SUPPLEMENTAL MATERIALS AND METHODS

Generation of GM-K562 cells

K562 cells were purchased from the American Type Culture Collection (ATCC, Manssas, VA) (Cat. No. CCL-243) and grown in RPMI-1640 medium (Life Technologies, Carlsbad, CA) supplemented with 10% heat-inactivated fetal bovine serum (FBS). GM-CSF-secreting K562 cells (GM-K562) were generated in the Vector Core Laboratory of the Harvard Gene Therapy Initiative (HGTI) by co-transfecting the parental cell line with 3.8 μg of a human GM-CSF expression vector (pUMD.hGMCSFa) and 2 μg of a puromycin selection plasmid (pJ6Omega-puro). pUMD.hGMCSFa was constructed by subcloning pMD.hGMCSF into pUC to remove the SV40 origin and sequence junctions. Transfected cells were selected with 2 μg/ml puromycin and cloned by limiting dilution. Individual clones were expanded and screened for GM-CSF secretion using a human GM-CSF ELISA kit (Thermo Scientific, Rockford, IL). The highest expressing clone was subjected to a second round of limiting dilution in puromycin-containing medium, the highest expressing subclone was chosen for manufacture of a master cell bank and clinical production lots at the HGTI Gene Vector Laboratory under cGMP conditions. The GM-K562 clinical lot secreted 13 μg GM-CSF/10^6 cells/24 hours.

Clinical factor analysis

Metaphase karyotype analysis and fluorescence *in situ* hybridization for the most common CLL abnormalities was performed on bone marrow aspirates or peripheral blood (Cytogenetics Laboratory, Brigham & Women's Hospital, Boston, MA), as described previously (1). For analysis of *IGHV* hypermutation status, the clonotypic IgH

sequence of study subjects was identified using a panel of VH-specific PCR primers, as previously described (2). Sequences were aligned to the closest *IGHV* germline gene sequence in the IMGT/GENE-DB database (3). 'Mutated' and 'unmutated' CLL cases were distinguished based on a 98% homology cutoff. ZAP70 expression in leukemia samples was analyzed by staining cells at 4˚C for 20 min with CD19- and CD3-specific mAbs. Cells were then fixed and permeabilized with Cytofix/CytoPerm solution (BD Bioscience, Franklin Lakes, NJ) and incubated with Alex488-conjugated anti-ZAP-70 mAb (clone 1E7.2; BD Biosciences) for 45 minutes at 4˚C. A ZAP-70 level above 20% within the CD19+ cell population was defined as positive (4). Data were collected on a Beckman Coulter FC500 flow cytometer (Brea, CA) and analyzed using the FlowJo (Tree Star, Inc.) software.

Chimerism analysis

The extent of overall donor engraftment in PBMC and CD3+ T cells isolated by immunomagnetic bead selection (Miltenyi, Auburn, CA) was determined by quantitative PCR analysis of informative polymorphic regions in genomic DNA (Tissue Typing Laboratory, Brigham & Women's Hospital, Boston, MA).

Immunophenotyping

Erythrocytes in freshly drawn blood samples were lysed using a TQ-Prep workstation and ImmunoPrep reagents (Beckman Coulter, Brea, CA). Blood cells were subsequently stained using monoclonal antibodies (mAb) specific for: CD3, CD8, CD4, CD45, CD45RO, CD25, CD127, and CD28 (all from Beckman Coulter), CCR7 (R&D Systems

(Minneapolis, MN), and CD57 (Abcam; Cambridge, UK) at 4˚C for 20 minutes in the dark. Data were collected on a Beckman Coulter FC500 flow cytometer (Brea, CA) and analyzed using the CXP (Beckman Coulter) software.

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3. Lefranc MP. IMGT databases, web resources and tools for immunoglobulin and T cell receptor sequence analysis, http://imgt.cines.fr. *Leukemia*. 2003;17(1):260-266.
4. Rassenti LZ, Huynh L, Toy TL, Chen L, Keating MJ, Gribben JG, Neuberg DS, Flinn IW, Rai KR, Byrd JC, et al. ZAP-70 compared with immunoglobulin heavy-chain gene mutation status as a predictor of disease progression in chronic lymphocytic leukemia. *N Engl J Med*. 2004;351(9):893-901.

SUPPLEMENTAL TABLES AND FIGURES

Suppl. Table 1. Presenting features and clinical outcome of the 22 study subjects. BM, bone marrow; CR, complete remission; DOD, died of disease; F, female; IF, induction failure; *IGHV*, immunoglobulin heavy chain variable region; LN, lymph node; M, male; MRD, matched-related donor; mut, mutated; n/a, not available; N/A, not applicable; NED, no evidence of disease; PB, peripheral blood; PR, partial remission; SD, stable disease; UNK, unknown; unmut, unmutated; URD, matched-unrelated donor

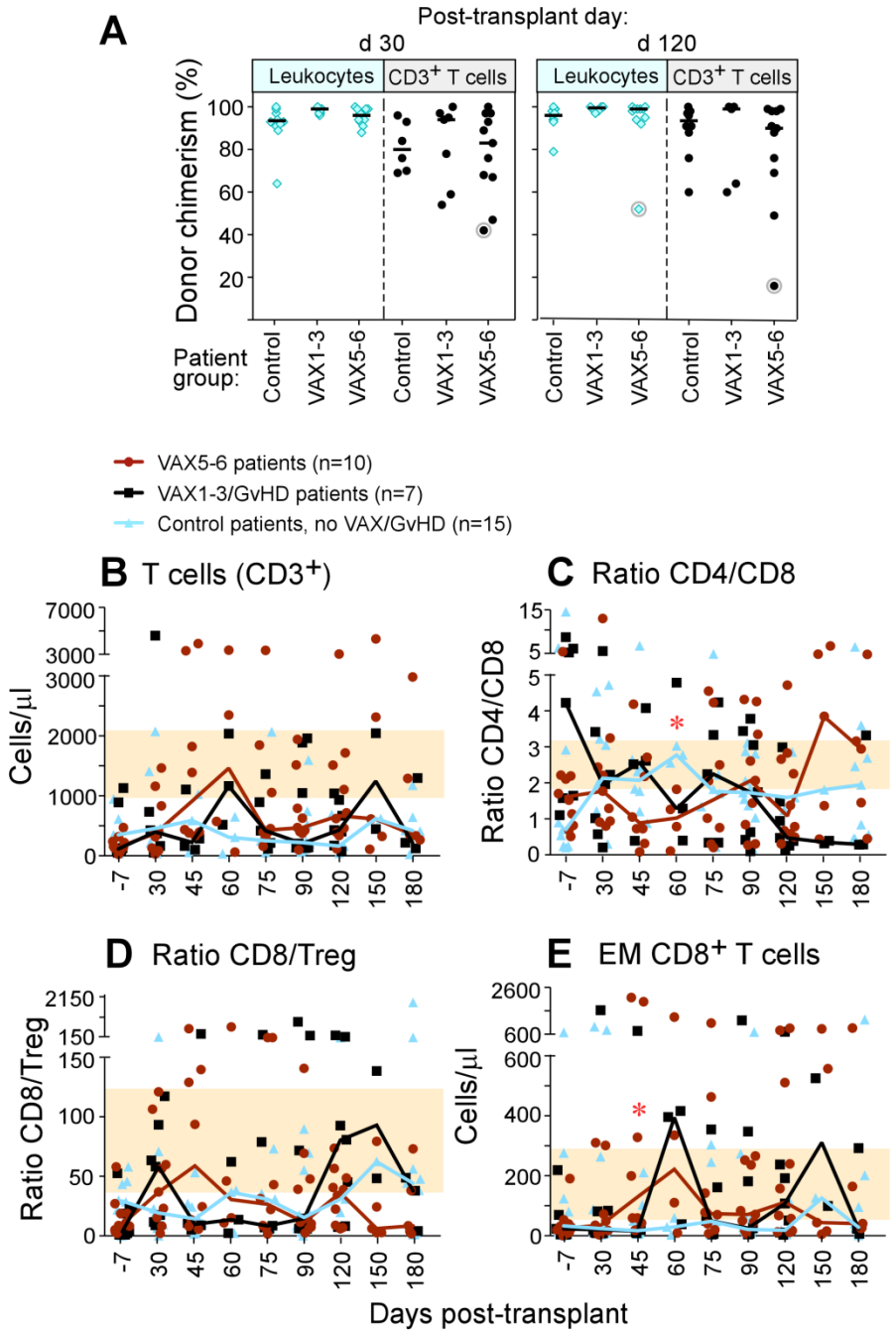
Patient ID	Age (Sex) at HSCT	Donor source	# Prior Therapies	% Marrow involvement at HSCT	ZAP-70	*IGHV* Mutation Status	Cytogenetics	# (Source) of Vaccines	Clinical disease status at HSCT	Clinical disease status at 6 months post-transplant	Days to aGVHD onset	Days to cGVHD onset	Time to relapse (months)	Follow-up time (years)	Clincial status at follow-up
VAX5-6															
1	41 (M)	MRD	2	<5	Positive	unmut	11q-, 13q-	6 (LN)	PR	CR	N/A	N/A	N/A	3	CR
2	46 (M)	URD	7	10	Negative	n/a	11q-	6 (PB)	PR	PR	N/A	157	N/A	2	died, unknown cause
3	41 (M)	MRD	3	<5	Positive	unmut	17p-, 14q-	5 (PB)	PR	CR	188	209	N/A	1	CR
4	68 (F)	URD	6	<5	Negative	unmut	17p-, 13q-	6 (PB)	PR	CR	N/A	393	N/A	3	CR
5	40 (M)	URD	2	<5	Positive	unmut	13q-	5 (PB)	PR	CR	N/A	N/A	N/A	4	CR
6	68 (M)	URD	5	<5	Positive	unmut	13q-	6 (PB)	CR	CR	N/A	208	N/A	3	CR
7	65 (M)	MRD	3	60	Positive	mut	+12	6 (PB)	PR	PR	N/A	N/A	9	1	2nd malignancy
8	70 (F)	URD	9	10	Positive	mut	17p-, +12 , 13q-, 11q-	6 (BM)	PR	Relapse	N/A	N/A	4	1	DOD
9	39 (F)	URD	3	<5	Negative	mut	17p-	6 (PB)	CR	CR	33	N/A	N/A	2	CR
10	49 (M)	MRD	3	10	Positive	unmut	11q-, 13q-	6 (LN)	IF	CR	N/A	302	N/A	3	CR
11	63 (M)	URD	3	80	Positive	unmut	17p-	6 (BM)	PR	PR	N/A	371	15	1	DOD
Median	49		3					6				255.5		2	
(Range)	(39-70)		(2-9)					(5-6)				(157-393)		(1-4)	
VAX1-3/GvHD															
12	63 (M)	URD	3	80	Positive	unmut	11q-, 13q-	3 (PB)	PR	PR	49	756	N/A	3	CR
13	49 (M)	URD	3	10	Positive	unmut	11q-	2 (BM)	IF	SD	52	N/A	N/A	1.5	SD
14	50 (M)	URD	5	<5	Positive	unmut	11q-, 13q-	1 (LN)	PR	CR	41	545	N/A	3	CR
15	58 (M)	URD	5	70	Positive	unmut	11q-, 13q-	1 (PB)	PR	PR	36	223	N/A	3	CR
16	46 (M)	MRD	4	30	Negative	unmut	11q-, 13q-	2 (PB)	PR	PR	56	326	N/A	1	CR
17	60 (M)	URD	11	<5	Positive	mut	13q-	1 (PB)	PR	CR	59	493	N/A	2	CR
18	52 (M)	MRD	8	<5	Positive	unmut	17p-, 13q-, 11q-, 7q-	1 (LN)	PR	CR	47	173	N/A	3	CR
Median	52		5					1			49	409.5		3	
(Range)	(46-63)		(3-11)					(1-3)			(36-56)	(173-756)		(1-3)	
VAX0/GvHD															
19	48 (F)	MRD	2	80	Negative	mut	11q-, 13q-	0 (PB)	PR	CR	56	N/A	N/A	3	CR
20	52 (M)	URD	2	50	Positive	unmut	17p-, 11q-, +12	0 (BM)	PR	CR	26	399	N/A	1	died, severe GvHD
21	61 (M)	URD	3	10	Positive	unmut	17p-, 13q-	0 (BM)	PR	CR	42	196	N/A	4	CR
22	54 (F)	URD	4	40	n/a	mut	17p-, 11q-, 13q-	0 (BM)	PR	CR	27	N/A	N/A	1	CR
Median	53		2.5					0			34.5	298.5		2	
(Range)	(48-61)		(2-4)								(26-55)	(198-399)		(1-4)	

Suppl. Table 2. Vaccine site skin reactions. Number of study subjects with skin reactions (mild erythema/warmth/induration/swelling) in response to each vaccine dose is depicted. #, skin reaction is unknown for one patient at this time point

Vaccine dose	**Skin reaction in response to vaccination** Number of cases/vaccinated patients (%)
1	11/18 (61)
2	9/13 (69)[#]
3	7/12 (58)
4	7/11 (64)
5	9/11 (82)
6	6/9 (67)

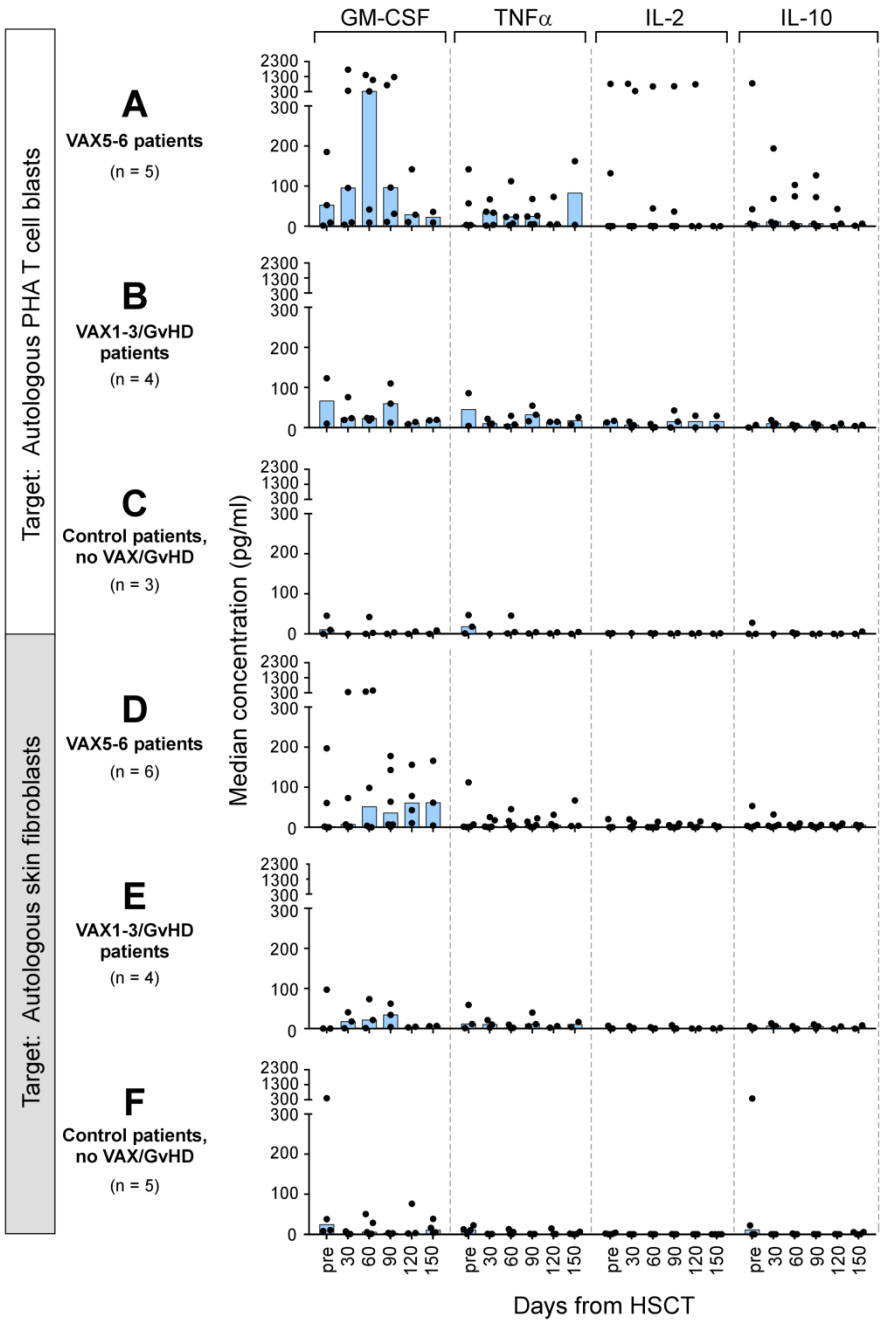
Suppl. Table 3. Observed toxicities with attribution to CLL/GM-K562 cell vaccination. Toxicity grade 3 – severe; grade 4 – life threatening

Patient ID	Post-transplant day at toxicity initiation	Toxicity	Grade	Attribution
3	67	Neutrophils	4	Possible
	87	Leukocytes	3	Possible
4	62	Platelets	3	Possible
10	108	Rash/Desquamation	3	Possible
16	102	Platelets	3	Unlikely
	102	Leukocytes	3	Unlikely
	111	Neutrophils	3	Unlikely



Suppl. Figure 1. Reconstitution of total CD3+ T cells and T cell subpopulations in study subjects receiving early post-transplant CLL/GM-K562 vaccination and patient controls. (**A**) Percentage of donor leukocyte and CD3+ T cell engraftment at post-transplant days 30 and 120 in study subjects in VAX5-6 (n=10), VAX1-3/GvHD (n=7) and control patients that neither received CLL/GM-K562 vaccines nor developed GvHD within the 100 days following RIC allo-HSCT for advanced CLL (n=15). Grey

circles refer to data points from Pt 8 who exhibited disease relapse 4 months following transplant. Horizontal bars indicate median value. (**B-E**) Flow cytometric analysis of T cell populations in serial pre- and post-HSCT peripheral blood samples obtained from the same VAX5-6, VAX1-3/GvHD and control patients. The median and individual values are displayed. The shaded areas represent the interquartile range obtained for peripheral blood samples from healthy subjects (n=20). *, $p<0.05$ (two-sided Wilcoxon rank-sum test) (**B**) Recovery of the absolute T cell (CD3+) counts; (**C**) the ratio of total CD4 to CD8 T cells (VAX5-6 vs. control at day 60: $P=0.052$); (**D**) the ratio of CD8 T cells to regulatory T cells (CD4+CD25+CD127-) and (**E**) the absolute number of effector memory T cells (CD45RO+CCR7-/CD62L-) (VAX5-6 vs. control at day 45: $P=0.041$) between post-transplant days 30 and 180 is shown.



Suppl. Figure 2. Effector cytokine secretion by CD8+ T cell populations in response to alloantigen-expressing target cells. (**A**) The median concentration of GM-CSF, TNFα, IL-2 or IL-10 in culture supernatant after 24-hour co-culture of serial post-HSCT CD8+ T cell samples obtained from VAX5-6 (n=5), (**B**) VAX1-3/GvHD (n=4) or (**C**) transplanted control patients (no vaccine/no GvHD) (n=3) in response to autologous PHA T cell blasts expressing hematopoietically-restricted alloantigens is depicted as bars. Individual values are shown as filled circles. (**D**) Additionally, CD8+ T cell samples isolated at serial time points following HSCT from VAX5-6 (n=6), (**E**) VAX1-3/GvHD (n=4) or (**F**) control patients (n=5) were assayed for cytokine secretion in response to autologous fibroblasts bearing broadly expressed alloantigens.

Suppl. Table 4. Clinical characteristics and transplant-related features of the control patient cohort. All patients within the control cohort received a reduced-intensity fludarabine and busulfan-based conditioning regimen and subsequently allogeneic peripheral blood stem cells. C, multiplexed cytokine analysis; CR, complete remission; E, IFNγ-ELISpot assay; IF, induction failure; *IGHV*, immunoglobulin heavy chain variable region; MMUD, mismatched-unrelated donor; MRD, matched-related donor; MTX, methotrexate; n/a, not available; N/A, not applicable; P, Immunophenotyping; PR, partial remission; RAP, rapamycin/sirolimus; SD, stable disease; TAC, tacrolimus; URD, matched-unrelated donor

Patient ID	Age (Sex) at HSCT	Donor source	GvHD prophylaxis medication	# Prior Therapies	*IGHV* Mutation Status	Cytogenetics	Clinical stage at HSCT	Days to aGVHD onset	Days to cGVHD onset	Time to relapse (months)	Follow-up time (months)	Immune assay
C1	48 (F)	URD	MTX, TAC, RAP	3	mutated	13q-	PR	N/A	N/A	20.5	39	E, C, P
C2	41 (F)	URD	MTX, TAC, RAP	4	mutated	13q-	CR	N/A	192	N/A	24	E, C
C3	43 (M)	MRD	MTX, TAC	n/a	n/a	13q-	PR	N/A	448	N/A	72	E,C
C4	35 (F)	MMUD	MTX, TAC, RAP	2	mutated	11q-	PR	210	189	N/A	39	E, C, P
C5	53 (F)	URD	MTX,TAC, RAP	2	n/a	13q-, 17p-	CR	N/A	N/A	N/A	7.5	P
C6	61 (M)	URD	MTX, TAC	5	n/a	+12	IF	N/A	N/A	N/A	10	P
C7	55 (F)	MRD	MTX, TAC	2	n/a	11q-	CR	N/A	182	N/A	19	P
C8	73 (M)	URD	MTX, TAC, RAP	2	n/a	+12, 17p-	CR	N/A	N/A	N/A	5	P
C9	59 (M)	URD	MTX, TAC, RAP	2	n/a	+12, 17p-	CR	N/A	N/A	N/A	4	P
C10	47 (M)	URD	MTX, TAC, RAP	2	unmutated	11q-, 13q-, +12	PR	N/A	N/A	N/A	1	P
C11	59 (F)	MRD	MTX, TAC, RAP	3	n/a	13q-, 17p-	PR	N/A	181	18	28	P
C12	63 (M)	MMUD	MTX, TAC, RAP	3	n/a	17p-	CR	N/A	105	N/A	61.5	P
C13	73 (M)	URD	MTX, TAC, RAP	3	unmuated	13q-, 17p-	CR	N/A	314	N/A	41	P
C14	59 (M)	MRD	MTX, TAC, RAP	3	n/a	n/a	PR	N/A	N/A	N/A	44	P
C15	44 (M)	MRD	MTX, TAC, RAP	2	n/a	n/a	PR	N/A	N/A	N/A	64	P
C16	50 (F)	MRD	MTX, TAC	2	unmuated	13q-, 17p-	SD	N/A	N/A	46	63	E, C, P
C17	64 (M)	URD	TAC, RAP	1	n/a	17p-	CR	N/A	161	N/A	59	P

Reduced intensity stem cell transplantation for advanced chronic lymphocytic leukemia followed by vaccination with lethally irradiated autologous tumor cells admixed with granulocyte macrophage-colony stimulating factor secreting K562 cells

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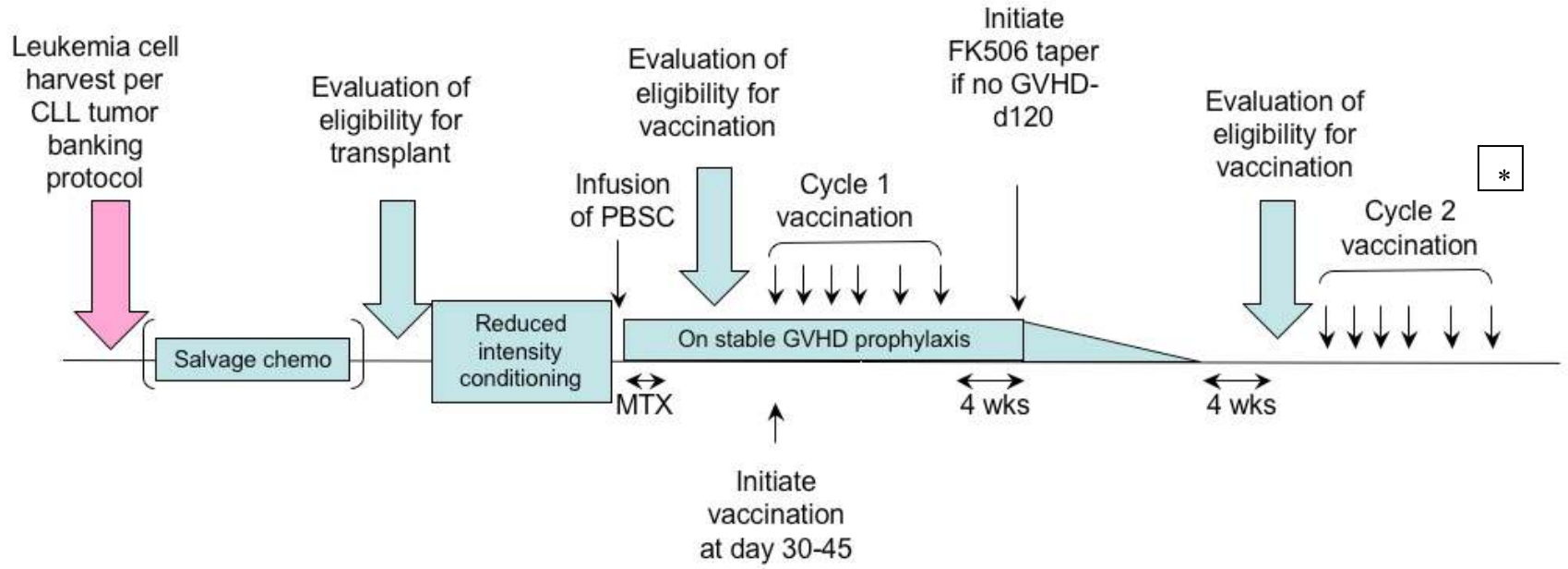
PROTOCOL SCHEMA



∗ With Amendment #21, the second phase of vaccination was deleted because it was unclear that the second phase of vaccination provides added clinical benefit and it had low feasibility (based on lack of subject willingness and high frequency of chronic graft versus host disease that is common to our DFCI transplant population in general).

