NATIONAL HUMAN GENOME RESEARCH INSTITUTE Division of Intramural Research

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES | NATIONAL INSTITUTES OF HEALTH | genome.gov/DIR

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.

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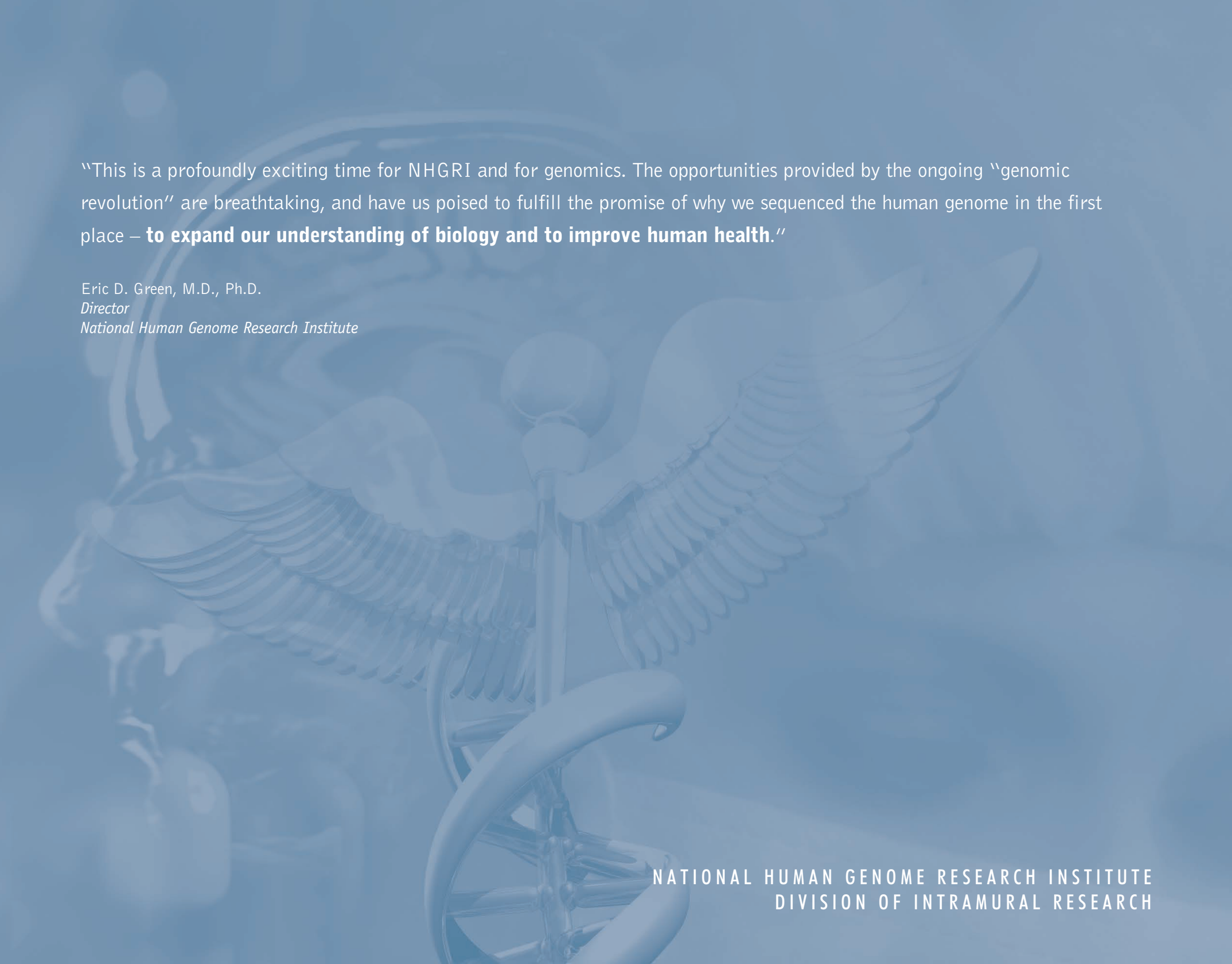

"This is a profoundly exciting time for NHGRI and for genomics. The opportunities provided by the ongoing "genomic revolution" are breathtaking, and have us poised to fulfill the promise of why we sequenced the human genome in the first place – **to expand our understanding of biology and to improve human health**."

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Director
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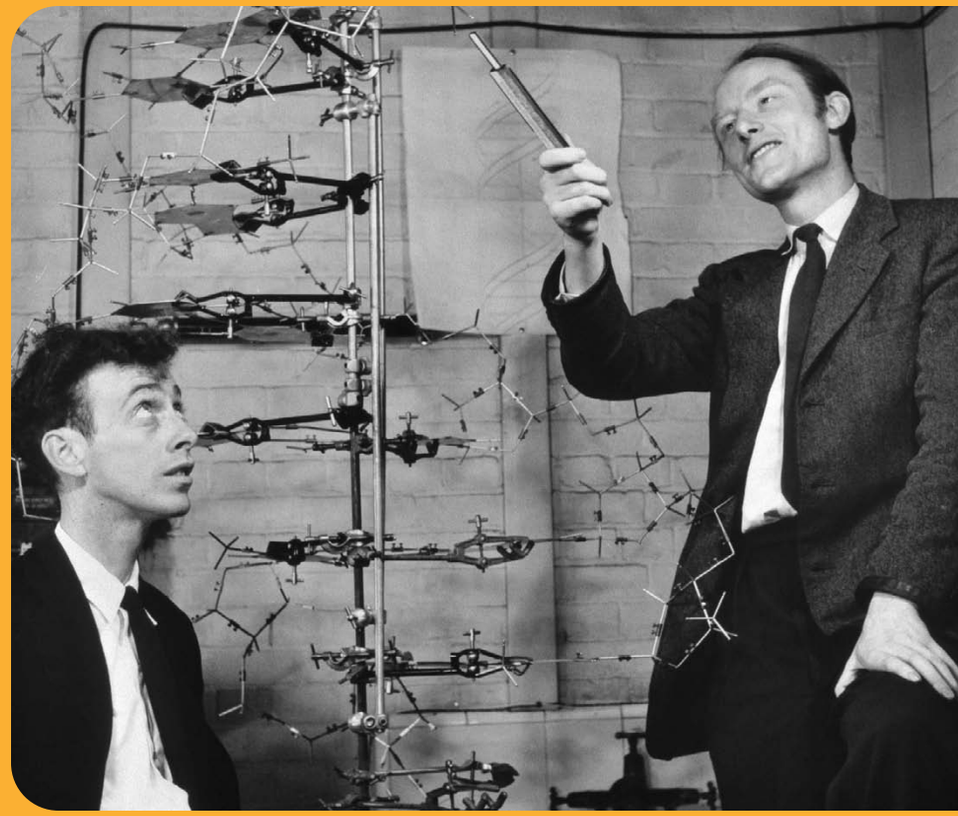
NATIONAL HUMAN GENOME RESEARCH INSTITUTE
DIVISION OF INTRAMURAL RESEARCH



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.

NHGRI's Scientific Director provides leadership for all research and related activities within the Institute's Division of Intramural Research. Jeffrey Trent served as founding Scientific Director from 1993 until 2002. Upon Dr. Trent's departure, Eric Green was appointed DIR's second Scientific Director. Dr. Green served in this role until he was selected to become the new Director of NHGRI in 2009 — succeeding Dr. Collins, who had been appointed Director of NIH earlier that year. In 2010, Daniel Kastner became the third Scientific Director to lead the Institute's Intramural Program.

With its tradition of scientific excellence, the Institute continues to infuse genomics into all areas of biomedical research and to translate genomic discoveries into medical advances.

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.

"Genomics has truly allowed us, in less than a generation, to cut through the Gordian knots of cell biology and biochemistry to get at some of the root causes of human suffering. The NHGRI Division of Intramural Research serves as a crucible not only for advancing science, but for applying the discoveries made here to a host of rare and common diseases."

Daniel L. Kastner, M.D., Ph.D.

The NHGRI Intramural Program: Vision, Mission, and Values

VISION

The goal of the NHGRI Intramural Program is to advance the frontiers of genetics and genomics. We aim to be world leaders in the translation of genomic knowledge into tools and approaches for improving the treatment, prognosis, and prevention of rare and common diseases. The study of genomic variation and its effects on phenotype at the species, population, and individual levels is central to our scientific pursuits. NHGRI researchers view the genome as a window to understanding the human condition, including factors influencing human history and health, disease susceptibility, and common principles of biology.

MISSION

The NHGRI Intramural Program is a broad and highly integrated research enterprise that aims to explore human and model organism biology at all levels of organization using state-of-the-art approaches. These efforts involve genome-wide comparisons at the species level, studies of healthy and diseased populations, and phenotype-genotype comparisons. We pursue ambitious interdisciplinary projects because of our strengths in basic, clinical, social, and behavioral research. Achieving our goals requires innovative and, at times, high-risk strategies that utilize a wide range of genomic, genetic, computational, and high-throughput methodologies. Our ability to rapidly pursue cutting-edge research initiatives allows us to tackle the most compelling biomedical problems of our time.

The NHGRI Intramural Program has become a model for successfully translating genetic and genomic discoveries into the clinical care arena. We study an array of disorders — rare as well as common, simple as well as complex — selected for their tractability and applicability to broader problems in biology. Our social and behavioral research is further integrating genomic medicine into community and individual health care. This type of work is critical for realizing the benefits of personalized medicine, addressing health disparities, and improving global health.

Our research is grounded by a number of fundamental tenets. For example, a full understanding of genetic and genomic variation extends from the principles of evolutionary biology, since we believe that the experiments of nature are as important as our own. Similarly, a detailed understanding of genome architecture and function is central to our mission. Finally, studies of development biology, animal models, and basic molecular mechanisms are critical for testing our scientific hypotheses and setting the stage for translational endeavors.

We effectively capitalize on the unique environment provided by the broader NIH Intramural Program and its more than 1,000 investigators who possess remarkable depth and breadth of expertise. In particular, the NIH Clinical Research Center provides an unparalleled infrastructure for supporting our diverse set of clinical research projects. We further contribute to the NIH and larger scientific community by generously disseminating genomic, computational, and high-throughput technologies to others. Finally, an important hallmark of our program is the inclusion of high-risk, imaginative, and potentially high-impact projects in our research portfolio, studies that would be difficult to pursue elsewhere.

VALUES

Guiding the NHGRI Intramural Program is a set of core values that include:

Being international leaders in genomics and associated translational, social, and behavioral research. We lead by encouraging our talented investigators to pursue a range of projects that span multiple scientific disciplines.

Fostering trans- and multidisciplinary research. We value collaborations among scientists in different disciplines to build the strongest possible research teams and to maximize the impact of their resulting discoveries.

Training researchers and clinicians. We support the education and training of basic, translational, behavioral, social, and clinical investigators in genomics, genetics, and related areas.

Maximizing data sharing. We strive to share data with other investigators and the general public in a timely, accessible, and appropriate fashion.

Promoting diversity. Diversity among the scientific staff, trainees, and research subjects is critical for enhancing the research process and the implementation of scientific findings.

Reducing health disparities and improving global health. We seek to use genomic- and genetic-based strategies to reduce health disparities and improve the health of people around the world.

Serving the public interest. We believe that, as public servants, we are obligated to study scientific and medical problems for which genomic approaches can improve health and the quality of life.

Educating the general public. Effective communication about the implications of genetic and genomic discoveries is essential for improving health literacy and informed decision-making.

Conducting ethical research. We are leaders in the ethical treatment of human subjects, the humane treatment of research animals, and the conduct of science with the highest possible integrity.

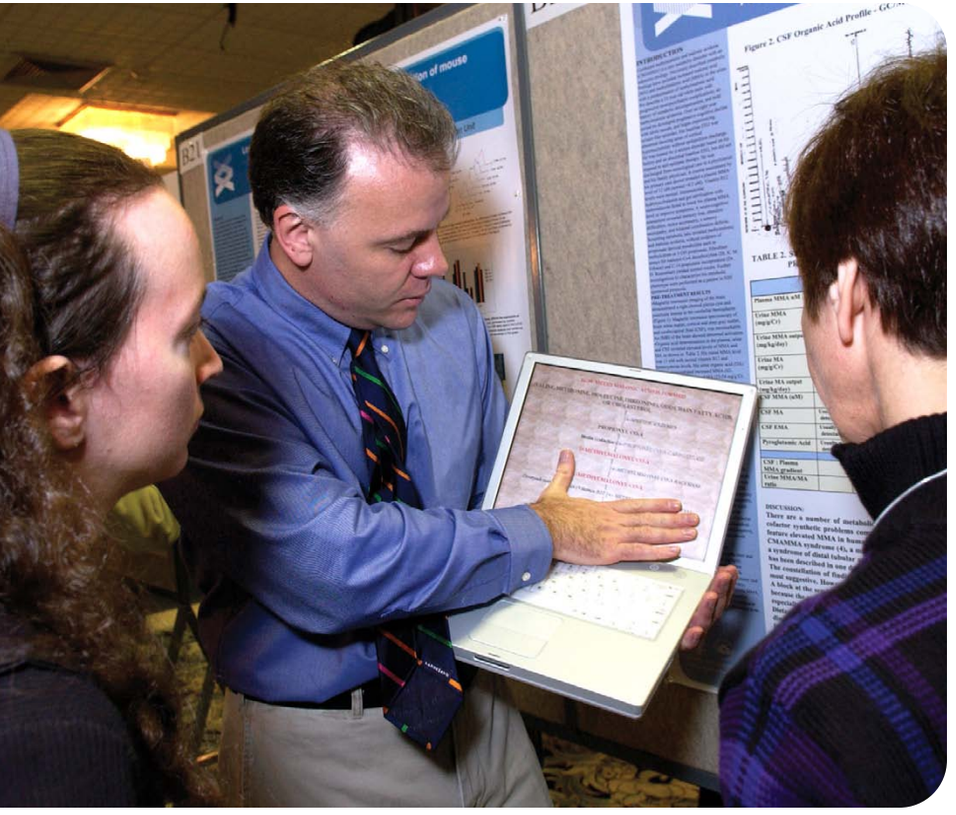
Organization and Structure

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.

An NIH scientist or clinician whose primary appointment is with another NIH institute can be appointed as an *Adjunct Investigator* within the NHGRI Intramural Program. These individuals have a close association with NHGRI Investigators and bring special expertise to NHGRI's Intramural Research Program. Adjunct Investigators participate in DIR events, serve on DIR committees, and teach in NHGRI-sponsored courses.

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.

BOARD OF SCIENTIFIC COUNSELORS

The Board of Scientific Counselors reviews and evaluates the Intramural Research Program of the National Human Genome Research Institute. This group, comprised of recognized experts in their respective fields, advises the Scientific Director on a wide variety of scientific and programmatic issues. Board members play a key role in strategic planning, as well as providing rigorous scientific peer review of the work of individual investigators in DIR. Each Board member is appointed to a five-year term.

Sean Eddy, Ph.D.
Group Leader
Janelia Farms Research Campus, Howard Hughes Medical Institute
Term ends June 2014

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Chair and Director, Genomic Medicine Institute
Director, Center for Personalized Genetic Healthcare
Cleveland Clinic Lerner Research Institute
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E. Desmond Lee Professor of Racial and Ethnic Diversity
George Warren Brown School of Social Work
Washington University Institute for Public Health
Term ends June 2015

Gary Gibbons, M.D.
Professor of Medicine
Director, Cardiovascular Research Institute
Chair, Department of Physiology
Morehouse School of Medicine
Term ends June 2011

Thomas Hudson, M.D.
President and Scientific Director
Ontario Institute for Cancer Research
Term ends June 2015

Alexandra Joyner, Ph.D.
Courtney Steel Chair in Pediatric Cancer Research
Member, Sloan-Kettering Cancer Center
Developmental Biology Program
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Bruce R. Korf, M.D., Ph.D.
Wayne H. and Sara Crews Finley Professor of Medical Genetics
Chair, Department of Genetics
University of Alabama at Birmingham
Term ends June 2014

Timothy J. Ley, M.D., Chair
Professor, Department of Medicine
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Department of Genetics
Washington University School of Medicine
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Stephanie L. Sherman, Ph.D.
Professor, Department of Human Genetics
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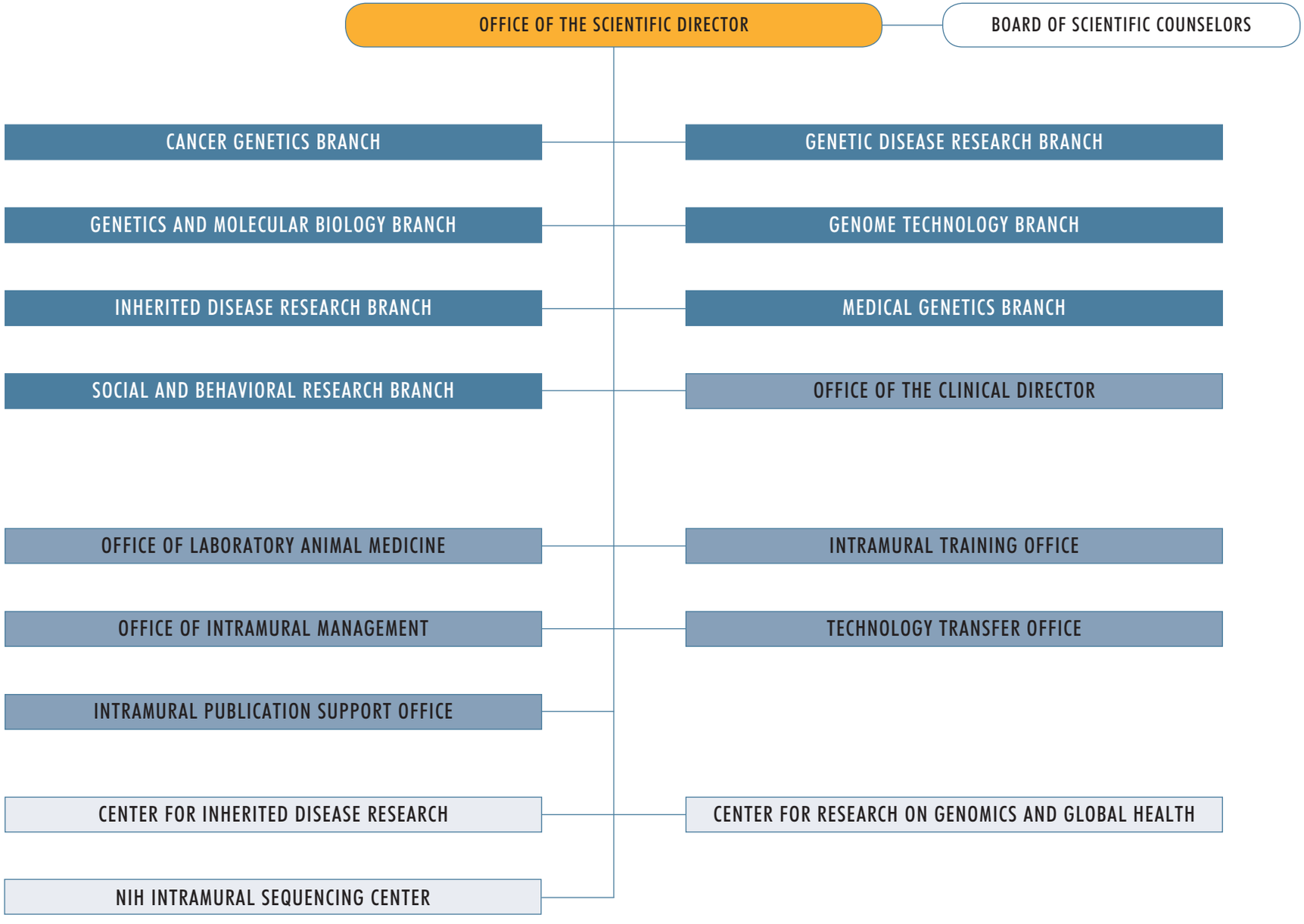
Term ends June 2013

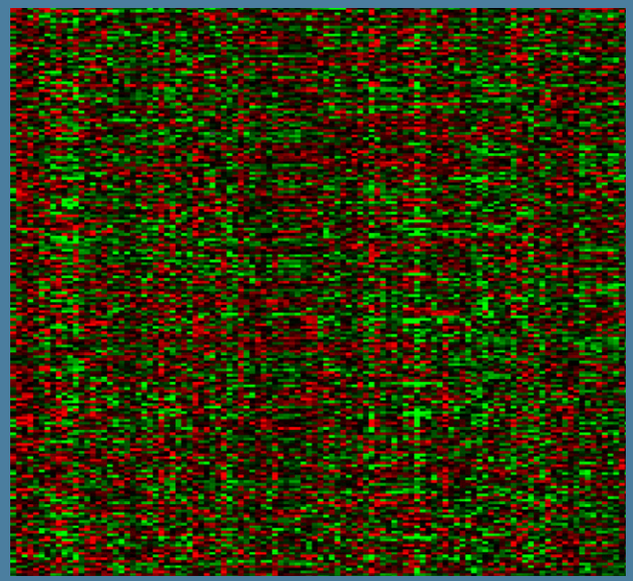
NHGRI DIVISION OF INTRAMURAL RESEARCH

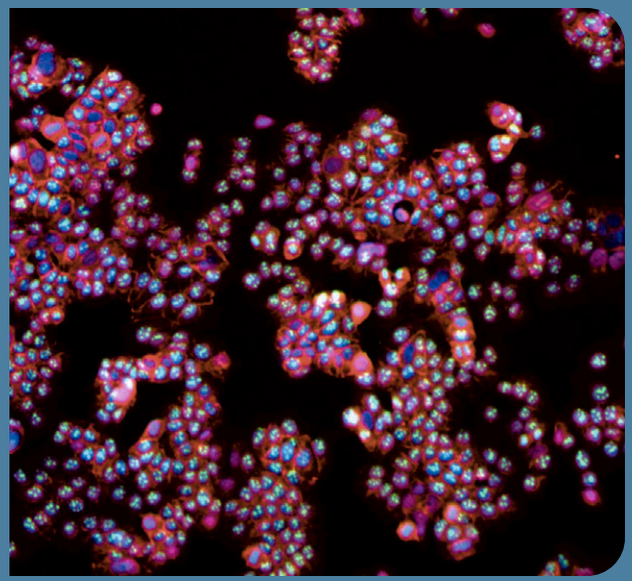


"This is **a fascinating time to be involved in cancer genetics**. We now have the tools and resources to understand the ways in which cancer both develops and progresses through the human body."

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

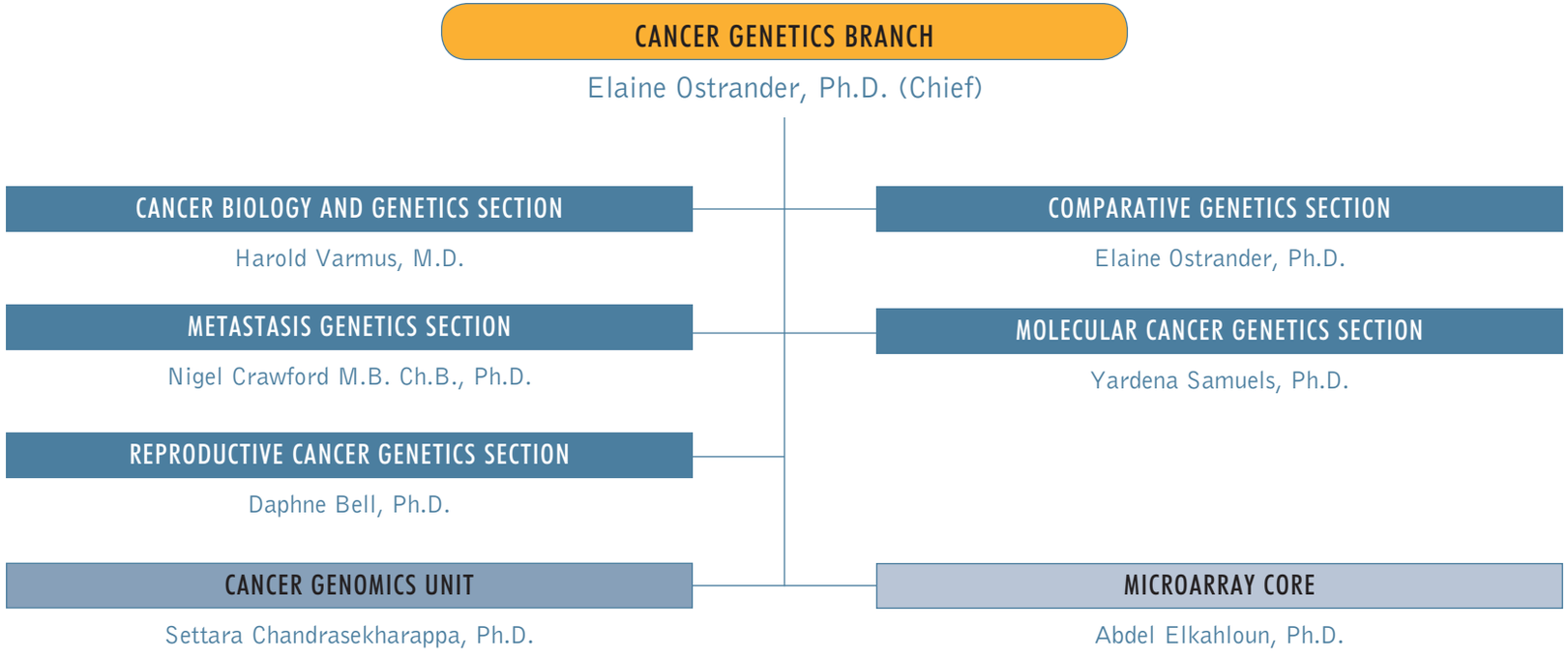
CANCER GENETICS BRANCH





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.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ELAINE A. OSTRANDER, Ph.D.

Dr. Ostrander's laboratory is interested in the study of genes important in growth regulation, particularly as it pertains to disease states in humans and canines. Her group aims to find genes that control the morphologic body plan of the domestic dog, which shows an extraordinary level of variation between breeds, and to identify disease susceptibility genes in dogs. Her group's work also focuses on the identification of genes that relate to susceptibility to, progression of, and specific outcomes in individuals with breast and prostate cancer.

Using a strategy that exploits the breed structure of dogs to investigate the genetic basis of body morphology, Dr. Ostrander's laboratory mapped the *IGF-1* locus on canine chromosome 15 as the major controller of small size. A single *IGF1* haplotype is common to all small dog breeds and nearly absent from giant breeds, suggesting that the same causal sequence variant is a major contributor to body size in all small dogs. Subsequent studies have identified genes controlling leg length and fur type, as well as loci controlling leg width, skull shape, ear position, and back arch. At least four additional loci associated with controlling body size have been identified and are a major focus of ongoing fine mapping studies.

Dog pedigrees are large, multigenerational, and the result of directed matings, all of which favor the expression of recessive disorders such as cancer. The clinical presentation, histology, and biology of many canine cancers very closely parallel those of human malignancies; comparative studies of canine and human cancer will be of significant clinical benefit to the health of both humans and companion animals. Towards that end, Dr. Ostrander's group has constructed high-density comparative maps of the canine genome and, in combination with a 7.5x whole-genome assembly of the dog, has been able to map loci for bladder cancer, malignant histiocytosis, Addison's disease, osteoarthritis, and other disorders. Cancer is of particular interest to her group and is the major focus of its canine disease studies.

Dr. Ostrander's laboratory is also studying human prostate cancer loci involved in susceptibility and progression in high-risk prostate cancer families, in an effort to determine the importance of those loci in increasing disease risk in the general population. Towards that end, her group has been involved in linkage studies using high-risk families, as well as genome wide association studies (GWAS) involving large numbers of cases and controls. While loci on chromosomes 8, 4, 11, 15, and 17 are also of interest, Dr. Ostrander's group has most vigorously pursued fine mapping of the locus on chromosome 22. In addition, through GWAS studies involving 43,671 SNPs in 3,650 prostate cancer cases and 3,940 controls, the laboratory has identified new loci of interest on chromosomes 2, 4, 8, 11 and 22. Many of these regions are being studied by collaborators in the International Consortium for Prostate Cancer Genetics.

Dr. Ostrander's laboratory has also analyzed candidate genes in a population-based case-control study of middle-aged men, investigating the role of several hundred candidate SNPs that may affect specific pathways of interest. Among the most interesting findings to date have been those associated with variants in *megalin*, an endocytic receptor expressed by prostate cells that can internalize bound active androgens. In a study of 553 Caucasian men with prostate cancer and 535 controls, Dr. Ostrander's group found

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three single nucleotide polymorphisms (SNPs) that were associated with both disease recurrence, progression and mortality. Risk of recurrence/progression alone was also associated with five additional SNPs, and six other SNPs showed evidence of modification by primary androgen deprivation therapy.

With regard to breast cancer, initial interest focused on understanding the distribution and frequency of *BRCA1* and *BRCA2* mutations in women drawn from the general population. The most recent study examined the prevalence and predictors of *BRCA1* and *BRCA2* mutations in women with breast cancer. Numerous familial and demographic factors were found to be significantly associated with *BRCA1* and, to a lesser extent, *BRCA2*-carrier status. However when all predictors were considered together, early age of diagnosis in cases and relatives, family history of ovarian cancer, and Jewish ancestry remained strongly and significantly predictive of *BRCA1* carrier status, whereas *BRCA2* predictors were less clear. Dr. Ostrander's laboratory is also interested in studies that validate models for predicting *BRCA1* and *BRCA2* mutation status. Finally, her laboratory is conducting fine mapping studies focused on breast cancer loci of lower penetrance, such as *FGFR2*.

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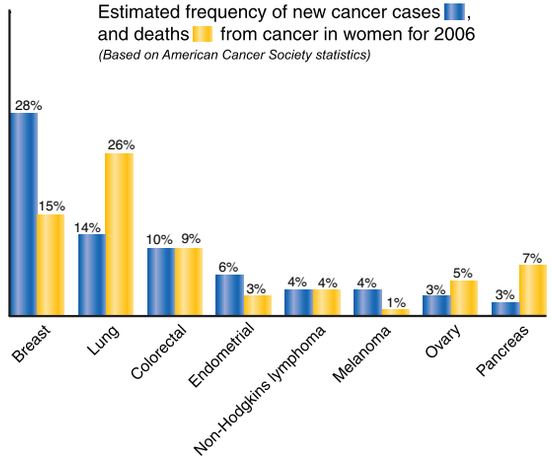
DAPHNE W. BELL, Ph.D.

The goals of Dr. Bell's laboratory are to identify the genetic alterations that lead to clinically aggressive subtypes of endometrial cancer and to apply this knowledge to improve the clinical management of women with endometrial cancer.

Endometrial cancer, which affects the endometrium (the lining of the uterus), is the most commonly diagnosed gynecological malignancy and the eighth leading cause of cancer death among American women. In the United States, about 43,000 new cases of endometrial cancer are diagnosed, and about 7,900 deaths are attributable to this disease annually. Worldwide, approximately 50,000 women die of endometrial cancer each year. While most patients present with "type I" tumors with endometrioid histology and have a good prognosis, around one in every seven patients is diagnosed with a "type II" serous or clear cell tumor. These type II tumors are the most clinically aggressive form of endometrial cancer and, as a result, contribute disproportionately to mortality. Type II tumors cause about 40% of all endometrial cancer deaths even though they represent only a small fraction of diagnosed cases.

Most human tumors are caused by the accumulation of genetic and epigenetic alterations in so-called cancer genes. Over the past few years, it has become evident that some genetic alterations may be exploited as therapeutic targets in cancer treatment. For example, the drug imatinib is highly effective in the treatment of chronic myelogenous leukemias with an underlying BCR-ABL chromosome translocation. Likewise, 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. Therefore, uncovering the genetic basis of human tumors is the first step towards personalized medicine using molecularly targeted therapeutics.



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 taking an integrated approach to catalog the genomic alterations in type II tumors. They are using high-density, single nucleotide polymorphism (SNP) genotyping to identify genome-wide copy number changes in type II endometrial tumors. In complementary studies, Dr. Bell's laboratory is searching for changes in gene expression in these tumors. Through an extensive collaboration with the NIH Intramural Sequencing Center performing high-throughput mutational screens, the Bell group is looking for changes in gene sequence.

Two strategies are used for these mutational analyses. The first involves a candidate gene approach in which high-throughput Sanger sequencing is used to identify genes whose protein products have the potential to be targeted by drugs (small-molecules). The second strategy employs next-

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generation sequencing to systematically interrogate type II tumors for somatic mutations in the exons of more than 18,000 protein-coding genes. The copy number, expression and mutation data are then integrated to identify genes or functional pathways that are recurrently altered in type II endometrial cancer. Once specific genetic alterations are found, follow-up studies are performed to determine whether — and how — they affect the function of the encoded proteins. Individual genes or functional pathways are prioritized for analysis based on their potential therapeutic relevance.

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 in lung cancer patients to the tyrosine kinase inhibitor gefitinib; her group plans similar evaluations of potential therapies for type II endometrial cancer.

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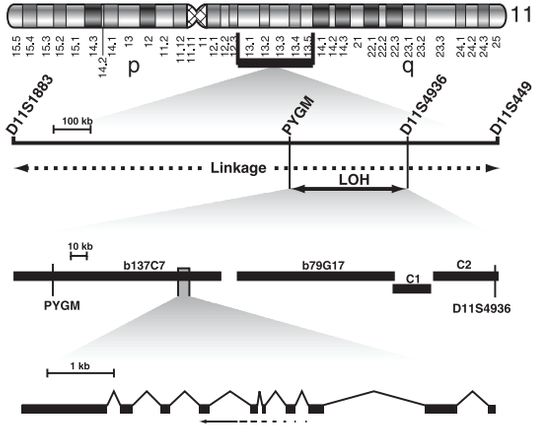
SETTARA C. CHANDRASEKHARAPPA, Ph.D.

Dr. Chandrasekharappa's research focuses on the development and use of genome technologies to advance research in human genetics. Current efforts of his laboratory are focused primarily on studies related to Fanconi anemia (FA).

Fanconi anemia is a recessive disorder characterized by congenital abnormalities, life-threatening bone marrow failure, and a predisposition to myeloid malignancies, as well as squamous cell carcinoma of the head, neck, and gynecological system. FA is a genetically heterogeneous disease as well, and complementation analysis is used to assign FA patients to one of the thirteen known groups. Genes for all these groups have been identified, and all appear to cooperate and participate in a common DNA repair pathway. While these 13 genes can account for most FA cases, the research efforts of the laboratory are focused on the identification of the remaining FA gene(s).

Congenital abnormalities associated with FA vary in terms of severity and the organs affected. The age of onset of bone marrow failure and incidence of malignancies also vary. Determining the precise molecular defect for a large number of samples should help reveal genotype-phenotype correlations, and should enhance our understanding of the disease, including its pathogenesis and clinical management. Dr. Chandrasekharappa's group intends to pursue this study using resources from The International Fanconi Anemia Registry, which was established in 1982 at Rockefeller University, and contains entries for nearly 1,100 individuals representing more than 600 FA families. Somatic mosaicism, a genotypic reversion resulting in restoration of a functional allele in the reverted lymphocytic cell populations (LCL), has been observed in nearly a third of FA patients. The laboratory, therefore, intends to identify the molecular changes in DNA from LCL that restore normal function to the previously disabled protein. This analysis will illuminate the precise nature, frequency, and mechanism of these reversions and, in doing so, shed light on the implications for bone marrow transplantation.



Searching for the two mutations responsible for disease in each patient, from thirteen FA genes spanning nearly a million base pairs, clearly requires development of a new and efficient methodology for mutation scans. Therefore, another area of interest for Dr. Chandrasekharappa's research lies in evaluating high-density hybridization arrays and next-generation sequencing technologies, with the goal of developing a comprehensive mutation detection approach for FA patients. Heterozygous mutations in some of the known FA genes are known to predispose an individual to

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familial breast (BRCA2, FANCJ, FANCN) and pancreatic (FANCN) cancers. The laboratory plans to explore the involvement of FA genes in other cancers and, conversely, the incidence of cancer in FA families.

Previous large-scale mapping efforts in Dr. Chandrasekharappa's laboratory led to the positional cloning of the genes responsible for Alagille syndrome and multiple endocrine neoplasia type 1.

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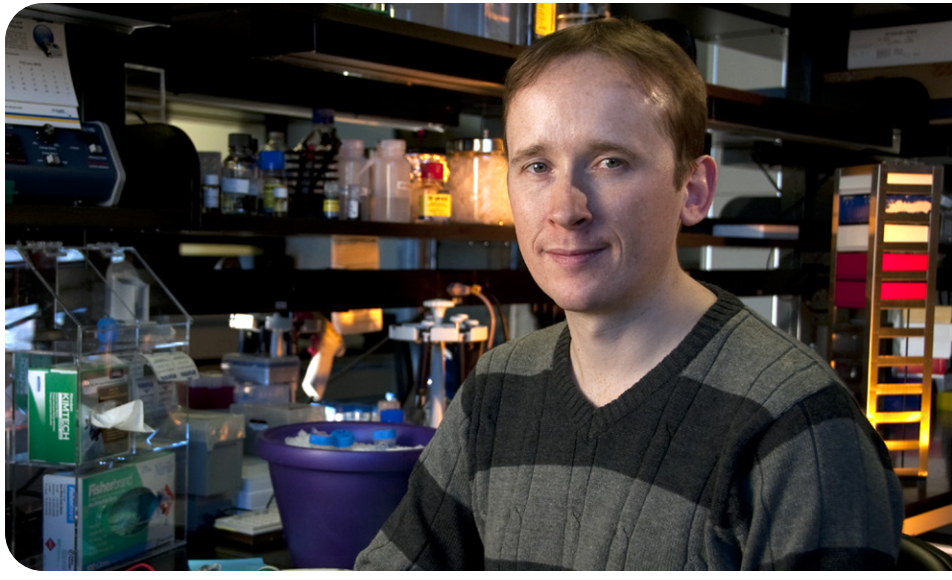
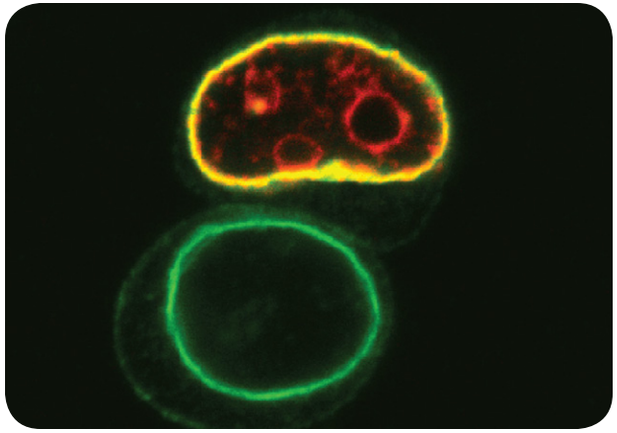
NIGEL CRAWFORD, M.B. Ch.B., Ph.D.



Dr. Crawford's research seeks to define how genetic variation among individuals influences tumor progression and metastasis in prostate and breast cancer. The overall aim of his research is to identify, at the point of diagnosis, those individuals at greater risk for developing more aggressive cancers. With this knowledge, physicians could consider implementing more aggressive therapeutic regimens.

Prostate carcinoma is a common disease; for example, in 2007 in the United States, 220,000 men were diagnosed with this type of cancer, but only a small proportion of these men (typically ~30,000) will actually succumb to the disease. However, the clinical course of prostate cancer is variable, with some men presenting with more aggressive forms of the disease at the time of diagnosis. Genetic predisposition plays an important role in prostate cancer development, and it has been estimated that 5-10% of cases have a familial component.

These observations form the basis of the research performed in Dr. Crawford's laboratory. His studies explore whether individual genetic variation promotes the development of prostate cancers that are more prone to metastasizing and resistant to therapeutic interventions. He characterizes the differences in tumor growth and metastasis that result when germline polymorphisms are introduced, through selective breeding, into mice prone to developing prostate cancer. His laboratory uses a well-characterized number of transgenic mouse models of prostate tumorigenesis called TRAMP (for "transgenic adenoma mouse prostate"). Transgenic mouse models of prostate cancer TRAMP mice are crossed with a strain of recombinant inbred mouse called the "Collaborative Cross," which incorporates a broad spectrum of allelic variants that are present in a number of inbred strains. It is anticipated that Collaborative Cross mice will be widely used in the study of complex traits.



