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Dendritic Cells in Hematopoietic Stem Cell Transplantation

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1. Introduction

Dendritic cells (DC) are highly specialized antigen-presenting cells (APC) that are pivotal in regulating the balance between immune tolerance and protective immunity. This functional versatility is highlighted in the context of allogeneic hematopoietic stem cell transplantation (allo-HSCT), where DC are crucial for the induction and modulation of graft-versus-host reactions. Furthermore, in the process of immune restoration after allo-HSCT, DC play a central role in generating protective immunity against pathogens. The importance of DC in directing the immune system during the complex immunological situation after allo-HSCT warrants further research, aimed at uncovering the therapeutic potential they hold in this setting.

2. Role of dendritic cells in the development of acute graft-versus-host disease following allogeneic hematopoietic stem cell transplantation

Allo-HSCT is a well-established and valuable therapeutic option for a variety of life-threatening malignant and non-malignant diseases (Gratwohl et al., 2010). In cancer, allo-HSCT has been mainly applied to treat leukemia and lymphoma patients (Gratwohl et al., 2010). Immunologic graft-versus-leukemia (GVL) effects mediated by allogeneic lymphocytes present in the graft are major contributors to its success. A number of distinct donor cell subsets have been identified that may play a role in the GVL responses after allo-HSCT. These include natural killer cells (Gill et al., 2009; Ruggeri et al., 2007), T cells reactive to tumor-specific or tumor-associated antigens (TAA; Molldrem et al., 2002; K. Rezvani & Barrett, 2008), and T cells reactive to host minor histocompatibility (miHC) antigens (Falkenburg et al., 2002, 2003; Riddell et al., 2002, 2003).

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2.1 Development of acute graft-versus-host disease following allogeneic hematopoietic stem cell transplantation

A major obstacle that substantially limits the therapeutic potential of allo-HSCT is the occurrence of graft-versus-host reactions against healthy host tissues, resulting in graft-versus-host disease (GVHD). GVHD is a major cause of morbidity and mortality following allo-HSCT. The overall incidence lies between 30% and 60% with a mortality rate of approximately 50% (Barton-Burke et al., 2008). It is a complex multi-step process, involving innate and adaptive immunity and affecting many organs, including skin, liver and the gastrointestinal tract (Ball & Egeler, 2008; Ferrara et al., 2009).

Billingham was the first to describe GVHD (Billingham, 1966). According to the Billingham criteria, three conditions must exist in order for GVHD to occur after allogeneic transplantation: (1) the donor graft must contain viable and immunologically functional effector cells, (2) the donor and recipient must be histoincompatible, and (3) the recipient must be immunocompromised.

The series of events that contribute to the development of acute GVHD (as described by Ferrara & Reddy, 2006; Goker et al., 2001) can be divided in three phases (Goker et al., 2001). The first phase – conditioning phase – starts before the engraftment. This phase involves tissue damage caused by pre-transplantation myeloablative radiation/chemotherapy regimens, followed by release of lipopolysaccharide and secretion of proinflammatory cytokines, upregulation of adhesion molecules and enhanced expression of major histocompatibility complex (MHC) molecules on recipient tissues. The proinflammatory environment will also activate APC. The second phase – induction and expansion phase – starts with the recognition of the histoincompatible host tissue antigens by donor T cells. This phase involves T cell activation, stimulation, proliferation and differentiation. Activated host APC play a key role in the second phase of the graft-versus-host reaction by presenting mismatched recipient antigens to donor T cells. The first two phases constitute the afferent phase of GVHD. Finally, the third phase – effector phase – represents the actual clinical phase of acute GVHD and involves direct and indirect damage to host cells contributing to aggravation of GVHD.

From these models, it is clear that donor T cells play a crucial role in evoking GVHD after allo-HSCT. Simultaneously, donor T cells represent major mediators of GVL effects. Therefore, research efforts are aimed at separating GVL reactions from GVHD (Li et al., 2009a; Mackinnon et al., 1995; A.R. Rezvani & Storb, 2008). A key question is whether GVL activity and GVHD are fundamentally different mechanisms, or whether they are both clinical manifestations of similar graft-versus-host reactions.

