Cell Therapies for Parkinson's Disease from Discovery to Clinic

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I. EXECUTIVE SUMMARY

In March of 2013, the California Institute for Regenerative Medicine (CIRM) in collaboration with the Centre for Regenerative Medicine (CRM) of the National Institutes of Health (NIH) held a two-day workshop on cell therapies for Parkinson's Disease (PD) with the goals of reviewing the state of stem cell (SC) research for the treatment of PD and to discuss and refine the approach and appropriate patient population(s) in which to plan and conduct new clinical trials using stem cell–based therapies for PD.

The group comprised approximately 50 scientists, clinicians, cell manufacturers, clinical trial and regulatory experts, as well as members of biotechnology and pharmaceutical industries, funding agencies and patient advocates (see Appendix A for list of attendees). Pioneers and worldwide leaders in the field presented their work and discussed the challenges and opportunities they have encountered in bringing experimental cell therapies for PD to the clinic.

Workshop participants identified priorities for research, development and funding, discussed existing resources and initiatives, and outlined a path to the clinic for a stem cell-based therapy for PD. A consensus emerged among participants that the development of cell replacement therapies for PD using stem cell-derived products could potentially offer substantial benefits to patients. As with all stem cell-based therapeutic approaches, however, there are many issues yet to be resolved regarding the safety, efficacy, and methodology of transplanting cells as therapies for patients. Workshop participants agreed that designing an effective stem cell-based therapy for PD will require further research and development in the following areas:

(1) Identifying the best cell type(s) to use as a source for the cellular therapeutic in future clinical trials (e.g., human induced pluripotent stem cells (hiPSCs) versus human embryonic stem cells (hESCs) versus adult stem cells (SCs)) and the degree of cell differentiation and purification required before transplantation;

(2) Optimizing conditions for the engraftment, survival, and integration with existing neural circuitry *in vivo*;

(3) Understanding the ongoing glial and neuroinflammatory effects of progressive PD on the local environment and the effects on transplanted neurons and discussing the optimal immunotherapy needed to support the grafted cells;

(4) Standardizing the protocols and processes for optimal cell manufacturing;

(5) Developing standard surgical methods for cell transplantation that accurately and effectively distribute the cells while causing minimal damage to the target region of the brain;

(6) Developing biological assays to assess the survival and efficacy of transplanted cells *in vivo*;

(7) Designing new functional clinical assessments to evaluate the success of potential interventions; and

(8) Identifying the most relevant considerations for the design of successful clinical trials (patient population, endpoints, monitoring, length of follow-up).

Breakout sessions provided a forum for participants to discuss all these points and to suggest additional opportunities where synergy of efforts could improve the probability for success in bringing SC therapies to the clinic. Although participants agreed that collaboration is crucial for the success in the field, they also indicated that supporting multiple approaches might increase the chance that a stem cell therapy for PD will make it to the clinic. The regulatory approval of a safe and effective product must first advance down the development pathway through a series of clinical trials. The workshop identified the following critical initial steps to facilitate development of a Phase 1/ 2 clinical trial for stem cell therapy:

1. ***Define the cell source*:** Either hiPSCs or hESCs could be used in the first stem cell trial. hESCs provide a more beneficial commercial model as a single hESC line can be banked in large quantities to treat multiple patients. hiPSCs can be autologous or allogeneic. Ideally, pluripotent stem cell banks should be matched to patients to minimize immune effects. Experiments to evaluate the different cell sources are underway and several approaches are under investigation. Currently the effort is focused on prioritizing the different approaches and moving forward into clinical trials with the highest priority.
2. ***Choose a differentiation protocol that can produce functional authentic nigral A9 dopaminergic (DA) neurons:*** It will be critical to select a differentiation protocol that produces the right type of DA neuron, both *in vitro* and *in vivo* in animal models. The method of differentiation is currently being optimized in different laboratories. Specifically, during characterization of cells through differentiation stages, there is a need to show robust expression of mDA neuron lineage markers (TH, Nurr1, Foxa2, Lmx1a, Pitx3, Engrailed1, Engrailed2) as well as of mature neuronal markers in the final product including Tuj1, synapsin, dopamine transporter (DAT), and G-protein coupled, inwardly rectifying potassium channel (GirK2). An important observation is that TH expression is shared among all catecholaminergic lineages and is not specific to midbrain. Other neuronal and non-neuronal fates should also be ruled out through marker expression.

3. ***Develop biological assays that predict in vivo functional activity and biological action:*** The likelihood of an effective approach for clinical application will increase when the functional features of authentic nigral A9 DA neurons are shown in the cell candidate, namely: A) Appropriate neurophysiological profile; Autonomous pacemaking or hyperpolarizing activated (ih) currents are primarily observed in A9 mDA neurons and represent a very important functional assay to be included in the in vitro characterization of the candidates in development; and B) DA production and release in response to physiological stimuli; Measuring DA production and release as well as its metabolites (DOPAC and HVA) with specific and sensitive techniques such as HPLC is necessary as part of the functional characterization assays of the candidate cell for transplantation. Finally, animal models should be used to optimize conditions for cell survival, show integration (significant fiber outgrowth with synapse formation) and functional benefits. Long-term engraftment (minimum 6 months) in an appropriate rodent model of PD (ex. 6-hydroxy-dopamine (6-OHDA) lesioned rat) and complete restoration of amphetamine-induced rotation behavior as well as significant improvements in at least two other motor performance behavioral need to be shown with the candidate cells. Further research is needed to define additional biomarkers and develop potency assays that provide correlations between cell survival and predictive functional outcome.
4. ***Develop purification strategies:*** Purification of DA cells from other cells in order to further enrich for DA neurons and obtain fully uniform populations at an optimized stage for transplantation is also necessary. This will allow for a better control of the ratio of serotoninergic (SER) to DA neurons in graft preparations and avoid dyskinesias as well as preclude tumor formation.
5. ***Determine the minimal effective dose and the maximum feasible dose in large animal models:*** Preclinical experiments in large animal models should be conducted on the selected cell to optimize integration with existing neural circuitry and restoration of function. Although the number of cells required to replace the nigral cell loss is unclear, other cell therapy projects and fetal transplant experiments indicate that it is likely to be around 100,000 DA neurons, assuming they have the same innervation potential as fetal nigral DA cells.
6. ***Develop a consistent transplantation protocol that shows low risk of hemorrhage and no tumor formation:*** The first trial should involve bilateral transplantation into the putamen. The physician conducting the transplant would select the optimal method of transplantation, which may include the use of new transplantation devices, but the device for cell delivery is not thought to be a rate-limiting step for the phase 1/ 2 trial
7. ***Select target patients for the Phase 1/2 trial:*** Given the results from the fetal transplants trials, it seems clear that the target patients should ideally be younger patients early in their disease course and responsive to oral DA replacement

therapies.

