Review Article

Application of nanomaterials in heart transplantation: a narrative review

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Background and Objective: Heart transplantation (HT) is a therapeutic option for end-stage heart disease. Still, it faces many challenges, especially the shortage of donor sources and the poor durability of grafts, which are the two critical issues. In this review, we generalize the application of existing nanomedicine technologies in donor management as well as prevention and diagnosis of post-transplantation complications, also including the current preclinical studies of nanomaterials in cardiac tissue engineering and gene-editing xeno-donor grafts. Finally, we discuss the remaining problems and future directions of nanomaterials in the field of HT.

Methods: A narrative review using current search of the most recent literature on the topic. The terms "nanomaterials", "nano medicine", "Heart transplantation (HT)", "Nano-drug delivery system (NDDS)" or their combination were searched in PubMed and Google Scholar. The specified timeframe began from 1990, and we prioritized publications mainly from the last 10 years.

Key Content and Findings: Nano-systems integrating therapeutic and diagnostic functions have been applied to cardiovascular diseases (CVDs) with their unique advantages in multiple fields such as drug delivery, tissue engineering, gene editing, imaging, biomarker editing, and many other aspects. In terms of transplantation, the preservation, transportation, and pretreatment of donor hearts machine perfusion (MP) provide the possibility for nano-systems with unique features, and therapeutic and diagnostic functions to be directly and passively targeted in order to improve the functional status of the transplanted organs or to increase the ability to tolerate the graft of patients. The development of nano-imaging, nanosensor, and nano biomarker technologies are also being applied to monitor the status of transplant recipients for early prevention and treatment of post-transplantation-related complications. Nanomaterials combined with cardiac tissue engineering and gene editing technologies could also expand graft sources and alleviate donor shortages.

Conclusions: Although the overall research on nanomaterial applications in the field of HT is in its infancy, its role in improving the prognosis of transplant recipients and breaking the current dilemma of HT is clear. However, before nanotechnologies can be translated into clinical applications in the future, they must be aimed at ensuring the drug delivery system's safety and pose a challenge in the direction of the ability to intervene with multiple drugs in combination.

Keywords: Heart transplantation (HT); nanomaterial; drug delivery; tissue engineering

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Introduction

The number of deaths caused by cardiovascular diseases (CVDs) worldwide reached 18,562,510 in 2019 (1). Not only the CVDs have a high incidence rate, but they always develop into end-stage heart failure (HF) (2). Heart transplantation (HT) has been proved to improve the long-term prognosis and quality of life of patients with advanced HF, improve the survival rate of patients, and has become the preferred treatment for patients with end-stage HF (3). However, HT faces many challenges, especially the shortage of donor sources and the poor durability of grafts, which are the two critical issues. So, new means are urgently needed to break the barriers of diagnosis and treatment. At present, nanotechnology is widely used in the biomedical field (4), and it shows great potential in overcoming many limitations of cardiovascular medicine because of its advantages such as relatively low toxicity, biodegradability, good mechanical properties, and biocompatibility (5). It is also expected to become a powerful tool to help overcome the barriers of HT in the future.

Nanosystems integrating therapeutic and diagnostic functions are applied in CVD with their unique advantages, specifically in drug delivery, tissue engineering, gene editing, imaging, and biomarkers. Nanoparticle (NP) delivery systems offer tremendous advantages in improving bioavailability and enhancing the activity of immunosuppressants (ISAs). On the other hand, the preservation, transportation, and preconditioning aspects of the donor heart with machine perfusion (MP) offer the possibility of direct passive targeting of nanomaterials to improve the functional status of the transplanted organ or to increase the ability of the recipient to tolerate the graft. Besides, the development of diagnostic nanomaterials, such as nano-imaging, nano-sensor, and nano-biomarker technologies, also has huge advantages in monitoring the status of transplant recipients and achieving early prevention and treatment of post-transplantation complications (6-8), while the application of cardiac tissue engineering and gene editing technology combined with nanotechnology has made it possible to gain artificial donors and xenografts (9,10). To some extent, patients with HF may also be able to avoid transplantation or delay transplantation time.

In this review, we generalize the applications of existing nanomedicine technologies for donor management as well as the prevention and diagnosis of post-transplant complications. These applications also include current preclinical studies of nanomaterials for cardiac tissue engineering and gene-editing xenografts. Nanomedicine defined here involves a variety of nano-biomedical materials and their medical applications, specifically include nanomaterials for treatment and imaging after direct myocardial injection, coronary perfusion, or intravenous injection, nanomaterials for assessing diagnostic information from body fluids or tissues, and nanomaterials applied on implantable biomaterials or tissue engineering. Finally, we will further aim to discuss the remaining issues and future directions of nanomaterials in the field of HT (*Figure 1*). We present this article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1506/rc).

Methods

We searched PubMed and Google Scholar for references with the terms “nanomaterials”, “nano medicine”, “Heart transplantation (HT)”, “Nano-drug delivery system (NDDS)” or their combination in the title or abstract. As the concept of nanomedicine was put forward the 1990s, our specified time frame began from 1990, and we prioritized publications from the last 10 years but cited other references where historically relevant and necessary. The search strategy is summarized in *Table 1*.

Nanomedicine and its properties

Nanostructured units are the basic units that make up nanomaterials and are generally defined as composition or crystal structure with length dimensions of less than 100 nm. Nanotechnology refers to any product created or modified by manipulating substances at the nanoscale (11). Nano-biomedical materials can be developed at 1–100 nm in at least one dimension critical for applications with nanotechnology, which have characteristics such as small size, large specific surface area, high surface energy, and a large proportion of surface atoms, and different from the general materials with the same composition in physical, chemical properties, and biological properties. The commonly used types of bionanomaterials and their features are summarized in *Table 2* (12,13).

