Welcome 2011-2012
1. A wild type Drosophila eye antennal disc stained for Emc (red), Da (green) and Sens (blue; Baker laboratory).

2. A mouse embryonic heart expresses green fluorescent protein in the endocardium (Zhou laboratory).

3. Mef2c muscle staining: Mef2 proteins are important for the development of skeletal muscle. The antibody against Mef2c marks the nuclei of the segmented somites, which contains the differentiating muscle progenitors. A one-day-old zebrafish larva is shown in the image (the head is on the left; Ozbudak laboratory).

4. Head of a live C. elegans hermaphrodite in which neurite specific heparan sulfate sugar structures are labeled (courtesy of Matthew Attreed, Buelow laboratory).

5. Spectral karyotyping of a mouse tumor metaphase (Montagna laboratory).

6. A composite image of a pancreatic neuroendocrine tumor (insulinoma) in an Men1 conditional knockout mouse. A PET scan showing the tumor in a live mouse and a confirmatory IHC section staining for insulin (red) and endothelial cells (green; Libutti laboratory).

7. Snapshot of a three dimensional model of three sex-specific neurons and their associated synapses in the C. elegans male tail. Volumetric reconstructions like the one above, along with wiring diagrams of the nematode nervous system, are used to address questions about nervous system development, synaptic specificity, the relationships between neuronal form and function, the neural circuits for goal-oriented behavior, and the genetics underlying these phenomena. (Emmons laboratory).

8. Fate mapping neural crest cells in Tbx1+/- embryo @ E10.5 (Morrow laboratory).

9. The HELP assay to study cytosine methylation genome-wide. Shown are data from mouse brain (red) and spermatogenic cells (green; Greally Laboratory).

10. The compound eye of Drosophila melanogaster can be used as a powerful genetic tool. (Secombe laboratory).
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2011-2012

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## POSTDOCTORAL FELLOWS

Department of Genetics

2011-2012

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**GRADUATE STUDENTS**

Department of Genetics

2011-2012

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*M.D./Ph.D. Students

**Visiting Ph.D. students from China
BRETT S. ABRAHAMS, Ph.D.

The Autism Spectrum Disorders: From Genetics to Biology

My work is aimed towards understanding how disorders of human cognition, and the Autism Spectrum Disorders (ASDs) in particular, are influenced by genetic variation. Defined entirely in terms of behavior, the ASDs represent a unique class of clinical conditions involving deficits in language use, impaired social behavior, and a circumscribed range of interests.

Work in my lab employs a blend of molecular genetics and developmental neurobiology to identify disease-related genes and understand how they operate functionally. Drawing on both hypothesis-based and discovery-driven methodologies, we have multiple studies directed focusing on Contactin-Associated Protein-like 2 (CNTNAP2). In addition to the potential importance of this molecule to ASD biology, we and others have obtained data to support a role for this gene in related disorders of cognition including specific language impairment, intellectual disability, and schizophrenia. And so our findings from cell, mouse, and human-based systems are likely to be of broad interest.

Looking forward, we will direct substantial effort towards understanding how individual molecular variants work alongside one another to modulate risk. New insights around how seemingly distinct molecules converge to shape disease-related processes will prove important in the development of potential therapeutics.


Recent Publications:
Examples of epigenetic regulation of genome architecture and gene expression are paved across the evolutionary lineage. Even if only a small proportion of human genes are subject to similar effects, they may still play a major role in the phenotypic variation and susceptibility to diseases. My long-term research goal is to investigate changes in the epigenetic control of gene expression which may be one of the central mechanisms by which aging predisposes to many age-related diseases and therefore lifespan.

Despite some early work, the role of epigenetics in human life span and age related diseases has remained unexplored. Discovering that methylated loci are involved in the genetic control of cellular existence, modify the risk for age-related disease and influence mortality is a novel and extremely important concept that would significantly enhance our understanding of the biology of aging. In addition, accumulating evidence supports the notion that major age-associated diseases (such as diabetes, metabolic syndrome and cancer) are regulated by epigenetic alterations. Epigenetic changes may provide information on the pivotal points between healthy and sick stages in the lifespan of an individual. Hence, epigenetic changes could serve as landmarks of events such as onset of disease and these events can be tracked long after its occurrence (forms of epimutation and the Barker theory).

To test our hypothesis, we propose to employ a novel high-throughput genome-wide methylation assay, HELP-tag. Additionally, we will utilize a combination of large-scale epigenomic analysis (EWAS) to identify the most distinctive epigenetic loci that show greatest differential methylation. We will then perform Multi-locus validation for methylation status using MassARRAY. And finally we will test expression of candidate loci to explore possible mechanisms of methylation regulation.

This research will further our understanding of the complexity of healthy lifespan process by identifying loci that when altered epigenetically have important ramifications for age-related diseases and lifespan. Validating the genes whose function is modulated epigenetically could lead to interventions to delay or even prevent the development of age-associated diseases.

Recent Publications:
Cells in developing tissues interact with one another. These interactions can be studied through genetic manipulation of intact animals. We use the fruitfly *Drosophila melanogaster*, which permits in vivo studies not yet possible in most other organisms. We are also employing mathematical models to understand such processes fully.

We are studying how developmental signals control the development of the nervous system, and how growth and proliferation are regulated within tissues on a cellular level. Growth and development must involve the coordinate regulation on a cellular basis of biosynthetic rate, cell cycle, metabolism, and turnover of cellular components. Growth must be down-regulated on terminal cell cycle exit, and up-regulated for regeneration. Little is known about how these processes are regulated in vivo, and how the cell or organism detects and responds to defects in their coregulation. One unexpected aspect is that differences in growth between cells can trigger cell competition, a process that seems to select for the fittest progenitor cells in vivo. It is strongly suspected that cell competition occurs during the early development and progression of cancer. In addition to the relevance to cancer, defects in the control of growth and development are related to degenerative diseases, including neurodegenerative diseases such as Alzheimer’s Disease, Huntington’s Disease, Ataxia Telangiectasia, and are relevant to the replacement and repair of tissues in regenerative medicine.

Our current projects include:
- developmental networks controlling neurogenesis, especially in the eye;
- mathematical modeling of neurogenesis and lateral inhibition;
- discovery and characterization of transcription factors and signaling pathways regulating growth;
- the mechanisms of growth and cell cycle regulation in multiple cell types;
- how tissues respond to inappropriate growth regulation through mechanisms including cell competition and neurodegeneration.

For more details, and complete list of publications, please see our website at http://fruitfly4.aecom.yu.edu/index.html

**Selected Recent publications**

Searching for Longevity Genes in Humans

Why do some people live much longer than others? What allows these individuals to escape age-associated diseases that contribute to mortality in the elderly? Is this a result of favorable genes or merely a healthy life style? If the genome does play a role, what are the mechanisms?

To address these questions, we recruited over 1500 Ashkenazi Jews. The Ashkenazi Jewish population is unique as it is derived from a small number (several thousands) of founders and therefore it is genetically homogeneous. This population has been utilized for identification of several genes, a prominent example being the breast cancer gene. The subjects fall into three groups; probands, subjects with exceptional longevity (1:10000 in the general population); their offspring; and a control group consisting of spouses of the offspring and other Ashkenazi Jewish people recruited from the Einstein Aging Study.

Studying the clinical and metabolic phenotype, revealed certain physiological characteristics in the centenarians and their offspring such as high levels of high-density lipoprotein (HDL), high adiponectin levels, and high IGF-1 levels. In collaboration with Dr. Atzmon and Suh, we showed that each of those phenotype is now associated with a genotype that has a functional meaning, and each of those genotypes have been validated independently in at least one other population of centenarians. One of the genotypes is also specifically protective from cognitive decline, and this was also validated as an Alzheimer’s protective gene. Recently, we studied telomere length in our population, demonstrating longer telomeres in our longest living subjects and their offspring compared to control. These finding may indicate longer telomeres at birth or slower attrition rate in their length, and this was associated with a specific haplotype of the telomere gene. Most important, since the trait of longer telomeres is associated with protective lipoprotein profile and less age-related disease, this test may be used as a predictor for longevity.

Using an un-biased approach we have employed an Affimetrix 6.0 platform with almost 2MM markers and across the genome. Comparing the centenarian genotype to a younger un-related control, we established 35 genotypes that increase monotincally with aging (from age 60 to 112)) and were linked significantly (p<10-6) to genes that have not been previously linked to aging. In collaboration with Dr. Bergman, using system biology approach we have found pattern of markers that are associated with aging and that are protected by specific longevity genes. In collaboration with Drs. Greally and Atzmon, we have used high throughput methylation assay (HELP) to demonstrate that centenarians methylation pattern across the genome is significantly different than in younger un-related subjects.

Our lab has trained many graduates and post-doc, and the latest graduate, Reid Thompson, MD PhD student, can be a reference. We offer a clinical platform for variety of genomic studies in collaboration with many of the Einstein faculty.

Recent Publications:
My lab uses the small nematode *C. elegans* with its simple and well characterized nervous system as a genetic model. We are trying to understand how growing axons navigate the extracellular space in order to connect to their appropriate partners. The extracellular space is filled with a complex mixture of proteins and proteoglycans e.g. heparan sulfate (HS) proteoglycans which are a particular focus of the lab. We are asking how specific modification patterns of the polysaccharide HS determine the path of developing axons.

