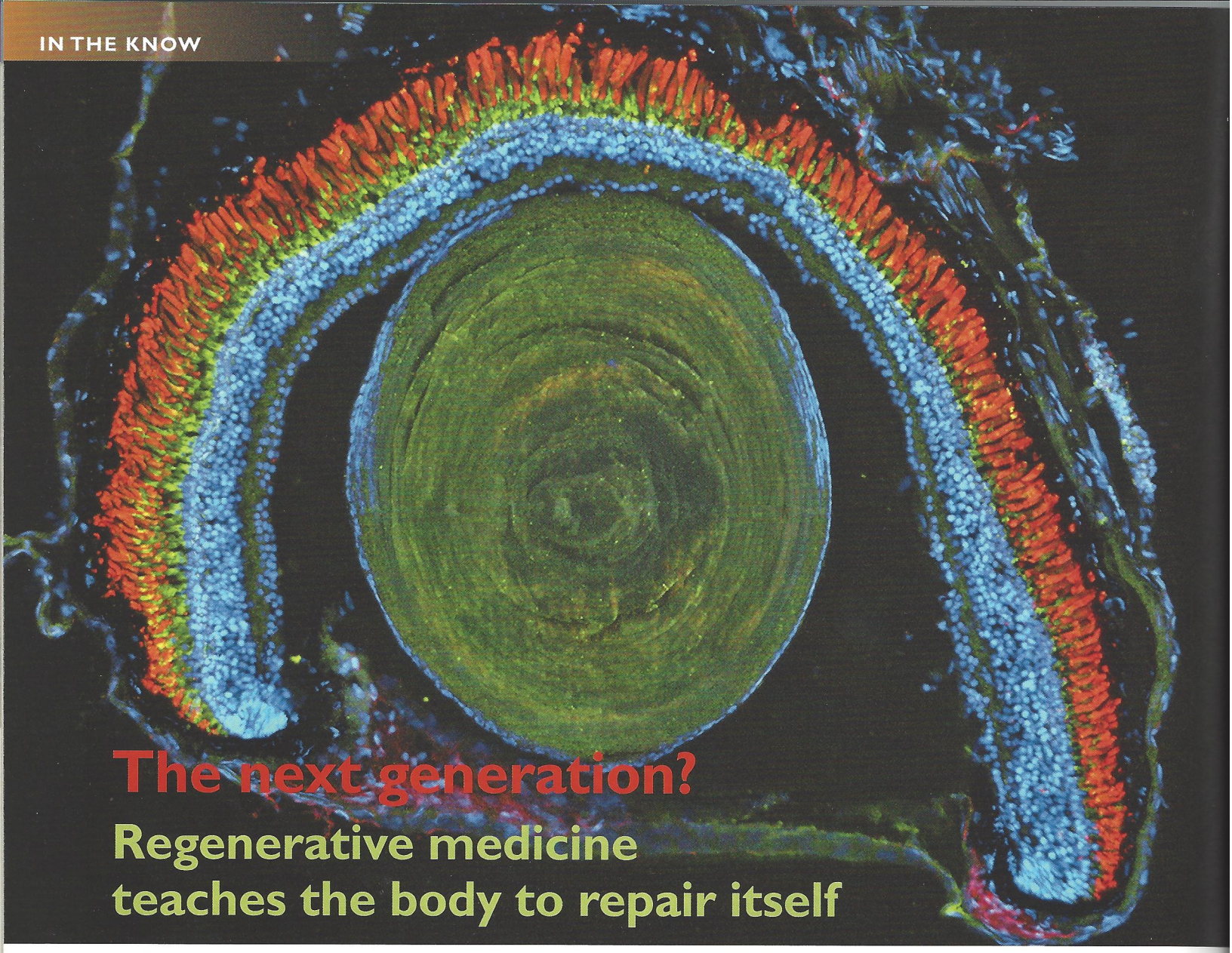

The next generation?

Regenerative medicine teaches the body to repair itself

This slice of a frog retina is stained with antibodies that recognize rods (red), cones (green) and cell nuclei (blue). Frogs have the same retinal cell types as the human retina.

FROM THE LAB OF MICHAEL ZUBER, PHD

Imagine your grandfather develops trouble with his vision. Straight lines appear distorted. The center of whatever he looks at turns blurry and dark. His color perception diminishes. You bring him to a doctor, in hopes that he doesn't go blind.

What will the doctor do to help?

A solution is not clear yet, but Michael Zuber, PhD, believes it may one day be possible. He's part of the exciting field known as "regenerative medicine," learning how to prompt the body to grow new tissues and organs to replace those that wear out and die.

Like many vision researchers across the country, Zuber and his colleague Reyna Martinez-De Luna, PhD, embrace the goals of the National Institutes of Health's National Eye Institute, to regenerate neurons and neural connections in the eye and visual system, in response to the increasing prevalence of blinding diseases such as age-related macular degeneration, glaucoma and diabetic retinopathy.

Zuber and Martinez-De Luna, who work in the Center for Vision Research at Upstate Medical University, focus on the retina, the light-sensitive layer at the back of the eye. They want to find a way to prompt regeneration in the retina to prevent blindness due to injury or disease.

Animals other than mammals can regenerate retinal cells when the original cells die, but somehow that ability was lost through evolution, Zuber said. The African clawed frog that he studies is one of the animals that has retained the ability to regenerate. If the retina is surgically removed from a tadpole or from an adult frog, it grows back in as little as a month. The newly regenerated retina contains the same architecture and cell types as the original retina.

