



Annual
Report
2013



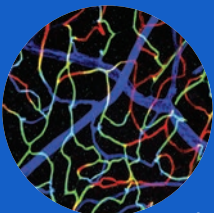
Research to Prevent Blindness



Dr. Stein Goes to Washington

Pictured above, National Eye Institute director Dr. Paul Steiving (*right*) accepts a bust of Dr. Jules Stein on behalf of the NEI. The bust, created by renowned Cubist sculptor Jacques Lipchitz, was a gift from RPB. On hand for the unveiling are RPB representatives (*from left*) Ambassador William vanden Heuvel, Katrina vanden Heuvel (Dr. Stein's granddaughter) and RPB President Brian F. Hofland, PhD.

The event was an occasion for rekindling ties that naturally unite RPB and the NEI through Dr. Stein, who was the founding force behind both organizations. Follow-up plans include joint communications to elevate public awareness of the need for increased support for eye research and the treatments it produces.



On the cover: A color-coded, confocal microscope image of the arrangement of blood vessels within the retina: blue for the blood vessels on the vitreal surface of the retina, green for the central layer of capillaries, and red for the deep layer of capillaries.

Advances in imaging technology allow researchers and eye care specialists to observe the early development of retinal diseases and to track the effectiveness of emerging, targeted therapies.

Image produced by Amir Rattner, PhD, in the laboratory of Jeremy Nathans, MD, PhD, The Johns Hopkins University School of Medicine. Dr. Nathans received a 2013 RPB Innovative Ophthalmic Research Award (see p17).



Research to Prevent Blindness

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***RPB expresses its gratitude to John Kusmiersky, who rotated off of the Board of Trustees in 2013, having completed 10 years of service.*

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Letter from the Chairman



It has been quite a year at RPB. Dr. Brian Hofland began as RPB's new dynamic president at the beginning of the year and was a catalyst for many exciting changes. We reviewed and made substantial and strategic upgrades to our Grants Program. We approved funding for a survey of the unmet needs of the vision research community. We re-energized our relationship with the National Eye Institute. We entered into strategic partnerships to expand resources for researchers. We welcomed new Board and Scientific Advisory Panel Members, while thanking departing Members for their invaluable service.

Changes to our Grants Program address current realities in conducting vision research. By increasing grant dollar amounts across the board and extending the duration of many grants across several years, we increase the likelihood that RPB awards will have an impact on two levels: on the research knowledge generated and on the trajectory of the career of the researcher.

With the national survey of unmet needs of the vision research community, conducted by a health economist at The Johns Hopkins University, RPB is reprising a role played in our early days. The findings from early surveys guided RPB for decades and helped shape arguments for increased federal support for eye research. We expect similar outcomes and more, because the current survey is also designed to complement other research that describes the financial impact of blindness both on individuals and on national productivity.

There is also a changing of the guard taking place at the department of ophthalmology chair level, and I am pleased to see so many researchers whose careers were supported by RPB assume leadership positions in our field. In 2013, alone, new chairs included: J. Timothy Stout, MD, PhD, at Baylor; Douglas Rhee, MD, at Case Western; Quan Nguyen, MD, MSc, at Nebraska; and Todd Margolis, MD, PhD, at Washington University in St. Louis.

Amidst this activity, we also mourned the loss of several true giants in eye science: Dr. Stephen J. Ryan, Dr. Lorenz E. Zimmerman, Dr. David L. Epstein and Dr. Ronald E. Smith. They gifted us with their leadership, their insights, their discoveries, and a cadre of men and women whom they mentored and who are maturing into today's leading investigators...for all of which we are grateful.

Have I forgotten to mention that eye science is advancing at a pace and in ways we could only imagine just a short time ago? In fact, 1,679 published studies cited RPB support in 2013—the most we have ever reported in a single year. You will read about these developments in the pages that follow.

I am proud to say that RPB is making rapid progress towards fulfillment of the lofty vision it was created to pursue. All of this activity is evidence that we are effective and inspiring others in fulfilling our mission.

A handwritten signature in black ink that reads "Diane S. Swift". The signature is written in a cursive, flowing style.

Diane S. Swift
Chairman

Letter from the President



Innovation is the principle upon which Research to Prevent Blindness was founded and it is the theme of this annual report. The element of innovation always has been a key component in the science we have supported. It is the means by which our researchers push the boundaries of knowledge regarding the causes of blinding conditions. And it is a catalytic ingredient in RPB's evolution, which was evident in 2013 as we undertook a strategic review of our Grants Program.

A Special Advisory Committee, comprised of chairs of departments of ophthalmology from across the country, was charged with analyzing RPB's current Grants Program and developing recommendations to help RPB better address the needs of the very vision research community we have cultivated over time. Those recommendations—consciously built on RPB's history and strengths—were refined by RPB's Scientific Advisory Panel of distinguished scientists and unanimously approved by RPB's Board of Trustees. This consensus-building process produced innovative changes for the organization.

Several awards, including the Jules and Doris Stein RPB Professorship (previously RPB's largest individual grant), were folded into an exciting, new award. Starting this fall, a portfolio of RPB Stein Innovation Awards will provide venture capital and seed money to scientists for innovative, high-risk/high-gain vision science research not previously funded.

We acted on another recommendation that RPB provide a greater platform for and increase the likelihood of innovative breakthroughs by lengthening the duration of many of our awards and increasing total grant amounts. At the same time, we laid out an enhanced accountability system for all grants, involving regular performance reviews.

Throughout 2013, RPB launched strategic and innovative partnerships with co-funders to better leverage RPB's resources. Among these, the highlight is the just-announced RPB Catalyst Award, which will bring together funding from the International Retina Research Foundation, the Sybil B. Harrington estate, and an anonymous donor to support three awardees (each receiving \$250,000 over four years) conducting novel stem cell studies for the treatment of age-related macular degeneration. An innovative aspect of this one-time series of awards calls for cross-award collaboration among the recipients. This is to incentivize researchers to work with people not normally in their laboratory sphere.

We also entered into a partnership with the Heed Ophthalmic Foundation to co-sponsor its Residents Retreat which provides a valuable professional development experience and training to second- and third-year residents in ophthalmology who have expressed interest in an academic research career. In addition, we are providing support to and partnering with the Alliance for Eye and Vision Research in its important work to educate the public and policymakers about the value of federally funded vision research.

The very concept of a public foundation that would bring together all sources of support—individual, government and business—in an expansive yet efficient research enterprise was Dr. Jules Stein's founding innovation for RPB. Our mission has not changed, but our tactics must and will. New grants, new partnerships, new researchers and new discoveries—these reflect the ability of this organization to adapt and, yes, to innovate.

A handwritten signature in black ink that reads "Brian F. Hofland". The signature is written in a cursive, flowing style.

Brian F. Hofland, PhD
President

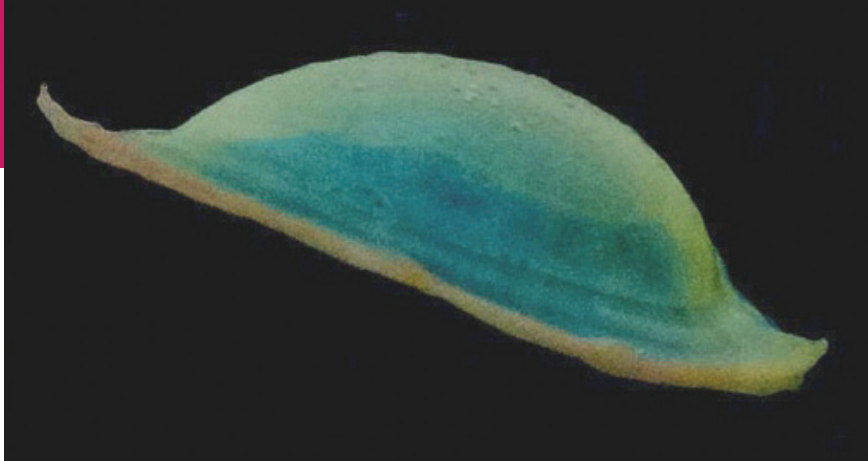
Innovations in Eye Research

RPB's intense focus is on innovative solutions to the challenges presented by sight stealing eye diseases—either through the testing of novel hypotheses, new applications of existing technologies, or the discovery of previously unknown mechanisms underlying the factors that affect vision. The support of this high-risk/high-reward work has not only connected RPB to nearly every advance in eye science in the past half century, it has accelerated the development of those advances.

Every year, RPB invests significant resources in scientists who have invested a large portion of their lives in developing treatments and cures for eye disorders. Following are some of the more innovative studies reported to us in grantees' updates.



