CRISPR/Cas9 and Blood Transfusions: Advancing HLA Class I-Deleted Blood Products to Prevent Rejection

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ABSTRACT

In adults, normal hematopoiesis occurs in the bone marrow, producing leukocytes, red blood cells, and platelets. Recently, megakaryocytes have been found in mouse lungs and spleen, where they release platelets by blood flow force. Blood products are used to treat a multitude of diseases and conditions that generate cytopenia. The blood transfusion system must be enhanced due to a drop in blood donors due to low birth rate and changing attitudes among young people, pathogen contamination, and rising demand due to chronic blood diseases that are prevalent among the elderly. Pluripotent stem cells, such as embryonic stem (ES) cells, may proliferate in vitro indefinitely and are a prospective source for blood transfusions to replace blood donations.

Platelet preparations can be maintained at room temperature to sustain platelet function, but only have a statutory expiry date of five days. Platelets are anucleate cells, thus irradiation before blood donation can lessen the risk of iPS cell infection. Effective treatment requires HLA-compatible platelet transfusions, although supply limits often leave patients underserved. CRISPR/Cas9 has made it viable to make HLA class I-deleted blood products to avoid rejection and lower the odds of platelet-expressed human leukocyte antigen Class I cancer-causing iPS cells (HLA-I). This article discusses the production of megakaryocyte cell lines, bioreactors, and scale-up cultures, as well as identifying viable drugs in manufacturing. HLA-null, iPSC-derived platelet products' universal potential will also be explored.

1 INTRODUCTION

Leukocytes, red blood cells, and platelets are all created in the bone marrow during normal hematopoiesis in adults. This process takes place in the bone marrow. On the other hand, fetal hematopoiesis takes place in unique places and at different phases of development than adult hematopoiesis. Primitive hematopoiesis happens briefly in the yolk sac during the early stages of embryo development. Definitive hematopoiesis starts after primary hematopoiesis and moves from the aorta-gonad-mesonephros (AGM) to the liver, and then to the bone marrow. These are the two stages of the development of fetal hematopoiesis. Our bodies are kept alive and protected by our circulatory system, which is responsible for three essential functions: oxygen delivery, coagulation, and immunity. Platelets are anucleate blood cells that play a role in clotting and are released from megakaryocytes in the bone marrow. Platelets are responsible for the clotting process. In typical thrombocytosis, mature megakaryocytes will have an extended cytoplasmic structure that is referred to as the proplatelet. The tip of the proplatelet extends into the bone marrow sinus, which is where it is sheared and changed into a platelet by the circulation (Junt et al., 2007; Kosaki, 2008; Machlus & Italiano, 2013; Thon et al., 2010). (Junt et al., 2007; Kosaki, 2008; Machlus & Italiano, 2013; Thon et al., 2010). (Lefrancais et al., 2017) Recent research has shown that megakaryocytes may be found in the lung and spleen of mice. These cells, when stimulated by the movement of blood, can then produce platelets.

According to Estcourt et al. (2017), blood products obtained from blood donors are utilized in the treatment of a variety of diseases and conditions that can result in cytopenia. On the other hand, the system for blood transfusions needs to be improved because there has been a decline in the number of people willing to donate blood as a result of declining birthrates and shifting attitudes among the younger population. Additionally, there has been an increase in demand because of the prevalence of chronic blood disorders among the elderly. Platelet preparations can be maintained at room temperature without losing their function, although they have a statutory expiration date that is only five days after they are made. As a direct consequence of this, platelet preparations are notoriously difficult to keep in stock. In addition, some individuals have alloantibodies that are directed against platelet-expressed human leukocyte antigen class I (HLA-I). This can lead to a condition known as alloimmune platelet transfusion refractoriness, or allo-PTR (Stanworth et al., 2015). Platelet transfusions that are HLA-compatible are necessary for optimal treatment; yet, supply shortages frequently result in patients not being adequately supplied. Pluripotent stem cells, which include embryonic stem (ES) cells (Thomson, 1998) and induced pluripotent stem (iPS) cells (Takahashi et al., 2007), have the potential to grow in vitro indefinitely and are a prospective source for the development of blood transfusion products that can serve as a replacement for blood donations. Irradiation of platelets prior to blood donation can help lower the risk of cancer caused by iPS cell contamination.

