RESEARCH GRANTS
2019-2022
Vessels and Nerves of the Choroid and Iris, seen from above. The Sclerotic and Cornea have been largely removed. (Testut.)
The Glaucoma Foundation is dedicated to improving the lives of people with glaucoma. The Foundation works to encourage and support basic and applied research in glaucoma with a goal of preserving and restoring vision.

The Foundation offers grants to researchers striving to improve the lives of glaucoma patients through novel innovations and scientific advances.

The areas of current focus for TGF’s Grant Research program are exfoliation syndrome, exfoliation glaucoma and intraocular pressure-independent mechanisms of optic nerve degeneration in glaucoma. Examples of research that may be considered range from basic science to clinical interventions, such as genetics and genomic medicine, disease modeling, assessment of ocular perfusion, artificial intelligence, and clinical research. Priority is given to novel proposals with a viable study hypothesis that can lead to impactful results that are fundable at the NIH level.
Unraveling the Proteolytic Landscape Regulating LOXL1 Implications in the Development of Pseudoexfoliation Syndrome

Principal Investigator: Fernando Rodriguez Pascual, PhD
Centro de Biologia Molecular “Severo Ochoa” (CSIC/UAM)
Madrid, Spain

While precise pathogenesis of PEX syndrome remains unknown, the identification of genetic variants in the LOXL1 gene strongly associated to the disease has opened new avenues for the investigation on its molecular causes. The protein product of the LOXL1 gene belongs to the lysyl oxidase (LOX) family, a group of enzymes contributing to build the extracellular matrix (ECM) by promoting the covalent association (cross-linking) of elastin and collagens. In particular, LOXL1 plays an important role in the formation of elastic fibers, the ECM scaffold mostly imparting elasticity to animal tissues, an observation very consistent with its identification as an integral part of the PEX deposits.

With the support of a previous grant from TGF, we initiated a line of research aiming to investigate the proteolytic processing of LOXL1 and its potential implications in the development of PEX syndrome. Far from being completed, our results provide a glimpse of the complexity of the proteolytic landscape regulating LOXL1 expression and activity, anticipating exciting findings potentially important for the development of PEX syndrome. Here we apply for a renewal of the support from TGF to accomplish the characterization of LOXL1 proteolytic regulation and to investigate its pathological relevance in the development of PEX syndrome.
Growth Differentiation Factor 15 Levels in Pseudoexfoliation Glaucoma

Principal Investigator:
Rajendra Apte, MD, PhD
Washington University, St. Louis, MO

There are several kinds of glaucoma, all of which can lead to the death of cells in the eye that send visual information to the brain. Preventing these cells from dying is an important part of the treatment for glaucoma. However, it can be difficult for physicians to identify which patients are at highest risk of developing glaucoma, or having their glaucoma get worse over time.

Finding a marker, such as a protein in the eye whose presence might predict whether glaucoma will get worse, would make it possible for physicians to better determine whether a patient should have surgery or another treatment.

This project will study a protein called ‘growth differentiation factor 15’ (GDF-15), which is associated with retinal stress in rodents and humans. By measuring the levels of this protein in human patients with glaucoma before and after surgery, we hope to understand whether there is a relationship between GDF-15 levels in the eye, the severity of glaucoma, and success of glaucoma surgery. If high GDF-15 levels are linked with more severe glaucoma, it could be used as a marker to help determine treatment for patients at the highest risk of developing severe glaucoma.

“With support from TGF, we are investigating whether a protein called Growth Differentiation Factor-15 is a molecular biomarker for pseudoexfoliation (PXG). These human pilot studies in patients with PXG can only be executed because of this generous grant support. We are analyzing the data and hope to publish our findings before the end of the year.”
Metabolomic Analyses of Aqueous Humor of Pseudoexfoliation Glaucoma

Principal Investigator:
Sanjoy K. Bhattacharya, M. Tech, PhD
Bascom Palmer Eye Institute
University of Miami
Miller School of Medicine, Miami, FL

We will identify the small molecules in the clear fluid of the front part of the eye termed aqueous humor. These small molecules are involved in all day-to-day functions of biological tissues in the eye.