We have shown that distinct modification patterns in HS serve specific and instructive functions during neural development leading us to formulate the ‘HS code’ hypothesis. We propose that defined combinations of modifications in the sugars of HS contain information and generate a molecular map that helps shaping the nervous system. Our goal is to decipher the information contained in HS, determine the factors that create and modulate it and describe the genes that respond to it.

In a related project we are investigating a pathological dimension of HS by studying Kallmann Syndrome, a human genetic disease with specific neurological defects. Using *C. elegans* as a model, we have shown that *kal-1*, the nematode orthologue of the gene mutated in human Kallmann patients, has a role in axon branching and requires HS with specific modifications for these functions. Our goal here is to understand how KAL-1 functions on a molecular level during disease and development. We approach this by conducting genetic screens to identify novel genes that interact with *kal-1*.

In summary, our studies are directed towards an understanding of how heparan sulfate and its modifications (the ‘HS code’) functions during development and disease of the nervous system.

**Recent Publications:**
My team has developed a unique mouse model of human dry eye syndromes via blockade of neurotransmission in tear production within the lacrimal gland. To accomplish this goal, we use botulinum toxin (the same compound used to remove facial wrinkles!). The resulting dry eye at the ocular surface mimics that found in humans and allows simple high throughput testing of preclinical therapeutics and devices for dry eye. In extreme dry eye damage states, the ocular surface can become stem cell deficient. Because my group is one of but a few that performs corneal epithelial stem cell replacement surgery regularly in humans, utilization of this titratable animal model of ocular surface damage will allow for better understanding of human stem cell deficiency as it affects ocular surface disease. The other arm of my team’s research program employs our expertise in bioengineering to create new tools and devices for laboratory investigation and surgical therapy. Among the devices which we have developed are a non-invasive microscopic tool for mitochondrial detection and potential stem cell isolation, laser systems for corneal transplantation currently in early clinical use, an implantable intraocular pressure monitor which would allow for continuous monitoring of intraocular pressure, and the Trabectome, a new and increasingly popular surgical approach for glaucoma treatment now in widespread clinical use in the United States.

Recent Publications:
ALES CVEKL, Ph.D.

Genetic and Epigenetic Regulatory Mechanisms in Mammalian Eye Development and Ocular Diseases

We are studying molecular mechanism of temporal and spatial regulation of expression of tissue-specific genes during mammalian development. We use an integrative approach to identify and characterize specific DNA-binding transcription factors and their co-activators interacting with proximal and distal regulatory regions of genes whose expression is coordinately regulated during development. We also study the dynamics of covalent modifications of core histones associated with these genes. Finally, we are interested in the developmental roles of ATP-dependent chromatin remodeling enzymes Brg1 and Snf2h and histone acetyltransferases CBP and p300.

Our model system is the ocular lens. Because of its unique morphology, lens is an advantageous tissue to study molecular mechanisms of embryonic induction, cellular differentiation, intercellular signaling and aging. Lens progenitor cells are formed as a result of multiple signals exchanged between the head surface ectoderm surrounding the anterior neural plate, the pre-placodal region, and lateral mesoderm. Lens precursor cells and terminally differentiated lens cells are marked by the expression of crystallin genes. Lens development as well as crystallin gene expression are regulated by a sparse number of genes encoding transcription factors such as Pax6, large Mafs, Prox1, Six3, Sox1, Sox2 and Hsf4 expressed in the lens. These genes act in concert with various signal transduction pathways notably FGFs, BMPs/TGF-β and Wnts. These genes either control the entire process of eye development (Pax6) or its specific stages. Mutations in these genes are responsible for a wide spectrum of human congenital eye diseases (aniridia, early onset cataract, and glaucoma) affecting both the anterior segment (cornea, lens, iris, and trabecular meshwork) and retina. Our primary focus is on the genetic network regulated by Pax6. Pax6/eyeless is considered a "master" gene for eye development. Thus, studies of Pax6's function are important for understanding of eye development and evolution of visual systems.

Finally, we recently developed a procedure to generate large quantities of lens progenitor cells from human ES cells. This finding allows us to investigate the molecular mechanisms of lens lineage formation and to develop procedures to differentiate these cells into lentoid bodies. We plan to develop induced pluripotent cells (iPS) from patients with early onset senile cataract and from individual that do not develop cataract between age 65-80 and to use these materials to study mechanism of cataractogenesis. We are also interested to employ retinal pigment epithelial cells from age-related macular degeneration patients for similar studies. Our long-term goal is to identify genes and pathways involved in this disease and identify genes with protective roles in age-onset cataract and in age-related macular degeneration.

Recent Publications:
WINFRIED EDELMANN, Ph.D.

Genomic Instability and Cancer

The maintenance of genomic integrity in all organisms requires multiple DNA repair pathways that are involved in the processes of DNA replication, repair and recombination. Perturbations in these pathways can lead to increased mutation rates or chromosomal rearrangements that ultimately result in cancer. MMR is one of the repair systems that mammalian cells employ to maintain the integrity of its genetic information by correcting mutations that occur during erroneous replication. Mutations in MMR genes are linked to one of the most prevalent human cancer syndromes, Lynch syndrome and a significant number of sporadic colorectal cancers. At the molecular level tumors that develop in these patients display increased genomic mutation rates as indicated by increased instability at microsatellite repeat sequences (termed microsatellite instability, MIN). MMR in eukaryotes is complex and involves several homologs of the bacterial MutS and MutL proteins. In mammals, the initiation of the repair process requires two complexes formed by three different MutS homologs (MSH): A complex between MSH2-MSH6 for the recognition of single base mismatches and a complex between MSH2-MSH3 for the recognition of insertion/deletions. The repair reaction also requires a complex between the two MutL homologs MLH1 and PMS2 that interacts with the MSH complexes to activate subsequent repair events which include the excision of the mismatch carrying DNA strand and its re-synthesis. These steps are carried out by exonucleases, polymerases and a number of replication associated proteins. In addition to correcting DNA mismatches, the MMR system mediates an apoptotic response to DNA damage and suppresses recombination between non-identical sequences in mammalian genomes. All of these functions are thought to be important for genome maintenance and tumor suppression. We have generated knockout mouse lines with inactivating mutations in all the different MutS and MutL homologs, and also in genes that function in the later MMR steps to study their roles in genome maintenance and tumor suppression. In addition, we have generated knock-in mouse lines with missense mutations and conditional knockout mouse lines that inactivate specific MMR functions and/or model mutations found in humans. Our studies indicate that specific MMR functions play distinct roles in maintaining genome stability and that defects in these functions have important consequences for tumorigenesis and the response of tumors to chemotherapeutic treatment. They have also revealed that some of the MMR proteins play essential roles in the control of meiotic recombination in mammals.

Selected References:

How complex neural circuits form and how they function are major unsolved problems in neurobiology. We use the nematode *Caenorhabditis elegans* to study these questions at the cellular and genetic levels. We are currently completing a comprehensive description of the synaptic interactions in the nervous system of the *C. elegans* adult male—the male connectome. We identify synapses and the trajectories of neurons in serial section electron micrographs and construct neural maps using a novel software platform. Our male wiring diagram, together with that of the adult hermaphrodite, which was published in 1986, completes the description of nervous system connectivity for the adults of this species, the only animal species for which this information is available.

We are now investigating how the male circuits generate the male’s behavior and how the circuits are genetically specified. The *C. elegans* male nervous system contains a set of circuits located in its tail that generates the male’s copulatory behavior. The neural network containing these circuits consists of the processes of some 185 neurons and over 5,000 synapses. We analyze the patterns of connectivity within this network using computational methods to identify pathways that subserve particular steps of behavior. Hypotheses regarding neuron function are experimentally tested by cell killing techniques. We probe the functions of classical and peptide neurotransmitters, their receptors, and gap junctions by genetic methods.

To determine how the network is genetically specified, we make use of transgenes that express fluorescent proteins targeted to specific synapses. We plan to use these synapse-specific labels to identify mutants and genes that affect formation of particular cellular synaptic contacts. In these experiments we hope to uncover the still elusive class of proteins that encode the molecular determinants of synaptic specificity.

Visit our website: worms.aecom.yu.edu.

Selected Recent Publications:


AARON GOLDEN, Ph.D.
Genome, Epigenome and Microbiome Informatics

The digitization of genetic information, and the subsequent developments in high throughput sequencing technologies, has without question revolutionized the life sciences, and the discipline of genetics in particular. The collection, processing and interpretation of such diverse and information rich data remains an ongoing area of research from an informatics perspective, combining many different strands in computational science ranging from algorithmic development and hardware optimization, to the application of techniques in artificial intelligence and computer vision. The importance of such work cannot be understated as if we are to be able to deal with the exponential growth in raw sequence data, combined with increasing diversity of sequence assays, we need smart, innovative and scaleable computing solutions to keep pace. My lab is devoted to the development of such solutions applicable to a range of problems in genome, epigenome and microbiome analysis. Specific work areas are as follows:

Self Organizing Maps & Evolutionary Computing
The application of the Self-Organizing Map (SOM) neural network algorithm to various pattern recognition problems in DNA sequences remains a core bioinformatics activity for the lab. We are currently investigating potential applications of the SOM in such areas as gene prediction and regulatory motif identification, ChIP-chip and ChIP-seq enrichment, characterizing genomic and epigenomic states based on sequence annotation discriminants, and the annotation of microbiomes using analysis platforms based on this technology.