Preclinical model systems and clinical trials designed to investigate the possibility of selectively activating graft-versus-host reactions that result in GVL effects without GVHD, have led to new insights in the pathophysiology of GVL responses and GVHD after allo-HSCT (Li et al., 2009a; A.R. Rezvani & Storb, 2008). In a more complex model of human GVHD and GVL pathophysiology (Li et al., 2009a), differentiation of activated T cells into the distinct subsets T helper (Th)1/cytotoxic T cell (Tc)1, Th2/Tc2, Th17 or regulatory T (Treg) cells is taken into account. These T cell subsets differ both in cytokine profiles and in their graft-versus-host activities. Activated Th1/Tc1 cells can directly attack host tissue and initiate specific inflammatory immune responses that lead to both GVL responses and acute GVHD. Th2 cells on the other hand, evoke antigen-specific cellular and humoral immune responses resulting in GVL responses, but also in chronic GVHD. Notably, Th2 cytokines may inhibit the development of acute GVHD. Activated Th17 cells potentiate inflammation

and lead to acute GVHD, whereas the Th1 cytokine interferon (IFN)-γ can suppress Th17 responses to decrease GVHD. Donor Treg cells suppress GVHD, but the effect of Treg cells on GVL responses remains to be further elucidated. The T cell subsets that are most likely associated with shifting the balance away from GVHD towards GVL responses are Th1/Tc1, γδ T and Treg cells (Li et al., 2009a).

2.2 Dendritic cells in the development of acute graft-versus-host disease

Early models have mainly focused on the central role of T cell activation and cytokine release in the pathophysiologic process of GVHD. The 1966 Billingham criteria clearly accounted for the presence of viable and immunologically functional effector cells as a prerequisite for the development of GVHD (Billingham, 1966). More recent models of GVHD (Choi et al., 2010; Ferrara & Reddy, 2006; Goker et al., 2001; Li et al., 2009a) also take into account the key role of antigen presentation in its development by stating that activation of APC precedes activation and clonal expansion of T cells in the immune cascade. Host APC play a crucial role in the graft-versus-host reaction by presenting mismatched recipient antigens to donor T cells (Goker et al., 2001). In allo-HSCT with a histocompatible donor, the relevant antigens are miHC antigens (Falkenburg et al., 2002, 2003; Ridell et al., 2002, 2003). APC digest miHC antigens into short peptides that are linked to MHC molecules and presented on the surface of APC as allopeptide-MHC complexes. Physical interaction between the allopeptide-MHC complexes and antigen-specific T cell receptors (TCR) then leads to recognition and activation of antigen-specific T cells (Clark & Chakraverty, 2002; Goker et al., 2001).

Following allo-HSCT, a unique situation is created in which both host- and donor-derived APC co-exist within the host. Thus, foreign miHC antigens can be presented by either host-derived or donor-derived APC. The latter case implies effective cross-presentation of recipient miHC antigens by donor-derived APC (Shlomchik, 2003). The roles of host- and donor-derived APC in the development of GVHD have been examined in experimental mouse studies. In a murine allogeneic bone marrow transplantation (BMT) model, Shlomchik and colleagues showed that host-derived APC were necessary and sufficient to initiate GVHD (Shlomchik et al., 1999). Donor APC on the other hand, while redundant for the onset of GVHD, were required to maximize the GVHD (Matte et al., 2004). A model focusing on the role of host-derived APC in the effector phase of GVHD demonstrated that tissue-resident APC control migration of alloreactive donor T cells into the tissues and subsequent local development of GVHD (Zhang et al., 2002).

APC represent a heterogeneous population of cells with varying antigen-presenting capacities. As the most specialized and professional APC of the immune system, DC are highly efficient in processing and presenting antigens (Mellman & Steinman, 2001). The role of DC in GVHD has been investigated and confirmed in various experimental settings (Mohty, 2007; Mohty & Gaugler, 2008; Xu et al., 2008).

