NEI (T-35) Summer Research Fellowship
Mentors and Their Areas of Research

Jose-Manuel Alonso, Ph.D.	Functional Circuitry of the Thalamus and Cortex
Alexandra Benavente-Perez, Ph.D.	Myopia and Ocular Vascular Function
Stewart Bloomfield, Ph.D.	Functional Roles of Gap Junctions in Retinal Physiology and Pathology
Mitchell Dul, O.D., M.S.	Perimetry/Visual Fields/Psychophysics/Glaucoma
Robert McPeek, Ph.D.	Neural Mechanisms Underlying Attention and Visually-Guided Actions
Tracy Ngyuyen, O.D., Ph.D.	Molecular Mechanisms Involved in the Pathogenesis of Various Ocular Surface Disorders
Mark Rosenfield, B.Sc. (Optom), Ph.D.	Computer Vision by Syndrome
Miduturu Srinivas, Ph.D.	Gating and Pharmacology Lens Gap Junction Channels
David Troilo, Ph.D.	Visual Development, Accommodation, Refractive Error, Myopia
Suresh Viswanathan, O.D., Ph.D.	Retinal Ganglion Cell Function, Glaucoma, Traumatic Brain Injury
Stefanie Wohl, Ph.D.	The Role of MicroRNAs in Retinal Glia Function
Qasim Zaidi, Ph.D.	Color Perception, Three-Dimensional Shape Perception
Xiaoying Zhu, O.D., M.D., Ph.D., M.S.	Emmetropization, Visual development and Myopia

Brief Descriptions of Mentor Research Programs

Jose-Manuel Alonso, Ph.D.

My laboratory is interested in understanding how the brain processes visual information. We pursue this general goal by investigating how neurons connect to each other and the role of these connections in constructing precise representations of the visual world in the brain. Most of our work focuses on two main structures early in the visual pathway: the thalamus and the primary visual cortex. These two structures have the most detailed representation of visual space in the brain and constitute the entrance of visual information to the cerebral cortex.

Disruption of the circuits from thalamus and primary visual cortex leads to cortical blindness: a lack of vision that cannot be treated by restoring eye function. Disruption of thalamic and cortical circuits can result as a consequence of eye disease, neurodegenerative disorders and brain insults. In my laboratory, we investigate the neuronal circuits of thalamus and visual cortex by using state-of-the-art technology that includes multielectrode/imaging recording from neuronal populations and computational modeling. Specific approaches are: a) study visual responses from multiple neurons under different stimulus conditions; b) identify neurons that are directly connected and study the response properties at the two poles of the connection; c) measure synchronous firing generated by different types of neurons and investigate its role in visual processing; d) study the role of populations of neurons in encoding visual information; e) study the role of alertness, visual attention and task difficulty in modulating neuronal responses; f) study changes in thalamo-cortical circuits that result from the local inactivation (or stimulation) of small groups of neurons.

Our laboratory is proud to collaborate with other outstanding research teams within and outside SUNY Optometry. Two of our most productive, current collaborations are with Prof. Swadlow at the University of Connecticut and Qasim Zaidi at SUNY Optometry. A better understanding of how neural circuits process visual information is essential to develop new strategies for the treatment and prevention of visual disorders. The long-term goal of our laboratory is to generate breakthroughs that make these new treatment and prevention approaches possible.

Alexandra Benavente, Ph.D.

From experimental studies, we know that eyes use visual information to adjust their growth and how they are focused. My two of my main research lines focus on studying this visual control of eye growth, in particular the role that the peripheral retina and eye shape might have as predictors of future changes in refraction; and understanding the development of pathological retinal changes in myopia. Our lab has found that the timing and duration of imposed defocus across the retina is important for affecting eye growth and refractive development. Brief daily interruption periods to negative defocus in emmetropic eyes prevent compensatory myopic growth, but once the eye starts to compensate, the same brief interruptions are not enough to slow the myopia progression. In addition, interactions between the refractive asymmetry of the peripheral retina and the visual defocus experienced may be associated with axial growth changes suggesting that peripheral refraction is a factor in the progression of myopia, and offer a means to control it. Another of my research interests is to understand the interaction between eye size and vascular physiology. The structural characteristics of a myopic eye include an elongated vitreous chamber, which in high myopia is related to a stretched and progressively thinned choroid and sclera. This increases the risk of choroidal and retinal changes, and a variety of other ocular diseases including macular degeneration, choroiditis and glaucoma among others. Because