Predicting/Classifying Genomic States using Probabilistic Models
Hidden Markov Models and Support Vector Machines are two of the best known and widely used approaches to characterize regions of the genome previously identified as having a particular biological status using analytical/statistical techniques. The lab is interested in exploring these and other graph based approaches to identify and characterize various ‘omic’ states based on studying multiple next-generation sequencing datasets associated with specific cellular conditions.

High Performance & Accelerated Computation
Many existing and widely used bioinformatics tools are constrained by their poor computational performance when used with large datasets. The lab is interested in developing 'hybrid' codes utilizing MPI/OpenMP and Graphics Processing Units on standard graphics cards, the optimization of existing parallelized software on multi-core machines, and the development of novel algorithmic variants to utilize 'cloud' computing resources.

Selected Recent Publications


The genome is used in different ways in multicellular organisms to establish and to maintain cellular differentiation and fates. Transcriptional programming of this type requires some ability to maintain a memory of a differentiation state through cell division, a property usually described as epigenetic. The mediators of such epigenetic regulation potentially include the positioning, types and post-translational modifications of histones within nucleosomes, the methylation of DNA, the influence of short RNAs and chromatin looping in three dimensions.

The malleability of the epigenetic and transcriptional programs in the cell allow adaptation to the environment. However, the same adaptive and flexible processes used to the cell’s advantage can acquire errors and lead to pathological changes. As a consequence, genome-wide epigenetic studies (referred to as epigenomic studies) can give insights into disease states, originally exemplified by cancer, but now including everything from diabetes mellitus to Alzheimer’s disease.

The Greally lab has interests in both basic science and clinical research, focusing on epigenomic processes. We have a long-standing interest in cytosine methylation, having developed genome-wide assays that interrogate not only promoters of genes but also the other genomic contexts that are usually ignored, finding patterns of regulation in normal cells that serve to guide understanding of changes observed in human disease states. The question of how this methylation mark is read by the cell has prompted us to initiate a program in structural epigenomics with colleagues in Biochemistry, and the development of a new approach to identify R-loop forming DNA in mammalian cells. Our human disease interests include type 2 diabetes mellitus arising as a consequence of intrauterine growth restriction, chronic kidney disease, Huntington’s disease, asthma and allergy, breast cancer, and viral infection of cells.

We recognize that computational skills are now an essential part of epigenomics research, making this a major focus of the lab. The same combination of molecular and computational approaches to study basic science and clinically-relevant questions defines Einstein’s Center for Epigenomics, directed by the PI, bringing new technological and computational resources to Einstein as a whole.

Recent Publications:
Early in development, the brain starts off as a simple sheet of neuroepithelial cells. My lab is interested in understanding how this simple sheet of progenitor cells develops into the adult forebrain and in particular into the adult cerebral cortex, the part of our forebrains that we use for our highest cognitive and perceptual functions. Essential to this understanding is the identification of the signals that pattern the early forebrain and that regulate the proliferation, cell fate choices, and differentiation of neural stem cells and progenitor cells. The primary approach we are using to test the roles of candidate signaling molecules directly \textit{in vivo} is a conditional genetic approach in the mouse using CRE/loxP technology. Our goals are: 1) to further characterize the roles and intracellular pathways of signaling molecules of the FGF, BMP, and WNT families in prenatal forebrain development; 2) to examine the roles of these factors at postnatal ages and in adult forebrain homeostasis; and 3) to establish paradigms to regenerate glutamatergic neurons in the adult neocortex using endogenous or transplanted neural precursors.

\textbf{Selected Recent Publications:}


The primary aim of this laboratory is to more fully understand the genetic bases of nicotine dependence and 22q11 syndrome.

**Nicotine dependence**: Among those who initiate smoking, only one-third develop dependence and addiction. Individuals who develop dependence often exhibit pre-existing behavioral traits. There are many genes that likely contribute, in complex ways, to individual variations in the development of nicotine dependence. Identification of such genes has been difficult in humans. Nicotine dependence includes tolerance, withdrawal, cue reactivity, and many other elements. These elements are likely to have distinct neural and genetic substrates. Additionally, it is thought that multiple genes affect nicotine dependence in a complex way. Mouse models provide a unique opportunity to examine the precise ways that individual genes alter different elements of nicotine dependence. We use diverse behavioral paradigms to examine how specific genes contribute to elements of nicotine dependence. Our studies have revealed that the transcription factor FosB, monoamine oxidase A, and cGMP-dependent protein kinase (PKG) are required for nicotine cue reactivity and stress-related behavioral traits. We are currently using lentiviral vectors to identify specific brain regions in which genes mediate the expression of nicotine cue reactivity.

**22q11 and neuropsychiatric disorders**: The human genome includes many variations, ranging from duplications and deletions of full chromosomes to single nucleotide polymorphisms. Moreover, a large number of kilo- to mega-base copy number variations (CNVs) are associated with autism spectrum disorder, mental retardation, and schizophrenia. Human chromosome 22q11.2 contains CNVs. Children and adolescents with 22q11.2 duplications and deletions consistently exhibit these neuropsychiatric disorders, along with associated cognitive and intellectual impairments during development. However, the diagnosis of these neuropsychiatric disorders is challenged by variations in diverse cognitive and intellectual capacities. Thus, patients with the same diagnosis may vary greatly in specific symptoms. Moreover, because duplications and deletions of 22q11.2 encompass 1.5 Mb or larger regions, it is not possible to determine whether segments or single genes are responsible for specific phenotypes in humans. To circumvent these obstacles, our laboratory examines the role of individual 22q11 genes in distinct aspects of behavior in genetically engineered mice. We have identified two small human 22q11.2 segments whose over-expression during development causes behavioral phenotypes consistent with neuropsychiatric disorders. Our current work examines the role of each of the genes encoded in the segments in behavioral phenotypes relevant to neuropsychiatric disorders in mice.

**Recent Publications:**


WILLIAM R. JACOBS, JR., Ph.D.

Molecular Genetic Approaches Towards Controlling Multi-Drug Resistant Tuberculosis

Tuberculosis, caused by *Mycobacterium tuberculosis*, causes one in four avoidable deaths in the Third World and kills more adults than malaria, AIDS, and all tropical diseases combined. In recent years, there has been a dramatic increase in the number of new TB cases worldwide - one of the consequences of the AIDS epidemic. In addition to these increasing incidences of TB, there has been an emergence of *M. tuberculosis* strains that are resistant to all seven anti-tuberculosis agents. These alarming trends have caused the World Health Organization to declare tuberculosis a global health emergency, a distinction never accorded another disease. My laboratory has focused on developing systems to genetically manipulate mycobacteria, particularly *M. tuberculosis*. These tools have allowed us to 1) develop the luciferase reporter phage assay for rapid assessment of drug susceptibilities; 2) analyze the genes involved in resistance to tuberculosis drugs such as isoniazid, ethionamide, ethambutol, and pyrazinamide, 3) to identify specific phenotypic properties associated with tuberculosis pathogenesis, and 4) develop recombinant mycobacteria vaccines. Current research efforts are employing a newly developed transposon mutagenesis system to identify genes of *M. tuberculosis* that are required for growth and persistence in mice. Additionally we have developed a high-throughput system for knocking out each gene in *M. tuberculosis*. This set of knockouts is a valuable resource for understanding important pathways and gene functions in *M. tuberculosis*. This knowledge should lead to the development of novel tuberculosis drugs and attenuated mutants of *M. tuberculosis* that can be used as live-cell tuberculosis vaccines. In addition, we have used genes from mycobacteriophages to make *Plasmodium falciparum*, the causative agent of malaria, more genetically tractable.


Recent Publications:


Epithelial cells are polarized in multiple ways. Apical-basolateral polarity (perpendicular to the plane of the epithelial sheath) enables a cell to directionally transport molecules across a cell layer (e.g. in the gut, kidney and glands) and selectively secrete extracellular matrix components to form a basal lamina. To perform many of their functions, epithelia frequently also have to be polarized within the plane of the epithelium. The latter polarization is commonly referred to as epithelial planar cell polarity (PCP) or tissue polarity and allows a cell to form structures that require not only positional, but also vectorial information. The cellular consequences of PCP signaling range from coordinated organization of cytoskeletal elements in single cells to complex migration of groups of cells. Examples of PCP in vertebrates can be very obvious, as in the ordered arrangement of scales on fish or hairs of mammalian skin. Less visible examples are the cilia of the respiratory tract and oviduct as well as the stereocilia of the sensory epithelium of the organ of Corti in the vertebrate inner ear. Aberrant PCP can lead to left/right asymmetry defects, open neural tubes, deafness and kidney disease.

PCP signaling is, however, best studied in *Drosophila melanogaster*, mainly because of the versatility of the fly as model system. In *Drosophila*, PCP can easily be seen on several external adult structures such as the bristles on the thorax or the precisely aligned hairs on wing cells. In addition, the facet eye also shows characteristics of PCP with its precise arrangement of each building block, the ommatidium, with respect to each other and the general axes in each eye. Genetic and molecular studies in *Drosophila* led to the identification of a signaling network – the non-canonical Wnt/Frizzled-PCP pathway – directing PCP establishment. In recent years it has become apparent that the PCP signaling module is highly conserved from insects to ascidians and mammals and is one of the most exciting topics of developmental biology today.

