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Universal Donor: From Serologic Compatibility to Genomic Bioengineering

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ABSTRACT

In this paper, we analyze how the idea of universal donors has developed from the classic serological ABO system through to the novel approaches in genomic bioengineering. First, we discuss the existing paradigm of type O blood being used as universal donors and the drawbacks associated with the use of serological matching, particularly in the context of organ transplantation. Then, using a literature review on the latest advancements, we describe new approaches for making universal donors, such as blood group antigen enzymatic conversion and CRISPR-Cas9 gene editing, which make it possible to produce hypoimmunogenic cells. Main barriers to developing these technologies lie in the balance between T lymphocytes and natural killer (NK) cell immune response, genetic diversity within a population, and implementation of novel bioengineering approaches in a clinical setting.

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Abbreviations

ABO, ABO blood group system; AI, Artificial Intelligence; AML, Acute Myeloid Leukemia; APC, Antigen-Presenting Cell; B2M, Beta-2 Microglobulin; CAR, Chimeric Antigen Receptor; ECM, Extracellular Matrix; HLA, Human Leukocyte Antigen; iPSC, Induced Pluripotent Stem Cell; NK cells, Natural Killer cells; PDX, Patient-Derived Xenograft; PSC, Pluripotent Stem Cell; RBC, Red Blood Cell; RhD, Rhesus D antigen; TAM, Tumor-Associated Macrophages

Introduction

The concept of "universal donor" in blood transfusion has been defined based on the ABO (ABO blood group) system, with O- blood as the universal donor (1). This classic definition, even though it is vital for emergency crises and time-critical cross-matching situations such as trauma, due to excessive demands in solid organ transplantation, is increasingly considered inadequate with the progress of research on immunology and genetics (2). Minor antigen incompatibilities, alloimmunization in patients requiring repeated transfusions, and limitations of type O blood resources have indicated that being "universal" in the serological scale cannot guarantee complete immunologic compatibility (2).

On the other hand, in cell and tissue transplantation, the immunization of HLA antigens (Human Leukocyte Antigens) as primary determinants of immune reaction have challenged the concept of a universal donor (3). Even in the presence of ABO system compatibility (3), Incompatibility of HLA antigens can result in rejection of the transplanted organ, T lymphocyte activation, and onset of numerous side effects (4).

The concept of a "universal donor" in earlier concepts can be traced back to Greek and Hindu myths, such as Hydra and Kama. Kama, who is often cited as the symbol of generosity, gave the natural armor that made him invincible to Kavacha, who had disguised himself as a beggar. Hydra, also with the power to regenerate its internal organs, could heal its men by giving them these organs. Today, this concept can be seen in Rhd (Rhesus D antigen) null blood types, rare but just as selfless. However, as mentioned above, limitations of blood O- have led researchers to more innovative methods to overcome challenges in developing the concept of a universal donor.

In recent years, innovative methods have been developed to reshape this concept. The concept is known today as a universal donor. In different blood groups, biochemical methods like enzymatic removal of terminal sugars from A and B antigens have been proposedto convert these types into a functional type O blood group (5).

RBCs (Red Blood Cells) without antigens A or B, also known as type O, and especially those lacking antigen D, are defined in the RhD system as the "universal donor." (6), This classic definition is still remaining scientifically accurate based on acute hematological reactions between natural antibodies and antigens A or B. In patients who require repeated injections, like thalassemia patients or those diagnosed with sickle cell anemia, alloimmunization against minor antigens has become a serious clinical issue (7). This exact problem is what led methods of "widespread antigen accommodation" to progress at a rapid pace, and for researchers to use molecular genotyping to increase the accuracy and compatibility of blood transfusions (6, 8, 9).

A recent study at the University of British Columbia has demonstrated a successful utilization of enzymes to convert blood type A to universal type O in a donor kidney. The kidney then was transplanted into a brain-dead patient and monitored for 48 hours with no hyperacute reaction (10, 11). The importance of this matter is not only hidden in the lack of resources for type O blood group and the safety of blood transfusions, but also in developing "off-the-shelf" and "ready-to-use" products for instant application in urgent cases.

