ELSEVIER

Journal of Autoimmunity xx (2008) 1–5

journal of autoimmunity

www.elsevier.com/locate/jautimm

Review

Hematopoietic stem cell transplantation for autoimmune diseases: What have we learned?

Richard K. Burt [a,*], Alessandro Testor [a], Robert Craig [b], Bruce Cohen [c], Robert Suffit [c], Walter Barr [d]

[a] *Division of Immunotherapy, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL 60611, USA*
[b] *Division of Gastroenterology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL 60611, USA*
[c] *Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL 60611, USA*
[d] *Division of Rheumatology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL 60611, USA*

Abstract

Numerous individuals and institutions throughout the world have contributed to the development of hematopoietic stem cell transplantation (HSCT) for autoimmune diseases. In this review, we will summarize what we have learned at our own institution (Northwestern University), and how it has guided our therapy. An emphasis will be placed on both the scientific basis for the development of autologous hematopoietic stem cell transplantation and a summary of the data in a variety of human diseases.

Keywords: Hematopoietic stem cell transplantation (HSCT); Autologous HSCT; Animal models; Human trials

1. Animal models

Autologous hematopoietic stem cell transplantation (HSCT) for autoimmune diseases is based on the rationale of using chemotherapy for ablation of an aberrant or ''self-reactive'' immune system and regeneration of a new and hopefully self-tolerant immune system from hematopoietic stem cells (HSC). Pre-clinical data to support this rationale was derived from animal models of autoimmune diseases. In some cases, the disease is predominately a genetically pre-ordained HSC defect that arises spontaneously and in other examples requires environmental stimuli such as immunization with self-peptides or adjuvant. Examples of the former include type I diabetes in NOD (non-obese diabetic) mice, while the latter includes EAE (experimental autoimmune encephalomyelitis) a demyelinating multiple sclerosis like disease induced by immunization with myelin peptides. Animal autoimmune diseases that arise spontaneously require an allogeneic stem cell transplant using a disease resistant donor for cure. In comparison, environmentally induced autoimmune diseases may be cured with syngeneic (the animal analogy for autologous) HSCT.

In our experience at Northwestern University, performing HSCT in EAE, an environmentally induced autoimmune disease, and in NOD mice, a spontaneous onset autoimmune diabetes, we have gleaned some insights that may also be applicable to humans. While animal HSC are collected by flushing bone marrow cells from a surgically amputated femur, most human HSCT utilize peripheral blood stem cells (PBSC) mobilized into the blood with a growth factor/cytokine and collected by leukopheresis. It is standard practice to use a growth factor such as neupogen (G-CSF) to mobilize hematopoietic stem cells (HSC) in normal donors and in patients with cancer. These growth factors may, depending on the disease, exacerbate or flare an autoimmune disease. We, therefore, evaluated the effect of various cytokines on disease severity in EAE, the animal model for multiple sclerosis [1]. Most cytokines including G-CSF caused irreversibly deterioration in neurologic function and some such as flt-3L caused lethal disease exacerbation [1]. A notable exception was thrombopoietin (TPO) that mobilizes stem cells without flaring EAE [1].

* Corresponding author.
E-mail address: rburt@northwestern.edu (R.K. Burt).

0896-8411/$ - see front matter © 2008 Published by Elsevier Ltd.
doi:10.1016/j.jaut.2007.12.010

While EAE, an animal model of multiple sclerosis, enters durable remission following syngeneic HSCT, we found that auto-reactive myelin-specific T cell clones remain *in vivo* after transplantation [2]. These clones proliferate ex vivo to the disease initiating protein as well as spread epitopes of myelin [2], and disease may recur with re-immunization to myelin peptides. Self-reactive T cells persisted or recurred *in vivo* despite utilizing an intense myeloablative total body irradiation (TBI) conditioning regimen. This implies that autologous HSCT achieves immune reset and disease remission but does not eliminate autoreactive repertoires that may, under appropriate conditions, reactivate disease, either because these repertoires are normal and regenerate after the transplant, albeit are initially self-tolerant, are reintroduced with the graft, or are memory T cells that survive the conditioning regimen even after intense myeloablative TBI. We also demonstrated that for EAE, an immune-mediated demyelinating disease, neurologic improvement after autologous HSCT depends on disease stage at the time of transplant [2]. Neurologic disability markedly improves when syngeneic HSCT is performed during the early acute phase of disease but has no discernable beneficial clinical effect in chronic EAE [2]. In other words, autologous HSCT is effective for the inflammatory but not degenerative stages of disease.