Due to the available tools and the possibility to use a combination of genetic and biochemical approaches, *Drosophila* is ideally suited to further dissect the PCP pathway and define its relationship to the cytoskeleton.

My lab is particularly interested in how the Fz-adapter protein Dsh regulates the canonical and non-canonical (PCP) Wnt pathways. We have identified candidate kinases and a phosphatase modifying Dsh in a systematic molecular screen based on RNAi. We currently characterize these kinases in vitro and in vivo using genetic and immunohistochemical tools. Furthermore, we study two additional kinases, Nemo and Rho kinase that have previously been shown to be required for the migration aspect of PCP establishment (and – in case of Rock – also for tumor cell migration). We have systematically identified targets of Nemo and Rock and use genetic and molecular approaches to integrate these substrates into the PCP signaling pathway and cell migration in general.

It is our goal to use *Drosophila* as model system to address fundamental questions that are relevant for development and disease in general.

Lab homepage: [http://jennylab.aecom.yu.edu/](http://jennylab.aecom.yu.edu/)

Selected References:


IN11/hSNF5 is a component of the chromatin remodeling SWI/SNF complex. It is an interacting partner for HIV-1 integrase (IN) and also a tumor suppressor biallelically mutated in rhabdoid tumors, a rare but highly aggressive pediatric malignancy. The two major areas of focus in the laboratory are: (i) understanding the role of IN11 in HIV-1 replication and exploring its potential as a drug target for intervention of AIDS; and (ii) understanding the mechanism of tumor suppression by IN11/hSNF5 and developing novel and effective therapeutic strategies for rhabdoid tumors.

IN11 in HIV-1 replication: We have found that IN11/hSNF5 directly binds and recruits components of Sin3a-histone deacetylase (HDAC) complex into the HIV-1 virions and this HDAC1 complex appears to be required for viral infectivity. We are currently isolating and characterizing IN and IN11 mutants defective for binding to HDAC1 complex and testing their effect on HIV-1 replication. We have found that HIV-1 harboring IN mutants defective or binding to IN11 are severely compromised for replication. Furthermore, we have found that IN11 mutants defective for binding to HDAC1 complex dominant negatively inhibit HIV-1 but not SIV replication. These studies are likely to open up a new paradigm for role of IN11 in HIV-1 replication and may provide novel strategies to inhibit viral replication.

Mechanism of Tumor suppression by IN11/hSNF5: By using a series of genetic systems developed in our laboratory and by isolating cancer-associated mutations of IN11, and a wealth of protein-protein interaction defective mutants of IN11, we are dissecting the exact mechanism of IN11-medaited G0/G1 cell cycle arrest, mitotic arrest, and senescence and tumor suppression. Furthermore, characterizing the IN11-associated HDAC1 complex has revealed an unanticipated role of IN11 in interferon signaling and tumor suppression.

Development of targeted therapies for rhabdoid tumors based on IN11 function: One of the goals of our laboratory is to develop molecularly targeted therapies based on the understanding of genesis of rhabdoid tumors. Majority of rhabdoid tumors have biallelic inactivation of IN11 gene. Our previous studies demonstrated that Cyclin D1 is a direct downstream target of IN11-mediated repression and that rhabdoid tumors are exquisitely dependent on Cyclin D1 for genesis and survival. Our preclinical studies have provided proof of principle for our hypothesis that targeting Cyclin/cdk axis is an effective means of inhibiting rhabdoid tumors in vitro and in vivo. The current goal is to develop novel strategies to facilitate clinical translation of laboratory findings to establish an effective therapy for these tumors. For this purpose, we are using non-invasive imaging technology such as microPET to monitor the therapeutic efficacy in primary mouse tumor models, developing novel drugs to target these tumors and investigating the interaction between Cyclin D1, the cdk pathway and In11 in mouse models.

Identification of downstream pathways regulated by IN11 has been instrumental in novel biomarkers and therapeutic targets for these tumors. Aurora A is repressed by IN11 and it is de-repressed in rhabdoid tumors due to loss of IN11. We have found that Aurora A is a novel therapeutic target as siRNA-mediated depletion of this gene resulted in potent mitotic catastrophe and cell death in rhabdoid tumors.

Recent Selected Publications:


Induced pluripotent stem (iPS) cells for disease modeling in schizophrenia

Schizophrenia (SZ) is a common psychiatric disorder affecting ~1% of humanity, leading to a lifetime of disability for a majority of patients. Twin studies show a high level of heritability (between 60-80%). However, lack of complete concordance in monozygotic twins suggests that environmental and epigenetic factors might play a substantial role in disease pathogenesis. A significant obstacle in studying the molecular basis of SZ and other neuropsychiatric disorders is the inaccessibility of the human brain, which has restricted molecular studies, such as gene expression profiling and epigenetic analysis, to autopsy samples. While some interesting findings have been made using postmortem brain, interpreting the data is associated with numerous confounding factors. In addition, since SZ is believed to be a developmental disorder, studying molecular events in postmortem samples is limiting. The discovery of iPS cells, which essentially allows investigators to reprogram somatic cells into pluripotent stem cells capable of differentiating into neurons and other cell types, provides an opportunity to create patient-specific neurons in vitro. The Lachman lab has begun to develop iPS cells from controls and patients with SZ, including a subset that carries a well characterized 22q11.2 del found in ~1% of patients. These cells are being induced to differentiate into glutamatergic neurons and are being subjected to gene expression profiling and epigenetic analysis to identify patient vs control differences. We are using next generation sequencing available through the Einstein Epigenetics Core facility. Gene expression profiling using next generation sequencing (RNA-Seq) carried out on a subset of our samples is providing us with a wealth of molecular data relevant to disease pathogenesis as well as human neurogenesis. Noteworthy so far is discovery of several novel long non-coding RNAs (IncRNAs) that appear to be involved in regulating HOX gene expression and early neurogenesis. In addition, based on disease mapping studies using genome wide association and our preliminary RNA-Seq data, we identified two IncRNAs that we suggest are involved in the development of SZ in a small subgroup of patients.

Epigenetic analysis and knockdown of SZ candidate genes coding for transcription factors and chromatin modifying enzymes followed by gene expression profiling are in the process of being carried out in differentiating human neurons derived from iPS cells.

Selected Recent Publications:
Erika Pedrosa, Vladislav Sandler, Abhishek Shah, Reed Carroll, Chanjung Chang, Shira Rockowitz, Xingyi Guo, Deyou Zheng, Herbert M. Lachman Development of patient-specific neurons in schizophrenia using induced pluripotent stem cells. (in press, Journal of Neurogenetics)
Retroviruses are associated with a variety of diseases in humans and other vertebrates including cancer and immunodeficiency. The major goals of the laboratory are focused on understanding the molecular basis of retroviral diseases. Mouse retroviruses cause tumors by a mechanism of insertional activation of oncogenes where the viral DNA integrates adjacent to an oncogene, and enhancer elements in the virus activate transcription of the adjacent host gene. We use these viruses as tools for high-throughput identification of cancer-causing genes in the mouse genome. Using sophisticated PCR techniques combined with massively parallel DNA sequencing, the viruses have been used as molecular tags to identify over 60 different genes that cause lymphomas, many of which have not been associated with a cancer-causing role previously, and we are also investigating the molecular mechanisms by which these genes act. Since retrovirus gene therapy vectors cause tumors in human patients by the identical mechanism, we have developed strategies to prevent retroviruses (or any other gene therapy vector that integrates into the human genome) from activating oncogenes and causing cancer. Our newly developed strategies can block most tumors, and are being adapted to human gene therapy use, and we are striving for even greater success.

8% of the human genome is retrovirus DNA. Human endogenous retrovirus K (HERV-K) the newest of all the retroviruses to enter the germline DNA of humans that is transmitted from parents to children. All humans are born with about 20 distinct HERV-K proviruses (the form of retroviral DNA that is integrated into the host genome) in their germlines. We are investigating whether this retrovirus can reinfect humans today. We have shown that most HERV-K proviruses in the human formed relatively recently in human evolution, long after the divergence of the human and chimpanzee lineages approximately 6 million years ago. We identified several proviruses that formed so recently that they are not yet fixed in the human genome. We have also identified two HERV-K proviruses that have full length open reading frames for all viral proteins, and are the best candidates to be infectious retroviruses in the human genome today. We are now asking whether HERV-K can indeed replicate in humans today, and whether it might be associated with any diseases.

In collaboration with Drs. Larry Herbst and Robert Burk, we are also studying a herpesvirus and a papillomavirus that are associated with fibropapillomas in endangered and threatened species of marine turtles. We are investigating the evolutionary histories of these viruses, how they are transmitted, the nature of turtle immune responses to them, and the roles of the viruses in causing tumors.

References:
STEVEN K. LIBUTTI, M.D.

