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Direct delivery of gene- and cell-based therapies to the nervous system. Image-Guided Biologic Therapies: Neurosurgeons Innovating Treatment Excellence Summit summary

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Direct convective delivery of gene therapy (intraparenchymal perfusion) and cell-based (intraparenchymal cell injection) therapeutics in the central nervous system are rapidly growing approaches for the treatment of neurological disorders that were not previously correctable. Increasing utilization of these advanced therapeutics underscores new insights into the molecular biological mechanisms underlying neurological disorders, advances in viral vector/cell-based therapies, and innovations in delivery technology. Consistent with emerging treatment paradigms, widespread adoption will require understanding of the variables necessary for therapeutic success. Specifically, there are several potential barriers to consistent, effective, and widespread adoption of these therapies. These include preclinical and clinical trial development/implementation, training, technology harmonization, and reimbursement. To define and address these issues, international experts in nervous system drug delivery, gene therapy, and cell-based therapy convened two summits—Image-Guided Biologic Therapies: Neurosurgeons Innovating Treatment Excellence (IGNITE) I and II—to develop strategies to drive the field forward. Presentations and discussions focused primarily on treatments for neurodegenerative disorders, rather than pathologies such as stroke or tumor, and the following report summarizing findings from the summit meetings maintains this focus.

Summit Meetings

The inaugural IGNITE I Summit (August 23, 2023) working group included international experts in nervous system drug delivery, neurological disorders, functional neurosurgery, and coding/reimbursement, as well as related industry representatives. Summary reports from presentations defined focus areas and the group analysis was generated. These served as the basis for the strategic topics and planning for IGNITE II (March 16, 2024) across intraparenchymal gene and cell-based therapies. The barriers identified and recommendations generated at IGNITE II will form the basis of the defined goals to be developed by subcommittees within each emerging treatment paradigm.

Gene Therapy

Overview

Nervous System Gene Therapy. Gene therapy is the use of genetic material to biologically modify cells and/or organ targets for therapeutic effect.[1,2] As the genetic basis for neurological disorders is defined, new potent gene therapy targets have been identified. Gene therapy offers the

ABBREVIATIONS AAV = adeno-associated virus; AMA = American Medical Association; CPT = Current Procedural Terminology; CRO = contract research organization; ESC = embryonic stem cell; IGNITE = Image-Guided Biologics Therapies: Neurosurgeons Innovating Treatment Excellence; IND = investigational new drug; iPSC = induced pluripotent stem cell; MSC = mesenchymal stem cell; NSC = neural stem cell.

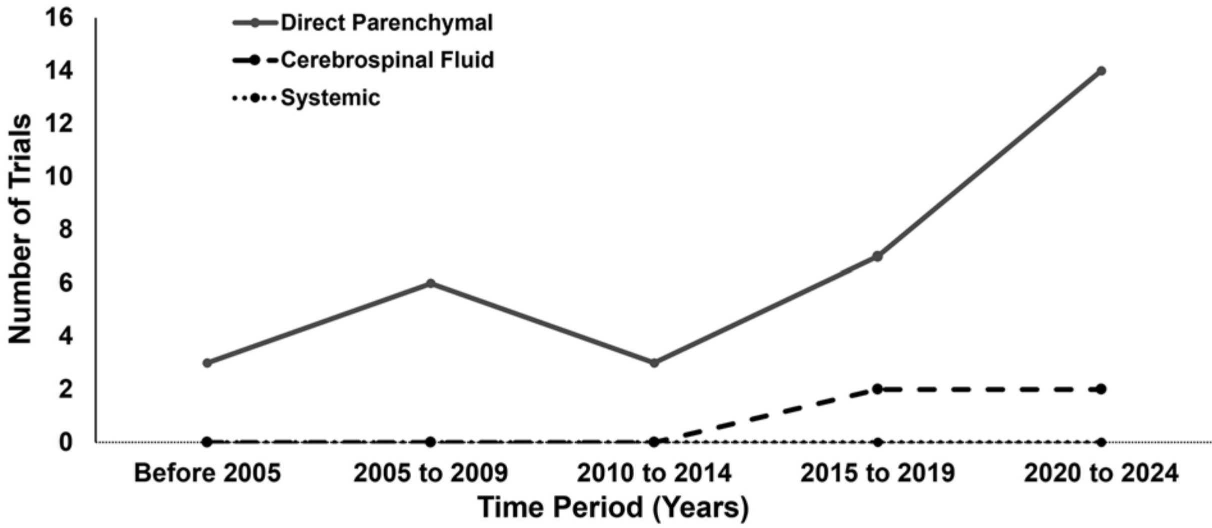

FIG. 1. Clinical trial initiation for gene therapy for neurodegenerative disorders as defined by method of delivery over time.

potential for permanent disease modification with a single treatment, most frequently using a viral vector carrying therapeutic transgenes delivered to a disease target. The rapid increase in gene therapy for neurological diseases has been driven by recent data that demonstrate the safety of this paradigm and that 80% (adeno-associated virus [AAV]–based gene therapy trials alone) of nervous system disease trials have met their primary efficacy endpoints.[2] Because the most frequently used (and growing) delivery method for nervous system gene therapy is convective intraparenchymal delivery of viral vectors carrying transgenes to specific targets, this was a focus of the IGNITE I and II Summit Meetings.