The application of nano-biomedical materials mainly focuses on the diagnosis and treatment of diseases. Therapeutic nanomaterials have the ability to carry drugs with targeted and controlled-releasing functions. Therefore, various nano-drug delivery system (NDDS) (*Figure 2*) are being continuously developed and improved. Diagnostic

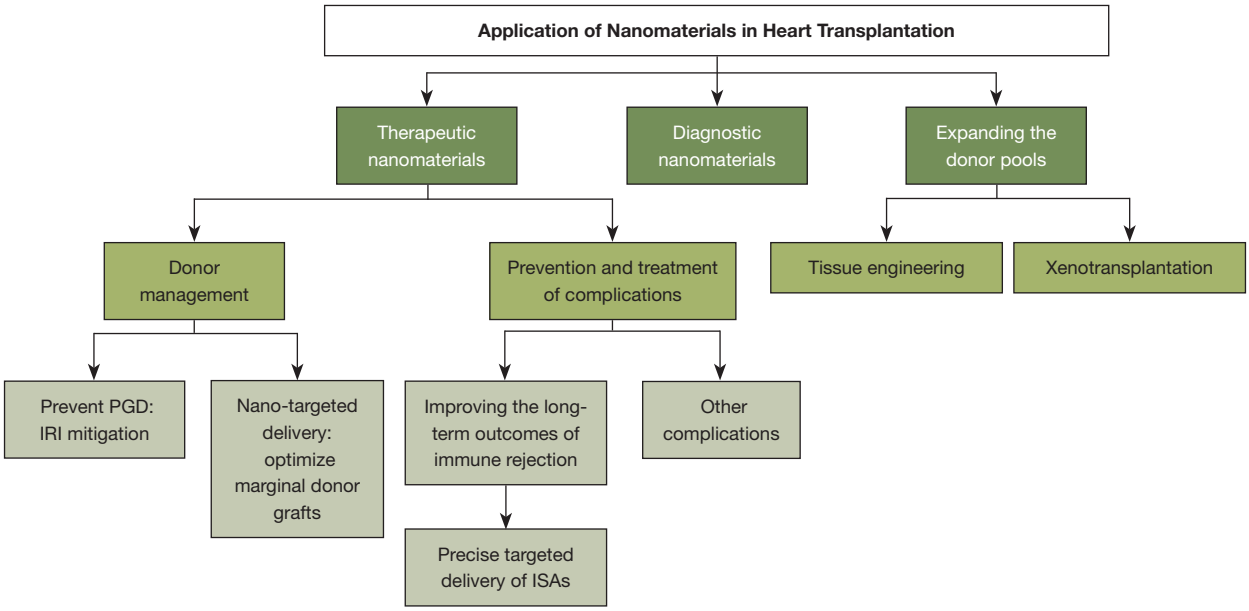

Figure 1 Application of nanomaterials in heart transplantation. PGD, primary graft dysfunction; IRI, ischemia-reperfusion injury; ISAs, immunosuppressants.

Table 1 The search strategy summary

Items	Specification
Date of search	May 4th, 2023
Databases and other sources searched	PubMed, Google Scholar
Search terms used	"nanomaterials", "nano medicine", "Heart transplantation (HT)", "Nano-drug delivery system (NDDS)"
Timeframe	1990 to May 2023
Inclusion and exclusion criteria	Inclusion criteria included the following: prioritized English-language; preclinical studies of nanomaterials for cardiac tissue engineering and gene-editing xenografts; nano-biomedical materials and their medical applications; human or non-human studies for treatment and imaging after direct myocardial injection, coronary perfusion, or intravenous injection with nanomaterials; human or non-human studies for using nanomaterials to assess diagnostic information from body fluids or tissues. Exclusion criteria included: abstracts without full article available; studies not available in English
Selection process	Two senior authors reviewed the search results and completed a manual full text review. Studies were marked for inclusion or exclusion with exclusion reasons independently based on the pre-defined criteria. In instances of disagreement, a third reviewer was utilized independently and resolved any disputes

nanomaterials have the advantage of generating signals through a variety of physical and chemical modalities, with the ability to visualize site-specific accumulations to show cellular or molecular states (14). There are also means of integrating therapeutics and diagnostics nanotechnologies, which are applied in CVD with their unique advantages (15).

However, nanomaterials may also adversely affect biological systems due to their toxicity, which may harm human beings. It is precisely based on the uncertainty of nanomedicine that the conflict of risk and value between

Table 2 Types and applications of commonly used bionanomaterials

Types	Applications features
Nanomaterials for cell separation or staining	Composite NPs: stable performance and easy separation from cells
	Gold NPs: mixing with different antibodies to prepare a various of complexes that can improve intracellular tissue resolution
Nano-matrix for drug delivery	NPs (liposomes, virions, etc.) or a matrix composed of nanofibers can control the release of drugs to improve the bioavailability of drugs
Nanobiofilm	Used to encapsulate biological specimens (electrodes, etc.)
	Plays an antibacterial role in implantable devices or using wound dressings
Bio-imaging and Bio-sensors	NPs are used as contrast agents to improve biodistribution and contrast
	Sensors based on nanotubes, nanowires and chemically modified NPs improve analytical sensitivity and speed
Bionanomaterials in tissue engineering	Nanomaterials can be used in the study of tissue and organ construction *in vitro* due to its biocompatibility
Nanoscale particles with biologically active therapeutic properties	Biomolecules can be mimicked to make the material surface reactive

NPs, nanoparticles.

