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INNOVATIVE APPROACHES IN IMMUNOMODULATION FOR CELL-BASED THERAPIES

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ABSTRACT

The field of medicine is on the verge of transforming with the help of cellular therapies, which can address a wide range of diseases by restoring dysfunctional tissues more dynamically than conventional drugs. These therapies include stem and non-stem cells sourced from different places and apply to diverse therapeutic areas, such as cancer, immune disorders, and regenerative medicine. Cellular therapies have received numerous clinical approvals, and many trials are underway. In these therapies, the recipient immune reaction remains a significant hindrance to favorable results. This review analyzes the latest investigations regarding immune system modulators to reduce immune rejection or enhance immune ability to tolerate cellular therapies. We talk over the capacity of these interventions to accelerate translation for productive results of cellular therapies to succeed in medical settings.

***Keywords*:** Cellular therapy, Immune modulation, Stem cells, Transplantation

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1. INTRODUCTION

The scope of cellular therapies has significantly expanded due to the revolution in biotechnology and immunology (Cubillos-Ruiz et al. 2021). These strategies focus on addressing or controlling various diseases by grafting living cells into the body and re-establishing or removing malfunctioned cells. These strategies involved the use of either unaltered or genetically modified somatic cells (SCs) or cells from autogenic, allogeneic and xenogeneic sources. Hematopoietic stem cell (SC) and CAR-T cell therapies for blood disorders and malignancies are the primary cellular therapeutics approved for clinical use. As of August 2022, over 3000 clinical experiments are underway for cell therapies. These experiments mainly involve the use of somatic cells, RBCs, WBCs, and platelets for a wide range of clinical applications, like malignancies, blood disorders, immunologic diseases, cardiac diseases, and vascular diseases, etc. A summary of the current state of clinical experiments for cyto-therapies is reported by Wang et al. (2021). Despite the growing number of cellular therapy options in development, the body defense to these therapies is always challenging and potentially resistant for clinical acceptance and desired results (Petrus-Reurer et al. 2021). Graft vs host reaction can also occur while using allogeneic graft with matched HLA due to differences in negligible alleles (Petrus-Reurer et al. 2021). To minimize rejection, immunosuppressants are frequently used. These treatments can be classified into three categories: induction, maintenance and rejection. Induction therapy refers to the administration of high-intensity immunosuppressive drugs immediately after therapy. Maintenance therapy uses long-term immunosuppressive drugs to avoid chronic rejection. Rejection treatment, on the other hand, is employed to treat acute rejection episodes. These treatments involve using various immunosuppressants like calcineurin inhibitors, corticosteroids etc. The immunosuppressants target these cells as B and T cells play an important role in body defense. However, systemic immunosuppressants are not ideal as they

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increase the chances of communicable diseases, malignancies, and organ malfunction. Thus, to achieve favorable long-term therapeutic outcomes for cellular therapies requires innovations in promoting and maintaining immune acceptance (Slepicka et al. 2021). This review focuses on the latest strategies to modulate immune functions to prevent rejection.

2. MANIPULATION OF CRISPR-CAS9 GENOME

The CRISPR-Cas9 system, a DNA editing technology, has facilitated the development of genetically modified cyto-therapies with low or no antigenicity, commonly referred to as "off-the-shelf" or "universal" therapies. By this system we can precisely break both DNA strands at the desired location in the genome, which the cell can automatically restore. Non-homologous end joining (NHEJ) repairs can knock out the intended gene. If we have donor DNA template, we can do homology directed repair (HDR), resulting in the insertion of exogenous genes at the desired location. The approach to gene editing for immune recognition avoidance varies depending on the intended application. In some cases, the focus is on removing genes that encode for surface markers like HLAs and TCRs, which can trigger an immune response. For regenerative therapies that utilize induced pluripotent stem cells (iPSCs), the emphasis is on deleting genes like B2M and CIITA, which are necessary for the expression of class I and II HLA genes. These genes are mainly responsible for driving immune reactions to foreign cells. While completely knocking out HLA can prevent identification from helper and cytotoxic T cells, that can also trigger transplant rejection by activating recipient natural killer (NK) cells, especially when HLA-1 is deficient (Duygu et al. 2021). To overcome this issue, scientists have utilized allele-specific modification of heterogenic HLA-1 to express common HLA-C alleles which can crossmatch > 90% of the people. In addition, they have eliminated HLA-II expression to generate iPSCs that can evade both NK and T cell recognition (Xu et al. 2019). HLA-E (a non-heterogenic HLA-1) expression can be increased in stem and progenitor cells to inhibit NK cell lysis activity (Gornalusse et al. 2017; Sugita et al. 2018). In addition, researchers have modified iPSCs to disrupt the expression of HLA-1 while also overexpressing CD47, a signal that effectively prevents phagocytosis and transplant rejection mediated by macrophages and NK cells (Deuse et al. 2019). CD7 and TRAC elimination have been done genetically in human T cells to create readily available CAR-T cells for therapeutic use. The elimination of TRAC prevents T cell receptor (TCR)-mediated signaling that can cause GVHD (Cooper et al. 2018). T cell acute lymphoblastic leukemia (T-ALL) destruction in vivo has been done with these modified CAR-T cells without xenogeneic GVHD. When CAR-T cells are further modified by eliminating TCR and HLA-1, then there is a decrease in alloreactivity and GVHD along with deletion of PD1 (Ren et al. 2017). By deletion of the PD1 inhibitory pathway, the activity of CAR-T cells increases as there is no programmed cell death. By Cas9, immunomodulatory properties have been imparted in the insulin-secreting cells of rat (INS-1E). Through precise engineering of INS-1E, IL-10 is continuously produced in response to glucose (Fig. 1). This modification is done in the region of c-peptide (Lim et al. 2020). The IL-10 secretion can reduce fibrosis and is anti-inflammatory to β cell with little systemic effects in the host. Safety concerns should require careful consideration in genetically modified cellular therapies. Double-strand breaks (DSBs) formed by CRISPR-Cas in the genome, can cause mutation and chromosomal abnormalities, which ultimately lead to harmful pathologies (Fig. 1 & 2) (Kosicki et al. 2018; Nahmad et al. 2022). These concerns are particularly crucial in cell therapies synthesized to evade immune detection because of their risk of transforming into malignancies. So, researchers are increasingly interested in base editors, prime editors and epigenetic editing tools because of their less risk to form DSBs to reduce immunogenicity (Bashor et al. 2022).