1.0 INTRODUCTION

1.1 Poor prognosis factors in chronic lymphocytic leukemia (CLL).

Chronic lymphocytic leukemia (CLL) is a disease of clonal B cells, in which affected individuals demonstrate significant heterogeneity in clinical course. Whereas some patients experience an indolent disease course, others succumb to the disease rapidly despite intensive treatment. Conventional prognostic factors for CLL, established some 20-30 years ago, have included age, sex, clinical stage, degree of bone marrow infiltration, and lymphocyte doubling time. [1-3] Response to treatment also has high prognostic significance. Prognosis is poor in patients who have chemo refractory disease, or who have received more than 3 prior regimens. Keating et al. has reported that patients who have failed to respond to fludarabine or other purine analogs have a median survival of 8 months, and a 1 year survival of 40%. [4]

Previous studies examining genetic prognostic factors such as Ig V_H mutational status, interphase cytogenetics and p53 status have demonstrated that each influence time from initial CLL diagnosis to treatment initiation and overall survival (OS) [5,6 7,8 9,10]. Recently, these factors have been demonstrated to also have adverse clinical impact following receipt of clinically highly effective chemoimmunotherapy (fludarabine/rituxan) [11] and suggest that survival for poor risk patients may be improved if they are treated more aggressively at the outset. This concept is supported by recent studies describing the ability of intensive therapy such as autologous and allogeneic transplant to overcome the poor prognosis associated with unmutated immunoglobin variable heavy-chain gene status and chromosomal abnormalities. [12-14] Clinical trials utilizing risk stratification according to the presence of at least two poor prognostic factors for assigning therapy at diagnosis are presently underway in Europe[15].

1.2 Myeloablative hematopoietic allogeneic stem cell transplantation (HSCT) for CLL induces graft-versus-leukemia (GVL), but is associated with high treatment related mortality. Myeloablative allogeneic stem cell transplantation is potentially curative for several types of hematologic malignancies, including CLL. Several studies have supported the critical role of donor-derived immunity against CLL following allogeneic HSCT in generating cure against this disease. Rondon et al. observed clinical remission of CLL following the withdrawal of immunosuppression [16]. More recently, Toze et al. observed clinical remissions associated with the induction of graft-versus-host disease (GVHD) [17]. While CLL patients typically have detectable minimal residual disease following autologous transplants and uniformly develop recurrent disease [14,18], plateau in survival curves after one year have been observed following myeloablative allogeneic HSCT. Michallet et al. reported the EBMT experience of treating young patients with CLL with HLA-matched siblings[19] and noted stable OS of ~46% after one year, indicating the presence of a GVL effect. Khouri et al. described a PFS of 78% at 5 years for chemosensitive patients following matched related and unrelated myeloablative transplant [20]. Paveletic et al. reported 30% progression free survival at more than 5 years for 38 CLL patients treated by myeloablative bone marrow transplantation using matched unrelated donors identified through the NMDP. [21] Esteve et al. furthermore demonstrated that successful treatment with allogeneic HSCT for CLL is associated with undetectable

minimal residual disease. [22] Finally, Collins et al. surveyed outcomes of donor lymphocyte infusion (DLI) at 40 North American centers and found that 40% of patients with CLL responded to DLI, thus directly demonstrating the effectiveness of donor-derived tumor immunity against CLL.[23]

Taken together, these studies demonstrate that lasting remissions can be achieved following myeloablative transplant for patients with advanced CLL. These encouraging results, however, have been offset by the observation of high treatment related mortality rates (38-50%) and high rates of GVHD (50-85%) in this patient population [17,19-21]. Donor T cells appear to be important to this GVL effect, since T cell depleted myeloablative transplant for CLL results in some improvement in this TRM rate (24%), as noted by Gribben et al. at DFCI, but is also associated with loss of beneficial effect on progression-free survival. [24] In conclusion, while myeloablative HSCT has curative potential for CLL, enthusiasm for this approach has been dampened by the prohibitively high levels of treatment associated complications associated with unmanipulated grafts.

1.3 Nonmyeloablative conditioning regimens for CLL are well tolerated, but are associated with high relapse-related mortality. In recent years, non-myeloablative conditioning regimens have proven to be effective in establishing donor engraftment without the morbidity and mortality associated with ablative conditioning regimens used in conventional allogeneic HSCT [25-28]. These non-myeloablative transplants (NST) have allowed allogeneic transplantation to be performed in patients with advanced age or co-morbid medical conditions. Because the conditioning regimen is non-myeloablative, they rely on GVL in order to be effective.

At Dana-Farber Cancer Institute (DFCI), we undertook a program to treat patients with advanced CLL with NST. Between January 2001 and August 2004, 46 patients with advanced CLL underwent NST consisting of a conditioning regimen of fludarabine (30 mg/m^2 x 4 days) and intravenous busulfan (0.8 mg/kg/d x 4 days). 94% received G-CSF mobilized peripheral blood stem cells while 6% received bone marrow. Graft vs host disease (GVHD) prophylaxis included tacrolimus plus low dose methotrexate (65%) or cyclosporine plus prednisone (35%) based regimens. Most patients had a HLA-matched unrelated donor (67%); 33% had a HLA-matched related donor. The patients were heavily pretreated, with a median of 5 prior therapies; 98% of patients had received fludarabine, 96% alkylating agents, 80% rituximab, and 32% alemtuzumab. 22% of patients had relapsed after prior autologous stem cell transplant. Most patients had active disease at time of NST, with only 17% in complete remission and 26% in partial remission. 50% of patients were in active relapse and 7% had failed to respond to any attempted therapy (induction failures). At two years, the overall and progression-free survival rates in this patient population were 54% and 34%, respectively, with a median follow-up of 20 months. Relapse was the principal cause of treatment failure,with a two-year cumulative incidence of 48%. Treatment related toxicity was minimal. These data support the use of nonmyeloablative transplant earlier in the disease course to achieve improved long-term disease control. Moreover, it is possible that better outcomes after transplantation can be attained by inducing more robust GVL responses.[29]

1.4 GM-CSF based vaccines to improve antigen presentation

Several animal tumor models have demonstrated potent and specific anti-tumor immune responses with appropriate immune stimulation. The local release of immuno-modulatory cytokines has been shown to be a useful adjuvant to tumor cell-based vaccine strategies. This can be most effectively achieved by transfection of the cytokine gene into the tumor cell, which is then irradiated and injected into the animal as a tumor-specific vaccine. In one study in which over 10 cytokines were compared in poorly immunogenic murine tumors, GM-CSF was identified as the most potent cytokine capable of generating systemic immunity that was CD4+ and CD8+ T cell dependent[30]. This vaccine approach has been shown to cure mice of small tumor burdens, and suggests that it is effective in treating minimal disease states.

The use of GM-CSF as a vaccine adjuvant has been explored in several phase I clinical trials, in diseases such as AML, melanoma, hepatocellular carcinoma, pancreatic cancer, prostate cancer and renal cell carcinoma [31-35]. These GM-CSF augmented vaccines were safe and well tolerated in patients. The vast majority of adverse events were grade 1-2 injection site reactions characterized by erythema, induration, tenderness and localized pruritis. Systemic adverse events have included generalized pruritis, rash, fatigues, fever, headache and malaise.

At DFCI, a series of vaccination studies using GM-CSF based vaccines have been performed [36-38]. In one phase I clinical trial, irradiated autologous melanoma cells engineered by retroviral mediated gene transfer to secrete GM-CSF were used to vaccinate 21 patients with metastatic melanoma[37]. In subsequent studies, irradiated autologous tumor cells engineered to secrete GM-CSF by adenoviral mediated gene transfer were administered by intradermal and subcutaneous injection at weekly and biweekly intervals in 34 patients with metastatic melanoma [39] and 34 patients with metastatic lung cancer [36] (average GM-CSF secretion 745 ng/10^6 cells/24 hours and 513 ng/10^6 cells/24 hours, respectively). In each of these studies, a common feature was the development of intense localized skin reaction at the vaccine injection sites, associated with a dramatic influx of dendritic cells, macrophages, eosinophils and T lymphoyctes which were not present prior to vaccination. These reactions were associated with subsequent immune mediated tumor rejection at distant metastatic sites. Collectively, these studies showed that local production of GM-CSF improves tumor antigen presentation by increasing the number and activity of professional antigen presenting cells in the tumor microenvironment. In the adenoviral melanoma trial, at a minimum follow up of 36 months, 10 patients are alive (29%) and 4 with NED[39]. Recent studies to elucidate the targets of the immune response have provided evidence of the presence of a coordinated humoral and cellular response to disease specific antigens[40,41].

1.5 GM-K562 cells as a bystander line

In the aforementioned trials, tumor cells were directly transduced with a retroviral or adenoviral construct encoding GM-CSF such that the tumor was the source of both antigen and GM-CSF production. This approach has many limitations, including the observation that the transduction efficiency of lymphoid cells is poor, making the production of a CLL secreting GM-CSF tumor vaccine not practical. To make the

secretion of GM-CSF more reliable and less susceptible to variables associated with virus production, K562 cells, stably transfected with a plasmid encoding GM-CSF and a puromycin resistance gene, was generated by the Harvard Gene Vector Laboratory. K562 is a CML cell line that has low level of class I and class II expression that is not inducible with IFNγ and therefore would be associated with a low likelihood of allogeneic response[42]. It is also a cell line grown in suspension culture, and thus is amenable to large-scale manufacturing. These GM-K562 cells (Type II Master Drug File #BB-MF-11209) secrete relatively high levels of GM-CSF in vitro (9-13 μg of GM-CSF per 10^6 cells over 24 hours, during the first 24 hours after thawing). 100% growth arrest occurs at radiation doses of 10,000 cGy, but GM-CSF secretion persists for at least 7 days.

At DFCI, a current study using irradiated GM-K562 cells to vaccinate patients with CML with evidence of persistent PCR-positivity for *BCR-ABL*, despite optimized treatment on imatinib has recently opened, and active patient recruitment is in progress (DFHCC 04-126). Preliminary results of the safety and effectiveness of a similar K562 Bystander GM-CSF based vaccine (manufactured by Cell Genesys) in CML patients has been recently reported[43] and support the biologic activity of the vaccine. The Cell Genesys K562 Bystander GVAX product secretes 250 ng GM-CSF/10^6 cells/24 hours. Nineteen patients were treated with 4 vaccines of 1 x 10^8 irradiated K562/GM-CSF cells once every three weeks. Five of 19 developed molecular remission (PCR negativity) following vaccination. Another 4 of 19 demonstrated a greater than one log reduction in *BCR-ABL* transcript level. Of the remaining 10 patients, 9 of 10 maintained stable disease or developed a less than 1 log decrement in *BCR-ABL* transcript level. No hematologic or autoimmune toxicities were noted. In another clinical trial using the Cell Genesys K562 Bystander cells, in which DFCI participated, AML patients with minimal residual disease in first remission were vaccinated with K562 Bystander cells admixed with autologous tumor before and after high dose chemotherapy with autologous peripheral blood stem cell rescue. No dose limiting toxicities were reported, and reduction in WT-1 transcript levels following the pre-transplant vaccine were observed, suggesting the anti-leukemic activity of this GM-CSF based vaccine platform.[44]

1.6 Study rationale: Reduced intensity allogeneic stem cell transplantation as a platform for stimulation of donor-derived tumor immunity. The current study proposes to develop the combination of GM-CSF based vaccination with allogeneic stem cell transplantation as a potentially curative treatment strategy in patients with poor risk CLL. Pre-clinical experiments in murine tumor model systems have demonstrated that administration of a GM-CSF based vaccine following T-cell depleted allogeneic bone marrow transplantation stimulates potent anti-tumor immunity without the exacerbation of graft-versus host disease.[45]

CLL, for many reasons, is an ideal disease in which to explore this treatment approach. First, allogeneic transplantation results in the reconstitution of normal donor immunity, which has the potential to overcome the immune deficiencies inherent to the disease and which are exacerbated by conventional CLL therapies (rituxan, fludarabine, CAMPATH), and that otherwise compromise the ability to mount effective tumor

immunity against CLL. Second, longstanding clinical experience has already demonstrated the susceptibility of CLL to donor-derived GVL effects, including response to DLI. Third, while the disease course of CLL is heterogeneous, a subset of patients clearly demonstrate indolent disease kinetics, which is advantageous for providing adequate time for mounting an effective immune response. Fourth, conventional and newer prognostic factors can readily identify a subset of CLL patients with poor risk, in whom aggressive therapy is warranted. Fifth, in a large subset of patients, tumor cells can be readily harvested from the peripheral blood or marrow of these patients, thus removing the barrier of feasibility for obtaining adequate numbers of tumor cells for vaccine generation. Finally, several recent gene expression studies of CLL have been completed, and thus target antigens that are overexpressed in CLL can be potentially identified against which vaccine-induced immune responses can be monitored [46-48].

This study is divided into three treatment phases: (1) non-myeloablative hematopoietic allogeneic stem cell transplantation; (2) cycle 1 GM-CSF based vaccination in the early post-transplant period; and (3) cycle 2 GM-CSF based vaccination following discontinuation of immunosuppression. Autologous leukemia cells for vaccine development will be collected on a separate tumor cell banking protocol (DF/HCC Protocol 06-200). Several critical issues need to be addressed in order to render any post-allograft immune-based intervention effective. First, the conditioning regimen must effectively minimize the amount of residual disease and yet have an acceptable toxicity profile. A reduced intensity regimen will likely best balance toxicity with good disease control, as suggested by a number of studies by other investigators. [49] [50] [51] [52] The proposed conditioning regimen uses the backbone of fludarabine and busulfex, already developed at DFCI, with intensification of the dose of busulfex from 25 to 50% of the full myeloablative dose. A second issue concerns patient selection. Our prior DFCI experience with nonmyeloablative transplant (section 1.3) revealed treatment-responsive disease to be the primary predictor of outcome. Because the proposed study requires a significant length of time from leukemia cell harvest and banking for vaccine development until completion of vaccine administration after allogeneic transplant, it is critical that patients have adequately controlled disease prior to initiating transplant. If disease is poorly controlled, then it can be anticipated that the likelihood of successfully initiating vaccination becomes severely diminished. For this reason, only patients with advanced CLL who have low volume disease or demonstrate stable or responding disease following salvage chemotherapy are eligible to reduced intensity transplant and thereafter, vaccination.

The current study proposes to administer two cycles of vaccinations, each consisting of a series of 6 vaccinations, following donor engraftment. The first cycle is administered during the early post-transplant period, during which it has been hypothesized that homeostatic mechanisms drive the rapid expansion of donor T cells as immune reconstitution is established following donor engraftment.[53] For this reason, this first cycle of vaccination will occur while on stable immunosuppression, and may serve to prime immune responses. The second phase of vaccination will occur following discontinuation of immunosuppression. With Amendment #21, the second phase of vaccination was deleted because it was unclear that the second phase of vaccination

provides added clinical benefit and it had low feasibility (based on lack of subject willingness and high frequency of chronic graft versus host disease that is common to our DFCI transplant population in general).

Paracrine secretion of GM-CSF by the irradiated/modified K562 cells should attract professional antigen presentation cells (APCs), such as dendritic cells, to the leukemia cell milieu, and stimulate these APCs to present leukemia antigens to donor lymphocytes, thereby triggering a leukemia specific allo-immune effect. This study will enroll patients to receive a vaccine comprised of a stable dose of GMCSF-secreting cells admixed with 1 x 10^7 of autologous tumor cells (CD5+CD19+). Of note, a recent study using tumor cells in this range as part of a retrovirally expressed GM-CSF vaccine for patients with metastatic melanoma observed the development of vitiligo, suggesting the effective immune targeting of melanocyte antigens [35].

A potential concern of our vaccination schema is how these interventions will interact with the new donor immune system, and whether it may increase the frequency and/or severity of GVHD. Thus, evaluations of the safety and toxicity of vaccination constitute the primary objectives of the study. Of note, no excessive GVHD has been observed in patients enrolled on an ongoing DFCI study (DFHCC 04-023), evaluating the safety of a vaccine consisting of autologous tumor, adenovirally transduced to secrete GM-CSF, administered following NST for aggressive myeloid leukemias. If this trial reveals significant biologic activity without substantive toxicity, then these results will provide the foundation for future vaccination trials at a single dose level in larger numbers of patients. In addition, further enhancement of antitumor immune effects may be achieved by combining GM-CSF based vaccination with other interventions such as donor lymphocyte infusion, or novel agents that may work by bypassing the action of endogenous negative regulators (i.e. blocking antibodies to CTLA4, or PD-L1) or by directly enhancing innate and adaptive immunity (i.e. adjuvants such as Toll-like receptor agonists).

2.0 STUDY OBJECTIVES

2.1 Primary Objectives:

2.1.1 To assess the safety and toxicity of vaccination with lethally irradiated autologous CLL cells (CD5+CD19+) admixed with GM-K562 cells following reduced intensity allogeneic stem cell transplant for CLL patients with advanced disease.

2.2 Secondary Objectives

2.2.1 To characterize the biologic activity in response to vaccination with lethally irradiated autologous CLL cells (CD5+CD19+) admixed with GM-K562 cells, following reduced intensity allogeneic stem cell transplant.

2.2.2 To estimate duration of disease response, disease free and overall survival.

3.0 **CONDITIONS OF ELIGIBILITY**

3.1 Conditions of inclusion

3.1.1 Advanced CLL, defined as

3.1.1.1 No response or progressive disease during a standard nucleoside analogue based regimen; or, evidence of progressive disease within 24 months of the completion of a nucleoside analogue based regimen, or

3.1.1.2 Intolerance to fludarabine, or

3.1.1.3 Failure to achieve complete remission (CR) following a salvage regimen (refer to Appendix 6 for definition of CR)

3.1.2 Subjects must have no sites of adenopathy > 5 cm

3.1.3 (8/8) HLA matched <u>related</u> or <u>unrelated</u> donor available. Unrelated donors will be analyzed by molecular typing at HLA Class I and Class II (A, B, C and DR loci)

3.1.4 Must have prior banked tumor, collected by peripheral blood draw, leukapheresis, bone marrow biopsy or by lymph node dissection, per DF/HCC protocol 06-200.

3.1.5 ECOG performance status 0-2

3.2 Conditions of exclusion

3.2.1 Serum creatinine ≥ 2.0 mg/dl

3.2.2 ALT or AST ≥ 3X ULN

3.2.3 Total bilirubin ≥ 2.0 mg/dl (except for patients with Gilbert's syndrome)

3.2.4 Cardiac ejection fraction<30%

3.2.5 HIV infection

3.2.6 Pregnancy

4.0 SUBJECT ENROLLMENT

Patients identified as being appropriate for this trial will be assessed by one of the clinical investigators for evaluation. During the assessment, participation in this study as well as other treatment alternatives will be presented and discussed. If a candidate patient desires to proceed further with this trial, informed consent will be obtained. After eligibility is confirmed, the eligibility checklist and signed informed consent form will be submitted to the DF/HCC Quality Control Center (632-3761) for official registration of the patient.

5.0 TREATMENT PLAN

5.1 Pre-transplant Evaluation

5.1.1 All study subjects will proceed with standard pre-transplant evaluations before the transplant date as required by FACT regulations. These studies will include standard pre-transplant viral testing. Other tests will include PFTs, and cardiac evaluation, including EKG and assessment of LV ejection fraction by echocardiogram or radionuclide scan. All subjects will also receive a PPD, with candida control. The pre-transplant PPD and *Candida* control and other standard pre-transplant testing above may be performed by local treating physicians.

5.2 Mobilization and Apheresis of Donor PBSC

5.2.1 Donors harvested at DFCI will be consented on institutional donor consent forms prior to therapy. The first day of G-CSF administration is day 1 for the donor. Daily injections of ~10 mcg/kg/day of G-CSF will be administered subcutaneously (SC) up to and including the day before or the day of the last apheresis. The daily dose of G-CSF should not exceed 1200 mcg/day. The dose may be rounded to the nearest convenient dose based on vial size. See Appendix 4 for guidelines. The donor weight is defined as the weight of the donor on the day that G-CSF is prescribed. Please see Appendix 3 for dose reductions.

5.2.2 Starting on day 4, CBC with differential and platelet count will be obtained daily and continued until the apheresis procedures are completed. The peripheral blood WBC should increase to 30-50 x 10^9 cells/L after 3 doses of G-CSF. If the WBC on Donor Day 4 is >65 x 10^9 cells/L, the Donor Day 5 dose should be reduced to 5 mcg/kg/day. If the WBC count reaches >100 x 10^9/L on any day on which the G-CSF is due to be administered, dosing of G-CSF should be withheld.

5.2.3 On day 5, apheresis will be started. Peripheral venous access is preferable and will be used whenever possible. Ideally, 3 total blood volumes will be

processed per session. The goal will be to collect 5 x 10^6 CD34+ cells/kg recipient weight, with a minimum of 2 x 10^6 CD34+ cells/kg recipient weight. In cases where the product is cryopreserved, if $\geq$2 x 10^6 CD34+ cells/kg are obtained, the cells will be infused and the patient will be evaluable. If less than 2 x 10^6 CD34+ cells/kg are collected after 4 apheresis sessions, the patient will be removed from the study.

5.2.4 Apheresis will not be performed if the donor's platelet count prior to a scheduled apheresis collection drops below 80 x 10^9/L. The donor will be re-evaluated on the next day.

5.2.5 The apheresis product may be cryopreserved and stored in the stem cell processing/cryopreservation laboratory. Starting on Day 0 of the protocol for the patient the products will be thawed and infused per institutional guidelines. Products not cryopreserved will be administered as per institutional guidelines.

5.2.6 For PBSC products collected from unrelated donors though the NMDP or other donor registries, G-CSF administration and cell collection practices will be those used by the local donor center. The NMDP has provided guidelines to donor centers for the collection of PBSC, which are similar to those used at our institution.

5.3 Patient Conditioning for Allogeneic PBSCT

5.3.1 Drug Formulation, Preparation and Administration. Commercial supplies of fludarabine, and Busulfex will be utilized. The formulation, preparation and route of administration will be as per package insert. The dose of each drug is indicated in sections 5.3.3 and 5.3.4.

5.3.2 For clinical purposes, day 0 is defined as the final day of infusion of donor PBSC, and therefore methotrexate will be given on day +1. For data recording purposes (such as case report forms for the QACT), day 0 is defined as the initial day of infusion of donor PBSC.

5.3.3 Fludarabine (30 mg/m^2/d, based on actual body weight) will be administered as a bolus infusion over approximately 30 minutes as per BWH policy for 4 days on days -5, -4, -3, -2. Days of administration are subject to change based on attending physician clinical assessment.

5.3.4 Busulfex (0.8 mg/kg/q12hours; total dose 6.4 mg/kg; based on actual body weight) will be administered twice daily by IV infusion over approximately 3 hours as per BWH policy on days -5, -4, -3, -2. Days of administration are subject to change based on attending physician clinical assessment.

5.3.5 In conjunction with chemotherapy, patients will receive intravenous fluids and/or diuretics as needed. Antiemetics will be administered as per institutional guidelines.

5.4 GVHD prophylaxis

5.4.1 Tacrolimus (FK506)

5.4.1.1 Tacrolimus will begin day –3 and continue until Day 90. FK506 taper will begin between Day 90-100. If there is no GVHD, the goal will be to taper off tacrolimus by day 150. The suggested initial tacrolimus dose is 0.05 mg/kg PO bid and will be adjusted to maintain levels between 5-10 ng/ml. Tacrolimus dose will be rounded to the nearest 0.5 mg. The initial tacrolimus dose may be adjusted as needed to reflect renal and hepatic function. The dose will be replaced if the patient vomits within 15 minutes of taking a dose.

5.4.1.2 Tacrolimus taper:

5.4.1.2.1 No tacrolimus taper will be allowed while receiving vaccines during the 1st cycle of vaccination. Taper may commence after the sixth vaccination has been given, at the discretion of the transplant physician.

5.4.1.2.2 Tacrolimus taper for patients with progressive disease before completion of vaccination. Patients with evidence of progressive disease requiring additional therapy or rapid taper of immune suppression will be removed from the study and receive no further vaccinations. In these cases, the tacrolimus taper will be performed at the discretion of the treating physician

5.4.2 Methotrexate (MTX)

5.4.2.1 MTX will be administered on days +1,3,6, and 11 at a dose of 5 mg/m^2 IV, and infused over approximately 15-30 minutes.

5.4.2.2 Suggested dose adjustments for MTX-related toxicity: Patients believed to be at the greatest risk for MTX related toxicity (i.e. late engraftment, hepatic dysfunction, severe mucositis) are those with either decreased real function (i.e. serum creatinine > 1.5x baseline or >2.0 mg/dL) or significant fluid collections (i.e. ascites, pleural effusions, etc) where MTX can accumulate and thus delay MTX

clearance). For patients with the above high risk features or significant mucositis, methotrexate doses may be held or leucovorin administered according to the following schedule.

5.4.2.3 Leucovorin rescue:

5.4.2.3.1 12 hours after day +1 MTX, give leucovorin at 10 mg/m2 IV or PO q6 hours x 3 doses (max single dose= 25 mg)

5.4.2.3.2 12 hours after day +3, 6 or 11 MTX, give leucovorin 10 mg/m2 IV or PO q6 hours x 6 doses (max single dose= 25 mg)

5.4.2.3.3 MTX levels should not be measured. Hyperbilirubinemia is not an indication for leucovorin therapy. Leucovorin rescue is not indicated if risks no longer exist; e.g. creatinine improved, fluid collection resolved.

5.5 Allogeneic PBSC infusions

5.5.1 Donor PBSC will be infused intravenously beginning on Day 0 through a PICC line or central catheter. The targeted/requested goal for infused cells will be 5 x 10^6 CD34+ cells/kg. The calculated cell dose is based on the recipient's weight on Day 0. Tylenol (650 mg, oral) and benadryl (25-50 mg, oral or intravenous) will be administered as premedications prior to stem cell infusion.

5.5.2 G-CSF at ~5 mcg/kg (dose rounded to nearest vial size) will be administered subcutaneously from Day 1 until the ANC is greater than 1000 cells/μL following initial PBSC infusion.

