Supplementary Information:

Trial Summary: Seven patients were treated on study and two patients remain alive. Five patients enrolled in the study have died due to disease progression; P3, P4, P7 developed rapid disease progression after the 3rd vaccine dose and were taken off study and offered other treatment options which included combination chemotherapy, vemurafenib, ipilimumab, and adoptive T cell therapy prior to succumbing from metastatic melanoma. P2 had disease progression after 6 vaccine doses and was given ipilimumab without response; he subsequently developed brain metastases treated with whole brain radiation and died of disease progression. P6 had a partial response to treatment and then had disease progression after 12 mo. on study; he developed lung metastases treated with ipilimumab followed by brain metastases that required whole brain radiotherapy and dexamethasone. P6 died of disease progression 3 months after the development of intra-cranial metastases. There are 2 patients that remain alive but are no longer receiving the study vaccine. P5 had a partial response to treatment and eventually had disease progression after 11.5 mo on study and received ipilimumab (4 doses) that was associated with a partial response; this patient remains alive and stable with no further treatment. P1 received a total of 11 vaccine doses (last dose administered 1.5 yr ago) and remains alive in complete remission with no other therapy provided.

Supplementary Figures:

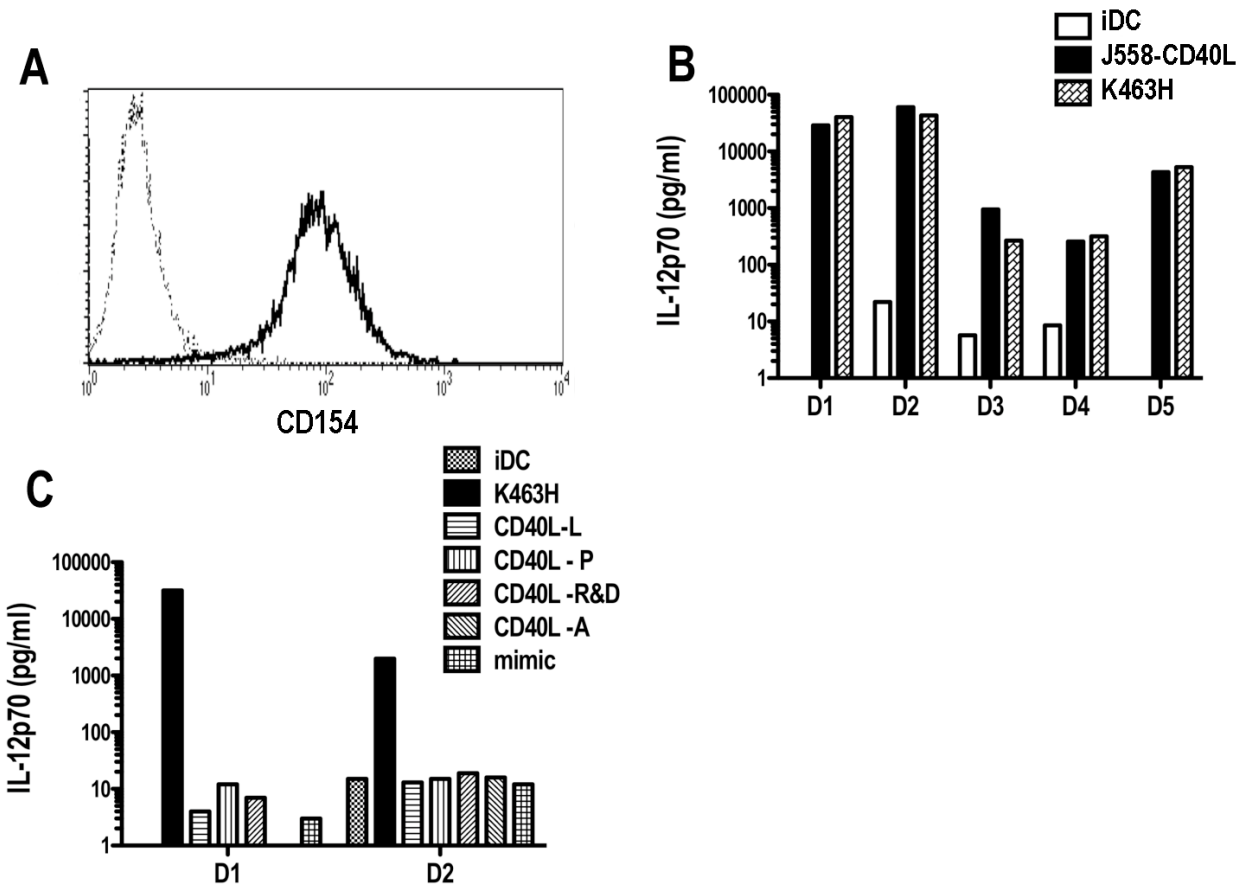

Figure S1 *Generation of a GMP-grade CD40L-expressing cell line (K463H) for clinical studies.* Human CD40L (CD154) was obtained from Origene (catalog #NM000074) and using standard methods a PCR product (809bp) was generated, cloned into the pCR2.1 vector, sequence verified and cloned into the pMIH vector for retroviral production. Using standard spin inoculation techniques, K562 (human leukemia cell line from ATCC) was transduced with concentrated virus supernatants and a stable cell line (designated K463H) was selected by hygromycin resistance. (A) CD154 expression by K463H line as characterized by flow cytometry (anti-human CD154 mAb, thick dark line; isotype control, dotted thin line). Microbiology and mouse antibody production testing demonstrated the cell line to be free of infectious agents and common murine pathogens and electron microscopy confirmed the absence of viral particles. Both adventitious virus testing and tumorigenicity testing were negative. GMP-grade K463H line was generated, selected and maintained under serum-free (Stemline S1694 media, Sigma, St Louis, MO) conditions. A master cell bank was stored in the GMP facility. The CD40L-expressing line (K463H) was compared to (B) J558-CD40L cells (a murine CD40L expressing cell line) (1) or (C) indicated research grade CD40L reagents for induction of IL-12 by DC. Experiments were performed in RMPI 1640 supplemented with 1% human AB sera. In the presence of human IFN-γ (100 U/mL), K463H is equipotent to J558-CD40L; none of the other reagents or a cytokine cocktail (mimic, ref. 49), induced significant IL-12 levels (<15pg/ 10^6 cells/24h). Results were obtained with DC derived from a healthy donor and is representative of 3 experiments performed.

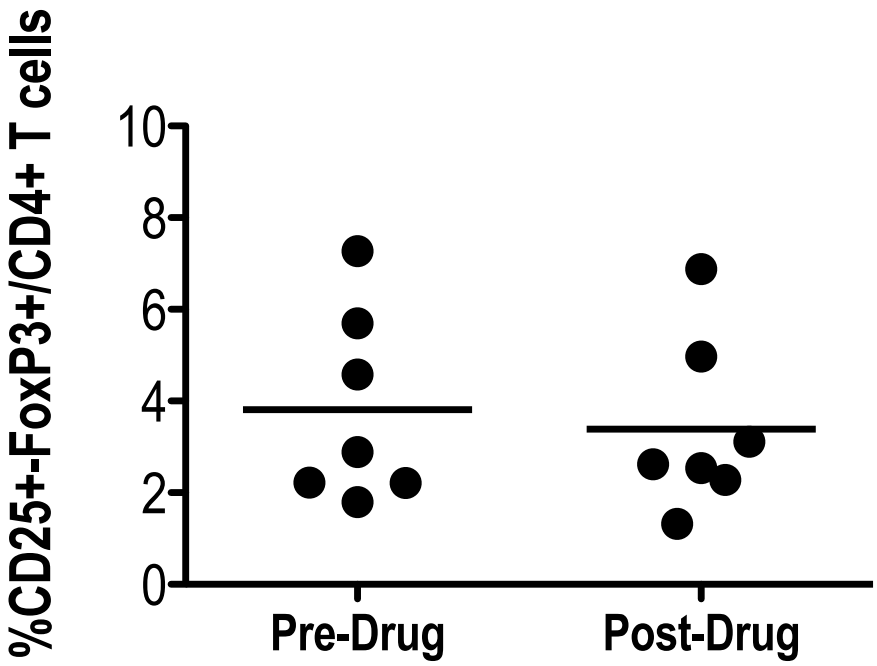

Figure S2 *Effect of single-dose cyclophosphamide on regulatory T cell (Treg) frequencies*. Patients were treated with a single-dose of cyclophosphamide (300mg/m^2) 72 h prior to the first DC vaccination. Blood was drawn pre- and 72 h post-drug treatment, PBMC isolated and Treg characterize as CD4+/CD25+/FoxP3+ by immuno-phenotyping. Frequency of Treg was determined by flow cytometry using a hierarchical gating strategy that included FSC/SSC, CD4 and CD25/FoxP3. Each dot represents an individual patient, and the horizontal line represents the mean value. p= 0.375, paired two-tailed t-test.