Since platelets are nucleolus-free cells, this risk can be mitigated. In addition, there is the possibility of improving the current blood transfusion system, which is dependent on donors, by using stored iPS cells that are homozygous for HLA in order to maintain a constant supply of HLA-compatible platelets. In more recent times, genetic editing techniques such as the CRISPR/Cas9 approach have made it possible to create HLA class I-deleted blood products in order to prevent rejection (Cong et al., 2013; Mali et al., 2013). This has allowed for the elimination of the need for HLA class I-deleted blood products to be used in transplantation. This paper discusses a number of topics, including the production of megakaryocyte cell lines, bioreactors, and scaled-up cultures, as well as the locating of potentially useful drugs during the manufacturing process. In addition to this, we will talk about the universal applicability of platelet products produced from iPSCs that lack HLA.

2 MEGAKARYOCYTE HEMATOPOIESIS DEVELOPMENT

Primitive hematopoiesis is the first step in the process of hematopoiesis, which takes place during ontogeny. Researchers have spent a significant amount of time and effort, primarily on mice, investigating hematopoietic development. According to Moore and Metcalf's 1970 research, the first occurrence of hematopoiesis in mice was the formation of structures known as blood islands in the yolk sac. The yolk sac is an extrafetal membrane tissue that surrounds the embryo beginning somewhere around day 7 of the fetal phase. The majority of fetal red blood cells containing fetal hemoglobin are formed in blood islands (Silver & Palis, 1997), but macrophages (Palis et al., 1999) and megakaryocytes (Tober et al., 2007) are also formed.Around day 10 of the fetal phase, definitive hematopoiesis begins with the generation of hematopoietic stem cells (HSCs) from the AGM area in the fetus, with the produced HSCs moving to the liver (Medvinsky & Dzierzak, 1996). On day 16 of the fetal phase, the HSCs begin to continually self-renew and differentiate (Ema & Nakauchi, 2000), developing both themselves and a variety of adult blood cells at the same time. This process is documented in the research of Ema & Nakauchi. The fetal liver is the primary site of hematopoiesis immediately after birth, but HSCs migrate to the bone marrow shortly before birth, where hematopoiesis also occurs, and in adults is the site of hematopoiesis throughout life.Long-term (LT) HSCs may be transplanted into mice with diminished hematopoietic capability (Osawa et al., 1996), whereas short-term (ST) HSCs have pluripotency but only transitory self-renewal ability (Osawa et al., 1996). (Christensen & Weissman, 2001). As the cells progress from stem-like HSCs into multipotent progenitors (MPPs), they lose the capacity to undergo self-renewal throughout this stage of development. In the not too distant future, MPPs will serve as the progenitors of all blood cells. After that, the common lymphoid progenitors (CLP), granulocyte/monocyte progenitors (GMP), megakaryocyte/erythroblast progenitors (MEP), and common myeloid progenitors (CMP) were purified and identified, and the pathways of their hematopoietic differentiation system were clarified (Akashi et al., 2000; Kondo et al., 1997). In accordance with the conventional understanding of megakaryopoiesis, HSCs are capable of differentiating into megakaryocyte progenitors known as MPPs, CMPs, and MEPs after undergoing the process of megakaryopoiesis.

According to research conducted by Bartley et al. and Kaushansky et al. in 1994, thrombopoietin (TPO), which is mostly produced by the liver, is an important cytokine for the development of megakaryocytes. In addition, cytokines such as interleukin (IL)-3 (Teramura et al., 1988), IL-6 (Navarro et al., 1991), IL-11 (Broudy et al., 1995), GM-CSF (Briddell et al., 1991), SCF (Briddell et al., 1991), and LIF (Metcalf et al., 1991) have been found to promote TPO interacts to a single transmembrane receptor called c-MPL, which dimerizes when TPO attaches. After that, the phosphorylation of tyrosine residues on the c-MPL receptor activates the JAK2/STATs pathway, in addition to MAPKs and PI3K/Akt via RAS, which ultimately results in the synthesis of a collection of megakaryocyte differentiation genes (Beer et al., 2008; Drachman et al., 1995; Grozovsky et al., 2015). transcription factors GATA-1 and FLI-1 are engaged in megakaryocyte differentiation (Deveaux et al., 1996; Frontelo et al., 2007; Stachura et al., 2006). These factors are also involved in the modulation of mpl gene expression and the differentiation of MEP fractions into erythrocytes and megakaryocytes (Deveaux et al., 1996; Frontelo et al., 2007). During the maturation of megakaryocytes, the FOG1/GATA1 complex, RUNX1, and FLI-1 have been related to the transcriptional regulation of megakaryocyte differentiation (Lordier et al., 2012; Shimizu et al., 2004, 2009; Wang et al., 2002). These findings were published in Lordier et al.