3. IMMUNE TOLERANCE BY RNA THERAPEUTICS

By the use of RNA therapeutics like RNA interference (RNAi), we can reduce the immunogenicity in cellular therapies. RNAi allows for targeted silencing of immunogenic allo-antigens by degrading or inhibiting translation of mRNA transcripts. The dsRNAs and endogenous RNA-induced silencing complex work synergistically to silence genes at the post-transcriptional level. As gene editing can leads to harmful pathologies which can be avoided by the use of RNAi that removes the MHC molecules on the cell surface (Fig. 2). In cellular therapies of blood vessels, rejection of transplant due to immune responses from the host's peripheral blood mononuclear cells (PBMCs) can occur when graft endothelial cells (ECs) express non-matched human leukocyte antigens (HLA). Ex vivo treatment of donor blood vessels with small interfering RNA (siRNA) targeting CIITA can avoid the rejection by adoptively transferred donor PBMCs in immunocompromised mice by eliminating HLA-II expression in ECs (Cui et al. 2017). While siRNA can provide initial immune tolerance by transiently knocking down HLA, prolonged immune tolerance may require permanent elimination. For the permanent knockdown of HLA-1, we require the stable expression of RNAi, which can be achieved by short hairpin RNA (shRNA), that targets the B2M gene, through lentiviral delivery. By this, we get HLA-1 knocked down cells which can prevent cytotoxic T cell response,

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and the residual expression of HLA-1 prevents the NK cell response (Figueiredo et al. 2006). Additionally, HLA-1 knocked down induced pluripotent stem cells (iPSCs) can be generated through shRNA that have the ability to produce platelets in a model of mouse having platelet refractoriness (Börger et al. 2016). After the use of mRNA in the vaccines for SARS-CoV-2, the curiosity to use mRNA in immunological tolerance for cyto-therapies is enhanced (Barbier et al. 2022) (Fig. 1). One approach involves using mRNA to activate and increase the number of regulatory T cells (Tregs) that suppresses the body defense to prevent GVHD (Guo et al. 2021). To achieve this, researchers have designed mRNA encoding for a modified version of human IL-2, which selectively binds to IL-2Rα on Tregs to avoid the activation of helper and cytotoxic T cells (de Picciotto et al. 2022). In mice, the mRNA successfully activates and increases Tregs to prevent acute GVHD. As IL-2 can also promote proinflammatory T cells, we have to monitor the T cell count to prevent the body's defense against cellular therapies. Specific alloantigen tolerance can be produced by using tolerogenic mRNA vaccines that are chemically purified to eliminate dsRNA fragments. These encoded antigen vaccines can induce immune tolerance through T cells without co-stimulatory molecules (Karikó et al. 2005; Karikó et al. 2011; Krienke et al. 2021). While their use has so far been limited to inducing autoantigen-specific Treg responses for preventing multiple sclerosis onset in a mouse model (Krienke et al. 2021), we anticipate the use of tolerogenic mRNA vaccines that encode donor HLA so donor HLA-specific suppressor T cells are activated to immune against HLA mismatched cellular therapies (Fig. 3).

