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REVIEW

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Pharmacological modulation of stem cells signaling pathway for therapeutic applications

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Abstract

Stem cells have an exceptional capacity for self-renewal and differentiation and are at the forefront of therapeutics, offering promising solutions for repairing tissues, cancer treatment and the cure of degenerative diseases. Stem cell fate is tightly regulated by key signaling pathways like Hedgehog, TGF-β, Wnt, Hippo, FGF, BMP and Notch, making these pathways prime targets for precision interventions. Despite significant advancements, challenges such as immune rejection, tumorigenesis, and inefficient tissue integration continue to limit clinical success. Pharmacological strategies are emerging as powerful tools to overcome these barriers by enhancing stem cell survival, directing differentiation, and modulating the stem cell niche. Small molecules can activate endogenous stem cells, reducing the need for transplantation while promoting in situ regeneration. Additionally, advancements in gene-editing technologies and biomaterials are further refining stem cell-based therapies. This paves the way for safer, more effective, and personalized therapies. Nevertheless, transforming these innovations into clinical practice entails overcoming regulatory hurdles, optimizing delivery methods, and ensuring long-term safety and efficacy. A multidisciplinary approach integrating personalized medicine, pharmacological modulation, and tissue engineering holds the key to addressing these limitations. Advancing research and refining previous strategies utilizing stem cell therapies has the prospective to revolutionize regenerative and onco-medicine, providing more targeted and sustainable treatment options for a wide range of diseases.

Keywords Stem cell therapy, Medicine, Signaling pathways, Pharmacological modulation

Introduction

Stem cells are undifferentiated cells having the unique ability to proliferate and differentiate into various specialized cell types [1]. These cells are primarily derived from two sources: (i) early embryos, known as embryonic stem cells (ESCs), and (ii) adult tissues, referred to as adult stem cells (ASCs). The defining characteristics of stem cells include self-renewal, clonality, and potency, as illustrated in Fig. 1 [2, 3]. ESCs are totipotent, meaning they can differentiate into all three embryonic germ layers: endoderm, mesoderm, and ectoderm. In contrast, ASCs are multipotent, with a more restricted differentiation potential limited to specific cell types [4].

Stem cell research began in the 1960s with the discovery of hematopoietic stem cells (HSCs), the first identified ASCs. This was followed by the identification of mesenchymal stem cells (MSCs), which led to the recognition of stem cells in various tissues and organs [5]. The primary function of ASCs is to maintain and repair damaged tissues. Among ASCs, MSCs have gained significant interest because of their immunomodulatory properties and ability to differentiate into mesoderm-derived tissues. These features make them useful therapeutic

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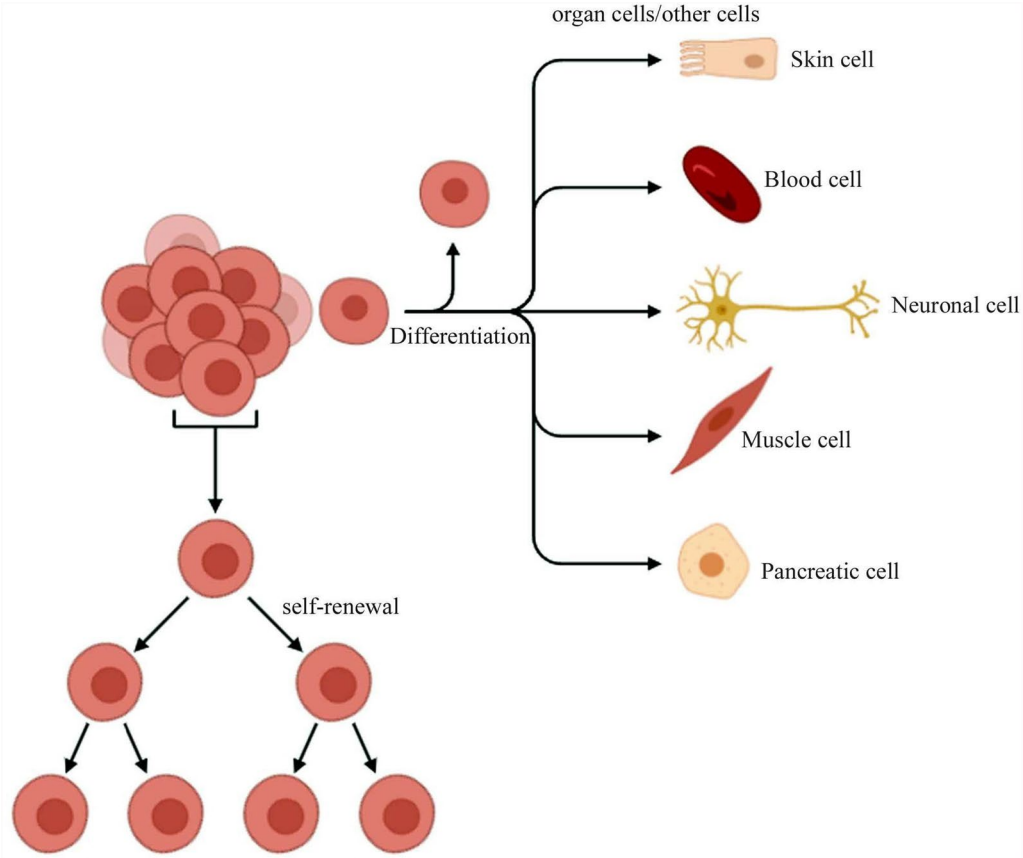


Fig. 1 Self-Renewal and differentiation characteristics of stem cells. Pluripotent stem cells differentiate into multiple lineages, including muscle, blood, skin, neuronal, and pancreatic cell types. Image created with icons from biorender.com

candidate for treating autoimmune and degenerative disorders [6]. MSCs are multipotent, self-renewing cells, primarily obtained from bone marrow but can also be sourced from other tissues, including adipose tissue, umbilical cord blood and compact bone [7] (Fig. 2). Figure created with icons from biorender.com.

Classification of stem cells

Stem cells are classified based on their potency, which determines their ability to differentiate into different cell types or their source. The simplest classification is based on potency, which divides stem cells into five categories: totipotent, pluripotent, multipotent, oligopotent, and unipotent, as described in Table 1 [8].

Stem cells can also be classified based on their source into three categories: ESCs, ASCs, and induced pluripotent stem cells (iPSCs), as outlined in Table 2 [8].

Stem cells and their potential in medicine

The use of stem cells in therapy holds the potential to transform the treatment of degenerative diseases, injuries, cancer and congenital disorders [12]. The main objective of regenerative medicine is to repair, replace, or regenerate cells, tissues, or organs to restore lost or impaired function, allowing the body to heal damaged tissues. Preclinical and clinical studies have shown the therapeutic potential of MSCs in treating conditions such as Alzheimer's disease, autoimmune disorders, diabetes, and spinal cord injuries, offering hope for patients with these debilitating conditions [13]. In cardiovascular medicine, stem cells and engineered cardiac patches are used to regenerate myocardium and improve heart function post-myocardial infarction [14]. Musculoskeletal applications include the repair of osteoarthritic cartilage and bone fractures using MSCs and bone morphogenetic proteins (BMPs). Ophthalmologic interventions employ stem-cell-derived retinal and limbal cells for treating degenerative eye diseases [15]. Hepatic and pancreatic regeneration is being investigated using hepatocyte-like cells and insulin-producing β-cells derived from iPSCs. Furthermore, stem-cell-based therapies are utilized in chronic wound healing, skin regeneration, and pulmonary diseases such as COPD, where they aid in reducing inflammation and promoting tissue repair [16]. Due