5.6 Supportive care

5.6.1 Levofloxocin 500 mg PO QD (or 250 mg PO QD if CrCl <50) will be given until ANC is >500 for 2 days.

5.6.2 Antibacterial prophylaxis and treatment should follow conventional post transplant guidelines. For example, patients should be treated with PCP prophylaxis for one year following transplantation using bactrim. If the patient is bactrim intolerant, atovaquone or pentamidine are acceptable agents.

5.6.3 Antiviral prophylaxis and treatment should follow conventional post transplant guidelines. HSV and VZV prophylaxis using acyclovir is recommended for one year after transplantation. Monitoring of CMV reactivation and disease is also required.

5.7 Administration of Lethally Irradiated Autologous CLL/GM-K562 Cell vaccine

5.7.1 The vaccination phase will commence between day +30 and day +45 following transplant. At any time between day +30 and day +45, the patient will receive a DTH (irradiated leukemia cell and *Candida* control) and undergo a bone marrow aspirate/biopsy.

5.7.2 Vaccination with lethally irradiated autologous CLL cells (CD5+CD19+) admixed with GM-K562 cells can commence provided the following criteria are satisfied:

5.7.2.1 No evidence of active grade II-IV acute GVHD

5.7.2.2 No systemic corticosteroid therapy

5.7.2.3 No <u>uncontrolled</u> active infection

5.7.2.4 ANC > 500/microliter off G-CSF

5.7.2.5 No CTC grade >=3 non-hematologic toxicity

5.7.2.6 ECOG performance status 0-2

5.7.2.7 No other significant medical, surgical or psychiatric condition that may interfere with compliance with protocol regimen.

5.7.2.8 No unexplained absolute eosinophil count <u>></u> 1.5x10^9/L.

5.7.3 If patients are deemed not eligible for vaccination, they will be taken off treatment and off study. If they must stop vaccination at any time, they will be taken off treatment. Patients will remain on study, however, and will be followed for outcomes through appointments scheduled based on standard of care including an evaluation one month after their last vaccination. Research tests may be added when deemed appropriate by the PI. All patients, whether or not they ever received vaccination, will be followed for life, and is standard for all HSCT patients.

5.7.4 GM-K562 cells are provided by the Harvard Gene Vector Laboratory. A master cell bank has been prepared that will provide the clinical grade material for this trial. These cells have been prepared under GMP conditions, and cryopreserved under controlled-rate conditions in DMSO,

human serum albumin (HSA), Dextran and Plasmalyte-A. Vials are stored in vapor-phase liquid nitrogen (LN2). Details of the cell line are included in Appendix I.

5.7.5 Starting between transplant day +30 to +45, patients will be administered a series of 6 vaccinations. Each vaccine will contain 1 x 10^7 irradiated GM-K562 cells admixed with 1 x 10^7 irradiated autologous tumor cells (CD5+CD19+). Vaccinations will be administered once a week (+/- 1 day) for three weeks, and then every other week (+/- 1 day) x 3 doses, until all 6 vaccinations are given.

5.7.6 GM-K562 cells and autologous tumor will be thawed in a 37^{o}C water bath, washed, irradiated at 10,000 cGy, and resuspended in sterile saline. The vaccine will be drawn up in 1 ml syringes to a final volume of 1 ml. Vaccine will be released to a member of the study team for immediate injection according to CMCF standard operating procedure.

5.7.7 Information regarding the number and location of the injections, the date of vaccine administration, and the total volume of vaccine administration will be collected for each vaccination and dictated in the patients chart by the provider.

5.7.8 A treating physician, RN, PA or NP will administer the injections in the outpatient facilities of the Dana-Farber Cancer Institute. Injections will be administered according to standard nursing procedure in the patient's arms or thighs on a rotating basis. Injections must be performed without the prior application of EMLA or other topical or local anesthetics, as such compounds both could obscure local reactions to the vaccination and could cause reactions that might be interpreted as vaccine reactions. Upon administration, the total volume of the vaccine will be divided in 2, such that 1/2 dose of the vaccine will be administered subcutaneously, and 1/2 dose of the vaccine will be administered intradermally.

5.7.9 Delay in vaccine administration: If severe hematologic toxicity (defined as ANC <500, platelet < 10K/ul, or absolute eosinophil count $\geq$1.5 x 10^9/L), CTC grade $\geq$ 3 non-hematologic toxicity, grade $\geq$ 2 allergic reaction (restricted to urticaria or bronchospasm), or $\geq$ grade 2 neurologic event develops during the vaccination period, vaccination may be delayed up to 14 days until the event has improved by at least 1 CTC grade. If condition is not improved after 14 days in the opinion of the treating physician and/or study PI, or if the toxicity recurs upon re-initiation of vaccination, no further vaccination will be given and the patient will be considered "off treatment", but will still be followed on study for toxicity and survival end points.

5.8 Monitoring during the course of vaccination.

5.8.1 All patients receiving at least three vaccines will be evaluable for toxicity assessment. Patients will be considered evaluable for immune activity if at least six vaccinations have been administered.

5.8.2 All patients will be monitored for adverse events. Dose limiting toxicity (DLT) will be defined as the occurrence of any grade 4 or higher toxicity (including both hematologic or non-hematologic), an absolute eosinophil count $\geq$ 1.5x10^9, or any allergic reaction that is grade 2 (restricted to urticaria and bronchospasm) or higher; any grade 2 or higher neurologic event; or any other grade 3 toxicity which does not resolve to grade 0 or 1 within 2 weeks, as defined by the NCI-CTC criteria (Version 3.0). If any DLTs are observed, then dose modifications will be implemented, as delineated in Section 8.0.

5.8.3 Disease response to irradiated autologous CLL/GM-K562 vaccination will be monitored by the following methods.

5.8.3.1 *Vaccination reactions.* Punch skin biopsies (4-6 mm) of vaccination sites will be obtained 2-3 days after the first and fifth vaccination. If a reaction is observed at the vaccination site following the other vaccinations, a skin biopsy is recommended. Histologic analysis of macrophages, dendritic cells, eosinophils and lymphocytes will be performed as a research test.

5.8.3.1.1 The skin biopsy material is processed by the CMCF, the same facility that processes the tumor tissue and manufactures the vaccine. All tissues processed by that laboratory are done so according to CMCF SOP and as such, are coded and stored in a secure area accessible only to appropriate laboratory and research study team members.

5.8.3.2 DTH: If sufficient cells are available, injections of irradiated autologous tumor cells (CD5+CD19+) ($1x10^6$) will be given with the first vaccination, with the fifth vaccination, and four weeks after the 6^{th} vaccination of for evaluation of baseline and vaccine induced delayed-type hypersensitivity. These cells will be resuspended in a volume of 0.5 ml and injected intradermally. A skin biopsy (4-6 mm) will be obtained for histologic and laboratory correlative examination 2-3 days after each DTH administration.

5.8.3.3 *Serologic responses to CLL cells*. Patient sera may be tested by ELISA after the 3rd, 6th, and 9th vaccination for evidence of an antigen-specific antibody response, as a research test.

5.8.3.4 *T cell responses to CLL cells*. Patient cellular responses against autologous CLL tumor may be tested after the 3rd, 6th, and 9th vaccination, as a research test.

5.9 Rules for Discontinuation of irradiated autologous CLL/GM-K562 Vaccination

5.9.1 Disease relapse or progression requiring additional therapy

5.9.2 Grade II-IV acute GVHD, or extensive chronic GVHD requiring systemic steroid therapy.

5.9.3 Development of any CTC grade ≥ 4 toxicity.

5.9.4 Development of an increased absolute eosinophil count to ≥ 1.5x10^9/L. If this occurs, further vaccines will be held until the eosinophilia has normalized (<0.4 x 10^9/L). In the event that the absolute eosinophil count remains ≥ 1.5 x10^9/L for more than 2 weeks despite being off vaccination, no further vaccinations will be given, and the PI and Sponsor must be notified within 24 hours of notification of the occurrence and initiation of corticosteroids and/or tyrosine kinase inhibitor therapy will be considered.[56] Since a mild, self-limited eosinophilia (<1.5 x10^9/L) is a well recognized and expected response to vaccine, an increase in absolute eosinophil count is not an automatic cause for halting all future vaccinations. In this scenario the patient's eosinophil counts and clinical course will be followed closely, and vaccination may be delayed for up to 2 weeks until the eosinophil count is normalized. If the absolute eosinophil count rises ≥ 1.5 x 10^9/L again with subsequent vaccination, then no further vaccinations will be given.

5.10 Post-vaccination Follow-up

5.10.1 Follow up visits will be conducted on a monthly basis for 6 months after the last vaccination for immunologic monitoring. Patients who receive all 6 study vaccinations and complete the 6-month follow-up will have completed the study requirements.

5.10.2 During the 6 months following final vaccine administration blood will be obtained on a monthly basis. . This blood will be used for research purposes to analyze for immunocompetence, and generation of tumor-specific immune responses. Patients who receive at least 6 vaccinations will be considered evaluable for clinical and immunologic endpoints.

5.10.3 Since this trial involves the use of genetically modified tumor cells, patients (who receive at least one vaccine) will be followed at least once a year for a minimum of 15 years to monitor any long-term toxicities of therapy. In addition, patient records and patient samples will be kept indefinitely.

6.0 REPORTING REQUIREMENTS FOR ADVERSE REACTIONS

6.1 Dana-Farber Cancer Institute/Harvard Cancer Care guidelines for reporting SAEs will be followed. These guidelines require the following events to be reported to the DFCI IRB:

6.1.1 Grade 2 (moderate) and Grade 3 (serious) Events -- Only events that are Unexpected and Possibly, Probably or Definitely Related/Associated with the Intervention

6.1.2 ALL Grade 4 (life-threatening) Events -- Unless specifically listed in protocol as not requiring reporting. For this protocol, the following transplant-related expected grade 4 events do not require reporting: cytopenias and mucositis.

6.1.3 ALL Grade 5 (Fatal) Events -- When subject is enrolled and actively participating in the trial or when event occurs within 30 days of the last study intervention. These SAE's will be reported to the principal investigator Catherine Wu, MD at (617) 632-5943. Full written SAE reports will be submitted to OPRS as soon as possible, but no later than 10 working days from notification of the event.

6.2 Human Gene Transfer

Any serious adverse event that is fatal or life-threatening, that is unexpected and associated with the use of the gene transfer product must be reported to the NIH OBA as soon as possible, but no later than 7 calendar days after the investigator's initial receipt of the information (i.e. at the same time the event must be reported to the FDA).

In addition, OBA reporting guidelines will be followed as well. See OBA guidelines appendix M-I-C-4 and M-I-C-4b, which specify that any SAE that is both unexpected and associated with the use of the vaccine must be reported. Reports must be sent within 15 days if unexpected and associated; and within 7 days if fatal or life-threatening, unexpected and associated. Follow-ups for previously reported events must be sent no later than 15 days of receipt by the investigator. Any event that occurs after the end of the trial and is associated with the use of the vaccine must be reported within15 days of the determination.

In the event of an SAE, the Principal Investigator will report to the DFCI OHRP and the IND holder on the DFCI IRB SAE reporting form. The Principal Investigator will then notify the DFCI Biosafety Officer and the Harvard Institutional Biosafety Officer when

the SAE is both unexpected and associated with the use of the gene transfer product. Where required, the IND holder will notify NIH/OBA and the FDA according to their reporting guidelines

The Dana-Farber Cancer Institute Data Safety Monitoring Committee will review the trial. The DSMC reviewers will assign a review time based on the outcome of their previous review

7.0 ANTICIPATED TOXICITY

7.1 Reduced intensity allogeneic stem cell transplantation

7.1.1 Fludarabine- The most common adverse events include myelosuppression (neutropenia, thrombocytopenia and anemia), fever and chills, infection, and nausea and vomiting. Other commonly reported events include malaise, fatigue, anorexia, and weakness. Serious opportunistic infections have occurred in CLL patients treated with fludarabine.

7.1.2 Busulfex- The most frequent, serious, toxic effect of busulfan is myelosuppression resulting in leukopenia, thrombocytopenia, and anemia. Hepatic veno-occlusive disease, which may be life-threatening, has been reported following the use of very high doses of busulfan in combination with cyclophosphamide or other chemotherapeutic agents prior to bone marrow transplantation. Possible risk factors for the development of hepatic veno-occlusive disease include: total busulfan dose exceeding 16 mg/kg based on ideal body weight, high busulfan levels, and concurrent use of multiple alkylating agents. A clear cause-and-effect relationship with busulfan has not been demonstrated. At high doses, busulfan has been shown to induce clinical seizures. Interstitial pulmonary fibrosis has been reported rarely. Busulfan is capable of inducing cataracts in rats and there have been several reports indicating that this is a rare complication in humans. In the few cases reported in humans, cataracts have occurred only after prolonged administration of busulfan. Hyperpigmentation is the most common adverse skin reaction and occurs in 5% to 10% of patients, particularly those with a dark complexion..

7.1.3 Tacrolimus - Primary toxicities include renal insufficiency, hypertension, hyperglycemia, hypomagnesemia, hypokalemia, and neurologic toxicity, including seizure and visual blindness. Tacrolimus could cause a condition called hemolytic uremic syndrome, characterized by acute renal failure, anemia and thrombocytopenia.

7.1.4 Methotrexate – The dose of methotrexate used in this study is lower than the dose typically used in myeloablative allogeneic transplantation. The primary toxicities expected are myelosuppression and mucositis. These effects are expected to be mild since the dose of methotrexate used will be reduced

compared to the full dose commonly used with conventional BMT. At high doses, MTX is also known to cause liver and/or renal damage. MTX can collect in extra-cellular fluid compartments, leading to delayed clearance and increased side effects. Therefore, in patients with significant third space fluid collections (e.g. ascites, pleural, pericardial effusions), MTX should be held or leucovorin rescue administered (see section 5.4.2.3).

7.1.5 G-CSF- Side effects associated with G-CSF include bone pain described as mild-moderate. Additional symptoms include myalgia, fatigue, headache, and insomnia. Fever, nausea and vomiting are less common.

7.1.6 Pancytopenia- Despite the administration of non-myeloablative chemotherapy, prolonged pancytopenia may be experienced. All patients will receive G-CSF after PBSC transfusion. If pancytopenia is prolonged, patients may require infusion of additional allogeneic stem cells or re-infusion of stored autologous stem cells (if available). Patients who have not engrafted by day +45 will be removed from study and not receive and vaccination.

7.1.7 Graft versus Host Disease (GVHD)- The principal target organs of acute GVHD are skin, gastrointestinal tract, and liver. Treatment in most cases will consist of increased doses of prednisone with or without the addition of other immune suppressive agents. Acute GVHD will be graded according to the Keystone convention (see Appendix 2).[54] Chronic GVHD can also affect skin, gut, and liver, but in addition, can affect mucosal membranes (dry eyes, dry mouth, vaginal dryness), joints (stiffness), and lungs (dry cough, dyspnea). Chronic GVHD will be graded as limited or extensive based on the original Seattle criteria (Appendix 5).[55]

7.2 Vaccination with irradiated autologous CLL admixed with GM-K562 cells

7.2.1 Localized skin reaction. In previous studies using GM-CSF secreting tumor cell vaccines, little toxicity other than injection site discomfort was observed. The most common adverse events were injection site reaction with erythema, induration, and local pruritis that was easily controlled with topical emollients. Grade I fatigue and nasal congestion were occasionally noted. No organ toxicities or autoimmune events were noted. GM-K562 is an investigational product and may have other side effects that are unknown at this time.

7.2.2 Potential toxicities of GM-CSF. GM-K562 cells secrete GM-CSF. We expect that initially a maximum of 100 μg of total GM-CSF will be secreted locally per 24 hours, and will diminish as invading inflammatory cells kill the bystander cells. Toxicities might be similar to what is seen when GM-CSF is given with subcutaneous administration. Side effects of GM-CSF injection include local toxicities such as pustular eruption, necrotizing

vasculities, erythema, hypersensitivity reactions including but not limited to pruritus, recall erythema at previous injection sites, general papular rash and phlebitis, and systemic toxicities, such as fever, asthenia, headache, bone pain, chills and myalgia. Infrequent side effects include dyspnea, peripheral edema and rash. GM-CSF may have more severe side effects when administrated to patients with normal bone marrow function. Theoretically, neutralizing antibodies could develop that could diminish its effectiveness. There is a rare risk of persistence of the GM-K562 cells causing high levels of GM-CSF. In one case elevated levels of GM-K562 cells caused a hypereosinophilic syndrome that ultimately resulted in extensive thrombosis involving major organs, including the heart, lungs and spleen, which proved to be fatal.

7.2.3 Auto-immune Diseases. This is a theoretic possibility, for which patients will be monitored. In principle, the mechanisms that allow the immune system to recognize tumor antigens could also lead to breakdown of tolerance to normal or self-antigens, generating an autoimmune reaction. In the B16 murine melanoma model, vaccination with GM-CSF expressing tumor has been associated with depigmented patches of skin, an indication of tissue-specific autoimmunity. K562 is an erythro-leukemia cell line. Immune response to K562 could theoretically lead to autoimmune anemia or leukopenia. No examples of autoimmunity were seen in previous GVAX trials in AML, melanoma, renal cell carcinoma, prostate cancer, pancreatic cancer and lung cancer.

7.2.4 Acute and chronic GVHD. While we hypothesize that this vaccine may elicit a leukemia specific response by the donor immune system, the possibility that it may elicit or aggravate GVHD also exists. Clinically significant (grade II-IV) acute and chronic GVHD are common complication after allogeneic HSCT. Based on the literature and our experience at the DFCI, the expected rate of grade II-IV acute GVHD after allogeneic NST by day +100 is approximately 40-60%, with grade III-IV aGVHD about 20%, and the expected chronic GVHD rate is about 70%. However, only a small proportion of patients would be expected to develop chronic GVHD before the end of the study period (around day +120 to +150). Therefore, we can expect a combined 40-60% incidence of acute and chronic GVHD before day +180. This trial will be designed such that it will be stopped only if a higher than expected rate of severe (grade III-IV) acute GVHD is observed.

7.2.5 Infection. K562 is a cell line. The master cell banks from which the vaccine is derived have tested negative for the following human viruses: CMV, hepatitis B, hepatitis C, HIV-1, HIV-2, human T cell lymphotrophic viruses type 1 and 2, human herpes virus type 6 and 7, human parvovirus B19, EBV and adeno-associated virus (AAV). The master cell banks have also been shown to be sterile and free of mycoplasma. The working cell banks have also been shown to be sterile and free of mycoplasma.

7.2.6 DMSO toxicity. This toxicity is unlikely since the irradiated, autologous CLL cells and the GM-K562 cells will be washed prior to administration. The cells are cryopreserved in 10% DMSO. DMSO is a hydrophilic molecule, which diffuses through tissue rapidly. Although toxicities associated with intradermal administration of 10% DMSO in humans have not been published, toxicities associated with topical administration of 50% or more DMSO include skin irritation (vesiculation, urticaria, erythema, induration, pruritus, pain, bleeding, scaling, heat generation), garlic-like taste and odor on the breath and skin, transient disturbances of color vision, photophobia and diarrhea. The FDA has authorized the use of 50% DMSO for the treatment of interstitial cystitis in humans. Numerous studies in humans have demonstrated the relative safety of intravenous infusion of cells cryopreserved in 10% DMSO solutions, as this has become standard medical practice for infusion of cryopreserved peripheral blood and bone marrow stem cell collections in the setting of stem cell transplantation.

7.2.7 Unexpected vaccine related toxicity: Any severe adverse event (CTC grade $\geq$ 3) that is not readily explained as a transplant or disease associated complication will be assessed as possible vaccine related toxicity. As this is a gene therapy study, all patients will be followed for a minimum of 15 years (at least on a monthly basis) in order to assess any delayed toxicities potentially related to the use of the gene transfer product.

8.0 **VACCINE DOSE MODIFICATIONS**

8.1 There will be no dose adjustments for Grade 1 and 2 toxicities, with the exception of grade 2 allergic reactions, (that are restricted to urticaria or bronchospasm) or grade 2 neurologic events, seen on this study.

8.2 If a patient develops grade 3 non-hematologic toxicity, or grade 2 allergic (restricted to urticaria or bronchospasm) or grade 2 neurologic toxicity, additional treatment will be withheld unless toxicity resolves to grade 0 or 1 within 2 weeks, as defined by NCI-CTC criteria (version 3.0). Then, he or she may be re-treated at every 2 week intervals if toxicity occurred while vaccinations were given on a weekly schedule. If toxicity was observed while vaccinations were given on an every 2 week schedule, then the patient can be re-treated at monthly intervals. Should further toxicity occur, the patient will receive no further therapy on this study. The patient will continue to participate in biologic studies if willing. If a patient develops grade 4 toxicity, he or she will be removed from the study. If two or more grade 4 or greater toxicities are observed, the trial will be suspended to investigate the causes of these unexpected toxicities.

8.3 Treatment of toxicities will be supportive.

9.0 REQUIRED EVALUATIONS

The following studies will be performed.

Required Evaluations				
Evaluations	Pre-transplant	Pre-vaccine #1	During vaccination	During the 6 months following final vaccine administration
Informed Consent	X			
Medical History	X	X	On days of vaccination	Q month
Physical Exam	X	X	On days of vaccination	Q month
GVHD assessment		X	On days of vaccination	Q month
Pre-transplant testing$^{\gamma}$	X			
CBC with differential$^{\Sigma}$	X	X	On days of vaccination	Q month
Bun/Cr, LFTs, LDH	X	X	On days of vaccination	Q month
CMCF/Immune Bloods$^{\infty}$	X	X	Q Month	Q month
Marrow Asp/BX	X*	X^		Month 1^ and 6 ± 3^
Peripheral blood whole cell and T cell chimerism		X		Month 1, 3 and 6
DTH $^{\delta}$		X	Vaccine 5	Month 1
Skin bx (4-6 mm) of vaccination or leukemia DTH sites		DTH 1 Site	Vaccine 1 Site, Vaccine 5 Site DTH 2 Site	DTH 3 Site
CT scans	X			
Peripheral blood 4 color flow cytometry	X	X		Month 3 and 6
β-HCG$^{\varepsilon}$	X$^{\beta}$			

* Marrow aspirate to be sent for FISH/cytogenetics, flow cytometry, and banking for assessment of DTH and disease-specific T cell responses

^ Marrow aspirate to be sent for FISH/cytogenetics, chimerism

∞ Approximately 50cc blood

γ PFTs, EKG, Echo or MUGA, PPD with controls, HIV, HTLV-1, hepatitis serologies

δ DTH will include irradiated leukemia cells and candida as controlε Only for female subjects

β Required only for women of child-bearing potential

∑ CBC with differential must be resulted before administering each vaccine.

10.0 ENDPOINTS

10.1 Primary Endpoints:

10.1.1 Safety and toxicity of vaccination with irradiated autologous CLL cells admixed with GM-K562 will be measured by the development of

10.1.1.1 Grade III-IV acute GVHD, or
10.1.1.2 CTC grade ≥ 3 non-hematologic toxicity, or
10.1.1.3 Grade >=4 hematologic toxicity attributable to the vaccine

10.2 Secondary endpoints

10.2.1 Development of immune response, as measured by the development of a skin vaccination response, DTH response and antibody and T cell responses to CLL cells following vaccination, as detected in research tests.

10.2.2 Disease free and overall survival.

11.0 DATA AND SAFETY MONITORING

11.1 This study will be conducted under BB-IND 11923 held by Dr. Glenn Dranoff. This study will be monitored by an independent Data and Safety Monitoring Committee of the Dana-Farber Harvard Cancer Center. Continuing reviews summarizing adverse events recorded during the study period will be submitted to the IRB annually. Patients will be enrolled at the Dana-Farber Cancer Institute and will be centrally registered by the QACT. Eligibility and consent are checked by the QACT prior to enrollment. A data manager will be assigned to this protocol to ensure that data is collected and reviewed on a continuous basis.

12.0 STATISTICAL CONSIDERATIONS

This is a phase I study to determine the feasibility of administering irradiated autologous CLL cells admixed with GM-K562 cells during and after recovery from reduced-intensity nonmyeloablative transplant without excessive incidence of overall grade III-IV aGVHD associated with the administration of these cells. The first vaccination cycle will be initiated approximately day 30 to 45 following infusion of donor PBSC. The original study also proposed initiating a second vaccination cycle approximately day 210, or later, depending on the timing and completion of the FK506 taper. However, cycle 2 has been discontinued because of feasibility.

The proposed total sample size for this study is 40 patients We anticipate that, because patients eligible for this transplant protocol must be have stable or responding disease at enrollment, all patients will be potentially eligible for the first vaccination cycle. We will, however, track the reasons for ineligibility to receive the initial vaccination study as a component of feasibility, as well as any GVHD resulting from it as a measure of the safety of the vaccination strategy. Similar assessments of feasibility and toxicity will be applied to the second vaccination cycle as well.

Phase I Design for Safety

The initial phase I safety component of this study includes all patients who receive cells at 30 to 45 days post transplant. Dose limiting toxicity is defined as overall grade III or IV GVHD. Patients will enroll in two stages of accrual. In the first stage of accrual, we will enroll 20 patients in this study and assume at least 16 will be eligible to initiate vaccination in cycle 1. After examining the feasibility and safety of this treatment regimen in the first stage of accrual, we will enroll 20 additional patients to ensure that a total of 30 patients will initiate vaccination in cycle 1. With these additional patients, we will further evaluate the safety of this treatment regimen, as well as the secondary endpoints of the trial.