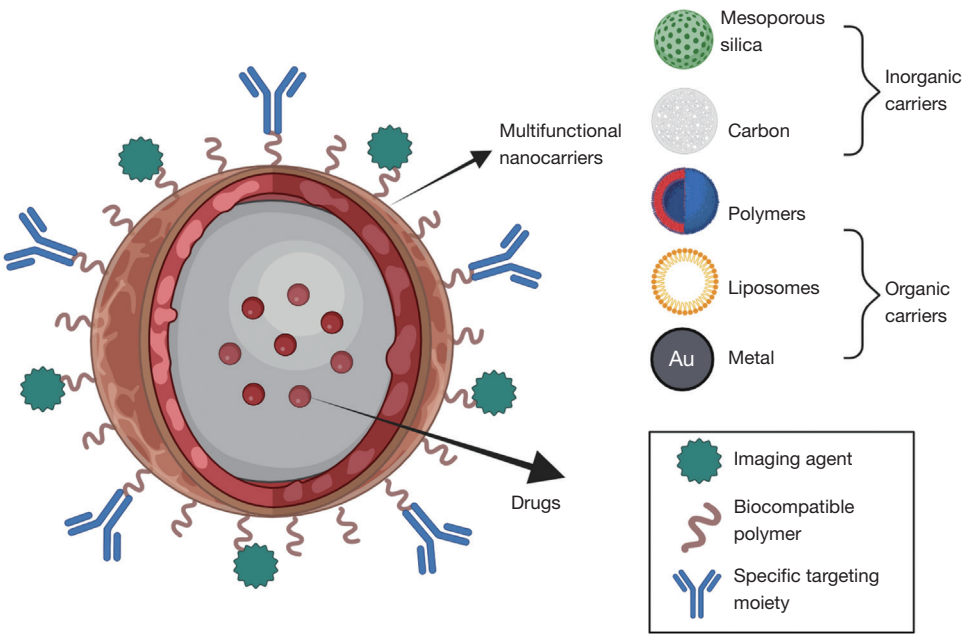

Figure 2 NDDS—multifunctional NPs system for drug delivery. Au, aurum; NDDS, nano-drug delivery system; NPs, nanoparticles.

nanotechnology research and application arises, but the study and use of bionanomaterials are crucial to the progress of medical development, which also motivates active cooperation and communication among various disciplinary fields, assuming their responsibilities and making solid contributions to the research of bionanomaterials.

Therapeutic nanomaterials applied in HT

Graft-related complications are the leading cause of

postoperative death after HT, which are presented by damaged graft parenchyma and vasculature, as well as micro thrombosis, and ultimately leading to ischemia, hypoxia, and tissue necrosis and contribute to cardiac pumping dysfunction in the transplanted heart due to the complex interactions between immune-mediated and non-immune-mediated mechanisms. These complications include primary graft dysfunction (PGD), acute allograft rejection, and cardiac allograft vasculopathy (CAV) (16). With the development of modern medical technology, acute immune rejection is no longer a direct threat to HT. However, it faces entirely new challenges: (I) PGD is the direct cause of many HT failures, and its mechanisms in the acute phase after operation are still unclear, so, how to minimize PGD and improve the success rate of transplantation is a major barrier. (II) Since long-term and systemic immunosuppression can cause tremendous adverse effects in patients, how to reduce and possibly resolve immunosuppression indefinitely needs to be tackled.

NPs can encapsulate various therapeutic molecules and are capable of being modified to active-targeting and control-releasing, such as loading drugs or genetic materials to enter the cells of the target organ (17). NPs hold great promise for improving bioavailability and enhancing the activity of ISAs. Nanomaterial-targeted therapeutic delivery systems have the potential to increase the ability of patients to tolerate the graft by improving the functional status of the transplanted heart or enhancing post-transplant immunomodulation (18). Here we will focus on the latest application progress of nanomedicine in improving PGD and optimizing the long-term immune rejection therapy regimen after transplantation. However, due to the high cost, inadequate reproducibility, and potential problems with the delivery system itself, there are currently no nano-delivery systems undergoing clinical trials or being approved for clinical treatment of complications after HT, but it can be boldly speculated that the application of nanomedicine in the treatment of HT patients will gradually realize clinical transformation in the near future as more and more studies continue to be refined.

Donor management

Preservation, transportation, and donor heart preconditioning are critical to utilize the donor resource fully. Currently, the standard method of donor preservation is still to preserve the heart from brainstem death patients by static cold storage (SCS). SCS combines the advantages of cardioplegia and hypothermia and achieves preservation by significantly decreasing the energy requirements of the donor heart, but the 4–6 h of cold ischemia time and ischemia-reperfusion injury (IRI) are considered essential causes of graft failure, particularly leading to an increased incidence of PGD. Meanwhile, as donor shortage is one of the main problems currently faced by HT (19), the concept of marginal donor grafts has emerged (20). However, due to the inherent defects of marginal donor grafts and the potential for more severe consequences of immune rejection, means are needed to optimize the quality of marginal donor grafts. Moreover, hypoxia caused by IRI can lead to gap junction damage in endothelial cells (ECs), which is also an important cause of graft rejection.

Donor management aims to improve the long-term survival of recipients who received marginal donor grafts, ameliorate donor preservation before transplantation, and minimize the damage to organs caused by ischemia. MP, as non-oxygenated perfusion of organs at cold or ambient temperatures, aims to maintain donor heart perfusion, for meeting the metabolic demands of the myocardium to reduce irreversible ischemic cell damage and death (21). MP can serve as a platform for resuscitation, preservation, evaluation, and possibly even repair of cardiac function before transplantation and is considered an ideal method for expanding the donor pool and improving donor resource utilization (22). The great potential of MP lies in the application of specific therapies to improve the quality of the donor heart during the perfusion period, and localized, sustained, and controlled delivery of nanotherapeutic agents to the donor heart during this critical period is a not-to-be-missed opportunity (23). MP provides an ideal passive targeting platform to enhance the potential utility of nano-targeting by simplifying administration kinetics during the period between donor harvesting and replacement to the acceptor.

Although there is no direct evidence or studies showing that nanomedical means can reduce the incidence of PGD after HT or treat PGD that has already occurred after HT, we summarize studies related to the application of nanomaterials to ameliorate donor IRI injury or the implementation of sustained and controllable nano-immuno-delivery therapies to the donor heart, which serve as circumstantial evidence that nano-biomedical materials can optimize donor quality, and also provide the basis for the future development of nano-delivery systems that can

be translated into clinical applications.

