



Research Member Abstracts

Hoda Anton-Culver, PhD

Professor & Chair, Department of Epidemiology
Director, Genetic Epidemiology Research Institute

During the past twenty nine years at UCI, Dr. Anton-Culver has established a major research program in cancer epidemiology and genetics. She is the principal investigator on many NIH/NCI and other research grants in epidemiology. She served on several NIH Study Sections including EDC2. She is a member of NCI's Board of Scientific Advisors (BSA) of the National Cancer Institute (NCI) since 1999. She is an advisor in NCI's Division of Cancer Biology (DCB) under the Intergovernmental Personnel Act (IPA). Dr. Anton-Culver is a highly regarded and accomplished scientist with a long list of peer-reviewed publications (more than 170) to her credit, largely in areas of cancer epidemiology and cancer genetics. Research contributions by Dr Anton-Culver are in cancer epidemiology with special emphasis on etiology, molecular genetic characterization, evaluation of genetic-phenotype correlation, and genotype-environment interaction using large populations of cancer patients, their relatives, and unaffected controls. Dr Anton-Culver's research theme takes advantage of population genetics, to predict the proportion of cancers that can be attributed to genetic variation and exposure to environmental risk factors in the population. She developed and has been successful in implementing this research theme in the understanding of several cancers, particularly breast, colorectal, ovarian, and prostate cancers. Gene-environment interactions are important components in several cancers in human populations and the knowledge generated from this research will help in planning of cancer prevention and control. Her current projects include early on-stage pancreatic cancer, Hereditary Breast and ovarian cancer, and Young Adolescent cancers.

Francisco J. Ayala, PhD

Bren Professor of Biological Sciences
Ecology and Evolutionary Biology

Research

The concept of the molecular clock has revolutionized evolutionary studies. DNA and protein sequences thus can be used for reconstructing evolutionary history and timing events of the past. How good is the clock? We are investigating a number of genes and testing new models of rates of gene evolution.

Another major research effort focuses on the population structure and evolution of parasitic protozoa, such as the agents of malaria and Chagas. We have shown that the four species of Plasmodium that cause human malaria diverged many million years ago; they became human parasites independently, by lateral transfer from other hosts. However, the world populations of *P. falciparum*, the agent of malignant malaria, originated from a single propagule only a few thousand years ago. We have shown that *P. falciparum* parasites are genetically virtually identical, except for the genes responding to the human immune system or to antimalarial drugs.

A third area of investigation is the evolution of molecular adaptation. The main lines of research are: the evolution of gene regulatory regions, the molecular adaptation of duplicated genes, ectopic expression, the evolution of pseudogenes, and the origin and evolution of introns.

Additionally, I am interested in the philosophy of biology and in bioethics, as well as in the relationships between science and religion, including the teaching of evolution in the schools.

Dean Baker, MD, MPH

Professor and Chief, Occupational and Environmental Medicine
Director, UCI Center for Occupational and Environmental Medicine

Research

Dr. Baker has more than two decades of experience conducting environmental and occupational epidemiological research. His research during the past several years has focused on two areas. One area is developmental toxicity and children's environmental health. He has conducted a series of epidemiological research studies examining chronic and latent effects on neurological and immunological function of gestational and childhood exposure to heavy metals, such as lead and mercury, and organochlorine chemicals, such as DDT and heptachlor. The other area of research has been on the physiological and adverse chronic health effects of psychosocial stressors in the workplace and in communities potentially exposed to environmental hazards. This research has focused primarily on hypertension and cardiovascular disease, although recent projects have considered effects of psychosocial factors on immune system function.

Pierre Baldi, PhD

Professor

Director, Institute for Genomics and Bioinformatics

Research

Areas: Artificial Intelligence: Automated Reasoning / Machine Learning / Data Mining
Large-Scale Data Analysis: Information Access & Management / Databases /
Information Infrastructure / Bio-Medical Informatics / Computational Biology

Dr. Baldi's research focuses in several areas of AI, data mining, machine learning, bioinformatics and communication networks. Projects in his group include understanding and predicting protein structures, analyzing and modeling gene expression data and regulatory networks, developing a computer GO player, analyzing and designing communication networks (Internet, Ultra Wide Band Radio), and quantifying information.

Scott Bartell, PhD

Assistant Professor,

Department of Epidemiology, College of Public Health

Research

Dr. Bartell's research interests are in probabilistic models and statistical methods for environmental epidemiology, exposure assessment, risk assessment, and decision analysis. Dr. Bartell has conducted research related to child environmental health, chronic beryllium disease susceptibility, applications of toxicokinetic and toxicodynamic models to risk assessment, and other topics. His current research efforts include development of statistical approaches for estimating time-varying exposures using biomarkers, two-stage epidemiologic study design, and epidemiologic studies of environmental and occupational exposures to silica, polychlorinated biphenyls, methyl mercury, and perfluorooctanoic acid. Dr. Bartell received an M.S. in environmental health from the University of Washington, and an M.S. in statistics and Ph.D. in epidemiology from the University of California at Davis.

Bruce Blumberg, PhD

Associate Professor

Department of Developmental and Cell Biology

Research

Studies of gene regulation and intercellular signaling during embryonic development. We study a family of regulatory proteins called nuclear hormone receptors and their ligands. These receptors are all members of the steroid receptor superfamily and are ligand-regulated transcription factors that regulate important events during embryonic development and adult physiology.

Peter Bryant, DPhil

Director, Development Biology Center

Research

Dr. Bryant's main research goal has been to use the genetic methods available in *Drosophila* to identify tumor suppressor genes and genes encoding growth factors, and to use the results to identify candidate human disease genes. In our laboratory and others, 21 tumor suppressor genes have been identified in *Drosophila* by showing that loss-of-function mutations cause an imaginal-disc overgrowth phenotype, characterized by a hyperplastic or neoplastic mode of growth. We have been involved in cloning and characterizing six of these *Drosophila* genes.

We have also used genetic methods to introduce mutations into five of the six members of a gene family encoding **Adenosine Deaminase-related Growth Factors**, which were discovered in my laboratory and shown to promote growth by depleting extracellular adenosine. We also discovered another entire family of six novel **Imaginal Disc Growth Factors** related to chitinases; these may be important in understanding more human diseases. Recently we initiated direct studies of some of our candidate genes in human disease & finding very high somatic mutation rates in three of our candidate genes in human **breast cancer**, and the evidence indicates that at least some of these mutations are functionally significant in tumorigenesis.

