

## Devices for cell transplantation into the central nervous system: Design considerations and emerging technologies

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### Abstract

Successful use of cell-based therapies for the treatment of neurological diseases is dependent upon effective delivery to the central nervous system (CNS). The CNS poses several challenges to the delivery of cell-based therapeutics, including the blood-brain barrier, anatomic complexity, and regional specificity. Targeted delivery methods are therefore required for the selective treatment of specific CNS regions. In addition, CNS tissues are mechanically and physiologically delicate and even minor injury to normal brain or spinal cord can cause devastating neurological deficits. Targeted delivery methods must therefore minimize tissue trauma. At present, direct injection into brain or spinal cord parenchyma promises to be the most versatile and accurate method of targeted CNS therapeutic delivery. While direct injection methods have already been employed in clinical trials of cell transplantation for a wide variety of neurological diseases, there are many shortcomings with the devices and surgical approaches currently used. Some of these technical limitations may hinder the clinical development of cell transplantation therapies despite validity of the underlying biological mechanisms. In this review, we discuss some of the important technical considerations of CNS injection devices such as targeting accuracy, distribution of infused therapeutic, and overall safety to the patient. We also introduce and discuss an emerging technology – radially branched deployment – that may improve our ability to safely distribute cell-based therapies and other therapeutic agents to the CNS. Finally, we speculate on future technological developments that may further enhance the efficacy of CNS therapeutic delivery.

**Key Words:** Cell transplantation, Parkinson's disease, radially branched deployment, stereotactic injection

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### INTRODUCTION

In animal models of a wide variety of neurological disorders – including Parkinson's disease (PD), epilepsy, stroke, and spinal cord injury – cell transplantation to the central nervous system (CNS) has led to significant

improvements in neurological function.<sup>[2,30,46,65]</sup> The success of these preclinical studies has been a result of our ability to produce appropriate cell types for specific pathological conditions and effectively distribute the cells to the target location. While much effort has been expended testing neural cell transplantation in animal

models of disease and producing relevant human cell types in appropriate quantities, there has been limited development of tools and techniques that facilitate the surgical delivery of cell-based therapies. Over the past two decades, preclinical animal studies have been translated into clinical trials testing cell transplantation for a multitude of CNS disorders including PD,<sup>[27,40,59,71]</sup> Huntington's disease,<sup>[6-8,11,26,29,33,49,62,64,69]</sup> stroke,<sup>[15,39,70,77]</sup> spinal cord injury,<sup>[2,25,34,37,48,58,84]</sup> amyotrophic lateral sclerosis (ALS),<sup>[22,50,67]</sup> Alzheimer's disease,<sup>[80]</sup> and malignant gliomas.<sup>[73]</sup> To date, most cell therapies have been delivered to the human brain or spinal cord with a stereotactically inserted straight cannula. While straight cannula transplantation has been effective for small animal experimental models, this cell delivery method falters when scaled up for human therapy. There is a growing recognition that current cell transplantation tools and techniques have substantial shortcomings that may compromise clinical translation.<sup>[14,17,51]</sup> Notably, the variable clinical outcomes observed in two double-blind, sham surgery-controlled transplantation trials for PD<sup>[27,59]</sup> have been partially attributed to a failure to properly distribute cells to the target region.<sup>[24,45]</sup> Our current inability to recapitulate the efficient cell distribution achieved in preclinical models may precipitate the failure of ongoing and future clinical trials despite validity of the underlying biological mechanisms. In this review, we first discuss some of the fundamental challenges with cell delivery to the human CNS. These difficulties include the blood-brain barrier (BBB), the anatomical complexity to the brain and spinal cord, the need for delivery to specific regions, and the delicate nature of CNS tissue. We also discuss issues inherent to the cellular therapeutics themselves, such as their lack of diffusion through CNS tissues. Next, we summarize current cell delivery devices and discuss some of their technical limitations as well as introduce an emerging technology – radially branched deployment – that may provide a solution to many of these shortcomings. Finally, we speculate on what future technologies may be required to close this clinical-translational gap.

