Idiotype-specific immunotherapy in multiple myeloma: suggestions for future directions of research

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Multiple myeloma (MM) remains a difficult-to-cure cancer and less than 20% of patients achieve long-term survival irrespective of the treatment delivered, including high-dose chemotherapy. Thus, new treatment modalities are urgently needed. Myeloma cells produce a monoclonal immunoglobulin (Ig) which is a truly tumor-specific antigen. The tumor-specific antigenic determinants are localized in the variable regions of the monoclonal Ig and are termed idiotopes (Id). Id-vaccination, i.e., vaccination with the autologous monoclonal Ig, has been performed in MM patients in order to elicit tumor-specific immune responses and possibly elimination of myeloma cells. However, clinical trials have not given the promising results obtained in mice. This review focuses on tolerance mechanisms that might hinder Id-specific immune responses in MM patients. New strategies for Id vaccination in MM are discussed.

Key words: T cells, idiotype, tolerance, immunosurveillance, cancer.

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High-dose chemotherapy and autologous[1] and allogeneic[2,3] stem cell transplantation and new drugs such as thalidomide and bortezomib[4,5] have improved the treatment of multiple myeloma (MM). Despite this, MM is still considered an essentially incurable cancer[6] and new therapies are undoubtedly warranted. This paper reviews immunotherapy approaches in MM with special emphasis on idiotype as a tumor-specific antigen to raise tumor-specific immune responses.

Introductory remarks: shared tumor antigens in MM and their limitations in immunotherapy

Immunotherapy of cancer rests on the premise that tumor cells express antigens serving as targets for immune-mediated attack. These antigens can be differentiation antigens, such as cancer-testis antigens, or over-expressed antigens.[7,8] Examples of general tumor antigens shared among MM cells from different patients are cancer-testis antigens such as MAGE and NY-ESO-1,[9-12] Muc-1,[13,14] sperm protein 17,[15] transcription factors PRDI-BF1 and XBP-1,[16] and the differentiation antigen CD138.[17] However, the clinical usefulness of these antigens for vaccination of MM patients remains to be determined. A major obstacle is likely to be immune tolerance, since these types of tumor antigens are also expressed to some extent in normal tissues as self-antigens.[16] An additional problem is that cancer-testis antigens are preferentially expressed late in the course of MM disease, and their expression is often restricted to subsets of myeloma cells. Finally, immune responses against cancer-testis antigens and differentiation antigens could have unwanted side effects such as autoimmunity, as is the case for anti-melanoma vaccines that have been shown to induce vitiligo.[18]

The problem of immune tolerance to shared tumor antigens in MM may be overcome by passive immunotherapy with antibodies. However, anti-CD20 monoclonal antibodies appear less useful in MM than in B lymphoma,[19] while monoclonal antibodies such as anti-CD138 (syndecan-1), anti-CD38, and anti-HM1.24 have so far not met clinical expectations or entered clinical trials.[17,20,21] Passive immunotherapy may also be performed as adoptive transfer of T cells. Thus, adoptive immunotherapy with allogeneic T cells (called donor lymphocyte infusion) is a therapeutic option for MM patients undergoing allogeneic stem cell transplantation.[22] Autologous MM-reactive T cells expanded *ex vivo* might also be used.[23-26] However, in these cases, the identity of MM antigen(s) targeted by T cells remains largely unknown and large scale preparation of clinical grade autoreactive T cells has not yet been performed.

A highly tumor-specific antigen in MM: myeloma protein idiotype

Given the problems of immunotherapy directed against shared tumor antigens described above, it is fortunate that MM cells express a highly tumor-specific antigen, i.e. the variable (V) regions of the clonally unique myeloma protein (monoclonal immunoglobulin) that each myeloma tumor secretes. This is so because the V regions vary for different myeloma proteins, due to the vast diversity of immunoglobulin (Ig) V-

regions generated by clonal rearrangements of V(D)J gene segments and by somatic hypermutation.[27] These V-region antigenic determinants are called idiotopes, and the sum of the idiotopes represents the idiotype (Id) of the monoclonal Ig. Id expressed by the monoclonal Ig in MM has distinct advantages as a tumor-specific antigen. Firstly, consistent with being derived from post-germinal B cells, myeloma cells usually contain numerous somatic mutations in their rearranged Ig V(D)J genes.[28] Secondly, the somatic mutation process appears to have stopped in MM so that cells do not acquire further amino acid replacements in their V regions.[28] Thus, since myeloma protein V regions do not change over time, Id is a stable tumor-specific marker. Id also has certain practical advantages as a tumor-specific antigen. Firstly, because assembled V(D)J gene segments of Ig heavy (H) and light (L) chains may be relatively easily amplified and sequenced from bone marrow samples, tailor-made DNA-based Id vaccines can be constructed for each patient without too much effort. Secondly, because monoclonal Ig can easily be purified from patient serum or transfected cells, protein-based Id vaccines can readily be prepared.

Id as a tumor-specific target for immune attack: basic immunological mechanisms

Prophylactic Id vaccination of mice protects against tumor challenge with Id-positive myeloma, as demonstrated by Eisen and colleagues[29] and confirmed by a number of other investigators. However, in order to design effective strategies for Id vaccines, it is crucial to understand the molecular and cellular mechanisms by which Id-specific immune responses are capable of eradicating myeloma cells. Experiments in mice have shown that Id-specific antibodies do not play a major role in tumor eradication, the reason being that the large quantities of soluble monoclonal Ig secreted by myeloma cells block Id-specific antibodies before they can reach the surface of myeloma cells. Even if Id-specific antibodies could escape peripheral blockade and reach the vicinity of myeloma cells, they are unlikely to be effective since myeloma cells usually express little or no surface Ig (Figure 1A). Id-specific CD8$^+$ T cells could have a role in immunosurveillance because MM cells usually express major histocompatibility complex (MHC) class I molecules. Moreover, studies in mice have demonstrated that myeloma cells process their endogenous Ig and present Id peptides on their MHC class I molecules to CD8$^+$ T cells[30] (Figure 1B). However, there is not yet much information on the role of Id-specific CD8$^+$ T cells *in vivo* in MM. Id-specific CD4$^+$ T cells have been considered unlikely to play a role in MM since myeloma cells usually do not express many MHC class II molecules. However, extensive studies in mice, reviewed by Corthay *et al.*,[31] have shown that Id-specific CD4$^+$ T cells clearly play a role in eradication of MHC class II-negative MOPC315 myeloma cells.[32,33,34] As a mechanism, it was demonstrated that monoclonal Ig secreted by the tumor was endocytosed and processed by antigen-presenting cells in the draining lymph node and within the tumor. Such antigen-presenting cells presented Id-peptides on their MHC class II molecules to Id-specific CD4$^+$ T cells of the Th1 type.[35,36] The activated tumor-infiltrating Id-specific CD4$^+$ T cells produced interferon-γ that stimulated macrophages so that these latter cells became tumoricidal and killed myeloma cells (Figure 1C).[37]

