NEI T-35 Mentors for the Summer Research Fellowship Program and Their Research Program Areas

Jose-Manuel Alonso, Ph.D.	Functional Circuitry of the Thalamus and Cortex
Benjamin Backus, Ph.D.	Learning in Visual Perception
Alexandra Benavente-Perez, Ph.D.	Myopia and Ocular Vascular Function
Stewart Bloomfield, Ph.D.	Functional Roles of Gap Junctions in Retinal Physiology and Pathology
Kenneth Ciuffreda, Ph.D.	Abnormal Oculomotor Systems/Head Trauma
Mitchell Dul, O.D., M.S.	Perimetry/Visual Fields/Psychophysics/Glaucoma
Philip Kruger, O.D., Ph.D.	Stimuli for Accommodation/Wavefront Aberration
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
Kathryn Richdale, O.D., Ph.D.	Patient-based Research in Cornea & Contact Lenses
Harold Sedgwick, Ph.D.	Perception of Spatial Layout in Low Vision
Miduturu Srinivas, Ph.D.	Gating and Pharmacology Lens Gap Junction Channels
David Troilo, Ph.D.	Visual Development, Accommodation, Refractive Error, Myopia
Suresh Viswanathan, BOpt., Ph.D.	Retinal Ganglion Cell Function, Glaucoma
Qasim Zaidi, Ph.D.	Color Perception, Three-Dimensional Shape Perception

Brief Descriptions of T35 Pre-doctoral Summer Fellowship Mentor Research Programs at SUNY College of Optometry

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, Prof. Stanley at Georgia Tech 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. Facilities include 2 research rooms (each 20' x 20') that are fully equipped to do electrophysiological recordings in awake and anesthetized animals. Sufficient office space is available for the principal investigator, students and visiting faculty.

Ben Backus, Ph.D.

Work in the Backus Lab focuses on three inter-related areas: perceptual learning,
binocular vision in normally sighted individuals, and abnormal binocular vision, especially amblyopia (lazy eye) and strabismus (binocularly misaligned eyes). Most T35 trainees focus on amblyopia, especially the effects of training to improve stereopsis or acuity, or physiologically motivated methods of characterizing binocular function, especially suppression during binocular combination. Adults retain significant plasticity in their visual systems. Over the last 8 years we have characterized many different aspects of this plasticity in dozens of “cue recruitment” experiments, wherein a visual signal comes to be utilized during perception so that it controls some aspect of the appearance of the stimulus that it did not control before. For example, the apparent rotation direction of a 3D rotating Necker (wire frame) cube can be trained to be contingent on the shape of the rotating object, and some of these effects last at least four weeks. We are now applying these ideas to the re-training of binocular neuron receptive fields, as a theoretically motivated way to treat amblyopia. Dr. Cristina Llerena Law, OD, is a PhD student in the lab who collaborates intensively with me on clinical studies; I am the mentor for

her NIH Loan Repayment and K-23 awards. In 2013 I completed a 10-year R01-funded project on binocular vision and cue recruitment. The lab has over 800 sq. ft. of space, including two mirror stereoscopes; large 6' x 8' rearprojection stereo display; RAPDx pupil size monitor; LCD shutter goggle stereoscopes; and access to shared state-of-the-art VEP apparatus with high precision display, eye tracking, Grass electrodes, and Plexon hardware/software.

Alexandra Benevente, Ph.D.

From experimental studies we know that eyes use visual information to adjust their growth and how they are focused. My main research interest is to understand the visual signals that trigger these eye growth changes that eventually lead to myopia. In particular, I am very interested in studying the role that the peripheral retina and eye shape might have as predictors of future changes in refraction. Another of my research interests is to understand the interaction between ocular 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. In this field, I am an external collaborator with the Vascular Imaging and Research Laboratory at Aston University, Birmingham, UK to study the vascular characteristics of the eyes in patients with Alzheimer's disease, and with SUNY IT to model ocular blood flow in myopia.

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, channelrhodopsin 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. My lab space is ~2000 sq. ft.

Kenneth Ciuffreda, O.D.-Ph.D.

