



Protocol Page

PHASE II TRIAL OF ID-SPECIFIC DONOR VACCINATED LYMPHOCYTE INFUSION FOR PATIENTS WITH MYELOMA RELAPSING OR FAILING TO ACHIEVE A COMPLETE REMISSION AFTER AN ALLOGENEIC TRANSPLANT

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Core Protocol Information

<b>Short Title</b>	ID-SPECIFIC DLI FOR MYELOMA
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<b>Full Title:</b>	PHASE II TRIAL OF ID-SPECIFIC DONOR VACCINATED LYMPHOCYTE INFUSION FOR PATIENTS WITH MYELOMA RELAPSING OR FAILING TO ACHIEVE A COMPLETE REMISSION AFTER AN ALLOGENEIC TRANSPLANT
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**Which Committee will review this protocol?**

The Clinical Research Committee - (CRC)

## Protocol Body

### 1.0 Objectives

1. Primary
  - 1.1 Determine whether transfer of myeloma specific immunity is enhanced by vaccinating donors prior to donor lymphocyte infusion with an id-specific vaccine.
2. Secondary
  - 2.1 To determine the rate of partial response (PR) and complete response (CR) in patients receiving donor lymphocytes (recipients) from an id-specific vaccinated donor.
  - 2.2 To determine the GVHD rates after donor lymphocyte infusion from an id-specific vaccinated donor.

### 2.0 Background

#### Current Results with Allografting in Myeloma

Although high dose chemotherapy and autologous transplant has improved the outcome for myeloma patients (1), most patients with myeloma will eventually relapse after high-dose therapy and autologous transplantation and die of their disease. Allogeneic transplantation has been explored in younger patients as a mean for overcoming stem cell contamination with myeloma cells and with the hope of obtaining a graft-versus tumor effect that could eradicate the malignant clone. A large report from the European Transplantation Registry showed disappointing results for patients undergoing allogeneic transplantation. Median survival was only 18 months, and the transplant-related mortality (TRM) was prohibitive at 41% (2,3). The HOVAN group recently published the results of its initial experience using T cell depleted myeloablative bone marrow transplant in patients with HLA identical sibling donors. After initial therapy with VAD regimen, patients younger than 55 with an HLA-identical sibling underwent allogeneic transplantation with cyclophosphamide (Cy) and TBI (N=47) or Cy/TBI plus idarubicine (N=5). All patients received ex-vivo T-cell depleted transplantation with the goal of reducing TRM. Eleven percent of patients developed grade III acute graft-versus host disease (GVHD), and 30% developed chronic extensive GVHD. Transplant-related mortality was 34%; median OS was 25 months from the time of transplantation and was significantly inferior to survival for same patients in other arms of the trial (47 months). Despite T-cell depletion, TRM remained elevated and a graft-versus myeloma effect was not apparent in this trial (4). Thus high transplant-related mortality precludes the use of myeloablative conditioning regimens for myeloma patients.

Allogeneic stem cell transplantation with reduced-intensity or non-myeloablative conditioning regimens has been attempted in patients with multiple myeloma. Table 1 summarizes the results of various phase two trials that have been published over the past few years. (5-11) Relapse was the most important cause of treatment failure, particularly for patients with chemorefractory disease. However, the observation that a small percentage of refractory myeloma patients can achieve long term disease control support further exploration of reduced intensity allografting as a curative strategy for myeloma. Patients receiving a non ablative allograft as part of their initial therapy, have been reported to have TRM of less than 15%, however, relapse is a common cause of treatment failure with 33% of patients receiving reduced intensity allografts as part of their initial therapy.

**Table 1: Results Of Nonmyeloablative Transplantation.**

Reference	N	Regimen	RR (CR)	Agyhd > Grade II	CGVHD	TRM	DFS	OS @ 2years
5	22	FM	72% (32)	46%	27%	40%	19% @ 2 years	30%
6	45	Mel 100 FM/TBI	61% (31)	42%	58%	38%	13% @ 3 years	36%
7	29	FM	45%	52%	51%	21%	33% @ 2 years	60%
8	41	Fbu ATG	50% (25)	40%	51%	17%	NR	62%
9	64	FM/ATG	90% (45)	39%	47%	23%	38% @ 2years	55%
10	31	Mel FM/TBI	61%	58%	NR	30%	31% @ 2 years	31%
11	54	TBI	52%	39%	46%	15%	55% @ 2 years	78%

RR: Response Rate. CR: Complete Response. aGVHD: acute Graft-Versus-Host Disease. cGVHD: chronic Graft-Versus-Host Disease. TRM: Transplant Related Mortality. DFS: Disease-Free Survival. OS: Overall Survival. FM: Fludarabine/Melphalan. TBI: Total Body Irradiation. ATG: Anti-Thymocyte Globulin. NR: Not Reported.

Non-myeloablative transplantation for myeloma is increasingly being explored as part of a tandem strategy, in which patients are treated with autologous transplantation followed by planned allogeneic transplantation. Maloney et al, recently published their experience with fifty-four patients receiving an autologous transplantation with melphalan (200 mg/m<sup>2</sup>), and after a median of two months, low-dose total body irradiation (single fraction 2Gy) followed by stem cell transplantation from an HLA-identical sibling. Estimated 2-year overall survival and disease-free survival were 78% and 52%, respectively (11). This, although encouraging, these results show that myeloma relapse will continue to be a major cause of treatment failure post-allograft, treatment of relapse with donor lymphocyte infusion has been successful but only in a minority of patients. Therefore strategies aimed at enhancing the graft vs myeloma effect without increasing toxicity need to be developed.

#### **Donor Lymphocyte Infusions (DLI) for Myeloma**

Interest in allografting for myeloma increased due to the demonstration of a graft versus myeloma effect (GVM) demonstrated by responses to donor lymphocyte infusions. (12-16) Up to 50% of patients respond to DLI, including some with sustained complete remission; however, incidence of acute and chronic GVHD is elevated and limits the widespread use of this strategy (15). The results of the largest DLI series for myeloma are summarized in Table 2.