Platelet activity can be modulated by NF-E2, which also contributes to the creation of platelets and enhances the formation of proplatelets in mature megakaryocytes (Levin et al., 1999; Shivdasani et al., 1995). These findings were published in two separate studies. Although the above describes the classic model for the generation of megakaryocytes and platelets, it was recently discovered that HSCs contain megakaryocyte repopulating progenitors (MKrPs) (Yamamoto et al., 2013). This contradicts the model described above. Straight from the HSCs, MKrPs are destined to develop into megakaryocytes in their mature state. In addition, certain HSCs that express von Willebrand factor (vWF), a protein that is present on megakaryocytes, have been demonstrated to develop directly into megakaryocytes (Sanjuan-Pla et al., 2013). This was discovered by the researchers that worked on the study. Additionally, MPPs were divided into four distinct groups (MPP1-4), each of which possessed a unique skew differentiation lineage. According to Pietras et al.'s (2015) research, MPP2 is especially predisposed to megakaryocyte and erythrocyte differentiation. According to Rodriguez-Fraticelli et al. (2018), it has also been discovered that MPP2 can develop into megakaryocytes in a direct manner.

3 BENEFITS OF BLOOD PRODUCTS MADE FROM iPS CELLS

Pluripotent stem cells, also known as iPS cells, have the capacity to self-renew and can proliferate indefinitely when cultured in vitro. Reconstructing the hematopoietic system with iPS cells in order to gain a better understanding of the developmental mechanism could be beneficial. In addition, iPS cells that are produced from specific individuals have the potential to be used for disease modeling, which can aid in the investigation of pathology and the testing of medications. Because of the simplicity with which iPS cells may be genetically changed via CRISPR/Cas9 and other technologies, it is possible to explore the function that particular genes play in the process of development as well as disease. In the field of regenerative medicine, patients' own cells as well as highly immunocompatible iPS cells could serve as potential source cells. iPS cells have been successfully differentiated into several different types of blood cells, including lymphocytes (Nishimura et al., 2013; Themeli et al., 2013; Vizcardo et al., 2013); myeloid cells (Haruta et al., 2013); erythrocytes (Hirose et al., 2013; Kurita et al., 2013); the nonpathogenicity of iPS cell-derived Induced pluripotent stem (iPS) cells may be used to generate a wide variety of blood cell lines, each of which would be capable of both self-replication and cryopreservation. This would result in an enormous number of blood cell lines that are both safe and functional and could be stored in a master cell bank. By adhering to good manufacturing practice or good gene, cellular, and tissue-based products manufacturing practice (GCTP) standards for the manufacturing process after freezing, it would be possible for it to manufacture blood products of an assured clinical grade quality.

4 PLATELET DIFFERENTIATION WITH ES AND iPS CELLS

A single platelet transfusion in Japan consists of 10 units, which is equivalent to around 200 billion platelets. Utilizing the capacity of iPS cells to self-renew indefinitely has allowed us, together with other groups, to devise a method for vastly increasing the quantity of iPS cells used in the production of megakaryocytes and platelets. This method was developed in order to meet the demand for these products. By co-culturing mouse fetal 10T1/2 cells with ES/iPS cells in the presence of vascular endothelial growth factor (VEGF), our differentiation method is able to produce ES/iPS cell-derived sac-like structures. These structures are referred to as ES/iPS-sac. Blood progenitor cells are contained within the sac's interior. According to Takayama et al. (2008) and Takayama et al. (2010), it is possible for these progenitor cells to directly develop into megakaryocytes and platelets if they are grown in the presence of soluble factors such as SCF and TPO.

The acquired platelets are responsible for the formation of thrombi in vivo. Feng et al. were able to develop iPS cells directly into megakaryocytes and platelets by using the EB approach (Feng et al., 2014). This was accomplished in a medium that lacked a feeder, included no serum, and contained no animal components. In addition, they utilized the TALEN technique to generate genetically altered HLA-null iPS cells into megakaryocytes and platelets, revealing that the platelets are capable of performing their intended role. (Hansen et al., 2018) Hansen et al. used a monolayer differentiation system to convert single iPS cells into blood progenitor cells in an environment free of feeder cells and serum.

