THE HARTWELL FOUNDATION

2017 Individual Biomedical Research Award

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Stem Cell Cytoplasmic Transfer to Cure Inherited Blindness

The retina is the light sensitive layer lining the inside surface of the eye. It contains specialized photoreceptor cells responsible for converting light into nerve signals that travel via the optic nerve to the brain where a visual image is formed. Each year, approximately 10,000 children in the United States inherit a genetic mutation that degrades the functional capacity of their retinal photoreceptor cells, resulting in blindness. There are more than 250 known genetic subtypes of inherited retinal degeneration, differing in the time of onset and rate of progression — some result in blindness at birth, while others allow the retention of some vision until the teenage years. Unfortunately, because there is no available treatment for this form of blindness, affected children are sight impaired or blind by the time they reach adulthood. Based upon Mandeep's recent discovery that retinal photoreceptor cells can be repaired through a novel approach called stem cell cytoplasmic transfer, he proposes to reverse retinal degeneration and loss of visual function by photoreceptor cell-transplantation. While performing mouse experiments to develop retinal cell transplantation as a treatment for retinal degeneration, he observed that the donor photoreceptor cells behaved in a completely unexpected way when transplanted into a diseased recipient retina. Contrary to accepted dogma, instead of repairing damage by replacing dead retinal photoreceptor cells, the normal donor cells merged with dysfunctional recipient cells and transferred their disease-free cellular material directly, cell-by-cell, to effectively repair malfunctioning recipient cells and reactivate the retina. For these observations to be translated for the benefit of children however, it is necessary to know more about the efficiency of cytoplasmic transfer and how to make it work in a larger retina, equivalent to the normal human eye. Specifically, to acquire dose-response kinetics of the cytoplasmic transfer process, Mandeep will transplant different doses of healthy primary mouse donor photoreceptor cells into recipient mice with retinal degeneration and examine the efficiency of the repair process over time by super-resolution confocal holographic microscopy. Similarly, in order to validate stem cell cytoplasmic transfer in a large mammalian retina, he will examine the time course requirements for optimal transfer efficiency using human stem-cell-derived photoreceptor cells transplanted into a pig retina. His focus will be to develop an acceptable delivery method and robust quality control of donor cells, which will enable the launch of a Phase I clinical trial as soon as possible. If Mandeep is successful, cytoplasmic transfer therapy will become an accepted intervention to repair dysfunctional retinal cells in cases of inherited blindness. Restoration of sight in those affected children will profoundly improve their quality of life.