**Table 2: Results of Largest Donor Lymphocyte Infusion Series for Myeloma**

Reference	N	Response Rate CR+PR	GVHD ≥2 (>Grade 2)	Comments
13	27	52% (22+30)	56% (15%)	Primarily T cell depleted transplant recipients
14	25	44% (28+16)	48% (24%)	Only 3 responders without GVHD
15	54	52% (17+35)	46% (20%)	T cell depleted patients primarily
16	11	90% (54+36)	50%	CD8 depleted DLI

Thus, in myeloma graft versus tumor responses seem to correlate with GVHD, possibly due to the fact that myeloma associated antigens that have been shown to be targets for the GVM effect are also

expressed in other tissues (17). Therefore, one possible strategy is to divert the GVM effect towards targets that are expressed primarily in myeloma cells and not in other tissues. This could increase the therapeutic efficacy of donor lymphocyte infusions. Vaccination with myeloma specific antigens is such an approach.

### **Vaccination therapy for Myeloma**

Vaccination against tumor specific antigens could enhance the graft versus myeloma effect of donor lymphocyte infusions. Immunoglobulin (Ig) molecules are composed of heavy and light chains, which possess highly specific variable regions at their amino termini. These variable regions contain determinants (molecule shapes) that can themselves be recognized as antigens or idiotypes, and are patient specific. Thus the idiotypic determinants of the surface Ig of a B-cell lymphoma or myeloma can thus serve as a tumor-specific marker for the malignant clone.

Studies in experimental animals, as well as in man, have demonstrated that active immunization against idiotypic determinants on malignant B-cells can produce resistance to tumor growth in a number of syngeneic experimental tumor models, as well as specific anti-tumor therapy against established tumors (18-27). These results, taken together, provided the rationale for testing autologous tumor-derived idiotypic surface Ig (Id) as a therapeutic "vaccine" against human B cell malignancies. Furthermore, preclinical studies in subhuman primates demonstrated that optimal immunization with human lymphoma-derived Id required conjugation of the protein to an immunogenic protein carrier (keyhole limpet hemocyanin; KLH) and emulsification in an adjuvant (28).

Kwak et al immunized nine patients with B cell lymphoma with autologous idotype protein. These patients received no anti-tumor therapy during the time of the study. They were either in complete remission or in a state of minimal residual disease following conventional chemotherapy. In addition, three patients with rapidly progressive recurrent lymphoma were enrolled in a separate safety study; all three required re-institution of chemotherapy shortly after enrollment, did not complete the immunization series, and were not studied further. They received intramuscular injections of 0.5 mg of Id conjugated to KLH at 0, 2, 6, 10, and 14 weeks, followed by two booster injections at 24 and 28 weeks. The KLH carrier provided a convenient internal control for immunocompetence of the patients, and all patients demonstrated both humoral and PBMC proliferative responses to the KLH protein, with the exception of one patient, who demonstrated only the latter. Seven of the nine patients demonstrated either a humoral (n=2) or a cell-mediated (n=4) anti-idiotypic immunological response, or both (n=1) (29). Toxicity was minimal in all twelve patients. All patients experienced transient local reactions characterized by mild erythema, induration, and discomfort, without skin breakdown, at the injection s. Id immunization was associated with a mild elevation (less than twice the normal value) of serum creatine phosphokinase 24 hours after immunization in an occasional case. These results demonstrate that patients with B cell lymphomas can be induced to make sustained idotype-specific immune responses by active immunization with purified autologous tumor-derived surface Ig. They show that autologous Id, made immunogenic by conjugation to KLH, can serve as an immunogen (antigen) to elicit host immunological responses.

Similar clinical results were observed in multiple myeloma patients. At the University of Turin 12 patients with myeloma received high-dose chemotherapy and autologous stem cell transplantation followed by vaccination with Id-specific proteins conjugated to KLH and GM-CSF or IL-2 as immunoadjuvants (30). Id-specific T cell proliferative responses were documented in 2 patients, and a positive Id-specific delayed-type hypersensitivity reaction was observed in 8 of the 10 patients studied. Twelve patients with multiple myeloma were treated at Stanford University with high-dose therapy and peripheral blood stem cell transplantation followed by Id immunizations (31). Following transplantation patients received a series of monthly immunizations consisting of Id-pulsed autologous dendritic cells followed by subcutaneous (S.C.) boosts of Id conjugated to KLH. The administration of Id-pulsed DC and Id-KLH vaccines was well tolerated with patients experiencing only minor and transient side effects. Two of 12 patients developed an Id-specific, cellular proliferative immune response, and one of three patients studied developed a transient but Id-specific cytotoxic T cell response. Similarly, investigators at the University of Wales were able to generate dendritic cells from six patients with IgG myeloma, and the cells were pulsed with the

autologous Id (32). Id-specific responses were also observed. PBMC proliferative responses to Id were observed in five of the six patients following treatment. These initial trials demonstrate that the vaccination of patients was relatively safe and capable of producing Id-specific T cell responses.

Granulocyte-macrophage colony-stimulating factor (GM-CSF; sargramostim) has emerged as a promising adjuvant for idiotypic Ig antigen. Syngeneic mice (10 mice per group) were immunized with 50 mcg Id-KLH derived from the tumor either alone or in combination with GM-CSF mixed together with the antigen and administered subcutaneously. Three additional daily doses of GM-CSF were administered S.C. as close to the original of immunization as possible. Mice immunized with an irrelevant Id-KLH (4C5 IgM) served as negative controls for the vaccine. Two weeks after this single immunization, all mice were challenged with a single preparation of 38C13 tumor cells ( $5 \times 10^3$  cells i.p.) and followed for survival. The results demonstrate that the augmented survival benefit afforded by immunization with relevant Id-KLH alone can be significantly enhanced by the addition of GM-CSF at either the 100 or 10,000 unit dose. A curious but reproducible observation has been the loss of this protective effect at a higher dose of GM-CSF of 50,000 units (data not shown). These data suggest that GM-CSF may have a potent adjuvant effect in vivo for Id-KLH antigen, especially at relatively low doses (33).

Idiotype protein vaccine in combination with GM-CSF as an adjuvant was evaluated in 20 lymphoma patients in first clinical complete remission (34). GM-CSF administration was well tolerated with minimal side effects. Tumor-specific cytotoxic CD8+ and CD4+ T cells were found in 19 of 20 patients. This data seem to indicate that GM-CSF may be an essential component of this vaccine formulation's potency.