This analysis will show a difference in small molecules between pseudoexfoliation glaucoma and normal eyes. Their addition (for example the molecules that provide energy) or removal (for example known toxic molecules) may be early intervention strategies for treating pseudoexfoliation glaucoma.

“This grant has supported our critical experiments of metabolite profiling and machine learning, and opened up the prospect for an extramural federal grant to fully investigate the initial mechanisms leading to deposit formation.”
New Understanding from Mouse Lines with Features of Pseudoexfoliation Syndrome

Principal Investigator:
Yong Yuan, PhD
College of Medicine,
University of Cincinnati,
Cincinnati, Ohio

Pseudoexfoliation syndrome is the most identifiable cause of open-angle glaucoma. Animal models are critical tools for finding the cause of the disease and for testing potential treatment regimens. Currently, no animal model is available that can recapitulate the symptoms of this disease.

We found features of pseudoexfoliation syndrome in several mouse lines with genetic defects affecting cellular functions. The objective of this proposal is to find what is the common cause of the disease among these mouse lines. New knowledge obtained from this study will lead to a better understanding of the disease as well as new strategies for combating the disease.

“As a new investigator to the glaucoma field, I am blessed to have the trust and the support from The Glaucoma Foundation in the form of grant awards and intellectual support at the Think Tank meetings. The grant helped me to collect critical data for a competitive NIH grant.”
Abnormal Extracellular Matrix Homeostasis of Trabecular Meshwork Cells in Pseudoexfoliation Syndrome and Glaucoma

Principal Investigator: Katy Liu, MD, PhD
Duke Ophthalmology, Duke University School of Medicine

Pseudoexfoliation glaucoma is the most common glaucoma with an identifiable cause. However, there is no targeted treatment for pseudoexfoliation glaucoma.

The trabecular meshwork lies within the drain of the eye, and it has the highest resistance to outflow of eye fluid or aqueous humor. Many scientists theorize that the trabecular meshwork cells put down dysfunctional surrounding matrix, or extracellular matrix, which provides support for the cells. There is no suitable model to study the extracellular matrix of trabecular meshwork cells. For the first time, we have grown trabecular meshwork cells from pseudoexfoliation donors. This powerful tool will allow us to determine alterations the trabecular meshwork extracellular matrix, and we have preliminary data to support this idea. We will also determine the effect of extracellular matrix on the biomechanical properties of trabecular meshwork cells, or the cell’s rigidity, which directly affects resistance to outflow of aqueous humor.

This study is critical to further our understanding the role of the extracellular matrix in the mechanism of pseudoexfoliation disease. With this knowledge, the extracellular matrix could be targeted by future drug and medical therapies.

“Support from The Glaucoma Foundation is allowing us to substantiate and expand upon our preliminary findings of abnormal extracellular matrix homeostasis in pseudoexfoliation syndrome and glaucoma. Using newly established trabecular meshwork cell lines, we are beginning in vitro experiments.”
The proposed research is designed to investigate the regulatory role of the LOXL1 protein that is associated with risk of pseudoexfoliation glaucoma. We are interested in how LOXL1 activity contributes to elevation in eye pressure that is typical of pseudoexfoliation glaucoma. Specifically, we will investigate the relationship between LOXL1, a signaling molecule called TGF-beta 1 (Transforming Growth Factor) and eye pressure, using a mouse model.

TGF-beta 1 is often elevated in eyes of people with pseudoexfoliation glaucoma, and it is known to induce “scarring” that causes elevated eye pressure. Results from this project will provide a better understanding of disease mechanism and may lead to targeted clinical interventions for pseudoexfoliation glaucoma.

“This grant has provided critical funding for technician salaries, biological materials, and animal care to complete these experiments. We believe that the results of this study will give us new insight into the role of LOXL1 in TGF-beta 1-mediated fibrosis in pseudoexfoliation glaucoma, potentially qualifying LOXL1 as a suitable drug target for pseudoexfoliation glaucoma treatment.”
Identifying Glaucoma Risk Alleles in the LOXL1 Promoter Using a Massive Parallel Promoter Assay

Principal Investigator:
John H. Fingert, PhD
University of Iowa

Exfoliation syndrome is a disease that causes accumulation of fibrillar material (exfoliation material) in tissues throughout the body, including the eye. Patients with exfoliation syndrome are at high risk for glaucoma and vision loss, thus exfoliation syndrome is a public health problem.

