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COMMENTARY

Cell Therapies for Parkinson's Disease

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Today we can treat many diseases symptomatically using both small molecules and biologics, and although effective, our repertoire of medicines that focuses on treating the cause of the disease is limited. Few therapeutic approaches have been designed to truly restore function. If done right, they can be very effective, often bringing lifelong therapeutic benefit to the patient. In this commentary, we will discuss how these principles are applied to living cell therapies for Parkinson's disease.

What makes "live" therapies special and so attractive? We need to appreciate that they rely, in part, on using the native function of the cell. They incorporate into the patient and follow the same logic as healthy cells: responding to the same environmental inputs and reacting with the same (bio) logical outputs. This is a fundamentally different mechanism of action when compared with small molecules and other biologics. These therapies, in contrast, address the symptoms of cells that have either weakened and died or otherwise behaved in a nonphysiological manner. For example, we treat patients with sickle cell disease symptomatically with pain-relieving medications during times of acute crisis; in contrast, a cell therapy can provide nonfaulty cells and correct the disease for the lifetime of the patient. As such, bone marrow transplantation has become a pillar of modern medicine not just for sickle cell disease, and the concept of transplanting blood cells has recently been expanded using "designer blood cells," immune cells that have been genetically engineered to target specific cancer cells. These designer cells, carrying an artificial recognition element, use their intrinsic cytotoxic activity to eliminate cancerous blood cells.[1] In summary, living cell therapies offer the tantalizing opportunity to provide life-long treatment administered in a single session.

Significant loss of functional cells is a critical feature of the pathology in a broad range of disorders of the central nervous system; the consequences of this degeneration are grave and exacerbated by the limited capacity of the brain and spinal cord to spontaneously regenerate. In Parkinson's disease, large numbers of cells within the substantia nigra pars compacta are lost. This degeneration is slowly progressive, developing silently over time, until an intervention comes too late to halt the disease progression or to rescue the cells or their neuronal circuit. Dopaminergic cell loss leads to the degeneration of nigra-striatal connections and subsequent, profound loss of striatal or putaminal dopaminergic circuits.[2]

The histopathological hallmark of Parkinson's disease is the Lewy body, an intracellular protein aggregate of mainly α-synuclein. The clinical signs are the classic triad of bradykinesia, rigidity, and resting tremor, as well as other nonmotor symptoms, which together diminish the quality of life of patients and their caregivers. The current standard therapeutic approach is to provide exogenous dopamine or to raise endogenous dopamine levels pharmacologically.[3] These therapies become less and less effective over time, though, and patients struggle with daily fluctuations in their symptoms. Some patients benefit from the implantation of a device for deep-brain stimulation, a therapy that counteracts tremors with electrical stimuli. Experimental gene therapies also are being investigated in early clinical trials to improve the survival of residual dopaminergic cells or to convert other brain cells into dopamine-producing cells.[4]

A few experimental "living" treatments have been tested that rely on transplantation and, in some cases, on the survival of cells. The earliest studies in humans were performed with adrenal medullary tissue with the rationale that this type of tissue, among other catecholamines, produces low levels of dopamine. A small series of trials were built upon these early findings, but the approach was eventually abandoned because of lack of efficacy and complications related to the cell source. Nonetheless, it captured the field's imagination of what cell therapies could potentially do and that the transplantation procedure itself may be safe. After unsuccessful trials with human retinal pigmented epithelial cells, autologous carotid body cells, and porcine ventral mesencephalic cells, the scientific and clinical community began to explore the potential of human fetal material.[5] The concept was sound: take the precursors of what would eventually become the dopaminergic system in an adult from an early gestation embryo and transplant the material into the affected area of the brain in a patient with Parkinson's disease. An estimated 400 patients worldwide have undergone this therapy as of today. In some case studies, long-term clinical benefits have been reported that were clearly linked to the surviving grafts postmortem and durable for up to 24 years. Yet, in controlled clinical trials, these therapies had less favorable outcomes. Furthermore, in some autopsies and limited to some transplants, the disease pathology had spread to the grafted cells, in line with the prion-like spread of Parkinson's disease. How relevant this spread is to the newly grafted cells remains to be seen in larger cohorts.[5] This highlighted that patient selection, patient conditioning, clinical end points, and cell preparation play critical roles in the outcome of cell-based therapies. While it

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Table 1 Current cell therapies for Parkinson's disease

Cell therapy	Group/developer	Location	Development stage	Animal POC published
Pluripotent stem cell–derived dopaminergic neurons	BlueRock Therapeutics/Memorial Sloan Kettering Cancer Center & Weill-Cornell School of Medicine	US	Phase I planned	Yes
	University of Lund/Novo Nordisk	Sweden	Preclinical	Yes
iPSC-derived dopaminergic neurons	Kyoto University/Sumitomo Dainippon Pharma	Japan	Phase I/II (08/2018, JMA-IIA00384)	Yes
	Cellular Dynamics International/Fujifilm	US	Preclinical	Yes
	https://www.summitforstemcell.org/	US	Preclinical (planned phase I 2019)	No
Human parthenogenetic stem cell–derived neural stem cells	International Stem Cell Corporation/ University of Melbourne	Australia	Phase I (NCT02452723)	No
ES–derived neural progenitors	First Affiliated Hospital of Zhengzhou University	China	Phase I (2017, NCT03119636)	No

