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Review

A Half-Century of Heterotopic Heart Transplantation in Mice: The Spearhead of Immunology Research

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Abstract: Since the success of solid organ transplants, such as human kidneys, livers and hearts, from the 50s to the 60s in the last century, the field of organ transplantation has progressed rapidly. Mainly due to modifications in surgical operation techniques and improvements in immunosuppressive therapy regimes, organ survival time can now be greatly prolonged. This progress has also been dependent upon the availability of appropriate animal models for organ transplantation. Therefore, the mouse heart transplantation model has developed into an irreplaceable research model for solid organ transplantation, providing indelible contributions to the field. In this review, we will provide an overview of the technical developments in murine heart transplantation, as well as its historical and current role for alloimmune research. Further, we will describe its current fields of application and its scientific achievements before we discuss potential future applications.

Keywords: murine transplantation; heterotopic heart transplantation; immunology

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1. The Historic Implementation of Animal Models for Transplantation Research

Since the success of solid organ transplants, such as human kidneys, livers and hearts, from the 50s to the 60s in the last century [1–3], the field of organ transplantation has progressed rapidly. Mainly due to modifications in surgical operation techniques and improvements in immunosuppressive therapy regimes, organ survival time can now be greatly prolonged. This progress has also been dependent upon the availability of appropriate animal models for organ transplantation.

Beginning in 1907, Carrel et al. invented the vascular anastomosis technique and tried to apply it to the transplantation of solid organs, such as forelimbs, ears and kidneys, in dogs [4,5]. Thus, he can be viewed as one of the founders of solid organ transplantation because he successfully tackled one of the biggest surgical obstacles, enabling organ transplantation. For this achievement, he subsequently received the Nobel Prize in 1912.

During the next fifty years, scientists were continuously trying to establish and optimize the transplantation of various solid organs. However, due to alloimmune reactions leading to acute or chronic transplant rejection, the long-term survival of donor organs after transplantation represented a major limitation for broad applications. Hence, various experimental models mimicking transplantation in animal models were established to find a solution for this problem. Before the 1960s, avascular skin grafts were the only successful animal model to study alloimmunity after transplantation [6], but since then, rat kidney organ transplantation models have been established. This model used the so-called porto-cavity shunt technique developed by Lee et al. [7,8]. In 1964, the first rat heart transplantation model was reported by Abbott and colleagues [9]. Initially, Abbott's model was performed with end-to-end anastomoses between the vessels of the donor and recipient. In 1969, Ono and Lindsey refined Abbott's model from end-to-end anastomoses to end-to-side anastomoses [10], thus eliminating the risk of paraplegia in the recipient. This technique significantly improved the model and, subsequently, made it more popular. Based on this technique, Corry et al. established the first successful mouse heart transplantation model in 1973 [11]. Also, in the same year, a mouse kidney transplantation model was successfully established by Sknoskiewicz et al. [12].

Compared with other animal model organisms (e.g., dogs, pigs, baboons) [13–16], mouse models display certain advantages in terms of experimental costs, the possibility of genetic manipulations and a higher reproducibility of experimental results. This is the major reason why they quickly became the mainstream animal model in the area of transplantation research. However, the technique to successfully transplant mouse kidneys is relatively complicated. Hence, its availability is limited and restricted to a few expert groups. Therefore, it is less widely applied to scientific studies [17]. Other mouse organ transplantation models, such as those of the liver, pancreas, small intestine, ear, artery and cornea, were subsequently developed in the 1980s and 1990s [18–25]. Thus, there are various problems, such as low success rates, complicated operation techniques and unstable graft perfusions. In contrast, the heart transplantation technique in mice is easier to perform, displays fewer complications and enables more stable and reproducible long-term graft survival. Therefore, it is currently more widely applied by various scientists [26–28].

2. Surgical Procedures of Mouse Heart Transplantation

Mouse heart transplantation is characterized by delicate microsurgery. The operation requires a lot of practice to achieve satisfactory success rates [29], which is also the biggest factor for limiting its use. In order to reduce the difficulty of the operation and improve its success rate, researchers have been ambitious in improving the applied surgical techniques. With continuous efforts for half a century, the operation time and success rate of this technique has been greatly improved. The main transplant methods are summarized in Figure 1 and described in the following subsections in chronological order based on their first application in the field.

2.1. The Cervical Heterotopic Heart Transplantation Technique

In 1991, Chen et al. reported on a cervical anastomosis technique where the innominate artery of the donor heart and the right common carotid artery of the recipient were anastomosed first using a 11/0 suture (Figure 2a). Subsequently, the pulmonary artery of the donor heart and the external jugular vein of the recipient were anastomosed using a 14 µm suture [30]. This technique has not been used on a large scale due to mismatching between the donor and recipient vessel lumen, leading to difficulties during the operation. In addition, vascular distortion, thrombosis and obstruction of the vessel anastomosis are more likely and have been reported to limit the surgical success rate of this technique [31]. Hence, this method is less used nowadays.

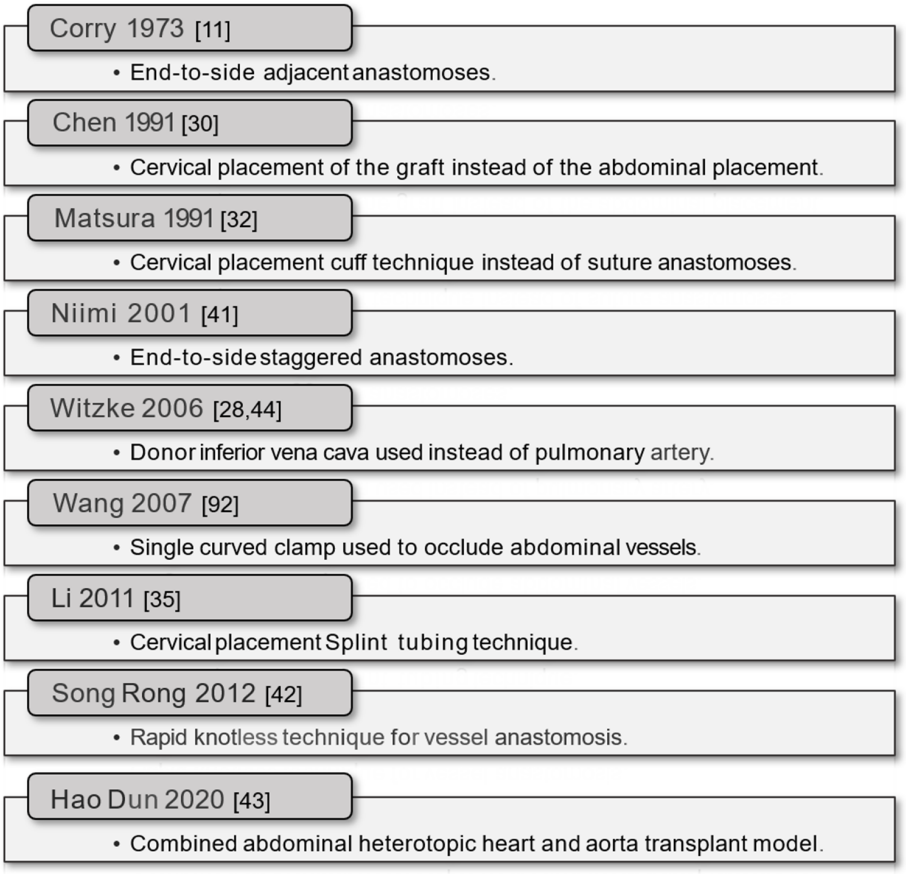

Figure 1. Timeline of key breakthrough events for this technology in mice.

