

Research Summaries for Faculty Trainers

Drew Adams, Ph.D., Genetics

The Adams lab uses chemical biology approaches to address problems at the interface of chemistry, biology, and medicine. A special emphasis is on the use of high-throughput screening to identify new small-molecule probes targeting proteins involved in disease, including diseases of the eye. An initial protein target for small-molecule inhibitor development is glutaredoxin 1, which has been characterized by Prof. John J. Mieyal of the CWRU School of Medicine Department of Pharmacology to promote diabetic retinopathy through its regulation of NFκB signaling.

Matthias Buck, Ph.D., Physiology & Biophysics

Dr. Buck's research program characterizes the structures and the dynamics of proteins involved in protein-protein interactions with a concentration on the plexin and the Eph-A1 and Eph-B1 transmembrane receptors. Protein interactions determine the basic mechanisms by which proteins transmit signals in cells and how signaling is disrupted by mutation in diseased states. Knowing at near-atomic resolution which residues interact in protein complex formation will allow them to rationalize their interaction affinity and specificity. Furthermore, it will provide an opportunity for them to alter the proteins for diagnostic or therapeutic purposes. Recently we have become interested in the role of Neuropilin and its co-receptors (incl. plexins) in the visual system, specifically in angiogenesis in the retina. An R21 was awarded for pilot work from the Eye Institute (2014-15).

William Bush, Ph.D., Epidemiology & Biostatistics

My research program applies statistical and bioinformatics approaches toward the analysis of genomic data for age-related macular degeneration (AMD). Specifically, we have developed an approach for looking at cumulative genetic effects and genetic interactions among disease pathways relevant to AMD.

Sudha Chakrapani, Ph.D., Physiology & Biophysics

My research focus over the last 15 years has been to understand the structure and function of ion channels, particularly the members of voltage- and ligand-gated channel family that are critical for the function of retinal ganglion cells and rod photoreceptors. I have expertise in membrane protein expression and purification, site-directed labeling and spectroscopy (electron paramagnetic resonance and fluorescence), X-ray crystallography, single-channel and macroscopic current measurements in reconstituted liposomes and heterologous expression systems. My research interests and expertise align well with the goals of this training program.

John Crabb, Ph.D., CWRU Chemistry, CCF Ophthalmic Research, Cole Eye Institute

Proteomic biomarker discovery for ocular diseases is a major focus of our laboratory. Age-related macular degeneration (AMD) is a leading cause of blindness worldwide. Complex genetic and environmental factors contribute to the disease and presently there are no cures. The prevalence of advanced AMD is increasing and early identification of AMD risk could help slow or prevent disease progression. Recently our AMD biomarker study of plasma protein advanced glycation endproducts (AGEs) has shown the adducts to discriminate between AMD and control subjects with accuracy $\geq 80\%$. Other projects in the laboratory using proteomic technology include mechanistic studies of AMD, primary open angle glaucoma, diabetic retinopathy, uveal melanoma and the visual cycle.

Evan Deneris, Ph.D., Neurosciences

My primary research is focused on the gene regulatory networks that control the development and maintenance of brain serotonin neurons. As a trainer in the Visual Science Training Program, my expertise is applicable to studies of dysfunctional neuronal transmission associated with disorders of the eye.

George Dubyak, Ph.D., Physiology & Biophysics

The Dubyak lab studies innate immune signaling pathways in different models of tissue infection or injury. A current emphasis is on how caspase-1 inflammasome signaling platforms are regulated to mediate production of inflammatory cytokines and pyroptotic cell death. Our recent studies have characterized roles for these signaling pathways during corneal infection by bacteria and in diabetic retinopathy.

David Friel, Ph.D., Neurosciences

My areas of expertise are: electrophysiology, calcium signaling, P/Q Ca²⁺ channelopathies, and mathematical modeling. Dysfunction of the P/Q-type voltage dependent calcium channels is associated with ocular motor abnormalities; e.g., involuntary eye movements (nystagmus).

