NINE YEARS OF INNOVATION
CATALYST FOR A CURE REPORT
2002 TO 2010

GLAUCOMA
RESEARCH FOUNDATION
SAN FRANCISCO, CALIFORNIA
First Printing
Copyright © 2011 Glaucoma Research Foundation
All rights reserved.
No parts of this publication may be reproduced without written permission
from the Glaucoma Research Foundation.

Front cover: The Catalyst For a Cure Principal Investigators
(Clockwise From Top Left) Philip Horner, PhD,
Nicholas Marsh-Armstrong, PhD, Monica Vetter, PhD, and David Calkins, PhD
ABSTRACT

The Catalyst For a Cure (CFC) research consortium was conceived as an multidisciplinary, collaborative, and sustained effort to achieve a better understanding of glaucoma. Four principal investigators were selected for their expertise in neuroscience, molecular biology, genetics and immunology as well as their willingness to work collaboratively. Funding began in January 2002 and was extended for a total of nine years and just over $7 million. In January 2011 the CFC’s Scientific Advisory Board credited the consortium with reshaping the direction of glaucoma research, with showing that glaucoma shares a number of similarities with Parkinson’s disease, amyotrophic lateral sclerosis, and Alzheimer’s disease, and with taking a pioneering approach that should become a model for research in other diseases.
EXECUTIVE SUMMARY

In 2001, Glaucoma Research Foundation (GRF) partnered with the Steven and Michele Kirsch Foundation to establish the Catalyst For a Cure (CFC) research consortium. The CFC effort was intended to be multidisciplinary, collaborative, and sustained, initially for a period of at least three years, contingent on satisfactory progress. The objective was to achieve a better understanding of glaucoma, progress in treatment, and a possible cure.

GRF established a Scientific Advisory Board (SAB) to assist the CFC in identifying target objectives and to monitor progress. Four Principal Investigators (PIs) were selected for their expertise in neuroscience, molecular biology, genetics and immunology as well as their willingness to work collaboratively. They were located at four U.S. universities and they had neither previously done research in glaucoma nor worked together. The first meeting of the consortium, with the SAB and representatives of the foundations, produced a functional research plan, a concise statement of the goal, and an explicit understanding of the requirements for collaboration and reporting. In turn, the PIs were to expect assistance with strong planning, oversight, and funding that, once allocated, was unrestricted.

Funding for year one was made in January 2002, was extended in years two and three, and then, by GRF alone, for two additional three-year terms, each year’s funding approved on the basis of reported results. Funds provided to the CFC over the nine-year period were just over $7 million.

The consortium has described the last decade of glaucoma research as “defined by the recognition that glaucoma is an age-related neurodegenerative disorder of the central nervous system.” The CFC efforts were guided by three main approaches in their non-traditional and multidisciplinary investigations:

- Fundamental mechanism of neurodegeneration in glaucoma
- Interventional studies and target validation
- Development and novel use of enabling technologies

Summarizing the results of the nine-year effort, the SAB has credited the CFC with reshaping the direction of glaucoma research by focusing on the earliest molecular events of the disease, with showing that glaucoma shares a number of similarities with Parkinson’s disease, amyotrophic lateral sclerosis, and Alzheimer’s disease, and with taking a pioneering approach that should become a model for research in other diseases.
INTRODUCTION

Glaucoma Research Foundation History.................................................................9
Catalyst Meetings.....................................................................................................9
Early Research Highlights.....................................................................................10
Establishing the Catalyst for a Cure......................................................................11

SECTION I
CONCEPT, IMPLEMENTATION, ACCOUNTABILITY, AND FUNDING

Concept..................................................................................................................15
  Guidelines: Multidisciplinary, Collaborative, Sustained
  Kirsch Foundation Model for Collaborative Consortia

Implementation.......................................................................................................16
  Assembly of the CFC Scientific Advisory Board
  Selection of the Principal Investigators
  The First Consortium Meeting and the Plan

Accountability......................................................................................................21
  Terms of Engagement
  Formal Annual Meetings and Written Reports
  Interim Meetings and Other Collaborative Tools
  Strengthening the Scientific Advisory Board
  Additional Reporting – Beyond the Original Design

Funding..................................................................................................................24
  The First Three Years, 2002-2004
  The Second Three Years, 2005-2007
  The Third Three Years, 2008-2010

SECTION II
RESULTS AND EVALUATIONS

Results of the Research – Reports from the CFC Team.........................................29
CFC Scientific Advisory Board Evaluation..............................................................35
Glaucoma Research Foundation Evaluation...........................................................37
Principal Investigators’ Comments on the Process...................................................39
Postscript: The CFC work continues....................................................................42

LIST OF INDIVIDUALS NAMED AND THEIR AFFILIATIONS..........................43
CFC RESEARCH BIBLIOGRAPHY: PAPERS AND ABSTRACTS.........................45
ACKNOWLEDGEMENTS.......................................................................................55
CATALYST CIRCLE DONORS..............................................................................56
NINE YEARS OF INNOVATION
CATALYST FOR A CURE REPORT

The Founders of the Glaucoma Research Foundation
Robert Shaffer, MD, H. Dunbar Hoskins, Jr., MD,
and John Hetherington, Jr., MD in 1989
INTRODUCTION

Glaucoma Research Foundation: Our History

The Glaucoma Research Foundation (GRF) seeks to prevent vision loss from glaucoma by investing in innovative research, education, and support with the ultimate goal of finding a cure. GRF was founded in 1978, originally as the Foundation for Glaucoma Research, by Robert N. Shaffer, MD, John Hetherington, Jr., MD, and H. Dunbar Hoskins, Jr., MD of the Shaffer Associates clinical practice at the University of California San Francisco’s Glaucoma Clinic. Initial funding for GRF consisted of two gifts, almost a million dollars each, from a grateful patient, Blanche Matthias and her good friend, Berenice Hauck.

The year it was founded, GRF awarded its first grant, the 1978 Shaffer Glaucoma Fellowship. In subsequent years GRF funded additional fellowships. These provided specialized training for visiting ophthalmologists from throughout the United States and a number of foreign countries. Early on GRF also launched 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. These grants were also intended to encourage new scientists to continue their work in the field of glaucoma.

Catalyst Meetings

To stimulate communication and further accelerate progress toward a cure, GRF initiated periodic Catalyst Meetings to Support Glaucoma Research in 1984. One of the explicit objectives of these meetings was to lure non-opthalmologists into the field of glaucoma. The emphasis on bringing in scientists from other fields was at least partly inspired by the experience of GRF founder, Robert N. Shaffer, MD. From 1950 through 1955 Dr. Shaffer was a participant in the Glaucoma Forums, multidisciplinary meetings sponsored by the Josiah Macy, Jr. Foundation at Princeton University. Dr. Shaffer described these as “undoubtedly the most important scientific meetings that I attended.”

These GRF Catalyst meetings were therefore gatherings of glaucoma experts and scientists from other fields. Although it was perhaps an unnecessary carrot, GRF made funds available for grants to participants that might be driven by
the outcome of the meetings. Seven of sixteen Catalyst meetings held between September 1984 and April 2000 resulted in the award of 33 grants in the total amount of $2 million. Awards went to researchers at institutions in 15 U.S. states, 3 provinces of Canada, the United Kingdom, and Israel. A review of the meeting and grant topics over the history of these meetings shows increasing focus on retinal ganglion cells, the optic nerve, and genetics.

Paul L. Kaufman, MD, with the Department of Ophthalmology and Visual Sciences at the University of Wisconsin, was a frequent participant in the Catalyst meetings and as a result of the first of them he shared a grant award with a researcher at the Weizmann Institute of Science, Rehovot, Israel. He later joined GRF’s Scientific Advisory Board, serving as its chair from 1998 to 2001, and was a strong supporter of collaborative work. At the same time, from his entry into the field of glaucoma in the early 1940’s, Dr. Shaffer had cultivated friendships and encouraged the sharing of knowledge among glaucoma experts. It became a charge of the Catalyst meetings to develop ideas for collaborative research projects.

