

NATIONAL HUMAN GENOME RESEARCH INSTITUTE *Division of Intramural Research*





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

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

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

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

Sincerely,

Eric D. Green, M.D., Ph.D.  
*Scientific Director*  
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Francis S. Collins, M.D., Ph.D.  
*Director*  
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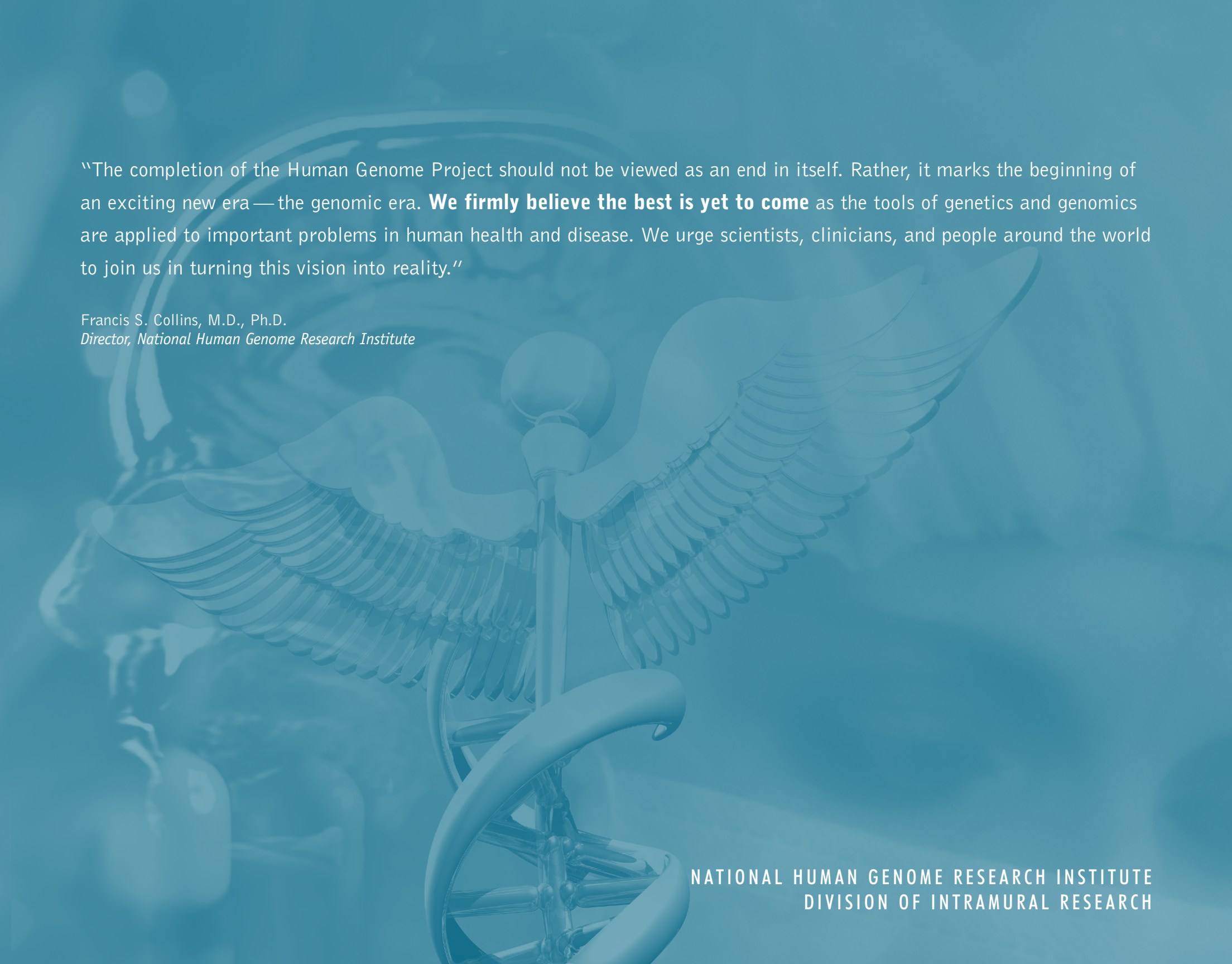
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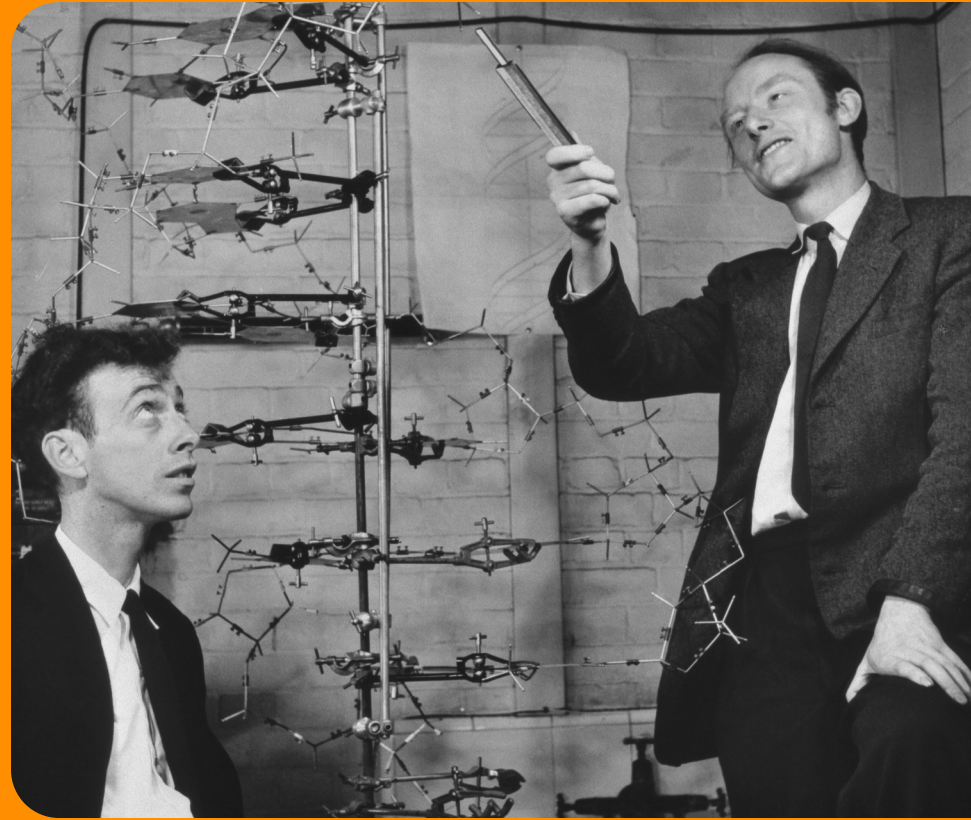


“The completion of the Human Genome Project should not be viewed as an end in itself. Rather, it marks the beginning of an exciting new era—the genomic era. **We firmly believe the best is yet to come** as the tools of genetics and genomics are applied to important problems in human health and disease.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

Francis S. Collins, M.D., Ph.D.  
*Director, National Human Genome Research Institute*

NATIONAL HUMAN GENOME RESEARCH INSTITUTE  
DIVISION OF INTRAMURAL RESEARCH





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

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

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

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

These landmark accomplishments convinced many in the worldwide scientific community that there was an urgent and compelling need to obtain the complete sequence of all 24 human chromosomes—roughly three billion bases in total. In **1988**, the U.S. Congress funded both the National Institutes of Health (NIH) and the Department of Energy (DOE) to "coordinate research and technical activities related to the human genome."

NIH established the Office of Human Genome Research in **1989**, appointing James Watson as its first Director. Together, the NIH and DOE programs joined forces with international partners and launched the Human Genome Project.

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

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



## THE DIVISION OF INTRAMURAL RESEARCH From Base Pairs to Bedside

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

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

- Identification of the genes responsible for numerous human genetic diseases
- Development of new paradigms for mapping, sequencing, and interpreting the human and other vertebrate genomes

- Development and application of DNA microarray technologies for large-scale analyses of gene expression
- Creation of innovative computational tools for analyzing large quantities of genomic data
- Generation of animal models critical to the study of human inherited disorders
- Design of novel approaches for diagnosing and treating genetic diseases

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



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

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

*Scientific Director  
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## Organization and Structure

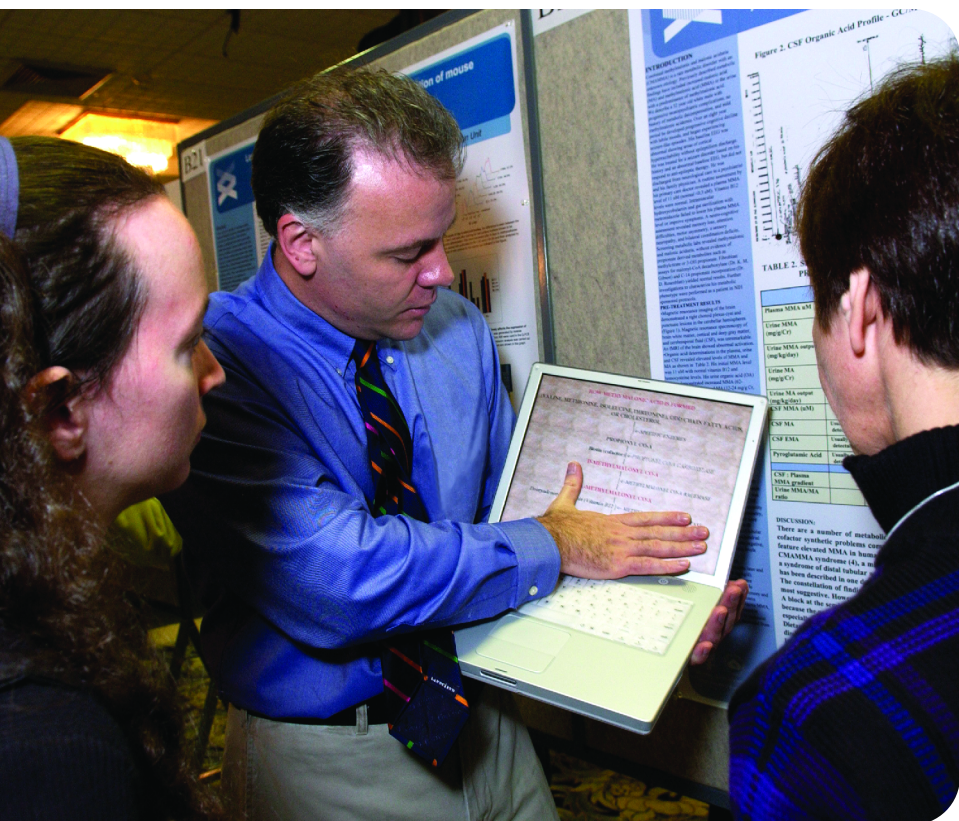
The NHGRI Division of Intramural Research plans and conducts a broad program of laboratory and clinical research on the main NIH campus in Bethesda, Maryland, as well as at other sites such as the Bayview campus in Baltimore, Maryland and the Twinbrook complex in Rockville, Maryland. The Division is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

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

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

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

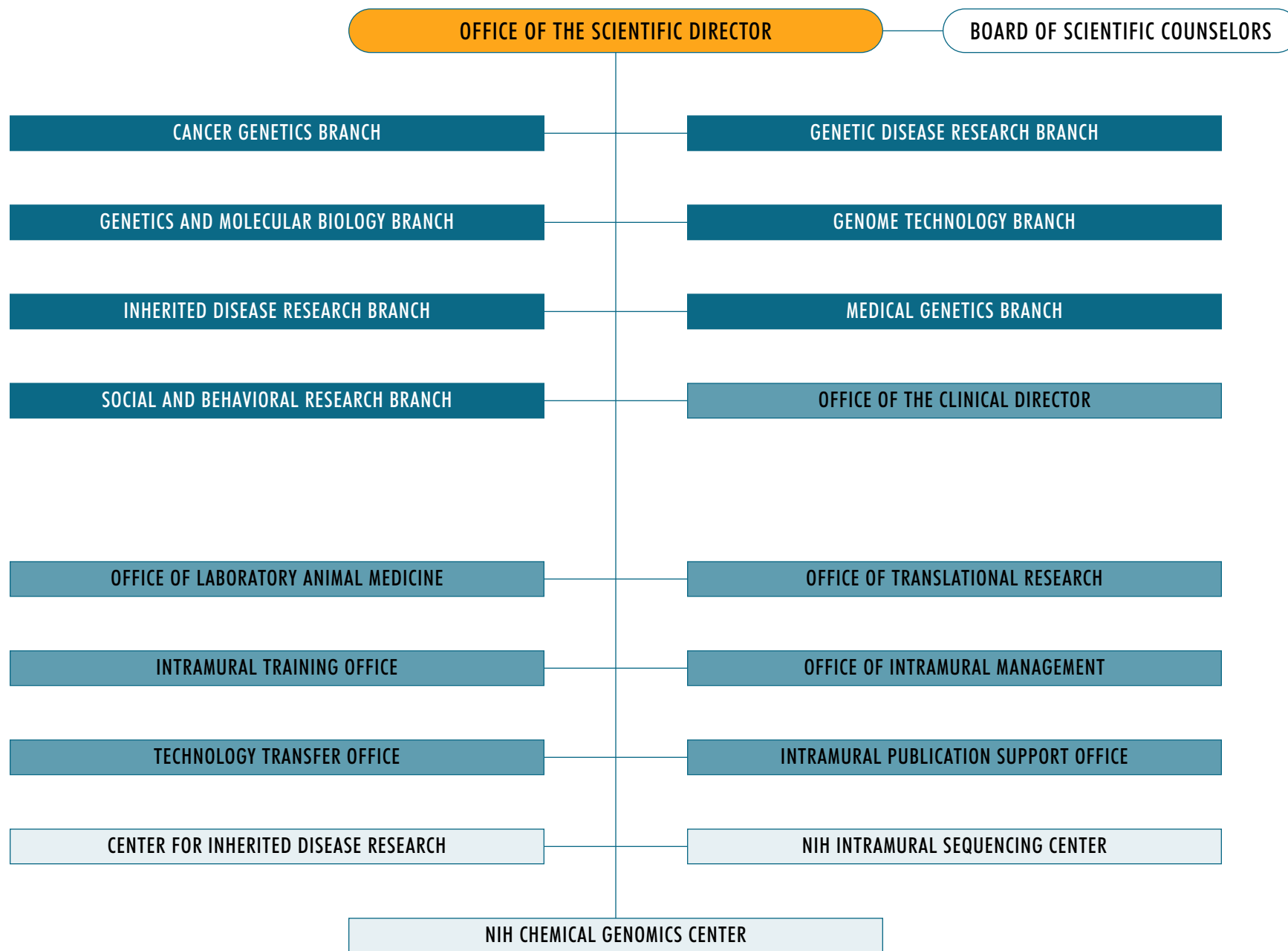




academic research departments. *Senior Investigators* have tenured positions at NIH. Individuals currently on the tenure track (but not yet tenured) are called *Investigators*. All Senior Investigators and Investigators lead Sections, which are individual laboratories within the Branches. *Associate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

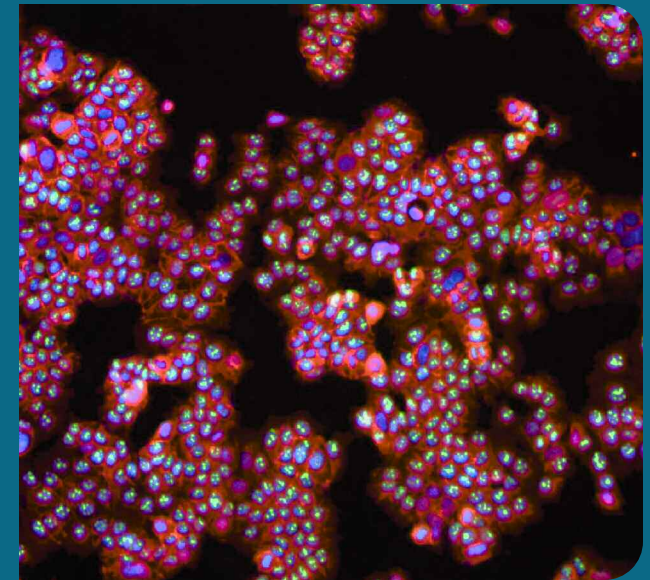
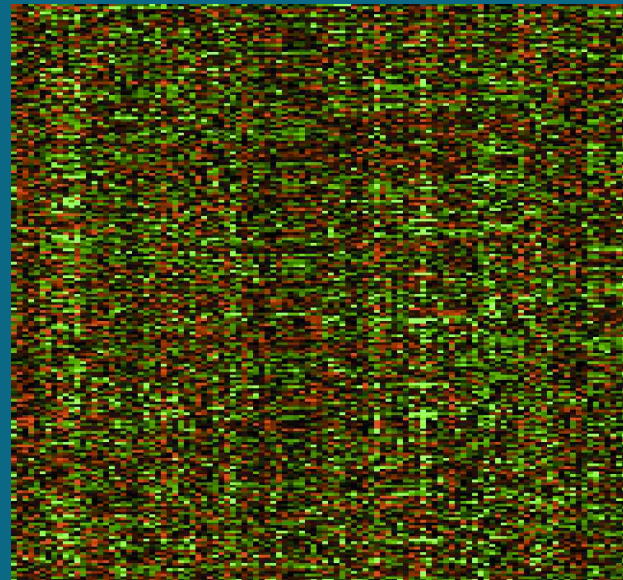
The NHGRI Division of Intramural Research is also supported by a number of other scientific and administrative entities, including a series of cores, centers, and offices. Together, all of the elements of the NHGRI Division of Intramural Research share a common aim—to deliver on the promise of genetics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

## NHGRI DIVISION OF INTRAMURAL RESEARCH



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

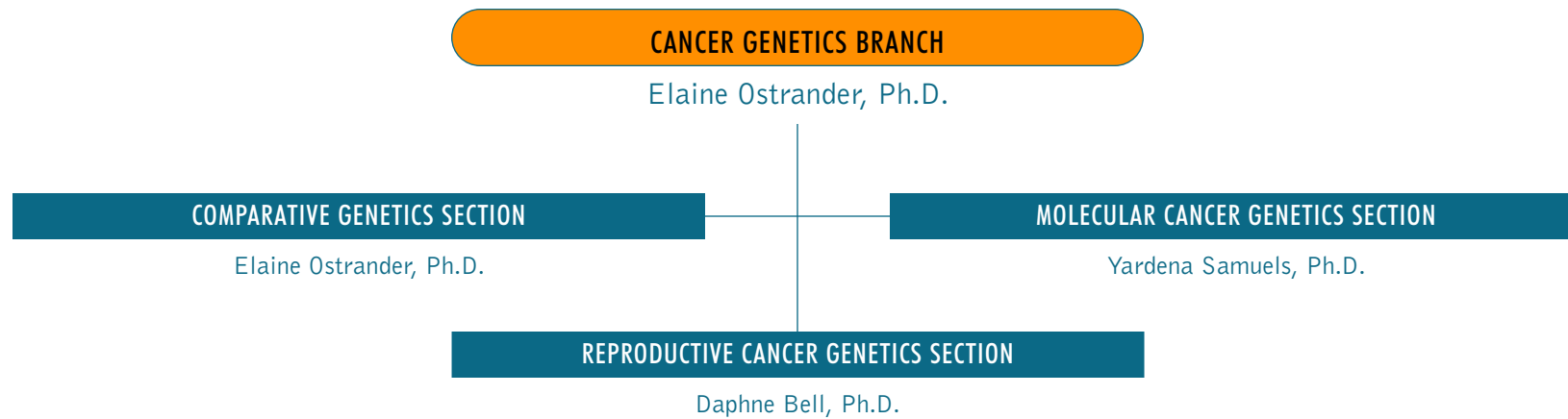
Elaine Ostrander, Ph.D.  
*Chief, Cancer Genetics Branch*



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.







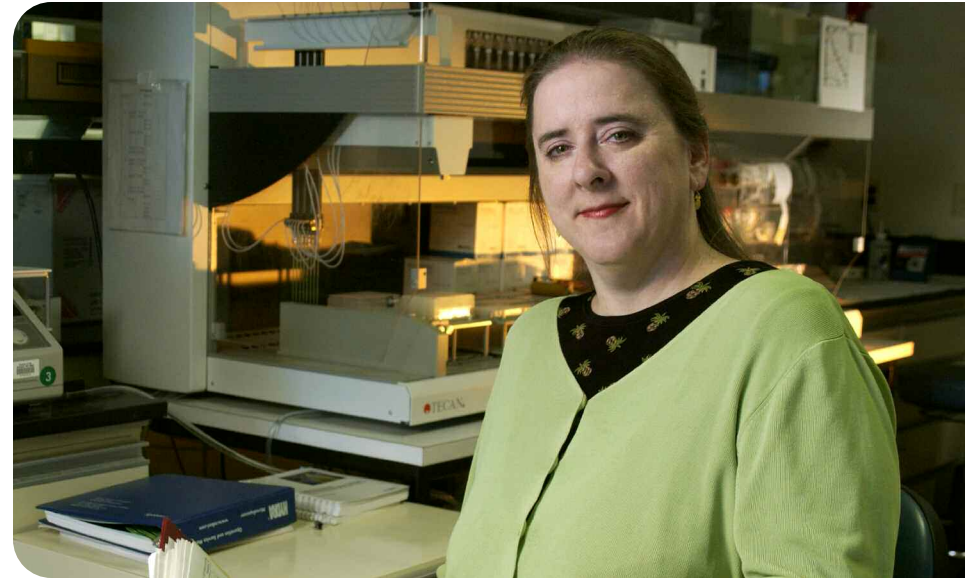
## ELAINE A. OSTRANDER, Ph.D.

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

Pedigrees of dogs are large, multigenerational, and the result of directed matings, all of which favor the expression of recessive disorders, such as cancers. Using information from these pedigrees, Dr. Ostrander's laboratory has constructed high-density comparative maps of the canine genome, and is using those resources as well as the 7.5x whole genome assembly of the dog to map genes for bladder cancer, Addison's disease, hip dysplasia and osteoarthritis. Her group has also undertaken a polymorphism study to determine the interrelatedness of dog breeds. This study demonstrated that differences among breeds account for about 30% of genetic variation within dogs, and that genotyping could be used to assign 99% of individual dogs to their correct breeds. Phylogenetic analysis also allows several breeds with ancient origins to be separated from the remaining breeds with modern European origins. This work sets the stage for Dr. Ostrander and her collaborators to begin the cloning of genes identified in linkage studies by identifying ancestral chromosomes that contribute the same genetic mutation to a multitude of dog breeds. Genes controlling morphology have been of particular interest. Dr. Ostrander's group recently demonstrated that a single *IGF1* haplotype is common to all small



breeds but nearly absent from giant breeds. Data from >3,200 dogs representing 143 breeds demonstrated that *IGF1* accounts for >50% of the variance in average breed mass. These results suggest that the evolutionary mechanics of size variation in dogs is relatively simple and uniquely dependent on the appearance of a single ancient variant. Ongoing studies include mapping loci for leg length and width, as well as skull shape.



Other traits of interest include athletic performance. Dr. Ostrander's laboratory recently showed that whippet dogs carrying a single copy of a protein-truncating mutation in the myostatin gene (*MSTN*) are more heavily muscled and race significantly faster than do their wild-type counterparts. This example of a performance enhancing polymorphism is likely to be one of a large class of genetic variants affecting behavior and performance.

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

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Finally, Dr. Ostrander's laboratory is interested in the frequency and distribution of mutations in known cancer susceptibility genes in the general population. They recently completed two screening studies looking for *BRCA1* and *BRCA2* mutations in women from the general population with breast cancer. The first study, an analysis of 1,600 women, was performed as part of the Shanghai Breast Self Examination Trial, involving 267,000 women in Shanghai, China. The second study is an ancillary project studying data from 2,300 Caucasian and African American women aged 35–64, built on the foundation of the large National Institute of Child Health and Human Development Women's CARE Study. Dr. Ostrander's group is currently analyzing the data to identify both protein-truncating and missense changes that may be associated with disease. To accomplish the latter, they are using comparative genomics—cloning and sequencing the *BRCA1* and *BRCA2* genes from lower mammals and identifying regions that are either highly conserved or evolving under positive selection to identify missense changes likely to be disease-associated. Such changes may represent weakly penetrant disease alleles for breast cancer, and will be the focus of new functional studies.

## SELECTED PUBLICATIONS

Parker HG, Kim LV, Sutter NB, Carlson S, Lorentzen TD, Malek TB, Johnson GS, DeFrance HB, Ostrander EA, Krygylak L. Genetic structure of the purebred domestic dog. *Science* 304:1160–1164, 2004.

Sutter ND, Eberle MA, Parker HG, Pullar BJ, Kirkness EF, Kruglyak L, Ostrander EA. Extensive and breed specific linkage disequilibrium in *Canis familiaris*. *Genome Res* 12:2388–2396, 2004.

Lindblad-Toh K, Wade CM, Mikkelsen T, Karlsson EK, Jaffe DB, Zody MC, Clamp M, Kamal M, Kulbokas III EJ, Chang JL, Mucelli E, Xie X, Breen M, Wayne R, Ostrander EA, et al. Genome sequence, comparative analysis and haplotype structure of the domestic dog. *Nature* 438:803–819, 2005.

VonHoldt BM, Ostrander EA. The singular history of a canine transmissible tumor. *Cell* 126:445–447 2006.

Malone KE, Daling JR, Doody DR, Hsu L, Bernstein L, Coates RJ, Marchbanks PA, Simon MS, McDonald JA, Norman SA, Strom BL, Burkman RT, Ursin G, Deapen D, Weiss LK, Folger SF, Madeoy JJ, Friedrichsen DF, Suter NM, Humphrey MC, Spirtas R, Ostrander EA. Prevalence and predictors of *BRCA1* and *BRCA2* mutations in a population-based study of breast cancer in white and black American women ages 35 to 64 years. *Cancer Res* 66:8297–8308 2006.

Agalliu I, Kwon E, Zadory D, Thompson J, Stanford JL, Ostrander EA. Germline mutations in the *BRCA2* gene and susceptibility to hereditary prostate cancer. *Clin Cancer Res* 13:839–843, 2007.

Suuriniemi M, Agalliu I, Schaid DJ, Johanneson B, McDonnell SK, Iwasaki L, Stanford JL, Ostrander EA. Confirmation of a positive association between prostate cancer risk and a locus at chromosome 8q24. *Cancer Epidemiol Biomarkers Prev* 16:809–814, 2007.

Sutter NB, Bustamante CD, Chase K, Gray MM, Zhao K, Zhu L, Padhukasahasram B, Karlins E, Davis S, Jones PG, Quignon P, Johnson GS, Parker HG, Fretwell N, Mosher DS, Lawler DF, Satyaraj E, Nordborg M, Lark KG, Wayne RK, Ostrander EA. A single *IGF1* allele is a major determinant of small size in dogs. *Science* 316:112–115, 2007.

Schaid DJ, Stanford JL, McDonnell SK, Suuriniemi M, McIntosh L, Karyadi DM, Carlson EE, Deutsch K, Janer M, Hood L, Ostrander EA. Genome-wide linkage scan of prostate cancer Gleason score and confirmation of chromosome 19q. *Hum Genet* 121:729–735, 2007.

Mosher D, Quignon P, Sutter NB, Mellersh CS, Ostrander EA. A mutation in the myostatin gene increases muscle mass and enhances racing performance in heterozygote dogs. *PLoS Genet* 3:e79, 2007.

Parker HG, Kukekova AV, Akey DT, Goldstein O, Kirkness EF, Baysac KC, Mosher DS, Aguirre GD, Acland GM, Ostrander EA. Breed relationships facilitate fine mapping studies: a 7.8 Kb deletion cosegregates with collie eye anomaly across multiple dog breeds. *Genome Res* 17:1562–1571, 2007.

Wayne RK, Ostrander EA. Lessons learned from the dog genome. *Trends Genet* 23:557–567, 2007.

Johanneson B, McDonnell SK, Karyadi DM, Hebring SJ, Wang L, Deutsch K, McIntosh L, Kwon EM, Suuriniemi M, Stanford JL, Schaid DJ, Ostrander EA, Thibodeau SN. Fine-mapping of hereditary prostate cancer families narrows the interval for a susceptibility locus on chromosome 22q12.3 to 1.36 Mb. *Hum Genet*, in press.

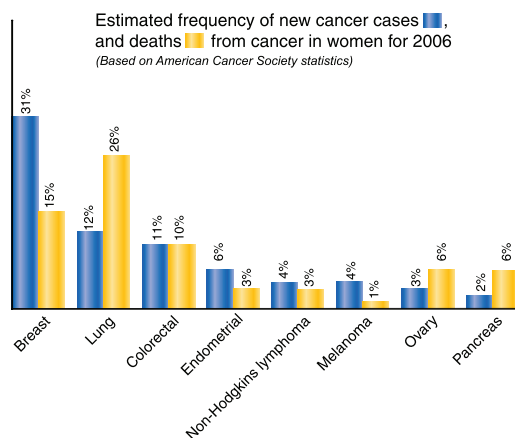
## DAPHNE W. BELL, Ph.D.

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

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

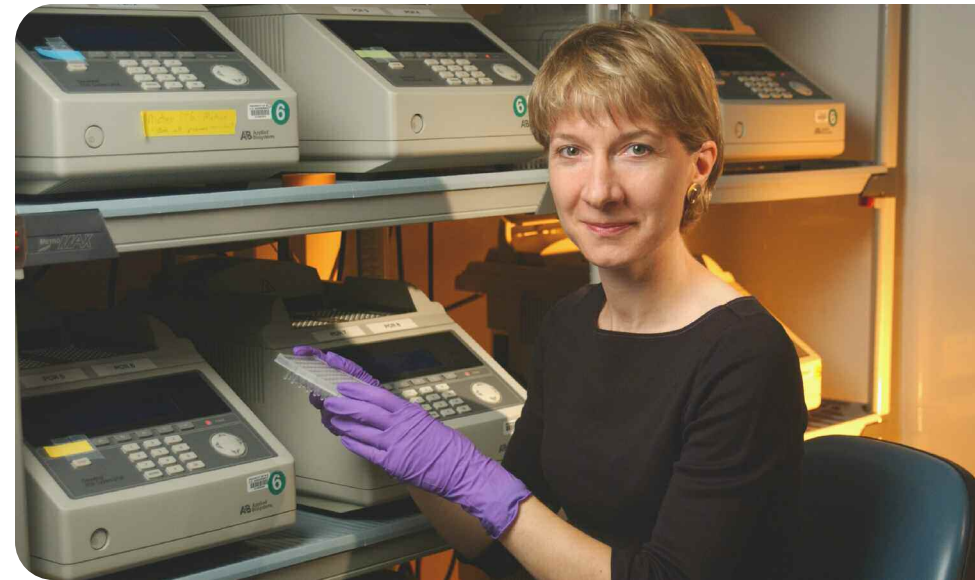
Over the past few years, it has become evident that certain types of chromosomal and genetic alterations may be exploited as therapeutic targets in the treatment of certain malignancies. For example, the drug imatinib is highly effective in the treatment of chronic myelogenous leukemia with an underlying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

Towards that end, her research group is using high-density single-nucleotide polymorphism (SNP) genotyping to identify genome-wide copy-number changes and loss-of-heterozygosity events in type II endometrial tumors. Parallel studies include extensive collaborations with the NIH Intramural Sequencing Center for performing mutational screens of all exons that encode the catalytic domains of 90 known tyrosine kinases. In addition, these efforts include searching for structural chromosomal alterations in endometrial tumors. Once specific genetic alterations are found to be associated with tumor development,



more extensive examination of the clinicopathologic features of mutation-harboring tumors will be performed in an attempt to implicate individual genes or functional pathways that could be targeted for therapeutic intervention.

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



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**HEAD**  
Reproductive Cancer Genetics Section

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

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

## SELECTED PUBLICATIONS

Bell DW, Varley JM, Szydlo TE, Kang DH, Wahrer DCR, Shannon KE, Lubratovich M, Verselis SJ, Isselbacher KJ, Fraumeni JF, Birch JM, Li FP, Garber JE, and Haber DA. Heterozygous germline *hCHK2* mutations in Li-Fraumeni Syndrome. *Science* 286:2528–2531, 1999.

Cantor S, Bell DW, Ganesan S, Kass E, Drapkin R, Grossman S, Wahrer DCR, Sgroi DC, Lane W, Haber DA, and Livingston DM. BACH1, a novel helicase-like protein, interacts with BRCA1 and contributes to its biochemical and clinical functions. *Cell* 105:149–160, 2001.

Moberg KH, Bell DW, Wahrer DCR, Haber DA, and Hariharan IK. Archipelago regulates cyclin E levels in *Drosophila* and is mutated in human cancer cell lines. *Nature* 413:311–316, 2001.

Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, Harris PL, Haserlat SM, Supko JG, Haluska FG, Louis DN, Christiani DC, Settleman J, and Haber DA. Specific activating mutations in the epidermal growth factor receptor determine responsiveness of non-small cell lung cancer to gefitinib. *N Engl J Med* 350:2129–2139, 2004.

Sordella R, Bell DW, Haber DA, and Settleman J. Gefitinib-sensitizing EGFR mutations in lung cancer activate anti-apoptotic pathways. *Science* 305:1163–1167, 2004.

Kwak EL, Sordella R, Bell DW, Godin-Heymann N, Okimoto RA, Brannigan BW, Harris PL, Driscoll DR, Fidias P, Lynch TJ, Rabindran SK, McGinnis JP, Wissner A, Sharma SV, Isselbacher KJ, Settleman J, and Haber DA. Irreversible inhibitors of the EGF receptor may circumvent acquired resistance to gefitinib. *Proc Natl Acad Sci USA* 102:7665–7670, 2005.

Bell DW, Lynch TJ, Haserlat SM, Harris PL, Okimoto RA, Brannigan BW, Sgroi DC, Muir B, Riemenschneider MJ, Bailey Iacona R, Krebs A, Johnson DH, Giaccone G, Herbst RS, Manegold C, Fukuoka M, Kris MG, Baselga B, Ochs JS, and Haber DA. Epidermal growth factor receptor mutations and gene amplification in non-small cell lung cancer: molecular analysis of the IDEAL/INTACT gefitinib trials. *J Clin Oncol* 23:8081–8092, 2005.

Bell DW, Gore I, Okimoto RA, Godin-Heymann N, Sordella R, Mulloy R, Sharma SV, Brannigan BW, Mohapatra G, Settleman J, and Haber DA. Inherited susceptibility to lung cancer may be associated with the T790M drug resistance mutation in EGFR. *Nat Genet* 37:1315–1316, 2005.

Kwak EL, Janowski J, Thayer S, Lauwers G, Brannigan BW, Harris PL, Okimoto RA, Haserlat SM, Driscoll DR, Ferry D, Muir B, Settleman J, Fuchs CS, Kulke M, Ryan DP, Clark JW, Sgroi DC, Haber DA, and Bell DW. EGFR kinase domain mutations in esophageal and pancreatic adenocarcinomas. *Clin Cancer Res* 12:4283–4287, 2006.

Rivera MN, Kim WJ, Wells J, Driscoll DR, Brannigan BW, Han M, Kim JC, Feinberg AP, Gerald WL, Vargus SO, Chin L, Iafrate AJ, Bell DW, Haber DA. An X chromosome gene, *WTX*, is commonly inactivated in Wilms tumor. *Science* 315:642–645, 2007.

Bell DW, Kim SH, Godwin AK, Schiripo TA, Harris PL, Haserlat SM, Wahrer DCR, Haiman CA, Daly MB, Nieldorf KB, Smith MR, Sgroi DC, Garber JE, Olopade OI, Le Marchand L, Henderson BE, Altshuler D, Haber DA, Freedman ML. Genetic and functional analysis of *CHEK2* (*CHK2*) variants in multiethnic cohorts. *Int J Cancer* 121:2661–2667, 2007.

Nagrath S, Sequist L, Maheswaran S, Bell DW, Irimia D, Ulkus L, Smith MR, Kwak EL, Gigumathy S, Muzikansky A, Ryan P, Balis UJ, Tompkins RG, Haber DA, Toner M. Isolation of rare circulating epithelial cells in cancer patients by microchip technology. *Nature*, in press.







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

## SELECTED PUBLICATIONS

Samuels-Lev Y, O'Connor DJ, Bergamaschi D, Trigiante G, Hsieh JK, Zhong S, Campargue I, Naumovski L, Crook T, Lu X. ASPP proteins specifically stimulate the apoptotic function of p53. *Mol Cell* 8:781–794, 2001.

Bergamaschi D, Samuels Y, O'Neil NJ, Trigiante G, Crook T, Hsieh JK, O'Connor DJ, Zhong S, Campargue I, Tomlinson ML, Kuwabara PE, and Lu X. iASPP oncoprotein is a key inhibitor of p53 conserved from worm to human. *Nat Genet* 33:162–167, 2003.

Samuels Y, Wang Z, Bardelli A, Silliman N, Ptak J, Szabo S, Yan H, Gazdar A, Powell SM, Riggins GJ, Willson JK, Markowitz S, Kinzler KW, Vogelstein B, Velculescu VE. High frequency of mutations of the *PIK3CA* gene in human cancers. *Science* 304:554, 2004.

Samuels Y, Velculescu VE. Oncogenic mutations of *PIK3CA* in human cancers. *Cell Cycle* 3:1221–1224, 2004.

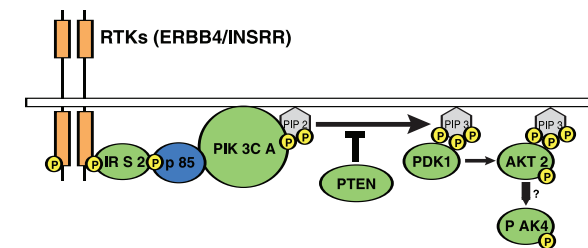
Samuels Y, Diaz LA, Jr., Schmidt-Kittler O, Cummins JM, DeLong L, Cheong I, Rago C, Huso DL, Lengauer C, Kinzler KW, Vogelstein B, Velculescu VE. Mutant *PIK3CA* promotes cell growth and invasion of human cancer cells. *Cancer Cell* 7:561–573, 2005.

Parsons DW, Wang TL, Samuels Y, Bardelli A, Cummins JM, DeLong L, Silliman N, Ptak J, Szabo S, Willson JK, Markowitz S, Kinzler KW, Vogelstein B, Lengauer C, Velculescu VE. Colorectal cancer: mutations in a signalling pathway. *Nature* 436:792, 2005.

Samuels Y, Ericson K. Oncogenic PI3K and its role in cancer. *Curr Opin Oncol* 18:77–82, 2005.

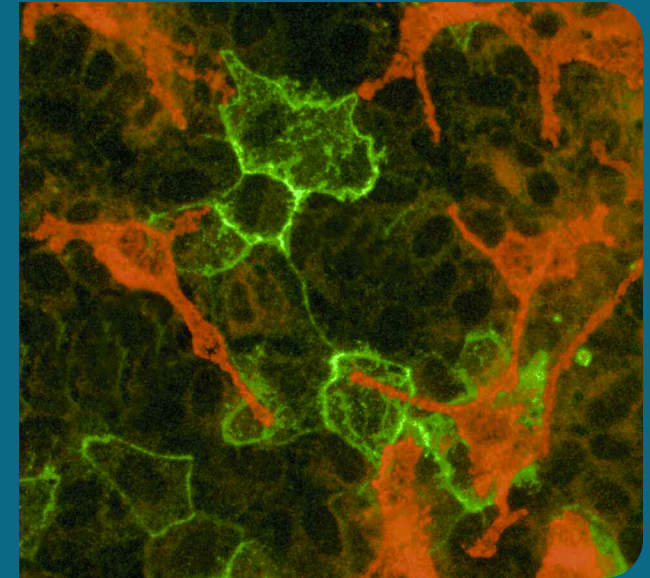
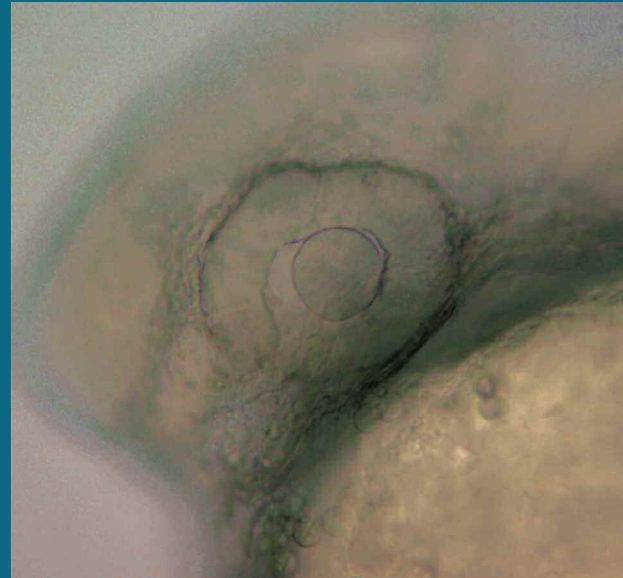
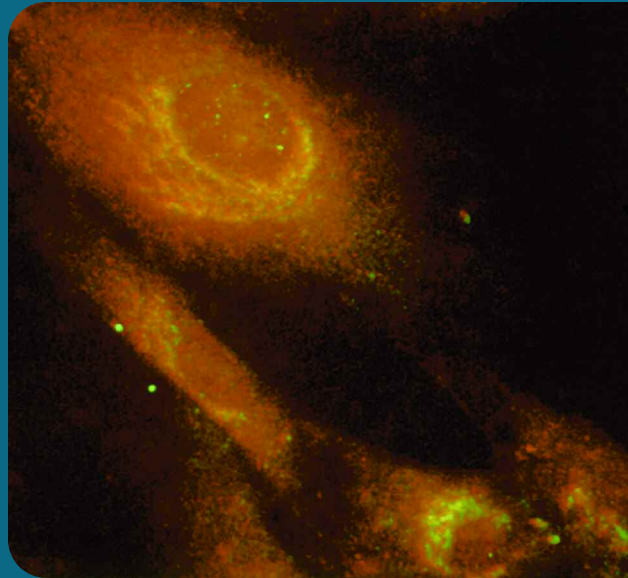
Samuels Y, Zhu J, Lengauer C. Inhibiting phosphoinositide 2-kinases. *Cancer Bio Ther* 4:538–545, 2005.