Allo-HSCT can change the origin (host- versus donor-derived), number, lineage and activation level of DC in the host (Clark & Chakraverty, 2002). Several studies have examined the role of DC counts and subsets in the development and severity of GVHD. Based on their immunophenotype and functional properties, DC can be classified into myeloid conventional DC (cDC) and plasmacytoid DC (pDC) (Liu, 2001). A murine BMT model demonstrated that host-derived DC are necessary and sufficient for priming donor T cells to cause acute GVHD (Duffner et al., 2004). In humans, peripheral blood DC

chimerism experiments have been performed following allo-HSCT to analyze the contribution of different DC subsets to GVHD (Boeck et al., 2006; Chan et al., 2003; Pihusch et al., 2005). Findings of Chan et al (Chan et al., 2003) confirmed the importance of host DC, because persistence of the DC at day 100 after allo-HSCT was correlated with GVHD. On the other hand, graft-versus-host reactions were also detected in patients that had DC exclusively of donor origin (Boeck et al., 2006). Lower counts of cDC and pDC in patients were associated with an increased risk for acute GVHD (Horváth et al., 2009; Lau et al., 2007; Rajasekar et al., 2008; Reddy et al., 2004; Vakkila et al., 2005). In addition, higher numbers of donor pDC following allo-HSCT decreased the risk of developing chronic GVHD, but also increased the risk of relapse, possibly due to interference with GVL reactions (Waller et al., 2001). In contrast to these data, higher pDC numbers in the graft or in the recipient after allo-HSCT have also been found to correlate with the development of chronic GVHD (Clark et al., 2003; Rossi et al., 2002). Next to absolute numbers, also activation status can be predictive of GVHD, with activated cDC being highly correlated with acute GVHD (Lau et al., 2007). Taken together, experimental data suggest that different DC subsets have different effects on GVHD and GVL reactions, but further research is required to unravel the exact role of each subset.

3. Dendritic cell-based therapy and allogeneic hematopoietic stem cell transplantation

Over the past decade several approaches of DC-based therapy in allo-HSCT settings have been scrutinized, yielding some promising results with regard to decreasing GVHD, optimizing GVL reactions and restoring protective immunity against pathogens.

3.1 Dendritic cell-based therapy to reduce graft-versus-host-disease and enhance graft-versus-leukemia effects

Allogeneic T cells have the capacity to kill residual malignant cells in the host, but also to destruct normal host tissue contributing to GVHD, which can be life-threatening and limits the use of allo-HSCT. While T cell depletion of the graft is a very effective way of reducing the risk of GVHD, it also diminishes the GVL effect, thereby increasing the risk of relapse. Hence, a more refined approach is needed to balance graft-versus-host reactions after allo-HSCT. Given the inherent key regulatory function of DC, DC-based therapy is considered an attractive approach to shift the balance in favor of GVL reactions.

3.1.1 Dendritic cell-based therapy to reduce graft-versus-host-disease

The finding in murine BMT models that host APC are necessary for GVHD to develop (Matte et al., 2004; Shlomchik et al., 1999), led the authors to suggest that depletion of host APC before the conditioning regimen should prevent GVHD without the need for prolonged immunosuppressive treatment.

Antibody-mediated depletion of DC was investigated in a chimeric human/mouse model of GVHD, in which severe combined immunodeficient (SCID) mice received a xenogeneic transplantation with human peripheral blood mononuclear cells (PBMC) (Wilson et al., 2009). Antibodies against the DC activation marker CD83 were injected in host mice 3 hours before injection of human PBMC. This therapeutic intervention almost completely prevented lethal GVHD, whereas negative control mice all developed severe GVHD.

Moreover, mice treated with anti-CD83 antibodies required no further immunosuppressive therapy and possessed functional T cell immunity *in vitro* (Wilson et al., 2009).

These data support further investigation of *in vivo* depletion of host and/or donor APC as a way of preventing GVHD in allo-HSCT recipients. This strategy makes redundant both T cell depletion, thereby preserving the memory T cell pool, and T cell-targeted immunosuppression, which greatly hampers GVL responses and protective immunity. However, the effect of DC depletion on GVL responses still needs to be investigated in animal allo-HSCT models including *in vivo* leukemic challenge. Some concern can be raised about potential interference of DC depletion with the GVL effect, because in mice studies antigen-presentation by host APC has been shown to be important in mediating GVL responses following donor lymphocyte infusions (DLI) (Chakraverty et al., 2006; Mapara et al., 2002). Furthermore, DC depletion might result in a delayed restorage of immunity against pathogens (Clark & Chakraverty, 2002).

More thorough elucidation of the role of distinct DC subsets in allo-antigen responses after allo-HSCT will pave the way to depletion of undesirable or expansion of desirable DC subsets. In this context, a study of Li et al. (Li et al., 2009b) has shown that manipulating the content of donor APC subsets in allo-HSCT grafts can enhance the GVL effect without increasing GVHD. In their study, leukemia-bearing mice that received hematopoietic stem cells (HSC) and CD11b-negative donor APC had substantially enhanced survival compared to recipients of HSC alone, HSC and T cells, or HSC and CD11b-positive APC.