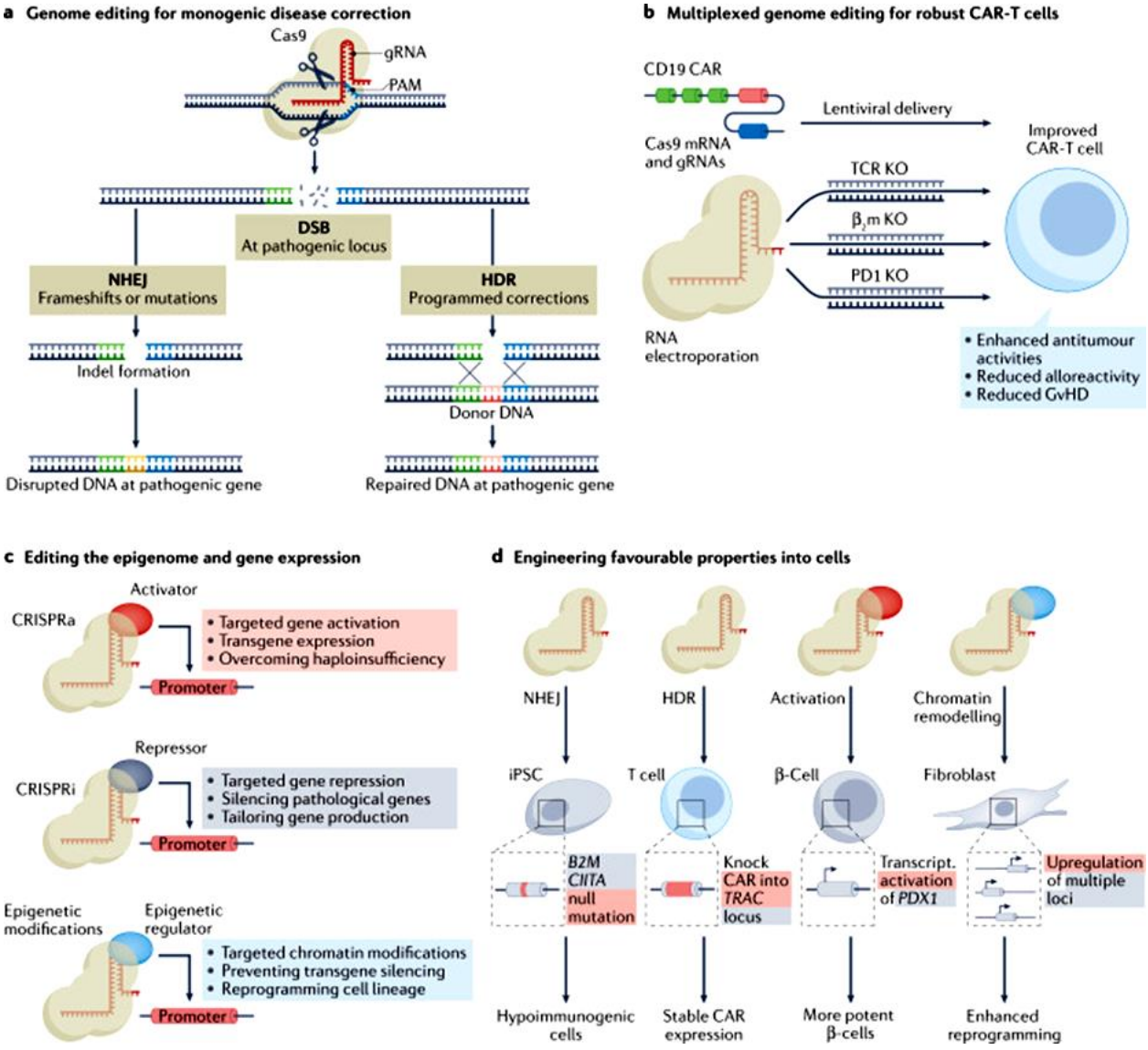

Fig. 1: Leveraging CRISPR–Cas-mediated genome and epigenome editing for improved cell-based therapeutics (Bashor et al. 2022).

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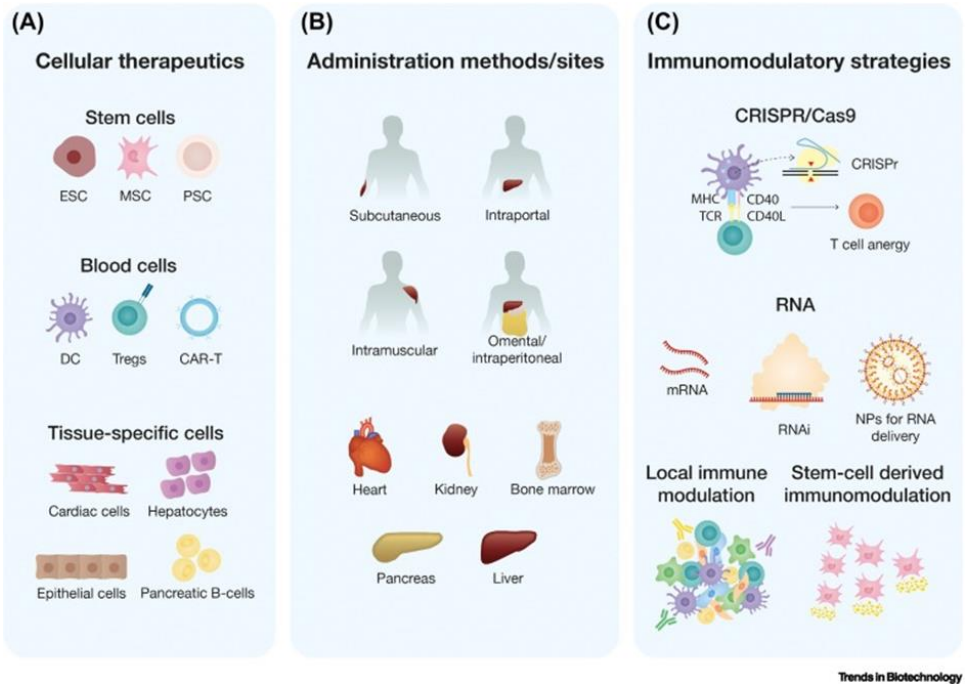