Our work on **human neuronal stem cells** also follows the philosophy of using *Drosophila* genetics to identify human homologs that are candidates for important functional roles in development and disease. We have used this approach to show at the molecular level that human neural stem cells undergo **asymmetric cell division**, a key feature of stem cells in general. There are many more genes to investigate in this respect, and the results will lead to a better understanding of how stem cell development is controlled, and will help in the effort to make stem cell therapy for trauma and diseases and safer and more effective.

Robin Bush, PhD

Assistant Professor

Ecology and Evolutionary Biology

Research

Studies in the evolution of infectious disease using the techniques of molecular phylogenetics and population genetics. In particular, we develop and apply computational techniques to study how antigenic proteins on the surfaces of pathogens evolve in response to host immune defenses. Her research currently focuses on two pathogens: the influenza virus, which with subsequent pneumonia is the sixth leading cause of death in the US, and the bacteria *Chlamydia*, which is the major cause of human blindness and venereal disease. Most of my efforts constitute basic research: Development and testing of hypotheses about evolutionary processes. Collaborate with scientists at public health agencies such as the CDC in applying our results to current efforts in disease surveillance, prediction and vaccine development.

Albert Cerussi, PhD

Project Scientist, Laser Beckman Institute

Susan Turk Charles, PhD

Assistant Professor

Department of Psychology and Social Behavior

Research

Experience with genetically informed data has been with large twin studies collected and housed within the Karolinska Institute in Stockholm, Sweden and with the MacArthur Midlife Study, MIDUS. Although my experience has been limited to twin samples, I am interested in molecular genetics and would welcome collaborations with people examining the association between psychosocial processes and specific polymorphisms, specifically mood or behavioral disorders. My contributions to research include the study of psychosocial processes that may be responsible for environmental variance, or possibly genetic and environmental interactions.

Judith Chung, MD

Gynecologic Oncology

Carl Cotman, PhD

Professor, Department of Neurology

Director, Institute for Brain Aging and Dementia

Research

Dr. Cotman laboratory is aimed toward understanding the mechanisms causing neuronal degeneration in Alzheimer's disease (AD) and the development of interventions to promote successful aging. We have been investigating the possibility that the accumulation of risk factors in the aged brain such as beta-amyloid and oxidative damage activate pathways associated with apoptosis. As predicted from cell culture models, caspases and related pathways are up regulated and caspase cleavage products of proteins such as fodrin; APP and tau accumulate in the AD brain. In the case of fodrin the accumulation parallels that of tangle formation, suggesting that like tangles this mechanism correlates with cognitive decline (Rohn, 2000).

In parallel, research is investigating possible behavioral interventions that may aid the brain in aging successfully. We suggest that exercise and environmental enrichment can have beneficial effects on brain function & health. Our findings show that Brain Derived Neurotrophic Factor (BDNF), a trophic factor known to support neuronal survival and plasticity, is induced with a few days of voluntary running in animal studies. In rodents & aged canines (dogs), current studies are investigating the mechanisms and functional consequences of this simple and widely practiced behavior (Cotman and Berchtold, 2002). We are finding that environmental enrichment particularly if combined with antioxidants can result in a slowing of rate of decline in learning and memory in the aged canine (Milgram, et al. in press). One of the current goals of our research is to evaluate such intervention strategies in elderly humans in collaboration with other investigators in the field. Specific training. Training is provided in basic cell culture biochemical methods as well as neuroanatomical methods applied to the study of the aging and AD brain. We also participate in the design and performance of clinical trials in collaboration with others. Collaborators include Kawas, Tenner, Glabe, and Sheu.

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Dwight Culver, MD

Clinical Professor, Department of Epidemiology

Research

Dr. Culver's primary interests are in the areas of biomarkers of susceptibility, early detection, and progression of disease in humans and Environmental and lifestyle factors that influence basic processes associated with evolutionary biology and disease trends in populations.

Most of Dr. Culver's research and scientific interest has been in trying to characterize with precision possible human exposure to environmental agents and relate these measures to physiological change and disease. My focus has been in the exposure of occupational groups to chemical and physical agents. It is among these groups that the most and easily characterized exposures occur. Thus, for some questions of gene-environment interaction, answers will come from studying these groups.

Ralph Delfino, MD, PhD

Associate Professor

Department of Epidemiology

GERI Scientific Council Member

Research

Dr. Delfino's major research interests have been in understanding the effects of community air pollutants on respiratory health. At McGill University, he found temporal associations between respiratory ER visits among the elderly in Montreal and summertime levels of ozone and particulate air pollutants well below U.S. air quality standards. He continues to contribute to this area of research at UCI by conducting panel studies in southern California. This has involved following cohorts of asthmatics (panels) with daily repeated measures for 2-3 months using spirometers, exhaled NO as a marker of airway inflammation, and daily diaries for reporting asthma symptoms, medication use, spatial location and physical activity. Several studies have involved detailed exposure assessments involving personal air monitoring systems that subjects carry with them during their daily activities. His studies were among the first panel studies to show associations of daily asthma severity in children with personal ozone exposure and outdoor fungal spores. Other research with asthmatic children showed strong associations of increased asthma symptoms, lung function deficits and increased exhaled NO with increases in personal exposures to particulate air pollution. Associations were greater among asthmatics not taking anti-inflammatory medications, consistent with suspected pro-inflammatory effects of air pollutants.

He has expanded his research to include the effects of air pollutants on cardiovascular health, including elderly subjects with coronary heart disease. The research involves an extensive effort at achieving accurate exposure assessment to include particle components, ultrafine particles, and pollutant source tracers. Compared with larger regulated particles, ultrafine particles have magnitudes higher particle number concentration and surface area, and larger concentrations of adsorbed or condensed toxic air pollutants (oxidant gases, organic compounds and transition metals) per unit mass. We aim to advance knowledge on air pollution health effects with new work on size-fractionated particle mass and number concentration as well as the chemical composition and *in vitro* redox activity of ultrafine particles collected at retirement homes of recruited subjects. Aims are to test whether pollutant exposures are associated with a wide range of inter-related health outcomes, using ambulatory ECG and blood pressure data, exhaled NO and blood draws for circulating biomarkers of inflammation, thrombosis and oxidative stress. He will also evaluate genetic polymorphisms expected to modify these repeated measures responses. His findings are expected to help generate new data on susceptibility to the adverse effects of air pollutants and the role that toxic pollutants in urban air play in adverse acute effects on respiratory and cardiovascular health.