Jennifer Elisseeff, PhD, is the Jules and Doris Stein RPB Professor of Ophthalmology at the Wilmer Eye Institute, The Johns Hopkins University. In her lab, surgeons, biologists, chemists and engineers work together to develop biomaterials and design new technologies for regenerative medicine.



Shown here, a biosynthetic cornea (tinted for purposes of illustration) created in the Elisseeff lab. Dr. Elisseeff has also created a novel bio-adhesive to treat corneal injuries and contact lenses that bind a natural lubricant.

Rebuilding the Eye

Transplanting an entire, healthy donor eye is still a holy grail for ophthalmology. When people “donate” their eyes to eye banks they are donating their corneal tissue for use in corneal grafts for patients who have damage to the clear surface of the eye due to infection, disease or trauma. There is a worldwide shortage of corneal tissue in eye banks, and scientists—including RPB scientists—are developing approaches to generating new sources of corneal tissue to meet demand.

Jules and Doris Stein RPB Professor Jennifer H. Elisseeff, PhD, The Johns Hopkins University School of Medicine, runs a lab where they are doing that and more, and combining several technologies in the process: “Our work aims to rebuild all of the tissues in the eye. This moves the field from synthetic materials, such as those for intraocular lenses, to actually rebuilding tissues that look similar to the native tissue. Our goal is to provide surgeons with a new paradigm in treating tissue loss.”

So far, they have succeeded in creating clear, corneal substitutes by engineering nano materials to mimic the normal cornea structure. They have also engineered conjunctival tissue (the conjunctiva is the mucous membrane lining the

eyelid) by placing conjunctival cells on biomaterials and allowing them to proliferate. In experiments, this fabricated tissue has successfully repaired conjunctival defects and produced a structure almost identical to surrounding tissue.

But tissue replacement, while extremely valuable in certain treatments for eye diseases, is not the only goal of the Elisseeff lab. “Synthetic biology allows us to create ocular tissues with new functions, such as the ability to secrete therapeutic proteins,” she says. “In our concept, for instance, reconstructed corneal or conjunctival tissues might be able to treat a variety of eye diseases.”

To that end, they have successfully incorporated synthetic circuits into stem cells. Eventually, says Elisseeff, “by incorporating synthetic biology into ocular tissue engineering, we envision new treatment paradigms where we can turn on a therapeutic gene simply using specifically designed eye drops.”

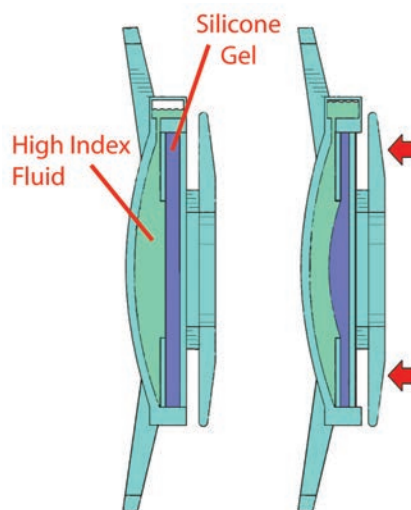
A Better Intraocular Lens

A revolutionary design is in the works for intraocular lenses (IOLs), the artificial lenses implanted into the human eye following cataract surgery. If successful, the new

IOLs will restore not only the clarity provided by current IOLs, but the ability to focus near and far (called accommodation) in response to brain impulses in a manner similar to a natural lens.

RPB Innovative Ophthalmic Research Awardee James T. Schwiegerling, PhD, Ophthalmology and Vision Science, University of Arizona College of Optical Sciences, and his team have completed a second generation prototype in which a gel material is pushed through a small opening into a chamber containing fluid of a different density. The interface between the two materials changes curvature and bends light to create a change in lens power.

As seen in the illustration, the new accommodating IOL



consists of a front lens that has a traditional refracting surface, with tabs for holding the lens in place. A separate, rear lens also has a refracting surface. It fits inside the front part and serves as a piston for the internal gel/fluid accommodating structure.

In the “Schweigerling” design, the capsular bag (the tissue that once held the patient’s natural lens) wraps around the rear portion of the IOL and remains connected to the eye’s ciliary muscle. When the ciliary muscle constricts or relaxes in response to brain impulses, the capsular bag pushes or pulls the back piece of the IOL, which pushes or pulls the gel, changing focus.

“Our innovation is including the high index fluid which en-

ables the IOL to work much like the natural lens. It works with our brain’s natural response,” says Schweigerling. “Existing accommodating IOL designs have shown modest ability to accommodate. We have demonstrated the ability to achieve significant accommodation, potentially eliminating presbyopia in eyes requiring an IOL. In addition, our design avoids loss of contrast sensitivity associated with traditional multifocal diffractive IOLs.”

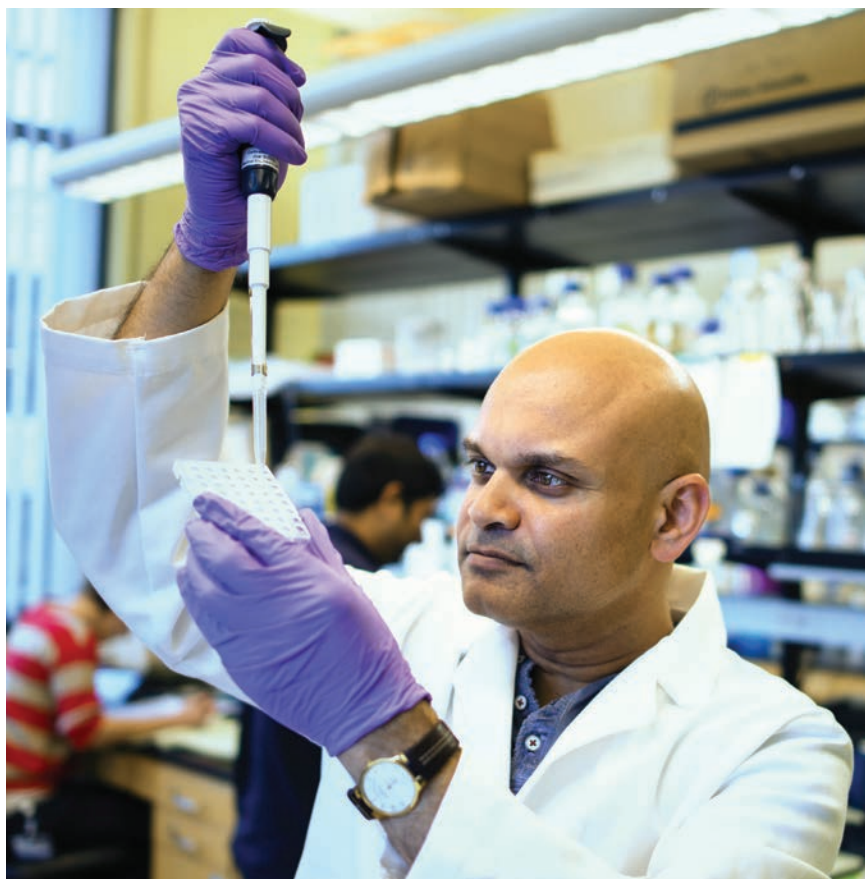
“It is the closest thing I have seen to restoring natural vision yet,” says Joseph M. Miller, MD, MPH, Chair of the Department of Ophthalmology and Vision Science, University of Arizona.

Eye Drops for AMD

Currently, most patients with the wet form of age-related macular degeneration (AMD) are treated with intraocular injections every four to 12 weeks under local anesthesia at the offices of an ophthalmologist. The benefits of slowing or halting vision loss—and, in some cases, restoring some lost sight—clearly outweigh the negatives. There are, however, serious risks created by injections into the eye, including spikes in intraocular pressure, infection and retinal detachment. There are also substantial costs either to patients or the health care system. A treatment that eliminates such injections, and the frequent office visits involved, would be far preferable.

A unique alternative shows promise, *in vivo* in lab experiments.

“We have developed an eye-drop therapy for both the dry and wet forms of AMD that could be self-administered by the patient,” says Rajendra Kumar-Singh, PhD, Department of Ophthalmology, Tufts University School of Medicine, whose work is supported by RPB’s Unrestricted Grant to Tufts. “Our studies were motivated primarily by the current limitations in the treatment procedure as well as by the potential to have



According to Dr. Kumar-Singh, experimental eye drops have been able to inhibit activation of complement, a part of the immune system implicated in both the dry and wet forms of AMD.

According to Dr. Wong, melanopsin cells are highly relevant to health and disease:

“During daytime, it is desirable to maximally stimulate them to enhance alertness and nighttime sleep quality; by contrast, nocturnal stimulation disrupts sleep quality and can cause other disorders such as depression.”

