Communication

Glaucoma at the Hamilton Glaucoma Center and the University of California, San Diego

Robert N. Weinreb, MD
Hamilton Glaucoma Center, University of California, San Diego La Jolla, CA, 92093 USA

Known for its unique cross-disciplinary investigative programs and clinical excellence, the scientists and clinicians at the Hamilton Glaucoma Center of the University of California, San Diego seek to enhance the discovery and translation of innovative research to clinical glaucoma care to prevent and cure glaucoma blindness. With state of the art laboratory and clinical facilities located on the La Jolla campus (Figure 1), the Center is a home for a world-renowned team of scientists and staff. More than 100 post-doctoral fellows in Glaucoma, many of whom hold distinguished academic positions throughout the world, have been trained at the Hamilton Glaucoma Center and the University of California, San Diego. At the core of Hamilton Glaucoma Center activities are the outstanding faculty that are described below.

Figure 1 The Hamilton Glaucoma Center research building opened in 2003.

Robert N. Weinreb, M.D.

Robert N. Weinreb, M. D. (Figure 2), is a clinician, a surgeon and scientist. He is Distinguished Professor of Ophthalmology and holds the Morris Gleich MD Chair at the University of California, San Diego. He oversees all clinical aspects of glaucoma diagnosis and treatment within the Department of Ophthalmology at the Shiley Eye Center. Patients from throughout the world seek his diagnostic and surgical expertise. Dr. Weinreb is also the Director of the Hamilton Glaucoma Center and oversees research activities there.

A graduate of the Harvard Medical School, Dr. Weinreb has made important scientific contributions to several aspects of glaucoma including imaging of the optic disc and retinal nerve fiber layer, aqueous dynamics and outflow biology, glaucoma surgical wound healing and medical therapy of glaucoma. His research laboratories are funded by the National Eye Institute and the National Institues of Health to study optic nerve biology, neuroprotection and aqueous outflow biology.

Dr. Weinreb has served as President of the Association for Research in Vision and Ophthalmology (2002 ~2003), President of the World Glaucoma Association (WGA) (2004~2006) and President of the American Glaucoma Society (2007~2009). He is Chief Editor of the International Glaucoma Review.

Figure 2 Robert N. Weinreb, MD, Distinguished Professor and Morris Gleich Chair, Director of the Hamilton Glaucoma Center, rweinreb@ucsd. edu.

Corresponding author: Robert N.weinreb, MD
E-mail: rweinreb@ucsd.edu

Linda Zangwill, Ph.D.

Linda Zangwill, Ph. D. (Figure 3), Professor and co-Director Clinical Research, is investigating new methods for detecting and measuring glaucomatous optic neuropathy and monitoring its progression. She also studies the relationship between structural changes in the optic nerve and alteration of visual function, as well as the characteristics of persons at an increased risk of developing glaucoma. Dr. Zangwill is Principal Investigator of several National Eye Institute funded studies including the "Diagnostic Innovations in Glaucoma Study (DIGS): Structural Assessment" evaluating the ability of new diagnostic imaging instruments to detect glaucomatous damage to the optic nerve and to monitor its progression and the African Descent and Glaucoma Evaluation Study (ADAGES), a multi-center study of structure and function in African Americans, a population with an elevated risk of developing glaucoma. As Director of the Imaging Data Evaluation and Analysis (IDEA) Center, she has developed procedures for utilization of diagnostic imaging instruments including confocal scanning laser ophthalmoscopy, scanning laser polarimetry, and spectral domain optical coherence tomography in national and international mutli-center clinical trials of glaucoma and ocular hypertension.

Figure 3 Linda M.Zangwill, PhD, Professor, zangwill@glaucoma.ucsd.edu

John Liu, Ph.D.