Convection-Enhanced Delivery. Because convective tissue perfusion is driven by bulk flow properties, it permits the interstitial targeted delivery of therapeutic infusate across the blood-brain barrier in a safe, homogeneous, and reliable manner.[3,4] Real-time MRI of a gadolinium-based agent coinfused during convective perfusion of nervous system structures can be used to accurately confirm cannula placement, ensure adequate target coverage, minimize/eliminate off-target infusion, and anatomically shape distribution (“infuse-as-you-go”),[5] as well as predict viral vector distribution and transgene expression.[6] Specifically, convective perfusion of nervous system targets with viral vectors carrying putative therapeutic genes has been used for gene therapy for a variety of disorders that are currently incompletely treated or untreatable with currently available medical and/or surgical paradigms, including neurodegenerative disorders, metabolic diseases, tumor, enzymatic deficiencies, and epilepsy.

Based on the delivery properties of convective delivery and the ability to image perfusion in real time (Video 1), convective delivery is the most common method used for viral vector distribution in nervous system gene therapy trials.[2,4]

VIDEO 1. Time-lapse video showing convection-enhanced delivery of AAV2-GDNF (glial cell line–derived neurotrophic factor) coinfused with gadoteridol into the right putamen via parietal trajectory. The cannula is progressively advanced anteriorly (deeper) during the infusion. The cannula depth and rate of infusion are adjusted “on-the-fly” to shape the volume of distribution with the goal of maximizing volumetric coverage of the putamen. © J. Bradley Elder, published with permission. Click here to view.

Overall, direct parenchymal delivery is used in 44% of all nervous system gene therapy trials, followed by intravenous (35%), intramuscular (13%), and cerebrospinal fluid (6%) delivery.[4] For neurodegenerative disorders specifically, direct parenchymal delivery is most common (Fig. 1). Among the ongoing and recent direct delivery trials listed in the US National Library of Medicine database (clinicaltrials.gov) that have approval from the US Food and Drug Administration (FDA) Center for Biologics Evaluation and Research, at least 61% use convective perfusion (Table 1).

AAV is the most common viral vector used in convective gene therapy (approximately 90% of clinical trials) and is capable of retro- and/or anterograde transport from the site of perfusion.[4] AAV is capable of transfecting nondividing cells with strong neuronal tropism. After AAV transfection, the transgene forms an extrachromosomal episome for gene transcription that does not integrate into the host genome. Transgene expression is durable for decades.[7]

Preclinical and Clinical Trial Development

Potential Limitations/Barriers. Because direct delivery of viral vectors for nervous system gene therapy is an emerging field with unique biological/therapeutic features, is being applied to a wide range of neurological disorders, and is a distinct surgical paradigm, it requires early multidisciplinary collaboration for therapeutic success. Delays or failure in the successful translation of viable gene therapy paradigms is often the result of lack of early involvement of expert multidisciplinary teams with independent investigators and/or industry partners to develop viable treatment paradigms (e.g., investigational new drug [IND]–enabling studies). Specifically, many

TABLE 1. Summary of central nervous system gene therapy clinical trials for neurodegenerative disorders