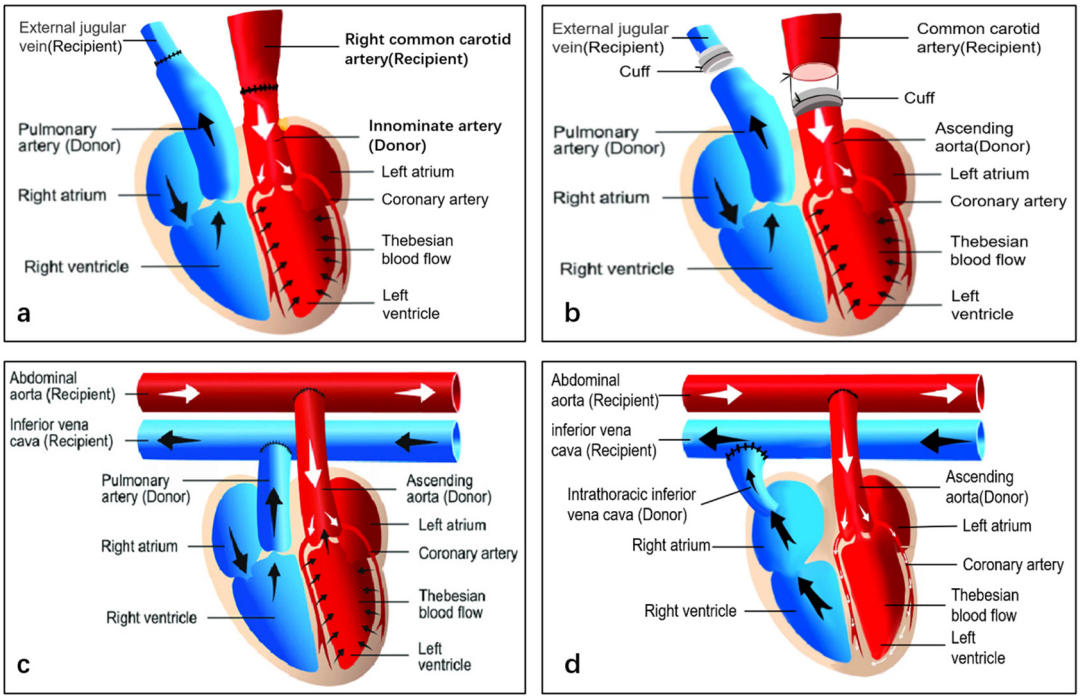

Figure 2. Surgical procedures of mouse heart transplantation. The cervical heterotopic heart transplantation technique (**a**). The cuff cervical heart transplantation technique (**b**). The heterotopic abdominal heart transplantation technique (**c**). The modified heterotopic abdominal heart transplantation technique (**d**). Arrows depict the direction of blood flow.

2.2. The Cuff Cervical Heart Transplantation Technique

In the same year as Chen et al., Matsura and colleagues invented a simplified mouse cuff cervical heart transplantation technique (Figure 2b) [32]. This method uses Teflon cuffs placed onto the recipient's external jugular vein/common carotid artery and the donor's pulmonary artery/aorta and ties a suture ligature around the connection. The cuff technique is the simplest surgical operation technique for a heart transplantation, and the model is less invasive [33,34]. However, the technique was mostly used for short- and medium-term experiments. In 2011, Li et al. reported a modified splint tube technique (STT) based on the cuff technique (CT) [35]. With the development of new vascular materials and the increasing availability of 3D printing technologies [36,37], this and other modifications to the cuff technique are expected to lead to considerable enhancements in surgical outcomes still to be proven in future studies.

2.3. The Heterotopic Abdominal Heart Transplantation Technique

The heterotopic abdominal heart transplantation technique was initially developed in rats [9] but is most widely used for murine heart transplantations. In this technique, the donor aorta and the recipient abdominal aorta are anastomosed, while the pulmonary artery is anastomosed to the recipient's inferior vena cava (Figure 2c) [29,38–40]. This technique achieves long-term survival of the transplanted heart in the recipient's abdominal cavity through end-to-side anastomosis, and it avoids complications caused by differences in the size of the vascular lumen in end-to-end anastomosis. Improvements in this technique are also quite elaborate and progressive. Niimi et al. (2001) proposed that the opening positions of arteries and veins should be staggered [41], Song Rong et al. (2012) proposed a continuous suture technique without a knotted end at the end-to-side anastomosis for the abdominal vessels [42] and Dun et al. (2020) reported a combined abdominal heterotopic heart and aorta transplantation model for mice [43]. Although this traditional way of operating is considered difficult and requires that the surgeon has extensive training, the complications are relatively small.

2.4. The Modified Heterotopic Abdominal Heart Transplantation Technique

In 2006, Witzke et al. invented a modified method of heterotopic abdominal transplantation using the intrathoracic inferior vena cava (IIVC), instead of the pulmonary artery of the donor heart, for the anastomosis to the inferior vena cava of the recipient (Figure 2d) [28,44]. After a long-term comparative study by our team, we found that even though there are no differences in long-term survival rates for this model compared with traditional pulmonary artery anastomosis, this modified technique facilitates anastomotic vessel reconstruction, thus reducing the difficulty of abdominal heart transplantation in mice [45]. In addition, the length of the donor inferior vena cava is significantly longer than that of the pulmonary artery, which also provides anatomical possibilities to use tissue engineering techniques, such as "nanofiber scaffolds" and 3D micro-stent printed "chimney" technologies [46–48], for more rapid intraperitoneal transplantation in the future.

3. Application Fields of Mouse Heart Transplantation

Heart transplant models in mice represent an important tool to investigate a variety of scientific aspects that are current or emerging obstacles in transplantation medicine. To provide a comprehensive overview of these research fields, we performed a medicine database search, as depicted in Figure 3. Published articles involving the use of this technology within the past 20 years were summarized, highlighting the applications and the achievements of this technology.

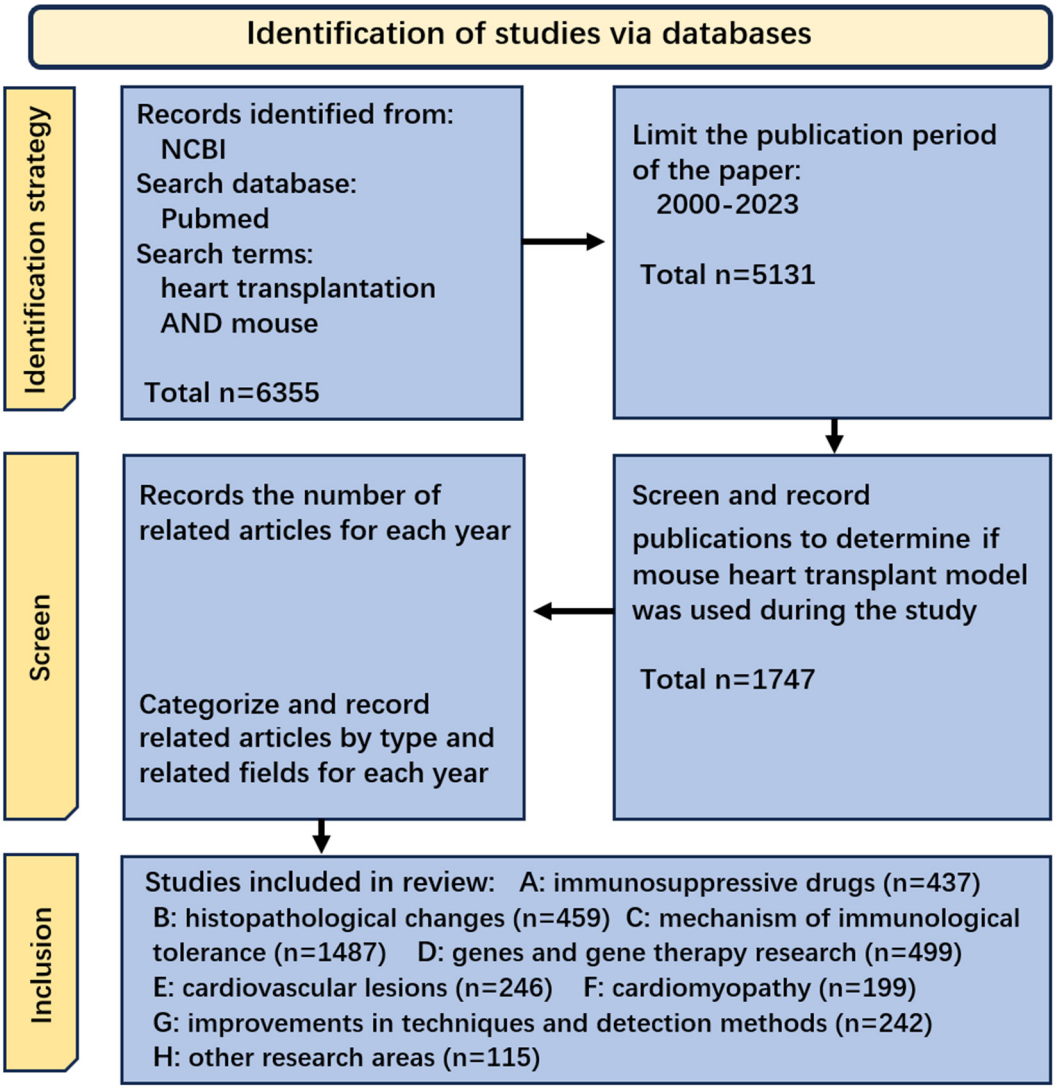

Figure 3. Identification of relevant scientific articles.