Indirect evidence for nanomedicine to prevent PGD: IRI mitigation

PGD is defined as unexplained univentricular or biventricular dysfunction that occurs within 24 h after HT, and excludes known secondary factors such as hyperacute rejection, pulmonary hypertension, and surgical complications (24). Specific risk factors for PGD include the pathological status, the gender and age matching degree of the donors and recipients, which most importantly depend on the time of heart exposure to ischemia injury, including brain stem death, cold ischemia, warm ischemia, and IRI (25). Using NPs targeting the cascade of reactions involved in destroying the organ to reduce the effects of IRI provides a new opportunity to mitigate IRI during MP of isolated organs.

Direct passive targeted preconditioning by local delivery can alleviate myocardial injury, such as direct myocardial injection or reperfusion means. Using nano-complex systems with loading and control-releasing functions to mitigate IRI, which can effective deliver various therapeutic molecules and can be reactive oxygen species (ROS)-response, has faster absorption, and wider distribution than virus delivery systems (26-29). In addition to the delivery of drugs with direct therapeutic effects, nano complexes as carriers can solve the bottleneck of molecular applications of certain gas state molecules. For example, mesoporous silica nanoparticles (MSNs) loaded with diallyl trisulfide (DATS) can make a compound DATS-MSN, which can also act as a stabilizing donor of hydrogen sulfide (H_2S) and has been found to promote the proliferation and differentiation of ECs *in vitro* to alleviate reoxygenation-induced inflammatory responses, and has been shown to protect the endothelium of aortic allografts from IRI (28). Meanwhile, timely oxygen supply can also significantly improve the prevention of myocardial ischemia and prevent oxygen overload from causing oxidative damage to myocardial cells (MCs), but ordinary cardioprotective fluids do not provide oxygen. Nano-oxygen drugs with an excellent ability to carry or release oxygen and facilitate perfusion of ischemic and hypoxic tissues, can effectively and promptly supply oxygen to hypoxic organs and tissues and reduce IRI (29). In addition, nanomaterials can also be combined with other new biomedical materials to reduce IRI based on the principle of ROS response, and can facilitate the rapid transmission of electrical signals between MCs while delivering agents (30). With the improvement of mechanistic investigations at the gene level related to IRI (31,32) and the development of gene therapies such as RNA interference (RNAi) and transgenic technology, silencing the mRNA of relevant molecules and thus alleviating IRI is a feasible strategy (33). Nano complexes are more stable than traditional viral or cationic gene carriers, and overcome the myocardial delivery challenge with dense fiber bundle structure and high-density negative charge through electrostatic and hydrophobic interactions (34). At the same time, compared with siRNA-mediated gene silencing, DNAzymes gold nano complexes also have additional advantages of enhanced stability and limited immune response, which can be a promising strategy for gene silencing against IRI in HT (35). Although similar clinical studies have not yet been carried out in the field of HT, it is foreseen that the combination of nano-carriers and gene-silencing technology will be a very promising field of application.

Nano-targeted delivery to optimize marginal donor grafts

Another effective key paradigm for donor management to expand donor sources includes nano-immuno-therapy, aiming to optimize the conditions of marginal donor grafts by means such as targeted delivery, avoiding post-transplant immune rejection caused by its own insufficiency. In addition, controlling early immune activation in organs and reducing organ immunogenicity during MP to pre-treat the donor heart can minimize the need for immunosuppression.

Tietjen *et al.* suggest that NPs target ECs more efficiently during isolated organ perfusion because ECs play an important role as the contact interface of immune response between the grafts and the recipients (36), and treatment of isolated grafts with NPs does not need to worry about systemic effects. For example, the synthesis of targeted rapamycin micelles (TRaM) and further customization of the micelles using a targeted peptide (cRGD) can improve the uptake efficiency of TRaM NPs, and avoid systemic effects. Rapamycin is delivered to the endothelium in a concentrated manner via a pH-sensitive triggered release mechanism to inhibit the ECs damage response and also to confer a local immunosuppressive effect (37). Adding TRaM to organ preservation solutions can protect aortic allografts from endothelial and epithelial activation, which significantly reduces organ damage and potentially induces a tolerant graft microenvironment (38). Besides, controlling early immune activation events within the transplanted organs and improving long-term graft

outcomes remain a significant focus of transplantation research. Perfusion of the donor heart with morpholino-loaded polyethylene glycol-poly lactic acid-co-glycolic acid (PEG-PLGA) NPs [manganese magnesium ferrite (MMF)-NPs] before transplantation may be a clinically feasible method to reduce chronic allograft transplant rejection through inhibiting proinflammatory cytokines and chemokines in heart grafts (39). These studies suggest that treating transplanted organs with ISAs loading with NPs before transplantation can reduce the incidence of post-transplant rejection while targeting a damaging immune response. An alternative feasible strategy is that targeted therapies that control induced alloimmunity with IRI can reduce IRI while reducing immune rejection. The novel anti-IL-6 NPs can control the release of anti-IL-6 over time, not only protecting the transplanted heart from IRI, but local delivery of anti-IL-6 also significantly reduces chronic immune rejection reaction (40). And compared with the systemic use of IL-6 antibody, isolated MP of PLGA NPs against IL-6 antibody resulted in reduced chronic rejection rates of mouse heart allografts, alleviating the adverse consequences of autophagy induced by resident dendritic cells (DCs) in grafts (40).

In the case of genetic defects, the donor organ can also be treated with *ex vivo* gene therapy during MP and then automatically transplanted back into the recipient, thus eliminating the need for lifelong immunosuppression. A vital issue of this approach is how to safely and effectively reduce the expression of major histocompatibility complex (MHC) molecules on grafted ECs during transplantation, whereas small interfering RNAs (siRNAs) can transiently reduce the presentation of the proteins in allogeneic grafts. Single transfection of siRNA-releasing poly(amine-co-ester) NPs targeting class II transactivators after transplantation into immunodeficient mice can attenuate MHC II expressions on ECs to reduce *in vitro* and *in vivo* allogeneic T-cell responses, suggesting that the use of poly(amine-co-ester) NPs during ordinary temperature MP of isolated organs can modify ECs and protect them from rejection by over-transferred allogeneic T cells (41).