Another promising strategy to modulate allo-antigen responses following allo-HSCT involves DC engineered to boost their tolerogenic or regulatory capacities.

In a study of Reichardt et al (Reichardt et al., 2008), DC were isolated directly from mice bone marrow and spleen cells using positive magnetic cell selection and exposed to rapamycin for 24 hours. Adoptive transfer of rapamycin-treated DC of host origin, but not donor origin, administered together with the bone marrow transplant, reduced GVHD severity and led to improved survival of recipient mice in a dose-dependent way. The reduced expansion of alloreactive T cells could account for the beneficial effects on GVHD and survival, but carries the risk of reducing the GVL effect.

In two other studies with similar methodology (Chorny et al., 2006; Sato et al., 2003), DC were generated from murine bone marrow cells using granulocyte macrophage colony-stimulating factor (GM-CSF) and either interleukin (IL)-10 and transforming growth factor (TGF)-β1 or vasoactive intestinal peptide (VIP) for 6 days. Then, lipopolysaccharide (LPS) was added for 2 days to induce activation, followed by injection of the DC 2 days after BMT. Results of both studies demonstrated that host-matched DC, but not host-mismatched DC, prevented the onset of severe GVHD in recipient mice in a dose-dependent way. In order to study the effect of DC therapy on GVL responses, mice were challenged with P815 or A20 malignant cells. BMT recipient mice that received host-matched DC were not only protected from lethal GVHD, but also maintained a strong GVL effect and survived significantly longer than control animals (Chorny et al., 2006; Sato et al., 2003).

In conclusion, the administration of specifically engineered DC appears to be a favorable means of modulating alloreactivity after allo-HSCT, because they are able to reduce the risk of severe GVHD, while maintaining the benefits of the GVL effect. Clinical trials will have to show if these beneficial effects can also be seen in humans. Considering that only host-matched DC were able to protect the recipient from severe GVHD and conserve a strong GVL effect in these murine models, it seems likely that the DC will have to be tailored to

every individual patient. Although this will be costly and labor-intensive, it can be cost-effective if proven beneficial in allo-HSCT.

3.1.2 Dendritic cell-based therapy to enhance the graft-versus-leukemia effect without aggravating graft-versus-host-disease

Donor alloreactive T cells responsible for the GVL effect target a broad range of allogeneic antigens and may thereby lead to GVHD. Hence, there is much interest in developing strategies that can direct the immune reaction towards specific antigens only or primarily expressed on malignant cells, so-called TAA.

As key regulators of the immune system, DC are inherently capable of inducing tumor-specific immune responses (Steinman & Banchereau, 2007). Various clinical studies have already explored the use of DC loaded with TAA as cellular cancer vaccines for hematological malignancies (Smits et al., 2011; Van de Velde et al., 2008). Thus far, results are often modest, but there is proof of principle that a DC vaccine can lead to eradication of malignant cells in an antigen-specific manner. Promisingly, in a phase I/II study by our group, vaccination with autologous monocyte-derived DC loaded with Wilms' tumor 1 (WT1) protein-encoding mRNA was able to convert partial remission into complete molecular remission in two patients in the absence of any other therapy (Van Tendeloo et al., 2010). These clinical responses were correlated with vaccine-associated increases in WT1-specific CD8+ T cell frequencies.

While DC vaccines are thoroughly being investigated in clinical trials for their capacity to induce tumor-specific immune responses, only few trials addressed their use in the setting of HSCT. In the context of autologous hematopoietic stem cell transplantation (auto-HSCT) for multiple myeloma (MM), a clinical trial in 27 patients suggested a benefit in overall survival of vaccination with autologous idiotype-pulsed APC, given at 4 time points after auto-HSCT, compared to historical controls (Lacy et al., 2009).