Although diagnosis and treatment of glaucoma depend upon the measurements of IOP, we now know that IOP readings during regular office visits may not be an ideal indicator of what really happens during daily life. Under the direction of John Liu PhD (Figure 4a), Professor, the Sleep Research Laboratory of the Hamilton Glaucoma Center is seeking to demonstrate that the 24 hour IOP, and not the IOP during usual office hours, is a better indicator for the diagnosis and treatment of glaucoma. The time influence of the 24-hour day on IOP is being systematically investigated under highly controlled conditions in a state-of-the-art sleep laboratory on the UCSD campus (Figure 4b). This innovative research studies the 24-hour IOP patterns and determines the treatments that are most effective during the night as well as during the day. Contrary to traditional belief, research conducted in the laboratory has demonstrated that more than ninety percent of the healthy eyes register their highest IOP peak at night. In untreated glaucoma patients, IOP is found to be always higher than the normal level at night as well as during the day. Various IOP-lowering medications that have similar efficacies in lowering IOP during the day show very different IOP-lowering efficacies at nighttime. These evidence-based laboratory results

Figure 4a The Sleep Laboratory has private rooms for 24 hours testing

Figure 4b John H.K. Liu, PhD, Professor, joliu@ucsd.edu

have made a significant impact on our understanding of how IOP is regulated during the nocturnal/sleep period. A recently initiated project is to investigate whether a lower 24-hour intracranial pressure could be an additional risk factor for glaucoma. Dr. Liu's research research has been supported by the National Eye Institute and the National Institutes of Health.

James Lindsey, Ph.D.

Under the direction Of James D. Lindsey, Ph.D. (Figure 5), Professor, the Laboratory for Outflow Biology has demonstrated how prostaglandin analogues that lower intraocular pressure alter and reduce collagens within the uveoscleral outflow pathway via metalloproteinases. Recently, the Laboratory has discovered that different size macromolecules within the uveoscleral outflow exit the eye via alternative routes. Because many of the mechanisms for drug-induced alterations of intraocular pressure appear to involve changes in the physical dimensions of outflow pathways, different drugs that lower intraocular pressure may have differential effects upon this partitioning of macromolecules within aqueous outflow.

Within the Sophie and Arthur Bordy Laboratory for Optic Nerve Biology, Dr. Lindsey focuses on understanding the mechanisms of retinal ganglion cell (RGC) injury and recovery from axonal damage. A confocal scanning laser ophthalmoscope has been developed that allows imaging of fluorescent neurons in transgenic mice that express cyan fluorescent protein under the control of an RGC marker protein promoter.In the laboratory, it has been demonstrated that corresponding retinal areas before and after optic nerve crush can be repeatedly re-imaged to allow for the longitudinal evaluation of fluorescence diminution following optic nerve crush or following ischemia reperfusion injury.This capability has allowed experiments showing that progression of damage can differ depending upon the insult. Within the Laboratory, the survival and recovery of injured RGCs is being studied, and methods for protecting them are being evaluate.

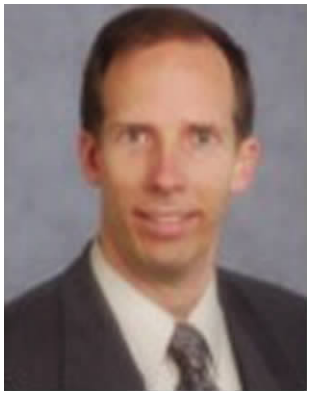

Figure 5 James D. Lindsey, PhD, Professor, lindsey@eye-center.ucsd.edu

Michael H. Goldbaum, M.D.

Under the direction of Michael Goldbaum, MD (Figure 6), Professor, the Glaucoma Informatics Laboratory at the Hamilton Glaucoma Center is conducting research that seeks to improve the diagnosis of glaucoma and enhance the detection of glaucomatous progression by the application of state-of-the-art pattern recognition methods, specifically machine learning classifiers (MLCs), to a variety of sensory and structural imaging tests.Dr Goldbaum has pioneered this field of vision research.

Figure 6 Michael H.Goldbaum, MD, Professor, mgoldbaum@ucsd.edu.