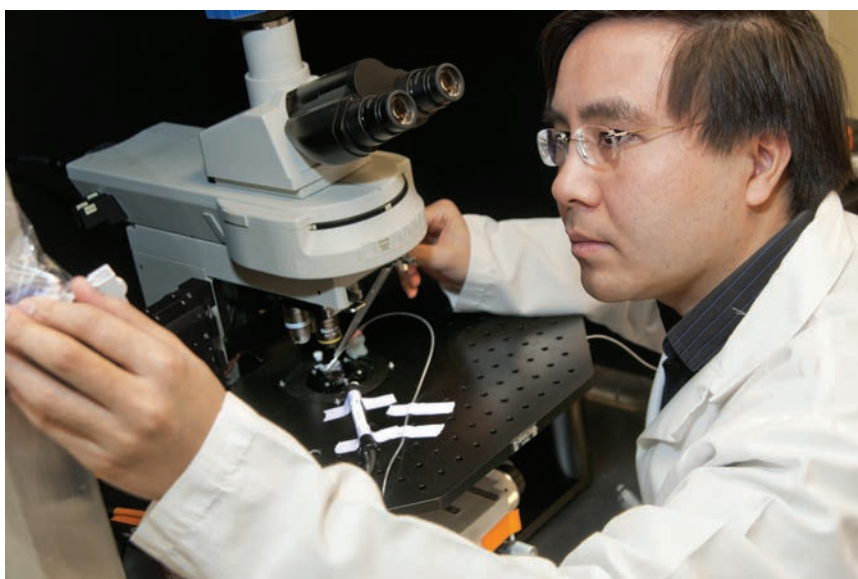
patients treat themselves before the dry form turns into wet AMD.”

The new topical treatment interrupts the AMD disease process at a much earlier point than the current eye injection treatments, which deliver an anti-VEGF agent to prevent the growth of leaky blood vessels in the retina. According to Kumar-Singh, this is another plus because VEGF (a blood vessel growth promoter) also plays significant roles in maintaining the health of retinal tissue.

“Bringing this product to market will still take several years,” says Kumar-Singh, “but we believe that it will be a ‘game-changer’ for patients. Given that this same therapy also works for the treatment of dry AMD, it will have substantial impact on the more than seven million Americans at risk of going blind from AMD.”

Revealing the Forgotten Photoreceptor

How many types of photoreceptors are there in the eye? Rods give us peripheral vision and help



us see in low light. Cones provide color vision, central vision, visual acuity and contrast sensitivity. Together, they allow us to see images, patterns, motion and color.

But the retina actually has three types of photoreceptors: rods and cones ... *and* melanopsin-expressing ganglion-cell photoreceptors. Like rods and cones, these melanopsin cells deliver visual information to the brain. Instead of sight, however, they drive non-image-forming photoreponses such as enhancing alertness and synchronizing sleep timing to the light/dark cycle.

In fact, it's even more complex than that. Five types of melanopsin cells have been discovered but their functional properties are poorly understood. One thing is known about them, however: they do interact with rods and cones to enhance vision.

RPB Career Development Awardee Kwoon Y. Wong, PhD, University of Michigan School of Medicine, investigates melanopsin cells' light-evoked responses, their modulation by neuroactive

substances such as dopamine, and their role in neural circuits. His findings suggest that it may be possible to use certain chemicals to regulate non-image-forming vision in humans.

“Reactions to light persist in many blind patients, since melanopsin cells remain functional in these individuals,” says Wong. “Thus, a better understanding of these cells' light responses, and of how various substances affect these responses, may lead to lighting technologies and pharmacological agents that appropriately modulate melanopsin cell responses at different times of day. Lights that strongly activate melanopsin cells could also improve the visual capability of people who are blind.”

The Corneal Infection Hunter

RPB-supported researcher James Chodosh, MD, MPH, Harvard Medical School, is an infectious eye disease hunter. Previously

1,679 published studies cited RPB support in 2013—the most we have ever reported in a single year.

supported by an RPB Career Development Award, an RPB Lew Wasserman Award and an RPB Physician-Scientist Award, and currently supported by an RPB Unrestricted Grant, he tracks viruses that cause corneal infection—but not the viruses we already know about. His goal is to identify the source of new, severe corneal pathogens in order to find ways to combat them before they evolve and spread in the population.

“In the last decade, almost 20 new or emergent adenoviruses have been whole genome sequenced and analyzed,” according to Chodosh. “Three of those were associated with corneal infection. In the last year, we have made important discoveries regarding how those viruses evolved, how they enter corneal cells, and how they cause inflammation in the cornea.” Through a combination of computer, laboratory and *in vivo* studies, researchers in his lab have not only demonstrated a way to identify an adenovirus as a potential corneal pathogen before it is found in patients, they have determined that different adenoviruses use distinctly different means of entry into the cells they infect.

“If we can predict a potentially infectious virus and understand how it enters corneal tissue, maybe we can equip eye specialists with tools to block its entry,” says Chodosh.

He also has a vision-robbing amoeba in his sights. Chodosh and colleagues at another RPB-supported institution, the University of California, Davis, led by Min Zhao, PhD, are pursuing new possibilities for treating *Acanthamoeba* keratitis,

a debilitating eye infection caused by an amoeba that finds its way to the cornea. Exposure to this pathogen frequently is due to contact lens wear, swimming (especially while wearing contact lenses), poor hygiene while handling contact lenses, corneal trauma, and chronic ocular surface diseases.

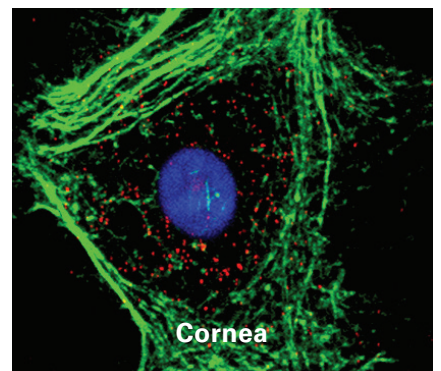
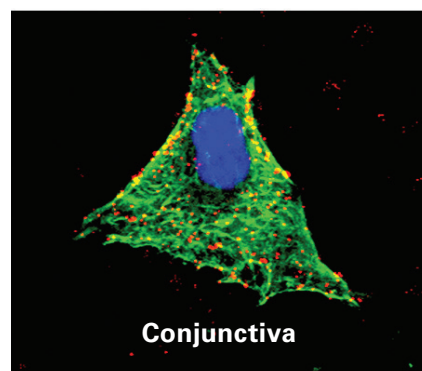
According to Chodosh, infection rates from *Acanthamoeba* have been rapidly rising for the past few decades. The organism is found widely in our environment, including contaminated contact lens solutions, bottled water, public water supplies, freshwater lakes, and even in the air. Once it gets into your eye and makes its way through the tough surface of the cornea, it forms drug-resistant cysts deep in the stromal layer.

Patients with this condition—which can lead to blindness—often have extreme sensitivity to light, pain and discomfort of the

ocular surface, and constant tearing. Treating the infection with drugs is difficult, and the amoebas can reemerge from their cysts, causing a recurrence of the infection. A corneal transplant is often the only way to eliminate the condition.

The Zhao lab is taking a unique approach, based on a suggestion from Chodosh: using electrical fields to coax the amoebas to move in a specific direction, closer to the ocular surface, where treatments have a better chance of working. So far, in the lab, it works.

“Everything on this planet is evolving or has evolved in a remarkable fashion,” says Chodosh. “Our intent is to expand our understanding of that process for various eye infections and find innovative ways to capture and eliminate the culprits.”



Entry of a fluorescently labeled adenovirus (red color) into human cell lines derived from conjunctival and corneal epithelial cells.

Figure adapted from Robinson, et al. Predicting the next eye pathogen: analysis of a novel adenovirus. MBio. 2013 Apr 9;4(2):e00595-12.

Profile: A Career Retooled

"I recently came up with this crazy idea," says David Beebe, PhD, Department of Ophthalmology, Washington University in St. Louis and Editor-in-Chief of *Investigative Ophthalmology and Visual Science*. "When you turn 35, the best thing we can do for you is stabilize the structure of the vitreous and separate it from the retina. After that, you would be good for the rest of your life."

Maybe not so crazy, the concept comes out of Beebe's findings as a developmental biologist whose clinically-based studies of the vitreous body—the gel that fills the eye—are aimed at identifying the mechanism responsible for age-related nuclear cataracts and open angle glaucoma.

"The way I got into this is quite strange," says Beebe. "Eighteen years ago, before I came to Washington University, my research teammates and I at USUHS, the Defense Department medical school, made a chance observation. We were investigating growth factors in chicken embryo lens development and to our surprise we identified the receptor for vascular endothelial growth factor (VEGF). At that time, it was thought that VEGF receptor was only expressed in blood vessels, where VEGF plays a role in the growth of new capillaries, so finding it in the blood-free lens was weird. Why would it be there?"

