



University of Washington

Medical Genetics Training Program

2003



The University of Washington Medical Genetics Training Program offers postdoctoral fellowships to individuals with the MD or MD/PhD degree.

The program is designed to train individuals for academic careers in human and medical genetics. The philosophy of the program is to use the most advanced concepts and techniques of genetics and cellular/molecular biology in the elucidation of problems in human and medical genetics. Research as well as clinical competence is stressed. Research activities span a wide spectrum of topics in basic and clinical human genetics.

Training is usually undertaken for a three-year period. The first year is supported by the UW residency program while years 2 and 3 are supported by NIH.

Trainees are expected to choose a research mentor soon after they start training in the program. The first year is divided between clinical and research activities while the subsequent years are devoted principally to research. The training faculty belongs to seven departments of the University of Washington (Medicine, Pediatrics, Genetics, Pathology, Environmental Health, Biochemistry, Molecular Biotechnology) and the Fred Hutchinson Cancer Research Center.

TRAINING IN CLINICAL GENETICS

The Program provides well-rounded clinical training leading to eligibility for certification in Clinical Genetics by the American Board of Medical Genetics. Training leading to eligibility for certification in Cytogenetics, Biochemical Genetics and Clinical Molecular Genetics is also available.

During the first year, fellows rotate among the Medical Genetics Clinic at the University Hospital, the Medical Genetics Clinic at Children's Hospital and Medical Center, and the Biochemical Genetics Clinic at University Hospital, all of which meet weekly. The Medical Genetics Clinic at the University has specialty clinics in neurological genetics, connective tissue genetics, and cancer genetics, in addition to the all-inclusive clinics. Several hundred families with developmental genetic and dysmorphic phenotypes are seen, counseled and studied each year in the Medical Genetics Clinic at Children's Hospital and Medical Center. The Biochemical Genetics Clinic is the major center in the states of Washington and Alaska for the study of patients with a wide range of metabolic genetic disorders, and has unique responsibility for the long-term supervision of medical care for these children and adults.

Specialty clinics in muscular dystrophy, cystic fibrosis and coagulation disorders are held at the Children's Hospital and are staffed, in part, by our clinical geneticists and genetic associates.

Our program also provides genetic services to the state of Alaska. There are six visits yearly to Alaska. Each fellow can expect to make one trip to Alaska, usually during the second year of training.

Exposure to cytogenetic evaluations is an important part of the Medical Genetics Training Program. Cytogenetics facilities at the University Hospital and the Children's Hospital process more than 2000 samples each year as part of cytogenetic evaluation of children and adults with congenital anomalies and for prenatal studies.

Training in fetal genetics and prenatal diagnosis is available through the Prenatal Diagnosis Clinic of the Department of Obstetrics. In addition, the fellows attend in-patient and out-patient consultations and a weekly conference on fetal diagnosis and management.

RESEARCH OPPORTUNITIES

Research of the training faculty covers most areas of Human and Medical Genetics and modern molecular biology. Fifteen members of our faculty are Diplomats of the American Board of Medical Genetics. Six are members of the National Academy of Sciences.

Basic Molecular Genetics and Developmental Genetics. Braun, Fields, Gartler, Hartwell, Olson, Palmiter, Tapscott, Soriano.

Human Molecular and Developmental Genetics. Byers, Deeb, Hartwell, Horwitz, King, Lynch, Stamatoyannopoulos, Stephens, Tait, Tapscott.

Cancer Genetics: Hartwell, Horwitz, King, Yeung

Gene Therapy. Blau, Emery, Lieber, Miller, Russell, Stamatoyannopoulos, Tapscott.

Genome Research. Chance, Horwitz, Jarvik, King, Lynch, Olson, Schellenberg, Stephens

Genetic Epidemiology. Austin, Jarvik, King, Wijsman

Clinical Genetics. Burke, Byers, Chance, Cheng, Horwitz, Jarvik, Motulsky, Pagon, Scott, Sybert

Clinical Molecular Genetics: Byers, Stephens, Tait

Neurogenetics. Bird, Chance, Lynch, Tapscott

Statistical Genetics. Jarvik, Wijsman

Cytogenetics and Molecular Cytogenetics. Disteche, Raskind, Trask.

Biochemical Genetics. Byers, Furlong, Scott

Pharmacogenetics and Ecogenetics. Furlong, Motulsky

Genetics of Aging. Bird, Deeb, Schellenberg

APPLICATIONS

Requests for further information and applications should be addressed to the program director, George Stamatoyannopoulos, Medical Genetics, Box 357720, University of Washington, Seattle, WA 98195-7720, (206-543-3526, FAX 206-543-3050), gstam@u.washington.edu.

MELISSA AUSTIN, M.S., Ph.D.

Research Program:

Dr. Austin's research program focuses on lipoproteins and genetic susceptibility to atherosclerosis, with an emphasis on triglyceride and low-density lipoprotein heterogeneity. Dr. Austin's current NIH-funded projects include two large-scale family studies investigating the familial forms of hyperlipidemia and the genetics of risk factors for coronary heart disease and diabetes in the Japanese American community. She also serves as a core director for the University of Washington Center for Ecogenetics and Environmental Health.

In her role as director, Dr. Austin leads a multidisciplinary group of faculty members from seven different schools and colleges in developing the Public Health Genetics program. Curriculum-related activities have already resulted in a new Masters of Public Health degree track in Public Health Genetics, and a new Ph.D. degree is planned. The Public Health Genetics Program also facilitates new research and dialogues among professionals in this emerging discipline. Dr. Austin leads the Genetics in Public Health Training Collaboration; a nationwide effort of five universities, the Centers for Disease Control and Prevention, and the National Institutes of Health; to identify career opportunities for graduates of public health genetics programs.

Investigator: Dr. Melissa Austin is Professor of Epidemiology in the School of Public Health and Community Medicine, Adjunct Professor in the Division of Metabolism, Endocrinology and Nutrition in the Department of Medicine, and Director of the new University-wide Public Health Genetics Program at the University of Washington. She is currently an Established Investigator of the American Heart Association.

Representative Publications:

- Austin MA, Mykkänen L, Kuusisto J, Edwards KL, Nelson C, Haffner SM, Pyörälä K, Laakso M: A prospective study of small, dense LDLs and non-insulin dependent diabetes in the elderly. *Circulation* 92:1770-1778, 1995
- Hokanson JE, Austin MA: Triglyceride is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol: A meta-analysis of population-based prospective studies. *J Cardio Risk* 3:213-219, 1996
- Austin MA, Ordovas JM, Eckfeldt JH, Tracy R, Boerwinkle E, Lalouel J-M, Printz M: Guidelines of the National Heart, Lung and Blood Institute Working Group on Blood Drawing, Processing and Storage for Genetic studies. *Am J Epidemiol* 144:437-441, 1996
- Edwards KL, Newman B, Mayer E, Selby JV, Krauss RM, Austin MA: Heritability of the insulin resistance syndrome in women twins. *Genet Epidemiol* 14:241-253, 1997
- Austin MA, Friedlander Y, Newman B, Selby JV, Edwards KL, Mayer-Davis EJ, King MC: Genetic influences on changes in body mass index. A longitudinal analysis of women twins. *Obesity Res* 5:326-331, 1997
- Friedlander Y, Sisovick DS, Weinmann S, Austin MA, Psaty BM, Lemaitre R, Arbogast P, Raghunathan TE, Cobb LA: Family history as a risk factor for primary cardiac arrest. *Circulation* 97:155-160, 1998
- Austin MA, Talmud PJ, Luong L-A, Haddad L, Day INM, Newman B, Edwards KL, Krauss RM, Humphries SM: Candidate gene studies of the atherogenic lipoprotein phenotype: A sib-pair linkage analysis of dizygous women twins. *Am J Hum Genet* 62:406-419, 1998
- Austin MA, Stephens K, Wijsman E: Linkage analysis of candidate genes and the small, dense low-density lipoprotein phenotype. *Atherosclerosis* 142:79-87, 1999
- Hokanson JE, Brunzell JD, Jarvik GP, Wijsman E, Austin MA: Lipoprotein lipase heterozygosity is a cause of small low-density lipoproteins: Linkage analysis in families with structural mutations in the lipoprotein lipase gene. *Am J Hum Genet*, in press

THOMAS D. BIRD, M.D.

Research Program:

Dr. Thomas D. Bird is a clinical neurogeneticist with interests in a wide range of hereditary disorders of the nervous system. Dr. Bird supervises adult neurogenetic clinics at the University of Washington Hospital and the Seattle Veterans Administration Medical Center. These clinics provide a rich source of material for investigations into the nosology and pathogenesis of hereditary neurological disease. Dr. Bird's specific research interests have included genetic studies of hereditary neuropathy (the Charcot-Marie-Tooth syndrome) and familial Alzheimer's disease. Hereditary neuropathy has proven to be very heterogeneous with loci on chromosomes 1, 17, X and others. Dr. Bird and colleagues have also provided clinical, neuropathological and linkage analysis evidence for both phenotypic and genetic heterogeneity in familial Alzheimer's disease. An ongoing detailed study of Volga German kindreds with Alzheimer's disease is a special focus of this research group. In addition, Dr. Bird has a clinical research interest in myotonic dystrophy, the hereditary ataxias, spastic paraplegia, familial ALS, the numerous genetic causes of chorea and families with Frontotemporal dementia having a variety of mutations in the tau gene.

Investigator: Dr. Bird is a Professor of Neurology and Medical Genetics and Research Investigator in the Geriatrics Section of VA Puget Sound Health Care System.

Representative Publications:

Chance PF, Alderson MK, Leppig KA, Lensch MW, Matsunami N, Smith B, Swanson PD, Odelberg SJ, Distèche CM, Bird TD: DNA deletion associated with hereditary neuropathy with liability to pressure palsies. *Cell* 72:143-151, 1993

Hayasaka K, Himoro M, Sato W, Takada G, Uyemura K, Shimizu N, Bird TD, Conneally PM, Chance PF: Charcot-Marie-Tooth neuropathy type 1B is associated with mutations of the myelin P0 gene. *Nature Genet* 5:31-33, 1993

Levy-Lahad E, Wasco W, Poorkaj P, Romano EM, Oshima J, Pettingell WH, You C, Jondro PD, Schmidt SD, Wang K, Crowley AC, Fu Y-H, Guenette SY, Galas D, Nemens E, Wijsman EM, Bird TD, Schellenberg GD, Tanzi RE: Candidate gene for the chromosome 1 familial Alzheimer's disease locus. *Science* 269:973-977, 1995

Poorkaj P, Bird TD, Wijsman E, et al: Tau is a candidate gene for chromosome 17 frontotemporal dementia. *Annals of Neurology* 43:815-825, 1998

Benson KF, Horwitz M, Richards RI, Mangelsdorf M, Wolff J, Raskind WH, Bird TD: Analysis of autosomal dominant familial spastic paraparesis families for CAG repeat expansion at common loci identifies novel expansion in a subset of patients. *Hum Molec Gen* 7:1779-1786, 1998

Hong M, Zhukaeva V, Vogelsberg-Ragaglia V, Wszolek Z, Reed I, Miller BI, Geschwind DH, Bird TD, et al: Mutation-Specific Functional Impairments in Distinct Tau Isoforms of Hereditary FTDP-17. *Science* 282:1914-1917, 1998

ROBERT BRAUN, Ph.D.

Research Program:

Dr. Braun's research interests address various aspects of germ cell development in the mouse. One major area of interest is in the mechanism of posttranslational control of gene expression. The lab is studying several genes that are under translational control in meiotic and haploid cells. Sequences controlling translational repression and translational activation have been identified in transgenic mouse studies. Several genes involved in regulating translation have been cloned and current efforts are directed at creating mutations in these genes in the mouse. The lab is currently characterizing phenotypes in Prbp, Zfr, and Tenr mutants. A second area of interest is in the characterization of the germ cell defect in a mouse model for Fanconi Anemia. Mice that have a mutation in the FAC gene are sterile. The lab is interested in determining the nature of the germ cell defect in FAC deficient mice and in understanding the function of the other FA genes in germ cell development. Lastly, the lab is assessing the likelihood of infection of the germ line by several vectors currently being used for gene therapy.

Investigator: Dr. Braun is an Associate Professor of Genetics.

Representative Publications:

Braun RE, Behringer RR, Peschon JJ, Brinster RL, Palmiter RD: Genetically Haploid Spermatids are Phenotypically Diploid. *Nature* 337:373-376, 1989

Lee K, Haugen HS, Clegg CH, Braun RE: Premature Translation of Protamine 1 mRNA Causes Precocious Nuclear Condensation and Arrests Spermatid Differentiation in Mice. *Proc Natl Acad Sci USA* 92:12451-12455, 1995

Lee KS, Fajardo MA, Braun RE: A testis cytoplasmic RNA binding protein that has the properties of a translational repressor. *Mol Cell Biol* 16:3023-3034, 1996

Fajardo MA, Haugen HS, Clegg CH, Braun RE: Separate elements in the 3 untranslated region of the mouse protamine 1 mRNA regulate translational repression and activation during murine spermatogenesis. *Dev Biol* 191:42-52, 1997

Braun RE: Every sperm is sacred-or is it? *Nature Genetics* 18:202-204, 1998

Zhong J, Lee K, Peters AHFM, Braun RE: A double-stranded RNA binding protein required for activation of repressed messages in mammalian germ cells. *Nature Genet* 22:171-174, 1999

Davies HG, Giorgini F, Fajardo MA, Braun RE: A sequence-specific RNA binding complex expressed in murine germ cells contains MSY2 and a novel protein, MSY4 (submitted)

Meagher MJ, RE Braun: A murine zinc-finger protein required during the mitotic proliferative phase of gastrulation (submitted)

PETER BYERS, M.D.

