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# Somatic Cell-Fusion and/or Co-Culturing: A Mechanism for Cell Re-Programming Prior to Cell Therapy of Neurodegenerative Diseases

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## Abstract

Alzheimer's disease (AD) and Parkinson's disease (PD) are the two most prevalent neurodegenerative diseases which generally start after 50-55 ages of life where the brain neural cell gets destroyed. Transplantation of the dopaminergic (DA-ergic) neuronal cells, though, could help the diseases but the most obstacle is the availability of a sufficient number of such cells for replacement therapy. Neural stem cells (NSCs) are able to produce DA-ergic neurons and also have the capacity to act as a useful vehicle for genetic and molecular therapies within the central system (CNS), however, the sustainability of slowly and senescence NSCs must be ensured through genetic manipulation both *in vitro* and *in vivo*. NSCs grow very occurs after a few passages. Here we'll discuss many options to modify the NSC cells for a better growth, and increased survival length, as well as their ability to control the release of dopamine within the neural synaptic cleft. Cell-Cell interactions in terms of co-culturing or cell fusion are commonly known to change the cells' fate by genetic reprogramming, and thus discussed here for evaluation of their use in the transplantation process.

**Keywords:** Neurodegenerative Diseases, Cell therapy, Cell-fusion, Gene reprogramming

## Introduction

Cell replacement therapy can be best described as the replenishment of cell loss by transplantation of a new cell of that type. The cell to be transplanted should be either genetically modified or modified by cell-cell interaction to create a modified cell type for the desired activities. Here we'll discuss neural cell reprogramming within the scenario of cell replacement therapy for neurodegenerative diseases where active cell loss is prominent. Alzheimer's disease (AD) and Parkinson's disease (PD), which generally starts in the mid-age of life and shows the loss of neural dopaminergic (DA-ergic) cells within the hippocampus and neural synaptic cleft at the Substantia nigra (SN), respectively [1, 2]. Supplementation of dopamine, a neural cell-derived product, from can ameliorate the disease symptoms temporarily, however, long time treatment with this neurotransmitter may cause motor neuron defect, dyskinesia etc. [3, 4]. Therefore, a controlled release of dopamine may be possible only by transplantation of the DA-ergic neural cells in there [5]. The biggest obstacle in such therapy of AD and PD, is the availability of the right cell type in sufficient amounts. Most of the cells, which may come on the list, have various negativities like the formation of teratomas in the future, or may differentiate to other cells. Besides, immune rejection, moral issues of using those cells, and availability in sufficient amounts for transplantation, are the added obstacles. Therefore, the selection

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of isogenic cells and reprogramming them to a differentiated neural cell may be the most effective thought for cell preparation for therapeutic purposes [6].

## Concept of Cell Reprogramming

Cell reprogramming concepts have been classically developed in the fields of developmental and stem cell biology and are currently being explored for regenerative medicine, given their potential to generate desired cell types for replacement therapy. Cell reprogramming refers to the ability to redefine the identity of a cell by changing its epigenetic and transcriptional landscapes, reflected in the acquisition of new morphological, molecular, and functional features [7]. These changes entail a complete reversion of cell fate or modification of somatic cellular identity.

Somatic cells can be reprogrammed to pluripotency, acquiring self-renewal and pluripotent features similar to embryonic stem cells (ESCs) [8]. Alternatively, lineage reprogramming involves the conversion of specialized cells into a different somatic cell type without transiting through pluripotency [9]. This process can occur directly (transdifferentiation or direct cell reprogramming) or progress through an intermediate progenitor state that re-differentiates into different cell types.

The discovery of iPSCs now becoming a hope to replace the cell loss caused by the disease [8-10]. In fact, somatic cells could be reprogrammed into induced pluripotent stem cells (iPSCs) and these cells could be used to model Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), Huntington disease (HD), and Parkinson's disease (PD) [11-14]. The foremost promising reprogramming technique for the generation of induced pluripotent stem cells (iPSCs) is the transduction of defined transcription factors like OCT4, SOX2, and KLF4 [8, 15, 16]. In general, the efficiency of iPSCs generation is extremely low, and also reprogrammed clones often show differences in the amount of the epigenome and transcriptome compared with the stem cells derived from the embryos [17-19].

