Magna Neurologica Vol. 4, No. 1 January 2026

https://journal.uns.ac.id/magna-neurologica
DOI: 10.20961/magnaneurologica.v4i1.2601
e-ISSN 2985-3729 p-ISSN 2963-6027

REVIEW ARTICLE **OPEN ACCESS**

OLIGODENDROCYTE DIFFERENTIATION FROM HUMAN IPSCS: STRATEGIES BASED ON SIGNALING PATHWAYS, TRANSCRIPTION FACTORS, AND NOVEL MODULATORS FOR RESEARCH AND THERAPY

Maria Maylyn Evangelina Wong*, Michelle Angelica Subrata

***Correspondence**: maria.wong@student.i3l.ac.id*
Department of Biomedicine, Indonesia International Institute for Life Sciences, Jakarta, Indonesia

Article History:
Received: July 25, 2025
Accepted: August 19, 2025
Published: January 1, 2026

Cite this as:
Wong MME, Subrata MA. Oligodendrocyte Differentiation from Human iPSCs: Strategies Based on Signaling Pathways, Transcription Factors, and Novel Modulators for Research and Therapy. Magna Neurologica. 4(1) January 2026: 75-83. 10.20961/magnaneurologica.v4i1.2601

ABSTRACT

Background: Oligodendrocytes (OLs) are vital for central nervous system (CNS) function, producing myelin sheaths and maintaining axonal integrity. However, their limited accessibility in human disease-relevant contexts has historically hindered progress in research. The advent of induced pluripotent stem cell (iPSC)-derived OLs has transformed the study of myelin-related diseases and regenerative therapies.
Objective: This review aims to provide a comparative overview of strategies for generating OLs from human iPSCs, emphasizing their mechanisms, efficiency, scalability, and translational applications.
Methods: We analyzed three major differentiation approaches described in recent literature. Signaling-based protocols replicate developmental processes by modulating TGF-β, SHH, and Wnt pathways. Transcription factor-driven methods accelerate lineage specification by directly inducing OL fate. Modulator-enhanced strategies incorporate epigenetic, metabolic, or environmental cues to improve efficiency and adaptability.
Results: Each approach offers distinct strengths and limitations. Signaling-based methods closely mimic in vivo development but require long culture times. Transcription factor-driven strategies enable rapid OL generation, although sometimes at the expense of physiological relevance. Modulator-enhanced protocols represent an emerging avenue, offering flexibility and potential for higher efficiency. Collectively, these strategies expand opportunities for disease modeling, therapeutic screening, and cell replacement therapies.
Conclusion: Advances across signaling, transcriptional, and modulatory domains have significantly advanced iPSC-based OL generation. Integration of these approaches may enable more efficient, scalable, and physiologically relevant OL production. Such progress holds significant potential to accelerate the development of myelin targeted therapeutics and enhance translational research in demyelinating diseases.

Keywords: based strategy, classical signaling, iPSC, oligodendrocyte differentiation, transcription factor-myelin regeneration

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Introduction

Oligodendrocytes (OLs) are essential glial cells in the central nervous system (CNS), responsible for producing the myelin sheath that insulates axons and facilitates rapid nerve impulse transmission. In addition to their structural role, OLs contribute to neuronal survival and metabolic support. Their dysfunction or loss is a defining feature of various neurological disorders, including multiple sclerosis (MS), leukodystrophies, and other neurodevelopmental and neurodegenerative conditions.[1,2] Despite the clinical burden of these diseases, access to functional human oligodendrocytes,

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particularly at defined developmental stages, remains limited, posing a significant challenge for studying disease mechanisms and developing targeted therapies.[3,4]

Human induced pluripotent stem cells (iPSCs) offer a promising platform for generating patient-specific oligodendrocytes in vitro, with potential applications ranging from disease modeling and drug screening to regenerative medicine. Over the past decade, numerous protocols have been developed to direct the differentiation of induced pluripotent stem cells (iPSCs) toward the oligodendrocyte lineage. However, unlike protocols for neurons or astrocytes, which are generally faster and more robust, oligodendrocyte differentiation remains relatively inefficient, time-consuming, and technically demanding.[5] Classical approaches attempt to mimic in vivo developmental signals through stepwise exposure to morphogens such as retinoic acid (RA), Sonic Hedgehog (SHH), and thyroid hormone (T3). While biologically faithful, these protocols often require several months to yield mature oligodendrocytes and are associated with high variability and limited scalability.[6,7]