Research Program:

The underlying objective of research in Dr. Byers laboratory is to understand the *molecular pathogenesis of inherited disorders of connective tissue*. Dr. Byers has concentrated on disorders in which the mutations occur in fibrillar collagen genes, particularly the COL1A1 and COL1A2 genes that encode the chains of types I and III procollagens. He has identified more than 150 mutations in the genes that encode type I procollagens, more than 130 in the COL3A1 gene that encodes type III procollagen, as well as mutations in the type V collagen genes in forms of Ehlers-Danlos syndromes, and the lysyl hydroxylase gene in Ehlers-Danlos syndrome type VI. These mutations affect mRNA processing and transport, protein assembly and folding, molecular transport within the cell, and molecular processing and fibril aggregation in the extracellular matrix. Mutations in these disorders give rise to the common phenotypes of osteogenesis imperfecta and forms of Ehlers-Danlos syndrome type as well as to some uncommon phenotypes, such as arterial aneurysms. The Byers lab is now trying to understand the mechanisms by which the cell recognizes and adapts to mutations that affect splicing, chain assembly and molecular transport as well as to define the manner in which mutations produce the phenotypes. The strategies to reach these goals include the analysis of the normal and altered order of splicing in complex genes, isolation of procollagen binding proteins by direct immunoprecipitation of bound proteins, analysis of pathways of intracellular degradation, and analysis of changes in gene expression within cells that harbor these mutations.

Investigator: Dr. Byers is Professor of Pathology and Medicine (Medical Genetics).

Representative Publications:

Chessler SD, Wallis GA, Byers PH: Mutations in the carboxyl-terminal propeptide of the pro α 1(I) chain of type I collagen result in defective chain association and produce lethal osteogenesis imperfecta. *J Biol Chem* 268:18218-18225, 1993.

Chessler SD, Byers PH: BiP binds type I procollagen pro α chains with mutations in the carboxyl-terminal propeptide synthesized by cells from patients with osteogenesis imperfecta. *J Biol Chem* 268:18226-18233, 1993.

Byers PH: Disorders of collagen structure and synthesis. In *The Metabolic Basis of Inherited Diseases*, CR Scriver, A Beaudet, W Sly, D Valle, eds. McGraw-Hill, New York, 2805-2842, 1994.

Willing MC, Deschenes SS, Scott D, Byers PH, Slayton RL, Pitts SH, Arikat H, Roberts R: Osteogenesis imperfecta type I: molecular heterogeneity for COL1A1 null alleles of type I collagen. *Am J Hum Genet* 55:638-647, 1994.

Byers PH, Duvic M, Atkinson M, Robinow M, Smith SL, Krane SM, Greally MT, Ludman M, Matalon R, Pauker S, Quanbeck D, Schwarze U. Ehlers-Danlos syndrome type VIIA and VIIB result from splice junction mutations or genomic deletions that involve exon 6 in the COL1A1 and COL1A2 genes of type I collagen. *Am J Med Genet* 72:94-105, 1997.

Schwarze U, Goldstein JA, Byers PH. Splicing defects in the COL3A1 gene: marked preference for 5' (donor) splice site mutation in patients with exon-skipping mutations and Ehlers-Danlos syndrome type IV. *Am J Hum Genet* 61:1276-1286, 1997.

Qi M, Byers PH. Constitutive skipping of an alternatively spliced exon 10 in the *ATP7A* gene abolishes Golgi localization of the Menkes protein and produces the occipital horn syndrome. *Hum Molec Genet* 7:465-469, 1998

PHILLIP F. CHANCE, M.D.

Research Program:

Dr. Chance has established a laboratory with an interest in the molecular basis of inherited neurologic disorders, especially diseases of peripheral nerves including various forms of Charcot-Marie-Tooth neuropathy and amyotrophic lateral sclerosis (ALS; also called Lou Gehrig's disease). Through work in Dr. Chance's laboratory the chromosomal location or molecular basis of several different peripheral nerve disorders has been defined. The observations have advanced the genetic nosology within peripheral nerve diseases, have immediate relevance to the practice of clinical medicine and may provide a critical prelude to the development of rational therapies for patients. Dr. Chance's current projects include positional cloning of the genes for inherited brachial plexus neuropathy and for a juvenile-onset form of ALS. Other current projects in Dr. Chance's lab focus on the identification of genetic abnormalities in malformation syndromes affecting the cerebellum and an analysis of the structure and ontogeny of a transposon-associated repeat sequence on the short arm of chromosome 17.

Investigator: Dr. Chance is a Professor of Pediatrics and Neurology

Representative Publications:

Chance PF, Abbas N, Lensch MW, Pentao L, Roa BB, Patel PI and Lupski JR: Two autosomal dominant neuropathies result from reciprocal duplication/deletion of a region of chromosome 17. *Human Molecular Genetics* 3; 223-228, 1994.

Kiyosawa H, Lensch MW and Chance PF: Analysis of the CMT1A-REP repeat: Mapping crossover breakpoints in CMT1A and HNPP. *Human Molecular Genetics* 4: 2327-2334, 1995.

Scherer SS and Chance PF: Myelin Genes: getting the dosage right. *Nature Genetics* 11:226-229, 1995.

Pellegrino JE, Rebbeck TR, Brown MJ, Bird TD and Chance PF: Mapping of hereditary neuralgic amyotrophy (familial brachial plexus neuropathy) to distal chromosome 17q. *Neurology* 46:1128-1132, 1996.

Kiyosawa H and Chance PF: Primate origin of the CMT1A-REP repeat and analysis of a putative transposon-associated recombinational hotspot. *Human Molecular Genetics* 5:745-754, 1996.

Chance PF: Inherited Demyelinating Neuropathy: Charcot-Marie-Tooth Disease and Related Disorders in *The Molecular and Genetic Basis of Neurological Disease*, R.N. Rosenberg, S.B. Prusiner, S. DiMauro, R.L. Barchi and LM Kunkel, eds., Oxford, Butterworth-Heinemann, 1996.

Chance PF, Rabin BR, Ryan SG, Ding Y, Scavina M, Crain B, Griffin JW and Cornblath DR: Linkage of the gene for an autosomal dominant form of juvenile amyotrophic lateral sclerosis to chromosome 9q34. *American Journal of Human Genetics* 62:633-641, 1998.

Gossett JG and Chance PF: Evaluation and review of the familial carpal tunnel syndrome. *Muscle and Nerve* 21:1533-1536, 1998.

SAMIR S. DEEB, Ph.D.

Research Program:

Dr. Deeb's group is presently involved in two major projects: 1) *The molecular genetics of red/green color vision*. A high degree of variation in the ability to discriminate between colors in the middle-to-long wavelengths has been observed in the general population. This phenotypic variation was observed among individuals who are classified as either color vision defective or normal. Dr. Deeb and colleagues have determined the molecular basis for the two major phenotypic classes among individuals with normal color vision to be a single amino acid polymorphism in the red pigment gene. A partial understanding of the molecular basis of the various classes and severity of color vision deficiency was achieved by gross analysis of the red/green pigment gene assays. 2) *The molecular basis of dyslipoproteinemia*. Dr. Deeb's laboratory is investigating variants of candidate genes involved in plasma lipoprotein metabolism that may be associated with elevated low density or diminished high density lipoprotein levels. Apolipoproteins A-I and B-100 and the enzyme lipoprotein lipase are the main candidates being investigated using techniques of linkage analysis and DNA sequence determination. In addition, cis-regulatory elements of the lipoprotein lipase gene are being extensively studied by introduction of various regulatory regions driving the expression of Lac Z into cell lines and transgenic mice.

Investigator: Dr. Deeb is a Research Professor of Medicine (Medical Genetics) and Genetics.

Representative Publications:

Winderickx J, Lindsey DT, Sanocki E, Teller EY, Motulsky AG, Deeb SS: A Ser/Ala polymorphism in the red photopigment underlies variation in color matching among color-normal individuals. *Nature* 356:431-433, 1992

Winderickx J, Battisti L, Motulsky AG, Deeb SS: Selective expression of the X-linked green visual pigment genes. *Proc Natl Acad Sci USA* 89:9710-9714, 1992

Deeb SS, Lindsey DT, Hibiya Y, Sanocki E, Winderickx J, Teller DY, Motulsky AG: Genotype-phenotype relationships in human red/green color vision defects: Molecular and psychophysical studies. *Am J Hum Genet* 51:687-700, 1992

Laakso M, Malkki M, Kekäläinen P, Kuusisto J, Deeb SS: Insulin receptor substrate-11 variants in non-insulin-dependent diabetes. *J Clin Invest* 94:1141-1146, 1994

Meagher M, Jorgensen AL, Deeb SS: Sequence and evolutionary history of the length polymorphisms in intron 1 of the human red photopigment gene. *J Mol Evol* 43:622-630, 1996

Yamaguchi T, Motulsky AG, Deeb SS: Visual pigment gene structure and expression in human retinae. *Hum Mol Genet* 6:981-990, 1997

Crognale MA, Teller DY, Yamaguchi T, Motulsky AG, Deeb SS: Analysis of red/green color discrimination in subjects with a single X-linked photopigment gene. *Vision Res* 39:707-719, 1998

Hu Q, Kukull WA, Bressler SL, Gray MD, Cam JA, Larson EB, Martin GM, Deeb SS: The human FE65 gene: genomic structure and an intronic biallelic polymorphism associated with sporadic dementia of the Alzheimer type. *Hum Genet* 103:295-303, 1998

Deeb SS, Fajas L, Nemoto M, Pihlajamäki J, Mykkanen L, Kuusisto J, Laakso M, Fujimoto W, Auwerx J: A pro12Ala substitution in PPAR γ 2 associated with decreased receptor activity, lower body mass index and improved insulin sensitivity. *Nat Genet* 20:284-287, 1998

CHRISTINE DISTECHE, Ph.D.

Research Program:

Our main interest is the study of the structure and function of the X and Y chromosomes in mammals. The sex chromosomes play important roles in the development of males and females. The mammalian X chromosome is subject to X inactivation early in embryogenesis, which ensures the same dosage of gene expression between males and females. We are specially interested in features of this process in terms of establishment and maintenance of X inactivation. Genes that escape X inactivation have been found in human and in mouse and many of these genes have Y homologues. The laboratory is presently investigating the mechanisms of escape from X inactivation in terms of epigenetic changes during development. Evolutionary aspects of X/Y gene pairs are also an active area of study. Their findings of more genes that escape X inactivation in human, as compared to mouse, have special relevance to Turner Syndrome which is characterized by the presence of a single X chromosome and associated with infertility in human females but not in mice. Features associated with Turner Syndrome are likely to result from haploinsufficiency of genes that escape X inactivation. Individuals with sex chromosome abnormalities have been extensively studied by the laboratory to define critical regions of the X or Y chromosomes which play specific roles in these disorders.

Investigator: Dr. Disteche is a Professor of Pathology and Adjunct Professor of Medical Genetics.

Representative Publications:

Tsuchiya K, Reijo R, Page DC, Disteche CM: Gonadoblastoma: molecular definition of the susceptibility region on the Y chromosome. *Am J Hum Genet* 57:1400-7, 1995

Disteche CM: The great escape. *Am J Hum Genet* 60:1312-1315, 1997

Adler DA, Rugarli EI, Lingenfelter PA, Tsuchiya K, Poslinski D, Liggitt HD, Chapman VM, Elliott RW, Ballabio A, Disteche CM. Evidence of evolutionary up-regulation of the single active X chromosome in mammals based on *Clc4* expression levels in *Mus spretus* and *Mus musculus*. *Proc Nat Acad Sc. USA.* 94:9244-9248, 1997

Schwartz A, Chan DC, Brown LG, Alagappan R, Pettay D, Disteche C, McGillivray B, de la Chapelle A, Page DC: Reconstructing hominid Y evolution: X-homologous block, created by X-Y transposition, was disrupted by Yp inversion through LINE-LINE recombination. *Hum Mol Genet* 7:1-11, 1998.

Lingenfelter PA, Adler DA, Poslinski D, Thomas S, Elliott RW, Chapman VM, Disteche CM: Escape from X inactivation of *Smcx* is preceded by silencing during mouse development. *Nature Genet* 18:212-213, 1998

Dal Zotto L, Quaderi NA, Elliott R, Lingenfelter PA, Carrel L, Valsecchi V, Montini E, Yen CH, Chapman V, Kalcheva I, Arrigo G, Zuffardi O, Thomas S, Willard HF, Ballabio A, Disteche CM, Rugarli EI: The mouse *Mid1* gene: implications for the pathogenesis of Opitz syndrome and the evolution of the mammalian pseudoautosomal region. *Hum Mol Genet* 7:489-499, 1998

DAVID W. EMERY, Ph.D.

Research Program:

Dr. Emery's general research interests focus on the field of hematopoietic stem cell gene therapy. This includes a broad interest in the mechanisms of gene regulation and the transplantation biology of hematopoietic stem cells. Past studies include the manipulation of transplantation immunity in mice and miniature swine using retrovirus vectors for major histocompatibility genes, and the enhancement of hematopoietic stem cell transplantation across xenogeneic barriers. Current studies have focussed on: 1) The systematic comparison of various nonhuman primates as pre-clinical large animal models for hematopoietic stem cell gene therapy research; 2) The development and testing of retrovirus vectors for human hemoglobin genes in transplanted mice; and 3) The investigation of chromatin insulators for minimizing negative position effects on retrovirus vector expression. Dr. Emery is also the Director of a clinical Gene and Cell Therapy Core Laboratory under construction at the University of Washington's General Clinical Research Center. This Core Laboratory will support ongoing and future clinical trials at the University of Washington Medical Center and affiliated hospitals which require the genetic modification and/or *ex vivo* manipulation of patient tissues under strict clinical standards.

Investigator: Dr. Emery is a Research Assistant Professor in the Department of Medicine (Medical Genetics).

Representative Publications:

Emery DW, Sablinski T, Shimada H, Germana S, Gianello P, Foley A, Shulman S, Arn S, Fishman J, Lorf T, Nিকেleit V, Colvin RB, Sachs DH, LeGuern C: Expression of an allogeneic MHC DRB transgene, through retroviral transduction of bone marrow, induces specific reduction of alloreactivity. *Transplantation* 64:1414-23, 1997

Emery DW, Shimada H, Germana S, Sachs DH, and LeGuern C: Transfer of porcine MHC DR α into IE α -deficient murine bone marrow results in reduced IE-restricted V β usage. *Transplantation* 66:1081-1088, 1998

Emery DW, Chen H, Li Q, and Stamatoyannopoulos G. 1998. Development of a condensed Locus Control Region cassette and testing in retrovirus vectors for Λ γ -globin. *Blood Cells Mol Dis* 24:322-339

Sablinski T, Emery DW, Monroy R, *et al.* Long-term discordant xenogeneic (porcine-to-primate) bone marrow engraftment in a monkey treated with porcine-specific growth factors. *Transplantation* 67:972-977

Emery DW, Morrish F, Li Q, Stamatoyannopoulos G: Development of an optimal Λ γ -globin expression cassette in retrovirus vectors. *Hum Gene Therapy* 10:877-888, 1999

Emery DW, and Stamatoyannopoulos G. Stem cell gene therapy for the β -chain hemoglobinopathies - problems and progress. *Ann New York Acad Sci* 872:94-107, 1999

Emery DW, Holley K, Sachs DH: Enhancement of swine progenitor chimerism in mixed swine/human bone marrow cultures with swine cytokines. *Exp Hematol* (in press)

STANLEY FIELDS, Ph.D.

