Center for Advanced Biotechnology and Medicine
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and by
The University of Medicine and Dentistry of New Jersey
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Director’s Overview

The community of research scientists at CABM is always looking forward to new experimental findings that will promote our mission – advancing basic knowledge in the life sciences to improve human health. On this occasion, the completion of our 15th year, it is appropriate and reassuring to reflect on some of our recent accomplishments in research, teaching and service.

CABM in its short lifetime has already become an important contributor to the biosciences revolution. As described in the following pages, CABM scientists continued to report the results of their latest research, designed to understand better and ultimately prevent AIDS, cancer, neurological disorders and other life-threatening diseases. During the past year nearly 100 peer-reviewed publications from CABM laboratories have appeared in high impact international journals including *Development, Genes and Development, EMBO Journal, Molecular Cell, Molecular and Cellular Biology, Nature, Nature Structural Biology, Proceedings of the National Academy of Sciences* and *Science*.

Generous support for this important work was provided by competitive awards from numerous public and private sources. We are grateful to the National Institutes of Health (NIH), U.S. Army Medical Research & Materiel Command, National Science Foundation (NSF), Veterans Administration, N.J. Commission on Science and Technology R&D Excellence Program, N.J. Commission on Cancer Research and Governor’s Council on Autism; the Howard Hughes Medical Institute (HHMI), American Association for Cancer, American Heart Association, Leukemia and Lymphoma Society, March of Dimes, Kimmel Foundation for Cancer Research and Sinsheimer Fund; the Ara Parseghian Medical Research, Burroughs Wellcome, AHEPA Cancer Research, Cure for Lymphoma, Emerald, Janssen Research, National Ataxia, and Whitehall Foundations; and Janssen-Cilag, Johnson & Johnson, Roche, Genzyme, GeneFormatics, Human Genome Sciences, Merck, Aventis and Genencor. In addition to two NIH MERIT awards and two HHMI investigators, CABM is home to the NIH-funded Northeast Structural Genomics Consortium.

Besides their strong commitment to classroom teaching in courses for undergraduate, graduate and medical students, CABM researchers trained and mentored many postdoctoral fellows and students in their laboratories in preparation for positions of scientific leadership in academia and industry. The
Annual Retreat and CABM Lecture Series have again this year provided opportunities for students to present and defend their work and to hear and interact with exciting speakers visiting from other leading educational institutions. The 15th Annual CABM Symposium, “Structural Genomics in Pharmaceutical Design”, was sponsored by 18 organizations and enjoyed by nearly 250 participants. The meeting fostered productive collaborations and licensing of intellectual property for industrial development, adding to CABM’s economic impact in New Jersey and across the nation.

CABM investigators served on various advisory, faculty search, departmental and other committees at Rutgers University and UMDNJ-Robert Wood Johnson Medical School. To foster translational aspects of our mission, several also have appointments and leadership roles in clinical departments and in the Cancer Institute of New Jersey, e.g. as Associate Director for Basic Research and Scientific Director of the Gallo Prostate Cancer Center. At the national and international levels, CABM faculty participate in meetings as invited speakers, serve on many journal editorial boards and meeting organizational committees, several grant review panels of the NIH and NSF, the National Cancer Institute Board of Counselors, the HHMI Cell Biology Review Panel and advisory boards of other government agencies, professional societies, foundations and companies.

This has been a challenging and productive year, with CABM scientists working at the frontiers of structural biology, molecular genetics and cell and developmental biology, using and creating novel systems to translate genomic sequences into protein function and gaining information and insights that are having positive impacts on human health. After 1-1/2 decades of outstanding progress, 2002 promises exciting, new scientific advances at CABM.

Aaron J. Shatkin, Professor and Director

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Research Programs and Laboratories
## Cell & Developmental Biology

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Cory Abate-Shen, Ph.D.
Resident Faculty Member, CABM; Professor, UMDNJ Robert Wood Johnson Medical School, Department of Neuroscience and Cell Biology and Department of Medicine, Scientific Director of the Dean and Betty Gallo Prostate Cancer Institute, Cancer Institute of NJ; Head, Division of Developmental Medicine and Research-Department of Medicine

Molecular Neurobiology Laboratory

Dr. Cory Abate-Shen joined CABM in August 1991 after spending three years as a postdoctoral and research fellow in Tom Curran’s laboratory at the Roche Institute of Molecular Biology. Her work at Roche contributed to characterization of the DNA binding and transcriptional properties of the regulatory proteins Fos and Jun. Dr. Abate-Shen received her Ph.D. from Cornell University Medical College where she was awarded the Vincent du Vigneaud Award for Excellence in Graduate Research. She is a recipient of a Sinsheimer Scholar Award and an NSF Young Investigator Award and received a career recognition award from The American Society for Cell Biology. Dr. Abate-Shen is a member of the NIH Study Section on Cell Development and Function. She was recently appointed head of a new division in the Department of Medicine.

My long-term interests are to understand the molecular mechanisms underlying homeobox gene function during embryogenesis and how aberrant homeobox function contributes to oncogenesis. A major focus of my recent work has been the development of animal models to elucidate the roles of particular homeobox genes in development, oncogenesis and embryogenesis. We have found that homeobox genes Msx1 and Pax3 are co-expressed in migrating limb muscle precursors, which are committed myoblasts that do not express myogenic differentiation genes such as MyoD. Msx1 negatively regulates differentiation of migrating limb muscle precursor cells through its ability to antagonize the myogenic activity of Pax3. Forced misexpression of Msx1 in cell culture and in chicken embryos inhibits MyoD expression as well as muscle differentiation. Conversely, forced misexpression of Pax3 activates MyoD expression and myogenesis, while this effect is counteracted by Msx1. Moreover, the Msx1 protein product interacts with Pax3, thereby inhibiting the DNA binding activity of Pax3 as well as its ability to transcriptionally activate MyoD regulatory elements. A major focus of our current research is the elucidation of additional protein partners that form functional associations with Msx proteins in vivo. Analysis of a functional role for Msx in breast and other carcinomas, as well as the identification of downstream targets for Msx, represent another important focus of our current studies. Our Msx1 transgenic mice provide an excellent resource to pursue these studies.

Prostate cancer is the most commonly diagnosed neoplasm, and ranks second to lung cancer as the leading cause of cancer death in American men. To investigate early stages of initiation and progression of prostate cancer, we have developed a mouse model using the Nkx3.1 homeobox gene, which is expressed specifically in the developing and adult prostate, and whose targeted disruption results in defects of prostate differentiation and function. Notably, human NKX3.1 maps to chromosomal region 8p21, which is deleted in ~60-80% of prostate tumors. Moreover, loss of 8p21 represents an early event in carcinogenesis since it is also deleted in prostatic intraepithelial neoplasia (PIN), the major precursor of prostate carcinoma in humans. We have found that Nkx3.1 mutant mice display lesions that resemble human PIN with respect to their histological appearance as well as the molecular changes that occur in early stages of
carcinogenesis, such as loss of the basal cell layer of the prostate epithelium. Based on our findings we have proposed that interactions between tissue-specific regulators, such as Nkx3.1, and broad-spectrum tumor suppressors, such as Pten, underlie the distinct phenotypes of different cancers. By utilizing mouse models, we are beginning to assemble a molecular pathway for prostate carcinogenesis that includes loss of NKKX3.1 as an initiating event followed by loss of PTEN as a later event leading to progression. Future goals include the identification of additional molecular alterations that characterize early stage prostate carcinogenesis, further elucidation of a molecular pathway for prostate carcinogenesis through the generation of new mutant mouse models, and the application of these mutant mouse models for the design of new therapeutics.

Publications:


Isaac Edery, Ph.D.
Resident Faculty Member, CABM; Associate Professor, Rutgers University, Department of Molecular Biology and Biochemistry

Molecular Chronobiology Laboratory

Dr. Isaac Edery completed his doctoral studies in biochemistry as a Royal Canadian Cancer Research Fellow under Dr. Nahum Sonenberg at McGill University in Montreal. His Ph.D. research focused on the role of the eukaryotic mRNA cap structure during protein synthesis and precursor mRNA splicing. Subsequently, he was in the laboratory of Dr. Michael Rosbash at Brandeis University where he pursued postdoctoral studies aimed at understanding the time-keeping mechanism underlying biological clocks. He joined CABM in 1993, and his research is supported by NIH. Dr. Edery is a member of the editorial board of Chronobiology International.

A wide range of organisms from bacteria to humans exhibit daily or circadian rhythms in physiological and behavioral phenomena that are controlled by endogenous pacemakers or clocks. Circadian clocks are precisely synchronized to the 24-hr solar day by the daily light-dark and temperature cycles, enabling organisms to perform activities at advantageous times and manifest appropriate seasonal responses. We use the fruitfly Drosophila as our model system to understand the cellular and biochemical bases underlying clock function.

The isolation of "clock genes" has provided significant insights into the molecular underpinnings governing circadian rhythms. A common theme in clocks from bacteria to humans is that at the "heart" of these pacemakers lie transcriptional-translational feedback loops. The best characterized animal model system for a circadian clock is Drosophila melanogaster, where four clock proteins termed PERIOD (PER), TIMELESS (TIM), dCLOCK (CLK) and CYCLE (CYC) function in a negative transcriptional autoregulatory loop. CLK and CYC are members of the basic-helix-loop-helix (bHLH)/PAS (PER-ARNT-SIM) superfamily of transcription factors and are required for the daily stimulation of per and tim expression. PER and TIM form a complex in the cytoplasm that enters the nucleus in a temporally gated manner where they bind the CLK-CYC heterodimer, blocking its DNA binding activity. In the absence of denovo synthesis, the concentrations of PER and TIM in the nucleus decrease below threshold levels, relieving autoinhibition and enabling the next round of per and tim transcript accumulation. Posttranscriptional mechanisms play an important role because they introduce "biochemical time constraints" that stretch the transcriptional feedback loop to ~24 hr and also allow it to respond to external stimuli. For example, light evokes the rapid degradation of TIM, the primary clock-specific photoresponse resetting the oscillatory mechanism. A blue-light photoreceptor called CRYPTOCHROME (CRY) has been implicated in transducing photic signals to TIM. Furthermore, the cytoplasmic phosphorylation of PER by the kinase DOUBLE-TIME (DBT) renders PER unstable. Cytoplasmic PER is stabilized by interacting with TIM which ensures that the accumulation and nuclear entry of the PER-TIM complex is a slow process, creating a time-window for daily increases in the levels of per and tim transcripts.

