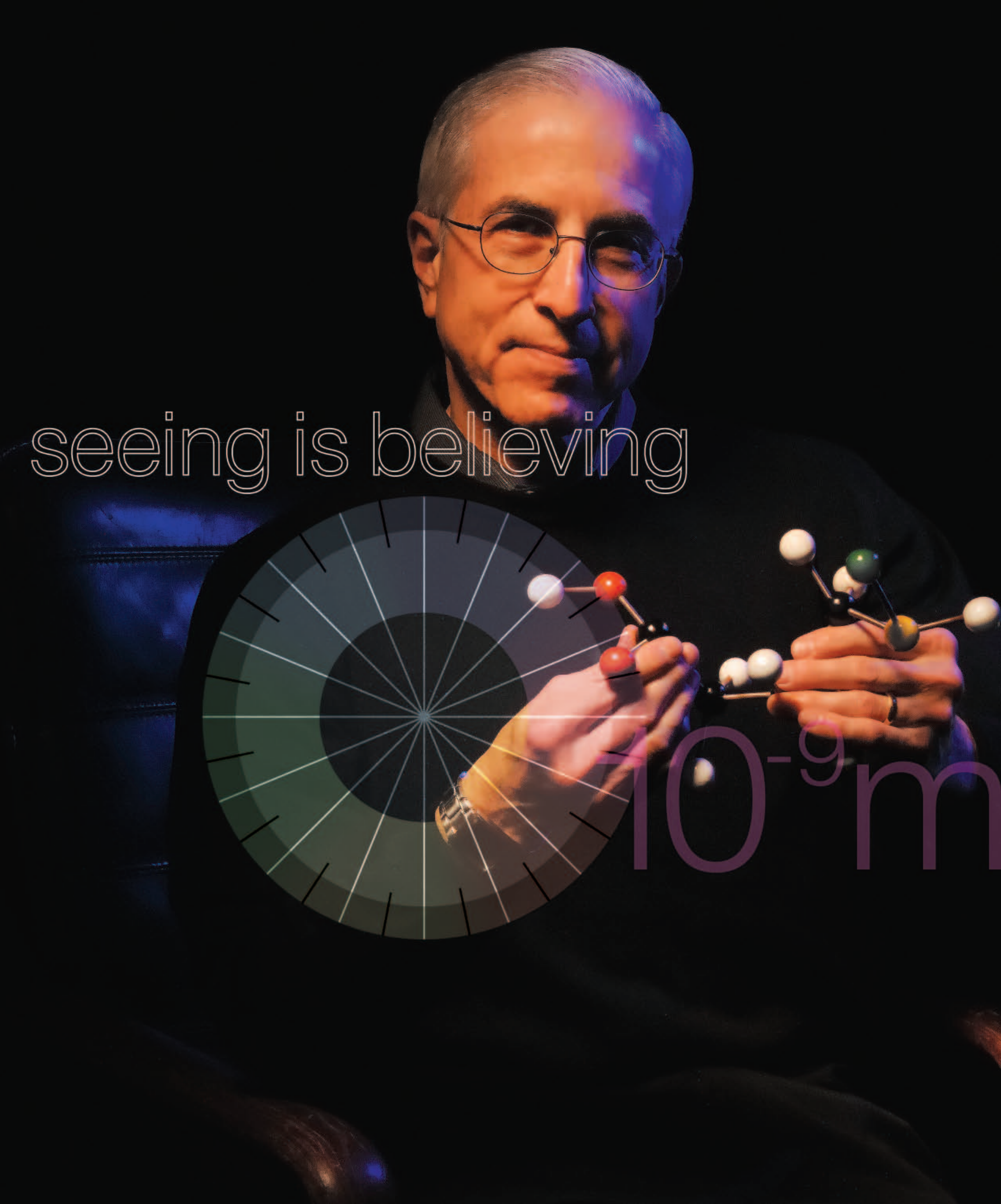
seeing is believing



by Kevin McKeough

[PRINCIPAL **INVESTIGATOR**]
At left, David R. Pepperberg, PhD, studies molecular sciences in the Lions of Illinois Eye Research Institute.

nanotechnology@UIC:

a cross-disciplinary team of researchers is exploring the use of nanotechnology to restore vision to damaged retinal cells

After decades of judging fashion models in competitions, Ave Green recently had to quit working due to the deterioration in her vision caused by age-related macular degeneration. The 77-year-old south suburban Chicagoan also can't see well enough anymore to apply her make-up or tell the colors of her clothes. She can no longer drive and must rely on her husband or friends for transportation.

"I see less and less. It's terrible," laments Green, who also despairs at the current lack of a cure for her illness.