#### **Donor Vaccination with Idiotype-KLH vaccine**

Most vaccination protocols have attempted to vaccinate the patient against their own malignancy. Intuitively, however, this strategy has the main obstacle that the patients immune system has already failed to respond to the tumor in an effective manner. The availability of a vaccine derived from the immunoglobulin idiotype as a tumor-specific antigen, opened the opportunity to study the transfer of antigen-specific antitumor immunity from an immunized stem cell donor to the SCT recipient. Kwak et al have explored this strategy of transferring tumor idiotypic-specific immunity with bone marrow from specifically immunized donors in a preclinical murine model (35). The 38C13 B cell tumor is a carcinogen-induced C3H cell line, which both expresses and secretes idiotypic Ig both in vitro and in vivo. Thus, it can serve as a model for well differentiated B cell malignancies, such as lymphomas or myelomas. Mice serving as syngeneic marrow donors were immunized with tumor-derived Id protein or with a control immunoglobulin of matched isotype. Naive lethally irradiated recipients reconstituted with marrow from immune donors showed serologic tumor idiotype-specific immunity, as well as protection against subsequent lethal tumor challenge. The immunoprotective effect of immune marrow was also shown in the setting of combined donor and recipient immunizations. These results demonstrate the successful transfer of tumor antigen-specific immunity with immune marrow as a protective element and provide support for testing this approach in humans.

This approach has been tested in a single human patient with myeloma; however, a myeloablative conditioning regimen was used (36). The goal of BB-IND 4999 was to induce myeloma idiotype-specific immunity in the allogeneic donor and to evaluate the transfer of idiotype-specific immunity to the myeloma patient following allogeneic bone marrow grafting. FDA approval was granted for this study. Idiotype-specific humoral and cellular immunity in both the donor and the recipient were evaluated using the serum antibody and peripheral blood mononuclear cell proliferative assays already established and described in the phase I lymphoma trial. This was the first time a normal BMT donor was immunized against a tumor protein. Successful donor immunization was demonstrated by serum antibodies, which bound specifically to patient-derived myeloma IgG and specific proliferation of peripheral blood mononuclear cells (PBMC) to the IgG in vitro. Donor toxicity consisted only of mild reactions at injection s. Bone marrow was used as the stem cell source. Engraftment was normal and accompanied by grade 2 skin GVHD responsive to therapy. 60 days post-SCT, recipient PBMC proliferated both to the KLH control protein (stimulation index [S.I.] 48.3 at 50 mcg/ml) and to Id (S.I. 4.8) when assayed independently in 5 day in vitro cultures. An Id-specific T-cell line has also been established from recipient PBMC. Specificity was demonstrated by the lack of proliferation to a panel of isotype-matched Ig of unrelated idiotypes. No

humoral anti-idiotypic response has been detected in the recipient. The recipient demonstrated complete clinical response (absence of M-protein, absence of dysplastic marrow plasma cells at day 100).

Dr Michael Bishop at the NCI together with Dr. Kwak have gone on to immunize 9 donors and proceed to stem cell collection and transplantation using a non ablative transplant regimen. In this study donor immunity was documented in all 9 donors, however the effects of donor immunization on transplant outcomes will be difficult to assess in the context of the primary allograft.

Thus, in order to define the role of id-specific donor vaccinations, we propose to do a phase II trial of donor lymphocyte infusions coming from an id-specific-KLH vaccinated donor. Such a trial will allow us to answer the following questions which are essential to move the field of id-specific vaccination forward.

- 1) Will id specific donor vaccination translate into a skewing of lymphocyte repertoire to a more myeloma specific spectrum?
- 2) Is it possible to quantify the degree that myeloma specific immunity is enhanced by id-specific vaccination?
- 3) Do ex-vivo measures of id-specific immunity correlate with disease control?
- 4) Will id specific vaccination of donors prior to lymphocyte collection enhance the efficacy of donor lymphocyte infusions for myeloma patients not in remission after allogeneic transplantation without increasing the risk of GVHD.

### 3.0 Background Drug Information

#### **3-A Id-KLH Vaccine Myeloma Immunoglobulin Idiotypic Vaccine (NSC-678327, BB IND 5779)**

Availability - Individual Myeloma immunoglobulin are obtained from each patient and individual vaccine is prepared for each patient at the **GMP Facility of MDACC**.

Idiotypic Vaccine Preparation - Idiotypic vaccines are prepared using a recipient's idiotype protein. The patient-specific protein will be isolated from the recipient's plasma (via plasmapheresis), purified by protein A or anti-Hu IgA affinity chromatography, and covalently coupled to a keyhole limpet hemocyanin (KLH) as described in **Appendix G**. The preparation of the final vaccine product (myeloma idiotype protein conjugated with KLH) will be performed by **GMP Facility of MDACC**. Each batch of patient-specific vaccines will be produced according to Good Manufacturing Practices (GMP) standards and will be tested for sterility, endotoxin contamination, and general safety, prior to its use in any patient. The final vaccine product (myeloma idiotype protein conjugated with KLH) will be manufactured (and vialled) by **the GMP Facility of MDACC**. Each patient-specific vaccine will be labeled to include the following information:

- a) myeloma immunoglobulin idiotype vaccine: patient-specific lot
- b) final volume and concentration of vaccine product
- c) KLH and patient-specific immunoglobulin subtype
- d) storage conditions
- e) fill date
- f) patient identification (first name/last initial)

Storage and Stability - The final product is available as a solution containing 1.1 mls of conjugated protein diluted in sodium chloride 0.9% (NS). The solution is contained in a 1.8 ml insert inside a sterile vial. The final solution contains 0.5 mg/ml of KLH conjugated to 0.5 mg/ml of the patient-specific immunoglobulin idiotype protein. Intact vials are stored at -20° C.

Administration - The patient (recipient) and donor will receive 3 subcutaneous injections of the patient-specific vaccine preparation containing 0.5 mg of the myeloma protein at the protocol specified timepoints. Both individuals will receive GM-CSF as an adjuvant to the vaccine preparation. GM-CSF will be administered as a subcutaneous injection at a dose of 250 mcg/m<sup>2</sup> (rounded up to the nearest vial)

daily for four consecutive days (day 0-day 3).

Adverse events- described with Id-KLH vaccine administration include local reactions (erythema, induration, swelling and tenderness), fever, chills, rash, myalgias and arthralgias. Mild elevations in creatinine phosphokinase (CPK) have been observed. Fever and chills, associated with vaccine administration will be treated with acetaminophen and/or meperidine.