Another result of the Catalyst meetings and reflection on the funding of Catalyst and other pilot grants was GRF’s determination that such short-term projects often provided inadequate time for development of significant results. GRF thus established three key concepts for the guidance of its continuing research endeavors:

- Multidisciplinary
- Collaborative
- Sustained

**Early Research Highlights**

The 1984 Catalyst meeting was constituted as an 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 the University of California at San Francisco, collaborating with scientists at the University of Iowa, isolated the TiGR gene. This gene was found to be one of those responsible for the onset of some forms of juvenile and adult glaucoma.
Establishing the Catalyst For a Cure

In 2001, GRF partnered with the Steven and Michele Kirsch Foundation in establishing the Catalyst for a Cure (CFC) research consortium. Four principal investigators were selected for their expertise in neuroscience, molecular biology, genetics, and immunology as well as their willingness to work collaboratively, sharing their expertise, toward a better understanding of glaucoma, progress in treatment, and a possible cure. The two foundations committed equally to funding the consortium for three one-year periods, the second and third years’ funding contingent on reports of satisfactory effort and progress. GRF established a Scientific Advisory Board to assist the CFC in identifying target objectives and to monitor its progress.

The following report provides greater detail on the conception, implementation, accountability, and funding of the CFC through the initial three years of Phase I and the six years of Phases II and III (Section I) and the results of the research and evaluations of the work (Section II). A list of individuals named with their affiliations and a bibliography of CFC papers and abstracts follow the text of the report.

Steven (left) and Michele Kirsch present the Catalyst Award to David Pyott of Allergan in 2006.
SECTION I

CONCEPT, IMPLEMENTATION, ACCOUNTABILITY AND FUNDING OF THE CATALYST FOR A CURE CONSORTIUM
CONCEPT

GRF guidelines: Multidisciplinary, Collaborative, Sustained

GRF's groundwork had persuaded its leaders that what was needed was a sustained, collaborative, multidisciplinary research project to speed the search for a cure for glaucoma. Such an effort would take advantage of laboratories working outside the mainstream of the research topic, ensuring that new and valuable expertise would be brought to bear, providing a fresh perspective, with principal investigators who could work together in a collaborative structure. The traditional approach to medical research – with individual scientists working on separate projects at their own institutions and sharing advances only at conferences and through publications – would not be followed.

In 2000 GRF’s Director of Scientific Affairs, Tara Steele, attended a gathering at the Cosmos Club in Washington, DC. Convened by Dr. Robert A. Goldstein of the Juvenile Diabetes Research Foundation, representatives of a dozen institutions and foundations, most much larger than GRF, discussed ways to fund research and to do more with the research funds available. Among perhaps thirty participants in discussion around the table was Sarah Caddick, PhD. In 2000, Dr. Caddick had a history of successfully assembling and supporting collaborative research teams and had just been recruited as Director of Medical & Scientific Programs for the Steven and Michele Kirsch Foundation of Mountain View, California. Ms. Steele subsequently engaged Dr. Caddick in conversation about ways in which the two foundations might work together. Exploratory discussions followed during which Dr. Caddick moved to the West Coast, taking up her new assignment.

Kirsch Foundation Model for Collaborative Consortia

The Kirsch Foundation had developed a model for setting up collaborative programs, largely based on the success of the model developed by Susan Howley, Executive Vice President for Research at the Christopher and Dana Reeve Foundation. The Kirsch Foundation sought to fund investigators with multi-year, collaborative consortium grants. Its goals included encouraging researchers from diverse fields to bring a fresh outlook to specific topics and provide them with a financial incentive and a common focus for work with others. It sought to act as initiator/catalyst of true, functional collaborative research and established guidelines for implementation that included assembling a scientific advisory board, providing a mechanism for the researchers to remain in close contact, and convening each consortium annually to review progress with its advisory board.

Dr. Caddick suggested to Ms. Steele that the foundations consider jointly setting up a consortium. The idea was presented to GRF’s Scientific Advisory Committee and found a champion in one of its members, Martin B. Wax, MD, Washington
University, St. Louis and Pharmacia Corporation. The idea was taken to GRF’s Board of Directors and the eventual result was an agreement between the Kirsch Foundation and the Glaucoma Research Foundation to launch the Catalyst For a Cure.

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. The plan was to engage experts willing to collaborate on an ongoing basis, sharing information and techniques, discussing obstacles, and shaping strategies. The project was also designed to permit relatively ambitious planning and continuity of effort by extending to at least three years, contingent on satisfactory progress. The participation of the Kirsch Foundation was also explicitly limited to three years, consistent with that foundation’s purpose to support the initiation and early stages of new research efforts.

IMPLEMENTATION

Assembly of the CFC Scientific Advisory Board

The CFC Scientific Advisory Board (2001)
Martin Wax, MD, Constance Cepko, PhD, Moses Chao, PhD, and Jack Antel, MD
Critical to the success of this unconventional project would be oversight and mentoring from highly qualified senior scientists in related disciplines. A new GRF Scientific Advisory Board (SAB) was to be created specifically for the CFC initiative. It was to consist of up to four senior researchers, including one clinician, who would commit to three assignments:

- Selection of the participants for the research consortium
- Mentoring the functional collaboration necessary for the consortium to meet its goals
- Reviewing progress annually

Essential qualifications for this role were a senior level of research expertise, some knowledge in the field of glaucoma, and a willingness to envision the progress that might be made with a non-traditional approach. This approach envisioned selecting a group of investigators who would tackle a problem they had never thought about. In addition, it was to be collaborative, multidisciplinary, and goal-oriented.

Together, Dr. Wax and Dr. Caddick identified a small number of highly regarded leaders to act as advisors and begin the process of creating the Catalyst For a Cure consortium. In August of 2001 the following were named to the Scientific Advisory Board for the CFC. They are listed with their affiliations at that time:

- Constance L. Cepko, PhD, Professor, Department of Genetics, Harvard Medical School, Boston. Dr. Cepko 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.

- 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.

- Moses V. Chao, PhD, Professor of 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.
• Martin B. 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.

Selection of the Principal Investigators

The concept behind the CFC dictated the essential qualifications of those who were to be chosen as its principal investigators:

• Demonstrated and highly promising research training and expertise
• Relative youth, offering the possibility that an intriguing problem might catch their attention and shift a new generation of scientists to work on it
• Willingness of the investigators and ability of their laboratories to work in a collaborative structure
• Representation of the desired disciplines, outside the mainstream of the research topic, ensuring that new and valuable expertise would be brought to bear

The conventional approach to finding outside researchers for a proposed project involves broadcasting a 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 with the proposal. The CFC was not to be a conventional project and the selection of its principal investigators was also atypical.

Dr. Caddick worked with the four members of the Scientific Advisory Board, GRF staff, and GRF board members to identify, approach, and interview candidates for the research team. They began by identifying leading senior scientists in different fields and asked for recommendations of young investigators who could contribute to the proposed collaboration. For the thirty-some individuals who were suggested, they then gathered information (biographies, publications, and research) and invited them to be considered. The invitation was not sent with an RFP. Instead, the concept and purpose of the proposed consortium were described and each of the candidates was asked to respond to three deceptively simple questions:

1. What focus/expertise could you/your lab bring to the consortium?
2. What would your "value-added" be to the overall effort?
3. How well could you work in a collaborative group? Are you comfortable working with other labs and sharing expertise/research?

As Dr. Caddick described it later, “The responses split the group in half, those who got it and those who didn’t.” Those who “didn’t get it” were eliminated. The CFC Scientific Advisory Board and Dr. Caddick evaluated the 16 remaining responses, along with the investigators’ scientific credibility, background, and references, and in September 2001 selected the four individuals who would constitute the CFC team. 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

Principal Investigators for the Catalyst for a Cure Consortium
Philip Horner, PhD, David Calkins, PhD, Monica Vetter, PhD, and Nicholas Marsh-Armstrong, PhD (2004)
The First Consortium Meeting and The Plan

In October of 2001 a dinner was held in San Francisco for the four principal investigators (PIs) of the CFC consortium, the CFC Scientific Advisory Board, and the CEOs and Boards of the co-sponsoring foundations, the Kirsch Foundation and the Glaucoma Research Foundation. The investigators and their advisors devoted all of the following day to their first consortium meeting, this one to develop a plan that focused directly on the research questions and a collaborative research agenda. The PIs, who had never worked together, needed to evaluate their respective skills and resources and determine how to work most effectively in pursuit of their now common objective. Again, as Dr. Caddick described it later, “We literally locked everyone in a room for the day and focused on creating a functional research plan that everyone contributed to. We encouraged an open dialogue, eliminated “issues” that might prevent them from truly working together, and made sure they understood that if they had a problem along the way, changes they needed to make, additional funds they might need, they had to tell us right then, not three years later when it would be too late to do a thing about it.”