Now a cross-disciplinary team of UIC researchers has begun a five-year study that eventually may help the rapidly growing number of people such as Ave Green who suffer from degenerative retinal diseases. Funded by a $6.3 million grant from the National Eye Institute, part of the National Institutes of Health, the team is working to develop a nanotech structure—that is, an artificially generated molecule—that can compensate for the damage such blinding diseases cause to cells in the retina.

"Down the road, if everything works as proposed, we'll have a device that can be introduced into the eye and that can repair vision loss," says David R. Pepperberg, PhD, Searls-Schenk professor in the department of ophthalmology and visual sciences and the study's principal investigator. If successful, the therapy also could pave the way for treatments for other neurodegenerative conditions.

Pepperberg cautions, however, that the study's outcome is uncertain and many challenges must be met for it to be successful. "We are many hurdles away from our ultimate goal," he says. "To get it to work is like building a rocket to go to the moon. It's a process that evolves in stages."

The project puts UIC at the vanguard of nanotech, the emerging technology used to create devices a nanometer—one billionth of a meter—in size. These nanotech devices can interact with molecules on the surfaces of cells, presenting a vast array of potential clinical applications.

"The NIH grant is an endorsement of the high quality of science this collaborative effort presents," says Dimitri T. Azar, MD, professor and head of the department of ophthalmology and visual sciences. "The grant and this project differentiate the UIC department of ophthalmology and put it among the leading institutions of eye research not only in the United States, but worldwide."

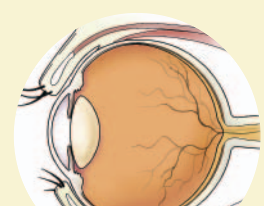
It's indicative of the project's enormous complexity that the study's co-investigators and collaborators include 10 other UIC faculty members from eight different departments, including ophthalmology and visual sciences, biochemistry and molecular genetics, bioengineering, biological sciences, biopharmaceutical sciences, medicinal chemistry and pharmacognosy, pharmacology and physics. The UIC team also is collaborating with scientists at Oak Ridge National Laboratory, the University of California at San Francisco and Vanderbilt University.

"This is a genuinely interdisciplinary approach to finding a solution for a major health problem," observes co-investigator Jack Kaplan, PhD, Benjamin Goldberg professor and head of the department of biochemistry and molecular genetics.

"Our goal is to augment our research efforts by focusing on four to six major areas of translational research that will lead to breakthroughs and, possibly, cures of important eye diseases in our community."
Dimitri T. Azar, MD, professor and head, department of ophthalmology and visual sciences

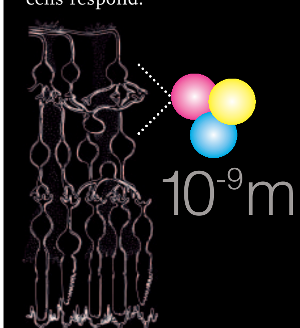
[**AGE-RELATED MACULAR DEGENERATION (AMD)**]

- By age 75, the risk of developing AMD reaches more than 25 percent.
- By 2020, approximately 3 million U.S. residents are projected to have AMD.
- Over 15 million people worldwide presently have this disease.



[**NANOSCALE MOLECULES**]

At one billionth of a meter, $10^{-9}m$, the implanted structures would respond to light the same way electrochemical signals from healthy rod and cone cells respond.



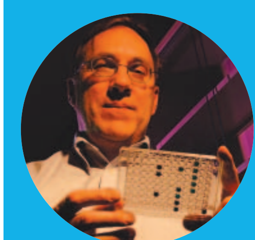
Medical illustrations by Lisa J. Birmingham and Adrienne J. Boutwell

Support of the Lions

The generosity of the Lions of Illinois to the UIC College of Medicine's department of ophthalmology and visual sciences was the primary source of support for the creation of the Lions of Illinois Eye Research Institute in 1985. Lions philanthropy raised nearly $6.5 million for the construction of the building and for an endowed research professorship in honor of Charles Young. The Lions of Illinois, by virtue of these extraordinary commitments, is one of the largest donors to the university and the largest single contributor to the department of ophthalmology and visual sciences. This legacy of giving is deeply appreciated by the university and it is particularly meaningful as it is in keeping with the Lions' historic mission of being "the Knights of the blind" that was established 80 years ago in collaboration with the legendary Helen Keller.