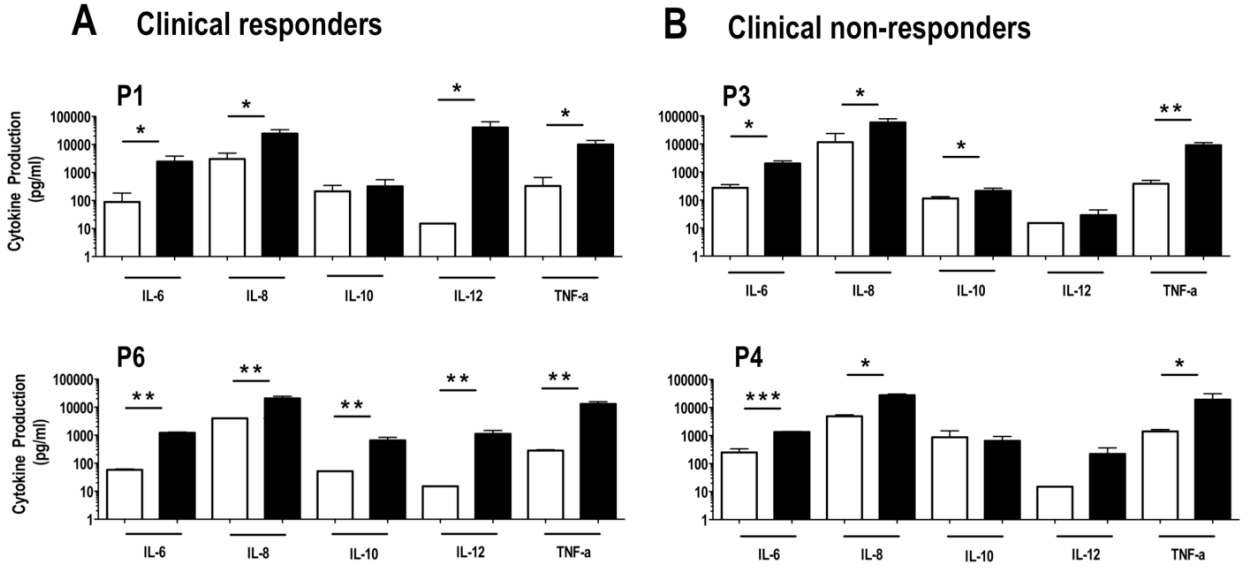

Figure S3 *Cytokine production by patient DC upon CD40L/IFN-γ activation.* Supernatants collected from iDC (open bars) and mDC (closed bars) were analyzed for cytokine and chemokine production using a 42-cytokine multiplex bead assay (EMD Millipore, Billerica, MA). Results for selected cytokines produced by DC derived from high/normal (IL-12>1ng, P1 and P6) and low (IL-12<1ng, P3 and P4) IL-12 producers are shown. Results are representative of those obtained in 2 vaccine doses and are presented in log scale. p= ***<0.001, **<0.01, *<0.05, paired two-tailed t-test.

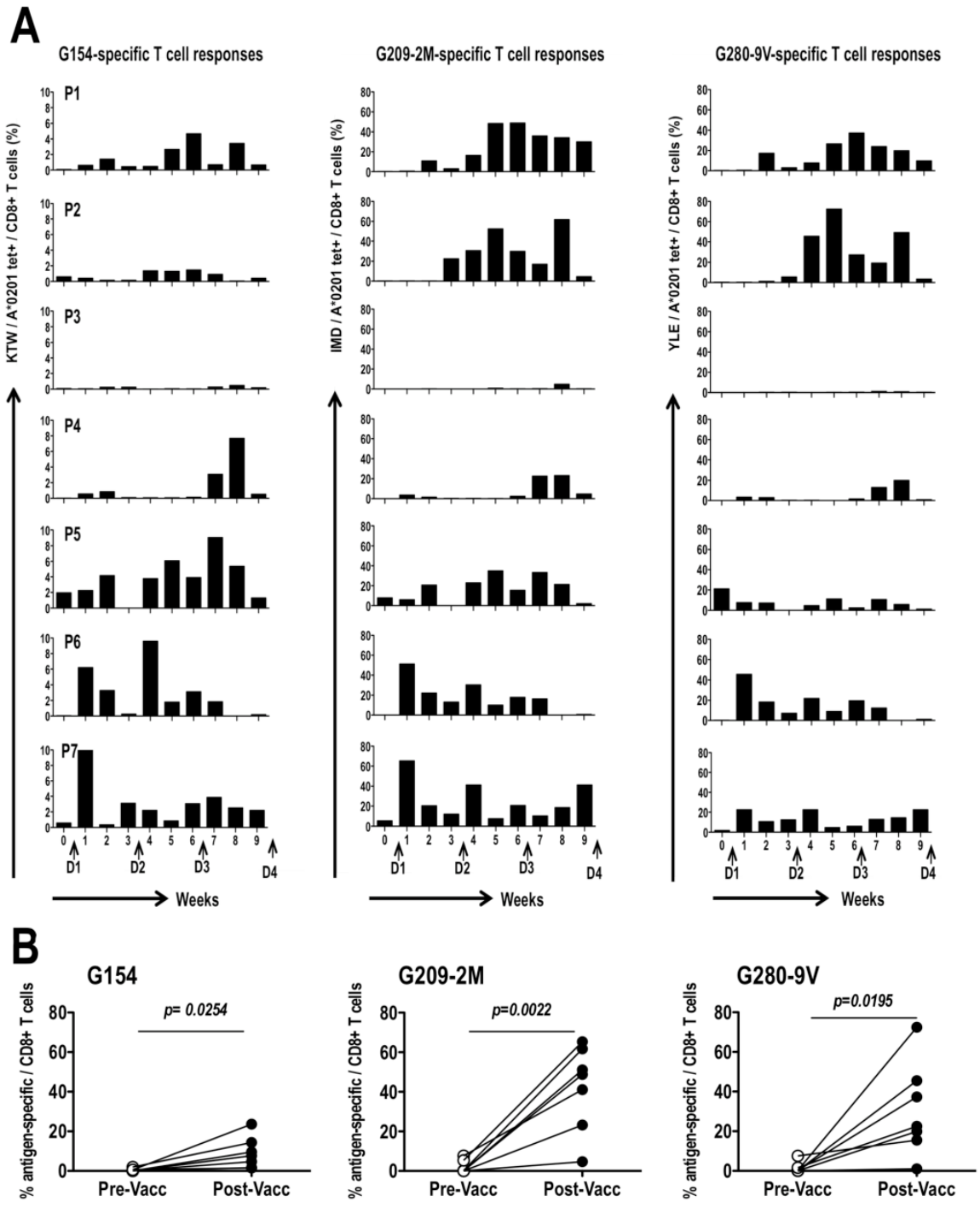

Figure S4 *Kinetics of T cell response to gp100 after vaccination with CD40L/IFN-γ-activated DC.* (A) Time is recorded in weeks (0 indicates pre-vaccination); DC vaccinations are denoted D1-D4. For culturing methods refer to legend of Fig 2. Please note the scale (y-axis) for G154 is different than that for G209-2M and G280-9V. (B) Comparison of gp100-specific frequencies pre-vaccination and at peak responses. Each dot represents results obtained with an individual patient. p values are indicated, paired two-tailed t-test.