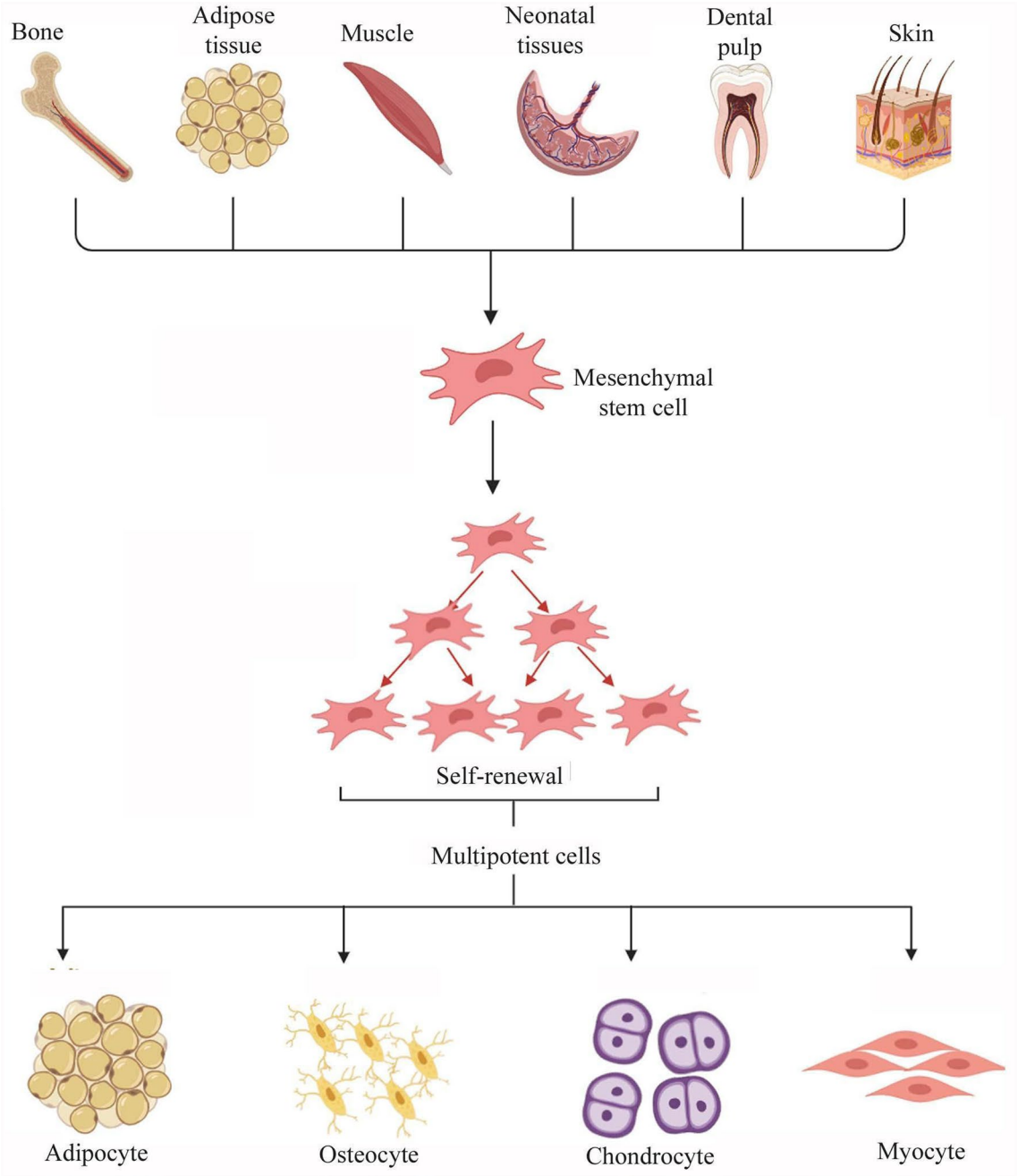


Fig. 2 Overview of MSC sources, self-renewal and differentiation into various mesodermal lineages such as adipocytes, osteoblasts, chondrocytes, and myocytes upon stimulation. MSCs can be derived from multiple tissues, including bone marrow (gold standard), adipose tissue, umbilical cord, placenta, dental pulp, menstrual blood, and amniotic fluid. Each source varies in invasiveness, cell yield, and differentiation potential. Bone marrow- and adipose-derived MSCs are extensively studied, while umbilical cord and placental MSCs offer non-invasive, ethically favorable alternatives with high proliferative capacity. MSCs are widely explored for regenerative therapies, including musculoskeletal repair, immunomodulation, and tissue engineering. Figure created with icons from biorender.com

to their inherent tumor-homing capabilities, MSCs can serve as delivery vehicles for anti-cancer agents. iPSCs offer a promising platform for generating patient-specific immune cells, such as dendritic cells and cytotoxic T lymphocytes, which can be used in adoptive immunotherapy [17]. Targeting cancer stem cell (CSC) specific signaling pathways such as Notch, Wnt, and Hedgehog, has emerged as a strategic approach to prevent tumor

Table 1 Stem cells classification based on their potency [9]

Types of SCs	Definition
Totipotent	It can differentiate into all cell types, including extraembryonic tissues (e.g., zygote)
Pluripotent	It can differentiate into nearly all cell types (e.g., ESCs)
Multipotent	It can differentiate into a limited range of closely related cell types (e.g., HSCs)
Oligopotent	It can differentiate into only a few cell types (e.g., lymphoid or myeloid stem cells)
Unipotent	It can produce only one cell type but retain self-renewal capacity (e.g., muscle stem cells)

Table 2 Stem cells classification based on source of cells

Types of SCs	Definitions
ESCs	Pluripotent cells derived from the inner cell mass of a 4–5 day-old blastocyst
ASC	Multipotent or unipotent cells involved in tissue maintenance and repair, found in bone marrow, skin, muscle, adipose tissue, and hematopoietic systems [8, 10]
iPSCs	Produced by genetically reprogramming somatic cells into a pluripotent state, mimicking the properties of ESCs [11]

recurrence and improve long-term outcomes. Moreover, stem cell models are increasingly being used to study tumor microenvironment interactions and to screen for anti-cancer drugs in vitro, facilitating precision oncology. Additional applications include gastrointestinal repair, urogenital tissue engineering, and even post-oncology tissue regeneration, illustrating the broad and transformative impact of stem cell-based regenerative medicine in modern healthcare. Current approaches in stem cell-based medicine utilize tissue engineering technologies that combine material science, cell transplantation, and microengineering to develop functional organoids for tissue and organ repair. These advancements aim to replicate the native cellular environment, providing structural and biochemical support to enhance regeneration and improve clinical outcomes [18, 19].

Role of signaling pathways in regulating stem cell behavior

The behavior of stem cells, including self-renewal, differentiation, and migration, is collectively regulated by essential signaling pathways (Fig. 3). These include Hedgehog (Hh), Wnt, Hippo, transforming growth factor-beta (TGF-β), fibroblast growth factor (FGF), BMP and Notch, among others [2, 20]. The Hh pathway plays a critical role in embryonic development, particularly in limb and bone formation via regulation of epithelial-mesenchymal interactions [21]. The Wnt pathway is crucial for tissue homeostasis, supporting both stem cell self-renewal & differentiation and is considered a key regulator of stem cell function [22]. FGF signaling supports embryonic development, angiogenesis, and wound healing through its regulation of proliferation and survival [23]. These pathways often exhibit complex crosstalk, where modulation of one can influence others, providing multiple pharmacological entry points to fine-tune stem cell behavior for therapeutic purposes. Understanding these signaling pathways is crucial for manipulating stem cells for therapeutic applications, as they offer potential targets for pharmacological modulation to enhance stem cell efficacy in regenerative or other medicinal applications [20].

Pharmacological enhancement of stem cell therapy

Pharmacological interventions play a crucial role in optimizing stem cell therapies. They enhance the survival, proliferation, and functionality of stem cells, ensuring their successful integration and performance in damaged tissues. Pharmacological compounds are key in directing stem cell differentiation, steering them to develop into specific cell types needed for tissue regeneration, such as cardiac or neural cells [24]. This targeted differentiation is essential for achieving the desired therapeutic outcomes. Moreover, pharmacological agents address the risk of tumorigenesis associated with pluripotent stem cells, such as ESCs and iPSCs, by promoting controlled differentiation and suppressing tumorigenic tendencies. This is crucial for ensuring the safety and effectiveness of stem cell therapies [25]. Immune rejection, a significant challenge in stem cell transplantation, can be mitigated through the use of immunosuppressive and immunomodulatory drugs. These agents prevent immune-mediated rejection and enhance tolerance, thereby improving the success rate of stem cell therapies [26]. Pharmacological agents also improve tissue integration by promoting angiogenesis (blood vessel formation) and reducing fibrosis [27]. This facilitates the connection

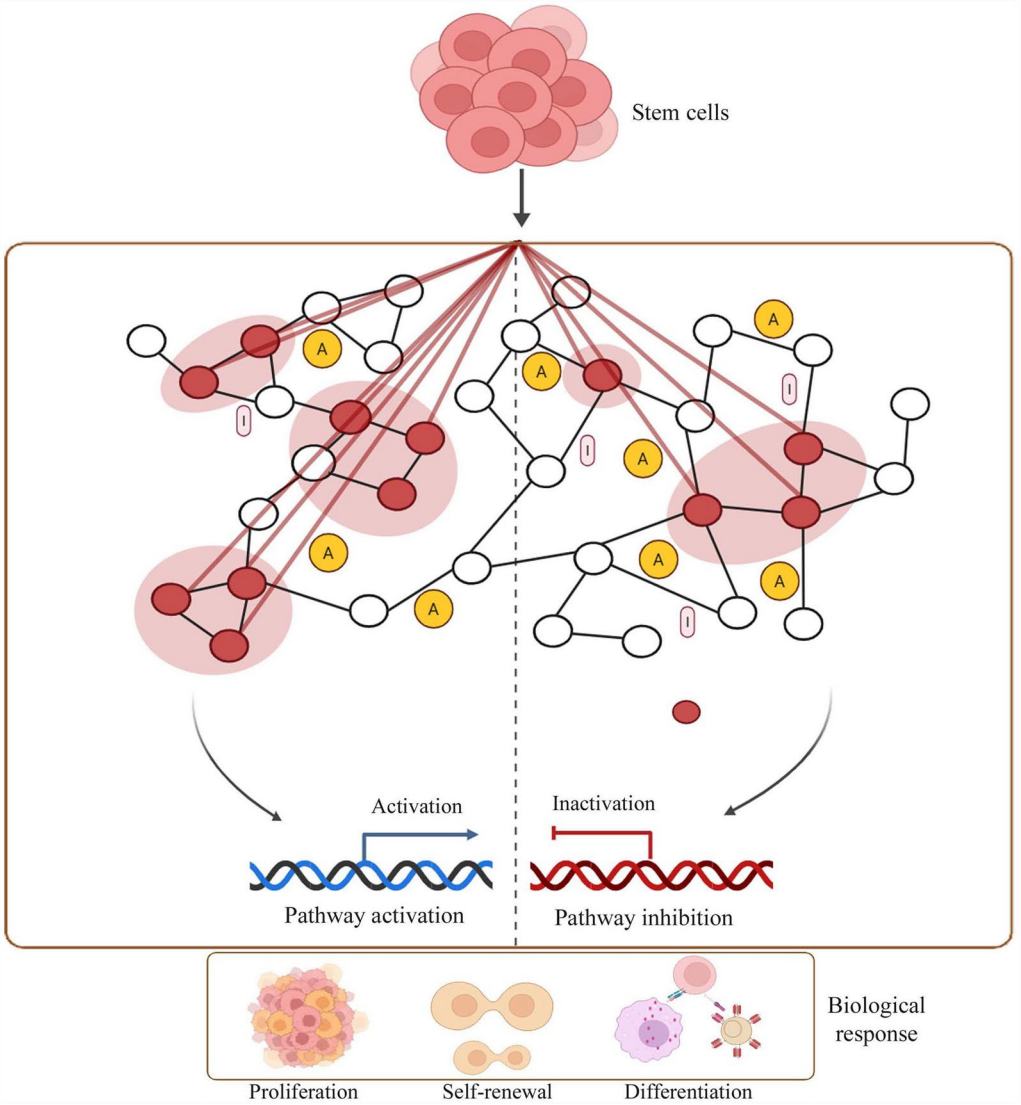


Fig. 3 General overview of the stem cell signaling pathway regulation by inhibitors (shown by I in red) and activators (shown by A in yellow). They modulate key cellular responses, including stemness, proliferation, and differentiation. Figure created with icons from biorender.com

between transplanted stem cells and host tissues, enhancing the overall effectiveness of the treatment. Furthermore, modulating the stem cell microenvironment (niche) through pharmacological means creates a supportive milieu that enhances stem cell survival, function, and regenerative potential. In some cases, pharmacological agents can stimulate the endogenous stem cells of the body to participate in tissue repair, reducing the need for external stem cell transplantation. This approach has shown promise in treating conditions such as brain injury and heart disease, offering new avenues for therapeutic intervention. In summary, pharmacological interventions are essential for unlocking the full potential of stem cell therapies in medicine, facilitating safer and more effective treatments for a broad spectrum of diseases and injuries [28].