They subsequently differentiated the blood progenitor cells into megakaryocyte, erythroid, and myeloid cells. None of these methods have been proven to be useful for actual clinical practice since the procedures are so complicated and the incubation times are so long. As a solution to the problems described in the introduction, our team devised an innovative strategy for immortalizing megakaryocytes.

5 The Generation of Immortal Megakaryocyte Cell Lines from Individual Primary Stem Cells

Using our previous ES/iPS cells differentiation approach, we found that the expression of c-MYC is repressed during the maturation phase of megakaryocytes, whereas it is raised during the proliferation phase of megakaryocyte progenitor cells (Takayama et al., 2010). This was something that we observed. As a consequence of this, c-MYC transgenic mice had a greater population of megakaryocytes than wild type mice, although there was no discernible difference in the quantity of platelets (WT; Thompson et al., 1996). On the other hand, c-MYC knockout animals had megakaryocytes with a low ploidy level (8N) and platelets with a high MPV. In addition to this, c-MYC knockout animals had a greater number of megakaryocytes and platelets than wild-type mice did (Guo et al., 2009). According to these findings, it appears that carefully managed expression of c-MYC is necessary for the maturation and proliferation of megakaryocytes. When ES cells were used to create blood progenitors, overexpression of c-MYC led to a temporary increase in megakaryocyte proliferation. However, this was followed by cellular senescence and eventually death. Because the polycomb complex component BMI1 and the BCL2 family member BCL-XL repress the cellular senescence-inducing INK4A/ARF gene locus and apoptosis, we were able to create immortalized megakaryocyte cell lines (imMKCLs) by transferring the c-MYC and BMI1 genes, followed by the BCL-XL gene, into human iPS/ES-derived hematop (Nakamura et al., 2014). Adding doxycycline leads imMKCLs to proliferate with the expression of the three genes switched on (designated as DOX ON), but removing doxycycline allows imMKCLs to mature and release platelets (designated as DOX OFF). This is due to the fact that these three genes are controlled by the Tet-On system in our system. We proposed a method to produce a large number of clinically applicable platelets from these imMKCL master cells through liquid culture in accordance with good manufacturing practice or GCTP clinical grade standards. This would be accomplished by stocking a large quantity of imMKCL strains as a master cell bank and confirming both their safety and their high level of productivity.

The high cost, on the other hand, makes it necessary to find ways to improve the conditions of the cultural media. In the first iteration of the imMKCL medium, we needed to use pricey recombinant proteins such stem cell factor (SCF) and thrombopoietin (TPO). However, we have only recently developed a TPO-like agonist in the form of the small molecule TA-316 (Aihara et al., 2017). KP-457 was found to block a disintegrin and metalloprotease 17 (ADAM17) activity at culture temperatures of 37 degrees Celsius (Hirata et al., 2017). This activity cleaves the extracellular surface of the vWF receptor GPIb (CD42b). KP-457 was discovered under these conditions.

Moreau et al. forced the expression of GATA1, FLI1, and TAL1 during the differentiation of iPS cells into megakaryocytes (Moreau et al., 2016). This resulted in the creation of forward programmed megakaryocytes (fopMKs), which is a cryopreservable and expandable megakaryocyte cell line. Overexpressing NF-E2, Maf-G, and Maf-K in human and mouse fibroblasts was the method that Ono et al. utilized in order to develop megakaryocytic cells. This method did not involve the use of iPS cells. (Ono et al., 2012). (Tozawa et al., 2019) They also produced megakaryocytes from a human adipose-derived mesenchymal stem cell line that proliferated for over two months. These cell lines have the potential to become a useful source of material if the conditions for growth on a big scale are optimized.

SIX NEW PHYSICAL FACTORS IN THE PRODUCTION OF PLATELETS IN VIVO HAVE BEEN DISCOVERED

Feeder cells are necessary for the culture of imMKCL throughout the proliferation and maturation stages (adhesion dependent), however a culture that does not require feeder cells is necessary for therapeutic usage. Throughout the whole growth phase, we were able to cultivate imMKCLs successfully in a 100-ml flask and a 1–20-L WAVE bag system with a moderate rocking motion but without the need of feeder cells. It was revealed that the combination of Rho-associated protein kinase (ROCK) inhibitors and aryl hydrocarbon receptor (AhR) antagonists could permit platelet formation in feeder-free circumstances throughout the maturation phase (Ito et al., 2018). This was reported by Gobbi et al. (2013) and Strassel et al. (2016), respectively.

