



Review Article

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Autologous Versus Allogeneic Induced Pluripotent Stem Cell Therapies: Immunologic, Manufacturing, and Translational Trade-Offs

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Abstract

Induced Pluripotent Stem Cell (iPSC)-derived therapies are entering clinical evaluation across endocrine, neurologic, ophthalmologic, and other regenerative indications, renewing debate over whether patient-specific autologous products or banked allogeneic products provide the more viable translational model. The distinction is not simply one of manufacturing scale. Autologous products can reduce classical alloimmune rejection because the donor and recipient are the same individual, but they retain important risks related to disease-specific autoimmunity, acquired genomic variation, differentiation heterogeneity, product-release testing, and individualized manufacturing. Allogeneic products offer batch standardization and inventory-based deployment yet may require immunosuppression or immune-evasive engineering to achieve durable engraftment in immunocompetent recipients. Recent human studies sharpen this comparison. Autologous stem-cell-derived islet products have produced prolonged insulin independence in individual patients with type 1 and type 2 diabetes, although interpretation is constrained because the reported recipients were already receiving immunosuppression for prior organ transplantation. In parallel, allogeneic stem-cell-derived islets have restored endogenous insulin secretion and insulin independence in most evaluable participants in a phase 1–2 study under systemic immunosuppression, while early gene-edited hypoimmune islet data suggest that immune-evasion strategies may eventually reduce this requirement. In Parkinson disease, both autologous iPSC-derived and allogeneic pluripotent-stem-cell-derived dopaminergic progenitors have shown clinical feasibility. Manufacturing advances in closed processing, automation, quality-by-design, and Good Manufacturing Practices (GMP)-compliant iPSC banking are also narrowing historical barriers to individualized production. Collectively, current evidence does not support a universal autologous or allogeneic winner. Platform choice should instead be indication-specific and should integrate immune biology, manufacturing reproducibility, time-to-treatment, safety testing, durability, and lifetime treatment burden.

Keywords: Induced pluripotent stem cells, Autologous cell therapy, Allogeneic cell therapy, Regenerative Medicine, Immune Rejection, Manufacturing, Pancreatic islets, Parkinson disease

Introduction

Loss, dysfunction, or irreversible depletion of specialized cell populations is central to the pathophysiology of numerous chronic and degenerative diseases, including diabetes mellitus, neurodegenerative disorders, retinal degeneration, cardiac injury, and some hematologic and immune conditions [1,2]. Conventional pharmacologic therapies can modify disease pathways or compensate for impaired function, but they generally do not restore the differentiated cell population responsible for normal tissue physiology. Cell-replacement strategies therefore offer a fundamentally different therapeutic paradigm. Rather than chronically modulating downstream consequences of disease, the strategy seeks to reconstitute missing or dysfunctional cellular function through transplantation of viable, lineage-appropriate cells [3]. Human pluripotent stem cells represent a particularly important platform for this approach because they combine extensive proliferative capacity with the ability to generate differentiated derivatives representing all three embryonic germ layers [4]. Induced Pluripotent Stem Cells (iPSCs) extend this concept by permitting somatic cells to be reprogrammed to pluripotency without requiring an embryonic source and by providing a renewable substrate that can be clonally expanded, genetically characterized, engineered when necessary, and differentiated into therapeutically relevant cell populations [5]. These properties have enabled development of iPSC-derived dopaminergic progenitors, pancreatic islet cells, retinal cells, cardiomyocytes, and hematopoietic or immune-cell products, among others. iPSC technology is no longer confined to disease modeling or preclinical experimentation, and early clinical studies have now provided evidence that pluripotent-stem-cell-derived products can survive transplantation, engraft, and produce measurable physiological effects in humans [6]. Clinical translation, however, converts the biological versatility of iPSCs into a complex product-development problem. Therapeutic iPSC platforms must preserve genomic and epigenomic integrity during reprogramming, clonal expansion, banking, and differentiation; reproducibly generate the intended lineage; minimize residual undifferentiated or off-target cell populations; and satisfy predefined criteria for identity, purity, potency, sterility, stability, and long-term safety [4,7-9]. Acquired genomic abnormalities, differentiation heterogeneity, incomplete maturation, and tumorigenic potential remain particularly important because prolonged self-renewal and developmental plasticity also create safety liabilities if inadequately controlled [4,7-9]. Autologous derivation and immunologic invisibility are not synonymous. The culture-associated changes, reprogramming-associated alterations, somatic mutations, aberrant antigen expression, or disease-associated genetic variants may modify the immunologic or functional properties of an ostensibly self-derived product [10].

