

Stem Cell Therapy for Pediatric Type 1 Diabetes: Current Evidence, Challenges, and Future Directions

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Abstract Type 1 diabetes mellitus (T1DM) in children poses significant lifelong challenges. Current insulin-based therapies effectively manage glycemic control but do not offer a cure. Stem cell therapy has been investigated as a promising treatment for T1DM. This review consolidates current evidence regarding stem cell therapies for managing T1DM in children, focusing on stem cell sources, mechanisms of action, clinical outcomes, and associated challenges. **Methods:** A structured narrative review was conducted. Relevant studies, clinical trials, and reports were sourced from PubMed and other scientific databases. Priority was given to pediatric studies, mixed-population studies with extractable pediatric data, and clinical trials assessing efficacy, safety, and feasibility. **Results:** Evidence suggests that various stem cell types including hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), and pluripotent-derived β -like cells have the potential to enhance C-peptide levels, reduce the need for exogenous insulin, and modulate autoimmunity. In one study of autologous HSCs transplantation, 59% of participants achieved insulin independence within 6 months, while 32% remained insulin independent at the last follow-up. HbA1c decreased accompanied by an increase in C-peptide. However, these effects have largely been demonstrated in small studies involving adolescents, young adults, or mixed-age populations and have been achieved using immunosuppressive regimens associated with toxicity, whereas MSCs based studies generally demonstrate more improvements in β -cell function and insulin requirements. These findings must be interpreted cautiously because pediatric-specific studies are still limited, and outcomes vary considerably depending on the disease stage, cell type, delivery method, and immunosuppression protocols. **Conclusion:** Stem cell therapy represents a promising yet still experimental approach for pediatric T1DM. Well-designed pediatric clinical trials are essential to establish efficacy and ensure safety before these therapies can be widely implemented in clinical practice. Future pediatric trials should consequently prioritize approaches that achieve immune modulation or β -cell replacement without myeloablative or intensive immunosuppressive conditioning.

Key Words Type 1 DM, Children, Stem Cell Therapy, Mesenchymal Stem Cells, Hematopoietic Stem Cells, iPSCs

INTRODUCTION

T1DM is a prevalent endocrine metabolic disorder that affects children and adolescents globally. It results from the autoimmune destruction of pancreatic β -cells, leading to hyperglycemia [1]. The age of onset for childhood T1DM typically peaks between 4 to 6 years and again during early puberty (10 to 14 years). There is an increasing incidence of T1DM in infants, affecting children as young as six months [2,3]. Autoimmune diabetes often occurs with significant acute and long-term complications. Symptoms usually manifest during childhood or adolescence, although they may occasionally appear later in life, with most patients requiring lifelong insulin injection treatment [4]. Exogenous

insulin use cannot replicate the endogenous insulin produced by a healthy pancreas. Complications such as hypoglycemia, weight gain, and dyslipidemia are among the consequences of standard insulin therapy [5, 6]. T1DM imposes a significant psychosocial and economic burden on affected children and their families, leading to a reduced quality of life and increased healthcare costs [7].

In the past two decades, treatment has seen major advancements, including the identification of new autoantibodies and the development of advanced insulin delivery and glucose monitoring devices. However, no effective methods have been approved to prevent or delay T1DM in young people, and the number of affected children

continues to rise [8]. Advances in diabetes technology have substantially improved the management of pediatric T1DM. Continuous glucose monitoring (CGM), insulin pumps, sensor-augmented pump therapy, and automated insulin delivery (AID) systems can improve glycemic control, increase time in range, and reduce hypoglycemia while decreasing some aspects of treatment burden. However, these technologies remain replacement rather than disease-modifying therapies. They require continuous device use, insulin administration, behavioral engagement, and access to specialized care. Technical failures, sensor or infusion-site problems, alarm burden, skin reactions, cost and access disparities, and the need for meal-related insulin input remain important limitations. Thus, despite major advances in diabetes technology, current treatment does not restore endogenous β -cell function or eliminate the underlying autoimmune process [8,9].

Progress in regenerative medicine—particularly β -cell replacement and stem cell-based immunomodulatory approaches—has generated considerable interest. Early experimental and clinical studies suggest that stem cell therapies may preserve residual β -cell function, restore immune tolerance, or replace destroyed β -cells. Preservation of residual β -cell function is associated with improved metabolic stability and reduced diabetes-related complications. Consequently, two major therapeutic strategies have emerged: immunomodulatory approaches designed to interrupt β -cell destruction and cell-replacement approaches intended to restore insulin-producing β -cell mass. Stem cell-based therapies encompass both strategies and therefore represent a distinct therapeutic concept rather than simply an alternative method of insulin delivery [8,10].

While clinical trials for adults provide robust evidence that enhances the care and outcomes of DM, pediatric clinical trials remain scarce. Therefore, it is crucial to synthesize emerging evidence specific to children. Recent narrative reviews have summarized the emerging role of stem cell therapy in pediatric T1DM. However, important uncertainties remain regarding the distinction between pediatric-specific evidence and findings extrapolated from adults, the durability of treatment effects, and the balance between metabolic benefit and treatment-related toxicity.

This narrative review critically evaluates current studies on stem cell-based therapies for type 1 DM, comparing HSCs, MSCs, pluripotent stem cell-derived β -cell replacement, and stem cell educator therapy with respect to their mechanisms, clinical efficacy, durability of β -cell function, safety, pediatric applicability, and translational feasibility, with particular emphasis on pediatric applicability, long-term remission, the requirements for safe clinical implementation in children and the ethical and regulatory requirements for future clinical use.

METHODS

An extensive examination of existing literature was performed on PubMed, Scopus, and Web of Science published from 2000–2025 using relevant keywords (e.g.,

“type 1 diabetes,” “children,” “stem cell therapy,” “ β -cell regeneration,” “mesenchymal stem cells,” “hematopoietic stem cells,” “iPSC”). The clinical trials, cohort studies, case series, and mechanistic research related to stem cell therapy for pediatric T1DM were included. Studies involved participants ≤ 18 years or contained pediatric-specific analyses were included. Adult studies were referenced only when it is essential to contextualize mechanisms or highlight gaps in pediatric evidence. Only articles published in English were included in the search.