Marcin Golczak, Ph.D., Pharmacology

My lab focuses on the role of Vitamin A in blinding eye diseases, focused on the elucidation of biochemical principles governing vitamin A metabolism in the eye. Our work has contributed substantially to understanding the mechanistic principles of RPE65-dependent 11-*cis*-retinal regeneration with special emphasis on the function of lecithin:retinol acyltransferase (LRAT). Applying organic chemistry, protein biochemistry, cell biology, and analytical techniques we have developed and tested novel pharmacological strategies for the treatment of progressive retinal diseases.

Beata Jastrzebska, Ph.D., Pharmacology

The focus of my research is to address the functional implications of rhodopsin dimerization and its role in signal propagation and termination by studying complexes of rhodopsin with its partner proteins.

Jonathan Haines, Epidemiology & Biostatistics

My lab has developed and applied computational methods to big data with a focus on data reduction and integration of different data types. These methods involve the use of genomic and computational approaches to understand the pathophysiology of human disease, including disorders of the eye which is the focus of the Visual Sciences Training Program.

Yoshikazu Imanishi, Ph.D., Pharmacology

My research program has been focused on the process of photoreceptor membrane morphogenesis and organization of the rhodopsin-mediated signaling cascade. The research is relevant to the pathogenic mechanisms of blinding disorders.

Sudha Iyengar, Ph.D., Epidemiology & Biostatistics

Dr. Iyengar's interests lie in sequencing, mapping and analyzing a wide range of research (patient) samples with a focus on genomic technology. These technologies are creating large volumes of data, quickly adding up from terabytes to petabytes and more. Analyses are performed with high density genome-wide linkage, genome-wide association, and next-generation sequencing type data, including workflows and quality control for Exome Sequencing, RNA-Seq and ChIP Seq. Her laboratory has trained pre- and post-doctoral students on the genetics/genomics of many ocular disorders.

Timothy Kern, Ph.D., Medicine and Pharmacology, VSTP co-Director

The major focus of research in the Kern laboratory is to learn what causes retinopathy in diabetes, and how it can be prevented. Diabetic retinopathy takes many years to develop in most patients, so studies using research animals have been fundamental to present understanding of this problem. The retinal lesions that develop in streptozotocin-diabetic animals are indistinguishable from those that develop in patients, and include microaneurysms, obliterated capillaries, pericyte loss and hemorrhage. The Kern group has also developed a second model of diabetic retinopathy in which blood hexose levels are elevated in nondiabetic

animals by feed-ing the sugar, galactose. These animals develop a retinopathy identical to that which develops in diabetes, in-dicating that elevated blood hexose is a major cause of diabetic retinopathy. Efforts currently are directed at identifying how hyperglycemia causes retinopathy, so that new, improved treatment may be devised to inhibit the loss of vision in diabetes.

Ahmad Khalil, Genetics:

My laboratory studies the role of long intergenic non-coding RNAs (lincRNAs) in human health and disease. We previously, in collaboration with Dr. Kris Palczewski identified evolutionary conserved lincRNAs in the eye. We will continue to collaborate with Dr. Palczewski to understand the functional roles of these lincRNAs in eye development and eye related disorders.

Philip Kiser, Ph.D., Pharmacology

Our research focuses on the structure and function of enzymes that carry out renewal of 11-cis-retinal for use by rod and cone photoreceptor visual pigments, a process essential for human vision. We are especially interested in the enzymology of the retinoid isomerase of this pathway, RPE65, as well as its relatives involved in carotenoid processing, the carotenoid cleavage oxygenases. X-ray crystallography, enzyme kinetics, and various spectroscopic methods are the primary methods we use to study these enzymes.

Jonathan Lass, M.D., Ophthalmology & Visual Sciences

Dr. Lass is the Charles I Thomas Professor in the Department of Ophthalmology and Visual Sciences at CWRU. He is a member of the Center for Anterior Segment Diseases and Surgery at University Hospitals Eye Institute, and Medical Director of the Cleveland Eye Bank, and Medical Director of the Case/UH Cornea Image Analysis Reading Center. His clinical research program is recognized as an international leader in the field of ophthalmology and the diseases and transplantation of the cornea.

Danny Licatalosi, RNA Center

The major focus of my lab is the study of tissue-specific RNA binding proteins and post transcriptional control of gene expression. Most of our recent work has been on post transcriptional regulation in mouse germ cell development and in the embryonic brain. My interests also include collaborating with other investigators interested in investigating how post-transcriptional events are regulated during eye development, particularly since multiple studies have indicated essential roles for specific RNA-binding proteins in the ocular system.