One of the most consequential design decisions is whether the therapeutic product is generated as an autologous, patient-

specific product or as an allogeneic product manufactured from a selected donor or master iPSC line. Autologous development preserves histocompatibility between the donor and recipient and therefore has the potential to substantially reduce classical alloimmune rejection [11]. In contrast, allogeneic development permits extensive characterization of a common starting line, larger manufacturing campaigns, standardized inventories, and potentially more rapid treatment [12]. These advantages are counterbalanced by biologically distinct liabilities. Autologous products require patient-specific reprogramming, differentiation, quality assessment, and release, creating challenges in turnaround time, manufacturing consistency, and comparability across individual products. Conventional allogeneic products introduce recipient recognition of non-self Human Leukocyte Antigens (HLA) and other alloantigens, potentially compromising persistence or requiring systemic immunosuppression [13]. HLA matching, physical immune isolation, local immunomodulation, and genome engineering to generate hypoimmunogenic or immune-evasive cell lines are increasingly being investigated as strategies to alter this balance [14]. The choice between autologous and allogeneic development therefore cannot be treated solely as a manufacturing question or reduced to the conventional distinction between "one batch per patient" and "one batch for many patients." The optimal architecture depends on the interaction among disease biology, transplantation site, expected graft longevity, consequences of immune rejection, susceptibility to recurrent autoimmunity, urgency of treatment, required cell dose, feasibility of repeat dosing, genomic-engineering burden, manufacturing reproducibility, and the clinical consequences of immunosuppression. A strategy that is appropriate for transplantation into the Central Nervous System (CNS) may not be appropriate for pancreatic islet replacement, just as the requirements of a durable cell-replacement product differ from those of a transient or readily redosable cellular therapy. Moreover, advances in closed-system manufacturing, automation, process analytical technologies, quality-by-design approaches, and immune engineering are progressively changing the practical boundaries of both development models [6]. These issues have become increasingly tractable because clinical experience is beginning to provide direct evidence rather than theoretical comparisons. Recent studies of stem-cell-derived pancreatic islets and dopaminergic-cell transplantation have demonstrated biologic activity and engraftment while simultaneously highlighting the importance of immune compatibility, immunosuppressive exposure, transplantation site, manufacturing strategy, and long-term product surveillance. Together with rapidly evolving hypo immune engineering and Good Manufacturing Practices (GMP)-manufacturing technologies, these studies provide an opportunity to reconsider how autologous and allogeneic iPSC therapies should be evaluated as alternative, rather than intrinsically competing, development architectures. In this review, we examine the biological, immunologic, manufacturing, and clinical factors that determine the relative suitability of autologous and allogeneic iPSC-derived therapies. Rather than asking which platform is universally

superior, we consider the conditions under which each architecture may provide the more favorable benefit–risk profile. We integrate evidence from recent stem-cell-derived pancreatic islet and dopaminergic-cell clinical programs with contemporary literature on immune engineering, genomic safety, manufacturing control, and scalability, and propose an indication-dependent framework for selecting among patient-specific, conventional allogeneic, and immune-engineered allogeneic strategies.

Immunologic Architecture of Autologous and Allogeneic iPSC-Derived Products

The principal immunologic rationale for autologous iPSC-derived therapy is minimization of classical donor–recipient alloimmune incompatibility. Because the starting cells and recipient are genetically matched at the major histocompatibility loci, autologous products avoid the broad HLA disparity that drives direct and indirect allorecognition after conventional transplantation. This may be particularly important for long-lived, nonhematopoietic grafts in which durable therapeutic benefit depends on sustained cell survival. However, autologous derivation does not guarantee complete immune tolerance. Reprogramming, prolonged culture, clonal selection, genomic or epigenomic alteration, lineage differentiation, and aberrant antigen expression can theoretically create neoantigens or alter immune recognition, and experimental evidence indicates that immunogenicity can vary among iPSC lines and differentiated derivatives [15,16]. Disease-specific immunity is an additional and biologically distinct problem. In type 1 diabetes, beta-cell replacement does not eliminate the autoreactive immune repertoire that contributed to destruction of endogenous beta cells. Autologous derivation can therefore address all immunity without necessarily addressing recurrent beta-cell-directed autoimmunity. The therapeutic problem is not simply whether immunosuppression can be avoided, but whether broad anti-rejection therapy can be replaced by more selective immune modulation that preserves graft function while limiting systemic immune toxicity. Future trials should therefore distinguish alloimmune, autoimmune, and innate inflammatory responses rather than combining them under a single “rejection” endpoint. Allogeneic cell replacement has the opposite trade-off. A banked, standardized product can be manufactured from a well-characterized source and used across many recipients, but immune rejection remains a core obstacle in immunocompetent hosts. Contemporary approaches include pharmacologic immunosuppression, encapsulation or local immune isolation, HLA matching, and genetic engineering to create hypoimmune cells. Reviews published in 2024–2025 describe rapid progress in immune-evasive engineering but also emphasize that safety, durability, and escape from both adaptive and innate immune surveillance must be demonstrated clinically rather than assumed from preclinical models [17,18]. Moreover, eliminating or reducing HLA expression may attenuate T-cell recognition while increasing susceptibility to natural-killer-cell-mediated clearance, requiring coordinated engineering of both adaptive and innate