The answer to that question led Dr. Beebe on a fruitful path of discovery, paved by RPB.

Moving the bench closer to the bedside

"I had been chairman of a basic science department, but I had arrived at a mid-career point and I was looking for a new trajectory. The Jules and Doris Stein RPB Professorship gave me the opportunity to move into ophthalmology," says Beebe.*

"As a basic scientist moving to a clinical/research department, I needed to learn the language of the clinic. Since I've been here, I've gone to grand rounds every week. Today, I can understand what the issues are. Many of the people training in my



lab go to grand rounds to be exposed to clinical problems that they might not have encountered earlier in their education. I may never have taken this approach to research if it were not for the Stein Professorship."

The lab support portion of the Stein Professorship made it easier for him to reestablish his lab and to embark on some of his clinical work: "Today, half of my lab is devoted to early eye development. The other half is focused on clinically relevant research—particularly the role played by oxygen in the development of cataracts and glaucoma."

When oxygen goes awry in the eye

"Over time, we learned that VEGF and its receptors increase in expression when you have hypoxia [low oxygen]. We went on to show that the lens makes VEGF all the time. That gave me the idea that, maybe, the lens requires a low oxygen environment for optimum health."

Beebe was aware of other studies indicating that oxygen could be toxic to the lens. In many studies, patients who'd had a vitrectomy [removal of most of the vitreous in preparation for retina surgery] developed nuclear cataracts with very high probability within two years of the surgery. But no one had explained why. The Stein RPB

Professorship supported Beebe's initial work, which helped him apply for and receive an NIH grant to continue his investigations.

"We developed a hypothesis," he continues. "If oxygen comes from the blood vessels that feed the retina, and the lens needs to be in a low oxygen environment, then the vitreous body, which sits between the lens and retina, might be important in moderating lens exposure to oxygen and the development of cataracts.

"About that time, I received the RPB Senior Scientific Investigator Award and we used it to obtain eye-bank eyes to look at the state of the vitreous. We measured vitreous degeneration and found that, as we age, the vitreous gel becomes more liquid."

They found that even though developing a nuclear cataract is a normal part of aging, if you have a more liquid vitreous it hastens the process. Not only are people who have more vitreous degeneration going to have more problems with nuclear cataracts, a degenerating vitreous can also pull on the retina and cause retinal detachment or macular hole.

"We are currently working with scientists at Purdue University on a way to restore the structure of the vitreous. They have developed compounds to stabilize cartilage in patients with osteoarthritis and the vitreous body is actually like dilute cartilage."

Tracking oxygen levels across the eye

Next, still using money from the RPB Senior Scientific Investigator Award, "We wanted to know what happens to oxygen levels in the eye after removal of the vitreous by vitrectomy" says Beebe. "In collaboration with Dr. Nancy Holekamp, a vitreoretinal surgeon, we used a fiber optic device to measure oxygen in the eyes of patients and, sure enough, exposure of the lens to oxygen increased after vitrectomy."

A healthy vitreous, it turns out, acts as an oxygen sponge. As it degenerates and loses its oxygen-absorbing capacity, or if it is removed via surgery, surrounding tissues in the eye are exposed to higher oxygen.

The oxygen conundrum

"The vitreous separates two domains, the oxygen-rich retina and the oxygen-poor lens," explains Beebe.

"An intact, healthy vitreous is going to keep the lens hypoxic, but it may also contribute to retinal hypoxia. This can actually be problematic once we hit 40 or 45, because age-related degenerations can start in our retina, such as wet AMD or diabetic retinopathy. Under those conditions, the vitreous is potentially harmful because it maintains a low oxygen environment and these conditions are promoted by low oxygen.

"This is what led me to my crazy idea. At a certain point, maybe the best thing that can happen is to have your vitreous separate from the retina with the anterior vitreous remaining intact to protect the lens. In fact, if you have posterior vitreous detachment, you're protected against the wet form of AMD. And our research indicates that you're probably going to be protected against diabetic macular edema and diabetic retinopathy, too."

Another oxygen complication: glaucoma?

"Recently, we've taken our clinical investigations a step further—again, quite by surprise. Dr. Stanley Chang [one of the country's leading retina surgeons and former department Chair] at Columbia noted that if you have a vitrectomy and then cataract surgery, you have a much higher risk of open-angle glaucoma. Based on our studies, he suggested that the lens is protecting the anterior segment against oxygen damage, right where the outflow system resides in the eye, potentially initiating or exacerbating glaucoma. Together with Dr. Carla Siegfried, we recently provided evidence for Stanley's idea. Being an observant clinician is incredibly important for medical research. It's why I have such close collaborations with clinicians.

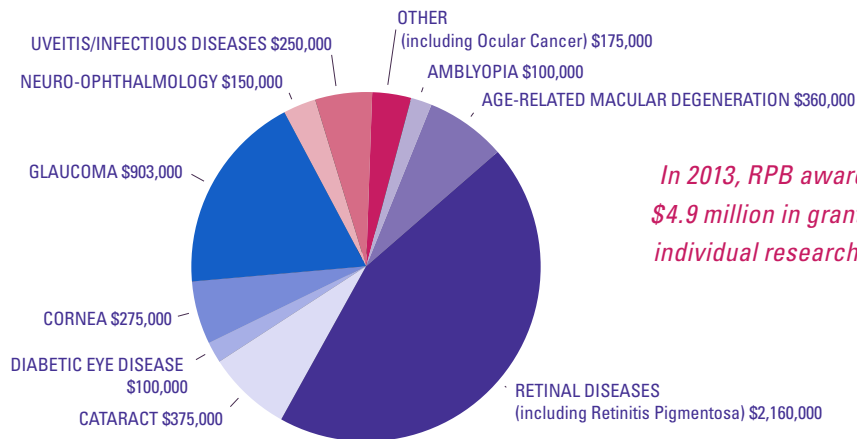
"RPB support has been a game changer for me, both the continuity of funding and the lack of restrictions on the direction of your studies, which lets you turn surprises into sound scientific sense."

**The Jules and Doris Stein RPB Professorship encouraged established, basic scientists to bring their expertise into a department of ophthalmology. It provided additional funds for lab support. In 2014, the Stein Professorship will be folded into the new Stein Innovation Award.*

RPB Grants Program

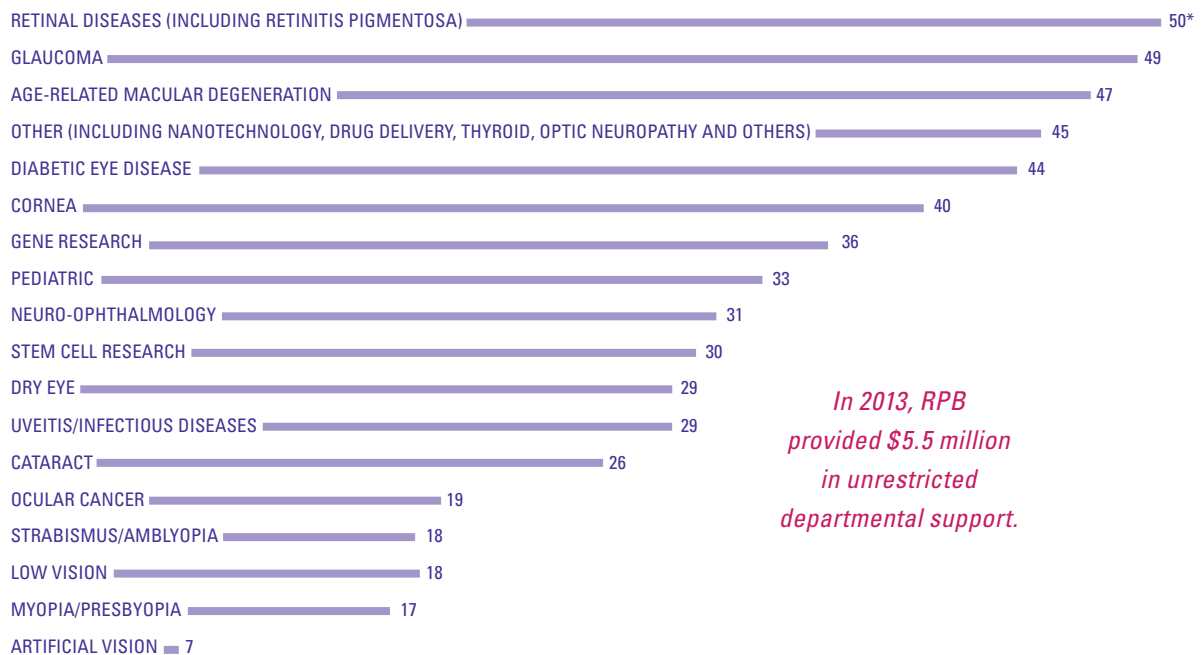
Research to Prevent Blindness awards grants to benefit both individual vision researchers and departments of ophthalmology. RPB grants can be used to support basic lab research (molecular biology, genetics, biochemistry, etc.), clinical studies (to determine the safety and effectiveness of new medications or devices), and translational research (that finds medical applications for basic research). In 2013, RPB approved 87 new grants: 54 departments of ophthalmology received Unrestricted Grants; and 33 researchers received individual awards. To date, RPB's total investment in cutting edge vision research is \$316 million.

