Protocol
985.03

FRED HUTCHINSON CANCER CENTER
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1. Protocol to Participate as a Donor of Peripheral Blood Mononuclear Cells to Provide Cells for Laboratory Research and Process Development Studies (Activation 1/17/95)

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2. INTRODUCTION

There are several reasons why the Center needs to acquire large numbers of peripheral blood mononuclear cells for research studies by leukapheresis. First, research examining peripheral blood hematopoietic stem cells (PBSC) collected by leukapheresis has provided the foundation for life-saving autologous, syngeneic, and allogeneic transplantation at our Center and others.[1-12] Second, research examining mononuclear cells obtained by leukapheresis have been essential to the development of novel adoptive immunotherapies that are now being utilize to successfully treat patients with cancer.[13-17] Third, large cell numbers are required for *ex vivo* and *in vivo* experimental models. Fourth, mononuclear cells remain essential for providing feeder layers to support the generation of other cellular components (e.g., antigen-specific T-cell populations).[24-26] For each of these types of research, along with other future applications, these larger cell quantities can only be obtained from patient or normal donors where the entire product can be used in the research effort. This protocol has been designed to allow for the collection of these cells for researchers at this Center, as well as for outside institutions and commercial enterprises.

3. BACKGROUND

A. Mobilization of PBSC for transplantation:

Hematopoietic stem cells circulate in the peripheral blood, but at considerably lower levels than are found in the bone marrow.[27] This has hindered the use of peripheral blood collections as a source of stem cells for transplantation because of the difficulty in obtaining adequate numbers of stem cells to rescue the recipient from the marrow-ablative chemo-radiotherapy administered. The numbers of hematopoietic progenitor cells can be greatly increased in the peripheral blood by administering recombinant human hematopoietic cytokines to the donor,[27]

by collecting cells during the initial hematologic rebound from marrow-hypoplasia producing chemotherapy,[28,29] or, especially, by combining the two.[29-31] Chemotherapy and hematopoietic cytokine mobilization is the basis for a number of autologous bone marrow transplantation protocols at this center, and we are able to obtain adequate numbers of stem cells for transplantation in 2 or less apheresis collections for most patients.[8,10,32]

Obviously, however, we cannot administer chemotherapy to a healthy donor to mobilize PBSC. For syngeneic or allogeneic transplantation, we administer hematopoietic cytokines (G-CSF, 10 mcg/kg/day for up to 7 days) to these donors, which is in keeping with the latest American Society for Blood and Marrow Transplant Guidelines.[33] Fortunately, the normal donor generally has a prolific response to the cytokines, and we have successfully transplanted dozens of patients with cells collected from one or two apheresis.[4,34-38] The donors have tolerated the administration of the cytokine and the apheresis with minimal toxicity

We have also administered hematopoietic cytokines to healthy donors to stimulate the level of granulocytes in the peripheral blood for collection and transfusion to transplant recipients with refractory infections during the neutropenic period after transplantation.[39] This regimen has involved daily administration of cytokines and apheresis for up to 14 days.[39]

B. Administration of Hematopoietic Cytokines to Healthy Donors:

As discussed above, we have administered recombinant human G-CSF to a large number of donors for mobilization of PBSCs for clinical and research purposes. Overall, the G-CSF has been well tolerated with the most frequent complaints being bone pain that is usually controlled with mild, non-prescription analgesics.[1-12,27,32] Other less frequent side effects noted in studies include flu-like symptoms (malaise, nausea, low grade temperatures). Perhaps most importantly, under this study we have successfully collected PBSCs by leukapheresis from greater than 921 donors over a more than 24 year period, either utilizing G-CSF at a dose of ≤ 10 mcg/kg/day to successfully mobilize or collecting non-mobilized mononuclear cells, all without a serious adverse event.

In healthy donors studies, there have been some reports of slight increase in spleen size, which normally resolves within a few weeks. There have been 6 reported cases of potentially deadly complication of splenic rupture out of the thousands of healthy donors receiving G-CSF. All of these 6 healthy donors received a daily dose of G-CSF between 10 – 20 mcg/kg, and in 3 of the 6 cases, the G-CSF was continued for 6 days.[40] As such, we will dose the G-CSF ≤ 10 mcg/kg/day and subjects will receive a maximum of 5 days of G-CSF. All these potential complications have been described in the written consent to ensure that donors are aware of these risks.