## Reprogramming using somatic cell nuclear transfer (SCNT)

The differentiated state of a somatic cell may be reversed experimentally to that of another cell type by a process termed as somatic cell nuclear transfer (SCNT) [20]. SCNT enables the direct generation of organisms from single donor cells. Although both the SCNT and the iPSC technologies can reprogram differentiated somatic cells into cells of embryonic state, the paths to achieve pluripotency are likely different. SCNT reprogramming is very fast, within an hour [21, 22], whereas the establishment of a stable iPSC takes several days to weeks to establish a stable cell. Furthermore, SCNT reprogramming, at least for chromatin accessibility and transcriptome reprogramming, is much more efficient than that of iPSCs [19].

## Co-culturing of Cells Induces Cellular Behavior

Co-culturing of two different types of cells give the opportunity to go for cell-cell interaction, which may lead to going for the generation of a new cell type with altered functions as well as altered capabilities [23-25]. Many such references are available in the literature with somatic cells, cancer cells, etc. [25]. Proliferation and differentiation of NSCs to neurons were induced when co-cultured with glioblastoma cells (Wang et. al. 2010). Cell survival and neuronal differentiation of transplanted NSCs noticeably improved in the ischemic striatum of the middle cerebral artery occlusion (MCAO) rat model system [27]**.** Sertoli cells (SCs) secreted neurotropic factors, and co-culturing with NSCs showed neurite outgrowths [28].

Microglia can stimulate the proliferation of NSCs in culture, increase the release of mitogenic factors, promotes differentiation to neurons, and also the formation of oligodendrocytes. Bone marrow-derived mesenchymal stem cells (BM-MSCs) that release chemokine ligand-2 (CCL-2) stimulate proliferation and differentiation of NSCs and also can protect the later cells from neurotoxic effect of 6-hydroxy dopamine [29, 30]. Olfactory ensheathing cells (OECs) are specialized glial cells that have properties of both SCs and astrocytes [31]. They have been shown to promote the differentiation of NSCs proliferation in co-culture [26], although not all astrocytes do so [27]**.** We showed before that hNSCs produce increased amounts of BDNF, GDNF, and Dopamine (DA) when co-cultured with human normal melanocytes (hNMCs) [32].

## Cell Fusion and Reprogramming may be Studied with Rigor in Cell Culture System

In one instance, hybrid cells were generated when mouse bone marrow cells were grown on mitotically-inactive fibroblast feeder cells. These hybrids contained genetic markers from both cell types and expressed endothelial markers when plated on a matrigel matrix [33]. In another study, neurosphere cells derived from embryonic day 14.5 mouse forebrain spontaneously fused with ESCs under conditions of co-culture [34]. The fused cells had markers from both fusion partners, grew with ESC-like morphology, and contained a tetraploid complement of chromosomes. These neurosphere/ESC hybrids contributed readily to chimeras. Spontaneous cell fusion was also detected when hygromycin-sensitive mouse ESCs were co-cultured with hygromycin-resistant primary murine brain cells for five days [35]. The resulting hybrid cells formed hygromycin-resistant colonies and expressed the stem-cell-specific Foxd3 gene from the chromosome originally present within the neural cells. Furthermore, these hybrid cells contributed to all or

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any three germ layers in chimeras. Spontaneous fusion of cancer cells with the host cells form a hybrid cell as shown in murine models similar to human *in vivo*, and people hybrids present host cell marker genes and showed an increased metastatic potential in them [35-38].