HOW RPB GRANTS TO INDIVIDUALS WERE APPLIED IN 2013



In 2013, RPB awarded \$4.9 million in grants to individual researchers.

HOW RPB UNRESTRICTED GRANTS WERE APPLIED IN 2013



In 2013, RPB provided \$5.5 million in unrestricted departmental support.

*Number of schools researching in this area out of total 54.

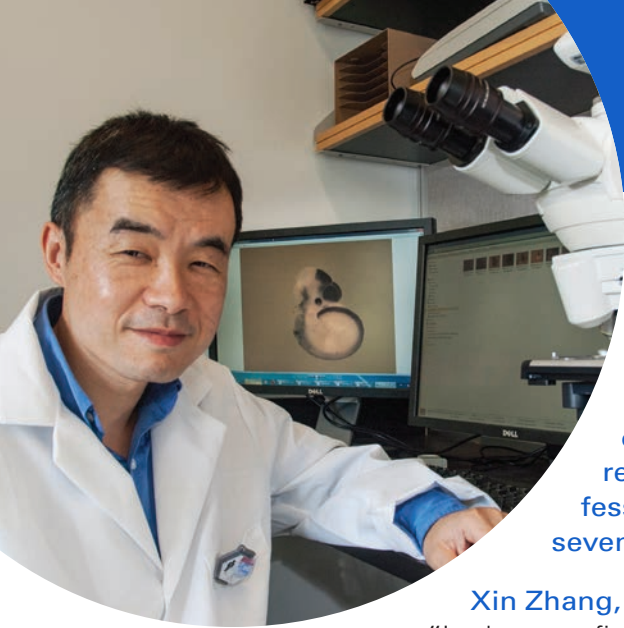
New Grants

The element of flexibility was one of the core qualities that our 2013 Strategic Review Process identified as a “keeper” in any changes we made to grants. Flexibility allows a researcher to purchase a piece of necessary equipment, supplement other restricted-use dollars, or complete unexpected aspects of a study. So, as you read the following descriptions of the 2013 awardees’ proposed research, keep in mind that they eventually may deliver findings other than those proposed—surprise discoveries that they encountered and pursued—and *that* is part of the plan.

You also will see that we gave out six Innovative Ophthalmic Research Awards—up from three in 2012. The focus on innovation reflected by that sharp increase will become further institutionalized at RPB as we roll out new awards in years to come. We will continue to support the most promising research but, necessity being the mother of innovation, we will address an urgency to move as quickly as possible toward new treatments as we confront the increasing age-related risk exposure of the Baby Boom generation.



Jerry Y. Niederkorn, PhD, University of Texas Southwestern Medical Center, uses RPB’s Unrestricted Grant to study the role of the immune system in controlling the metastasis of intraocular melanoma, a cancer that originates in the eye.



Jules & Doris Stein RPB Professorship

Designed to foster translational research by recruiting outstanding basic scientists to conduct clinically relevant research in a department of ophthalmology, the Stein Professorship provides a potential \$1,025,000 over a possible seven-year period.

Xin Zhang, PhD, Columbia University College of Physicians & Surgeons

"In the next five years, I will investigate growth factor signaling in the matrix outside of cells and at the cell surface. Inside the cell, I will test the potential for selective signal activation to rescue retinal degeneration."

Jules & Doris Stein RPB Professorship Extension

Irina A. Pikuleva, PhD, Case Western Reserve University School of Medicine

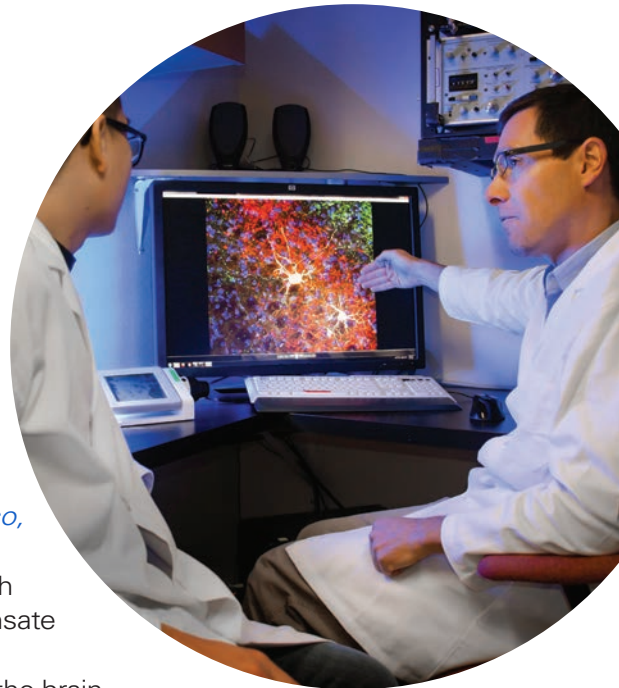
"I will investigate the benefits of combining antioxidant supplement therapy with drugs that target the accumulation of oxidized fat products found in drusen, which develop in dry age-related macular degeneration."

RPB Walt and Lilly Disney Award For Amblyopia Research

Created through a pledge from The Walt and Lilly Disney Foundation for research into improved detection, treatment or cures for amblyopia, the leading cause of childhood vision loss, the Disney Award provides \$100,000 annually.

Erik Ullian, PhD, University of California, San Francisco, School of Medicine

"Our work focuses on the mechanisms and rules by which cells projecting from one eye compete with, and compensate for, input from the other eye. This will shed light on the mechanisms underlying amblyopia, a condition in which the brain ignores inadequate input from a diseased eye and favors the better eye's information. We will use new genetic tools to manipulate genes in retinal ganglion cells to determine the feasibility and critical period for gene-delivery based treatment of amblyopia."



RPB Physician-Scientist Awards

\$100,000 to nationally recognized MDs and MD/PhDs who bring to the lab a practical understanding of patients' needs while their research efforts yield new knowledge in treating patients.

Szilard Kiss, MD, Weill Cornell Medical College

"While anti-VEGF injections may improve vision for patients with wet age-related macular degeneration (AMD), they require repeated re-injections as frequently as monthly. The goal of our RPB-funded research is to develop a single injection gene therapy with an anti-VEGF agent that would result in sustained, long-term treatment."

Stephen Tsang, MD, PhD, Columbia University College of Physicians & Surgeons

"Our RPB studies are already demonstrating the potential for using gene therapy to treat human patients with retinitis pigmentosa (RP) caused by PDE6A mutations. The next step will be a human clinical trial to treat RP patients with PDE6A mutations."

Demetrios Vavvas, MD, PhD, Harvard Medical School

"Treatments targeting apoptosis—a mechanism of cell death in many retinal diseases—have been developed, but they fail to show effective neuroprotection. My group recently demonstrated that necrosis, a distinct cell death mechanism, also mediates photoreceptor death. Our RPB studies will identify specific therapeutic targets for both apoptosis and necrosis."



RPB Mildred Krahrmer Sanders & William Clifford Sanders Laboratory for Vision Research

The *University of Florida College of Medicine* received this one-time \$600,000 grant, as fulfillment of the wishes of Mr. and Mrs. Sanders who, in their will, named RPB to conduct the competitive application process for the construction of an eye research lab.

"This space is purpose-designed to house key modules of our vision core," said William Driebe, MD, former Chair, "with a primary focus on developing new gene therapies. Members of our group will also use the lab to develop a next generation of viral vectors that can be used to deliver larger genes, and vectors that can target photoreceptors and other tissue by intravitreal injection. We have begun finalizing construction contracts and have held meetings on the design and scope of work."





RPB Career Development Awards

\$250,000 over four years for outstanding young clinical and basic scientists.

Daniel R. Saban, PhD,
Duke University School of Medicine

"My research team has detected a unique population of immune cells which likely contribute to chronic, severe ocular allergy, a vision-threatening condition with unmet medical needs. Our goal is to reveal new insights for novel therapeutics."

Cagri G. Besirli, MD, PhD, *The Regents of the University of Michigan School of Medicine*

"One of the underlying mechanisms of photoreceptor injury in retinal disorders involves the separation of photoreceptors from the tissue that nourishes them, the retinal pigment epithelium (RPE). The long-term goal of my laboratory is to develop pharmacologic and biologic neuroprotective agents to enhance the survival of photoreceptors."