Targeting the Tumor Microenvironment to Treat Cancer

The goal of Dr. Libutti’s research program is to develop novel cancer therapies through a better understanding of the complex interactions within the tumor microenvironment. In order to better understand the relationship between the tumor and its microenvironment, their research is focused on the interaction between tumor-derived factors and host cells developing in the context of the tumor microenvironment. By understanding this interaction they hope to be able to design novel treatment strategies to inhibit both the growth and the spread of tumors. They are currently studying a variety of tumor-derived factors with effects on tumor-associated vasculature as well as tumor stromal elements. Dr. Libutti’s approach to the study of these interactions has been through the utilization of a variety of in vitro and in vivo model systems. His team is using genetic approaches such as gene expression profiling and methylation analysis to understand the changes that occur in cells within the tumor exposed to tumor-derived factors. They have developed techniques, which allow them to isolate endothelial cells, fibroblasts and cancer stem cells from tumor tissue. This has resulted in their ability to study tumor-derived cells directly, and has led to the observation that tumor associated endothelial cells and stromal cells have epigenetic changes compared to normal cells from the same tissue type. This approach has also allowed them to identify specific genes such as FILIP1L (formerly DOC1), which appear to play a role in the ability of cancer cells to invade and migrate through tissues.

The laboratory has also developed mouse models of human cancers that recapitulate the tumors seen in human conditions. The laboratory is particularly interested in endocrine and neuroendocrine tumors and has developed mouse models of MEN1 and vHL. The tumors that result are similar to those seen in patients with these syndromes and serve as a useful tool for studying biomarkers and target genes. A human biospecimen repository for endocrine and neuroendocrine tumors with over 400 samples has also been developed for correlative studies. Endocrine and neuroendocrine tumors are extremely vascular and therefore serve as an ideal model for studies of tumor angiogenesis and the tumor microenvironment.

Various methods of delivering anti-tumor agents, including targeted gene therapy approaches and the use of tumor targeted nanoparticles are being pursued. Dr. Libutti was the first to administer TNF bound colloidal gold nanoparticles as targeted therapy to cancer patients. The overall goal of Dr. Libutti’s work is to translate a better understanding of tumor cell-host cell interactions, within the context of the tumor microenvironment, into better therapies for patients with cancer.

Selected Publications:
SRIDHAR MANI, M.D.

Phenotyping Orphan Nuclear Receptors

Orphan nuclear receptors (those that lack a well defined physiologic ligand) control nearly every major physiologic and biochemical process in eukaryotes - cell metabolism (e.g., cholesterol, energy, bile acids), xenobiotic detoxification, cell differentiation (e.g., gastrulation, retinal development), circadian rhythm, and cancer cell growth and apoptosis (e.g., NURR77). Alterations in the receptor are directly linked to human disease (e.g., NOR1 and extraskeletal myxoid chondrosarcomas). Of these receptors, the steroid and xenobiotic receptor (SXR or PXR) is a key regulator of genes encoding drug metabolizing and transport proteins. In addition, PXR has been implicated in cancer drug resistance, carcinogenesis and pathophysiologic states like osteomalacia. Our laboratory focuses on defining the role of PXR and other orphans in: (i) xenobiotic metabolism and pharmacology (ii) carcinogenesis, organogenesis, host defense and anticancer drug resistance using classical techniques in genetics and pharmacology.

Also see: http://sridharmanilab.googlepages.com/

Recent Publications:
Mukherjee S, Wang H, Mani S. Novel physiologic implications for the Pregnan X Receptor in gut innate immunity. submitted
CRISTINA MONTAGNA, Ph.D.

Genes Regulating Normal Breast Differentiation and Identification of Novel Biomarkers for the Detection and Classification of Breast Cancer

Project 1- Role of Septin 9 in Breast Carcinogenesis.
A comparative cytogenetic approach aimed to identify recurrent DNA copy number variations in a panel of murine models for breast cancer resulted in the identification of Septin 9 (Sept9) as potential novel oncogene. The septin family of genes codes for a highly redundant and conserved family of GTP-binding proteins that assemble into filaments and bind to microfilaments and microtubules. At the locus of genomic amplification deregulation of Sept9 expression occurs by a complex pattern of genetic and epigenetic alterations affecting several Sept9 isoform variants. Our hypothesis is that during malignant transformation, breast epithelial cells undergo genomic amplification of the Sept9 locus and over-express Sept9 mRNA and protein. Additionally, aberrant cytosine methylation occurs at specific alternative promoters within the Sept9 locus resulting in an abnormal pattern of Sept9 isoform variants. We are currently studying how the expression of various Sept9 isoforms is regulated in normal and cancer cells and the functional differences between these isoforms.

Project 2- Stage- and Cell Subtype-Specific Epigenetic Regulation of Mammary Gland Development and breast tumorigenesis.
We are interested in investigating the DNA methylation changes occurring in the development of the normal mammary gland during puberty, adult age, pregnant, lactating and undergoing mammary gland involution. This approach has the final goal of dissecting the molecular processes that mediate methylation changes in the morphogenesis and differentiation of the normal breast and to identify “hot spot” loci for gene silencing in breast carcinogenesis.

Project 3- Aneuploidy in aging.
Polyplody and aneuploidy are the most frequent cytogenetic events observed in mammalian cells. Polyplodization is a widely accepted mechanism for increasing genetic variation in unicellular organisms and for the acquisition of new properties in a variety of cell types (e.g., osteoclast fusion in bone resorption and myoblast fusion in muscle development) and is considered a physiological process. Aneuploidy on the contrary is linked to pathological states. It is a hallmark of spontaneous abortions and birth defects and is observed virtually in every human tumor. While the catastrophic consequence of high levels of aneuploidy observed in abortions is self-explanatory, the role of aneuploidy under physiological conditions is a question waiting for answers. The major goal of this project is to explore a possible correlation between age-associated genome instability in a variety of tissues and functionality of these cells.

Recent Publications:


Our lab is interested in discovering genes required for organogenesis, a process by which organs form during embryonic development, with the purpose to understand the cause of birth defects. Our research begins with collecting DNAs from affected individuals with genetic disorders having known chromosomal gains or losses, and moves to looking at gene function in model organisms. This process runs full circle back to humans to provide at minimum better prenatal screening, ideally, to discover ways to reduce symptoms. The reason for studying chromosomal disorders is that regions in the genome containing large duplications or deletions of DNA, will pinpoint the location of causative genes whose function in organogenesis is sensitive to altered copy number. To identify the responsible ones, among dozens of genes in each interval, we have turned to using mouse and zebrafish model organisms. The model organisms further help to determine gene function.

Our main focus is on a disorder termed chromosome 22q11.2 deletion syndrome (22q11DS). Most affected children have a similar sized 3 million base pair deletion encompassing 40 genes. Children with the syndrome have learning disabilities, cleft palate, hearing loss and cardiovascular defects. One gene in the region termed Tbx1, a transcription factor, was found in mouse models, to be responsible for many of the defects in patients with the syndrome. Using knockout and gain-of-function mutant mice, we have begun to understand its function. Since it’s a transcription factor, we are interested in genes it can regulate. Our mission is to build a genetic pathway downstream of Tbx1. Since we don’t know what pathways are regulated, we took an unbiased gene discovery approach. To do this, we isolated RNA from normal and mutant mouse embryos at various developmental stages and performed microarray gene profiling. From this analysis, it appears that Tbx1 promotes cell survival and restricts differentiation. We are validating these findings by doing real-time RT-PCR and in situ hybridization of probes to genes uncovered on staged mouse and zebrafish embryos. We eventually want to perform molecular studies including chromatin immunoprecipitation followed by next-generation sequencing. To identify genes regulating Tbx1, we are screening putative mouse enhancers in zebrafish using the tol2 transposon system. This approach requires injection of enhancers connected to fluorescent reporters into fertilized zebrafish eggs and watching where the reporter is expressed in live embryos.

Although most patients have the same sized 3 Mb deletion, the severity varies dramatically. While some are mildly affected, others are very sick. In order to go full circle with our research program, we are taking genes discovered in the mouse or zebrafish and are seeing if DNA variations in them could alter the overall phenotype in affected individuals. In addition to the candidate gene effort, we are also taking unbiased approaches by performing a whole genome association study using Affymetrix microarrays containing 1.8 million single nucleotide and copy number DNA variations.

Recent Publications:
HARRY OSTRER, M.D.

Human Genomics in Development and Disease

Genetic differences play an important role in normal human development and disease. These differences can also play a role in the progression of disease and in individual responses to therapy. The research mission of our laboratory is to use of modern genomics to help understand the roles of human genetic variation in these processes.

Genetic variation in human populations. We have characterized genetic variation in a number of human populations (Hispanics and Latinos, Jewish HapMap Project) to understand the origins and migrations of these populations. Currently, we are exploring the role of natural selection in the formation of some of these populations. We are carrying the work forward to understand disease susceptibilities within these groups. A key feature of this work is translating new findings into clinical practice to promote personalized medicine.

Human developmental disorders. We study the genetic basis of rare genetic disorders, notably disorders found in isolated populations and disorders of sex development, to identify not only the mutational basis, but also the molecular mechanisms. Recently, we identified mutations in genes in the MAP kinase pathway in abnormal testicular development and now are investigating the roles of members of this pathway in normal testicular development.