Using a statistical method for studying genetic variation called quantitative trait locus (QTL) mapping, Dr. Crawford analyzes DNA from the offspring of transgenic mouse models of prostate tumorigenesis TRAMP and Collaborative Cross mice. His goal is to identify multiple sites, called modifier loci, in the mouse genome that drive the development of more aggressive forms of tumorigenesis and metastasis. The researchers in his laboratory use a combination of methodologies to identify individual candidate genes at each modifier locus. The role of these candidate modifier genes in tumor progression and metastasis is explored in human prostate tumor progression through a combination of functional analyses and epidemiological association studies.

In addition, Dr. Crawford's laboratory is investigating the role of the *RRP1B* gene in tumor progression and metastasis in breast cancer. By using a well-characterized transgenic model of mouse mammary tumorigenesis, *RRP1B* was identified as a candidate modifier QTL gene for metastasis efficiency. Subsequent experimentation using *in vitro* and *in vivo* modeling in mice demonstrated that activation of the *Rrp1b* gene suppresses tumor growth and metastasis, yielding a gene expression signature that can be accurately

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used to predict survival in human breast cancer. Dr. Crawford was part of a research consortium demonstrating that the human *RRP1B* gene contains variants associated with markers of metastasis and survival in multiple breast cancer epidemiological cohorts.

In recent breast cancer studies, Dr. Crawford has focused on the function of RRP1B, which had previously been a poorly characterized protein. His analyses have explored the interaction of RRP1B with other proteins, particularly with a number of nucleosome-binding proteins that are potent modulators of gene expression and chromatin structure. The laboratory is using chromatin immunoprecipitation and 'next-generation' DNA sequencing methodologies to identify promoter sequences that bind RRP1B. Dr. Crawford expects these studies to provide greater insight into the function of this metastasis efficiency modifier, and to shed light on how dysregulation of *Rrp1b* gene expression has such potent effects on global gene expression.

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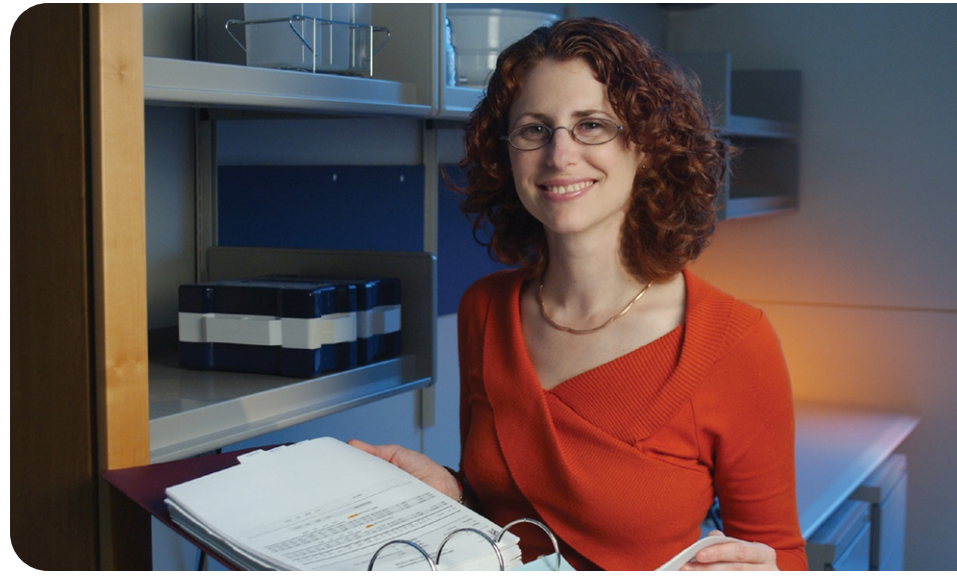
YARDENA SAMUELS, Ph.D.

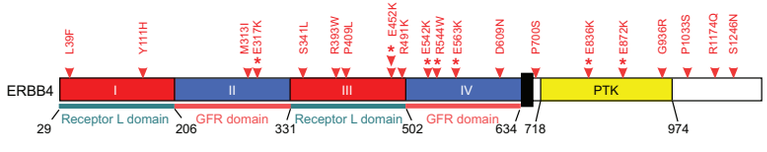


Dr. Samuels uses a variety of genomic approaches to identify novel somatic mutations in late-stage cutaneous melanoma. Genetic alterations, including point mutations, deletions and amplifications, occur in every cancer cell. These changes are known to occur in oncogenes, tumor suppressor genes, and stability genes. Although many of these genes have been identified for certain types of tumors, most still remain to be discovered.

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, over 60,000 people are diagnosed with malignant melanomas and more than 8,000 die of the disease.

In early stage disease, in its radial growth phase (RGP), the melanoma tumor stays on the skin's surface; however, once the malignancy advances to the vertical growth phase (VGP), it penetrates through the skin and is able to metastasize. As melanomas penetrate farther into the skin, treatment options as well as cure and survival rates decrease. In fact, 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. Genes that have been implicated in the development of melanomas include *CDKN2A, NRAS, and BRAF*. Comprehensive cancer genome sequencing may identify recurring genetic alterations that will ultimately lead to targeted approaches for the diagnosis and treatment of melanoma, enabling personalized treatment.



Dr. Samuels' group aims to discover recurrent tumor-specific mutations in gene families within melanoma tumors. Once these mutations are identified, her group focuses on characterizing the biochemical, functional, and clinical aspects of the most highly mutated genes. To facilitate this search, the Samuels laboratory has established a library of metastatic melanoma tumors and matched normal tissues in collaboration with the National Cancer Institute. Dr. Samuels uses candidate approaches as well as whole exome and whole genome sequencing to identify novel somatic mutations.

The Samuels laboratory has recently examined the genes encoding matrix metalloproteinases and tyrosine kinases, both of which play important roles in regulating the cellular events that lead to tumor formation. Importantly, the Samuels laboratory's research on tyrosine kinases has revealed that *ERBB4* is somatically mutated in 19% of melanoma cases. Studies of seven missense mutations in *ERBB4* showed that all mutants exhibited increased kinase activity. Exposure of melanoma cells to the FDA-approved ERBB inhibitor lapatinib resulted in a greater reduction in cell proliferation in cells containing endogenous *ERBB4* mutations than in cells containing endogenous wild-type *ERBB4*. Based on these results, and in collaboration with Dr. Rosenberg, a phase II clinical study will be conducted in which melanoma patients harboring *ERBB4* mutations will be treated with lapatinib.

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Since solid tumors can result from genetic alterations in a large number of genes that function through a relatively small number of pathways, therapeutic development may lie in the discovery of agents that target the physiologic effects of these altered pathways. Thus, inhibitors that broadly target downstream mediators or nodal points may be the most effective. The Samuels group's whole exome and whole genome research may not only lead to the discovery of novel highly mutated genes, but may also help determine which pathways are altered in melanoma, and how these genes and pathways interact. Ultimately, Dr. Samuels aims to decipher the genetic landscape of melanoma in order to enhance biological insight into the disease, and to point to novel strategies for better patient care.

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 human 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 and is the focus of several targeted therapy trials.

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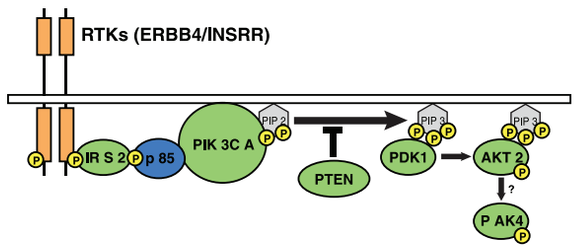


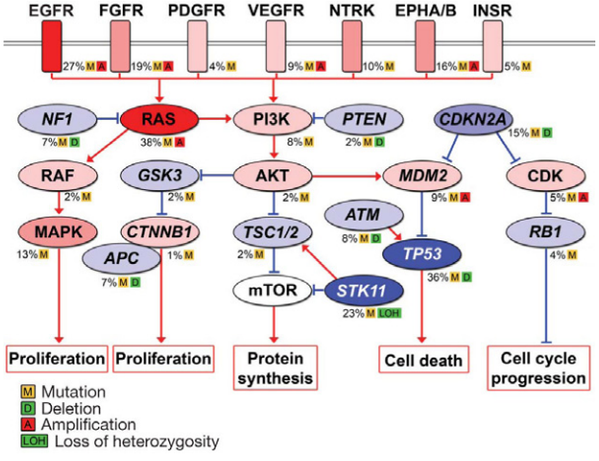
HAROLD E. VARMUS, M.D.

The Varmus laboratory uses a variety of experimental approaches to understand the molecular mechanisms of oncogenesis, with an emphasis on the use of mouse models of human cancer and human lung adenocarcinomas.

In its work on mouse models, the group has focused on the functions required to maintain the oncogenic state, the relationship between normal development lineages and oncogenic events, the molecular basis of tumor progression, and strategies for targeted therapeutics.

Dr. Varmus's group joined the NHGRI Intramural Research Program in 2010. Over the past decade at Memorial Sloan-Kettering Cancer Center, the Varmus group addressed these issues through the creation and study of models for cancers of the breast, pancreas, lung, ovary, mesenchymal tissues, and plasma cells and other hematopoietic lineages. They used a variety of methods to generate oncogenic mutations that included conventional and regulated transgenes, non-conditional and conditional null mutations, and tissue-specific delivery of genes with retroviral vectors.

Current work on these issues follows two approaches. In the context of a mouse model for acute myeloid leukemia, the laboratory conducts studies of the Bcl-2 family of proteins, with an emphasis on the novel factors that control their abundance and the contribution that the six anti-apoptotic Bcl-2 proteins make to oncogenesis. Using mice carrying stage-specific transgenes and retroviral vectors, the laboratory is making efforts to determine the stages in the development of B-cells — a well-characterized cell lineage — at which cells are susceptible to the oncogenic influences of known cancer genes c-Myc and p53.



For the past eight years, the laboratory has devoted special efforts to an understanding of human lung cancer, especially adenocarcinomas driven by mutations in the gene encoding the epidermal growth factor receptor (EGFR). This work was triggered by dramatic remissions observed in some patients with lung adenocarcinomas – especially non-smokers – after treatment with tyrosine kinase inhibitors, and led to the description of lung-specific somatic mutations of EGFR.

Various approaches to this important medical problem have since been pursued by Dr. Varmus's group. The laboratory recapitulated EGFR-induced cancers and K-Ras-induced lung cancers in mouse models in which the oncogene is temporally controlled by doxycycline-dependent regulatory elements. In a large collaboration that later became The Cancer Genome Atlas project, Dr. Varmus's group identified additional mutations in human lung adenocarcinomas; identification of those mutations in mouse models followed as part of a collaboration sponsored by the Starr Cancer Consortium. Resistance to tyrosine kinase inhibitors that occurs inevitably during cancer treatment was explained by the identification of a second mutation in the EGFR tyrosine kinase domain and recapitulating drug resistance in mouse models. The role of other members of the EGFR family in lung carcinogenesis has been examined as well.

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Using high-throughput screening methods, the Varmus group identified small molecules that inhibit the growth of human lung cancer cell lines and investigated molecular targets of those compounds. The laboratory has studied the inflammatory response that often accompanies lung adenocarcinomas in mice and humans. They are harnessing mass spectroscopy and other proteomic methods to look for proteins (especially phosphoproteins) involved in oncogenic signaling pathways in EGFR- and K-Ras-driven lung tumor cells. Their efforts have extended to seeking plasma proteins that might serve as biomarkers for lung cancers induced by mutant K-Ras or EGFR genes. The biomarker effort is a component of collaborative mouse model studies conducted with the Canary Foundation.

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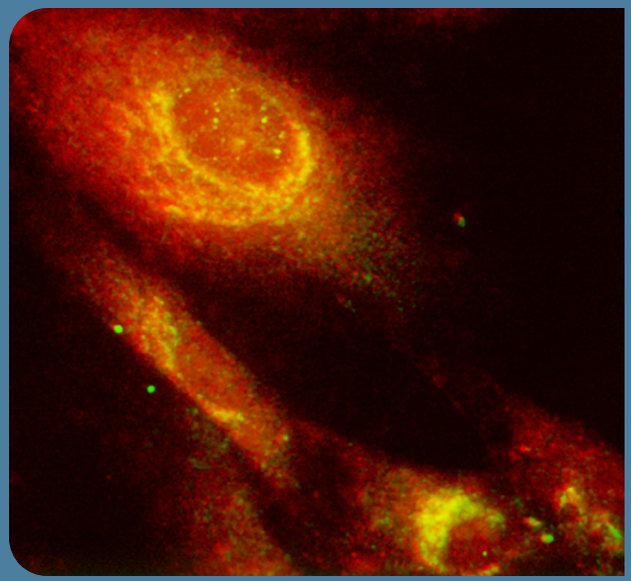
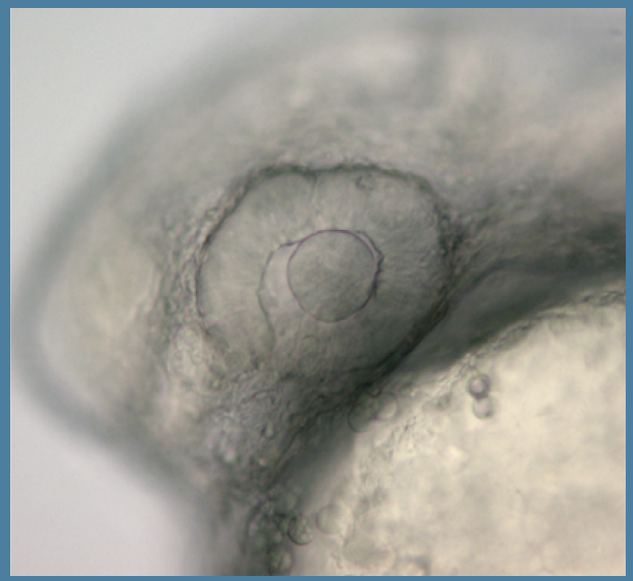
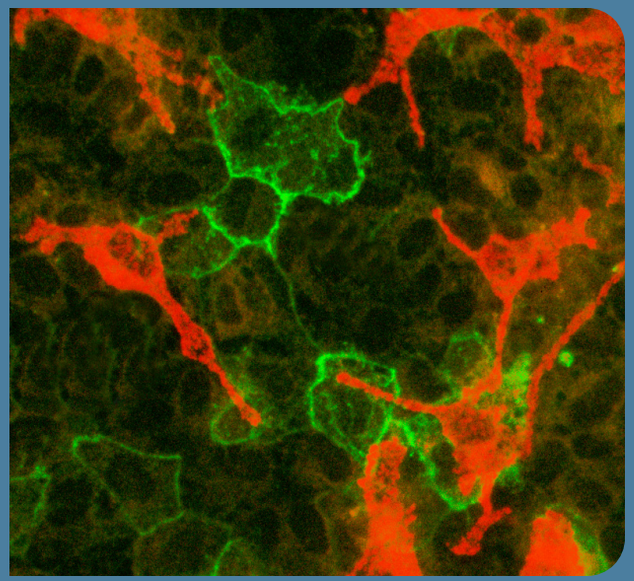
"Understanding the molecular and genomic basis of disease requires putting together many different pieces of the puzzle-**basic molecular research, animal studies, and clinical investigations**. One of the exciting things about NHGRI is that we can do all of these things in a collaborative atmosphere."

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

GENETIC DISEASE RESEARCH BRANCH

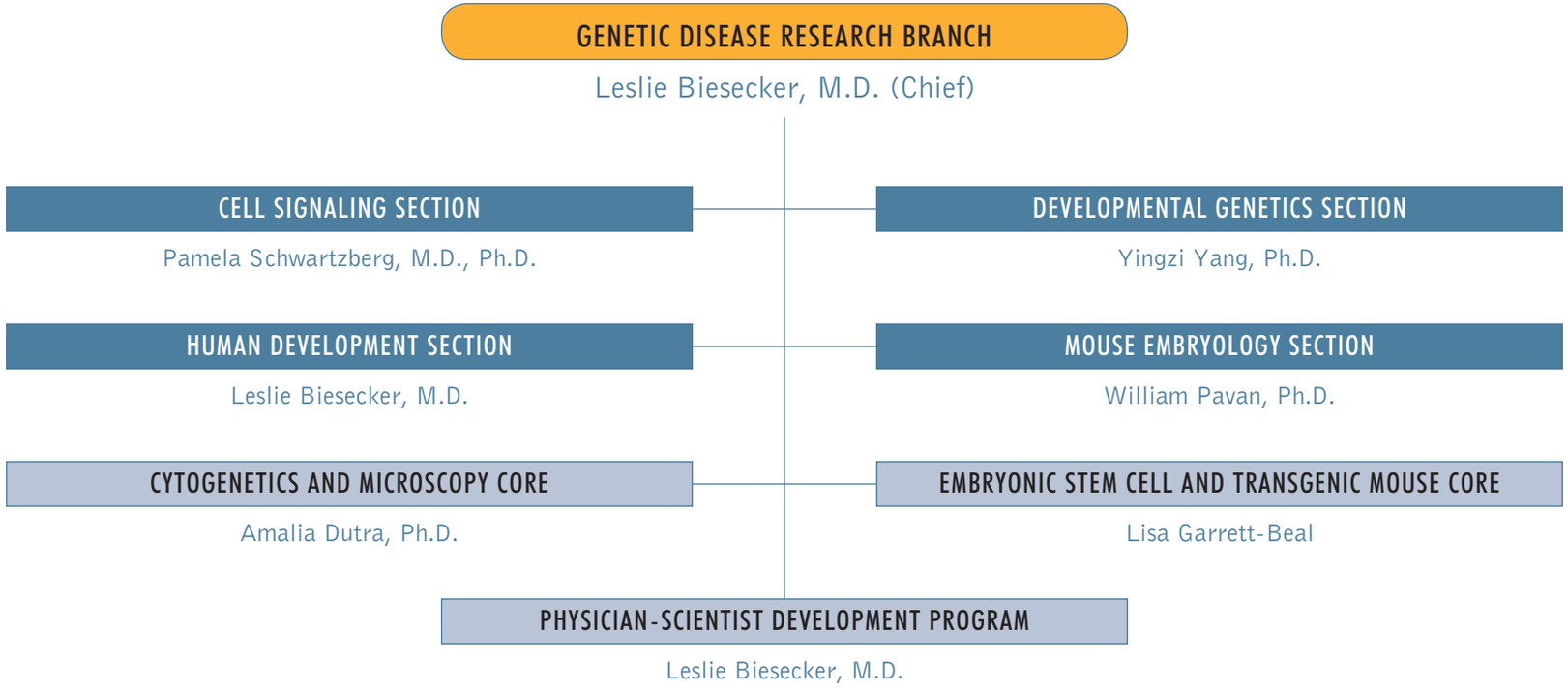






The Genetic Disease Research Branch (GDRB) uses human and mouse genetics to study the genes and proteins involved in a variety of normal developmental processes and related diseases. Branch investigators study normal and abnormal bone and limb development, pigment cell development and neurocristopathies, T-helper cell maturation and defects in host defense, and the role of rare variants in common disease. These studies aim to characterize normal developmental 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 pathways, 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.


GENETIC DISEASE RESEARCH BRANCH
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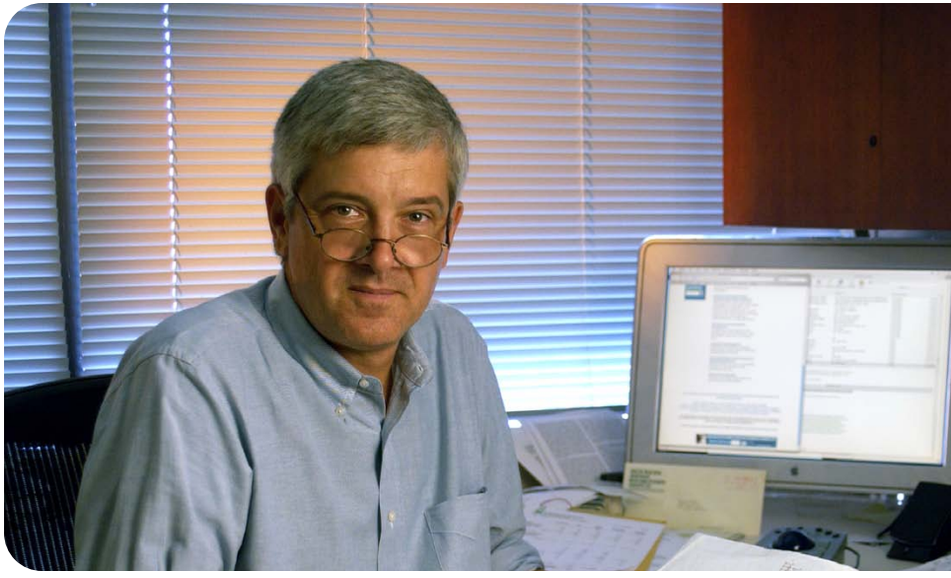
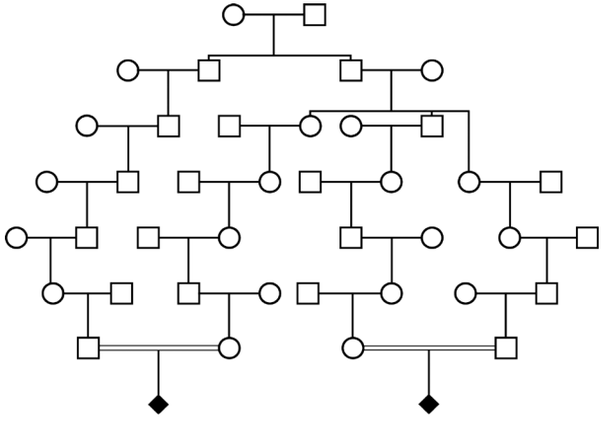


Dr. Biesecker's research focuses on understanding the relationship of genomic variation to health and disease. Currently, his laboratory is engaged in studies in two main areas: classic genotype-phenotype studies of genetic disorders of development and growth, and new approaches to hypothesis-generating clinical genomics research. 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 genetic disease, and better understand basic mechanisms of normal and abnormal human development and physiology.

Dr. Biesecker's group studies several multiple anomaly syndromes, including Pallister-Hall syndrome, Greig cephalopolysyndactyly syndrome, McKusick-Kaufman syndrome, Bardet-Biedl syndrome, oral-facial-digital syndrome, Lenz microphthalmia syndrome, Proteus syndrome, and non-syndromic polydactyly. Patients with these disorders exhibit various 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. The Human Development Section has been recognized as an international leader in finding novel diagnostic and management approaches to these disorders, many of which are extremely rare. To further elucidate the clinical manifestations of these multiple anomaly syndromes, Dr. Biesecker's group takes advantage of the clinical resources available through the Mark O. Hatfield Clinical Research Center on the main NIH campus.



In order to find the genes that are altered in these syndromes, Dr. Biesecker's group performs classical laboratory-based positional cloning studies, determines genotype-phenotype correlations, and uses animal models to investigate the pathogenetic mechanisms of these disorders. Protocols aimed at understanding the disorders listed above, as well as other disorders having manifestations that overlap with these disorders, are actively recruiting individuals for study. Many patients are invited for evaluation at the Clinical Research Center, where they undergo extensive and sophisticated phenotypic assessments to generate data essential for understanding the range and variability of these rare disorders.

The second area of research is a highly collaborative large-scale medical sequencing project aimed at developing and exploring novel methods for conducting hypothesis-generating clinical genomics research. This project, aptly named ClinSeq™ (see *genome.gov/clinseq*), uses massively parallel sequencing and other genomic interrogation methods as a tool for clinical research. The ClinSeq™ study enrolls patients with a range of phenotypes from healthy through diseased, and the study will initially focus on cardiovascular disease. Patients undergo an initial medical evaluation for a common set of cardiovascular phenotypic features, including coronary

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artery calcification and blood pressure; DNA isolated from these patients then enters a high-throughput sequencing pipeline. Through a combination of standard capillary-based sequencing and massively parallel sequencing, billions of base pairs of sequence are being generated. The goal of the protocol is to use genomic characterization as a tool to identify novel phenotypes and explore the genetic architecture of disease. The study will contribute to our understanding of the relative contributions of rare versus common genetic variants to common disease. The clinical focus of the ClinSeq™ initiative will later be expanded to include additional sets of genes. This project is one of the leading international efforts in this exciting new area of research and is establishing new approaches to study design, informed consent, and subject participation for clinical genomics research.

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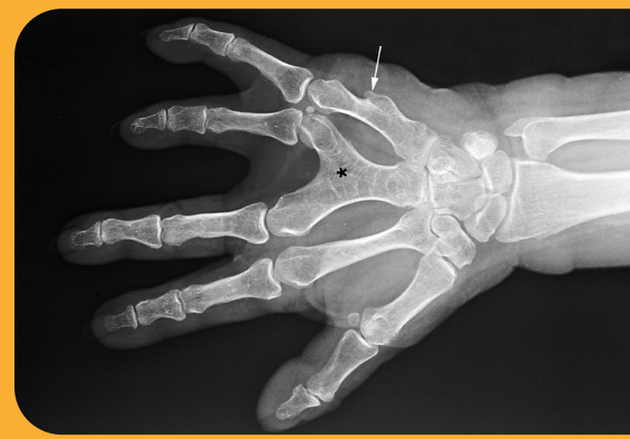
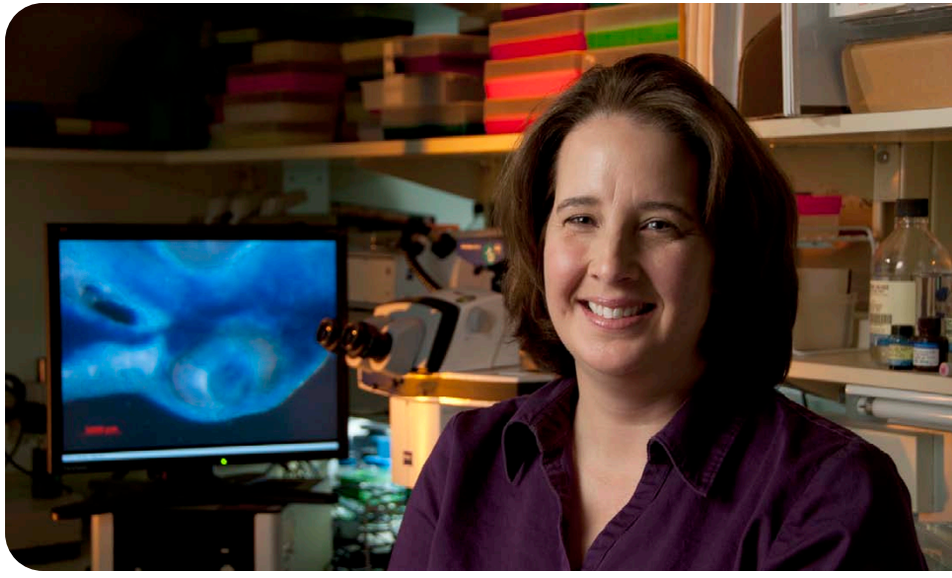
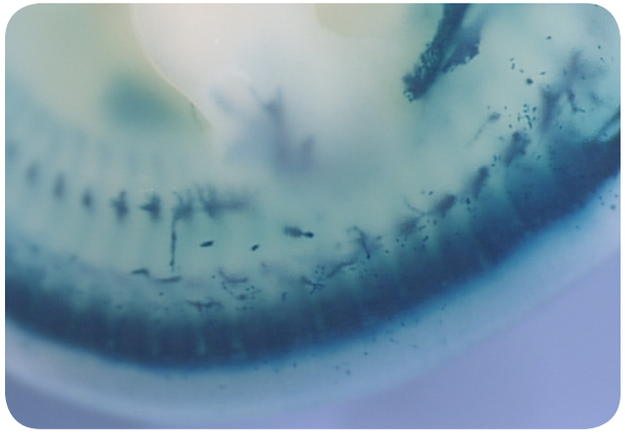


STACIE K. LOFTUS, Ph.D.



Dr. Loftus' research is conducted within the Mouse Embryology Section, led by Dr. William Pavan. Her work focuses on the genetic and cellular processes that control mammalian development, with the goals of understanding both inborn errors of embryonic development as well as diseases that strike later in life. Although finding the gene(s) responsible for such conditions does not automatically lead to a cure, research findings can give important clues about anomalies at the cellular level, both during development and during maintenance of mature cell functions.

Dr. Loftus is analyzing the molecular and genetic basis of neural crest development. Neural crest cells, which appear along the dorsal surface 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. The Mouse Embryology Section is particularly interested in understanding the role that neural crest cell-expressed genes play in regulating a migrating cell's fate to either continue migration to another location, or to stop migrating, proliferate, and proceed with differentiation into distinct cell types. Disruption of these genes during neural crest cell development can lead to a variety of congenital disorders such as albinism and neurocristopathies, while disruption at later stages can contribute to cancers such as melanoma.



One example of a neurocristopathy is 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 may lack peripheral nervous system innervation of the gut. Several years ago, Dr. Pavan's laboratory found that mutations in the 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 an additional transcription factor, MITF, both of which are altered in Waardenburg syndrome and melanoma tumors.

In order 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 and are involved in both developmental disorders and cancer progression. She is specifically interested in finding the genes that start neural crest cell migration through the embryo, and ascertaining the role these same genes play in causing primary melanoma tumor cells to proliferate, invade surrounding tissues and metastasize to other locations in the body. She is also investigating how to mark and distinguish the individual cells undergoing this process in vivo.

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In addition, Dr. Loftus uses mouse disease models to identify and understand the underlying defects in 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 molecular and genetic defects responsible for this condition.

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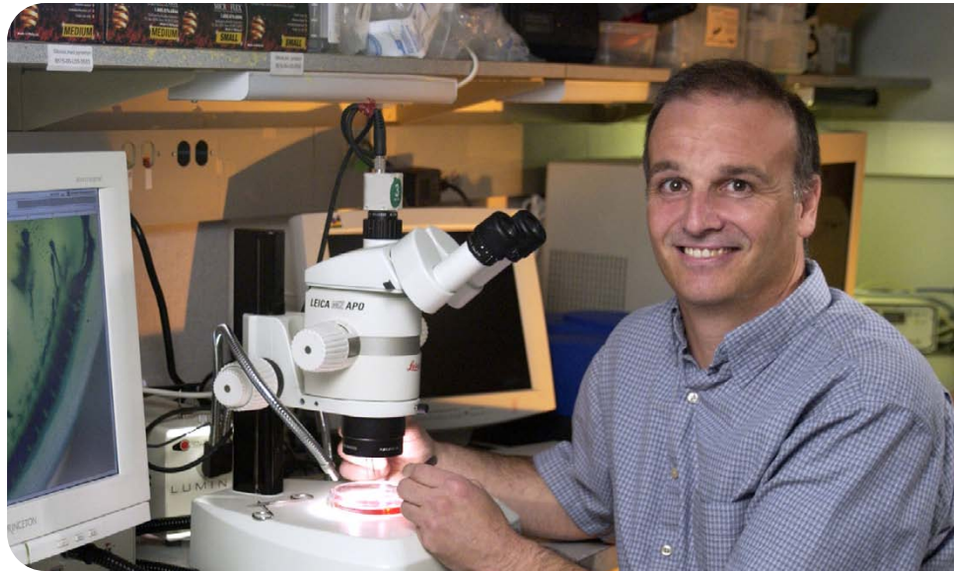
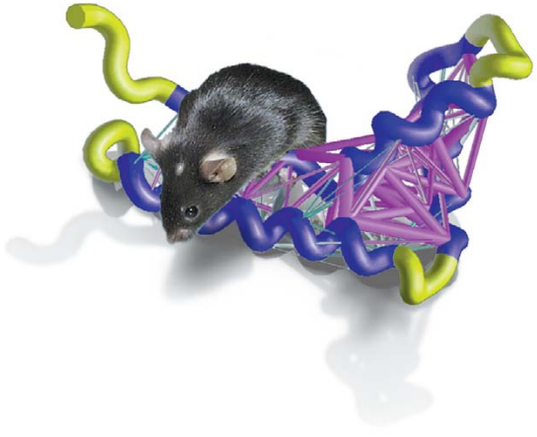
WILLIAM J. PAVAN, Ph.D.



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 mammal — and looking for similarities in genes and in their regulatory regions.

SELECTED PUBLICATIONS

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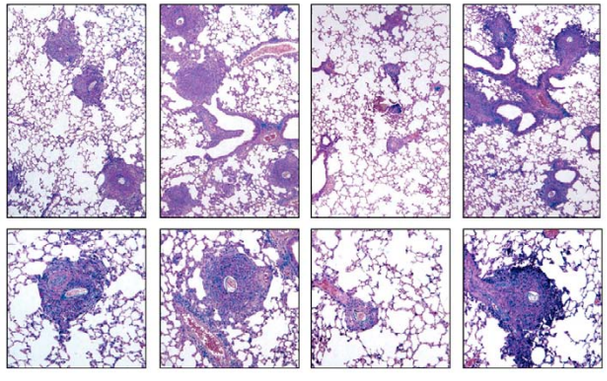
PAMELA L. SCHWARTZBERG, M.D., Ph.D.

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. Another Tec — family kinase member, Rlk, may be important for T helper

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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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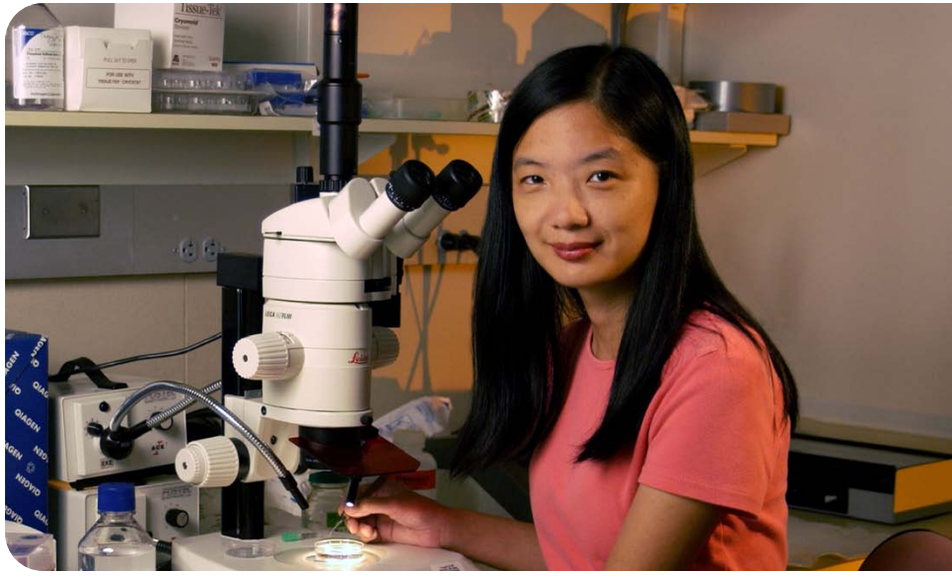
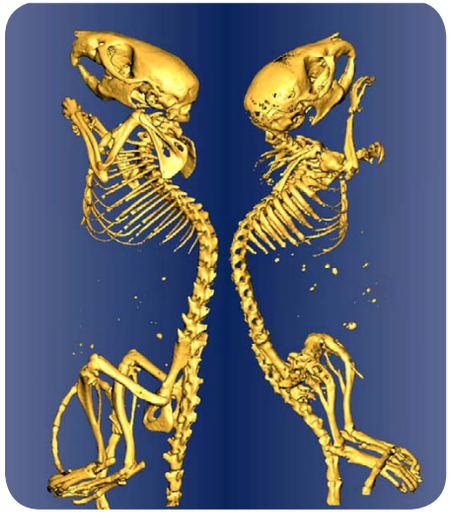
YINGZI YANG, Ph.D.



Dr. Yang studies vertebrate embryonic development, with a specific focus on limb and skeletal morphogenesis. Her goal is to understand the mechanisms by which molecular signals are transduced and integrated in a regulatory network to control key events during mammalian embryonic development and adult homeostasis. To that end, her group focuses on the molecular mechanisms of two major families of signaling molecules — Wnt and Hedgehog (Hhs) — in both normal developmental processes and adult diseases, including tumor formation.

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, skeleton, limbs, and many other organs. Disruptions in Wnt and Hedgehog signaling can also promote a variety of cancers. In fact, disrupted Wnt signaling is a leading cause of colon cancer, breast tumors, and brain tumors in adults. Misregulated Wnt and Hedgehog signaling is also involved in bone diseases such as osteoarthritis, osteoporosis, and bone tumors.

Skeletal morphogenesis is a typical example of vertebrate organogenesis. It starts from mesenchymal condensation, in which mesenchymal progenitor cells differentiate into either osteoblasts, which form bone, or chondrocytes, which form cartilage, depending on the ossification mechanism. Later, cartilage and bone develop through a precisely coordinated process with the sequential maturation of chondrocytes and osteoblasts and the invasion of blood vessels. Early patterning signals, which include Hhs, Wnts, FGFs, and TGF-superfamily members, provide temporal and spatial information to instruct skeletal anlagen formation, long before overt skeletogenesis. These signaling pathways also play major roles in regulating cell proliferation, differentiation, and organization in the formed skeletal system. Dr. Yang's previous work provided insight into several fundamental aspects of tissue patterning and cell fate determination in the limb and skeletal system. Her current research addresses how signaling pathways exert specific effects in skeletal and other developmental processes, and in stem cell self-renewal/differentiation, and how disruption of these events leads to various diseases and tumors.



To test the function of Wnt and Hedgehog proteins, Dr. Yang's group is using both genetic and biochemical approaches. They have engineered a series of mice with specific genetic mutations that lead to the incorrect expression of specific protein-coding genes. The resulting mouse phenotypes provide powerful clues about 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*, then exposes the cells to particular molecules or growth factors, singly or in combination, to observe the effects. Using these approaches, they seek to understand fundamental events in skeletal morphogenesis, and have made several discoveries in their current research efforts. For example, Dr. Yang has found that different Wnt proteins 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

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osteogenesis. This work indicates that the Wnt pathway may be an important diagnostic and therapeutic target for cartilage and bone diseases, such as arthritis and osteoporosis.

Previously, Dr. Yang's laboratory 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, therefore, be a tumor suppressor in adults. In addition, Dr. Yang found that the Hedgehog signaling pathway also plays important roles in postnatal skeletal homeostasis; Wnt5a has also been shown to control vertebrate morphogenesis by regulating cell polarity.

Dr. Yang's group is continuing to study how Wnt and Hedgehog signaling pathways control fundamental aspects of 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 embryonic morphogenesis.

