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FALL WINTER 2017

# TGF's 24th Annual International Think Tank

The Glaucoma Foundation's Annual International Think Tank provides a unique opportunity for scientists and clinicians around the world to apply their research and progress to the challenges of glaucoma. Collaboration is the key to the success of the Think Tank, which strives to create an open and effective dialogue among those attending. The hope is to foster new relationships among the participants that will lead to communication and collaboration across disciplines and between laboratories - long after the meeting has ended.

Beginning in 2012, the Glaucoma Foundation sharpened its focus on exfoliation syndrome (XFS), the most common recognizable cause of open-angle glaucoma worldwide, comprising the majority of cases in some countries. XFS is characterized by deposits of а flaky, dandruff-like material in many ocular tissues. Four facets of XFS have been singled out for investigation - genetics, genomics, and gene-environment interactions; biomarkers – looking for specific molecules that may be elevated or decreased in the eye or blood; developing animal models of the disease; and further exploring



The 2017 Annual International Think Tank in session.

molecular and cellular mechanisms involved in the production of exfoliation material.

This summer's Think Tank in New York City was the fifth to deal with exfoliation, with some 60 participants from the United States as well as Australia, Canada, China, Germany, Japan, Singapore and Spain.

The Annual Think Tank has stimulated research at a geometric level, and TGF's grants program now focuses specifically on XFS. The result is the concentration of the research efforts of The Glaucoma Foundation into advances in XFS. The number of researchers working on XFS has increased markedly and publications are increasing steadily. Robert Ritch, MD, founder of The Glaucoma Foundation and Chairman of the Scientific Advisory

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### **LETTER FROM THE PRESIDENT**



**Dear Friends:** 

It was 100 years ago that a young Finnish ophthalmologist at the University of Helsinki, John G. Lindberg, published his thesis on a new phenomenon, exfoliation syndrome (XFS). Long thought to be a Scandinavian disease and largely ignored by Americans, it is now known to be the most common recognizable cause of open-angle glaucoma worldwide, affecting some 80 million

people, and comprising the majority of glaucoma in some countries. We observed this anniversary in June, at the annual meeting of the World Glaucoma Congress in Finland.

Exfoliation syndrome has been the focus of TGF's efforts since 2012. On these pages you will read how our sharpened focus is making a real impact through our Annual Think Tank and research grants we have funded this year.

In related news, TGF has just raised its grant stipend to \$60,000 in response to the increasing costs of research and to maximize the effect of the scientific research being performed. We are very encouraged that by concentrating our entire research program on XFS, the number of researchers working on exfoliation has increased markedly with impressive results.

This year's Think Tank was the fifth to focus on exfoliation syndrome. On that occasion, The Foundation presented its 2017 Robert Ritch Award for Excellence and Innovation in Glaucoma to clinician scientist Tin Aung of Singapore, whose extensive research efforts have greatly furthered the understanding of angle-closure glaucoma and glaucoma genetics. The award honors Dr. Ritch, founder of TGF and its Medical Director and Chairman of the Think Tank since its inception.

As you all know, finding a cure for glaucoma is the compelling impetus for everything we do. We are encouraged by the significant support we have received to reach that goal and thank you, our valued friends. We are counting on your continued generosity.

Sincerely,

Scott R. Christensen President Chief Executive Officer

### **TGF's 24th Annual International Think Tank**

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At the Think Tank Dinner Professor Tin Aung of Singapore received the 2017 Robert Ritch Award for Excellence and Innovation in Glaucoma.

Board, is spearheading this global effort.

In 2007 scientists identified genetic variants in the lysyl oxidase-like 1 (LOXL1) gene that have been strongly associated with XFS, but do not alone cause the condition. Environmental effects appear to play a role in whether or not someone predisposed to the disease will develop it. Collaborations have already advanced the understanding of exfoliation and yielded important new findings.

Several new genes have now been discovered and associations with elastic tissue disorders are being described. New information about the LOXL1 gene and its variations offer the possibility of devising treatment approaches directed toward the gene. Altogether, recent studies have provided new insights into the genetics, pathology and biology of XFS, opening the door to new approaches to preventing or reversing or even curing XFS.

Growing patient-derived XFS cells in cell culture has revealed that similar to other age-related diseases such as age-related macular degeneration and Alzheimer's, the cellular machinery that degrades protein aggregates is not working properly. In the case of XFS, the theory is that exfoliation material cannot be degraded leading to an accumulation of "cellular trash" both inside and outside the cell that becomes toxic.