To address these challenges, newer strategies have emerged to improve the efficiency and speed of oligodendrocyte generation. These include methods using transcription factor–mediated lineage instruction and protocols incorporating small molecules or epigenetic modulators to enhance plasticity and streamline differentiation.[8] Although these approaches have shown promise in accelerating the production of oligodendrocyte lineage cells, questions remain regarding their developmental fidelity, functional maturity, and suitability for clinical translation.[9]

As the field continues to expand, there is a growing need to synthesize current differentiation strategies into a cohesive framework, evaluating their underlying mechanisms and practical implications for modeling disease and designing therapeutics.[10] This review offers a comparative overview of three principal frameworks used to generate oligodendrocytes from human iPSCs: (1) classical signaling-based protocols that emulate developmental patterning, (2) acceleration strategies that incorporate transcriptional or chemical cues, and (3) emerging modulator-enhanced approaches involving epigenetic, metabolic, or environmental factors. We examine the relative advantages, limitations, and translational relevance of each strategy and discuss how these methodologies can be integrated and optimized to advance research and therapeutic development in myelin-related disorders.

Methods

Classical Signaling-Based Differentiation

The stepwise generation of oligodendrocytes from human induced pluripotent stem cells (iPSCs) through signaling-based protocols is designed to recapitulate embryonic development, relying on the precise temporal modulation of morphogens and growth factors. This approach typically progresses through three primary stages: neural induction, patterning into oligodendrocyte progenitor cells (OPCs), and maturation into functional oligodendrocytes (OLs).[5]

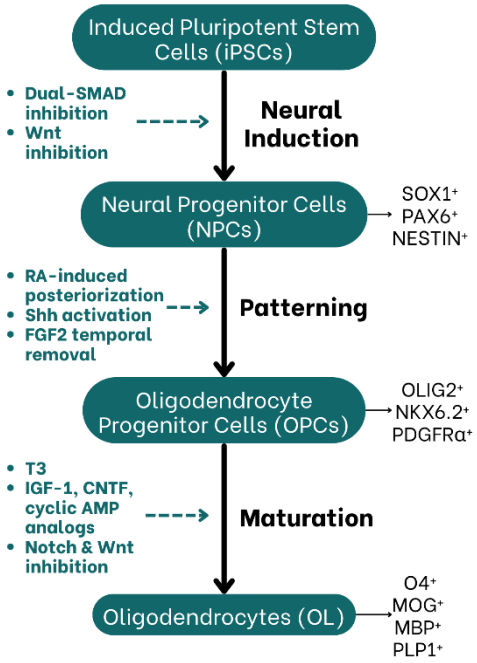

Figure 1. Stepwise representation of classical signaling-guided differentiation of human iPSCs into oligodendrocytes

As illustrated in Figure 1, the first step involves directing iPSCs toward a neuroectodermal fate. This is most commonly achieved through dual-SMAD inhibition, which involves the use of a combination of SB431542 (an inhibitor of TGF-β/Activin/Nodal signaling via ALK5) and Noggin or LDN193189 (inhibitors of the BMP pathway).[11] Dual-SMAD inhibition not only effectively suppresses non-neural lineages and promotes neural induction by mimicking the in vivo process of neural plate specification but also demonstrates a several-fold increase in neural conversion efficiency over single-inhibitor protocols, routinely achieving greater than 80% neural conversion.[12] Mechanistically, Noggin inhibits BMP signaling, preventing the default pathway toward non-neural fates, while SB431542 blocks TGF-β/Activin/Nodal pathways in parallel, collectively fostering rapid and efficient neuralization.[13,14]

This synergistic action is markedly more effective than either inhibitor alone, resulting in robust and reproducible neural induction. During this process, the extinction of the pluripotency marker OCT4 and the emergence of the neural marker PAX6 commonly occur by day 7–8 of differentiation, marking a swift and significant commitment to the lineage. Dual-SMAD inhibition is thus a foundational step in nearly

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all directed differentiation protocols toward neural and glial lineages, including oligodendrocytes.[15,16]

In some protocols aimed at generating forebrain-type oligodendrocytes, additional inhibition of the Wnt/β-catenin pathway (e.g., XAV939) is employed. This pathway plays a role in neural patterning, where its activation promotes posterior (spinal) neural identities, while its inhibition favors anterior (forebrain) fate specification.[17] By inhibiting Wnt/β-catenin signaling during early neural induction, these protocols anteriorize neural progenitors and reduce posterior bias, thus enriching for progenitors committed to developing into forebrain-type oligodendrocytes.[18] This precise modulation is critical, as Wnt activity also influences subsequent OPC specification and maturation stages in a context- and timing-dependent manner, underscoring the need for tightly controlled pathway regulation throughout differentiation.[19]