## CHALLENGES OF CELL DELIVERY TO THE CENTRAL NERVOUS SYSTEM

For cell-based therapies, successful translation of preclinical research into clinical practice requires a means of cell delivery effective at the scale of the human patient. For some organ systems, innovation of new approaches is not required. For example, hematopoietic stem cells are generally delivered to human patients via intravenous (IV) infusion, the same route used in early rodent studies. However, unlike the “liquid organ” of blood, the CNS does not present such convenient access for cell delivery or an environment permissive for cell distribution by diffusion and hemodynamics. The BBB

is a major physiological obstacle to cell delivery from the intravascular compartment. In general, the BBB severely restricts the passage of charged molecules, proteins, viral particles, and cells.<sup>[9,60]</sup> Under normal conditions, only certain immune cell types are able to cross the BBB and enter the CNS.<sup>[1]</sup> Reports of CNS delivery of bone marrow-derived stem cells after IV infusion have been controversial,<sup>[5,16,53,78,83]</sup> and this route is unlikely to achieve clinical utility. While the administration of certain osmotic agents such as mannitol can partially disrupt the BBB, this strategy has been useful only for increasing permeability to pharmacological agents, such as chemotherapy.<sup>[60]</sup> Intrathecal or intraventricular injections bypass the BBB by placing cells in the cerebrospinal fluid (CSF) compartment. Interestingly, this route of administration has been sufficient to produce benefit in various animal models of neurological disease, such as multiple sclerosis<sup>[10]</sup> and stroke.<sup>[44]</sup> Many forms of cell-based therapies have been administered by intrathecal injection,<sup>[35,47]</sup> but it is unclear whether this cell delivery approach is clinically efficacious. There are perhaps circumstances in which this route of delivery is adequate, such as if implanted cells act by secreting neurotrophic or immunomodulatory factors instead of direct incorporation into the CNS. However, intrathecal or intraventricular injections will not likely enable cell engraftment into specific CNS regions. Similarly, intraarterial delivery methods have been investigated as a way of targeting cell-based therapies to ischemic regions for the treatment of stroke.<sup>[28,54]</sup> Such an approach, however, is limited to specific vascular territories (which may include non-target regions) and may also depend upon a disrupted BBB. Thus, with current technologies, cell transplantation to specific CNS regions in general requires some form of direct injection into the neural tissue.

## THE STRAIGHT CANNULA: DIFFICULTIES SCALING UP TO HUMAN THERAPY

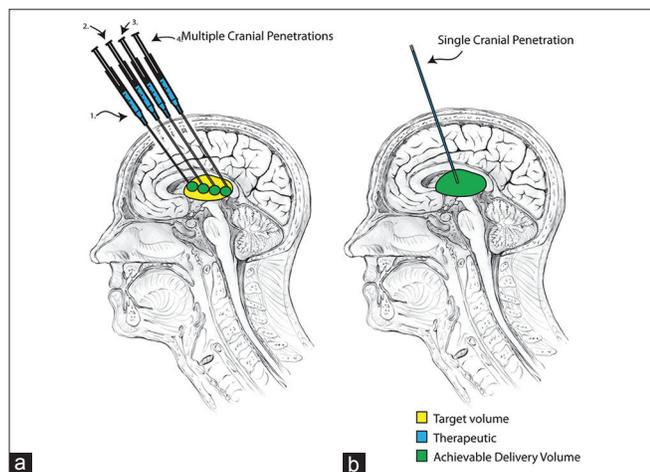
In preclinical animal studies, transplanted cells are usually delivered into the brain or spinal cord with a stereotactically guided straight cannula or needle. In general, this cannula is coupled to some form of syringe used to dispense a cellular suspension. For the small brain targets of rodent preclinical models, a single, small volume injection per hemisphere is often sufficient to achieve a therapeutic effect. However, the human brain is over 2000 times larger than that of the mouse. This vast difference in scale creates a fundamental problem with the straight cannula transplantation strategy. To enable transplantation to larger target volumes, cell distribution performed with a straight cannula can be increased by making multiple injections – both along a single needle tract and through adjacent brain penetrations [Figure 1]. To facilitate this basic strategy, Breeze, *et al.*<sup>[18]</sup> developed