Key signaling pathways of stem cell regulation

TGF-β signaling

TGF-β is broadly regarded as one of the most important factors in extensively distributed profibrogenic mediators in the human body [29]. The TGF-β superfamily consists of a diverse range of proteins, including TGF-β (1–3), activins (A, B), inhibins (A, B), BMPs 1–20, growth differentiation factors (such as myostatin), nodal, leftys, and Müllerian-inhibiting substance [30]. This superfamily plays a crucial role in regulating tissue homeostasis, tissue repair, immune and inflammatory responses,

extracellular matrix (ECM) deposition, cell differentiation, and growth [31]. Furthermore, TGF-β is vital for the maintenance and differentiation of stem cells [31]. The TGF-β signaling pathway mainly divides into three distinct pathways: the SMAD1/5/8, SMAD2/3, and TAB/TAK pathways [31].

TGF-β, especially TGF-β1, regulates HSCs and progenitor cells. It has been recognized as a powerful inhibitor of the growth of early multipotent progenitor populations [32]. This inhibition occurs through the downregulation of cytokine receptors, including those for interleukin(IL)−1, granulocyte-monocyte colony-stimulating factor (GM-CSF), IL-3, granulocyte colony-stimulating factor (G-CSF), and stem cell factor (SCF), along with the modulation of genes involved in the cell cycle [32]. Research indicates that TGF-β primarily slows proliferation by employing growth-inhibitory mechanisms rather than triggering apoptosis. However, it also contributes to the apoptotic process in bone marrow progenitors.

TGF-β, along with Activin A and Nodal signaling pathways, is crucial for stimulating the self-renewal of primed pluripotent stem cells [33]. These pathways, together with BMP, GDF, and SMAD signaling branches (including SMAD1, SMAD5, and SMAD8), play a crucial role in maintaining both naive and primed pluripotent states while directing differentiation into diverse embryonic and extraembryonic lineages [33]. Notably, nodal and activin receptors, as well as SMAD proteins are heavily expressed in undifferentiated ESCs, underscoring their role in ES cell maintenance [34]. BMP-4, in particular, is crucial for the self-renewal of ES cells, and deficiencies in TGF-β signaling in mice have been concomitant to defective and delayed growth [34]. Disruption of this pathway has been implicated in multiple diseases, including malignancies, autoimmune disorders, and impaired wound healing, making it a"double-edged sword"[32]. Changes in TGF-β superfamily pathways, whether caused by mutations or variations in signaling component expression, are associated with human diseases, including developmental disorders, vascular conditions, and cancer [30]. This dual function underscores the complexity of TGF-β signaling and its profound influence on both physiological health and disease progression.

Notch signaling

Identified over a century ago, the Notch gene is a crucial element of a highly conserved signaling pathway essential for tissue development and maintaining homeostasis [35]. The Notch mechanism begins with the interaction of Notch receptors with specific ligands. In humans, there are four Notch receptors (Notch1-4), which are synthesized in the endoplasmic reticulum and processed in the Golgi apparatus by the enzyme Furin (S1 cleavage) [36]. These receptors are then transported to the cell membrane, where they interact with ligands from neighboring cells, such as Delta-like proteins (DLL1, DLL3, DLL4) or Jagged proteins (JAG1, JAG2) [36, 37]. This interaction initiates a sequence of proteolytic cleavages, beginning with the ADAM family of metalloproteases performing the S2 cleavage of the receptor. This is followed by the γ-secretase enzyme complex carrying out the S3 and S4 cleavages, ultimately releasing the active intracellular domain of Notch (NICD) [38]. The NICD subsequently moves to the nucleus, where it interacts with the CSL transcription factor (CBF1/RBP-Jκ, Su(H), Lag-1) to modulate the expression of target genes [39].

The Notch signaling begins when Notch receptors undergo three sequential cleavages, enabling the NICD to enter the nucleus and regulate target gene transcription [40]. This pathway is essential for maintaining the balance and function of various tissues and organs. Notch signaling plays a vital role in regulating cell fate decisions, including the self-renewal of ASCs and the differentiation of progenitor cells into distinct lineages [41]. Disruptions in Notch signaling can result in various diseases, including both cancerous and non-cancerous conditions, with the impact being highly dependent on the specific context. It can promote or suppress tumor growth depending on the cellular and environmental context [42]. Additionally, it affects cell survival and proliferation, highlighting its complex role in cellular processes. Overall, the Notch pathway governs self-renewal, differentiation, proliferation, and apoptosis in various cell types and developmental stages.

Notch signaling also plays a pivotal role in controlling stem cell behavior across different organisms. In fruit flies, intestinal stem cells rely on Notch signaling to determine whether their daughter cells differentiate into enterocytes or enteroendocrine cells [41]. It helps maintain stem cells in an undifferentiated state, particularly in low-oxygen (hypoxic) environments, by activating specific genes [43]. In mammals, this pathway is vital for maintaining intestinal stem cells and regulating their differentiation into secretory or absorptive cell types, highlighting its role in stem cell behavior and tissue development [37]. The context-dependent nature of this pathway enables it to perform diverse roles in development, homeostasis, and disease, making it a crucial focus of research in stem cell biology and medicine.

Hh signaling

The Hh signaling pathway is an intricate system that plays an essential role in development, tissue homeostasis, and the maintenance of stem cells. It is tightly regulated through mechanisms such as protein

trafficking and feedback loops, ensuring precise control over its activity [44]. This pathway is essential for processes like tissue patterning, cell fate determination, and stem cell self-renewal. Its dysregulation contributes to the pathogenesis of various cancers, particularly through its effects on CSCs, making it a promising target for therapeutic intervention. The pathway includes several key components: three secreted Hh ligands: Sonic (Shh), Desert (Dhh), and Indian (Ihh), along with their corresponding receptor, Patched (PTCH), the transmembrane protein Smoothened (SMO), and three Gli transcription factors (Gli1–3) [45]. In the absence of Hh ligands, the Patched receptor continuously inhibits SMO, preventing its activation. This inhibition leads to the proteolytic processing of Gli3 and Gli2 into their repressor forms (Gli3-R and Gli2-R), which suppress the transcription of target genes [46]. However, when Hh ligand binds to Patched, this repression is relieved, allowing SMO to become active. Activated SMO subsequently triggers the conversion of Gli2 and Gli3 into their active forms (Gli2-A and Gli1), which then translocate to the nucleus and initiate the transcription of Hh target genes [47] (Fig. 4).

The Hh pathway is crucial for the development and proper patterning of several organs during embryogenesis, such as the nervous system, skeleton, limbs, lungs, heart, and gut. It directs these processes by controlling cellular proliferation, differentiation, and migration [48]. Beyond development, Hh signaling is crucial for maintaining resident stem and progenitor cell populations in various tissues, ensuring tissue repair and regeneration. The role of Hh signaling in CSCs has been widely explored in various malignancies, including basal cell carcinoma, multiple myeloma, glioblastoma, chronic myeloid leukemia, and colon cancer [49]. Pharmacological modulation of the Hh pathway involves drugs that either activate or inhibit this pathway. For example, Cyclopamine is a SMO antagonist used to inhibit Hh signaling, which has been explored for its potential in cancer treatment [50]. Cyclopamine promotes terminal differentiation of multiple myeloma stem cells rather than inducing cytotoxicity which reduces clonogenic potential and slows tumor progression [51]. Clinically approved SMO inhibitors such as vismodegib and sonidegib are used in the treatment of advanced basal cell carcinoma and medulloblastoma [52]. These agents work by blocking