Huang CH, Mandelker D, Schmidt-Kittler O, Samuels Y, Velculescu VE, Kinzler KW, Vogelstein B, Gabelli SB, Amzel LM. The structure of a human p110 $\alpha$ /p85 $\alpha$  complex elucidates the effect of oncogenic PI3K $\alpha$  mutations. *Science* 318:1744–1748, 2007.



“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.”

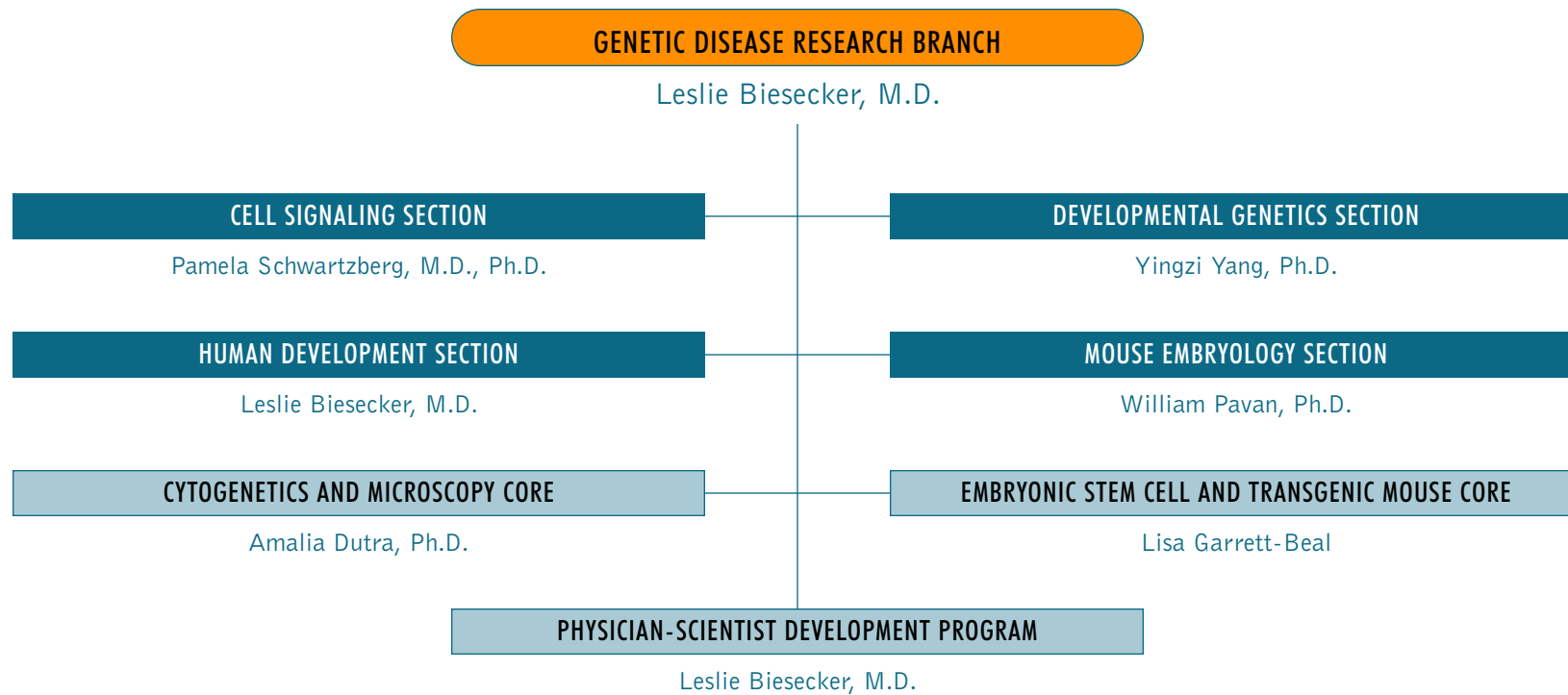
Leslie Biesecker, M.D.  
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The Genetic Disease Research Branch (GDRB) uses human and mouse genetics to study the genes and proteins involved in a variety of normal developmental processes and related diseases. Branch investigators study normal and abnormal 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.





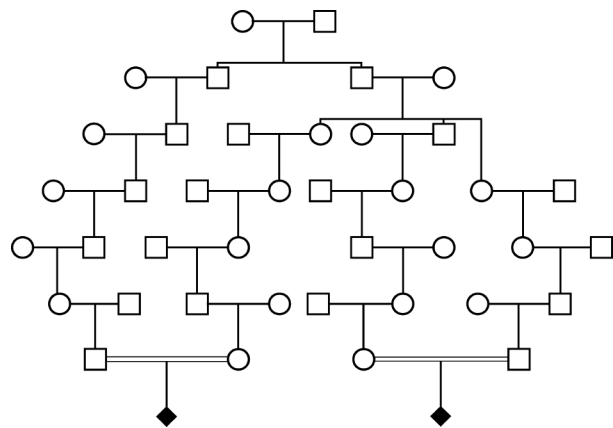


## LESLIE G. BIESECKER, M.D.

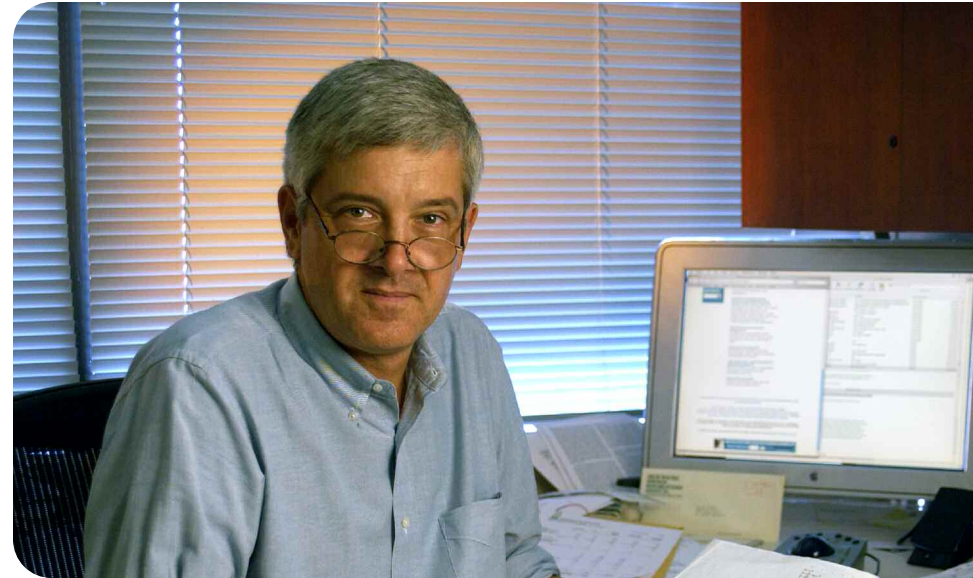
Dr. Biesecker's research focuses on the role of rare genomic sequence variants in human disease. Currently, his laboratory is studying the role of rare variants in two classes of disorders: rare multiple congenital anomaly syndromes and common diseases of the cardiovascular system. The goals of his research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

Dr. Biesecker's group studies several multiple congenital anomaly syndromes, including Pallister-Hall syndrome, Greig cephalopolysyndactyly syndrome, McKusick-Kaufman syndrome, Bardet-Biedl syndrome, and Lenz microphthalmia syndrome. These disorders exhibit combinations of central nervous system malformations, visceral malformations, and polydactyly (extra fingers and toes). Some patients have functional complications, such as mental retardation, seizures, and visual loss. To further elucidate the clinical manifestations of multiple congenital anomaly syndromes and improve treatment approaches, Dr. Biesecker's group conducts clinical research in the Mark O. Hatfield Clinical Research Center.

In the laboratory, his group performs classical positional-cloning studies to find the genes that are altered in these syndromes, determines genotype-phenotype correlations, and uses animal models to investigate the pathogenetic mechanisms of these disorders. For example, they determined that two multiple congenital anomaly syndromes—



oculofaciocardiodental syndrome (OFCD) and MAA2-associated Lenz microphthalmia—are allelic because of their phenotypic overlap. This investigation identified a single-base substitution in the *BCOR* gene (encoding BCL-6-interacting corepressor) on chromosome Xp11.4 in affected males from a family with Lenz syndrome, and different loss-of-function mutations in the *BCOR* gene in seven families affected with OFCD.



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

A new area of research for Dr. Biesecker's group, the ClinSeq project, is studying the use of large-scale medical sequencing (LSMS) in a clinical

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

## SELECTED PUBLICATIONS

Kang S, Graham JM, Olney AH, Biesecker LG. *GLI3* frameshift mutations cause the Pallister-Hall syndrome. *Nat Genet* 15:266–268, 1997.

Shin SH, Kogerman P, Lindstrom E, Toftgard R, Biesecker LG. *GLI3* mutations in human disorders mimic *Drosophila* Cubitus interruptus protein functions and localization. *Proc Natl Acad Sci USA* 96:2880–2884, 1999.

Slavotinek AM, Stone EM, Heckenlively JR, Green JS, Heon E, Musarella MA, Parfrey PS, Sheffield V, Biesecker LG. Mutations in *MKKS* cause Bardet-Biedl syndrome. *Nat Genet* 26:15–16, 2000.

Stone DL, Slavotinek A, Bouffard GG, Banerjee-Basu S, Baxevanis AD, Barr M, Biesecker LG. Mutations in a putative chaperonin cause the McKusick-Kaufman syndrome. *Nat Genet* 25:79–82, 2000.

Biesecker LG. The multifaceted challenges of Proteus syndrome. *JAMA* 285:2240–2243, 2001.

Rosenberg MJ, Agarwala R, Bouffard G, Davis J, Fiermonte G, Hilliard MS, Koch T, Kalikin LM, Makalowska I, Morton DH, Petty EM, Weber JL, Palmieri F, Kelley RI, Schaffer AA, Biesecker LG. Mutant deoxynucleotide carrier is associated with congenital microcephaly. *Nat Genet* 32:175–179, 2002.

Ng D, Thakker N, Corcoran CM, Donnai D, Perveen R, Schneider A, Hadley DW, Tiffit C, Zhang L, Wilkie AOM, van der Smagt JJ, Gorlin RJ, Burgess SM, Bardwell VJ, Black GCM, Biesecker LG. Oculofaciocardiodental and Lenz microphthalmia syndromes result from distinct classes of mutations in *BCOR*. *Nat Genet* 36:411–416, 2004.

Lindhurst MJ, Fiermonte G, Song S, Struys E, DeLeonardis F, Schwartzberg PL, Chen A, Castegna A, Verhoeven N, Mathews CK, Palmieri F, Biesecker LG. Knockout of *Slc25a19* causes mitochondrial thiamine pyrophosphate depletion, embryonic lethality, CNS malformations, and anemia. *Proc Nat Acad Sci USA* 103:15927–15932, 2006.

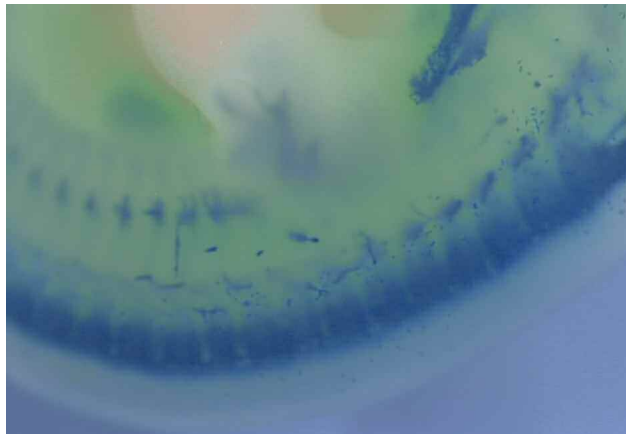


## STACIE K. LOFTUS, Ph.D.

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

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

The Mouse Embryology Section is particularly interested in Waardenburg syndrome, a congenital peripheral nervous system disorder that can cause facial abnormalities, lack of pigment in several regions, and deafness. Patients with Waardenburg syndrome also may lack peripheral nervous system innervation of the gut. Several years ago, Dr. Pavan's laboratory found that mutations in a transcription factor, SOX10, disrupt neural crest development in mice and are



responsible for neural crest defects in some individuals with Waardenburg syndrome. Dr. Loftus has been developing technologies to clarify the relationship between SOX10 and two other transcription factors that are altered in Waardenburg syndrome (MITF and PAX3), identify their downstream target genes, and specify the effects those gene products have on normal neural crest cell development.



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

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

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

## SELECTED PUBLICATIONS

Loftus SK, Morris JA, Carstea ED, Gu JZ, Cummings C, Brown A, Ellison J, Ohno K, Rosenfeld MA, Tagle DA, Pentchev PG, Pavan WJ. Murine model of Niemann-Pick C disease: mutation in a cholesterol homeostasis gene. *Science* 277:232–235, 1997.

Loftus SK, Chen Y, Gooden G, Ryan JF, Birznieks G, Hilliard M, Baxevis AD, Bittner M, Meltzer P, Trent J, Pavan W. Informatic selection of a neural crest-melanocyte cDNA set for microarray analysis. *Proc Natl Acad Sci USA* 96:9277–9280, 1999.

Loftus SK, Larson DM, Watkins-Chow D, Church DM, Pavan WJ. Generation of RCAS vectors useful for functional genomic analyses. *DNA Res* 8:221–226, 2001.

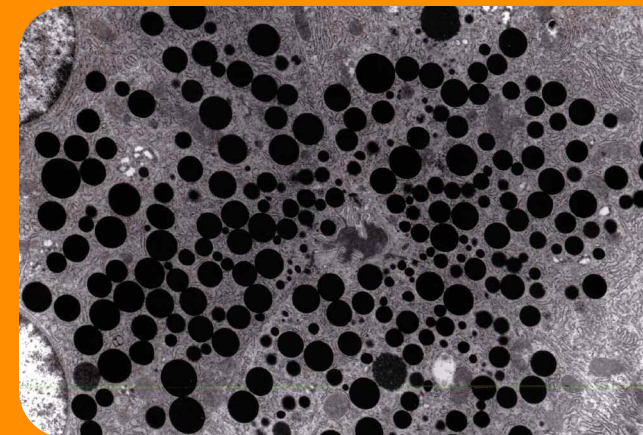
Loftus SK, Erickson RP, Walkely SU, Bryant MA, Incao A, Heidenreich RA, Pavan WJ. Rescue of neurodegeneration in Niemann Pick-C mice by a prion-promoter-driven *Npc1* cDNA transgene. *Hum Mol Genet* 11:3107–3144, 2002.

Loftus SK, Larson DM, Baxter LL, Antonellis A, Chen Y, Wu X, Jiang Y, Bittner M, Hammer JA III, Pavan WJ. Mutation of the melanosomal protein RAB38 in chocolate mice. *Proc Natl Acad Sci USA* 99:4471–4476, 2002.

Rao C, Foernzler D, Loftus SK, Liu S, McPherson JD, Jungers KA, Apte SS, Pavan WJ, Beier DR. A defect in a novel ADAMTS family member is the cause of the belted white-spotting mutation. *Development* 30:4665–4672, 2003.

Hou L, Loftus SK, Incao A, Chen A, Pavan WJ. Complementation of melanocyte development in SOX10 mutant neural crest using lineage-directed gene transfer. *Dev Dyn* 229:54–62, 2004.

Loftus SK, Cannons JL, Incao A, Pak E, Chen A, Zerfas PM, Bryant MA, Biesecker LG, Schwartzberg PL, Pavan WJ. Acinar cell apoptosis in *serpini2*-deficient mice models pancreatic insufficiency. *PLoS Genet* 1:e38, 2005



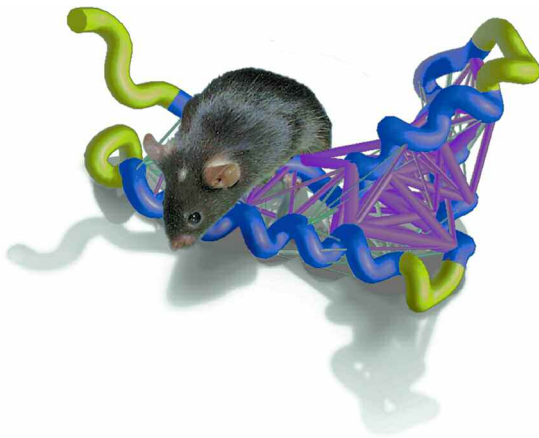


## WILLIAM J. PAVAN, Ph.D.

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

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

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



Mice are particularly good models for studying melanocyte genetics because many strains with differing coat patterns have been preserved over the past two centuries, and each coat pattern



reflects a different, spontaneous mutation in a gene or genes governing melanocyte development. Thus, no sophisticated assays are required to identify different phenotypes; researchers simply look at coat colors and patterns.

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

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

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

## SELECTED PUBLICATIONS

Loftus SK, Morris JA, Carstea ED, Gu JZ, Cummings C, Brown A, Ellison J, Ohno K, Rosenfeld MA, Tagle DA, Pentchev PG, Pavan WJ. Murine model of Niemann-Pick C disease: mutation in a cholesterol homeostasis gene. *Science* 277:232–235, 1997.

Southard-Smith EM, Kos L, Pavan WJ. Sox10 mutation disrupts neural crest development in Dom Hirschsprung mouse model. *Nat Genet* 18:60–64, 1998.

Dunn KJ, Williams BO, Li Y, Pavan WJ. Neural crest directed gene transfer demonstrates Wnt1 role in melanocyte expansion and differentiation during mouse development. *Proc Natl Acad Sci USA* 97:10050–10055, 2000.

Potterf SB, Furumura M, Dunn KJ, Arnheiter H, Pavan WJ. Transcription factor hierarchy in Waardenburg syndrome: regulation of MITF expression by SOX10 and PAX3. *Hum Genet* 107:1–6, 2000.

Potterf SB, Mollaaghababa R, Hou L, Southard-Smith EM, Hornyak TJ, Arnheiter H, Pavan WJ. Analysis of SOX10 function in neural crest-derived melanocyte development: SOX10-dependent transcriptional control of dopachrome tautomerase. *Dev Biol* 237:245–257, 2001.

Loftus SK, Larson DM, Baxter LL, Antonellis A, Chen Y, Wu X, Bittner M, Hammer JA, Pavan WJ. Mutation of melanosome protein RAB38 in *chocolate* mice. *Proc Natl Acad Sci USA* 99:4471–4476, 2002.

Pollock PM, Cohen-Solal K, Sood R, Namkoong J, Koganti A, Zhu H, Robbins C, Makalowska I, Martino JJ, Shin S-S, Marin Y, Roberts KG, Yudit LM, Chen A, Cheng J, Incao A, Pinkett HW, Graham CL, Dunn K, Crespo-Carbone SM, Mackason KR, Ryan KB, Sinsimer D, Goydos J, Reuhl KR, Eckhaus M, Meltzer PS, Pavan WJ, Trent JM, Chen S. Melanoma mouse model implicates metabotropic glutamate signaling in melanocytic neoplasia. *Nat Genet* 34:108–112, 2003.

Rao C, Foerzler D, Liu S, Loftus S, McPherson J, Apte S, Pavan WJ, Beier DR. A defect in a novel ADAMTS family member is the cause of the belted white-spotting mutation. *Development* 130:4665–4672, 2003.

Baxter LL, Pavan WJ. Pmel17 expression is *Mitf*-dependent and reveals cranial melanoblast migration during murine development. *Gene Expr Patterns* 3:703–707, 2003.

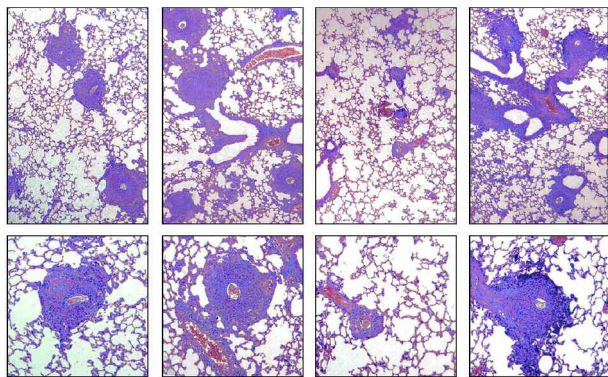
Hou L, Loftus SK, Incao A, Chen A, Pavan WJ. Complementation of melanocyte development in SOX10 mutant neural crest using lineage-directed gene transfer. *Dev Dynamics* 229:54–62, 2004.

## 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  $\text{NF}\kappa\text{B1}$ , a transcription factor that plays a key role in the regulation of cellular genes involved in immune and inflammatory responses. In addition to pointing toward new lines of research for treating the disease, these insights may aid in



the development of vaccines, because the generation of long-term persisting antibodies against a particular infectious agent is a crucial requirement for successful vaccine development.

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



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

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

## SELECTED PUBLICATIONS

Debnath J, Chamorro M, Czar MJ, Schaeffer EM, Lenardo MJ, Varmus HE, Schwartzberg PL. *rlk/TXK* encodes two forms of a novel cysteine string tyrosine kinase activated by Src family kinases. *Mol Cell Biol* 19:1498–1507, 1999.

Schaeffer EM, Debnath J, Yap G, McVicar D, Liao XC, Littman DR, Sher A, Varmus HE, Lenardo MJ, Schwartzberg PL. Requirement for Tec kinases Rlk and Itk in T cell receptor signaling and immunity. *Science* 284:638–641, 1999.

Schaeffer E, Broussard C, Debnath J, Anderson S, McVicar D, Schwartzberg P. Tec family kinases modulate thresholds for thymocyte development and selection. *J Exp Med* 192:987–1000, 2000.

Czar MJ, Kersh EN, Mijares LA, Lanier G, Lewis J, Yap G, Chen A, Sher A, Duckett CS, Ahmed R, Schwartzberg PL. Altered lymphocyte responses and cytokine production in mice deficient in the X-linked lymphoproliferative disease gene *SH2D1A/DSHP/SAP*. *Proc Natl Acad Sci USA* 98:7449–7454, 2001.

Schaeffer EM, Yap GS, Lewis CM, Czar MJ, McVicar DW, Cheever AW, Sher A, Schwartzberg PL. Mutation of Tec family kinases alters T helper cell differentiation. *Nat Immunol* 2:1183–1188, 2001.

Crotty S, Kersh EN, Cannons J, Schwartzberg PL, Ahmed R. SAP is required for generating long-term humoral immunity. *Nature* 421:282–287, 2003.

Labno CM, Lewis CM, You D, Leung DW, Takesono A, Kamberos N, Seth A, Finkelstein LD, Rosen MK, Schwartzberg PL, Burkhardt JK. Itk functions to control actin polymerization at the immune synapse through localized activation of Cdc42 and WASP. *Curr Biol* 13:1619–1624, 2003.

Takesono A, Horai R, Mandai M, Dombroski D, Schwartzberg PL. Requirement for Tec kinases in chemokine-induced migration and activation of Cdc42 and Rac. *Curr Biol* 14:917–922, 2004.

Cannons JL, Hill B, Yu LJ, Mijares LA, Dombroski D, Nichols KE, Antonellis A, Koretzky GA, Gardner K, Schwartzberg PL. SAP regulates TH2 differentiation and PKC- $\tau$ -mediated activation of NF- $\kappa$ B1. *Immunity* 21:693–706, 2004.

Dombroski D, Houghtling R, Labno CM, Burkhardt J, Schwartzberg PL. Kinase-independent functions for Itk in the regulation of Vav and the actin cytoskeleton. *J Immunol* 174:1385–1392, 2005.

Schwartzberg PL, Finkelstein LD, Cook JA. Tec kinases: regulators of T helper cell differentiation. *Nature Rev Immunol* 5:284–295, 2005.

Cannons JL, Yu LJ, Jankovic D, Crotty S, Horai R, Kirby M, Anderson S, Cheever AW, Sher A, Schwartzberg PL. T cell-mediated humoral immune regulation by SAP: evidence for a mechanism independent of cytokine regulation. *J Exp Med* 203:1551–1565, 2006.

Broussard C, Fleischacker C, Horai R, Chetana M, Venegas AM, Sharp L, Hedrick S, Fowlkes BJ, and Schwartzberg PL. Altered development of CD8+ T cell lineages in mice deficient in the Tec kinases Itk and Rlk. *Immunity* 25:93–104, 2006.

Adriani M, Aoki J, Horai R, Thornton AM, Konno A, Kirby M, Anderson SM, Siegel RM, Candotti F, Schwartzberg PL. Impaired in vitro regulatory T cell function associated with Wiskott-Aldrich syndrome. *Clin Immunol* 124:41–48, 2007.

Horai R, Mueller KL, Handon RA, Cannons JL, Anderson SM, Kirby MR, Schwartzberg PL. Requirements for selection of conventional and innate T lymphocyte lineages. *Immunity* 27:775–785, 2007.

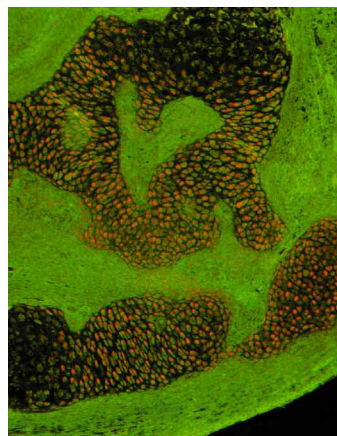


## YINGZI YANG, Ph.D.

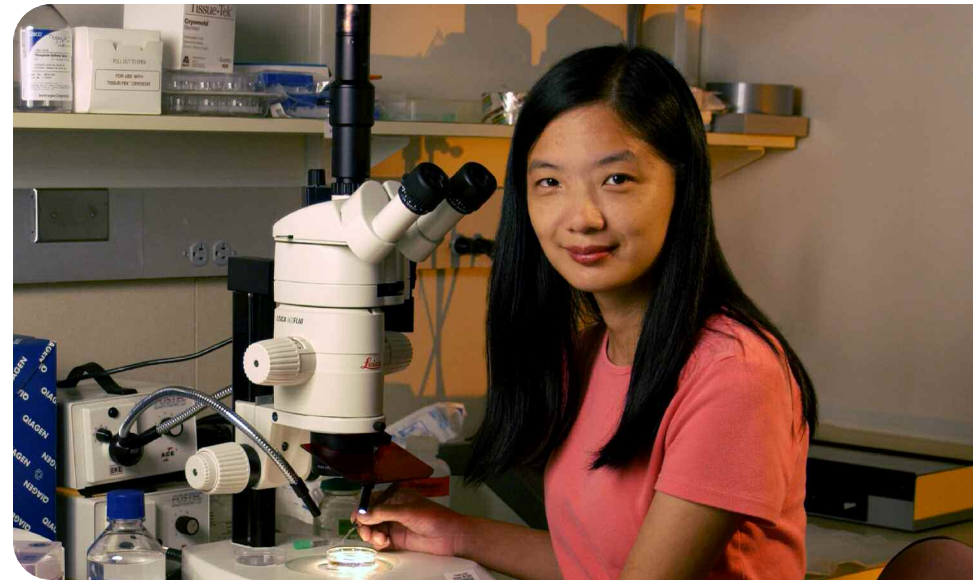
Dr. Yang studies cell-to-cell signaling in vertebrate limb development and skeletal morphogenesis. In particular, she concentrates on the Wnt and Hedgehog groups of signaling molecules, which play important roles in the formation of many organs and tissues in the developing embryo. Her goal is to understand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

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

Limb and skeletal development are excellent models for the study of these signaling molecules because abnormalities can be easily observed. Moreover, embryos can survive with severe abnormalities in limb development, which allows scientists to study genetically the function of Wnt and Hedgehog signaling in the limb and correlate this information with



human birth defects. Limb development can be divided into the early patterning phase and the late skeletal morphogenesis phase. Dr. Yang's previous work provided insight into the regulation of early limb-patterning events, while her current research addresses how signaling molecules regulate the formation of skeletal elements in the limb—a later morphogenetic process.



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

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

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

## SELECTED PUBLICATIONS

Yang Y, Guillot P, Boyd Y, Lyon MF, McMahon AP. Evidence that preaxial polydactyly in *Doublefoot* mutant is due to ectopic Indian Hedgehog signaling. *Development* 125:3123–3132, 1998.

Kundu M, Javed A, Jeon JP, Horner A, Eckhaus M, Muenke M, Lian JB, Yang Y, Nuckolls GH, Stein GS, Liu PP. Cbfb interacts with Runx2 and has a critical role in bone development. *Nat Genet* 32:639–644, 2002.

Topol L, Jiang X, Choi H, Garrett-Beal L, Carolan PJ, Yang Y. Wnt-5a inhibits the canonical Wnt pathway by promoting GSK-3-independent beta-catenin degradation. *J Cell Biol* 162:899–908, 2003.

Yang Y. Wnts and wing: Wnt signaling in vertebrate limb development and musculoskeletal morphogenesis. *Birth Defects Res Part C Embryo Today* 69:305–317, 2003.

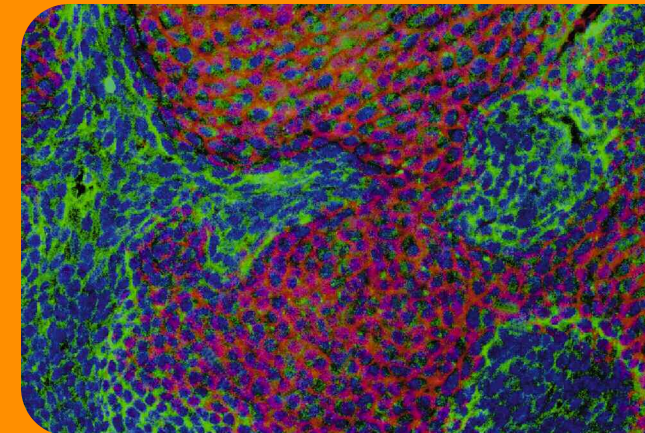
Yang Y, Topol L, Lee H, Wu J. Wnt5a and Wnt5b exhibit distinct activities in coordinating chondrocyte proliferation and differentiation. *Development* 130:1003–1015, 2003.

Guo X, Day T, Jiang X, Garrett-Beal L, Topol L, Yang Y. Wnt/beta-catenin signaling is sufficient and necessary for synovial joint formation. *Genes Dev* 18:2404–2417, 2004.

Day T, Guo X, Garrett-Beal L, Yang Y. Wnt/beta-catenin signaling in mesenchymal progenitors controls osteoblast and chondrocyte differentiation during vertebrate skeletogenesis. *Dev Cell* 8:739–750, 2005.

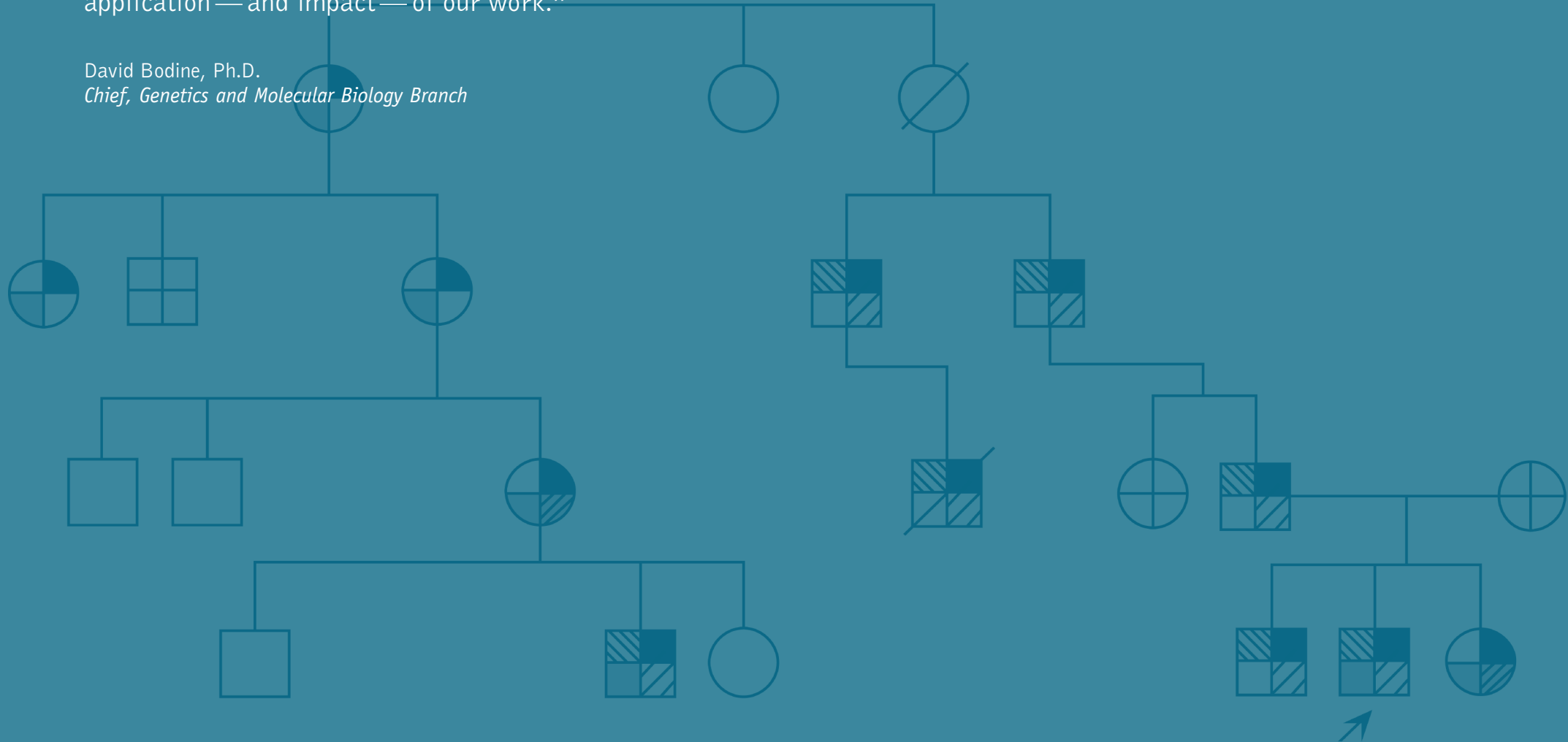
Mak KK, Chen MH, Day TF, Chuang PT, Yang Y. Wnt/b-catenin signaling interacts differentially with Ihh signaling in controlling endochondral bone and synovial joint formation. *Development* 133:3695–3707, 2006.

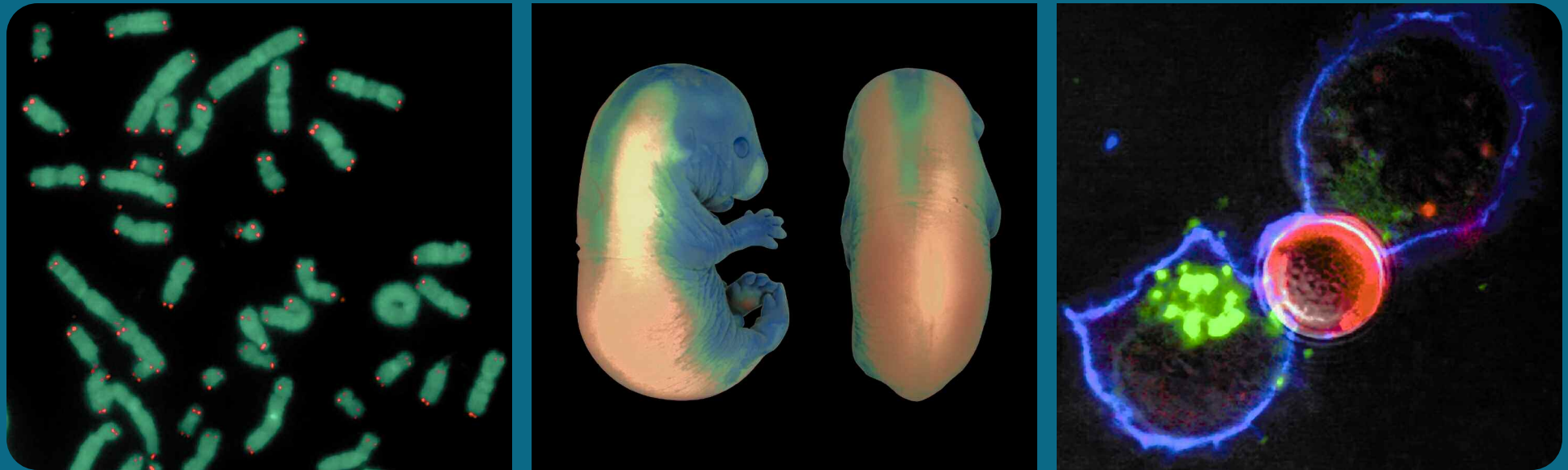
Nemeth MJ, Topol L, Anderson SM, Yang Y, Bodine DM. Wnt5a inhibits canonical Wnt signaling in hematopoietic stem cells and enhances repopulation. *Proc Natl Acad Sci USA* 104:15436–15441, 2007.



“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*





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.



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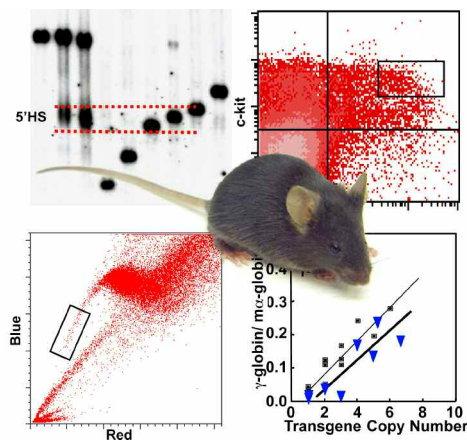
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## DAVID M. BODINE, Ph.D.

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

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



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



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

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

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

## SELECTED PUBLICATIONS

Frazar TF, Weisbein JL, Anderson SM, Cline AP, Garrett LJ, Felsenfeld G, Gallagher PG, Bodine DM. Variegated expression from the murine band 3 (AE1) promoter in transgenic mice is associated with mRNA transcript initiation at upstream start sites and can be suppressed by the addition of the chicken  $\beta$ -globin 5' HS4 insulator element. *Mol Cell Biol* 23:4753–4763, 2003.

Gallagher PG, Nilson DG, Wong C, Weisbein JL, Garrett-Beal LJ, Eber SW, Bodine DM. A dinucleotide deletion in the ankyrin promoter alters gene expression, transcription initiation and TFIID complex formation in hereditary spherocytosis. *Hum Mol Genet* 14:2501–2509, 2005.

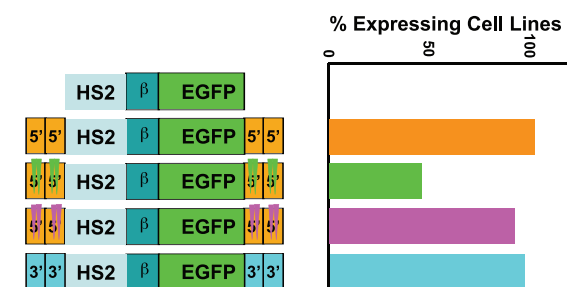
Lucas ML, Seidel NE, Porada CD, Quigley JG, Anderson SM, Malech HL, Abkowitz JL, Zanjani ED, Bodine DM. Improved transduction of human sheep repopulating cells by retrovirus vectors pseudotyped with feline leukemia virus type C or RD114 envelopes. *Blood* 106:51–58, 2005.

Nemeth MJ, Kirby MR, Bodine DM. Hmgb3 regulates the balance between hematopoietic stem cell self-renewal and differentiation. *Proc Natl Acad Sci USA* 103:13783–13788, 2006.

Pilon AM, Nilson DG, Zhou D, Sangerman J, Townes TM, Bodine DM, Gallagher PG. Alterations in expression and chromatin configuration of the alpha hemoglobin-stabilizing protein gene in erythroid Kruppel-like factor-deficient mice. *Mol Cell Biol* 26:4368–4377, 2006.