The plan that resulted began with a statement of the goal:

**Our goal is to have significant new progress in finding the cause(s) and critical mechanisms that result in the onset of glaucoma.**

Five strategies were outlined. They were set up as three-year targeted plans toward implementing the goal, and were supported by recital of proposed tactics, that is, specific research goals (experimental strategies). Those five strategies from the original plan, and the labs that were to execute them, were as follows:

1. Investigate the occurrence and mechanisms of a proliferative repair response in glaucoma and the role/reaction of astrocytes in this process. Horner Lab.
2. Create a molecular profile of retinal ganglion cells (RGCs) as glaucoma progresses. Vetter Lab, Calkins Lab.
4. Investigate the neuronal-neuronal and neuronal-glial signaling mechanisms in a glaucoma model. Horner Lab, Calkins Lab.

As well as their initial agenda, the strategic plan would serve as the basis of the annual review process. It was to be updated after each review to reflect progress and, if appropriate, changes in direction. The plan was finalized in the last two months of the year, reviewed by the Advisory Board, and signed off. The Catalyst
For a Cure consortium was to be funded and begin its research in January of 2002.

ACCOUNTABILITY

The Terms of Engagement

Accountability was a key component of the collaborative model for the CFC. Key elements and responsibilities of this accountability were explicitly stated:

- The researchers were mandated to share their expertise and information so that the consortium could address issues more efficiently and effectively. This was expected to result in earlier identification of promising new research routes and elimination of dead ends.
- The advisors and funders were to assist with strong planning, due diligence, and oversight to ensure that the collaboration had adequate support and remained focused on core issues.
- Funding, once allocated, was to be unrestricted in return for active reporting of results and regular, open communication between consortium members and the funding partnership.

During the late 2001 planning process each CFC participant had reaffirmed his or her commitment to the expected regular and open communication. The plan to fund all four principal investigators equally for three years promoted the commitment to collaboration by reducing this element of competitiveness. An interactive email group was created for the members of the consortium to remain in close contact throughout the course of each year, to share information and provide each other with assistance.

In May of 2002, Dr. Wax and Dr. Caddick hosted a lunch for the CFC principal investigators and their assistants at the annual meeting of the Association for Research in Vision and Ophthalmology (ARVO) in Fort Lauderdale, Florida. Although it had been only four months since funding began, the PIs were already visiting each other’s labs, sharing results, and corresponding regularly. The Scientific Advisory Board had also been responding to questions and offering assistance when needed. The CFC was up and running in accordance with its design.

Formal Annual Meetings and Written Reports

The requirement for formal annual meetings of the CFC investigators and reviews by the Scientific Advisory Board set expectations consistent with full accountability. The meeting agendas called for presentations by the PIs to the members of the advisory board covering the work of the prior twelve months,
the results of that work, and any appropriate changes proposed to the longer-term plan. The members of the Scientific Advisory Board had the opportunity to question, comment, and challenge assumptions and were to serve as expert resources in discussions to follow the presentations. The SAB was also to provide a written evaluation of the work along with any recommendations on research direction or funding to the investigators and to the funding foundations.

These expectations for reporting and review have been met during the nine-year history of the consortium. Full and formal annual meetings, with the expected PI presentations for SAB review and followed by SAB evaluations, have been held each year. Initially these meetings were held in December. From 2006, they were held in January to coincide with a CFC team presentation at GRF’s annual benefit. As the proposed term of the project was extended initially by three years and then an additional three years, meetings at the end of each three-year term were also the forum for presentation of prospectuses covering the next three years.

Interim Meetings and other Collaborative Tools

As early as May of 2002, five months in, the principal investigators agreed that they would like to meet more often than annually and proceeded to do so. In most cases team members took advantage of conferences, such as ARVO, that
were already on their mutual agendas. Additional meetings were specifically convened for CFC purposes.

The PIs expanded upon regular telephone conference calls by sharing data and discussing findings as a group using network meeting software. The software enabled remote control of any computer (Mac or PC, desktop client or server), either via the Internet or over a local network. Multiple users were able to log in simultaneously and view or even control the same desktop.

The team participated in the purchase of a server to provide a central repository for data files and other information. A virtual bank was also created for tissues from the animal models. Often samples of tissue from the same animal were required for different experiments in different laboratories. The group coordinated efforts so that tissue prepared in one laboratory was openly shared with the other laboratories as needed.

**Strengthening the Scientific Advisory Board**

In 2005, as expected, the Kirsch Foundation ceased its funding and oversight of the CFC. Sole responsibility for both funding and oversight was undertaken by GRF. Accordingly, the CFC Scientific Advisory Board was strengthened 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 study of optic nerve cells, cell death, and clearance of self-destructive calls by phagocytes. He was a strong advocate of sharing information and materials, even with competitors.

**Additional Reporting to Supporters – Beyond the Original Design**

The apparent success of the CFC principal investigators in forming an effective collaboration and exploring new ground was of great interest to GRF board members. Two years into the work, in January of 2004, David Calkins, PhD, one of the PIs, attended the quarterly meeting of the GRF Board of Directors and provided an overview of the CFC: the team members, their current specific goals, their collaboration (conference calls on strategy, planning, designing the
experiments). He reported on the exchange of material between the labs (data, tissue, reagents) and the three group meetings that had been held during the preceding twelve months. He talked about retinal ganglion cells, gene expression, and of course the DBA/2J mouse.

That was only one of many occasions when one or another of the PIs was the featured speaker for gatherings of GRF supporters and potential donors. Subsequently, a series of moderated telephone presentations was initiated. Each of the PIs made time for a conversation with GRF’s CEO on the “President’s Teleconference” and responded to live questions from donor-listeners. Without exception the PIs were engaging as well as informative, managing to effectively convey the essence and the newness of what they were doing, as well as their enthusiasm, to largely non-scientist audiences.

In January 2006, and in conjunction with its annual meeting in San Francisco, the entire CFC team provided a detailed scientific briefing to a larger gathering of GRF supporters and in January 2007 this presentation became the centerpiece of GRF’s first (and profitable) benefit event.

To many who attended these briefings, the investigators soon became “Phil,” “David,” “Nick” and “Monica.” The investigators have reported that such a close relationship with the supporters of their work, many of them glaucoma patients, was uncommon and that it was inspiring. These meetings with supporters appear to have contributed to the openness of the enterprise, the collegiality of the various relationships involved, and the commitment of the investigators.

**FUNDING**

**The First Three Years, 2002-2004, Phase I: $1.5 million total**

Both foundations initially committed to funding the three-year project at a total of $1,150,000, half to come from each foundation. The Kirsch Foundation funded its share with a three-year grant to GRF of $575,000. GRF channeled annual funding, including its own $575,000 share, to the CFC laboratories in January of each year, beginning in 2002 and continuing, after the required reviews and approvals, through 2004. This core funding amount was equally divided among the four laboratories.

Two supplemental grants were also made, funded equally by the two foundations. The first, made in year two and paid over years two and three, was for $110,000 to establish the consortium’s DBA/2J mouse colony, located at the Horner lab, University of Washington. The second, made in year three, was for $200,000 to support an additional post doc at each institution in order to increase the effort toward a successful conclusion of the first phase.
The Second Three Years, 2005-2007, Phase II: $2.8 million total

The Kirsch Foundation had indicated from the beginning that, consistent with its own mandate, it would not fund the project after the initial three-year period. In 2004, the consortium’s third year, GRF weighed results to date and determined that it would take on the challenge of entirely funding the CFC consortium for another three years, each year again contingent on satisfactory reviews of progress.

At the same time, GRF determined to seek protection and any financial benefits related to intellectual property that might be created by the CFC. Pro bono assistance was provided by Michael Ladra, an intellectual property specialist at the Palo Alto law firm Wilson Sonsini Goodrich & Rosati. As a result, GRF’s exclusive rights and royalty sharing terms were included in grant agreements with the four CFC institutions for 2005 and subsequent years.

GRF’s total three-year commitment to the CFC for 2005-2007 was set at $2,500,000, which included $65,000 per year for the mouse colony. To support this undertaking, as well as its pilot grants, educational programs, and other activities, the foundation launched a three-year $7.5 million capital campaign. GRF’s Board of Directors alone pledged $2.6 million and the campaign ultimately raised a total of $8.6 million. Funding to the laboratories was again delivered in January of each year, from 2005 through 2007, and again subsequent to the required reviews and approvals in the second and third years.