Research in the field of regenerative medicine has concentrated mostly on reprogramming stem cells into retinal neurons that can be used to restore vision.

Zuber and Martinez-De Luna are taking a different approach. They want to identify the signals and molecules that instruct the retina how to replace its lost or dying cells.

To accomplish this goal, they are studying the African clawed frog because this non-mammalian vertebrate regenerates retinal cells. These frogs have what scientists call intrinsic progenitors, a pool of cells that constantly produce new cells as needed. In addition, the frogs' mature cells have the ability to turn themselves into a different cell type in a process called transdifferentiation.

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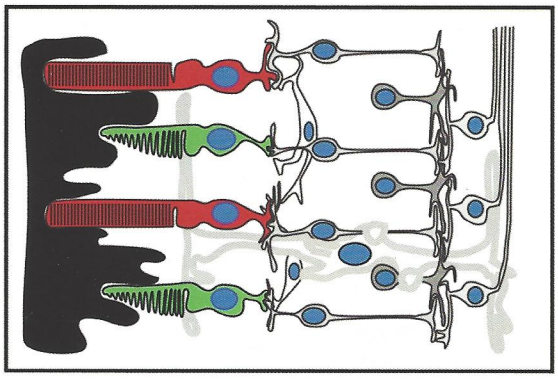
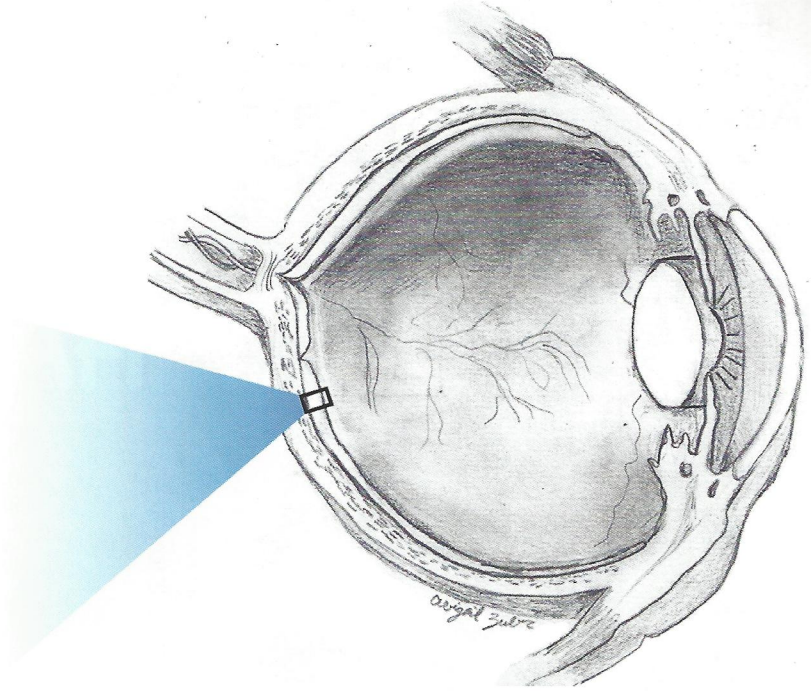
RETINA





The retina is the light-sensing tissue at the back of the eye that converts light into electrical signals that are interpreted as visual images by the brain. Animals that have backbones, called vertebrates — which includes humans, as well as frogs — have the same types of retinas, comprised of six major neurons, or nerve cells, and one glial cell: ganglion cells, horizontal cells, cone photoreceptors, rod photoreceptors, amacrine cells, bipolar cells and Muller glial cells. The retinal pigmented epithelium is the pigmented cell layer outside the neural retina that supports photoreceptor function. Whether due to age or an inherited condition, retinal diseases that lead to blindness usually affect a particular cell type first. Death of one type of cell leads to subsequent loss of other neurons in the retina, progressive retinal degeneration and, often, blindness.

EYE DRAWING COURTESY OF ABIGAIL ZUBER AND ADAPTED FROM AN EYE DIAGRAM FROM THE NATIONAL EYE INSTITUTE. THE RETINA SCHEMATIC IS COURTESY OF ANDREA VICZIAN, PHD.

Regenerative medicine

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For a review paper in the Journal of Ophthalmic Vision Research last year, Zuber and Martinez-De Luna summarized the current knowledge of endogenous mechanisms of regeneration in frogs and how understanding those mechanisms could lead to new approaches for repairing the human retina. "The mammalian retina has the potential to initiate a program of regeneration under favorable conditions," they wrote.

They are studying how new rods, the cells responsible for night vision, regenerate after the original rods are eliminated and how retinal degeneration caused by prolonged rod death affects this regeneration. Some of the questions they are exploring include:

- How long does it take for rods to regenerate after they are eliminated?
- Where do the regenerated rods come from? Do they come from the retinal pigmented epithelium or from the intrinsic pool of progenitors present in the frog retina?
- What are the cellular and molecular events that define the critical point beyond which regeneration is no longer possible?

"Understanding how animals such as the frog can regenerate new retinal cells will help us to identify the reasons our own retina cannot repair itself, and in the long term lead to new therapies for replacing retinal cells in patients who have lost their vision due to damage or disease," explains Zuber.

Reyna Martinez-De Luna, PhD, and Michael Zuber, PhD, at the Center for Vision Research in Upstate's Neuroscience Research Building.

PHOTO BY SUSAN KAHN

It's a scientific challenge they are up for. Ultimately, Zuber and Martinez-De Luna are optimistic that their work will help find a regenerative solution, someday giving doctors a way to help patients who face blindness. ●

Hear an interview at www.upstate.edu/healthlinkonair by searching "regenerative."