The specific causes of exfoliation syndrome are unknown, but hereditary is important. The genetic basis of exfoliation syndrome is complex and involves the interaction of many genetic and environmental factors. Seven genetic risk factors have been discovered, and one of these genes, LOXL1, is a potent risk factor for disease. In this application, we propose experiments to determine the mechanism by which the LOXL1 gene confers risk for exfoliation syndrome. Our hypothesis is that dozens of different genetic mutations together cause an abnormal amount of LOXL1 protein to be produced in the eye, which in turn damages the drainage structures of the eye and leads to glaucoma.

With our proposal we will identify dozens of mutations that alter LOXL1 production in the eye using a DNA sequencing technique known as BiT-STARR-seq. The overall goal of these experiments will be to identify the specific cause of exfoliation syndrome at the molecular level (i.e. LOXL1 gene mutations).
Anti-Fibrotic Potential of All-Trans Retinoic Acid in Pseudoexfoliation Syndrome and Glaucoma

Principal Investigator:
Ursula Schlötzer-Schrehardt, PhD
University of Erlangen-Nürnberg

The causes underlying the development of pseudoexfoliation syndrome and its associated glaucoma, which is the most common type of secondary open angle glaucoma associated with a high risk of blindness, are not fully understood, and there is no specific treatment.

This project addresses the current need for a better understanding of the mechanisms of PEX pathogenesis and identification of therapeutic targets. It proposes to test the hypothesis that impaired retinoic acid signaling is causally involved in the abnormal fibrotic matrix process.

It is further suggested that compounds stimulating retinoic acid signaling have a potential to reverse the adverse fibrotic effects of disease. It is anticipated that the findings will identify novel pathomechanisms involved in the development of PEX glaucoma and advance the development of novel therapeutic approaches for the treatment of pseudoexfoliation syndrome and glaucoma.

Dr. Schlötzer-Schrehardt is a member of TGF’s Scientific Advisory Board. She is a professor at the University of Erlangen - Nürnberg’s Department of Ophthalmology where she has been cited as the world’s leading expert on the pathogenetic mechanisms causing PEX and lauded for her tremendous contributions to our knowledge of the cellular and molecular mechanisms that cause this disease. This named grant was awarded in 2020.
Role of IGFBPL1 on Retinal Ganglion Cell Survival in an IOP-independent Injury Model

Principal Investigator:
Kin-Sang Cho, PhD
Schepens Eye Research Institute

Glaucoma is a globally unmet medical challenge because of its prevalence, devastating consequences and lack of effective treatment. The disease leads to progressive loss of retinal ganglion cells and vision. Our recent study identified a protein called insulin-like growth factor binding protein like-1 (IGFBPL1) that is a novel regulator of retinal ganglion cells survival and nerve growth. Progressive loss of retinal ganglion cells and their axons in the optic nerve is a characteristic feature of glaucoma, leading to vision loss.

We recently observed lack of IGFBPL1 in mice exhibits progressive degeneration of retinal ganglion cells, which mimics the pathogenesis of IOP-independent glaucoma. It suggests that IGFBPL1 is a key player to maintain RGC survival in the adult. The proposed study will investigate the regulatory networks of IGFBPL1 and the long-term effect of IGFBPL1 on the survival in a IOP-independent glaucoma model. After completion of the proposed studies, we anticipate uncovering novel molecular targets for glaucoma therapy.
Retinal Organoids to Study Disease Progression and Intervention in Glaucoma

Principal Investigator: Miriam Kolko, MD, PhD
University of Copenhagen

Glaucoma is characterized by the progressive loss of the retinal ganglion cells (RGCs), and while IOP clearly plays a role, several lines of research have indicated that dysfunction of the Müller glia (MG) play a key role in the pathophysiology.

We hypothesize that vulnerability to RGC loss depends on MG’s ability to protect the RGCs and that MG dysfunction due to glaucoma will affect the essential partnership between RGCs and the MG. We will look at two patients’ groups, denoted normal tension glaucoma (NTG) and ocular hypertension (OHT). In NTG patients, IOP is within the normal range, but patients still experience glaucomatous RGC loss.