Fig. 2: Key figure. Cellular therapies, administration, and immunomodulatory strategies (Chua et al. 2023).

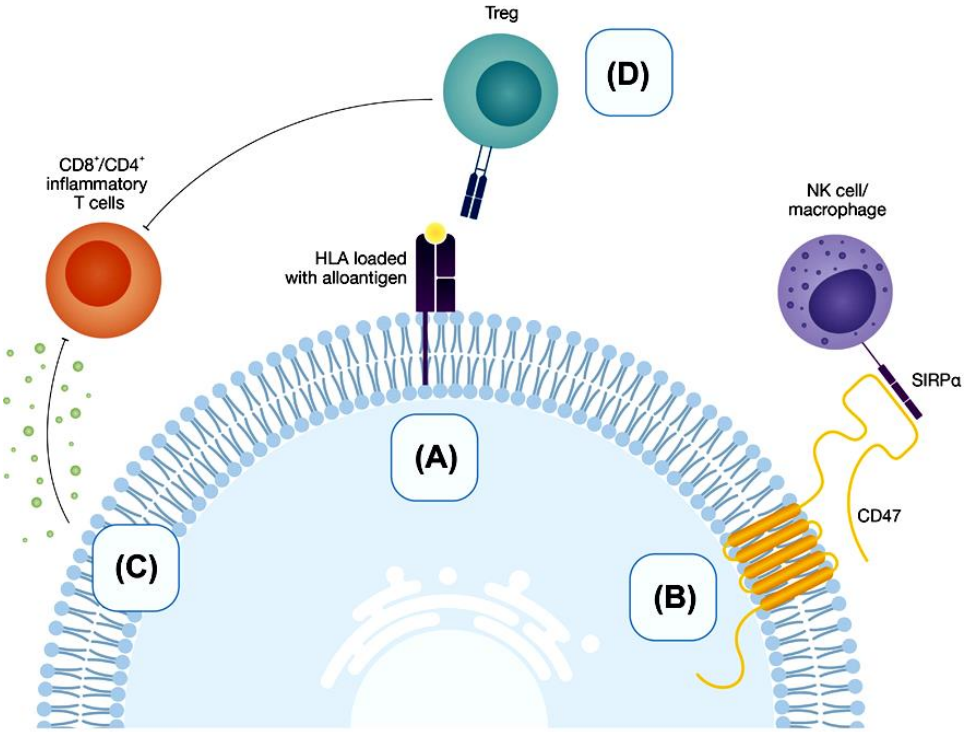

Fig. 3: CRISPR- and RNA-based technologies for immunomodulation (Chua et al. 2023).

These technologies can be applied to either (A–C) reduce the immunogenicity of cell therapies or (D) induce tolerance toward the cell therapy by the host immune system. Strategies to reduce donor immunogenicity include (A) CRISPR-Cas9 editing of donor cells to express common or nonpolymorphic HLAs or knockout of immunostimulatory HLA gene through CRISPR-Cas9 or RNAi therapies. Additionally, donor cells can also be genetically engineered to (B) overexpress immunosuppressive surface markers such as CD47 or (C) secrete anti-inflammatory cytokines such as IL-10 to modulate the local immune environment. (D) Additionally, recipient tolerance toward allogeneic cell therapies can be achieved through targeted activation of Tregs using mRNA-based IL-2 production or tolerogenic vaccines. Abbreviations: CRISPR-Cas9, clustered regularly interspaced short palindromic repeats-associated protein 9; HLA, human leukocyte antigen; IL, interleukin; NK, natural killer; Tregs, regulatory T cells.

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4. IMMUNE-MODULATION OF LOCAL MICROENVIRONMENT

Interventions aimed at creating a favorable immune microenvironment for cellular therapy can be achieved through the localized delivery of immunomodulators instead of systemic administration (Campa-Carranza et al. 2022). Furthermore, the combined administration of tolDCs and Tregs in situ has demonstrated potential. Another approach involves the use of mesenchymal stem cells (MSCs) for localized applications, which will be discussed further in the stem cell-derived immune-modulators section.