For this purpose, a literature search was performed using PubMed over the years 2000–2023. The search terms used were heart transplantation AND mouse. Publications were filtered and included as depicted Figure 3 (identification of studies). In the identified articles, the achievements from using this technology and the respective research scope which can mainly be categorized by several aspects (see Figure 4) will be discussed in the following subsections.

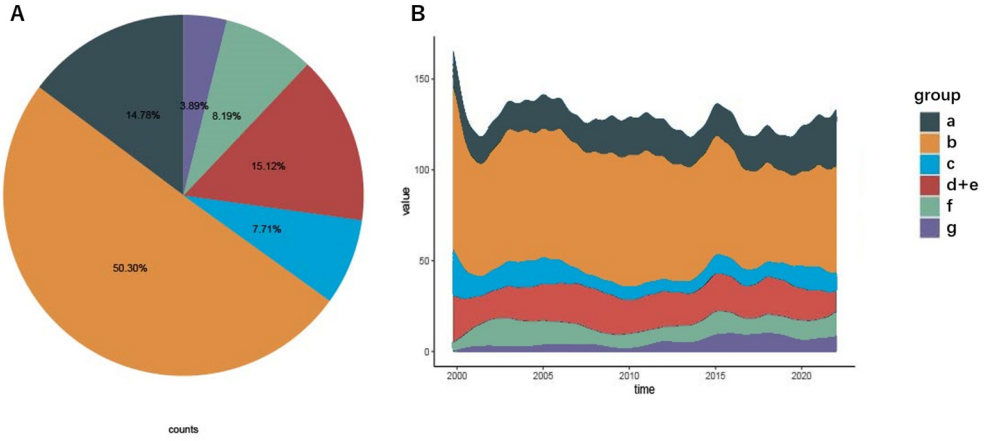

Figure 4. Review of the heart transplant literature. Categorization of the research scope in mouse heart transplantation (**A**), dynamic heat map of articles published over time with respect to research background (**B**). In the last two decades, nearly half of the applications of mouse heart transplantation technologies have focused on studying the mechanism and/or induction of immune tolerance (**A**). By examining the year–quantity heat map, we see that the application of this technology in the mechanism of immunological tolerance has a large compartment and is stable compared with two decades ago, and its application in other emerging fields has also increased (**B**). We identified 1747 identified articles that used mouse heart transplantation model technology. These reports were categorized into eight groups based on topic (**a**–**g**): articles focused on research investigating the efficacy of immunosuppressive drugs (**a**); articles studying the mechanism of immunological tolerance (**b**); articles conducting research on the role of transplant-relevant genes and gene therapy (**c**); articles conducting research on cardiovascular lesions (**d**); articles conducting research on cardiomyopathy (**e**); articles describing improvements in surgical techniques, novel therapeutics or the development of new inspection and detection methods (**f**); articles focusing on other research areas (e.g., age and sex factors, side effects of radiotherapy, transfusion blood group research) (**g**).

3.1. Alloimmune Response and Immune Tolerance Mechanisms

One of these aspects is the investigation of the alloimmune response or the targeted development of tolerance mechanisms. The heart transplantation model in mice is of great value, as the HLA (human leukocyte antigen) system and H − 2 in mice are similar to each other. A large number of various mouse strains implemented for the clarification of a variety of immunological research queries have been cultivated [49], and it can be said that the understanding and progress of modern human immunology is based on a variety of these findings. Mouse heart transplantation models, especially those using various immunodeficient mouse strains, provide an excellent and reproducible quantification tool for studying the complexity of the immune system. According to our statistics, in the past 20 years, 499 papers related to mouse heart transplantation technology used special transgenic/gene-deficient mouse strains, accounting for 29% of the total. A few to mention are the Scid and RAG-2 mouse strains lacking functional T cells and B cells [50], nude mice lacking functional T cells, 129/Sv mice demonstrating B cell dysfunction and beige mice showing poor NK cell function. Scientists have extensively used various specific strains of mouse HTX models to study the alloimmune response and immune tolerance mechanisms [49–54]. For instance, by using this model, Hasgur et al. revealed the essential role of B cell-derived IL-1β and IL-6 during homeostatic T cell expansion [50]. Sharma et al. reported that they used a mouse HTX model to study the relationship between myocardial myosin and cardiac graft failure (acute immune rejection) [51]. Young et al. reported the use of this model to study the effect of Listeria (Lm) bacterial infections on immune tolerance in cardiac allografts [52]. On the other hand, it is important to note that some groups have performed heart transplantation between rats and mice to investigate the immunological mechanism of acute rejection in a xenotransplantation setting [53–56].

3.2. Gene Therapy and the Impact of Genes and Gene Mutations on Long-Term Survival

Another research aspect is the topic of genetic engineering, gene therapy and the impact of genes and gene mutations on long-term survival. It is an invaluable advantage that mouse heart transplantation models can be used to study organ transplantation in syngeneic, transgenic and knockout strains [57,58]. Knockout of a single selected gene can cause a specific immunodeficiency in mice [59–61], while activation/insertion of a new gene of interest can alter a certain immune function [62,63]. Today, the number of molecular genetic knockout models in mice has exceeded 1200, and some special transgenic "humanized mouse models" have been developed to better research human diseases [64–66]. Research on these specific genes represents an irreplaceable reference value for human organ transplantation, as well as autoimmune and hereditary diseases caused by gene defects [67–70]. Roussoulieres et al. successfully used a mouse heart transplantation model to identify key genes implicated in the acute rejection of heart allografts [58]. Just recently, the first short-term success of a pig-to-human heart xenotransplantation attracted a lot of attention. The lack of galactose-α1, 3-galactose epitope (GTKO) [71–73] (α1, 3-galactosyltransferase knockout) used in donor GT-KO pigs for transplantation was initially studied on the basis of a mouse heart transplant model. It was McKenzie et al. who described in mice the rejection of Gal+ mouse hearts by mice lacking Galα(1,3)Gal (Gal−/−) and, subsequently, raised attention that the α1, 3-galactosyltransferase epitope is a major trigger for xenogeneic hyperacute rejection (HAR) and that its pathogenesis more closely reflects the combination of pig and primate [74]. To study the crossmatch of humans with pigs, many transplant research groups have used the GALT/KO humanized mouse HTX model for further preliminary studies [65,71,73,75]. The establishment of a reliable heart transplantation technique in mice has inestimable value, for which genetically modified mice have provided profound proof. For instance, transgenic expression of CD39, CD47, tissue factor pathway inhibitor (TFPI) and endothelial protein C receptor (EPCR), the key components of thromboregulation that affect hemostasis, have also been reported in previous studies using mouse heart transplantation technology [76,77].

Many more examples can be mentioned here for using gene knockout mouse transplantation models, such as Zhang et al., who determined the site and mechanism of suppression by regulatory T (Treg) cells using KO-chemokine receptor mice for CCR2, CCR4, CCR5 and CCR7. They investigated the homing behavior of alloantigen-specific Foxp3$^+$ Tregs migrating sequentially from the transplant into the secondary lymphatic organs of tolerant animals. Zhang et al. showed that sequential migration from blood to the target tissue and to the draining lymph nodes is required for Treg cells to differentiate and fully execute their suppressive function. The Bromberg group further, and more elegantly, showed in subsequent work that L-selectin (CD62L)-dependent T cells homing to lymph nodes (LNs) are required for heart allograft tolerance induction, clearly showing the important role of lymphoid compartments [78,79]. Hu et al. found that p53 is involved in the cardiac apoptosis that is triggered in the process of an alloimmune reaction and that prolonged survival of heart allografts can be achieved when p53 is lacking [80].

3.3. Immune Activating/Suppressing Drug Research

Various new drug compounds that are generated with the purpose of selectively activating regulatory or inhibitory components of the immune reaction must undergo a large number of repeated animal tests during research and development. Including molecular probes, monoclonal antibodies and various other reagents, these application tests in mice are far more extensive than in other experimental animal settings [81–83]. Moreover, due to the small size of mice, these tests typically cost a third as much due to reduced costs to raise and house them in comparison to rats, and the tests require only a tenth of the drug's dose. Therefore, from the perspective of drug development costs, the mouse experimental setup is currently one of the most favorable, cost-effective and, from the immunological point of view, ideal mammalian models. Therefore, the mouse heart transplantation model has also been extensively used in the research and development

of drugs for organ transplantation, such as cyclosporine, cyclophosphamide, tacrolimus and rapamycin [84–88]. There are also some reports in which scientists used this model to investigate pharmacokinetic drug delivery. For instance, when Zhou et al. used this model, they observed that prodrug-assembled nanoparticle scaffolds carrying the mammalian target of rapamycin complex kinase inhibitor (TORKinib) compounds can significantly extend the survival of grafts through inducing immune suppression [89]. Another example is the work of Zhang et al., who reported that this model was used to study allograft tolerance in cyclophosphamide-induced tolerance [90]. Furthermore, Zhang et al. used this model to study the combined use of a blocking monoclonal antibodies against CD45RB and cyclophosphamide after transplantation and found a significant prolongation in xenograft survival [91]. Wang et al. reported that they used this model to study the role of cytokines in regulating the pattern of rejection and recipient susceptibility to cyclosporine (CsA) in a mouse cardiac allograft model [92]. Last but not least, Moffatt et al. used this model to investigate the effect of tacrolimus on tolerance induction in a model implementing a CD4/CD8 blockade [93].