Our studies are geared towards isolating all the components that comprise a circadian timekeeping device, characterizing their interactions within the various feedback loops and
understanding how the daily changes in visible light modulate the oscillatory mechanism. In addition, we recently showed that the splicing efficiency of an intron in the 3' untranslated region of per is thermosensitive. At lower temperatures this intron is spliced more efficiently leading to higher levels of per mRNA and mainly daytime activity. By regulating the splicing efficiency of this intron flies are active during the warmer daytime hours during autumn/winter days typical of temperate zones and avoid the midday sun by manifesting mainly nocturnal activity during the warmer spring/summer seasons. We are continuing these studies to understand how a clock helps measure calendar time by adapting to seasonal changes in temperature and daylength.

Given the similarities in the circadian timing mechanisms operating in Drosophila and mammals, we anticipate that our findings will continue to provide important insights into disorders associated with clock malfunction in humans, including manic-depression, seasonal affective disorders (SAD or winter depression), chronic sleep problems in the elderly and symptoms associated with trans-meridian flight ("jet-lag") and shift-work.

Publications:


Céline Gélinas, Ph.D.
Resident Faculty Member, CABM; Professor, UMDNJ-Robert Wood Johnson Medical School, Department of Biochemistry

Tumor Virology Laboratory

Dr. Céline Gélinas came to CABM in September 1988 from the University of Wisconsin where she conducted postdoctoral studies with Nobel laureate Dr. Howard M. Temin. She earned her Ph.D. at the Université de Sherbrooke in her native country, Canada, and received a number of honors including the Jean-Marie Beauregard Award for Academic and Research Excellence and the National Cancer Institute of Canada King George V Postdoctoral Fellowship. Her work is currently funded by the NIH and The Cure for Lymphoma Foundation.

Our laboratory has a long-standing interest in the role of the Rel/NF-κB proteins in the onset and progression of hematopoietic and solid tumors. Proteins in the Rel/NF-κB-family of transcription factors play fundamental roles in immune and inflammatory responses, and are implicated in the control of cell proliferation, the inhibition of apoptosis and in oncogenesis. Experimental evidence linking deregulated Rel/NF-κB activity to human cancer has emerged in recent years, consistent with the acute oncogenicity of the Rel/NF-κB oncoprotein v-Rel in inducing fatal leukemias/lymphomas in animal models. Aberrant Rel/NF-κB activity is found in various human leukemias, lymphomas, myelomas and Hodgkin’s disease. Chromosomal amplification, rearrangement, overexpression and/or constitutive activation of the rel and nf-κB genes are also observed in breast, colon, lung, ovarian and prostate cancer. The viral and cellular Rel proteins offer a powerful system to study how the Rel/NF-κB factors function in normal lymphoid cells and to understand how their aberrant activities lead to cancer. Our research focuses on the transcriptional activity and regulation of the Rel/NF-κB factors, on their role in cell growth, apoptosis and oncogenesis, and on the cellular genes that they control.

In prior studies, we demonstrated that the transcriptional and anti-apoptotic activities of the v-Rel oncoprotein were necessary for its oncogenic function. Our analyses characterizing Rel-mediated effects on cell survival and neoplasia have recently demonstrated the ability of a subset of mammalian cellular Rel/NF-κB factors to malignantly transform primary lymphoid cells. Detailed analyses of the determinants required for this activity are starting to provide important insights into the mechanisms involved in tumors associated with aberrant Rel/NF-κB function. Our recent experiments suggest that the specificity of target gene activation is likely to play a critical role in the oncogenic conversion of cellular Rel/NF-κB factors. Our ongoing functional characterization of the Rel/NF-κB target genes Bfl-1/A1 and TAPIR and the analysis of their transcriptional regulation by Rel/NF-κB offers new avenues to characterize the Rel/NF-κB signaling pathway and its role in cell survival. This comprehensive approach will help to clarify the mechanism by which Rel/NF-κB proteins function in the immune system and in oncogenesis. In addition, since Rel/NF-κB activity has been implicated in various disease conditions, the systematic analysis of Rel/NF-κB regulation and relevant Rel/NF-κB target genes may also provide important insights into novel approaches for therapeutic intervention.
Céline Gélinas

Publications:


Fang Liu, Ph.D.
Resident Faculty Member, CABM; Assistant Professor, Rutgers University, Susan Lehman Cullman Laboratory for Cancer Research, Department of Chemical Biology, Ernest Mario School of Pharmacy

Growth and Differentiation Control Laboratory

Dr. Fang Liu obtained her B.S. in biochemistry from Beijing University and Ph.D. in biochemistry from Harvard University working with Dr. Michael R. Green. She conducted postdoctoral research with Dr. Joan Massagué at Memorial Sloan-Kettering Cancer Center and joined CABM in 1998. Dr. Liu has received awards from the American Association for Cancer Research-National Foundation for Cancer Research, the Pharmaceutical Research and Manufacturers of America Foundation, the Burroughs Wellcome Fund, and the Sidney Kimmel Foundation for Cancer Research. She also obtained fellowships from the K.C. Wong Education Foundation and the Jane Coffin Childs Memorial Fund for Medical Research.

Inhibition of SMAD Transcriptional Activity by Cyclin-Dependent Kinase Phosphorylation: TGF-β is the most relevant physiological inhibitor of cell proliferation of a wide variety of cell types. During the earliest stage of tumorigenesis, the ability of TGF-β to inhibit cell growth enables it to act as a potent tumor suppressor. TGF-β inhibits cell proliferation by causing cell cycle arrest at the G1 phase. SMAD proteins are candidate tumor suppressors and can mediate the TGF-β growth-inhibitory effects by regulating the expression of several cell cycle-related genes. We have recently discovered that certain SMAD proteins are major substrates for cyclin-dependent kinases (CDKs). We expect that our findings will have a major impact in the cancer research field and may be useful for therapeutic applications.

TGF-β-Inducible Gene Regulation: SMAD proteins can mediate transforming growth factor-β (TGF-β) inducible transcriptional responses. In an effort to search for TGF-β/SMAD inducible genes, we identified Smad7, which is rapidly upregulated by TGF-β and can antagonize TGF-β signaling by binding to and inhibiting the TGF-β receptor function. We found that TGF-β can stabilize Smad7 mRNA as well as activate Smad7 transcription. The Smad7 promoter is the first TGF-β responsive promoter identified in vertebrates that contains the 8 base pair palindromic SMAD binding element (SBE), an optimal binding site for SMAD. We are using Smad7 promoter as a model system to elucidate the molecular mechanisms of TGF-β-inducible gene regulation. We have also identified SMAD interreacting proteins that may regulate SMAD transcription activity and are in the process of characterizing these interacting proteins.

Characterization of SMAD4 as a pancreatic tumor suppressor: SMAD4 is a pancreatic tumor suppressor. More than 50% of pancreatic cancers bear mutations in the SMAD4 locus (~30% homozygous deletions and ~22-25% mutations with loss of heterozygosity). The mechanism of how SMAD4 functions as a pancreatic tumor suppressor is not completely defined. Our work is directed towards addressing this important issue.
Publications:


**Peter Lobel, Ph.D.**
Resident Faculty Member, CABM; Professor, UMDNJ-Robert Wood Johnson Medical School, Department of Pharmacology

**Protein Targeting Laboratory**

Dr. Peter Lobel trained at Columbia University and Washington University in St. Louis and joined CABM in 1989. He is currently conducting research on lysosomes and associated human hereditary metabolic diseases. This work recently led to the identification of a disease gene that causes a fatal childhood neurodegenerative disorder. At CABM he was the first faculty member of UMDNJ to be named a Searle Scholar, a prestigious award given to newly appointed faculty members who show outstanding promise in biomedical research.

Our laboratory has developed new methods for disease discovery and identified the molecular bases for three fatal neurodegenerative disorders based on our research on lysosomal enzyme targeting. Lysosomes are membrane-bound, acidic organelles that are found in all eukaryotic cells. They contain a variety of different proteases, glycosidases, lipases, phosphatases, nucleases and other hydrolytic enzymes, most of which are delivered to the lysosome by the mannose 6-phosphate targeting system. In this pathway, lysosomal enzymes are recognized as different from other glycoproteins and are selectively phosphorylated on mannose residues. The mannose 6-phosphate serves as a recognition marker that allows the enzymes to bind mannose 6-phosphate receptor which ferry the lysosomal enzyme to the lysosome. In the lysosome, the enzymes function in concert to break down complex biological macromolecules into simple components. The importance of these enzymes is underscored by the identification of over thirty lysosomal storage disorders (e.g., Tay Sach's disease) where loss of a single lysosomal enzyme leads to severe health problems including neurodegeneration, progressive mental retardation, and early death. Our approach to identify the molecular basis for unsolved lysosomal storage disorders is based on our ability to use mannose 6-phosphate receptor derivatives to visualize and purify mannose 6-phosphate containing lysosomal enzymes. For instance, we can fractionate proteins in normal and disease specimens by 2-dimensional gel elecetrophoresis and then, in a manner analogous to Western blotting, use a radiolabeled mannose 6-phosphate receptor derivative to selectively visualize phosphorylated lysosomal enzymes. This allows us to compare the spectrum of lysosomal enzymes present in normal and disease specimens. If the disease specimen lacks a given lysosomal protein, this may be responsible for disease. To investigate this, we purify and sequence the normal protein, clone the corresponding gene, and examine patients for mutations associated with disease. In this manner, we found that a fatal childhood neurodegenerative disease called LINCL (late infantile neuronal ceroid lipofuscinosis) is caused by mutations in a gene encoding a previously undiscovered lysosomal protease.

