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Sections of retinas regenerated and visual function increased with stem cells from skin

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Scientists from Schepens Eye Research Institute are the first to regenerate large areas of damaged retinas and improve visual function using IPS cells (induced pluripotent stem cells) derived from skin. The results of their study, which is published in *PLoS ONE* this month, hold great promise for future treatments and cures for diseases such as age-related macular degeneration, retinitis pigmentosa, diabetic retinopathy and other retinal diseases that affect millions worldwide.

"We are very excited about these results," says Dr. Budd A. Tucker, the study's first author. "While other researchers have been successful in converting skin cells into induced pluripotent stem cells (iPSCs) and subsequently into retinal neurons, we believe that this is the first time that this degree of retinal reconstruction and restoration of visual function has been detected," he adds. Tucker, who is currently an Assistant Professor of Ophthalmology at the University of Iowa, Carver College of Medicine, completed the study at Schepens Eye Research Institute in collaboration with Dr. Michael J. Young, the principle investigator of the study, who heads the Institute's regenerative medicine center.

Today, diseases such as retinitis pigmentosa (RP) and age-related macular degeneration (AMD) are the leading causes of incurable blindness in the western world. In these diseases, retinal cells, also known as photoreceptors, begin to die and with them the eye's ability to capture light and transmit this information to the brain. Once destroyed, retinal cells, like other cells of the central nervous system have limited

capacity for endogenous regeneration.

"Stem cell regeneration of this precious tissue is our best hope for treating and someday curing these disorders," says Young, who has been at the forefront of vision stem cell research for more than a decade.

While Tucker, Young and other scientists were beginning to tap the potential of embryonic and adult stem cells early in the decade, the discovery that skin cells could be transformed into "pluripotent" cells, nearly identical to embryonic cells, stirred excitement in the vision research community. Since 2006 when researchers in Japan first used a set of four "transcription factors" to signal skin cells to become iPSCs, vision scientists have been exploring ways to use this new technology. Like embryonic stem cells, iPSCs have ¬the ability to become any other cell in the body, but are not fraught with the ethical, emotional and political issues associated with the use of tissue from human embryos.

Tucker and Young harvested skin cells from the tails of red fluorescent mice. They used red mice, because the red tissue would be easy to track when transplanted in the eyes of non-fluorescent diseased mice.

By forcing these cells to express the four Yamanaka transcription factors (named for their discoverer) the group generated red fluorescent IPSCs, and, with additional chemical coaxing, precursors of retinal cells. Precursor cells are immature photoreceptors that only mature in their natural habitat—the eye.

Within 33 days the cells were ready to be transplanted and were introduced into the eyes of a mouse model of retina degenerative disease. Due to a genetic mutation, the retinas of these recipient mice quickly degenerate, the photoreceptor cells die and at the time of transplant electrical activity, as detected by ERG (electroretinography), is absent.

Within four to six weeks, the researchers observed that the transplanted "red" cells had taken up residence in the appropriate retinal area (photoreceptor layer) of the eye and had begun to integrate and assemble into healthily looking retinal tissue.

The team then retested the mice with ERG and found a significant increase in electrical activity in the newly reconstructed retinal tissue. In fact, the amount of electrical activity was approximately half of what would be expected in a normal retina. They also conducted a dark adaption test to see if connections were being made between the new photoreceptor cells and the rest of the retina. In brief, the group found that by stimulating the newly integrated photoreceptor cells with light they could detect a signal in the downstream neurons, which was absent in the other untreated eye.

Based on the results of their study, Tucker and Young believe that harvesting skin cells for use in retinal regeneration is and will continue to be a promising resource for the future.

The two scientists say their next step will be to take this technology into large animal models of retinal degenerative disease and eventually toward human clinical trials.

Provided by Schepens Eye Research Institute

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