C. Collection of Blood by Leukapheresis:

Leukapheresis techniques are widely used for the collection of plasma, platelets, or granulocytes from healthy blood donors. As described above, the Leukapheresis Unit for the Fred Hutchinson Cancer Center (FHCC) has performed thousands of these procedures, and the FHCC Leukapheresis Unit is registered with the Food and Drug Administration for the collection of blood cells from both patients and healthy donors. The units are staffed by dedicated nursing and technical personnel experienced in apheresis.

D.

The apheresis technology used to collect the peripheral blood mononuclear cells has been shown to be very safe for both healthy donors and patients. Reported adverse reactions during leukapheresis include mainly vasovagal reactions (<1 %) and citrate toxicity (<0.4%), which are usually mild.[41] Other adverse effects mostly resolve around the insertion and removal of the peripheral blood IV lines, which can cause some mild discomfort, bruising and rarely bleeding. As part of the overall process, the leukapheresis process will collect or destroy some other cells in the blood, including platelets (about 6 units, Table 1). We examined the effect of leukapheresis on platelet counts immediately before and after the procedure, and found, on average, a 30-50% drop.

Table 1. Apheresis Components Collected at FHCC:

PARAMETER	MEAN ± STD	NUMBER OF COLLECTIONS
Mononuclear Cell Yield	2.11 ± 1.58 x 10E10	108
WBC Purity	52.9 ± 27.2% MNC	108
Collected Volume	412 ± 95 ml	108
CD34++ Cell Yield	9.33 ± 8.10 x 10E7	60
Platelet Yield	3.21 ± 1.99 x 10E11	108

This drop is compounded by repetitive apheresis procedures so that after two daily apheresis collections, the platelet count drops by 43.5%, and after three procedures by 57.5% from the pre-collection baseline level. The standard practice of the autologous transplant group is to transfuse patients undergoing apheresis to maintain a platelet count of ≥29,000/uL. For healthy allogeneic donors, we frequently will separate the platelets from the apheresis product for re-infusion back to the donor.

Severe thrombocytopenia can be avoided by requiring a minimum platelet count before apheresis. Platelet counts rebound the day after apheresis, and return to baseline levels about 7-10 days after the apheresis procedures are concluded. Nevertheless, subjects on this study will be screened to ensure that they have normal counts, including platelet count, prior to moving forward as a candidate for either G-CSF or non-GCSF leukapheresis.

4. OBJECTIVES

The overall objective of the protocol is to obtain mononuclear cells from healthy subjects for critical research that has and will continue to save lives of patients with cancer. To achieve this overarching goal, we will obtain these mononuclear cells from healthy subjects who are undergoing G-CSF mobilization for a patient receiving hematopoietic stem cell transplant and healthy volunteers from the community at large who wish to participate in the research study. Therefore, the specific objectives are as follows.

A. To collect G-CSF mobilized PBSC from healthy volunteers for use in laboratory research at the Center. These cells may also be provided to researchers at other institutions and commercial entities.

B. To collect G-CSF mobilized PBSC from healthy subjects undergoing leukapheresis for syngeneic or allogeneic transplantation. These cells may also be provided to researchers at other institutions and commercial entities.

C. To collect non-mobilized peripheral blood mononuclear cells from non-mobilized healthy volunteers for use in laboratory research and possible clinical production at the Center. These cells may also be provided to researchers at other institutions and commercial entities.

5. SUBJECT POPULATION

The overall subject population will be similar (i.e., otherwise healthy individuals) who wish to participate in the proposed research, but the procedures and entry for the study will be slightly different. Therefore, we have developed inclusion and exclusion criteria for all three subject and procedure types.

A. Inclusion and Exclusion for G-CSF Mobilized Volunteers

Eligibility Criteria

- Age 18- 70.