a template containing a  $2 \times 9$  array of holes that guide insertion of an injection cannula. This template was mounted to a stereotactic head frame and aligned to guide cannula insertions along the anterior–posterior axis of the putamen. Transplantation was accomplished by simultaneously retracting the cannula and depressing the plunger of the attached syringe. Grafts were thus deposited over a distance of 10 mm. A buffered saline solution was then injected over the next 10 mm to prevent grafted tissue from being pulled upward as the cannula was withdrawn. Similar multiple transcortical brain penetration transplantation strategies have been used for a wide range of clinical trials.<sup>[5,27,33,40,59,70,80]</sup> In one previous clinical trial, some patients with PD had received a total of 16 separate transcortical penetrations for transplantation to the putamen.<sup>[18,27]</sup> This relatively large number of brain penetrations is a cause for concern, as each cannula “pass” through brain parenchyma carries a risk of intracranial hemorrhage, which is the most serious complication associated with this type of procedure. Hemorrhage rates associated with deep brain stimulation (DBS) lead placement are dependent upon location but typically range from <1 to <5%, with up to half of such procedure-related hematomas causing permanent neurological deficits.<sup>[12,13,85]</sup> While the one report of intraoperative hemorrhage associated with cell transplantation for PD did not result in any apparent neurological injury, it did prevent completion of the cell transplantation for that patient.<sup>[52]</sup> A device that minimizes the number of cortical penetrations for a given target volume could therefore reduce the

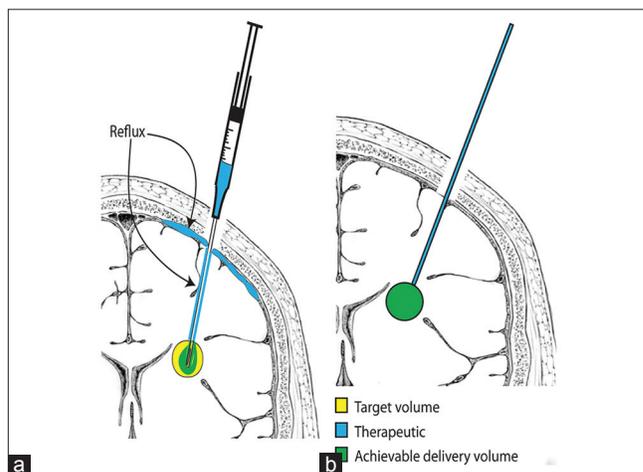
morbidity associated with cell transplantation to the CNS [Figure 1]. Another approach to translational scale-up has been to deliver a very large number of cells to a single location or along a short segment of the cannula tract.<sup>[72]</sup> Unfortunately, the transplantation of a large mass of cells can severely impair graft viability. In a study of myoblast transplantation, increasing cellular density within grafts resulted in increasing cell death and central necrosis within the graft site.<sup>[75]</sup> This cell density-related necrosis was attributed to the limitations of oxygen and nutrient diffusion through the larger cellular masses. Furthermore, large injection volumes (i.e. greater than 100  $\mu$ l per site) can mechanically increase damage to the surrounding host CNS tissue<sup>[61]</sup> and are more likely to result in reflux of infusate along the penetration tract.<sup>[81,82]</sup>

### The problem of infusate reflux

One significant issue with the injection of any fluid into a tissue is reflux, which is the return of infusate back up the path of the cannula [Figure 2].<sup>[81]</sup> Reflux with injections into CNS tissues is particularly problematic due to the low elastic modular properties of the brain and spinal cord parenchyma. During injection, the infusate initially expands the surrounding tissue to create a potential space. If the volume injected exceeds the capacity of that potential space, the infusate then travels in the path of least resistance, which is invariably along the cannula tract. In the case of injections of a cell suspension, reflux can lead to unintended deposition of cells to non-target locations, unpredictable cell dosing at the intended target



**Figure 1: The need for neurosurgical instrumentation that minimizes cranial penetrations. (a) Current straight cannula cell delivery devices require multiple cranial penetrations to increase cell distribution (green) within a target region (yellow). Each penetration carries a distinct risk of hemorrhage and as many as eight penetrations per hemisphere have been performed in clinical trials of cell transplantation to the CNS. Since this is the most serious complication associated with procedures of this type, a more ideal injection device would require only a single transcortical penetration to distribute cells to the entire target region, as in (b). Image provided in part by Kenneth Xavier Probst of XavierStudio**