Nemeth MJ, Topol L, Anderson SM, Yang Y, Bodine DM. Wnt5a inhibits canonical Wnt signaling in hematopoietic stem cells and enhances repopulation. *Proc Natl Acad Sci USA* 104:15436–15441, 2007.

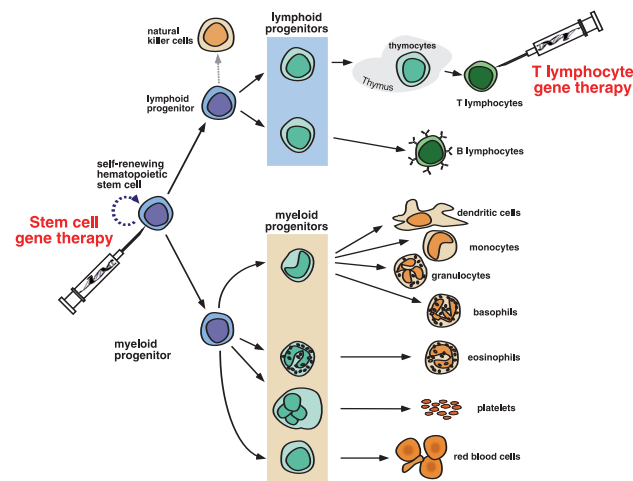
Stefanovic M, Markham NO, Parry EM, Garrett-Beal LJ, Cline AP, Gallagher PG, Low PS, Bodine DM. An 11-amino acid beta-hairpin loop in the cytoplasmic domain of band 3 is responsible for ankyrin binding in mouse erythrocytes. *Proc Natl Acad Sci USA* 104:13972–13977, 2007.



## FABIO CANDOTTI, M.D.

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

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



Genetic correction of a patient's own hematopoietic stem cells, therefore, could be a beneficial therapeutic alternative.

Dr. Candotti's laboratory is evaluating novel retroviral vectors as gene transfer tools for correcting ADA deficiency. A major obstacle to this approach has been the low level of expression of the inserted genes and often eventual loss of expression. To overcome this problem, his group



has constructed improved retroviral vectors that provide a higher level of transgene expression in human lymphoid cells, as compared with previously used vectors. They currently are conducting a clinical trial to determine whether these improved vectors will provide better reconstitution of the immune system.

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



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

Finally, Dr. Candotti's group is evaluating T cell- and hematopoietic stem cell-directed gene therapy for a rare form of immune deficiency caused by a genetic mutation of the  $\beta 1$  chain of the interleukin-12 receptor (IL12R $\beta 1$ ). This disease is characterized by increased vulnerability to weakly pathogenic organisms. Even with aggressive treatment, IL12R $\beta 1$ -deficient patients can succumb to such infections. Experiments with retroviral-mediated gene correction of T cells from IL12R $\beta 1$ -deficient patients have shown restored expression of IL12R $\beta 1$  and a reconstituted, functional IL-12 signaling pathway. As with ADA deficiency and WAS, these results indicate that the biological defects of T cells caused by IL12R $\beta 1$  deficiency can be corrected by gene transfer.

## SELECTED PUBLICATIONS

Wada T, Schurman SH, Otsu M, Garabedian EK, Ochs HD, Nelson DL, Candotti F. Somatic mosaicism in Wiskott-Aldrich syndrome suggests *in vivo* reversion by a DNA slippage mechanism. *Proc Natl Acad Sci USA* 98:8697-8702, 2001.

Wada T, Jagadeesh GJ, Nelson LD, Candotti F. Retrovirus-mediated WASP gene transfer corrects Wiskott-Aldrich syndrome T cell dysfunction. *Hum Gene Ther* 13:1039-1046, 2002.

Muul LM, Tuschong LM, Soenen SL, Jagadeesh GJ, Ramsey WJ, Long Z, Carter CS, Garabedian EK, Alleyne M, Brown M, Bernstein W, Schurman SH, Fleisher TA, Leitman SF, Dunbar CE, Blaese RM, Candotti F. Persistence and expression of the adenosine deaminase gene for twelve years and immune reaction to gene transfer components: long-term results of the first clinical gene therapy trial. *Blood* 101:2563-2569, 2003.

Shcherbina A, Candotti F, Rosen FS, Remold-O'Donnell E. High incidence of lymphomas in a subgroup of Wiskott-Aldrich syndrome patients. *Br J Haematol* 121:529-530, 2003.

Schurman SH, Candotti F. Autoimmunity in the Wiskott-Aldrich syndrome. *Curr Opin Rheumatol* 15:446-453, 2003.

Wada T, Konno A, Schurman SH, Garabedian EK, Anderson SM, Kirby M, Nelson DL, Candotti F. Second-site mutation in the Wiskott-Aldrich syndrome (WAS) protein gene causes somatic mosaicism in two WAS sibs. *J Clin Invest* 111:1389-1397, 2003.

Bosticardo M, Witte I, Fieschi C, Novelli F, Casanova JL, Candotti F. Retroviral-mediated gene transfer restores IL-12 and IL-23 signaling pathways in T cells from IL-12 receptor  $\beta 1$  deficient patients. *Mol Ther* 9:895-901, 2004.

Konno A, Wada T, Schurman SH, Garabedian EK, Kirby M, Anderson SM, Candotti F. Differential contribution of Wiskott-Aldrich syndrome protein to selective advantage in T and B cell lineages. *Blood* 103:676-678, 2004.

Wada T, Schurman SH, Jagadeesh GJ, Garabedian EK, Nelson DL, Candotti F. Multiple revertant patients in a single Wiskott-Aldrich syndrome family. *Blood* 104:1270-1272, 2004.

Fieschi C, Bosticardo M, de Beaucoudrey L, Dupuis S, Feinberg J, dos Santos O, Bustamante J, Levy J, Candotti F, Casanova JL. A novel form of complete IL-12/IL-23 receptor  $\beta 1$ -deficiency with cell surface-expressed non-functional receptors. *Blood* 104:2095-2101, 2004.

Wada T, Schurman SH, Garabedian EK, Yachie A, Candotti F. Analysis of T-cell repertoire diversity in Wiskott-Aldrich syndrome. *Blood* 106:3895-3897, 2005.



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

## SELECTED PUBLICATIONS

Castilla LH, Wijmenga C, Wang Q, Stacy T, Speck NA, Eckhaus M, Marin-Padilla M, Collins FS, Wynshaw-Boris A, Liu PP. Failure of embryonic hematopoiesis and lethal hemorrhages in mouse embryos heterozygous for a knocked-in leukemia gene *CBFB-MYH11*. *Cell* 87:687–696, 1996

Castilla LH, Garrett L, Adya N, Orlic D, Dutra A, Anderson S, Owens J, Eckhaus M, Bodine D, Liu PP. Chromosome 16 inversion-generated fusion gene *Cbfb-MYH11* blocks myeloid differentiation and predisposes mice to acute myelomonocytic leukemia. *Nat Genet* 23:144–146, 1999.

Blake T, Adya N, Oates A, Zon L, Chitnis A, Weinstein BM, Liu PP. Zebrafish homolog of the leukemia gene *CBFB*: its expression during embryogenesis and its relationship to *scl* and *gata-1* in hematopoiesis. *Blood* 96:4178–4184, 2000.

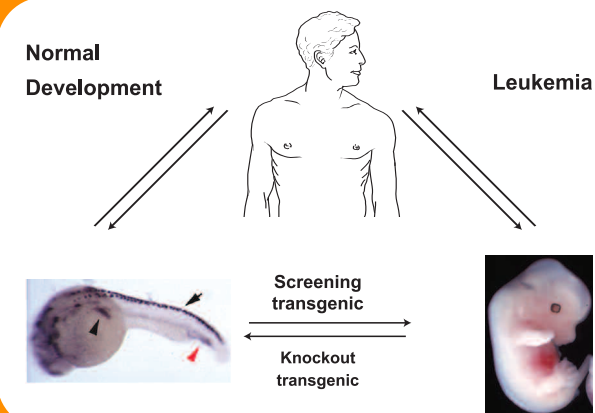
Kundu M, Chen A, Anderson S, Kirby M, Xu L-P, Castilla LH, Bondine D, Liu PP. Role of *Cbfb* in hematopoiesis and perturbations resulting from expression of the leukemogenic fusion gene *Cbfb-MYH11*. *Blood* 100:2449–2456, 2002.

Lyons SE, Lawson ND, Lei L, Bennett PE, Weinstein BM, Liu PP. A nonsense mutation in zebrafish *gata-1* causes the bloodless phenotype in *Vlad Tepes*. *Proc Natl Acad Sci USA* 99:5454–5459, 2002.

Kundu M, Javed A, Jeon J-P, Horner A, Shum L, Eckhaus M, Muenke M, Lian JB, Yang Y, Nuckolls GH, Stein GS, Liu PP. *Cbfb* interacts with *Runx2* and has a critical role in bone development. *Nat Genet* 32:639–644, 2002.

Castilla LH, Perrat P, Martinez NJ, Landrette SF, Keys R, Oikemus S, Flanagan J, Heilman S, Garrett L, Dutra A, Anderson S, Pihan GA, Wolff L, Liu PP. Identification of genes that synergize with *Cbfb-MYH11* in the pathogenesis of acute myeloid leukemia. *Proc Natl Acad Sci USA* 101:4924–4929, 2004.

Sood R, English MA, Jones M, Mullikin J, Wang DM, Anderson M, Wu D, Chandrasekharappa SC, Yu J, Zhang J, Liu PP. Methods for reverse genetic screening in zebrafish by resequencing and TILLING. *Methods* 39:220–227, 2006.

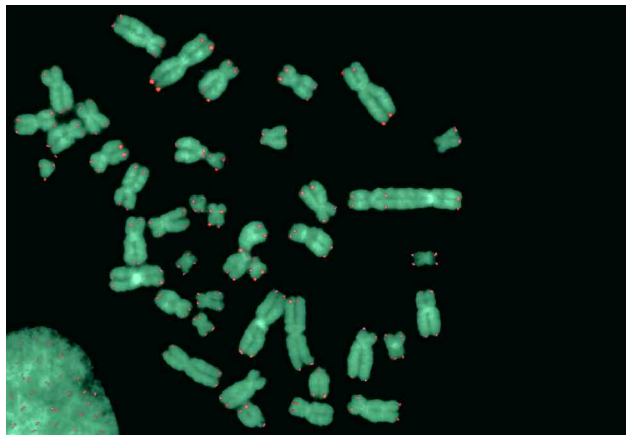


## KYUNGJAE (KJ) MYUNG, Ph.D.

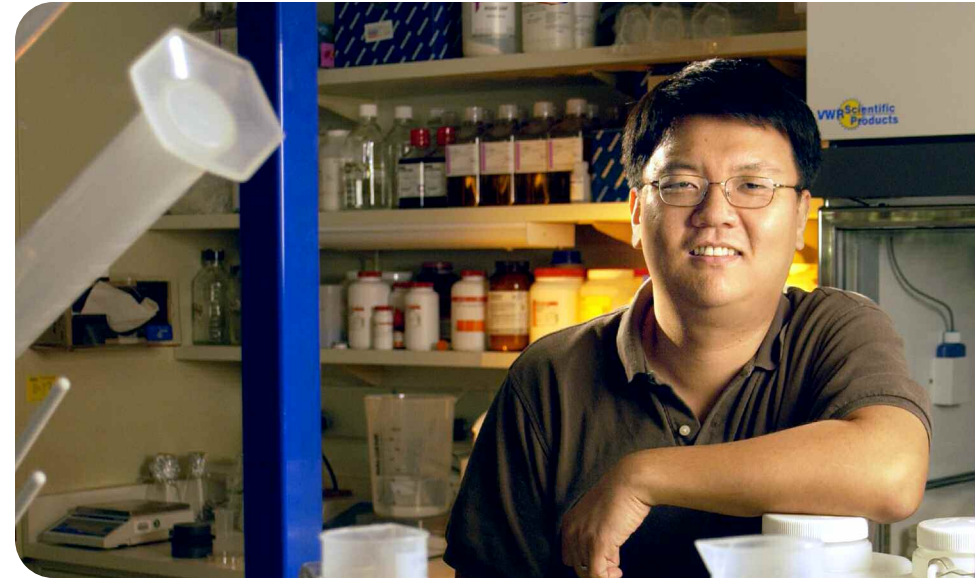
Dr. Myung's laboratory is investigating genome instability by examining the mechanisms of DNA repair and replication, as well as their roles in the production and suppression of gross chromosomal rearrangements (GCRs). Specifically, his group is studying how previously identified mutator genes regulate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

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

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



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



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

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

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



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

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

## SELECTED PUBLICATIONS

Myung K, Datta A, Chen C, Kolodner RD. SGS1, the *Saccharomyces cerevisiae* homologue of BLM and WRN, suppresses genome instability and homeologous recombination. *Nat Genet* 27:113–116, 2001.

Myung K, Chen C, Kolodner RD. Multiple pathways cooperate in the suppression of genome instability in *Saccharomyces cerevisiae*. *Nature* 411:1073–1076, 2001.

Myung K, Kolodner RD. Suppression of genome instability by redundant S-phase checkpoint pathways in *Saccharomyces cerevisiae*. *Proc Natl Acad Sci USA* 99:4500–4507, 2002.

Kolodner RD, Putnam CD, Myung K. Maintenance of genome stability in *Saccharomyces cerevisiae*. *Science* 297:552–557, 2002.

Myung K, Pennaneach V, Kats ES, Kolodner RD. *Saccharomyces cerevisiae* chromatin-assembly factors that act during DNA replication function in the maintenance of genome stability. *Proc Natl Acad Sci USA* 100:6640–6645, 2003.

Myung K, Ghosh G, Fattah FJ, Li G, Kim H, Dutra A, Pak E, Smith S, Hendrickson EA. Regulation of telomere length and suppression of genomic instability in human somatic cells by Ku86. *Mol Cell Biol* 24:5050–5059, 2004.

Myung K, Smith S, Kolodner R. Mitotic checkpoints function in the formation of gross chromosomal rearrangements in *Saccharomyces cerevisiae*. *Proc Natl Acad Sci USA* 101:15980–15985, 2004.

Smith S, Hwang JY, Banerjee S, Majee A, Gupta A, Myung K. Mutator genes for suppression of gross chromosomal rearrangements identified by a genome-wide screening in *Saccharomyces cerevisiae*. *Proc Natl Acad Sci USA* 101:9039–9044, 2004.

Banerjee S, Myung K. Increased genome instability and telomere length in the *elg1*-deficient *Saccharomyces cerevisiae* mutant are regulated by S-phase checkpoints. *Eukaryot Cell* 3:1557–1566, 2004.

Smith S, Gupta A, Kolodner RD, Myung K. Suppression of gross chromosomal rearrangements by the multiple functions of the Mre11-Rad50-Xrs2 complex in *Saccharomyces cerevisiae*. *DNA Repair* 4:606–617, 2005

Motegi A, Kunts K, Majeed A, Smith S, Myung K. Regulation of gross chromosomal rearrangements by ubiquitin and SUMO ligases in *Saccharomyces cerevisiae*. *Mol Cell Biol* 26:1424–1433, 2006.

Banerjee S, Smith S, Myung K. Suppression of gross chromosomal rearrangements by yKu70-yKu80 heterodimer through DNA damage checkpoints. *Proc Natl Acad Sci USA* 103:1816–1821, 2006.

Motegi A, Sood R, Moinova H, Markowitz S, Liu P, Myung K. Human SHPRH suppresses genomic instability through proliferating cell nuclear antigen polyubiquitination. *J Cell Biol* 175:703–708, 2006.

Motegi A, Myung K. Assays to measure the rate of gross chromosomal rearrangement formation in *Saccharomyces cerevisiae*: a practical approach to study genomic rearrangements observed in cancer. *Methods* 41:168–176, 2007.

## JULIA A. SEGRE, Ph.D.

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

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

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



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



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

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

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

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in the wound healing process and, when impaired, can result in psoriasis. The ultimate goal of the Segre laboratory is to understand the skin's response to the many environmental stresses, such as exposure to ultraviolet light and chemicals. Normally, there is an orderly progression of differentiation in the skin. However, when the skin is injured, it activates a stress response that upregulates the expression of structural proteins to erect a temporary barrier until a more permanent one can be built. Her laboratory is investigating whether clusters of genes are held together in the genome to respond in a coordinated fashion to environmental stresses. Dr. Segre is currently leading a project to examine the bacterial diversity that resides on human skin and its contribution to both health and disease. Her efforts involve the use of genomic methods to sequence the genomes of skin microflora in order to shed light on their role in common skin diseases, such as eczema.

## SELECTED PUBLICATIONS

Segre JA, Nemhauser JL, Taylor BA, Nadeau JH, Lander ES. Positional cloning of the nude locus: genetic, physical, and transcription maps of the region and mutations in the mouse and rat. *Genomics* 28:549–559, 1995.

Segre JA, Bauer C, Fuchs E. Klf4 is a transcription factor required for establishing the barrier function of the skin. *Nat Genet* 22:356–360, 1999.

Fuchs E, Segre JA. Stem cells: a new lease on life. *Cell* 100:143–155, 2000.

Patel S, Kartasova T, Segre JA. Mouse *Sprr* locus: a tandem array of coordinately regulated genes. *Mamm Genome* 14:140–148, 2003.

Jaubert J, Cheng J, Segre JA. Ectopic expression of Kruppel like factor 4 (Klf4) accelerates formation of the epidermal permeability barrier. *Development* 130:2767–2777, 2003.

Segre JA. Complex redundancy to build a simple epidermal permeability barrier. *Curr Opin Cell Biol* 15:778–784, 2003.

Dai X, Segre JA. Transcriptional regulation of epidermal differentiation and development. *Curr Opin Genet Dev* 14:485–491, 2004.

Jaubert J, Patel S, Cheng J, Segre JA. Tetracycline-regulated transactivators driven by the involucrin promoter to achieve epidermal conditional gene expression. *J Invest Dermatol* 123:313–318, 2004.

Martin N, Patel S, Segre JA. Long-range comparison of human and mouse *Sprr* loci to identify conserved noncoding sequences involved in coordinate regulation. *Genome Res* 14:2430–2438, 2004.

Djalilian A, McGaughey D, Patel S, Seo EY, Cheng J, Tomic M, Ishida-Yamamoto A, Segre JA. Connexin 26 regulates epidermal barrier, wound remodeling and promotes psoriaform progression. *J Clin Invest* 116:1243–1253, 2006.

Segre JA. Epidermal barrier formation and recovery in skin disorders. *J Clin Invest* 116:1150–1158, 2006.

Segre JA. Epidermal Differentiation Complex yields a secret: mutations in the cornification protein Filaggrin underlie ichthyosis vulgaris. *J Invest Dermatol* 126:1202–1204, 2006.

Patel S, Xi ZF, Seo EY, McGaughey D, Segre JA. Klf4 and corticosteroids activate an overlapping set of transcriptional targets to accelerate in utero epidermal barrier acquisition. *Proc Natl Acad Sci USA* 103:18668–18673, 2006.

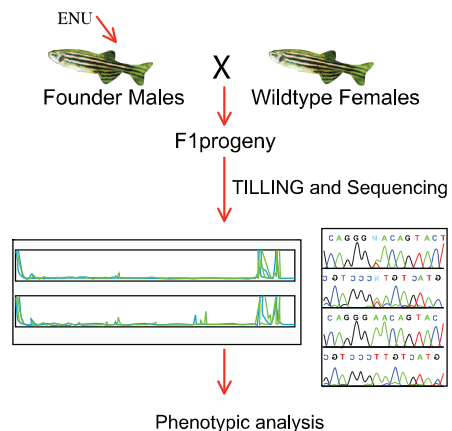
Strong C, Wertz PW, Wang C, Andl T, Yang F, Meltzer PS, Millar SE, Ho I-C, Pai S-Y, Segre JA. Lipid defect underlies selective barrier deficiency in an epidermal-specific deletion of *Gata-3*. *J Cell Biol* 175:661–670, 2006.

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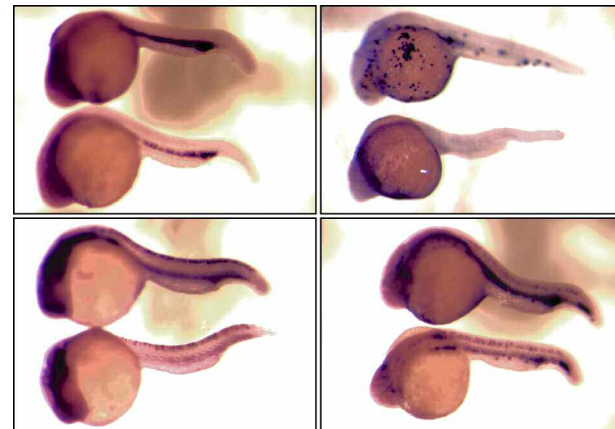
Dr. Sood's research is focused on generating a resource for NHGRI investigators that will allow them to perform functional analyses of genes of interest using zebrafish as a model organism. Dr. Sood is performing large-scale *N*-ethyl-*N*-nitrosourea (ENU) mutagenesis in zebrafish, which produces random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

To identify potentially interesting mutations in the collection of ENU-treated zebrafish, Dr. Sood is employing sequencing in combination with TILLING (for "targeting induced local lesions in genomes"), which

provides a cost-effective alternative to sequencing large numbers of samples.



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





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

## SELECTED PUBLICATIONS

Sood R, Bonner TI, Makalowska I, Stephan DA, Robbins CM, Connors TD, Morgenbesser SD, Su K, Faruque MU, Pinkett H, Graham C, Baxevis AD, Klinger KW, Landes GM, Trent JM, Carpten JD. Cloning and characterization of 13 novel transcripts and the human RGS8 gene from the 1q25 region encompassing the hereditary prostate cancer (HPC1) locus. *Genomics* 73:211–222, 2001.

Carpten J, Nupponen N, Isaacs S, Sood R, Robbins C, Xu J, Faruque M, Moses T, Ewing C, Gillanders E, Hu P, Bujnovszky P, Makalowska I, Baffoe-Bonnie A, Faith D, Smith J, Stephan D, Wiley K, Brownstein M, Gildea D, Kelly B, Jenkins R, Hostetter G, Matikainen M, Schleutker J, Klinger K, Connors T, Xiang Y, Wang Z, De Marzo A, Papadopoulos N, Kallioniemi O-P, Burk R, Meyers D, Gronberg H, Meltzer P, Silverman R, Bailey-Wilson J, Walsh P, Isaacs W, Trent J. Germline mutations in the ribonuclease L gene in families showing linkage with HPC1. *Nat Genet* 30:181–184, 2002.

Makalowska I, Sood R, Faruque MU, Hu P, Robbins C, Eddings EM, Mestre JD, Baxevis AD, Carpten JD. Identification of six novel genes by experimental validation of GeneMachine predicted genes. *Gene* 284:203–213, 2002.

Pollock PM, Cohen-Solal K, Sood R, Namkoong J, Martino JJ, Koganti A, Zhu H, Robbins C, Makalowska I, Shin S-S, Marin Y, Roberts KG, Yudit LM, Chen A, Cheng J, Incao A, Pinkett HW, Graham CL, Dunn K, Crespo-Carbone SM, Mackason KR, Ryan KB, Sinsimer D, Goydos J, Reuhl KR, Eckhaus M, Meltzer PS, Pavan WJ, Trent JM, Chen S. Melanoma mouse model implicates metabotropic glutamate signaling in melanocytic neoplasia. *Nat Genet* 34:108–112, 2003.

Gillanders E, Juo SH, Holland EA, Jones M, Nancarrow D, Freas-Lutz D, Sood R, Park N, Faruque M, Markey C, Kefford RF, Palmer J, Bergman W, Bishop DT, Tucker MA, Bressac-de Paillerets B, Hansson J, Stark M, Gruis N, Bishop JN, Goldstein AM, Bailey-Wilson JE, Mann GJ, Hayward N, Trent J, Lund Melanoma Study Group, Melanoma Genetics Consortium. Localization of a novel melanoma susceptibility locus to 1p22. *Am J Hum Genet* 73:301–313, 2003.

Sood R, Makalowska I, Galdzicki M, Hu P, Eddings E, Robbins CM, Moses T, Namkoong J, Chen S, Trent JM. Cloning and characterization of a novel gene, SHPRH, encoding a conserved putative protein with SNF2/helicase and PHD-finger domains from the 6q24 region. *Genomics* 82:153–161, 2003.

Walker GJ, Indsto JO, Sood R, Faruque MU, Hu P, Pollock PM, Duray P, Holland EA, Brown K, Kefford RF, Trent JM, Mann GJ, Hayward NK. Deletion mapping suggests that the 1p22 melanoma susceptibility gene is a tumor suppressor localized to a 9-Mb interval. *Genes Chromosomes Cancer* 41:56–64, 2004.

Veeramachaneni V, Makalowski W, Galdzicki M, Sood R, Makalowska I. Mammalian overlapping genes: the comparative perspective. *Genome Res* 14:280–286, 2004.

Zhang J, Wheeler D, Yakub I, Wei S, Sood R, Rowe W, Liu PP, Gibbs RA, Buetow KH. SNPdetector: a software tool for sensitive and accurate SNP detection. *PLoS Comput Biol* 1:395–404, 2005.

Sood R, English MA, Jones M, Mullikin J, Wang DM, Anderson M, Wu D, Chandrasekharappa SC, Yu J, Zhang J, Liu PP. Methods for reverse genetic screening in zebrafish by resequencing and TILLING. *Methods* 39:220–227, 2006.

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

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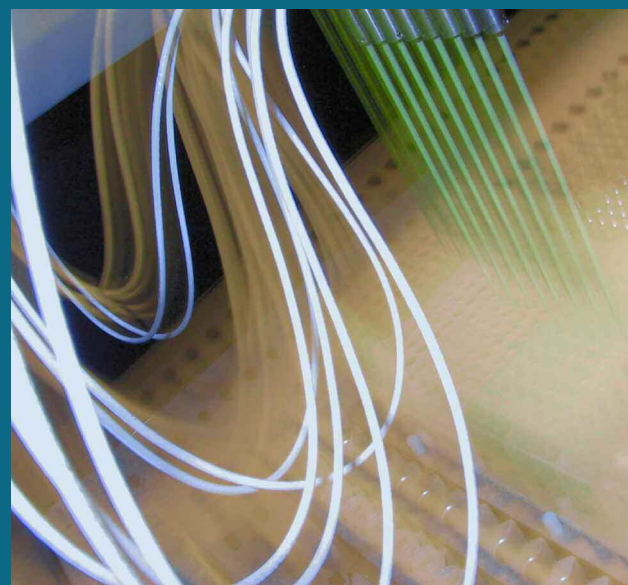
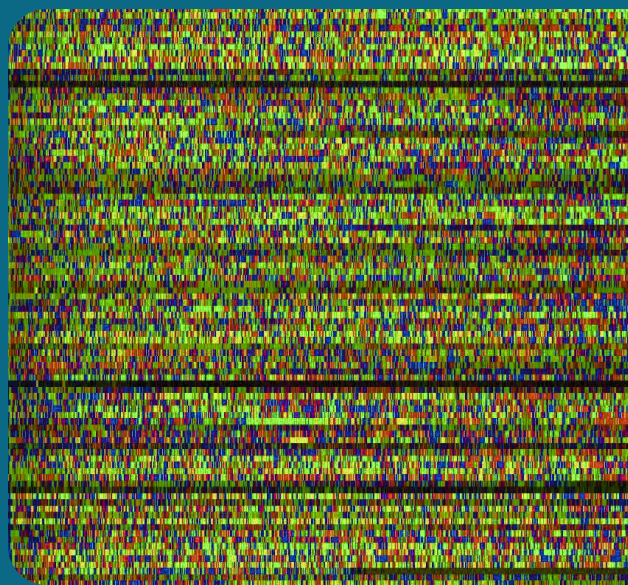
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Investigators in the Genome Technology Branch (GTB) study the structure and function of genomes in disease and normal states. Over the years, GTB researchers have developed world-class expertise in a wide range of genomic techniques, including the 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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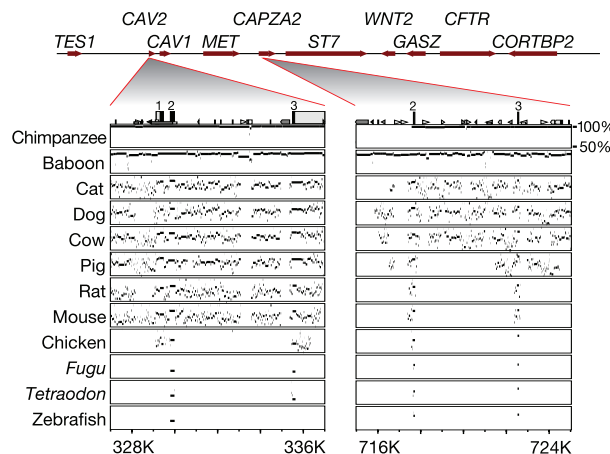


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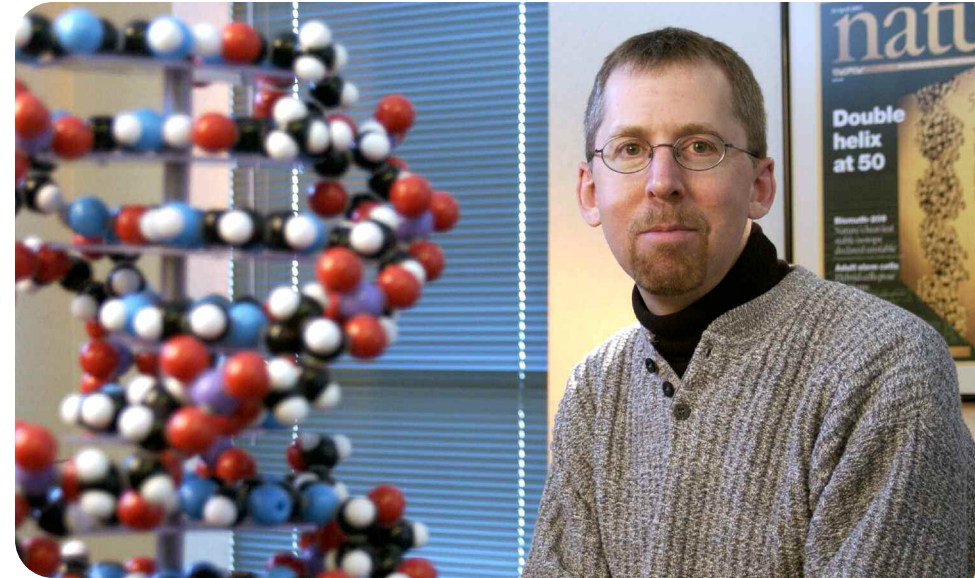
Dr. Green's research focuses on three major areas: (1) sequencing and comparing targeted stretches of DNA from a wide variety of animal species *en route* to unraveling the complexities of genome function; (2) developing innovative research tools and technologies for performing genome analysis; and (3)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

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

In some cases, Dr. Green and his colleagues search for sequences conserved over tens of millions of years of evolution; such sequences are more likely to play important functional roles.



In other cases, they examine sequence differences among closely related species (such as groups of primates), revealing more recent genomic changes. In essence, Dr. Green's group uses the detailed records of evolution embedded within all species' DNA to help decode the human genome.



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

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

## SELECTED PUBLICATIONS

DeSilva U, Elnitski L, Idol JR, Doyle JL, Gan W, Thomas JW, Schwartz S, Dietrich NL, Beckstrom-Sternberg SM, McDowell JC, Blakesley RW, Bouffard GG, Thomas PJ, Touchman JW, Miller W, Green ED. Generation and comparative analysis of approximately 3.3 Mb of mouse genomic sequence orthologous to the region of human chromosome 7q11.23 implicated in Williams syndrome. *Genome Res* 12:3–15, 2002.

Thomas JW, Prasad AB, Summers TJ, Lee-Lin S-Q, Maduro VV, Idol JR, Ryan JF, Thomas PJ, McDowell JC, Green ED. Parallel construction of orthologous sequence-ready clone contig maps in multiple species. *Genome Res* 12:1277–1285, 2002.

Antonellis A, Ellsworth RE, Sambuughin N, Puls I, Abel A, Lee-Lin SQ, Jordanova A, Kremensky I, Christodoulou K, Middleton LT, Sivakumar K, Ionasescu V, Funalot B, Vance JM, Goldfarb LG, Fischbeck KH, Green ED. Glycyl tRNA synthetase mutations in Charcot-Marie-Tooth disease type 2D and distal spinal muscular atrophy type V. *Am J Hum Genet* 72:1293–1299, 2003.

Thomas JW, Touchman JW, Blakesley RW, Bouffard GG, Beckstrom-Sternberg SM, Margulies EH, Blanchette M, Siepel AC, Thomas PJ, McDowell JC, Maskeri B, Hansen NF, Schwartz MS, Weber RJ, Kent WJ, Karolchik D, Bruen TC, Bevan R, Cutler DJ, Schwartz S, Elnitski L, Idol JR, Prasad AB, Lee-Lin SQ, Maduro VV, Summers TJ, Portnoy ME, Dietrich NL, Akhter N, Ayele K, Benjamin B, Cariaga K, Brinkley CP, Brooks SY, Granite S, Guan X, Gupta J, Haghighi P, Ho SL, Huang MC, Karlins E, Laric PL, Legaspi R, Lim MJ, Maduro QL, Masiello CA, Mastrian SD, McCloskey JC, Pearson R, Stantripop S, Tiongson EE, Tran JT, Tsurgeon C, Vogt JL, Walker MA, Wetherby KD, Wiggins LS, Young AC, Zhang LH, Osoegawa K, Zhu B, Zhao B, Shu CL, De Jong PJ, Lawrence CE, Smit AF, Chakravarti A, Haussler D, Green P, Miller W, Green ED. Comparative analyses of multi-species sequences from targeted genomic regions. *Nature* 424:788–793, 2003.

Margulies EH, Blanchette M, NISC Comparative Sequencing Program, Haussler D, Green ED. Identification and characterization of multi-species conserved sequences. *Genome Res* 14:673–678, 2003.

Schueler MG, Dunn JM, Bird CP, Ross MT, Viggiano L, NISC Comparative Sequencing Program, Rocchi M, Willard HF, Green ED. Progressive proximal expansion of the primate X chromosome centromere. *Proc Natl Acad Sci USA* 102:10563–10568, 2005.

Antonellis A, Lee-Lin S-Q, Wasterlain A, Leo P, Quezado M, Goldfarb LG, Myung K, Burgess S, Fischbeck KH, Green ED. Functional analyses of glycyl-tRNA synthetase mutations suggest a key role for tRNA-charging enzymes in peripheral axons. *J Neurosci* 26:10397–10406, 2006.

Hurle B, Swanson W, NISC Comparative Sequencing Program, Green ED. Comparative sequence analyses reveal rapid and divergent evolutionary changes of the *WFDC* locus in the primate lineage. *Genome Res* 17:276–286, 2007.

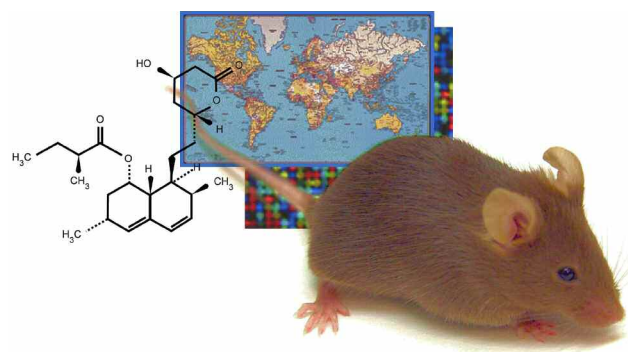
The ENCODE Project Consortium. Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project. *Nature* 447:799–816, 2007.

## 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](http://pubchem.ncbi.nlm.nih.gov)). Its activities are intended to catalyze the understanding of gene function and the development of therapeutics based on genomic targets. NCGC has developed a novel titration-based screening method, called Quantitative High-Throughput Screening (qHTS), which generates comprehensive activity and pharmacological data on hundreds of thousands of compounds. Using this and related techniques, NCGC has generated chemical probes for a wide variety of targets from the human genome and that of various model and pathogenic organisms. In turn, these compounds are being used to investigate target function and physiology. Where targets have therapeutic potential, NCGC is

focused on “orphan” diseases (rare genetic diseases) and diseases of the developing world. After each qHTS screen is completed, NCGC cheminformatics scientists use algorithms developed in-house to identify the compounds with pharmacological activity, and to compare these activities with those in other screens in order to determine selectivity and identify compounds for chemical optimization.



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

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

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

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

## SELECTED PUBLICATIONS

Morris JA, Kandpal G, Ma L, Austin CP. DISC1 (Disrupted-In-Schizophrenia 1) is a centrosome-associated protein that interacts with MAP1A, MIPT3, ATF4/5 and NUDEL: regulation and loss of interaction with mutation. *Hum Mol Genet* 12:1591–1608, 2003.

Austin, CP. The impact of the completed human genome sequence on the development of novel therapeutics for human disease. *Ann Rev Med* 55:1–13, 2004.

Austin CP, Battey JF, Bradley A, Bucan M, Capecchi M, Collins FS, Dove WF, Duyk G, Dymecki S, Eppig JT, Grieder FB, Heintz N, Hicks G, Insel TR, Joyner A, Koller BH, Lloyd KC, Magnuson T, Moore MW, Nagy A, Pollock JD, Roses AD, Sands AT, Seed B, Skarnes WC, Snoddy J, Soriano P, Stewart DJ, Stewart F, Stillman B, Varmus H, Varticovski L, Verma IM, Vogt TF, von Melchner H, Witkowski J, Woychik RP, Wurst W, Yancopoulos GD, Young SG, Zambrowicz B. The knockout mouse project. *Nat Genet* 36:921–924, 2004.

Austin CP, Brady LS, Insel TR, Collins FS. NIH Molecular Libraries Initiative. *Science* 306:1138–1139, 2004.

Inglese J, Auld DS, Jadhav A, Johnson RL, Simeonov A, Yasgar A, Zheng W, Austin, CP. Quantitative high-throughput screening: a titration-based approach that efficiently identifies biological activities in large chemical libraries. *Proc Natl Acad Sci USA* 103:11473–11478, 2006.

Zheng W, Padia J, Urban DJ, Jadhav A, Goker-Alpan O, Simeonov A, Goldin E, Auld D, LaMarca ME, Inglese J, Austin CP, Sidransky E. Three classes of glucocerebrosidase inhibitors identified by quantitative high-throughput screening are chaperone leads for Gaucher disease. *Proc Natl Acad Sci USA* 104:13192–13197, 2007.

Inglese J, Johnson RL, Simeonov A, Xia M, Zheng W, Austin CP, Auld DS. High-throughput screening assays for the identification of chemical probes. *Nat Chem Biol* 3:466–479, 2007.

Xia M, Huang R, Witt KL, Southall N, Fostel J, Cho M-H, Jadhav A, Smith CS, Inglese J, Portier CJ, Tice RR, Austin CP. Compound cytotoxicity profiling using quantitative high-throughput screening. *Environ Health Perspect* doi:10.1289/ehp.10727, 2007.

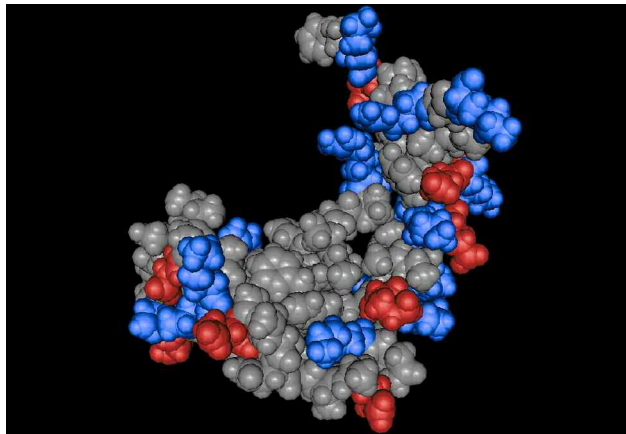




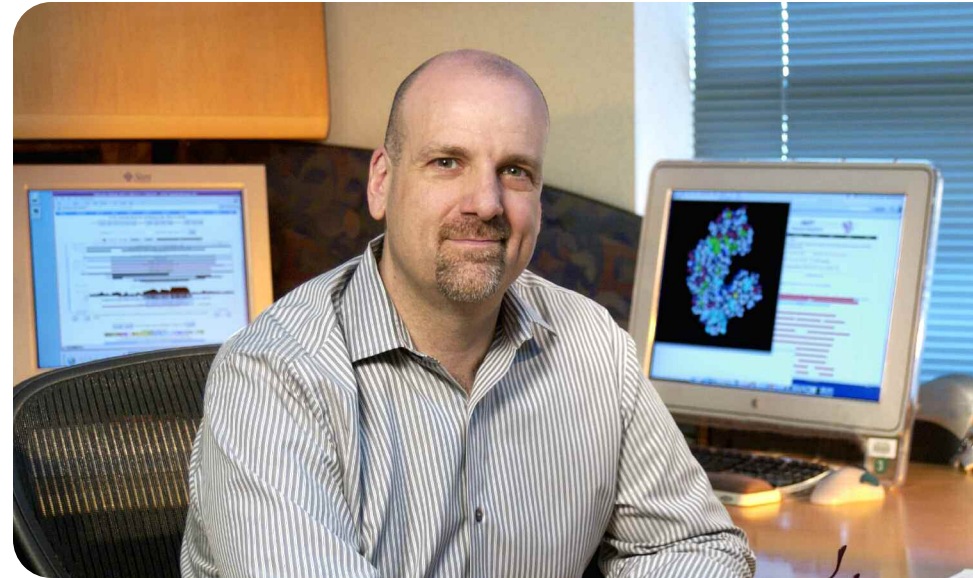
## ANDREAS D. BAXEVANIS, Ph.D.