### **3-B Unconjugated KLH**

Availability – KLH according to GMP standards as described above, will also be vialled as a separate product by the MDACC GMP facility and will be supplied by the investigational pharmacy. This vialled product will be tested separately for sterility, endotoxin, and general safety, prior to its use in any patient. Each vial of KLH will be labeled to include the following information:

- a) Patient-specific lot
- b) Final volume and concentration of product
- c) Patient-specific immunoglobulin subtype
- d) Storage conditions
- e) Fill date
- f) Patient identification (first name/last initial)

Adverse events– The toxicities associated with the administration of unconjugated KLH are anticipated to be identical to those described with the Id-KLH vaccine. The safety issues regarding the injection of heterologous idiotype protein isolated from other patients' B-cell tumors have already been fully addressed in CC Protocol 96-C-0133 (NCI T93-0164; Id Vaccination in Previously Untreated Patients with Follicular Lymphoma) and are felt to be minimal, because of the highly purified nature of the protein. Briefly an immune response of any consequence to the isotype used as a negative control during the skin test is not likely, based on:

- a) Any immune response specifically directed against the idiotype (i.e., variable region) on the control idiotype protein is not likely to cross-react with host cells and is therefore not likely to be of any consequence.
- b) An autoimmune response against constant region or allotype determinants shared between the idiotype of patient's own tumor and that of the control idiotype is theoretically possible. However, no evidence of such autoimmune responses have been observed either in vivo or in vitro during the course of immunization of the normal donors so far treated or in the patients who underwent autologous transplantation. Furthermore, a safety precedent exists for immunizing patients with material derived from tumor cells from other patients. For example in attempting to develop immune responses against metastatic melanomas, patients were immunized with 1) intact melanoma cells: 2) shed antigens fractionated by detergent treatment and ultracentrifugation: 3) melanoma cells infected with vaccinia virus and melanoma cells freeze thawed and mechanically disrupted, all using a pool of allogeneic melanoma cell lines.

### **3-C Sargramostim (granulocyte-macrophage colony-stimulating factor; NSC - 613795; BB-IND 2632, Leukine)**

Availability - The GM-CSF to be used in this study is a glycosylated, recombinant human GM-CSF. This GM-CSF is an altered form of the native molecule; the position 23 arginine has been replaced with a leucine to facilitate expression of the protein in yeast (*Saccharomyces cerevisiae*). Manufactured by Immunex. GM-CSF will be provided by the protocol from a commercial source.

Storage and Stability - The GM-CSF is formulated as a white lyophilized cake and is provided in vials containing 500 mcg of the GM-CSF protein as well as 10.0 mg of sucrose, 40.0 mg of mannitol, and 1.2 mg of Tris (Trimethylamine). The unreconstituted material should be kept refrigerated at 2-8°C and is stable for at least eighteen months. Once reconstituted, the solution is stable for at least 24 hours at 2-8°C or at

18-25° C. Because the product does not contain a preservative, vials should be treated as unit-dose containers; reconstituted solution should be held at 2-8° C and discarded after no more than six hours. Do not freeze GM-CSF.

**Preparation** - To prepare a vial of GM-CSF for direct subcutaneous use, aseptically inject 1.0 ml of Sterile Water for Injection, USP, into the vial to dissolve the lyophilized cake. The diluent should be directed against the side of the vial to avoid excess foaming. Avoid vigorous agitation of the vial; do not shake. This yields a solution containing 500 mcg/ml.

**Administration** - The appropriate total dose is withdrawn into and administered from a plastic tuberculin syringe. The GM-CSF will be injected subcutaneously as close as possible to the Id-KLH injection. All GM-CSF doses for each patient will be administered by the nursing staff in the outpatient unit.

**Adverse events**- Toxicities described in patients receiving GM-CSF include: fever, chills, diaphoresis, myalgias, fatigue, malaise, headache, dizziness, dyspnea, bronchospasm, pleural effusion, anorexia, indigestion, nausea, vomiting, diarrhea, injection tenderness, urticaria, rash, pruritus, hypersensitivity reactions, bone pain, thromboembolic events, phlebitis, hypotension, peripheral edema, leukocytosis, thrombocytosis or thrombocytopenia, hepatic enzyme abnormalities, and bilirubin elevation. The first administration of GM-CSF has provoked a syndrome of dyspnea and hypotension within two hours after GM-CSF injection in a single patient receiving yeast-derived GM-CSF; this type of reaction has more frequently been observed in patients receiving GM-CSF produced in *E. coli*. One report of a vascular leak-like syndrome occurring after autologous bone marrow transplant in a patient receiving continuous IV (intravenous) infusion of GM-CSF has been recorded.

## 4.0 Patient Eligibility

### Recipient Criteria for Vaccine Production

1. Recipient for vaccine production: Patient with IgG1, IgG2, or IgG4 Multiple Myeloma who has received or is planning to receive an allogeneic progenitor cell transplant from a HLA compatible related donor (either 6/6 or 5/6 related donor).
2. Recipient for vaccine production: Have evidence of persistent or relapsing disease as demonstrated by persistent serum peak (by either standard protein electrophoresis, immune fixation or free light chain assays) or marrow infiltration. Serum peak must be greater or equal than 0.2 gm/dl and represent more than 70% of the specific immunoglobulin subtype. Patients who have adequate amount of monoclonal idiotype protein previously cryopreserved on prior departmental laboratory protocols are also eligible to be registered for vaccine production using the cryopreserved samples.
3. Able to sign written informed consent.
4. Age up to 70 years.
5. Zubrod PS  $\geq$ 2.
6. Have no serious organ dysfunction as defined by serum creatinine  $<$ 2.5 mg/dL, serum bilirubin  $<$ 3 x upper limit of normal, SGPT  $<$ 4 x upper limit of normal.
7. Negative donor infectious disease panel:
  - Hepatitis B surface antigen (HBsAg)
  - Anti-Hepatitis B core antibody (HBcAb)
  - Anti-Hepatitis C Virus antibody (HCV Ab)
  - Anti-Human Immunodeficiency Virus (HIV) antibody (HIV 1/2 type O Ab)
  - Anti-Human T cell lymphotropic Virus (HTLV) antibody (HTLV I/II Ab)
  - Rapid Plasma Reagen (RPR)
  - Cytomegalovirus antibody (CMV)
  - HCV/HIV Nucleic Acid Test
  - West Nile Virus Nucleic Acid Test
  - Sickledex
  - T Cruzi AB



Additional tests shall be performed as required to assess the possibility of transmission of other infectious or non-infectious diseases.