We assume that NTG patients may have a specific MG dysfunction leading to RGC loss. In contrast to NTG patients, patients with OHT have increased IOP but no evidence of glaucomatous damage. These patients may have a resistance due to a sustained healthy MG and are therefore able to withstand the high IOP. Unlike NTG patients, patients with OHT have increased IOP but no evidence of glaucomatous injury. They may have a resistance due to continued healthy MG and therefore are able to withstand the high IOP.

Our hypothesis is that we can detect new neuroprotective targets from MG derived from OHT patients as well as further identify both toxic and neuroprotective targets in RGCs that have been exposed to MG from NTG or OHT patients, respectively.
Schlemm’s Canal Catheterization and Substance Delivery in Live Monkeys

Principal Investigator:
Paul L. Kaufman, MD
University of Wisconsin Madison

Glaucoma is the leading cause of irreversible blindness. Its prevalence increases with age. Lowering pressure inside the eye is critical to glaucoma therapy, and slows progression of optic nerve damage and visual loss. Self-administered eye drops utilize various drugs that enhance fluid outflow from or decrease fluid formation by the eye, reducing eye pressure.

Most patients will require several classes of drop therapy, each self-administered one to three times daily. Unfortunately, patient adherence to self-administered drop regimens is poor, because of age-related infirmities and the complexity of medical regimens for co-existing conditions.

In live monkeys, we will inject viruses carrying genes that enhance fluid outflow into the small drainage channel (Schlemm’s canal) that encircles the front part of the eye, permanently reducing the flow resistance of the major outflow pathway, reducing the viral load, avoiding off-target local and systemic adverse side effects, assuring consistent therapeutic efficacy, and relieving the patient’s physical and psychological burden. We have designed and fabricated the tiny catheters, mastered the microscopic injection technique, constructed virus-gene vectors that work in cells and in organ-cultured monkey eyes, and are ready to move into live monkeys (this project) and then hopefully into human clinical trials.
DNA Methylation and RGC Degeneration in Glaucoma

Principal Investigator:
Shahid Husain, PhD
University of South Carolina

Glaucoma is the second leading cause of blindness worldwide. Nearly 80 million people worldwide are believed to have glaucoma, including an estimated 3 million in the USA. Approximately 120,000 people are blinded by glaucoma accounting for 9-12% of all cases of blindness. Vision loss is caused by damage to the optic nerve, which connects eye to the brain for image formation and recognition. In most cases of glaucoma, vision loss is coincident with elevated eye pressure. This pressure imbalance in the eye over a long period of time causes degeneration of eye neuron, which ultimately leads to the blindness.

During the progression of glaucoma, numerous factors including epigenetics play crucial role. Chemical reactions with the help of enzymes can modify DNA. Once DNA is chemically modified it will become tightly packed and reduces it activity for the production of certain beneficial factors such as neurotrophins. Neurotrophins are essential components for the neuron of healthy eye. When DNA is tightly packed it will not allow machinery to produces neurotrophins, as a result neurons will be deprived of neurotrophins and start to degenerate. Once sufficient number of neurons are degenerated, it will lead to the blindness, as seen in glaucoma.
Mouse Strain Specific Differences in Intracranial Pressure and Susceptibility to Glaucoma

Principal Investigator:
Colleen M. McDowell, PhD
University of Wisconsin Madison

Glaucoma is a silent, underdiagnosed, costly and debilitating disease and the only treatment options for the disease include reducing elevated pressure within the eye. However, patients are sometimes resistant to current established treatments and it is crucial to identify therapies and develop new treatments for glaucoma that can directly save the visual neurons from dying.

We will utilize mouse models to study changes in pressure occurring on the eye neurons from both inside the eye and from the brain side of the eye in glaucoma to identify new protection therapies.
Targeting Neuronal NAD Production Through NMNAT2 Activity for Neuroprotection in Glaucoma

Principal Investigator:
Pete A. Williams, PhD
St Erik Eye Hospital

Our research program has identified metabolic dysfunction in the retina and optic nerve in experimental glaucoma animals and human glaucoma patients. We have discovered that an important molecule, ‘NAD’, declines in the retina and optic nerve during glaucoma, and increasing NAD levels using nicotinamide (a form of vitamin B3 and a precursor to NAD) prevents glaucoma in animals.