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

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



Dr. Baxevanis' group also studies the evolutionary relationships between members of the homeodomain family of proteins. His group has deduced a family tree that shows the relationship between 129 different human homeodomain proteins; these 129 proteins segregate into six distinct groups, with each group characterized by similar structural and functional features. His group also maintains a publicly available database called the



Homeodomain Resource, which is used extensively worldwide by researchers studying these proteins. It contains full-length homeodomain sequences and data on experimentally derived structures, protein-protein interactions, DNA binding sites, and mutations linked to human disorders.

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

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

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

## SELECTED PUBLICATIONS

Banerjee-Basu S, Baxevanis AD. Threading analysis of the Pitx2 homeodomain: predicted structural effects of mutations causing Rieger syndrome and iridogoniodysgenesis. *Hum Mutat* 14:312–319, 1999.

Banerjee-Basu S, Baxevanis AD. Molecular evolution of the homeodomain family of transcription factors. *Nucleic Acids Res* 29:3258–3269, 2001.

Makalowska I, Ryan JF, Baxevanis AD. GeneMachine: gene prediction and sequence annotation. *Bioinformatics* 17:843-844, 2001.

Saleem RA, Banerjee-Basu S, Berry FB, Baxevanis AD, Walter MA. Analyses of the effects that disease-causing missense mutations have on the structure and function of the winged-helix protein FOXC1. *Am J Hum Genet* 68:627–641, 2001.

Banerjee-Basu S, Baxevanis AD. Molecular modeling of mutations in the DNA-binding domain of the oncoprotein Qin. *Mol Cancer Ther* 1:1237–1241, 2002.

Banerjee-Basu S, Moreland T, Hsu BJ, Trout KL, Baxevanis AD. The Homeodomain Resource: 2003 Update. *Nucleic Acids Res* 31:304-306, 2003.

Saleem RA, Banerjee-Basu S, Berry FB, Baxevanis AD, Walter MA. Structural and functional analyses of disease-causing missense mutations in the forkhead domain of FOXC1. *Hum Mol Genet* 12:2993–3005, 2003.

Wolfsberg TG, Wetterstrand KA, Guyer MS, Collins FS, Baxevanis AD. A user’s guide to the human genome. *Nat Genet* 35 Suppl 1:4, 2003.

Banerjee-Basu S, Baxevanis AD. Structural analysis of disease-causing mutations in the P-subfamily of forkhead transcription factors. *Proteins* 54:639–647, 2004.

Saleem RA, Banerjee-Basu S, Murphy TC, Baxevanis AD, Walter MA. Essential structural and functional determinants within the forkhead domain of FOXC1. *Nucleic Acids Res* 32:4182–4193, 2004.

Gillanders EM, Masiello A, Gildea D, Umayam L, Duggal P, Jones MP, Klein AP, Freas-Latz D, Ibay G, Trout K, Wolfsberg TG, Trent JM, Bailey-Wilson JE, Baxevanis AD. GeneLink: a data management system designed to facilitate genetic studies of complex traits. *BMC Genomics*. 5:81, 2004.

The ENCODE Consortium. The ENCODE (Encyclopedia of DNA Elements) project. *Science* 306:636-640, 2004.

Baxevanis AD, Ouellette BFF (Eds). *Bioinformatics: A Practical Guide to the Analysis of Genes and Proteins*, 3rd ed. New York: John Wiley & Sons, 2005.

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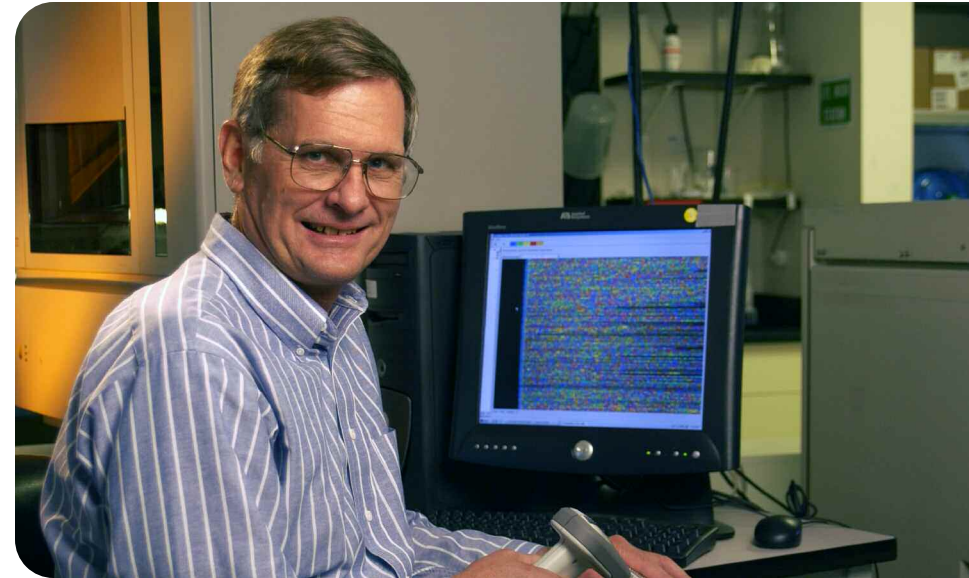
Dr. Blakesley directs the Sequencing Group of the NIH Intramural Sequencing Center (NISC). Established in 1997, NISC is a multi-disciplinary genomics facility that emphasizes the generation and analysis of DNA sequences.

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

Dr. Blakesley oversees NISC's role in several large DNA sequencing efforts. For example, the NISC Comparative Sequencing Program involves generating genomic sequences from multiple vertebrates for comparative analyses. In this project, targeted genomic regions are selected for



study and then sequenced. The resulting data consist of sets of orthologous sequences for the same large genomic region from multiple species. This project aims to generate data for use in developing and refining computational tools for comparing genomic sequences from different vertebrates. These efforts likely will inform decisions about the selection of additional species for systematic genome sequencing.



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

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

## SELECTED PUBLICATIONS

Fuchs R, Blakesley R. Guide to the use of type II restriction endonucleases. *Methods Enzymol* 100:3–38, 1983.

Thompson JA, Blakesley RW, Doran K, Hough CJ, Wells RD. Purification of nucleic acids by RPC-5 ANA-LOG chromatography: peristaltic and gravity-flow applications. *Methods Enzymol* 100:368–399, 1983.

Chatterjee DK, Hammond AW, Blakesley RW, Adams SM, Gerard GF. Genetic organization of the KpnI restriction-modification system. *Nucleic Acids Res* 19:6505–6509, 1991.

Wang G, Blakesley RW, Berg DE, Berg CM. pDUAL: a transposon-based cosmid cloning vector for generating nested deletions and DNA sequencing templates in vivo. *Proc Natl Acad Sci USA* 90:7874–7878, 1993.

Blakesley RW. Cycle sequencing. *Methods Mol Biol* 167:101–112, 2001.

DeSilva U, Elnitski L, Idol JR, Doyle JL, Gan W, Thomas JW, Schwartz S, Dietrich NL, Beckstrom-Sternberg SM, McDowell JC, Blakesley RW, Bouffard GG, Thomas PJ, Touchman JW, Miller W, Green ED. Generation and comparative analysis of approximately 3.3 Mb of mouse genomic sequence orthologous to the region of human chromosome 7q11.23 implicated in Williams syndrome. *Genome Res* 12:3–15, 2002.

Shevchenko Y, Bouffard GG, Butterfield YS, Blakesley RW, Hartley JL, Young AC, Marra MA, Jones SJ, Touchman JW, Green ED. Systematic sequencing of cDNA clones using the transposon Tn5. *Nucleic Acids Res* 30:2469–2477, 2002.

Thomas JW, Touchman JW, Blakesley RW, Bouffard GG, Beckstrom-Sternberg SM, Margulies EH, Blanchette M, Siepel AC, Thomas PJ, McDowell JC, Maskeri B, Hansen NF, Schwartz MS, Weber RJ, Kent WJ, Karolchik D, Bruen TC, Bevan R, Cutler DJ, Schwartz S, Elnitski L, Idol JR, Prasad AB, Lee-Lin SQ, Maduro VV, Summers TJ, Portnoy ME, Dietrich NL, Akhter N, Ayele K, Benjamin B, Cariaga K, Brinkley CP, Brooks SY, Granite S, Guan X, Gupta J, Haghghi P, Ho SL, Huang MC, Karlins E, Laric PL, Legaspi R, Lim MJ, Maduro QL, Masiello CA, Mastrian SD, McCloskey JC, Pearson R, Stantripop S, Tiongson EE, Tran JT, Tsurgeon C, Vogt JL, Walker MA, Wetherby KD, Wiggins LS, Young AC, Zhang LH, Osoegawa K, Zhu B, Zhao B, Shu CL, De Jong PJ, Lawrence CE, Smit AF, Chakravarti A, Haussler D, Green P, Miller W, Green ED. Comparative analyses of multi-species sequences from targeted genomic regions. *Nature* 424:788–793, 2003.

Crawford GE, Holt IE, Mullikin JC, Tai D, Green ED, Wolfsberg TG, Collins FS, National Institutes of Health Intramural Sequencing Center. Identifying gene regulatory elements by genome-wide recovery of DNase hypersensitive sites. *Proc Natl Acad Sci USA* 101:992–997, 2004.

Blakesley RW, Hansen NF, Mullikin JC, Thomas PJ, McDowell JC, Maskeri B, Young AC, Benjamin B, Brooks SY, Coleman BI, Gupta J, Ho SL, Karlins EM, Maduro QL, Stantripop S, Tsurgeon C, Vogt JL, Walker MA, Masiello CA, Guan X, Bouffard GG, Green ED; NISC Comparative Sequencing Program. An intermediate grade of finished genomic sequence suitable for comparative analyses. *Genome Res* 14:2235–2244, 2004.

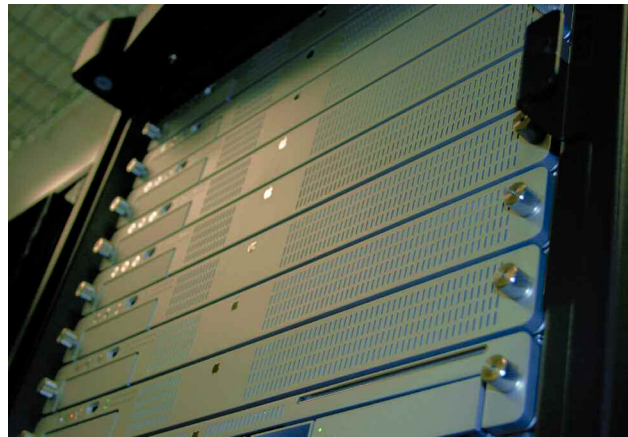


## GERARD G. BOUFFARD, Ph.D.

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

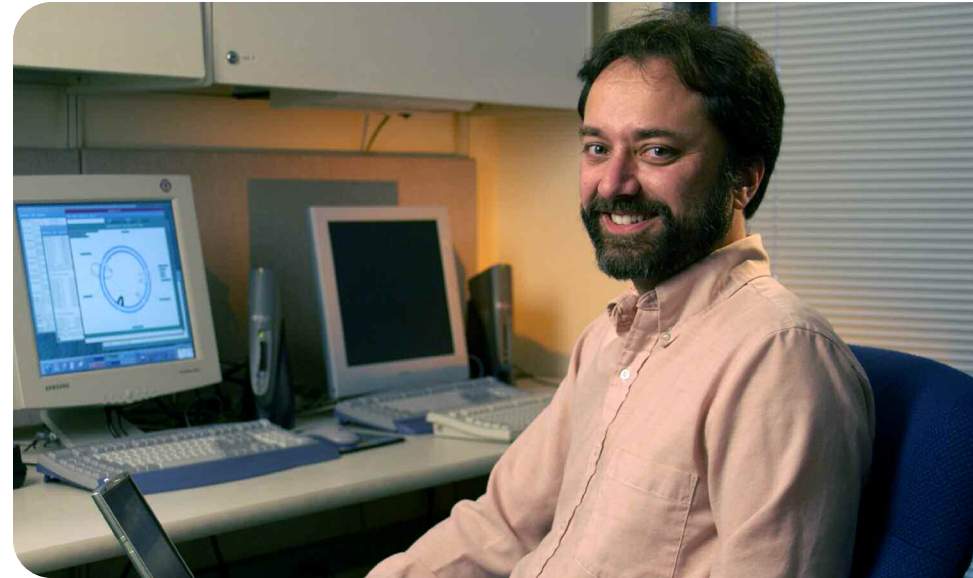
To cope with NISC's large sequencing throughput and data generation, Dr. Bouffard has directed the development of a customized, NISC-specific Laboratory Information Management System. This system controls the flow of samples and materials through the laboratory, identifies reagents and equipment with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

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



comparing sequences from primates, other mammals, marsupials, monotremes, birds, and fish.

He also is involved in NHGRI's ENCODE (*Encyclopedia of DNA Elements*) project, aimed at identifying all the functional elements in the human genome. For this project, scientists at NHGRI and elsewhere are applying current technologies—and testing potential new technologies—to study 44 regions that, taken



together, comprise 1% of the human genome. Dr. Bouffard's group is helping to generate and analyze sequences of these regions in multiple other species.

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

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

## SELECTED PUBLICATIONS

Bouffard GG, Rudd KE, Adhya SL. Dependence of lactose metabolism upon mutarotase encoded in the *gal* operon in *Escherichia coli*. *J Mol Biol* 244:269–278, 1994.

Bouffard GG, Idol JR, Braden VV, Iyer LM, Cunningham AF, Weintraub LA, Touchman JW, Mohr-Tidwell RM, Peluso DC, Fulton RS, Ueltzen MS, Weissenbach J, Magness CL, Green ED. A physical map of human chromosome 7: an integrated YAC contig map with average STS spacing of 79 kb. *Genome Res* 7:673–692, 1997.

Gubin AN, Njoroge JM, Bouffard GG, Miller JL. Gene expression in proliferating human erythroid cells. *Genomics* 59:168–177, 1999.

Andrews J, Bouffard GG, Cheadle C, Lu J, Becker KG, Oliver B. Gene discovery using computational and microarray analysis of transcription in the *Drosophila melanogaster* testis. *Genome Res* 10:2030–2043, 2000.

Shevchenko Y, Bouffard GG, Butterfield YS, Blakesley RW, Hartley JL, Young AC, Marra MA, Jones SJ, Touchman JW, Green ED. Systematic sequencing of cDNA clones using the transposon Tn5. *Nucleic Acids Res* 30:2469–2477, 2002.

Strausberg RL, Feingold EA, Grouse LH, Derge JG, Klausner RD, Collins FS, Wagner L, Shenmen CM, Schuler GD, Altschul SF, Zeeberg B, Buetow KH, Schaefer CF, Bhat NK, Hopkins RF, Jordan H, Moore T, Max SI, Wang J, Hsieh F, Diatchenko L, Marusina K, Farmer AA, Rubin GM, Hong L, Stapleton M, Soares MB, Bonaldo MF, Casavant TL, Scheetz TE, Brownstein MJ, Usdin TB, Toshiyuki S, Carninci P, Prange C, Raha SS, Loquellano NA, Peters GJ, Abramson RD, Mullahy SJ, Bosak SA, McEwan PJ, McKernan KJ, Malek JA, Gunaratne PH, Richards S, Worley KC, Hale S, Garcia AM, Gay LJ, Hulyk SW, Villalón DK, Muzny DM, Sodergren EJ, Lu X, Gibbs RA, Fahey J, Helton E, Kettelman M, Madan A, Rodrigues S, Sanchez A, Whiting M, Madan A, Young AC, Shevchenko Y, Bouffard GG, Blakesley RW, Touchman JW, Green ED, Dickson MC, Rodriguez AC, Grimwood J, Schmutz J, Myers RM, Butterfield YS, Krzywinski MI, Skalska U, Smailus DE, Schnerch A, Schein JE, Jones SJ, Marra MA, Mammalian Gene Collection Program Team. Generation and initial analysis of more than 15,000 full-length human and mouse cDNA sequences. *Proc Natl Acad Sci USA* 99:16899–16903, 2002.

Thomas JW, Touchman JW, Blakesley RW, Bouffard GG, Beckstrom-Sternberg SM, Margulies EH, Blanchette M, Siepel AC, Thomas PJ, McDowell JC, Maskeri B, Hansen NF, Schwartz MS, Weber RJ, Kent WJ, Karolchik D, Bruen TC, Bevan R, Cutler DJ, Schwartz S, Elnitski L, Idol JR, Prasad AB, Lee-Lin SQ, Maduro VV, Summers TJ, Portnoy ME, Dietrich NL, Akhter N, Ayele K, Benjamin B, Cariaga K, Brinkley CP, Brooks SY, Granite S, Guan X, Gupta J, Haghghi P, Ho SL, Huang MC, Karlins E, Laric PL, Legaspi R, Lim MJ, Maduro QL, Masiello CA, Mastrian SD, McCloskey JC, Pearson R, Stantripop S, Tiangson EE, Tran JT, Tsurgeon C, Vogt JL, Walker MA, Wetherby KD, Wiggins LS, Young AC, Zhang LH, Osoegawa K, Zhu B, Zhao B, Shu CL, De Jong PJ, Lawrence CE, Smit AF, Chakravarti A, Haussler D, Green P, Miller W, Green ED. Comparative analyses of multi-species sequences from targeted genomic regions. *Nature* 424:788–793, 2003.

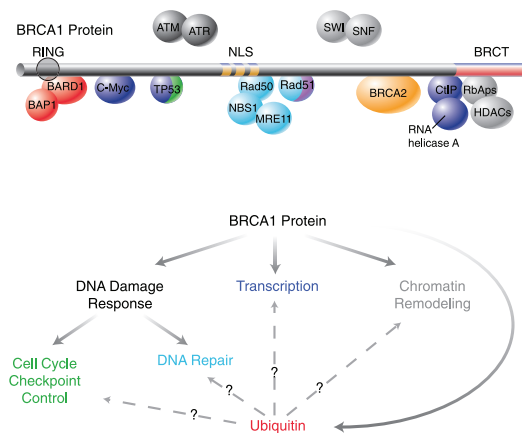
Blakesley RW, Hansen NF, Mullikin JC, Thomas PJ, McDowell JC, Maskeri B, Young AC, Benjamin B, Brooks SY, Coleman BI, Gupta J, Ho SL, Karlins EM, Maduro QL, Stantripop S, Tsurgeon C, Vogt JL, Walker MA, Masiello CA, Guan X, Bouffard GG, Green ED; NISC Comparative Sequencing Program. An intermediate grade of finished genomic sequence suitable for comparative analyses. *Genome Res* 14:2235–2244, 2004.

## LAWRENCE C. BRODY, Ph.D.

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

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

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



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



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

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

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

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

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

## SELECTED PUBLICATIONS

Yarden RI, Pardo-Reoyo S, Sgagias M, Cowan KH, Brody LC. BRCA1 regulates the G2/M checkpoint by activating Chk1 kinase upon DNA damage. *Nat Genet* 30:285–289, 2002.

Kanaan Y, Kpenu E, Utley K, Adams-Campbell L, Dunston GM, Brody LC, Broome C. Inherited BRCA2 mutations in African Americans with breast and/or ovarian cancer: a study of familial and early onset cases. *Hum Genet* 113:452–460, 2003.

Coyne RS, McDonald HB, Edgemon K, Brody LC. Functional characterization of BRCA1 sequence variants using a yeast small colony phenotype assay. *Cancer Biol Ther* 3:453–457, 2004.

Kirke PN, Mills JL, Molloy AM, Brody LC, O'Leary VB, Daly L, Murray S, Conley M, Mayne PD, Smith O, Scott JM. Impact of the MTHFR C677T polymorphism on risk of neural tube defects: case-control study. *BMJ* 328:1535–1536, 2004.

Swanson DA, Pangilinan F, Mills JL, Kirke PN, Conley M, Weiler A, Frey T, Parle-McDermott A, O'Leary VB, Seltzer RR, Moynihan KA, Molloy AM, Burke H, Scott JM, Brody LC. Evaluation of transcobalamin II polymorphisms as neural tube defect risk factors in an Irish population. *Birth Defects Res A Clin Mol Teratol* 73:239–244, 2005.

Parle-McDermott A, Mills JL, Kirke PN, Cox C, Signore CC, Kirke S, Molloy AM, O'Leary VB, Pangilinan F, O'Herlihy C, Brody LC, Scott JM. The MTHFD1 R653Q polymorphism is a maternal genetic risk factor for severe abruptio placentae. *Am J Med Genet* 132:365–368, 2005.

Parle-McDermott A, Pangilinan FJ, Mills JL, Signore CC, Molloy AM, Cotter A, Conley M, Cox C, Kirke PN, Scott JM, Brody LC. A polymorphism in the MTHFD1 gene increases a mother's risk of having an unexplained second trimester pregnancy loss. *Mol Hum Reprod* 11:477–480, 2005.

Parle-McDermott A, Kirke PN, Mills JL, Molloy AM, Cox C, O'leary VB, Pangilinan F, Conley M, Cleary L, Brody LC. Confirmation of the R653Q polymorphism of the trifunctional C1-synthase enzyme as a maternal risk for neural tube defects in the Irish population. *Eur J Hum Genet* 14:768–772, 2006.

Parle-McDermott A, Mills JL, Molloy AM, Carroll N, Kirke PN, Cox C, Conley MR, Pangilinan FJ, Brody LC, Scott JM. The MTHFR 1298CC and 677TT genotypes have opposite associations with red cell folate levels. *Mol Genet Metab* 88:290–294, 2006.

## BREAST CANCER MUTATION DATABASE

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

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



## SHAWN M. BURGESS, Ph.D.

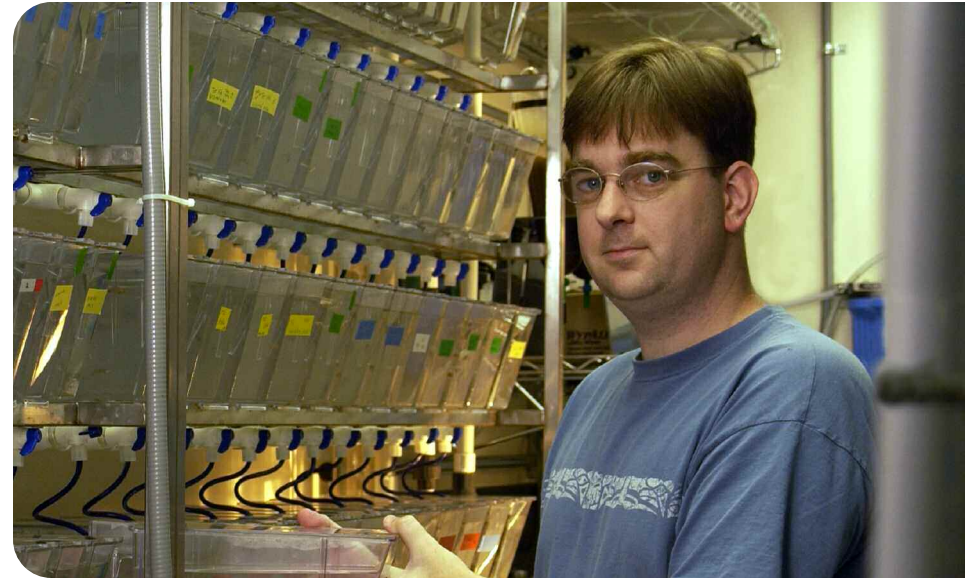
Dr. Burgess' laboratory studies developmental processes and their relationship to human genetic disease. His group employs a variety of modern molecular biology methods to identify and functionally characterize novel developmental genes involved in organogenesis of the ear and maintenance of stem cell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

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

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



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



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

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

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

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

### SELECTED PUBLICATIONS

Burgess S, Hopkins N. Use of pseudotyped retroviruses in zebrafish as genetic tags. *Methods Enzymol* 327:145–161, 2000.

Burgess S, Reim G, Hopkins N, Brand M. The zebrafish *spiel-ohne-grenzen* (*spg*) gene encodes the POU domain protein Pou2 related to mammalian *Oct4* and is essential for formation of the midbrain and hind-brain, and for pre-gastrula morphogenesis. *Development* 129:905–916, 2002.

Golling G, Amsterdam A, Sun Z, Antonelli M, Maldonado E, Chen W, Burgess S, Haldi M, Artzt K, Farrington S, Lin SY, Nissen RM, Hopkins N. Insertional mutagenesis in zebrafish rapidly identifies genes essential for early vertebrate development. *Nat Genet* 31:135–140, 2002.

Nissen RM, Yan J, Amsterdam A, Hopkins N, Burgess SM. Zebrafish foxi one modulates cellular responses to Fgf signaling required for the integrity of ear and jaw patterning. *Development* 130:2543–2554, 2003.

Wu X, Li Y, Crise B, Burgess SM. Transcription start regions in the human genome are favored targets for MLV integration. *Science* 300:1749–1751, 2003.

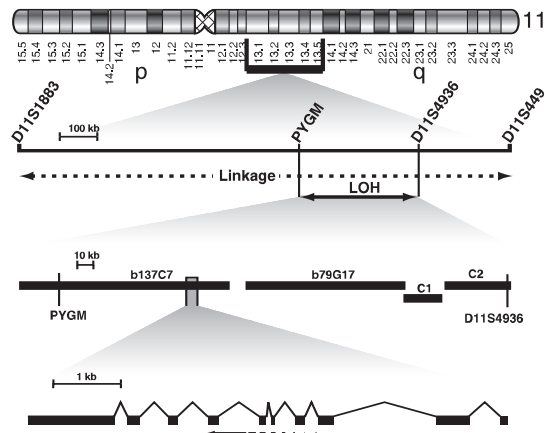
Kurita K, Burgess SM, Sakai N. Transgenic zebrafish produced by retroviral infection of *in vitro*-cultured sperm. *Proc Natl Acad Sci USA* 101:1263–1267, 2004.



## SETTARA C. CHANDRASEKHARAPPA, Ph.D.

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

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



Dr. Chandrasekharappa and colleagues discovered the genes responsible for both disorders in 1997. AGS is caused by mutations in the human *JAG1* gene, which encodes a ligand (Jagged 1) for the Notch transmembrane receptor. The Notch signaling pathway, originally discovered in fruit flies, is important in determining the early fate of the cell. MEN1 is caused by mutations in the tumor suppressor gene, *MEN1*. This gene encodes a protein called



menin, which is expressed very early in development, resides in the cell nucleus, and appears to bind several different proteins including the transcription factor JunD. When bound to menin, JunD represses cell growth; without menin, JunD promotes cell growth.

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

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

## SELECTED PUBLICATIONS

Chandrasekharappa SC, Guru SC, Manickam P, Olufemi SE, Collins FS, Emmert-Buck MR, Debelenko LV, Zhuang Z, Lubensky IA, Liotta LA, Crabtree JS, Wang Y, Roe BA, Weisemann J, Boguski MS, Agarwal SK, Kester MB, Kim YS, Heppner C, Dong Q, Spiegel AM, Burns AL, Marx SJ. Positional cloning of the gene for multiple endocrine neoplasia-type 1. *Science* 276:404–407, 1997.

Oda T, Elkahlon AG, Pike BL, Okajima K, Krantz ID, Gennin A, Piccoli DA, Meltzer PS, Spinner NB, Collins FS, Chandrasekharappa SC. Mutations in the human *Jagged1* gene are responsible for Alagille syndrome. *Nat Genet* 16:235–242, 1997.

Guru SC, Goldsmith PK, Burns AL, Marx SJ, Spiegel AM, Collins FS, Chandrasekharappa SC. Menin, the product of the *MEN1* gene, is a nuclear protein. *Proc Natl Acad Sci USA* 95:1630–1634, 1998.

Agarwal SK, Guru SC, Heppner C, Erdos MR, Collins RM, Park SY, Saggari S, Chandrasekharappa SC, Collins FS, Spiegel AM, Marx SJ, Burns AL. Menin interacts with the AP1 transcription factor JunD and represses JunD-activated transcription. *Cell* 96:143–152, 1999.

Manickam P, Vogel AM, Agarwal SK, Oda T, Spiegel AM, Marx SJ, Collins FS, Weinstein BM, Chandrasekharappa SC. Isolation, characterization, expression and functional analysis of the zebrafish ortholog of MEN1. *Mamm Genome* 11:448–454, 2000.

Agarwal SK, Novotny EA, Crabtree JS, Weitzman JB, Yaniv M, Burns AL, Chandrasekharappa SC, Collins FS, Spiegel AM, Marx SJ. Transcription factor JunD, deprived of menin, switches from growth suppressor to growth promoter. *Proc Natl Acad Sci USA* 100:10770–10775, 2003.

Itoh M, Kim CH, Palardy G, Oda T, Jiang YJ, Maust D, Yeo S-Y, Lorick K, Kenworthy A, Lippincott-Schwartz J, Weissman AM, Lewis J, Chandrasekharappa SC, Chitnis AB. Mind bomb is a ubiquitin ligase that is essential for efficient activation of Notch signaling by Delta. *Dev Cell* 4:67–68, 2003.

Lorent K, Yeo SY, Oda T, Chandrasekharappa S, Chitnis A, Matthews RP, Pack M. Inhibition of Jagged-mediated Notch signaling disrupts zebrafish biliary development and generates multi-organ defects compatible with an Alagille syndrome phenocopy. *Development* 131:5753–5766, 2004.

Cerrato A, Parisi M, Santa Anna S, Missirlis F, Guru S, Agarwal S, Sturgill D, Talbot T, Spiegel A, Collins F, Chandrasekharappa S, Marx S, and Oliver B. Genetic interactions between *Drosophila melanogaster* Menin and Jun/Fos. *Dev Biol* 298:59–70, 2006.

Rodriguez V, Chen Y, Elkahlon A, Dutra A, Pak E, Chandrasekharappa S. Chromosome 8 BAC array comparative genomic hybridization and expression analysis identify amplification and overexpression of a novel gene TRMT12 in breast cancer. *Genes Chromosomes Cancer* 46:694–707, 2007.

Ji Y, Prasad NB, Novotny EA, Kaur S, Elkahlon A, Chen Y, Zhang RZ, Chu ML, Agarwal SK, Marx SJ, Collins FS, Chandrasekharappa SC. Mouse embryo fibroblasts lacking the tumor suppressor menin show altered expression of extracellular matrix protein genes. *Mol Cancer Res* 5:1041–1051, 2007.



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

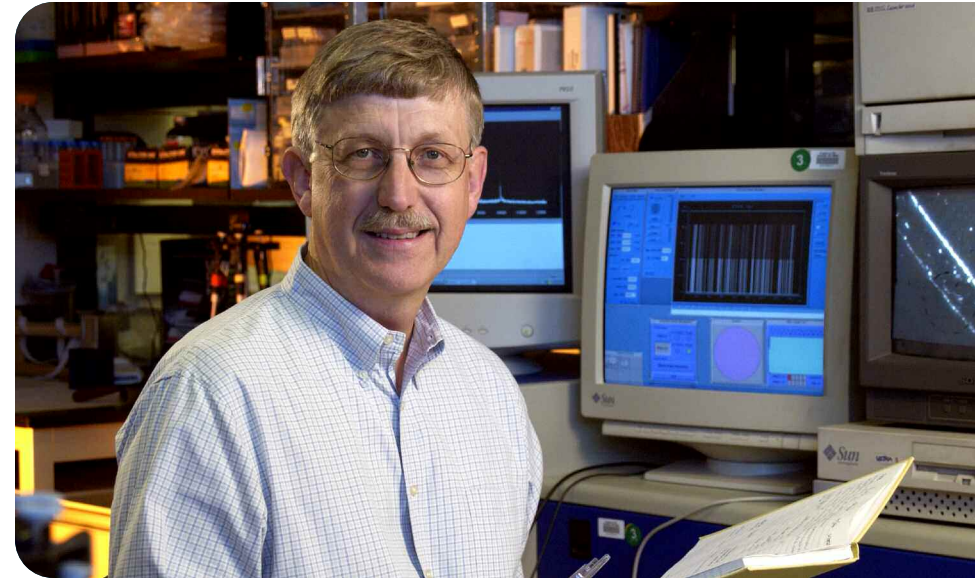
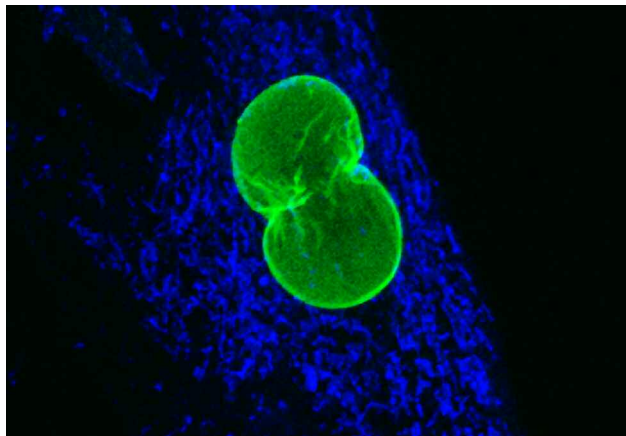
Dr. Collins' laboratory seeks to identify and understand the function of genes involved in a range of human diseases. His group is also developing animal models of genetic disorders to test potential therapeutic approaches.

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

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

laboratory have shown that farnesyltransferase inhibitors (FTIs) can significantly ameliorate the nuclear-shape abnormalities seen in HGPS cells.

Because most progeria patients are in extremely fragile health, there are few opportunities to conduct human trials of potential therapies. Dr. Collins' group has developed an animal model of progeria by reengineering human *LMNA* to carry the HGPS



mutation, and inserting it into the germline of a mouse. The mouse develops normally, without progeroid features in skin, hair, or bone, but demonstrates progressive cardiovascular disease that closely resembles the disease seen in HGPS patients, most of whom die of heart attack or stroke in their early teenage years. Specifically, these mice exhibit progressive loss of vascular smooth muscle cells in the media of their large arteries. This mouse model now offers a valuable resource for screening potential progeria therapies; in fact, early results from treating the progeria mice with FTIs show considerable promise.

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

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

## SELECTED PUBLICATIONS

Eriksson M, Brown WT, Gordon LB, Glynn MW, Singer J, Scott L, Erdos MR, Robbins CM, Moses TY, Berglund P, Dutra A, Pak E, Durkin S, Csoka AB, Boehnke M, Glover TW, Collins FS. Recurrent *de novo* point mutations in lamin A cause Hutchinson–Gilford progeria syndrome. *Nature* 423:293–298, 2003.

Goldman RD, Shumaker DK, Erdos MR, Eriksson M, Goldman AE, Gordon LB, Gruenbaum Y, Khuon S, Mendez M, Varga R, Collins FS. Accumulation of mutant lamin A causes progressive changes in nuclear architecture in Hutchinson–Gilford progeria syndrome. *Proc Natl Acad Sci USA* 101:8963–8968, 2004.

Silander K, Mohlke KL, Scott LJ, Peck EC, Hollstein P, Skol AD, Jackson AU, Deloukas P, Hunt S, Stavrides G, Chines PS, Erdos MR, Narisu N, Conneely KN, Li C, Fingerlin TE, Dhanjal SK, Valle TT, Bergman RN, Tuomilehto J, Watanabe RM, Boehnke M, Collins FS. Genetic variation near the hepatocyte nuclear factor-4 $\alpha$  gene predicts susceptibility to type 2 diabetes. *Diabetes* 53:1141–1149, 2004.

Capell BC, Erdos MR, Madigan JP, Fiordalisi, Varga R, Conneely KN, Gordon LB, Der CJ, Cox AD, Collins FS. Inhibiting farnesylation of the progerin protein prevents the characteristic nuclear blebbing of HGPS. *Proc Natl Acad Sci USA* 102:12879–12884, 2005.

Crawford GE, Holt IE, Whittle J, Webb BD, Tai D, Davis S, Margulies EH, Chen Y, Bernat JA, Ginsburg D, Zhou D, Luo S, Vasicek TJ, Daly MJ, Wolfsberg TG, Collins FS. Genome-wide mapping of DNase hypersensitive sites using Massively Parallel Signature Sequencing (MPSS). *Genome Res* 16:123–131, 2006.

Varga R, Eriksson M, Erdos MR, Olive M, Harten I, Kolodgie F, Capell BC, Cheng J, Faddah D, Perkins S, Avallone H, San H, Qu X, Ganesh S, Gordon LB, Virmani R, Wight TN, Nabel EG, Collins FS. Progressive vascular smooth muscle cell defects in a mouse model of Hutchinson–Gilford progeria syndrome. *Proc Natl Acad Sci USA* 103:3250–3255, 2006.

Bonnycastle LL, Willer CJ, Conneely KN, Jackson AU, Burrill CP, Wantanabe RM, Chines PS, Narisu N, Scott LJ, Enloe ST, Swift AJ, Duren WL, Stringham HM, Erdos MR, Reibow NL, Buchanan TA, Valle TT, Tuomilehto J, Bergman RN, Mohlke KL, Boehnke M, Collins FS. Common variants in *MODY* contribute to risk of type 2 diabetes in Finns. *Diabetes* 55:2534–2540, 2006.

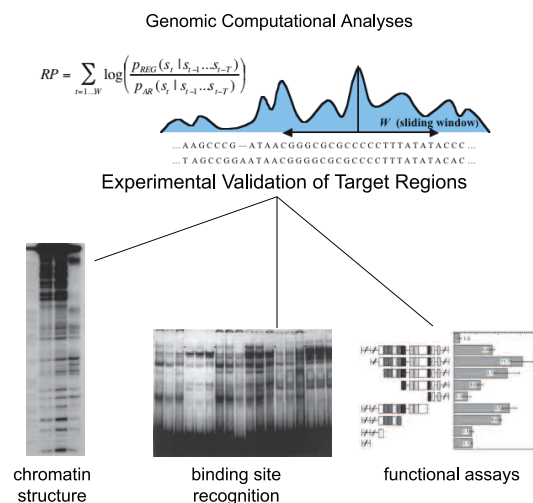
Scott LJ, Bonnycastle LL, Willer CJ, Sprau AG, Jackson AU, Narisu N, Duren WL, Chines PS, Stringham HM, Erdos MR, Valle TT, Tuomilehto J, Bergman RN, Mohlke KL, Collins FS, Boehnke M. Association of transcription factor 7-like 2 (*TCF7L2*) variants with type 2 diabetes in a Finnish sample. *Diabetes* 55:2649–2653, 2006.

Scott LJ, Mohlke KL, Bonnycastle LL, Willer CJ, Li Y, Duren WL, Erdos MR, Stringham HM, Chines PS, Jackson AU, Prokunina-Olsson L, Ding CJ, Swift AJ, Narisu N, Hu T, Pruim R, Xiao R, Li XY, Conneely KN, Riebow NL, Sprau AG, Watkins L, Xiang F, Saramies J, Buchanan TA, Watanabe RM, Valle TT, Kinnunen L, Abecasis GR, Pugh EW, Doherty KF, Bergman RN, Tuomilehto J, Collins FS, Boehnke M. A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. *Science* 316:1341–1345, 2007.

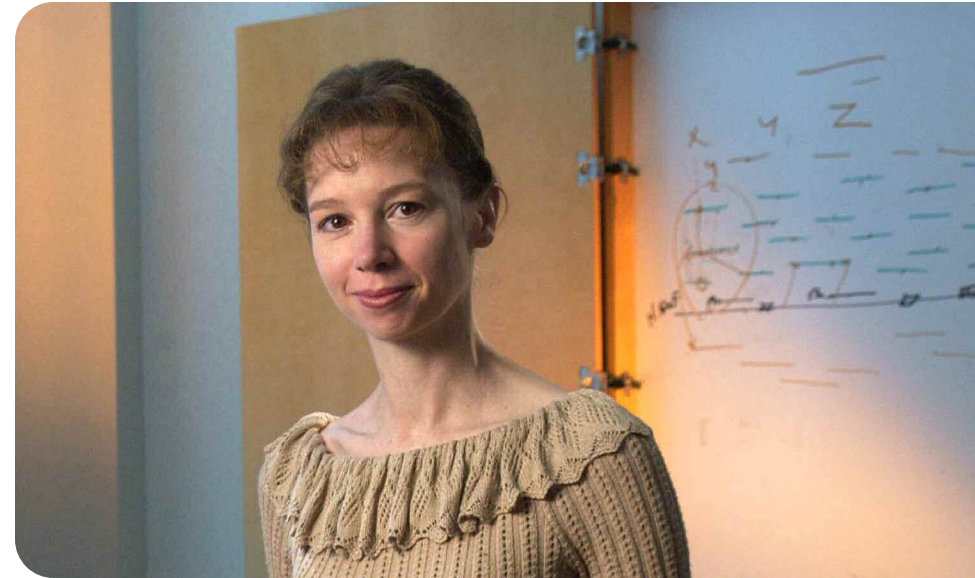
## LAURA L. ELNITSKI, Ph.D.