- Capable of understanding the risk and benefits of the study.
- Completion of initial health screening evaluation (initial donor screening questionnaire submitted with application) without any past medical history that would prevent them from being a donor as per the NMDP guidelines, which are in keeping with criteria found in the United States Code of Federal Regulations and in the Standards of the American Association of Blood Banks. Please see Appendix A for the guidelines.
- Sign Consent 985.03M.
- Adequate veins for placement of leukapheresis IVs as per screening by the leukapheresis nurse staff.
- A normal physical performed by FHCC provider.
- A CBC will be drawn after the 1st day of apheresis. To proceed with the 2nd day of apheresis the volunteer must have a platelet count greater than 150,000/uL and must have a HCT ≥ 36% for females or an HCT ≥ 38% for males.

Exclusion Criteria

- Age <18 or >70
- Unable to provide informed consent
- History of adverse reaction to growth factors such as G-CSF.
- Pregnancy
- Breast feeding
- Currently taking anticoagulation therapy. Aspirin at a dose up to 325 mg a day are allowed.
- Abnormal CBC
- Current infection
- Uncontrolled diabetes
- Uncontrolled hypertension
- Current treatment for cancer other than non-melanoma skin cancer
- History of cancer other than non-melanoma skin cancer.
- History of heart disease including coronary artery disease or arrhythmia
- History of stroke or TIA
- History of autoimmune disease in subject or their parents
- A positive Hepatitis B or C test indicating a previous exposure or current infection.
- A positive HIV test indicating previous exposure or current infection.
- Any medical condition that would prevent them from being a transplant donor as per NMDP guidelines as demonstrated in Appendix A.
- Any potential health or psychological condition, which in the clinical judgement of the PI or the Medical Director of the FHCC Leukapheresis Center, would place the volunteer at an unacceptable risk.
- A CBC will be drawn after the 1st day of apheresis. A platelet count < 150,000/uL or HCT < 36% for females or an HCT < 38% for males will exclude the donor from a 2nd day of leukapheresis.

B. Inclusion and Exclusion for G-CSF Mobilized Subjects for Allogeneic Transplantation
The overall inclusion and exclusion criteria for this population is very similar to the other two populations with the exception that subjects will only be eligible if they are already donating for a transplant and only one day of leukapheresis is required, such that the second day can be obtained for research purposes. In addition, some of these subjects may have central line access due to clinical reasons, and as such, adequate peripheral vein access will not be a requirement, given the line would be already placed for clinical indications, if needed.

Eligibility Criteria

- Age 18-70.
- Capable of understanding the risk and benefits of the study.
- Completion of initial health screening evaluation (initial donor screening questionnaire submitted with application) without any past medical history that would prevent them from being a donor as per the NMDP guidelines, which are in keeping with criteria found in the United States Code of Federal Regulations and in the Standards of the American Association of Blood Banks. Please see Appendix A for the guidelines.
- Sign Consent 985.03A.
- Agreed to donate G-CSF mobilized MNCs for an allogeneic transplant and met all inclusion criteria appropriate for the clinical donation of these cells.
- Not required to undergo leukapheresis for more than one day for patient collection.
- A normal physical performed by FHCC provider.
- A CBC will be drawn at the after the 1st day of apheresis. To proceed with the 2nd day of apheresis the volunteer must have a platelet count greater than 150,000/uL and must have a HCT $\geq$ 36% for females or an HCT $\geq$ 38%.

Exclusion Criteria

- Age <18 or >70
- Unable to provide informed consent
- History of adverse reaction to growth factors such as G-CSF.
- Pregnancy
- Breast feeding
- Currently taking anticoagulation therapy. Aspirin at a dose up to 325 mg a day are allowed.
- Abnormal CBC
- Current infection
- Uncontrolled diabetes
- Uncontrolled hypertension
- Current treatment for cancer other than non-melanoma skin cancer
- History of cancer other than non-melanoma skin cancer.
- History of heart disease including coronary artery disease or arrhythmia
- History of stroke or TIA
- History of autoimmune disease that would prevent donation according to NMDP guidelines.
- A positive Hepatitis B or C test indicating a previous exposure or current infection.

- A positive HIV test indicating previous exposure or current infection.
- Any medical condition that would prevent them from being a transplant donor as per NMDP guidelines as demonstrated in Appendix A.
- Any potential health or psychological condition, which in the clinical judgement of the PI or the Medical Director of the FHCC Leukapheresis Center, would place the volunteer at an unacceptable risk.
- A CBC will be drawn at the after the 1st day of apheresis. A platelet count < 150,000/uL or HCT < 36% for females or an HCT < 38% for males will exclude the donor from a 2nd day of leukapheresis.