8. ***Select outcomes and follow-up studies for Phase 1/2 trial:*** Most participants agreed that the patients must be followed for at least 3 years after transplantation. Outcome parameters should include a range of clinical measures along with MRI and PET.

Participants proposed that CIRM and NIH prioritize their funding efforts in the area of PD to support projects that will advance these research goals, especially around the generation of sufficiently large numbers of authentic DA nigral neurons such that stem cell-based therapies can be more rapidly developed as treatment options for PD.

Document Contacts

Many researchers provided inputs during this workshop. Readers seeking more information about particular details and contacting researchers in certain areas may access that information by contacting:

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II. BACKGROUND

OVERVIEW OF THE INCIDENCE, ANATOMY, AND SYMPTOMATOLOGY OF PD

Parkinson's disease (PD) is the second most common neurodegenerative disorder in the world, affecting 1 to 2% of the population over 65 and reaching a prevalence of almost 4% in those aged 85 years old or above. It is characterized by progressive motor dysfunction, expressed as a classical "resting tremor", slowness of movements (bradykinesia), muscle rigidity, and difficulties with gait and balance [3]. PD patients also exhibit a variety of non-motor features, including mood disturbances (i.e., depression, anxiety), dementia, pain, and sleep disturbances. Autonomic problems, including bladder/bowel dysfunction, sexual dysfunction, and sweating abnormalities, as well as gastrointestinal abnormalities, are also common. These non-motor aspects arise at any stage of the disease and often present before motor features develop [4].

The primary signs of PD arise from damage to neuronal circuits in the basal ganglia involved in the precise control of motor function [1, 2, 5] (see Figure 1). The basal ganglia are a collection of nuclei comprised of the striatum (STR), globus pallidus (GP), subthalamic nucleus (STN), and substantia nigra (SN). DA neurons of the substantia nigra *pars compacta* (SNc), the neurons progressively lost in PD, project to striatal medium spiny neurons (MSNs) and influence the activity of motor circuits running through the basal ganglia to the thalamus, and cortex. Degeneration of DA neurons leads to a disruption of the delicate balance of excitatory and inhibitory feedback that is necessary for appropriate motor function (Figure 1).

Clinically, the severity in PD is measured using the modified Unified Parkinson's Disease Rating Scale (UPDRS), a rating scale used to follow the longitudinal course of PD. This scale is the most commonly used in the clinical study of PD and tracks both motor and non-motor features of the disease [6, 7]. The modified UPDRS consists of four broad scales that evaluate (1) non-motor experiences with daily living, (2) motor experiences with daily living, (3) motor features, and (4) motor complications. A need for further research on the current clinical outcome measures is also required, as difficulty interpreting the results of studies in recent years has been attributed to problems with the chosen outcome given the natural variability in the scores that arise out of UPDRS assessments [8].

Post-mortem, the PD disease process in the brain can be staged using the Braak classification [9] by analyzing fixed tissue sections for the accumulation and regional distribution of alpha synuclein and Lewy bodies (LBs), the classical pathological hallmark of PD. LBs are large, insoluble protein aggregates that result from the accumulation and aggregation of misfolded proteins, particularly (α)-synuclein [10]. The Braak system has been proposed as a method to stage the severity of PD based on observations of the regional distribution of LBs in the central nervous system [9, 11, 12].

However, a relationship between Braak staging and clinical severity has been difficult to establish, particularly given the fact that LBs are not universally observed in all forms of PD (reviewed in [13]) and they might just not be in the right distribution of his classification.

PATHOGENESIS OF PD: CELLULAR MECHANISMS, GENETICS, AND IMMUNE EFFECTS

For many decades, PD was thought to be an idiopathic, late adult–onset disease resulting from unknown environmental factors [14]. However, the identification of Mendelian mutations in the SNCA gene in 1997 [15], which codes for the α-synuclein protein that is deposited in the classic pathological lesion of PD, the LB [10], was key to uncovering the role of genetics in the disease. Since then, a number of other loci have been implicated; several genes have been found to underlie dominant or recessive forms of PD. These include recessive mutations in the *PINK1, Parkin* and *DJ-1* genes which cause early-onset forms of PD, and the *LRRK2* gene, which is an autosomal-dominant risk factor for PD [14]. Although these genetic forms of PD are rare, comprising approximately 3-5% of cases [16], and can lack LB pathology new and powerful genome-wide association studies (GWAS), have mapped many new gene variants that alter the risk for PD, and geneticists predict that more may be discovered [16-19]. Therefore, genetic risk factors do contribute to the etiology of even typical forms of PD [16].

What are the mechanisms responsible for the highly selective death of the SNc DA neurons in PD patients? Post-mortem evaluation and more recently genetic and molecular studies have helped uncover the evidence for many possible mechanisms to explain the cellular pathogenesis of sporadic PD, which is likely to be complex, involving altered metabolism and possible spread of α-synuclein, lysosomal dysfunction, mitochondrial dysfunction and possibly a dysregulated inflammatory response (reviewed in [20]). In terms of mitochondrial defects, these were found to be associated with the occurrence of classical PD symptoms that developed in young adults after self-exposure to the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Later, mechanistic studies revealed that MPP+ (the actively toxic metabolite of MPTP) inhibits mitochondrial metabolism [21]. Substantial progress towards understanding the role of mitochondria in the disease process has been made by the identification and characterization of genes causing familial variants of PD. Studies on the function and dysfunction of these genes have revealed that various aspects of mitochondrial biology appear to be affected in PD, comprising mitochondrial biogenesis, bioenergetics, dynamics, transport, and the fidelity of the mitochondrial quality control systems [22].