David Lodowski, Ph.D., Proteomics

The Lodowski laboratory takes an integrative approach to understanding the molecular dynamics of proteins within the visual signaling system, combining X-ray crystallography, mass spectrometry and *in vivo* studies. A translational extension of our studies combines principles of structure based drug design inspired by natural products to rationally develop inhibitors suitable for the treatment of diabetic retinopathy.

Zheng-Rong Lu, Ph.D., Biomedical Engineering

Our laboratory focuses on molecular imaging and drug delivery using novel nanotechnology. We are interested in using biodegradable materials and organic nanomaterials to design and develop targeted, safe and effective imaging agents and drug delivery systems for diagnostic imaging, treatment of human diseases and image-guided therapy. Our ongoing research projects include biodegradable macromolecular MRI contrast agents and targeted nanoglobules. We are poised to interact with other investigators associated with the Visual Sciences Training Program to pursue advanced diagnosis and treatment of ocular disorders.

Akiko Maeda, M.D, Ph.D., Ophthalmology & Visual Sciences

Dr. Maeda's research focuses on understanding the inflammatory elements, including Toll-like receptors and chemokine receptors, which contribute to retinal degenerative diseases. In

addition, she has generated mice with mutations in visual cycle enzymes, resulting in delayed clearance of all-trans-retinal from the retina; and these mice develop cone-rod dystrophy.

Danny Manor, Ph.D., Nutrition

A number of projects in the Manor lab directly relate to the mission of the Visual Sciences Training Program. In particular, we are studying the molecular mechanisms and pathological outcomes of heritable defects in regulators of vitamin E status. Specifically, we are studying the outcomes of mutations in the tocopherol transfer protein (TTP), manifesting in CNS deficits especially in the cerebellum and the retina. Using genetic mouse models we are studying how alpha-tocopherol protects these tissues from functional deficits presented by affected humans, namely cerebellar ataxia and retinitis pigmentosa.

Jason Mears, Ph.D., Pharmacology

Within eukaryotic cells, mitochondria continually divide and fuse. Defects in these processes are associated with an increasing number of human diseases, including cancer, neurodegeneration and aging. Research in the Mears lab is focused on understanding of the cellular machinery that regulates mitochondrial dynamics in yeast and mammalian cells. Cryo-electron microscopy along with biochemical and computational methods are used to elucidate the structural and mechanistic roles of proteins in the eukaryotic fission machinery. Mitochondrial dysfunction has recently been associated with age related retinal disease including macular degeneration and glaucoma. Therefore, understanding how changes in mitochondrial dynamics contribute to these diseases is an important priority.

Vincent Monnier, Ph.D., Pathology

My lab is currently involved in research to decipher the role of the Maillard reaction *in vivo* on the destabilization of lens crystallins in the aging lens and the formation of age-related nuclear cataracts. In addition we are characterizing the basis for selective uptake of glutathione into the lens and how this process changes with aging, likely serving as a contributing factor to cataract formation.

Tingwei Mu, Physiology & Biophysics

My research focuses on studying the protein biogenesis and function of GABA(C) receptors. They are highly expressed in the retina. A study of mice in which these receptors are knocked out demonstrated that elimination of the GABA(C) receptors led to abnormal visual processing in the retina and resulted in changes in vascular permeability similar to the symptoms of retinal hypoxic conditions. Our research aims to gain insights into the process of GABA(C) receptor maturation, and the mechanisms by which the function of these receptors are regulated.

Marvin Nieman, Ph.D., Pharmacology

Circulating and membrane bound proteases from diverse cell types control vascular integrity and contribute to angiogenesis by initiating signaling pathways through Protease Activated Receptors (PARs), which belong to the family of 7-transmembrane domain G protein-coupled receptors (GPCRs). The PARs are also involved in tissue degeneration and repair upon injury. Expression of all four PAR subtypes has been observed in the postnatal eye and in retina of the adult rat. The Nieman laboratory focuses on the structure and function of PARs with a special emphasis on the physical interactions that regulate their activation and signaling specificity.