Disorder	NCT No.	Phase	Year	Transgene	Target	Viral Vector
Parkinson's disease	NCT03562494	1	2018	AADC	Putamen*	AAV2
Parkinson's disease	NCT03065192	1	2017	AADC	Striatum*	AAV2
Parkinson's disease	NCT04167540	1	2020	GDNF	Putamen*	AAV2
Parkinson's disease	NCT05822739	1	2023	Unclear	Unclear	Undefined
Parkinson's disease	NCT00252850[41]	1	2005	NTN	Putamen	AAV2
Parkinson's disease	NCT00985517[42]	1/2	2009	NTN	Putamen/SN	AAV2
Parkinson's disease	NCT01621581[43]	1	2013	GDNF	Striatum*	AAV2
Parkinson's disease	NCT05603312	1/2	2022	GAD	STN	AAV2
Parkinson's disease	NCT05894343	1/2	2023	GAD	STN	AAV2
Parkinson's disease	NCT00643890[44,45]	2	2008	GAD	STN	AAV2
Parkinson's disease	NCT03720418	1/2	2018	AADC, TH, GTPCH	Putamen*	LV
Parkinson's disease	NCT00195143[46]	1	2003	GAD	STN	AAV2
Parkinson's disease	NCT06285643	2	2024	GDNF	Putamen*	AAV2
Parkinson's disease	NCT01973543[11,12]	1	2013	AADC	Striatum*	AAV2
Parkinson's disease	NCT00627588	1/2	2008	AADC, TH, & GTPCH	Striatum*	LV
Parkinson's disease	NCT04127578	1/2	2020	GBA	Cisternal	AAV9
Parkinson's disease	NCT02418598	1/2	2015	AADC	Putamen*	AAV2
Parkinson's disease	NCT00400634[47]	2	2006	NTN	Putamen	AAV2
Parkinson's disease	NCT00229736[13,48]	1	2004	AADC	Putamen	AAV2
Alzheimer's disease	NCT00087789[9]	1	2004	NGF	Nucleus basalis of Meynert	AAV2
Alzheimer's disease	NCT00876863[10]	2	2008	NGF	Nucleus basalis of Meynert	AAV2
Alzheimer's disease	NCT05040217	1	2022	BDNF	Entorhinal cortex*	AAV2
Alzheimer's disease	NCT03634007	1/2	2019	Apolipoprotein E2	Intrathecal	AAVrh.10
Alzheimer's disease	NCT04133454	1	2019	TERT	Intrathecal	AAV
Frontotemporal dementia	NCT06064890	1/2	2023	GRN	Thalamus*	AAV9
Frontotemporal dementia	NCT04747431	1/2	2021	GRN	Cisterna magna	AAV1
Huntington's disease	NCT05541627	1/2	2022	Cholesterol 24-hydroxylase	Striatum*	AAVrh.10
Huntington's disease	NCT04120493	1/2	2019	miRNA targeting HTT mRNA	Striatum*	AAV5
Huntington's disease	NCT05243017	1/2	2021	miRNA targeting HTT mRNA	Striatum*	AAV5
Huntington's disease	NCT04885114	1	2021	miRNA targeting HTT mRNA	Putamen, thalamus*	AAV1
AADC deficiency	NCT01395641[49]	1/2	2014	AADC	Putamen*	AAV2
AADC deficiency	NCT02852213[50]	1	2016	AADC	SN/VTA*	AAV2
AADC deficiency	NCT02926066[49]	2	2016	AADC	Putamen*	AAV2
AADC deficiency	NCT04903288	2	2021	AADC	Putamen*	AAV2
AADC deficiency	NCT05765981	1	2023	AADC	Putamen	AAV9
AADC deficiency	NCT06432140	1	2024	AADC	Putamen	AAV9
Multisystem atrophy	NCT04680065	1	2023	GDNF	Putamen*	AAV2

AADC = aromatic L-amino acid decarboxylase; BDNF = brain-derived neurotrophic factor; GAD = glutamic acid decarboxylase; GBA = glucosylceramidase beta; GDNF = glial cell–derived neurotrophic factor; GRN = granulin; GTPCH = guanosine triphosphate cyclohydrolase; HTT = huntingtin; LV = lentiviral vector; miRNA = micro RNA; mRNA = messenger RNA; NCT = National Clinical Trial; NGF = nerve growth factor; NTN = neurturin; SN = substantia nigra; STN = subthalamic nucleus; TERT = telomerase reverse transcriptase; TH = tyrosine hydroxylase; VTA = ventral tegmental area.
* Indicates convection-enhanced delivery.

IND-enabling studies do not accurately mirror feasible and effective clinical trials due to the lack of critical expert input. Similarly, barriers to successful clinical trial implementation have been the lack of multidisciplinary expert participation into trial design and the infrastructure needed for execution.

Recommendations. To address potential barriers to successful preclinical and clinical trial advancement, the summit attendees developed critical recommendations. First, multidisciplinary teams of experts including neurosurgeons with convective perfusion expertise (and understanding of the biological features of gene therapy), clinician disease-specific experts, and scientists with critical understanding of viral vector biology need to engage investigators and/or industry partners early in the translation process (i.e., before IND-enabling studies). Second, dur-

