GLAUCOMA
RESEARCH FOUNDATION

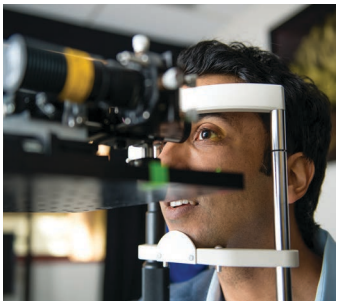
CATALYST FOR A CURE REPORT

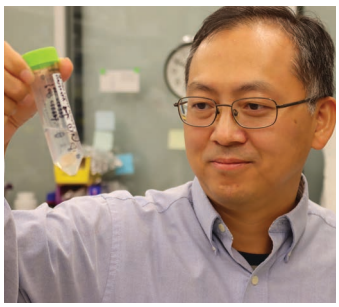
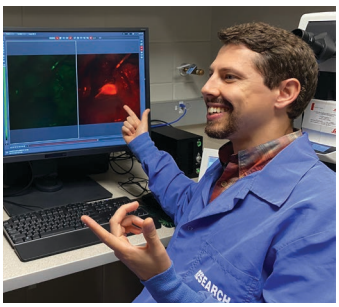
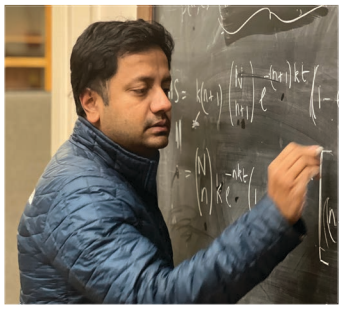
TWENTY YEARS OF INNOVATION

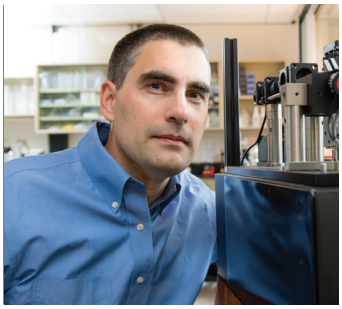
2002 TO 2022

A GUIDE FOR COLLABORATIVE RESEARCH







SAN FRANCISCO, CALIFORNIA

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Collaboration Accelerates Medical Research
A "How to" Manual

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SAN FRANCISCO, CALIFORNIA

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Front Cover: Catalyst for a Cure Principal Investigators (L-R):
Row 1: Jeffrey L. Goldberg, MD, PhD (CFC 2); Anna La Torre, PhD (CFC 3);
Vivek Srinivasan, PhD (CFC 2)
Row 2: Milica Margeta, MD, PhD (CFC 4); Yang Hu, MD, PhD (CFC 3);
Sandro Da Mesquita, PhD (CFC 4)
Row 3: Karthik Shekhar, PhD (CFC 4); Monica Vetter, PhD (CFC 1); Alfredo Dubra, PhD (CFC 2)

Dedicated to our scientists, donors, and volunteers
committed to finding a cure, and to glaucoma patients
who inspire our work each and every day.

With very special thanks to Steven & Michele Kirsch and
Ted & Melza Barr for their extraordinary support
and enduring partnership.

ABSTRACT

The unique Catalyst for a Cure (CFC) collaborative approach to basic medical research was launched in 2002 with the first CFC. More than twenty years and four CFC teams later, this book provides our proven step-by-step recipe for successful research collaborations along with summaries of results and an extensive bibliography. As more institutions, including the National Eye Institute, fund collaborative research initiatives, we encourage you to learn from our experience and perfect your own collaborative approach to accelerate medical research for better treatments and cures for glaucoma, neuro-degenerative diseases like Alzheimer's, and other debilitating diseases.

Collaboration Accelerates Medical Research
A "How to" Manual

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**Active, continuation contingent on annual reviews and approvals*

FOREWORD

Welcome! This book tells a story of scientific success, of how the Catalyst for a Cure (CFC) transformed the way we think about biomedical research. As I think about the 20 years that have passed since I was fortunate enough to join the first CFC, I also reflect on what I have learned about progress in science. When we break it down, science is really all about time travel. After all, even as we push forward towards innovation, every new viewpoint evolves through a lens focused ever deeper into the journeys of those who came before us. To understand what is in front of us often necessitates referral to yesterday's results. Finding truth in science is a constant tug of war between what we are trying to see and what we thought we understood already. In the end, we hold on to what holds water over time and leave behind the rest. Through this process of iteration, reconciliation, and abandonment, science brings us to greater understanding and another step forward.

Today as I time travel in celebration of CFC, I am struck by just how much we got right. By "we" I mean both the scientists and the wonderful and diverse community of people that support us. There are plenty of accolades to go round. The CFC itself remains a triumph of collaboration, proving that, with the proper ingredients, researchers are more effective working as a true consortium rather than a loose affiliation with independent ideas and approaches. We got the ingredients right as well. The backbone of the CFC is accountability at all levels. Each iteration of the CFC includes an expert advisory board of partners and stakeholders that provides oversight, mentorship, and guidance. Continuation of the generous funding so critical to CFC innovation is contingent upon a rigorous annual review and measurement against meaningful milestones. These are designed with intention to move the research ever closer to our goal: new treatments to restore vision and protect against the devastating neurobiological effects of glaucoma.

We got another special ingredient right as well. The CFC at its roots is all about people. From the start, an intimate partnership with patients and their families and friends affected by glaucoma has defined the CFC. Their basic need for new treatments and their commitment to support innovation in the search itself have fueled scientific success. The CFC began with an exciting collaborative vision shared between Steven and Michele Kirsch and Glaucoma Research Foundation. The result of this first iteration was an amazing 11-year run that produced some of the most highly cited publications in glaucoma research. About mid-way through, Ted and Melza Barr with son Terence joined our efforts, providing critical support that allowed CFC to make new forays.

The Kirschs' generosity continued with the third CFC, for which I was honored to serve as chair of the scientific advisory board. For the fourth CFC, now also at work, the Barr family has once again taken a leadership role in providing support as CFC branches out to find commonalities among age-related neurodegenerative disorders. By doing so, we hope to impel a quantum leap forward in finding new ways to restore vision in glaucoma.

Here is one last lesson, as I look back. Successes are far sweeter and mistakes less painful when experienced as a team. This book tells how we created consortiums of like-minded people that became so much more than the sum of their parts. These pages tell the story of a paradigm shift, one I know will inspire others to truly collaborative efforts. Stories like this constantly evolve into new chapters and new beginnings. Where will CFC go next on its exciting journey? Well, only time will tell.

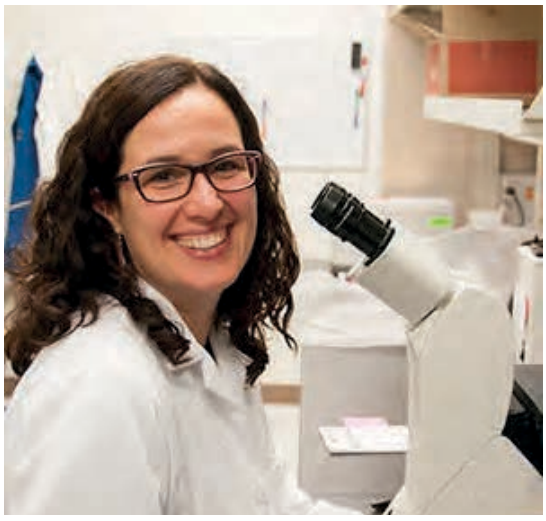
David J. Calkins, PhD
Vanderbilt University Medical Center

INTRODUCTION

After twenty years and four Catalyst for a Cure initiatives, Glaucoma Research Foundation is sharing its experience and results in this "How to" manual with the hope that more foundations and institutions will incorporate collaborative research in their medical research portfolios. Truly collaborative research is highly productive and rewarding for all concerned – patients, donors, doctors, and scientists - all looking for better treatments and cures. Collaboration just works! But it requires unique planning and execution. Hence this book.

Collaboration is the future of medical research. It accelerates research by creating an environment for innovative thinking and rapid testing of new ideas. It brings together scientists and clinicians with diverse backgrounds to challenge each other's thinking and develop new approaches to understanding the underlying mechanisms of disease, with the goal to prevent and cure debilitating diseases. Done as we have done it, this collaboration engages patients in the process as well, for the benefit of all.

In this book you will find specific steps for a successful research collaboration, from defining the overarching goal to identifying an advisory board and selecting investigators, and then recognizing when it's finished. The history of GRF and its dedication to collaborative research illuminates the process with specific examples and observations from participants. Actual Catalyst for a Cure collaborations are shared with details of funding, research results, and bibliographies. We urge you to adopt this proven model and to incorporate your own improvements to optimize it for your unique environment.



Anna La Torre, PhD, brings her expertise in stem cells and organoids to the CFC 3 Vision Restoration.

Jeffrey Goldberg, MD, PhD, at the microscope with Andrew Huberman, PhD, discovering new glaucoma biomarkers in CFC 2.

Part I

How We Do It

How it Works:
The Essential Elements and Process of the CFC Model – in Brief (Details Later)

"This pioneering approach to disease research should become a model for research in other diseases, including other neurodegenerative diseases."

- Scientific Advisory Board, CFC 1

The first members of the CFC Scientific Advisory Board recruited for their expertise in ophthalmology, genetics, neuroscience, cell biology, and neuroimmunology. Left to right: Martin Wax, MD, Constance L. Cepco, PhD, Moses V. Chao, PhD, Jack P. Antel, MD.

The Catalyst for a Cure (CFC) research model brings together the essential scientists within a framework that provides accountability while offering the opportunity for creative teamwork.

- Skilled investigators with a fresh outlook
- Representing diverse fields
- Focused on specific goals
- Committed to collaboration
- Required to report regularly
- Supported with expert oversight and mentoring
- Funded long enough to develop significant results

With sponsorship and funding as a given, the essential elements of the CFC model are two small groups of individuals: (1) the scientific advisors, who form the Scientific Advisory Board (SAB) and (2) the principal investigators (PIs), the CFC research team.

The scientific advisors:

- Each CFC research initiative (four have been launched to date) has had its own SAB
- SAB numbers have been variously set from four to seven advisors
- The advisors are eminently qualified and highly regarded senior research scientists
- They can imagine the success that might result from this non-traditional approach

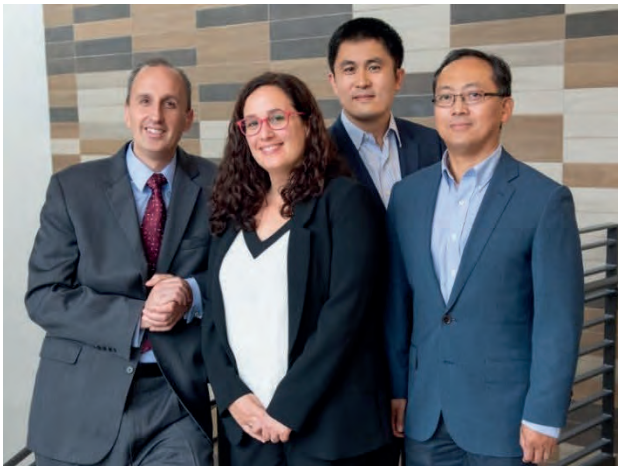
The principal investigators:

- Each CFC research team to date has consisted of four scientists
- They are from different laboratories and represent different disciplines
- They are early in their careers but have promising training and demonstrated expertise
- They are willing to commit themselves and their laboratories to a collaborative structure

The CFC Consortiums – Principal Investigators (2002 to Present)

CFC 1 – Redefining Glaucoma
2002 - 2012

CFC 2 – Biomarker Initiative
2012 - 2018



CFC 3 – Vision Restoration
2019 - Present

CFC 4 – Prevent and Cure Neurodegeneration
2022 - Present

The CFC process, very briefly, is as follows:

- Initial term – set at 3 years, each year's funds dependent on required reports and approvals
- Launch – PIs and advisors meet, set preliminary objectives, agree on year-one agenda
- During term – PIs communicate often, work together, report to SAB at required intervals
- During term – SAB members are available to PIs, meet with PIs no less than annually
- Annually and at term's end – SAB reports to sponsors, may recommend continued funding

The launch meeting for CFC3 with the Principal Investigators and their Scientific Advisors to set preliminary goals and discuss plans for the first year of the collaboration.

Left to right: Yang Hu, MD, PhD, Zhigang He, PhD, BM, Larry Benowitz, PhD, Tom Brunner, Jeffrey Goldberg, MD, PhD, Anna La Torre, PhD, Derek Welsbie, MD, PhD, Valeria Canto-Soler, PhD, David Calkins, PhD, Xin Duan, PhD.

Photo by Nancy Graydon

Significant Goals
And How We Set Them

"The CFC consortium has reshaped the direction of glaucoma research."
- Scientific Advisory Board, CFC 1

Launching a truly collaborative research effort is not a trivial exercise. It draws upon talented scientists and valuable resources. It merits a meaningful goal, not merely an obvious incremental advance. A successful outcome should be a significant addition to the state of science.

What's more, setting a significant goal has indirect but related benefits. It will:

- Attract the attention of senior scientists for the scientific advisory board
- Engage the interest of bright, ambitious candidates for the investigative team
- Not so incidentally, help to involve potential supporters and donors

For the four Catalyst for a Cure initiatives launched to date, we have defined the goals using information and guidance from a variety of sources. To set the general direction and then narrow the focus we have drawn from:

- Historically developed and recognized needs
- Internal management and board of directors' discussions
- Guidance from a specially convened meeting of our research committee
- Discussions with constituents, patients, and supporters
- Informal gatherings at professional conferences
- Formal symposiums created to review the science in a proposed target area
- Discussions of and with the scientific advisory boards at and after recruitment
- SAB and PI discussions at team launch meetings

CFC 1 The objective of the first CFC consortium, "Redefining Glaucoma," arose naturally from our long-recognized need to understand the basic mechanism and progression of glaucoma. The work from pilot grants and early collaborative efforts had produced successes but a broader and deeper understanding of the nature of the disease was still missing from the body of knowledge. A tentative statement of that objective was improved by the scientific advisory board after it was established, then enhanced by the advisors and the newly selected principal investigators at the team's launch meeting.

CFC 2 Emboldened by the success of the first CFC initiative, we convened a formal symposium, a "catalyst meeting," to consider next steps. The topic was *"Retinal Ganglion Cell Deterioration in Glaucoma."* A consensus at the symposium and the urging of constituent physicians and patients/supporters set the general direction of the second CFC team, the Biomarker Initiative. As always now, at the launch meeting, the members of the scientific advisory board for this initiative and the principal investigators refined the stated goal.

The launch meeting for CFC2 included both the Principal Investigators and their Scientific Advisors to outline the consortium's initial research objectives to identify new glaucoma biomarkers. The investigators are joined by GRF President and CEO, Tom Brunner (left) and SAB Chair, Martin Wax, MD (right).

Photo by Phillip Van Nordstrom

CFC 3 The goal of CFC 3, "Vision Restoration," arose both naturally and audaciously. GRF leadership organized a gathering of the foundation's research committee members (outside advisors, very senior research scientists, and physicians) who were attending a scientific meeting. They decided it was time to leverage CFC's results to date, and to answer the call of constituent physicians and patients who had no recourse for vision that had already been lost. At the launch meeting and beyond, the principal investigators have taken a strong lead in defining the specific objectives and experiments that will contribute to achieving their goal.

GRF Research Committee met in November 2017 to decide on the overarching goal of CFC3 – vision restoration. Members included: Left to right: David J. Calkins, PhD, Cynthia Grosskreutz, MD, PhD, Robert Stamper, MD, Adrienne Graves, PhD, Joel Schuman, MD, Tom Brunner. November 10, 2017 (New Orleans, LA)

The SAB for CFC3 met in July 2018 to discuss the most promising areas of investigation for vision restoration and noted possible PIs. It was agreed that a Request for Applications would be distributed to the vision science research community. Photos by Nancy Graydon

CFC 4 The goal of the fourth CFC initiative, to Prevent and Cure Neurodegeneration, was inspired by a purposeful longtime supporter. It also sprang naturally from the nature of the CFC model and the curve of its progress. We staged another special-purpose catalyst meeting, "Solving Neurodegeneration," to review the latest research results and consider opportunities for collaboration on common roots of different neurodegenerative diseases. Consensus at the symposium confirmed the potential of such an effort and, following later discussions, sponsoring boards of directors signed on in support of another audacious initiative. At launch, both scientific advisors and principal investigators enthusiastically drafted the details of the first year's work.

In short, goals can be set in a variety of ways. Done right, involving and engaging the imagination of the key participants, setting meaningful goals is a prelude to significant achievement.

The "Solving Neurodegeneration" Catalyst Meeting held virtually in April 2021 led to a published white paper, and a unique multi-disease CFC to prevent and cure neurodegeneration (CFC4). In addition to the general session with all 32 participants, break-out sessions allowed for additional focused discussions.

Three Premises to Keep in Mind
They Ground the Model and Guide the Process

"The four groups represent a model for how research can be pushed forward through collaborative and multidisciplinary approaches."

- Scientific Advisory Board, CFC 1

"The team science approach…revealed synergies and enabled progress that could not have been achieved by any individual laboratory alone."

- Principal Investigators' Final Report, CFC 2

Underlying the CFC model for collaborative research are three premises to keep in mind:

- True collaboration is essential
- Multidisciplinary teams spark more ideas
- Significant results require sustained effort

True collaboration is essential

True collaboration is open and inventive. It liberates creative spirits in a dynamic working relationship. It re-ignites the sense of fun that a curious child enjoys. Truly collaborative investigators leave their traditional research silos, reaching out to investigators in other laboratories. They pose the questions that are puzzling them to others who might have an inkling. They imagine projects they can do together, better than what they might do alone. They discuss what they've learned, and how they learned it, early and often. They share ideas, data, slides, mounts, tissues, and scarce materials. They work on publications together, giving credit where credit is due.

It requires trust. The CFC model structure enables that trust (1) by engaging teams of investigators who can conceive that real collaboration might be useful, (2) by obtaining their commitment to the process and to each other, as well as the research objective, and (3) by providing the means and incentives for the investigators to meet often and communicate regularly.