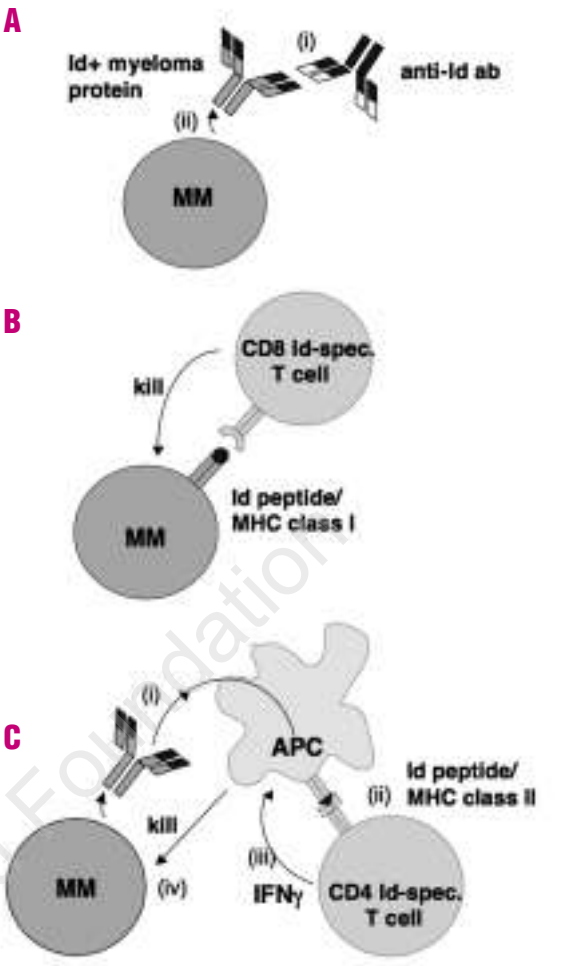

Figure 1. Role of Id-specific antibodies, CD8$^+$ and CD4$^+$ T cells in the eradication of MM cells. A. Id-specific antibody is likely to be blocked by the high concentration of myeloma protein and will thus not reach the MM cells, indicated by (i). Moreover, MM cells usually express little or no surface Ig and are therefore a poor target (ii). Consistent with this, Id-specific antibodies on their own seem to be of little therapeutic value.[107,108] B. MM can process their endogenous Ig and present Id-peptide on their MHC class I molecules to CD8$^+$ T cells.[30] C. MM cells are usually MHC class II-negative and thus cannot be recognized directly by CD4$^+$ T cells. However, secreted myeloma protein (i) is endocytosed and processed by tumor antigen presenting cells (dendritic cells, macrophages) which present Id peptides on their MHC class II molecules to Id-specific CD4$^+$ T cells that become activated (ii)[32-36] and secrete interferon-γ (iii) that stimulates macrophages. Activated macrophages become tumoricidal (iv) to MM cells.[37]

Evidence for naturally occurring Id-specific T-cell responses in MM patients

The observation that Id-specific CD4$^+$ T cells protect mice against MM raises the question as to whether Id-specific T cells have relevance in human disease. MM patients have perturbations of their αβ T-cell receptor

(TCR) repertoire with clonal and oligoclonal expansions particularly in the CD8+ populations.[38-41] Dendritic cells, too, have been shown to be dyfunctional.[42-44] These abnormalities are expected to generally lower the efficiency of T-cell responses in MM patients. Despite this, even in the absence of Id vaccination, low frequencies of Id-specific T cells have been detected by adhesion, proliferation, and cytokine secretion (ELISPOT) assays in patients with monoclonal gammopathy of undetermined significance (MGUS) and MM.[45-47] These low frequency Id-specific T cells do not appear to be related to the clonally or oligoclonally expanded T cells. Such Id-specific T cells responded to synthetic peptides corresponding to the complementarity determining regions (CDR) of both H and L chains of the monoclonal Ig.[48-50] Id-specific T cells appeared to be more frequent among CD4+ cells than among CD8+ cells. While Th1 cells that produced interferon-γ dominated in the early stages of the disease, Th2 cells that produced interleukin-4 dominated with disease progression.[51] Id-specific cytotoxic T-cell lines with the capacity to kill autologous primary myeloma cells were also generated *in vitro*.[52,53] The cytotoxic T-cell lines consisted of both CD4+[53] and CD8+[52,53] T cells. Killing of MM was in one report solely MHC class I-restricted[52] while in the other report both class I- and class II-restriction was observed.[53] Collectively, these results suggest that Id-specific T cells can naturally occur in MGUS and MM patients and can be involved in controlling the progression of the disease. T cells with other specificities may also play a role in both MGUS and MM.[24]

However, an alternative interpretation is that in MM patients most high avidity Id-specific T cells have been deleted and that only low avidity T cells remain (*see below)*. Although such low avidity Id-specific T cells are detected by sensitive techniques *in vitro*, their significance *in vivo* is not known. It is, in fact, difficult to test whether high avidity Id-specific T cells are tolerized in MM patients, simply because the Id-specific repertoire prior to disease is unknown.

Id-specific vaccination in MM patients

Since Id vaccination confers protection against MM in mice,[29] it has been important to investigate the effects of Id vaccination in MM patients. A number of different strategies for Id-vaccination have been employed. In some studies, untreated patients with early stage MM were immunized with autologous alum-precipitated myeloma protein, either with[54] or without[55] granulocyte-macrophage colony-stimulating factor (GM-CSF). In other studies, Id vaccination was performed with conjugates of Id-keyhole-limpet hemocyanin (Id-KLH) in association with GM-CSF or interleukin-2,[56] or with Id-pulsed dendritic cells.[57-62] Some of these studies were performed in untreated patients while others were performed after high-dose chemotherapy and stem cell transplantation. Id-specific T- and B-cell responses were detected with variable frequency, but clinical responses were unsatisfactory and not correlated with the induction of tumor-specific immune responses. Thus, it is too early to say whether Id-vaccination and elicitation of Id-specific immune responses might improve the prognosis of MM patients.[63,64] It should be emphasized that the same vaccine formulations, i.e., Id/KLH conjugates or dendritic cell-based Id vaccines, induced Id-specific immune responses with higher frequency in patients with B-cell lymphoma, with clear evidence of tumor burden reduction and/or improvement of clinical outcome.[65,66] The effectiveness in B-cell lymphomas is a proof of principle of the validity of Id as a tumor-specific target for immune attack, but it also strongly suggests that the immune competence status and mechanisms of Id tolerance play a much more important role in MM than in lymphoma, as discussed below.