Research Program:

Dr. Fields' laboratory uses the yeast *Saccharomyces cerevisiae* to investigate macromolecular interactions, both those between proteins and those between RNA and protein. Protein-protein interactions are analyzed with the yeast two-hybrid system which uses gene expression to detect the association of proteins fused to DNA-binding and transcriptional activation domains. One of their goals is to use this technique to develop a "protein linkage map" for yeast, which would be a description of all the protein-protein interactions that occur in this organism and that are detectable by this method. A related three hybrid method can be used as a simple genetic assay to study RNA-protein interactions, and another aim in the laboratory is to apply this method to understand the basis for some of the RNA-protein interactions that underlie RNA metabolism in yeast. In addition, these methodologies are being applied to analyze viral genomes and the proteins they encode. The laboratory is also interested in studying proteins in human disease using yeast-based assays.

Investigator: Dr. Fields is a Professor of Genetics and Medicine (Medical Genetics)

Representative Publications:

Fields S and Song O: A novel genetic system to detect protein-protein interactions. *Nature* 340:245-246, 1989

Fields S and Jang SK: Presence of a potent transcription activating sequence in the p53 protein. *Science* 249:1046-1048, 1990

Chien C-T, Bartel PL, Sternglanz R, and Fields S: The two-hybrid system: a method to identify and clone genes for proteins that interact with a protein of interest. *Proc Natl Acad Sci USA* 88:9578-9582, 1991

Yuan YO, Stroke IL, and Fields S: Coupling of cell identity to signal response in yeast: Interaction between the $\alpha 1$ and STE12 proteins. *Genes Dev* 7:1584-1597, 1993

Iwabuchi K, Bartel PL, Li B, Marraccino R and Fields S: Two cellular proteins that bind to wild type but not mutant p53. *Proc Natl Acad Sci USA* 91:6098-6102, 1994

Fields S and Sternglanz R: The two-hybrid system: an assay for protein-protein interactions. *Trends in Genetics* 10:286-292, 1994

Yang M, Wu Z, and Fields S: Protein-peptide interactions analyzed with the yeast two-hybrid system. *Nucleic Acids Res* 23:1152-1156, 1995

Bartel PL, Roecklein JA, SenGupta D, and Fields S: A protein linkage map of *Escherichia coli* bacteriophage T7. *Nature Gen* 12:72-77, 1996

SenGupta DJ, Zhang B, Kraemer B, Pochart P, Fields S, Wickens M: A three-hybrid system to detect RNA-protein interactions in vivo. *Proc Natl Acad Sci USA* 93:8496-8501, 1996

Fields S: The future is function. *Nature Genet* 15:325-327, 1997

Schwartz H, Alvares CP, White MB, Fields S: Mutation by a two-hybrid assay. *Hum Mol Genet* 7:1029-1032, 1998

CLEMENT E. FURLONG, Ph.D.

Research Program:

Dr. Furlong's laboratory is investigating the *function of the polymorphic, HDL-associated enzyme human serum paraoxonase (PON1)* in the detoxication of organophosphorus compounds. Insecticides such as parathion, chlorpyrifos and diazoxon are bioactivated to highly toxic oxon forms by the cytochrome P450 systems. The toxic oxons are potent inhibitors of acetylcholinesterase. These oxons are hydrolyzed by paraoxonase. Direct testing of paraoxonase's protective effects against organophosphate poisoning in a model system supports the role of PON1 in detoxication *in vivo*. PON1 exhibits a substrate-dependent polymorphism in human populations. At least two allelic forms of the enzyme have been observed. One isoform (PON1_{R192}) hydrolyzes paraoxon (the toxic metabolite of parathion) with a high turnover rate and the other (PON1_{Q192}) with a low turnover rate. The effect of the polymorphism is reversed for other organophosphorus compounds such as diazoxon, soman and sarin. In addition to hydrolyzing organophosphates, PON1 appears to play an important role in metabolizing oxidized lipids. A number of recent studies have reported that the R192 variant of this protein is a risk factor for coronary artery disease. Studies aimed at understanding the consequences of the PON1 polymorphism in human populations are underway. A second interest of Dr. Furlong is the *development of protein-based surface plasmon resonance biosensors* that have broad application in the fields of medicine, biotechnology and environmental monitoring. A third area of interest in the laboratory is the *development of bacterial-based protein producing bioreactors*.

Investigator: Dr. Furlong is a Research Professor of Medicine (Medical Genetics) and Genetics.

Representative Publications:

- Humbert R, Adler DA, Disteché CM, Hassett C, Omiecinski CJ, Furlong CE. 1993. The molecular basis of the human serum paraoxonase activity polymorphism. *Nature Genetics* 3:73-76.
- Li W-F, Costa LG, Furlong CE. Serum paraoxonase status: a major factor in determining resistance to organophosphates. 1993. *J. Toxicol. Environ. Health.* 40:337-346.
- Li, W-F, Furlong CE, Costa LG. 1995. Paraoxonase protects against chlorpyrifos toxicity in mice. *Toxicol. Lett* 76:219-226.
- Davies H, Richter RJ, Keifer M, Broomfield C, Sowalla J, Furlong CE. 1996. The effect of the human serum paraoxonase polymorphism is reversed with diazoxon, soman and sarin. *Nature Genetics* 14:334-336.
- Li, W-F, Costa LG, Furlong CE. 1997. Paraoxonase (*Pon1*) gene in mice: sequencing, chromosomal location, and developmental expression. *Pharmacogenet.* 7:137-144.
- Shih, DM, Gu L, Xia Y-R, Navab M, Li W-F, Hama S, Castellani LW, Furlong CE, Costa LG, Fogelman AM, Lusis AJ. 1998. Serum paraoxonase knockout mice are susceptible to organophosphate insecticides and lipoprotein oxidation. *Nature* 394:284-287.
- Woodbury RG, Wendin C, Clendenning J, Melendez J, Elkind J, Bartholomew D, Brown S, Furlong CE. 1998. Construction of surface plasmon resonance biosensors using a gold-binding polypeptide and a miniature integrated sensor. *Biosensors & Bioelectronics* 13:1117-1126.

STANLEY M. GARTLER, Ph.D.
And R. SCOTT HANSEN, Ph.D.

Research Program:

Dr. Gartler's laboratory has two main areas of activity: X-chromosome inactivation and autosomal imprinting. *X-chromosome inactivation*. In mammals the two X chromosomes in the female become equivalent to the single X chromosome in the male through the mechanism of X-chromosome inactivation, a form of dosage compensation. This system is critical for normal development and results in monallelic expression in females for X-linked loci subject to X-chromosome inactivation. These active and inactive alleles differ in chromatin configuration, DNA methylation, XIST expression, histone acetylation and replication timing. At present, the work is focused on replication timing differences. Dr. Gartler's lab has shown that the fragile X syndrome, which is characterized by an X-chromosome cytological aberration and mental retardation, exhibits delayed replication and hypermethylation. Further analysis has shown that the replication delay may extend millions of bases beyond the borders of the fragile X gene. How this very late zone of replication develops is one of the projects being pursued at present. In the course of this work Dr. Gartler's lab has determined the replication timing of genes near the border of late and early replicating bands. These genes appear to constitute a special group, in that their replication timing changes depending on the tissue under study. This finding may have considerable evolutionary significance and constitutes a major laboratory project. *Imprinting*. Monoallelic expression is also known in some autosomal genes, which is said to result from imprinting. That is, the expression of such genes is dependent on parent of origin. The alleles at an imprinted locus will differ in replication timing, as for alleles subject to X-inactivation. Using a method based on replication timing differences, a procedure to detect imprinted genes in the human genome has been developed. Development of a methylation screen to find imprinted genes is underway.

Investigator: Dr. Gartler is a Professor of Medicine (Medical Genetics) and Genetics. He is a member of the National Academy of Sciences. Dr. Hansen is a Research Assistant Professor of Medicine (Medical Genetics).

Representative Publications:

Hansen RS, Canfield TK, Lamb MM, Gartler SM, Laird CD: Association of fragile X syndrome with delayed replication of the FMR1 gene. *Cell* 73:1403-1409, 1993

Hansen RS, Canfield TK, Gartler SM: Unusual replication timing for the XIST gene in human fibroblasts. *Hum Mol Genet*: 4:813-820, 1995

Kawame H, Gartler SM, Hansen RS: Allele-specific replication timing in imprinted domains: Absence of asynchrony at several loci. *Hum Mol Genet* 4:2287-2293, 1995

Hansen RS, Canfield TK, Fjeld AD, Gartler SM: Role of late replication timing in the silencing of X-linked genes. *Hum Mol Genet* 5:1345-1353, 1996

Hansen RS, Canfield TK, Fjeld AD, Munn S, Laird CD, Gartler SM: A variable domain of delayed replication of FRAXA fragile X chromosomes: X inactivation-like spread of late replication. *Proc Natl Acad Sci USA* 94:4587-4592, 1997

Hansen RS, Canfield TK, Stanek AM, Keitges EA, Gartler SM: Reactivation of *XIST* in normal fibroblasts and a somatic cell hybrids: Abnormal localization of XIST RNA in hybrid cells. *Proc Natl Acad Sci USA* 95:5133-5138, 1998

Widrow RJ, Hansen RS, Kawame H, Gartler SM, Laird CD: Very late DNA replication in the human cell cycle. *Proc Natl Acad Sci USA* 95:11246-11250, 1998

LELAND H. HARTWELL, Ph.D.

Research Program:

Dr. Hartwell's research program uses yeast genetics to study the control of the cell cycle by checkpoints, control circuits that arrest progression of the cell cycle when chromosomal damage is present. Two checkpoints are being investigated, one that controls mitosis in response to DNA double strand breaks and another that controls DNA replication in the presence of DNA alkylation damage. The Hartwell lab studies *two aspects of yeast cell biology, the control of the cell cycle and the development of cell polarity*. 1) The cell cycle is controlled in response to DNA damage and other perturbations by controls discovered in the Hartwell Lab, called checkpoints. Checkpoints arrest progress through the cell cycle so that damage can be repaired before the cell continues on. Checkpoints are responsible for the high fidelity of mitotic chromosome replication and segregation providing surveillance at the G1 to S transition, during S phase, and at the G2 to M transition. Loss of the G1 checkpoint in human cells is an important element in the generation of cancer cells since this loss unleashes an instability of the genome permitting rapid tumor cell evolution. 2) During mating, yeast cells polarize toward one another in response to pheromone signals. The Hartwell lab is investigating the functions needed for a cell to reorient its polarity in response to an external signal. They have found that a pheromone receptor and trimeric G protein play important roles. How the receptor communicates with the cell's cytoskeleton to direct polarity is an issue of central concern. The Hartwell group has also discovered that a yeast cell has two mating pathways, one that is used when pheromone gradients can be detected and another that the cell uses when the pheromone concentration saturates the cell's detection system. Another issue of current study is how the cell switches from one behavior to another. In both of these areas yeast genetics is exploited to identify the components that function in the process under consideration and to determine the particular role that a gene product plays.

Investigator: Dr. Hartwell is President and Director of the Fred Hutchinson Cancer Research Center and Research Professor of Genetics at the University of Washington. He is also a member of the National Academy of Sciences.

Representative Publications:

Weinert TA, Hartwell LH: The *RAD9* gene controls the cell cycle response to DNA damage in *Saccharomyces cerevisiae*. *Science* 241: 317-322, 1988

Hartwell LH, Weinert T: Checkpoints: Controls that ensure the order of cell cycle events. *Science* 246: 629-634, 1989

Hartwell LH and Kastan MB: Cell cycle control and cancer. *Science* 266:1821-1828, 1994

Paulovich AG and Hartwell LH: A checkpoint regulates the rate of progression through S phase in *S. cerevisiae* in response to DNA damage. *Cell* 82:841-847, 1995

Toczyski DP, Galgoczy DJ, Hartwell LH: *CDC5* and *CKII* control adaptation to the yeast DNA damage checkpoint. *Cell* 90:1097-1106, 1997

Hartwell LH, Szankasi P, Roberts CJ, Murray AW, Friend SH: Integrating genetic approaches into the discovery of anticancer drugs. *Science* 278:1064-1068, 1997.

Paulovich AG, Armour CD, Hartwell LH: The *Saccharomyces cerevisiae* *RAD9*, *RAD17*, *RAD24* and *MEC3* genes are required for tolerating irreparable, ultraviolet-induced DNA damage. *Genetics* 150:75-93, 1998.

MARSHALL HORWITZ, M.D., Ph.D.

Research Program:

Dr. Horwitz's research interests are focused in two areas: 1) Inherited disorders of hematopoiesis. We are working to positionally clone genes responsible for autosomal dominant acute myelogenous leukemia (AML) and cyclic neutropenia. 2) Novel approaches to gene therapy. We are investigating non-viral mechanisms in which DNA is efficiently transfected and generalized strategies for negating gene activity at the protein level.

Investigator: Dr. Horwitz is an Associate Professor of Medicine (Medical Genetics) and Investigator in the Markey Molecular Medicine Center.

Representative Publications:

Horwitz M, Goode E, Jarvik GP: Anticipation in familial leukemia. *Am J Hum Genet* 59:990-998, 1996

Horwitz M: Hypermethylated myoblasts specifically deficient in MyoD autotransformation as a consequence of instability of MyoD. *Exp Cell Res* 226:170-182, 1996

Gogos J, Thompson R, Lowry W, Sloan BF, Weintraub H, Horwitz M: Gene trapping in differentiating cell lines: regulation of the lysosomal protease cathepsin B in skeletal myoblast growth and fusion. *J Cell Biol* 134:837-847, 1996

Li F-Q, Coonrod A, Horwitz M: Preferential MyoD homodimer formation demonstrated by a general method of dominant negative mutation employing fusion with a lysosomal protease. *J Cell Biol* 135:1043-1067, 1996

Horwitz M, Benson KF, Li F-Q, Wolff JW, Leppert MF, Hobson L, Mangelsdorf M, Yu S, Hewett D, Richards RI, Raskind WH: Genetic heterogeneity in familial acute myelogenous leukemia: Evidence for a second locus at chromosome 16q21-23.2. *American Journal Human Genetics*, 61: 873-881, 1997

Coonrod A, Li F-Q, Horwitz M: The mechanism of DNA transfection: Efficient gene transfer without viruses. *Gene Therapy* 4:1313-1321, 1997

GAIL JARVIK, M.D., Ph.D.

