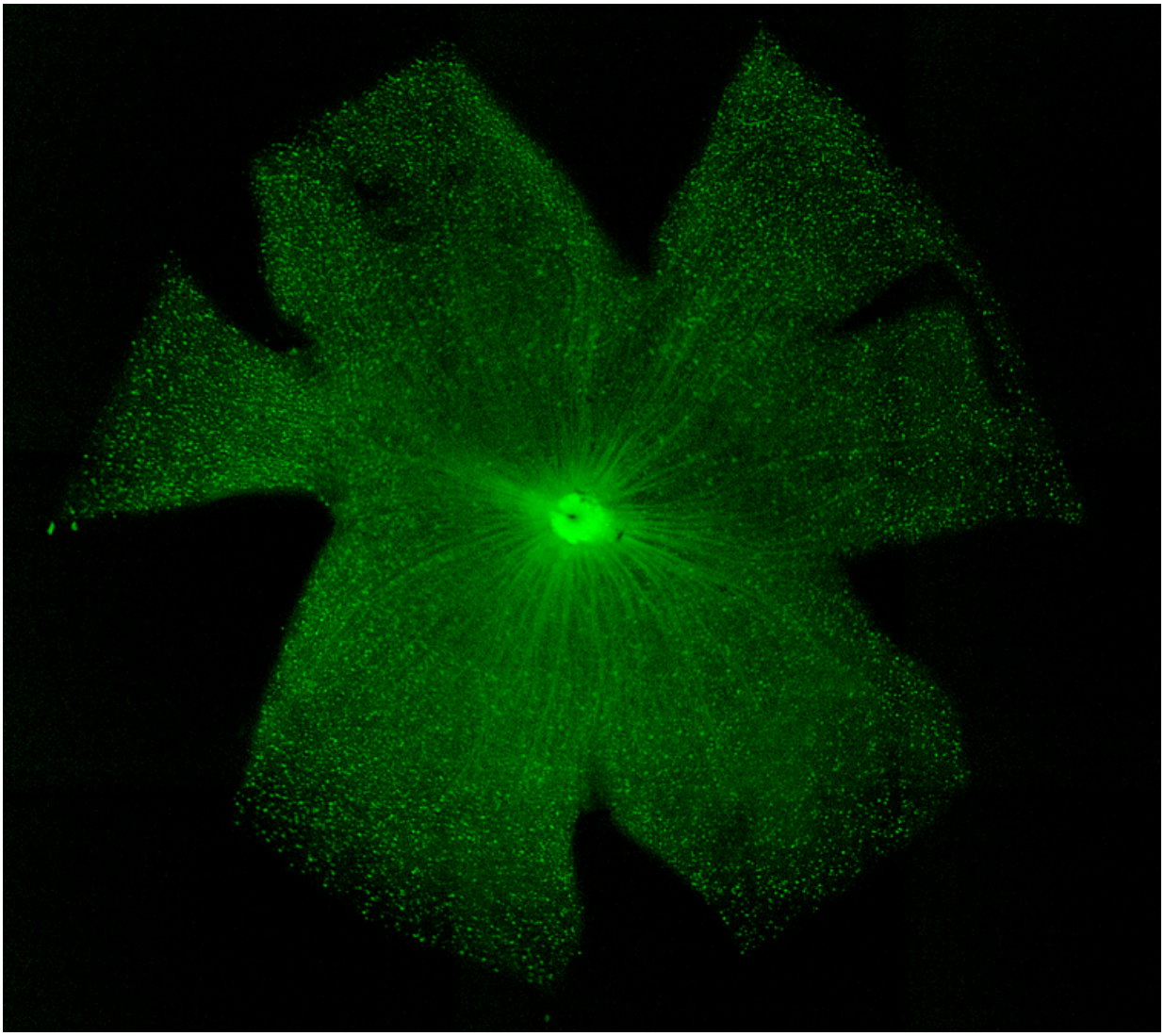
Promising new compound protects neurons and vision in mice with glaucoma

April 19 2016



Representative retinal flatmount images of the 12 month-old GLAST (+/-) mice, a glaucoma model, administered KUS 121. Each dot represents a spared retinal

ganglion cell. Rays converging at the center (the optic nerve head) represent spared nerve fibers. The retina treated with KUS121 has more retinal ganglion cells and nerve fibers, as compared with that of the non-treated control mouse. Credit: Noriko Nakano and Hanako Ikeda

Early tests of a novel compound in mice with glaucoma should come as welcome news to millions of people around the world now suffering with this leading cause of vision loss. Researchers reporting in the journal Heliyon have shown that a compound they've developed might help to prevent the nerve damage that leads people with glaucoma to lose their sight.