4.1. Localized Delivery of Immune-Modulators

Biomaterials like hydrogels and micelles find growing applications in immunomodulation, also in cellular therapies, owing to their capacity for customization, biocompatibility and adaptability (Fig. 2) (Adu-Berchie and Mooney 2020; Whitaker et al. 2021; Anggelia et al. 2022; Bu et al. 2022). For the niches of local immunomodulation, biomaterial-based scaffolds have been proved to be useful (Adu-Berchie and Mooney 2020; Anggelia et al. 2022; Antmen et al. 2021). Apoptosis can be triggered in inflammatory cells by Fas receptor/Fas ligand (FasL) pathway that can induce immune tolerance to self-antigens. Allogeneic islets and FasL-modified microgels have been co-transplanted showing long-term islet engraftment and normoglycemia in diabetic mice and other animals, indicating an alternative tool to systemic tolerance (Headen et al. 2018; Skoumal et al. 2019; Lei et al. 2022). Transplant immunomodulation can be done by immune checkpoint modulators which are commonly used to block immune checkpoints in oncology. Cytotoxic T cells and suppressor T cells play a key role in transplant rejection. By programmed cell death-1 (PD-1)/PD-ligand 1 (PD-L1) pathway, we can suppress cytotoxic T cell response and promote suppressor T cell response. Co-administration of PD-L1-eluting microgel and transient rapamycin was used to create immunosuppressive microenvironment for islet transplantation (Coronel et al. 2020). Micelles having dexamethasone when combined with cytotoxic T lymphocyte associated antigen-4-Ig (CTLA4Ig), in diabetic mice, have been shown to reduce proinflammatory cytokines and enhance allogeneic islet survival (Razavi et al. 2021). Additionally, dexamethasone-eluting graphene scaffolds have been used to achieve co-transplantation of islets and adipose tissue-derived MSCs by creating a localized immunosuppressive microenvironment (Girão et al. 2020; Bellet et al. 2021; Wang et al. 2019). Neo-vascularized implantable cell Homogenization and encapsulation (NICHE) implant with drug reservoir also has a localized immunosuppressive approach that sustains the release of immune suppressants. By eluting cytotoxic T lymphocyte associated antigen-4-Ig (CTLA4Ig) and/or anti-lymphocytic serum immunosuppressants, the NICHE creates a locally immune-protected environment where host vasculature can ensure engraftment of Leydig's cells and islets (Paez-Mayorga et al. 2020; Paez-Mayorga et al. 2022). In addition, MSCs with islets can be co-transplanted within NICHE to provide local immune-suppression and inhibit graft rejection (Paez-Mayorga et al. 2022).

4.2. Co-Administration of TolDCs

Tolerogenic dendritic cells are a type of immature DCs that exhibit immunosuppressive properties. These cells have the ability for immune tolerance by suppressing cytotoxic T cells, promoting apoptosis, and decreasing sensitivity, while also favoring the generation of Tregs. Thus, TolDCs have great potential for inducing graft tolerance and promoting graft survival. TolDCs can be targeted inside body or synthesized for therapeutic applications (Ochando et al. 2020; Que et al. 2020).

Tacrolimus-loaded microspheres and Clodronate liposomes were co-administered for the in situ generation of TolDCs, in case of xenogeneic beta cells dermatological engraft (Pathak et al. 2021). This approach resulted in the down-regulation of membrane receptors indicating it's transformation to TolDC phenotype. TolDCs have less antigen-presenting capacity leading to decreased activation of T cells and overexpress suppressor T cells for 520 days after engraftment, indicating long-term immune tolerance. Ex vivo generation of TolDCs involves culturing DCs derived from BM/ blood with various cytokines and immunosuppressive agents. According to research by Madelon et al. (2020), when both TolDCs and islets derived from rats are co-engrafted under renal capsule of mice led to long term xenograft survival with no immunosuppression. There are some challenges regarding the use of TolDCs like maturation, destruction by natural killer cells and translocation etc.

4.3. Cotransplantation with Suppressor T Cells

Regulatory T cells, a type of T cell expressing CD4, CD25, and FoxP3, with long-lasting immunosuppressive effects and have key importance in self-tolerance. Treg cell therapy has been investigated in number of clinically active trials (Ferreira et al. 2019). One notable study involves simultaneous autologous Treg infusion and allogeneic islet transplantation through the portal vein, which has shown to be safe and feasible (NCT04820270) (Bergström et al. 2021). Studies have shown to decrease the needs of immune-suppressants by infusing Tregs after 6 weeks of islet transplantation (NCT03444064).

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4.4. Co-Engraftment with Sertoli Cells

Sustentacular cells of Sertoli have a crucial role in creating an immune-privileged environment in the testes by forming a barrier that restricts the movement of lymphocytes and antibodies. Additionally, they have the ability to produce immunomodulatory molecules that suppress IL-2 production, B and T cells proliferation. This unique characteristic of Sertoli cells has led to investigations of their potential use in co-transplantation with exogenous cell grafts. For instance, Sertoli cells have been co-transplanted with allogeneic islets in diabetes mellitus type 1 models (Paez-Mayorga et al. 2022), mesencephalic tissue graft in Parkinson's disease models (Jhao et al. 2019), and dermatological grafts in other models (Luca et al. 2018).