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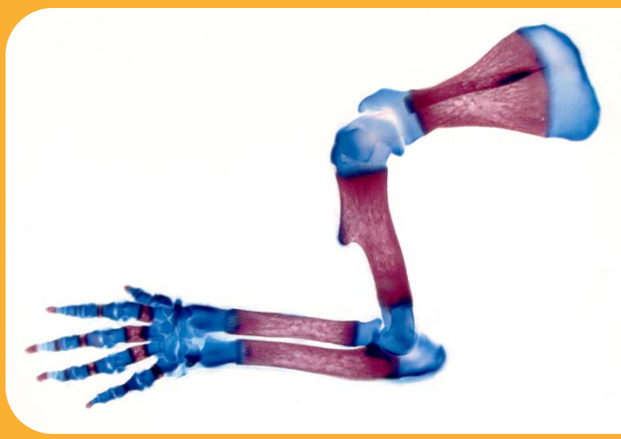
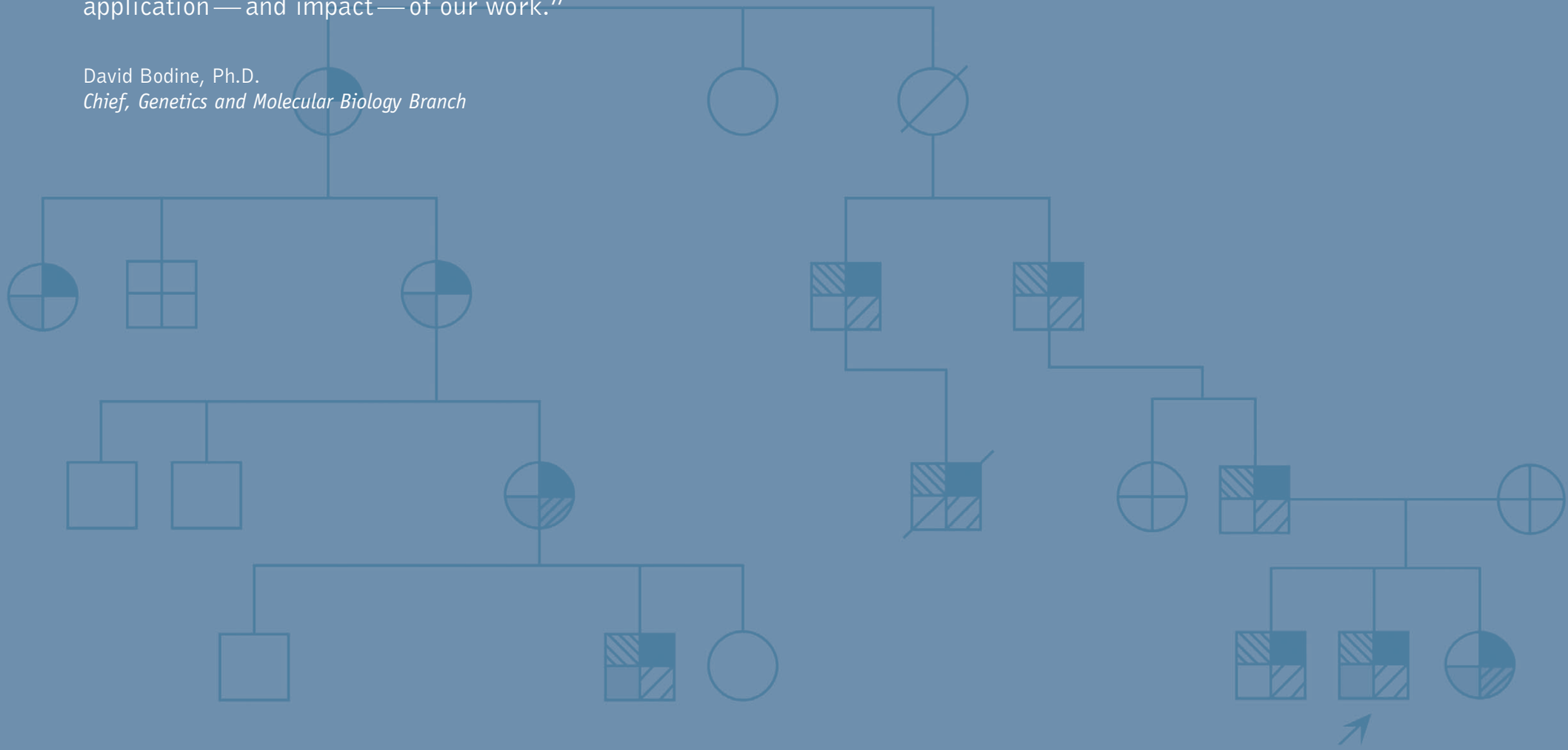
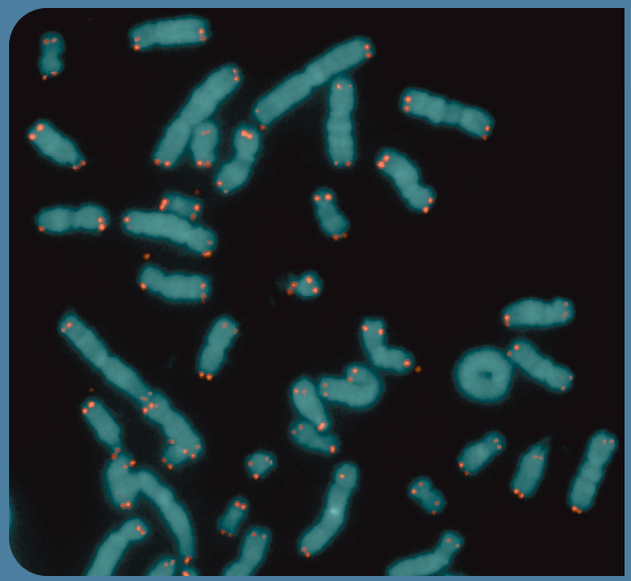


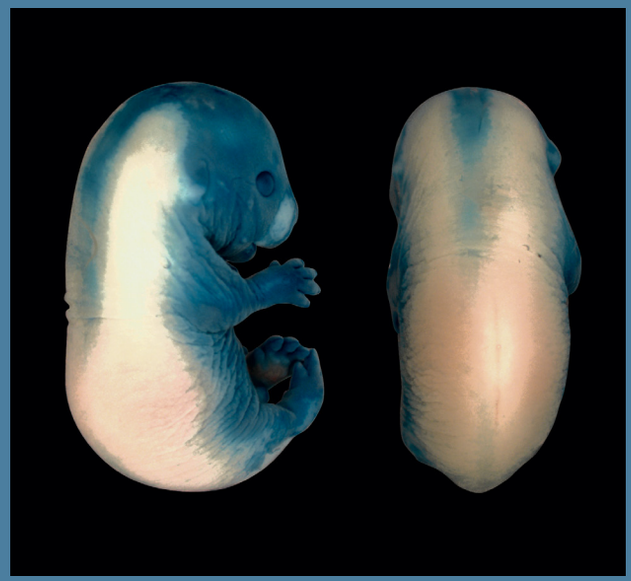
"One of the most fascinating aspects of what we do involves **understanding not only the relationship between genes and diseases, but also the role these genes play in normal individuals**. This approach significantly increases the potential application — and impact — of our work."

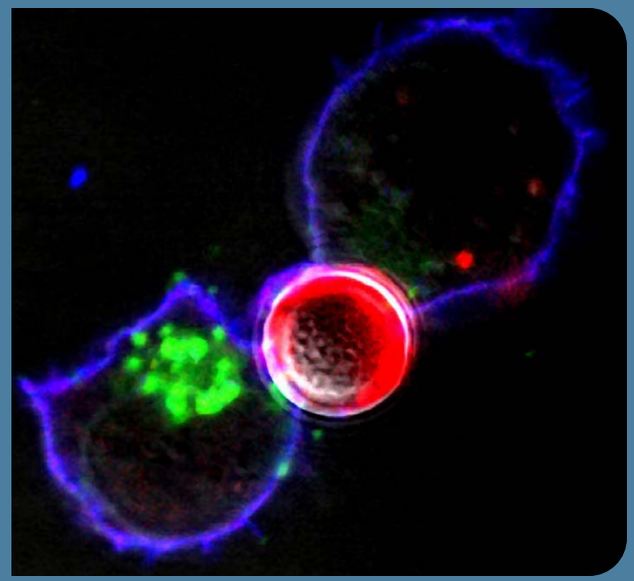
David Bodine, Ph.D.
Chief, Genetics and Molecular Biology Branch



GENETICS AND MOLECULAR BIOLOGY BRANCH

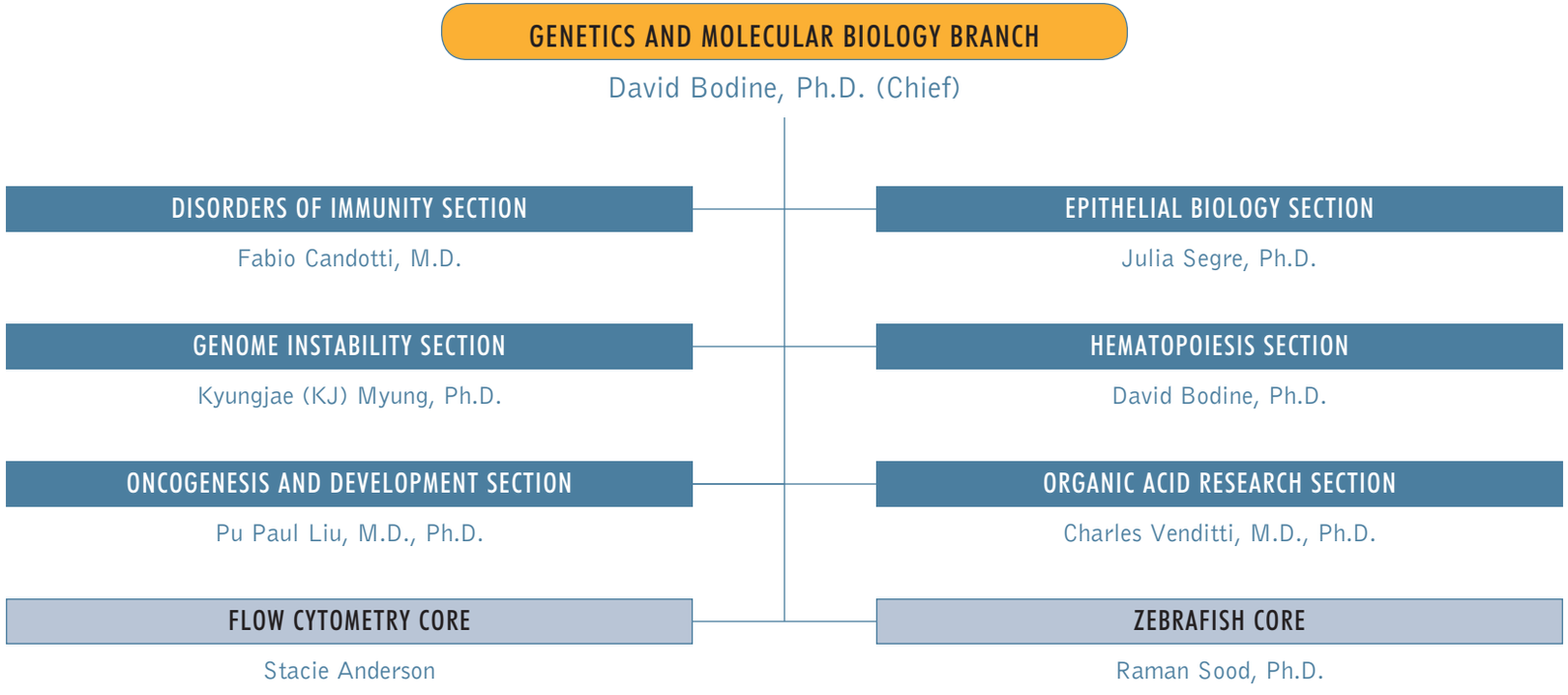






Investigators in the Genetics and Molecular Biology Branch (GMBB) use molecular genetic and genomic approaches to understand the development and function of different tissues and the mechanisms of genetic disease. The Branch integrates technologies and informational resources produced by the Human Genome 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, the immune system, and the environment. GMBB investigators perform translational and clinical studies of primary immune disorders, leukemia, solid tumors, anemia, eczema, and psoriasis. Branch investigators are also conducting a clinical trial of gene therapy and stem cell transplantation for severe combined immune deficiency. 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. GMBB supports two Cores that enable research across the NHGRI Intramural Program — the Flow Cytometry Core and the Zebrafish Core.


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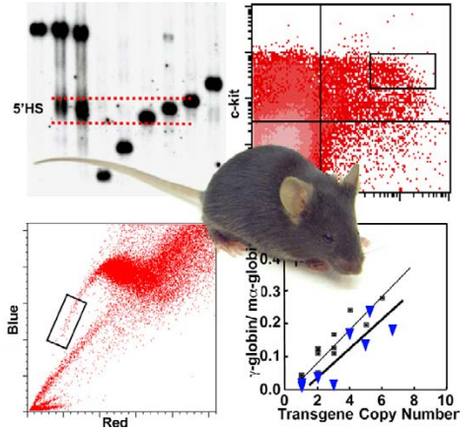
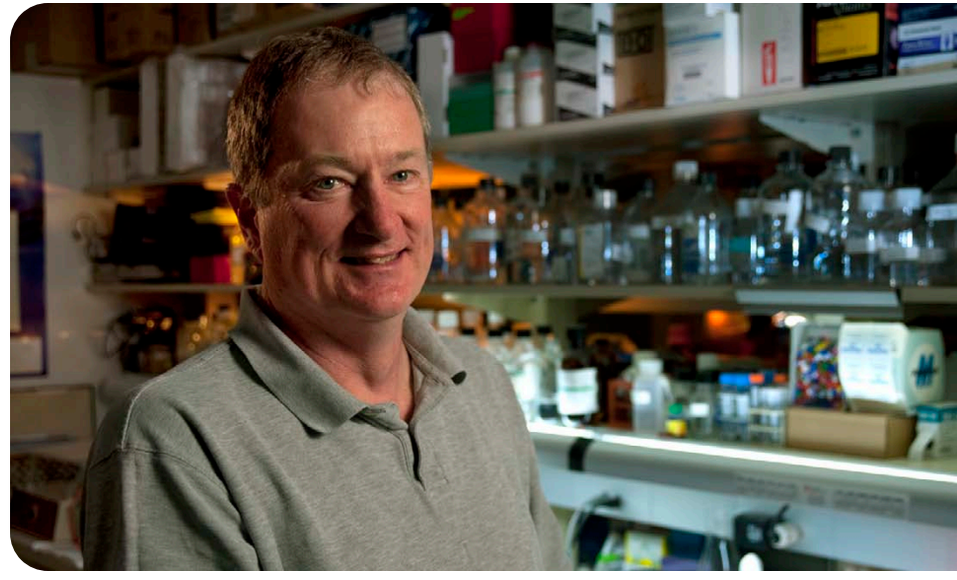
DAVID M. BODINE, Ph.D.

Dr. Bodine's research focuses on hematopoiesis, the regenerative process in which a small pool of undifferentiated hematopoietic stem cells (HSC) proliferate and differentiate into all of the different types of cells found in the peripheral blood. As the progeny of HSC multiply, they become restricted to specific hematopoietic lineages, eventually becoming committed to maturing into one single type of cell that then circulates in the blood. Perturbations of this process cause a variety of disorders ranging from hematologic malignancy to anemia.

One of Dr. Bodine's research objectives is to understand the changes in epigenetic factors affecting hematopoiesis. To this end, his group is involved in work designed to extend the *ENC*yclopedia *O*f *D*NA *E*lements (ENCODE) Project into the study of primary cells. ENCODE was developed to identify all functional elements in the human genome, including epigenetic factors and transcription factor binding sites, and has primarily analyzed cell lines or cells in culture. The hematopoietic system provides a unique opportunity because, unlike cell lines, hematopoietic cells can be sorted into nearly homogeneous populations that are clearly defined by their *in vivo* and *in vitro* properties using flow cytometry. Researchers are thereby able to take "snapshots" of the state of the genome at different stages of hematopoiesis. In addition, although transcriptional profiles of many well-defined hematopoietic cells exist, changes at the DNA and chromatin level are likely to reflect changes in differentiating cells better and more accurately than changes in the steady-state level of mRNA.



Dr. Bodine's group is using new sequencing technologies that have made it possible to conduct genome-wide analysis of epigenetic marks on primary cells. They are particularly interested in discovering genes that have different epigenetic marks in HSC and common myeloid progenitors. Dr. Bodine's laboratory hopes to discover candidate genes and pathways that could be exploited to enhance HSC self-renewal, leading to safer and more effective bone marrow transplants.



Dr. Bodine and colleagues also study two genetic anemia syndromes. The first is caused by a deficiency of the transcription factor EKLF. By examining the genome-wide binding of EKLF in differentiating erythroid cells, they seek to identify EKLF-mediated steps in the differentiation process. These data will be merged with information about the binding of other erythroid transcription factors to identify "regulatory signatures" for different genes expressed in red blood cells. Dr. Bodine's group is studying the second of these syndromes in a mouse model for human Diamond Blackfan anemia, which is caused by expression of a mutant RPS19 gene. Mice expressing the mutant allele fail to complete erythropoiesis – the terminal differentiation of proliferating red cell progenitors into enucleated circulating red blood cells. With the hypothesis that the mutant RPS19 gene inhibits protein translation, Dr. Bodine's laboratory is conducting a proteomic analysis of mutant and wild-type cells to better understand the net effect of RPS19 mutations.

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In chromosomes, individual loci and the chromatin surrounding them become active in specific cells while remaining silent in others. This activation may be associated with specific cis-acting sequences that are responsible for the establishment and maintenance of active chromatin. While certain DNA regulatory elements, such as promoters and enhancers, are well described in the literature, other critical cis-acting elements that prevent gene silencing (barriers) or the activation of neighboring genes (enhancer blockers) are not well defined. Dr. Bodine's group is conducting an in-depth analysis of barrier and enhancer blocking elements of two loci (ANK-1 and SLC4A1) that are expressed in red blood cells. His group has identified point mutations in a novel promoter element and in a barrier element at the ANK-1 locus that are associated with ANK-1 deficiency. They speculate that they will be able to use the same approach to identify barriers and enhancer blockers at the SLC4A1 locus. Knowledge of how these barrier and enhancer blocking elements function can ultimately be used to improve the safety and efficiency of vectors used in gene therapy approaches for treating specific diseases, such as sickle cell disease.

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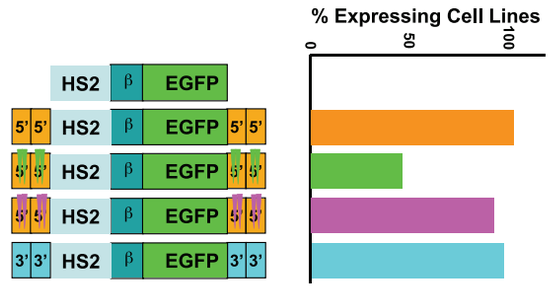
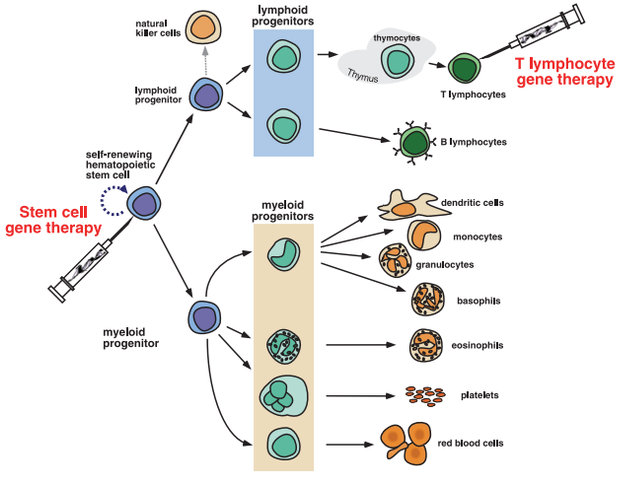


FABIO CANDOTTI, M.D.

Dr. Candotti's laboratory studies the molecular basis of inherited disorders of the immune system with the aim of developing better treatments for these conditions. For many inherited immune deficiency disorders, the only available therapeutic option is hematopoietic cell transplantation (HCT), currently an intensive procedure that carries a number of risks. Dr. Candotti is seeking treatment alternatives to HCT, 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 have enough residual enzyme activity to prevent toxic adenosine metabolites from accumulating. Their immune deficiency is therefore milder, and may not be diagnosed until later in childhood or even adulthood. Although HCT from a matching sibling donor can cure ADA deficiency, most patients do not have a matched donor; HCT for them carries increased risks. Genetic correction of a patient's own hematopoietic stem cells, therefore, could be a beneficial therapeutic alternative.



Dr. Candotti's laboratory is evaluating novel viral vectors as gene transfer tools for correcting ADA deficiency. A major obstacle to this approach has been the low efficiency of the procedure due to the complex

steps necessary in the collection, genetic manipulation and administration of adequate numbers of gene-corrected hematopoietic stem cells. Results from current trials carried out by Dr. Candotti's group using murine retroviral vectors are promising. With the goal of improving the timing and quality of immune reconstitution, Dr. Candotti's laboratory is evaluating the use of vectors based on human lentiviruses that should be available for human experimentation in late 2011.

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. As with ADA deficiency, most WAS patients do not have an ideal donor for HCT and development of alternative therapeutic approaches is therefore needed. Dr. Candotti's group is building on *in vitro* and *in vivo* studies indicating that retroviral-mediated gene transfer

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can correct the biological defects observed in cells from patients with WAS and in animal models of the disease. In addition, observations in WAS patients with spontaneous correction of their genetic defects have confirmed that gene-corrected cells have a selective advantage over their mutated counterparts. These findings provide a positive outlook for the prospects of gene therapy in this disease.

Dr. Candotti's laboratory has demonstrated that WAS patients carry defective regulatory T-cells, an important subset of T-lymphocytes responsible for the maintenance of immune tolerance. These findings may explain the autoimmune problems that develop in this disease and may allow development of new therapeutic avenues. Other research efforts by Dr. Candotti's group have demonstrated that novel gene transfer vectors based on Foamy virus can be used to correct the constellation of immunological problems characteristic of WAS mouse models. Because of their safety profile, these new vectors are good candidates for clinical development, which could provide new alternative therapeutic options in the near future.

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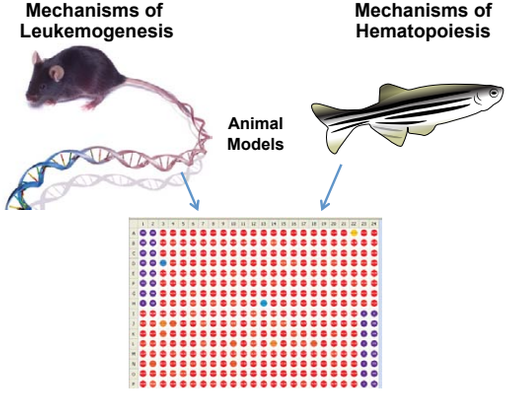
PU PAUL LIU, M.D., Ph.D.

Dr. Liu's laboratory investigates the molecular mechanism of leukemia, a disease that strikes approximately 43,000 Americans each year. His group has a particular interest in 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.

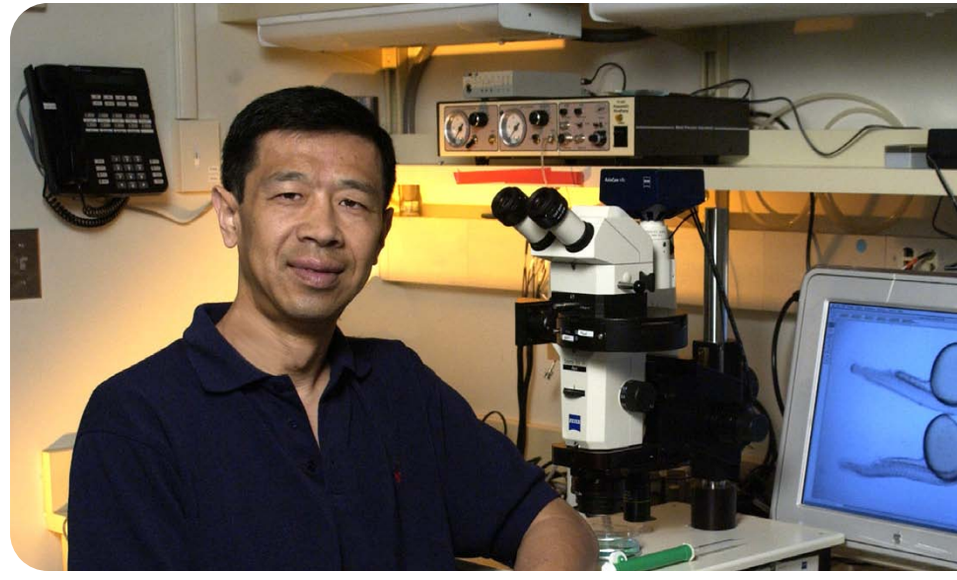
Leukemia is an example of hematopoiesis gone awry and, when it develops, the body produces large numbers of abnormal blood cells, or blasts. In acute leukemia, these blasts are too immature to carry out their normal functions, and symptoms of dysfunction appear quickly. Leukemias are frequently associated with chromosome abnormalities and defects such as translocations, inversions, and deletions. One form of human acute myeloid leukemia (AML) is associated with an inversion of 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.

To study the *CBFB-MYH11* fusion gene, Dr. Liu's group generated transgenic mouse models. With these models, they demonstrated that the fusion gene blocks normal hematopoiesis through its encoded fusion protein (CBFβ-SMMHC), leading to AML susceptibility. Dr. Liu's group has determined the importance of functional domains in the mouse *Cbfb-MYH11* fusion gene by generating and analyzing mice expressing truncated CBFβ-SMMHC. They made the novel observation that *Cbfb-MYH11* induces AML without dominant repression of another gene called *RUNX1*, which was previously believed to be the key function of this fusion gene.



Translational studies – develop novel leukemia drugs

More recently, Dr. Liu's laboratory has identified novel *CBFB-MYH11* target genes during leukemia development using mouse models. With the identified target genes, his group was able to identify and enrich for leukemia stem cells, which are responsible for initiating leukemia and for relapse after treatments. Characterization of such leukemia stem cells may help to develop approaches to leukemia cell eradication in patients. In fact, through a collaboration with the NIH Chemical Genomics Center, Dr. Liu's group conducted a chemical library screen and is in the process of developing and testing novel anti-leukemia compounds in transgenic mouse AML models.



In parallel, Dr. Liu's group is studying genetic control of hematopoiesis in the zebrafish, which is an excellent vertebrate model for embryonic development and for conducting systematic genetic screens. Using chemical mutagenesis techniques, zebrafish mutants are generated that carry defects in hematopoiesis. 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*, 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

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vlad tepes fish. In mammals, the transcription factor GATA1 is required for normal erythroid development. This first *gata1* mutation identified in the zebrafish demonstrates significant functional conservation between mammalian and zebrafish hematopoiesis, and offers a powerful tool for future studies of hematopoiesis in zebrafish.

Dr. Liu's laboratory has more recently used high-throughput reverse genetic screening systems to efficiently generate fish lines carrying mutations in any genes of interest, which can then be used for further phenotypic and genetic studies. Using this approach, the group generated a fish line with a mutation in the *runx1* gene, which is frequently mutated in human leukemias. This novel zebrafish mutant enabled Dr. Liu's group to more accurately determine the gene's function in hematopoiesis. In addition, the *runx1* mutant fish as well as other transgenic fish lines have been used successfully in the screening of novel compounds that target the leukemia-related *runx1* and *cbfb* genes. This technology will therefore 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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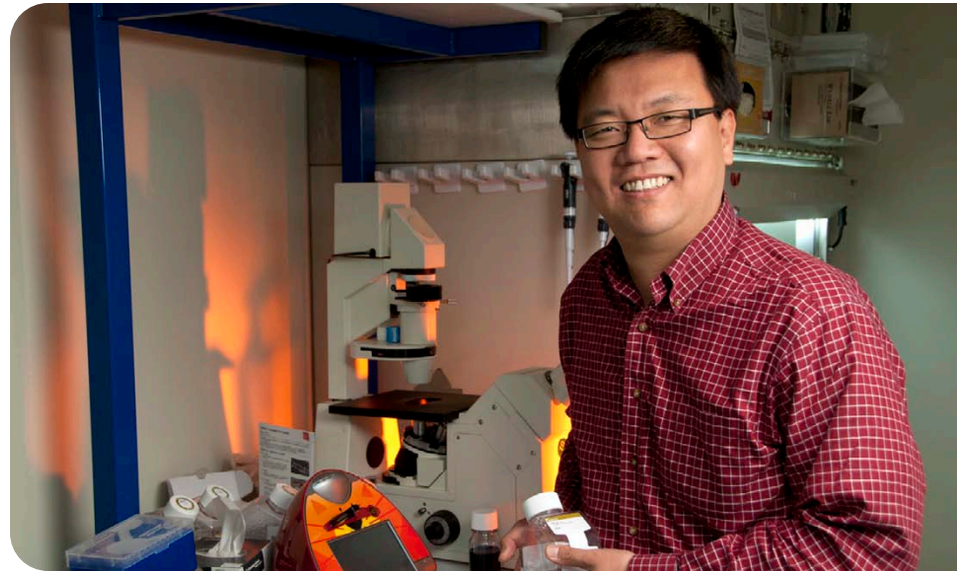
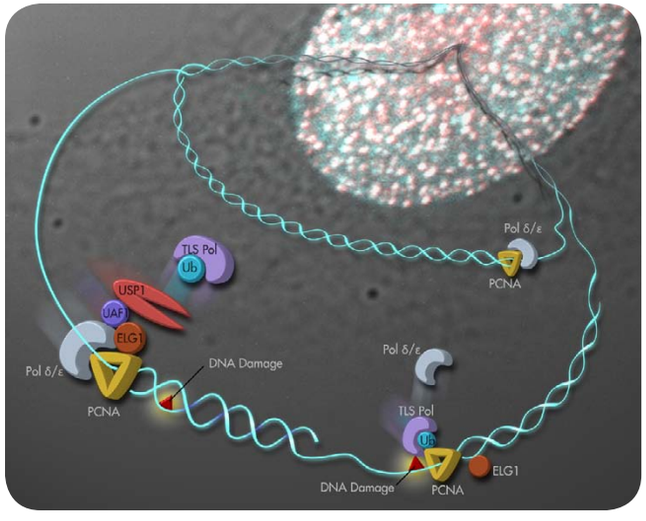
KYUNGJAE (KJ) MYUNG, Ph.D.



Dr. Myung's laboratory investigates 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. The major goals of his group are to develop new model systems to aid in this research and to use information from his studies to develop potential chemotherapeutic agents.

Genome instability is observed 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, suggesting that genome instability defects are probably involved in tumor development.

Using a whole-genome screening method in yeast developed by his group, Dr. Myung's laboratory is studying the pathways that maintain genome stability in mammals, as well as in yeast. Currently, his group is focusing on the mechanism of action for three of these genes: *ELG1, RAD5, and MPH1*.



Dr. Myung's group found that GCRs are suppressed by a template-switching mechanism that involves a post-replication repair pathway principally regulated by Rad5-dependent proliferating cell nuclear antigen (PCNA) polyubiquitination. His group also recently identified mammalian *RAD5* genes, called *SHPRH* and *HLTF;* the scientific community has been searching for these genes for the last 20 years. Both *SHPRH* and *HLTF* redundantly promote PCNA polyubiquitination and suppress GCR formation. Mutation or silencing of these genes has been observed in several cancers.

Dr. Myung's laboratory found that the yeast Elg1 (Enhanced level of genome instability 1) protein is involved in DNA repair, and that mutations in *elg1* enhance spontaneous DNA damage, which then increases the rate of GCRs. Dr. Myung's group also identified the mammalian ELG1 that shares similar functions with yeast Elg1. Interestingly, they found that the mammalian ELG1 generates DNA damage-induced nuclear foci in response to stresses of DNA replication. Using gene-knockout and RNAi-based methods, they found that mammalian *ELG1* has a unique function in regulating the level of ubiquitinated PCNA and thereby suppressing tumorigenesis.

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Dr. Myung's laboratory is conducting early-stage screenings to identify small molecules that potentiate DNA replication stresses and inhibitors of ELG1-dependent DNA repair pathways. These small molecules could be potential chemotherapeutic agents.

Over the past several years, Dr. Myung and his colleagues have identified many genes that enhance GCRs when overexpressed. One of the more 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. Using yeast as a model organism, his group is currently exploring a DNA repair mechanism to repair DNA adducts produced by cross-linking agents. This particular mechanism is defective in patients with Fanconi anemia.

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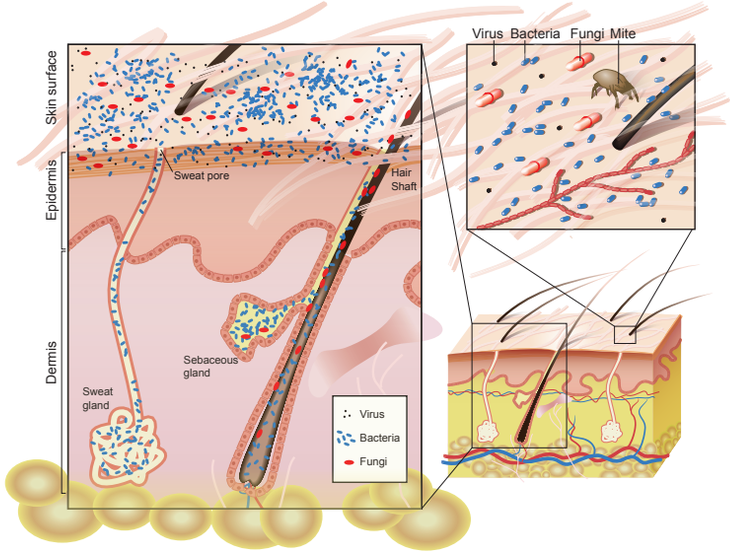
JULIA A. SEGRE, Ph.D.

Dr. Segre's research has historically focused on how the epidermis — the exposed layer of the skin — creates a barrier at the interface of the body and the environment. Using animal models, her laboratory explored the genetic pathways involved in building and repairing this skin barrier. They found that, in response to skin perturbations, epidermal cells express high levels of antimicrobial peptides, proteins that can both directly kill microbes (e.g., bacteria and fungi) and stimulate the body's immune system. This observation has led Dr. Segre to shift her research focus to identifying the microbes that inhabit the skin. As the largest organ of the human body, skin serves as a critical barrier to invasion by microbes, while at the same time providing a major home to them.

Dr. Segre's research program is now exploring the bacteria and other microbes that constitute the skin microbiome. Using contemporary genomic methodologies, she is focusing on the role that these microbes may play in human health and disease. The Segre laboratory estimates that approximately one million bacteria reside on each square centimeter of skin; many common skin conditions are associated with both impaired skin barrier function and increased microbial colonization. By sequencing the DNA of bacteria collected from the skin of humans and mouse models of human disease, Dr. Segre's group investigates how these bacteria contribute to health and, conversely, how changes in the bacterial community structure might contribute to chronic skin disorders, such as eczema and psoriasis.



Eczema, also called atopic dermatitis, is characterized by red, itchy patches of skin. Its prevalence has doubled in the United States over the last 30 years, with approximately 15% of children and about 2% of adults currently affected. Medical management of atopic dermatitis in the United States is associated with an estimated 7.4 million physician visits and over $1 billion in direct costs annually, posing a significant financial and medical burden. Cognizant of this rise in atopic dermatitis incidence and its consequences, Dr. Segre's laboratory has launched a clinical study of the microbiome associated with the skin of eczema patients.

Analysis of microbial diversity has traditionally been based on culturing samples; however, this method detects only a limited fraction of the bacteria that are actually present. New genomic tools are now available that identify bacteria based on species-specific sequences in the 16S rRNA ribosomal genes. In collaboration with clinical dermatologists from the National Cancer Institute, Dr. Segre's group is using such new techniques to perform an initial study to catalog the resident skin microbiota of healthy humans. Initially, the group is collecting samples from the bend of the elbow, which is often affected in patients with eczema. The samples are then analyzed with high-throughput sequencing by the NIH Intramural Sequencing Center (NISC). Many thousands of 16S rRNA sequences are being generated in order to identify both dominant and rare species of bacteria that reside in this area. Many of the bacterial species detected so far were previously unknown to be present on human skin.

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Microbial studies are being extended to a broad range of human skin sub-sites, including the navel, the sole of the foot, and the forehead. These skin sub-sites are commonly affected in skin diseases, and are associated with a wide range of physiological properties, including the density of hair follicles and sweat glands. In collaboration with the Microbiology Laboratory of the NIH Clinical Center, Dr. Segre's group is culturing large numbers of aerobic and anaerobic bacteria from these skin sub-sites; she plans to then determine the complete genomic sequence of novel isolates. Sequencing will be performed at NISC using powerful new DNA sequencing platforms. The generation of genome sequences from large numbers of newly-isolated microbes will facilitate downstream studies involving metagenomic analyses of samples from patients with different skin diseases.

Dr. Segre is an active participant in the Human Microbiome Project, an effort launched as part of the NIH Roadmap for Medical Research to comprehensively characterize human microbiota (nihroadmap.nih.gov/hmp).

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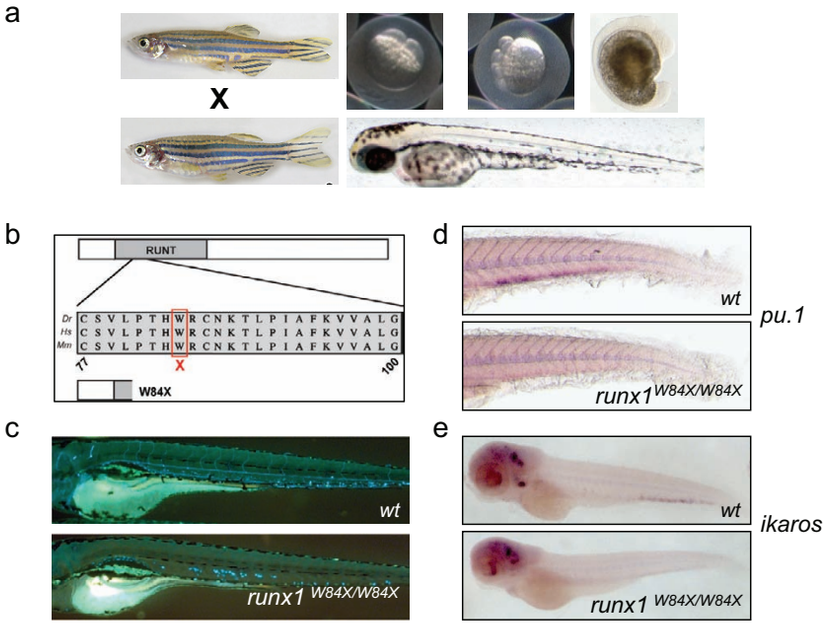
RAMAN SOOD, Ph.D.

Dr. Sood's research is aimed towards developing resources and adopting new technologies to facilitate the functional analysis of genes involved in human genetic diseases using the zebrafish as a model organism. Her goal is to adopt new technical developments in the field of zebrafish research so that all NHGRI investigators can capitalize on these cutting-edge methodologies.

Animal models with gain or loss of function mutations in genes play an important role in functional genomic studies, developing models for understanding the pathophysiology of diseases, and novel therapeutic approaches. To achieve this goal using the zebrafish as a model system, Dr. Sood utilizes two complementary approaches: TILLING (for "targeting induced local lesions in genomes") and zinc-finger nuclease mediated mutagenesis. Both of these methods can be used to generate genetic mutants in genes of interest for her group and other NHGRI investigators.



For the first method, known as TILLING, Dr. Sood's laboratory undertook a large-scale N-ethyl-N-nitrosourea (ENU) mutagenesis approach to generate ~3500 zebrafish males heterozygous for random point mutations throughout their genomes. Reverse genetic approaches involving polymerase chain reaction (PCR) and sequencing of exons coding for functional domains are used to identify mutants for genes of interest. Once candidate mutations are identified, new fish lines are then generated and bred to homozygosity in an effort to better understand the resulting phenotypes. To date, Dr. Sood has generated over a dozen lines with missense and truncation mutations in genes involved in diverse cellular and developmental processes such as DNA repair, hematopoiesis, gastrulation, and cancer.

In the other method of mutant generation, Dr. Sood's group microinjects mRNA-encoding zinc finger nucleases specifically targeting the gene of interest into one-cell stage zebrafish embryos. The injected embryos, or "founders," are grown to adulthood, which takes approximately three months, and are screened for germline transmission of mutations induced by the zinc finger nucleases. The phenotypes are then analyzed by crossing

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the heterozygous mutant fish. Using this method, Dr. Sood has identified several different mutants with frame-shift mutations and premature truncations in cbfb, a gene involved in regulation of hematopoiesis.

Dr. Sood has a long-standing interest in understanding the process of cancer development and progression. In parallel with the technical development work being conducted in the Zebrafish Core, Dr. Sood has collaborated with Dr. Paul Liu to characterize the phenotypes of zebrafish mutations in genes involved in hematopoiesis; mutations in several genes that control hematopoiesis cause leukemias and lymphomas.

Through the study of novel zebrafish mutations in gata1 and runx1, two of the major regulators of primitive and definitive hematopoiesis, respectively, Drs. Sood and Liu have demonstrated differential requirements of these genes during different waves of hematopoiesis. These mutants provide tools for clarifying the mechanism of hematopoiesis and developing new therapeutics by high-throughput chemical screening.

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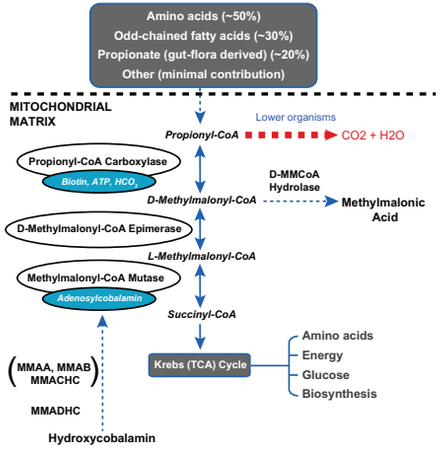
CHARLES P. VENDITTI, M.D., Ph.D.