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

In addition, Dr. Elnitski's laboratory is investigating less characterized functional elements in the human genome. In one project, her group is looking at 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 influence the process of RNA splicing, in which introns are removed from a primary transcript and exons are joined to produce a mature transcript. ESEs also influence the selection of correct splice sites (or signals) located at the boundaries between exons and introns during precursor messenger RNA (mRNA) editing. The correct choice is essential not only



for the production of proteins derived from the right combination of exons, but also for alternative splicing choices—such as exon skipping—that occur in specialized tissues or at different developmental stages. As part of this project, Dr. Elnitski seeks to investigate the role of ESEs in unnatural exon skipping and their relevance to several cancers and inherited diseases in humans. For example, exon skipping is caused by genetic mutations in the *BRCA1* and *CFTR* genes, which are associated with breast cancer and cystic fibrosis, respectively. For this analysis, she will build probabilistic models to identify mutation that disrupt splicing.

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

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

Finally, Dr. Elnitski is extensively involved in NHGRI's ENCODE (*Encyclopedia of DNA Elements*) project, which aims to produce a comprehensive catalog of functional elements in the human genome. She is involved in addressing the role of silencer elements in regulated gene transcription and identifying networks of bidirectional promoters.

## SELECTED PUBLICATIONS

Hillier LW, International Chicken Genome Sequencing Consortium, et al. Sequence and comparative analysis of the chicken genome provide unique perspectives on vertebrate evolution. *Nature* 432:695–716, 2004.

ENCODE Project Consortium. The ENCODE (ENCyclopedia Of DNA Elements) Project. *Science* 306:636–640, 2004.

Elnitski L, Giardine B, Shah P, Zhang Y, Riemer C, Weirauch M, Burhans R, Miller W, Hardison RC. Improvements to GALA and dBERGE II: databases featuring genomic sequence alignment, annotation and experimental results. *Nucl Acids Res Database* issue:D466–470, 2005.

Wu J, Iwata F, Grass JA, Osborne CS, Elnitski L, Fraser P, Ohneda O, Yamamoto M, Bresnick EH. Molecular determinants of NOTCH4 transcription in vascular endothelium. *Mol Cell Biol* 25:1458–1474, 2005.

Giardine B, Riemer C, Hardison RC, Burhans R, Elnitski L, Shah P, Zhang Y, Blankenberg D, Albert I, Miller W, Kent WJ, Nekrutenko A. Galaxy: a platform for interactive large-scale genome analysis. *Genome Res* 15:1451–1455, 2005.

King DC, Taylor J, Elnitski L, Chiaromonte F, Miller W, Hardison RC. Evaluation of regulatory potential and conservation scores for detecting cis-regulatory modules in aligned mammalian genome sequences. *Genome Res* 15:1051–1060, 2005.

Walters E, Altman NS, Elnitski L. Clustering of gene locations. *Comput Stat Data Anal* 50:2920–2932, 2005.

Elnitski L, King D, Hardison RC. Computational prediction of cis-regulatory modules from multispecies alignments using Galaxy, Table Browser and GALA. *Methods Mol Biol* 338:91–103, 2006.

Elnitski L, Jin VX, Farnham PJ, Jones SJM. Locating mammalian transcription factor binding sites: a survey of computational and experimental techniques. *Genome Res* 16:1455–1464, 2006.

Elnitski LL, Shah P, Umamay L, Wolfsberg TG, and Baxeavanis AD. The ENCODEdb Portal: simplified access to ENCODE Consortium data. *Genome Res* 7:954–959, 2007.

Giardine B, Riemer C, Hefferon T, Thomas D, Hsu F, Zielenski J, Sang Y, Elnitski L, Cutting G, Trumbower H, Kern A, Kuhn R, Patrinos GP, Hughes J, Higgs D, Chui D, Scriver C, Phommarinh M, Patnaik SK, Blumenfeld O, Gottlieb B, Kent J, Miller W, Hardison RC. PhenCode: connecting ENCODE data with mutations and phenotype. *Hum Mutat* 28:554–562, 2007.

Yang MQ, Koehly LM, Elnitski LL. Comprehensive annotation of bidirectional promoters identifies co-regulation among breast and ovarian cancer genes. *PLoS Comput Biol* 3:e72, 2007.

Yang MQ, Elnitski L. A computational study of bidirectional promoters in the human genome. In: Zhang Y (Ed), *Springer Verlag Lecture Notes in Bioinformatics*. Heidelberg, Germany: Springer Verlag, pp. 361–371, 2007.



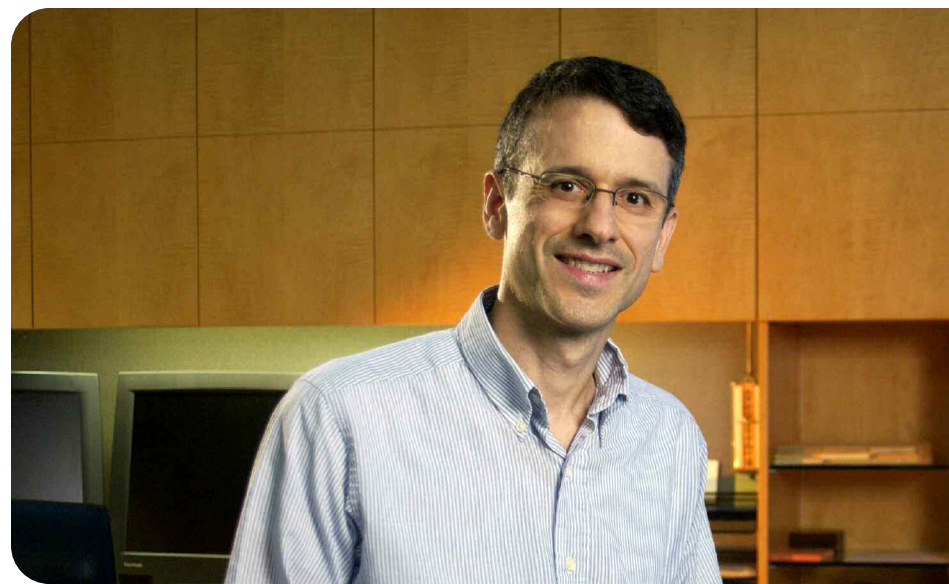
## JAMES INGLESE, Ph.D.

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

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



A veteran of the pharmaceutical and biotechnology industry, Dr. Inglese has developed many biological assay methods, including one of the first high-sensitivity fluorescence G protein-coupled receptor assays. He pioneered the use of laser-scanning imaging, a technology that enables the use of cellular and particle-based assays in whole cell ligand-binding studies. He also developed chemical methodologies to incorporate cAMP-dependent protein kinase



(PKA) sites into proteins, peptides, and small molecules permitting straightforward PKA-dependent labeling of ligands for use in radiometric assays. Most recently, he explored the use of naturally occurring protein domains, in combination with protein evolution techniques, to create antibody surrogates for the detection of post-translationally modified peptides and proteins. Such engineered domains have been used successfully in the development of protease and phosphatase assays for HT screening.

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

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

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

## SELECTED PUBLICATIONS

Inglese J, Samama P, Patel S, Stroke IL, Burbaum JJ, Appell KC. Chemokine receptor-ligand interactions measured using time-resolved fluorescence. *Biochemistry* 37:2372–2377, 1998.

Inglese J, Glickman JF. Radiolabeling of receptor ligands by chemical incorporation of phosphorylation sites. *Anal Biochem* 274:104–109, 1999.

Zuck P, Lao Z, Skwish S, Glickman JF, Burbaum J, Inglese J. Ligand-receptor binding measured by laser-scanning imaging. *Proc Natl Acad Sci USA* 96:11122–11127, 1999.

Ferrer M, Hamilton A, Inglese J. A PDZ domain-based detection system for enzymatic assays. *Anal Biochem* 301:207–216, 2002.

Inglese J. Engaging science and technology for drug development. *Assay Drug Dev Technol* 1:1, 2002.

Inglese J. Expanding the HTS paradigm. *Drug Discov Today* 7:S105–S106, 2002.

Whitney M, Stack JH, Darke PL, Zheng W, Terzo J, Inglese J, Strulovici B, Kuo LC, Pollock BA. A collaborative screening program for the discovery of inhibitors of HCV NS2/3 cis-cleaving protease activity. *J Biomol Screen* 7:149–154, 2002.

Ferrer M, Zuck P, Kolodin G, Mao SS, Peltier RR, Bailey C, Gardell SJ, Strulovici B, Inglese J. Miniaturizable homogenous time-resolved fluorescence assay for carboxypeptidase B activity. *Anal Biochem* 317:94–98, 2003.

Hamilton A, Inglese J, Ferrer M. A PDZ domain-based assay for measuring HIV protease activity: assay design considerations. *Protein Sci* 12:458–467, 2003.

Kunapuli P, Ransom R, Murphy KL, Pettibone D, Kerby J, Grimwood S, Zuck P, Hodder P, Lacson R, Hoffman I, Inglese J, Strulovici B. Development of an intact cell reporter gene  $\beta$ -lactamase assay for G protein-coupled receptors for high-throughput screening. *Anal Biochem* 314:16–29, 2003.

Kornienko O, Lacson R, Kunapuli P, Schneeweis J, Hoffman I, Smith T, Alberts M, Inglese J, Strulovici B. Miniaturization of whole live cell-based GPCR assays using microdispensing and detection systems. *J Biomol Screen* 9:186–195, 2004.

Inglese J, Auld DS, Jadhav A, Johnson RL, Simeonov A, Yasgar A, Zheng W, Austin CP. Quantitative High-Throughput Screening (qHTS): a titration-based approach that efficiently identifies biological activities in large chemical libraries. *Proc Natl Acad Sci USA* 103:11473–11478, 2006.

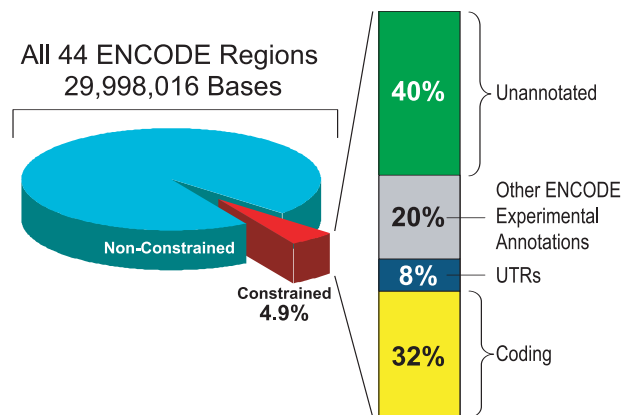
Auld DS, Johnson RL, Zhang Y, Veith H, Jadhav A, Yasgar A, Simeonov A, Zheng W, Martinez ED, Westwick JK, Austin CP, Inglese J. Fluorescent protein-based cellular assays analyzed by laser scanning microplate cytometry in 1536-well plate format. *Methods Enzymol* 414:566–589, 2006.

## ELLIOTT MARGULIES, Ph.D.

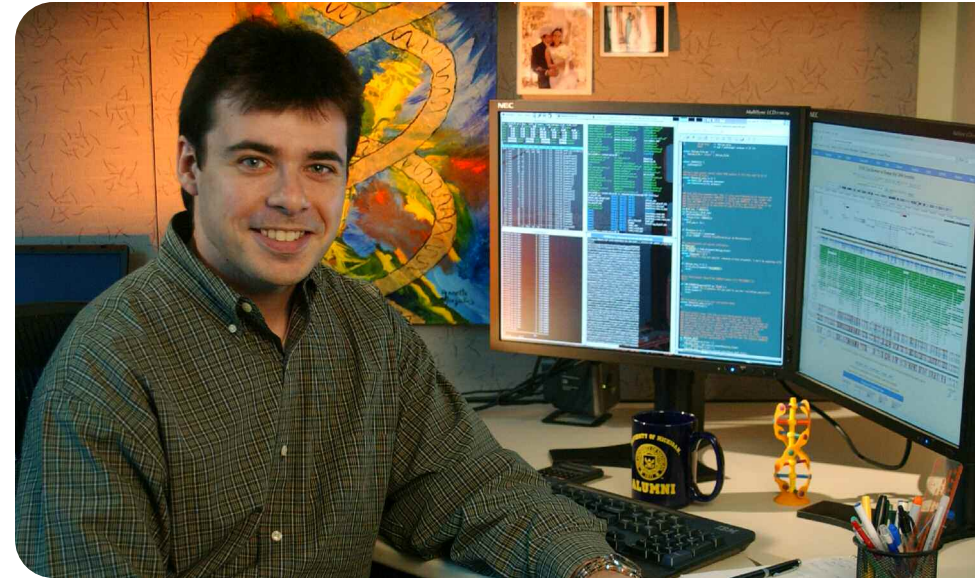
Dr. Margulies develops bioinformatics approaches for identifying and characterizing regions of the human genome that are evolutionarily conserved across multiple species. The conservation of these sequences over millions of years of evolution is strong evidence that they play important roles in biology,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

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

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



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

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

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

## SELECTED PUBLICATIONS

Thomas JW, Touchman JW, Blakesley RW, Bouffard GG, Beckstrom-Sternberg SM, Margulies EH, Blanchette M, Siepel AC, Thomas PJ, McDowell JC, Maskeri B, Hansen NF, Schwartz MS, Weber RJ, Kent WJ, Karolchik D, Bruen TC, Bevan R, Cutler DJ, Schwartz S, Elnitski L, Idol JR, Prasad AB, Lee-Lin SQ, Maduro VVB, Summers TJ, Portnoy ME, Dietrich NL, Akhter N, Ayele K, Benjamin B, Cariaga K, Brinkley CP, Brooks SY, Granite S, Guan X, Gupta J, Haghighi P, Ho SL, Huang MC, Karlins E, Laric PL, Legaspi R, Lim MJ, Maduro QL, Masiello CA, Mastrian SD, McCloskey JC, Pearson R, Stantripop S, Tiogson EE, Tran JT, Tsurgeon C, Vogt JL, Walker MA, Wetherby KD, Wiggins LS, Young AC, Zhang LH, Osoegawa K, Zhu B, Zhao B, Shu CL, Jong PJD, Lawrence CE, Smit AF, Chakravarti A, Haussler D, Green P, Miller W, Green ED. Comparative analyses of multi-species sequences from targeted genomic regions. *Nature* 424:788–793, 2003.

Margulies EH, NISC Comparative Sequencing Program, Green ED. Detecting highly conserved regions of the human genome by multispecies sequence comparisons. *Cold Spring Harb Symp Quant Biol* 68:255–263, 2003.

Margulies EH, Blanchette M, NISC Comparative Sequencing Program, Haussler D, Green ED. Identification and characterization of multi-species conserved sequences. *Genome Res* 13:2507–2518, 2003.

ENCODE Project Consortium. The ENCODE (ENCyclopedia Of DNA Elements) Project. *Science* 306:636–640, 2004.

Angata T, Margulies EH, Green ED, Varki A. Large-scale sequencing of the CD33-related Siglec gene cluster in five mammalian species reveals rapid evolution by multiple mechanisms. *Proc Natl Acad Sci USA* 101:13251–13256, 2004.

Margulies EH, NISC Comparative Sequencing Program, Maduro VVB, Thomas PJ, Tomkins JP, Amemiya CT, Luo M, Green ED. Comparative sequencing provides insights about the structure and conservation of marsupial and monotreme genomes. *Proc Natl Acad Sci USA* 102:3354–3359, 2005.

Margulies EH, Vinson JP, NISC Comparative Sequencing Program, Miller W, Jaffe DB, Lindblad-Toh K, Chang JL, Green ED, Lander ES, Mullikin JC, Clamp M. An initial strategy for the systematic identification of functional elements in the human genome by low-redundancy comparative sequencing. *Proc Natl Acad Sci USA* 102:4795–4800, 2005.

Margulies EH, Chen CW, Green ED. Differences between pair-wise and multi-sequence alignment methods affect vertebrate genome comparisons. *Trends Genet* 22:187–193, 2006.

ENCODE Project Consortium. The ENCODE pilot project: functional annotation of 1% of the human genome. *Nature* 447:799–816, 2007.

Margulies EH, Cooper GM, Asimenos G, Thomas DJ, Dewey CN, Siepel A, Birney E, Keefe D, Schwartz AS, Hou M, Taylor J, Nikolaev S, Montoya-Burgos JI, Loytynoja A, Whelan S, Pardi F, Massingham T, Brown JB, Bickel P, Holmes I, Mullikin JC, Ureta-Vidal A, Paten B, Rosenbloom KR, Kent WJ, NISC Comparative Sequencing Program, Baylor College of Medicine Human Genome Sequencing Center, Washington University Genome Sequencing Center, Broad Institute, UCSC Genome Browser Team, British Columbia Cancer Agency Genome Sciences Center, Antonarakis SE, Batzoglu S, Goldman N, Hardison R, Haussler D, Miller W, Pachter L, Green ED, Sidow A. Analyses of deep mammalian sequence alignments and constraint predictions for 1% of the human genome. *Genome Res* 17:760–774, 2007.



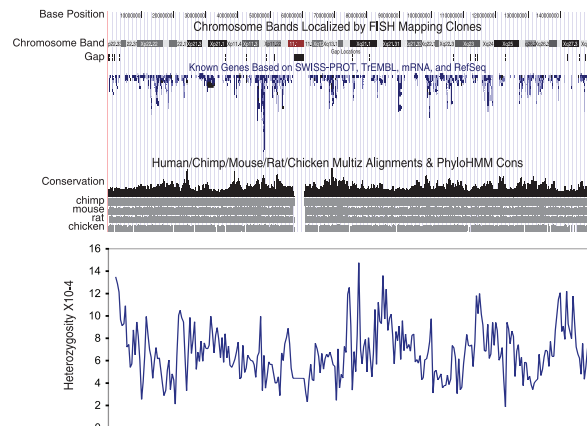
## JAMES C. MULLIKIN, Ph.D.

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

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

Dr. Mullikin’s group also provides computational support to major NHGRI efforts, such as the International Haplotype Map (HapMap) Project, which is primarily focused on determining genes and genetic variations that affect health and disease susceptibility. In the initial

phase of the project, investigators aim to produce a working HapMap consisting of about 600,000 polymorphic sites roughly 5 kb apart from one another. Some particularly complex regions will need even higher resolution. When completed, the HapMap Project will give researchers a powerful tool for isolating and identifying disease genes through association studies.



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

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

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

## SELECTED PUBLICATIONS

Mullikin JC, McMurray AA. DNA sequencing: sequencing the genome, fast. *Science* 283:1867–1869, 1999.

Mullikin JC, Hunt SE, Cole CG, Mortimore BJ, Rice CM, Burton J, Matthews LH, Pavitt R, Plumb RW, Sims SK, Ainscough RM, Attwood J, Bailey JM, Barlow K, Bruskiwich RM, Butcher PN, Carter NP, Chen Y, Clee CM, Coghill PC, Davies J, Davies RM, Dawson E, Francis MD, Joy AA, Lambie RG, Langford CF, Macarthy J, Mall V, Moreland A, Overton-Larty EK, Ross MT, Smith LC, Steward CA, Sulston JE, Tinsley EJ, Turney KJ, Willey DL, Wilson GD, McMurray AA, Dunham I, Rogers J, Bentley DR. An SNP map of human chromosome 22. *Nature* 407:516–520, 2000.

Ning Z, Cox AJ, Mullikin JC. SSAHA: a fast search method for large DNA databases. *Genome Res* 11:1725–1729, 2001.

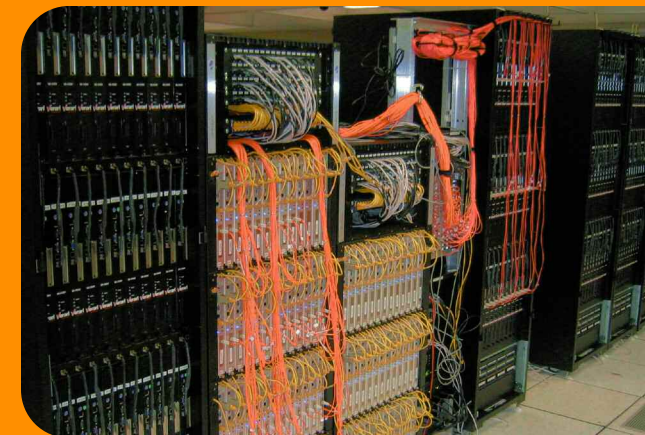
Mullikin JC, Ning Z. The Phusion assembler. *Genome Res* 13:81–90, 2003.

Eichler EE, Nickerson DA, Altshuler D, Bowcock AM, Brooks LD, Carter NP, Church DM, Felsenfeld A, Guyer M, Lee C, Lupski JR, Mullikin JC, Pritchard JK, Sebat J, Sherry ST, Smith D, Valle D, Waterston RH. Completing the map of human genetic variation. *Nature* 447:161–165, 2007.

Keinan A, Mullikin JC, Patterson N, Reich D. Measurement of the human allele frequency spectrum demonstrates greater genetic drift in East Asians than in Europeans. *Nat Genet* 39:1251–1255, 2007.

The International HapMap Consortium. A second generation human haplotype map of over 3.1 million SNPs. *Nature* 449:851–861, 2007.

Pontius JU, Mullikin JC, Smith DR, Agencourt Sequencing Team, Lindblad-Toh K, Gnerre S, Clamp M, Chang J, Stephens R, Neelam B, Volfovsky N, Schäffer AA, Agarwala R, Narfström K, Murphy WJ, Giger U, Roca AL, Antunes A, Menotti-Raymond M, Yuhki N, Pecon-Slattery J, Johnson WE, Bourque G, Tesler G, NISC Comparative Sequencing Program, O'Brien SJ. Initial sequence and comparative analysis of the cat genome. *Genome Res* 17:1675–1689, 2007.

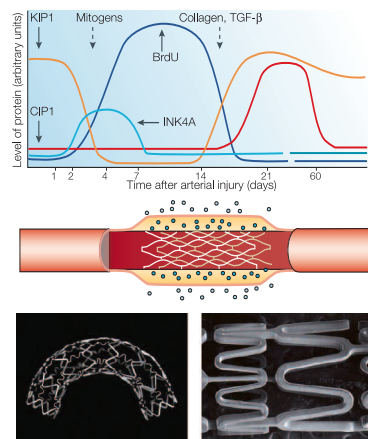


## ELIZABETH G. NABEL, M.D.

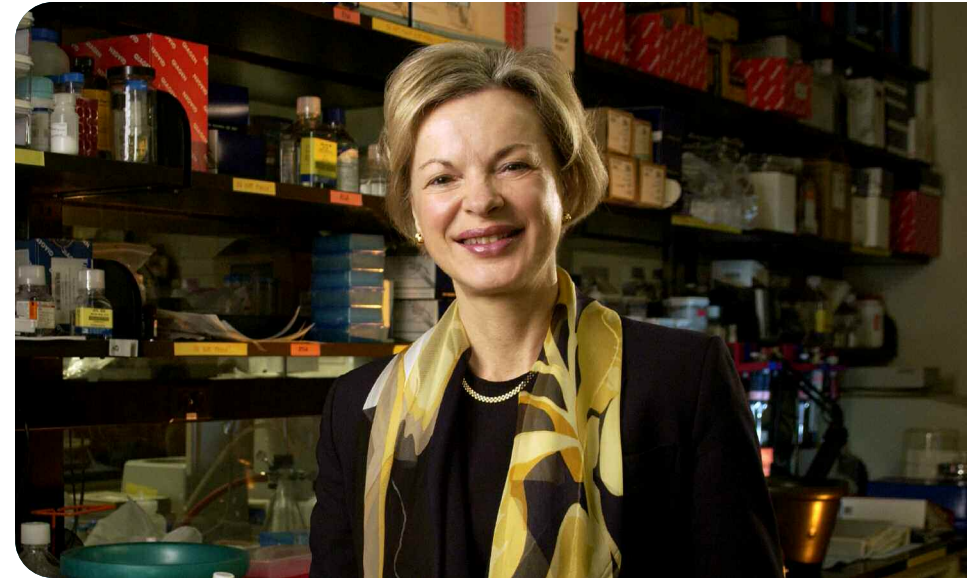
Dr. Nabel's laboratory seeks to identify the molecular, cellular, and genetic mechanisms that cause vascular disorders. In particular, her research focuses on defining the pathways that regulate cell growth in the vasculature, remodel the vasculature after injury, and lead to genetic susceptibility to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

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

Given the role of cyclins in vascular health, one major focus of Dr. Nabel's laboratory is the study of CKIs, which are primarily involved in inhibiting the proliferation of a variety of normal cell types. Dr. Nabel's laboratory previously identified a particular CKI, known as  $p27^{Kip1}$ , as a major regulator of vascular cell proliferation during arterial remodeling.



In one set of studies, her group found that  $p27^{Kip1}$  plays a major role in cardiovascular disease through its effects on the proliferation of bone marrow-derived immune cells that migrate into vascular lesions. To demonstrate whether  $p27^{Kip1}$  regulates arterial wound repair, Dr. Nabel and coworkers recently subjected  $p27^{-/-}$  (homozygous knockout),  $p27^{+/-}$  (heterozygous knockout), and  $p27^{+/+}$  (wild-type) mice to a wire injury in the femoral artery and examined subsequent cell proliferation and lesion formation. Cell proliferation was significantly increased in the innermost lining of the blood vessels of  $p27^{-/-}$  mouse arteries compared with  $p27^{+/+}$



arteries. Arterial lesions also were markedly increased in the  $p27^{-/-}$  mice compared with those of  $p27^{+/+}$  mice. The heterozygous knockout mice ( $p27^{+/-}$ ) had an intermediate phenotype. These findings suggest that vascular repair and regeneration are regulated by the proliferation of hematopoietically and nonhematopoietically derived cells through a  $p27^{Kip1}$ -dependent mechanism, with immune cells largely mediating these effects.

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

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

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

## SELECTED PUBLICATIONS

Boehm M, Yoshimoto T, Crook MF, Nallamshetty S, True A, Nabel GJ, Nabel EG. A growth factor-dependent nuclear kinase phosphorylates p27Kip1 and regulates cell cycle progression. *EMBO J* 21:3390–3401, 2002.

Nabel EG. CDKs and CKIs: molecular targets for tissue remodeling. *Nat Rev Drug Discov* 1:587–598, 2002.

Boehm M, Nabel EG. The cell cycle and cardiovascular diseases. *Prog Cell Cycle Res* 5:19–30, 2003.

Nabel EG. Genomic Medicine: cardiovascular disease. *N Engl J Med* 349:60–72, 2003.

Boehm M, Olive M, True AL, Crook MF, San H, Qu X, Nabel EG. Bone marrow-derived immune cells regulate vascular disease through a p27Kip1-dependent mechanism. *J Clin Invest* 114:419–426, 2004.

Ganesh SK, Skelding KA, Mehta L, O'Neill K, Joo J, Zheng G, Goldstein J, Simari R, Billings E, Geller NL, Holmes D, O'Neill WW, Nabel EG. Rationale and study design of the CardioGene Study: genomics of in-stent restenosis. *Pharmacogenomics* 5:952–1004, 2004.

Ganesh SK, Nabel EG. Genomics of in-stent restenosis: early insights into a complex disease. *Circulation* 112:2378–2379, 2005.

Nallamshetty S, Crook M, Boehm M, Yoshimoto T, Nabel EG. The cell cycle regulator p27<sup>Kip1</sup> interacts with MCM7, a DNA replication licensing factor, and inhibits initiation of DNA replication. *FEBS Lett* 579:6529–6536, 2005.

Varga R, Eriksson M, Erdos MR, Olive M, Harten I, Kolodgie F, Capell BC, Cheng J, Faddah D, Perkins S, Avallone H, San H, Qu X, Ganesh S, Gordon LB, Virmani R, Wright TN, Nabel EG, Collins FS. Progressive vascular smooth muscle cell defects in a mouse model of Hutchinson-Gilford progeria syndrome. *Proc Natl Acad Sci USA* 103:3250–3255, 2006.

Ganesh L, Yoshimoto T, Moorthy NC, Akahata W, Boehm M, Nabel EG, Nabel GJ. Protein methyltransferase 2 inhibits NK- $\kappa$ B function and promotes apoptosis. *Mol Cell Biol* 26:3864–3874, 2006.

Yoshimoto T, Boehm M, Olive M, Crook MF, San H, Langenickel T, Nabel EG. The arginine methyltransferase PRMT2 binds RB and regulates E2F function. *Exp Cell Res* 312:2040–2053, 2006.

Nakahira K, Kim HP, Geng XH, Nakao A, Wang X, Murase N, Drain PF, Wang X, Sasidhar M, Nabel EG, Takahashi T, Lukacs NW, Rytter SW, Morita K, Choi AMK. Carbon monoxide differentially inhibits TLR signaling pathways by regulating ROS-induced trafficking of TLRs to lipid rafts. *J Exp Med* 203:2377–2389, 2006.

Capell BC, Collins FS, Nabel EG. Mechanisms of cardiovascular disease in accelerated aging syndromes. *Circ Res* 101:13–26, 2007.

True AL, Olive M, Boehm M, San H, Westrick RJ, Raghavachari N, Xu X, Lynn EG, Sack MN, Munson PJ, Gladwin MT, Nabel EG. Heme oxygenase-1 deficiency accelerates formation of arterial thrombosis through oxidative damage to the endothelium, which is rescued by inhaled carbon monoxide. *Circ Res* 101:893–901, 2007.

Crook MF, Olive M, Xue HH, Langenickel TH, Boehm M, Leonard WJ, Nabel EG. GA-binding protein regulates KIS gene expression, cell migration, and cell cycle progression. *FASEB J* 22:225–235, 2008.

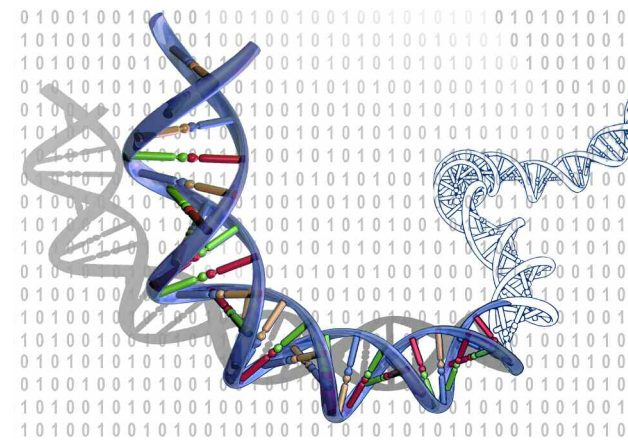


## TYRA G. WOLFSBERG, Ph.D.

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

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

Dr. Wolfsberg has devised an approach for analyzing putative DNase-sensitive regions and establishing whether they represent transcriptionally active regions. Her analyses have shown that such hypersensitive sites do indeed reside more frequently in regions known to contain regulatory elements, such as segments upstream of genes, sequences within CpG islands (unmethylated regions of the genome that are associated with the 5' ends of most housekeeping genes and many tissue-specific genes), and regions where the human and mouse



genomes are similar. Dr. Wolfsberg and her colleagues are now scaling up this process to deal with up to 100,000 such sites in the human genome. This scale-up involves the development of new computer protocols for handling the sheer volume of raw data in a way that is computationally efficient and tractable.

In another line of research, Dr. Wolfsberg is working with other NIH laboratories to determine



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

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

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

## SELECTED PUBLICATIONS

Wolfsberg TG, McEntyre J, Schuler GD. Guide to the draft human genome. *Nature* 409:824–826, 2001.

Wolfsberg TG, Schafer S, Tatusov RL, Tatusova TA. Organelle genome resources at NCBI. *Trends Biochem Sci* 26:199–203, 2001.

Wolfsberg TG, Wetterstrand KA, Guyer MS, Collins FS, Baxeavanis AD. A user's guide to the human genome II. *Nat Genet Suppl* 35:4, 2003.

Crawford GE, Holt IE, Mullikin JC, Tai D, Blakesley R, Bouffard G, Young A, Masiello C, Green ED, Wolfsberg TG, Collins FS, National Institutes of Health Intramural Sequencing Center. Identifying gene regulatory elements by genome-wide recovery of DNase hypersensitive sites. *Proc Natl Acad Sci USA* 101:992–997, 2004.

The ENCODE Project Consortium. The ENCODE (Encyclopedia of DNA Elements) project. *Science* 306:636–640, 2004.

Gillanders EM, Masiello A, Gildea D, Umayam L, Duggal P, Jones MP, Klein AP, Freas-Lutz D, Ibay G, Trout K, Wolfsberg TG, Trent JM, Bailey-Wilson JE, Baxeavanis AD. GeneLink: a database to facilitate genetic studies of complex traits. *BMC Genomics* 5:81–95, 2004.

Hematti P, Hong BK, Ferguson C, Adler R, Hanawa H, Sellers S, Holt IE, Eckfeldt CE, Sharma Y, Schmidt M, von Kalle C, Persons DA, Billings EM, Verfaillie CM, Nienhuis AW, Wolfsberg TG, Dunbar CE, Calmels B. Distinct genomic integration of MLV and SIV vectors in primate hematopoietic stem and progenitor cells. *PLoS Biol* 2:e423, 2004.

Scacheri PC, Rozenblatt-Rosen O, Caplen NJ, Wolfsberg TG, Umayam L, Lee JC, Hughes CM, Shanmugam KS, Bhattacharjee A, Meyerson M, Collins FS. Short interfering RNAs can induce unexpected and divergent changes in the levels of untargeted proteins in mammalian cells. *Proc Natl Acad Sci USA* 101:1892–1897, 2004.

White JM, Bridges LC, DeSimone DW, Tomczuk M, Wolfsberg TG. Introduction to the ADAM family. In: Hooper NM, Lendeckel U (Eds), *The ADAM Family of Proteases: Proteases in Biology and Disease, Vol 4*. Dordrecht, The Netherlands: Springer, p. 1–28, 2005.

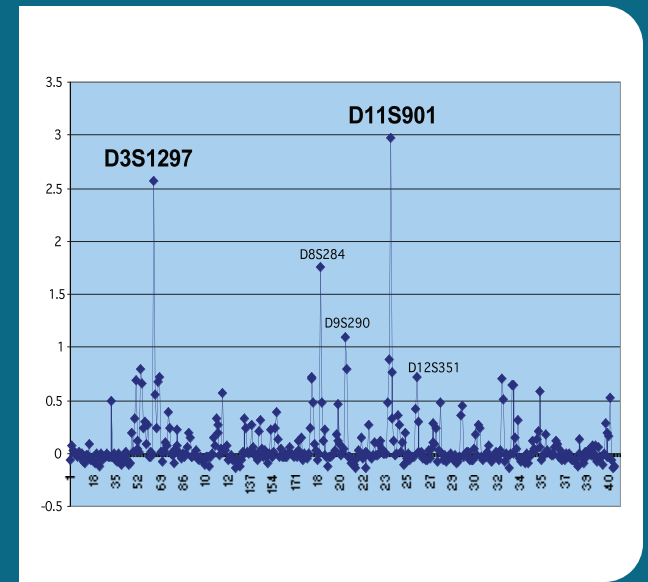
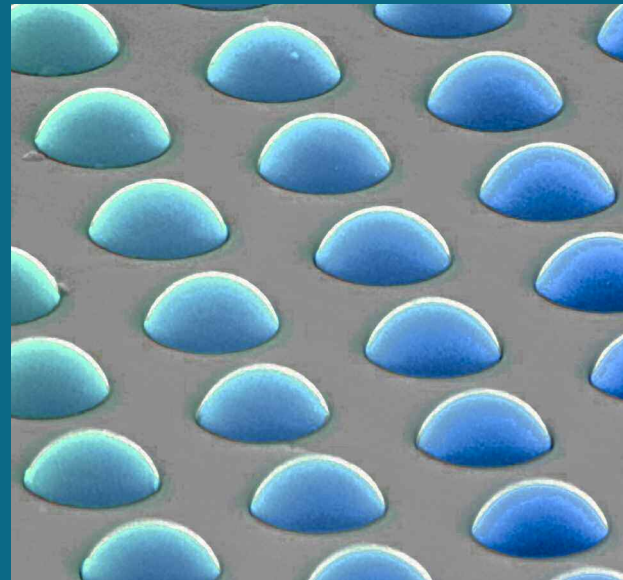
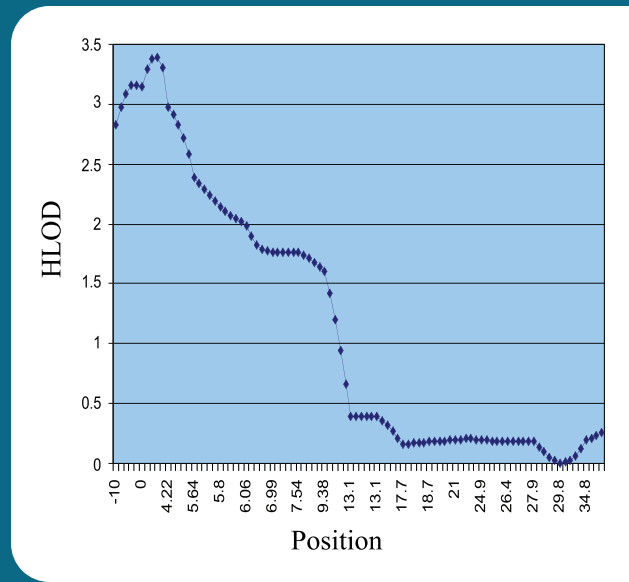
Crawford GE, Holt IE, Whittle J, Webb BD, Tai D, Davis S, Margulies EH, Chen Y, Bernet JA, Ginsburg D, Zhou D, Luo S, Vasicek TJ, Wolfsberg TG, Collins FS. Genome-wide mapping of DNase hypersensitive sites using massively parallel signature sequencing (MPSS). *Genome Res* 16:123–131, 2006.

Crawford GE, Davis S, Scacheri PC, Renaud G, Halawi MJ, Erdos MR, Green R, Meltzer PS, Wolfsberg TG, Collins FS. DNase-chip: a high-resolution method to identify DNase I hypersensitive sites using tiled microarrays. *Nat Methods* 3:503–509, 2006.

Baxter LL, Hsu BJ, Umayam L, Wolfsberg TG, Larson DM, Frith MC, Kawai J, Hayashizaki Y, Carninci P, Pavan WJ. Informatic and genomic analysis of melanocyte cDNA libraries as a resource for the study of melanocyte development and function. *Pigment Cell Res* 20:201–209, 2007.

Elnitski LL, Shah P, Moreland RT, Umayam L, Wolfsberg TG, Baxeavanis AB. The ENCODEdb portal: simplified access to ENCODE Consortium data. *Genome Res* 17:954–959, 2007.





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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**STATISTICAL GENETICS SECTION**

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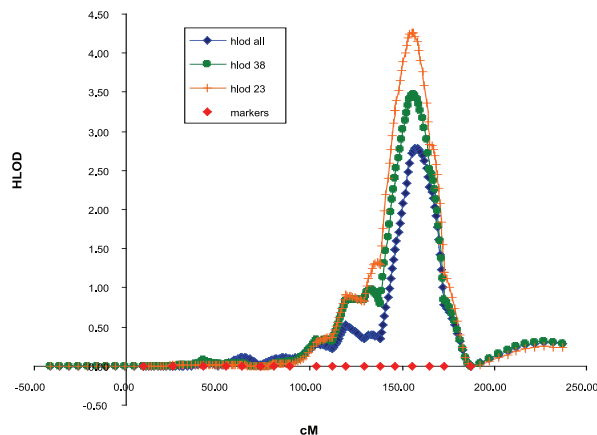
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## JOAN E. BAILEY-WILSON, Ph.D.

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

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

Dr. Bailey-Wilson and others have used similar approaches to locate other cancer-related genes. For example, in the mid-1990s, she and her collaborators published evidence that



genes involved in prostate cancer reside on specific regions of chromosomes 1, 8, and X. These findings have been replicated, and two candidate genes have been cloned: *HPC1*, which encodes ribonuclease L, and *MSRI*, which encodes the macrophage scavenger receptor 1. In ongoing studies, Dr. Bailey-Wilson and her collaborators are looking for additional susceptibility genes for these and other cancers.



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

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

## SELECTED PUBLICATIONS

Sellers TA, Bailey-Wilson JE, Elston RC, Wilson AF, Ooi WL, Rothschild H. Evidence for mendelian inheritance in the pathogenesis of lung cancer. *J Natl Cancer Inst* 82:1272–1279, 1990.

Bailey-Wilson JE, Sorant AJM, Malley JD, Presciuttini S, Redner RA, Severini TA, Badner JA, Pajevic S, Jufer R, Baffoe-Bonnie A, Kao L, Doan BQ, Goldstein JL, Holmes TN, Behnemann D, Mandal DM, Turley TN, Weissbecker KA, O'Neill J, Pugh EW. Comparison of novel and existing methods for detection of linkage disequilibrium using parent-child trios in the GAW12 genetic isolate simulated data. *Genet Epidemiol* 21:S378–S383, 2001.

