UCSD Researcher Receives NIH Transformative R01 Award for Stimulation of Neuron Regeneration in the Retina

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Proposed research will facilitate the development of therapies to restore vision to human patients with severe blindness

A research team led by principal investigator Kang Zhang, MD, PhD, professor of ophthalmology at the University of California, San Diego's Shiley Eye Center and director of UCSD's Institute of Genomic Medicine, has been awarded a five year, $4.66 million NIH Transformative Award.

Kang Zhang, MD, PhD

Zhang and co-principal investigators Sheng Ding, PhD, from The Scripps Research Institute, and Thomas Reh, PhD from the University of Washington, received the highest possible scores for their proposal to investigate the regenerative potential of retinal cells. Their long-term goal is to

restore visual function lost through diseases such as macular degeneration and retinitis pigmentosa.

"The success of this work could mean a paradigm shift in how retinal disease is treated, and could have broad and profound impact on human disease therapies by utilizing the regenerative power of our own cells," said Zhang.

Some vertebrates, such as goldfish and newts, have a remarkable ability to regenerate a lost limb or eye – something it was thought no mammal can do. However, they recently showed proof of principle at a small scale level in mice by turning Muller cells into a type of retinal neuron.

"The human genome is quite similar to that of a newt, but we humans seem to have lost the potential to regenerate our own cells, possibly due to some inhibitory mechanims," Zhang said. "We are seeking small molecule chemicals that can block these inhibitions and consequently unlock humans' regenerative potential."

The Transformative Award program, funded through the Office of the NIH Director and the Common Fund, is intended "to support research that has the potential to transform the way we think about and conduct science, so the recipients represent an elite few with truly bold ideas," according to Francis Collins, Director of the National Institutions of Health.

The researchers are looking at particular kinds of cells called Muller cells, which are abundant and have the ability to regenerate nerve cells after retinal injury in fish, they usually play a supporting role in the central nervous system neurons of humans, such as those present in the eye or brain. This study proposes to use chemicals to turn Muller cells into photoreceptors in the eye – cells that are lost in two diseases that are leading causes of blindness, macular degeneration and retinitis pigmentosa.

Identification of chemicals for Muller cells reprogramming and differentiation will provide new avenues in developing cell-based therapy as well as small molecule drugs for regenerative medicine, and facilitate new understanding of the mechanisms of trans-differentiation, according to the scientists. They plan to screen more than 100,000 compounds in order to identify the chemicals that prompt mouse Muller glia to develop new neurons, conferring the power of regeneration to the mammalian retina.

"Our ultimate goal is to use a chemical approach to turn on the regenerative potential of hibernating stem cells such as Muller cells by introducing a small molecule directly into the eye, perhaps even by eye drop or pill," said Zhang. He added that, since there is no need to transplant cells instead the body's own cells would be used, the therapy wouldn't have the risk of rejection or tumors.

Larry Goldstein, PhD, director of UC San Diego's stem cell program commented, "If this approach proves successful, it will have important applications in the field of regenerative medicine. If a patient's cells could be safely and effectively reprogrammed into retinal cells, it would serve as valuable first step towards developing novel treatments for vision loss.

Project Summary

Retinal photoreceptors are light-sensing cells that convert complex external visual stimuli to electrical and chemical signals. Degeneration of these photoreceptors is the end point of the most common forms of irreversible blindness in humans, including age-related macular degeneration and retinitis pigmentosa, which affect more than 50 million people worldwide.

In non-mammalian vertebrates such as fish, resident Muller glia cells in the retina have the ability to proliferate and differentiate into all retinal cell types, including photoreceptors; as a result, visual function is restored. However, this regenerative potential is almost non-existent in mammals.

By developing and applying high-throughput screening, the team hopes to identify small molecules that will enhance Muller glia cells' ability to reprogram and differente into retinal neurons in mammals. Identification, optimization and characterizations of chemical tools will provide new avenues for development of cell-based therapy as well as conventional small molecule therapeutics for regenerative medicine – with the hoped-for result of restoring visual function lost in patients with severe blindness.

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