ES, embryonic stem; iPSC, induced pluripotent stem cell; POC, proof of concept.

remains debated how the failed studies should be interpreted, the underlying concept holds value, and an ongoing clinical trial is revisiting many of the questions that remain open. The TRANSEURO study aims to test a living fetal cell product with optimized sample preparation, sample storage, patient enrollment, and follow-up characteristics.[6] However, even under the best circumstances, therapies based on fetal cell material may face challenges to widespread use because of the limited availability of the tissue: a more scalable and better-defined cell source will be needed for successful cell therapy approaches. Human embryonic stem cells and human induced pluripotent stem cells taken together as pluripotent stem cells, are capable of indefinite self-renewal and can differentiate into virtually any native cell type of the human body, including those needed as cell therapies to replace the functional cells lost in many disease states.[7] In a series of studies, it was shown that pluripotent stem cells can generate native midbrain dopaminergic neurons, the very cells lost in Parkinson's disease. Importantly, for the first time, these cells showed long-term survival and function in established models of Parkinson's disease.[8] A variety of efforts worldwide are currently underway to find a more suitable cell source for dopaminergic cell transplantation (**Table 1**). All focus on providing a better cellular product, one that can be manufactured, possibly stored, and used at scale for the estimated 6–10 million patients with Parkinson's disease worldwide. Therapies include dopamine-producing cells, or precursors, derived from human embryonic stem cells, human induced pluripotent stem cells, and parthenogenetic stem cells. Some, but not all, studies have shown convincing preclinical data, and it is noteworthy that in the past, efficacy in the 6-OHDA lesioned rodent offered a reasonably good prediction of clinical function, with weak preclinical signals leading to poor clinical outcomes, whereas a strong effect in rodents suggested a benefit to patients. It remains to be seen how these different cell sources and manufacturing protocols will compare in the clinic. Such comparisons will have to rely on the use of common clinical outcome measures such as positron emission tomography imaging, quantitative rating scales, and quality of life measures but may also include emerging tools, such as new biomarkers and wearable devices. A recent review by Barker *et al.*[9] provided guidance on how to evaluate the readiness of several therapeutic approaches on their fitness for clinical translation. Beyond clinical testing, and because these cells can be produced at scale and allow researchers to evaluate the material with relative ease in the laboratory, we see a series of studies addressing the biology and mechanism of such cell products. Genetic tools have been used to track synaptic connectivity of the grafted cells, demonstrating that grafted human embryonic stem cell–derived dopaminergic progenitors have the capacity to innervate their forebrain targets, integrate into the host circuitry, and bring functional recovery in animal models. Furthermore, graft-dependent modulation of host glutamatergic synaptic transmission onto striatal medium spiny neurons was demonstrated to be reminiscent of endogenous midbrain dopaminergic neurons.[10]

We are optimistic that the right cellular therapy, one that capitalizes on cells that can be manufactured at high quality and in sufficient numbers to address the clinical need, one that demonstrates safety and efficacy in established preclinical models, and one that is given to the right patient population will bring much-anticipated results to those in need. We will see several of these approaches enter the clinic over the next few years. It will be important to establish a network of clinical sites capable of delivering this new class of therapies to patients, and active discussions with payers are needed to ensure appropriate reimbursement of such therapies: does the higher initial cost outweigh the cost of a multiyear treatment? How will living cell therapies compare with emerging gene therapies and other therapies on the horizon? Importantly, we need to deliver treatments that improve patient quality of life and the lives of those surrounding them. It is important not to speak of "a cure" in this context, as Parkinson's disease is more than the failure of the dopaminergic motor system. Patients have additional nonmotor symptoms, and we will continue to evaluate how cell therapies may address nonmotor symptoms, and how significant these aspects of the disease will be if the motor symptoms are adequately controlled. It remains to be seen if the restoration of the dopaminergic system will have disease-modifying effects. We begin to imagine developing cell therapies that deliver augmented

function, for example, using cells that may be resistant to the spread of disease (e.g., α-synuclein knockout neurons) or that secrete disease-modifying antibodies; those may be even more efficacious at addressing the unmet clinical need. Furthermore, we need to develop better clinical outcome measures, including biomarkers that will let us compare the different therapeutic approaches, and we have to use novel tools such as machine learning on large data sets, to link the cell product to clinical outcomes, all while monitoring the patients on an ongoing basis.

In summary, a new class of cell therapies is on the horizon and will undoubtedly change the quality of life of patients with diseases such as Parkinson's.

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