3.4. Ischemia–Reperfusion(I/R) Injury and Cardiovascular Disease Research

The mouse heart transplantation model is also widely implemented in the study of ischemia and reperfusion (I/R) injuries, as well as to investigate the development of cardiovascular lesions [94–98]. The model supports researchers to investigate specific time frames in the damaging patterns after ischemia–reperfusion in the transplanted organ to study the effects of ischemia [29,99]. Fukunaga et al. used this model and discovered that the antagonistic translation factor nuclear factor erythroid 2-related factor 2 (Nrf2) is protective in the I/R injury setting and in cardiac allogamy vasculopathy [98]. Ban et al. found that I/R injury was closely related to the downregulation of the β-catenin pathway and the upregulation of ROCK1 and PTEN expression using a mouse heart model [100]. Hasegawa et al. applied it to study the difference between cardiac allograft vasculopathy (CAV) and atherosclerosis [101]. Sumi et al. and Benke et al. both described the application of this technique in their studies of cardiac remodeling caused by heart failure, which can be used to study cardiac remodeling in mechanically unloaded hearts in order to address the underlying mechanisms [29,102].

3.5. Other Fields

The mouse heart transplantation model has also been applied to investigate sex and age differences after transplantation [103–105], the effect of diet and exercise on transplant function and survival outcomes [106,107], research on ABO-incompatible transplantation [108,109], the identification of cellular and protein functions [110–113], the invention and validation of new testing technologies [114–117] and many more. For instance, Daly et al. applied this model to prove the potential of positron emission tomography (PET) to be a specific, sensitive and quantitative diagnostic test in the detection of transplant rejection [115]. Flögel et al. reported this model to investigate the MRI-based noninvasive detection of allograft rejection in the early posttransplant stage [116].

Habertheuer et al. also used this model to find that donor tissue-specific exosome analysis can noninvasively monitor early acute rejection after transplantation with high precision [118].

4. Current Problems and Prospects for the Future

Current immunosuppressive therapies have been clinically effective in preventing and reversing acute rejection after transplantation. However, the ultimate goal of long-term transplant survival has not been fulfilled by developing this revolutionary breakthrough in the past two decades [119], so there is still a long way to go. Many researchers and clinicians are convinced that xenotransplantation and the induction of immune tolerance will be an important development to substantially improve transplantation medicine in the future. The establishment of a suitable animal model that mimics human organ

transplantation is an indispensable condition to achieve this goal, and all the researchers contributing to the supply and optimization of the mouse heart transplant model have helped to make great progress in this direction. Unfortunately, there is no animal model that truly meets 100% of the ideal criteria reflecting the clinical setting. Although the HTX model in mice truly is accompanied by some problems, such as technically complex and delicate surgery compared with other large animal transplant settings, this can be met by long-term microsurgical training to reach sufficient success [29]. A perspective to improve this obstacle will be the founding and support of a specific mouse transplantation training class to impart the required expert knowledge. Importantly, to study and tease out different mechanisms of acute and chronic alloimmune rejection, as well as to determine aspects in evolving techniques that can induce immune tolerance for bench-to-bedside transfer in humans, it is still an irreplaceable animal model at this stage, as it offers an almost unlimited variety with which to implement genetic engineering to inactivate or remove one or more specific genes of interest. We believe that, with the development of genetic engineering technology, microsurgery technology and new biomaterials technology, the mouse HTX organ transplantation model will become easier to use and surgery procedures more effective, which will lead to wider applications and, thus, will continue to promote the development of transplantation research in humans.

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References

1. Harrison, J.H.; Merrill, J.P.; Murray, J.E. Renal homotransplantation in identical twins. *Surg. Forum* **1956**, *6*, 432–436.
2. Murray, J.E.; Merrill, J.P.; Harrison, J.H. Kidney transplantation between seven pairs of identical twins. *Ann. Surg.* **1958**, *148*, 343–359. [CrossRef]
3. Starzl, T.E.; Marchioro, T.L.; Porter, K.A.; Brettschneider, L. Homotransplantation of the liver. *Transplantation* **1967**, *5*, 790–803. [CrossRef] [PubMed]
4. Carrel, A. The surgery of blood vessels etc. *Bull. Johns Hopkins. Hosp.* **1907**, *18*, 18–28.
5. Plenter, R.J.; Zamora, M.R.; Grazia, T.J. Four decades of vascularized heterotopic cardiac transplantation in the mouse. *J. Investig. Surg.* **2013**, *26*, 223–228. [CrossRef] [PubMed]
6. Billingham, R.E.; Krohn, P.L.; Medawar, P.B. Effect of cortisone on survival of skin homografts in rabbits. *Br. Med. J.* **1951**, *1*, 1157–1163. [CrossRef] [PubMed]
7. Lee, S. An improved technique of renal transplantation in the rat. *Surgery* **1967**, *61*, 771–773. [PubMed]
8. Lee, S.H.; Fisher, B. Portacaval shunt in the rat. *Surgery* **1961**, *50*, 668–672. [PubMed]
9. Abbott, C.P.; Lindsey, E.S.; Creech, O., Jr.; Dewitt, C.W. A Technique for Heart Transplantation in the Rat. *Arch. Surg.* **1964**, *89*, 645–652. [CrossRef] [PubMed]
10. Ono, K.; Lindsey, E.S. Improved technique of heart transplantation in rats. *J. Thorac. Cardiovasc. Surg.* **1969**, *57*, 225–229. [CrossRef]
11. Corry, R.J.; Russell, P.S. New Possibilities for Organ Allografting in the Mouse. In *Immunological Aspects of Transplantation Surgery*; Calne, R.Y., Ed.; Springer: Dordrecht, The Netherlands, 1973; pp. 279–295.
12. Skoskiewicz, M.; Chase, C.; Winn, H.J.; Russell, P.S. Kidney transplants between mice of graded immunogenetic diversity. *Transplant. Proc.* **1973**, *5*, 721–725. [PubMed]
13. Pabst, R. The pig as a model for immunology research. *Cell Tissue Res.* **2020**, *380*, 287–304. [CrossRef] [PubMed]
14. Pressler, B.M. Transplantation in small animals. *Vet. Clin. N. Am. Small Anim. Pract.* **2010**, *40*, 495–505. [CrossRef]
15. Dehoux, J.P.; Gianello, P. The importance of large animal models in transplantation. *Front. Biosci.* **2007**, *12*, 4864–4880. [CrossRef] [PubMed]