Research Program:

Dr. Jarvik's major interest is in the genetics of common disease. She is involved in a number of research projects which address *the inheritance of diseases of complex etiology*. These projects use statistical genetics methods such as linkage analysis, complex segregation analysis, and association and interaction tests, in large data-sets collected in collaboration with molecular biologists and epidemiologists. She is particularly interested in the analysis of risk factors for coronary artery disease, including lipid disorders. A major focus of research is the study of gene-by-gene interactions in the inheritance of familial combined hyperlipidemia and elevated levels of apolipoprotein B. That study is also directed at mapping an apolipoprotein B elevating locus. A second major project involves lipid and oxidative risk factors in a case-control study of carotid artery disease. Associations between lipid factors, the HDL-associated antioxidant enzyme paraoxonase activity and genotype, and susceptibility of LDL to oxidation are being evaluated. Changes in gene effects with age, Alzheimer Disease, and prostate cancer are also areas of study.

Investigator: Dr. Jarvik is an Associate Professor of Medicine (Medical Genetics), a member of the Markey Molecular Medicine Center and an Affiliate Member of the Fred Hutchinson Cancer Research Center.

Representative Publications:

Jarvik G, Austin M, Fabsitz R, Auwerx J, Reed T, Christian J, Deeb, S. Genetic influences on age-related change in total cholesterol, low density lipoprotein-cholesterol and triglyceride levels: Longitudinal apoE genotype effects. *Genetic Epidemiology* 11:375-384, 1994

Jarvik G, Brunzell J, Austin M, Krauss R, Motulsky A, Wijsman E. Genetic predictors of familial combined hyperlipidemia in four large pedigrees: influence of apolipoprotein B major locus predicted genotype and low density lipoprotein phenotype. *Arteriosclerosis and Thrombosis*, 14:1687-1694, 1994

Jarvik GP, Wijsman EM, Kukull WA, Schellenberg GD, Yu C, Larson EB. Interactions of apolipoprotein E genotype, total cholesterol level, age, and sex in the prediction of Alzheimer disease in a case-control study. *Neurology*, 45:1092-1096, 1995

Jarvik GP, Larson EB, Goddard K, Kukull WA, Schellenberg GD, Wijsman EM. Influence of apolipoprotein E genotype on the transmission of Alzheimer disease in a community-based sample. *American J Human Genetics* 58:191-200, 1996

Jarvik GP, Goode EL, Austin MA, Auwerx J, Deeb S, Schellenberg GD, Reed T. Evidence that the apolipoprotein E genotype effects on lipid levels can change with age in males: a longitudinal analysis. *Am J Human Genetics* 61:171-181, 1997

Jarvik GP. Genetic predictors of common disease: Apolipoprotein E genotype as a paradigm. *Annals of Epidemiology* 7:357-62, 1997

Graham J, Chapman NH, Goddard KAB, Goode EL, Wijsman EM, Jarvik GP. Segregation and linkage analysis of a quantitative versus a qualitative trait in large pedigrees. *Genetic Epidemiology* 14:999-1004, 1997

Gibbs M, Stanford JL, McIndoe RA, Jarvik GP, Kolb S, Goode EL, Chakrabarti L, Schuster EF, Buckley VA, Miller EL, Brandzel S, Li S, Hood L, Ostrander EA. Evidence for a Rare Prostate Cancer Susceptibility Locus at Chromosome 1p36. *Amer J Hum Genet* 64:776-787, 1999

Jarvik GP. Complex Segregation Analyses: Uses and Limitations. *Am J Hum Genet* 63: 942-946, 1998

MARY-CLAIRE KING, Ph.D.

Research Program:

Dr. King's group studies the genetics of complex, common human conditions. Their primary areas of interest are breast and ovarian cancer and inherited deafness. Their approach is to apply human genetics and genomics to identification and characterization of critical genes in informative families and populations. Because these conditions are not purely genetic, they also study the interaction between genetic and environmental influences on human traits. Dr. King's lab also applies genomic sequencing to the identification of victims of human rights abuses.

Investigator: Dr. King is a Professor of Medicine (Medical Genetics) and Genetics and an American Cancer Society professor.

Representative Publications:

Holt JT, Thompson ME, Szabo CI, Robinson-Benion C, Arteaga CL, King MC, Jensen RA:
Growth retardation and tumor inhibition by BRCA1. *Nature Genet* 12:298-302, 1996

Smith TM, Lee M, Szabo CI, Jerome N, McEuen M, Taylor M, Hood L, King MC: Complete
genomic sequence and analysis of 117 kb of human DNA containing the gene BRCA1.
Genome Res 6:1029-1049, 1996

King MC: Leaving Kansas...finding genes in 1997. (Editorial) *Nature Genet* 15:8-10, 1997

Schubert EL, Lee MK, Mefford HC, Argonza RH, Morrow JE, Hull J, Dann JL, King MC:
BRCA2 in American families with breast or ovarian cancer. *Amer J Human Genet* 60:
1031-1040, 1997

Czabo CI, King MC: Population genetics of BRCA1 and BRCA2. *Amer J Human Genet*
60:1013-1020, 1997

Lee MK, Lynch ED, King MC. SeqHelp: a program to analyze molecular sequences utilizing
common computational resources: *Genome Research*. 8:306-312, 1998

Newman B, Mu H, Butler LM, Millikan RC, Moorman PG, King MC: Frequency of breast
cancer attributable to BRCA1 in a population-based series of American women. *JAMA*
279:915-921, 1998

Mu H, King MC, Criswell LA: Relative predispositional effects and mode of inheritance of
HLA-DRB1 alleles among community-based Caucasian females with rheumatoid arthritis.
Genetic Epidemiol 15:123-134, 1998

Lynch ED, Ostermeyer EA, Lee MK, Arena JF, Ji H, Dann J, Swisshelm K, Suchard D,
MacLeod PM, Kvinnsland S, Gjertsen BT, Heimdal K, Lubs H, Moller P, King MC.
Inherited mutations in PTEN that are associated with breast cancer, Cowden disease, and
juvenile polyposis. *Am J Hum Genet* 61:1254-1260, 1997

Lynch ED, Lee MK, Morrow JE, Welsh PL, Leon PE, King MC. Nonsyndromic deafness
DFNA1 associated with mutation of a human homolog of the *Drosophila* gene *diaphanous*:
Science 278:1315-1318, 1997

ANDRÉ LIEBER, Ph.D.

Research Program:

The main objective of research in Dr. Lieber's laboratory is to modify adenoviruses for gene therapy. The work is currently focused on three main areas. 1) Oncolytic adenoviruses for the treatment of cervical carcinoma. Dr. Lieber has found that E1-deleted adenoviruses replicate specifically within HPV-associated cervical carcinoma cells but not within normal cells. This is the basis for an anti-tumor approach, which has potential application for other malignancies including those with deregulated pRb/p16 functions that also allow for replication of E1-deleted Ad vectors. Current emphasis is to establish a viral delivery and expression system with maximal tumor-specificity that can be applied systemically. Specifically, the lab is testing whether a unique Adeno-AAV-hybrid vector (Ad.AAV) can be used to activate gene expression from a tumor-specific promoter only upon viral DNA replication which, in turn, will occur selectively in tumor cells. This system is being used to express gene products that kill tumor cells selectively by viral cytolysis or p53-independent apoptosis. In this context, it was demonstrated that insulator elements shield heterologous promoters from non-specific transactivation by adenoviral enhancers. Other studies are being undertaken to facilitate viral dissemination throughout the tumor. 2) Integrating adeno-AAV hybrid vectors for sickle cell gene therapy. Dr. Lieber has developed a novel, integrating Δ Ad.AAV hybrid vector devoid of all viral genes that combines features of adenoviral vectors including high titer, high infectivity, and large capacity with the integration capability of AAV ITRs. This vector is able to accommodate large transgene expression cassettes and to stably transduce cells in vitro with a 100% efficiency without associated toxicity. Ongoing studies focus on the improvement of integration frequency of Δ Ad.AAV vectors and on the stimulation of site-specific integration by incorporating the AAV Rep function into hybrid vectors. 3) Adeno- or Adeno-AAV vectors with modified tropism. Dr. Lieber has developed a strategy to specifically retarget adenoviruses to any cell type of interest. This approach involves creating a library of adenoviruses displaying random peptides in their fiber knobs as ligands and screening this library for adenovirus variants with tropism to a particular cell type in vitro and potentially in vivo. There are two areas of application: One is to change the tropism of oncolytic vectors based on Ad5 so that they will infect only tumor cells but not the surrounding normal liver tissue after intraportal virus application or infusion into the hepatic artery; the other is to retarget Adeno-AAV vectors to cell types that are refractory to Ad5 infection, including CD34+ cells and lung epithelial cells.

Investigator: Dr. Lieber is Research Assistant Professor of Medicine (Medical Genetics).

Representative Publications:

- Lieber A, Sandig V, Bähring S, Sommer W, Strauss M: Stable high level expression in mammalian cells by T7 phage RNA polymerase. *Methods in Enzymology* 217:47-66, 1993
- Lieber A, Strauss M: Selection of efficient cleavage sites in target RNAs by using a ribozyme expression library. *Mol Cell Biol* 15:540-551, 1995
- Lieber A, Vrancken Peeters MJ, Meuse L, Fausto N, Perkins J, Kay M: Adenovirus-mediated urokinase gene transfer induces liver regeneration and allows for efficient retrovirus transduction of hepatocytes in vivo. *Proc Natl Acad Sci (USA)* 92, 6210-6214, 1995
- Lieber A, He C-Y, Polyak S, Gretsch D, Barr D, Kay MA: Elimination of hepatitis C viral RNA in infected hepatocytes by adenovirus-mediated expression of ribozymes. *J Virol* 70:8782-8791, 1996
- Lieber A, He C-Y, Kay MA: Adenoviral preterminal protein stabilizes mini-adenoviral genomes in vitro and in vivo. *Nature Biotech*, 15:1383-1387, 1997
- Lieber A, He C-Y, Meuse L, Himeda C, Wilson C, Kay MA: Inhibition of NF- κ B in combination with bcl-2 expression allows for persistence of first-generation adenovirus vectors in mouse liver. *J Virol* 92:9267-9277, 1998

ERIC D. LYNCH, Ph.D.

Research Program :

The focus of Dr. Lynch's research is to identify and characterize the genes involved in hearing loss. In 1997 his research efforts, in collaboration with Dr. Mary-Claire King at the University of Washington and Dr. Pedro Leon at the University of Costa Rica, led to the identification of a mutation in the Human Diaphanous 1 (HDIA1) gene, as being associated with hearing loss in DFNA1-linked individuals in a large Costa Rican family. Functional characterization of the HDIA1 gene and its protein product are a large part of the current work in his laboratory. Ongoing efforts include the development of a transgenic mouse with the pertinent human DFNA1 mutation in the HDIA1 mouse ortholog p140mDia, in an attempt to recapitulate the progressive hearing loss phenotype in a model organism. If this is successful, Dr. Lynch will have proven that the diaphanous gene is involved in hearing loss and will have a system to investigate further the role of diaphanous in hearing and for gene therapy studies. Concurrent to the development of the Knock-in mouse, Dr. Lynch is developing a p140mDia Knock-out mouse with the goal of further understanding the role of diaphanous, as a down stream effector of Rho in the regulation of actin filament formation during such basic cellular processes as cytokinesis.

Following the identification of the DFNA1 gene, a collaboration with Dr. Karen Avraham led to the mapping and cloning of the DFNA15 gene (POU4F3). The DFNA15 gene is a known transcription factor with expression limited to the hair cells of the inner ear, the retinal ganglion cells, and the dorsal root ganglion. Ongoing studies with this gene include the development of rapid screening assays for mutations in this gene in additional families. Using direct sequencing, Dr. Lynch is screening additional families for mutations in the DFNA15 gene. Dr. Lynch's goal is to characterize the degree to which POU4F3 plays a role in genetically influenced hearing loss in families with a clear genetic predisposition to hearing loss. This work is parallel to the analysis of the DFNA1 gene in families with sensory neural hearing loss of presumed genetic origin. Additionally, Dr. Lynch is developing cell lines with POU4F3 under inducible control for the analysis of cDNA arrays to identify genes whose expression is regulated by POU4F3.

Dr. Lynch continues to seek out and study additional families with hereditary hearing loss in the hopes of identifying additional deafness genes. A recent collaboration to map the gene for syndromic hearing loss in Perrault's syndrome has led to the identification of a candidate region of linkage. Perrault's syndrome involves sensory neural hearing loss in men and sensory neural hearing loss with ovarian dysgenesis in women. Dr. Lynch is currently seeking additional families with Perrault's syndrome in an attempt to confirm the map location and to further narrow the linked region with the goal of positionally cloning the responsible gene(s).

Investigator: Dr. Lynch is a Research Assistant Professor in the Division of Medical Genetics within the Department of Medicine, and an affiliate of the Virginia Merrill Bloedel Hearing Research Center at the University of Washington.

Representative Publications:

Lee MK, Lynch ED, King MC. SeqHelp: A procedure to analyze molecular sequences using common computational resources. *Genome Res*: 8:306-312, 1998

Vahava O, Morell R, Lynch ED, Weiss S, Kagan ME, Ahituv N, Morrow JE, Lee MK, Skvorak AB, Morton CC, Blumenfeld A, Frydman M, Friedman TB, King M-C, Avraham KB: Mutation in transcription factor POU4F3 causes inherited progressive hearing loss in humans. *Science*: 279:1950-1954, 1998

Lynch ED, Lee MK, Morrow JE, Welsh, PL, Leon PL, King M-C: Non-syndromic deafness DFNA1 associated with mutation of a human homolog of the Drosophila gene diaphanous. *Science*: 278:1315-1318, 1997

A. DUSTY MILLER, Ph.D.

Research Program:

Advances in molecular biology have made it feasible to cure genetic disease by transfer of corrective genes to somatic tissues of humans. Dr. Miller has focused on the use of viral vectors derived from retroviruses and parvoviruses (including adeno-associated virus) to develop efficient gene transfer systems, and has demonstrated gene transfer and expression in many somatic cell types in culture and in animals. Dr. Miller is currently using these vectors in gene transfer trials in humans, but much development work remains to make gene therapy an effective treatment. Other ongoing studies focus on the basic biology and properties of parvovirus vectors and their potential for use in gene therapy, and on retrovirus biology, including the nature of the receptors used for entry of retroviruses into cells and the evolution of the retrovirus envelope proteins that interact with these receptors.