My current research is in the areas of normal and abnormal oculomotor
systems, which include both versional and vergence eye movements, as well as accommodation. This broadly includes both experimental aspects and bioengineering-based system modeling/computer simulations. The accommodation studies are in the areas of myopia, where we have developed a retinal-based biochemical model of refractive error development related to retinal defocus and nearwork, and the human depth-of focus,
where we have studied blur detection in the near retinal periphery and have correlated it with retinal neuroanatomy/neurophysiology, optical aberrations, and visual attention. The studies on eye movements are in the areas of nystagmus, where we are investigating the effectiveness of various forms of feedback (visual, auditory, and/or proprioceptive) in the development of new treatment paradigms and devices for both adults and very young children, and in acquired brain injury, where we are investigating the use of visual and auditory treatment modalities to improve reading eye movements and reading ability with inferences regarding possible sites of residual neural plasticity; this will be followed in the future with a direct neurological assessment using brain-imaging techniques. There are four laboratory areas (22' x 12'; 10' x 12'; 22' x 8'; and 10' x 8') on the vision sciences and clinical sciences floors. These laboratories (total) contain 4 infrared eye movement recording devices (one with and/or auditory feedback), 4 static optometers, 4 dynamic objective infrared optometers (one with auditory biofeedback), 1 head movement system, 4 computers, and a clinical refracting unit. Computer simulation/modeling capability is also available. Office space, some shared, is available for all investigators.

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.

Philip Kruger, Ph.D.

We are examining the broad range of stimuli that control ocular accommodation. The standard view is that luminance contrast *per se* is the stimulus for reflex (blur-driven) accommodation, and that blur feedback is an essential part of the accommodative process. Our findings disagree with this conventional view, and suggest that the effects of the chromatic aberration of the eye, and the angle of incidence of light at the retina, provide directional information that specifies the sign of defocus of the eye (myopic or hyperopic). High-speed infrared optometry is used to monitor accommodation continuously while a variety of stimuli (including dioptric and non-dioptric depth cues) are presented in a Badal optometer under computer control. A principal goal is to better understand the chromatic and achromatic directional stimuli for reflex accommodation, which result from the refraction and chromatic dispersion of the light entering the eye. Measurements of the Stiles-Crawford effect and wavefront aberrations of the eye are used to create images that simulate defocus behind and in front of the retina, and the simulations are used to drive accommodation. The approach assumes that the optical information that controls accommodation also controls the process of emmetropization (coordinated growth and development of the optical components of the eye). Our findings disagree with the standard view of aberrations as imperfections or noise that must be removed from the retinal image. Instead aberrations like defocus and chromatic aberration provide information for depth perception, accommodation and emmetropization. Facilities include two 15' x 20' light-tight laboratories, and a 15' x 15' foot lab housing a computer graphics facility; investigators have offices adjacent to the three laboratories. There are 6 computers and a computer-graphics facility. Special equipment includes: A high speed infrared optometer and Maxwellian view Badal stimulus system; Two channel Maxwellian view optical system for measuring the Stiles-Crawford function, Sharp XGE-800U Video-projector; Barco Calibrator color display; Joyce display scopes; graphics computers for 3-D animation.

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.

Kathryn Richdale, O.D.-Ph.D.

I conduct patient-based research primarily in contact lenses and anterior segment disease. This includes the study of contact lens complications, presbyopia and myopia contact lens correction, and anterior segment inflammation due to dry eye and infiltrative keratitis. My research is supported by a Mentored Research Career Development Award from the National Eye Institute (K23-EY019097) and industry partners. Our research is conducted in the Clinical Vision Research Center (CVRC) which is located within the College of Optometry. The CVRC has designated research exam rooms, a special testing room, administrative offices, locked storage areas, and private waiting and subject interview areas to ensure compliance with guidelines for Good Clinical Practices. In 2014 I worked with two optometry students selected for the T35 program at SUNY. One student studied accommodative and binocular changes associated with multifocal contact lenses for myopia control, and the other examined tear protein changes associated with contact lens-related infiltrative keratitis. Both students are also co-advised by senior researchers at the College with expertise in myopia and cell biology.

Harold Sedgwick, Ph.D.