C. **Inclusion and Exclusion for Non-G-CSF Mobilized Volunteer Subjects.**
The overall inclusion and exclusion criteria for this population is very similar to the other two populations with the exception that volunteers will not be required to receive G-CSF, and as such, a previous reaction to G-CSF is not an exclusion criteria. Moreover, these volunteers will only receive 1 day of leukapheresis.

Eligibility Criteria

- Age 18-70.
- Capable of understanding the risk and benefits of the study.
- Completion of initial health screening evaluation (initial donor screening questionnaire submitted with application) without any past medical history that would prevent them from being a donor as per the NMDP guidelines, which are in keeping with criteria found in the United States Code of Federal Regulations and in the Standards of the American Association of Blood Banks. Please see Appendix A for the guidelines.
- Sign Consent 985.03NM.
- Adequate veins for placement of leukapheresis IVs as per screening by the leukapheresis nurse staff.
- A normal physical performed by FHCC provider.

Exclusion Criteria

- Age <18 or >70
- Unable to provide informed consent
- Pregnancy
- Breast feeding
- Currently taking
- Currently taking anticoagulation therapy. Aspirin at a dose up to 325 mg a day are allowed.
- Abnormal CBC
- Current infection
- Uncontrolled diabetes
- Uncontrolled hypertension
- Current treatment for cancer other than non-melanoma skin cancer
- History of cancer other than non-melanoma skin cancer.
- History of heart disease including coronary artery disease or arrhythmia
- History of stroke or TIA

- History of autoimmune disease that would prevent donation according to NMDP guidelines.
- A positive Hepatitis B or C test indicating a previous exposure or current infection.
- A positive HIV test indicating previous exposure or current infection.
- Any medical condition that would prevent them from being a transplant donor as per NMDP guidelines as demonstrated in Appendix A.
- Any potential health or psychological condition, which in the clinical judgement of the PI or the Medical Director of the FHCC Leukapheresis Center, would place the volunteer at an unacceptable risk.

6. APPROACH, EVALUATION AND COUNSELING OF VOLUNTEER AND TRANSPLANT SUBJECTS

Volunteer subjects will be recruited by advertisement. These volunteers will approach the study staff about possible donation of either G-CSF mobilized MNCs and/or non-G-CSF mobilized MNCs.

In the case of donors donating G-GCSF mobilized cells for a transplantation, these donors will be approached about their potential involvement during their arrival and/or data review clinic on the transplantation service located on the 6th floor of the FHCC (formerly SCCA).

Potential volunteers will undergo a health questionnaire by the research coordinator to assess for potential exclusion/inclusion criteria. For the transplant subjects, this questionnaire is performed prior to HLA typing by the CIL lab.

All volunteers will have to provide written consent during a face to face conference with an attending physician. At this conference, all questions and concerns must be addressed. Clinical providers at the FHCC will perform a physical exam. Blood will be drawn and sent to VRL Eurofins or the Fred Hutchinson Cancer Center Lab for appropriate screening laboratory results as indicated in Section 5.0 Inclusion and Exclusion Criteria. In mobilized donors, an optional small additional amount of blood may be drawn both before and after administration of G-CSF for the purpose of examining the impact of G-CSF on blood cells.

Volunteers and transplant subjects will meet with a staff member of the FHCC Apheresis Center before initiation of cytokine administration or proceeding to non-mobilized leukapheresis. This nurse will determine the suitability of the subject using the criteria listed in 5.0 above.

7. PROTOCOL REGISTRATION

Not applicable.

8. STUDY DESIGN

A. Subject Identification:

Participants donating under protocol 985.03M and 985.03NM are recruited via flyers and our lab website. Participants donating under consent 985.03A and 985.03H are approached by an attending physician at the FHCC.

B. Subject Health Screen:

All subjects will undergo evaluation for suitability for this protocol by the staff of the FHCC Apheresis Center. This will involve determining the health of the subject in accordance to the criteria listed in section 6.0 above.

