



2008 Grant Recipients

Gustavo Aguirre, D.V.M., Ph.D.

Dept of Genetics, School of Veterinary Medicine, University of Pennsylvania

Project: Developing Retinal Therapies in Models of Retinal Degeneration

Proof of principle *studies* in retinal disease models have demonstrated that experimental therapies can be evaluated and transitioned into clinical trials for retinal diseases in human patients (e.g., gene therapy for LCA; CNTF via encapsulated cell based therapy technology). Dr. Aguirre will continue to use disease relevant models to develop or evaluate novel therapies that have the potential for restoring sight or preventing/slowing down the loss of vision in human patients.

Tomas Aleman, M.D.

Scheie Eye Institute, University of Pennsylvania

Project: Retinitis Pigmentosa: Paving the Path to Treatments Through Detailed Understanding of Disease Expression

Summary: Success of ongoing gene therapy trials for Leber Congenital Amaurosis has raised expectations that other forms of inherited retinal degeneration may also be treatable. Detailed characterizations of patients, part of the groundwork that was necessary to initiate these trials, will be performed in other inherited retinal degenerative disorders to increase understanding of human disease expression and mechanism. The knowledge gained will be used to ask specific questions relevant for the planning of future treatment trials for these conditions.

Muayyad Al-Ubaidi, Ph.D.

Dept of Cell Biology, University of Oklahoma

Project: To evaluate pharmacological and neurotrophic agents to rescue photoreceptor cells in RP animal models.

Summary: Since a greater proportion of retinal degenerative diseases are still of unknown causes, there exist the need to further study other aspects of normal retinal function. Furthermore, in most cases where the mutation is known, it is not known how that mutation has altered the function of the protein leading to the degenerative disease phenotype. Dr. Al-Ubaidi and his team chose to understand how modulations in a post-translational modification can alter retinal function. The gained knowledge will help them understand how a protein functions and therefore, how a mutation would alter that function leading to a blinding disease. They will identify all sulfated retinal proteins and will choose those that have been involved in retinal disease for further study. They will then study how lack of sulfation altered that function. This will allow them to develop strategies, gene based or pharmacological, to counter the effects of the mutation.

Jonathan Ash, Ph.D.

Dept of Ophthalmology, University of Oklahoma

Project: To perform research on neuroprotection that would be relevant to genetic photoreceptor degenerations

Summary: In most cases of retinal degeneration, photoreceptor death is the result of long-term inflammation, exposure to environmental insults, and genetics. While disease causing genes are present before birth, patients with retinitis pigmentosa or age related macular degeneration typically do not develop disease for 50 to 80 years. The protracted time to develop symptoms suggests that retinal neurons have an endogenous mechanism for protection from chronic injury. The main focus of Dr. Ash's work is to identify the mechanism of stress-induced endogenous protection of photoreceptors, and once identified, he and his team will develop these protective mechanisms into new therapeutics, with the goal of delaying or preventing blindness resulting from inherited retinal degenerations.

Joseph Carroll, Ph.D.

Eye Institute, Medical College of Wisconsin

Project: Advanced Retinal Imaging and Improving the Success of Gene Therapy

Summary: Dr. Carroll and his team will use adaptive optics, allowing them to see individual photoreceptor cells in the retina, and optical coherence tomography, allowing them to see the layers of the retina. This information will be combined with genetic data and clinical data on each patient to develop a high-resolution genotype-phenotype correlation that carries with it significant predictive power with regard to treating this and other retinal degenerations.

Arlene Drack, M.D.

University of Iowa Hospitals and Clinics

Project: To perform clinically-relevant molecular genetics research in syndromic and non-syndromic RP

Summary: Dr. Drack's research is focused on treatment strategies for mouse models of human retinitis pigmentosa and Bardet Biedl syndrome (BBS). Dr. Drack's group was the first to demonstrate genetic heterogeneity of BBS by identifying linkage to three different chromosomal locations in three large consanguineous tribes of Bedouin Arabs from Israel. Furthermore, her laboratory has independently identified seven of the twelve known BBS genes and recently developed knockout mouse models of many of those genes. In the next few years, Dr. Drack and her team intend to develop and test viral-mediated gene replacement therapy in mouse models of these diseases; and clinically and molecularly characterize a large number of patients affected with BBS to establish the natural history of the vision loss in this disease as well as to identify a large number of individuals who could be invited to participate in a future human clinical trials of gene therapy for these diseases.

Jacque Duncan, M.D.