8. Negative serum Beta HCG test in a women with child bearing potential (not post-menopausal for 12 months or no previous surgical sterilization) and willing to use an effective contraceptive measure while on study. Mothers should not breastfeed during the study.

#### **Exclusion Criterion**

1. Recipient with IGg3 Multiple Myeloma.

#### **Donor Criteria**

1. Able to sign written informed consent and be willing to provide donor lymphocytes.
2. Age 18 – 75 years
3. No physical contraindications to lymphocyte collection (i.e., severe atherosclerosis, auto-immune disease, cerebrovascular accident, prior malignancy less than 5 years ago other than non-melanoma skin cancer treated with surgery). Donors with severe atherosclerosis by history will receive a cardiology consult and be judged eligible on a case by case basis.
4. Negative donor infectious disease panel:
  - Hepatitis B surface antigen (HBsAg)
  - Anti-Hepatitis B core antibody (HBcAb)
  - Anti-Hepatitis C Virus antibody (HCV Ab)
  - Anti-Human Immunodeficiency Virus (HIV) antibody (HIV 1/2 type O Ab)
  - Anti-Human T cell lymphotropic Virus (HTLV) antibody (HTLV I/II Ab)
  - Rapid Plasma Reagen (RPR)
  - Cytomegalovirus antibody (CMV)
  - HCV/HIV Nucleic Acid test

Additional tests shall be performed as required to assess the possibility of transmission of other infectious or non-infectious diseases.

5. Negative serum Beta HCG test in a woman with child bearing potential (not post-menopausal for 12 months or no previous surgical sterilization) must use an effective method of contraception until at least 1 month after lymphocyte collection. Mothers should not breastfeed during the study.

### **Donor Eligibility Undetermined**

All products obtained from donors where eligibility has not been determined must be stored in quarantine until eligibility has been assessed. Products in quarantine are clearly labeled to prevent release. If product must be released prior to eligibility determination then urgent medical need must be documented. These products must be labeled "NOT EVALUATED FOR INFECTIOUS SUBSTANCES" and "WARNING: Advise patient of communicable disease risks".

### **Release of Products from Ineligible Donor**

The release of products from an ineligible donor requires the documentation of urgent medical need and the consent of the patient. Products are labeled with a "Biohazard" Label including "WARNING: Advise patient of communicable disease risks". Screening and test results must accompany the product and provided to the infusing physician in an envelope for review. These documents are to be properly disposed of after infusion to protect the privacy of the donor.

### **Ineligible Donors**

If donor is deemed to be ineligible, finding must be documented on the Donor Certificate.

An "Urgent Medical Need" order including reason for ineligibility must be provided to the laboratory.

## **5.0 Pretreatment evaluation**

The procedures and tests listed below are standard of care and are performed to determine recipient and donor eligibility.

### **A. Both recipient and donor:**

- 1) History and physical (H&P).
- 2) Albumin, total protein, calcium, glucose, BUN, creatinine, bilirubin, ALT, alkaline phosphatase, LDH, CBC with differential, PT/PTT. Serum B-HCG for female donor and recipient.

### **B. Recipient only:**

- 1) Immunodeficiency panel: Quantitative immunoglobulins, quantification of lymphocyte subsets (CD4 and CD8).
- 2) Cyclosporine or tacrolimus level as appropriate.
- 3) Disease restaging: SPEP, UPEP, serum and immunofixation electrophoresis, serum for free kappa and lambda light chain assay, Beta 2 Microglobulin, and C reactive protein.
- 4) Bone survey, Magnetic resonance imaging (MRI), or Positive Emission Tomography (PET)/Computed tomography(CT) as clinically indicated.
- 5) Bone marrow aspiration and biopsy for cytogenetics, chimerism, myeloma panel, and IgG subpanel.
- 6) Negative donor infectious disease panel:
  - Hepatitis B surface antigen (HBsAg)
  - Anti-Hepatitis B core antibody (HBcAb)
  - Anti-Hepatitis C Virus antibody (HCV Ab)
  - Anti-Human Immunodeficiency Virus (HIV) antibody (HIV 1/2 type O Ab)
  - Anti-Human T cell lymphotropic Virus (HTLV) antibody (HTLV I/II Ab)
  - Rapid Plasma Reagen (RPR)
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  - HCV/HIV Nucleic Acid Test
  - West Nile Virus Nucleic Acid Test
  - Sickledex
  - T Cruzi AB

Additional tests shall be performed as required to assess the possibility of transmission of other infectious or non-infectious diseases.

**C. Donor only:**

- 1) Negative donor infectious disease panel:
  - Hepatitis B surface antigen (HBsAg)
  - Anti-Hepatitis B core antibody (HBcAb)
  - Anti-Hepatitis C Virus antibody (HCV Ab)
  - Anti-Human Immunodeficiency Virus (HIV) antibody (HIV 1/2 type O Ab)
  - Anti-Human T cell lymphotropic Virus (HTLV) antibody (HTLV I/II Ab)
  - Rapid Plasma Reagen (RPR)
  - Cytomegalovirus antibody (CMV)
  - HCV/HIV Nucleic Acid test

Additional tests shall be performed as required to assess the possibility of transmission of other infectious or non-infectious diseases.

## 6.0 Treatment Plan

### Idiotype Procurement

6.1 Recipient will undergo steady state plasmapheresis procedure to provide idiotype protein necessary to produce the vaccine. This is a standard procedure. Plasma (60-100 cc) from the plasmapheresis procedure will be sent to the MD Anderson Cancer Center GMP lab where it will be processed. The MDACC GMP lab will be responsible for producing the id-KLH conjugated vaccine according to the supplied standard operating procedure (see PDOL Appendices H and I). The vaccines will be kept in the GMP lab until requested. Alternatively vaccine can be produced using previously collected idiotype monoclonal protein collected on ongoing laboratory protocols and cryopreserved.

6.2 Donor will be vaccinated with an id-KLH vaccine 0.5 cc subcutaneously, once during weeks -8, -6, and -2 prior to donor lymphocyte collections.

The preferred site for the vaccine injection are the deltoid area (upper arm) and thigh. Sites should be alternated with each vaccine administration.

All donors will be observed in the clinic for two hours following vaccine administration. During the observation period, vital signs will be taken every 15 minutes during the first hour and then every 30 minutes during the second hour following vaccine administration.