16. Graves, S.S.; Mathes, D.W.; Storb, R. Induction of Tolerance Towards Solid Organ Allografts Using Hematopoietic Cell Transplantation in Large Animal Models. *OBM Transplant.* **2019**, *3*, 24. [CrossRef] [PubMed]
17. Mannon, R.B.; Griffiths, R.; Ruiz, P.; Platt, J.L.; Coffman, T.M. Absence of donor MHC antigen expression ameliorates chronic kidney allograft rejection. *Kidney Int.* **2002**, *62*, 290–300. [CrossRef] [PubMed]
18. Qian, S.G.; Fung, J.J.; Demetris, A.V.; Ildstad, S.T.; Starzl, T.E. Orthotopic liver transplantation in the mouse. *Transplantation* **1991**, *52*, 562–564. [CrossRef] [PubMed]
19. Squiers, E.C.; Kelley, S.E.; West, J.C. Small bowel transplantation in the mouse: Development of a model. *Microsurgery* **1992**, *13*, 345–347. [CrossRef]
20. Purcell, L.J.; Mottram, P.L.; Green, M.K.; Mandel, T.E. Transplantation of the segmental pancreas in STZ-treated diabetic mice. *Transplant. Proc.* **1992**, *24*, 236–237. [PubMed]
21. Jiang, J.; Humar, A.; Gracia, B.; Zhong, R. Surgical technique for vascularized ear transplantation in mice. *Microsurgery* **1998**, *18*, 42–46. [CrossRef]
22. Chereshnev, I.; Trogan, E.; Omerhodzic, S.; Itskovich, V.; Aguinaldo, J.G.; Fayad, Z.A.; Fisher, E.A.; Reis, E.D. Mouse model of heterotopic aortic arch transplantation. *J. Surg. Res.* **2003**, *111*, 171–176. [CrossRef] [PubMed]
23. Dietrich, H.; Hu, Y.; Zou, Y.; Dirnhofer, S.; Kleindienst, R.; Wick, G.; Xu, Q. Mouse model of transplant arteriosclerosis: Role of intercellular adhesion molecule-1. *Arterioscler. Thromb. Vasc. Biol.* **2000**, *20*, 343–352. [CrossRef] [PubMed]
24. Zhang, E.P.; Schulte, F.; Bulfone-Paus, S.; Hoffmann, F. The effect of corticosteroid and cyclosporin A on murine corneal allograft rejection. *Graefe's Arch. Clin. Exp. Ophthalmol.* **2000**, *238*, 525–530. [CrossRef] [PubMed]
25. Boardman, D.A.; Philippeos, C.; Fruhwirth, G.O.; Ibrahim, M.A.; Hannen, R.F.; Cooper, D.; Marelli-Berg, F.M.; Watt, F.M.; Lechler, R.I.; Maher, J.; et al. Expression of a Chimeric Antigen Receptor Specific for Donor HLA Class I Enhances the Potency of Human Regulatory T Cells in Preventing Human Skin Transplant Rejection. *Am. J. Transplant.* **2017**, *17*, 931–943. [CrossRef] [PubMed]
26. Nagano, H.; Libby, P.; Taylor, M.K.; Hasegawa, S.; Stinn, J.L.; Becker, G.; Tilney, N.L.; Mitchell, R.N. Coronary arteriosclerosis after T-cell-mediated injury in transplanted mouse hearts: Role of interferon-gamma. *Am. J. Pathol.* **1998**, *152*, 1187–1197. [PubMed]
27. Tao, R.; Wang, L.; Han, R.; Wang, T.; Ye, Q.; Honjo, T.; Murphy, T.L.; Murphy, K.M.; Hancock, W.W. Differential effects of B and T lymphocyte attenuator and programmed death-1 on acceptance of partially versus fully MHC-mismatched cardiac allografts. *J. Immunol.* **2005**, *175*, 5774–5782. [CrossRef] [PubMed]
28. Wu, K.; Zhang, J.; Fu, J.; Wu, S.; Philipp, T.; Uwe, H.; Kribben, A.; Witzke, O. Novel technique for blood circuit reconstruction in mouse heart transplantation model. *Microsurgery* **2006**, *26*, 594–598. [CrossRef]
29. Westhofen, S.; Jelinek, M.; Dreher, L.; Biermann, D.; Martin, J.; Vitzhum, H.; Reichenspurner, H.; Ehmke, H.; Schwoerer, A.P. The heterotopic heart transplantation in mice as a small animal model to study mechanical unloading—Establishment of the procedure, perioperative management and postoperative scoring. *PLoS ONE* **2019**, *14*, e0214513. [CrossRef] [PubMed]
30. Chen, Z.H. A technique of cervical heterotopic heart transplantation in mice. *Transplantation* **1991**, *52*, 1099–1101. [CrossRef]
31. Li, W.; Shepherd, H.M.; Krupnick, A.S.; Gelman, A.E.; Lavine, K.J.; Kreisel, D. Mouse Heterotopic Cervical Cardiac Transplantation Utilizing Vascular Cuffs. *J. Vis. Exp.* **2022**, *184*, e64089. [CrossRef]
32. Matsuura, A.; Abe, T.; Yasuura, K. Simplified mouse cervical heart transplantation using a cuff technique. *Transplantation* **1991**, *51*, 896–898. [CrossRef] [PubMed]
33. Schramm, R.; Schäfers, H.J.; Hamacher, J.; Menger, M.D. Simplified technique for heterotopic vascularized heart transplantation in mice. *Microsurgery* **2006**, *26*, 212–213. [CrossRef] [PubMed]
34. Wang, Q.; Liu, Y.; Li, X.K. Simplified technique for heterotopic vascularized cervical heart transplantation in mice. *Microsurgery* **2005**, *25*, 76–79. [CrossRef]
35. Li, C.; Luo, L.; Lu, J.; Feng, L.; Shan, J.; Long, D.; Guo, Y.; Wu, W.; Li, S.; Li, Y. A modified splint tubing technique for heterotopic heart transplantation in mouse. *Transpl. Immunol.* **2011**, *25*, 82–87. [CrossRef] [PubMed]
36. Lan, D.; Shang, Y.; Su, H.; Liang, M.; Liu, Y.; Li, H.; Feng, Q.; Cao, X.; Dong, H. Facile Fabrication of Hollow Hydrogel Microfiber via 3D Printing-Assisted Microfluidics and Its Application as a Biomimetic Blood Capillary. *ACS Biomater. Sci. Eng.* **2021**, *7*, 4971–4981. [CrossRef]
37. Song, H.G.; Rumma, R.T.; Ozaki, C.K.; Edelman, E.R.; Chen, C.S. Vascular Tissue Engineering: Progress, Challenges, and Clinical Promise. *Cell Stem Cell* **2018**, *22*, 340–354. [CrossRef]
38. Laschinger, M.; Assfalg, V.; Matevossian, E.; Friess, H.; Hser, N. Potential of Heterotopic Cardiac Transplantation in Mice as a Model for Elucidating Mechanisms of Graft Rejection. In *Cardiac Transplantation*; InTech Open: Rijeka, Croatia, 2012. Available online: https://www.intechopen.com/chapters/28052 (accessed on 10 February 2024).
39. Wang, C.; Wang, Z.; Allen, R.; Bishop, G.A.; Sharland, A.F. A modified method for heterotopic mouse heart transplantion. *J. Vis. Exp.* **2014**, *88*, 51423. [CrossRef]
40. Ren, H.; Zhang, J.; Wang, H.; Zhou, S. Everted Suturing of the Inferior Vena Cava Is Addressed in the Abdominal Mouse Heart Transplant Model. *Exp. Clin. Transplant.* **2018**, *16*, 588–591. [CrossRef]
41. Niimi, M. The technique for heterotopic cardiac transplantation in mice: Experience of 3000 operations by one surgeon. *J. Heart Lung Transplant.* **2001**, *20*, 1123–1128. [CrossRef]
42. Rong, S.; Lewis, A.G.; Kunter, U.; Haller, H.; Gueler, F. A knotless technique for kidney transplantation in the mouse. *J. Transplant.* **2012**, *2012*, 127215. [CrossRef] [PubMed]

