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## **\$1.4 Million Grant Helps Professor See The Light**

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DURHAM, N.H. -- University of New Hampshire professor Rick Cote has received \$1.4 million from the National Institutes of Health (NIH) to continue research into the central enzyme that controls initial steps of vision and that, when defective, can result in retinitis pigmentosa, a leading inherited cause of blindness.

Retinitis pigmentosa, or RP, affects 1.5 million people worldwide. Typically, symptoms begin in childhood or early adulthood and progress from impairments in night vision to tunnel vision. The degree of vision loss varies, but in some cases RP leads to total blindness.

Cote, a professor of biochemistry and molecular biology who has received NIH funding through the National Eye Institute for 18 years, conducts fundamental research into visual signaling pathways in the photoreceptors of the retina. "Until you know how the retina functions normally, you're not going to be able to understand how genetic or environmental defects in the visual pathway can cause vision loss or total blindness, or how to slow or prevent disease progression," he says.

Normal functioning of the retina begins with light being absorbed by the photoreceptor cells, called rods and cones. Cones are responsible for color perception, daylight vision, and visual discrimination tasks like reading, while rods provide peripheral vision and vision in low light.

Central to rod and cone visual signaling is the phosphodiesterase (PDE) protein. This enzyme is activated by light and is directly responsible for the nerve impulse that signals the perception of light. "It's therefore not surprising that this exquisitely light-sensitive enzyme can also cause retinal disease when its regulation or catalytic activity is impaired by a genetic mutation, as in certain forms of RP," says Cote. Most of Cote's research career has focused on better understanding how PDE functions. With such knowledge, he says, "we might someday be able to intervene therapeutically to prevent defects in PDE from causing retinal disease."

Working with graduate and undergraduate students in his lab, along with three full-time research scientists, Cote uses a variety of molecular, biochemical, cell biological and pharmacological approaches to understand the structure of PDE and how it is regulated in darkness and in the light. This latest four-year NIH award will support several new directions in Cote's research program. One project involves a collaboration with Tom Laue, professor of biochemistry and molecular biology, to use novel biophysical techniques to determine how small molecules and proteins bind to PDE and alter its structure and regulatory properties.

In another strand of his research, conducted in partnership with Karen Carleton, research associate professor with UNH's Hubbard Center for Genome Studies, Cote is exploring the evolution of vertebrate rod and cone cells in the retina. By focusing on the evolution of the

PDE protein, Cote and Carleton hope to better understand its functioning – and malfunctioning – in humans. “The basic plan for the human retina evolved at the time when vertebrates evolved from the invertebrates,” he says. In their preliminary work, Cote and Carleton have identified rod and cone photoreceptor PDE in species ranging from fish to humans, and their amino acid sequences are very similar.

Yet another line of work is to evaluate a newly discovered PDE binding protein (called GARP2) for its potential to turn off the PDE in rods during daytime – “rods are so light-sensitive that they can’t function in bright light,” Cote says – to conserve metabolic energy.

Cote is also exploring PDE’s sexier side: its relationship to Viagra and other drugs that treat erectile dysfunction. Of the 11 families of phosphodiesterases, the photoreceptor PDE – named PDE6 – is most closely related to PDE5, an enzyme abundant in smooth muscle tissue in our bodies. Viagra and similar drugs (Levitra, Cialis) work by inhibiting PDE5, but most of these drugs also potentially inhibit PDE6, causing temporary alterations in vision. A better understanding of the differences between PDE5 and 6 will result in creating drugs that selectively target PDE5 but do not affect PDE6 or the visual process. While Cote does not foresee an immediate role for these drugs in combating retinal diseases, PDE inhibitors have profound therapeutic potential in treating cardiovascular disease, asthma, diabetes, and cancer, making the development of PDE inhibitors with no adverse effects on vision very desirable.

After two decades of research on PDE, Cote remains fascinated with how rods and cones, and the proteins contained within these light-detecting cells, translate light into sight. “The activity of all these photoreceptor proteins – especially PDE - have to be coordinated on the millisecond time scale so we can see. It’s a miracle that it all works,” he says.

**Rick Cote can be reached at [rick.cote@unh.edu](mailto:rick.cote@unh.edu) or 603-862-2458. For more detailed information on Cote’s research, visit [www.cote.unh.edu](http://www.cote.unh.edu).**

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