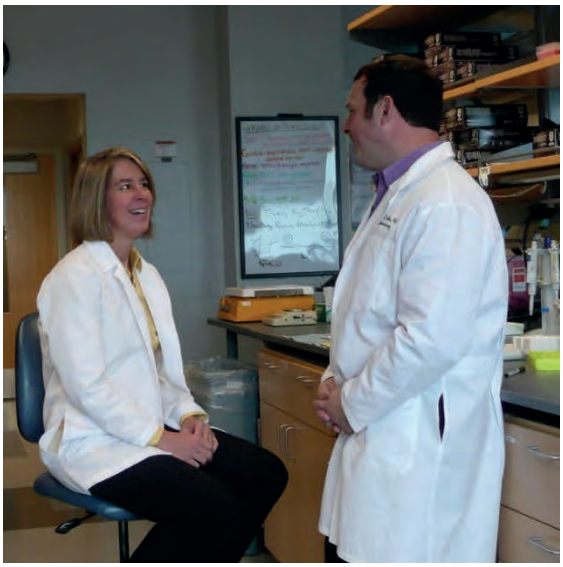
Multidisciplinary teams spark more ideas

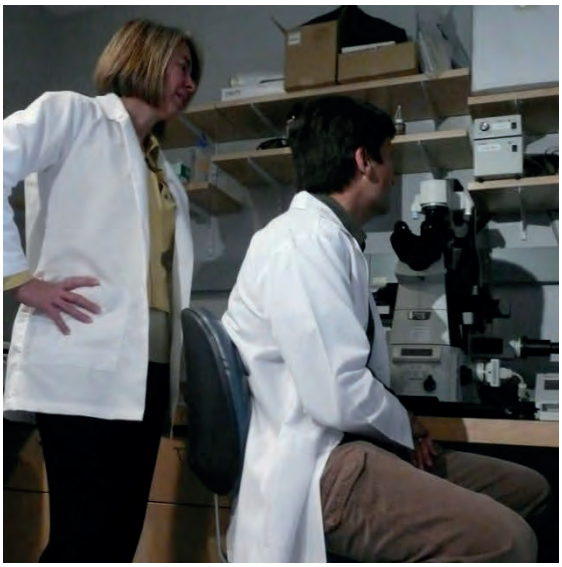
Just as outside experts can provide a fresh take on the subject at hand, experts in related but different fields can provide different perspectives as well as different skills and tools to advance a project. This is particularly the case where investigators are still working with processes and mechanisms not fully understood. Looking from a different angle or thinking from a different mindset offers the prospect of new insights or better questions.

Selecting the right combination of disciplines for a common focus, the job of the scientific advisors, requires imagination as well as an advanced level of scientific expertise. The investigators themselves are usually intrigued by the prospects of working with team members from different specialties and they relish the opportunity to learn from experts outside their own niches.

Significant results require sustained effort

GRF's early history of sponsoring catalyst meetings and pilot grants led to our conviction that short-term projects provide inadequate time for the development of significant results. The CFC model establishes a relatively longer three-year term with each year's funding contingent on annual reviews and approvals. Further, in practice, we have been prepared to renew CFC grants for additional terms and have done so when team progress and possibilities compel it.





The annual CFC grant allowed for travel funding so the team members could visit each other's laboratories to facilitate collaboration. Members of the CFC1 team meet at the lab of David J. Calkins, PhD, at Vanderbilt University (2012).

Finding and Engaging the Scientific Advisors: CFC's Advisors Have Volunteered Their Time

"When I was first approached, I thought someone had made a mistake."
- Jack P. Antel, MD, Scientific Advisory Board, CFC 1

"It's like having a panel of experts to think about what we propose, sometimes having one say, "I tried that a long time ago and…."
- A principal investigator, CFC 3

With a meaningful goal, underlying premises in mind, and funding assumed, the next step in the process is enlisting the first set of key players, the scientific advisors**.** Their CFC assignment, as the Scientific Advisory Board (SAB), is to:

- Select the principal investigators (PIs) for the consortium
- Mentor and oversee the collaboration
- Review progress annually

The assignment dictates their qualifications:

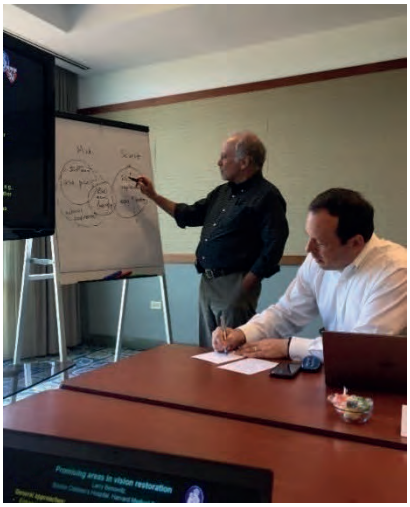
- A senior level of research expertise
- Some knowledge in the field to be investigated
- The ability to envision progress that might be made with a non-traditional approach

We have identified potential scientific advisors for the CFC in various ways:

- On our Research Committee, already outside advisors to the foundation
- Suggested by scientist friends and supporters on our committees or our board
- Among senior research leaders our leadership has met at professional meetings
- By word of mouth, as we asked specialists in the field to suggest likely candidates
- Among scientists and physicians who have participated in our Catalyst symposiums
- Most recently, among PIs from earlier CFC initiatives

The candidates we have identified for CFC scientific advisory boards have come from across the United States, Canada, and the United Kingdom. They are eminently qualified, successful, and highly regarded. They are busy but, after explaining the CFC model to the most likely candidates, we have succeeded in engaging them and all have volunteered their time, because they are:

- Intrigued by the possibilities for truly collaborative research
- Eager to be part of a potentially important research success (those significant goals)
- Interested in keeping up with developments in their own and related fields
- Glad to meet and work as colleagues with other eminent research scientists
- Keen to learn and to teach



Left: Larry Benowitz, PhD and David J. Calkins, PhD at the Advisory Board planning meeting for the CFC3. Right: Members of the CFC4 Advisory Board at the July 2022 launch meeting with the principal investigators: Adriana Di Polo, PhD and Shane Liddelow, PhD.

Photos by Nancy Graydon and Michelle de Elizalde, DVM

In Their Own Words:
Scientific Advisors Say Why They Volunteer

We recently asked several of our scientific advisors, given their professional eminence and the demands on their time, why they agreed to serve on a CFC advisory board. They answered as follows:

"I started as an SAB member in 2000 by invitation by Sarah Caddick. The SAB was highly experienced in neurobiology and in mentoring young investigators. Several high-ranking scientists participated. They included Marty Wax, Eugene Johnson, and Martin Raff, whose opinions are frequently sought after by other foundations. Their participation and experience were a huge attraction.

The other reason for joining the CFC effort was the innovative way that science was being conducted. The original CFC had four young investigators from four different institutions. One advantage of this strategy is to have younger investigators as part of the CFC. Each had not worked on glaucoma per se, but each brought different approaches and new ideas to the CFC. They synergized their interests to demonstrate that the 'whole is greater than the sum of the parts.' I was honored to participate as an advisor to the CFC."

- Moses V. Chao, PhD
NYU Langone Medical Center, New York, NY
SAB Chair, CFC 1 – Redefining Glaucoma

"Very good question—in brief, the opportunity to help a foundation I deeply believe in, and the opportunity to stay connected to some of the brightest and best scientists in all of glaucoma research."

- Jeffrey L. Goldberg, MD, PhD
Stanford University School of Medicine, Stanford, CA
Principal Investigator, CFC 2 – Biomarker Initiative
SAB Chair, CFC 3 – Vision Restoration

"The Catalyst for a Cure program of GRF funds important and exciting scientific work that can lead to new understanding, diagnostics, and treatments for glaucoma – perhaps even a cure. The opportunity to be involved in the advisory board allowed me to interact in a meaningful way with the researchers working on the development of new biomarkers for glaucoma that could enable detection of glaucoma and its progression earlier than ever before. This is important, as the earlier glaucoma is treated, the better progression of the disease can be avoided, and vision can be saved. Additionally, early detection means that glaucoma can often be treated less aggressively throughout an individual's lifetime, exposing that person to less risk in the process."

- Joel S. Schuman, MD, FACS
NYU Langone Health, NYU Grossman School of Medicine
SAB, CFC 2 – Biomarker Initiative

"When I was first approached, I thought someone had made a mistake. I was unaware of Glaucoma Research Foundation, and I wasn't a specialist in glaucoma. But I was impressed when I learned that GRF was extremely committed, had done its homework, identified a significant problem in glaucoma, and laid out a rather novel way to get a group of scientists to work together. It was a serious undertaking, bringing people in from outside glaucoma for objective opinions. The novel structure, the qualifications of the others selected for the advisory board, and the focus on the progressive loss of nerve fibers and myelin in the optic nerve represented a coming together of interests for me.

I never regretted having committed. The scientists were given leeway to address the problem in novel ways, but they were expected to meet quality standards. The model worked well and I learned a lot, from the scientists who were young when they started and from the other members of the board, amazing people such as Marty Wax and Martin Raff.

Congratulations to GRF for devising the Catalyst for the Cure program and for sustaining the effort through the multiple cycles."

- Jack P. Antel, MD
Montreal Neurological Institute, McGill University, Montreal, CA
SAB, CFC 1 – Redefining Glaucoma

"To be truthful, I said yes because, with Sarah Caddick, I assembled the first Scientific Advisory Board for the Catalyst for a Cure. And frankly, it's hard to ask eminent scientists to serve on a board if you do not!

However, to address the more relevant question of the value of a superb SAB, there are several aspects to consider. When we created the Catalyst for a Cure, it was a fundamental change in the way research was conducted among a group of scientists. The premise of selecting the best scientists who would work together as a consortium rather than competitors in isolation was novel. GRF should be deeply proud that model has since been validated as a productive medical research model subsequently adopted by other institutions including the National Institutes of Health.

Among the distinctions of our model is that the candidates were not selected by application but rather identified and selected by fully independent senior scientists from different fields. It was the caliber of the young CFC members chosen and their specific mission that attracted prominent senior scientists to serve on the CFC's Scientific Advisory Board. It is particularly noteworthy that we intentionally sought out CFC scientists who did not have any expertise in glaucoma, but who we hoped would focus their future research endeavors in our field. Fortunately, many have. I have been gratified to receive notes from several that say the CFC significantly changed their careers and I suspect that future CFC members will enjoy the same attraction to a lifelong commitment in glaucoma research as those in the first two CFCs whose SABs I chaired or was a member.

Finally, I would be remiss if I didn't mention that the CFC was only made possible by the vision of GRF founders (Bob Shaffer, Dunbar Hoskins, and Jack Hetherington), the capability of its leadership (Tom Brunner), and the resources of generous donors such as the Kirsch and Barr families among many others."

- Martin Wax, MD
CEO and Chairman, Mimetogen, Inc., Montreal, QC
SAB organizer, CFC 1 – Redefining Glaucoma
SAB Chair, CFC 2 – Biomarker Initiative

Selecting the Principal Investigators: Senior Level Networking Plus a Process (Mostly)

[Editor: Ten years ago, you famously said, "It was for the money."]
"Yes, and I'd still say that. I was recently asked what got me interested in glaucoma. It was my first grant!"
- Nicholas Marsh-Armstrong, PhD, Principal Investigator, CFC 1

"The selection process was very different from anything that I had experienced before. It was very fast, from nomination to selection, which is unusual in science, but I think it was a good thing. It got people working together quickly."
- Principal Investigator, CFC 1

An early photo of the first CFC team (left to right): Philip Horner, PhD, David Calkins, PhD, Monica Vetter, PhD, and Nicholas Marsh-Armstrong, PhD.

The first job of the CFC scientific advisors, working together as the SAB, is to select the principal investigators. They are looking for scientists who are:

- Relatively early in their careers, offering the possibility that an intriguing problem might catch their attention and shift a new generation to work on it
- Well-trained and have already demonstrated research expertise
- Willing and able to commit themselves and their laboratories to work in a collaborative structure
- Representative of the needed disciplines, outside the mainstream of the research topic, ensuring that new and valuable expertise will be brought to bear
- Goal-oriented

To help identify and recruit the scientists, the SAB has the use of:

- The roughly defined research objective
- A general understanding of the several disciplines that should be included
- Committed funding for an initial three-year term
- Their professional associations among leading and senior scientists and their ability to network within and across disciplines at the same senior level
- Staff support from the sponsoring foundation(s)

Deliberately NOT used in our search for CFC principal investigators is the classic request for proposals (RFP). RFPs typically generate the return of lengthy grant proposals from an assortment of aspirants anxious to pursue their own research interests and hoping to fit those to the request. The scientific advisors, understanding the nature of the CFC, know that won't work.

Instead, CFC's scientific advisors have typically identified their peers, senior level scientists in the relevant disciplines. Then they have used their networking skills to reach those scientists, within and across disciplines, to explain the opportunity and ask them to suggest promising candidates**.** Senior level networking at its best, with fortuitous encounters along the way, has provided the rosters of potential CFC investigators.

One exception: In the case of one CFC team, CFC 2, those fortuitous encounters along the way happily preempted much of our usual process. Three of the four principal investigators were involved in and distinguished themselves at the catalyst meeting that roughed out the objective for the second CFC initiative. They also provided most of the multidisciplinary components expected to contribute to achieving the goal. The scientific advisors, several of whom were at the same meeting, thus had three parts of a highly promising quartet almost in hand. It only remained to search out the fourth investigator in a complementary discipline who would complete the team.

Our typical process: For three of the CFC's four initiatives to date, selection of the PIs has relied on a longer step-by-step process, now fairly well-defined. Following identification of usually two dozen or more possibilities through their networking, the SAB and foundation staff next:

- Gather more information about the candidates (biographies, publications, research)
- Send the likely prospects a Call for Scientific Proposal or an RFA (request for application) which includes a description of the concept and purpose of the proposed consortium and outlines the application requirements:
    - A single page proposal that explicitly includes:
        - A brief description of scientist's background and training
        - Statement of scientific expertise and its relevance to the topic
        - Demonstration or evidence of collaboration
    - Complete CV, contact information for two professional references, and the candidate's anticipated ability to attend the planned launch meeting scheduled a few months out
- Publish the RFA at the same time through the Association of University Professors of Ophthalmology and other applicable sites
- Review responses to select the finalists
- Interview the finalists and select the principal investigators

With the selection of the principal investigators, the two teams are in place to begin the research initiative.

Launching the Research Initiative, Reviewing the Terms of Engagement

"Being asked to tackle a tough problem through unconventional means forced me and others in the group to go places where we would not have dared (or been able) to go without the freedom that this structure afforded."

- Principal Investigator, CFC 1

Our CFC research initiatives are launched at a two-day meeting. That usually begins with a festive dinner where major donors and foundation directors join in to celebrate the selection of the principal investigators and the beginning of their research efforts. The next day, it's all day. Consider the challenges:

- The four members of the new "team" had never met until the night before
- They don't know each other's personalities, circumstances, skill sets, or lab resources
- They are expected to begin working together closely to achieve the initiative goal

The PIs hold the first meeting of the day, getting to know each other and assessing the possibilities.

The formal launch meeting, with all CFC hands on deck, consumes most of the rest of the day. Its purpose is to:

- Launch a team of bright and purposeful adventurers in high spirits
- Maintain accountability for the investigators, their advisors, and those who fund their efforts

To accomplish that purpose, and to cover the details required for execution, our agenda is a full one:

- Introductions and welcome from the SAB and the sponsoring foundation(s)
- A brief review of the grant conditions and investigator responsibilities, including focus on the overarching goal, active collaboration (meetings, teleconferences, updates), semi-annual and annual progress reports to the SAB, annual meetings, and annual reports on expenditure of grant award funds
- A reminder about the nature of the collaboration expected of the principal investigators – probably the most important item on the agenda.
- A general discussion about the nature and meaning of the initiative's goal
- Suggestions from the advisors for possible investigative approaches and interim goals for accountability, and another reminder that the advisors are there to question, recommend, and advise, not to direct
- A reminder to bring to the SAB or to the foundation(s) any special requests for equipment, consultants, or other needs for possible additional funding
- A request for a one- or two-page report within 30 days outlining the team's planned approach and achievable goals for the first year. This report is required to release funding for the year.

Members of the CFC4 team met for the first time in San Francisco in July 2022 at the "launch meeting" to discuss focus areas and priorities for the first year of the collaboration.
Left to right: Humsa Venkatesh, PhD, Karthik Shekhar, PhD, Milica Margeta, MD, PhD, and Sandro Da Mesquita, PhD.

If the year ahead includes professional meetings that most of the participants are likely to attend, interim meetings-at-meetings may be suggested for quick updates.

Again, accountability and all the details that contribute to it are essential, but for this launch meeting what matters most is the takeaway spirit of the day: This is special. The money is committed, the mission is set, the scientists are ready…for something different. Maintain that enthusiasm! This is not just about joining forces to get funding, or to pool scarce lab material, or to write an article. This is to be a remarkable collaboration, bringing diverse skills and experience to do research that no single lab could accomplish on its own. The scientists have the authority to set their own research and experimental goals and to take risks, to fail early and often, to re-set those goals when necessary, and move on to new possible solutions.

Tom Brunner, GRF President and CEO, would meet with CFC investigators at meetings including the American Academy of Ophthalmology Annual Meeting (Left with Dr. Jeffrey Goldberg) and the Association for Research in Vision and Ophthalmology or ARVO (Right with Dr. Alfredo Dubra).

The Principal Investigators:
Figuring out Collaboration

"Prior to CFC I was not doing anything related to disease, nothing translational. My pitch was that I would be the team member who could contribute [my particular] understanding. And, yes, that's how it worked."

- Xin Duan, PhD, Principal Investigator, CFC 3

"I can honestly say, the best science that my lab has done has been in collaboration with people who don't do what we do."