6.3 GM-CSF 250 mcg/m<sup>2</sup> (dose rounded up to the nearest vial) S.C. will be given daily for four days (days 0-3) after each vaccine. All GM-CSF injections will be given in close proximity to the vaccination, as close to the exact site of injection as possible to ensure optimal recruitment of dendritic cells. The first dose of GM-CSF will be given by a nurse, and the remaining three doses will be given by the donor. Research staff will provide educational instructions regarding subcutaneous injection administration.

6.4 Recipient must meet the following criteria in order to receive the vaccine:

- Recipient to receive vaccine must be greater or equal than 3 months post allograft and with 5% or greater donor cell engraftment
- On a prednisone or prednisone equivalent dose of no more than 10 mg every other day at the time of registration, and with tacrolimus levels of <5 ng/dl or cyclosporine levels of < 100 ng/dl.
- Have no uncontrolled GVHD.

- Negative serum Beta HCG test in a woman with child bearing potential (not post-menopausal for 12 months or no previous surgical sterilization) and willing to use an effective contraceptive measure while on study.

If the recipient does not meet the above "pre-vaccine" criteria, the recipient and donor will be taken off the study. The donor will have follow-up tests and procedures performed, as described in Section 7.0.

- 6.5 On day 0 (day of lymphocyte collection) donors will undergo a steady state pheresis to obtain lymphocytes. Donor target cell dose will be to  $\geq 2 \times 10^7$  CD3+ cells /kg recipient weight. If the target dose is not reached after 3 collections, then the donor and the recipient will be taken off the study and the apheresis product will be discarded.
  - 6.6 If successful collection, on day 0:  $1 \times 10^7$  CD3+/cells per kg will be infused into the recipient. The rest of the cells will be cryopreserved in  $5 \times 10^7$  CD3+ cells /kg recipient weight aliquot. Premedication will include only acetaminophen 650 mg po (orally) and benadryl 25 mg iv once.
- NO STEROIDS ARE TO BE GIVEN PRIOR TO LYMPHOCYTE INFUSION.
- 6.7 After DLI on same day, recipient will receive id-KLH vaccine. The vaccine will be also administered on week 4 and week 8 post DLI. The recipient will receive a total of 3 vaccines.
  - 6.8 For the donor the time of active treatment will begin the day of the first vaccine and finish 30 days after donor lymphocyte collection.
  - 6.9 For the recipient the time of active treatment will begin the day of the donor lymphocyte infusion and finish 30 days after the last vaccination.
  - 6.10 Recipients will receive GM-CSF 250 mcg/m<sup>2</sup> (rounded up to the nearest vial) S.C.daily for four days (days 0-3) after each vaccine. All GM-CSF injections will be given in close proximity to the vaccination, as close to the exact site of injection as possible to ensure optimal recruitment of dendritic cells. The first dose of GM-CSF will be given by a nurse, and the remaining three doses will be given by the recipient. Research staff will provide educational instructions regarding subcutaneous injection administration.
  - 6.11 Donors and/or recipients: Fever and chills associated with vaccine administration and/or GM-CSF will be treated with acetaminophen and/or meperidine. The use of non-steroidal anti-inflammatory drugs and/or steroids should be avoided.
  - 6.12 Recipients should not receive steroid premeds, or high dose steroids for other indications unless approved by the Study Chair or his designee.
  - 6.13 Recipients failing to respond 6 months after the last vaccination can receive up to 3 subsequent doses of  $5 \times 10^7$  CD3+ cells/kg of the remaining cryopreserved cells, if no active GVHD is present. The additional lymphocyte infusions and follow up will be exactly like the first infusion.

## 7.0 Evaluation During Study

### A. Donor:

#### Prior to each vaccination: Within 72 Hours:

- 1) H&P, vital signs.
- 2) Albumin, total protein, calcium, glucose, BUN, creatinine, bilirubin, ALT, alkaline phosphatase, LDH, CBC with differential, PT/PTT.

- 3) Toxicity assessment after first vaccination.
- 4) Immunodeficiency panel: Quantitative immunoglobulins, and quantification of lymphocyte subsets (CD4 and CD8).
- 5) Negative serum pregnancy test if of child bearing potential if of child bearing potential.
- 6) Leukopheresis will be performed to obtain  $2 \times 10^9$  mononuclear cells (MNC) from donor and recipient.
- 7) Collect 10 cc serum and 60 cc whole blood in preservative-free heparin for idiotype-specific antibody and cellular proliferative responses once during weeks -8, -6, -4, -2, and 0.
- 8) Negative donor infectious disease panel:
  - Hepatitis B surface antigen (HBsAg)
  - Anti-Hepatitis B core antibody (HBcAb)
  - Anti-Hepatitis C Virus antibody (HCV Ab)
  - Anti-Human Immunodeficiency Virus (HIV) antibody (HIV 1/2 type O Ab)
  - Anti-Human T cell lymphotropic Virus (HTLV) antibody (HTLV I/II Ab)
  - Rapid Plasma Reagen (RPR)
  - Cytomegalovirus antibody (CMV)
  - HCV/HIV Nucleic Acid Test

Additional tests shall be performed as required to assess the possibility of transmission of other infectious or non-infectious diseases.

**Prior to lymphocyte collection:** Within 72 Hours:

- 1) H&P, vital signs.
- 2) Albumin, total protein, calcium, glucose, BUN, Creatinine, bilirubin, ALT, Alkaline phosphatase, LDH, CBC with differential, PT/PTT.
- 3) Toxicity assessment.
- 4) Collect 10 cc serum and 60 cc whole blood in preservative-free heparin for idiotype-specific antibody and cellular proliferative responses.
- 5) Negative donor infectious disease panel:
  - Hepatitis B surface antigen (HBsAg)
  - Anti-Hepatitis B core antibody (HBcAb)
  - Anti-Hepatitis C Virus antibody (HCV Ab)
  - Anti-Human Immunodeficiency Virus (HIV) antibody (HIV 1/2 type O Ab)
  - Anti-Human T cell lymphotropic Virus (HTLV) antibody (HTLV I/II Ab)
  - Rapid Plasma Reagen (RPR)
  - Cytomegalovirus antibody (CMV)
  - HCV/HIV Nucleic Acid Test

Additional tests shall be performed as required to assess the possibility of transmission of other infectious or non-infectious diseases.