## Cell-Cell Fusion as a Method of Cell Reprogramming

Another major technique of reprogramming is a cell-cell fusion that had been reported earlier between somatic cells and hESCs [39, 40]. In brief, this method allows the melding of two or more cells into one cell called a heterokaryon (or homokaryon, if fusion occurs between identical cell types), and this state persists for two to three days, after which the nuclei fuse and produce a hybrid cell. This hybrid cell contains a single polyploid/tetraploid nucleus capable of reentering cell division [41-43]. In particular, fusogens are mandatory for the contribution to the steric formation of several cell fusion-related lipid intermediates named "the hallmarks of cell-cell fusion" [44]. In one study, hybrids were generated by a fusion of male murine Hprt-/- ESCs with female mouse splenocytes [45]. Fused cells were selected in the HAT medium. The resulting hybrid cells exhibited near-tetraploid karyotypes and formed a variety of embryonic bodies containing cell types corresponding to all three germ layers [46]. In addition, these cells contained synchronously replicating X chromosomes, suggesting that the inactive X chromosome of splenocyte origin was reprogrammed to a pre-inactivation state. In another study, a fusion of thymocytes from an adult female mouse, harboring a silent GFP transgene, with ESCs from a male mouse yielded hybrids that expressed GFP [47]. The thymocyte/ ESC hybrids contained reactivated X chromosome of thymocyte origin as judged by fluorescent *in situ* hybridization for Xist RNA. The pluripotency factor *nanog* is expressed in morula, blastocyst stage embryos, and in ESCs, but not in differentiated somatic cells. The silent *nanog* gene, however, can be reactivated upon the fusion of somatic cells with ESCs or when somatic nuclei are transplanted into oocytes [48]. Cell–Cell fusion-mediated reprogramming is a faster and more efficient method than the iPSCs method, because the hESC used for cell fusion provides all the factors required for the maintenance of pluripotency. However, the fused and reprogrammed cells retain both the somatic and ES cell genomes, a visible barrier to their application in anything apart from mechanistic studies. Cell fusion is one of all the several approaches that allow differentiated cells to return to a pluripotent state [49-51]. Cell fusion is a very important physiological process that is required for discrete events *in vivo* like fertilization, tissue repair, and immune defense [52]. Outside these settings, cell-to-cell fusion is comparatively uncommon, but will be induced experimentally, for instance, using agents like inactivated Sendai virus [53], polyethylene glycol (PEG) [54], or electrical charge, in an *ex vivo* setting. Cell fusion hybrids between mouse ESCs and human fibroblasts are often identified as each of the parental nuclei may be distinguished and monitored. Cell types may be labeled with different fluorescent tags before cell fusion and flow cytometry is accustomed to select the heterokaryons that are formed (Villafranca et. al. 2020), additionally as following how they alter over time.

## Fusion-Mediated Reprogramming Using Other Embryonic Cells

Primordial germ cells (PGCs) contain interesting reprogramming activities since they undergo imprint erasure shortly after migration to the genital ridge but before the establishment of male or female gonadal fates. PGCs are identified by the expression of an Oct4-GFP transgene, which allows their purification by fluorescence-activated cell sorting (FACS). Analysis of DNA contained within PGCs prepared in this way revealed demethylation at multiple genetic loci including both imprinted and non-imprinted genes [55, 56]. This finding makes PGC cells and their cultured derivatives, embryonic germ cells (EGCs), attractive candidates for intentional fusion with somatic cells to cause reprogramming. Indeed, when PGCs marked with ROSA26βgeo were electro-fused to thymocytes, Several imprinted and non-imprinted genes underwent demethylation, adopting a state observed in normally-derived EGCs [47]. In overall morphology, the hybrids resembled EGCs but inspection of the hybrid karyotype revealed a tetraploid complement of chromosomes. When EGC/T-cell hybrids were injected into host blastocysts and implanted into pseudo-pregnant mothers, β-galactosidase expression was widely observed in chimeric embryos on days between 9 and 10. Though EGCs contain potent demethylating activities, it remains unclear if the expected loss of imprints in PGC/somatic fusions would have consequences for cell-based therapies.

## Mouse Embryonic Carcinoma Cells (ECCs) Can Reprogram Somatic Cells

Human T- lymphoma cells could be reprogrammed upon fusion with mouse embryonic carcinoma cells. During this instance, the hybrids expressed human Oct4 and Sox-2 genes, showing that human genes involved in pluripotency were de-repressed by the hybridization event. In addition, the CD45 surface protein was reduced in ECC/T-lymphoma hybrids. This suggested an alteration of lymphocytic characteristics in the hybrids. A comparison of different reprogramming methods is shown in Table 1.

Such a comparison would indicate whether cytoplast fusion is a feasible alternative to iPS cell generation, and would provide some insight into how transduction of a few key pluripotency factors compares with provision of the complete pluripotent cytoplasmic or cytoplasmic plus nuclear environment in cell reprogramming. The cell fusion system also offers an opportunity to explore gene reactivation and

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**Table 1:** Comparison of Different Reprogramming Methods