The laboratory has demonstrated that: 1.the detection of glaucoma with automated perimetry, optic nerve topography, and retinal nerve fiber layer thickness measurement is improved by the application of MLCs; 2.there is information in early visual fields that indicate whether an eye is at risk of glaucomatous progression; 3.a novel modification of Independent Component analysis, learning from data without human intervention, can identify patterns of visual field defects resembling the classic glaucoma-

tous patterns plus new patterns not previously discovered with human experience; and, 4.a new MLC method developed in the laboratory, progression of patterns (POP), is able to detect more eyes with progressive glaucomatous deterioration of visual fields than current progression-detecting algorithms, which is important knowledge for glaucoma specialists deciding which treatment an eye needs.

The goal of this research is a set of applications for the various functional and structural testing instruments to bring to the glaucoma practitioner intuitive information in real time that will help the practitioner decide whether an eye has glaucoma and which treatment is most appropriate for preventing glaucomatous deterioration.

Kang Zhang, M.D., Ph.D.

Although the exact disease mechanisms are not fully understood, the pathogenesis of glaucoma involves a complex interplay of a variety of environmental, metabolic, and genetic risk factors. The laboratories of Kang Zhang, MD, PhD (Figure 7), Professor and Director, UCSD contributions to glaucoma. His laboratory has documented that first-degree relatives of individuals with POAG have a three-to nine-fold greater risk than that of the general population of developing POAG. Further, the laboratory has identified a gene that predisposes individuals with high risk for POAG in the Barbados (Caribbean) population. The biological pathways that could lead to the development of glaucoma also are being investigated by Dr. Zhang and his team. By reprogramming fibroblast derived stem cells (induced pluripotent stem cells (iPS)) from the same patient with POAG, it is hoped that functional retinal neurons, such as retinal ganglion cells, can be programmed and eventually reintroduced into the patient's eyes to restore vision in glaucoma.

Terry Gaasterland, Ph.D.

Terry Gaasterland, PhD (Figure 8), Professor, is seeking genetic determinants of risk for glaucoma through genome sequencing and computational data analysis. Under National Eye Institute funding, her laboratory is reading DNA sequences for all protein coding regions genome-wide in glaucoma patients, affected relatives, and unaffected controls. The laboratory is sequencing DNA from subjects who were included in a large Genome-Wide Association Study (GWAS), called NEIGHBOR. NEIGHBOR is a multi-institutional, national project, and the Hamilton Glaucoma Center is a major contributor of DNA samples. The approach employed is to use DNA hybridization in single-tube solution reactions to recover DNA from exons genome-wide ("exome capture"). Exome capture, combined with next generation sequencing, allows for greater depth and breadth of coverage compared to conventional GWAS.The sequence data reveals changes at the DNA level that turn into changes at the protein level, including changes in three-dimensional structure, biochemical properties of active sites, or affinity for other essential carrier, transport, or catalytic proteins. The laboratory's expertise is the bioinformatic analysis of DNA and protein sequences in an evolutionary context. It is expected that novel and rare changes in conserved protein regions will highlight genes that

Figure 7 Kang Zhang, MD, PhD, Professor, k5zhang@ucsd.edu.

Figure 8 Terry Gaasterland, PhD, Professor, Scripps Institute, tgaasterland@ucsd.edu.

when altered, confer risk to glaucomatous damage to the optic nerve or disease progression.

Felipe Medeiros, M.D., Ph.D.

Felipe Medeiros, MD, PhD (Figure 9), Associate Professor and Medical Director of the Hamilton Glaucoma Center, is a clinician and clinical researcher. His research encompasses identification of risk factors for development and progression of glaucoma, and methods and strategies for diagnosis, follow-up and management. His past research on risk factors has contributed to elucidate and integrate the role of many different risk factors in glaucoma, culminating with the development of the first validated risk calculator to predict the risk of disease development in subjects with ocular hypertension.Currently, his laboratory is expanding refining existing models and developing others that could be used to assess risk of disease progression in those already diagnosed with glaucoma.

Figure 9 Felipe A. Medeiros, MD, PhD, Associate Professor, fmedeiros@glaucoma.ucsd.edu.

