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	Owner: Dave Schwering (Manager-Lab)	**Next Review:** 08/31/2025
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Procedure Packaging and Shipment of MNC Product to Manufacturing Facility for Preparation of CD4CAR Cells for Protocol #CTO-IUSCCC-ICG122-101

I. PURPOSE

This SOP details the steps for packaging and shipment of the autologous Apheresis MNC product to a manufacturing facility for preparation of CD4CAR cells.

II. SCOPE

This procedure applies to the packaging and shipment of autologous Apheresis MNC for patients enrolled on IRB Protocol # CTO-IUSCCC-ICG122-101. All Cellular Therapy Laboratory Technologists will follow this procedure

III. STATEMENTS/REQUIREMENTS

Any exceptions to this policy must be approved by the CTL Processing Facility Medical Director. Any exceptions that deviate from the study protocol must be approved by the Study PI.

- This procedure is used to support
  - Protocol #CTO-IUSCCC-ICG122-101, A Phase I, Multicenter Study of CD4- directed chimeric antigen receptor engineered T-cells (CD4CAR) in patients with Relapsed or Refractory CD4 Positive Lymphoid Hematological Malignancies.
  - CD4CAR T CELL THERAPY FOR CMML Protocol Number: CTO-IUSCCC-0840
- Cryopreservation of the leukapheresis material must occur within 24 hours of the end of apheresis collection.
  - Leukapheresis material can be stored at room temperature for a maximum of 1 hour following the end of apheresis collection.
- All study forms are found in the corresponding confidential study binder.
- Always contact study site manager for any questions or concerns.
- Any deviation that has the potential to impact the quality, purity, safety or testing of the MNC product must be reported to the study site manager.
  - Deviations must be reported within 24 hours of discovery.

IV. DEFINITIONS

AABB: Association for the Advancement of Blood and Biotherapies

AWB: Air Waybill

CTL: Cellular Therapy Laboratory

CIT: Indiana University Simon Comprehensive Cancer Center (Coordinating Center)

Louisville Manufacturer: University of Louisville Brown Cancer Center

FACT: Foundation for the Accreditation of Cellular Therapy

FDA: Food and Drug Administration

HPC(A): Hematopoietic Progenitor Cells by Apheresis

ISBT: International information standard for coding and labeling of cell therapy products

MNC: Mononuclear Cells PI: Principal Investigator RC: Research Coordinator

PBMC: Peripheral Blood Mononuclear Cells

SOP: Standard Operating Procedure

V. EQUIPMENT/RESOURCES

Autologous MNC Product

VeriCor Transport Cooler Shipping Container

Shipping Address Label

Bubble Wrap

Temperature Monitoring Device

Biohazard Bag

Absorbent Pads

'Do Not X-Ray' labels

Courier Shipping Documentation

VI. PROCEDURE

A. Apheresis Notification of MNC, Apheresis Product Pick-up
    i. Apheresis RN will notify CTL that the product is ready for pick-up.
    ii. The product will be immediately picked up by CTL.
B. Maintaining Chain of Custody from Apheresis RN to CTL Technologist
C. After the Apheresis RN completes the collection procedure, the RN will complete Appendix 10.4 Apheresis Tracking Log.
    i. "Gram staining result on apheresis product:_____" will be left blank by Apheresis.
        1. This will be filled in by CTL, see "Product Sampling" section below.
    ii. Keep a copy of Appendix 10.4 Apheresis Tracking Log in the CTL chart.
D. The Apheresis RN releasing the product must also sign and record time of release on the Autologous Product Description & Quality Certificate form F-561a.
    i. The CTL Technologist will then sign the F-561a form to document taking custody of the product.
E. Apheresis product will be received by the Cellular Therapy lab and then transferred to the Cellular Immunotherapy and Transduction lab for manufacturing (or shipping if Louisville will be manufacturing) within one hour of collection end time.

i. If more time is required, please place into appropriate temperature monitored storage (2-8 °C) until the time of transfer occurs.

ii. Provide temperature graph of the refrigerator used to store the product to CTL QA.

F. The product will be transported at room temperature to the Cell Therapy Lab in the VeriCor transport cooler.

G. Product Receipt into CTL

i. The product will be received and logged into the F-001 CTL Activity Log according to SOP PST 005 Procedure Receipt of Cellular Therapy Products

H. Product sampling

i. The MNC product will have a sample removed via the sampling bulb attached to the Apheresis collection bag.

1. Do not spike the bag or create an open system. The sample must be taken in a manner that maintains a closed system.

ii. Close one of the slide clamps on the tubing between the sample bulbs and the Y connector.

iii. Mix product thoroughly before sampling to ensure a representative sample.

iv. Open the slide clamp on the line between the product bag and the Y connector on the sample bulb assembly.

v. Gently squeeze the sample bulb attached to the tubing with the open slide clamp to withdraw only the amount of product sample needed which is approximately 0.5mL.To express any excess product sample back into the product bag:

1. Invert the sample bulb and hold it above the fluid level of the product bag.

2. Gently squeeze the sample bulb to express excess sample back into the product bag.

3. To clear the tubing between the product bag and the sample bulb:

a. Hold the sample bulb upright and below the product bag.

b. Gently squeeze the sample bulb and use residual air in the sample bulb to push product sample from the tubing into the product bag.

vi. While maintaining pressure on the sample bulb, close the slide clamp completely just below the Y connector.

vii. Before removing the product sample, permanently seal the tubing twice between the sample bulb and the Y connector just below the slide clamp.

viii. Disconnect the sample bulb at the lower permanent seal.

ix. Approximately 2.5 mL of product will be needed for testing.