- Before administration of the cytokine, the subject must have a CBC and chemistry profile obtained for review by the medical director of the FHCC Apheresis Center. Blood samples will undergo routine blood bank tests for viruses that include screening for HIV, Hepatitis B and C, Syphilis and testing of liver function. Blood specimens may also be tested for ABO and/or HLA typing.
- Women subjects of child-bearing potential must have a pregnancy screening (HCG test). If positive, subject would be excluded from the study.
- Women subjects who are breast feeding will be excluded from the Mobilized study.

C. Administration of Hematopoietic Cytokine:

a. Recombinant human G-CSF will be administered by a nurse in the FHCC Clinic The dose will be ≤ 10 mcg/kg subject weight per day and use adjusted body weight for subjects at > 120% of ideal body weight, administered by subcutaneous injection. The G-CSF will be started 3 to 5 days before the first apheresis, and will be given for up to a total of 5 days.

D. Apheresis Collection of PBSC:

Collection of PBSC will be performed in accordance with the standard practices of the FHCC Apheresis Center. Cells will be collected either as a single day collection or over two consecutive days. If it is a single day collection, typically 18L of blood will be processed for young healthy donors using peripheral veins for venous access. This single collection will occur on Day 5 after starting the GCSF and take up to 6 hours. If the cells are to be collected over two consecutive days, donors will have collections on days 4 and 5 after starting the GCSF. Each of these collections will typically process 12 liters of blood over about 3 to 4 hours, although smaller blood volumes and shorter collection times are permissible. The blood will be anti-coagulated with a mixture of ACD-A and heparin, again in accordance with standard practice at the Apheresis Center. A maximum of two collections on two consecutive days will be performed for volunteer mobilized subjects. Donors scheduled for two collections will evaluated to see if they qualify for the second day collection. In some cases, donors may not qualify for the second day collection.

Subjects that are collected without G-CSF mobilization may undergo apheresis a maximum of 12 times per year, in accordance with Federal regulations regarding apheresis platelet donors.

A CBC will be obtained at the start of each collection to monitor hematocrit and platelet levels. If the hematocrit or platelet level falls below the standard guidelines for the Apheresis Center, the apheresis procedure will be halted immediately.

E. Subject Reimbursement:

Subjects will not be reimbursed for any wages lost during or after the procedure, nor for hospitalization or long-term health costs resulting from their donation.

Subjects will be compensated varying amounts for their donation based upon administration of G-CSF and number of leukapheresis sessions. The breakdown of this compensation can be found in section 10 of this protocol.

F. Evaluation and response criteria

Not applicable.

9. RISKS TO VOLUNTEER AND TRANSPLANT SUBJECTS

Subjects experiencing adverse effects beyond malaise, mild bone pain controlled with non-narcotic analgesia, or other mild constitutional symptoms will be withdrawn from the study. The subject will be evaluated daily by a member of the Apheresis Center during administration of the cytokine and the apheresis collections.

The risks of this protocol are outlined below and in all consent forms, and will be discussed with the subjects during the consenting process.

A. Risks for Non-G-CSF Mobilized Volunteers.

- The blood draw may briefly cause subjects to feel faint, lightheaded, or nauseated.
- There may be some discomfort and bruises from the leukapheresis needles.
- The citrate in the anticoagulant used in the apheresis procedure may cause subjects to experience a sour taste in the mouth and/or numbness and tingling around the mouth, feet or hands as a result.
- The anticoagulant will typically clear the subject's body within about four hours, However, there could be a small risk of bleeding from this anticoagulant until it clears. The risk of bleeding from the anticoagulant is less than one in a hundred. If bleeding occurs, it is usually mild oozing from the IV site. The risk of a serious or life-threatening bleed from some other part of your body is less than one in 5,000 subjects. [42-43]
- The leukapheresis procedure may cause a decrease in platelets. This is usually minimal and typically will not affect the blood's ability to form clots in the event of subsequent cuts or injuries.
- Some subjects can show a decrease in red blood cell count for 1-2 days after, but this should cause no symptoms as the subject's body should quickly replace ant blood cells removed by the leukapheresis procedure.