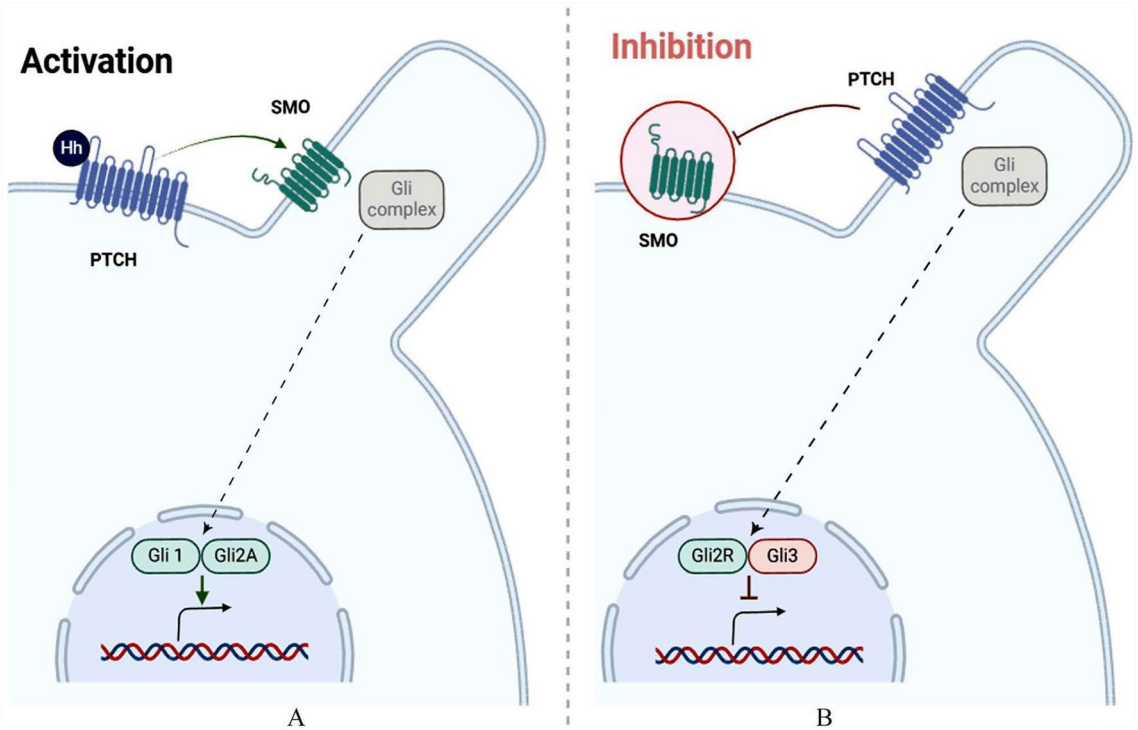


Fig. 4 Hh activation (left panel) and inhibition (right panel) signaling pathways [45]. Binding of Hh ligands, SHh, IHh, or DHh to PTCH at the cell surface causes PTCH to exit the primary cilium, thereby relieving its inhibition of SMO. Activated SMO enters the cilium and initiates a signaling cascade that converts Gli transcription factors into their active forms. These activated Gli proteins translocate to the nucleus, promoting the expression of Hh target genes. (B) In the absence of Hh ligands, PTCH remains localized in the primary cilium and inhibits SMO, blocking downstream signaling. Gli transcription factors are maintained in their repressor forms, preventing Hh target gene expression. Figure created with icons from biorender.com

downstream Hh signaling, thereby suppressing the self-renewal capacity of CSCs and limiting tumor growth.

Wnt signaling

The Wnt signaling pathway is categorized into two distinct sub-pathways: the canonical and non-canonical pathways. The canonical Wnt pathway mainly directs cell fate determination, whereas the non-canonical pathway is involved in regulating cell movement and tissue polarity [53].

Canonical Wnt signaling pathway

The canonical Wnt signaling pathway is initiated through the β-catenin signaling cascade, beginning with the activation of the Frizzled (FZD) receptor family and the low-density lipoprotein receptor-related protein 5/6 (LRP5/6) co-receptor [54]. In the absence of Wnt activation, β-catenin forms a complex with adenomatous polyposis coli and AXIN. Within this complex, β-catenin is phosphorylated at its NH2-terminal degradation motif by casein kinase 1α (CK1α) and glycogen synthase kinase 3β (GSK3β) [55]. This phosphorylation marks β-catenin for polyubiquitination by the β-TRCP1 or β-TRCP2 complex, leading to its subsequent degradation by the proteasome [55]. However, in the presence of canonical Wnt signaling, the pathway is activated. Dishevelled (DVL), a key cytoplasmic protein, becomes phosphorylated by CK1α and binds firmly to frequently rearranged in advanced T-cell lymphomas (FRAT) for stabilization [56]. This interaction disrupts the β-catenin destruction complex. Specifically, the Wnt signal triggers the formation of the FZD-DVL complex and the LRP5/6-AXIN-FRAT complex, preventing the phosphorylation of β-catenin by CK1α and GSK3β [57, 58]. As a result, β-catenin accumulates in the cytoplasm and translocates to the nucleus, where it forms a complex with T-cell factor/lymphoid enhancer factor (TCF/LEF) family transcription factors, Legless family docking proteins (BCL9 and BCL9L), and PYGO family coactivators (PYGO1 and PYGO2) [59]. The TCF/LEF-β-catenin-Legless-PYGO nuclear complex activates the transcription of target genes, such as FGF20, DKK1, WISP1, MYC, and CCND1, which are involved in regulating cell proliferation, differentiation, and survival.

Non-canonical Wnt signaling pathway

The non-canonical Wnt signaling pathway is transduced through FZD family receptors and co-receptors, including RYK and ROR2 [60]. This pathway operates through two main branches: Ca^{2+}-dependent signaling and planar cell polarity signaling [61]. The Ca^{2+}-dependent branch involves effector molecules such as Nemo-like kinase (NLK) and nuclear factor of activated T cells (NFAT), while the planar cell polarity signaling branch relies on small G proteins (e.g., RHOA, RHOU, RAC, and CDC42) and c-Jun NH2-terminal kinase (JNK), which are dependent on DVL [62].

Small G proteins are essential in regulating cytoskeletal rearrangements during processes like cancer cell invasion and metastasis [63]. NLK, a Ca^{2+}-dependent effector, inhibits the canonical Wnt pathway by phosphorylating TCF/LEF transcription factors, thereby modulating their activity. NFAT, a Ca^{2+}-dependent effector, is associated with both metastasis in cancer and convergent extension during early embryogenesis [64]. The planar cell polarity signaling pathway, which intersects with the non-canonical Wnt pathway, is transduced through DVL- or Ca^{2+}-dependent cascades and plays a vital role in regulating tissue polarity and cell movement [65].

FGF Signaling

FGF signaling plays a crucial role in regulating a wide range of biological processes vital for embryonic development and adult tissue homeostasis [66]. These include cell survival, proliferation, migration, differentiation, embryonic patterning, organogenesis, tissue regeneration, and metabolic regulation. The FGF family comprises 22 ligands that bind to four high-affinity receptors (FGFR1–4), triggering diverse intracellular signaling pathways that are fundamental to stem cell maintenance and function [67]. Ligand binding induces FGFR dimerization and autophosphorylation, initiating activation of several canonical pathways, including the RAS-MAPK, PI3K-AKT, phospholipase Cγ (PLCγ), and STAT pathways [68]. Specifically, the RAS-MAPK pathway primarily regulates proliferation and differentiation, the PI3K-AKT pathway supports survival and growth via downstream mTOR signaling, the PLCγ pathway modulates calcium-dependent intracellular signaling and the STAT pathway is involved in transcriptional regulation and self-renewal. Furthermore, FGF signaling sustains the expression of core pluripotency transcription factors such as SOX2, OCT4, KLF4, NANOG, and c-MYC, thereby reinforcing stem cell identity [66].

In ESCs, FGF2 is routinely added to culture media to preserve the primed pluripotent state mediated via the PI3K-AKT pathway. Pharmacological modulation of FGF signaling is widely explored in both regenerative medicine and oncology [23, 69]. Inhibition of FGF signaling using selective and non-selective small molecule FGFR inhibitors has emerged as a therapeutic strategy in various cancers, including those of the lung, breast, and bladder [70]. In addition, monoclonal antibodies (mAbs) targeting FGFRs can block ligand-receptor binding, preventing receptor activation, while ligand traps sequester extracellular FGFs, disrupting autocrine and paracrine signaling loops that sustain tumor growth [71].

Combination therapies that integrate FGFR inhibitors with other targeted agents, such as imatinib in gastrointestinal stromal tumors, have shown promising results in overcoming drug resistance [72].

Hippo signaling

The Hippo signaling pathway is a conserved kinase cascade essential for regulating stem cell fate, organ size, and tissue homeostasis [73]. It is centered on MST1/2 and LATS1/2 kinases, which phosphorylate YAP/TAZ to prevent nuclear entry and gene activation. When inactive, unphosphorylated YAP/TAZ enter the nucleus, bind TEADs, and promote self-renewal and inhibit differentiation [74]. In ESCs and iPSCs, active YAP/TAZ signaling sustains pluripotency by upregulating core transcription factors like Oct4 and Nanog. Similarly, in tissue-specific stem cells such as those in the intestine or skin, YAP enhances self-renewal and proliferation, while its loss impairs progenitor maintenance [75]. Hippo signaling also integrates with other pathways like Wnt, BMP, Notch, and TGF-β to coordinate stem cell behavior. This pathway acts as a central mechanotransducer in stem cells, integrating diverse upstream cues such as cell density, mechanical forces, cell polarity, and GPCR signaling to regulate YAP/TAZ activity [76]. Mechanical sensors like integrins, Piezo channels, and plexins, along with cytoskeletal regulators such as Rho GTPase, Jub, and LIMD1 transmit signals to the Hippo cascade. RAP2 GTPase further conveys ECM stiffness, modulating YAP/TAZ localization and function [77]. This mechanosensitive control of Hippo signaling is essential for stem cell proliferation, organ size regulation, and tissue regeneration, while its dysregulation contributes to tumor progression and impaired repair [78].

Hippo pathway activators like YL-602 enhance MST1/2 activity to suppress YAP/TAZ, exerting anti-cancer effects [79], while inhibitors such as Verteporfin disrupt YAP/TAZ-TEAD interactions to block oncogenic transcription [80]. Chronic inhibition of the Hippo pathway carries considerable risks due to prolonged activation of YAP and TAZ, which are recognized oncogenes associated with tumorigenesis and fibrosis [81]. While transient Hippo pathway suppression to activate YAP/TAZ holds promise in regenerative medicine by enhancing tissue repair and stem cell-driven regeneration, systemic or sustained inhibition may disrupt immune homeostasis, compromise normal tissue function, and impair organ development [82]. Owing to the involvement of the Hippo pathway in immune regulation, inflammation, and tissue architecture, these potential adverse effects highlight the critical need for precise, context-specific modulation to harness its therapeutic potential while mitigating oncogenic and fibrotic risks.