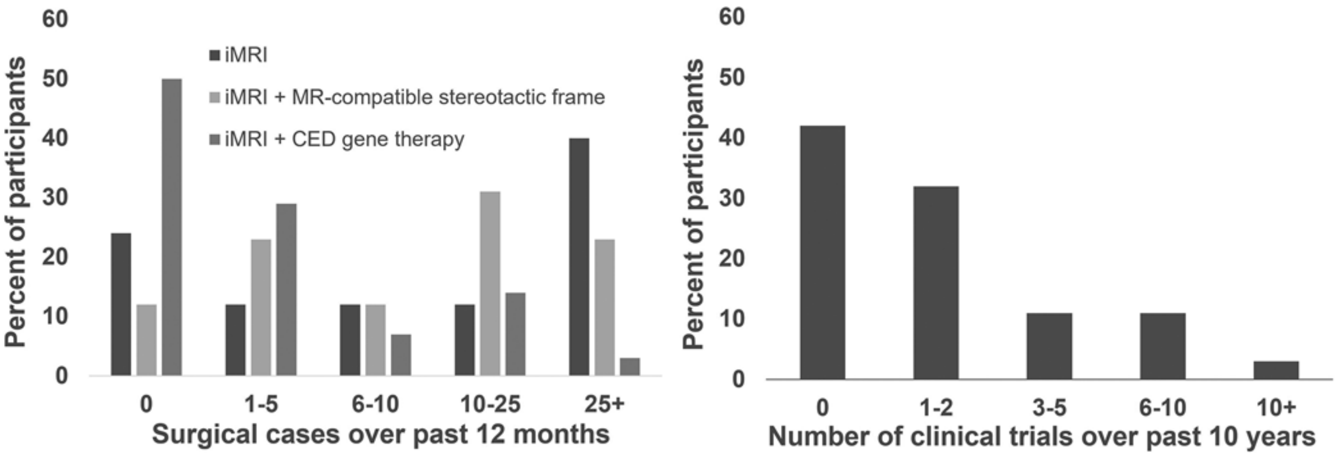

FIG. 2. Left: Self-reported experience with convective perfusion for gene therapy by neurosurgeons attending the IGNITE II Summit. Most respondents reported little or no experience with real-time image monitoring of convective delivery. The x-axis shows the number of cases over the prior 12 months, and the y-axis shows the percent of summit participants. **Right:** Institutional experience with convective perfusion for gene therapy clinical trials among respondents over the past 10 years. The x-axis shows the number of clinical trials over the 10-year period. The y-axis shows the percent of summit participants. CED = convection-enhanced delivery; iMRI = intraoperative MRI.

ing preclinical studies, prioritization of the understanding of the biological and surgical variables that optimize the biological effects of gene therapy should be employed, including therapeutic coverage, viral serotype, and delivery approach to target.[8] For example, a recent series of gene therapy clinical trials in Parkinson's disease describes an evolution toward improved surgical efficiency and target coverage using fewer trajectories and higher volume of infusate, which demonstrates the importance of continued evolution and optimization of the surgical paradigm.[8] Without direct input from experienced multidisciplinary experts, investigators/companies risk developing preclinical protocols that are not viable clinical trial designs. Third, because this is an emerging technique, contract research organizations (CROs) often lack the expertise to effectively implement the convection-enhanced delivery technique and are often unfamiliar with the associated technology. When a CRO is used for IND-enabling studies, it is important to engage neurosurgeon experts to assess and ensure that the surgical approach mirrors the clinical trial application in these regulatory investigations. Fourth, teams of experts (ideally the same team involved in preclinical trial design) will also be essential to clinical trial design and implementation. Finally, it is essential that the clinical trial sites possess expertise and infrastructure to perform these procedures successfully.

Surgical Training

Potential Limitations/Barriers. Clinical results from recent direct delivery gene therapy clinical trials in neurodegenerative disorders such as Parkinson's disease and Alzheimer's disease underscore the importance of the evolution of the surgical technique from small-volume stereotactic bolus injection[9,10] to MRI-guided convection-enhanced delivery and use of higher infusion volumes.[11–13] However, this more complicated surgical paradigm requires adequate training to achieve proficiency. The importance of surgical training is underscored by the results from the PRECISE study, in which the lack of therapeutic success was potentially attributable to surgeon experience and suboptimal catheter positioning.[14]

Convective delivery of gene therapy in the nervous system is a new surgical approach to the treatment of neurological disorders not typically operated by neurosurgeons (Fig. 2). It involves placement of a specially designed infusion cannula to nervous system targets using an MRI-compatible stereotactic frame. An infusion pump delivers the gene therapy infusate coinfused with gadolinium-DTPA (diethylenetriamine pentaacetate) via infusion tubing to the cannula and target. The shape and volume of distribution is monitored in real time with intraoperative MRI.[15,16] With the use of real-time image guidance, the cannula and infusion rate can be adjusted to conform the pattern of infusion to the shape of the target, avoid leak back, and minimize off-target perfusion.[5] Because the technique for convective perfusion is not routinely part of neurosurgical training and requires on-the-fly adjustments for optimal target perfusion, defined surgical expertise is critical for optimal outcome.

Recommendations. To ensure surgical training and the threshold experience needed for the successful implementation of convective delivery of gene therapy to the nervous system, the summit attendees developed the following recommendations. First, defining training requirements will help ensure that all surgeons participating in clinical trials have achieved and demonstrated a threshold level of experience to ensure uniformity in surgical outcomes. Training will need to include experience in key gene therapy technologies (i.e., intraoperative MRI, MR-compatible stereotaxis and infusion equipment) and observation of a minimum number of cases (defined by data from early trials). Second, after observing the defined number of cases, the surgeon will then complete a specified number of gene therapy cases with oversight by an experienced surgeon. Finally, continued assessment of expertise would include an annual minimum of gene therapy cases and assessment of surgical effectiveness measured by objective radiographic measures (target coverage).[17]

Technology Harmonization

Potential Limitations/Barriers. Convective delivery for gene therapy in the nervous system requires a stereotactic frame, infusion cannula, infusion pump, and MR scanner. Each technology was originally developed for other purposes and has been adapted for use in gene therapy, creating opportunities for innovation and harmonization. For example, infusion cannula design has evolved to incorporate reflux-resistant technology to reduce risk of backflow and allow higher infusion rates.[18] Also, MR scanners with a larger bore size (70 cm) reduce the risk of collision and increase freedom in patient positioning compared to smaller bore MR scanners. Because intraoperative MRI is used for delivery, MR-compatible stereotactic frames, infusion pumps, and cannulas are necessary.[14,19,20] These technologies need to be vector compatible for successful delivery. Unique institutional differences across technologies create potential for loss of consistency across a trial.