- Shane A. Liddelow, PhD, Scientific Advisor, CFC 4

True collaboration in a highly competitive (sometimes cut-throat) field where success depends on the insights of individual minds is truly different, but we've discovered true collaboration isn't all that hard. Particularly when the right pieces are in place:

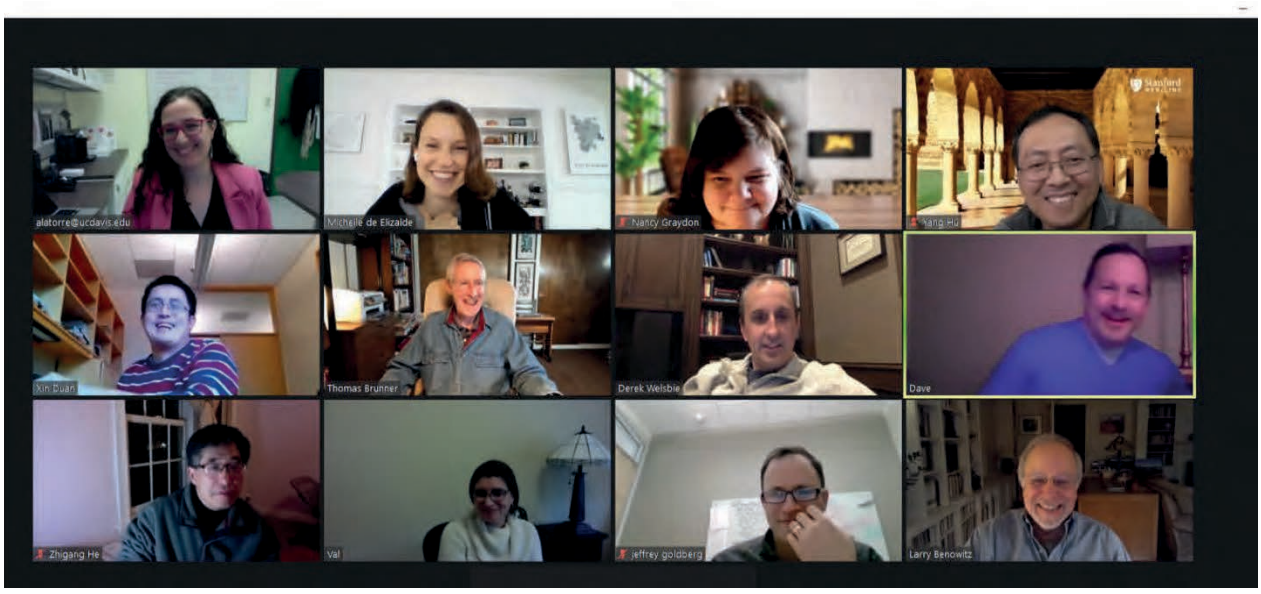
- The right research scientists
    - They have provided evidence of previous collaborative work on their applications
    - They have explicitly committed to working together for this initiative
    - They have professional reputations for integrity and responsibility
    - They become creative when confronted with challenges to teamwork

- The right framework
    - CFC is driven by the concept that true collaboration speeds discovery
    - CFC engages scientific advisors who are enthusiastic about the team's collaboration
    - CFC expects frequent team communication, sharing, combined efforts and reports
    - CFC apportions funds for travel to each other's labs and team meetings
    - CFC funds the researchers equally to reduce that element of competitiveness

With the right pieces in place, collaboration works and feeds on itself to get even better.

When they began work in 2002, prepared to meet the design expectations, CFC 1 promptly raised the bar. Less than 6 months in, the team decided that the mandated annual meetings weren't enough. They took advantage of conferences that were already on their mutual agendas. They convened additional meetings for CFC purposes. They expanded upon regular telephone conference calls by sharing data and discussing findings as a group using network meeting software, which was fairly primitive by today's standards. They participated in the purchase of a server to provide a central repository for data files and other information. They managed a virtual bank for tissues from their animal models. When samples of tissue from the same animal were needed for different experiments in different labs, they coordinated efforts so that tissue prepared in one lab was openly shared with the other labs as needed.

Each of the teams that followed has found this a useful pattern, adding their own variations and taking advantage of improvements in technology. That became critical for CFC 3, confronted with COVID-19 lockdowns. For a time, their labs were closed, then extremely short-staffed. Travel was inadvisable. The usual conferences at which they might have met were cancelled or became virtual only. They "got really good at Zooming," and shifted their agenda to aspects of their plans that depended less upon fully functioning labs until those were available again.



Despite the COVID-19 pandemic and the inability to meet in person, mid-year and annual meetings were held virtually with the CFC3 team, their Scientific Advisors and GRF staff to review plans and results and set new research goals for the coming year.

In Their Own Words:
CFC Principal Investigators on Why and How They Collaborate

The traditional habits of research labs, working in "silos" and sharing information only in carefully presented and protected formats and forums, are long established and deeply ingrained. That prompted us to ask each of the principal investigators of CFC 1, 2, and 3 how they bring themselves to share their best ideas with three bright and well-situated strangers. Among their answers:

CFC requires the commitment

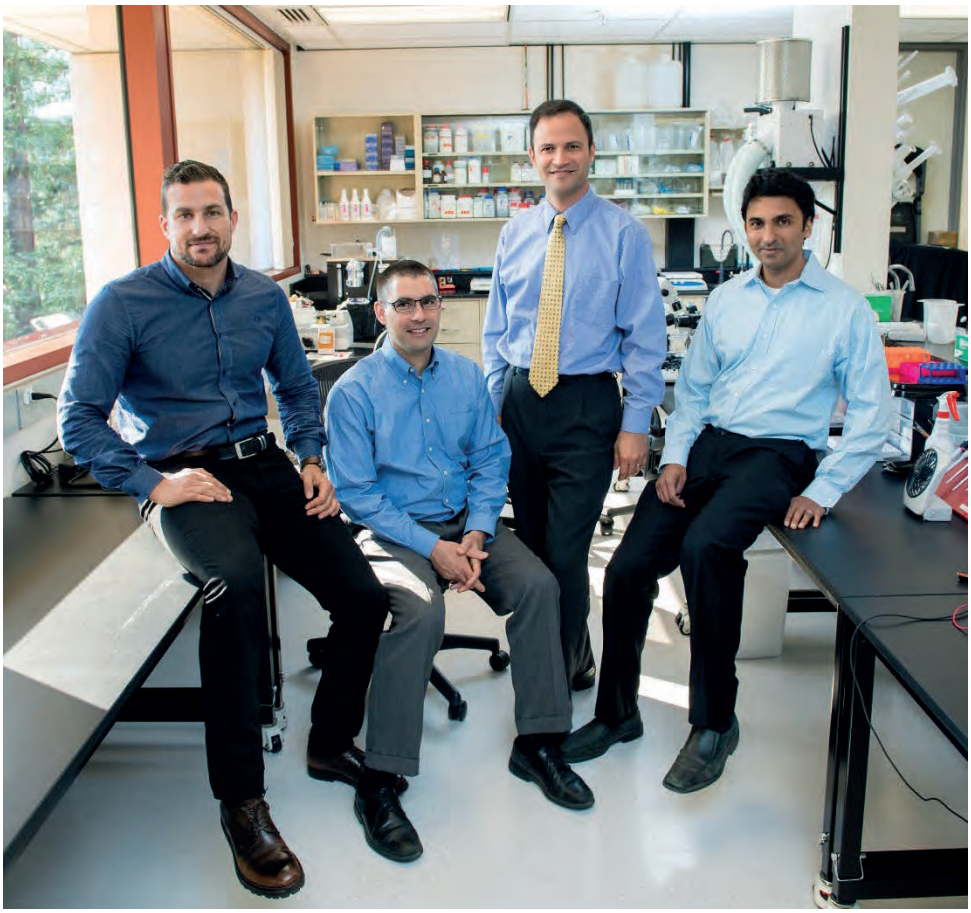
- *Funding was contingent on collaboration; it required an intentional decision to be open.*
- *Sharing your best ideas? Typically, you wouldn't do that. You live or die by your ideas. What made it different was that it was a given. We were told the conditions.*
- *We had made a strong commitment.*
- *It wasn't hard. I was already an enthusiastic acolyte of collaborative science, had done that, been part of multiple-PI grants.*

Trust is key

- *The hardest part about true collaboration is developing trust.*
- *We met regularly. We did a lot of travel. We did meetings at meetings, and we created meetings. Back then Skype didn't work all that well and we didn't have Zoom, so in-person was really critical.*
- *I had reservations. I didn't know them. So much depends on personalities. It went really well, a win/win situation. We were all on the same page from day one.*
- *It needs chemistry, and there was good chemistry. I remember the first time I felt that: I hadn't done retina work for years and Dave said, "Come on up, we'll do a boot camp."*
- *[My three colleagues] came across as extremely trustworthy…and they were a knowledgeable group.*
- *GRF made a lot of effort to pick people who would click.*

We made it work

- *The different disciplines, different skill sets gave us something very important to our careers, learning how to communicate across fields and to learn while trying to add value.*
- *We identified specific experiments that would be strengthened by shared effort and collaboration.*
- *Team members developed distinct projects that could contribute to the consortium while being managed on a day-to-day basis within their individual labs, maintaining member commitments to the training and development of students, postdocs, and staff.*



At the start of CFC2, all four investigators were in different states. But at the end, all four were in California with three at Stanford University.

Left to right: Andrew Huberman, PhD, Alfredo Dubra, PhD, Jeffrey L. Goldberg, MD, PhD, Vivek Srinivasan, PhD

Photo by Genevieve Shiffrar

The Scientific Advisors:
Mentoring the Principal Investigators

"The annual meeting was a very important time for us to present our findings and lay out our new ideas for discussion with the advisory board. This is unusual and very valuable."

- Principal Investigator, CFC 1

"Focus on experiments that can most rapidly disqualify a proposal and allow concentration on only the most promising opportunities."

- Scientific Advisors to Principal Investigators

In addition to the annual and mid-year meetings, the investigators often traveled to each other's labs and met at research conferences such as ARVO.

The CFC initiatives are not science as usual, but neither are they intellectual free-for-alls. They call for spirited adventurers, but with a specific destination in mind. The senior scientists who form the Scientific Advisory Board (SAB) hold the researchers accountable for the rigor and direction of their work. To provide this oversight, the scientific advisors:

- Review the research team's semi-annual reports and annual meeting presentations
- Provide an evaluation and recommendation on funding following the annual meeting
- Consult and advise as needed throughout the consortium's term
    - To ensure that the team remains focused on core issues
    - To ensure that intermediate goals contribute to achieving the overarching goal
    - To question, comment, and challenge assumptions
    - To serve as expert resources in discussions

During CFC's 20-plus year experience, the senior advisors have:

Questioned and cautioned:

- Questioned (not for the first time) whether the model is the most appropriate one for human glaucoma
- Described what seemed an overload of information and analytical overkill that overlooked several crucial questions
- Noted the breadth and number of new observations and urged the investigators to identify specific aims that will yield definitive answers in the next year
- Observed that interventional trials often generate more questions than answers, given the limited time, resources, and manpower available

Prodded and encouraged:

- Strongly recommended that future team research go deeper into the mechanism of the earliest events that appear in the model and the intervention trials
- Encouraged them to widen the studies beyond the current model, to validate and confirm findings in another animal model
- Recommended that the team measure both nerve cell survival and function since useful drug strategies must ultimately improve vision

The senior advisors have also:

Requested improved reporting:

- Requested an annual report be revised to provide more information and more detailed plans for the following year
- Recommended initiation of quarterly conference calls to improve communication between scientists and advisors

Complimented collaboration:

- Appreciated evidence of serious collaboration among the scientists and their laboratories, sharing ideas and materials and doing combined experiments
- Commended the team's high productivity in experimental results and publications
- Complimented the team on excellent progress and amazing images

Principal Investigators took every opportunity to connect with their Scientific Advisors, who provided key insights and direction to the team. Andrew D. Huberman, PhD (CFC2) with Martin Wax, MD (CFC1 and CFC2 SAB) at a GRF donor event.

The mentoring process not only achieves results; it is welcomed, as evidenced by the comments of the principal investigators on the following page.

Principal Investigators Comment
On the Work of the Scientific Advisory Board

- *They are not junior scientists with time on their hands. They are great to work with.*
- *It was great but scary. I was new, green, and these were luminaries. It was stressful being asked about our accomplishments because they paled in comparison.*
- *They provided encouragement, probing questions, some helpful suggestions, but they were also a very diverse group. Nobody knows the research like the researchers.*
- *They were invaluable. They were never heavy handed, knew they were there to advise, not mandate. They provided guidelines and resources.*
- *They were free-er earlier, which made sense. As time passed and expectations increased it went from more mentoring to regulatory, narrowing the focus, but we were determined.*
- *If I could change anything, it would be to have more time with them, for the exposure to the "names" in the field, to their expertise. My exposure to [one of them] was like a tease, just not nearly enough.*
- *It's been very helpful to my development, especially with the paper. They've read it, taught me how to deal with editors, et cetera.*

The guidance provided by the Scientific Advisors, particularly at the CFC Annual and mid-year meetings, is critical to the process. From CFC3 Annual Meeting in San Francisco (February 2020)

Photo by Nancy Graydon

Principal Investigators Meeting Their Supporters: A Lesson for Us and Unexpected Rewards

"I was an optics engineer, enjoying technical challenges, had a career, but never fully appreciated [the need]. Meeting the patients changes the way you think about the problem, heightens the sense of importance and urgency…. it's now a more personal thing for me to work on."

- Alfredo Dubra, PhD, Principal Investigator, CFC 2

By the end of year one, CFC 1 was delivering as we had hoped. Collaborative planning, joint experiments, shared data, extra meetings, frequent communications, a proposal for their own mouse colony, designs for division of labor between the labs to advance their mutual objective. Year two saw results beginning to come in. Smiles all around, but there was an unexpected bonus to come. We invited David Calkins, one of the PIs, to provide an overview to GRF's board of directors. He reported on group meetings, the exchange of lab material, retinal ganglion cells, gene expression, and the DBA/2J mouse we'd heard so much about.

That report to supporters, many of whom were patients, was a hit and only the first of many that "Dave," "Monica," "Phil," and "Nick" provided to board meetings, potential donors, and GRF's first full-on (and profitable) benefit event. And we produced moderated teleconferences with live questions from donor-listeners.




Each year, the CFC1 scientists would report their progress to Board members, donors, and friends. This annual event was then transformed into an annual fundraising gala in 2007. To date, more than $8 million has been raised from the Gala to support GRF's research and education programs.

We discovered that:

- The principal investigators are knowledgeable and informative "in-house" specialists
- They are excited to be on the leading edge of research in their field
- They enjoy celebrating what they are doing and easily convey their enthusiasm
- They become very good at explaining their work to non-scientist audiences

This has multiple benefits:

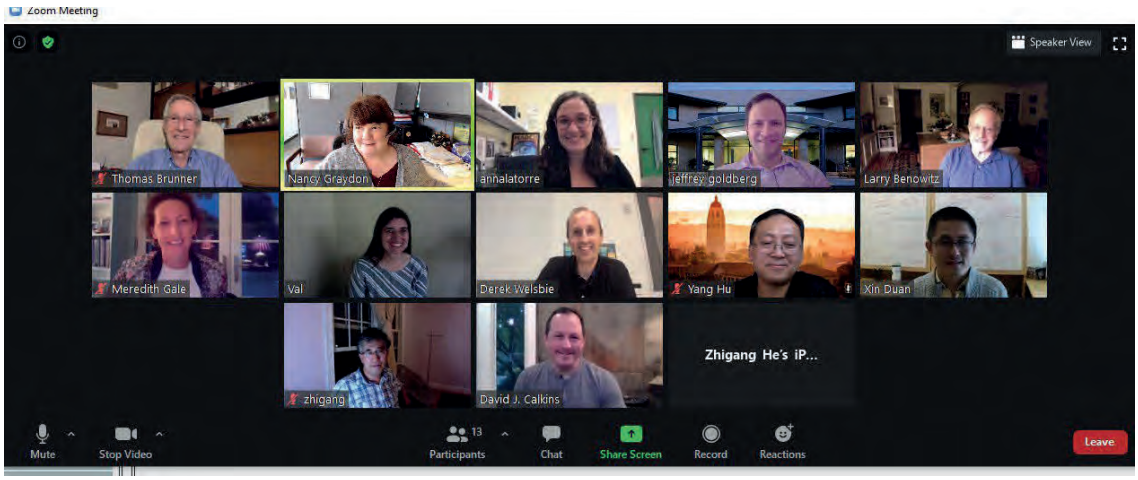
- The meeting of researchers and supporters contributes to the openness of the enterprise
- The researchers say that such a close relationship with supporters is uncommon and inspiring
- That some of the supporters are patients adds to the researchers' sense of urgency
- Potential donors are better informed about the work of the foundation

GRF's Annual Gala offered a unique experience for donors, Board members, and patients to meet with CFC scientists. Members of CFC1: Nick Marsh-Armstrong, PhD, Monica Vetter, PhD, Andrew Iwach, MD (Board Chair) and David Calkins, PhD.

We have learned this lesson, enjoyed the benefits, and continued to engage the principal investigators in reporting what they are doing. As foundation supporters took to the PIs of CFC 1, so have they become well acquainted with "Alf", "Jeff", "Vivek" and "Andy" of CFC 2 who attended donor gatherings, did teleconferences, and became adept at providing video materials for meetings and the GRF website.

Donors, Board members and Gala attendees welcome the opportunity to meet the CFC researchers and hear first-hand about the progress of their investigations. Here members of CFC2 are with Board member, Adrienne Graves, PhD (center).

The CFC 3 team, constrained by pandemic limitations, has had the countervailing advantage of continuously improving technology and has added to GRF's recorded library of resources during 2020 and 2021. With in-person meetings happening again, "Xin," "Yang," "Anna" and "Derek" are now building their own congenial and enriching relationships with supporters and potential donors.



In addition to live events, an ongoing webinar series "Innovations in Glaucoma" is held regularly to keep donors and patients updated on the CFC's progress. Recordings are then posted online and viewed by patients around the world.

The combined efforts over the years have provided us with unplanned opportunities and valuable assets:

- Knowledgeable and engaging speakers and panel discussions at foundation meetings
- Online moderated teleconferences and responses to live questions from listeners
- Recorded video reports and explanations of research progress for use at meetings
- All the above and more for use on the website

And enriched the experiences of the principal investigators.

The Catalyst for a Cure consortium is highlighted at donor events as well as other GRF meetings including Glaucoma 360, an annual forum highlighting new innovations in glaucoma.

Teams Meeting Teams:
Still Another Multiplier

In early 2023, as this publication was being made ready to print, we enjoyed another happy surprise. We should have expected it by then.

We had two CFC teams at work. CFC 3 was scheduled to report on its fourth full year and CFC 4 was to report on its initial efforts after only six months. Members of both teams and their scientific advisory boards were to be in San Francisco within the same time frame for their (as *initially* planned) separate reports and evaluations.

One of the scientific advisors, among the staunchest advocates of collaboration, suggested that the teams and advisors meet in joint session. There was some thoughtful hesitation. These were two very different sets of teams, with decidedly different (although complementary) assignments. One team had four years of experience taking the kinks out of collaboration; the other had barely begun. On the other hand, they had all committed to the collaborative program, and they all knew a great deal about the science each of the others was exploring and advancing.

A joint session was scheduled. It began with an early breakfast, was moderated as a forum open to questions from all and continued through lunch with each team reporting in detail to its advisors, in the presence of the other team and its advisors across the table. After the first ice-breaking question, no more encouragement was needed. There was an easy flow of questions, answers, suggestions, explanations, thoughtful probes, and generous clarifications – from, to, and among investigators and advisors of both teams. At one point a CFC 3 team member was asked how something he was doing actually worked. He gave a wry smile, shrugged his shoulders, and said, "I don't know," although the gleam in his eye suggested that he intended and expected to find out. The distance across the table seemed less and less, the collaborative possibilities more and more.