43. Dun, H.; Ye, L.; Zhu, Y.; Wong, B.W. Combined abdominal heterotopic heart and aorta transplant model in mice. *PLoS ONE* **2020**, *15*, e0230649. [CrossRef]
44. Su, S.; Türk, T.R.; Wu, S.; Fan, H.; Fu, J.; Wu, K.; Flögel, U.; Ding, Z.; Kribben, A.; Witzke, O. Modified suture technique in a mouse heart transplant model. *Asian J. Surg.* **2011**, *34*, 86–91. [CrossRef]
45. Yin, D.; Fu, J.; Allabauer, I.; Witzke, O.; Rong, S.; Hoerning, A. Blood Circuit Reconstruction in an Abdominal Mouse Heart Transplantation Model. *J. Vis. Exp.* **2021**, *172*, e62007. [CrossRef]
46. Smit, F.E.; Dohmen, P.M. Cardiovascular tissue engineering: Where we come from and where are we now? *Med. Sci. Monit. Basic Res.* **2015**, *21*, 1–3. [CrossRef] [PubMed]
47. Joanne, P.; Kitsara, M.; Boitard, S.E.; Naemetalla, H.; Vanneaux, V.; Pernot, M.; Larghero, J.; Forest, P.; Chen, Y.; Menasché, P.; et al. Nanofibrous clinical-grade collagen scaffolds seeded with human cardiomyocytes induces cardiac remodeling in dilated cardiomyopathy. *Biomaterials* **2016**, *80*, 157–168. [CrossRef] [PubMed]
48. Jang, J.; Park, H.J.; Kim, S.W.; Kim, H.; Park, J.Y.; Na, S.J.; Kim, H.J.; Park, M.N.; Choi, S.H.; Park, S.H.; et al. 3D printed complex tissue construct using stem cell-laden decellularized extracellular matrix bioinks for cardiac repair. *Biomaterials* **2017**, *112*, 264–274. [CrossRef] [PubMed]
49. Muller, A.M.; Fischer, A.; Katus, H.A.; Kaya, Z. Mouse models of autoimmune diseases—*Autoimmune* myocarditis. *Curr. Pharm. Des.* **2015**, *21*, 2498–2512. [CrossRef]
50. Hasgur, S.; Fan, R.; Zwick, D.B.; Fairchild, R.L.; Valujskikh, A. B cell-derived IL-1β and IL-6 drive T cell reconstitution following lymphoablation. *Am. J. Transplant.* **2020**, *20*, 2740–2754. [CrossRef]
51. Sharma, M.; Liu, W.; Perincheri, S.; Gunasekaran, M.; Mohanakumar, T. Exosomes expressing the self-antigens myosin and vimentin play an important role in syngeneic cardiac transplant rejection induced by antibodies to cardiac myosin. *Am. J. Transplant.* **2018**, *18*, 1626–1635. [CrossRef] [PubMed]
52. Young, J.S.; Daniels, M.D.; Miller, M.L.; Wang, T.; Zhong, R.; Yin, D.; Alegre, M.L.; Chong, A.S. Erosion of Transplantation Tolerance After Infection. *Am. J. Transplant.* **2017**, *17*, 81–90. [CrossRef] [PubMed]
53. Fryer, J.P.; Leventhal, J.R.; Pao, W.; Stadler, C.; Jones, M.; Walsh, T.; Zhong, R.; Zhang, Z.; Wang, H.; Goodman, D.J.; et al. Synthetic peptides which inhibit the interaction between C1q and immunoglobulin and prolong xenograft survival. *Transplantation* **2000**, *70*, 828–836. [CrossRef]
54. Dujovny, N.; Varghese, A.; Shen, J.; Yin, D.; Ji, S.; Ma, L.; Finnegan, A.; Chong, A.S. Acute xenograft rejection mediated by antibodies produced independently of TH1/TH2 cytokine profiles. *Am. J. Transplant.* **2002**, *2*, 526–534. [CrossRef]
55. Hosiawa, K.A.; Wang, H.; DeVries, M.E.; Garcia, B.; Jiang, J.; Zhou, D.; Cameron, M.J.; Zhong, R.; Kelvin, D.J. Regulation of B- and T-cell mediated xenogeneic transplant rejection by interleukin 12. *Transplantation* **2006**, *81*, 265–272. [CrossRef] [PubMed]
56. Chen, D.; Weber, M.; Lechler, R.; Dorling, A. NK-cell-dependent acute xenograft rejection in the mouse heart-to-rat model. *Xenotransplantation* **2006**, *13*, 408–414. [CrossRef] [PubMed]
57. Yannoutsos, N.; Ijzermans, J.N.; Harkes, C.; Bonthuis, F.; Zhou, C.Y.; White, D.; Marquet, R.L.; Grosveld, F. A membrane cofactor protein transgenic mouse model for the study of discordant xenograft rejection. *Genes Cells* **1996**, *1*, 409–419. [CrossRef]
58. Roussoulières, A.L.; Raisky, O.; Chalabreysse, L.; Dureau, G.; Cerutti, C.; Thieblemont, C.; Boissonnat, P.; Sebbag, L.; Obadia, J.F.; Ninet, J.; et al. Identification and characterization of two genes (MIP-1beta, VE-CADHERIN) implicated in acute rejection in human heart transplantation: Use of murine models in tandem with cDNA arrays. *Circulation* **2005**, *111*, 2636–2644. [CrossRef] [PubMed]
59. Fry, J.W.; Morris, P.J.; Wood, K.J. Adenoviral transfer of a single donor-specific MHC class I gene to recipient bone marrow cells can induce specific immunological unresponsiveness in vivo. *Gene Ther.* **2002**, *9*, 220–226. [CrossRef] [PubMed]
60. Zhang, A.; Wang, K.; Zhou, C.; Gan, Z.; Ma, D.; Ye, P.; Sun, Y.; Wu, J.; Huang, X.; Ren, L.; et al. Knockout of microRNA-155 ameliorates the Th1/Th17 immune response and tissue injury in chronic rejection. *J. Heart Lung Transplant.* **2017**, *36*, 175–184. [CrossRef] [PubMed]
61. Zhang, M.; Zheng, Y.; Sun, Y.; Li, S.; Chen, L.; Jin, X.; Hou, X.; Liu, X.; Chen, Q.; Li, J.; et al. Knockdown of NEAT1 induces tolerogenic phenotype in dendritic cells by inhibiting activation of NLRP3 inflammasome. *Theranostics* **2019**, *9*, 3425–3442. [CrossRef]
62. Min, W.P.; Gorczynski, R.; Huang, X.Y.; Kushida, M.; Kim, P.; Obataki, M.; Lei, J.; Suri, R.M.; Cattral, M.S. Dendritic cells genetically engineered to express Fas ligand induce donor-specific hyporesponsiveness and prolong allograft survival. *J. Immunol.* **2000**, *164*, 161–167. [CrossRef] [PubMed]
63. Schnickel, G.T.; Hsieh, G.R.; Kachikwu, E.L.; Garcia, C.; Shefizadeh, A.; Fishbein, M.C.; Ardehali, A. Cytoprotective gene HO-1 and chronic rejection in heart transplantation. *Transplant. Proc.* **2006**, *38*, 3259–3262. [CrossRef] [PubMed]
64. Buszko, M.; Cardini, B.; Oberhuber, R.; Oberhuber, L.; Jakic, B.; Beierfuss, A.; Wick, G.; Cappellano, G. Differential depletion of total T cells and regulatory T cells and prolonged allotransplant survival in CD3ε humanized mice treated with polyclonal anti human thymocyte globulin. *PLoS ONE* **2017**, *12*, e0173088. [CrossRef] [PubMed]
65. Yin, D.; Ma, L.; Shen, J.; Byrne, G.W.; Logan, J.S.; Chong, A.S. CTLA-41g in combination with anti-CD40L prolongs xenograft survival and inhibits anti-gal ab production in GT-Ko mice. *Am. J. Transplant.* **2002**, *2*, 41–47. [CrossRef] [PubMed]
66. Hofmann, I.; Geer, M.J.; Vögtle, T.; Crispin, A.; Campagna, D.R.; Barr, A.; Calicchio, M.L.; Heising, S.; van Geffen, J.P.; Kuijpers, M.J.E.; et al. Congenital macrothrombocytopenia with focal myelofibrosis due to mutations in human G6b-B is rescued in humanized mice. *Blood* **2018**, *132*, 1399–1412. [CrossRef]