BMP signaling

BMP signaling is a fundamental regulator of stem cell fate, with pivotal roles in osteogenic differentiation, skeletal tissue development, and regeneration [83]. BMPs, which belong to the TGF-β superfamily, initiate signaling by binding to type I and type II serine/threonine kinase receptors (BMPRI and BMPRII) located on the cell surface [84]. This receptor complex phosphorylates Smad1/5/8, which pair with Smad4 and enter the nucleus to activate osteogenic genes like RUNX2, SP7, and DLX5, guiding stem cell differentiation and bone formation. In MSCs, BMP signaling is indispensable for commitment to the osteoblast lineage and for the maturation of cells responsible for synthesizing and mineralizing bone matrix [85]. Several BMP isoforms, including BMP-2, BMP-4, BMP-6, BMP-7, and BMP-9, are known to induce osteogenic differentiation by activating both canonical Smad-dependent pathways and non-canonical routes such as MAPK, PI3K/Akt, and Rho-GTPase signaling [86]. This dual signaling architecture enables precise spatial and temporal regulation of osteogenesis and supports complex developmental processes such as craniofacial morphogenesis and maintenance of the calvarial stem cell niche. The intensity and duration of BMP signaling are critical determinants of cell differentiation, with recent studies indicating that cumulative signaling history shapes fate decisions via transcriptional regulators like SOX2. Aberrant BMP signaling has been implicated in skeletal malformations and impaired tissue regeneration, underscoring its importance as a therapeutic target in regenerative and onco-medicine. BMP-9 has emerged as one of the most potent BMPs for bone formation and is notably resistant to inhibition by endogenous antagonists such as noggin [87]. Modulation of BMP signaling via agonists or antagonists (e.g., noggin, chordin, gremlin) offers refined control over stem cell fate decisions and enhances the efficacy of tissue engineering strategies. BMP activators like SY-LB-35 and recombinant BMPs facilitate bone healing and stem cell-based regeneration.

Pharmacological modulation of stem cell signaling pathways

TGF-β signaling modulators

TGF-β signaling modulators either enhance or inhibit the TGF-β pathway, with a crucial role in controlling stem cell self-renewal, differentiation, and tissue homeostasis. Given the dual role of TGF-β in maintaining stem cell populations and its involvement in diseases such as cancer and fibrosis, modulating this pathway has significant therapeutic potential. TGF-β inhibitors, such as small molecule inhibitors (e.g., galunisertib and SB431542), mAbs (e.g., fresolimumab), and soluble TGF-β receptors, are widely studied for their ability to block

TGF-β-mediated fibrosis, tumor progression, and immunosuppression [88, 89]. Galunisertib is a selective ALK5 inhibitor and has demonstrated potential in clinical trials for advanced cancers by reducing TGF-β-driven metastasis [90]. It blocks Smad2/3 phosphorylation, reversing TGF-β–mediated immune suppression and CSC-driven epithelial-mesenchymal transition (EMT) by enhancing $CD8^+$ T cell activity and reprogramming the tumor microenvironment toward an immunologically active and less invasive phenotype [91, 92]. Hence, it improves responses to both immunotherapy and chemotherapy by promoting anti-tumor immunity and reducing treatment resistance. LY2109761 is a dual inhibitor targeting both TGF-β receptor I and II kinases, primarily studied in metastatic cancers such as pancreatic and breast cancer [93, 94]. It functions by stabilizing the inactive conformations of TGF-β receptors, thereby preventing Smad2/3 nuclear translocation and downstream transcriptional activity. This effectively disrupts TGF-β-driven pro-metastatic processes, including EMT, angiogenesis, and fibrosis [95, 96]. Similarly, fresolimumab, a pan-TGF-β neutralizing antibody, has been investigated for its anti-fibrotic effects in systemic sclerosis and chronic kidney disease [97]. It prevents TGF-β isoform (TGF-β1, TGF-β2, TGF-β3) interaction with cell surface receptors, reverses immunosuppression and cancer stem cell maintenance [93]. It has shown promising results in early clinical trials for skin cancer, glioblastoma, and metastatic breast cancer. It also enhances radiosensitivity in glioblastoma [96].

On the other hand, TGF-β activators, such as recombinant TGF-β proteins and BMPs (e.g., BMP2 and BMP7), are used to promote tumor-suppressive and tissue-repair functions. BMP7, in particular, thwarts TGF-β1-induced fibrosis and promote stem cell differentiation in preclinical models [98]. Hp-TGM, a TGF-β mimic from the parasitic worm *Heligmosomoides polygyrus*, selectively activates Smad2/3 signaling by binding mammalian TGF-β receptors and promotes stable regulatory T cell induction. It offers a novel immunomodulatory approach for autoimmune disorders like colitiss [99]. Additionally, gene therapy approaches, including antisense oligonucleotides and siRNA/shRNA, offer targeted strategies to modulate TGF-β signaling at the genetic level. These modulators allow TGF-β signaling regulate the balance between self-renewal and differentiation (Table 3). For example, TGF-β and its downstream effectors, such as Smad2/3, are essential for maintaining the pluripotency of ESCs and inducing differentiation into specific lineages [100].

Despite their potential, TGF-β modulators face challenges due to the context-dependent role of the pathway. In cancer, for instance, TGF-β can act as both a tumor suppressor and promoter, necessitating precise modulation to avoid adverse effects [108]. Combination

Table 3 TGF-β signaling modulators currently in clinical trials, FDA-approved or under development

Compound	Type	Target	Clinical trial status	Cancer types
Galunisertib (LY2157299) [101]	Small-molecule kinase inhibitor	TβRI	Phase 1/2	Hepatocellular carcinoma (HCC), Metastatic Prostate Cancer, TNBC, Advanced HCC, Rectal Cancer, Recurrent Glioblastoma
Vactosertib (TEW-7197) [102]	Small-molecule kinase inhibitor	TβRI	Phase 1/2	Advanced Solid Tumors, Desmoid Tumors, Multiple Myeloma, Metastatic Colorectal cancer (CRC), Metastatic Pancreatic Ductal Adenocarcinoma (PDAC), Gastric Cancer, Urothelial Carcinoma, Non-Small Cell Lung Cancer (NSCLC)
LY3200882 [103]	Small-molecule kinase inhibitor	TβRI	Phase 1	Advanced/Metastatic Cancers
PF06952229 [104]	Small-molecule kinase inhibitor	TβRI	Phase 1	Advanced/Metastatic Breast Cancer, Castration-Resistant Prostate Cancer
Trabedersen (AP 12009) [105]	Antisense oligonucleotide	TGF-β2	Phase I/II	Pancreatic Cancer, CRC, Glioma, Malignant Melanoma
AVID200 [106]	Ligand trap	TGF-β	Phase 1	Advanced solid tumors
NIS793 [107]	Pan anti-TGF-β-neutralizing antibody	TGF-β	Phase 2	Metastatic PDAC
SRK-181-mIgG1	Selective antibody	Latent TGF-β1	Phase 1	Advanced solid tumors
ABBV151	Anti-GARP:TGFβ1 mAb	TGF-β1	Phase 1	Advanced solid tumors
Luspatercept	TGF-β ligand trap	TGF-β superfamily ligands (e.g., GDF11)	FDA-approved but not for cancer	Anemia in myelodysplastic syndromes

therapies, such as pairing TGF-β inhibitors with immune checkpoint inhibitors, are being explored to enhance therapeutic efficacy [109]. Furthermore, advancements in nanoparticle-based delivery systems aim to improve the specificity and reduce off-target effects of TGF-β modulators [110]. Overall, pharmacological modulation of TGF-β signaling holds great promise for targeting stem cell-related diseases, including cancer, fibrosis, and degenerative disorders, while also providing tools to manipulate stem cell behavior for medicinal applications [111].

Notch signaling modulators

Notch signaling is essential for regulating stem cell maintenance, differentiation, and tissue regeneration [41]. Pharmacological modulation of this pathway has become a promising strategy for treating a range of diseases, including cancer, tissue damage, and regenerative disorders [112]. Several agents have been made to modulate Notch signaling, including γ-secretase inhibitors, Notch receptor antibodies, and peptides, each offering distinct mechanisms and therapeutic applications [113, 114]. γ-secretase inhibitors, such as DAPT (N-[N-(3,5-difluorophenacetyl)-l-alanyl]-s-phenylglycine-butyl ester), have shown potential in enhancing the efficacy of chemotherapy drugs. DAPT improves the effectiveness of cisplatin in treating drug-resistant osteosarcoma cells, suggesting its utility in overcoming chemotherapy resistance [115]. Inhibitors like Compound E and MRK-003 have shown promise in preclinical models of Notch-driven breast cancer by significantly reducing tumor proliferation and metastasis [43]. Mechanistically, these inhibitors disrupt the Notch-TGFβ signaling crosstalk involved in EMT, a key process in cancer stem cell self-renewal and metastatic behavior [116]. As a result, treatment with these inhibitors lead to decreased tumor growth and a reduction in cancer stem cell enriched side populations, highlighting their potential in targeting aggressive, treatment-resistant cancer subtypes. Compound E also induces G_0/G_1 cell cycle arrest and promote apoptosis in leukemia cell lines [43]. Its mechanism involves the downregulation of pro-survival genes such as HES1 through Notch1 inhibition. It depicts synergistic effects when used in combination with therapies like dexamethasone and imatinib, significantly enhances treatment efficacy and lowers the risk of relapse. Another γ-secretase inhibitor, RO4929097, has demonstrated promise in treating solid tumors by blocking Notch receptor activation, thereby slowing tumor growth and targeting CSCs [117]. These findings highlight the potential of γ-secretase inhibitors as adjuncts to conventional cancer therapies. In addition to small molecule inhibitors, mAbs targeting Notch receptors are being explored as therapeutic agents. These antibodies, such as the anti-Notch1 antibody OMP-52M51 (brontictuzumab) prevent the interaction between Notch receptors and their ligands [118]. This approach has shown potential in reducing tumor growth by targeting CSCs that depend on Notch signaling for survival and proliferation (Table 4).