Dr. Venditti studies a group of inherited metabolic disorders that cause increased methylmalonic acid and homocysteine to accumulate in body fluids. The conditions are generally caused by impaired intracellular metabolism of vitamin B12 or by defects in two enzymes — methylmalonyl-CoA mutase (MUT) and methionine synthase — that require the vitamin to function. Dr. Venditti and his colleagues conduct clinical research aimed at defining the natural history of these conditions, as well as laboratory studies that use metabolic, genetic, and genomic approaches to better understand the basic biology underlying these disorders.

Isolated methylmalonic acidemia (MMA) is one of the most common inborn errors of organic acid metabolism. The American College of Medical Genetics recommends newborn screening for MMA. With diverse clinical manifestations, affected patients are medically fragile and suffer from multisystem complications ranging from developmental delay to metabolic stroke to end-stage renal failure. The frequency of these complications and their precipitants remains undefined. Aberrant intracellular metabolism of vitamin B12 produces another group of conditions that feature both increased MMA and/or hyperhomocysteinemia; these disorders are named after their corresponding cellular complementation class — either cobalamin C, D, E, F, or G — and are also clinically and biochemically heterogeneous.

Dr. Venditti conducts clinical research in pursuit of a comprehensive understanding of the natural history of these disorders while developing new insights into their pathophysiology. Future efforts will involve studying patients using stable isotopes and metabolic tracers to monitor in vivo metabolism by mass spectrometry and magnetic resonance spectroscopy.



In the laboratory, Dr. Venditti uses model organisms to study MMA pathophysiology. By examining a mouse model of vitamin B12-nonresponsive MMA that displays neonatal lethality, his group has determined that mitochondrial dysfunction is a cardinal feature of the disorder and may underlie the tissue-specific manifestations seen in patients. In addition, Dr. Venditti has found that a large source of methylmalonic acid derives from skeletal muscle, which may explain the clinical observation of persistent MMA in patients after solid organ (liver or liver-kidney) transplantation. Dr. Venditti's group plans to use transgenic knockout and *Mut*-partial-deficiency mouse models to examine organ-specific contributions to methylmalonic acid metabolism and to further explore disease mechanisms.

Mouse models of MMA have also provided a platform for testing gene and cell therapies. Dr. Venditti's laboratory produced and validated lentiviral, adenoviral, and adeno-associated viral vectors for delivering the *Mut* gene to the liver and skeletal muscle in mice. They have also recently found evidence for viral correction in enzyme-deficient human liver cells and in *Mut*-knockout mice. Furthermore, gene-delivery studies using adeno-associated virus serotype 8 vectors have been successful in mice, and have encouraged the pursuit of similar approaches in patients. Dr. Venditti plans to undertake cell therapy experiments in future studies.

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Another focus of Dr. Venditti's laboratory involves the study of cobalamin metabolism. In collaboration with the NHGRI Zebrafish Core and as an extension of previous efforts using *C. elegans* to study MMA and cobalamin disorders, Dr. Venditti and his colleagues have developed a zebrafish model of cobalamin C deficiency. The cobalamin C (*cblC*) disorder, a form of combined MMA and hyperhomocysteinemia, is thought to be the most common inborn error of intracellular cobalamin metabolism. While its clinical manifestations are diverse — ranging from intrauterine effects, such as congenital microcephaly, to cognitive deterioration in adulthood — the underlying explanation for the pathophysiology in patients is unknown. One particularly devastating disease-related complication is progressive retinal degeneration leading to medical blindness. This occurs in only some patients affected with *cblC*. Dr. Venditti plans to use the *cblC* zebrafish model for genomic and proteomic studies in an effort to shed light on this human disorder.

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"**The confluence of creative thinking and unprecedented technological advances is accelerating genetics and genomics at an ever-increasing pace**. Diverse technologies, from single molecule sequencing to *in vivo* imaging, combined with state-of-the-art bioinformatic approaches, allow us to extract and analyze information as never before. It is an extraordinary time to be in this cutting-edge field."

Lawrence Brody, Ph.D.
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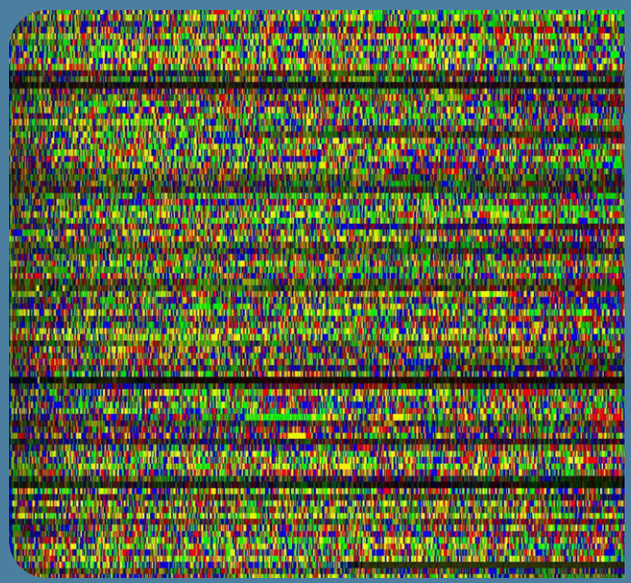
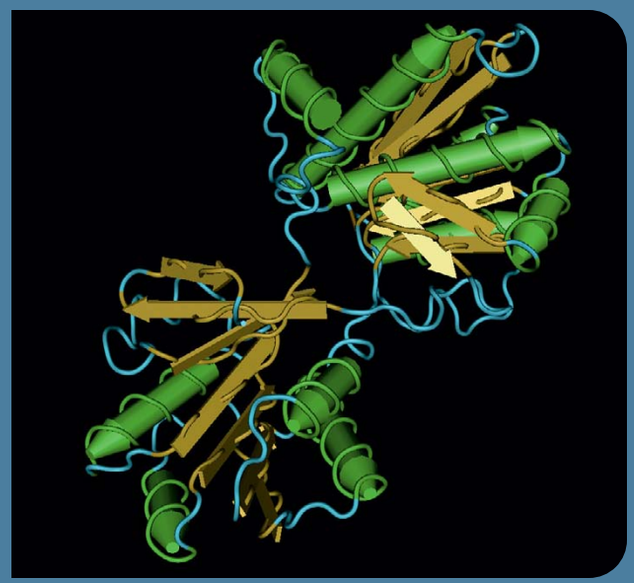
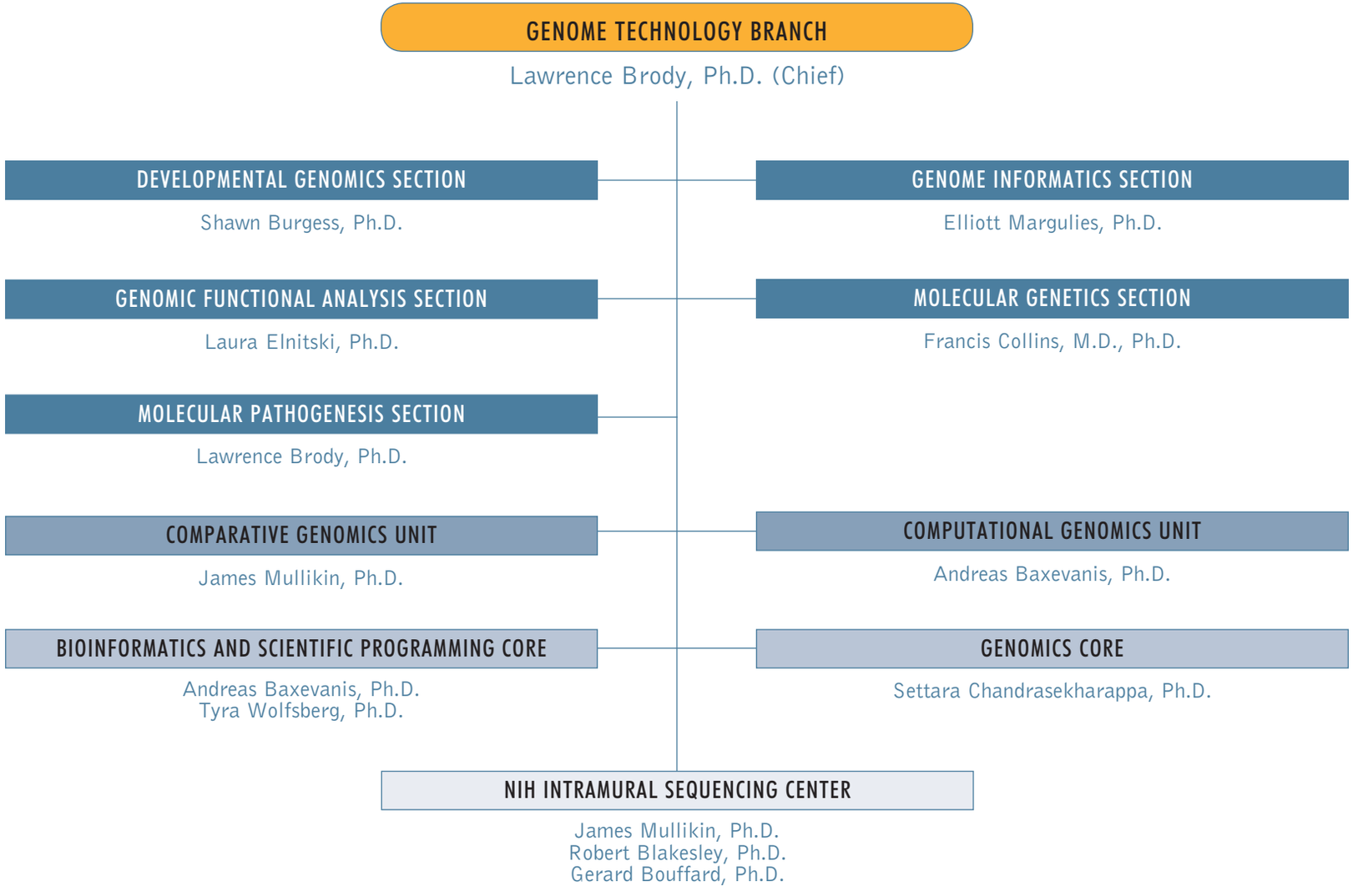
GENOME TECHNOLOGY BRANCH





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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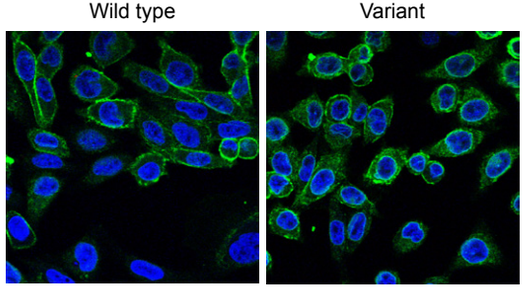
LAWRENCE C. BRODY, Ph.D.

Dr. Brody studies the inherited components of human disease. As head of the 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 focuses on identifying genetic variants that alter an individual's risk of developing specific conditions. These variants fall roughly into two categories. Some are associated with a very high risk of developing a disease; variants of this type, such as those in known breast cancer-linked genes, are of great medical importance. The second category of variants is associated with more modest risk. The medical significance of variants in the latter group is not yet known, but their isolation and identification can lend insight into the mechanism of complex conditions.

Dr. Brody's major area of investigation focuses on the genetics of neural tube defects (NTDs) and other birth defects. NTDs and congenital heart defects are some of the most common birth defects in the United States. Spina bifida, the most common NTD, results in the exposure of the spinal cord through an opening in the vertebrae. It is often corrected by surgery, but those affected may face lifelong medical complications, including paralysis. Dr. Brody's laboratory is collaborating with researchers at Trinity College in 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. Dr. Brody's laboratory was the first to connect genetic variants in genes involved in vitamin B12 metabolism to neural tube defects.



A major focus of the Brody laboratory involves the study of folate and vitamin B12 metabolism. This "pathway" is central to DNA metabolism, DNA methylation, and approximately one hundred different metabolic steps that involve the transfer of a methyl group between molecules. Given its central role, genes involved in the folate and vitamin B12 pathway are likely to be involved in many disease states. In addition to birth defects, the laboratory

has already found that inherited variants in this pathway contribute to medical conditions ranging from miscarriage to diseases of old age. Dysfunction of folate and vitamin B12 metabolism is extremely common in the elderly. Why some aged individuals suffer degenerative disease while others do not is not well understood — there is the possibility that certain combinations of vitamin levels and genetic makeup may lead to premature disease. In an attempt to understand all of the genetic elements that regulate folate and vitamin B12 metabolism, the Brody laboratory is carrying out a genome-wide association study in a large sample of healthy individuals; an international team of collaborators has already measured dozens of metabolites in these same individuals. The genetic and metabolic data will be merged in order to identify variants in genes that control metabolism. Since these same genes are likely to be involved in the disease process, they will be tested in large samples of individuals with birth defects and with diseases of aging such as anemia and dementia.

Dr. Brody is also interested the application of genetic information to public health and disease prevention. With investigators in NHGRI's Social and Behavioral Research Branch, he initiated and co-directs the Multiplex Initiative. This transdisciplinary project was designed to test some elements of personalized genetic risk profiling by providing individuals with a personalized

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genetic profile. The project is addressing questions aimed at determining the demographics of participation in genetics studies and how individuals perceive and utilize their genetic risk profile.

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. His team has studied how these genes function in cells and determined 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. While the laboratory no longer studies *BRCA1* and *BRCA2* at the bench, Dr. Brody continues to carry out bioinformatic studies on these genes. He collects information on mutations identified in patients undergoing genetic testing. More than 2,000 distinct *BRCA1* and *BRCA2* mutations have been identified to date, and have been cataloged to facilitate further study. Dr. Brody and others have used this information to better understand the range of cancer risk associated with these genetic mutations.

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BREAST CANCER MUTATION DATABASE

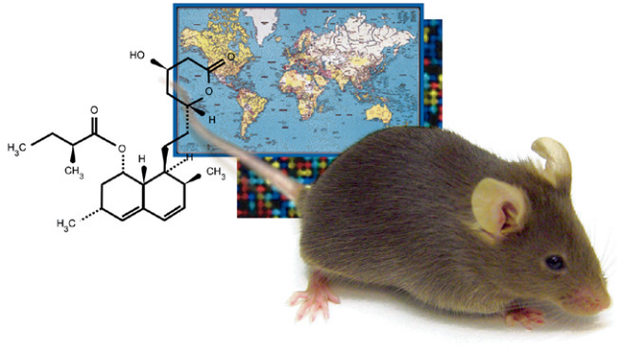
To identify and categorize all of the possible variations in both BRCA1 and BRCA2, and to help speed up the discovery of additional mutations around the world, Dr. Brody's laboratory has established the Breast Cancer Information Core (BIC) database. The database is a repository for mutations found worldwide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

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

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 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.

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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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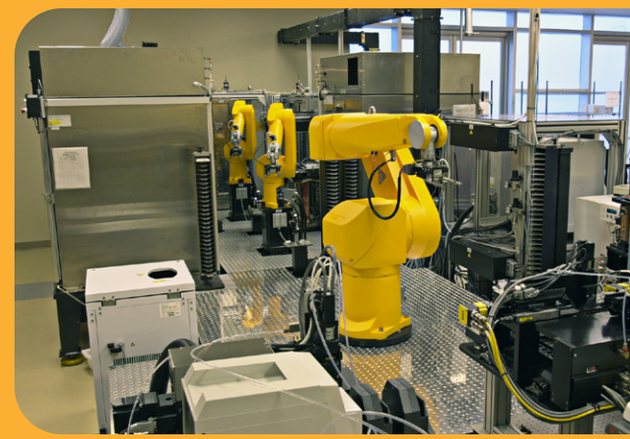
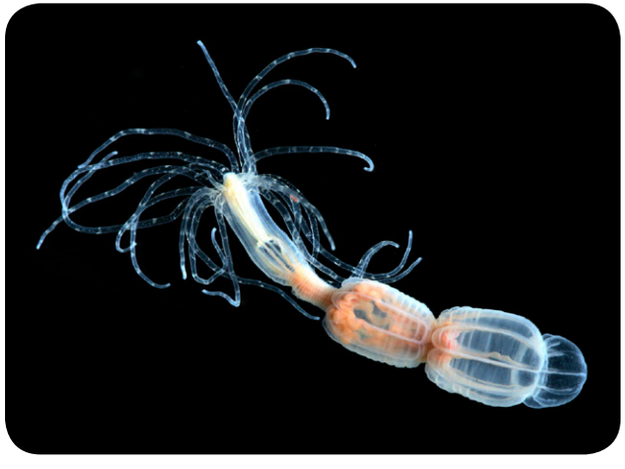


ANDREAS D. BAXEVANIS, Ph.D.

Dr. Baxevanis' research focuses on the computational analysis of the homeodomain group of proteins, which play a fundamental role in the specification of body plan, pattern formation, and cell fate determination during metazoan development. His group uses a variety of bioinformatic approaches aimed at understanding the evolution and function of these proteins and their role in human disease.

Homeobox (or Hox) genes are organized in conserved genomic clusters across a range of phylogenetic taxa and are considered partially responsible for patterning the primary body axis. Over evolutionary time, the functional diversification of these Hox genes has contributed to the diversification of animal body plans. To investigate the origin and early evolution of Hox genes and the "Hox code," Dr. Baxevanis' group has focused on the sea anemone *Nematostella*. Cnidarians, including corals, sea anemones, and jellyfish, constitute an outgroup to bilaterians – animals having bilateral symmetry – and have the potential to provide unique insights into early Hox evolution. Dr. Baxevanis and his collaborators have found phylogenetic evidence suggesting that a rudimentary Hox code in the cnidarian-bilaterian ancestor played a role in patterning the animal's primary (and possibly secondary) body axis. Moreover, thanks to strong stabilizing selection on this Hox code, certain core characteristics have been maintained despite being deployed in a bewildering array of animal forms for over a half billion years. In addition, Dr. Baxevanis' group has examined the possible role of Wnt genes in ancestral metazoan axial patterning, gene functions thought to pre-date the Hox system. Strong evidence suggests that Hox genes were "co-opted" into this pathway sometime between their origin and the last common ancestor of cnidarians and bilaterians.



The Baxevanis group also maintains the Homeodomain Resource, a publicly available database used extensively worldwide by researchers studying the homeodomain family of proteins. This database contains full-length homeodomain sequences and data on experimentally derived structures, protein-protein interactions, DNA binding sites, and mutations linked to human disorders.

Dr. Baxevanis' group devotes significant effort to developing computer software that will aid biomedical researchers. For example, early in the development of microarrays, his group developed the first publicly available software program designed to easily store and analyze microarray data. More recently, his group developed GeneLink, which enables researchers to analyze large data sets from studies of complex genetic disorders. Specifically designed to be used with large-scale linkage or association studies, GeneLink allows genotype data to be merged easily with pedigree and phenotype data, and an unlimited number of phenotypes to be stored and analyzed. His group has also developed ENCODEdb, a Web site that provides a unified, single point-of-access to data not only generated by the ENCODE Consortium, but also from other source databases within ENCODE pilot-project regions, providing the user a complete view of all known data in a particular region of interest.

Finally, Dr. Baxevanis has played a key role in the Multiplex Initiative, a large, multidisciplinary research collaboration to examine the effects of genetic susceptibility testing. Specifically, this project aims to explore

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why patients elect (or decline) to undergo testing, how they interpret test information and results, and how they will ultimately use this knowledge in future health care decisions. To study these and similar questions, Dr. Baxevanis and his colleagues have designed and deployed a prototype multiplex genetic test for 15 polymorphisms associated with increased risk for eight common health conditions. Dr. Baxevanis' group led the creation of the complex computational infrastructure required for this type of multicenter study, which involved investigators at NHGRI, the Henry Ford Health System (HFHS) in Detroit, Michigan, and the Center for Health Studies in Seattle, Washington. His group developed the Multiplex Initiative's Web site, which serves as the primary tool for collecting survey data from participants, precisely recording what genetic testing information is sought, in what order, and how long participants spend in each area of the site. The ability to track and capture similar measurements is critical to answering many of the study's behaviorally related questions. Initial observations are already providing valuable insights into how genetic susceptibility testing can best be used for advancing personalized medicine and improving the health of individuals.

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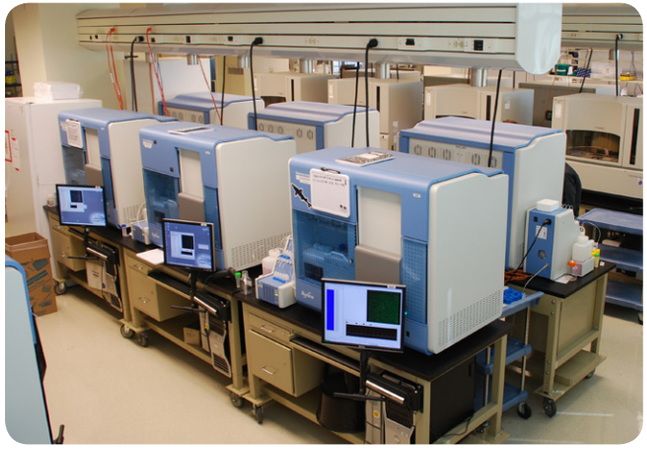
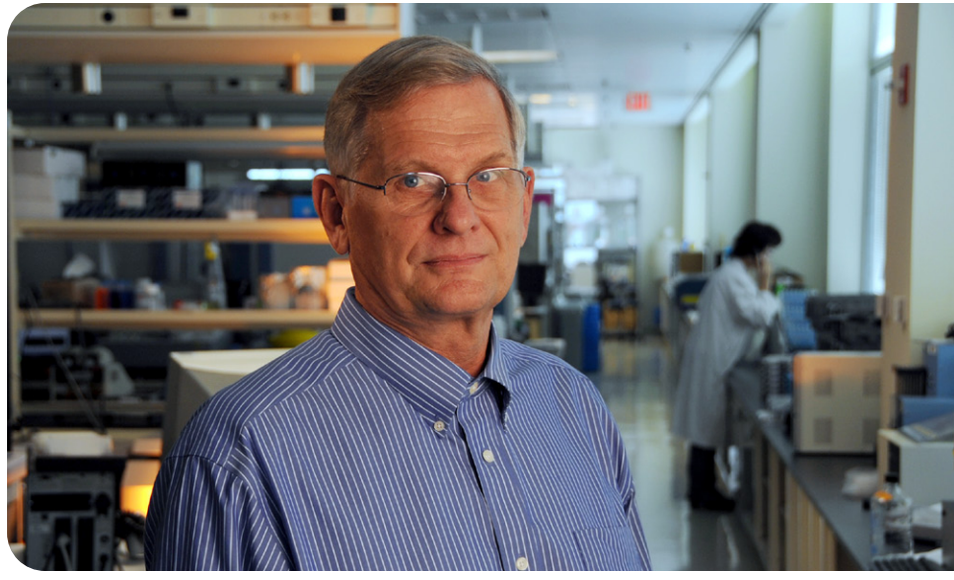
ROBERT W. BLAKESLEY, Ph.D.

Dr. Blakesley directs the Sequencing Group of the NIH Intramural Sequencing Center (NISC). His group is responsible for high-throughput generation of DNA sequence data using state-of-the-art automated instrumentation. Established in 1997, NISC is a multidisciplinary genomics facility tasked with 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 variety of areas, including nucleic acid enzymology, purification and manipulation of nucleic acids, apparatus and software design, and DNA sequencing. His current work focuses on increasing the value of NISC's sequencing pipeline by implementing new technologies that provide greater versatility and capacity while increasing overall operational efficiency, reducing costs, and applying good manufacturing principles.



Dr. Blakesley oversees NISC's role in several large DNA sequencing efforts. For example, the medical sequencing program at NISC is providing sequence data to many NIH investigators in order to discover a link between sequence variants and disease. NISC has provided ClinSeq, its largest collaborative project, with sequences of 250 genes from DNA of >500 volunteer subjects processed through the NIH Clinical Center who demonstrate various levels of atherosclerosis. In the next several years, NISC will expand sequencing to include data from nearly 18,000 human genes of 1000 participants. One of ClinSeq's first goals is to investigate some of the technical, medical and genetic counseling issues involved in implementation of large-scale DNA sequencing in the clinical setting. NISC



is also generating human sequence data for the NIH Undiagnosed Diseases Program, which integrates clinical and genomic research for patients with mysterious conditions that have long eluded diagnosis. A third area of medical sequencing involves genomic DNA from matched pairs of tumor and normal patient samples for investigators searching for somatic changes associated with several specific cancer types.

In another large effort for NISC, the Comparative Sequencing Program involves generating genomic sequences from multiple vertebrates – currently 75 species – for comparative analyses. In this project, targeted genomic regions (>200) 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. Through comparative sequence analysis, a number of discoveries of conserved noncoding elements are now targeted by collaborating investigators for functional studies. NISC also generated

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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 was a pilot-scale program that focused on 1% of the human genome, distributed across 44 discrete regions.

NISC is a major participant in the NIH Intramural Skin Microbiome Project. As part of this transdisciplinary collaboration, NISC is providing complete sequencing of microbial genomes from clinical isolates in order to catalog new clinically important species and to understand the variety and persistence of antibiotic resistance in known species. In addition, metagenomic sequencing of rRNA genes is being used to identify microbial community members and their relative abundance in and on the skin of patients with atopic dermatitis.

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GERARD G. BOUFFARD, Ph.D.

Dr. Bouffard directs the Bioinformatics Group at the NIH Intramural Sequencing Center (NISC). He oversees many aspects of project management, beginning with initial team contact and developing experimental design strategies with collaborative investigators. He and his staff have built and continue to develop a robust system for recording the receipt of biological samples and relevant metadata, laboratory process tracking, and raw DNA sequence data collection and processing. Working closely with NISC personnel, numerous quality control and integrity monitoring measures have been implemented, allowing for thorough review, reporting and process control.

To cope with NISC's large sequencing throughput and data generation, Dr. Bouffard has directed the development of a customized Laboratory Information Management System (LIMS). This system controls the flow of samples and materials through the laboratory, identifies reagents and equipment with barcodes, and records the people and tools involved at every stage. Efficient flow control, flexibility to prioritize tasks, and backtracking capability are achieved thereby. More recent enhancements have included the capabilities to capture and report the costs of reagents and services used for all projects. As a result, budgeting and cost projections have improved significantly, while allowing true cost comparisons of protocols and projects.

Since NISC's founding in 1997, Dr. Bouffard has played an active leadership role in planning and overseeing operational changes in response to rapid developments in molecular biology, DNA sequencing, and information technologies. The first large-scale sequencing project of the mouse genome using Sanger sequencing of BAC-based (bacterial artificial chromosome) shotgun libraries evolved, over time, into the widely-recognized Comparative Vertebrate Sequencing Program. This project targeted specific subgenomic regions across as many as 80 different species of primates, other mammals, marsupials, monotremes, birds, and fish. In addition, a number of significant scientific publications have been based on NISC's high-quality comparative genomic sequence data in the ENCODE (*ENC*yclopedia *O*f *D*NA *E*lements) project. Both established and novel technologies were used in identifying all the functional elements in ~1% of the human genome.

Shifting its emphasis from interspecies comparisons to the detection of medically significant human genetic variations, NISC established a robust PCR-based medical sequencing pipeline that targets specific genes and regions of interest. Extensive changes were made to the LIMS and DNA sequencing pipeline to accommodate the accurate tracking of over 2.5 million amplicons from over six thousand samples. In ClinSeq, the largest among several well-known projects, ~1,000 volunteers are providing DNA samples and undergoing laboratory tests aimed at understanding the genetic components of cardiovascular disease.

With the start of "NextGen" production DNA sequencing at NISC, attention has shifted from the well-established shotgun clone and PCR amplicon-based Sanger sequencing processes to the rapid design and construction of entirely new pipelines. Years of experience with Sanger sequencing have enabled Dr. Bouffard's group to anticipate the data and metadata collection needs of

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large-scale sequencing projects, and thereby implement practical approaches to process automation, historical tracking, and real-time quality assurance. The establishment of robust systems has been crucial to the rapid and successful deployment of sequencing technologies into exciting new areas, such as chromatin immunoprecipitation (ChIP-Seq), RNA sequencing, and both whole exome and whole genome sequencing. Use of new and improved interfaces and information technologies has positioned Dr. Bouffard's group to meet future challenges of increased sequence data complexity and volume.

Dr. Bouffard's graduate studies and continued interest are in the microbiological field. As a participant in the NIH Intramural Skin Microbiome Consortium, which endeavors to catalog the variety and relative abundance of microbial populations in and on the skin, he is actively involved with the study's microbial survey, the development of a whole-genome reference sequence, and the metagenomic sequencing of human skin samples.

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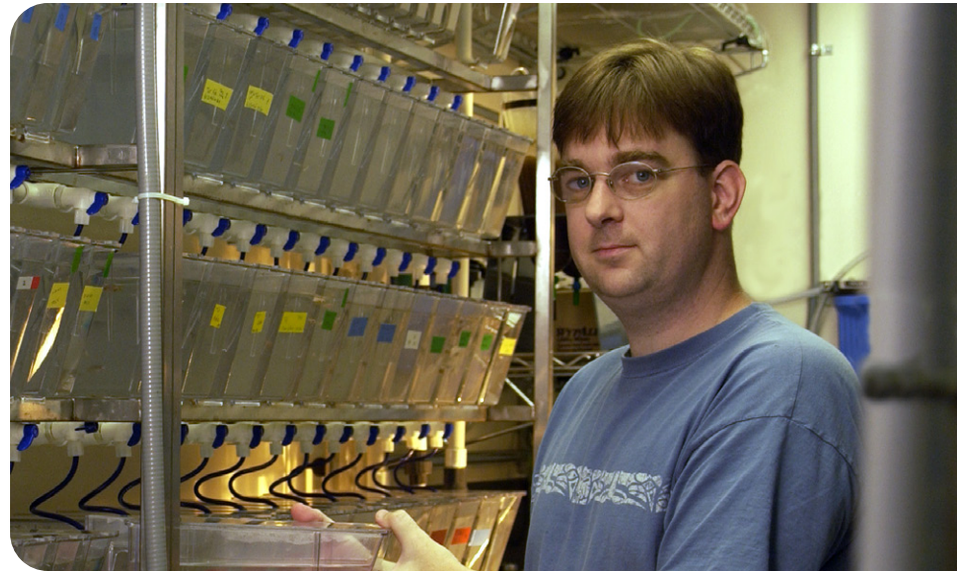
SHAWN M. BURGESS, Ph.D.

Dr. Burgess' laboratory studies developmental processes and their relationship to human genetic disease. Specifically, 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.

Hearing loss is one of the most common medical conditions affecting the human population, particularly in older adults. Twenty-eight million Americans, including one in three over the age of 60 and half over the age of 85, have some level of hearing loss. Unlike other vertebrates, mammals are unable to significantly regenerate the sensory neurons (hair cells) required for hearing and balance after losses caused by cell damage or cell death. Dr. Burgess' laboratory studies hair cell regeneration in the zebrafish (*Danio rerio*), which has a remarkable capacity for regeneration. Studies have shown that, after injury, zebrafish tissues as diverse as the retina, heart, fin, spinal cord, and inner ear are capable of complete recovery. Dr. Burgess uses a combination of genetic and genomic approaches to elucidate the gene network that is activated in the zebrafish inner ear stem cell population – known as "supporting cells"– during regeneration.

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 provided a major breakthrough in the ability to identify genes that are important in the early development of vertebrates. As opposed to chemical mutagens, the use of retroviruses reduces the time required for gene identification from years to weeks. The ability to expose zebrafish to these retroviruses and then quickly identify relevant mutations allows geneticists to perform large-scale mutagenesis and rapid phenotypic screening in a vertebrate system.



Two major projects are central to this research. One involves the transcriptional profiling of the zebrafish inner ear after sound exposure. Intense and extended sound exposure can damage and kill the hair cells of the inner ear. In this project, zebrafish hair cells are killed after 48 hours of sound exposure and then efficiently regenerate over the course of a week. Dr. Burgess' group has collected tissue from zebrafish inner ears at several intervals following sound exposure, and has then determined which genes exhibit significant increases or decreases in expression. Several phases of regeneration have been identified, and over 1,800 genes have been implicated in regeneration. Using these data as a foundation, Dr. Burgess' laboratory is now using a combination of genetics, embryology, and computational approaches to better define the critical genes involved in the regeneration process.

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A second related project involves classical genetic screening for genes involved in ear function and hearing regeneration. For this, retroviruses are being utilized as mutagens, and high-throughput analyses are being used to map the precise position of retroviral integrations. Akin to P-element mutations in *Drosophila*, this approach is creating a large zebrafish mutation pool that can be screened for phenotypes relevant to hearing function and inner ear regeneration. Once such mutations are identified, their roles in development, function, and tissue repair can be determined.

By integrating the information emerging from these different projects, a deeper understanding of the underlying network of tissue regeneration in the ear will emerge, potentially providing the basis for developing new therapeutic approaches for human hearing loss.

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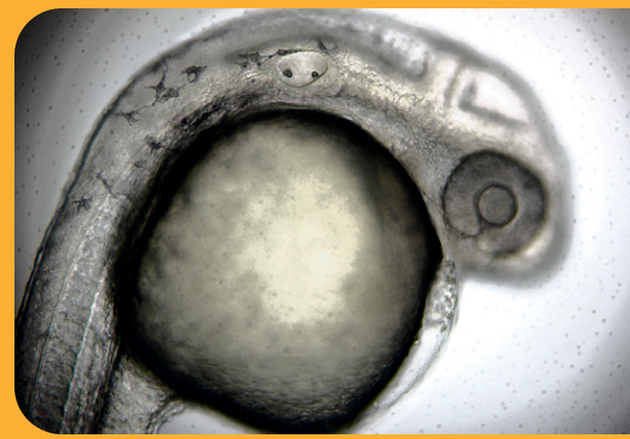
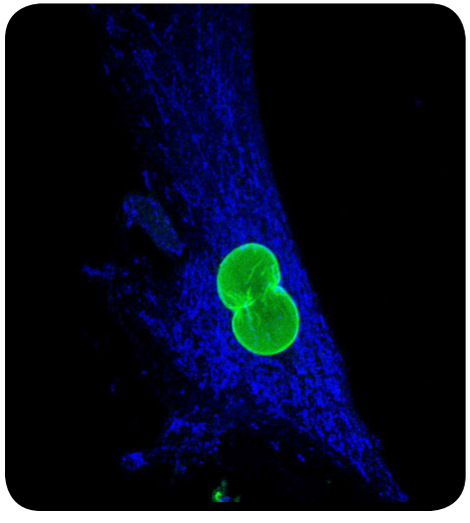


FRANCIS S. COLLINS, M.D., Ph.D.

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 in the lab 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 HGPS is caused by a point mutation in the lamin A gene (*LMNA*). This activates a cryptic splice donor, resulting in shortening of the normal version of the encoded protein by 50 amino acids near the C-terminus. 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. The mutant protein in HGPS, called progerin, is able to be farnesylated, but cannot be cleaved, rendering it permanently anchored in the nuclear membrane, sequestering other proteins and functioning as a dominant negative. Interestingly, progerin is also present in small amounts in normal individuals, and may contribute to the normal process of aging. Cell-culture experiments have shown that farnesyltransferase inhibitors (FTIs) can significantly ameliorate the nuclear-shape abnormalities seen in HGPS cells. Using a mouse model as a resource for screening potential therapies, the Collins laboratory has demonstrated that FTI treatment can prevent the onset of cardiovascular disease in young mice, and even reduce the progression of cardiovascular defects upon treatment in older mice. This research has complemented other data in support of a clinical trial administering FTIs to HGPS patients.



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 over 20,000 individuals to identify susceptibility factors for type 2 diabetes (T2D), formerly known as non-insulin-dependent diabetes mellitus (NIDDM). The FUSION project (*F*inland — *U*nited *S*tates *I*nvestigation *o*f *N*IDDM) began with linkage studies of affected sib pairs, and then moved on to perform a genome-wide association study (GWAS) on a total of 1,200 cases and 1,200 controls. Subsequently the FUSION project has become an integral part of several worldwide consortia studying T2D and quantitative traits. To date, these consortia have identified over 30 susceptibility loci for T2D and hundreds of loci affecting glucose, BMI, and lipid quantitative traits. Many of these T2D variants are associated with impaired insulin secretion or processing, and the vast majority reside in non-coding portions of the genome. These data suggest that altered regulatory function in the pancreatic islet may play an important role in T2D pathophysiology. Using ChIP-seq technology, the Collins lab is now investigating the islet epigenome to identify regulatory elements that are necessary for normal islet function and which, when altered, may lead to disease.

Recent seminal work has also identified a role for microRNAs (miRNAs) in lipid and glucose metabolism, but the extent of their influence in metabolic homeostasis is unknown. The Collins group is studying the underlying

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mechanism of miRNA targeting to establish the importance of miRNAs in regulating metabolic processes, especially in pancreatic islets and other tissues relevant to T2D.

Finally, the Collins laboratory is taking a bold step into the analysis of gene-environment interactions. Allergic asthma is the most common form of asthma and is the product of allergen exposure and underlying genetic susceptibility. The laboratory is investigating gene-environment interactions in allergic asthma using a physiological model of exposure to house dust mite allergen (HDMA), in which mice are sensitized and challenged with HDMA. This model is being investigated in a panel of genetically diverse mice, to identify genes that modulate asthma by positional cloning. The results from this study will be shared with collaborators in several epidemiologic research groups, in order to translate the findings from mice to humans.

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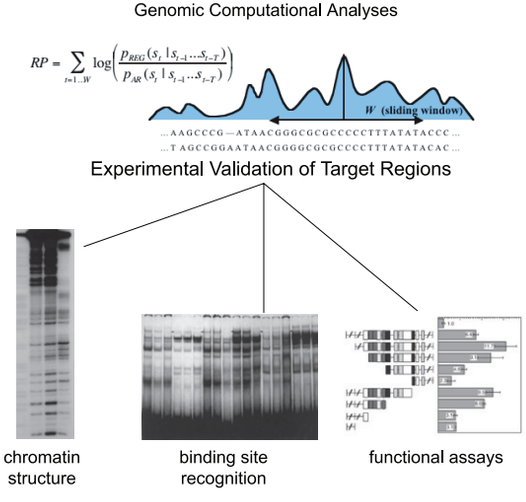
LAURA L. ELNITSKI, Ph.D.

Dr. Elnitski is a molecular and computational biologist who studies noncoding functional elements in vertebrate genomes. The functional sequences that encode proteins — genes — make up less than 2% of the human genome. Functional elements found in the remaining 98% of the genome, such as promoters, enhancers, silencers, and RNA-splicing signals, have important biological roles, particularly in regulating the temporal and spatial patterns of gene expression. The study of these noncoding functional elements is crucial for establishing a complete understanding of normal cell function.

Dr. Elnitski's group uses both bioinformatic and experimental approaches to identify noncoding functional elements in vertebrate genomes. For instance, they use cross-species comparisons to zero-in on sequences that have remained relatively unchanged throughout evolution; genomic regions with high degrees of conservation often contain functionally important sequences. These data are useful for training machine-learning algorithms that predict the potential of genomic sequences to be regulatory (i.e., those that control gene expression) or neutrally evolving (i.e., those that are not under selection to remain the same). Such predictions are used to narrow the amount of genomic material that must be examined to find important regulatory sequences.



In addition, Dr. Elnitski's laboratory is investigating less characterized functional elements in the human genome. In one project, her group is exploring mutations in exonic splicing enhancers (ESEs) that correlate with aberrant splicing patterns in coding regions of genes. Present in most mammalian exons, ESEs are short sequences that direct the process of RNA splicing, in which introns are removed from the primary transcript and the exons are then joined together, producing a mature messenger RNA (mRNA). ESEs play a role during precursor mRNA editing in the selection of correct splice sites, which are located at the boundaries between exons and introns. The correct choice of splice sites is essential not only for the proper production of proteins, but also for the generation of alternatively spliced mRNA forms (which represents regulated exon skipping) that often 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 study, her group has built probabilistic models to prioritize mutations that disrupt RNA splicing for experimental testing.