Investigator: Dr. Miller is a Member of the Division of Basic Sciences and the Program in Molecular Medicine of the Fred Hutchinson Cancer Research Center. He is an Affiliate Professor of Pathology at the University of Washington.

Representative Publications:

Blaese RM, Culver KW, Miller AD, Carter CS, Fleisher T, Clerici M, Shearer G, Chang L, Chiang Y, Tolstoshev P, et al.: T lymphocyte-directed gene therapy for ADA- SCID; initial trial results after 4 years. *Science* 270:475-480, 1995

Miller AD: Cell-surface receptors for retroviruses and implications for gene transfer. *Proc Natl Acad Sci USA* 93:11407-11413, 1996

Koeberl DD, Alexander IE, Halbert CL, Russell DW, Miller AD: Persistent expression of human clotting factor IX from mouse liver after intravenous injection of AAV vectors. *Proc Natl Acad Sci USA* 94:1426-1431, 1997

Kiem HP, Andrews RG, Morris J, Peterson L, Heyward S, Allen JM, Rasko JEJ, Potter J, Miller AD: Improved gene transfer into baboon marrow repopulating cells using recombinant human fibronectin fragment CH-296 in combination with interleukin-6, stem cell factor, FLT-3 ligand, and megakaryocyte growth and development factor. *Blood* 92:1878-1886, 1998

Halbert CL, Standaert TA, Wilson CB, Miller AD: Successful readministration of adeno-associated virus vectors to the mouse lung requires transient immunosuppression during the initial exposure. *J Virol* 72:9795-9805, 1998

Wolgamot G, Bonham L, Miller AD: Sequence analysis of *Mus dunni* endogenous virus reveals a hybrid VL30/gibbon ape leukemia virus-like structure and a distinct envelope. *J Virol* 72:7459-7466, 1998

Rasko JEJ, Battini JL, Gottschalk RJ, Mazo I, Miller AD: The RD114/simian type D retrovirus receptor is a neutral amino acid transporter. *Proc Natl Acad Sci USA* 96:2129-2134, 1999

ARNO G. MOTULSKY, M.D., D.Sci.

Research Program:

The principal theme of the work of Dr. Motulsky is the *role of heredity-environment interactions in the pathogenesis of disease*. Dr. Motulsky introduced the concept of genetically determined drug reactions (pharmacogenetics) and worked extensively on several pharmacogenetic traits. Current emphasis in Dr. Motulsky's laboratory deals with the extension of pharmacogenetics to other environmental agents (ecogenetics) in conjunction with a new UW center on ecogenetics. Previous studies on the frequency and genetics of hyperlipidemia in populations of patients with coronary heart disease led to the definition of the role of various genetic hyperlipidemias in coronary heart disease. Dr. Motulsky's current work in this field focuses on the study of lipid-related genes and is being carried out at the cellular, molecular and population levels. Recent work deals with the genetics of homocysteine elevations as a risk factor in arteriosclerotic vascular disease. Another aspect of Dr. Motulsky's work is on the molecular genetics of color vision genes. Much heterogeneity was found in the molecular make-up of color vision pigment genes in individuals with normal and with defective color vision. The psychophysical perception of color is correlated with molecular gene arrangement in collaboration with psychologists.

Investigator: Dr. Motulsky is a Professor (Emeritus-active) of Medicine (Medical Genetics) and Genetics. Dr. Motulsky is a member of the National Academy of Sciences.

Representative Publications:

Winderickx J, Lindsey DT, Sanocki E, Teller DY, Motulsky AG, Deeb SS: A Ser/Ala polymorphism in the red photopigment underlies variation in colour matching among colour-normal individuals. *Nature* 356: 431-433, 1992.

Deeb SS, Linsey DT, Hibiya Y, Sanocki E, Winderickx J, Teller DY, Motulsky AG: Genotype-phenotype relationships in human red/green color vision defects: Molecular and psychophysical studies. *Am J Hum Genet* 51:687-700, 1992.

Motulsky AG, Brunzell JD: The genetics of coronary atherosclerosis, in: *Genetic Basis of Common Diseases*, edited by RA King, JI Rottner, AG Motulsky. Chap 9, pp 150-169. Oxford University Press, 1992.

Motulsky AG, Deeb SS: Color vision and its genetic defects, in *The Metabolic and Molecular Bases of Inherited Disease*, 7th edition, edited by CR Scriver, AL Beaudet, WS Sly, D Valle, Chapter 143. New York, McGraw Hill, 1995

Motulsky AG: Nutritional ecogenetics: homocysteine-related arteriosclerotic vascular disease, neural tube defects, and folic acid. *Am J Hum Gen* (invited editorial). 58:17-20, 1996.

Yamaguchi T, Motulsky AG, Deeb SS: Visual pigment gene structure and expression in human retinae. *Hum Mol Genet* 6:981-990, 1997

Boushey SS, Beresford SAA, Omenn GS, Motulsky AG: A Meta-Analysis of Plasma Homocysteine as a Risk Factor for Arteriosclerotic Vascular Disease and the Potential Preventive Role of Folic Acid. *Proceedings from the International Conference on Homocysteine Metabolism*. Co. Claire, Ireland, July 26, 1995. Kluwer Academic Publishers. 1997.

Omenn GS, Beresford SAA, Motulsky AG: Preventing Coronary Heart Disease, B Vitamins and Homocysteine. *Circulation*, 97:421-424, 1998.

Hill AVS, Motulsky AG: Genetic Variation and Human Disease: The Role of Natural Selection. In, *Evolution in Health and Disease*, S. C. Stearns, editor, Chapter 5. New York, Oxford University Press, 1999, pp. 50-61.

MAYNARD OLSON, Ph.D.

Research Program:

Dr. Olson's research emphasizes large-scale genome analysis. He is Director of the Human Genome Center at the University of Washington, which has implemented an integrated approach to mapping and sequencing multi-megabase-pair, contiguous tracts of human DNA. This approach includes acquisition of redundant cloned coverage of the DNA, validation of the integrity of the clones, definition of a minimum-tiling path across the sequencing target, sequencing of individual clones by a random-sampling method, assembly of finished sequence, quality assessment, and biological annotation. In addition to this focus on the development of an efficient, generic approach to large-scale genomic sequencing, Dr. Olson is involved in studies of the phenotypic effects of natural, intra-species variation in DNA sequence. This research involves both human genes and model-organism studies in the yeast *Saccharomyces cerevisiae*. The emphasis is on understanding the role of variation amongst alleles that occur at high frequencies in natural populations.

Investigator: Dr. Olson is a Professor of Medicine (Medical Genetics) and Genetics at the University of Washington. He is a member of the National Academy of Sciences.

Representative Publications:

Olson MV: The human genome project. *Proc Natl Acad Sci USA* 90:4338-4344, 1993

Gnirke A, Iadonato SP, Kwok P-Y, Olson MW: Physical calibration of yeast-artificial-chromosome based genome maps by RecA-assisted restriction endonuclease (RARE) cleavage. *Genomics* 24:199-210, 1994

Olson MV: A time to sequence. *Science* 270:394-396, 1995

Gillett W, Hanks L, Wong G, Yu J, Lim R, Olson MV: Assembly of high-resolution restriction maps based on multiple complete digests of a redundant set of overlapping clones. *Genomics* 33:389-408, 1996

Wong GK-S, Yu J, Thayer EC, Olson MV: Multiple-complete-digest (MCD) restriction-fragment mapping: generating sequence-ready maps for large-scale DNA sequencing. *Proc Natl Acad Sci USA* 94:5225-5230, 1997

Thayer EC, Olson MV, and Karp RM: Error checking and graphical representation of multiple-complete-digest (MCD) restriction-fragment maps. *Genome Res* 9:79-90, 1999

Olson MV: When less is more: gene loss as an engine of evolutionary change. *Am J Hum Genet* 64:18-23, 1999

ROBERTA A. PAGON, M.D.

Research Program:

The research interests of Dr. Pagon focus on the nosology and delineation of genetic disorders and syndromes, and the development of electronic clinical genetics information resources. Her clinical research is made possible through an extensive clinical program involving in-patient and out-patient consultations at Children's Hospital and Regional Medical Center, the major tertiary-level pediatric hospital in the WWAMI (Washington-Wyoming-Alaska-Montana-Idaho) region, and a network of regional genetics clinics in Washington State. *Genetic eye diseases* and the diagnosis and management of children with *ambiguous genitalia* are special research interests. Dr. Pagon is interested in the *information needs of medical geneticists and genetic counselors* created by the discoveries of the Human Genome Project. She has developed Helix: Genetic Testing Resource, a database of genetic testing laboratories funded by the National Library of Medicine (NIH) and the Maternal Child Health Bureau (HSRA), that serves as the "yellow pages" for genetics laboratories (www.genetests.org). With funding from the National Library of Medicine and the National Human Genome Research Institute, she is developing GeneClinics, an electronic expert-authored information resource that relates genetic testing information to the diagnosis, management and risk assessment of patients and families with inherited disorders (www.geneclinics.org).

Investigator:

Dr. Pagon is Professor of Pediatrics and Adjunct Professor of Ophthalmology and Medicine (Medical Genetics). She is a consultant to the Regional Genetics Program of Washington State and an attending physician in the Children's Hospital and Regional Medical Center Genetics Clinic. She is a member of the Board of Directors of The American Board of Medical Genetics (ABMG) and a member of the clinical practice committee of The American College of Medical Genetics (ACMG).

Representative Publications:

Pagon RA, Graham JM, Zonona J, Yong SL: Coloboma, congenital heart disease and choanal atresia with multiple anomalies: CHARGE association. *J Pediatr* 99:223-227, 1981

Pagon RA: Retinitis pigmentosa: a review. *Surv Ophthalmol* 33:137-177, 1988

Dobyns WB, Pagon RA, Armstrong D, Curry CJR, Greenberg F, Grix A, Holmes LB, Laxova R, Michels VV, Robinow M, Zimmerman RL: Diagnostic criteria for Walker-Warburg Syndrome. *Am J Med Genet* 32:195-210, 1989

Leppig KA, Pagon RA: Phenotypic correlations of ocular coloboma with known cause. *Clin Dysmorphol* 2:322-331, 1992

Marymee K, Dolan CR, Pagon RA, Bennett RL, Coe S, Fisher NL: Development of the Critical Elements of Genetic Evaluation and Genetic Counseling for Genetic Professionals and Perinatologists in Washington State. *J Genet Counseling* 7: 133-165, 1998

Kawame H, Hannibal M, Pagon RA: Phenotypic spectrum and management issues in Kabuki syndrome. *J Pediatr* 134:480-485, 1999

Pagon RA: Genetic Diagnosis and Counseling in Scientific American Medicine. Eds. D.C. Dale and D.D. Federman, Chapter 9:VIII:1-9, 1999. Scientific American, Inc.: New York.

RICHARD D. PALMITER, Ph.D.

Research Program:

Dr. Palmiter's group has two research interests. One area involves the *role of catecholamines in the development and function of the mammalian nervous system*. By inactivating the dopamine β -hydroxylase (DBH) gene, mice were created that cannot synthesize norepinephrine or epinephrine. They die, apparently due to cardiovascular failure, between day 11 and 13 of gestation. However, they can be rescued to birth by providing the mothers with β -agonists or dihydroxyphenylserine, a norepinephrine precursor. After birth they do remarkably well as long as they are not stressed. The Palmiter lab is in the process of studying their physiological, metabolic and behavior deficits. The Palmiter lab has also made mice in which the dopaminergic neurons cannot make dopamine, but norepinephrine-producing neurons are normal, by inactivating the tyrosine hydroxylase (TH) gene and then restoring TH function in noradrenergic cells. These mice are born at normal frequency and begin to suckle and grow normally but after about 2 weeks they become hypoactive and stop feeding. They can be rescued to adulthood by daily administration of L-dopa, the product of the TH gene. The effect of dopamine deficiency on locomotion was expected; however, the profound effect on feeding behavior was not anticipated. These mice will provide ideal recipients of various gene therapy approaches. One approach will be to introduce the TH gene into specific neurons to determine which neurons control feeding and locomotor behaviors, the other involves systemic production of L-dopa to determine whether all the deficits can be reversed by chronic supply of L-dopa. Another project that is just beginning involves the role of neuropeptide Y, which is coexpressed with catecholamines in the sympathetic nervous system, in various physiological processes. The other research interest involves *the analysis of zinc homeostasis in mice and cultured cells*. Transporters involved in the influx and efflux of zinc from cells are being cloned and characterized. Other members of this family are involved in transport of zinc into intracellular vesicles. For example, zinc is stored in synaptic vesicles of certain neurons and may function as a neuromodulator. A central question relates to the molecular mechanism by which cells "sense" the concentration of intracellular zinc and regulate its abundance. One aspect of this regulation involves the transcriptional control of genes including the metallothionein genes. Various metallothionein genes have been disrupted by gene targeting as a means of discerning the function of these ubiquitous metal-binding proteins.

Investigator: Dr. Palmiter is a Professor of Biochemistry and Investigator of the Howard Hughes Medical Institute. He is also a member of the National Academy of Sciences.