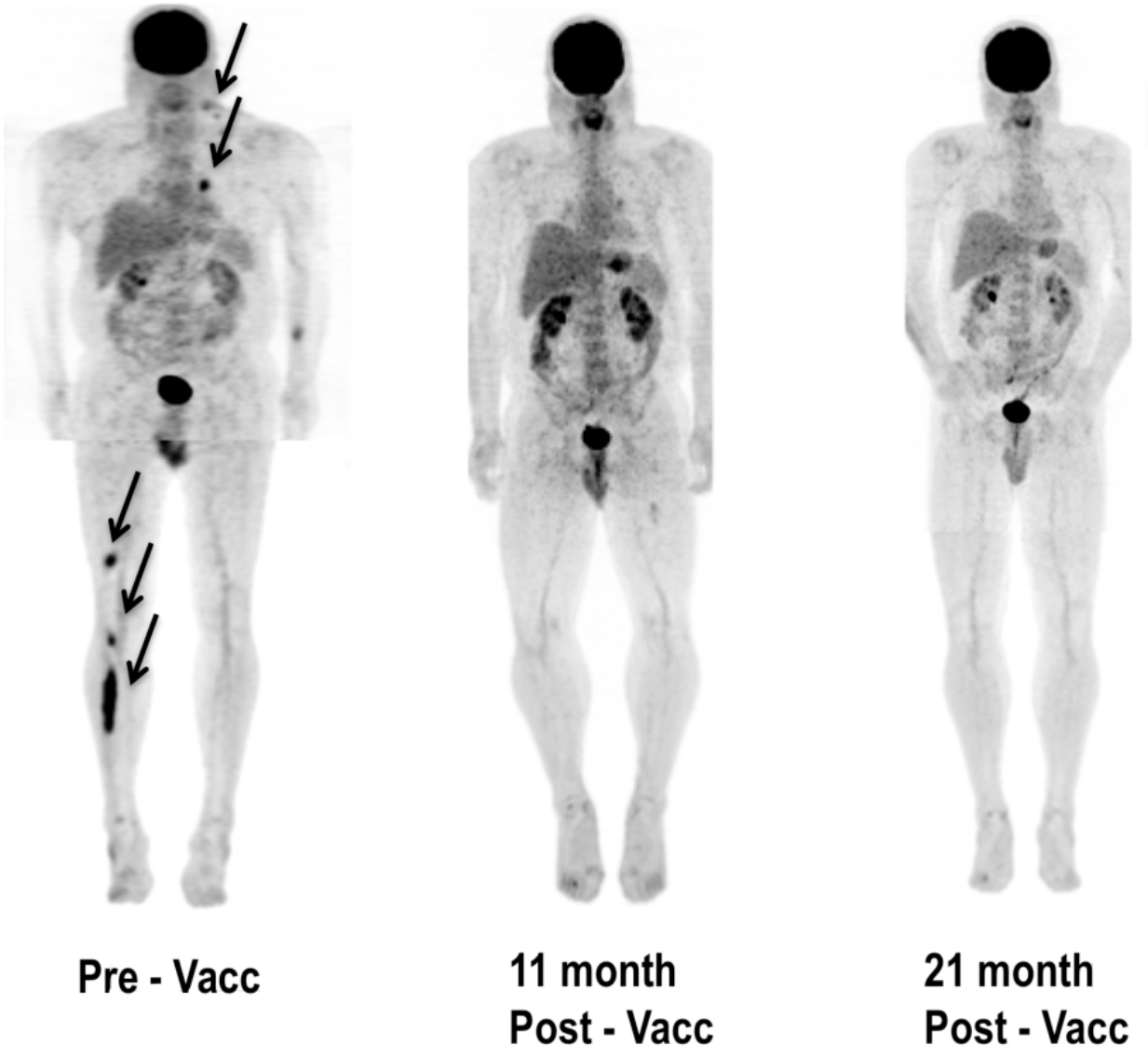

Figure S5 *Positron emission tomography*. Radiologic studies (FDG-PET/CT imaging) were obtained on Patient 1 before vaccination, 11 months and 21 months after treatment. Coronal whole body PET images show complete regression of left supra-clavicular and hilar lymph nodes as well as multiple subcutaneous lesions on the right leg. P1 remains in remission as of August 2012.

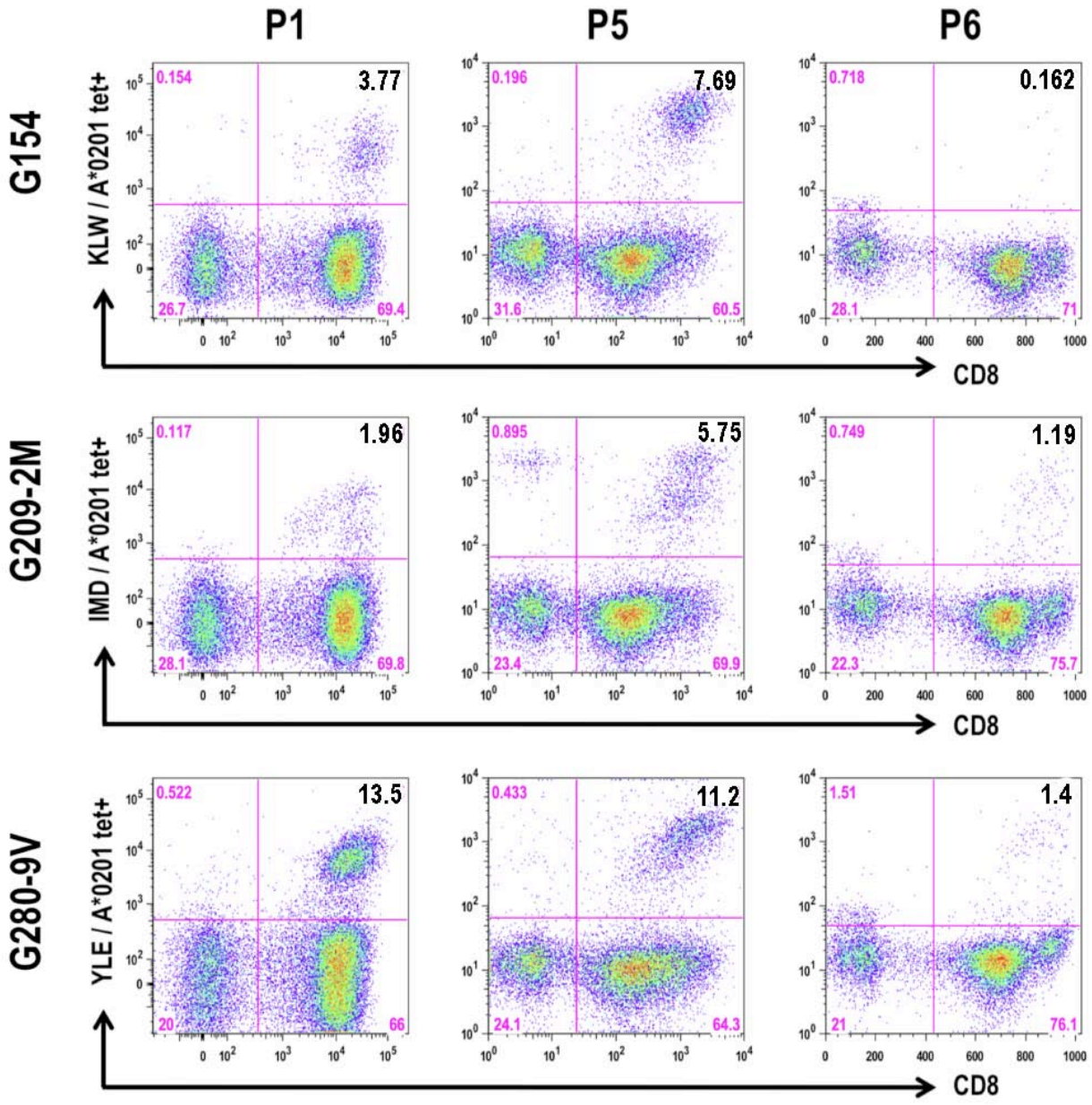

Figure S6 *gp100-specific T cell frequencies in clinical responders 6-12 months after last DC vaccination.* Antigen-specific CD8+ T cell frequencies obtained in cultures derived from PBMC obtained from clinical responders (patients P1, P5 and P6) at 6 to12 months after the last DC vaccination. The response in P6 is presumably blunted due to use of corticosteroids. P5 had recently completed a course of ipilimumab. P1 had received no therapy for 1 year after the final vaccine dose. Flow cytometric analysis and gating strategy is same as that described for Figure 2. Numbers on right-hand quadrant represent percentages of antigen-specific T cells in DUMP-/7-AAD-/CD8+-gated cells.

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Mature Dendritic Cell Vaccination Against gp100 in Patients with Advanced Melanoma

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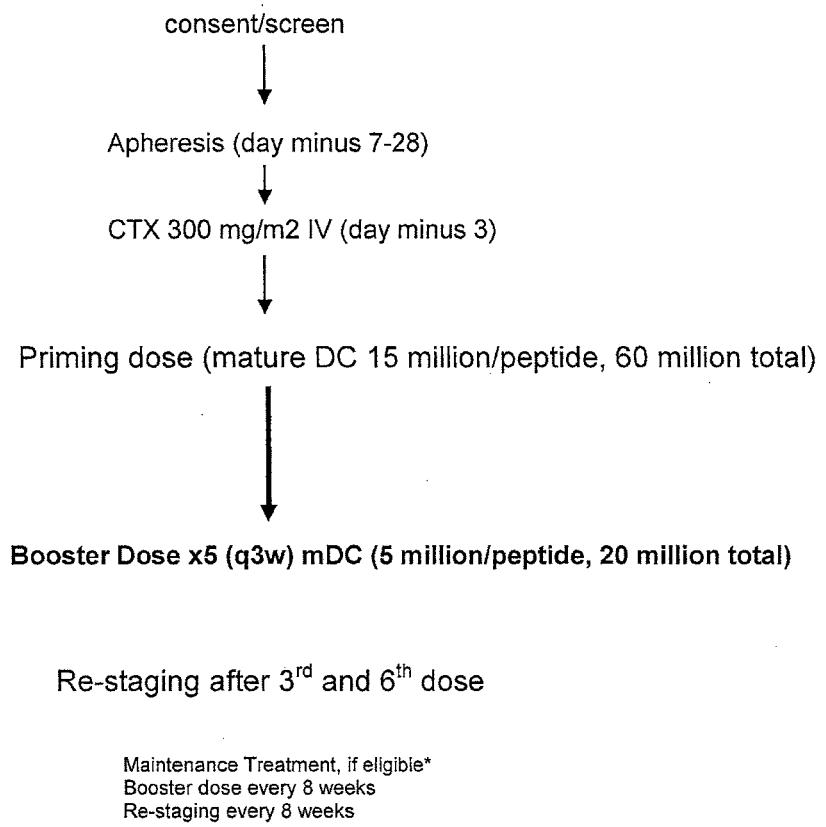
Schema



- For maintenance treatment, eligible patients include those with partial or complete response after 6 vaccine doses. Patients can continue to receive additional vaccine doses if there is no evidence of disease progression. A total of 12 patients will be accrued to this study.
- Immune monitoring. Blood is drawn every week from dose #1-dose #4 (day 0- day 64) and then every three weeks until day 190. Patients that receive maintenance treatment blood is drawn prior to each vaccine dose (every two months). Two BD vacutainer tubes (CPT 8 cc tubes, or alternatively, green top 8cc tubes) are drawn at each visit.

