific Counselors — an external group that provides expert oversight for all research and training ongoing in the NHGRI Division of Intramural Research. Clinical research is overseen by the Clinical Director, who provides guidance and support for all NHGRI investigators involved in patient-based research.

The NHGRI Division of Intramural Research has seven Branches, each organized around specific areas of scientific inquiry:

- Cancer Genetics Branch
- Genetic Disease Research Branch
- Genetics and Molecular Biology Branch
- Genome Technology Branch
- Inherited Disease Research Branch
- Medical Genetics Branch
- Social and Behavioral Research Branch

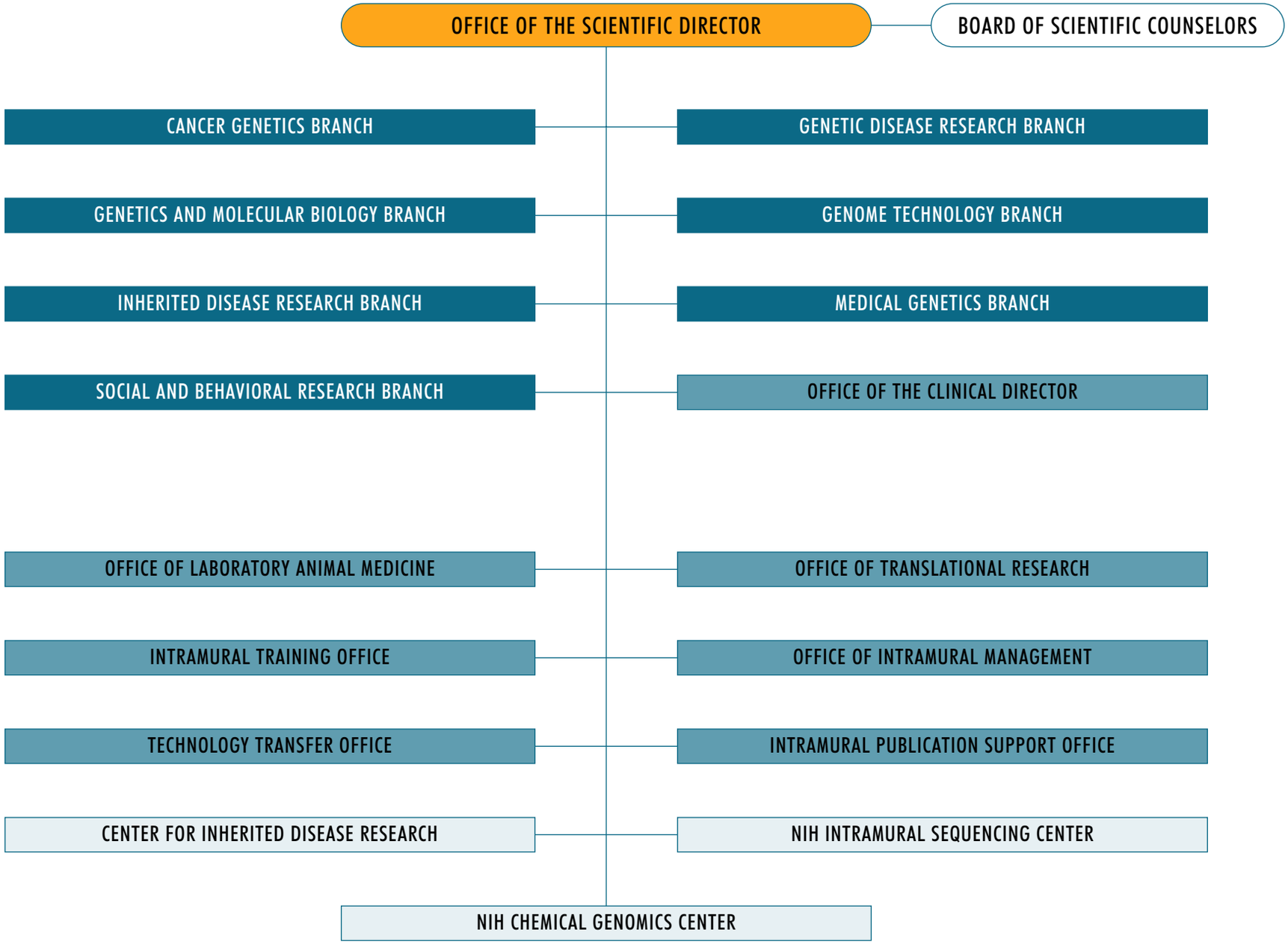
Each of the more than 40 NHGRI investigators is assigned to one of these Branches, although these boundaries are artificial in many ways since there are significant interactions among investigators and trainees in different Branches. There also is considerable overlap in their respective areas of research. NHGRI investigators have appointments similar to those in most



academic research departments. *Senior Investigators* have tenured positions at NIH. Individuals currently on the tenure track (but not yet tenured) are called *Investigators*. All Senior Investigators and Investigators lead Sections, which are individual laboratories within the Branches. *Associate Investigators* are akin to research- and clinical-track faculty at universities, serving a variety of critical roles within NHGRI (but are not part of the NIH tenure system). Some Associate Investigators head Units, which reflect their research groups. Finally, there are *Adjunct Investigators*, individuals with significant scientific interactions with NHGRI, but whose primary appointment resides in another NIH Institute.

The NHGRI Division of Intramural Research is also supported by a number of other scientific and administrative entities, including a series of cores, centers, and offices. Together, all of the elements of the NHGRI Division of Intramural Research share a common aim — to deliver on the promise of genetics and genomics by connecting the base pairs of the Human Genome Project to the bedside of those afflicted with a genetic disease.

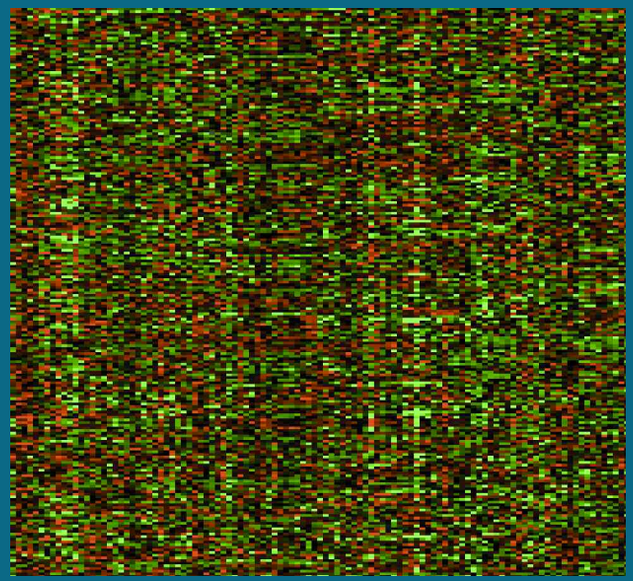
NHGRI DIVISION OF INTRAMURAL RESEARCH

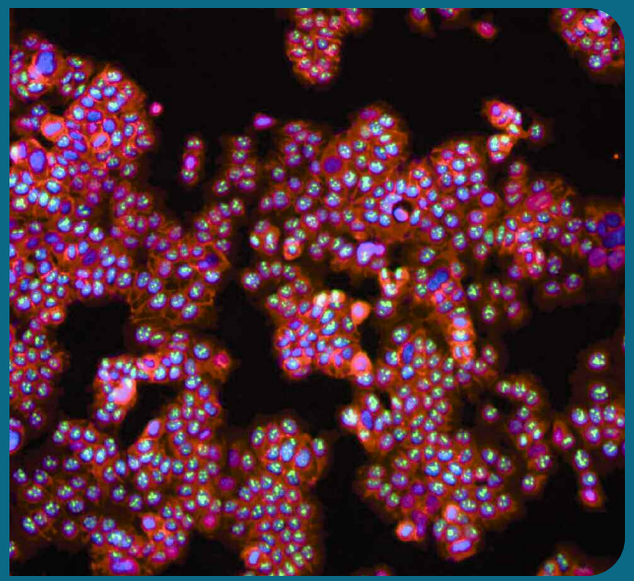


"This is **a fascinating time to be involved in cancer genetics**. We now have the tools and resources to understand the ways in which cancer both develops and progresses through the human body."

Elaine Ostrander, Ph.D.
Chief, Cancer Genetics Branch

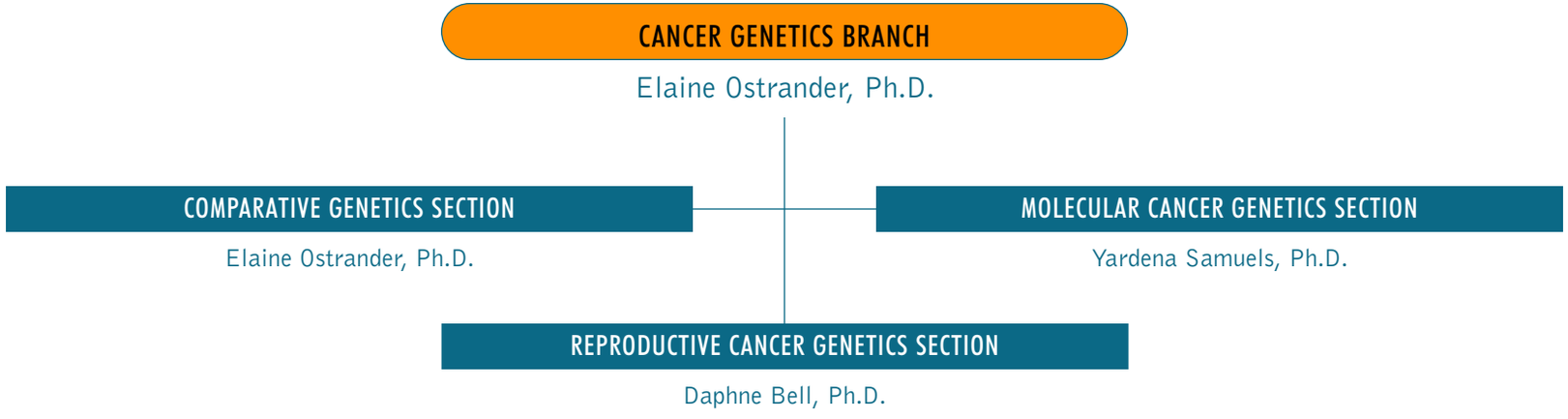
CANCER GENETICS BRANCH





Researchers in the Cancer Genetics Branch (CGB) seek to identify and study genes that contribute to cancer susceptibility and progression. CGB scientists are working to identify genetic variants involved in melanomas and in prostate, ovarian, and endometrial cancers. Their research aims to understand the relationship between genetic variation and cancer progression, as well as the functional role of specific genetic variants in normal and disease states.

Susceptibility to cancer may be inherited or result from the accumulation of specific genetic changes over time. CGB investigators are particularly interested in how genetic variants contribute to susceptibility to aggressive cancers in the general population. Towards that end, their projects focus on the use of high-risk families and population based case control studies to identify specific germline variants responsible for susceptibility to breast and prostate cancer. Studies of ovarian and endometrial tumors, as well as melanomas, are also underway to determine the genes responsible for both susceptibility and progression in these types of cancers. Studies of canine families that capitalize on new approaches in comparative genomics are providing the opportunity to identify susceptibility loci associated with other genetically complex cancers (such as sarcomas and bladder cancer) that have traditionally been difficult to study in human families. Ultimately, CGB scientists are seeking to understand the life history of tumors using state of the art genomic approaches.


CANCER GENETICS BRANCH
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ELAINE A. OSTRANDER, Ph.D.

Dr. Ostrander's laboratory maps genes responsible for cancer susceptibility in canines and humans. Cancer is the number one killer of dogs, and studying the major cancers in dogs provides a remarkably valuable approach for developing a better understanding of the development of cancer in humans. The clinical presentation, histology, and biology of many canine cancers very closely parallel those of human malignancies, so comparative studies of canine and human cancer genetics should be of significant clinical benefit to both.

Pedigrees of dogs are large, multigenerational, and the result of directed matings, all of which favor the expression of recessive disorders, such as cancers. Using information from these pedigrees, Dr. Ostrander's laboratory has constructed high-density comparative maps of the canine genome, and is using those resources as well as the 7.5x whole genome assembly of the dog to map genes for bladder cancer, Addison's disease, hip dysplasia and osteoarthritis. Her group has also undertaken a polymorphism study to determine the interrelatedness of dog breeds. This study demonstrated that differences among breeds account for about 30% of genetic variation within dogs. In addition, it demonstrated that genotyping could be used to assign 99% of individual dogs to their correct breeds. Phylogenetic analysis also allows several breeds with ancient origins to be separated from the remaining breeds with modern European origins. This work sets the stage for Dr. Ostrander and her collaborators to begin the cloning of genes identified in linkage studies by identifying ancestral chromosomes that contribute the same genetic mutation to a multitude of dog breeds. Related to this work are projects aimed at identifying genes controlling morphologic differences between breeds, such as the genes controlling overall body size, leg length and width, and skull shape.

Dr. Ostrander's laboratory is also interested in prostate and breast cancer susceptibility genes in humans. With their collaborators, they have undertaken a genome-wide scan for prostate cancer susceptibility genes in a cohort of 254 high-risk families. Their data thus far demonstrate that prostate cancer is genetically very heterogeneous and that multiple loci are likely to be important. Loci on chromosomes 1, 8, 17, and 22 are the focus of current studies. In a population-based, case-control study of middle-aged men and prostate cancer, Dr. Ostrander's group has investigated the role of several hundred candidate SNPs that comprise various pathways of interest. These data are currently under analysis.

Finally, Dr. Ostrander's laboratory is interested in the frequency and distribution of mutations in known cancer susceptibility genes in the general population (that is, other than in high-risk families). They recently completed two screening studies looking for *BRCA1* and *BRCA2* mutations in women from the general population with breast cancer. The first study, an analysis of 1,600

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women, was performed as part of the Shanghai Breast Self Examination Trial, involving 267,000 women in Shanghai, China. The second study is an ancillary project studying data from 2,300 Caucasian and African-American women between the ages of 35 and 64, built on the foundation of the large National Institute of Child Health and Human Development Women's CARE Study. Dr. Ostrander's group currently is analyzing the data to identify both protein-truncating and missense changes that are likely to be associated with disease. To accomplish the latter, they are using comparative genomics—cloning and sequencing the *BRCA1* and *BRCA2* genes from lower mammals and identifying regions that are either highly conserved or evolving under positive selection to identify missense changes likely to be disease-associated. Such changes are likely to represent weakly penetrant disease alleles for breast cancer, and will be the focus of new functional studies.

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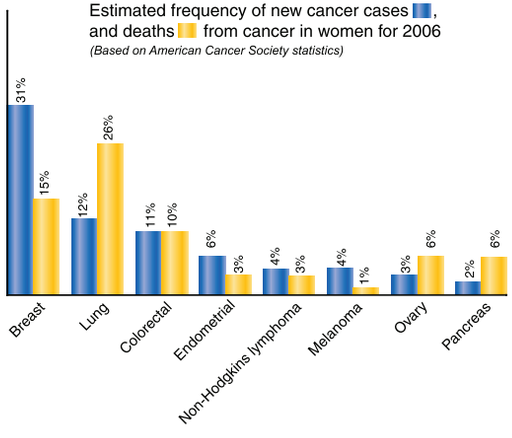
DAPHNE W. BELL, Ph.D.

The goals of Dr. Bell's laboratory are to understand the genetic alterations that lead to clinically aggressive subtypes of endometrial cancer, to determine whether there is a heritable basis for familial endometrial cancer, and to uncover the genetic risk factors that promote the development of endometrial cancer at a young age.

Endometrial cancer, which affects the endometrium (the lining of the uterus), is the most common gynecological malignancy in the United States. There are 41,200 new cases of endometrial cancer diagnosed each year, along with 7,350 deaths attributable to this disease. Most patients present with "type I" tumors with endometrioid histology and have a good prognosis, but around 15 percent are diagnosed with "type II" serous or clear cell tumors that are clinically aggressive. Patients with type II tumors have a five-year survival rate of less than 40 percent.

Over the past few years, it has become evident that certain types of chromosomal and genetic alterations may be exploited as therapeutic targets in the treatment of certain malignancies. For example, the drug imatinib is highly effective in the treatment of chronic myelogenous leukemia with an underlying BCR-ABL chromosome translocation. Similarly, a subset of non-small cell lung cancers with specific mutations that affect the catalytic domain of the epidermal growth factor receptor (EGFR) responds to the drugs gefitinib and erlotinib. Dr. Bell aims to identify the genetic alterations that cause serous and clear cell tumors of the endometrium en route to developing new therapies for type II endometrial cancers.

Towards that end, her research group is using high-density single-nucleotide polymorphism (SNP) genotyping to identify genome-wide copy-number changes and loss-of-heterozygosity events in type II endometrial tumors. Parallel studies include extensive collaborations with the NIH Intramural Sequencing Center for performing mutational screens of all exons that encode the catalytic domains of 90 known tyrosine kinases. In addition, these efforts include searching for structural chromosomal alterations in endometrial tumors. Once specific genetic alterations are found to be associated with tumor development, more extensive examination of the clinicopathologic features of mutation-harboring tumors will be performed in an attempt to implicate individual genes or functional pathways that could be targeted for therapeutic intervention.



An inherited susceptibility to endometrial cancer is usually associated with increased risk for hereditary non-polyposis colorectal cancer (HNPCC). In fact, endometrial cancer is the second most common form of malignancy diagnosed in women with HNPCC. Susceptibility to endometrial cancer is also associated with an increased risk for Cowden syndrome, which first produces symptoms in the late twenties and causes multiple noncancerous growths called hamartomas on the skin and mucous membranes. Cowden syndrome is also linked to the development of breast, thyroid, and endometrial malignancies. There are a few families that lack either the clinical manifestations or molecular characteristics of HNPCC or Cowden syndrome, yet still have a clustering of endometrial cancer cases, which suggests a tissue-specific etiology. It is possible that predisposition to endometrial cancer in these families is linked to one or more low-penetrance susceptibility alleles rather than a single highly-penetrant mutation.

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Dr. Bell brings valuable expertise to her studies of endometrial cancer. Previously, she discovered a cancer-susceptibility gene (*CHEK2*) that has been implicated in the development of breast and prostate cancer. She also defined the genetic alterations responsible for clinical sensitivity and resistance of lung cancer patients to the tyrosine kinase inhibitor gefitinib (Iressa); her group plans similar evaluations of the usefulness of potential therapies for type II endometrial cancer.

Within the general population, women with an increased risk of developing endometrial cancer usually have an imbalance of estrogens and progesterones that are caused by one or more risk factors, including obesity, diabetes mellitus, polycystic ovary syndrome, early menarche, nulliparity, and late menopause. Up to a quarter of endometrial cancer patients diagnosed before age 50 have one or more of these risk factors, but not all women with these risk factors develop endometrial cancer; thus, individual genetic variations appear to also affect disease susceptibility. To examine this phenomenon, Dr. Bell will perform case-control genetic association studies in order to establish what underlying genetic risk factors influence the development of endometrial cancer in premenopausal women, with the hope of making the predictive equation even more precise.

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YARDENA SAMUELS, Ph.D.

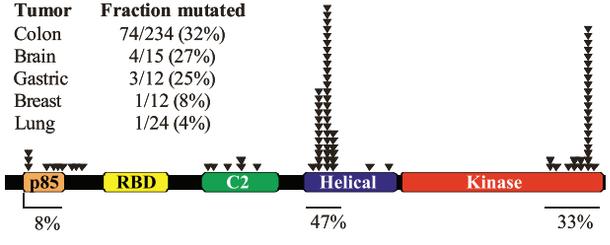
Genetic alterations, including point mutations, deletions, and amplifications, occur in every cancer cell. These changes are known to occur in oncogenes, tumor suppressor genes, and stability genes. Although many of these genes have been identified for certain types of tumors, most remain to be discovered. Dr. Samuels uses high-throughput DNA sequencing and whole-genome genotyping to identify novel mutations in gene families that regulate signal transduction in late-stage cutaneous melanoma.

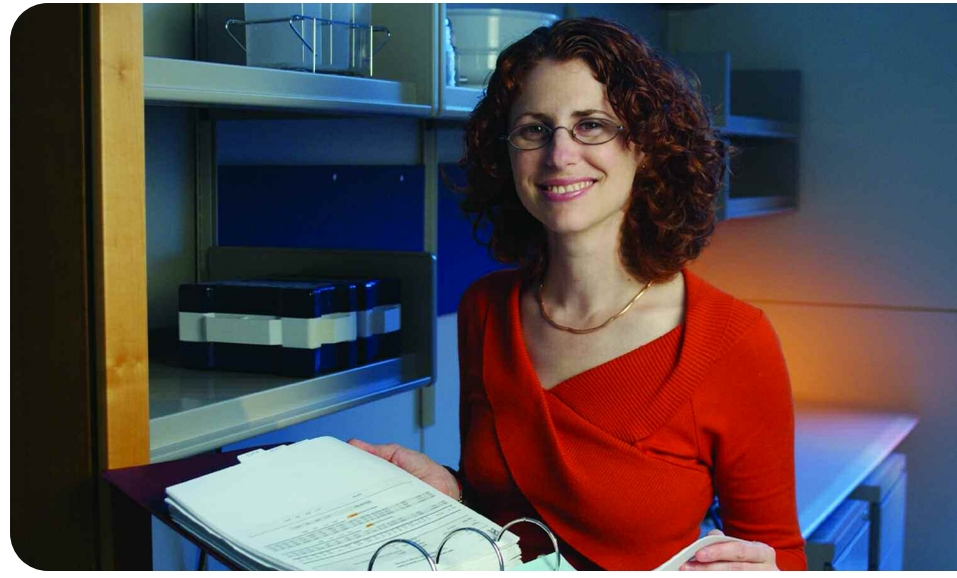
Melanoma arises as a result of the malignant transformation of melanocytes, the pigment-producing cells located in the bottom layer of human skin. It is the most common fatal skin cancer, and its incidence has increased 15-fold in the United States over the last 40 years, faster than any other malignancy. Each year in the United States, nearly 60,000 people are diagnosed with malignant melanomas and more than 8,000 will die of the disease.

As melanomas penetrate farther into the skin, treatment options, cure rates, and survival rates decrease. In early stage disease, the tumor is in its radial growth phase (RGP) and stays on the skin's surface. These tumors can usually be completely removed by simple surgery. Once the malignancy switches to the vertical growth phase (VGP), it penetrates through the skin and is able to metastasize to the lymph nodes and other sites in the body, rendering standard surgical interventions ineffective. Five-year survival rates for VGP melanoma range from 13 to 69 percent, and no treatment has yet been found to be universally effective.

Melanoma disease progression is assumed to be associated with the accumulation of genetic mutations over time. The genes that have already been implicated in the development of melanomas include *CDKN2A*, *NRAS*, and *BRAF*. Dr. Samuels is using high-throughput DNA sequencing to search for additional mutated genes in melanoma. She is currently examining the genes encoding tyrosine and serine protein kinases, which play important roles in regulating the cellular events that lead to tumor formation; these genes are associated with a variety of human cancers and may be targets for therapeutic intervention. Identifying melanoma-associated genetic alterations in specific genes may eventually allow clinicians to understand the clinical progression of the disease, allowing them to better predict clinical course and therapeutic response. Dr. Samuels also hopes to identify new targets for drug development.

Tumor	Fraction mutated
Colon	74/234 (32%)
Brain	4/15 (27%)
Gastric	3/12 (25%)
Breast	1/12 (8%)
Lung	1/24 (4%)





Dr. Samuels' earlier work has provided her strong expertise for these studies. Specifically, she previously used high-throughput DNA sequencing to analyze the phosphatidylinositol-3-kinase (PI3K) gene family, and discovered a large number of mutations associated with colorectal cancer in the lipid kinase-encoding gene *PIK3CA*. This gene is now known to be one of the most highly mutated oncogenes in human malignancies. *PIK3CA* plays an essential role in tumor cell proliferation, and is essential for invasion *in vitro* and metastasis *in vivo*. Treatment with the PI3K inhibitor LY294002 has been shown to reduce PIK3CA signaling and to preferentially inhibit the growth of cells producing mutant PIK3CA, suggesting that therapy directed at mutant PIK3CA or its downstream targets might be beneficial for some patients.

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To identify genes regulated by mutant *PIK3CA*, Dr. Samuels performed serial analyses of gene expression (SAGE) and microarray analyses on cells containing either wild-type or mutant *PIK3CA*. She discovered that a gene called *DDIT4* (also known as *Redd1*) was upregulated six- to ten-fold in all cells containing mutant *PIK3CA* (compared to cells contained wild-type *PIK3CA*). To examine the role of *Redd1*, which may be central to the PI3KCA pathway, Dr. Samuels is 'knocking out' the *Redd1* gene in human colorectal cancer cells that contain a mutant allele of *PIK3CA*, using homologous recombination techniques. She will then evaluate the effect of *Redd1* inactivation by performing *in vitro* analyses of cell growth, migration, and invasion, and by studying *in vivo* models of metastatic disease. By doing so, she hopes to find new targets for clinical intervention, as well as gain new insights into basic tumor biology.

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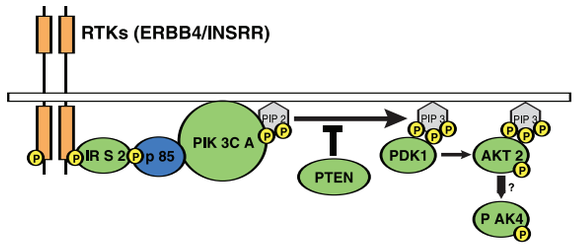
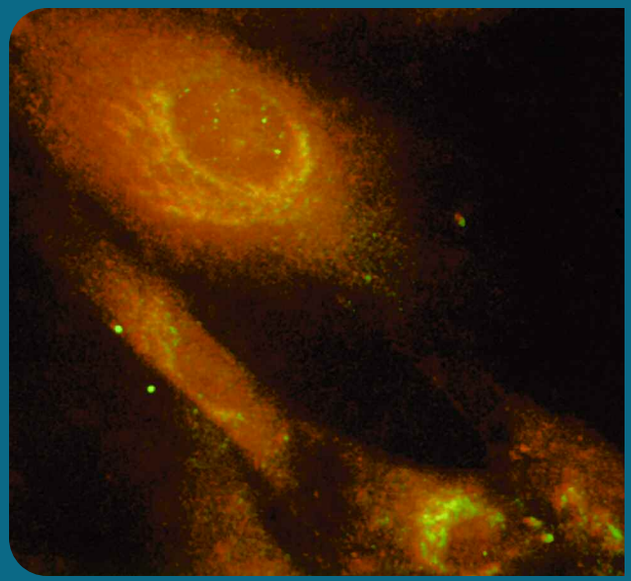
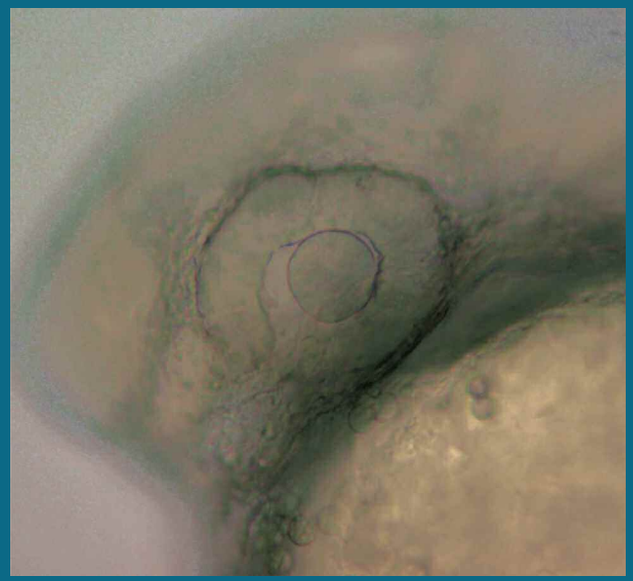


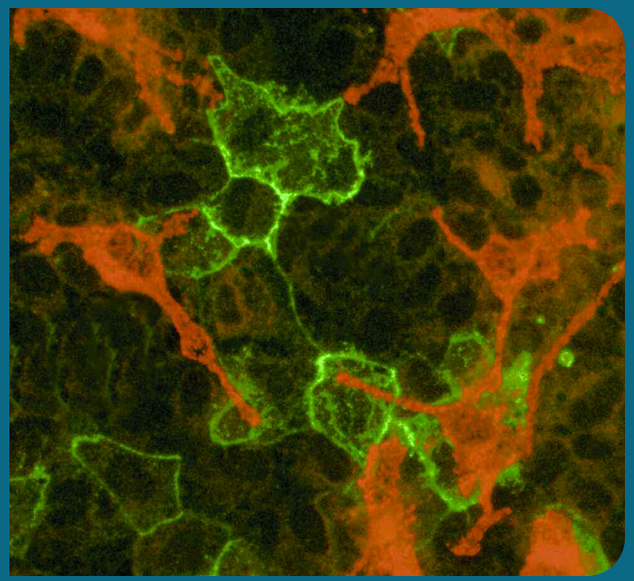
"Understanding the molecular and genomic basis of disease requires putting together many different pieces of the puzzle- **basic molecular research, animal studies, and clinical investigations**. One of the exciting things about NHGRI is that we can do all of these things in a collaborative atmosphere."

Leslie Biesecker, M.D.
Chief, Genetic Disease Research Branch

GENETIC DISEASE RESEARCH BRANCH

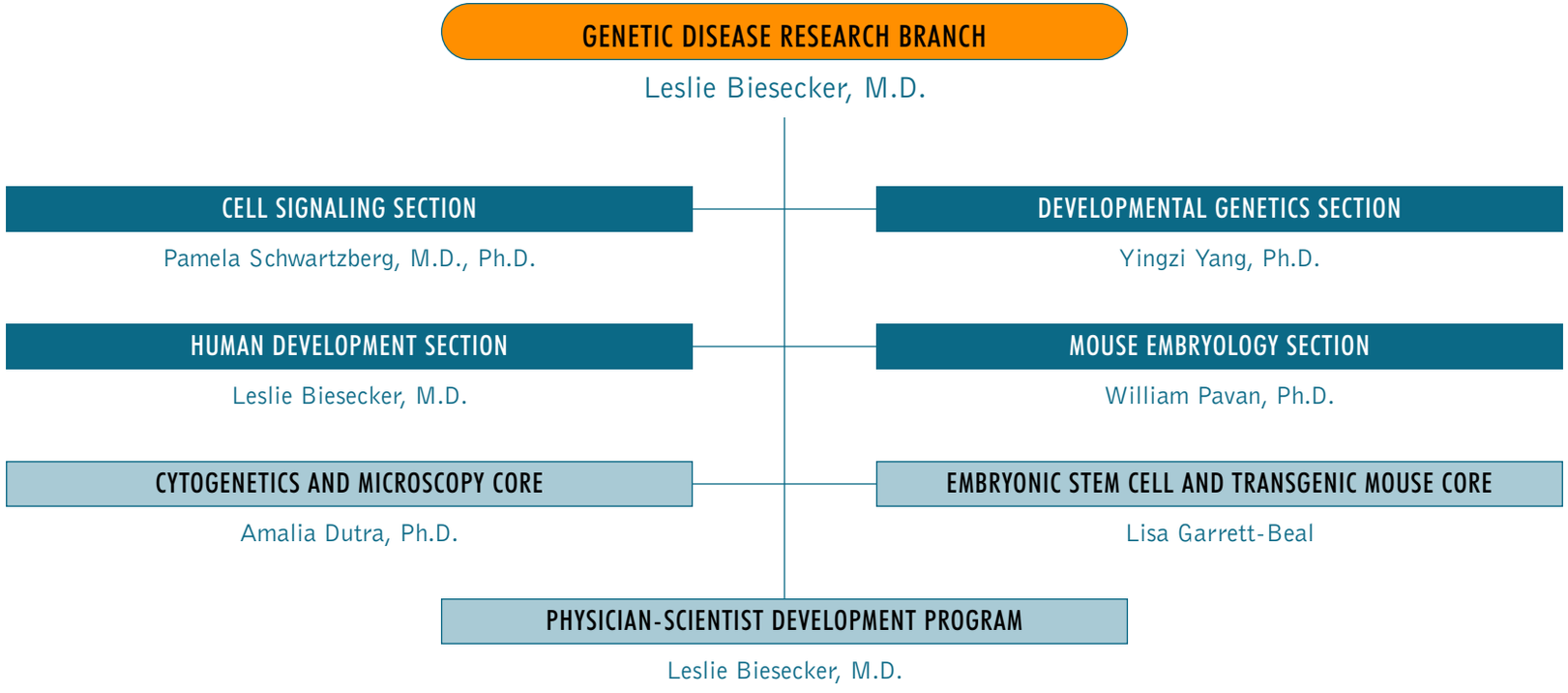






The Genetic Disease Research Branch (GDRB) uses human and mouse genetics to study the genes and proteins involved in a variety of normal developmental processes and related diseases. Branch investigators study normal and abnormal bone and limb development, pigment cell development and neurocristopathies, T helper cell maturation and defects in host defense, and the role of rare variants in common disease. These studies aim to characterize normal developmen tal and cellular pathways through the analysis of naturally occurring mutations in humans, as well as of spontaneous, engineered, and induced mutations in mice. Such efforts further our understanding of how particular mutations contribute to birth defects and diseases such as albinism, abnormal host responses, and atherosclerosis.

GDRB researchers study normal gene function, and examine the phenotypic consequences of mutations at the molecular, cellular, and whole organism level. They examine the ways in which these phenotypic effects manifest themselves through interactions with other genes and the environment. This research is accomplished through both clinical genetic studies and the use of mouse models. GDRB investigators are particularly interested in understanding normal signaling path-ways, and how defects in those pathways lead to abnormalities in morphogenesis, development, and homeostasis. The Branch also supports several more broadly defined scientific activities through its two Cores the Embryonic Stem Cell and Transgenic Mouse Core, and the Cytogenetics and Microscopy Core—and through the Physician Scientist Development Program.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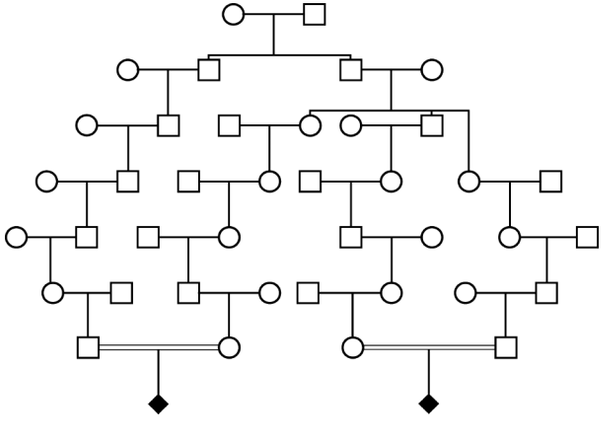
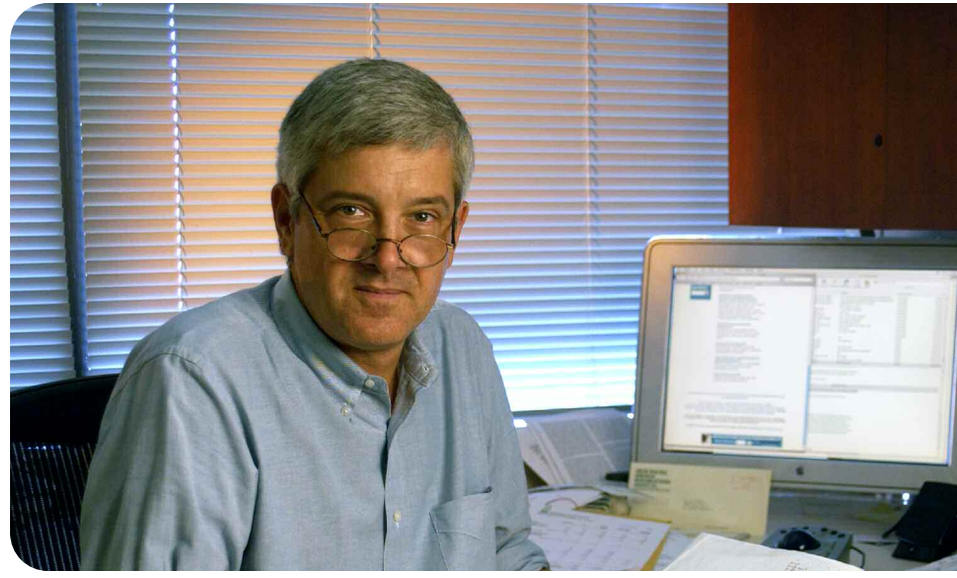
LESLIE G. BIESECKER, M.D.

Dr. Biesecker's research focuses on the role of rare genomic sequence variants in human disease. Currently, his laboratory is studying the role of rare variants in two classes of disorders: rare multiple congenital anomaly syndromes and common diseases of the cardiovascular system. The goals of his research program are to improve the medical care of patients affected by these disorders, provide generalized knowledge about the broad field of genomics and health, and better understand basic mechanisms of normal and abnormal human development.

Dr. Biesecker's group studies several multiple congenital anomaly syndromes, including Pallister-Hall syndrome, Greig cephalopolysyndactyly syndrome, McKusick-Kaufman syndrome, Bardet-Biedl syndrome, and Lenz microphthalmia syndrome. These disorders exhibit combinations of central nervous system malformations, visceral malformations, and polydactyly (extra fingers and toes). Some patients have functional complications, such as mental retardation, seizures, and visual loss. To further elucidate the clinical manifestations of multiple congenital anomaly syndromes and improve treatment approaches, Dr. Biesecker's group conducts clinical research in the Mark O. Hatfield Clinical Research Center. They also conduct field studies of populations to ascertain and evaluate patients. Several of these disorders occur frequently in closed religious sects — specifically, the Old Order Amish and Mennonites in Lancaster County, Pennsylvania and regions of Ohio and Kentucky. His group maintains close relationships with local clinics that serve these populations. In the laboratory, his group performs classical positional-cloning studies to find the genes that are altered in these syndromes, determines genotype-phenotype correlations, and uses animal models to investigate the pathogenetic mechanisms of these disorders. For example, they determined that two multiple congenital anomaly syndromes — oculofaciocardiodental syndrome (OFCD) and MAA2-associated Lenz microphthalmia — are allelic because of their phenotypic overlap. This investigation identified a single-base substitution in the *BCOR* gene





(encoding BCL-6-interacting corepressor) on chromosome Xp11.4 in affected males from a family with Lenz syndrome, and different loss-of-function mutations in the *BCOR* gene in seven families affected with OFCD.

In addition, Dr. Biesecker's group is working to improve the diagnosis and management of Proteus syndrome, a rare and severe type of segmental overgrowth. It is a complex disorder with multisystem involvement and great clinical variability. The patchy overgrowth manifestations of Proteus syndrome are believed to result from somatic mosaicism of a dominant lethal gene defect, but the gene locus has yet to be identified. Dr. Biesecker's laboratory is testing this hypothesis by comparing tissues of affected and unaffected patients, and screening those tissues for alterations in gene structure or expression. They are also determining the range of manifestations, severity, and natural history of Proteus syndrome with a longitudinal study. Through these investigations, Dr. Biesecker's group has found an association between Proteus syndrome and two serious complications — massive pulmonary embolism and tumor predisposition.

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A new area of research for Dr. Biesecker's group, the ClinSeq project, is studying the use of large-scale medical sequencing (LSMS) in a clinical research setting. By sequencing targeted regions of a person's genome and returning relevant and individual results to that person, this project is beginning to explore some of the technical, medical, and genetic counseling issues that accompany the implementation of LSMS in the clinical setting. Specifically, ClinSeq aims to develop the technological and procedural infrastructure to facilitate this type of research and demonstrate that it is feasible to sequence and interpret large amounts of genomic sequence data and return individual results to subjects. In this study, patients are evaluated in the NIH Clinical Research Center for a common set of cardiovascular phenotypic features, including coronary artery calcification, lipid profiles, and blood pressure. For each clinical subject, functional regions of several hundred candidate genes will be sequenced at the NIH Intramural Sequencing Center (NISC). This study will contribute to our understanding of the relative contributions of rare versus common genetic variants to common disease. In the future, ClinSeq's clinical focus will broaden, and additional sets of genes will be sequenced.

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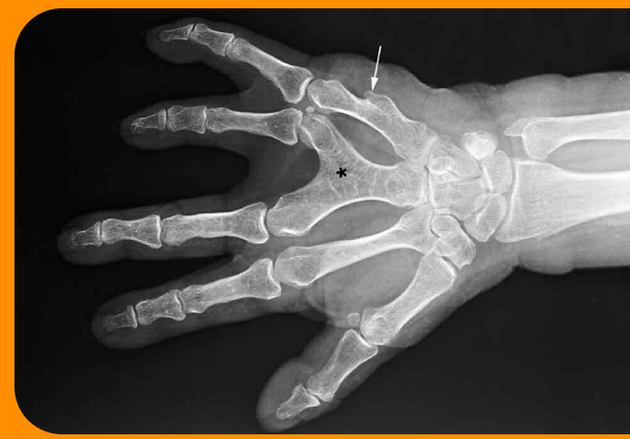
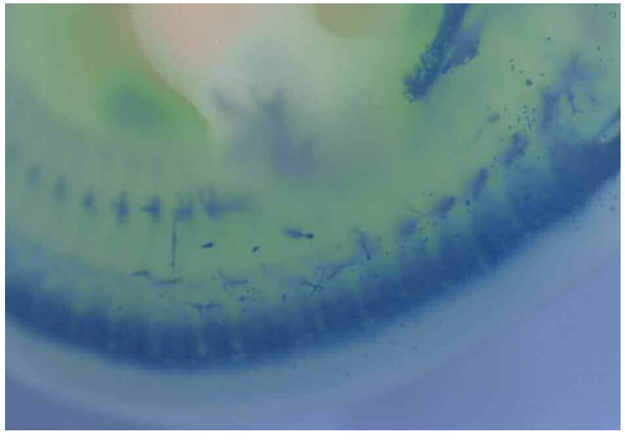


STACIE K. LOFTUS, Ph.D.

Dr. Loftus' research focuses on the genetic and cellular processes that control mammalian development, with the goal of developing a better understanding of inborn errors of embryonic development. Although finding the gene(s) responsible for such conditions does not automatically lead to a cure, such findings can give important clues about what is going wrong at the cellular level, and animal models carrying these genetic alterations can provide researchers with useful ways to test potential therapies.

As part of the Mouse Embryology Section, led by Dr. William Pavan, Dr. Loftus is analyzing the molecular and genetic basis of neural crest development. Neural crest cells, which appear at the top of the neural tube in early embryos, are pluripotent (i.e., able to differentiate into many cell types). They migrate through the body and develop into a variety of tissues, including cells of the peripheral nervous system, melanocytes, cartilage, and bone. Errors in neural crest cell development, thus, can lead to a wide array of human diseases, such as albinism, melanoma, and neurocristopathies.

The Mouse Embryology Section is particularly interested in Waardenburg syndrome, a congenital peripheral nervous system disorder that can cause facial abnormalities, lack of pigment in several regions, and deafness. Patients with Waardenburg syndrome also may lack peripheral nervous system innervation of the gut. Several years ago, Dr. Pavan's laboratory found that mutations in a transcription factor, SOX10, disrupt neural crest development in mice and are responsible for neural crest defects in some individuals with Waardenburg syndrome. Dr. Loftus has been developing technologies to clarify the relationship between SOX10 and two other transcription factors that are altered in Waardenburg syndrome (MITF and PAX3), identify their downstream target genes, and specify the effects those gene products have on normal neural crest cell development.



As a way to identify downstream targets of these transcription factors, Dr. Loftus uses DNA microarray analysis to study gene expression differences in neural crest-derived cell lines. Using this information, she seeks to identify genes (or combinations of genes) that govern neural crest cell development at each stage of the development process. She is specifically interested in finding the genes that encode the molecular signals that start neural crest cells migrating through the embryo, ascertaining whether the same genes determine the type of cell a neural crest cell ultimately becomes, and finding the contributing factors intrinsic to each cell in determining whether it becomes a glial cell, a melanocyte, or part of the jaw. She is also investigating how the extracellular environment, through which neural crest cells must pass, contributes to their development.

Dr. Loftus has developed a strain of transgenic mice that is useful for studying neural crest cells *in vivo* in normal and gene-defective disease states. In addition, she studies other mouse disease models to identify and

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understand the underlying defects in seemingly similar genetic disorders in humans. For example, in earlier work, Dr. Loftus used a mouse model to clone both the mouse and human gene responsible for Niemann-Pick C disease, a rare lipid storage disorder that severely damages the liver, spleen, and nervous system and is fatal to most patients by their teens. She continues to study the underlying defects in this condition. In addition, she is studying acinar cell apoptosis, or programmed cell death of the pancreatic cells that secrete digestive enzymes. This defect in mice leads to malnutrition, growth inhibition, and a compromised immune system. Using this mouse model, Dr. Loftus is working to identify the responsible gene and to determine whether a homologous gene in humans is responsible for a subset of Shwachman-Diamond syndrome patients who exhibit a similar clinical phenotype.

