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Title of Project: Post-Transplant Use of Irradiated Allogeneic Cells

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[redacted]	

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1) Research Introduction

a) *Purpose/Specific Aims*

This pilot study will determine the tolerance and anti-tumor efficacy of irradiated haploidentical blood mononuclear cells (irradiated allogeneic cells, IAC) in patients with high-risk hematologic malignancies who have undergone autologous or allogeneic hematopoietic stem cell therapy. There will be 2 cohorts:

-Cohort 1 will be composed of patients with high-risk non-Hodgkin lymphoma or multiple myeloma; they will have undergone high dose chemotherapy with ***autologous*** stem cell rescue but remain at high risk for relapse.

-Cohort 2 will be composed of patients with high-risk hematologic malignancies who have undergone an HLA-matched ***allogeneic*** hematopoietic stem cell transplant. The IAC will be administered either prophylactically (for those identified to be at high risk at the time of transplant) or after molecular, immunophenotypic or clinical relapse (if the patient is not a candidate for standard donor lymphocyte infusion or alternate standard therapy).

- **Primary Objective**

The primary objective is to determine the toxicity associated with the administration of IAC to patients with high-risk hematologic malignancies.

- **Secondary Objective**

To secondary objective is to determine if there is evidence of disease response associated with IAC. This will be determined by standard disease staging, use of minimal residual disease markers, and/or by clinical analysis by the Hematologic Malignancies Tumor Study Group as directed by disease and disease state.

- **Tertiary Objective**

To determine if treatment with the irradiated cells induces an immune response targeting tumor associated epitopes.

Hypotheses

-An "allogeneic effect" (enhancement of an immune reaction by the presence of a concurrent allogeneic reaction) has been demonstrated in animal studies, is operative in humans and, can be used to enhance anti-tumor responses (1-6).

-Treatment with IAC, as done previously at [redacted] will induce an "allogeneic effect" that results in a clinical anti-tumor response (6,7).

- IAC induce the production of T cells that target tumor associated epitopes (7).

Primary Endpoint(s)

- Determine the toxicities associated with administration of IAC. The anticipated/projected IAC-associated toxicities of greatest concern include:
  - Short-term toxicities: constitutional/systemic adverse events including fevers, hypotension, pulmonary infiltrates;
  - Long-term toxicities: autoimmune effects, graft-versus-host disease (GVHD), graft rejection;

- Disease response in patients who receive IAC.

Secondary Endpoint(s)

- Induction of host T cells reactive with tumor associated epitopes.

b) Research Significance

The ability of allogeneic cells to modulate host immunity was described > 40 years ago. In those studies, humoral immune responses in experimental animals were enhanced after infusion of allogeneic cells(1-3). These enhanced antibody responses were called an "allogeneic effect" because they were dependent upon graft - host allo-reactivity even though they were mediated by host cells. This theme of allogeneic reactivity activating host immunity was seen also in a guinea pig leukemia model(4). In those studies, passive transfer of allogeneic cells prolonged survival after challenge with leukemia cells of the same strain as the host.

Additional murine studies also demonstrate indirect anti-tumor effects of allogeneic cells. For example, in one model system, MHC mismatched T cells induced anti-tumor immunity against hematopoietic and non-hematopoietic tumors of the host tissue type(5). Utilizing various strain and tumor combinations, a direct graft versus tumor effect mediated by donor cells was shown NOT to be required for the anti-tumor effect. The investigators hypothesized that donor CD4+ cells cooperated with host CD8+ cells to overcome host CD4+ cell tolerance.

The above-cited animal studies demonstrate host immune stimulation by allogeneic cells. Clinical studies in *humans* present examples of tumor responses after allogeneic cell infusions without durable engraftment. One of the most direct examples of a host mediated anti-tumor effect in humans is provided by studies performed at [redacted]hich tested the anti-neoplastic effects of irradiated allogeneic cells (termed irradiated haploidentical cells (IAC) since they were obtained from siblings, parents or children that were 50% matched for HLA alleles) (6). Irradiation assured that there would be no engraftment or GVHD. The IAC were administered every 8 weeks. Fifteen patients were treated with sequential infusions of IAC with no pre-treatment. The disease profile included metastatic renal cell carcinoma, metastatic melanoma, and AML. No manifestations of GVHD were apparent. Three of eleven patients with metastatic renal cell carcinoma had partial tumor responses and two had stable disease. The tumor responses were delayed until after the second or third infusion. Two patients with metastatic melanoma had progressive disease after two treatments, however one of these patients had significant improvement in pulmonary metastatic disease and lung PET scan but developed new sites of soft-tissue and lymph node disease during treatment. Two patients with AML had stable disease for 4 months and came off study to participate in other clinical trials.