A related area of interest is the growing appreciation of the systemic nature of exfoliation. It has been known for decades that exfoliation material can be found in many tissues in patients affected by XFS and that numerous conditions, such as hearing loss, and cardiovascular and cerebrovascular disease, are associated with XFS.

A recent study looked at female patients in the large, inclusive Utah Population Data Base (UPDB) to see if there was a link between XFS and pelvic organ prolapse. Researchers found that women with pelvic organ prolapse were at approximately a 50% increased risk of having XFS and that women 30-65 years of age who had a pelvic organ prolapse diagnosis, when followed for 20 years, had a 48% increased risk of developing XFS during that time period. The findings could lead women with pelvic organ prolapse to get early screening for XFS, and potentially save their vision.

# **Doctor, I Have a Question**



QUESTION ANSWERED BY: Gregory K. Harmon, MD Board Chairman of The Glaucoma Foundation

### What is the relationship between cataracts, glaucoma and MIGS?

A cataract is a clouding of the eye's natural lens, allowing less light to pass through and blurring vision. Cataracts affect over 20 million Americans over the age of 40. By age 80, half of all Americans have cataracts. For many, they are an unavoidable part of aging.

It is very common for glaucoma and cataracts to coexist. In both conditions, the risk increases with age. In addition, there is a risk of developing cataracts or having them progress after any invasive glaucoma surgery. And cataracts, when advanced, can trigger angle-closure glaucoma in susceptible individuals. But while vision loss from glaucoma is still irreversible, loss of vision due to cataracts can usually be reversed by surgically removing the cloudy, cataract lens and implanting a clear artificial replacement intraocular lens.

When a cataract causes reduced or poor vision, with blur, glare or dimming of sight that interferes with everyday life's activities, it is usually time for surgical intervention. Today, surgeons view cataract surgery as an ideal opportunity to bring a patient's glaucoma under better control. They do this by combining cataract surgery with a minimally invasive glaucoma surgery (MIGS) procedure. The FDA's recent approval of several new MIGS procedures is increasing doctors' options. The greatest advantage to the concomitant use of a MIGS procedure with cataract surgery is the significant reduction of surgical and postoperative risks and complications, as compared to traditional glaucoma filtration surgery (trabeculectomy).

Cataract surgery with MIGS is particularly important in patients with mild to moderate glaucoma. Patients with advanced and severe glaucoma may still require traditional filtration surgery or tube shunt surgery because IOP levels typically need to be much lower in these patients.

A growing number of surgeons are combining cataract surgery with newer MIGS, which in clinical trials have been shown to significantly decrease IOP. Among these technologies are the iStent, Trabectome, Kahook dual blade goniotomy, the CyPass Micro-Stent device and the Xen gel stent. All of these MIGS have shown that they can lower IOP and reduce topical glaucoma medication with a greatly reduced rate of the inherent risks of traditional drainage surgery. Another promising MIGS device, the InnFocus micro shunt, is currently under investigation and FDA trials. Most importantly, clinical research has shown that by performing a MIGS procedure at the same time as removing the cataract, the surgeon can usually bring the patient's mild to moderate glaucoma under better control, lower the IOP and/or reduce the medications required to control the IOP.

The advent of MIGS has reduced the necessity of combining cataract and trabeculectomy surgeries, thereby reducing the associated risk of vision threatening complications especially infections that can occur long after the trabeculectomy has been performed. Although trabeculectomy surgery is performed far less often than a decade ago, it can be well suited for patients with glaucoma that is severe and advanced. These patients typically need much lower IOP levels which are often best provided by performing the more traditional glaucoma surgery, trabeculectomy or tube shunt procedures.

Special situations can impact cataract surgery. Patients with exfoliation glaucoma often have cataracts. It is best to perform the removal of these cataracts earlier rather than later to minimize risk of complications. In exfoliation glaucoma, the delicate fibers that hold the eye's natural lens in place (zonules) can become weakened and loose. If cataract surgery is delayed in these individuals, allowing the lens to become harder and zonules to become weaker, the eye's natural lens could fall into the back of the eye during surgery. In fact, exfoliation syndrome is the largest most significant complicating factor in all of cataract surgery. On the positive side, cataract surgery done in patients with exfoliation often lowers the IOP level more than the IOP lowering that results from cataract surgery in the patient who does not have exfoliation syndrome.

The use of a MIGS procedure when performing cataract surgery in patients with exfoliation

syndrome further enhances the IOP lowering effect.