Catherine Diamond, MD, MPH

Assistant Professor

Department of Epidemiology, Infectious Diseases

Research

Research area is AIDS-related malignancies such as lymphoma, Kaposi's sarcoma and anal cancer. I am currently investigating the effect of antiretroviral therapy on the pathogenesis and histology of AIDS-related lymphoma. I also have an ongoing project researching the influence of antiretroviral therapy on survival and quality of life among patients with AIDS-related lymphoma. In addition, I am responsible for the University of California Irvine Medical Center-based trials of the California Collaborative Treatment Group, a clinical research consortium funded by the University wide AIDS Research Program.

Rufus Edwards, PhD

Assistant Professor

Department of Epidemiology, Infectious Diseases

Research

Human Exposure assessment to air pollution where susceptibility clearly has a genetic basis

Pauline Filipek, MD

Associate Professor

Clinical Pediatrics & Neurology

Research

Autism and Methylation epigenetic etiology

Walter M. Fitch, PhD

Professor

Ecology and Evolutionary Biology

Research

Molecular evolutionary studies can shed much light on a vast array of interesting biological problems. My research is eclectic, and tries to answer any and all of these problems to the extent that the sequence information in proteins and/or nucleic acids is available and the methods are suitable.

To perform such studies one must detect significant similarity among sequences, align them homologously, and infer ancestral relationships and sequences. I spend a considerable amount of time inventing new and improving old ways of accomplishing such tasks. I am especially interested currently in ways of assigning weights to different nucleotide positions so that one may have greater confidence in the resulting phylogeny (evolutionary tree). An associated problem is how to allow for the fact that some amino acids may not be allowed to vary among insects but are variable among vertebrates and vice versa.

The best part of research is when a new improvement permits one to see new things. New things we've seen recently include the following:

1. An analysis of 350 isoaccepting tRNA's for eight amino acids from all the kingdoms showed that the various isoacceptors evolved by gene duplications that occurred prior to the most recent common ancestor of everything that is alive today.
2. An analysis of the genes of the influenza virus isolated from 1933 to the present has permitted us to study the evolution of flu where the "fossils" are accurately dated. The rate of evolution for the hemagglutinin gene turns out to be as fast as for any known gene, 10^{-2} substitutions/site/year with a rate so constant that I can determine the year of the virus' isolation if given the sequence.

Steven Frank, PhD

Professor

Ecology and Evolutionary Biology

Research

Dr. Frank uses mathematical and computational models to study complex phenotypes. Earlier in his career, he focused on the population genetics and evolution of reproductive and behavioral traits, summarized in his 1998 book, *Foundations of Social Evolution*. As molecular biology developed and provided more information about the relation between genotypes and phenotypes, Dr. Frank followed with studies on population and evolutionary aspects of immunology and pathogen evolution, leading to his 2002 book on *Immunology and Evolution of Infectious Disease*. Recently, he has moved into cancer research, with emphasis on how the dynamics of cell lineages affect cancer progression, and how the processes of progression influence the epidemiological patterns of age-specific cancer incidence. He is currently focusing on the population genetics of cancer predisposition.

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Jay Gargus, MD

Professor, Physiology & Biophysics
GERI Scientific Council Member

Research

There are two major research thrusts ongoing in the lab. The first is broadly a functional genomics approach to ion channels as candidate genes in common complex polygenic disease, and the other is broadly the molecular pathophysiology of inborn errors in signal transduction via growth factor receptors and channels. Our approach to both places a heavy reliance upon functional biophysical studies and molecular pathophysiology in addition to more traditional human molecular genetics.

Our most recent project, funded by a new NIH project grant, is a translational integrative clinical genomics approach to identifying stress response candidate genes in autism. It is based upon a metabolic phenotype, first identified in my clinic in 2 rare atypical subsets of patients with autism, those with a 15q inverted duplication and those with a familial form at risk for SIDS. Follow-on studies by our group of investigators suggest related abnormalities in a subset of more typical cases of autism.

Our other project aimed at complex polygenic neuropsychiatric disease has been a collaborative effort that resulted in the cloning and characterization of a novel CAG-repeat containing potassium channel implicated in schizophrenia.

In addition, we have participated in the use of this gene to produce a transgenic mouse ataxia model, have sequenced the complete human genomic locus and defined its key promoter elements, defined the functional consequences of a rare truncation allele of the gene found in schizophrenia, and have localized the gene's expression to the dopaminergic neurons of the mid-brain, where it plays a critical role in pacing, bursting and dopamine release, findings potentially involved in a pathophysiological model of the disease.

We have three active projects dealing with very different aspects of growth factor signal transduction using perspectives ranging from translational biophysical studies in human inborn errors to gene isolation in model systems.

Older projects within this general area have been the isolation and characterization of genes encoding the transporters underlying the kidney concentrating mechanism. They first took advantage of a rare human inborn error in red cell function (Kidd antigen null cells) to isolate a human urea transporter, and the second involved the cloning of functional components of the mammalian Na/K/Cl cotransporter using somatic cell mutants.

Chad P. Garner, PhD

Assistant Professor
Department of Epidemiology
GERI Scientific Council Member

Research

Dr. Garner's work is focused on developing powerful statistical approaches for studying genetic variation and complex human phenotypes. He is currently working on methodology to incorporate models of epistasis in linkage analysis and methodology for DNA sequence-based analysis of candidate disease genes in population studies. Dr. Garner's group works on a range of genetic and environmental problems, including; a field study to identifying the social and environmental risk factors for type 2 diabetes in Hispanic girls, the development of effective tools for educating specific populations about antibiotic resistance and prescription compliance, and the development of new statistical genetic approaches for studying gene-environment interactions. Dr. Garner collaborates with several Investigators at UCI that are studying specific diseases. He is an Honorary Senior Lecturer at King's College London where his work is focused on identifying the genetic mechanisms underlying several hematological variables and diseases, including; normal variation in platelet counts, the developmental switch from fetal to adult hemoglobin, and stroke among children with sickle cell disease.

Daniel L. Gillen, PhD

Assistant Professor
Department of Statistics

Research

Professor Gillen's research focuses on the development of statistical methods for the analysis of survival time data and group sequential methods for the design and monitoring of clinical trials. In particular, Gillen's interests include the development of methods that robustly incorporate time-varying effects on survival in the settings of observational cohort studies and clinical trials. His primary areas of application are in nephrology and cancer.