In a related study of IAC therapy at [redacted]or patients with refractory hematologic malignancies, the development of a host CD8+ T-cell anti-AML epitope (a component of the malignant cell membrane that is subject to immune attack) (PR-1) response was detected in a patient with AML who had a CR after treatment with allogeneic cells (7). The development of a *host* derived CD8 anti-tumor response confirms an "allogeneic effect" in this patient.

In the present study we propose to extend these studies to patients with very high-risk hematologic malignancies who have undergone ***autologous*** or ***allogeneic*** hematopoietic stem cell therapy. The hematologic malignancies tumor study group at [redacted] has identified 2 cohorts of patients to be studied. The first cohort has very high-risk multiple myeloma or non-Hodgkins lymphoma and will have been treated with high dose chemotherapy followed by ***autologous*** stem cell rescue. They have been chosen for study because the risk of relapse is very high and, in the case of multiple myeloma, disease monitoring is straight-forward. The second cohort of patients has a very high-risk hematologic malignancy that has been treated with an ***allogeneic*** transplant from an HLA-matched donor. These patients are chosen for study because they have a projected disease free survival of <25% following allogeneic transplant. In both cases it is hoped that the infused IAC induce and/or enhance an anti-tumor response, as was seen in the earlier [redacted].

c) Research Design and Methods

This is an open label study designed to determine whether IAC therapy should be developed further for patients with very high-risk hematologic malignancies undergoing hematopoietic stem cell therapy. Consenting patients will have *potential* haploidentical donors (full and half siblings, genetic parents, genetic children) who might be interested in participating identified. Potential donors will be interviewed for participation and evaluated and consented by an investigator who is not the primary treatment investigator or care provider for the patient.

Patients will receive transfusions, infection prophylaxis, nutritional support, protective isolation, and all treatment-related care per standards of the Blood & Marrow Transplant Program.

The duration of the study will be 3 years. Patients and donors will be consented up to 90 days before anticipated first treatment with irradiated cells. Patients and donors will be registered within 7 days of anticipated first treatment with irradiated cells.

Treatment Plan:

Registration: Once a potential donor has been identified for respective patient, both the patient / recipient and the relative/ donor will sign consent to participate in the study. Upon signing the consent, donor will undergo protocol mandated screening for eligibity. Once donor's eligibility is confirmed both patient and donors will be registered for the study by OHRS research staff.

Each participant will be given a unique identifier code. No patient will start treatment prior to registration.

All eligible patients will be treated at [redacted] and receive standard treatment per Blood & Marrow Transplant Program Policies.

1. Patients in cohort 1 will be treated initially with IAC within 42 days after hematopoietic engraftment (both neutrophils and platelets). Engraftment is

[redacted]

defined by 3 consecutive measurements with absolute neutrophil count > 500/mm3 and platelets > 20,000/mm3 without transfusion.