After we identified the gene and determined the function of corresponding protein, we developed rapid biochemical and DNA-based assays for definitive pre-and postnatal diagnosis and carrier screening. This allows for genetic counseling to prevent further occurrence of the disease.

However, in the absence of universal carrier testing, new cases will continue to arise so it is important to develop effective therapies that can halt and reverse disease progression. To this end,
we have produced recombinant enzyme in a form that can be taken up by affected cells in culture to correct the primary defect. We are also working to develop a LINCL mouse model that should allow detailed studies of disease pathophysiology and evaluation of potential therapeutics strategies.

Another research program in the laboratory is to identify the spectrum of lysosomal enzymes encoded by the human genome. This research is particularly timely given the current effort towards determining the complete sequence of the human genome. Our approach is to purify mannose 6-phosphorylated proteins and then analyze each protein by peptide mapping, mass spectrometry, and chemical sequencing. This information is used to search sequence databases to determine if a given protein corresponds to a known lysosomal enzyme or if it represents a previously unidentified species. We recently used this approach to determine the molecular basis for Niemann Pick type C2 disease, a fatal cholesterol storage disorder. In addition to their roles in human inherited diseases, alterations in the lysosomal system have been implicated in a variety of disease processes such as tumor invasion and metastasis in cancer, tissue destruction in arthritis, and early changes associated with Alzheimer’s disease. Once we develop the tools to visualize and characterize the players, our ultimate goal will be to understand the role that lysosomal proteins play in these widespread pathological processes.

Publications:


James H. Millonig, Ph.D.
Resident Faculty Member, CABM; Assistant Professor, UMDNJ-Robert Wood Johnson Medical School, Department of Neuroscience and Cell Biology

Developmental Neurogenetics Laboratory

Dr. James H. Millonig came to CABM in September 1999 from the Rockefeller University where he was a postdoctoral fellow in the laboratory of Dr. Mary E. Hatten. His postdoctoral research combined neurobiology and mouse genetics to characterize and clone the dreher mouse locus. He did his doctoral research at Princeton University with Dr. Shirley M. Tilghman. Dr. Millonig is a recipient of the March of Dimes Basil O’Connor Starter Research Award and grants from the Whitehall Foundation, the National Ataxia Foundation and N.J. Governor’s Council on Autism.

My laboratory studies the development of the dorsal CNS by combining mouse molecular genetics and neuroanatomical approaches. The dorsal CNS includes the cerebrum, hippocampus, cerebellum and sensory neurons of the spinal cord. These structures play an important role in cognition, learning, memory, motor movement and sensation. During development, millions of different types of neurons are generated which are involved in controlling these neural functions. Our ultimate goal is to understand the molecular pathways that lead to the generation of different types of dorsal neurons in two simple dorsal anatomical structures, the spinal cord and cerebellum.

The entire dorsal CNS arises from the lateral neural plate very early in development. At this stage, the epidermal ectoderm is adjacent to the lateral neural plate and dorsalizes it through the action of secreted proteins. This results in the delamination of the neuroectoderm from the epidermis and the eventual folding of the neural plate into a neural tube. Failure of this to occur results in spina bifida, a common human disorder that has an incidence of 1:1000.

Once the neural tube forms, another transitory signaling center called the roof plate that is situated on the dorsal midline is believed to instruct neighboring cells to a particular lineage again through the action of secreted factors. As a postdoctoral fellow at The Rockefeller University, we identified the first mouse mutation to lack a roof plate. It is a spontaneous mouse mutation called dreher (dr). Our positional cloning of the locus determined that a gene called Lmx1a is responsible for the loss of roof plate in dr/dr embryos (Millonig et al, 2000).

Expression analysis of Lmx1a indicated that it was expressed just in the roof plate. Dr can then be used as a mouse model to determine the role of the roof plate during dorsal CNS development. Any perturbation to dorsal neurons in dr/dr embryos must be due to loss of roof plate signaling. Our phenotypic analysis has determined that the roof plate is necessary to generate the normal complement of dorsal neurons and is required even after their commitment for their initial steps of differentiation, neuronal migration and axon extension (Millonig, unpublished results).

We are now investigating the possible cellular mechanisms that result in the decrease of dorsal neurons in dr/dr embryos. There are at least three possibilities: decrease in the rate of proliferation of progenitors, increased cell death or progenitors spend a longer time in the cell.
cycle. Preliminary data suggests that the last could be true, indicating that the roof plate coordinates the withdrawal of cells from the cell cycle (Tanya Borusk, unpublished results). *Splotch* (*Sp*), another mouse mutant, exhibits a similar cell cycle withdrawal phenotype, providing us with two mutations that together should lead to insights into the molecular mechanisms that control dorsal neuronal generation.

Another spontaneous mouse mutation, *vacuolated lens* (*vl*), appears to have the opposite phenotype to *dr*, too much roof plate. *Vl/vl* embryos have an expanded dorsal midline and exhibit phenotypes consistent with too much roof plate, such as an increase in the number of dorsal neurons and overgrowth of the dorsal vertebrae that lie above the roof plate. In *dr*, this part of the vertebrae is missing. *Vl* maps near the *dr* locus but sequencing of *Lmx1a* from *vl/vl* embryos indicates that *Lmx1a* is not responsible for the mutation (Jigar Desai, unpublished results). We are now in the process of positionally cloning the locus.

We have also been focusing on identifying genes that are downstream of roof plate signaling. To this end, we have identified transcription factors that are expressed in nested domains in the developing cerebellum that appear to be restricted to particular cellular populations (Max Tischfield, unpublished results). Phenotypic analysis of *dr* embryos and in vitro explants are being used to determine if roof plate signaling is necessary and sufficient for the expression of these dorsal markers. The function of these genes is being tested through a combination of mouse genetics and the forced misexpression in the cerebellum during chick embryogenesis. Through these different approaches the pathways involved in dorsal CNS development will be ascertained.

**Publications:**

Michael M. Shen, Ph.D.
Resident Faculty Member, CABM; Associate Professor, UMDNJ-Robert Wood Johnson Medical School, Department of Pediatrics

Mammalian Embryogenesis Laboratory
Dr. Michael Shen completed his doctoral work in genetics under Dr. Jonathan Hodgkin at the MRC laboratory of Molecular Biology in Cambridge, England. He then performed postdoctoral work at Harvard Medical School under Dr. Philip Leder before joining CABM in 1994. He is a former recipient of a Leukemia Society of America Special Fellowship, a Howard Hughes Medical Institute Post-doctoral Fellowship, a Jane Coffin Childs Post-doctoral Fellowship, and a National Science Foundation Graduate Fellowship. Dr. Shen is a member of the NIH Study Section on Cell Development and Function and of the National Cancer Institute Steering Committee for the Mouse Models of Human Cancer Consortium.

The research in our laboratory is directed towards understanding the molecular mechanisms involved in (i) formation of the embryonic anterior-posterior and left-right axes in the mouse embryo, (ii) signal transduction by EGF-CFC proteins and the TGF-beta-related factor Nodal, and (iii) prostate development and carcinogenesis.

To address the first two areas, we are pursuing studies of the recently identified EGF-CFC gene family, whose members encode novel extracellular proteins. We have used gene targeting approaches in mice to demonstrate that EGF-CFC genes play essential roles in embryonic axis formation, namely that Cripto is required for correct orientation of the anterior-posterior (A-P) axis, while Cryptic is necessary for determination of the left-right (L-R) axis. Thus, targeted disruption for Cripto results in a 90 degree mis-orientation of the A-P axis, indicating that Cripto is essential for an axial rotation that converts a proximal-distal asymmetry into an orthogonal A-P axis during pre-gastrulation stages. In contrast, null mutation for Cryptic results in L-R laterality defects, including randomized abdominal situs, pulmonary right isomerism, and severe cardiac defects, as well as lack of expression of regulatory genes in the L-R pathway, suggesting that Cryptic is essential for a key step in L-R axis specification. Our results also support an interaction of EGF-CFC proteins with the TGF-beta-related factor Nodal and with activin receptors, which we are currently examining using biochemical and cell culture approaches.

In another major area of interest, we are investigating prostate development and cancer (in collaboration with Dr. Cory Abate-Shen's lab). We are focusing on the role of the Nkx3.1 homeobox gene, which displays restricted expression in the embryonic and adult mouse prostate. We have demonstrated that homozygous Nkx3.1/- mice created by gene targeting display progressive defects in prostate histology with advancing age, resulting in epithelial hyperplasia and dysplasia. These lesions in aged mutant mice resemble human prostatic intraepithelial neoplasia (PIN), which is believed to represent the precursor to prostate carcinoma. These observations are noteworthy given the mapping of human NKX3.1 to the minimal deleted interval of chromosome 8p21, which is lost as an early and frequent event in human prostate cancer. Our findings show that Nkx3.1 plays a critical role in the normal morphogenesis and function of the prostate, and suggest that it may represent a prostate-specific tumor suppressor gene.
Publications:


Review articles (peer-reviewed):


Book chapters/technical articles/reviews:


Eileen White, Ph.D.
Associate Investigator, Howard Hughes Medical Institute; Resident Faculty Member, CABM; Professor, Rutgers, Department of Molecular Biology and Biochemistry

Viral Transformation Laboratory

Dr. Eileen White transferred her research program to CABM in July 1990 from Cold Spring Harbor Laboratory where she was a staff investigator. She conducted postdoctoral research at the Cold Spring Harbor laboratory as a Damon Runyon – Walter Winchell Fellow, working with Dr. Bruce Stillman. Her work is currently funded by a MERIT Award from NIH and Howard Hughes Medical Institute. Dr. White is a member of the National Cancer Institute Board of Scientific Counselors.