We will base the discontinuation of this study on the development of overall grade III or IV aGVHD during cycle 1, as a putative toxicity of vaccination; and death by day 100 as both an assessment of toxicity of vaccination in the context of nonmyeloablative transplant and feasibility of implementing early vaccination in this patient population. Stopping rules will be based on the outcomes in the first 6 patients to initiate vaccination. If 2 or more of the first 6 vaccinated patients develop overall grade III or IV GVHD during the vaccination period prior to immunosuppressive taper, we will declare vaccination to be too toxic to continue. If the true rate of overall grade III/IV aGVHD is 20%, then the probability that 3 or more patients develop this severity of GVHD is 0.34; if the true rate is 30% this probability is 0.58, and if the true rate is 10%, the probability is 0.11. The table below presents the probability of no more than 2 patients with overall grade III/IV GVHD:

	5%	10%	15%	20%	25%	30%
Pr(at most 1 grade III/IV GVHD in 6 pts)	0.97	0.89	0.78	0.66	0.53	0.42

We are also concerned about the number of patients dying by day 100, either of causes unrelated to vaccination or of non-GVHD consequences of vaccination. This assessment will be conducted in all patients undergoing transplant on this protocol. We will conduct an interim analysis of survival after 10 patients have enrolled and been following for 120 days. We will tally the numbers of patients who die by day 120, along with the causes of those deaths and whether the patient initiated vaccination. This speaks to the feasibility of vaccination with this schedule in this population, as well as to the tolerability of this transplant regimen. If there are 3 or more deaths in which vaccination cannot be ruled out as a contributory factor, we will discuss termination of the trial with the DSMC.

Secondary Endpoints

Based on our historical experience, the progression-free survival rate of a cohort of CLL patients reported in Brown et al (BBMT 2006) and transplanted at DFCI from 2001-2004, was 44% at 1 year following nonmyeloablative transplant. Additionally, in a larger cohort of CLL patients receiving allogeneic transplant at the DFCI from 1998-2008 (data unpublished), the progression-free survival at 1 year post-transplant was 50%. If we enrolled 30 patients who received at least one vaccine, we would have 89% power to detect a difference in the disease-free survival rate at one year post-transplant from 50 to 75% using a one-sided test at the 0.05 significance level. Additionally, we will estimate the overall survival rate at 1 year post-transplant using the method of Kaplan and Meier. We will also tally the number of patients in cycles 1 who achieve a response (CR and PR) and quantify the biologic activity of this treatment regimen using a variety of immunologic assays.

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14.0 APPENDICES

14.1 **Appendix 1**.

14.1.1 Vector and Cell Line Construction

The K562 cell line, a human erythroleukemia line, was purchased from American Type Culture Collection (ATCC; catalogue #CCL-243). This cell line was tested by ATCC and found to be negative for bacterial, fungal, and mycoplasma contamination. It is also Epstein-Barr virus nucleic acid free. The species has been verified as human by isoenzyme analysis and short tandem repeat analysis. The cells are grown in suspension in RPMI 1640 media supplemented with 10% heat-inactivated fetal bovine serum.

The K562 GM-CSF cell line (K562GM) was constructed in the Vector Core Laboratory of the Harvard Gene Therapy Initiative (HGTI). The K562GM line was constructed by co-transfecting the parental cell line with 3.8 μg of a human GM-CSF expression vector (pUCMD.hGMCSFa) and 0.2 μg of a puromycin selection plasmid (pJ6Omega-puro). pUCMD.hGMCSFa was constructed by subcloning pMD.hGMCSF into pUC to remove the SV40 origin and sequenced junctions. The letter "a" refers to the orientation of the GM-CSF gene.

Transfected cells were selected with 2 μg/ml puromycin. Surviving cells were cloned by limiting dilution in 96-well plates with puromycin selection. Approximately 35% of the wells were found to contain proliferating cells. In total, 117 clones were picked for further analyses. Individual clones were expanded both with and without puromycin selection and then screened for GM-CSF secretion using a Human GM-CSF ELISA kit (Endogen #EH-GMCSF). The highest expressing clone (Clone #19), maintained in the presence of puromycin, secreted 61.6 μg GM-CSF/10^6 cells/24 hours. The same clone grown in the absence of puromycin produced 50.9 μg GM-CSF under the same assay conditions. Further analysis of the six top secreting clones, maintained for longer periods with, or without puromycin indicated that clones maintained with puromycin continued to secrete high-level GM-CSF, while clones maintained in the absence of puromycin showed dramatic decreases in GM-CSF expression.

To ensure that the cell population was derived from a single cell and to attempt to select stable, high level GM-CSF-secreting clones, Clone #19 cells were subjected to a second round of limiting dilution cloning in puromycin-containing media. In the second round of cloning, 44% of the wells contained proliferating cells. Fifteen of these subclones were then analyzed for GM-CSF secretion. In these experiments, the best clone was again Clone #19 which produced 40 μg GM-CSF/10^6 cells/24 hours. The best secreting subclone (Clone #19-5), produced 22 μg GM-CSF/10^6 cells/24 hours. Based on its consistent, high level of expression, Clone #19 was chosen for clinical production. These cells were transferred to the HGTI Gene Vector Laboratory (GVL) for production of a master cell bank (MCB) and clinical production lots.

14.1.2 Manufacturing

14.1.2.1 Facilities and Operations

Clinical grade K562GM cells were manufactured at the HGTI Gene Vector Laboratory (GVL). The GVL is a 1200 ft^2 controlled access facility with Class 10,000 air. The facility is used to manufacture cell and viral vectors under cGMP conditions. The GVL facility and its operations are covered under a Type V Drug Master File (# BB-MF 10367 "Harvard Gene Therapy Initiative Gene Vector Laboratory, Boston, Massachusetts.") submitted to the FDA in March of 2002. The key components of the GVL and it operations are briefly described below. A comprehensive description of the GVL is contained in the Type V Drug Master File.

The GVL is divided into 5 functional areas: Process Development (PD), Clinical Manufacturing (CD), Quality Control (QC), Quality Assurance (QA), and Facility Support (FS). The QA group is independent of the manufacturing group. In addition, two independent consultants provide advice on clinical, manufacturing, QA, and regulatory issues.

The function of the PD group is to develop the products and processes that will be used during clinical production and testing. Generally, vectors are initially developed in research laboratories and then transferred to the PD group to for scale-up and GMP development. Once the GMP process has been developed, then the SOP's, Batch Records, and other process control documents are written. The products and processes are then transferred to the CD group for clinical production.

CD personnel manufacture, purify, and cryopreserve the clinical grade material. They also monitor production equipment (such as incubators, freezers, refrigerators), maintain control over an automatic electronic recording and alarm system, maintain control over vector inventories, and prepare all production records. CD personnel also perform all in-process product testing.

The main function of the QC group is to perform environmental monitoring of the GVL, and to perform characterization tests on manufactured products. The tests performed by QC primarily involve those for drug Function, Identity, and Potency (e.g., viral titer, vector structure, gene expression assays, etc.). All tests for product Safety and Sterility are performed by contract laboratories under GLP conditions. Samples sent to outside testing laboratories are shipped and tracked by QC personnel. Assay development is also performed by the QC staff with assistance from other groups.

QA controls the release and storage of all raw materials, and drug components, containers and closures. QA is responsible for controlling the release and use of all SOP's, Batch Records, or other Quality System documents, QA reviews completed documents for any errors and is responsible for investigating any deviations from proscribed procedures. QA maintains records of deviations, any changes in procedures, and equipment calibration and maintenance logs. QA is responsible for the final review of product files, and the release of products for clinical use, QA and/or independent consultants

periodically perform internal audits of GVL facilities and operations, as well as external audits of suppliers of critical raw materials and contract testing laboratories.

FS personnel are responsible for cleaning, maintenance, and decontamination of the facilities and equipment in the GVL. FS staff also provide routine laboratory maintenance and waste disposal functions.

14.1.2.2 SOPs and Forms Covering the Production of K562GM Cells

The SOP's and production documents that are directly related to the manufacturing of K562GM cells are listed below. General SOPs and forms related to GVL operations are reported in the Type V Drug Master File.

GP002.02	Cell Culture Logs
GP003.02	Cell Thawing
GP005.02	Passaging of Suspension Cells
GP008.02	Proportional Aliquoting of Cells
GP018.02	Cell Bank Reproduction
GP022.02	Freezing Cells Using the Controlled Rate Freezer
FR003.00	Culture Log for Cell Amplification (for GP002)
FR034.00	Cell Bank Freezing & QC Test Article Preparation (for GP018)
2005	Cell Counting
2501	Batch Record for Production of Cell Banks and Clinical Lots of Cells
4007	GM-CSF ELISA
5007	Lot Number Assignment

14.1.2.3 Master Cell Bank (MCB) Production

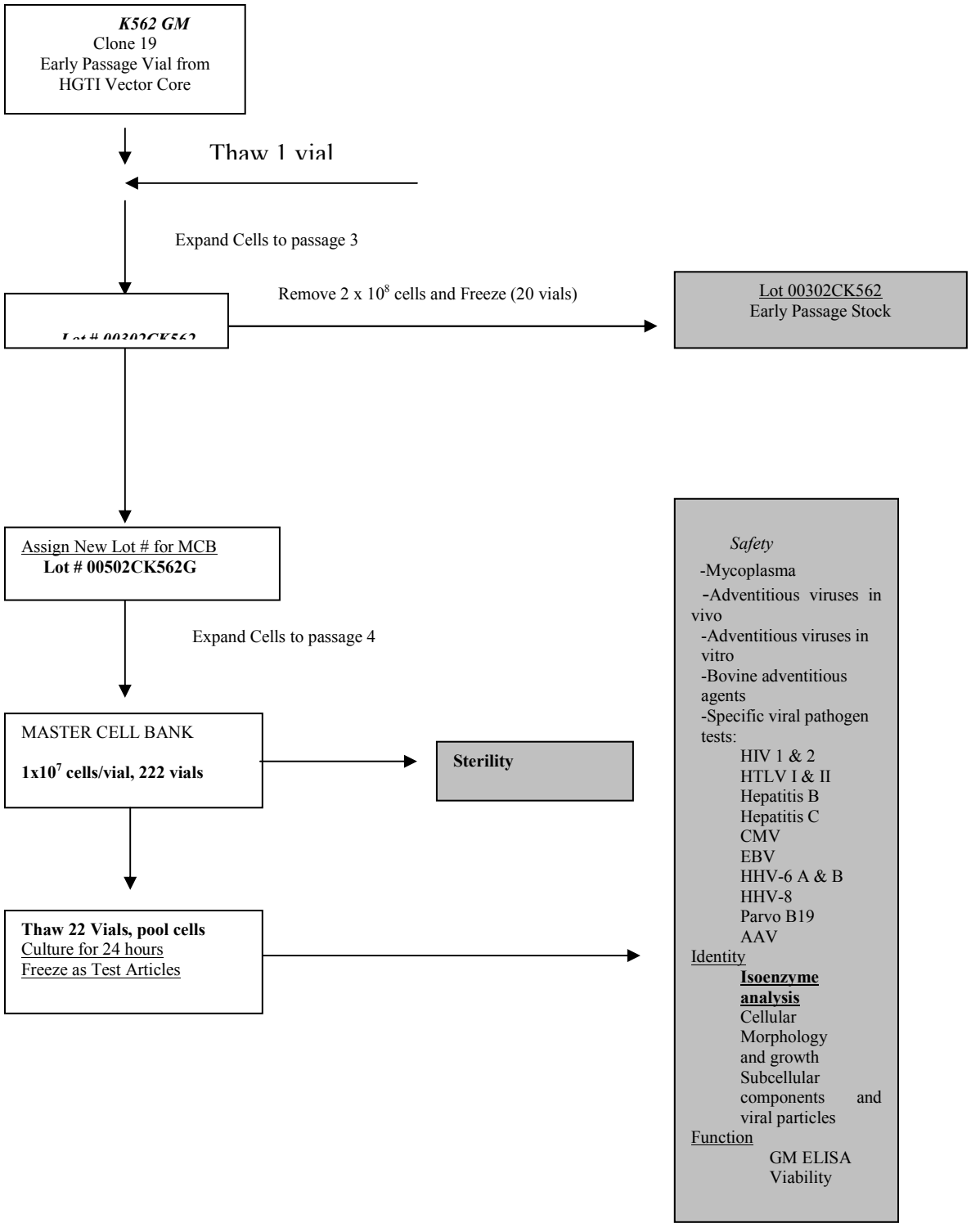
One frozen vial of early passage Clone #19 cells was obtained from the HGTI Vector Core Laboratory on 3/29/02, and thawed in cleanroom #2 in the Class 10,000 facility. Cells were expanded in RPMI 1640 medium supplemented with 10% fetal bovine serum (FBS), and 2 μg/mL of puromycin. Puromycin was included to maintain high expression of the transgene, since previous studies had shown an approximately ten-fold drop in GM-CSF expression in cell banks made in the absence of puromycin.

Cells were expanded for 3 passages at which time 2×10^8 cells were removed from the passage 3 cell pool and frozen in 20 vials. These early passage stock cells were named lot #00302CK562 and were retained to have some early passage cells, if needed for future studies. The remaining cells were expanded in culture to passage 4. A total number of 2.5×10^9 cells were then harvested by centrifugation at 850 x g for 5 minutes. Cell pellets were washed 4 times with RPMI 1640 without additives to remove any residual puromycin. Final cell pellets were then resuspended in a small volume of medium for final cell counting prior to freezing.

Cells were frozen in conditioned RPMI 1640 medium containing 5% DMSO. Conditioned medium was obtained from a tissue culture vessel of the same lot of K562 cells that were carried in parallel to the MCB cells. This parallel vessel contained RPMI 1640 medium supplemented with 10% FBS but without puromycin. After 24 hours in

contact with the K562 cells, the conditioned medium was collected and filtered through a 0.22µm filter prior to use in the freezing medium. 2.2 x 10^9 total cells were resuspended at a final concentration of 1 x 10^7 cells/mL in freezing medium and aliquoted in to 222 labeled cryovials. Cells were then frozen in a controlled rate freezer. A schematic representation of the MCB production process is in Figure 1.

Figure 1 – Schematic Representation of Production and Characterization of K562GM Master Cell Bank: Lot # 00502CK562



14.1.2.4 Production of Clinical Lots

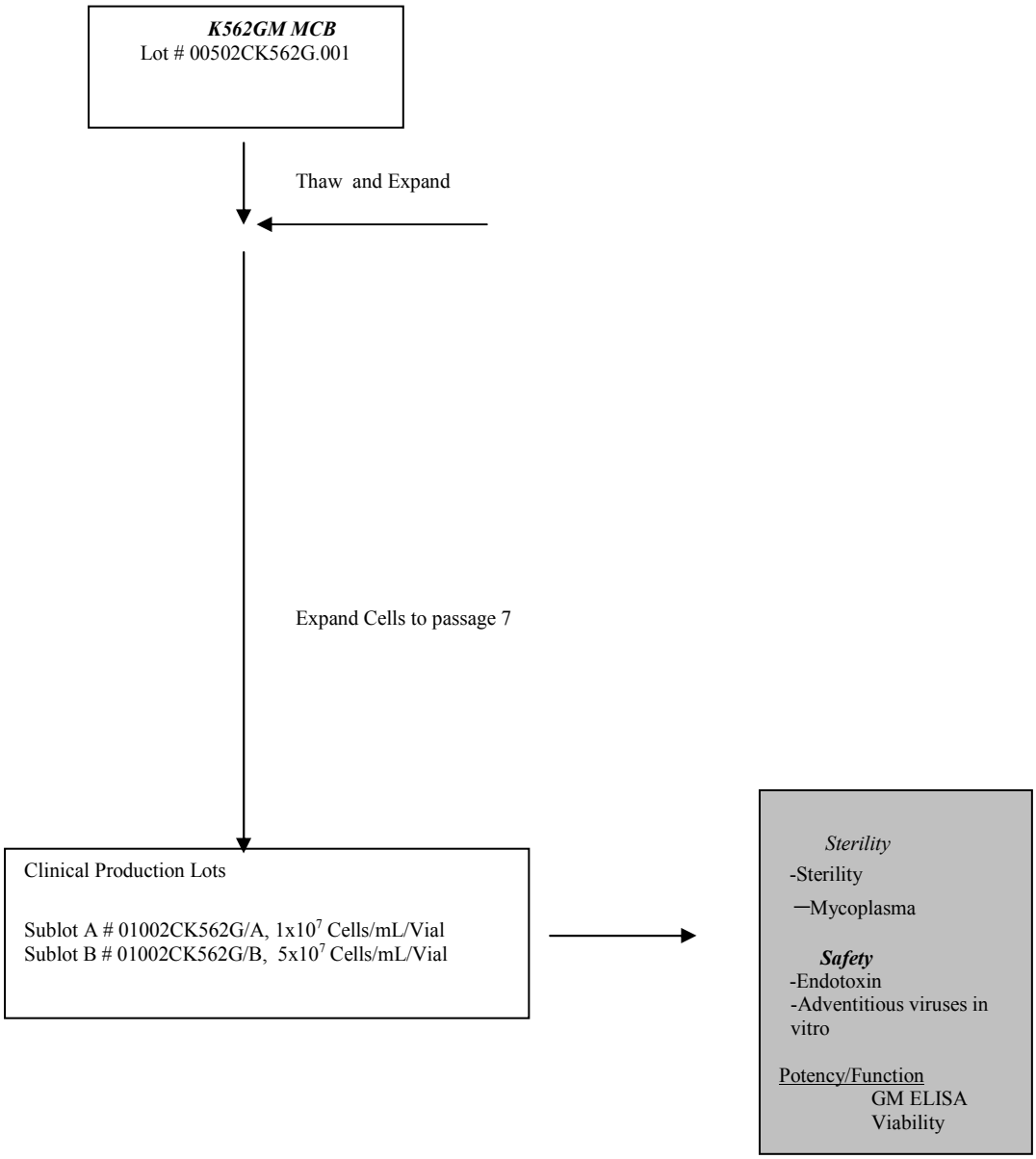
One vial of the MCB Lot # 00502CK562 was thawed on 10/1/02. Cells were expanded in RPMI 1640 medium supplemented with 10% FBS, and 2 μg/mL of puromycin. As with the MCB, puromycin was used in the production of the clinical lot to maintain high expression of the transgene, since previous studies had shown an approximate ten-fold drop in GM expression in cell banks made in the absence of puromycin.

Cells were expanded in culture for 3 cell passages (to passage 7), to a total number 1.0 x 10^{10} cells. Cells were then harvested by centrifugation at 850 x g for 5 minutes. Cell pellets were washed 4 times with RPMI 1640 without additives to remove any residual puromycin. Final cell pellets were then resuspended in a small volume of medium for final cell counting.

The total cell harvest was partitioned into two separate containers that were used to formulate sublots A and B. Sublot A was prepared using 2.5 x 10^9 total cells, and vialed at 1 x 10^7 cells/vial in 250 vials. Sublot B was prepared using 7.5 x 10^9 cells total, and vialed at 5 x 10^7 cells/vial in 150 vials.

Cells were frozen in conditioned RPMI 1640 medium containing 5% DMSO. Conditioned medium was obtained from a tissue culture vessel of the same lot of K562 cells that were carried in parallel to the clinical production lot cells. This parallel vessel contained RPMI 1640 medium supplemented with 10% FBS but without puromycin. After 24 hours in contact with the K562 cells, the conditioned medium was collected and filtered through a 0.22μm filter prior to use in the freezing medium. Cells were the frozen in a controlled rate freezer. A schematic representation of the clinical lot production process is in Figure 2.

Figure 2 – Schematic Representation of Production and Characterization of K562GM Clinical Lots: Lot #01002CK562G



14.1.3 Controls

14.1.3.1 Characterization of K562GM Master Cell Bank

Table 1: Certificate of Analysis- K562 GM-CSF, Master Cell Bank, Lot: # 00502CK562GM

Test	Method/Laboratory	Specification	Result
SAFETY/STERILITY			
Bacterial Culture (at vialing)	14 day culture on pooled test article (Children's Hospital, Boston)	No growth	No growth
Fungal Culture (at vialing)	14 day culture on pooled test article (Children's Hospital, Boston)	No growth	No growth
Sterility including B+F (for release)	AppTec Protocol #30045	No Growth	*No Growth*
In Vitro Viral culture (at vialing)	Viral culture (Children's Hospital, Boston)	No virus detected	No virus detected
In Vitro Adventitious Virus (for release)	AppTec Protocol # 30519	Negative	*Negative*
In Vivo Adventitious Virus	AppTec Protocol # 30027.12 CRL Protocol # NALS-ATPL-001	Negative	Negative @ Apptec Negative @ CRL
Mycoplasma (PTC)	AppTec Protocol # 30055.13	Negative	Negative
Detection of Bovine Adventitious Agents	AppTec Protocol # 30236.02	Negative	*Negative*
specific pathogen tests			
AAV-2	AppTec Protocol # 30307.04	Negative	Negative
HIV-1	AppTec Protocol # 30272.05	Negative	Negative
HIV-2	AppTec Protocol # 30614.03	Negative	Negative
HTLV I & II	AppTec Protocol # 30615.01	Negative	*Negative*
HBV	AppTec Protocol # 30703.01	Negative	Negative
HCV	AppTec Protocol # 30173	Negative	Negative
CMV	AppTec Protocol # 30705.00	Negative	Negative
EBV	AppTec Protocol # 30713.00	Negative	Negative
HHV-6 A	AppTec Protocol # 30719.00	Negative	Negative
HHV-6 B	AppTec Protocol # 30720.00	Negative	Negative
HHV-8	AppTec Protocol # 30702.00	Negative	*Negative*
Parvo B19	AppTec Protocol # 30619.01	Negative	Negative
IDENTITY AND FUNCTION			
Identification of Cell Line Species	AppTec Protocol # 30330.02	Human	Human
Determination of Cellular Morphology and Growth	AppTec Protocol # 30117.05	Anchorage-independent,	*Anchorage-independent,*

14.1.3.2 Characterization of K562GM Clinical Lots

The QC testing and specifications for the Clinical Lots are shown in Table 2 below.

Table 2: Certificate of Analysis- K562 GM-CSF, Clinical Lots
Lot: # 01002CK562G/A (sublot A)
Lot: # 01002CK562G/B (sublot B)

Test	Method/Laboratory	Specification	Result
Sterility including B+F	AppTec Protocol #30045	Negative	*Negative* (Sublots A and B)
In Vitro Adventitious Virus	AppTec Protocol # 30519.04	Negative	*Negative* (Sublots A and B)
Endotoxin	AppTec Protocol # 30518	< 5 EU/mL	< 0.5 EU/mL (Sublots A and B)
Function	HGTI SOP # 4007 GM ELISA	Expresses GM-CSF	*Expresses GM-CSF* Irradiated Sublot A: 13 μg/10^6 cells/24 hr. Irradiated Sublot B: 9 μg/10^6 cells/24 hr.
Viability	HGTI SOP # 2005	≥ 70% Viable	*Sublot A: 82 % Viable after Irradiation* Sublot B: 82 % Viable after Irradiation
Mycoplasma (PTC)	AppTec Protocol # 30055.13	Negative	Negative (Sublots A and B)

14.1.3.3 Irradiation studies

Irradiation studies have been initiated to study the amount of γ-irradiation needed to halt cell division but maintain high cell viability and GM-CSF secretion by the K562 GM-CSF cells. Irradiation was performed using a Gammacell 1000 γ-irradiator with a ^{137}Cs source. The irradiator is located in the Dana-Farber Cancer Institute and is under the control of the Cell Manipulation Core Facility.

The Gammacell 1000 irradiator that was used for the irradiation experiments is the same irradiator that will be used to irradiate K562 GM-CSF cells for administration to patients. This irradiator is currently used to irradiate cell and blood products for administration to patients. The irradiator has a standard operating procedure for its operation. Preventive maintenance and calibration are performed by a contractor on an annual basis. This includes dose mapping and a determination of the time needed to achieve a 3300 rad central dose. Monthly calculations of the decay rate are also performed and the results are posted near the irradiator. Members of Harvard Gene Therapy Initiative QA group audited the irradiator and its records in April 2004.

Several irradiation studies were performed on the K562 GM-CSF cells. These studies include: 1) Dose response studies to determine the most effective dose to ensure 100% lethality; 2) Experiments to determine the effects of irradiation on the potency of the cells 3) Assays on the lots produced to establish their specifications, and 4) Irradiation studies using ^{3}H-thymidine incorporation to measure cell replication. The results of these studies are described below.

A dose response was performed to measure the amount of γ-radiation required to halt cell division and induce complete lethality (Figure 3). K562 GM-CSF cells were irradiated at 1, 10, 20, 50, and 100 Gray (100 to 10,000 rads). Cell viability was measured by trypan blue exclusion while cell division was measured by counting a fixed number of cells at various time points after irradiation. The number of viable cells after irradiation is shown in Figure 3.

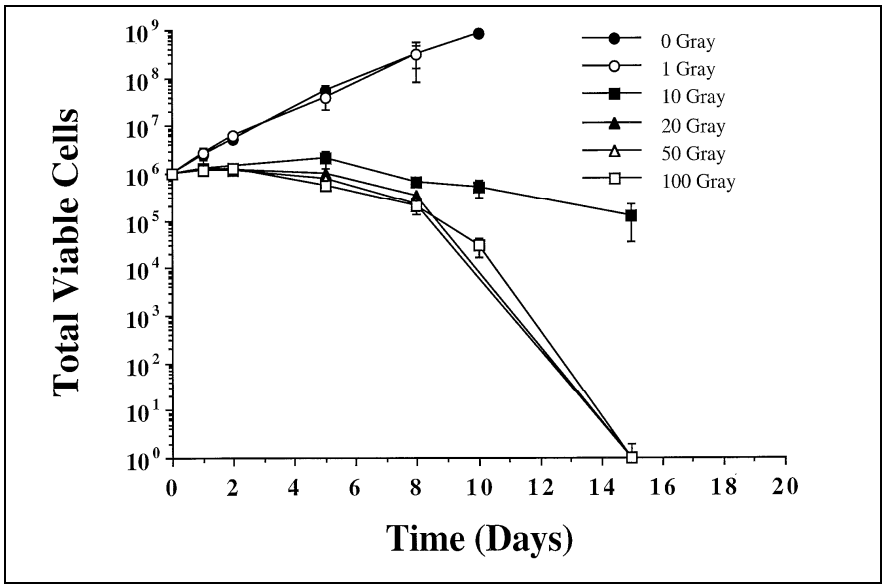
As can be seen in Figure 3, cells irradiated at 1 Gy showed very little cell death and proliferated at the same rate as non-irradiated controls. Cells that were irradiated at 10 Gy increased in number approximately 2-fold over a 5 day period, after which the cell number gradually declined over the remainder of the experiment. Long-term cultures of these cells (> 2 months) indicated that none of these cells ultimately survive this dose and go on to resume normal cell proliferation (data not shown).

