

Cell based therapy for the treatment of neuropsychiatric disorders



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Introduction

Worldwide, neuropsychiatric illnesses have a significant negative impact on the economy, health care system, and wellbeing of affected patients and their dependents (1). Neuropsychiatric disorders, such as major depressive disorder (MDD), schizophrenia (SZ), or bipolar disorder (BD), is thought to affect at least one in four members families. Mental illness and substance use disorders accounted for a combined 173.1 million disability-adjusted life years (DALYs), or roughly 7.1% of the total disease burden worldwide (2). Due to the COVID-19 pandemic, the number of people who suffer from anxiety and depressive disorders significantly increased in 2020 (3). According to studies from India, depression and anxiety are very common in both the general population and COVID-19 infected patients as well as in the post-COVID-19 infection stage (4).

The term "potency" describes a stem cell's capacity to multiply and differentiate into various cell types. In many ways, stem cells have revolutionized how we study and treat diseases (5). Due to the central nervous system's (CNS) poor capacity for regeneration, stem cell therapies are widely used in regenerative medicine, particularly in neurological pathologies. Numerous pre-clinical animal models have demonstrated the safety and efficacy of stem cell therapy, spurring an increase in clinical trials (6). Stem cell (SC) therapies benefit the CNS through a number of mechanisms, including cell replacement, inflammation control, and neuroprotection. Depending on where stem cells are coming from, these mechanisms change. Human pluripotent stem cells (hPSCs), fetal-derived neural progenitor stem cells (fNPCs), and mesenchymal stem cells (MSCs) are the three types of stem cells that are frequently used (7).

Human Pluripotent Stem Cells

Stem cells, like hPSCs, are helpful in regenerative medicine because they can self-renew and differentiate into specific tissue types. Human embryonic stem cells (hESCs) and human induced pluripotent stem cells (hiPSCs) are the two types of hPSCs that are most frequently used. In the clinical setting, cell expansion and replacement are the main uses of hPSCs. Due to the high risk of cancer caused by mutations accumulated during the proliferation of undifferentiated tissues as well as the effects of the local microenvironment, this cannot occur by direct implantation.

Prior to transplantation, the cells should ideally be cultured and differentiated into tissue (2).

Fetal-Derived Neural Progenitor Stem Cells

Cells from the fetal brain and spinal cord are used to create fNPCs. These stem cells are advantageous for treating CNS pathologies because they can differentiate into different CNS cell types, including neurons, glial cells, and neuroectodermal cells. The availability of fNPCs is a significant limiting factor, though; for some transplantations, ten aborted fetuses may be needed for each patient. Cell replacement is the main therapeutic strategy for treating fNPCs, with encouraging outcomes in rat models of Parkinson's disease, Huntington's disease, traumatic brain injury, and stroke (7).

Mesenchymal Stem Cells

Multipotent self-renewing stem cells known as mesenchymal stem cells (MSCs) can also be found in the umbilical cord, peripheral blood, and adipose tissue. MSCs are typically taken from bone marrow. Animal models of pathologies of the heart, liver, eye, and blood have been used primarily in MSC testing. A meta-analysis found that there was no increase in acute infusional toxicity, organ system complications, infection, death, or malignancy when MSCs were administered intravenously (8).

Cell therapy employed for neuropsychiatric disorders

Depression

Stem-cell therapy targets the hippocampus in an effort to improve neuronal plasticity. The hippocampal grey matter is severely reduced in patients with depression. In depressed people, this diminution results in fewer neurons and decreased brain communication. Many of the symptoms of depressive episodes are caused by the loss of interneurons in the hippocampus' anterior cingulate cortex (1). The outcomes of various experimental studies strongly support stem cells' potential therapeutic use in the treatment of depression. Although data from experimental models has demonstrated beneficial effects in treating depression, there are still open questions (8).

Autism Spectrum Disorder

The basis for the potential use of stem cells in ASD therapy has been provided by the molecular and cellular changes that underlie ASD. Most importantly, the paracrine effects and immunomodulatory properties of SC have made it possible for clinical applications in the treatment of ASD. SC option therapy may offer significant advantages for restoration therapy through the secretion of, secretome, a complex tool of macromolecules (interleukins, growth factors, and extracellular vesicles) which is responsible for the recovery of damaged tissues, and plays a significant role in the paracrine effect of stem cells (27).