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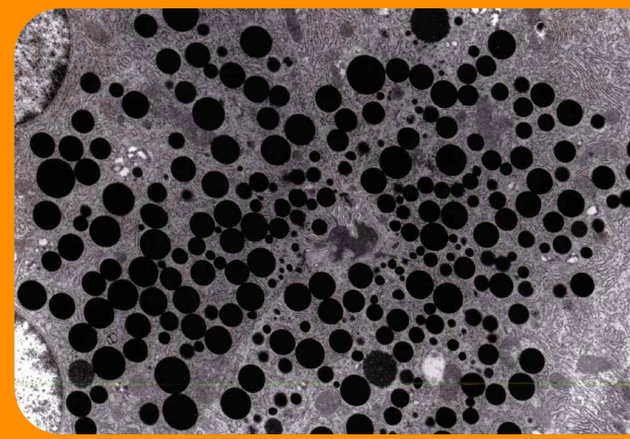
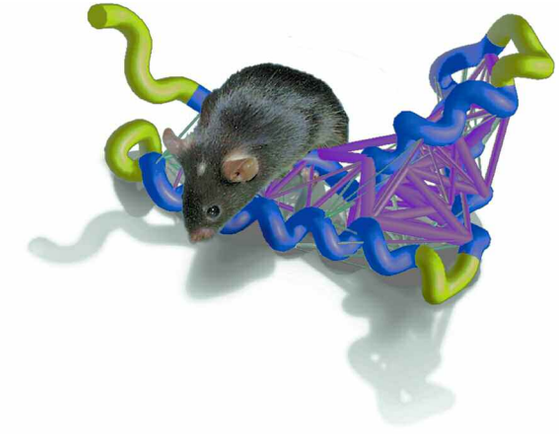


WILLIAM J. PAVAN, Ph.D.

Dr. Pavan's laboratory uses genomic tools to study how an embryo develops into a functioning organism. His group focuses on neural crest cells, a group of stem cells that differentiates into a wide variety of tissues throughout the body. This research is relevant to a range of human developmental disorders.

In vertebrate development, neural crest cells form at the top of the neural tube, which later becomes the spinal cord. They then migrate throughout the body to populate the entire peripheral nervous system and form other tissues, such as craniofacial structures, part of the adrenal gland, and melanocytes — cells that, among other functions, determine skin, hair, and eye color. When the genetic machinery that controls neural crest cell development goes awry, it can cause many human diseases, ranging from Waardenburg syndrome to cleft lip and palate.

At least 15 genes have been shown to be important for the development of neural crest cells and their descendants, but hundreds of genes are probably involved. Dr. Pavan's laboratory uses animal models — most often mice — of neural crest cell disorders to identify the genes required for normal development. His laboratory is investigating how these genes function and whether the corresponding genes in humans are responsible for any human diseases. For example, many of the genes and mechanisms involved in normal melanocyte development also are involved in the progression of melanoma, a particularly aggressive type of skin cancer. Reactivation of the genetic pathways that enable neural crest-derived cells to migrate through the embryo may be responsible for melanoma's high metastasis rate.



Mice are particularly good models for studying melanocyte genetics because many strains with differing coat patterns have been preserved over the past two centuries, and each coat pattern reflects a different, spontaneous mutation in a gene or genes governing melanocyte development. Thus, no sophisticated assays are required to identify different phenotypes; researchers simply look at coat colors and patterns.

Dr. Pavan's team has identified a number of genes important to proper neural crest formation, including, for example, the gene for the transcription factor SOX10. Their studies found that SOX10 interacts with two other transcription factors, PAX3 and MITF. All three have human counterparts, and mutations in any of them can upset the normal differentiation of neural crest cells into melanocytes and other tissues. Dr. Pavan's laboratory also isolates and cultures undifferentiated mouse neural crest stem cells *in vitro*. This makes it possible both to study precisely how specific genetic mutations derail normal development and to insert genes in the cells in an effort to correct a mutation or to make the cells differentiate in specific directions. In addition to screening existing mouse strains,

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Dr. Pavan's laboratory runs a large-scale mutagenesis-screening program, generating new mutants and seeking to find other genes that, when mutated, cause additional neural crest defects. These genes then become candidates for study as possible human disease genes.

Utilizing another set of genomic research tools, Dr. Pavan's laboratory has generated complementary DNA (cDNA) libraries representing expressed genes in several melanocyte-derived cells and cell lines. They use the cDNA data in microarray studies to find genes with similar expression patterns across different melanoma cell lines and then look for the same expression patterns in developing mouse embryos. This process has pointed the way to several previously unidentified genes that may be involved in human developmental diseases. His laboratory is now comparing genomic sequences from a wide variety of species — ranging from fish to birds to mammals — and looking for similarities in genes and in their regulatory regions.

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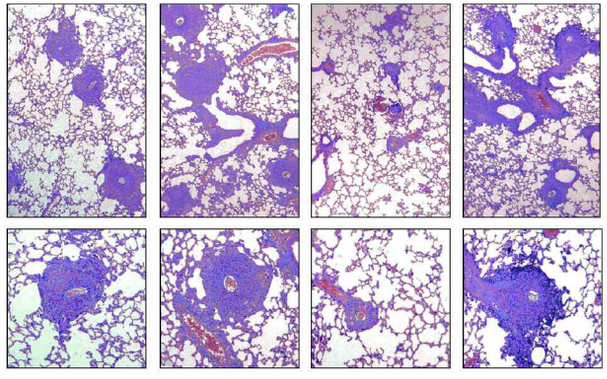
PAMELA L. SCHWARTZBERG, M.D., Ph.D.

Dr. Schwartzberg's laboratory studies signal transduction in T lymphocytes, with a particular focus on signaling molecules that affect T lymphocyte function and their ability to respond to infection. Her group generates mouse models that lack genes affecting a variety of signaling molecules to see how the loss of a particular gene affects the immune system.

They have generated "knockout" mouse models for genes involved in or related to several primary human immunodeficiency syndromes, including X-linked lymphoproliferative syndrome and X-linked agammaglobulinemia. They challenge these knockout mouse models with a wide array of infectious agents, including parasites, to study the effect of the loss of gene function on the overall immune system *in vivo* and to analyze cells from the animals *in vitro* to examine what has happened at both a biochemical and a cellular level. Studies such as these can not only help explain what is going wrong in human immune diseases, but also advance basic scientific understanding of immune system function in general, and often identify likely pathways for therapeutic research.

X-linked lymphoproliferative syndrome is a severe (and usually fatal) immune disorder characterized by a hyperactive response to viral infection, low serum antibodies, and lymphoma. It is caused by mutations in the *SH2D1A* gene, which encodes a small signaling molecule called SLAM-associated protein, or SAP. Dr. Schwartzberg's laboratory has found that mutations affecting SAP in mice cripple long-term serum antibody production. Specifically, mutations in SAP prevent T cells from signaling B cells — the antibody-forming cells of the immune system — to differentiate and form a persistent defense against infectious agents. Dr. Schwartzberg's group has further demonstrated that SAP-deficient T cells show abnormal activation of nuclear factor NFκB1, a transcription factor that plays a key role in the regulation of cellular genes involved in immune and inflammatory responses. In addition to pointing toward new lines of research for treating the disease, these insights may aid in the development of vaccines, because the generation of long-term persisting antibodies against a particular infectious agent is a crucial requirement for successful vaccine development.



X-linked agammaglobulinemia is a severe immunodeficiency characterized by very low serum antibodies and defective B cell development and function. It is caused by mutations in a Tec family tyrosine kinase called Btk, which is a key signaling molecule in B lymphocyte development. Dr. Schwartzberg's laboratory is investigating whether the Tec kinases play equivalent roles in T lymphocytes. They have generated mice carrying mutations that affect the major Tec kinases expressed in T cells to answer this question. One of these — Itk — appears to be the major Tec kinase involved in T cell function; it is required for proper intracellular calcium signaling, activation of the regulation of T cell actin cytoskeleton, activation of downstream transcription pathways, and activation of T helper 2 cell responses against parasites and allergens. Itk, therefore, is a highly promising target for research into treatments for asthma and hypersensitivity.

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Another Tec — family kinase member, Rlk, may be important for T helper 1 (TH1) cell responses and is a potential target for developing therapies for TH1-mediated diseases, including autoimmune disorders.

Finally, Dr. Schwartzberg's group investigates the genetics of Wiskott-Aldrich syndrome, a severe immunodeficiency syndrome marked by increased susceptibility to infections, eczema, and autoimmune disorders. It is caused by mutations in a gene known as *WASP* (for Wiskott-Aldrich syndrome protein). The WASP protein appears to play an important role in the T cell's actin cytoskeleton, which is required for organizing signaling molecules to permit effective T cell function. Dr. Schwartzberg's laboratory found that *WASP* fails to be activated properly in T cells from Itk-deficient mice. They are now investigating the responses of WASP-deficient mice to parasitic challenges *in vivo* to determine whether some of the observed phenotypes can be understood in the context of what is known about Itk.

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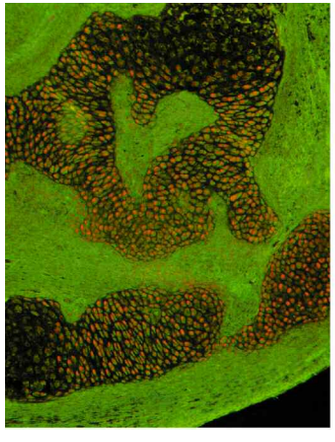
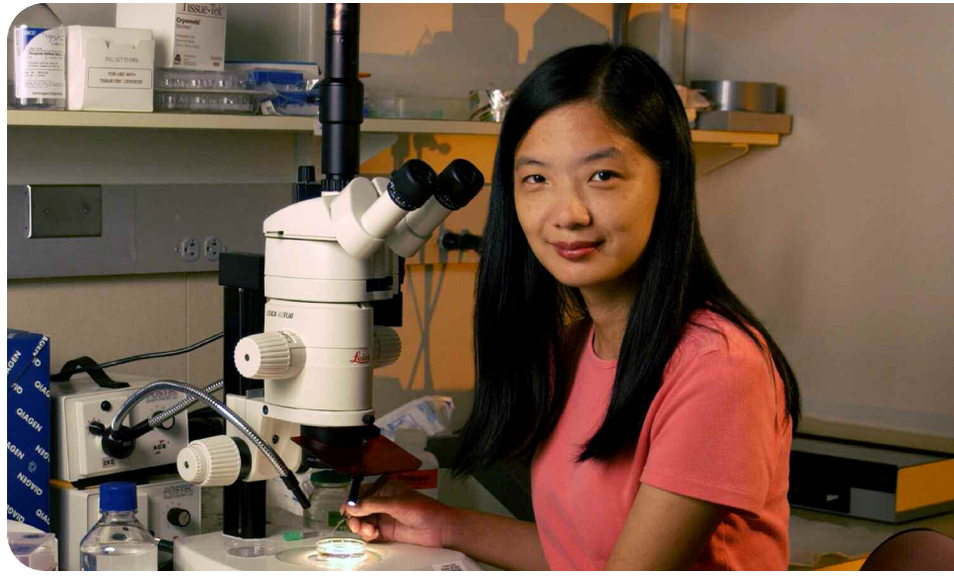
YINGZI YANG, Ph.D.

Dr. Yang studies cell-to-cell signaling in vertebrate limb development and skeletal morphogenesis. In particular, she concentrates on the Wnt and Hedgehog groups of signaling molecules, which play important roles in the formation of many organs and tissues in the developing embryo. Her goal is to understand precisely how these signaling pathways act and interact with each other and with other signaling molecules in regulating vertebrate embryonic development.

In humans and in mice, the 19 members of the Wnt group and the three members of the Hedgehog group are critically important signaling molecules that control cell proliferation and differentiation — processes essential to the developing embryo. Mutations in the genes that code for these molecules can cause devastating birth defects, including debilitating abnormalities of the central nervous system, axial skeleton, limbs, and other organs. Disruptions in Wnt and Hedgehog signaling also can promote a variety of cancers. In fact, disrupted Wnt signaling is a leading cause of colon cancer, breast tumors, and brain tumors in adults. Likewise, mutations in Hedgehog genes have been implicated in skin, brain, and pancreatic tumors. Misregulated Wnt and Hedgehog signaling also is involved in bone diseases such as osteoarthritis and bone tumors.

Limb and skeletal development are excellent models for the study of these signaling molecules because abnormalities can be easily observed. Moreover, embryos can survive with severe abnormalities in limb development, which allows scientists to study genetically the function of Wnt and Hedgehog signaling in the limb and correlate this information with human birth defects. Limb development can be divided into the early patterning phase and the late skeletal morphogenesis phase. Dr. Yang's previous work provided insight into the regulation of early limb-patterning events, while her current research addresses how signaling molecules regulate the formation of skeletal elements in the limb — a later morphogenetic process.





Dr. Yang's group is using the tools of both genetics and biochemistry to test the function of Wnt and Hedgehog proteins. They have engineered a series of mice with specific genetic mutations; the mice either lack a protein or they misexpress it in a particular pattern. The resulting phenotypes — such as a shortened limb or reduced bone formation — provide evidence of a particular protein's function. To understand how these signaling molecules work, Dr. Yang's laboratory cultures cells from mutant and normal animals *in vitro*, and exposes the cells to particular molecules or growth factors, singly or in combination, to observe the effects. In doing so, they seek to understand fundamental events in skeletal morphogenesis, and have made several discoveries in their current research efforts. Dr. Yang found that different Wnts play distinct roles in regulating chondrocyte differentiation. The canonical Wnt pathway induces synovial joint formation and determines cell differentiation of mesenchymal progenitors by inhibiting chondrogenesis while promoting osteogenesis. This work indicates that the Wnt pathway may be an important diagnostic and therapeutic target for

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cartilage and bone diseases, such as arthritis and osteoporosis. Dr. Yang's laboratory also found that non-canonical Wnt5a promotes chondrocyte differentiation by inhibiting canonical Wnt signaling activity. Overactive canonical Wnt signaling is considered a possible cause of some human cancers, particularly colon cancer. Wild-type Wnt5a may thus be a tumor suppressor in adults. In addition, Dr. Yang found that the canonical Wnt pathway interacts with the Indian hedgehog (Ihh) signaling pathway in distinct ways during different processes of skeletal morphogenesis, and Wnt5a acts in parallel pathways with Ihh to coordinate chondrocyte maturation.

Dr. Yang's group is continuing to study how Wnt and Hedgehog signaling pathways are integrated with other pathways in skeletal development and bone diseases. Dr. Yang is also actively investigating the molecular mechanisms underlying the control of cell and tissue organization by the planar cell polarity pathway in both embryonic development and adult tissue homeostasis.

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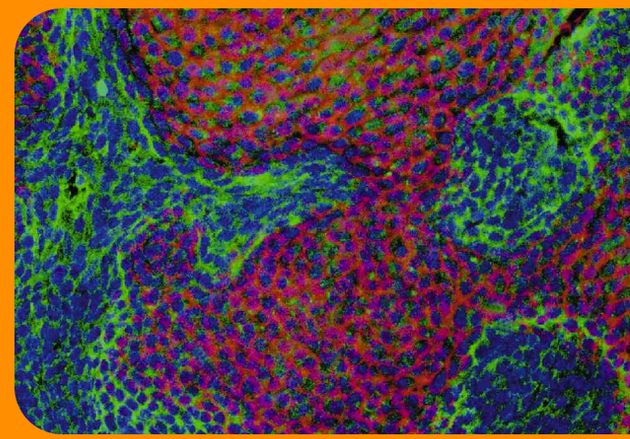
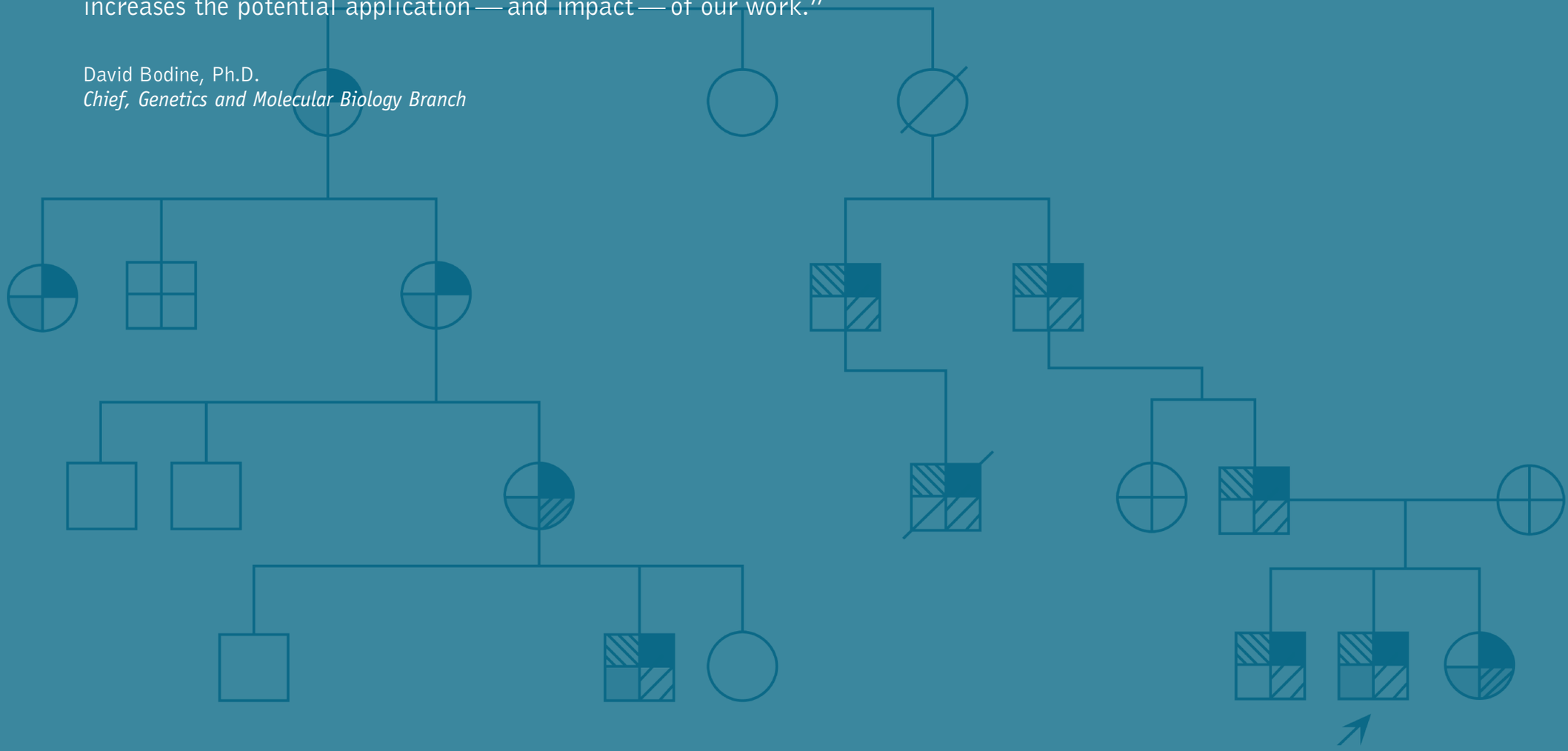
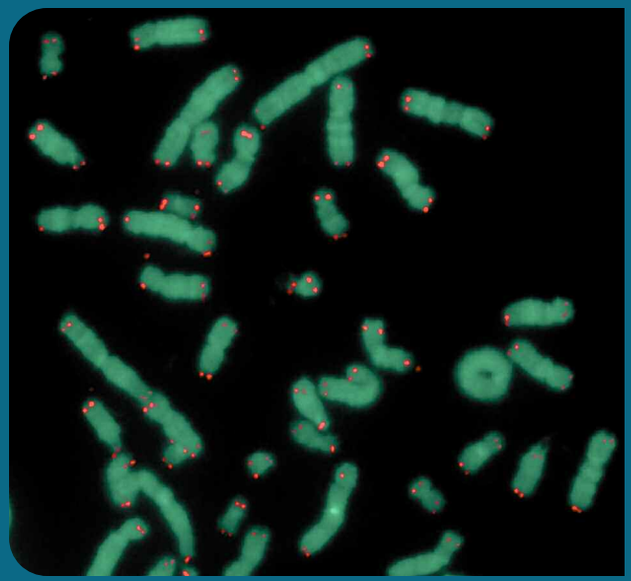


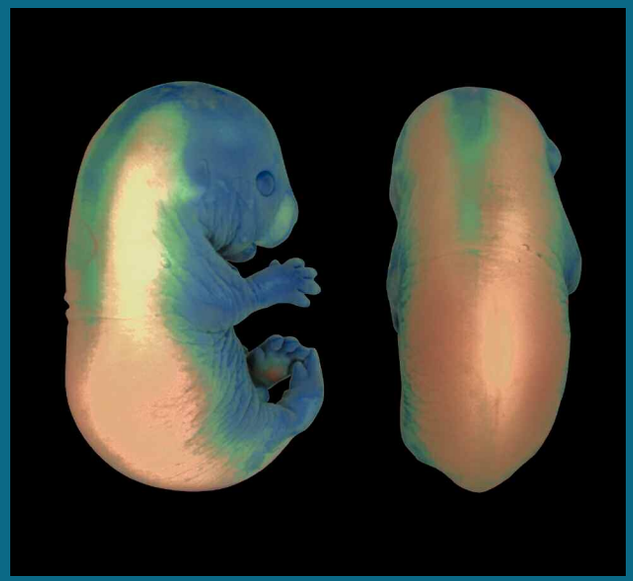
"**One of the most fascinating aspects of what we do involves not only understanding the relationship between genes and diseases, but understanding the roles these genes play in normal individuals** as well. This approach significantly increases the potential application — and impact — of our work."

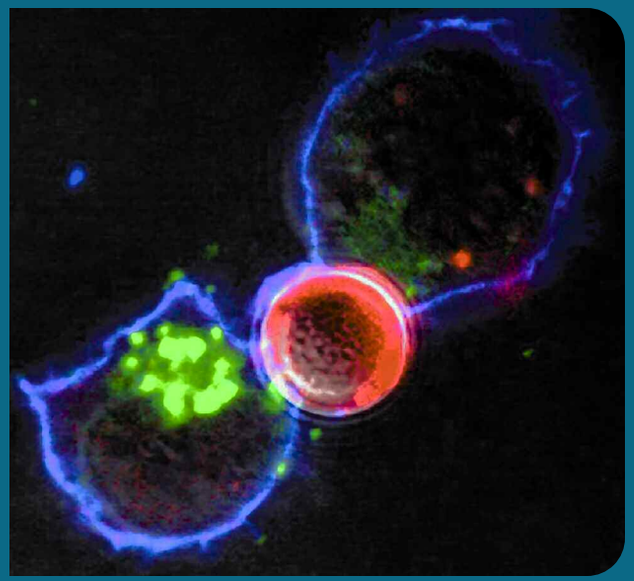
David Bodine, Ph.D.
Chief, Genetics and Molecular Biology Branch



GENETICS AND MOLECULAR BIOLOGY BRANCH

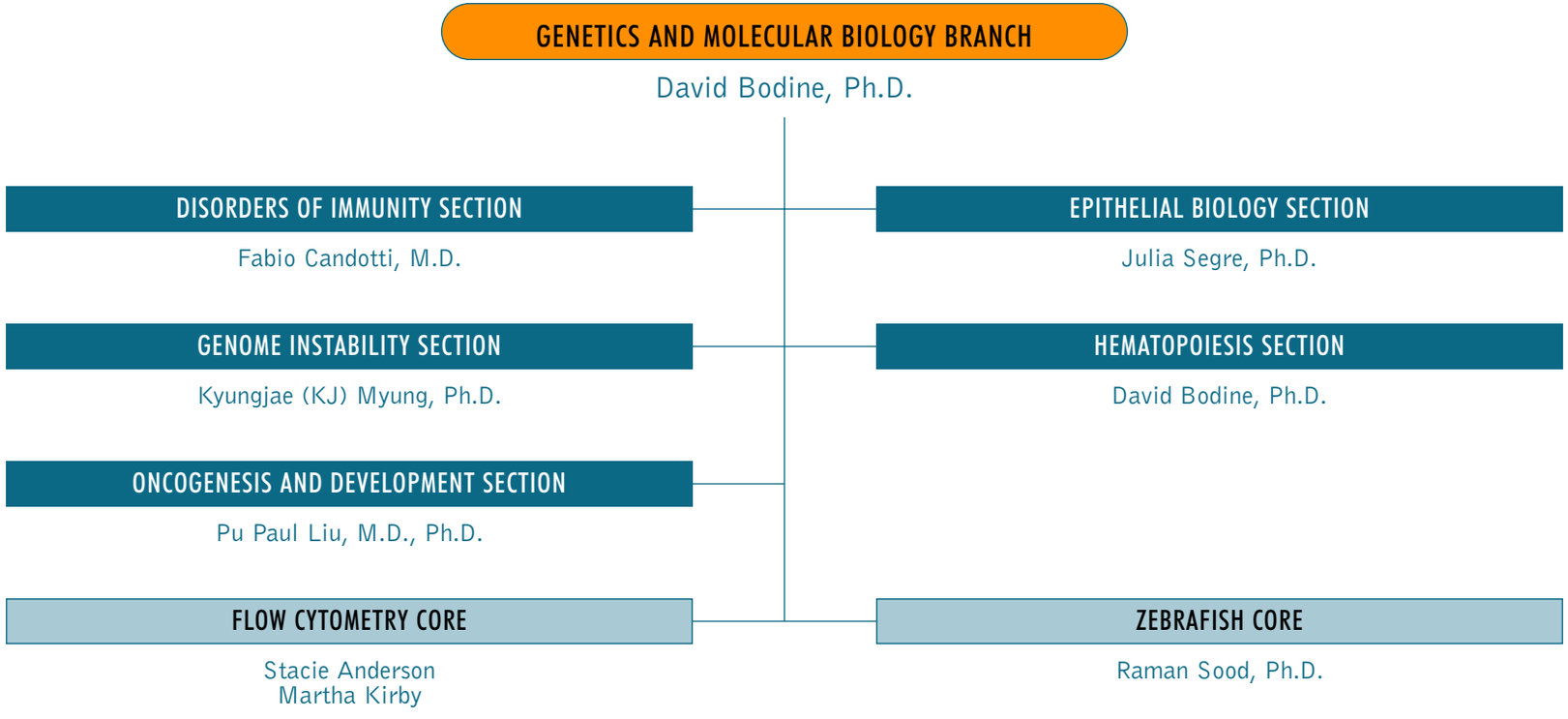






Investigators in the Genetics and Molecular Biology Branch (GMBB) use molecular genetic and genomic approaches to understand the development and function of different cells and tissues, with the goal of elucidating the mechanisms of genetic disease. The Branch integrates technologies and informational resources produced by the Human Genome Project with state-of-the-art animal models and the first-rate facilities of the NIH Clinical Center in order to develop effective treatments for both inherited and acquired diseases.

GMBB investigators conduct basic research on DNA repair and the development of skin, blood, and the immune system. Ongoing basic research in the Branch is investigating novel gene regulatory elements, new anti-leukemia drugs, novel DNA repair mechanisms, and the interaction of the skin and the immune system. GMBB investigators also perform translational and clinical studies of primary immune disorders, leukemia, solid tumors, anemia, eczema, and psoriasis. In the clinic, Branch investigators conduct clinical trials of gene therapy and stem cell transplantation for severe combined immune deficiency. These studies are augmented by two Cores within the Branch the Flow Cytometry Core and the Zebrafish Core that also serve the needs of investigators across the NHGRI Intramural Program. Future efforts of the Branch will focus on initiatives aimed at translating basic research findings so as to improve the diagnosis and treatment of human diseases.


GENETICS AND MOLECULAR BIOLOGY BRANCH
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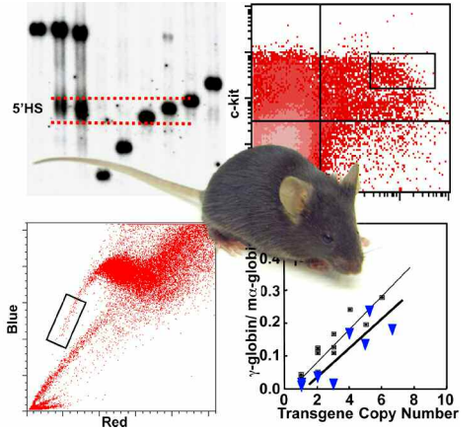
DAVID M. BODINE, Ph.D.

Dr. Bodine's laboratory investigates the genetics of pluripotent hematopoietic stem cells (PHSCs) to improve the effectiveness of bone marrow transplantation and to find better ways to use these unique cells for gene transfer therapy. A major limitation to bone marrow transplantation is the lack of availability of stem cells. His laboratory seeks to understand and control the self-renewal of PHSCs in order to amplify them, thereby improving stem cell transplantation and gene therapy techniques.

PHSCs are found mainly in bone marrow. These cells (and their progeny) proliferate extensively and differentiate into all the cell types of the peripheral blood, a process known as hematopoiesis. PHSCs also can self-renew without differentiating. These two properties allow clinicians to transplant a small number of PHSCs into a bone marrow recipient, where the PHSCs can replicate and completely reconstitute the recipient's blood and immune systems. Dr. Bodine's laboratory is investigating how PHSCs decide whether to differentiate or self-renew when they divide. To this end, he and his colleagues are comparing the genes expressed in hematopoietic stem cells to the genes expressed in stem cells from other organs to find gene products common to multiple stem cells. They hypothesize that the shared gene products may regulate stem cell self-renewal or differentiation. The function of the genes they have identified is being tested in knockout and transgenic mouse models.



Dr. Bodine's laboratory also investigates the genetic causes of acquired and inherited blood disorders. His group has used transgenic mice to demonstrate that point mutations in an insulator element of the human ankyrin locus can cause hereditary spherocytosis, a blood disorder characterized by severe anemia that requires frequent transfusions. A similar analysis of a second hereditary spherocytosis mutation has demonstrated where the RNA polymerase complex binds to the red cell ankyrin promoter. Ankyrin has two other promoters besides the one that is

active in red blood cells. The Bodine laboratory is now conducting an analysis of the chromatin structure surrounding the three ankyrin promoters to define the sequences required to activate the red-cell-specific ankyrin promoter and to suppress the other two.

Finally, his group is working to perfect the use of PHSCs as a vehicle for gene therapy. They previously demonstrated that genes can be successfully inserted into mouse and primate PHSCs with retrovirus vectors and, through self-renewal and proliferation, the new genes are passed along to all the progeny of the transduced stem cell. Unfortunately, gene therapy trials with this approach have been hampered by the instability of the vectors and the variable expression of gene products in PHSCs. For a treatment approach to be valuable, the transduced gene must be expressed at

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the appropriate level in the correct cell type. Dr. Bodine's laboratory is developing new retrovirus vectors designed to be more stable, allowing more efficient gene transfer into PHSC. For example, his group substituted the erythrocyte ankyrin promoter for globin promoters in retrovirus vectors, and found that these vectors are stable and produce near-therapeutic levels of globin RNA and protein in animal models. Further refinement of these vectors may lead to gene therapy for sickle cell disease and β-thalassemia.

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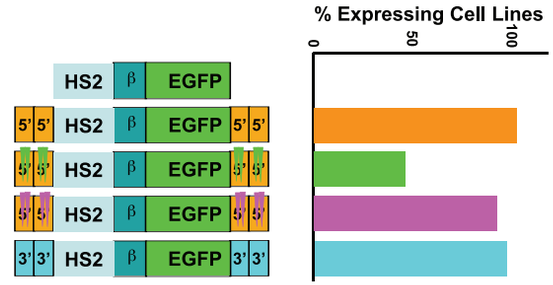
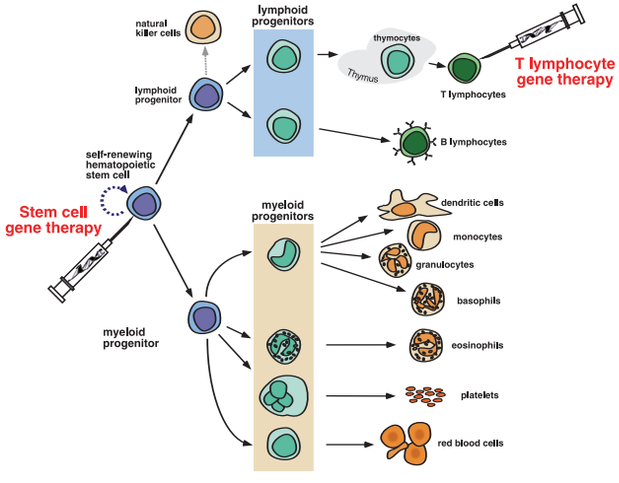


FABIO CANDOTTI, M.D.

Dr. Candotti's laboratory studies the molecular basis of inherited disorders of the immune system in order to develop better treatments for these conditions. For many inherited immune deficiency disorders, the only available therapeutic option is hematopoietic stem cell transplantation (HSCT), currently an intensive procedure that carries a number of risks. Dr. Candotti is seeking treatment alternatives to HSCT, with a particular interest in gene replacement approaches. His laboratory is developing gene therapies for two rare immune deficiency syndromes: adenosine deaminase (ADA) deficiency and Wiskott-Aldrich syndrome (WAS).

ADA is a key enzyme in the purine salvage pathway that catalyzes the deamination of adenosine and deoxyadenosine to inosine and deoxyinosine, respectively. Genetic loss of ADA causes a significant increase in adenosine and deoxyadenosine levels, with toxic effects on lymphocytes. Most individuals with this disorder develop severe combined immune deficiency (SCID) soon after birth due to the absence of T and B lymphocytes and consequent lack of immune protection. Left untreated, individuals with ADA-deficient SCID usually die within the first two years of life from multiple opportunistic infections. Some patients do have enough residual enzyme activity to prevent toxic adenosine metabolites from accumulating. They, therefore, have a milder form of immune deficiency, which may not be diagnosed until later in childhood or even adulthood. Although HSCT from a matching sibling donor can cure ADA deficiency, most patients do not have a matched donor and, thus, face substantial risks from HSCT. Genetic correction of a patient's own hematopoietic stem cells, therefore, could be a beneficial therapeutic alternative.



Dr. Candotti's laboratory is evaluating novel retroviral vectors as gene transfer tools for correcting ADA deficiency. A major obstacle to this approach has been the low level of expression of the inserted genes and often eventual loss of expression. To overcome this problem, his group has constructed improved retroviral vectors that provide a higher level of transgene expression in human lymphoid cells, as compared with previously used vectors. They currently are conducting a clinical trial to determine whether these improved vectors will provide better reconstitution of the immune system.

WAS is an X-linked recessive disorder characterized by very low numbers of platelets that are unusually small. It is associated with eczema of the skin and immune deficiency. WAS patients have an increased chance of developing a malignancy and, in as many as 40% of cases, also have an autoimmune disorder. However, WAS is associated with a milder form of immune deficiency than that observed in ADA deficiency. Thus, WAS patients usually do not develop overwhelming infections at an early age. As with ADA deficiency, however, most WAS patients do not have an ideal donor for HSCT. Dr. Candotti's group is building on *in vitro* studies indicating that retroviral-mediated gene transfer can correct the biological

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defects observed in cell lines from patients with WAS. In addition, observations in WAS patients with spontaneous *in vivo* correction of their genetic defects have confirmed that gene-corrected cells have a selective advantage over their mutated counterparts. These findings suggest that the prospects for the success of gene therapy in this disease are relatively good.

Finally, Dr. Candotti's group is evaluating T cell- and hematopoietic stem cell-directed gene therapy for a rare form of immune deficiency caused by a genetic mutation of the β1 chain of the interleukin-12 receptor (IL12Rβ1). This disease is characterized by increased vulnerability to weakly pathogenic organisms. Even with aggressive treatment, IL12Rβ1-deficient patients can succumb to such infections. Experiments with retroviral-mediated gene correction of T cells from IL12Rβ1-deficient patients have shown restored expression of IL12Rβ1 and a reconstituted, functional IL-12 signaling pathway. As with ADA deficiency and WAS, these results indicate that the biological defects of T cells caused by IL12Rβ1 deficiency can be corrected by gene transfer.

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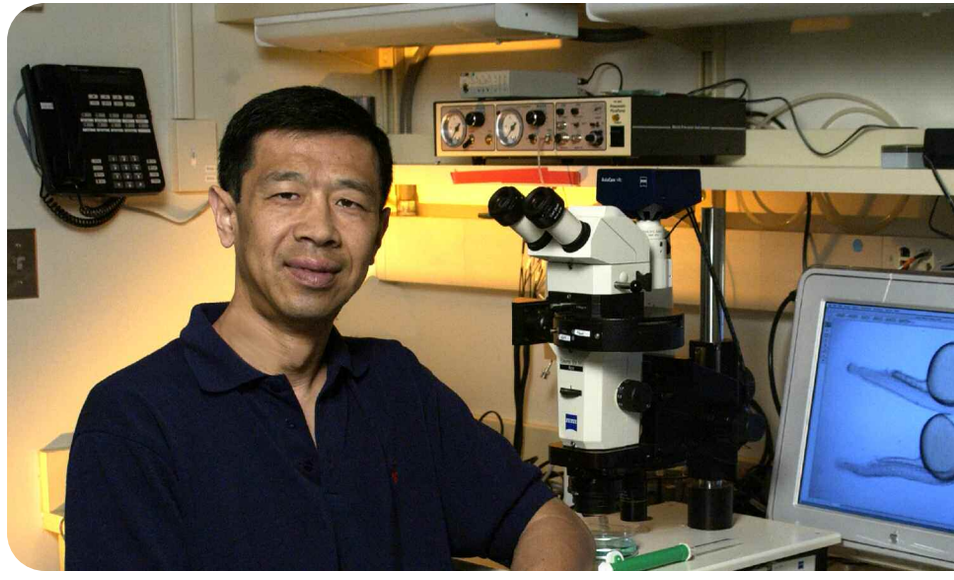
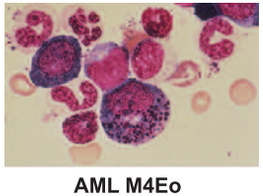
PU PAUL LIU, M.D., Ph.D.

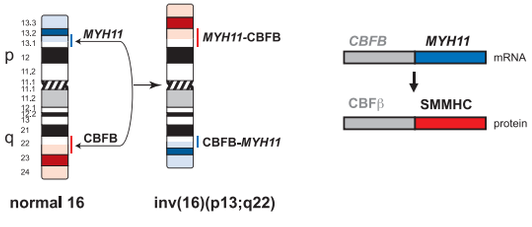


Dr. Liu's laboratory investigates the genetic control of hematopoiesis, the process through which pluripotent hematopoietic stem cells differentiate into all of the types of mature cells that circulate in the bloodstream. His group has a particular interest in leukemia, which strikes an estimated 26,000 Americans each year. Leukemia is an example of hematopoiesis gone awry, and when it develops, the body produces large numbers of abnormal blood cells, or blasts. In acute leukemia, the blasts are too immature to carry out their normal functions, and symptoms of dysfunction appear rapidly.

Leukemias frequently are associated with abnormalities of chromosomes, such as translocations, inversions, and deletions. In one form of human acute myeloid leukemia (AML), the genetic defect is an inversion on chromosome 16. Dr. Liu's laboratory found that this inversion generates a fusion gene between the core binding factor β gene (*CBFB*) and *MYH11*, the gene encoding smooth muscle myosin heavy chain. His group also demonstrated that the *CBFB-MYH11* fusion gene, through its encoded fusion protein, CBFβ-SMMHC, blocks normal hematopoiesis in transgenic mice and makes them susceptible to leukemia. They further demonstrated in transgenic mice that the expression of the *CBFB-MYH11* fusion gene is necessary but not sufficient for leukemia to develop; they have identified a number of other genes that may act in concert with the fusion gene to cause AML. Dr. Liu's laboratory is looking for downstream target genes of the CBFβ-SMMHC fusion protein and are testing new therapeutic approaches for AML in mice that specifically counteract the function of *CBFB-MYH1*.



AML M4Eo



To determine the role of *CBFB* in hematopoiesis and other developmental processes, Dr. Liu's group has generated mice with a *CBFB-GFP* "knock-in" fusion. They used the mice to examine the expression pattern of the CBFβ protein in different lineages of adult hematopoietic cells and found that it is expressed uniformly in all cell lineages except B lymphocytes and erythroid cells. CBFβ expression decreases during maturation of B cells in the adult bone marrow; it is not expressed at all in nucleated erythroid precursors. Thus, CBFβ is required for myeloid and lymphoid differentiation, but it does not play a critical role in erythroid differentiation. Recent studies from Dr. Liu's laboratory have provided more direct evidence that CBFβ plays an important role in T lymphocyte differentiation. They also found that CBFB-GFP mice have reduced CBFβ activity, and homozygous mice display bone formation defects similar to those in a human disease called cleidocranial dysplasia. This suggests that CBFβ plays a very important role in bone formation, which is a focus of further study in Dr. Liu's laboratory.

In parallel, Dr. Liu's group is studying genetic control of blood formation in the zebrafish, which is an excellent vertebrate model for embryonic development and for conducting systematic genetic screens. The group uses

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chemical mutagenesis techniques to generate zebrafish mutants with defects in blood formation. Through genetic mapping and positional cloning, Dr. Liu's laboratory seeks to identify the genes that are altered in these mutants. One zebrafish mutant, *vlad tepes* (the historical name for Dracula), has few or no blood cells at the onset of circulation. Dr. Liu's group identified a novel nonsense mutation in the *gata1* gene as the cause for the bloodless phenotype in the *vlad tepes* fish. As the first *gata1* mutation identified in the zebrafish, this finding demonstrates significant functional conservation between mammalian and zebrafish hematopoiesis, and offers a powerful tool for future studies of hematopoiesis in zebrafish. Finally, Dr. Liu's laboratory recently developed a high-throughput reverse genetic screening system to efficiently generate fish lines carrying mutations in any genes of interest, which can then be used for further phenotypic and genetic studies. This technology will be highly useful for generating fish models of human disease and complex traits, as well as for the development of novel treatments.

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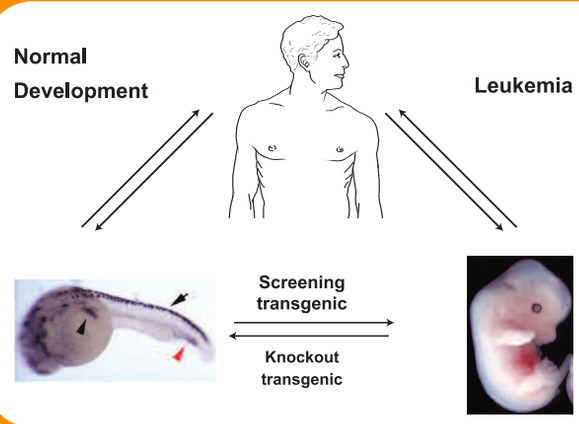
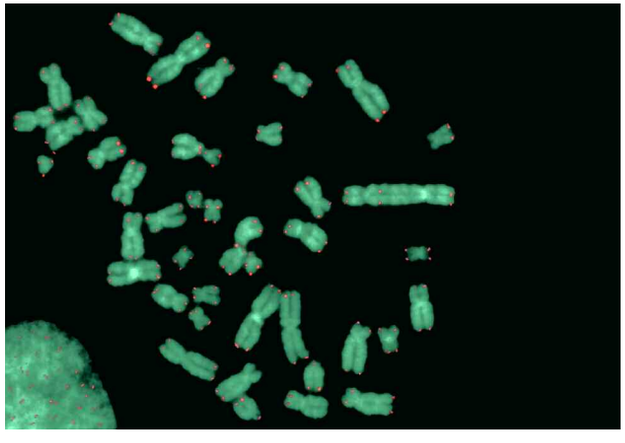


KYUNGJAE (KJ) MYUNG, Ph.D.

Dr. Myung's laboratory is investigating genome instability by examining the mechanisms of DNA repair and replication, as well as their roles in the production and suppression of gross chromosomal rearrangements (GCRs). Specifically, his group is studying how previously identified mutator genes regulate the process of genome instability, with an emphasis on exploring the instability suppression mechanism of the proteins they encode. One of the major goals of his group is to develop new model systems to aid in this research.

Genome instability is found in many genetic disorders and cancer. Different types have been identified, including the accumulation of mutations, chromosomal rearrangements, and aneuploidy (an abnormal number of chromosomes). These defects have been linked to faulty DNA repair and responses to DNA damage. Many are seen in tumors harboring mutations in DNA-repair genes, which suggests that genome-instability defects are probably involved in tumor development.

Using a whole-genome screening method developed by his group, Dr. Myung's laboratory is studying the pathways that maintain genome stability and, when perturbed, contribute to the occurrence of GCRs. Recently, their genome-wide screen in yeast revealed ten more genes encoding proteins that suppress GCRs; they then established the mechanism of action for three of these genes: *ELG1*, *RAD5*, and *RAD18*.



Dr. Myung's laboratory found that the Elg1 protein is involved in DNA repair and that mutations in *elg1* enhance spontaneous DNA damage, which then increases the rate of GCRs. They also found that the DNA damage that results from inactivating the Elg1 protein then activates a feedback mechanism (called the intra-S checkpoint) that further suppresses the rate at which GCRs occur. Interestingly, they also discovered that *elg1* mutations lead to

increased telomere sizes, independent of other previously known telomere-maintenance proteins. Using gene-knockout and RNAi-based methods, they found that mammalian *ELG1* shares similar functions with yeast Elg1.

Dr. Myung's group also found that GCRs are suppressed by a template-switching mechanism that involves a post-replication repair pathway principally regulated by Rad18 and Rad5-dependent proliferating cell nuclear antigen (PCNA) polyubiquitination. In the absence of this template-switching mechanism, GCRs are caused by Siz1-dependent PCNA sumoylation and Srs2 helicase recruitment. The group also recently identified a mammalian *RAD5* gene, called *SHPRH;* others in the scientific community have been searching for this gene for the last 20 years. *SHPRH* promotes PCNA polyubiquitination and suppresses GCRs; it is also mutated in several cancer cell lines.

Over the past several years, Dr. Myung and his colleagues have identified many genes that enhance GCRs when overexpressed. One of the more

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dramatic examples of this overexpression is *MPH1*, which is highly homologous to a Class M gene implicated in Fanconi anemia, and enhances GCRs by partially inactivating Rad52-dependent homologous recombination.