In contrast to environmentally induced autoimmune diseases, spontaneous onset autoimmune diseases require an allogeneic HSCT for sustained disease remission. The immune suppressive conditioning regimen not only allows for immune reset but facilitates engraftment of allogeneic HSC and regeneration of a new immune system from a genetically distinct and hopefully disease resistant stem cell compartment that should prevent disease recurrence. The phenomena by which engrafted allogeneic HSC prevent autoimmune disease recurrence has been termed graft versus autoimmunity (GVA) [3,4].

Allogeneic lymphocytes facilitate full donor engraftment by eliminating residual host hematopoiesis, but also cause graft versus host disease (GVHD), a potentially lethal immune-mediated disorder. In malignancies, the benefit from lymphocyte depletion of the allograft in terms of less GVHD is obscured by recurrence of leukemia from residual host hematopoiesis. In autoimmune diabetes, we have demonstrated in NOD mice that diabetes may be prevented and islet cell tolerance induced, that is a GVA phenomena may occur, without GVHD by using embryonic stem cell-derived HSC that are completely devoid, by virtue of ex vivo production, of any contaminating lymphocytes [5]. Thus allogeneic mixed chimerism, that is co-existence of both donor and host hematopoiesis, appears to be sufficient to achieve and maintain remission of autoimmune diseases without GVHD.

In summary, depending on the disease, growth factors used for mobilization may flare symptoms. Since, TPO is not commercially available for clinical usage in America, depending upon disease, a therapeutic mobilization using cyclophosphamide (2 g/m^2) prior to G-CSF to ameliorate disease activity during mobilization should be considered. Second, an autologous HSCT, even when using an intense myeloablative regimen, does not completely eliminate all self-reactive T cells but does allow an immune reset that induces disease remission. Therefore, the rationale for using intense and more toxic myeloablative regimens that is based on the supposition of completely ablating autoreactive repertoires is suspect. Thus, our approach, knowing that complete immune ablation cannot be achieved, is to achieve immune reconstitution and thus ''immune reset'' by designing optimal autologous non-myeloablative immune-specific regimens. Third, allogeneic HSCT should be designed to minimize the risk of GVHD by utilizing *in vivo* or ex vivo lymphocyte depletion which despite achieving only low level donor mixed chimerism can, in animal models, induce self tolerance without GVHD.

2. Human trials

At Northwestern University, we have performed 200 HSCT for immune-mediated diseases. The most common indications for HSCT at our center are systemic lupus erythematous, multiple sclerosis, systemic sclerosis, and Crohn's disease. Other indications have included chronic inflammatory demyelinating polyneuropathy, myasthenia gravis, rheumatoid arthritis, polymyositis, autoimmune related retinitis and optic neuritis (ARRON syndrome), vasculitis (Behçet's, Sjögren's, Wegner's), and sarcoidosis. Through this experience we have drawn several general conclusions.