Jason I. Comander, MD, PhD, *Harvard Medical School*

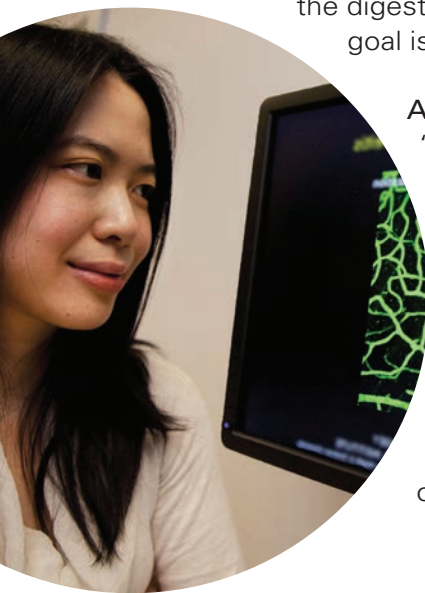
"I am currently developing new techniques to speed methods of determining which DNA variants in patients are disease-causing and which are benign."

Anna Demetriades, MD, PhD, *Weill Cornell Medical College*

"My laboratory is dedicated to finding new treatments for glaucoma by using a cell-specific gene therapy approach to provide sustained delivery of therapeutic agents to the eye and by exploring the role of neuroprotective proteins in preventing retinal ganglion cell loss."

Phoebe Lin, MD, PhD, *Oregon Health & Science University School of Medicine*

"I am studying how the microbiome—the many microorganisms that live symbiotically in the digestive tract—affects ocular inflammation by training the immune system. My goal is to pharmacologically manipulate this process to treat ocular inflammation."



Ala Moshiri, MD, PhD, *University of California, Davis, School of Medicine*

"My objectives are to develop and test molecular fluorescence resonance energy transfer (FRET) sensors of the visual cycle in order to non-invasively measure the health and functioning of the visual cycle in healthy and diseased states."

Derek Welsbie, MD, PhD, *The Johns Hopkins University School of Medicine*

"Using a technique known as RNA interference we have screened a collection of 'druggable' genes and identified one that might mediate retinal ganglion cell death in glaucoma. Our goal is to develop a new class of glaucoma therapeutics."

RPB Innovative Ophthalmic Research Awards

\$100,000 to basic scientists (PhD or MD/PhD) actively engaged in out-of-the-box research in collaboration with the school's department of ophthalmology. This award is intended to bring basic science into ophthalmology and new collaborations between ophthalmology and other scientific disciplines.

Joshua R. Sanes, PhD, *Harvard University*

"The majority of apparently 'disease-free' individuals experience some degree of age-associated decline in vision. Some of these alterations can be attributed to optical changes, for example in the lens and cornea, but others clearly involve alterations in neurons, including those in the retina. We will investigate the molecular basis of age-related synaptic decline in pursuit of new treatments."

Joseph C. Corbo, MD, PhD, *Washington University in St. Louis School of Medicine*

"I propose to genetically reprogram adult rod photoreceptors into cones [the cells that provide visual acuity, color perception and contrast sensitivity] in order to treat retinal diseases that affect cones, for which there are currently no effective therapies."

Daniel J. Goldman, PhD, *The Regents of the University of Michigan School of Medicine*

"Disease or injury of the mammalian retina leads to irreparable vision loss, while the injured zebrafish retina mounts a regenerative response that restores lost sight. Key to this regenerative response are Müller glia cells. We hope to develop a novel cell culture model to help identify factors in the injured retina environment that stimulate Müller glia reprogramming."

Steven R. Little, PhD, *University of Pittsburgh School of Medicine*

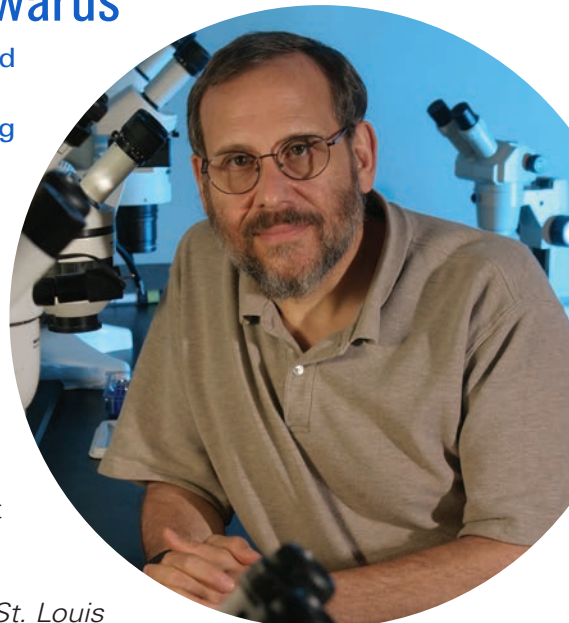
"Topical eye drop treatment for glaucoma is extremely inefficient, with compliance rates as low as 50%. Using a novel, thermo-gelling eye drop, we will apply new, computer-aided design methods to produce controlled release formulations for delivery of a glaucoma medication."

Jeremy Nathans, MD, PhD, *The Johns Hopkins University School of Medicine*

"Our primary goal is to characterize patterns and mechanisms of retinal cell-type specific changes in the DNA and proteins that make up the contents of the nucleus of a cell in response to photoreceptor stress, disease, and neuroprotection. We are particularly interested in the possibility that long-lasting epigenetic changes might be induced by photoreceptor stress."

Eric A. Newman, PhD, *University of Minnesota, Academic Health Center, Medical School*

"In the retinas of diabetic patients, well before overt retinopathy is observed, there is a reduction in light-evoked increases in blood flow in retinal vessels. We will determine whether oral administration of aminoguanidine (AG) reverses the loss of light-evoked blood flow increases and reverses the decrease in contrast sensitivity in patients with type 1 diabetes."





RPB Senior Scientific Investigator Awards

\$150,000 to extend the productivity of seasoned vision scientists who can play a crucial role in training the next generation of vision scientists.

Wallace B. Thoreson, PhD, University of Nebraska Medical Center

“We are studying the mechanisms that regulate chemical communications across the gap between nerves from rods and cones. Our goal is to learn how the information is converted into a neural code for the brain and how this process shapes what we see in order to develop effective therapies that repair damage to the eye.”

J. William Harbour, MD, University of Miami Miller School of Medicine

“There are many uveal melanoma tumors with features that make them suspicious for malignancy, but which are not large enough to biopsy. We propose to develop a non-invasive ‘optical biopsy’ for suspicious uveal nevi—hopefully, a routine office procedure—that would identify suspicious nevi that have undergone transformation.”

Robert W. Nickells, PhD, University of Wisconsin-Madison School of Medicine

“We have learned that even though we can prevent 100% retinal ganglion cell (RGC) death in glaucoma, these cells completely shut down normal function and become quiescent. We believe that this provides a unique opportunity to reactivate RGCs by introducing key transcription factors.”

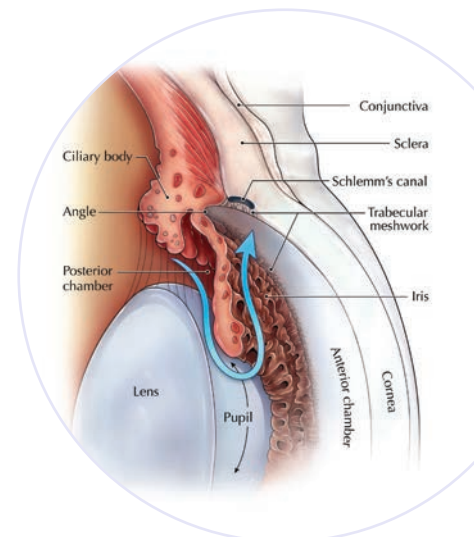
W. Daniel Stamer, PhD, Duke University School of Medicine (see profile on next page)

“Our primary research goal is the development of novel therapies for ocular hypertension that will act on the blood-aqueous barrier in the area of Schlemm’s Canal.”

Outflow pathway of the aqueous humor

Aqueous humor (shown here as a blue arrow) is a fluid secreted by the ciliary body. It maintains intraocular pressure and nourishes ocular tissue, exiting the eye after filtering through the trabecular meshwork and draining through Schlemm’s canal.

“In glaucoma, the tissue that makes up the main outflow pathway goes bad,” says Dr. Stamer. “So far, we don’t have a drug that targets that tissue.”