2. Patients in cohort 2 with *high-risk* disease will be treated initially with IAC within 120 days after hematopoietic engraftment (neutrophils and platelets). Chimerism studies must reveal engraftment of donor CD3+ cells > 80% and there must not be any evidence of > grade I *acute* GVHD or *severe* chronic GVHD, per standard CIBMTR staging.
3. Patients in cohort 2 being treated for *relapsed* disease may receive initial treatment with irradiated allogeneic cells any time after relapse documented. They may receive disease specific therapy prior to the experimental cell therapy, but they must have recovered from the disease-specific therapy prior to the experimental cell therapy.
4. All treated patients who do not have evidence of relapse or progressive disease may be treated q 8-12 weeks for up to 3 treatments with delays up to 8 weeks as clinically indicated.
5. Donor will undergo evaluation at RWJ Blood Services within 7 days of each infusion.
6. Donors meeting eligibility requirements will be harvested by leukapheresis with targeted CD3+ (0.5-3.0 x 10^8/kg); harvesting will be done according to FACT and AABB guidelines.
7. Donor cells (0.5-3 x 10^8 CD3+/kg) will be irradiated (25 Gy) and infused no more than 24 hours after harvesting of the cells; in case of ABO incompatibility either RBC depletion will be undertaken or the product will be split to assure infusion of $\leq$ 10 ml ABO incompatible RBC/day.
8. Management of cytopenias, infections, and other complications will conform to standard procedures at the discretion of the physician.
9. Disease status: Disease status will be evaluated every 8 weeks by history, physical examination, laboratory studies and bone marrow aspirate and biopsy as indicated by disease state and clinical parameters.
10. Rh- recipients of child bearing potential who are anticipated to receive a Rh+ product will receive Rhogam at standard dose.
11. Anti-coagulant treatment of any form (Heparin/ Warfarin/ Apixaban etc. will be withheld for one day prior to harvesting of cells from the donor
12. IAC products will meet preparation and release criteria as outlined below:
    a. Donor leukapheresis volume will be 2.5-3.0 blood volumes or as determined by blood services.
    b. The leukapheresis product will be appropriately labeled with: 2 patient-specific identifiers, the name of the product, the product unit number, the expiration date, donor Rh/ABO type, and the statement: "Caution: New Drug – Limited By Federal Law To Investigational Use Only".
    c. If there is a major ABO incompatibility, the product will either be split so that no more than 10 ml ABO incompatible RBC be infused/day or undergo RBC depletion to ≤ 10 ml of RBC.
    d. The product will be transported to the [redacted] Hospital Transfusion Services where it will undergo irradiation (25 Gy)

[redacted]

according to standard operating procedures. A label indicating irradiation will be attached.

e. The product will then be assigned to the patient and the released product will be transported to and administered to the patient at [redacted]er pre-medication of the patient with acetaminophen 650 mg PO and diphenhydramine-HCl 25 mg PO.

d) Preliminary Data

See the research significance section above and references. IAC is an effective therapy for selected patients with renal cell carcinoma. Individual responses have also been seen in AML and CML (6, Strair personal observation). There is also evidence that allogeneic cells can induce a host CD8+ T cell response directed an AML-associated epitope (7).

e) Sample Size Justification/Statistical Analysis

The primary aim of this pilot study is to see if there is acceptable tolerance (no irreversible grade 3 or higher) experimental treatment-related serious adverse effects and any disease response for 10 patients in each cohort. This will ensure that there is at least an 80% chance that the true unacceptable rate is less than 30%. The study will be closed if there is >1 irreversible grade 3 or higher experimental treatment related adverse effect in either cohort.

If there is (1) a steroid refractory GVHD or (2) graft failure in cohort 2, then the study will stop.

The secondary aim is to determine if there is evidence of disease response to IAC. If there is evidence of disease response in either arm, additional studies will be planned.

f) Study Variables

- ***Independent Variables or Interventions***

IAC infusion every 8-12 weeks as tolerated and feasible.

Toxicity will be measured by occurrence of any experimental treatment-related Adverse Events (AE) up to 12 weeks of completion of therapy. The CTCAE Version 4.0 will be utilized for the description and grading of the AE. All symptoms, signs, or diseases assessed as experimental treatment-related will be captured and graded by a study investigator and an attribution will be associated to the experimental therapy (IAC).

Attribution of the AE:

- Definite – The AE is clearly related to the experimental therapy
- Probable – The AE is likely related to the experimental therapy
- Possible – The AE may be related to the study treatment
- Unlikely – The AE is doubtfully related to the study treatment
- Unrelated – The AE is clearly NOT related to the study treatment

Any experimental treatment-related irreversible grade 3 or higher AE (definite, probable or possible) will result in that patient not receiving any further treatment. If the AE corrects completely or to Grade 1 within 2 weeks, repeat treatment as directed by protocol may be utilized. If there is more than one such irreversible experimental treatment-related Grade 3 adverse event, the study will be terminated for that cohort.

Since a major concern is that the IAC might trigger an immune response that results in steroid-refractory GVHD OR graft failure (in cohort 2), specific parameters to diminish the likelihood of these events are included in the inclusion criteria (e.g. durable engraftment and high donor chimerism). Furthermore, the study will be terminated if even a single episode of these events occurs.