(1) Treatment-related mortality needs to be very low for non-malignant diseases. To minimize mortality, the regimens we generally utilized for autologous HSCT of autoimmune diseases are non-myeloablative. Non-myeloablative regimens are safer than myeloablative regimens. The rationale of an autologous HSCT for immune-mediated disorders is maximal suppression of the immune system without irreversible ablation of the entire bone marrow compartment [6]. Following a non-myeloablative regimen, hematopoietic recovery *will* occur without infusion of HSC; however autologous HSC provide support and shorten the duration of chemotherapy induced neutropenia. White blood cell and platelet engraftment is more rapid following a non-myeloablative regimen compared to a TBI containing myeloablative regimen [7]. It is probable that the longer the duration of disease, the more organ systems damaged, and the longer accumulated duration of prior therapies, the higher the risk differential between myeloablative and non-myeloablative regimens. Myeloablative regimens used to treat breast cancer had 2% TRM in patients generally not immune suppressed and with otherwise normal organ function. In comparison, initial experience in autologous HSCT for autoimmune diseases in the EBMT registry was 11% TRM [8] and most recently with more experience and more careful patient selection TRM is 7% with higher TRM from more intense, i.e. myeloablative regimens [9]. TRM has fluctuated widely between centers and regimens. In one American study using a TBI containing myeloablative regimen for scleroderma, TRM was reported to be 23% (8 of 34 patients) [10]. At

Please cite this article in press as: Richard K Burt et al., Hematopoietic stem cell transplantation for autoimmune diseases: What have we learned?, Journal of Autoimmunity (2008), doi:10.1016/j.jaut.2007.12.010

Northwestern University, the TRM using non-myeloablative regimens is 1.6% (3 of 180 patients).

(2) Although it is possible that a percentage of patients may be cured, until and unless proven otherwise, autologous HSCT for autoimmune diseases should not be viewed as a cure but rather as changing the natural history of the disease. Investigators should consider this more realistic expectation in justifying mortality endpoints from myeloablative versus non-myeloablative regimens. In fact, similar to syngeneic HSCT in animal models, autologous HSCT, even when using aggressive myeloablative regimens containing TBI, does not completely eliminate serologic markers or clonal repertoires. Autologous HSCT achieves an immune reset and immune regeneration after HSCT [11,12], and the new immune system's default is to regenerate self-tolerance. However, true immune ablation with elimination of all autoreactive memory cells does not occur even with aggressive TBI containing myeloablative regimens.

(3) Depending on disease, growth factor alone or therapeutic mobilization utilizing cyclophosphamide (2 g/m^2) and G-CSF may be used to collect HSC. Therapeutic mobilizations may be associated with infectious complications but tend to ameliorate autoimmune disease activity and has been reported to decrease relapse compared to PBSC mobilization with growth factor alone [9].

(4) Avoid conditioning agents that will further damage already injured organs. Unlike what happens in cancer, in which visceral organ dysfunction is a contraindication for HSCT, in immune-mediated diseases some organ damage often provides the indication for HSCT. Similarly, avoid late toxicities of the conditioning regimen such as life-threatening malignancies that occur years later. Immune-mediated diseases, may, despite significant morbidity, spontaneously remit or ''burn out''. While probability of bad outcome can be determined for a given population, individual patients who will remit spontaneously cannot be excluded *a priori*. It is not appropriate to expose a subset of patients who will remit without HSCT to agents such as total body irradiation that cause a relatively high incidence of a more lethal disease, i.e. myelodysplastic syndrome (MDS)/leukemia. The incidence of second malignancies in follicular (low grade) lymphomas treated with autologous HSCT is currently the best analogy for anticipated transplant induced malignancies in autoimmune diseases. Using a TBI regimen for low grade lymphomas, one study reported a 28% incidence of secondary malignancies, 10% due to MDS (leukemia) [13]. Another study compared TBI to non-TBI autologous HSCT regimens for low grade lymphomas with a 8.5% incidence of MDS/leukemia following a TBI regimen compared to 1.7% for non-TBI regimens [14]. Treatment of systemic sclerosis and multiple sclerosis with TBI containing regimens has already been reported to be complicated by MDS/leukemia [10,15]. Of 34 patients with systemic sclerosis treated with a myeloablative TBI containing regimen, 8 died from treatment, 4 died from disease progression, and 2 of the surviving 22 patients (10%) developed MDS [10]. A TBI regimen used for autologous HSCT of multiple sclerosis was complicated by 1 of 14 patients developing MDS/leukemia [15]. The incidence of MDS, leukemia, and secondary cancer in autoimmune diseases treated with myeloablative TBI containing conditioning agents is probably being under-estimated since most initial publications do not have long term follow-up. Secondary malignancies from different conditioning regimens, correlated with prior long-term exposure to cyclophosphamide and chronic immune suppressive agents, needs to be evaluated and reported from registry data.