of the known vascular features of many of these conditions associated with pathological myopia, my research also focuses on describing the vascular changes that a non-pathological myopic eye undergoes prior to the development of posterior pole pathologies. This is of significant clinical importance, as degenerative myopia is a leading cause of blindness. Our clinical work has described compromised ocular hemodynamics and thinner choroids in moderate myopic eyes with no degeneration, later confirmed by others. Also in low and moderate human myopes, but not in high myopes, the ocular perfusion pressure is higher when the choroid is thinner. In experimental myopia, the ocular perfusion pressure remains stable within the first six months of life, but it increases as myopia develops. I hypothesize that these early vascular anatomical and functional changes in both experimental animal and human eyes may be early indicators of the development of irreversible posterior pole complications associated with myopia progression.

Stewart Bloomfield, Ph.D.

Historically, the work in our laboratory has been directed at understanding the cellular mechanisms of information processing and cell-to-cell communication in the mammalian retina. The retina is an exquisite model system to study signal processing in the CNS, owing to its relative simplicity of organization, accessibility, and the ability to be maintained in an in vitro environment while still remaining responsive to natural light stimulation. We use a wide range of techniques in the lab, including patch clamp and multi-electrode array recordings, confocal and multi-photon microscopy, channel rhodopsin expression, histological and morphological staining paradigms as applied to transgenic and knockout mouse models. Most recently, my lab has focused on the role of gap junctions and electrical synaptic transmission in the retina. The wide distribution and diverse connexin subunit makeup of gap junctions in the retina is unique in the CNS and, as a result, it has become arguably the best model system for the study of electrical neurotransmission in the brain. We have shown the electrical transmission via gap junctions plays a multitude of roles in image processing, including contrast sensitivity, neural adaptation, synchronization of ganglion cell activity, and direction selectivity critical to the optokinetic response. Further, we have shown that gap junction coupling between neurons is highly plastic and light dependent. For example, we recently reported that during daylight the electrical coupling between ganglion cells is increased, thereby altering their Activity so that additional visual information can be passed across the limited bandwidth of the optic nerve. In the past few years, we have translated our basic research in a more clinical direction. Neuronal loss through cell death is a hallmark of many pathological conditions in the nervous system, including Alzheimer's and Huntington's disease in the brain and diabetic neuropathy, ischemic retinopathy, retinitis pigmentosa (RP) and glaucoma in the retina. The major pathways underlying cell death have been well characterized and they include a number of molecularly regulated cascades. In addition, converging evidence indicates that intercellular communication through gap junctions underlies secondary or bystander neuronal death in a variety of neurodegenerative diseases. In this scheme, gap junctions form conduits by which toxic metabolites are transferred from a dying cell to its neighbors leading to their death. Interestingly, our data indicate that gap junction-mediated secondary cell
death is responsible for ~75% of the total loss of ganglion and amacrine cells in the retina under ischemic and excitotoxic conditions. Our results also suggest that the cohort of gap junctions, based on the connexins they express, play differential roles in secondary cell death dependent on the type of initial insult. Taken together, these data support the novel hypothesis that gap junction-mediated secondary cell death is responsible for most of the cell loss in the retina associated with a variety of primary insults. The long-term goal of this new phase of our research is to elucidate novel therapeutic

strategies for targeting specific gap junctions to limit the cell loss associated with a number of retinal neurodegenerative diseases.

Mitchell Dul, O.D.