Overall response rate will be defined as the proportion of patients meeting the criteria for partial response (PR), very good partial response (VGPR) and complete response (CR). Disease response will be determined by Standards of Blood and Marrow Transplant Program disease-specific parameters.

- ***Dependent Variables or Outcome Measures***

Toxicity and disease response will be measured. Disease response will use standard disease-specific parameters.

g) Drugs/Devices/Biologics

Irradiated allogeneic cells are administered under a FDA awarded IND.

h) Primary Specimen Collection

-Standard disease monitoring q 3 months
-Immunologic studies immediately prior first infusion and 30 days after each IAC infusion; if no additional infusions administered samples will be obtained also at day +60 and day +90. No samples will be repeated within 21 days of each other.

i) Interviews, Focus Groups, or Surveys

N/A

- ***Administration***

N/A

- ***Study Instruments***

Standard policies and procedures of the Hematologic Malignancies and Blood & Marrow Transplant Programs of Rutgers Cancer Institute of New Jersey

[redacted]

Timetable/Schedule of Events: Patients and donors will be consented when they meet eligibility criteria, up to 90 days prior to anticipated first treatment. Patients and donors will be registered in ONCORE within 7 days of anticipated first treatment.

Patient Procedures	Screening (within 14 days of registration- unless otherwise noted)	Pre each cycle of IAC (- 7 days)	Q 30 days (+/- 7 days) after each IAC infusion[6]	Completion of therapy (within 8 weeks of last protocol treatment and monitoring)
Informed Consent[1]	X			
Inclusion/Exclusion	X			
Hx, PE, ECOG Performance Status	X	X	X	X
Toxicity Assessment	X	X	X	X
Hematologic and Biochemical Profile[2]	X	X	X	X
Serum Pregnancy Test (if of childbearing potential)	X	X		
Disease staging BMasp/biopsy[3]	X		X	
HLA and ABO/Rh Typing	X			
Infectious Disease Screening[4]	X	X		
Ancillary studies: immune function[5]	X	X[7]	X	X

1. Patients will be consented within 90 days of anticipated first treatment with irradiated cells.
2. Standard CBC, chemistry profile
3. Disease staging as clinically indicated per standards of Blood & Marrow Transplant Program
4. Infection Disease Screening per RWJ transplant services within 7 days of harvesting.
5. For patients for whom there is a disease specific epitope that can be monitored during therapy four tubes of EDTA anticoagulated blood will be collected at each time point and sent to the Immune Laboratory. No need to wait for results. These patients will be identified at baseline evaluation for collection beginning prior to 1st cycle of IAC.
6. These assessments will be performed Q 30 days until the patient receives their next IAC infusion, completes protocol therapy or comes off study.
7. No need to repeat if prior sample dawn within 21 days.

Donor Procedures	Screening	Within 7 days of each donor leukapheresis	Day of Collection

[redacted]

Informed Consent[1]	X		
HLA-Typing[2]	X		
Donor Evaluation[3]	X		
Ancillary studies: Immune function[6]	X		
RWJ Blood Services Evaluation[4]		X	
CBC w/diff[5]			X

1. Donors will be consented within 90 days prior to the patient's first treatment.
2. HLA typing may be low resolution class I. May occur at any time prior to donor evaluation.
3. Donor evaluation will occur after HLA typing and will include physician evaluation to assure all donor eligibility criteria are met.
4. To be performed as per the policies of the RWJ Blood services program. Donors will provide five 7.5ml green top tubes for ancillary studies at time of initial donation.
5. Pre-collection CBC w/diff.
6. Only for selected donors whose corresponding patient has a disease related epitope that can be monitored immunologically. Four EDTA anticoagulated tubes will be collected at screening only and sent to the Immune Laboratory.

2) Project Management

a) Research Staff and Qualifications

[redacted]

b) Resources Available

(1) Facilities

[redacted].

(2) Medical Or Psychological Resources

[redacted]

[redacted]

Blood and Marrow Transplantation Program. There are no anticipated psychological effects of the experimental treatment. Any psychological or behavioral issues that arise will be addressed with available resources.