The goal of our research program is to examine viral oncogenes and mechanisms of mammalian cell growth. Specifically, the White lab is working to determine the mechanisms by which oncogenes of the DNA tumor virus adenovirus stimulate cell proliferation and inhibit cell death which leads to malignant transformation.

We study the mechanisms by which human DNA tumor viruses deregulate cell cycle and apoptosis (programmed cell death) control in the development of cancer and during productive viral infection. Understanding pathways that control cell proliferation and cell death will lead to better treatments for cancer and viral infections.

Description of Research

The DNA tumor virus adenovirus infects human cells, recruits them into a proliferative state, and borrows elements of the host cell transcription, translation, and DNA replication machinery to reproduce viral proteins and DNA. In rodent cells which are semipermissive for adenovirus infection, cell growth is deregulated but virus replication is ineffective. As the viral infection does not progress to completion, the deregulation of cell growth control produces transformation. The viral genes required for oncogenic transformation are the E1A and E1B oncogenes. Understanding how the products of these viral oncogenes alter cell growth control pathways is important for establishing how cancer develops.

Regulation of programmed cell death (apoptosis) by E1A and E1B is necessary for sustaining a productive infection in human cells and is an integral part of the transformation process in rodent cells. The E1A proteins are responsible for initiating a proliferative response, and an indirect consequence of this required function of E1A is the induction of apoptosis. The E1B gene encodes overlapping, redundant functions to suppress apoptosis, the 19K and 55K proteins. Thus, E1A expression and subsequent growth deregulation can occur unimpeded by cell death in the presence of E1B expression. Without inhibition of apoptosis by E1B, transformation of rodent cells is rare, and premature death of the host cell impairs virus yield in productively infected human cells. The human bcl-2 proto-oncogene, which is known to inhibit apoptosis in other systems, will also suppress apoptosis induced by E1A expression and cooperate with E1A to transform primary rodent cells. Thus, inhibition of apoptosis is an important step in the progression of the transformed state.
There is substantial evidence that the product of the p53 tumor suppressor gene mediates the induction of apoptosis by E1A and that the E1B and bcl-2 gene products function by disabling p53. Expression of the E1B 19K or bcl-2 genes will prevent p53-dependent apoptosis by modifying p53 function indirectly, whereas the E1B 55K protein acts by a direct interaction with p53. bcl-2 may be the cellular equivalent of the E1B 19K gene, with its oncogenic and anti-apoptotic activity, in all or in part, attributed to bypassing the function of p53.

One of the most important, recently identified events in humans and other life forms is programmed cell death or apoptosis. Failure of this process can result in excessive cell growth as in cancer or abnormal development; inappropriate induction of programmed cell death is responsible for many other diseases including neurodegenerative disorders. By studying the oncogenes of the DNA tumor virus, adenovirus, we have determined that malignant transformation requires (i) stimulation of proliferation by viral E1A proteins (ii) inhibition by E1B proteins of the apoptosis that results from the inappropriate stimulation, (iii) inhibition by E1B proteins of the apoptosis that results from the inappropriate E1A induction of apoptosis is mediated through the cellular p53 tumor suppressor, and E1B products prevent p53-dependent cell death both directly (55 Kd protein) and indirectly (19 Kd protein).

Results
Our recent studies have demonstrated that E1B 19 Kd protein is the equivalent of the cellular product of the bcl-2 gene. Both have oncogenic and anti-apoptotic activity, all or in part, attributed to bypassing the function of the p53 tumor suppressor. We have found that the E1B 19 Kd protein blocks apoptosis by interacting with and inhibiting the p53 inducible and death promoting Bax protein. An E1B 19 Kd interacting human protein called Nbk/Bik has been identified, shown to contain a BH3 domain, and demonstrated to induce apoptosis.

E1A promotes apoptosis by interacting with and inhibiting negative regulators of cell cycle control. Binding of E1A to, and inhibition of, the transcriptional coadaptor p300 promotes accumulation of the p53 tumor suppressor protein which induces apoptosis. By inhibiting p300, E1A prevents the transcriptional activation of mdm-2, the product of which interacts with and promotes the degradation of p53. Thus the E1A-p300 interaction disables the negative feedback loop to control p53 levels, which left unrestrained, causes apoptosis rather than growth arrest. The E1B 19K protein functions analogously to Bcl-2 to inhibit apoptosis by E1A, p53, and multiple other stimuli. The E1B 19K protein functions by at least two independent mechanisms to inhibit apoptosis. First, the E1B 19K protein binds to the pro-apoptotic Bax protein to prevent loss of mitochondrial membrane potential, caspase activation, and apoptosis. Second, the E1B 19K protein inhibits caspase interaction by interfering with the function of adaptor molecules such as FADD and Ced-4 that interact with and activate caspases. By inhibiting FADD-dependent activation of the caspase FLICE, the E1B 19K protein can disable both the TNF-α and Fas-mediated death signaling pathways which play an important role in immune surveillance against virus infection and cancer. The E1B 19K protein binds to Ced-4, and presumably mammalian Ced-4 homologues, and thereby prevents caspase activation. Thus, the study of the
mechanism of regulation of apoptosis by the adenovirus transforming proteins has revealed important regulatory steps in death signaling pathways.

Our findings have been reported in several original research reports and review articles and at numerous international symposia.

**Future Directions**
The current aim is to determine the molecular basis by which apoptosis is regulated by E1A, p53, E1B and Bcl-2. Establishing how the transforming genes of DNA tumor viruses subvert p53 function will provide insight into the cause and prevention of cancer and lead to new strategies in anticancer therapy.

**Publications:**


Mengqing Xiang, Ph.D.
Resident Faculty Member, CABM; Assistant Professor, UMDNJ-Robert Wood Johnson Medical School, Department of Pediatrics

Molecular Neurodevelopment Laboratory

Dr. Mengqing Xiang came to CABM in September 1996 from the Johns Hopkins University School of Medicine where he conducted postdoctoral studies with Dr. Jeremy Nathans. He earned his Ph.D. at the University of Texas M.D. Anderson Cancer Center and has received a number of honors including a China-U.S. Government Graduate Study Fellowship, a Howard Hughes Medical Institute Postdoctoral Fellowship, a Basil O’Connor Starter Scholar Research Award, and a Sinsheimer Scholar Award. His work is currently supported by NIH and the Alexandrine and Alexander L. Sinsheimer Fund.

Our laboratory investigates the molecular mechanisms that govern the determination and differentiation of highly specialized sensory cells and neurons. We employ molecular genetic approaches to identify and study transcription factors that are required for programming development of the retina, inner ear, and somatosensory ganglia. A major focus of our work is to develop animal models to study roles of transcription factor genes in normal sensorineural development, as well as to elucidate how mutations in these genes cause sensorineural disorders such as blindness and deafness. Current projects in my laboratory are centered on studies of biological roles of two small families of transcription factor genes – Brn3 POU domain genes and Barhl homeobox genes. During the past year we made significant progress in three projects. First, our studies have shown that Brn3a plays a key role in the control of soma size, target field innervation, and axon pathfinding of inner ear sensory neurons. Second, our work has identified an important transcriptional cascade involved in the control of retinal ganglion cell development. Finally, we have generated knockout mice to demonstrate that Barhl1 is specifically required for the maintenance of cochlear outer hair cells.

Publications:


## Structural Biology

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Edward Arnold, Ph.D.
Resident Faculty Member, CABM; Professor, Rutgers, Department of Chemistry and Chemical Biology, Adjunct Professor, UMDNJ-RWJMS, Department of Molecular Genetics and Microbiology

Biomolecular Crystallography Laboratory
Dr. Arnold obtained his Ph.D. in organic chemistry with Professor Jon Clardy at Cornell University in 1982. From 1982 to 1987, he did postdoctoral work with Professor Michael G. Rossmann at Purdue University and was a central member of the team that solved the structure of a human common cold virus by X-ray crystallography. Among the awards and fellowships Arnold has received are a National Science Foundation Predoctoral Fellowship, Damon Runyon–Walter Winchell and National Institutes of Health Postdoctoral Fellowships, an Alfred P. Sloan Research Fellowship, a Johnson and Johnson Focused Giving Award, and a Board of Trustees Award for Excellence in Research at Rutgers. Dr. Arnold is the director of a multi-center NIH Program Project. He received an NIH MERIT Award in 1999 and was elected a Fellow of the American Association for the Advancement of Science in 2001. The laboratory is supported by grants from NIH and industrial collaborators, and by research fellowships.

Many of the underlying biological and chemical processes of life are being detailed at the molecular level, providing unprecedented opportunities for the development of novel approaches to the cure and prevention of human disease. A broad base of advances in chemistry, biology, and medicine has led to an exciting era in which knowledge of the intricate structure of life’s machinery can help to accelerate the development of new small molecule drugs and biomaterials such as engineered viral vaccines. Drs. Eddy Arnold and Gail Ferstandig Arnold and their colleagues are working to develop and apply structure-based drug and vaccine designs for the treatment and prevention of serious human diseases. In pursuit of these goals, their laboratory takes advantage of cutting-edge research tools, including X-ray crystallography, molecular biology, virology, protein biochemistry, and macromolecular engineering.

The approaches being developed in the Arnold laboratory are applicable to a wide array of human health problems, ranging from infectious diseases to cancer and diseases caused by hereditary genetic defects. Much of the Arnold lab’s research effort to date has focused on the development of drugs and vaccines for the treatment and prevention of AIDS. Examples of the results of these studies include: 1) collaborative development of drugs for the treatment of AIDS, some of which appear to be more effective than treatments in current use; and 2) production of AIDS vaccine candidates that have elicited protective immune responses against HIV.