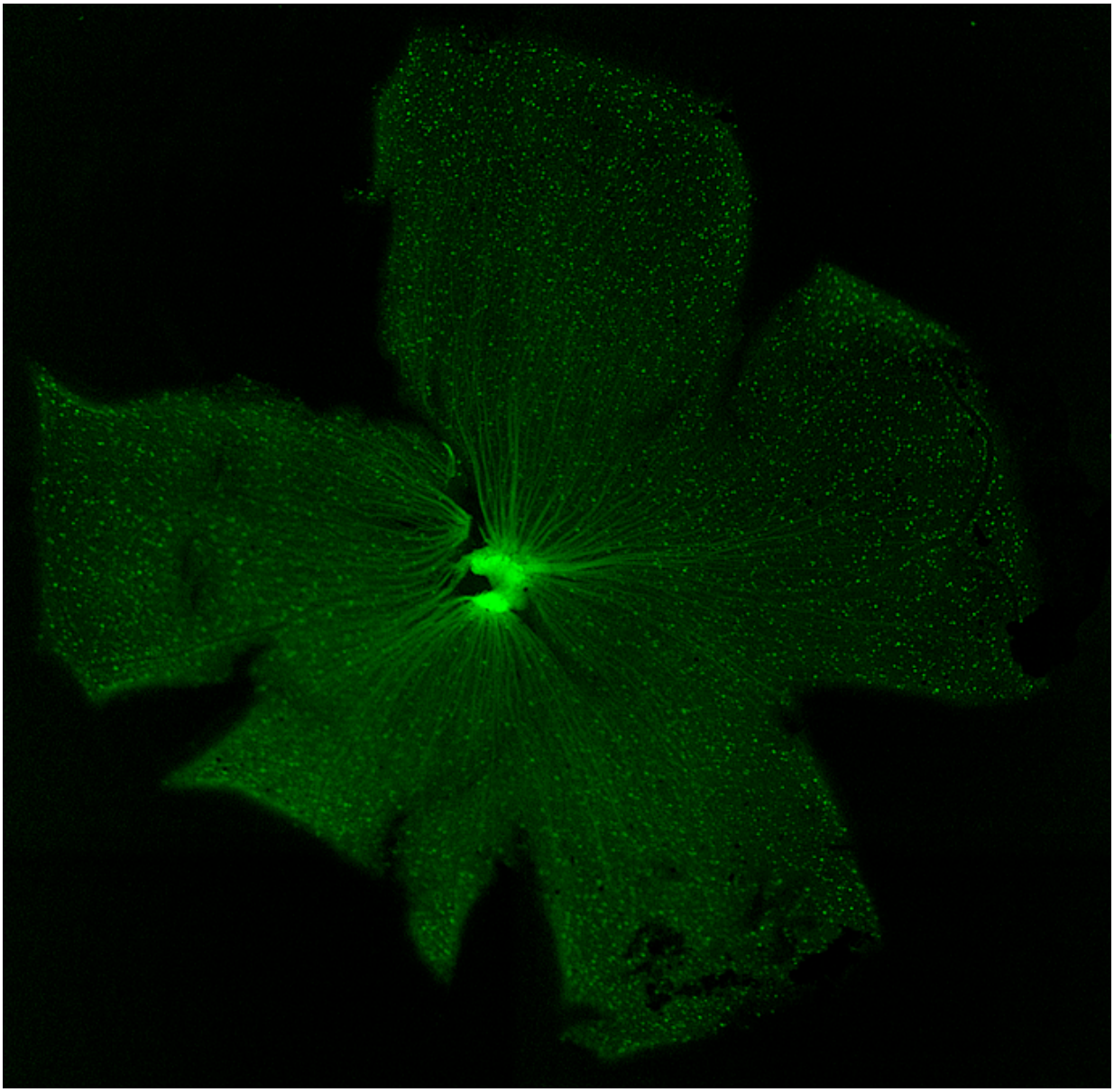
The only treatments available for glaucoma today include surgery or drugs used to reduce pressure in the eye. However, many patients continue to experience gradual vision loss despite those treatments.

"Our newly developed small compounds prevented the progression of glaucoma in three different mouse models," said Hanako Ikeda of Kyoto University in Japan.

The findings in mice suggest that these compounds, dubbed KUSs [Kyoto University Substances] "might slow down disease progression and prolong normal or near-normal vision [in people with glaucoma]; ideally, KUSs might prevent the eventual loss of eyesight," she added.

Ikeda and her colleagues have worked for years to understand what causes the death of neural cells in the eye. They previously uncovered strong evidence for a role of an enzyme called VCP (valosin-contianing protein). This enzyme acts as an ATPase, breaking down ATP molecules that serve as the cellular currency for energy.

"We thus assumed that specific inhibitors of the VCP ATPase activity would prevent neuronal cell death and the disease symptoms as well," Ikeda said.



Representative retinal flatmount images of the 12 month-old GLAST (+/-) mice, a glaucoma model administered PBS as a control (vehicle). Each dot represents a spared retinal ganglion cell. Rays converging at the center (the optic nerve head) represent spared nerve fibers. The retina treated with KUS121 has more retinal

ganglion cells and nerve fibers, as compared with that of the non-treated control mouse. Credit: Noriko Nakano and Hanako Ikeda

She and her colleagues went in search of a compound with the right activity. The search led them to KUSs. Earlier studies in cells suggested that these KUSs could help to maintain ATP levels, reduce cellular stress, and protect neurons.

Now, they show that KUSs delivered orally or through injections also protect neurons of the retina in mice with glaucoma. Mice with glaucoma treated with KUSs showed less thinning of the retinal nerve fiber layer than did those treated with a control. KUSs also helped to preserve visual functions, apparently by maintaining ATP levels.

"In cells that are dying, an almost universal phenomenon is that ATP levels gradually decrease," Ikeda said. "KUSs maintain cellular ATP levels by inhibiting the ATPase activity of VCP. In other words, inhibiting the ATPase activity of VCP frees up ATP for other essential cellular processes and consequently prevents or retards cell death."

The researchers say their compounds could offer neural protection in glaucoma and perhaps other neurodegenerative diseases as well. Their next step is to study the mechanisms of cell protection in the mice in greater detail. Plans are underway for a phase I/II clinical trial to test the safety and efficacy of KUSs in people with an acute ocular disease. They say it will take at least another three to five years before a trial of KUSs in people with glaucoma could begin.

More information: "Neuroprotective effects of VCP modulators in mouse models of glaucoma" by Nakano et al.
dx.doi.org/10.1016/j.heliyon.2016.e00096

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