**B. Recipient:**

**Within 10 days prior to lymphocyte infusion and within 72 hours prior to each vaccine:**

- 1) H&P, vital signs.
- 2) Albumin, total protein, calcium, glucose, BUN, creatinine, bilirubin, ALT, alkaline phosphatase, LDH, CBC with differential, PT/PTT.
- 3) GVHD assessment.
- 4) Immunodeficiency panel.
- 5) Negative serum pregnancy test if of child bearing potential.
- 6) Disease specific assessment:
  - SPEP, UPEP, serum and immunofixation electrophoresis, serum for free kappa and lambda light chain assay, Beta 2 Microglobulin, and C reactive protein.

- 7) Collect 10 cc serum and 60 cc peripheral blood in preservative-free heparin for idiotype-specific antibody and cellular proliferative responses, immediately prior to donor lymphocyte infusion, 1 hour after the donor lymphocyte infusion.
- 8) Idiotype-specific humoral and cellular responses will be assessed in both donor and in the recipient post-transplantation.
- 9) Negative donor infectious disease panel:
  - Hepatitis B surface antigen (HBsAg)
  - Anti-Hepatitis B core antibody (HBcAb)
  - Anti-Hepatitis C Virus antibody (HCV Ab)
  - Anti-Human Immunodeficiency Virus (HIV) antibody (HIV 1/2 type O Ab)
  - Anti-Human T cell lymphotropic Virus (HTLV) antibody (HTLV I/II Ab)
  - Rapid Plasma Reagen (RPR)
  - Cytomegalovirus antibody (CMV)
  - HCV/HIV Nucleic Acid Test
  - West Nile Virus Nucleic Acid Test
  - Sickledex
  - T Cruzi AB

Additional tests shall be performed as required to assess the possibility of transmission of other infectious or non-infectious diseases.

### **C. Donor Long-Term Follow-Up:**

#### **Procedures and Tests:**

Donors will have the following procedures and tests at 1, 12, and 24 ( $\pm$  1 week) post donor lymphocyte collection at MD Anderson Cancer Center if possible.

- 1) H&P, vital signs.
- 2) Albumin, total protein, calcium, glucose, BUN, creatinine, bilirubin, ALT, Alkaline phosphatase, LDH, CBC with differential, PT/PTT.
- 3) Immunodeficiency panel.

If the donor is not able to return to MD Anderson Cancer Center for long-term follow-up, the donor should have the procedures and tests performed with a local physician, as approved by the Study Chair. The results should be sent to research staff at MD Anderson Cancer Center.

#### **Telephone Follow-Up:**

Donors will receive a telephone follow-up call once a year for 5 years, starting at month 24 ( $\pm$  1 week) post donor lymphocyte infusions. The telephone follow up will include questions regarding interim history, hospitalizations, new medications, and new allergies.

### **D. Recipient Long-Term Follow-Up:**

#### **Procedures and Tests:**

Recipients will have the following procedures and tests at 3, 6, 12, 18, and 24 months post last vaccine ( $\pm$  1 week)

- 1) H&P, vital signs.
- 2) Albumin, total protein, calcium, glucose, BUN, creatinine, bilirubin, ALT, alkaline phosphatase, LDH, CBC with differential, PT/PTT.
- 3) GVHD assessment.
- 4) Immunodeficiency panel
- 5) Disease specific assessment:
  - SPEP, UPEP, serum and immunofixation electrophoresis, serum for free kappa and lambda light chain assay, Beta 2 Microglobulin, and C reactive protein.

-Bone marrow aspiration and biopsy for cytogenetics, chimerism, and myeloma panel: Kappa, Lambda, CD138 staining.

6) Collect 10 cc serum and 60 cc peripheral blood in preservative-free heparin for idiotype-specific antibody and cellular proliferative responses, immediately prior to donor lymphocyte infusion, and months ( $\pm$  1 week) 1, 2, 3, 4, 6, 12, 18 and 24.

7) Idiotype-specific humoral and cellular responses will be assessed in both donor and in the recipient post-transplantation.

If the recipient is not able to return to MD Anderson Cancer Center for long-term follow-up, the recipient should have the procedures and tests performed with a local physician, as approved by the Study Chair. The results should be sent to research staff at MD Anderson Cancer Center.

**Telephone Follow-Up:**

Recipients will receive a telephone follow-up call once a year for 5 years, starting at month 24 ( $\pm$  1 week) post donor lymphocyte infusions. The telephone follow up will include questions regarding interim history, hospitalizations, new medications, and new allergies.

**OPTIONAL PROCEDURE**

Recipients will be asked for permission to obtain additional blood samples for future testing as well as a punch skin biopsy using standard techniques in an area around the vaccination to identify types of cellular infiltrates.

Unused cells or vaccines generated for this study which are not infused into the recipients will be used for research purposes.

**E. Evaluation of Toxicity and Data Collection (Donors and Recipients)**

The severity of the adverse events observed in the proposed treatment will be graded according to the Common Terminology Criteria v3.0 (CTCAE).

Events not included in the CTCAE chart will be scored as follow:

General grading:

Grade 1: Mild: discomfort present with no disruption of daily activity, no treatment required beyond prophylaxis.

Grade 2: Moderated: discomfort present with some disruption of daily activity, require treatment.

Grade 3: Severe: discomfort that interrupts normal daily activity, no responding to first line treatment.

Grade 4: Life Threatening: discomfort that represents immediate risk of death.

Expected adverse events (AEs) related to the vaccine injection :

1. Local reactions (erythema, induration, swelling and tenderness),
2. Fever, chills,
3. Rash,
4. Myalgias and arthralgias.
5. Mild elevations in creatinine phosphokinase (CPK).

Expected adverse events (AEs) related to GM-CSF:

1. Fever, chills, diaphoresis
2. Myalgias, fatigue, malaise
3. Headache, dizziness
4. Dyspnea, bronchospasm, pleural effusion
5. Anorexia, indigestion, nausea, vomiting, diarrhea

6. Urticaria, rash, pruritus, hypersensitivity reactions
7. Bone pain
8. Thromboembolic events, phlebitis
9. Hypotension
10. Peripheral edema
11. Leukocytosis, thrombocytosis or thrombocytopenia
12. Hepatic enzyme abnormalities and bilirubin elevation have been recorded.