Even if more robust clinical findings are not available, the therapeutic potential of nano-targeted drug delivery during MP is evident. MP can continuously administer nano-immune delivery therapy and constantly supply oxygen and nutrients to organs, and remove toxic metabolites to enhance transplant assessment, preservation, and resuscitation. Thus, the repertoire of organs can be expanded. This opens up the possibility to ultimately improve the long-term transplant outcome.

Prevention and treatment of complications after HT

Despite the increasing survival of HT patients in recent years, graft-related complications, including allograft rejection, and CAV remain the leading cause of patient mortality after transplantation (42). Due to complex interactions between immune-mediated and non-immune-mediated mechanisms, graft parenchyma and vasculature are damaged, and micro thrombosis is formed, which ultimately leads to ischemia, hypoxia, and tissue necrosis and contributes to cardiac pumping dysfunction in the transplanted heart. Because of the need to use immunosuppression to treat graft-related complications, non-graft-related complications are also on the rise. Infections have become one of the most common causes of death in post-transplant follow-up (43), thromboembolic complications in recipients are also a significant cause of late death (44,45), and the risk of developing a new solid malignancy after transplantation is 10% in 1–5 years (46). One of the main clinical approaches to improve the long-term outcome of the graft is to improve the therapeutic index of immunotherapy, namely, increased efficacy and decreased toxicity. Targeted nano-delivery systems can enhance the bioavailability of ISAs and make various modifications of passive targeting and active targeting, which is considered a new means to benefit the above problems.

Improving the long-term outcomes of immune rejection: precise targeted delivery of ISAs

One of the critical sites of immuno-therapy delivery is the cells responsible for initiating immunity. A key target for intra-organ delivery of NPs is the inhibition of Toll-like receptor (TLR) activation in antigen-presenting cells (APCs). The innate immune response can be moderated by various antibody-modified NPs targeting APCs (47,48) or the self-features of macrophages and DCs that can extend dendrites into the vascular lumen to capture the characteristics of NPs from the blood circulation (49). For example, coating the surfaces of NPs with antibodies against the macrophage antigen CD11b and the DCs antigen CD11c can target the macrophages and DCs (50,51). NPs composed of high-density lipoproteins and lipids loaded with mTOR-specific inhibitors can target macrophages and reduce aerobic glycolysis, thereby promoting immune tolerance of HT (47). This suggests that targeted nano-

therapy of macrophages and DCs has great potential for application in transplantation medicine.

Immune allogeneic recognition-activated T cells are the main contributing factor in triggering the rejection of transplanted organs, while immune checkpoints are key modulators of the immune system for self-tolerance and prevention of autoimmunity (52). Dual targeting of immune checkpoint proteins by bispecific antibodies offers the possibility of immunosuppressive interventional drug development (53).

In addition, the current membrane-based nanovesicles (NVs) that are easy to prepare on a large scale have been shown to show the characteristics of long circulation, eliminating the disadvantage that traditional nanomaterials which are easy to be quickly removed from the blood circulation, and improving the clinical efficacy of nanomaterials. The functional properties of the cell membrane are retained in the membrane coating process, and they can effectively target or interact and bind with different protein molecules (54). Thus, the investigators designed the PD-L1/CTLA-4 dual-targeted exosome-like NVs. Additionally, they demonstrated that these NVs could enhance the immunosuppressive pathways of two key immune checkpoints, PD-L1/PD-1 and CTLA-4/CD80, which jointly inhibit T-cell activation and maintain peripheral tolerance and prolong the survival period of cardiac grafts (55). In addition, the targeted peripheral immune organs self-assembled NPs of the passive targeted delivery system can improve heart allograft rejection (56), and combined with ultrasonic means, nanobubbles loading with drugs can make the drug concentration increases, so as to improve the therapeutic effect of heart transplant rejection (57).

Macrophage-derived PD-L1/CTLA-4 NVs were also found to have a high potential to metastasize to lymphoid tissues (55). Actively targeted delivery of immunosuppressive drugs to lymph nodes (LNs) represents a major advance towards more effective treatment of immune-mediated diseases. Drainage LNs are the main site of immune activation, but so far, the chance is still rare to deliver drug molecules to the LNs after systemic administration. Active targeting of the LNs is a difficult task, and a larger difficult is the deeper visceral LNs may be the main effective site for transplantation therapy. High endothelial venule (HEV) is the unique postcapillary micro vein in lymphoid tissue (58). The MECA79 antibody can recognize peripheral node address in molecules expressed in endothelial veinlets (HEV) of LNs. Researchers have developed MECA79-encapsulated particles containing the immunosuppressive drug tacrolimus (TAC), and found it demonstrated the features of targeted delivery to LNs and found shown to prolong the survival of cardiac allografts in transplantation when injected intravenously (59). Selective delivery of NPs containing anti-CD40L encapsulated with MECA-79 antibody to LNs also significantly delayed the onset of allograft rejection while increasing the number of regulatory T cells (Tregs). Combined MECA-79-anti CD40L-NPs treatment with rapamycin resulted in a significant prolongation of allograft survival compared to soluble anti-CD40L and rapamycin respectively (60). Heterogeneous nano-delivery vectors modified with a chemokine CCL21-specific aptamer for LNs targeting significantly enhanced the accumulation of the loaded ISAs FTY720 in draining LNs and attenuated immunosuppression of distant peripheral immune organs, thus effectively prolonging long-term survival in a chronic mouse HT model (61). These studies demonstrate that LN-targeted drug delivery can achieve LN-specific immunomodulation to improve survival after HT through precise and localized immunomodulation, while minimizing the side effects of immunosuppression, providing a theoretical basis for the development of LNs-targeted nano-delivery systems and their translational applications.