(5) Limit HSCT to the inflammatory stage of the disease. Degenerative non-inflammatory stages of the disease will probably not respond. The outcome of myeloablative TBI containing regimens in late secondary progressive multiple sclerosis, which is predominately an axonal degenerative disease, is similar to syngeneic HSCT in chronic EAE, that is of no benefit [16]. In contrast for systemic sclerosis, depending on type of graft, fibrosis may reverse following HSCT. There is some data that an allogeneic HSCT can reverse dermal fibrosis [17] and may reverse pulmonary fibrosis and lower pulmonary artery pressure [18].

(6) Treating earlier in the disease course while the disease is still inflammatory, before organ dysfunction, and before exposure to long term immunosuppression will likely improve safety and efficacy for both myeloablative and non-myeloablative regimens.

(7) Manipulation or CD34 selection of the graft will increase infections [19] and to date has not been demonstrated to improve efficacy. The only publication comparing selected to unselected grafts suggests that this maneuver may even shorten remission duration [20]. However, the conditioning regimen and method of mobilizing PBSC may affect the need for CD34 selection. For example, it is conceivable that CD34 selection may decrease relapse if therapeutic mobilization with cyclophosphamide which has an *in vivo* purging effect is not used to collect HSC, and if antibodies such as antithymocyte globulin that lymphocyte deplete the reinfused graft *in vivo* are not utilized in the regimen. There currently exists virtually no firm data on the benefit of CD34 selection, that is lymphocyte depletion, of the autograft.

(8) Secondary autoimmune disorders may arise from the conditioning regimen itself. Our standard non-myeloablative regimen of cyclophosphamide (200 mg/kg) and rabbit antithymocyte globulin (rATG) was well tolerated. Our second generation regimen utilized cyclophosphamide and a broader and longer acting agent, alemtuzumab, instead of rATG. Secondary immune-mediated cytopenias including idiopathic thrombocytopenic purpura, neutropenia, and autoimmune hemolytic anemia occurred from 2 to 18 months after HSCT, necessitating discontinuation of that regimen [21]. Our current third generation non-myeloablative regimen is termed ''rituximab sandwich'' in which one dose of rituximab (500 mg) is given before and after cyclophosphamide (200 mg/kg) and rATG (6.0 mg/kg). To date this regimen has been well tolerated.

Please cite this article in press as: Richard K Burt et al., Hematopoietic stem cell transplantation for autoimmune diseases: What have we learned?, Journal of Autoimmunity (2008), doi:10.1016/j.jaut.2007.12.010

(9) Besides the above experience in autologous HSCT for autoimmune diseases, we have initiated non-myeloablative allogeneic HSCT protocols for selected patients with HLA matched siblings. The number of patients treated is too small for definitive conclusions, but a potent GVA affect, similar to our animal experiments, with stable mixed chimerism and disease remission including serologic remissions have occurred without any GVHD [18,22]. Either $CD34^+$ selection and/or inclusion of alemtuzumab in the conditioning regimen for *in vivo* donor lymphocyte depletion are used to prevent GVHD. After allogeneic HSCT, we maintain patients on cyclosporine for 1 month and cellcept for 9 months to minimize host versus graft disease, i.e. to prevent graft rejection.