Another surgical challenge, especially among exfoliation patients, is when glaucoma patients have small pupils that do not dilate well. Fortunately, today's cataract surgeons have many options to help them temporarily enlarge the patients' pupils during cataract surgery so that the surgery can be performed more easily and with less risk.

Finally, another breakthrough which has made cataract surgery in the presence of glaucoma much safer is the femtosecond laser. Femtosecond laser-assisted cataract surgery is very helpful in patients with exfoliation syndrome, narrow angles or angle-closure glaucoma. This is particularly true if the cataract is more advanced, requiring more ultrasound energy to break it up. By softening the cataract lens with the laser before the lens is removed. the risk of complications is reduced, making the cataract surgery safer. In exfoliation patients, by softening the cataract lens prior to its removal, stress on the eye's delicate zonules is reduced and, therefore, the risk of the lens falling into the back of the eye is reduced. In patients with narrow angles or angle-closure glaucoma, the associated risk of damage to the iris and the cornea are greatly reduced as well.

Cataract surgery in patients with glaucoma continues to make great progress! The advent of MIGS procedures is helping cataract surgeons provide their patients with *safer* surgery that provides better glaucoma control and/ or a reduced need for glaucoma medications. Many surgeons now feel that combining MIGS procedures with a cataract surgery is an opportunity that should never be missed. By better controlling glaucoma at the time of cataract surgery, patients may be able to avoid the traditional, more risky, invasive glaucoma surgeries.

# Living with Glaucoma



"This is an exciting time. There are lots of possibilities and it's really frustrating that there is research going unfunded."

Twenty-six year old Ryan Gedney, who was born with open-angle glaucoma, is well on his way to becoming an ophthalmologist and giving back to the visually impaired community.

A second year medical student at the Medical University of South Carolina, Ryan credits his parents and a great doctor who was able to stabilize his condition very early. In fact, it was the doctor who treated Ryan throughout his childhood and teen years who inspired him to become a physician. "Now I want to help people who weren't as lucky as I am," he says.

In Ryan's case, his parents realized there was something wrong with his eyes shortly after his birth as he was sensitive to light, his eyes were runny, he didn't want to be outside and looked away from people. They researched the possibilities and suspected he may have glaucoma, which the doctor confirmed. When Ryan was a toddler he had a goniotomy – a surgical procedure used in congenital glaucoma to relieve eye pressure. "Today my pressure is stable, and despite poor vision, I've had no major problems. I need glasses to function and I always wear sunglasses when I go outside. The pressure spikes that occurred when I was a baby damaged my vision, but luckily nothing else."

When Ryan graduated from Clemson University with a degree in bioengineering, he worked in medical device design and development, specifically on neuro (brain and nervous system) devices. He also began volunteering at local eye clinics – helping visually impaired and blind people with tasks and errands. "I saw what they have to go through – and realized how fortunate I am. "I also started a program of my own called the Young Eyes Project, where I collect new and used glasses in local schools in Charleston, and then work with a physician at MUSC to give those glasses to children who couldn't otherwise afford them."

Appropriately for his desired profession, Ryan will graduate from medical school in 2020 and then will begin residency work. "I'll always be involved in research – it's the most important part of medicine... that's where everything starts. I also want to be the kind of doctor who is personable. People want a connection and they want to be able to trust that their doctor is doing the right thing for them.

"When I start practicing, I'll draw on my own experience to help others with vision problems, having been in their shoes."

Ryan is currently working on a research project involving medical shunts to relieve pressure in the brain, which can arise from an abnormal buildup of cerebrospinal fluid. The buildup is often caused by an obstruction which prevents proper fluid drainage.

"I think every day about applying this technology to relieve eye pressure in glaucoma. This is life-changing stuff, even when it might not sound exciting. There are lots of possibilities and it's really frustrating that there is important research going unfunded.

"The chance that I might lose my vision is always in the back of my mind. But I think I'll be fine. What I want is to now focus on helping other people."

### **Joseph M. La Motta** 1932 – 2017



The Glaucoma Foundation was deeply saddened by the death of our devoted friend, longtime Board Member and former Chairman and CEO, Joseph M. La Motta, on May 16. Joe joined the Board in 1990 and served as Chairman and CEO from 1992 to 1999.

A leader during a time of expansion, he helped initiate pivotal new programs, among them the International Think Tank, with its goal of optimizing the success of glaucoma research and speeding the search for cures.

