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# Autologous Peripheral Blood Purified Stem Cells Transplantation for Treatment of Systemic Lupus Erythematosus

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## 1. Introduction

"Lupus", from the Latin in the 19th century, had appeared in the West before and after the medical literature. In 1828, the French dermatologist Bette (Bielt) firstly reported such a patient: facial skin has erythema the same as the the wolf bites. To the mid-19th century, there was a doctor named Carson Musharraf formally using the "lupus" (lupus erythematosus, LE) as the medical terminology, which only referred to skin lesions of discoid lupus erythematosus then. With the development of medical science and clinical practice, more and more doctors found that lupus is not only skin damage, but also associated with kidney, brain, heart, lungs, nerves, muscles and joints, blood and other systemic diseases. To the 1890s, American doctor Osler (Osler) proposed the disease as "systemic lupus erythematosus" (systemic lupus erythematosus, SLE) [1]. Systemic lupus erythematosus (SLE), a common autoimmune disease without explicit etiology, has a high incidence of secondary infection, treatment difficulties and high mortality, arousing the focus of domestic and foreign scholars. According to the prevalence rate from 70 to 100/10 million people [2], China has reached to 1.12 million patients which is constituted mainly by young women. In addition to involving the outer skin, the disease violates various body organs, including vital organs such as the nervous system, heart, kidney and so on, the central nervous system such as meningitis, encephalitis, acute cerebrovascular disease, spinal cord inflammation and subarachnoid hemorrhage, even to death. It is the most common when occurring cardiac involvement, such as pericarditis, pericardial effusion heart attack, and life-threatening acute cardiac tamponade, which affect the quality of life. Involving the kidneys, it may be kidney failure. Respiratory system involvement includes bronchial pneumonia, pleurisy, atelectasis and respiratory failure. Secondary infection is a common complication of SLE, causing death at worst.

SLE is considered a typical multi-organ involvement autoimmune disease, as a result of the disorder of immune system[3,4]. Before the 1960s, the 5-year survival rate was below 50%. With the progress of the treatment and the development of therapeutic drugs, especially corticosteroids and cytotoxic drugs for SLE, the survival rate has improved significantly, has

reached 93% to the 1990s, while 10 and 20 year survival rate has reached 92%, 68%, respectively[5,6].

In treatment, we begin with corticosteroid and cytotoxic at large doses the most, in order to suppress the disease, in 1-2 weeks, if necessary, plus corticosteroid pulse therapy or immunosuppressive therapy. Glucocorticoid inhibits T lymphocytes mainly through the production of growth factors and Fc receptor expression [7,8]. However, the dosage of corticosteroids varies with the insensitivity of the patients. In addition, due to large amount of medication for a long time, it prones to side effects and complications, such as: infection (viruses, bacteria, fungi, etc.), induced diabetes, peptic ulcer, perforation or gastrointestinal bleeding, fractures and avascular necrosis, mental disorders, Cushing's syndrome, acne, hirsutism, etc. More than 60% of patients died of hormonal side effects, which has bad impact on life quality [7]. Therefore, it is still a medical problem without effective cure. The latest research reports, it is an effective and new treatment for SLE by hematopoietic stem cell transplantation [4], the evaluation of long-term efficacy of which remains to be seen. Since the pathological immune T, B lymphocytes from the common lymphoid stem / progenitor cells, it may be an effective way to cure the disease by the application of certain tools (such as chemotherapy or radiotherapy) to destroy pathological immune and re-establish normal immune system by hematopoietic stem cell transplant[3,7]. In recent years, it gradually become a hot topic in international research for autologous peripheral blood stem cell transplantation for treatment of SLE and other autoimmune diseases, whose exact mechanism is not fully clear, only defined to the level of the original autoimmune cell clones completely destroyed, while normal one re-established [7 10]. Autoimmunity and self-tolerance is a dynamic equilibrium between the process, in which, we use immunosuppressive agents to weaken the strength of their immune, while hematopoietic stem cell transplantation to support the power of self-tolerance and eventually make the body's immune system normal [11]. Theoretically, it is possible to cure SLE and other autoimmune disease, and may achieve the purpose of healing.