Search Strategy

The literature search combined terms related to type 1 diabetes, pediatric populations, and stem cell-based therapies using Boolean operators. The core search strategy was: (“type 1 diabetes” OR “type 1 diabetes mellitus” OR T1D OR T1DM) AND (child OR pediatric OR paediatric* OR adolescent*) AND (“stem cell” OR “stem cell therapy” OR “mesenchymal stem cell” OR MSC OR “hematopoietic stem cell” OR HSC OR “induced pluripotent stem cell” OR iPSC OR “embryonic stem cell” OR ESC OR “stem cell educator” OR “ β -cell replacement”). The search strategy was adapted to the syntax and indexing requirements of each database. Searches were limited to studies published in English between 2000 and 2025.

A total of 512 records were identified through database searches (PubMed, Scopus, Web of Science). After removing 72 duplicates, 440 titles/abstracts were screened. Of these, 398 records were excluded for not meeting the inclusion criteria (animal studies, non-clinical, review articles, irrelevant outcomes). The full texts of 42 articles were assessed for eligibility. Thirty-four (34) articles were excluded for the following reasons: Adult-only population ($n = 14$), No clinical outcomes reported ($n = 9$), Laboratory/mechanistic only ($n = 7$), Insufficient or inaccessible data ($n = 4$). Ultimately, 8 studies were included in the qualitative analysis. Other studies used for results interpretation and discussion. The study identification and selection process is summarized in a PRISMA 2020-style flow diagram (Figure 1) to improve transparency of the literature search and screening process. Although this study was designed as a structured narrative review rather than a systematic review, the PRISMA-style diagram [11] was used to transparently present the identification, screening, eligibility assessment, and inclusion of studies.

The methodological quality and risk of bias of the included clinical studies were assessed using design-specific critical appraisal approaches. Randomized controlled trials were evaluated using the Cochrane Risk of Bias 2 (RoB 2) tool, non-randomized comparative intervention studies were assessed using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool, and observational or case-level studies were assessed using the appropriate Joanna Briggs Institute (JBI) critical appraisal checklist. The appraisal considered study design, participant selection, comparability of groups, allocation procedures, confounding, outcome measurement, follow-up, and

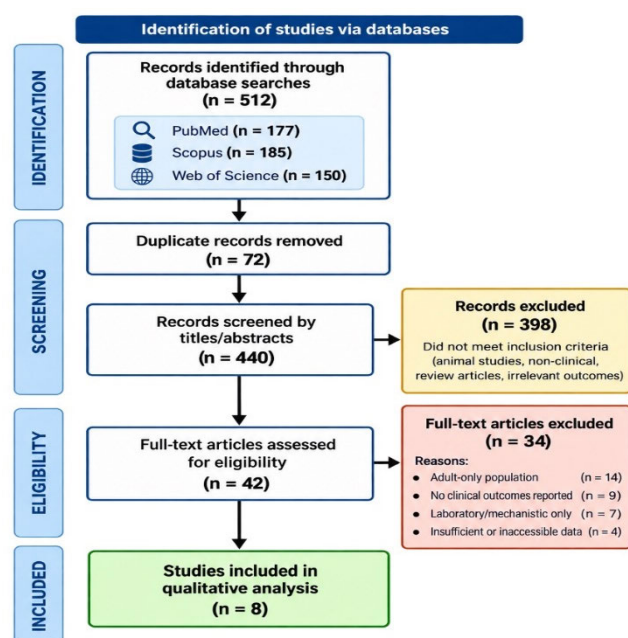


Figure 1: PRISMA 2020 Flow Diagram of Study Selection Process, Shows the Number of Records Identified, Screened, assessed for Eligibility, excluded with Reasons and the Final Number of Studies Included in the Quantitative Analysis

completeness of outcome data. The findings were used to contextualize the strength and limitations of the available evidence and to guide cautious interpretation of clinical outcomes rather than to generate a pooled effect estimate.

Because of substantial heterogeneity in populations, interventions, outcome definitions, follow-up duration, and study designs, quantitative meta-analysis was not attempted, and the findings were synthesized narratively. For each eligible study, data were extracted using a predefined framework including study design, participant characteristics, age range, disease duration, stem cell source and type, cell dose where reported, route of administration, conditioning or immunosuppressive regimen, follow-up duration, C-peptide, HbA1c, insulin requirement or insulin independence, immune markers, and treatment-related adverse events (Table 1).

To ensure methodological rigor, the quality of the included narrative reviews was evaluated using the Scale for the Assessment of Narrative Review Articles (SANRA) [12]. Two independent reviewers scored each article across SANRA's six items: importance, aims, literature search, referencing, scientific reasoning, and endpoint data presentation. Each item was rated from 0 (low standard) to 2 (high standard), resulting in a maximum sum score of 12. Any scoring discrepancies between reviewers were resolved through consensus or consultation with a third reviewer.

Pathophysiology of T1DM in Children:

T1DM results from autoimmune destruction of pancreatic beta cells caused by complex interaction of genetic and environmental factors, including exposure to viruses, the

host microbiome, diet. Exposure to these factors recruit antigen-presenting cells to transfer self-reactive beta-cell antigens to self-reactive T cells ultimately leading to progressive β -cell failure, absolute insulin deficiency, and metabolic instability. About one-third of newly diagnosed pediatric type 1DM are present with diabetic ketoacidosis which has a mortality rate of around 0.3-0.5%, despite aggressive treatment. The life expectancy of many individuals is reduced by 10-20 years. Pediatric-onset diabetes differs from adult diabetes in its unique epidemiology, pathophysiology, developmental factors, and responsiveness to treatment, [13].

The management of diabetes in children should not be inferred from the care of diabetes in adults. Clinicians must be aware of the child's changing developmental phases while providing care for children and adolescents and modify their treatment to fit the child's requirements and situation. Exogenous insulin is currently the most common treatment for type 1 diabetes but doesn't cure the disease [14]. Over the past few decades, treatments have focused on normalizing glucose levels while reducing the risk of hypoglycemia, monitoring chronic complications, and acknowledging the important psychosocial factors affecting children during periods of growth and development [15]. The physiological characteristics of pediatric patients must be considered when designing clinical trials for stem cell therapy for diabetes. Children's immature immune systems predispose them to type 1 DM and affect their response to immunomodulatory therapies [16,17]. Careful trial design is therefore essential to ensure safety while evaluating the potential of stem cell-based interventions in children.