Dr. Myung's laboratory is conducting several early-stage investigations into other potential enhancers of GCRs. In one of these studies, his group is investigating examining how overexpression of Spt2, which functions as part of the transcription machinery, leads to an increase in GCRs. The group is also using knockout-mouse models of *RAD5* and *ELG1* to determine whether these genes are involved in tumor formation, and trying to create new ways of measuring GCRs in mammals when DNA replication is challenged.

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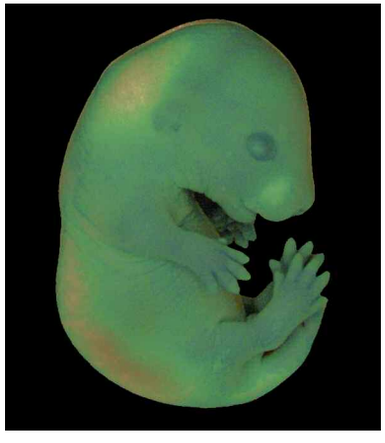
JULIA A. SEGRE, Ph.D.

Dr. Segre's research focuses on the dynamic process by which skin cells maintain a proper balance between proliferation and differentiation. Combining classical genetics techniques and modern genomic tools, her laboratory uses mouse models to investigate the function of novel genes important for *in utero* human skin development, the normal process of wound healing, and chronic skin disorders, such as psoriasis and eczema.

Located at the interface between the body and its surrounding environment, the skin acts as a barrier to infectious agents and protects against the loss of critical bodily fluids. The major barrier activity resides within the epidermis, the exterior layer of the skin, which is sloughed off and repopulated from dividing cells in inner layers. This process of differentiation is maintained throughout life as part of epidermal regeneration. However, in infants that are born prematurely, immaturity of the skin, which does not develop its major and necessary function as a barrier until 34 weeks *in utero*, places them at great risk of disease. This is because their poorly developed epidermis is a portal of entry for infection and potential toxins.

For humans, maternal injections of glucocorticoids are recommended to accelerate lung and epidermal maturation before an anticipated premature delivery. However, glucocorticoids are extremely potent medications that can be associated with the rapid development of many side effects, including immune suppression, low birth weight, and a host of other metabolic problems. Accordingly, Dr. Segre hopes to discover more specific therapies to replace systemic glucocorticoid treatment for premature births.



To find better strategies for promoting epidermal development, Dr. Segre's group seeks to answer fundamental questions about the mechanism by which epidermal cells produce this barrier. Previously, Dr. Segre discovered that the DNA-binding protein Kruppel-like factor 4 (Klf4) protein was necessary for barrier acquisition. While genetically engineered mice that lacked the *Klf4* gene looked identical to normal mice, they lost weight rapidly and died 12 hours after birth; when immersed in a dye solution, these newborn mice absorbed the dye and turned blue, indicating a lack of epidermal barrier development. Dr. Segre's laboratory

has demonstrated that ectopic expression of *Klf4* in mice is sufficient to accelerate barrier acquisition, suggesting that Klf4 must be a crucial factor for the skin to achieve barrier function. These genetically engineered mice, therefore, are an important animal model for studying how to accelerate this process in premature infants.

Dr. Segre's laboratory identified the overlapping downstream targets of both the Klf4 protein and glucocorticoids in the skin so they can test specific molecules that may enhance epidermal barrier acceleration. The ultimate goal is to identify genes that have the positive effect of stimulating barrier acquisition without the negative effects of glucocorticoids.

In addition to investigating the process of barrier acquisition during embryonic development, Dr. Segre studies the regeneration of the epidermis that occurs with normal wound healing. Recently, her laboratory used an animal model to show that restoration of the skin's barrier is a key step

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in the wound healing process and, when impaired, can result in psoriasis. The ultimate goal of the Segre laboratory is to understand the skin's response to the many environmental stresses, such as exposure to ultraviolet light and chemicals. Normally, there is an orderly progression of differentiation in the skin. However, when the skin is injured, it activates a stress response that upregulates the expression of structural proteins to erect a temporary barrier until a more permanent one can be built. Her laboratory is investigating whether clusters of genes are held together in the genome to respond in a coordinated fashion to enviromental stresses.

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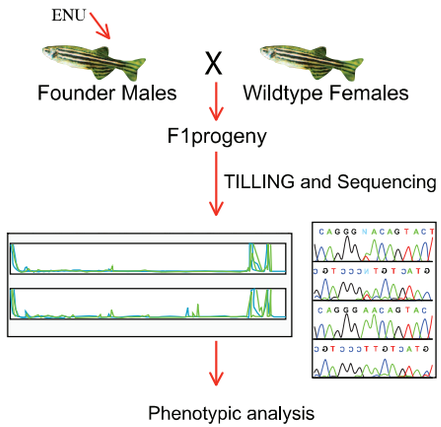
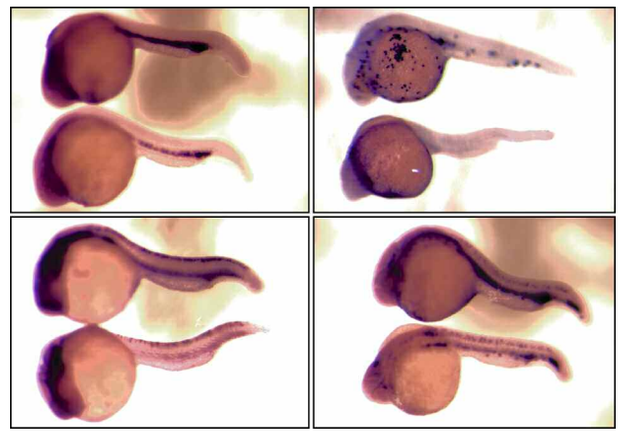
RAMAN SOOD, Ph.D.

Dr. Sood's research is focused on generating a resource for NHGRI investigators that will allow them to perform functional analyses of genes of interest using zebrafish as a model organism. Dr. Sood is performing large-scale *N*-ethyl-*N*-nitrosourea (ENU) mutagenesis in zebrafish, which produces random point mutations throughout the organism's genome. Her goal is to develop approximately 5,000 F1 male fish bearing such mutations, a number that makes it highly likely that there will be an individual in the collection carrying a mutation in every gene that researchers may wish to study. Dr. Sood uses reverse genetic approaches to identify mutants for genes of interest. Her major focus is to identify mutations in genes involved in hematopoiesis and cancer and to study their phenotype to understand the function of these genes. She does this by generating lines of zebrafish for mutations of functional significance and breeds them to homozygosity to study the phenotype.

To identify potentially interesting mutations in the collection of ENU-treated zebrafish, Dr. Sood is employing sequencing in combination with TILLING (for "targeting induced local lesions in genomes"), which provides a cost-effective alternative to sequencing large numbers of samples.



In high-throughput TILLING, regions of interest are amplified by polymerase chain reaction (PCR). Heteroduplexes between wild-type fragments and fragments harboring an induced mutation are formed by denaturing and reannealing PCR products. These heteroduplexes are



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cleaved by an endonuclease, Cel I. Cleaved products are then resolved using denaturing polyacrylamide gel or capillary electrophoresis. To increase throughput, samples are pooled fourfold. Upon detection of a mutation in a pool, the individual DNA samples are sequenced to identify the individual carrying the mutation and the nature of the mutation. This rapid screening procedure determines the location of a mutation to within ± 10 bp for PCR products that are 300 to 600 bp in size.

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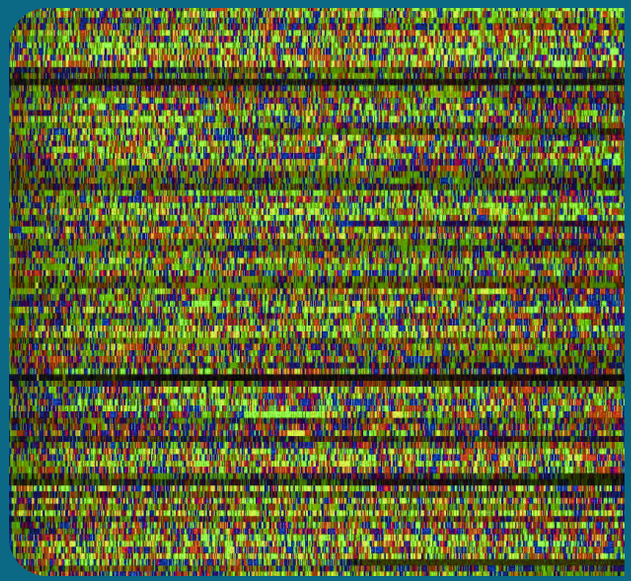
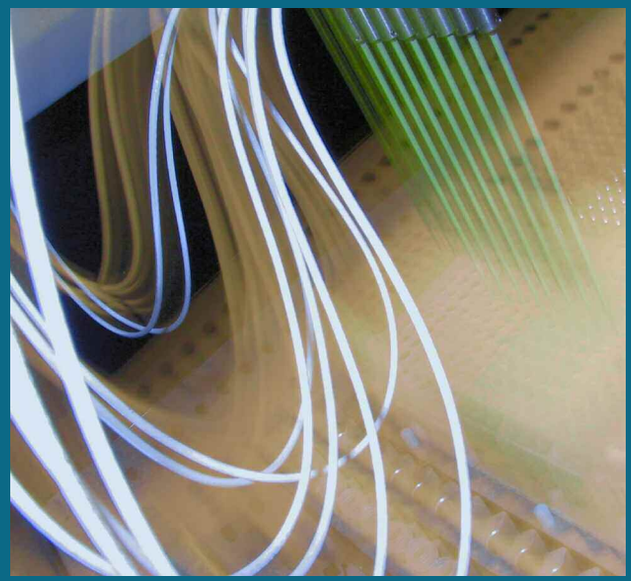
"A major reason we have been so successful is that **we can move quickly to develop a new technology, even if it is risky**. Another key ingredient to our success is creatively partnering with other NIH Institutes and outside research institutions, interactions that have led to remarkable accomplishments."

Eric Green, M.D., Ph.D.
Chief, Genome Technology Branch

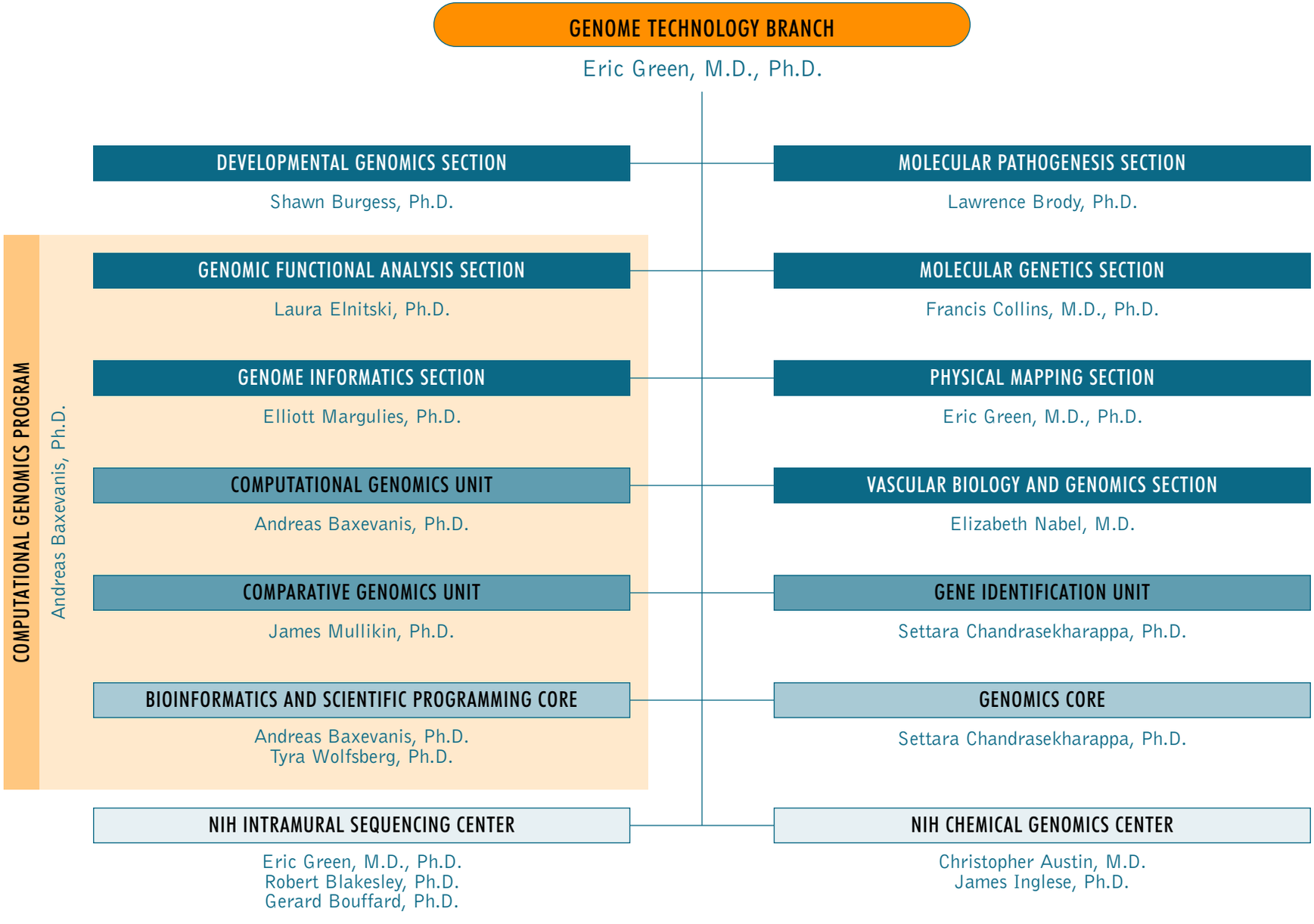
GENOME TECHNOLOGY BRANCH





Investigators in the Genome Technology Branch (GTB) study the structure and function of genomes in disease and normal states. Over the years, GTB researchers have developed world class expertise in a wide range of genomic techniques, including the mapping and sequencing of mammalian chromosomes, gene isolation, systematic mutagenesis, developmental genomics, chemical genomics, and the computational analysis of DNA and protein sequences. This work has been applied to the development, testing, and implementation of innovative technologies for performing genome sequencing, chemical screenings, and analyzing and characterizing genes and their encoded proteins.

GTB researchers are actively seeking to identify the genetic causes of rare disorders, such as hereditary deafness, progeria, and peripheral neuropathies. They also study the genetic contributions relevant to more common conditions, such as type 2 diabetes, breast cancer, neural tube defects, and cardiovascular disease, and are investigating how particular genes may influence normal health and even longevity. The research programs of Intramural scientists at NHGRI make productive use of GTB's two Cores—the Genomics Core and the Bioinformatics and Scientific Programming Core. The broader NIH research community has benefited from the Branch's expertise in large scale DNA sequencing, chemical genomics, disease gene identification, and computational genomics. GTB investigators are involved in a number of joint ventures with other NIH Institutes to develop resources, including genome analysis tools and data sets, that are made available to others via the Internet.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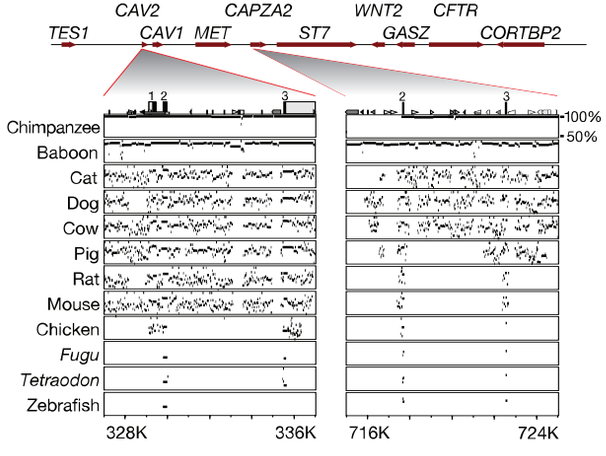
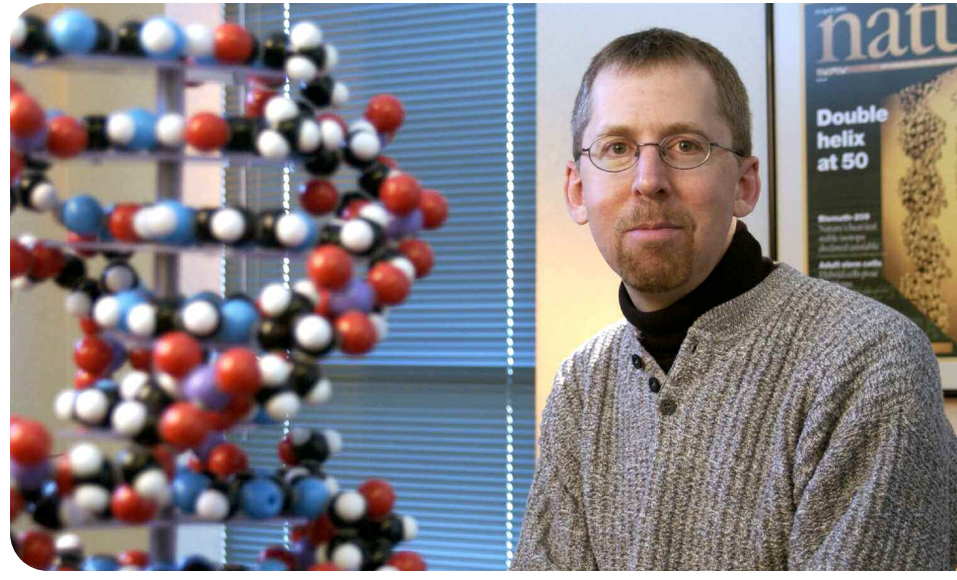
ERIC D. GREEN, M.D., Ph.D.

Dr. Green's research focuses on three major areas: (1) sequencing and comparing targeted stretches of DNA from a wide variety of animal species *en route* to unraveling the complexities of genome function; (2) developing innovative research tools and technologies for performing genome analysis; and (3) identifying and characterizing genes associated with human disease. In his multiple roles as Scientific Director of NHGRI, Chief of the Genome Technology Branch, and Director of the NIH Intramural Sequencing Center (NISC), he has fundamental interests in mapping, sequencing, and interpreting vertebrate genomes.

The major activities in Dr. Green's laboratory, performed in partnership with NISC, center on a novel comparative sequencing program. Specifically, targeted regions of the human genome are selected and then mapped and sequenced in multiple other vertebrates, including a diverse set of primates, numerous other mammals (including marsupials and monotremes), birds, fish, amphibians, and reptiles. The resulting data sets are providing unprecedented abilities to perform evolutionarily diverse sequence comparisons.

In some cases, Dr. Green and his colleagues search for sequences conserved over tens of millions of years of evolution; such sequences are more likely to play important functional roles. In other cases, they examine sequence differences among closely related species (such as groups of primates), revealing more recent genomic changes. In essence, Dr. Green's group uses the detailed records of evolution embedded within all species' DNA to help decode the human genome.





Although Dr. Green's comparative sequencing program is extensive and produces large amounts of new data, it is essentially a reconnaissance effort to identify the most promising genomes to sequence, develop new analytical methods for extracting biological information from sequence comparisons, and forge new paths to facilitate the comprehensive understanding of complex genomes. His program also has laid important groundwork for NHGRI's ENCODE (*Enc*yclopedia *o*f *D*NA *E*lements) project, an effort to identify all functional elements in the human genome. ENCODE's initial goals involve the focused study of a selected 1% (~30 Mb) of the human genome, distributed across 44 regions. As major participants in ENCODE, Dr. Green's laboratory and NISC are responsible for most of the multispecies sequencing of these genomic regions.

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In parallel with unraveling the complexities of genome function through large-scale comparative genomics, Dr. Green's laboratory also seeks to understand the genetic basis for certain human diseases. To date, his group has identified genes associated with hereditary deafness (Pendred syndrome), vascular disease, cancer, and neurological disease (Charcot-Marie-Tooth disease). Such discoveries have provided new opportunities to study the function of individual genes and the proteins they encode, to define the pathological consequences of disease-associated mutations, and to generate animal models of these disorders.

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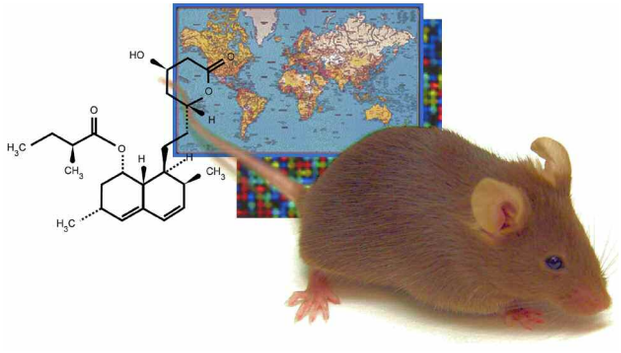
CHRISTOPHER P. AUSTIN, M.D.

Dr. Austin is Director of the NIH Chemical Genomics Center (NCGC), and is also Senior Advisor for Translational Research in the NHGRI Office of the Director. Dr. Austin founded NCGC in 2003, and has built it into one of the leading centers for high-throughput screening, chemical probe development, and chemical genomics — the use of small-molecule compounds to understand the organization and function of genes and genomes.

NCGC works with investigators throughout the world to develop chemical probes of genes and pathways, establish new paradigms for screening and chemical probe development, and make high-quality chemical genomic data freely available in public databases (see *pubchem.ncbi.nlm.nih.gov*). Its activities are intended to catalyze the understanding of gene function and the development of therapeutics based on genomic targets. NCGC has developed a novel titration-based screening method, called Quantitative High-Throughput Screening (qHTS), which generates comprehensive activity and pharmacological data on hundreds of thousands of compounds. Using this and related techniques, NCGC has generated chemical probes for a wide variety of targets from the human genome and that of various model and pathogenic organisms. In turn, these compounds are being used to investigate target function and physiology. Where targets have therapeutic potential, NCGC is focused on "orphan" diseases (rare genetic diseases) and diseases of the developing world. After each qHTS screen is completed, NCGC cheminformatics scientists use algorithms developed in-house to identify the compounds with pharmacological activity, and to compare these activities with those in other screens in order to determine selectivity and identify compounds for chemical optimization.



NCGC chemists perform technology-enabled high-throughput chemistry on these compounds to optimize their biological activities, and to produce optimal probes for the biology being studied. NCGC scientists then work with collaborators to investigate novel biology using these probes.

At a higher level of analysis, NCGC's screening throughput and precision is producing a database of chemical activities that, over the next several years, will begin to define general principles of chemical structure-biological activity relationships. The ultimate goal of this work is to predict biological activity based on gene and compound structure, and to define relationships between gene products based on the small molecule compounds with which they interact. This approach is a fundamentally new way of defining the

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structural and functional organization of genomes, driven by the fact that small molecules interact with the gene-encoded protein products that are most proximate to function, in addition to mRNAs and DNAs.

A developmental neurogeneticist by training, Dr. Austin came to NHGRI in 2002 from the private sector, where his work focused on genome-based discovery of novel targets and drugs. As Senior Advisor for Translational Research, he is responsible for initiation of programs to determine gene function and therapeutic potential across the genome; in this role, he has initiated the Knockout Mouse Project (KOMP), a large-scale transcriptome study of mouse tissues, and the Molecular Libraries Roadmap Initiative, of which NCGC is a part.

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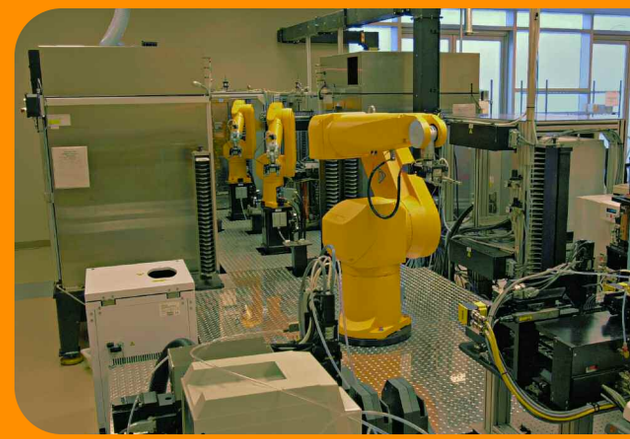
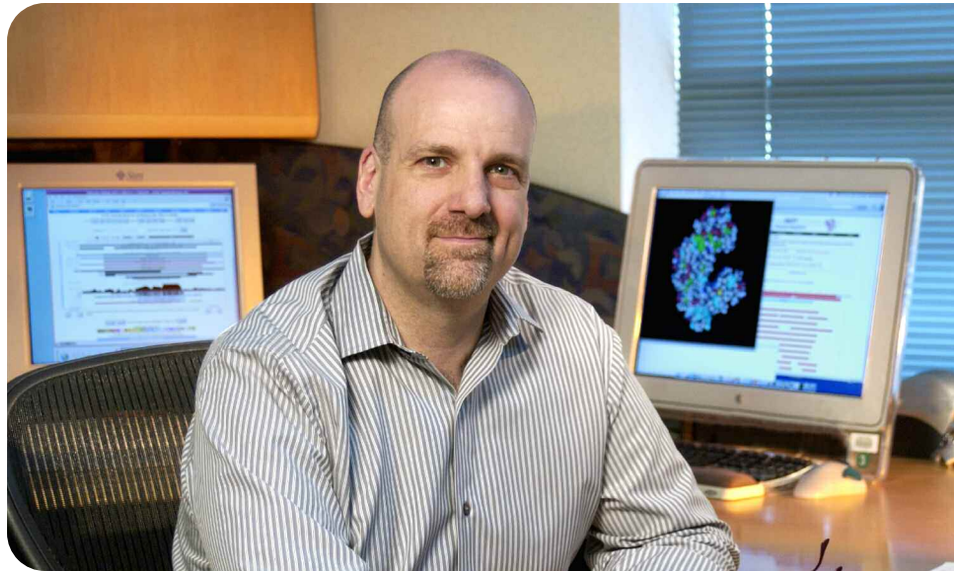
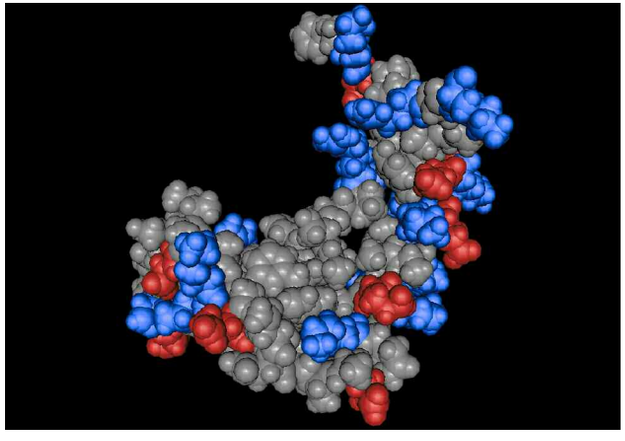


ANDREAS D. BAXEVANIS, Ph.D.



Dr. Baxevanis' research focuses on the computational analysis of disease-causing mutations from a structural standpoint, using innovative techniques to deduce the precise structural changes in a protein caused by a particular genetic mutation. This kind of bioinformatics approach provides a powerful window into understanding the fundamental cause of phenotypes in people afflicted with a given genetic disorder. The same approach can be used to predict structural changes that a hypothetical mutation would cause, enabling laboratory researchers to design experiments more effectively.

Dr. Baxevanis' group recently elucidated the differing molecular effects of five missense mutations in the *FOXC1* gene, which causes an array of eye, ear, skeletal, and cardiac disorders. In other analyses, Dr. Baxevanis' group helped elucidate the mechanism by which specific mutations alter a protein's ability to bind to a target DNA sequence. Depending on the protein involved, the disease phenotypes that result from its inability or reduced ability to bind to DNA can be quite different. For example, mutations in a gene called *FOXP2* are responsible for a severe speech and language disorder, while *FOXP3* mutations can lead to severe immune dysfunction.



Dr. Baxevanis' group also studies the evolutionary relationships between members of the homeodomain family of proteins. His group has deduced a family tree that shows the relationship between 129 different human homeodomain proteins; these 129 proteins segregate into six distinct groups, with each group characterized by similar structural and functional features. His group also maintains a publicly available database called the Homeodomain Resource, which is used extensively worldwide by researchers studying these proteins. It contains full-length homeodomain sequences and data on experimentally derived structures, protein-protein interactions, DNA binding sites, and mutations linked to human disorders.

Because such computational analyses must always be confirmed by laboratory experiments, the ability to combine laboratory and computational approaches in a synergistic manner is critical to being able to perform cutting-edge biological research in the future. Such synergism also will allow investigators to more effectively design experiments and analyze data sets being generated through large-scale studies.

Dr. Baxevanis' group devotes significant effort to developing computer software that will aid other biomedical researchers. For example, early in the

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development of microarrays — devices that can detect the expression of thousands of genes in a tissue sample — his group developed the first publicly available software program designed to easily store and analyze microarray data. More recently, the group developed a software program known as GeneLink, which enables researchers to analyze large data sets from studies of complex-trait genetic disorders, such as cancer, diabetes, and hypertension. Unlike cystic fibrosis and Huntington's disease, which are caused by mutations in a single gene, complex-trait disorders involve many genes along with environmental factors. Gene-mapping studies involving families with an unusually high incidence of such diseases become complicated, requiring the identification and comparison of hundreds — and perhaps thousands — of DNA markers in thousands of individuals. GeneLink enables researchers to store this information and mine it for relationships that might not be immediately apparent.

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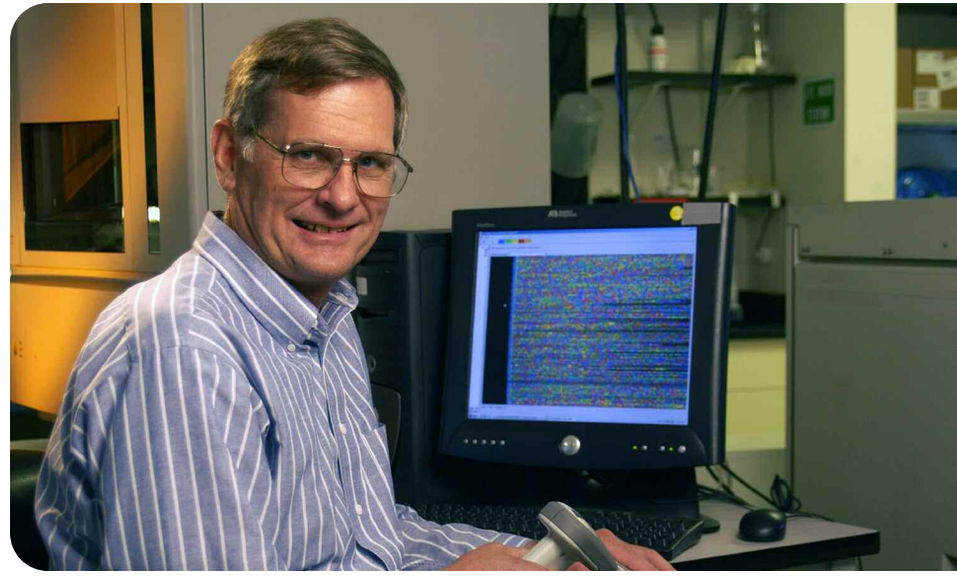
ROBERT W. BLAKESLEY, Ph.D.

Dr. Blakesley directs the Sequencing Group of the NIH Intramural Sequencing Center (NISC). Established in 1997, NISC is a multi-disciplinary genomics facility that emphasizes the generation and analysis of DNA sequences.

Dr. Blakesley has had a career-long scientific interest in providing practical technological solutions to research problems. He spent more than 20 years in an industrial molecular biology research and development laboratory developing products in a number of areas, including nucleic acid enzymology, purification and manipulation of nucleic acids, apparatus and software design, and DNA sequencing. His current work focuses on improving NISC's sequencing pipeline by developing more consistent large-scale DNA purification methods, using robotics to increase overall efficiency and reduce costs, and applying good manufacturing principles to the sequencing process.

Dr. Blakesley oversees NISC's role in several large DNA sequencing efforts. For example, the NISC Comparative Sequencing Program involves generating genomic sequences from multiple vertebrates for comparative analyses. In this project, targeted genomic regions are selected for study and then sequenced. The resulting data consist of sets of orthologous sequences for the same large genomic region from multiple species. This project aims to generate data for use in developing and refining computational tools for comparing genomic sequences from different vertebrates. These efforts likely will inform decisions about the selection of additional species for systematic genome sequencing.



Another major priority for NISC is generating sequence data for the ENCODE (*Enc*yclopedia *o*f *D*NA *E*lements) project, an NHGRI-led initiative that aims to identify all the functional elements in the human genome. Its initial sequencing effort is a pilot-scale program that is focusing on 1% of the human genome, distributed across 44 discrete regions. A major component of the ENCODE project is the comparative sequencing of these regions in multiple vertebrate species. In partnership with other NHGRI investigators, NISC is extensively involved in generating these multi-species sequences and analyzing the resulting data.

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NISC also is a major participant in the Mammalian Gene Collection (MGC) program, an NIH-funded effort to generate a publicly available resource of sequenced full-length complementary DNAs (cDNAs) for all human, mouse, and other species' genes. This program involves constructing new cDNA libraries, screening clones by expressed sequence tag generation to identify those that contain putative full-length cDNAs, determining the complete sequence of candidate full-length clones, and establishing repository and distribution systems for the resulting clone collections. As part of the MGC program, NISC has developed a robust pipeline for generating the sequence of full-length cDNA clones.

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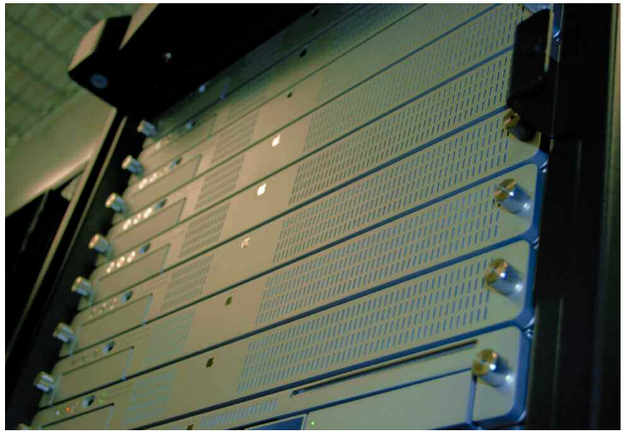
GERARD G. BOUFFARD, Ph.D.

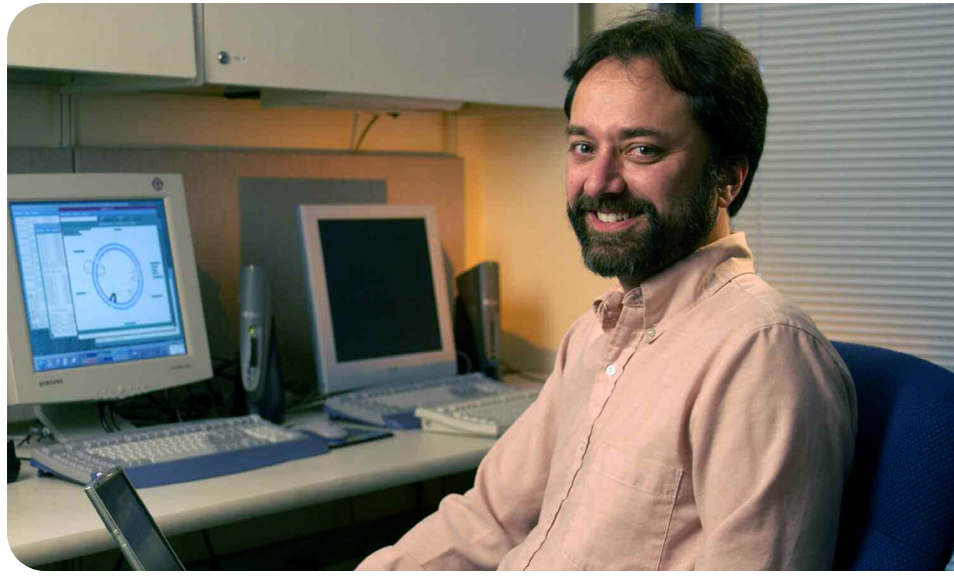
Dr. Bouffard directs the Bioinformatics Group at the NIH Intramural Sequencing Center (NISC). In this role, he oversees the management and analysis of data from one of the country's premier DNA sequencing facilities. His main focus is a major comparative genomics project—an effort to compare the human genome with that of other vertebrates to reveal important, unrecognized common sequences and to begin unraveling their function. He also is engaged in helping several other NIH investigators whose research requires analyses of DNA sequences.

To cope with NISC's large sequencing throughput and data generation, Dr. Bouffard has directed the development of a customized, NISC-specific Laboratory Information Management System. This system controls the flow of samples and materials through the laboratory, identifies reagents and equipment with bar codes, and records the people and tools involved at every stage. This detailed control is aimed at providing efficient flow control, the flexibility to rush high-priority tasks through the system, and a backtracking capability for monitoring sequence quality.

The NISC Comparative Sequencing Program is a large-scale effort to compare discrete segments of various species' genomes. So far, it is confined to vertebrates, with tens of species spanning millions of years of evolution. Dr. Bouffard's bioinformatics staff is assimilating and comparing sequences from primates, other mammals, marsupials, monotremes, birds, and fish.



He also is involved in NHGRI's ENCODE (*Enc*yclopedia *o*f *D*NA *E*lements) project, aimed at identifying all the functional elements in the human genome. For this project, scientists at NHGRI and elsewhere are applying current technologies—and testing potential new technologies—to study 44 regions that, taken together, comprise 1% of the human genome. Dr. Bouffard's group is helping to generate and analyze sequences of these regions in multiple other species.



His group's other major project is the Mammalian Gene Collection (MGC), which is an effort to build a repository of clones and associated sequences representing every human gene and to make them available to scientists worldwide. MGC has now expanded to include mouse, rat, zebrafish, and *Xenopus* genes. Initially, MGC scientists scoured existing complementary DNA (cDNA) libraries to build their collection. Now that those sources are rarely turning up novel, previously unseen cDNAs, they are using more directed strategies, such as generating cDNA libraries from different tissues to find genes that might be expressed only in particular tissues under specific conditions.

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Dr. Bouffard also collaborates with other NIH scientists on an as-requested basis. For example, his group recently analyzed a large number of expressed sequence tags (ESTs) for researchers at the National Eye Institute who are trying to identify all the genes that are expressed in tissues related to vision. In addition, his group analyzed about 5,000 blood cell ESTs for the National Institute of Diabetes and Digestive and Kidney Diseases in a study that identified the gene responsible for a clinically important blood group system. This finding paved the way for tests that will reduce transfusion dangers for certain people.

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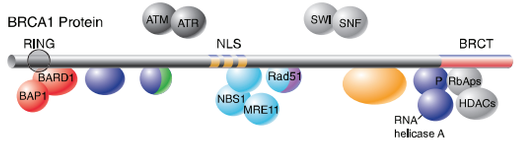
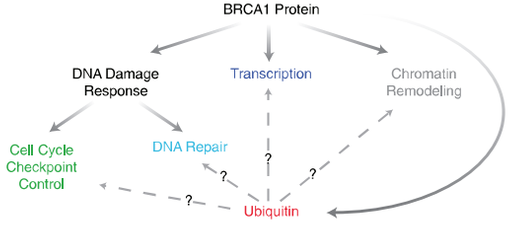
LAWRENCE C. BRODY, Ph.D.

Dr. Brody investigates the genetics of breast cancer and neural tube defects. As head of GTB's Molecular Pathogenesis Section, he is interested in studying genetic mutations that lead to perturbations in normal metabolic pathways and cause disorders such as cancer and birth defects.

His laboratory investigates mutations in two known breast cancer-linked genes, breast cancer gene 1 (*BRCA1*) and breast cancer gene 2 (*BRCA2),* and their roles in inherited breast and ovarian cancer susceptibility. In 1994, Dr. Brody's laboratory was among the first to report that women carrying *BRCA1* or *BRCA2* mutations have a higher risk of developing both breast and ovarian cancer than women without such mutations. His group also discovered an unusually high frequency of specific *BRCA1* mutations in the Jewish population. They recently helped identify eight distinct protein-shortening mutations and another six rare variations of *BRCA2* in a group of African-American breast and ovarian cancer patients.

His team is continuing to study these two populations to better understand the risk of cancer associated with specific mutations and is collecting information on all identified mutations in these two genes worldwide (see sidebar). More than 2,000 distinct *BRCA1* and *BRCA2* mutations have been identified to date. Because women with *BRCA1* mutations account for only 5% of all breast cancer cases diagnosed every year, there is a growing scientific consensus that not all *BRCA* mutations carry the same risk of cancer.





Dr. Brody's group also is investigating how normal *BRCA* genes help maintain healthy cells. The group demonstrated that the normal BRCA1 protein regulates key effectors that control the G2/M DNA damage checkpoint, a cell-cycle checkpoint that prevents cells with genomic damage from entering mitosis and reproducing. The carboxyl terminus of BRCA1 contains two motifs found in several DNA-repair and cell-cycle checkpoint proteins. Dr. Brody's laboratory demonstrated that these

motifs also bind to a number of other nuclear proteins critical to DNA replication. This segment of BRCA1 also interacts with several histone deacetylases, proteins that modulate the transcriptional activity of genes leading to cell growth arrest, cellular differentiation, and apoptosis (programmed cell death).

Research has found that the amino terminus of BRCA1 is a RING finger protein, a class of proteins that have E3 ligase activity. E3 ligase catalyzes a key enzymatic step in the ubiquitination pathway, a cellular pathway that recognizes misfolded proteins in the nucleus and targets them for degradation, thus keeping the cell functioning normally. Defects in the normal ubiquitination pathway are implicated in a range of illnesses, including cancer. Dr. Brody's team is working to identify all the molecules in the ubiquitination pathway that interact with BRCA1.

Dr. Brody's other major area of investigation is the genetics of neural tube defects (NTDs), one of the most common birth defects in the United States. Spina bifida, the most common NTD, results in the exposure of the spinal cord

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through an opening in the vertebrae. It often is corrected by major surgery, but it still can lead to life-long medical complications, including paralysis.

Dr. Brody's laboratory is collaborating with researchers at Trinity College in Dublin, Ireland — a country with an historically high rate of NTDs — and at the National Institute of Child Health and Human Development at NIH to identify genes controlling NTD risk in a large series of affected Irish families. This team has identified human genetic variants in the majority of the genes encoding the constituents of folate, vitamin B12, and homocysteine metabolic pathways. The team also established that genetic variants in folate metabolic pathway genes account for a large fraction of NTD cases. Folate, vitamin B12, and homocysteine metabolism will be a major focus of the Brody laboratory in the future. This "pathway" is central to DNA metabolism and DNA methylation, and is likely to be involved in many disease states. The laboratory has already found that inherited variants in this pathway contribute to medical conditions ranging from miscarriage to diseases of old age.

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BREAST CANCER MUTATION DATABASE

To identify and categorize all of the possible variations in both BRCA1 and BRCA2 and to help speed up the discovery of additional mutations around the world, Dr. Brody's laboratory has established the Breast Cancer Information Core (BIC) database. The database is a repository for mutations found worldwide in the BRCA1 and BRCA2 genes.

For more information on BIC, go to: *http://research.nhgri.nih.gov/bic/*

SHAWN M. BURGESS, Ph.D.

Dr. Burgess' laboratory studies developmental processes and their relationship to human genetic disease. His group employs a variety of modern molecular biology methods to identify and functionally characterize novel developmental genes involved in organogenesis of the ear and maintenance of stem cell populations.

Before coming to NHGRI, Dr. Burgess was part of a group at the Massachusetts Institute of Technology that pioneered the use of pseudotyped retroviruses for mutagenesis in zebrafish. This technology represented a major breakthrough in the ability to quickly identify genes important in the early development of vertebrates. The use of retroviruses, as opposed to chemical mutagens, reduces the time for gene identification from years to weeks. The ability to expose zebrafish to these retroviruses and then quickly identify resultant mutations is allowing geneticists to perform large-scale mutagenesis and rapid phenotypic screening in a vertebrate system.

Dr. Burgess was involved in a three-year, large-scale screening effort that used retroviral mutagenesis to produce over 525 mutations that visibly affect the development of the zebrafish embryo. Of these mutations, more than 20 affect the development of the zebrafish ear and vestibular system. His group is now studying this set of mutations to identify genes involved in the development of the vertebrate ear and establish their role in disease and normal health.

One of these genes encodes a transcription factor known as forkhead class I-1 (*foxi1*), which is required for ear and jaw development in zebrafish, and zebrafish *foxi1* has an analog in both humans and mice. In fact, the mouse knockout model of *foxi1* is deaf and has balance problems. Therefore, *foxi1* is a strong candidate gene for some forms of human congenital deafness, which occurs in one per 1,000–2,000 births.

Dr. Burgess' group is using various techniques in zebrafish to define the developmental pathway in the ear and jaw that is affected by *foxi1* mutations. During the first few days of development, zebrafish are relatively transparent and all their internal structures are visible. In addition, zebrafish have a robust startle response — if they do not respond to a tapping stimulus, they likely are functionally deaf. Thus, the ability to combine sophisticated embryology with high-throughput genetics makes the zebrafish an ideal animal model for studying this kind of developmental malformation.

Dr. Burgess continues to expand the functionality of the pseudotyped retroviruses for use in new large-scale screens for gene function. The next challenge his laboratory faces is devising screens that are not based solely on knocking out genes; these new approaches will allow for conditional expression, misexpression, or rapid tissue expression screening. For example, his group recently helped produce a transgenic zebrafish from cultured sperm infected with a pseudotyped retrovirus *in vitro*. The collected sperm was used to perform the *in vitro* fertilizations, and transgenic embryos were identified.