Dr. Elnitski's group is also examining the regulation of transcript initiation in the human genome. One project focuses on the role of bidirectional promoters, which are defined as the regulatory regions between two adjacent genes whose transcription initiation sites are neighboring but oriented away from each other. This promoter architecture is often found in DNA repair genes and genes that are implicated in somatic cancers. Thus, the identification of

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all genes associated with this promoter structure might provide new insights into human disease. Dr. Elnitski has identified tumor suppressor genes regulated by bidirectional promoters that are coexpressed and have common transcription factor-binding sites involved in their regulation. Furthermore, aberrant methylation of these promoters can lead to silencing of their expression; in the case of bidirectional promoters, expression of both flanking genes is affected. Dr. Elnitski has mapped all bidirectional promoters in the human genome using computational techniques, and these results 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. Specifically, she is mapping silencer elements using a novel experimental system. She is also identifying networks of bidirectional promoters across species to develop the first regulatory maps of orthologous promoter elements in sequenced mammalian genomes.

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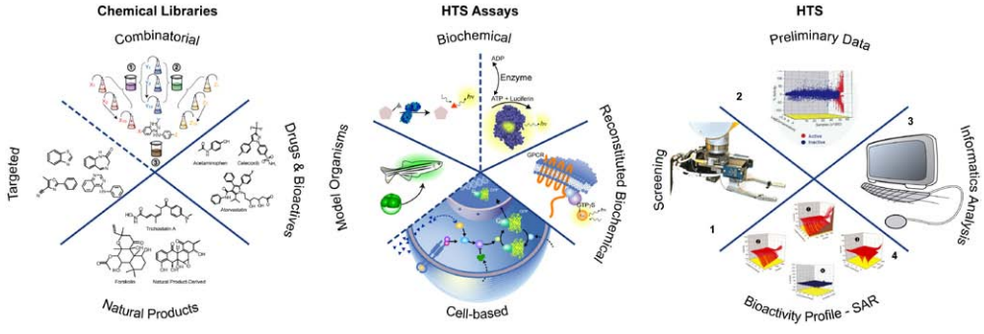
JAMES INGLESE, Ph.D.

Today's pharmaceuticals are directed toward fewer than 2% of the proteins encoded by the human genome's approximately 25,000 genes, yet thousands of genes have been implicated in the broad spectrum of rare diseases that affect humanity. Facilitating the discovery and development of drugs for treating rare and underserved diseases is an important area of focus for the NIH.

In collaboration with disease foundations and individual investigators, Dr. Inglese's laboratory develops and implements strategies to identify chemical modulators targeting the molecular underpinnings of disease pathophysiology. Applying his expertise in enzymology, cell and molecular biology, and chemistry, Dr. Inglese develops and validates biochemical and cell-based phenotypic assays for use in the screening of chemical libraries. He also uses gene silencing technologies and chemogenomic libraries to reveal secondary targets mediating the function of primary genetic abnormalities. Assays used for these purposes can range widely in concept and be enabled by various technologies. Assay designs encompass the measurement of gene expression, epigenetic and post-translational regulation, cell-surface and nuclear receptor binding, signal transduction, and metabolic enzymes, as well as the biological activity of entire pathways and the functional variation resulting from the genomic diversity of pathogenic organisms.

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 cytometry, a technology that enables the use of cellular and particle-based assays in whole cell ligand-binding studies. He has developed chemical methodologies to incorporate phosphorylation sites into proteins, peptides, and small molecules, permitting PKA-dependent labeling of ligands for use in radiometric assays. Using naturally occurring



protein domains in combination with protein evolution techniques, he has created antibody surrogates for the detection of post-translationally modified peptides and proteins. Such engineered domains have been used successfully in the development of assays for high throughput screening (HTS). Currently, he and his colleagues are developing methodologies coupling microscopy-based assays with laser scanning cytometry to enable these information-rich phenotypic assays for HTS.

Dr. Inglese has extensive experience in leading multidisciplinary research teams at both biotechnology and major pharmaceutical companies, and as a founding member of the NIH Chemical Genomics Center (NCGC, which will become an integral part of the NIH Center for Translational Therapeutics). For example, a current program focused on an inherited neuropathy called Charcot Marie Tooth disease (CMT) brings together leading investigators in peripheral nerve myelination, neurologists, and patient advocates. CMT type 1A, the most prevalent form of this autosomal dominant disease, has been linked to overexpression of the PMP22 gene. Leveraging the expertise of this network, Dr. Inglese's group has embarked on the design, development and optimization of assays tailored to monitoring the regulation of the PMP22 gene locus.

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From a comprehensive collection of approved drugs, large libraries of diverse chemical matter, and natural products derived from plants and microorganisms, using state-of-the-art HTS technologies, his team searches for candidate compounds that suppress PMP22. Through these efforts, Dr. Inglese and his team endeavor to facilitate the discovery and development of therapies for CMT and related disorders.

In order to support the development of a more efficient drug discovery paradigm, Dr. Inglese's laboratory engages in the evaluation, development, and refinement of high throughput techniques and novel assay technologies for small molecule discovery. For example, he and his colleagues developed an improved process for testing large chemical libraries by integrating the resolving power of the pharmacologic dose-response relationship with the speed and accuracy of automated HTS. The resulting technology has been a fundamental asset enhancing the productivity of hundreds of programs conducted at NCGC.

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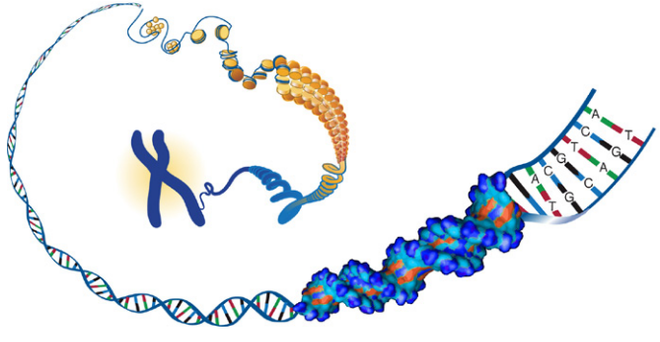
ELLIOTT H. MARGULIES, Ph.D.

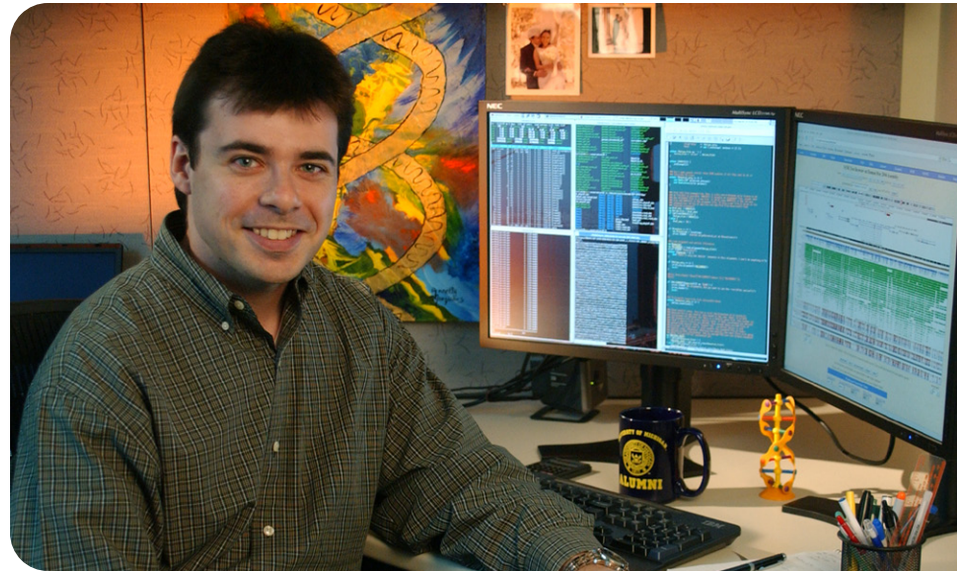
Dr. Margulies develops bioinformatic approaches that utilize ultra-high-throughput DNA sequencing technologies to sequence and characterize genomes. His group combines the application of these new sequencing technologies with bioinformatic studies that aim to examine a variety of scientific questions, ranging from those aimed at better understanding basic genome biology to those helping to address important clinical problems. In aggregate, these efforts seek to enhance our ability to decipher the information encoded within genomes.

Dr. Margulies' group combines experimental and bioinformatic approaches to identify and characterize the genetic information that confers biological function. Indeed, many of the functional elements encoded within the human genome are yet to be discovered; however, uncovering how basic biological phenomena are encoded within genomes is essential for understanding human development and disease. Many of the projects being pursued in Dr. Margulies' laboratory involve high-throughput experiments that generate large amounts of data; such data are then analyzed computationally to quantify gene expression, DNA-protein interactions, and genomic variation.

Another component of Dr. Margulies' research program involves developing and using analytical methods for detecting evolutionarily constrained sequences and determining their functional significance. The conservation of such sequences over millions of years of evolution is strong evidence that they play important biological roles, such as coding for critical genes or functioning as regulatory elements.

Toward that end, Dr. Margulies is developing new methods for detecting cross-species conservation that take into account the important role of the chromatin structure in genome function. Two approaches are currently being pursued. The first involves an in-depth analysis of the "molecular topograph" of DNA. Recently, it was 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 to establish the role of DNA topography in genome function. 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 proteins) that occur at the same relative position in multiple species can be identified. In some cases, the identified sequences are quite different between species, yet they seem to confer a 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.

In addition to computational projects, Dr. Margulies is developing high-throughput methods to assay large regions of the genome for transcriptional regulatory activity. For example, he recently developed a new approach that couples in vitro cell-based transfections with cell sorting to identify candidate enhancer sequences; he hopes to expand the use of these methods to allow an

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entire genome to be assayed at once. By coupling the data generated in the laboratory with various computational analyses, his group hopes to establish multidisciplinary approaches for studying genome function.

Finally, Dr. Margulies' laboratory has been instrumental in implementing "next-generation" DNA sequencing technologies at NHGRI. These new platforms can generate significantly larger amounts of sequence data at a fraction of the cost and time compared to traditional methods. His group has been working closely with the NIH Intramural Sequencing Center (NISC) and other NHGRI Investigators to apply these new sequencing technologies to a variety of biomedical research projects. Other applications are also being pursued in Dr. Margulies' laboratory, including new approaches for whole-genome sequencing and the sequencing of unknown microbial pathogens.

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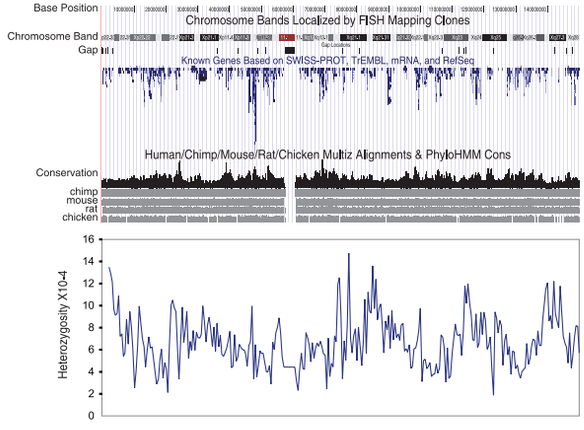
JAMES C. MULLIKIN, Ph.D.

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

His main research focus involves the development of algorithms for performing complex computations. One such program, called Sequence Search and Alignment by Hashing Algorithm (SSAHA), is used to dramatically accelerate the speed at which gigabases of DNA sequence are searched for single nucleotide poymorphisms (SNPs). Even though this program was first developed several years ago, Dr. Mullikin continually refines SSAHA in response to the changing needs of genomic scientists, and SSAHA remains the key tool that he and others use to detect sequence variants. He also developed a program called Phusion (pronounced "fusion"), which is used to assemble genome sequences from whole-genome shotgun data. Both the mouse and nematode genome sequences were assembled using Phusion.

Dr. Mullikin's group provides computational support for major NHGRI efforts such as the International Haplotype Map (HapMap) Project, which is primarily focused on determining genes and genetic variants that affect health and disease susceptibility. During the initial phase of this project, investigators produced a working haplotype map, consisting of ~600,000 polymorphic sites spaced an average of ~5 kilobase pairs apart. With the second phase of the project completed, investigators can now access a map of human variation in three populations, which contains over three million polymorphic sites across the human genome. Indeed, this landmark project has provided the foundation for the rapid completion of a large number of genome-wide association studies (GWAS; a list of published GWAS studies is available at *genome.gov/gwastudies/*).



Dr. Mullikin's group also provides critical computational support and guidance for a large-scale medical sequencing (LSMS) program based at the NIH Intramural Sequencing Center (NISC). Dr. Mullikin works with collaborating investigators to generate preliminary feasibility assessments for their projects by evaluating the genomic regions that they wish to target, whether it be a specific list of genes or entire genomic intervals. He then develops an initial design of PCR assays across the regions of interest. If a project is deemed feasible, it is then entered into the NISC sequencing pipeline which, in the end, produces a large number of DNA sequence reads. The reads are then automatically analyzed for the presence of genetic variants.

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Dr. Mullikin's group is currently preparing for a flood of new data that will be produced by "next-generation" DNA sequencers. These new sequencing machines, which utilize novel approaches significantly different from traditional "Sanger-based" instruments, are capable of exponentially higher throughput than previously possible. Some medical sequencing projects will be adapted to capitalize on the strengths of these new sequencing platforms, and many more projects will become feasible as sequencing costs decrease. In order to utilize these new instruments most effectively, Dr. Mullikin's group is testing methods for genomic enrichment that can be used in purifying specific regions of the genome prior to sequencing. His group is also developing new analytical methods to accurately detect genetic variants using data generated by these next-generation instruments.

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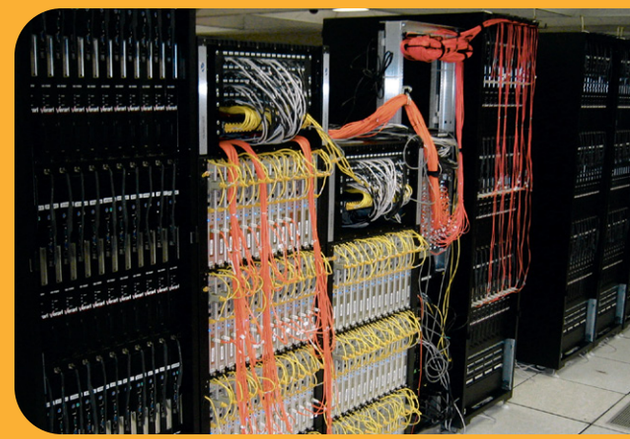

TYRA G. WOLFSBERG, Ph.D.

Over the last several years, the number of publicly available complete genome sequences and annotations has increased dramatically. At the same time, advances in technology have allowed individual researchers to perform experiments that generate tens of thousands of data points. This massive increase in data poses challenges for the individual biologist, requiring large-scale data analysis capabilities that are best handled using computational approaches. Dr. Wolfsberg's research focuses on developing methodologies to integrate sequence, annotation, and experimentally-generated data to assist bench biologists in quickly and easily analyzing results from their large-scale experiments.

Several recent projects have required that short sequences be mapped back to the genome or transcriptome from which they were derived. As neither existing heuristics nor simple pattern-matching approaches are well-suited for the task, Dr. Wolfsberg's group has developed a suite of algorithms to rapidly align sequences under 25 nucleotides in length. One of these programs is designed to map tens of thousands of sequence tags to whole genomes in only a few minutes, allowing for mismatches. A faster version has been developed for use when the sequence tags start or end with a common pattern, such as a specific restriction enzyme site. A third program is optimized to search for a single degenerate sequence, such as a consensus transcription factor-binding site, in a complete genome.

A related research effort has been to determine the genomic context of a set of coordinates, such as those obtained using one of the alignment algorithms described above. Graphical genome browsers themselves cannot be practically used for analyzing large sets of coordinates. Thus, Dr. Wolfsberg's group has developed algorithms that compare the positions of interest to the coordinates of features displayed in a genome browser, such as genes or conserved sequences. Based on a set of genomic regions as input, the programs identify either overlapping or the closest genomic annotation. For example, they can provide a list of coordinates that are upstream or downstream of genes, or highlight regions that are conserved across species. In order to evaluate the statistical significance of the computationally determined findings, Dr. Wolfsberg's laboratory has developed methods for extracting sequences at random that have the same biological characteristics as the sequences being analyzed in a given experiment. The genomic context of these control sequences is then determined, with the resulting information then used to establish p-values associated with the experimental data.

Dr. Wolfsberg's group has used these sequence mapping and annotation programs for a wide range of projects. For example, they have collaborated with researchers in locating transcriptionally active regions of DNA by finding sites that are sensitive to deoxyribonuclease (DNase), and in exploring gene expression patterns by identifying genome-wide consensus binding sequences for selected transcription factors. She is currently collaborating with researchers at the National Heart, Lung, and Blood Institute in assessing the efficacy and safety of retroviruses used as vectors in gene therapy studies.

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More specifically, Dr. Wolfsberg's group is studying the positions at which retroviruses and retroviral vectors integrate into the host genome during retroviral gene therapy. Recent studies have shown that one of the common retroviruses used in gene therapy, the Moloney murine leukemia virus (MLV), can integrate into genes and disrupt their function. In a clinical trial of retroviral gene therapy, four patients with X-linked severe combined immunodeficiency developed leukemia after the MLV vector integrated near a proto-oncogene, thereby activating it. In an attempt to identify alternate vectors for retrovirus-mediated gene therapy, Dr. Wolfsberg's group has performed a systematic analysis of the integration patterns of avian sarcoma leukosis virus (ASLV) in the rhesus macaque, and has followed three macaques for more than four years following treatment with a vector based on simian immunodeficiency virus (SIV). These studies have shown that both ASLV and SIV appear to be safer alternatives to MLV for gene therapy. Thus, optimized vectors based on either of these viruses may be considered for future gene therapy trials.

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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.
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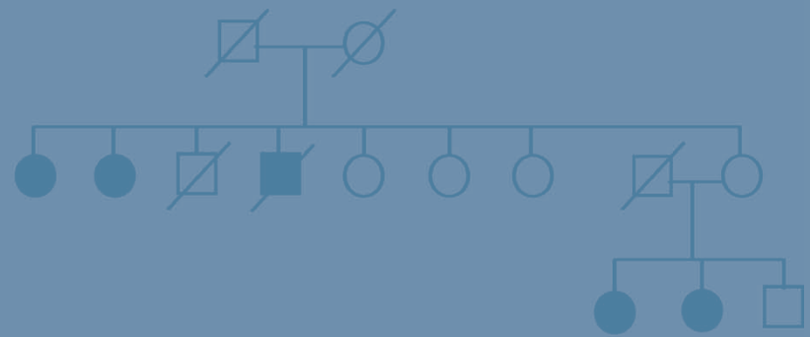
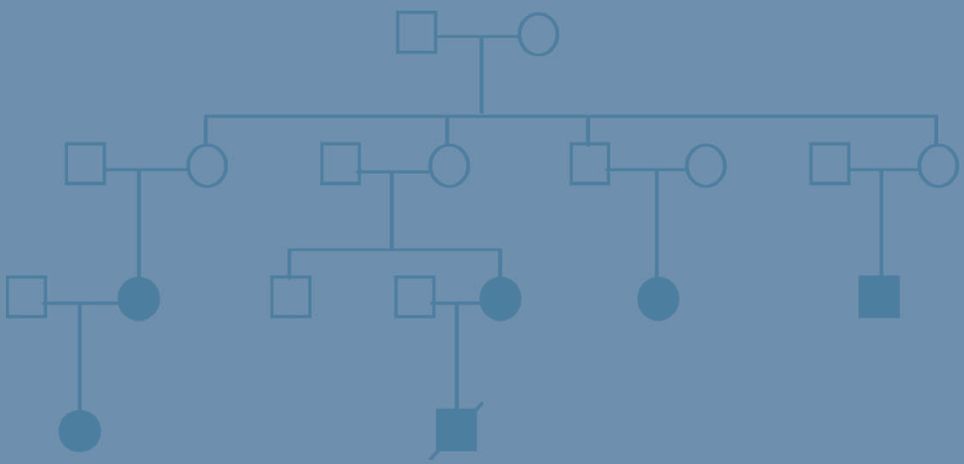
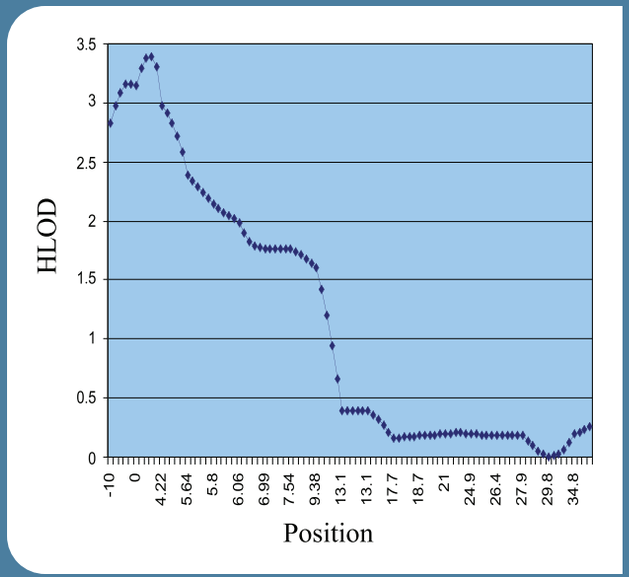
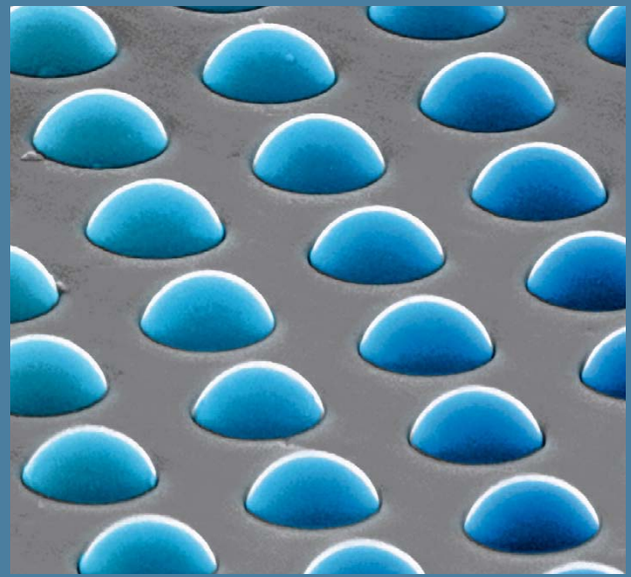
Co-Chiefs, Inherited Disease Research Branch

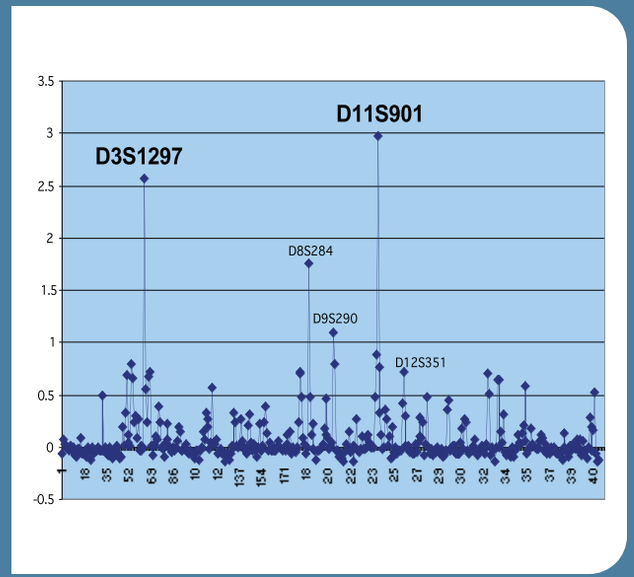




INHERITED DISEASE RESEARCH BRANCH

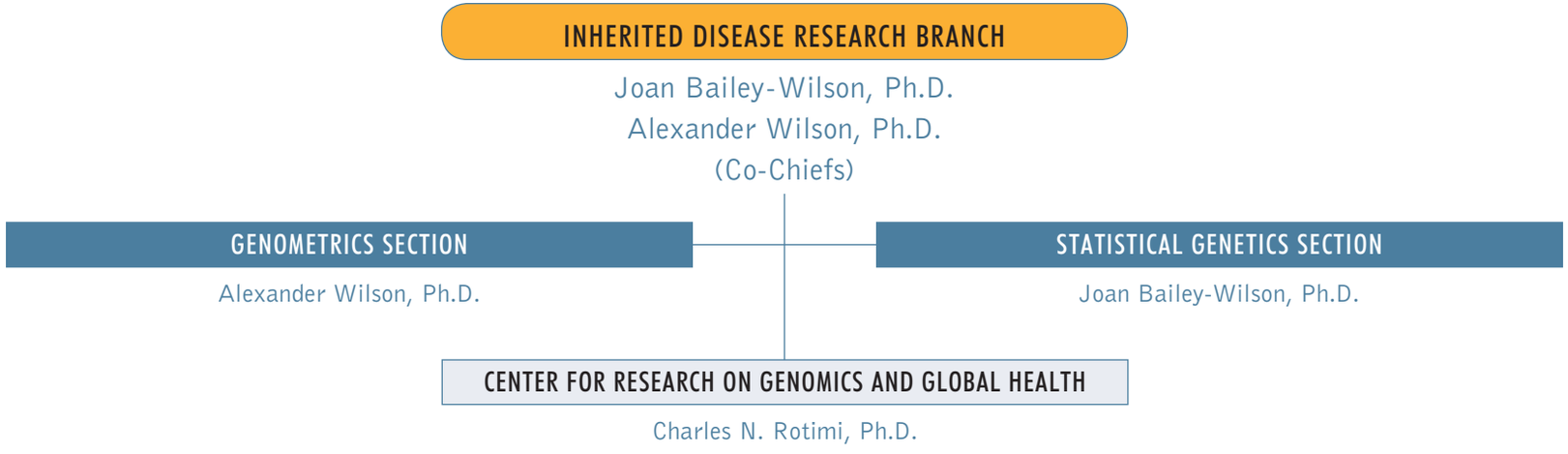






The Inherited Disease Research Branch (IDRB) develops and applies new methods and tools to identify genetic contributions to human disease, with particular emphasis on the study of common multi-factorial disorders. IDRB investigators specialize in statistical genetics and genetic epidemiology, which 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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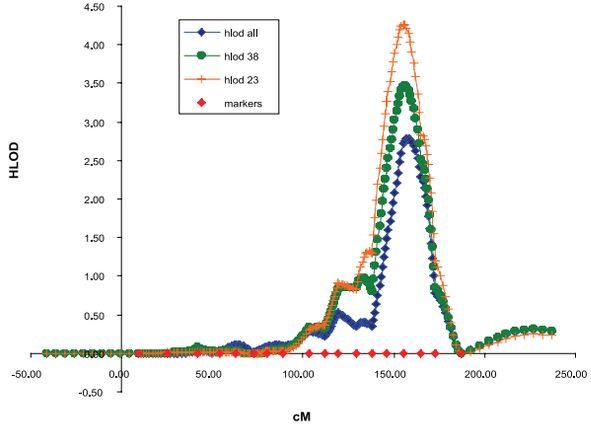
Dr. Bailey-Wilson develops new statistical methods and performs analyses that guide other genome scientists in their hunt for disease-associated genes. Trained in statistical genetics, she is interested in understanding the genetics of complex diseases and developing novel methodologies to disentangle the roles that genes and environment play in disease causation.

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 has been particularly interested in lung cancer since the early 1980s — a time when very few scientists believed there might be a genetic link to the condition. 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. In a collaboration called the Genetic Epidemiology of Lung Cancer Consortium, Dr. Bailey-Wilson and others recently narrowed down the location of a potential lung-cancer gene to a region of chromosome 6. She and her collaborators are continuing the search for this and other lung cancer susceptibility loci.

Dr. Bailey-Wilson has used similar approaches to locate other cancer-related genes. For example, 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 MSR1, which encodes the macrophage scavenger receptor 1. Dr. Bailey-Wilson is focusing on additional susceptibility genes for these and other cancers in ongoing studies.



To keep pace with the analysis of the exponentially increasing number of genetic markers, Dr. Bailey-Wilson also develops and tests novel computational methods. Until relatively recently, fewer than 100 of these "signposts" along the genome had been identified. Now, there are millions of known markers and genome scientists identify more each day. She is also working to address the issue 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 linkage 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 is using association methods that take advantage of linkage disequilibrium data, HapMap data, and the sequence of the human genome to determine the location of genetic loci that increase risk for various diseases. She has used these and other analytical methods to determine, for example, whether alleles at specific marker loci are transmitted along with a disease through generations in families with several affected members. She has also 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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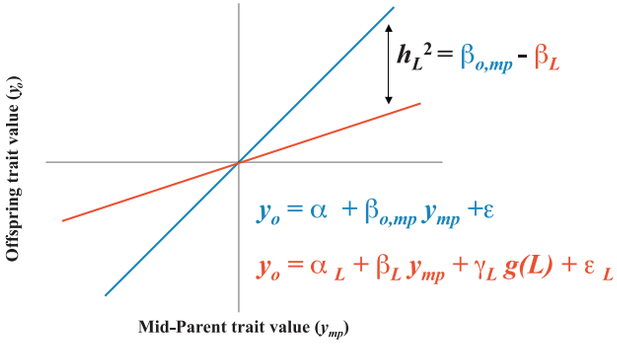
ALEXANDER F. WILSON, Ph.D.

Along with his background in medical genetics and biology, Dr. Wilson uses statistical, mathematical, and computer science approaches to develop new methodologies for performing statistical genetic analysis. He studies continuous or quantitative traits that are caused by both genetic and environmental factors, which are quite different from simple discrete single-gene Mendelian disorders. By analyzing the patterns of hundreds of thousands to millions of genetic markers or variants, Dr. Wilson's group identifies chromosomal regions where the genes for these traits most likely reside.

Dr. Wilson's research covers a wide range of disorders, from scoliosis (extreme curvature of the spine) to obesity and cardiovascular disease. Working with investigators at the University of Colorado, Dr. Wilson's group recently identified five regions that may be responsible for the development of scoliosis, two of which have already been confirmed by other researchers. These discoveries are significant, because scoliosis affects about one in 200 people, most often girls between 10 and 16 years of age. Although many cases of scoliosis are mild, some can be crippling.

Dr. Wilson's group has also been involved with Investigators from the Sequenced Treatment Alternatives to Relieve Depression study in a large collaborative effort aimed at finding genetic factors underlying response to a drug used in treating major depression. In this study, a genetic marker was found in the serotonin 2A receptor 5HTR2A that was associated with patients' response to citalopram, a selective serotonin reuptake inhibitor. Earlier animal studies have shown citalopram to downregulate the 5HTR2A receptor. The identification of this and other markers may lead to a personalized treatment for individuals with depression, a significant departure from the current trial-and-error approach to prescribing antidepressive medications.



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 Mid-Parent (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; obtaining phenotypes of the parents is sufficient when using this method. In a study of high blood pressure, for example, scientists would use ROMP to genotype the offspring while only checking the parents' blood pressures. ROMP is then used to estimate the heritability of the trait and determine whether the locus being studied contains a gene that affects the trait.

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Recent theoretical efforts focus on the development of linear regression methods that use multiple and/or stepwise regression in regions that are bounded by recombination hotspots (areas of increased recombination) over the entire genome. This "tiled regression" approach is being used to test for trait-marker associations in genome-wide association studies and in sequence data; it allows for the inclusion of genetic markers that are physically very close together (in linkage disequilibrium). With this approach, it becomes practical to analyze millions of markers and their significant gene x gene interaction terms.

Dr. Wilson also created a software program called GASP (Genometric Analysis Simulation Program), which enables scientists to create artificial populations or families with different mixtures of genetic and environmental influenced diseases. Because real 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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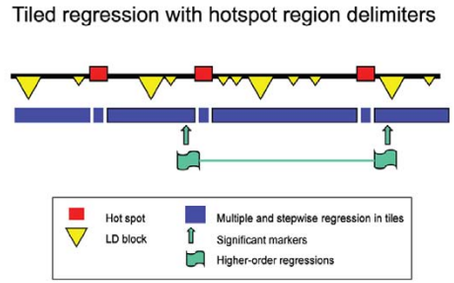


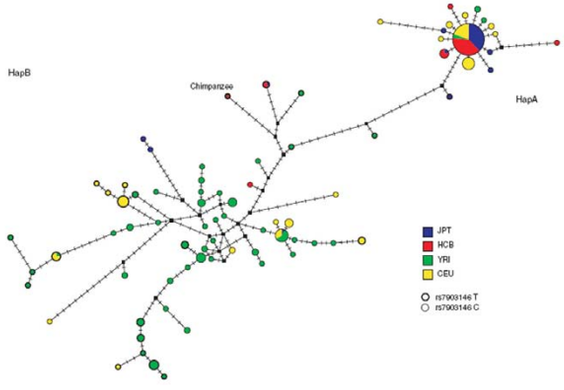
CHARLES N. ROTIMI, Ph.D.

Dr. Rotimi is the Director of the Center for Research on Genomics and Global Health, whose mission is to advance research into the role of culture, lifestyle, genetics, and genomics in health disparities. Dr. Rotimi develops genetic epidemiology models and conducts population genetics research that explores the patterns and determinants of common complex diseases in the African diaspora and other human populations.

A key focus of Dr. Rotimi's research is understanding the triangular relationship between obesity, hypertension, and diabetes, which together account for more than 80% of the health disparity between African Americans and European Americans. Genetic epidemiology models developed by his group are helping to address whether high disease rates are the result of exposure to environmental risk factors, genetic susceptibility, or an interaction between the two.

Dr. Rotimi has been extensively involved in a number of genetic epidemiology projects that are being conducted in several African countries and in the United States. These projects have included the Africa America Diabetes Mellitus (AADM) study, the Howard University Family Study, the Genetics of Obesity in Blacks Study, and the Engagement of African Communities for the International HapMap Project.

Begun in 1998, the AADM study draws upon the expertise of an international group under Dr. Rotimi's leadership that is exploring how genes and lifestyle factors interact to increase diabetes risk or resistance. Study participants have included more than 4,000 West Africans either with diabetes or as part of a control group, with the goal of identifying diabetes susceptibility genes in populations whose ancestors gave rise to most African Americans. In collaboration with colleagues at deCODE Genetics in Iceland, Dr. Rotimi's group recently identified three genes — *TCF7L2*, *CDKAL1*, and *TCF2* (*HNF1*β) — that likely play important roles in diabetes risk.



Dr. Rotimi's group is also engaged in the first genome-wide scan of an African American cohort, with the goal of identifying genes associated with obesity, hypertension, diabetes, and metabolic syndrome. More than 2,000 participants from multigenerational African American families are enrolled in this large-scale genetic epidemiology study. In collaboration with investigators at the Coriell Institute for Biomedical Research, this research will explore how the genome-wide association study (GWAS) approach can inform complex disease mapping in a genetically admixed population such as African Americans.

Dr. Rotimi's group is also participating in the Black Women's Health Study, a national longitudinal study begun in 1995 to determine the underlying cause of selected illnesses in black women. It includes 59,000 women aged 21-69 at the time of enrollment. Over 25,000 DNA samples have been processed to date, and the data derived from these samples are being used in a number of scientific investigations, including those examining the genetic bases of cancer, diabetes, and lupus.

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Since much of his research activity is focused on vulnerable populations, Dr. Rotimi is collaborating with investigators at Case Western Reserve University and the University of Ibadan in Nigeria to study issues related to informed consent in genetics studies. These efforts are investigating whether subjects perceive their participation as voluntary, and whether consented individuals understand the purpose of the genetic studies in which they are participating.

Dr. Rotimi's scientific approach takes broader societal context into account, recognizing both the independence required for good scholarly investigation and researchers' responsibility not to alienate individuals from the scientific process. His group gives particular thought to ways in which scientists document and describe the nonrandom pattern of human genetic variation and its link to disease risks in different populations. By engaging in constructive conversation on these issues, Dr. Rotimi has positioned his group to untangle the complexities of genetic variation within the context of health disparities and group identity.

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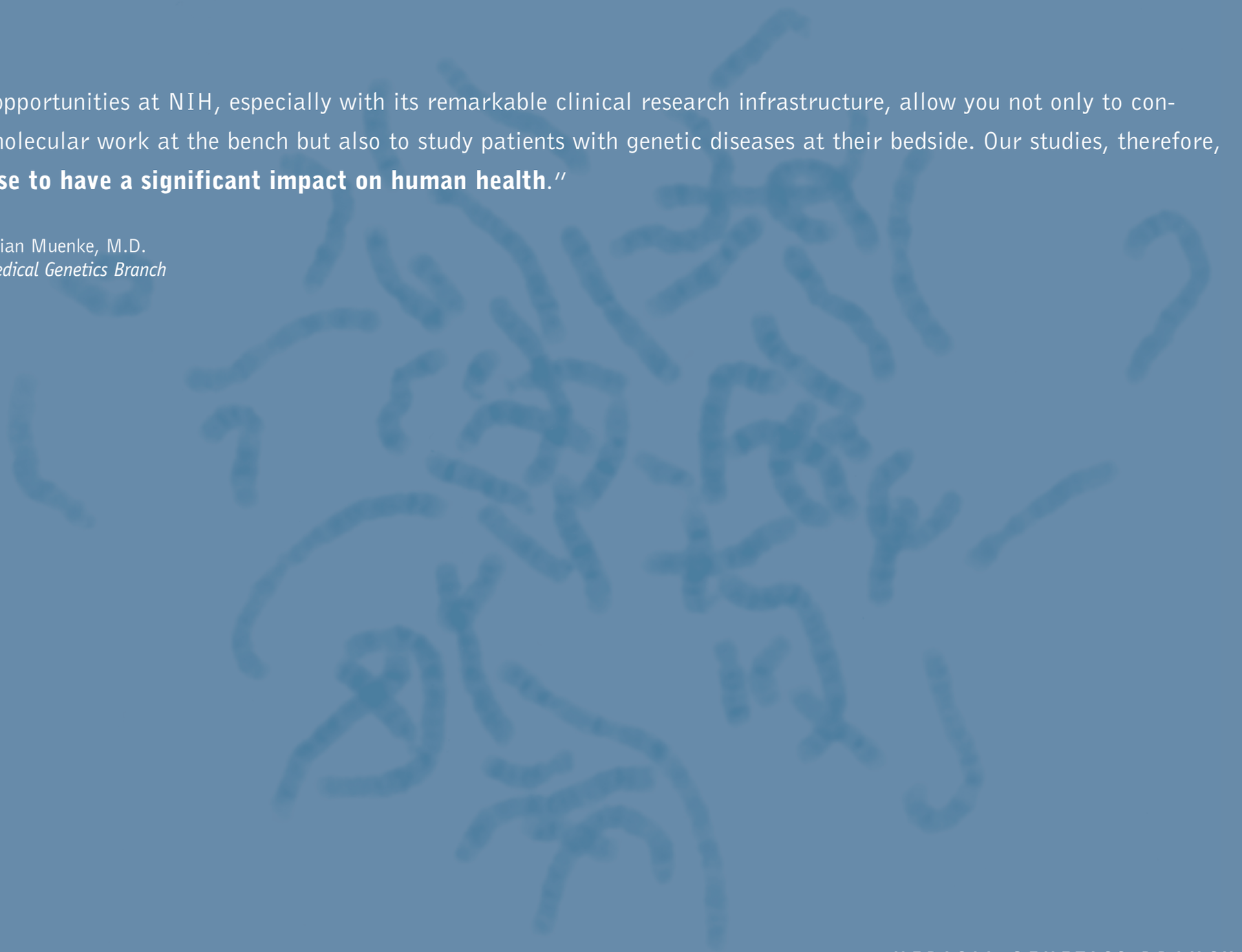
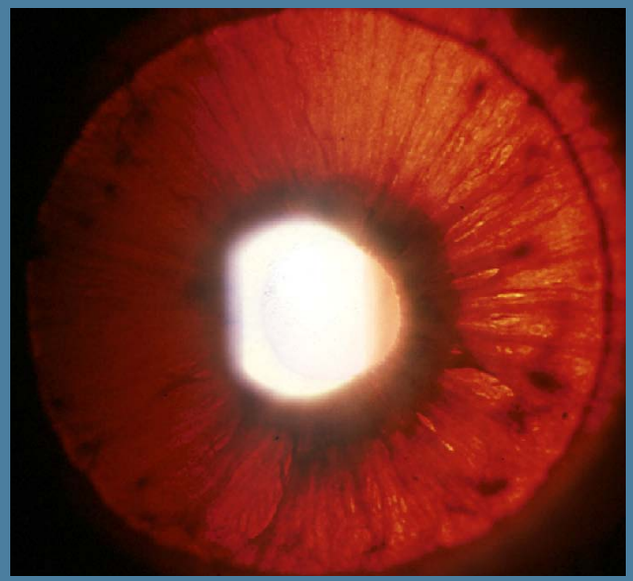
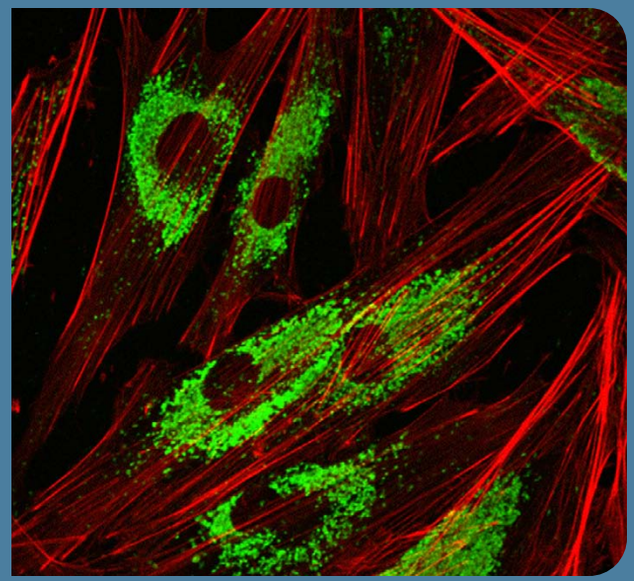
"The opportunities at NIH, especially with its remarkable clinical research infrastructure, allow you not only to conduct molecular work at the bench but also to study patients with genetic diseases at their bedside. Our studies, therefore, **promise to have a significant impact on human health**."