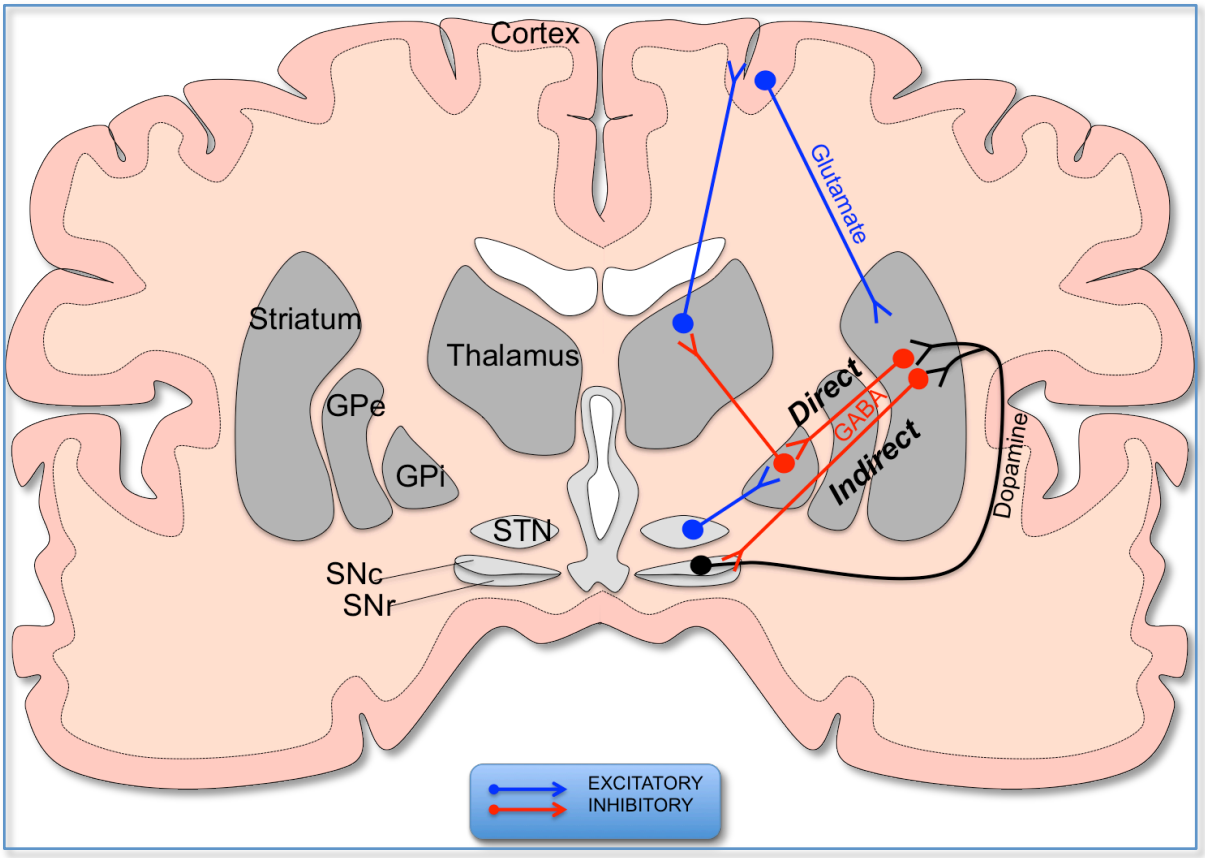

FIGURE 1. Coronal section of the human brain showing the relevant regions (left) and circuits (right) underlying the *direct* and *indirect* motor pathways under normal physiologic conditions. Neurons in the primary motor cortex synapse with medium spiny neurons (MSNs) in the striatum, which in turn regulate motor activity via two mutually antagonistic circuits known as the *direct* and *indirect* pathways (reviewed in [1, 2]).

Some genetic forms of PD directly impair mitochondrial function and thereby cause bioenergetic failure. Indeed, studies published over the last seven years have established a model for the PINK1/Parkin pathway of mitochondria quality control [23]. Furthermore, data from iPSC-derived neural cells from PD patients with LRRK2/PINK1 mutations have shown altered bioenergetic profiles and mitochondrial dynamics [24]. However, the precise mechanisms linking mitochondrial dysfunction to neuronal death in PD remain unclear. As described above, affected neurons in PD tend to accumulate large amounts of α-synuclein in the form of LBs [10]. LBs are one of several known types of insoluble protein aggregates that form in a number of neurodegenerative disorders, the composition of which varies according to specific disease (i.e., Beta-amyloid and tau in Alzheimer's disease, TDP-43 in amyotrophic lateral sclerosis, and mutant huntingtin in Huntington's disease (HD); reviewed in [25]). Whether LBs actually cause disease or are a secondary coping response to disease pathogenesis is a matter

of intense debate (reviewed in [13]). Early hypotheses, based on post-mortem observations of PD brains, suggested that LBs within the neurons themselves might be linked to DA cell death [26]. However, recent evidence suggests that LBs might instead be essential for sequestering misfolded or dysfunctional proteins that otherwise cause cellular damage, and thus might be protective [27], similar to observations in HD models [28]. Other cellular mechanisms designed to manage the accumulation of such proteins, such as proteosomal degradation and autophagy have been shown to be dysregulated in PD [24, 29, 30]. Indeed in this last area the recognition that GBA mutations are so common in sporadic PD has suggested that lysosomal dysfunction may be a much more important pathway for disease than previously thought.

DA neurons are also disproportionately vulnerable to oxidative damage and inflammatory effects. A distinguishing feature of nigrostriatal DA neurons is their increased reliance on intracellular oxidative processes related to the synthesis of dopamine [31], which makes them particularly susceptible to oxidative stress. This aspect was directly revealed in studies with hiPSC-derived neurons from PD patients with PINK1/LRRK2 mutations, whereby patient-derived DA neurons were more vulnerable to pharmacologically induced oxidative stress than DA neurons from healthy controls [24, 32]. DA neurons also have increased iron content [33] and reduced levels of the antioxidant glutathione [34], which increases their susceptibility to oxidative stress (reviewed in [35]) as well as having specific calcium channels that may in some way link to disease [36]. In addition, there are more microglia, the resident macrophages of the central nervous system (CNS), in the SN relative to other regions of the brain. Because activated microglia produce increased levels of inflammatory cytokines and chemokines and generate reactive oxygen species that harm DA neurons [35], immune activation in the SNc may influence the onset and progression of the disease, leading to accelerated DA neuron damage and death in PD patients.

TREATMENT FOR PD: CURRENT STANDARD OF CARE

Presently, there is no cure for PD. The current landscape of development activity in the US PD therapeutics market is shown in Figure 2. Current treatments in the market provide some symptomatic relief but do not act to reverse disease progression. There is a high unmet medical need to develop disease-modifying treatments that address the underlying biological causes of the disorder and halt disease progression.

Early-stage PD is typically treated pharmacologically with therapies that replace the dopamine normally secreted by DA neurons in the SNc. These include (1) levodopa, a dopamine precursor that is transformed into dopamine in the brain, which is always given with carbidopa, a peripheral dopamine decarboxylase inhibitor that inhibits the metabolism of L-dopa outside the central nervous system (CNS), thereby enhancing its delivery to the brain. Combination carbidopa-levodopa therapies have proven

particularly effective at reducing disease symptoms while minimizing side effects of the drugs in the short term; however, these drugs are associated with severe adverse effects in long term use. Other therapies for early stage PD include dopamine agonists, which mimic the effect of L-dopa by binding directly to striatal dopamine receptors. Dopamine agonists are often used as first-line therapies and their early use delays the appearance of motor complications and other dopamine-related symptoms. However, recent reports link them to a range of behavioral problems [37]. Other adjunctive therapies, such as monoamine oxidase–B inhibitors (to prolong dopamine signaling by blocking dopamine metabolism), COMT inhibitors which work in a similar way and anti-cholinergic agents (which have classically been used in younger patients to treat their tremor) can provide added relief [38, 39].