The functional assessment of patients with glaucoma is typically conducted with conventional (white on white) perimetric analysis. A significant drawback to this form of testing is the high degree of variability of results from one test to another. As a consequence, it is difficult to differentiate stability or progression of the disease from normal variability without several sets of data, aggregated over several years. The primary purpose of my research program is to apply a quantitative cortical pooling model to the analysis of perimetric damage produced by glaucoma, with the goals of reducing perimetric variability and improving relations between clinical measures of glaucomatous damage. We have been using a customized form of contrast sensitivity perimetry (CSP), with a low spatial frequency stimulus which we have shown to reduce the effects of prereceptoral factors such as refractive error, pupil size, and increased density of the human crystaline lens associated with age. We have also demonstrated that this stimulus in its present form, produces less variable results in areas of decreased sensitivity. We have continued to work to optimize contrast sensitivity perimetry (CSP) for clinical use in patients with glaucoma-specifically to detect pattern and diffuse loss that have clinical significance; to quantitatively compare this form of perimetry to conventional and other non-conventional assessment tools under various clinical conditions; to reduce test-retest variability; and to maintain or enhance sensitivity to change associated with glaucoma. Two research rooms approximately 300 sq. feet.

Robert McPeek, Ph.D.

Visual scenes are often crowded with many different objects. As a result, goal-directed actions require the selection of a single target from a field of many possible targets. A similar selection process is thought to underlie our ability to covertly shift visual attention to a target object of interest while ignoring distracting objects. The long-term goal of my research is to elucidate the neural mechanisms underlying this target selection process, both for covert visual attention and for visually-guided actions, including eye movements and reaching movements. To pursue this goal, my laboratory uses a range of techniques: we perform psychophysical studies in both humans and monkeys, we investigate the neural correlates of visual selection using multi-electrode recordings of neuronal spiking activity and local field potentials, and we test causal relationships between activity and behavior using pharmacological and electrical manipulations of neural activity in monkeys. We have found that the primate superior colliculus (SC), a midbrain structure, plays an important role not only in the execution of saccadic eye movements, but also in the higher-level process of eye-movement target selection. Moreover, our experiments have revealed that perturbing SC activity causes striking target selection deficits for reaching movements as well as eye movements. These results demonstrate that the SC is part of an abstract, effector-independent “priority map” that governs target selection for a variety of actions. In addition to the SC, target selection is also subserved by a network of other cortical and subcortical brain areas, but we still have little idea of how activity across these different areas is coordinated. Current work investigates the functional interactions between two key areas involved in target selection: the SC and the frontal eye field (FEF), a cortical region that communicates bidirectionally with the SC. The results of these studies will not only provide new information about the functional architecture of the target selection system; they will also lead toward a better understanding

of how cortical and subcortical brain areas interact in performance of a cognitive task. Facilities include two independent awake-behaving monkey neurophysiology labs of approx. 300 sq. feet each, a separate lab of approx. 300 sq. feet for studying human psychophysics and motor behavior, and sufficient office space for the principal investigator, students, and post-doctoral fellows.

Tracy Nguyen, O.D., Ph.D.

The aim in my lab is to understand the molecular mechanisms involved in the pathogenesis of various ocular surface disorders with the goal of developing therapeutic treatments. We are currently focusing on the molecular protein markers for dry eye disease. Dry eye develops as a result of alteration in the quantity and/or quality of tear fluid which can lead to tear instability, osmotic stress and disruption in the corneal epithelium barrier function. It is often associated with ocular surface inflammation. We are currently investigating the role of extracellular matrix metalloproteinase inducer (EMMPRIN, also termed CD147) in the pathogenesis of dry eye disease. EMMPRIN is a highly glycosylated protein that is a member of the immunoglobulin superfamily and is involved in various physiological an pathophysiological processes. It plays a role in tumor development, inflammation and pH homeostasis. We hypothesize that the soluble form of EMMPRIN can be found in tear fluid and that it plays a major role in the inflammatory process of dry eye disease. We will use molecular techniques such as western blotting, immunofluorescence staining, microwell based protein array and protein chain reaction to test our hypothesis. Laboratory space is approximately 400 sq. feet. Two other shared facilities (both approximately 325 sq. feet) house equipments needed for the experiments.

Mark Rosenfield, B.Sc. (Optom), Ph.D.

The use of computers and digital electronic devices for both vocational and non-vocational activities including e-mail, internet access and entertainment is almost universal in modern society. Today's visual requirements may include viewing laptop and tablet computers, electronic book readers, smartphones and other electronic devices both in the workplace, at home or in the case of portable equipment, in any location. Some screen sizes may necessitate very small text which the observer frequently positions at a closer viewing distance than had previously been adopted for hard copy printed materials. These increased visual demands may give rise to a variety of symptoms which have been termed computer vision syndrome (CVS). Up to 90% of computer users experience visual symptoms including eyestrain, headaches, ocular discomfort, dry eye, diplopia and blurred vision either at near or when looking into the distance after prolonged computer use. Research in our laboratory is evaluating both the causes and potential treatments for this highly prevalent condition. An inability to satisfy the visual requirements will present significant lifestyle difficulties for patients.