Krzysztof Palczewski, Ph.D., Chair of Pharmacology, VSTP Director

An internationally acclaimed leader in vertebrate vision research, Dr. Palczewski has led his team to multiple seminal contributions, including solving the structure of the light sensitive G protein-coupled receptor, rhodopsin; discovering and characterizing the role of new elements such as miRNA, non-coding RNA, and massive parallel RNA sequencing of transcripts in the eye; characterizing critical visual cycle proteins; contributing novel imaging and functional

assays of the retina; identifying blinding genetic mutations; and devising pharmacological therapies for treatment of retinal dysfunction/disease.

Paul Park, Ph.D., Ophthalmology & Visual Sciences

Current research in the Park lab focuses on the biology of the retina and structure-function studies of rhodopsin and other G protein-coupled receptors (GPCRs) using cutting-edge biochemical, biophysical and genetic technologies. Structure-function studies of rhodopsin are designed to better understand photoreceptor biology and retinal degeneration.

Brian Perkins, Ph.D., Cole Eye Institute, CCF

Current research in the Perkins lab is designed to learn how the basal body localizes and is maintained at the correct position on the apical surface of photoreceptors. To achieve this goal, we use zebrafish to test the *in vivo* mechanisms that position basal bodies, including the role of cytoplasmic dynein motors, the Planar Cell Polarity (PCP) pathway, and the interactions between PCP signaling and the Joubert Syndrome protein Arl13b. With more than 10 years of experience using zebrafish as a model system for retinal degeneration, Dr. Perkins is a valued member of the training faculty.

Irina Pikuleva, Ph.D., Ophthalmology & Visual Sciences

The research program of the Pikuleva lab is focused on the role of cholesterol in retinal structure and function. Cholesterol maintenance in the retina is important to delineate because of the link between retinal cholesterol and age-related macular degeneration, a common blinding disease. We identified the major enzymes eliminating cholesterol from the retina (CYP27A1 and CYP46A1) and the major homeostatic mechanisms controlling cholesterol levels in this organ. We established that CYP27A1 and CYP46A1 deficiency leads to significant accumulations of retinal cholesterol and a wide variety of vascular retinal abnormalities, thus linking cholesterol metabolism to the status of retinal vasculature. We are now moving to studies of cholesterol transport and storage in the retina and pharmacologic modulation of retinal pathways that control retinal cholesterol.

Douglas Rhee, M.D., Chair, Ophthalmology & Visual Sciences

Dr. Rhee a clinician-scientist whose laboratory investigates the mechanisms of extracellular matrix synthesis and turnover in the trabecular meshwork, and their relationship to intraocular pressure. Clinically, Dr. Rhee specializes in rare syndromes and the surgical management of high risk or complex patients, and he has incorporated innovative strategies, techniques, and devices for both glaucoma and cataract surgery.

Arne Rietsch, Ph.D., Molecular Biology & Microbiology

The Rietsch laboratory studies how the bacterial pathogen *Pseudomonas aeruginosa* causes disease. In particular, we are focusing on the type III secretion system that allows *P. aeruginosa* to deliver protein toxins directly into the cytoplasm of targeted host cells. Secretion is triggered by cell contact, often referred to as contact-dependent secretion. The pathogenesis of *P. aeruginosa* is especially important to understand in the context of keratitis, inflammation of the cornea.

Andrew Rollins, Ph.D., Biomedical Engineering

Dr. Rollins' research interests are in the development and application of advanced biomedical optical technologies, especially optical coherence tomography (OCT), and including optical stimulation and imaging of electrophysiology. OCT is especially useful in diagnosing many retinal conditions and disorders of the optic nerve, as well as monitoring response to therapeutic interventions.

Phoebe Stewart, Ph.D., Pharmacology; Director, CCMSB

Our laboratory is pursuing cryo-electron microscopy and crystallography projects to understand the molecular mechanisms underlying visual phototransduction. Specific projects include visualizing the rhodopsin/transducin complex and the phosphodiesterase-6 (PDE6)/transducin alpha-subunit complex. Additional projects involve cryo-electron tomography of murine rod outer segments to compare wild-type morphology with that found in mouse models of human visual disorders.