67. Matsuura, R.; Maeda, A.; Sakai, R.; Eguchi, H.; Lo, P.C.; Hasuwa, H.; Ikawa, M.; Nakahata, K.; Zenitani, M.; Yamamichi, T.; et al. Human HLA-Ev (147) Expression in Transgenic Animals. *Transplant. Proc.* **2016**, *48*, 1323–1325. [CrossRef]
68. Xie, C.; Zhang, Y.P.; Song, L.; Luo, J.; Qi, W.; Hu, J.; Lu, D.; Yang, Z.; Zhang, J.; Xiao, J.; et al. Genome editing with CRISPR/Cas9 in postnatal mice corrects PRKAG2 cardiac syndrome. *Cell Res.* **2016**, *26*, 1099–1111. [CrossRef]
69. Chhabra, M.; Alsughayyir, J.; Qureshi, M.S.; Mallik, M.; Ali, J.M.; Gamper, I.; Moseley, E.L.; Peacock, S.; Kosmoliaptsis, V.; Goddard, M.J.; et al. Germinal Center Alloantibody Responses Mediate Progression of Chronic Allograft Injury. *Front. Immunol.* **2018**, *9*, 3038. [CrossRef]
70. Wedel, J.; Stack, M.P.; Seto, T.; Sheehan, M.M.; Flynn, E.A.; Stillman, I.E.; Kong, S.W.; Liu, K.; Briscoe, D.M. T Cell-Specific Adaptor Protein Regulates Mitochondrial Function and CD4(+) T Regulatory Cell Activity In Vivo following Transplantation. *J. Immunol.* **2019**, *203*, 2328–2338. [CrossRef] [PubMed]
71. Gock, H.; Salvaris, E.; Murray-Segal, L.; Mottram, P.; Han, W.; Pearse, M.J.; Goodman, D.J.; Cowan, P.J.; d'Apice, A.J. Hyperacute rejection of vascularized heart transplants in BALB/c Gal knockout mice. *Xenotransplantation* **2000**, *7*, 237–246. [CrossRef] [PubMed]
72. Salvaris, E.; Gock, H.; Han, W.; Murray-Segal, L.; Barlow, H.; Mottram, P.; Pearse, M.; Cowan, P.; Goodman, D.; d'Apice, A.J. Naturally acquired anti-alpha Gal antibodies in a murine allograft model similar to delayed xenograft rejection. *Xenotransplantation* **2000**, *7*, 42–47. [CrossRef] [PubMed]
73. Tector, A.J.; Mosser, M.; Tector, M.; Bach, J.M. The Possible Role of Anti-Neu5Gc as an Obstacle in Xenotransplantation. *Front. Immunol.* **2020**, *11*, 622. [CrossRef] [PubMed]
74. McKenzie, I.F.; Li, Y.Q.; Patton, K.; Sandrin, M.S. Fucosyl transferase (H) transgenic heart transplants to Gal−/− mice. *Transplantation* **2000**, *70*, 1205–1209. [CrossRef] [PubMed]
75. Chiang, T.R.; Fanget, L.; Gregory, R.; Tang, Y.; Ardiet, D.L.; Gao, L.; Meschter, C.; Kozikowski, A.P.; Buelow, R.; Vuist, W.M. Anti-Gal antibodies in humans and 1, 3alpha-galactosyltransferase knock-out mice. *Transplantation* **2000**, *69*, 2593–2600. [CrossRef]
76. Imai, M.; Takigami, K.; Guckelberger, O.; Kaczmarek, E.; Csizmadia, E.; Bach, F.H.; Robson, S.C. Recombinant adenoviral mediated CD39 gene transfer prolongs cardiac xenograft survival. *Transplantation* **2000**, *70*, 864–870. [CrossRef]
77. McGregor, C.G.A.; Byrne, G.W. Porcine to Human Heart Transplantation: Is Clinical Application Now Appropriate? *J. Immunol. Res.* **2017**, *2017*, 2534653. [CrossRef] [PubMed]
78. Zhang, N.; Schröppel, B.; Lal, G.; Jakubzick, C.; Mao, X.; Chen, D.; Yin, N.; Jessberger, R.; Ochando, J.C.; Ding, Y.; et al. Regulatory T cells sequentially migrate from inflamed tissues to draining lymph nodes to suppress the alloimmune response. *Immunity* **2009**, *30*, 458–469. [CrossRef] [PubMed]
79. Ochando, J.C.; Yopp, A.C.; Yang, Y.; Garin, A.; Li, Y.; Boros, P.; Llodra, J.; Ding, Y.; Lira, S.A.; Krieger, N.R.; et al. Lymph node occupancy is required for the peripheral development of alloantigen-specific Foxp3+ regulatory T cells. *J. Immunol.* **2005**, *174*, 6993–7005. [CrossRef]
80. Hu, Y.; Zou, Y.; Hala, M.; Dietrich, H.; Wick, G.; Xu, Q. Prolonged survival of heart allografts from p53-deficient mice. *Transplantation* **2000**, *69*, 2634–2640. [CrossRef]
81. Zheng, X.X.; Gao, W.; Donskoy, E.; Neuberg, M.; Ruediger, M.; Strom, T.B.; Moll, T. An antagonist mutant IL-15/Fc promotes transplant tolerance. *Transplantation* **2006**, *81*, 109–116. [CrossRef]
82. Dai, H.; Peng, F.; Lin, M.; Xia, J.; Yu, S.; Lan, G.; Wang, Y.; Xie, X.; Fang, C.; Corbascio, M.; et al. Anti-OX40L monoclonal antibody prolongs secondary heart allograft survival based on CD40/CD40L and LFA-1/ICAM-1 blockade. *Transpl. Immunol.* **2015**, *32*, 84–91. [CrossRef]
83. Van Aelst, L.N.; Summer, G.; Li, S.; Gupta, S.K.; Heggermont, W.; De Vusser, K.; Carai, P.; Naesens, M.; Van Cleemput, J.; Van de Werf, F.; et al. RNA Profiling in Human and Murine Transplanted Hearts: Identification and Validation of Therapeutic Targets for Acute Cardiac and Renal Allograft Rejection. *Am. J. Transplant.* **2016**, *16*, 99–110. [CrossRef]
84. Kosuge, H.; Haraguchi, G.; Koga, N.; Maejima, Y.; Suzuki, J.; Isobe, M. Pioglitazone prevents acute and chronic cardiac allograft rejection. *Circulation* **2006**, *113*, 2613–2622. [CrossRef]
85. Shimizu, I.; Tomita, Y.; Iwai, T.; Kajiwara, T.; Okano, S.; Nomoto, K.; Tominaga, R. Sequential analysis of anti-alpha Gal natural antibody-producing B cells in GalT knockout mice in cyclophosphamide-induced tolerance. *Scand. J. Immunol.* **2006**, *63*, 435–443. [CrossRef]
86. Yu, Z.; Zhou, X.; Yu, S.; Xie, H.; Zheng, S. IL-15 is decreased upon CsA and FK506 treatment of acute rejection following heart transplantation in mice. *Mol. Med. Rep.* **2015**, *11*, 37–42. [CrossRef] [PubMed]
87. Urbanellis, P.; Shyu, W.; Khattar, R.; Wang, J.; Zakharova, A.; He, W.; Sadozai, H.; Amir, A.Z.; Shalev, I.; Phillips, M.J.; et al. The regulatory T cell effector molecule fibrinogen-like protein 2 is necessary for the development of rapamycin-induced tolerance to fully MHC-mismatched murine cardiac allografts. *Immunology* **2015**, *144*, 91–106. [CrossRef] [PubMed]
88. Gong, W.; Liu, B.; Chen, J.; Liu, C.; Shen, Z. Impact of Regulatory T Cells on Innate Immune Cells in a Pre-Sensitized Heart Transplant Model. *Ann. Transplant.* **2018**, *23*, 246–251. [CrossRef] [PubMed]
89. Zhou, K.; Chen, X.; Zhang, L.; Yang, Z.; Zhu, H.; Guo, D.; Su, R.; Chen, H.; Li, H.; Song, P.; et al. Targeting peripheral immune organs with self-assembling prodrug nanoparticles ameliorates allogeneic heart transplant rejection. *Am. J. Transplant.* **2021**, *21*, 3871–3882. [CrossRef]