Miduturu Srinivas, Ph.D.

The multi-gene family of proteins called connexins form intercellular gap junctions that directly mediate signaling between adjacent cells. These cell–cell channels consist of two hemichannels or connexons from adjacent cells. In addition to forming gap junctions, some members of the connexin family can also function as transmembrane ion channels in the undocked state. Both cell-cell channels and hemichannels formed by connexins play a wide variety of roles in a number of different cell types and tissues, including the eye, and mutations in human connexins underlie a variety of disorders, including deafness, skin disease, demyelinating neuropathies, and cataracts. One major goal of our

laboratory is to determine the physiological roles of connexin channels in the eye, specifically the lens. Using electrophysiological recordings and cellular/molecular techniques, our studies with Dr. Thomas White at SUNY Stony Brook indicate that factors that influence lens growth and transparency (e.g. growth factors and oxidative stress, respectively) have potent effects on connexin channel function. The potential ramifications for lens function and the mechanism by which they affect coupling is currently being pursued. A second major goal is to identify highly specific and selective inhibitors for connexin channels. Such inhibitors are likely to be useful for unraveling the physiological role of connexins and provide new and promising pharmacological targets in the treatment of several pathologies including epilepsy, cardiac arrhythmia and essential tremor. In collaboration with Dr. Heike Wulff at UC Davis, whose laboratory specializes in the design of small molecule ion channel modulators, we identified four new small molecule chemotypes that inhibit connexin channels in the low micromolar range. Structure-activity studies of these compounds are a current focus of interest. A third goal is to identify domains that are involved in gating of connexin channels by phosphorylation, pH and voltage. Using a combination of electrophysiological and molecular biology techniques, our collaborative studies with Vytas Verselis at AECOM indicate that amino acids in the first extracellular loop undergo significant rearrangements during channel closure by voltage and pH. Laboratory space approximately 800 sq. feet.

David Troilo, Ph.D.

My research interest is in the visual regulation of postnatal eye growth and the development of refractive state. The eye continues to develop from birth to maturity in such away that it normally adjusts growth to match eye size to optical power thereby achieving focused images on the retina. It is unclear how this works and why it sometimes results in eyes that become nearsighted (myopic) or farsighted (hyperopic). We know from earlier experimental work that eye growth and refractive state can be visually guided. My work, and that of others, has established that experimentally imposing defocus on the retina can influence the growth of the eye and the development of refractive state. I am currently working in collaboration with Alexandra Benavente on the spatial and temporal characteristics of the visual stimuli influencing eye growth. I am also collaborating with Stewart Bloomfield on studies of the retinal biochemical basis of the ocular growth response to light using a new experimental paradigm. These studies have relevance to tens of millions of patients with refractive errors.

References:

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Benavente-Perez, A., Nour, A., & Troilo, D. (2014). Axial eye growth and refractive error development can be modified by exposing the peripheral retina to relative myopic or hyperopic defocus. *Invest Ophthalmol Visual Sci, 55* (10), 6765-6773.

Suresh Viswanathan, O.D., Ph.D.

Research in my lab focuses on understanding the mechanisms underlying visual dysfunction in glaucoma and mild traumatic brain injury and in developing clinical tests for the early detection and monitoring of

neuronal dysfunction in these conditions. These investigations use electrophysiological, psychophysical and in vivo imaging techniques. The total research space add up to 348 square feet.

Stefanie Wohl, Ph.D.