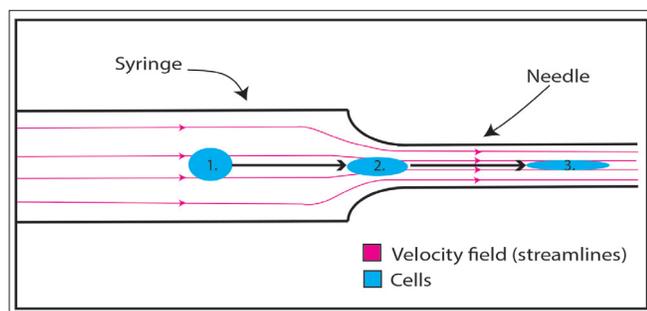


**Figure 2: Problems associated with infusate reflux. (a) Direct injection of a cell suspension (blue) into the target region (yellow) with a straight cannula device can result in reflux of infusate up the penetration tract (see arrows). This inability to accurately distribute therapeutics minimizes the achievable distribution volume (green) and results in a loss of therapeutic material. Moreover, reflux along the penetration tract delivers cells to unintended target locations, which may have adverse effects and lead to negative or mixed therapeutic results. (b) An ideal injection device would minimize reflux and achieve delivery to the entire target region (green). Image provided in part by Kenneth Xavier Probst of XavierStudio**

site, and even substantial loss of cell suspension at the surface of the brain or spinal cord.

### Disadvantages of the syringe-coupled cannula for cell delivery

Cell delivery cannulas are generally connected to an external syringe via a Luer lock or similar coupling mechanism.<sup>[18,27,51]</sup> This design has several disadvantages. First, for most syringes, small movements of the plunger dispense relatively large volumes, making the delivery of small, precise doses of cell suspension difficult to achieve manually. To address this issue, incorporation of mechanical or electrical drives to control the translational movements of the plunger could prove beneficial. Second, mechanical forces at the transition point between syringe and catheter can damage cells. The inner diameter of a syringe is typically larger than that of an injection cannula. Cells and fluid thus experience a considerable increase in linear velocity as they pass from syringe to cannula. This generates differential velocities along the length of a cell, known as an extensional force, which is thought to be a significant contributor to cell injury during injection [Figure 3].<sup>[4]</sup> Cells also experience a concomitant drop in pressure during passage from a syringe to a smaller bore cannula, although this effect may not be as damaging.<sup>[4]</sup> Furthermore, cells are also exposed to shear stresses as cells and fluid in the middle of a cannula travel at a higher velocity than those at the outer boundary. These mechanical effects may be inconsequential for standard needle sizes (i.e. 16–22 gauge),<sup>[79]</sup> but may become critical if the inner diameter of an injection cannula is made smaller. Third, the use of a syringe for multiple injections can make cell dosing unpredictably variable due to the sedimentation of cells in the carrier fluid [Figure 4]. Unlike small molecules and viral particles that easily dissolve in a fluid, cells in suspension naturally sediment in a time-dependent manner. For example, normal erythrocytes

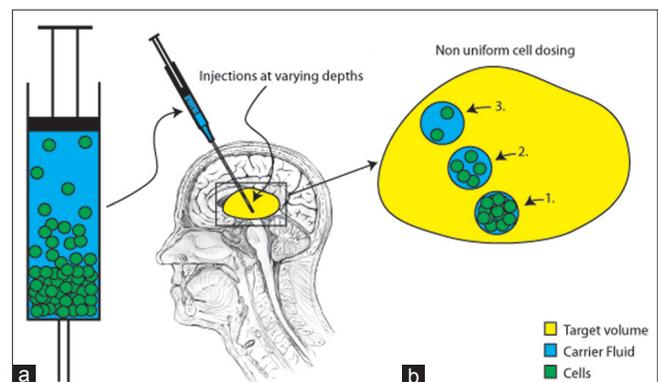


**Figure 3: Extensional forces experienced by cells upon injection through a syringe and needle.** The diameter of an injection syringe is typically larger than that of the attached needle. As a cell (blue) passes from a syringe to a needle, it will experience increasing velocities along its length, causing the cell to stretch and possibly rupture. These extensional forces may therefore decrease cell viability during injection. A greater differential between the diameters of the syringe and needle will result in greater extensional forces, while a longer needle will increase the time a cell experiences extensional forces