5. STEM CELL DERIVED IMMUNE-MODULATORS

Stem cells have the potential to be engineered and transformed into specific cell types, and also utilized as living therapies for immune modulation in cell-based treatments. Their unlimited cell source could eliminate the concerns associated with restricted donor tissue availability in cell transplantation.

5.1. Therapeutics Derived through iPSC

The use of human pluripotent stem cells (hPSCs), which include both hESCs and hiPSCs, is being elaborately studied for numerous medical anomalies like cardiovascular, neurodegenerative, spinal cord injury and T1D. Despite being derived from the patient's own cells or having HLA matching, transplant rejection can still take place, limiting their outcomes (Deuse et al. 2019; Todorova et al. 2020). Moreover, the expenditures associated with this procedure is a major hurdle. Finally, autoimmune reactions, such as those that occur in T1D, remain a significant obstacle to overcome.

Recent advancements in immune engineering have created hypoimmune cells (HIP). Study by Cai et al. (2020) has shown that beta cells derived from iPSCs were protected from autoimmunity and maintained their function through CRISPR-mediated deletion of the Rnls gene in a murine model of T1D (Cai et al. 2020). Another research revealed that hiPSCs can be manipulated by lentivirus to overexpress PD-L1, which suppressed the transplant rejection of islet-like xenografts and maintained normoglycemia in immunocompetent mice with T1D (Yoshihara et al. 2020). A study on MI in murine model showed that when biotechnologically engineered HIP-iPSCs were engrafted in infarct zone it led to suppression of MHC class I/II and overexpression of CD47, and ultimately led to differentiation into HIP-iECs (Deuse et al. 2021). This successful cardiac engraftment improved cardiac output, and prevented rejection. These research demonstrate the use of iPSCs to overcome immune rejection in cell-based therapies.

5.2. DC-Like Cells

Researchers have explored using DC-like (DCL) cells derived from SC to induce immune tolerance. Todorova et al. (2020) reported that hESCs can be used to generate DCL cells that express CTLA4-Ig/PD-L1 (Todorova et al. 2020). These DCL cells work similar to tolDCs, resulting in long-term survival of allografts of smooth and cardiac muscles derived from hPSC. Importantly, immune tolerance is given to specific alloantigens expressed by DCL cells, hence minimizing the need for immunosuppression.

5.3. Mesenchymal Stem Cells

Mesenchymal stem cells can secrete various molecules regulating inflammation and immune responses such as cytokines, chemokines, and growth factors (Song et al. 2020). These cells can impede the response of T cells to foreign antigens and foster the production of regulatory T cells. Additionally, MSCs can steer the differentiation of dendritic cells into tolerogenic DCs, changing M1 macrophages, which are pro-inflammatory, to M2 phenotype, which is anti-inflammatory, and causes suppression of NK cells. These features make mesenchymal stem cells a promising candidate for co-administration in cellular therapies, including those aimed at treating islets (as evidenced by the clinical trial NCT02384018). The immunosuppressive properties of MSCs have been leveraged in various preclinical studies investigating their role in cellular therapies. According to research on retinal degenerative disease in the murine model, fetal retinal pigment epithelial (RPE) cells are co-engrafted with mesenchymal stem cells resulting in prolonged graft survival by suppressing host immunoreaction and preserving retina function (Pan et al. 2020). In another study on acute liver failure in a murine model, hepatocyte nuclear factor-4 alpha (HNF4α) which overexpresses MSCs are co-encapsulated with hepatocytes, promoted M2 macrophage leading to reduced inflammation (Kong et al. 2020). In iPSC-derived cardiomyocytes transplantation, Isograft of MSCs can provide immune tolerance by promoting suppressor T cells and inducing apoptosis in cytotoxic T cells (Yoshida et al. 2020). In study on MI in murine model showed that when iPSC-derived cardiomyocytes are co-transplanted with MSCs improved heart functions (Neef et al. 2022). When human umbilical cord perivascular MSCs are co-engrafted with islets in mice with diabetes showed suppression in T cells and

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maintained tight glucose level (Forbes et al. 2020). Finally, for allogeneic beta cell engraftment in rats with no need of systemic immunosuppression, MSCs are synthesized to express PD-L1/CTLA4-Ig leading to local immunosuppression (Wang et al. 2022). Although SCs offer significant potential for cell therapies, several challenges must be overcome, including maturation, long-term survival, immunogenic potential, cost effectiveness, manufacturing, quality control, and maintaining stable phenotype during transplantation (Levy et al. 2020). For further insights on these topics, we encourage readers to refer to the section titled "Concluding remarks and future perspectives."

