

RESEARCH TOWARDS A CURE

Scott R. Christensen
President & CEO



We have prepared this interim newsletter to give you a view into the progress of our *Cure Glaucoma Now* program, specifically our focus on exfoliation syndrome (XFS), and the strides the TGF research program is making in its efforts to find a cure for this disease.

You will hear from Dr. Robert Ritch, our medical director who is a pioneer and world expert in the field, as well as from three of the researchers who are currently working on projects funded by The Glaucoma Foundation.

Exfoliation syndrome is an age-related systemic disease characterized by the production and accumulation of a whitish material in many ocular as well as non-ocular tissues. Worldwide, XFS is the most common identifiable cause of open-angle glaucoma, comprising the majority of glaucoma in some countries. Some 80 million people worldwide have the disorder.

We are encouraged by the significant financial support we have already received for this bold initiative to find a cure for exfoliation syndrome. The Glaucoma Foundation is uniquely positioned for this most ambitious project and welcomes underwriting support from the public and the medical community. We are very heartened about this journey to a cure.

Robert Ritch, MD
TGF Founder and Medical Director



Three years ago we made a decision to devote the efforts of The Glaucoma Foundation to curing exfoliation syndrome. I had decided that this was a potentially reversible disorder – that it was potentially curable or could be eliminated. And so we turned The Glaucoma Foundation's research funding and the Think Tank over to exfoliation syndrome.

I have been interested in this field for over 20 years, and long bemoaned the lack of interest, in spite of the fact that exfoliation is the single most identifiable glaucoma affecting millions of people around the world. Now the tide is turning. The first Think Tank devoted to XFS was in 2012, the second in 2013, and another was this year. As a result of this new focus we have significantly increased the number of people who are working in this disease and areas relating to this disease. We have gained more professional awareness and in the last three years have probably tripled the number of people doing research in this field.

Coming out of the Think Tank, we now have four working groups focused on different facets of exfoliation. One is looking at genetics and genomics, at gene environment and gene interactions. A second group is working on biomarkers – looking for characteristic molecules, looking at what molecules or compounds are elevated or decreased in the eye with XFS and systemic molecules or systemic markers that we can detect, even for a blood test for XFS. Another group is working on animal models, finding ways to create better models. And the fourth group is trying to explore further the mechanism in the production of exfoliation material by the cells in the eye, and growing cells in three-dimensional tissue culture to try to harvest exfoliation material. And if we can get exfoliation material, can we find ways to disaggregate it or eliminate it or can we find ways to stop cells from producing it?

The level of activity we have today is all very exciting!

TO
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Michael G. Anderson, PhD
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Dept. of Molecular Physiology & Biophysics
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Dr. Anderson in his lab

Several of TGF's current research grants aim at better understanding the role of the LOXL1 gene, which has been identified as clearly associated with the risk for exfoliation syndrome. Michael Anderson at the

University of Iowa is creating a new mouse model in which the human LOXL1 gene will be added into the mouse genome to test the role of LOXL1 in the eye and simultaneously create a lasting resource for future experiments. Here's what Dr. Anderson says:

The first step was finding that the LOXL1 gene was a major player – a discovery in 2007 that gave us a toehold to the next step. That is to figure out how LOXL1 promotes the pathology so we then can work to stop that progression.

It's actually shocking that exfoliation syndrome hadn't been studied by more researchers as such a huge number have the disorder. Exfoliation is also ripe for study because it's distinguishable from other glaucomas – there is more certainty about findings about this disease.

The Foundation has been fabulous – the new focus allows science to stage itself for a major hypothesis. In this transition to the next stage, tools and people have to be refocused. We need to go from asking "what genes contribute to exfoliation" toward "how does LOXL1 contribute to exfoliation." In the process, we can test new ideas and bring cures closer to reality. Unfortunately, the NIH is not good at refocusing; TGF has that longer vision.

A small grant can feed a big idea. Our challenge is to develop a mouse model that has as many of the disease features as possible. That's one of the missing tools that is needed in the field and will make it easier for other new people to enter this field of research.

I think The Foundation's new focus is playing a huge role in bringing us closer to finding a cure for exfoliation syndrome. I'm very grateful for the support.

Terete Borrás, PhD
Professor of Ophthalmology
Gene Therapy Center
University of North Carolina School of
Medicine at Chapel Hill



Professor Terete Borrás

My laboratory is interested in developing gene therapy protocols for the treatment of glaucoma. This includes developing effective gene

glaucoma is extremely important. Glaucoma is a broad field and focusing on the exfoliation type of the disease will bring the possibility of finding a cure. The new focus stimulated my thinking and set me into gear to apply the tools I have in the lab towards the achievement of this goal.

Seed money grants, like those TGF funds, are small – to develop just a given idea. These grants are ideal to target a specific goal using the specific expertise of a given laboratory. The overall projects of my lab use gene transfer viral vectors to deliver different amounts of normal and mutated protein to specific cells in living rats, monitor their IOP and look at their effect on eye tissues. This technology seemed totally suitable to initiate a project on the search for the treatment of exfoliation glaucoma.

delivery technology to glaucoma-related eye tissues. The new emphasis of The Foundation on exfoliation

My expertise is gene therapy for glaucoma. My final goal is to be able to treat exfoliation by delivering the corrected LOXL1 protein into specific cells of the iris that are suspected of producing the exfoliation material. For that, we would first need to reproduce the formation of the exfoliation material in an experimental system, so we could then see it disappearing after our gene delivery treatment. If the iris is really producing this material, we have the

tools to deliver the good gene to these cells. We believe the results of our experiments will provide a first glimpse into the direct involvement of LOXL1 with the known causative effects of XFS.

I am really enthusiastic. The Glaucoma Foundation is unique in letting us work on one aspect of the whole. These are special projects to test things that haven't been tested – it's a very good way to go.

Mansoor Sarfarazi, PhD, FARVO
Head, Molecular Ophthalmic Genetics
Laboratory, Divisions of
Ophthalmology & Surgical Research
University of Connecticut Health Center
(UConn Health)



Dr. Mansoor Sarfarazi with his Research Assistant, Roshanak Sharafieh, PhD, CG(ASCP)

I am very encouraged by The Glaucoma Foundation (TGF) that has actively been funding researchers like myself to initiate types of research projects that have less of a chance of getting funded by the NIH. Without TGF's support, my research investigation into the genetic causes of exfoliation syndrome (XFS) would not have been possible at all.

The funding that we received from TGF allowed us to simultaneously screen over 25,000 different genes in a group of 73 XFS-affected subjects. To the best of my knowledge, this is the largest group of XFS families and sporadic subjects that have ever been screened for gene mutations in such a large number of genes.

Although several genes have been shown to be "associated" with XFS, so far no actual XFS-causing genes have been identified. We believe that identification of one or more specific XFS-causing genes through our conducted study will pinpoint the first gene that is involved in the etiology of this condition. If so, this will open up many new research ideas and perhaps, lead us to various biochemical-biological pathways that are directly involved in the etiology of XFS.

Even when the first gene for XFS is identified, we still need to understand its biological properties and further investigate how such a gene, when mutated, leads to the XFS phenotype. The science of finding a cure is complicated and requires expertise from many different disciplines. Therefore, there are urgent research and development requirements before any cure can be identified.

Unfortunately, exfoliation syndrome has been largely ignored by major funding agencies such as NIH. Other organizations, like The Glaucoma Foundation, have provided the opportunity to find answers and eventually cure conditions like XFS, which afflict our worldwide aging population. In turn, TGF depends highly on donations from Samaritans and caring people who may have or know someone affected with these types of devastating eye disorders.

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