Much of our behavior depends upon accurate perception of the three-dimensional spatial layout of the environment. Multiple sources of visual information are available to specify this layout, including stereopsis, motion parallax, shading, and perspective. This raises the question of how the visual system combines these sources of information, which is also referred to as the problem of sensory fusion. I and Dr. Barbara Gillam (U. of New South Wales in Australia) are exploring the role of perceptual surfaces in mediating the integration of two kinds of information for space perception: stereopsis and perspective. By integrating the local stereoscopic information relating an object to a surface with the stereoscopic and perspective information operating across the entire extent of the surface, the visual system can potentially greatly enhance the accuracy and precision with which the object's spatial location is perceived. It has already been shown that the perceived slant of a background surface can influence the perceived relative depth of two probes suspended in front of the surface. Our projects use this paradigm to investigate the processes by which local depth signals and surface slant signals are integrated. We use computer generated stereoscopic displays. The first questions relate to what surface characteristics facilitate surface mediated integration of information for probe depths. Another area of interest is the "topography of surface mediation". A third series of questions looks at the relative effects on perceived probe depth of different types of information specifying surface slant. They examine perspective, gradients of stereoscopic discontinuity at surface boundaries, and a closely related form of information produced by gradients of texture discontinuity at surface boundaries. Finally, we are also interested in studying the perceptual response to inconsistent information about the relative depth of the probes. Facilities include one combined office and research preparation room (approx. 18' x 20'), two research cubicles (approx. 8' x 10'), and one storage/file room (approx. 6' x 13'). We have two research computers running PC NT with software for 3D image generation & animation (one equipped for stereo image generation), as well as a number of older PCs suitable for some projects. One research cubicle is equipped with a large rear projection screen and several slide projectors for creating wideangle displays.

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 laboratory works on 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 as it grows in size it undergoes adjustments of its optical components and its refractive state. These adjustments are usually coordinated so that eyes grow toward emmetropia (emmetropization). Occasionally emmetropization does not occur and the eye becomes nearsighted (myopic) or farsighted (hyperopic). We are interested in how emmetropization works and why it occasionally leads to refractive errors. Our earlier work, and that of others, has established that imposed defocused images can influence the growth of the eye and the development of refractive errors. We are currently interested in several aspects of this experimental ocular growth regulation including the characteristics of the visual stimuli influencing eye growth, the way the stimuli are spatially and temporally integrated, how accommodation interacts with this integration. In collaboration with Dr. Jody Summers Rada (University of Oklahoma) we are also studying the biochemical basis of the ocular growth response. We hypothesize that the development of refractive state is determined by a confluence of several interacting factors including the shape of the eye, the spatial pattern of refractive state across the retina, and the temporal characteristics of visual stimuli experienced. In addition to these, there may be individual inherited differences in eye shape and peripheral refractive state as well as the area of retina involved in the integration of the visual growth signal, and the gain of the eye growth controller. Such a multifactorial system would explain why it is so difficult to predict who will become myopic, and who will progress (and how to treat them effectively). These studies have relevance to tens of millions of patients with refractive errors. Myopia is a leading cause of blindness but its control is an old and still controversial topic. We believe that our current work will help provide answers to several clinically relevant questions regarding the development and control of myopia, the association between near work and myopia, and the identification of
risk factors and predictors. Laboratory space approximately 800 sq. feet.

Suresh Viswanathan, Ph.D.

The research focus of my laboratory is to develop tests for the early detection
and reliably monitoring progression of optic neuropathy in conditions like glaucoma or trauma to the optic nerve. In earlier studies we identified a retinal ganglion cell component of the electroretinogram called the Photopic Negative Response (PhNR). More recently, we have evidence from animal studies that soon after traumatic optic nerve injury the intensity response function of the PhNR demonstrates sensitivity reduction and
with further progression of the condition the sensitivity reduction is accompanied by reduction in saturated responses as well. In related studies we also found that animals that were treated with Brain Derived Nerve Growth Factor during stages when there was a selective reduction in the sensitivity of the PhNR, but no significant change in saturated amplitude, demonstrated best preservation of retinal ganglion cell function. These findings indicate that the different

parameters of the PhNR intensity response function can serve as a biomarker for identifying the severity of optic nerve dysfunction that can be used to tailor treatment strategies.
Based on these findings we are currently testing hypothesis that patients with mild to moderate glaucoma or traumatic optic nerve injury who demonstrate reduction in PhNR sensitivity, but normal saturated amplitudes have the best prognosis for improvement in visual function. The total research space add up to 348 square
feet.

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.