Rationale for Stem Cell Therapy in Pediatric T1DM:

Stem cells are self-renewal cells that can give rise to at least one type of highly differentiated progeny. Based on the potential for development, stem cells are classified into unipotent, oligopotent, multipotent, pluripotent, or totipotent. Based on the origin of stem cells, they are grouped into embryonic stem cells (ESCs), adult stem cells (ASCs), and induced pluripotent stem cells (iPSCs). iPSCs and ESCs are pluripotent stem cells, whereas ASCs are unipotent or oligopotent. iPSCs, hematopoietic stem cells (HSCs), human blood-derived multipotent stem cells, and MSCs were used for the preservation of B-cells [18,19]. Recent rapid advancements in stem cell technology have led to stem cell therapy as an option for a wide range of diseases, including diabetes [20]. The underlying mechanisms include the ability of stem cells to increase the β cell proliferation, stimulation of β cell neogenesis which is the formation of insulin-producing β cells. Another approach of Stem cells therapy is to reconstitute immunotolerance, re-establish peripheral tolerance toward b-cells through remodeling of the immune response as well as through inhibition of the immune response of T cell through TGF- β and inflammatory pathways. Early intervention is recommended in pediatrics to maintain residual β cell function and prevent the disease progression. As a result, stem-cell therapy is being investigated as a potential approach to preserve or restore β -cell function. [21].

Table 1: Clinical Studies of Stem Cell-Based Therapies Involving Pediatric Participants or Providing Relevant Evidence For Pediatric T1DM

Study reference*	Study design	Population /age group	Sample size	Stem cell type/ intervention route/cell dose	Follow up	Main outcomes	Adverse outcomes	Pediatric relevance/limitation
D'Addio <i>et al.</i> [33]	Multicenter pooled cohort (nonmyeloablative AHST)	New onset T1DM; Mixed (including adolescents and adults)	65	Autologous hematopoietic stem cells were mobilized with cyclophosphamide. infusion of autologous CD34+ cells are injected intravenously	Up to 48 months	decrease in HbA1c levels (from 10 to 6%) increase in C-peptide levels (from 0.5 to 1.2 ng/ml) 59% achieved insulin independence within 6 months	52% experienced adverse effects, as culture negative-bilateral pneumonia in 1 patient and late endocrine dysfunction (hypothyroidism or hypogonadism) in 2 others. There is no mortality	Not pediatric specific High efficacy signal must be balanced against conditioning-related toxicity
Thakkar <i>et al.</i> [28]	Prospective clinical study	Mixed (adolescents + adults)	20: (10 autologous; 10 allogeneic)	Autologous bone marrow-derived MSCs Approximately 2.7×10^4 differentiated cells/kg in autologous group and 2.1×10^4 kg in allogeneic group; infused into portal/thymic circulation and subcutaneous tissue after nonmyeloablative conditioning.	24 months	Improved metabolic control; partial insulin independence in some cases HbA1c changed from 10.99 ± 2.10 to $7.75 \pm 1.05\%$; insulin requirement changed from 63.90 ± 20.95 to 39.66 ± 9.37 IU/day.	No major safety concerns; well tolerated	Young-adult rather than pediatric evidence; should not be interpreted as pediatric efficacy
Gu <i>et al.</i> [40]	1:2 matched case-control study	newly diagnosed children with type 1 DM	42: 28 treated + 14 controls	Autologous- HST. with immune ablation	3-5yr Long term follow up	insulin stopped in three cases only. No sustained insulin independence. At long-term follow-up, no significant advantage in daily insulin dose, HbA1c, or C-peptide compared with controls	90% of the patients presented serious adverse events; to secondary cyclophosphamide including gastrointestinal symptoms, hair loss, leukopenia and neutropenia,	Direct pediatric evidence; small nonrandomized study; important to counterpoint to positive adult HSC studies
Yamauchi <i>et al.</i> [39]	Case report	16-year-old adolescent	1	allogeneic hematopoietic stem cell transplantation (HSCT)	At least 20 months recorded	Insulin independence; euglycemia maintained at 15 mo; and C-peptide improved from 1.0 to 3.4 ng/mL at 20 mo	Single-case; HSCT transplant-related risks	Highly specific case of T1DM associated with IPEX; cannot be generalized to ordinary pediatric T1DM
Izadi <i>et al.</i> [26]	A triple-blind parallel randomized placebo-controlled trial	newly diagnosed T1DM children	21	two doses of autologous BM-MSCs transplantation; 1×10^6 MSCs/kg per infusion, at weeks 0 and 3 were injected intravenously (IV)	12 months	significantly reduces the number of hypoglycemic episodes improved glycated hemoglobin (HbA1c), shifted serum cytokine patterns from pro-inflammatory to anti-inflammatory, increased the number of regulatory T-cells in the peripheral blood, and improved quality of life.	Mild reaction, urticaria and mild lymphocyte increase No major complications and adverse events were reported	Mixed pediatric/adult study; pediatric-specific numerical outcomes should be reported separately if available

Table 1: Clinical Studies of Stem Cell-Based Therapies Involving Pediatric Participants or Providing Relevant Evidence For Pediatric T1DM (Continue)

Study reference*	Study design	Population /age group	Sample size	Stem cell type/ intervention route/cell dose	Follow up	Main outcomes	Adverse outcomes	Pediatric relevance/limitation
Mesplès <i>et al.</i> [27]	Pilot study	children (age 6–10 years, average 8 years) recently diagnosed with type 1 diabetes mellitus	6	autologous hematopoietic stem cell transplantation $>180 \times 10^6$ kg; CD34+ cells $>0.22\%$ without immune ablation used to suppress the transplanted by intravenous (i.v.) infusion.	6 months	significantly decreasing the production and effect of autoantibodies against ICA, GAD, and IA2, as well as decreased blood sugar levels and HbA1c.	No adverse effects	Direct pediatric evidence but extremely small sample and uncontrolled design
Leão <i>et al.</i> [32]	Retrospective cohort, 36-month follow-up study	Mixed children and adult range (15–40 years)	28	Allogeneic adipose-derived stromal/stem cells (ASC) infusion + cholecalciferol	36 months	Signals of improved partial clinical remission (IDAA1c), lower insulin needs at some timepoints Decreased insulin requirements after three years of follow-up.	few severe adverse events were reported.	Young-adult/mixed population; minimum age 15; not pediatric-specific and includes a combination intervention
Zhao <i>et al.</i> [58]	Early clinical device-based immunomodulation pilot study	Mixed 15 to 41 years average age	15	Cord blood-derived multipotent stem cells used ex vivo to “educate” patient lymphocytes (device)	Up to 40 wk	Improved fasting/stimulated C-peptide, immunologic markers ($\uparrow$ Tregs), sustained metabolic improvements in some patients through 40 weeks Stem Cell Educator	Reported as safe in small cohorts; longer studies and larger cohorts needed	Adolescent/young-adult evidence; very small study; experimental device-based immunomodulation

*Studies were included because they either enrolled pediatric participants or provided clinically relevant evidence informing the potential pediatric application of stem cell-based therapies. Adult and mixed-age studies are explicitly identified and should not be interpreted as direct evidence of efficacy or safety in children.