So, if you should have more than one team at work, make sure they meet.

Funding:
Sustained and Supplemental

"The unrestricted nature of the CFC funding and its consortium structure has allowed us to pursue highly imaginative, non-traditional and multidisciplinary investigations."

- 2010 Interim Report, Principal Investigators, CFC Team 1

Because we believe that collaborative, multidisciplinary research efforts must be sustained long enough to achieve their objectives, GRF has been prepared to see CFC initiatives extend beyond the initial three-year term. These longer-term research programs, in addition to GRF's pilot grants, educational programs, and other activities, have been supported by:

- GRF's continuously maintained program inviting donor gifts
- Three intensive capital campaigns, two exceeding their goal
- Grants for the CFC program from other foundations

Sustaining the Core Funding

Funding Catalyst for a Cure's first eleven years went like this:

- CFC 1, launched in 2002, was funded in a 50/50 partnership with the Steven and Michele Kirsch Foundation for the first three years. A second three-year term, 2005-2007 was tagged at $2,500,000 and was all on GRF. We launched a three-year $7.5 million capital campaign. The Board of Directors alone pledged $2.6 million and the campaign ultimately raised a total of $8.6 million.

- In 2007, when GRF discussed the possibility of renewing CFC 1 and funding a third three-year term, at a cost of $3,000,000, the Melza M. and Frank Theodore Barr Foundation offered a matching grant through GRF of $1.5 million over three years. The Barr gift kicked off a new three-year $12 million capital campaign. GRF's Board of Directors provided increased support and the foundation boosted its efforts to generate support from allied organizations and affiliated glaucoma practices. This campaign was less successful, due to the 2008 recession, and foundation investment losses served to further reduce available funds. Total revenue for 2008-2010 was $7.8 million, far short of the $12 million goal. We fully funded CFC but payments were shifted to quarterly installments in 2009 and 2010 to better match cash flows.

- CFC 1's final two-year extension for 2011-2012, with total transitional funding of $1,600,000, was provided with an additional commitment of the Melza M. and Frank Theodore Barr Foundation through GRF.

Then came CFC 2, CFC 3, and CFC 4:

- The extension of the Catalyst for a Cure program with the launch of CFC 2 required more ambitious fund raising and in 2014 GRF launched another capital campaign with an initial goal of $15 million. By 2018 that goal had been exceeded, but so had the scope of the CFC effort and the campaign was extended with an increased goal of $25 million. In June of 2020 the campaign reached that goal with more than 27,500 contributions from donors.

- The Kirschs had continued to follow the progress of the Catalyst for a Cure program which they had helped to launch in 2002. In 2021 they offered a $1,500,000 challenge grant from the Steven and Michele Kirsch Foundation to extend the CFC 3 initiative for another three-year term. With matching funds through GRF, that effort could be renewed to run now for a total of six years, through 2024.

- At about the same time, Ted Barr expressed an interest in furthering work on neurodegeneration, including its agency in other neurodegenerative diseases. After a 2021 Catalyst meeting, production of a detailed white paper, and continued discussions, Ted Barr and his son Terence Barr proposed a $2.4 million grant from the Melza M. and Frank Theodore Barr Foundation through GRF to fund the fourth CFC initiative, launched in July 2022.

Supplemental Funding

The terms of the CFC grants permit and encourage the principal investigators to propose additional work and request supplemental funds to support it. The teams have exercised this option and, to date, each request has been granted, the supplemental funds all provided by GRF, with the endorsement of the Scientific Advisory Board and the approval of GRF's Board of Directors:

- In 2003, its second year at work, the CFC 1 team, Redefining Glaucoma, requested funds to establish a mouse model colony, to be located at the Horner lab, University of Washington. The initial request was for $110,000, to be paid over years two and three. The mouse colony was further supported and expanded during years four through nine with an additional $444,225.

- In 2004, the CFC 1 team requested a supplemental $200,000 to support the successful conclusion of its three-year effort with an additional post-doc at each institution.

- For year five, 2006, $80,000 was requested to provide the CFC 1 team with additional personnel to do tissue analysis at the Calkins lab, Vanderbilt.

- In 2010, year nine of CFC 1's work, a symposium was held at Vanderbilt and a final supplement of $15,000 was requested by the Calkins lab.

- In 2012, the first year of CFC 2's work, the Biomarker Initiative team requested a supplemental $80,000 equipment grant to support the purchase of a light source at the Medical College of Wisconsin for the Dubra lab's effort to improve its adaptive optics.

- In 2022, the fourth year of CFC 3's work, the Vision Restoration team requested supplemental equipment grants of (1) $100,000 for the purchase of a suite of instruments to measure vision in rodent models at the Duan lab, UCSF, assessing the impact of various treatments and (2) $75,000 for specialized diagnostic instrumentation at the Hu lab, Stanford.

- In late 2022, during the first six months of CFC 4's work, the Neurodegeneration Initiative team requested a supplemental grant of $33,510 to fund purchase of equipment and supplies to isolate cells for RNA sequencing. The equipment will be located at the Venkatesh lab and shared by the Margeta lab, both at Harvard.

Tables on the following pages show years and amounts of core and supplemental funding for CFC 1, CFC 2, and CFC 3 to date.

CFC1 - REDEFINING GLAUCOMA - Funding

Date	Year	Description	Amount	Per year	Total Per Year	Total Per term
2002	1	Core funding per PI/Lab	85,000	340,000	340,000	
2003	2	Core funding per PI/Lab	85,000	340,000		
		DBA/2J mouse colony	54,144	54,144	394,144	
2004	3	Core funding per PI/Lab	85,000	340,000		
		DBA/2J mouse colony support	54,144	54,144		
		Additional post-doc per lab	50,000	200,000	594,144	1,328,289
2005	4	Core funding per PI/Lab	192,500	770,000		
		DBA/2J mouse colony support	65,075	65,075	835,075	
2006	5	Core funding per PI/Lab	192,500	770,000		
		DBA/2J mouse colony support	65,075	65,075		
		Mouse colony expansion	54,000	54,000		
		Additional post-doc, tissue analysis	80,000	80,000	969,075	
2007	6	Core funding per PI/Lab	192,500	770,000		
		Mouse colony support	65,075	65,075	835,075	2,639,225
2008	7	Core funding per PI/Lab	233,750	935,000		
		Mouse colony support	65,000	65,000	1,000,000	
2009	8	Core funding per PI/Lab	233,750	935,000		
		Mouse colony support	65,000	65,000	1,000,000	
2010	9	Core funding per PI/Lab	233,750	935,000		
		Mouse colony support	65,000	65,000		
		Vanderbilt symposium	15,000	15,000	1,015,000	3,015,000
2011	10	Core transitional funding per PI/lab	200,000	800,000	800,000	
2012	11	Core transitional funding per PI/lab	200,000	800,000	800,000	1,600,000
		Eleven-year total				8,582,514

Years 1-3 Core funding of $1,150,000 was provided half by the Steven and Michele Kirsch Foundation and half by GRF.

Years 7-9 Baseline funding of $3,000,000 was provided half by a grant from the Melza M. and Frank Theodore Barr Foundation through Glaucoma Research Foundation and half by GRF.

Years 10-11 Transitional funding of $1,600,000 was provided by a grant from the Melza M. and Frank Theodore Barr Foundation through Glaucoma Research Foundation.

CFC 2 - BIOMARKER - Funding

Date	Year	Description	Amount	Per year	Total Per year	Total Per term
2012	1	Core funding per PI/Lab	150,000	600,000		
		Suppl. Equip. Grant, Dubra lab	80,000	80,000	680,000	
2013	2	Core funding per PI/Lab	200,000	800,000	800,000	
2014	3	Core funding per PI/Lab	250,000	1,000,000	1,000,000	2,480,000
2015	4	Core funding per PI/Lab	250,000	1,000,000	1,000,000	
2016	5	Core funding per PI/Lab	250,000	1,000,000	1,000,000	
2017	6	Core funding per PI/Lab	250,000	1,000,000	1,000,000	3,000,000
2018	7	Transitional funding per Pi/Lab	100,000	400,000	400,000	400,000
		Seven-year total				5,880,000

CFC 3 - VISION RESTORATION - Funding*

Date	Year	Description	Amount	Per year	Total Per year	Total Per Term
2019	1	Core funding per PI/Lab	150,000	600,000	600,000	
2020	2	Core funding per PI/Lab	200,000	800,000	800,000	
2021	3	Core funding per PI/Lab	250,000	1,000,000	1,000,000	2,400,000
2022	4	Core funding per PI/Lab	250,000	1,000,000		
		Suppl. Equip. Grant, UCSF/Duan	100,000	100,000		
		Suppl. Equip. Grant, Stanford/Hu	75,000	75,000	1,175,000	
2023	5	Core funding per PI/Lab	250,000	1,000,000	1,000,000	
2024	6	Core funding per PI/Lab	250,000	1,000,000	1,000,000	3,175,000
		Six-year total commitment*				5,575,000

Years 4-6 core funding of $3,000,000 is being provided half by a challenge grant from the Steven and Michele Kirsch Foundation and half by GRF.

**Active, continuation contingent on annual reviews and approvals*

Extend the Run? Or Call It a Wrap?
Determining the Length of the Initiative and Closing it Down

Just as they are not intellectual free-for-alls, CFC initiatives are not open-ended invitations to perpetual studies. There are times when terms should be renewed. And there comes a time when each initiative has peaked, and the project should be brought to an orderly finish. How do we know? We look at the basics, already built in.

- The original statement of the goal
- Progress toward the goal, as reported by the teams' semi-annual and annual reports
- Team plans for further research and experiments
- The evaluations and recommendations of the Scientific Advisory Board regarding:
    - Progress to date
    - Prospects for significant further progress

The research goal that we set for each initiative is expected to be largely achievable. Therefore, each team that is making solid progress should be given adequate time to realize the results of its efforts. Extend the run. By the same token, a record of successful work and substantial achievement of the goal should spell the natural end of the specific funded project. Call it a wrap.

To manage an orderly end of CFC initiatives and respect the researchers' transitional needs:

- The SAB anticipates the pending close by encouraging the teams to focus on concluding and reporting on their key experiments or studies
- The foundation(s) to date have adjusted funding for a transitional period that enables the teams to finish up and write their final reports while beginning to secure other funding for their labs

The following table shows the years and funded terms of CFC's four initiatives to date, two of them still active. Grant renewals are generally for additional three-year terms except the final extensions.

CFC TEAM YEARS AND TERMS

Team	Research Topic	Years Funded	Terms of Years	Total Years	Total Funds
CFC 1	**Redefining Glaucoma**	2002 - 2012	3 + 3 + 3 + 2	11	$8.6 mil.
CFC 2	**Biomarker Initiative**	2012 - 2018	3 + 3 + 1	7	$5.9 mil.
CFC 3	**Vision Restoration**	2019 - 2024*	3 + 3*	6*	$5.6 mil.*
CFC 4	**Prevent and Cure Neurodegeneration**	2022 h2 - 2025 h1*	3*	3*	$2.4 mil.*

*Active, continuation contingent on annual reviews and approvals.

Part II

The Scientists and Supporters Who Know How

Glaucoma Research Foundation
Early Research Work

"Blanche Matthias gave of herself generously throughout her life. We shall do our best to make the ongoing work of the Foundation a continuing tribute to her memory."

– GRF Founders

Glaucoma Research Foundation (GRF) was founded in 1978 by Robert N. Shaffer, MD, John Hetherington, Jr., MD, and H. Dunbar Hoskins, Jr., MD. The initial funding consisted of two gifts, almost a million dollars each, from a grateful patient, Blanche Matthias, and her good friend, Bernice Hauck. GRF awarded its first grant in the year it was founded, the 1978 Shaffer Glaucoma Fellowship, and additional fellowships in the years that followed. These grants provided specialized training for visiting ophthalmologists from the United States and several foreign countries.

With philanthropic support from two of their patients, San Francisco based glaucoma specialists Left to right: John "Jack" Hetherington, Jr., MD, Robert N. Shaffer, MD, FACS, and H. Dunbar Hoskins, Jr., MD, established Glaucoma Research Foundation in 1978 with the mission to help patients through innovative research.

Research grants also began early on with a continuing program of pilot grants, generally for one year, to explore research ideas that had breakthrough potential but were not yet qualified for funding from traditional sources. The grants were also intended to encourage new scientists to continue their work in the field of glaucoma.

To date, Glaucoma Research Foundation has funded close to 300 pilot grants, now known as Shaffer Grants for Innovative Glaucoma Research. Each year at the Annual Gala, the Shaffer Prize is awarded to the best research project from the previous year. This coveted award is a great source of pride and validation for awardees.

Due to the COVID-19 pandemic, two Shaffer Prizes were awarded at the 2023 Annual Gala to: Lev Prasov, MD, PhD, and Rachel Wang Kuchtey, MD, PhD.

"As an early career clinician-scientist, the Shaffer Prize represents a validation that my lab's work is meaningful to the glaucoma community and that our progress is appreciated by patients, researchers, and clinicians. This is a true honor for our laboratory and helps motivate us to continue our work in identifying pathogenic mechanisms for glaucoma that could be targeted in the future with therapeutics."

- Lev Prasov, MD, PhD, University of Michigan, 2023 Shaffer Prize

To stimulate communication and further accelerate progress toward a cure, GRF initiated multidisciplinary catalyst meetings in glaucoma research in 1984. One of the explicit objectives of these meetings was to lure non-ophthalmologists into the field. GRF also made funds available for grants to catalyst meeting participants. Between September 1984 and April 2000, catalyst meetings resulted in the award of 33 grants in the total amount of $2 million to researchers at institutions in 15 U.S. states, 3 Canadian provinces, the United Kingdom, and Israel. A review of meeting and grant topics over their history shows increasing focus on retinal ganglion cells, the optic nerve, and genetics.

Paul L. Kaufman, MD shared receipt of a catalyst meeting grant in 1984, was a frequent participant in catalyst meetings, later joined GRF's Scientific Advisory Committee, and was a strong supporter of collaborative work. As Dr. Shaffer had cultivated friendships and encouraged the sharing of knowledge from his entry into the field in the early 1940's, it naturally became a charge of the catalyst meetings to develop ideas for collaborative research projects.

The first of the catalyst meetings, in 1984, was constituted as a multidisciplinary discussion of normal tension glaucoma. As a result of the discussion, GRF sponsored the *Collaborative Normal Tension Glaucoma Study* beginning in 1986. This was a ten-year collaborative study and controlled clinical trial. It involved 24 study centers around the world and was monitored by an institutional review board. Completed in 1998, it was the first study to document that lowering intraocular pressure in people with normal tension glaucoma slows the progression of the disease.

In 1997 GRF-funded researchers at UCSF, collaborating with scientists at the University of Iowa, succeeded in isolating the TIGR gene. This gene was found to be one of those responsible for the onset of some forms of juvenile and adult glaucoma.

The Catalyst for a Cure Research Consortiums
2002 – 2022

Not yet properly introduced here are the scientists and supporters who have demonstrated for us, and continue to demonstrate, that collaborative research works. They are the scientific advisors, the principal investigators, the supporters, and the major donors of the Catalyst for a Cure consortiums. Highly condensed, here are the stories, those already told and those still being written, of their CFC initiatives:

CFC 1 – Redefining Glaucoma

CFC 2 – Biomarker Initiative

CFC 3 – Vision Restoration

CFC 4 – Prevent and Cure Neurodegeneration

CFC 1
Redefining Glaucoma
2002 - 2012

"…to identify the origins of glaucoma, with emphasis on genetics and neurodegeneration of the optic nerve, define new therapy targets, and move closer to a cure."

- From an early GRF statement of the research objective

In 2001, Glaucoma Research Foundation (GRF) partnered with the Steven and Michele Kirsch Foundation to establish the first consortium of the Catalyst for a Cure (CFC). The specific objective was to assemble and support a consortium of scientists who would use recent breakthroughs in neuroscience, molecular biology, genetics, and immunology to answer key questions about the causes and mechanisms of glaucoma.

Michele and Steven Kirsch partnered with GRF in 2001 to establish the first CFC team. They continued to provide their philanthropic support over 20 years including a $1.5 million pledge to support CFC3.

The CFC 1 Scientific Advisors

Martin Wax, MD, who had championed the idea at GRF, and Sarah Caddick, PhD, representing the Kirsch Foundation, recruited the scientific advisors who together, became the Scientific Advisory Board (SAB). Those named to the SAB in August of 2001 with their affiliations at that time, were:

- **Moses V. Chao, PhD**, Chair, Professor Cell Biology, Physiology and Neuroscience, New York University School of Medicine, NYU Medical Center/Skirball Institute of Biomolecular Medicine, New York. Dr. Chao was a renowned expert on the function of growth factors in neurons and glia. He pioneered early molecular analysis of the quintessential nerve growth factor receptor and was a respected editor and scientific consultant with the ability to critically evaluate scientific ideas.

- **Jack P. Antel, MD**, Professor of Neurology, Montreal Neurological Institute, McGill University, Montreal. Dr. Antel was a clinical scientist whose work has led to new hypotheses and potential targets for the treatment of another devastating degenerative disease, multiple sclerosis. He had successfully bridged the gap between basic and clinical research and therefore provided perspective on the design and evaluation of studies aimed at human disease.

- **Constance L. Cepco, PhD**, Professor, Department of Genetics, Harvard University Medical School, Boston. Dr. Cepco was a leading expert and innovator in the biology of retinal development and was working on complex problems with which others had made only slow progress. Her eye on innovation and technology provided important guidance and thrust for the CFC team.

- **Martin Wax, MD**, Washington University, St. Louis, Senior Director & Head, Ophthalmology Discovery Research, Pharmacia. Dr. Wax was an ophthalmologist specializing in the management and study of glaucomatous disease and was recognized as a leading expert in the field. His research knowledge and experience in glaucoma provided historical perspective, essential to prevent the CFC from repeating failed approaches and to keep the focus of the research directed toward the clinical issues.