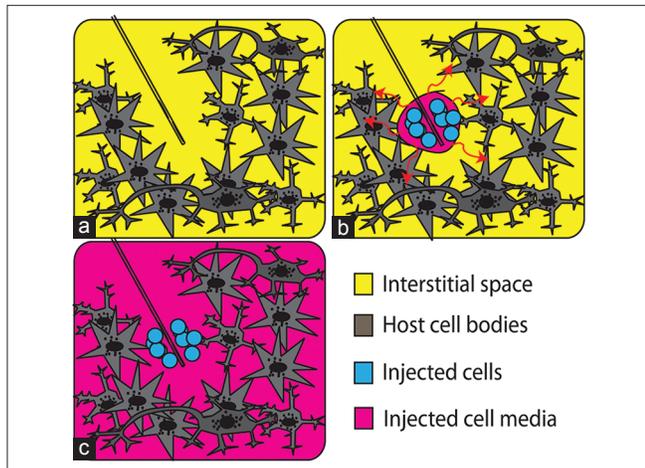
sediment at up to 20 mm per hour, and when cells are aggregated, this rate can exceed 110 mm per hour.<sup>[31]</sup> Unless the syringe is kept in constant motion, cell sedimentation creates a density gradient with the greatest concentration of cells toward the end attached to cannula.<sup>[38]</sup> Thus, the first partial injection volume from a syringe may contain far more cells than those dispensed later.

### Cell suspensions do not behave like a solution

An important consideration for any injectable therapeutic is the composition of the infusate. Most drugs that are dissolved in the carrier fluid distribute as a solution during brain infusion. Similarly, suspensions of very small particles (e.g. gene therapy viruses) also act as solutions. Cells, on the other hand, are typically injected within a suspension. As discussed above, this has consequences related to sedimentation, but it also affects the way in which cells can be deposited within a tissue. The brain and spinal cord can be considered a biphasic material consisting of a deformable porous matrix (CNS parenchyma) and a penetrating fluid within the interstitium [Figure 5].<sup>[57]</sup> Injected drugs and viral particles can easily diffuse into the interstitium, and the rate and extent of such mass transfer is partially dependent upon the average pore size of the parenchyma. Continuous positive pressure, as used with convection enhanced delivery (CED), can further enhance the distribution of a solution throughout the interstitial space using bulk flow instead of passive diffusion.<sup>[55]</sup> Cells, however, are much larger than the average pore size of CNS tissue. Thus, with the injection of a cell suspension, the cells are more likely to remain within the potential space created by mechanical deformation of the injection cannula while the carrier fluid disperses throughout the interstitium [Figure 5]. Unless we can “instruct” grafted



**Figure 4: Inconsistencies in cell dosing related to the sedimentation of cells in suspension.** (a) Cells (green) in a carrier fluid (blue) sediment over time, increasing the cellular concentration of the suspension at the most dependent portion of the delivery syringe. This gradient of cell density can lead to inconsistent cell dosing if multiple injections are performed from the same syringe, as is commonly done when grafting multiple cellular deposits along a single penetration tract (b). Sedimentation may therefore result in a higher cell density at the first injection site (1) and decreasing cell densities at the subsequent injection sites (2 and 3). Such variability is difficult to predict and may adversely affect outcomes



**Figure 5: Diffusion of a cell suspension after injection into the brain. (a) Host cell bodies (gray) and interstitial space (yellow) comprise the CNS parenchyma. During an injection procedure, a cannula can mechanically create a potential space within the interstitium. A cell suspension (blue and magenta) can be deposited into this potential space, as shown in (b). The carrier fluid (magenta) will begin to diffuse into the interstitium, while the cells will only experience limited, if any, movement into the interstitial space (c)**

cells to migrate through the interstitial space to disperse specifically within the target region, we must develop surgical devices and techniques to “manually” distribute cellular grafts.