Dr. Eddy Arnold and coworkers study the structure and function of reverse transcriptase (RT), an essential component of the AIDS virus and the target of many of the most widely used anti-AIDS drugs. Using the powerful techniques of X-ray crystallography, his team has solved the three-dimensional structures of HIV-1 RT in complex with a variety of antiviral drugs and small segments of the HIV genome. These studies have revealed the workings of an intricate and fascinating biological machine in atomic detail and have yielded numerous novel insights into polymerase structure-function relationships, detailed mechanisms of drug resistance, and structure-based design of RT inhibitors. Synthesis of this information has led to the development of a number of inhibitors that show great promise as potential treatments for AIDS.
Drug development and structural studies of a molecule as complex as HIV RT require immense and highly coordinated resources. Dr. Eddy Arnold has been fortunate to have highly successful collaborations with the groups of Dr. Stephen Hughes (NIH NCI, Frederick, MD) and Dr. Paul Janssen (Center for Molecular Design, Janssen Research Foundation, Belgium), and generous access to synchrotron X-radiation sources (CHESS, APS, and BNLS). Hughes and his group have contributed expertise in protein engineering, production, and biochemistry at every stage of the RT project. Janssen and his coworkers (including chemists at Janssen Research Foundation, Springhouse, PA) have synthesized hundreds of molecules from a number of chemical families in search of optimal drug candidates, eventually leading to the discovery of agents effective against isolates of HIV containing drug-resistance mutations that can cause the currently available drugs to fail. Crystallographic work from the Arnold and Hughes laboratories has allowed precise visualization of how potential anti-HIV drug candidates latch onto RT, their molecular target. Janssen and colleagues at the Center for Molecular Design have used this structural information to guide the design and synthesis of new molecules with improved properties. Following further evaluation against drug-resistant variants, scientists at Tibotec-Virco (Mechelen, Belgium) have coordinated testing of two of the molecules with highly promising results in Phase II clinical trials. Some of these anti-HIV compounds are inexpensive to make, potently and broadly effective, non-toxic, and simple to administer. These molecules have the potential to be widely accessible for treating AIDS in underdeveloped nations.

Vaccines have proven to be the most effective tools for worldwide control of infectious diseases. Our laboratory’s vaccine development project, jointly directed by both of us, involves engineering a human common cold virus, rhinovirus, to display immunogenic segments from more dangerous pathogens for the purpose of developing vaccines against these pathogens. This work involves generating “combinatorial libraries” of chimeric human rhinoviruses using a technique called random systematic mutagenesis. Foreign sequences are linked to the HRV sequences via adapters of randomized sequences and lengths, leading to a constellation of presentations. Large sets of such viruses presenting the foreign sequences in many conformations are generated and then selected with appropriate antibodies aimed at the target pathogen, allowing for the isolation of vaccine candidates with the most effectively reconstructed foreign segments. Our combinatorial approach to the vaccine problem is akin to buying many tickets for a lottery: the chances of winning the jackpot are increased by having more tickets.

Chimeric rhinovirus constructs have been made that elicit antibodies (in guinea pigs) capable of potently neutralizing the AIDS virus in cell culture. Virus libraries incorporating immunogens from the HIV gp120 and gp41 envelope glycoproteins have been constructed. We are also working collaboratively with Professor John Taylor of the Rutgers Chemistry and Chemical Biology Department to probe the immunogenic determinants of an epitope from gp41 using synthetic peptides. In addition to looking for chimeric viruses and peptides capable of eliciting the most potent and broad immune responses possible, we are also interested in elucidating the molecular determinants of immunogenicity. Knowledge of the relationship between structure and function (i.e., neutralization) would give us the opportunity to develop better vaccine candidates. The laboratory team is also using X-ray crystallography to analyze the structures of...
some of the engineered viruses (and soon peptides), alone and in complex with anti-HIV antibodies. Ultimately we hope to identify three-dimensional correlates of immunogenicity, and use this information to develop a structural basis for design of more effective human vaccines. There is every reason to expect that a structure-based approach to vaccine development will become as important to vaccinology as has structure-based drug design to drug discovery and development.

In addition to working to develop novel vaccines and chemotherapeutic agents, the laboratory aims to gain greater insights into the basic molecular processes of living systems. Other projects currently being pursued in the lab include structural studies of: 1) the human mRNA capping enzyme and its associated factors (with Dr. Aaron Shatkin at CABM); 2) the TNF-like cytokine BLYsS (B lymphocyte stimulator, with Yuling Li and colleagues at Human Genome Sciences); 3) and hantavirus proteins (with Dr. Colleen Jonssen at University of New Mexico). The structural group also collaborates with Dr. Gaetano Montelione (CABM) on crystallography of proteins targeted by the Northeast Structural Genomics Consortium.

Publications:


reverse transcriptase are resistant to lamivudine triphosphate (3TCTP) in vitro. *J. Virol.* **75**:6321-6328.


Protein NMR Laboratory
Dr. Gaetano Montelione did graduate studies in protein physical chemistry with Professor Harold Scheraga at Cornell University. He learned nuclear magnetic resonance spectroscopy at the Swiss Federal Technical Institute in Zürich where he worked with Dr. Kürt Wüthrich, the first researcher to solve a protein structure with this technique in 1985. Two years later Dr. Montelione solved the structure of epidermal growth factor. He has developed new NMR techniques for refining 3D structures of proteins and triple resonance experiments for making \(^{1}H\), \(^{13}C\), and \(^{15}N\) resonance assignments in intermediate-sized proteins. His laboratory has determined 3D solution structures for epidermal growth factor, type-\(\alpha\) transforming growth factor, RNA-binding proteins involved in cold-shock response, and immunoglobulin-binding proteins. He is a member of the NSF Molecular Biophysics Study Section. Dr. Montelione has received the Searle Scholar Award, the Dreyfus Teacher-Scholar Award, a Johnson and Johnson Research Discovery Award, the American Cyanamid Award in Physical Chemistry, the NSF Young Investigator Award, and the Michael and Kate Bárány Award of the Biophysical Society.

Goals of our work involve developing high-throughput technologies suitable for determining many new protein structures from the human genome project using nuclear magnetic resonance spectroscopy (NMR) and X-ray crystallography. These structures provide important insights into the functions of novel gene products identified by genomic and/or bioinformatic analysis. The resulting knowledge of structure and biochemical function provides the basis for collaboration with pharmaceutical companies to develop drugs useful in treating human diseases that are targeted to these newly discovered functions. The approach we are taking is opportunistic in the sense that only proteins which express well in bacterial expression systems are screened for their abilities to provide high quality NMR spectra or well-diffracting protein crystals. Those that provide good NMR or X-ray diffraction data are subjected to automated analysis methods for structure determination. The success of our approach relies on our abilities to identify, clone, express, and analyze hundreds of biologically-interesting proteins per year; only a fraction of the initial sequences chosen for cloning and analysis result in high-resolution 3D structures. However, this “funnel” process can yield new functions for tens of new structures per year and can thus have tremendous scientific impact. A New Jersey Commission on Science and Technology Excellence Award has been made to a research team organized jointly by Montelione and Steve Anderson to pursue an Initiative in Structural Bioinformatics and Genomics based on these ideas. Montelione is also director of the NIH-funded Northeast Structural Genomics Consortium, a multi-year $25 million inter-institutional pilot project in large scale structural proteomics.

Publications:


**Stanley Stein, Ph.D.**

Resident Faculty Member, CABM; Adjunct Professor, UMDNJ-Robert Wood Johnson Medical School, Department of Genetics and Microbiology and Department of Neuroscience and Cell Biology; Graduate Faculty Member, Rutgers University, Department of Chemistry

**Protein Microchemistry Laboratory**

Dr. Stanley Stein has held research positions at Hoffmann-LaRoche and Schering Corporation where he participated in the discovery and development of the prominent anti-viral and anti-cancer therapeutic protein, interferon. His interests in biological and analytical chemistry are directed toward both proteins and oligonucleotides. He has also contributed in several ways to academic-industrial technology transfer, including fee-for-service analyses, long-term research contracts and entrepreneurial enterprises.

The Stein laboratory focuses on improving technologies for delivering therapeutic drugs. These include enhanced cell uptake of drugs against intracellular targets, preferential delivery to target cells such as to macrophages for treating AIDS and tuberculosis, sustained drug release over periods of weeks or months to overcome problems of patient noncompliance, oral delivery of protein/peptide drugs and oral delivery of water-insoluble small molecule drugs for cancer and other life-threatening diseases.

**Publications:**


Ann Stock, Ph.D.
Associate Investigator, Howard Hughes Medical Institute; Resident Faculty Member, CABM; Professor, UMDNJ-Robert Wood Johnson Medical School, Department of Biochemistry

Protein Crystallography Laboratory

Dr. Ann Stock performed graduate work on the biochemistry of signal transduction proteins with Professor Daniel E. Koshland, Jr. at the University of California at Berkeley. From 1987 to 1991 she pursued structural analysis of these proteins while a postdoctoral fellow with Professor Clarence Schutt at Princeton University and Professor Gregory Petsko at the Structural Biology Laboratory in the Rosenstiel Center at Brandeis University. Her CABM laboratory has solved structures of several signal transduction proteins, including receptor modification enzymes and members of the two-components family of signal transduction proteins. Stock has received National Science Foundation Predoctoral and Damon Runyon-Walter Winchell Postdoctoral Fellowships, a Lucille P. Markey Scholar Award in Biomedical Science, the NSF Young Investigator Award and a Sinsheimer Scholar Award. She is an associate investigator of the Howard Hughes Medical Institute.