The CFC 1 Principal Investigators

Dr. Caddick, Dr. Wax, the other members of the SAB, and GRF selected the four individuals who would form the first CFC team of principal investigators (PIs). With their affiliations at that time, they were:

David Calkins, PhD
University of Rochester Medical Center
Rochester, New York

Philip Horner, PhD
University of Washington
Seattle, Washington

Nicholas Marsh-Armstrong, PhD
Kennedy-Krieger Institute/Johns Hopkins University
Baltimore, Maryland

Monica Vetter, PhD
University of Utah
Salt Lake City, Utah

At the end of 2004, when the CFC 1 grant was renewed for a second three-year term, the Kirsch Foundation had fulfilled its three-year commitment. With sole responsibility for oversight as well as funding, GRF moved to strengthen the SAB with the addition of three more members:

- **Eugene M. Johnson, PhD,** Washington University Medical School, St. Louis. Dr. Johnson's laboratory work focused on neurobiology and, in particular, neurodegeneration in aging and in such diseases as Alzheimer's and Parkinson's.

- **Dennis D.M. O'Leary, PhD,** Salk Institute, La Jolla. Dr. O'Leary's work included the study of axon guidance and neural mapping, particularly between the eye and the brain, and his goals included the design of effective strategies to overcome neurological diseases.

- **Martin Raff, MD, Emeritus Professor,** Department of Biology, University College London. Dr. Raff's work involved the study of optic nerve cells, cell death, and clearance of self-destructive cells by phagocytes. He was a strong advocate of sharing information and materials, even with competitors.

Additional members of the Scientific Advisory Board were added in 2004 to provide additional insights and guidance to the team. Top row, left to right: Martin Raff, MD, Martin Wax, MD, Eugene M. Johnson, PhD; Bottom row, left to right: Dennis D.M. O'Leary, PhD, Sarah Caddick, PhD, Moses V. Chao, PhD.

The three new SAB members joined the original four and, together, they mentored and encouraged the PIs throughout the eight additional years that followed.

* * *

During their eleven years as Catalyst for a Cure researchers, the CFC 1 primary investigators became a remarkably effective team as they sought to understand glaucoma. They pursued their best ideas, abandoned some lines of work that seemed less promising, and left others as outside the reach of their tight focus. Tables on the following two pages capture selected statements of the team's goals and accomplishments from their periodic reports to the SAB and comments in other forums.

CFC 1 – REDEFINING GLAUCOMA
SELECTED TEAM STATEMENTS OF INTERIM GOALS

2002 Each team to work on 2 of 5 strategies intended to reveal early progression: innate repair response; molecular profile of RGCs; promoters specific to RGCs or retinal stem cells; interaction between RGCs and surrounding glial cells; regulatory regions of human glaucoma predisposition genes.

2003 Establish centralized breeding facility of rodent model * analyze stem cell activity in the mouse retina during progression * Develop tools and methods to study gene expression during progression.

2004 Disseminate tissue and animals to all labs * Develop full molecular analysis of mechanisms of progression * Establish broader core structure: Horner, mouse core; Calkins, retinal pathology, RNA extraction; Vetter, screening; Marsh-Armstrong, manipulating RNA for genomic studies.

2005 Define the fundamental cellular events underlying disease onset and progression, centering on DBA/2J model, with emphasis on most likely sites for therapeutic intervention.

2006 Investigate three basic mechanisms involved in disease progression: pressure mediated injury, RGC pathology leading to axonal transport dysfunction; and gliosis/innate immunity * Initiate interventional studies in DBA/2J model and analyze multiple markers to shed light on the mechanisms.

2007 Complete the interventional studies underway in the DBA/2J model * Continue to investigate 3 mechanisms involved in disease progression.

2008 Continue to test roles of specific proteins, genes, and the three cascades that contribute to RGC axonal and somatic degeneration * Initiate studies on mitochondrial dysfunction in the optic nerve.

2009 Continue to chase down the mechanisms underlying transport loss, oxidative stress, and loss of connections * Determine if gliosis is supportive or detrimental of RGC degeneration in DBA/2J mice * Complete and publish analysis of mitochondrial fusion in the DBA model and extend it to the micro bead model.

2010 Given time and funding limits, per SAB recommendation, focus on establishing more precise timing and sequence of events in the DBA/2J model.

2011 and 2012 Test inhibition of stress response protein kinase in squirrel monkeys * Test new apparatus' visual recording of RGC cell response to drugs and stressors in rodent model in vivo * Test whether anti-gliosis and/or pro-metabolic therapies can reverse RGC vulnerability * Test whether human induced pluripotent stem cell-derived cells function as retina neurons and glia * Collect retinal tissue and image labeled retinas by confocal microscopy for assessment of RGC decline.

CFC 1 – REDEFINING GLAUCOMA
SELECTED TEAM STATEMENTS OF INTERIM ACCOMPLISHMENTS

2002 Determined that microarrays are most practical for profiling gene expression * Optimized procedures for defining stem cell promoters and modifying DNA inserts in candidate glaucoma genes * Initiated plans to breed and maintain a colony of DBA/2J mice * Eliminated strategy #5.

2003 Prepared and tested equipment and personnel to analyze microarrayed gene expression data during progression in DBA/2J mice * Established colony, determined that the model actually develops glaucoma, not just symptoms * Completed histopathological characterization of tissue from aged mice.

2004 Identified failure of transport in optic nerve * Identified window of persistence and self-repair * Research indicated glaucoma is not a disease of the eye but the central nervous system.

2005 Now focused on 3 favored hypotheses for disease initiation and potential therapeutic targets: (1) pressure-induced calcium injury, (2) axonal transport dysfunction, and (3) innate immunity/gliosis.

2006 Made several key findings in testing 3 favored hypotheses, confirming destruction of axonal function occurs early, further likening glaucoma to other neurodegenerative diseases * Now doing in vitro experiments, including in DBA/2J mice, to determine potential for rescue of sick RGCs.

2007 Completed first intervention trials in DBA/2J model, validating several hypotheses * Developed rodent microbead occlusion model (shorter timing and IOP elevations more akin to those in glaucoma.

2008 Evidenced early involvement of microglia in glaucoma-like changes and demonstrated that gliosis can be tempered under raised IOP.

2009 Accumulated more data on earliest pathological changes in DBA/2J model: greatly reduced axonal transport, progressive dendritic pruning of RGCs, activation of microglia, and aggregation of gamma-synuclein protein * Contrary to expectations, found that TRPV1, activated by RGCs under pressure, may be neuroprotective.

2010 Team published 5 papers in 2009-2010 and have another 8 submitted or in revision; more than 9 joint abstracts presented at national conferences.

2011 and 2012 Proved in principle that induced pluripotent stem cells can be used to develop neural cell lines * Confirmed that clusters of activated microglia, spreading from the central retina, foreshadow patterns of later RGC disease * Demonstrated that early detection of microglia activation is possible in vivo * Completed all live imaging at multiple stages in a large cohort of mice for quantitative analysis * Completed characterization of a new micro bead primate model of glaucoma.

In January 2013 the CFC 1 team, Redefining Glaucoma, submitted its final report.

Executive Summary, January 2013
David Calkins, Monica Vetter, Nick Marsh-Armstrong, and Philip Horner

The Catalyst for a Cure consortium was originally tasked with applying our collective expertise as neuroscientists to achieve better understanding of glaucoma, with the ultimate goal of developing novel strategies for treatment. To achieve this, we have 1) developed and characterized animal models of glaucoma and developed tools for analysis, 2) performed a detailed characterization of the disease at the cellular and molecular level, 3) defined Important and novel events in the progression of glaucoma, and 4) tested the effectiveness of interventions that target these events. Through this work we have obtained a detailed understanding of this complex disease and have revealed novel approaches for slowing disease progression. The CFC has made major contributions that have changed how we think about glaucoma.

Importantly, we characterized glaucoma as a progressive, neurodegenerative disease, and provided significant evidence that targeting early events has the greatest therapeutic potential. We showed that RGCs undergo functional decline and genetic deprogramming before they are permanently lost, and we defined a window of "vulnerability" for RGCs during which there Is the potential for rescue. We also showed that glia are key players in these early events and can be effectively targeted for therapeutic Intervention.

Through this work we find that multiple factors contribute to neurodegeneration in glaucoma. We propose that multiple insults and the failure of intrinsic protective mechanisms ultimately lead to blindness. In the future, we propose that maximal benefit in this complex degenerative disease will likely come from a combinatorial therapy that targets molecular pathways in the neurons as well as in surrounding glia.

The work of the CFC has resulted in 28 publications, including some that are the most highly cited in the field of glaucoma research. GRF, Kirsch, and Barr Foundation support has led to roughly $4.5M in additional federal funding for glaucoma research, not including trainees who have gone on to secure independent funding. We have provided training to some 25 students or fellows, many of whom are continuing glaucoma research. Overall, we have had a significant impact upon the field and contributed to a shift in thinking about how to effectively slow or halt vision loss. We are committed to continuing with this Important work.

In 2012, the CFC pursued several important lines of investigation:

1. We have delved deeper into understanding the novel process by which optic nerve astrocytes (glia) internalize axonal material in the nerve head, and how this is altered in glaucoma. We have identified a secreted protein that may play a role in this internalization process. These pathways may lead to therapeutic targets in glaucoma.

2. We have further investigated how microglia contribute to pathology in glaucoma. We reported that high dose irradiation, which is neuroprotective, depletes activated microglia at early stages of disease and are targeting molecular pathways that regulate microglia activation. In addition, we showed that early detection of microglia activation predicts later patterns of RGC degeneration and are pursuing live imaging of microglia as a biomarker of early glaucoma.

3. We investigated how RGCs respond to pressure-related stress and find that they upregulate proteins to help them maintain calcium levels and adapt to stress. We explored the relationship between axon loss and pruning of synapses and dendrites in the retina and found that these were independent events in RGC decline. Finally, we adapted the microbead-occlusion model to the squirrel monkey, whose visual system structurally parallels that of human beings. This model could be used to test clinically-relevant mechanisms to speed FDA translation of CFC-derived treatments.

4. We have probed the metabolic vulnerability of RGCs, and changes in mitochondria since changes have been identified in early-stage glaucoma. We found misregulation of a key protein that controls the transport of mitochondria in axons, which may underlie the decline in metabolic function. Since we have shown that glial activation is pathogenic in chronic glaucoma, we have focused on finding the signals released by damaged nerves that ignite glial activity. We have identified a key target that may be a critical component for blocking the spread or amplification of glial activation that exacerbates the disease.

In summary, we have honed in on critical mechanisms driving neurodegeneration in glaucoma and identified components that we are targeting for therapeutic intervention as a foundation for pre-clinical testing.

The team's research bibliography is contained in the appendix that follows.

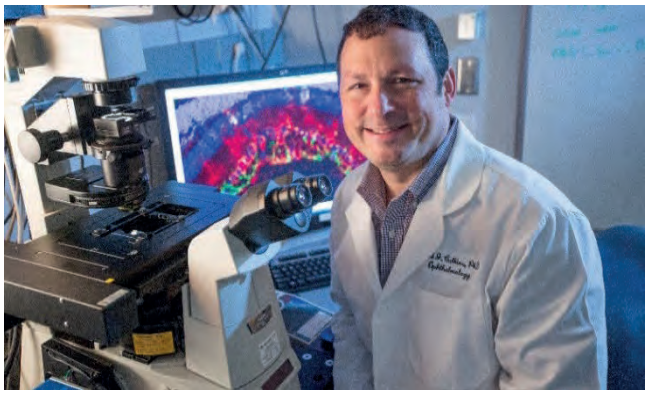
Comments on
CFC 1 - Redefining Glaucoma

The Catalyst for a Cure initiative Redefining Glaucoma was the first of GRF's research efforts to operate using the fully imagined Catalyst for a Cure model. The principal investigators worked together from 2002 through 2012, beginning with the goal of finding the causes and critical mechanisms of glaucoma. They concluded with a detailed understanding of the disease and changed the conventional view of glaucoma as an eye disease to a more complete understanding of glaucoma as a neurodegenerative disease, revealing the possibility of new therapeutic approaches. Specifically, the team was able to show that the first sign of injury in glaucoma actually occurs in the brain when the axons in the optic nerve lose their ability to communicate with their projection site in the mid-brain.

In its 2011 evaluation of the CFC 1 consortium, the Scientific Advisory Board stated that "the CFC initiative has exceeded expectations when it began as a collective enterprise to study glaucoma. The CFC scientists have become a unique collaborative and collegial partnership, which has been able to address key questions about the pathogenesis of glaucoma. It has been gratifying to see the four groups working closely together and sharing information throughout the past decade. It has attracted numerous new students and fellows to the field. Its multidisciplinary approach is enhanced by the synergism of the four laboratories, each of which uses distinctive technologies and approaches and has now established its own specific niche in the field."

The SAB credited the team with becoming experts in the field and "reshaping the direction of glaucoma research by focusing on the earliest molecular events of the disease, which occur well before the demise of retinal ganglion cells." Further, "the findings made by the CFC scientists have shown that glaucoma shares a number of similarities with Parkinson's disease, amyotrophic lateral sclerosis, and Alzheimer's disease," using "a pioneering approach that should become a model for research in other diseases."

The first CFC team worked together for 11 years and helped to define glaucoma as a neurodegenerative disease like Alzheimer's, Parkinson's, and ALS.



The first CFC team identified some of the earliest biological changes of glaucoma. As such, their findings are among the most cited in the field of glaucoma.

CFC 2
Biomarker Initiative
2012 – 2018

"…to determine what we should be measuring and then invent better ways to measure it."
- Principal investigator, CFC 2 – Biomarker Initiative

To build on the success of the first CFC team, still working, in 2010 GRF initiated plans to sponsor a second team of investigators and hasten the pace of discovery. We convened a catalyst meeting to explore the possibilities. Eighteen scientists and physicians from across the country and beyond met in San Francisco in September 2010 to discuss "*Retinal Ganglion Cell Degeneration in Glaucoma*." The discussion was wide-ranging but focused on the need to develop new imaging techniques that would take advantage of the eye's unique access to direct visualization of retinal ganglion cell bodies and axons. Such images might identify new biomarkers – objective, measurable indicators of the disease. The September catalyst meeting thus broadly defined the next grant objective for Catalyst for a Cure:

> *To conduct research to identify new, sensitive, and specific, clinically applicable markers for glaucoma detection, progression, and therapeutic intervention.*

The CFC 2 Scientific Advisory Board

Momentum from the catalyst meeting made the selection process for CFC 2's scientific advisors and primary investigators an exception to our now-usual pattern. The SAB was quickly established and included four of the participants in the catalyst meeting that set the objective. Those named for the CFC 2 SAB, with their affiliations at that time were:

- **Martin Wax, MD, Chair,** Chief Medical Officer and EVP R&D, PanOptica, Inc., Mount Arlington, NJ; Glaucoma Research Foundation Board of Directors; SAB CFC 1 – Redefining Glaucoma
  Dr. Wax was an expert in the field of glaucoma and grounded in the history of work on both research and clinical issues as well as an early advocate for the creation of Catalyst for a Cure.

- **Ben Barres, MD, PhD,** Neurobiology Department, Chair, Stanford University School of Medicine, Stanford, CA
  Dr. Barres' research focused on the interaction between neurons and glial cells in the central nervous system.

- **Scott Fraser, PhD**, Provost Professor of Biological Sciences and Biomedical Engineering, Director of Science Initiatives, University of Southern California, Los Angeles, CA
  Dr. Fraser's work was committed to quantitative biology, applying the tools of chemistry, engineering, and physics to problems in biology and medicine.

- **Martin Raff, MD**, Emeritus Professor, Department of Biology, University College London, London, England, UK; SAB CFC 1 – Redefining Glaucoma
  Dr. Raff's work involved study of optic nerve cells, cell death, and clearance of self-destructive cells by phagocytes.

- **Joel Schuman, MD, FACS**, Professor, Chairman of Ophthalmology,
  UPMC Eye Center, Pittsburgh, PA; Glaucoma Research Foundation, Research Committee
  An ophthalmologist expert in testing for glaucoma, Dr. Schuman and his colleagues were the first to identify a molecular marker for glaucoma, published in 2001.

- **Russ Van Gelder, MD, PhD**, Boyd K. Bucey Professor of Ophthalmology; Chair, Uveitis & Ocular Inflammation; University of Washington, Seattle, WA
  Dr. Van Gelder's research was at the forefront of two fields, non-visual photoreception and pathogen detection in uveitis.

- **Monica Vetter, PhD**, George and Lorna Winder Professor of Neuroscience; Chair, Neurobiology and Anatomy, University of Utah, Salt Lake City, UT; Principal Investigator, CFC 1
  Dr. Vetter continued her focus, following CFC 1 – Redefining Glaucoma, on understanding molecular pathways controlling neural development and degeneration in the retina.

Among those attending the September catalyst meeting were three younger investigators who, in the estimation of the newly established SAB, had distinguished themselves as likely candidates for the new CFC consortium. Considering the skill sets the complete team would need, the fourth principal investigator was recruited, and the team was complete.

The CFC 2 Principal Investigators

The CFC Biomarker Initiative brought together four scientists from prestigious academic centers chosen for their expertise in biomedical imaging, physics, retinal cell biology, neurobiology, and clinical ophthalmology. They were, with their affiliations at that time:

Alfredo Dubra, PhD
Assistant Professor of Ophthalmology and Biophysics
Department of Ophthalmology, The Eye Institute
Medical College of Wisconsin, Milwaukee, WI

Jeffrey L. Goldberg, MD, PhD
Associate Professor of Ophthalmology
Walter G. Ross Distinguished Chair in Ophthalmic Research
Bascom Palmer Eye Institute, Interdisciplinary Stem Cell Institute
University of Miami, Miami, FL

Andrew D. Huberman, PhD
Assistant Professor of Neurosciences, Biology and Ophthalmology
University of California San Diego, San Diego, CA

Vivek J. Srinivasan, PhD
Instructor in Radiology at Harvard Medical School
The Martinos Center for Biomedical Imaging
Assistant in Biomedical Engineering, Department of Radiology,
Massachusetts General Hospital, Charlestown, MA

Photos by Greg Pio

The launch meeting was held in November 2011 for the first three-year term, 2012-2014. Based on the team's progress, reported and reviewed regularly, and with the endorsement of its scientific advisory board, GRF renewed the team's grant for another three years, 2015-2017, and then again, with transitional funding, for one more year, 2018.

The principal investigators of the Biomarker Initiative pursued their agenda together for seven years. Despite the challenges of their particularly diverse specialties, they found ways to improve each other's toolkits while adding to each other's expertise. With customized optical equipment that non-invasively produced clearer images of cellular structures than previously available, they moved research into the clinic and closer to influence on patient outcomes.

CFC 2 launch meeting in November 2011.

Tables on the following two pages include selected statements of the team's goals and accomplishments from their regular reports to their scientific advisory board and their remarks on other occasions during their time as Catalyst for a Cure investigators.