Recommendations. The summit attendees believe technology harmonization in gene therapy surgery can improve reliability when comparing data between sites and streamline surgical training. Although harmonization includes establishing minimum standards (e.g., intraoperative MR scanner field strength, vector-compatible infusion tubing/pumps, frameless MR-compatible stereotaxis, and MR bore size), it should include flexibility in noncritical variables if the goals of surgery are achievable. The IGNITE Summit participants concurred that real-time MR monitoring is critical to monitor infusions, optimize infusion distribution, enhance safety, and correlate outcomes with target coverage. However, the exploitation of technological advances (including other imaging technologies, robotics, and predictive software) in the future may significantly change operative workflow and eliminate or reduce the need for real-time MR monitoring.

Reimbursement

Potential Limitations/Barriers. Widespread adoption of new therapies will require defined coding and associated reimbursement. Although gene therapies can have potent therapeutic impact, gene therapy procedures for direct tissue perfusion can be lengthy, complex, and resource intensive. Currently, the only existing brain infusion codes that closely mirror gene therapy treatment (e.g., code 61517) involve implantation of chemotherapy in the brain and require brain tumor removal. Without a framework for adequate reimbursement, financial barriers could significantly limit widespread adoption of these treatments.

Recommendations. Summit attendees identified potential reimbursement options for direct delivery of gene therapy in the nervous system. One option could be the use of an American Medical Association (AMA) category III code. Category III codes are temporary codes used to track physician use of emerging techniques and technologies. A code requires a study protocol and support from applicable specialties, peer-reviewed literature, and data from prior studies. The AMA collects data to decide if a category III code should become a permanent Current Procedural Terminology (CPT) code. Another option could be to obtain an ICD-10 code for delivery to the nervous system. Previously, an ICD-9 code was approved (2006) for stereotactic creation of burr holes for placement of a therapeutic agent. However, a CPT code was not issued because there were no approved therapies and no relative value units were assigned due to the lack of procedural data. Another possible reimbursement pathway is the application for the FDA breakthrough therapy designation. This mechanism streamlines the steps for a product to achieve market clearance and can accelerate the reimbursement process. Finally, other FDA mechanisms that can expedite approval of therapeutics and reimbursement decisions include priority review, accelerated approval, regenerative medicine advanced therapy designation, and fast track.

Cell-Based Therapy

Overview

Nervous System Cell–Based Therapy. Cell-based therapy in the nervous system involves implantation of therapeutic cells directly in the parenchyma, systemic circulation, or cerebrospinal fluid. Nervous system cell–based therapies are used to treat neurodegenerative disorders, metabolic diseases, traumatic brain injury, stroke, and tumor. Central nervous system cell–based trials have used cells that can potentially integrate into neural circuitry for repair, neuroprotection, and/or restoration.[21–24] Recently, cell-based nervous system trials have focused on the treatment of neurodegenerative disorders (Fig. 3). Specifically, Parkinson's disease trials represent 49% of all cell-based therapies, and 89% of these disease-specific trials employ direct parenchymal injection of cells. This trend reflects advancements in understanding of mechanisms of cell therapy, improved stem cell production, and enhancements in direct cell delivery to the nervous system.[25]

Therapeutic Cells. Various pluripotent cells have been investigated for potential roles in neurological restoration and/or other therapy, including neural stem cells (NSCs), embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and multipotent mesenchymal stem cells (MSCs).[25] NSCs are derived from embryonic or human brain tissue (fetal or adult) and differentiate into nervous system cells, including neurons and astrocytes. ESCs are derived from blastocysts, and iPSCs are derived from reprogrammed human tissue. ESCs and iPSCs can differentiate into all somatic cell types.[26,27] MSCs are derived from reprogrammed adult tissues. They can differentiate into specific cell types including hepatocytes, adipocytes, osteoblasts, and neurons.[27] MSCs, ESCs, and iPSCs have a high risk of tumor formation compared to NSCs.

Delivery of Cell-Based Therapy. Cell-based clinical trials involve systemic, intraventricular/intrathecal, and direct parenchymal delivery methods.[28,29] Although systemic and intrathecal delivery of cell therapies are less invasive, the distribution of cells is not efficient due to blood-brain/cerebrospinal fluid barriers, dilutional effects of