90. Zhang, Q.W.; Tomita, Y.; Matsuzaki, G.; Yoshikawa, M.; Shimizu, I.; Nakashima, Y.; Sueishi, K.; Nomoto, K.; Yasui, H. Mixed chimerism, heart, and skin allograft tolerance in cyclophosphamide-induced tolerance. *Transplantation* **2000**, *70*, 906–916. [CrossRef] [PubMed]
91. Zhang, Z.; Lazarovits, A.; Gao, Z.; Garcia, B.; Jiang, J.; Wang, J.; Xing, J.J.; White, M.; Zhong, R. Prolongation of xenograft survival using monoclonal antibody CD45RB and cyclophosphamide in rat-to-mouse kidney and heart transplant models. *Transplantation* **2000**, *69*, 1137–1146. [CrossRef] [PubMed]
92. Wang, H.; Hosiawa, K.A.; Min, W.; Yang, J.; Zhang, X.; Garcia, B.; Ichim, T.E.; Zhou, D.; Lian, D.; Kelvin, D.J.; et al. Cytokines regulate the pattern of rejection and susceptibility to cyclosporine therapy in different mouse recipient strains after cardiac allografting. *J. Immunol.* **2003**, *171*, 3823–3836. [CrossRef] [PubMed]
93. Moffatt, S.D.; Metcalfe, S.M. Comparison between tacrolimus and cyclosporine as immunosuppressive agents compatible with tolerance induction by CD4/CD8 blockade. *Transplantation* **2000**, *69*, 1724–1726. [CrossRef] [PubMed]
94. Isobe, M.; Suzuki, J.; Morishita, R.; Kaneda, Y.; Amano, J. Gene therapy for heart transplantation-associated coronary arteriosclerosis. *Ann. N. Y. Acad. Sci.* **2000**, *902*, 77–83. [CrossRef] [PubMed]
95. Gu, H.; Xie, M.; Xu, L.; Zheng, X.; Yang, Y.; Lv, X. The protective role of interleukin-18 binding protein in a murine model of cardiac ischemia/reperfusion injury. *Transpl. Int.* **2015**, *28*, 1436–1444. [CrossRef] [PubMed]
96. Tuuminen, R.; Dashkevich, A.; Keränen, M.A.; Raissadati, A.; Krebs, R.; Jokinen, J.J.; Arnaudova, R.; Rouvinen, E.; Ylä-Herttuala, S.; Nykänen, A.I.; et al. Platelet-derived Growth Factor-B Protects Rat Cardiac Allografts From Ischemia-reperfusion Injury. *Transplantation* **2016**, *100*, 303–313. [CrossRef] [PubMed]
97. Liu, G.; Zhang, H.; Hao, F.; Hao, J.; Pan, L.; Zhao, Q.; Wo, J. Clusterin Reduces Cold Ischemia-Reperfusion Injury in Heart Transplantation Through Regulation of NF-kB Signaling and Bax/Bcl-xL Expression. *Cell. Physiol. Biochem.* **2018**, *45*, 1003–1012. [CrossRef] [PubMed]
98. Fukunaga, N.; Kawajiri, H.; Badiwala, M.V.; Butany, J.; Li, R.K.; Billia, F.; Rao, V. Protective role of Nrf2 against ischemia reperfusion injury and cardiac allograft vasculopathy. *Am. J. Transplant.* **2020**, *20*, 1262–1271. [CrossRef] [PubMed]
99. Yao, L.; Lv, X.; Wang, X. MicroRNA 26a inhibits HMGB1 expression and attenuates cardiac ischemia-reperfusion injury. *J. Pharmacol. Sci.* **2016**, *131*, 6–12. [CrossRef]
100. Ban, Q.; Qiao, L.; Xia, H.; Xie, B.; Liu, J.; Ma, Y.; Zhang, L.; Zhang, M.; Liu, L.G.; Jiao, W.; et al. β-catenin regulates myocardial ischemia/reperfusion injury following heterotopic heart transplantation in mice by modulating PTEN pathways. *Am. J. Transl. Res.* **2020**, *12*, 4757–4771.
101. Hasegawa, T.; Visovatti, S.H.; Hyman, M.C.; Hayasaki, T.; Pinsky, D.J. Heterotopic vascularized murine cardiac transplantation to study graft arteriopathy. *Nat. Protoc.* **2007**, *2*, 471–480. [CrossRef]
102. Benke, K.; Sayour, A.A.; Mátyás, C.; Ágg, B.; Németh, B.T.; Oláh, A.; Ruppert, M.; Hartyánszky, I.; Szabolcs, Z.; Radovits, T.; et al. Heterotopic Abdominal Rat Heart Transplantation as a Model to Investigate Volume Dependency of Myocardial Remodeling. *Transplantation* **2017**, *101*, 498–505. [CrossRef]
103. Oberhuber, R.; Heinbokel, T.; Cetina Biefer, H.R.; Boenisch, O.; Hock, K.; Bronson, R.T.; Wilhelm, M.J.; Iwakura, Y.; Edtinger, K.; Uehara, H.; et al. CD11c+ Dendritic Cells Accelerate the Rejection of Older Cardiac Transplants via Interleukin-17A. *Circulation* **2015**, *132*, 122–131. [CrossRef]
104. Heinbokel, T.; Quante, M.; Iske, J.; Nian, Y.; Maenosono, R.; Minami, K.; Liu, Y.; Azuma, H.; Elkhal, A.; Tullius, S.G. CTLA4-Ig prolongs graft survival specifically in young but not old mice. *Am. J. Transplant.* **2021**, *21*, 488–502. [CrossRef] [PubMed]
105. Maenosono, R.; Nian, Y.; Iske, J.; Liu, Y.; Minami, K.; Rommel, T.; Martin, F.; Abdi, R.; Azuma, H.; Rosner, B.A.; et al. Recipient sex and estradiol levels affect transplant outcomes in an age-specific fashion. *Am. J. Transplant.* **2021**, *21*, 3239–3255. [CrossRef] [PubMed]
106. Molinero, L.L.; Yin, D.; Lei, Y.M.; Chen, L.; Wang, Y.; Chong, A.S.; Alegre, M.L. High-Fat Diet-Induced Obesity Enhances Allograft Rejection. *Transplantation* **2016**, *100*, 1015–1021. [CrossRef] [PubMed]
107. Uchiyama, M.; Yin, E.; Yanagisawa, T.; Jin, X.; Hara, M.; Matsuyama, S.; Imazuru, T.; Uchida, K.; Kawamura, M.; Niimi, M. Yogurt Feeding Induced the Prolongation of Fully Major Histocompatibility Complex-Mismatched Murine Cardiac Graft Survival by Induction of CD4(+)Foxp3(+) Cells. *Transplant. Proc.* **2017**, *49*, 1477–1482. [CrossRef] [PubMed]
108. Galili, U. Xenotransplantation and ABO incompatible transplantation: The similarities they share. *Transfus. Apher. Sci.* **2006**, *35*, 45–58. [CrossRef]
109. Park, S.; Lee, J.G.; Jang, J.Y.; Ryu, J.H.; Kim, D.J.; Chang, S.J.; Kim, H.; Chung, J.; West, L.; Yang, J. Induction of Accommodation by Anti-complement Component 5 Antibody-based Immunosuppression in ABO-incompatible Heart Transplantation. *Transplantation* **2019**, *103*, e248–e255. [CrossRef] [PubMed]
110. Ballard, V.L.; Sharma, A.; Duignan, I.; Holm, J.M.; Chin, A.; Choi, R.; Hajjar, K.A.; Wong, S.C.; Edelberg, J.M. Vascular tenascin-C regulates cardiac endothelial phenotype and neovascularization. *FASEB J.* **2006**, *20*, 717–719. [CrossRef]
111. Shen, H.; Heuzey, E.; Mori, D.N.; Wong, C.K.; Colangelo, C.M.; Chung, L.M.; Bruce, C.; Slizovskiy, I.B.; Booth, C.J.; Kreisel, D.; et al. Haptoglobin enhances cardiac transplant rejection. *Circ. Res.* **2015**, *116*, 1670–1679. [CrossRef] [PubMed]
112. Xu, X.; Li, X.; Gu, X.; Zhang, B.; Tian, W.; Han, H.; Sun, P.; Du, C.; Wang, H. Prolongation of Cardiac Allograft Survival by Endometrial Regenerative Cells: Focusing on B-Cell Responses. *Stem Cells Transl. Med.* **2017**, *6*, 778–787. [CrossRef]

113. Zhao, Y.; Chen, S.; Lan, P.; Wu, C.; Dou, Y.; Xiao, X.; Zhang, Z.; Minze, L.; He, X.; Chen, W.; et al. Macrophage subpopulations and their impact on chronic allograft rejection versus graft acceptance in a mouse heart transplant model. *Am. J. Transplant.* **2018**, *18*, 604–616. [CrossRef] [PubMed]
114. Fischer, K.; Ohori, S.; Meral, F.C.; Uehara, M.; Giannini, S.; Ichimura, T.; Smith, R.N.; Jolesz, F.A.; Guleria, I.; Zhang, Y.; et al. Testing the Efficacy of Contrast-Enhanced Ultrasound in Detecting Transplant Rejection Using a Murine Model of Heart Transplantation. *Am. J. Transplant.* **2017**, *17*, 1791–1801. [CrossRef] [PubMed]
115. Daly, K.P.; Dearling, J.L.; Seto, T.; Dunning, P.; Fahey, F.; Packard, A.B.; Briscoe, D.M. Use of [18F]FDG Positron Emission Tomography to Monitor the Development of Cardiac Allograft Rejection. *Transplantation* **2015**, *99*, e132–e139. [CrossRef] [PubMed]
116. Flögel, U.; Su, S.; Kreideweiss, I.; Ding, Z.; Galbarz, L.; Fu, J.; Jacoby, C.; Witzke, O.; Schrader, J. Noninvasive detection of graft rejection by in vivo (19) F MRI in the early stage. *Am. J. Transplant.* **2011**, *11*, 235–244. [CrossRef] [PubMed]
117. Cao, Y.A.; Bachmann, M.H.; Beilhack, A.; Yang, Y.; Tanaka, M.; Swijnenburg, R.J.; Reeves, R.; Taylor-Edwards, C.; Schulz, S.; Doyle, T.C.; et al. Molecular imaging using labeled donor tissues reveals patterns of engraftment, rejection, and survival in transplantation. *Transplantation* **2005**, *80*, 134–139. [CrossRef]
118. Habertheuer, A.; Korutla, L.; Rostami, S.; Reddy, S.; Lal, P.; Naji, A.; Vallabhajosyula, P. Donor tissue-specific exosome profiling enables noninvasive monitoring of acute rejection in mouse allogeneic heart transplantation. *J. Thorac. Cardiovasc. Surg.* **2018**, *155*, 2479–2489. [CrossRef]
119. Rodriguez-Barbosa, J.I.; Schneider, P.; Graca, L.; Bühler, L.; Perez-Simon, J.A.; Del Rio, M.L. The Role of TNFR2 and DR3 in the In Vivo Expansion of Tregs in T Cell Depleting Transplantation Regimens. *Int. J. Mol. Sci.* **2020**, *21*, 3347. [CrossRef] [PubMed]