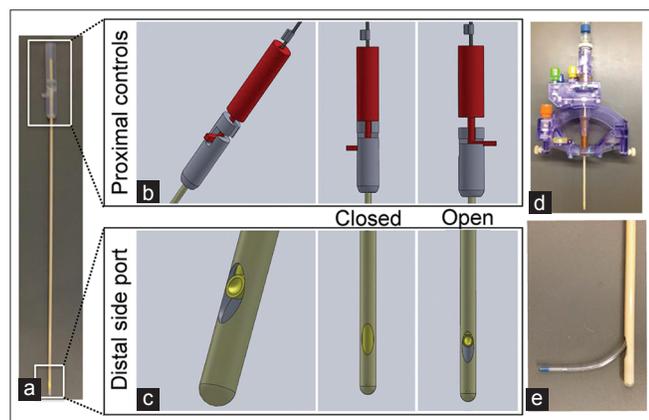
## CURRENT PLATFORMS FOR TARGETING CELL DELIVERY

Accurate targeting to a specific CNS location is often critical to the success of cell-based therapies, and several methods currently exist to achieve this goal. The most basic method is direct visualization of the entry point (e.g., by craniotomy, dural opening, and even CNS tissue dissection) and injection with a handheld syringe. This non-stereotactic, “freehand” method has been used to inject anti-tumor gene therapies into the walls of brain tumor resection cavities.<sup>[19,20,32]</sup> In these studies, the surgeons employed an insulin or tuberculin syringe to make 8-10 injections into the brain parenchyma adjacent to the brain tumor resection cavity. The injection entry points were selected under direct visualization, allowing the surgeons to avoid critical structures such as cerebral vessels, ventricles, or eloquent brain. With this approach, however, brain structures deep to the entry point are not visible to the surgeon and are thus at risk of inadvertent injury by needle insertion. Furthermore, the hand is not a particularly stable platform for syringe manipulation and even small movements of the syringe can injure CNS tissue after insertion of the needle into the parenchyma. Finally, handheld injection may prevent accurate targeting of small structures (e.g., the ventral horn of the spinal cord for treatment of ALS). Most cell transplantation

trials have employed a frame-based stereotactic platform for the insertion of a cell delivery cannula.<sup>[8,7,27,33,40,59,70,80]</sup> Such rigid fixation eliminates undesirable movement of the cannula and can be integrated with magnetic resonance imaging (MRI)-based, computer-aided stereotactic targeting systems. In the brain, modern stereotactic platforms are capable of introducing the tip of a straight cannula to essentially any target location with submillimeter accuracy using plans developed from preoperative MRI. Until recently, similarly stable and accurate stereotactic platforms did not exist for injections into the spinal cord, and freehand injections with tuberculin or insulin syringes were generally used.<sup>[25,34,37,48]</sup> Some investigators have used an operating room table-mounted arm to stabilize the syringe and needle.<sup>[25,48,50]</sup> More recently, Boulis and colleagues<sup>[63,68]</sup> have developed a novel “frame-based” stereotactic platform to enhance accuracy and safety of spinal cord injections. The device frame is secured with percutaneous translamina screws rostral and caudal to the level of injection. A micropositioner platform is suspended on rails over the exposed spinal cord and provides precise control of the cannula insertion angle and location in the  $x$ ,  $y$ , and  $z$  planes. Furthermore, the design includes a “floating cannula” to allow the injection needle to move with pulsations of the spinal cord. This device is currently being used for a phase I clinical trial evaluating the safety of neural stem cell injections into the ventral horns of the upper lumbar cord to treat ALS.<sup>[67]</sup> In this ongoing trial, stereotactic targeting to the ventral horns is based on preoperative MRI and a total of five injections, either unilaterally or bilaterally, are made to varying depths. A volume of 10  $\mu\text{l}$  is injected over 2 min and the needle is left in place for 1 min after completion of the injection to reduce reflux. Overall, this device represents a significant advance in cell transplantation to the spinal cord as it has greatly improved targeting accuracy. Most stereotactic surgery relies upon imaging obtained before surgery for targeting. After the operation begins, however, the CNS tissues can shift unpredictably due to a loss of CSF and accumulation of air within the subdural space. Thus, the actual brain target may move in relation to the stereotactic frame and platform, resulting in surgical inaccuracy. Interventional MRI (iMRI) has recently been developed to provide real-time imaging for stereotactic procedures. For instance, it is now possible to implant DBS leads into anatomical structures as defined by MR images obtained in the operating room after the start of surgery.<sup>[43,66,76]</sup> Other preclinical studies have demonstrated the utility of iMRI for the monitoring of gene therapy infusions in real time, providing the ability to confirm adequate delivery to the target region.<sup>[23,41]</sup> Thus, iMRI will likely be a powerful tool for both targeting and monitoring of cell transplantation to the CNS.