Nicotinamide is also low in the blood of glaucoma patients and we have now demonstrated that nicotinamide treatment can increase visual function in glaucoma patients. NAD production is an ideal target for drug discovery for glaucoma and we have now generated a number of novel drugs that target these processes.

This research program will further these studies by designing and testing new NAD-generating drugs with an aim to raise NAD in the retina and optic nerve. This will provide novel glaucoma treatments that are not reliant on, but can be used in combination with, existing pressure lowering treatments.
Retinal ganglion cells (RGC), the neurons that die in glaucoma, are metabolically active and require a precise regulation of blood supply to meet their high oxygen and nutrient demand. The vascular theory of glaucoma proposes that insufficient blood flow contributes to RGC neurodegeneration.

Glaucoma patients suffer from vascular deficits including decreased blood flow in the retina and optic nerve, reduced vessel caliber, and capillary defects. Notably, vascular autoregulation and flicker-induced neurovascular coupling, a key process that matches blood flow to the metabolic demand of active neurons, are severely compromised in this disease. However, the cellular mechanisms underlying vascular dysfunction in glaucoma and their impact on neuronal damage are currently unknown. Pericytes, the ensheathing cells that wrap around capillary walls, have emerged as key regulators of microcirculatory blood flow and neurovascular coupling. Pericytes are centrally positioned within the neurovascular unit, contain contractile proteins, and respond rapidly to neuronal stimulation. The retinal microvasculature is rich in pericytes, with >90% pericyte coverage in human retinal capillaries. We recently reported that inter-pericyte tunneling nanotubes (IP-TNTs), fine tubular processes that connect retinal pericytes on distal capillary systems, are essential for neurovascular coupling in the retina. These findings were published in the impactful journal Nature (2020) and were lauded as critically important by the scientific community at large. Despite this, the role of pericytes and IP-TNTs in vascular dysregulation in glaucoma has not been investigated.

To fill this knowledge gap, we recently developed a novel two-photon laser scanning microscopy (TPLSM) technique to visualize retinal pericytes and single capillary blood flow in living mice).
Progressive loss of retinal ganglion cell (RGC) neurons of optic nerve causes glaucoma leading to complete blindness. Currently, over 3 million Americans are suffering from glaucoma without any cure.

Lowering high eye pressure provides temporary relief but without the cure. Till date no therapy is available for RGC neuroprotection in glaucoma. Thus, there is a critical need to develop therapy to protect the RGC neurons. Studies in glaucoma patients’ retina and in animal models of glaucoma have widely found presence of elevated reactive oxygen species (ROS) which are toxic chemicals and cause oxidative stress, potentially leading to RGC death in glaucoma.

Mitochondria are the energy source for cells, but damaged mitochondria are the primary source of toxic ROS chemicals. In healthy cells, ROS are cleared by activation of Nrf2 transcription factor. Several of Nrf2 activators are under FDA clinical trials for neurodegenerative diseases. Though ROS accumulation observed in glaucoma patients’ retina, nothing is known if Nrf2 activation could remove ROS and protect human RGC neurons as a potential therapy for glaucoma.

In this proposal we will use human stem cell derived RGC neurons and test if Nrf2 activation could serve as neuroprotectant under glaucomatous condition.
2021 ARTIFICIAL INTELLIGENCE GRANT

Forecasting Glaucoma Progression and the Need for Surgical Intervention using Artificial Intelligence

Principal Investigator: Linda Zangwill, PhD
Sally Baxter, MD, MSc (Co-Principal Investigator)
Mark Christopher, PhD (Co-Principal Investigator)
Viterbi Family Department of Ophthalmology
Shiley Eye Institute, Hamilton Glaucoma Ctr.
UC San Diego

Primary open angle glaucoma is a leading cause of blindness in the United States and worldwide. However, there is no way to predict in advance which individuals are at greatest risk of progressing to vision loss in patients who are diagnosed and then medically treated for glaucoma. Such patients might then be considered for surgical intervention to delay vision loss.

There have been important innovations in artificial intelligence (AI) applications in healthcare, in general, and particularly in ophthalmology. Although considerable progress has been made in developing AI algorithms to detect glaucoma using imaging and visual field data, few have integrated these results in one model. Even fewer have incorporated information from clinical examinations and electronic medical records to support clinical decision-making. This study is designed to address this important unmet need.