Cells that were irradiated at higher doses (20-100 Gy) showed a small, but consistent increase in cell number in the first 1-3 days after irradiation. After the first couple of days, the number of viable cells gradually declines until day 10. After day 10, the number of viable cells decreases rapidly.

An overall increase in cell number after lethal irradiation is not unexpected since even very large doses of γ-rays do not immediately halt all cell processes. Much of the lethal effects of irradiation only become manifest after the cells have progressed through S-phase and mitosis and the lesions introduced into the DNA become fixed as point mutations, chromosome breaks, or other permanent types of chromosomal damage. While not all cells will complete their passage through mitosis and cell division, a significant proportion will successfully complete one round of cell division after irradiation, particularly at doses that, while lethal, do not induce massive amounts of DNA damage (e.g., 10 Gy).

Irradiation did not have a marked effect on GM-CSF secretion in the first three days following irradiation, and in general gm-csf secretion appears to depend on cell viability. Vials of clinical production lots 01002CK562G/A and 01002CK562G/B were irradiated at 100 Gy either after thawing or in the frozen state. Results are presented in Table 3. As can be seen, irradiation at 100

Figure 3 - γ-Irradiation Doses Needed to Induce Complete Lethality in K562 GM-CSF Cells



Gy appears to be suitable to maintain viability and GM-CSF expression. The final protocol requires irradiation of frozen vials at 100 Gy prior to thawing and dosing.

TABLE 3 – VIABILITY AND GM-CSF EXPRESSION AFTER IRRADIATION AT 100 GY

Lot #	Irradiation Treatment	Viability @ Thaw	Viability @ 24 hrs.	GM-CSF
01002CK562G/A	Unirradiated	90%	96%	15 μg/10^6 Cells/24 hrs.
	Thaw then Irradiate	86%	82%	11.7 μg/10^6 Cells/24 hrs.
	Irradiate Frozen	89%	90%	15 μg/10^6 Cells/24 hrs.
01002CK562G/B	Unirradiated	86%	ND	ND
	Thaw then Irradiate	86%	82%	8.8 μg/10^6 Cells/24 hrs.
	Irradiate Frozen	ND	ND	ND

Cell viability after irradiation was also assessed by measuring the amount of DNA replication occurring in the cells following irradiation. DNA replication was measured using ^{3}H-thymidine incorporation assays.

In these types of studies it is important to distinguish between the different mechanisms by which ^{3}H-thymidine becomes incorporated into the DNA. Immediately after irradiation, significant amounts of ^{3}H-thymidine will be incorporated into the DNA solely due to DNA repair. While DNA repair mechanisms play a key role in cell survival, the amount of ^{3}H-thymidine incorporated by DNA repair is unrelated to whether or not the cells will survive long term. Long term survival depends upon the ability of the cells to successfully undergo S-phase DNA replication. As such, it is S-phase ^{3}H-thymidine incorporation that is important to measure in assessing the lethality of the irradiation. Accurately measuring S-phase replication requires that the assay be performed after most DNA repair activity has ceased. DNA repair processes are generally completed by the time the cells transition through one complete round of the cell cycle. This is generally around 24 hours after irradiation although some cell cycle delay can occur in heavily damaged cells. After this period, most ^{3}H-thymidine incorporation will be primarily due to any S-Phase replication that is occurring. To eliminate the ^{3}H-thymidine signal due to DNA repair, the assay was run 48 hours after irradiation.

Furthermore, even in lethally irradiated cells, there is often a significant amount of S-phase DNA replication that will occur that does not correlate with long term cell survival. This is because radiation-induced lesions do not block cell entry into S-phase and mitosis. A significant proportion of the irradiated cells will progress through S-phase and enter mitosis even though there are numerous, un-repaired lesions in the DNA (termed error-prone DNA replication). A significant number of lethally irradiated cells will also successfully complete a single round of cell division. This post-irradiation round of cell division can be detected as a transitory increase in the total number of cells 1-2 days after irradiation (see Fig. 3, for example). It is in fact this error-prone DNA replication process that results in the lethal effects of irradiation since S-phase replication is where any un-repaired lesions are fixed into the mutations that cause lethality. Although this error-prone DNA replication can result in high cpms in ^{3}H-thymidine incorporation assays it is not necessarily indicative of long term cell viability. Long term viability requires that the cells be able to successfully passage through an indefinite number of replicative cycles. To get an accurate measure of long term DNA replication, the ^{3}H-thymidine assay was run a second time 18 days after irradiation.

The experiments were performed as follows. Three vials from each sublot were irradiated while frozen with 100 Gray. A fourth vial from each sublot was irradiated with 200 Gray to provide a lethally irradiated control. A fifth vial from each sublot was left un-irradiated to provide for a fully replication-competent control. Cells were thawed after irradiation and placed in culture. At 48 hours, and at 18 days after irradiation, aliquots of the cells were removed from each treatment group and used for ^{3}H-thymidine incorporation assays. The cell cultures were further maintained for another 4-5 weeks to determine if any outgrowth of cells would occur.

^{3}H-thymidine incorporation assays were performed by incubating cells in media containing 1 μCi/ml of ^{3}H-thymidine for 24 hours. After incubation, cells were harvested and the DNA isolated by phenol/chloroform extraction. Purified DNA was then spotted

onto filters and the amount of ^{3}H-thymidine incorporated determined in a 2000CA Liquid Scintillation Analyzer (Packard, Downers Grove, IL).

The results of these experiments are shown below in Table 4. Results are expressed as cpm/1x10^{5} cells. At 48 hours, the levels of incorporation in the un-irradiated controls were more than 10-fold greater than in any irradiated sample. This indicates that the majority of the irradiated cells are not actively replicating their DNA at this time point. However, there were low levels of incorporation in some of the irradiated samples. This most likely represents incorporation of thymidine from error-prone DNA replication that is associated with the first round of cell division following irradiation. By day 18, counts in all irradiated samples had declined to background levels, with no significant difference between cells irradiated at 100 Gray verses the 200 Gray control sample. Levels of cpm's in un-irradiated cells at 18 days were more than 200-fold greater than in any irradiated sample. Periodic observation of the cultures for a total of 7 weeks after irradiation has given no indication of any cell growth in the irradiated samples.

Table 4 – ^{3}H-thymidine Incorporation in K562GM-CSF cells

Sublot	Time After Irradiation	Dose	cpm/1 x 10^{5} Cells
Sublot A (1 x 10^{7} cells/mL)	48 hours	None	681,200
		100 Gray (replicate 1)	2,415
		100 Gray (replicate 2)	1,961
		100 Gray (replicate 3)	1,944
		200 Gray	6,649
Sublot B (5 x 10^{7} cells/mL)	48 hours	None	398,450
		100 Gray (replicate 1)	20,724
		100 Gray (replicate 2)	21,536
		100 Gray (replicate 3)	26,471
		200 Gray	11,317
Sublot A (1 x 10^{7} cells/mL)	18 Days	None	476,400
		100 Gray (replicate 1)	1,516
		100 Gray (replicate 2)	1,699
		100 Gray (replicate 3)	2,005
		200 Gray	1,279
Sublot B (5 x 10^{7} cells/mL)	18 Days	None	434,462
		100 Gray (replicate 1)	1,286
		100 Gray (replicate 2)	1,515
		100 Gray (replicate 3)	1,174
		200 Gray	1,173

14.2 **Appendix 2**.

Keystone Convention for grading of Acute GVHD[54]

ORGAN STAGE	SKIN*	LIVER	GUT
1	Rash < 25%	Bilirubin 2-2.9 mg/dl	Diarrhea 500-1000cc/d or biopsy-proven upper GI involvement
2	Rash 25-50%	Bilirubin 3-6 mg/dl	Diarrhea 1000-1500cc/d
3	Rash > 50%	Bilirubin 6.1-15 mg/dl	Diarrhea 1500-2000cc/d
4	Generalized erythroderma with bullae	Bilirubin > 15 mg/dl	Diarrhea > 2000 cc/d or severe abdominal pain with or without ileus
OVERALL GRADE			
I	Stage 1-2	None	None
II	Stage 3 or	Stage 1 or	Stage 1
III	-	Stage 2-3 or	Stage 2-4
IV	Stage 4 or	Stage 4	-

* Use “rule of nines” to determine body surface area

13.3 **Appendix 3** :

Safety Monitoring of Donors and Suggested Guidelines for Symptom Management

1.0 Adverse events associated with G-CSF administration

Side effects generally occur 1-2 days after the first dose of G-CSF and last 1-2 days after the final dose. Most donors experience bone pain, beginning after the second dose and described as mild-moderate. Additional symptoms include myalgia, fatigue, headache, and insomnia. Fever, nausea and vomiting are less common. Approximately 10-15% of donors experience a flu-like syndrome. All of these symptoms are usually treated with oral acetaminophen or occasionally narcotics.

Side effects of Apheresis

2.0.1 The apheresis procedure for PBSC collection is also a source of side effects and potential complications. The peripheral venous access may produce bruising, hematoma or mild bleeding.

Use of a citrate-based anticoagulant (e.g. ACD-A) may elicit symptoms of hypocalcemia: perioral numbness, paresthesias and carpopedal spasms. These symptoms may be treated with oral or IV calcium administration or by decreasing the ACD requirement by supplementing anticoagulation with heparin.

2.0.3 PBSC products contain large numbers of platelets, similar to a platelet apheresis product. It is common to encounter platelet counts < 100 x 10^9/L after two apheresis collections. Counts < 50 x 10^9/L are occasionally reported. Following completion of apheresis, platelet counts remain depressed for 3-5 days before rebounding to above normal levels

3.0 Treatment of donor symptoms

3.0.1 Some donors will experience bone pain. Acetaminophen, ibuprofen, naproxen and similar analgesics may be taken for bone pain. Rarely donors may require orally administered prescription analgesics. Because the donor's platelet count will fall with the collection of PBSC products, aspirin and aspirin-containing, drugs should be avoided during G-CSF administration and for 14 days following apheresis. Other symptoms that occur less frequently but may require treatment include headache, nausea, chills, night sweats, and body aches.

3.0.2 Symptoms that are intolerable may qualify for adjustment of the G-CSF dosage as below. Most often the daily dose of G-CSF will be decreased to ~5 μg/kg/day (see Table Appendix 1). If the symptoms are severe or persisting in spite of dose reduction, G-CSF may be stopped. All symptoms should disappear or diminish markedly 48 to 72 hours after the final G-CSF dose.

Guidelines for G-CSF dose reductions for donor symptoms (adapted from NMDP guidelines for PBSC collection from volunteer donors) are in Appendix 2, Table 1.

Appendix 3; Table 1

Guidelines for G-CSF dose reductions for donor symptoms

Symptom	Severity	G-CSF Dose Adjustment
Pain	Intolerable	~5 mcg/kg/day. If not improved in 24 h, hold G-CSF
Nausea	No significant oral intake	Hold
Vomiting	2-5 episodes in 24h	~5 mcg/kg/day
	>5 episodes in 24 h	Hold
Headache	Unrelenting and severe	~5 mcg/kg/day. If not improved in 24h, hold G-CSF
Insomnia	Difficulty sleeping despite medication	~5 mcg/kg/day. If not improved in 24 h, hold G-CSF
Leukocytosis	WBC >65 x 10^9	~5 mcg/kg/day
	WBC >100 x 10^9	Hold

13.4 Appendix 4: Guidelines for 10 mcg/kg/day G-CSF Dosing of Donors

Number of G-CSF Vials Given Per Day

Donor Weight (kg)	1.0mL (300mcg)Vials	1.6mL (480mcg)Vials	Daily G-CSF Dose (mcg/day)	Daily G-CSF Dose (mcg/kg/day)
45 to 54	0	1	480	10.6 to 8.9
55 to 69	2	0	600	10.9 to 8.7
70 to 85	1	1	780	11.1 to 9.2
86 to 95	3	0	900	10.5 to 9.5
96 to100	0	2	960	10.1 to 9.6
101 to 115	2	1	1080	10.6 to 9.4
116 and greater	4	0	1200	10.3 or less

13.5 Appendix 5. Staging of Chronic GVHD [55]

Table 2 Classification of Chronic Graft-Versus-Host Disease

Subclinical graft-versus-host disease:
Histologically positive but no clinical symptoms

Clinical limited chronic graft-versus-host disease:
Either or both
—Localized skin involvement
—Hepatic dysfunction (due to chronic GVHD)

Extensive chronic graft-versus-host disease:
Either
—Generalized skin involvement
or
—Localized skin involvement or hepatic dysfunction due to chronic GVHD or both
plus
—Liver histology showing chronic aggressive hepatitis, bridging necrosis, or cirrhosis
or
—Involvement of eye (Schirmer's test with less than 5 mm wetting; or
—Involvement of minor salivary glands or oral mucosa demonstrated on labial biopsy
or
—Involvement of any other target organ (lung, kidney)

13.6 Appendix 6

Disease Response Criteria

COMPLETE RESPONSE

All of the following are required for a period of at least 2 months:

- Absence of lymphadenopathy, hepatomegaly, or splenomegaly by physical examination and by appropriate radiographic techniques, if done.
- No constitutional symptoms.
- Polymorphonuclear leukocytes ≥1,500/μL.
- Platelets >100,000/μL.
- Hemoglobin >11.0 g/dL (untransfused).
- Bone marrow normocellular for age, lymphs <30%, no lymphoid nodules; if hypocellular marrow, repeat in 4 weeks.

PARTIAL RESPONSE

The following are required for a period of at least 2 months.

- ≥50% decrease in peripheral blood lymphocyte count from baseline, and
- ≥50% reduction in lymphadenopathy, and/or
- ≥50% reduction in the size of the liver and/or spleen (if abnormal before treatment).

Plus ≥1 of:

- Polymorphonuclear leukocytes ≥1,500/μL or 50% increase over baseline
- Platelets >100,000/μL or 50% increase over baseline
- Hemoglobin >11.0 g/dL or 50% increase over baseline (untransfused)

Otherwise CR with persistent nodules classified as nodular PR

Otherwise CR with persistent anemia or thrombocytopenia due to drug toxicity classified as PR and monitored prospectively.

PROGRESSIVE DISEASE

- ≥50% increase in sum of products of at least two lymph nodes on two consecutive exams 2 weeks apart (at least one node must be ≥2 cm); appearance of new palpable lymph nodes
- ≥50% increase in the size of the liver and/or spleen; appearance of palpable hepatomegaly or splenomegaly, which was not previously present.
- ≥50% increase in the absolute number of circulating lymphocytes to at least 5,000/μL.
- Transformation to a more aggressive histology (e.g., Richter's syndrome or PLL with >55% prolymphocytes).

STABLE DISEASE

- Patients who have not achieved a CR or PR but have not exhibited PD will be considered to have SD.

Source: Cheson B, Bennett J, et al. NCI-sponsored working group guidelines for chronic lymphocytic leukemia: revised guidelines for diagnosis and treatment. *Blood* 1996;87:4990-4997.

Research Consent Form
Dana-Farber/ Harvard Cancer Center
BIDMC/BWH/CH/DFCI/MGH/Partners Network Affiliates OPRS 01-17-06

Protocol Title:
Reduced intensity stem cell transplantation for advanced chronic lymphocytic leukemia followed by vaccination with irradiated autologous tumor admixed with GM-K562 cells

DF/HCC Principal Research Doctor / Institution:
Catherine Wu, MD/ DFCI

DF/HCC Site-Responsible Research Doctor(s) / Institution(s):
Jennifer Brown, MD PhD/ DFCI
Edwin P. Alyea, MD/ DFCI

A. INTRODUCTION

We are inviting you to take part in a clinical trial, a type of research study, because you have advanced chronic lymphocytic leukemia (CLL). Research is a way of gaining new knowledge. A person who participates in a research study is called a "subject" rather than a patient. This research study is evaluating whether the addition of a vaccine after reduced intensity transplant will be safe and beneficial as a possible treatment for advanced CLL. The vaccine used in this trial consists of your own leukemia cells (collected and banked on the companion study, DF/HCC # 06-200) mixed together with additional cells (called GM-K562 cells), that have been altered in the laboratory to secrete a hormone known as granulocyte macrophage-colony stimulating factor (GM-CSF). GM-CSF stimulates the cells of the immune system to attack tumor cells. It is expected that about 20 people will take part in this research study through the Dana-Farber Harvard Cancer Center (DF/HCC).

An organization that is supporting a research study either by giving money or supplying a treatment agent is called the "sponsor." The sponsor of this protocol is the Cancer Vaccine Center of the Dana-Farber Cancer Institute, and they are providing the GM-K562 cells.

This research consent form explains why this research study is being done, what is involved in participating in the research study, the possible risks and benefits of the research study, alternatives to participation, and your rights as a research subject. The decision to participate is yours. If you decide to participate, please sign and date at the end of the form. We will give you a copy so that you can refer to it while you are involved in this research study.

DFCI Protocol Number: 06-196	Date DFCI IRB Approved this Consent Form: September 20, 2012
Date Posted for Use: September 24, 2012	Date DFCI IRB Approval Expires: September 19, 2013
OHRS Version Date: 04/24/2012	

If you decide to participate in this research study, some tests will be done to see if you are eligible to be in the research study. These tests are called screening tests. The research study has certain requirements that must be met. If the screening tests show that you can be in the research study, you will be able to start on the study treatment.

If the tests show that you cannot be in the research study, you will not be able to participate in this research study. If you are not able to participate in the research study, the study doctors will discuss with you other treatment options and/or refer you back to your regular doctor.

We encourage you to take some time to think this over and to discuss it with other people and your doctor and to ask questions now and at any time in the future.

B. WHY IS THIS RESEARCH STUDY BEING DONE?

This research study is a Phase I clinical trial. Phase I clinical trials test the safety of an investigational intervention, in this case, vaccination with GM-K562 bystander cells together with your own leukemia cells, after transplantation. Phase I studies also try to define the appropriate dose of the study treatment to use for further studies. "Investigational" means that the vaccine, in this case, is still being studied and that research doctors are trying to find out more about it. It also means that the FDA (U.S. Food and Drug Administration) has not approved the vaccine for use for your type of cancer.

You are being asked to participate in this trial because you have advanced chronic lymphocytic leukemia (CLL). There is ample evidence to suggest that allogeneic (cells donated from a sibling or other compatible person) marrow or stem cell transplant can be effective therapy for CLL. This is because the new donor's immune system, that develops after transplantation, unlike a CLL patient's own immune system before transplantation, can have the ability to recognize and kill the leukemia cells. This powerful immune reaction against leukemia that is performed by the donor immune cells (or the "graft") is called the "graft-versus-leukemia" or GVL effect. In the past, allogeneic stem cell transplantation required the use of high dose chemotherapy and/or radiation just prior to stem cell infusion, and success in controlling or eliminating cancer was attributed to a combination of the high dose chemotherapy/radiotherapy and the GVL effect. However, this type of allogeneic transplant is limited due to the toxic nature of the chemotherapy/radiation, and its use is restricted to young patients

without other significant medical problems. Recently, allogeneic transplantation has been successfully performed using lower doses of chemotherapy and without radiation. These transplants are referred to as non-myeloablative or "reduced intensity" transplants. This approach has now made this form allogeneic stem cell transplantation possible for older patients and patients with other medical conditions.

Your doctor has determined that you are a candidate for a reduced intensity transplant as treatment for your CLL. One of the potential disadvantages of this approach is that the low dose chemotherapy used in this setting may not be sufficient to control your cancer, and there is a higher probability of early disease relapse. Previous studies with reduced-intensity transplantation in patients with advanced CLL (i.e. not in remission after chemotherapy) have indeed demonstrated high relapse and mortality within the first year. Part of the reason for this may be that the new donor immune system often takes several months to develop after transplantation, and in patients with refractory disease at transplant, the leukemia often recurs or progresses before any beneficial "graft-vs-leukemia" effect can be established. Therefore, one strategy to attack this problem would be early boosting of anti-tumor immunity through tumor vaccinations.

In recent years, researchers at the Dana-Farber Cancer Institute (DFCI) have discovered that vaccines made from a patient's own cancer cells, that have been engineered in the laboratory to produce a protein called GM-CSF, can be effective in stimulating a powerful immune response specific to that cancer. GM-CSF is a naturally occurring hormone in the body that helps our immune system fight infections and diseases. In these studies, vaccine was genetically engineered in the laboratory by using a virus to insert the GM-CSF gene into tumor cells. The cells were then irradiated, which means that they were placed in a machine that delivered a specific amount of radiation to the cells. This irradiation procedure allows the cells to be still capable of secreting GM-CSF for a period of time following injection, but causes them to be unable to grow and divide. Previous clinical trials performed at DFCI and other centers using these GM-CSF based vaccines have shown them to be safe in patients with advanced melanoma (a type of skin cancer), lung and ovarian cancer, as well as AML, and immune activity was observed in some patients.

One of the challenges of the initial studies was the process of inserting the GM-CSF gene into the patient's tumor cells. Some of the types of tumor cells were not very efficient at secreting the GM-CSF. A newer method utilizes a "cell line", which is a pure culture of cells maintained in the laboratory. In this case, we use a cell line known as K562 cells to carry the GM-CSF producing gene. These "GM-K562" cells

are myeloid leukemia cells, that lack immune markers that would otherwise cause them to be rapidly rejected by your own immune system. In order to use GM-K562 cells in a vaccine specific for CLL, the current study proposes to mix irradiated GM-K562 cells with your own leukemia cells (also irradiated) as a vaccine.

By combining your irradiated leukemia cells with the GM-CSF secreting K562 cells in one vaccine, we hope that the secretion of GM-CSF will attract cells of your new donor immune system to the vaccine site. Once there, when your donor's immune cells "see" your irradiated CLL cells they will attack them and hopefully any other remaining CLL cells that they may encounter in your body.

The purpose of this research study is to assess the safety and immune activity of the tumor vaccine, when administered after a reduced intensity transplant. All study participants will receive vaccines consisting of GM-K562 cells, combined with the same number of their own CLL cells. The first vaccination will occur early after transplant starting approximately 4-6 weeks after your transplant. One of the goals of this study is to determine whether these vaccinations will improve and accelerate your new immune system's ability to recognize and destroy your leukemia cells.

C. WHAT OTHER OPTIONS ARE THERE?

Taking part in this research study is voluntary. Instead of being in this research study, you have the following options:

- Standard treatment including chemotherapy alone without transplant.
- Reduced intensity allogeneic transplant without GM-CSF based vaccination. An allogeneic transplant means that the blood stem cells are donated from a sibling or other compatible person, not from the study subject him or herself.
- Allogeneic stem cell transplant using high dose chemotherapy or radiation
- Participation in another research study, using standard or investigational drugs/ vaccines.
- No therapy for your cancer.
- Receive comfort care, also called palliative care. This type of care may help to reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to treat your symptoms.

Please talk to the research doctor about your options before you decide whether you will take part in this research study.

D. WHAT IS INVOLVED IN THE RESEARCH STUDY?

Sometimes it is hard to keep track of all of the details and procedures that are part of a research study. We will describe them in this consent form and you can refer to this at any time during the research study. We will also provide you with a chart or a calendar that will be an easy reference for you to keep track of the procedures and treatments in this research study.

This trial can be divided into four phases: 1) Screening; 2) Reduced intensity transplant phase; 3) Vaccinations; and 4) Vaccine completion; as detailed below:

1. Screening phase

After signing this consent form, you will be asked to undergo some screening tests or procedures to find out if you can be in the research study. These tests and procedures are likely to be part of regular cancer care and may be done even if it turns out that you do not take part in the research study. If you have had some of these tests or procedures recently, they may or may not have to be repeated. Many of these tests must take place up to 21 days prior to the start of your treatment. Women of childbearing age will have a pregnancy test during their transplant workup.

If these tests show that you are eligible to participate in the research study, you will begin the study treatment. If you do not meet the eligibility criteria, you will not be able to participate in this research study.

The tests included for screening are:

- **A complete medical history**: This includes any information about any other illnesses you may have as well as a record of all the medications you are taking and a measurement of difficulty you may have performing everyday tasks.
- **Physical examination**: A member of the study team will conduct a physical examination, including measurement of your blood pressure, temperature, heart rate, height, weight as well an oxygen saturation test which is measured by a monitor that is placed around your index finger
- **Current status of your CLL** will be assessed so that the study team can determine how your disease has responded to chemotherapy.

Tests to evaluate this include CAT scans, analysis of bone marrow, and blood tests.

- **Blood tests**. These include routine blood chemistries and blood counts, as well as a blood test for the Human Immunodeficiency Virus (HIV) or the virus that causes AIDS. Blood tests for HIV are done to make sure it is safe for you to receive the vaccine. If the HIV test is positive, you will not be eligible for the study. If the HIV test is positive, you will be informed of the result and counseled regarding appropriate follow up with your physician.
- **Electrocardiogram**
- **Pregnancy test:** This is to make sure that you are not pregnant at the time of starting the study.
- **Immune assessment**: Approximately 4 tablespoons of blood to study the way your CLL and immune system react to the vaccine. Additional bone marrow may be taken (10-20 ml) at the time of bone marrow aspiration for purposes of future studies to measure the immune response against your leukemia.

If, in addition to these tests, you can show that:

(1) your CLL is unchanged (stable) or improved after additional chemotherapy to control your disease, which will be measured by CT scans, bone marrow tests and/or blood tests,; and
(2) you have an appropriate transplant donor, and
(3) that you have collected and stored on a previous research study your leukemia cells and these cells are available for vaccine generation.

then ***these screening procedures confirm that you are eligible to participate in the research study*** and the following tests described below will be performed to confirm the safety of your proceeding with reduced-intensity stem cell transplantation:

- **Pre-transplant evaluations**: The pre-transplant evaluations include:
  - **Heart function test (ECHO or MUGA)**- To perform this test you will be exposed to either ultrasound or a radioactive drug to determine how your heart is working. These tests will not affect you or the treatment of your disease.
  - **Pulmonary function test**- To perform this test you will be asked to blow into a tube connected to a machine that will measure how your lungs are working.