***(3)* Research Staff Training**

[redacted]

c) Research Sites

[redacted]

3) Multi-Site Research Communication & Coordination

N/A

a) Outside Research

N/A

4) Research Data Source/s

b) Primary Data-Subjects and Specimens

- **Subject Selection and Enrollment Considerations**

(1) Recruitment Details

[redacted]

(2) Source of Subjects

Patients will be patients of the Blood & Marrow Transplantation practice

(3) Method to Identify Potential Subjects

Patients under a transplant physician's care will be identified by the investigators on the study.

***(4)* Subject Screening - PATIENT**

(a) Inclusion Criteria - PATIENT

- Age 18 or over
- Patient with disease (stage) eligible per cohort:
- **COHORT 1**: Patients undergoing high dose chemotherapy with ***autologous*** stem cell rescue and "high-risk" disease as defined below:
  - Diffuse large cell lymphoma or peripheral T cell lymphoma (including specified WHO subtypes) not in CT-PET complete remission at time of high dose therapy

[redacted]

- Diffuse large cell lymphoma with "double hit" or "double expressor" features
- Diffuse large cell lymphoma or peripheral T cell lymphoma (including WHO specified subtypes) refractory to standard induction therapy OR relapsing within 1 year of treatment OR in greater that second CR
- Mantle cell lymphoma not in CR1
- Multiple myeloma with ONE (or more) of the following high risk features:
  - Less than very good partial remission at time of high dose therapy
  - High R-ISS (Stage III – beta 2 microglobulin ≥5.5 plus LDH > ULN and/or del17p, t(4;14), t(14;16)) at time of diagnosis
  - Cytogenetics or FISH del17p

- **COHORT 2**: Patients with high risk disease having undergone an ***allogeneic*** hematopoietic stem cell transplant from a 10/10 HLA matched donor with one of the following disease subtypes:
  - AML in CR1 with high risk features (ELN) at presentation
    - Diagnostic sample with either t(6;9), t(9;22), 11q23, inv 3, -5, -7, del17p, complex cytogenetics, NPMwt-flt3ITD+, OR p53 mut. Patients whose samples have mutations in RUNX1 or ASXL1 are also eligible (unless the patient has favorable cytogenetics).
  - AML in CR1 with measurable minimal residual disease (MRD) by molecular (e.g., myeloid mutation profile, PCR for NPM1, CBF, MLL) or flow cytometry
  - AML not in CR1(including patients with morphologic CR but with incomplete recovery, CRi)
  - MDS with complex cytogenetics, 17p deletion or p53 mutation, or JAK2 or RAS mutation
  - Treatment-related MDS or AML
  - ALL not in CR1
  - ALL with MRD
  - Any hematologic malignancy relapsed or with persistent disease after ***allogeneic*** hematopoietic stem cell transplant.
  - Multiple myeloma
  - NHL with chemoresistant disease at time of transplant
  - Any patient undergoing ***allogeneic*** hematopoietic stem cell transplant and an anticipated rate of relapse >80% based upon published data and for which there is consensus amongst the Hematologic Malignancies Tumor Study Group that enrollment is appropriate
- Availability of a genetic child, genetic parent or sibling as a potential HLA haploidentical donor
- Meets standard eligibility requirements for high dose chemotherapy with autologous stem cell rescue (COHORT 1) or allogeneic hematopoietic stem cell transplant (COHORT 2) and has signed consent for those procedures

- Male and female and all ethnic groups are eligible provided they are fluent in English.

(b) Exclusion Criteria

- Non-English speaking person
- Patients undergoing haploidentical allogeneic hematopoietic stem cell transplants are not eligible; patients undergoing < 10/10 HLA allele matched allogeneic transplant are not eligible
- Pregnant women
- Children are not eligible as the transplant program is certified as an adult only transplant program.