Sudhir Gupta, MD

Professor, Medicine, Microbiology & Molecular Genetics, & Pathology

Research

Our laboratory is investigating the molecular signaling of apoptosis in human lymphocytes, especially with regard to human aging. We have demonstrated increased susceptibility of both CD4+ and CD8+ T cells from aged humans to CD95- and TNF- α -induced apoptosis and there appears to be an age-dependent increase in apoptosis; aged > young > cord blood. Furthermore, we have demonstrated that increased CD95- and TNF- α -induced apoptosis was due to over expression of FADD because expression of dominant negative FADD normalized the apoptosis in aged. Increased TNF- α -induced apoptosis was also, in part, due to decreased NF- κ B activation secondary to decreased I κ B as over expression of I κ B resulted in normalization of apoptosis. Currently, we are studying both the death receptor induced and the mitochondrial pathway of apoptosis in 4 distinct subsets of CD8+ T cells. Preliminary study shows that terminal differentiated effector CD8+ T cells are resistant to apoptosis. We are investigating molecular basis of resistance to apoptosis. We are also investigating a role of ATM gene in increased susceptibility of lymphocytes from ataxia telangiectasia to apoptosis. Another focus of my research is to define and discover novel gene mutations in patients with rare primary immunodeficiency diseases. Recently, we have discovered a novel Rag-2 mutation in a patient with Omenn syndrome (a rare form of severe combined immunodeficiency) and characterized his oligoclonal T cells. We are also investigating first cases of autosomal dominant agammaglobulinemia with no B cells (father and daughter). Initial studies suggest a defect in Pax 5 and IL-7R genes. Finally, we are investigating genetic basis of hyper IgM syndrome in a patient in whom all known gene defects appear to be normal and therefore a possibility of discovering a novel gene defect.

Barbara A. Hamkalo, PhD

Professor, Molecular Biology & Biochemistry

School of Biological Sciences

Research

The research in Professor Hamkalo's laboratory is directed toward understanding the relationship between eukaryotic chromosome structure, organization, and function. There are two major areas of interest.

One major area of interest is in the composition, structure, and function of centromeric heterochromatin in the chromosomes of vertebrates. We are attempting to identify centromeric satellite DNA-specific binding proteins that may be involved in differential condensation using a novel method that permits isolation of sequences as nucleoprotein complexes. In addition, we are using histone H1 subtype-specific antibodies which we have generated in order to determine the distribution of different subtypes relative to chromosome organization and to investigate the possibility that specific subtype(s) may be heterochromatin-specific.

A second major emphasis is the identification of homologous proteins and genes in yeast so that it will be possible to assess function in a genetically tractable system. Finally, in collaboration with Los Alamos National Laboratory, we are characterizing a mini-chromosome in mouse 3T3 cells which appears to be little more than a centromere region as a starting material to identify mammalian centromere functional sequences.

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G. Wesley Hatfield, PhD

Professor, Microbiology & Molecular Genetics and Chemical Eng & Materials Science
Associate Director, UCI Institute for Genomics and Bioinformatics (IGB)
Director, Computational Biology Research Laboratory of the IGB

Research

Systems Biology - Researchers in the Hatfield laboratory employ computational and modern genomic methods to study global gene regulation and mechanisms of pathogenesis in the model organism *Escherichia coli* K12 and pathogenic bacteria. They are using these data to develop non-linear dynamic mathematical models of metabolic pathways and metabolic and genetic regulatory networks [Yang C.R., Shapiro B.E., Mjolsness E.D., Hatfield, G.W. "An enzyme mechanism language for the mathematical modeling of metabolic pathways. *Bioinformatics*. 2005 (6): 774-80].

Effects of Chromosome Structure and Topology on Gene Expression - Dr. Hatfield and his colleagues were the first to demonstrate that superhelical energy is stored at many supercoiling-induced DNA duplex destabilized (SID) sites around the chromosome, and that DNA architectural proteins such as the IHF protein can alter the structure of the chromosome in ways that redistribute this energy among SID sites to lower the activation energy for biochemical reactions such as DNA replication, recombination, and transcription initiation. Hatfield, G.W. and Benham, C. J. (2002). "DNA topology-mediated control of global gene expression in *Escherichia coli*. *Annu. Rev. Genet.* 36: 175-203.

Functional Genomics and Bioinformatics - Researchers in the Hatfield lab are using computational and genomic methods to define DNA topology-dependent global regulatory mechanisms. They also have developed novel computational methods based on protein-induced DNA helix deformation energy to identify highly sequence-degenerate protein-DNA binding. For example these methods have been used to find all of the chromosomal, high-affinity, binding sites for the DNA architectural proteins IHF and FIS [Steffen N.R., Murphy S.D., Lathrop R.H., Opel M.L., Toller L, Hatfield G.W. "The role of DNA deformation energy at individual base steps for the identification of DNA-protein binding sites." *Genome Inform*; 13: 153-62 (2002)].

DNA Microarrays – Together with the Long and Baldi labs, the Hatfield group pioneered the use of Bayesian statistics and beta-mixture modeling methods for the analysis of DNA microarray data based on experiment-wide false positive and negative levels. This resulted in the development of Cyber-T, a widely used DNA microarray data analysis program available for online use at the IGB website. [Baldi, P. & G.W. Hatfield. 2002. *DNA Microarrays and Gene Expression: From Experiments to Data Analysis and Modeling*. Cambridge University Press. Cambridge U.K.

The UCI Computational Biology Research Laboratory- The ability to produce a synthetic gene rapidly that encodes a protein of interest and is optimized for desirable sequence properties, such as optimal translation kinetics for folding and expression in a chosen target organism, has been elusive, since most genes are hundreds to thousands of nucleotides long and it is not possible accurately to synthesize DNA molecules longer than fifty to eighty nucleotides. Hatfield (with Prof. Rick Lathrop) has developed and secured UC patent protection on a computational method to accomplish this very task. This technology has been licensed by the University to CODA Genomics, Inc. Irvine CA.

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Randall Holcombe, MD

Associate Professor
Chief, Division of Hematology and Oncology

Research

Dr. Holcombe's research includes both basic and clinical and are focused toward colon cancer in the areas of cancer immunology, intracellular signaling via the Wnt pathway, and clinical therapeutics.