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



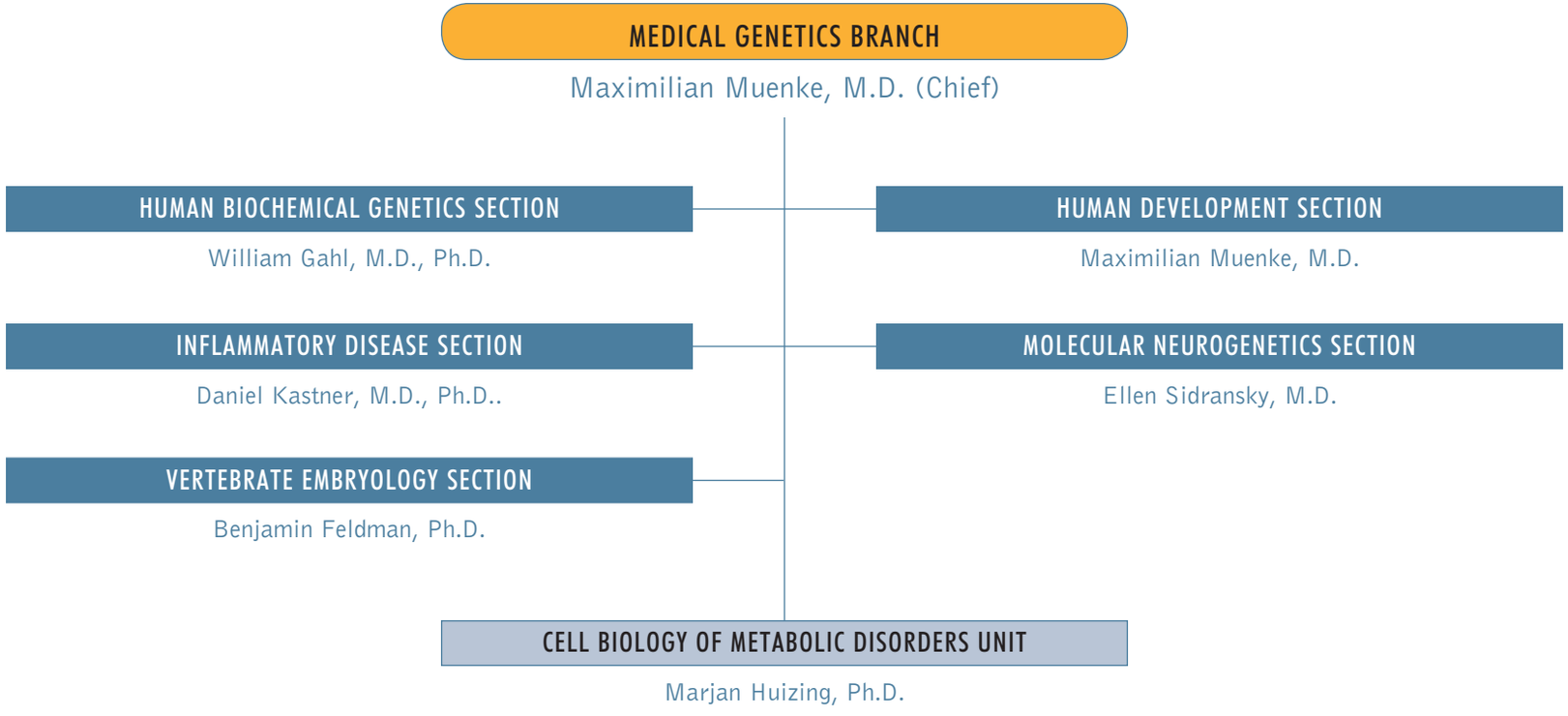
MEDICAL GENETICS BRANCH





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
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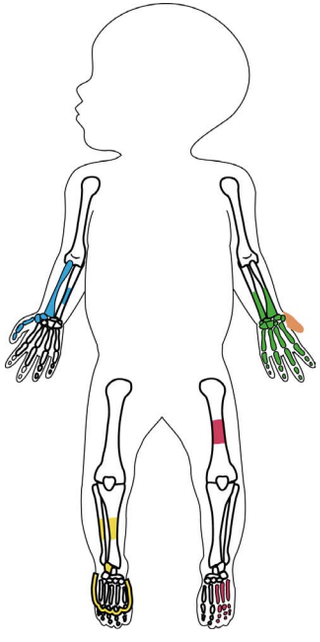
MAXIMILIAN MUENKE, M.D.

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 involve holoprosencephaly (HPE) and attention deficit hyperactivity disorder. HPE, a common brain birth defect that occurs in one in 250 embryos, 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; consequently, the live birth rate is low – approximately one in 10,000. Children born with the disorder show various degrees of developmental disabilities and mental retardation.

Dr. Muenke's laboratory has discovered over ten genes associated with HPE and, in doing so, illuminated a number of key 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 together only account for 20% of documented HPE cases. Thus, Dr. Muenke and colleagues are continuing their hunt for additional genes and other causes contributing to HPE.



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 researchers have found an association in animal models between low maternal cholesterol during pregnancy and birth defects. There have also 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 development, resulting in the growth of some organs 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 4-6% of school-age children and five times as many boys as girls. Characterized by impulsiveness, hyperactivity, and attention problems, ADHD has been recognized as a distinct disorder for many years. Its cause has remained a mystery, although environmental factors were long considered the most likely culprits. Over the past decade, studies of twins, adopted children, and families with a high prevalence of this disorder have shown instead that genetic factors are the major underlying cause of ADHD.

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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 with other behavioral disorders, such as nicotine dependence. By studying this population, Dr. Muenke's laboratory has now identified several candidate genomic regions for ADHD and is currently performing fine-mapping studies to identify specific contributing genes. His group is 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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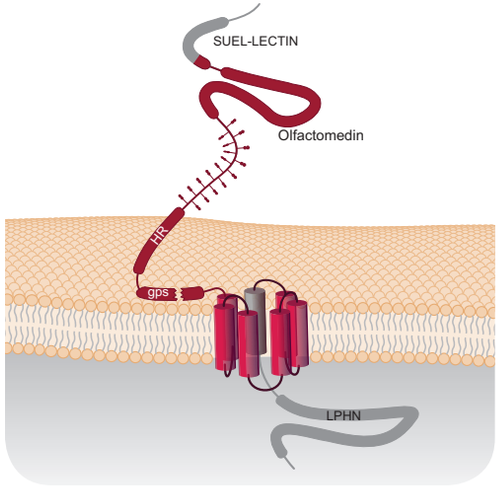
MAURICIO ARCOS-BURGOS, M.D., Ph.D.

Dr. Arcos-Burgos studies neurodevelopmental disorders and related conditions using approaches from the fields of clinical genetics, genetic epidemiology, and population genetics. The main focus of his research is on understanding the genetic basis for attention deficit hyperactivity disorder (ADHD), the most common childhood behavioral disorder.

ADHD affects more than 4.4 million people in the United States. Affected individuals are at an increased risk for poor educational achievement, low income, underemployment, legal difficulties, and impaired social relationships. The cost ascribed to ADHD in the United States is an estimated $42.5 billion per year. Genetic factors are strongly implicated in ADHD's etiology, and it is estimated that up to 70% of the ADHD phenotype is explained by genetic factors. Dr. Arcos-Burgos endeavors to dissect and study the biological component of ADHD.

Dr. Arcos-Burgos used positional cloning approaches to discover a gene called *LPHN3;* a common variant of this gene confers a major risk of susceptibility to developing ADHD. Functional studies revealed that *LPHN3* variants are expressed in key brain regions related to attention and activity. Further, these variants affect metabolism in neural circuits implicated in ADHD and are associated with response to stimulant medication. Preliminary studies suggest that incidence of ADHD in the general population would be reduced by about 9% if the effect of the *LPHN3* variant that confers susceptibility to ADHD were controlled. These findings were replicated in samples obtained from around the world, opening a window into the evaluation of molecular substrates of ADHD and the development of new drugs targeting specific genes and developmental pathways in the brain involved in the disorder.



With colleagues in the Human Development Section of NHGRI's Medical Genetics Branch, Dr. Arcos-Burgos is engaged in an array of additional ADHD research projects. This collaborative work involves the study of endophenotypes, which are new phenotypic constructs

associated with ADHD. Deep sequencing of regions potentially associated with regulation and generation of *LPHN3* mRNA isoforms will also be performed. Using functional assessment magnetic resonance imaging, the group hopes to identify brain patterns associated with ADHD. Additional loci conferring susceptibility to ADHD will be cloned in order to dissect any potential interactions with *LPHN3*, and pharmacogenetic studies to identify the individual genetic background associated with response to treatment in ADHD patients will be undertaken.

Over the past 20 years, Dr. Arcos-Burgos has conducted population genetics studies of the genetically isolated Paisa community of Colombia. He has recruited thousands of members of multigenerational and extended families, in which complex genetic conditions such as idiopathic epilepsy, Alzheimer's disease, nonsyndromic facial clefting (NSFC) and vitiligo have clustered with high prevalence. Using information from more than 600 pedigrees of families in which NSFC has been observed, he has been able to identify several loci conferring susceptibility to facial malformation through positional cloning approaches; these loci include *IRF6* and *FOXE1*.

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Dr. Arcos-Burgos has also participated in several whole-genome linkage and association projects aimed at cloning genes responsible for Mendelian and non-Mendelian inherited conditions. He coordinated the physical cloning of the *SLC6A19* gene, the human homolog of a well-characterized mouse gene called B0AT1. The mutant allele of this gene is one of the genes responsible for Hartnup disorder, a metabolic disorder characterized by impaired transport of neutral amino acids across epithelial cells in the kidney and intestines. People with the disorder experience transient rashes, cerebellar ataxia, and psychosis. He also participated in cloning the *KCNJ10* gene, which encodes a potassium channel expressed in the brain, inner ear, and kidney. Sequencing of this candidate gene revealed homozygous missense mutations in the DNA of infants affected by a combination of epilepsy, ataxia, deafness, and kidney disease.

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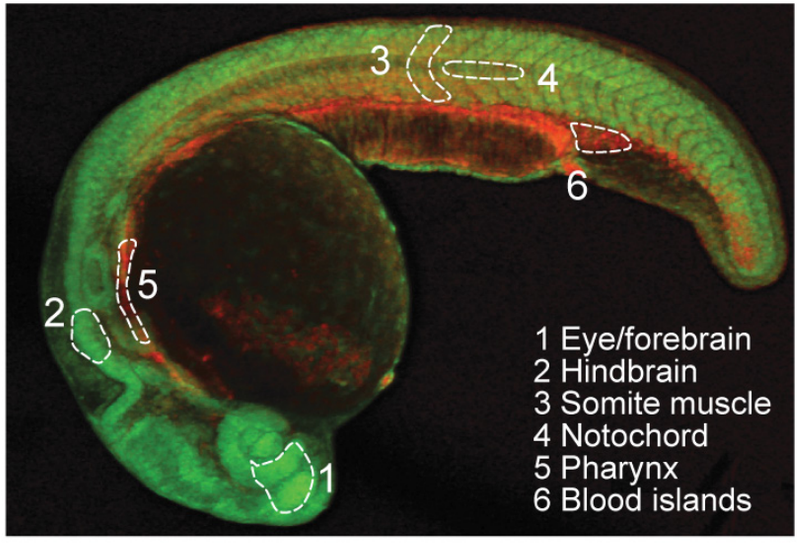
BENJAMIN FELDMAN, Ph.D.

Dr. Feldman utilizes genomic, molecular and developmental biology strategies to investigate the genetic basis of germ layer formation during early embryogenesis, and how errors in this process cause common birth defects. He is pursuing this research in zebrafish, a vertebrate model organism with embryos that are amenable to a wide range of experimental interventions. Germ layer formation establishes the mesoderm, endoderm and ectoderm lineages during gastrulation and is evolutionarily conserved in animals ranging from flatworms to humans. Elucidating the genetic basis of germ layer formation is essential to understanding the human genome and to identifying the genetic risks for gastrulation-related birth defects and pregnancy loss.

In vertebrates, normal mesoderm and endoderm (mesendoderm) formation requires the controlled production and delivery of Nodal-related ligands (Ndrs), which are members of the TGF beta superfamily. Prior to joining NHGRI, Dr. Feldman contributed to this understanding through his analysis of zebrafish with mutations in two Nodal-related genes: *ndr1*, also called *squint*, and *ndr2*, also called *cyclops*. Zebrafish with mutations in either of these genes develop holoprosencephaly; Dr. Feldman showed that *ndr1;ndr2* compound mutants lack all endoderm and anterior mesoderm. He also found that two Nodal antagonists, Lefty1 and Lefty2, are essential for limiting excess Ndr1 signaling and excess mesoderm and endoderm formation.



At NHGRI, Dr. Feldman has continued his investigations into Nodal signaling. His studies in this area have focused on Foxh1, a transcription factor that plays a key role in the Nodal-signaling pathway. Dr. Feldman's laboratory has shown that maternal Foxh1 found in developing embryos controls production of certain keratin proteins that are essential for viable gastrulation. The role of Foxh1 in this process is distinct from its role in Nodal signaling. His laboratory has also identified a number of environmental and genetic factors, such as temperature and the heat shock protein Hsp90, that influence the frequency of holoprosencephaly in zebrafish with a mutation in the *ndr1* gene. In addition, and in line with NIH and NHGRI's mission in promoting translational research, Dr. Feldman has worked with colleagues in the Medical Genetics Branch to elucidate risk factors for human holoprosencephaly and congenital heart defects, and to develop a model for Costeff syndrome that he used to shed light on biochemical aspects of this infantile-onset metabolic disorder.

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Dr. Feldman's principal research efforts have focused on the early embryonic mechanisms that initiate, complement and respond to signaling by Ndrs. As a starting point, Dr. Feldman and colleagues developed a flexible method for embryonic dissection which they used to identify genes expressed in newly formed mesoderm and endoderm and in the adjacent yolk, where uncharacterized RNAs with mesoderm and endoderm-inducing activity reside. The Feldman laboratory's future work is dedicated to determining the functions of proteins encoded by these genes. Using a novel high-throughput time-lapse documentation system they created, they will identify developmental anomalies that arise in zebrafish embryos in which translation of signaling proteins or transcription factors has been blocked via introduction of antisense nucleic acid analogs. They also plan to systematically analyze the expression and cross-regulation of the transcription factors expressed in the newly formed mesoderm and endoderm, with the goal of defining a comprehensive gene regulatory network underlying their specification.

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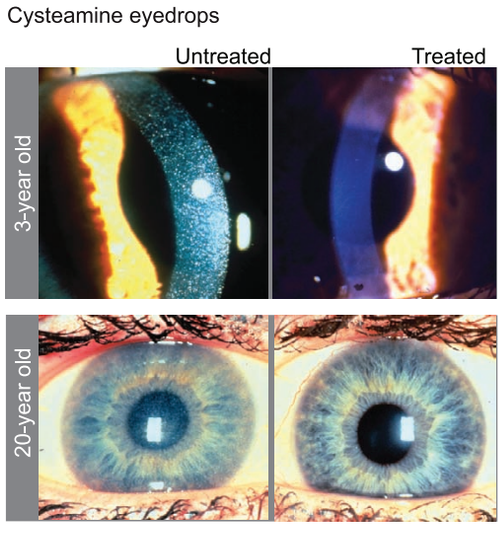
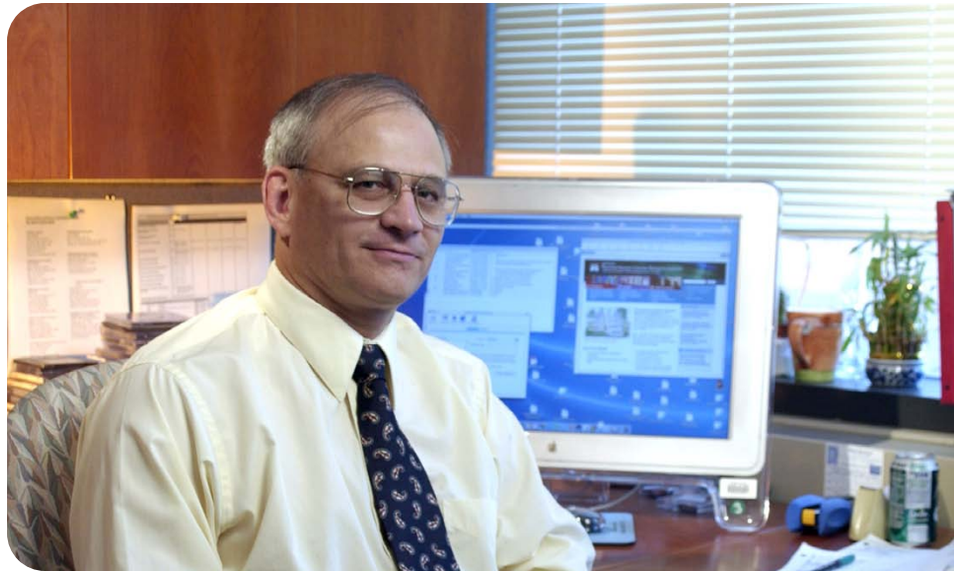
WILLIAM A. GAHL, M.D., Ph.D.

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 diseases, including cystinosis, Hermansky-Pudlak syndrome, alkaptonuria, and disorders of sialic acid metabolism.

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 improved the future for many cystinosis patients from a life filled with debilitating complications to one marked by chronic yet manageable symptoms. Dr. Gahl's group is following about 125 pre- and post-transplant cystinosis patients to track their clinical course, identify additional mutations, and document complications of the disease and therapy.



Another of Dr. Gahl's major research areas is Hermansky-Pudlak syndrome (HPS), a group of vesicle formation and transport disorders characterized by albinism and bleeding. In some cases, HPS is also 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 demonstrated that an anti-fibrotic agent shows promise in slowing the development of the fatal lung disease of some HPS patients.

His laboratory also studies alkaptonuria, a condition in which mutations in the HGD gene cause a buildup of homogentisic acid (HGA), which discolors the eyes and damages the connective tissues in major joints and cardiac valves. Dr. Gahl's group conducted a three-year clinical trial of nitisinone, an inhibitor of HGA production; the results are currently being analyzed for publication.

Dr. Gahl also studies disorders of sialic acid, a charged sugar. Deficiency of sialic acid production causes a severe muscle-wasting disease that often forces patients into wheelchairs, ultimately leading to death by respiratory

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failure. Excess sialic acid is also 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.

Dr. Gahl's group includes national experts in autosomal recessive polycystic kidney disease and congenital hepatic fibrosis, Chediak-Higashi syndrome, and Gray Platelet syndrome, and additional expertise is accruing in different types of albinism.

Dr. Gahl also directs the NIH Undiagnosed Diseases Program (UDP), an initiative that attempts to obtain a diagnosis for patients who have long been unable to achieve that goal. The UDP intends to identify new diseases that will provide insights into normal cell biology, biochemistry, and physiology.

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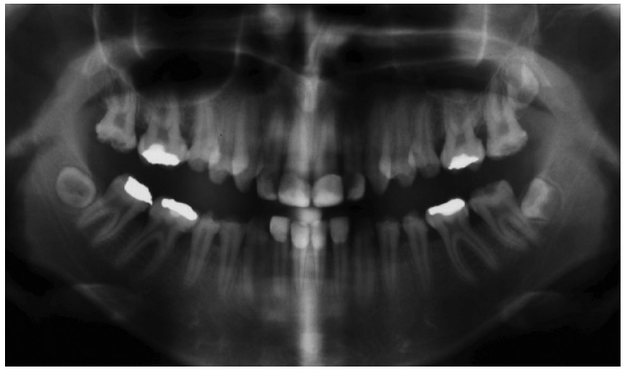
SUZANNE HART, Ph.D.

An American Board of Medical Genetics-certified clinical biochemical geneticist and medical geneticist, Dr. Hart uses molecular and biochemical techniques to understand genetic diseases of the teeth, the oral cavity, and the kidney.

Gingival tissue plays an important role in tooth development, with gum health contributing to overall well-being, appearance, and the ability to eat and speak properly. Overgrowth of the gums can occur as an isolated inherited condition, as part of a genetic syndrome, or as a side effect of certain medications. In 2002, Dr. Hart and colleagues discovered the only gene mutation known to be involved in hereditary gingival fibromatosis (HGF), a rare autosomal dominant form of gum overgrowth. The mutated gene, *SOS1*, normally encodes a protein that activates the ras pathway, a key growth signaling pathway in cells. The Hart laboratory is also studying syndromic forms of gingival overgrowth, such as Zimmerman-Laband syndrome and juvenile hyaline fibromatosis, as well as gingival overgrowth attributed to various medications.

In a related area of study, Dr. Hart investigates the molecular causes of disorders that affect the enamel or dentin inside teeth. Of particular interest to her research are isolated tooth defects, as well as syndromes where tooth anomalies occur. The genes expressed in the developing tooth are difficult to analyze; teeth are mineralized structures. Therefore, the isolation of RNA needed to study gene expression in teeth is difficult. Her group conducts mutation analysis and uses linkage-type approaches to study genes involved in normal tooth development, and has discovered mutations in a number of these (e.g., *AMELX, ENAM, KLK4, MMP20,* and *DSPP*). A large collection of samples compiled by Dr. Hart's group since 1991 forms the foundation for this research. These samples are routinely re-examined as new genomic technologies become available, enabling the identification of additional genes involved in the development of tooth defects.



Dr. Hart collaborated with the research group that identified the *CTCS* gene, which was found to be mutated in Papillon-Lefevre syndrome. This autosomal recessive disorder is characterized by keratosis of the palms and soles of the feet, as well as pronounced periodontal disease. Children with this condition suffer mouth inflammation and problems with their newly erupted teeth. Primary teeth are typically lost by age 4, with further exfoliation and loss of permanent teeth by age 20.

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Dr. Hart also conducts research on medullary cystic kidney disease (MCKD), an inherited disorder associated with gradual loss of kidney function. In 2002, Dr. Hart and colleagues identified *UMOD* on chromosome 16 as the causative gene in MCKD type 2, a hereditary endoplasmic reticulum storage disease associated with kidney failure. They have also identified *REN* mutations as the cause of one form of anemia and chronic kidney failure. Currently, her laboratory is actively trying to identify the causative gene for MCKD type 1, a disorder in which patients have normal kidney function through childhood but later develop renal failure and ultimately require kidney transplantation. The identification of the underlying genetic causes of various forms of kidney disease may lead to new therapeutic approaches.

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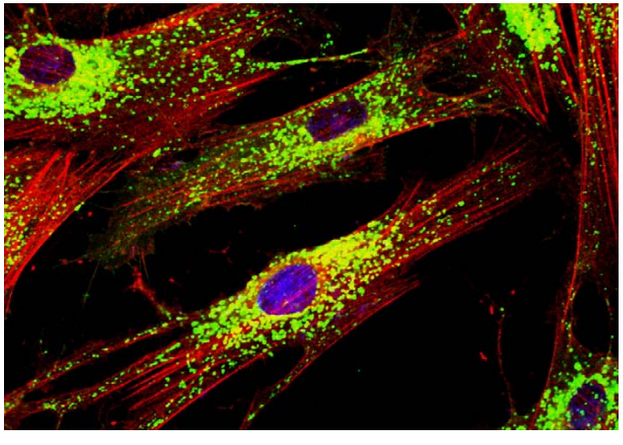
MARJAN HUIZING, Ph.D.

Dr. Huizing's group investigates rare human genetic disorders and associated intracellular processes in order to gain insight into the changes in molecular function that underlie various genetic metabolic disorders, with the hope of developing treatments for these illnesses. Her research focuses on disorders of sialic acid metabolism and of lysosome-related organelles.

Sialic acid is a negatively charged sugar localized at the end of glycoconjugate chains on glycoproteins and glycolipids. These chains are present on the cell surface and are crucial for many biological processes, including cell adhesion and signal transduction. Sialic acid synthesis is tightly regulated; defects in this pathway cause a variety of disorders, including hereditary inclusion body myopathy (HIBM), sialuria, infantile sialic acid storage disease (ISSD), and Salla disease.

HIBM is caused by mutations in the gene encoding the key enzyme in sialic acid synthesis, UDP-GlcNAc 2-epimerase/ManNAc kinase, which in turn leads to sialic acid deficiency. Without adequate supplies of sialic acid, progressive muscle degeneration (or myopathy) sets in. Dr. Huizing's group has demonstrated that muscle α-dystroglycan, an integral component of the muscle transmembrane dystrophin-glycoprotein complex, is low in sialic acid in HIBM patients. Based on this observation, they developed a mouse model mimicking HIBM. These mice die of unexpected glomerular disease due to hyposialylation of kidney glycoproteins, leading to severe proteinuria and hematuria. Oral administration of the sialic acid precursor N-acetyl-mannosamine (ManNAc) partially rescues the kidney defect, allowing the mutant mice to survive. Dr. Huizing's group is currently evaluating the use of ManNAc not only as a treatment for HIBM, but also for renal disorders involving glomerular disease-associated proteinuria and hematuria.



Dr. Huizing also studies other sialic acid-related diseases, including sialuria, a progressive disease in which patients produce excess sialic acid. Symptoms can include developmental delay, coarse features, and liver enlargement. Sialuria appears to be due to a single mutation that causes a change in the three-dimensional structure of the active site of the UDP-GlcNAc 2-epimerase/ManNAc kinase enzyme. Dr. Huizing's group demonstrated that elimination of the single mutant allele using a synthetic small interfering RNA (siRNA) rescued the abnormal phenotype in cultured cells from sialuria patients. In ISSD and Salla disease, other sialic acid-related conditions, a transport malfunction causes sialic acid to accumulate in lysosomes. Dr. Huizing's group is evaluating possible steps to alleviate this sialic acid accumulation in cultured cells from ISSD and Salla patients.

Dr. Huizing is also investigating the causes of and potential treatments for disorders of lysosome-related organelles (LROs), including Hermansky-Pudlak syndrome (HPS), Chediak-Higashi syndrome, and Griscelli syndrome. A rare inherited disorder that has been identified in about 400 people worldwide, HPS is mainly characterized by decreased pigmentation

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(ocular or cutaneous albinism) and a lack of platelet dense bodies that causes bleeding problems. The disease can lead to prolonged bleeding and poor function of the lungs and intestine; fatal pulmonary fibrosis is a possible complication. An ongoing clinical trial at NHGRI is testing the drug pirfenidone as a potential HPS treatment for symptoms associated with pulmonary fibrosis.

Dr. Huizing's group continues to search for novel genes causing LRO disorders, with the hope of better understanding the biological causes of these conditions. She played a major role in identifying six distinct genetic subgroups of HPS patients by cataloging relevant clinical and genetic characteristics. To study the effects of LRO-related gene mutations, Dr. Huizing is performing fluorescent protein expression studies using patients' cells in order to examine defective intracellular trafficking. These results will be instructive for elucidating the complex vesicular transport processes that are involved in the biogenesis of LROs.

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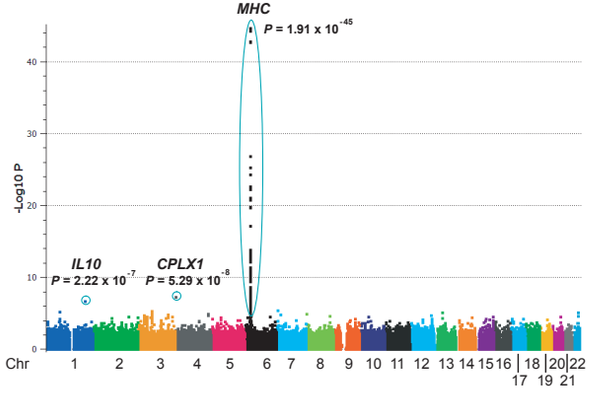
DANIEL L. KASTNER, M.D., Ph.D.

The Inflammatory Disease Section studies the genetics, pathophysiology, and treatment of inherited disorders of inflammation through an integrated clinical and laboratory program. Having recently moved to NHGRI from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the group has investigated Mendelian and genetically complex inflammatory disorders for the last twenty years, and proposed the now widely-accepted concept of autoinflammatory disease for a class of disorders of innate immunity.

Many of the Section's most important projects began with patient encounters in the NIH Clinical Center. As a rheumatology fellow, Dr. Kastner saw a patient with familial Mediterranean fever (FMF), a recessively inherited disorder characterized by episodes of fever, serositis, arthritis, and skin rash. The Kastner group utilized classical linkage analysis to map the FMF gene to chromosome 16p, and subsequently led an international consortium that identified the underlying gene by positional cloning in 1997. The gene encodes a protein (pyrin) that is the prototype for a motif found in some 20 human proteins involved in inflammation and apoptosis. Animal model studies carried out in the laboratory demonstrated that the pyrin protein regulates inflammation through interleukin 1 (IL-1), a cytokine produced in white blood cells. This finding has advanced new therapies targeting IL-1 in FMF patients who are unresponsive to, or intolerant of colchicine, the previously established treatment for this illness.

Following an Irish patient with prolonged febrile episodes similar to FMF, the Kastner group discovered that mutations in the 55 kDa receptor for tumor necrosis factor (TNF) define a dominantly-inherited syndrome that the group named TNF receptor-associated periodic syndrome, or TRAPS. Drawing upon functional immunologic studies of TRAPS patients, the group pioneered the use of etanercept, a recombinant TNF receptor fusion protein, for the treatment of TRAPS. Based on another patient seen in the clinic, the group discovered that mutations in *NLRP3*, which encodes a pyrin domain-containing regulator of IL-1, cause a devastating inflammatory disorder of the skin, bones, and central nervous system known as neonatal-onset multisystem inflammatory disease, or NOMID. Mutations in another protein identified in the Section as a pyrin-binding molecule cause the dominantly inherited syndrome of pyogenic arthritis, pyoderma gangrenosum, and acne. Subsequently, a therapeutic trial conducted at the NIH Clinical Center established that anakinra, a recombinant IL-1 receptor antagonist, dramatically attenuates inflammation in patients with NOMID. More recently, in collaboration with colleagues at NIAMS, the Kastner group discovered a recessively inherited, anakinra-responsive illness known as DIRA (deficiency in the IL-1 receptor antagonist), which is caused by mutations in the endogenous IL-1 receptor antagonist gene.



With the North American Rheumatoid Arthritis Consortium, the Section discovered that variants in the T-cell signaling molecule STAT4 predispose to rheumatoid arthritis, systemic lupus erythematosus, and Sjögren's syndrome. In 2010, the Section completed a genome-wide association study demonstrating that variants of the genes encoding interleukin 10 (IL-10) and the interleukin 23 (IL-23) receptor predispose an individual to Behçet's disease, a genetically complex disorder characterized by the triad of oral, ocular, and genital inflammation.

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The Section continues to pursue a vigorous program in translational research. Its clinicians have seen a total of over 1300 patients with various autoinflammatory diseases at the NIH Clinical Center. In the laboratory, work aimed at better understanding the genetics of Behçet's disease is ongoing, now focusing on disease subsets, common copy number variants, and deep resequencing for rare variants. Members of the group are currently leading an international consortium searching for susceptibility loci for systemic onset juvenile idiopathic arthritis (also known as Still's disease) using a genome-wide association approach. Whole-exome sequencing is being used in selected families with apparent monogenic disorders to discover new inherited disease loci. The group continues to study pyrin and related proteins, using animal models and biochemical approaches. In collaboration with NIAMS, the Kastner group also continues active therapeutic clinical protocols in several autoinflammatory diseases.

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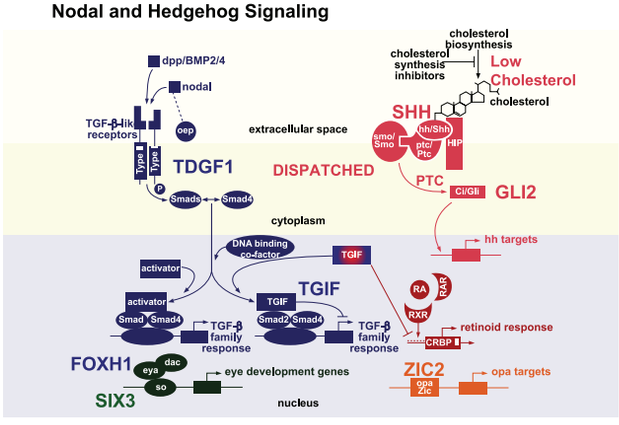
ERICH ROESSLER, M.D., Ph.D.

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. One of his main areas of interest is on the genetics of early embryonic development of the vertebrate axial midline and forebrain, and establishment of the left-right axis (laterality).

These crucial developmental steps occur during the first month in the life of a human fetus, and are critical for proper human development and cognitive function. Studies of the complex interplay between genetic and environmental influences on early development of the forebrain are an important foundation for future advances in molecular medicine and our detailed understanding of complex genetic mechanisms and signaling networks. Dr. Roessler has worked for many years with Dr. Muenke studying holoprosencephaly (HPE), a 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 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), which results when forebrain cleavage never occurs. Working with Dr. Muenke and others, Dr. Roessler identified the first gene behind HPE in humans, known as *Sonic Hedgehog*, and demonstrated that the condition in well over a hundred affected families can be attributed to mutations in this gene. Since this discovery, over a dozen human genes have been shown to play a significant role in HPE. Dr. Roessler runs the clinical diagnostic laboratory performing mutation testing for a large number of these HPE genes, providing his expertise to clinicians worldwide.

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Dr. Roessler also focuses on identifying new human genetic mutations within coding and regulatory elements that contribute to common birth defects, and demonstrating how these mutations lead to developmental disturbances. To specifically understand more about human birth defects, Dr. Roessler investigates and extrapolates from the basic mechanisms involved in vertebrate body plan development, since these conserved processes are directly implicated in the causation of human birth defects. Furthermore, these essential human-based studies demonstrate the similarities and differences between humans and model organisms with respect to the genetic and environmental influences on birth defect causation.

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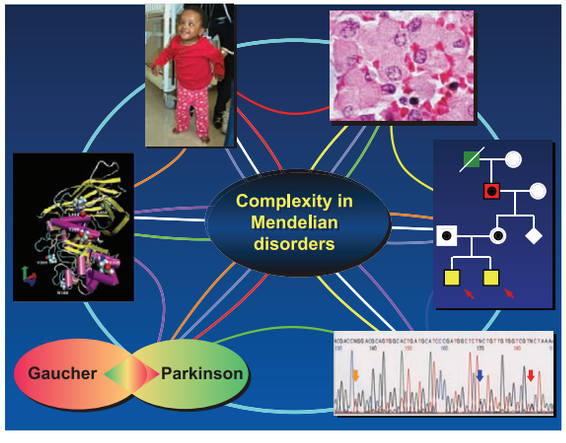
ELLEN SIDRANSKY, M.D.

Dr. Sidransky's research focuses on Gaucher disease, a rare recessively inherited condition 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, her research goal is the translation of basic research findings into new therapeutic approaches for this and other inherited diseases. She and her colleagues have also discovered potential links between Gaucher disease (a single-gene disorder) and Parkinson disease (a multi-gene disorder).

Gaucher disease results from mutations in the *GBA* gene, which codes for the enzyme glucocerebrosidase. This lysosomal enzyme is responsible for breaking down a fat called glucocerebroside. People with Gaucher disease cannot properly produce this enzyme; therefore, glucocerebroside in their cells is not degraded 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 of the lysosomal storage disorders. It is the most prevalent hereditary disorder among Ashkenazi Jews, of whom about 1 in 15 are carriers, compared with about 1 in 100 in the general population. Currently, the primary treatment for Gaucher disease is enzyme replacement therapy, requiring life-long intravenous infusions every two weeks, a regimen that is inconvenient and extremely expensive.

For reasons still not well-understood, the manifestations of Gaucher disease vary dramatically. Some people with glucocerebrosidase deficiency have no symptoms, whereas some have enlarged spleens and livers, bone problems, blood abnormalities, and growth retardation. Others have devastating lung, skin and nervous system manifestations. Although almost 300 different disease-associated mutations in *GBA* have been identified, patients with the same genotypes can have variable clinical manifestations (or phenotypes). Thus, patient genotyping is not always a reliable guide for prognosis, therapy or genetic counseling. Rather, researchers have to rely on careful phenotyping to guide their studies.



Dr. Sidransky's research has shown that, while patients have traditionally been classified into three distinct

phenotypes, their symptoms actually form a continuum; her laboratory has described several new Gaucher phenotypes along this spectrum. For example, studies of a *GBA*-knockout mouse model helped her group identify a previously unrecognized phenotype involving prenatal or immediate postnatal death. They also described the clinical and genetic characteristics of a rare Gaucher phenotype with myoclonic epilepsy, characterized by quick jerks of the arms, shoulder and legs.

Dr. Sidransky and her colleagues continue to explore the vast phenotypic heterogeneity associated with Gaucher disease by sequencing and comparing the *GBA* gene and nearby genomic regions in patients who share atypical phenotypes, with the hope of improving our understanding of the genotype-phenotype relationship. Their studies show that the GBA gene lies in a gene-rich region of chromosome 1q. Interestingly, a closely related pseudogene nearby plays a role in causing some mutations that result in Gaucher disease.

A second major project in Dr. Sidransky's laboratory involves investigating an association between mutations in the GBA gene and Parkinson disease. Her group discovered that patients and families carrying GBA

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mutations had an increased incidence of this disorder. In several subsequent studies, analyses of samples from patients with Parkinson disease and Lewy body dementia showed that *GBA* mutations were more frequent than anticipated. Additional studies performed at centers around the world confirm that heterozygosity for *GBA* mutations is an important risk factor for Parkinson disease and related disorders. A multicenter collaborative study among Parkinson disease patients demonstrates *GBA* mutations are the most common inherited risk factor identified to date. Indeed, subjects with Parkinson disease are over five times more likely than their healthy counterparts to carry a *GBA* mutation . This insight has given Parkinson disease researchers a new exciting avenue for studying the mechanisms and treatment of different neurodegenerative disorders.

In collaboration with the NIH Chemical Genomics Center, Dr. Sidransky's laboratory has also screened collections of thousands of small molecules to discover potential new therapies for patients with Gaucher disease. Their initial screening has identified three novel classes of drugs that may allow the mutant enzyme to function. This approach offers promise for new treatments for Gaucher disease patients, and may also have implications for the treatment of some individuals with Parkinson disease.

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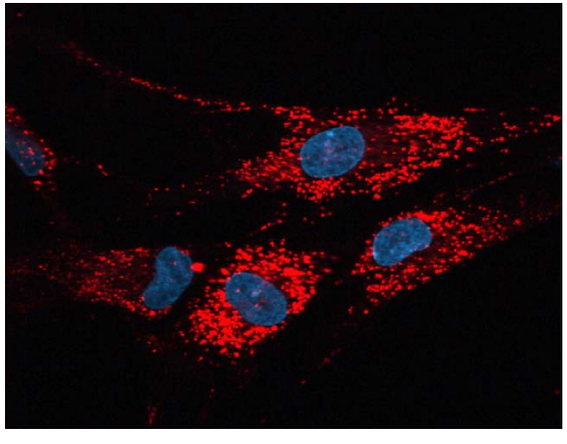
CYNTHIA J. TIFFT, M.D., Ph.D.