Schizophrenia

iPSC may be a more effective option in schizophrenia. Interneurons, which are damaged in schizophrenia, are created using embryonic stem cells in several studies to serve as a disease model. In addition, stem cell-derived interneurons may one day be used to treat schizophrenia in patients by being transplanted into their bodies. Patients with schizophrenia have fewer GABAergic cells in their prefrontal cortex (PC) therefore implantation of interneurons in PC region could improve connectivity (1).

Bipolar Disorder

Neuropsychiatric disorders including bipolar disorder, have been linked to microRNAs (miRNAs), which play a critical role in brain development and plasticity. Additionally, it has been reported that changes in neural stem cell numbers, distribution, and differentiation capacity have a significant impact on brain homeostasis and neuroplasticity. Therefore, it may be important to identify target miRNAs to understand the future prospects of neural stem cells in maintaining brain homeostasis as a promising therapeutic tool for stem-cell-based therapy and as a promising potential therapeutic tool suitable for BD therapy (28).

Obstacles in bench to bed progress of cell therapy

Efficacy issues

Numerous cells are being used for cell therapy, however, the therapeutic effectiveness is one of the important factors of any transplanted cell. Cell therapy alone is not sufficient to produce desired therapeutic effects, therefore, supportive treatments such as rehabilitation, pharmacological agents, and electrical/magnetic stimulation are required to enhance the effectiveness of cell therapy (29).

Safety issues

Safety issues are not the problem in case of autologous patient-derived cells. Reprogrammed or genetically modified cells have increased stemness potential but these cells are associated with the risk of uncontrolled proliferation. As an alternative, allogenic transplants from healthy donors may avoid the cell proliferation issues, however, these cells have a risk of rejection from immune system. Failsafe procedures should be verified using a variety of techniques in clinical settings even after extensive testing (29).

Evaluation procedure issues

Several methods are employed during the clinical testing to ensure the safety and efficacy of the cell therapy. The significant criteria of the stem cells, quality and well-defined characteristics, should be checked before their clinical use. Dose, route, time, and non-invasive procedure to administer cells, and well-designed clinical trials play significant role in ensuring the safety and efficacy of cell therapy (29).

Patient's rights issues

Privacy of the patients, involved in the testing of cell therapy, must be protected. Problems may arise from the transplanted cells, cell associated factors, and cell therapy procedure during the clinical trials. Patient complications should be monitored in invasive procedure, as well as during transplantation and post-transplantation period to ensure long term safety (29).

Conclusion

Cell based therapy is the promising therapy for various neuropsychiatric disorders including depression, ASD, schizophrenia, bipolar disorders. Stem cells including hPSCs, fNPCs, and MSCs are frequently used, and provide their effects through neuroestoration (release of neurotransmitter), activation of neurogenesis, anti-inflammation, and neuroprotection mechanisms. Despite of several advantages, cell therapy also has numerous obstacles such as poor efficacy, safety issues, investigational problems, and patient's rights issues which hinder

translation of safe and effective cell-based therapies from bench to bed. Further, cell-based therapies might be good therapeutic options for the treatment of neuropsychiatric disorders, however, extensive research in this area is required.