Beckman Vision Center, University of California - San Francisco

Project: High resolution retinal imaging in patients with retinal degenerations

Summary: Dr. Duncan and her team will correlate the images of retinal structure produced by the Adaptive Optics Scanning Laser Ophthalmoscope (AOSLO) with standard measures of retinal structure created with an instrument known as Optical Coherence Tomography (OCT). OCT images provide information about retinal structure in cross-section, while AOSLO gives en face images of individual cones. By combining these two techniques Dr. Duncan hopes to learn more about how changes in cone structure relate to vision loss in patients with retinal degenerations. In addition, Dr. Duncan will correlate the images of cone structure obtained using AOSLO with standard clinical measures of retinal function used in Ophthalmology clinics, including visual acuity, automated perimetry, fundus photography including fundus autofluorescence and multifocal electroretinography (mfERG), to learn how well the cones work or are able to see.

Erica Farber, Ph.D.

Jules Stein Eye Institute, University of California – Los Angeles

Project Title: Characterization of microRNAs in stem cell microvesicles

Summary: Fish and amphibians retain stem cells with the ability to regenerate the retina after injury. However, mammals have lost this ability. Recently, dormant stem cells were discovered in the mammalian eye. Further elucidation of the communication role of microvesicles within stem cell niches may reveal ways for microvesicles to awaken these dormant stem cells and lead to retina repair. Additionally, microvesicles released from cells engineered to express mRNA, proteins, or siRNA may be useful to deliver these small molecules to the eye. Dr. Farber and her colleagues will characterize the micro RNAs in stem cell microvesicles and establish a way to use microvesicles as vehicles for the transfer of specific small molecules to retinas affected by degenerative disease.

Jeffrey Goldberg, M.D., Ph.D.

Bascom Palmer Eye Institute, University of Miami

Project: Research leading to the development of therapeutic tools for photoreceptor diseases

Summary: Retinal degenerations such as retinitis pigmentosa often end with the death of retinal neurons such as rod and cone photoreceptors. Although it may be possible to salvage these cells before they die, for the many patients who have lost these cells, we must figure out a way to replace them. Little is known about how to harvest retinal stem cells, how to direct them to the proper location in the retina, how to push

them to differentiate into photoreceptors, and how to integrate them into the retina. Dr. Goldberg and his team are now attempting to address retinal degenerative disease by combining cell culture and nanotechnology to provide novel approaches to stem cell and cell replacement therapy. Dr. Goldberg's hope with these experiments is to enhance the efficacy of stem cell and photoreceptor transplantation and integration into the retina, and thereby bring back vision in retinal degenerative diseases.

Michael Grassi, MD

University of Chicago

Project: Collaborative effort to facilitate the discovery and testing of effective compounds to treat retinal degenerative disease.

Summary: Dr. Grassi has developed a multidisciplinary, inter-institutional collaboration between basic scientists and clinicians in Chicago to investigate the mechanisms that may result in apoptotic photoreceptor death in RP. Using a cellular model of RP, the research team will screen hundreds of thousands of small molecules to identify those compounds and genes that retard or prevent apoptosis. In addition, the cell culture system will enable a genome scale screen using RNA interference to assess the role of over 25,000 individual genetic perturbations in photoreceptor cell survival. Results from the screenings will be extended to animal models, which will enable the development and introduction of new therapies to better treat, and perhaps even prevent RP.

Neena Haider, PhD

University of Nebraska

Project: Research into genetic modifiers of retinal degenerations

Summary: Dr. Haider's research uses molecular genetics to identify and characterize genes important in vision loss. The goal of her lab is to identify novel genes associated with retinal disease, determine the gene networks that regulate retinal stem cells, and identify modifier genes that can prevent retinal degeneration and restore vision in degenerating retinas. The goal of this project is to evaluate the efficacy of molecular and genetic modifiers in a degenerating retina. Her studies will greatly enhance understanding of genetic factors that influence severity of retinal disease, and provide potentially powerful targets for improved therapies to treat or prevent multiple forms of retinal disease.

Yuk Fai Leung, Ph.D.

Dept of Biological Sciences, Purdue University

Project: Research in gene regulatory networks in retina and RPE

There have been many research studies that have identified the underlying genetic causes of retinal degenerative diseases. However, without a fundamental understanding of the development of retina and retinal pigment epithelium (RPE), it would be difficult to elucidate the developmental mechanisms that are altered by these genes, not to mention designing effective treatments. Dr. Leung and his team are studying a novel *irx7* (gene) regulatory network and its function in retinal development of zebra fish. Dr. Leung's work will (1) elucidate the extent to which *irx7* is regulating cellular differentiation in retina, and (2) clarify a framework of the *irx7* regulatory network. This will greatly facilitate the investigation of molecular controls of normal zebra fish retinal development, which will in turn establish a strong scientific foundation for studying disease genes that cause retinal degeneration, and ultimately assist the design of better treatments for retinal degeneration.