In this context, in the early 2010s, gene editing technologies such as CRISPR-Cas9 have been introduced to modify HLA genes to generate hypoimmunogenic cells in cell-based therapies and regenerative medicine (12). These advanced modalities have changed the concept of "universal donor" and increased expectations. This approach has updated this subject from a simple serological matter to a full complex bioengineering project.

Future perspective of universal donor can increase the pace of transition from conventional to bioengineered immune compatibility, a transition that will have a widespread effect on addressing some limitations in donated organs, such as a lack of enough donors, economics, and medical ethics (9).

Since HLA molecules play a key role in antigen-presenting and activating T lymphocytes, in transplantation, HLA class I and II are more prominent than in other areas of medicine (3). Incompatibility between HLA molecules can lead to transplantation rejection or the onset of numerous pathologies in the recipient (11, 13, 14).

At present, the concept of a "universal donor" in clinical practice remains largely limited to type O blood, particularly in emergency situations. (11). However, the increase in demand for blood group O and limitations of its resources have put quite a pressure on blood transfusion systems (15-17). A retrospective 12-year study, in three academic hospitals from April 2000 to March 2014, calculated the total transfusion number, which is equal to 314,968. Out of these transfusions, 48.1% was dedicated to type O blood group, which is almost half of all transfusions, and out of this number, 8.9% had been given to ABO non-identical patients. At the same time, we are now aware of alloimmunization in patients with repeated transfusions and must consider this issue.

Two innovative methods have been explored in the following sentences. Firstly, the biochemical method of enzymic elimination of antigens A and B from the red blood cell's surface using bacterial glycosidase allows us to generate a functional type O blood group (11, 18, 19).

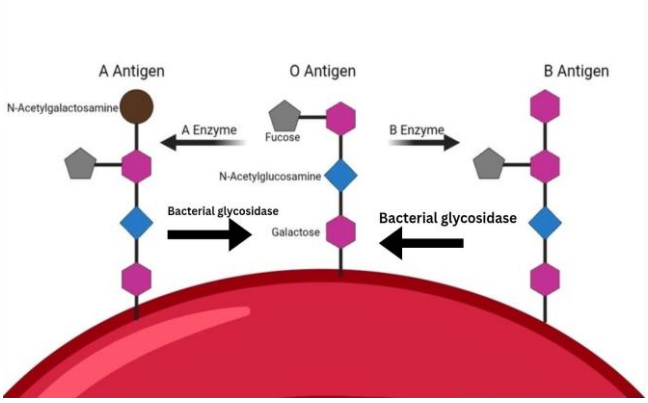

Figure 1. Using bacterial glycosidases to remove the terminal sugar from antigens A and B to form a functional type O blood group.

Secondly, the genomic and medical bioengineering method using CRISPR-Cas9. This innovation enables researchers to eliminate genes related to expressing HLA subunits, including beta-2 microglobulin (B2M) or special alleles of HLA class I (7, 20, 21). The goal of these interventions is to produce a hypoimmunogenic cell, particularly pluripotent stem cells (PSCs), that are less recognized by active T lymphocytes. PSCs literally have unlimited proliferation capacity and can differentiate into all somatic cell types. The differentiation ability is also checked by assessing the differentiation of PSCs into all germinal layers, including ectoderm, mesoderm, and endoderm. This method is used especially in generating cells driven from induced pluripotent stem cells (iPSCs) for treatment usage, and it speaks of a future perspective of making ready-to-use platforms and personalized medicine (22-24). Especially with the progression of CRISPR and gene editing, identifying more widespread variables is possible, as shown in Figure 2.