Unfortunately, the effectiveness of carbidopa-levodopa-based therapies decreases as the disease progresses, typically within 5 years of treatment initiation [40, 41]. Fluctuations in the response to medication as well as alterations in the production of endogenous L-dopa result in “on-off” states in which the medication produces alternating phases of good responses and periods of no response and/or the development of involuntary movements resulting from dysregulation of dopamine balance. These involuntary movements, dyskinesias, worsen over time, requiring additional therapies to control them, such as amantadine or more aggressive enteral or surgical treatments [39-41]. Deep brain stimulation (DBS) is a relatively new and increasingly utilized therapy among physicians. In DBS, one or more electrodes are surgically implanted into one of two specific regions of the basal ganglia, the subthalamic nucleus or the GPi [40]. An impulse generator delivers electrical stimuli to the cells and fibers located closest to the implanted electrode, thereby modulating the firing rate and patterns of neurons within the basal ganglia, which in turn influences thalamocortical circuits. DBS is a surgical technique typically employed in patients with moderately advanced PD who have disabling on-off fluctuations, dyskinesias and tremor, who remain responsive to L-dopa [39, 40]. It has been shown to be very effective at reducing the motor symptoms of PD in patients, with numerous clinical trials demonstrating significant relief [39, 40, 42].

The mechanism(s) by which DBS relieves PD symptoms remain unclear [40, 43], and the procedure carries risks that concern physicians and patients. Foremost are the potential for infection or intracranial hemorrhage, which often require device removal and an extended waiting period before consideration of further implantation surgery. Hardware-related complications, including electrode lead fractures, also occur at a high frequency. Finding the optimal DBS stimulation patterns for each patient is also a challenging process of trial and error [43].

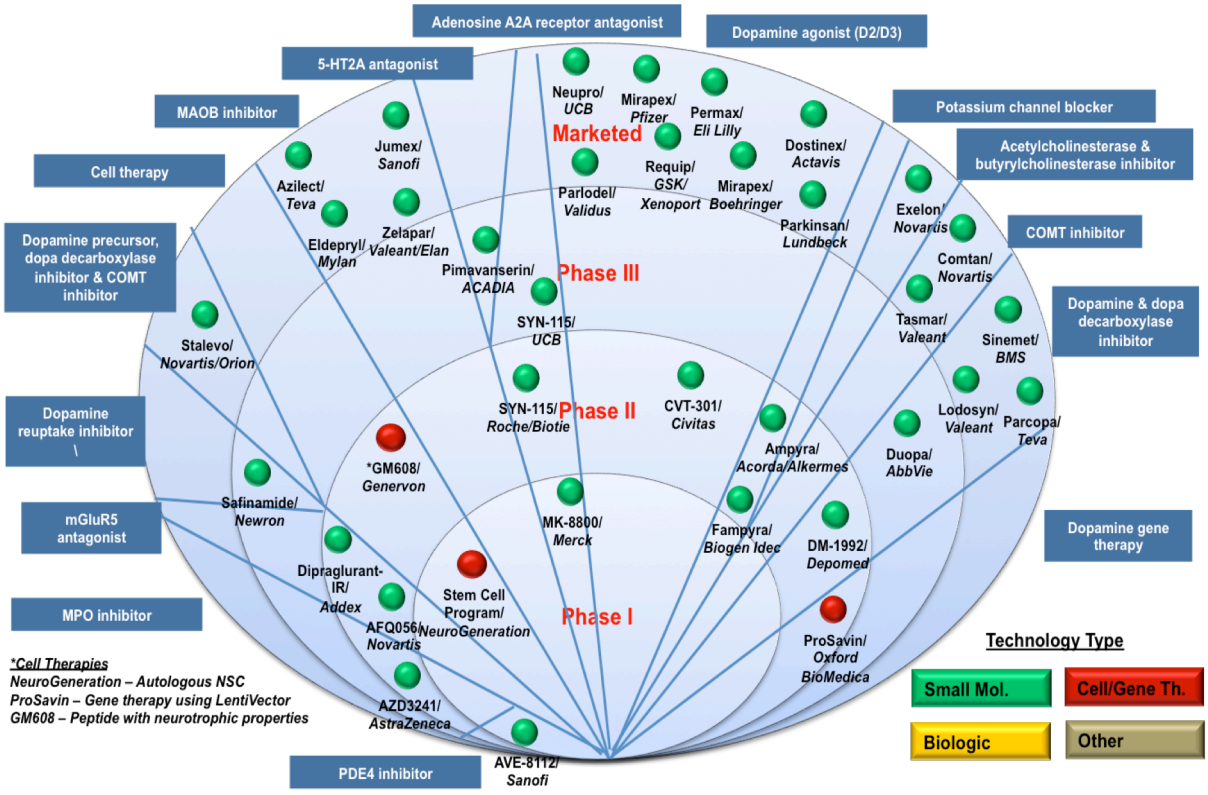

FIGURE 2. SNAPSHOT OF DEVELOPMENT ACTIVITY FOR PD (2013). This snapshot of the PD therapeutics pipeline is not comprehensive but these 36 candidates are representative of activity in various phases of development.
Source: EvaluatePharma (September 2013)

Furthermore, a number of other neurological and neuropsychiatric issues can occur with DBS, including cognitive impairment, speech disturbances (particularly with respect to verbal fluency), memory loss, sensory disturbances and mood disturbances [40, 44, 45]. While some of these effects may be corrected by adjusting the location of the implant and electrical stimulation; others are either permanent or only relieved by cessation of the therapy. Finally, DBS treatment carries significant ongoing expense beyond the initial surgery, owing to the cost of device and battery replacements and ongoing physician visits to monitor stimulation efficacy [43]. In summary, although dopamine-replacement therapies and DBS can provide relief of motor symptoms in patients with PD, they present some important disadvantages, have been received with mixed patient acceptance and do not treat the underlying causes of the disease.

In addition to the degradation of motor function, PD patients often display a range of cognitive and psychiatric symptoms, including dementia, hallucinations, anxiety and

depression; disturbances in sleep, bowel/bladder and sexual function; and pain [39, 41]. These symptoms significantly diminish patient quality of life [4, 41]. However, despite their impact, few clinical trials have directly addressed these issues, and current management of these symptoms in late-stage PD is often poor [39, 40]. Although data from fetal cell transplants suggest that replacing DA neurons will likely not affect these non-motor symptoms [46], cell replacement may be a clinically competitive option that could lead to significant improvements in the quality of life for patients [47].