Kristina Narfstom, D.V.M.

Dept of Veterinary Medicine, University of Missouri

Project: Research in large animal models of retinal degeneration with an emphasis on proof-of-concept

Summary: Dr. Narfstom is investigating the implantation of light-sensing microchips in the retinas of animal models. The chips contain thousands of miniature solar cells that turn light into electrical current and early studies show that they may have even further benefits for people with RP in that they seem to actually slow progression of the disease. In addition, Dr. Narfstom hopes to use gene replacement therapy to restore sight in the same animal model. Success with animal models would pave the way for using this approach in people with RP. Narfstom already has had success using gene therapy to restore sight to French sheepdogs that suffer from another inherited retinal disorder. The dogs, called Briards, are born with night blindness and poor daylight vision that get progressively worse with age.

David Pepperberg, PhD

University of Illinois at Chicago

Project: Exploring the use of nanotechnology to restore vision to damaged retinal cells.

Photoreceptor degenerative diseases such as age-related macular degeneration (AMD) destroy the ability of rod and cone photoreceptors to respond to light and to transmit visual signals to “post-photoreceptor” nerve cells in the inner layers of the retina. However, the post-photoreceptor nerve cells themselves often appear to remain healthy in the diseased retina. As a possible therapy for AMD and related retinal diseases, Dr. Pepperberg and his colleagues are working to develop implantable, nanoscale molecular structures that can directly stimulate the post-photoreceptor nerve cells in response to light, and thus bypass the non-functioning photoreceptors. The immediate focus of their research is to develop prototypes of the desired molecular device, and to test the activities of these prototypes in two kinds of biological systems: (1) single, isolated cells that have been engineered to express a given type of postsynaptic receptor protein; and (2) retinal tissue obtained from animal models. We anticipate that this research will identify structures ultimately suitable for testing in human subjects.

Vladlen Slepak, Ph.D.

Bascom Palmer Eye Institute, University of Miami

Project: The role of light-dependent movement of transducin in retinal rods.

Summary: Bright light damages photoreceptor cells because the eye focuses reflected sunlight on the retina. It is also known that light can exacerbate retinal degeneration. The exact molecular mechanisms that protect photoreceptor cells and the reasons these protective mechanisms malfunction in disease are not completely understood. Several years ago scientists discovered that a crucial protein responsible for light reception, transducin, which in darkness localizes to the rod outer segments, and then re-localizes across the cell in bright light. Dr. Slepak’s research will uncover new information about photoreceptor cell biology that will allow us to understand how rod cells protect themselves from damaging levels of light. Specifically, this project will test the current hypothesis that the translocation of transducin to the inner compartments of rod cells has a cytoprotective function. Potentially, this research will identify novel proteins that influence cell survival, which can be targeted pharmacologically or through gene therapy.

Alexander Sumaroka, Ph.D.

Scheie Eye Institute, Univ of Pennsylvania

Project: Retinal Mapping For Targeting Treatment in Retinitis Pigmentosa

Summary: Inherited retinal degenerations in the family of diseases known as retinitis pigmentosa will be studied with optical coherence tomography, mainly to inquire about the integrity of the photoreceptor layer. Structural abnormalities of the inner retina, suggesting the process of retinal remodeling, will also be defined. The present work will use state-of-the-art high-resolution instrumentation. Mapping of the photoreceptor layer has already been used in the University of Pennsylvania gene therapy clinical trial to target appropriate retinal regions for treatment and this approach has proven valuable.

Veena Theendakara, Ph.D.

Jules Stein Eye Institute, UCLA

Project: To perform research into novel cone photoreceptor gene and mechanisms of ZBED4, a novel protein with mutations causing cone-rod dystrophy

Summary: Dr. Theendakara and her colleagues have recently identified ZBED4, a novel protein present in the nucleus and cytoplasm of cone photoreceptors. In addition, they found a mutation in the *ZBED4* gene associated with disease in patients with cone-rod dystrophy. The objectives of their work are to investigate the movement of the ZBED4 protein between the nucleus and cytoplasm of cone photoreceptor cells; and to screen patients for mutations in the *ZBED4* gene and establish genotype-phenotype correlations for early detection of disease and future intervention.