For 2006 and 2007, with the endorsement of the Scientific Advisory Board, the CFC issued a supplemental budget request. An additional $54,000 in 2006 and $44,000 in 2007 were to support further expansion of the mouse colony and a further $80,000 in each of the two years was to support additional personnel at the Calkins lab to analyze the additional tissue. GRF authorized the supplemental payments, bringing the three-year funding to $2.8 million.

The Third Three Years, 2008-2010, Phase III: $3.0 million total

In 2007, the CFC’s sixth year, GRF again evaluated progress and discussed the possibility of funding for another three years. With the offer of major support from the Melza M. and Frank Theodore Barr Foundation, a matching grant through GRF of $1.5 million over three years, GRF elected to fund CFC for the years 2008 through 2010, subject to the now-usual annual reviews. The Barr gift served to kick-off a new three-year $12 million capital campaign. GRF’s Board of Directors provided increased funding and the foundation increased its efforts to generate support from regional chapters and affiliated glaucoma practices.

The 2008-2010 capital campaign was less successful due to the recession, and investment losses, included in the foundation’s total revenues, served to further
reduce available funds. For the three-year period, total revenue was $7.8 million, far short of the $12 million goal.

For 2008, the laboratories were funded for the year in January but in 2009 and 2010, to better match cash flows for the foundation, funding was delivered in quarterly installments.
SECTION II

RESULTS AND EVALUATIONS
Results of the Research

The CFC Approach – From a CFC Team Report dated June 2010

The last decade in glaucoma research was defined by the recognition that glaucoma is an age-related neurodegenerative disorder of the central nervous system. Finding neuro-protective and neuro-enhancing strategies to abate vision loss in glaucoma for those patients who do not respond to IOP-lowering regimens depends upon establishing the sequence and mechanisms of key degenerative events in the disease. The CFC was part of this growing effort in many important ways that are documented in our published work, recent progress reports, and presentations at national and international conferences.

The unrestricted nature of the CFC funding and its consortium structure has allowed us to pursue highly imaginative, non-traditional and multidisciplinary investigations. Early on we adopted three main approaches that have guided our efforts. These can be summarized as:

1. **Fundamental mechanisms of neurodegeneration in glaucoma:**
   - cellular, molecular and physiological cascades
   - genetic regulation and transcriptional events

2. **Interventional studies and target validation:**
   - pharmacological agents
   - transgenic and viral delivery of genes
   - systemic modulations (e.g., dietary, irradiation)

3. **Development and novel use of enabling technologies:**
   - new animal models of glaucoma
   - cell-type specific reporter strains
   - imaging technologies, both cellular and systemic
   - physiological tools

The use of these three approaches in combination has proven to be very powerful for developing and testing specific hypotheses. In particular, the various hypotheses we have tested over the tenure of the CFC have evolved into four primary themes of studies:

1. **Key progressive events in degeneration:**
   - Distal injury at target sites in the brain
   - Deficits in axonal transport and optic nerve function
   - Morphological (dendritic) and transcriptional changes in the retina
2. Intrinsic RGC Response:
- Oxidative stress and metabolic dysfunction
- Gene expression changes
- Gamma-synuclein aggregation

3. Microglial Modulation of RGC Survival:
- Role of microglia activation in chronic and acute glaucoma
- Activation/recruitment of microglia by RGC intrinsic signals
- Live imaging of microglia activation and gliosis in the central retina

4. Astrocyte-RGC Interactions in the Nerve Head
- Expression of trophic factors in the RGC projection
- Regulation of extracellular calcium in the RGC milieu
- Synucleins and other components of intracellular degradation
- Lipid metabolism and aggregation

Summary Report of Results – From a CFC Team Report of February 2011

A. Focus of Investigation and Major New Knowledge Created

1. Overview. At the inception of the CFC, the prevailing viewpoint of vision loss in glaucoma was that with aging, elevated intraocular pressure (IOP) elicited mechanical damage to retinal ganglion cells (RGCs), thereby inducing apoptotic cell death. The CFC challenged this viewpoint immediately on two fronts. First, in line with emerging clinical studies, we proposed that sensitivity to pressure, rather than elevated pressure, was a characteristic of the retina, optic nerve head, and RGC projection to the brain. Thus, rather than passive bystanders in mechanical injury, the system as a whole could respond actively to stress in glaucoma and that this response included early as of yet unknown cascades intrinsic to the RGCs themselves. Second, rather than playing a late role in managing post-apoptotic scavenging, we proposed that retinal and optic nerve head glia (microglia and astrocytes in particular) are active very early in progression and provide a response extrinsic to the RGCs influential for system maintenance, trophic support, and key interactions with RGC axons. Our view is that these programs – intrinsic and extrinsic – interact during progression of the disease and together influence outcome. This viewpoint guided the CFC through Phases 1-3 and informed both our mechanistic studies (why RGCs degenerate) and our interventional studies (slowing RGC degeneration).

2. Mechanisms of Progression: Intrinsic Pathway. Consistent with our central viewpoint, we established in the DBA/2J mouse that RGC axons in the optic nerve are highly sensitive to subtle differences in IOP so that even at young ages, axons could be lost with sufficient stress (Inman et al., 2006). Even RGCs in
isolation without glial or vascular influence demonstrate this sensitivity, including robust changes in the expression of genes involved in intrinsic stress pathways (Sappington et al., 2006). This response can be ameliorated by the addition of particular glial signals (interleukin-6), showing that extrinsic glial signals early on might be protective. Part of the RGC intrinsic program includes an early challenge to axons in the optic nerve, with loss of retrograde and anterograde transport occurring prior to structural depletion of either RGC cell bodies in the retina (Buckingham et al., 2008) or synaptic connections in the brain (Crish et al., 2010). These changes in axonal function are concurrent with a remarkable program of transcriptional changes, evoking large-scale reorganization of the expression profile of RGCs in the retina (Soto et al., 2008). Further evidence suggests that RGCs and their axons express an actual mechanism via the transient receptor potential channel TRPV1 to respond directly to pressure-related signals through changes in intracellular calcium concentrations (Sappington et al., 2009). These signals may influence metabolic and oxidative cascades, since we have now shown an early component of axon dysfunction is loss of metabolic activity influencing subsets of axons (Baltan et al., 2010).

3. Mechanisms of Progression: Extrinsic Pathway. A broad screen of genetic changes in the DBA/2J retina illuminated several important cascades (Steele et al., 2006). Among these were genes involved in the innate immune response, which influences interactions between microglia cells, RGCs and the immune system. This is reflected with the highly reactive nature of microglial and astrocyte populations early in the DBA/2J retina (Inman and Horner, 2007). While
certain microglia-derived signals may be protective (Sappington et al., 2006), inhibiting these interactions early in progression using minocycline, a broad spectrum tetracycline antibiotic, reduces not only microglia activation, but also much of the axonopathy associated with RGC degeneration in the DBA/2J (Bosco et al., 2008). Subsequent work shows that not only are microglia activated early, but represent a highly dynamic population of glia particularly near the optic nerve head, where RGC axons pass unmyelinated in forming the nerve proper (Bosco et al., 2011). This region of the retina-nerve junction is also a critical locus for astrocyte interactions with RGC axons (Son et al., 2010). Recently, we demonstrated that astrocytes in the unmyelinated zone of the nerve head form phagocytotic relationships with RGC axons and that these interactions increase in glaucoma and require intact gamma-synuclein signaling (Nyguyen et al., 2011).

B. Tool Development

1. Animal Models. Much work prior to the CFC utilized acute models in which elevated IOP is induced by an injury to the aqueous fluid pathways. At the time, these were not readily available to new laboratories without considerable surgical experience. As well, the nature of the IOP elevations often exceeded magnitudes seen in the human disease, calling into question their relevance. Thus, we developed a colony of DBA/2J mice at the University of Washington run by the Horner laboratory (Inman et al., 2006). This mouse shows an age-dependent tendency towards elevated IOP through specific gene defects that affect aqueous dynamics in the anterior eye. Because there is variability at every age, the effects of IOP can be teased from those due to aging. For several years, this colony supplied CFC investigators with all of the animal tissue necessary for experiments. It also became a valuable resource for other laboratories across the country in need of specific tissues and preparations.