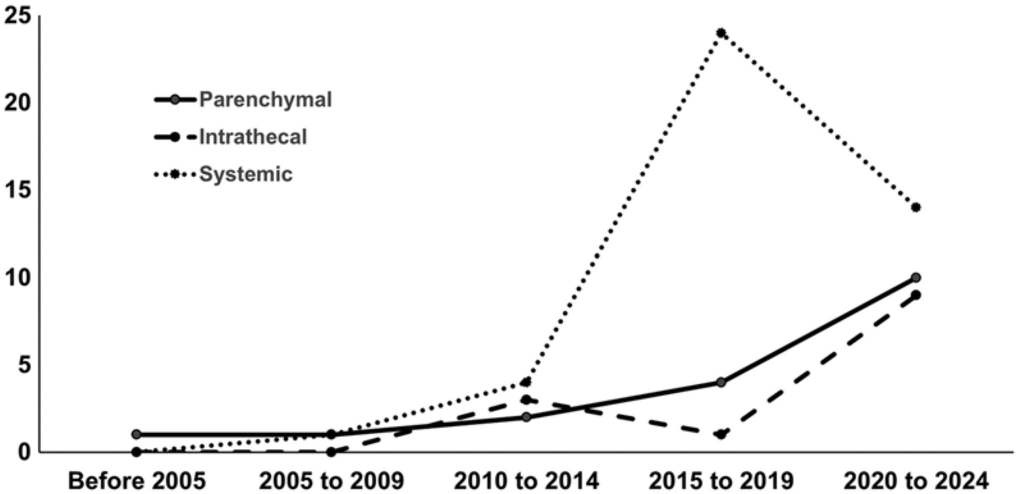

FIG. 3. Clinical trial initiation for cell-based therapies for neurodegenerative disorders as defined by method of delivery over time.

blood/cerebrospinal fluid, and lack of targeted placement into disease neural circuits.[30] While most (58%) cell-based trials for neurodegenerative disorders utilize intravenous delivery, direct brain (24%) and intrathecal/intraventricular (18%) delivery are becoming more common (Fig. 3). MSCs are the most frequently (70% of clinical trials) used cell type and are delivered using systemic (75%), cerebrospinal fluid (19%), or direct intraparenchymal (6%) routes. Recently (last 4 years), 60% of cell-based trials have used ESCs, NSCs, or iPSCs for neurodegenerative disorders, and 92% of these trials used direct parenchymal delivery (Table 2).

A critical component of cell-based therapy is immune suppression to mitigate graft-host response.[31] Intraparenchymal cell survival is compromised by infiltration of T cells, B cells, and natural killer cells and the immune response to the trauma associated with surgical delivery cells.[32] Further work is ongoing to define the optimal immunosuppressive regimens after transplantation.

Preclinical and Clinical Trial Development

Potential Limitations/Barriers. Because the direct intraparenchymal delivery of therapeutic cells is increasing rapidly, development of clinical trials that employ optimized cell production/handling, surgical technique, and immunosuppression are critical. Unlike direct delivery of viral vectors for gene therapy, transplanted stem cells are sensitive to delivery-associated mechanical injury. Because implanted stem cells do not migrate significantly from the implantation site, target selection and total target number are carefully determined. Posttransplant cell survival is impacted by the host immune response and requires mitigation via immune modulating medications and/or the use of autologous iPSCs. Finally, clinical trial design will account for the 3D connections and architecture of the targeted brain region.[33,34]

Because direct delivery of cell-based therapies is an emerging field with unique biological/therapeutic/surgical features applied across a wide range of neurological disorders, it requires multidisciplinary collaboration. Like gene therapies, delays or failure in the successful translation of viable cell-based therapy paradigms is often the result of the lack of early involvement of expert multidisciplinary teams with independent investigators and/or industry partners to develop viable treatment paradigms. Often IND-enabling studies do not accurately mirror feasible and effectively designed clinical trials due to the lack of expert input. Barriers to successful clinical trial implementation have often been due to the lack of multidisciplinary expert participation in trial design and the infrastructure needed for execution.

Recommendations. To best address potential barriers to successful preclinical and clinical trial advancement, the summit attendees developed the following recommendations. First, multidisciplinary teams of experts including neurosurgeons with cell-based delivery expertise (including biological understanding of pluripotent cells), neuroimmunologists, disease-specific experts, and stem cell scientists need to engage investigators and/or industry partners early in the translation process (i.e., before IND-enabling studies). Second, during preclinical studies, prioritization of understanding of the biological and surgical variables that optimize the biological effects of cell-based therapies should be employed, including immunosuppression, cell viability, and delivery.[8] Third, because this is an emerging technique, CROs often lack the expertise to effectively implement cell-based therapy techniques and are often unfamiliar with the associated technology. When a CRO is used for IND-enabling studies, it is important to engage neurosurgeon experts to assess and ensure that the approach matches the clinical trial application. Fourth, teams of experts (ideally the same team involved in preclinical trial design) will also be essential to clinical trial design and implementation. Finally, it is essential that clinical trial sites possess expertise and infrastructure to perform these procedures successfully.

Surgical Training

Potential Limitations/Barriers. Because cell-based nervous system therapies are emerging, typically neuro-

TABLE 2. Summary of central nervous system cell–based therapy clinical trials for neurodegenerative disorders