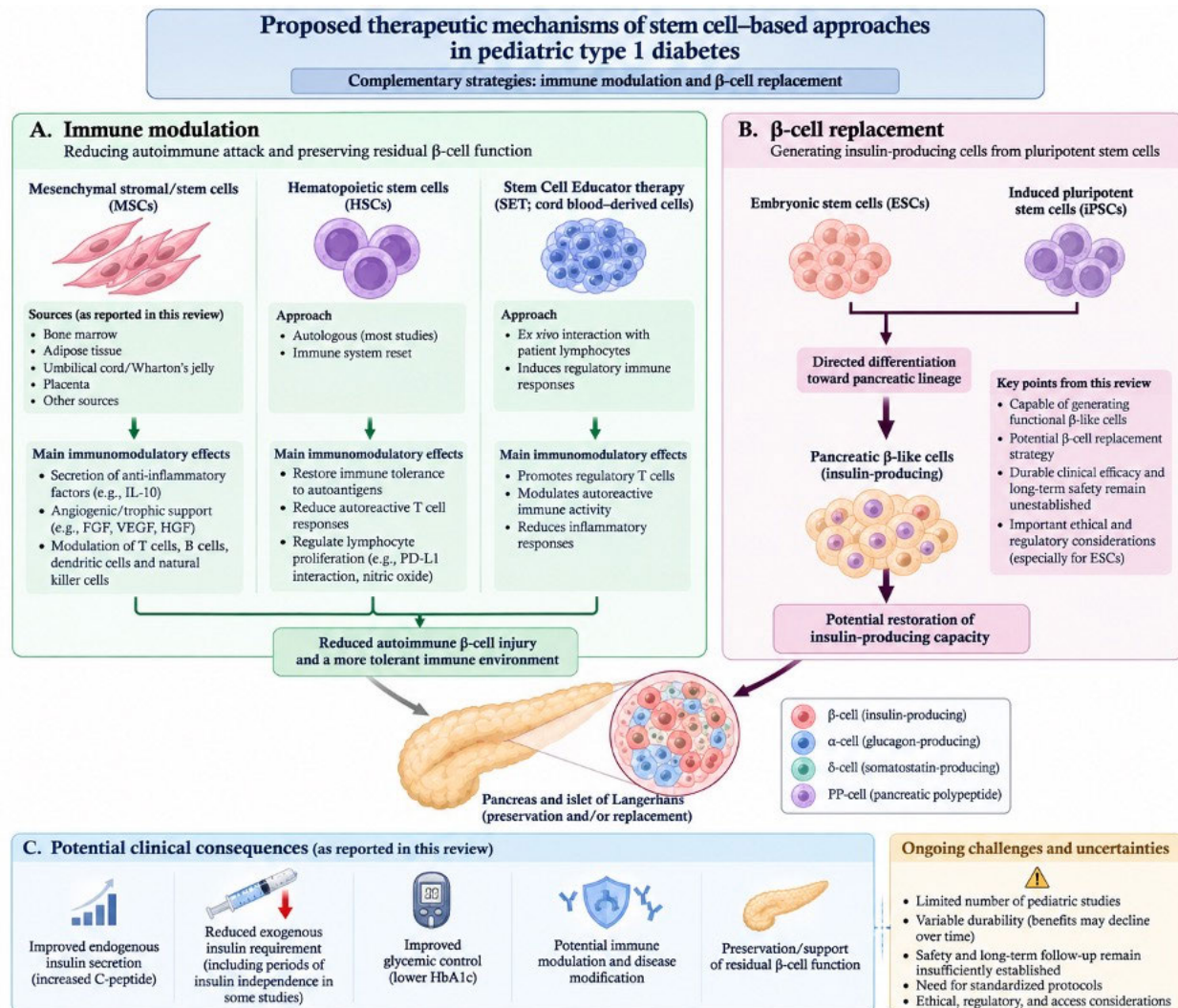


Figure 2: Proposed Therapeutic Mechanisms of Stem Cell-Based Approaches in type 1 Diabetes. (A) MSCs, HSCs, and Stem Cell Educator Therapy may Modulate Immune Responses and Preserve Residual β -Cell Function. (B) ESCs and iPSCs can Generate Pancreatic B-Like Cells as a Potential B-Cell Replacement Strategy. (C) These Approaches may Improve Insulin Secretion, Reduce Insulin Requirements, and Improve Glycemic Control, although Long-Term Efficacy and Safety Remain Uncertain

Types of Stem Cell Therapy in Clinical Trials Including Pediatrics T1DM

The clinical trials focusing on pediatric T1DM are limited in comparison to the adult trials. However, stem cells are currently engaged in pediatric research and have led to improvements in clinical outcomes in some pediatric diseases or in quality of life [22]. To date, specific types of stem cells are under evaluation for these purposes, with the potential for differentiation and proliferation varying considerably among sources [23]. The available clinical trials are presented in table no (1). These include mesenchymal stem cells (MSCs), umbilical cord stem cells, hematopoietic stem cells (HSCs), induced pluripotent stem cells (iPSCs), embryonic stem cells.

The proposed complementary mechanisms of these approaches, including immune modulation and potential β -cell replacement, are summarized in Figure 2.

Mesenchymal Stem Cells (MSCs)

MSCs are multipotent, non-hematopoietic extracted from many sources, including stroma of bone marrow, adipose tissue, umbilical cord blood, Wharton's jelly, placenta, and even endometrial tissue. MSCs can be used to repopulate damaged tissues. The anti-inflammatory and immunomodulatory effects of MSCs aid in the protection of existing β cells from autoimmune attack. Their angiogenic and immunomodulatory properties make them ideal for generating functional β cells tailored for personalized medicine [10,24,25].