The CFC also developed a new acute model with a less invasive mode of elevating IOP that elicits elevations more akin to the human disease (25-30%). This “microbead occlusion model” uses a simple injection of polystyrene microbeads into the anterior chamber to block aqueous flow (Sappington et al., 2010). Much of the early pathology in this model resembles that of the DBA/2J, but without much variability in IOP (Crish et al., 2010). It is being used by several other groups around the world, with the Calkins laboratory at Vanderbilt providing training on an on-demand basis. The model is being used by CFC laboratories now to test specific mechanistic hypotheses involving transgenic mice.

2. Quantitative Monitoring of Disease Progression. One of the challenges facing the CFC early on was the field’s nearly total reliance on the use of a single assay of RGC survival: retrograde labeling of RGCs from injections in the superior colliculus. This technique is fraught with difficulties, not the least of which is the underlying assumption that lack of signal in the retina translates to loss of RGCs. We immediately began a methodical program to develop new tools to (1)
measure intact axonal transport to and from the brain (Crish et al., 2010), (2) quantify the spatial pattern of RGC-specific markers in the retina (Soto et al., 2008; Buckingham et al., 2008; Wax et al., 2008), (3) track axon survival in the optic nerve (Inman et al., 2006), and (4) assess functionality of the RGC projection in living animals (Calkins et al., 2008). Moreover, with the growing importance of understanding glial-dependent extrinsic mechanisms, we also developed tools for tracking microglial and astrocyte proliferation and migration (Bosco et al., 2011; Nyguyen et al., 2011). These and other quantitative tools and assays were not available to the field at the inception of the CFC; they have become one of the recognizable standards of our collaboration.

C. The Road Less Traveled: Avenues Not Pursued

1. Cell-Specific Microarrays. Following our microarray experiment in which we probed gene expression in the DBA/2J retina (Steele et al., 2006), we explored the possibility of repeating the experiment for specific cell types. Earlier we had devised protocols for isolating purified populations of (1) RGCs, (2) microglia, and (3) astrocytes (Sappington et al., 2006). Our plan was to use these protocols to isolate these cells from the DBA/2J retina. However, ultimately we abandoned the project because (1) yield was too low for microarray screening and (2) we questioned how representative of the living state isolated cells really are. We believed that our efforts were better directed at testing specific mechanistic hypotheses regarding RGC-glial interactions, and certainly this has proven successful. To this end, for genes of interest we have been successful in developing specific probes for in situ hybridization.

2. Biomarkers. In certain forms of glaucoma, antibodies and other blood serum proteins serve as markers for the disease (Wax et al., 2008). Our work indicates broad changes in retinal and nerve levels of various markers for both RGCs and glia (Buckingham et al., 2008; Soto et al., 2008; Bosco et al., 2011; Nyguyen et al., 2011). It was natural to pose the question of whether these markers could (1) breach the blood-retinal barrier and (2) if so, serve as serum biomarkers for disease progression in either protein form or as auto-antibodies. Of particular interest was gamma-synuclein, which was found to aggregate in dystrophic RGCs of the DBA/2J. If indeed gamma-synuclein formed a toxic substrate, it might be feasible to detect it or antibodies against it in blood serum. This is indeed the case for gamma-synuclein in Parkinson’s disease. However, the investigation did not demonstrate consistent results. Ultimately, we decided that a thorough and quantitative screening of serum from our animal models might indeed illuminate biomarkers of progression, but that to follow up on mechanistic studies to identify the earliest markers would require resources beyond the capacity of a highly focused consortium.

3. RGC-specific Promoters. One of our most imaginative hypotheses was that by identifying and cloning RGC-specific genetic promoters, we could develop
tools to re-program stressed RGCs to modify expression of pro-survival genes and to develop RGC-like stem cells for transplantation. While we were successful in identifying novel retina-specific promoters for progenitor cells, we ultimately realized that the quest for an RGC-specific promoter gene would require years more of highly focused effort. We also realized that by using viral vectors, we could introduce new genes (or inhibitory genes) into RGCs with far greater efficacy – especially given the RGC-preference of AAV2 vectors. In terms of stem cells, recent technology indicates that the use of inducible pluripotent stem cell lines could represent a far easier path, since these are easier to harvest, as is influencing their neuronal or glial cell fate. Furthermore, we found very little evidence for a proliferative repair response in glaucoma, indicating that our efforts to induce such a response using stem cells would likely not be fruitful (Inman and Horner, 2007).
Evaluations

CFC Scientific Advisory Board Evaluation

The Scientific Advisory Board for the CFC, chaired by Moses Chao, PhD for nine years, began the evaluation section of its January 2011 report as follows:

“The CFC consortium has completed nine years of support from the Glaucoma Research Foundation and, in its first years, from the Kirsch Foundation. 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 feels this pioneering approach to disease research should become a model for research in other diseases, including other neurodegenerative diseases.”

More specifically, in this report the SAB wrote that “the CFC consortium has reshaped the direction of glaucoma research by focusing upon the earliest molecular events of the disease, which occur well before the demise of retinal ganglion cells. A major emphasis has been on studying changes in the glial environment during disease progression.” 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.”

In its annual reports during the nine years of the collaboration, the SAB has also noted the effectiveness of the CFC at prioritizing its work, given the number of attractive avenues for research and the limited resources available.

SAB comments in its annual reports have marked the progress of the CFC effort:

December 2003:
The group presented a clear and concise overview of how the four labs work together and complement each others’ specific skills to achieve a fluid transfer of knowledge and ideas that has resulted in significant progress and breakthrough ideas over the last twelve months.

January 2004:
A major accomplishment has been the establishment of four intertwined core facilities, including the DBA/2J mouse colony (Horner lab), a histopathology core facilities,
(Calkins lab), transgenic genomic and gene expression core (Marsh-Armstrong lab) and a microarray core (Vetter lab). The four laboratories have organized the cores to minimize overlap and maximize the distribution of tissues and reagents in the consortium. The four cores were integrated seamlessly.

January 2006:
During 2005 the consortium was successful in making considerable progress on the specific aims outlined in the December, 2004 meeting. They include documenting glial and neuronal responses in the DBA/2J retina; assessing gene expression by RNA profiling during increased IOP; utilizing promoter-specific DNA sequences for RGC expression and verifying the specific axonal defects in the DBA/2J retina. Based upon the progress made in the last year, the consortium has made a decided emphasis in moving toward intervention studies.

December 2006:
In the past four years, the number of personnel in the four groups has grown to 30 investigators, including over a dozen PhD fellows. Four papers have been published and another six manuscripts have been either submitted or are under preparation. Over 35 abstracts describing work supported by the Glaucoma Research Foundation have been presented at national conferences. The CFC has become a highly visible research team, whose findings have now become publicized in meetings and in journals. The four groups represent a model for how research can be pushed forward through collaborative and multidisciplinary approaches.

December 2008:
It is strongly recommended that the course of future research go deeper into the mechanism of the earliest events that appear in the DBA/2J model and in the intervention trials.

January 2010:
The major accomplishment of the consortium has been to document a preliminary time course of the molecular and cellular changes in the DBA/2J model. The methods now in place should allow the investigators to generate a more precise timeline and sequence of events in this model.

January 2011:
The CFC consortium has reshaped the direction of glaucoma research by focusing upon the earliest molecular events of the disease, which occur well before the demise of retinal ganglion cells.

With respect to the collaboration, the SAB recognizes that all the investigators have become experts in the field of glaucoma, and they are now working more independently than when the consortium started, with their own projects. The SAB feels the independence of each group is a healthy outcome.
Glaucoma Research Foundation Evaluation

By Thomas M. Brunner, President & CEO

The Glaucoma Research Foundation Board and its President and Chief Executive Officer have had many opportunities to review and evaluate the progress of the Catalyst For a Cure scientists. Under the terms of the grant agreements, each year the board and president determined if progress merited continued funding and subsequently approved funding for the succeeding year. Also at the end of each three-year phase, a major review was made by the board and president together with input from the CFC scientists and the CFC SAB to determine if another three-year grant should be made to extend the collaborative research effort. At every step of the way, both annually and at the end of the three-year intervals, there was overwhelming support for continuing to fund the work of this productive team.

Another way to evaluate the success of the Catalyst For a Cure is to compare it to the impact it has on the accomplishment of the mission of the Glaucoma Research Foundation “to prevent vision loss from glaucoma by investing in innovative research, education and support with the ultimate goal of finding a cure”. To accomplish our mission, the GRF Board defined a group of strategic imperatives with each imperative including specific actionable items. One of the key research imperatives was to “Fund large, multi-year, collaborative research programs to better understand the mechanisms of glaucoma.” The satisfaction with the early results of the Catalyst For a Cure collaboration led to the board’s making such programs key strategies for implementation of the Glaucoma Research Foundation mission.