Expected adverse events (AEs) related to the vaccine:

1. Autoimmune reactions (hypogammaglobulinemia, collagen vascular diseases, cytopenias).
2. Local reactions

Expected adverse events (AEs) related to the DLI:

1. Graft versus host disease

#### **Casualty Assessment:**

For the purpose of this study adverse events known to be caused by the vaccine administration, GM-CSF, donor lymphocyte infusion and to the vaccine and its direct consequences will be scored as definitive related.

Adverse events known to be related to drugs used for the treatment of Medical problems arise as direct consequences of known adverse events will be scored as probable related.

When the relationship of the adverse event cannot be ruled out with certainty the AE may be considered possible related.

#### **Adverse Events Data Collection :**

At each evaluation time point adverse events will be assessed and only those related to the vaccine and donor lymphocyte infusion will be collected.

The donor and recipient will be provided a diary to collect any adverse events following administration of the vaccines and GM-CSF. The donor and recipient will bring the diary to each scheduled visit for review by research staff.

Adverse events related to the injection site and GM-CSF won't be capture unless these are considered serious. The data collection will reflect the onset and resolution date and maximum grade; beyond this point some events considered late complications post treatment might be recorded with the first date of its awareness and grade or resolution date when able to be documented.

Intermittent events should be labeled as such and followed until resolution. If a patient is taken off study while an event still ongoing, this will be followed until resolution unless another therapy is initiated. Pre-existing medical conditions will be recorded only if an exacerbation occurs during the active treatment period. Co-morbid events will not be scored separately.

#### **Serious Adverse Event Reporting (SAE)**

A serious adverse event is – any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience



that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity – a substantial disruption of a person's ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, the Investigational New Drug (IND) Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy on Reporting Serious Adverse Events". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND office, regardless of attribution (within 5 working days of knowledge of the event).
- All life-threatening or fatal events, expected or unexpected, and regardless of attribution to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office. -
- The MDACC "Internal SAE Report Form for Prompt Reporting" will be used for reporting to the IND Office.
- Serious adverse events will be captured from the time the patient signs consent until 30 days after the last dose of drug. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- A research nurse will document information regarding the adverse event into the patient's/donor's medical record. The Study Chair will review and sign the documentation.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study

treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

#### **Reporting to FDA:**

· Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the Study Chair and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

## **8.0 Criteria for Response**

1. The primary clinical endpoints for this study are anti-myeloma response to donor lymphocyte infusions and GVHD.
2. CRITERIA FOR RESPONSE: Consensus EBMT/IBMTR Response Criteria for Myeloma are to be used. Appendix E.(37)
3. Acute and Chronic GVHD will be graded according to Appendix F. Patients who develop any form of GVHD may be treated according to standard care or any extant protocol.
4. RELAPSE/PROGRESSION will be recorded by the day of detection.
5. SURVIVAL will be recorded by the day and cause of death, and measured from the date of DLI.

## **9.0 Criteria for Removal from the Study**

1. Patient/Donor withdrawal of informed consent
2. Patient death
3. Disease progression requiring anti-myeloma therapy
4. Patient/ Donor not being compliant
5. 5 years post donor lymphocyte infusion
6. If the recipient does not meet the "pre-vaccine" criteria in Section 7.0 B., the recipient and donor will be taken off the study.
7. Donor lymphocyte collection failure
8. An increasing or unexpected pattern of toxicity observed deemed unacceptable by the study chairman
9. Investigator judgment when the well being and best interest of the patient is compromised.
10. Inability of donor to provide lymphocytes after study registration

## **10.0 Statistical Considerations**

**Preliminaries.** This is a single-arm feasibility trial of Id Specific vaccinated DLI for treatment of multiple myeloma patients post allograft from a matched sibling donor who are not in CR or relapsing after transplant at least 3 months after stem cell transplant. The last myeloma therapy must be at least 3 weeks prior to entry. Labeling time of DLI as week 0, each donor will be vaccinated at weeks -8, -6, -2 and each patient will be vaccinated at weeks, 0, 4, and 8. Toxicity (TOX) will be defined as the event that the patient suffers grade 2, 3 or 4 GVHD or death within 6 months post DLI. The historical rate of TOX is 50% (54/107). The primary aim is to determine whether transfer of myeloma specific immunity is enhanced by vaccinating donors prior to donor lymphocyte infusion with an id-specific vaccine.

**Trial Conduct.** A maximum of 10 patients will be treated.

**Analysis of Myeloma Specific CTLs over time.** A generalized linear mixed model (Diggle, et al., 1998) will be fit to the longitudinal measurements of myeloma specific CTLs. For patient  $j = 1, \dots, 20$  at observation time  $t = -8, -6, -2, 0, 4, 8, 12$ , denote the myeloma specific CTL count by  $Y_{j,t}$  and covariate vector by  $Z_j$ . The model is given by

$$g\{E(Y_{j,t})\} = m + f_j(t) + b Z_j + \text{error}$$

where  $g$  is a suitable link function,  $m$  is the overall mean,  $f_j$  is a patient-specific function of  $t =$  time from day of DLI, accounting for the manner in which  $Y$  varies over time and includes a patient effect to account for correlation among the successive observations on each patient,  $Z_j$  is a component accounting for patient covariates with  $b$  is a covariate parameter vector, and "error" is the usual measurement of error.

Additional analyses of the final data will include analysis of survival times as functions of the treatments and patient prognostic covariates using an appropriate survival regression model determined by goodness-of-fit analyses.

**Toxicity Monitoring Rule.** For the purpose of safety monitoring, "toxicity" will be defined as Grade 2-4 acute GVHD within 6 months of DLI. Based on an historical toxicity rate of 50%, denoting  $q = \text{Pr}(\text{toxicity})$ , it will be assumed that  $q$  follows a beta(.50, .50) prior. The trial will be stopped early for safety if  $\text{Pr}(Q > .50 | \text{data}) > .90$ . This rule will stop the trial early if  $[\# \text{ toxicities}] / [\# \text{ patients}]$  is greater than or equal to 2/2, 3/3, 4/4, 5/6, 6/7, or 7/9. The operating characteristics of this rule are as follows:

True Pr(Toxicity)	Pr(Stop Early)	Median Sample Size
.50	.35	10
.60	.52	8
.70	.70	5
.80	.88	2

**PROTOCOL COMPLIANCE** Patients will be reviewed by the study investigators who will score the patient for toxicity, and GVHD. Data must be entered in PDMS and the Study Chairman will be the final arbiter of toxicity and other outcomes should a difference of opinion exist.

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