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The transgenic fish transmitted the proviral integration to the next generation in a Mendelian fashion. This approach for generating transgenic animals opens the door for the rapid generation of transgenic lines in model organisms that are otherwise intractable to transgenesis.

Another aspect of development being studied by Dr. Burgess' group involves stem cell biology. His group has isolated a mutant stem cell gene in zebrafish that is a homolog of a gene in mice called *Oct4*. In mice, the *Oct4* gene product maintains stem cell pluripotency by activating and repressing multiple downstream genes. Although the precise mechanism by which the Oct4 protein represses downstream genes remains unknown, when it is removed from stem cells, they begin to differentiate. Dr. Burgess' group has developed an *Oct4*-deficient zebrafish and is conducting trans-species transcriptional profiling in both zebrafish and mice to compare the genetic profiles of the two species.

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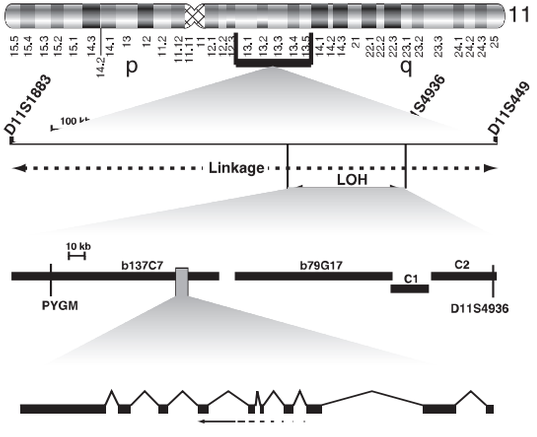
SETTARA C. CHANDRASEKHARAPPA, Ph.D.

Dr. Chandrasekharappa's research focuses on the development and use of genome technologies to advance research in human genetics. For more than a decade, he has been involved in the large-scale mapping and positional cloning of disease genes, with particular emphasis on the genes responsible for Alagille syndrome (AGS) and multiple endocrine neoplasia type 1 (MEN1).

AGS is a congenital disorder characterized by fewer bile ducts than normal in the liver and abnormalities of the heart, eyes, vertebrae, and face. Thus, multiple organ systems are affected, but the extent to which each is affected varies from individual to individual. MEN1 is a rare hormonal disorder also known as multiple endocrine adenomatosis or Wermer's syndrome. In MEN1, hormone-producing glands develop multiple tumors. The affected glands in MEN1 are primarily the parathyroid, pituitary, and pancreas; in many individuals, all three are affected. Although the symptoms may vary, they are often severe. For example, an overactive parathyroid gland can produce excess calcium in the blood, leading to kidney damage. A hyperactive pituitary gland can produce an array of symptoms, including infertility and excessive growth. A hyperactive pancreas can promote severe ulcers in the stomach and intestine, and some of these tumors may become cancerous.



Dr. Chandrasekharappa and colleagues discovered the genes responsible for both disorders in 1997. AGS is caused by mutations in the human *JAG1* gene, which encodes a ligand (Jagged 1) for the Notch transmembrane receptor. The Notch signaling pathway, originally discovered in fruit flies, is important in determining the early fate of the cell. MEN1 is caused by mutations in the tumor suppressor gene, *MEN1*. This gene encodes a protein called menin, which is expressed very early in development, resides in the cell nucleus, and appears to bind several different proteins including the transcription factor JunD. When bound to menin, JunD represses cell growth; without menin, JunD promotes cell growth.

The basic biological function of menin is not entirely clear. However, it is known that the Jagged 1 protein is involved in various developmental processes. A total loss of menin is needed to cause tumors in MEN1 patients, whereas a partial loss of Jagged 1 is sufficient to cause AGS. One of the major activities of Dr. Chandrasekharappa's laboratory is studying the function of both proteins, particularly to understand how their loss leads to the respective diseases. These efforts include developing a model of AGS in zebrafish and models of MEN1 in fruit flies, zebrafish, and mice.

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Dr. Chandrasekharappa often collaborates with other scientists to locate and clone human disease genes. His expertise in the applications of genomic technologies to positional cloning has led to collaborations with scientists interested in defects in zebrafish development. He is also working on adapting microarray technology to a new use: searching for chromosomal alterations or deletions that might be involved in many human diseases. Microarrays traditionally have been used for detecting gene expression changes in particular tissues. However, if stretches of genomic DNA are used, the microarray can detect chromosomal deletions or amplifications in cancer cells. Dr. Chandrasekharappa believes such higher-resolution searches for potential genomic alterations might pay off by detecting chromosomal changes in a number of diseases whose molecular defects have not yet been characterized.

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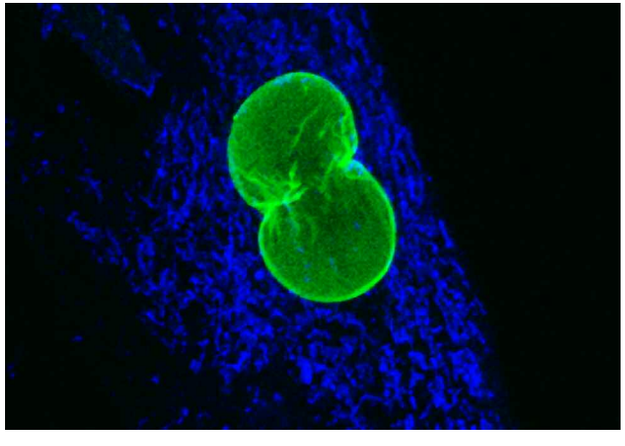
FRANCIS S. COLLINS, M.D., Ph.D.

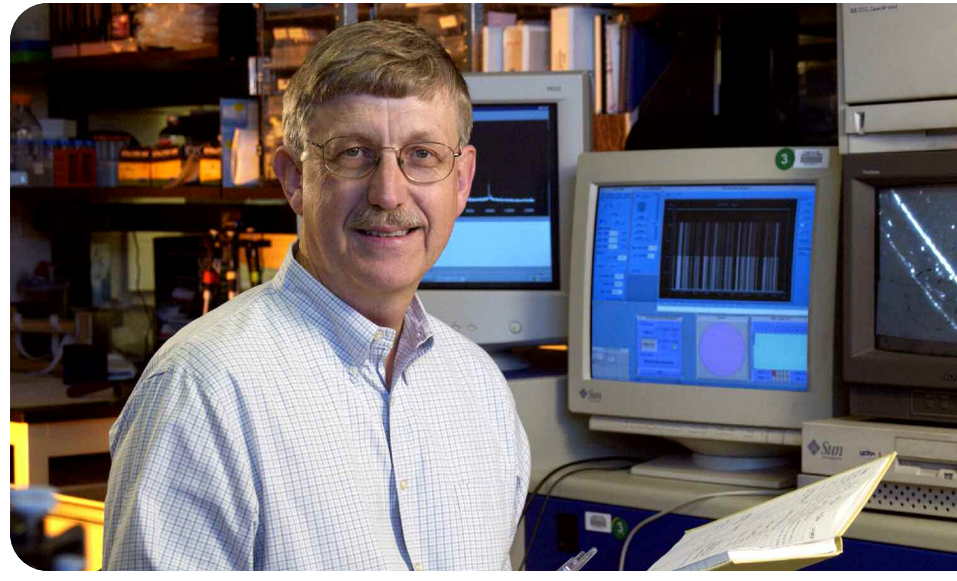
Dr. Collins' laboratory seeks to identify and understand the function of genes involved in a range of human diseases. His group is also developing animal models of genetic disorders to test potential therapeutic approaches.

A significant project that Dr. Collins directs focuses on Hutchinson-Gilford progeria syndrome (HGPS), a rare genetic disorder characterized by rapid premature aging. HGPS patients typically die from cardiovascular complications in their teens. Dr. Collins' laboratory recently discovered that a point mutation in the lamin A gene (*LMNA*) activates a cryptic splice donor, resulting in shortening of the normal version of the encoded protein by 50 amino acids near the C-terminus. They also found that HGPS is associated with significant changes in the shape of the nucleus; these structural defects worsen as HGPS cells age in culture. The severity of nuclear changes correlates with an increase in the mutant protein, called progerin; introducing progerin into normal cells induces the same nuclear changes. Recent work also implicates progerin in disrupting the normal process of mitosis.

The lamin A protein is normally farnesylated at its C-terminus, which apparently helps target the prelamin to the inner surface of the nuclear membrane. A subsequent protease cleavage releases this C-terminal fragment, allowing lamin A to join other proteins in the scaffold that lies just under the nuclear membrane. Progerin is able to be farnesylated, but cannot be cleaved, rendering it permanently anchored in the nuclear membrane, binding other proteins to it as well, and functioning as a dominant negative. Cell-culture experiments in the Collins laboratory have shown that farnesyltransferase inhibitors (FTIs) can significantly ameliorate the nuclear-shape abnormalities seen in HGPS cells.



Because most progeria patients are in extremely fragile health, there are few opportunities to conduct human trials of potential therapies. Dr. Collins' group has developed an animal model of progeria by reengineering human *LMNA* to carry the HGPS mutation, and inserting it into the germline of a mouse. The mouse develops normally, without progeroid features in skin, hair, or bone, but demonstrates progressive cardiovascular disease that closely resembles the disease seen in HGPS patients, most of whom die of heart attack or stroke in their early teenage years. Specifically, these mice exhibit progressive loss of vascular smooth muscle cells in the media of their large arteries. This mouse model now offers a valuable resource for screening potential progeria therapies; in fact, early results from treating the progeria mice with FTIs show considerable promise.



The Collins laboratory is also applying positional-cloning techniques to more difficult, non-Mendelian conditions. In a major long-term project involving researchers at the Finnish National Public Health Institute, the University of Michigan, the University of Southern California, and the University of North Carolina, Dr. Collins and his collaborators are studying nearly 10,000 individuals to identify susceptibility factors for type 2 diabetes (T2D). The FUSION project (Finland — United States Investigation Of NIDDM), using linkage studies of affected sib pairs, initially identified

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regions of chromosomes 6, 11, 14, 20, and 22 that may harbor diabetes-susceptibility genes. On chromosome 20, specific variations in the region of an alternative promoter of the *HNF4A* gene have been found to confer susceptibility to T2D, a result that has been confirmed by several other groups. The project has also confirmed the association of variants in the *TCF7L2* gene with T2D, and developed interesting new data to suggest how the variations (which are outside the coding region) might affect gene function. Furthermore, with the advent of the HapMap and the ability to undertake genome-wide association (GWA) studies, the search for T2D-susceptibility genes in the FUSION project has accelerated dramatically. In stage 1 of this GWA study, a total of 1,200 cases and 1,200 controls have been studied using the Illumina 317K genome-wide single-nucleotide polymorphism (SNP) panel; several interesting associations are now being tested in a stage 2 analysis of an even larger number of cases and controls. These results are being compared with those of other large association studies of T2D. Based on extensive experience in molecular biology, cell biology, genetics, and animal models, the Collins laboratory is ready to plunge into functional analyses of any T2D variants as soon as they are convincingly validated.

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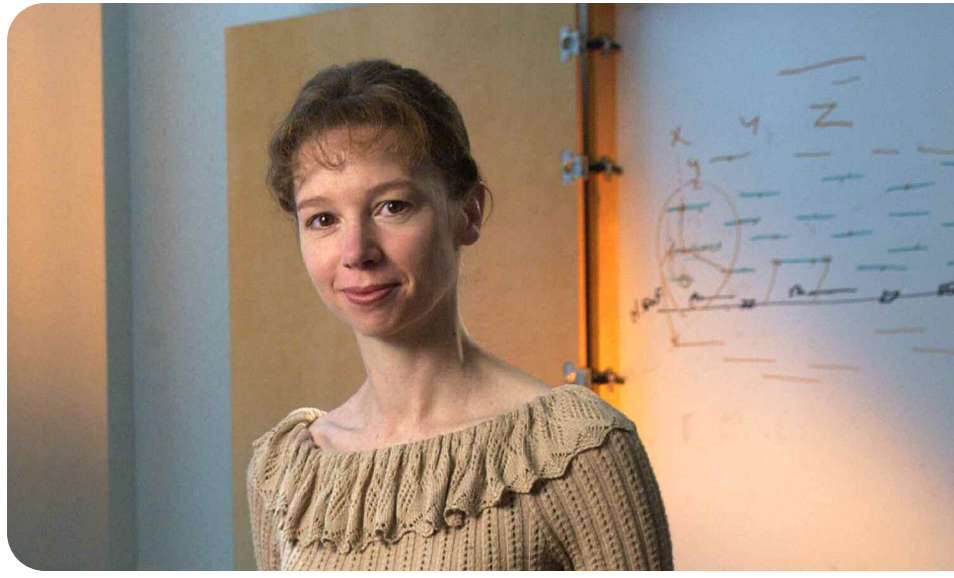
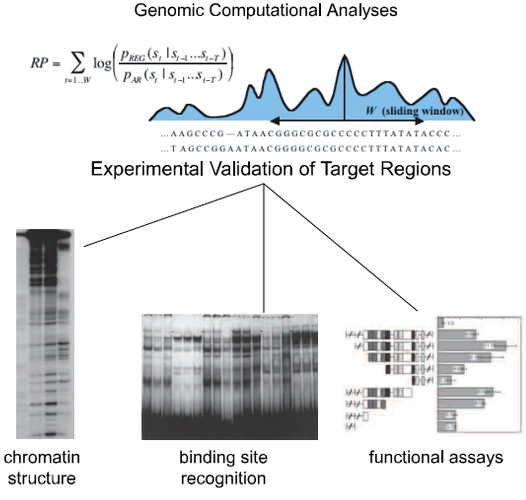
LAURA L. ELNITSKI, Ph.D.



Dr. Elnitski is a molecular and computational biologist who uses experimental and bioinformatic methods to discover noncoding functional elements in the human genome. Genes, which are the functional elements that encode proteins, make up less than 2% of the human genome. Other functional elements such as promoters, enhancers, repressors, and RNA-splicing signals have important biological roles, particularly in regulating temporal and spatial patterns of gene expression. Still in its infancy, the science of identifying and understanding these noncoding functional elements is crucial to providing a full understanding of the human genome. Dr. Elnitski uses sequence conservation among species as a guide to finding functional elements. Cross-species comparisons enable scientists to zero in on sequences that have been highly constrained to remain the same throughout evolution, often reflecting the most functionally important regions in the genome. Dr. Elnitski's group develops computational approaches that discriminate regulatory regions (i.e., sequences that control gene expression) from those that are neutrally evolving (i.e., sequences that are not under selection to remain the same). Researchers can use these approaches to investigate the regulatory regions influencing the expression of selected genes.

In addition, Dr. Elnitski's laboratory is investigating less characterized functional elements in the human genome. In one project, her group is looking at how exonic splicing enhancers (ESEs) correlate with alternative splicing patterns in multispecies sequence alignments. Present in most mammalian exons, ESEs are short sequences that influence the process of RNA splicing, in which introns are removed from a primary transcript and exons are joined to produce a mature transcript. ESEs also influence the selection of correct splice sites (or signals) located at the boundaries between exons and introns during precursor messenger RNA (mRNA) editing. The correct choice is essential not only for the production of proteins derived from the right combination of exons, but also for alternative splicing choices — such as exon skipping — that occur in specialized tissues or at different developmental stages. As part of this project, Dr. Elnitski seeks to investigate the role of ESEs in unnatural exon skipping and their relevance to several cancers and inherited diseases in humans. For example, exon skipping is caused by genetic mutations in the *BRCA1* and *CFTR* genes, which are associated with breast cancer and cystic fibrosis, respectively. For this analysis, she will study human mutations that fall within predicted ESEs and result in improper splicing.



Dr. Elnitski's group is also examining the regulation of gene expression in the human genome. One project examines bidirectional promoters, which are defined as the regulatory regions falling between two adjacent genes whose transcription initiation sites are neighboring but oriented away from each other. These promoters are often associated with genes that are implicated in somatic cancers. Thus, identification of all genes with this promoter structure could provide new insight into human disease. Genes regulated by

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bidirectional promoters can be coexpressed, suggesting that common transcription factor-binding sites are involved in their regulation. Furthermore, aberrant methylation of these promoters can lead to silencing of their expression. This event would affect expression of both genes flanking the bidirectional promoter. Dr. Elnitski has computationally mapped all bidirectional promoters in the human genome. The results of this analysis are being used to find targets of aberrant methylation in ovarian cancer tumor samples.

Finally, Dr. Elnitski is extensively involved in NHGRI's ENCODE (*Enc*yclopedia *o*f *D*NA *E*lements) project, which aims to produce a comprehensive catalog of functional elements in the human genome, starting with a pilot phase focusing on 1% of the genome. She is particularly interested in developing a database to query and store functional data generated from analyses performed using multispecies sequence alignments.

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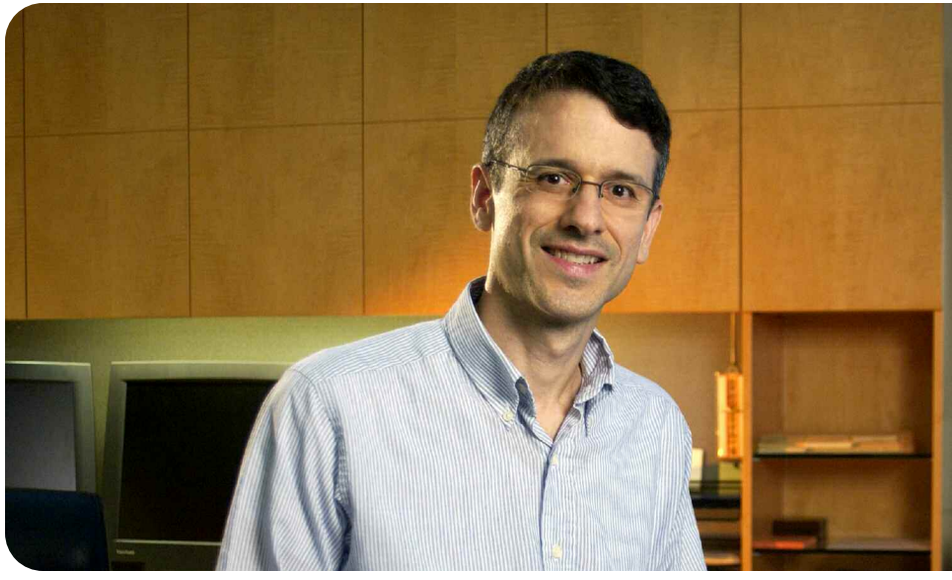
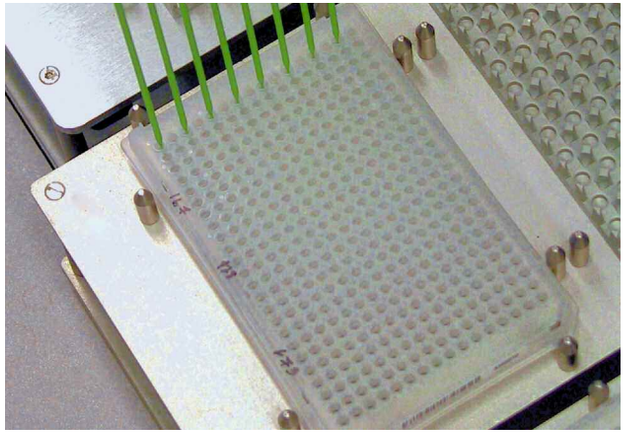
JAMES INGLESE, Ph.D.



Dr. Inglese investigates the interactions of small molecules with biological targets. His expertise is in developing, optimizing, and miniaturizing biochemical and cell-based assays for studying cell-surface and nuclear receptors, signal transduction and metabolic enzymes, and targeted pathways and genomes. Currently, he is developing the infrastructure of the NIH Chemical Genomics Center (NCGC), the first component of a nationwide network of screening centers that will produce innovative chemical probes for use in biological research and drug discovery.

Today's pharmaceuticals are directed toward fewer than 2% of the proteins encoded by the human genome, leaving ample opportunity for the discovery of myriad novel disease-intervention options. Of the approximately 25,000 human genes unearthed by genomic sequencing, those capable of modulating human disease remain relatively unknown. Identifying proteins involved in disease without the insights gained from years of intensive biomedical research is a daunting task. In an attempt to overcome such obstacles, Dr. Inglese applies state-of-the-art, high-throughput (HT) screening and assay technologies to the search for novel chemical probes that can regulate protein-protein interactions and gene expression.



A veteran of the pharmaceutical and biotechnology industry, Dr. Inglese has developed many biological assay methods, including one of the first high-sensitivity fluorescence G protein-coupled receptor assays. He pioneered the use of laser-scanning imaging, a technology that enables the use of cellular and particle-based assays in whole cell ligand-binding studies. He also developed chemical methodologies to incorporate cAMP-dependent protein kinase (PKA) sites into proteins, peptides, and small molecules permitting straightforward PKA-dependent labeling of ligands for use in radiometric assays. Most recently, he explored the use of naturally occurring protein domains, in combination with protein evolution techniques, to create antibody surrogates for the detection of post-translationally modified peptides and proteins. Such engineered domains have been used successfully in the development of protease and phosphatase assays for HT screening.

For NCGC, Dr. Inglese is developing and refining HT techniques for novel assay technologies and small molecule discovery processes. These assays may include bioactivity confirmation assays, potency determinations, and phenotypic cell-based assays focused on small molecule modulators of protein-protein interactions. To aid in the identification of chemical ligands for proteins of unknown function, he will lead a major effort to amass and

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analyze a diverse spectrum of interesting compounds that may not have been tested in the past because they were not considered to have drug-like potential. This collection will include many of the natural products classified as cellular metabolites and biosynthetic intermediates.

HT technologies, which allow for simultaneous collection of data from thousands of individual assays, often involve a fusion of biology, automation, and complex data analysis. Thus, their success is contingent on assembling a multidisciplinary team of scientists, engineers, and bioinformatics experts. For this reason, when fully developed, NCGC will have a large, technically diverse staff with expertise in several areas, including biomolecular screening and profiling, chemistry, and informatics.

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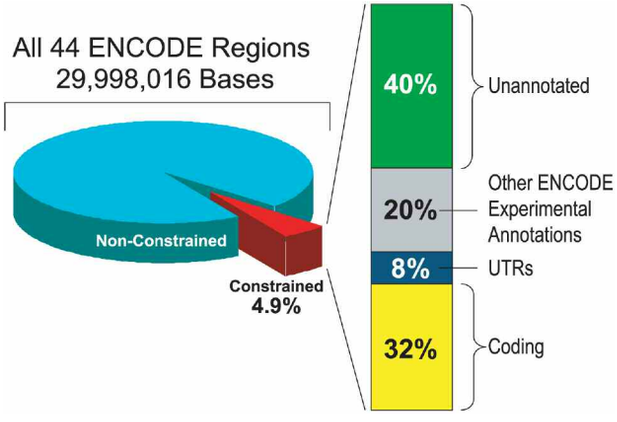
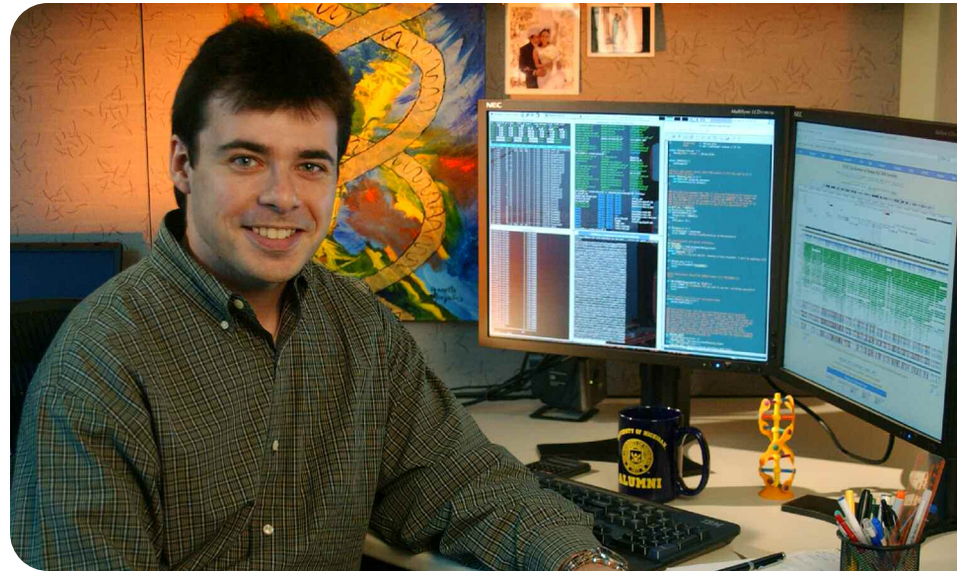
ELLIOTT MARGULIES, Ph.D.

Dr. Margulies develops bioinformatics approaches for identifying and characterizing regions of the human genome that are evolutionarily conserved across multiple species. The conservation of these sequences over millions of years of evolution is strong evidence that they play important roles in biology, such as coding for genes or functioning as regulatory elements. He has played an important role in advancing the goals of the NISC Comparative Sequencing Program over the past several years.

Dr. Margulies' group utilizes both high-performance computational analyses and laboratory-based high-throughput genomic methods to decipher the genetic information that confers biological function. Indeed, many functions encoded within the genome are likely yet to be discovered; however, uncovering these basic biological phenomena is essential for understanding human development and disease. A major component of Dr. Margulies' research program involves developing and implementing analytical methods for detecting evolutionarily conserved sequences and determining their functional significance. As more vertebrate genomes are sequenced, the evolutionary depth of sequence data sets allows Dr. Margulies to refine algorithms that can detect different kinds of conserved sequences, such as those present only in a subset of species (e.g., primates or certain lineages of mammals).

To better understand the relationship between evolutionary sequence constraint and the functional elements encoded in the human genome, Dr. Margulies is developing approaches to characterize conserved sequences. Through his participation in the ENCODE consortium, he is examining the patterns of overlap between constrained sequences and specific genomic functions, such as RNA transcription, chromatin accessibility, or DNA-protein interactions. The results emanating from this work not only highlight the functional significance of evolutionarily conserved sequences, but they also point to new approaches for assessing evolutionary conservation.





Toward that end, Dr. Margulies is also developing new methods for detecting cross-species conservation that take into account the important role the three-dimensional chromatin structure of DNA plays in genome function. Two approaches are currently being pursued. The first involves looking at structural conservation, as it has been shown that different DNA sequence patterns can produce similar three-dimensional structures. Using this information, Dr. Margulies is analyzing the structural similarity of orthologous genomic regions from different species. The second approach involves evaluating functional conservation across different species. Using multi-species sequence alignments as a framework, specific functions (e.g., the binding of certain protein) can be found that occur in the same relative position in multiple species. In some cases, these sequences are quite different among species, yet they confer similar function. By analyzing these sequences more carefully, Dr. Margulies hopes to uncover how the genome can encode function in ways other than through its primary sequence.

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In addition to these computational-based projects, Dr. Margulies is developing comprehensive high-throughput methods to assay large regions of the genome for transcriptional regulatory activity. He eventually hopes to expand these methods so that an entire genome can be assayed at once. By coupling the data generated in the laboratory with the various computational methods, his group hopes to create synergistic, multidisciplinary approaches for revealing the myriad functions encoded in the human genome.

Finally, Dr. Margulies plans to establish computational and experimental tools to analyze the data that will be produced by the next generation of DNA sequencing technologies. These new sequencing platforms will generate several orders of magnitude more data than current DNA sequencing technologies can, at greatly reduced costs. They will therefore be of great interest to smaller, investigator-driven research programs and potentially to clinical laboratories.

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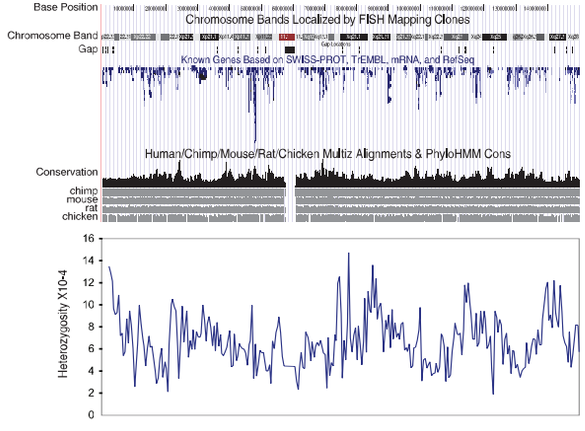
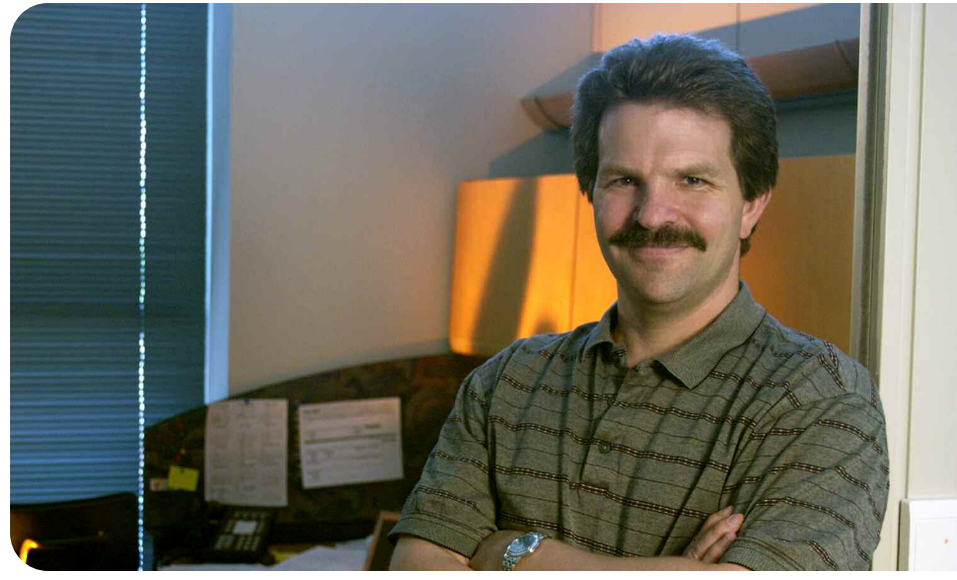
JAMES C. MULLIKIN, Ph.D.

Dr. Mullikin develops and utilizes computer programs to analyze large data sets generated through systematic DNA sequencing projects. A highly skilled computational geneticist, he collaborates extensively with other genomic researchers, analyzing data others collect or that are available in public databases.

His main work involves creating algorithms for performing complex computations. He designed one such program, called Sequence Search and Alignment by Hashing Algorithm (SSAHA), to dramatically accelerate the speed at which gigabases of DNA sequence are searched for single nucleotide poymorphisms (SNPs). The program was developed several years ago, and Dr. Mullikin is still refining SSAHA in response to the continually changing needs of genomic scientists. SSAHA remains the key tool that he and others use to detect genetic variation. He also developed a program called Phusion — pronounced "fusion" — for assembling a genomic sequence from a whole-genome shotgun data. The genomic sequences of both mouse and the nematode (*Caenorhabditis elegans*) were assembled using Phusion.

Dr. Mullikin's group also provides computational support to major NHGRI efforts, such as the International Haplotype Map (HapMap) Project, which is primarily focused on determining genes and genetic variations that affect health and disease susceptibility. In the initial phase of the project, investigators aim to produce a working HapMap consisting of about 600,000 polymorphic sites roughly 5 kb apart from one another. Some particularly complex regions will need even higher resolution. When completed, the HapMap Project will give researchers a powerful tool for isolating and identifying disease genes through association studies.





In addition, Dr. Mullikin is developing algorithms for NHGRI's comparative sequencing efforts, which involve the sequencing of many additional vertebrate genomes to help annotate the human sequence. Because only 1% to 2% of the human genome codes for protein, comparing the human genome with that of other vertebrates is key to highlighting other regions that are functionally important. In humans and mice, for example, as much as 3% of the noncoding sequence seems to have been conserved. Dr. Mullikin and other scientists are working to determine what these conserved, noncoding sequences are doing; some probably are involved in gene regulation, while others may have structural roles.

In one project, he is developing signal processing algorithms for sorting out the confusion that can result when polymerase chain reaction technology is used to amplify a segment of the genome for subsequent SNP discovery.

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During such a process, two copies of every chromosomal region (except for those on the X and Y chromosomes in males) can get sequenced. This can be confusing in heterozygous cases, where the regions contain different SNPs. Simply allowing for the possibility of a heterozygous state is not the answer; it merely increases the error rate. Dr. Mullikin is trying to devise software for unraveling the signals so the correct information can be captured. To take the algorithm a step farther, he is working on methods for reliably detecting insertion-deletion polymorphisms — situations where an entire sequence is inserted or deleted, which creates a much more complicated signal than does an individual base change. His work should make it possible to extract that information from the mixed signals.

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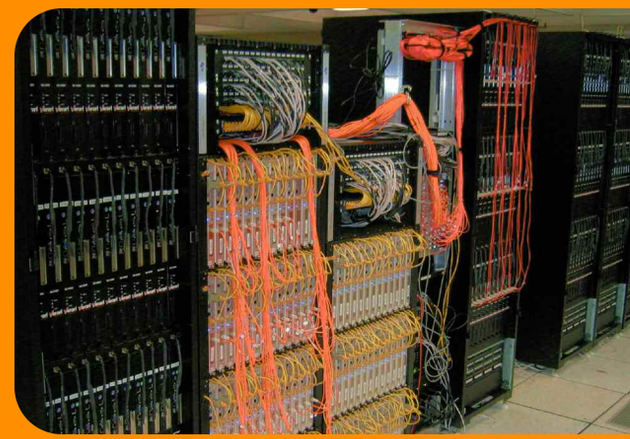
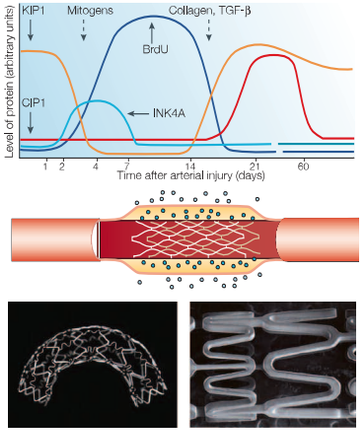


ELIZABETH G. NABEL, M.D.

Dr. Nabel's laboratory seeks to identify the molecular, cellular, and genetic mechanisms that cause vascular disorders. In particular, her research focuses on defining the pathways that regulate cell growth in the vasculature, remodel the vasculature after injury, and lead to genetic susceptibility to vascular diseases. Taken together, these studies focus on the molecular genetics of vascular diseases, with an emphasis on cell cycle regulation of proliferation, inflammation, and apoptosis.

Cardiovascular diseases are the leading cause of morbidity and mortality in industrialized countries. Most cardiovascular diseases result from complications of atherosclerosis, which is a chronic and progressive inflammatory condition characterized by excessive cellular proliferation of vascular smooth muscle cells, endothelial cells, and inflammatory cells that leads to occlusive vascular disease, myocardial infarction, and stroke. Recent studies have revealed the important role of cyclins, cyclin-dependent kinases (CDKs), and cyclin-dependent kinase inhibitors (CKIs) in vascular and cardiac tissue injury, inflammation, and wound repair. Dr. Nabel's research seeks to understand the circuitry of the cyclin-CDK-CKI interactions in normal physiology and disease pathology, providing a better understanding of the molecular mechanisms of cardiovascular diseases. This approach will hopefully lead to the rational design of new classes of therapeutic agents.

Given the role of cyclins in vascular health, one major focus of Dr. Nabel's laboratory is the study of CKIs, which are primarily involved in inhibiting the proliferation of a variety of normal cell types. Dr. Nabel's laboratory previously identified a particular CKI, known as $p27^{Kip1}$, as a major regulator of vascular cell proliferation during arterial remodeling. In one set of studies, her group found that $p27^{Kip1}$ plays a major role in cardiovascular disease through its effects on the proliferation of bone marrow-derived immune cells that migrate into vascular lesions. To demonstrate whether $p27^{Kip1}$ regulates arterial wound repair, Dr. Nabel and coworkers recently subjected $p27^{-/-}$ (homozygous knockout), $p27^{+/-}$ (heterozygous knockout), and $p27^{+/+}$ (wild-type) mice to a wire injury in the femoral artery and examined subsequent cell proliferation and lesion formation. Cell proliferation was significantly increased in the innermost lining of the blood vessels of $p27^{-/-}$ mouse arteries compared with $p27^{+/+}$ arteries. Arterial lesions also were markedly increased in the $p27^{-/-}$ mice compared with those of $p27^{+/+}$ mice. The heterozygous knockout mice ($p27^{-/+}$) had an intermediate phenotype. These findings suggest that vascular repair and regeneration are regulated by the proliferation of hematopoietically and nonhematopoietically derived cells through a $p27^{Kip1}$-dependent mechanism, with immune cells largely mediating these effects.



A related area of Dr. Nabel's program focuses on the structural and functional analysis of a serine-threonine kinase called kinase interacting stathmin, or KIS. A nuclear protein that binds the C-terminal domain of $p27^{Kip1}$, KIS phosphorylates a serine residue at position 10 (Ser 10) in the sequence and thereby promotes its export to the cytoplasm. KIS is activated by mitogens during G0/G1, and expression of KIS overcomes growth arrest induced by $p27^{Kip1}$. Depletion of KIS with small interfering RNA (siRNA) inhibits Ser 10 phosphorylation and enhances growth arrest. In addition, treating $p27^{-/-}$ cells with KIS siRNA causes them to grow and progress to S/G2, similar to control-treated cells, implicating $p27^{Kip1}$ as the critical target for KIS. Dr. Nabel's laboratory previously cloned and characterized the

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gene encoding this kinase and is now conducting studies to examine its structure and function, including the transcriptional control of the KIS promoter, the phenotypic consequences of knockout of the KIS gene in mice, and the effect of knock-in mutations at different phosphorylation sites of p27.

Dr. Nabel's group is also involved in a clinical study of the genetics of restenosis, which is the recurrence of a blockage in an artery after it has been manually reopened with an artificial stent. Restenosis is a major limitation of stent therapy for coronary artery disease. In this study, the investigators are following patients who have received bare metal stents for the treatment of a blocked coronary artery and then comparing the genetic profiles of patients with restenosis with those of patients with no restenosis. The genetic analyses include gene expression profiling, serum proteomics, and genotyping using candidate gene and genome-wide scanning approaches. The goal is to identify gene, RNA, and protein profiles of patients with recurrent restenosis, so as to advance our understanding of the pathogenesis of this problem and to target potential therapies.

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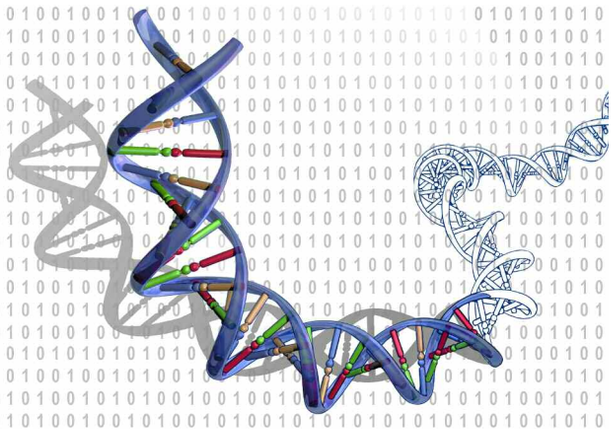
TYRA G. WOLFSBERG, Ph.D.

Dr. Wolfsberg applies bioinformatics techniques to a variety of genomic research questions, such as identifying gene-regulatory sequences on a genome-wide basis and understanding the behavior of retroviruses used as vectors in gene-therapy experiments. As Associate Director of NHGRI's Bioinformatics and Scientific Programming Core, she also devotes part of her time to overseeing the day-to-day operation of this state-of-the-art computing facility (see *Cores, Centers, and Offices*).

Dr. Wolfsberg's research primarily involves collaborations with other NHGRI and outside scientists. For example, she is collaborating with Dr. Francis Collins' group to develop a genome-wide library of gene-regulatory sequences. This effort aims to scale up a proven but labor-intensive method of finding gene-regulatory elements — locating transcriptionally active regions of DNA by finding sites that are sensitive to deoxyribonuclease (DNase).

Dr. Wolfsberg has devised an approach for analyzing putative DNase-sensitive regions and establishing whether they represent transcriptionally active regions. Her analyses have shown that such hypersensitive sites do indeed reside more frequently in regions known to contain regulatory elements, such as segments upstream of genes, sequences within CpG islands (unmethylated regions of the genome that are associated with the 5′ ends of most housekeeping genes and many tissue-specific genes), and regions where the human and mouse genomes are similar. Dr. Wolfsberg and her colleagues are now scaling up this process to deal with up to 100,000 such sites in the human genome. This scale-up involves the development of new computer protocols for handling the sheer volume of raw data in a way that is computationally efficient and tractable.



In another line of research, Dr. Wolfsberg is working with other NIH laboratories to determine whether the retrovirus vectors currently used in *ex vivo* gene-therapy experiments integrate preferentially into the DNA of their target cells or at random. The answer to this question could have a major bearing on the prospects for gene therapy using these vectors. Originally, it was believed that the retroviruses used to carry therapeutic genes in *ex vivo* gene therapy would integrate themselves in a random manner and that the chances of their disrupting a gene or interfering with gene expression were remote.

However, in 2002, it was revealed that three out of ten children who had been treated for X-linked severe combined immunodeficiency type 1 in a French gene-therapy experiment had developed uncontrolled proliferation of mature T cells — a leukemia-like disorder. In both cases, some of the recombinant retroviruses had inserted themselves near the promoter of the *LMO2*

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oncogene, which encodes a transcription factor involved in hematopoiesis. In late 2003, the French team carrying out the trial concluded that integration of the virus at that site led to uncontrolled overexpression of the gene. Since then, research into whether particular retrovirus vectors favor certain sites in the genome over others has produced mixed results. Dr. Wolfsberg is helping her collaborators at NHGRI and at the National Heart, Lung, and Blood Institute to determine whether these viral vectors integrate randomly or preferentially.

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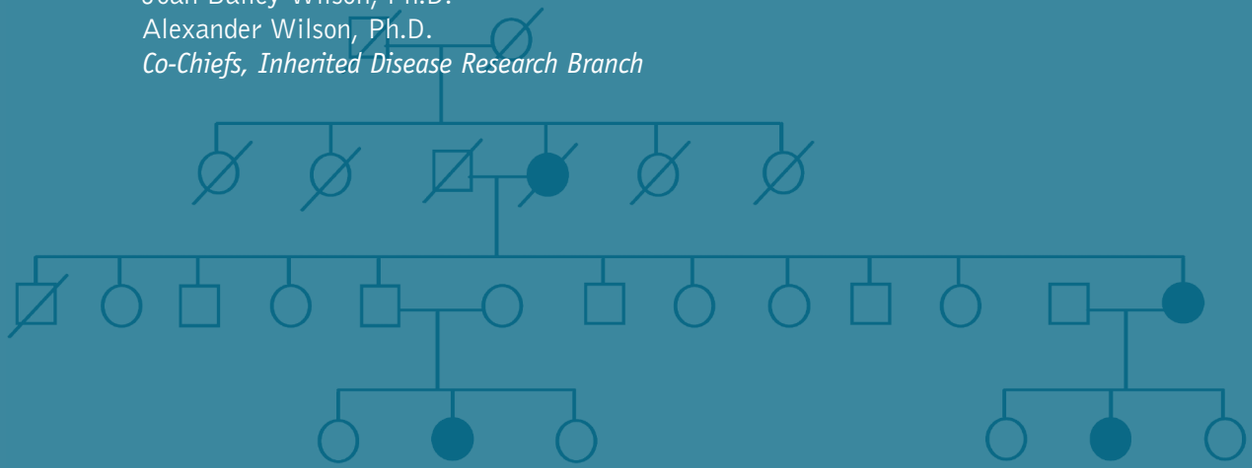
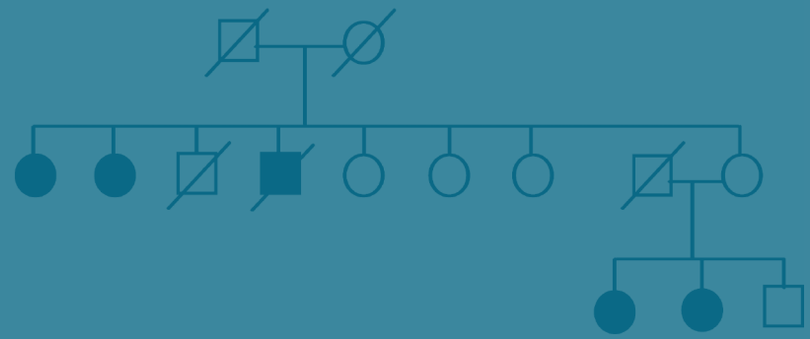
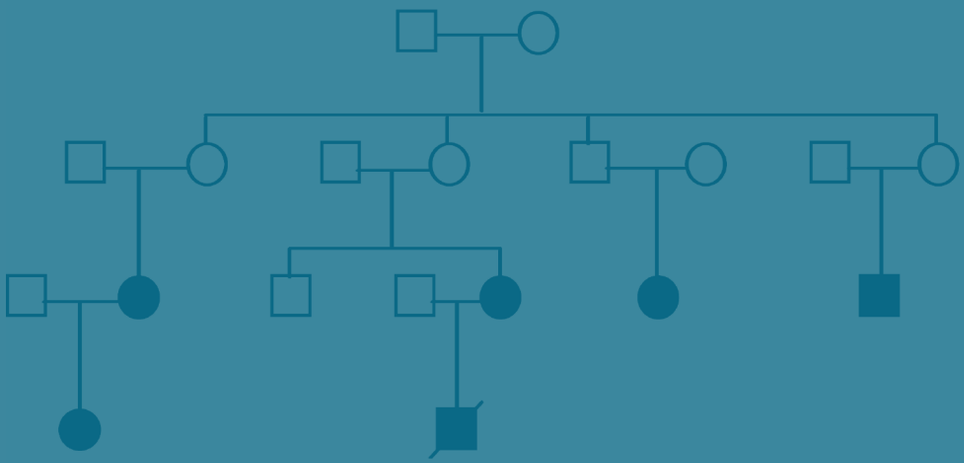
"The field of **statistical genetics is reaching a critical stage** in its ability to inform our understanding of the genetic contributions to complex diseases. Indeed, we are to the point where we can now identify specific genetic variations as contributing factors to a specific disease."

