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# Integrative Perspectives on In Vitro Neurogenesis; From Fundamental Mechanisms to Clinical Potential

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## Abstract

In vitro neurogenesis, defined as the differentiation of stem cells into functional neurons under controlled laboratory conditions, represents a pivotal tool in contemporary neuroscience research and regenerative medicine. This approach enables precise modeling of neurodevelopmental processes and neurodegenerative disorders, while also supporting the exploration of novel therapeutic strategies. Stem cell–based platforms, including embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and neural stem cells (NSCs), provide versatile and well-characterized sources for generating diverse neuronal lineages. Experimental in vitro models such as neuronal rosettes and neurospheres offer valuable insights into early neural commitment, spatial organization, and lineage specification during neural differentiation. Furthermore, recent advances have highlighted stem cell–derived exosome therapy as a promising cell-free approach for central nervous system (CNS) regeneration. Collectively, this review summarizes major cellular sources, key molecular markers, differentiation mechanisms, and translational applications of in vitro neurogenesis, while also addressing current limitations and outlining future directions in this rapidly evolving field.

**Keywords:** Embryonic stem cells (ESCs), Exosome therapy, In vitro neurogenesis, Induced pluripotent stem cells (iPSCs), Neural stem cells (NSCs), Progenitors

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## Introduction

Neurogenesis occurs both during embryonic development and in limited regions of the adult brain, such as the subventricular zone (SVZ) and subgranular zone (SGZ) of the hippocampus (1). In vitro neurogenesis allows scientists to recreate these processes under controlled conditions, bypassing the complex and variable in vivo environment (2). This approach facilitates a deeper understanding of neural development, disease modeling, and central nervous system (CNS) repair strategies.

## Literature Search Strategy

A structured literature search was conducted to identify relevant publications on in vitro neurogenesis and related translational applications. The primary databases used were PubMed and Google Scholar. The search covered studies published between 1990 and 2025. Search terms included combinations of the following keywords: “in vitro neurogenesis,” “neural stem cells,” “embryonic stem cells,” “induced pluripotent stem cells,” “neuronal rosettes,” “neurospheres,” “neuronal differentiation,” and “exosome therapy in CNS.” Only peer-reviewed articles published in English were included. Both original research articles and review papers relevant to neural differentiation mechanisms, cellular markers, disease modeling, and regenerative medicine applications were considered. In addition, the reference lists of selected articles were manually screened to ensure comprehensive coverage of the topic.

## Cellular Sources for In Vitro Neurogenesis

### Embryonic Stem Cells (ESCs)

ESCs exhibit pluripotency (3, 4) and can differentiate into various neuronal subtypes, including dopaminergic, cholinergic, and GABAergic neurons (5). Their ability to model early neurodevelopment is valuable, though their clinical use is limited by tumorigenicity and ethical concerns.

### Induced Pluripotent Stem Cells (iPSCs)

IPSCs share similar properties with ESCs but are reprogrammed from adult somatic cells, making them ethically viable and patient-specific (6, 7). IPSC-derived neurons are now widely used in modeling disorders such as Alzheimer’s, Parkinson’s, and Huntington’s disease (8).

### Neural Stem Cells (NSCs)

NSCs derived from fetal or adult CNS tissues can self-renew and give rise to neurons, astrocytes, and oligodendrocytes. They are commonly maintained as neurospheres and have shown potential in CNS regeneration models (9).

## Mechanisms of Neuronal Differentiation

### Role of Growth Factors

Neurotrophic factors such as brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and fibroblast growth factor-2 (FGF-2) are critical for supporting neuronal survival, synaptogenesis, and differentiation (10, 11, 12).

### Transcriptional and Epigenetic Control

Key transcription factors— Neuronal Differentiation 1 (NEUROD1), Achaete-Scute Family BHLH Transcription Factor 1 (ASCL1), and POU Class 3 Homeobox 2 (BRN2)—initiate neuronal lineage specification. REST/NRSF acts as a repressor

and must be downregulated for neuronal gene expression to proceed (13, 14). Epigenetic mechanisms like DNA methylation and histone acetylation further fine-tune differentiation (13).

**Culture Systems: 2D vs. 3D Models**

Traditional 2D cultures are valuable but limited in mimicking brain complexity. Three-dimensional (3D) systems such as neurospheres and brain organoids provide more physiologically relevant environments, promoting natural cell–cell interactions and layered architecture (15).