Clinical studies suggested that MSCs transplantation can improve metabolic outcomes in pediatric T1DM. Early transplantation of autologous MSCs is proved by Izadi *et al.* [26] to significantly improve HbA1c and C-peptide level and shift pro-inflammatory cytokines to anti-inflammatory cytokines. The study concluded that early transplantation of

MSCs significantly reduces the number of hypoglycemic events in recipients and can greatly improve metabolic indices and alleviate immune responses by increasing anti-inflammatory cytokines and decreasing pro-inflammatory cytokines compared to late transplantation of MSCs.

Another recent study on autologous BM-MSCs concluded the promising therapeutic effect in pediatric T1DM [27]. The study protocol includes stimulation of BM-MSCs proliferation with colony-stimulating factors (Filgrastim) which do not require immune ablation and can be immediately implanted into the subject. They reported a significant decline in the autoantibodies, blood sugar levels and (HbA1c) with no reported complications.

Allogenic transplantation of AMSCs is proved to be easy protocol, safe therapy for preserving β cells' function and, consequently, prolonging clinical remission. Several studies working on ASCs documented their safety without serious reported adverse events in T1DM [28,29], and other autoimmune diseases, such as rheumatoid arthritis [30], systemic lupus erythematosus, inflammatory bowel disease, and multiple sclerosis [31]. A trial by Leão *et al.* [32] on young T1DM patients aged 15 years and older demonstrated that the intervention with combined infusion of AMSC and vitamin D supplementation was associated with partial clinical remission at 6 months and a lower total daily insulin requirement. With consideration of the complex pathophysiology of T1DM, combined interventions are more likely to yield favorable outcomes. Patients who received treatment showed a higher rate of clinical remission and required a lower total insulin dose over a three-year follow-up period, indicating improved glycemic stability and long-term benefits from the intervention.

Previous research indicated that MSCs promote angiogenesis through the secretion of cytokines like fibroblast growth factors and vascular endothelial growth factor and through secretion of peptides, such as hepatocyte growth factor, which possess local immunosuppressive properties [33]. Additionally, interleukin-10 (IL-10) is expressed by MSCs and plays a significant role in regulating T cells and promoting a suppressive phenotype by counteracting the effects of interleukin-12 (IL-12) during the onset of an inflammatory immune response [25, 34]. Furthermore, MSCs contribute to immunomodulation by altering the phenotype of dendritic cells, T cells, B cells, and natural killer cells [24].

MSCs originated from either bone marrow or adipose tissue have been proved to play an essential role in lowering levels of fasting blood sugar, hemoglobin A1c (HbA1c), and C-peptide, and in treating microvascular complications [26, 34]. However, some of the disadvantages of its use in clinical practice are limited to its method of collection, proliferation rate, cell activity with age, and the risk of tumor formation as demonstrated by El-Sawah *et al.* [35]. Overall, emerging pediatric evidence suggests that MSC therapy is safe and may prolong partial remission, but long-term effects remain unknown

Hematopoietic Stem Cells (HSCs)

HSCs exhibit immunomodulatory capacities through interactions with CD4+ and CD8+ T cells, mediated by the surface molecule programmed death ligand 1 (PD-L1). They also secrete nitric oxide (NO) and regulate lymphocyte proliferation by inhibiting mitogen activity [36]. Another study demonstrated a significant reduction in the proliferation of T cell clones upon stimulation by antigen-presenting cells and glutamic acid peptide decarboxylase. These attributes have spurred interest in autologous HSC (auto-HSCs) transplantation. The immunomodulatory functions of autologous HSCs have been linked to substantial insulin independence, improved metabolic control, and increased C-peptide levels in both short- and medium-term follow-up of T1DM. Additionally, a cost-effectiveness analysis comparing type 1 diabetic patients undergoing autologous hematopoietic cell transplantation with those on insulin therapy indicated economic benefits [37].

D'Addio *et al.* [38] explored high-dose immunosuppression followed by nonmyeloablative autologous HSCs transplantation in newly diagnosed type 1 diabetes, observing enhanced B-cell function and prolonged insulin independence. In another case, Yamauchi *et al.* [39] reported on a 16-year-old with late-onset FOXP3 R347H mutation-associated IPEX syndrome and T1D, where insulin dependency improved following HSC transplantation, allowing the patient to cease insulin infusion and maintain euglycemia 15 months post-treatment. Conversely, a study by Gu *et al.* [40] on 42 children newly diagnosed with T1DM found conventional insulin therapy more advantageous for HbA1c control and diabetic complications, highlighting its preference for treating newly diagnosed children. The key distinction lies in the absence of cyclophosphamide-induced immune ablation in this study.

Research on HSCs in pediatric T1DM treatment has shown that autologous HSCs regenerate immune tolerance to autoantigens and reset the immune system rather than regenerate B cells, aiming to halt the immune-mediated destruction of insulin-producing cells. Auto-HSCT is potentially the only treatment associated with sustained and complete remission for T1DM. Clinical trials have reported periods of insulin independence in treated patients, but challenges such as immunosuppression to prevent graft-versus-host disease, long-term efficacy, and patient selection remain [41,42].

A recent study by Mesplez *et al.* [27] demonstrated that HSCs transplantation influenced production of pancreatic antibody, reduced pancreatic tissue inflammation, and enhanced metabolic control over a six-month follow-up in children recently diagnosed with T1DM associated with ketoacidosis. The procedure, involving IV infusion of auto-HSCs without cyclophosphamide, was low-risk and had no ethical issues, as no observed complications during the transplant or follow-up period. Furthermore, combining HSCs with MSCs transplantation in a study by Madani *et al.* [43] revealed significant improvement in daily insulin dosage, HbA1c levels, and C-peptide levels.

Pluripotent Stem Cells

The discovery of pluripotent embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) has opened new avenues for β -cell replacement therapy [43,45,46,47,48]. ESCs originate from inner cell mass of the embryo blastocyst, while iPSCs are derived from reprogramming somatic cells through the ectopic expression of factors like OCT3/4, SOX2, KLF4, and c-MYC. Both ESCs and iPSCs are pluripotent, capable of differentiating into various cell types, including cardiomyocytes, neurons, and pancreatic β -cells [49].