The issue of T-cell tolerance to Id in MM

If Id vaccination is to be useful in MM patients, T cells have to be able to respond. This is an issue that has been largely ignored despite theoretical and experimental evidence of its importance. First, in order to elicit any T-cell responses at all, Id peptides derived from the myeloma must be able to bind the MHC molecules of the individual,[67,68] and this might often not be the case. Second, even if Id peptides are able to bind MHC molecules of the individual, one should consider that T cells can either respond, or become tolerant. The tolerance issue can be further divided into two scenarios: (i) tolerance to germline encoded Id peptides prior to disease, and (ii) emergence of tolerance to Id peptides with disease development.

As to the first issue, a number of basic immunological experiments strongly suggest that CD4+ T cells are tolerant to germline encoded Id peptides,[69-73] in part due to deletion in the thymus.[71,74] Thus, Id-specific CD4+ T cells should selectively focus on Id peptides dependent on somatic mutation of rearranged V(D)J in the myeloma cells. This might not be a major problem in MM, since V gene regions are usually heavily mutated. As to the second issue, which is of the utmost importance, it appears that Id-specific CD4+ T cells become tolerant as MM disease progresses. This evidence was obtained in Id-specific TCR-trangenic mice challenged with such high amounts of MOPC315 MM cells that the resistance conferred by Id-specific CD4+ T cells was overcome.[75,76] Such experiments demonstrated that if T cells failed to eliminate myeloma cells upon their initial encounter, T-cell tolerance ensued and MM tumors progressed.[75,76] More specifically, Id-specific CD4+ T cells were progressively deleted once the serum myeloma protein concentration exceeded 50 μg/mL. Deletional tolerance was evident not only in the thymus, but also in peripheral lymphoid organs, and even in the MM tumor itself.[75,76] Based on this model, one would expect that MM patients in whom the myeloma protein concentration is much higher than 50 μg/mL at diagnosis would have no functional Id-specific CD4+ cells left due to tolerance development prior to disease detection. Even individuals with MGUS, whose monoclonal component serum levels are typically less than 3 mg/mL in the absence of any symptoms, may have undergone the same tolerance process as that in MM patients.

Close to nothing is known about the tolerance of Id-specific CD8+ T cells. However, it has been argued that CD8+ T-cell responses to influenza hemagglutinin are

reduced due to tolerance to the cross-reactive V_H49-58 sequence of the V_H gene segment used in the MOPC21 plasmacytoma; this Ig V-region sequence differs by only one amino acid from the relevant hemagglutinin sequence.[30,77]

Suggestions for future directions of research

Better characterization of Id-specific T-cell responses in humans

As referenced above, many investigators have described Id-specific T cells occurring naturally, as well as after Id immunization, in MM patients. These findings appear to contradict the studies on T-cell tolerance done in two different Id-specific TCR-transgenic strains of mice in which tolerance development can be easily monitored.[75,76] To reconcile these seemingly contradictory findings, it is reasonable to suggest that Id-specific T cells should be better characterized in humans. Preferably, Id-specific T cells should be cloned, and their specificity for Id should be documented both with synthetic peptides as well as with the complete monoclonal Ig. The MHC restriction elements should also be defined. These requirements are not unreasonable as they are usually met by T-cell immunologists working with other antigens in humans. Finally, the avidity of Id-specific T cells should be investigated, e.g. by establishing dose-response curves. It is entirely possible that a more detailed investigation in MM patients will actually reveal that there is a substantial degree of T-cell tolerance to Id in MM as in TCR-transgenic mouse models.

Besides a better characterization of Id-specific T cells, it is important to investigate the role of inhibitory mechanisms such as those mediated by regulatory T cells (Tregs). Relief of inhibitory signals mediated by Tregs has been shown to improve the potency of vaccine-induced antitumor immune responses.[78] Thus, in the MOPC315 plasmacytoma model, it was observed more than 20 years ago that large subcutaneous tumors could be cured by either low (15 mg/kg) or high (300 mg/kg) doses of cyclophosphamide. However, only mice treated with low dose cyclophosphamide were able to reject a lethal challenge with MOPC315 cells following chemotherapy, strongly suggesting the establishment of antitumor immunity.[79] Since Tregs are sensitive to low dose cyclophosphamide,[80] these data would suggest, though indirectly, their involvement in control of immune responses against myeloma. Very little is known about Tregs in human MM, and whether they can influence Id-specific immune responses. Recently, two conflicting reports have been published, one describing Treg dysfunction,[81] the other suggesting an increased frequency and normal immunosuppressive function of Tregs isolated from patients.[82]

The tolerance problem: should only patients in complete remission be vaccinated?

If there is actually a substantial degree of T-cell tolerance to Id in MM patients, it should be of overriding importance to reverse T-cell tolerance prior to Id-vaccination. As judged from the results in an Id-specific TCR-transgenic model, reversal might be obtained once the serum myeloma protein concentration has dropped below <50 μg/mL. However, this estimate is based on results obtained in a single Id-specific TCR transgenic model.[75,76] It might well be that in patients with a polyclonal Id-specific TCR repertoire, the serum concentration required for relief of tolerance could vary for individual Id-specific T cells. Likewise, the monoclonal Ig concentration needed for induction of T-cell tolerance could differ between mice and men, and even between individual MM patients. Stem cell transplantation is considered the treatment of choice for MM patients up to the age of 65 years old.[1,59,83] The complete remission rate varies from 20 to 40%, depending on the criteria used to define complete remission. Recently, it has been proposed that the monoclonal Ig must no longer be detectable by immunofixation, which has a sensitivity level of about 50-200 μg/mL of serum myeloma protein, in order for the patient to qualify as having complete remission.[84] However, since the amount of residual circulating monoclonal Ig in immunofixation-negative patients in complete remission has not been systematically examined, it is unknown whether such patients really have myeloma protein concentrations below the critical <50 μg/mL threshold. Thus, more sensitive techniques should be developed to determine the degree of complete remission, e.g. patient-specific ELISA and PCR methods. Patients in molecular complete remission, as defined by PCR methods based on tumor-specific V(D)J PCR primers, may indeed have very low amounts, or no, circulating monoclonal Ig, but these patients probably represent a very small minority after stem cell transplantation. Even if the serum levels of the monoclonal Ig do not fall below the 50 μg/mL threshold during remission, it might still be advisable to vaccinate at a time-point when the monoclonal Ig concentration is low or very low. This suggestion is based on experimental data indicating that the higher the antigen concentration, the more profound the T cell tolerance.[75,76,85] Thus, once the monoclonal Ig concentration has been reduced, low avidity Id-specific T cells could regain some of their Id-responsiveness.

