

# Eye Damage In Premature Babies May Be Prevented By Promising Protein

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A protein long thought to be one of the body's supporting players has quietly been taking a lead role in healthy eyesight, a discovery that could rapidly lead to treatments for babies born before their eyes are finished growing, University of Florida and Harvard Medical School researchers have found.

The finding, described in separate, back-to-back papers published in the June 19 *Proceedings of the National Academy of Sciences*, offers a new target for therapies for retinopathy of prematurity, a potentially blinding disease that annually affects about 15,000 babies.

In newborns with the disease, oxygen-starved areas of the retina compensate by quickly growing new blood vessels. But these new vessels are fragile and leaky.

"We've identified a protein that is part of the body's natural defenses in oxygen-deprived conditions," said Maria B. Grant, M.D., a professor of pharmacology and therapeutics at UF's College of Medicine. "When babies are born before levels of this protein are normal, blood vessels spread abnormally throughout the retina. But if we can increase the protein to more normal levels in premature babies, it should result in healthier blood vessel growth."

The protein - insulin-like growth factor binding protein-3, or IGFBP-3 - was thought to exist exclusively to regulate insulin-like growth factor-1, a molecular growth factor that is necessary for the development of nerve, muscle, bone, liver, kidney, lung, eye and other body tissues.

But in studies of mice and of human cells in cultures, scientists from the Program in Stem Cell Biology and Regenerative Medicine at UF's McKnight Brain Institute found that IGFBP-3 activates stem cells and other reparative cells of the bone marrow and the lining of blood vessels.

Researchers from Harvard Medical School and the University of Goteborg in Sweden arrive at essentially the same conclusion in *PNAS*, identifying the protein IGFBP-3 as a promising therapeutic agent after analyzing data from mouse and human studies.

"This discovery has a big future in helping premature babies," said Alexander V. Ljubimov, Ph.D., a professor of medicine at UCLA and director of Ophthalmology Research Laboratories at Cedars-Sinai Medical Center. "The idea is to administer this already clinically available protein to premature babies to stabilize the existing vessels in the retina, prevent their loss and block the compensatory growth of new, aberrant vessels. Finding the right dose may enable babies to cope with the first phases of their life without becoming blind."

Retinopathy of prematurity affects infants weighing less than 2.75 pounds who are born within the first 31 weeks of pregnancy, according to the National Eye Institute. More than 1,000 require medical treatment and about 500 become legally blind.

Treatments based on IGFBP-3 could advance relatively quickly because it is a natural protein and presumably safe, Ljubimov said.

"The discovery has added credibility because independent research groups took different approaches to show essentially the same thing," said Ljubimov, who was not involved in the research. "There is independent confirmation from totally different research teams within the same journal."

At UF, researchers infused IGFBP-3 into one eye of each of nine mice before placing the animals into a high-oxygen chamber for five days. When scientists compared vascular growth within the retinas, they found blood vessels were closer to normal in eyes treated with IGFBP-3.

When UF scientists repeated the experiment in 18 mice treated with bone marrow stem cells expressing IGFBP-3, they found the treated eyes developed normally.

In addition to studies in mice, Harvard research collaborators in Sweden examined infants with retinopathy of prematurity in a prospective clinical study and found that the IGFBP-3 levels were lower than those of healthy infants, further suggesting that the protein helps prevent oxygen-induced blood vessel loss and promotes healthy vascular regrowth.

"The implications for retinopathy are that IGFBP-3 appears to have benefit in preventing vessel loss independent of insulin-like growth factor-1 in both the mouse model of oxygen-induced retinopathy and in infants with retinopathy of prematurity," said Lois E.H. Smith, M.D., Ph.D., an associate professor of ophthalmology at Harvard Medical School and senior author of the Harvard study. "Supplementation to increase IGFBP-3 in premature infants at risk for ROP to normal levels in utero may prove beneficial in this disease.

"Harvard Medical School researchers and collaborators at the University of Goteborg are currently conducting a phase 1 clinical study to evaluate the use of IGFBP-3 in combination with IGF-1 to examine the effects on prevention of retinopathy in premature infants, based on the clinical findings in our study," Smith said. "This work suggests that both IGF-1 and IGFBP-3 acting independently help prevent retinopathy."