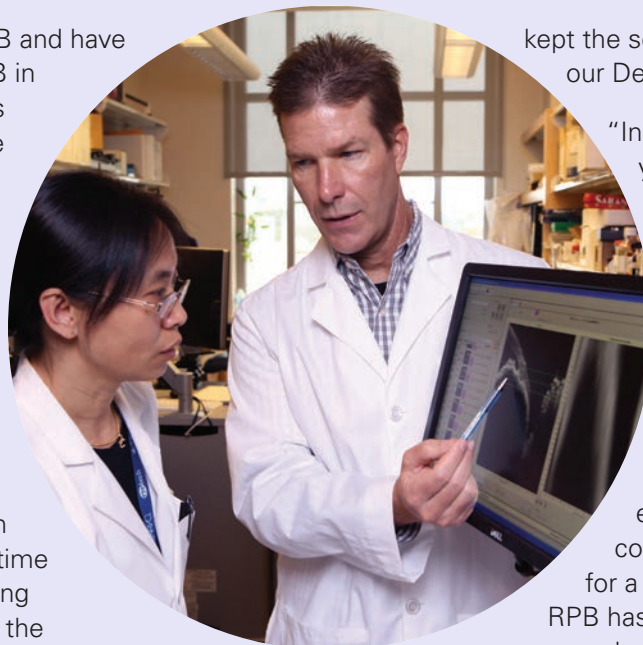
Profile: A Career Refocused

"I have worked with RPB and have been supported by RPB in a variety of ways," says Dan Stamer, PhD, Duke University. "When I was just starting my research career, at the University of Arizona, I received an RPB Career Development Award (CDA). The impact was immediate. Within months I added a technician to my team and could spend more time thinking about and testing new ideas. My focus is the primary outflow pathway of the eye, which is the main mechanism for regulating intraocular pressure [IOP]."

There are many normal daily activities (rubbing your eye, squinting or just waking up) that raise IOP, according to Stamer. The primary outflow pathway is pressure sensitive, and acts like a shock absorber. In most people, the shock absorber dampens IOP spikes and keeps IOP within a very narrow range over your whole life. "If you have glaucoma, the shock absorber wears out over time, causing elevated IOP and bigger pressure spikes are transmitted to the delicate nerves in the back of the eye, which causes you to lose vision," he says.

"The CDA-supported work allowed me to compete successfully for National Eye Institute grants and publish high impact papers—all on different aspects of this mechanism.

"After some time I became Research Director at Arizona. In that role, I helped manage the Unrestricted Grant from RPB, providing gap support for unfunded scientists, pilot research, equipment purchase and maintenance, etc. RPB



kept the science moving forward for our Department.

"In science, as in anything else, you can get comfortable and complacent. I was awarded an RPB Sabbatical Grant to visit a distant laboratory where I learned a new technique for measuring outflow facility. This new technology now drives much of what I do in the lab, creating a multiplier effect for my group and my colleagues who now use it. So, for a relatively small investment, RPB has made a significant impact on me and others who study glaucoma.

"While I was on sabbatical, it became clear that I had to make a move with my career. I realized I was missing key colleagues with whom I could work to develop a better glaucoma treatment, which is my ultimate goal. RPB was the catalyst for the process of understanding and decision making that led me to move to Duke.

"Now, at Duke, with my recent Senior Scientific Investigator Award, I feel like I am coming full circle with RPB's support. I will be screening for compounds that modify the shock absorber in glaucomatous eyes, and developing technology to monitor the impact of treatment and progression of disease. I am confident that I am now poised to help get a new drug on the market and save vision for those who have glaucoma.

"Mine is just one of many RPB career support success stories. Very few funders will help you when you are just starting out, or have a non-conventional idea, or encourage you to reinvent yourself. RPB gets it."

RPB Special Scholar Awards

\$25,000 - \$100,000 given to promising young scientists of exceptional merit, in honor of former RPB trustees and others who have made generous contributions of time, energy and financial resources in support of eye research.



Nawajes Mandal, PhD, Ernest & Elizabeth Althouse Scholar - University of Oklahoma Health Sciences Center

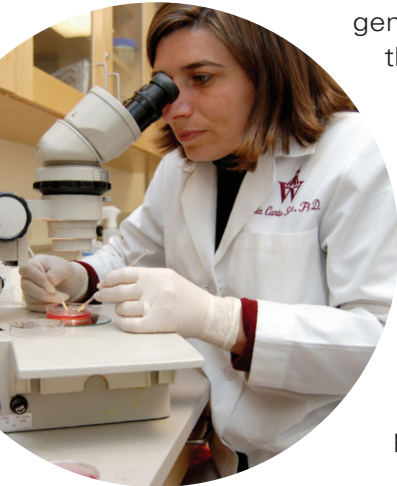
"DHA, an omega-3 fatty acid, has been tested as a neuroprotective treatment for age-related macular degenerations, but has been found to be harmful under some conditions. Our goal is to identify the true role of DHA in the retina and provide guidelines for its use in specific eye diseases."

Jun Yang, PhD, Nelson Trust for Retinitis Pigmentosa Scholar - University of Utah School of Medicine

"My research team and I are developing a gene therapy for a devastating form of retinitis pigmentosa, Usher syndrome, which produces combined blindness-deafness."

Maria Valeria Canto-Soler, PhD, William & Mary Greve Scholar - The Johns Hopkins University School of Medicine

"In our studies, human induced pluripotent stem cells (hiPSCs) are generated from adult skin or blood cells obtained from patients through a routine clinical biopsy. In the lab, these cells are re-directed to become retinal cells from which we intend to form three-dimensional, patient-specific models for treatment testing."



Wei Li, PhD, Sybil B. Harrington Scholar - University of Miami Miller School of Medicine

"Through a process known as phagocytosis, the retinal pigment epithelium (RPE) clears photoreceptor debris from the retina. In the aged RPE, there is significantly reduced phagocytosis activity, which contributes to RPE death and AMD. Using newly developed technology, we will identify valuable targets for future therapies to prevent RPE death and AMD."

Kip M. Connor, PhD, Sybil B. Harrington Scholar (Macular Degeneration) - Harvard Medical School

"Our studies are designed to determine if dietary intake of omega-3 long-chain polyunsaturated fatty acids protects against AMD. Early indications are that they have anti-blood vessel-overgrowth and anti-inflammatory effects."

Ashwath Jayagopal, PhD, Dolly Green Scholar - Vanderbilt University School of Medicine

"One goal of this research is to develop imaging technologies capable of detecting molecular disease biomarkers in diabetic retinopathy and wet AMD very early in disease progression. We further aim to engineer nanoparticles targeting these molecules."

RPB Medical Student Eye Research Fellowships

This \$30,000 stipend enables a student to take a year off to pursue a laboratory research project within a department of ophthalmology.

Qinyun Wang, *University of California, San Francisco, School of Medicine*

"We are working to expand the clinical applications of Adaptive Optics Scanning Laser Ophthalmoscopy (AOSLO) by combining it with microperimetry, a novel technique that delivers visual stimuli to targeted retinal regions of interest with single-cone precision."

Philip DeSouza, *Duke University School of Medicine*

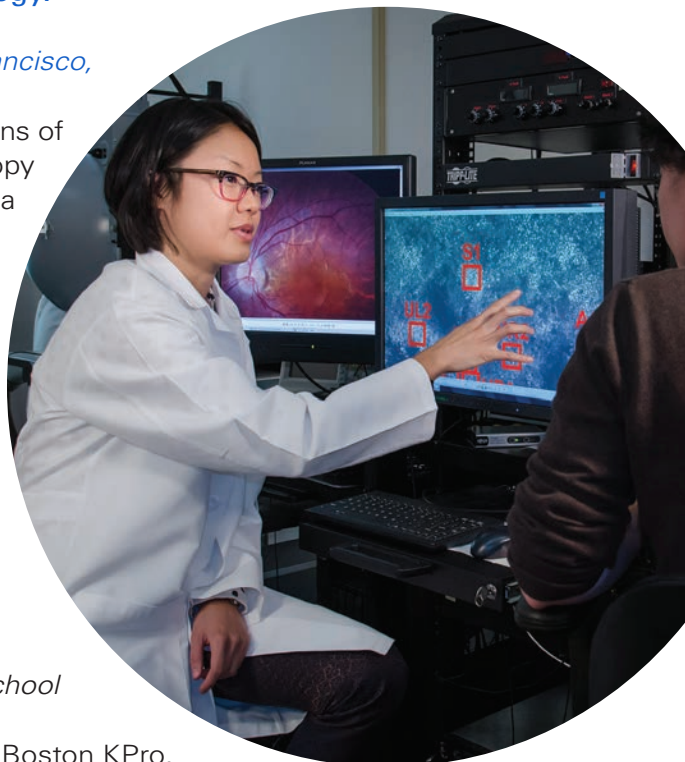
"My research will investigate whether or not a surgeon's assessment of ocular microanatomy and ability to perform surgical maneuvers in a wetlab is improved when using microscope-integrated-OCT rather than traditional viewing alone."