Representative Publications:

Kelly EJ, Palmiter RD: A Murine Model of Menkes Disease Reveals a Physiological Function of Metallothionein. *Nature Genet* 13:219-222, 1996

Erickson JC, Clegg KE, Palmiter RD: Sensitivity to Leptin and Susceptibility to Seizures of Mice Lacking Neuropeptide Y. *Nature* 381:415-418, 1996

Palmiter RD, Cole TB, Quiafe CJ, Findley SD: ZnT-3, a Putative Transporter of Zinc into Synaptic Vesicles. *Proc Natl Acad Sci USA* 93:14934-14939, 1996

Thomas SA, Palmiter RD: Thermoregulatory and Metabolic Phenotypes of Mice Lacking Noradrenaline and Adrenaline. *Nature* 387:94-97, 1997

Thomas TA, Palmiter RD: Impaired Maternal Behavior in Mice Lacking Norepinephrine and Epinephrine. *Cell* 91:583-592, 1997

Marsh DJ, Hollopeter G, Kafer KE, Palmiter RD: Role of the Y5 Neuropeptide Y Receptor in Feeding and Obesity. *Nature Med.* 4:718-721, 1998

Palmiter RD: Perspective: The Elusive Function of Metallothioneins. *Proc Natl Acad Sci USA* 95:8428-8430, 1998

WENDY H. RASKIND, M.D. Ph.D.

Research Program:

The focus of Dr. Raskind's research is the study of neurobehavioral disorders, both single gene and complex in etiology. She is Co-Principal Investigator for an NIH-funded multidisciplinary learning disabilities center involving faculty from the College of Education and several departments in the School of Medicine. Multigenerational families are being studied to characterize, model and map genetic subtypes of dyslexia. To unravel the genetic contributions to this complex disorder, the quantitative measures used in the clinical assessment of reading disabled children are studied individually and in combination. These include measures of executive function as well as reading and related processes. Parametric and nonparametric genetic modeling and linkage analyses are employed. The laboratory also engages in mapping and positional cloning of genes responsible for Mendelian neurologic diseases, including cerebellar ataxias, spastic paraparesis, myokymia, choreas and episodic disorders. They have identified a mutated protein kinase as the cause of SCA14 and plan functional studies as well as creation of a mouse model.

Investigator: Dr. Raskind is Professor of Medicine (Medical Genetics), Professor of Psychiatry and Behavioral Sciences (Joint with Medicine), Adjunct Professor of Genome Sciences and Adjunct Professor of Orthopaedics.

Representative Publications:

Fernandez, M, Raskind W, Wolff J, Matsushita M, Yuen E, Graf W, Lipe H, Bird T: Familial dyskinesia and facial myokymia (FDFM): A novel movement disorder. *Ann Neurol* 49:486-492, 2001.

Raskind WH, Hsu L, Berninger VW, Thomson JB, Wijsman EM: Familial aggregation of phenotypic subtypes in dyslexia. *Behavior Genetics* 30:385-399, 2000.

Yu C, Niakan KK, Matsushita M, Stamatoyannopoulos G, Orkin SH, and Raskind WH: X-linked thrombocytopenia with thalassemia due to a mutation in the amino-finger of GATA-1 affecting DNA-binding rather than FOG-1 interaction. *Blood* 100: 2040-2045, 2002.

Hsu L, Berninger VW, Thomson JB, Wijsman EM, Raskind WH. Familial aggregation of dyslexia phenotypes: paired correlated measures. *Am J Med Genet (Neuropsych Genet)* 114:471-478, 2002.

Chen D-H, Brkanac Z, Verlinde CLMJ, Tan X-J, Bylenok L, Nochlin D, Matsushita M, Lipe H, Wolff J, Fernandez M, Cimino PJ, Bird TD, Raskind WH. Missense mutations in the regulatory domain of PKC γ : a new mechanism for dominant nonepisodic cerebellar ataxia. *Am J Hum Genet* 72:839-849, 2003.

DAVID W. RUSSELL, M.D., Ph.D.

Research Program:

Dr. Russell's research program focuses on the development of improved methods for transducing mammalian cells with viral vectors. The technologies being developed will find applications in somatic cell genetics, the engineering of mutant animals, and gene therapy. Transduction by adeno-associated virus (AAV) vectors is an active area of investigation, including the cloning of new AAV serotypes and the development of vectors based on them, designing improved methods for vector production, testing of vectors in pre-clinical animal disease models, and studies on the molecular mechanisms of AAV-mediated transduction. A major focus of the lab at present is the development of homologous gene targeting strategies based on AAV vectors, with the ultimate goal of therapeutic gene correction.

Vectors based on foamy viruses (an alternative retroviral vector system) are also under investigation. Foamy virus vectors offer many possible advantages, including improved transduction of non-dividing cells, wide host range, and large packaging capacity. In addition to studies on the basic biology of foamy viruses, the potential of foamy virus vectors for gene therapy applications is being explored, including the development of improved vector production methods, and the testing of vectors in pre-clinical animal models. Recent findings from the laboratory have shown that foamy virus vectors can efficiently transduce hematopoietic stem cells in *ex vivo* strategies, and also other cell types after *in vivo* administration.

Investigator: Dr. Russell is an Assistant Professor in the Department of Medicine (Hematology) and an Investigator of the Markey Molecular Medicine Center.

Representative Publications:

Russell DW, Miller AD, Alexander IE: Adeno-associated virus vectors preferentially transduce cells in S phase. *Proc Natl Acad Sci USA* 91:8915-8919, 1994

Russell DW, Berger MS, Miller AD: The effects of human serum and cerebrospinal fluid on retroviral vectors and packaging cell lines. *Hum Gene Ther* 6:635-641, 1995

Russell DW, Alexander IE, Miller, AD: DNA synthesis and topoisomerase inhibitors increase transduction by adeno-associated virus vectors. *Proc Natl Acad Sci USA* 92:5719-5723, 1995

Russell DW, Miller AD: Foamy virus vectors. *J Virol* 70:217-222, 1996

Hirata RK, Miller AD, Andrews RG, Russell DW: Transduction of hematopoietic cells by foamy virus vectors. *Blood* 88:3654-3661, 1996

Rutledge EA, Russell DW: Adeno-associated virus vector integration junctions. *J Virol* 71:8429-8436, 1997

Rutledge EA, Halbert CL, Russell DW: Infectious clones and vectors derived from adeno-associated virus (AAV) serotypes other than AAV Type 2. *J Virol* 72:309-319, 1998

Russell DW, Hirata RK: Human gene targeting by viral vectors. *Nat Genet* 18:25-330, 1998

Inoue N, Russell DW: Packaging cells based on inducible gene amplification for the production of adeno-associated virus vectors. *J Virol* 72:7024-7031, 1998

Trobridge GD, Russell DW: Helper-free foamy virus vectors. *Hum Gene Ther* 9:2517-2525, 1998

Gerard D. Schellenberg

Research Program:

Dr. Schellenberg's research program focuses on neurodegenerative diseases and behavioral disorders. The neurodegenerative diseases he is studying include Alzheimer's disease, frontotemporal dementia, progressive supranuclear palsy and related tauopathies, and amyotrophic lateral sclerosis/parkinsonism dementia complex (ALS/PDC) of Guam. He is using linkage and disequilibrium analysis to identify genetic loci for late-onset Alzheimer's disease and ALS/PDC. Recently his laboratory identified tau as the gene responsible for inherited forms of frontotemporal dementia. Dr. Schellenberg's laboratory is now determining how these mutations affect tau gene regulation and the biochemical function of the tau protein, and how different mutations lead to different disease phenotypes. Work is now in progress to identify the *cis* and *trans*-acting factors that regulate the tau gene.

Dr. Schellenberg's group is also using linkage analysis to identify the genes responsible for two behavioral disorders, autism and schizophrenia. The autism project is identifying families with two or more affected subjects with autism. For each family, in addition to the affected siblings, the parents and unaffected siblings are being evaluated by an extensive battery of neuropsychological tests. The results will be used for quantitative trait analysis to identify autism genes. Linkage analysis is also being used to identify schizophrenia genes.

Investigator:

Dr. Schellenberg is a Research Professor in the Division of Gerontology and Geriatric Medicine, Department of Medicine and is an adjunct Professor in the Departments of Pharmacology and Neurology.

Representative Publications:

- Levy-Lahad E, Wijsman EM, Nemens E, Anderson L, Goddard KAB, Weber JL, Bird TD, Schellenberg GD: A familial Alzheimer's disease locus on chromosome 1. *Science* 269:970-973, 1995
- Levy-Lahad E, Wasco W, Poorkaj P, Romano DM, Oshima J, Pettingell WH, Yu C, Jondro PD, Schmidt SD, Wang K, Crowley AC, Fu Y-H, Guenette SY, Galas D, Nemens E, Wijsman EM, Bird TD, Schellenberg GD, Tanzi RE: Candidate gene for chromosome 1 familial Alzheimer's disease locus. *Science* 269:973-977, 1995
- Yu C-E, Oshima J, Fu Y-H, Hisima F, Wijsman EM, Martin GM, Mulligan J, Schellenberg GD: Positional cloning of the Werner's Syndrome Gene. *Science* 272:258-262, 1996
- Bird TD, Levy-Lahad E, Poorkaj P, Sharma V, Nemens E, Lampe T, Schellenberg GD: Wide range in age of onset for chromosome 1-related familial Alzheimer's disease. *Ann Neurol* 40:932-936, 1996
- Yu CE, Oshima J, Wijsman EM, Nkura J, Miki T, Puissan C, Matthews S, Fu YH, Mulligan J, Martin GM, Schellenberg GD: The Werner's Syndrome Collaborative Group. Mutation in the Consensus domains of the Werner's syndrome gene. *Am J Hum Genet* 60:330-341, 1997
- Poorkaj P, Bird TD, Wijsman EM, Nemens E, Garruto RM, Anderson L, Andreadis A, Wiederholt WC, Raskind M, Schellenberg GD: Tau is a Candidate Gene for Chromosome 17 Frontotemporal Dementia. *Ann Neurol* 43:815-825, 1998
- Hong M, Zhukareva V, Vogelsberg-Ragaglia V, Wszolek Z, Reed L, Geschwind DH, Bird TD, McKeel D, Morris JC, Wilhelmsen KC, Schellenberg GD, Trojanowski JQ, Lee VM-Y: Mutation-specific functional impairments in distinct tau isoforms of hereditary frontotemporal dementia and Parkinsonism linked to chromosome 17: Genotype predicts phenotype. *Science* 282:1914-1917, 1998

C. RONALD SCOTT, M.D.

Research Program:

Laboratory research interest has recently focused on the *mutational events that are responsible for the X-linked disorder, hemophilia B*. In collaboration with Drs. Hans Chen and Arthur Thompson, the molecular defects involving the factor IX gene have been shown to involve deletions, insertions and single base pair changes. The specific mutations are usually unique for each family and can be used for carrier detection and prenatal diagnosis. The mutations that affect the factor IX locus are being used as a model to address questions of mutation rate in male and female gametes and mechanisms of recombination for X-linked genes. Dr. Scott is a clinical biochemical geneticist and investigates *the molecular basis of human metabolic disorders*. He supervises a clinic committed to the diagnosis and management of children affected with inborn errors of metabolism, and is responsible for the supervision of a laboratory devoted to the accurate analysis of biological specimens submitted for the chemical or molecular detection of genetic disease. Diagnostic techniques in biochemical genetics using gas chromatography/mass spectroscopy, high pressure liquid chromatography, and enzyme analyses are available for training of post doctoral fellows. A molecular diagnostic laboratory focusing on common disorders affecting children (fragile-X, muscular dystrophy, cystic fibrosis, Prader-Willi/Angelman) is also available for training. In collaboration with investigators at the Fred Hutchinson Cancer Research Center, a clinical trial has been initiated on the efficacy of gene therapy for patients with Gaucher disease. This program uses isolated bone marrow stem cells that have been transfected with retroviral vectors containing the normal β -glucocerebrosidase gene.

Investigator: Dr. Scott is a Professor of Pediatrics, and an Associate of the Center on Human Development and Disability.

Representative Publications:

Torrioni A, Chen Y-S, Semino O, Santachiara-Beneceretti AS, Scott CR, Lott ML, Winter M, Wallace DC: mtDNA and Y-chromosome polymorphisms in four Native American populations from Southern Mexico. *Am J Hum Genet* 54:303-318, 1994

Wildin RS, Antush MJ, Bennett RL, Schoof JM, Scott CR. Heterogeneous AVPR2 Gene Mutations in Congenital Nephrogenic Diabetes Insipidus. *Am J Hum Genet* 55:266-277, 1994

Herrinton LJ, Weiss NS, Beresford SAA, Stanford JL, Wolfla DM, Feng Z, Scott CR: Lactose and galactose intake and metabolism in relation to the risk of epithelial ovarian cancer. *J Epidemiol*, 141:407-416, 1995

McKinnis EJR, Sulzbacher S, Rutledge JC, Sanders J, Scott CR: Bone marrow transplantations in Hunter Syndrome. *J Pediat* 129:145-148, 1996

Chen S-H, Schoof RM, Buroker NE, Scott CR: The identification of a (CGG) AGG insertion within the CGG repeat of the FMR1 gene in Asians. *Hum Genet* 99:793-795, 1997

Cederbaum SD, Scott CR, Wilcox WR: Amino acid metabolism. In, *Principles and Practice of Human Genetics*, Third ed, Rimoin DL, Connor JM, Pyeritz RE (Eds), pp 1867-1895, 1996

PHILLIPPE SORIANO, Ph.D.

Research Program:

Research in this laboratory is centered on the genetic analysis of mouse development, with a particular emphasis on genes implicated in growth factor signaling pathways. To identify such genes, we have produced a large number of developmental mutants using gene traps in embryonic stem (ES) cells. In this approach, a promoterless reporter gene encoding β galactosidase activity is introduced in ES cells. Selection for expression of the gene requires transcription from a cellular promoter, and consequently a mutation in a cellular gene, and the activity of the tagged gene can be followed by staining for β galactosidase activity. About 40% of the mutations derived by this approach result in embryonic lethality at different stages of development. Dr. Soriano has adapted this method to derive mutations in genes induced or repressed by a variety of growth factors or retinoids, and thus hope to identify genes in specific signal transduction pathways which play critical roles in embryonic development.

Genes playing roles in growth responses might be subject not only to transcriptional control, but also encode proteins which may be regulated by phosphorylation. One such gene, Hrs, has been implicated in growth factor receptor internalization. Hrs deficient embryos fail to undergo ventral fusion morphogenesis during development, leading to a defect in the fusion of the heart primordia and cardia bifida. Dr. Soriano has also examined the role of growth factors in development by generating targeted mutations in the genes encoding both receptors for platelet-derived-growth-factors (PDGF), a small family of growth factors involved in proliferation, survival, migration and chemotaxis of a number of mesenchymal cell types. During embryonic development, PDGFs appear to play important roles in all muscle cell types, as well as in the formation of the skeleton. We are presently examining the role of these factors along with that of members of the fibroblast growth factor (FGF) family in regulating chondrogenesis and muscle development downstream of the myogenic regulatory transcription factor Myf5. We are also engineering mice carrying small mutations in the PDGF receptor genes that prevent various effectors from docking to the receptors, to try to unravel the role of various signal transduction pathways in a physiological context.