Dr.Medeiros and his team also have investigated the role of structural evaluation of the optic nerve and nerve fiber layer in glaucoma. He was the first to demonstrate that early structural changes in the optic nerve are predictive of development of future functional losses in glaucoma, a result that has significant implications for the clinical management of patients with the disease and for the incorporation of structural endpoints in clinical trials. He has also conducted extensive investigations on the role of imaging technologies for diagnosing and monitoring glaucoma progression. His studies were the first to evaluate rates of disease progression using new technologies such as scanning laser polarimetry and optical coherence tomography. Currently, he is expanding the work on this area with the development of methods to combine structural and functional tests in order to improve detection of disease progression and estimation of rates of change. Dr. Medeiros also is focused on the methodological and statistical aspects of the use of clinical tests in glaucoma, and is investigating the potential of Bayesian statistics to improve the evaluation of imaging and functional tests in the disease.

More recently, Dr. Medeiros' laboratory is evaluating performance-based measures and quality of life in patients with glaucoma. This research involves investigating the ability of glaucoma patients to perform activities of daily living with methods such as driving simulation, and studying the relationship between measures of functional impairment and results of standard clinical tests.The main goal of this research is to develop models that could effectively predict which patients are at risk for functional impairment and decrease in quality of life from glaucoma.

Rigby Slight, M.D.

Rigby Slight, MD (Figure 10), Associate Professor, is a clinician and glaucoma specialist. He oversees resident and post-doctoral clinical training at the Veterans Administration Hospital in La Jolla.Dr. Slight also is an investigator in many of the ongoing clinical trials at the Hamilton Glaucoma Center.

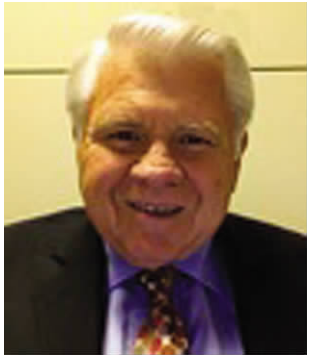

Figure 10 J. Rigby Slight, MD, Associate Clinical Professor, kissamutt@aol.com

Won-Kyu Ju, Ph.D.

Won-Kyu (Daniel)Ju, PhD (Figure 11), Assis-

Figure 11 Won-Kyu Ju, PhD, Assistant Professor, danielju@glaucoma.ucsd.edu

tant Professor, studies oxidative damage and the role of the mitochondria in glaucomatous optic neuropathy. Although high IOP may be causative in many individuals, the cellular and molecular mechanism (s)by which it damages the optic nerve and RGCs are unknown. Growing evidence suggests that mitochondrial dysfunction can play a major role in neuronal cell death in a wide variety of neurodegenerative disorders, suggesting a possible role in glaucomatous optic neuropathy. Increased mitochondrial susceptibility to IOP-induced damage in certain individuals may predispose them to the development of glaucomatous optic neuropathy. His team has shown that increased pressure can directly damage RGC mitochondria and that this damage is correlated with progressive RGC degeneration in murine glaucoma. In healthy cells, mitochondria are autonomous and morphologically dynamic organelles that structurally reflect a balance of ongoing fission and fusion within a cell. Recent studies have indicated that this balance shifts towards mitochondrial fragmentation prior to and during apoptosis. This balance is regulated by a family of dynamin-related GTPase that exert opposing effects. Optic atrophy type 1 (OPA1)and the mitofusins are required for mitochondrial fusion, while dynamin-related protein 1(Drp1)regulates mitochondrial fission. His team has found that elevated pressure triggers mitochondrial fragmentation and abnormal cristae depletion in the ON axons, as well as altering cytochrome c oxidase gene and protein, and mitochondrial fusion/fission mediators such as OPA1 and Drp1 in the ON head in glaucomatous DBA/2J mice. Further, elevated IOP compromises both respiratory capacity and oxidative phosphorylation, as well as alters OPA1 and Drp1 expression, and RGC death. These observations led to his hypothesis that interventions to protect against mitochondrial fission-related dysfunction will be beneficial for reducing glaucomatous neurodegeneration and RGC loss. His laboratory also has shown that increased OPA1 expression using recombinant OPA1-adeno-associated viral construct protects RGCs by 25% in a mouse model of glaucoma. This observation indicates that OPA1 can directly modulate RGC survival, and that increasing OPA1 expression may protect against RGC death in glaucomatous optic neuropathy. This approach may provide a new strategy to protect against RGC death in various optic neuropathies, including glaucoma. Dr. Ju's research is supported by the National Eye Institute and the National Institutes of Health.

