Using an Adaptive Trial Design to Examine the Safety and Feasibility of Deploying Cell Therapy in Patients with Parkinson's Disease

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We have developed a strategy to address several of the regulatory, practical, and ethical issues that arise from designing clinical trials examining biological therapies requiring surgical delivery. We are in the process of carrying out two Phase I studies with the primary goal of examining the safety and feasibility of autologous peripheral nerve grafts delivered to target brain areas at the time of deep brain stimulation (DBS) surgery in patients with Parkinson's disease. DBS therapy is FDA approved for the treatment of several conditions including Parkinson's disease. We chose peripheral nerve tissue as donor material because Schwann cells, after injury, transdifferentiate to become "repair cells," activate antioxidant response element signaling pathways, and release a host of neurotrophic factors. Our cell therapy delivery strategy has helped us clear many of the hurdles encountered in early-stage clinical trials. Three key advantages of our design are 1) participants have their own sural nerve removed and transplanted at the time of DBS surgery, without any significant modifications, thus the delivery of the grafts does not require FDA oversight; 2) DBS surgery is an insurance reimbursable procedure, thus greatly reducing trial costs, and 3) DBS is a standard of care for Parkinson's disease thus patients do not have to forego the therapeutic benefits of DBS to participate in the trial. We have implanted grafts (~ 5 pieces of sural nerve) into the substantia nigra (SN) of 37 participants. Initially, we implanted to a single target, unilaterally to the contralateral SN of the most affected side (based on motor performance) in 8 participants. Next, we implanted 18 participants. Subsequently, we escalated the dose in 11 participants by progressing from two targets in the unilateral SN, to two targets in one SN plus one target in the contralateral SN, and finally two targets to each SN. No serious adverse events related to the grafting have been seen and the adverse event profile has been comparable to that of DBS alone, but we have seen evidence for therapeutic benefits in some participants who have had the grafts for over 12 to 24 months While dedicated efficacy studies are needed to assess the potential efficacy of this therapy, we are finding that this approach of combining cell therapy at the time of DBS surgery provides substantial advantages.