Besides, long-term drug delivery using intravenous injection can bring financial and mental burden to patients, so researchers have also developed an oral LN-DDS, which uses bio-inspired β-glucan microcapsules (β-GM) to target low-dose TAC to LNs via the oral route, which can alleviate the acute rejection of cardiac allografts and exhibits low nephrotoxicity (62). The above studies show that the various antibodies or cell membrane modified nano-targeted delivery systems can effectively promote the tolerance of cardiac allografts by inhibiting the activation of immune cells and the activation of LNs.

Prevention and treatment of other complications after HT

In the long run, the success of HT is also limited by many other complications. CAV is an inflammatory-proliferative process that has uniquely diffused, with concentric stenosis as a hallmark of its pathology, which needs to reduce macrophage infiltration, inhibit pro-inflammatory factors, and stimulate gene expression of anti-inflammatory factors. On the other hand, due to the need to use immunosuppression to treat graft-related complications, non-graft-related complications are also on the rise. Infections have become one of the most common causes of

death in post-transplant follow-up (43). The microvascular deposition of fibrin and capillary antithrombin binding in the later stages of HT leads to coronary thrombosis, coronary occlusion, and coronary stenosis as well as cardiac enlargement which jointly leads the graft failure is the leading cause of late death (44,45,63,64). And the risk of developing new solid malignancies in 1–5 years after transplantation is up to 10% (46). Organic polymers can be developed as drug delivery carriers or drug release systems with good histocompatibility and low toxicity, improving drug bioavailability, delaying elimination half-life, and reducing drug dosage. Modification based on organic nanomaterials can also confer better stability, targeting, and traceability (65). Natural nanomaterials in the organism, such as liposomes, not only have a sizeable drug-loading capacity but also can deliver drugs efficiently via endocytosis (66). These nanotechnologies undoubtedly provide new ideas and approaches for the diagnosis and treatment of complications after HT.

Lipid nanoparticles (LDEs) can carry drugs in the circulation and targeted heart, and intravenous administration of either LDE-methotrexate (MTX) or LDE-paclitaxel (PACLI) has been shown to contribute to the improvement of CAV to varying degrees (67). In transplanted hearts, LDE-PACLI treatment reduced the width of the intima-media layer and inhibited the destruction of the medial layer without observing biotoxicity (68), whereas LDE-MTX treatment strongly ameliorated the stenosis of the vessels and their necrotic grades, which are the most typical features of CAV (69). In conclusion, organic polymers, natural nanomaterials, and antibody-modified nanocarriers enable the sustained release and high targeting of drugs such as immunosuppressive or inflammation ameliorating agents *in vivo*, as well as increase the uptake of therapeutic agents by cardiovascular tissues, which ultimately results in an effective prolongation of the drug's half-life, maintenance of immunosuppressive status, and antiproliferative effects. Non-invasive nanomedicine strategies can improve EC adhesion, spreading, and proliferation by affecting lipid levels, angiogenesis, inflammatory response modulation, and intra-arterial thrombosis. Meanwhile, smooth muscle cell proliferation and platelet cell adhesion are inhibited *in vitro*, which effectively improves the state of the hypercoagulable microvascular system *in vivo* after transplantation (70-74). In addition, the development of nanotechnology has facilitated the use of NPs as antimicrobial nanomedicines in the antimicrobial treatment of chronic and biofilm-associated infections (75). Due to their unique properties, nanomaterials are expected to be a powerful means of post-transplantation anti-infection, especially as effective antioxidants for treating sepsis, including sustainable nanosheets and cerium dioxide NPs (76,77). For example, due to the excellent reducing ability of nanoFe, researchers have developed nanoFe as a potential tool for the treatment of sepsis and septic myocardial injury, which has shown beneficial effects in treating myocardial injury mainly by reducing inflammation, inhibiting oxidative stress, improving mitochondrial function, and inhibiting apoptosis (78). Although there are no specific reports on clinical studies on nanomaterials science targeting the diagnosis and treatment of complications after HT, related nanomaterials targeted delivery systems are still under investigation, and are likely to be successfully transformed in the near future.

Diagnostic nanomaterials applied in HT

In addition to treatment, the key to preventing complications after transplantation is to closely monitor the patient's condition. HT recipients must undergo long-term follow-up after surgery to prevent and detect early post-transplant immune rejection and the adverse complications mentioned above. However, endomyocardial biopsy (EMB), the gold standard for diagnosing immune rejection, is an invasive and invasive test (79). Therefore, the monitoring of cardiovascular physiology, cardiac structure, and blood markers to determine the cardiovascular physiology, cardiac structure, and blood markers of post-transplantation patients through the use of nanotechnological means is necessary to reduce the frequency of the use of EMB, among which nano-imaging, nano-sensors, and nano-biomarkers are highly favored by researchers. Because of the particular pathogenesis of CVD, identifying unique, specific targets valuable for imaging in the cardiovascular is challenging. Moreover, when choosing the mode of *in vivo* cardiovascular imaging, the penetration depth and spatial resolution requirements as well as the invasive nature of the clinical imaging mode should also be considered (80). The primary imaging target remains the activated cells and molecules in inflammatory and immune responses.