## Experimental Models in In Vitro Neurogenesis

**Neuronal Progenitor Cells and Early Neural Commitment**

Neuronal progenitor cells (NPCs) represent an intermediate stage between pluripotent stem cells and fully differentiated neural cells (Fig. 1). These cells have restricted potential compared to NSCs but are capable of differentiating into major neural lineages, including neurons, astrocytes, and oligodendrocytes. NPCs are essential for early neurodevelopment, contributing to both neural patterning and regional specification.

The early commitment of stem cells to a neural lineage is driven by intrinsic genetic programs and extrinsic signals such as FGF2, BDNF, and retinoic acid, which influence the transcriptional and epigenetic landscape of the cells (16–18). During this stage, cells express characteristic neural progenitor markers including Nestin, PAX6, SOX1, and SOX2, are reflecting their identity and developmental stage (19–22, 1). Morphologically, NPCs often exhibit a bipolar or radial glia-like structure and form organized arrangements in vitro, which serve as the foundation for downstream differentiation models such as rosettes and neurospheres. These models retain the multipotency and self-renewal capacity of NPCs, thereby serving as ideal systems for studying early neurogenesis (23).

**Neuronal Rosettes**

Neuronal rosettes are radial arrangements of columnar neural progenitor cells that arise during early stages of in vitro differentiation from ESCs or iPSCs. These structures resemble the embryonic neural tube and are considered hallmark indicators of early neuroectodermal commitment (24). They express typical neuroepithelial markers such as PAX6, SOX1, and Nestin (1, 25) , and can be isolated to derive more mature populations of NSCs for further differentiation.

**Neurospheres**

Neurospheres are spherical clusters (26) of neural stem or progenitor cells grown in suspension cultures, typically in serum-free media supplemented with epidermal growth factor (EGF) and fibroblast growth factor-2. This model allows for expansion, self-renewal, and multipotency testing of NSCs (9, 27). Upon exposure to differentiation conditions (e.g., withdrawal of mitogens), cells from neurospheres can give rise to neurons, astrocytes, and oligodendrocytes. Neurosphere assays are widely used to assess neurogenic potential and study stem cell responses to various stimuli.

**Marker Profiles of In Vitro Models**

Neuronal rosettes and neurospheres, as representative in vitro models of neurogenesis, exhibit distinct marker expression patterns that reflect their


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developmental status (Table 1). Neuronal rosettes characteristically express early neuroepithelial markers such as PAX6, SOX1, and Nestin, indicating their primitive neural identity and radial organization reminiscent of the neural tube structure (28, 29). In contrast, neurospheres predominantly maintain stemness-associated markers including Nestin, SOX2, and Musashi-1 during their undifferentiated state (27, 30, 31). Following induction of differentiation, these 3D cultures give rise to multiple neural lineages, as demonstrated by the emergence of neuronal, astrocytic, and oligodendroglial markers (32–34), confirming the multipotent capacity of neural stem cell populations.

## Neuronal Lineage Markers

The identification of lineage-specific markers plays a crucial role in validating successful neural differentiation in vitro (Table 2).

### Nestin

Nestin is an intermediate filament protein expressed predominantly in undifferentiated neural stem cells and early progenitor populations. It serves as a widely accepted indicator of early neural commitment in stem cell-derived cultures (1, 25). As differentiation progresses, Nestin expression gradually declines, reflecting the transition from proliferative progenitors to lineage-restricted cells.

### βIII-Tubulin (TUJ1)

βIII-tubulin, detected by the TUJ1 antibody, represents one of the earliest and most reliable markers of neuronal differentiation (35). Its expression indicates post-mitotic neuronal commitment and cytoskeletal reorganization associated with neuronal polarization. Quantification of TUJ1-positive cells is commonly employed to assess neurogenic efficiency in vitro systems.

## Applications of In Vitro Neurogenesis

### Disease Modeling

Induced PSC-derived neurons have been used to model neurodevelopmental and neurodegenerative diseases, including autism, ALS, and multiple sclerosis (8, 36). These models enable the dissection of molecular pathology and high-throughput drug screening.

### CNS Regeneration

NSCs have shown potential in preclinical models of CNS repair. In vitro, they can be directed to generate neurons and glial cells; in vivo, transplanted NSCs can integrate into host circuits and aid functional recovery (9, 37).