Dr. Tifft's research focuses on lysosomal storage disorders (LSDs), particularly those that affect the central nervous system. With more than 20 years of experience as a clinical geneticist, Dr. Tifft is expert in the diagnosis and treatment of LSDs. In collaboration with colleagues at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), she is using mouse models to elucidate the pathophysiology of disease progression in a number of these conditions.

Her research has shown neurodegeneration to be an inflammatory process involving the activation of microglia and astrocytes, a process that can be slowed by bone marrow transplantation or treatment with small molecules such as migluatat and other selected anti-inflammatory agents. Her findings are directly applicable to the study of two LSDs in particular — Tay-Sachs and Sandhoff diseases — and have been extended to other glycosphingolipid storage disorders, including GM1 gangliosidosis.

Tay-Sachs disease is an autosomal recessive disorder caused by a deficiency of the enzyme hexosaminidase A, which leads to the accumulation of a lipid called GM2 ganglioside, predominantly in brain tissues. Incidence had historically been high among Ashkenazi Jews, but effective carrier screening introduced in the mid-1970s has reduced incidence in this group by more than 90 percent. Currently, only a third of the 20 to 25 patients diagnosed with Tay-Sachs each year in the United States are of Jewish heritage.



In the classic infantile form of Tay-Sachs disease, a child experiences normal development for the first six months, reaching a plateau in skills development and the onset of seizures usually before the child's first birthday. Relentless neurodegeneration continues, leading to death between two and five years of age. Sandhoff disease and GM1 gangliosidosis are related ganglioside storage disorders that have no strong ethnic predilection. There are no effective therapies for these diseases.

Dr. Tifft is conducting an ongoing natural history study of glycosphingolipid storage disorders to identify biomarkers in cerebrospinal fluid and other tissues that correlate with disease progression. She applies her knowledge of biomarkers and disease progression as a member of the Scientific Advisory Group for the Tay-Sachs Gene Therapy Consortium, where she designs outcome measures for clinical trials that use gene therapy and other therapeutic modalities.

Dr. Tifft also is interested in diagnosis and surveillance of children with neurofibromatosis type 1. Her clinical research has shown that screening with magnetic resonance imaging of the brain in newly diagnosed patients detects clinically significant pathology prior to the onset of symptoms.

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She has participated in multi-center clinical trials of enzyme replacement therapy for the treatment of Gaucher, Fabry, and Pompe diseases and has recently completed an investigator-initiated study on the treatment of GM2 gangliosidosis using substrate reduction therapy.

Dr. Tifft serves as the Director of Pediatrics for the NIH Undiagnosed Diseases Program. In this role, she applies her expertise in cell biology and storage disorders to design screening assays of tissues from patients referred to the program. Her study of structural abnormalities in lysosomes and other cellular organelles is applied in combination with other functional and gene sequencing studies to heighten the potential for identifying new diseases.

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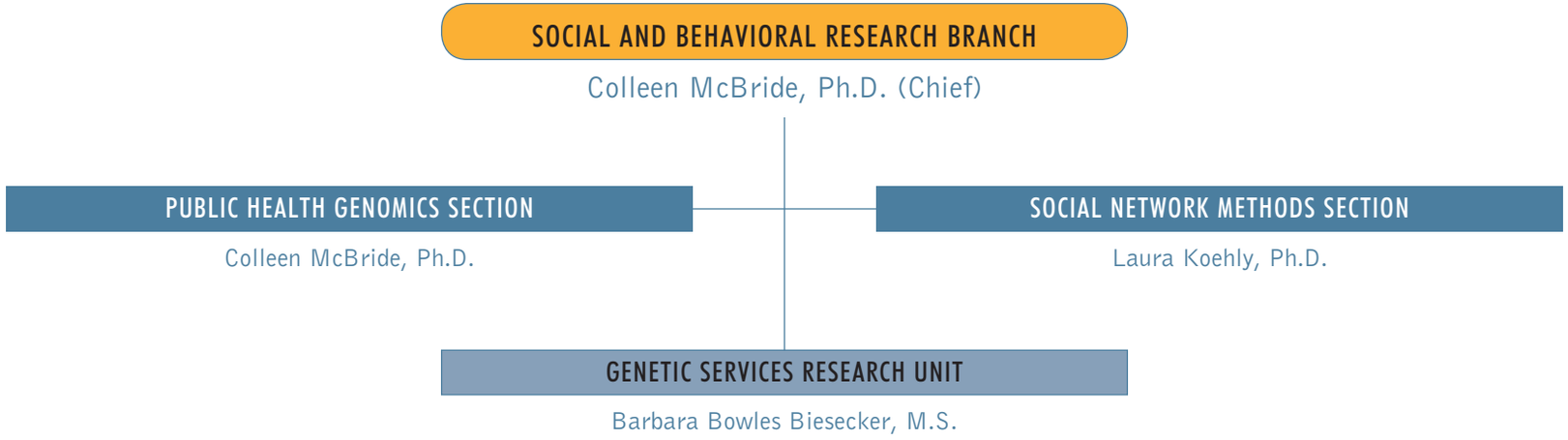
"This field is wide open, full of mystery, evolving rapidly, and divergent. **Our charge is to be among the trailblazers**. We all have the ultimate objective to promote public health and well-being."

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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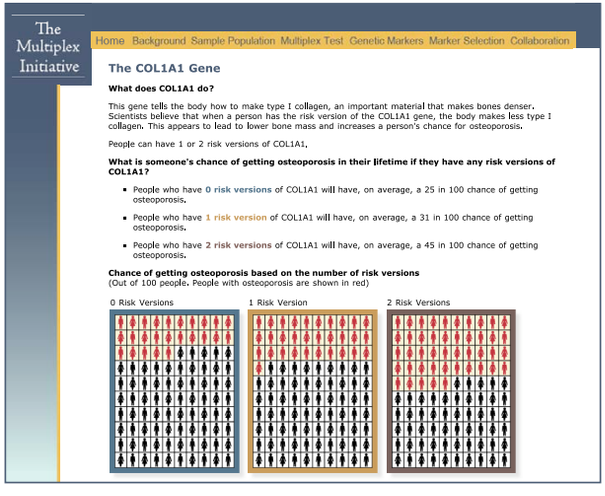
COLLEEN M. McBRIDE, Ph.D.

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. A central assumption regarding genetic discovery is that it will eventually allow lifestyle interventions to be personalized in ways that make compliance easier which, in turn, would make them more effective in lowering disease risk. Currently, new genetic information is primarily being used to personalize risk communications under the assumption that, given this individualized information, people will then be motivated to adopt healthier lifestyles.

Private companies have recently started marketing genetic tests called "multiplex" genetic profiles. These profiles test simultaneously for multiple gene variants, suggesting that these variants increase one's risk for a variety of common diseases. A number of laboratories are advertising and/or offering multiplex tests direct-to-consumer with little regulatory or clinical oversight. Little is known about the populations that are seeking testing or the effects on their behavioral and health outcomes. In 2005, Dr. McBride and colleagues launched the Multiplex Initiative, a large pilot study to explore healthy young adults' interest in "multiplex testing". The prototype multiplex test assessed an individual's genetic susceptibility to eight common health conditions (*e.g.*, heart disease and several cancers) based on 15 genetic variants. Individuals who are insured by the Henry Ford Health System in Detroit, Michigan were offered the testing as part of a research study. Those who opted to undergo testing were followed to determine whether receipt of genetic risk information prompted them to seek other risk information, such as that based on family history and any behavioral risk factors. This is the first study to inform the public debate about the effects of genetic susceptibility testing among healthy populations.



In two other studies, Dr. McBride is evaluating the potential of genetic risk information to motivate parents to positively influence their children's health behaviors. In the first study, parents who enrolled in the Multiplex Initiative were asked to complete additional surveys that asked them to hypothetically consider multiplex testing for one of their children, selected randomly. In a second study, overweight parents are provided with information about their child's genetic risk of becoming overweight as adults. Following receipt of this information, the parent is observed in a virtual cafeteria making food choices for that child. The objective of both studies is to evaluate whether, and under what circumstances, genetic risk information could be used to prompt parenting practices that facilitate family-based health promotion.

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Lastly, Dr. McBride is evaluating public health models for using genetic information to categorize populations according to risk level. Dr. McBride is working with Dr. Gail Davey, a colleague at Addis Ababa University in Ethiopia and the Mossy Foot Foundation to address podoconiosis, a debilitating rare tropical disease seen in genetically susceptible farmers who work barefoot in clay soil. An effective intervention for reducing the occurrence of podoconiosis is to encourage those deemed to be "at risk" to wear protective footwear. However, Ethiopia's high poverty rate means that access to footwear is limited and, under these circumstances, wearing shoes would publicly identify those "at risk", leading to social stigma. Dr. McBride, and her colleagues are comparing approaches to distributing footwear based on genetic risk profiles that increase the likelihood of compliance and make best use of these limited resources.

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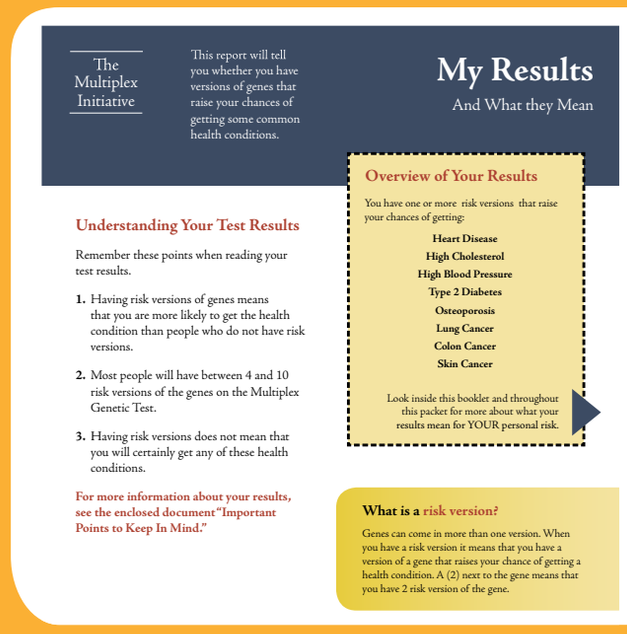


The Multiplex Initiative

This report will tell you whether you have versions of genes that raise your chances of getting some common health conditions.

My Results
And What they Mean

Overview of Your Results

You have one or more risk versions that raise your chances of getting:

Heart Disease
High Cholesterol
High Blood Pressure
Type 2 Diabetes
Osteoporosis
Lung Cancer
Colon Cancer
Skin Cancer

Look inside this booklet and throughout this packet for more about what your results mean for YOUR personal risk.

Understanding Your Test Results

Remember these points when reading your test results.

1. Having risk versions of genes means that you are more likely to get the health condition than people who do not have risk versions.
2. Most people will have between 4 and 10 risk versions of the genes on the Multiplex Genetic Test.
3. Having risk versions does not mean that you will certainly get any of these health conditions.

For more information about your results, see the enclosed document "Important Points to Keep In Mind."

What is a risk version?

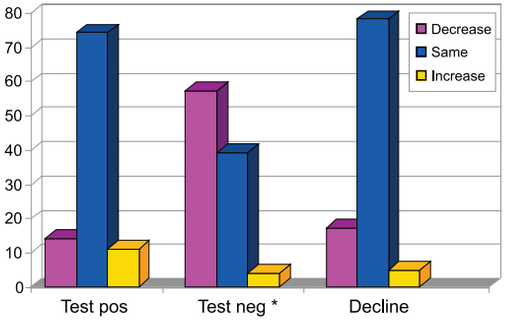
Genes can come in more than one version. When you have a risk version it means that you have a version of a gene that raises your chance of getting a health condition. A (2) next to the gene means that you have 2 risk version of the gene.

BARBARA BOWLES BIESECKER, M.S.

Ms. Biesecker's research and teaching activities focus on making genetic counseling as effective as possible. This is an area of growing importance, as the application of new genetic technologies brings an avalanche of information and questions. Currently, behavioral researchers have little empirical evidence to establish best practices toward helping people choose how to use their own genetic information in making health and reproductive decisions. Ms. Biesecker's training as a genetic counselor greatly informs her research program, which focuses on identifying cutting-edge approaches that have high clinical significance and the potential for directly improving clinical practice.

To that end, the major focus of Ms. Biesecker's research is determining how genetic counseling can improve people's decision-making and coping abilities. Her work is centered on three major thematic areas: (1) the role of ambivalence in deciding whether to undergo prenatal testing; (2) how clients adapt to living with a genetic condition or being at increased risk; and (3) psychological factors that influence decisions about multiplex genetic testing.

Ms. Biesecker is widely recognized as one of a small group of clinical researchers exploring psychological adaptation to a variety of rare genetic disorders. Her previous work included studying the factors influencing adaptation to living at risk for Huntington disease or neurofibromatosis type I, and to parenting a child with a pervasive developmental disorder or Down syndrome. In each of these scenarios, adaptation was measured as an outcome of the process of coping with the condition. In collaboration with Dr. Lori Erby at The Johns Hopkins University and collaborators from the Patient-Reported Outcomes Measurement Information System (PROMIS) NIH Roadmap Initiative, Ms. Biesecker has developed an adaptation scale that includes four sub-domains: self-esteem, spiritual and psychological well-being, response to coping, and social integration. The scale has been evaluated with confirmatory factor analyses and appears to reliably measure the multiple facets of adaption; further, it can be used to understand adaptation across different populations. Each of these studies has identified predictors of adaptation, and future studies of potential interventions to improve adaptation are planned.



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 to inform a larger, randomized control trial investigating women's ambivalence toward prenatal testing and how a genetic counseling intervention might benefit them. Genetic prenatal testing has been available for several decades, primarily to determine whether a developing fetus has a chromosomal abnormality. Ambivalence about such testing (endorsing both pros and cons) has been shown to influence decisions and lead to less-informed choices. This study is aimed at exploring ways to reduce ambivalence and enhance informed choices.

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Genetic Counseling Training Program

In the early 1990s, Ms. Biesecker and her colleagues established 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 Washington Metropolitan Area. Its goal is to train genetic counselors skilled in therapeutic counseling and in genetic counseling research methods.

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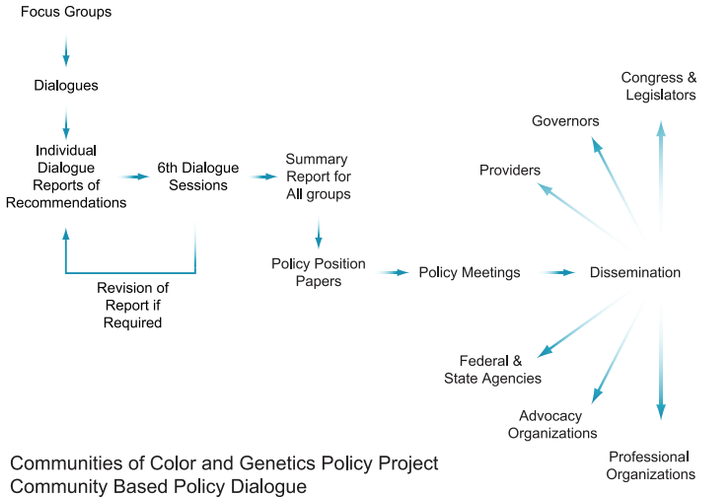
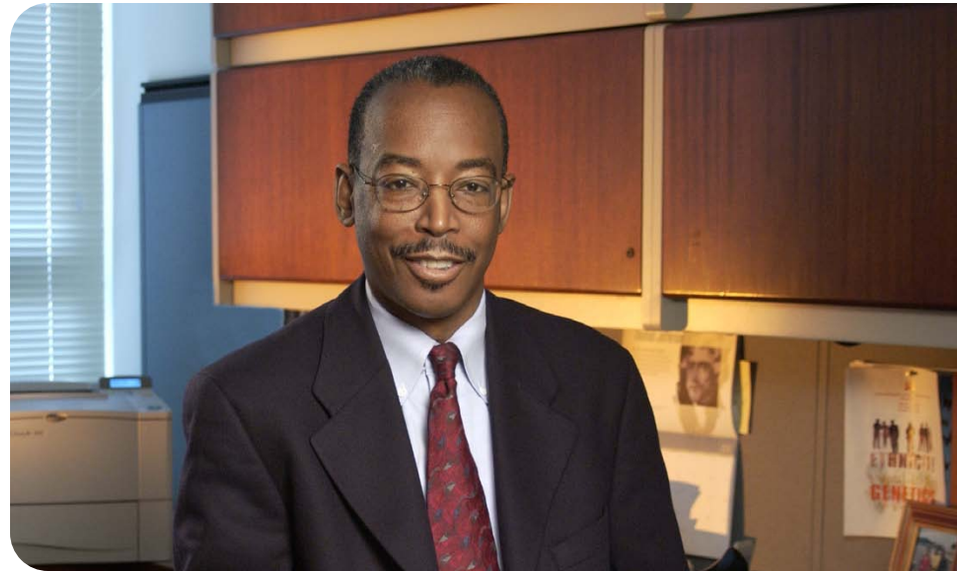
VENCE L. BONHAM, J.D.

Mr. Bonham is a health care services and policy researcher whose work is at the intersection of public policy, health care, and genetics. His research, conducted within the Public Health Genomics Section, focuses primarily on the social influence of new genomic knowledge, particularly in communities of color. Mr. Bonham is interested in how genomic discoveries influence social identity, how genomics might influence the use of the constructs of race and ethnicity in biomedical research, and the role of genetics and genomics in understanding racial and ethnic health disparities.

Mr. Bonham is leading the Physicians' Understanding of Human Genetic Variation Study,which is a large multi-year research project. Its goal is to investigate factors that influence health care providers' decisions about providing genetic services. As an initial step in this research, Mr. Bonham and his colleagues conducted an Internet-based survey of family physicians to explore differences in treatment recommendations for genetic testing for white and black women. Specifically, it delved into the physicians' approaches to women seeking reproductive counseling. Results of that study suggested that physicians considered race in deciding which genetic tests to request. Drawing from that experience, Mr. Bonham and his team have used a mixed-methods research approach, beginning with a series of structured interviews and focus groups aimed at further exploring health professionals' knowledge of human genetic variation, their beliefs about genetic differences based upon race and ethnicity, and the roles that race and ethnicity may play in clinical practice. Based on this research, Mr. Bonham is developing an assessment tool, the Health Professionals' Genetic Education Needs Exploration (HP GENE) Survey, that can be used in studies related to genetics and health disparities. Mr. Bonham and his colleagues are currently undertaking a large national survey of primary care physicians using the HP GENE Survey.



Communities of Color and Genetics Policy Project
Community Based Policy Dialogue



All of Mr. Bonham's research projects actively involve trainees. Mr. Bonham has worked closely with his trainees to expand the range of research questions addressed within his research group. He has directed a study of basic genetic scientists, examining their use of population descriptors (including race and ethnicity) in their research. Additional projects have investigated self-identified mixed race individuals' perceptions of identity, their views of genetics, and their experiences with clinical care – questions that Mr. Bonham also plans to explore in immigrant populations and individuals that are carriers for single gene conditions.

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In addition to his work in the Social and Behavioral Research Branch, Mr. Bonham serves as the Senior Advisor to the NHGRI Director on the Societal Implications of Genomics. Mr. Bonham lends his expertise to training state and federal judges on the social implications of genomics research and new technologies. Mr. Bonham also heads the Education and Community Involvement Branch (ECIB), which leads.NHGRI's public outreach and community involvement initiatives. As Chief of ECIB, Mr. Bonham is responsible for structuring how NHGRI involves and engages various communities, including those who are underserved in biomedical research participation.

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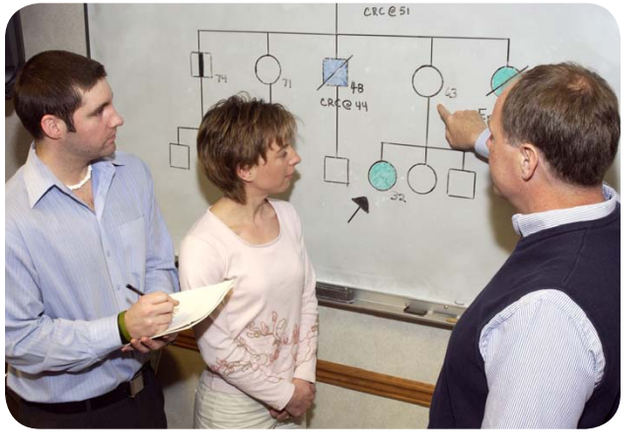
DONALD W. HADLEY, M.S., C.G.C.

Mr. Hadley is a clinical researcher in the Social Network Methods Section of the Social and Behavioral Research Branch and a genetic counselor in the Office of the Clinical Director. In the latter capacity, he provides education and counseling to people participating in NIH clinical protocols that have or are at risk for inherited diseases.

As a researcher, Mr. Hadley focuses on understanding the factors that influence interest in and uptake of genetic services, including genetic education, counseling, and testing; he is particularly interested in psychological and behavioral outcomes. Specifically, his research examines the significant role of the family in influencing an individual's knowledge, attitudes, and behaviors related to genetic testing, with the ultimate goal of defining the individual and family variables affecting the psychological and behavioral impact of such testing. An understanding of these issues will inform the development of clinical interventions aimed at improving family communication related to disease risk and health behaviors, adaptation of those experiencing difficulty, and adherence to recommendations for health screening and disease prevention.

Mr. Hadley's work has focused on studying families with an inherited cancer susceptibility syndrome known as hereditary nonpolyposis colorectal cancer (HNPCC; also known as Lynch Syndrome). His group collects data from patients who choose to receive genetic counseling services and to consider the option of genetic testing for the disease-causing mutation in their families. Participants complete a baseline questionnaire that assesses their interest in and attitudes toward genetic testing prior to receiving genetic information. This survey documents their general mood, level of worry about cancer and genetic testing, cancer screening practices, spiritual beliefs, and feelings about their familial communication practices and support. A follow-up questionnaire is administered at six-month, one-year, and three-year intervals after receiving their genetic test results or choosing not to undergo testing.



Using the resulting data, Mr. Hadley's group analyzes the ways in which the genetic counseling and testing process influences participants' psychological well-being and communication about genetic risk, and evaluates how such factors guide their cancer screening choices. As only about half of the eligible family members have chosen to participate in the HNPCC study, Mr. Hadley's group now hopes to detail the perspectives and attitudes of those who opted out of genetic testing and to gain insight into their cancer screening practices.

Mr. Hadley is expanding his research to more carefully consider the influence of the immediate and extended family on individual family members' knowledge and feelings about HNPCC. Genetic testing typically begins with a single individual who is affected with a disease and receives genetic testing. If a disease-causing mutation is found, then biologically close and eventually more distant relatives seek out genetic services as knowledge about the disease and testing options spreads within the family. The periodic provision of genetic information and the associated family communication has

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the potential to influence thoughts and behaviors of those who later come to receive genetic services. This research intends to examine whether previous experiences with genetic services and communication within the family are associated with an increase or decrease in psychological distress, perceptions of risk, genetic knowledge, and adoption of appropriate cancer screening practices. Gaining insights into social influences that may occur within the family may yield critical information for developing innovative genetic- and genomic-based education and counseling programs for families.

To extend his research portfolio, Mr. Hadley plans to include the study of families with more common diseases that affect larger segments of the population. His future studies will include diseases with genetic contributions that are also influenced by factors such as the environment, lifestyle, and diet.

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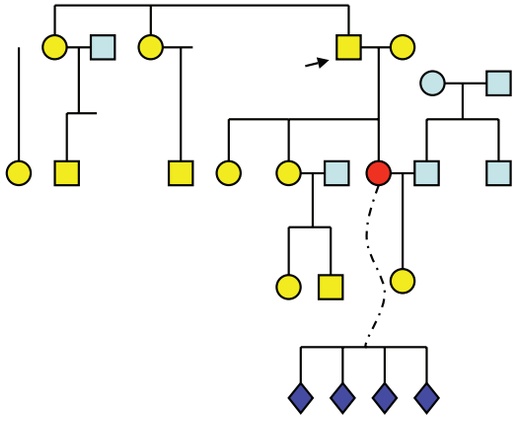
LAURA KOEHLY, Ph.D.

Dr. Koehly's research focuses on developing and applying social network methods to the study of complex social systems, such as families and communities. Her current research examines the influence of social context on coping responses to communication of hereditary risk and evaluates the effects of social context on improving health outcomes. To that end, she seeks to develop effective family-based interventions to encourage communication among family network members about genetic risk information, as well as to mobilize related social support processes that increase appropriate screening regimens and health-promoting behaviors.

In order to better understand the impact of the interpersonal environment on behaviors, Dr. Koehly also develops statistical methods to examine the perspectives of all members within a family system, thereby considering the social context in which genetically at-risk individuals live. This approach is in contrast to previous research in this field that has maintained a more limited and biased focus on individuals' perspectives as if they were independent of the broader social network.

Recently, Dr. Koehly has focused on the dissemination of and adaptation to genetic risk information for a number of hereditary cancer syndromes, such as Lynch syndrome (inherited colon cancer) and hereditary breast and ovarian cancer. Communication within families about cancer risk, particularly in the context of these rare cancer syndromes, fosters an appreciation of shared disease risk that can lead to cooperative, family-based approaches for reducing distress and improving both screening and health-promoting behaviors. Indeed, Dr. Koehly's work has shown that optimal dissemination of genetic risk communication occurs primarily among at-risk individuals and their first-degree relatives and spouses, although optimistic individuals tend to enlist more biological family and social kin in their discussions of cancer risk. Her work has also shown that an interconnected system of emotional support among its members is associated with less anxiety within the family. Additionally, families with interpersonal connections in which cancer screening is encouraged are more likely to engage in appropriate screening behaviors. Dr. Koehly and her team continue to explore ways to maximize the reach of cancer communication beyond first-degree relatives.



Dr. Koehly is also leading a study known as Project RAMA (Risk Assessment in Mexican Americans) to develop culturally sensitive family-centered interventions to motivate health behaviors such as cancer screening and changes in lifestyle habits. The goal is to lower risk for common diseases that "run in families." This project targets multi-generational Mexican American households by providing members with family history feedback about common health conditions in an effort to engage family members in adaptive cooperative coping. Dr. Koehly is exploring whether an intervention that provides risk feedback to multiple household members can stimulate discussion regarding family risk of diseases such as diabetes, and whether these discussions encourage associated risk-reducing behaviors among family members (*e.g.*, blood glucose testing or increased physical activity).

Additionally, Dr. Koehly is in the early stages of research to examine the system of family caregiving in families affected by Alzheimer's disease (AD). Caregiving is an interpersonal process that involves communication about a shared problem and the development of cooperative approaches among family members to address the problem. Research aimed at understanding this process to date has focused on the perspective of individual caregivers. Dr. Koehly will examine whether patterns of caregiving differ based on factors such as the number of relatives affected by AD and their age at diagnosis.

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Among other questions, Dr. Koehly is interested in addressing whether the individual's perceived risk of developing AD is associated with their level of involvement in providing care to other affected family members. Finally, Dr. Koehly will investigate whether the structure of the caregiving family member's support network is helpful in reducing the strain of this role.

In the future, Dr. Koehly intends to obtain information based on family history regarding the social context of families with varying levels of disease risk, to explore if patterns of communication, support, and encouragement are common across diseases. Additionally, she is interested in examining whether these patterns vary across families from different ethnic and racial backgrounds, in order to guide the development of network-oriented interventions that are culturally sensitive.

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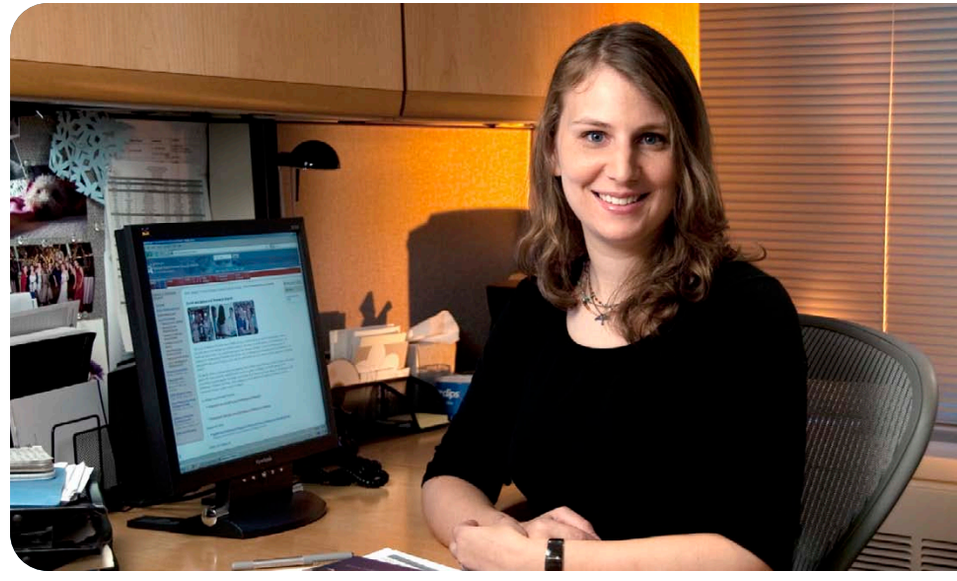
SUSAN PERSKY, Ph.D.

Dr. Persky is a social psychologist whose work examines the use of new genomic knowledge in interactions between health care providers and patients, as well as in the discourse that occurs in other social contexts. Dr. Persky is particularly interested in how new genomic information might influence social stigma, health disparities, and other unequal treatment. She uses a number of novel research methods, including immersive virtual environment technology and quantitative content analysis of online media sources (e.g., online forums and blogs), with the aim of increasing the applicability of her research findings to real-world processes and behavior. Dr. Persky also leads the Immersive Virtual Environment Testing Area facility at the NIH Clinical Center.

One of the major themes of Dr. Persky's work is the exploration of how general (non-personalized) information about genetic predisposition for body weight and obesity influences attitudes and behavior amongst both health care providers and members of the public. Information about gene discovery related to weight and obesity receives a widespread attention from the media and in scientific publications; however, little is known about how this information affects those who are exposed to it. In one study, Dr. Persky and colleagues are exploring how this knowledge affects health care providers' attitudes towards overweight patients and any subsequent treatment recommendations. In this study, she "immerses" medical students in a virtual clinical scenario where they interact with a virtual patient; they then make recommendations for the virtual patient's treatment.



In another study, Dr. Persky is exploring the public impact of genetic information related to the causes of obesity as it circulates in online communities (i.e., discussion forums). This work focuses on using quantitative content analysis techniques to observe and categorize natural, real-world discussions about weight, weight management, and health behavior that occur in these forums. Both of these projects aim to draw a clearer picture of how dissemination of information about discoveries related to genetic predisposition for overweight and obesity will impact the beliefs and health behavior of individuals, as well as the quality of the healthcare they receive.

Dr. Persky collaborates on several other research projects outside the context of body weight and obesity. One immersive virtual environment-based project explores how social characteristics of health care providers can influence patients' responses to disease risk information presented during a clinical visit. In addition, she is currently conducting a quantitative content analysis project that examines the universe of genetics blogs as online sources of information for the public about genetic susceptibility tests marketed

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directly to consumers. In this project, Dr. Persky is analyzing the sources of information available to consumers as they make decisions about whether to order these tests.

In her role as leader of the Immersive Virtual Environment Testing Area, Dr. Persky provides scientific oversight for projects conducted within the facility. She serves as a technical expert and liaison, and also as a social psychology content expert and collaborator.

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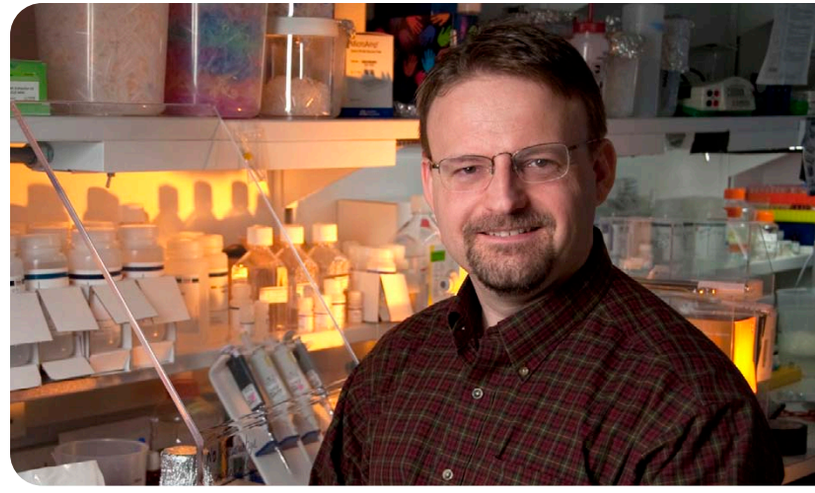
ADJUNCT INVESTIGATORS

BRIAN P. BROOKS, M.D., Ph.D.



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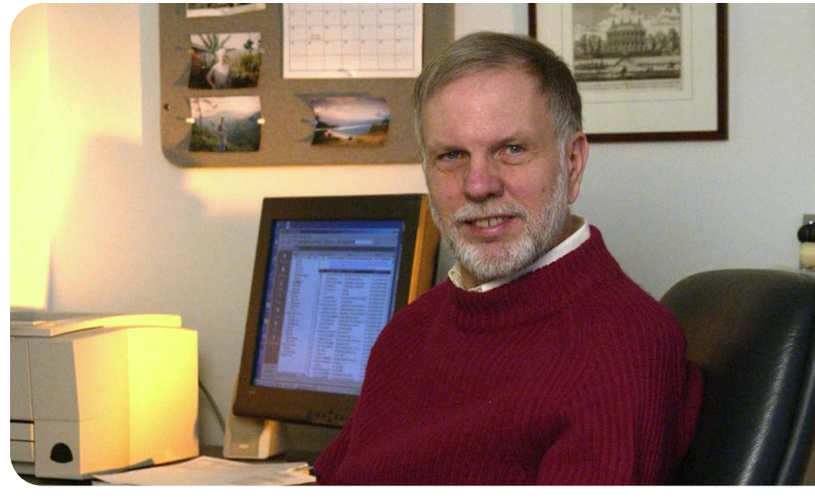
Dr. Brooks studies uveal coloboma, a potentially blinding congenital eye malformation caused by failure of the optic fissure to close during the fifth week of human gestation. Although the embryology leading to coloboma has been well-characterized for decades, less is known about the genetic and developmental processes involved. The Brooks laboratory integrates clinical and genetic data from uveal coloboma patients with molecular, developmental, and biochemical studies of normal and faulty optic fissure closure in model systems, with the ultimate goal of devising molecular diagnosis, prevention, and treatment strategies. His group has identified a unique syndrome in which abnormal vertebral segmentation cosegregates with coloboma in an autosomal dominant fashion. With state-of-the-art clinical tools, Dr. Brooks is leading efforts to define the clinical phenotypes of coloboma patients, thereby identifing potential clinical risk factors and coloboma microforms. Using laser-capture microdissection and gene expression analysis, Dr. Brooks has identified 221 genes that are differentially regulated at the closing edges of the optic fissure. Using this approach, he discovered that *Nlz1* and *Nlz2* are important in regulating closure via a *Pax2*-dependent mechanism. He is currently exploring how these genes interact with other transcriptional regulators during development and the role of these genes in human disease and development.

KENNETH H. FISCHBECK, M.D.



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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.

EDWARD GINIGER, Ph.D.

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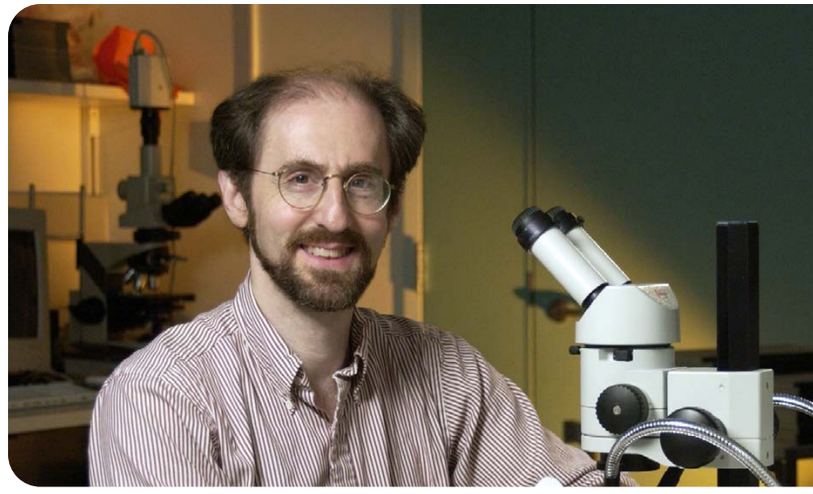

Information processing in the brain is done by specialized neural circuits. Every neuron has an axon, which carries information to its synaptic partners within these circuits. Dr. Giniger seeks to understand the molecular mechanisms that guide an axon, allowing it to find just the right partners from 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.

PAUL S. MELTZER, M.D., Ph.D.

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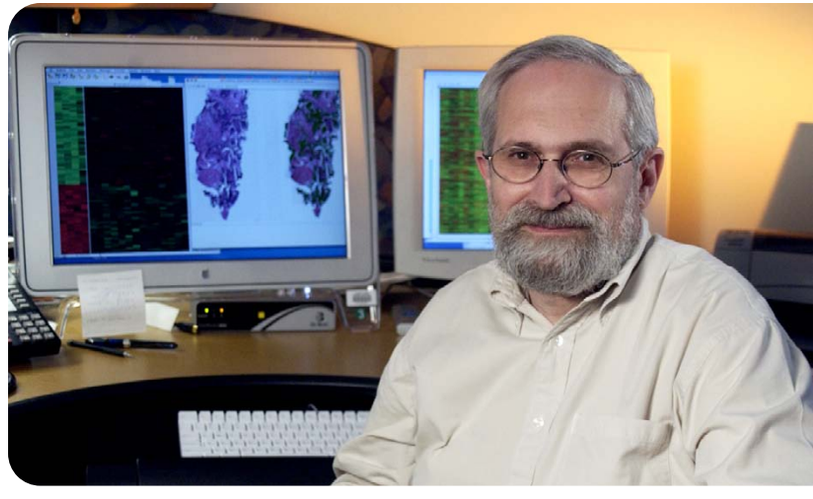

Dr. Meltzer uses cutting-edge technologies to analyze the abnormalities in genome structure and function that occur in cancers. These methods include various types of microarray analyses, which allow him to scan the entire genome and examine how genes that cause cancer start tumor progression and affect 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.

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Dr. Milgram studies cell signaling and protein trafficking in polarized cells, including kidney and airway epithelial cells. Epithelial cells form a lining at the surface of the skin and along membranes within the body. This lining is essential for cell defense, nutrient absorption and ion transport. Her research group investigates how the topmost membrane receptors regulate the activity of ion channels, including the epithelial sodium channel (ENaC) and the cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel. Focused initially on the airway epithelium, Dr. Milgram's research program has now expanded to study other epithelial cells and model systems, including the kidney and gastrointestinal tract. Her laboratory's findings suggest that receptors, signaling intermediates and effectors are compartmentalized into regulatory complexes that increase the fidelity and efficiency of cell signaling. These studies utilize diverse approaches, ranging from in vitro biochemical assays to physiological assays in knockout mice.