The TCR repertoire and antigen-presenting cell function post-transplantation

In addition to obtaining a complete remission, patients undergoing Id vaccination would need to educate new Id-specific T cells in the thymus from committed thymocyte precursors. It will therefore be a challenge to find the best time-point after stem cell transplantation to vaccinate: (i) monoclonal Ig concentration should be at its nadir while (ii) new antigen-presenting cells (such as dendritic cells) and (iii) a new T-cell repertoire should have emerged. The second requirement could be a problem since MM patients have been reported to have quantitatively and qualitatively deficient dendritic cells. However, sufficient dendritic cells have been obtained from MM patients to perform Id-vaccination after stem cell transplantation.[57-62] As concerns the qualitative defects, one signaling pathway leading to dendritic cells dysfunction following exposure to MM cells, or their conditioning culture medium,

has recently been identified. Thus, *ex vivo* generated dendritic cells treated with specific inhibitors of p38 mitogen activated protein kinase (MAPK) regained full functionality and established Id-specific immunity in mice.[86] The third requirement mentioned above, namely development of a new T-cell repertoire, might be difficult to fulfill as the T-cell receptor repertoire has been reported to be severely and long-lastingly altered in MM patients both before[38-41] and after[39] stem cell transplantation. Development of a new T-cell repertoire after transplantation could be a particular problem in MM patients, given their advanced age and thymic involution.

A recent study has shown that the immune competence of MM patients can be restored following high-dose chemotherapy and autologous stem cell transplantation by a combination of vaccination and adoptive T-cell therapy. Patients vaccinated against *Streptococcus pneumoniae* both before T-cell harvest and after adoptive T-cell transfer shortly following transplantation had improved immune reconstitution.[87] However, the relevance of such results to vaccination of MM patients is not straightforward. Firstly, vaccination to prime T cells before harvest might not be successful because of tolerance, due to a high tumor burden prior to the high-dose chemotherapy. Secondly, Id-specific T cells deleted by myeloma progression would not be expected to reappear following autologous T-cell transfer.

The possibility of inducing complete remission with a combination of targeted therapy and conventional drugs is emerging as an alternative to stem cell transplantation. For instance, the association of thalidomide with melphalan and prednisone (MPT regimen) induces a complete remission rate comparable to that achieved by autologous stem cell transplantation.[88] It is currently under investigation whether the remission status achieved by MPT or other regimens with immunomodulatory drugs such as revlimid or bortezomib preserves the immune competence status of MM patients better than stem cell transplantation does.[89] It should be pointed out that allogeneic stem cell transplantation has the potential advantages of providing recipients with a non-tolerized T-cell repertoire. In addition, donor-derived, fully functional dendritic cells could be used for vaccination. The latter strategy has recently been tested in a pilot clinical trial.[90]

Id vaccines and methods of delivery

There are many different approaches to Id-vaccination. Since the monoclonal Ig can readily be purified from serum prior to cytoreductive therapy, protein-based vaccines have been widely used in clinical trials. Id has been conjugated to carrier proteins such as KLH, and delivered in the presence of adjuvants such as alum, GM-CSF, or interleukin-12, or delivered by dendritic cells alone or with the same adjuvants. As an alternative, it is relatively easy to amplify rearranged V(D)J genes from myeloma cells and produce tailor-made Id-vaccines in DNA format. Injection of Ig-genes as naked plasmids[91,92] or Id-encoding recombinant adenovirus[93] induced anti-Id antibody responses and tumor protection in mice. Moreover, monoclonal antibodies or single chain Fv have been genetically conjugated to GM-CSF,[94] chemokines[95] CD40L,[96] tetanus toxin fragment C[97] and interleukin-1β,[98] and used as protein vaccines[94-98] or DNA vaccines[95,97,98] for vaccination against myelomas and B-cell lymphomas in mice. In the years to come, novel innovative Id-containing molecules, and more efficient means of DNA vaccination, such as electroporation,[99,100] are likely to further boost this approach. For example, novel bivalent molecules (*vaccibodies*) that target antigen-presenting cells via antigen-presenting cell-specific single chain Fv for efficient delivery of idiotypic single chain Fv have been constructed. When vaccibodies were delivered as an intramuscular DNA vaccine combined with electroporation, antigen-presenting cells in draining lymph nodes became Id-primed and stimulated Id-specific $CD4^+$ T cells.[100] Vaccinated mice mounted an Id-specific immune response and resisted a challenge with MOPC315 tumor.[100] The vaccibody technology has recently also been applied to MM patients (*Frøyland M, Bogen B, unpublished data*).

Should all patients be Id-vaccinated, regardless of V(D)J sequences of the myeloma protein?

If V(D)J sequences do not contain peptide binding motifs for MHC molecules of the individual, no Id-specific T-cell responses can be expected. In this case, immunization of patients with their own monoclonal Ig would be futile. Likewise, due to T-cell tolerance, only Id peptides expressing somatic mutations or N-region diversity are expected to be immunogenic, but only in patients with very good complete remission. Thus, Ig-sequencing, HLA typing, and analyses of V regions for mutations and peptide-binding motifs are important prerequisites to increase the chances of successful Id vaccination.

Id-specific T-cell therapy?

Since Id-specific T cells can be tolerized or display low avidity as a consequence of long-term exposure to myeloma cells, an alternative strategy is the transfer of allogeneic Id-specific T cells concomitantly with the allotransplantation procedure. If generated with an appropriate vaccine formulation in a healthy immunocompetent donor, it is theoretically possible to generate high avidity Id-specific T cells. The exquisite tumor-specificity of Id makes this antigen an ideal candidate for normal donor immunization. This approach will circumvent both Id tolerance and the disrupted T-cell receptor repertoire of MM patients. When the stem cell donor is immunized against the recipient's Id, anti-Id humoral and cellular immunity is expected to be transferred with the graft. Although patient series are very small, results are promising[101] and clinical trials are ongoing.