The overall objective of this proposal, “Forecasting Glaucoma Progression and the Need for Surgical Intervention using Artificial Intelligence”, is to use multimodal AI and deep learning strategies to predict which glaucoma patients will need glaucoma surgery. We will leverage existing data from diverse research datasets and real-world clinical glaucoma populations for the development and testing of the deep learning models. Data from clinical examinations, electronic health record data, optical coherence tomography imaging and visual field testing will be used as input for the development and testing of the AI algorithms that can predict which patients will likely need glaucoma surgery.
FORECASTING GLAUCOMA PROGRESSION

Linda Zangwill, Ph.D., is Professor of Ophthalmology and co-Director of Clinical Research and Director of the Imaging Data Evaluation and Analysis (IDEA) Center at the Hamilton Glaucoma Center. Dr. Zangwill received her M.S. at the Harvard School of Public Health and her Ph.D. from Ben-Gurion University of the Negev.

Dr. Zangwill’s research focuses on improving our understanding of the complex relationship between structural and functional change over time in the aging and glaucoma eye, developing computational and statistical techniques to improve glaucomatous change detection, and identifying risk factors that can predict rapidly progressing glaucoma.

As Director of the Imaging Data Evaluation and Analysis (IDEA) Center, Dr. Zangwill has developed and implemented protocols for utilizing diagnostic imaging instruments in national and international multi-center clinical trials of glaucoma and ocular hypertension.

The three UCSD Principal Investigators, Linda Zangwill, PhD, Sally Baxter, MD, MSc and Mark Christopher, PhD are joined by investigators Robert N. Weinreb MD (UCSD), Christopher Garkin MD, MPH and Massimo Fazio, PhD (University of Alabama, Birmingham), and Jeffrey Liebman MD (Columbia University) to complete this important work.

This proposal will build upon the prior work conducted by this research team to develop AI algorithms that incorporate a variety of data types to improve forecasting of clinical outcomes for glaucoma patients.
Elastic Fibers and Exfoliation Glaucoma

Principal Investigator:
Rachel W. Kuchtey, MD, PhD
Vanderbilt Eye Institute

Exfoliation glaucoma (XFG) is one of the most common types of secondary glaucoma, which will lead to irreversible blindness if left without treatment. In order to effectively treat this disease, precise understanding of its molecular mechanisms is needed.

The breakthrough genetic discoveries over the last decade have paved the pathways leading toward our goal. LOXL1, encoding lysyl oxidase-like 1 protein is the most significant gene associated with XFG and the interaction between lysyl oxidase-like 1 and fibrillin-1 has been increasingly recognized as they are two essential elements for proper elastic fiber formation and function.

We propose to use our newly created mouse model supported by The Glaucoma Foundation during the first funding cycle to investigate the roles of those two molecules in XFG. If successful, new treatments could be quickly tested in our model in the near future.

“As a glaucoma clinician, I have deep appreciation on how the disease impacts a patient's life and I will draw great satisfaction when we can get the disease under control one patient at a time. However, my decade and a half experience in the clinic also tells me we need a permanent fix. It is clear to me that only through in-depth basic science research can we make the cure of glaucoma possible.”
New Tools to Understand Intraocular Pressure Regulation at the Level of Aqueous Veins and Sclera Complex

Principal Investigator:
Guan Xu, PhD
University of Michigan

A great proportion of patients with glaucoma, especially those with exfoliation glaucoma that progresses rapidly, require surgical intervention to avoid blindness. However, the lack of knowledge of how aqueous drainage paths behave when pressure in the eye fluctuates is a critical barrier to the accurate prediction of surgical outcomes. The goal of this proposed project is to fill this knowledge gap using an advanced imaging technology combined with an established mechanical analysis method.