Carlos Subauste, Ph.D., Medicine; Ophthalmology & Visual Sciences

We pursue two areas of research in our laboratory. We study how genetic and pharmacologic manipulation of molecules that regulate autophagy enhances protection against ocular toxoplasmosis. We also examine the role of CD40-TRAF signaling in the development of diabetic and ischemic retinopathies. We study whether inhibitors of CD40 signaling have beneficial effects in these diseases.

Loretta Szczotka-Flynn, M.D., Ophthalmology; Epidemiology & Biostatistics

With over 25 years experience in the treatment and research of keratoconus, Dr. Szczotka-Flynn's longstanding interest in keratoconus and corneal topography has led to numerous studies and publications. She has vast experience in successful recruitment of many subjects in single and multi-centered trials, and she directs the Coordinating Center for the Cornea Preservation Time Study which recently completed enrollment of 1330 eyes for endothelial keratoplasty across 40 sites in the US. Dr. Szczotka-Flynn can facilitate interactions of clinical fellows with basic scientists for the transitional vision research. For example Drs. Pikuleva and Maeda have projects that require clinical samples and interactions with patients.

Johannes von Lintig, Ph.D., Professor, Pharmacology

The von Lintig laboratory has a long standing experience in studying carotenoid and retinoid metabolism related to vision. We were among the first who molecularly identified genes encoding key components of this pathway such as the vitamin A forming enzyme as well as membrane channels for carotenoids and retinoids. Mutations in these genes can cause a broad spectrum of blinding disease. We have generated small animal models to clarify the etiology of these diseases and to establish treatments for their cure. The continuation of these projects presents a challenge with high relevance for clinical applications.

Horst von Recum, Ph.D., Biomedical Engineering

Research in the von Recum lab is directed at engineering mechanisms for the delivery of small molecule drugs, proteins, and DNA in the treatment of ocular disorders. Therapeutics are targeted against infection, inflammation, cell proliferation, and retinoid metabolism disorders.

Daniel Wesson, Ph.D., Neurosciences

My research explores the central processing of sensory information among ensembles of neurons in animals engaged in sensory tasks. As such, my laboratory possesses expertise in theoretical principles of sensory information processing (in both health and disease) as well as expertise in methods for developing psychophysical operant behavioral assays for use in rodents, large scale neural recordings from both single neurons and neural networks, and analysis of multivariate physiological and behavioral data captured from animals. These approaches are applicable to studies of ocular disorders in collaboration with other investigators associated with the Visual Sciences Training Program.

Steven E. Wilson, M.D., Ophthalmology, Cole Eye Institute

My research focuses on stromal-epithelial-bone marrow-derived cell interactions in the cornea and especially cytokine-mediated processes in corneal wound healing and disease. A major area of investigation has become epithelial basement membrane regeneration and its role in myofibroblast generation associated with corneal scarring in wound healing, infection and disease.

Anthony Wynshaw-Boris, M.D., Ph.D., Professor and Chair, Genetics

Research in the Wynshaw-Boris laboratory is focused on understanding genetic and biochemical pathways important for the development and function of the mammalian central nervous system, primarily using mouse models of human and mammalian diseases to define pathways disrupted in these diseases, including ocular disorders. There are currently three main projects in the laboratory: the study of mouse mutants for each of three Dishevelled genes; the genetics of autism, with particular emphasis on pathways responsible for brain overgrowth; and the study of *in vivo* mouse models and human cellular models of human neuronal migration defects such as Baraitser–Winter syndrome (BRWS), a well-defined disorder characterized by distinct craniofacial features, ocular colobomata and neuronal migration defect.

Alex Yuan, M.D., Ph.D., CCF Ophthalmology

The Yuan lab studies retinal degeneration and scar formation. Using the Zebrafish model, recent studies have focused on *in vivo* imaging of retinal vasculature using confocal laser ophthalmoscopy; in addition, optical coherence tomography (OCT)-guided laser injury was used to study retinal regeneration.

Richard Zigmond, Ph.D., Professor, Neurosciences

The Zigmond laboratory focuses on neuronal plasticity in the superior cervical ganglion, the sympathetic ganglion that innervates structures in the eye, including the iris. We are interested in how neurons in this ganglion respond to axonal injury and what cells and molecules foster the ability of these neurons to regenerate, re-innervate their targets, and restore normal function.