Because PD progresses slowly over a period of years to decades, patients often require extensive medical and home care, thereby placing an enormous burden on the individual, their families, and society that has been estimated to be on the order of $25 billion annually in the US alone [48]. Although a variety of therapies treat the motor features of PD, these treatments diminish in efficacy over time. Furthermore, they do not reverse the underlying biological defect, nor do they modify disease progression. Stem cell-based replacement therapies could therefore represent a revolutionary approach to slow, halt, or reverse many of the motor aspects of PD. In the long term, they might be the best path to a disease modifying therapy for this devastating neurodegenerative disorder.

WHERE HAVE WE BEEN? HISTORY OF CELL TRANSPLANTATION IN PD

The potential of cell-replacement therapies for significant long-term relief of PD symptoms without the need for continued pharmacological or surgical therapy provided the early rationale to conduct transplantation trials using fetal ventral mesencephalic (VM) tissue [49, 50]. The results from these studies will be critical for informing the design of clinical trials to assess the effectiveness of stem cell-based transplantation for PD.

Early open-label trials in Europe and the US showed substantial clinical improvement in some patients receiving fetal cell transplants grafted into the basal ganglia. Studies reported improved motor symptoms [51-55], improved ^{18}F-DOPA uptake [53-58] and robust, long-term graft survival and reinnervation of the grafted site in these patients [56, 59]. However, two placebo-controlled trials conducted in the US, known as the Colorado-Colombia (CC) and Tampa/Mount Sinai/Rush (TMR) trials, showed only modest benefit, if that [60, 61]. Of concern, a significant proportion of patients appeared to develop graft-induced diskynesias (GIDs) that persisted even in the absence of levodopa medication [60-62]. These results led to a halt of all cell therapy trials for PD.

Subsequent long-term evaluation of secondary endpoints by positron emission tomography (PET), ^{18}F-DOPA and UPDRS scoring, combined with stratification of patients by age and severity, showed a statistically significant benefit of fetal tissue transplantation for certain patient populations. Specifically, younger or less severely

affected patients who had been responsive to dopamine replacement therapy at the time of transplantation showed marked improvement starting 2–4 years after transplantation, in line with reports from the open-label trials [56, 63-66]. Details such as methods for tissue preparation, surgical technique, and immunosuppressive therapy seemed to have particular impact on the success of the intervention as did the nature of the primary end point chosen for use in the study.

In the end, the CC and TMR trials revealed the importance of patient selection, trial design and rigorous follow-up in clinical trials using cell-replacement therapies. In addition, the clinical endpoints chosen, particularly in the CC trial, were later realized to be problematic and revealed the importance of defining objective, quantifiable measures as primary endpoints that are assessed some time after surgery when the graft has had a chance to mature and integrate into the host brain. Furthermore, we now understand the importance of controlling the transplantation procedure itself, including surgical transplantation methods and immunotherapy, to assure successful outcomes. Finally, studies revealing that patients continued to improve years and even decades after transplantation of fetal VM tissue [63, 67, 68] underscores the importance of including long-term rigorous follow-up of patients to monitor ongoing changes and improvements in motor symptoms.

To reflect on these findings, the workshop discussed the current efforts to optimize clinical trial design for cell transplantation in PD. A European consortium, TRANSEURO, will conduct the first fetal cell transplantation study since the CC and TMR trials. The principal objective of TRANSEURO is to develop a safe, long-lasting, and efficacious approach to treating PD patients using fetal cell-based therapeutics that can serve as a template for future clinical trials, including those for other stem cell–based therapies. This clinical trial is being designed using a very tightly controlled approach to minimize procedural variables. It includes specific criteria for selection of the patients (defined age range, stage and type of PD), tissue preparation (specified number of cells grafted, standardized methods for tissue collection to assure a high percentage of DA neuroblasts and to limit the number of serotoninergic neurons), defined methods for tissue placement, graft support and improved trial design (number of patients, follow up time and endpoints). A very careful consideration of the discussions and analysis that have led to this new clinical trial has been reviewed elsewhere [69]. The primary endpoints for the clinical study are safety and motor effects, but the intent is to evaluate the effects of “tissue preparation and delivery, patient selection and immunosuppressive treatment” and to show that consistency and efficacy of DA cell replacement in PD can be improved by careful attention to those parameters (www.transeuro.org.uk). This study, informed by previous challenges and setbacks, will serve as a valuable resource to inform future stem-cell transplantation studies.

III. CHALLENGES AND OPPORTUNITIES IDENTIFIED IN THE WORKSHOP

A. THERAPEUTIC CANDIDATE PROFILE FOR STEM CELL THERAPIES

Stem cell-based replacement therapies could potentially provide lifetime reversal of many of the symptoms of PD. Given the availability of other therapeutic options for PD patients (L-dopa, enzyme inhibitors, dopamine agonists, DBS) and the risks incurred by surgery, in order to be clinically competitive, a DA cell therapy should provide long lasting, major improvement (>60-70%) of motor symptoms and suppression of dyskinesias. Participants of the workshop proposed the following therapeutic profile should be expected for an ideal candidate for a cellular therapy (see also Executive Summary for further detail):

- First, transplanted cells **must have the potential to recreate the characteristics of neurons lost to the disease**. The principal cell type lost in PD is the A9 DA neuron, found selectively in the SNc. Cell therapy should aim to replace this particular group of DA neurons, supported by *in vitro* and *in vivo* data in preclinical animal models. Candidate cells must express the features of authentic nigral A9 DA neurons, such as the right transcriptional and neurophysiological profile (i.e. pacemaker potentials), dopamine production and release in response to physiological stimuli and significant fiber outgrowth with synapse formation.

- Once transplanted into the right anatomical location, DA neurons **must survive, re-innervate the striatum and functionally integrate into the host's neural circuitry.** Therefore, rigorously defining and determining the number of cells required for successful implantation will be essential to achieving lasting survival and integration.

- Transplanted neurons **must provide measurable, biological outcomes** in terms of dopamine synthesis and regulated release upon physiological stimuli. The field must place emphasis on the development of potency assays to establish correlations between cell properties in vitro and predictive functional outcomes in vivo. The tools necessary to assess the survival and function of transplanted DA neurons are being developed, and some of these features must be inferred by analyzing the activity of the cells in culture and in large animal models.

- **Safety issues must be addressed:** (1) tumor formation; (2) graft induced dyskinesias (GIDs), either through the presence of serotoninergic neurons

hyperinnervating the striatum or uneven distribution of transplanted material in the target region; (3) host immunological reactivity to the grafted material; and (4) Inappropriate stem cell migration.

– Finally, the therapy **must result in the significant improvement of motor deficits** in patients that is robust and sustained over a period of years to decades.

The following sections highlight avenues of current development in stem cell research that were presented and discussed during the workshop and that directly or indirectly are contributing to development of cells with this therapeutic candidate profile.