Allogeneic transplantation is also an ideal platform to test the efficacy of Id-specific immunomanipulated donor lymphocyte infusion. This suggestion is based on the observation that donor lymphocyte infusion has an effect in MM.[22] However, because the effect seems to be mediated by alloreactive T cells, it has been difficult to separate *graft-versus-myeloma* and *graft-versus-host* effects. If highly tumor-reactive Id-specific T cells could

be transferred, the problem of *graft-versus-host* disease might be reduced while retaining the *graft-versus-myeloma* effect. Indeed, Id-specific T cells for transfer could be obtained by immunizing related donors, followed by *in vitro* expansion and enrichment. To avoid any potential risk associated with the exposure of a healthy donor to a cancer product, which might be ethically acceptable in the case of related,[101] but not of unrelated, donors, *in vitro* priming and education of allogeneic donor T cells should also be considered. There is published evidence suggesting the feasibility of this approach.[52,102,103,104] However, whether infusion of Id-specific T cells has any clinical effect is not known. The finding that transfer of Id-specific $CD4^+$ T cells[105] or an Id-specific T-cell line[106] could cure mice of previously injected Id^+ B lymphoma cells suggest that this could be a valuable strategy in MM.

All authors contributed significantly to this manuscript and declare that they have no potential conflicts of interest.

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References

1. Harousseau JL. Stem cell transplantation in multiple myeloma (0, 1, or 2). Curr Opin Oncol 2005;17:93-8.
2. Corradini P, Voena C, Tarella C, Astolfi M, Ladetto M, Palumbo A, et al. Molecular and clinical remissions in multiple myeloma: role of autologous and allogeneic transplantation of hematopoietic cells. J Clin Oncol 1999; 17:208-15.
3. Crawley C, Lalancette M, Szydlo R, Gilleece M, Peggs K, Mackinnon S, et al. Outcomes for reduced-intensity allogeneic transplantation for multiple myeloma: an analysis of prognostic factors from the Chronic Leukaemia Working Party of the EBMT. Blood 2005;105:4532-9.
4. Bruno B, Giaccone L, Rotta M, Anderson K, Boccadoro M. Novel targeted drugs for the treatment of multiple myeloma: from bench to bedside. Leukemia 2005;19:1729-38.
5. Bruno B, Rotta M, Giaccone L, Massaia M, Bertola A, Palumbo A, et al. New drugs for treatment of multiple myeloma. Lancet Oncol 2004;5:430-42.
6. Durie BG, Kyle RA, Belch A, Bensinger W, Blade J, Boccadoro M, et al. Myeloma management guidelines: a consensus report from the Scientific Advisors of the International Myeloma Foundation. Hematol J 2003;4:379-98.
7. Van den Eynde BJ, van der Bruggen P. T cell defined tumor antigens. Curr Opin Immunol 1997;9:684-93.
8. Novellino L, Castelli C, Parmiani G. A listing of human tumor antigens recognized by T cells: March 2004 update. Cancer Immunol Immunother 2005; 54:187-207.
9. Pellat-Deceunynck C, Mellerin MP, Labarriere N, Jego G, Moreau-Aubry A, Harousseau JL, et al. The cancer germline genes MAGE-1, MAGE-3 and PRAME are commonly expressed by human myeloma cells. Eur J Immunol 2000;30:803-9.
10. van Baren N, Brasseur F, Godelaine D, Hames G, Ferrant A, Lehmann F, et al. Genes encoding tumor-specific antigens are expressed in human myeloma cells. Blood 1999;94:1156-64.
11. Jungbluth AA, Ely S, DiLiberto M, Niesvizky R, Williamson B, Frosina D, et al. The cancer-testis antigens CT7 (MAGE-C1) and MAGE-A3/6 are commonly expressed in multiple myeloma and correlate with plasma-cell proliferation. Blood 2005;106:167-74.
12. van Rhee F, Szmania SM, Zhan F, Gupta SK, Pomtree M, Lin P, et al. NY-ESO-1 is highly expressed in poor-prognosis multiple myeloma and induces spontaneous humoral and cellular immune responses. Blood 2005; 105:3939-44.
13. Treon SP, Mollick JA, Urashima M, Teoh G, Chauhan D, Ogata A, et al. Muc-1 core protein is expressed on multiple myeloma cells and is induced by dexamethasone. Blood 1999; 93: 1287-98.
14. Choi C, Witzens M, Bucur M, Feuerer M, Sommerfeldt N, Trojan A, et al. Enrichment of functional CD8 memory T cells specific for MUC1 in bone marrow of patients with multiple myeloma. Blood 2005;105:2132-4.
15. Lim SH, Wang Z, Chiriva-Internati M, Xue Y. Sperm protein 17 is a novel cancer-testis antigen in multiple myeloma. Blood 2001;97:1508-10.
16. Lotz C, Mutallib SA, Oehlrich N, Liewer U, Ferreira EA, Moos M, et al. Targeting positive regulatory domain I-binding factor 1 and X box-binding protein 1 transcription factors by multiple myeloma-reactive CTL. J Immunol 2005;175:1301-9.
17. Dhodapkar KM, Krasovsky J, Williamson B, Dhodapkar MV. Antitumor monoclonal antibodies enhance cross-presentation of cellular antigens and the generation of myeloma-specific killer T cells by dendritic cells. J Exp Med 2002;195:125-33.
18. Overwijk WW, Lee DS, Surman DR, Irvine KR, Touloukian CE, Chan CC, et al. Vaccination with a recombinant vaccinia virus encoding a "self" antigen induces autoimmune vitiligo and tumor cell destruction in mice: requirement for $CD4^{(+)}$ T lymphocytes. Proc Natl Acad Sci USA 1999;96:2982-7.
19. Treon SP, Pilarski LM, Belch AR, Kelliher A, Preffer FI, Shima Y, et al. CD20-directed serotherapy in patients with multiple myeloma: biologic considerations and therapeutic applications. J Immunother 2002;25:72-81.
20. Tassone P, Goldmacher VS, Neri P, Gozzini A, Shammas MA, Whiteman KR, et al. Cytotoxic activity of the maytansinoid immunoconjugate B-B4-DM1 against CD138+ multiple myeloma cells. Blood 2004;104:3688-96.
21. Ozaki S, Kosaka M, Wakahara Y, Ozaki Y, Tsuchiya M, Koishihara Y, et al. Humanized anti-HM1.24 antibody mediates myeloma cell cytotoxicity that is enhanced by cytokine stimulation of effector cells. Blood 1999;93: 3922-30.
22. Lokhorst HM, Schattenberg A, Cornelissen JJ, Thomas LL, Verdonck LF. Donor leukocyte infusions are effective in relapsed multiple myeloma after allogeneic bone marrow transplantation. Blood 1997;90:4206-11.
23. Dhodapkar MV, Krasovsky J, Olson K. T cells from the tumor microenvironment of patients with progressive myeloma can generate strong, tumor-specific cytolytic responses to autologous, tumor-loaded dendritic cells. Proc Natl Acad Sci USA 2002;99:13009-13.
24. Dhodapkar MV, Krasovsky J, Osman K, Geller MD. Vigorous premalignancy-specific effector T cell response in the bone marrow of patients with monoclonal gammopathy. J Exp Med 2003;198:1753-7.
25. Noonan K, Matsui W, Serafini P, Carbley R, Tan G, Khalili J, et al. Activated marrow-infiltrating lymphocytes effectively target plasma cells and their clonogenic precursors. Cancer Res 2005;65:2026-34.
26. Hayashi T, Hideshima T, Akiyama M, Raje N, Richardson P, Chauhan D, et al. Ex vivo induction of multiple myeloma-specific cytotoxic T lymphocytes. Blood 2003;102:1435-42.
27. Tonegawa S. Somatic generation of antibody diversity. Nature 1983; 302: 575-81.
28. Sahota SS, Leo R, Hamblin TJ, Stevenson FK. Myeloma VL and VH gene sequences reveal a complementary imprint of antigen selection in tumor cells. Blood 1997;89:219-26.
29. Lynch RG, Graff RJ, Sirisinha S, Simms ES, Eisen HN. Myeloma proteins as tumor-specific transplantation antigens. Proc Natl Acad Sci USA 1972; 69:1540-4.
30. Cao W, Myers-Powell BA, Braciale TJ. Recognition of an immunoglobulin VH epitope by influenza virus-specific class I major histocompatibility complex-restricted cytolytic T lymphocytes. J Exp Med 1994;179:195-202.
31. Corthay A, Lundin KU, Munthe LA, Froyland M, Gedde-Dahl T, Dembic Z, et al. Immunotherapy in multiple myeloma: Id-specific strategies suggested by studies in animal models. Cancer Immunol Immunother 2004; 53:759-69.
32. Lauritzsen GF, Bogen B. The role of idiotype-specific, CD4+ T cells in tumor resistance against major histocompatibility complex class II molecule negative plasmacytoma cells. Cell Immunol 1993;148:177-88.
33. Lauritzsen GF, Weiss S, Dembic Z, Bogen B. Naive idiotype-specific CD4+ T cells and immunosurveillance of B-cell tumors. Proc Natl Acad Sci USA 1994;91:5700-4.
34. Bogen B, Munthe L, Sollien A, Hof-