3. Summary

In America there are two philosophically divergent approaches towards autologous HSCT for autoimmune diseases. One group advocates aggressive myeloablative regimens that contains total body irradiation which they believe may be more effective than non-myeloablative regimens [6,10]. We, on the other hand, advocate non-myeloablative regimens that do not have radiation [6,23–25]. It is our concern that myeloablative regimens are too toxic and their risk benefit is not justified for autoimmune diseases. While patient selection, e.g. treating very early after disease onset, with limited organ dysfunction, and before therapy with other immune suppressive agents will certainly diminish the transplant morbidity of any conditioning regimen, there remains an undetermined but possibly significant late risk of MDS/leukemia and solid tumors from TBI. It is also our bias from animal models and clinical experience that autologous HSCT, no matter what the regimen, does not cause complete *in vivo* lymphodepletion. Autoreactive memory cells survive and autoantibodies, while significantly diminished, generally remain positive. In terms of risk benefit, autologous HSCT should be viewed as changing the natural history of disease rather than a cure.

On the other hand, allogeneic HSCT by altering genetic predisposition is more likely to ‘‘cure’’ autoimmune diseases. Again, in America, there are two divergent philosophical approaches to allogeneic HSCT for autoimmune diseases. One group utilizes an unmanipulated allograft which has resulted in GVHD-related mortality [17]. In contrast, it is our bias that GVHD is an unacceptable risk for autoimmune diseases. We, therefore, advocate either an *in vivo* or *ex vivo* lymphocyte depleted allograft [18,22]. In animal models GVA may occur without GVHD despite relatively low level (5–10%) donor engraftment. The safety and superiority of these different approaches for both autologous and allogeneic HSCT, and the ‘‘optimal’’ conditioning regimen and graft composition will only be clarified with time and may perhaps require randomized comparative trials. More additional information on hematopoietic stem cell transplantation is provided in other papers in this special issue of the *Journal of Autoimmunity* [26–36]. We have not attempted to focus on mechanisms of autoimmunity or related papers on various autoimmune diseases but refer to recent literature published in this journal [37–57].

References

[1] Verda L, Luo K, Kim DA, Bronesky D, Kohm AP, Miller SD, et al. Effect of hematopoietic growth factors on severity of experimental autoimmune encephalomyelitis. Bone Marrow Transplant 2006;38(6):453–60.
[2] Burt RK, Padilla J, Begolka WS, Canto MC, Miller SD. Effect of disease stage on clinical outcome after syngeneic bone marrow transplantation for relapsing experimental autoimmune encephalomyelitis. Blood 1998;91(7):2609–16.