In allo-HSCT, the dynamic immunological situation that follows transplantation due to the scollision of donor and host immune system adds complexity to the development of DC-based therapy. Hitherto, it is unclear whether donor- or host-derived DC would be best suited for use in immunotherapy aimed at increasing GVL responses. In this regard, murine models demonstrated that host APC are crucial for GVL reactions and that donor APC, although not strictly necessary, can contribute to the GVL effect (Matte et al., 2004; Reddy et al., 2005). This is similar to what is observed in GVHD, which is not surprising given that both are manifestations of graft-versus-host immunity. Therefore, avoiding aggravation of GVHD is an important concern when developing DC-based strategies aiming to augment GVL immunity after allo-HSCT.

Next to GVHD, another concern regarding DC vaccination to boost GVL responses is its effectiveness when given shortly after allo-HSCT, considering the immunosuppressive state of patients at that time. Murine vaccination studies have shown, however, that tumor lysate-pulsed bone marrow-derived DC administered early after auto- or allo-HSCT can elicit effective anti-tumor immunity (Asavaroengchai et al., 2002; Moyer et al., 2006). Furthermore, DC vaccination around the time of HSCT could have some benefits, such as lower tumor burden, donor T cells that are not tolerant to host antigens and low numbers of host Treg cells (Hashimoto et al., 2011).

A total of 6 patients have been involved in three clinical reports of DC vaccines after allo-HSCT. Donor monocyte-derived DC were used for vaccination, pulsed with recipient tumor

cells (Fujii et al., 2001; Tatsugami et al., 2004) or with WT1 peptide (Kitawaki et al., 2008). Only one trial reported clinical, but transient responses in 4 relapsed patients with hematological malignancies in the absence of GVHD (Fujii et al., 2001). There were no detectable responses nor GVHD in the other two cases (renal cell carcinoma and acute myeloid leukemia). In the trial reporting clinical responses, patients were infused both with donor monocyte-derived DC pulsed with irradiated patient tumor cells and with donor T cells primed by these DC, which might both have contributed to the observed responses.

A fourth study involving 20 MM patients investigated DLI and/or host-derived DC vaccination (Levenga et al., 2010). The authors concluded that partial T cell-depleted allo-HSCT can be combined with pre-emptive DLI and recipient monocyte-derived DC vaccination to increase graft-versus-myeloma effects with limited GVHD.

In conclusion, early results of clinical DC vaccination in the context of HSCT are promising with no or limited GVHD, but because of the small study populations and lack of controls, further research is required.

Instead of engineering DC *ex vivo* and then transferring them to patients, another approach is to directly target them *in vivo*. To our knowledge, this approach has not been tested yet in the allo-HSCT setting.

However, in 8 patients with Hodgkin disease, non-Hodgkin lymphoma or advanced-stage breast cancer, auto-HSCT was followed by immunotherapy with fms-like tyrosine kinase receptor-3-ligand (Flt3-L) for 6 weeks (Chen et al., 2005). Flt3-L is a hematopoietic growth factor, essential for the development of DC from progenitor cells. This phase I study demonstrated that vaccination with Flt3-L was safe and well-tolerated, resulting in increased frequencies and absolute numbers of circulating immature DC and their precursors in patients' blood without affecting other mature cell lineages. The expanded DC were mostly pDC and were shown here to enhance T cell activation and NK cell cytotoxicity against tumor cells *in vitro* after Toll-like receptor 9-ligand administration, but are also known to play a role in antiviral immunity and in preventing GVHD (Arpinati et al., 2003). In correspondence with these data, others have also suggested that mobilization of specific DC subsets through Flt3-L administration might be a feasible way to target DC *in vivo* (Eto et al., 2002; Teshima et al., 2002), but more research is needed to unravel the functional diversity of these mobilized DC.

3.2 Dendritic cell-based therapy to restore protective immunity against pathogens

Viral and fungal infections are an important cause of morbidity and mortality in patients following HSCT (Gratwohl et al., 2005). These patients have increased susceptibility for primary infection, reinfection and also reactivation of latent viruses due to hampering of their immune system by two main factors (Smits & Berneman, 2010). Firstly, there is the immunosuppressed state accompanying HSCT, often further increased by medication given to prevent GVHD. Secondly, the intense pre-transplantation chemotherapy conditioning regimen, intended to destroy a large part of blood cells, is believed to eliminate memory T cells. Furthermore, early after HSCT dysfunctional DC lead to severely impaired development of antigen-specific T cells (Safdar, 2006). Considering their central role in innate and adaptive immunity, DC seem the ideal candidate for immunotherapy aimed at bringing about the swift restoration of immunity against pathogens in this particular setting.