immune pathways [17,18]. The translational objective is therefore not complete immunologic invisibility per se, but sufficient immune compatibility to support durable function without creating unacceptable risks of immune escape, malignant transformation, or impaired host surveillance [17,18].

Human Proof-of-Concept in Pancreatic Islet Replacement

Autologous Stem-Cell-Derived Islets: Two recent reports provide complementary human proof-of-concept for personalized stem-cell-derived islet replacement, although the cellular platforms were not identical. Wang et al. reported transplantation of autologous chemically induced pluripotent stem-cell-derived islets in a patient with type 1 diabetes and transplanted beneath the abdominal anterior rectus sheath. The recipient achieved sustained insulin independence, beginning 75 days after transplantation and maintained near-normal glycemic measures through one year [19]. In a separate study, Wu et al. generated personalized islet tissue from expandable autologous endoderm stem cells rather than a conventional iPSC intermediate and demonstrated insulin independence in a patient with long-standing type 2 diabetes [20]. These findings establish feasibility and clinically meaningful beta-cell function, but they do not yet prove that autologous stem-cell-derived islets can routinely achieve durable insulin independence without immunosuppression. Both reported recipients had prior solid-organ transplants and were receiving immunosuppressive therapy. Accordingly, these studies establish personalized manufacturing feasibility, graft survival, and endocrine function, but they do not yet establish that autologous stem-cell-derived beta-cell replacement can avoid systemic immune therapy in immunocompetent patients. Trials in non-transplant recipients will need prospective assessment of recurrent beta-cell autoimmunity, graft-specific cellular and humoral immunity, C-peptide durability, metabolic function, and long-term graft surveillance.

Allogeneic Stem-Cell-Derived Islets and Immune-Evasive Strategies: Allogeneic stem-cell-derived islets have advanced further in formal multicenter clinical testing. In the phase 1–2 FORWARD study, zimislecel, an allogeneic stem-cell-derived islet product, produced detectable C-peptide in all 14 participants with at least 12 months of follow-up. Among 12 participants who received the full dose, all were free of severe hypoglycemic events with glycated hemoglobin below 7%, and 10 of 12 were insulin-independent at day 365. The study therefore establishes that pluripotent-stem-cell-derived allogeneic islets can provide clinically meaningful beta-cell replacement, while simultaneously demonstrating that, in its current form, efficacy is coupled to systemic immune suppression [21]. These results demonstrate strong biological activity but also illustrate the current immune-management burden of conventional allogeneic replacement. A 2025 first-in-human report provided an important proof-of-concept for immune-engineered allogeneic cell replacement. Carlsson et al. transplanted CRISPR/Cas12b- and lentiviral-engineered allogeneic donor islet cells into a patient with

type 1 diabetes without systemic immunosuppression. At 12 weeks, the cells remained detectable, showed glucose-responsive insulin secretion, and elicited no measurable immune response against the edited graft [22]. These data are preliminary, derive from a single recipient, and do not establish long-term metabolic efficacy or safety, but they demonstrate that engineered immune evasion can alter the fundamental immunologic assumptions underlying allogeneic transplantation. Longer follow-up will be required to determine whether immune evasion remains stable, whether graft function is durable, and whether reduced immune surveillance introduces new safety concerns, particularly if similar engineering is applied to proliferative pluripotent-cell-derived products [6,22].