Research in the Stock laboratory focuses on structure/function studies of signal transduction proteins. Effort is concentrated on bacterial histidine protein kinases and response regulator proteins that mediate the majority bacterial signaling processes. These systems are important for virulence in pathogenic organisms and are currently targets for development of new antibiotics in several pharmaceutical companies. During the past year the Stock laboratory determined the first structure for a full-length member of the OmpR family of transcription factors, the largest subfamily of response regulator proteins. The structure provides insight into the mechanism of regulation of the protein by phosphorylation and suggests a limit to the extent of mechanistic similarities between proteins of similar structure and function.

Publications:


### Molecular Genetics

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Stephen Anderson, Ph.D.
Resident Faculty Member, CABM; Associate Professor, Rutgers University, Department of Molecular Biology and Biochemistry

Dr. Stephen Anderson conducted his postdoctoral research under Nobel laureate Dr. Frederick Sanger at the MRC Laboratory of Molecular Biology in Cambridge, England. That project involved the sequencing of human and bovine mitochondrial genomes. He went on to a position at the California-based biotechnology start-up company Genentech. Anderson has held research or teaching positions at Harvard University, the MRC Laboratory of Molecular Biology, Genentech, Inc., University of California, San Francisco, and Rutgers University. While at Genentech he was responsible for all specialty chemical projects and second generation tissue plasminogen activator research. He is an associate editor of the journal SEQUENCE. Currently Dr. Anderson is on leave at GeneFormatics, Inc.

Protein Engineering Laboratory

Our laboratory is focusing on the study of protein folding and molecular recognition. We are particularly interested in the role these processes may play in the pathophysiology of Alzheimer’s disease. The Alzheimer’s β amyloid precursor protein (APP) is a large, membrane-bound glycoprotein that is expressed in the body from several different alternatively-spliced mRNAs. Contained within this precursor protein is the amyloid β peptide which has been strongly implicated as a causal agent in Alzheimer’s disease. Our laboratory is currently using a protein engineering strategy to dissect the structure and function of the APP molecule as well as its component domains. We are also seeking to identify and isolate other proteins in the body that bind to APP. We have discovered that amyloid β peptide fibrils bind and activate both tissue plasminogen activator and plasminogen in a manner remarkably similar to the known physiological cofactor, fibrin. This phenomenon may shed light on the involvement of amyloid peptide fibrils in cerebral amyloid angiopathy and hemorrhagic stroke.

Recently the laboratory has been using a combination of protein expression and biophysical approaches to create a new structure-based functional genomics paradigm for analyzing “orphan” gene sequences. We have embarked on an ambitious, multidisciplinary, collaborative project to develop new methods for analyzing protein 3D structure and function. These methods, termed structural genomics, will be used to interpret the flood of novel gene sequence data being produced by the human genome project. The work on structural genomics, in collaboration with Professor Gaetano Montelione at CABM and other colleagues at Rutgers, UMDNJ-Robert Wood Johnson Medical School, CABM and HHMI, has picked up momentum during the last year. Significant progress has been made in understanding the structure and dimerization properties of the BRCT domain, which is found in the human breast cancer gene, BRCA1. We are also working on highly conserved bacterial gene products that are found in Mycobacterium tuberculosis and other human pathogens but not in humans themselves – understanding the structure and function of these may suggest strategies for developing novel antibiotics. Finally, we have embarked upon the scaled-up expression and biophysical characterization, in a pilot-study mode, of a series of small orphan gene products from the roundworm, C. elegans. Our work on molecular recognition has centered on the well-characterized protease-protease inhibitor interaction. The specific model system we have employed is the interaction of avian ovomucoid third domains (OM3D) with members of the trypsin family of serine proteases. Our
approach is the expression of recombinant turkey OM3D in *E. coli* and specific mutagenesis of reactive site residues. Mutant inhibitors are then tested for binding affinity with a panel of serine proteases. Our goal is to provide a complete, canonical set of ovomucoid third domain (OM3D) variants with every amino acid at the reactive site mutagenized, individually, to every other amino acid. This project is virtually complete, with the last mutants currently being made. The work is being conducted in collaboration with Dr. Michael Laskowski Jr.’s laboratory at Purdue University and Dr. Michael James’ laboratory at Edmonton, Alberta. The resultant database will represent an unparalleled resource for drug design groups and other users interested in rationalizing the energetics of protein-protein interactions.

We also have a long-term effort aimed at developing improved industrial methods for synthesizing vitamin C. We are working on increasing the activity of a crucial enzyme in the pathway from glucose to 2-keto-L-gulonic acid [a precursor of vitamin C], 2,5-diketo-D-gluconic acid (2,5-DKG) reductase, using protein engineering techniques and extensive mutagenesis of the enzymes’ substrate and cofactor binding sites.

**Publications:**


Arnold B. Rabson, M.D.
Resident Faculty Member, CABM; Professor, UMDNJ-Robert Wood Johnson Medical School, Department of Molecular Genetics and Microbiology; Adjunct Professor, UMDNJ-RWJMS, Department of Pathology

Viral Pathogenesis Laboratory

Dr. Rabson joined CABM in the summer of 1990. Previously, he performed his residency in pathology at Brigham and Women’s Hospital in Boston. He was a medical staff fellow and a senior staff fellow in Malcolm Martin’s laboratory at the National Institute of Allergy and Infectious Diseases from 1981 to 1990. Dr. Rabson has served on a number of federal grant review boards, including an NIH Special Review Committee for AIDS. He is a member of the NIH Pathology B study section and has served as Chairman of several Special Emphasis Panels of the NIH Center for Scientific Review. He is on the editorial board of the Journal of Virology, Clinical Cancer Research and the Journal of Biomedical Science. Dr. Rabson is also the Associate Director for Basic Research of the Cancer Institute of New Jersey (CINJ) and directs the Transcriptional Regulation and Oncogenesis Program of CINJ.

Dr. Rabson’s laboratory focuses on the molecular basis of cancer and human retroviruses. His research program encompass studies of the viral and cellular mechanisms that regulate the expression of human retroviruses that cause cancer and AIDS, the human T-cell leukemia virus type 1 (HTLV-1) and the human immunodeficiency virus (HIV). A second aspect of the laboratory studies the roles of cellular transcription factors in the development and progression of human malignancies, including leukemia, lymphomas, and prostate cancer.

Previous studies in Dr. Rabson's laboratory identified the frequent occurrence of molecular alterations in the gene encoding the NFkB2 transcription factor in the malignant cells of patients with cutaneous T-cell lymphoma (CTCL). Over the past year, Dr. Rabson’s laboratory has demonstrated that the tumor associated NF-κB-2 mutants also gain new gene regulatory functions. Regulated expression of these aberrant proteins can prevent T cell death and increase proliferation; thus the lymphoma associated rearrangements lead to both a loss of function and a gain of new transcriptional regulation. Dr. Rabson is now identifying the target genes of the tumor associated mutant proteins that may explain how this genetic alteration leads to T cell lymphomas.

Dr. Rabson's laboratory has demonstrated inappropriate, constitutive, activation of NF-κB in a series of aggressive, tumorigenic, human prostate cancer cell lines and has shown inappropriate activation of NF-κB in focal areas of primary prostate cancer samples from patients with the disease. He has further shown that constitutive, inappropriate activation of NF-κB in the prostate cancer cells is due to activation of regulatory kinases such as the IkappaB kinases and the NF-κB kinase. He is continuing to study the consequences of NF-kB expression in prostate cancer cells. This work offers possible new approaches for therapy of the disease.
Collaborative studies with Drs. Strair (CINJ) and White (CABM) are evaluating the potential utility of highly attenuated adenoviruses as cytotoxic agents for the therapy of different subsets of leukemias and lymphomas since mutated, highly attenuated adenoviruses may be useful in the therapy of this disease. In collaboration with Dr. R. Strair (CINJ) and Dr. A. Conney (Rutgers University), Dr. Rabson is studying the molecular mechanisms by which the phorbol ester, TPA, can induce differentiation of human leukemic cells. The collaborative studies at CABM have focused on the effects of TPA on NF-kB and on chromatin structure during the induction of differentiation.

The Rabson laboratory has identified and characterized models of latent HTLV-1 infection and demonstrated that immune activation stimuli can potently induce HTLV-1 gene expression. This suggests that stimulation of particular T cell clones through their T cell receptor could lead to enhanced HTLV-1 gene expression, resulting in increased T cell proliferation. This could explain the polyclonal to oligoclonal proliferation of infected T cells that characterizes HTLV-1-associated diseases. Over the last year, Dr. Rabson’s laboratory has demonstrated that the HTLV-1 Tax protein is the target of the T cell activation stimuli. These results suggest that inhibition of T cell signaling might alter the progression of HTLV-1 infection.

Publications:


Aaron J. Shatkin, Ph.D.
Director, CABM; University Professor of Molecular Biology at Rutgers University and Professor, UMDNJ-Robert Wood Johnson Medical School, Department of Molecular Genetics and Microbiology

Molecular Virology Laboratory
Dr. Aaron J. Shatkin, a member of the National Academy of Sciences, has held research positions at the National Institutes of Health, The Salk Institute, and the Roche Institute of Molecular Biology. He has taught at, among other institutions, Georgetown University Medical School, Cold Spring Harbor Laboratory, The Rockefeller University, UMDNJ-Newark Medical School, University of Puerto Rico, and Princeton University. He was editor of the Journal of Virology from 1973-1977, founding editor-in-chief of Molecular and Cellular Biology from 1980-1990, and is currently an editor of Advances in Virus Research and a member of the editorial board of the Proceedings of the National Academy of Sciences. Shatkin serves on the advisory boards of a number of organizations including the Howard Hughes Medical Institute, and in 1989 he was recognized by New Jersey Monthly magazine with a New Jersey Pride Award for his contributions to the State’s economic development. In 1991 the State of N.J. awarded Shatkin the Thomas Alva Edison Science Award. He was elected Fellow of the American Academy of Arts and Sciences in 1997, and the American Association for the Advancement of Science in 1999.