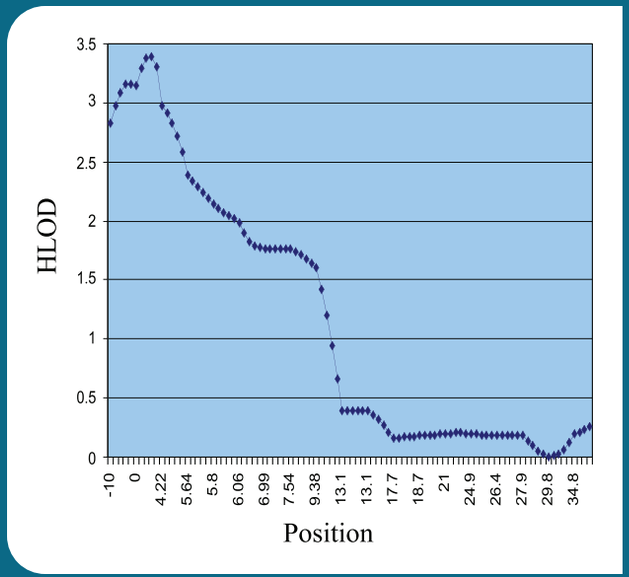
Joan Bailey-Wilson, Ph.D.
Alexander Wilson, Ph.D.
Co-Chiefs, Inherited Disease Research Branch

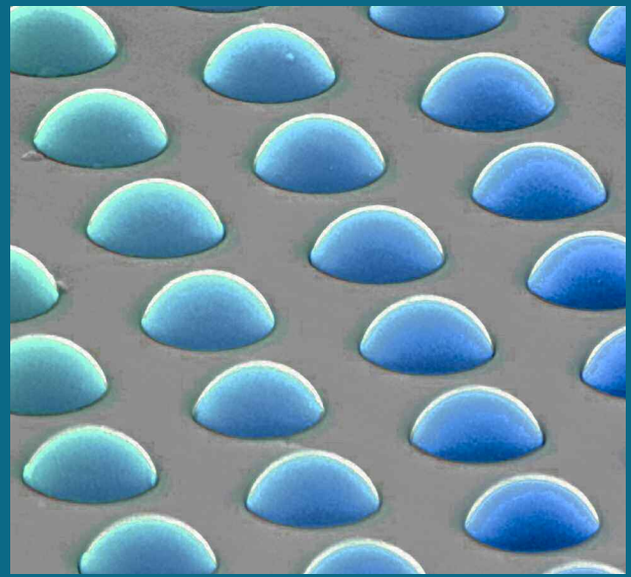


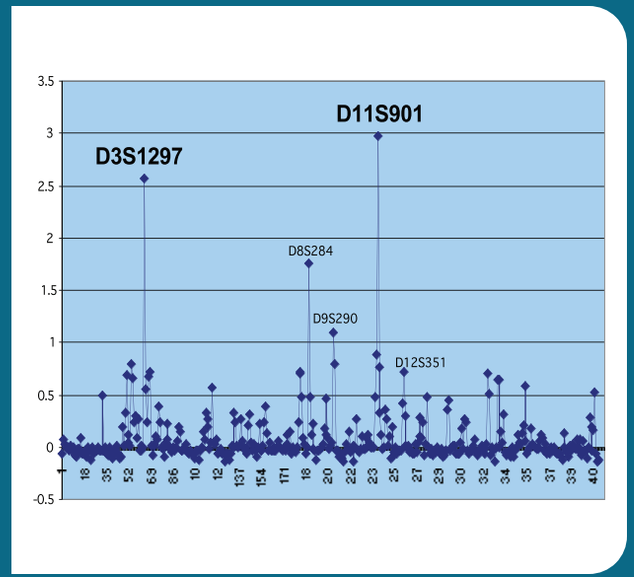




INHERITED DISEASE RESEARCH BRANCH







The Inherited Disease Research Branch (IDRB) develops and applies new methods and tools to identify genetic contri butions to human disease, with particular emphasis on the study of common multi factorial disorders. IDRB investigators specialize in statistical genetics and genetic epidemiology, which are disciplines of genetics that combine statistics, epidemiology, mathematics, molecular genetics, and computer science to identify genetic variants responsible for increased susceptibility to disease and variation of phenotypic traits. The Branch also serves as a major link between NHGRI and the Center for Inherited Disease Research (CIDR), a Federally supported facility located at The Johns Hopkins University in Baltimore, Maryland that provides high throughput genotyping to scientists at NIH and at research institutions around the world.

Statistical genetics approaches are becoming increasingly important due to the availability of prodigious amounts of genomic data being collected from individuals. Moreover, the rapidly growing catalog of single nucleotide polymorphisms in the human population, the decreasing cost of genotyping, and the recent completion of a haplotype map of the entire human genome are giving this area of research unprecedented opportunities for advancing the study of complex genetic diseases. IDRB scientists capitalize on these opportunities by actively developing new statistical theories and software to analyze data sets emanating from large scale genetic association and linkage studies. They also use these innovative approaches to distinguish genuine genetic influences from random background noise.


INHERITED DISEASE RESEARCH BRANCH
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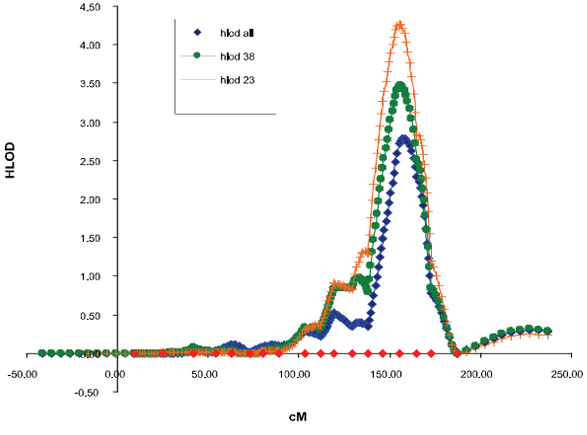
JOAN E. BAILEY-WILSON, Ph.D.

Dr. Bailey-Wilson develops new statistical methods and software and performs analyses that guide other genome scientists in their hunt for disease-associated genes. Trained in statistical genetics, she is interested in understanding the genetics of complex diseases and developing novel methodologies that can be used to disentangle the roles that genes and environment play in causing these diseases.

Collaborating with other researchers, Dr. Bailey-Wilson studies a range of diseases, including lung cancer, prostate cancer, breast cancer, myopia and other eye diseases, and cleft lip and palate. She is particularly interested in lung cancer, a research focus for her since the early 1980s — a time when very few scientists believed there might be a genetic link to lung cancer. Today, significantly more data support the idea that there are susceptibility alleles for one or more unknown genes that dramatically increase certain smokers' risk of developing lung cancer. Dr. Bailey-Wilson, working recently with both NIH and non-NIH scientists in a collaboration called the Genetic Epidemiology of Lung Cancer Consortium, narrowed down the location of a potential lung-cancer gene to a region of chromosome 6.

Dr. Bailey-Wilson and others have used similar approaches to locate other cancer-related genes. For example, in the mid-1990s, she and her collaborators published evidence that genes involved in prostate cancer reside on specific regions of chromosomes 1, 8, and X. These findings have been replicated, and two candidate genes have been cloned: *HPC1*, which encodes ribonuclease L, and *MSRI*, which encodes the macrophage scavenger receptor 1. In ongoing studies, Dr. Bailey-Wilson and her collaborators are looking for additional susceptibility genes for these and other cancers.



To keep pace with the analysis of the exponentially increasing number of genetic markers, Dr. Bailey-Wilson also develops novel computational methods. Just a few years ago, fewer than 100 of these "signposts" along the genome had been identified. Now, there are hundreds of thousands of known markers, and genome scientists identify more each day. Current computer programs cannot handle such large numbers of markers, so Dr. Bailey-Wilson is working with her colleagues to come up with tractable ways of addressing this problem. She also is working to address the problem of linkage disequilibrium, or the nonrandom association of closely spaced loci. Linkage disequilibrium can be caused by a low frequency of recombinations between two loci when they are very close together on a chromosome. The closer two loci are, the more likely they are to exhibit linkage disequilibrium. Thus, markers that are only 100 kb apart display significantly greater linkage disequilibrium than markers that are between 100 to 5,000 kb apart.

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Because standard statistical analysis methods typically assume no linkage disequilibrium exists between loci, Dr. Bailey-Wilson is adapting these methods to study sets of dense genetic markers. She has used these and other analytic methods to determine, for example, whether alleles at specific marker loci are transmitted along with a disease through the generations in families with several affected members. She and her coworkers also have used statistical methods to determine the marker alleles that people with a specific disease carry more frequently — and disease-free people carry less frequently — than can be explained by chance. This work has helped to greatly reduce the number of target regions through which investigators need to search for potential disease-related genes.

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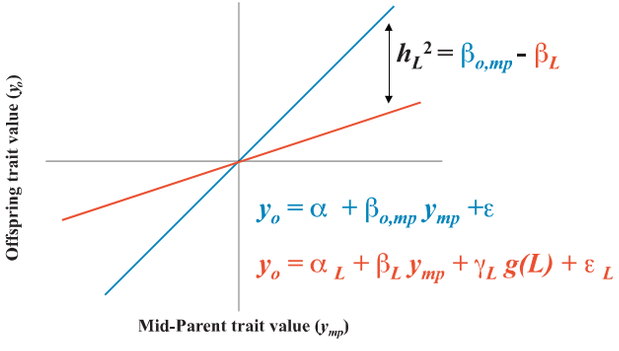
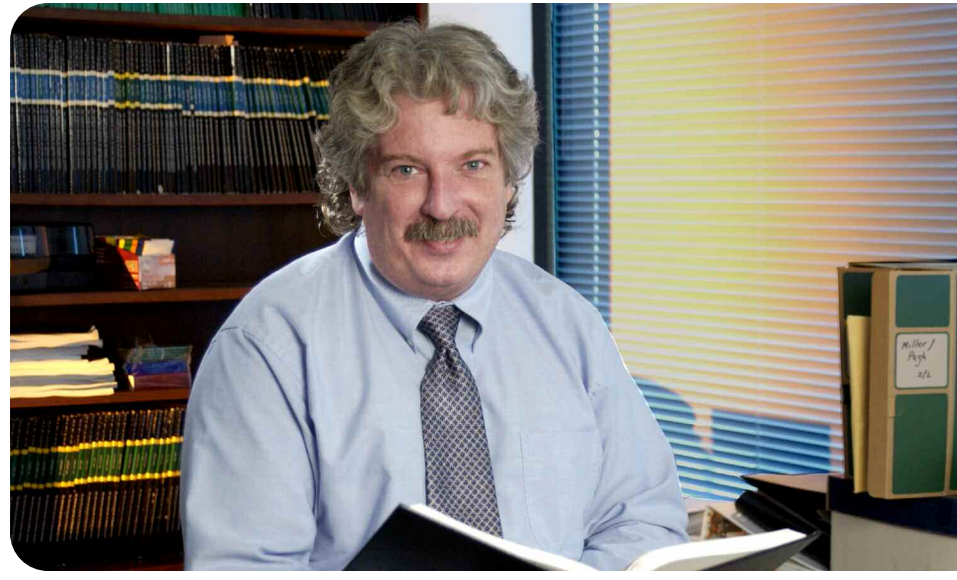
ALEXANDER F. WILSON, Ph.D.

Along with his background in medical genetics and biology, Dr. Wilson uses statistics, mathematics, and computer science to develop new methodologies for performing statistical genetic analysis. Most of the traits he studies are multifactorial, not Mendelian single-gene diseases. By analyzing the patterns of genetic markers in people with a disease and people who are healthy, Dr. Wilson's group identifies chromosomal regions where disease genes most likely reside.

Dr. Wilson's research covers a wide range of disorders, ranging from scoliosis (extreme curvature of the spine) to obesity and cardiovascular disease. Working with investigators at The Johns Hopkins University, Dr. Wilson's group recently determined that at least some cases of scoliosis are linked to a gene on the X chromosome, paving the way for research to identify the causative gene (or genes). This is a significant discovery, because scoliosis affects about one in 200 people, most often girls between 10 and 16 years of age. Although most cases are mild, some can be crippling.

Similarly, by analyzing data from an ongoing genotyping study of traits related to obesity in the Old Order Amish in Pennsylvania, Dr. Wilson's group recently found candidate regions for obesity-related genes on five chromosomes. The strongest signal was found on a region on chromosome 7 — in an area that holds a dozen or more genes encoding taste and smell receptors. Moreover, Dr. Wilson's group has collaborated in other studies that have provided evidence for the presence of genetic factors influencing body mass index (BMI), the standard measure of obesity. Ironically, BMI was once considered the prime example of a purely environmental factor that contributed to heart disease; researchers can now begin to elucidate the influence of genetics on an individual's BMI.





Dr. Wilson also helps to develop important new methodologies to bolster statistical geneticists' toolkits. For example, he combined a traditional test of heritability with a standard analysis of variance test in a way that simplifies and significantly reduces the cost of testing for the heritability of quantitative traits. This methodology is called regression of offspring on midparent (ROMP). Tests of association for quantitative traits traditionally have required genotyping parents and offspring in large numbers of families, a process that can be extremely costly. However, ROMP requires investigators only to genotype the offspring while phenotyping the parents. In a study of high blood pressure, for example, scientists would use ROMP to genotype the offspring while only checking the parents' blood pressures. When a series of computerized calculations is performed, ROMP can use

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these tests to estimate the heritability of the trait and determine whether the locus being studied contains a gene that affects the trait.

Dr. Wilson also created a software program called GASP (for Genometric Analysis Simulation Program), which enables scientists to create models of populations or of families with different mixtures of genetic and environmental influenced diseases. Because such data are often "noisy," GASP allows the creation of sample situations without extraneous factors, with one or more genes plugged in for analysis by various statistical methods. In this way, statistical geneticists can use GASP to try out new analytical approaches. Investigators at more than 70 institutions in at least 14 countries are using GASP to test new methodologies and as a teaching tool.

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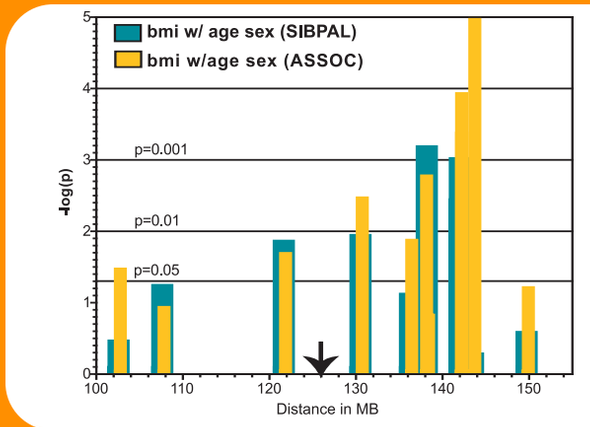
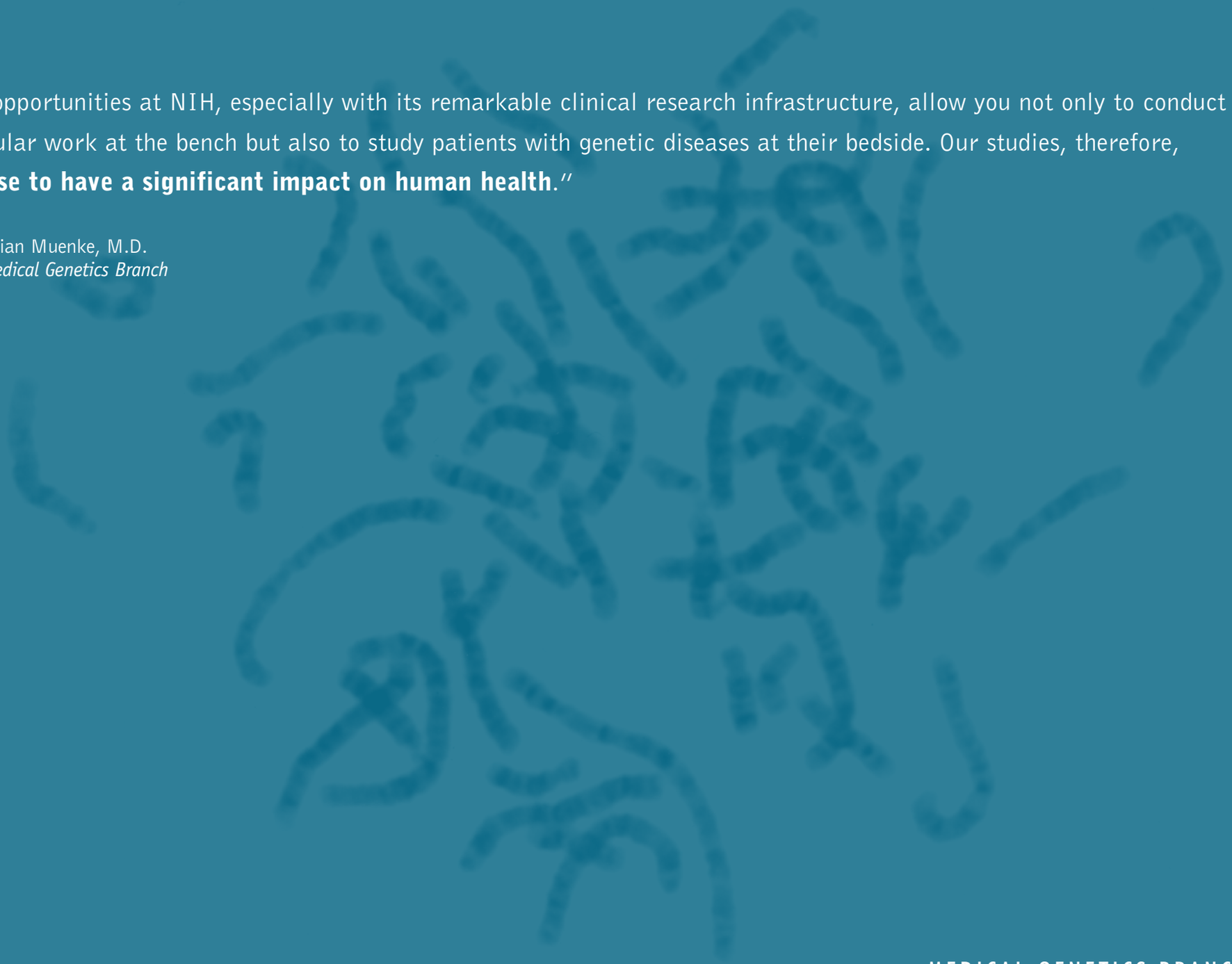
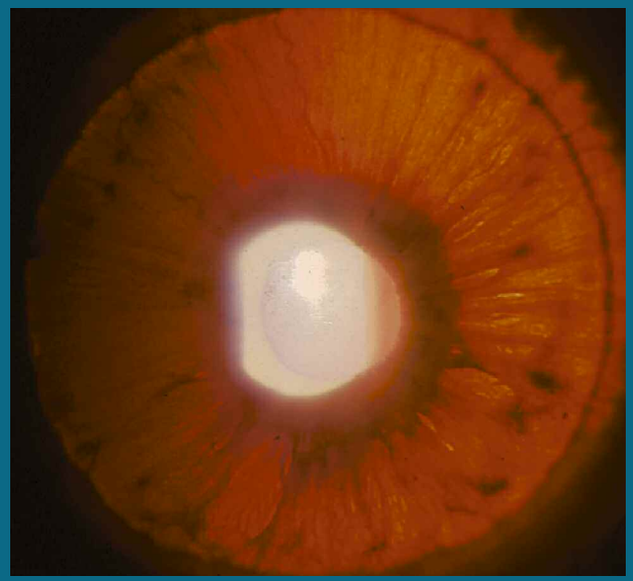


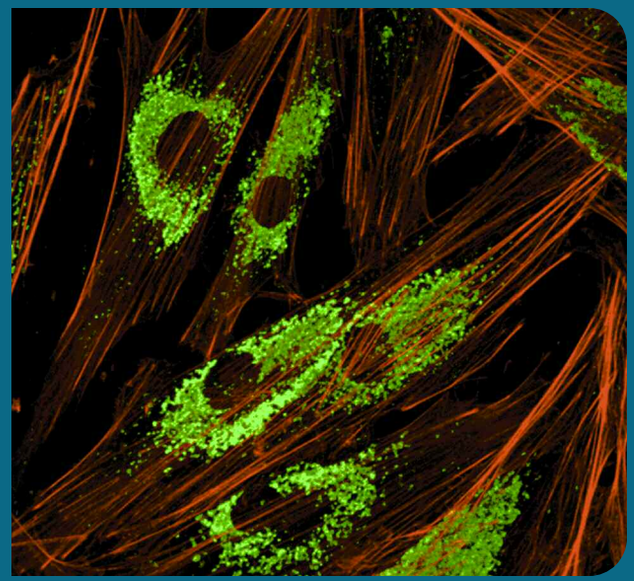
"The opportunities at NIH, especially with its remarkable clinical research infrastructure, allow you not only to conduct molecular work at the bench but also to study patients with genetic diseases at their bedside. Our studies, therefore, **promise to have a significant impact on human health**."

Maximilian Muenke, M.D.
Chief, Medical Genetics Branch



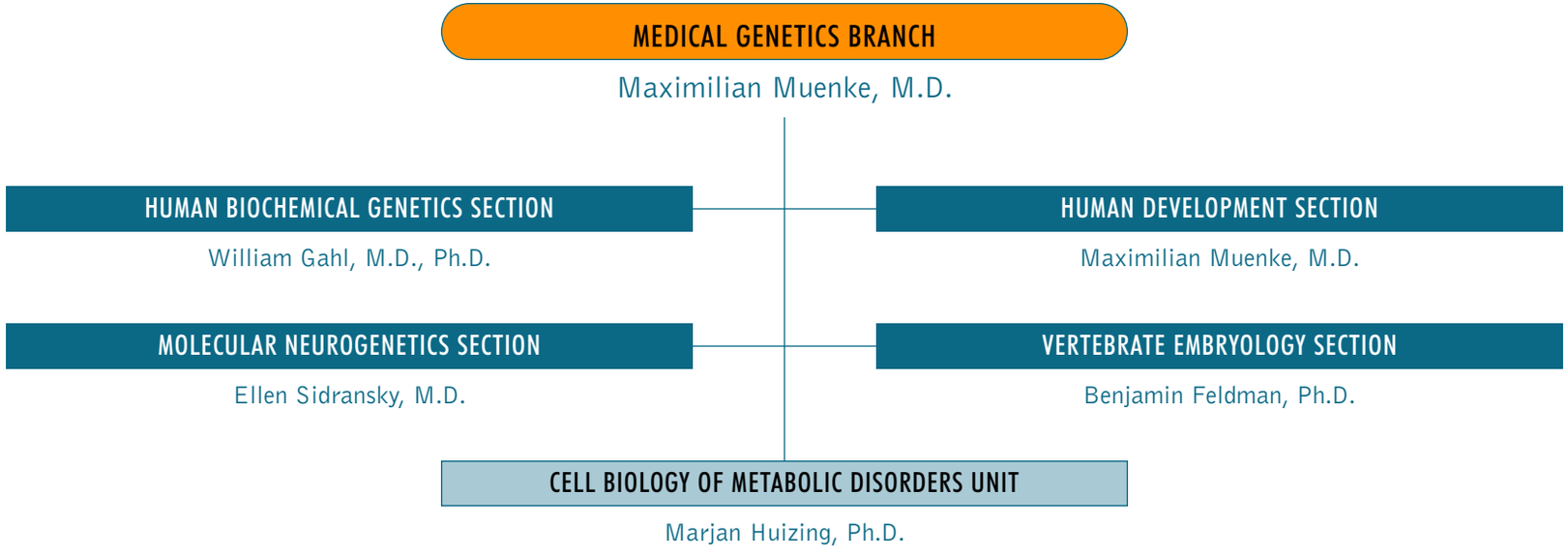
MEDICAL GENETICS BRANCH





The Medical Genetics Branch (MGB) seeks to identify and understand inherited disorders of metabolism and of human development. MGB investigators focus on human genetics, vertebrate embryology, inborn errors of metabolism, and neurogenetic disorders. Projects performed at the biochemical, molecular, and cell biological levels involve the direct study of human subjects as well as the development and use of experimental model systems, such as zebrafish and mouse. The Branch fosters outstanding basic research and serves as a model for translational research, emphasizing the compassionate and scientifically rigorous application of basic science discoveries at the bedside. Branch researchers develop and test new diagnostic tests and treatments for patients with rare genetic disorders in the NIH Clinical Center.

To achieve their goals, MGB investigators use a variety of cutting edge techniques to address questions regarding disease pathophysiology and human development. In addition to making extensive and selective use of genomic data, MGB researchers routinely capitalize on partnerships with key laboratories at NHGRI, NIH, and worldwide. The Branch attracts patients with rare disorders and engages in collaborations that have led to the acquisition of large sample sets from unique populations. Studies of these rare patients and populations have proven invaluable for advancing the mission of the Branch.


MEDICAL GENETICS BRANCH
Maximilian Muenke, M.D.
HUMAN BIOCHEMICAL GENETICS SECTION
William Gahl, M.D., Ph.D.
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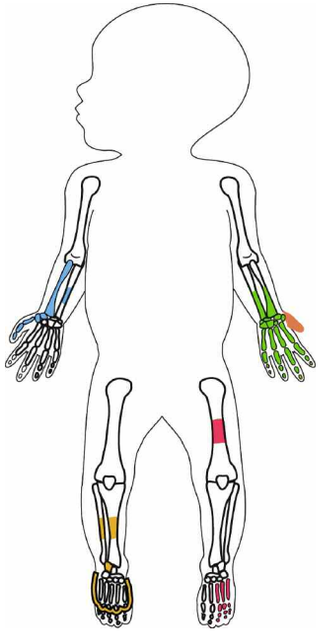
MAXIMILIAN MUENKE, M.D.

Dr. Muenke's research program seeks to improve knowledge about the formation of the central nervous system and to elucidate the origin of developmental disabilities and mental retardation. Specifically, his laboratory investigates birth defects that affect normal embryonic development and lead to neurological impairment. His two major areas of focus are holoprosencephaly and attention deficit hyperactivity disorder.

Holoprosencephaly (HPE) is a common brain birth defect that occurs in one in 250 embryos. HPE is characterized by the failure of the embryonic brain to divide properly into left and right hemispheres during early development. It frequently results in fetal demise, so the live birth rate is extremely low: approximately one in 10,000. Children born with the disorder show various degrees of developmental disabilities and mental retardation.

Dr. Muenke's laboratory discovered several genes associated with HPE and, in doing so, illuminated many of the molecular processes involved in early embryonic development. The first human HPE-related gene his group identified was Sonic Hedgehog (*SHH*), a gene initially found in fruit flies and named for the prickly appearance it gives them. Dr. Muenke and other investigators have since identified a number of additional genes in the Sonic Hedgehog and Nodal signaling pathways that are implicated in HPE. However, these genes still account for only 20% of documented HPE cases. Dr. Muenke's laboratory, thus, continues its hunt for new HPE-associated genes.



Dr. Muenke's group is also studying environmental factors that may affect the development of HPE, particularly cholesterol. It is well-known that cholesterol is necessary for the activation of *SHH*, and, in animal models, researchers have found an association between low maternal cholesterol during pregnancy and birth defects in their offspring. There have been reports of babies with various birth defects, including HPE, being born to women who took cholesterol-lowering statin drugs during pregnancy. One of Dr. Muenke's goals is to conduct a larger study to determine whether low maternal cholesterol can indeed adversely affect embryonic development. In related research, Dr. Muenke is studying laterality defects, or abnormal left-right positioning of body organs. In vertebrates, laterality defects occur very early in developmental processes, allowing some organs to end up on the wrong side of the body. Many people are unaware that they are affected by these disorders, but severe symptoms can (and often do) arise in their children.

Another major research area for Dr. Muenke's group involves understanding the genetic basis of attention deficit hyperactivity disorder (ADHD). ADHD is the most common behavioral disorder in children; it affects at least 4% to 6% of school-age children and five times as many boys as girls. ADHD, which is characterized by impulsiveness, hyperactivity, and attention problems, has been recognized as a distinct disorder for many years. Its cause has remained a mystery, although environmental factors were considered the most likely culprits. Over the past decade, however, studies

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of twins, adopted children, and families with a high prevalence of ADHD have shown that genetic factors, rather than environmental factors, are the major underlying cause of ADHD.

Building on research by investigators in Colombia studying 18 large, multigenerational families with a high incidence of ADHD, Dr. Muenke's laboratory conducted detailed phenotyping and genotyping of this population. His group found strong evidence for familial ADHD, including comorbidity to other behavioral disorders, such as nicotine dependence. Dr. Muenke's laboratory has now identified several candidate regions for ADHD in this population and is fine-mapping these regions to help identify specific contributing genes. They are conducting a similar study of more than 1,000 families in the United States. Because of the typically smaller size of American families, this second arm of the study focuses on families with only two children, at least one of whom has ADHD.

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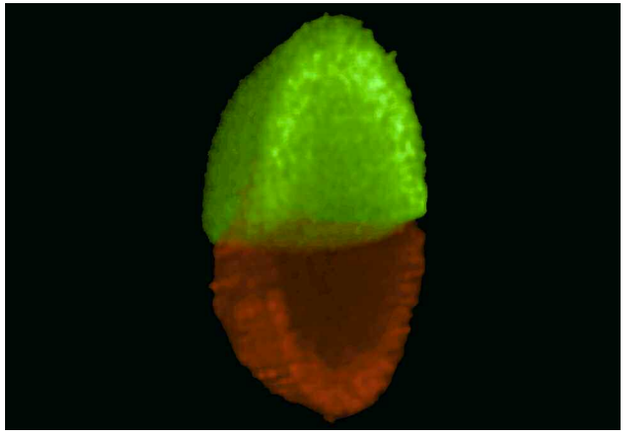
BENJAMIN FELDMAN, Ph.D.

Dr. Feldman's laboratory uses basic research approaches to investigate the genetic and biochemical causes of human genetic embryonic diseases. His main areas of research include elucidating the molecular and cellular mechanisms of gastrulation, developing models of human genetic diseases in zebrafish, and improving embryology research techniques.

Gastrulation is the process in which embryos undergo dramatic morphogenesis from a simple assembly of homogenous cells into highly diversified organisms with a recognizable body plan. Elucidating the molecular and cellular mechanisms of gastrulation is an important research goal, because genetic mutations or environmental insults during gastrulation can lead to significant developmental deformities and miscarriages. A more precise understanding of this process and how it is affected by genetic mutations should help scientists develop diagnostic and therapeutic tools for dealing with human developmental disorders.

Studies have shown that several signaling pathways act in concert during gastrulation, an important example of which is the Nodal signaling pathway. Dr. Feldman's group is using various approaches to illuminate this pathway's role. They are currently focusing on a transcription factor named FoxH1, which is known to mediate Nodal signaling. Another group of molecules the Feldman laboratory is studying is the RhoGEFs (Rho guanine nucleotide exchange factors). RhoGEFs are important for regulating cell movement. Dr. Feldman's laboratory is trying to determine whether these molecules have a role in gastrulation. They have identified a number of RhoGEF genes that are upregulated in gastrulation.



Using antisense nucleic acid analogs to prevent these genes from being translated into proteins, they have identified three RhoGEFs that are essential for key cellular movements during gastrulation.

Dr. Feldman is also studying human genetic diseases in zebrafish. For example, he is collaborating with various investigators to study 3-methyl glutaconic aciduria (MGA) type III, a genetic disease found in certain families of Iraqi Jewish descent. MGA type III involves defects in the optic nerve, and symptoms include compromised vision in infancy and impaired mobility. It is caused by mutations in the *OPA3* gene, and previous research identified a close homolog of this gene in zebrafish. Dr. Feldman and colleagues are employing antisense strategies to establish a zebrafish model of MGA type III, with a focus on the causes of the disease's metabolic imbalances.

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Finally, Dr. Feldman is developing new tools for embryology research. For example, his team has devised a technique called FACS-assisted microdissection of photolabeled cells (FAM-P) to isolate cells from specific embryonic regions. To achieve this, Kaede, a protein that has a base state of green fluorescence, is injected into the embryonic yolk of embryonic cells. Upon photoconversion with a particular wavelength of light, Kaede undergoes cleavage, and its fluorescence shifts from green to red. In this way, specific regions of embryonic cells are labeled. Embryonic cells are then dissected from each other by enzymatic treatment, and red and green cells are subsequently separated based on their fluorescence colors. Using FAM-P as a starting point, Dr. Feldman's laboratory has explored the composition of early cells belonging to the mesoderm and endoderm lineages, identifying ten new genes specific to these lineages. Dr. Feldman's lab is now investigating the function of these ten genes as well as the behavior of mesoderm and endoderm cells isolated by FAM-P.

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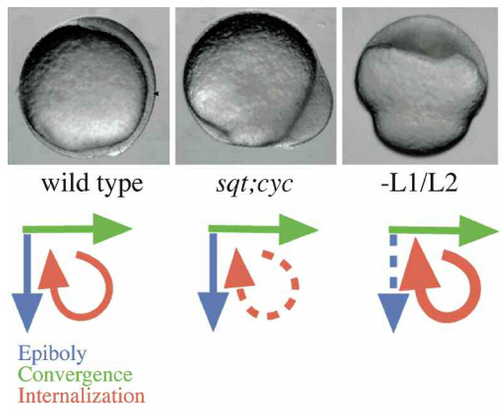
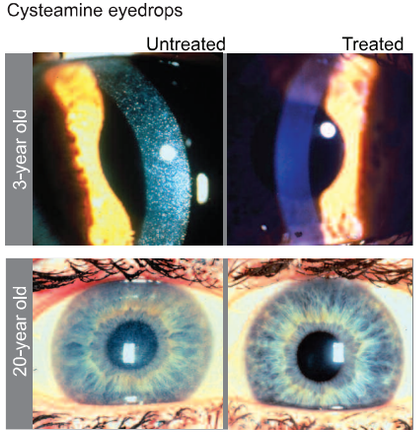


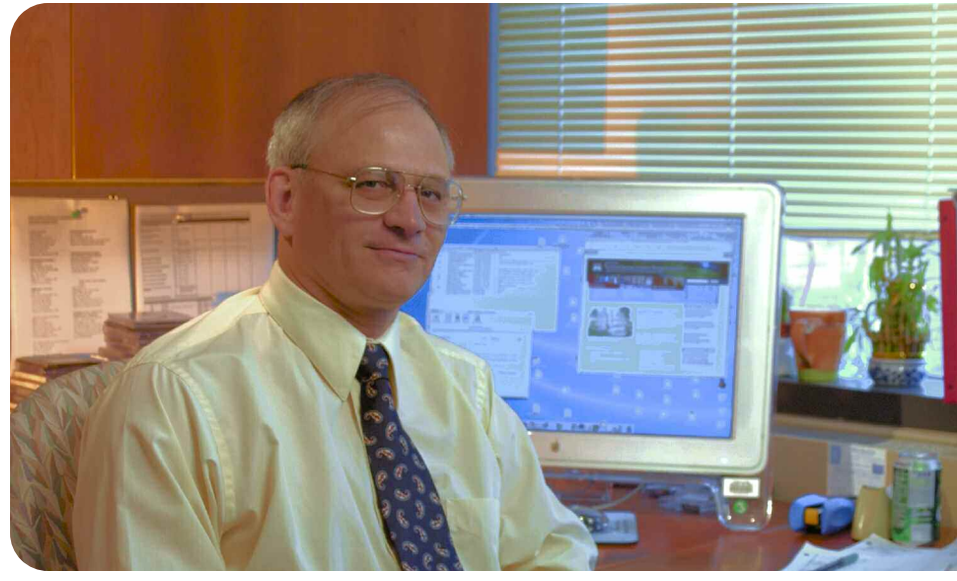
WILLIAM A. GAHL, M.D., Ph.D.

Dr. Gahl studies rare inborn errors of metabolism through the observation and treatment of patients in the clinic and through biochemical, molecular biological, and cell biological investigations in the laboratory. His group focuses on a number of disorders, including cystinosis, Hermansky-Pudlak syndrome, alkaptonuria, and sialic acid diseases.

Dr. Gahl has a long-standing research interest in cystinosis, a lysosomal storage disorder caused by a mutation in the *CTNS* gene that occurs in one in every 100,000 to 200,000 live births. The *CTNS* gene encodes the protein cystinosin, and mutations in *CTNS* lead to impaired transport of cystine out of lysosomes and the formation of cystine crystals in most cells in the body. Untreated, the disease causes kidney failure in childhood, along with a host of other severe complications. Over the past two decades, Dr. Gahl's laboratory has elucidated the pathogenesis of this disease and demonstrated the safety and efficacy of cysteamine (β-mercaptoethylamine) therapy, a treatment that depletes cells of cystine. In fact, cysteamine therapy, along with kidney transplantation, has changed the life course of many cystinosis patients from one filled with debilitating complications to one marked by chronic, yet manageable symptoms. His group is following about 125 pre- and post-transplant cystinosis patients to track their clinical course, identify additional mutations, and document any complications of their cysteamine therapy.



Another major research focus for Dr. Gahl is Hermansky-Pudlak syndrome (HPS), a group of vesicle formation and transport disorders characterized by albinism and bleeding. In some cases, HPS also is characterized by pulmonary fibrosis or colitis. HPS was first described in 1959 and was thought to be a single-gene disorder affecting vesicles involved in intracellular transport. Since then, eight human genes — including two discovered by Dr. Gahl's group — have been identified as causes of HPS. Because some HPS patients have no identifiable genetic mutation, it is believed that proper vesicle formation and movement may require other genes. No treatment has been developed for the underlying disorder, but Dr. Gahl's group has had success in slowing the development of some HPS symptoms in a small group of patients.



His laboratory also studies alkaptonuria, a condition in which mutations in the *HGO* gene cause a buildup of homogentisic acid (HGA), which discolors the eyes and damages the connective tissues in major joints and cardiac valves. By closely monitoring 58 alkaptonuria patients, Dr. Gahl's group produced the first modern characterization of the disease and found a potential therapy involving small doses of the drug nitisinone, which decreases HGA production. The next step is a three-year clinical trial to determine whether the drug can slow or halt the hip damage caused by the disease.

Dr. Gahl also studies sialic acid disorders, as his laboratory is a reference laboratory for this rare group of conditions. Sialic acid deficiency causes a severe muscle-wasting disease that often forces patients into wheelchairs,

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ultimately leading to death by respiratory failure. Excess sialic acid is equally detrimental to health. Three rare childhood diseases, characterized by growth retardation and developmental delays, are caused by excess sialic acid. One of these diseases is so rare that only seven patients have been identified worldwide; Dr. Gahl's laboratory has done mutation analysis on six of them. Research on treating sialic acid disorders is just beginning. In the meantime, Dr. Gahl's group has developed phenotypic descriptions of the different disorders and provides diagnostic assistance to other laboratories.

Dr. Gahl's laboratory is also developing a strong research interest in other genetic disorders. These include autosomal recessive polycystic kidney disease and congenital hepatic fibrosis, Chediak-Higashi syndrome, gray platelet syndrome, Hutchinson-Guilford progeria syndrome, and various forms of renal Fanconi syndrome.

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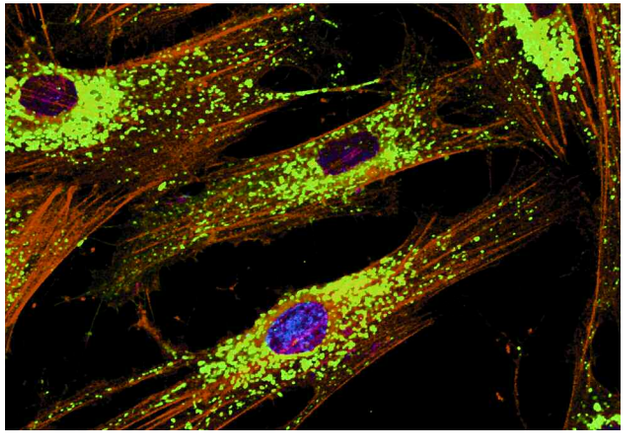
MARJAN HUIZING, Ph.D.

Dr. Huizing's laboratory investigates rare human genetic disorders and normal and abnormal intracellular processes. Her goal is to gain insight into changes in molecular function that underlie various genetic metabolic disorders and developing treatments for these illnesses. Her research focuses on hereditary inclusion body myopathy (HIBM) and Hermansky-Pudlak syndrome.

HIBM is caused by mutations in the gene encoding the enzyme UDP-GlcNAc 2-epimerase/ManNAc kinase. Defects in this enzyme, which catalyzes two committed steps in sialic acid biosynthesis, cause sialic acid deficiency. Without new supplies of sialic acid, progressive muscle degeneration, or myopathy, sets in. The typical course of the disease involves a steady deterioration of arm and leg muscles until, eventually, patients are unable to walk.

Sialic acid is a negatively charged sugar localized at the end of glycoconjugate chains on glycoproteins and glycolipids. These chains are expressed at the cell surface and are crucial for many biological processes, including cell adhesion and signal transduction. Research has shown that dystroglycan, an integral component of the muscle transmembrane dystrophin-glycoprotein complex, is involved in the pathogenesis of many forms of myopathy, including muscular dystrophy. Dr. Huizing's group demonstrated that muscle α-dystroglycan in patients with HIBM is low in sialic acid. They are now investigating the use of *N*-acetyl-D-mannosamine (ManNAc), a neutral sugar and specific substrate for sialic acid synthesis, as a therapy for HIBM; they also are developing a mouse model for testing such a therapy. Another treatment involves infusing mice with immunoglobulin, which is high in sialic acid content.



Dr. Huizing also studies other sialic acid-related diseases, including sialuria, a progressive disease in which patients produce too much sialic acid. Symptoms may include developmental delay, coarse features, and enlargement of the liver. Sialuria appears to be caused by a single mutation that causes a change in the three-dimensional structure of the active site of the enzyme UDP-GlcNAc 2-epimerase/ManNAc kinase. A third sialic acid-related disease, infantile free sialic acid storage disease, involves a transport malfunction that causes sialic acid to accumulate in lysosomes.

In addition, Dr. Huizing is investigating the causes of and potential treatments for Hermansky-Pudlak syndrome (HPS), a rare inherited disorder that has been identified in about 400 people worldwide. Affected individuals are characterized by decreased pigmentation (ocular or cutaneous albinism), a lack of platelet dense bodies (causing bleeding problems), and their storage of an abnormal fat-protein compound, called ceroid, which leads to dysfunction in some organs. The disease can cause prolonged bleeding and poor function of the lungs and intestine; fatal pulmonary fibrosis also is a possible complication. An ongoing clinical trial at NHGRI

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is testing the drug pirfenidone as a potential HPS treatment. The purpose of the trial is to find out whether pirfenidone can relieve symptoms associated with pulmonary fibrosis.

Dr. Huizing's group continues to look for additional HPS-causing genes, with the hopes of better understanding the biology of the disease. She played a major role in identifying seven distinct genetic subgroups of HPS patients by cataloguing relevant clinical and genetic characteristics. She also helped discover the mutated gene associated with the HPS-3 subgroup. Scientists subsequently discovered several other HPS-related genetic mutations in mice. To study the effects of HPS mutations, Dr. Huizing's group is using fluorescent protein expression studies to examine the defective intracellular trafficking to lysosome-related organelles in HPS patients' cells. It has been shown that such cells fail to transport certain lysosomal proteins to their correct destination, and *HPS* gene products somehow are involved in recognizing specialized vesicles key to lysosomal biogenesis.

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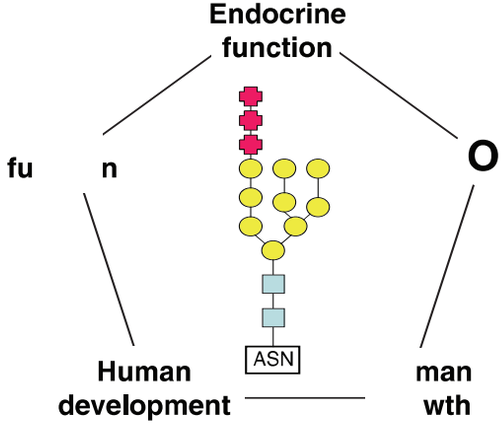
DONNA M. KRASNEWICH, M.D., Ph.D.

Dr. Krasnewich investigates metabolically and biochemically based developmental disorders, especially those involving defects in sugar metabolism. This work is performed within the Section on Human Biochemical Genetics, led by Dr. William Gahl.