gaard P, Omholt H, Dagnaes F et al. Naive CD4+ T cells confer idiotype-specific tumor resistance in the absence of antibodies. Eur J Immunol 1995;25:3079-86.
35. Dembic Z, Schenck K, Bogen B. Dendritic cells purified from myeloma are primed with tumor-specific antigen (idiotype) and activate CD4+ T cells. Proc Natl Acad Sci USA 2000; 97: 2697-702.
36. Dembic Z, Rottingen JA, Dellacasagrande J, Schenck K, Bogen B. Phagocytic dendritic cells from myelomas activate tumor-specific T cells at a single cell level. Blood 2001;97:2808-14.
37. Corthay A, Skovseth DK, Lundin KU, Rosjo E, Omholt H, Hofgaard PO, et al. Primary antitumor immune response mediated by CD4+ T cells. Immunity 2005;22:371-83.
38. Halapi E, Werner A, Wahlstrom J, Osterborg A, Jeddi-Tehrani M, Yi Q, et al. T cell repertoire in patients with multiple myeloma and monoclonal gammopathy of undetermined significance: clonal CD8+ T cell expansions are found preferentially in patients with a low tumor burden. Eur J Immunol 1997;27:2245-52.
39. Mariani S, Coscia M, Even J, Peola S, Foglietta M, Boccadoro M, et al. Severe and long-lasting disruption of T-cell receptor diversity in human myeloma after high-dose chemotherapy and autologous peripheral blood progenitor cell infusion. Br J Haematol 2001;113:1051-9.
40. Sze DM, Giesajtis G, Brown RD, Raitakari M, Gibson J, Ho J, et al. Clonal cytotoxic T cells are expanded in myeloma and reside in the CD8(+)CD57(+)CD28(-) compartment. Blood 2001;98:2817-27.
41. Sze DM, Brown RD, Yang S, Gibson J, Ho J, Fazekas de St GB, et al. Prediction of high affinity class I-restricted multiple myeloma idiotype peptide epitopes. Leuk Lymphoma 2003;44:1557-68.
42. Brown RD, Pope B, Murray A, Esdale W, Sze DM, Gibson J, et al. Dendritic cells from patients with myeloma are numerically normal but functionally defective as they fail to up-regulate CD80 (B7-1) expression after huCD40LT stimulation because of inhibition by transforming growth factor-β1 and interleukin-10. Blood 2001;98:2992-8.
43. Ratta M, Fagnoni F, Curti A, Vescovini R, Sansoni P, Oliviero B, et al. Dendritic cells are functionally defective in multiple myeloma: the role of interleukin-6. Blood 2002;100:230-7.
44. Fiore F, Nuschak B, Peola S, Mariani S, Muraro M, Foglietta M, et al. Exposure to myeloma cell lysates affects the immune competence of dendritic cells and favors the induction of Tr1-like regulatory T cells. Eur J Immunol 2005;35:1155-63.
45. Osterborg A, Yi Q, Bergenbrant S, Holm G, Lefvert AK, Mellstedt H. Idiotype-specific T cells in multiple myeloma stage I: an evaluation by four different functional tests. Br J Haematol 1995;89:110-6.
46. Yi Q, Bergenbrant S, Osterborg A, Osby E, Ostman R, Bjorkholm M, et al. T-cell stimulation induced by idiotypes on monoclonal immunoglobulins in patients with monoclonal gammopathies. Scand J Immunol 1993; 38:529-34.
47. Dianzani U, Pileri A, Boccadoro M, Palumbo A, Pioppo P, Bianchi A, et al. Activated idiotype-reactive cells in suppressor/cytotoxic subpopulations of monoclonal gammopathies: correlation with diagnosis and disease status. Blood 1988;72:1064-8.
48. Fagerberg J, Yi Q, Gigliotti D, Harmenberg U, Ruden U, Persson B, et al. T-cell-epitope mapping of the idiotypic monoclonal IgG heavy and light chains in multiple myeloma. Int J Cancer 1999;80:671-80.
49. Hansson L, Rabbani H, Fagerberg J, Osterborg A, Mellstedt H. T-cell epitopes within the complementarity-determining and framework regions of the tumor-derived immunoglobulin heavy chain in multiple myeloma. Blood 2003;101:4930-6.
50. Wen YJ, Ling M, Lim SH. Immunogenicity and cross-reactivity with idiotypic IgA of VH CDR3 peptide in multiple myeloma. Br J Haematol 1998; 100:464-8.
51. Yi Q, Osterborg A, Bergenbrant S, Mellstedt H, Holm G, Lefvert AK. Idiotype-reactive T-cell subsets and tumor load in monoclonal gammopathies. Blood 1995;86:3043-9.
52. Li Y, Bendandi M, Deng Y, Dunbar C, Munshi N, Jagannath S, et al. Tumor-specific recognition of human myeloma cells by idiotype-induced CD8(+) T cells. Blood 2000;96:2828-33.
53. Wen YJ, Barlogie B, Yi Q. Idiotype-specific cytotoxic T lymphocytes in multiple myeloma: evidence for their capacity to lyse autologous primary tumor cells. Blood 2001;97:1750-5.