## **2. Materials and methods**

### **2.1 Clinical data**

A total of 16 patients consistent with the diagnostic criteria for SLE by American College of Rheumatology in 1982 were recruited, for whom corticosteroids and immunosuppressive therapy ineffective. There are 4 males and 12 females, aging from 11-37 years old, and the type of renal pathology, II, III, IV, V were 3, 3, 6, 4 cases, respectively. SLEDAI scores are 14-35 points.

### **2.2 Reagents**

CD34<sup>+</sup> cell isolation kit, Germany Miltenyi Biotec Company; Lymphocyte separation medium, Beijing Ding Guo; Antibody (mouse IgG1-PE, mouse anti-human CD34-PE), American Gene Company; 3 - aminopropyl triethoxy silane solution, a company in Kyoto, Japan

### **2.3 Main instruments**

Immunomagnetic separation system, company Miltenyi Biotec, Germany; Blood cell separator, U.S. BAXTER Company; BD's flow cytometry, U.S.; Low-speed desktop

centrifuge, Beijing Medical Centrifuge Factory Hettich, Germany's low-temperature high-speed centrifuge

#### **2.4 Hematopoietic stem cell mobilization, collection, purification and cryopreservation**

Mobilization plan: cyclophosphamide + granulocyte colony stimulating factor. We use cyclophosphamide intravenous 4g/m<sup>2</sup>, divided into 2 to 3 days, and urine alkalization and hydration to protect the heart, liver and kidney. When WBC <1.0 × 10<sup>9</sup> / L, give Recombinant Human Granulocyte Colony-stimulating Factor Injection 5ug/kg, until WBC > 5.58 × 10<sup>9</sup> / L and CD34 <sup>+</sup> > 2% we start collecting with CS3000Plus blood cell separator (BAXTER products). After dilution and volume adjustment, plus CD34 monoclonal antibody in cells in 19 ~ 25 °C for 30 minutes, then wash 2 times by PBS buffer to pre-sort on MiniMACS separator, at last cool and liquid nitrogen froze immediately.

#### **2.5 Pre-treatment**

Cyclophosphamide 50mg/kg daily, intravenous infusion, once every 4 days (-5 to -2 days); ATG 2.5mg/kg.d, intravenous infusion, once every 3 days, while urine alkalization and hydration to protect the heart, liver and kidney.

#### **2.6 Hematopoietic stem cell reinfusion**

Transplant day 0, recover the frozen stem cells in 37 °C ~ 40 °C water bath, then rapid transfusion through subclavian vein cannulation.

#### **2.7 Follow-up indicators**

Dynamic monitoring hematopoietic and immune indicators of clinical manifestations of SLE patients after transplantation.

#### **2.8 Statistical analysis**

We use software package SPSS10.0 processing repeated measurements analysis of variance of autoantibodies, immune function monitoring indicators in patients with SLE who underwent autologous peripheral blood stem cell transplantation.

### **3. Results**

#### **3.1 Autologous peripheral blood stem cell mobilization**

The total number of collected CD34 <sup>+</sup> cells ranged from (2.06-9.9) × 10<sup>8</sup>, higher than the required 2 × 10<sup>6</sup>/kg, is the success of hematopoietic stem cell collection for the 16 patients.

#### **3.2 Mobilization-related complications**

The total of 16 patients have leukopenia and gastrointestinal adverse reactions, and all with varying degrees of fever, but blood cultures were negative. 1 case has severe edema, but alleviate after the supplement of albumin and furosemide. 1 case has atopic dermatitis (specific reasons unknown), the anti-histamine treatment effective. All the patients were in stable condition after mobilization without the original mobilization-related illness or death.

### 3.3 Changes in clinical transplantation

Within 1 month after transplantation, the facial rash, joint pain and other symptoms disappeared completely in all patients. 13 patients with proteinuria disappeared completely in three months, 3 cases of the four V-type, still urinary protein in a year, but the 24-hour urine protein continued to decline. One patient, 1 year after transplantation, had the recurrence of oral ulcers, arthralgia, leukopenia and elevated titers of autoantibodies. The other patient, 2 and a half years after transplantation, had facial erythema, leukopenia and elevated titers of autoantibodies.

### 3.4 Hematopoietic reconstitution after transplantation

The number of peripheral blood leukocytes is  $> 1.0 \times 10^9 / L$  after 7 to 15 days, platelets is  $> 20 \times 10^9 / L$  0 to 21 days.