Mature Dendritic Cell Vaccination Against gp100 in Patients with Advanced Melanoma

ELIGIBILITY: (See Section 3.0)

Unresectable stage III and stage IV M1a/M1b melanoma. Patients with stage IV M1c are not eligible. Prior systemic cytotoxic chemotherapy is not allowed. Prior adjuvant Interferon or investigational (non-cytotoxic) therapy is permitted. Patients must be HLA-A2 positive and each tumor must express gp100 antigen. A total of 12 patients will be accrued to this study over 2 years.

TREATMENT: (See Section 6.0)

Eligible patients that provide written informed consent will undergo apheresis to collect blood mononuclear cells for vaccine production. All patients will be given cyclophosphamide 300mg/m2 IV three days prior to vaccine dose #1 in order to deplete regulatory T cells. All patients will receive mature DC for each dose of vaccine. For each dose all patients will receive autologous dendritic cells pulsed with 3 melanoma peptides (gp100 antigen) and one control (CMV) peptide. All patients will receive booster doses with mature DC. The DC vaccine will be given intravenously every three weeks for a total of six vaccine doses. Peripheral blood (16 ml) will be taken weekly to monitor the immune response to each peptide by tetramer assay. Apheresis is repeated after vaccine dose #3 and dose #6 in order to collect PBMC for immune monitoring. Restaging is performed after three and six vaccine doses. Patients with stable disease or better (partial response/complete response) after six doses will be eligible to receive additional vaccinations as maintenance therapy every 2 months until progression.

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Mature dendritic cell vaccination against gp100 in patients with advanced melanoma

1.0 BACKGROUND AND RATIONALE

1.1 Overview

In 2007, it is estimated that 59,940 new cases of melanoma will be diagnosed in the US (1). Although many individuals will be detected early and cured with surgery, approximately 8,110 patients will die from metastatic melanoma. Patients with metastatic (stage IV) melanoma suffer a poor prognosis and conventional therapy for these patients offers little benefit. The median survival of patients with metastatic melanoma is 9 months; patients with brain metastasis suffer a significantly poorer prognosis with a median survival of 3 months despite definitive treatment with radiation and steroids (2). No therapy has been proven to prolong survival and thus, new treatment approaches are needed for melanoma (3, 4).

1.2 Chemotherapy for melanoma

Chemotherapy has little impact on the natural history of metastatic melanoma. Dacarbazine received FDA approval in 1975 and remains the standard of care as treatment for patients with stage IV melanoma. The response rate to dacarbazine in most studies is 10-15%, primarily partial responses that tend to be of short (2-3 months) duration. Few durable complete responses are seen after treatment with dacarbazine. A meta-analysis of 74 studies published between 1974-1995 reviewed the ineffectiveness of dacarbazine-based chemotherapy as the median survival of enrolled patients was 8.8 months (5). Addition of other cytotoxic agents to dacarbazine adds little clinical benefit and increases toxicity (6). The randomized Intergroup study led by ECOG evaluated dacarbazine versus dacarbazine plus BCNU, cisplatin, and tamoxifen revealed no significant differences in progression-free survival and overall survival (7). Addition of Interferon and Interleukin-2 to dacarbazine, vinblastine, cisplatin (CVD) is not superior to CVD alone as studied in the largest randomized clinical trial in North America (8).

1.3 Cytokines for melanoma

Interleukin-2 received FDA approval in 1998 as treatment for metastatic melanoma despite concerns about toxicities and poor tolerability. In a series of single arm (uncontrolled) clinical trials (n=270 patients), the response rate to high dose Interleukin-2 is 16% (6% complete response rate). As reported, ten of the 16 patients who achieved a complete response remain disease free at a median follow up of 5 years (9). Six deaths occurred due to toxicity. This published experience using high dose IL-2 suggests that immunomodulation has a role in the treatment of this disease and in fact, may be curative in a small group of patients.

1.4 Vaccines for melanoma

Since 1970, investigators have pursued the hypothesis that melanoma is inherently immunogenic and elicits an immune response that can be, in some instances, protective (10, 11). As a result, therapeutic immunization strategies have evolved over the past decade to develop more contemporary approaches

based on molecular techniques of antigen identification and immune monitoring (12). As one example, the molecular cloning of several melanocyte-lineage antigens (MLA) has prompted investigators to identify and isolate immunogenic peptides that can be used in vaccination protocols (13). These candidate melanoma tumor antigens include: gp100/pMel17, MART-I, Melan-A, tyrosinase as well as antigens from the cancer-testis family (MAGE family) which are known to be expressed only in testis and placenta in normal tissues (14, 15). In normal adult issues, each MLA is expressed at low levels with expression restricted to melanocytes and retina pigmented epithelium (16). Various vaccine formulations are under investigation world wide and include viral vector based (ie, vaccinia virus), DNA based, and peptide based approaches (17, 18).

1.5 Gp100 melanoma antigen vaccines

The gp100 antigen has been studied in detail. Three candidate peptides that bind HLA-A2 (the most common class I allele expressed by ~50% of the population) have been identified and each is known to be immunogenic in patients with melanoma (19-22). One peptide named (G209-2M (also called gp100:209-217) has been studied extensively and shown to be immunogenic when given subcutaneously with adjuvant (23). In our work, the (G280-9V (also called gp100:280-288) peptide was given with autologous dendritic cells (without IL-2 or any other cytokine) and shown to be immunogenic in patients with advanced melanoma (24). The third peptide epitope named G154 has also been studied in some detail (25). Other gp100 related peptides that are restricted to HLA-A3 are known but are less well studied (26).

1.6 Dendritic cells

Dendritic cells (DC) serve a critical role in capturing and presenting antigen in the initiation of immunity against infectious pathogens and neoplasia (27). A variety of technical advances involved the isolation of human DC as well as an improved understanding of DC biology have led investigators to propose using autologous DC as adjuvant for peptide vaccination in cancer, including melanoma (28). The initial clinical reports (29-31) conclude that DC immunization is safe and well tolerated; serious adverse events related to DC vaccination are rare. Interestingly, clinical responses have been documented by numerous investigators in a variety of malignancies including melanoma (32, 33). While most clinical investigators concede that the optimal dose, schedule, and route for DC vaccination are unknown, further clinical evaluation is justified based on clinical activity in the setting of minimal toxicity. In our prior study of 12 patients with advanced melanoma (study 98-057), two patients had a partial response using RECIST criteria and three patients had stable disease after six vaccine doses (24). The median survival of the entire cohort was 37.6 months (median follow up 48.3 mo) with three patients still alive and one patient that continues to respond to DC vaccination without additional treatment. All 12 patients had detectable immunity to gp100 antigen as measured by elispot assay, tetramer analysis, and specific lysis of gp100+ melanoma tumor cells. This result supports continued development of DC based immunization strategies using gp100 antigen peptides.

1.7 Regulatory T cells

Recent advances in immunology confirm the presence of a small population of circulating CD4+CD25+ T cells (known as regulatory T cells or Treg) that function to suppress T cell immunity toward nominal and self antigens (34). In healthy adults, approximately 5% of peripheral blood CD4+ T cells are Treg based on co-expression of CD25 and the transcription factor FoxP3 (35). Elimination of Treg permits more effective immunity after vaccination in a variety of experimental models (36-

40). Depletion of Treg either with anti-CD25 monoclonal antibodies or administration of low dose cyclophosphamide is sufficient to allow tumor rejection after peptide vaccination in model systems. This strategy was attempted clinically in the 1980's using cyclophosphamide together with a first generation (whole cell, irradiated) vaccine and shown to be safe and well tolerated (41). Several randomized trials later confirmed that vaccine given with cyclophosphamide is more immunogenic (42, 43). Currently, the use of low dose cyclophosphamide which can be safely administered in the outpatient infusion area is the most cost effective strategy to eliminate Treg in patients prior to vaccination and is currently being evaluated at multiple centers. Humanized anti-CD25 monoclonal antibodies have not been shown to effectively deplete Treg in patients with solid organ transplants.

1.8 Study rationale

Tumor vaccines represent a promising area of clinical investigation in melanoma and other solid tumors based on evidence of clinical activity and minimal toxicity (44, 45). One example of a DC vaccine in late stage clinical development is Sipuleucel-T (Provenge, Dendreon). Sipuleucel-T administration to men with hormone refractory prostate cancer has been shown to prolong survival in a controlled randomized study (46). The underlying hypothesis of this research is that repeated immunization is effectively required to elicit antigen-reactive T cells capable of eradicating melanoma. Moreover, both quantitative and qualitative improvements in CD8 immunity are necessary (but not sufficient) for clinical response and improved survival. The goal of this study is to build on our prior clinical trial results (study 98-057) together with incorporating two important advances in this area of research. First, it is now apparent that Treg cells can impair immunization against tumor antigens in model systems; however, limited data in humans given cancer vaccines supports this conclusion. Second, the maturational status of DC appears critical for optimal induction of immunity. Compelling evidence from numerous groups suggests that mature DC serve as better adjuvants compared to immature DC(47); however, no conclusive data in humans exists showing the superiority of mature DC when used in vaccine trials. Intensive immunologic monitoring is essential to understand the effects of Treg depletion and the generation of peptide-specific CD8 immunity in a longitudinal manner. The current study proposes to use three known immunogenic HLA-A*0201 restricted peptides derived from the gp100 MLA together with a control CMV peptide for immunization of patients with advanced melanoma. Inclusion of a control peptide will allow one to measure the response after a booster immunization in an individual with pre-existing immunity; in non-immune (CMV seronegative) individuals, CMV peptide immunization will permit assessment of a primary immune response directed against a strong antigenic viral peptide that has been well characterized (48). In this study, all patients will receive a single IV dose of cyclophosphamide (300 mg/m^2) given prior to the initial priming dose with mature DC pulsed with three melanoma and one control CMV peptide. Patients will then receive booster immunizations with mature dendritic cells. Booster mDC doses will be administered every 3 weeks. A total of six mDC doses (priming dose and 5 booster doses) will be provided to each patient. A total of 12 patients will be accrued to this study over a 24 month period.