Following neural induction, the next phase involves patterning the neural progenitor cells into OPCs. This is typically guided by a combination of retinoic acid (RA) and Sonic Hedgehog (SHH) or its agonists, such as purmorphamine or SAG (Smoothened agonist).[16] RA promotes posteriorization, while activation of SHH signaling specifies ventral identity, leading to upregulation of key transcription factors such as OLIG2 and NKX6.2, critical for oligodendroglial lineage commitment.[20,21] In parallel, FGF2 (basic fibroblast growth factor) is frequently used to expand the pool of neural progenitors, although its timing and concentration require careful control.[22,23] It has opposing effects at different stages, promoting early OPC expansion but inhibiting later differentiation. This makes the temporal removal of FGF2 critical for the OPC to oligodendrocyte transition. Furthermore, as cells acquire an OPC phenotype, characterized by markers such as PDGFRα and NG2, the addition of PDGF-AA promotes their survival and proliferation.[24]

The final phase involves the maturation of OPCs into fully functional OLs. A different set of cues drives this transition to promote myelin protein expression and morphological maturation. Among the most essential factors is triiodothyronine (T3). This thyroid hormone upregulates significant myelin genes such as MBP, MOG, and PLP1.[25,26.] Additional growth factors, including insulin-like growth factor 1 (IGF-1), ciliary neurotrophic factor (CNTF), and cyclic AMP analogs (e.g., dbcAMP), further enhance the maturation process and promote myelination.[27] Importantly, inhibition of the Notch signaling pathway is often incorporated at this stage, as Notch activity maintains OPCs in an undifferentiated state and suppresses terminal differentiation.[28] As it does to the OPC specification, Wnt pathway modulation also plays a nuanced role in OL maturation. While Wnt inhibition is beneficial during early stages to promote neural and glial commitment, its activity during OL maturation must be tightly regulated, as inappropriate activation or suppression can hinder myelin gene expression.[8,5]

Together, these signaling cascades represent a coordinated and time-sensitive roadmap for deriving oligodendrocytes from induced pluripotent stem cells (iPSCs). However, variability in timing, dosage, and cell line responsiveness remains a significant challenge for standardizing protocols and translating them into clinical applications.

Transcription Factor-Based Acceleration

An alternative to classical morphogen-driven differentiation is transcription factor (TF)-based reprogramming, which seeks to bypass the lengthy and complex signaling cascades required for oligodendrocyte maturation. This approach uses forced expression of lineage-defining TFs to instruct neural progenitors directly toward an oligodendrocyte fate.[29] One widely studied system is the SON protocol, involving the forced overexpression of SOX10, OLIG2, and NKX6.2 in neural progenitor cells.[30,31] Initially demonstrated by Zhang et al and subsequently refined and validated by Ehrlich et al, this combination drives efficient and rapid oligodendrocyte lineage commitment.[29,8]

The SON protocol dramatically shortens the differentiation timeline. While classical signaling-based approaches typically require 70 to 120 days to generate mature oligodendrocytes, TF-driven protocols can achieve comparable results in as little as 28 to 35 days.[7] Ehrlich et al.[8] reported over 70% of cells expressing the OPC marker O4 at four weeks post-induction, alongside expression of maturation markers like MBP and SOX10. Morphological analysis confirmed the presence of cells with pre-myelinating and myelinating oligodendrocyte characteristics. Crucially, upon transplantation into the mouse brain, SON-derived cells engrafted, migrated, and formed compact myelin sheaths, demonstrating functional myelination in vivo. Moreover, the SON approach has been successfully applied to patient-derived iPSCs, such as those modeling multiple system atrophy, highlighting its relevance for disease-specific applications.[32]

While multi-factor systems such as SON have showcased impressive efficiency, single-factor overexpression approaches have also been explored. García-León et al.[33] demonstrated that sole overexpression of SOX10, a master regulator of oligodendrocyte development, can be sufficient to induce oligodendrocyte progenitor cells (OPCs) from human neural progenitor cells in chemically defined conditions. SOX10 directly activates downstream regulatory networks, including OLIG2, NKX2.2, and MYRF, critically coordinating oligodendrocyte