Cancer Immunology: Dr. Holcombe's laboratory research focus on the immunology of colon cancer and a specific immunomodulatory medication, levamisole, which was utilized clinically for adjuvant therapy of colon cancer patients.

Wnt Signaling: Aspects of the signal transduction pathway were being studied in *Drosophila* by Drs. Lawrence Marsh and Marian Waterman. The research focused on non-APC components of the Wnt pathway and their alterations, and importance, in the pathogenesis of colon cancer. These studies suggest that components of the Wnt pathway may be utilized as diagnostic or prognostic markers in colon cancer. Translational studies in Dr. Holcombe's laboratory have also expanded to the investigation of Wnt signaling in other malignancies including melanoma.

Lan Huang, PhD

Assistant Professor
Department of Developmental & Cell Biology and Physiology & Biophysics

Research

Protein ubiquitination and proteasome-mediated protein degradation are essential for the regulation of many important biological processes including cell cycle progression, apoptosis, DNA repair, etc. Disruption of normal ubiquitin-proteasome degradation pathways has been implicated in a wide range of human disease, incl. cancer & neurological degeneration. Although the ubiquitin-proteasome system has been intensively investigated, many key questions remain unanswered concerning its components and the regulation of their activities. Currently, there is little consensus as to the number or identity of the relevant ubiquitin receptors. It is unclear whether such receptors are intrinsic proteasome subunits, "shuttling" factors that bind ubiquitinated species and escort them to the proteasome, or if a combination of both types are involved. The three different classes of proteins identified so far as candidate receptors include two proteasome subunits, Rpn10 (a non-ATPase subunit), Rpt5 (an ATPase subunit), and proteins with Ubl-UBA domains (e.g. Rad23, Dsk2). Rpn10 and Rad23 are not essential for viability, but recent studies indicate that they serve as alternative ubiquitin receptors and are involved in degradation of only a subgroup of substrates. Thus, our hypothesis is that unknown ubiquitin receptors or alternative pathways are present and responsible for regulating substrate recognition by and transport to the 26S proteasome for degradation. To test this hypothesis, we will employ a novel mass spectrometry-based proteomics approach to globally map the 26S proteasome interacting networks under different biological conditions, e.g. at different cell cycle phases. We propose to develop and employ a novel integrated proteomics approach to capture both stable and transient protein interactions and to identify proteasome interacting proteins and characterize their interaction interfaces using novel mass spectrometry methodologies. This strategy will provide an unprecedented opportunity to elucidate dynamic protein interaction networks under physiological conditions.

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Taosheng Huang, MD, PhD

Assistant Professor

Director, Cardiovascular Genetics Clinic Division of Genetics & Metabolism

Research

The primary interest of our lab is to study the molecular basis of genetic syndromes, and apply discoveries from genetic syndromes to common diseases. Currently, our lab is focusing on the following areas.

1. To study the role of TBX3 in breast cancer. TBX3 is also a T-box transcription factor. Mutation of TBX3 causes Ulnar-Mammary syndrome characterized by hypoplasia and absence of the mammary gland. Oveexpression of TBX3 plays an important role in breast cancer. To study the role of TBX3 in breast cancer, we created an animal model, and analyzed TBX3 expression in human breast cancer tissue. By working with animal and breast cancer tissue, our research aims to optimize the clinical relevance of our work
2. To identify the disease-causing gene associated with noncompaction of the ventricular myocardium (spongy heart), we are studying a family with balanced translocation with this condition, and are also performing a linkage study for a large family with this disease.
3. The intracellular pathway to study TBX5. TBX5 is a T-box transcription factor. Mutations of TBX5 cause Holt-Oram syndrome characterized by congenital heart diseases and limb anomalies. By studying the intracellular network of TBX5, including the upstream transcription factor that controls TBX5 expression cofactor that interacts with TBX5 and downstream target whose genetic regulation is dependent on TBX5. We anticipate identifying many genes associated with congenital heart disease, a most common malformation¹ in humans, and contributes significantly to the mobility and mortality in pediatric populations.
4. The genetic basis of optic atrophy. Two larger kingdom were identified with autosomal dominant inherited optic atrophy. We are performing linkage analysis and candidate gene mutation analysis to elucidate the genetic cause of this condition.

Claudia Kawas, MD

Professor

Departments of Neurology and Neurobiology and Behavior

Research

Her work is concentrated on the epidemiology of aging and Alzheimer's disease, developing research in the determinants of successful aging, longitudinal and clinical pathological investigations, and most recently, studies in cognitive and functional abilities of the Oldest Old (over 90 years of age).

Abraham Lee, PhDProfessor, [Biomedical Engineering](#)Professor, [Integrated Nanosystems Research Facility](#)Professor, [Mechanical and Aerospace Engineering](#)**Research**

Dr. Lee's research interest focuses on the development of integrated micro and nano fluidic chip processors for the manipulation and self-assembly of biomolecules and other synthesized nanoparticles. These integrated chip processors will also be designed for the sample preparation of biological fluids to extract the required ingredients for on-chip transducers. Applications for these fluidic processors include programmable precision production of biological reagents for nanomedicine, biomolecular nanosystems that utilize biophysics principles, and platforms to perform controlled studies of molecule-molecule/cell-molecule interactions. With the research community's recent focus on nanotechnology, nanotransducers with unique functions are being developed for various biological applications. Examples include quantum dots for molecular beacons, synthetic peptides to mimic cellular functions, carbon nanotubes for electronic detection of biomolecules, DNA-based transducers produced by directed self-assembly, and liposomes for targeted drug delivery. Professor Lee's research group is developing integrated microfluidic platforms with the goal of generating programmable synthesis of multifunctional nanotransducers.

Other research interests include microtools for real-time, minimally invasive therapy and imaging of the brain and micro devices for distributed surveillance in liquid-based environments.

Eva Lee, PhD

Professor, Department of Developmental & Cell Biology
and Department of Biological Chemistry

Research

Research objective in the Lee laboratory is the understanding of molecular events underlying tumorigenesis. Study of familial clustered cancers and hereditary cancers in the past two decades has facilitated the identification of tumor suppressor genes whose mutation results in cancer predisposition. Many of these tumor suppressor proteins are involved in these cellular processes.