The primary endpoint is immunological response based on tetramer assays performed on longitudinal blood samples obtained at multiple time points. Immunological response is based on measuring increased numbers of peptide specific CD8+ T cells as measured by the tetramer assay (49). In the proposed study, the tetramer assay will be performed at the designated time points (n=18). The additional laboratory correlative assays such as the ^{51}Cr release assay and elipsot assays will be performed after the 3rd and 6" vaccination. The primary endpoint will also include evaluating the safety and tolerability of the mature dendritic cell vaccine. Secondary endpoints in the study include objective response rate (RECIST) and time to progression. Since repeated doses of CD40

ligand/interferon-γ activated mDC have not yet been administered to patients, the safety and side effect profile of mDC immunization will be documented (50).

In addition, we propose to obtain tumor tissue to evaluate various biomarkers (including the expression of HLA-A*0201 and gp100) and perform exploratory studies to discover markers of resistance and progression (51). These correlative laboratory studies are viewed as a high priority that will allow scientists to better understand the natural history of patients treated with novel therapies.

2.0 OBJECTIVES

2.1 Primary Objective

2.1.1 To determine the immunological response based on measuring increased numbers of peptide specific CD8+ T cells as calculated by the tetramer assay.

2.1.2 To assess the safety and tolerability of the mature dendritic cell vaccine.

2.2 Secondary Objectives

2.2.1 To determine the clinical response rate using RECIST criteria

2.2.2 To determine the time to progression

2.2.3 To assess regulatory T cell depletion after cyclophosphamide administration.

2.2.4 To perform exploratory biomarker analysis of accessible tumors

2.2.5 To determine the safety and side effect profile of mDC administered to patients given after a single dose of cyclophosphamide.

3.0 ELIGIBILITY CRITERIA

Patients must fulfill the following eligibility requirements:

3.1 Inclusion Criteria

3.1.1 Unresectable stage III and stage IV M1a/M1b melanoma including patients with uveal melanoma

3.1.2 Age ≥ 18 years

3.1.3 Life expectancy ≥ 4 months

3.1.4 ECOG performance status 0-2

3.1.5 HLA-A2 positive

3.1.6 gp100 expression >6% in primary lesion or metastasis

3.1.7 At least 28 days from prior treatment (including adjuvant interferon)

3.1.8 Required initial laboratory values (submitted within 14 days prior to registration):

WBC >3,000/mm3
Hg ≥ 9.0 gm/dl
Platelets >75,000/mm3
Serum Bilirubin < 2.0 mg/dl
Serum Creatinine < 2.0 mg/dl

3.1.9 Sexually active women of childbearing potential must use effective birth control during the trial and for at least two months following the trial.

3.1.10 Men must be willing to avoid fathering a new child while receiving therapy.

3.2 Exclusion Criteria

3.2.1 Prior treatment with cytotoxic chemotherapy
3.2.2 Active untreated CNS metastasis
3.2.3 Active infection
3.2.4 Prior malignancy (except non-melanoma skin cancer) within 3 years
3.2.5 Pregnant or nursing
3.2.6 Concurrent treatment with systemic corticosteroids, however local (inhaled or topical) steroids are permitted.
3.2.7 Inability to provide adequate informed consent
3.2.8 Patients with known allergy to eggs
3.2.9 Patients with a prior history or uveitis or autoimmune inflammatory eye disease.
3.2.10 Patients who are known to be positive for hepatitis BsAg, hepatitis C antibody, or HIV antibody.

4.0 REGISTRATION

4.1 Registration: Patients may be enrolled on this study by calling the Clinical Research Associate. A total of 12 patients will be accrued over a 2 year period.

The following information must be provided:

- Patient's name, date of birth, race, ethnicity and sex
- Responsible physician
- Diagnosis and date of diagnosis
- Date Informed Consent signed

5.0 AGENT INFORMATION

5.1 Drug: Autologous dendritic cells pulsed with three melanoma peptides and a CMV (control) peptide is the vaccine. For dose #1 only, inactivated Influenza vaccine is added to the DC preparation to provide a source of class II antigen to induce CD4+ helper T cells.

5.1.1 Mechanism of Action: Induction of antigen-specific CD8+ T cells that function to cause tumor regression through multiple mechanisms including 1) direct tumor cytolysis requiring cell to cell contact; 2) secretion of cytokines such as Interferon-γ and Tumor necrosis factor. Administration of cyclophosphamide three days prior to the first immunization will deplete regulatory T cells that serve to inhibit the generation of immunity. Multiple immunizations are necessary to elicit and sustain CD8+ T cell immunity.

5.1.2 Pharmacodynamics/kinetics: Immunological monitoring is planned to assess the response to DC immunization. Regulatory T cell (Treg) counts will be assessed pre-treatment and at weekly intervals.
5.1.3 Formulation: Synthetic peptides (>95% purity) will be obtained commercially.
5.1.4 Availability: Product will be obtained by apheresis prior to start of treatment.

5.1.5 Preparation: Product will be prepared in the SCC GMP manufacturing facility using SOP and GMP grade materials.

5.1.6 Storage and Stability: Vaccine will be made starting from fresh Peripheral Bone Marrow Cells (PBMC). For each dose, PBMC will be thawed and placed in culture with GM-CSF/IL-4. For all patients receiving mDC, immature DC will be co-cultured with CD40 ligand plus Interferon-g for 24 hrs to generate mDC. Each dose will undergo sterility testing and phenotypic analysis for quality control. Each DC preparation will be pulsed with soluble peptide for 2 hr and washed prior to administration. DC preparations that fail to pass each release criteria will be held and not released for patient administration.

5.1.7 Administration: intravenously

5.1.8 Toxicities: Common: rash, fatigue, nausea. Less common: rigors/chills, cough, allergic rhinitis, skin hypopigmentation. Rare: allergic reaction/hypersensitivity.

5.2 Drug: cyclophosphamide (CTX)

5.2.1 Mechanism of Action: an alkylating agent which is biochemically inert until it is metabolized to its active components by the liver phosphamidases.

5.2.2 Pharmacodynamics/kinetics: The drug and its metabolites are excreted by the kidney after iv administration. The plasma half-life ranges from 4 to 6.5 hours.

5.2.3 Formulation: 2-[bis(2-chloroethyl)amino] tetrahydro-2H-13,2-oxazaphosphorine 2-oxide monohydrate, Molecular weight is 279.1.

5.2.4 Availafbility: commercially available and formulated as a sterile white lyophilized powder containing 75 mg mannitol per 100 mg cyclophosphamide.

5.2.5 Preparation: resuspended in sterile water for injection.

5.2.6 Storage and stability: after reconstitution, cyclophosphamide is stable at room temperature for 24 hours.

5.2.7 Adminstration: intravenously

5.2.8 Toxicities: Common: alopecia, infertility, nausea, vomiting, anorexia, diarrhea, mucositis, stomatitis, hemorrhagic cystitis, and leucopenia. Less common: headache, facial flushing, rash, nasal congestion, syndrome of inappropriate diuretic hormone release, renal tubular necrosis. Rare: CHF, hemorrhagic myocarditis, cardiac necrosis, anaphylactic reactions, dizziness, skin/nail hyperpigmentation, hypokalemia, hyperuricemia, hepatotoxicity, jaundice, neutrophilic eccrine hidradenitis, toxic epidermal necrolysis, renal tubular acidosis, interstitial pneumonitis, pulmonary fibrosis, secondary malignancy, radiation recall response.

5.2.9 Pre-Medication: All patients receiving cyclophosphamide must be premedicated with an anti-emetic. The choice of premedication will be left to discretion of the treating physician.

6.0 TREATMENT PLAN

6.1 Histologic Confirmation

6.1.1 Patients who have not had histologic documentation of metastatic disease will undergo biopsy or surgical resection as deemed clinically appropriate by the principal investigator. Expression of gp100 by immunohistochemistry is required for eligibility. If excess tumor is available, it will be saved for biomarker analysis and tissue culture. For patients with metastatic melanoma that is not accessible to biopsy, gp100 expression by the primary

lesion must be documented. Patients with gp100 negative tumors are not eligible. Tumor gp100 antigen expression greater than 6% is required.

6.1.2 Patients who have had histologic documentation of metastatic disease at an outside institution will be required to have the histopathology reviewed at BJH/Washington University.

6.2 Dendritic Cell Preparation

6.2.1 After biopsy, patients will undergo apheresis at the BJH blood bank according to standard procedures. The apheresis product will be transported to the SCC GMP laboratory (7" floor Southwest Tower). PBMC will be obtained by Ficoll-Hypaque gradient centrifugation and cryopreserved in 7.5% DMSO according to standard procedures.