[UIC CO–INVESTIGATORS]

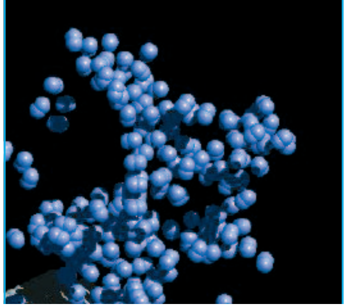
Jack Kaplan, PhD,
Benjamin Goldberg professor and head, biochemistry and molecular genetics



Brian Kay, PhD,
professor and head, biological sciences

Haohua Qian, PhD,
associate professor, ophthalmology and visual sciences

>The Future of Nanotechnology
Personalized medicine
Drug delivery
New composite materials
Nanomachines



This team is trying to accomplish nothing less than engineering a molecule to perform a crucial step in what Pepperberg calls "the exquisite process" of sight itself. In a healthy eye, light enters through the cornea and strikes the neural tissue in the back of the eye known as the retina. The approximately 100 million rod and cone photoreceptor cells in each retina respond to the presence of light by producing electrochemical signals that are sent to other types of cells in the retina in a chain of communication that ultimately reaches the brain.

Degenerative retinal disease can destroy these photoreceptors while leaving other retinal cells intact, resulting in a breakdown of communication that Pepperberg likens to a malfunctioning cell phone not transmitting a caller's speech to the relay tower. "Other cell types in the retina frequently remain healthy and capable of function," Pepperberg explains. "The problem is that those remaining healthy cells are no longer receiving signals from the photoreceptors."

In their attempt to solve this problem, Pepperberg's team is developing a molecular structure that would be only several nanometers in size but would be able to perform a breathtakingly complex combination of functions. If they succeed, millions of these molecular structures would be introduced into each patient's eyes in a fluid. The structures then would find and affix themselves to specific binding sites on the surfaces of the retinas' healthy cells, the "downstream" links in the chain of visual communication. These structures would respond to light by changing shape, twisting in a way that stimulates the cells in the same way that the electrochemical signals from healthy rod and cone cells would.

As if it weren't enough of a challenge to design and construct a molecular structure that can perform all these tasks, the team ultimately hopes to create multiple variations of it, each one customized to different types of synapses, or connections, between retinal cells. "It's not merely designing and making workable a single type of photoreceptive structure, but a multiplicity of these structures that can be introduced together and can operate at the different synapses that function in the healthy eye," Pepperberg says.

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Pepperberg is both animated and meticulously detailed as he explains the project in his office in the Lions of Illinois Eye Research Institute, where photos, drawings and even coffee cups bearing the image of Albert Einstein line shelves along with stacks of documents. A large photo of the legendary scientist riding a bicycle rests on an easel by the door.

His affinity with Einstein reflects Pepperberg's own academic background. He earned a BS in physics and a PhD in biophysics from the Massachusetts Institute of Technology, and he has a physicist's fascination with light, which drew him in turn to his lifelong study of the molecular processes of vision.

This study is the culmination of his decades of research in the cellular processes of the retina, but Pepperberg also is relying on the expertise of his UIC colleagues, who have divided responsibility between them for the nanoscale structures' crucial functions: attaching the structures to the desired cells and being compatible with them; responding to light; and changing shape in a way that will allow light to produce a visual response in the target retinal cells.

"We think we know how to engineer molecules to perform the individual functions, but now we're trying to build one to do them all together in a way that doesn't interfere with the target cell's other functions," explains co-investigator Brian Kay, PhD, professor and head of the department of biological sciences.

Kay is responsible for finding ways to make the molecule attach to the target retinal cells as desired. "If you find something that binds with everything, that's no good. You might find something that binds weakly or too tightly—that's no good. You need to find something that binds selectively and with specificity," he says.

To achieve that result, Kay generates billions of different DNA sequences and introduces them into bacteria, which then go on to secrete molecules with different binding properties. These molecules are combined with test target cells in the lab to see if they'll attach. The combinations then are washed with a buffer, clearing away the molecules that don't bind. More bacteria then are used to increase the quantity of the remaining molecules. The process is repeated until the number of molecule types is winnowed down from billions to tens.

To make the nanotech structure light-sensitive, Karol Bruzik, PhD, associate professor of medicinal chemistry, is conducting experiments with azobenzene, a class of molecules that responds to light. One challenge he faces is that azobenzene only reacts to short wavelengths of light, including ultraviolet wavelengths that are invisible to the human eye.

"This is not adequate. It has to be responsive to a broader spectrum of light," he says. Therefore, Bruzik is combining azobenzene molecules with certain chemical residues to produce chemical "photoswitches" that will undergo structural change when they absorb visible light.