Neurologic Cell Replacement Shows That Tissue Context Matters

Parkinson's disease provides a complementary example because the central nervous system differs immunologically and clinically from the portal or systemic environments relevant to islet replacement. In a 2020 report, personalized iPSC-derived dopaminergic progenitor cells were implanted in a patient with Parkinson's disease without immunosuppression. PET imaging demonstrated increased dopaminergic signal consistent with graft survival and function were stable or improved over 18–24 months [23]. This single-patient experience showed that a GMP-compatible autologous iPSC workflow could be executed for a complex neural product. More recent trials have demonstrated that allogeneic approaches can also be feasible in the brain. Sawamoto and colleagues reported a phase I/II study of allogeneic iPSC-derived dopaminergic progenitors in seven patients, with no serious adverse events, no tumor formation on imaging, increased fluorodopa uptake, and motor improvement in several participants over 24 months [24]. Tabar and colleagues similarly reported a phase I study of an off-the-shelf human embryonic stem-cell-derived dopaminergic progenitor product in 12 patients; participants received one year of immunosuppression, graft survival was supported by imaging, and no product-related serious adverse events were observed [25]. The neurologic experience is particularly informative because it illustrates that immune-management burden depends not only on donor–recipient compatibility but also on anatomical site, blood–brain barrier biology, local immune surveillance, graft size, and the consequences of partial graft loss. The ability to use limited-duration immunosuppression in some CNS transplantation protocols should therefore not be generalized to endocrine, cardiac, hepatic, or other systemic replacement strategies. Conversely, the absence of immunosuppression in a single autologous Parkinson disease case should not be interpreted as proof that all autologous iPSC-derived neural products will be non-immunogenic.

Manufacturing: Scale-Out and Scale-Up are Different Engineering Problems

The manufacturing argument against autologous iPSC therapy is substantial but should be stated precisely. Patient-specific

production requires repeated starting-material acquisition, reprogramming or retrieval from a personalized bank, clone or bank qualification, lineage differentiation, product testing, release, scheduling, and chain-of-identity control. Inter-individual differences in cell growth and differentiation propensity can create process variability. Recent GMP-focused reviews identify sterility, identity, genomic and epigenomic integrity, pluripotency, differentiation competence, potency, residual undifferentiated cells, and tumorigenicity as critical control domains [26,27]. These requirements are not removed by automation. The manufacturing landscape is changing. GMP-compliant platforms have now been described for generating and banking iPSC lines suitable for both autologous and allogeneic derivatives, including validated donor screening, reprogramming, in-process controls, release assays, stability testing, and multilineage differentiation [28]. The field is also moving toward closed systems, automated handling, suspension culture, bioreactors, digital process monitoring, and quality-by-design. A 2021 review specifically identifies advanced automation and cost-of-goods analysis as central to market readiness [7], while a 2026 manufacturing review highlights closed and automated systems as an important route to improving reproducibility for autologous products [29]. A critical regulatory distinction is that characterization occurs at multiple levels. The parental somatic-cell source, reprogrammed iPSC clone, master or working cell bank, differentiated intermediate, and final therapeutic product each present distinct critical quality attributes. Genomic stability and pluripotency may be central release or characterization attributes for the iPSC intermediate, whereas lineage identity, purity, functional potency, residual undifferentiated cells, sterility, viability, and dose consistency become increasingly important at the differentiated-product stage [7,9,10,30]. The appropriate testing strategy must therefore be linked to process stage and intended mechanism of action rather than applying an undifferentiated checklist to every manufacturing intermediate. Genomic surveillance deserves particular emphasis because reprogramming, clonal selection, prolonged expansion, and genome engineering can each select or introduce variants with potential consequences for growth, differentiation, or tumorigenicity. Conventional karyotyping alone may be insufficient to detect sub chromosomal copy-number changes or potentially consequential sequence-level variants. Contemporary development programs increasingly incorporate complementary genomic essays and predefined procedures for evaluating variants of concern, although consensus thresholds for clinical relevance remain incomplete [7,9,10,30]. Potency remains another major translational challenge with assays necessitating linking potency to a biological function causally related to the intended clinical effect. For example, glucose-responsive insulin secretion for beta-cell products or lineage-appropriate dopaminergic function for neural products are critical, rather than relying exclusively on phenotypic markers. Because complex cellular products often require orthogonal assays, potency strategies may combine functional, molecular, and

phenotypic measures across development [7,9,10,30]. Autologous CAR T-cell therapy provides a useful operational precedent showing that individualized cellular products can be manufactured, released, distributed, and administered at commercial scale [31]. However, CAR T-cell therapy is not an economic surrogate for iPSC-derived replacement products, which may require clonal banking, substantially longer culture and differentiation, additional genomic surveillance, and distinct tumorigenicity and potency assessments. The relevant lesson is therefore that patient-specific manufacturing

is operationally feasible, not that its cost structure or manufacturing-risk profile is equivalent across cellular modalities.