Human ESCs was utilized to treat three adult diabetic patients in a study by Shroff [50]. They recorded improvement in blood glucose levels and reduction in secondary high blood sugar effects, such as cardiac, renal, neuropathic, and vision issues, without adverse events or teratoma formation. While ESCs-based therapies are progressing, they face significant ethical and regulatory challenges, especially in contexts where human embryo destruction is contentious [51]. In contrast, iPSCs offer an ethically viable alternative, by passing these debates [52]. Patient-specific iPSCs can be derived from an individual's cells, potentially eliminating the need for immune suppression and paving the way for personalized cell therapy [53]. iPSCs hold the promise of generating healthy tissue for transplantation, including heart cells for cardiac repair, neurons for neurodegenerative diseases, and pancreatic beta cells for diabetes treatment [54]. They uniquely allow for the generation of patient-specific, fully differentiated insulin-producing β cells, potentially providing a future strategy for restoring insulin-producing cell function, although durable clinical efficacy and safety remain unestablished [19].

Despite progress, iPSC-based therapies face challenges, such as complex differentiation protocols, tumor formation risks, and immunosuppression requirements for allogeneic iPSCs. Although autologous iPSC-derived β cells could mitigate immunosuppression needs, the process remains costly and time consuming [55]. Most iPSC trials in diabetic patients are in early stages, emphasizing the necessity for prolonged follow-ups and large-scale multicenter validation. Observed outcomes suggest temporary insulin independence rather than a definitive cure, with long-term monitoring required to confirm sustained beta-cell function and safety [56]. A recent study examined autologous iPSC-islet transplantation in patients with T1DM experiencing severe hypoglycemia episodes, showing promising metabolic outcomes and insulin independence within three months post transplantation [57].

Stem Cell Educator Therapy (SET)

Zhao *et al.* [58] developed a procedure for Stem Cell Educator therapy (SET) in which a patient's blood is circulated through a closed-loop system that separates lymphocytes from the whole blood and briefly co-cultures them with adherent CB-SCs (Cord Blood-derived

multipotent Stem Cells) before returning them to the patient's circulation. In an open label, phase1/phase 2 study, 15 patients with age started from 15 and older received one treatment with the SCE. Treatment markedly improves C-peptide levels, reduces the median glycated hemoglobin A1C (HbA1C) values, and decreases the median daily dose of insulin in patients. Successful immune modulation by CB-SCs and the resulting clinical improvement in patient status may have important implications for other autoimmune and inflammation-related diseases without the safety and ethical concerns associated with conventional stem cell-based approaches.

The methodological quality and risk of bias of the included studies were assessed using design-specific appraisal tools. Randomized trials were assessed using the Cochrane Risk of Bias 2 (RoB 2) tool, non-randomized intervention studies using ROBINS-I, and observational or case-level studies using the appropriate Joanna Briggs Institute (JBI) critical appraisal checklist.

The methodological appraisal demonstrated substantial heterogeneity in the evidence base, with randomized evidence limited to small trials and several studies being non-randomized, uncontrolled, retrospective, or case-level. These limitations, together with the small sample sizes, mixed-age populations, and limited follow-up of pediatric participants, reduce the certainty and generalizability of reported metabolic benefits (Supplementary Table S1).

Importantly, stem-cell-based interventions should be evaluated against contemporary pediatric standard care rather than against conventional insulin therapy alone. CGM, insulin pumps and automated insulin-delivery systems can substantially improve time in range and reduce hypoglycemia without exposing children to the conditioning, transplantation, tumorigenicity, or immunological risks associated with experimental cell therapies. Therefore, any future stem-cell intervention would need to demonstrate clinically meaningful additional benefit over optimized technology-supported insulin therapy while maintaining an acceptable long-term safety profile.

In general, most available clinical studies are early-phase (Phase I/II) investigations, with safety and feasibility representing major objectives and efficacy outcomes generally considered exploratory. Study populations are often small and heterogeneous, limiting statistical power and generalizability. Only a limited number of studies specifically include children, resulting in insufficient age-specific evidence regarding both efficacy and long-term safety. Among the investigated approaches, MSCs represent one of the most frequently studied cell types because of their immunomodulatory and anti-inflammatory properties [36,37,41,42]; however, substantial variation exists in cell dose, treatment frequency, timing, and route of administration [26,31,57]. Randomized controlled trials remain scarce [36,37,41,42].

Clinical evidence for HSCs-based therapy is heterogeneous. The multicenter study by D'Addio *et al.* [38]

Supplementary Table S1: Quality Appraisal and Methodological Limitations of Clinical Studies Included in the Qualitative Synthesis

Study	Study design	Appraisal tool	Key appraisal findings	Overall assessment
D'Addio <i>et al.</i> [37]	Multicenter pooled prospective clinical cohort; single intervention group	JBICohort Checklist	Multicenter recruitment, clearly defined intervention and outcomes, and 48-month follow-up are strengths. However, there was no concurrent control group, conditioning immunosuppression was used, and the cohort included adolescents and young adults, limiting pediatric-specific interpretation and causal inference.	Moderate methodological strength; important limitations due to absence of comparator and mixed-age population
Thakkar <i>et al.</i> [27]	Prospective, open-label, two-arm non-randomized clinical study	ROBINS-I	Prospective design and predefined metabolic outcomes are strengths. However, allocation was not randomized, the sample was very small (10 participants per arm), participants had long-standing T1DM, and treatment differed between autologous and allogeneic groups. The open-label design may also introduce outcome-assessment bias.	Serious risk of bias; low certainty
Gu <i>et al.</i> [39]	1:2 matched case-control study	JBICase-Control Checklist	Matching and a contemporaneous control group are strengths. However, treatment was not randomized, with potential selection and confounding bias. The treated group was small (n=14), and long-term results did not demonstrate significant advantages in HbA1c, insulin dose, or C-peptide.	Moderate-to-low methodological strength; important risk of selection and confounding bias
Yamauchi <i>et al.</i> [38]	Single case report	JBICase Report Checklist	Detailed clinical course, intervention, and post-treatment outcomes were reported. However, the evidence is based on a single adolescent with IPEX-associated T1DM and no comparator; therefore, generalizability to conventional pediatric T1DM is extremely limited.	Low level of evidence; hypothesis-generating
Izadi <i>et al.</i> [25]	Triple-blind, randomized, placebo-controlled Phase I/II trial	Cochrane RoB 2	Randomization, placebo control, and triple blinding are major strengths. However, the sample was small (n=21), follow-up was approximately one year, two participants were lost/excluded from analysis, and the trial was retrospectively registered.	Some concerns; comparatively stronger evidence among included studies
Mesples <i>et al.</i> [26]	Pediatric pilot study; six children; single intervention group	JBICase Series Checklist	A clearly defined pediatric population and clinical outcomes are strengths. However, the sample was very small (n=6), there was no control group, follow-up was limited to six months, and the design cannot establish comparative efficacy or long-term durability.	Low methodological strength; preliminary evidence
Leão <i>et al.</i> [31]	Retrospective cohort with intervention and control groups; 36-month follow-up	ROBINS-I	Long follow-up and a contemporaneous comparison group are strengths. However, retrospective selection, non-randomized treatment allocation, a small intervention group (n=7), potential selection/confounding, and the combined ASC + vitamin D intervention limit causal inference.	Serious risk of bias; low certainty
Zhao <i>et al.</i> [57]	Open-label Phase I/II Stem Cell Educator study with randomized treatment/sham allocation; very small control group	Cochrane RoB 2	Random allocation and sham control are strengths. However, the sample was small (n=15), only three participants were assigned to the control group, the study was open-label, and the population was predominantly adult (15–41 years), limiting pediatric applicability and precision of efficacy estimates.	Some concerns/high risk of bias; very low certainty for pediatric efficacy