Tumor suppressor genes linked to familial clustered cancers and hereditary cancers include genes in all categories. We have investigated the function of several of these genes including gene mutated in ataxia telangiectasia (ATM) and its related kinase, ATR; genes mutated in Nijmegen breakage syndrome, NBS1 and A-T like syndrome, Mre11; and Li-Fraumeni syndrome (p53). The organization of these tumor suppressors in DNA damage response and the roles of phosphorylation in the regulation of checkpoint activities and cell survival upon DNA damage are being investigated. Our studies firmly establish protein networks between cell cycle checkpoint ATM and DNA repair proteins, NBS1 and Mre11. Ongoing and future studies will provide insights into how the checkpoint proteins interact with the repair protein in the maintenance of genome stability.

Breast cancer is both a genetic and an endocrine disease. We have developed a new mouse mammary tumor model using the Cre/loxP system for tissue-specific inactivation of p53 -- mice carrying MMTV-Cre and floxed p53 alleles develop mammary tumors with nearly complete penetrance with quantifiable latency periods. Lung and liver metastasis occurs at high frequency. Our studies show that multiple cell types including epithelial and myoepithelial cells could give rise to mammary tumors. Importantly, tumor progression is associated with the loss of estrogen receptor expression, and metastatic potential is intrinsic to the primary tumors. Using this model system, we will study the contribution of estrogens to mammary tumorigenesis, mechanisms leading to deregulated ER expression, and molecular profiles that provide a distinction between metastatic and non-metastatic mammary tumors. There is a great need for a physiological test system to evaluate therapeutic efficacy for breast cancer. In this regard, mouse models which closely resemble human cancers are considered to be advantageous. We will validate the use of p53 model for treatment of early and advanced stage breast cancer. Improved models for sensitive, quantitative, and non-invasive measurement of treatment efficacy over time will be established.

Ellis Levin, MD

Professor, Department of Medicine

Research

Genetic epidemiology of Breast Cancer, estrogen receptors.

Steven Lipkin, MD, PhD

Associate Professor, Departments of Biological Chemistry and Medicine
GERI Scientific Council Member

Research

DNA mismatch repair (MMR) is critical for maintaining both mitotic and meiotic genomic integrity. Defective MMR leads to carcinogenesis of the colorectum, endometrium, stomach, small bowel, ovary, brain and kidney. Mutations in five MMR genes (MLH1, MSH2, MSH6, PMS2 and MLH3) cause cancer susceptibility. Germline MMR gene mutations underlie the most common cancer genetic syndrome, Hereditary Non-Polyposis Colon Cancer (HNPCC). Furthermore, somatic MMR defects are attributable for ~17,000 sporadic colorectal cancer (CRC) and ~10,000 endometrial cancer new diagnoses each year in the United States.

Previously, my group cloned MLH3, the last uncharacterized mammalian MMR gene. MLH3 has higher amino-acid identity with homologues in *S. cerevisiae*, *Arabidopsis*, and *C. elegans* than to any other human protein. This conservation suggests it may perform unique functions in mammalian MMR. My initial studies revealed a role for MLH3 in human and mouse CRC susceptibility.

In addition, we are working to define whether MLH3 participates in meiotic checkpoint recognition and is a plausible candidate gene for mutation analyses in idiopathic human infertility or genetic aneuploidy disorders such as Down or Turner Syndromes.

Larry Marsh, PhD

Professor, Department of Developmental & Cell Biology

Research

We are engineering the fruit fly to express human neurodegenerative (and other) disease genes and using these animals to identify genetic mechanisms that affect disease and to identify possible therapeutics. Some therapeutics are now in clinical trials. We are also using the fly to uncover the mechanisms of oncogene regulation as it relates to the ability of tissues to regenerate and to become cancerous.

Christine McLaren, PhD

Professor, Department of Epidemiology
Director of Biostatistics, Chao Family Comprehensive Cancer Center

Research

Statistical models provide insight into the structure of data. Models of biological processes can assist with distinguishing between health and disease. Dr. McLaren's statistical modeling research has concentrated on mixture distribution analysis, goodness-of-fit testing, and hierarchical regression modeling of longitudinal data. Medical applications including disease prevalence and estimation of iron overload and hemochromatosis, analysis of distributions of red blood cell volume and hemoglobin concentration in iron deficiency anemia, detection of cisplatin-induced anemia in patients undergoing cancer chemotherapy, and screening for hepatocellular carcinoma. As a result of her experience with statistical modeling and collaborative medical research, in January of 2000, Dr. McLaren received a \$4 million 5-year contract awarded by NIH/NHLBI, Screening for Iron Overload and Hereditary Hemochromatosis Field Center.

Susan Neuhausen, PhD

Professor, Department of Epidemiology

Associate Director, Genetic Epidemiology Research Institute

Research

My primary research interest is to identify genes that cause and/or increase susceptibility to common diseases. Thus, I am actively involved in numerous research projects devoted to the study of breast cancer, prostate cancer, colorectal cancer, and celiac disease.

In collaboration with distinguished researchers around the world, I am continuing to study women who carry *BRCA1* and *BRCA2* mutations in order to identify gene variants that modify their risks of developing cancer. In addition, we are studying this group of carriers in order to assess the cancer risks that their family members are subject to, and to determine if prophylactic and preventative treatments will significantly reduce their risk of developing breast and ovarian cancers. Our focus is *BRCA1/2* mutation carriers who, because of their high risk of developing cancer at an early age, are the group for whom these results would first be applied. This information can be used to assist women and their physicians in individual risk assessment, as well as target women for prevention or treatment strategies.

For prostate, colorectal, and non-familial breast cancer studies, we are using case-control studies to investigate genetic and lifestyle factors that cause increased susceptibility to developing these diseases. For these studies, my objective is to elucidate pathways and genes that have not been previously explored in this context. My current studies are case-control and case-case studies investigating the associations of genetic variants and haplotypes (in genes likely involved in cancer) with occurrence and/or progression of the disease. In the near future, I would like to perform functional studies to determine what the effects of associated variants are.

For celiac disease, our primary objective is to identify non-HLA genes that predispose to the disease. Towards that end, we have ascertained more than 200 families with from two to thirteen cases of celiac disease and have performed a genome-wide search. We are currently performing additional genotyping in regions of interest. We are also planning to investigate the prevalence of other auto-immune diseases within families and to follow the natural history of the disease in those affected individuals who do not follow a gluten-free diet.