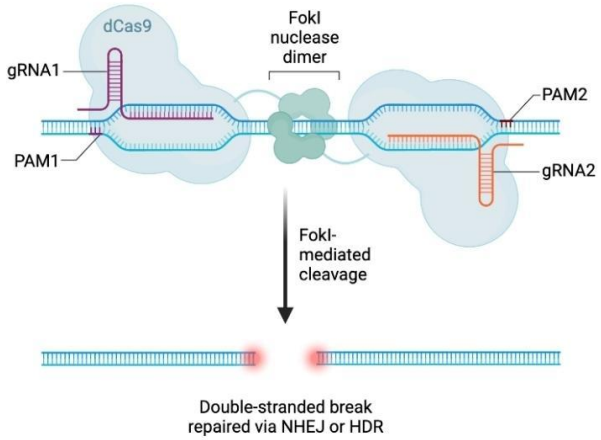

Figure 2. CRISPR-Cas9 gene-editing mechanism showing guide RNA-directed targeting and modification of a specific DNA sequence.

However, eliminating HLA creates new challenges, such as NK (Natural Killer) cell activation due to "missing self" recognition. NK cells operate based on detecting whether HLA molecules are present, eliminating the HLA expressing gene may resolve T cell recognition; due to the fact that they check HLA patterns, not its whole existence, but it will still trigger NK cells (4). Overall, the current status shows the concept of universal donor is shifting from a simple ABO blood system to molecular genetics and immune reactions.

Critical analysis and discussion

One of the main challenges in redefining the concept of universal donor in genomic context is creating a delicate balance between the two main players of the immune system, meaning T lymphocytes and NK cells. Most of the genetic methods, especially eliminating HLA class I, have been designed to reduce recognition by cytotoxic T cells. Since activation of T cells is dependent on recognizing peptides being presented on HLA on a cellular level, by eliminating HLA molecules, we can reduce immune reactions (8, 25, 26).

However, this creates an immunological paradox.

NK cells operate based on the 'missing self' method, meaning the lack of HLA molecule naturally creates an activation signal for NK cells. Concludingly, eliminating HLA molecules may seem to reduce immune reaction, but they increase the risk of NK cell activation, thus increasing the risk for transplant rejection.

Ultimately, the primary obstacle in producing universal donor products in the genomic context is not simply optimizing CRISPR or other gene editing technologies but a deep understanding and intellectual design to provide a balance between the T and NK cells. A balance that, if constructed correctly, may raise the concept of compatibility from an individual level to a universal level (18).

Another challenge that has been discussed less along this complex path is population-level genetic diversity. Widespread polymorphisms in HLA genes and even in subsidiary blood groups show that the concept of a "universal donor" is controversial, depending on the population studied. A bioengineered cell that may result in the least immune reaction in one population may show alloreactivity in other populations. Therefore, efforts to develop universal donor platforms must take population genetics and epidemiological variation into account.

On the other hand, we also need to pay attention to the practical and structural dimensions of this problem. Even if enzymic innovations or gene editing tools look promising, challenges of mass production, standardization, quality control, and expenses are still in place.

Translation of information from basic and preclinical studies to real widespread clinical applications needs accurate platforms, precise monitoring and long-term evaluation (27). From this perspective, achieving the concept of universal donor is more than just a biological innovation and seems to be a multidimensional challenge in certain disciplines, including public medicine, socioeconomic considerations, and medical ethics (9).

Emerging Horizons: From AI-Bio-Engineered Universal HLA to donors derived from Xenogeneic Organs

The future concept of a universal donor seems to be moving from a simple method to a multilayered and complex solution. In blood transfusion, the enzymatic elimination of AB antigens may be more practical and available for clinical use, especially considering the recent discovery of bacterial glycosidase. If obstacles such as the complete elimination of immunogens, RBC membrane stability, and industrial scale-up are solved, it may be possible to rely on universal blood banks instead of simply using group O blood type. This outcome can reduce this pressure on type O resources and increase flexibility of choices in emergencies (17). Furthermore, one of the futuristic solutions given is In-vitro manufactured red blood cells as substitutes for donor blood. These cultured RBCs could potentially become the new universal donor by avoiding specific blood group antigens using bioreactor systems and 3D culture materials (28).