6. IMMUNE MODULATION OF SPECIFIC SITE FOR CELL DELIVERY

Certain organs or tissues naturally have reduced immunological surveillance, making them ideal for receiving cellular therapy (Parmar et al. 2020). These anatomical locations, like CNS, eye, testes, placenta and hematopoietic niches, have limited/ slow regeneration capacity. However, it's important to note that immune protection does not necessarily extend in all organ tissues like blood-ocular barrier protecting the intraocular compartment and blood-brain barrier protecting the brain's parenchyma (Chen et al. 2019). Therefore, to protect GVHD researchers often investigate cell replacement therapy in the immune protected sites.

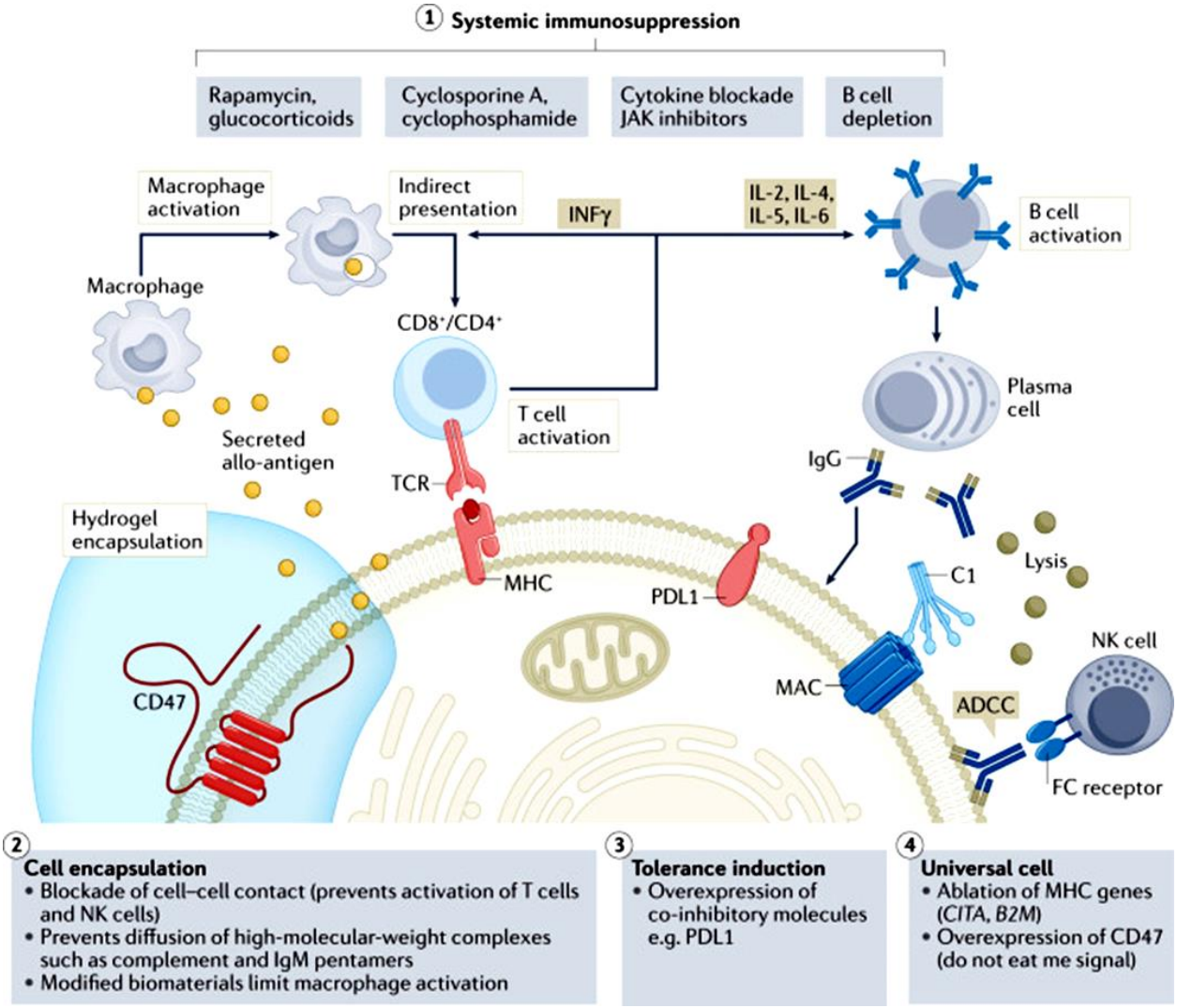

Fig. 4: Strategies to overcome immune rejection for allogeneic cell therapy (Bashor et al. 2022).

6.1. Dopamine Progenitor Cells Derived through iPSC

According to research on Parkinson's disease model of rhesus macaque, both autologous and allogeneic dopamine neural progenitor cells derived through iPSC placed in immune privileged site of brain parenchyma (Tao

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et al. 2021) which found that only autologous transplantation resulted in recovery of motor and depressive dysfunction for over 2-year with no need of immunosuppressive drugs. Thus, non-autologous engraftments, even in immune modulated sites, require immunosuppression for successful graft. A recent clinical trial on a patient with idiopathic Parkinson's disease by intracranial administration of autologous dopamine neural progenitor cells derived through iPSC showed improvements for over 2-years with no immunosuppression (Schweitzer et al. 2020).