One of the earliest steps in the cascade of controls that regulate mRNA formation and function is the addition of a 5'-terminal "cap." This structural hallmark is present on all eukaryotic cellular mRNAs and is essential for viability. The cap enhances several downstream events in gene expression including splicing of pre-mRNAs, initiation of protein synthesis and mRNA stability. Recently we have cloned and sequenced the mouse and human capping enzymes (CE) and mapped the human protein to 6q16, a region implicated in tumor suppression. The mammalian CE are 597-aa polypeptides consisting of two functional domains, N-terminal RNA 5' triphosphatase (RT) and C-terminal guanylyltransferase (GT). Mutational analysis demonstrated that the GT active site lysine is present in one of several highly conserved motifs characteristic of a nucleotidyltransferase superfamily. A haploid strain of S. cerevisiae lacking GT was complemented for growth by the mouse wild type cDNA clone but not by a clone containing alanine in place of the active-site lysine. The results demonstrate the functional conservation of CE from yeast to mammals.

We found that mammalian CE binds via its GT domain to the hyperphosphorylated C-terminal domain (P-CTD) of RNA polymerase II, accounting for the selective capping of pre-mRNAs. The CE N-terminal RT contains the sequence VHCHTHGFNRTG which corresponds to the conserved active-site motif in protein tyrosine phosphatases (PTPs). Mutational analyses indicate that removal of phosphate from RNA 5' ends and from protein tyrosines occurs by a similar mechanism. We have also cloned, mapped to 18p11.22-p11.23 and characterized the third essential enzyme for capping--mRNA (guanine-7-) methyltransferase (MT). Sequence alignment of the 476-aa human MT with the corresponding yeast, worm and fly enzymes demonstrated several required, conserved motifs including one for binding S-adenosylmethionine.

Yeast two-hybrid screening with CE yielded transcription elongation factor SPT5 which stimulated GT, but the effects were not additive with SPT5, suggesting a common binding site

Center for Advanced Biotechnology and Medicine
on CE. We also found that MT interacts with the nuclear transporter, importin-alpha (Impa). MT selectively bound and methylated RNA containing 5'-GpppG, and both activities were stimulated several-fold by Impa. MT/RNA/Impa complexes were dissociated by addition of Imp-beta (Impb) which also blocked Impa stimulation of RNA cap methylation. RanGTP but not RanGDP prevented these effects of Impb. The results suggest that, in addition to a linkage between capping and transcription, mRNA biogenesis and nucleocytoplasmic transport are functionally connected, a possibility we are exploring further.

Publications:


Education, Training & Technology Transfer
CABM Lecture Series

January 24
James Manley, Biological Sciences, Columbia University
“mRNA Processing and the Integration of Nuclear Events”

February 14
Heiner Westphal, NIH
“How Mouse LIM Homeobox Genes Control Organogenesis”

March 29
Rick Young, MIT
“Lessons from Global Expression Profiling of Yeast and Human Cells”

April 18
Nadia Rosenthal, Harvard Medical School
“Retinoic Acid and Heart Development”

May 16
Se-Jin Lee, Johns Hopkins University
“Novel Growth and Differentiation Factors Related to TFG-β”

September 19
Jon Clardy, Chemistry and Chemical Biology, Cornell University
“Natural Products and Natural Product Libraries”

October 24 & 25
15th Annual CABM Symposium
“Structural Genomics in Pharmaceutical Design”

December 6
Michael B. Kastan, Hematology-Oncology, St. Jude’s Children’s Research Hospital
“DNA Damage Response Pathways in the Genesis and Treatment of Cancer”

-- The CABM Lecture Series is supported in part by Aventis --

ANNUAL CABM RETREAT, June 11th, 2001

FOREST LODGE, Warren, NJ

Program

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<td>Professor and Director, CABM</td>
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<tr>
<td>9:10 AM</td>
<td>Proteomics: Protein Structure, Engineering and Applications</td>
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<td>Chair: Hunter Moseley – Protein NMR Spectroscopy Lab (Guy Montelione)</td>
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<td>Tom Acton – Protein NMR Spectroscopy Lab (Guy Montelione)</td>
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<td>&quot;The Northeast Structural Genomics Consortium, a Pilot Project Focusing on Eukaryotic Organisms&quot;</td>
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<td></td>
<td>Scott Banta – Protein Engineering Lab (Stephen Anderson)</td>
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<td>“Alteration of the Cofactor Specificity of Corynebacterium 2,5-diketo-D-gluconic Acid Reductase”</td>
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<td>Shahriar Pooyan – Protein Microchemistry Lab (Stanley Stein)</td>
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<td>“PEG Carrier for Drug Targeting”</td>
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<td>Li Lin – Protein Targeting Lab (Peter Lobel)</td>
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<td>“The Human CLN2 Protein/Tripeptidyl-peptidase I Is A Serine Protease”</td>
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<td>David Buckler – Protein Crystallography Lab (Ann Stock)</td>
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<td>“X-ray Crystal Structure of An OmpR Homolog from Thermotoga maritima&quot;</td>
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<td>Deena Oren – Biomolecular Crystallography Lab (Eddy Arnold)</td>
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<td>“Determining the Structure of the Human B Lymphocyte Stimulator BlyS”</td>
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<td>10:40 AM</td>
<td>Coffee Break</td>
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<td>11:00 AM</td>
<td>Gene Expression and Cancer</td>
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<td>Chair: Leonard Edelstein – Tumor Virology Lab (Céline Gélinas)</td>
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<td>Priya Srinivasan – Molecular Virology Lab (Aaron J. Shatkin)</td>
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</table>
“Analysis of C. elegans mRNA Capping Machinery by RNA Interference”

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**Annual CABM Retreat**

Wen-Feng Chen – Molecular Chronobiology Lab (Isaac Edery)
"Analysis of Locomotor Activity and Per mRNA Splicing in Flies from Different Latitudes"

Paul Lizzul – Tumor Virology Lab (Céline Gélinas)
“TAPIR is a Novel NF-κB-inducible Gene, Distinct from IκB, Which Suppresses NF-κB-mediated Transactivation in Response to TNFα and IL-1β Signaling”

Junghan Suh – Viral Pathogenesis Lab (Arnold Rabson)
"Mechanisms of NF-κB Activation in Prostate Cancer Cells"

Isao Matsuura – Growth and Differentiation Control Lab (Fang Liu)
“Phosphorylation of SMAD by Cyclin-dependent Kinases”

Kurt Degenhardt – Viral Transformation Lab (Eileen White)
“Adenovirus Induces DNA Fragmentation through a DFF-45/ICAD Dependent Mechanism That Is Inhibited by E1B 19K”

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12:30-3:30 PM  **Lunch and Free Time**

3:30 PM  **Poster Presentation (odd numbers)**

5:00 PM  **Mammalian Development**

**Chair: Yu-Ting Yan** – Mammalian Embryogenesis Lab (Michael Shen)

Jixiang Ding – Mammalian Embryogenesis Lab (Michael Shen)
“Eyes Wide Apart - Cripto and Midline Formation”

Hansol Lee – Molecular Neurobiology Lab (Cory Abate-Shen)
"Searching for the Regulatory Network of Msx1 Homeobox Protein"

Shengguo Li – Molecular Neurodevelopment Lab (Mengqing Xiang)
“Functional Analysis of the Barhl1 Homeobox Gene during Development of the Mouse Nervous System”

Ahmed Usmani – Developmental Neurogenetics Lab (James Millonig)
“Dorsal CNS Development in the Mutant Mouse Dreher”
6:00 PM  Poster Presentation (even numbers) and Buffet Reception

15th Annual CABM Symposium

Structural Genomics in Pharmaceutical Design
Princeton Forrestal Conference Center
Princeton, New Jersey
October 24-25, 2001

CABM Organizing Committee
Edward Arnold
Gaetano Montelione
Aaron J. Shatkin
Ann Stock

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-Rigaku/MSC, Inc.
-TKR Biotech Products
-Upstate Biotechnology
15th Annual CABM Symposium

Program

Wednesday, October 24, 2001

8:00 AM  Registration and Continental Breakfast

8:45 AM  Opening Remarks
          Aaron Shatkin, Director, Center for Advanced Biotechnology and Medicine

EXPERIMENTAL STRUCTURAL GENOMICS
Chair: Edward Arnold, Rutgers University and CABM

9:00 AM  Vim Hol, University of Washington
          “Protein Structures from Tropical Parasites: A Drug Design Perspective”

9:40 AM  Gaetano Montelione, Rutgers University and CABM
          “Structural Proteomics of Eukaryotic Gene Families”

10:20 AM  Sean Buchanan, Structural GenomiX
          “New Bacterial Drug Targets from Structural Genomics”

10:40 AM  Refreshment Break

INFORMATICS FOR STRUCTURAL GENOMICS
Chair: Casimir Kulikowski, Rutgers University

11:10 AM  Helen Berman, Rutgers University and Protein Data Bank
          “The Protein Data Bank”

11:50 AM  Mark Gerstein, Yale University
          “Structural Genomics: Surveys of a Finite Parts List”

PROTEIN PRODUCTION AND DRUG DESIGN
Chair: Masayori Inouye, Robert Wood Johnson Medical School
2:00 PM  
*David Waugh*, National Cancer Institute, Frederick  
“Generic Protein Expression and Purification Strategies for Structural Genomics”

15th Annual CABM Symposium

2:40 PM  
*Edward Arnold*, Rutgers University and CABM  
“Optimization of Multiple Factors in Developing Potent HIV Reverse Transcriptase Inhibitors as Potential Anti-AIDS Drugs”

3:40 PM  
Refreshment Break

IDENTIFYING BIOCHEMICAL FUNCTIONS  
Chair: *Gaetano Montelione*, Rutgers University and CABM

4:10 PM  
*Jeffrey Skolnick*, Danforth Plant Science Center  
“Prediction of Protein Structure and Function on a Genomic Scale”