In our preliminary study, we have already shown that our approach can resolve the deformation of aqueous drainage paths and the surrounding tissue in the eye in 3 dimensions, which has not been achieved by any existing technology. During the funding period, we will further validate our approach by comparison to standard tissue measurement tools. After the validation, we will analyze the deformation of the aqueous drainage path and their surrounding sclera under well-controlled pressure in pig eyes and human donor eyes. These analyses will provide us with the knowledge needed for selecting appropriate surgical procedures for the most desirable patient outcomes.
The Role of Left-Right Determination Factor 2 (LEFTY2) in Exfoliation Glaucoma

Principal Investigator:
Steven Bassnett, PhD
Washington University School of Medicine

Exfoliation glaucoma is a potentially blinding condition affecting millions of people worldwide. Unfortunately, patients are often unaware of this disease until a significant portion of their vision has been lost irretrievably.

One of the goals of this project is to determine whether the levels of a protein called LEFTY2 can be used to diagnose the condition or predict which patients are likely to be affected most severely. The study will also examine which cells produce LEFTY2 and its effect on cells in the drainage pathway of the eye.
Molecular Mechanisms of Reactive Astrocyte Neurotoxicity to Human Retinal Ganglion Cells

Principal Investigator:
Xitiz Chamling, PhD
Johns Hopkins University School of Medicine

Glaucoma, the second leading cause of blindness, has no therapeutic approaches available except for lowering intraocular pressure. Drugs that can protect retinal ganglion cells (RGCs), the neuronal cells whose death leads to vision loss in glaucoma, is a potential therapeutic option to prevent vision loss. However, developing such drugs has been difficult because the cause of RGC death in glaucoma is not fully understood.

Several studies are now suggesting that another cell type, called astrocytes, that populate the brain and optic nerve (bundle of nerves that connect the eye to the brain), can release toxic factors when they are stressed and not functioning normally. Such stressed astrocytes are called reactive astrocytes and the factors secreted by them can kill the RGCs. In our lab, we have established methods to convert human stem cells to human RGCs and human reactive astrocytes in a dish. Using these cells, we plan to study how reactive astrocytes cause RGC death. By studying the cause of human RGCs death, we hope to identify targets for developing drugs to protect RGCs and prevent glaucoma-related vision loss.
A Novel Transcription Factor for Neurodegeneration Therapy in Glaucoma and Optic Neuropathy

Principal Investigator:
Kun-Che Chang, PhD
University of Pittsburgh

Glaucoma is the second leading cause of blindness worldwide, estimated to affect ~80 million people in 2020. So far there is no permeant therapy for glaucoma. However, vision restoration through gene delivery strategies could be potential solutions for such a disease.

In this proposal, we identify a novel therapeutic gene and will apply it to a glaucomatous animal model, which will not only provide us a deeper understanding of the molecular mechanism of this gene in neuroregeneration therapy but also a foundation of the translational experiment for preclinic study.
Optic Nerve Head Perfusion in a Murine Model of Pathological Myopia

Principal Investigator:
Rachel Shujuan Chong, MBBS, MMed(Ophth), PhD
Singapore Eye Research Institute

Myopia is an important risk factor for glaucoma – high myopia in particular has been suggested to increase the risk of developing this sight-threatening disease by 3 to 7-fold. Elongation of the eyeball that occurs in myopia often results in deformation of structures in the eye, including the optic nerve head where glaucoma damage occurs. It is possible that myopia-associated changes to the eye shape also affects the blood vessels that supply retinal ganglion cells at the optic nerve head, although this has not been studied in great detail to date.

We aim to investigate how myopia can alter blood vessel structure and function around the optic nerve head using state-of-the-art methods of ocular imaging and tissue analysis in a mouse model of high myopia that demonstrates similar characteristics as human myopia. Our study will enable deeper insight into the mechanisms that underlie myopia-associated glaucoma, which may help clinicians to identify patients who are most at risk of losing sight in future.
The most important test to detect progression is visual field testing. Visual field testing is the reference standard to measure visual function in glaucoma. It is called called standard automated perimetry (SAP). However, this test is very subjective, often unreliable, and variable. One of the main causes of unreliable tests is the lack of attentiveness or concentration during the test.

Previous studies have shown that listening to Mozart or taking vitamin B12 can improve the reliability of this test. Recent studies have suggested that over-the-counter medications such as nicotinamide (vitamin B3) and pyruvate can also improve the performance during this test. This can ultimately reduce costs due to repeated testing and increase doctor’s certainty when analyzing the results of this test.