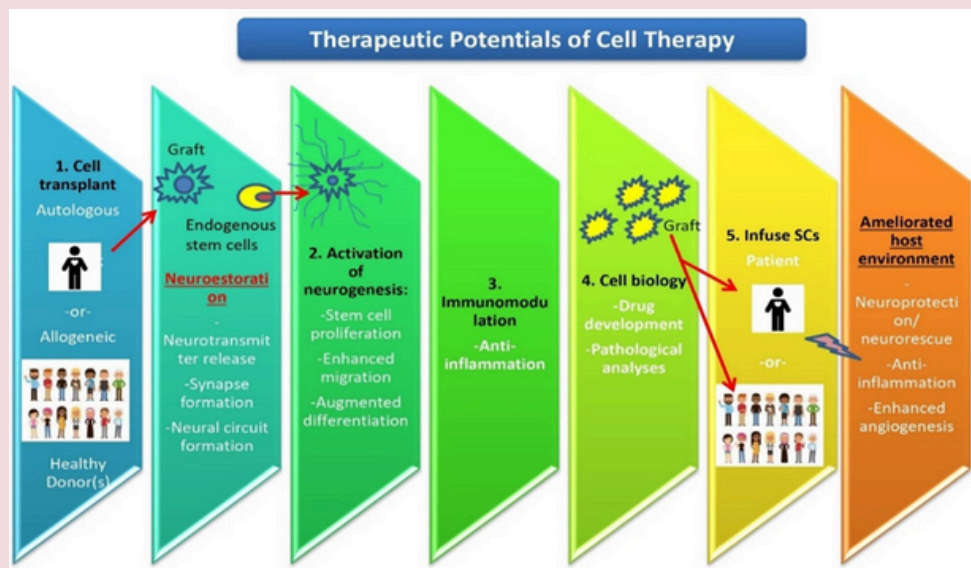


Figure 1: The therapeutic potentials of cell therapy

Table 1. Stem cell models to study neuropsychiatric disorders

S. No.	Neuro-psychiatric Disorders	Animal model details	Major findings	References
1.	Depression	Wistar rats; depression, induced with Chronic mild stress (CMS)	Anti-inflammatory effects; ↓pro-inflammatory cytokines; ↑expression of anti-inflammatory cytokines; BMMCs ↓ 8'2-deoxyguanosine level	(9)
		C57BL/6 mice; depression-induced with CMS	Improves depressive-like behaviors. ↓expression of inflammatory factors in the serum. ↓microglial activation in the hippocampus	(10)
		Wistar Kyoto rats model of treatment-resistant depression	MSCs encapsulation ↑treatment effects	
		Mice model depression induced by CUMS	The hUC-MSCs treatment improves anxiety-like behaviors, ↓pro-inflammatory factor levels, and ↑anti-inflammatory factor levels. Inhibit microglial M1 polarization and the level of inflammation factors. C3a-C3aR signaling inhibition alter polarization of microglia results ↓neuroinflammation. ↓neuronal damage and synaptic deficits.	(11)
		Sprague Dawley rats; Depression model by corticosterone injection	BMSCs-derived exosomes improved hippocampal neuron injury of rats with depression by upregulating miR-26a.	(11)

Table 1. Stem cell models to study neuropsychiatric disorders (continued...)

		Male BALB/c mice depression, induced by CS	miRNA ↓levels of pro-inflammatory cytokines (IL-1 β , IL-6, and TNF α) released by astrocytes <i>in vivo</i> ; Exosomes with ↓ miR-207 levels showed ↓antidepressant activity <i>in vivo</i> experiments. ↓antidepressant activity MiR-207 could ↓release of pro-inflammatory cytokines <i>in vitro</i> .	(12)
		iPSC-derived serotonergic neurons	Treatment of serotonergic neurons with short interfering RNA (siRNA) targeting PCDHA6/PCDHAB ↑neurite length in serotonergic neurons.	(13)
2.	Autism Spectrum Disorders (ASD)	BTBR mice; MSC derived exosomes	Ameliorating autistic-like behaviors.	(14)
		BTBR mice and control wild type C57BL mice; MSC derived exosomes	↑Social-interaction and ↓repetitive behaviors; ultrasonic vocalization and maternal pup retrieval were also improved	(14)
		iPSC-derived telencephalic organoids	↓ levels of GABAergic neuronal differentiation	(15)
		iPSC-derived NPCs and neurons	↓Proliferation; neurons showed a rescue of network defects	(16)
		iPSC-derived neurons and astrocytes	↑Synaptic puncta	(17)
		iPSC-derived excitatory neurons	↓Synaptic 1 puncta, synaptic connections, dendrite length, branch complexity	(18)
3.	Schizophrenia	Rodent; phencyclidine (PCP) model of schizophrenia	Improved novel object recognition and normalized pre-pulse inhibition	(19)
		MAM rodent model	Normalized latent inhibition, ↑social interaction time, ↑reversal learning and extradimensional set shifting, normalized dopamine population activity, ↓hippocampal hyperactivity, ↓amphetamine-induced locomotor activity, ↑contextual fear conditioning normalized dopamine population activity, and ↓hippocampal hyperactivity.	(1)
		Cyclin D2 knock-out	↓Amphetamine-induced locomotor activity, ↑contextual fear conditioning normalized dopamine population activity, and ↓hippocampal hyperactivity	(20)
		iPSC-derived neurons	Neurons showed an ↑connectivity and expression of glutamate receptors	(21)
		iPSC-derived NPCs, excitatory neurons	FURIN rs4702: control and CRISPR-Cas9-edited excitatory neuron FURIN RNA expression made more similar	(22)
4.	Bipolar Disorder	iPSC-derived hippocampal dentate gyrus (DG) granule-like neurons	LiCl responder neurons exhibited ↓number of action potentials and ↓hyperexcitability	(23)
		iPSC-derived hippocampal DG granule-like neurons and CA3 pyramidal neurons	Treatment with α -dendrotoxin, Tetraethylammonium chloride, or 4-aminopyridine: ↓neuronal excitability in LiCl responder and non-responder lines treatment with LiCl: ↓ excitability of LiCl responder neurons	(24)
		iPSC-derived hippocampal DG-like neurons	↑Wnt/b-catenin signaling activity, ↓ hyperexcitability	(25)
		iPSC-derived astrocytes and neurons	Recovered neuronal activity	(26)

