THE HARTWELL FOUNDATION

2006 Individual Biomedical Research Award

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Hair Cell Regeneration by Inactivating Genes in the Rb Pathway in Supporting Cells in Mice

This innovative proposal is about recovery of hearing at the most fundamental level of auditory reception: regeneration of the hair cells (HC) present in the inner ear that convert sound vibrations to nerve impulses. Many genetic and environmental factors can cause irreversible damage to auditory HC, including chemotherapy and antibiotics that leave many sick children at risk. Mammalian HC, unlike those in certain lower vertebrates (chicken, fish, and amphibians), do not undergo spontaneous regeneration, even though neighboring supporting cells (SC) retain a limited capacity to divide and adopt sensory cell characteristics. Consequently, damage to HC usually results in irreversible deficits in hearing and balance. Remarkably, Dr. Zuo recently identified a unique cell-cycle regulator called p16Ink4a that makes mammals unable to regenerate HC, which is coincidentally absent in chickens. Utilizing a unique mouse model where the animals will have had their hearing destroyed by chemotherapeutic drugs or antibiotics, he will genetically remove the cell-cycle inhibitor to explore the molecular pathways responsible for restoring hearing. His theory is that that inactivation of appropriate genes in the pathway normally preventing conversion of SC to HC will unblock the natural stimuli for their regeneration as HC, in a manner analogous to lower vertebrates. If HC regeneration occurs under these manipulations, it would be the first example of HC regeneration in mice, making it possible to develop targeted drug therapy to restore hearing in deaf children and adults.