CFC 2 – BIOMARKER INITIATIVE
SELECTED TEAM STATEMENTS OF INTERIM GOALS

2012 Determine (1) if there is/are early cellular/molecular/metabolic markers for glaucoma or glaucoma progression and (2) if novel, non-invasive imaging approaches can be used to visualize them.

2013 Design non-invasive human and mouse imaging techniques and instruments with unprecedented resolution, wider field of view, requiring less time/exposure to light * Test hypothesis that inner retina synapse loss is the earliest change in human glaucoma that can be directly imaged.

2014 Continue study of vascular changes in rodents, glaucoma suspects and patients, and optimize in vivo probe in animal models * Examine non-invasive imaging of human synapses by exploring fluorescence output using viral and other probes.

2015 Continue testing and validating 5 proposed biomarkers for disease onset and progression: (1) retinal microvasculature imaging, (2) structural imaging of melanopsin in RGCs, (3) structural and spectroscopic imaging of the inner retina, (4) metabolic optical imaging of blood flow and oxygenation, (5) in vivo mouse imaging using advanced structural and functional tools for animal and human use.

2016 Further explore structural and metabolic candidate biomarkers in animal models (mitochondrial structure and metabolism, retinal oxygen metabolism, imaging of the inner retina), paying particular attention to Off-pathway function * Emphasize moving testing toward human subjects.

2017 Develop and implement Westheimer Effect visual field test * Use visible light OCT spectroscopy to examine IPL structure and oxygen saturation * Use AO imaging for putative mitochondrial dynamics/metabolic state. All above to include testing/data gathering from patients and normal subjects.

2018 As recommended by the SAB, concentrate on most promising biomarkers to gain sufficient data to determine true potential and bring some closure to the team's research.

CFC 2 – BIOMARKER INITIATIVE
SELECTED TEAM STATEMENTS OF INTERIM ACCOMPLISHMENTS

2012 Completed systematic analysis of variation among each of the major RGC subtypes in normal adult mouse retina, as a baseline for comparison of control and glaucomatous RGCs * Developed imaging and testing protocol for studying the inner retina of glaucoma suspects and patients.

2013 Discovered that dendritic changes occur in some RGC types as early as 7 days after IOP elevation, robustly in large field, Off-alpha RGCs * Completed a new imaging instrument for small and large animal imaging based on novel deformable mirror technology.

2014 Pursued metabolic imaging with spectroscopic OCT, which we recently showed can quantify oxyhemoglobin and deoxyhemoglobin concentrations in blood, and completed ex vivo validation. Began unbiased exploration of cell type and regional changes in the eyes of glaucomatous patients.

2015 Continued efforts to better characterize mitochondrial dynamics in RGCs as well as their relationship with RGC survival and axon growth * Began studies of vascular and inner retinal changes in patients and built a metabolic imaging system (AOSLO) for humans * *Journal of Neuroscience* selected cover story stemming from CFC work.

2016 Concentrated on three aspects of RGC changes: mitochondrial structure and metabolism; retinal oxygen metabolism; and vascular, nerve fiber, and ganglion cell components of the inner retina.

2017 Measured Westheimer effect on normal subjects and glaucoma patients * Using visible light OCT ophthalmoscope, made progress toward visualizing synaptic sublayers of the retina * Developed additional data on mitochondrial response to axon growth therapies in animal models.

2018 Using improved visible light OCT instrumentation, provided images in the IPL which contains the On/Off RGCs identified as the earliest cells damaged in glaucoma * Using further improved AOSLO, continued to study microcysts found in the inner nuclear layer, looking for correlation with early and progressive changes in RGCs.

The CFC 2 team, the Biomarker Initiative, submitted its final report in February 2019.

Final Report, February, 2019
Alfredo Dubra, Jeffrey L. Goldberg, Andrew Huberman, Vivek Srinivasan

Summary

This is the final report of the 7-year Catalyst for a Cure (CFC) Biomarker Initiative. Starting from fundamental biology of glaucoma, the CFC team developed new structural and functional diagnostic tests to assess the very earliest changes in glaucoma, prior to death of ganglion cells, in humans. The team also developed new therapeutic strategies for salvaging vision loss and engaging plasticity in glaucoma patients. The team is now validating these approaches during glaucoma progression and in patients receiving candidate therapies, with encouraging early results. Some of the ideas conceived by the CFC team under the Biomarker Initiative have already received funding from the National Institutes of Health (National Eye Institute), with additional promising collaborative grant applications pending. At the same time, the team is refining their approaches and pursuing pathways towards commercialization and widespread adoption of their approaches in clinical practice.

Throughout the Biomarker Initiative, the critical feedback and engagement of the Scientific Advisory Board was essential in honing the team's line of attack. The team science approach, promoted by the GRF, revealed synergies and enabled progress that could not have been achieved by any individual laboratory alone. The CFC members thank the GRF for the opportunity to participate in this unique research model. The experience has pointed the way forward for the investigators to continue to improve glaucoma progression detection and management, and prevent further loss of vision from this disease.

Detailed Report

Here, we highlight a few findings and innovations from the CFC Biomarker Initiative that the team believes to be the most impactful. A more comprehensive summary of the findings can be found in previous annual reports, publications listed below, and an invited review article, "Discovery and Clinical Translation of Novel Glaucoma Biomarkers," Progress in Retinal and Eye Research, Volume 80, January 2021.

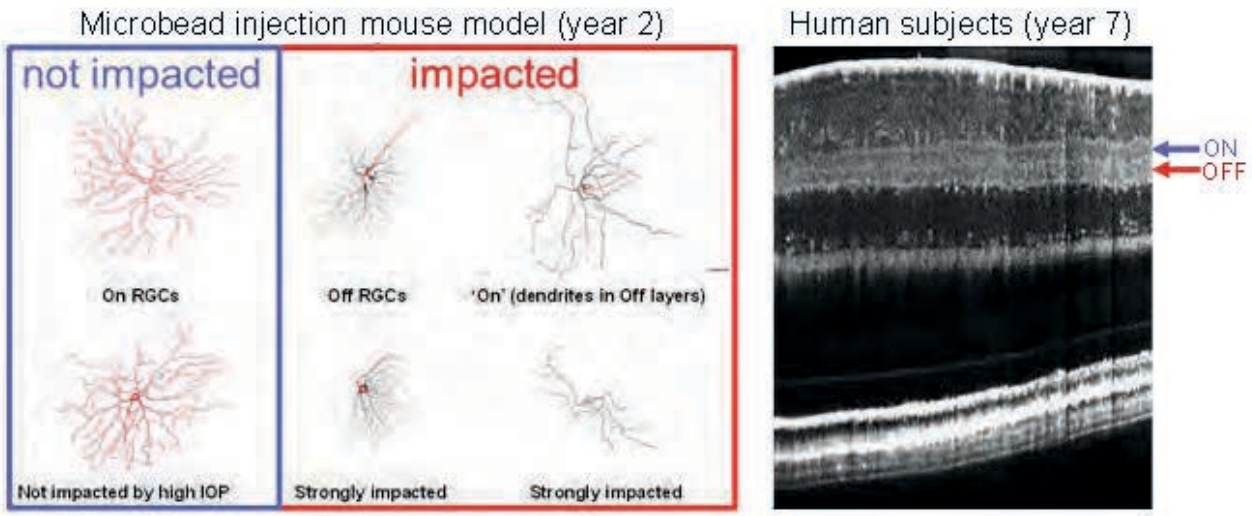


Figure 1. In year 2, the team identified dendritic retraction as a very early biological change in stressed ganglion cells, and found earliest changes in the off sublamina of the inner plexiform layer (IPL). The former finding has since been confirmed by multiple laboratories. In year 7, the team developed a novel approach that uses visible light Optical Coherence Tomography (OCT) to visualize and quantify subtle differences in reflectivity in the inner plexiform layer that are indicative of synaptic organization, providing the first opportunity to assess these putative early changes quantitatively in living humans with glaucoma.

Experimental mouse studies performed early by the CFC team (Figure 1) suggested that the dendritic morphology of ganglion cells and possibly their synaptic partners change in early glaucoma, and more specifically, that these changes are earliest and most predictive in the off sublamina of the inner plexiform layer (IPL). The IPL, comprising dense connections between bipolar cell axons, amacrine cells, and ganglion cell dendrites, is moderately reflective on Optical Coherence Tomography (OCT) images, but its internal structure has been visualized only anecdotally. In years 4-7, by custom designing an optimized visible light OCT system, the team demonstrated the ability to clearly image the internal structure of the IPL by its intrinsic reflectivity. The 3 hyper-reflective bands and 2 hypo-reflective bands observed with visible light OCT correspond well with the standard anatomical division of the IPL into 5 layers (Figure 1). Synapse density or neurite orientation, size, and density, which vary across sublaminae, may generate this reflectivity contrast. If the anatomical strata coincide with the reflective bands as the data suggest, the on- and off- sublaminae can now be quantified in human subjects. Thus, our results suggest IPL sublamina thickness, reflectivity, and contrast (the variation between layers) as promising human biomarkers for early subtle morphological changes seen in experimental glaucoma.

Ongoing improvement in imaging hardware, as well as optimization of scanning protocols and image processing, will lead to further improvements in image quality in glaucoma

patients. In addition to high-end research instrumentation, we are retrofitting commercially available OCT instruments to provide similar images, albeit with lower resolution, but with the potential to have a more immediate and widespread impact on glaucoma management.

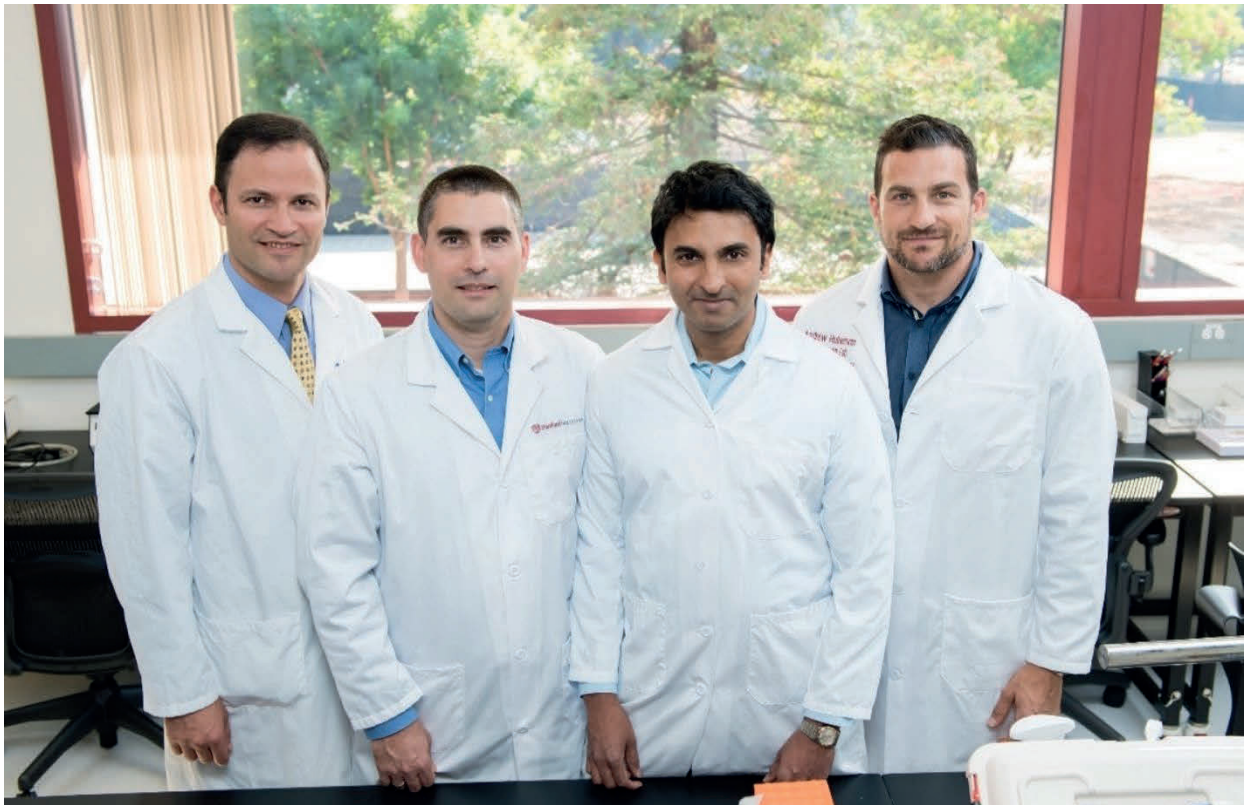
A second biomarker that grew out of the findings that OFF RGCs degenerate early in glaucoma is a functional assay for ON and OFF visual pathway probing in glaucoma patients. We first determined whether electrophysiological response properties of the ON and OFF visual pathways observed in animal experimental models can be observed in humans. Visual evoked potentials (VEPs) were recorded in response to contrast increments and decrements presented using sawtooth temporal waveforms and a facilitating stimulus that leveraged the previously described Westheimer effect. VEP responses were analyzed as a function of stimulus size and visual field location initially in healthy adult participants and subsequently in glaucoma patients in a range of severities. We found that the VEP responses were larger in amplitude and shorter in latency for contrast decrements than for contrast increments in normal patients, suggesting that normal patients have a preferential OFF pathway sensitivity. Remarkably patients with mild or severe glaucoma show an increasing level of OFF preference loss, paralleling the data from animal models. Thus specific stimuli elicit VEP responses that allow differential detection of ON and OFF pathways in human, an approach that may be applied in future work to glaucoma detection and measures of progression. We are continuing this work collaboratively now with follow-on funding from the National Eye Institute, measuring OFF pathways using the novel VEP and measuring IPL with visible light OCT in the same patients.

On the non-invasive imaging front, we have established non-confocal (split detection) adaptive optics scanning laser ophthalmoscopy (AOSLO) of inner nuclear layer microcysts as a potential predictive biomarker in glaucoma. We showed that high resolution AOSLO provides higher sensitivity (20% vs 5%) for detection of microcystic changes, which may be missed on conventional imaging techniques such as OCT. Monitoring these changes can be a useful biomarker for glaucoma progression potentially aiding in the evaluation of new therapies and routine patient care management. Additionally, we have developed a way to visualize axonal transport from high frame rate AOSLO reflectance imaging of the nerve fiber layer. We are investigating these and other imaging biomarkers in a recombinant human nerve growth factor clinical trial for glaucoma.

Finally, we designed a novel immersive virtual reality technology to stimulate the human retina in specific locations, using RGC subtype specific stimuli to trigger maximal firing of the RGCs most vulnerable in glaucoma. After receiving IRB approval for this study last year, we have already enrolled a handful of glaucoma subjects. The overall design of the study includes patients with and without nerve growth factor implants and in patients with varying degrees of retinal degeneration. We expect to have data from 200 patients within 2 years, pending securing of additional funding to support this work.

The team's research bibliography is contained in the appendix that follows.

Comments on
CFC 2 – Biomarker Initiative



For the CFC2 Biomarker Initiative, it was important to have a clinician-scientist on the team. Jeffrey Goldberg, MD, PhD, brought a unique and important perspective to the consortium due to his clinical background.

Photo by Genevieve Shiffrar

The principal investigators of the Catalyst for a Cure Biomarker Initiative (CFC 2) worked together from 2012 through 2018. The scientists' goal was to identify new, clinically applicable markers for glaucoma detection, progression, and therapeutic intervention. In aid of this objective, the team developed state-of-the-art imaging equipment to non-invasively measure the structural and biological changes in the nerve cells of the eye due to glaucoma.

An adaptive optics scanning laser ophthalmoscope (AOSLO) was improved technically and used to provide extremely high-resolution images of the retina, making it possible to see a patient's retinal ganglion cells directly and to visualize the transport of mitochondria within the cells. Changes in routine cell activity may be useful as indicators of deteriorating cell health.

The team also developed an improved optical coherence tomography (OCT) ophthalmoscope, using visible light to image specific layers in the retina with unprecedented depth resolution and contrast. These layers include the inner plexiform layer (IPL) which contains the ON/OFF neurons.

The CFC Biomarker team also discovered that certain retinal ganglion cells, in particular the OFF neurons, were more susceptible to damage from glaucoma than others, a potential "canary in the coal mine." The images of these cell subtypes reveal changes that may serve as an early biomarker to predict glaucoma and/or early glaucoma progression before vision loss occurs. In addition, the team designed a new test to specifically assess the functioning of these cell subtypes. The test is more objective and may be both more sensitive to glaucoma and easier for patients than the conventional visual field test. Functional tests for these retinal ganglion cells and other newly identified biomarkers have been validated in models of glaucoma and, by the end of the CFC 2 team effort, were being tested in patients.

At the final review meeting in February 2019 their advisors complimented the team on excellent progress and images shown. They also observed that the level of collaboration among the PIs and their labs had continued to increase while they brought new skills and technology to glaucoma research. The advisors were also pleased to learn that a recommended biomarker review article was in its final stages preparatory to submission in the coming weeks and that the scientists looked forward to continuing their research to preserve and restore vision.

Jeffrey Goldberg, MD, PhD was the first clinician-scientist on a CFC team. With the advantages of a glaucoma specialist on the team both CFC3 and CFC4 teams also have clinician-scientists as principal investigators.

Photo by Genevieve Shiffrar

CFC 3
The Steven and Michele Kirsch Vision Restoration Initiative
2019 – 2024*

**Active, continuation contingent on annual reviews and approvals*

In November 2017, as the CFC 2 Biomarker Initiative was approaching its 7th and final year, some of GRF's leadership and members of GRF's Research Committee were attending an ophthalmic industry meeting in New Orleans.

GRF's Research Committee:

David J. Calkins, PhD, Chair
Cynthia Grosskreutz, MD, PhD
Robert Stamper, MD
Martin Wax, MD
Adrienne Graves, PhD
Joel Schuman, MD
Monica Vetter, PhD

GRF Leadership:

Tom Brunner, President & CEO
Nancy Graydon, EDD & COO

They gathered to discuss next steps for the Catalyst for a Cure program and agreed that it was time to leverage the results from the first two CFC teams:

CFC 1 – Redefining Glaucoma had clarified the mechanisms of progression
CFC 2 – The Biomarker Initiative enabled clearer clinical outcomes

The CFC's "Audacious Goal"

The next step was to set CFC's own "audacious goal" of restoring vision that has already been lost to glaucoma. *

** In 2013, the National Eye Institute (NEI) launched a program with an unconventional goal. The NEI challenged the ophthalmic and vision research community to seek creative and pioneering initiatives that would fundamentally advance research over the next 10 to 15 years. Competitive grants were intended to give researchers more room to be ambitious and truly "audacious."*

At about the same time, in another institutional turnabout, the NEI specifically endorsed "cross-functional groups" and collaboration.