reported substantial metabolic improvement, including insulin independence in a proportion of participants; however, the cohort included predominantly adolescents and young adults, and treatment was associated with clinically important adverse events related to conditioning and immunosuppression. In contrast, the pediatric study by Gu *et al.* [40] demonstrated only transient insulin independence in a small number of children, without sustained improvement in β -cell function during longer-term follow-up and with a high frequency of treatment-related adverse events. These findings indicate that the metabolic benefits reported with HSC transplantation should be interpreted cautiously in pediatric patients, particularly when potential efficacy is considered alongside conditioning-related toxicity [38,40].

Several clinical studies have reported short-term improvements in β -cell function, reflected by increased C-peptide levels, reduced insulin requirements, or improved glycemic control [36–38,41,42]; however, the durability of these effects remains uncertain and inconsistent. Some

autologous HSC transplantation studies have reported relatively prolonged metabolic benefits, including insulin independence extending over several years [38,39], whereas similar sustained effects have not been consistently demonstrated in pediatric populations [40]. The attenuation of therapeutic effects observed in some studies over 6–24 months may reflect several non-mutually exclusive mechanisms, including incomplete suppression of the underlying autoimmune response, failure to establish durable antigen-specific immune tolerance, limited restoration of functional β -cell mass, progressive loss of residual β -cells, and heterogeneity in cell source, dose, route of administration, timing relative to diagnosis, and concomitant immunosuppression. Therefore, early improvements in C-peptide should not be interpreted as evidence of permanent restoration of β -cell mass or durable disease remission [36,38,40].

Regarding safety, MSC-based therapies have generally demonstrated a more favorable short-term safety profile, with adverse events typically being mild or transient

[36,37,41,42]; however, their long-term safety and efficacy remain insufficiently established. In contrast, autologous HSC-based approaches may provide greater metabolic benefit in selected patients but require conditioning and, in some protocols, immunosuppression, which can result in substantial hematological, infectious, and other treatment-related complications [38, 40]. These risks are particularly important in children and raise significant ethical concerns because the long-term benefit remains uncertain while treatment-related toxicity may be immediate and potentially serious [40]. Emerging pluripotent stem cell-derived therapies offer the potential for direct β -cell replacement but remain experimental, with important unresolved concerns regarding tumorigenicity, immune rejection, graft survival, cellular differentiation, and long-term safety surveillance. Consequently, none of the currently investigated approaches has yet established a sufficiently favorable and durable risk-benefit profile to support routine clinical use in children [38–45].

The quality of the available clinical evidence remains an important limitation. Although the randomized placebo-controlled MSC trial provides comparatively stronger evidence, most other studies were non-randomized, uncontrolled, retrospective, or based on very small pediatric cohorts. The absence of randomization in several studies increases the potential for selection and confounding bias, while the small sample sizes and limited follow-up restrict the precision of efficacy and safety estimates. In addition, the inclusion of adolescents, young adults, and adults in several studies limits direct extrapolation to children. Accordingly, observed improvements in C-peptide, HbA1c, insulin requirements, or insulin independence should be interpreted as preliminary evidence rather than definitive proof of durable disease modification in pediatric T1DM.

Comparative Analysis According to Cell Type, Disease Duration, and Follow-Up

The available clinical evidence varies considerably by stem cell type, disease duration, and follow-up, limiting direct comparison between therapeutic approaches. HSC-based therapies have shown notable metabolic responses, including periods of insulin independence, particularly in recent-onset T1DM; however, these effects are inconsistent and may be associated with significant conditioning- and immunosuppression-related toxicity [38–40]. MSC-based therapies generally demonstrate better short-term tolerability, with variable improvements in C-peptide, HbA1c, and insulin requirements, but their long-term efficacy remains uncertain [26–28,32]. Pluripotent stem cell-derived therapies remain largely experimental because of concerns regarding immune rejection, graft survival, and tumorigenicity [43–45].

Disease duration and follow-up also influence treatment outcomes. Studies involving recent-onset T1DM may benefit from preservation of residual β -cell function,

whereas evidence in established disease does not demonstrate reliable restoration of β -cell mass [26,27]. Although improvements in C-peptide have been reported following several stem cell-based interventions, durable preservation of endogenous β -cell function has not yet been reliably demonstrated in pediatric populations [26–28,38–40]. Transient improvement in C-peptide should therefore be distinguished from durable β -cell restoration or disease remission. Moreover, initial improvements in C-peptide, insulin requirements, or glycemic control may diminish during longer follow-up, with sustained benefits beyond 24 months remaining particularly limited in children [38–40]. Overall, current evidence is insufficient to establish a superior stem cell type or optimal treatment window for pediatric T1DM, and reported short-term metabolic improvements should not be interpreted as durable disease remission.

Safety, Ethical, and Regulatory Considerations in Children

The potential to modify disease progression using regenerative medicine, especially through stem cell therapies, presents a range of ethical and regulatory dilemmas. The principal safety, pediatric evidence, and translational considerations of the stem cell-based approaches reviewed are summarized in Table 2.