As a glaucoma sufferer himself, Joe La Motta truly understood the importance of The Glaucoma Foundation's mission and his role as a dedicated leader. The Glaucoma Foundation's Joseph M. La Motta Endowment Fund, established in 2000, will perpetuate his memory and his many achievements.

### Be Social and Find us at:

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Funding for this newsletter was provided by The Delta Gamma Foundation Service for Sight Grant.

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### **KAREN LING JOINS TGF BOARD OF DIRECTORS**

Karen Ling is the Executive Vice President and Chief Human Resources Officer (EVP, CHRO) at Allergan. As EVP, CHRO at the pharmaceutical company, Ling is responsible for leading the human resources organization, including talent management, leadership development, compensation & benefits and staffing.

Ling has extensive global human resources experience in pharmaceuticals and consumer health care. She previously was Senior Vice President, Human Resources, for Merck & Co., Inc.'s Global Human Health and Consumer Care businesses worldwide. Prior to that role at Merck, she was Vice President, Compensation and Benefits. Prior to Merck, Ling was Group Vice President, Global Compensation & Benefits at Schering-Plough. Ling also spent 14 years at Wyeth in various positions of responsibility in human resources.

Prior to joining Wyeth, Ling practiced corporate law in Boston. She is a graduate of Yale University, with a degree in economics, and Boston University School of Law.

### **TWO NEW MEMBERS FOR SCIENTIFIC ADVISORY BOARD**

Jonathan G. Crowston, BSc, MBBS, PhD, FRCOphth, FRANZCO, is the Ringland Anderson Professor of Ophthalmology, University of Melbourne, and Managing Director of the Centre for Eye Research Australia (CERA). He is a practicing glaucoma specialist clinician at the Royal Victorian Eye and Ear Hospital.

Crowston gained his ophthalmology training at Moorfields Eye Hospital, London and was awarded a PhD for work on ocular fibrosis at the Institute of Ophthalmology, University College London (2000). He subsequently completed Glaucoma Fellowships at the University of Sydney and UC San Diego where he then joined the glaucoma faculty, prior to moving to Australia in 2006.

He serves on a number of boards including the Centre for Eye Research Australia (CERA), and the World Glaucoma Association. His research is focused on understanding why aging predisposes to optic nerve disease and in particular on neuroplasticity and the potential for retinal ganglion cell recovery. He has published broadly and received awards for his research and training. Among them was the inaugural 2016 ARVO David L Epstein Award recognizing outstanding research in glaucoma and for mentoring young clinical investigators. Since 2015, Baldo Scassellati-Sforzolini MD, PhD, MBA, has been Senior Vice President Clinical Development at Allergan, where he is responsible for all therapeutic areas globally with 70 projects and 200 studies in Phase I to Phase IIIb in dermatology, aesthetics, eye care, CNS, gastroenterology / epathology, anti-infective, internal medicine, urology and women's health. He is a member of the R&D Leadership Team and the Global Operational Leadership Teams (top 35 leaders at Allergan).

From 2013 to 2015 he served as Vice President Development Eye Care & Dental at Valeant Pharmaceuticals where he was responsible for Medical Affairs, Clinical Development and Device Safety for the Eye Care Division (Bausch + Lomb) and for the Dental Division (Orapharma).

Beyond his extensive R&D experience at these and other drug companies, he worked for nine years in academic hospitals in the EU and US and was investigator in multi-centric clinical trials in Parkinson's disease and macular degeneration.

### **2017 Research Grants**

### Functional Analysis of Rare Protective Coding Variants in LOXL1

### Principal Investigator: R. Rand Allingham, MD

#### Duke Eye Center, Durham, North Carolina

Exfoliation glaucoma (XFS) is the most common cause of identifiable open-angle glaucoma worldwide. This form of glaucoma is caused, at least in part, by genetic variants in an enzyme called lysyloxidase-like 1 (LOXL1). This grant project will study how some rare variants of LOXL1 that have been found to be highly protective for exfoliation glaucoma in the Japanese population affect LOXL1 protein function.

### LOXL1-Associated Pathomechanisms Predisposing to Optic Nerve Damage in Pseudoexfoliation Glaucoma

### Principal Investigator: Ursula Schlotzer-Schrehardt, PhD

### **University of Erlangen-Nurnberg, Germany**

This project aims to uncover pathomechanisms associated with dysregulation of LOXL1 that result in the development of exfoliation glaucoma. It tests the working hypothesis that XFS-associated risk variants of the LOXL1 gene are causally related to elastic fiber abnormalities in the lamina cribrosa and are influenced by pathophysiologic factors, such as mechanical stress and strain. This would further suggest that compounds stimulating expression of LOXL1 have a potential to reverse the adverse effects of disease and stress on elastic tissue function.