To further the discussion, GRF put together a brief white paper, *Exciting Areas in Vision Restoration and Optic Nerve Regeneration.* The paper opened and then closed as follows (references omitted):

> *Following the second Catalyst for a Cure (CFC) initiative's focus on identifying new biomarkers for glaucoma, Glaucoma Research Foundation and its advisors have identified vision restoration and optic nerve regeneration as potential areas of focus for the third CFC.*
>
> *Among the wide range of work being done in RGC replacement for vision restoration, we think the most compelling areas of focus include (1) the generation of induced pluripotent stem cell (iPSC) -derived RGCs and (2) strategies to promote the growth and integration of axons post-RGC regeneration/transplantation toward target tissues in the brain.*

After further discussions in San Francisco, GRF's Board of Directors unanimously agreed to support the next CFC collaboration which would focus on vision restoration.

The CFC 3 Scientific Advisory Board

By May of 2018 a new Scientific Advisory Board, composed of leading experts in neurodegeneration, was established for CFC 3. They would oversee the direction of the research and identify principal investigators for the initiative, to be launched in January 2019. With their affiliations at that time, the five SAB members named were:

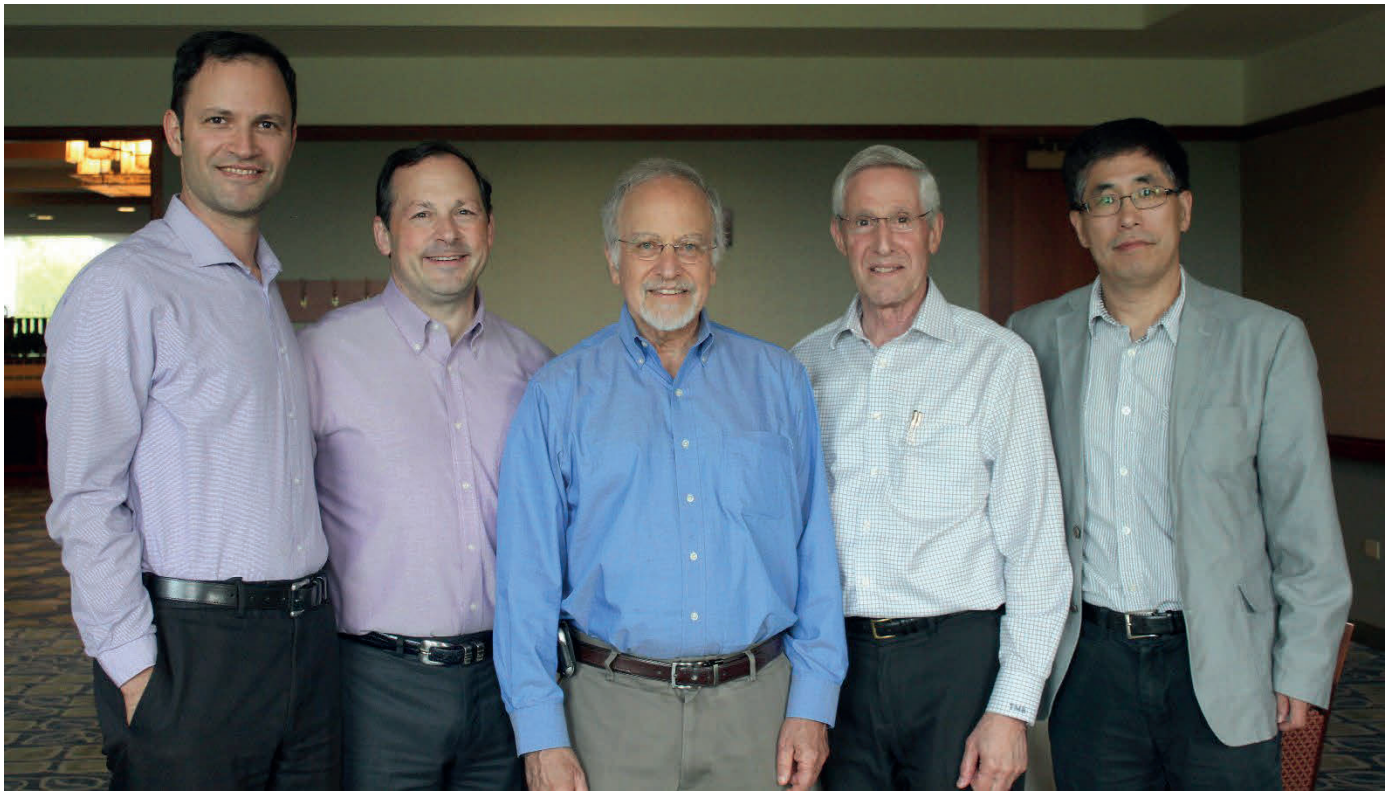
- **David J. Calkins, PhD, Chair**, Denis M. O'Day Professor of Ophthalmology and Visual Sciences, Vice Chairman and Director for Research, The Vanderbilt Eye Institute; Director, Vanderbilt Vision Research Center, Vanderbilt University Medical Center, Nashville, TN; Principal Investigator, CFC 1 – Redefining Glaucoma; Chair, GRF Research Committee
  Dr. Calkins' lab continued to focus on the molecular mechanisms of neurodegeneration in glaucoma.

- **Larry Benowitz, PhD**, Professor of Neurosurgery and Ophthalmology, Harvard Medical School; Neurosurgical Innovation and Research Endowed Professor, Boston Children's Hospital, Boston, MA
  Dr. Benowitz's lab seeks to discover basic mechanisms that control the growth of nerve connections.

- **Valeria Canto-Soler, PhD**, Doni Solich Family Chair in Ocular Stem Cell Research; Director of CellSight, University of Colorado School of Medicine, Aurora, CO
  Dr. Canto-Soler's research aims to understand mechanisms governing eye development and establish novel stem-cell based therapeutics to treat ocular diseases.

- **Jeffrey L. Goldberg, MD, PhD**, Professor and Chair, Department of Ophthalmology, Stanford University School of Medicine, Stanford, CA; Principal Investigator CFC 2 – Biomarker Initiative
  Dr. Goldberg continues research on neuroprotection and regeneration of RGCs and focuses his clinical efforts on patients in need of medication or surgery for optic nerve disease and cataract.

- **Zhigang He, PhD, BM,** Professor of Neurology and Ophthalmology, Harvard Medical School; Research Associate, Boston Children's Hospital, Boston, MA
  Dr. He's lab seeks to restore lost function after CNS injuries by promoting axon regeneration and enhancing neuronal plasticity.



Tom Brunner (second from right) with members of the CFC 3 Scientific Advisory Board at their planning meeting in July 2018.

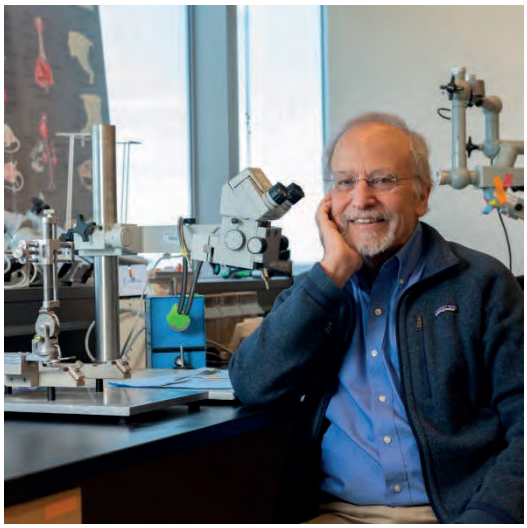
Photo by Nancy Graydon

The CFC3 Scientific Advisors

Top:
David Calkins, PhD (Chair, 2018 – 2021)

Middle:
Larry Benowitz, PhD
Valeria Canto-Soler, PhD

Bottom:
Jeffrey L. Goldberg, MD, PhD
(Chair, 2022 – Present)
Zhigang He, PhD, BM



The CFC 3 Principal Investigators

The advisors for the Vision Restorative Initiative held their first meeting in July 2018 at Chicago, Illinois and set about identifying prospects for the research team, this time using the CFC's now regularized process (described earlier). The PIs were chosen for their expertise in retinal ganglion cell restoration, replacement or repair, neuroprotection, and clinical ophthalmology. With their affiliations at the time, they were:

Xin Duan, PhD, Assistant Professor, Department of Ophthalmology and Physiology, Weill Institute for Neurosciences, University of California, San Francisco

Dr. Duan's laboratory investigates retinal ganglion cells subtype-intrinsic factors and tests their roles in optic nerve regeneration and vision recovery.

Yang Hu, MD, PhD, Assistant Professor, Department of Ophthalmology, Stanford University School of Medicine, Stanford, CA

The Hu laboratory studies the mechanisms responsible for neuronal degeneration and axon regeneration, focusing on clinically relevant scenarios and therapies for vision restoration.

Anna La Torre, PhD, Assistant Professor, Department of Cell Biology and Human Anatomy, School of Medicine, University of California, Davis

Dr. La Torre's laboratory generates retinal ganglion cells from stem cells to enhance axonal growth and cell survival and, ultimately, to use as donor cells for disease modeling and therapy.

Derek Welsbie, MD, PhD, Assistant Professor of Ophthalmology, San Diego Shiley Eye Institute, University of California, San Diego

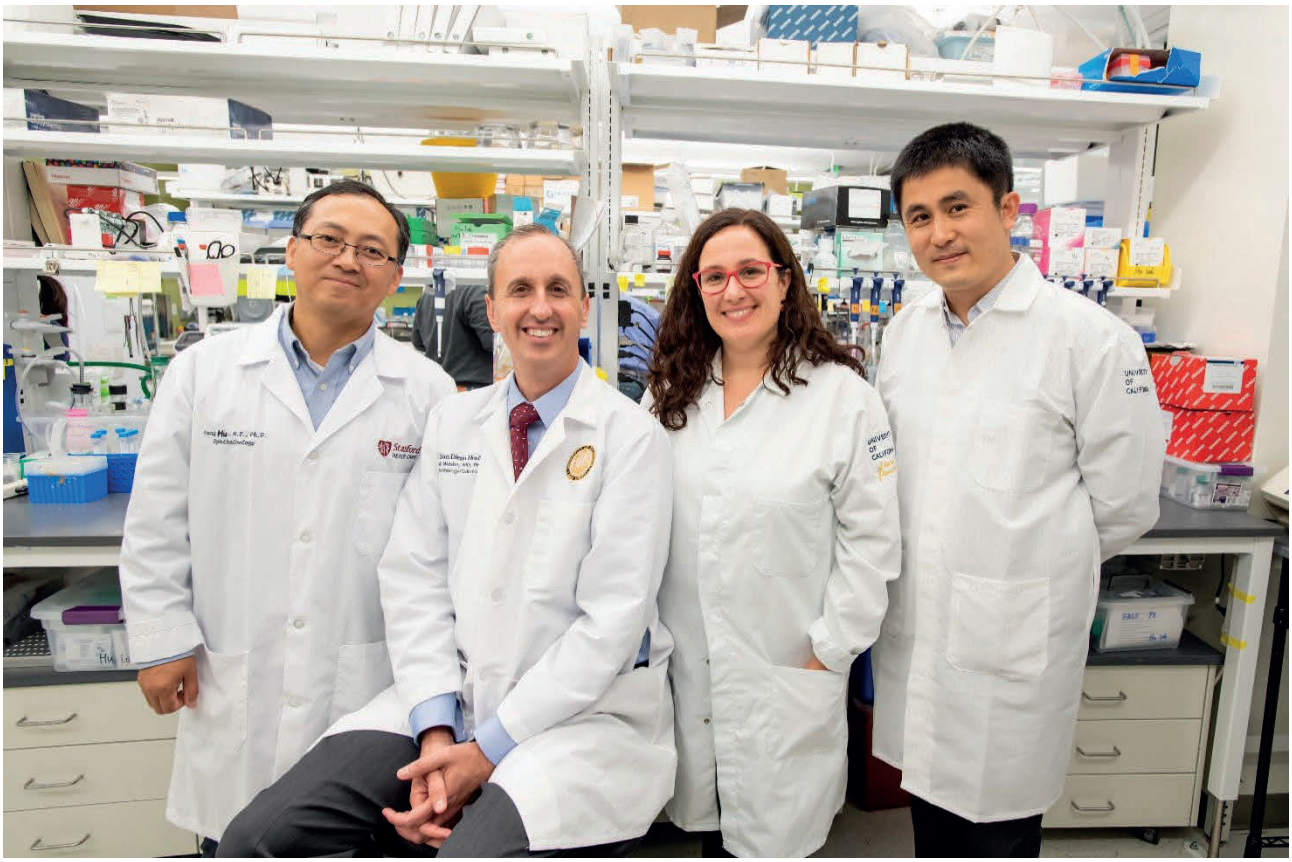
The Welsbie lab focuses on identifying genes that are causally involved in retinal ganglion cell death, degeneration, and regeneration, as well as neuroprotective drug therapies for RGCs.

Photos by Genevieve Shiffrar

With a grant agreement that described their engagement to conduct research to identify new therapeutic interventions to restore vision lost to glaucoma, the new Vision Restoration team held its launch meeting in February 2019 and outlined its approach and achievable goals for the first year.

The first three years' work resulted in recommendations for renewal from both the SAB and GRF's research committee. GRF's board of directors voted to extend for 2022-2024. At about the same time, David Calkins took on a more senior role at Vanderbilt that required him to relinquish his work with GRF. GRF asked Jeff Goldberg, already on the SAB for CFC 3 and formerly a principal investigator for CFC 2, to take on the role of CFC 3 SAB chair.

The principal investigators of CFC 3, Vision Restoration, at this writing, are in the fourth year of their collaboration, doing what Jeff Goldberg calls "team science." Tables on the following pages show their interim goals and accomplishments to date:



CFC3 was launched with the goal to solve one of the greatest unmet medical needs expressed by glaucoma doctors and patients, vision restoration. This team is making excellent progress in both neuroprotection and stem cell replacement of lost retinal nerve cells. Left to right: Yang Hu, MD, PhD, Derek Welsbie, MD, PhD, Anna La Torre, PhD, Xin Duan, PhD

Photo by Genevieve Shiffrar

CFC 3 – THE STEVEN AND MICHELE KIRSCH VISION RESTORATION INITIATIVE*
SELECTED TEAM STATEMENTS OF INTERIM GOALS

2019 (1) Better understand intrinsic properties of RGCs in order to optimize for engraftment and (2) screen select mouse cells to identify (a) genes whose manipulation may improve donor RGC survival and integration and (b) neuroprotective strategies that prevent RGC death and axon degeneration. More specifically: Complete first round of RGC transplantations (using a subtype already known to be expressed in retinal organoids) * Use CRISPR-based screening to identify genes whose activation / inactivation improves donor RGC survival and integration * Begin trial evaluation of neuroprotective strategies and targets with AAV/CRISPR knockouts in the pupillary block mouse model.

2020 We have consolidated research aims to focus on development of (1) a regenerative therapy and (2) a neuroprotective / neuroenhancement therapy * Expand efforts to characterize the developmental trajectories of different RGC subtypes * Expand on recent discovery of GCK-IV kinase inhibition as a strategy to promote axon regeneration * Test axon-regeneration strategies in combination with GCK-IV knockout to look for robust endogenous RGC regeneration.

2021 Test whether surgical disruption of the ILM improves RGC transplantation * Validate whether GCK-IV kinase inhibition improves survival and neurite extension * Test whether overexpression of OPN (osteopontin), a protein more prevalent in resistant RGCs, can elicit neuroprotective effects in stem cell-derived RGCs in culture and in transplantation * Screen about 20 of 40 genes identified as possible neuroprotection targets in the SOHU mouse model.

2022 Continue measuring response of transplanted RGCs to various potential treatments and monitoring electrical activity to determine if they are connected appropriately to provide functional vision * Test two key candidate neuroprotection strategies in Rhesus macaque cultures * Validate whether inhibition of DLK/LZK in large animal (pig) model of glaucoma improves RGC survival and neurite extension * The collaborative goal is to have a comprehensive road map for functional restoration in three to five years.

2023 Extend efforts to promote transplanted RGC survival with additional molecules as well as combinatorial treatments * Shift testing of transplanted RGC function by screening with several molecules normally involved in the stability of the ILM and cell migration pathways * Relate single-cell resolution tracings of axonal regeneration cues to tracings linking eye to brain targets in order to understand regenerating axon targets * The collaborative goal remains to have a comprehensive road map for functional restoration in three to five years.

**Active, continuation contingent on annual reviews and approvals*

CFC 3 – THE STEVEN AND MICHELE KIRSCH VISION RESTORATION INITIATIVE*
SELECTED TEAM STATEMENTS OF INTERIM ACCOMPLISHMENTS

2019 Created specialized biological tools to identify the different types of RGCs, then to label and monitor * Building expertise in single cell RNA-sequencing analysis related to identification that many subtypes are not yet developed in stem cell cultures * Started transplantation experiments using mice and organoid-derived donor cells * Identified a new molecular pathway (GCK-IV kinase inhibition) that increased survival of RGCs *and* promoted growth of new axons.

2020 Showed that inhibition of GCK-IV kinases led to significant improvement in both survival and neurite outgrowth of RGCs in mouse retinal organoids * Adjusted to an imaging lab closure (due to COVID-19) and, based on work indicating that the internal limiting membrane (ILM) is a significant barrier, improved surgical techniques for transplantation * Used remote meetings to discuss and study additional collaborative projects following release from various shelter-in-place orders * Developed an imaging technique to test whether transplanted cells are making useful connections with the rest of the retina.

2021 Confirmed that scraping the retina creates breaks in the ILM and increases penetration of neurites from transplanted RGCs *Created new RGCs and implanted in model retinas * Tested treatments to improve nerve cell survival * Developed imaging that can evaluate RGC function in vivo and tracers to visualize neurons functioning in retina circuits * Collaborated with another lab to develop differentiation protocols for large mammal induced pluripotent stem cells (Rhesus macaque iPSCs).

2022 Showed that GCK-IV kinase inhibition highly promotes donor RGC survival within a host eye * While transplanted donor RGC survival has been improved, an unbiased screening strategy failed to show ability of these cells to engraft with the host * Discovered axonal regenerating cues at single-cell resolution and developed a new tracing method linking the eye to the brain targets at single-neuron resolution * All labs are aiming to translate basic knowledge from mouse retinal neuron diversity to human and non-primate models with plans to broaden the investigation using neuroprotective strategies previously identified.