Oladele Ogunseitan, PhD

Professor, Department of Population Health and Disease Prevention
Program in Public Health

Research

My research concerns the exploration of genetic diversity in microbial communities and how this diversity correlates and changes with fluctuating environmental conditions, including the presence of toxic environmental pollutants. I place emphasis on the use of phylogenetically conserved genes as indicators of toxicant bioavailability. In particular, I am interested in genes that are also implicated in human response to toxic chemicals. Therein lays my interest in the Genetic Epidemiology Research Institute. For example, my laboratory has investigated the interaction between genes encoding for delta-aminolevulinatase (ALAD) and toxic metal contamination in microbial communities. ALAD polymorphisms have also been linked to differences in human susceptibility to high blood Pb concentrations under uniform conditions of environmental Pb exposure. I have also done some work on polymorphisms in cytochrome P450 family of enzymes, and in this regard, we are investigating the metabolism of caffeine in microorganisms under various environmental conditions. Because microorganisms have short generation times, they are excellent models for tracking the influence of environmental selective pressures on genetic diversity. Information gathered through microbial population models is meaningful for tracking the evolutionary origins and fate of genetic polymorphisms in human populations. In addition to my research, I teach courses in the School of Social Ecology that introduce non-specialists to the implications of research findings in genetic epidemiology for public perception of environmental risk.

Sai-Hong Ignatius Ou, MD, PhD

Assistant Clinical Professor
Hematology/Oncology

Research

Research interest in the epidemiology of bronchioalveolar (BAC) carcinoma. It is a distinct subtype of adenocarcinoma of the lung, affects primarily elderly non-smoking women. There may be a distinct genetic mutations in the epidermal growth factor receptor that lead to the genetic mutation. My goal is to identify available BAC tissue in the California Cancer Registry and to sequence that region in the EGFR to characterize and categorize the various mutation.

Steven G. Potkin, MD

Professor, Department of Psychiatry and Human Behavior

Research

Dr. Potkin's career has been devoted to understanding the causes of, and developing new treatments for, schizophrenia. Dr. Potkin has approached decreasing stigma for those suffering from mental illness in a variety of ways. His brain imaging and biological studies provide evidence that schizophrenia is a brain illness. In addition to communicating to the general public, family members, and patients with schizophrenia, he has made many presentations to the California Legislature to educate legislators on mental illness and advocate for the needs of the mentally ill. Dr. Potkin played a key role in passing legislation which allowed treatment-resistant patients to receive new treatments and provided funding for model integrated service programs, such as the Village.

Thomas Poulos, PhD

Chancellor's Professor, Molecular Biology & Biochemistry

School of Biological Sciences

Co-Director Center for Chemical and Structural Biology

GERI Executive Committee Member

Research

Our laboratory uses three approaches to study protein structure and function: x-ray crystallography for protein structure determination, recombinant DNA methods to generate mutant proteins, and biochemical methods for characterization of both mutant and native proteins. The primary focus is on heme containing enzymes and related redox proteins. Protein engineering is used to study structure-function relationships and address the question of how these enzymes activate molecular oxygen and peroxides and how interprotein electron transfer reactions operate. For example, does the protein participate in the electron transfer process and how are the oxidizing equivalents of oxygen/peroxide stored in the active site? A longer range goal is to use structural information and mutagenesis to design novel redox catalysts. To increase the structural data base required, new peroxidase and P450 structures are being determined using diffraction methods. More recently, studies on nitric oxide synthase (NOS) have been initiated. NOS is responsible for producing nitric oxide, a critically important regulatory molecule involved in the immune, nervous, and cardiovascular systems. The design of isoform specific inhibitors is an important practical goal in NOS research. Toward this end, the lab has succeeded in crystallizing the heme domain of the three main NOS isoforms and the structure of one solved to 1.9A resolution. This opens the way for structure based drug design.

Elizabeth Rugg, PhD

Associate Researcher
Dermatology

Research

Primary Research Interests: 1) The genetic basis of epithelial diseases particularly those resulting from mutations in keratins and keratin associated proteins. 2) Understanding the function of the keratin cytoskeleton and the functional consequences of keratin gene mutations and polymorphisms 3) Developing therapies for keratin disorders

Other relevant research interests and areas of expertise: 1) Skin disorders caused by mutations in connexin genes 2) Polymorphic variations in keratin genes in relation to human evolution 3) The application of DHPLC in screening for genetic variations.

Rainer Reinscheid, PhD

Assistant Adjunct Professor
Pharmacology

Research

Our group is interested in the function of G protein coupled receptors under normal and pathological conditions. Recently, we focused on a novel GPCR that is associated with an increased risk in asthma and other atopic diseases. We are currently studying the pharmacological properties of mutant forms of this GPCR and their physiological correlation to asthma. Also, we are testing patient DNA samples for the mutation and investigate a possible contribution of the mutant receptor to psychiatric disorders, since this receptor is mainly expressed in the CNS. We have collaboration on this project with the Department of Psychiatry at Chiba University, Chiba, Japan, and would like to include and discuss with other groups in the field here at UCI.

Maike Sander, MD

Developmental & Cell Biology

Research

My research interests entail mouse genetics to identify factors that control the formation of insulin-producing beta-cells in the pancreas. To define the pathways that underlie beta-cell development, we analyze pancreas development in mice, in which specific genes have been inactivated. Specifically, our research aims to identify genes that mark and maintain pancreatic stem cell, as these cells could be a potential source for transplantable replacement beta-cells for patients with diabetes. Similar to the cancers of the hematopoietic system or colon cancer, which are thought to originate from tissue stem cells, pancreatic stem cells may also be involved in the pathogenesis of pancreatic adenocarcinoma. In our research, we are investigating whether genes that control the maintenance of old pancreatic stem cells in the embryo also play a role in pancreatic cancer.

Leonard Sender, MD

Clinical Professor of Medicine

Medical Director, Clinical Oncology Svcs., Chao Family Comprehensive Cancer Center

Research

Dr. Sender's research interests are adolescent and young adult cancers with a major emphasis on young adult sarcomas and leukemia; issues related to epidemiology and health disparity related to adolescent and young adult cancers. Dr. Sender is a nationally known expert in disorders of the blood and lymphatic systems, such as leukemia and non-Hodgkin's lymphoma.

Hal Stern, PhD

Professor and Chair, Department of Statistics

GERI Executive Committee Member

Research

Dr. Stern's research interests include: statistical inference using Bayesian methods, assessing the fit of statistical models, applications of statistics in the social and biological sciences, and statistics in sports. He has authored more than 50 publications (more than 30 referred publications), and is a co-author of the graduate level statistics text "Bayesian Data Analysis".