Peptide-based modulators of Notch signaling have also gained attention as they promote cell differentiation and tissue regeneration. Certain peptides have been shown to regenerate hair cells in the cochlea, offering hope for treating hearing loss and other regenerative disorders [124]. In the skin, Notch signaling controls stem cell proliferation and differentiation, and its dysregulation can impair wound healing. Studies have demonstrated that inhibiting Notch signaling with agents like DAPT can accelerate wound healing and improve tissue repair in preclinical models [125].

Notch signaling is also crucial for the regeneration of organs such as the liver and pancreas. In the liver, Notch signaling promotes regeneration by regulating cell

Table 4 Notch signaling modulators currently in clinical trials, FDA approved or under development

Compound	Type	Target	Clinical Trial Status	Cancer Types
γ-secretase inhibitors (GSIs)[119]	Small-molecule inhibitors	Notch signaling pathway	Pre-clinical/Clinical	NSCLC, HCC, Breast Cancer, CRC, Prostate Cancer
mAbs[120]	Targeted antibodies	Notch receptors or ligands	Clinical trials	CRC, Other solid tumors
Notch ligand-targeting agents	Small molecules or antibodies	Notch ligands (e.g., DLL3)	Pre-clinical/Clinical	SCLC, Other cancers
Notch receptor-targeting agents	Small molecules or antibodies	Notch receptors (e.g., Notch1, Notch2)	Pre-clinical/Clinical	Various cancers
NMK-T-057[121]	Triazole compound	γ-Secretase-mediated Notch signaling	Pre-clinical	Breast Cancer
GSI-I + IL-24[122]	Combination therapy	Notch signaling and apoptosis induction	Pre-clinical	HCC
Nirogacestat[123]	Small molecules inhibitor	γ-Secretase	FDA-approved	Desmoid Tumors

proliferation and differentiation. Research has shown that modulating the Notch-IGF1 pathway can enhance liver regeneration by promoting the growth of specific cell populations while inhibiting others [126]. Similarly, in the pancreas, Notch signaling is essential for the regeneration of exocrine cells, which are vital for digestion. Blocking Notch signaling has been shown to delay the recovery of these cells after acute pancreatitis, suggesting that Notch modulators could be used to support pancreatic healing [127]. In summary, Notch signaling modulators, including γ-secretase inhibitors, mAbs, and peptides, offer versatile tools for targeting cancer, enhancing tissue repair, and promoting organ regeneration. Their ability to regulate stem cell behavior and tissue homeostasis makes them valuable candidates for therapeutic development in regenerative medicine and oncology.

Hh signaling modulators

The Hh signaling pathway is a critical regulator of embryonic development, tissue homeostasis, and stem cell maintenance. However, aberrant activation of this pathway is frequently observed in various human cancers, including breast cancer, lung cancer, bladder cancer, pancreatic cancer, chondrosarcoma, rhabdomyosarcoma, neuroblastoma, medulloblastoma, and gastric cancer [128]. The role of Hh signaling in cancer is complex and context-dependent, with its activation mechanisms varying across different tumor types. For instance, Gorlin syndrome (basal cell nevus syndrome), an autosomal dominant condition caused by germline loss of the PTCH1 gene, is strongly associated with basal cell carcinoma, rhabdomyosarcoma, and medulloblastoma [129]. Mutations in other Hh pathway components, such as Gli1 and Gli3 in pancreatic adenocarcinoma, Gli1 gene amplification in glioblastoma, and SUFU (suppressor of fused) mutations in medulloblastoma, further underscore the Hh pathway involvement in tumorigenesis [130]. Additionally, regulatory proteins like speckle-type POZ protein, an E3 ubiquitin ligase adaptor, can inhibit Hh signaling by promoting the degradation of Gli2 in gastric cancer [131].

Hh signaling contributes to cancer progression through three primary mechanisms: driving tumor initiation, promoting tumor growth, and regulating residual cancer cells after therapy [132, 133]. These roles highlight its significance in CSCs, where Hh signaling is often hyperactive. For example, in lung adenocarcinoma, Hh signaling enhances the maintenance, proliferation, self-renewal, and tumorigenicity of CSCs [134]. Furthermore, proto-oncogenes and tumor suppressor genes can modulate Hh signaling to influence CSC proliferation and migration. The SCUBE2 protein, a member of the SCUBE family, has been shown to inhibit glioma stem cell proliferation and migration by downregulating Hh signaling [135].

Given its central role in cancer, the Hh pathway has become a key target for therapeutic intervention. The pathway primarily regulates target gene expression through smoothened (SMO)-mediated nuclear transfer of transcription factors, making SMO a prime target for inhibition. Three oral SMO antagonists i.e. vismodegib (GDC-0449), sonidegib (LDE225), and glasdegib (PF-04449913) have been approved by the FDA for clinical use [136]. These drugs have demonstrated significant efficacy in treating locally advanced and metastatic basal cell carcinoma, as well as acute myeloid leukemia (AML) [137, 138]. In summary, Hh signaling modulators, particularly SMO inhibitors, represent a promising therapeutic strategy for targeting cancers driven by aberrant Hh pathway activation. Their ability to disrupt CSC maintenance and tumor growth makes them valuable tools in oncology, with ongoing research exploring their potential in combination therapies and other cancer types (Table 5).

Wnt signaling modulators

The Wnt signaling pathway is a crucial regulator of stem cell behavior, affecting cell fate, proliferation, and differentiation [146]. his highly conserved pathway functions through two main mechanisms: the canonical (β-catenin-dependent) and non-canonical (β-catenin-independent) pathways, each vital for specific cellular functions. Dysregulation of Wnt signaling is associated with various diseases, including cancer, fibrosis, and neurodegenerative disorders [62, 147]. Pharmacological modulation of Wnt signaling, through either activation or inhibition, has emerged as a promising therapeutic strategy for these conditions.

Activation of Wnt signaling

Activating Wnt signaling is a strategy to promote stem cell renewal and tissue regeneration. One approach involves inhibiting glycogen synthase kinase-3β (GSK-3β), a key regulator of β-catenin degradation. Small molecules such as lithium chloride, a GSK-3β inhibitor, prevent the breakdown of β-catenin, allowing it to accumulate in the cytoplasm, translocate to the nucleus, and activate Wnt-responsive genes [148]. Another strategy involves enhancing receptor availability at the cell surface. R-spondins, secreted proteins that stabilize FZD and LRP5/6 receptors, reduce receptor turnover and improve ligand-receptor interactions, thereby amplifying canonical Wnt signaling [149]. Additionally, small molecules targeting endogenous Wnt inhibitors, such as Dickkopf (DKK) proteins and secreted FZD-related proteins (sFRPs), have shown promise. These

Table 5 Hh signaling modulators that are FDA-approved, currently in clinical trials, or under development

Compound	Type	Target	Clinical Status	Cancer Types
Vismodegib (GDC-0449)[139]	SMO inhibitor	SMO	FDA-approved	Basal Cell Carcinoma (BCC), Medulloblastoma
Sonidegib (LDE-225)[140]	SMO inhibitor	SMO	FDA-approved	Locally Advanced BCC
Glasdegib (PF-04449913)[141]	SMO inhibitor	SMO	FDA-approved	Acute Myeloid Leukemia (AML)
Arsenic Trioxide (ATO)[142]	GLI inhibitor	GLI transcription factors	FDA-approved for APL	Acute Promyelocytic Leukemia (APL)
Itraconazole[143]	SMO inhibitor	SMO	Clinical trials	Breast Cancer, Prostate Cancer, NSCLC, Pancreatic Cancer
Taladegib (LY2940680)[144]	SMO inhibitor	SMO	Clinical trials	Solid tumors
Saridegib (IPI-926)	SMO inhibitor	SMO	Clinical trials	Solid tumors
BMS-833923 (XL-139)	SMO inhibitor	SMO	Clinical trials	Solid tumors
GANT-61[143, 144]	GLI inhibitor	GLI transcription factors	Pre-clinical/Clinical	Breast Cancer, Pancreatic Cancer, CRC
GANT-58[143, 144]	GLI inhibitor	GLI transcription factors	Pre-clinical/Clinical	Breast Cancer, Pancreatic Cancer, CRC
5E1 mAb[145]	SHH ligand inhibitor	Sonic Hh (SHH)	Pre-clinical/Clinical	Medulloblastoma, Glioblastoma, Pancreatic Cancer

compounds counteract the inhibitory effects of DKK and sFRPs, increasing Wnt ligand activity and promoting downstream signaling [150, 151]. GSK-3β inhibitors CHIR99021 and lithium chloride activate canonical Wnt/β-catenin signaling, promoting osteogenesis and bone repair [152]. CHIR99021 increases β-catenin levels, directing MSCs toward osteoblast differentiation and improving bone mineral density in preclinical models. Lithium chloride also supports bone regeneration by upregulating essential Wnt target genes like RUNX2 and OSTERIX, enhancing fracture healing. CHIR99021 also promotes neuronal morphology in human neural precursor cells and, when combined with neurotrophic factors such as BDNF and GDNF, facilitates dopaminergic neuron differentiation. These neurogenic effects hold therapeutic promise for neurodegenerative diseases and central nervous system injuries by supporting neural regeneration and functional recovery [153].