6.2.2 PBMC will be resuspended in media and dispersed in TI75 culture flasks. After 2 hour at 37C, non-adherent cells will be removed by three washes with PBS. Adherent cells will then be cultured in media containing 1% autologous plasma containing GM-CSF 100 ng/ml (Berlex) and Interleukin-4 20 ng/ml (CellGenix). Fresh media containing GM-CSF and IL-4 is added every 2-3 days. On day 6, iDC will be harvested.

6.2.3 In this study, mDC will be obtained by exposure of day 6 iDC to CD40 ligand and interferon-γ for an additional 24 hours. On the day of harvest, DC will be collected, washed twice in media and resuspended at $5x10^6$/ml. An aliquot is removed for phenotyping and check viability.

6.2.4 In this study there will be four peptide antigens (G154, G209, G280, C495) administered for each vaccine dose. Peptides noted by the prefix "G" are derived from gp100 melanoma antigen with the number indicating the position of the first amino acid. C495 is the CMV derived peptide encoded by the pp65 (residues 495- 503) viral matrix protein. Each peptide antigen is pulsed separately on DC and hence, there will be 4 tubes for each vaccine dose. For the initial priming dose, patients receive 15 million DC per peptide (60 million DC total). For the remaining (booster) doses, patients receive 5 million DC per peptide (20 million DC total). Either 3 mls of DC suspension (DC#1 dose) or 1 ml of DC suspension (DC#2-6 dose) is added to each sterile tube. Peptide solution to added to each tube at a final concentration of 50 ug/ml and maintained at 37C in a shaker water bath.

6.2.5 After 2 hours, an aliquot of supernatant is removed for sterility testing. Each tube is centrifuged and resuspended in RT PBS and washed twice. The cells will be resuspended in 1 ml PBS and checked for viability. Pulsed DC from each group is then mixed together in 50 ml normal saline and 5% human serum albumin. If the DC vaccine product passes each release criteria, the product is transported to the CAM infusion center for administration.

6.3 Treg depletion

6.3.1 Patients will report to the Infusion center (Siteman Cancer Center treatment area-CAM 7" floor). CTX is given on day -3 (-72 hours prior to dose 1) to deplete circulating Treg prior to dose #1. Immediately prior to CTX administration, two CPT tubes (BD vacutainer, 8ml) are drawn for a baseline determination of Treg count. Patients will be given dolasetron 30 minutes prior to administration of CTX 300mg/m2 given intravenously in 250 ml normal saline over 60 min. Only a single dose of CTX is given to each patient. No CTX will be given to any patient after the DC dose #1.

6.4 DC vaccine administration

6.4.1 Each DC vaccine is administered over 30 minutes by intravenous infusion through either a peripheral venous line or a central venous line. Patients will be observed for 2 hours after the first dose and vital signs recorded every 30 minutes beginning at the start of the infusion. For

each dose thereafter, patients will be observed in the treatment area for 30 minutes after the infusion. If patients develop temperature greater than 38 degrees centigrade, acetaminophen 650mg po should be given and the PI notified the same day. After the observation period, patients may be discharged to home from the treatment area.

6.5 Immune Monitoring

6.5.1 Starting on day 0 and weekly thereafter until day 64, two CPT tubes (BD vacutainer CPT tube, 8 ml) is obtained by venipuncture for immune monitoring. After day 64, peripheral blood is collected every 3 weeks until day 190 for immune monitoring. If patients continue on the maintenance dosing, patients will continue to have immune monitoring every 4 weeks. These blood samples will be used for tetramer assay and determination of Treg cell counts. The blood samples will be transported to the PI's laboratory (located in Southwest Tower Room 632) within two hours (notify Michelle Becker-Hapak at 362-9406 or John Steel, RN at 747-2125).

6.5.2 Apheresis is obtained for each patient after the third vaccine dose and after the sixth vaccine dose. Patients will undergo apheresis at the BJH blood bank according to standard procedures to collect lymphocytes for functional laboratory assays to determine immunity against the melanoma peptides.

6.6 Assessment of Clinical Response

6.6.1 Patients will undergo routine clinical monitoring and follow up with blood work (in addition to immune monitoring) and physical examination performed by the investigators every three weeks while on study. The RECIST criteria [56] will be used for tumor response assessment after three and six vaccine doses (18 weeks of treatment). CT of the chest, abdomen, and pelvis is the preferred imaging modality for assessment. In certain instances, MRI scan is acceptable. For cutaneous lesions, direct measurement is also acceptable and visible lesions should be photographed.

6.6.2 Immune monitoring will be performed as outlined in section 6.5

6.6.3 Patients deemed to have a clinical response (partial response/complete response) after six DC immunizations will be eligible to receive further treatment. Eligible patients will receive maintenance DC vaccinations every 2 months. Patients will undergo clinical follow up every 4 weeks with physical examination and blood work (CBC, CMP, LDH). Restaging evaluations will be performed every 8 weeks for tumor response assessment. Patients will continue to receive treatment until there is evidence of disease progression.

6.6.4 Patients will be followed until disease progression according to the maintenance schedule.

7.0 POTENTIAL TOXICITY AND DOSE MODIFICATIONS

Life-threatening or any Unexpected Toxicities: Any toxicities of grade 2 or higher should be reported immediately to the Principal Investigator and to the Cancer Center Clinical Trials Office as indicated in Section 11.0. No subsequent treatment course is to begin until all toxicities greater or equal to Grade 2 have abated.

Treatment delays of up to 21 days will be allowed; however, if administration of the next planned dose is delayed greater than 21 days, the patient will discontinue the study vaccine and will not be eligible to receive additional treatment on this protocol. Treatment delays should be to be kept to a minimum and every effort is to he made to maintain a planned schedule.

7.1 Allergic Reactions: none expected

7.2 Hematological Toxicity: none expected

7.3 Cardiovascular Toxicity: none expected

7.4 Cutaneous Toxicity: rash

7.5 Gastrointestinal/Hepatic Toxicity: none expected

7.6 Neurologic Toxicity: none expected

7.7 Renal Toxicity: none expected

7.8 Respiratory Toxicity: none expected

7.9 Other Toxicities: fatigue, chills, fever

7.10 Dose Limiting Toxicity is defined as:

- Any Grade 3 or greater hematological and non hematological toxicities
- Any Grade 3 or greater allergic reaction
- Any Grade 3 or greater autoimmunity that involves vital organ (heart, kidneys, brain, eye, liver, colon and adrenal gland).

8.0 STUDY CALENDAR AND DATA SUBMISSION

8.1 Pre-Treatment and Treatment: All laboratory work must be completed within 14 days prior to treatment. Any x-ray, scan of any type or ultrasound, which is utilized for tumor measurement per protocol, must be completed within 30 days prior to registration.

Tests and Observations	Pre-Treatment	Prior to each DC dose (every 3 weeks)	After 3rd and 6th DC dose	Maintenance[g]		Follow-up[h]
				4 wks	8 wks	
Signed informed consent	X					
Biopsy/pathology	X[a]		X[b]			X[b]
History & Physical	X	X		X		X
Apheresis	X[c]		Xd			
Tumor Measurements (CT scans)	X		X		X	X
CBC, CMP, LDH	X	X		X		X
PT/PTT	X					
Immune monitoring[e]	X	X	X	X		
Pregnancy test	X[f]					

a. gp100 expression must be confirmed.
b. Optional biopsy for biomarker analysis.
c. To obtain mononuclear cells for DC generation obtained 7-28 days prior to the start of treatment.
d. To obtain mononuclear cells for immune monitoring obtained no sooner than 7 days after the 3rd or 6th dose.
e. Immune monitoring studies will be drawn in CPT (BD vacutainer tube) or green top tube. Starting on day 0, two tubes will be drawn weekly until day 64. Thereafter, two tubes will be drawn every 21 days until day 190. For patients receiving maintenance treatment, blood is drawn every two months. Contact person is Michelle Becker-Hapak (phone 314-362-9406).
f. Non-pregnant status will be determined in all women of childbearing potential.
g. For patients that continue to receive the vaccine past the 6th dose.
h. Patients will have a physical exam and standard bloodwork at 30 days post their last DC dose. Patients who are removed from therapy for reasons other than progressive disease will be followed according to standard of care procedures until disease progression.

8.2 Data Submission Schedule:

Form	**Submission Schedule**
Original Consent Form	Prior to starting treatment
Eligibility Checklist/patient registration	Within 2 weeks of registration
Medical/Surgical History Prior Treatment On study Physical On study Hematology On study Chemistry On study Radiology	Within 4 weeks of registration
Treatment Form Treatment Physical Exam Treatment Hematology Treatment Chemistry Toxicity Form Immune Monitoring Form	Q cycle
Treatment Summary	EOS
Tumor Measurement Form	Pre and post study
Concomitant Medications	Pre-study and as needed
Apheresis Form	7 days post apheresis
Follow up Form	1 and 6 months post treatment
SAE Reporting Form	Within 7 days of notification event

9.0 CRITERIA FOR RESPONSE (RECIST Criteria)

9.1 Tumor measurement

9.1.1 Measurable disease: the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

9.1.2 Measurable lesions: lesions that can be accurately measured in at least one dimension with the longest diameter ≥2.0 cm. With a spiral CT scan, the lesion must be ≥1.0 cm in at least one dimension.