The Catalyst For a Cure is clearly an innovative approach to research and we believe its success may lead to other true collaborative research efforts. In terms of the return on investment, in addition to the many publications, presentations, and discoveries which have changed how glaucoma is viewed by the research community, the scientists have been acknowledged with significant funding from the National Institutes of Health and other granting organizations. They have also been recognized with career advancement. Dr. Monica Vetter has been named Department Chair for Neurology and Anatomy at the University of Utah,
Dr. David Calkins has been promoted to Director of Research for the Vanderbilt Eye Center, and both Dr. Horner and Dr. Marsh-Armstrong have advanced in their academic careers. In addition to the founding PIs, other scientists who have worked with the program have expanded their interest in glaucoma and continued their research at other organizations and in new laboratories dedicated to glaucoma research.

When I joined GRF as its new President and CEO in February 2003, I was introduced to the Catalyst For a Cure as a unique research opportunity jointly sponsored by GRF and the Kirsch Foundation. I was told it was one of the most important research efforts at GRF. Consequently I made it a priority to meet the scientists and learn more about the Catalyst For a Cure which also represented a significant amount of our expense budget. I first met the scientists at their May 2003 joint meeting in Las Vegas. I was supposed to get half an hour to introduce myself but instead we ended up spending the better part of the morning discussing their program and their objectives. I came away impressed with the energy, knowledge, and enthusiasm of the team. In particular, I remember their commitment to undertaking only research that could benefit from their collaboration, i.e., their multiple talents, as opposed to projects that any one of them could undertake independently. Thus, they came up with their four research cores with each core group contributing its particular expertise to jointly solving a problem.

Since that first meeting I have continued to be impressed with each of the scientists and what they bring to the consortium and by the effectiveness with which they work together. The team has certainly exceeded my expectations and I believe the expectations of the Glaucoma Research Foundation. They have stimulated the whole field of glaucoma research toward a greater understanding of the earliest changes in the glaucoma disease process. This understanding is our hope for identifying possible new therapies and ultimately curing glaucoma.

Finally, I believe it is also important to acknowledge that not only do the board and CEO of the Glaucoma Research Foundation recognize the success of the CFC, but also an outside independent reviewer found compelling evidence of their progress and successful collaboration. As part of the consideration for a third phase of CFC funding, at the January 2010 GRF board meeting an outside reviewer who examined the reports and publications of the CFC stated that the program had made significant accomplishments. At the same board meeting Martin Raff, MD, a member of the CFC SAB, related his personal satisfaction with CFC research progress and answered questions of the board. As a result of these reviews and the commitment of two years of full funding from the Melza M. and Frank Theodore Barr Foundation, the GRF Board decided to renew the CFC funding for a third time with a two-year phase IV.

These commitments of funding and support reflect the strong belief that the CFC has been an extremely successful program. The CFC exemplifies the
early principles of the Glaucoma Research Foundation advancing innovative, collaborative and sustained research toward better understandings of glaucoma with the ultimate goal of helping patients.

**Principal Investigators’ Comments on the Process**

*Your comments on the selection process?*

“I think that having really smart scientists nominate a small group of young promising scientists is a great idea since there is the likelihood that you are going to end up with really good people. By design or by luck, or both, it worked out well for the current group, and maybe such thinking went into the original selection process. I would urge those nominating people to consider both the quality of the investigator as well as their likelihood to work well in a group. I would also urge the selection of young scientists starting their careers, as there is the highest likelihood of them bonding and of hooking them into the study of glaucoma.”

“The selection process must emphasize openness, collaboration, and willingness to work as part of a team. This needs to be probed deeply before a commitment is made. As well, the recruits should be very close in career level – just beginning is best – so that excitement and energy is shared on an even playing field.”

“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.”

*Individual reasons for signing up?*

“It was money. Even more today than it was when we were selected, scientists cannot afford to turn down money. Now, I am totally hooked. You want to repeat that aspect of it.”

“I was busy studying the basic science of visual neural processing, but found this less and less satisfying – so I jumped at the chance to broaden my research program to include a neurodegenerative disease.”

“I signed up for several reasons. First of all – I very much enjoy collaboration, and find working with other scientists to be very stimulating. Second – it seemed to be a serious effort backed by an esteemed advisory group, which gave me confidence that it would lead to something. Third – it was an opportunity to think about something new, and with potential translational
impact. I think that it is important for basic scientists to actively think about problems related to human health.”

Expectations for the CFC and how well the program has met them?

“Initially, I had no expectations. Over the years, the expectations have fluctuated considerably. Being a perfectionist, I think we could have done better at various junctions. But, we could have done a lot worse. The expectations for success on a scientific front had to be balanced with the expectations of success on many other fronts (meeting the career advancement needs of PIs and trainees, the GRF, needs for increased fundraising, etc.). Looking back at the launch of the program, I think we have done exceedingly well.”

“Expectations have been exceeded by the quality of the work emerging, the friendliness of the team, and the commitment of the individual labs to glaucoma.”

“My expectations were most definitely exceeded. I initially expected that the CFC would provide short-term seed funding for us to start working in a new area. But I was impressed and pleased that the support continued long enough for us to become established in the field and make real progress. The group worked (and continues to work) remarkably well together. The advisory group has been very energetic and committed. It has been an amazing opportunity to interact with great scientists both as colleagues and advisors.”

An effective research process for the individual principal investigators?

“Generally yes. It got me into this area of study which I care so passionately about. The collaborative nature of the project, while not perfect, was in sum highly beneficial, especially in the beginning (where the collective thinking was necessary to stay on the right track). I personally think that being forced to tackle a tough problem through unconventional means, as we were asked to do, 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. Such approach is great in the long term, but not necessarily in the short term, as we are judged by the outside (and somewhat by GRF itself) by the short-term results. Since we find ourselves now in a position of doing truly transformative science (with huge potential of preventing vision loss), I think it was a great success.”

“Absolutely. I enjoy collaborative efforts and teamwork, and really found my niche in the CFC model. I have received back completely what I put into the effort.”
“This has definitely been an effective research process. The most important aspect was to have flexible funding to permit exploratory research. This enabled us to pursue several possible directions, and identify the most relevant aspects of the disease to be targeted for intervention. This flexibility is rare and allows a more creative scientific process.

The CFC effort has brought 4 active labs into the glaucoma field working on neurobiological problems. These are labs that were not previously working in glaucoma. This will have lasting impact. It is generally very difficult for investigators to start working in a new field since NIH funding requires a track record of publication and significant preliminary data for projects to be funded. In addition, there are not straightforward mechanisms to support collaborative work. So this was a rare opportunity to do science in a different way.

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.”

Modifying the process for a group of new, young PIs to make it better? Advice for GRF as funder? For the SAB? For PI teammates?

“The key thing is finding the right people. One bad apple will spoil everything. Focus on getting good people with passion for science and making a difference (and that can work together).

For GRF: I like the fact that [GRF’s CEO] now joins us in conference calls, as frequent and regular communication is good for all involved. In general, the GRF should avoid setting a precise direction of the research. For SAB: It has been so supportive and helpful that it is hard to ask anything more of very busy people who give so much of their time. However, any more frequent contact (semi-annual conference calls, informal 1:1 mentorships, etc.) would be even better.”

“I am not sure I would modify anything substantially. I think the collaborative nature of the work has to be continuously reinforced by the SAB. Less emphasis on “cure” and more emphasis on “moving forward”. Cures arise from solid mechanistic studies. One reason disease studies have had less impact is because the search for the magic bullet has distracted the search for understanding.

The power of the CFC lies in its capacity to perform non-traditional research that is unappealing to the NIH. We do work that otherwise could not be funded – high risk, high pay-off, and some purely imaginative whose use may not be apparent. Such experiments often comprise paradigm shifts –
but this is not known for quite a while, and the payoff is not apparent in the short term. I think this should be reiterated and kept as a focus. In terms of the SAB, we have enjoyed nearly 100% dedication and participation. I would encourage the SAB to take the time consistently to keep up on our publications and progress reports in detail.”

“What the CFC effort has underscored is that diseases are complex and a “cure” is not possible without first understanding the disease. This takes time and significant investment, and is not a trivial undertaking.