### Spinal Cord Injury

Stem cell therapies for spinal cord injury (SCI) aim to replace lost neurons, promote axonal regrowth, and restore synaptic connections. Animal studies suggest improved motor function post-transplantation of ESC- or NSC-derived neural precursors (15).

### Exosome Therapy as a Product of Stem Cells in Neural Regenerative Therapy

Exosomes are small extracellular vesicles (30–150 nm) secreted by various cell types, including stem cells. These vesicles carry diverse molecular cargos such as proteins, lipids, mRNAs, and microRNAs, enabling intercellular communication and modulation of recipient cell function. In recent years,


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**Table 1.** Comparative summary of key morphological features, molecular markers, and functional roles of in vitro neurogenesis models. These models represent progressive stages in neural differentiation, starting from early progenitor arrangements (rosettes) to multipotent neurospheres and lineage-specific derivatives.

| Model | Structure & Growth | Key Markers | Function | References |
|---|---|---|---|---|
| **Neuronal Rosettes** | 2D radial neural structure | PAX6, SOX1, Nestin | Indicates early neuroectodermal commitment | (24), (25), (28) |
| **Neurospheres** | 3D NSC cluster | Nestin, SOX1, Musashi-1 | Allows NSC expansion and multipotency testing | (27), (30) |
| **Differentiated Neurons** | Neurite-bearing post-mitotic cells | TUJ1 (βIII-tubulin) | Indicate successful neuronal commitment | (32), (35) |
| **Glial Derivatives** | Mixed adherent cells | GFAP (astrocytes), O4 (oligodendrocytes) | Reflect glial lineage outcome of NSC differentiation | (31), (34) |

**Table 2.** A summary of major components, mechanisms, and translational implications of in vitro neurogenesis based on the integrated content of the updated review article.

| Category | Example / Item | Role / Function | Key Reference(s) |
|---|---|---|---|
| **Stem Cell Sources** | ESCs, iPSCs, NSCs | Source cells for neuronal differentiation | (5–9) |
| **Differentiation Signals** | BDNF, NT-3, FGF-2, Retinoic Acid | Promote survival, synaptogenesis, and neuronal lineage specification | (10), (11), (12), (17) |
| **Transcription Factors** | NEUROD1, ASCL1, BRN2 | Drive neural fate commitment | (13, 14) |
| **Epigenetic Regulators** | REST, DNA methylation, histone acetylation | Repress/activate gene expression for neurogenesis | (13, 14) |
| **Culture Models** | 2D cultures, 3D organoids | Mimic physiological conditions for neuronal development | (15) |
| **Structural Models** | Neuronal Rosettes, Neurospheres, Brain Organoids | Models to examine NSC behavior and early differentiation | (24–27), (28), (30) |
| **Neuronal Markers** | Nestin, PAX6, TUJ1, GFAP, O4 | Identify early progenitors and lineage-specific neural cells | (25), (29), (32–34), (35) |
| **Applications** | Disease models, CNS repair, SCI therapy, Exosome-based therapy | Translational uses of in vitro-derived neurons and cell-free regenerative strategies via exosome | (8), (9), (35–38), (40–49) |
| **Challenges** | Maturation, reproducibility, microenvironment | Current limitations in achieving clinical-grade neurons | (7, 13, 50) |
| **Future Directions** | Bioengineering, CRISPR, patient-specific models | Improve fidelity, personalization, and regenerative potential | (51) |

exosomes derived from stem cells have emerged as promising therapeutic tools in neural regenerative medicine due to their capacity to mimic many of the paracrine effects of their parent cells without the associated risks of cell transplantation (38, 39). One major advantage of stem cell-derived exosomes is their ability to cross the blood-brain barrier, allowing them to deliver therapeutic agents directly to affected areas of the CNS (40, 41). Moreover, exosomes exhibit low immunogenicity and eliminate the risks of tumorigenicity or uncontrolled differentiation associated with live stem cell