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- **Tuberculosis test (TB skin test)**- This will be a small injection under the skin. Two to three days after the small injection, you must return to the clinic for your doctor or nurse to examine the site of injection in order to determine if the TB test is positive or not.
- **Blood tests**- These include routine blood chemistries and blood counts to make sure that it will be safe for you to proceed to with transplantation. These tests do not form part of the assessment of your disease status.

If insufficient numbers of your leukemia cells to generate vaccine were collected on the CLL collection and banking study (DFHCC study #06-200), then you will not be eligible for this research study.

2. ALLOGENEIC REDUCED INTENSITY STEM CELL TRANSPLANT - The transplant phase of the study will begin when you are admitted to the hospital to receive the chemotherapy and stem cell transplant. The minimum duration of hospitalization for the procedure is approximately 8 days. Your hospital stay could be prolonged based on your medical conditions or complications. Undergoing transplant involves the following procedures and treatments during your hospital stay:

- **Central intravenous (into a vein) catheter (large i.v.)**: If you do not already have a large i.v. that is placed into a vein, such as a Hickman line or a Port-a-cath, you will need one to be placed in your chest at the time of hospital admission. These are intravenous catheters that can remain under your skin for several weeks that are placed while under general anesthesia, and provide a way to easily and safely give medications or cells to you. Both the chemotherapy you will receive to prepare your body to accept your donor's stem cells, and the stem cells themselves will be given through this catheter.

- **Chemotherapy-** These drugs include fludarabine, once daily over 30 minutes each day for 4 days and Busulfex twice daily for the same 4 days. These will all be given through your central intravenous line. The goal of this chemotherapy is to both control your cancer and suppress your immune system, so that your body will not reject the donor stem cells.

- **Medications to prevent graft versus host disease (GVHD)**. Just prior to and immediately following infusion of stem cells, you will receive two medications to help prevent graft-versus-host disease

(GVHD), a common complication of transplant where your donor's immune cells attack your body (see risk section below). One drug you will be given to prevent GVHD is called tacrolimus. Tacrolimus is an oral (taken by mouth) medication that you will start taking 3 days before the transplant and continue for about 5-6 months. By approximately 6 months after transplant, you will discontinue the tacrolimus. The second drug is called methotrexate, will be given as a 15 minute intravenous infusion on days 1, 3, 6 and 11 after the transplant. If you have been discharged from the hospital, you will receive this medication in clinic.

- **Medications to prevent infections**. After your transplant, you will also take antibiotic medications to help prevent possible infections (e.g. acyclovir, levofloxacin, etc.). G-CSF (Neupogen, Filgrastim), a white blood cell growth factor, will be given daily subcutaneously (injection under the skin) starting the day after the stem cell transplant until your blood counts have recovered.

- **Physical Exams**: During your hospitalization for transplant and following discharge to the outpatient clinic, you will have physical exams and you will be asked questions about your general health and specific questions about any problems that you might be having as well as any medications you may be taking.

- **Blood tests**. These include routine blood chemistries, blood counts and other blood tests to determine what percentage of cells in your blood are derived from your donor.

- **Bone marrow aspirate and biopsy**- Between 30-45 days after your transplant, a bone marrow aspirate and biopsy will be performed to assess the status of your disease and to look for evidence of your donor's cells in your bone marrow.

3. Vaccination Phase

Vaccinations will be given in approximately seven weeks and will begin approximately one month after your stem cells have been infused (at approximately day 30-45), provided that you have no evidence of significant GVHD.

- **CLL/GM-K562 vaccination**. Vaccines will consist of your own irradiated leukemia cells mixed with GM-K562 cells.

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- The irradiated CLL cells are your own leukemia cells that were collected, processed and stored in the DFCI Cell Manipulation Core Facility (CMCF) prior to your transplant.

- The GM-K562 cells are derived from a K562 cell line that has been modified at the Harvard Gene Therapy Initiative such that the gene for GM-CSF has been inserted into these cells. Thus, these cells have the ability to reliably secrete GM-CSF in effort to stimulate the immune system, but have been irradiated so that they do not have the ability to grow. These cells have also been collected and stored on a previous research study in our cell bank in the DFCI CMCF.

  When it is time for your vaccinations, the CMCF staff will prepare the vaccine by thawing a specific number of the CLL cells and a specific number of the GM-K562 cells and combining them in one syringe according to the protocol procedure.

  You will receive vaccines consisting an equal number of irradiated GM-K562 cells and your leukemia cells. The vaccine will be given 6 times over a period of 2 months. The vaccine will be injected subcutaneously and intradermally (injections under and into the skin). The locations of the vaccinations will be rotated at each visit between the arms and thighs. You will receive vaccination shots once weekly for 3 vaccines and then every other week for 3 vaccines until you have received a total of 6 vaccinations. You will not be allowed to use topical numbing cream before the injections as this could confuse the possibility of a reaction at the site of the vaccination. As a result, you might experience local pain. All vaccinations may be given as an outpatient in the clinic. During this period of time, you will continue to be followed closely by the study team on at least a biweekly basis to monitor for side effects. If, during the course of therapy, side effects develop that your doctors feel pose a threat to you, treatment will be stopped. You may stop treatment at any time whether or not side effects develop.

- **Skin biopsies.** Before the first vaccination, after the fifth vaccination, and four weeks following the sixth vaccination, a small amount of your own leukemia cells (killed) will be injected under your skin (like a TB test) to see if your donor's immune system will react against it and cause redness and swelling. For each of the

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leukemia cell injections and for the first and fifth vaccinations, you will be required to return to clinic two to three days after the injection, so that your doctor or nurse can examine the skin around the site of injection and perform a skin biopsy. If you develop a local skin reaction to any of the other vaccines, you may be asked to undergo a small skin biopsy for additional laboratory/pathologic evaluation. All skin biopsies are relatively simple outpatient procedures that will take 5-10 minutes to perform. A biopsy means that a small piece of skin tissue is removed. The area will be numbed first with a local anesthetic. A small stitch will be placed after the biopsy.

- **Current status of your CLL** will be assessed so that the study team can determine how your disease has responded to transplant and vaccination. Tests to evaluate this include analysis of bone marrow, and blood tests.

- **Immune assessment**. During the course of this study, we will be also be drawing your blood monthly to evaluate immune cells and the effect that the vaccinations may have on your new immune system.

The biopsies and blood tests we have discussed above will provide important information in helping to discover how the vaccine is working in you. We are also requesting permission to collect medical information from your chart and link this information to your specimens so that we may better understand how your treatment and response to treatment may affect the results of the laboratory studies. For samples obtained prior to beginning therapy, this information might also allow us to develop new ways of predicting responses to therapy. Finally, we are requesting your permission to store these samples to establish a specimen bank for future research. Studies from your samples may yield new information regarding your disease.

4. Vaccine Completion

After you completed vaccination, you will return to the outpatient clinic for monthly check-ups, to monitor the effects of the vaccine. The majority of these procedures are part of standard post-transplant cancer care. However, we are requesting additional blood tests for research purposes. During your monthly visit, you will undergo the following treatments and procedures:

- **A complete medical history**: This includes any information about any other illnesses you may have as well as a record of all the

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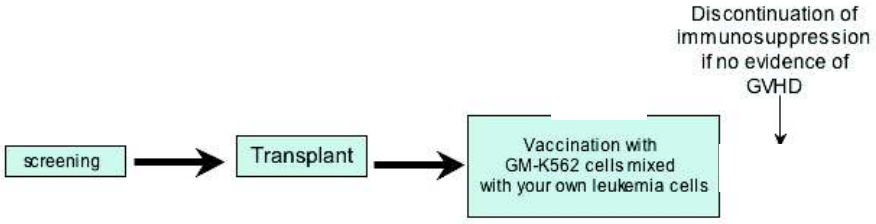
medications you are taking and a measurement of difficulty you may have performing everyday tasks.

- **Physical examination**: A member of the study team will conduct a physical examination, including measurement of your blood pressure, temperature, heart rate, height, weight as well an oxygen saturation by oximetry (which entails using a monitor that is put around your index finger). We will look to see if there are any signs of GVHD.
- **Blood tests**. These include routine blood chemistries and blood counts, and blood tests to determine to what extent your blood cells come from your donor.
- **Immune assessment**: Approximately 4 tablespoons of blood will be collected per visit to examine the way your CLL and immune system react to the vaccine.

Since this trial involves the use of genetically modified cells (GM-K562), it is recommended that subjects on this trial undergo annual checkups for at least 15 years, in order to monitor for long term effects of the vaccination treatment. While not required, it is preferred that study subjects return to the DFCI clinic for their annual check up. Keeping in touch with you and checking your condition every year helps us look at the long-term effects of the research study.

RESEARCH STUDY PLAN



E. HOW LONG WILL I BE IN THIS RESEARCH STUDY?

Since the study is planned for a total of twelve vaccines with six months of follow-up afterwards, it is expected that you will remain on study treatment and close follow-up for approximately one year from the time that you begin your vaccines. In addition, since this trial involves the use of genetically modified cells (GM-K562), it is recommended that subjects on this trial undergo annual checkups for

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at least 15 years if they receive vaccine, in order to monitor for long term effects of the vaccination treatment.

The research doctor may decide to take you off the research study treatment (vaccination) for many reasons including if:

- It is considered to be in your best interest
- The study treatment or procedures are found to be unsafe or ineffective
- There is any problem with following study treatments and procedures
- There are any problems with research funding or drug supply
- Your condition worsens
- Or any unforeseen reason

If you are removed from the research study treatment, the research doctor will explain to you why you were removed.

In addition, you can stop participating in the research study at any time. However, before you decide to stop participating in this research study, we encourage you to talk to the research doctor and your regular doctor first.

Disposition of your donor (allogeneic) transplant stem cells

At times more cells are collected from a donation than are needed to do the transplantation. If your physician determines that it is preferable to administer a dose of cells that is less than the complete collection, the extra cells will be frozen and stored in our freezers for your future use. After 10 years, the laboratory will discard any remaining stored cells if your doctor determines that they are no longer clinically useful to you. Alternatively, if your donor is related to you, you may request in writing that we transfer these frozen cellular products to another facility of your choice. If your donor is unrelated to you, these remaining cells will be discarded.

Disposition of your own (autologous) tumor cells used for vaccine production

The tumor cells that are collected from you prior to your transplant will be frozen to preserve them. If you are eligible for vaccine after your transplant, some of these cells will be used to manufacture your vaccine. Some of these tumor cells that are frozen may not be needed by you. Any cells you do not use will be stored in our freezers. The remaining stored cells will be discarded if your physician determines that you have no further clinical need for these cells. After 10 years, the laboratory will discard any remaining stored cells. Alternatively,

you (the recipient) can request in writing that we transfer the remaining tumor cells to another facility of your choice.

F. WHAT ARE THE RISKS OR DISCOMFORTS OF THE RESEARCH STUDY?

There are risks to taking part in any research study. One risk is that you may get a drug or dose of a drug that does not help treat your disease or that makes your condition or disease worse. Another risk is that there may be side effects.

All chemotherapy drugs have side effects, which can range from mild and reversible to severe, long lasting and possibly life-threatening. There is a great deal of variability among side effects of different drugs and between individuals. For investigational drugs, in this case, the vaccine, all of the risks are not known at this time. **You need to tell the research doctor or a member of the study team immediately if you experience any side effects.** You should also notify your regular doctor as soon as possible.

Since many drugs used to treat cancer are designed to cause the rapidly dividing cancer cells in your body to slow down or die, these drugs can also cause other rapidly dividing normal cells in your body to slow down or die. These include the blood cells that help to fight infection (white blood cells), the blood cells that help the blood clot (platelets), and the blood cells that carry oxygen in your body (red blood cells). When anticancer drugs cause a decrease in these blood cells, it is called bone marrow suppression. While you are participating in this research study, your blood cell levels will be monitored closely.

Please notify the research doctor, and your regular doctor if possible, if any of the following occur:

- A fever of 100.5 or above.
  This could be a sign of an infection. If you have a low white blood cell count, this can be serious, life-threatening or fatal. You may have to take antibiotics or be admitted to the hospital.

- Low energy or shortness of breath.
  This could be a sign of anemia (not enough red blood cells). If this becomes severe, you may need to come into the clinic or hospital to have a transfusion of red blood cells.

- You bruise easily, or, when injured, you do not stop bleeding.
  This could be a sign that your platelets (blood cells that help with clotting) are low. This can be serious or life-threatening. You may need to come into the clinic or hospital for a transfusion of platelets.

Many cancers are associated with an increased risk of blood clots forming that could lead to swelling in the legs and arms. These clots may travel to the lungs causing shortness of breath or to the brain causing a stroke. This may become serious and life threatening. Some chemotherapeutic drugs can increase this risk. It is important to let your research doctor and regular doctor know if you have increased shortness of breath or difficulty breathing.

Other common side effects include nausea, vomiting, and loss of appetite. You may also experience constipation, loose stools or diarrhea. It is important to increase your fluid intake if diarrhea occurs. If this becomes severe, you may have to be hospitalized and receive intravenous fluids.

Everyone in the research study will be watched carefully for side effects. You will be monitored during your chemotherapy to keep track of your blood counts and organ function, particularly your kidney and liver function. If you experience side effects, they may go away after you stop taking the study drug. Some side effects can be mild; but others can be long lasting and may never go away. Some may be life-threatening or fatal. You should talk to the research doctor about any side effects you may be experiencing.

During the research study, you will be notified of newly discovered side effects, which may affect your health or willingness to participate. You may be asked to sign a new consent form that shows that you have been informed of new information relating to this research study.

Since the effect of the study drug(s), in this case, the vaccine, taken with other medications may not be known, it is important that you tell the research doctor about all drugs, prescription and non-prescription drugs, herbal preparations and nutritional supplements that you are taking or planning to take.

While on the study, you are at risk for the side effects described below. You should discuss these with the researcher and/or your doctor. There may also be other side effects that we cannot predict. You may receive other drugs to make side effects less serious and uncomfortable. Many side effects go away shortly

after the vaccinations are stopped, but it is possible that side effects may develop which may be serious, long lasting or permanent.

Allogeneic transplantation (without vaccination) is a procedure with significant side effects, and carries a risk of mortality of approximate 20% at one year. Because this is a genetic engineering study, in the event of a fatal outcome, we are mandated to ask your family for permission to perform a post-mortem examination (or autopsy). This examination will help us ascertain the cause of death, and determine if the vaccinations had any beneficial or deleterious effect.

A significant risk to taking part in this study is the likelihood of receiving a vaccine that is not effective in helping to treat your disease. This means that you may spend time and experience side effects taking a vaccine that does not provide you with any health-related benefits.

Risks involved in this study may be divided into risks associated with the reduced intensity transplant (these risks would be the same even if you do not receive vaccinations), and risks associated with the vaccine (which is the investigational part of this trial). These risks are detailed below:

RISKS ASSOCIATED WITH REDUCED INTENSITY ALLOGENEIC TRANSPLANTATION:

Side effects common to all chemotherapy medications you will receive as preparation for your transplant:

Chemotherapy related side effects

Side effects associated with both Busulfex and Fludarabine:

Very Likely (>50%)

- Low blood counts
- Nausea
- Vomiting
- Diarrhea
- Fever
- Loss of appetite
- Loss of hair
- Infertility

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Unlikely (<20%)
- Lung, liver, and/or kidney problems
- Inflamed intestines which can cause diarrhea, abdominal pain, and nausea.

Rare side effects specifically associated with Fludarabine (<10%):
- Tissue swelling (edema)
- Tiredness, confusion
- Seizures
- Numbness and/or temporary partial paralysis of the legs

Rare side effects associated with Busulfex (<10%):
- Seizures
- Fluid around the heart
- Inflammation, scarring of the lungs (pulmonary fibrosis)

Risks associated with other medications:

Side effects of Tacrolimus
- Reversible liver damage- often associated with jaundice.
- Reversible kidney damage, which may lead to acute kidney failure and require hospitalization, possibly dialysis, and may lead to permanent kidney failure
- Tremors
- High blood pressure
- Diabetes

Side effects of Methotrexate
- Inflammation or ulceration of the stomach.
- Mouth sores
- Low blood counts
- Liver damage (uncommon at the dose used in this trial)
- Kidney damage (uncommon at the dose used in this trial)
- Lung damage (uncommon at the dose used in this trial)

Likely side effects associated with G-CSF (Filgrastim, Neupogen)
- Bone or joint pain
- Headache
- Fever/chills
- Nausea/vomiting

- Fatigue

Unlikely side effects associated with G-CSF (Filgrastim, Neupogen)
- Rash
- Diarrhea
- Abdominal Pain
- Liver dysfunction
- Injection site reaction

Using these drugs together or with other drugs not listed here may cause other side effects that are not seen when each drug is given alone. If any doctor other than your transplant doctor prescribes drugs for you, you must tell the transplant doctor right away.

Risks associated with stem cell infusion:
During your stem cell infusion, you will be closely monitored. Most people have no immediate reaction to the stem cell infusion. However, there are some risks associated with stem cell infusion.

Very Likely (>50%)
- Unpleasant taste and a disagreeable odor that may last for a few days if your donor's cells were frozen and then thawed prior to infusing them into you. In order to freeze the stem cells without damaging them, chemicals (preservative) are added. These sensations are a result of the preservative for freezing the cells.

Rare side effects associated with stem cell infusion (<10%):
- Low-grade fevers or chills in the first 24 hours after the infusion.
- A temporary drop in blood pressure, if the donor stem cells were previously frozen in the preservative
- Headache, if the donor stem cells were previously frozen in the preservative
- Severe allergic reaction

Risk of Non-Engraftment or Graft Rejection (failure of the donor blood cells to grow):

It is possible that the cells from your donor may not grow properly and that your own blood cells may not recover after the chemotherapy. If this occurs your blood counts will remain low and you will be at increased risk of infection and

bleeding which may be life threatening. Your doctors may recommend one of several steps to improve your blood counts including, but not limited to, increasing the growth factor medication dose, use of other growth factors or a second infusion of donor cells.

Risks associated with GVHD:

GVHD is the most common serious complication after allogeneic transplant. GVHD may involve the skin (rash or blisters), bowel (nausea, diarrhea, bowel pain) or cause inflammation of the liver (resulting in jaundice [yellow discoloration of your skin]). You will be followed closely to detect the presence, if any, of GVHD. GVHD can be a serious disease and can be fatal. If you develop GVHD, you may require treatment with drugs such as other immune suppressing agents. You will be taking medications in an attempt to prevent GVHD after the transplant. Medications that are given to prevent or treat GVHD suppress the immune system, and a person may get serious infections while on these medications. Some of these infections can be fatal.

Risks Related to Infection:

Following transplant, your immune function will likely recover slowly over the course of months, even as the number of cells in your blood becomes normal. In addition, as part of the treatment plan, you will be receiving medications that suppress the immune system in order to prevent GVHD. Together, these factors can put you at risk for a variety of bacterial, viral and fungal infections. As a preventive measure, you will be put on an antibiotic and antiviral medication after the transplant. However, even with this preventive step, you may still develop a serious infection, that could require prolonged treatment with medications to fight infections, such as antibiotics, antiviral drugs, or anti-fungal drugs, and even hospitalization. These infections can be fatal, and it is important to contact your doctor should you develop any symptoms of infection, such as fever, fatigue, chills, sweats, cough, headache, or any other signs that are not usual for you.

RISKS ASSOCIATED WITH GM-K562 CELL VACCINATIONS:

Common (>50%)

- Skin reactions at the injection site, such as redness, swelling or itching.

Unlikely (<10%)

- Reactions to the GM-CSF produced by the vaccine cells:

- Fever
- Joint pain or swelling
- Shortness of breath
- Fluid retention (weight gain or ankle swelling)
- Diarrhea
- Fatigue
- Elevated white blood cell counts (cells that help fight infection)
- Decrease in red blood cells (anemia)
- Thyroid gland abnormalities (elevation or decrease in thyroid blood tests)
- Kidney damage (abnormal urine production)
- Liver damage
- Allergic reaction that may include a rash, hives, fever, difficulty breathing, and low blood pressure. Although usually reversible with treatment, it can be severe or life threatening.

- It is theoretically possible that vaccination with GM-K562 cells mixed with your own tumor cells may increase your risk or worsen graft-versus-host disease (GVHD) after your transplant, see section on GVHD.
- Vaccination might lead to an autoimmune reaction in which an immune attack is made against normal body tissues. This might result in thyroid abnormalities, diabetes, or other conditions.
- Although your tumor cells will be irradiated to prevent their growth in you, it is possible, though unlikely, that they may grow after being injected in you causing new tumors.

Rare (<1%)

- There is a rare risk that even though the GM-K562 cells are irradiated to kill them, they may survive after injection for a prolonged period of time. This could cause high levels of GM-CSF to develop in your body. Many hundreds of doses of this vaccine have been given without any problem with the GM-K562 cells, but in 1 case the GM-K562 cells did survive after injection. These cells made increased levels of GM-CSF which caused a very high increase in a type of white blood cell (called eosinophils) (hypereosinophilic syndrome) this increase resulted in blood clots (extensive thrombosis) involving major organs including the heart, lungs and spleen which proved to be fatal. We will check your white blood cell count and the types of white blood cells, especially the type called "eosinophils", before you start the vaccine and we will check them frequently while you are receiving the vaccine. If we see a large increase in your white blood cell count or especially your eosinophil count we may

need to stop the vaccines and if necessary, we may need to treat you with steroids and or other medications.

- There is a rare risk of liver problems or failure which can cause fatigue, and jaundice (yellowing of the skin and eyes). Although this is usually mild and reversible, this can be serious or life threatening and may require hospitalization and surgery.

Due to the limited experience using this vaccine to treat patients, it is not possible to predict the exact likelihood of experiencing side effects.

RISK OF OTHER PROCEDURES:

Risks Associated with Bone Marrow Tests:
The side effects of bone marrow tests may include bleeding, bruising, and or pain in the hip-bone area. The pain may last for a couple of days. Less common side effects include infection at the place where the needle enters the skin. There may be an allergic reaction to the drug used to numb the area.

Risks Associated with Blood Tests:
Blood samples are drawn for the purpose of looking for many of these possible side effects and to study your body's reaction to the vaccine. Likely side effects of having your blood drawn are bleeding at the site, bruising and slight pain. Less likely effects are fainting and infection with inflammation of the vein at the site where the blood is drawn.

Risks of Skin Biopsy:

This procedure may be associated with complications such as pain, bleeding, infection, scarring and problems with wound healing. Local anesthetic numbing agents may be associated in unusual cases with central nervous system effects, including lightheadedness, dizziness, blurred vision, ringing in the ears, seizures, or respiratory arrest, or cardiovascular effects including a slow heart rate or low blood pressure. Allergic reactions may also occur rarely.

Reproductive Risks:
Because the drugs in this study can affect an unborn baby, you should not become pregnant or father a baby while on this study. You should also not nurse your baby while on this study. Let your doctor know if you become pregnant or find out that you are going to be the father of a child. If you have any questions

about the reproductive issues or about preventing pregnancy, please discuss them with the investigator or your doctor.

Radiation Risks Associated with Scans and X-Rays:
While you are in this research study, CT scans may be used to evaluate your disease. The total amount of radiation that you will get from these tests is relatively small and is not likely to be harmful to you or affect your disease.

Other Risks:
There is a possibility that a rare or previously unknown side effect may occur. It is not possible to measure the chances of such occurrences or their severity.

With chemotherapy given at standard doses for bone marrow transplant, there is a small risk of developing a secondary cancer. This risk seems to be most correlated with the administration of total body irradiation, which has not been included in the proposed regimen. While it is unlikely that a secondary cancer would occur as a result of the proposed regimen since the chemotherapy doses are much less than the standard transplant regimen, we cannot absolutely exclude this possibility.

Non-Physical Risks:
Because of side effects or the time required for tests and clinic visits while you are on this research study, you may be unable to keep up with your normal daily activities.

G. WHAT ARE THE BENEFITS OF THE RESEARCH STUDY?

Taking part in this research study may or may not make your health better. We hope the information learned from this research study will help doctors learn more about the CLL/GM-K562 vaccination following reduced intensity allogeneic stem cell transplantation as a treatment for CLL in the future.

H. CAN I STOP BEING IN THE RESEARCH STUDY AND WHAT ARE MY RIGHTS?

You have the right to choose not to sign this form. If you decide not to sign this form, you cannot participate in this research study.

You can stop being in the research study at any time. Tell the research doctor if you are thinking about stopping or decide to stop. He or she will tell you how to

stop. Leaving the research study will not affect your medical care. You can still get your medical care from your hospital or doctor.

If you choose to not participate, or if you are not eligible to participate, or if you withdraw from this research study, this will not affect your present or future care and will not cause any penalty or loss of benefits to which you are otherwise entitled.

It is important to tell the research doctor if you are thinking about stopping so risks from the GM-K562 vaccination following reduced intensity allogeneic stem cell transplantation can be evaluated by your research doctor. In some cases, the abrupt stopping of a drug can have risks in itself. Another reason to tell your research doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

I. WHAT ARE THE COSTS?

Taking part in this research study may or may not lead to added costs to you or your insurance company.

You will not be charged for the following parts of this research study:

- Laboratory costs associated with the preparation of the vaccine
- Costs of vaccine administration
- Costs of vaccine site and DTH skin biopsies
- Costs of research procedures involving material from the required bone marrow biopsies

Your insurance company will be charged for other portions of your care during this research study that are considered standard care. These include routine blood tests, physician examinations, radiological studies, and surgical procedures that are associated with your care. All costs related to your transplant, and medical treatment for transplant related complications will be billed through your insurance company. We will obtain prior approval from your insurance before you are admitted for transplantation. You may be responsible for co-payments and deductibles that are standard for your insurance coverage.

If you have questions about your insurance coverage, or the items you might be required to pay for, please call financial services for information. The contact information for financial services:

- Dana-Farber Cancer Institute: (617) 632-3455
- Brigham and Women's Hospital: (617) 732-5524 or (617) 732-7485

You will be responsible for the following additional costs:

- Parking
- Meals
- Travel and lodging

The National Cancer Institute provides an online resource to help people participating in cancer clinical trials understand which services their insurance company is required by law to pay. This can be found at the website below.

http://www.cancer.gov/clinicaltrials/learning/insurance-coverage

J. WHAT HAPPENS IF I AM INJURED OR SICK BECAUSE I TOOK PART IN THIS RESEARCH STUDY?

We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them.