(5) **Subject Screening - DONOR**

(a) Inclusion Criteria - DONOR

- Donor must be related to patient and be partially (≥ 3/6 antigen) HLA-matched.
- Donor must meet all RWJ Blood Services requirements for hematopoietic stem cell donation including:
  - Age ≥ 18 years old;
  - normal hemogram (WBC 4.0-10.0 x $10^3/mm^3$; platelet count 150,000 to 440,000/ mm^3 ; Hemoglobin/Hematocrit; 12.5-18 g/dl, 38 to 54%
  - not pregnant or lactating;
  - not HIV-1, HIV-2, HCV, Hepatitis B core or HTLV-I/II seropositive; HB S ag (-); meet other infectious disease screening criteria utilized by RWJ Blood Services;
  - no uncontrolled infections, other medical or psychological/social conditions, or medications that might increase the likelihood of patient or donor adverse effects or poor outcomes;
  - meet other blood bank criteria for blood product donation (as determined by RWJ Blood Center screening history and laboratory studies).
- Male and female and all ethnic groups are eligible provided they are fluent in English.

(b) Exclusion Criteria

- Non-English speaking person
- Pregnant women
- Children are not eligible as the transplant program is certified as an adult only transplant program.

(6) Recruitment Materials

N/A

[redacted]

(7) **Lead Site Recruitment Methods**

N/A

- **Subject Randomization**

  N/A

- **Secondary Subjects**

  N/A

- **Number of Subjects**

  (1) Total Number of Subjects

  A total of 20 subjects will complete the study. There will be 10 patients in each cohort. There will be a donor corresponding to each patient. There may be additional potential; donors screened if a donor fails the screening.

  (2) Total Number of Subjects If Multicenter Study

  N/A

  (3) Require Number of Subjects to Complete Research

  The number of subjects needed to complete the research procedures (i.e., numbers of subjects excluding screen failures.) is 40 (twenty patients and twenty donors). Each patient will participate in the study for 3 infusions and then be followed until disease progression or 3 years. Patients will be enrolled over a 3 year period of time.

  (4) Feasibility Of Recruiting

  We expect to enroll 7 subjects per year onto this study.

- **Consent Procedures**

  (1) Consent

  (a) Documenting Consent

  An IRB approved informed consent form will be provided to eligible patients and donors for participation. Written Informed consent will be obtained prior to commencing any research procedures.

  (b) Waiver of <u>Documentation</u> Of Consent

  N/A

  (c) Waiver or <u>Alteration</u> of Consent <u>Process</u>

  N/A

  (i) Waiver or <u>Alteration</u> Details

[redacted]

N/A

(ii) Destruction of Identifiers

N/A

(iii) Use of Deception/Concealment

N/A

(2) Consent Process

[redacted]

(a) Location of Consent Process

During adult Hematologic Malignancies and Blood & Marrow Transplant clinical practices, the potential participant will be approached by the Investigator for interest onto this study. Consent will take place in private consulting room. If the patient and/or donor wishes to enroll on the study, he or she will sign the informed consent in the presence of the principal investigator or sub-investigator.

(b) Ongoing Consent

During the course of the study, subjects will be updated about any new information that may affect whether they are willing to continue taking part in the study. If there are any changes to the study, subjects will be re-consented.

(c) Individual Roles for Researchers Involved in Consent

The Principal Investigator and sub-investigators will consent the patients and donors.

(i) Consent Discussion Duration

The Informed consent process will commence prior to any research procedures. The Investigator shall seek such consent only under circumstances that provide the prospective patient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The length of time that will be devoted to the consent discussion is an ongoing process.

(ii) Coercion or Undue Influence

The informed consent document will not include any exculpatory language through which the subject or representative is made to waive any of the subject's

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

N/A

(iii) [redacted]

N/A

(b) Parental Permission

N/A

***(c)* Non-Parental Permission**

N/A

(d) Assent Process

N/A

(i) Documentation of Assent

N/A

(e) Non-English Speaking Subjects

N/A

(i) Process for Non-English Speaking Subjects

[redacted]

If a subject who does not speak English presents, they will not be eligible for this study. This is an investigator-initiated pilot study that does not have financial resources for translation of consent at this time. If this study indicates that the intervention has potential utility, national funding will be sought. At that time funds would be anticipated to pay for a translation of the consent.

(f) Short Form Consent for Non-English Speakers

N/A

(2)* Adults Unable to Consent / Cognitively Impaired Adults (*for interventional studies)

(a) NJ Law-Assessment of Regaining the Capacity To Consent

N/A

(b) Capacity To Consent

N/A

(c) NJ Law-Selecting A Witness

N/A

(d) Removing a Subject

Subjects will be removed from the study if:

- They are non-compliant with protocol requirements
- If subject condition worsens

If subject withdraws consent.