B. Risks for G-CSF Mobilized Subjects for Allogeneic/Syngeneic Transplantation

These subjects do not receive additional G-CSF as part of 985.03 and are mobilized as part of their allogeneic donation. Risks pertaining to their mobilization are addressed in their allogeneic/syngeneic donation consent.

Under protocol 985.03, these subjects will face the same risks as non-G-CSF mobilized volunteers (see above).

C. Risks for G-CSF Mobilized Volunteer Subjects

G-CSF mobilized volunteer subjects face all of the above specified risks for non-mobilized subjects as well as the following risks that are a result of G-CSF administration.

- There may be some discomfort and bruising from needle sticks during the G-CSF administration.
- Occasionally subjects complain about bone aches, flu-like symptoms, headache, nausea and light-headedness due to the G-CSF. These symptoms are dose and schedule related. The symptoms are usually mild and treatable with analgesics.

- There may be an increased risk of autoimmune exacerbation as a result of G-GCSF administration, therefore, subjects with autoimmune disease or a family history of such, are excluded.

- Rupture of the spleen has been reported as a very rare and unusual occurrence. Splenic rupture can be serious and life threatening, however, it has only been reported to occur in approximately one out of ten thousand subjects.[40] This risk is discussed further in section 3B of the protocol. Cases of spleen rupture in patients receiving G-CSF are generally correlated with larger and more numerous doses of G-CSF than are administered under this protocol.
- Although long-term complications have not been observed in patients following G-CSF administration, this possibility cannot be excluded.

D. Universal Risks

Confidentiality

With all research there is the risk of potential loss of subject confidentiality. All precautions to maintain the confidentiality of subjects will be taken and all subject samples will be de-identified prior to distribution outside of the study team. This study is funded by the NIH, and is therefore, covered by a certificate of confidentiality which provides an additional layer of protection for all subjects.

This certificate means that the study team would generally not have to give out identifying information about subjects, even if requested by a court of law.

This protection has some limits. We would voluntarily provide the information:

- To a member of the federal government who needs it in order to audit or evaluate the research.
- To the funding agency and groups involved in review of the research, if they need the information to make sure the research is being carried out correctly.
- To the federal Food and Drug Administration (FDA), if required by the FDA.
- To someone who is accused of a crime, if he or she believes that our research records could be used for defense.
- To authorities, if we learn of child abuse, elder abuse, or if participants might harm themselves or others.

Genomic Sequencing

Some subjects may agree to have their samples undergo genomic sequencing. There is a very low risk of the release of genetic information as all personal subject information is kept private. If the results of genomic sequencing were to become known, subjects would be protected by the Genetic Information Nondiscrimination act (GINA). GINA restricts health insurance companies from requesting genetic information provided in research studies. However, GINA does not protect subjects from genetic discrimination by companies that sell life, disability or long-term care insurance.

10. BENEFITS TO VOLUNTEERS AND TRANSPLANT SUBJECTS

There are no direct medical benefits to the volunteers and transplant subjects other than their knowledge that their cells may be used for research to potentially improve the care of future patients. Subjects will be compensated for their time and inconvenience accordingly:

- Non-Mobilized volunteer subjects (consent 985.03NM): $300 for completed single day non-mobilized collection.
- G-CSF mobilized volunteer subjects (consent 985.03M): $200 for receiving full series of 4 G-CSF injections ($50 per dose received), $300 per leukapheresis donation, for a total of
  $800 for a complete two day mobilized donation with 4 G-CSF injections.
- G-CSF mobilized allogeneic/syngeneic subjects (consent 985.03A): $500 for a single leukapheresis donation.

RECORDS

All subject records will be maintained in the Apheresis Centers in accordance with applicable law regarding the maintenance of records for blood donor centers.

11. STATISTICAL CONSIDERATIONS

Not applicable to this study. This is an ongoing protocol for collection of cells for research with no projected sample size or study duration.

12. TERMINATION OF STUDY

Accrual onto this study will be suspended if any subject develops severe toxicity from the cytokine administration or the apheresis procedures. This toxicity is defined as any requiring acute medical intervention. Subject accrual will not be resumed without review of the toxicity by the Institutional Review Board.

No limit to the number of subjects that may be entered is established.

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