BYPASSING THE HLA SYSTEM IN ORGAN TRANSPLANTATION: OPPORTUNITIES TO ACHIEVE UNIVERSAL COMPATIBILITY VIA FULL SUPPRESSION AND ARTIFICIAL IMMUNOBIOCODING

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Annotation: This study explores innovative strategies to overcome HLA incompatibility in organ transplantation, a major cause of graft rejection. Two promising approaches are highlighted: CRISPR/Cas9-mediated deletion of HLA genes and artificial immunobiocoding to create universal donor cells. Gene editing to suppress classical HLA expression, while preserving non-classical molecules like HLA-E, has shown reduced immune recognition in preclinical models. Additionally, the expression of immunomodulatory molecules such as PD-L1 and CD47 further enhances immune evasion. Ongoing clinical efforts, including iPSC banks and universal stem cell lines, indicate substantial progress toward safer, more accessible transplantation without long-term immunosuppression.

Keywords: HLA, organ transplantation, CRISPR/Cas9, universal donor, immunobiocoding, iPSC, immune evasion, NK cells, immunosuppression.

In organ transplantation, the human leukocyte antigen (HLA) system represents one of the key immunological barriers. HLA incompatibility between donor and recipient often leads to graft rejection. This study examines novel strategies, including CRISPR/Cas9-mediated suppression of HLA genes and artificial immunobiocoding, as approaches to achieve universal donor compatibility while minimizing the need for long-term immunosuppression.

Conventional transplantation relies on HLA compatibility and immunosuppressive drugs, but rejection remains a major challenge. With more than 150,000 transplants performed annually worldwide [1], the development of universal donor approaches could dramatically improve access and outcomes. Two strategies are currently under study: (1) genetic suppression of HLA molecules using CRISPR, and (2) artificial immunobiocoding to mimic “self” signals and evade immune detection.

CRISPR/Cas9 suppression of HLA: Deleting HLA-A, HLA-B, and CIITA genes eliminates classical HLA class I/II molecules. Xu et al. (2019) demonstrated that such iPSC lines are not recognized by T cells, while maintaining HLA-E expression to avoid NK cell attack [2]. Deuse et al. (2021) showed HLA-deficient cardiomyocytes survived long-term in humanized mice without rejection [3]. Artificial immunobiocode: Since complete HLA deletion triggers NK-mediated

"missing self" recognition, additional strategies are applied. These include expression of HLA-E/G, immune checkpoint molecules (PD-L1, CD47), and engineered β2m-HLA fusion proteins that transmit immunosuppressive signals. Gornalusse et al. (2017) confirmed that HLA-E expressing pluripotent stem cells evade NK lysis.

Clinical progress: Kyoto University (CiRA) developed an iPSC bank with 27 clinical-grade HLA-homozygous lines, covering up to 90% of the Japanese population [4]. Current SARs-T clinical trials are testing universal iPSCs in cardiac, hepatic, and spinal cord transplantation.

CRISPR-mediated HLA suppression and artificial immunobiocoding represent promising strategies toward universal donor transplantation. These technologies can reduce dependence on immunosuppressive drugs, shorten waiting lists, and expand access to transplantation. Large-scale clinical studies are essential to confirm safety and efficacy in humans.

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