Disorder	NCT No.	Phase	Start	Target	Cell Type
Parkinson's disease	NCT01860794	1/2	2013		NPC
Parkinson's disease	NCT03550183	1	2018	IV	MSC
Parkinson's disease	NCT05887466	1/2	2023	Putamen	ESC
Parkinson's disease	NCT04506073	2	2020	IV	MSC
Parkinson's disease	NCT00976430	NA	2009	Striatum	MSC
Parkinson's disease	NCT05901818	1	2023	Striatum	NPC
Parkinson's disease	NCT05435755	1	2022	Ventricle	ESC
Parkinson's disease	NCT04414813	1	2020	Ventricle	ESC
Parkinson's disease	NCT05691114	1	2023	Ventricle	ESC
Parkinson's disease	NCT04802733	1	2021	Putamen	ESC
Parkinson's disease	NCT06145711	NA	2023	Gpi	iPSC
Parkinson's disease	NCT02611167	1	2017	IV	MSC
Parkinson's disease	NCT01453803	NA	2014	IV & intranasal	MSC
Parkinson's disease	NCT05699161	1/2	2021	Face	MSC
Parkinson's disease	NCT03309514	1/2	2022	Basal ganglia	NSC
Parkinson's disease	NCT03119636	1/2	2017	Striatum	ESC
Parkinson's disease	NCT02369003[51]	1	2015	STN, SN, putamen, basal forebrain	Peripheral nerve
Parkinson's disease	NCT06142981	NA	2019	IV	PRP & VSEL
Parkinson's disease	NCT04146519	2/3	2017	IV	MSC
Parkinson's disease	NCT03815071	1	2019		iPSC
Parkinson's disease	NCT05152394	1	2022	IV	MSC
Parkinson's disease	NCT06056427	NA		IV	MSC
Parkinson's disease	NCT03684122	1/2	2018	IV	MSC
Parkinson's disease	NCT04772378	NA		IV	MSC
Parkinson's disease	NCT04928287	2	2021	IV	MSC
Parkinson's disease	NCT04995081	2	2021	IV	MSC
Parkinson's disease	NCT05635409	1	2022	Putamen	ESC
Parkinson's disease	NCT02780895	1	2014	Putamen	NPC
Parkinson's disease	NCT05094011	1	2025	Striatum	MSC
Parkinson's disease	NCT01446614	1/2	2011	IV	MSC
Parkinson's disease	NCT06167681	1/2	2024	Striatum	iPSC
Parkinson's disease	NCT06482268	1	2024	Putamen	iPSC
Parkinson's disease	NCT03128450	2/3	2017	Intranasal	NSC
Parkinson's disease	NCT02538315	NA	2016		NSC
Parkinson's disease	NCT06141317	1/2	2023	IV	MSC
Parkinson's disease	NCT04928287	2	2021	IV	MSC
Parkinson's disease	NCT06422208	1	2024	Putamen	iPSC
Parkinson's disease	NCT02452723	1	2016	Striatum, SN	NSC
Huntington's disease	NCT01834053	1/2	2014	Intrathecal	MSC
Huntington's disease	NCT02728115	1	2017	IV	MSC
Huntington's disease	NCT04219241	2/3	2020	IV	MSC
Huntington's disease	NCT03252535	2	2018	IV	MSC
Huntington's disease	NCT06097780	3	2024	IV	MSC
Huntington's disease	NCT03724136	NA	2018	IV	MSC
Huntington's disease	NCT00190450[52]	2	2002	Striatum	NPC
Alzheimer's disease	NCT02899091	1/2	2016	IV	MSC
Alzheimer's disease	NCT04040348	1	2019	IV	MSC
Alzheimer's disease	NCT02672306	1/2	2017	IV	MSC
Alzheimer's disease	NCT04228666	1/2	2020	IV	MSC

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TABLE 2. Summary of central nervous system cell–based therapy clinical trials for neurodegenerative disorders

Disorder	NCT No.	Phase	Start	Target	Cell Type
Alzheimer's disease	NCT05016427	1	2020	IV	Treg
Alzheimer's disease	NCT05667649	1	2023	Intraventricular	MSC
Alzheimer's disease	NCT04482413	2	2023	IV	MSC
Alzheimer's disease	NCT03117738	1/2	2017	IV	MSC
Alzheimer's disease	NCT03724136	NA	2018	IV	MSC
Alzheimer's disease	NCT02795052	NA	2016	IV, intranasal	MSC
Alzheimer's disease	NCT03899298	1	2019	IV, intranasal	MSC
Alzheimer's disease	NCT01297218[53]	1	2011	brain	MSC
Alzheimer's disease	NCT02833792	2	2016	IV	MSC
Alzheimer's disease	NCT02600130	1	2016	IV	MSC
Alzheimer's disease	NCT04855955	NA			MSC
Alzheimer's disease	NCT04954534	NA	2021	Intraventricular	MSC
Alzheimer's disease	NCT02054208[54]	1/2	2014	Intraventricular	MSC
Alzheimer's disease	NCT03172117[54]	1/2	2017	Intraventricular	MSC
Alzheimer's disease	NCT02912169	1/2	2015	IV, intranasal	MSC
Alzheimer's disease	NCT01547689	1/2	2012	IV	MSC
Alzheimer's disease	NCT03117738	1/2	2017	IV	MSC
Alzheimer's disease	NCT04388982	1/2	2020	Intranasal	MSC
Alzheimer's disease	NCT03297177	NA	2020	IV	MSC
Multisystem atrophy	NCT05167721	2	2021	Intrathecal	MSC
Multisystem atrophy	NCT05698017	1/2	2022	Intrathecal	MSC
Multisystem atrophy	NCT02315027[55]	1/2	2012	Intrathecal	MSC
Multisystem atrophy	NCT02795052	NA	2016	IV, intranasal	MSC
Multisystem atrophy	NCT04876326	NA	2020	Intrathecal	MSC
Multisystem atrophy	NCT00911365	2	2008	Arterial	MSC
Multisystem atrophy	NCT03265444	1	2018	Arterial	MSC
Frontotemporal dementia	NCT05315661	1	2022	Intraventricular	MSC
Frontotemporal dementia	NCT02795052	NA	2016	IV, intranasal	MSC