54. Osterborg A, Yi Q, Henriksson L, Fagerberg J, Bergenbrant S, Jeddi-Tehrani M, et al. Idiotype immunization combined with granulocyte-macrophage colony-stimulating factor in myeloma patients induced type I, major histocompatibility complex-restricted, CD8- and CD4-specific T-cell responses. Blood 1998;91:2459-66.
55. Bergenbrant S, Yi Q, Osterborg A, Bjorkholm M, Osby E, Mellstedt H, et al. Modulation of anti-idiotypic immune response by immunization with the autologous M-component protein in multiple myeloma patients. Br J Haematol 1996;92:840-6.
56. Massaia M, Borrione P, Battaglio S, Mariani S, Beggiato E, Napoli P, et al. Idiotype vaccination in human myeloma: generation of tumor-specific immune responses after high-dose chemotherapy. Blood 1999;94:673-83.
57. Cull G, Durrant L, Stainer C, Haynes A, Russell N. Generation of anti-idiotype immune responses following vaccination with idiotype-protein pulsed dendritic cells in myeloma. Br J Haematol 1999;107:648-55.
58. Lim SH, Bailey-Wood R. Idiotypic protein-pulsed dendritic cell vaccination in multiple myeloma. Int J Cancer 1999;83:215-22.
59. Reichardt VL, Okada CY, Liso A, Benike CJ, Stockerl-Goldstein KE, Engleman EG, et al. Idiotype vaccination using dendritic cells after autologous peripheral blood stem cell transplantation for multiple myeloma-a feasibility study. Blood 1999;93:2411-9.
60. Titzer S, Christensen O, Manzke O, Tesch H, Wolf J, Emmerich B, et al. Vaccination of multiple myeloma patients with idiotype-pulsed dendritic cells: immunological and clinical aspects. Br J Haematol 2000;108:805-16.
61. Wen YJ, Ling M, Bailey-Wood R, Lim SH. Idiotypic protein-pulsed adherent peripheral blood mononuclear cell-derived dendritic cells prime immune system in multiple myeloma. Clin Cancer Res 1998;4:957-62.
62. Yi Q, Desikan R, Barlogie B, Munshi N. Optimizing dendritic cell-based immunotherapy in multiple myeloma. Br J Haematol 2002;117:297-305.
63. Coscia M, Mariani S, Battaglio S, Di BC, Fiore F, Foglietta M, et al. Long-term follow-up of idiotype vaccination in human myeloma as a maintenance therapy after high-dose chemotherapy. Leukemia 2004;18:139-45.
64. Rasmussen T, Hansson L, Osterborg A, Johnsen HE, Mellstedt H. Idiotype vaccination in multiple myeloma induced a reduction of circulating clonal tumor B cells. Blood 2003;101:4607-10.
65. Bendandi M, Gocke CD, Kobrin CB, Benko FA, Sternas LA, Pennington R, et al. Complete molecular remissions induced by patient-specific vaccination plus granulocyte-monocyte colony-stimulating factor against lymphoma. Nat Med 1999;5:1171-7.
66. Timmerman JM, Czerwinski DK, Davis TA, Hsu FJ, Benike C, Hao ZM, et al. Idiotype-pulsed dendritic cell vaccination for B-cell lymphoma: clinical and immune responses in 35 patients. Blood 2002;99:1517-26.
67. Bogen B, Malissen B, Haas W. Idiotope-specific T cell clones that recognize syngeneic immunoglobulin fragments in the context of class II molecules. Eur J Immunol 1986; 16: 1373-8.
68. Bogen B, Lambris JD. Minimum length of an idiotypic peptide and a model for its binding to a major histocompatibility complex class II molecule. EMBO J 1989;8:1947-52.
69. Bogen B, Jorgensen T, Hannestad K. T helper cell recognition of idiotopes on λ2 light chains of M315 and T952: evidence for dependence on somatic mutations in the third hypervariable region. Eur J Immunol 1985;15:278-81.
70. Bogen B, Snodgrass R, Briand JP, Hannestad K. Synthetic peptides and β-chain gene rearrangements reveal a diversified T cell repertoire for a λ light chain third hypervariable region. Eur J Immunol 1986;16:1379-84.
71. Bogen B, Dembic Z, Weiss S. Clonal deletion of specific thymocytes by an immunoglobulin idiotype. EMBO J 1993;12:357-63.
72. Eyerman MC, Zhang X, Wysocki LJ. T cell recognition and tolerance of antibody diversity. J Immunol 1996; 157:1037-46.
73. Guo W, Smith D, Guth A, Aviszus K, Wysocki LJ. T cell tolerance to germline-encoded antibody sequences in a lupus-prone mouse. J Immunol 2005;175:2184-90.
74. Snyder CM, Aviszus K, Heiser RA, Tonkin DR, Guth AM, Wysocki LJ. Activation and tolerance in CD4(+) T cells reactive to an immunoglobulin variable region. J Exp Med 2004;200:1-11.
75. Bogen B. Peripheral T cell tolerance as a tumor escape mechanism: deletion of CD4+ T cells specific for a mono-

