ENHANCING THE INJURED BRAIN’S CAPACITY FOR RECOVERY

The Steinberg Lab: An Opportunity for Impact

Conventional medical wisdom has long held that after the first months following a stroke or other cerebrovascular event, recovery of impaired functions would be minimal; that the brain had little capacity for repair. For the millions of people left with impaired movement, speech, or cognition, this was a devastating new reality. And for physicians, a hard message to deliver.

With years of clinic and operating room observations, coupled with the emergence of the field of stem cell and regenerative medicine, Dr. Gary Steinberg is challenging this conventional paradigm in his laboratory. He believes that stem cell therapeutics hold the key to the recovery of function he has long believed possible -- and that he has a responsibility to his patients to accelerate research and bring hope back into the equation. In fact, in an industry-sponsored early clinical trial, Dr. Steinberg has already shown stem cells can promote recovery of function in patients years post-stroke.

However, still unknown is precisely how brain stem cells promote recovery. Elucidating these mechanisms of recovery are critical for the development of effective clinical therapies.

Neurons are specialized cells in the brain that process information. Like all cells, they are unbelievably complicated in their own right. Painstaking, fundamental research in the Steinberg Lab has demonstrated that transplanted stem cells in mice and humans promote recovery.

The Steinberg Lab has shown that neuronal stem cells introduced into the brains of animals do not become new brain cells as originally hypothesized by many. Rather, the recovery of function seen in these animals is in fact due to secretion of powerful proteins, growth and angiogenesis factors, and molecules that enhance native recovery. The lab has developed a promising human neuronal stem cell (NR1) that does in fact enhance native recovery in animals. To receive approval from the Federal Drug Administration to advance this promising cell to the clinic and optimize treatment in patients, requires demonstration of the mechanisms of action—how the cells recover function—and data supported protocols for the right dosage, timing of delivery, and best route of delivery.

Philanthropic Priorities in the Steinberg Lab

Dr. Steinberg has identified the lab’s NR1 human neuronal stem cell research as priorities for philanthropic investment. The brain is an exceptionally complex system. It follows then that each of the strategies outlined below is complex in their execution, requiring funding at a minimum of $2M over the next 8 months and then $500,000 per year over a five-year period.
Priority: NR1 Stem Cell Strategies

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The three-pronged attack described below (in order of priority) will test the hypothesis that NR1 cells trigger post-stroke recovery by modulating brain inflammation and plasticity, and the inflammatory changes drive the plasticity changes. Inflammation can have both positive and negative consequences. Plasticity is the extraordinary ability of the brain to change and adapt based on experience or its environment.

Once this hypotheses is confirmed and commercialized in the United States, there is potential to expand it to other countries through Dr. Steinberg’s various connections in academic medicine.

All of this work will be preclinical—in the laboratory—in preparation for human clinical trials. These studies will proceed in parallel with research funded by other sources focused on safety, toxicity, and stability of the NR1 stem cells.

Strategy 1: NR1 Secreted Factors that have the Most Impact on Recovery

Dr. Steinberg has identified this project as his highest priority. The team will investigate which of a number of NR1 secreted factors are important for modulating post-stroke inflammation or plasticity. The team can progress incrementally, one factor at a time, or in an accelerated multiple factor synchronized scenario depending on the level of funding available. As work proceeds, the team may narrow its focus on either inflammation or plasticity depending on which parameters look most relevant.

Impact: Optimizing the best stem cell therapy for clinical trial by identifying the factors which have the most robust action, or greatest demonstration of mechanisms, and extent of recovery.
Strategy 2: Immune Cell Response and Neuro-Inflammation after NR1 Transplantation

In this project, the team will investigate the effects of NR1 on the post-stroke inflammatory response and determine how this relates to NR1-induced functional recovery and plasticity changes. Immune cells have a central role in protecting the host, but also contribute to the pathogenesis of inflammatory and degenerative diseases. They will profile the response of immune cell sub-populations in brain, blood, and spleen after NR1 transplantation, modify the early immune cell response to determine the effect on functional recovery and plasticity changes.

Impact: Enable specific strategies to enhance or mitigate the inflammatory response in patients after stroke to prevent further injury and promote recovery.

Strategy 3: Modulation of Inflammatory Changes after NR1 Transplantation to Recover Neurologic Function after Stroke

The team will determine which brain regions show inflammatory changes after hNSC transplantation following chronic stroke, and which of these immune hotspots best correlate with neurologic recovery. They will use MRI and PET imaging of a TSPO (inflammation) tracer to monitor inflammation throughout the brain and correlate changes in PET and FLAIR signal over time and brain region with functional recovery.

Impact: To enable more precise targeting within the brain of transplantation, elucidate recovery mechanisms, as well as develop potential dual strategies involving brain stimulation.

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