Meanwhile, Pepperberg is working with fellow ophthalmology faculty member Haohua Qian, PhD, to test prototype molecules that have the potential to activate postsynaptic receptors. Pepperberg and Qian are studying the receptor interactions of these chemicals in a laboratory near Pepperberg's office, where racks hold plastic containers, each holding a specific chemical being evaluated. Long, slender tubes extend from each vial, coming together in an apex beneath a microscope (which is needed to see the cellular preparation as the test is set up). The cell to be tested is placed in a chamber beneath the microscope, a given test chemical is introduced through the thin tubes to the vicinity of the cell, and sensors attached to the cell measure the electrophysiological response that results.

It will be a long time before all the components of the molecular structure are assembled and functioning together as desired, let alone ready for clinical trials in human patients. Yet Pepperberg and his colleagues believe their study holds great promise to spare future patients the devastating effects of degenerative retinal disease.

Their efforts also may someday have applications to other neurodegenerative diseases. For example, molecular structures akin to those under study in the project might be able to restore the chain of neural communication in tissues that are degraded by Parkinson's disease, re-enabling patients' motor functions. Similarly, research by Pepperberg's team might also lead to the development of replacement nerve cell components as a therapy for Alzheimer's disease.

"We think our approach takes us in the right direction," Pepperberg says. "The technology that we're seeking to develop is rational and promising. Even if the ultimate goal is not fully accomplished in the current project, it will be achieved someday."

[AN **INTERDISCIPLINARY** APPROACH]

David Pepperberg is leading a multidisciplinary research team that includes faculty from 10 UIC departments and three other academic institutions. The team members include:

[**Co-Investigators**]

Haohua Qian, PhD,
Ophthalmology and Visual Sciences, UIC

Nalin Kumar, DPhil,
Ophthalmology and Visual Sciences, UIC

Brian Kay, PhD,
Biological Sciences, UIC

Karol Bruzik, PhD,
Medicinal Chemistry and Pharmacognosy, UIC

Jack Kaplan, PhD,
Biochemistry and Molecular Genetics, UIC

Guy LeBreton, PhD,
Pharmacology, UIC

Jie Liang, PhD,
Bioengineering, UIC

Sandra Rosenthal, PhD,
Chemistry, Vanderbilt University

Robert Standaert, PhD,
Chemistry, Oak Ridge National Laboratory

Tejal Desai, PhD,
Bioengineering, University of California at San Francisco

[**Collaborators at UIC**]

Christoph Grein, PhD,
Physics

Hayat Onyuksel, PhD,
Biopharmaceutical Sciences and Bioengineering

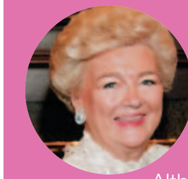
Arnon Lavie, PhD,
Biochemistry and Molecular Genetics

Rice Foundation

Challenge Grant

The Daniel F. and Ada L. Rice Foundation has issued a $100,000 challenge grant to support the research of David Pepperberg, PhD, as he develops a molecular therapy for age-related macular degeneration. The foundation will award $100,000 if an additional $200,000 can be raised by April 30, 2007. Dan and Ada Rice, longtime Wheaton and Chicago residents and philanthropists, established the foundation in 1947.

For more information or to make a contribution, please contact Patricia Wager at the College of Medicine at (312) 413-9763 or pwager@uic.edu.



The effect is devastating. "You're heartbroken," Ave Green says. Although treatments can slow the progression of the illness in its early stages, no cure is available for the vision loss that results from late-stage macular degeneration. "Nothing gets you better," Green says. "If you could see a little bit more, you'd be thrilled. It'd be everything in my life to see better."

Vision Loss's Effect

Even into her mid-90s, Miriam Levi remained active, taking part in a daily exercise class and reading newspapers to keep up with current events.

Since the 97-year-old Levi developed age-related macular degeneration a few years ago, though, she has lost most of her sight. She no longer can manage her own finances or read her date book to know when to send birthday cards and gifts to her friends and relatives, including her four grandchildren and six great-grandchildren. Levi now needs assistance bathing and keeping track of her medications, and may need to move into an assisted-living facility.

"Without question, the macular degeneration has really knocked her for a loop," says her son, Allan Levi, associate director for administration in the department of medical education. "Before the vision problems she wasn't slowing down, she was very much with it."

Miriam Levi and Ave Green are typical of people with macular degeneration. The disease is the leading cause of vision loss in Americans age 60 or older. A 2004 study published in the *Archives of Ophthalmology* found that 1.75 million U.S. residents at the time had AMD and projected that 3 million people in this country would have the illness by 2020.

"With the baby boomer segment of the population aging, macular degeneration—already a huge public health concern—will grow even larger," David Pepperberg observes.

Named for its effect on the macula, the center of the retina, macular degeneration reduces central vision to a blurry smudge (although peripheral vision remains). "What surprises most people is that such a tiny diseased area can severely diminish one's ability to read and drive," Pepperberg notes.