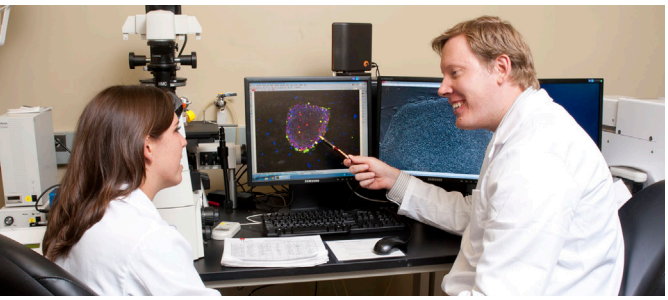
INNOVATE
EVIDENCE-BASED MENTAL HEALTH RESEARCH



Transplantation of Brain Cells to Treat Cognitive Decline

Cognitive decline, disruptions in the way humans learn, understand and perceive the world around them, is a reoccurring theme in behavioral and mental health issues. Brain injury and cognitive decline can occur after substance abuse, and in particular chronic alcoholism, when circuitry in the brain is damaged, sometimes severely. Researchers at UC Davis are exploring a unique solution to treat cognitive decline by transplanting neurons. What if we can restore cognitive function as commonly as knee or hip replacements?

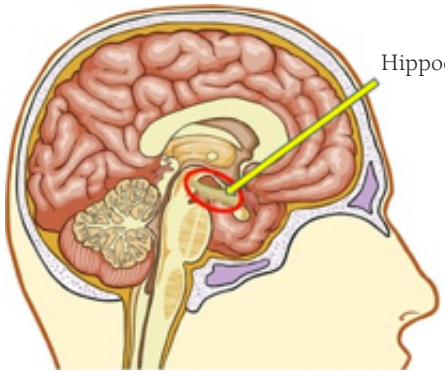
While neuron regeneration is more complicated than knee replacement and won't be available for a long time, Ben Waldau, Ph.D., is taking the first steps toward seeking solutions for those with cognitive decline. Waldau recently received one of 23 Pilot Award grants from the UC Davis Behavioral Health Center of Excellence to study the development of regenerative therapies to repair damaged circuits in the brain and restore cognitive function. Waldau is Assistant Professor in the Department of Neurological Surgery at UC Davis School of Medicine. His pilot award is entitled, "Transplantation of Induced Pluripotent Stem and Neural Progenitor Cells derived from a UC Davis Patient with Mental Illness into a Mouse Model of Endogenously Deficient Dentate Neurogenesis."

A Clinician and Basic Scientist

Waldau is a vascular neurosurgeon at UC Davis Health System who mainly operates on ruptured aneurysms. "Nearly every patient who has a ruptured aneurysm has some degree of cognitive disorder and every patient mentions memory problems," expressed Waldau. He sees patients on a regular basis, yet his research is focused on basic science and providing a broader understanding of what goes on inside the brain. Waldau explains, "The main reason I came to this university in 2012 was not only to take care of patients, but also to advance basic science. This pilot award has made it possible for me to continue my work with a leading stem cell research center and collect preliminary data to seek larger grants."

How it Works

Waldau collected brain tissue during a routine brain surgery from a patient with Traumatic Brain Injury (TBI) and severe cognitive decline due to chronic alcoholism. He and assistant



brainmadesimple.com

"Dr. Ben Waldau is not only a talented surgeon but also a dedicated physician-scientist. His innovative research uses cutting-edge techniques that could ultimately help the lives of his patients."

- Jan Nolta, Ph.D. Director, Stem Cell Program and Institute for Regenerative Cures at UC Davis

researcher, Whitney Cary, are now proliferating and differentiating those cells into types that can be implanted into the hippocampus of mouse models with decreased ability to create new neurons, called neurogenesis. The ability to create new neurons is most prominent in the dentate gyrus of the hippocampus. The dentate gyrus is typically known as being responsible for episodic memories. Episodic memories are the autobiographical memories that make up our personal life stories, such as memories of your first kiss and where you were on significant dates like Sept. 11, 2001. Waldau's goal is to enhance learning and memory and restore neurogenesis by transplanting cells from a human patient into a mouse's dentate gyrus. Eventually, this research aims to help patients with cognitive decline due to degeneration of the hippocampus by transplanting the patient's own cells into the dentate gyrus to restore learning and memory.

This study uses a Cyclin D2-KO mouse, which has very few progenitor cells, a type of cell that has the ability to differentiate into specific types of cells, and very limited ability to create new neurons through neurogenesis. This causes three observable responses in these mice; first, KO mice perseverate which means they have a decreased ability to adjust to new information or repeat actions during platform reversal, second, impaired long-term memory acquisition, and third, mood disorders shown through decreased normal behaviors such as nest construction and burying marbles.

Enriched Environment

Upon implantation, the cells are not guaranteed to survive. However, there are two factors that may increase the rate of survival and integration[1]. The first is an enriched environment, which stimulates the brain, like a playground for children with areas to explore and social stimuli. Neurogenesis is stimulated by this environmental enrichment. The second factor is a Laminin-rich environment. Laminin is a fibrous protein important for cell survival. The survival rate for cells is higher when they are implanted near blood vessels, which are high in Laminin. Once the cells have been implanted and given time to reproduce within the brain, the mice will again be assessed in their performance on water maze trials and behavioral indicators such as nest building.

A main concern for this study is whether or not the transplanted cells can successfully find their final locations upon migration into the dentate gyrus of the hippocampus. The obstacles at the level of basic science are numerous. Even still, there is a broad spectrum of possible clinical applications for this research including the ability to address cognitive decline, depression and aging.

1. Jamal AL, Walker TL, Nguyen AJ, Berman RF, Kempermann G, Waldau B. Transplanted dentate progenitor cells show increased survival in an enriched environment, but do not exert a neurotrophic effect on spatial memory within 2 weeks of engraftment. Cell Transplant. 2015 Jan 23. [Epub ahead of print] PubMed PMID: 25621922

Behavioral Health Center of Excellence at UC Davis

UC Davis launched the Behavioral Health Center of Excellence in October 2014 to advance mental health research and policy with initial funding from the Mental Health Services Act. The Innovate series highlights the Center's $4.3 million Research Pilot Award program.

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