| Queries | Cell-Cell Fusion | Transduction of transcription factors | Somatic Cell Nuclear Transfer (SCNT) |
|---|---|---|---|
| **Mechanisms** | The melding of two or more cells into one cell called a heterokaryon [49, 57] | Reprogramming factors, OCT4, SOX2, KLF4, c-MYC, NANOG, and LIN-28 were transiently transfected simultaneously with the nuclear-localized ECFP (ECFP-nuc) expression vector into the OGIH HDFf or MRC5 [42, 43] | SCNT is a technique by which the nucleus of a differentiated cell is introduced into an oocyte from which its genetic material has been removed by a process called enucleation [62] |
| **Efficiency** | hESC cytoplast fusion could initiate reprogramming but was never able to complete reprogramming [58]. | Enucleated hESC-fusion initiates reprogramming but does not yield completely reprogrammed cells [58] | The cloning efficiency is varying within relatively low values between 0.5% and 5% offspring per transferred SCNT embryos [63]. |
| **Viability of the Processes** | Cell fusion provides relatively efficient reprogramming [58, 59]. | Nuclear transfer, reprogramming through direct introduction of a somatic nucleus into the environment of a pluripotent cell provides relatively efficient reprogramming [58, 61] | Low efficiency in creating normal viable offspring in animals by SCNT (1–5%) and the high number of abnormalities in these cloned animals is due to epigenetic reprogramming failure [64] |
| **Merits/ Demerits** | Cell-Cell fusion methods takes less than 10 days to make the hybrids and efficiency is more than 0.005% [60] | High throughput single-cell multi-omics methods are potential to understand the transcription factors and chromatin changes necessary for cell type conversion [59] | Ability to confirm *in vitro the desired genetic* modification in the somatic cells prior to animal production [65] |
| | Identify the earliest events in reprogramming, and enable to distinguish the stages before and after cell division [49] | iPSC generation is very low and reprogrammed clones often show differences at the level of the epigenome and transcriptome when compared with stem cells derived from embryos and the efficiency was less than 0.001% [43] The reprogramming process of iPSC generation required more than 4 weeks for emergence of hESC-like colonies, and the efficiency was less than 0.001% [9, 15, 61] | There are ethical and practical barriers to apply in humans [65] |
| | Reprogramming by cell fusion with hESC is much more efficient and faster than virus transduction of reprogramming factors [43] | | |
| | Fusion yielded almost no partially reprogrammed cell colonies. However, the fused cells were tetraploid or aneuploidy [58, 61] | | |

silencing which is useful in the context of designing strategies to reverse certain disease states. The goal of regenerative medicine is to restore form and function to damaged tissues. While the fused cells are unlikely to be directly suitable for medical use, they can offer an important experimental tool to examine the pathways of cell conversion, genome repurposing, and locus reactivation, which can be imitated for therapeutic benefit.

## Polyethylene Glycol (PEG)-Mediated Cell Fusion

Cell fusion may therefore be considered an efficient method of reprogramming where the hESCs partner provides a completely functional network of pluripotency factors and cell signaling molecules. However, fully reprogrammed colonies appeared in cell fusion-mediated reprogramming much faster than in four-factor-mediated iPSCs generation [66, 67]. Much PEG-mediated fusion reprogramming were reported before as mouse ESCs/iPSCs were fused with neurospheres cumulus cells, splenocytes, mesenchymal stem cells (MSCs), and mouse embryonic fibroblasts (mEFs) [46, 68-70]. Human ESCs are PEG-fused to fibroblasts and myeloid precursors [39, 40, 43]. In cancer biology, PEG-mediated fusion between non metastatic melanoma cells with macrophages reprogrammed to metastatic cancer cells [71-73]. Further, mouse non-metastatic melanoma cells when fused with human leukocytes expressed human genes within the hybrid together with their increased metastatic potential [71].

## Spontaneous Fusion

Interest was stirred within the field of adult somatic cell research when engraftments of marked bone marrow stem cells (BMSCs) displayed remarkable lineage plasticity following engraftment. However, subsequent studies demonstrated that the fusion of ESCs and somatic cells occurs

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spontaneously under conditions of co-culture [34, 75]. These findings suggested alternative interpretations during which endogenous somatic cells acquired somatic cell markers through simple fusion events. Though these findings raised concerns, later studies that controlled for cell fusion revealed that adult stem cells do possess a stimulating degree of developmental plasticity. For example, bone marrow-derived cells possessed the power to turn out to be cells with epithelial character, apparently without fusion, as judged by a sensitive *crelox* strategy to detect fusion events [54]. Taken together, these results indicate a promising future for investigations of adult vegetative cell plasticity, but such research should be conducted in conjunction with robust methods to detect fusion events.