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lineage progression.[34] By combining SOX10 overexpression with a medium enriched in thyroid hormone (T3), IGF-1, and cyclic AMP analogs, the authors generated OPC-like populations expressing markers such as OLIG2, PDGFRα, and NG2 within significantly reduced timeframes.[35]

Despite having lower myelin gene expression relative to SON-based OPCs, this method offers advantages in terms of decreased genetic manipulation complexity and improved scalability. Other research supports SOX10's role as a master regulator activating critical downstream genes (NKX2.2, MYRF) required for oligodendroglial specification.[33] Minimal TF combinations like OLIG2 plus SOX10 have also proven sufficient to generate myelinating oligodendrocytes from iPSCs, underscoring the potency of selective TF cocktails.[36]

Beyond lineage-specific transcription factors, emerging evidence suggests that classical pluripotency-associated factors, such as OCT4, can enhance oligodendroglial differentiation by increasing cellular plasticity and remodeling the epigenetic landscape. Kim et al.[37] demonstrated that sustained OCT4 expression in somatic cells and defined OPC-induction conditions could directly reprogram cells into induced oligodendrocyte progenitor cells (iOPCs). These iOPCs expressed key OPC markers and efficiently differentiated into MBP^+ oligodendrocytes in vitro and following transplantation, without forming tumors. Notably, reprogramming occurred without passing through an intermediate stage of neural progenitors, suggesting a direct lineage conversion facilitated by OCT4-mediated chromatin remodeling.

Further supporting this mechanism, Yun et al.[30] found that OCT4 reconfigures chromatin accessibility at glial gene loci, promoting recruitment of transcriptional machinery associated with oligodendrocyte fate. When combined with a small-molecule cocktail, TGF-β and HDAC inhibitors, and cAMP activators, OCT4 expression rapidly generated cells expressing OLIG2, SOX10, and ultimately MBP within weeks. Genome-wide analysis indicated that OCT4's role was not to specify lineage directly but to prime the chromatin environment, establishing a permissive epigenetic state for downstream glial differentiation. This concept aligns with broader epigenetic models, wherein the transient expression of pluripotency factors, such as OCT4, can act as pioneer factors, opening previously inaccessible chromatin regions and facilitating more efficient lineage commitment without inducing full pluripotency.[38]

While TF-based approaches offer rapid and high-efficiency oligodendrocyte generation, challenges persist. Many protocols rely on integrating viral vectors, which raises safety concerns related to genomic insertion and limits translational potential.[39] Furthermore, bypassing natural developmental checkpoints may compromise physiological fidelity and regional identity of generated oligodendrocytes.[34] To overcome these issues, ongoing efforts explore transient, non-integrative delivery methods and combine TF strategies with small molecule modulators to enhance safety, maturation, and scalability.[40] Overall, TF-driven oligodendrocyte differentiation, from multi-factor protocols like SON to single-factor and epigenetic priming approaches, represents a rapidly evolving toolkit.[41] Optimizing these methods to balance speed, fidelity, safety, and scalability remains critical to advancing disease modeling and regenerative applications.

Novel and Emerging Modulators

In addition to classical signaling cues and transcription factor overexpression, recent studies have identified emerging molecular modulators that enhance the efficiency, speed, and fidelity of oligodendrocyte differentiation from induced pluripotent stem cells (iPSCs). These include endocannabinoid signaling, epigenetic regulators, and biophysical cues, all of which provide promising avenues for protocol refinement.[9,42]

One such example is the endocannabinoid system, which has been shown to play a role in both OPC proliferation and differentiation. The cannabinoid receptor agonist WIN55212-2, which activates CB1 and CB2 receptors, was recently reported to enhance oligodendrocyte maturation in vitro by inhibiting the GLI1 effector of the Sonic Hedgehog pathway, thereby promoting the transition from OPCs to mature OLs.[43,44] This highlights the potential of crosstalk modulation, rather than direct activation or inhibition of canonical pathways, as a strategy to fine-tune differentiation outcomes.

Another emerging area of interest is epigenetic regulation. Histone modifications such as H3K27me3 and H3K9me3 are associated with transcriptional repression of myelin genes and must be dynamically regulated during the transition from OPCs to myelinating OLs.[45] Studies have shown that histone deacetylase inhibitors (HDACis) and chromatin remodeling factors can promote the expression of oligodendrocyte lineage genes, enhance maturation, and improve remyelination capacity.[46] Targeting such mechanisms offers an orthogonal approach to traditional growth factor-based strategies.