B. TOOLS FOR MODELING PD *IN VITRO* (i.e., iPSCs in a dish).

The ability to create iPSCs from human skin biopsies has revolutionized the ability to model numerous neurodegenerative diseases *in vitro*. Models of Alzheimer's disease [70, 71], HD [72-75], ALS [76, 77], and autism [78, 79], among others, provide an experimental platform for researchers to investigate disease-specific phenotypes at the cellular and molecular level, which could provide invaluable insights for determining the underlying mechanisms of disease, and a cell culture system for screening for new therapeutic treatments.

However, significant challenges accompany this approach. For example, the ability to overcome clonal variability and minimize the genomic and phenotypic changes that cell lines present over passage and time. One of the proposed solutions for monogenic and genetically defined disorders is to generate isogenic control lines that harbor defined genetic alterations [80] through the use of advanced genome-editing technologies, including zinc-finger nucleases (ZFNs), transcription activator–like effector nucleases (TALENs), and clustered/regularly interspaced palindromic repeats (CRISPRs), specific sequences can be inserted into the cellular genome to introduce defined mutations (or mutation-corrected) sequences for study (reviewed in [78, 81]). By otherwise preserving all other genetic features of an hiPSC line, these technologies allow for superior experimental control and can be used to address the challenges associated with clonal variability.

In PD, recent studies using neural cell types derived from human LRRK2-G2019S hiPSCs have revealed increased expression of oxidative stress–response genes and alpha-synuclein protein [32], increased susceptibility to proteosomal [82] and oxidative [24] stress, as well as key genes and signaling pathways involved in *in vitro* pathogenesis [83] of the disease. Some of these studies have also shown how isogenic correction of this mutation could reverse several of the identified *in vitro* phenotypes [82, 83].

A different challenge that the field faced was the need for a repository of well characterized, publicly available and diverse hiPSC lines derived from genetic PD patients. In response, the NINDS PD iPSC Consortium (www.pdips.org) initiated the development of such a resource in 2009 [84]. The Consortium has already generated iPSCs from patients with disease-causing mutations for analysis of how cells with different PD-associated genotypes and phenotypes that respond to cellular stressors, such as oxidative stress. In addition, although it is unclear whether DA neurons from patients with sporadic PD exhibit the same cellular perturbations observed in genetic forms of the disease, hiPSC studies can provide an important framework for studying different types of PD. hiPSC models from patients with a diversity of genetic and idiopathic forms will be essential for extracting clinically meaningful information related to disease phenotypes and potential treatments. For example, promising neuroprotective molecules could be tested in patient-derived cells to identify an individual's responsiveness to a given therapy and understand mechanisms of disease. hiPSC-derived neurons could also be used to assess the efficacy of cell-based treatments *in vivo* and develop new targets for drug development. Studying these models might lead to new insights into the cellular defects underlying the death of SNc neurons in PD patients. Finally, hiPSC-based models can be used to optimize neuronal differentiation protocols (e.g., to generate the A9 SNc neurons needed for stem cell transplantation) and identify conditions that optimize cell survival.

These patient-derived lines can also provide a powerful tool for drug discovery. By grouping the genetic PD iPSC lines according to shared cellular phenotypes and the clinical features of the donor patients, this platform could be used for screening of small molecule libraries, to identify candidate drugs that modify specific phenotypes, thereby providing a tool to identify patients and at-risk cohorts who may be amenable to specific treatments. Expanding the resource to include data from idiopathic patient hiPSC lines may provide a means to extrapolate the findings to predict drug responsiveness for different cohorts of this sporadic disorder.

C. TECHNOLOGIES FOR STEM CELL TRANSPLANTATION

Recent advances in stem cell technologies, animal models of PD, and clinical tools will greatly facilitate the goal of stem cell-based therapies for PD. Although workshop participants were optimistic, highlighting a number of key breakthroughs in these areas, they also discussed the ongoing issues that must be addressed in order to make stem cell–based therapies a viable clinical option. These are summarized below.

***Stem cell source*:** Since the availability of fetal tissue is restricted, a range of cell sources suitable for generating midbrain DA (mDA) neurons has emerged in the past

two decades including *in vitro* expanded midbrain neural precursors [85-87] and various neural stem cell lines [88-90]. However, all these cell sources and strategies have disadvantages (reviewed in [91]). One is the limited potential of neural stem cell (NSC) lines to generate authentic mDA neurons. Thus, the group discussed the need for a stem cell source that offers access to the earliest stages of embryonic development (which would allow control of regional specification during their cell differentiation).

Human pluripotent stem cells may push the field in a new direction, as they provide an alternative source of cells for derivation of DA neurons for therapeutic application and can readily bypass some of the limitations inherent to NSCs [91, 92]. Importantly, translation of any stem cell-based candidate to the clinical setting will require evidence for efficacy, safety and long term functional efficacy in preclinical models of disease. Presently, both hiPSC- and hESC-derived sources are being developed as candidates for clinical application.

The history of derivation of mDA neurons provides an object lesson in the challenges inherent in achieving clinical application. Differentiation of this cell type from hESC was reported nearly a decade ago [22], however the field struggled with demonstrating *in vivo* functional engraftment of these cells. It was not until the development of floor plate-based neural differentiation protocols [93-95] that the field made a significant step forward towards the use of these cells for potential clinical cell therapies. Transplantation of these neurons results in robust *in vivo* survival and therapeutic benefit across rodent and primate PD models, demonstrating both therapeutic efficacy and scalability to large animal models [94].

This differentiation strategy is based on the direct conversion of ESCs to floor plate precursors that, upon exposure to Shh and Wnt signaling agonists, are efficiently converted to mDA neurons. Molecular profiling of these cells confirmed a developmental progression of hESCs consistent with the mDA lineage, whereby they correctly co-expressed the transcription factors Foxa2 and Lmx1a at the floor-plate precursor stage and Pitx3 and Nurr1 at later stages of differentiation [94].

This approach has been adopted by other labs, introducing variations and refinements that have lead to some interesting alternatives [93]. Participants felt that work in this area suggests that the floor plate protocol may have translational potential for the development of a candidate therapeutic DA cells for transplantation in humans.