David Timberlake, PhD

Assistant Professor, Program in Public Health

Department of Epidemiology

Research

David Timberlake, PhD, is an Assistant Professor with a joint appointment in both the Program in Public Health and the Department of Epidemiology. His major research interest is in the genetic basis for the use and misuse of licit and illicit substances in which it will be converted in twin and family-based samples. The objective is to test the hypothesis of Environmental factors such as upbringing, education, and Behavioral traits and the underlying genetic basis for the use of various substances. This basis is a possible function of a genetic predisposition to behavioral disorders, such as antisocial personality disorder.

David van Dyk, PhD

Associate Professor, Department of Statistics, ICS

Research

His scholarly work focuses on methodological and computational issues involved with Bayesian analysis of highly structured statistical models and emphasizes serious interdisciplinary research. He is particularly interested in improving the efficiency of computationally intensive methods involving data augmentation, such as EM-type algorithms and various Markov chain Monte Carlo methods. Professor van Dyk's primary area of interdisciplinary work is Astro-statistics; he coordinates the [California-Harvard Astrostatistics Collaboration](#). The group includes Astronomers and Statisticians and provides an open forum for discussing statistical issues that arise in astrophysical research, for example at the Harvard-Smithsonian Astrophysical Observatory. The group's current work focuses on constructing and fitting highly structured models for data obtained with the [Chandra X-ray Observatory](#).

Paul Vrana, PhD

Assistant Professor, Department of Biological Chemistry

Research

Dr. Vrana's research interests is centered on a development of mammalian system for studying the effects of natural genetic and epigenetic variation. The hope is that this research can forge an important link between biomedical and ecological/organism research. This is important for at least two reasons: 1. ablating gene function via transgenic technology reveals processes requiring gene function and downstream targets, it does not predict the effects of coding-region or regulatory variants. 2. Common alleles underlie the predisposition to many human diseases.

Pathik Wadhwa, MD, PhD

Associate Professor, Department of Psychiatry & Human Behavior

Research

Research interests are: biobehavioral processes in human pregnancy and life-span development, effects of maternal stress on fetal development and birth outcomes, maternal-placental-fetal endocrinology and the biology of the stress response in pregnancy, infection and immune function in pregnancy, gene-environment interactions in human fetal development, racial/ethnic disparities in perinatal health outcomes, utero-placental perfusion and fetal vascular hemodynamics, and influences of socio-demographic and psycho-social factors and health behaviors.

Deborah A. Wing, MD

Associate Professor and Director, Division of Maternal-Fetal Medicine
Department of Obstetrics-Gynecology

Research

Dr. Wing's areas of research include the physiology of human labor and delivery, focusing on cervical ripening and labor induction. Her clinical research trials have been conducted in both inpatient and outpatient settings and have used chemical and mechanical approaches. This research focus is timely in today's healthcare environment, addressing cost-effectiveness and innovation in antepartum/intrapartum care. She was the driving force in the research efforts that defined the "standard of care" in which the amount and dosing regimen were concluded.

Dr. Wing is currently participating in other projects evaluating differing approaches to cervical ripening and labor induction, including the use of an anti-progestational agent known as mifepristone and other approaches to the use of misoprostol for the same purpose. Another research focus looks at different facets of urinary tract infection in pregnancy and the effects of these infections on newborns, she has conducted trials comparing outpatient to inpatient therapy for acute pyelonephritis in pregnancy, and other trials comparing the efficacy of differing antibiotics for upper urinary tract infection in pregnancy. Future investigation in this area will look at short-course therapies for uncomplicated urinary tract infections during pregnancy and preventative alternative medicine approaches.

Dominik Wodarz, PhD

Associate Professor, Department of Ecology and Evolutionary Biology
GERI Scientific Council Member

Research

Main research interests include: dynamics of virus infections, the immune system, and therapy; models of cancer progression, host defenses against tumors, and cancer therapy; prions; evolution of immune system and pathogens; bioinformatics and computational biology as applied to the immune system and infectious agents.

Jun Wu, PhD

Assistant Professor, Program in Public Health
Department of Epidemiology

Research

Major research interest is in air pollution exposure assessment and air pollution epidemiology. The goal of her research is to reduce exposure estimation errors and examine the impacts of air pollutants on respiratory and birth outcomes. Her other interests are to examine host susceptibility to air pollutants, including genetic variability.

GERI Members
Research Abstracts

Zhaoxia Yu, PhD
Assistant Professor
Department of Statistics

Research

Research interests include genome-wide association, haplotype-based analysis, gene-gene and gene-environment interaction, gene regulatory network, genetic pathway, and genetic epidemiology.

Jason Zell, DO, MPH
Assistant Adjunct Professor, Hematology/Oncology
Department of Medicine

Research

Research interests include breast cancer epidemiology, including molecular/genetic markers of oncogenesis and metastasis; genetic epidemiology of non small cell lung cancer; including bronchoalveolar carcinoma

Argyrios Ziogas, PhD
Associate Adjunct Professor
Department of Epidemiology

Research

Research is in the development of statistical methodology of doing family studies. I am concentrating on three important areas: 1) statistical models for analysis in genetic (family based) data; 2) development of statistical methods that deal with ascertainment bias; and 3) the examination of gene-environment and gene-gene interactions that may be involved in the etiology of breast, colorectal, or prostate cancer. Applications of my research include the use of efficient designs that allow for the testing of hypotheses concerning gene-environment interactions or effect modifications related to the etiology of breast, ovarian, and colon cancer; estimation of the frequency of susceptibility or metabolic genes in the general population; and the estimation of the attributable risk of genetic and environmental factors for breast, ovarian, and colorectal cancer. Other areas of interest include analysis of epidemiologic studies of cancer and other chronic diseases. In particular, I am interested in the development of efficient sampling for the analysis of case-control and cohort studies as applied to the genetic epidemiology. These designs include nested case-control, case-cohort, and counter-match case control designs. My interest is in determining the efficiency of such designs and comparing the relative efficiency across different study designs. Other research interests include developing methods of correction for measurement error in case-control and cohort studies. In particular, I am concerned with situations where information on exposure data (measured and true) exists in part of the subjects but not in all participants. Another area related to the above is my interest in developing statistical methods for family validation studies.