To put this into context: The “War on Cancer” was launched in 1971. Thousands of labs and billions of dollars have been poured into this effort, yet 40 years later cancer remains a major cause of death. Significant progress has been made, but diseases are complex and not easily tractable. In many ways, diseases of the nervous system are even more complex.

Remarkably little was known about the neurobiology of glaucoma at the outset of this effort. A very strong case can be made that we know a whole lot more now than when we started, and that we are on the right track towards that important end of curing glaucoma. We all have our eyes on that, and this should remain the primary goal of any new consortium that is formed.”

**Postscript: The CFC Work Continues**

The CFC work has continued into 2011 and, subject to the requirements for annual funding, prospectively into 2012. This additional work has been funded by the continuing commitment of the Melza M. and Frank Theodore Barr Foundation through GRF.

Ted and Melza Barr
at the Glaucoma Research Foundation Benefit in 2010
INDIVIDUALS CITED AND AFFILIATIONS

ANTEL, Jack P, MD, Montreal Neurological Institute, McGill University
BARR, Melza M. and Frank Theodore, Foundation
BRUNNER, Thomas M., GRF
CADDICK, Sarah, PhD, Gatsby Charitable Foundation
CALKINS, David, PhD, Vanderbilt Eye Institute, Vanderbilt University
CEPKO, Constance L, PhD, Harvard University
CHAO, Moses V, PhD, Skirball Institute, New York University
GOLDSTEIN, Robert A, MD, PhD, Juvenile Diabetes Research Foundation
HAUCK, Berenice, Inaugural (1978) Funder, GRF
HETHERINGTON, John, MD, Glaucoma Center of San Francisco
HORNER, Philip, PhD, University of Washington
HOSKINS, H. Dunbar Jr, MD, Glaucoma Center of San Francisco
HOWLEY, Susan, Christopher and Dana Reeve Foundation
JOHNSON, Eugene M, PhD, Washington University Medical School
KAUFMAN, Paul L, MD, University of Wisconsin
KIRSCH, Steven and Michele, Foundation
LADRA, Michael, Wilson Sonsini Goodrich & Rosati
MACY, Josiah Jr, Foundation
MARSH-ARMSTRONG, Nicholas, PhD, Johns Hopkins School of Medicine
MATTHIAS, Blanche, Inaugural (1978) funder, GRF
O’LEARY, Dennis D M, PhD, Salk Institute
RAFF, Martin, MD, University College, London
SHAFFER, Robert N, MD (1912-2007), Founder, GRF
STEELE, Tara, GRF Director of Scientific Affairs in 2000
VETTER, Monica L., PhD, University of Utah
WAX, Martin B, MD, Pan Optica Inc
Papers and manuscripts:


Abstracts:


ACKNOWLEDGEMENTS

The production of this report was also a collaborative effort. I had the privilege of drafting the textual framework, using GRF archives and aided by the memories of those who first established the foundation and then the CFC. Robert N. Shaffer, MD at 90, An Oral History and Memoir provided insights into the development of the beliefs and commitment that underpin GRF and its support for research.

Tara Steele and Rita Loskill sketched the background for establishment of the CFC in several conversations. Sarah Caddick patiently filled in essential details and emailed copies of early documents.

At GRF Jennifer Rulon organized and sent a decade’s worth of CFC reports for review. Tanya Marino handled copyediting, design and production. Carmen Torres provided creative guidance and Elizabeth DeMartini proofread.

Thanks to each of them, to the writers of the materials in Section II, to those who reviewed the draft for completeness and accuracy, and to Ted Barr who, with his usual foresight, urged preparation of the report to preserve information that might be useful for future research efforts.

Deirdre Porter
March 2011
CATALYST CIRCLE DONORS

Glaucoma Research Foundation gratefully acknowledges the following Catalyst Circle members for their generous support of the Catalyst For a Cure research consortium from July 1, 2001 through March 31, 2011.

INDIVIDUALS

Visionaries
($500,000 to $5,000,000)

Mr. & Mrs. F.T. Barr
Deirdre Porter and Bradford Hall
Virginia and Robert N. Shaffer, MD
Charlot and Dennis E. Singleton

Benefactors
($200,000 to $499,999)

Steven L. Merrill
Ann and Emmett Skinner, Jr.

Founders
($100,000 to $199,999)

Jill and Michael Chmura
Joan F. and Clarence B. Coleman
Eleanore Compagno 1989 Trust
Germaine and Timothy Dwyer, Wendy Dwyer Memorial
Ernest and Virginia Esberg Trust
Jack F. Flowers and V. Fern Flowers Marital Trust
Richard K. Hirayama
Frank Stein and Paul S. May
Mona and Edward Zander
Pacesetters
($50,000 to $99,999)
Don O. Bedford
Frederick and Cynthia Brinkmann
Thomas M. and Wallace Brunner
M. Helen W. Davis Trust
Walter H. Girdlestone
Ann and H. Dunbar Hoskins, Jr., MD
Iris and Lawrence E. Lerner
Kate Obstgarten Private Foundation
Gladys and George M. Weston, DDS

Patrons
($25,000 to $49,999)
Maria V. Altmann
Lori and Allen Bouch
Sarah and Bill Brown
Lois Cane
John J. Clifford
Nora P. Cooks
Joy and Dinesh Desai
Eugene H. Gray and Stephanie S. Gray Irrevocable Trust
Susan and John Hetherington, MD
Robert Karp
David and Janet Kline
Lawrence S. Lipkind, DDS
William D. McDonald
Judith and Charles Munnerlyn, PhD
Robert C. Nevins
Angela Nomellini and Kenneth E. Olivier
June and Sean Otto
Sam and Denise Polakoff
F. Tracy Schilling
W.B. Seaton
Madeline Smith
Robert L. Stamper, MD
Matthew Tate, PhD
Robert N. Thayer
Warren B. Williamson
Dr. James and Elizabeth Wise
Sponsors
($10,000 to $24,999)

Jeanette and Weston Anderson
Dorothy and Richard Annesser
Anonymous
Arlene R. Anthony
Karla and George Barber
J. Bronwyn Bateman, MD and Douglas Hershey, MD
Frances T. Beaumont
Dr. Joseph and Mrs. Helen Bernstein
Richard C. Blum
Robert L. Border
Kelvin L. Davis
Sharon Dow
Robert J. Drabkin
Maurine Ehrlich
Betsy S. Erdman
Enid and Martin Gleich
Margaret and Joseph Govednik
Irene Harris
Beverly and Andrew Honzel
Andrew G. Iwach, MD
Jo Ann and George Jenkins
Roberta R. W. Kameda
Marjorie A. Nevitt
Madeline G. Okano
Alfred Ollagnier
Sanders M. Orr
Ron Payne
Michael L. Penn, Sr
Mary Helen Pidgeon
Janet and Cary R. Rayment
William L. Ridgway
Guy Rounsaville
Shigemi Sugiki, MD, FACS
Arthur S. Takahara
Patricia and George Thomas
Martin B. Wax, MD
Catherine and Charles Wilmoth
Contributors
($5,000 to $9,999)

Misato Adachi, MD
Jeanne G. Baer
Arthur A. Basham, MD
Virgene and James Beam
Charles K. Bobrinskoy
Richard Bondurant
Tim Brown
Courtney Brunn
Lisa Moscaret-Burr and Curtis Burr
Paul W. Cannon
Charles H. Clark
Nobuko Saito Cleary
and Gary Cleary, PharmD, PhD
Jerome M. Cohen
C. Seth Cunningham
Frank J. DeAlessandro
Molly and Brett Dick
Mark Eckstein
Alfred L. Fenaughty
Danielle, Maureen and Dan Fiarito
Anthony R. Fisher, PhD
Margaret and Russell Garvin
Adrienne L. Graves, PhD
Christopher Green
Larry and Carie Haimovitch
Carol M. Hall
Dorothy C. and Leonard A. Hatley
Ken Hedrick
Betty I. Jenkins
Manraj Johl
Debora and Keith Kaback, MD
Clarice and Raymond I. Kandel
Cynthia Harper and Steve Karas
Frances and Jerry G. Leigh
Linda and Donald Linck, DDS
Michael MacDougall
Andi Mallinckrodt
Inge and Harold Marcus
Paul Margolis
Janet R. Martin
Frances Marie Miller
Christopher M. Morgan
James and Rebecca Morgan
Seymour and Pearl Moskowitz
Vincent E. O’Brien
Hiro and Betty Jean Ogawa
Judy F. Oliphant
Flora P. Olmo
Charles J. Philipps
Elda and Richard Phillips
Richard Pon, CPA
Barbara J. Ritzenthaler
Irl R. Robinson
N. D’Arcy Roche
and Stephanie Twomey
Karen and Harry Roth
Barbara Rothman
David J. Roux
John Russell
Richard P. Schifter
David and Rosy Schwartz
Dorothy and Dean W. Skanderup
Stephen E. Smith
Dorris and Bill Stewart
Donald J. Stewart
Stephen M. Sullivan
Catherine and Richard Tate
Lydia and John T. Vidovich
Vincent A. Wallace
Brian Walsh
Barbara H. Wilson
Ratna K. Yadla, MD
B.J. and Michael P. Zimprich
Jan Zones
The President's Club
($1,000 to $4,999)