Cancer genetics and genomics. We have explored the roles of low and high-penetration variants in risk of human cancers and have developed models for predicting risk. Through genome wide association studies, we have identified common variants that increase risk of adverse outcomes (erectile dysfunction, urinary dysfunction, proctitis) for men treated with radiation therapy for prostate cancer. We have also developed a molecular signature based on acquired somatic copy number alterations that is highly predictive of risk of metastasis and may account for this increased risk among African-American men.

Recent publications
Spatiotemporal regulation of vertebrate axis segmentation, stem cell proliferation and muscle differentiation

Vertebrate body axis is composed of repetitive structures, called vertebrae. These metameric structures are established during embryonic development by a process called somitogenesis, where the precursors of vertebrae and associated muscles are laid down as sequential tissue segments (somites). The rhythmic production of the somites is controlled by the “segmentation clock” that reveals itself as oscillatory gene expression at the posterior (tail) end of the vertebrate embryos. Fgf, Wnt, Notch and Retinoic Acid (RA) signaling pathways interact with each other to regulate the somite segmentation and differentiation. Defects in somite segmentation and differentiation result in vertebral anomalies, congenital scoliosis, and mispatterning of intersomitic blood vessels and peripheral nerves. It is important to identify genes involved at different stages of segmentation in order to develop future gene- and cell-therapies for the patients. Cells segmented into somites differentiate into vertebrae and muscles. Muscle wasting (muscular atrophy) and muscular dystrophy develop due to genetic mutations, metabolic disorders and aging. It is crucial to discover the gene regulatory network that controls the differentiation of muscle cells to be able to induce adult muscle stem cells (satellite cells) to proliferate and differentiate. Also, the regulation of metabolism in muscle cells needs deeper understanding to prevent and cure metabolic defects, such as insulin resistance in muscle cells.

In my lab, we focus on three major research areas:
1- Regulation of differentiation, growth and metabolism of muscles during embryogenesis
2- Control of vertebrate anterior-posterior axis extension: proliferation of stem cells at the posterior end of the embryo
3- Quantitative developmental biology: somite segmentation, gene expression oscillations, morphogen gradients

We are trying to understand how these processes are controlled by the signaling pathways and their transcription factor targets. Genome-wide studies, molecular temporal-perturbation experiments and imaging will be coupled with bioinformatics tools and mathematical modeling to achieve these objectives and zebrafish will be utilized as the main model organism during these studies.

Recent Publications:
How does a cell respond rapidly to changes in its environment? How does an organism develop from a single cell into specialized cell types and into tissues and organs? The answers to these broad questions often boil down to two principal mechanisms: regulation of gene expression and post-translational signaling that alters protein activity. Historically, the long-term interest of our lab has been to understand how the general transcription factors and their regulators combine to generate such exquisitely flexible yet consistent patterns of gene expression. Recent genetic selections in our lab, however, established links between transcription and post-translational modification by the ubiquitin family, drawing our lab into the intersection of the transcription, ubiquitin, and SUMO fields.

So what are the ubiquitin and SUMO pathways and why are they important? Ubiquitin and SUMO are the two most prominent members of the ubiquitin protein family. Both of these small regulatory proteins (less than 100 amino acids long) are covalently conjugated to other cellular proteins and regulate their activity, analogous to the role that phosphorylation performs in other signaling pathways. Ubiquitin and SUMO are conserved and essential for viability of most eukaryotic cells, and they post-translationally modify many proteins that are important for normal cell growth and human disease. Conjugation with ubiquitin often targets substrates for proteosome-mediated degradation, and it can also serve as a signaling modification that stimulates protein-protein interactions, whereas SUMO conjugation has less predictable biological outcomes, presumably mediated by recruitment of different SUMO-binding effector proteins. Modification with SUMO can: (1) directly alter protein activity, (2) alter cellular localization, and (3) affect protein stability, but the molecular determinants of these different outcomes need to be investigated in greater detail. The lack of a clear understanding of the roles and regulation of this essential pathway is one of the major elements that has drawn us to study it further. The ongoing projects in our lab have three goals: (1) to investigate the roles of two newly identified ubiquitin ligases in general transcriptional regulation, (2) to identify downstream effectors of SUMO pathway signaling, and (3) to identify small molecule inhibitors of the SUMO pathway.

**Recent Publications:**


CHARLES E. ROGLER, PhD

Roles of long non-coding RNAs and microRNAs in gene silencing in mammalian cells

**Overall Research Program:** The Rogler laboratory investigates functions and mechanisms of action of long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) in gene silencing in mammalian cells.

**Background:** Recent work in our laboratory has focused on the development of a protocol for the direct biochemical identification of microRNA (miRNA) targets in RNA Induced Silencing Complexes (RISC). This has led us to discover that long non-coding RNAs (lncRNAs) have a highly enriched presence of in RISC. We have also identified a new class of RNAs involved in gene silencing, that have been designated as *silencing long-non-coding derived RNAs* or *silondRNAs*.

**Major Projects in the laboratory:**
1. Studies of the biogenesis of silondRNAs in the nucleus.
2. Studies on the regulation of silondRNA biogenesis by microRNAs.
3. Biochemical identification of silondRNA targets in cell lines.
4. Studies on silondRNA biogenesis and targets in healthy and diseased liver tissue.
5. Roles of miRNAs in control of liver stem cell differentiation.
6. Role of miRNAs in targeting components of the TGFβ signaling pathway.
7. Roles of miRNAs in regulation of the RHOB tumor suppressor in liver cancer.

**Selected publications most relevant to current research:**


*Erin C. Connolly, Koenraad Van Doorslaer, Leslie Rogler, and Charles E. Rogler* Over-expression of microRNA-21 promotes a metastatic phenotype by targeting the tumor suppressor, RHOB *Mol Cancer Res;* 8: 691-700, 2010

*D. Moskowitz, B Kosmyna, LE Rogler, B Calder, J Matarlo, R Beawee, and CE Rogler*, Roles for Ago2-RNPs in nuclear and cytoplasmic functions of essential long non-coding RNAs, *2011, manuscript in Review*
During the past decade, liver-directed cell therapy and gene therapy for inherited metabolic disorders has progressed to a point where successful clinical application is in sight. Our current preclinical targets are inherited hyperbilirubinemia (Crigler-Najjar syndrome, CN-1) and alpha-1 antitrypsin (AAT) deficiency. We have been pursuing several approaches for liver-directed gene therapy as follows.

**Subproject 1. Hepatocyte-based therapies for genetic liver diseases.** The conventional source for human hepatocytes is livers from deceased allogeneic donors. Hurdles to broad clinical application of this highly promising approach include the scarcity of usable donor organs and the need for prolonged immunosuppression. To overcome these limitations, we are developing methods to abrogate allograft rejection of hepatocytes by transferring into donor hepatocytes ex vivo specific genes derived from the adenoviral DNA that down-regulate cell surface death receptors, thereby preventing killing by effector T-cells. In a different approach, we are exploring host tolerization by inhibiting costimulatory pathways between antigen-presenting cells and T-lymphocytes.

In other studies, we are developing pharmacological approaches to augment the engraftment of transplanted hepatocytes into the liver. In addition, we are optimizing the use of preparative hepatic irradiation (originally developed in our laboratory) to induce preferential proliferation of the engrafted hepatocytes. Our work has been translated into the first successful hepatocyte allotransplantation in a patient with CN-1. Regiospecific hepatic irradiation has been employed to augment the benefit of hepatocyte transplantation in an infant with urea cycle disorder (collaboration with University of Pittsburgh).

AAT deficiency (AATD) is one of the most common potentially lethal inherited disorders in the Western world. The classic form AATD arises from the inheritance of the misfolded AAT-Z variant, which is not secreted efficiently from hepatocytes into plasma. The resulting circulatory deficiency results in uninhibited neutrophil elastase activity in the lung, causing severe pulmonary emphysema. AAT-Z molecules retained in the hepatocyte endoplasmic reticulum as polymerized globules cause liver disease. We have shown that wildtype hepatocytes transplanted into recipient mice expressing human AAT-Z proliferate spontaneously, repopulating the liver, correcting the histological abnormality. The mechanism of hepatic repopulation by transplanted normal hepatocytes in AATD, has major implications for therapeutic application of hepatocyte transplantation for the treatment of liver and lung components of the disease, and is a focus of our laboratory.

**Subproject 2. Human embryonic and pluripotent stem cells as sources of hepatocytes:** Shortage of liver donors is a major obstacle to liver transplantation, as well as hepatocyte transplantation. As a novel renewable source of human hepatocytes, we have differentiated human embryonic stem cells into hepatocytes by manipulating human embryonic stem cells in culture. We have also generated induced pluripotent cells (iPSCs) from skin fibroblasts of normal subjects and patients with inherited metabolic diseases, and differentiated them into hepatocytes in culture. By transplanting hepatocytes derived from normal human iPSCs in the jaundiced Gunn rat model of human CN1, we have shown for the first time that these hepatocyte-like cells express mature (postnatal) functions of human hepatocytes, engraft in the liver and proliferate under appropriate stimuli. This is also the first demonstration of amelioration of an inherited metabolic disorder of the liver by transplantation of stem cell-derived hepatocytes.

Ongoing studies are focused on generating disease-specific iPSCs without integration of any exogenous DNA. Genetic lesions in these cells will be corrected by homologous recombination or supervised gene addition. The genetically corrected cells will be differentiated into hepatocytes and tested in preclinical studies by transplantation into animal models of the respective diseases.