## The Future of Cell Reprogramming for Cell Therapy of Neurodegenerative Diseases

Different types of reprogramming can result in producing undifferentiated cells with varying degrees of "stemness". Technically, somatic cell nuclear transfer (SCNT) is the only method that can reprogram a somatic cell into a totipotent cell capable of creating a complete organism. However, as described above, cellular reprogramming methods usually involve induced pluripotency via *in vivo* or *in vitro* manipulation, which is expensive, time- consuming, and involves cumbersome techniques. Finding a way to produce iPS cells that are near "biological equivalent" embryonic stem cells is of interest to the research community because this would allow iPS cells to be created from patients for immediate use in transplantation. For many medical conditions, this is a difficult goal, because a patient's cells have often been affected by their own disease. A non-genetic and PEG-mediated cell fusion of DA-ergic neural cells with other selectively chosen partner cells (based on research, and also see the recent review) which is our current research of interest to improve the growth potential and differentiation of the NSCs may remove the need for immunosuppressive drugs and eliminate the rejection of transplanted cells.

## Evidence of Using NSCs for PD and AD Cell Therapy

NSCs may provide a virtually unlimited sources of self-renewing progenitors for transplantation. The potential applications and technical challenges of this approach have been critically reviewed [76]. It has been reported that transplanting differentiated monkey embryonic NSCs into the monkey putamen leads to their proliferation into fully functional DA neurons [77]. Implantation of these DA neurons caused sustained improvement of MPTP-induced motor symptoms that was significant over a 10 –14-week follow-up period compared with a sham group. Proliferation into fully differentiated DA neurons has been observed following the implantation of undifferentiated human NSCs into MPTP-lesioned monkeys [78].

## Progress in Dopaminergic Cell Replacement and Regenerative Strategies for Parkinson's Disease [79]

Understanding of Parkinson's disease therapy through the use of cell reprogramming becomes evident. Interestingly, direct reprogramming using just one pluripotent factor can generate expandable stem/progenitor cells [80-83]. Recently, human iNPCs (hiNPCs) have been successfully differentiated into the motor and dopaminergic neurons using specific patterning molecules [84, 85] transplanted mouse iNSCs into the brains of toxin-induced mouse models of PD. Restoration of brain tissue led to enhanced functional recovery of the animals in behavioral assessment. Another study investigating the effects of iNSC engraftment in the 6-OHDA-induced mouse model of PD found restored dopamine production and improved motor behavior, despite low survival rates of engrafted cells [86]. Transplantation of mouse iNSCs into the hippocampus of the APP/PS1 mouse model of AD can significantly improve the spatial learning and memory of APP/PS1 AD mice [87]. In cynomolgus monkey, iPSC-derived dopaminergic neurons were transplanted into the putamen of a non-human primate Parkinsonian brain. The reprogrammed neurons survived and underwent extensive outgrowth into the transplantation site and surrounding putamen; improved motor function and increased motor activity without immune suppression [88]. The transplantation of these neurons into the rat striatum lesioned by 6-OHDA, a functional model of PD, successfully demonstrated improvements in motor function post-neuron engraftment [89].

## DA-ergic Neuron-based Replacement Therapy for AD

Similarities among Alzheimer's disease, Parkinson's disease, and Dementia may call for a similar treatment [90-97]. In fact, in mouse AD models, transplantation of NSCs was reported to improve cognition function mediated by the neurotropic factor BDNF [97-99]. Further, transplantation of growth factor-secreting NSCs increased neurogenesis and cognitive function in a rodent AD model [98], and aged primate brains [100]. Other recent AD rodent model studies have reported that NSC transplantation decreased neuroinflammation [101], attenuation of *tau* and Aβ in AD neuropathology [102], promotion of neurogenesis and synaptogenesis [103, 104], and reversal of cognitive deficits [101, 103, 104].

Dopamine therapy improves cognitive function in Alzheimer's disease. The study is supported by the Alzheimer's Drug Discovery Foundation and published in *JAMA Network Open*. The study provides the first evidence that "rotigotine", a drug that acts on dopamine transmission in the brain, improves cognitive function in Alzheimer's disease [105]. In brief, hNSCs being are equipped with both Tyrosine hydroxylase, a key rate-limiting enzyme for

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Dopamine production, moreover, as its scavenging enzymes (DAT and MAO-B) which might efficiently control the physiologic level of that neurotransmitter [106]. hNSCs become the primary choice for cell replacement therapy. Furthermore, hNSCs can produce brain derived neural factors (BDNF) and glial-cell-derived neural factors (GDNF) which might influence the expansion and Dopamine production ability of hNSCs in an autocrine manner [107-109]. While the therapeutic mechanisms behind these changes are not yet fully understood, they are likely mediated by both the paracrine release of neuro-protective or immune modulatory factors [93], and by direct neuronal differentiation [110, 111], although the widespread generation of non-neuronal glial cell types from transplanted NSCs remains a major limiting factor for neuro-replacement strategies [111]. A modified neural cell, after reprogramming by any of the above-mentioned methods, may well be used for transplantation within the brain for cell therapy. Since spontaneous PEG-mediated fusion or co-culturing-mediated reprogramming showed plenty of advantages over genetic or virus-mediated reprogramming, we will keep hope for the long-run development of the therapeutic achievement for AD/PD cell therapy.