Christina Marsica Grassi, *Harvard Medical School*

"The damaged cornea can be replaced with a keratoprosthesis (artificial cornea), such as the Boston KPro. The goal of this project is to enable refinement of the device for increased use in patients who would benefit from an artificial cornea."

Huy Nguyen, *Columbia University College of Physicians & Surgeons*

"Knobloch Syndrome is a rare, untreatable disease caused by a mutation in the gene coding for Collagen XVIII. This causes dysfunctional retinal pigment epithelium (RPE) cells and severe vision loss in the teenage years. We hope to create a procedure to successfully introduce Collagen XVIII into the deficient RPE, restoring their function."



RPB International Research Scholar Award

This award of up to \$10,000 enables foreign researchers to travel to the U.S. for collaboration with U.S. researchers.

Chunyan Qiao, MD, PhD, *collaborating with researchers at Harvard Medical School*

"The CDKN2B-AS gene region is important for maintaining retinal ganglion cells in a state of health that allows them to maintain visual processing throughout life. Our study will assess the association between the CDKN2B-AS rs3217992 locus variants and glaucomatous progression."

2013 RPB APPROVED GRANTS TOTAL: \$12,483,000*

U.S. medical schools receiving new 2013 departmental and/or individual investigator awards

STATE	RPB GRANTEE INSTITUTIONS	TOTAL GRANTS 2013	TOTAL SUPPORT INCLUDING 2013
ALABAMA	University of Alabama at Birmingham School of Medicine	\$110,000	\$3,855,000
ARIZONA	University of Arizona College of Medicine	110,000	2,265,000
CALIFORNIA	University of California, Davis, School of Medicine	360,000**	3,743,900
	David Geffen School of Medicine at UCLA	110,000	8,660,750
	University of California, San Diego, School of Medicine	110,000	3,285,000
	University of California, San Francisco, School of Medicine	240,000	7,069,256
	Keck School of Medicine of the University of Southern California	110,000	5,273,500
CONNECTICUT	Yale University School of Medicine	110,000	3,287,224
FLORIDA	University of Florida College of Medicine	710,000	4,305,600
	University of Miami Miller School of Medicine	315,000	4,600,200
GEORGIA	Emory University School of Medicine	110,000	3,707,100
ILLINOIS	Northwestern University Feinberg School of Medicine	110,000	2,780,000
	University of Illinois at Chicago	110,000	4,026,712
IOWA	University of Iowa Carver College of Medicine	110,000	4,352,425
KENTUCKY	University of Louisville School of Medicine	110,000	3,844,800
LOUISIANA	Louisiana State University Health Sciences Center in New Orleans	110,000	2,602,100
MARYLAND	The Johns Hopkins University School of Medicine	520,000**	8,885,140
MASSACHUSETTS	Harvard Medical School	648,000**	8,755,315
	Tufts University School of Medicine	110,000	3,413,697
MICHIGAN	The Regents of the University of Michigan School of Medicine	460,000**	6,953,050
	Wayne State University School of Medicine	110,000	3,913,000
MINNESOTA	Mayo Medical School	110,000	3,054,600
	University of Minnesota, Academic Health Center, Medical School	210,000	3,248,701
MISSOURI	Washington University in Saint Louis School of Medicine	210,000	6,994,981
NEBRASKA	University of Nebraska Medical Center	260,000	2,010,000
NEW YORK	Albert Einstein College of Medicine of Yeshiva University	110,000	1,977,500
	Columbia University College of Physicians & Surgeons	1,015,000#	5,618,167
	Weill Cornell Medical College	460,000**	4,893,700
	Mount Sinai School of Medicine	110,000	4,068,200
	University of Rochester School of Medicine & Dentistry	110,000	2,775,250
	SUNY at Buffalo School of Medicine & Biomedical Sciences	110,000	900,000
	SUNY Upstate Medical University	110,000	2,630,000
NORTH CAROLINA	Duke University School of Medicine	540,000**	7,070,150
	University of North Carolina at Chapel Hill School of Medicine	110,000	1,630,500
OHIO	Case Western Reserve University School of Medicine	360,000	3,512,500
	Cleveland Clinic Lerner College of Medicine	110,000	2,735,000
	University of Cincinnati College of Medicine	110,000	1,710,250
OKLAHOMA	University of Oklahoma Health Sciences Center	185,000	5,011,600
OREGON	Oregon Health & Science University School of Medicine	360,000**	4,842,150
PENNSYLVANIA	University of Pennsylvania School of Medicine	110,000	5,638,500
	University of Pittsburgh School of Medicine	210,000	4,398,372
SOUTH CAROLINA	Medical University of South Carolina	110,000	2,397,500
TENNESSEE	University of Tennessee Health Science Center	110,000	2,655,000
	Vanderbilt University School of Medicine	135,000	2,745,500
TEXAS	Baylor College of Medicine	110,000	4,354,060
	University of Texas Southwestern Medical Center at Dallas	110,000	4,116,000
UTAH	University of Utah Health Sciences Center	210,000	5,335,300
WASHINGTON	University of Washington School of Medicine	110,000	3,557,638
WISCONSIN	Medical College of Wisconsin	110,000	4,334,215
	University of Wisconsin-Madison School of Medicine	260,000	4,628,750

*Includes commitments for special grants to: The Association of University Professors in Ophthalmology; The Johns Hopkins University for a "Sight Survey"; and University of Alabama at Birmingham School of Medicine for a special endowed chair.

** Includes a four-year \$250,000 Research to Prevent Blindness Career Development Award, payable at the rate of \$62,500 per year.

#Includes a five-year \$625,000 Jules and Doris Stein Research to Prevent Blindness Professorship payable at \$125,000 per year and a \$150,000 Stein Professorship Laboratory renovation grant.

Schools that received RPB support but no new grants in 2013: State University of New York Downstate Medical Center, University of Texas Health Science Center at Houston, University of Missouri - Kansas City School of Medicine, New York University School of Medicine.

The RPB grant approval process is highly competitive. A standing Scientific Advisory Panel (SAP) and rotating Ad Hoc Committees convene each spring and fall to review all grant applications. Ad Hoc Committees are comprised of selected ophthalmology department chairs whose recommendations are forwarded to the SAP for further evaluation. The SAP includes distinguished scientists representing a broad range of scientific disciplines and interests. Their recommendations are presented to the RPB Board of Trustees for final approval.

2013 RPB SCIENTIFIC ADVISORY PANEL

Robert Eugene Anderson, MD, PhD

Professor, Departments of Cell Biology and Ophthalmology, Dean McGee Professor of Ophthalmology, George Lynn Cross Research Professor, University of Oklahoma Health Sciences Center, Director of Research, Dean McGee Eye Institute

John E. Dowling, PhD

Gordon and Llura Gund Professor of Neurosciences, Department of Molecular and Cellular Biology, Harvard University

Robert Folberg, MD

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Eve Higginbotham, SM, MD

Vice Dean, Inclusion and Diversity, Senior Fellow, Leonard Davis Institute of Health Economics, Professor of Ophthalmology, Scheie Eye Institute, University of Pennsylvania

Roderick R. McInnes, CM, MD, PhD, FRSC

Director, Lady Davis Research Institute, Jewish General Hospital, Canada Research Chair in Neurogenetics, Alva Chair in Human Genetics, Professor of Human Genetics, Professor of Biochemistry, McGill University

Anthony Moore, MA, FRCS, FRCOphth, FMedSci

Professor of Ophthalmology, Department of Ocular Biology and Therapeutics, Institute of Ophthalmology, University College London

Krzysztof Palczewski, PhD

Professor and Chair, Department of Pharmacology, Case Western Reserve University

John S. Penn, PhD

Phyllis G. and William B. Snyder Professor and Vice Chairman, Department of Ophthalmology and Visual Sciences, Assistant Dean for Faculty Development Vanderbilt University School of Medicine

Sheila West, PhD

Professor, Vice Chair for Research, Wilmer Eye Institute, The Johns Hopkins School of Medicine, Department of Epidemiology, The Johns Hopkins Bloomberg School of Public Health

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University of Kentucky College of Medicine

Jayne Weiss, MD

Louisiana State University Health Sciences Center in New Orleans

David J. Wilson, MD

Oregon Health & Science University School of Medicine

In 2013, John E. Dowling, PhD, Robert Folberg, MD and Eve Higginbotham, SM, MD rotated off of RPB's SAP, having provided years of invaluable guidance in the selection of grantees and the shaping of RPB's grant programs. RPB is deeply grateful for their service. Dr. Dowling continues as the Scientific Advisor to RPB's Board of Trustees and Special Advisor to RPB staff.



Research to Prevent Blindness

RPB's mission is to preserve and restore vision by supporting research to develop treatments, preventives and cures for all conditions that damage and destroy sight.