### 3.5 Transplant-related complications

All patients suffered from uneven serum sickness-like reactions, 1 case severe renal failure and heart failure, 3 cases hemorrhagic cystitis, 1 case psychogenic mental disorders, 1 case perineal candidiasis, 1 case acute pulmonary edema, 1 case septic shock, but all recovered after active treatment. 2 patients had fever after transplantation because of tuberculosis infection (see Chapter VII). One case with fever in October after transplantation, had chest CT showing: 1, multiple new lung nodules; 2, left lung consolidation; 3, pericardial thickening, small left pleural effusion. According to CT, it was much as the invasive nature of purulent bacterial or fungal infection, in combination with other manifestations, at last diagnosed as fungal infections, alleviated after itraconazole injection. 12 cases of cytomegalovirus infection became negative after ganciclovir treatment (see Chapter VI). 3 cases of herpes zoster, 1 case of generalized herpes zoster, were recovered after treatment by ganciclovir. 1 case in the purification of autologous peripheral blood stem cell transplantation in August, appeared Evans syndrome (also known as idiopathic thrombocytopenic purpura with autoimmune hemolytic anemia). Check ENA polypeptide: ANA 70.50u/ml, ds-DNA 18.65u/ml, RNP 49.90u/ml, Sm 15.44u/ml, Coomb's test showed: more than a single specific anti-human globulin (++), specific anti-C3 (+), monospecific anti-IgG (+). Bone marrow pathology: bone marrow dysfunction, three lines of hematopoietic cells can be seen, the proportion of red tablets was normal, megakaryocyte number and morphology were without exception. Be double filtration plasmapheresis and methylprednisolone injection pulse therapy, Coomb's test showed: more specific anti-human globulin (+), single-specific anti-C3 (+), I (-). Plus immunosuppressive agents cyclosporine and vincristine, while reducing the hormone dosage, it is stable in clinical and laboratory condition.

### 3.6 Post-transplant changes in autoantibody

After transplantation ANA, anti Ds-DNA antibodies, anti-Sm antibodies, anti-RNP antibody titers decreased than those before transplantation, but among the different phases they showed no significant ( $P > 0.05$ ), while ANA, anti-RNP antibody titers were significantly lower than before transplantation ( $P < 0.05$ ), specifically in chapter IV.

### 3.7 Post-transplant immune reconstitution

It is different for CD3 +, CD45RA + CD4 +, CD45RA + CD8 +, CD45RO + CD4 + expression when 3 months, 6 months and 1 year after transplantation ( $P < 0.05$ ). (1) 3, 6 month after

treatment, CD3 + expression levels were significantly lower than that before transplantation (P <0.05); (2) 6,12months after transplantation, CD45RA + CD4 + expression levels were significantly higher than that 3 months after transplantation (P <0.05), but no significant difference than before treatment (P> 0.05); (3) 3,6 months after transplantation when CD45RA + CD8 + expression levels were significantly lower than before transplantation ( P <0.05). (4) 3,6, 12 months after transplantation, the CD45RO + CD4 + expression levels were significantly lower than that before transplantation (P <0.05). Detailed in Table 1. and Chapter.

| time                      | CD <sub>3</sub> <sup>+</sup> | CD <sub>45</sub> RA <sup>+</sup> CD <sub>4</sub> <sup>+</sup> | CD <sub>45</sub> RA <sup>+</sup> CD <sub>8</sub> <sup>+</sup> | CD <sub>45</sub> RO <sup>+</sup> CD <sub>4</sub> <sup>+</sup> |
|---------------------------|------------------------------|---|---|---|
| Before<br>transplantation | 74.49±9.79                   | 5.80±3.96   | 28.95±11.28   | 16.66±5.60  |
| 3 months later            | 58.04±20.61*                 | 3.41±4.46   | 20.29±11.11*  | 8.43±3.32*  |
| 6 months later            | 62.75±17.09*                 | 6.33±4.87 <sup>Δ</sup>  | 18.89±8.18*   | 10.26±4.84*   |
| 12 months<br>later        | 67.28±14.16                  | 7.84±3.63 <sup>Δ</sup>  | 23.14±10.15   | 11.55±5.25*   |
| F                         | 3.727                        | 4.457   | 4.539   | 8.325   |