Bailey-Wilson JE, Amos CI, Pinney SM, Petersen GM, de Andrade M, Wiest JS, Fain P, Schwartz AG, You M, Franklin W, Klein C, Gazdar A, Rothschild H, Mandal D, Coons T, Slusser J, Lee J, Gaba C, Kupert E, Perez A, Zhou X, Zeng D, Liu Q, Zhang Q, Seminara D, Minna J, Anderson MW. A major lung cancer susceptibility locus maps to chromosome 6q23-25. *Am J Hum Genet* 75:460–474, 2004.

Baffoe-Bonnie AB, Smith JR, Stephan DA, Schleutker J, Carpten JD, Kainu T, Gillanders EM, Matikainen M, Teslovich TM, Tammela T, Sood R, Balshem AM, Scarborough SD, Xu J, William B, Isaacs WB, Trent JM, Kallioniemi O-P, Bailey-Wilson JE. A major locus for hereditary prostate cancer in Finland: localization by linkage disequilibrium of a haplotype in the *HPCX* region. *Hum Genet* 117: 307–316, 2005.

Klein AP, Tsai Y, Duggal P, Gillanders EM, Barnhart M, Mathias RA, Dusenberry IP, Turiff A, Chines PS, Goldstein J, Wojciechowski R, Hening W, Pugh EW, Bailey-Wilson JE. Investigation of altering SNP density on the power to detect trait loci and frequency of false positive in non-parametric linkage analyses of qualitative traits. *BMC Genet* 6:S20, 2005.

Doan BQ, Frangakis CE, Shugart YY, Bailey-Wilson JE. Application of the propensity score in a covariate-based linkage analysis of the collaborative study on the genetics of alcoholism. *BMC Genet* 6:S33, 2005.

Duggal P, Gillanders EM, Mathias RA, Ibay GP, Klein AP, Baffoe-Bonnie AB, Ou L, Dusenberry IP, Tsai Y, Chines PS, Doan BQ, Bailey-Wilson JE. Identification of tag single-nucleotide polymorphisms in regions with varying linkage disequilibrium. *BMC Genet* 6:S73, 2005.

Doan B, Sorant AJ, Frangakis C, Bailey-Wilson JE, Shugart YY. Covariate-based linkage analysis: application of a propensity score as the single covariate consistently improves power to detect linkage. *Eur J Hum Genet* 14:1018–1026, 2006.

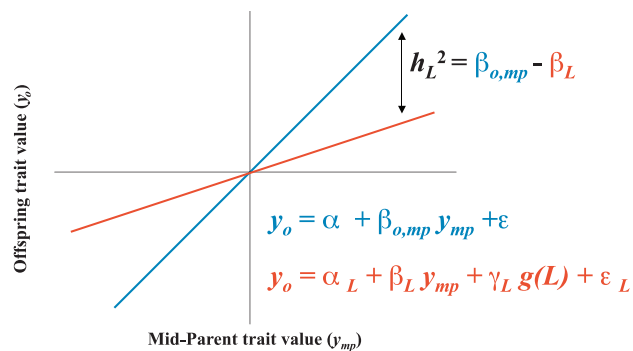
Kim Y, Duggal P, Gillanders EM, Kim H, Bailey-Wilson JE. Examining the effect of linkage disequilibrium between markers on the Type 1 error rate and power of nonparametric multipoint linkage analysis of two-generation and multigenerational pedigrees in the presence of missing genotype data. *Genet Epidemiol* 32:41–51, 2008.

## ALEXANDER F. WILSON, Ph.D.

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

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

Similarly, by analyzing data from an ongoing genotyping study of traits related to obesity in the Old Order Amish in Pennsylvania, Dr. Wilson's group recently found candidate regions for obesity-related genes on five chromosomes. The strongest signal was found on a region on chromosome 7—in an area that holds a dozen or more genes encoding taste and smell receptors. Moreover, Dr. Wilson's group has collaborated in other studies that have provided



evidence for the presence of genetic factors influencing body mass index (BMI), the standard measure of obesity. Ironically, BMI was once considered the prime example of a purely environmental factor that contributed to heart disease; researchers can now begin to elucidate the influence of genetics on an individual's BMI.



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



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

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

## SELECTED PUBLICATIONS

Wilson AF, Elston RC, Siervogel RM, Tran LD. Use of the robust sib-pair method to screen for single locus, multiple-locus, and pleiotropic effects: application to traits related to hypertension. *Am J Hum Genet* 48:862–872, 1991.

Wilson AF, Sorant AJ. Equivalence of single- and multilocus markers: power to detect linkage with composite markers derived from biallelic loci. *Am J Hum Genet* 66:1610–1615, 2000.

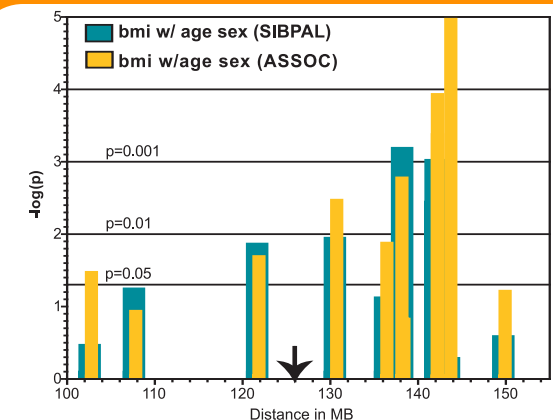
Platte P, Papanicolaou GJ, Johnston J, Klein CM, Doheny K, Pugh EW, Roy-Gagnon M-H, Stunkard AJ, Francomano CA, Wilson AF. A study of linkage and association of body mass index in the Old-Order Amish. *Am J Med Genet C Semin Med Genet* 121:71–80, 2003.

Matise TC, Sachidanandam R, Clark AG, Kryglyak L, Wijsman E, Kakol J, Buyske S, Chui B, Cohen P, de Toma C, Ehm M, Glanowski S, He CS, Heil J, Markianos K, McMullen I, Pericak-Vance MA, Silbergleit A, Stein L, Wagner M, Wilson AF, Winick JD, Winn-Deen ES, Yamashiro C, Cann HM, Lai E, Holden AL. A 3.9 centimorgan- resolution human single-nucleotide polymorphism linkage map and screening set. *Am J Hum Genet* 73:271–284, 2003.

Miller NH, Justice CM, Marosy B, Doheny KF, Pugh E, Zhang J, Wilson AF. Identification of candidate regions in familial idiopathic scoliosis. *Spine* 30:1181–1187, 2005.

Papanicolaou GJ, Justice CM, Kovac IP, Sorant AJM, Wilson AF. Critical values and variation in type I error along chromosomes in the COGA dataset using the applied pseudo-trait (APT) method. *BMC Genet* 6:S54, 2005.

Roy-Gagnon M-H, Mathias RA, Wilson AF. Application of the regression of offspring on mid-parent (ROMP) method to detect associations between SNPs and the beta 2 EEG phenotype in the COGA data. *BMC Genet* 6:S56, 2005.



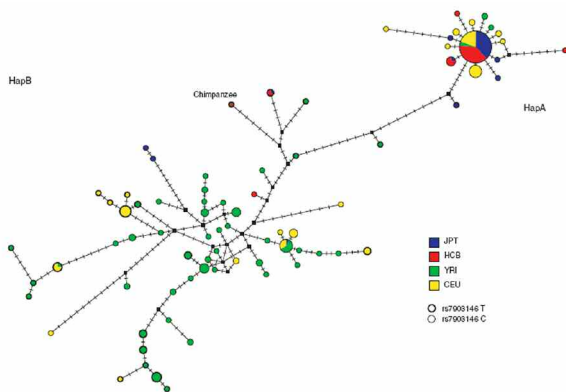
## CHARLES N. ROTIMI, Ph.D.

Dr. Rotimi is the Director of the NIH Intramural Center for Genomics and Health Disparities (NICGHD), 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 $\beta$* ) — 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 non-random 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.

## SELECTED PUBLICATIONS

Rotimi CN, Comuzzie AG, Lowe WL, Luke A, Blangero J, Cooper RS. The quantitative trait locus on chromosome 2 for serum leptin levels is confirmed in African Americans. *Diabetes* 48:643–644, 1999.

Gabriel SB, Schaffner SF, Nguyen H, Moore JM, Roy J, Blumenstiel B, Higgins J, DeFelice M, Lochner A, Faggart M, Liu-Cordero SN, Rotimi C, Adeyemo A, Cooper R, Ward R, Lander ES, Daly MJ, Altshuler D. The structure of haplotype blocks in the human genome. *Science* 296:2225–2229, 2002

Rotimi CN, Chen G, Adeyemo AA, Furbert-Harris P, Parish-Gause D, Zhou J, Berg K, Adegoke O, Amoah A, Owusu S, Acheampong J, Agyenim-Boateng K, Eghan BA Jr, Oll J, Okafor G, Ofoegbu E, Osotimehin B, Abbiyesuku F, Johnson T, Rufus T, Fasanmade O, Kittles R, Daniel H, Chen Y, Dunston G, Collins FS; the Africa America Diabetes Mellitus Study. A genome-wide search for type 2 diabetes susceptibility genes in West Africans: the Africa America Diabetes Mellitus (AADM) Study. *Diabetes* 53:838–841, 2004.

Rotimi CN. Are medical and nonmedical uses of large-scale genomic markers conflating genetics and 'race'? *Nat Genet* 36 Suppl:S43–47, 2004.

Rotimi CN. Inauguration of the African Society of Human Genetics. *Nat Genet* 36:544, 2004.

Yuan A, Chen G, Rotimi C, Bonney GE. A statistical framework for haplotype blocks inference. *J Bioinform Comput Biol* 3:1021–1038, 2005.

Rotimi CN, Chen G, Adeyemo AA, Jones LS, Agyenim-Boateng K, Eghan BA Jr, Zhou J, Doutamey A, Lashley K, Huang H, Fasanmade O, Akinsola FB, Ezepue F, Amoah A, Akafo S, Chen Y, Oll J, Johnson T. Genome wide scan and fine mapping for quantitative trait loci for intraocular pressure on 5q and 14q in West Africans. *Invest Ophthalmol Vis Sci* 47:3262–3267, 2006.

Helgason A, Palsson S, Thorleifsson G, Grant SF, Emilsson V, Gunnarsdottir S, Adeyemo A, Chen Y, Chen G, Reynisdottir I, Benediktsson R, Hinney A, Hansen T, Andersen G, Borch-Johnsen K, Jorgensen T, Schafer H, Faruque M, Doumatey A, Zhou J, Wilensky RL, Reilly MP, Rader DJ, Bagger Y, Christiansen C, Sigurdsson G, Hebebrand J, Pedersen O, Thorsteinsdottir U, Gulcher JR, Kong A, Rotimi C, Stefansson K. Refining the impact of TCF7L2 gene variants on type 2 diabetes and adaptive evolution. *Nat Genet* 39:218–225, 2007.

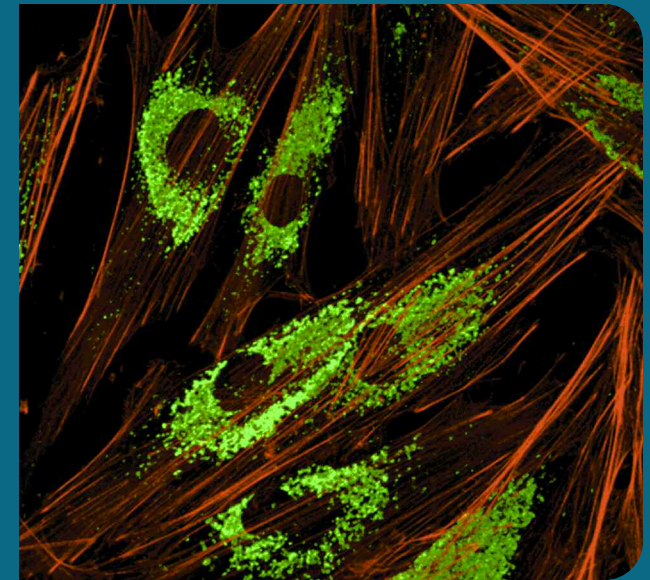
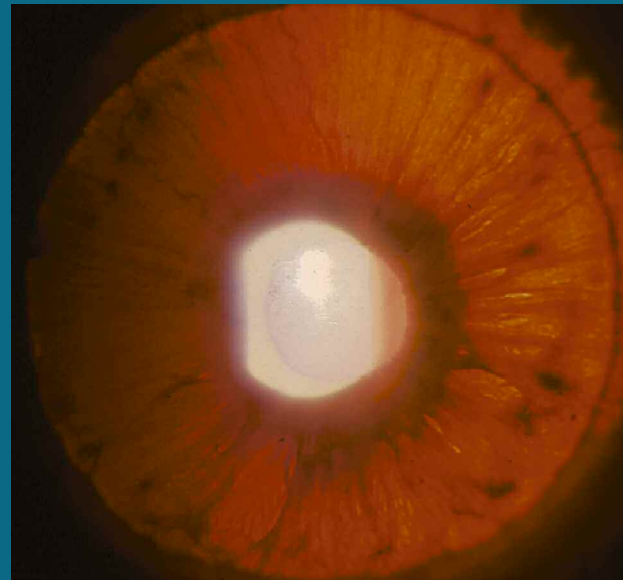
Steinthorsdottir V, Thorleifsson G, Reynisdottir I, Benediktsson R, Jonsdottir T, Walters GB, Styrkarsdottir U, Gretarsdottir S, Emilsson V, Ghosh S, Baker A, Snorraddottir S, Bjarnson H, Ng MC, Hansen T, Bagger Y, Wilensky RL, Reilly MP, Adeyemo A, Chen Y, Zhou J, Gudnason V, Chen G, Huang H, Lashley K, Doumatey A, So WY, Ma RC, Andersen G, Borch-Johansen K, van Vliet-Ostaptchouk JV, Hofker MH, Wijmenga C, Christiansen C, Rader DJ, Rotimi C, Gurney M, Chan JC, Pedersen O, Sigurdsson G, Gulcher JR, Thorsteinsdottir U, Kong A, Stefansson K. A variant in the CDKAL1 gene influences insulin response and the risk of type 2 diabetes. *Nat Genet* 39:770–775, 2007.

International HapMap Consortium. A second generation human haplotype map of over 3.1 million SNPs. *Nature* 449:851–861, 2007.

“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.**”

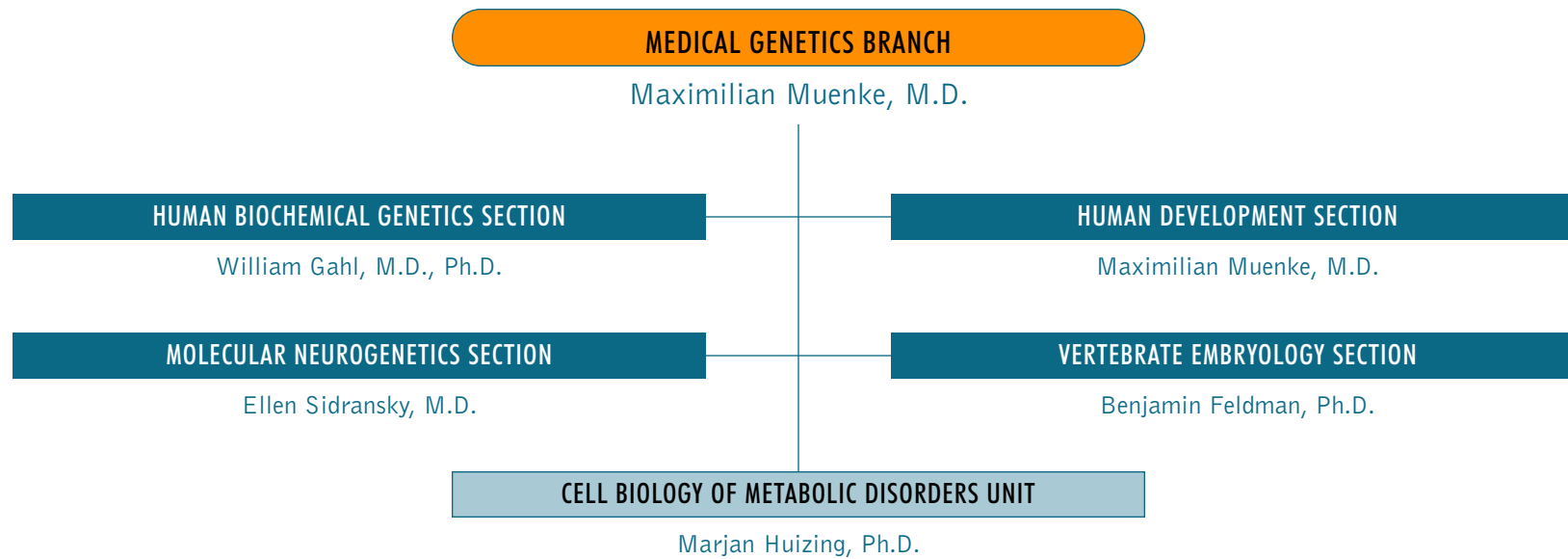
Maximilian Muenke, M.D.  
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The Medical Genetics Branch (MGB) seeks to identify and understand inherited disorders of metabolism and of human development. MGB investigators focus on human genetics, vertebrate embryology, inborn errors of metabolism, 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.

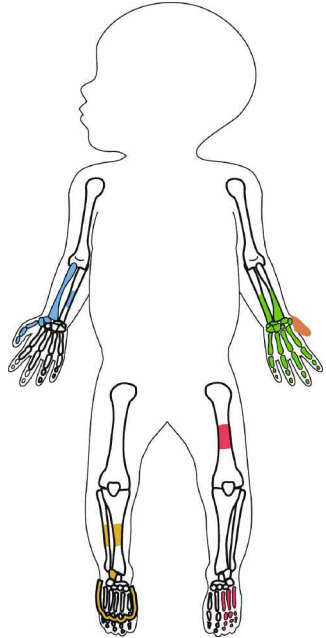


## MAXIMILIAN MUENKE, M.D.

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

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

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



Dr. Muenke's group is also studying environmental factors that may affect the development of HPE, particularly cholesterol. It is well-known that cholesterol is necessary for the activation of *SHH*, and, in animal models, researchers have found an association between low maternal cholesterol during pregnancy and birth defects in their offspring. There have been reports of babies with various birth defects, including HPE, being born to women who took cholesterol-lowering statin drugs during pregnancy. One of Dr. Muenke's goals is to conduct a larger study to determine



whether low maternal cholesterol can indeed adversely affect embryonic development. In related research, Dr. Muenke is studying laterality defects, or abnormal left-right positioning of body organs. In vertebrates, laterality defects occur very early in developmental processes, allowing some organs to end up on the wrong side of the body. Many people are unaware that they are affected by these disorders, but severe symptoms can (and often do) arise in their children.

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

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

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

## SELECTED PUBLICATIONS

Gripp KW, Wotton D, Edwards MC, Roessler E, Ades L, Meinecke P, Richieri-Costa A, Zackai EH, Massagué J, Muenke M, Elledge S J. Mutations in *TGIF* cause holoprosencephaly and link Nodal signaling to human neural axis determination. *Nat Genet* 25:205–208, 2000.

Bamford R, Roessler E, Burdine RD, Saplakoglu U, dela Cruz J, Splitt M, Goodship JA, Towbin J, Bowers P, Ferrero GB, Marino B, Schier AF, Shen MM, Muenke M, Casey, BM. Loss-of-function mutations in the EGF-CFC gene *CFC1* are associated with human left-right laterality defects. *Nat Genet* 26:365–369, 501, 2000.

Arcos-Burgos M, Castellanos FX, Konecki D, Lopera F, Pineda D, Palacio JD, Rapoport JL, Berg K, Bailey-Wilson J, Muenke M. Pedigree disequilibrium test (PDT) replicates association and linkage between *DRD4* and ADHD in multigenerational and extended pedigrees from a genetic isolate. *Mol Psych* 9:252–259, 2004.

Arcos-Burgos M, Castellanos FX, Lopera F, Pineda D, Palacio JD, Palacio LG, Rapoport JL, Berg K, Bailey-Wilson J, Muenke M. ADHD in a population isolate: linkage to loci at 4q13.2, 5q33.3, 11q22, and 17p11. *Am J Hum Genet* 75:998–1014, 2004.

Edison RJ, Muenke M. Central nervous system and limb anomalies in case reports of first trimester statin exposures. *New Engl J Med* 350:1579–1582, 2004.

Edison RJ, Muenke M. Mechanistic and epidemiologic considerations in the evaluation of adverse birth outcomes following gestational exposure to statins. *Am J Med Genet* 131A:287–298, 2004.

Palacio JD, Castellanos FX, Pineda DA, Lopera F, Arcos-Burgos M, Quiroz YT, Henao GC, Puerta YC, Ramirez DL, Rapoport JL, Bailey-Wilson J, Berg K, Muenke, M. Attention-deficit/hyperactivity disorder and comorbidities in 18 Paisa Colombian multigenerational families. *J Am Acad Child Adolesc Psych* 43:1506–1515, 2004.

Roessler E, Ermilov AN, Grange DK, Wang A, Grachtchouk M, Dlugosz AA, Muenke M. A previously unidentified amino terminal domain regulates transcriptional activity of wild-type and disease-associated human *GLI2*. *Hum Mol Genet* 14:2181–2188, 2005.

Bendavid C, Haddad BR, Griffin A, Huizing M, Gicquel I, Dubourg C, Cavalli CR, Long R, Ouspenskaia M, Odent S, Lacbawan F, David V, Muenke M. Multicolor FISH and quantitative PCR can detect submicroscopic deletions in holoprosencephaly patients with normal karyotype. *J Med Genet* 43:496–500, 2005.

Jeong Y, El-Jaick K, Roessler E, Muenke M, Epstein DJ. A functional screen for Sonic hedgehog regulatory elements across a 1 MB interval identifies long-range ventral forebrain enhancers. *Development* 133:761–772, 2006.

Russell HF, Wallis D, Mazzocco MM, Moshang T, Zackai E, Zinn AR, Ross JL, Muenke M. Increased prevalence of ADHD in Turner syndrome with no evidence of imprinting effects. *J Pediatr Psych* 31:945–955, 2006.

Jain M, Palacio LG, Castellanos FX, Palacio JD, Pineda D, Restrepo MI, Muñoz JF, Lopera F, Wallis D, Berg K, Bailey-Wilson JE, Arcos-Burgos M, Muenke, M. Attention-deficit/hyperactivity disorder and comorbid disruptive behavior disorders: evidence of pleiotropy and new susceptibility loci. *Biol Psychiatry*, in press.

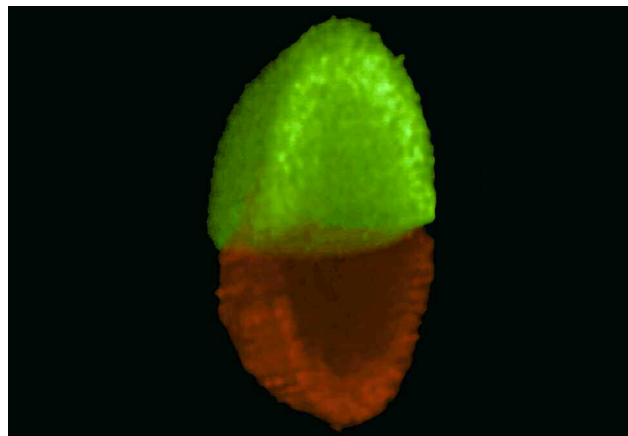


## BENJAMIN FELDMAN, Ph.D.

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

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

Studies have shown that several signaling pathways act in concert during gastrulation, an important example of which is the Nodal signaling pathway. Dr. Feldman's group is using various approaches to illuminate this pathway's role. They are currently focusing on a transcription



factor named FoxH1, which is known to mediate Nodal signaling. Another group of molecules the Feldman laboratory is studying is the RhoGEFs (Rho guanine nucleotide exchange factors). RhoGEFs are important for regulating cell movement. Dr. Feldman's laboratory is trying to determine whether these molecules have a role in gastrulation. They have identified a number of RhoGEF genes that are upregulated in gastrulation.



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

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

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

## SELECTED PUBLICATIONS

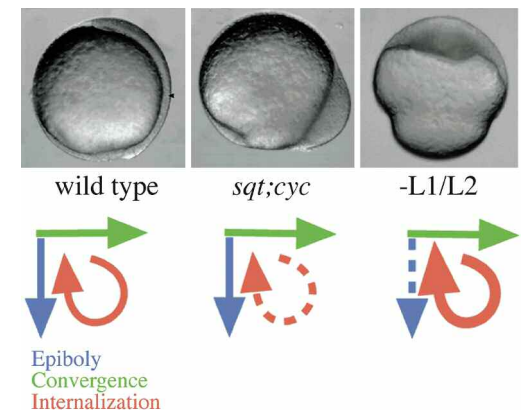
Feldman B, Gates MA, Egan E, Dougan ST, Rennebeck G, Sirotkin HI, Schier AF, Talbot WS. Zebrafish organizer development and germ-layer formation require nodal-related signals. *Nature* 395:181-185, 1998.

Feldman B, Dougan ST, Schier AF, Talbot WS. Nodal-related signals establish mesendodermal fate and trunk neural identity in zebrafish. *Curr Biol* 10:531-534, 2000.

Feldman B, Concha M, Saude L, Parsons MJ, Adams R, Wilson S, Stemple DL. Lefty antagonism of squint is essential for normal gastrulation. *Curr Biol* 12:129-135, 2002.

Pei W, Williams PH, Clark MD, Stemple DL, Feldman B. Environmental and genetic modifiers of squint penetrance during zebrafish embryogenesis. *Dev Biol* 308:368-378, 2007.

Pei W, Noushmehr H, Costa J, Ouspenskaia MV, Elkahlon AG, Feldman B. An early requirement for maternal FoxH1 during zebrafish gastrulation. *Dev Biol* 310:10-22, 2007.

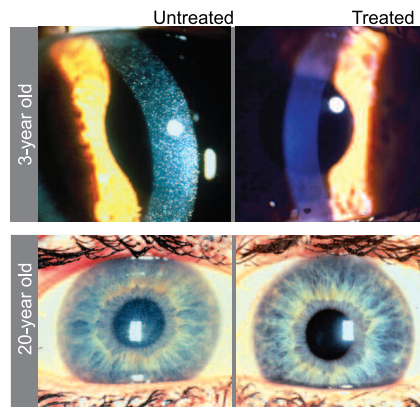


## WILLIAM A. GAHL, M.D., Ph.D.

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

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

Cysteamine eyedrops



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



disorder, but Dr. Gahl's group has had success in slowing the development of some HPS symptoms in a small group of patients.

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

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

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

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

## SELECTED PUBLICATIONS

Gahl WA, Thoene JG, Schneider JA. Cystinosis. *N Engl J Med* 347:111–121, 2002.

Phornphutkul C, Introne WJ, Perry MB, Bernardini I, Murphey MD, Fitzpatrick DL, Anderson PD, Huizing M, Anikster Y, Gerber LH, Gahl WA. Natural history of alkaptonuria. *N Engl J Med* 347:2111–2121, 2002.

Kleta R, Romeo E, Ristic Z, Ohura T, Stuart C, Arcos-Burgos M, Dave MH, Wagner CA, Camargo SRM, Inoue S, Matsuura N, Helip-Wooley A, Bockenauer D, Warth R, Bernardini I, Visser G, Eggermann T, Lee P, Chairoungdua A, Jutabha P, Babu E, Nilwarangkoon S, Anzai N, Kanai Y, Verrey F, Gahl WA, Koizumi A. Mutations in SLC6A19, encoding B0AT1, cause Hartnup disorder. *Nat Genet* 36:999–1002, 2004.

Kleta R, Bernardini I, Ueda M, Varade WS, Phornphutkul C, Krasnewich D, Gahl WA. Long-term follow-up of well-treated nephropathic cystinosis patients. *J Pediatr* 145:555–560, 2004.

Sonies BC, Almajid P, Kleta R, Bernardini I, Gahl WA. Swallowing dysfunction in 101 patients with nephropathic cystinosis: benefit of long-term cysteamine therapy. *Medicine* 84:137–146, 2005.

Suwannarat P, O'Brien K, Perry MB, Sebring N, Bernardini I, Kaiser-Kupfer MI, Rubin BI, Tsilou E, Gerber LH, Gahl WA. Use of nitisinone in patients with alkaptonuria. *Metabolism* 54:719–728, 2005.

Helip-Wooley A, Westbroek W, Dorward H, Mommaas M, Boissy R, Gahl WA, Huizing M. Hermansky-Pudlak syndrome type-3 protein interacts with clathrin. *BMC Cell Biol* 6:33, 2005.

Sparks SE, Ciccone C, Lalor M, Orvisky E, Klootwijk R, Savelkoul PJ, Dalakas MC, Krasnewich DM, Gahl WA, Huizing M. Use of a cell-free system to determine UDP-N-acetylglucosamine 2-epimerase and N-acetylmannosamine kinase activities in human hereditary inclusion body myopathy. *Glycobiology* 15:1102–1110, 2005.

Ueda M, O'Brien K, Rosing DR, Ling A, Kleta R, MacAreavey D, Bernardini I, Gahl WA. Coronary artery and other vascular calcifications in cystinosis patients after kidney transplantation. *Clin J Am Soc Nephrol* 1:555–562, 2006.

O'Brien K, Hussain N, Warady B, Kleiner DE, Kleta R, Bernardini I, Heller T, Gahl WA. Nodular regenerative hyperplasia and severe portal hypertension in cystinosis. *Clin Gastroenterol & Hepatol* 4:387–394, 2006.

Sparks S, Rakocevic G, Joe G, Manoli I, Shrader J, Harris-Love MH, Sonies B, Ciccone C, Dorward H, Krasnewich D, Huizing M, Dalakas MC, Gahl WA. Intravenous immune globulin in hereditary inclusion body myopathy: a pilot study. *BMC Neurol* 7:3, 2007.

Helip-Wooley A, Boissy RE, Westbroek W, Dorward H, Koshoffer A, Huizing M, Gahl WA. Improper trafficking of melanocyte-specific proteins in Hermansky-Pudlak syndrome type-5. *J Invest Dermatol* 127:1471–1478, 2007.

Galeano B, Klootwijk R, Manoli I, Sun M, Ciccone C, Darvish D, Starost MF, Zervas PM, Hoffmann VJ, Hoogstraten-Miller S, Krasnewich DM, Gahl WA, Huizing M. Mutation in the key enzyme of sialic acid biosynthesis causes severe glomerular proteinuria and is rescued by N-acetylmannosamine. *J Clin Invest* 117:1585–1594, 2007.

Gahl WA, Balog JZ, Kleta R. Nephropathic cystinosis in adults: natural history and effects of oral cysteamine therapy. *Annals Intern Med* 147:242–250, 2007.



## 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 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 known gene mutation involved in hereditary gingival fibromatosis (HGF), a rare form of gum overgrowth. The gene, *SOS1*, 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.

Dr. Hart also investigates the molecular causes of disorders that affect the enamel or the 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 since teeth are mineralized structures, making the isolation of RNA needed to study gene expression 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



Hart's group since 1991 forms the foundation for this research; these samples are routinely re-examined as new genomic technologies are developed that enable the identification of additional genes involved in the development of tooth defects.

Dr. Hart collaborated with the research group that identified the gene (*CTCS*) shown to be mutated in Papillon-Lefevre syndrome. This inherited 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, with exfoliation and loss of the teeth by age 20.

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Another area of Dr. Hart's research is related to medullary cystic kidney disease, a hereditary endoplasmic reticulum storage disorder caused by mutations in the *UMOD* gene. People with this rare dominant condition have a 50% risk of passing the disorder to their children. Currently, this project involves mapping the gene for the type 1 form of the disease, in which patients have normal kidney function through childhood but develop renal failure and ultimately require a kidney transplant. Her group is achieving promising results correcting protein defects in cell culture — progress that could lead to new therapeutic approaches.

## SELECTED PUBLICATIONS

Hart TC, Zhang Y, Gorry MC, Hart PS, Cooper M, Marazita ML, Marks JM, Cortelli JR, Pallos D. A mutation in the *SOS1* gene causes hereditary gingival fibromatosis. *Am J Hum Genet* 70:943–954, 2002.

Hart TC, Gorry MC, Hart PS, Woodard AS, Shihabi Z, Sandhu J, Shirts B, Xu L, Zhu H, Barmada MM, Bleyer AJ. Mutations of the *UMOD* gene are responsible for medullary cystic kidney disease 2 and familial juvenile hyperuricaemic nephropathy. *J Med Genet* 39:882–892, 2002.

Hart PS, Michalec MD, Seow WK, Hart TC, Wright JT. Identification of the enamelin (g.8344delG) mutation in a new kindred and presentation of a standardized ENAM nomenclature. *Arch Oral Biol* 48:589–596, 2003.

Hart TC, Hart PS, Gorry MC, Michalec MD, Ryu OH, Uygur C, Ozdemir D, Firatli S, Aren G, Firatli E. Novel ENAM mutation responsible for autosomal recessive amelogenesis imperfecta and localised enamel defects. *J Med Genet* 40:900–906, 2003.

Hart PS, Hart TC, Michalec MD, Ryu OH, Simmons D, Hong S, Wright JT. Mutation in kallikrein 4 causes autosomal recessive hypomaturation amelogenesis imperfecta. *J Med Genet* 41:545–549, 2004.

Kim JW, Simmer JP, Hart TC, Hart PS, Ramaswami MD, Bartlett JD, Hu JCC. MMP-20 mutation in autosomal recessive pigmented hypomaturation amelogenesis imperfecta. *J Med Genet* 42:366–370, 2005.

Hart PS, Hart TC. Disorders of human dentin. *Cells Tissues Organs* 186:70–77, 2007.

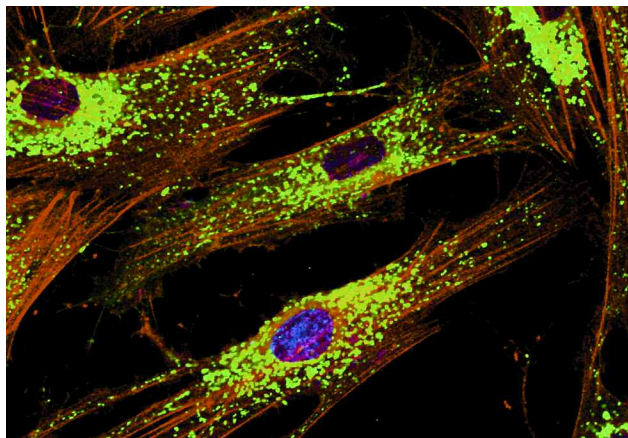
Jang SI, Lee EJ, Hart PS, Ramaswami M, Pallos D, Hart TC. Germ line gain of function with *SOS1* mutation in hereditary gingival fibromatosis. *J Biol Chem* 282:20245–20255, 2007.

## MARJAN HUIZING, Ph.D.

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

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

Sialic acid is a negatively charged sugar localized at the end of glycoconjugate chains on glycoproteins and glycolipids. These chains are expressed at the cell surface and are crucial for many biological processes, including cell adhesion and signal transduction. Research has shown that dystroglycan, an integral component of the muscle transmembrane dystrophin-glycoprotein complex, is involved in the pathogenesis of many forms of myopathy, including muscular dystrophy. Dr. Huizing's group demonstrated that muscle  $\alpha$ -dystroglycan in patients with HIBM is low in sialic acid. They are now investigating the use of *N*-acetyl-D-mannosamine (ManNAc), a neutral sugar and specific substrate for sialic acid synthesis, as



a therapy for HIBM; they also are developing a mouse model for testing such a therapy. Another treatment involves infusing mice with immunoglobulin, which is high in sialic acid content.

Dr. Huizing also studies other sialic acid-related diseases, including sialuria, a progressive disease in which patients produce too much sialic acid. Symptoms may include developmental delay, coarse features,



and enlargement of the liver. Sialuria appears to be caused by a single mutation that causes a change in the three-dimensional structure of the active site of the enzyme UDP-GlcNAc 2-epimerase/ManNAc kinase. A third sialic acid-related disease, infantile free sialic acid storage disease, involves a transport malfunction that causes sialic acid to accumulate in lysosomes.

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

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

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

## SELECTED PUBLICATIONS

Huizing M, Anikster Y, Fitzpatrick DL, Jeong AB, D'Souza M, Rausche M, Toro JR, Kaiser-Kupfer MI, White JG, Gahl WA. Hermansky-Pudlak syndrome type 3 in Ashkenazi Jews and other non-Puerto Rican patients with hypopigmentation and platelet storage pool deficiency. *Am J Hum Genet* 69:1022–1032, 2001.

Huizing M, Gahl WA. Disorders of vesicles of lysosomal lineage: the Hermansky-Pudlak syndromes. *Curr Mol Med* 2:451–467, 2002.

Huizing M, Scher CD, Strovel E, Fitzpatrick DL, Hartnell LM, Anikster Y, Gahl WA. Nonsense mutations in ADB3A cause complete deficiency of the B3A subunit of adaptor complex-3 and severe Hermansky-Pudlak syndrome type 2. *Pediatr Res* 51:150–158, 2002.

Huizing M, Rakocevic G, Sparks SE, Mamali I, Shatunov A, Goldfarb L, Krasnewich D, Gahl WA, Dalakas MC. Hypoglycosylation of  $\alpha$ -dystroglycan in patients with hereditary IBM due to GNE mutations. *Mol Genet Metab* 81:196–202, 2004.

Huizing M, Hess R, Dorward H, Claassen DA, Helip-Wooley A, Kleta R, Kaiser-Kupfer MI, White JG, Gahl WA. Cellular, molecular and clinical characterization of patients with Hermansky-Pudlak syndrome type 5. *Traffic* 5:711–722, 2004.

Helip-Wooley A, Westbroek W, Dorward H, Mommaas M, Boissy R, Gahl WA, Huizing M. Hermansky-Pudlak syndrome type-3 protein interacts with clathrin traffics lysosome-related organelles. *BMC Cell Biol* 6:33, 2005.

Sparks SE, Ciccone C, Lalor M, Orvisky E, Klootwijk R, Savelkoul PJ, Dalakas MC, Krasnewich DM, Gahl WA, Huizing M. Use of a cell-free system to determine UDP-N-acetylglucosamine 2-epimerase and N-acetylmannosamine kinase activities in human hereditary inclusion body myopathy. *Glycobiology* 15:1102–1110, 2005.

Huizing M. Disease mechanisms associated to mutations of the GNE gene. *Drug Discov Today* 2:519–527, 2005.

Huizing M, Brooks BP, Anikster Y. Optic neuropathies in inherited metabolic disorders. *Pediatr Endocrinol Rev* 3:97–103, 2005.

Savelkoul PJM, Manoli I, Sparks S, Ciccone C, Gahl WA, Krasnewich DM, Huizing M. Normal sialylation of N-linked and O-GalNAc-linked glycans in hereditary inclusion-body myopathy. *Mol Genet Metab* 88:389–390, 2006.

Huizing M, Parkes JM, Helip-Wooley A, White JG, Gahl WA. Platelet alpha granules in BLOC-2 and BLOC-3 subtypes of Hermansky-Pudlak syndrome. *Platelets* 18:150–157, 2007.

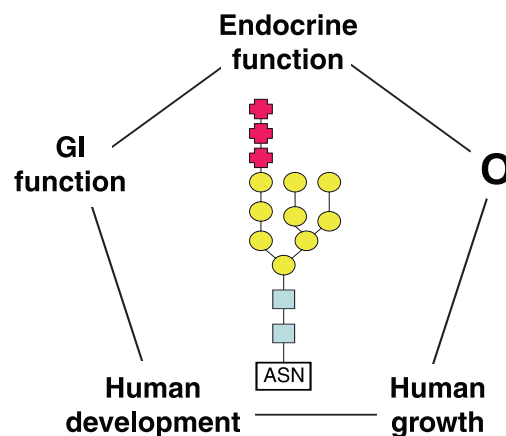
Galeano B, Klootwijk R, Manoli I, Sun M, Ciccone C, Darvish D, Starost MF, Zervas PM, Hoffmann VJ, Hoogstraten-Miller S, Krasnewich DM, Gahl WA, Huizing M. Mutation in the key enzyme of sialic acid biosynthesis causes severe glomerular proteinuria and is rescued by N-acetylmannosamine. *J Clin Invest* 117:1585–1594, 2007.



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

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

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



The most common form of the 21 CDG types identified so far, CDG type Ia, results from a deficiency in the enzyme phosphomannomutase. Less-common forms result from defective enzyme activities at other steps in the N-linked oligosaccharide synthetic pathway. CDG type Ib is the only treatable form of the disorder, but Dr. Krasnewich hopes research will lead to treatment strategies for other forms of CDG as well.



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

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

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

**SELECTED PUBLICATIONS**

Krasnewich DM, Holt GD, Brantly M, Skovby F, Redwine J, Gahl WA. Abnormal synthesis of dolichol linked oligosaccharides in carbohydrate-deficient glycoprotein syndrome. *Glycobiology* 5:503–510, 1995.