Investigator: Dr. Soriano is a Member in the Division of Basic Sciences, Fred Hutchinson Cancer Research Center.

Representative Publications:

Chen Z, Friedrich G A, Soriano P: Transcriptional Enhancer Factor-1 disruption by a retroviral gene trap leads to heart defects and embryonic lethality in mice. *Genes Dev* 8:2293-2301, 1994

Lowell CA, Soriano P: Knockouts of Src-family kinases: stiff bones, wimpy T cells, and bad memories. *Genes Dev* 10:1845-1857, 1996

Gertler FB, Niebuhr K, Reinhard M, Wehland J, Soriano P: Mena, a relative of Vasp and Drosophila Enabled, is implicated in the control of microfilament dynamics. *Cell* 87:227-239, 1996

Zambrowicz BP, Imamoto A, Fiering S, Herzenberg LA, Kerr WG, Soriano P: Disruption of overlapping transcripts in the ROSA β geo 26 gene trap strain leads to widespread expression of β galactosidase in mouse embryos and hematopoietic cells. *Proc Natl Acad Sci USA* 94:3789-3794, 1997

Friedrich GA, Hildebrand JD, Soriano P: The secretory protein Sec8 is required for paraxial mesoderm formation in the mouse. *Dev Biol* 192:364-374, 1997

Crosby JR, Seifert RA, Soriano P, Bowen-Pope DF: Chimaeric analysis reveals role of Pdgf receptors in all muscle lineages. *Nature Genet* 18:385-388, 1998

GEORGE STAMATOYANNOPOULOS, M.D., Dr.Sci.

Research Program:

Dr. Stamatoyannopoulos's lab works on three areas: 1) *The control of human globin genes during development and differentiation.* The lab has defined two molecular mechanisms of switching, gene silencing and competition among globin genes for interaction with a powerful upstream regulatory element, the locus control region. Concerning the *cis* control of switching current studies focus on the analysis of sequences involved in silencing; the delineation of the mechanism of LCR/gene interactions; and the identification of sequences involved in the developmental clock of globin gene switching. We have obtained evidence that the trans control of globin gene switching is combinatorial and involves interactions between specific *cis* elements and ubiquitous as well as erythroid specific transcriptional factors. Current emphasis is on the cloning of developmental stage-specific trans acting factors and the production of *in vivo* binary systems which will allow analysis of the combinatorial control. Experimental systems used include transgenic mice, genetic knockouts and YAC transfers into mammalian cells. 2) *The development of treatments for sickle cell disease through pharmacologic induction of fetal hemoglobin.* The laboratory has a long-standing interest in this field. The currently used cytotoxic drug treatment for induction of fetal hemoglobin in sickle cell disease is based on investigations carried out in this lab. Current emphasis is on the delineation of the mechanism of fetal hemoglobin induction by short chain fatty acids. 3) *the development of somatic gene therapy for β chain hemoglobinopathies.* Sickle cell disease and β thalassemia will be cured if normal globin genes could be efficiently transferred into the patient's hemopoietic stem cells. The lab focuses on two aspects related to therapeutic viral vectors: a) The identification of chromatin insulators which could seal the therapeutic genes from the effects of the site of integration; b) the development of new systems of dominant selectable genes which could be used for *in vivo* selection of stem cells transduced with therapeutic genes.

Investigator: Dr. Stamatoyannopoulos is a Professor of Medicine (Medical Genetics) and Genetics and Adjunct Professor of Pathology. He is the head of the Division of Medical Genetics, and Director of the Markey Molecular Medicine Center.

Representative Publications:

Peterson, K.R., Li, Q., Clegg, C.H., Furukawa, T., Navas, P.A., Norton, E.J., Kimbrough, T.G., Stamatoyannopoulos G: Use of YACs in studies of development: Production of β -globin locus YAC mice carrying human globin developmental mutants. *Proc Natl Acad Sci USA* 92:5655-5659, 1995

Raich N, Clegg CH, Grofti J, Romeo P-H, Stamatoyannopoulos G: GATA1 and YY1 are developmental repressors of the human ϵ -globin gene. *EMBO J* 14:801-809, 1995

Li Q, Clegg C, Peterson K, Shaw S, Raich N, Stamatoyannopoulos G: Binary transgenic mouse model for studying the trans control of globin gene switching. *Proc Natl Acad Sci USA* 94:2444-2448, 1997

Asano H, Stamatoyannopoulos G: Activation of β -globin promoter by erythroid Krüppel-like factor. *Mol Cell Biol* 18:102-109, 1998

Navas PA, Peterson KR, Li Q, Skarpidi E, Rohde A, Shaw SE, Clegg CH, Asano H, Stamatoyannopoulos G: Developmental specificity of the interaction between the locus control region and embryonic or fetal globin genes in transgenic mice with an HS3 core deletion. *Mol Cell Biol* 18:4188-4196, 1998

Li Q, Emery DW, Fernandez M, Han H, Stamatoyannopoulos G: Development of viral vectors for gene therapy of β chain hemoglobinopathies: Optimization of an A_γ -globin gene expression cassette. *Blood* 93:2208-2216, 1999

KAREN STEPHENS, Ph.D.

Research Program:

Karen Stephens's research interests include the genetic basis of tumorigenesis, gene expression during normal and pathological skin differentiation, gene mapping, and molecular diagnosis of inherited diseases.

Investigations into the genetics of tumorigenesis are focused on patients with neurofibromatosis type 1 (NF1), the most common inherited disorder predisposing to both benign and malignant neoplasia. Based on our observation that NF1 patients with contiguous gene deletions consistently show an earlier age at onset of benign neurofibromas and are probably at increased risk for malignancies, Dr. Stephens hypothesized that an adjacent unknown gene predisposes these patients to tumor development. Current efforts are directed at mapping and identifying this modifying gene, understanding the molecular mechanism that explains why the deletion breakpoints of patients are tightly clustered, mosaicism for contiguous NF1 gene deletions. In addition, Dr. Stephens is also investigating secondary genetic events in leukemic cells of children with NF1, who are at about 200 fold increased risk for developing malignant myeloid disorders. Gene expression in the skin has focused on cytoskeletal defects that cause epidermal fragility and underlie skin blistering diseases, the identification of nuclear and cytosolic proteins that interact with the cytoskeleton, and the role of unique nucleolar proteins in skin differentiation. As a Director of the Clinical Genetics Laboratory, Dr. Stephens is actively involved in the development and implementation of clinical tests for the definitive diagnosis of inherited disorders.

Investigator: Dr. Stephens is a Research Associate Professor of Medicine (Medical Genetics) and Laboratory Medicine, Adjunct Research Associate Professor of Pathology, and Director of the Clinical Genetics Laboratory, Laboratory Medicine.

Representative Publications:

Stephens K, Zlotogorski A, Smith L, Ehrlich P, Wijsman EM, Livingston RL, Sybert VP. Epidermolysis bullosa simplex: A certain 5 mutation is a fully dominant allele in epidermal cytoskeleton function. *Am J Hum Genet* 56:577-585, 1995

Sawada S, Florell S, Purandare S, Ota M, Stephens K, Viskochil D. Identification of NF1 mutations in both alleles of a dermal neurofibroma. *Nat Genet* 14:110-112, 1996

Miles DK, Freedman MH, Stephens K, Pallavicini M, Sievers EL, Weaver M, Grunberger T, Thompson P, Shannon K: Genetic analysis and patterns of hematopoietic lineage involvement in children with neurofibromatosis type 1 and malignant myeloid disorders. *Blood* 88:4314-4320, 1996

Stephens K, Ehrlich PE, Weaver M, Le R, Sybert VP: Primers for exon-specific amplification of the KRT5 gene: identification of novel and recurrent mutations in epidermolysis bullosa simplex patients. *J Invest Dermatol* 108:349-353, 1997

Leppig KA, Kaplan P, Viskochil D, Weaver M, Ortenberg J, Stephens K: Familial NF1 contiguous gene deletions: cosegregation with distinctive facial features and early onset of cutaneous neurofibromas. *Am J Med Genet* 73:197-204, 1997

Sybert VP, Frances JS, Corden LD, Smith LT, Weaver M, Stephens K, McLean WHI: Cyclic ichthyosis with epidermolytic hyperkeratosis: a phenotype conferred by mutations in the 2B domain of keratin 1. *Am J Hum Genet* 64:732-738, 1999

Maruyama K, Weaver M, Leppig K, Aylsworth AS, Farber R, Ortenberg J, Rubenstein A, Immken L, Curry C, Stephens K. NF1 microdeletions with clustered breakpoints identified by quantitative PCR. Submitted.

VIRGINIA P. SYBERT, M.D.

Research Program:

Dr. Sybert pursues two major areas of research. The first is a *long-term study of the sex chromosome disorder, Turner syndrome*. She has established a large (480 patients) clinic for children and adults with Turner syndrome. Through this clinic, she has investigated several aspects of the natural history of Turner syndrome. Current projects include recommendations for care, description of long-term complications, and evaluation of psychosexual and self-image attitudes in adults with Turner Syndrome. The second general area of research is in the *inherited disorders of the skin*: disorders of keratinization, the blistering conditions (epidermolysis bullosa) and the ectodermal dysplasias. Specific studies include the molecular bases for epidermolysis bullosa, biochemical evaluations of Harlequin ichthyosis and other inherited disorders of scaling and cell adhesion.

Investigator: Dr. Sybert is a Professor of Medicine (Dermatology) and Adjunct Professor of Medicine (Medical Genetics).

Representative Publications:

Sybert VP: Hypomelanosis of Ito: A description, not a diagnosis. *J Invest Dermatol* 103:141S-143S, 1994

Stephens K, Zlotogorski A, Smith L, Ehrlich P, Wijsman E, Livingston RJ, Sybert VP: Epidermolysis bullosa simplex – A keratin 5 mutation is a fully dominant allele in epidermal cytoskeleton function. *Am J Hum Genet* 56:577-585, 1995

Ehrlich P, Sybert VP, Spencer A, Stephens K: A common keratin 5 gene mutation in epidermolysis bullosa simplex-Weber-Cockayne. *J Invest Dermatol* 104:877-879, 1995

Pavlidis K, McCauley E, Sybert VP: Psychosocial and sexual functioning in women with Turner syndrome. *Clin Genet* 47:85-89, 1995

Koeberl DD, McGillivray B, Sybert V: Prenatal diagnosis of 45,X/46,XX mosaicism and 45,X: implications for postnatal outcome. *Am J Hum Genet* 47:661-666, 1995

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Vanderhooft SL, Francis JS, Pagon RA, Smith LT, Sybert VP: Prevalence of hypopigmented macules in a healthy population. *J Pediatr* 129:355-361, 1996

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Sybert VP: *Genetic Skin Disorders*. Oxford University Press, New York, 1997

Sybert VP: Cardiovascular malformations and complications in Turner syndrome. *Pediatr* 101:E111-E117, 1998

Larralde M, Gardner SA, Torrado MV, Fernhoff PM, Munoz AES, Spraker MK, Sybert VP: Lymphedema as a postulated cause of cutis verticis gyrata in Turner syndrome. *Pediatr Dermatol* 15:18-22, 1998

Sybert VP, Francis JS, Corden LD, Smith LT, Weaver M, Stephens K, McLean WHI: Cyclic ichthyosis with epidermolytic hyperkeratosis: A phenotype conferred by mutations in the 2B domain of keratin 1. *Am J Hum Genet* 64:732-738, 1999

JONATHAN F. TAIT, M.D., Ph.D.

Research Program:

Dr. Tait's laboratory has two related areas of interest: studies of the human blood clotting system, and studies of the annexin family of calcium-dependent phospholipid binding proteins. The long-range goal of this research is to develop better means to diagnose and treat disorders of hemostasis and thrombosis, and to understand the functions of annexins. The interaction of annexin V with phospholipids, platelets, and erythrocytes has been characterized quantitatively. These results show that annexin V is an excellent probe for detection and functional inhibition of cellular procoagulant phospholipid (primarily phosphatidylserine). Annexin V is now being developed as a means to image thrombi and apoptotic cells in vivo. Annexin V is also being used for measurement of surface-exposed phosphatidylserine in blood cells in the clinical laboratory setting.

Investigator: Dr. Tait is an Associate Professor of Laboratory Medicine and an Adjunct Associate Professor of Pathology and Medicine/Medical Genetics. He also directs the clinical molecular genetics laboratory in Laboratory Medicine at the University of Washington Medical Center, which provides DNA-based clinical testing for genetic diseases.

Representative publications:

Tait JF, Gibson D, Fujikawa K. Phospholipid binding properties of human placental anticoagulant protein I, a member of the lipocortin family. *J Biol Chem* 264:7944-7949, 1989

Thiagarajan P, Tait JF. Binding of annexin V/placental anticoagulant protein I to platelets. Evidence for phosphatidylserine exposure in the procoagulant response of activated platelets. *J Biol Chem* 265:17420-17423, 1990

Tait JF, Smith C, Xu L, Cookson BT. Structure and polymorphisms of the human annexin III (ANX3) gene. *Genomics* 1993; 18:79-86 Stratton JR, Dewhurst TA, Kasina S, Reno JM, Cerqueira MD, Baskin DG, Tait JF. Selective uptake of radiolabeled annexin V on acute porcine left atrial thrombi. *Circulation* 92:3113-21, 1995

Tait JF, Engelhardt S, Smith C, Fujikawa K. Prourokinase-annexin V chimeras: construction, expression, and characterization of recombinant proteins. *J Biol Chem* 270:21594-99, 1995

Wood BL, Gibson DF, Tait JF. Increased phosphatidylserine exposure in sickle cell disease: flow-cytometric measurement and clinical associations. *Blood* 88:1873-80, 1996

Hofgaertner WH, West Keefe SF, Tait JF. Frequency of deletional alpha-thalassemia genotypes in a predominantly Asian-American population. *Am J Clin Pathol* 107:576-581, 1997

Blankenberg FG, Katsikis PD, Tait JF, Davis RE, Naumovski L, Ohtsuki K, Kojiwada S, Abrams MJ, Darkes M, Robbins RC, Maecker HT, Strauss HW. In vivo detection and imaging of phosphatidylserine expression during programmed cell death. *Proc Natl Acad Sci USA* 95:6349-6354, 1998

Hofgaertner WT, Tait JF. Frequency of problems during clinical molecular-genetic testing. *Am J Clin Pathol* 112:14-21, 1999

Tait JF, Smith C. Phosphatidylserine receptors: role of CD36 in binding of anionic phospholipid vesicles to monocytic cells. *J Biol Chem* 274:3048-3054, 1999

STEPHEN TAPSCOTT, M.D., Ph.D.