## Other Importance of Using NSCs for Cell Therapy of Neurodegenerative Diseases

NSCs can also act as a vehicle or career of genetic material. NSCs stably transduced with human nerve growth factor genes survive and integrate into the cerebral cortex of AD animal model (Rat) upon transplantation and enhance cognitive performance. This survival and integration were not observed in the same rat model transplanted with NSCs without genetic modification [112, 113]. Transplantation of NSCs is also used as a vehicle to deliver potential therapeutic agents, including neprilysin, insulin-degrading enzyme, plasmin, and cathepsin B, to decrease Aβ levels in AD mouse models [114]. Neural stem cells (hNSCs) can be an efficient candidate to deliver neurotropic factors or enhance gene expression to modify the course of the disease [115-117]. These cells also have been considered for use in cell replacement therapies in various neurodegenerative diseases, as well as in other brain-related diseases such as ischaemic and neoplastic lesions. Here, we speculate on ways in which neural stem cells [118].

## Limitations of Somatic Cell Fusion Reprogramming Methods for Cell Therapy

Although the fusion hybrid cells show pluripotential characteristics, the fusion hybrid cells are not identical to the pluripotent fusion partner cells. The fusion hybrid cells can form chimera but not contribute to the germline. Although fusion-induced reprogramming is very efficient (about 95%), the resultant hybrid cells lack therapeutic potential because of their tetraploidy and the presence of exogenous genes from the pluripotent fusion partner cells [119].

A critical issue for bringing iPSCs into the presetting clinic is the non-sufficient scale and preservation of neurons. Cryopreservation of a large number of cells will interfere with this challenge. Functional and non-tumorigenic dopaminergic neurons lost with extensive fiber innervation in the midbrain of PD can be retained with regenerative medicine and iPSCs derived dopaminergic neurons. It seems not only the donor cells but also the host niche is important for accepted transplantation [120], PD is multiple neuronal subtype damage such as midbrain dopaminergic neurons. Dopamine agonist treatment side effects open a new therapeutic strategy based on stem cells [121]. Recently, in a study, the researchers created a library of iPSCs from Parkinson's disease as a useful source to focus on common and divergent pathogenic mechanisms of neurodegenerative disorders [122]. Wide and practical iPSCs studies of PD treatment, establish a new alternative to knowing and treat it deeply. Further, due to the number of divisions that the cells underwent, there are difficulties in the conservation of genomic instability. Finally, we know that no developed technology is perfect, but it is possible to eliminate the negativities in our hands by continuing to progress [123].

## Challenges with Clinical Translation and Potential Solutions

There are several major difficulties associated with using trans-differentiated cells in clinical applications. The most glaring issue is the use of lentiviruses to infect cells, due to the small possibility of unintended insertional mutagenesis [124]. These mutations, while unlikely, could cause drastic, unforeseen consequences in the host, such as the emergence of cancer [125]. Understandably, many government agencies take precautions due to this risk. Non-integrating viruses and other methods that do not integrate DNA into the host genome do not pose these threats but have much lower reprogramming efficiencies. Therefore, there is a need to efficiently transdifferentiate cells while avoiding the possibility of mutagenesis.

The advent of dCas9 allows for a drastic reduction of the chance of mutagenesis through its ability to multiplex. When lentiviral vectors are used to overexpress multiple exogenous transcription factors, more than one vector may be used due to the cargo capacity limitations of lentiviruses. However, trans-differentiation methods utilizing dCas9 only need to use one vector to efficiently express the dCas9. Once the cells express dCas9, several gRNAs targeting various genes can be added through non-integrating methods, allowing the dCas9 to regulate the expression of several genes despite the cells receiving a single lentivirus infection [126].

Thus, reducing the number of DNA-integrating viruses needed to trans-differentiate cells lowers the chance for

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insertional mutagenesis. Another alternative that would completely remove the potential for mutagenesis would be through the delivery of dCas9/ gRNAs ribonucleoprotein complexes (dCas9 RNPs). dCas9 RNPs consist of dCas9 preloaded with gRNAs, which are then directly delivered to cells using electroporation or transfection techniques, eliminating the need for DNA integration into the genome. However, dCas9 RNPs come with a major drawback; they are cleared rapidly from the cell through protein degradation pathways [127]. Therefore, the dCas9 RNPs would need to be re-introduced into the source cells at regular intervals to effectively trans-differentiate the cells.