Inhibition of Wnt signaling

Diseases like cancer and fibrosis, characterized by hyperactive Wnt signaling require pathway inhibition. Several inhibitors have been developed to target different components of the Wnt pathway. LGK974, a porcupine inhibitor, blocks the lipidation of Wnt proteins, preventing their secretion and effectively targeting Wnt-driven cancers such as breast and pancreatic cancer [154]. At the transcriptional level, PRI-724, a small molecule that disrupts the interaction between β-catenin and its coactivator CBP, has shown promise in clinical trials for treating fibrotic diseases [155]. Extracellular modulators, such as sFRPs and DKK proteins, inhibit Wnt signaling by binding to Wnt ligands or their receptors, preventing the formation of active signaling complexes. DKK proteins, for instance, directly inhibit LRP5/6, suppressing canonical Wnt signaling [156].

Intracellular inhibitors target key signaling components, such as DVL proteins, which are essential for signal transduction. By disrupting DVL interaction with FZD receptors, these inhibitors prevent downstream signaling [157]. Additionally, small molecules that block β-catenin nuclear translocation or increase the expression of Axin, a component of the β-catenin destruction complex, effectively downregulate Wnt signaling and promote β-catenin degradation [143]. Wnt signaling modulators offer versatile tools for targeting diseases driven by pathway dysregulation. Activators like GSK-3β inhibitors and R-spondins hold promise for regenerative medicine by promoting stem cell renewal and tissue repair. Inhibitors such as LGK974, PRI-724, and DKK proteins provide therapeutic options for cancers and fibrotic diseases characterized by hyperactive Wnt signaling [158]. Continued research into these modulators and their mechanisms will further advance their clinical applications (Table 6).

FGF signaling modulators

FGF signaling regulates stem cell pluripotency, tissue repair, and disease progression primarily through interactions with FGF receptors and activation of downstream pathways, including RAS-MAPK, PI3K-AKT, PLCγ, and STAT. Both activators and inhibitors of this pathway offer significant therapeutic potential in regenerative medicine, oncology, and inflammatory disorders. Activators of FGF signaling include several ligands, such as FGF2, FGF4, FGF7, and FGF9, which help maintain pluripotency in human ESCs and induce differentiation in mouse ESCs [66]. FGF-binding proteins further enhance this pathway by stabilizing ligands and facilitating receptor

Table 6 Wnt signaling modulators in clinical development. Pyrvinium is FDA-approved against pinworms and Celecoxib as NSAID

Compound	Type	Target/Mechanism	Status	Cancer Types
Pyrvinium[159]	Small molecule	Activates CK1α (β-catenin destruction)	Phase II (repurposed)	ER + breast cancer (high INPP4B expression)
Celecoxib[160]	NSAID	COX-2/Wnt inhibitor (indirect)	Phase II (repurposed)	Breast, CRC
LGK-974 (WNT974)[161]	Small molecule (PORCN inhibitor)	Blocks Wnt ligand secretion	Phase I/II	Pancreatic, BRAF-mutant CRC, TNBC, head/neck squamous cell carcinoma
PRI-724[155]	Small molecule	Disrupts β-catenin/CBP interaction	Phase I/II	CRC, hepatitis-related cirrhosis
OMP-18R5 (Vantictumab)[162]	mAb	Binds FZD1/2/5/7/8 receptors	Phase I	Advanced solid tumors, pancreatic cancer
DKN-01[163]	mAb	Inhibits DKK1 (Wnt antagonist)	Phase I/II	Esophageal, gastric, biliary tract, prostate, liver cancers
Foxy-5[164]	WNT5A-mimicking peptide	Mimics WNT5A to block signaling	Phase I	Breast, colon, prostate cancers
OMP-54F28[165]	Fusion protein	Decoy receptor (FZD8-Fc)	Phase I	Hepatocellular, ovarian, pancreatic cancers
CWP232291[166]	Small molecule	Induces apoptosis via caspase activation	Phase I/II	AML, myelodysplastic syndrome, multiple myeloma
90Y-OTSA-101[167]	Radiolabeled antibody	Targets FZD10	Pre-clinical/Phase I	Synovial sarcoma

engagement, thereby supporting tissue repair across multiple systems [168]. Pharmacological agents like lovastatin indirectly augment FGF signaling by upregulating endogenous ligand expression, contributing to processes such as bone regeneration [169].

Inhibitors of the pathway include small molecule FGFR inhibitors such as PD166866 (FGFR1-specific) and AZD4547 (FGFR1-3 inhibitor), which block receptor kinase activity and downstream signaling via MAPK/ERK and STAT. These inhibitors have demonstrated efficacy in reducing neuroinflammation, particularly in Lyme disease, by downregulating pro-inflammatory cytokines including IL-6, CCL2, and CXCL8 [170]. Synthetic sulfonic acid polymers (e.g., PSS, PAS, PAMPS) function as heparan sulfate mimetics to sequester FGF2, thereby preventing FGFR1 activation and suppressing angiogenesis in preclinical tumor models [171]. Endogenous antagonists such as Sprouty proteins and SEF also modulate FGF signaling by attenuating RAS-MAPK activation. FGF signaling exhibits notable crosstalk with other pathways, such as TGFβ. In this context, FGF antagonizes TGFβ-driven smooth muscle cell differentiation by repressing TGFβR1 and Smad2/3. Conversely, inhibition of FGF signaling can promote contractile SMC phenotypes and limit pathological vascular remodeling [172]. Therapeutically, FGFR inhibitors like AZD4547 are being developed to target cancers with FGFR amplifications or mutations, including those resistant to conventional therapies [170]. In regenerative contexts, FGF2 supplementation enhances stem cell-mediated tissue repair, particularly for bone and neural injuries. Furthermore, FGFR inhibition offers promising anti-inflammatory effects in conditions such as neuroinflammatory Lyme disease. Several FGFR-targeting therapies are in various stages of clinical development or approved for cancer treatment. Investigational small molecules such as Derazantinib [173]. AZD4547 [174], LY2874455, Debio 1347 [175] and RLY-4008 [176] are currently in Phase I–III trials for various solid tumors, including breast, gastric, and lung cancers. In addition, FP-1039 [177], a peptide-based FGFR decoy, and mAb Bemarituzumab [178] targeting FGFR2, are being explored in early and late-stage clinical trials, respectively. Several FGFR inhibitors have received FDA approval, including Pemigatinib, Futibatinib [179], Erdafitinib [180], and Infigratinib [181], primarily for the treatment of FGFR-altered cholangiocarcinoma and urothelial carcinoma.

Despite its therapeutic relevance, targeting FGF signaling poses challenges due to its dual role in promoting tissue repair and contributing to fibrosis or tumor progression when dysregulated. Off-target effects of some inhibitors (e.g., PD166866) further underscore the need for selective modulation strategies [182]. Nonetheless, precise targeting of FGF signaling nodes enables controlled regulation of stem cell fate, tissue homeostasis, and disease outcomes, with broad applications across oncology, neurology, and regenerative medicine.

Hippo signaling modulators

Modulation of the Hippo pathway is a promising strategy for treating diseases such as cancer, where YAP/TAZ hyperactivity is common [183]. Several antipsychotics

and mood stabilizers, including amisulpride, aripiprazole, clozapine, quetiapine, and risperidone, have been shown to downregulate expression of Hippo pathway genes (e.g., NF2, WWC1) and modulate pathway activity in neuronal cells [184]. Both repurposed drugs (e.g., antipsychotics) and novel small molecules are under investigation to restore normal Hippo signaling in disease contexts. Among the most prominent inhibitors are the small molecules that modulate core kinase components such as MST1/2 and LATS1/2 [184]. XMU-MP-1, an ATP-competitive MST1/2 inhibitor, has been shown to activate YAP/TAZ signaling and enhance tissue regeneration in preclinical models [185]. Similarly, LATS1/2 inhibitors such as GA-017, TRULI, and TDI-011536 stabilize YAP/TAZ, promoting their nuclear translocation and stimulating proliferation and organoid growth, with TRULI demonstrating high potency but some off-target effects [184, 185]. In contrast, inhibitors targeting the YAP/TEAD interaction serve primarily as anti-cancer agents [186]. Verteporfin, originally used for photodynamic therapy, has been repurposed to disrupt YAP/TEAD binding and suppress transcriptional activity. Other emerging compounds like JM7 and CA3 inhibit TEAD palmitoylation or block YAP-TEAD complex formation, respectively, and are under preclinical investigation [187]. Additionally, the MST1/2 activator YL-602 represents a novel approach to directly enhance Hippo pathway activity, inducing apoptosis and reducing tumor growth in vivo. Peptide-based strategies, such as SHAP (a STRIPAK-modulating peptide), offer upstream activation of Hippo signaling, while theoretical decoy peptides are being designed to inhibit key protein–protein interactions within the pathway. Beyond chemical modulators, gene editing and overexpression of components like MST1/2, LATS1/2, and SAV1 provide genetic means of activating Hippo signaling in preclinical research [188]. Other small molecules targeting upstream regulators such as MAP4Ks and WWC proteins are also in early-stage development.

BMP signaling modulators

Several classes of small molecules, peptides, and biologics have been developed to modulate BMP signaling, a pathway critical for embryogenesis, bone formation, and tissue repair. Small molecule activators such as flavonoids, chalcones (e.g., isoliquiritigenin, 4'-hydroxychalcone), and the carbazole derivative PD407824 have demonstrated the ability to enhance BMP-responsive gene expression and induce Smad1/5/8 phosphorylation in preclinical studies [189, 190]. Of particular interest are benzoxazoles and benzimidazoles like SY-LB-35 and SY-LB-57, which function as allosteric agonists of BMP receptors and simultaneously activate multiple signaling pathways, including PI3K/Akt and MAPKs, thus improving cell viability [191]. These compounds offer promising alternatives to recombinant BMPs by potentially avoiding issues of delivery, cost, and systemic side effects.