Providing your care does not mean that DF/HCC or the research doctors are at fault, or that there was wrongdoing. There are no plans for DF/HCC to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

If you think you have been injured as a result of taking part in this research study, tell the person in charge of this research study as soon as possible. The research doctor's name and phone number are listed in this consent form.

K. WHAT ABOUT CONFIDENTIALITY?

We will take measures to protect the privacy and security of all your personal information, but we cannot guarantee complete confidentiality of study data.

Medical information created by this research study may become part of your hospital medical record. Information that does not become part of your medical

record will be stored in your study file. It may also become part of a DF/HCC research database called CORIS.

The results of this research study may be published. You will not be identified in publications without your permission.

L. WHOM DO I CONTACT IF I HAVE QUESTIONS ABOUT THE RESEARCH STUDY?

If you have questions about the study, please contact the research doctor or study staff as listed below:

Dana-Farber Cancer Institute

- Catherine J. Wu, MD 617 632-5943
- Edwin P. Alyea, MD 617-632-3903
- Jennifer Brown, MD, PhD 617 525-1326

24-hour contact: DFCI: Catherine Wu, MD, page at 617-632-2337 beeper 45385.

For questions about your rights as a research participant, please contact a representative of the Office for the Protection of Research Subjects at DFCI (617) 632-3029. This can include questions about your participation in the study, concerns about the study, a research related injury, or if you feel/felt under pressure to enroll in this research study or to continue to participate in this research study.

M. PRIVACY OF PROTECTED HEALTH INFORMATION

Federal law requires Dana Farber/Harvard Cancer Center (DF/HCC) and its affiliated research doctors, health care providers, and physician network to protect the privacy of information that identifies you and relates to your past, present, and future physical and mental health conditions ("protected health information"). If you enroll in this research study, your "protected health information" will be used and shared with others as explained below.

1. **What protected health information about me will be used or shared with others during this research?**

   - Existing medical records
   - New health information created from study-related tests, procedures, visits, and/or questionnaires

2. **Why will protected information about me be used or shared with others?**

   The main reasons include the following:
   - To conduct and oversee the research described earlier in this form;
   - To ensure the research meets legal, institutional, and accreditation requirements;
   - To conduct public health activities (including reporting of adverse events or situations where you or others may be at risk of harm); and
   - Other reasons may include for treatment, payment, or health care operations. For example, some medical information produced by this research study may become part of your hospital medical record because the information may be necessary for your medical care. (You will also be given a notice for use and sharing of protected health information.)

3. **Who will use or share protected health information about me?**

   - DF/HCC and its affiliated research doctors and entities participating in the research will use and share your protected health information. In addition, other DF/HCC offices that deal with research oversight, billing or quality assurance will be able to use and share your protected health information.

4. **With whom outside of DF/HCC may my protected health information be shared?**

   While all reasonable efforts will be made to protect the confidentiality of your protected health information, it may also be shared with the following entities:

   - Outside individuals or entities that have a need to access this information to perform functions on behalf of DF/HCC and its affiliates (for example, data storage companies, insurers, or legal advisors).
   - The sponsor(s) of the study, its subcontractors, and its agents: DFCI Cancer Vaccine Center

- Other research doctors and medical centers participating in this research, if applicable
- Federal and state agencies (for example, the Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, and/or the Office for Human Research Protections), or other domestic or foreign government bodies if required by law and/or necessary for oversight purposes. A qualified representative of the FDA and the National Cancer Institute may review your medical records.
- Hospital accrediting agencies
- A data safety monitoring board organized to oversee this research, if applicable

Some who may receive your protected health information may not have to satisfy the privacy rules and requirements. They, in fact, may share your information with others without your permission.

5. For how long will protected health information about me be used or shared with others?

- There is no scheduled date at which your protected health information that is being used or shared for this research will be destroyed, because research is an ongoing process.

6. Statement of privacy rights:

- You have the right to withdraw your permission for the research doctors and participating DF/HCC entities to use or share your protected health information. We will not be able to withdraw all the information that already has been used or shared with others to carry out related activities such as oversight, or that is needed to ensure quality of the study. To withdraw your permission, you must do so in writing by contacting the researcher listed above in the section: “Whom do I contact if I have questions about the research study?”
- You have the right to request access to your protected health information that is used or shared during this research and that is related to your treatment or payment for your treatment, but you may access this information only after the study is completed. To request this information, please contact the researcher listed above in the section: “Whom do I contact if I have questions about the research study?”

N. DOCUMENTATION OF CONSENT

My signature below indicates:

- I have had enough time to read the consent and think about participating in this study;
- I have had all of my questions answered to my satisfaction;
- I am willing to participate in this study;
- I have been told that my participation is voluntary and I can withdraw at any time

Signature of Participant or Legally Authorized Representative

Date

Relationship of Legally Authorized Representative to Participant

DFCI Protocol Number: 06-196	Date DFCI IRB Approved this Consent Form: September 20, 2012
Date Posted for Use: September 24, 2012	Date DFCI IRB Approval Expires: September 19, 2013
OHRS Version Date: 04/24/2012	

Adult Participants

To be completed by person obtaining consent:

The consent discussion was initiated on _____ (date).

Signature of individual obtaining consent: _____

Printed name of above: _____

Date: _____

☐ A copy of this signed consent form will be given to the participant or legally authorized representative, or, where the participant is a minor, the participant's parent or legal guardian.

For Adult Participants

☐ 1) The participant is an adult and provided consent to participate.

☐ 1a) Participant (or legally authorized representative) is a non-English speaker and signed the translated Short Form in lieu of English consent document:

As someone who understands both English and the language spoken by the participant, I interpreted and/or witnessed, in the participant's language, the researcher's presentation of the English consent form. The participant was given the opportunity to ask questions.

Signature of Interpreter/Witness: _____

Printed Name of Interpreter/Witness: _____

Date: _____

☐ 1b) Participant is illiterate

The consent form was read to the participant who was given the opportunity to ask questions.

Signature of Witness: _____

Printed Name of Witness: _____

Date: _____

☐ 2) The participant is an adult who lacks capacity to provide consent and his/her legally authorized representative:

☐ 2a) gave permission for the adult participant to participate

☐ 2b) did not give permission for the adult participant to participate

DFCI Protocol Number: 06-196	Date DFCI IRB Approved this Consent Form: September 20, 2012
Date Posted for Use: September 24, 2012	Date DFCI IRB Approval Expires: September 19, 2013
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Banking of chronic lymphocytic leukemia tumor cells for vaccine generation

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Protocol version 9.0; 8/12/2010

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1.0 INTRODUCTION

This trial will serve as a companion banking study to DFCI protocol # 06-196 "Reduced intensity stem cell transplantation for advanced chronic lymphocytic leukemia followed by vaccination with lethally irradiated autologous tumor cells admixed with granulocyte macrophage-colony stimulating factor secreting K562 cells." The purpose of the current study is to harvest and bank leukemia cells collected from patients with advanced CLL for future generation of autologous tumor cell vaccines.

Chronic lymphocytic leukemia (CLL) is a disease of clonal B cells, in which affected individuals demonstrate significant heterogeneity in clinical course. Whereas some patients experience an indolent disease course, others succumb to the disease rapidly despite intensive treatment. Conventional prognostic factors for CLL, established some 20-30 years ago, have included age, sex, clinical stage, degree of bone marrow infiltration, and lymphocyte doubling time.[1-3] Response to treatment also has high prognostic significance. Prognosis is poor in patients who have chemo refractory disease, or who have received more than 3 prior regimens. Keating et al. have reported that patients who have failed to respond to fludarabine or other purine analogs have a median survival of 8 months, and a 1 year survival of 40%. [4]

Vaccine approaches to the treatment of advanced CLL may have the potential to improve outcome for this disease. CLL, for many reasons, is an ideal disease in which to explore this immune-based therapeutic approach. First, while the disease course of CLL is heterogeneous, a subset of patients clearly demonstrate indolent disease kinetics, which is advantageous for providing adequate time for mounting an effective immune response. Second, conventional and newer prognostic factors [5-11] can readily identify a subset of CLL patients with poor risk, in whom more aggressive and/or novel therapeutic approaches may be warranted. Third, in a large subset of patients, autologous tumor cells, which are the best source of leukemia-associated antigens against which an anti-tumor immune response can be mounted, can be readily harvested from the peripheral blood or marrow of these patients, thus removing the barrier of feasibility for obtaining adequate numbers of tumor cells for vaccine generation.

2.0 STUDY OBJECTIVES

2.1 To collect up to 100 patient samples that could potentially be used to prepare autologous tumor cell vaccines

3.0 CONDITIONS OF ELIGIBILITY

3.1 Conditions of inclusion

3.1.1 Ability to harvest CLL cells from peripheral blood, lymph nodes or bone marrow, defined as >30% involvement of bone marrow intratrabecular space, or peripheral blood lymphocytosis >5000/microliter, or surgically accessible lymph nodes of $\geq$2 cm

3.1.2 ECOG performance status 0-2

3.1.3 Age ≥18 years

3.2 Conditions of exclusion

3.2.1 Uncontrolled infection

3.2.2 Leukemia with active CNS involvement

4.0 SUBJECT ENROLLMENT

Patients identified as being appropriate for this trial will be assessed by one of the clinical investigators for evaluation. After eligibility is confirmed and informed consent is obtained, the eligibility checklist and signed informed consent form will be submitted to the DF/HCC Quality Control Center (632-3761) for official registration of the patient.

5.0 TREATMENT PLAN

5.1 Patient leukemia cells will be collected for (a) potential vaccine development, (b) banking for potential future assessment of DTH response following vaccination, and (c) banking for potential future assessment of disease specific T cell responses following vaccination.

5.2 A goal of a minimum of 1.3×10^8 leukemia (CD5+CD19+) cells will be harvested.

5.3 Within 10 days prior to leukemia cell harvest, the following procedures will be performed:

5.3.1 CBC with differential

5.3.2 Peripheral blood flow cytometry to evaluate percent CLL cells (CD19+CD5+) that are circulating in the peripheral blood

5.3.3 Blood for infectious disease markers (IDMs) will be drawn according to CMCF policy as per AABB and FDA guidelines.

5.4 Leukemia cell harvest from peripheral blood: If the patient has peripheral blood lymphocytosis >5000/microliter, and peripheral leukemia cells are present, an appropriate volume of blood will be collected based on the subject's white blood cell count, with a minimum of 50 cc of blood, but no more than 250 cc blood collected per day.

5.4.1 Tumor cells can be collected by peripheral blood over no more than 2 different days, separated by no more than 10 days

5.4.2 Mononuclear cells from tumor-bearing peripheral blood will be isolated by Ficoll-Hypaque separation under GMP conditions, and cyropreserved under controlled-rate conditions in 10% DMSO, PlasmalyteA, and human serum albumin. Vials stored in vapor-phase liquid nitrogen (LN2).

5.5 If the tumor cell number collected by peripheral blood as described above is insufficient (i.e. $< 1.3 \times 10^8$ leukemia cells) for vaccine generation and DTH testing, then additional leukemia cell can be harvested via one or more of the following methods:

5.5.1 Leukapheresis

5.5.2 Dissociation of tumor cells from a surgically excised lymph node

5.5.3 Bilateral bone marrow aspiration under local anesthesia- no more than 200cc marrow should be aspirated from each side of the pelvis.

5.5.4 Cells collected by leukapheresis, dissociation of surgically excised lymph node or bone marrow aspiration will be processed as detailed in section 5.4.2.

5.6 Tumor cells for vaccination and immunologic evaluation will be cryopreserved and stored in vapor phase liquid nitrogen. At least 12 individual tumor aliquots will be prepared for each patient. Cell dose per aliquot will be fixed per individual patient at 1×10^7 tumor cells (CD5+CD19+) per aliquot. For cell yields greater than 1.3×10^8 leukemia (CD5+CD19+) cells, extra aliquots will be cryopreserved according to standard lab practice.

5.7 Tumor cells will also be banked for the DTH studies and will be cryopreserved at approximately 1×10^6 cells per aliquot.

5.8 Additional aliquots of CLL cells that are not used for vaccine preparation or DTH may be used for research studies, including studies of immune responses against CLL, of gene expression and of immunophenotyping.

6.0 **ANTICIPATED TOXICITY**

6.1 Risks associated with blood draws: Pain and erythema and/or ecchymosis at the needle insertion site. Possibility of fainting at the time of blood draw.

6.2 Risks associated with leukapheresis: These reactions or side effects are usually reversible when the procedure is stopped or with the correct medical care, and may include:

6.2.1 Light-headedness or dizziness while blood is being drawn or processed during apheresis.

6.2.2 In individuals with a history of migraines or asthma, apheresis could cause symptoms of these problems to recur.
6.2.3 Tingling of lips and fingers, sensations of feeling faint or mild chest tightness, and cough related to the anticoagulant used in apheresis.
6.2.4 Low blood pressure, high blood pressure, or a slow pulse can occur. These reactions can also be due to the anticoagulant used in apheresis.
6.2.5 Bruising or infection may occur at the sites where needles are inserted.
6.2.6 Anemia may occur if red cells and plasma cannot be returned due to problems with IV lines or apheresis equipment.
6.2.7 Rare, serious or life-threatening allergic reactions.

6.3 Risks associated with bone marrow aspiration: The side effects of bone marrow tests may include bleeding, bruising, and or pain in the posterior iliac area. The pain may last for a couple of days. Less common side effects include skin infection at site of needle entry. There may be an allergic reaction to lidocaine, which is used for local anesthesia.

6.4 Risks associated with lymph node biopsy: Pain and erythema and/or ecchymosis at the biopsy site. The pain may last for a couple of days. Less common side effects include skin infection at the biopsy site. There may be an allergic reaction to lidocaine, which is used for local anesthesia.

6.5 Special care will be taken to ensure that patients understand that storage is for potential vaccine production and does not guarantee participation in the vaccine trial. If less than the goal number of tumor cells are collected, then the patient will be unable to participate on DFHCC 06-196.

7.0 REQUIRED EVALUATIONS

The following studies will be performed.
:

Evaluations	At study enrollment
Informed Consent	X
Medical History	X
Physical Exam	X
CBC with differential	X
Bun/Cr, LFTs, LDH	X
Peripheral blood flow cytometry	X
Beta-2- microglobulin	X
Approximately 50 cc peripheral blood to CMCF	X

8.0 REFERENCES

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Research Consent Form
Dana-Farber/ Harvard Cancer Center
BIDMC/BWH/CH/DFCI/MGH/Partners Network Affiliates

OPRS 01-1706

Protocol Title:
Banking of chronic lymphocytic leukemia tumor cells for vaccine generation

DF/HCC Principal Research Doctor / Institution:
Catherine Wu, MD / DFCI

DF/HCC Site-Responsible Research Doctor(s) / Institution(s):
Jennifer Brown, MD PhD / DFCI;
Edwin P. Alyea, MD / DFCI

A. INTRODUCTION

We are inviting you to take part in a clinical trial, a type of research study, because you have advanced chronic lymphocytic leukemia (CLL) that is not in clinical remission. Research is a way of gaining new knowledge. A person who participates in a research study is called a "participant" rather than a patient.

An organization that is supporting a research study either by giving money or supplying a treatment agent is called the "sponsor." The sponsor of this protocol is the Cancer Vaccine Center of the Dana-Farber Cancer Institute, and they are providing a new vaccine for CLL.

This research consent form explains why this research study is being done, what is involved in participating in the research study, the possible risks and benefits of the research study, alternatives to participation, and your rights as a research participant. The decision to participate is yours. If you decide to participate, please sign and date at the end of the form. We will give you a copy so that you can refer to it while you are involved in this research study.

If you decide to participate in this research study, some tests will be done to see if you are eligible to be in the research study. These tests are called screening tests. The research study has certain requirements that must be met. If the screening tests show that you can be in the research study, you will be able to start on the study treatment.

If the tests show that you cannot be in the research study, you will not be able to participate in this research study. If you are not able to participate in the research study, the study doctors will discuss with you other treatment options and/or refer you back to your regular doctor.

We encourage you to take some time to think this over and to discuss it with other people and your doctor and to ask questions now and at any time in the future.

DFCI Protocol Number: 06-200	Date DFCI IRB Approved this Consent Form: 01/29/2013
Date Posted for Use: 01/29/2013	Date DFCI IRB Approval Expires: 01/28/2014

B. WHY IS THIS RESEARCH STUDY BEING DONE?

You are being asked to participate in this trial because you have chronic lymphocytic leukemia (CLL) that is not in clinical remission.

The purpose of the current research study is to collect, freeze and store leukemia cells from your blood or bone marrow. These cells may be used to prepare CLL tumor cell vaccines in the future. This study is a companion study to clinical trial, DF/HCC clinical trial 06-196 in which your own CLL cells may form part of a vaccine treatment for your leukemia. There is a separate consent form for this vaccine study and it will be given to you for you to read. It is important to understand that even if you consent to allow us to save your leukemia cells, we cannot guarantee that you may be able to receive a vaccine. First, we may not be able to make enough vaccine from your collected cells. Second, you may not be able to participate in a vaccine study in the future, for reasons related to the status of your overall health. Third, an appropriate vaccine trial may not be available in the future. Leftover leukemia cells that are not used to make a vaccine may be banked for future studies for research purposes.

C. WHAT OTHER OPTIONS ARE THERE?

Taking part in this research study is voluntary. Instead of being in this research study, you have the option of not allowing your leukemia cells to be stored to make a vaccine and for other research.

Please talk to the research doctor about your options before you decide whether you will take part in this research study.

D. WHAT IS INVOLVED IN THE RESEARCH STUDY?

Screening phase – If you choose to take part in this study, and after you have given your consent, you will first undergo a series of tests or procedures to find out if you can be in the research study. These tests and procedures are likely to be part of regular cancer care and may be done even if it turns out that you do not take part in the research study. If you have had some of these tests or procedures recently, they may or may not have to be repeated. Many of these tests must take place up to 30 days prior to the start of your treatment. Women of childbearing potential may undergo pregnancy testing closer to the time of cell collection.

If these tests show that you are eligible to participate in the research study, you will begin the study treatment. If you do not meet the eligibility criteria, you will not be able to participate in this research study.

The tests included for screening are:

- **A complete medical history**: This includes any information about any other illnesses you may have as well as a record of all the medications you are taking and a measurement of difficulty you may have performing everyday tasks.
- **Physical examination**: A member of the study team will conduct a physical examination, including measurement of your blood pressure, temperature, heart rate, height, weight as well as oxygen saturation as measured by a monitor placed on the outside of your index finger.
- **Current status of your CLL** will be assessed so that the study team can estimate if it will be possible to collect enough of your leukemia cells to make future vaccine. Tests to evaluate this include blood tests.
- **Blood tests**. These include routine blood chemistries and blood counts, as well as a blood test for the Human Immunodeficiency Virus (HIV) or the virus that causes AIDS. Blood tests for HIV are done to make sure it is safe for you to receive the vaccine. If the HIV test is positive, you will not be eligible for the study. If the HIV test is positive, you will be informed of the result and counseled regarding appropriate follow up with your physician.
- **Electrocardiogram**

After the screening procedures confirm that you are eligible to participate in the research study: you will undergo the following tests and treatment, as described below:

- **Leukemia cell collection**- In order to make the vaccine, leukemia cells will be collected by one or more of the following methods:
    - drawing blood (up to 16-18 tablespoons per day) during one to two visits to the clinic. Within two days before the clinic visit to draw blood, some blood tests will be performed to determine the percent of leukemia cells in your blood.
    - If the leukemia cell number collected by blood draw is insufficient, you may undergo a procedure called leukapheresis, Leukapheresis is a procedure in which your blood will be allowed to flow out of an intravenous (i.v.) catheter in one arm, run through a machine where the leukemia cells will be removed, and the remaining blood returned to you through an i.v. in the opposite arm.

- By ***bone marrow aspiration***. Bone marrow aspiration is a procedure in which a needle is put in your rear hip bone under anesthesia (may be local or general), and bone marrow, which contains the leukemia cells, is pulled out using a syringe

  By ***surgery to remove a lymph node*** that has CLL cells. In this procedure, anesthesia (may be local or general) is given, and a lymph node that contains leukemia cells is cut out. Subsequently, the skin over the area where the lymph node was removed is sewn back together.

Your physician will discuss with you which approach is best in your case to ensure the highest number of tumor cells is collected. We anticipate that for most patients, sufficient leukemia cells will be obtained either with the blood draws or by leukapheresis. After collection, the leukemia cells will be transported to the Cell Manipulation Core Facility (CMCF) at the Dana-Farber Cancer Institute, where they will be frozen until the time of vaccine administration.

E. HOW LONG WILL I BE IN THIS RESEARCH STUDY?

You will be in this study until we extract the leukemia cells.

If an insufficient amount of cells are collected to make the vaccine, you may not be eligible to partcipate in the DF/HCC clinical trial 06-196. If you become ineligible for a vaccine study, then your frozen cells will be stored indefinitely for purposes of research studies for 10 years for the purpose of research studies.

F. WHAT ARE THE RISKS OR DISCOMFORTS OF THE RESEARCH STUDY?

There are risks to taking part in any research study.

The following include some of the physical risks associated with participating on this study*:*

Risks associated with blood draws: Blood samples are drawn for the purpose of looking for many of these possible side effects.

Likely side effects of having your blood drawn are:

- Bleeding at the site of blood draw
- Bruising at the site of blood draw
- Slight pain at the site of blood draw

Less likely effects are:

- Fainting
- Infection with inflammation of the vein at the site where the blood is drawn.

Risks associated with leukapheresis: These reactions or side effects are usually reversible when the procedure is stopped or with the correct medical care, and may include:

- Light-headedness or dizziness while blood is being drawn or processed during leukapheresis.
- In individuals with a history of migraines or asthma, leukapheresis could cause symptoms of these problems to recur.
- Tingling of lips and fingers, sensations of feeling faint or mild chest tightness, and cough related to the anticoagulant used in leukapheresis.
- Low blood pressure, high blood pressure, or a slow pulse can occur. These reactions can also be due to the anticoagulant used in leukapheresis.
- Bruising or infection may occur at the sites where needles are inserted.
- Anemia may occur if red cells and plasma cannot be returned due to problems with IV lines or leukapheresis equipment.
- Rare, serious or life-threatening allergic reactions.

Risks associated with bone marrow aspiration: The side effects of bone marrow tests may include:

- Bleeding
- Bruising, and/or
- Pain in the posterior iliac area (back of the hip). The pain may last for a couple of days

Less common side effects include:

- Skin infection at site of needle entry.
- An allergic reaction to lidocaine, which is used for local anesthesia.

Risks associated with lymph node biopsy: The side effects of lymph node biopsy may include:

- Pain, inflammation, irritation or bruising at the biopsy site. The pain may last for a couple of days.

Less common side effects include:

- Skin infection at the biopsy site;
- An allergic reaction to lidocaine, which is used for local anesthesia

Non-physical risks include the possibility that you will not receive vaccine because your medical condition changed in a way that made you ineligible for the vaccine study or there were technical problems with the processing and storage of the collected leukemia cells. Another risk is that the vaccine treatment may not provide you with any health related benefits.

G. WHAT ARE THE BENEFITS OF THE RESEARCH STUDY?

Taking part in this research study may or may not make your health better. We hope the information learned from this research study will help doctors learn more about the use of patients' own leukemia cells as a vaccine as a treatment for CLL in the future.

H. CAN I STOP BEING IN THE RESEARCH STUDY AND WHAT ARE MY RIGHTS?

You have the right to choose not to sign this form. If you decide not to sign this form, you cannot participate in this research study.

You can stop being in the research study at any time. Tell the research doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop. Leaving the research study will not affect your medical care. You can still get your medical care from your hospital or doctor.

If you choose to not participate, or if you are not eligible to participate, or if you withdraw from this research study, this will not affect your present or future care and will not cause any penalty or loss of benefits to which you are otherwise entitled.

I. WHAT ARE THE COSTS?

Taking part in this research study may or may not lead to added costs to you or your insurance company.

You will not be charged for the following that are part of this research study:

- Collection, processing and storage of your cells.

Your insurance company will be charged for other portions of your care during this research study that are considered standard care. These include routine blood tests, physician examinations, radiological studies, and surgical procedures, including biopsies, that are associated with your care. You may be responsible for co-payments and deductibles that are standard for your insurance coverage.

If you have questions about your insurance coverage, or the items you might be required to pay for, please call financial services for information. The contact information for financial services:

- Dana Farber Cancer Institute: (617) 632-3455
- Brigham and Women's Hospital: (617) 732-5524 or (617) 732-7485

The National Cancer Institute provides an online resource to help people participating in cancer clinical trials understand which services their insurance company is required by law to pay. This can be found at the website below.

http://www.cancer.gov/clinicaltrials/learning/insurance-coverage

J. WHAT HAPPENS IF I AM INJURED OR SICK BECAUSE I TOOK PART IN THIS RESEARCH STUDY?

We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them.

Providing you with medical care does not mean that DF/HCC or the research doctors are at fault, or that there was wrongdoing. There are no plans for DF/HCC to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

If you think you have been injured as a result of taking part in this research study, tell the person in charge of this research study as soon as possible. The research doctor's name and phone number are listed in this consent form.

K. WHAT ABOUT CONFIDENTIALITY?

We will take measures to protect the privacy and security of all your personal information, but we cannot guarantee complete confidentiality of study data. Medical information created by this research study may become part of your hospital medical record. Information that does not become part of your medical record will be stored in your study file. It may also become part of a DF/HCC research database called CORIS.

The results of this research study may be published. You will not be identified in publications without your permission.

L. WHOM DO I CONTACT IF I HAVE QUESTIONS ABOUT THE RESEARCH STUDY?

If you have questions about the study, please contact the research doctor or study staff as listed below:

Dana-Farber Cancer Institute

- Catherine J. Wu, MD: 617 632-5943
- Jennifer Brown, MD PhD: 617 632-6692
- Edwin P. Alyea, MD: 617-632-3903

24-hour contact: DFCI: Catherine Wu, MD, page at 617-632-2337 beeper 45385.