According to two-photon microscopy (Junt et al., 2007), the cytoplasm extends from megakaryocytes in the bone marrow to the lumen of blood vessels. There, the terminals of the protrusions are split by blood flow stimulation. It is believed that shear stress is the fundamental factor responsible for cytoplasmic cleavage. Shear stress has been used as the foundation for the construction of bioreactors by a number of different organizations, including our own (Avanzi et al., 2016; Di Buduo et al., 2015; Nakagawa et al., 2013). A microfluidic platelet bioreactor that imitated the environment of bone marrow was built by Thon et al. by loading human umbilical vein endothelial cells (HUVECs) and extracellular matrix components onto a chip (Thon et al., 2014). This allowed the researchers to study how platelets behave in the bone marrow. Blin et al. developed a bioreactor that has a number of vWF-coated micropillars that work as megakaryocyte anchors (Blin et al., 2016). This bioreactor efficiently enables shear stress to be applied to megakaryocytes. Since platelet production efficiency was low across the board for the reactors, we made the assumption that shear stress alone does not adequately portray the environment of the bone marrow. As a consequence of this, we decided to further explore the areas in the bone marrow where platelets are manufactured by employing two-photon microscopy and particle image velocimetry (PIV). Platelets were sheared and freed from proplatelets at a bloodstream site that was subjected to turbulence, which indicates that turbulence plays a physical function in the production of platelets as well (Ito et al., 2018).

PLATELET PREPARATIONS MADE FROM iPS CELLS THAT ARE USED IN THE PRODUCTION

On the basis of the findings that turbulence promotes to platelet production in vivo, we cultured imMKCLs in a vertical reciprocal motion liquid culture bioreactor (VerMES) with adjustable turbulent physical circumstances. The VerMES has a capacity of 2.4 liters and can produce turbulent physical conditions of varying degrees. Using this technique, we were able to generate iPS cell-derived platelets that functioned very similarly to platelets in vivo in a very efficient manner (approximately 80 platelets per megakaryocytes).

An investigation into the effects of varying levels of turbulence on the physical features of culture vessels as well as the formation of platelets was carried out with the use of 0.3-L and 2.4-L VerMES. It was determined that the volume of the VerMES culture vessel has no bearing on the appropriate quantities of shear stress and turbulent energy that should be present. As a consequence of this, we adjusted the shear stress and turbulent energy in an 8-L VerMES in order to generate 100 billion platelets that are functional. Through the use of electron microscopy, it was discovered that the ultrastructures of platelets produced from iPS cells and platelets seen in vivo are completely identical. Watanabe et al. (2017) used thrombocytopenic mouse and rabbit models to establish that the iPS cell-derived platelets exhibited a hemostatic capability similar to donor platelets (Ito et al., 2018). This was demonstrated by the fact that the iPS cell-derived platelets were able to clot blood in the same manner as donor platelets.

Since an examination of imMKCLs cultivated in VerMES and static cultures indicated practically no difference in gene expression patterns (Ito et al., 2018), our team came up with the hypothesis that key components that stimulate platelet synthesis may be released from imMKCLs in VerMES cultures. Proteomic examination of the culture supernatant revealed an increase in the secretion of six proteins in the VerMES culture as compared to the culture that was maintained in static conditions. This was determined by examining the difference between the two cultures. It was surprising to find that adding the VerMES culture supernatant to the static culture did not have much of an effect on the creation of platelets. This finding suggests that soluble factors and physical stimuli, including shear stress, work together to stimulate platelet development. Platelet production can be stimulated by sardilysin (NRDC; Nishi, 2013), macrophage migration inhibitory factor (MIF; Strußmann et al., 2013), and insulin-like growth factor binding protein 2 (IGFBP2; Coppé et al., 2008). All three of these factors have been shown to have this effect. In cultures where neither MIF nor IGFBP2 was present, proplatelet generation was shown to be much lower, as determined by observations performed in a microfluidic chip environment. Further investigation found that the absence of MIF and IGFBP2 resulted in a reduction in the amount of extracellular matrix that was secreted, which in turn inhibited proplatelet formation. According to Nishi (2013), NRDC was discovered in a turbulent environment around proplatelets, and it is hypothesized that it plays a role in the endopeptidase-mediated fragmentation of the proplatelets. In conclusion, it is believed that stimulation of turbulent flow prompts the growth of proplatelets by means of an autocrine mechanism. This process ultimately results in shear stress cleaving the cell membrane, which is necessary for the production of platelets.