4:50 PM  
*Ming-Ming Zhou*, Mount Sinai School of Medicine  
“Structure and Function of Protein Modular Domains”

5:30 PM  
*F. Raymond Salemme*, 3-Dimensional Pharmaceuticals  
“Protein Thermal Stability Measurements for High-Throughput Drug Screening and Target Decryption”

6:15 PM  
Reception

Thursday, October 25, 2001

8:00 AM  
Continental Breakfast

HIGH-THROUGHPUT STRUCTURE DETERMINATION  
Chair: *Ann Stock*, Robert Wood Johnson Medical School and CABM

9:00 AM  
*Andrzej Joachimiak*, Argonne National Laboratories  
“Structural Gemonics: from Genome Sequence to Proteome Structure”

9:40 AM  
*Stephen Burley*, Rockefeller University  
“Structural Genomics of Sterol/Isoprenoid Biosynthesis”

10:20 AM  
*Clemens Anklin*, Bruker NMR Instruments
“New Approaches to Biomolecular NMR Using Ultra High Field Systems and Cryoprobes”

10:40 AM Refreshment Break

15th Annual CABM Symposium

STRUCTURAL BIOINFORMATICS
Chair: Donna Bassolino, Bristol-Myers Squibb Pharmaceutical Research Institute

11:10 AM Cyrus Chothia, Cambridge University
“Protein Repertoires in Genomes: the Immunoglobulin Superfamily in Humans”

11:50 AM Ronald Levy, Rutgers University
“Recent Developments in Protein Fold Recognition, Determination, and ab initio Prediction”

12:30 PM Lunch

NEW TARGETS FOR PHARMACEUTICAL DESIGN
Chair: Stephen Anderson, GeneFormatics, Inc.

2:00 PM Peter Lobel, Robert Wood Johnson Medical School and CABM
“Lysosomal Proteomics and the Indentification of Human Disease Genes”

2:40 PM Martin Rosenberg, GlaxoSmithKline
“Microbial Genomics: Opportunities and Hurdles”

3:20 PM John Chiplin, GeneFormatics, Inc.
“Considerations for Target Selection and Drug Discovery in the Postgenomic Era”

3:40 PM L. Patrick Gage, Wyeth Research
“The Future of Molecular Medicine”
Closing Remarks
GRADUATE, UNDERGRADUATE STUDENTS AND POSTDOCTORAL FELLOWS INCLUDING COMPETITIVE FELLOWSHIP AWARDS

CABM faculty members also participate in UMDNJ and Rutgers University graduate student rotation programs that place students in CABM labs each year in order to give them education and experience in a range of research methods and subjects.

Graduate Students
- Priti Bachhawat, Protein Crystallography
  - NIH Biotech Training Grant
- Scott Banta, Protein Engineering
  - NIH Biotech Training Grant
- Joseph Bauman, Biomolecular Crystallography
- Annerban Bhattacharya, Protein NMR Spectroscopy
- Wen-Feng Chen, Molecular Chronobiology
- Natalia Denissova, Growth & Differentiation Control
- Jui Dutta, Tumor Virology
- Chaosu E, Mammalian Embryogenesis
  - USAMRMC
- Leonard Edelstein, Tumor Virology
  - NIH Biotech Training Grant
- John Everett, Protein NMR Spectroscopy
  - NIH Biotech Training Grant
- Jayita Guhaniyogi, Protein Crystallography
- Gezhi Hu, Molecular Neurobiology
  - American Heart Association
- Hyuk Wan Ko, Molecular Chronobiology
- Gregory Kornhaber, Protein NMR Spectroscopy
- Lynn Lagos, Tumor Virology
- Jung Eun Lee, Molecular Chronobiology
- Wei Liu, Molecular Neurodevelopment
- Paul F. Lizzul, Tumor Virology
- Denise Perez, Viral Transformation
  - NIH–NCI
- Eduardo Perez, Protein Crystallography
  - NIH Biochem Training Grant
- Shahriar Pooyan, Protein Microchemistry
- Yan Shen, Viral Transformation
- Matthew Simmons, Tumor Virology
  - NIH Biochem Training Gran
- David Snyder, Protein NMR Spectroscopy
  - NIH Biotech Training Grant
Graduate and Postdoctoral Students

-Priya Srinivasan, Molecular Virology
-Stacey Stein, Molecular Neurobiology
-NJCCR
-Junghan Suh, Viral Pathogenesis

-Ramya Sundararajan, Viral Transformation
-Alejandro Toro, Protein Crystallography
-NIH Biophysics Training Grant
-Paola Velasco, Biomolecular Crystallography
-Gang Xiao, Protein Targeting
-Cuifeng Yin, Protein NMR Spectroscopy
-Guobao Zhang, Protein Microchemistry
-Yujie Zhao, Viral Pathogenesis
-Deyou Zheng, Protein NMR Spectroscopy

Postdoctoral Students
-Dr. Andrew Bendall, Molecular Neurobiology
-Dr. David Buckler, Protein Crystallography
-Dr. Rajula Bhatia-Gaur, Molecular Neurobiology
-Neuroscience & Cell Biology NIH Training Grant
-UMDNJ Foundation
-Dr. Andrea Cuconati, Viral Transformation
-Howard Hughes Medical Institute
-Dr. Kalyan Das, Biomolecular Crystallography
-Dr. Kurt Degenhardt, Viral Transformation
-Dr. Jianping Ding, Biomolecular Crystallography
-Dr. Jiexiang Ding, Mammalian Embryogenesis
-Dr. Bonnie Lynn Dixon, Protein Engineering
& Protein NMR Spectroscopy
-Dr. Yongjun Fan, Tumor Virology
-Dr. Kristin Gunsalus, Protein NMR Spectroscopy
-NIH Postdoctoral Fellowship
-Dr. Daniel Himmel, Biomolecular Crystallography
-Dr. Holly Henry, Viral Transformation
-Howard Hughes Medical Institute
-Dr. Jiux doctoral Jin, Protein Crystallography
-Howard Hughes Medical Institute
-Dr. Natalia Khlebtsova, Protein Crystallography
-Howard Hughes Medical Institute
-Dr. Eun Young Kim, Molecular Chronobiology
-Dr. Minjung Kim, Molecular Neurobiology
-Dr. Jerome Kucharczak, Tumor Virology
-Dr. Hansol Lee, Molecular Neurobiology
-Dr. Hsin-Ching Lin, Viral Pathogenesis
-Dr. Li Lin, Protein Targeting
-Dr. Heng-Ling Liou, Protein Targeting
-Dr. Yuanpeng Huang, Protein NMR Spectroscopy

**Graduate and Postdoctoral Students**

-Dr. Jan-Jan Liu, Mammalian Embrogenesis
-Dr. Jianyin Long, Growth & Differential Control
-Dr. Xuejun Ma, Biomolecular Crystallography
-Dr. Isao Matsuura, Growth & Differential Control
-Dr. Daniel Monleon, Protein NMR Spectroscopy
-Dr. Hunter Moseley, Protein NMR Spectroscopy
-Dr. Deena Oren, Biomolecular Crystallography
-Dr. Rajan Paranji, Protein NMR Spectroscopy
-Dr. Beatrice Rayet, Tumor Virology
  Cure for Lymphoma Foundation Fellowship and UMDNJ Foundation
-Dr. Victoria Robinson, Protein Crystallography
  Howard Hughes Medical Institute
-Dr. Stefan Sarafianos, Biomolecular Crystallography
-Dr. Anju Thomas, Viral Transformation
-Dr. Steven Tuske, Biomolecular Crystallography
  NIH Postdoctoral Fellowship
-Dr. Yingxia Wen, Molecular Virology
-Dr. Yu-Ting Yan, Mammalian Embryogenesis

**Undergraduate Students**

-Alan Anschel, Viral Transformation
  Howard Hughes Medical Institute
-Antonious Attallah, Protein Crystallography
-Jisook Baek, Viral Transformation
-Angelo Banaria, Lab Management
-Marvin Bayro, Protein NMR Spectroscopy
-Michael Chen, Protein Crystallography
-Helen Chow, Protein NMR Spectroscopy
-Bonnie Cooper, Protein NMR Spectroscopy
-Gaurev Davé, Biomolecular Crystallography
-Michelle DeFreese, Lab Management
-Kate Drahos, Protein NMR Spectroscopy
-Robert Faltas, Biomolecular Crystallography
-Manju Goyal, Protein NMR Spectroscopy
-April Graham, Molecular Neurobiology
  Biomedical Careers Fellowship
-Michelle Hickey, Viral Pathogenesis
-Hui Yun Ho, Administration
-Lydia Hsu, Viral Pathogenesis
-Hyunmi Kim, Molecular Virology
-Rebecca Liu, Protein NMR Spectroscopy
-Nicholas Lumia, Lab Management
-Meera Mani, Protein Crystallography

Undergraduate Students

-Ram Mani, Protein NMR Spectroscopy
   Howard Hughes Medical Institute Fellowship
   Rutgers University Undergraduate Research Fellowship
-Raehum Paik, Molecular Chronobiology
-Hammad Rizvi, Mammalian Embryogenesis
-Gurmukh Sahota, Protein NMR Spectroscopy
-Beth Shafers, Molecular Virology
-Rachel Siegel, Biomolecular Crystallography
   Howard Hughes Medical Institute Fellowship
-Jennifer Staley, Administration
-Max Tischfield, Developmental Neurogenetics
-Melanie Vishnu, Lab Management
-Deborah Weintraub, Protein Crystallography
-Karlvin Wong, Molecular Neurobiology
-Zeba Wunderlich, Protein NMR Spectroscopy
**PATENTS**


**Lobel, P.** and Sleat, D “Human lysosomal protein and methods of its use” U.S. Patent #6,302,685.


**Stein, S.** “Site-specific 13C-enriched reagents for diagnostic medicine by magnetic resonance imaging”. U.S. Patent #6,210,655.


Fiscal Information