Lastly, biophysical and environmental cues such as oxygen tension, extracellular matrix stiffness, and 3D organoid platforms are increasingly integrated into OL differentiation protocols.[47] Moderate hypoxic conditions have been reported to improve oligodendrocyte output, likely by mimicking the developmental CNS microenvironment.[48,49] These insights highlight the need to consider molecular signals and microenvironmental context when designing next-generation protocols.

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Results

Comparative Analysis of Differentiation Protocols

The diverse methodologies for differentiating oligodendrocytes from human induced pluripotent stem cells (iPSCs) were categorized into classical signaling-driven protocols, transcription factor-based acceleration, and emerging chemical or epigenetic modulation approaches. Table 1 summarizes their predominant features.

Table 1. Summary of key characteristics of signaling-driven, transcription factor-based, and novel modulator-enhanced differentiation strategies for oligodendrocyte generation from human iPSCs

Feature	Signaling-Driven	Transcription Factor-Based	Novel Modulator-Enhanced
Key drivers	Morphogens (e.g., RA, SHH)	TFs (e.g., SON, SOX10)	OCT4, CB1/CB2 activation, epigenetics
Timeline to OLs	~70–120 days	~28–35 days	Variable (typically 30–75 days)
OLs yield ($O4^+$ cells)	Moderate (~30–60%)	High (~70%)	Moderate to high (protocol dependent)
Fidelity to developmental stages	High	Moderate	Low to moderate
Genetic manipulation requirement	Not required	Required (viral TF delivery)	Often, but may use small molecules
Best suitability	Mechanistic studies	Drug screening, transplantation	Protocol enhancement, hybrid systems
Limitations	Long, variable, expensive	Integration risk, maturity	Early-stage, poorly standardized

OLs: Oligodendrocytes, RA: Retinoic Acid, SHH: Sonic Hedgehog, TF: Transcription Factor

Classical signaling approaches, rooted in recapitulating developmental morphogen gradients, generally offer high fidelity to the natural oligodendroglial lineage but require extended culture periods and yield moderate purity. In contrast, transcription factor-driven protocols significantly reduce differentiation time and increase oligodendrocyte yield, albeit with the caveats of genetic manipulation and potential compromises in physiological maturation. Novel modulators, including endocannabinoid agonists and epigenetic regulators, represent promising adjuncts or alternatives that may enhance efficiency or developmental accuracy, though their application remains in early stages. When selecting the optimal differentiation strategy, researchers must weigh these factors and project-specific needs, such as scalability, safety, and model relevance.

Discussion

Applications in Disease Modeling and Repair

The capability to generate mature oligodendrocytes (OLs) from human induced pluripotent stem cells (iPSCs) has revolutionized the study of myelin-related diseases and regenerative medicine. Unlike traditional rodent models, iPSC-derived OLs retain patient-specific genetic variants and human-specific epigenetic and transcriptomic profiles, enabling unparalleled modeling of disease pathophysiology and drug responses in a personalized context.[50]

One of the most illustrative examples is Pelizaeus-Merzbacher disease (PMD), a rare leukodystrophy caused by mutations in the PLP1 gene, which encodes proteolipid protein one a crucial component of myelin.[51] Inoue et al.[16] generated oligodendrocytes from PMD patient iPSCs and identified hallmark cellular phenotypes, including mislocalization of mutant PLP1 protein, activation of endoplasmic reticulum (ER) stress pathways, and increased oligodendrocyte apoptosis. Importantly, this human cellular model recapitulated molecular features of PMD that were previously inaccessible in animal models, permitting a detailed dissection of ER stress signaling as a pathogenic mechanism. Moreover, this platform provided a preclinical system for testing therapeutic agents targeting proteostasis and intracellular trafficking defects.[16,52]

Beyond inherited leukodystrophies, iPSC-derived oligodendrocytes have been utilized to investigate demyelinating diseases, such as multiple sclerosis (MS), which is characterized by immune-mediated destruction of myelin and incomplete remyelination.[53] Despite the complexities introduced by immune and microenvironmental factors, generating oligodendrocyte progenitor cells (OPCs) and mature OLs from MS patient-derived iPSCs allows investigation of intrinsic cellular deficits in OL differentiation, survival, and myelination capacity.[4] Kerkering et al.[11] used MS patient iPSC-derived OPCs to identify impaired maturation and reduced responsiveness to pro-myelinating agents, providing insight into disease heterogeneity and identifying patient-specific therapeutic responses.[54] These findings underscore the utility of patient-tailored OL models for screening remyelination-promoting drugs and investigating repair mechanisms.