Mauchly test of sphericity, P> 0.05, the spherical assumption is not rejected, without correction with correction factor ε freedom.  
\* Compared with the pre-transplant, P <0.05; Δ compared with 3 months after transplant, P <0.05

Table 1. Alternation of immune function in patients with SLE before and after AHSCT

4. Discussion

Systemic lupus erythematosus is an autoimmune disease, without clear cause and difficult to cure. In recent years, with the increasing levels of health care, new drugs and treatments are emerging for treatment. Particularly glucocorticoids and cytotoxic drugs for SLE, the survival rate has improved significantly. To the 1990s, 5,10,20-year survival rate has reached 93%, 1 92%, 68%,respectively [5,6].  
Though corticosteroid treatment with cytotoxic drugs is still the preferred solution, However, due to the large amount of medication for a long time, prone to side effects and complications and make 60% of patients eventually die from side effects o [7]. Therefore, it is still medical problem at home and abroad.  
In 1985, Ikehara confirmed Allo-BMT to treat mice autoimmune disease. In 1991 Knaan-Shanzer confirmed their bone marrow transplant for adjuvant arthritis in rats. At the same time,it was discovered that receiving Allo-BMT or autologous bone marrow transplantation can achieve remission for autoimmune disease such as the blood system or other malignancies [12]. Karussis et al [13] firstly used cyclophosphamide and granulocyte colony-stimulating factor to stimulate the bone marrow to release hematopoietic stem cells into the blood, and isolated, purified and separate mouse hematopoietic stem cells in vitro. After sorting the total number of CD34<sup>+</sup> cells greater than 2.0 × 10<sup>6</sup>/kg, use large doses of immunosuppressive agents in the second step for abnormal immune cells elimination, then reinfuse the CD34<sup>+</sup> cells into mice. After the reconstruction of immune system, and long term follow up, it was found that it has achieved remarkable results in animal models.



In recent years, it is effective that autologous peripheral blood stem cell transplantation for autoimmune diseases and becoming a hot topic in international research. Firstly, we use doses of immunosuppressive agents or radiation in patients to finish a strong immune suppression, and then rebuild the patient's immune system by autologous hematopoietic stem cell transplantation. The use of peripheral blood transplantation, hematopoietic stem cells has no anesthesia, trauma and has an earlier immune reconstitution compared to bone marrow transplantation. The patient's immune regulation in the reconstruction process can reach a new equilibrium and (or) immune tolerance, may complete remission or even completely cured [7 ~ 11].

Hematopoietic stem cell transplantation (HSCT) for the treatment of SLE has opened up a new way, however, there is a certain risk, which confined its use. Combined with existing research and the experience, the performance of at least one of the following may be considered for HCST treatment; ① epileptic seizures or psychiatric symptoms; ② lung involvement at one of the following: pulmonary hemorrhage, infiltration and no infection is present, within the last 6 months is greater than 15% lower forced vital capacity, pulmonary hypertension; ③ refractory hemolytic anemia, reticulocyte count is greater than 3%, hemoglobin less than 100g / L; or the decreaseing of other fatal blood cells; ④ SLE disease activity index greater than 16 points; ⑤ serious anti-cardiolipin antibody syndrome. Nephritis and has one of the following persons: proteinuria greater than 1g / d and albumin less than 30 g / L, serum creatinine greater than 15mg / L, and hematuria, cellular casts, renal biopsy with acute proliferative damage. Patients also need the following therapy: oral prednisone 0.5mg/kg at least 2 months, last 6 months or intravenous methyl poured nylon 1g, 3 times; application CTX 500 mg/m<sup>2</sup>, 3 times/month [3,7].