Gpi = globus pallidus internus; IV = intravenous; NA = not applicable; NPC = neural progenitor cell; PRP = platelet-rich plasma; Treg = regulatory T cell; VSEL = very small embryonic-like stem cell.

surgeons are unfamiliar with the surgical approach required for direct delivery of therapeutic cells in the central nervous system.[35] The procedure includes highly specialized handling and targeted injection of cells to the brain. Unlike convective perfusion of viral vectors in gene therapy, cells are often delivered as a series of deposits along a cannula track.[36] Critical for the successful intraparenchymal delivery of cells to specific brain targets is accurate delivery and cell survival. The surgical implantation process has several challenges, including the sensitivity of cells to mechanical injury. The delivery device materials that the cells are exposed to during infusion also directly impact survivability. Columnar injection, in which cells are deposited into the cannula track as the cannula is removed, reduces cellular trauma and enhances survival.[37]

Recommendations. To ensure surgical training and the threshold experience needed for the successful implementation of direct injection of cell-based therapies to the nervous system, the summit attendees developed the following recommendations. First, defining training requirements will help ensure that all surgeons participating in clinical trials have achieved and demonstrated a threshold level of experience to ensure uniformity in surgical outcomes. Training will need to include experience in key cell-based therapy technologies (e.g., intraoperative stereotaxis, injection equipment) and an observation of the minimum number of cell-based therapy cases. Second, after observing the defined number of cases, the surgeon will then complete a specified number of cell-based therapy cases with oversight by an experienced surgeon. Finally, continued assessment of expertise would include an annual minimum of cell-based therapy cases and assessment of surgical effectiveness measured with objective measures (imaging and/or clinical).

Technology Harmonization

Potential Limitations/Barriers. The summit attendees noted that successful cell-based therapies will incorporate resource-intensive technologies to develop and differentiate stem cells, need to have quality control testing performed and timing of delivery defined, and precisely deliver cells to target structures with minimal surgical trauma. Cell-based therapies require a stereotactic frame and injection cannula. Unlike direct infusion gene therapy, an intraoperative MR scanner is not needed for cell-based therapies. Each technology used in cell implantation was originally developed for other purposes and has been adapted for use in cell-based therapies, creating opportunities for innovation and harmonization. These technologies need to be optimized for cell survival for successful delivery. Unique institutional differences across technologies create potential for loss of uniformity and result interpretation across a trial. To optimize the opportunity for successful trial implementation, it will be critical to harmonize technology across centers.

Recommendations. For direct brain delivery of cell therapies, summit participants felt that near-term harmonization efforts should focus on establishing minimum specifications for surgical devices (e.g., cannula), optimization of surgical protocols (number of trajectories per target, number of cell deposits, timing of injections, flow rates), and development of immune suppression protocols, as well as developing a consensus for ideal surgical outcome related to the anatomical distribution of cells delivered and their survival.[38] Consensus is needed regarding primary endpoints, duration, and long-term follow-up for neurological outcome and immune suppression in clinical trials. Methods for immune suppression may influence the surgical devices used to deliver cells, thereby informing preferred technology. Ultimately, defining the specific goals of cell delivery surgery and better understanding of optimal immune suppression will allow development of a standardized surgical platform that can be more broadly deployed in clinical trials.

Simultaneously, the need for ongoing innovation was recognized, and harmonization should coexist with flexibility for incorporating novel surgical strategies and improved devices. For example, needle trajectories traversing the long axis of a structure may improve clinical outcomes due to the higher number of cells delivered across a larger volume of the target. Early work delivering embryonic dopamine neurons for Parkinson's disease described delivery along the long axis of the putamen, foreshadowing future shifts in approaches to gene therapy drug delivery.[39] However, the potential benefit of increasing cells delivered to the target and target coverage are not clear and any benefits may be outweighed by increased neuroimmune response to trauma associated with longer needle tracks. Similarly, alternative catheter designs with potential for increased spatial distribution of cells without additional needle trauma should be studied.[40]

Reimbursement

Widespread adoption of new cell-based therapies will require defined coding and associated reimbursement. While cell-based therapies can have potent therapeutic impact, direct cell implantation procedures can be lengthy, complex, and resource intensive. Coding and reimbursement barriers and recommendations to address these barriers are similar to gene therapy.

Direct convective perfusion for nervous system gene therapy and injection of cell-based therapies represent potentially transformative neurosurgical platforms to treat neurological disorders that were not previously treatable. To fully realize the potential of these treatment paradigms, it will be critical to address the barriers to consistent, effective, and widespread adoption of these therapies, including preclinical and clinical trial development/implementation, training, technology harmonization, and reimbursement.

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Supplemental Information

Videos

Video 1. https://vimeo.com/1058275861.

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