A Comparative Framework for Platform Selection

The appropriate platform should be selected at the level of the indication and product, rather than from a universal presumption that either autologous or allogeneic manufacturing is intrinsically superior. (Table 1) summarizes the principal dimensions that should be considered.

Table 1: Indication-dependent comparison of autologous and allogeneic pluripotent-stem-cell-derived therapeutic architectures.

Dimension	Autologous Ipsc-Derived Product	Allogeneic Ipsc/PSC-Derived Product
Cell source and product architecture	Patient-specific somatic cells are reprogrammed and differentiated for return to the same individual; alternatively, a previously established patient-specific iPSC bank may serve as the starting material.	A selected donor-derived or established master pluripotent stem-cell bank provides starting material for products intended for multiple recipients.
Immune compatibility	Minimizes classical donor-recipient HLA mismatch and the associated alloimmune response. Autologous origin does not guarantee complete absence of product-specific immunogenicity.	HLA and minor-histocompatibility mismatch may activate adaptive and innate immune responses unless controlled by matching, pharmacologic immunosuppression, physical immune isolation, or immune engineering.
Disease-specific autoimmunity	Does not eliminate an underlying autoimmune process. In type 1 diabetes, for example, autologous beta-cell replacement may remain susceptible to recurrent beta-cell-directed autoimmunity.	May face both alloimmunity and recurrence of disease-specific autoimmunity, depending on the indication and cellular target.
Immune-management strategy	May reduce or eliminate the need for anti-rejection immunosuppression, although disease-specific immunomodulation may still be required.	Conventional products may require systemic or local immunosuppression. Alternative approaches include HLA matching, encapsulation, immune isolation, or immune-evasive engineering.
Immune engineering	Generally unnecessary solely to overcome donor-recipient HLA mismatch; however, genetic correction or disease-specific engineering may be required in selected indications.	May incorporate HLA modification, modulation of immune checkpoints, or strategies addressing T-cell and NK-cell recognition. Such modifications add safety, genomic, CMC, and surveillance requirements.
Genetic-disease liability	Patient-derived cells retain the patient's germline genotype. This can be advantageous for histocompatibility but problematic when the pathogenic variant affects the intended therapeutic lineage. Gene correction may therefore be required for inherited disorders.	A selected donor/master line can be chosen to exclude disease-causing variants and other predefined liabilities, although donor-specific genomic abnormalities and variants arising during culture remain relevant.
Genome-editing burden	No editing is intrinsically required for histocompatibility. Editing may nevertheless be necessary to correct pathogenic variants or introduce therapeutic properties.	Immune-evasive architectures may require one or multiple genomic modifications, increasing the burden of off-target assessment, clonal characterization, genomic stability testing, and comparability.
Starting-material variability	Patient age, genotype, disease state, prior treatment, somatic-cell source, and acquired cellular abnormalities may influence reprogramming, proliferation, and differentiation performance.	Selection of a highly characterized source line can substantially reduce donor-to-donor variability before large-scale manufacturing.
Manufacturing paradigm	Predominantly scale-out: repeated patient-specific manufacturing or differentiation from individualized banks.	Predominantly scale-up: larger standardized manufacturing campaigns derived from common master and working cell banks.
Manufacturing reproducibility	Inter-individual variation can affect reprogramming efficiency, proliferation kinetics, differentiation propensity, yield, and potentially final-product attributes.	A common starting bank improves standardization, but batch-to-batch variability, process drift, scale-dependent effects, and comparability after manufacturing changes still require control.
Time to treatment	Potentially prolonged when somatic-cell collection, reprogramming, clone selection, banking, differentiation, testing, and release occur after treatment eligibility is established. Time can be reduced if a qualified patient-specific bank already exists.	Potentially rapid when qualified intermediate or final product is manufactured in advance, cryopreserved, and available from inventory.
Chain of identity/custody	Critical throughout collection, reprogramming, banking, differentiation, release, and administration because each product is assigned to a specific recipient.	Conventional chain-of-custody controls remain essential, but individual patient identity is generally not linked to the starting cell line in the same manner as an autologous product.