This study seeks to test whether these over-the-counter nutritional supplements have an impact on patients’ performance during visual field testing.
The Genetic Landscape of Blinding Exfoliation Glaucoma

Principal Investigator:
Chiea Chuen Khor, MB, BS, DPhil
Singapore Eye Research Institute

Exfoliation syndrome is a major cause of irreversible blindness throughout the world. This condition was found to be heritable and accordingly, genetic variants showing significant associations with risk of exfoliation syndrome have been discovered. However, comparatively little has been done to investigate the potential role of human genes and propensity for progression towards blinding exfoliation glaucoma.

We first asked whether CYP39A1, a gene where carriers of mutations had a 2-fold increased risk of exfoliation syndrome, would also be involved in exfoliation glaucoma-related blindness. We observed that persons with exfoliation syndrome carrying a loss-of-function CYP39A1 variant have >7-fold risk of blindness compared to persons with exfoliation syndrome who did not carry any CYP39A1 variant. When only patients with exfoliation glaucoma were considered, carriers of CYP39A1 G204E were observed to have 5.9-fold increased risk of blindness compared to non-carriers.

Although we were encouraged that genetic variants conferring such high odds of blindness actually exist, the association with CYP39A1 only explained between 10 to 20 percent of blindness due to exfoliation glaucoma. We hypothesize that additional genes could be involved in this irreversible, debilitating process. To address this question, we propose to perform long read sequencing mapping and search specifically for structural variants that are strongly associated with blindness. Structural variants has yet to be systematically studied, and will be accessible using long-read sequencing. Data from this proposal has the potential to uncover genetic markers that may be useful for identifying individuals at high risk of exfoliation syndrome related blindness.
Biochemical Characterization of LOXL1 and Effect of Variants Associated with Exfoliation Syndrome

Principal Investigator:  
Raquel L. Lieberman, PhD  
Georgia Institute of Technology

Exfoliation syndrome (XFS) is a leading risk factor for secondary glaucoma, a major cause of blindness worldwide. Genetic changes in LOXL1 were discovered in connection with XFS 15 years ago, yet how the LOXL1 gene product contributes to disease is still unknown.

In this proposal we will use state of the art biochemical techniques to characterize LOXL1 and elucidate the changes that occur with genetic changes proposed either to cause or prevent XFS. In the long term, this study will result in new insights into how LOXL1 contributes to XFS/XFG, as well as new directions for therapeutics.
Role of LOXL1 Variants in Elastic Fiber Formation

Exfoliation syndrome (XFS) manifests as excessive deposits of abnormal elastic fiber proteins in various organs, especially in the eye where it can lead to blindness. XFS is linked to the LOXL1 gene giving rise to the enzyme lysyl oxidase-like 1 (LOXL1) which is responsible to polymerize elastic fibers. Small changes in LOXL1 termed “variants”, can either promote or protect from XFS.

The objective of this proposal is to analyze the consequences of specific LOXL1 variants with either protective or risk profiles on the function and development of elastic fibers. We will analyze the structure and aggregation of these LOXL1 variants, their interaction with elastic matrix proteins, and their contribution to elastic fiber formation. We expect from the results of this project to better understand how LOXL1 variants can either promote or reduce the risk of getting XFS. The project may even open new avenues for therapies for XFS.
Nicotinamide and Pyruvate for Neuroenhancement in Open-Angle Glaucoma: A Phase 2 Randomized Clinical Trial

Principal Investigator:
Simon John PhD
Columbia University Irving Medical Center

Glaucoma is the leading cause of irreversible blindness worldwide. The most important test to detect progression is visual field testing. Visual field testing is the reference standard to measure visual function in glaucoma. It is called standard automated perimetry (SAP). However, this test is very subjective, often unreliable, and variable. One of the main causes of unreliable tests is the lack of attentiveness or concentration during the test.

Previous studies have shown that listening to Mozart or taking vitamin B12 can improve the reliability of this test. Recent studies have suggested that over-the-counter medications such as nicotinamide (vitamin B3) and pyruvate can also improve the performance during this test. This can ultimately reduce costs due to repeated testing and increase doctor’s certainty when analyzing the results of this test. This study seeks to test whether these over-the-counter nutritional supplements have an impact on patients’ performance during visual field testing.
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