Nano-imaging, especially the adoption of magnetic, acoustic, and optical nanomaterials and their combinations can produce signal contrast that matches their homologous imaging modalities. For example, NPs can carry a high concentration of targeted imaging tracers to yield higher

sensitivity and specificity, and it has the possibility of combining different optical or vibrational signatures for multiplexed imaging (6). Because of these advantages, it has become the prime candidate for therapeutic and diagnostic applications of CVD. The tracer effect of radioactive elements and the superparamagnetic property of iron oxide make inorganic nanomaterials as a potential imaging material (81). Based on a developed magnetic resonance imaging (MRI) visible light and T cell-targeted multifunctional polymeric nanocarrier, effective co-delivery of pDNA and superparamagnetic iron oxide NPs into primary T cells expressing CD3 molecular biomarkers was demonstrated. Moreover, in a rat model of HT, this multifunctional nanocarrier showed high efficiency in detecting acute post-transplantation immune rejection, where T-cell aggregation could be seen at the endocardium of the transplanted heart as a linear strong low-signal region on the MRI image. Meanwhile, noninvasive MRI could easily monitor the therapeutic effect during targeted gene therapy for immune rejection in heart transplant rats (82). In addition to MRI, imaging tests such as ultrasound and positron emission tomography/computed tomography (PET/CT), enhanced with nano contrast agents, have been endowed with the ability to monitor immune rejection after HT (83,84). Nano-sensors based on enzymatic cleavage or temperature can be stimulated to generate imaging signals after nanomaterials encounter with a molecular or physicochemical trigger. Immediate non-invasive enzyme cleavage nano-sensors [GzmB-responsive nanosensors (GBRNs)] can also be used for acute graft immune rejection detection, which can predict immune responses in transplanted mice with insufficient immunosuppressive treatment by utilizing the catalytic activity of ultra-small gold nanoclusters (AuNC) in combination with a urine assay, and it is a sensitive and rapid way of routinely monitoring transplanted allogeneic grafts (85). Implantable nano micro sensors can also be used for continuous disease monitoring and diagnosis in conjunction with molecular communication for health monitoring and drug delivery. In this way, early detection of released molecules associated with the shedding of arterial ECs *in vivo* as an early marker of adverse biological reactions to graft abnormalities becomes possible (8).

Developing post-transplantation cardiac adverse effects such as infarction and HF should also be possible for early prediction. Preferred biomarkers for diagnostic tests such as cardiac troponin (cTnT and cTnI) and natriuretic peptide [brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-pro-BNP)] usually require invasive modalities such as drawing of venous blood, which is inconvenient for long-term monitoring of patients. However, the detection of endogenous biomarkers in clinical samples (including blood, saliva, and urine) is usually hindered by background signals, requiring more sensitive and specific strategies. Nanomaterials have the advantage of detecting CVD-related molecules and cellular biomarkers by using magnetic and other physical and chemical properties to amplify signals and improve their sensitivity. Using nanomaterials to construct electroanalytical sensing platforms for the electroanalysis of emerging cardiac biomarkers can meet long-term patient monitoring needs and potentially benefit critical patient intensive care (7). For example, Radha Shanmugam *et al.* reported a multi-sensor based on a gold electrochemical platform decorated with zinc oxide nanorods, which could be used to determine cTnT and cTnI levels (86). A nano molecularly imprinted polymer (N-MIP) was developed and assembled on reduced graphene oxide (rGO) modified screen-printed graphite electrodes, which can also be used to detect cTnT (87). Hu *et al.* reported a novel enhanced photoelectrochemical sensor platform based on the sequential deposition of Nitrogen-doped ZnO nanopolyhedra and protoporphyrin IX to monitor BNP levels (88). The development of electrochemical sensing platforms in the field of monitoring the biomarkers of adverse cardiovascular reactions undoubtedly provides a feasible new scheme for monitoring the status of the cardiovascular system in patients after HT.

Expanding the donor pool: tissue engineering and xenotransplantation

Donor shortage is one of the main problems currently faced by HT (19). According to the statistics of The Global Observatory on Donation and Transplantation, by the end of 2021, there were 2,026 patients in European countries undergoing HT, while the number of recipients on the active waiting list in the same year was 8,548, of whom 362 died while waiting (89). How to expand the donor pool and solve the problem of increasing shortage of human organs suitable for transplantation is an urgent issue to be solved.

The cardiac tissue engineering strategy aims to combine functional cells with scaffold biomaterials to regenerate or repair damaged myocardium. The main challenge is to get appropriate cell sources with enhanced regenerative capacity and suitable biomaterials. The extracellular matrix (ECM) of myocardial tissue is well-organized and has

an anisotropic structure that supports and guides tissue formation of dissociated cells. However, direct printing of ECM proteins has proved to be difficult due to the failure of conventional *in vitro* culture systems to adequately mimic *in vivo* micro-environmental properties (85). The integration of nanotechnology and polymeric biomaterials can modulate interactions between natural cells and biomaterials, providing various dimensional cues within the cytoplasmic matrix to regulate the behavior of MCs or stem cells, and stimulate the rapid formation of functional tissues (90). A neonatal-scale human heart with collagen has been printed once, the reproduction of all anatomical structures contained in the 3D model of the heart is confirmed by μCT imaging, demonstrating that collagen printing is a platform that can be used to build advanced tissue scaffolds for a variety of organ systems (91). In the tissue-engineered erection of 3D artificial hearts, multiple micro-environmental cues play an indispensable role in stem cells' survival, self-renewal, and differentiation. A wide range of nanomaterials provides instructive signaling cues in the micro-environment to regulate stem cell fate into specific profiles for controlling its behavior. Among them, developing conductive biomaterials is crucial to realize the desired functions (92). Park *et al.* demonstrated that organic nanomaterials rGO sheets and that can improve cardiac repair when combined with human bone marrow mesenchymal stem cells (hMSCs), while Lee *et al.* doped graphene into the substrate of cultured human embryonic stem cells (hESCs) and demonstrated that it promotes gene expression of cardiac-specific ECM components (93-95). Using the metallic material aurum coated on microspheres and doping hESC-derived embryoid bodies (EBs) into it, the gene expression in mesodermal and cardiac mesodermal lineage cells is found to promote, possibly through enhanced Cx43 expression of hESC-derived EBs and electrically coupled to the recipient cardiomyocytes (96). Kim *et al.* produced substrates with nanoscale features to mimic the anisotropic structure of the natural cardiac ECM, and cardiac balloon-derived cells (CDCs) cultured on the substrates were able to align, mature, and differentiate into a monolayer of MCs, exhibiting features of intercellular junctions capable of spontaneous beating and interconnectivity. In addition, the inoculated cells showed increased expression of Cx43 cardiac markers with a corresponding increase in wall thickness and collagen organization (97,98). The above studies suggest that tuning the cell-nanomaterial interface is key to developing next-generation advanced scaffolds for cardiac tissue engineering. While a fully functional 3D bio-printed heart has not yet been realized, the ability to begin to build the structure, and realize the mechanical and biological properties of a complete heart is already in place.