**Recent Publications:**

NAMITA ROY-CHOWDHURY, Ph.D.

I. Inherited Disorders of Bilirubin Glucuronidation

UGT1A1 is a member of UDP-glucuronosyltransferases (UGT) family of enzymes, which is concentrated in the hepatic endoplasmic reticulum (ER). UGT1A1 mediates the glucuronidation of bilirubin and estrogens. UGT1A1-mediated glucuronidation is required for excretion of bilirubin in bile. We showed that the genetic lesions in any one of the five exons encoding UGT1A1 can abolish or reduce bilirubin glucuronidation, causing potentially lethal Crigler-Najjar syndrome type I (CN-I), or its less severe variant, Crigler-Najjar syndrome type II (CN-II). We also showed that Gilbert syndrome, a milder form of inherited hyperbilirubinemia, is caused by a promoter variation. We have been studying the regulation of UGT1A1 gene expression. Our objective is to develop novel therapies (gene and cell-based therapies) to cure this disease, using the jaundiced Gunn rat model of CN-1.

II. Primary Hyperoxaluria Type 1 (PH1)

PH1 is an autosomal recessive disease caused by mutations in the alanine:glyoxylate aminotransferase gene (AGXT). In humans, insufficient AGXT activity in liver peroxisomes leads to increased oxalate production that causes calcium oxalate stones in the kidney and then in blood, heart, bones, etc. It is a lethal disease unless combined liver and kidney transplantation is performed. We have developed a mouse model of PH1. Our plan is to cure this disease by (a) gene therapy (b) transplantation of adult primary hepatocytes or (c) hepatocytes derived from human embryonic (hESC) or induced pluripotent stem cell (iPSC). For the latter, fibroblasts from the skin of normal volunteers or patients with PH1 are used to generate IPS. Initially we used viral vectors to generate induced pluripotent stem cells. Our current focus is to use non-integrating factors to generate IPS cells.

Publications:
In the Human Genetics Laboratory at Jacobi Medical Center, under the medical directorship of Dr. Susan Gross, we provide clinical genetic testing as a service to hospital patients. Primarily the type of testing we offer identifies carriers who are at risk for having children affected with debilitating diseases such as Cystic Fibrosis. We also are engaged in research & development projects, including the recent development of a rapid and reliable targeted aneuploidy and microdeletion detection platform for use in the prenatal setting such as on amniotic fluid samples.

In separate efforts, over the past 5 years, we have been offering accessible and affordable genetic testing for Ashkenazi Jewish genetic diseases including but not limited to Tay Sachs-disease. These efforts recently led to the establishment of the Program for Jewish Genetic Health of Yeshiva University and Einstein. The overarching mission of the Program is to provide a centralized resource for the Jewish community and its future generations, addressing Jewish genetic health concerns from before birth to old age. Also see: http://www.yu.edu/genetichealth/

Recent Publications:
JULIE SECOMBE, Ph.D.

Transcriptional Control of Cell Growth and Development

My lab is interested in understanding the role of chromatin in the transcription of developmentally important processes such as cell growth using the model organism *Drosophila melanogaster*.

There are currently three main projects in the lab:

1. **The function of the histone demethylase Lid in animal development.** JmjC domain-containing histone demethylases were first described in 2005, making them the newest class of chromatin modifying enzyme. We are interested in understanding the function of Little imaginal discs (Lid), a JmjC domain-containing protein whose human orthologs are found misregulated in cancer and mental retardation patients. We are currently pursuing the role of Lid’s demethylase activity in regulating gene expression during development in addition to characterizing the function of Lid’s other domains implicated in chromatin and/or control of gene expression. Our studies characterizing Lid will enable us to gain insight into the role that dynamic covalent changes to chromatin play in regulated gene expression in vivo and will be directly relevant to understanding how this goes awry in cancer and mental retardation.

2. **The role of Lid in Myc-induced cell growth.** We isolated Lid in a genetic screen in *Drosophila* to identify novel effectors of Myc oncoprotein function. Based on the clinical importance of understanding the mechanisms by which Myc acts in tumorigenesis, we investigated the role of Lid in Myc-induced growth and showed that it is a novel co-factor required for dMyc-dependent transcriptional activation. Significantly, this occurs independently of Lid’s demethylase activity, leaving the mechanism by which Lid function in this context unknown. We are taking both genetic and cell biological approaches to determine the mechanism by which Lid functions in Myc-mediated activation of transcription.

3. **The mechanism by which Myc induces genomic instability.** Human cancer cells exhibit many chromosomal abnormalities (deletions, inversions, translocations etc) that are generated through genomic instability. Myc overexpression can lead to double-stranded DNA breaks and ultimately genomic instability, although the mechanism by which this occurs has remained elusive. We are investigating this question using lacZ mutation reporter transgenes. Using *Drosophila*, we aim to define precisely how Myc acts to promote genomic instability, a process that is key to understanding how Myc acts during tumor formation and subsequent metastasis.

Recent Publications:


SIMON SPIVACK, M.D., M.P.H.

Epigenetic Variability and Functional Impact on Gene Regulation

The goal of the Spivack laboratory is to understand differences in gene regulation among individuals, using genetic and epigenetic techniques. The mechanistic goal is to understand the subtleties of how specific high-resolution patterns of DNA methylation and microRNA expression regulate gene expression. We have developed several new functional genetic technologies to examine epigenetic function. We have recently completed initial genome-wide searches of the transcriptome, methylome, and micronome of lung cancers. The translational goal is to identify individuals at particularly high risk for lung cancer, to enhance prevention and early detection efforts.

There are both mechanistic and translational components to the studies:

Mechanistically, the role of promoter sequence and epigenetic variation in the regulatory region of carcinogenesis and oxidant pathway genes is being explored in vitro. We develop techniques in the lab, such as human genomic methyl-DNA reporter constructs, patch methylation strategies, in addition to studying native gene regulation models. Unique technologies include the realtime quantitation of native mRNA by the laboratory's RNA-specific strategy, microRNA:mRNA binding assay, tagged-bisulfite genomic sequencing strategy to determine high resolution CpG methylation maps at specific loci, and the respective functional consequence by patch methylation Luc reporter constructs.

Translationally, epigenetic and other biomarkers are being established by pairing laser capture microdissected human lung and several unique, non-invasively collected surrogate specimens developed in the laboratory, such as mRNA expression signatures from brush-exfoliated buccal mucosa cells, and DNA methylation and microRNA analyses from exhaled breath condensate, a first report for a new airway biomarker class. These airway-derived specimens continue to accrue from a sampling (currently n>750) of a population assembled in a lung cancer case-control context. The specimens are being studied for quantitative gene expression, and their regulatory substrates listed above, in multiple pathways. These expression, genetic, and epigenetic data are being linked to precise measurements of environmental exposure as an approach to putting a real metric to gene-environment interaction.

Selected Publications:
Brock GJ, Moschos S, Spivack SD, Hurteau GJ. The 3'paradigm of miR-200 family and other microRNAs. Epigenetics, 6:3, 1-5. PMID: 21242719, 2011.
Our long-term research goal is to investigate the genetic components of aging and aging-related disease using functional genomics approaches. We focus on the identification of gene sequence variation, i.e., single nucleotide polymorphisms (SNPs), in candidate genes and the assessment of their potential functional impact on aging-related phenotypes. Candidate genes include categories of genes implicated in the modulation of common causes of aging, e.g., free radical production, antioxidant defense, genome maintenance, and apoptosis, or more targeted pathways involved in specific aging-related diseases such as breast cancer. Any genetic variation found to be significantly associated with one or more defined aging phenotypes is then further investigated in specific functional tests, utilizing in silico modeling, in vitro cell culture models, and mouse models. We consider the assessment of the functional impact of SNP haplotypes, i.e., allelic variation caused by multiple SNPs in the same gene, in vitro and animal models as essential to confirm the link between genotype and phenotype in aging studies. This should ultimately result in an integrated approach to study the genetics of aging at different levels ranging from genetic determinants in the form of DNA sequence variations, through cell type- and tissue-specific gene expression profiles, to molecular and cellular endpoints in tissues, to impacts on quality and duration of life span. The results are expected to lead to the identification of functional pathways that control basic aging processes and the onset of age-related diseases. Insight into the functional impact of individual genetic variation on the aging process will lead to a better understanding of phenotypic variation in aging human populations, including susceptibility to aging-related diseases and exceptional longevity. Importantly, it will help close the long-held gap between the population genetics and molecular genetics of aging.

Four systematic multidisciplinary studies are currently underway. First, we have initiated a population-based association study to test genotype-phenotype correlations of genome maintenance genes in a breast cancer cohort. We currently focus on the tumor suppressor BRCA1, which is involved in double strand break repair with broad effects on cellular physiology and genomic stability. We have established a high-throughput mouse embryonic stem cell transgenesis to knock-in human BRCA1 haplotype variants for functional analysis in vivo. Second, in a cohort of longitudinal study of aging, we are testing the hypothesis that genetic variation at loci involved in genome maintenance mechanisms (e.g., DNA repair, antioxidant defense, cell cycle control, and apoptosis) can be related to individual differences in the rate and severity of aging-related phenotypes. Third, we are focusing on identification of functional SNP haplotypes of genes involved in the Growth Hormone/Insulin-like Growth Factor-1 (GH/IGF-1) pathway. Down-regulation of the GH/IGF-1 pathway is well-known to extend life span in model organisms varying from worms and flies to mice. We are investigating whether this evolutionarily conserved pathway play a role in human longevity using Ashkenazi Jewish centenarian cohorts. Fourth, we are studying mouse models that harbor human gene variations in DNA repair/genome maintenance and as a consequence manifest premature aging phenotypes. Our results from transcriptome analysis delineate a complex genetic network of cellular responses to endogenous DNA damage and suggest it as the cause of the premature aging phenotypes in these mice.