[3] Slavin S, Nagler A, Varadi G, Or R. Graft vs autoimmunity following allogeneic non-myeloablative blood stem cell transplantation in a patient with chronic myelogenous leukemia and severe systemic psoriasis and psoriatic polyarthritis. Exp Hematol 2000;28(7):853–7.
[4] Marmont AM, Gualandi F, Van Lint MT, Bacigalupo A. Refractory Evans’ syndrome treated with allogeneic SCT followed by DLI. Demonstration of a graft-versus-autoimmunity effect. Bone Marrow Transplant 2003;31(5):399–402.
[5] Verda L, An Kim D, Ikehara S, Statkute L, Bronesky D, Petrenko Y, et al. Hematopoietic mixed chimerism derived from allogeneic embryonic stem cells prevents autoimmune diabetes mellitus in NOD mice. Stem Cells; in press.
[6] Burt RK, Marmont A, Oyama Y, Slavin S, Arnold R, Hiepe F, et al. Randomized controlled trials of autologous hematopoietic stem cell transplantation for autoimmune diseases: the evolution from myeloablative to lymphoablative transplant regimens. Arthritis Rheum 2006;54(12):3750–60.
[7] Statkute L, Verda L, Oyama Y, Traynor A, Villa M, Shook T, et al. Mobilization, harvesting and selection of peripheral blood stem cells in patients with autoimmune diseases undergoing autologous hematopoietic stem cell transplantation. Bone Marrow Transplant 2007;39(6):317–29.
[8] Tyndall A, Fassas A, Passweg J, Ruiz de Elvira C, Attal M, Brooks P, et al. Autologous haematopoietic stem cell transplants for autoimmune disease—feasibility and transplant-related mortality. Autoimmune Disease and Lymphoma Working Parties of the European Group for Blood and Marrow Transplantation, the European League Against Rheumatism and the International Stem Cell Project for Autoimmune Disease. Bone Marrow Transplant 1999;24(7):729–34.
[9] Gratwohl A, Passweg J, Bocelli-Tyndall C, Fassas A, van Laar JM, Farge D, et al. Autoimmune Diseases Working Party of the European Group for Blood and Marrow Transplantation (EBMT). Autologous hematopoietic stem cell transplantation for autoimmune diseases. Bone Marrow Transplant 2005;35(9):869–79.
[10] Nash RA, McSweeney PA, Crofford LJ, Abidi M, Chen CS, Godwin JD, et al. High-dose immunosuppressive therapy and autologous hematopoietic cell transplantation for severe systemic sclerosis: long-term follow-up of the US multicenter pilot study. Blood 2007;110(4):1388–96.
[11] Traynor AE, Schroeder J, Rosa RM, Cheng D, Stefka J, Mujais S, et al. Treatment of severe systemic lupus erythematosus with high-dose chemotherapy and haemopoietic stem-cell transplantation: a phase I study. Lancet 2000;356(9231):701–7.
[12] Muraro PA, Douek DC, Packer A, Chung K, Guenaga FJ, Cassiani-Ingoni R, et al. Thymic output generates a new and diverse TCR repertoire after autologous stem cell transplantation in multiple sclerosis patients. J Exp Med 2005;201(5):805–16.
[13] Brown JR, Feng Y, Gribben JG, Neuberg D, Fisher DC, Mauch P, et al. Long-term survival after autologous bone marrow transplantation for follicular lymphoma in first remission. Biol Blood Marrow Transplant 2007;13(9):1057–65.
[14] Montoto S, Canals C, Rohatiner AZ, Taghipour G, Sureda A, Schmitz N, et al. Long-term follow-up of high-dose treatment with autologous