Peter N. Rosen, M.D.

Under the direction of Peter N. Rosen, MD (Figure 12), Assistant Professor, the laboratory for Vision and Driving Performance was recently established at the Hamilton Glaucoma Center to investigate the relationship between changes of structure and visual function in patients with glaucoma, and the psychophysics of task performance, using driving simulation. Driving simulation offers advantages beyond evaluating driver fitness: it is an interactive test of perceptual(vision), cognitive(vision processing, judgment, decision-making) and motor-control abilities that dynamically integrate spatial and temporal aspects of vision under controlled conditions of task performance.Correlating task performance to OCT and visual field deficits, while varying the

Figure 12 Peter Rosen, MD. Assistant Clinical Professor, prosen@cox.net

contrast of scenarios to simulate day, fog, or nighttime driving conditions, for example, may be a sensitive way to detect progression in terms that are meaningful for treatment decisions and patient understanding of glaucoma progression.Driving simulation engages and mimics visual and cognitive processes that are used in on-road driving and allows clinicians and researchers to assess reactions to risky situations without the risk. Its utility as a test of vision impairment depends on specific features entailed in driving scenarios that map back to and evoke specific visual functions not traditionally measured clinically, including motion, detection, kinetic depth perception, visual processing speed, divided attention, spatial and situational awareness, reaction time and others.

Madhusudhanan Balasubramanian, Ph.D.

Madhusudhanan Balasubramanian, PhD (Figure 13), Assistant Research Scientist, focuses his multidisciplinary research on developing computational tools to measure deformation of the optic nerve head from retinal images and to develop biomarkers of glaucoma progression for various retinal imaging instruments.

Figure 13 Madhusudhanan Balasubramanian, PhD. Assistant Professor, madhu@glaucoma.ucsd.edu

Current broad themes of Dr.Balasubramanian's research are: 1.Developing computer vision and image processing algorithms for quantifying deformation of the optic nerve head non-invasively from optical images of the retina in clinical population and in non-human primate eyes under experimental glaucoma. The algorithm development, which employs both mathematical and statistical techniques, have the central goals of: a)minimizing the number of follow-ups required for glaucoma diagnosis and management, b)early detection of glaucoma, and c)improving the specificity of detecting glaucoma progression by controlling type I statistical error; 2.Developing computational algorithms to estimate patient-specific intrinsic characteristics of the retina such as the reflectance of the optic nerve head and texture of the retinal nerve fiber layer. The working hypothesis is that intrinsic characteristics of the retina is less affected by changes in retinal illumination during follow-up and therefore can provide highly specific and sensitive detection of glaucoma progression; 3.Developing biomarkers of glaucoma progression for various optical imaging instruments such as the confocal scanning laser ophthalmoscope and spectral domain optical coherence tomograph (SD-OCT) using the measures of optic nerve head deformation estimated from retinal images; 4.Developing computationally efficient high-performance algorithms necessary for analyzing high-dimensional retinal datasets such as the SD-OCT volume scans.A CPU-/GPU-cluster computing environment is utilized to achieve high computational efficiency; 5. Translating the high-performance algorithms into clinical tools to assist with glaucoma diagnosis and management in clinics; 6.Developing optimal human-computer interfaces (hardware and software), graphics, and interactive stereoscopic visualization techniques for exploring high V dimensional ocular imaging datasets; and, 7.Developing algorithms for retinal image preprocessing, retinal image restoration and quality enhancement, and retinal image quality measurement.

Dr. Balasubramanian is a founding member of the new computational ophthalmology initiative under the graduate CSME program (Computational Science, Mathematics, & Engineering) at UCSD. The computational ophthalmology initiative is aimed at bridging ocular research with advanced engineering, computing, and optics, and also to facilitate cross-disciplinary training of clinical fellows in ophthalmology and undergraduate and graduate students at UCSD. Dr. Balasubramanian's research is supported by the National Eye Institute and the National Institutes of Health.