For questions about your rights as a research participant, please contact a representative of the Office for the Protection of Research Subjects at DFCI (617) 632-3029. This can include questions about your participation in the study, concerns about the study, a research related injury, or if you feel/felt under pressure to enroll in this research study or to continue to participate in this research study.

M. PRIVACY OF PROTECTED HEALTH INFORMATION

Federal law requires Dana-Farber/Harvard Cancer Center (DF/HCC) and its affiliated research doctors, health care providers, and physician network to protect the privacy of information that identifies you and relates to your past, present, and future physical and mental health conditions ("protected health information"). If you enroll in this research study, your "protected health information" will be used and shared with others as explained below.

1. **What protected health information about me will be used or shared with others during this research?**

   - Existing medical records
   - New health information created from study-related tests, procedures, visits, and/or questionnaires

2. **Why will protected information about me be used or shared with others?**

   The main reasons include the following:
   - To conduct and oversee the research described earlier in this form;
   - To ensure the research meets legal, institutional, and accreditation requirements;
   - To conduct public health activities (including reporting of adverse events or situations where you or others may be at risk of harm); and
   - Other reasons may include for treatment, payment, or health care operations. For example, some medical information produced by this research study may become part of your hospital medical record because the information may be necessary for your medical care. (You will also be given a notice for use and sharing of protected health information.)

3. **Who will use or share protected health information about me?**

   - DF/HCC and its affiliated research doctors and entities participating in the research will use and share your protected health information. In addition, other DF/HCC offices that deal with research oversight, billing or quality assurance will be able to use and share your protected health information.

4. **With whom outside of DF/HCC may my protected health information be shared?**

   While all reasonable efforts will be made to protect the confidentiality of your protected health information, it may also be shared with the following entities:

   - Outside individuals or entities that have a need to access this information to perform functions on behalf of DF/HCC and its affiliates (for example, data storage companies, insurers, or legal advisors).
   - The sponsor(s) of the study, its subcontractors, and its agents: DFCI Cancer Vaccine Center
   - Other research doctors and medical centers participating in this research, if applicable

- Federal and state agencies (for example, the Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, and/or the Office for Human Research Protections), or other domestic or foreign government bodies if required by law and/or necessary for oversight purposes. A qualified representative of the FDA and the National Cancer Institute may review your medical records.
- Hospital accrediting agencies
- A data safety monitoring board organized to oversee this research, if applicable

Some who may receive your protected health information may not have to satisfy the privacy rules and requirements. They, in fact, may share your information with others without your permission.

5. For how long will protected health information about me be used or shared with others?

- There is no scheduled date at which your protected health information that is being used or shared for this research will be destroyed, because research is an ongoing process.

6. Statement of privacy rights:

- You have the right to withdraw your permission for the research doctors and participating DF/HCC entities to use or share your protected health information. We will not be able to withdraw all the information that already has been used or shared with others to carry out related activities such as oversight, or that is needed to ensure quality of the study. To withdraw your permission, you must do so in writing by contacting the researcher listed above in the section: “Whom do I contact if I have questions about the research study?”
- You have the right to request access to your protected health information that is used or shared during this research and that is related to your treatment or payment for your treatment, but you may access this information only after the study is completed. To request this information, please contact the researcher listed above in the section: “Whom do I contact if I have questions about the research study?”

N. DOCUMENTATION OF CONSENT

My signature below indicates my willingness to participate in this research study and my understanding that I can withdraw at any time.

Signature of Participant
or Legally Authorized Representative

Date

DFCI Protocol Number: 06-200	Date DFCI IRB Approved this Consent Form: 01/29/2013
Date Posted for Use: 01/29/2013	Date DFCI IRB Approval Expires: 01/28/2014

To be completed by person obtaining consent:

The consent discussion was initiated on _____ (date).

☐ A copy of this signed consent form will be given to the participant or legally authorized representative, or, where the participant is a minor, the participant's parent or legal guardian.

For Adult Participants

☐ The participant is an adult and provided consent to participate.

☐ Participant is a non-English speaker and signed the translated Short Form in lieu of English consent document

As someone who understands both English and the language spoken by the participant, I interpreted, in the participant's language, the researcher's presentation of the English consent form. The participant was given the opportunity to ask questions.

Signature of Interpreter: _____

Printed name of Interpreter: _____

Date: _____

☐ The participant is an adult who lacks capacity to provide consent and his/her legally authorized representative:

☐ gave permission for the adult participant to participate

☐ did not give permission for the adult participant to participate

Signature of Individual obtaining consent: _____

Printed name of above: _____

Date: _____

DFCI Protocol Number: 06-200	Date DFCI IRB Approved this Consent Form: 01/29/2013
Date Posted for Use: 01/29/2013	Date DFCI IRB Approval Expires: 01/28/2014

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

ICMJE Form for Disclosure of Potential Conflicts of Interest

Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. Identifying information.

Enter your full name. If you are NOT the corresponding author please check the box "no" and a space to enter the name of the corresponding author in the space that appears. Provide the requested manuscript information. Double-check the manuscript number and enter it.

2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes". Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence,or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. Other relationships.

Use this section to report 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.

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): Catherine
2. Surname (Last Name): Wu
3. Effective Date (07-August-2008): 27-March-2013

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

5. Manuscript Title: Autologous CLL cell vaccination early after transplant induces leukemia-specific T-cells

6. Manuscript Identifying Number (if you know it): 69098-RG-1

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	☐	☐	☑	NCI R21 and NIH R01		×
1. Grant	☐	☐	☑	Claudia Adams Barr Program in Cancer Research		×
1. Grant	☐	☐	☑	Leukemia and Lymphoma Translational Research Program		×
1. Grant	☐	☐	☑	Early Career Physician-Scientist Award, Howard Hughes Medical Institute		×
1. Grant	☐	☐	☑	Damon-Runyon Cancer Research Foundation - Clinical Investigator		×
						ADD
2. Consulting fee or honorarium	☑	☐	☐			×
						ADD

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

ICMJE Form for Disclosure of Potential Conflicts of Interest

The Work Under Consideration for Publication

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

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Relevant financial activities outside the submitted work

Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
						ADD
3. Employment	☑	☐	☐			×
						ADD
4. Expert testimony	☑	☐	☐			×
						ADD
5. Grants/grants pending	☑	☐	☐			×
						ADD
6. Payment for lectures including service on speakers bureaus	☑	☐	☐			×
						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

* 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.

ICMJE Form for Disclosure of Potential Conflicts of Interest

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?

- [x] 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

Evaluation and Feedback

Please visit http://www.icmje.org/cgi-bin/feedback to provide feedback on your experience with completing this form.

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

ICMJE Form for Disclosure of Potential Conflicts of Interest

Instructions

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1. Identifying information.

Enter your full name. If you are NOT the corresponding author please check the box "no" and a space to enter the name of the corresponding author in the space that appears. Provide the requested manuscript information. Double-check the manuscript number and enter it.

2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes". Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. Relevant financial activities outside the submitted work.

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Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

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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): Ana
2. Surname (Last Name): Brusic
3. Effective Date (07-August-2008): 01-April-2013

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

5. Manuscript Title: Autologous CLL cell vaccination early after transplant induces leukemia-specific T-cells

6. Manuscript Identifying Number (if you know it): 69098-RG-1

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

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

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The Work Under Consideration for Publication

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

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

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

ICMJE Form for Disclosure of Potential Conflicts of Interest

Relevant financial activities outside the submitted work

Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
						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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1. Given Name (First Name): Ann
2. Surname (Last Name): Perrin
3. Effective Date (07-August-2008): 29-March-2013

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

Corresponding Author's Name: Catherine Wu

5. Manuscript Title: Autologous CLL cell vaccination early after transplant induces leukemia-specific T-cells

6. Manuscript Identifying Number (if you know it): 69098-RG-1

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

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7. Other	☑	☐	☐			✕
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Section 1. Identifying Information

1. Given Name (First Name): Anselmo
2. Surname (Last Name): Alonso
3. Effective Date (07-August-2008): 01-April-2013

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

5. Manuscript Title: Autologous CLL cell vaccination early after transplant induces leukemia-specific T-cells

6. Manuscript Identifying Number (if you know it): 69098-RG-1

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						ADD
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						ADD
5. Payment for writing or reviewing the manuscript	☑	☐	☐			×
						ADD
6. Provision of writing assistance, medicines, equipment, or administrative support	☑	☐	☐			×

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						ADD
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1. Given Name (First Name): Christine
2. Surname (Last Name): Canning
3. Effective Date (07-August-2008): 01-April-2013

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

5. Manuscript Title: Autologous CLL cell vaccination early after transplant induces leukemia-specific T-cells

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						ADD
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1. Given Name (First Name): Corey
2. Surname (Last Name): Cutler
3. Effective Date (07-August-2008): 29-March-2013

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

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						ADD
6. Provision of writing assistance, medicines, equipment, or administrative support	☑	☐	☐			×

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ICMJE Form for Disclosure of Potential Conflicts of Interest

The Work Under Consideration for Publication

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

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

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						ADD
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						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)	☑	☐	☐			×
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1. Given Name (First Name): Di
2. Surname (Last Name): Wu
3. Effective Date (07-August-2008): 29-March-2013

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Dr. Catherine J. Wu

5. Manuscript Title: Autologous CLL cell vaccination early after transplant induces leukemia-specific T-cells

6. Manuscript Identifying Number (if you know it): 69098-RG-1

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						ADD
2. Consulting fee or honorarium	☑	☐	☐			×
						ADD
3. Support for travel to meetings for the study or other purposes	☑	☐	☐			×
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4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	☑	☐	☐			×
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						ADD
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Section 1. Identifying Information

1. Given Name (First Name): Donna
2. Surname (Last Name): Neuberg
3. Effective Date (07-August-2008): 27-March-2013

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Catherine J Wu

5. Manuscript Title: Autologous CLL cell vaccination early after transplant induces leukemia-specific T-cells

6. Manuscript Identifying Number (if you know it): 69098-RG-1

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Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
1. Grant	☑	☐	☐			×
						ADD
2. Consulting fee or honorarium	☑	☐	☐			×
						ADD
3. Support for travel to meetings for the study or other purposes	☑	☐	☐			×
						ADD
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						ADD
5. Payment for writing or reviewing the manuscript	☑	☐	☐			×
						ADD
6. Provision of writing assistance, medicines, equipment, or administrative support	☑	☐	☐			×

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Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
						ADD
7. Other	☑	☐	☐			✕
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						ADD
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						ADD
5. Grants/grants pending	☑	☐	☐			✕
						ADD
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						ADD
8. Patents (planned, pending or issued)	☑	☐	☐			×
						ADD
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1. Given Name (First Name): Edwin
2. Surname (Last Name): Alyea
3. Effective Date (07-August-2008): 27-March-2013

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Corresponding Author's Name: Catherine Wu

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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): Glenn
2. Surname (Last Name): Dranoff
3. Effective Date (07-August-2008): 28-March-2013

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

Corresponding Author's Name: Catherine Wu

5. Manuscript Title: Autologous CLL cell vaccination early after transplant induces leukemia-specific T-cells

6. Manuscript Identifying Number (if you know it): 69098-RG-1

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

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

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Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
1. Board membership	☑	☐	☐			×
						ADD
2. Consultancy	☐	☑	☐	Novartis, Nextech, Selecta, Genentech, Merck		×
						ADD
3. Employment	☑	☐	☐			×
						ADD
4. Expert testimony	☑	☐	☐			×
						ADD
5. Grants/grants pending	☐	☑	☐	Novartis		×
						ADD
6. Payment for lectures including service on speakers bureaus	☑	☐	☐			×
						ADD

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Relevant financial activities outside the submitted work

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7. Payment for manuscript preparation	☑	☐	☐			×
						ADD
8. Patents (planned, pending or issued)	☐	☐	☑	MIT/Whitehead	to MIT from MIT invention years ago	×
						ADD
9. Royalties	☐	☐	☑	Innate Immune		×
						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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Hide All Table Rows Checked 'No' SAVE

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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): Jeng-Shin
2. Surname (Last Name): Lee
3. Effective Date (07-August-2008): 27-March-2013

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Catherine J. Wu

5. Manuscript Title: Autologous CLL cell vaccination early after transplant induces leukemia-specific T-cells

6. Manuscript Identifying Number (if you know it): 69098-RG-1

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

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

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

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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	
						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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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): Jennifer
2. Surname (Last Name): Brown
3. Effective Date (07-August-2008): 28-March-2013

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

5. Manuscript Title: Autologous CLL cell vaccination early after transplant induces leukemia-specific T-cells

6. Manuscript Identifying Number (if you know it): 69098-RG-1

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

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The Work Under Consideration for Publication

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

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Section 3. Relevant financial activities outside the submitted work.

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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	
1. Board membership	☑	☐	☐			✕
						ADD
2. Consultancy	☐	☑	☐	Pharmacyclics		✕
2. Consultancy	☐	☑	☐	Genentech		✕
2. Consultancy	☐	☑	☐	Celgene		✕
2. Consultancy	☐	☑	☐	Emergent		✕
2. Consultancy	☐	☑	☐	Onyx		✕
2. Consultancy	☐	☑	☐	Sanofi Aventis		✕
2. Consultancy	☐	☑	☐	Avila		✕
2. Consultancy	☐	☑	☐	Novartis		✕
2. Consultancy	☐	☑	☐	Vertex		✕
						ADD
3. Employment	☑	☐	☐			✕

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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	
						ADD
4. Expert testimony	☑	☐	☐			×
						ADD
5. Grants/grants pending	☐	☐	☑	Genzyme (now Sanofi)		×
5. Grants/grants pending	☐	☐	☑	Celgene		×
						ADD
6. Payment for lectures including service on speakers bureaus	☑	☐	☐			×
						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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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Jerome
2. Surname (Last Name): Ritz
3. Effective Date (07-August-2008): 27-March-2013

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

Corresponding Author's Name: Catherine Wu

5. Manuscript Title: Autologous CLL cell vaccination early after transplant induces leukemia-specific T-cells

6. Manuscript Identifying Number (if you know it): 69098-RG-1

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

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

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Relevant financial activities outside the submitted work

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

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

ICMJE Form for Disclosure of Potential Conflicts of Interest

Relevant financial activities outside the submitted work

Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
						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

* 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

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Jessica
2. Surname (Last Name): Wong
3. Effective Date (07-August-2008): 28-March-2013

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

5. Manuscript Title: Autologous CLL cell vaccination early after transplant induces leukemia-specific T-cells

6. Manuscript Identifying Number (if you know it): 69098-RG-1

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Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
1. Grant	☐	☐	☑	NCI R21, NIH R01		×
						ADD
2. Consulting fee or honorarium	☑	☐	☐			×
						ADD
3. Support for travel to meetings for the study or other purposes	☑	☐	☐			×
						ADD
4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	☑	☐	☐			×
						ADD
5. Payment for writing or reviewing the manuscript	☑	☐	☐			×
						ADD
6. Provision of writing assistance, medicines, equipment, or administrative support	☑	☐	☐			×

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						ADD
7. Other	☑	☐	☐			✕
						ADD

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						ADD
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						ADD
3. Employment	☑	☐	☐			✕
						ADD
4. Expert testimony	☑	☐	☐			✕
						ADD
5. Grants/grants pending	☑	☐	☐			✕
						ADD
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						ADD
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						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)	☑	☐	☐			×
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FAX To: ATTN: DIANA NG
617-632-3351

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): JOHN
2. Surname (Last Name): KORETH
3. Effective Date (07-August-2008): 27-March-2013

4. Are you the corresponding author? ☐ Yes ☒ No Catherine Wu

5. Manuscript Title
Autologous CLL cell vaccination early after transplant induces leukemia-specific T-cells

6. Manuscript Identifying Number (if you know it)
69098-RG-1

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

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Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
1. Board membership	☐	☒	☐	Spectrum Pharma	Advisory Board	× ADD
2. Consultancy	☐	☒	☐	Eleven Biotherapeutics		× ADD
3. Employment	☒	☐	☐			× ADD
4. Expert testimony	☒	☐	☐			× ADD
5. Grants/grants pending	☐	☐	☒	Millennium Pharmaceuticals		× ADD
6. Payment for lectures including service on speakers bureaus	☒	☐	☐	Prometheus Labs Otsuka Pharmaceuticals		× ADD
7. Payment for manuscript preparation	☒	☐	☐			×

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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 ×
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Section 1. Identifying Information

1. Given Name (First Name): Joseph
2. Surname (Last Name): Antin
3. Effective Date (07-August-2008): 27-March-2013

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

5. Manuscript Title: Autologous CLL cell vaccination early after transplant induces leukemia-specific T-cells

6. Manuscript Identifying Number (if you know it): 69098-RG-1

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1. Grant	☑	☐	☐			×
						ADD
2. Consulting fee or honorarium	☑	☐	☐			×
						ADD
3. Support for travel to meetings for the study or other purposes	☑	☐	☐			×
						ADD
4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	☑	☐	☐			×
						ADD
5. Payment for writing or reviewing the manuscript	☑	☐	☐			×
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						ADD
7. Other	☑	☐	☐			✕
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1. Board membership	☑	☐	☐			✕
						ADD
2. Consultancy	☑	☐	☐			✕
						ADD
3. Employment	☑	☐	☐			✕
						ADD
4. Expert testimony	☑	☐	☐			✕
						ADD
5. Grants/grants pending	☐	☑	☑	NCI	Graft vs Host Disease P01	✕
						ADD
6. Payment for lectures including service on speakers bureaus	☑	☐	☐			✕
						ADD
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						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
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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Kristen
2. Surname (Last Name): Stevenson
3. Effective Date (07-August-2008): 27-March-2013

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

Corresponding Author's Name: Catherine Wu

5. Manuscript Title: Autologous CLL cell vaccination early after transplant induces leukemia-specific T-cells

6. Manuscript Identifying Number (if you know it): 69098-RG-1

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

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

ICMJE Form for Disclosure of Potential Conflicts of Interest

The Work Under Consideration for Publication

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

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

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						ADD
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						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): Masayasu
2. Surname (Last Name): Naito
3. Effective Date (07-August-2008): 28-March-2013

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

Corresponding Author's Name: Catherine Wu

5. Manuscript Title: Autologous CLL cell vaccination early after transplant induces leukemia-specific T-cells

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1. Grant	☐	☐	☑	NCI R21 and NIH R01		×
						ADD
2. Consulting fee or honorarium	☑	☐	☐			×
						ADD
3. Support for travel to meetings for the study or other purposes	☑	☐	☐			×
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4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	☑	☐	☐			×
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5. Payment for writing or reviewing the manuscript	☑	☐	☐			×
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						ADD
7. Other	☑	☐	☐			✕
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						ADD
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						ADD
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						ADD
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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): Mildred
2. Surname (Last Name): Pasek
3. Effective Date (07-August-2008): 28-March-2013

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

5. Manuscript Title: Autologous CLL cell vaccination early after transplant induces leukemia-specific T-cells

6. Manuscript Identifying Number (if you know it): 69098-RG-1

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

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

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

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						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
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Section 1. Identifying Information

1. Given Name (First Name): Naa Norkor
2. Surname (Last Name): Hammond
3. Effective Date (07-August-2008): 29-March-2013

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

5. Manuscript Title: Autologous CLL cell vaccination early after transplant induces leukemia-specific T-cells

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1. Grant	☐	☐	☑	NCI R21		×
1. Grant	☐	☐	☑	NIH R01		×
						ADD
2. Consulting fee or honorarium	☑	☐	☐			×
						ADD
3. Support for travel to meetings for the study or other purposes	☑	☐	☐			×
						ADD
4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	☑	☐	☐			×
						ADD
5. Payment for writing or reviewing the manuscript	☑	☐	☐			×
						ADD

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Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
6. Provision of writing assistance, medicines, equipment, or administrative support	☑	☐	☐			×
						ADD
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						ADD
2. Consultancy	☑	☐	☐			×
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4. Expert testimony	☑	☐	☐			×
						ADD
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						ADD
7. Payment for manuscript preparation	☑	☐	☐			×
						ADD
8. Patents (planned, pending or issued)	☑	☐	☐			×
						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): Natalie
2. Surname (Last Name): Goldstein
3. Effective Date (07-August-2008): 29-March-2013

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

5. Manuscript Title: Autologous CLL cell vaccination early after transplant induces leukemia-specific T-cells

6. Manuscript Identifying Number (if you know it): 69098-RG-1

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

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						ADD
7. Other	☑	☐	☐			✕
						ADD

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

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						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)	☑	☐	☐			×
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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Philippe
2. Surname (Last Name): Armand
3. Effective Date (07-August-2008): 27-March-2013

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

5. Manuscript Title: Autologous CLL cell vaccination early after transplant induces leukemia-specific T-cells

6. Manuscript Identifying Number (if you know it): 69098-RG-1

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

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

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						ADD
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						ADD
3. Employment	☑	☐	☐			✕
						ADD
4. Expert testimony	☑	☐	☐			✕
						ADD
5. Grants/grants pending	☑	☐	☐			✕
						ADD
6. Payment for lectures including service on speakers bureaus	☑	☐	☐			✕
						ADD
7. Payment for manuscript preparation	☑	☐	☐			✕

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						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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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): Richard
2. Surname (Last Name): Mulligan
3. Effective Date (07-August-2008): 29-March-2013

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Catherine Wu, MD

5. Manuscript Title: Autologous CLL cell vaccination early after transplant induces leukemia-specific T-cells

6. Manuscript Identifying Number (if you know it): 69098-RG-1

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

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

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

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Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
						ADD
8. Patents (planned, pending or issued)	☐	☐	☑	MIT/Whitehead	to MIT from MIT invention years ago	×
						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)	☑	☐	☐			×
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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Robert
2. Surname (Last Name): Soiffer
3. Effective Date (07-August-2008): 01-April-2013

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

5. Manuscript Title: Autologous CLL cell vaccination early after transplant induces leukemia-specific T-cells

6. Manuscript Identifying Number (if you know it): 69098-RG-1

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

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

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Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
						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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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): Sean
2. Surname (Last Name): McDonough
3. Effective Date (07-August-2008): 28-March-2013

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Catherine Wu, MD

5. Manuscript Title: Autologous CLL cell vaccination early after transplant induces leukemia-specific T-cells

6. Manuscript Identifying Number (if you know it): 69098-RG-1

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

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Tetsuro
2. Surname (Last Name): Sasada
3. Effective Date (07-August-2008): 28-March-2013

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Catherine J. Wu

5. Manuscript Title: Autologous CLL cell vaccination early after transplant induces leukemia-specific T-cells

6. Manuscript Identifying Number (if you know it): 69098-RG-1

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

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Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
						ADD
7. Other	☑	☐	☐			✕
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						ADD
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						ADD
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						ADD
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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): Ursula
2. Surname (Last Name): Hainz
3. Effective Date (07-August-2008): 27-March-2013

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Catherine J Wu

5. Manuscript Title: Autologous CLL cell vaccination early after transplant induces leukemia-specific T-cells

6. Manuscript Identifying Number (if you know it): 69098-RG-1

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						ADD
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						ADD
3. Support for travel to meetings for the study or other purposes	☑	☐	☐			×
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5. Payment for writing or reviewing the manuscript	☑	☐	☐			×
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						ADD
7. Other	☑	☐	☐			✕
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Section 1. Identifying Information

1. Given Name (First Name): Ute E.
2. Surname (Last Name): Burkhardt
3. Effective Date (07-August-2008): 28-March-2013

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Catherine J. Wu

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1. Grant	☐	☐	☑	NCI R21, NIH R01		×
						ADD
2. Consulting fee or honorarium	☑	☐	☐			×
						ADD
3. Support for travel to meetings for the study or other purposes	☑	☐	☐			×
						ADD
4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	☑	☐	☐			×
						ADD
5. Payment for writing or reviewing the manuscript	☑	☐	☐			×
						ADD
6. Provision of writing assistance, medicines, equipment, or administrative support	☑	☐	☐			×

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The Work Under Consideration for Publication

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

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						ADD
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						ADD
3. Employment	☑	☐	☐			✕
						ADD
4. Expert testimony	☑	☐	☐			✕
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5. Grants/grants pending	☑	☐	☐			✕
						ADD
6. Payment for lectures including service on speakers bureaus	☑	☐	☐			✕
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						ADD
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						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)	☑	☐	☐			×
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Section 1. Identifying Information

1. Given Name (First Name): Vincent
2. Surname (Last Name): Ho
3. Effective Date (07-August-2008): 27-March-2013

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

5. Manuscript Title: Autologous CLL cell vaccination early after transplant induces leukemia-specific T-cells

6. Manuscript Identifying Number (if you know it): 69098-RG-1

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						ADD
2. Consulting fee or honorarium	☑	☐	☐			×
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3. Support for travel to meetings for the study or other purposes	☑	☐	☐			×
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7. Other	☑	☐	☐			✕
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						ADD
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Section 1. Identifying Information

1. Given Name (First Name): Wanyong
2. Surname (Last Name): Zeng
3. Effective Date (07-August-2008): 29-March-2013

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

Corresponding Author's Name: Catherine J. Wu, M.D.

5. Manuscript Title: Autologous CLL cell vaccination early after transplant induces leukemia-specific T-cells

6. Manuscript Identifying Number (if you know it): 69098-RG-1

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Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
1. Grant	☑	☐	☐			×
						ADD
2. Consulting fee or honorarium	☑	☐	☐			×
						ADD
3. Support for travel to meetings for the study or other purposes	☑	☐	☐			×
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						ADD
5. Payment for writing or reviewing the manuscript	☑	☐	☐			×
						ADD
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Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
						ADD
7. Other	☑	☐	☐			✕
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						ADD
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4. Expert testimony	☑	☐	☐			✕
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5. Grants/grants pending	☑	☐	☐			✕
						ADD
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						ADD
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						ADD
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1. Given Name (First Name): Quinlan
2. Surname (Last Name): Sievers
3. Effective Date (07-August-2008): 28-March-2013

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Corresponding Author's Name: Catherine J. Wu, MD

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						ADD
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