9.1.3 Non-measurable lesions: all other lesions, including small lesions (longest diameter < 2.0 cm with conventional techniques or <1.0 cm with spiral CT scans) and other non-measurable lesions. These include: bone lesions; leptomeningeal disease; ascites; pleural/pericardial effusion; inflammatory breast disease; lymphangitis cutis/pulmonis; abdominal masses that are not confirmed and followed by imaging techniques; and cystic lesions.

9.1.4 All measurements should be recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

9.1.5 The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

9.1.6 Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules, palpable lymph nodes). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesions is recommended.

9.2 Baseline documentation of target and non-target lesions

9.2.1 All measurable lesions up to a maximum of 10 lesions representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

9.2.2 Target lesions should be selected on the basis of their size (lesions with the longer diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically).

9.2.3 A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

9.2.4 All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present" or "absent."

9.3 Response Criteria

9.3.1 Evaluation of target lesions

9.3.1.1 Complete response (CR)–disappearance of all target lesions.

9.3.1.2 Partial response (PR)–at least a 30% decrease in the sum of the LD of the target lesions taking as reference the baseline sum LD.

9.3.1.3 Progression (PD)–at least a 20% increase in the sum of the LD of the target lesions taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.

9.3.1.4 Stable disease (SD)–neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD since the treatment started.

9.3.2 Evaluation of non-target lesions

9.3.2.1 Complete response (CR)–disappearance of all non-target lesions and normalization of tumor marker level.

9.3.2.2 Non-complete response (non-CR)/non-progression (non-PD)–persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.

9.3.2.3 Progressive disease (PD)–appearance of one or more new lesions. Unequivocal progression of existing non-target lesions. Although a clear progression of non-target lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by a review panel (or principal investigator).

9.4 Evaluation of best overall response

9.4.1 The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

9.4.2 Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

9.4.3 In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

9.5 Confirmation

9.5.1 To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat studies that should be performed no less than 4 weeks after the criteria for response are first met.

9.5.2 In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6-8 weeks.

10.0 REMOVAL OF PATIENTS FROM PROTOCOL THERAPY

Patients can be removed from Protocol Therapy for any of the following reasons:

- Patient withdraws consent and refuses to continue participation in the study
- The PI decides to remove the patient from the study (i.e. for non-compliance with the protocol or rapid clinical progression requiring urgent therapeutic intervention.
- The Siteman Cancer Center decides to close the study
- Patients who develop DLT
- Patients who develop an allergic reaction to investigational product will be removed from the study, and discontinue therapy.

11.0 SERIOUS ADVERSE EVENT REPORTING

Investigators are required to notify the Principal Investigator and the Siteman Cancer Center Clinical Trials Office of any serious adverse event (SAE). The investigator is also required to notify the Quality Assurance and Safety Monitoring Committee (QASM), and the Human Research Protection Office (HRPO) of any SAE.

11.1 Reporting Requirements for Adverse Events

11.1.1 Unexpected Toxicities:

Report of event must be made within 7 days for:

1. Death within 30 days of treatment regardless of cause.
2. Any unexpected or life-threatening event not mentioned in the consent form, drug brochure, or investigational drug data form, or an event which is more severe or frequent than described in the investigator's brochure (e.g. liver failure should be reported even if investigator brochure refers to elevated liver enzymes).
3. Any unexpected or life-threatening event resulting in discontinuation of treatment, even if potentially expected.
4. Any hospitalization or prolongation of existing hospitalization unless "preplanned" (e.g. all admissions for fever, neutropenia, dehydration, etc. must be reported regardless of whether they were expected. Admissions for scheduled chemotherapy or elective surgery do not need to be reported).
5. Any persistent or permanent physical or psychological disability.
6. Breach of confidentiality.
7. Second malignancy in participant or congenital anomaly in offspring of research subject who had taken a study drug. These must reported regardless of length of time between treatment completion and event occurrence.

11.1.2 Expected Toxicities:

a. Death on Study – regardless of cause: Telephone Report and Written Report
b. Grade 4 toxicities excluding myelosuppression and aplasia: Written Report
c. Grade 4 myelosuppression or aplasia: Report only as part of regular data submission
d. All other expected toxicities, grades 1-3: Report only as part of regular data submission.

11.2 Types of Report

11.2.1 Telephone Report

The PI should be notified within 24 hours of knowledge of the event at (314) 362-5677.

11.2.2 Written Report

Written report (MedWatch) should be sent to QASM and HSC within 7 working days.

To download the most current Medwatch form go to the following website: http://www.fda.gov/medwatch/safety/FDA-3500_fillable.pdf

You will need to complete the 3500 (voluntary reporting form), you can fill this out online and save it, or download the form first and then fill it in.

An attribution (not related, unlikely, possibly, probably, or definitely related) should be stated in section B.5 of the MedWatch form.

Once your have completed the form & the PI has signed it, Fax this form and attachments to 1-800-FDA-0178.

12.0 DATA AND SAFETY MONITORING

The principal investigator will review all patient data at least every six months, and provide a semi-annual report to the QASM Committee. This report will include:

1) the protocol title, IRB protocol number, and the activation date of the study.
2) the number of patients enrolled to date
3) the date of first and most recent patient enrollment
4) a summary of all adverse events regardless of grade and attribution
5) a response evaluation for evaluable patients, if applicable to the study.
6) a summary of any recent literature that may affect the ethics of the study.

The study principal investigator and study coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or study coordinator becomes aware of a serious adverse event, the SAE will be reported to the HRPO and QASM Committee within 15 working days.

13.0 STATISTICAL CONSIDERATIONS

Approximately 12 patients will be enrolled in this study over 2 years.

The primary end point of the study is to determine the post-vaccine immune response based on measuring increased numbers of peptide-specific CD8 T cells as calculated by the tetramer assay. For each peptide, the tetramer assay is performed on blood samples obtained at the indicated time points. In this clinical trial, a total of 18 time points are obtained. These 18 time points include 3 pre-treatment measurements, 9 weekly measurements (day 7 to day 64) and 6 additional measurements

obtained every 3 weeks (day 85 to day 190). Additional time points are collected for patients that receive maintenance therapy as defined by the protocol. Data are presented as the percentage of CD8+ T cells positive for tetramer binding based on gating variables set using the iMASC reagent kit (Beckman Coulter). The lower limit of detection (LLD) is 0.03% based on the acquisition of 100,000 gated events in the lin-CD8+ gate. The HIV gag HLA-A*0201 restricted peptide (SLYNTVATL) is used as the non-binding control peptide. Each sample is stained with the HIV gag tetramer and the number of HIV gag positive CD8+ T cells is subtracted from each experimental point (ref 24). The mean + 3SD at baseline (n=3 samples) is obtained for each patient. Based on our

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2. Surname (Last Name): Carreno
3. Effective Date (07-August-2008): 12-April-2013

4. Are you the corresponding author? ☑ Yes ☐ No

5. Manuscript Title: IL-12p70 Producing Patient DC Vaccine Elicits Tc1 Polarized T cells

6. Manuscript Identifying Number (if you know it): 68395-RG-RV-2

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						ADD
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3. Effective Date (07-August-2008): 15-April-2013

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Beatriz Carreno

5. Manuscript Title: IL-12p70 Producing Patient DC Vaccine Elicits Tc1 Polarized T cells

6. Manuscript Identifying Number (if you know it): 68395-RG-RV-2

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Corresponding Author's Name: Beatriz Carreno

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Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
8. Patents (planned, pending or issued)	☑	☐	☐			ADD ×
9. Royalties	☑	☐	☐			ADD ×
10. Payment for development of educational presentations	☑	☐	☐			ADD ×
11. Stock/stock options	☑	☐	☐			ADD ×
12. Travel/accommodations/ meeting expenses unrelated to activities listed**	☑	☐	☐			ADD ×
13. Other (err on the side of full disclosure)	☑	☐	☐			ADD ×

* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

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ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Megan
2. Surname (Last Name): Chan
3. Effective Date (07-August-2008): 15-April-2013

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Beatriz Carreno

5. Manuscript Title: IL-12p70 Producing Patient DC Vaccine Elicits Tc1 Polarized T cells

6. Manuscript Identifying Number (if you know it): 68395-RG-RV-2

Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

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The Work Under Consideration for Publication

Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
1. Grant	☑	☐	☐			X ADD
2. Consulting fee or honorarium	☑	☐	☐			X ADD
3. Support for travel to meetings for the study or other purposes	☑	☐	☐			X ADD
4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	☑	☐	☐			X ADD
5. Payment for writing or reviewing the manuscript	☑	☐	☐			X ADD
6. Provision of writing assistance, medicines, equipment, or administrative support	☑	☐	☐			X

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Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
						ADD
7. Other	☑	☐	☐			X
						ADD

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1. Board membership	☑	☐	☐			X
						ADD
2. Consultancy	☑	☐	☐			X
						ADD
3. Employment	☑	☐	☐			X
						ADD
4. Expert testimony	☑	☐	☐			X
						ADD
5. Grants/grants pending	☑	☐	☐			X
						ADD
6. Payment for lectures including service on speakers bureaus	☑	☐	☐			X
						ADD
7. Payment for manuscript preparation	☑	☐	☐			X