- **Economic Burden and/or Compensation for Subjects**

(1) Expenses

No additional cost will be incurred by the subjects participating in this study.

(2) Compensation/Incentives

Subjects will not be paid for study participation.

- **Risks to Subjects**

(1) Description of Subject Risk

For Recipient: The risks of irradiated allogenic haploid cells are not completely known. The possible risks are:

1. Fever

[redacted]

2. Chills
3. Night sweats
4. Shortness of breath
5. Potential for excessive activation of patients immunity resulting in organ damage

The known risks of standard allogenic or autologous transplant procedure are:

Bleeding

Infection and

Organ (lung liver, kidney, intestinal, heart, gastrointestinal, neurologic, oral & other) toxicity

Long term risk of graft versus host disease

For Donor: Possible risks from leukapheresis and related investigations

1. Possibility of identifying new infection/ illness donor is unaware of
2. Risk of pain and infection due to intravenous catheter
3. Risk of hypocalcemia
4. Fatigue
5. Vaso-vagal shock
6. Nausea & vomiting

(2) Procedures for Risks to Embryo, Fetus, and/or Pregnant Subjects

N/A

(3) Risks to Non-Subjects

N/A

(4) Assessment of Social Behavior Considerations

No additional social behavior risk is anticipated.

(a) Reasonably Foreseeable Risks

The infusion of irradiated cells may be associated with short-term effects such as fevers, chills, dyspnea and systemic inflammatory symptoms such as shortness of breath due to pneumonia or diarrhea due to colitis. Long-term effects may include infection or autoimmunity. For patients who have received an allogeneic transplant the manifestation of "autoimmunity" might be graft-versus host disease or graft rejection.

[redacted]

(b) Risk Of Imposing An Intervention On Subject With Existing Condition

N/A

(c) Other Foreseeable Risks

The patients receiving therapy with IAC have very high-risk diseases and are receiving IAC as an adjuvant to transplant therapy. It may be hard to determine the toxicity related to their disease, standard treatment (transplant therapy) or the experimental therapy (IAC). In this context all patients will be at risk for infection, bleeding, organ toxicity (including heart, lung, kidney, liver, oropharyngeal, gastrointestinal, neurologic, ophthalmic and bone marrow) some of which might be irreversible and some of which could lead to long-term morbidity and death. These risks are intrinsic to the disease and standard therapy and may be worsened by the experimental therapy.

(d) Observation And Sensitive Information

N/A

(5) Minimizing Risks

The experimental intervention (IAC) involves administration of irradiated Patients receiving IAC will be reviewed weekly at 2 meetings – a weekly transplant meeting and a weekly clinical research meeting. Any SAE considered likely related to IAC will be discussed and presented for biometric evaluation re:stopping rules.

(6) Certificate of Confidentiality

N/A

(7) Potential Benefits to Subjects

IAC may improve clinical outcomes by increasing disease response rates and disease control.

(8) Provisions to Protect the Privacy Interests of Subjects

Patient confidentiality will be strictly maintained according to NIH guidelines.

(a) Research Team Access To Subject Data

The subject's personal health information, identifiers and research data are stored and kept in a secure area in the [redacted]omputer screens containing personal health identifiers are inaccessible to public view. Only the study doctor and research team will have direct access.

c) Secondary Data – Records/Chart Reviews/Databases/Tissue Banks/etc.

[redacted]

N/A

Chart/Record Review Selection

N/A

- **Secondary Specimen Collection**

  Blood samples for immune studies will be frozen immediately prior to each infusion and at 30, 60 and 90 days following infusions if there is not a sample drawn within 21 days as part of pre-infusion sampling.

5) Special Considerations

d) Health Insurance Portability and Accountability Act (HIPAA)

Protected Health Information (PHI) under HIPAA means any information that identifies an individual and relates to at least one of the following:

- The individual's past, present or future physical or mental health
- The provision of health care to the individual
- The past, present or future payment for health care

Health information related to this study may be used or disclosed in connection with this research study, including, but not limited to, information in the patient medical record such as certain information indicating or relating to a particular medical condition, blood and other tissue samples and related records, physical examinations, x-rays, MRI's, etc. Personal identity, such as a name, address, and other identifiers, will be kept confidential.