Please cite this article in press as: Richard K Burt et al., Hematopoietic stem cell transplantation for autoimmune diseases: What have we learned?, Journal of Autoimmunity (2008), doi:10.1016/j.jaut.2007.12.010

haematopoietic progenitor cell support in 693 patients with follicular lymphoma: an EBMT registry study. Leukemia 2007 [Epub ahead of print].
[15] Samijn JP, te Boekhorst PA, Mondria T, van Doorn PA, Flach HZ, van der Meche FG, et al. Intense T cell depletion followed by autologous bone marrow transplantation for severe multiple sclerosis. J Neurol Neurosurg Psychiatry 2006;77(1):46–50.
[16] Burt RK, Cohen BA, Russell E, Spero K, Joshi A, Oyama Y, et al. Hematopoietic stem cell transplantation for progressive multiple sclerosis: failure of a total body irradiation-based conditioning regimen to prevent disease progression in patients with high disability scores. Blood 2003;102(7):2373–8.
[17] Nash RA, McSweeney PA, Nelson JL, Wener M, Georges GE, Langston AA, et al. Allogeneic marrow transplantation in patients with severe systemic sclerosis: resolution of dermal fibrosis. Arthritis Rheum 2006;54(6):1982–6.
[18] Loh Y, Oyama Y, Statkute L, Verda L, Quigley K, Yaung K, et al. Non-myeloablative allogeneic hematopoietic stem cell transplantation for severe systemic sclerosis: graft-versus-autoimmunity without graft-versus-host disease? Bone Marrow Transplant 2007;39(7):435–7.
[19] Witzens-Harig M, Heilmann C, Hensel M, Kornacker M, Benner A, Haas R, et al. Long-term follow-up of patients with non-Hodgkin lymphoma following myeloablative therapy and autologous transplantation of CD34+-selected peripheral blood progenitor cells. Stem Cells 2007;25(1):228–35.
[20] Moore J, Brooks P, Milliken S, Biggs J, Ma D, Handel M, et al. A pilot randomized trial comparing CD34-selected versus unmanipulated hemopoietic stem cell transplantation for severe, refractory rheumatoid arthritis. Arthritis Rheum 2002;46(9):2301–9.
[21] Loh Y, Oyama Y, Statkute L, Quigley K, Yaung K, Gonda E, et al. Development of a secondary autoimmune disorder after hematopoietic stem cell transplantation for autoimmune diseases: role of conditioning regimen used. Blood 2007;109(6). 2643–2548.
[22] Burt RK, Oyama Y, Verda L, Quigley K, Brush M, Yaung K, et al. Induction of remission of severe and refractory rheumatoid arthritis by allogeneic mixed chimerism. Arthritis Rheum 2004;50(8):2466–70.
[23] Oyama Y, Barr WG, Statkute L, Corbridge T, Gonda EA, et al. Autologous non-myeloablative hematopoietic stem cell transplantation in patients with systemic sclerosis. Bone Marrow Transplant 2007;40(6):549–55.
[24] Voltarelli JC, Couri CE, Stracieri AB, Oliveira MC, Moraes DA, Pieroni F, et al. Autologous nonmyeloablative hematopoietic stem cell transplantation in newly diagnosed type 1 diabetes mellitus. JAMA 2007;297(14):1568–76.
[25] Burt RK, Traynor A, Statkute L, Barr WG, Rosa R, Schroeder J, et al. Nonmyeloablative hematopoietic stem cell transplantation for systemic lupus erythematosus. JAMA 2006;295(5):527–35.
[26] Abraham N, Li M, Vanella L, Peterson S, Ikehara S, Asprinio D. Bone marrow stem cell transplant into intra-bone cavity prevent Type 2 diabetes: Role of heme oxygenase -adiponectin. J Autoimmun; this issue.
[27] Boren EJ, Cheema GS, Naguwa SM, Ansari AA, Gershwin ME. The emergence of progressive multifocal leukoencephalopathy (PML) in rheumatic diseases. J Autoimmun 2007;30(1–2):90–8.
[28] Deane S, Meyers F. Gershwin M. On reversing the persistence of memory: Hematopoietic stem cell transplant for autoimmune disease in the first ten years. J Autoimmun; this issue.
[29] Gershwin ME. Bone marrow transplantation, refractory autoimmunity and the contributions of Susumu Ikehara. J Autoimmun; this issue.
[30] Hara M, Murakami T. Kobayashi E. *In vivo* bioimaging using photogenic rats: fate of injected bone marrow-derived mesenchymal stromal cells. J Autoimmun; this issue.
[31] Ikehara S. Innovative BMT method for intractable diseases. Immunol Res 2007;38(1–3):251–60.
[32] Marmont A. Will hematopoietic stem cell transplantation cure human autoimmune diseases? J Autoimmun; this issue.