Thea Amberg
Robert F. Amrhein
Constance H. Andronico
Sylvia Ann Arey
Martha Armstrong
Michael Arnold
Dorothy Arnold
Fanny H. Arnold
Eileen B. Ayer
Gail Bales
Michael S. Barish
Johnella Barnett
Jason Baron
Walter R. Barry, Jr
The Beach Foundation
Joyce Beals
Lezlie Beam
Karen E. Belt
Joan and Burt Berry
Charles R. Bethge
Barbara J. Bethune
Roger Blank
Stephen E. Block
Marian E. Blum
Lawrence M. Borek
Gene R. Bouch
Peggy Bounds
Laird Broadfield and Joanne Stark
Robert and Jean Brock
Jeanette Brooks
Richard Burnley and Louise Spinelli
James E. Cafritz
Deepu Chacko
Justin T. Chang
Hu H. Chao
Stephen Clarke
Norma Clayton
Harvey W. Cohen
David Cohen
Pamela L. Colbert
Michael D. Couch
Patricia Crosby
Cynthia E. Davis
Libby and Eugene de Juan, Jr., MD
Joyce E. DeMercurio
Victoria and Donald F. DeMuth
Rose M. DiDenti
Lucy B. Dobson
Diane Duerr-Levine and Matt Levine
Arnold Dunkelman
Michael and Tracey Elfstrom
Entrekin Foundation
Albert D. Ernest
Blair Evans
Janice Ewenstein
Mary K. Fallas
Peter Falzon
John Farady
Frank B. Fehsenfeld
Marilyn A. Fenneman and Alex Forrester
John Frick
Paul Gacek
Sally and Mike Gallagher
Robin Q. Gates
Alla Gelbinovich
Marlene Gerbsman
Susanne Gerson
Vivian C. Ginty
William K. Glikbarg
Mr. and Mrs. Earl C. Gossett
Gary Greenberg
Henry Greenspan
John W. Grunden, PharmD
Roger J. Guidi
Sharlene L. and Alfred D. Hall, PharmD
Kinta Haller
Luana F. Hammett
Robert T. Harker
Gena Harper
Marjorie D. Hart
Neil M. Hay-Roe
Kristin Hebert and Bruce Potterton
Paul Heiman
Hal Heitzmann, PhD
CORPORATIONS AND FOUNDATIONS

Visionaries
($500,000 to $2,000,000)

Allergan, Inc
Edward Joseph Daly Foundation
Kirsch Foundation

Benefactors
($200,000 to $499,999)

The Alcon Foundation, Inc.
Alcon Laboratories, Inc.
Pfizer Inc.

Founders
($100,000 to $199,999)

The Allergan Foundation
Frank and Joseph Gila Fund
Mellam Family Foundation

Pacesetters
($50,000 to $99,999)

David Corporation
The Lebensfeld Foundation
Merck
Motorola Foundation
Neighbor to Nation
Santa Barbara Foundation
Santen, Inc.
Patrons
($25,000 to $49,999)

The Bodri Foundation of the Jewish Community Endowment Fund
Carol Young Brooke Foundation
California HealthCare Foundation
Citigroup
Delta Gamma Foundation
Dodge & Cox
OptiMedica Corporation
The Polakoff Foundation
Saul Family Fund
The Sun Microsystems Foundation
R. Jean & James D. Taylor Foundation
Union Bank
United Way of the Bay Area
Sponsors
($10,000 to $24,999)

Abbott Medical Optics
All Nippon Airways Co., Ltd.
Alloy Ventures, Inc.
Apricot Pit Apartments
K. Arakelian Foundation
Ballard Technology, Inc.
Bausch & Lomb
Boris Darling Productions
Canon USA, Inc.
Citigroup Foundation
Colliers International
Elsewhere Advertising
Heidelberg Engineering, Inc.
Rosanne and Al Levitt Philanthropic Fund
Lumenis, Inc.
Roy G. Michell Charitable Foundation and Trust
McBeth Foundation
Peninsula Community Foundation
Pfund Family Foundation
Pharmacia
Andrew & Lillian A. Posey Foundation
QLT Inc.
San Francisco Diamond Exchange
TBB Global Logistics
The Marian and Julius Tills Endowment Fund
UBS Investment Bank
Contributors
($5,000 to $9,999)

Albuquerque Community Foundation
AllianceBernstein
Allstate Life Insurance Company
Amorphex Therapeutics
ArtVision Portraiture
Bausch & Lomb Pharmaceuticals
Brady-Harbord-Payne
Chevron Humankind Employee Funds
DeMuth Family Fund
Donate For Charity, Inc.
Ellex
Glaukos Corporation
Imperial Hotel, Tokyo
Jane R. Lurie Philanthropic Fund
Mandarin Oriental, San Francisco
Mayo Foundation for Medical Education and Research
N.E. Eye Research Foundation
North American Elite Insurance
Novartis Ophthalmics Inc
Pearle Vision Foundation/Center
Suslov Family Trust
The Ghelfi Foundation
The Seelenfreund Family Fund
Topcon Medical Systems, Inc.
United Airlines
Versant Ventures
Wells Fargo Foundation
Y.H. Mirzoeff & Sons Foundation, Inc.
Zaffaroni Foundation
The President’s Club
($1,000 to $4,999)

Alnor Oil Company, Inc.
Altheos, Inc.
AT&T United Way
   Employee Giving Campaign
Bank of the West
Barclays Capital
Bay City Capital Foundation
Blackie Foundation
Concrete Technology Corporation
Daimler Financial Services
Delta Gamma, Diablo Valley
   Alumnae Chapter
Delta Gamma, Zeta Epsilon Chapter
Edward Jones Investments
Glaucoma Institute of Austin
Global Impact
Heidemann-Wuest Charitable Foundation
Hines Family Fund
Hospira Foundation
Intermedica, Inc.
Iridex Corporation
Ivantis, Inc.
J. Lohr Vineyards & Wines
Jay A. Martin Fine Images
Jenna Bayer Garden Design, Inc.
Jesup & Lamont Securities Corp.
John Hancock Matching Gifts Program
Joyce J. Cammilleri Family Fund
JustGive.org
Lawrence Schacht Foundation, Inc.
Loewenstern Foundation
Manika Jewelry
Merck Partnership For Giving
Michael and Susan Gaynon
   Family Charitable Fund
Morgan Stanley Smith Barney
NeoMedix Corporation
Network For Good
Park West Gallery
Physicians Interactive
Richard and Rhoda Goldman Fund
Saks Fifth Avenue, Union Square
San Francisco Rotary Foundation
Schlauch-Jen Family Fund
Silverado Country Club and Resort
Skadden, Arps, Slate,
   Meagher & Flom LLP
Sony Electronics
St. Francis Lutheran Church Foundation
The Boeing Company
   Gift Matching Program
The Bowers Family Charitable Fund
The Charles Schwab Corporation Foundation
The Harold L. & Jean C. Smith Charitable Foundation
The Howard Ray Hansen Charitable Gift Fund
The Magnum Group, Inc.
The Oliver Family Foundation
The Palace Hotel
Third Baptist Church of Portsmouth
Tobosa Exploration, Inc.
Transcend Medical Inc.
Vibro-Acoustic Consultants
Wachovia Securities, LLC
Wentworth, Hauser and Violich
Xerox Corporation
The Catalyst For a Cure Principal Investigators
Nicholas Marsh-Armstrong, PhD, Philip Horner, PhD,
David Calkins, PhD and Monica Vetter, PhD
at the 2010 Glaucoma Research Foundation Annual Benefit