Stem cells can self-renew, replicate to mature blood cells, has CD34 antigen expressed, including hematopoietic progenitor / unique cell populations. The cceptable number of CD34<sup>+</sup> cell transplantation cellsis in the range  $(2 \sim 5) \times 10^6/\text{kg}$ , but the number of peripheral blood stem cells often less than 0.1%. Therefore, we need a way to increase the concentration of peripheral blood stem cells, which is called stem cell mobilization. The key method is chemotherapy + granulocyte colony-stimulating factor or single granulocyte colony-stimulating factor. The former may alleviate the disease, while the later may deteriorate it. Joint mobilization is better than single granulocyte-colony stimulating factor, cyclophosphamide 4g/m<sup>2</sup> than 2g/m<sup>2</sup> [3,14,15]. The group of 16 patients were treated with cyclophosphamide 4g/m<sup>2</sup> combined granulocyte colony-stimulating factor 5ug/kg to make a success rate of 100%. But in the process of collecting peripheral blood stem cells, there are two important problems to be solved, that is, when to start and when to end. We need to keep abreast of peripheral blood mononuclear cells and stem cells numbers timely for clinical decisions. CD34<sup>+</sup> cell count is the most widely used in the determination of graft stem / progenitor cells of the indicators. The absolute count of which is closely related to content, to predict the effect of acquisition. The peripheral blood WBC, MNC count and the number of harvested CD34<sup>+</sup> cells were not significantly correlated, indicating which does not accurately reflect the level of peripheral blood stem cells, so it became the key that the absolute count of CD34<sup>+</sup> collection . In general, the best collection time should be when the peripheral blood CD34<sup>+</sup> cells is from 20 to 85 / uL, according to its cell surface antigen and labeled antibody to the tiny beads binded specifically. Some scholars [16] reported that CD34<sup>+</sup> cell graft up to a median of 49% by positive selection, compared with pre-separation concentration as 33 times. The main purpose is to remove the graft in the immune cells to

reduce the chance of a relapse transplant. We used the German company Miltenyi Biotec MACS immunomagnetic system in CD34<sup>+</sup> sorting [17].

Mobilization of patients with SLE-related complications included fever, hypotension, abdominal pain, joint pain, seizures, myocardial infarction, pulmonary edema [17]. The total of 16 patients mobilized had both leukopenia and gastrointestinal adverse reactions, with varying degrees of fever, while blood cultures negative, after CD34<sup>+</sup> cells collected the temperature returned to normal but its mechanism remains unclear, needing further study.

Pretreatment is one of the important part of autologous hematopoietic stem cell transplantation. Its main purpose is to destroy the abnormal cells in vivo in patients, minimize recurrence, and provided the necessary space to implant. Regimen should also have the function to suppress hematopoietic and immune, which often require multiple medications and / or radiotherapy combined.

Currently, there are no uniform for conditioning regimen for SLE. In general, the efficacy of pre-clinical and pre-treatment intensity have some relevance, for example, by cyclophosphamide / busulfan, cyclophosphamide or other drugs combined with systemic lymph node irradiation, the disease recurrence rate is low, but transplant-related mortality also increased. Because of the transplanted organ damage associated with SLE patients, most scholars do not advocate the use of intense myeloablative program, but the lymphatic clearance program. The current use of cyclophosphamide (200mg/kg) + anti-thymocyte globulin (ATG, 90mg/kg) is more common, while some individual case reports cyclophosphamide (120 ~ 150mg/kg) + systemic lymph node irradiation (400 ~ 600cGy, lung shielding to 400cGy) or cyclophosphamide (120mg/kg) + busulfan (16 mg / kg) and the BEAM program (BCNU 300mg / m<sup>2</sup>, VP16 400 ~ 800mg / m<sup>2</sup>, cytarabine 800 ~ 1600mg / m<sup>2</sup>, melphalan 140mg / m<sup>2</sup>) [10,15,18]. The whole body and lymph node irradiation can induce more tumor-related complications, should be taken seriously enough [15].

Conditioning regimen containing cyclophosphamide, 5% patients emerged life-threatening cardiac toxicity and severe cardiac toxicity, mainly showing low-voltage ECG, progressive heart failure or pericarditis with the drug doses. One case in our group occurred serious heart failure in use of drugs to support and pericardiocentesis when necessary.

Over 90% patients had the incidence of oral mucositis after hematopoietic stem cell transplantation, approximately the date of reinfusion, continuing until blood implanted. Some patients have severe pain and require total parenteral parenteral nutrition support and make fungal, bacterial, viral and other infections common.

Almost all patients have varying degrees of gastrointestinal reactions, mainly nausea, vomiting, or diarrhea. We can use 5 - hydroxy tryptophan-blockers to control gastrointestinal adverse reactions before chemotherapy.

Renal dysfunction is a common complication with amounts of pathogenic factors, such as direct drug toxicity, hypovolemia and use of nephrotoxic drugs. By disabling nephrotoxic drugs, paying attention to water and electrolyte balance, most patients can return to normal.