clonal immunoglobulin idiotype secreted by a plasmacytoma. Eur J Immunol 1996;26:2671-9.
76. Lauritzsen GF, Hofgaard PO, Schenck K, Bogen B. Clonal deletion of thymocytes as a tumor escape mechanism. Int J Cancer 1998;78:216-22.
77. Cao W, Myers-Powell BA, Braciale TJ. The weak CD8+ CTL response to an influenza hemagglutinin epitope reflects limited T cell availability. J Immunol 1996;157:505-11.
78. Dannull J, Su Z, Rizzieri D, Yang BK, Coleman D, Yancey D, et al. Enhancement of vaccine-mediated antitumor immunity in cancer patients after depletion of regulatory T cells. J Clin Invest 2005;115:3623-33.
79. Mokyr MB, Dray S. Some advantages of curing mice bearing a large subcutaneous MOPC-315 tumor with a low dose rather than a high dose of cyclophosphamide. Cancer Res 1983; 43:3112-9.
80. Ghiringhelli F, Larmonier N, Schmitt E, Parcellier A, Cathelin D, Garrido C, et al. CD4+CD25+ regulatory T cells suppress tumor immunity but are sensitive to cyclophosphamide which allows immunotherapy of established tumors to be curative. Eur J Immunol 2004;34:336-44.
81. Prabhala RH, Neri P, Bae JE, Tassone P, Shammas MA, Allam CK, et al. Dysfunctional T regulatory cells in multiple myeloma. Blood 2006; 107: 301-4.
82. Beyer M, Kochanek M, Giese T, Endl E, Weihrauch MR, Knolle PA, et al. In vivo peripheral expansion of naive $CD4^{+}CD25^{high}$ $FOXP3^{+}$ regulatory T cells in patients with multiple myeloma. Blood 2006;107:3940-9.
83. Reichardt VL, Okada CY, Stockerl-Goldstein KE, Bogen B, Levy R. Rationale for adjuvant idiotypic vaccination after high-dose therapy for multiple myeloma. Biol Blood Marrow Transplant 1997;3:157-63.
84. Blade J, Samson D, Reece D, Apperley J, Bjorkstrand B, Gahrton G, et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. Br J Haematol 1998; 102: 1115-23.
85. Singh NJ, Schwartz RH. The strength of persistent antigenic stimulation modulates adaptive tolerance in peripheral CD4+ T cells. J Exp Med 2003;198:1107-17.
86. Wang S, Yang J, Qian J, Wezeman M, Kwak LW, Yi Q. Tumor evasion of the immune system: inhibiting P38 map kinase signaling restores the function of dendritic cells in multiple myeloma. Blood 2006; 107:2432-9.
87. Rapoport AP, Stadtmauer EA, Aqui N, Badros A, Cotte J, Chrisley L, et al. Restoration of immunity in lymphopenic individuals with cancer by vaccination and adoptive T-cell transfer. Nat Med 2005;11:1230-7.
88. Palumbo A, Bertola A, Musto P, Caravita T, Callea V, Nunzi M, et al. Oral melphalan, prednisone, and thalidomide for newly diagnosed patients with myeloma. Cancer 2005; 104:1428-33.
89. Bae JE, Yu-Tzu T, Hidesima K, Catley L, Li X, Prabhala RH. Proteasome inhibitor does not affect the function of human immune system: effects on dendritic cells, T lymphocytes and NK cells. Blood 2005;106:[abstract 3930].
90. Bendandi M, Rodriguez-Calvillo M, Inoges S, Lopez-Diaz de CA, Perez-Simon JA, Rodriguez-Caballero A, et al. Combined vaccination with idiotype-pulsed allogeneic dendritic cells and soluble protein idiotype for multiple myeloma patients relapsing after reduced-intensity conditioning allogeneic stem cell transplantation. Leuk Lymphoma 2006;47:29-37.
91. Stevenson FK, Zhu D, King CA, Ashworth LJ, Kumar S, Hawkins RE. Idiotypic DNA vaccines against B-cell lymphoma. Immunol Rev 1995; 145:211-28.
92. Syrengelas AD, Chen TT, Levy R. DNA immunization induces protective immunity against B-cell lymphoma. Nat Med 1996;2:1038-41.
93. Timmerman JM, Caspar CB, Lambert SL, Syrengelas AD, Levy R. Idiotype-encoding recombinant adenoviruses provide protective immunity against murine B-cell lymphomas. Blood 2001; 97:1370-7.
94. Tao MH, Levy R. Idiotype/granulocyte-macrophage colony-stimulating factor fusion protein as a vaccine for B-cell lymphoma. Nature 1993;362:755-8.
95. Biragyn A, Tani K, Grimm MC, Weeks S, Kwak LW. Genetic fusion of chemokines to a self tumor antigen induces protective, T-cell dependent antitumor immunity. Nat Biotechnol 1999;17:253-8.
96. Huang HI, Wu PY, Teo CY, Chen MN, Chen YC, Silin D, et al. Improved immunogenicity of a self tumor antigen by covalent linkage to CD40 ligand. Int J Cancer 2004;108:696-703.
97. King CA, Spellerberg MB, Zhu D, Rice J, Sahota SS, Thompsett AR, et al. DNA vaccines with single-chain Fv fused to fragment C of tetanus toxin induce protective immunity against lymphoma and myeloma. Nat Med 1998;4:1281-6.
98. Hakim I, Levy S, Levy R. A nine-amino acid peptide from IL-1β augments antitumor immune responses induced by protein and DNA vaccines. J Immunol 1996;157:5503-11.
99. Buchan S, Gronevik E, Mathiesen I, King CA, Stevenson FK, Rice J. Electroporation as a "prime/boost" strategy for naked DNA vaccination against a tumor antigen. J Immunol 2005;174:6292-8.
100. Fredriksen AB, Sandlie I, Bogen B. DNA vaccines increase immunogenicity of idiotypic tumor antigen by targeting novel fusion proteins to antigen-presenting cells. Mol Ther 2006; 13:776-85.
101. Neelapu SS, Munshi NC, Jagannath S, Watson TM, Pennington R, Reynolds C et al. Tumor antigen immunization of sibling stem cell transplant donors in multiple myeloma. Bone Marrow Transplant 2005;36:315-23.
102. Kwak LW, Taub DD, Duffey PL, Bensinger WI, Bryant EM, Reynolds CW et al. Transfer of myeloma idiotype-specific immunity from an actively immunised marrow donor. Lancet 1995;345:1016-20.
103 .Kim SB, Baskar S, Kwak LW. In vitro priming of myeloma antigen-specific allogeneic donor T cells with idiotype pulsed dendritic cells. Leuk Lymphoma 2003;44:1201-8.
104. Geffroy-Luseau A, Moreau-Aubry A, Bataille R, Pellat-Deceunynck C. Allogeneic T lymphocytes as a source of peptide-dependent T cells specific for myeloma cells. Int Immunol 2005; 17:1193-200.
105. Lundin KU, Hofgaard PO, Omholt H, Munthe LA, Corthay A, Bogen B. Therapeutic effect of idiotype-specific $CD4^{+}$ T cells against B-cell lymphoma in the absence of anti-idiotypic antibodies. Blood 2003;102:605-12.
106. Armstrong AC, Dermime S, Mulryan K, Stern PL, Bhattacharyya T, Hawkins RE. Adoptive transfer of anti-idiotypic T cells cure mice of disseminated B cell lymphoma. J Immunother 2004; 27: 227-31.
107. Bridges SH. Participation of the humoral immune system in the myeloma-specific transplantation resistance. J Immunol 1978;121:479-83.
108. Bridges SH. Myeloma-specific transplantation resistance: a requirement for complete Freund's adjuvant stimulation of effectors. J Immunol 1978; 120:613-8.