6.2. Retinal Pigmented Epithelium Derived through Human Embryonic Stem Cells

Due to the presence of the retinal-immune barrier, research on cellular therapy for retinal diseases has gained momentum (Coco-Martin et al. 2021). A Phase 1/2 clinical trial demonstrated the allogeneic engraftment of hESC-RPE (OpRegen) in AMD and geographic atrophic patients resulted in improvement in vision for over 15 months (NCT02286089). Another phase utilized RPE derived through hESC (MA09-hRPE) transplantation for macular repair in patients with advanced Stargardt disease, which resulted in subretinal hyperpigmentation which indicates the survival of engraftment (NCT01344993) (Mehat et al. 2018). Despite the immune-privileged nature of the transplantation site, systemic immunosuppression was done to decrease the chances of rejection in both cases. hESC-RPE patch was also transplanted in AMD patients with intravitreal fluocinolone acetonide implant as a localized immunosuppressant, improving vision (da Cruz et al. 2018). Additionally, researches are currently being done on human retinal progenitor cells (hRPCs) for retinitis pigmentosa via intravitreal or retinal injection without immunosuppression (NCT02464436, NCT03073733).

6.3. Transplantation of Beta Cells in the Anterior Chamber of Eye

Research on mice with type 1 diabetes (T1D) has shown that intraocular transplantation of allogeneic beta cells did not require immunosuppression, but immunosuppression was needed for the baboon model (Abdulreda et al. 2019). Thus, a clinical trial was done in a blinded type 1 diabetic patient with beta cells engraftment in the eye's anterior chamber (NCT02846571). But revascularization can break the blood-ocular barrier by extending from the iris. However, maintenance immunosuppression is administered to trial participants for two years to prevent rejection. Researchers are investigating local immunosuppression like rapamycin microparticles to avoid systemic immunosuppression (Fan et al. 2019).

6.4. Role of Endothelial Cells in Site Specific Immune-Modulation

Recent research has shown that endothelial cells can also play immune-modulatory function, like immune tolerance and regulation of allo-immunity, beyond their primary role of recruiting immune cells (Johansson-Percival et al. 2018; Amersfoort et al. 2022). Endothelial subsets of specific tissues exhibit typical immune functions like production of cytokines, express co-stimulatory or co-inhibitory receptors, and induce apoptosis in other cells. ECs play a crucial function in maintaining tissue-specific immunity, such as the blood-brain barrier.

7. CONCLUSION

Numerous trials are underway to explore various immunomodulatory strategies for cell therapy. In 2021, the first CAR-Tregs trial in humans was done to induce and maintain immune tolerance in kidney transplant. A clinical trial aiming to prevent graft versus host disease without engraftment inhibition was done in Japan by combining cord blood transplantation with intra-BM injection of MSCs. Additionally, investigations on CRISPR-Cas9 and mRNA based immune therapeutics are in clinical process for innovation in immunomodulation. Before clinical applications, safety and ethical concerns need to be appropriately addressed. Other issues like reproducibility, manufacturing, implementation of standardization and quality control protocols need to be resolved. Thus, organizations in bio fabrication units have developed guidelines to produce good quality manufacturing, such as the Bio-Fab USA program. The program's goal is to make the manufacturing of cellular therapies scalable, consistent, and cost-effective. To achieve this, the program uses AI, robotics, IT, and computational sciences. These technological advancements can resolve the issues of ethical consideration, cost effectiveness, and accessibility. Because cellular therapies are living drugs, there should be proper supply chain monitoring like manufacturing, storage, transportation, and administration to ensure widespread and reproducible implementation. Developing safe and effective delivery methods is a significant challenge that must be addressed. A prime example of this challenge is seen in the delivery of SC-derived β cells, where the desired response of the graft is largely dependent on the delivery approach. Despite more than seven decades of research in this field, an optimal solution for cell delivery has not yet been identified. However, advances in biomaterials and nano-medicine may resolve this problem. Lastly, there are research opportunities to develop productive methods to trace cell therapeutics once they are delivered into the body and monitor their viability, functioning, and modification of immunological responses as needed. In this regard, innovation in radiological approaches like real-time imaging technologies and optogenetic methods that use light stimuli of specific wavelengths may be useful. Addressing these translational challenges is a

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monumental task that demands the integration of various areas of expertise and capabilities. The successful and prompt development and regulatory approval of COVID-19 vaccines, achieved through the collaboration of academia and industry on a global scale, demonstrate the impact of concerted efforts. Such joint endeavors hold the potential to unlock the full potential of cellular therapies.

Author's Contribution: MZZ: Conceptualization, Supervision; MZZ, MSI. and BRK: Data curation, Methodology, Supervision, Writing – original draft; AS, HA, MM and RN: Visualization, and Data curation; SAS, WH, SASh and MR: Writing – Review & Editing. All authors have read and approved the final version for publication.

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