My laboratory studies the neural retina at the cellular and molecular level. The cells we are interested in and focus on are called glia cells, more precisely Müller glia. Müller glia are the predominant glia in the neural retina and named after Professor Heinrich Müller (described in 1851). Glia cells per se are known as the support cells in the central nervous system but have a variety of other functions including maintaining the homeostasis of the tissue but also protection after injury or disease.
In mammals, including humans, the central nervous system i.e., the brain (including the retina) and the spinal cord, does not regenerate after injury or disease. We know that glia, as part of their protective function, undergo morphological changes to create a barrier and a non-permissive environment for regeneration. This glial response, called gliosis, is a very complex process and includes a variety of factors and mechanisms which are not fully understood.
Molecules known to play in role in Müller glia development and function are microRNAs. microRNAs are small molecules present in every cell of the body that act as translational repressors. That means mRNA (transcribed from DNA) is not translated into protein. About 1000 different microRNAs have been identified so far and it is known that they have a huge impact in development, independent from tissue origin and cell type. However, their expression pattern can vary between different cell types, developmental stages (maturation of a cell) as well as physiological and pathophysiological conditions. For the latter, there is increasing evidence that microRNAs play an important role in various diseases and can be used as a biomarker for certain diseases.
In my laboratory, we investigate the role of microRNAs in the glial response to injury/disease. The focus lies on Müller glia but will also include other glia types such as astrocytes and microglia. Specific approaches are

1. Transgenic models to visualize and isolate the different kind of glia
2. Cell and tissue culture to study cellular and molecular changes in glia
3. microRNA profiling and RNA analyses
4. Techniques to overexpress or inhibit microRNAs and alter protein expression

Investigating the impact of microRNAs in the different phases of glial activation after injury and/or disease will give us a better understanding of the underlying mechanisms of gliosis in order to develop strategies to minimize the inhibitory nature of this process. The long-term goal is to develop new approaches and therapies to attenuate the glial response after damage which might allow regeneration of the central nervous system including the neural retina.

Qasim Zaidi, Ph.D.

My research concentrates on unraveling the neural processes used in complex visual
tasks involving color and 3-D shape. In color, my lab uses a mixture of mathematical, computational and psychophysical techniques to unravel the geometry of perceptual color spaces, factors governing color saliency, and the tuning of central and peripheral color adaptation to everyday tasks. In addition, I have collaborations that use single-cell, multi-cell, local field potential and fMRI techniques in retina, and cortical areas V1 and IT to study cone-pathways, the perception of lights and darks, color induction, and the neural decoding of color. In 3-D perception, my lab studies the perception of material qualities and non-rigid shapes.
For these projects we are developing scale-space generalizations of differential geometry theorems to process high-resolution stereo movies. Based on our experimental results, we build neural models that

we are testing in an electrophysiology collaboration on the processing of velocity patterns in cortical areas MT and MST, and an fMRI collaboration on the perception of shiny and deforming objects. Previous work from my lab has found applications in philosophy, clinical procedures, computer graphics and machine vision.

Xiaoying Zhu, O.D., M.D., Ph.D., M.S.

My principle research interest is in emmetropization, visual development and myopia. Animal studies show that during early postnatal life, ocular growth is modulated by the visual input from the retina, resulting in the correction of refractive errors. Eyes use two compensatory mechanisms to reduce defocus: When the eye wears a positive lens, which would put the images of distant objects in front of the photoreceptors (myopic defocus), it slows its rate of elongation and thickens the choroid, pushing the retina forward toward the image plane. When the eye wears a negative lens, which would put the images of distant objects behind the photoreceptors (hyperopic defocus), it accelerates its rate of elongation and thins the choroid, pulling the retina back toward the image plane. My research focuses on possible signaling molecules that regulate emmetropization, using animal models to uncover potential measures to prevent and treat myopia in school-aged children. Specifically, I have discovered that glucagon acts as a stop signal to prevent myopic development and eye growth and that insulin acts as a grow signal to enhance myopic development and eye growth. I have also studied temporal integration of defocus in emmetropization. In normal life, most parts of the retina experience frequent episodes of myopic and hyperopic defocus depending on the spatial layout of the environment, the distance of the objects viewed, and the eye's refraction and its accommodative state. How does the retina sum together these episodes of defocus over time to determine the direction of the eye's growth toward emmetropia? My results show that the signals for the effects of both positive and negative lenses on both the rate of ocular elongation and choroidal thickness rise at a similar rate (within minutes), but they decline at slower, very different rates, with the signal regulating the rate of ocular elongation declining the slowest in the case of positive lens-wear, and the fastest in the case of negative lens-wear.