Application of Entropy-Guided Artificial Intelligence in HLA Design

At the cellular and transfusion level, futuristic paths will probably be directed towards generating safe cells with desired modifications regarding non-immunogenicity. Instead of eliminating HLA molecules, bioengineering specific alleles, preserving and using certain inhibitory molecules can result in universal platforms. Cells derived from induced pluripotent stem cells (iPSCs), while being genetically modified for a specific purpose, can provide the opportunity to produce a variety of cells and tissues in regenerative medicine with the least immunogenicity. Such platforms can transition the "off-the-shelf-therapy" concept from a mere idea to a more clinical reality (29).

However, one of the main futuristic practical approaches could be using artificial intelligence to predict compatibility patterns. The high number of variations of HLA genes in human populations creates mathematical probability and biological challenges. Using machine learning to go through a large genome database can help identify combinations that are most common in one population (24, 30). "Shannon Entropy" can evaluate variability and probability of certain polymorphisms and can be a valuable tool for creating bioengineered HLA molecules.

Using programming languages such as Python for genomic data analysis, stimulating receptor-antigen connection and stability will give us the ability to further predict the HLA molecules generated. Instead of trial and error in laboratories, first, we can eliminate different modalities by using big data (7, 31).

A newly experimented method has also been mentioned in some articles known as antigen masking or PEGylation, which allows us to add chemical modifications to cover the surface of AB antigens; however, it is still experimental, and no clinical data has been recorded so far (16).

CAR T cell approach

The concept of using CAR (Chimeric antigen receptor) T cells arose while trying to tackle Acute Myeloid Leukemia (AML). This fast-growing, often aggressive blood cancer was considered challenging and hard to cure due to its known heterogeneous nature. These cancer cells express different kinds of molecules, such as CD33, CLL-1, and CD7, which create the core treatment problems due to requiring multiple specific treatments. These advances in cell engineering also align with the broader goal of creating universally compatible donor platforms. Studies have utilized CAR T cells as an effective solution. This method allows T-cells to be genetically edited and to lack certain genes to prevent possible rejection. Pre-clinical studies conducted on PDX (Patient Derived Xenograft) models show that utilizing a customized combination of CAR T cells can reduce leukemia's burden and introduce "off-the-shelf" allogenic stem-cell transplantation (32). By genetically disturbing or deleting the endogenous T-cell receptor, this approach also minimizes the risk of graft-versus-host disease.

Macrophage and dendritic cell therapy

Turning M1 and M2 macrophages into one another, or at least in function, was introduced as a way to control TAM (Tumor-Associated-Macrophages) in cancer therapy. TAM cells function like M2 cells by enhancing tumor growth; therefore, using genomic reprogramming may be effective (33). With this knowledge that M2 cells can be utilized in fibrosis, this process can also be reversed, turning macrophages into M2 function ones to reduce inflammation and immune response in a universal donor (34). In the same way, these therapies support the universal donor concept by reducing the risk of immune rejection, offering a path to more universally compatible transplants.

APC (Antigen Presenting Cells), such as dendritic cells, can also be utilized in this way. By reprogramming dendritic cells to express inhibitory signals such as PD-L1, IL-10, and TGF-β instead of the traditional inflammatory cytokines, we can modulate immune reactions in dendritic cells and even T cells (35).

Bio printing and Synthetic organs

Another emerging strategy in transplantation involves tissue engineering and bioprinting, which apply engineering principles to the construction of functional tissues and organs. Synthetic organs can be made by seeding cells onto acellular scaffolds. Scaffolds are both made naturally from decellularized ECM (Extracellular Matrix) or hydrogel, and synthetically from gelatin and sodium alginate. To shape the wanted organ, pores, channels, and mechanical structures are embedded. Two main methods are known for planting cells onto this scaffold: static seeding and dynamic seeding. In static seeding, cells settle by gravity and migrate into pores according to the pore size, interconnectivity, and viscosity. Whereas in the latter, perfusion seeding is done by bioreactors and is more clinically important. Dynamic seeding provides uniform distribution and improves nutrition access to preserve an organ. This method allows bio-printing to seed donor cells without being present to the recipient (36, 37). By integrating bioprinting with advanced immune therapies, we further push the boundaries of the universal concept.

