Harnessing an innate repair mechanism enhances the success of retinal transplantation

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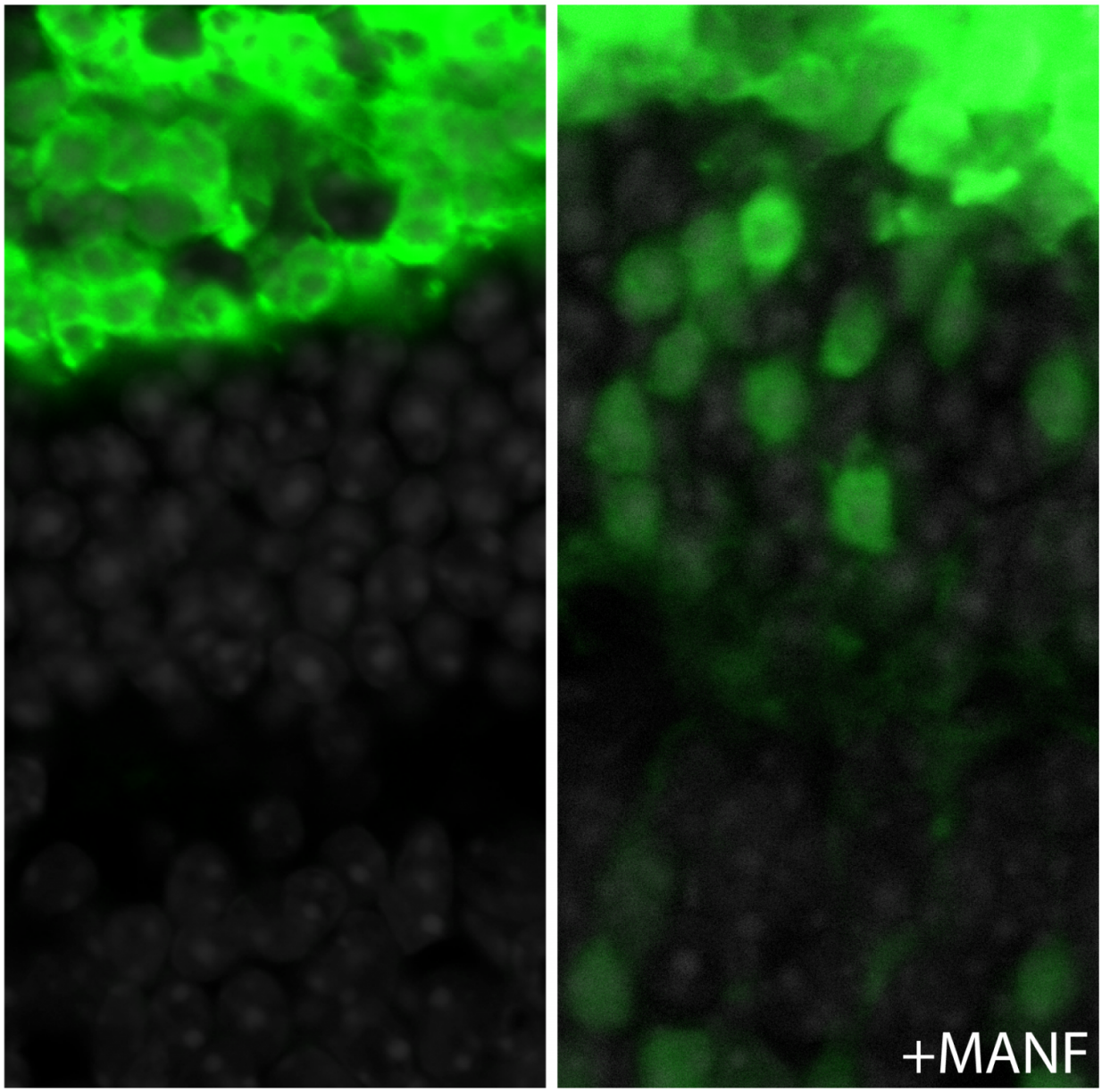

Photoreceptors transplanted into the sub-retinal space integrate better following supplementation with MANF. Credit: Joana Neves, Ph.D., Buck Institute for Research on Aging

Regenerative therapies, based on cell replacement, hold promise for a wide range of age-related diseases, but efforts to bring the therapies to patients have not been very successful - in large part because the newly-derived replacement cells can't integrate efficiently into tissues affected by the ravages of aging. Publishing in *Science*, researchers at the Buck Institute harnessed a naturally-occurring and evolutionarily ancient anti-inflammatory mechanism that repaired the eye and significantly enhanced the success of retinal regenerative therapies in mice. The results could be particularly significant for chronic inflammatory diseases of the eye, including macular degeneration.

The group discovered a previously unknown immunomodulatory property of an evolutionarily conserved factor, MANF (Mesencephalic Astrocyte-derived Neurotrophic Factor). MANF converts inflammatory immune cells into repairing immune cells; in this study it profoundly improved the endogenous repair capacity of the retina in both flies and mice. Strikingly, when the researchers used MANF as a supplement while transplanting photoreceptors into congenitally blind mice, MANF increased the efficiency of integration and accelerated and improved the recovery of visual function. "MANF promotes healing and helps create a microenvironment conducive to successful transplantation," said Buck faculty and co-senior author Deepak Lamba, PhD, MBBS, who is among those developing stem cell technologies to treat degenerative eye diseases. Lamba says that even though researchers around the world have successfully transplanted retinal stem cells in mice that success has not

benefited the millions of people who suffer from vision problems related to retinal degeneration, because only about 1 percent of the transplanted cells survive and integrate over time. "We are hoping to turn that statistic around," he said.

Lamba and co-senior author Heinrich Jasper, PhD, say the research also raises the possibility of using MANF as a treatment early in the disease process as a way of preventing further symptoms from developing, noting that they used MANF to protect photoreceptors in three mouse models of photoreceptor degeneration. "Our hope is that MANF will be useful for treatment of inflammatory conditions in many disease contexts," said Jasper, who is Chief Scientific Officer at the Buck Institute. "Focusing on immune modulation to promote a healthy repair response to tissue damage rather than a deleterious inflammatory response is a new frontier in aging research."

The initial discovery that fueled the project was made in genetic studies of fruit flies in the Jasper lab. Lead author Joana Neves, PhD, a Glenn Foundation for Medical Research postdoctoral research fellow who shares an appointment in both the Jasper and Lamba labs, found that MANF was secreted by the immune cells in the fly in response to damage to the retina. MANF then acted on the same cells to promote their transition from pro-inflammatory to anti-inflammatory repair cells, promoting retinal repair. Once the team determined that MANF acts similarly in mammals, the research moved into mice.

Jasper says the research demonstrates that combining genetic studies in invertebrates and vertebrates can lead to the rapid identification of new factors with promising therapeutic potential. "The early work in the fly allowed us to identify genes that led us to an immune modulator that is conserved among many species," said Jasper. "We were able to do that work relatively quickly at a low cost and it helped us set up the pre-clinical work that is now taking place in mice and human cells."

More information: Immune modulation by MANF promotes tissue repair and regenerative success in the retina, *Science*, DOI: 10.1126/science.aaf3646