References

1. Bartony MA, Gallicchio VS. Stem Cells, Lithium and Neuropsychiatric Disorders. *J Stem Cell Res.* 2022;3(1):1-13.
2. Soliman MA, Aboharb F, Zeltner N, Studer L. Pluripotent stem cells in neuropsychiatric disorders. *Molecular psychiatry.* 2017;22(9):1241-9.
3. WHO. Mental Health. [Fact Sheet]. 2022/accessed on January 6,2023.
4. Vaishnav M, Grover S, Vaishnav P, Sharma K, Avasthi A. Psychiatric and neuropsychiatric issues in persons with COVID-19 infection: A case-control online study from India Neorealists study. *Indian journal of psychiatry.* 2022;64(5):473-83.
5. Alessandrini M, Preynat-Seauve O, De Bruin K, Pepper MS. Stem cell therapy for neurological disorders. *South African Medical Journal.* 2019;109(8 Supplement 1):S71-S8.
6. Trounson A, McDonald C. Stem cell therapies in clinical trials: progress and challenges. *Cell stem cell.* 2015;17(1):11-22.
7. Gala D, Gurusamy V, Patel K, Damodar S, Swaminath G, Ullal G. Stem Cell Therapy for Post-Traumatic Stress Disorder: A Novel Therapeutic Approach. *Diseases.* 2021;9(4):77.
8. do Prado-Lima PANs, Costa-Ferro ZSM, de Freitas Souza BS, da Cruz IBM, Lab B. Is there a place for cellular therapy in depression? *World Journal of Psychiatry.* 2021;11(9):553.
9. do Prado-Lima PANs, Onsten GA, de Oliveira GN, Brito GC, Ghilardi IM, de Souza EV, et al. The antidepressant effect of bone marrow mononuclear cell transplantation in chronic stress. *Journal of Psychopharmacology.* 2019;33(5):632-9.
10. Huang X, Fei G-q, Liu W-j, Ding J, Wang Y, Wang H, et al. Adipose-derived mesenchymal stem cells protect against CMS-induced depression-like behaviors in mice via regulating the Nrf2/HO-1 and TLR4/NF- κ B signaling pathways. *Acta Pharmacologica Sinica.* 2020;41(5):612-9.
11. Li J, Wang H, Du C, Jin X, Geng Y, Han B, et al. hUC-MSCs ameliorated CUMS-induced depression by modulating complement C3 signaling-mediated microglial polarization during astrocyte-microglia crosstalk. *Brain Research Bulletin.* 2020;163:109-19.
12. Li D, Wang Y, Jin X, Hu D, Xia C, Xu H, et al. NK cell-derived exosomes carry miR-207 and alleviate depression-like symptoms in mice. *Journal of neuroinflammation.* 2020;17(1):1-19.
13. Vadodaria KC, Ji Y, Skime M, Paquola AC, Nelson T, Hall-Flavin D, et al. Altered serotonergic circuitry in SSRI-resistant major depressive disorder patient-derived neurons. *Molecular psychiatry.* 2019;24(6):808-18.
14. Perets N, Hertz S, London M, Offen D. Intranasal administration of exosomes derived from mesenchymal stem cells ameliorates autistic-like behaviors of BTBR mice. *Molecular autism.* 2018;9(1):1-12.
15. Mariani J, Coppola G, Zhang P, Abyzov A, Provini L, Tomasini L, et al. FOXG1-dependent dysregulation of GABA/glutamate neuron differentiation in autism spectrum disorders. *Cell.* 2015;162(2):375-90.
16. Marchetto MC, Belinson H, Tian Y, Freitas BC, Fu C, Vadodaria KC, et al. Altered proliferation and networks in neural cells derived from idiopathic autistic individuals. *Molecular psychiatry.* 2017;22(6):820-35.