Patient information will only be used in accordance with permission by the subject (IRB approved signed informed consent form) as required or allowed by law.

e) Family Educational Rights and Privacy Act (FERPA)

N/A

f) NJ Access to Medical Research Act

N/A

g) Code of Federal Regulations Title 45 Part 46 (Vulnerable Populations)

N/A

- **"Special" Classes Of Subjects**

  N/A

6) Research Data Protection and Reporting

a) Data Management and Confidentiality

Data will be collected as per the standard Bone Marrow Transplant procedures and research data will be stored in Oncore. Data will be analyzed by the PI. Patients participating in this study will have real-time data obtained from the Blood & Marrow Transplant Program weekly research meeting AND the weekly clinical research meeting of the Hematologic Malignancies Tumor Study Group. Additional data will be obtained from data forms for submission to the Center for International Bone Marrow Transplantation Registry (CIBMTR) as part of a separate IRB-approved protocol. If a patient participating in this study does not agree to have data collected for submission to the CIBMTR, data will be collected by the Investigator from the electronic medical record.

b) Data Security

The data collected will be stored on clinical trial management software - Oncore in Principal Investigator's computer. All Computers in OHRS are encrypted, password protected and on secured servers. Only the Principal Investigator and/or the research team will have access to the patient's data.

c) Data and Safety Monitoring

Minimal risk is anticipated however there is always the possibility of unanticipated effects. Institutional Data Safety Monitoring Board/ HROC will monitor the data form the research after initial 2-3 patients and based on their suggestions the research will be conducted as is/ Modified or discontinued.

- **Periodic Data Evaluation**

  Weekly at the Blood & Marrow Transplantation and Hematologic Malignancies Tumor Study group research meetings.

- **Type of Data Evaluated**

  Treatment related toxicities; unanticipated adverse events.

- **Collection of Safety Information**

  Patient safety data will be reviewed at both of the above cited weekly meetings.

- **Frequency Of Data Collection**

  Weekly. If there is no weekly meeting (e.g. holiday) data will be delayed until the next scheduled meeting.

- **Reviewer of Data**

  Principal Investigator reviews all data.

- **Schedule Of Review Of Cumulative Data**

Review of cumulative data will occur weekly at the Hematologic Malignancies Tumor Study Group weekly research meeting.

- **Tests for Safety Data**

  Weekly meetings of the Blood & Marrow Transplant Program and Hematologic Malignancies Clinical Research Tumor Study Group review each patient. Experimental treatment-related SAEs will reported for biometric review.

- **Suspension of Research**

  Suspension will take place based upon stopping rules

d) Reporting Results

- **Sharing of Results with Subjects**

  Clinical results can only be shared following completion of the study.

- **Individual Results**

  Patients will be notified of any abnormal findings or lab results.

- **Aggregate Results**

  N/A

- **Professional Reporting**

  It is expected that the results of this process will be submitted for publication in a timely manner following the conclusion. [redacted] all co-authors prior to submission or use, will review any abstract or manuscript.

- **ClinicalTrials.Gov Registration And Data Reporting**

  The study will be registered in accordance to applicable institutional guidelines.

7) Data and/or Specimen Banking

Specimen collection, processing and storage will follow standard Biospecimen Repository Services (BRS) procedures. All specimens will be de-identified and given a unique BRS number. Only pathological information for each corresponding samples will be recorded. Specimens will be labeled by a unique identification number and initials only; there will be no other link to the subject. This link, along with data and health information collected for the protocol, will be retained for a period of 6 years in the Office of Human Research Services (OHRS) on behalf of the principal investigator.

[redacted]

8) Other Approvals/Authorizations

[redacted]

There are no other applicable approvals that will be obtained prior to commencing the research. (e.g., school site authorization, data use agreements, external site authorization, funding agency, Bio-Safety, Radiation -Safety etc.)

[redacted]

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DO NOT MODIFY THIS SPACE

Form V[redacted]

Approval Date: 4/23/2021
Expiration Date: 4/22/2022

9) Bibliography

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5. Symons HJ, Levy MY, Wang J, Zhou X, Zhou G, Cohen SE, et al. The allogeneic effect revisited: exogenous help for endogenous, tumor-specific T cells. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2008;14(5):499-509.
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