## RADIALLY BRANCHED DEPLOYMENT FOR MORE EFFICIENT CELL DELIVERY TO THE HUMAN BRAIN

For cell transplantation to the brain, a more ideal device and neurosurgical strategy would enable the distribution of multiple, small cellular grafts to relatively large target regions via a single transcortical penetration. We have recently developed a modular cannula system capable of radially branched deployment (RBD) of a cell delivery catheter at trajectories “branched” from essentially any rotational angle and depth along a single transcortical penetration tract [Figure 6].<sup>[74]</sup> Cunningham and colleagues have also explored the use of radial trajectories for cell transplantation; their device deflects a straight but semi-flexible catheter 25° from the primary trajectory axis, allowing for radial transplantation distance of up to 8 mm.<sup>[14,21]</sup> The RBD device consists of a set of three nested tubes (an outer guide tube, an inner guide tube, and a cell delivery catheter).<sup>[74]</sup> In its “closed” condition, the RBD device resembles a standard stereotactic biopsy cannula in both dimensions and outward appearance [Figure 6] and has an outer diameter of 2.4 mm. The cell delivery catheter, however, has an outer diameter of only 1 mm. To achieve radial transplantation, the cell delivery catheter is deployed at a 90° angle from the primary trajectory axis and can be extended outward up to 20 mm. Depth of injection can be altered by raising or lowering the entire RBD device, while rotating the device allows for injections in any direction from the tip of the guide tube. Thus, by varying depth, rotation, and radial extension of the cell delivery catheter, it is possible to distribute cell deposits within very large (>4 cm<sup>3</sup>) target regions. The RBD device therefore provides a new delivery option for cell therapy. For example, in PD treatment, the putamen (or post-commissural putamen)

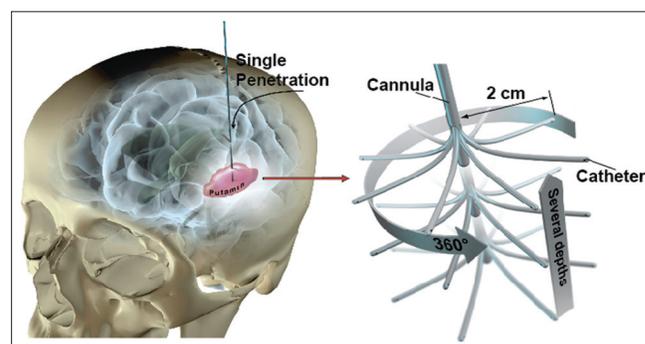


**Figure 6:** Interventional magnetic resonance imaging-compatible radially branched deployment device (a). All components are made of FDA-approved, non-paramagnetic materials (b). Proximal control elements allow simple opening and closing of the distal side port (c). (d) iMRI RBD with the Clearpoint SMARTframe platform. (e) Deployed cell delivery catheter

has been the primary target for dopaminergic cell transplantation in past clinical trials. However, this basal ganglia structure is a difficult target for a straight cannula delivery system as it is both volumetrically large and irregularly shaped [Figure 7]. Using volumetric MRI scans and a stereotactic planning system, we have been able to design surgical plans with RBD capable of “arborizing” the entire putamen via a single transcortical penetration. Preclinical studies of the RBD device have shown excellent precision with multiple cell delivery catheter placements through a single penetration in agar. Neural precursor cells can be passed through the device with high viability and preservation of differentiation potential. In addition, the device has been used in combination with a skull-mounted, MRI-compatible stereotactic platform (Clearpoint SMARTframe, MRI Interventions, Memphis, TN, USA) to test injections into subcortical white matter of live swine. Importantly, no hemorrhages or other complications were noted during RBD injections into swine brains. In addition, histological analysis after injection of fluorescent beads confirmed infusate delivery along the planned trajectories without reflux. In contrast, similar stereotactic injection of fluorescent beads through a 20G straight cannula resulted in reflux of over 75% of infusate. RBD therefore appears to resist reflux at the transition point between the deployed catheter and the outer guide tube side port. This reflux resistance may be a consequence of the directional change of the tract and/or the larger caliber of the outer guide tube. Similar reflux control has been observed with a “stepped” gene therapy delivery cannula, wherein reflux is inhibited at the point of caliber change.<sup>[42]</sup>

## Eliminating the need for a separate cell delivery syringe

The RBD device contains an integrated catheter-plunger



**Figure 7:** Schematic illustrating the use of RBD to deliver cells to a larger human brain target. A cylindrical cannula introduced by any modern stereotactic frame can be precisely rotated around the axis of the initial trajectory and retracted to more superficial brain regions without incurring additional neural damage. Thus, the ability to deploy a cell delivery catheter perpendicular to initial trajectory along multiple radii and depths allows one to efficiently “arborize” larger brain target regions such as the putamen (pink) via a single transcortical brain penetration. Image provided in part by Kenneth Xavier Probst of XavierStudio