Sugars are important for brain development and the proper functioning of other organs in the body. A group of genetic defects in sugar metabolism are termed congenital disorders of glycosylation (CDG), which result from abnormal carbohydrate metabolism — specifically, the abnormal synthesis of N-linked oligosaccharides. About 400 cases of CDG are known worldwide, although given the variable clinical presentations of CDG, many individuals likely go undiagnosed. Affected children may appear normal at birth, but as they age, the children develop problems that range in severity from mild to debilitating. Children with other forms of the condition may have only gastrointestinal symptoms and a failure to thrive; those at the other end of the spectrum may suffer severe central nervous system impairment and chronic complications, including liver disease, cardiac disease, and blood clotting problems.



The most common form of the 16 CDG genotypes identified so far, CDG type Ia, results from a deficiency in the enzyme phosphomannomutase. Less-common forms result from defective enzyme activities at other steps in the N-linked oligosaccharide synthetic pathway. CDG type Ib is the only treatable form of the disorder, but Dr. Krasnewich hopes research will lead to treatment strategies for other forms of CDG as well.

To study the underlying metabolic defects associated with CDG, Dr. Krasnewich and collaborators are using glycobiologic and cell biologic experimental tools. In clinical studies, they are examining the initial clinical presentation and course of CDG in patients to determine what the observed clinical spectrum of the disorder reveals about the role of glycobiology in human physiology. Understanding these enzyme defects will pave the way for candidate gene identification, mutation analysis, and prenatal diagnosis in appropriate families.

Dr. Krasnewich is also part of a team investigating other glycobiologic disorders, including those affecting sialic acid metabolism. NHGRI occupies

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a unique niche in the study of these disorders, because it is the only facility in the United States able to perform the necessary diagnostic tests. Clinical pathology can result from an individual having too much or too little sialic acid. When a person produces too little sialic acid, myopathy sets in — usually at 20 to 30 years of age — eventually causing affected individuals to become wheelchair bound. Dr. Krasnewich and her colleagues are working on potential therapies that involve administering compounds to increase the amount of sialic acid in muscles. Dr. Krasnewich also is interested in other sugar-based congenital myopathies that are just coming to light and the many she believes remain undiagnosed and unidentified. She hopes these studies will help advance the development of drugs that can be used to treat patients with these metabolic disorders.

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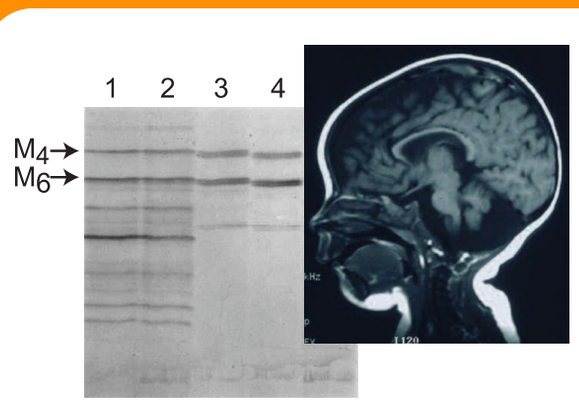
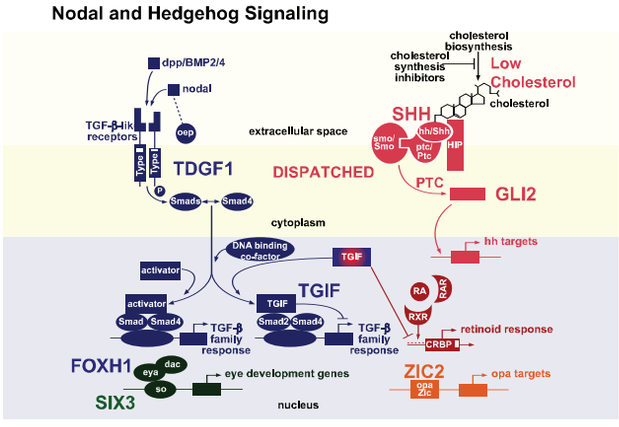


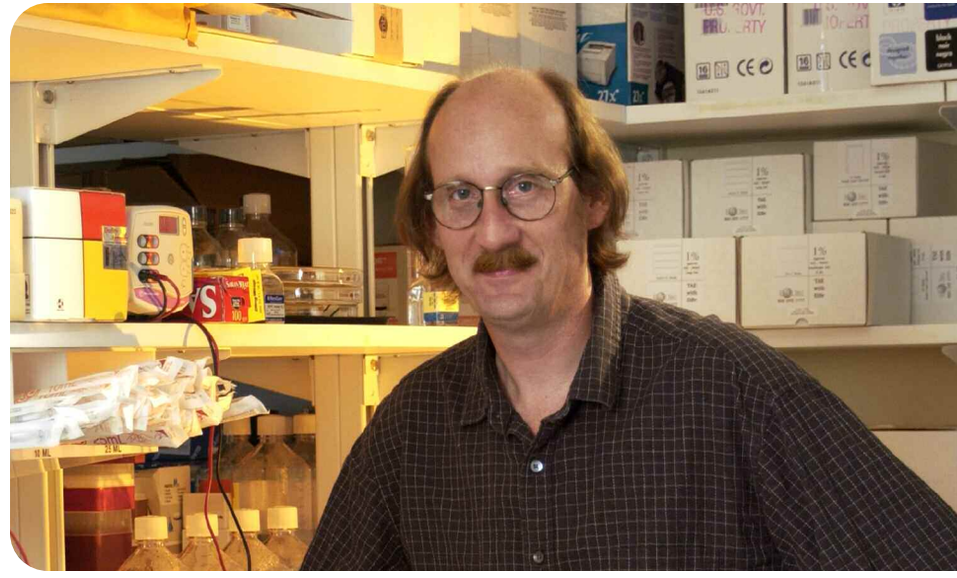
ERICH ROESSLER, M.D., Ph.D.

Dr. Roessler focuses on identifying human genetic mutations that contribute to birth defects and demonstrating how these mutations cause their pathophysiology. His work is performed within the Human Development Section, which is led by Dr. Maximilian Muenke, and involves detailed functional analyses of suspect genes and collaborations with scientists using model organisms to study equivalent genetic mutations. To understand more about birth defects, Dr. Roessler also investigates the basic mechanisms involved in body plan development, since these processes are directly affected by the alterations associated with birth defects.

Dr. Roessler's studies focus primarily on early embryonic development of the axial midline and forebrain and establishment of the left-right axis (laterality). These developmental steps occur in the first month of a human fetus's life and are critical for proper human development. He has worked for many years with Dr. Muenke studying holoprosencephaly (HPE), a laterality defect that occurs when the embryonic forebrain does not divide properly into the two lobes of the cerebral hemispheres.



HPE is the most common human structural birth defect affecting the brain. It occurs in one in every 250 conceptions and is associated with frequent fetal loss; only one case in 10,000 continues to birth. At birth, HPE can manifest itself in small head size, developmental delays, and facial deformities that range from cleft lip or closely set eyes to the much more severe condition, cyclopia (a single eye at the root of the nose); cyclopia



results when forebrain cleavage never occurs. Working with Dr. Muenke and others, Dr. Roessler identified the first gene behind HPE in humans, called Sonic Hedgehog.

Researchers studying HPE are now turning their focus from gene identification — an effort that has identified as many as 12 candidate loci — to understanding environmental factors that might contribute to HPE. This will require a better understanding of patterns of gene expression at key points during fetal development. Once contributing factors have been identified, they can be subjected to further, targeted study. In one example of the environment's potential role in HPE, Dr. Roessler plans to study the effects of low maternal cholesterol levels on embryonic development. In

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particular, he hopes to understand the influence of the cholesterol-lowering statin drugs on fetal development in women who become pregnant while taking these drugs.

Other laterality disorders being investigated by Dr. Roessler include congenital cardiac malformations, which are some of the most common human birth defects and often require surgical correction. He is examining the role of the Nodal signaling pathway, a key player in both midline and laterality development in vertebrates, although its complete role in these processes is not fully understood. He has investigated at least six genes in the Nodal pathway that are mutated and could be important genetic contributors to the mechanisms of the malformations associated with congenital heart disease.

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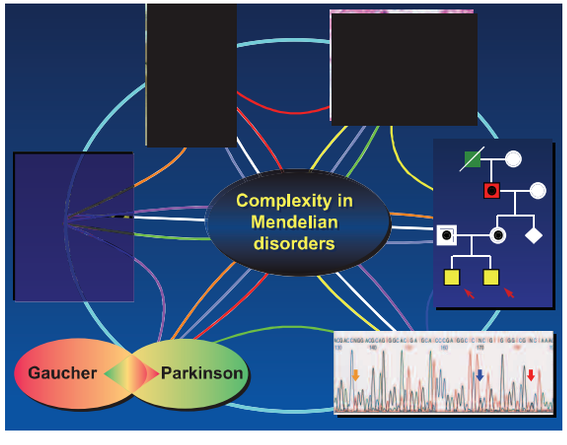
ELLEN SIDRANSKY, M.D.

Dr. Sidransky's research focuses on the genetics of Gaucher (pronounced "go-SHAY") disease, a rare, recessively inherited disorder with highly variable symptoms. Her work has been instrumental in uncovering the spectrum of symptoms and some of the mechanisms underlying the pathology of this disorder. Ultimately, the goal of her research is the translation of basic research findings into new therapeutic approaches for this and other inherited disorders. She and her colleagues have also discovered potential links between this single-gene disorder and the more common multi-gene disorder, Parkinson disease.

Gaucher disease results from mutations in the *GBA* gene, which codes for the enzyme glucocerebrosidase. This lysosomal enzyme is responsible for breaking down a specific kind of fat called glucocerebroside. People with Gaucher disease cannot properly produce this enzyme, so the glucocerebroside in their cells is not broken down and accumulates — mostly in the liver, spleen, and bone marrow cells. This accumulation can result in pain, fatigue, jaundice, bone damage, anemia, and even death. Gaucher disease is the most common lysosomal storage disorder in the general population, affecting an estimated 20,000 to 30,000 people in the United States, although many cases may go undiagnosed. It is the most prevalent hereditary disorder among Ashkenazi Jews; in this population, about 1 in 15 people are carriers, compared with about 1 in 100 in the general population. Currently, the primary treatment for Gaucher disease is enzyme replacement therapy, which has helped many patients but is inconvenient because it requires life-long intravenous infusions every two weeks. At a cost of roughly $300,000 a year, it also is extremely expensive.

For reasons still not well understood, the manifestations of Gaucher disease vary dramatically from one individual to another. Some people with glucocerebrosidase deficiency never have symptoms, whereas others have enlarged spleens and livers as well as bone problems, blood abnormalities, and growth retardation. Still others have devastating lung, skin, and nervous system manifestations. Although more than 200 different disease-associated mutations in *GBA* have been identified, patients with the same mutations (or genotypes) can have quite different clinical manifestations (or phenotypes). Thus, for this disease, patient genotyping is not a reliable guide for prognosis, therapy, or genetic counseling. Gaucher disease researchers have to rely more on the careful analysis of phenotypes to guide their studies.



Traditionally, patients with Gaucher disease have been classified into one of three very separate and distinct phenotypes. Dr. Sidransky's research, however, has shown that Gaucher disease phenotypes actually form a continuum, with the major distinction being the degree of neurologic damage involved. Dr. Sidransky's laboratory has described several new Gaucher phenotypes that lie along this continuum. For example, studies of a *GBA*-knockout mouse model helped her group identify a previously unrecognized phenotype involving prenatal or immediate postnatal death. Additionally, her laboratory described the clinical and genetic characteristics of a rare Gaucher disease phenotype in which myoclonic epilepsy (characterized by quick little jerks of the arms, shoulder, and legs) is a significant component.

Dr. Sidransky and her colleagues continue to explore the vast phenotypic heterogeneity in Gaucher disease by sequencing and comparing the *GBA* gene and nearby genomic regions in groups of patients who share atypical phenotypes. Their studies show that the *GBA* gene lies in a gene-rich region

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of chromosome 1q. Interestingly, there is a closely related pseudogene nearby that plays a role in causing some mutations that result in Gaucher disease. Dr. Sidransky believes that analyses of both the differences and similarities in the *GBA* sequences in different patient groups and in different organisms may improve our understanding of how genotype influences phenotype in patients with Gaucher disease.

A second major project in Dr. Sidransky's laboratory involves investigating a potential link between mutations in the *GBA* gene and Parkinson disease. Her group recently discovered that several families carrying *GBA* mutations had an unusually high incidence of Parkinson disease. In a complementary study, they analyzed brain tissue samples from patients with and without Parkinson disease and found that 14% of the Parkinson disease samples had at least one mutated *GBA* gene, compared with none in the non-affected samples. GBA mutations were also subsequently identified in patients with Lewy body dementia. Thus, heterozygosity for *GBA* mutations may be a risk factor for Parkinson disease and related disorders. This insight has given Parkinson disease researchers a new, exciting avenue for studying the mechanisms of the disease.

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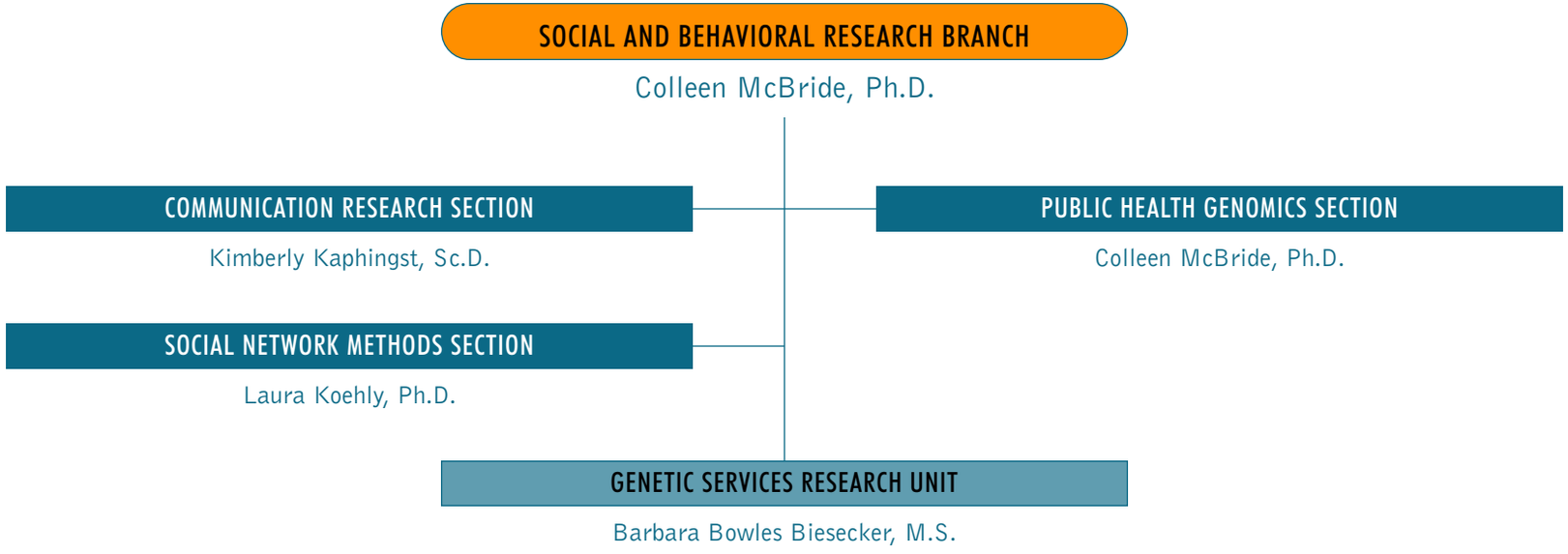
"This field is wide open, full of mystery, evolving rapidly, and divergent. **Our charge is to be among the trailblazers**. We all have the ultimate objective to promote public health and well-being."

Colleen McBride, Ph.D.
Chief, Social and Behavioral Research Branch

SOCIAL AND BEHAVIORAL RESEARCH BRANCH

The Social and Behavioral Research Branch (SBRB) has the overarching and broad objective of investigating social and behavioral factors that facilitate the translation of genomic discoveries for health promotion, disease prevention, and improvements in health care. The newest Branch in the NHGRI Intramural Program, SBRB is involved in studying a range of problems that are highly relevant to the eventual realization of health benefits from genetics and genomics research. SBRB research encompasses four conceptual domains: (1) testing the effectiveness of strategies for communicating information about genetic risks; (2) developing and evaluating behavioral interventions; (3) using genomic discoveries in clinical practice; and (4) understanding the social, ethical, and policy implications of genomic research. Together, these areas reflect NHGRI's long standing commitment to addressing the broader implications of the many recent advances in genetics and genomics.

The specific research challenges being investigated by SBRB investigators include improving methods of communication about genetic risk to lay populations, establishing best practices in genetic counseling, investigating approaches for successfully integrating genetics into primary care settings, and studying a broad set of issues relating to the appropriate public dissemination of genomic discoveries. SBRB investigators are also detailing bioethical considerations for the involvement of human subjects in genomic research. Together, the research performed by the Branch is providing an analytical framework for making practical decisions that will influence how genetic advances are translated into new clinical practices.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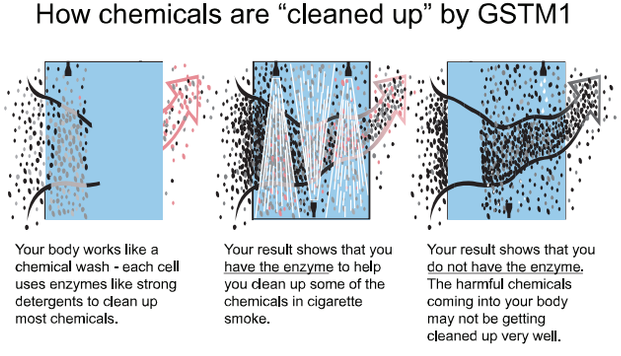
Dr. McBride's research focuses on developing innovative public health interventions to promote risk-reducing behaviors. Building on her behavioral epidemiology and genetics experience, she is investigating how genetic information can best be used to motivate people to behave in more healthful ways. Genetic testing is likely to become a leading medical tool for educating patients about their health risks and inspiring them to take preventive steps, although there are many obstacles to overcome before that can occur. Having the testing technology does not necessarily translate into better health behaviors.

Accurate family history information combined with genetic test results may help to personalize risk in a way that generalized health advice does not. Indeed, an important question is under what circumstances is it easiest to motivate people to take preventive actions. Studies have shown that some patients become motivated to change their behavior on learning their high-risk status. However, for many reasons, others discount such information despite their known risk. Because people are not passive recipients of health advice and have competing motives that drive their behavior, an individual's emotions, value systems, and other personal characteristics need to be considered when delivering health communication approaches. Unfortunately, such factors are not well understood by many health professionals, who may overestimate the impact genetic information will have on their patients. Researchers need to establish the most effective and efficient ways to bring these genetic discoveries to patients, communities, and health care professionals.



As Chief of SBRB, which was established in 2003, Dr. McBride currently is articulating research priorities for the Branch to help guide the use of genetics and genomics to improve the health and well-being of the population. Initially, SBRB is focusing on smaller studies that address the basic science of risk communication, best practices for genetic counseling and education, clinical integration of genetics,

techniques for involving communities in dissemination of genetic discoveries, and related bioethical and social policy issues.

In one study, Dr. McBride's group is investigating family physicians' attitudes and preferences related to integrating genetic information on complex diseases into their clinical practice. Other than oncology specialists, only a small fraction of physicians have any formal training in genetics, and there is very little dissemination of such information into primary care settings. Therefore, although many family physicians take patients' family histories, most of these histories are inadequate for genetic study purposes. Dr. McBride's team is partnering with the American Academy of Family Physicians (AAFP) to evaluate reactions of AAFP members who undertake a year-long genetics curriculum. The curriculum will include training on how to take an optimal family history that can be used in the context of genetic studies. The team will survey physicians before and after the AAFP course and will also survey physicians who choose not to enroll.

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In another study, Dr. McBride is investigating how genetic information influences smokers and how it can best be used to motivate them to stop smoking. The study is examining smokers who are blood relatives of a patient with late-stage lung cancer. The hypothesis is that these at-risk smokers may have an enhanced fear of developing lung cancer and may be especially receptive to prevention information. Study participants are being offered genetic testing to determine their susceptibility to lung cancer. Among those who choose to be tested, some will learn they are at high risk, and others will be reassured that they are not at high-risk for lung cancer. The study eventually will include about 150 relatives of cancer patients who are receiving care at the H. Lee Moffitt Cancer Center and Research Institute in southern Florida.

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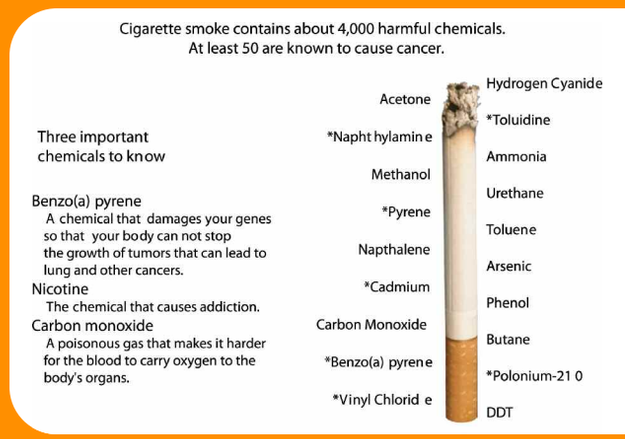
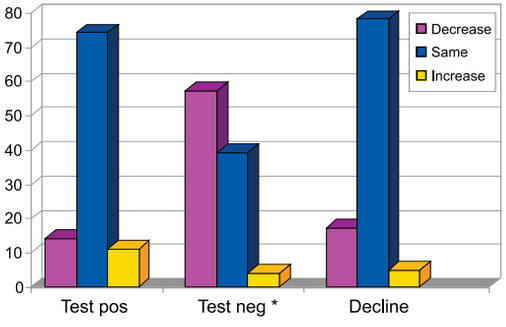


BARBARA BOWLES BIESECKER, M.S.

Ms. Biesecker's research and teaching activities focus on making genetic counseling as effective as possible, a growing challenge as new genetic technologies bring about an avalanche of data and questions about what testing of our genes can reveal. This tremendous amount of genetic information has highlighted the fact that behavioral researchers do not yet know enough empirically about the best ways to help people decide how to use their own genetic information in making health and reproductive decisions. Since genetic counseling has a relatively sparse amount of research to guide its professionals, Ms. Biesecker and her colleagues are on the cutting edge of genetic counseling research.

The major focus of Ms. Biesecker's investigations is determining how genetic counseling can improve people's decision-making and coping abilities. To this end, she is focusing on three major areas: (1) how a person's decision to undergo genetic testing affects his or her psychological well-being and family relationships; (2) how living with a genetic condition affects a person's quality of life; and (3) the overall effectiveness of genetic counseling.

Some of her past research has included studies of illness perception and of the quality of life of people who live with genetic conditions, such as achondroplasia and Marfan syndrome. She has also used qualitative methods to explore concerns and appraisals of girls and women with Turner syndrome — in which a female has only one X chromosome — and how they adapt to related social and medical problems. In one of her Turner syndrome studies, infertility was the most prevalent "challenge" among the 97 girls, adolescents, and adult women affected by this condition. Furthermore, about a third of participants said their parents and physicians hid from them the fact that infertility is a component of Turner syndrome, thus diminishing their trust in their relatives and health care providers. This study recommended that family members and health care providers be truthful and open with patients about the symptoms and consequences of Turner syndrome and to offer those affected by the condition social guidance and support to help them deal with these problems.



Change in breast cancer risk perception from baseline to follow up for those who tested positive, negative or declined testing for *BRCA 1/2*

*Significant change in risk perception from baseline to follow up (p=0.001)

Currently, Ms. Biesecker is conducting a pilot study in anticipation of a larger, randomized control trial investigating women's ambivalence toward prenatal testing and how a genetic counseling intervention might benefit them. It also is used to test the fetus via the amniotic fluid for disorders such as Down's syndrome and neural tube defects. However, no one has assessed the frequency of women's ambivalence towards such tests and how genetic counseling might help them before they potentially face decisions about whether to continue a pregnancy.

Because a vast majority of genetic counselors are trained as clinicians and not as researchers, research training is an important aspect of Ms. Biesecker's activities. In the early 1990s, she and her colleagues established

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The Johns Hopkins University/NHGRI Genetic Counseling Training Program, which she continues to direct. This graduate program brings together valuable resources from both institutions and from numerous clinical training sites throughout the region. Its goal is to produce genetic counselors skilled in therapeutic counseling and in genetic counseling research methods.

Overall, Ms. Biesecker hopes her work will help establish more effective clinical interventions to allow practitioners to improve the genetic counseling they offer patients. Teaching decision-making skills is an important component of genetic counseling in pediatric and adult genetics as well, and research aimed at improving the outcomes of genetic counseling has important implications for clinical care. New models for service delivery can be developed based on empirical evidence and tested in further studies.

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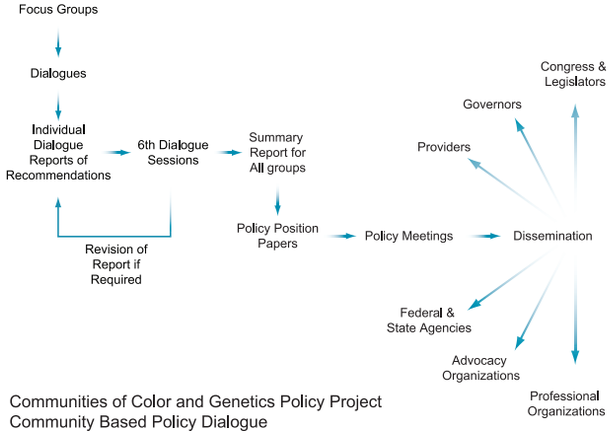
VENCE BONHAM, JR., J.D.

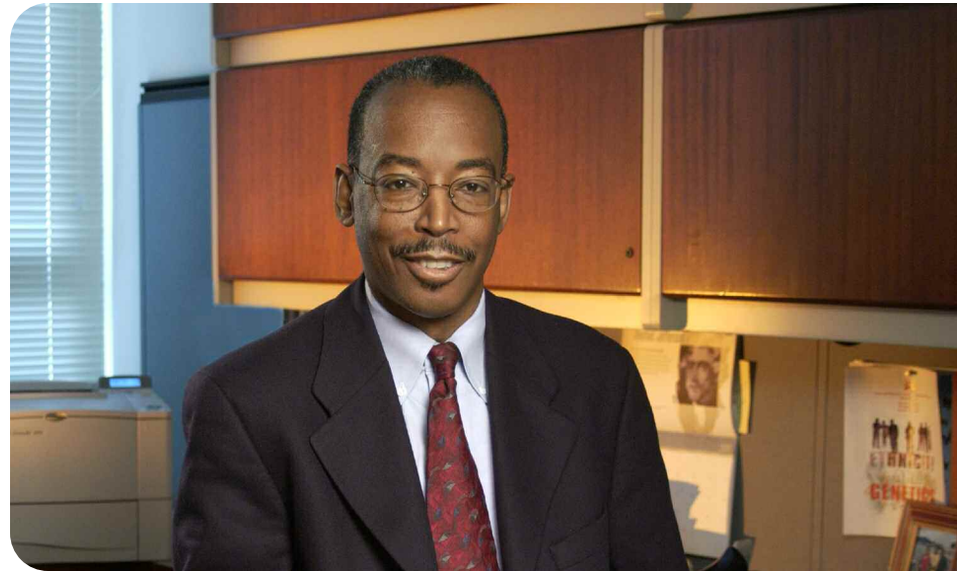
Mr. Bonham is a health care policy researcher whose work examines the intersection of public policy and genetics and the numerous questions that this prompts. Among the questions of interest to Mr. Bonham are the impacts of genetic discovery on the use of the constructs of race and ethnicity, health disparities, genetic discrimination, and medical decision-making and subsequent considerations for public policy development. His research is conducted within the Public Health Genomics Section, led by Dr. Colleen McBride. Mr. Bonham's primary research goal is to improve our understanding and use of genomics in communities, particularly in communities of color, and determine how genetic research will affect people in such communities.

Mr. Bonham's prior research explored differences in the health care experiences of African American and white patients. In one study, he and his colleagues found that African American patients were less likely than whites to receive adequate pain medication. He also has explored differences in the impact of socioeconomic status on health among African Americans, finding better physical health among high socioeconomic status African American men who have a behavioral predisposition to directly confront barriers to upward social mobility (John Henryism). Mr. Bonham also has conducted research on the use of community based dialogue as a model for establishing community engagement in African American and Latino communities on the topic of genomics policy-making and genetics education.



Communities of Color and Genetics Policy Project
Community Based Policy Dialogue

Since coming to the NHGRI in 2002, Mr. Bonham has focused on studying the connection between genomic research and health disparities. Currently, he is building a program of research relating to health care providers' decisions about genetic testing. He and his colleagues have conducted a large Internet-based survey of family physicians to assess their opinions and decisions related to genetic testing and the extent to which a patient's ethnic and racial background influences these decisions. Additionally, he and his colleagues are working to develop an assessment tool for gauging how health professionals use race and ethnicity to make decisions about providing genetic services and in assessing risk of genetic disease. An important aspect of this research will involve structured interviews and focus groups with a geographically dispersed sample of physicians to gain insights into their understanding of the concepts of race and ethnicity and how these concepts relate to the genetic basis of disease.



Mr. Bonham also serves as a Senior Advisor to NHGRI's Director on the Societal Implications of Genomics. He co-chairs the NHGRI Working Group on Race, Ethnicity, and Genetics. This group provides the Institute — and NIH as a whole — with guidance on issues that arise as genomics research begins to uncover the relationships between these factors. In addition, Mr. Bonham heads the Education and Community Involvement Branch (ECIB),

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which leads NHGRI's public education and community involvement and outreach initiatives.

As Chief of ECIB, he is responsible for leading public education initiatives and structuring how the Institute reaches out and engages various types of communities, such as those who are underserved in biomedical research participation. For example, ECIB staff members coordinate the annual DNA Day Ambassador Program, during which NHGRI scientists travel to high schools throughout the country to expand students' knowledge of genomic science. They also coordinate courses that bring diverse communities to the NIH campus to learn about current issues in genomics and to gain information about the genetics of rare diseases. One such program is the annual Current Topics in Genomics Research Short Course, in which college faculty and students from historically minority-serving institutions have the opportunity to learn about the latest advances in genomic research directly from NHGRI faculty.

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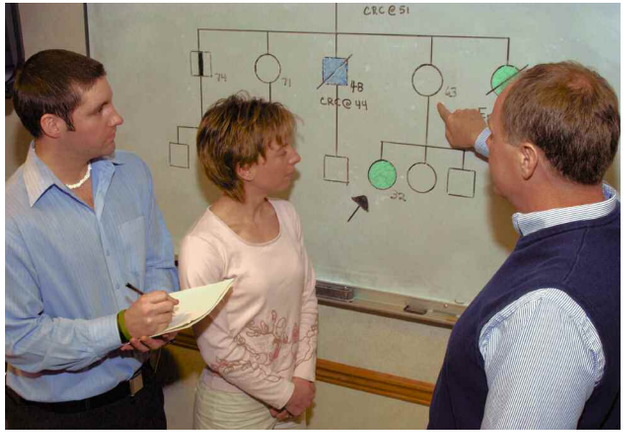
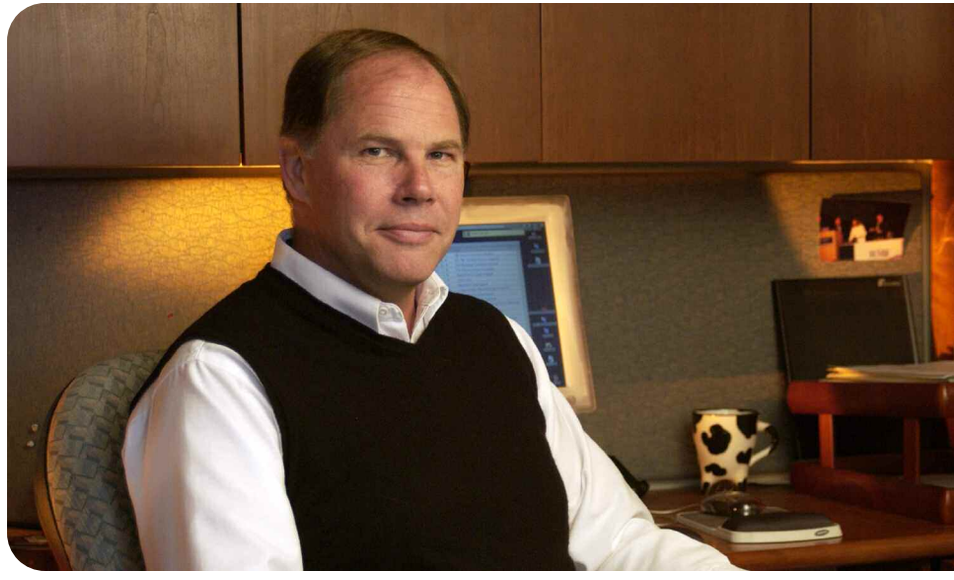
DONALD W. HADLEY, M.S., C.G.C.

Mr. Hadley is a genetic counselor and a clinical researcher. As a genetics counselor, he provides education and counseling for people with or at risk for genetic or inherited diseases participating in NIH clinical protocols. As a researcher, he evaluates methods for educating and counseling families with genetic conditions. His research is performed within the Social Network Methods Section of the SBRB.

Mr. Hadley strives to understand the psychological and behavioral outcomes of the counseling and testing process. His clinical role gives him insight into the concerns of families considering genetic testing and the many issues they deal with following their decisions and, for some, their subsequent test results. When Mr. Hadley arrived at NHGRI in 1993, genetic testing for single gene disorders was just becoming a reality, with scientists pinpointing genes for cystic fibrosis, Huntington's disease, and hereditary breast/ovarian and colon cancer. When these tests became widely available, there was an explosion of questions regarding families with identifiable genetic disorders — for example, how to help them make decisions about testing, what psychological and social factors might influence their decisions, and what might be the behavioral and psychological consequences of choosing or not choosing genetic testing.

Currently, Mr. Hadley's particular area of focus addresses the many questions surrounding genetic screening for hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch Syndrome, the most common form of hereditary colon cancer. Mr. Hadley is collaborating with investigators at the National Cancer Institute to collect information from families that are at risk for developing HPNCC. In addition to collecting information from these families through detailed questionnaires, the researchers ask participants to attend a genetic education session to help them understand





HNPCC and cancer screening recommendations for associated cancers, genetic testing for HNPCC, and the associated risks and benefits of these genetic tests.

His team follows both those who choose testing and those who do not and collects data from them at 6-month, and 1- and 3-year intervals to document how the genetic counseling and testing process influences them psychologically and guides their choices about cancer screening. Interestingly, only about half the eligible people in families with recognized mutations choose to participate in the study. It is important to understand what these people know about their cancer risks and what cancer screening practices they undergo, if any, among a host of other questions. To address these, the research team will recruit non-participating family members to complete questionnaires regarding their thoughts, attitudes, and cancer screening practices in order to gain insight into the cohort of family members not seeking genetic information.

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As a member of the Medical Genetics consult team, Mr. Hadley also works with families affected by other genetic diseases. For example, he is working with a large family known to carry a mutation in a gene for Familial Encephalopathy with Neuroserpin Inclusion Bodies (FENIB) which presents in mid-adulthood with behavioral changes and cognitive decline. His role is to assist them in considering the option of pre-symptomatic genetic testing for the known family mutation. His work has shown, however, that a host of issues complicate the family's decisions, including the lack of preventive treatments to delay or prevent this devastating disease.

Mr. Hadley plans to extend his research portfolio to include the study of families with more common diseases that affect larger portions of the population. These include diseases that are known to have genetic contributions but are also influenced by other factors such as environment, lifestyle, and diet. This will be an important area to explore as research continues to move genomics into the medical and public health arenas.

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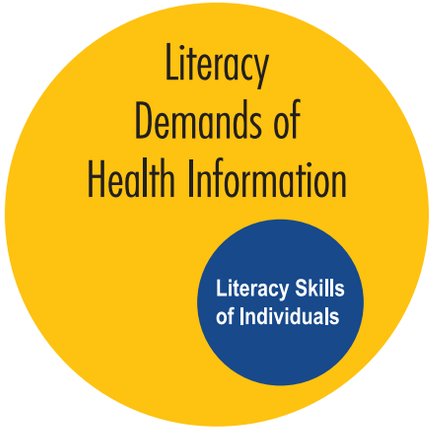
KIMBERLY A. KAPHINGST, Sc.D.

Dr. Kaphingst has a unique background that includes multidisciplinary training in bench and behavioral sciences, and her research reflects and capitalizes on this broad perspective. The bulk of Dr. Kaphingst's research focuses on developing ways to communicate information about genetics and genomics to the general public, particularly people who have limited education or literacy. This is an area in which little research has been done to date. Her goal is to test the relative effectiveness of different communication approaches, with the hope that these approaches ultimately can be incorporated into practical interventions designed to improve the public's health.

Dr. Kaphingst's previous research focused on the communication of various types of health information. She examined how direct-to-consumer prescription drug advertisements presented risk and benefit information via broadcast and print media. Dr. Kaphingst also investigated the communication of cancer information to patient- and community-based populations. One such study was conducted with breast cancer patients who had donated blood or tissue samples for breast cancer research, with the goal of understanding their perceptions of the donation process and their interest in receiving information about ongoing research studies. Although the donors expressed a strong interest in receiving information about studies using their samples, they had a limited understanding of genetic research and related vocabulary.



Communicating with the general public about genetics is likely to be a substantial challenge.

Nearly a quarter of the U.S. adult population has low levels of functional literacy skills, and another quarter has marginal skill levels. Existing research shows that these adults have more limited knowledge and skills related to chronic diseases, such as cancer, hypertension, diabetes, and asthma. For the Human Genome Project to fulfill its promise of improving the public's health, scientists must develop effective, research-based strategies that can convey health information to everyone, including those with limited literacy.

Dr. Kaphingst is currently conducting research in both an Immersive Virtual Environment Technology (IVET) laboratory and in community-based settings. Her IVET laboratory work focuses on examining variables

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that impact the effectiveness of strategies for communicating abstract genomic concepts. She is also partnering with community groups to design genetic communication strategies that are culturally and linguistically appropriate for various target populations.

Dr. Kaphingst is particularly interested in communicating with lay audiences in the context of common diseases, in which genes interact with other genes and the environment to contribute to the development of a chronic disease or disorder. She seeks to develop improved methods for effectively informing people about their disease susceptibility risk and about any preventive steps they can take to diminish their risk, with the hope that individuals will take concrete measures toward improving their health by changing their behaviors.

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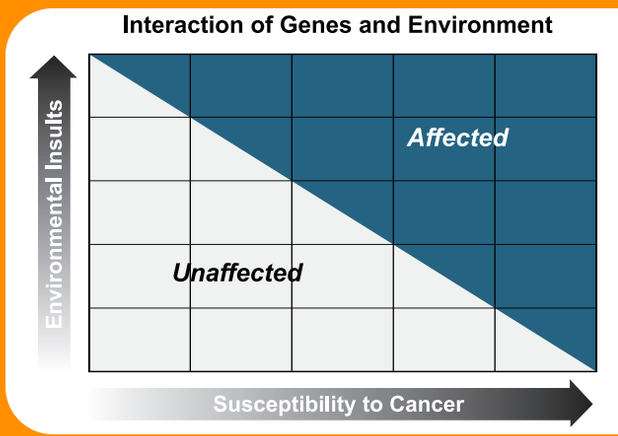


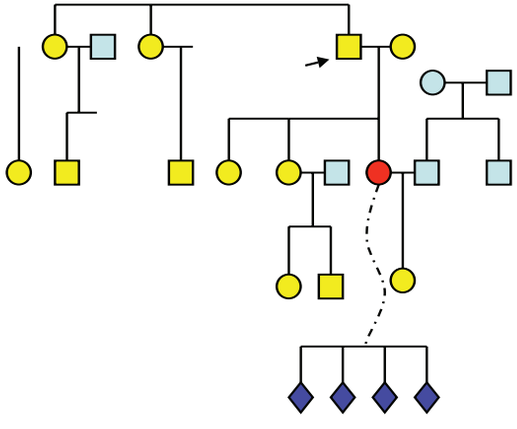
LAURA KOEHLY, Ph.D.

Dr. Koehly's research focuses on developing and applying social network methods to the study of complex social systems, such as families and communities. The ultimate goal of her research is to develop interventions for increasing the efficacy of health counseling, testing, and surveillance within family networks.

Her research is specifically directed to fostering individuals' willingness to initiate and share risk information throughout their family system, developing effective approaches to facilitate informed decision-making among all members of an at-risk family system about undergoing risk counseling, and overcoming barriers in reaching disconnected family members (e.g., due to estrangement or the death of a key family member). Ultimately, her research aims to develop effective strategies to help families effectively cope with disease-risk information and to increase patients' willingness to share such information with their personal physician and other health care personnel.

With the surge in availability of genetic testing and counseling services, medical practitioners need to understand how social networks operate and, in particular, how an individual disseminates relevant disease-risk information to other potentially susceptible family members. This kind of knowledge is particularly valuable to health care practitioners because it could help facilitate and refine the specific prevention and treatment approaches they use for their own patients.

Previous research in this field has focused primarily on the "index case" (the patient) and only one or two relatives. Unfortunately, this narrow view of social networks provides a biased perspective. Moreover, traditional statistical models have assumed that individuals in a social network respond to disease-risk information independently when, in fact, they do not. Dr. Koehly's research seeks to overcome such limitations by studying entire family systems and developing more appropriate social network models. In turn, these models should allow her to better understand the impact of the interpersonal environment on an individual's (or a system of individuals') behaviors.



In one of her research projects, Dr. Koehly is seeking a broader understanding of difficult-to-reach individuals in an index case's social network. Before devising contact systems to reach such individuals — typically those outside the nuclear family — she and her colleagues are studying how health information (including genetic-risk information) is conveyed through the family, identifying any significant barriers to this process. Dr. Koehly also is studying family members' knowledge of their close friends and relatives ("close others") and where within the family structure these close others are situated. The purpose of this investigation is to better understand how hard-to-reach family members and those who do not respond to health-risk information fit into the family's full social system.

In another project, Dr. Koehly is examining how families and their social systems might vary in their response to different genetic diseases. Initially, she is investigating whether the diffusion of information or coping processes differs by condition. For instance, there may be significant variation in responses to early-onset versus late-onset diseases or in responses to diseases with lower versus higher survival rates. For this research project, Dr. Koehly is using a social interaction model created for studying families at risk for hereditary nonpolyposis colon cancer (HNPCC). Although all family members

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in this study were generally willing to share information about HNPCC, those affected by HNPCC as well as mutation carriers were more likely to inform their extended family members and actively persuade them to seek counseling or testing. Furthermore, extended family members who were persuaded to seek such services by their affected kin were more likely to seek those services sooner than were extended family members who found out about their risk through unaffected individuals.

Dr. Koehly is also interested in obtaining baseline information about how "average families" — that is, those who are not affected by or identified as high-risk for a specific condition — communicate with one another and their degree of closeness to one another. These patterns could serve as control or reference groups in social network studies conducted in specific health contexts. Additionally, families from different ethnic and racial backgrounds might exhibit different patterns of family support and communicative relations. Understanding the multicultural aspects of the family support and communication structure will help in developing network-oriented interventions that are sensitive to these differences. In addition, understanding the family culture from a network perspective will provide important information for delivering genetic counseling and genetic-risk education.

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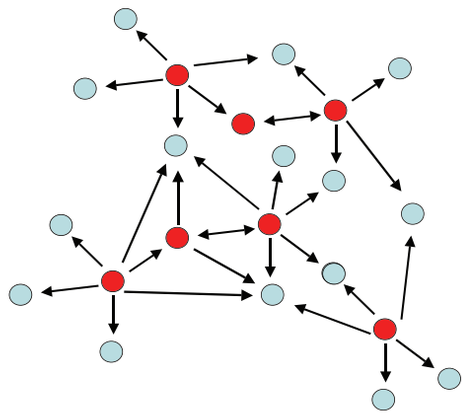

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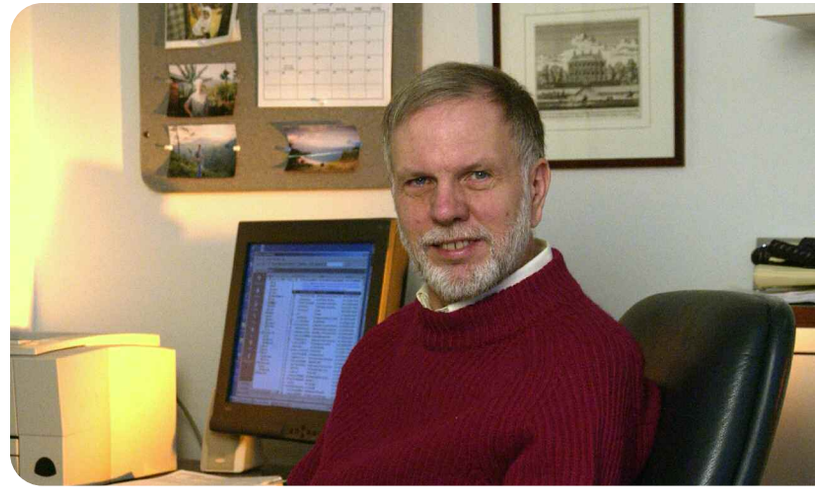

Dr. Fischbeck studies the mechanisms of hereditary neurological and neuromuscular disorders, with the goal of developing effective treatments for these conditions. His laboratory's areas of research include the polyglutamine expansion diseases (Huntington's disease, Kennedy's disease, and spinocerebellar ataxia), spinal muscular atrophy, Charcot-Marie-Tooth disease, muscular dystrophy, hereditary motor neuron disease, and Friedreich's ataxia. His laboratory studies the disease mechanisms of these conditions in cell culture and model systems. In addition, Dr. Fischbeck directs a genetic outreach program intended to identify and characterize patients and families with hereditary neurological diseases. His group has conducted a clinical trial of gentamicin treatment in patients with muscular dystrophy, and a trial of idebenone treatment for Friedreich's ataxia is ongoing. Efforts also are under way to develop new treatments for spinal muscular atrophy, muscular dystrophy, and the polyglutamine expansion diseases.