Another concern with trans-differentiated cells is their ability to completely mimic their desired cell phenotype, as it is likely that the trans-differentiated cells will not be identical to their native counter parts. Thus, more complete reprogramming processes are needed to generate trans-differentiated cells that more closely resemble the desired cell phenotypes. Through thorough testing and experimentation, the major characteristics of the reprogrammed cells can be analyzed and compared to native cells. Although *in vitro* assays will analyze some of the reprogrammed cells' properties, well-designed *in vivo* assays are necessary to fully characterize them in a physiological setting. Current *in vivo* studies are superficial and typically fail to detail more than a handful of reprogrammed cell capabilities; as such, more extensive testing in animal models is necessary before trans-differentiated cells see any translation to clinical applications [128, 129]. Lastly, reprogramming efficiency is another problem associated with the trans-differentiation process [128]. A low conversion efficiency generally leads to a lengthy period of time before there are enough reprogrammed cells for any clinical application, hindering the use of trans-differentiated cells in humans, as clinical situations are often time-sensitive [130]. Consequently, improving the efficiency and cell yield of the transdifferentiation process is vital to make the trans-differentiation more favorable for clinical applications. This can be done with a myriad of methods, which include optimizing biochemical [131], biophysical [132], and biomechanical [133] cues the cells experience during the reprogramming process, targeting additional transcription factors, and transitioning from exogenous overexpression to endogenous up-regulation via dCas9. Here we display a table showing some advantages and disadvantages of using stem cells in neurodegenerative cell therapies **(Table 2).** Each stem cell has a specific neurogenic potential and can achieve certain results, but there are still many problems to be solved before they can be used for clinical applications.

## Conclusions

Recent experiments that make use of spontaneous or intentional fusions of somatic cells with ESCs, ECCs, EGCs, or others, have shown that somatic nuclei can even be reprogrammed through cell fusion. Such reprogramming consists of the epigenetic remodeling of the somatic genome to yield a new (and typically more embryonic) state of chromatin organization and organic phenomenon. Performing assays of developmental potential like chimera formation can operationally assess the reprogramming of somatic/ embryonic cell hybrids.

Three conditions ought to be satisfied for proof of reprogramming in hybrid cells:

(1) The organic phenomenon in hybrids must carry with it the sum of individual patterns of organic phenomenon present in unfused parental cells.

(2) Gene silencing or activation in hybrids is best demonstrated with polymorphisms that mark the "parental" origin of reprogrammed organic phenomena.

**Table 2:** Advantages and Disadvantages of Stem Cells

| Cells | Sources | Advantages | Disadvantages |
|---|---|---|---|
| Neural stem cells (NSCs) | Primary tissues, (fetal, neonatal, and adult brain) Embryonic stem cells Induced pluripotent stem cells | Easy to access No ethical issues (but based on sources) No histocompatibility | Strong immunogenicity (but based on sources) The mechanism of cell proliferation, differentiation, and migration is unclear |
| Mesenchymal stem cells (MSCs) | Bone marrow, Adipose tissue, and Umbilical cord | Widespread sources Secrete multiple bioactive factors Directional migration | Bone marrow mesenchymal stem cells-limited raw materials Poor proliferation, and traumatic No unified identification standard for umbilical cord blood mesenchymal stem cells, and the culture technology in vitro and differentiation are not yet mature |
| Embryonic stem cells (ESCs) | Early embryo | Strong proliferation ability Abundant sources Can be passed on | Ethical issues The allograft produces a great rejection reaction Unrestrained differentiation Tumorigenicity |
| Induced pluripotent stem cells (iPCSs) | Gene recombination | No ethical issues No histocompatibility | Complex operation process Low reprogramming efficiency Mutation induction Tumorigenicity |