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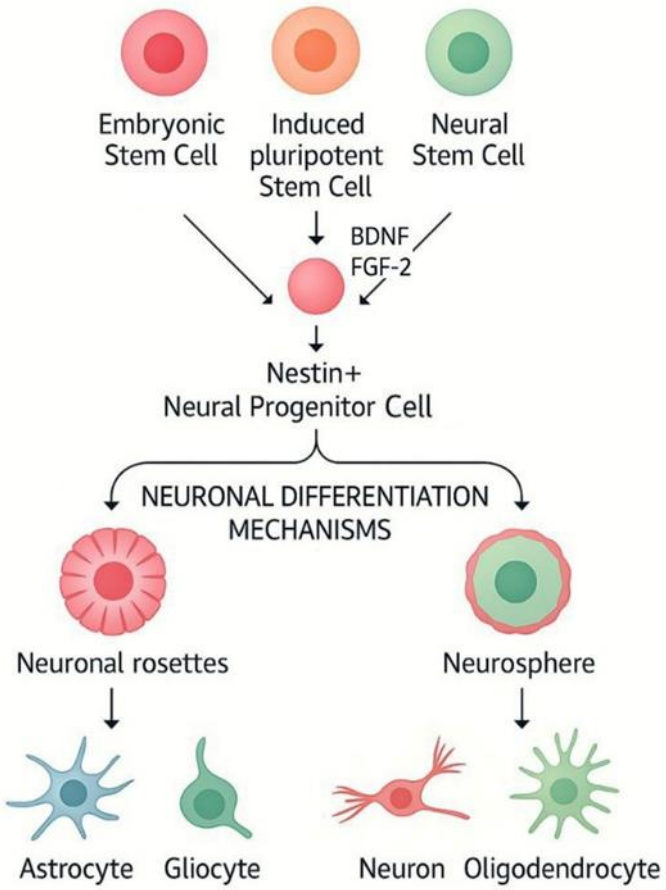


**Figure 1.** Schematic representation of in vitro neurogenesis. ESCs, iPSCs, and NSCs can differentiate through various neuronal differentiation mechanisms, such as neuronal rosettes and neurospheres. Under the influence of growth factors like BDNF and FGF-2, Nestin-positive neural progenitor cells are generated, which can further differentiate into neurons (TUJ1-positive) and glial lineage cells (GFAP-positive), including astrocytes, gliocytes, and oligodendrocytes.

therapies (38, 42). Their relatively high stability also facilitates storage and transport, which enhances their clinical feasibility (43).

In the context of neurological diseases, exosomes have shown therapeutic potential across several conditions:

- In Alzheimer's and Parkinson's diseases, mesenchymal stem cell (MSC)-derived exosomes have demonstrated neuroprotective effects, including reduced neuro-inflammation and promotion of neurogenesis (44–46).
- In SCI models, exosomes have been shown to support axonal regeneration and functional recovery by modulating local immune responses and stimulating neural repair (47).
- In traumatic brain injury (TBI), exosome treatment has resulted in improved neurological outcomes through enhanced

neurovascular remodeling and suppression of apoptosis (48).

Mechanistically, these effects are attributed to exosome cargo such as BDNF, FGF-2, and miRNAs like miR-133b, which modulate signaling pathways involved in neural differentiation and regeneration (42, 49).

Despite these advantages, several challenges remain. Standardization of isolation and purification methods is critical to ensure reproducibility and efficacy (43). The optimal dosage, frequency, and route of administration also need to be established through preclinical and clinical studies. Finally, deeper mechanistic understanding is necessary to refine and enhance exosome-based interventions for neurological applications (40, 47).

## Challenges and Limitations

Despite these advances, several issues remain:

- Maturation deficits: Many in vitro neurons exhibit immature electrophysiological properties (6, 7).
- Variability in differentiation: Protocol inconsistencies across labs affect reproducibility (50).
- Limited micro-environmental mimicry: Lack of vascularization, glial support, and extracellular matrix cues in simplified cultures can limit translational potential (13).

## Future Directions

Future work should aim to:

- Enhance neuronal maturation using long-term cultures, electrical stimulation, and co-culture with glial cells.
- Employ bioengineered scaffolds and organoids to better mimic the in vivo brain environment.
- Expand patient-specific applications using iPSC technologies and CRISPR-mediated genetic editing (51).

## Conclusion

In vitro neurogenesis stands at the interface of developmental neuroscience, disease modeling, and regenerative medicine. The integration of classical stem cell biology and emerging in vitro models has opened new frontiers for understanding the nervous system and treating its disorders. As challenges are addressed through advanced culture systems, personalized medicine, and bioengineering, the clinical translation of in vitro neurogenesis is steadily becoming a reality.

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