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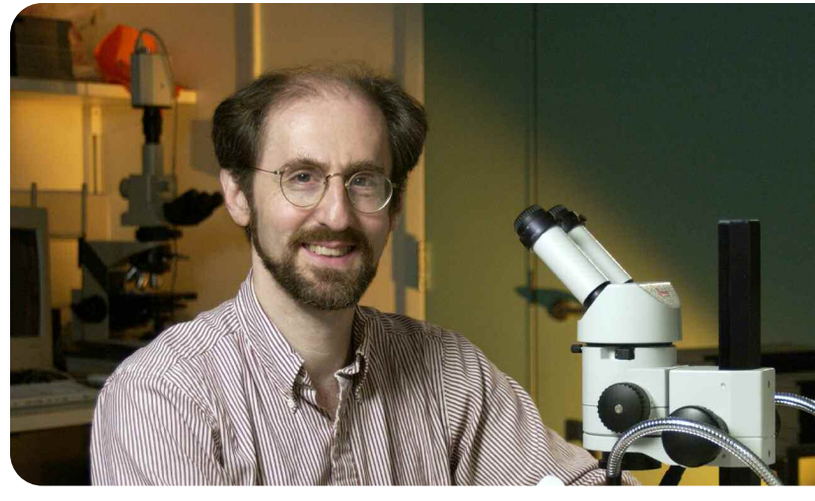

Information processing in the brain is done by specialized neural circuits. Every neuron has an axon, which carries information to its synaptic partners within these circuits. Dr. Giniger seeks to understand the molecular mechanisms that guide an axon, allowing it to find just the right partners from among the myriad cells of the nervous system. His laboratory also seeks to understand why axons do not make guidance mistakes, given the intricacy of the trajectories they need to navigate. To understand these processes in humans, Dr. Giniger studies neural circuits of fruit flies, a model system that allows biochemical and cell biological approaches to be merged with classical and molecular genetics. His laboratory has shown how a particular protein on the surface of fly nerve cells, called Notch, engages signaling proteins inside the axon that make it grow or turn when it encounters the Notch ligand — the *delta* protein. Notch is found in all multicellular animals, so this machinery almost certainly acts in construction of the human brain and nervous system.

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Dr. Hardy is a human geneticist and molecular biologist whose research focuses on neurological disease. In 1991, he and his colleagues described the first genetic mutations in the amyloid gene associated with Alzheimer's disease. His group also helped make many of the mouse models that are currently used in the study of Alzheimer's disease. Subsequently, his laboratory found mutations in the *tau* gene, which underlies Niemann-Pick C disease, a rare, inherited neurodegenerative childhood disease. The overarching goal of his laboratory is to continue to find and understand genes that cause or predispose individuals to neurodegenerative diseases and stroke. These efforts are pursued by three separate research groups. The Clinical Section Group works in collaboration with researchers at the National Institute of Neurological Disorders and Stroke to characterize families with neurological illness. The Cell Biology Group works largely on developing an understanding of the cellular effects of mutations that lead to neurological disease. Finally, the Transgenic Group uses animal models of neurodegenerative diseases to develop an understanding of disease mechanisms and eventually to test treatments.

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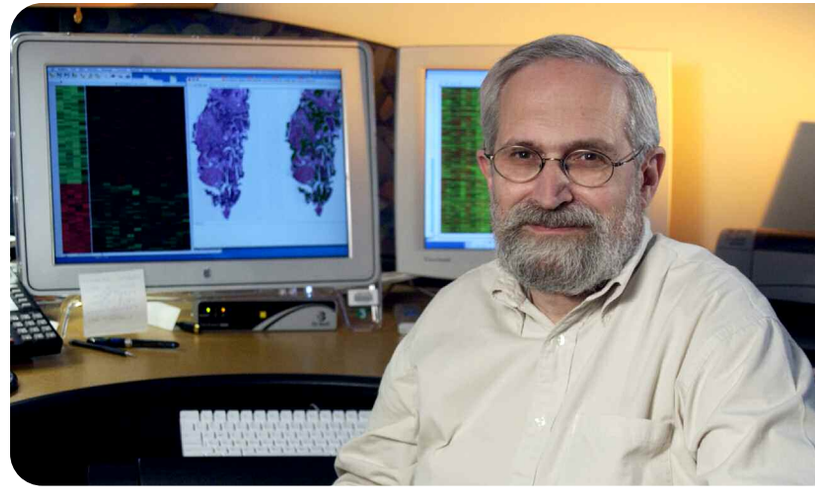


Dr. Meltzer uses cutting-edge technologies to analyze the abnormalities in genome structure and function that occur in cancers. These methods include various types of microarray analyses, which allow him to scan the entire genome and examine how genes that cause cancer start tumor progression and affect whether a tumor spreads to other parts of the body. He and his colleagues are refining the classification of cancers, increasing our understanding of how cancer develops at a cellular level, and identifying new targets for potential anticancer therapy. His most recent work has focused on sarcoma, breast cancer, and melanoma. Examining different sarcoma cell lines using microarray analysis revealed a set of genes with significantly different expression patterns in cells with high versus low metastatic potential. The use of similar technologies revealed diagnostic and predictive outcome patterns in breast cancer cells, and identified a genetic pattern associated with estrogen receptor expression in breast cancers. Distinct gene-expression profiles were associated with mutations in *BRCA1* and *BRCA2*, both known breast cancer genes. Dr. Meltzer's laboratory has also found mutations in the *BRAF* and *NRAS* genes in melanoma cell lines, as well as *BRAF* mutations in benign melanocytic lesions. These findings suggest that *BRAF* mutations play a role in early melanoma tumor progression.

CORES, CENTERS, AND OFFICES

CORES

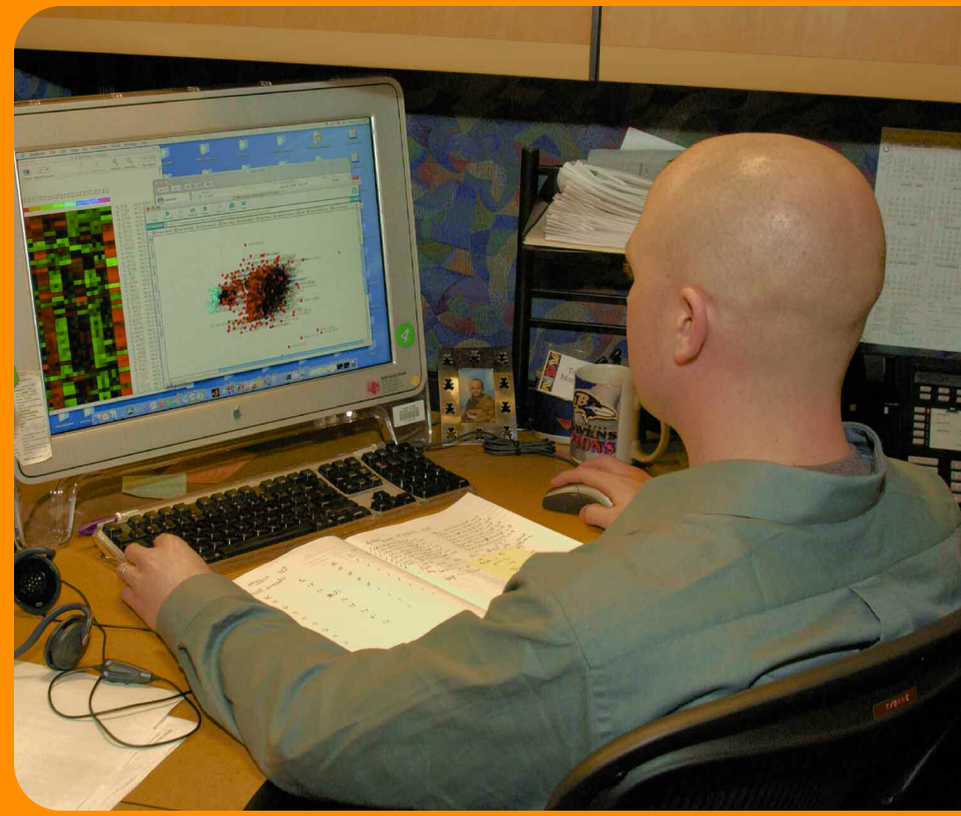
The Division of Intramural Research operates seven core facilities to support the work of NHGRI investigators and their collaborators. These cores maintain and utilize state-of-the-art instrumentation. In addition, the Cores provide access to experts in relevant areas, who then often play a key role in the design and execution of subsequent experiments.

Bioethics Core

Located in the Office of the Clinical Director, the Bioethics Core provides consultation, education, and administrative infrastructure in three key areas: the ethics of human subject research, the responsible conduct of research, and clinical bioethics. It also provides administrative support for the NHGRI Institutional Review Board (IRB), and provides education and consultation for investigators engaged in human subject research. Each year, the Core organizes a series of discussion groups on issues related to the responsible conduct of research, in keeping with the NIH requirement that all researchers participate annually in such training. The Core also addresses emergent needs in bioethics education and consultation and has a close working relationship with the NIH Clinical Center's Department of Clinical Bioethics, including joint appointments and shared physical space. This provides an interface with state-of-the-art scholarship in bioethics as well as networking opportunities with bioethics activities in other NIH Institutes.

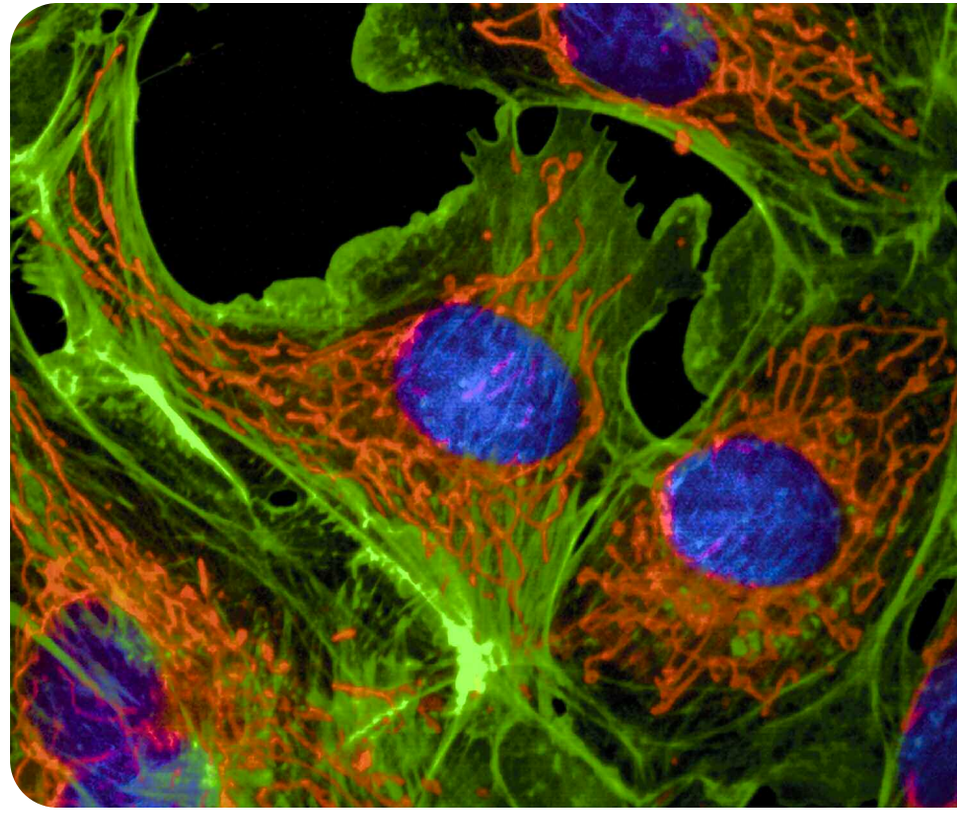
Bioinformatics and Scientific Programming Core

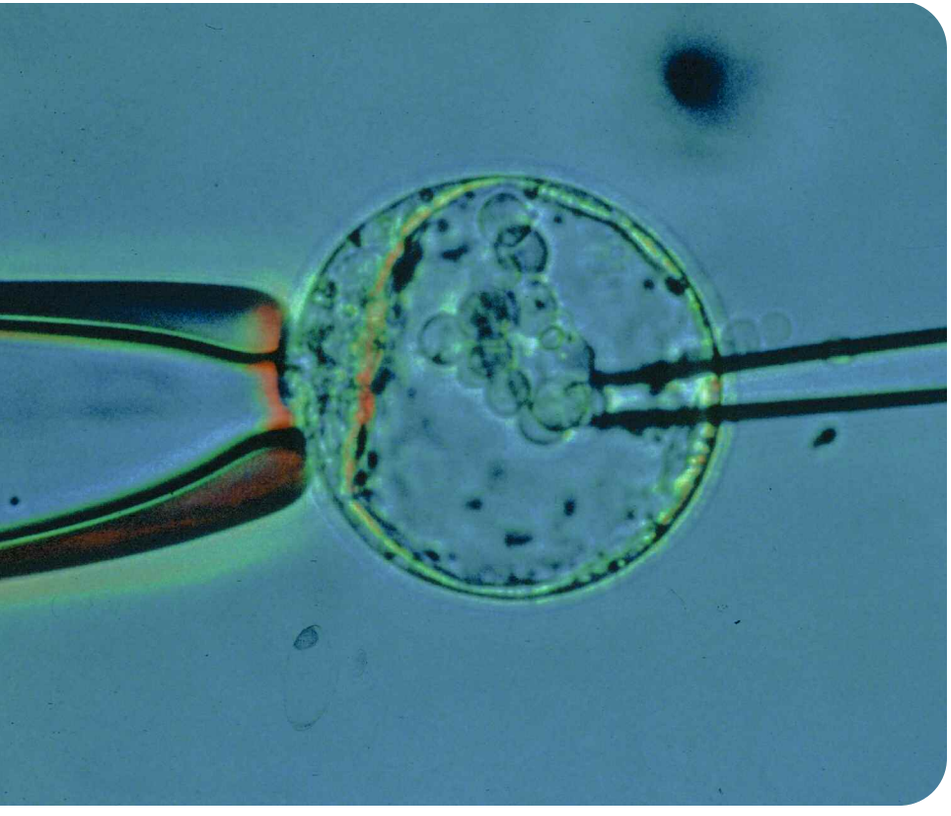
The Bioinformatics and Scientific Programming Core provides NHGRI investigators with expertise and assistance in bioinformatics and computational analysis for genome research. It develops computational tools for genome analysis, implementing them as "generalized solutions" that can then be tailored to the needs of individual investigators. Examples of Core-developed software include *GeneMachine*, an integrated tool that performs both comparative and predictive gene identification techniques, and *GeneLink*, a database solution designed to facilitate large-scale genetic linkage or association studies, allowing for complex trait mapping. The Core plays a key role in developing and maintaining sequence and mutation databases that allow for the efficient archiving and retrieval of genomic data generated by NHGRI investigators, such as the Breast Cancer Information Core (BIC; see *Lawrence Brody, Genome Technology Branch*). Core personnel collaborate with the numerous NHGRI laboratories that require intensive computational support. The Core maintains several high-end computer systems, including a 120-node Linux cluster; investigators also have access to the NIH Biowulf cluster, with more than 1250 compute nodes (2500 processors). NHGRI personnel can access commonly used sequence analysis software, often through Core-designed special interfaces; Core personnel provide basic assistance in using these computational tools. Finally, the Core is involved in a series of educational efforts, including hands-on bioinformatics training classes for NHGRI researchers, which are offered on a regular basis and cover the essentials of bioinformatics as related to genomic research.



Cytogenetics and Microscopy Core

The Cytogenetics and Microscopy Core performs fluorescence *in situ* hybridization (FISH) mapping of DNA clones, facilitating the visualization of defined nucleic acid sequences at the cellular and subcellular levels. Services include standard FISH mapping on high-resolution banded metaphase chromosomes (using G-banding or DAPI-banding); analyzing clones containing human, mouse, and other species' DNA (preferably genomic clones); high-resolution mapping of overlapping clones on extended chromatin structures (e.g., halo preparations or stretched DNA fibers); and high-sensitivity FISH mapping procedures based on the tyramide signal amplification system, such as for mapping cDNA clones. For karyotyping, the Core assists investigators in relevant techniques such as cell culture, metaphase chromosome preparation, and interpretation of rearranged karyotypes. The Core also offers both single-photon and multiphoton confocal scanning optical microscopy. Using this methodology, researchers can generate three-dimensional images of thick transparent objects, such as biological cells and tissues. The confocal approach facilitates the imaging of living specimens, enables the automated collection of three-dimensional data in the form of Z-series, and improves the images of multilabeled specimens. Time-lapse sequences of Z-series can also be collected from living preparations with the confocal microscope to produce four-dimensional data sets.





Embryonic Stem Cell and Transgenic Mouse Core

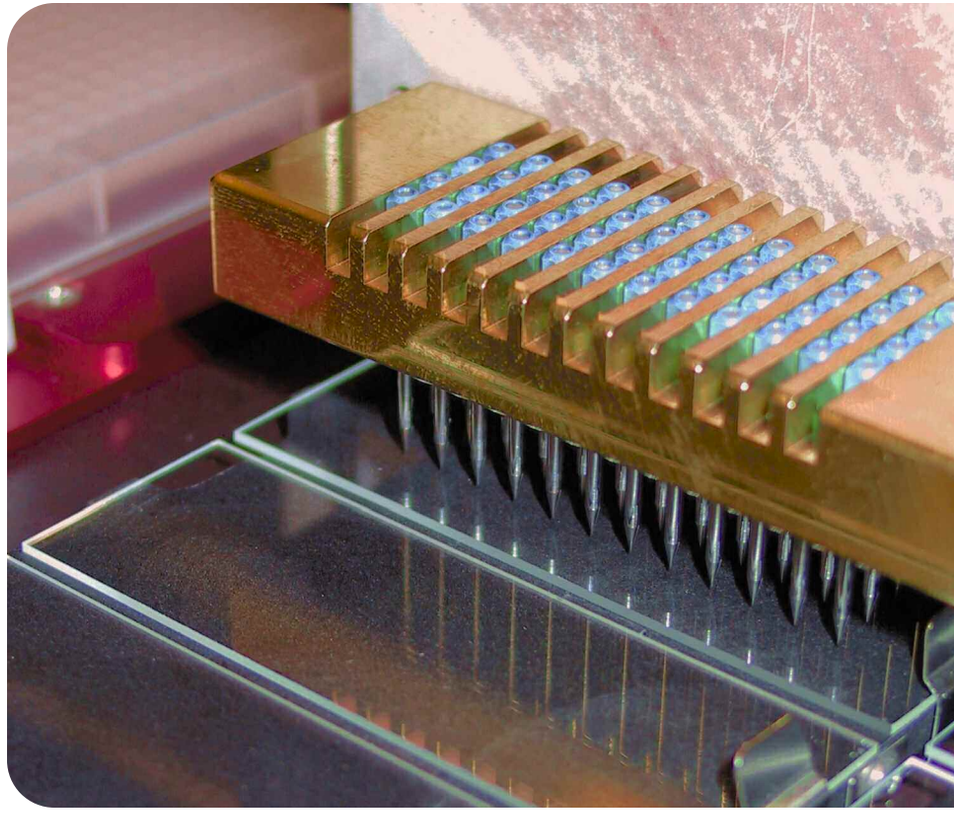
The Embryonic Stem Cell and Transgenic Mouse Core specializes in producing transgenic mouse models as a service to researchers studying gene function and human genetic diseases. Specific services include microinjection of DNA into the pronucleus, embryonic stem cell culture and electroporation, microinjection of embryonic stem cells into blastocysts, surgical embryo transfer, cryopreservation of sperm and embryos, *in vitro* fertilization, and rederivation of imported mice. Other services include perfusion of mouse tissues, dissection of mouse embryos and tissues, and mouse retro-orbital bleeding. The Core also provides information on mouse breeding and maintenance of mouse colonies, and assistance in designing DNA constructs and protocols for developing transgenic mice.

Flow Cytometry Core

The Flow Cytometry Core provides NHGRI researchers access to high-quality flow cytometry services. Flow cytometry can be used to analyze, identify, and isolate subpopulations of cells from mixed populations, and to classify cells that represent only 0.1% of the total sample. This technology can be used to analyze any cell type that can be prepared as a single-cell suspension. Multiple parameters can be measured simultaneously on thousands of cells per second, including cell size, cell complexity, and surface and intracellular markers. The Core is equipped with two three-laser, nine-color high-speed BD FACSArias™; one three-laser BD FACSVantage™ equipped with a UV laser; one three-laser, nine-color BD LSR II analyzer; two four-color FACSCalibur™ analyzers; and a Miltenyi AutoMACS™ for magnetic cell separation. Core personnel are available for training, development, and project execution.

Genomics Core

The Genomics Core offers physical mapping, genotyping, DNA sequencing, and microarray services. The physical mapping services include mapping, and accessing clones from various genomic libraries. Investigators may also scan the entire human genome with short tandem repeat polymorphism (STRP) markers and single nucleotide polymorphism (SNP) markers, and may fine-map regions identified by initial genome-wide scans. The Core provides equipment and expertise for fine-mapping regions identified by initial genome-wide scans. It also provides genotyping services for the mouse genome, and has plans to extend these services to the zebrafish genome. In addition, the Core offers access to several human DNA panels that are commonly used for determining allele frequencies. For DNA sequencing, investigators carry out the reactions, and then Core officers analyze the samples on sequencing instruments. In the areas of physical mapping, genotyping, and sequencing, Core personnel work with investigators to identify and meet their specialized needs. The Genomics Core provides several types of microarray services, including cDNA and oligonucleotide-based expression arrays for human, mouse, and zebrafish. In addition, the Core performs labeling and hybridization for smaller projects involving either slide arrays or Affymetrix™ arrays. Investigators also have access to equipment for RNA-based evaluations, hybridizations, scanning, and image analysis. The Core offers training in performing hybridizations, data analysis, and other aspects of microarray studies, both formally and on a one-on-one basis.



Zebrafish Core

The Zebrafish Core provides NHGRI investigators with the ability to study the function of genes of interest using zebrafish as a model organism. The Core performs whole-mount RNA *in situ* hybridizations using embryos from various stages of development in order to establish the spatial and temporal expression of genes, microinjections of morpholinos designed to block translation and/or splicing to study the phenotypic effects of gene knock-down, microinjections of RNA to study the phenotypic effects of gene overexpression, and resequencing/TILLING (Targeting Induced Local Lesions IN Genomes) to identify an allelic series of mutants in a target gene from a collection of ENU-mutagenized animals. The Core plans to collect 5,000 F1 males through repeated rounds of ENU mutagenesis and has already cryopreserved sperm and extracted DNA from 3,000 F1 males. Since the availability of mRNA sequence is a prerequisite for morpholino design and resequencing/TILLING, the Core also assists researchers in bioinformatics analyses to identify the zebrafish orthologs of genes of interest, deriving suitable cDNA clones for *in situ* hybridization, and determining target exons for resequencing/TILLING efforts. The Core also provides basic training in zebrafish handling and maintenance, including assistance with imaging to document *in situ* hybridization and morphant data. The Core maintains a backup of most commonly used zebrafish lines as well as mutants identified through resequencing/TILLING by sperm cryopreservation.

CENTERS

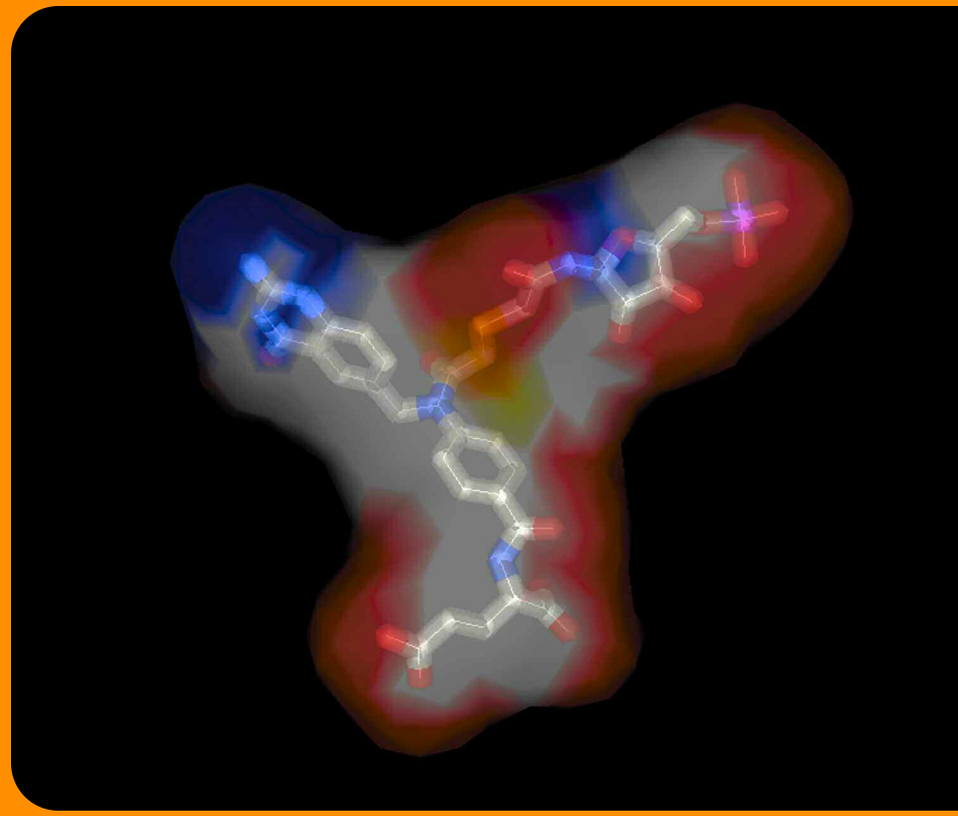
The Division of Intramural Research operates or oversees three centers that offer unique, high-throughput technologies for small-molecule screening, and genetic, genomic, and sequencing services to NHGRI investigators and their collaborators. Access to these centers allows NHGRI researchers to develop more comprehensive and higher-risk research portfolios.

Center for Inherited Disease Research

The Center for Inherited Disease Research (CIDR; *cidr.jhmi.edu*) provides high-throughput genotyping and statistical genetics services for researchers trying to identify loci and allelic variants that contribute to human disease. CIDR concentrates primarily on multifactorial hereditary diseases, although it can accommodate linkage analyses of single-gene disorders. The staff also helps investigators use marker-assisted breeding strategies to accelerate the production of congenic and consomic strains of mice, and conducts mapping studies with inbred mouse strains. Automated genotyping technologies are used to carry out genome-wide linkage scans with microsatellite and SNP-based markers. Custom SNP genotyping is available for fine mapping and candidate gene studies. CIDR recently added SNP panels for whole-genome association studies. Extramural researchers supported by one of the 13 participating NIH Institutes receive free genotyping services, while NIH Intramural investigators pay on a fee-for-service basis. Access to CIDR is open to all researchers through competitive peer review, and all data remain the property of the principal investigator.

NIH Chemical Genomics Center

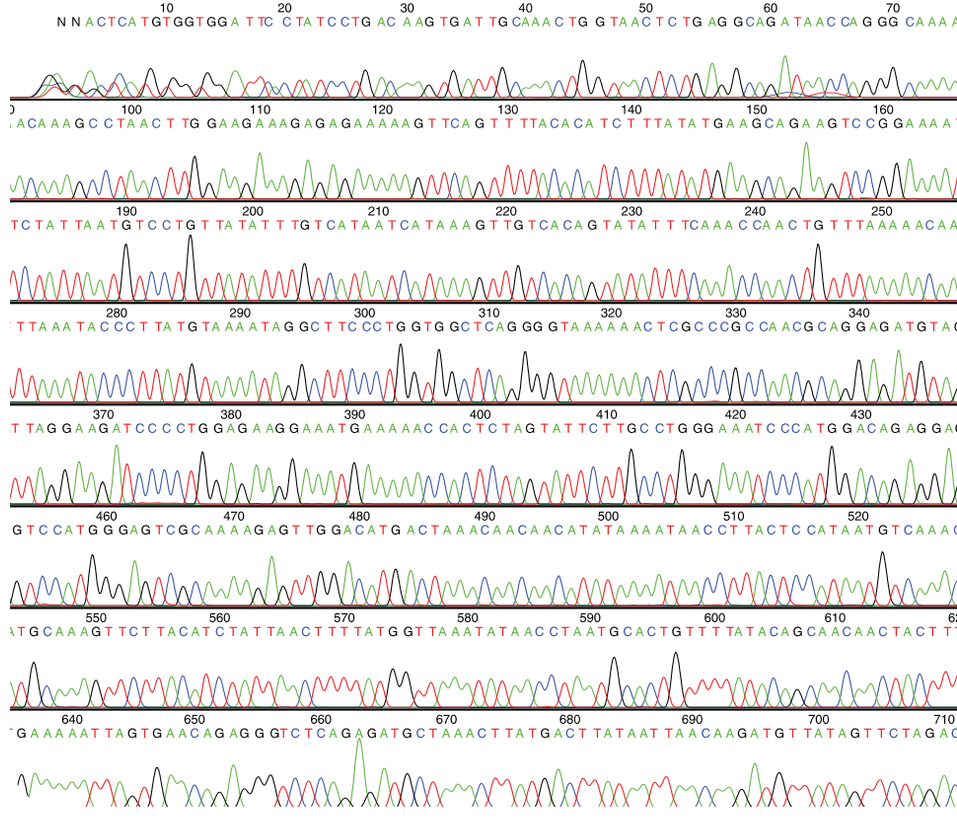
The NIH Chemical Genomics Center (NCGC; *ncgc.nih.gov*) is an ultrahigh-throughput small-molecule screening and chemistry center that discovers chemical probes of gene and cell functions across the genome using quantitative high-throughput screening (qHTS) technology, and develops new paradigms that enable chemical genomics and downstream drug development. NCGC collaborates with investigators worldwide to discover small-molecule chemical probes of basic and therapeutic importance. The probes that NCGC generates are defining the function of human and other genes, and the comprehensive datasets of chemical activity that NCGC generates on a wide range of assays are enabling true *chemical* genomics (i.e., the discovery of the general principles by which small molecules interact with gene products, and the definition of genomic organization on the basis of small-molecule interaction and biological function). NCGC also has explicit translational goals focused on



the identification of chemical starting points for the development of new drugs for rare genetic and orphan diseases. Located 10 minutes north of the Bethesda NIH campus, the Center has a staff of over 30 biologists, chemists, engineers, and informatics scientists, who together have enormous genomics, automation, and biopharmaceutical experience. The NCGC staff works with other NHGRI researchers and investigators throughout NIH and the world to translate genome sequence into biological function and therapeutics. NCGC is a founding member of the NIH Roadmap Molecular Libraries Screening Center Network (see *mli.nih.gov*).

NIH Intramural Sequencing Center

The NIH Intramural Sequencing Center (NISC; *www.nisc.nih.gov*) is a multidisciplinary genomics facility that emphasizes the generation and analysis of DNA sequence. The NISC Sequencing Group is responsible for high-throughput generation of DNA sequence data using state-of-the-art automated instrumentation, while the NISC Bioinformatics Group performs contemporary sequence assimilation and analysis. NISC is located in recently constructed research space within a cluster of NIH buildings near the Twinbrook Metro station, a short distance north of the NIH Bethesda campus. NISC performs DNA sequencing projects for NIH investigators on a fee-for-service basis; this includes both generation of the sequence and customized analysis of the resulting data by staff bioinformaticians. In addition, NISC is involved in several cutting-edge, large-scale genomics efforts, including the NISC Comparative Sequencing Program, the ENCODE project, and the ClinSeq large-scale medical sequencing project.



OFFICES

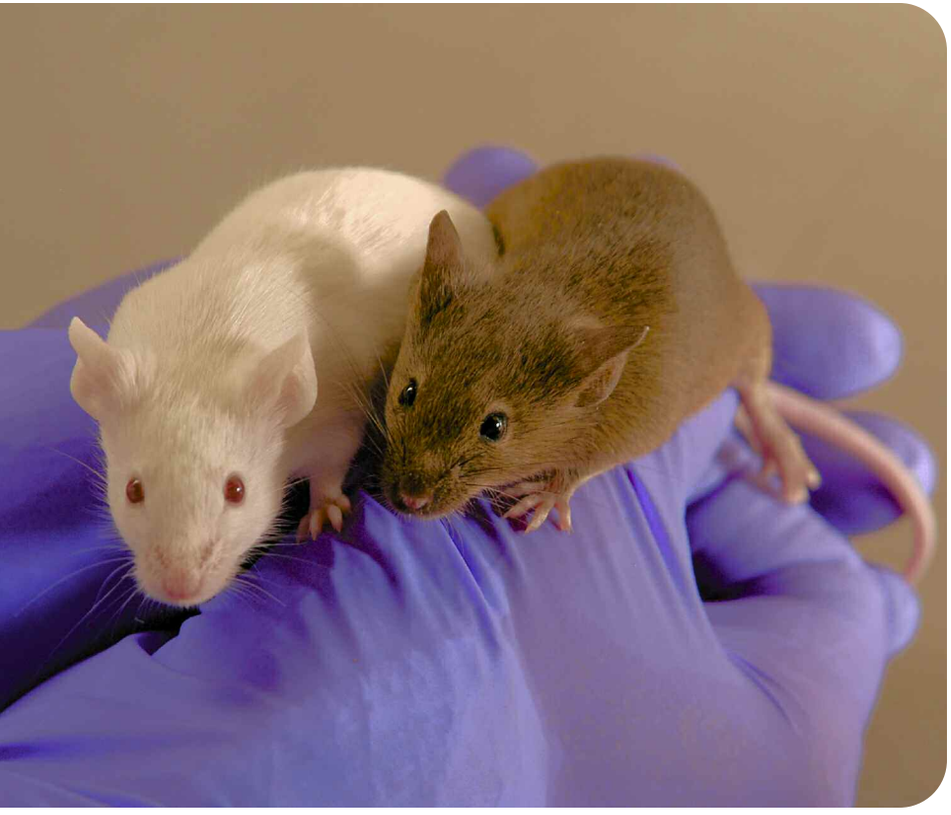
The Division of Intramural Research has several offices that support the work of NHGRI investigators. These offices provide a wide range of services, including administrative support, training and career development guidance, assistance in designing research protocols, and fostering the translation of scientific discoveries into products for improving human health.

Office of the Scientific Director

The NHGRI Office of the Scientific Director (OSD) provides leadership and managerial oversight for all research and related activities within the Institute's Division of Intramural Research. OSD creates and maintains a productive research environment through the effective management, coordination, and prioritization of NHGRI research activities. This is accomplished by providing overall scientific leadership and by overseeing activities that are central to the successful day-to-day operation of the NHGRI Intramural Program, primarily through the Office of Intramural Management. In conjunction with the NHGRI Board of Scientific Counselors, OSD has the primary responsibility for performing regular external reviews of all NHGRI research programs, ensuring their continued high quality and relevance. OSD staff (in particular, the Scientific Director and Deputy Scientific Director) serve important liaison roles between NHGRI and other NIH components by representing the Institute on various NIH-wide committees. Finally, OSD promotes activities intended to increase interactions among its scientific staff, through seminar series, the annual NHGRI scientific retreat, and other programs intended to highlight the Institute's investigators and their research.

Office of the Clinical Director

The NHGRI Office of the Clinical Director (OCD) is responsible for providing the infrastructure that makes possible innovative clinical research. A key goal of OCD is to encourage NHGRI clinical research and facilitate intramural scientists' ability to engage in clinical projects—for example, by arranging in-house or off-site consultations or special laboratory services. Among the top priorities of the Clinical Director are enhancing the Institute's overall clinical research program and increasing the number of protocols aimed at developing therapies. Currently, NHGRI investigators oversee more than 70 protocols at any one time. These range from genetic counseling projects to training protocols for clinical genetics residents to pathogenesis studies aimed at determining the effects of specific genetic mutations and treatment protocols. OCD also oversees a number of aspects of patient safety, such as ensuring the credentialing of personnel who come in contact with patients and maintaining the IRB that passes judgment on patient protection provisions of clinical trials. It also supports the Data Safety and Monitoring Board, which oversees trials in progress and intervenes to stop a trial if a therapy proves too risky to be of therapeutic benefit or so successful that it must be offered immediately to all participants. The Clinical Director also serves on the NIH-wide Medical Executive Committee, which sets general policies for the NIH Clinical Research Center, approves all NHGRI clinical protocols, and is ultimately responsible for the quality of patient care in all NHGRI clinical trials.



Office of Translational Research

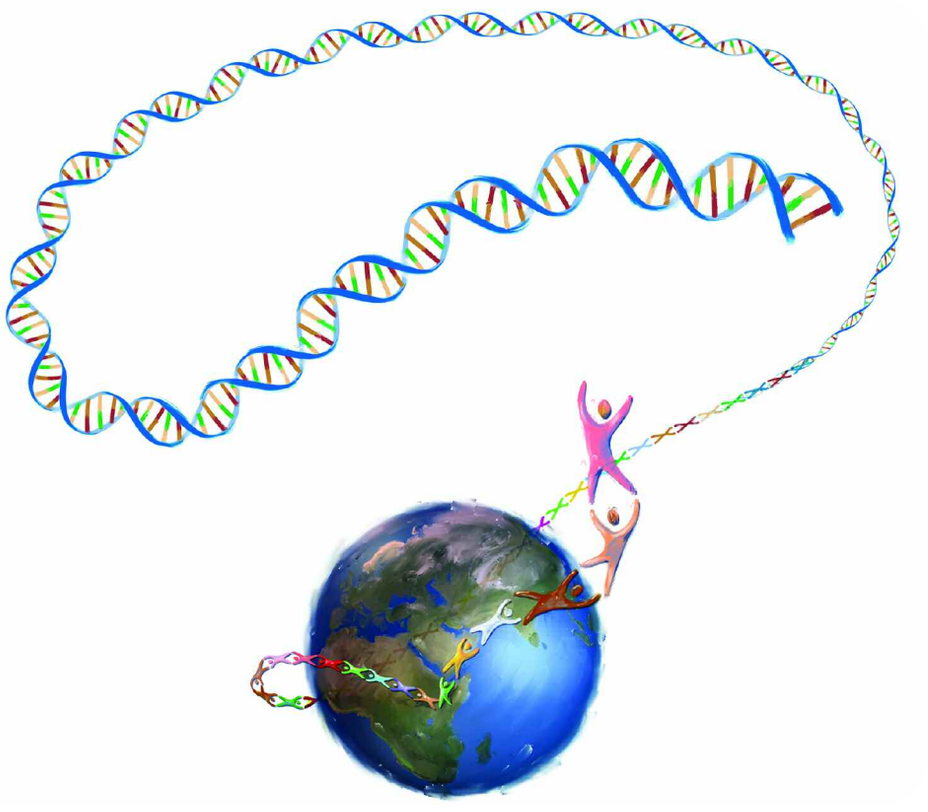
The NHGRI Office of Translational Research aims to facilitate translational and transdisciplinary approaches in an effort to bridge basic and clinical research within the Intramural Program. Recently established, the Office is now exploring different strategies for catalyzing translational research at NHGRI, including fellowships to develop expertise in understudied human diseases, the provision of clinical staff to basic science investigators to help them initiate new translational research projects, and a visiting clinical investigator program that couples extramural clinicians with intramural basic scientists. The Office seeks to provide consultative and infrastructure support to NHGRI researchers, so as to increase the number of projects that incorporate translational components.

Intramural Training Office

The NHGRI Division of Intramural Research provides an excellent environment for training the next generation of researchers and is proud to support training at all career levels. The Intramural Training Office (ITO) serves as the focal point for training and career development at NHGRI and offers a variety of information and resources related to mentoring, career development, and funding opportunities. It also assists in matching trainees to individual research laboratories. ITO focuses on a wide range of important training-related areas, including trainee orientations, mentorship programs, educational programs, conflict resolution and problem solving, and minority recruitment. It also serves as a clearinghouse for information about job opportunities. For more information about ongoing intramural training activities, see the *Training and Career Development Programs* section.

Office of Laboratory Animal Medicine

The mission of the NHGRI Office of Laboratory Animal Medicine (OLAM) is to promote the humane care and use of animals in biomedical and behavioral research, teaching, and testing. Because animals are an essential component of the research conducted at NHGRI, OLAM provides information and guidelines to NHGRI investigators on the proper care, use, and humane treatment of research animals. OLAM is responsible for housing and care of research animals and for enhancing their well-being. The animal program and animal laboratory areas are inspected and evaluated at least twice each year by the NHGRI Animal Care and Use Committee (ACUC), in compliance with federal regulations and guidelines.



Technology Transfer Office

The mission of the NHGRI Technology Transfer Office (TTO) is to build bridges between the Institute's research laboratories and the private sector for the benefit of public health. TTO carries out this mission by assisting in the transfer of NHGRI-developed technologies to the private sector for further development; it also facilitates the exchange of research resources between NHGRI and outside scientific groups. Since its inception, TTO has been an integral part of the NHGRI Division of Intramural Research, posting steady annual increases in technology licenses, Cooperative Research and Development Agreements (CRADAs), and Employee Invention Reports. TTO has a variety of mechanisms at its disposal to help achieve its technology transfer goals, including the evaluation, patenting, and licensing of novel technologies and methods invented by NHGRI investigators. TTO is also involved in negotiating Material Transfer Agreements and other legal documents that enable the sharing of materials and resources between NHGRI scientists and the academic and private sectors. This sharing may range from obtaining single, critical reagents to setting up formal research collaborations. TTO also facilitates CRADAs between NHGRI researchers and the private sector. In this capacity, it provides NHGRI researchers and administrators with general advice and guidance on copyrights, intellectual property, conflict of interest issues, and related matters.

Intramural Publication Support Office

NHGRI's Intramural Publication Support Office (IPSO) provides a variety of publication-related services intended to facilitate the dissemination of NHGRI research findings. Creative medical illustrators and graphics experts within IPSO provide full-service graphics and media support, create high-quality photographs and custom illustrations for journal publications, posters, slide presentations, and special events. As a service to NHGRI researchers, IPSO also maintains a library of images, including commonly used genetics illustrations and templates for slide presentations. Science writers within IPSO assist in developing lay summaries of research programs and editing abstracts and manuscripts. The writers and graphics experts within the Office work closely in developing brochures and other publications describing NHGRI's research and training programs.

TRAINING AND CAREER DEVELOPMENT PROGRAMS

TRAINING AND CAREER DEVELOPMENT PROGRAMS

NHGRI offers a wide range of programs aimed at furthering the professional training and career development of students, research scientists, health professionals, and educators. Training and educational opportunities available at NHGRI for individuals at different stages of their careers are described below. More in-depth information, including points of contact and application procedures, can be found on the NHGRI Research Training Opportunities Web page (*genome.gov/researchtraining*).

Summer Internship in Biomedical Research Program

The Summer Internship in Biomedical Research Program provides students at different levels the opportunity to perform biomedical research alongside some of the world's most accomplished scientists. The program immerses students in a unique environment devoted to understanding the underlying causes of human genetic disease, in order to develop novel methods for the detection, prevention, and treatment of heritable disorders. In addition to laboratory training and mentoring, participants attend the NIH Summer Seminar Series, where leading biomedical and clinical researchers present their latest findings at a level geared toward advanced high school and college students. NHGRI also conducts its own Summer Seminar Series, with an emphasis on career development and mentoring. At the end of the summer, students present their work at the annual NIH Summer Research Program Poster Day. This very important component of the program gives students the opportunity to showcase what they have accomplished over the summer, and allows them to meet investigators and students from other NIH Institutes. Participants earn a monthly stipend based on their educational level; however, they are responsible for their own travel and housing expenses. Information on local housing options is available to all accepted students. To be eligible, applicants must be: enrolled at least half-time in high school or college; citizens or permanent residents of the United States; and at least 16 years of age. The application deadline for the Summer Internship Program is March 1 of each year.