Krasnewich DM, Gahl WA. Carbohydrate-deficient glycoprotein syndrome. *Adv Pediatr* 44:109–140, 1997.

Krasnewich DM, Dietrich K, Bauer L, Ginns EI, Sidransky E, Hill S. Splenectomy in Gaucher disease: new management dilemmas. *Blood* 91:3085–3087, 1998.

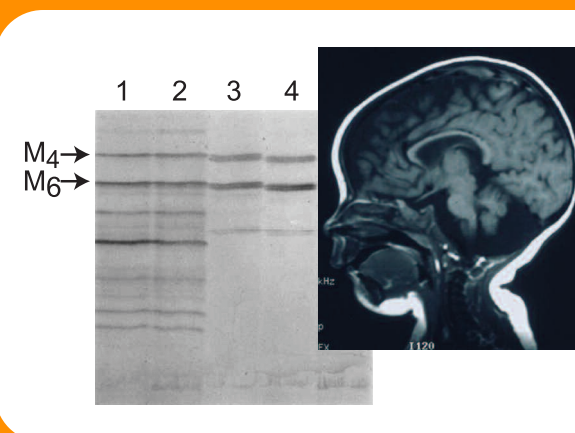
Pearl PL, Krasnewich D. Neurologic course of congenital disorders of glycosylation. *J Child Neurol* 16:409–413, 2001.

Orvisky E, Stubblefield B, Long RT, Martin B, Sidransky E, Krasnewich D. Phosphomannomutase activity in congenital disorders of glycosylation type 1a determined by direct analysis of the interconversion of mannose-1-phosphate to mannose-6-phosphate by high-pH-anion-exchange chromatography with pulsed amperometric detection. *Anal Biochem* 317:12–18, 2003.

Huizing M, Rakocevic G, Sparks S, Mamali I, Shatunov A, Goldfarb L, Krasnewich D, Gahl WA, Dalakas MC. Hypoglycosylation of  $\alpha$ -dystroglycan in patients with hereditary IBM due to *BNE* mutations. *Mol Genet Metab* 81:196–202, 2004.

Kleta R, Morse RP, Orvisky E, Krasnewich D, Alroy J, Ucci AA, Bernardini I, Wenger DA, Gahl WA. Clinical, biochemical, and molecular diagnosis of a free sialic acid storage disease patient of moderate severity. *Mol Genet Metab* 82:137–143, 2004.

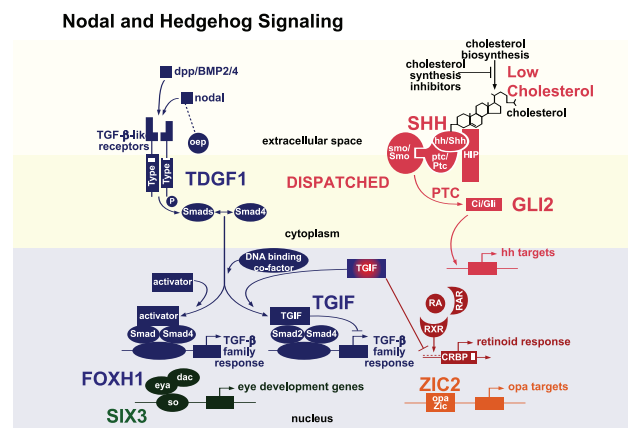
Sparks SE, Krasnewich DM. Congenital disorder of glycosylation type 1a. In: GeneReviews at GeneTests. University of Washington, Seattle: Medical Genetics Information Resource, 2005. [Available at [www.genetests.org](http://www.genetests.org)]



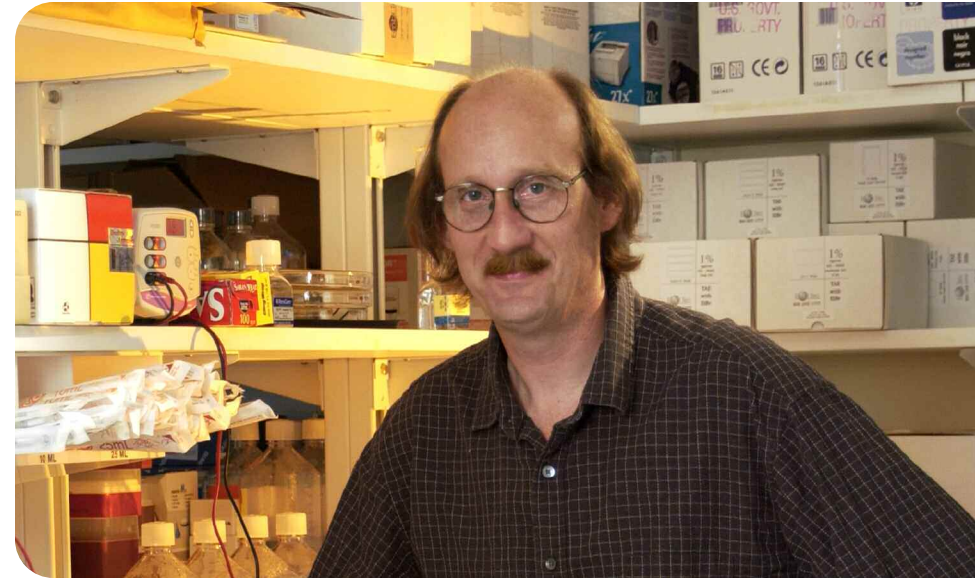
## ERICH ROESSLER, M.D., Ph.D.

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

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



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



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

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

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

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

## SELECTED PUBLICATIONS

Roessler E, Belloni E, Gaudenz K, Jay P, Berta P, Scherer SW, Tsui LC, Muenke M. Mutations in the human *Sonic Hedgehog* gene cause holoprosencephaly. *Nat Genet* 14:357–360, 1996.

Roessler E, Belloni E, Gaudenz K, Vargas F, Scherer SW, Tsui LC, Muenke M. Mutations in the C-terminal domain of Sonic Hedgehog cause holoprosencephaly. *Hum Mol Genet* 6:1847–1853, 1997.

Roessler E, Ward DE, Gaudenz K, Belloni E, Scherer SW, Donnai D, Siegel-Bartelt J, Tsui LC, Muenke M. Cytogenetic rearrangements involving the loss of the *Sonic Hedgehog* gene at 7q36 cause holoprosencephaly. *Hum Genet* 100:172–181, 1997.

Roessler E, Mittaz L, Du Y, Scott HS, Chang J, Rossier C, Guipponi M, Matsuda SP, Muenke M, Antonarakis SE. Structure of the human *lanosterol synthase* gene and its analysis as a candidate for holoprosencephaly (HPE1). *Hum Genet* 105:489–495, 1999.

Wallis DE, Roessler E, Hehr U, Nanni L, Wiltshire T, Richieri-Costa A, Gillessen-Kaesbach G, Zackai EH, Rommens J, Muenke M. Mutations in the homeodomain of the human *SIX3* gene cause holoprosencephaly. *Nat Genet* 22:196–198, 1999.

Bamford RN, Roessler E, Burdine RD, Saplakoglu U, dela Cruz J, Splitt M, Goodship JA, Towbin J, Bowers P, Ferrero GB, Marino B, Schier AF, Shen MM, Muenke M, Casey B. Loss-of-function mutations in the EGF-CFC gene *CFC1* are associated with human left-right laterality defects. *Nat Genet* 26:365–369, 2000.

Gripp KW, Wotton D, Edwards MC, Roessler E, Ades L, Meinecke P, Richieri-Costa A, Zackai EH, Massague J, Muenke M, Elledge SJ. Mutations in *TGIF* cause holoprosencephaly and link NODAL signaling to human neural axis determination. *Nat Genet* 25:205–208, 2000.

Roessler E, Du Y, Dutra A, Niehrs C, Muenke M. The genomic structure, chromosomal location, and analysis of the human DKK-1 head inducer gene as a candidate for holoprosencephaly. *Cytogenet Cell Genet* 89:220–224, 2000.

Goldmuntz E, Bamford R, Karkera JD, dela Cruz J, Roessler E, Muenke M. *CFC1* mutations in patients with transposition of the great arteries and double-outlet right ventricle. *Am J Hum Genet* 70:776–780, 2002.

Roessler E, Du YZ, Mullor JL, Casas E, Allen WP, Gillessen-Kaesbach G, Roeder ER, Ming JE, Altaba AR, Muenke M. Loss-of-function mutations in the human *GLI2* gene are associated with pituitary anomalies and holoprosencephaly-like features. *Proc Natl Acad Sci USA* 100:13424–13429, 2003.

Roessler E, Ermilov AN, Grange DK, Wang A, Grachtchouk M, Dlugosz AA, Muenke M. A previously unidentified amino terminal domain regulates transcriptional activity of wild-type and disease-associated human *GLI2*. *Hum Mol Genet* 14:2181–2188, 2005.

El-Jaick KB, Powers SE, Bartholin L, Myers KR, Hahn J, Orioli IM, Ouspenskaia M, Lachawan F, Roessler E, Wotton D, Muenke M. Functional analysis of mutations in *TGIF* associated with holoprosencephaly. *Mol Genet Metab* 90:97–111, 2007.



## ELLEN SIDRANSKY, M.D.

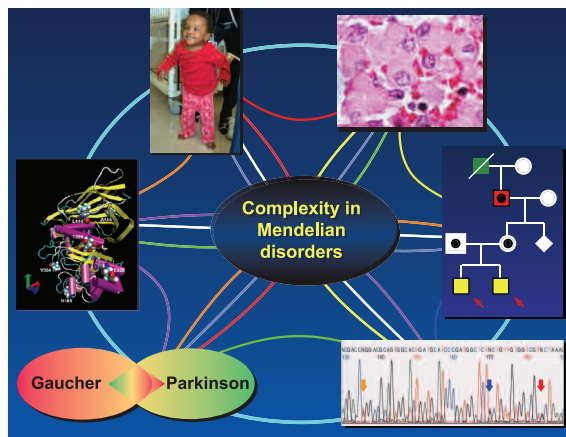
Dr. Sidransky's research focuses on the genetics of Gaucher disease, a rare, recessively inherited disorder with highly variable symptoms. Her work has been instrumental in uncovering the spectrum of symptoms and some of the mechanisms underlying the pathology of this disorder. Ultimately, her research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

Gaucher disease results from mutations in the *GBA* gene, which codes for the enzyme glucocerebrosidase. This lysosomal enzyme is responsible for breaking down a specific kind of fat called glucocerebroside. People with Gaucher disease cannot properly produce this enzyme, so the glucocerebroside in their cells is not broken down and accumulates—mostly in the liver, spleen, and bone marrow cells. This accumulation can result in pain, fatigue, jaundice, bone damage, anemia, and even death. Gaucher disease is the most common lysosomal storage disorder. It is the most prevalent hereditary disorder among Ashkenazi Jews, of whom about 1 in 15 are carriers, compared with ~1 in 100 in the general population. Currently, the primary treatment for Gaucher disease is enzyme replacement therapy, which requires life-long intravenous infusions every two weeks. It 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 quite different clinical manifestations (or phenotypes). Thus, patient genotyping is not 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 in Gaucher disease by sequencing and comparing the *GBA* gene and nearby genomic regions in patients who share atypical phenotypes. 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. Dr. Sidransky believes that analyses of both the differences and similarities in the *GBA* sequences in different patient groups and different organisms may improve our understanding of how genotype influences phenotype in patients with Gaucher disease.

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

Lastly, Dr. Sidransky's laboratory is working to develop better therapy for patients with Gaucher disease. In collaboration with the NIH Chemical Genomics Center, they used high-throughput screening of libraries containing tens of thousands of compounds to identify promising chemicals that interact with glucocerebrosidase and may have therapeutic potential. These small molecules may act as chemical chaperones to enable the mutant enzyme to reach its target.

## SELECTED PUBLICATIONS

Sidransky E, Sherer DM, Ginns EI. Gaucher disease in the neonate: a distinct Gaucher phenotype is analogous to a mouse model created by targeted disruption of the glucocerebrosidase gene. *Pediatr Res* 32:494–498, 1992.

Holleran WM, Ginns EI, Menon GK, Grundmann JU, Fartasch M, McKinney C, Elias PM, Sidransky E. Consequences of beta-glucocerebrosidase deficiency in epidermis: ultrastructure and permeability barrier alterations in Gaucher disease. *J Clin Invest* 93:1756–1764, 1994.

Koprivica V, Stone DL, Park JK, Frish A, Cohen I, Tayebi N, Sidransky E. An analysis and classification of 304 mutant alleles in patients with Type 1 and Type 3 Gaucher disease. *Am J Hum Genet* 66:1777–1786, 2000.

Orvisky E, Sidransky E, McKinney CE, LaMarca ME, Samimi R, Krasnewich D, Martin BM, Ginns EI. Glucosylsphingosine accumulation in mice and patients with type 2 Gaucher disease begins early in gestation. *Pediatr Res* 48:1–5, 2000.

Park JK, Orvisky E, Tayebi N, Kaneski C, LaMarca ME, Stubblefield BK, Martin BM, Schiffmann R, Sidransky E. Myoclonic epilepsy in Gaucher disease: genotype-phenotype insights from a rare patient subgroup. *Pediatr Res* 53:387–395, 2003.

Tayebi N, Stubblefield BK, Park JK, Orvisky E, Walker JM, LaMarca ME, Sidransky E. Reciprocal and nonreciprocal recombination at the glucocerebrosidase gene region: implications for complexity in Gaucher disease. *Am J Hum Genet* 72:519–534, 2003.

Tayebi N, Walker JM, Stubblefield BK, Orvisky E, LaMarca ME, Wong K, Rosenbaum H, Schiffmann R, Bembi B, Sidransky E. Gaucher disease with Parkinsonian manifestations: does glucocerebrosidase deficiency contribute to a vulnerability to Parkinsonism? *Mol Genet Metab* 79:104–109, 2003.

Goker-Alpan O, Schiffmann R, LaMarca ME, Nussbaum RL, McInerney-Leo A, Sidransky E. Parkinsonism among Gaucher disease carriers. *J Med Genet* 41:937–940, 2004.

Lwin A, Orvisky E, Goker-Alpan O, LaMarca ME, Sidransky E. Glucocerebrosidase mutations in subjects with parkinsonism. *Mol Genet Metab* 81:70–73, 2004.

Sidransky E. Gaucher disease: complexity in a "simple" disorder. *Mol Genet Metab* 83:6–15, 2004.

Sidransky E. Gaucher disease and Parkinsonism. *Mol Genet Metab* 84:302–304, 2005.

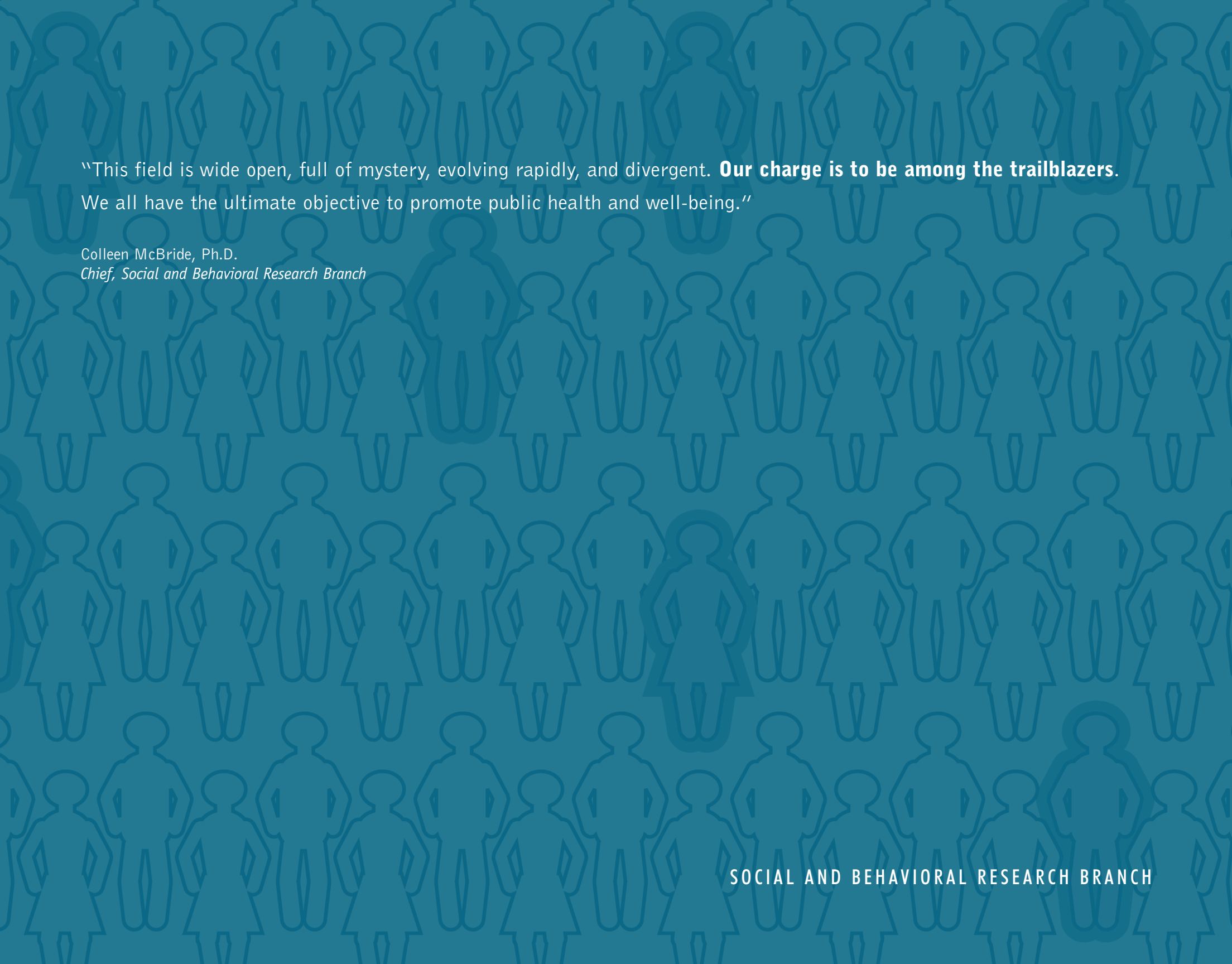
Goker-Alpan O, Hruska KS, Orvisky E, Kishnani PS, Stubblefield BK, Schiffmann R, Sidransky E. Divergent phenotypes in Gaucher disease implicate the role of modifiers. *J Med Genet* 42:e37, 2005.

Goker-Alpan O, Sidransky E. Risky business: Gaucher disease and multiple myeloma. *Blood* 105:4546–4547, 2005.

Sidransky E. Heterozygosity for a Mendelian disorder as a risk factor for complex disease. *Clin Genet* 70:275–282, 2006.

Goker-Alpan O, Giasson BI, Eblan MJ, Nyugen J, Hurtig HI, Lee VM-Y, Trojanowski JQ, Sidransky E. Glucocerebrosidase mutations are an important risk factor for Lewy body disorders. *Neuro* 67:908–910, 2006.

Zheng W, Padia J, Urban DJ, Jadhav A, Goker-Alpan O, Simeonov A, Goldin E, Auld D, LaMarca ME, Ingles J, Austin CP, Sidransky E. Three classes of glucocerebrosidase inhibitors identified by quantitative high-throughput screening are chaperone leads for Gaucher disease. *PNAS* 104:13192–13197, 2007.



“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

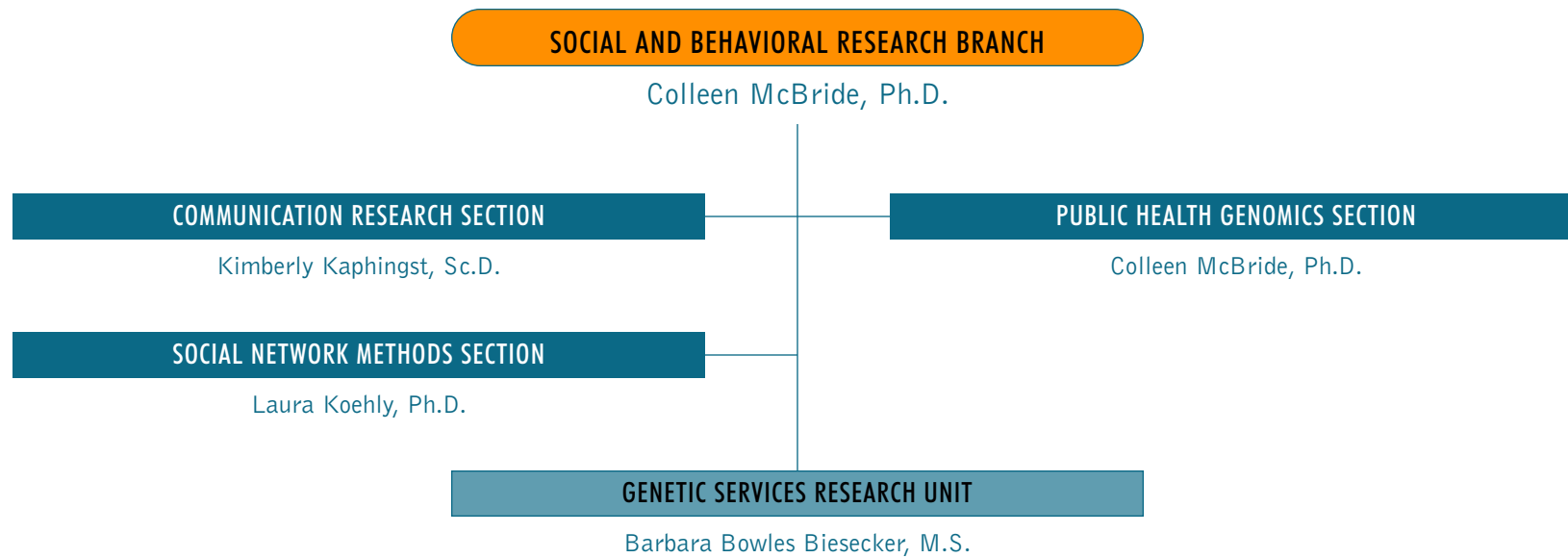




The Social and Behavioral Research Branch (SBRB) has the overarching and broad objective of investigating social and behavioral factors that facilitate the translation of genomic discoveries for health promotion, disease prevention, and improvements in health care. The newest Branch in the NHGRI Intramural 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.



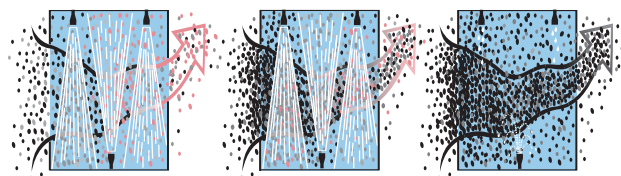


## COLLEEN M. McBRIDE, Ph.D.

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. Genetic testing is likely to become a leading medical tool for educating patients about their health risks and inspiring them to take preventive steps, although there are many obstacles to overcome before that can occur. Having the testing technology does not necessarily translate into better health behaviors.

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

### How chemicals are "cleaned up" by GSTM1



Your body works like a chemical wash - each cell uses enzymes like strong detergents to clean up most chemicals.

Your result shows that you have the enzyme to help you clean up some of the chemicals in cigarette smoke.

Your result shows that you do not have the enzyme. The harmful chemicals coming into your body may not be getting cleaned up very well.

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



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

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

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

## SELECTED PUBLICATIONS

McBride CM, Scholes D, Grothaus L, Curry SJ, Albright J. Promoting smoking cessation among women who seek cervical cancer screening. *Obstet Gynecol* 91:719-724, 1998.

McBride CM, Scholes D, Grothaus LC, Curry SJ, Ludman E, Albright J. Evaluation of a minimal self-help smoking cessation intervention following cervical cancer screening. *Prev Med* 29:133-138, 1999.

McBride CM, Halabi S, Bepler G, McIntyre L, Lipkus I, Albright J, O'Briant K. Maximizing the motivational impact of feedback of lung cancer susceptibility on smokers' desire to quit. *J Health Commun* 5:229-241, 2000.

McBride CM, Bastian LA, Halabi S, Fish L, Lipkus IM, Bosworth HB, Rimer BK, Siegler IC. Efficacy of a tailored intervention to aid decision-making about hormone replacement therapy. *Am J Public Health* 92:1112-1114, 2002.

McBride CM, Bepler G, Lipkus IM, Lyna P, Samsa G, Albright J, Datta S, Rimer BK. Incorporating feedback of genetic susceptibility into a smoking cessation intervention for African American smokers with low income. *Cancer Epidemiol Biomarkers Prev* 11:521-528, 2002.

McBride CM, Emmons KM, Lipkus IM. Understanding the potential of teachable moments for smoking cessation. *Health Educ Res* 18:156-170, 2003.

Lipkus IM, McBride CM, Lyna P, Pollak KI. Interpretation of genetic risk feedback among African-American smokers with low socioeconomic status. *Health Psychol* 23:178-188, 2004.

Bepler G, Zheng Z, Guatam A, Sharma S, Cantor A, Sharma A, Cress WD, Kim YC, Rosell R, McBride C, Robinson L, Sommers E, Haura E. Ribonucleotide reductase M1 gene promoter activity, polymorphisms, population frequencies, and clinical relevance. *Lung Cancer* 47:183-192, 2005.

McBride CM. Trail-blazing a public health research agenda in genomics and chronic disease. *Prev Chronic Dis* 2:A04, 2005.

Cigarette smoke contains about 4,000 harmful chemicals.  
At least 50 are known to cause cancer.

Three important chemicals to know

- Benzo(a) pyrene  
A chemical that damages your genes so that your body can not stop the growth of tumors that can lead to lung and other cancers.
- Nicotine  
The chemical that causes addiction.
- Carbon monoxide  
A poisonous gas that makes it harder for the blood to carry oxygen to the body's organs.

Acetone

Hydrogen Cyanide

\*Naphthylamine

\*Toluidine

Ammonia

Methanol

Urethane

\*Pyrene

Toluene

Naphthalene

Arsenic

\*Cadmium

Phenol

Carbon Monoxide

Butane

\*Benzo(a) pyrene

\*Polonium-210

\*Vinyl Chloride

DDT

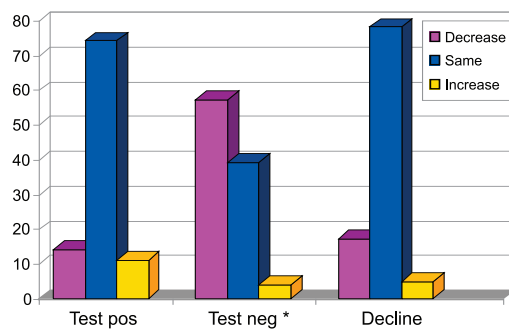
## BARBARA BOWLES BIESECKER, M.S.

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

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

Some of her past research has included studies of illness perception and of the quality of life of people who live with genetic conditions, such as achondroplasia and Marfan syndrome. She has also used qualitative methods to explore concerns and appraisals of girls and women with Turner syndrome — in which a female has only one X chromosome — and how they adapt to related social and medical problems. In one of her Turner syndrome studies, infertility was

the most prevalent "challenge" among the 97 girls, adolescents, and adult women affected by this condition. Furthermore, about a third of participants said their parents and physicians hid from them the fact that infertility is a component of Turner syndrome, thus diminishing their trust in their relatives and health care providers. This study recommended that family members and health care providers be



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 ( $p=0.001$ )



truthful and open with patients about the symptoms and consequences of Turner syndrome and to offer those affected by the condition social guidance and support to help them deal with these problems.

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

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



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Genetic Counseling Training Program

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

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

## SELECTED PUBLICATIONS

McInerney-Leo A, Biesecker BB, Hadley DW, Kase RG, Giambarrresi TR, Johnson E, Lerman C, Struewing JP. BRCA1/2 testing in hereditary breast and ovarian cancer families: effectiveness of problem-solving training as a counseling intervention. *Am J Med Genet* 130:221–227, 2004.

Gollust S, Apse K, Fuller B, Miller PS, Biesecker B. Community involvement in policy-making for genetic tests: assessing the interests and experiences of affected individuals. *Am J Public Health* 95:35–41, 2005.

Peters KF, Apse KA, Blackford A, McHugh B, Michalic D, Biesecker B. Living with marfan syndrome: coping with stigma. *Clin Genet* 68:6–14, 2005.

Sutton E, Young J, McInerney-Leo A, Bondy C, Gollust S, Biesecker B. Truth telling and Turner Syndrome: the impact of diagnostic disclosure. *J Peds* 148:102–107, 2006.

Gooding H, Organista K, Burack J, Biesecker B. Genetic susceptibility testing from a stress and coping perspective. *Soc Sci Med* 62:1880–1890, 2006.

Lipinski S, Lipinski M, Biesecker LG, Biesecker B. Uncertainty and perceived personal control among parents of children with rare chromosome conditions: the role of genetic counseling. *Am J Med Genet C Semin Med Genet* 142:232–240, 2006.

Gooding HC, Linnenbringer EL, Burack J, Roberts JS, Green RC, Biesecker BB. Genetic susceptibility testing for Alzheimer disease: motivation to obtain information and control as precursors to coping with increased risk. *Patient Educ Couns* 64:259–267, 2006.

McInerney-Leo A, Hadley D, Kase RG, Giambarrresi TR, Struewing JP, Biesecker BB. BRCA1/2 testing in hereditary breast and ovarian cancer families III: risk perception and screening. *Am J Med Genet A* 140:2198–2206, 2006.

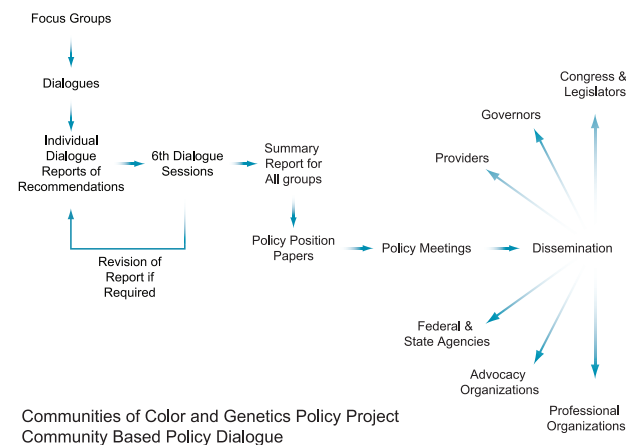
Turner J, Biesecker B, Leib J, Biesecker L, Peters KF. Parenting children with Proteus syndrome: experience with, and adaptation to, courtesy stigma. *Am J Med Genet A* 143:2089–2097, 2007.



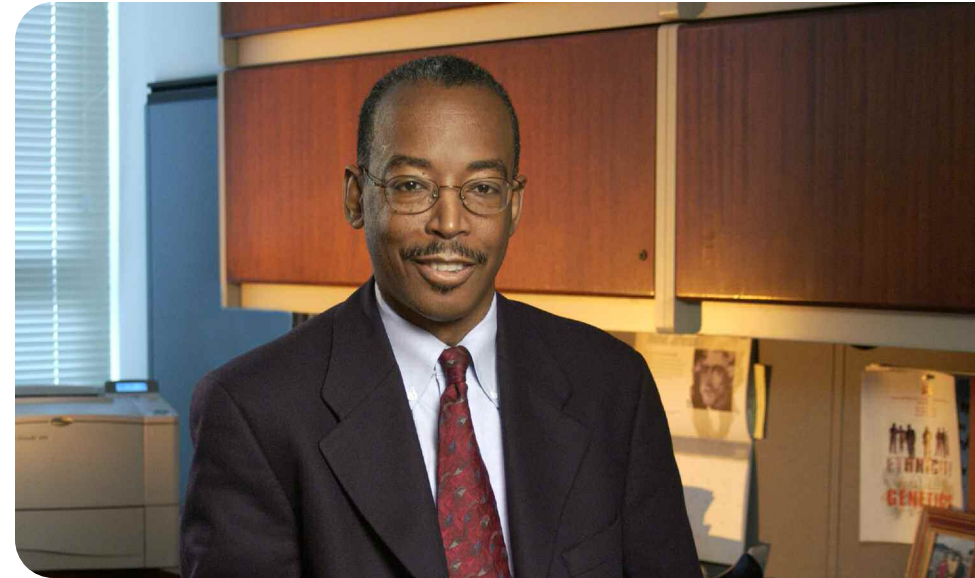
## VENCE BONHAM, JR., J.D.

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

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



Since coming to the NHGRI in 2002, Mr. Bonham has focused on studying the connection between genomic research and health disparities. Currently, he is building a program of research relating to health care providers' decisions about genetic testing. He and his colleagues have conducted a large Internet-based survey of family physicians to assess their opinions and decisions related to genetic testing and the extent to which a



patient's ethnic and racial background influences these decisions. Additionally, he and his colleagues are working to develop an assessment tool for gauging how health professionals use race and ethnicity to make decisions about providing genetic services and in assessing risk of genetic disease. An important aspect of this research will involve structured interviews and focus groups with a geographically dispersed sample of physicians to gain insights into their understanding of the concepts of race and ethnicity and how these concepts relate to the genetic basis of disease.

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

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

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

## SELECTED PUBLICATIONS

Bonham VL. Race, ethnicity, and pain treatment: striving to understand the causes and solutions to the disparities in pain treatment. *J Law Med Ethics* 29:52–68, 2001.

Nerenz DR, Bonham VL, Green-Weir R, Joseph C, Gunter M. Eliminating racial/ethnic disparities in health care: can health plans generate reports? *Health Aff* 21:259–263, 2002.

Bonham VL, Nathan VR. Environmental public health research: engaging communities. *Int J Hyg Environ Health* 205:11–18, 2002.

Bonham VL, Sellers SL, Neighbors HW. John Henryism and self-reported physical health among high socioeconomic status African American men. *Am J Public Health* 94:737–738, 2004.

Bonham V, Warshauer Baker E, Collins FC. Race and ethnicity in the genomic era: the complexity of constructs. *Am Psychol* 60:9–15, 2005.

Race, Ethnicity and Genetics Working Group. The use of racial, ethnic, and ancestral categories in human genetics research. *Am J Hum Genet* 77: 519–532, 2005.

Bonham VL, Haywood C, Gamble VN. Sickle cell disease: the past, present and future social and ethical dilemmas. In: *The Renaissance of Sickle Cell Disease in the Human Genome Era*. United Kingdom: Imperial College Press, p. 311–321, 2007.



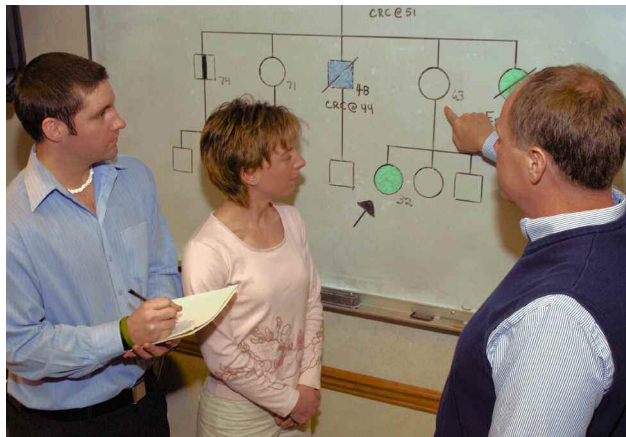
## DONALD W. HADLEY, M.S., C.G.C.

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

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

Currently, Mr. Hadley's particular area of focus addresses the many questions surrounding genetic screening for hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch

Syndrome, the most common form of hereditary colon cancer. Mr. Hadley is collaborating with investigators at the National Cancer Institute to collect information from families that are at risk for developing HPNCC. In addition to collecting information from these families through detailed questionnaires, the researchers ask participants to attend a genetic education session to help them understand



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

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



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

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

## SELECTED PUBLICATIONS

Hadley D, Jenkins J, Dimond E, Nakahara K, Grogan L, Liewehr D, Steinberg S, Kirsch I. Genetic counseling and testing in families with hereditary non-polyposis colorectal cancer. *Arch Intern Med* 163:573-582, 2003.

Hadley D, Jenkins J, deCarvalho M, Dimond E, Kirsch I, Palmer CGS. Colon cancer screening practices following genetic counseling and testing for hereditary non-polyposis colorectal cancer. *J Clin Oncol* 22:39-44, 2004.

McInerney-Leo A, Biesecker BB, Hadley DW, Kase RG, Giambarresi TR, Johnson E, Lerman C, Struewing JP. *BRCA1/2* testing in hereditary breast and ovarian cancer families: effectiveness of problem-solving training as a counseling intervention. *Am J Med Genet* 130:221-227, 2004.

McInerney-Leo A, Biesecker BB, Hadley DW, Kase RG, Giambarresi TR, Johnson E, Lerman C, Struewing JP. *BRCA1/2* testing in hereditary breast and ovarian cancer families II: impact on relationships. *Am J Med Genet A* 133:165-169, 2005.

McInerney-Leo A, Hadley D, Gwinn-Hardy K, Hardy J. Genetic testing in parkinson's disease. *Mov Disord* 20:1-10, 2005.

Palmer CGS, Hadley D. Evaluating the impact of genetic counseling and testing with signal detection methods. *J Genet Couns* 14:17-27, 2005.

Wattendorf DJ, Hadley DW. Family history: The three-generation pedigree. *Amer Fam Physician* 72:441-448, 2005.

Lindor NM, Petersen GM, Hadley DW, Kinney AY, Miesfeldt S, Lu KH, Lynch P, Burke W, Press N. Recommendations for the care of individuals with an inherited predisposition to Lynch Syndrome: a systematic review. *JAMA* 296:1507-1517, 2006.

McInerney-Leo A, Hadley D, Kase RG, Giambarresi TR, Stuewing JP, Biesecker BB. *BRCA1/2* testing in hereditary breast and ovarian cancer families III: risk perception and screening. *Am J Med Genet A* 140:2198-2206, 2006.

James CA, Hadley DW, Holtzman NA, Winklestein JA. How does the mode of inheritance of a genetic condition influence families? A study of guilt, blame, stigma, and understanding of inheritance and reproductive risks in families with X-linked and autosomal recessive diseases. *Genet Med* 8:234-242, 2006.

Hadley DW, Jenkins JF, Steinberg SM, Liewehr D, Moller S, Martin JC, Calzone KA, Soballe PW, Kirsch I. Perceptions of cancer risks and predictors of colon and endometrial cancer screening in women undergoing genetic testing for Lynch syndrome. *J Clin Oncol*, in press.

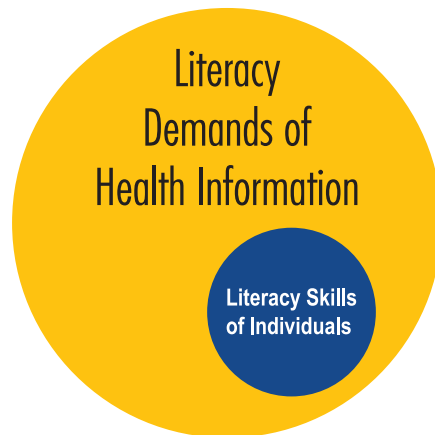
## KIMBERLY A. KAPHINGST, Sc.D.

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

Dr. Kaphingst's previous research focused on the communication of various types of health information. She examined how direct-to-consumer prescription drug advertisements presented risk and benefit information via broadcast and print media. Dr. Kaphingst also investigated the communication of cancer information to patient- and community-based populations. One such study was conducted with breast cancer patients who had donated blood or tissue samples for breast

cancer research, with the goal of understanding their perceptions of the donation process and their interest in receiving information about ongoing research studies. Although the donors expressed a strong interest in receiving information about studies using their samples, they had a limited understanding of genetic research and related vocabulary.

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



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

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

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

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

**SELECTED PUBLICATIONS**

Kaphingst KA, DeJong W. The educational potential of direct-to-consumer prescription drug advertising. *Health Affairs* 23:143-150, 2004.

Kaphingst KA, Rudd RE, DeJong W, Daltroy LH. Literacy demands of product information intended to supplement television direct-to-consumer prescription drug advertisements. *Patient Educ Couns* 55:293-300, 2004.

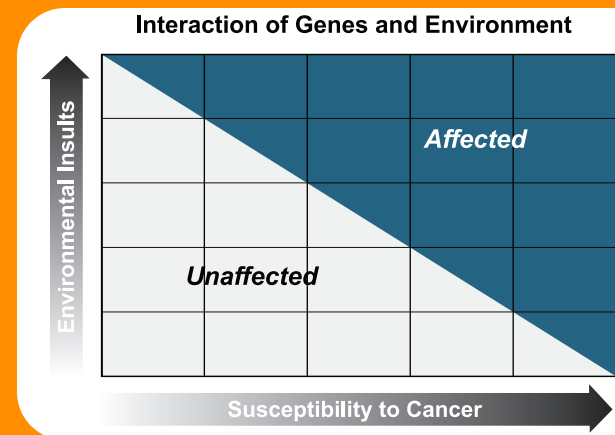
Rudd RE, Kaphingst K, Colton T, Gregoire J, Hyde J. Rewriting public health information in plain language. *J Health Commun* 9:195-206, 2004.