iPSC intermediate characterization	Each patient-specific line may require defined qualification for identity, pluripotency, genomic/epigenomic integrity, sterility, differentiation competence, and other critical attributes.	Extensive characterization can be concentrated at master- and working-cell-bank levels and leveraged across multiple manufacturing campaigns, subject to appropriate comparability controls.
Final-product quality control	Each patient-specific lot requires predefined release testing appropriate to the differentiated product, including identity, purity, viability, potency, sterility, residual undifferentiated cells, and other product-specific attributes.	The same fundamental final-product controls apply, but standardized manufacturing may permit greater accumulation of process-performance and lot-to-lot comparability data.
Genomic stability and tumorigenic risk	Reprogramming, clonal selection, prolonged expansion, differentiation, and any gene correction can introduce or select genomic abnormalities. Risk must be assessed for each manufacturing architecture and therapeutic lineage.	The same intrinsic PSC-related risks apply. Extensive characterization of a common bank is advantageous, but abnormalities arising in a master clone or during large-scale expansion could affect many doses. Additional editing may introduce further genomic risks.
Residual pluripotent cells/ectopic tissue risk	Requires sensitive control of residual undifferentiated cells and off-target differentiated populations in every patient-specific product.	Equivalent biological requirement; standardized processes may facilitate assay validation and accumulation of process knowledge across lots.
Potency assessment	Potency must be demonstrated for each individualized final product using assays linked to the intended mechanism of action; lot size may constrain destructive testing strategies.	Common manufacturing may facilitate standardized potency testing and establishment of broader product-performance datasets, although potency remains lineage- and indication-specific.
Dose consistency	Patient-specific manufacturing may introduce greater inter-lot variability in cell yield and functional attributes and therefore requires robust acceptance criteria.	Common source material and standardized production may improve dose consistency, although scale-up can itself alter cell phenotype or function and must be validated.
Manufacturing failure consequence	Failure generally affects an individual patient's product but may result in clinically important treatment delay, repeat collection, or loss of treatment opportunity.	Failure involving a master/working bank or systemic manufacturing process can affect multiple lots or patients, creating a potentially larger batch- or platform-level consequence.
Inventory and distribution	Usually limited finished-product inventory; individualized banking can create intermediate inventory but requires patient-specific storage and retrieval.	Amenable to inventory-based distribution of standardized intermediates or finished products and potentially broader geographic deployment.
Transplantation-site dependence	Particularly attractive when durable engraftment is required and avoidance of long-term anti-rejection immunosuppression is clinically important. The advantage depends on local tissue immunobiology.	Clinical feasibility depends strongly on transplantation site and immune environment. Time-limited immune management may be feasible in some relatively immune-protected sites, whereas systemic grafts may pose greater immune-management challenges.
Durability considerations	Histocompatibility may favor long-term persistence when alloimmune rejection would otherwise limit graft survival, but durability still depends on disease biology, graft quality, local inflammation, and recurrent autoimmunity.	Durable function requires sustained immune compatibility. Persistence may depend on immunosuppression, immune isolation, HLA matching, or durable performance of immune-evasive modifications.
Repeat dosing/replacement	Repeat manufacture may be possible from an established patient-specific bank, but repeated production remains individualized and resource intensive.	Inventory-based manufacturing may facilitate repeat dosing where biologically and clinically appropriate, although repeated exposure can alter alloimmune responses.
Long-term surveillance	Should address graft persistence and function, tumorigenicity, ectopic tissue formation, genomic abnormalities, disease recurrence, and late immune effects.	Requires the same surveillance plus assessment of alloimmune responses and, for immune-engineered products, persistence and consequences of immune-evasion phenotypes.
Scalability constraint	Primarily constrained by parallel manufacturing capacity, individualized QC/release, scheduling, labor, facility utilization, and process failure rates. Automation and closed systems may mitigate—but do not eliminate—these constraints.	Primarily constrained by scale-up, bioreactor/process performance, bank capacity, cryopreservation, distribution, and maintenance of product comparability during manufacturing expansion.
Economic determinants	Economics depend on manufacturing success rate, individualized testing, labor, facility utilization, time to release, logistics, storage, and whether avoidance of chronic immune management offsets production costs.	Manufacturing costs can be distributed across many doses, but total treatment cost may include immune-management drugs, monitoring, complications, engineering complexity, and long-term surveillance.
Principal development advantage	Patient-product histocompatibility with potential reduction of classical alloimmune rejection and associated treatment burden.	Standardized source material, extensive bank characterization, inventory-based availability, manufacturing scale-up, and potential distribution to large patient populations.

Principal development liability	Individualized manufacturing, patient-to-patient biological variability, repeated lot qualification/release, treatment lead time, and retention of patient-specific disease variants where relevant.	Donor–recipient immune incompatibility and the potential need for immunosuppression or additional immune engineering, with associated biological and regulatory complexity.
Most plausible indication fit	Particularly compelling when long-term graft persistence is essential, chronic systemic immunosuppression carries substantial lifetime burden, treatment can accommodate individualized manufacturing, and patient-specific genetic defects do not compromise the therapeutic lineage or can be corrected safely.	Particularly compelling when rapid availability, large patient numbers, standardized dosing, manufacturing scale, or repeatable distribution dominate and immune incompatibility can be controlled with an acceptable benefit–risk profile.