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8. Patents (planned, pending or issued)	☑	☐	☐			ADD ×
9. Royalties	☑	☐	☐			ADD ×
10. Payment for development of educational presentations	☑	☐	☐			ADD ×
11. Stock/stock options	☑	☐	☐			ADD ×
12. Travel/accommodations/ meeting expenses unrelated to activities listed**	☑	☐	☐			ADD ×
13. Other (err on the side of full disclosure)	☑	☐	☐			ADD ×

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ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Amer
2. Surname (Last Name): Alyasiry
3. Effective Date (07-August-2008): 07-August-2008

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Beatriz Carreno

5. Manuscript Title: IL-12p70 Producing Patient DC Vaccine Elicits Tc1 Polarized T cells

6. Manuscript Identifying Number (if you know it):

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4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	☑	☐	☐			X ADD
5. Payment for writing or reviewing the manuscript	☑	☐	☐			X ADD
6. Provision of writing assistance, medicines, equipment, or administrative support	☑	☐	☐			X

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7. Other	☑	☐	☐			X
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1. Board membership	☑	☐	☐			X
						ADD
2. Consultancy	☑	☐	☐			X
						ADD
3. Employment	☑	☐	☐			X
						ADD
4. Expert testimony	☑	☐	☐			X
						ADD
5. Grants/grants pending	☑	☐	☐			X
						ADD
6. Payment for lectures including service on speakers bureaus	☑	☐	☐			X
						ADD
7. Payment for manuscript preparation	☑	☐	☐			X

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8. Patents (planned, pending or issued)	☑	☐	☐			ADD / X
9. Royalties	☑	☐	☐			ADD / X
10. Payment for development of educational presentations	☑	☐	☐			ADD / X
11. Stock/stock options	☑	☐	☐			ADD / X
12. Travel/accommodations/ meeting expenses unrelated to activities listed**	☑	☐	☐			ADD / X
13. Other (err on the side of full disclosure)	☑	☐	☐			ADD / X

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Wen-Rong
2. Surname (Last Name): Lie
3. Effective Date (07-August-2008): 12-April-2013

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Beatriz M Carreno

5. Manuscript Title: IL-12p70 Producing Patient DC Vaccine Elicits Tc1 Polarized T cells

6. Manuscript Identifying Number (if you know it): 68395-RG-RV-2

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1. Grant	☑	☐	☐			X ADD
2. Consulting fee or honorarium	☑	☐	☐			X ADD
3. Support for travel to meetings for the study or other purposes	☑	☐	☐			X ADD
4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	☑	☐	☐			X ADD
5. Payment for writing or reviewing the manuscript	☑	☐	☐			X ADD
6. Provision of writing assistance, medicines, equipment, or administrative support	☑	☐	☐			X

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1. Board membership	☑	☐	☐			X / ADD
2. Consultancy	☑	☐	☐			X / ADD
3. Employment	☐	☑	☐	EMD Millipore Employee		X / ADD
4. Expert testimony	☑	☐	☐			X / ADD
5. Grants/grants pending	☑	☐	☐			X / ADD
6. Payment for lectures including service on speakers bureaus	☑	☐	☐			X / ADD
7. Payment for manuscript preparation	☑	☐	☐			X

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8. Patents (planned, pending or issued)	☑	☐	☐			ADD ×
9. Royalties	☑	☐	☐			ADD ×
10. Payment for development of educational presentations	☑	☐	☐			ADD ×
11. Stock/stock options	☑	☐	☐			ADD ×
12. Travel/accommodations/ meeting expenses unrelated to activities listed**	☑	☐	☐			ADD ×
13. Other (err on the side of full disclosure)	☑	☐	☐			ADD ×

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Rebecca
2. Surname (Last Name): Aft
3. Effective Date (07-August-2008): 12-April-2013

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Beatriz Carreno

5. Manuscript Title: IL-12p70 Producing Patient DC Vaccine Elicits Tc1 Polarized T cells

6. Manuscript Identifying Number (if you know it): reference 68395-RG-RV-2

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2. Consulting fee or honorarium	☑	☐	☐			X ADD
3. Support for travel to meetings for the study or other purposes	☑	☐	☐			X ADD
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5. Payment for writing or reviewing the manuscript	☑	☐	☐			X ADD
6. Provision of writing assistance, medicines, equipment, or administrative support	☑	☐	☐			X

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1. Board membership	☑	☐	☐			X
						ADD
2. Consultancy	☑	☐	☐			X
						ADD
3. Employment	☑	☐	☐			X
						ADD
4. Expert testimony	☑	☐	☐			X
						ADD
5. Grants/grants pending	☑	☐	☐			X
						ADD
6. Payment for lectures including service on speakers bureaus	☑	☐	☐			X
						ADD
7. Payment for manuscript preparation	☑	☐	☐			X

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8. Patents (planned, pending or issued)	☑	☐	☐			ADD ×
9. Royalties	☑	☐	☐			ADD ×
10. Payment for development of educational presentations	☑	☐	☐			ADD ×
11. Stock/stock options	☑	☐	☐			ADD ×
12. Travel/accommodations/ meeting expenses unrelated to activities listed**	☑	☐	☐			ADD ×
13. Other (err on the side of full disclosure)	☑	☐	☐			ADD ×

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Lynn
2. Surname (Last Name): Cornelius
3. Effective Date (07-August-2008): 15-April-2013

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Beatriz Carreno

5. Manuscript Title: L-12p70 Producing Patient DC Vaccine Elicits Tc1 Polarized T cells

6. Manuscript Identifying Number (if you know it): 68395-RG-RV-2

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						ADD
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						ADD
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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Kathryn
2. Surname (Last Name): Trinkaus
3. Effective Date (07-August-2008): 12-April-2013

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Dr. Beatriz Carreno

5. Manuscript Title: IL-12p70 Producing Patient DC Vaccine Elicits Tc1 Polarized T cells

6. Manuscript Identifying Number (if you know it): 68395-RG-RV-2

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1. Board membership	☑	☐	☐			X / ADD
2. Consultancy	☑	☐	☐			X / ADD
3. Employment	☑	☐	☐			X / ADD
4. Expert testimony	☑	☐	☐			X / ADD
5. Grants/grants pending	☑	☐	☐			X / ADD
6. Payment for lectures including service on speakers bureaus	☑	☐	☐			X / ADD
7. Payment for manuscript preparation	☑	☐	☐			X

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Relevant financial activities outside the submitted work

Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
8. Patents (planned, pending or issued)	☑	☐	☐			ADD ×
9. Royalties	☑	☐	☐			ADD ×
10. Payment for development of educational presentations	☑	☐	☐			ADD ×
11. Stock/stock options	☑	☐	☐			ADD ×
12. Travel/accommodations/ meeting expenses unrelated to activities listed**	☑	☐	☐			ADD ×
13. Other (err on the side of full disclosure)	☑	☐	☐			ADD ×

* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Section 4. Other relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☑ No other relationships/conditions/circumstances that present a potential conflict of interest

☐ Yes, the following relationships/conditions/circumstances are present (explain below):

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

Hide All Table Rows Checked 'No' SAVE

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Evaluation and Feedback

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Section 1. Identifying Information

1. Given Name (First Name): Gerald
2. Surname (Last Name): Linette
3. Effective Date (07-August-2008): 22-April-2013

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Beatriz M. Carreno

5. Manuscript Title: IL-12p70 Producing Patient DC Vaccine Elicits Tc1 Polarized T cells

6. Manuscript Identifying Number (if you know it): 68395-RG-RV-2

Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

The Work Under Consideration for Publication

Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
1. Grant	☐	☐	☑	Barnes-Jewish Hospital Foundation		X ADD
2. Consulting fee or honorarium	☑	☐	☐			X ADD
3. Support for travel to meetings for the study or other purposes	☑	☐	☐			X ADD
4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	☑	☐	☐			X ADD
5. Payment for writing or reviewing the manuscript	☑	☐	☐			X ADD

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The Work Under Consideration for Publication

Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
6. Provision of writing assistance, medicines, equipment, or administrative support	☑	☐	☐			X ADD
7. Other	☑	☐	☐			X ADD

* This means money that your institution received for your efforts on this study.
** Use this section to provide any needed explanation.

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

Relevant financial activities outside the submitted work

Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
1. Board membership	☑	☐	☐			X ADD
2. Consultancy	☐	☑	☐	Genentech		X
2. Consultancy	☐	☑	☐	BMS		X
2. Consultancy	☐	☑	☐	GSK		X ADD
3. Employment	☑	☐	☐			X ADD
4. Expert testimony	☑	☐	☐			X ADD
5. Grants/grants pending	☑	☐	☐			X ADD

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Relevant financial activities outside the submitted work

Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
6. Payment for lectures including service on speakers bureaus	☐	☑	☐	Genentech		×
						ADD
7. Payment for manuscript preparation	☑	☐	☐			×
						ADD
8. Patents (planned, pending or issued)	☑	☐	☐			×
						ADD
9. Royalties	☑	☐	☐			×
						ADD
10. Payment for development of educational presentations	☑	☐	☐			×
						ADD
11. Stock/stock options	☑	☐	☐			×
						ADD
12. Travel/accommodations/ meeting expenses unrelated to activities listed**	☑	☐	☐			×
						ADD
13. Other (err on the side of full disclosure)	☑	☐	☐			×
						ADD

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