



# Development of Novel Pyruvate Kinase Muscle Isoform 2 (PKM2) Activators for Photoreceptor Neuroprotection

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Therapeutics and Vaccines  
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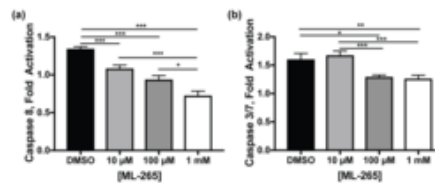
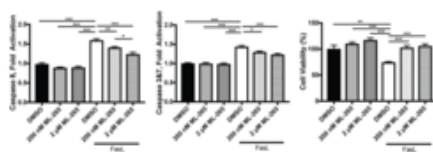
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## OVERVIEW

A novel treatment for photoreceptor diseases through activation of PKM2

- Small molecule activator ML-265 that induces changes in photoreceptor cells
- A means to address illnesses that currently lack therapy options

## BACKGROUND

Photoreceptor cells in the retina including rods, cones, and intrinsically photosensitive retinal ganglion cells are the neuroendocrine cells which sense light and influence circadian rhythm. Photoreceptor (PR) dysfunction or death is the cause of vision loss or blindness in nearly 18 million people in the United States. Common illnesses which adversely affect PR and that therefore cause vision loss include retinal detachment, retinal dystrophies, and age-related macular degeneration. The poor visual function and blindness patients experience results in life-long vision services, loss of productivity for patients and caregivers, and a reduced quality of life. Currently, no successful treatment options exist to prevent photoreceptor death in retinal diseases. So, there is an urgent need exists to discover neuroprotective modalities to improve photoreceptor survival.

## INNOVATION

Researchers at the University of Michigan have developed a novel treatment for photoreceptor diseases that targets Pyruvate Kinase Muscle Isoform 2 (PKM2). In contrast to terminally differentiated neurons, PR neurons perform aerobic glycolysis and maintain PKM2 expression. The inventors have determined that a small molecule activator of PKM2 named ML-265 can be activated to boost PR survival under stress. ML-265 is a small molecular activator that promotes

PKM2 to take a tetrameric form that displays a high catalytic activity and that is associated with ATP synthesis, catabolic metabolism, and induction of metabolic changes in photoreceptors. The researchers report that metabolic programming via genetic and pharmacologic PKM2 activation reduces PR cell death and increases cell viability in vitro and in an in vivo rat model. The inventors have formulated additional PKM2 activator compounds which may complement and augment the positive effects of ML-265. The clinical use of these compounds may therefore delay or prevent PR death and improve outcomes for patients with retinal disease.

## **ADDITIONAL DETAILS**

Figure 1: Photoreceptor cells treated with ML-265 in vitro display decreased caspase activation, a marker of cell death, in response to FasL treatment. FasL produces caspase activation similar to that observed in retinal detachment. A correlating increase in cell viability was observed with ML-265 treatment.

Figure 2: Similar to in vitro experiments, treatment with ML-265 showed reduced caspase activity after retinal detachment in rats.