8 DIFFERENCES IN MEGAKARYOCYTE MATURATION AND PLATELET PRODUCTION BETWEEN IN VITRO AND IN VIVO

Adult megakaryocytes in the bone marrow mature into giant polyploid cells with chromosome numbers ranging from 16N to 124N, migrate into the vascular niche, come into contact with collagen type IV in the vein's basement membrane, and form proplatelet protrusions in order to release platelets into the bloodstream (Semeniak et al., 2016). This process allows platelets to be released into the bloodstream. On the other hand, megakaryocytes generated from iPS cells almost exclusively consist of weakly polyploid cells, with numbers ranging from 2N to 32N. (Takayama et al., 2010). In a similar manner, the number of nucleosomes found in megakaryocytes that were produced in vitro from CD34+ cells isolated from peripheral blood can range anywhere from 2N to 32N. (Liu et al., 2011). The formation of proplatelets begins as protrusions at numerous places along the cell membrane in vitro. These protrusions elongate and release platelets.

It is estimated that a single MK in the bone marrow will generate between 800 and 2,000 platelets, whereas imMKCLs only produce between 60 and 80 platelets per cell. In addition, platelets generated from iPS can be anywhere from 2 to 10 times larger than those generated in vivo, which are just 2 to 4 times larger. After being injected into mice, it was noticed that the large iPS-derived platelets became broken due to the movement of blood (Ito et al., 2018).

It is currently believed that the involvement of the vascular niche and the environment of the bone marrow has not been sufficiently adapted to the growth conditions in vitro. This is due to the fact that the formation of polyploid cells and platelets is significantly lower in vitro than it is in vivo.

COMPATIBILITY OF 9 HLA ANTIGENS WITH iPS CELL-DERIVED PLATELETS

It is possible to become sensitized to non-self HLA-I and generate antibodies against it if one is pregnant or receives a significant number of platelet transfusions. As a direct consequence of this, between 5 and 15 percent of patients who undergo platelet transfusions experience allo-PTR, which is the rejection of transfused platelets due to an incompatibility with HLA-I. Platelets that are compatible with the individual's HLA are necessary for these patients, but they are not always readily available, especially in unusual circumstances or during medical emergencies (Stanworth et al., 2015). Platelets produced from iPS cells offer a number of potential solutions to the problem of allo-PTR. To get started, iPS cells taken from the patient can be used to make autologous platelets (https://jrct.niph.go.jp/en-latest-detail/jRCTa050190117). This will get the process off to a good start. This product is completely compatible with nature, including HLA and the human platelet antigen (HPA), which is an alloantigen on platelets that can generate allo-PTR and post-transfusion purpura (Semple et al., 2011; Stanworth et al., 2015). However, the production of autologous platelets for each individual is a time- and resource-intensive process that can be rather expensive.

Alternately, our laboratory along with a number of others have been stockpiling homozygous HLA haplotypes in iPS cells (Turner et al., 2013; Umekage et al., 2019). These cells are highly compatible with one another. The 10 most prevalent lines of induced pluripotent stem cells (iPSCs) that have homozygous HLA have the potential to cover around half of the Japanese population, according to estimations. These cells can be employed as a universal product without the necessity for a library of HLA haplotypes (Feng et al., 2014; Gras et al., 2013; Suzuki et al., 2020). In addition, they can be utilized as a substrate for the production of additional modified products, which may ultimately result in the development of novel platelet therapies.

10 CONSIDERATIONS

Since the announcement that human iPS cells had been developed in 2007, there have been a total of thirteen years pass. It has been demonstrated that adequate quantities of platelets derived from iPS cells can be created for use in therapeutic transfusions. As a direct consequence of this, a first-in-human clinical research utilizing autologous iPSC-derived platelets in patients with allo-PTR was initiated in 2019 (https://jrct.niph.go.jp/en-latest-detail/jRCTa050190117). One of the issues that are now being faced is bringing down the price of production. In this context, greater maturation of imMKCLs is necessary by building a culture system that simulates the environment seen in living organisms. In the future, further technological improvements will reach levels that are industrialized, making it possible to construct new medical systems that will make it possible to have safe and ready transfusion systems whenever they are needed.

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