### Morbidity and Mortality in Patients with Exfoliation Syndrome: A Large Database Analysis – Utah Project on Exfoliation Syndrome (UPEXS)

### Principal Investigator: Barbara Wirostko, MD

### John A Moran Eye Center, University of Utah, Salt Lake City, Utah

This project will utilize a large Utah Population Data Base (UPDB) containing over 8 million lives to determine the impact exfoliation syndrome (XFS) has on lifestyle and death. A number of studies have reported the increased risk of systemic disorders in patients with XFS. Using the Utah dataset, it was just reported that XFS is associated

with an increased risk of pelvic organ prolapse, a major common disorder in women. To date there has been no report of increased mortality in people with XFS in specific populations. Expanded utilization of this powerful resource will facilitate the ability to study how XFS increases or potentially reduces risk of major disease.

### Role of Lysyl Oxidase-Like-1 (LOXL1) Proteolytic Processing in the Development of Pseudoexfoliation Syndrome (PEX)

### Principal Investigator: Fernando Rodriguez Pascual, PhD

### Centro de Biologia Molecular, Madrid, Spain

Genetic variations in the LOXL1 gene have been strongly associated with exfoliation syndrome (XFS). The protein product of the LOXL1 gene belongs to a group of enzymes which contributes to building the extracellular matrix (ECM) by promoting the cross-linking of elastin and collagens. LOXL1 plays an important role in the formation of elastic fibers, the ECM scaffold imparting elasticity to animal tissues. LOXL1 must be proteolytically processed in order to fulfill its biological function, but how this process occurs, what cellular enzymes (proteases) are involved, and whether this contributes to XFS disease are not yet known, and are the main questions this research will investigate.

### Targeted Deep Sequencing of the FLT1 – POMP – SLC46A3 Susceptibility Locus for Exfoliation Syndrome and Exfoliation Glaucoma

### Principal Investigator: Chiea Chuen Khor, PhD Genome Institute of Singapore

An earlier investigation studied 13,620 XFS patients from 33 countries and identified five new genes contributing to XFS susceptibility. The most significant newly identified loci include a gene encoded for a protein called POMP, which is responsible for ensuring cellular well-being by cleaning up harmful oxidative radicals and degraded proteins. The genetic association mapping to this POMP locus shows clear evidence of interaction with geographical latitude, whereby genetic risk conferred increases with distance away from the equator. This grant, utilizing investigators from six continents, will be used to fully sequence this gene locus. The Glaucoma Foundation 80 Maiden Lane, Suite 700 New York, NY 10038 www.glaucomafoundation.org T 212.285.0080 F 212.651.1888

A copy of The Glaucoma Foundation's annual financial report may be obtained upon request by writing to The Foundation at 80 Maiden Lane, Suite 700, New York, NY 10038 or by residents of the states listed below from the appropriate state agency. Florida: A copy of the official registration and financial information may be obtained from the Division of Consumer Services by calling toll-free within the State. Registration Number - CH7263. Registration does not imply endorsement, approval, or recommendation by the State. Maryland: Information filed under the Maryland Charitable Organizations Laws can be obtained for the cost of postage and copies from the Office of the Maryland Secretary of State's Office, Charities registration, PO Box 136, Jackson, MS 39205-0136, 601-359-1633. New Jersey: Information filed with the Attorney General of the State of New Jersey by calling 201-504-6215. Registration with the Attorney General does not imply endorsement. New York: A copy of the last annual report filed may be obtained upon request in writing to the Office of the Attorney General, Department of Law, Charities Bureau, 120 Broadway, New York, NY 10271. North Carolina: A copy of the license to solicit charitable organization or sponsor and financial information may be obtained from the Pennsylvania Branch, by calling 919-733-4510. Registration does not imply endorsement, approval, or recommendation by the State. Pennsylvania: The official registration and financial information of The Glaucoma Foundation may be obtained from the Pennsylvania Department of State by calling toll free, within Pennsylvania, 1-800-732-0999. Registration does not imply endorsement. Tripina: Official registration and financial information and financial information of The Glaucoma Foundation may be obtained from the Pennsylvania Department of Agriculture & Consumer Services, P.O. Box 1163, Richmond, VA 23209. Washington: Registration and financial information and be obtained from the Charities Division of Consumer Affairs, Department of Agriculture