CORES, CENTERS, AND OFFICES

CORES

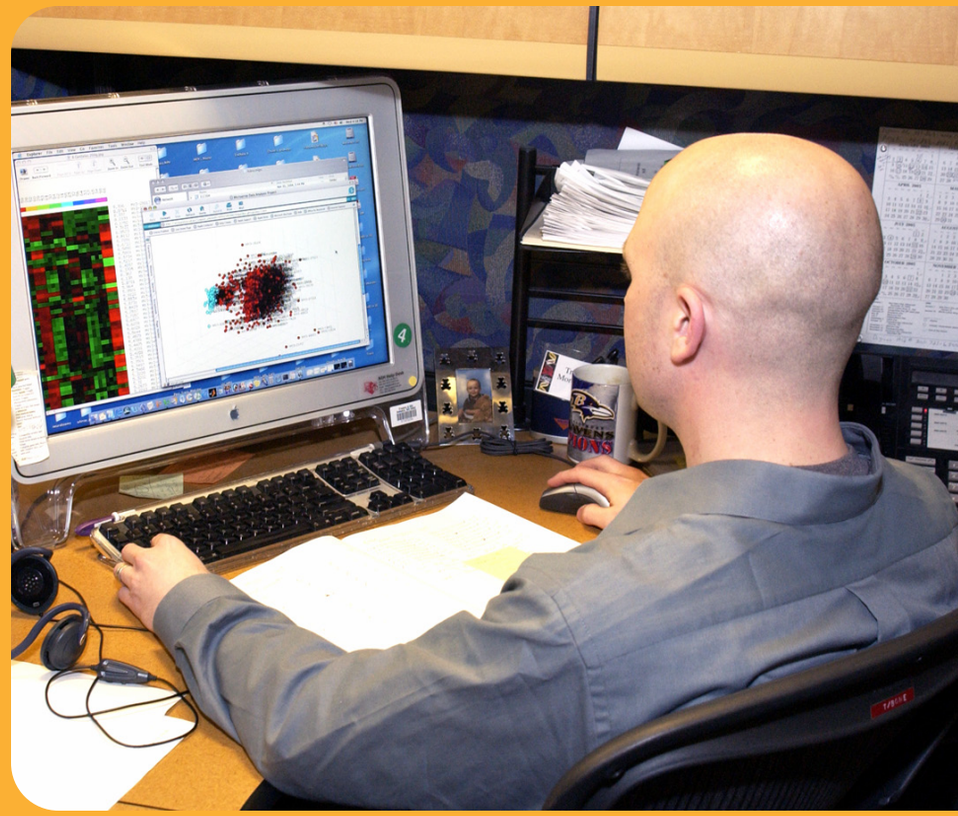
The Division of Intramural Research operates seven core facilities to support the work of NHGRI investigators and their collaborators. These cores maintain and utilize state-of-the-art instrumentation. In addition, the Cores provide access to experts in relevant areas, who then often play a key role 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. Core-developed software includes *GeneLink*, a database solution designed to facilitate large-scale genetic linkage or association studies, allowing for complex trait mapping, as well as numerous sequence-based utilities that aid in the analysis of transcription factor binding sites and next-generation sequencing data. In addition to software developed in-house, the Core makes available commonly used commercial and public-domain software for the analysis of sequence, expression, and structural data; Core personnel provide basic assistance in using these computational tools. The Core also 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



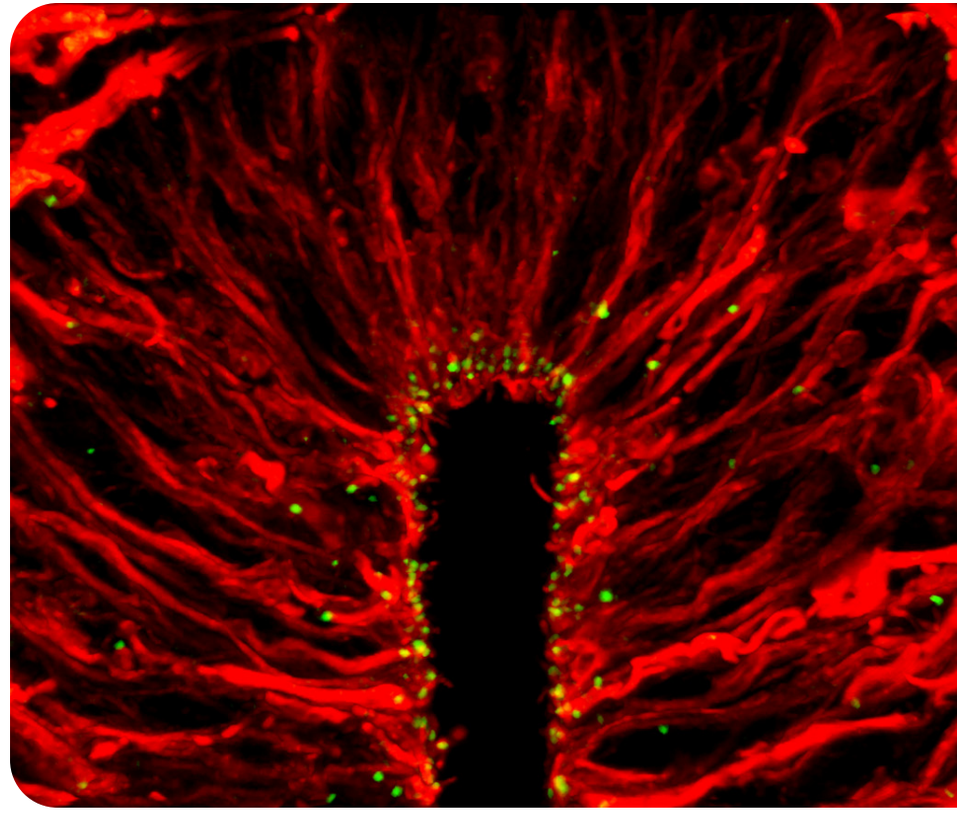
Core (BIC; see *Lawrence Brody, Genome Technology Branch*). To facilitate and support clinical studies, the Core has implemented Labmatrix, a Web-based, HIPAA-compliant database system that includes functionality for IRB protocol management, biological sample accessioning and storage management, workflow tracking, and handling of complex genotypic and phenotypic data. Core personnel collaborate extensively 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 2200 compute nodes (6500 processors). Finally, the Core is involved in a series of educational efforts, including hands-on training classes in bioinformatics for NHGRI researchers which are offered on a regular basis and cover the essentials of bioinformatics as related to genomic research.

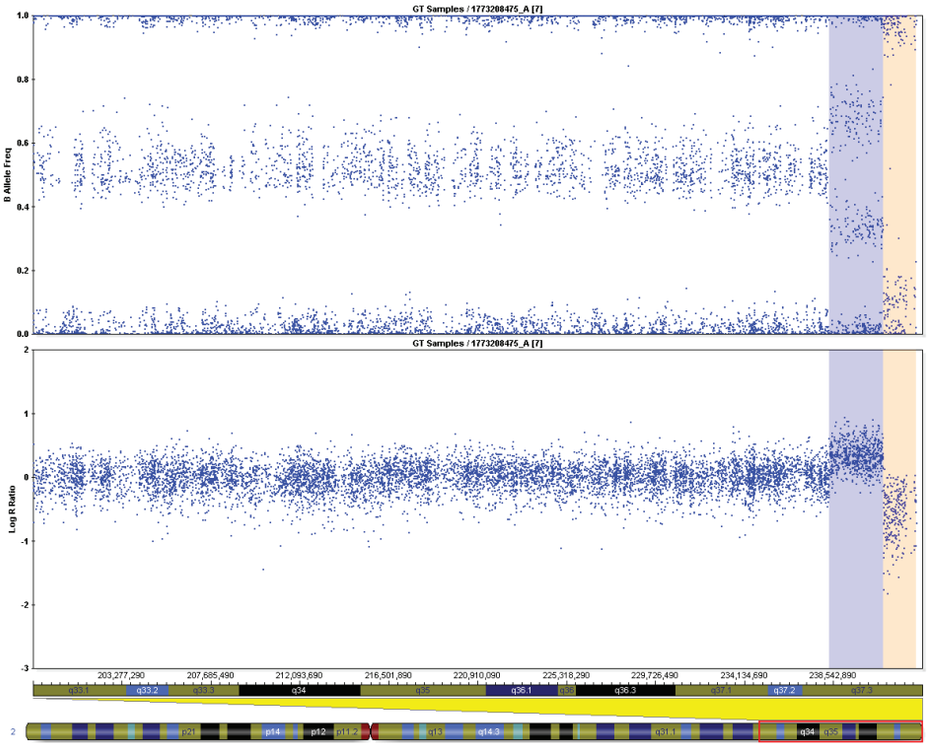
Cytogenetics and Microscopy Core

The Cytogenetics and Microscopy Core's mission is to provide NHGRI investigators access to imaging and cytogenetics resources that support and extend their abilities to discover the causes of disease and the mechanisms of normal development and physiology. The 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); analyses of clones containing human, mouse, and other species' DNA; and high-resolution mapping of clones on extended chromatin structures. For karyotyping, the Core provides services such as cell culture, metaphase chromosome preparation, and interpretation of abnormal karyotypes. The Core also offers single-photon and multi-photon confocal scanning microscopy, as well as spinning disk and wide-field microscopy designed for live cell imaging and time lapse Z-stack images. Using these methodologies, researchers can generate three-dimensional images of thick transparent objects, such as biological cells and tissues.

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, nine-color BD LSR II analyzer equipped with the High Throughput Sampler for analyses directly from a 96-well plate; two four-color FACSCalibur™ analyzers; a Compucyte iCys™ research laser scanning cytometer, and a Miltenyi AutoMACS™ for magnetic cell separation. Core personnel are available for training, development, and project execution.

Genomics Core

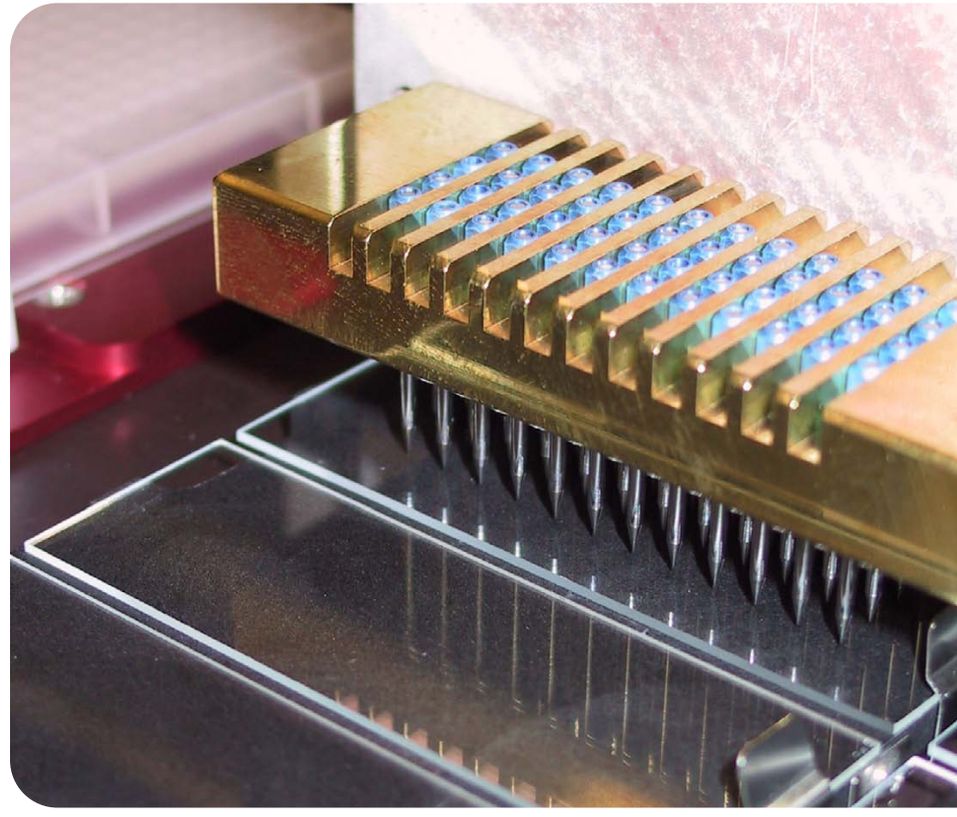
The Genomics Core offers genotyping, physical mapping, and DNA sequencing services. Physical mapping services provide investigators access to BAC clones from human, mouse, and zebrafish genomic libraries. For DNA sequencing, Core personnel utilize ABI 3100 sequencing instruments to analyze samples provided by investigators. In addition, the Core offers access to several human DNA panels that are commonly used for determining allele frequencies. Genotyping is the most significant activity of the Core and includes a variety of services using both short tandem repeat polymorphism (STRP) and single nucleotide polymorphism (SNP) technologies. The Core has a set of >400 STRP markers for whole human genome scanning and >500 markers for genotyping mouse DNA. New markers are identified to generate a dense map of a given focus region, as needed. SNP-based genotyping is also available, using both the Illumina GoldenGate and Infinium assays. The Core is quick to adopt newer and higher-density SNP chips as well as new SNP technologies for novel applications, thereby continually adding to the repertoire of offered services. These technologies are used for a variety of applications in exploring human, mouse, and other genomes, including linkage analysis, copy number changes, parental origin of deletions/duplications, speed congenics, methylation, and microRNA expression. The Core aids investigators in the utilization and adoption of available technologies and instrumentation specific to their needs.

Microarray Core

The NHGRI Microarray Core represents a consortium between NHGRI, the National Institute of Mental Health (NIMH), and the National Institute of Neurological Disorders and Stroke (NINDS). It was established in order to provide Intramural investigators with full service, cost-effective, and time-efficient access to state-of-the-art genomic and transcriptomic technologies for understanding genome copy number, patterns of gene expression, and single nucleotide polymorphisms (SNPs) identified in genome-wide association studies. The Core often performs the labeling and processing of isolated RNA/DNA samples provided by investigators. Investigators have access to the Agilent, Affymetrix, and Illumina Beadchip platforms, and custom, in-house slides are also available. Upon completion of an experiment, investigators are provided with a summary report including a data quality assessment, a preliminary analysis, and raw data output files. Core operations are based on instrumentation, protocols, and reagents that have been developed or adapted in-house. Costs associated with the purchase of commercial chips, as well as reagents for labeling probes, are the responsibility of the individual investigator. In addition to advising and assisting investigators in project design and implementation, the Core also provides hands-on training to interested investigators for all supported platforms and related protocols when requested.

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. Core services include whole-mount RNA *in situ* hybridization using embryos from various stages of development in order to establish the spatial and temporal expression of genes, microinjection of morpholinos designed to block translation and/or splicing to study the phenotypic effects of gene knock-down, microinjection of RNA to study the phenotypic effects of gene overexpression, microinjection of plasmid DNA to evaluate the regulatory potential of conserved noncoding sequences, resequencing/TILLING (*T*argeting *I*nduced *L*ocal *L*esions *IN G*enomes) to identify an allelic series of mutants in a target gene from a collection of ENU-mutagenized animals, and cryopreservation of backup of lines for future studies . Since the availability of mRNA sequence is a prerequisite for morpholino design and resequencing/TILLING, the Core also assists researchers in bioinformatic 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 microinjection data. The Core maintains a series of commonly used wild-type, mutant, and transgenic zebrafish lines.



CENTERS

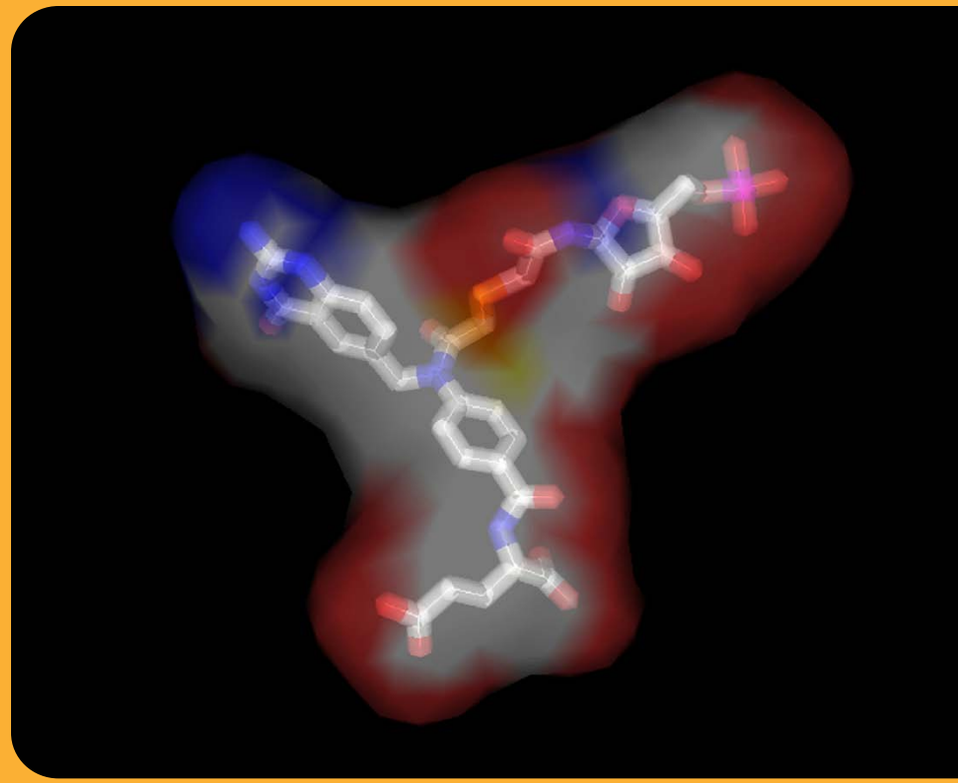
The Division of Intramural Research operates or oversees three centers that offer unique, high-throughput technologies for small-molecule screening, and genetic, genomic, and sequencing services to NHGRI investigators and their collaborators. Access to these centers allows NHGRI researchers to develop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

Center for Inherited Disease Research

The Center for Inherited Disease Research (CIDR; *www.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 is managed by NHGRI on behalf of 14 NIH Institutes. CIDR carries out linkage analyses of single-gene disorders, genotyping studies on complex multifactorial hereditary diseases and sequencing studies to discover novel disease-associated alleles. The staff also helps investigators use marker-assisted breeding strategies to accelerate the production of congenic and consomic strains of mice; they conduct mapping studies with inbred mouse strains. Automated genotyping technologies are used to carry out genome-wide scans with SNP-based markers for genome wide association studies (GWAS). These whole genome SNP arrays also include probes designed to detect copy number variants in the genome. Several other fixed content arrays are offered. Custom SNP genotyping is available for fine mapping and candidate gene studies. Next generation sequences services are provided to investigators requiring the sequence of selected genomic regions or the entire human exome. Extramural researchers supported by one of the 14 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 a competitive peer review process; reviews are carried out six times a year. The NIH Data Sharing Policy mandates that GWAS data be deposited in an investigator-accessible database. CIDR facilitates the deposition of GWAS data into the Database of Genotypes and Phenotypes (dbGaP). All non-GWAS datasets remain the property of the principal investigator.

Center for Research on Genomics and Global Health

The Center for Research on Genomics and Global Health (CRGGH; *crggh.nih.gov*) facilitates the study of human genetic variation and its relationship with disease on a global scale. Its mission is to explore the roles of culture, lifestyle, genetics and genomics in the causes and origins of disease in individuals and in populations. The Center's research informs science and policy addressing national and global health inequalities. Its investigations probe the role that genetic and genomic factors play in disease distribution differences among populations, and pursue ways this knowledge can be translated into policy. CRGGH seeks



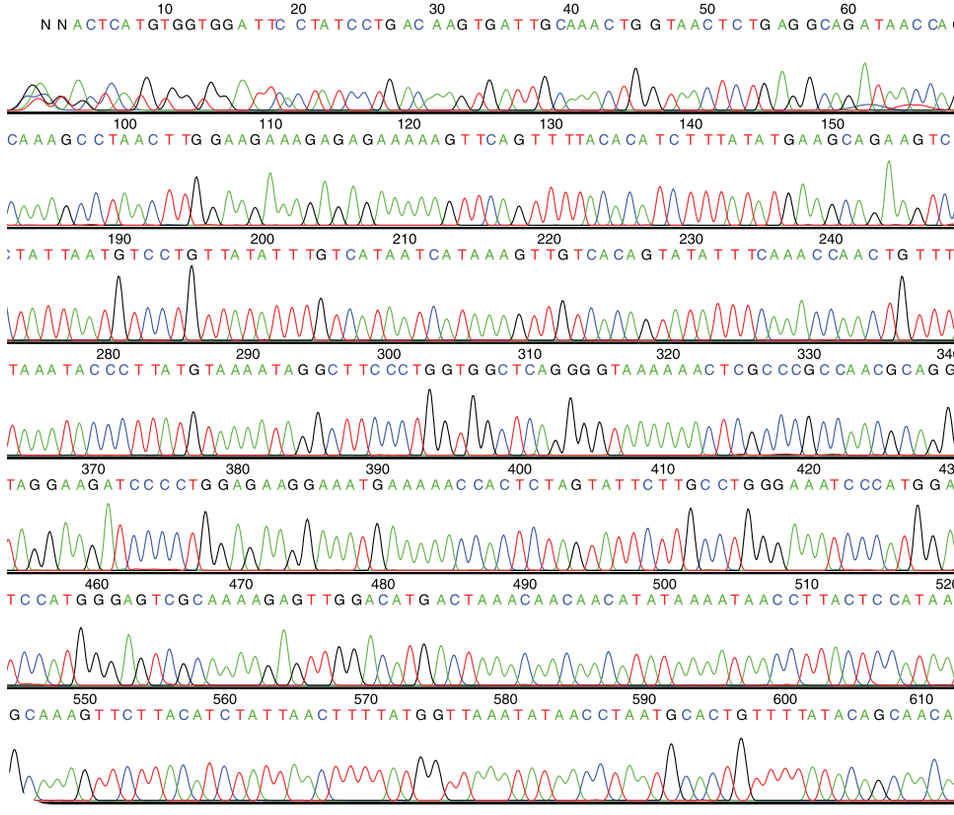
to raise public awareness about the role of genomics in health and human history.

To achieve these goals, investigators develop genetic epidemiology models that explore the patterns and determinants of common complex diseases in human populations in the United States and around the world. They study the roles that genetic and environmental factors play in the pathophysiology of common complex diseases and variable drug response.

CRGGH investigators are also developing strategic research resources to facilitate the study of genetic factors associated with disease susceptibility in the United States and globally, and are building upon strategic genomic resources that capture the widest variation of the human genome, especially from Africa. In addition, CRGGH has undertaken a comprehensive training program to facilitate the use of genomic approaches in the study of human health and population differences in disease distributions.

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 near the Twinbrook Metro station within a cluster of NIH buildings, 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, the ClinSeq large-scale medical sequencing project, microbial genomic and metagenomic sequencing for the NIH Intramural Skin Microbiome Project, and most recently human genome sequencing as part of the Undiagnosed Diseases Program.



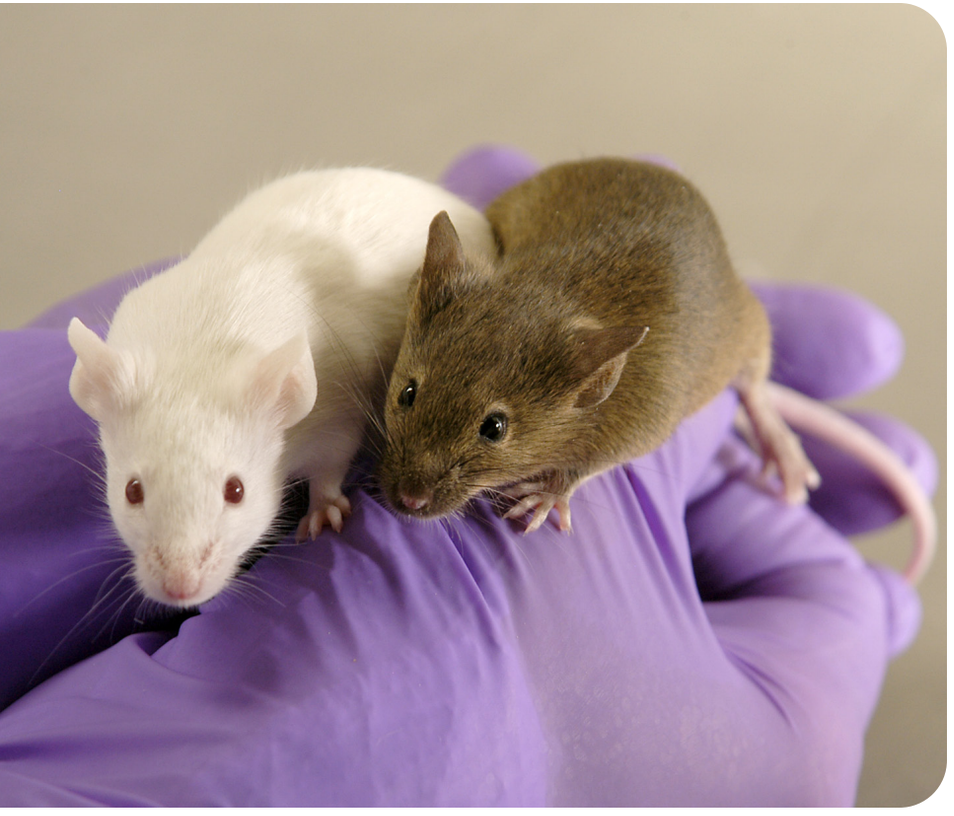
OFFICES

Office of the Scientific Director

The NHGRI Office of the Scientific Director (OSD) provides leadership and managerial oversight for all research, training, 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.

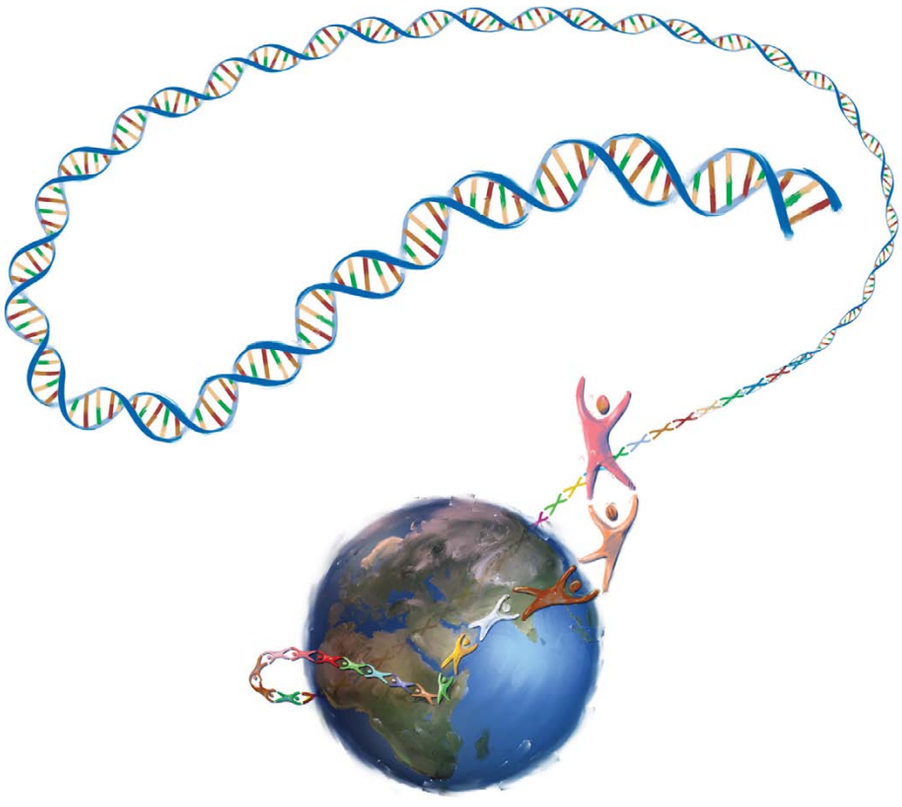


Intramural Training Office

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.

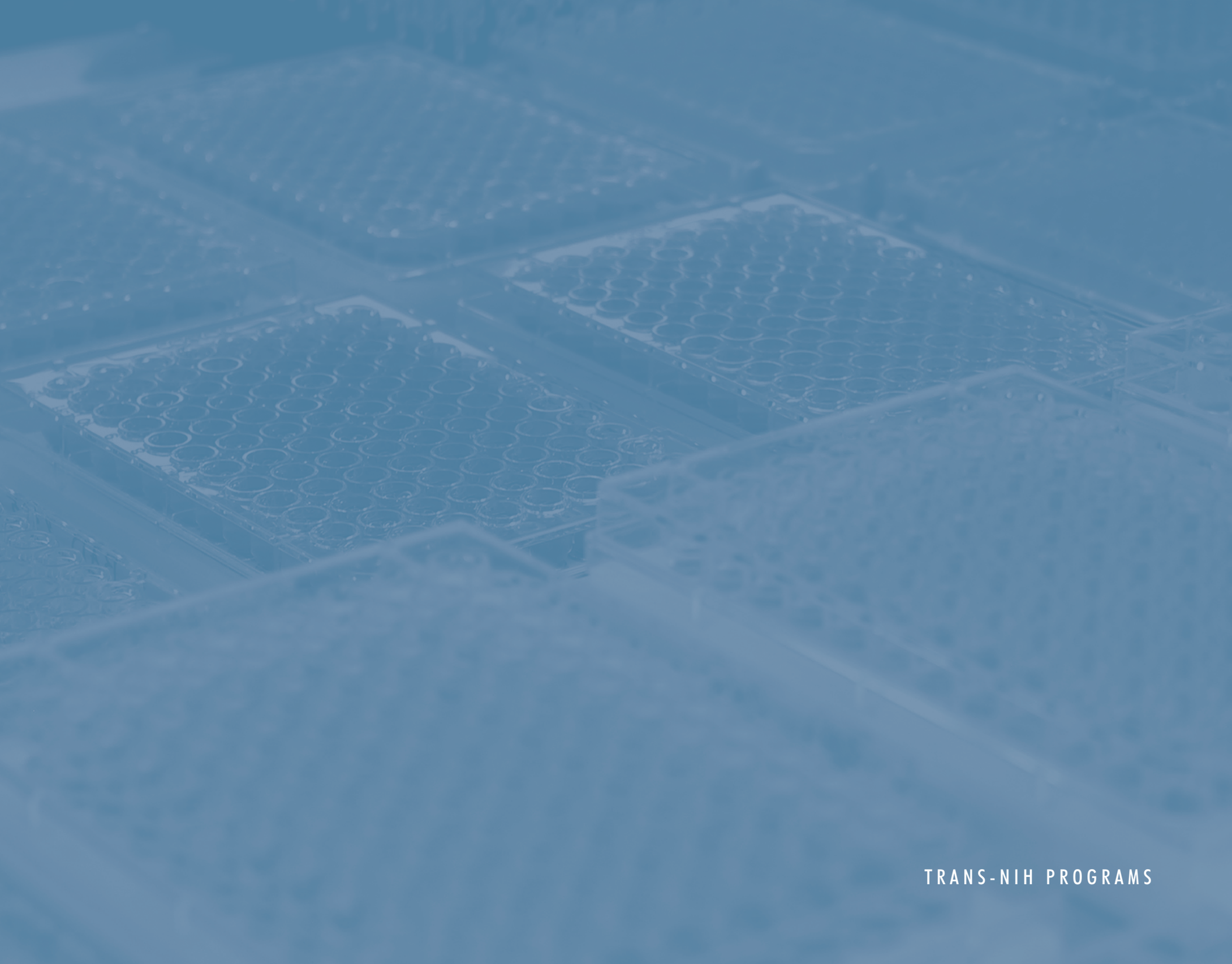


Technology Transfer Office

The Technology Transfer Office (TTO) is the focal point for the administration of all technology transfer-related activities, including collaborative research agreements, inventions, patents, royalties, licensing, marketing of NHGRI-owned technologies and oversight of associated intellectual property and related policy matters for the Institute. An important mission of the TTO is to foster productive research collaborations between Intramural scientists and the private sector and to facilitate the successful commercialization of NHGRI-developed biomedical technologies for the benefit of public health. The TTO is responsible for reviewing, evaluating and managing a diverse, ever-increasing and valuable invention and licensing portfolio of research reagents and technologies. It also negotiates and manages conditional gift funds (e.g., directed donations) and Cooperative Research and Development Agreements (CRADAs), as well as various types of non-NIH research grants and non-NIH derived fellowship monies. Each year, the TTO executes hundreds of transactional agreements on behalf of NHGRI scientists with universities, foundations, nonprofit organizations, and companies from around the world. Lastly, the TTO also serves as a resource for information and advice for both Intramural scientists and administrators on a wide range of technology transfer-related legal and policy issues, including on the transfer of human materials, authorship, copyrights, and the NIH Public Access Policy. The TTO staff also provides guidance regarding the manner and means by which intramural investigators are allowed to collaborate with university researchers on extramurally funded NIH grant projects and restrictions on the receipt and use of research grant, fellowship, and other gift funds.

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.



TRANS-NIH PROGRAMS

Undiagnosed Diseases Program

Using a unique combination of scientific and medical expertise and resources, the trans-NIH Undiagnosed Diseases Program (UDP) pursues the dual goals of providing answers to patients with mysterious conditions that have long eluded diagnosis while advancing medical knowledge about rare and common diseases. UDP is led jointly by NHGRI, the NIH Clinical Center, and the NIH Office of Rare Diseases Research.

Any longstanding medical condition that eludes diagnosis by a referring physician can be considered "undiagnosed" and may be submitted to UDP for further consideration. If invited, the patient is admitted to the NIH Clinical Center in Bethesda, Maryland, usually for a week of diagnostic consultations and tests. In addition to observations made during the week-long visit, the accumulated clinical and laboratory findings are studied in detail for diagnostic clues in the weeks and months of analysis that follow a patient's visit. Each case receives the attention of a multidisciplinary expert medical team drawn from a number of NIH Institutes and Centers. NIH experts consulting on UDP cases offer a collective base of knowledge about rare and common diseases and utilize the clinical and laboratory resources of one of the world's largest medical research institutions.

Through the study of each case, most of which have confounded experts elsewhere over a number of years, UDP offers the possibility of diagnosis and potential therapeutic strategies for patients accepted into the Program. In return, UDP researchers gain new insights about genetic and biochemical mechanisms of disease, and normal cell biology, biochemistry, and physiology.

Since its founding in 2008, UDP has encountered diseases that are difficult to diagnose, uncommon presentations of known disorders, complex disorders that are multisystemic, and new disorders that are diagnosed for the first time. Genomic advances offer new tools for UDP clinical researchers attempting to make often elusive diagnoses. These tools not only help in detecting defects in genes that point to known disorders, but also offer the potential for making discoveries about the role of newly understood molecular and biochemical events that can cause disease. Such new discoveries then have the potential to inform therapeutic approaches for more common diseases.

The UDP caseload is steadily growing, with more than 100 pediatric and adult patients added each year. The number of applications from patients has exceeded expectations, reflecting that UDP fills an unmet medical need. More information on UDP is available at *http://rarediseases.info.nih.gov/undiagnosed*

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 Program in Biomedical Research

The Summer Internship Program in Biomedical Research 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

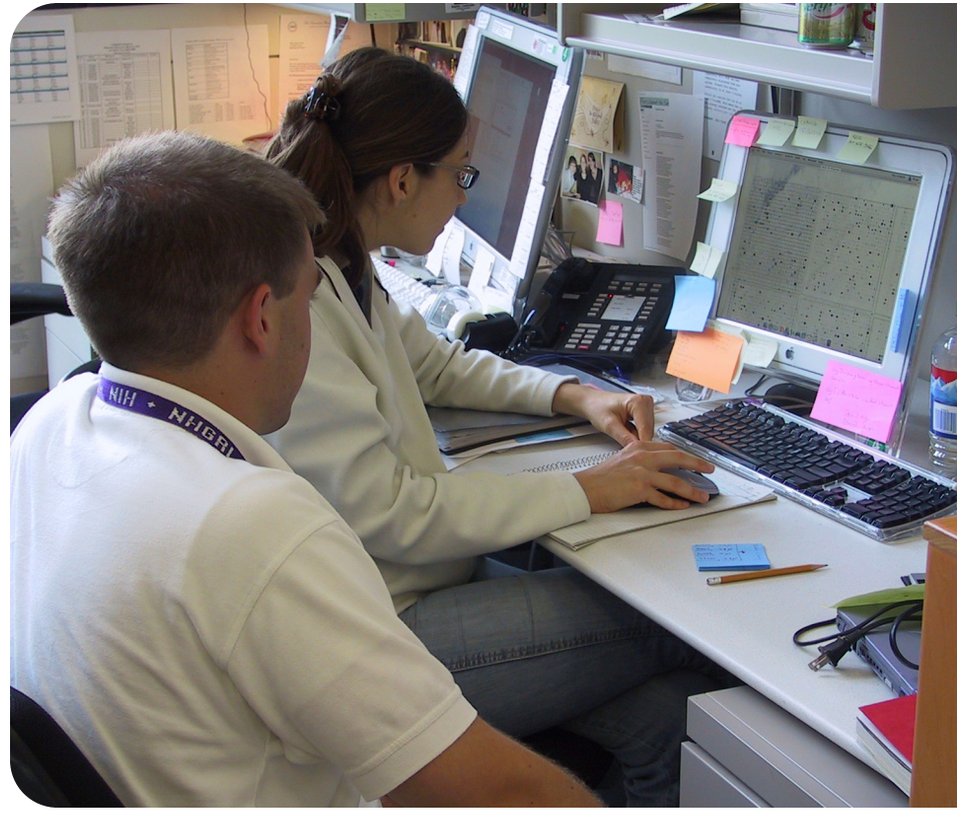
The Intramural Research Training Awards (IRTA) Program consists of four types of awards, each specifically designed to suit the needs of trainees at different stages of their education and/or professional training. These awards include stipends to those who have recently earned a bachelor's or master's 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 in the latest biomedical 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, but may 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 *https://ugsp.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 of the year preceding 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 capital. 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 license 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.

NHGRI Summer Workshop in Genomics Program

The NHGRI Summer Workshop in Genomics 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 $30 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 $3.2 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

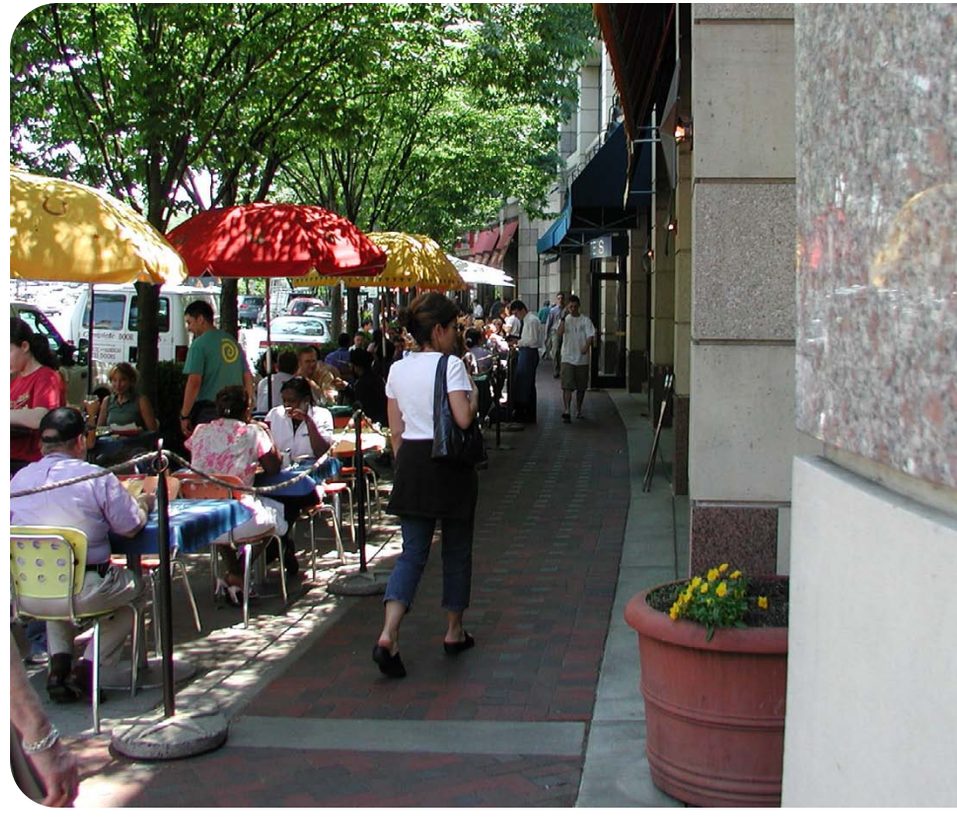
Bethesda, Maryland is a vibrant community surrounding the NIH campus. Its many dining options are legendary. No matter what you crave—from American to Vietnamese cuisine—you will find it in Bethesda. The Bethesda Urban Partnership Inc. makes it even easier to decide where to dine by offering a Web site (*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
metroopensdoors.com

ABOUT MONTGOMERY COUNTY
montgomerycountymd.gov

ABOUT BETHESDA
bethesda.org

ABOUT WASHINGTON-AREA RENTALS
washingtonpost.com/wp-dyn/content/rentals

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

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