Selected Publications:
Genome instability has since long been implicated as the main causal factor in cancer and aging. Exactly how loss of genome integrity may lead to increased cancer risk and loss of organ and tissue function with age remains unknown. We study genome instability as a function of age in various model organisms, including mouse and fruit fly, and its consequences in terms of alterations in tissue-specific patterns of gene regulation.

We developed transgenic reporter systems in mouse and fruit fly, which allows us to determine tissue-specific frequencies of various forms of genome instability, e.g., point mutations, deletions, translocations. By crossing the mutational reporter animals with mutants harboring specific defects in various genome maintenance pathways, the relevance of these pathways for the accumulation of specific forms of genome instability is assessed, in relation to the pathophysiology of aging. Similarly, by using knockdown approaches we assess the effect of specific genes, e.g., SOD, FOXO, SIR2, on genome integrity in cultured cells.

To improve our understanding of the possible role of stochastic alterations in genome or epigenome in aging and disease we have now begun to explore single-cell approaches. To access putative cell-to-cell variation in genome and epigenome during aging we developed procedures to analyze single cells or nuclei in a genome-wide manner for DNA sequence changes or alterations in DNA methylation. These procedures will allow us to directly measure the rate of mutations and epimutations in organs and tissues during aging.

Finally, as a spin-off from our more basic research we are developing, in collaboration with clinical departments, novel assays for measuring subtle genetic changes in single cells or very small number of cells, such as tumor needle biopsies.

Recent Publications:
ZHENGDONG ZHANG, Ph.D.

Computational analyses of gene regulation:
A next-gen sequencing approach

With recent resource and technology development, biology has entered a new data-driven phase in the 21st century. The research interest of my lab is computational biology and bioinformatics, focusing on algorithm development, data integration, and software implementation. With the advent of new DNA sequencing technologies, it is a particularly challenging and exciting time now to do such computational work, as more and more biological data are being generated at an ever-accelerating speed.

Gene expression in living cells is under strict spatial and temporal control, and its dysregulation is the direct cause of many human diseases. The primary focus of research in my lab is gene expression and its regulation, for which we take an integrated approach to study the following aspects on the whole genome scale:

- gene expression profiles
- transcriptional regulation of gene expression
- epigenetic mechanisms and long range control of gene expression
- gene copy number variation

The biological system currently under investigation is breast cancer metastasis, a complex multi-step process during which tumor cells spread from the primary tumor mass to distant organs. To study the genetic and biochemical determinations of this deadly aspect of cancer progression, we analyze various microarray and sequencing profiles to discover regulatory sub-networks, DNA binding of key regulators, and copy number variations during the progression.

For more details and a complete list of publications, please visit our lab web site at www.zdzlab.org

Recent Publications:
The research field of my group is Computational Genomics and Bioinformatics, with a strong focus of mining large-scale experimental genomic data to decipher the function of the human genome and the genomes of other model organisms. We develop and apply computational techniques for integrating data of comparative genomics and functional genomics (and epigenomics) to decode the structure, function, and evolution of the human genome. More generally, we are interested in bioinformatic and statistical approaches for exploiting novel and biologically significant patterns in high-throughput genomic data. Recently, we have become highly interested in the expression, regulation, and evolution of human genes (coding or non-coding) that are involved in the development, specification, maturation, and maintenance of human neural systems. Working extensively with experimentalists, our study will contribute important information to neurodegenerative diseases and many other brain diseases. Please see our website for more details: http://dain.aecom.yu.edu/zhenglab

Recent publications:
Molecular Mechanisms in Heart Development and Congenital Heart Disease

Our research focuses on molecular mechanisms in cardiovascular development and disease. We apply an integrated approach of mouse genetics, developmental embryology, cell and molecular biology to study specification and lineage development of cardiac cells, transcriptional regulation of cardiac development, and involved signaling pathways.

**Endocardial Cell Lineage Specification and Differentiation:** Our molecular model for studying endocardial cell specification and differentiation is the transcription factor NFATc1 (Nuclear Factors in Activated T-cells-1). It is the only known transcription factor specifically expressed by the endocardial cells during heart development. We have generated several endocardial specific Cre and lacZ transgenic mouse lines. We are now using the ‘Cre-loxP’ system to trace the evolution of endocardial cell lineages during heart development. Our data indicate that the endocardium is the origin of cardiac mesenchyme and coronary vascular endothelium, and that VEGF, Notch, and Calcineurin pathway regulates the endocardial to endothelial transition and subsequent coronary vascular formation.

**Transcriptional Regulation of Cardiac Development:** Our study of NFATc1 regulation has led to the discovery of an important auto-regulatory loop via a transcriptional enhancer during cardiogenesis. We are currently characterizing this enhancer paradigm by identifying its upstream regulators and downstream key components using DNA affinity pull-down, Mass-Spec, and cDNA microarrays. We are also using ES cell differentiation, early mouse embryos, and CHIP-Seq to identify the cis-elements for the early endocardial expression of NFATc1 when cardiac cells are specified. These studies will define the transcriptional hierarchy of endocardial specification.

**Modeling of Cardiovascular Disease:** Congenital heart valve disease is a common birth defect whereas senile aortic valve stenosis is a common disease in the elderly. We are generating and characterizing mouse models of congenital heart valve disease or senile aortic valve stenosis by ablation of endocardial cells or genes in the endocardium. These mouse models will allow us to better understand the endocardial role in these diseases.

**Epigenetic and genetic Mechanisms of Coronary Vessel Pattering:** Coronary vascular formation is a developmental mystery in terms of its origin and patterning. We are interested in the regulatory role of hypoxia and VEGF signaling in coronary vessel development. We generated a mouse model of coronary anomalies by deletion of VEGFA in the myocardium. We also created a hypoxic-responsive mouse model revealing that the myocardium surrounding the forming main coronary arteries is hypoxic. This model permits us to address the role of hypoxic myocytes and their hypoxic-dependent VEGFA production in coronary vessel development and patterning. In addition, we have begun to study epigenetic regulation of heart and coronary vascular development focusing on the hypoxia-inducible factor function.

**Recent Publications:**

Wu, H., Kao, S-C., Barrientos, T., Baldwin, H.S., Olson, E.N., Crabtree, G.R., Zhou, B. and Chang, C-P. 'DSCR1 is a transcriptional target of NFATc1 within the endocardium during heart development' *J. Biol. Chem.* 282:30673-9, 2007


CAPTIONS FOR THE BACK COVER

1. Patch-ligase DNA methylation functional assay results for the DAPK promoter showing the reporter construct without promoter, the reporter construct with unmethylated DAPK promoter (unM) and reporter constructs with DAPK promoter methylated at different CpG sites (MP1 to MP6; Spivack laboratory).

2. Mouse embryo showing the pattern of gene deletion (dark blue) obtained with a cre allele expressed mainly in the forebrain. (Hébert laboratory).

3. Digital and microPET images of an Ini1+-mouse bearing primary tumors before and after treatment with flavopiridol. Left two panels digital images and Right panels represents MicroPET images of the same mouse. The top two panels are before treatment and the bottom two panels are images of the same mouse after treatment (Kalpana laboratory).

4. Functional roles of genes can be assessed easily in zebrafish by morpholino oligonucleotide mediated gene knockdown and the phenotype can be rescued simply co-injecting mRNA of the targeted gene together with the targeting morpholinos. (Ozbudak laboratory).

5. LAM-PCR to amplify cancer-causing genes in retrovirus induced lymphomas (Lenz laboratory).

6. Hepatic steatosis in mouse infected with a mutant murine leukemia virus (Lenz laboratory).

7. An immuno-histochemical analysis of the heterozygous mucopolysaccharidosis mouse brain showing beta-glucuronidase activity in green, NeuN (a neuronal marker) in red and nuclei (DAPI) in blue (RoyChowdhury Laboratory).

8. Genome-wide sequence coverage and mutation localization in single S2 cells treated with or without ENU. (Vijg laboratory).

9. A genetic assay for cell competition in Drosophila. In the left panel, some pigmented cells have been generated in the eye, which are genetically defective and would normally be lost by ‘cell competition’, which has occurred in the eye shown in the right panel. On the left, however, the unpigmented cells are unable to recognize and eliminate the defective cells, because of a defect in a gene required for cell competition (Baker laboratory).

10. The binding of certain transcription factors can significantly alter the local histone modification profiles. Shown here is the decline of acetylation on histone H3 lysine 9 (H3K9ac) upon binding of a repressor. The profiles near transcription start sites (TSSs) are without (black) and with (colors) the binding of this repressor. (Zheng laboratory).