[33] Ozawa K, Sato K, Oh I, Ozaki K, Uchibori R, Obara Y, et al. Cell and gene therapy using mesenchymal stem cells (MSCs). J Autoimmun; this issue.
[34] Ratajczak MZ, Zuba-Surma EK, Wysoczynski M, Wan W, Ratajczak J, Wojakowski W, et al. Hunt for pluripotent stem cell - regenerative medicine search for almighty cell. J Autoimmun; this issue.
[35] Rezvani A. Storb R. Separation of graft-vs.-tumor effects from graft-vs.-host disease in allogeneic hematopoietic cell transplantation. J Autoimmun; this issue.
[36] Sonoda Y. Immunophenotype and functional characteristics of human primitive CD34-negative hematopoietic stem cells: The significance of the intra-bone marrow injection. J Autoimmun; this issue.
[37] Anaya JM, Castiblanco J, Tobon GJ, Garcia J, Abad V, Cuervo H, et al. Familial clustering of autoimmune diseases in patients with type 1 diabetes mellitus. J Autoimmun 2006;26:208–14.
[38] Avrameas S, Ternynck T, Tsonis IA, Lymberi P. Naturally occurring B-cell autoreactivity: A critical overview. J Autoimmun 2007;29:213–8.
[39] Cohen IR. Biomarkers, self-antigens and the immunological homunculus. J Autoimmun 2007;29:246–9.
[40] Lan RY, Mackay IR, Eric Gershwin M. Regulatory T cells in the prevention of mucosal inflammatory diseases: Patrolling the border. J Autoimmun 2007;29:272–80.
[41] Lang KS, Burow A, Kurrer M, Lang PA, Recher M. The role of the innate immune response in autoimmune disease. J Autoimmun 2007; 29:206–12.
[42] Milner J, Ward J, Keane-Myers A, Min B, Paul WE. Repertoire-dependent immunopathology. J Autoimmun 2007;29:257–61.
[43] Papadimitraki ED, Bertsias GK, Boumpas DT. Toll like receptors and autoimmunity: A critical appraisal. J Autoimmun 2007;29:310–8.
[44] Peng Y, Martin DA, Kenkel J, Zhang K, Ogden CA, Elkon KB. Innate and adaptive immune response to apoptotic cells. J Autoimmun 2007;29:303–9.
[45] Rowley B, Tang L, Shinton S, Hayakawa K, Hardy RR. Autoreactive B-1 B cells: Constraints on natural autoantibody B cell antigen receptors. J Autoimmun 2007;29:236–45.
[46] Ryan KR, Patel SD, Stephens LA, Anderton SM. Death, adaptation and regulation: The three pillars of immune tolerance restrict the risk of autoimmune disease caused by molecular mimicry. J Autoimmun 2007;29:262–71.
[47] Tsonis IA, Avrameas S, Moutsopoulos HM. Autoimmunity and pathophysiology. J Autoimmun 2007;29:203–5.
[48] Youinou P. B cell conducts the lymphocyte orchestra. J Autoimmun 2007;28:143–51.
[49] Zelenay S, Moraes Fontes MF, Fesel C, Demengeot J, Coutinho A. Physiopathology of natural auto-antibodies: The case for regulation. J Autoimmun 2007;29:229–35.
[50] Zhou ZH, Tzioufas AG, Notkins AL. Properties and function of polyreactive antibodies and polyreactive antigen-binding B cells. J Autoimmun 2007;29:219–28.
[51] Abbas AK, Lohr J, Knoechel B. Balancing autoaggressive and protective T cell responses. J Autoimmun 2007;28:59–61.
[52] Adamus G, Webb S, Shiraga S, Duvoisin RM. Anti-recoverin antibodies induce an increase in intracellular calcium, leading to apoptosis in retinal cells. J Autoimmun 2006;26:146–53.
[53] Bonfield TL, Barna BP, John N, Malur A, Culver DA, Kavuru MS, et al. Suppression of activin A in autoimmune lung disease associated with anti-GM-CSF. J Autoimmun 2006;26:37–41.
[54] Gao J, Killedar S, Cornelius JG, Nguyen C, Cha S, Peck AB. Sjögren's syndrome in the NOD mouse model is an interleukin-4 time-dependent, antibody isotype-specific autoimmune disease. J Autoimmun 2006;26:90–103.
[55] Ogawa N, Minamimura K, Kodaka T, Maki T. Short administration of polyclonal anti-T cell antibody (ALS) in NOD mice with extensive insulitis prevents subsequent development of autoimmune diabetes. J Autoimmun 2006;26:225–31.
[56] Rivadeneyra-Espinoza L, Ruiz-Arguelles A. Cell-penetrating anti-native DNA antibodies trigger apoptosis through both the neglect and programmed pathways. J Autoimmun 2006;26:52–6.
[57] Wu HY, Monsonego A, Weiner HL. The mechanism of nasal tolerance in lupus prone mice is T-cell anergy induced by immature B cells that lack B7 expression. J Autoimmun 2006;26:116–26.

Please cite this article in press as: Richard K Burt et al., Hematopoietic stem cell transplantation for autoimmune diseases: What have we learned?, Journal of Autoimmunity (2008), doi:10.1016/j.jaut.2007.12.010