Note*: Neither architecture has an intrinsic platform-level advantage across all applications. Selection depends on the interaction among disease mechanism, cellular lineage, transplantation site, anticipated graft longevity, immune biology, genetic background, manufacturing strategy, time-to-treatment requirements, product quality attributes, and acceptable lifetime treatment burden. Autologous derivation minimizes classical donor–recipient HLA mismatch but does not eliminate recurrent autoimmunity, product-specific immunogenicity, genomic risk, or manufacturing variability. Allogeneic development enables common-bank characterization and scalable inventory-based manufacturing but introduces alloimmune risk that may require pharmacologic, physical, matching, or genetic mitigation. Immune-engineered allogeneic products should therefore be considered a distinct and evolving development strategy rather than assumed to have the same benefit–risk profile as conventional allogeneic products.

Key Unresolved Questions for Clinical Translation

As autologous, conventional allogeneic, and immune-engineered allogeneic pluripotent stem-cell therapies advance clinically, comparison among these architectures will require prospective evaluation across several domains. Current studies establish feasibility and early biological activity but remain insufficient to determine which platform provides the most favorable long-term benefit–risk profile for a given indication. Five domains are particularly important for generating evidence that can support product development and platform selection.

Immune Compatibility and Longitudinal Immune Surveillance: Immune outcomes should be characterized according to mechanism rather than treated generically as “rejection.” For autologous products, the central questions are whether reprogramming, expansion, differentiation, or genetic manipulation creates clinically meaningful immunogenicity and whether disease-specific autoimmunity can recur against the transplanted lineage. For conventional allogeneic products, studies should distinguish cellular and humoral alloimmune responses and characterize their relationships to graft persistence and function. Immune-engineered allogeneic products introduce an additional challenge: modifications intended to reduce T-cell recognition may alter natural killer cell surveillance or other innate immune interactions, while broader immune-evasive phenotypes could theoretically impair recognition of abnormal or transformed graft cells [16]. Clinical protocols should therefore incorporate longitudinal assessment of graft-directed cellular and humoral immunity, disease-specific autoimmunity where relevant, innate immune activation, inflammatory responses associated with implantation, and the intensity and duration of any pharmacologic immune management. The clinically meaningful endpoint is not simply whether immunosuppression is used, but whether durable graft function can be achieved with an acceptable cumulative

immune-management burden.

Genomic Integrity, Tumorigenicity, and Consequences of Genetic Engineering: Genomic risk should be evaluated across the complete manufacturing history rather than solely in the final differentiated product. Reprogramming, clonal selection, prolonged expansion, cryopreservation, differentiation, and genome editing can introduce or select genetic abnormalities, some of which may confer proliferative or survival advantages [7,9,10,30]. This issue becomes particularly important when gene correction is incorporated into an autologous product or multiple modifications are introduced to create an immune-evasive allogeneic line. Development programs should define the complementary genomic methods used to characterize source cells, iPSC banks, relevant manufacturing intermediates, and final products, together with prespecified procedures for interpreting variants of potential concern. Long-term surveillance should extend beyond overt tumor formation to include abnormal graft expansion, ectopic tissue formation, altered differentiation, and other evidence of clonal behavior. For immune-engineered products, tumorigenic risk and immune surveillance are mechanistically linked: engineering that improves graft persistence should not inadvertently permit abnormal cells to evade host immune control [7,9,10,30].

Potency, Product Identity, and Prediction of Durable Clinical Function: A central challenge for iPSC-derived products is determining which pre-release measurements meaningfully predict therapeutic performance after transplantation. Phenotypic lineage markers establish identity but may not adequately demonstrate functional competence. Potency assays should therefore measure biological activities mechanistically linked to the intended therapeutic effect and should be sufficiently robust to detect clinically meaningful manufacturing variability [7,9,10,30]. Orthogonal combinations of functional, molecular, and phenotypic assays may be necessary for complex cellular products.

A particularly important unresolved question for autologous manufacturing is whether the same potency specification can reliably accommodate biologic variation among patient-specific lines. For allogeneic products, the corresponding challenge is demonstrating that potency remains stable across manufacturing scale-up, process changes, cryopreservation, and successive production campaigns. Establishing relationships among critical quality attributes, potency measures, engraftment, and longitudinal clinical function will be essential for both regulatory development and meaningful comparison of manufacturing architectures.