Safety: For cell-based therapies to be a viable option for treatment of PD, a number of safety issues must be addressed in preclinical rodent and larger animal models. The major issues appear to be the risk of (1) tumor formation; (2) graft induced dyskinesias (GIDs), either through the presence of serotoninergic neurons hyperinnervating the striatum or uneven distribution of transplanted material in the target region [although it is extremely hard to mimic this problem in the lab]; (3) host immunological reactivity to the grafted material; and (4) inappropriate stem cell migration. Undifferentiated NSCs have

the capacity to undergo extensive migration from the site of transplantation to non-target sites of the brain through white matter tract. The propensity of stem cells to migrate may result in a theoretical risk that they could cause seizure-like symptoms or other brain dysfunction. The purification (and efficient differentiation) of cell populations to remove undifferentiated cells, together with methods that yield differentiated precursor cells with high efficiency, will significantly lower the risk for tumor formation and inappropriate migration. Purification to remove serotonergic cells or at least ensure that their numbers are low relative to midbrain DA neurons, as well as improved surgical methods for distributing cells within the putamen (discussed below) are likely to reduce the incidence of GIDs in patients. Finally, the immune responses to cell transplantation in the brain, particularly the effects of local inflammation on the viability of transplanted cells, are being evaluated [96]. However, it remains unclear how, and to what degree, the immune system contributes to the long-term viability of grafted material, a question that will be critical to address in the future. This having been said it is known that human fetal allografts can survive long term in the adult PD brain in the absence of continuous long term immunosuppression.

Sorting & Purification: *To what degree will cells need to be sorted and purified prior to transplantation?* The workshop discussed this consideration in a number of contexts. First, pluripotent stem cell–derived populations may pose a risk for tumor formation after transplantation, since they can contain undifferentiated or proliferating non-neuronal cells [97, 98]. Furthermore, there is preclinical evidence to suggest that sorted allogeneic cell populations display improved survival and engraftment with reduced incidence of tumor formation [99]. Some procedures are being developed for purifying DA neurons from mixed cultures [99] to remove undifferentiated stem cells and enrich for cells expressing late differentiation stage markers, but these differentially purified cell types will need to be systematically tested *in vivo*. Second, follow-up studies of patients treated with fetal tissue grafts revealed that GIDs could be caused, in part, by the presence of serotonergic cells or at least a high ratio of SER to DA neurons [68, 100, 101]. This suggests that purification to remove this cell type, and to further enrich for cell types that produce A9 DA neurons, is desirable. The effects of sorting and purification on cell transplantation efficacy are therefore an important future area of study.

Scale Up**:** A crucial consideration for the clinical application of these cell-based therapies is the scale-up of laboratory protocols to manufacturing processes that are reproducible and predictable, and produce large numbers of cells that are clinically effective, cost effective, and compliant with current Good Manufacturing Practices (cGMP). Furthermore, the development of strategies for large-scale 3D manufacturing that more closely mimic the native developmental environment are underway and advances have been made in the development of small-scale 3D approaches using engineered, chemically-defined biomaterials (reviewed in [102, 103]). Importantly, these

synthetic environments offer superior control over cell culture conditions while producing desired cell types with significantly improved efficiency, consistency and reproducibility (reviewed in [103]). It is likely that these bioengineered platforms, together with improvements in small-molecule and other non-integration-based methods for cell differentiation, will lay the foundation for future large-scale cell bioprocessing. This latter step will likely involve partners in industry, as most academic labs lack the resources for such large-scale manufacturing. Furthermore, an effort should be placed in establishing collaborations between biology and bioengineering labs as it will be necessary to rigorously characterize and test the cells produced using these methods in preclinical models of PD. Nonetheless, the progress initiated and achieved by academic labs has been impressive and will be essential to continue.

Animal models to evaluate cell therapy for PD: Preclinical studies in disease models of PD are required to better define the risk-benefit ratio associated with investigational cell therapy products. In addition, use of disease/injury models provides the opportunity for possible identification of activity-risk biomarkers that may be applicable for monitoring in clinical trials (FDA Draft Guidance of Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products (11/2012)). Animal models of PD are good models for motor deficits, and include neurotoxic models using compounds [(6-hydroxydopamine (6-OHDA), 1-methyl-1,2,3,6-tetrahydropyridine (MPTP), paraquat, or rotenone] that damage to the DA system, and genetic models that express mutations linked to PD in humans (reviewed in [104]). Neurotoxin-based models produced by 6-OHDA or MPTP administration are the most widely used toxic models, while paraquat and rotenone are more recent additions to the stable of toxic agents used to model PD but can be difficult to use. Unilateral injection of 6-OHDA has been shown to cause nigral DA neuron loss, depletion of dopamine, and behavioral deficits that can easily be quantified (such as abnormal rotational behavior in response to amphetamines). Easy behavioral evaluation makes the rodent 6-OHDA lesion the most commonly used animal model. Indeed, in the 1980's the 6-OHDA model was used to establish proof-of-principle for human ventral mesencephalic tissue transplantation [105]. However, 6-OHDA lesion does not recapitulate the clinical features of PD and does not recreate pathologies such as Lewy-like inclusions but is a sensitive model to assay DA nigrostriatal integrity. Furthermore, the comparatively small size of rodent brains makes addressing the issue of scalability challenging in rodents alone. Nonetheless, these model systems are very valuable as a first step towards establishing preclinical proof of concept for cell-replacement therapies.

A second lesion model, involves the administration of the neurotoxin MPTP [106], a compound that is selectively taken up by catecholaminergic, including DA neurons, and causes them to die. In primates, MPTP exposure leads to the hallmark behavioral characteristics of PD, including tremors, motor dysfunction, SNc DA neuron damage, and responsiveness of symptoms to L-DOPA treatment ([106]; reviewed in [107]).

Important early studies by Redmond and colleagues [108, 109] were the first to demonstrate the efficacy of ventral mesencephalic grafts in primate MPTP models of PD. Similar primate models have since been used to show that hESC-derived DA precursors, generated by the floor-plate method, can also efficiently engraft and produce long-lasting benefit [94]. MPTP administration in non-human primates is therefore an important model system to validate therapeutic efficacy and scalability of cell-replacement therapies for PD.

Evaluation of the efficacy of a candidate in preclinical studies was identified as a critical issue in the development of cell therapies. The correlation of DA cell loss and striatal innervation with performance in a variety of tests provides a useful tool for the evaluation of the *in vivo* efficacy and performance of stem cell-derived DA neuron preparations. The most commonly used tests are the drug-induced (apomorphine, amphetamine) rotation tests, and the spontaneous motor tests (cylinder and stepping). Those tests are usually performed in the severe unilaterally lesioned rat model of 6-OHDA. In order to show preclinical efficacy, workshop participants agreed that the candidate cell therapy must show complete (100%) reversal of drug-induced rotation 6 months after transplantation (assuming the cells have been left in situ long enough to fully mature). Moreover, the candidate should preferably be tested in two additional motor tests showing robust recovery of function. Criteria for animal inclusion and animal numbers should be very clearly delineated in the experimental protocols.