With regard to DC-based therapy for antifungal immunity after allo-HSCT, much knowledge was obtained from research by the group of Romani. They showed in murine

models of allo-HSCT that DC discriminate between different fungal morphotypes or their corresponding RNA with regard to maturation, cytokine production and Th1 cell priming both *in vitro* and *in vivo* (Bacci et al., 2002; Bozza et al., 2003; d'Ostiani et al., 2000). Similarly, also human monocyte-derived DC were found to react differently in terms of cytokine production and activation of IFN-γ-producing T cells.

Subcutaneous vaccination of mice with DC pulsed with Candida yeasts or Aspergillus conidia (or transfected with the corresponding RNA) on days 1 and 7 after T cell-depleted allo-BMT dramatically increased the recovery of antifungal resistance to subsequent fungal challenge (Bacci et al., 2002; Bozza et al., 2003).

They also demonstrated that Flt3-L-expanded and thymosin α1-treated IL-4-expanded monocyte-derived DC were capable of inducing antifungal immunity as well as allogeneic transplant tolerance (Romani et al., 2006). Overall, the findings of the group of Romani suggest a role for active DC vaccination very shortly after allo-HSCT to restore antifungal immunity and show that expansion of distinct DC might allow more specific regulation of post-transplantation immunity (Montagnoli et al., 2008; Perruccio et al., 2004).

Over the last 10 years, DC have established a firm foothold in immune-based strategies aimed at restoring antiviral (and especially anti-CMV) immunity following allo-HSCT. Monocyte-derived DC from CMV-seropositive HSCT donors pulsed with CMV peptide/lysate or transfected with an adenoviral vector encoding CMV-peptide, have been used with great success to expand CMV-specific cytotoxic T lymphocytes (CTL) *ex vivo* (Micklethwaite et al., 2008; Peggs et al., 2001; Szmania et al., 2001). Clinical trials examining adoptive transfer of these DC-expanded CMV-specific CTL to allo-HSCT recipients demonstrated that this is a safe method capable of restoring functional anti-CMV immunity early after transplantation (Micklethwaite et al., 2007, 2008; Peggs et al., 2009). Although a minority of the patients developed GVHD after adoptive transfer of CMV-specific CTL, this was most likely not related to the infusion itself.

Another study showed that DC transfected with CMV pp65-encoding RNA can successfully expand autologous CMV-specific CTL *in vitro* from both seropositive and -negative patients after allo-HSCT, suggesting that CMV-loaded DC vaccination could provide a valid clinical alternative to adoptive CTL transfer (Heine et al., 2006).

Also for measles virus (MV), DC vaccination could be a favorable approach as results of an *in vitro* study with MV-loaded DC from HSCT patients showed that these DC significantly induced autologous MV-specific T cells from the naïve repertoire (Nashida et al., 2006). Clinical trials are needed, however, to validate whether viral antigen-loaded DC vaccination can indeed live up to the promising results obtained with adoptive virus-specific CTL transfer.

4. Conclusion

DC have been the subject of intensive investigation in mouse models to reduce the occurrence of GVHD and enhance GVL reactions following allo-HSCT. Also in humans, it is clear that DC play an important role in initiating and balancing graft-versus-host reactions. Further clarification of differences between DC subsets in their capacity to shift the balance away from GVHD towards GVL and anti-microbial reactions will help to translate the promising mouse data into clinical success. Questions to be solved are which would be the best time frame and strategy of immunotherapy to use in allotransplant patients. DC-based

approaches to be further investigated include DC vaccines, adoptive transfer of *in vitro* primed T cells and *in vivo* targeting of DC.

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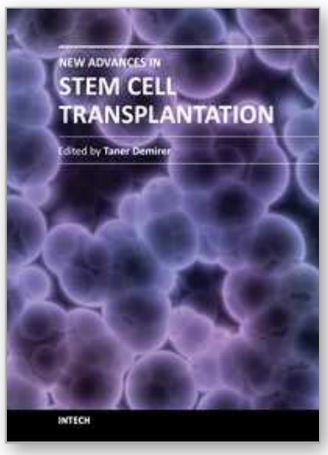

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This book documents the increased number of stem cell-related research, clinical applications, and views for the future. The book covers a wide range of issues in cell-based therapy and regenerative medicine, and includes clinical and preclinical chapters 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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