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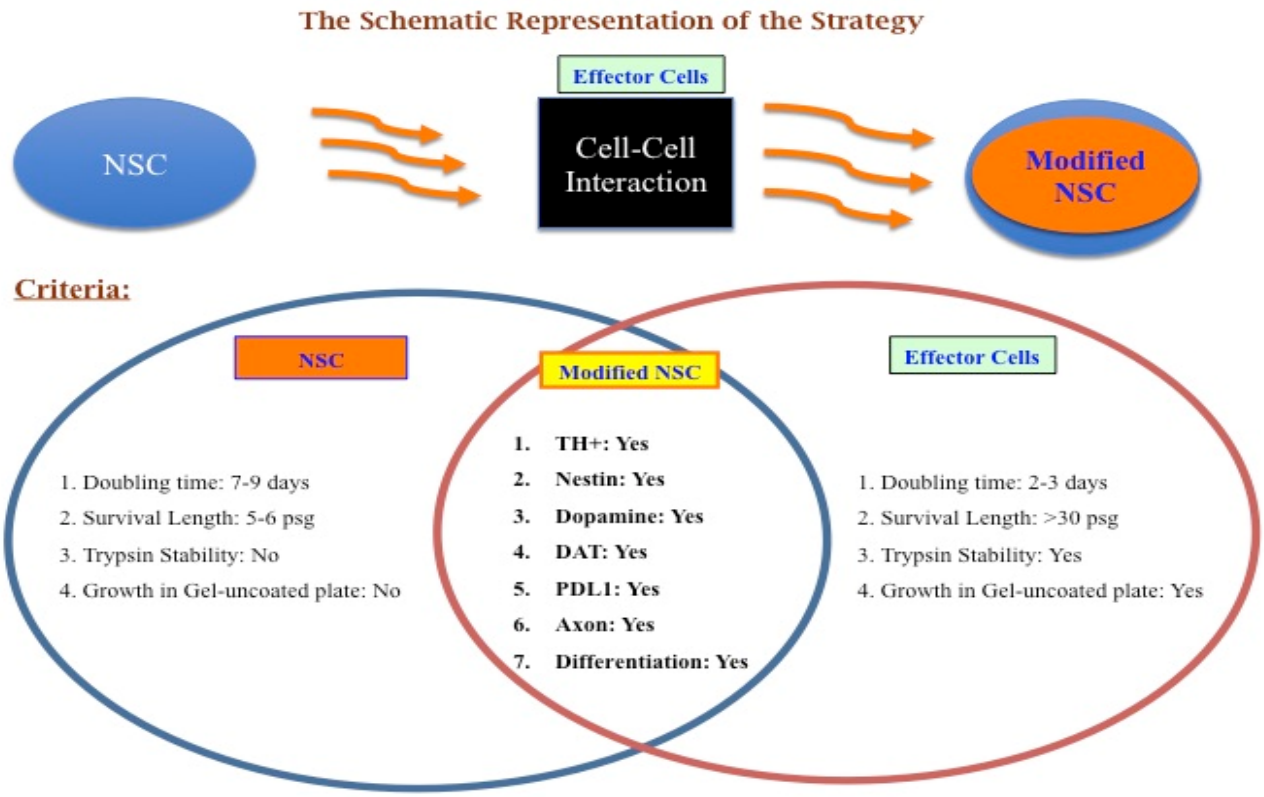


**Figure 1:** A Schematic Diagram

(3) Reprogrammed hybrid cells should exhibit unique developmental potential or biological characteristics.

Trans-differentiation is a powerful tool for generating functional cell phenotypes without the need for iPSCs or embryonic stem cells. Over the past several years, several techniques for cellular reprogramming have been developed and various targeted cell phenotypes have been generated, with encouraging results. Although current trans-differentiation methods are somewhat limited due to efficiency problems, there is ongoing research that aims to improve efficiency and there have been preliminary success with the emergence of dCas9 as an alternative to transgene overexpression methods. Regardless of efficiency limitations, a wide array of cells has been successfully generated and their ability to mimic physiological cells shows great promise, especially with the advent of trans-differentiating cells *in situ*. These cells still have a long way to go to achieve fully-functional states and see use in tissue engineering, as rigorous clinical testing needs to be conducted. Nevertheless, considering how infantile the fields of reprogramming and trans-differentiation are, it would not be surprising to see transdifferentiated cells have a place in personalized regenerative medicine and tissue engineering in the future [128]**.** This article is a review of our concept on the idea whether and how a cell can be modified for better efficacy in terms of Dopamine production and cell survival and can bypass the genetic defect in the host for PD therapy, but not on any Experimental Observations. A schematic diagram-1 is posted here to view the concept of our future strategy. Choice of effector cells is matter of selection based on the goals [6].

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## Author's Contribution

Both the authors have contributed equally to preparing this article, reading, and approving the final manuscript.

## Conflict of Interests

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## Consent for Publications

Both the authors have agreed to submit this paper for publication.

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Not applicable

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