The lack of rigorous investigations into dose finding and early identification of possible side effects is another of the potential contributors to clinical failures in translational research. In the case of cell therapies for PD, the evaluation of potency can be considered a surrogate for efficacy measurements and will play a key role in defining the quality of the cellular therapy product. Presently, the field does not have appropriate predictive potency assays available and participants agreed that identifying assays to measure correlations between *in vivo* cell survival and predictive functional outcome should remain a developmental focus for laboratories working in PD. Ideally, potency assays should be in place for early clinical development, and validated assays will be required for pivotal clinical trials. Long term efficacy measures will need to be carefully chosen for clinical trials and the field needs to assess whether preclinical imaging, or other assays can predict long-term functional outcomes.

New tools for transplanting cells into the human brain: Another point of discussion during the meeting was the evolution of new tools for transplantation. Analysis of fetal transplant studies suggested that the surgical technique has a great impact in the survival and viability of cell grafts and the expression of GIDs [64, 110]. Improved surgical techniques first pioneered by Ivar Mendez and colleagues, in which grafted material is distributed evenly across the striatum, appear to reduce the incidence of GIDs while preserving therapeutic efficacy [111-114]. Some of the meeting members

presented their new developments in this area. Dr. Lim from UCSF described a new surgical tool, known as a radially branched deployment device, that evenly distributes multiple, small cell grafts over a large target region within a single transcortical penetration. There was significant enthusiasm about this tool at the workshop, as this surgical approach reduces the likelihood of trauma to other brain regions that can arise with multiple brain penetrations and separate injections. When formulated with materials compatible with functional real-time imaging, such as interventional MRI, radially branched deployment tools may offer an unparalleled ability to monitor the accuracy of targeting during the surgical procedure itself, thereby minimizing the risk of off-target injection and damage to other brain regions [115, 116]. Importantly, by facilitating the even distribution of cell grafts, this delivery platform is likely to reduce the risk of "hotspots" of graft innervation that are thought to influence the development of GIDs. However the currently available delivery devices used in transplant trials to date are still probably adequate as the theory of GIDs induced by hot spots comes from a study using a transfrontal delivery approach with noodles of tissue. The development of GIDs may have had as much to do with the overall approach as with the device employed to deliver the cells.

Research suggests that the extracellular environment critically affects cell survival and differentiation. Dr. David Schaffer also discussed research to develop synthetic bioactive materials that emulate the extrinsic environment. These materials could potentially increase the number and differentiation status of cells generated *in vitro*, and could also be transplanted with cells as a way of affecting their survival and integration into the brain. These extracellular matrix materials have not been tested in animal models yet. This represents another important area where collaboration between bioengineers and PD researchers may prove valuable.

New tools to evaluate disease progression and functional recovery: Functional neuroimaging techniques such as positron emission tomography (PET) have been important tools for assessing the neuropathology of PD and has helped in understanding the mechanisms responsible for the success or failure of grafting human fetal tissue in clinical trials (reviewed in [117]). During the workshop, one of the requirements that emerged for the success of a future cell therapy trial is an optimized functional imaging protocol. Although functional imaging cannot currently be used as a primary endpoint in clinical transplantation trials, if used appropriately, it can provide researchers with an additional valuable *in vivo* tool alongside clinical observations. Of these neuroimaging methods, radiotracer imaging of the nigrostriatal DA system using [^{18}F]-fluorodopa (^{18}F-DOPA) PET is among the best-accepted methods for monitoring disease progression [118]. A bottleneck in the field is the search for a ligand tagging a specific DA presynaptic terminal location that would allow identification of the survival and growth of the DA-rich graft. To date, ^{18}F-DOPA PET remains the standard for monitoring survival and growth of grafted DA cells. Studies have shown a strong

relationship between striatal dopamine deficiency as measured by ^{18}F-DOPA PET and the severity of motor symptoms (reviewed in [117]). However, it is not possible to quantitatively assess DA neuron number using this approach; therefore, the true relationship between tracer uptake and tissue biology remains imperfect [119]. Still, the ability of [^{18}F]-fluorodopa PET to monitor ongoing disease progression that accurately tracks with progression of motor symptoms makes this a usable and reliable biomarker for some aspects of disease progression and monitoring [119], albeit an expensive one.

IV. CONCLUSIONS AND RECOMMENDATIONS

As indicated at the beginning of this document in the Executive Summary, the workshop identified a series of critical initial steps to facilitate development of a Phase 1/ 2 clinical trial for stem cell therapy:

1. ***Define the cell source*:** Either hiPSCs or hESCs could be used in the first stem cell trial. hESCs provide a more beneficial commercial model as a single hESC line can be banked in large quantities to treat multiple patients. hiPSCs can be autologous or allogeneic. Ideally, pluripotent stem cell banks should be matched to patients to minimize immune effects. Experiments to evaluate the different cell sources are underway and several approaches are under investigation. Currently the effort is focused on prioritizing the different approaches and moving forward into clinical trials with the highest priority.
2. ***Choose a differentiation protocol that can produce functional authentic nigral A9 DA neurons:*** It will be critical to select a differentiation protocol that produces the right type of DA neuron, both *in vitro* and *in vivo* in animal models. The method of differentiation is currently being optimized in different laboratories. Purification of DA cells from other cells is also necessary in order to control the ratio of serotoninergic (SER) to DA neurons in graft preparations and avoid dyskinesias as well as to preclude tumor formation. Animal models should be used to optimize conditions for cell survival, integration and functional benefits to the animal.
3. ***Determine the minimal effective dose and the maximum feasible dose in large animal models:*** Preclinical experiments in large animal models should be conducted on the selected cell to optimize integration with existing neural circuitry and restoration of function. Although the number of cells required to replace the nigral cell loss is unclear, other cell therapy projects and fetal transplant experiments indicate that it is likely to be around 100,000 DA neurons, assuming they have the same innervation potential as fetal nigral dopamine cells.
4. ***Develop biological assays that predict in vivo functional activity and biological action:*** The likelihood of an effective approach for clinical application will increase if cells express the features of authentic nigral A9 DA neurons, such

as the right transcriptional and neurophysiological profile (i.e. pacemaker potentials), dopamine production and release in response to physiological stimuli and significant fiber outgrowth with synapse formation. Further research is needed to define additional biomarkers and develop potency assays that provide correlations between cell survival and predictive functional outcome.

5. ***Develop a consistent transplantation protocol that shows low risk of hemorrhage and no tumor formation:*** The first trial should involve bilateral transplantation into the putamen. The physician conducting the transplant would select the optimal method of transplantation, which may include the use of new transplantation devices, but the device for cell delivery is not thought to be a rate-limiting step for the phase 1/ 2 trial.
6. ***Select target patients for the Phase 1/2 trial:*** Given the results from the fetal transplants trials, it seems clear that the target patients should ideally be younger patients early in their disease course and responsive to oral dopamine replacement therapies.
7. ***Select outcomes and follow-up studies for Phase 1/2 trial:*** Most participants agreed that the patients must be followed for at least 3 years after transplantation. Outcome parameters should include a range of clinical measures along with MRI and PET.

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