system that facilitates accurate and precise manual delivery of small infusate volumes. The lumen of the cell delivery catheter is fitted with a grade 5 titanium (Ti6Al4V) wire that serves as a plunger. The close fit between the inner walls of the catheter and the plunger wire provides a nearly gas-tight seal that allows both aspiration and dispensing of the cell suspension. This simple integration of catheter with its own flexible plunger eliminates the need for a separate syringe. In its current design, advancing the plunger wire 1 cm dispenses  $1.36 \pm 0.13 \mu\text{l}$  ( $n = 50$  trials), and up to  $100 \mu\text{l}$  can be delivered by a single catheter. Furthermore, the catheter-plunger system nearly eliminates dead volume. The catheter-plunger system is a modular component of the RBD device. That is, even with the outer and inner guide tube assembly inserted into the target region, the catheter-plunger system can be completely exchanged. This modularity eliminates cell dose variability that can arise from cell sedimentation in a syringe. For each radial catheter deployment, the surgeon dispenses the entire cell dose of the catheter-plunger. Then, with the RBD guide tube side port in the closed position, the depleted catheter-plunger is removed and replaced with another that has been pre-loaded with cells for deployment to another radial location. Since the catheter-plunger subassembly can be filled with different infusate volumes and/or cell concentrations, the user can tailor the distribution of cell doses.

### Interventional MRI for cell delivery

Ideally, cell transplantation to the CNS would be targeted and monitored with real-time imaging. To enable this method, we have recently fabricated the RBD device with materials compatible with use in the high-field magnetic environment of iMRI. The outer guide tube comprises polyetheretherketone (PEEK), both the inner guide tube and cell delivery catheter are formed from Nylon-12, and the plunger is derived from a nickel titanium (Nitinol) wire. Proximal user control elements are a combination of custom-designed thermoplastics and standard medical components. This “plastic” RBD device fits through the fluid-filled targeting cannula of the Clearpoint SMARTframe [Figure 6]. Our intent on “marrying” RBD with an available stereotactic platform is to facilitate the integration of cell transplantation with other, complementary stereotactic procedures. For instance, in the case of PD, we do not see cell transplantation as “competitive” to DBS therapy, gene therapy, or even medical therapy. Rather, we envision these distinct treatment modalities working together, each addressing a different aspect of the disease. It is our hope that a combined therapeutic approach will provide PD patients with durable, high quality of life.

### FUTURE CONCEPTS FOR CELL TRANSPLANTATION TO THE CNS

The RBD device is an early iteration in what we hope will

be a rapid evolution of neurosurgical devices designed for stereotactic therapeutic delivery to the CNS. While it represents an improvement over straight cannula injectors, RBD still does not fully recapitulate the cell distribution achieved in preclinical animal models. In a rat model of PD, three injections of  $\sim 1 \mu\text{l}$  of cell suspension to the rat striatum are sufficient to treat the animal. However, the relevant human brain target is over 500 times larger. Theoretically, to achieve the same distribution of dopaminergic neurons in the human brain, one would need to deposit  $1 \mu\text{l}$  of cell suspension at 1500 separate locations (per hemisphere). Such a feat is likely both impractical and unsafe with current injection technologies. One possible solution, however, is to reduce the RBD delivery catheter to very small dimensions. For rodent cell transplantation surgeries, we routinely use cannulas with outer diameters of  $\sim 50 \mu\text{m}$  that inflict minimal injury on the host brain. Perhaps it will be possible to create an RBD-like device that simultaneously deploys hundreds of such very fine cell delivery catheters according to surgical plan. In some cases, a straight initial trajectory is not ideal. For instance, critical brain structures might lie between the desired entry point and planned target region. A “steerable” injection device could solve this problem. Instead of being limited to a straight trajectory to a given target, perhaps future injection devices can take curved paths in order to circumvent injury to critical structures. In addition, future developments in material sciences may identify materials that are less traumatic to CNS tissues. The translational needs that exist at the surgical bedside are constantly evolving and change with discoveries made both in the basic science laboratories and the clinical setting. Certain breakthroughs in cell biology research may actually obviate the need for surgical cell dispersal. Certain stem cells themselves may have the innate ability to migrate toward tumors or injured regions within the brain,<sup>[3,36,56]</sup> and perhaps some day we will be able to engineer them to target other specific CNS loci for drug or viral delivery. Perhaps we may even learn how to manipulate the BBB to allow entry of cell therapeutics from the intravascular compartment. In any case, continued close interactions between the basic science community, bioengineers, and neurosurgeons will be key to facilitate the translation of preclinical research into clinical therapies.

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