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Several differentiation protocols, particularly those utilizing transcription factor (TF)-driven acceleration, have demonstrated that human iPSC-derived oligodendrocytes can functionally engraft and myelinate in vivo. Ehrlich et al.[8] showed that OLs produced via the SON protocol (overexpressing SOX10, OLIG2, and NKX6.2) grafted into neonatal mouse brains survived, migrated widely, and established compact, multilamellar myelin sheaths around host axons. These in vivo results validate the functional competence of iPSC-derived oligodendrocytes and provide a foundation for cell replacement therapies in disorders characterized by myelin loss, including MS, spinal cord injury, and white matter stroke.[55,9]

Although clinical trials specifically using iPSC-derived oligodendrocytes are not yet underway, multiple preclinical studies suggest strong therapeutic potential. Advances in differentiation protocols have increased cell purity, reduced timelines, and improved safety profiles by developing feeder-free, xeno-free, and integration-free methods.[56,3] Future translation will require rigorous characterization of graft safety, long-term functional integration, and scalable manufacturing compliant with good manufacturing practice (GMP) standards. The ability to generate patient-specific or HLA-matched oligodendrocytes also opens prospects for autologous or allogeneic transplantation to restore myelin and improve neurological function.[57]

Human iPSC-derived oligodendrocytes provide a versatile platform for mechanistic disease modeling, therapeutic drug discovery, and regenerative medicine applications. Continued refinement and validation of differentiation protocols and transplantation strategies will be critical to realize their full clinical potential for demyelinating and dysmyelinating disorders.

Challenges and Future Perspectives

While recent advances have expanded the toolkit for generating oligodendrocytes from human iPSCs, several key challenges that limit consistency, safety, and clinical scalability remain many protocols, whether signaling-based or transcription factor-driven, still suffer from batch-to-batch variability and inter-line heterogeneity. Differentiation efficiencies and maturation stages can vary substantially between iPSC lines derived from different donors or reprogramming methods, as well as between laboratories applying nominally similar protocols.[58,10] This variability complicates cross-study comparisons and undermines the reliability of disease modeling, where reproducible and standardized cell populations are critical.

Additionally, many current protocols still rely on animal-derived components, feeder layers, or undefined media supplements, which present regulatory and safety challenges for the production of clinical-grade cells.[59] Using xenogenic materials complicates scalability and human application due to contamination or immune rejection risks. Looking forward, hybrid differentiation approaches that combine precisely timed signaling molecules, transient TF expression (via non-integrative methods), and small-molecule epigenetic modulators hold promise for balancing differentiation speed with developmental fidelity.[37,38] The development of non-viral delivery systems, including mRNA transfection, recombinant proteins, or synthetic modified RNAs, to transiently express TFs in iPSCs or progenitors is an active area addressing safety and integration concerns.[60] Parallel advances in generating chemically defined, xeno-free media and automation platforms for differentiation and quality control will be essential to enable large-scale clinical manufacturing.[4]

Moreover, cutting-edge technologies such as single-cell transcriptomics and epigenomics allow detailed characterization of heterogeneity and maturation states, facilitating improved protocol optimization.[61,62] Three-dimensional organoid systems and biomimetic scaffolds increasingly replicate in vivo-like cellular environments and biomechanical cues, which can significantly enhance OL maturation and functional myelination capacity.[63] Ultimately, bridging the remaining gap between in vitro differentiation and robust in vivo functionality, including stable integration, long-term survival, and physiological myelination, will be crucial to realizing the full potential of iPSC-derived oligodendrocytes as regenerative medicine tools and precise, patient-specific platforms for disease modeling and drug development.[59]

Conclusion

The directed differentiation of human iPSCs into oligodendrocytes offers powerful tools for understanding CNS myelination, modeling disease, and developing novel therapeutics. While classical signaling-based protocols remain foundational for recapitulating developmental biology, they are limited by their long timelines and inherent variability. Transcription factor–driven strategies and emerging modulator-based approaches have introduced significant improvements in efficiency and scalability, though challenges related to genetic manipulation, standardization, and functional fidelity persist. Integrating these strategies through hybrid protocols, non-integrative delivery systems, and defined culture conditions holds promise for enhancing safety and clinical readiness. Concurrent advances in single-cell technologies, 3D modeling, and scalable manufacturing platforms will be crucial for supporting the translation into therapeutic settings. As differentiation methods evolve, iPSC-derived oligodendrocytes are poised to become indispensable tools for precision modeling of myelin disorders and the development of regenerative interventions targeting demyelinating diseases.

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