**Active, continuation contingent on annual reviews and approvals*

CFC 4
The Melza M. and Frank Theodore Barr Catalyst for a Cure Initiative To Prevent and Cure Neurodegeneration 2022 h2 – 2025 h1*

**Active, continuation contingent on annual reviews and approvals*

In April 2021, yet another catalyst meeting was convened, inspired by Ted and Melza Barr.

Due to the COVID-19 pandemic, the meeting was held virtually. Additional support was provided by BrightFocus Foundation. More than twenty leading scientists in glaucoma, Alzheimer's, and Parkinson's met to discuss the topic, "Solving Neurodegeneration." The meeting has been described as exceptionally productive and energizing, and a number of the participants created a lengthy white paper afterwards, *Solving Neurodegeneration: Common Mechanisms and Strategies for New Treatments.* *****

* Lauren K. Wareham, Shane A. Liddelow, Sally Temple, Larry I. Benowitz, Adriana Di Polo, Cheryl Wellington, Jeffrey L. Goldberg, Zhigang He, Xin Duan, Guojun Bu, Albert A. Davis, Karthik Shekhar, Anna La Torre, David C. Chen, M. Valeria Canto-Soler, John G. Flanagan, Preeti Subramanian, Sharyn Rossi, Thomas Brunner, Diane E. Bovencamp, and David J. Calkins

The following brief excerpts from the white paper, references omitted, reveal some of the premises and conclusions that drove the launch and purpose of the CFC 4 initiative, Prevent and Cure Neurodegeneration.

From the "Abstract"

> *Across neurodegenerative diseases, common mechanisms may reveal novel therapeutic targets based on neuronal protection, repair, or regeneration, independent of etiology or site of disease pathology. Glaucoma, which causes vision loss through degeneration of the optic nerve, likely shares early cellular and molecular events with other neurodegenerative diseases of the central nervous system. Here we discuss major areas of mechanistic overlap: aging, inflammation, bioenergetics and metabolism, and neurovascular interactions. We summarize important discussion points with emphasis on*

the research areas that are most innovative and promising in the treatment of neurodegeneration yet require further development. The research that is highlighted provides unique opportunities for collaboration that will lead to efforts in preventing neurodegeneration and ultimately vision loss.

From the "Conclusions"

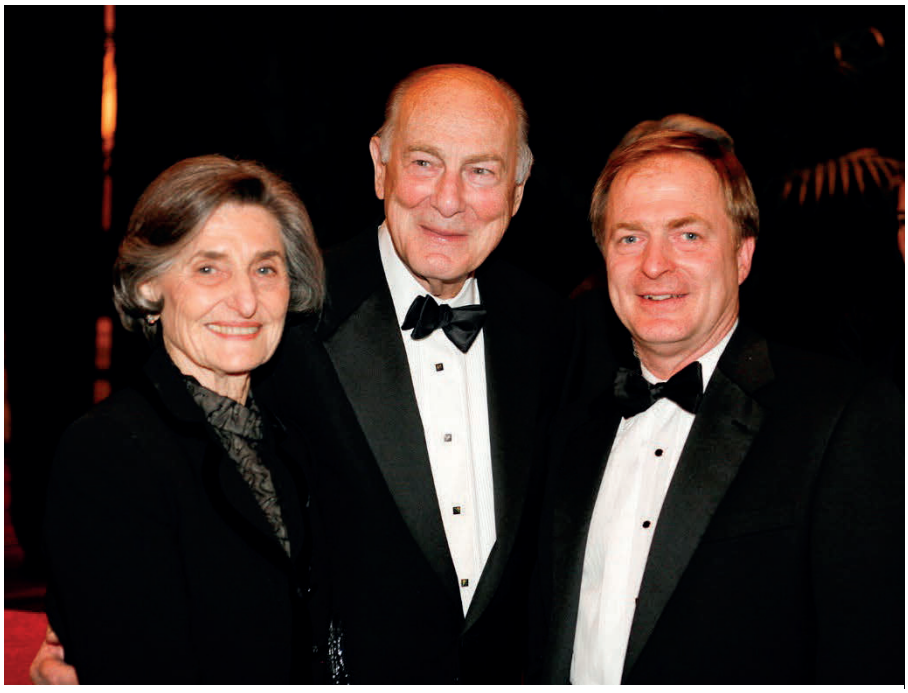
Providing patients with effective strategies to treat or prevent neurodegenerative disease is a monumental challenge that scientists and clinicians alike will increasingly face as the population ages and incidence of disease increases. Reaching these goals will rely on a greater understanding of the common pathological mechanisms across the entire spectrum of neurodegenerative diseases, which include diseases of the brain and by extension, the visual system. Focusing solely on linking molecular mechanisms to a single disease can lead to siloed thinking, unable or unwilling to make major leaps forward in the development of advanced treatments and cures applicable to the broader picture.

In this "think tank" style meeting, with multidisciplinary experts from all aspects of human CNS neurodegeneration, we have identified several common molecular mechanisms of disease that highlight the most promising avenues for fruitful collaboration. We believe that the commonalities among diseases provide new and exciting collaborative research opportunities that we can harness to discover new therapeutics and clinical strategies.

The Preliminary Goal for a Fourth CFC Consortium

As expected, GRF subsequently determined to build upon 20 years of CFC collaboration and leverage new technologies in regenerative medicine for neuroscience to create a fourth CFC consortium. The preliminary goal of this initiative is:

To harness multidisciplinary, collaborative, and integrative approaches to develop breakthrough strategies to cure neurodegeneration across diseases and, specifically, to prevent loss of visual function and restore vision in glaucoma.



Melza, Ted, and Terence Barr at a GRF Gala. Ted Barr inspired and supported the initial Catalyst Meeting in April 2021 that led to the establishment of the 4th Catalyst for a Cure team.

The CFC 4 Scientific Advisory Board

Membership of the scientific advisory board for CFC 4 was established by the end of 2021. Each of those named had participated in the April 2021 catalyst meeting that laid the groundwork for this effort and provides expertise in neurodegeneration and regenerative medicine. They and their affiliations are:

- **Adriana Di Polo, PhD, Chair,** Professor of Neuroscience, University of Montreal, Canada
  Dr. Di Polo's research focuses on the development of therapeutic strategies for neuroprotection in glaucoma, the identification of signaling pathways that regulate neuronal survival and regeneration, and the characterization of neuron-glia interactions in the injured retina.

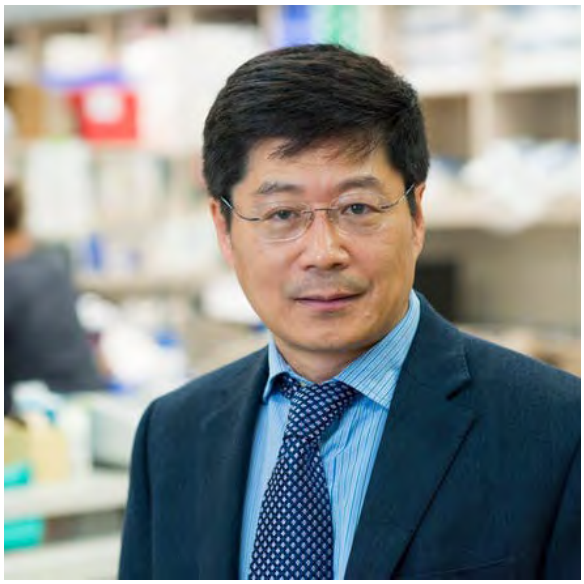
- **Guojun Bu, PhD,** Chief Scientific Officer, SciNeuro Pharmaceuticals and Editor-in-Chief, Molecular Neurodegeneration; Bu was the former Chair of Neuroscience at the Mayo Clinic, Jacksonville, FL
  Dr. Bu's research is centered on understanding the pathogenesis of Alzheimer's disease and related dementias. He also collaborates with Mayo Clinic's Center for Regenerative Medicine, studying the cellular mechanisms of brain disorders and developing future replacement therapy.

- **Shane A. Liddelow, PhD,** Assistant Professor, Department of Neuroscience, Physiology and Ophthalmology, New York University, NY
  The Liddelow lab focuses on mechanisms that induce different forms of reactive astrocytes and how these interact with other cells in the CNS. The lab uses high throughput single cell and bulk RNA sequencing, spatial transcriptomics, genetic engineering, and modern *in vitro* modeling to investigate disease mechanisms and, ultimately, to aid development of new therapies for CNS injury and diseases.

- **Sally Temple, PhD,** Scientific Director, Principal Investigator, and Co-Founder, Neural Stem Cell Institute, Albany, NY
  Dr. Temple's lab works on using neural stem cells to develop therapies for eye, brain, and spinal cord disorders. The lab contributes to stem cell research by characterizing neural stem cells and the intrinsic and environmental factors that regulate their behavior.

The CFC 4 Scientific Advisors

Adriana Di Polo, PhD, Chair



Guojun Bu, PhD

Shane A. Liddelow, PhD

Sally Temple, PhD

The CFC 4 Principal Investigators

The newly assembled scientific advisory board for CFC 4 met with leadership of GRF and the Barr foundation in January and March of 2022 to review the goals of this initiative, their roles as advisors, and the qualifications and recruitment of the principal investigators. The search for PIs was conducted with CFC's now-usual process (described in Part I above). Finalists were interviewed in late May and the CFC 4 principal investigators named in early June. With their affiliations, they are:

Sandro Da Mesquita, PhD, Assistant Professor, Department of Neuroscience, Meningeal Lymphatics and Neurological Disorders Lab, Mayo Clinic, Jacksonville, FL

Dr. Da Mesquita's unique expertise is in the field of brain vascular biology, which has implications for Alzheimer's and other neurodegenerative diseases.

Milica Margeta, MD, PhD, Physician and Surgeon, Massachusetts Eye and Ear; Assistant Professor of Ophthalmology, Harvard Medical School, Boston, MA

Dr. Margeta is a glaucoma clinician and surgeon and a leader in the biology of microglia (unique cells of the brain and spinal cord) and neuroinflammation.

Karthik Shekhar, PhD, Assistant Professor, Department of Chemical and Biomolecular Engineering; Faculty Scientist, Lawrence Berkeley Laboratory; Member, Helen Wills Neuroscience Institute; University of California, Berkeley

A leader in computational biology, Dr. Shekhar has played a key role in collaborations that span neuroscience, immunology, single cell genomics, genetics, and machine learning, with a focus on visual systems.

Humsa Venkatesh, PhD, Assistant Professor, Program in Neuroscience, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Dr. Venkatesh's discoveries have shaped the emerging field of cancer neuroscience, illuminating the nervous system's role in disease progression.

Photos by Jay Watson

The First CFC 4 Consortium Meeting

Members of the CFC4 met for the first time in person at a two-day launch meeting in San Francisco in July 2022. Left to right: Milica Margeta, MD, PhD, Karthik Shekhar, PhD, Sandro Da Mesquita, PhD, and Humsa Venkatesh, PhD.

Photo by Jay Watson

Team members met in person for the first time in July 2022. They devised an approach for the first year of their collaboration and a rough sketch of likely work for the three-year term.

The current statement of the team's overarching goal is*: To explore similarities and differences among glaucoma and other conditions that stem from the death of neurons in the eye, brain, or spinal cord, in search of potential preventive measures and cures for all neurodegenerative illnesses.*

The CFC 4 team's initial priority is: *To identify promising avenues of exploration, drawn from their areas of expertise, that could reveal how and why neurons die — the first step toward preventing and curing neurodegeneration.*

CFC 4 – THE MELZA M. AND FRANK THEODORE BARR FOUNDATION INITIATIVE TO PREVENT AND CURE NEURODEGENERATION*

Launched in July 2022

SELECTED TEAM STATEMENTS OF INTERIM ACCOMPLISHMENTS

2023 H1 (February): Generated protocol for pilot experiment, optimizing methods and techniques to efficiently isolate non-neural cells from different mouse central nervous system tissues (forebrain, retinas, and optic nerves) and to evaluate their transcriptome by single-cell and/or single-nucleus RNA sequencing * Established computational methods to analyze the data sets, including incorporation of glial transcriptions from several mouse models that have been previously analyzed.

Team members are also using the forum created by the GRF on collaborations outside the CFC 4 proposal: Shekhar and Margeta have each submitted proposals involving the other and focused on glaucoma to the BrightFocus Foundation. Additionally, Shekhar and Duan (CFC 3) are collaborating to apply spatial transcriptomics to retinal whole mounts with the aim of spatially mapping each of the approximately 45 types of mouse retinal ganglion cells. Their proposal, "*A spatial transcriptomics approach to identify molecular changes and multicellular interactions underlying retinal neurodegeneration in glaucoma,"* has been funded by BrightFocus Foundation. In addition, Shekhar received The Dr. Douglas H. Johnson Award from BrightFocus in April 2023 to recognize "exceptionally promising and forward-thinking ideas in the field of glaucoma."

At the CFC4 Launch Meeting in July 2022, the Principal Investigators devised an approach for their first year of their collaboration and made an initial outline of their work for the three-year term.

AFTERWORD

As David Calkins said in his foreword, scientific discovery is a continuous process building on all that goes before. Perhaps the key word is continuous. I would add that discovery benefits greatly from diversity of thought and resolution of conflict through collaboration. The real value of the Catalyst for a Cure collaborative research model is the recognition of that and the conscious effort to create small teams of scientists open to new ideas and willing to share their discoveries, affirming or surprising, to advance the science and provide real progress toward solving serious medical problems like glaucoma, vision loss, and neurodegeneration.

Looking back over Glaucoma Research Foundation's 45-year history, it's apparent that the founders' goal of pursuing research to save vision and improve quality of life for glaucoma patients is being achieved. In fact, in just the last ten years the number of new drugs and devices to save vision for glaucoma patients is truly amazing. Forty-five years ago, no one could have predicted the highly effective, innovative drugs with minimal side effects available now. Nor could anyone have imagined the "interventional" glaucoma strategies in use today, inserting drainage devices or sustained release drugs that preserve vision without any continuing patient effort. And most recently, studies have shown the effectiveness of using laser light energy to stimulate remodeling of the drainage tissues in the eye to preserve vision.

All these developments resulted from investment in research and scientific discovery. Each built on an innovative idea and the contributions of many others to develop and translate the ideas into products that doctors can use to better help patients. Today as we look to the future, we cannot predict the new approaches that will help patients, that will eradicate glaucoma, and that will restore lost vision. What we can do is continue to invest in collaborative and innovative research knowing that, just as in the past 45 years, those investments will lead to techniques and treatments we cannot imagine with benefits to patients that would be amazing today.

Philanthropy plays an essential role in innovation. We have been extremely fortunate to have visionary leadership over the past 45 years. Glaucoma Research Foundation was established in 1978 by two grateful patients and this legacy of giving continues. Cornerstone contributions from Steven and Michele Kirsch, followed by significant investments from Ted and Melza Barr, inspired and nurtured our collaborative research initiatives over two decades. In addition, thanks to more than 5,000 gifts received annually, we are able to make a real impact on the field of glaucoma research.

Volunteers, as well as donors, have been critical to our success. Our Scientific Advisors give generously of their time and expertise and serve as incredible mentors to our investigators. And our Board of Directors, committee members and other dedicated individuals, all come together to make our work possible.

We hope that this book, sharing our learning about the creation and implementation of collaborative research, will be helpful in the ongoing process of discovery. We invite readers to utilize and improve upon the techniques. Most of all we encourage continuing to build on the incredible research that has evolved in recent years with a focus on improving the quality of life for patients with debilitating conditions like glaucoma. Together we are making a difference. Together the future is bright!

Thomas M. Brunner
President and CEO
Glaucoma Research Foundation

Part III

Appendix

Current Positions and Affiliations of CFC 1, 2, 3 and 4 Principal Investigators

CFC 1

- **David Calkins, PhD**

  Assistant Vice President for Research, Vanderbilt University Medical Center
  Director, Vanderbilt Vision Research Center
  Vice-Chairman and Director of Research, Vanderbilt Eye Institute
  Denis M. O'Day Professor of Ophthalmology & Visual Sciences
  Professor of Psychology and Professor of Pharmacology, Vanderbilt University

- **Philip Horner, PhD**

  Scientific Director, Center for Neuroregeneration, Houston Methodist Research Institute
  Co-Director, Center for Regenerative and Restorative Neurosurgery
  Vice Chair, Research, Department of Neurosurgery
  Professor of Physiology, Weill Cornell Medical College

- **Nicholas Marsh-Armstrong, PhD**

  Daryl and Opal Geweke Endowed Chair in Glaucoma Research
  Professor, Department of Ophthalmology and Vision Science
  University of California, Davis

- **Monica Vetter, PhD**

  Professor and Chair, Department of Neurobiology and Anatomy
  Adjunct Professor of Ophthalmology & Visual Sciences
  University of Utah

CFC 2

- **Alfredo Dubra, PhD**

  Professor of Ophthalmology
  Stanford University

- **Jeffrey L. Goldberg, MD, PhD**

  Blumenkranz Smead Professor and Chair of Ophthalmology
  Byers Eye Institute, Stanford University

- **Andrew D. Huberman, PhD**

  Associate Professor, Neurobiology
  Stanford University

- **Vivek J. Srinivasan, PhD**

  Associate Professor, Department of Ophthalmology
  Associate Professor, Department of Radiology
  NYU Grossman School of Medicine

CFC 3

- **Xin Duan, PhD**
  Associate Professor, Department of Ophthalmology and Physiology
  Weill Institute for Neurosciences, University of California, San Francisco

- **Yang Hu, MD, PhD**
  Associate Professor, Department of Ophthalmology
  Stanford University School of Medicine

- **Anna La Torre, PhD**
  Associate Professor, Department of Cell Biology and Human Anatomy
  School of Medicine, University of California, Davis

- **Derek Welsbie, MD, PhD**
  Associate Professor of Ophthalmology
  San Diego Shiley Eye Institute, University of California, San Diego

CFC 4

- **Sandro Da Mesquita, PhD**
  Assistant Professor, Department of Neuroscience, Meningeal Lymphatics and Neurological Disorders Lab
  Mayo Clinic, Jacksonville, FL

- **Milica Margeta, MD, PhD**
  Physician and Surgeon, Massachusetts Eye and Ear
  Assistant Professor of Ophthalmology, Harvard Medical School

- **Karthik Shekhar, PhD**
  Assistant Professor, Department of Chemical and Biomolecular Engineering; Faculty Scientist, Lawrence Berkeley Laboratory; Member, Helen Wills Neuroscience Institute; University of California, Berkeley

- **Humsa Venkatesh, PhD**
  Assistant Professor, Program in Neuroscience
  Brigham and Women's Hospital, Harvard Medical School

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CFC 2

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