Intramural Research Training Awards Program

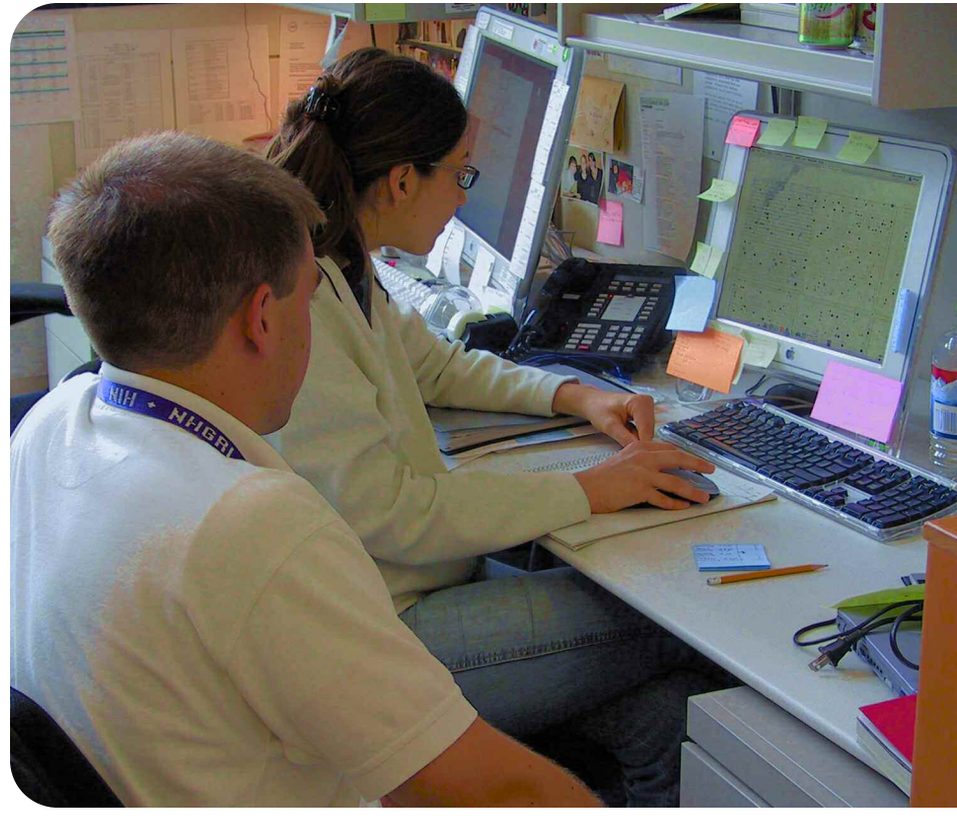
The Intramural Research Training Awards (IRTA) Program consists of four types of awards, each specifically designed to suit the needs of trainees at different stages of their education and/or professional training. These awards include stipends to those who have recently earned a bachelor's or master's degree and to pre- and postdoctoral trainees.

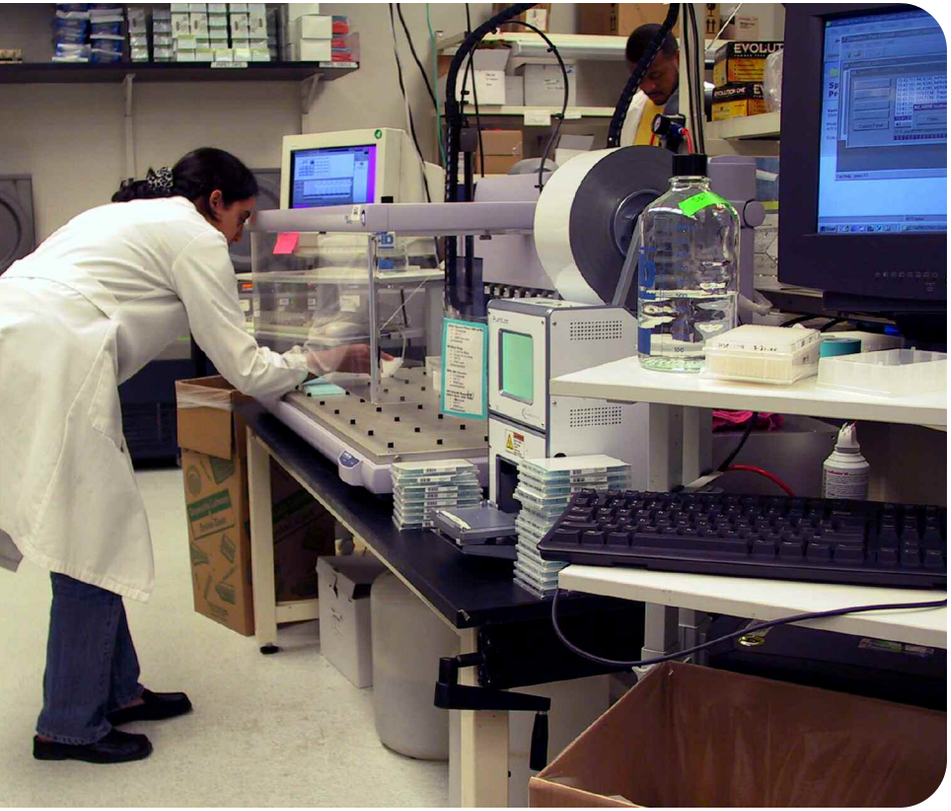
TECHNICAL INTRAMURAL RESEARCH TRAINING AWARD

The Technical Intramural Research Training Award (Tech IRTA) program is designed to train support professionals hands-on in the latest advanced research techniques. To be eligible for this program, candidates must have a bachelor's or master's degree from an accredited American college or university; they also must be U.S. citizens or permanent residents. The initial award is for two years and can be extended to a maximum of three years. Tech IRTA fellowships do not carry a service payback obligation, and stipend amounts depend on the applicant's educational level. Applications for this program are accepted throughout the calendar year.

POST-BACCALAUREATE INTRAMURAL RESEARCH TRAINING AWARD

The Post-Baccalaureate Intramural Research Training Award (Post-Bac IRTA) gives recent college graduates the opportunity to spend a year engaged in biomedical investigation in NHGRI laboratories. While in this program, participants work side-by-side with some of the leading scientists in genetics and genomics in an environment devoted exclusively to biomedical research. During their tenure in the program, Post-Bac IRTA fellows are expected to begin the application process for graduate or medical school. The duration of the fellowship is normally one year, which can be extended for an additional year, provided the trainee's performance is satisfactory and continued support by the laboratory is available. To be eligible, candidates must be U.S. citizens or permanent residents, have graduated from an accredited American college or university, and begin their training within two years of receiving an undergraduate degree. This program is intended for individuals who have not previously worked full-time in a research laboratory, with the exception of summer experiences. The Post-Bac IRTA program is also open to individuals who have been accepted into graduate or medical school and have written permission from their school to delay matriculation for up to one year. Stipend amounts depend on the candidate's educational level. Applications for this program are accepted throughout the calendar year.





PRE-DOCTORAL INTRAMURAL RESEARCH TRAINING AWARD

The Pre-Doctoral Intramural Research Training Award (Pre-Doc IRTA) helps to foster the professional development of future scientists by providing graduate and medical students the opportunity to work directly with top NHGRI researchers in some of the world's most advanced biomedical research facilities. To be eligible for consideration, applicants must be currently enrolled in a doctoral program in the biomedical sciences, *or* have been accepted into medical or graduate school, *or* be college graduates who earned their degree no more than 12 months prior to applying, and intend to apply to graduate or medical school within the year. Applicants must be U.S. citizens or permanent residents. Participants in this program receive a stipend based on their educational level and experience; partial travel allowances also may be available. Pre-Doc IRTAs are granted for one year, with the option of renewing for a second year, pending satisfactory performance and the availability of resources. Applications for this program are accepted throughout the calendar year.

POST-DOCTORAL INTRAMURAL RESEARCH TRAINING AWARD

The Post-Doctoral Intramural Research Training Award (Post-Doc IRTA) is available to promising researchers who are interested in pursuing full-time, semi-independent research in NHGRI laboratories. Post-doctoral fellows select laboratories that are compatible with their academic interests and career plans. An important aspect of the post-doctoral training experience at NHGRI is mentoring by an NHGRI investigator, including career counseling. Trainees also receive extensive support from the NHGRI Intramural Training Office, which serves as a focal point for training and career development and whose goal is to improve the overall training experience at NHGRI. All fellows are encouraged to participate in post-doctoral seminar series, activities offered through the NHGRI Fellows Committee, and other NHGRI- and NIH-sponsored career development programs. Post-Doc IRTAs are initially awarded for one or two years, and may be extended to a maximum of five years, depending on the annual assessment of the trainees' progress and the availability of institutional resources. Post-doctoral candidates must be U.S. citizens or permanent residents with a doctoral degree and less than five years of relevant postdoctoral experience. Applications for this program are accepted throughout the calendar year. Information on current openings in NHGRI laboratories can be found at the NHGRI Intramural Training Office's Web page (*genome.gov/ITO*).

Graduate Partnerships Program

The Graduate Partnerships Program (GPP) directly links NHGRI and NIH with major universities in the training of graduate students in biomedical and clinical research. GPP establishes and fosters graduate education partnerships with institutions dedicated to quality education in basic and clinical biomedical research, while providing the infrastructure and research support needed for productive graduate careers. Through these university partnerships, NHGRI and NIH are able to play a key role in training the next generation of biomedical scientists. While at NHGRI, GPP students interact extensively with a talented group of research faculty and numerous post-doctoral fellows. The GPP Office, NIH's Office of Intramural Training and Education, and NHGRI's Intramural Training Office provide individual career advisement, and training in scientific presentations and writing. They also sponsor events supporting the students' quality of life. GPP students spend their first year at their college or university taking graduate-level courses. In the second year, they move partially or completely to NHGRI for their research while continuing to take higher-level graduate courses. The final years in the program are dedicated completely to research at NHGRI. Fellows maintain an affiliation with their home university throughout the course of the program, and they receive their doctoral degree from their home university upon completion. Detailed information on eligibility, application procedures, and deadlines can be found at the GPP Web site (*gpp.nih.gov*).

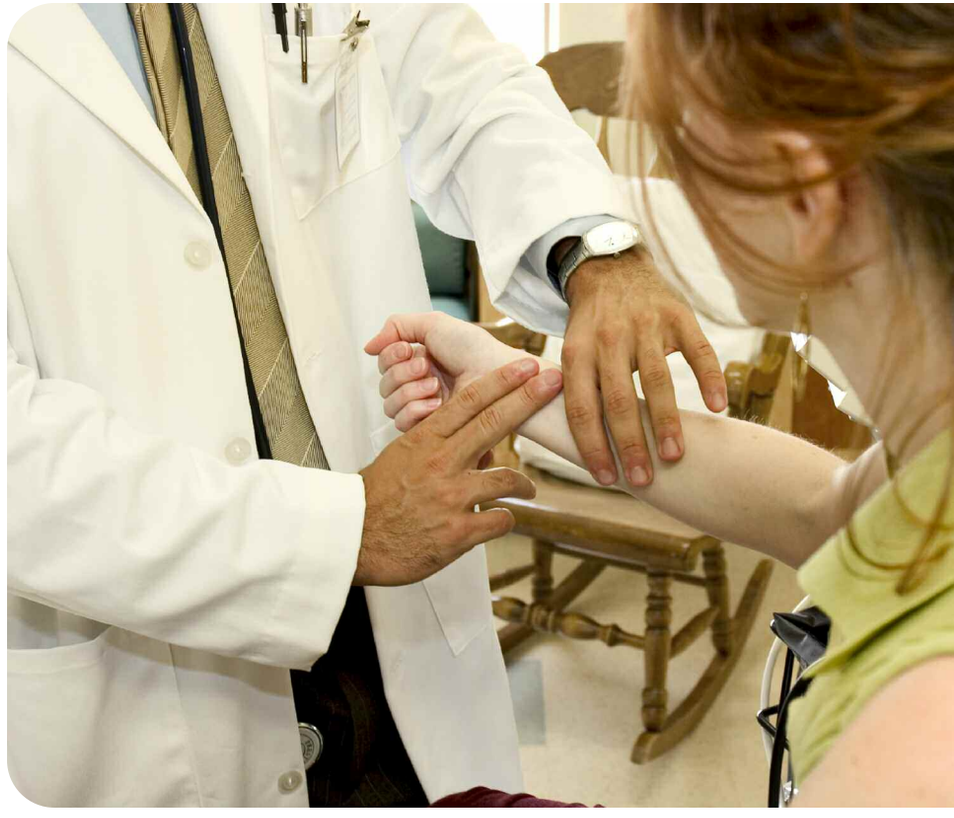
Undergraduate Scholarship Program

The NIH Undergraduate Scholarship Program (UGSP) offers competitive scholarships to students from disadvantaged backgrounds who are committed to careers in biomedical, behavioral, and social science health-related research. UGSP offers scholarship support, paid research training during the summer, and paid employment and training at NIH after graduation. Currently, UGSP provides up to $20,000 per academic year in tuition, educational expenses, and reasonable living expenses to scholarship recipients. Scholarships are awarded for one year and can be renewed up to a maximum of four years. For each full or partial scholarship year, UGSP awardees are committed to two service obligations: a ten-week summer laboratory experience under the mentorship of an NIH investigator and one full year of research in an NIH laboratory. To be eligible for UGSP, a student must be: enrolled or accepted for enrollment as a full-time student at an accredited, four-year undergraduate institution; a U.S. citizen, national, or qualified noncitizen (see *ugsp.info.nih.gov/citizenship.htm* for more information); from a "disadvantaged" background with demonstrable financial need; and either within the top 5% of his/her class, or having a grade-point average of 3.5 or higher (on a 4.0 scale). The application deadline for the UGSP is March 1 of each year.

Physician-Scientist Development Program

The NHGRI Physician-Scientist Development Program is designed for board-eligible or board-certified physicians who seek additional training to develop an independent research program that integrates the field of genomics with clinical investigation in genetic medicine. Participants have substantial protected time to develop their own integrated, clinical-basic research program that should serve as the basis for an independent research career.

The goal of the program is to train investigators who can compete for independent faculty positions at NHGRI, other NIH Institutes, and other top biomedical research institutions. The program provides support to design, implement, and pursue independent research. With the assistance of an NHGRI Intramural Program mentor, the participant designs a project that integrates the direct study and/or treatment of human subjects with a laboratory research project. The mentor advises and guides the participant in selecting a project, developing a study design, organizing a patient recruitment and analysis plan, conducting bench research, and all other aspects of training. The program provides a competitive salary for the participant, laboratory space and supplies, a clinical research budget, and funds for a research technician. Support is renewable annually, with demonstration of adequate progress, for up to five years. The program is open to physicians who are board-certified or board-eligible in any appropriate specialty and who have completed their training within the past five years. Applicants are not required to have substantial basic research experience but must demonstrate an aptitude for and commitment to research. The deadline for applications is October 31 or the year preceeding the July 1 starting date.



Metropolitan Washington D.C. Medical Genetics Residency Program

NHGRI offers a three-year residency program in medical genetics, which trains physicians to diagnose, manage, and counsel patients with genetic disorders. Participants gain broad experience in clinical and molecular genetics, metabolic diseases, and cytogenetics. This NHGRI-sponsored program gives students experience with rare genetic disorders that might not be seen in a more typical medical genetics program; is one of the few to emphasize clinical research; and grants access to the vast resources at NIH and at other highly-ranked medical institutions in the nation's capitol. During the first 18 months of training, residents spend most of their time seeing patients at various NIH facilities and in hospitals and outpatient clinics throughout metropolitan Washington. Clinical training addresses the role of genetics in general medicine, pediatrics, oncology, ophthalmology, dermatology, and perinatal medicine. During the second year, residents continue their patient care responsibilities, while performing laboratory research in any of the nearly 4,000 participating laboratories in the Washington area; during this time, they begin to devise their own basic or clinical research projects. Third-year residents spend most of their time conducting research and have minimal clinical responsibilities. Throughout the program, trainees attend a number of lecture-based courses as well as the weekly Clinical Genetics Case Conference and the biweekly Cytogenetics/Molecular Genetics Sign-Out Conference. M.D. candidates must have completed at least two years of training in a residency program accredited by the U.S. Accreditation Council for Graduate Medical Education and be board-eligible or board-certified in that specialty. Training is usually in pediatrics, internal medicine, or obstetrics and gynecology, but the program is open to M.D. candidates with other training. Applicants should submit materials 12 to 18 months before the proposed start date.

Metropolitan Washington D.C. Medical Genetics Training Program

NHGRI sponsors the Metropolitan Washington Medical Genetics Training Program, which offers two-year fellowships in medical genetics, cytogenetics, biochemical genetics and molecular genetics for individuals with M.D. or Ph.D. degrees. This program provides participants the opportunity to conduct genetic research in some of the world's most advanced laboratories; gain clinical experience in the Washington area; and develop expertise in basic and clinical genetics research and diagnostics. Fellows spend 18 months of the program at a laboratory of their choice. Six months of clinical experience is also required. Fellows see patients in various NIH facilities and in hospitals and outpatient clinics throughout metropolitan Washington. Training sites include the Children's National Medical Center and Research Institute, Georgetown University Medical Center, and Walter Reed Army Medical Center. Trainees attend a number of lecture-based courses as well as the weekly Clinical Genetics Case Conference and the biweekly Cytogenetics/Molecular Genetics Sign-Out Conference. Upon completion of the program, trainees will qualify for board certification by the American Board of Medical Genetics (ABMG) in one or more of the following areas of expertise: clinical biochemical genetics, clinical cytogenetics and clinical molecular genetics. Eligibility for this program has been established by ABMG. For training in clinical genetics, applicants must have spent two years in an accredited residency training program in the United States and be board-eligible or board-certified in the primary residency. For training in each of the other subspecialties, ABMG requires a Ph.D. degree earned from a U.S. university, or equivalent education with prior ABMG approval. For individuals with M.D. degrees, a medical licence from any U.S. State is also required. Applicants should submit materials 12 to 18 months before the proposed start date.

Combined Pediatrics and Medical Genetics Residency Program

NHGRI, in conjunction with the Children's National Medical Center (CNMC), offers a remarkable opportunity for medical school graduates to complete a five-year residency program in pediatrics and medical genetics. This program trains physicians in pediatric medicine and in the diagnosis, management, and counseling of patients with genetic disorders. Participants gain broad experience in pediatrics, clinical and molecular genetics, metabolic diseases, and cytogenetics. The Combined Pediatrics and Medical Genetics Residency Program is unparalleled in several respects: it trains residents in one of the nation's most prestigious children's hospitals, gives trainees the opportunity to observe rare genetic disorders they might not see in a more typical medical genetics program, is one of the few programs that emphasizes clinical research, and gives participants access to the vast resources at NIH and at other highly-ranked medical institutions in the nation's capital. Trainees spend their first 30 months in a pediatrics residency program at the world-renowned CNMC, located in the heart of Washington. Participants then receive 18 months of formal training in clinical genetics, which entails seeing patients in various NIH facilities and in hospitals and outpatient clinics throughout the metropolitan Washington, D.C. area. Clinical training highlights the role of genetics in general medicine, pediatrics, oncology, ophthalmology, dermatology, and perinatal medicine. During their final year, residents perform laboratory research on a project of their choosing. Upon completion of the program, trainees qualify for board certification by both the American Board of Pediatrics and ABMG. Interested applicants must have successfully completed medical training at an accredited medical school. Applicants should submit materials 12 to 18 months before the proposed start date, which is usually July 1.

The Johns Hopkins University/NHGRI Genetic Counseling Training Program

The Johns Hopkins University (JHU) and NHGRI together offer an opportunity to earn a master's degree (Sc.M.) in genetic counseling from the Department of Health Policy and Management at the JHU Bloomberg School of Public Health. Students have access to unparalleled resources in clinical settings throughout the Baltimore/Washington area. The program is unique in its emphasis on psychological aspects of genetic counseling and on research methodology and public policy issues. As part of this program, students complete at least 80 credit hours of course work in human genetics, genetic counseling, public policy, research methodology, ethics, and health communication. Supervised clinical rotations begin in the second quarter of the program and are required throughout. Students must also complete a thesis project. Upon completion, trainees qualify for board certification by the American Board of Genetic Counseling. NIH Intramural stipends are offered to all enrolled students who are U.S. citizens or permanent residents. An 85% scholarship is awarded by JHU the second and third years to students in good academic standing. Scholarships of $10,000 are offered by NHGRI to students with demonstrable financial need. In addition, loans are available through the financial aid office to students with residual financial need. Students are also granted a small budget from NHGRI to conduct their thesis research. To be eligible, applicants must have earned a bachelor's degree from an accredited U.S. college or university, completed undergraduate courses in biochemistry and genetics, have prior counseling experience (either paid or unpaid), and have some prior course work in statistics. The Sc.M. program in genetic counseling requires submission of the JHU Bloomberg School of Public Health general application. The application deadline for the program is January 15 for matriculation the following September.

Visiting Fellow Program

The Visiting Fellow Program provides postdoctoral research training to foreign scientists with five years or less of other relevant postdoctoral training. U.S. citizens are not eligible for the Visiting Fellow Program. Visiting fellows receive a monthly stipend during the award period, with the stipend level determined by the number of years of prior postdoctoral training. They are not considered employees of NIH. Visiting fellow awards generally are made for two years, although a one-year award is an option. Fellowships are renewable for up to five years, based on merit and subject to approval. All renewals are contingent upon visa limitations and compliance with U.S. immigration regulations. Prior to starting the program, candidates must provide a photocopy of their diploma (and translation, if not in English) or a letter from a university dean or registrar stating when the degree will be awarded. Coursework toward a degree does not, by itself, qualify a candidate for a fellowship.

Health Disparities Visiting Faculty Program

The NHGRI Health Disparities Visiting Faculty Program provides researchers focused on genomics and health disparities with the opportunity to spend 6 to 12 months at NHGRI. The visiting faculty member works directly with an NHGRI investigator and has the opportunity to learn new technologies, develop research collaborations, and conduct independent research while on sabbatical. Basic and social science researchers have access to NHGRI laboratories, core facilities, clinics, and training programs for study in any area of human genetic and genomic disease, including the ethical, legal, and social implications of such research. Researchers are expected to share their skills and experience upon returning to their home institutions, and applications will be evaluated based on this criterion. Applicants must possess a doctoral degree or professional terminal degree and propose a research project that is compatible with research being conducted in the NHGRI Division of Intramural Research. Candidates must be independent faculty-level investigators who have potential or demonstrated excellence in clinical or basic research or in a social science discipline. Finally, applicants must be: affiliated with a grantee of the National Center on Minority Health and Health Disparities (NCMHD) Centers of Excellence in Partnerships for Community Outreach, Research on Health Disparities and Training (Project EXPORT); affiliated with a grantee of NCMHD's Research Infrastructure in Minority Institutions Program; or employed by a predominantly minority-serving institution. The program provides funding of up to 75% of a researcher's current salary and a research budget for his/her work at NHGRI. Applications for this program are accepted throughout the calendar year.

Current Topics in Genomic Research Short Course Program

The Current Topics in Genomic Research Short Course Program is an intensive, five-day course for faculty at colleges and universities with substantial underrepresented minority, rural, and/or disadvantaged student enrollment. This course is designed to update instructors on genomic science and the continuing effort to find the genetic basis of diseases and to present current topics on the ethical, legal, and social implications of genomics. NHGRI investigators work closely with participants, offering both lecture- and laboratory-based presentations. An important part of the Course involves the development of curricula and teaching materials that participants can use upon returning to their own institutions. Class sizes are limited to facilitate interactions between participants and Course faculty. NHGRI pays expenses for room and board, while the participant's home institution is responsible for travel to and from the Bethesda campus. All accepted Course applicants are also asked to select one promising student from their schools to attend the associated Genome Scholars Program. This program parallels the Course, offering a close-up view of careers in genetic and genomic research along with an enhanced mentoring experience. Genome Scholars Program applicants must have a minimum grade-point average of 3.0, be currently enrolled at the sponsor's school in a science-related major, and successfully complete a formal application. NHGRI pays all expenses, including travel.

NIH AND SURROUNDING AREA

THE NATIONAL INSTITUTES OF HEALTH

As scientific and clinical research has become increasingly critical to human health and well-being, the National Institutes of Health (NIH) has grown in size and importance. In 1887, when NIH's predecessor (the Laboratory of Hygiene) was launched, the institution employed a single scientist, had an annual budget of just $300, and fit into a one-room laboratory at the U.S. Marine Hospital in Staten Island, New York. Today, located on a 300-acre campus in Bethesda, Maryland and at several other satellite venues, NIH consists of 27 individual Institutes and Centers, and boasts an annual budget of more than $28 billion. It is truly among the most prestigious research institutions in the world.

In addition to funding more than 40,000 individual research projects in all 50 states and throughout the world, NIH maintains a robust research program in its own on-campus laboratories and clinical research facilities. In fact, nearly $3 billion, or slightly more than 10% of NIH's annual budget, is dedicated to this "Intramural" Research Program. NIH Intramural investigators have access to state-of-the-art laboratory facilities, advanced research and computing tools, and a highly educated and diverse technical staff. Working in a comfortable collegial atmosphere, NIH Intramural scientists collaborate with each other regardless of Institute affiliation or discipline, and enjoy tremendous intellectual freedom to pursue their research interests.

Thanks to the world-class talent that NIH has attracted over the years, the agency currently boasts a roster of 16 Nobel laureates who have either trained or conducted research within its Intramural Program. More than 100 additional Nobel Prize winners — including Linus Pauling and James Watson — have been among NIH's longtime grantees. Today, a new generation of world-renowned researchers directs active laboratories at NIH.

The Mark O. Hatfield Clinical Research Center

The Mark O. Hatfield Clinical Research Center (CRC) is headquarters for the cutting-edge clinical research performed at NIH. Designed specifically for housing patients enrolled in carefully designed clinical trials, the CRC admits nearly 10,000 patients and logs more than 72,000 outpatient clinic visits each year. It is the largest hospital in the world devoted exclusively to clinical research and, since its inception in 1953, has served as an international model for the conduct of such research.

A unique feature of the CRC is its physical proximity to NIH's basic science laboratories, enabling NIH investigators to develop and deliver potential therapies to patients being treated at the Center. Because of its outstanding reputation for this "bench-to-bedside" approach to clinical research, patients throughout the world actively seek enrollment in NIH clinical trials. NIH is typically recruiting patients for more than 1,000 individual clinical studies for a variety of afflictions ranging from common ailments, such as breast cancer and heart disease, to rare genetic disorders, such as polycystic kidney disease and Hermansky-Pudlak syndrome.

Individuals admitted to the CRC may be physician-referred or self-referred to participate in specific studies. Once enrolled in a clinical trial, patients receive all care free of charge. There are more than 800 practicing physicians at the CRC, who work along with more than 1,000 other skilled healthcare professionals, including nurses, medical technicians, imaging specialists, and physical therapists, to care for patients enrolled in NIH clinical trials.

The NIH Libraries

The NIH Library offers on-campus scientists and clinicians a valuable research resource. In addition to possessing extensive print holdings, the library provides access to more than 1,000 electronic books and journals and to major biomedical and clinical research databases. Librarians are available to help researchers conduct literature searches in all the scientific databases available on campus, including specialized collections open only to library staff. A full-service facility assisting the entire NIH community, the library promptly fills online requests for copies of any journal articles in its collection, and most journal articles are available for download directly by any member of the NIH community.

In addition to the NIH Library, the NIH campus is home to the National Library of Medicine (NLM), the world's largest biomedical library. Begun in 1836 as a small series of medical volumes owned by the U.S. Army Surgeon General, NLM now operates under a nearly $300 million annual budget and possesses an unparalleled collection of books, journals, photographs, and rare historical materials. NLM is a magnificent resource for both the NIH community and the general public. In addition to maintaining its physical collection, NLM provides critical research tools to scientists and clinicians throughout the world via a series of electronic databases freely accessible through the Internet. Chief among these is MEDLINE, the world's premier biomedical literature database. Produced and maintained by NLM staff, MEDLINE provides references and abstracts from more than 4,600 biomedical journals indexed as far back as the early 1960s and citations for more than 12 million individual articles. Other NLM databases include GenBank, an international collection of all known DNA and protein sequences; ToxNet, a specialized database covering toxicology and environmental health; and MEDLINEplus, which features health information for the general public.

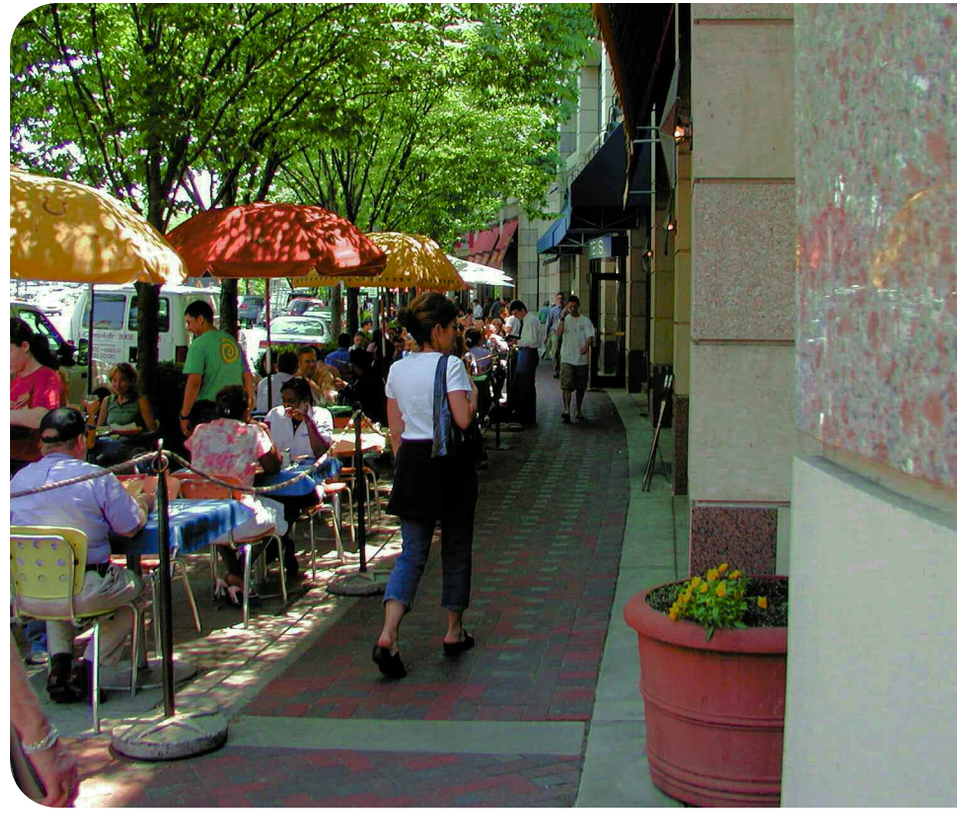
One of the components of NLM — the National Center for Biotechnology Information (NCBI) — serves as an international focal point for creating automated systems that disseminate large-scale biological data and facilitate biological discovery using these data. NCBI makes significant contributions to the biological community through its development of mathematical and computational methods that are widely used. These methods include BLAST, used to compare sequences of interest with one another; Entrez, used to seamlessly traverse a large set of biologically related databases; and Cn3D, which is used to analyze the structure of biologically important molecules. In addition to GenBank, NCBI oversees the development and curation of a number of critical biological databases, such as Online Mendelian Inheritance in Man (OMIM), the Gene Expression Omnibus (GEO), and the Cancer Genome Anatomy Project (CGAP). NCBI is engaged in numerous scientific collaborations with scientists at various NIH Institutes and regularly offers training to members of the NIH community in the effective use of these electronic resources and tools.

Amenities on the Bethesda Campus

The Bethesda NIH campus has eight food court-style eating facilities and several coffee bars and Internet cafés. There are shops on campus offering greeting cards, gifts, and photoprocessing services; a dry cleaning service is also available. A bookstore, operated by the Foundation for Advanced Education in Science, provides textbooks for staff members enrolled in the NIH Graduate School program; a selection of general interest books is also available. Other facilities include a weight room and exercise facility, barber and beauty shops, a credit union, a laundry, a flower shop, and numerous ATM machines. Green spaces and streams grace the Bethesda campus, where dozens of picnic tables and many sculptures and flower gardens dot the landscape.

The Surrounding Communities

The NIH campus is surrounded primarily by residential communities with small, eclectic business districts that offer NIH personnel easy and quick access to fine dining, entertainment, and quiet getaways.



BETHESDA

Bethesda, Maryland is a vibrant community surrounding the NIH campus. Its many dining options are legendary. No matter what you crave — from American to Vietnamese cuisine — you will find it in Bethesda. The Bethesda Urban Partnership Inc. makes it even easier to decide where to dine by offering a Web site (*bethesda.org*) and an Eat Here Guide describing the assortment of restaurants, their prices, and locations.

Bethesda is eminently walkable and very family-friendly. Throughout the year, residents and visitors enjoy outdoor music and arts events, gallery walks, food festivals, and a weekly community farmers' market. Its varied residences range from loft-type condominiums and apartments in the heart of Bethesda to gracious single-family homes in outlying residential neighborhoods. The staples of daily life — grocery stores, markets, pharmacies, and dry cleaners — are minutes away from nearly any corner of town. The city also possesses abundant arts and crafts galleries, specialty stores, bookstores, fashion boutiques, casual cafés, and ice cream parlors. For the outdoor lover, a paved bike path passes through Bethesda, traversing Rock Creek Park to the east and the C&O Canal to the west on its way to historic Georgetown, one of Washington's most charming neighborhoods.

MONTGOMERY COUNTY

In addition to Bethesda, other nearby Montgomery County communities within a short drive, Metro commute, or bike ride to NIH include Rockville, Gaithersburg, Kensington, Chevy Chase, Silver Spring, and Takoma Park, one of the most ethnically diverse areas of the county. For those who prefer a more rural lifestyle, upper Montgomery County and Frederick County are only a short distance away by car, bus, or commuter train.

Leisure-time and educational activities are abundant in Montgomery County. Residents and visitors can choose from a number of museums, public galleries, theaters, historic sites, and parks. For example, they can visit the Clara Barton National Historic Site in Glen Echo, catch an evening play at the Olney Theatre, explore the historic C&O Canal, or spend a day on the lake at Black Hills Regional Park in Boyds.

WASHINGTON, D.C.

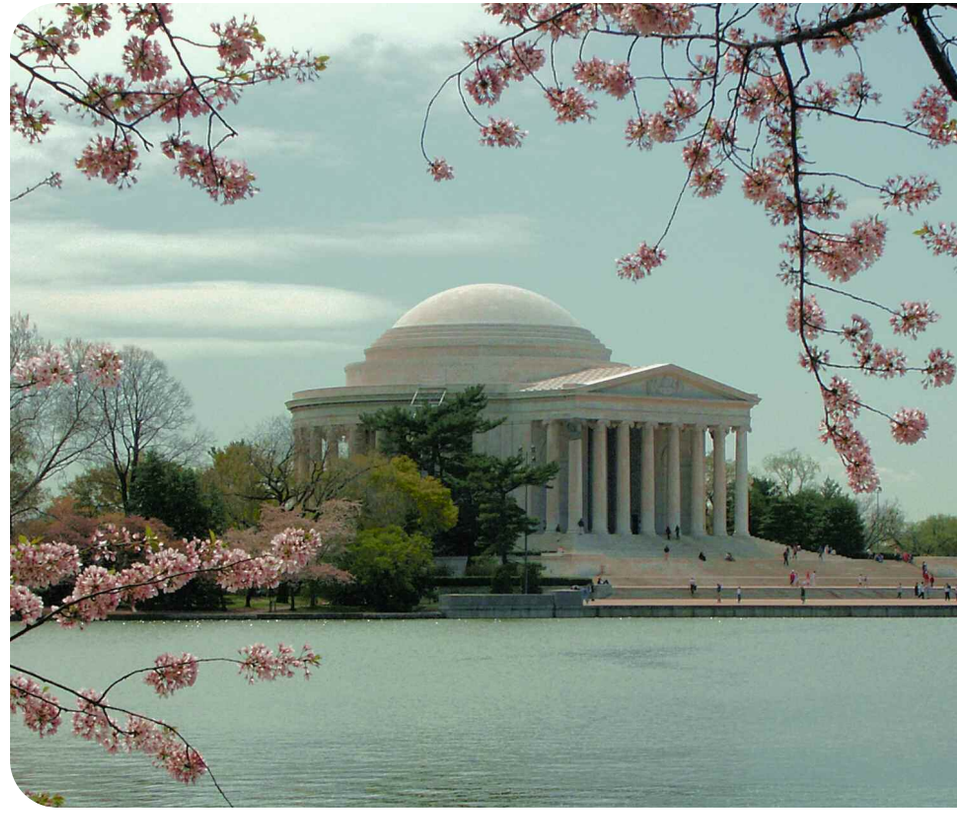
Washington is one of the world's grandest capitals — a city of impressive Federal architecture, inspiring monuments, and magnificent embassies. But Washington also has a local side — it is a lively, multicultural city filled with ethnic restaurants, late-night bars, bookstores, and more theater performances than any city except New York.

Washington combines the cultural vibrancy of urban America with the expansiveness and friendliness of the South. Residents can as easily jog along the banks of the Potomac as they can head for an all-night diner after a long evening of work or play. They can visit the Rotunda of the U.S. Capitol, buy seafood from waterside vendors on Maine Avenue, check out contemporary art at the galleries in Penn Quarter, dine elbow-to-elbow with the nation's lawmakers, and rent canoes to paddle down the Potomac. For living options, the city offers a wealth of modern and pre-war apartment complexes, luxury condominiums, exquisite brownstones in historic neighborhoods, and attractive single-family homes in quiet residential areas — all within easy access of commercial districts and Metro lines.

Georgetown is one of the liveliest neighborhoods in Washington. Its gracious Federal-style mansions and brownstones house Washington's elite, while Georgetown University students occupy modest rowhouses throughout the area. It is a neighborhood of designer boutiques and trendy stores, four-star restaurants and take-out pizza joints, rowdy nightclubs, and name-brand ice cream parlors.

Washington's cultural life is rich and varied. The Smithsonian Institution — with its 16 museums devoted to subjects as diverse as contemporary art, Native American history, natural history, and space flight — is an unparalleled national treasure. Boasting premier collections, the museums are free of charge to all visitors. In addition, Washington's majestic monuments and memorials draw travelers from all over the globe. The magnificent John F. Kennedy Center for the Performing Arts is home to both the world-renowned National Symphony Orchestra and the Washington Opera Company. The most successful Broadway plays bring their touring companies to the National and Warner Theatres. Aficionados of popular music can take in shows at a number of bars, clubs, and dinner theaters throughout the metropolitan area (see *Nightlife*).

Springtime comes early in Washington, when the city fills with downy pink cherry blossoms. People out for a stroll abound on neighborhood sidewalks, downtown on the National Mall, and on the walkways of the National Zoo. It's the perfect time to visit the National Arboretum and the beautifully landscaped gardens of Dumbarton Oaks in upper Georgetown.



Summer brings sultry evenings, late-afternoon jazz concerts around a fountain in the sculpture garden of the National Gallery of Art, Shakespeare in the park at the Carter Barron Amphitheatre, and many outdoor street festivals. Throughout the year, sports fans can cheer on Washington's many professional and college teams. Winters in Washington are relatively mild, with average daytime temperatures in the winter months ranging from the upper-30s to the mid-40s. One can drive a few hours north and enjoy winter sports such as skiing and snowboarding or drive a few hours south and still find a warm, sunny beach.

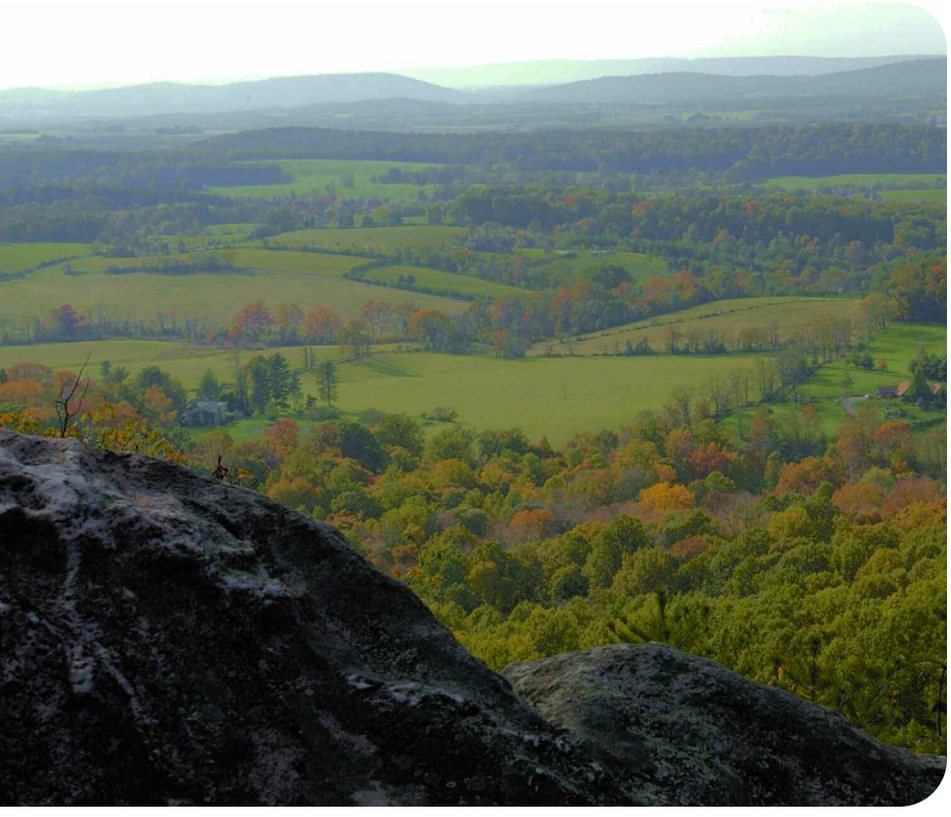
BALTIMORE

A quick 50-minute drive or commuter-rail trip connects Washington with Baltimore, Maryland. A bustling city in its own right, Baltimore provides a great day-trip or weekend getaway from Washington. The Inner Harbor is one of its most famous tourist destinations, featuring the world-class National Aquarium, the Maryland Science Center, several docked ships for exploring (including the U.S.S. Constellation, the last all-sail warship, built by the U.S. Navy in 1853), and the airy Harborplace shopping pavilion, all arranged around Baltimore's sparkling harbor. Nearby Fells Point — a historic district representing one of the oldest surviving maritime communities in the country — offers many eclectic restaurants, bars, galleries, and boutiques. Many of the area's brick rowhouses date from the early 1700s, and the restored cobblestone streets give the neighborhood an authentic ambience.

Other Baltimore resources make the city a commuter destination for Washington-area residents. The Baltimore Orioles playing at Camden Yards draw spectators from the entire metropolitan area. The Johns Hopkins University, one of the nation's finest institutions of higher learning, offers classes and degree programs in fields such as medicine, public health, business, and engineering.

Nightlife

The recent revival of Washington's economy has had a major impact on stimulating its nightlife. The historic National Theatre now offers a full lineup of acclaimed Broadway shows. People are staying out later and, in response, restaurants are staying open later for the after-hours crowd. The nightlife in the Washington metropolitan area offers something for everyone, a host of entertainment options, including dance clubs with an eclectic mix of music, theater, movies, shopping, pubs, live entertainment, and family fun. Washingtonians' tastes in entertainment run the entire gamut — this is a town where both Redskins tickets and seats at the opera are at a premium.



The Outdoors

For the outdoor enthusiast, the Washington metropolitan area provides virtually limitless options. Throughout Rock Creek Park, the largest urban park in America, you can find soccer fields and tennis courts, picnic sites, and areas in which to hike, bike, fish, and ride horseback. Visitors can also find excitement kayaking the white waters of the Potomac, unwind on the hundreds of miles of bike paths that crisscross the region, and navigate the many hiking trails in nearby Shenandoah National Park and the Appalachian Trail. Both lie within two hours of Washington's suburbs.

The Maryland and Delaware shores provide an easy getaway from the city. With multiple beaches to choose from, visitors can revel in the carnival-like atmosphere of Ocean City, Maryland; relax under an umbrella on family-friendly Bethany Beach, Delaware; or enjoy salt water taffy and cappuccino at Rehoboth Beach, Delaware. Charming bed and breakfasts and inns abound in the beach towns, as do condominiums and rental homes, often available for longer-term visits. Antiquing is a pleasant pastime in historic Lewes, Delaware and biking along the boardwalk in Rehoboth is an enjoyable way to see the town. The food scene is as varied as are the beaches, offering everything from fine seafood dishes and international cuisine to boardwalk fries and Maryland blue crabs.

The Delmarva Peninsula — the jagged crescent of land between the Chesapeake Bay and the Atlantic Ocean — provides as much interest for the naturalist as for the beachgoer. Cape Henlopen State Park features six miles of unspoiled beachfront, extensive nature trails, and sanctuaries for nesting birds. Visitors can also camp, fish, hunt, and picnic in park facilities. At the far edge of the peninsula lies Assateague Island, a narrow spit of land famous for its wild ponies and windswept beaches. The Assateague Island National Seashore occupies most of the 37-mile-long barrier island, and the National Park Service provides year-round camping as well as beaches and picnic areas for visitors. There are salt marshes to explore, quiet bayside waters to canoe, and pine forests to admire. On the southern half of the island, nature trails traverse the Chincoteague Wildlife Refuge, and rangers conduct guided tours and special programs for travelers of all ages.

Getting Around

Getting around the region is easy. Metro, the area's clean and safe subway system, has five lines connecting 84 stations throughout Maryland, Virginia, and Washington. More than 100 Metrobus routes expand the reach of the underground system.

Both Metro and multiple Metrobus lines stop directly on the NIH campus. From there, a 20- to 30-minute trip transports riders to Washington's major cultural, federal, shopping, and residential areas.

Washington's Union Station — a destination in itself with its soaring arches and majestic marble columns — is one of the stops on Metro's Red Line. From there, Amtrak and commuter-rail operators offer regular train service to Baltimore, Philadelphia, New York, and other points north and south.

For air travel, Washington has three major airports to choose from: Ronald Reagan Washington National Airport, which is accessible by Metro; Dulles International Airport, a 30- to 40-minute drive from NIH; and Baltimore/Washington International Airport (BWI), also a 30- to 40-minute drive from NIH. BWI is also accessible by Amtrak and commuter-rail service from Union Station.

Additional Information

For more information on NIH and the Washington metropolitan area, please visit the following Web sites:

ABOUT NIH
nih.gov

ABOUT WASHINGTON, D.C.
washington.org

ABOUT METRO
wmata.com

ABOUT MONTGOMERY COUNTY
montgomerycountymd.gov

ABOUT BETHESDA
bethesda.org

ABOUT WASHINGTON-AREA RENTALS
washingtonpost.com/wp-adv/classifieds/rentals/front.htm

ABOUT WASHINGTON-AREA ARTS AND LEISURE
washingtonpost.com/wp-dyn/artsandliving

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