Graft Durability and Long-Term Clinical Benefit-Risk:

Early evidence of engraftment or physiological activity should not be equated with durable therapeutic benefit. Cell-replacement products are generally intended to function for years and potentially decades, making longitudinal assessment central to their value proposition. Follow-up should evaluate persistence of the transplanted cells, stability of the intended phenotype, durability of physiological function, progressive or late graft loss, recurrent disease-related injury, ectopic tissue formation, graft overgrowth, delayed immune responses, and complications attributable to the transplantation procedure or immune-management regimen [19–25]. The determinants of durability are also likely to be indicated specifically. A neural graft implanted within the CNS and a beta-cell graft exposed to systemic metabolic and immune signals should not be expected to have equivalent immune or functional trajectories. Future studies should therefore determine not only whether a graft survives, but why function is maintained or lost and whether failure reflects product quality, immune injury, recurrent disease biology, implantation site, or other recipient factors. These distinctions will be necessary to determine whether the theoretical histocompatibility advantage of autologous therapy or the manufacturing consistency of allogeneic therapy translates into superior lifetime clinical benefit.

Manufacturing Performance, Scalability, and Total Treatment Burden: Claims of scalability should be evaluated using prospective manufacturing data rather than inferred from whether a platform is categorized as autologous or allogeneic. Relevant measures include manufacturing success and failure rates, process deviations, time from starting material to release, lot-release success, labor and facility requirements, capacity utilization, cryopreservation and distribution performance, patient waiting time, and comparability following process changes [32,33]. Autologous development must establish whether scale-out, automation, closed processing, and patient-specific banking can provide reproducible products without unacceptable treatment delays or failure rates. Allogeneic development must establish that scale-up preserves critical quality attributes and potency across larger campaigns and that the advantages of common-bank manufacturing are not offset by immune-management requirements or increasingly complex genome engineering. Economic evaluation should similarly extend beyond manufacturing cost per dose.

Comparative analyses should incorporate manufacturing failures, bridging treatment, immunosuppressive drugs and monitoring, immune-related complications, hospitalization, logistics, retreatment, long-term surveillance, durability of benefit, and the consequences of graft failure. Ultimately, the relevant comparison is the total lifetime treatment burden required to achieve durable functional replacement, rather than the production cost of the cellular product in isolation. Collectively, these domains provide a framework for moving the autologous–allogeneic comparison from platform-level assumptions to testable clinical and manufacturing hypotheses. The most informative future studies will prospectively integrate immune, genomic, functional, manufacturing, and longitudinal clinical endpoints within the same development programs.

Limitations of the Current Evidence

The available clinical evidence remains insufficient for definitive platform-level comparisons. Autologous experience is dominated by single-patient or very small studies, and the reported diabetes recipients received immunosuppression after prior organ transplantation, precluding direct estimation of the immune advantage of autologous derivation. Conventional allogeneic islet replacement has more advanced clinical evidence but remains based on early-phase cohorts, while human experience with immune-engineered allogeneic cells is presently limited to proof-of-concept observations. Cross-study interpretation is further constrained by differences in cell source, differentiation state, dose, transplantation site, disease severity, immune-management strategy, outcome definitions, and follow-up duration. Manufacturing literature similarly describes primarily process capability and enabling technologies rather than mature commercial performance. Accordingly, comparative claims regarding cost, throughput, scalability, durability, or immune superiority should be considered hypotheses requiring prospective product-specific validation.

Conclusions

Clinical translation of PSC-derived therapies has progressed sufficiently that autologous and allogeneic development can now be compared using emerging human data rather than theoretical assumptions alone. Autologous derivation offers a direct strategy for minimizing classical alloimmune mismatch but does not eliminate disease-specific autoimmunity, product-specific immunogenicity, genomic risk, or the complexity of individualized manufacturing. Allogeneic platforms provide manufacturing standardization and rapid product availability but require successful management of donor–recipient immune incompatibility through pharmacologic, physical, matching, or increasingly genetic approaches. The relevant scientific question is therefore not which platform is intrinsically superior, but which combination of cell source, immune strategy, manufacturing architecture, and clinical setting provides the most favorable lifetime benefit–risk profile for a specific indication. Future studies should prospectively integrate clinical efficacy,

immune monitoring, genomic safety, potency, manufacturing performance, and treatment burden. Such evidence will be necessary to determine whether patient-specific, conventional allogeneic, or immune-engineered allogeneic approaches offer the most durable and scalable therapeutic solution for individual cell-replacement applications.

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Conflicts of Interest

None.

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