Kaphingst KA, DeJong W, Rudd RE, Daltroy L. A content analysis of direct-to-consumer television prescription drug advertisements. *J Health Commun* 9:515-528, 2004.

Kaphingst KA, Rudd RE, DeJong W, Daltroy L. Comprehension of information in three direct-to-consumer television prescription drug advertisements among adults with limited literacy. *J Health Commun* 10:609-619, 2005.

Kaphingst KA, Zanfini C, Emmons KM. Accessibility of web sites containing colorectal cancer information to adults with limited literacy. *Cancer Causes Control* 17:147-151, 2006.

Kaphingst KA, Janoff JM, Harris LN, Emmons KM. Views of female breast cancer patients who donated biologic samples regarding storage and use of samples for genetic research. *Clin Genet* 69:393-398, 2006.



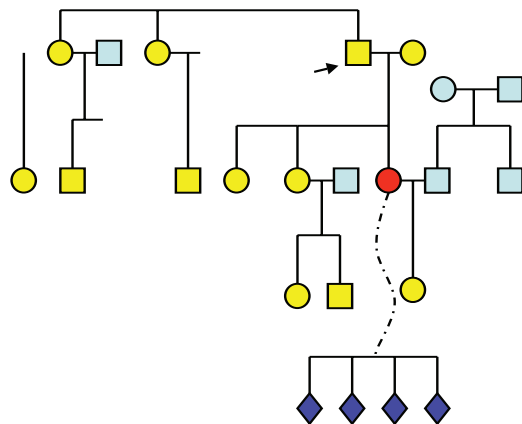
## LAURA KOEHLI, Ph.D.

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

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

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

Previous research in this field has focused primarily on the "index case" (the patient) and only one or two relatives. Unfortunately, this narrow view of social networks provides a biased perspective.



Moreover, traditional statistical models have assumed that individuals in a social network respond to disease-risk information independently when, in fact, they do not. Dr. Koehly's research seeks to overcome such limitations by studying entire family systems and developing more appropriate social network models. In turn, these models should allow her to better understand the impact of the interpersonal environment on an individual's (or a system of individuals') behaviors.



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

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



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

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

## SELECTED PUBLICATIONS

Koehly LM, Shivy VS. Social environments and social contexts: social network applications in person-environment psychology. In: Martin W and Swartz JL (Eds), *Person-Environment Psychology and Mental Health: Assessment and Intervention*. Mahwah, NJ: Lawrence Erlbaum Associates, pp. 59–87, 2000.

Koehly LM, Peterson SK, Watts BG, Kempf KG, Vernon SW, Gritz ER. A social network analysis of communication about hereditary nonpolyposis colorectal cancer genetic testing and family functioning. *Cancer Epidemiol Biomarker Prev* 12:304–313, 2003.

Peterson SK, Watts BG, Koehly, LM, Vernon SW, Baile WF, Kohlmann WK, Gritz ER. How families communicate about HNPCC genetic testing: findings from a qualitative study. *Am J Med Genet C Semin Med Genet* 119C:78–86, 2003.

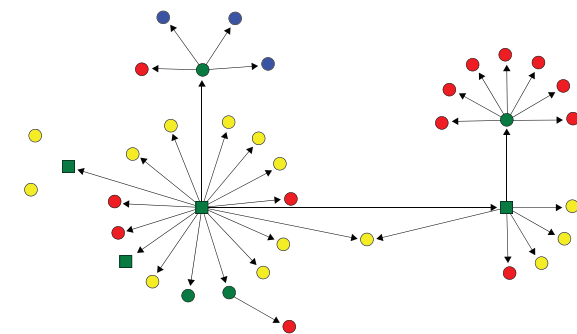
Koehly LM, Goodreau SM, Morris M. Assessing exponential family models for sampled and census network data. *Sociol Methodol* 34:241–270, 2004.

Koehly LM, Pattison P. Random graph models for social networks: multiple relations or multiple raters. In: Carrington P, Scott J, and Wasserman S (Eds), *Models and Methods in Social Network Analysis*. New York, NY: Cambridge University Press, pp. 162–191, 2005.

Pentz RD, Peterson SK, Watts B, Vernon SW, Lynch PM, Koehly LM, Gritz ER. HNPCC family members' perceptions about the duty to inform and health professionals' role in the dissemination of genetic information. *Genet Test* 9:261–269, 2005.

Yang MQ, Koehly LM, Elnitski LL. Comprehensive annotation of bidirectional promoters identifies co-regulation among breast and ovarian cancer genes. *PLoS Comput Biol* 3:e72, 2007.

Slaughter A, Yu J, Koehly L. Social network analysis: understanding the role of context in small groups and organizations. In: Salas E, et al. (Eds), *Team Effectiveness in Complex Organizations: Cross-disciplinary Perspectives and Approaches*. Mahwah, NJ: Lawrence Erlbaum Associates, in press.





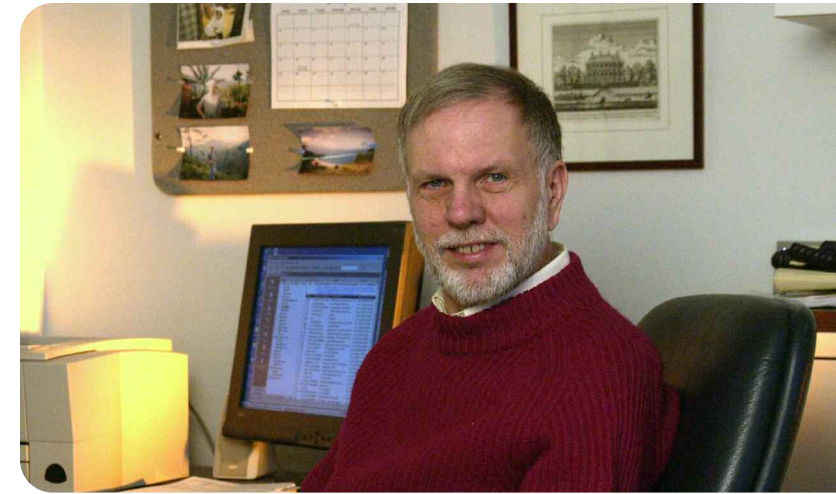
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Dr. Fischbeck studies the mechanisms of hereditary neurological and neuromuscular disorders, with the goal of developing effective treatments for these conditions. His laboratory's areas of research include the polyglutamine expansion diseases (Huntington's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



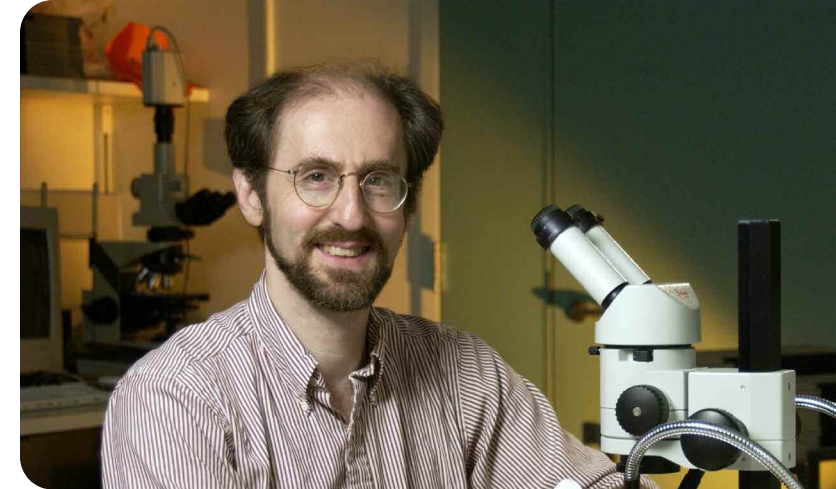
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Information processing in the brain is done by specialized neural circuits. Every neuron has an axon, which carries information to its synaptic partners within these circuits. Dr. Giniger seeks to understand the molecular mechanisms that guide an axon,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





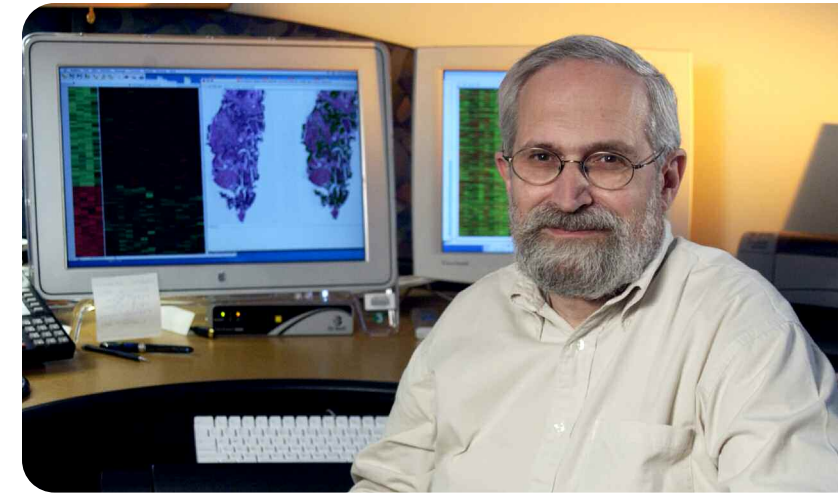
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Dr. Meltzer uses cutting-edge technologies to analyze the abnormalities in genome structure and function that occur in cancers. These methods include various types of microarray analyses, which allow him to scan the entire genome and examine how genes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



## SHARON L. MILGRAM, Ph.D.

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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. Examples of Core-developed software include *GeneMachine*, an integrated tool that performs both comparative and predictive gene identification techniques, and *GeneLink*, a database solution designed to facilitate large-scale genetic linkage or association studies, allowing for complex trait mapping. The Core plays a key role in developing and maintaining sequence and mutation databases that allow for the efficient archiving and retrieval of genomic data generated by NHGRI investigators, such as the Breast Cancer Information Core (BIC; see *Lawrence Brody, Genome Technology Branch*). Core personnel collaborate with the numerous NHGRI laboratories that

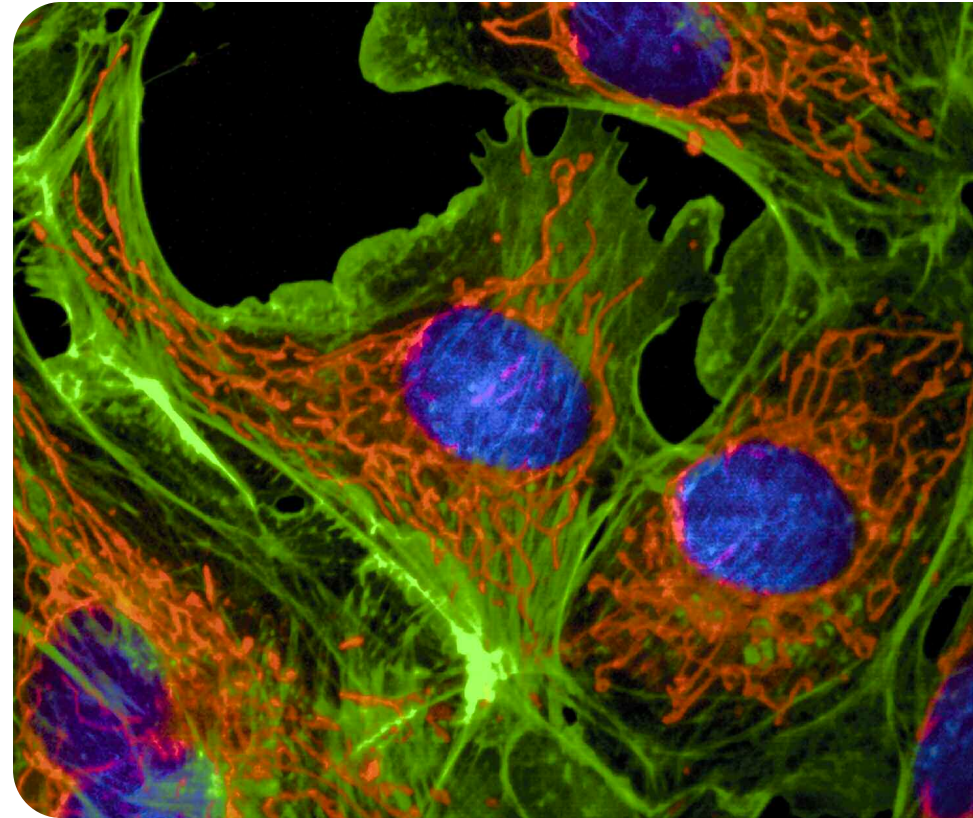


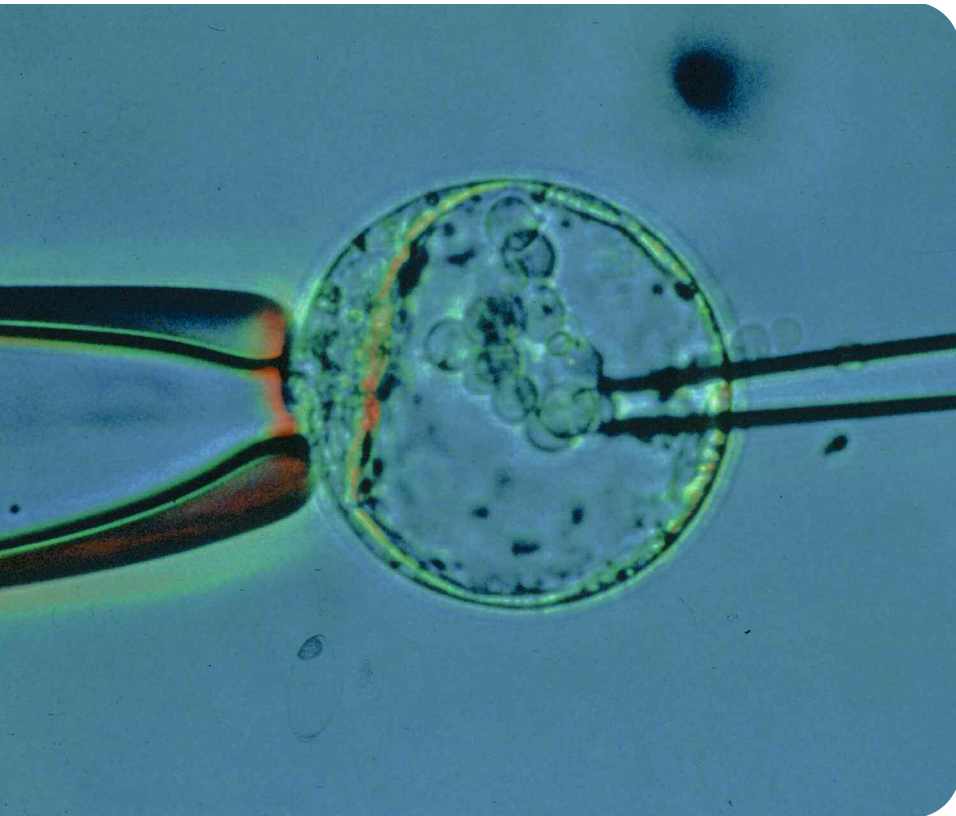
require intensive computational support. The Core maintains several high-end computer systems, including a 120-node Linux cluster; investigators also have access to the NIH Biowulf cluster, with more than 1250 compute nodes (2500 processors). NHGRI personnel can access commonly used sequence analysis software, often through Core-designed special interfaces; Core personnel provide basic assistance in using these computational tools. Finally, the Core is involved in a series of educational efforts, including hands-on bioinformatics training classes for NHGRI researchers, which are offered on a regular basis and cover the essentials of bioinformatics as related to genomic research.



## Cytogenetics and Microscopy Core

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





## Embryonic Stem Cell and Transgenic Mouse Core

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

## Flow Cytometry Core

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

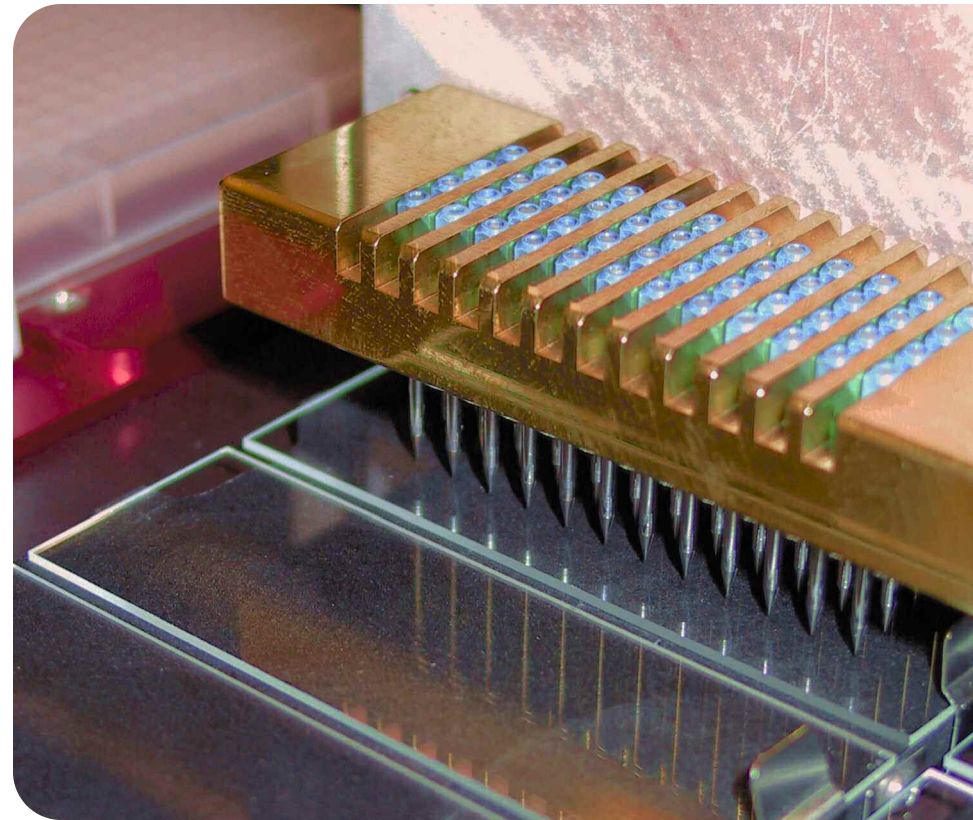


## Genomics Core

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

## Zebrafish Core

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



## CENTERS

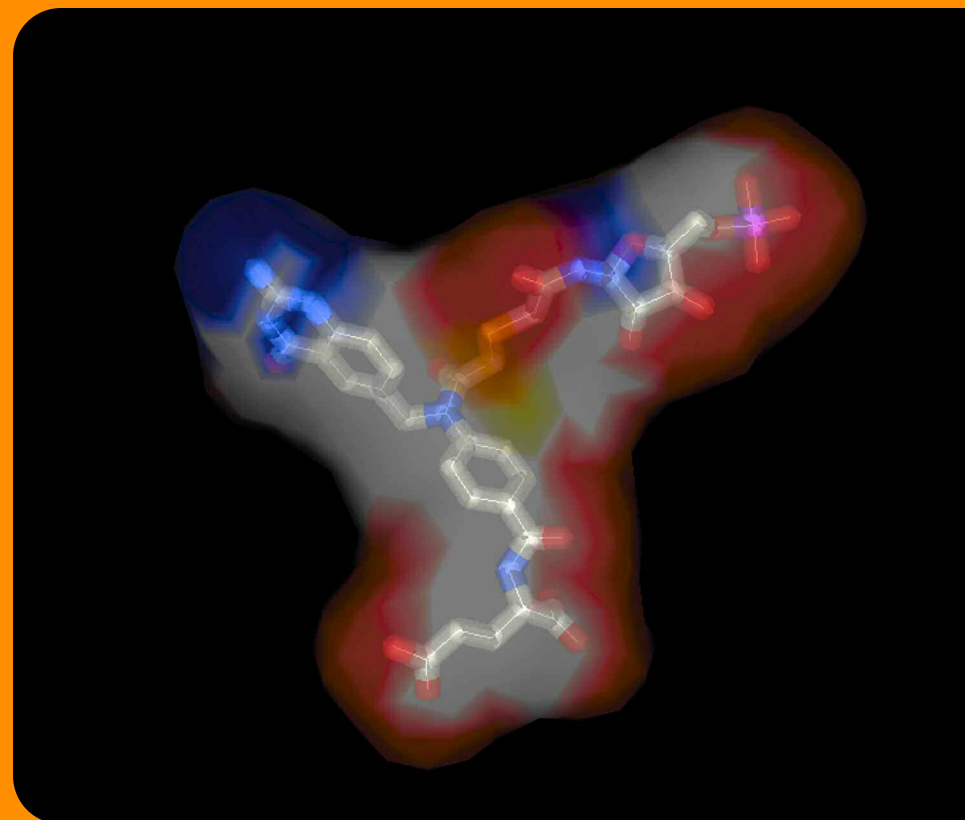
The Division of Intramural Research operates or oversees three centers that offer unique, high-throughput technologies for small-molecule screening, and genetic, genomic, and sequencing services to NHGRI investigators and their collaborators. Access to these centers allows NHGRI researchers to develop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

### Center for Inherited Disease Research

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

### NIH Chemical Genomics Center

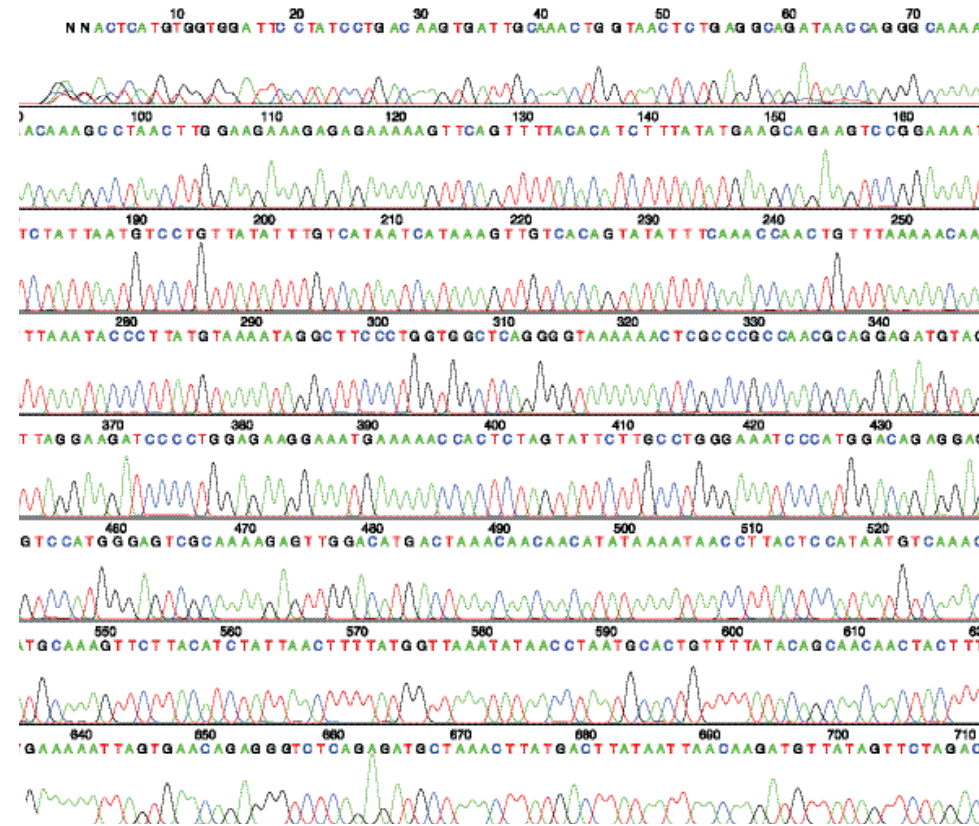
The NIH Chemical Genomics Center (NCGC; [ncgc.nih.gov](http://ncgc.nih.gov)) is an ultrahigh-throughput small-molecule screening and chemistry center that discovers chemical probes of gene and cell functions across the genome using quantitative high-throughput screening (qHTS) technology, and develops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



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

## NIH Intramural Sequencing Center

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



## OFFICES

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

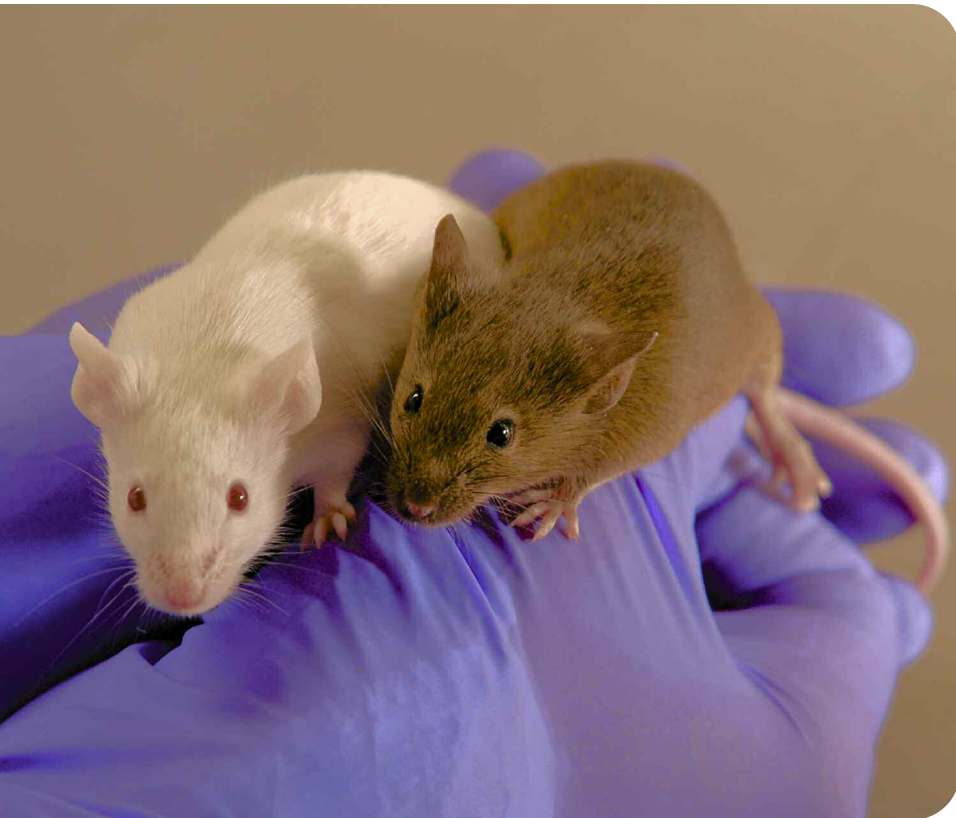
### Office of the Scientific Director

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

### Office of the Clinical Director

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





### Office of Translational Research

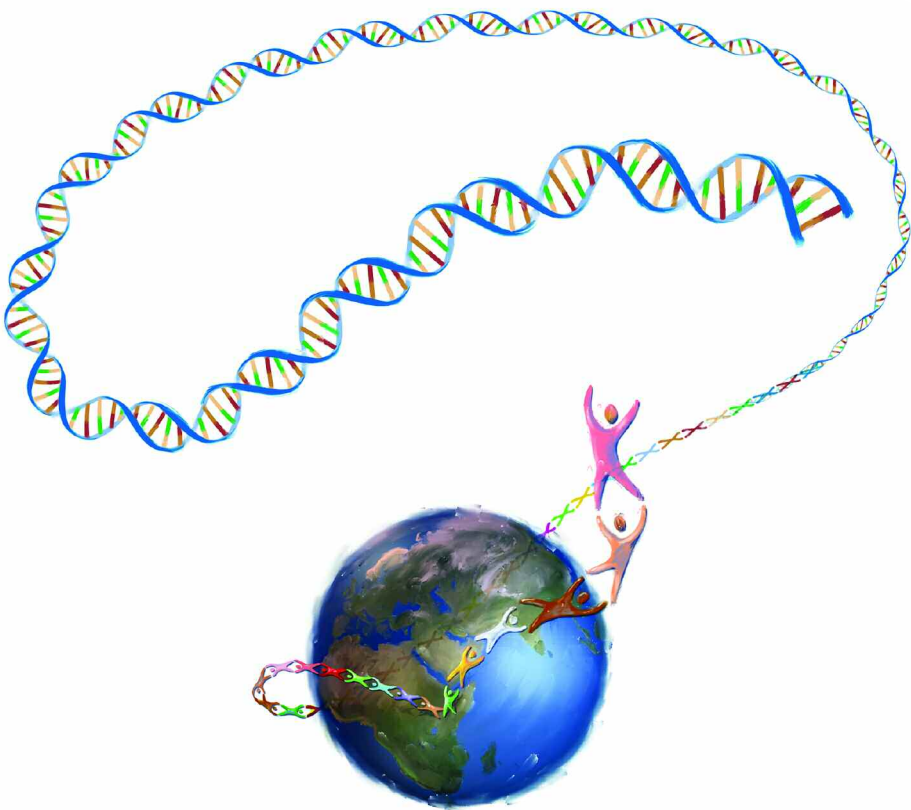
The NHGRI Office of Translational Research aims to facilitate translational and transdisciplinary approaches in an effort to bridge basic and clinical research within the Intramural Program. Recently established, the Office is now exploring different strategies for catalyzing translational research at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

### Intramural Training Office

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

### Office of Laboratory Animal Medicine

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



## Technology Transfer Office

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

## Intramural Publication Support Office

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





TRAINING AND CAREER DEVELOPMENT PROGRAMS

## TRAINING AND CAREER DEVELOPMENT PROGRAMS

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

### Summer Internship in Biomedical Research Program

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





## Intramural Research Training Awards Program

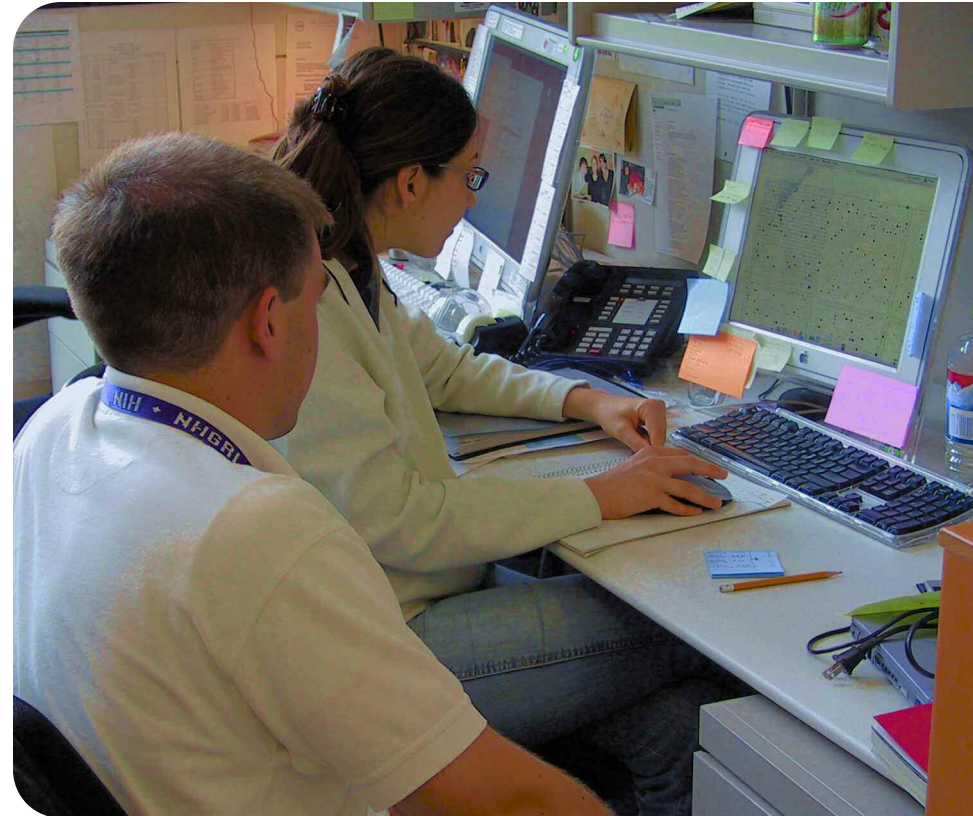
The Intramural Research Training Awards (IRTA) Program consists of four types of awards, each specifically designed to suit the needs of trainees at different stages of their education and/or professional training. These awards include stipends to those who have recently earned a bachelor's or master's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

### TECHNICAL INTRAMURAL RESEARCH TRAINING AWARD

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

### POST-BACCALAUREATE INTRAMURAL RESEARCH TRAINING AWARD

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





#### **PRE-DOCTORAL INTRAMURAL RESEARCH TRAINING AWARD**

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

#### **POST-DOCTORAL INTRAMURAL RESEARCH TRAINING AWARD**

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

## Undergraduate Scholarship Program

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



## Physician-Scientist Development Program

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

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





## Metropolitan Washington D.C. Medical Genetics Residency Program

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

## Metropolitan Washington D.C. Medical Genetics Training Program

NHGRI sponsors the Metropolitan Washington Medical Genetics Training Program, which offers two-year fellowships in medical genetics, cytogenetics, biochemical genetics and molecular genetics for individuals with M.D. or Ph.D. degrees. This program provides participants the opportunity to conduct genetic research in some of the world's most advanced laboratories; gain clinical experience in the Washington area; and develop expertise in basic

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



## Combined Pediatrics and Medical Genetics Residency Program

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



## The Johns Hopkins University/NHGRI Genetic Counseling Training Program

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

## Visiting Fellow Program

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

## Health Disparities Visiting Faculty Program

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

## Current Topics in Genomic Research Short Course Program

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





NIH AND SURROUNDING AREA



## THE NATIONAL INSTITUTES OF HEALTH

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

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

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



## The Mark O. Hatfield Clinical Research Center

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

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

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







## The NIH Libraries

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

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



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

### Amenities on the Bethesda Campus

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



## The Surrounding Communities

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

### BETHESDA

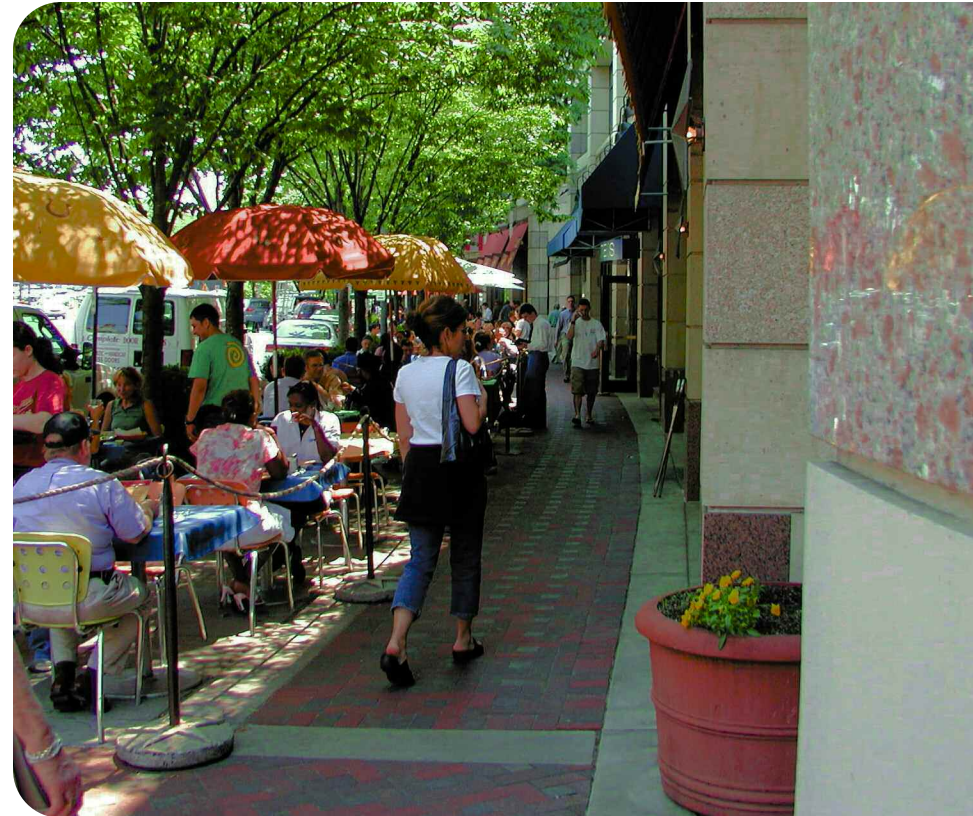
Bethesda, Maryland is a vibrant community surrounding the NIH campus. Its many dining options are legendary. No matter what you crave — from American to Vietnamese cuisine — you will find it in Bethesda. The Bethesda Urban Partnership Inc. makes it even easier to decide where to dine by offering a Web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

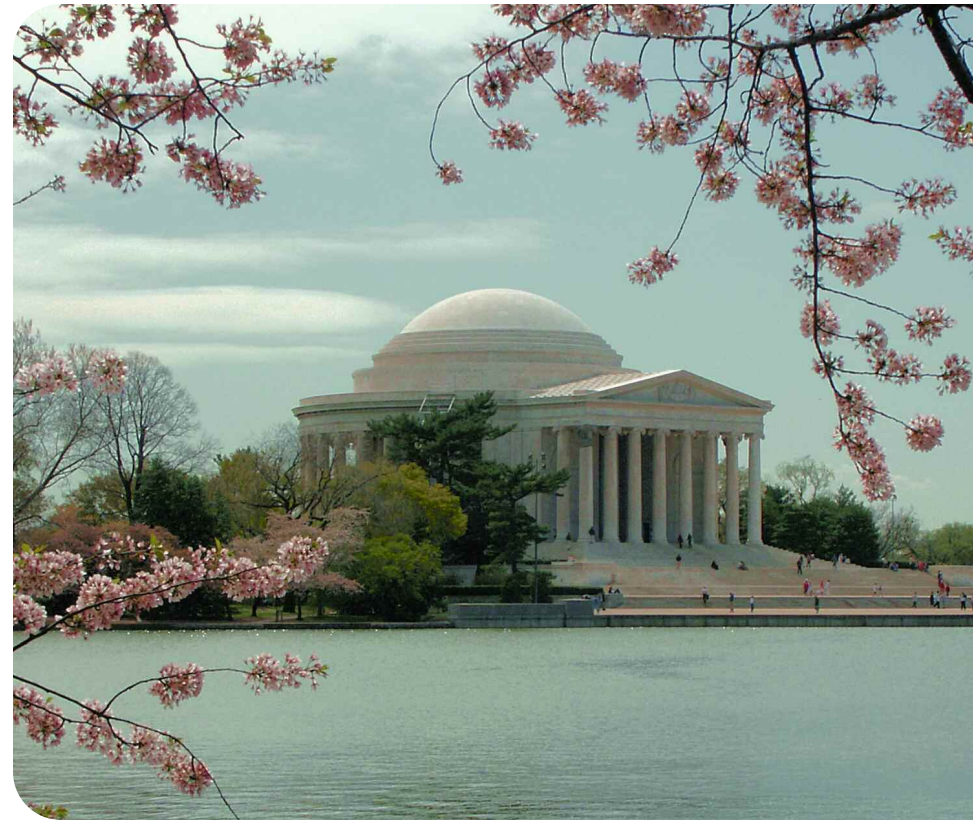
Washington is one of the world's grandest capitals—a city of impressive Federal architecture, inspiring monuments, and magnificent embassies. But Washington also has a local side—it is a lively, multicultural city filled with ethnic restaurants, late-night bars, bookstores, and more theater performances 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](http://nih.gov)*

### **ABOUT WASHINGTON, D.C.**

*[washington.org](http://washington.org)*

### **ABOUT METRO**

*[wmata.com](http://wmata.com)*

### **ABOUT MONTGOMERY COUNTY**

*[montgomerycountymd.gov](http://montgomerycountymd.gov)*

### **ABOUT BETHESDA**

*[bethesda.org](http://bethesda.org)*

### **ABOUT WASHINGTON-AREA RENTALS**

*[washingtonpost.com/wp-dyn/content/rentals](http://washingtonpost.com/wp-dyn/content/rentals)*

### **ABOUT WASHINGTON-AREA ARTS AND LEISURE**

*[washingtonpost.com/wp-dyn/artsandliving](http://washingtonpost.com/wp-dyn/artsandliving)*



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Page 29  
Southard-Smith EM et al. *Genome Res*  
9:215–225, 1999.

Page 31  
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Myung K et al. *Mol Cell Biol*  
24:5050–5059, 2004.

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Myung K et al. *Mol Cell Biol*  
24:5050–5059, 2004.

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Page 78  
CIT's Biowulf Group,  
<http://biowulf.nih.gov>

Pages 79  
Nabel EG *Nat Rev Drug Discov*  
1:587–598, 2002.

Page 84 (left image)  
Rokman A et al. *Hum Genet*  
116:43–50, 2005.

Page 84 (right image)  
Schleutker J et al. *The Prostate*  
57:280–289, 2003.

Page 86  
Bailey-Wilson JE et al. *Am J Hum Genet*  
75:460–474, 2004.

Page 88  
Stambolian D et al. *Am J Hum Genet*  
75:448–459, 2004.

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McInerney-Leo A et al. *Am J Med Genet A*  
140:2198–2206, 2006.

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