Research Program:

Myotonic Dystrophy: Myotonic dystrophy is caused by the expansion of a CTG repeat in the 5-prime non-translated region of a protein kinase gene, the dystrophin myotonia protein kinase (DMPK) gene. Dr. Tapscott has shown that the expansion of the repeat alters the local chromatin structure, making it less accessible to nuclear factors and eliminating a hypersensitive site that is adjacent to the triplet repeat. He proposes that the regulation of genes in the region of the expanded repeat is impaired as a result of the altered chromatin conformation, making myotonic dystrophy a disease of chromatin structure. He has recently identified an enhancer element in the hypersensitive region adjacent to the normal sized repeat and demonstrated that loss of the hypersensitive site enhancer suppresses expression of the adjacent DMAHP gene. He is currently studying the role of the DMAHP gene in myotonic dystrophy.

Chromatin Structure and the Regulation of Gene Transcription: Initiating gene transcription within native chromatin is a critical aspect of cell differentiation. He is studying the ability of MyoD to remodel chromatin at binding sites in several muscle and non-muscle genes. He has shown that MyoD can remodel chromatin and that this activity is dependent of two novel domains of MyoD. He is currently determining the factors that interact with these regions and the mechanism of chromatin remodeling.

Neurogenic bHLH proteins: The bHLH NeuroD protein is capable of inducing ectopic-neurogenesis when expressed in developing frog embryos. He has been studying NeuroD and two new bHLH proteins related to NeuroD, NeuroD2 and NeuroD3. His initial work has led to the recognition that there are at least two related sub-families of neurogenic bHLH genes. One group is expressed early in development and is highly related to the atonal homolog MATH1. This group is expressed in replicating progenitor cells and early neuroblasts, but not at high levels in the mature nervous system. The second group starts to be expressed at the time of neuronal birth and its expression persists in the adult nervous system and is highly related to the neurod gene. Currently, there are three members of this latter group, NeuroD, NeuroD2 and MATH2. These genes are expressed in a partially overlapping fashion and we have shown that NeuroD and NeuroD2 have differential transcriptional activity. Therefore these genes are good candidates for establishing and maintaining specific neuronal identities in subpopulations of neurons. Currently he is pursuing homologous recombination to mark and disrupt the expression of NeuroD2 and a related NeuroD3 gene, as well as using in vitro assays to identify direct target genes.

Investigator: Dr. Tapscott is an Assistant Member, Divisions of Clinical Research and Molecular Medicine, Fred Hutchinson Cancer Research Center and Assistant Professor, Department of Medicine, Division of Neurology, University of Washington

Representative Publications:

Otten AD, Tapscott SJ: Triplet repeat expansion in myotonic dystrophy alters the adjacent chromatin structure. Proc Nat Acad Sci USA 92:5465-5469, 1995

Klesert TR, Otten AD, Bird TD, Tapscott SJ: Trinucleotide repeat expansion at the myotonic dystrophy locus reduces expression of DMAHP. Nat Genet 16:402-406, 1997

Gerber AN, Klesert TR, Bergstrom DA, Tapscott SJ: Two domains of MyoD mediate transcriptional activation of genes in repressive chromatin: a mechanism for lineage determination in myogenesis. Genes Dev 11:436-450, 1997

Cook DL, Gerber AN, Tapscott SJ: Modeling stochastic gene expression: implications for haploinsufficiency. Proc Natl Acad Sci USA 95: 15641-15646, 1998

BARBARA TRASK, Ph.D.

Research Program:

The Trask group studies large-scale facets of genome organization. Their work relies on continued development of fluorescence in situ hybridization (FISH), a means of fluorescently tagging specific DNA sequences in chromosomes or nuclei, and flow cytometry, a technology for isolating specific chromosomes for molecular analyses based on their DNA content.

One aspect of genomic organization under study is the arrangement of DNA within the interphase nucleus. Two meters of DNA are packed within each nucleus in interphase, the stage when transcription, repair, and replication occur. FISH is used to mark sites of sequences lying at known distances from each other on the same chromosome (or on different chromosomes). By comparing interphase distances between these points to predictions of various physical models, such as that of a random-walk, we hope to learn which arrangements, if any, are dictated by functional constraints and which can be explained by the physical forces acting on these large molecules.

The structure, function, and evolution of some of the more complex and variable regions of the human genome are also under investigation. One project focuses on the subtelomeric regions of human chromosomes. These regions are a patchwork of sequence-blocks that are duplicated near the ends of multiple chromosomes. They exhibit remarkable polymorphism: the number and location of large blocks can vary among individuals. Because these segments can contain genes, the compositional variability of subtelomeric DNA may have phenotypic consequences. A combination of molecular and cytogenetic techniques is currently being used to unravel the structure and function of these highly dynamic regions of the genome.

In addition, they are studying the large and complex duplications encompassing members of the olfactory receptor gene family. Members of this large gene family are distributed over 40 sites in the human genome, yet each sensory neuron expresses only one gene. In order to determine how the expressed repertoire of olfactory receptors has evolved and is regulated, they are analyzing the genomic organization and function of these genes in mouse and man.

Investigator: Dr. Trask is Professor and Vice Chair of Molecular Biotechnology and Adjunct Professor of Genetics and Bioengineering.

Representative Publications:

Ma C, Martin S, Trask BJ, Hamlin JL: Sister chromatid fusion initiates amplification of the dihydrofolate reductase gene in Chinese hamster cells. *Genes Dev.* 7:605-620, 1993

Yokota H, van den Engh G, Hearst JE, Sachs, RK, Trask BJ: Evidence for the organization of chromatin in Mbp-sized loops arranged along a random-walk path in the human G0/G1 interphase nucleus. *J Cell Biol* 130:1239-1249, 1995

Mefford H, van den Engh G, Friedman C, Trask BJ: Analysis of the variation in chromosome size among diverse human populations by bivariate flow karyotyping. *Human Genet* 100:138-144, 1997

Trask BJ, Friedman C, Martin-Gallardo A, Rowen L, Akinbami C, Blankenship J, Collins C, Giorgi D, Iadonato S, Johnson F, Kuo WL, Massa H, Morrish T, Naylor S, Nguyen OTH, Rouquier S, Smith T, Wong DJ, Youngblom J, van den Engh GJ: Members of the olfactory receptor gene family are contained in large blocks of DNA duplicated polymorphically near the ends of human chromosomes. *Hum Mol Genet* 7:13-26, 1998

Trask BJ, Massa HF, Brand-Arpon V, Chan K, Friedman C, Nguyen OT, Eichler E, van den Engh G, Rouquier S, Shizuya H, Giorgi D: Large multi-chromosomal duplications encompass many members of the olfactory receptor gene family in the human genome. *Hum Mol Genet* 7:2007-2020, 1998

ELLEN WIJSMAN, Ph.D.

Research Program:

Dr. Wijsman's research is directed towards the development and application of quantitative methods for analysis of human genetic data, including techniques of gene mapping, modelling modes of inheritance, and identifying regions of identify-by-descent through linkage disequilibrium analysis. Disorders under investigation currently include Alzheimer's disease (AD), dyslexia, autism, cardiovascular disease, and ALS. Application of such methods in Dr. Wijsman's research group has lead to genes involved in Werner's syndrome and familial AD. Computational constraints in analyses of complex diseases has lead to a search for alternative methods of analysis. Dr. Wijsman is working on the development and evaluation of Monte Carlo Markov chain methods of analysis in situations where current methods are computationally impractical. Current studies indicate that these methods provide a mechanism for identifying both the number of underlying contributory loci and their genome locations, by providing a computationally tractable approach to multipoint analysis of large pedigrees in the presence of complex modes of inheritance.

Investigator: Dr. Wijsman is a Research Professor of Medicine (Medical Genetics) and Biostatistics.

Representative Publications:

Olson JM, Wijsman EM: Linkage between quantitative trait and marker loci: methods using all relative pairs. *Genet Epidemiol* 10:87-102, 1993

Levy-Lahad E, Wijsman EM, Nemens E, Anderson L, Goddard KAB, Weber, JL, Bird TD, Schellenberg GD: A familial Alzheimer's disease locus on chromosome 1. *Science* 269:970-973, 1995

Jarvik GP, Larson EB, Goddard K, Kukull WA, Schellenberg GD, Wijsman EM: Influence of apolipoprotein E genotype on the transmission of Alzheimer disease in a community-based sample. *Am J Hum Genet* 58:191-200, 1996

Goddard KAB, Yu C-E, Oshima J, Miki T, Nakura J, Piussan C, Martin GM, Schellenberg GD, Wijsman EM: Towards localization of the Werner syndrome gene by linkage disequilibrium and ancestral haplotyping: lessons learned from analysis of 35 chromosome 8p11.1-21.1 markers. *Am J Hum Genet* 58:1286-1302, 1996

Snow GL, Wijsman EM: Pedigree analysis package (PAP) vs. MORGAN: Model selection and hypothesis testing on a large pedigree. *Genet Epidemiol* 15:355-369, 1998

Wijsman EM, Brunzell JB, Jarvik GP, Austin MA, Motulsky AG, Deeb SS: Evidence against linkage of familial combined hyperlipidemia to the apolipoprotein AI-CIII-AIV gene complex. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 18:215-226, 1998

Chapman NH, Wijsman EM: Genome screens using linkage disequilibrium tests: optimal marker characteristics and feasibility. *Am J Hum Genet* 63:1872-1885, 1998

Daw EW, Heath SC, Wijsman EM: Multipoint oligogenic analysis of age-of-onset data with applications to Alzheimer disease pedigrees. *Am J Hum Genet* 64:839-851, 1999

RAYMOND S. YEUNG, M.D.

Research Program:

Dr. Yeung's research focuses on the genetic mechanisms of tumorigenesis with emphasis on tumor suppressor genes and hereditary cancers. With over 20 such genes cloned in humans, the diversity of their functions and mechanisms highlights novel pathways of tumor initiation. Dr. Yeung's work exploits a unique animal model of hereditary cancer to study the multi-step process of tumor development. Two such novel tumor suppressor genes of current interest relate to the disease tuberous sclerosis complex (TSC). Dr. Yeung's laboratory utilizes genetic, cell biologic and biochemical approaches to dissect the function of these genes. Recent studies evaluate the concept of protein transport/sorting and its mechanistic link to cell cycle control. Another aspect of Dr. Yeung's work deals with genetic factors that govern phenotypic heterogeneity. Genetic analyses are being carried out to identify quantitative trait loci that contribute to variation in tumor burden, multiplicity and metastatic potential. In collaboration with others, the role of TSC-related genes in cardiomyocytic proliferation and neuronal differentiation are also being investigated.

Investigator: Dr. Yeung is an Associate Professor of Surgery and Medicine (Medical Genetics).

Representative Publications:

- Yeung RS, Buetow KH, Testa JR, Knudson AG: Renal carcinoma susceptibility locus in the Eker rat involves a tumor suppressor gene mapping to chromosome 10. *Proc Natl Acad Sci USA* 90:8038-8042, 1993
- Yeung RS, Xiao GH, Jin F, Lee WC, Testa JR, Knudson AG: Predisposition to renal carcinoma in the Eker rat is determined by germ-line mutation of the tuberous sclerosis 2(TSC2) gene. *Proc Natl Acad Sci USA*, 91:11413-11416, 1994
- Jin F, Xiao GH, Wienecke R, DeClue JE, Yeung RS. Suppression of tumorigenicity by wild-type tuberous sclerosis 2 (Tsc 2) gene and its C-terminal region. *Proc Natl Acad Sci USA* 93:9154-9159, 1996
- Xiao GH, Shoarinejad F, Jin F, Golemis EA, Yeung RS: The tuberous sclerosis 2 gene product, tuberin, functions as a Rab5 GTPase activating protein (GAP) in modulating endocytosis. *J Biol Chem* 272:6097-6100, 1997
- Pajak L, Jin F, Xiao GH, Soonpaa MH, Field LJ, Yeung RS: Sustained proliferation in cardiomyocytes lacking the TSC2 gene product. *Am J Physiol* 273:H1619-H1627, 1997
- Yeung RS, Katsetos CD, Klein-Szanto AJ: Subependymal astrocytic hamartomas in the Eker rat model of tuberous sclerosis. *Am J Pathol* 151:1477-1486, 1997
- Henske EP, Wessner L, Golden J, Scheithauer BW, Volkmeyer A, Zuang P, Klein-Szanto AJ, Kwiatkowski DJ, Yeung RS: Loss of tuberin in subependymal giant cell astrocytomas and angiomyolipomas supports a two-hit model for the pathogenesis of tuberous sclerosis tumors. *Am J Pathol* 151:1639-1647, 1997
- Otterson GA, Xiao GH, Geradts J, Jin F, Chen WD, Niklinska W, Kaye FJ, Yeung RS: Expression of the FHIT gene fails to suppress growth and tumorigenicity of human carcinomas. *J Natl Cancer Inst* 90:426-432, 1998
- Plank TL, Yeung RS, Henske EP: Hamartin, the product of the tuberous sclerosis 1 gene, interacts with tuberin and appears to be localized to cytoplasmic vesicles. *Cancer Res* 58:4766-4770, 1998
- Rennebeck G, Anderson R, Kleymenova EV, Yeung RS, Artzt K, Walker C: Loss of function of the Tsc2 tumor suppressor gene results in embryonic lethality characterized by disrupted neuroepithelial growth and development. *Proc Natl Acad Sci USA* 95:15629-15634, 1998
- Soucek T, Yeung RS, Hengstschlager M: Inactivation of the cyclin-dependent kinase inhibitor p27 upon loss of the tuberous sclerosis complex gene-2. *Proc Natl Acad Sci USA* 95:15653-15658, 1998