17. Russo FB, Freitas BC, Pignatari GC, Fernandes IR, Sebat J, Muotri AR, et al. Modeling the interplay between neurons and astrocytes in autism using human induced pluripotent stem cells. *Biological psychiatry.* 2018;83(7):569-78.
18. Zaslavsky K, Zhang W-B, McCready FP, Rodrigues DC, Deneault E, Loo C, et al. SHANK2 mutations associated with autism spectrum disorder cause hyperconnectivity of human neurons. *Nature neuroscience.* 2019;22(4):556-64.
19. Tanaka EM, Reddien PW. The cellular basis for animal regeneration. *Developmental cell.* 2011;21(1):172-85.
20. Felgentreff K, Du L, Weinacht KG, Dobbs K, Bartish M, Giliani S, et al. Differential role of nonhomologous end joining factors in the generation, DNA damage response, and myeloid differentiation of human induced pluripotent stem cells. *Proceedings of the National Academy of Sciences.* 2014;111(24):8889-94.
21. Brennand KJ, Simone A, Jou J, Gelboin-Burkhardt C, Tran N, Sangar S, et al. Modelling schizophrenia using human induced pluripotent stem cells. *Nature.* 2011;473(7346):221-5.
22. Schrode N, Ho S-M, Yamamuro K, Dobbyn A, Huckins L, Matos MR, et al. Synergistic effects of common schizophrenia risk variants. *Nature genetics.* 2019;51(10):1475-85.
23. Stern S, Santos R, Marchetto MC, Mendes APD, Rouleau GA, Biesmans S, et al. Neurons derived from patients with bipolar disorder divide into intrinsically different sub-populations of neurons, predicting the patients' responsiveness to lithium. *Molecular psychiatry.* 2018;23(6):1453-65.
24. Stern S, Sarkar A, Stern T, Mei A, Mendes APD, Stern Y, et al. Mechanisms underlying the hyperexcitability of CA3 and dentate gyrus hippocampal neurons derived from patients with bipolar disorder. *Biological psychiatry.* 2020;88(2):139-49.
25. Santos R, Linker SB, Stern S, Mendes APD, Shokhirev MN, Erikson G, et al. Deficient LEF1 expression is associated with lithium resistance and hyperexcitability in neurons derived from bipolar disorder patients. *Molecular psychiatry.* 2021;26(6):2440-56.
26. Vadodaria KC, Mendes APD, Mei A, Racha V, Erikson G, Shokhirev MN, et al. Altered neuronal support and inflammatory response in bipolar disorder patient-derived astrocytes. *Stem cell reports.* 2021;16(4):825-35.
27. Alessio N, Brigida AL, Peluso G, Antonucci N, Galderisi U, Siniscalco D. Stem cell-derived exosomes in autism spectrum disorder. *International Journal of Environmental Research and Public Health.* 2020;17(3):944.
28. Coradduzza D, Garroni G, Congiargiu A, Balzano F, Cruciani S, Sedda S, et al. MicroRNAs, Stem Cells in Bipolar Disorder, and Lithium Therapeutic Approach. *International Journal of Molecular Sciences.* 2022;23(18):10489.
29. Yasuhara T, Kawauchi S, Kin K, Morimoto J, Kameda M, Sasaki T, et al. Cell therapy for central nervous system disorders: current obstacles to progress. *CNS neuroscience & therapeutics.* 2019;26(6):595-602.