On the other hand, small molecule inhibitors such as Dorsomorphin and LDN-193189 selectively block BMP type I receptor kinases, thereby inhibiting Smad1/5/8 activation and preventing ectopic ossification [192, 193]. Dalantercept, an ALK1-Fc fusion protein, targets BMP9/10 to inhibit angiogenesis and has shown promise in cancer trials [194]. Similarly, SJ000063181 serves as a potent probe for BMP-related studies [195]. Additionally, molecules like NPL1010 and NPL3008, which inhibit Chordin cleavage, suppress BMP activity at the level of upstream regulation [193]. Dorsomorphin, an early BMP receptor inhibitor, laid the foundation for more selective compounds such as LDN-193189, despite its broader kinase inhibition profile [194].

Challenges and limitations

Stem cell therapy holds immense promise but presents significant challenges and limitations that must be addressed for safe and effective clinical applications. One primary concern is the similarity between stem cells and tumor cells, as both exhibit rapid proliferation, genetic instability, increased telomerase expression, and self-renewal capabilities. For instance, pluripotent stem cells, such as ESCs and iPSCs, carry a risk of teratoma formation, with animal studies reporting the development of benign and malignant tumors following transplantation [196]. Additionally, a notable case report documented a patient developing a tumor-like mass in the spinal cord years after stem cell therapy, highlighting the potential long-term risks [197]. Immune rejection remains a critical barrier to successful stem cell transplantation. Even genetically matched autologous iPSCs can trigger immune responses [198]. In HSCT, complications like graft-versus-host disease (GVHD), hepatic veno-occlusive disease, and late-onset pulmonary disorders further hinder clinical outcomes [199, 200]. Biodistribution, survival, and signaling complexity present significant hurdles in stem cell therapy [201]. Transplanted cells may become trapped in microvasculature, raising risks like pulmonary embolism. Systemic delivery can cause off-target effects, while local delivery is invasive. Allogeneic transplants often require immunosuppression, increasing the risk of infections and malignancies. Additionally, stem cell behavior is governed by complex, interconnected signaling pathways (e.g., PI3K/Akt, Raf/Mek/Erk, Wnt/Gsk3β), where modulation of one pathway may disrupt others, leading to unpredictable outcomes [14].

The use of stem cell therapies and pharmacological modulators also raises significant ethical

concerns regarding patient safety, transparency, and equitable access. Translating findings from animal models to humans presents a dilemma. Preclinical results often fail to fully predict human outcomes, making early clinical trials inherently risky and necessitate careful regulation of first-in-human trials. Premature commercialization of unproven treatments fosters misinformation and therapeutic misconception. Misuse of the term"stem cell therapy"can mislead patients into believing they are receiving validated care [202]. Patient variability(genetic differences), cell source, dosage, and delivery route affect therapeutic outcomes [203]. Key concerns include tumorigenicity and unforeseen toxicities, especially with genetically modified or pharmacologically enhanced stem cells [204].

Regulatory oversight plays a crucial role in ensuring the safety, efficacy, and ethical application of regenerative medicine therapies. Despite efforts towards harmonization, significant differences remain between regulatory agencies of different countries, complicating multinational development programs. While the Regenerative Medicine Advanced Therapy (RMAT) designation by FDA accelerates approval for therapies addressing unmet medical needs, other regions adopt different approaches. Japan's Pharmaceuticals and Medical Devices (PMD) Act allows conditional, time-limited approval based on preliminary safety data, while South Korea's Act on the Safety and Support for Advanced Regenerative Medicine and Advanced Biopharmaceuticals (ARMAB) sets strict guidelines for clinical studies and approvals. The European Union classifies regenerative medicine products as Advanced Therapy Medicinal Products (ATMPs), requiring centralized approval by the European Medicines Agency (EMA), yet inconsistencies in international approvals persist. Another challenge is the classification of therapies based on their degree of manipulation and intended use. In the U.S., minimal manipulation criteria under 21 CFR 1271 determine whether a therapy requires premarket approval. However, this distinction can be ambiguous, particularly for therapies that involve intermediate levels of modification. Similarly, Japan and South Korea implement varying standards for determining whether a product qualifies for expedited approval or requires extensive clinical testing, creating disparities in regulatory expectations. Global regulatory alignment is necessary to facilitate broader adoption of regenerative medicine therapies.

Future perspective

The future of regenerative medicine is increasingly oriented towards the pharmacological modulation of stem cell signaling pathways to enhance therapeutic efficacy. Targeting critical pathways, such as Hh, Wnt, Notch, and TGF-β, can precisely regulate stem cell fate, improve survival, and drive controlled differentiation. Emerging strategies, such as small molecule screening and drug repurposing, have identified compounds like staurosporine and metformin, which promote stem cell functionality and enhance therapeutic outcomes. Epigenetic modulators, including histone deacetylase inhibitors like valproic acid and DNA methyltransferase inhibitors such as 5-azacytidine, are facilitating stem cell reprogramming by altering chromatin accessibility and gene expression profiles.

The next phase of development will focus on precision medicine, tailoring stem cell modulation to individual patient profiles to enhance efficacy and minimize adverse effects. This will involve targeted manipulation of signaling pathways, supported by gene editing technologies like CRISPR to optimize regenerative potential and reduce risks such as tumorigenesis. Immune modulation will remain crucial for improving stem cell engraftment and function. Future strategies will aim to create a pro-regenerative immune environment, balancing immune tolerance with tissue repair, enhancing safety and durability, especially for MSCs that rely on paracrine signaling and immune interactions. Combining pharmacological agents with gene therapies, biomaterials, and engineered scaffolds could further optimize stem cell environments and differentiation.

As of early 2025, around 116 interventional clinical trials are underway globally, involving 83 unique hPSC products. Among these, ~ 50% of hPSC trials are Phase I/II, focusing on safety and preliminary efficacy. These trials are mainly focused on treating eye disorders, central nervous system conditions, and various cancers. To date, over 1,200 patients have received hPSC-derived therapies, with more than 10^{11} cells administered, and no major safety issues have been reported [205]. While no hPSC-based therapy has yet received full regulatory approval, promising results are emerging, particularly for retinal and spinal cord conditions. Neural stem cells (Oligodendrocyte progenitor cells) based therapy is also being explored in a phase 1 clinical trial for spinal cord injury treatment [206]. HSCT remains widely approved and routinely applied SC therapy for haematological malignancies and immune disorders, with success rates nearing 70% [207, 208]. MSC therapies, though still largely experimental, show potential in autoimmune diseases and tissue regeneration, with some trials reporting efficacy rates ranging 60–80% [209]. The regenerative medicine market is driven by MSC research and projected to reach $13.66 billion by 2025. Nonetheless, key challenges persist, including variability in clinical outcomes, immunogenicity of allogeneic cells, and the need for scalable, tumour-free iPSC manufacturing. Emerging

trends such as the integration of iPSCs and CRISPR for personalised medicine and the increasing dominance of iPSC-based trials (>74% of current hPSC studies) reflect a shift towards precision regenerative therapies.

Developing multitarget inhibitors is essential to address pathway crosstalk and drug resistance, similar to strategies in cancer stem cell therapy [210]. The use of nano-drug delivery systems is an exciting advancement, allowing for targeted delivery of pharmacological agents and reducing systemic toxicity [211]. Engineered microenvironments mimicking natural stem cell niches will guide stem cell fate and integration, while vascularized grafts will improve graft survival and function, allowing for the creation of large, functional tissues. Pharmacological modulation will include exosome-based therapeutics and epigenetic modulators, offering safer, controllable alternatives by leveraging stem cell secretomes to stimulate endogenous repair mechanisms.

Future research should focus on optimizing drug delivery, minimizing off-target effects, and ensuring long-term safety. Enhancing immune tolerance and reducing rejection are key for allogeneic stem cell transplants, which can be addressed with immunosuppressive drugs or novel immune modulation techniques. Combining pharmacological strategies with biomaterials and precision medicine, such as coupling small-molecule inhibitors with hydrogels or CRISPR-based gene editing, could further refine treatments and improve outcomes. In addition, integrating high-throughput single-cell analyses and advanced disease models will enhance our understanding of stem cell heterogeneity and patient-specific responses, accelerating the translation of regenerative and therapies from the lab to clinical practice. Modern regulatory initiatives are improving toxicology assessments for regenerative therapies involving stem cells, promoting innovation in clinical trial design, and leveraging post-market data to enhance patient safety. Balancing innovation with strict safety measures will ensure responsible translation of regenerative therapies into clinical practice. Aligning regulatory frameworks globally and utilizing reliance and recognition mechanisms will streamline approvals and reduce uncertainty, fostering broader access to regenerative medicine products.

Conclusion

Stem cell therapies, when integrated with pharmacological modulation, represent a paradigm shift in regenerative medicine and oncology, offering novel solutions for a wide range of diseases. Key signaling pathways such as TGF-β, Notch, Hippo, BMP, Hh, Hippo and Wnt play fundamental roles in stem cell regulation, making them prime candidates for therapeutic intervention. However, their dual roles in both promoting and suppressing tumorigenesis, as well as their broader involvement in tissue homeostasis, present significant challenges that must be carefully addressed. Pharmacological modulators, including small molecule inhibitors, mAb, and gene-editing technologies, have demonstrated significant potential in enhancing therapeutic efficacy. Yet, challenges such as tumorigenicity, immune rejection, and the unpredictability of translating pre-clinical successes into clinical applications highlight the need for rigorous safety assessments and ethical considerations. Establishing robust regulatory frameworks, implementing long-term patient monitoring, and ensuring equitable access to advanced therapies are essential to maximizing their clinical impact. By integrating personalized medicine, combination therapies, and cutting-edge biotechnologies, regenerative medicine can move toward safer, more effective, and widely accessible treatments. Continued interdisciplinary research and innovation will be key to overcoming existing limitations and unlocking the full potential of regenerative approaches in modern healthcare.

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Use of AI in writing
"The authors declares that they have not use AI-generated work in this manuscript. Trinka and ChatGPT was used to improve the structure, syntax, language and coherence in writing only".

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