Stem-cell tourism is an additional concern, as families may be vulnerable to unproven commercial claims of cure. Such interventions may expose children to avoidable risks and financial burdens, emphasizing the need for treatment within regulated clinical trials and clear communication regarding evidence and safety. The ethical threshold for exposing children to experimental cell-based therapies should be particularly stringent because pediatric patients have long expected lifespans during which delayed adverse effects may become clinically relevant. Ethical concerns include informed consent, therapeutic misconceptions, and ensuring equitable access, highlighting the obligations of providers who offer experimental treatments. Special care is required when obtaining consent from vulnerable groups, such as children [59, 60].

Safety considerations for using stem cells in children with diabetes include the risk of tumorigenicity and immunological reactions. Other concerns are infections due to a weakened immune system, potential teratogenic effects from pluripotent cells, and unforeseen side effects from the cell products themselves [60,61]. Although stem cell therapy has the potential to reduce or eliminate insulin dependency, repeat dosing may be necessary, and results can vary based on patient-specific factors [62]. Risks of genetic instability or incomplete differentiation and cost effectiveness are greatly associated with iPSCs which need further study to make them widely available to patients [63,64].

Table 2: Comparative Safety and Translational Considerations of Stem Cell-Based Approaches for Pediatric T1DM

Stem cell approach	Main safety concerns	Pediatric evidence	Overall status
MSCs	Generally favorable short-term tolerability; mild injection-site reactions and urticaria reported. Long-term safety remains uncertain [23,27,31].	Limited pediatric studies; small sample sizes and short follow-up.	Promising, but experimental
HSCs	Conditioning-related toxicity, including leukopenia, neutropenia, gastrointestinal symptoms, and infections. Serious adverse events reported in pediatric patients [37,39].	Limited pediatric evidence; transient benefits reported.	Higher safety risk; experimental
iPSCs	Potential tumorigenicity, genetic instability, incomplete differentiation, and immune-related complications [54,53,62,63].	Very limited pediatric evidence; mainly early clinical/adult studies.	Experimental
ESCs	Potential teratoma/tumor formation, immune rejection, and long-term graft-related risks; ethical concerns [43–50].	No established pediatric clinical evidence in the reviewed studies.	Experimental
Stem Cell Educator (SET)	Reported as well tolerated in a small study; long-term and rare adverse events remain uncertain [57].	Limited adolescent/mixed-age evidence.	Experimental

CONCLUSION AND FUTURE RESEARCH DIRECTIONS

Stem cell therapy represents a potential therapeutic strategy for type 1 diabetes mellitus (T1DM) in children. Early clinical studies suggest that selected stem cell-based interventions may preserve residual β -cell function, modulate autoimmune responses, reduce insulin requirements, and, in some patients receiving intensive HSCs based interventions, achieve temporary periods of insulin independence. Importantly, future stem-cell therapies should demonstrate clinically meaningful benefits beyond those achievable with contemporary CGM, insulin pumps, and automated insulin-delivery systems, while maintaining an acceptable long-term safety profile. However, these benefits have not been consistently demonstrated in pediatric populations, and insulin independence should not, in isolation, be interpreted as evidence of restored endogenous insulin secretion.

Determining the most appropriate cell source and therapeutic approach remains a major research priority. Pediatric evidence remains limited, and children may exhibit a more aggressive autoimmune disease course that could influence treatment response. The few pediatric-focused studies, predominantly involving MSCs, have generally reported acceptable short-term tolerability but limited or inconsistent evidence of efficacy and no reliable evidence of sustained C-peptide preservation. Although autologous stem cell approaches, including autologous HSCs, may reduce the risk of alloimmune rejection, they remain associated with treatment-related risks and adverse effects. The recent generation of islet-like cells from autologous induced pluripotent stem cells (iPSCs) represents an important milestone, although the clinical efficacy, durability, and long-term safety of this approach remain to be established. Accordingly, the conclusions of this narrative review are intended to identify patterns in reported clinical outcomes, highlight uncertainties regarding efficacy and safety, and define priorities for future research rather than establish comparative treatment efficacy among different stem cell-based approaches.

Ongoing research is evaluating increasingly advanced cell-based approaches for diabetes in children and may inform the potential future integration of stem cell-based therapies into pediatric clinical practice. Nevertheless,

several challenges must be addressed before these therapies can be considered for broader clinical application. These include establishing the long-term safety, viability, and functional stability of transplanted cells; minimizing or eliminating the need for chronic systemic immunosuppression; and ensuring appropriate ethical and regulatory oversight. Additional concerns include genetic and epigenetic abnormalities acquired during cellular reprogramming or prolonged culture, incomplete or inappropriate differentiation, and the potential formation of abnormal cell populations, including teratomas in pluripotent stem cell-derived therapies.

Equitable and affordable access represents an additional ethical challenge. If effective cell-based therapies become clinically available, their complex manufacturing requirements and specialized delivery systems may initially limit access to patients treated at highly specialized centers. This may create disparities related to affordability, reimbursement, geographic access, and the distribution of specialized therapeutic resources. Future development should therefore incorporate health-economic evaluation and strategies for equitable implementation alongside assessments of efficacy and safety. In parallel, β -cell replacement strategies should prioritize immune-protective approaches, including encapsulation and other immunoisolation technologies, with the aim of reducing or avoiding systemic immunosuppression while maintaining graft survival and function.

Collectively, the available evidence indicates that stem cell-based therapy is a promising but still investigational approach for T1DM in children. Although some approaches, particularly MSC-based therapies, have demonstrated favorable short-term tolerability, the long-term efficacy, durability, and safety of these interventions remain insufficiently established. Progress toward pediatric clinical application will require larger, well-designed, adequately controlled, and pediatric-specific studies capable of determining which cell sources and therapeutic strategies provide clinically meaningful benefits. A clinically acceptable pathway toward pediatric application should proceed through five sequential requirements: (1) reproducible preclinical evidence demonstrating efficacy and safety; (2) standardized, GMP-compatible manufacturing with rigorous characterization of cell identity,

purity, potency, and genomic stability; (3) carefully designed and monitored pediatric clinical trials using clinically meaningful efficacy and safety endpoints; (4) independent regulatory and ethical oversight with transparent reporting of adverse events; and (5) long-term follow-up and registry-based surveillance to evaluate treatment durability and detect delayed or rare adverse outcomes.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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