Another prominent side effect caused by cyclophosphamide is hemorrhagic cystitis, mainly due to as cyclophosphamide metabolites acrolein from urine, causing extensive mucosal ulceration, necrosis and bleeding. The effective prevention measures include alkaline urine and application Gomez sodium, which can be combined with acrolein to reduce the cell toxicity in a total dose of 1.6 times of that of cyclophosphamide and divided in 4 times.



Animal experiments confirmed that the graft of T lymphocytes related to disease recurrence after transplantation [3,7,11]. At present, most foreign scholars are using cell sorting system to remove T-cell line in vitro, only can remove about 3 logarithmic T cells, which can be re-entered to arouse the body's own response to the disease clone. ATG is a kind of polyclonal immunoglobulin antibodies using the human thymus cells immunized animals to collect the serum extract, selective against human T lymphocytes. Anti-thymocyte globulin in the body can bind to T cells, swallowed by circulating monocytes, and fixed macrophages components, through the activation of complement to remove T cells [19]. We applied plenty of ATG in vivo to remove the residual T lymphocytes and memory cells to enhance the success rate and reduce the relapse rate.

The exact mechanism of autologous peripheral blood stem cell transplantation for autoimmune diseases is not fully clear, what can be certain is that the original autoimmune cell clones were completely destroyed while re-established a normal immune system [7-10]. By high dose systemic immunosuppressants or radiation, we eliminate its own mature immune cells, while stem cells, due to a large quantity of aldehyde dehydrogenase, can resist to cyclophosphamide. Pretreatment process can avoid the impact of memory T cell so that the new stem cells can develop into non-anti-self lymphocytes, inducing tolerance to the autoantigen. In addition, the mobilization and pre-processing stage eliminate autoimmune lymphocytes, reduce antibodies and immune complexes to allow healing of damaged tissue and normal immune.

Autoimmunity and self-tolerance is a dynamic equilibrium between the process. By using immunosuppressive agents and hematopoietic stem cell transplantation can eventually balance the body's immune system back to normal [11]. Theoretically, it is possible to cure autoimmune disease.

Since 1997, Marmont using autologous bone marrow stem cell transplantation for treatment of SLE has been successful, there have been a lot of research on bone marrow and peripheral blood stem cell transplantation for treatment of SLE at home and abroad, and have achieved encouraging clinical results. In 2003, ASH meeting reported the U.S. total number of cases is 681, of which 127 cases were systemic lupus erythematosus, mainly in remission. Van Lear have found that 45 SLE patients undergoing transplantation, 27 of which have significantly improved, 14 recurred after the initial alleviation, 7 deaths, for 5 have relation with the transplantation and the overall transplant-related mortality rate is 11% [20]. Traynor et al from North America [10] found 15 patients with SLE completing the study of autologous transplantation were alive, but 2 died after mobilization. In more than 1 year's follow-up, 12 patients, 8 cases completely withdrew, 2 have small doses of hormones to maintain, 2 had disease activity requiring the addition of immunosuppressive agents. Our studies show that it has an ideal short-term effect about autologous peripheral blood purified CD34 + cell transplantation for SLE, for all patients had hematopoietic reconstitution well, most of the clinical manifestations and related immunological parameters disappeared and were markedly improved in survival quality. But there are still many issues worth further reflection and research [3], such as: SLE multiple genetic abnormalities exist in the stem cell gene level, the transplanted stem cells will differentiate into the same self-reactive immune cells; whether disease recurrence are related to stem cells derived from the input; if the new input stem cells in the relatively normal environment can develop into self-tolerance T, B lymphocytes, and so on.

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## **New Advances in Stem Cell Transplantation**

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This book documents the increased number of stem cell-related research, clinical applications, and views for the future. The book covers a wide range of issues in cell-based therapy and regenerative medicine, and includes clinical and preclinical chapters from the respected authors involved with stem cell studies and research from around the world. It complements and extends the basics of stem cell physiology, hematopoietic stem cells, issues related to clinical problems, tissue typing, cryopreservation, dendritic cells, mesenchymal cells, neuroscience, endovascular cells and other tissues. In addition, tissue engineering that employs novel methods with stem cells is explored. Clearly, the continued use of biomedical engineering will depend heavily on stem cells, and this book is well positioned to provide comprehensive coverage of these developments.

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