In addition, many studies are devoted to using nanotechnology to improve and repair necrotic myocardium after a heart attack (99-102), suggest that the history of developing HF after a heart attack could be avoided to some extent, and more patients may be able to avert transplantation or delay that. And in transplantation, nano-tissue engineering can also provide opportunities for patients to improve heart function and promote myocardial regeneration and repair during recovery. Chen *et al.* made multilayered chitosan and silk protein-modified electrostatically spun cellulose nanofibers by using layer-by-layer coating technology and developed nanofiber patches to improve the micro-environment of ventricular remodeling (103). When applied to the infarct injury region during surgery, the patch may significantly inhibit ventricular remodeling and inhibit myocardial fibrosis. More surprisingly, Malki *et al.* developed a sutureless nano patch in which the NPs were locally heated under near-infrared irradiation, allowing the patch to be thermally immobilized to the cardiac defect, providing a sutureless method of cardiac patch implantation that minimizes the risk of additional intraoperative injury to the patient (104). During surgery, the intra-pericardial delivery techniques via nanomaterial-modified catheters, pumps, and patches for delivering targeted therapeutic drugs can facilitate increasing efficacy and drug bioactivity while reducing systemic adverse effects after transplantation (105). The emergence and application of these nano-consumables can help to increase the success rate of HT, reduce the incidence of postoperative complications, and improve the prognosis of transplant recipients.

And it is worth mentioning that obtaining allogeneic donors through gene editing techniques has also become a hot development in recent years. Advances in xenotransplantation confirm that transplantation of organs derived from pigs into non-human primates can survive for many years, stimulating interest in research on alleviating organ shortage. A 57-year-old patient with non-ischemic cardiomyopathy received a heart from a transgenic porcine-derived pig with 10 gene edits (106), which is undoubtedly a major milestone in xenograft HT. Xenotransplantation requires scientific advances to overcome the evolutionary distance between species, zoonotic spread to human reservoirs, hyperacute rejection, and allograft failure caused by thrombotic

microangiopathy. Gene editing can make cardiac xenografts more compatible for transplantation into humans. Based on the increasing use of transgenic pigs for biomedical purposes, the potential for integrating nanotechnology approaches into *in vitro* porcine embryo production systems is enormous, and it has already been applied in embryo labeling and characterization, gamete and embryo delivery, sperm enrichment and sorting, sperm-mediated gene transfer, and three-dimensional culture systems for secondary follicles (107). Due to the instability of most delivered substances, and the intracellular delivery efficiency of CRISPR/Cas9 is low, nanotechnology can also make full use of the delivery system to overcome the above biological obstacles and the targeted release of related substances (108,109). For example, extracellular vesicles are promising for transporting CRISPR-Cas9 RNA-guided nucleic acid endonucleases [ribonucleoproteins (RNPs)] throughout the body. Researchers have designed a tetrahedral DNA nanostructure (TDN) that is coupled to a DNA aptamer and can realize specific cellular targeting by cholesterol anchoring (110). In addition, NPs deliver plasmid DNA to simultaneously induce genome editing of two genes and transgene expression in ECs, suggesting it is a powerful tool that can be used for cardiovascular research and potentially gene therapy (111). Current researches are still limited to animal experiments or cellular level, and there is still a lot of room for exploration of unspecified mechanisms and pathways, including how to improve the targeting of nano complexes and reduce their biotoxicity through rational modification and other methods. Although some therapeutic techniques have been applied in clinical trials, they are still limited to the study of other organs, such as the liver and kidney, and the exploration of HT still has a long way to go in these aspects.

Conclusions

In summary, in current research, the preclinical studies of nanomaterials are more focused on the development of NDDS, increasing the supply of donor organs and preventing graft rejection, and inducing tolerance by maintaining graft viability, treating IRI, and preventing graft rejection. However, many issues still need to be solved. Firstly, many studies lack the long-term toxicological profile of NPs administration and characteristic information about their distribution, metabolism, and excretion, which poses specific difficulties in controlling the safety of DDSs (112). Whether nanomedicines accumulate in high concentrations in organs such as the liver, kidney, and spleen may lead to damage to the corresponding organs or an imbalance of elements in the body? These safety issues are complex problems that must be faced in future research (65,113). Secondly, most nanotherapeutic drugs must be administered intravenously, challenging patient compliance. Ideal nanotherapeutic drugs should be stable, easy to store, orally administered, with long dosing intervals and low dosing frequency, etc. The use of novel organic NP capsules (e.g., polysaccharide-glucan, starch, cellulose) may provide a solution for the biosafety of nanomaterials and improve patient compliance (62,114), and the research on the biodegradability and safety of these nanomaterials will be at the forefront in the future. Finally, many studies have focused on the delivery of single compounds. However, some clinical studies have shown that multi-drug strategies for deceased donor organs have shown improvement in other organs' transplantation (115), whereas there are no relevant studies in HT. Since immunosuppression also typically involves antibody therapy and pharmacologic intervention regimens, and long-term graft survival may also require more than one NPs delivery therapy, future research may have to be devoted to adding the ability for NPs to provide patients with multi-drug combination interventions. Although most of the researches in the field of HT are in the preclinical exploratory stage, their role in improving the prognosis of transplant recipients and breaking the current dilemma of HT is clear. Therefore, to continue to improve the preclinical research such as pharmacology and toxicology, and to carry out a large number of in-depth studies on the application of new nanotechnology or materials such as nano-robotics, nano-genetic engineering, carbon nano-tubes, and nano-photothermal materials in the field of HT, and to promote the entry of nanomedicines into the clinical research is the subject of our future attention.

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