Xenotransplantation

The concept of "Universal Donor" should not be limited to human donors. Recent studies, regarding the inadequate abundance of human heart donors for transplantation, have tried to utilize genetically modified pig hearts on human recipients, also known as xenotransplantation. Such usage could also be logically predicted due to the similarities between pig and human anatomy even often used as practice model for transplant surgeons. The study had 2 phases, known as "knock-outs" and "knock-ins". The first phase includes knocking out or down-regulating genes that trigger an immediate human immune reaction, and the second phase paints a picture of knocking in or up-regulating some genes to protect the transplanted heart. This new method was recently tested on 2 brain-dead patients and monitored for 66 hours with outstanding results, including continuous operating and pumping the heart, lack of hyperacute reaction, lack of antibody-mediated reaction, and no zoonotic infections. Even though this method is still experimental, it holds a bright promise (24, 38).

Conclusion

The concept of "universal donor" has changed from a simple serological transition to a complex immunological and genetic problem. Even though group type O still remains the backbone of emergencies in clinical use, evidence shows that this classic concept does not answer all the demands of immune compatibility (11, 17). Variability of RBC antigens, complexities in patients in need of repeated injections, and the critical role of HLA in transplantation show that the concept of a universal donor is multidimensional.

Recent progress in enzyme elimination and developments in widespread genotyping are evidence of ongoing efforts to improve immunological compatibility and transplantation outcomes. In the meantime, gene editing innovations such as CRISPR and proliferating cells derived from IPSCs are showcasing a bright prediction of producing hypoimmunogenic cells that are very valuable for regenerative medicine (3, 39). Recent studies display efforts in utilizing hypo-immunogenic bioengineering to create "off-the-shelf" regulatory T-cells. Using CRISPR gene-editing, and reducing the expression of HLA class I and II by silencing genes B2M and CIITA, respectively. By reducing the expression of HLA class I and II, they have successfully created a hypo-immunogenic universal regulatory T-cell safe from cytotoxic T-cell advances (40).

However, despite all these said efforts, challenges such as creating a balance between T cells and NK cells, stability of bioengineered cells in human body conditions, and ethical problems are still standing.

Table 1. Comparative overview of current and emerging strategies towards universal donor platforms.

Strategy	Biological target	Mechanism	Clinical status
Conventional O donation	ABO and RhD antigens	Neutrally lacks A, B, and RhD antigens	Widely used in emergency transfusion
Enzymatic ABO conversion	Terminal carbohydrate residue of AB antigen	Glycosidase-mediated cleavage	Experimental
CRISPR HLA knockout	HLA class I	Gene editing to eliminate HLA expression	Preclinical

RBC, red blood cell; HLA, human leukocyte antigen; iPSC, induced pluripotent stem cell; NK, natural killer cell; CRISPR, clustered regularly interspaced short palindromic repeats.

Ultimately, the future of a universal donor probably isn't hidden in eliminating immune cell identity but in precise immunological engineering. Transition from traditional accommodation to systematic design will open a new door to blood transfusion in cellular treatment. A beginning that will further blur the lines between immunology and genetics.

Declarations

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Authors' Contributions

Conceptualization of the study, literature review, article synthesis, and preparation of the initial draft of the manuscript were done by ER. The text underwent critical analysis and revision by SF with regard to structure, references, and academic tone. Overall supervision, analysis, and coherence of the manuscript at a scientific level were ensured by MV. All authors approved the final version.

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Conflicts of Interest

The authors declare that they have no competing interests.

Ethics Approval

Not applicable.

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