1. 0.5 mL will be sent to Microbiology for the gram stain.

a. The gram stain will be completed as a STAT test in the Microbiology Laboratory. CTL will get the results and fill out the result on the Apheresis Tracking Form.

b. Do not release the product to the courier until the gram stain result is complete.

2. 1.0 mL will be used by CTL for a CBC and CD3 flow cytometry.

3. 1.0 mL will be transferred to a cryovial and sent to CIT for T Cell subset testing.

a. All tubes must be properly labeled.

i. Patients name, DOB, MRN, DIN and study ID number at a minimum.

I. Product Testing

i. CTL will

1. Weigh the product bag to get an estimated volume.

2. Perform a CBC according to Procedure: Determining Product Parameters Using Beckman Coulter Unicel® DxH 600
3. Perform a manual differential according to Procedure: Manual Differential
4. Perform flow cytometry for CD3 according to Procedure Flow Cytometric Acquisition and Analysis Using the BD FACSLyric or Procedure: Flow Cytometric Acquisition and Analysis Using the BD FACSVia
5. Calculate the TNC and the MNC for the product.
    a. Document all processing and calculations on the F-013.
6. Document WBC/mL, TNC, MNC%, MNC Total, CD3 Total and gram stain results on the MNC Apheresis toe tag label.

J. Labeling the Apheresis Material

i. Prior to distribution the product should be labeled according to PST 008 Procedure: Product and Reagent Labeling .
ii. Use ISBT product code S1303 MNC, Apheresis Citrate/xx/Refrigerated/For Further Processing.
    1. Include the study identification number next to the MRN.
iii. A second technologist will verify the label is correct and document on F-406 Verification of Product Labeling: Autologous MNC
iv. Remove the Apheresis Collection Label and place in patient chart.
v. Affix final product label to bag
vi. Attach completed MNC Apheresis toe tag to the apheresis collection bag.
    1. Include Subject ID, Gram Stain Result, WBC, TNC, MNC and CD3 Total on the toe tag.
        a. Do not release the product without all of the required results.

K. Packaging of the Fresh Apheresis Material for Shipment

i. The product will be released to the CIT for manufacturing or for shipment to an outside facility for manufacturing.
    1. Call the **Director Cell Immunotherapy and Transduction (GMP Facility)** listed in the protocol specific Cellular Therapy Manual to schedule the product transfer.
ii. The product must not remain at room temperature longer than 1 hour.
    1. If there is a delay, store the product at 2-8 °C in appropriate temperature monitored storage.
iii. Include the pre-apheresis CBC results as well as the post apheresis CBC results.
    1. Print these results from Cerner.
iv. Include a copy of the IDMs.
    1. Label the product with a biohazard label and appropriate warning labels if the IDMs are reactive or incomplete.
v. Include a Circular of Information.
vi. Include Appendix 10.4 Apheresis Tracking Log.
    1. Keep a copy of Appendix 10.4 Apheresis Tracking Log in the CTL chart.

L. Product Release from CTL

i. The product will be released to CIT personnel for manufacturing or shipment to the appropriate manufacturer.

1. Apheresis product needs to arrive at manufacturing facility within 24 hours of collection.
2. CIT will complete (as needed)
    a. Appendix 10.1 CD4CAR T Cell Shipping Memo
    b. Appendix 10.5 Cell Product Receipt Form
    c. Appendix 10.2 CryoShipper Shipping Transport Label

ii. The release of the product will be documented on the F-001 CTL Activity Log according to SOP PST 006 Procedure Cellular Therapy Product Release .

iii. Complete Appendix 10.7 Chain of Custody Log
    1. Keep a copy and give the original to the CIT personnel.

VII. CLINICAL SIGNIFICANCE/SPECIAL CONSIDERATIONS

The experimental product described in this protocol will be given to subjects with unmet medical needs for which there are no effective therapies known at this time.

VIII. REFERENCES

AABB Standards for Cellular Therapy Product Services, current edition.

FDA CFR Title 21, Part 1271 Human Cells, Tissues and Cellular and Tissue Based Products

FACT Standards, current edition.

CTO-IUSCCC--ICG122-101 Cellular Therapy Manual

IX. FORMS/APPENDICES

CTO-IUSCCC--ICG122-101 Cellular Therapy Manual Forms (see secure drive protocol folder for current version)

- Appendix 10.1 CD4CAR T Cell Shipping Memo
- Appendix 10.2 CryoShipper Shipping Transport Label
- Appendix 10.4 Apheresis Tracking Log
- Appendix 10.5 Cell Product Receipt Form
- Appendix 10.6 Product Label examples
- Appendix 10.7 Chain of Custody Log

F-001 CTL Activity Log”

BMT Forms:

F-CL-2.00-1 Autologous Pre-CAR T-cell Therapy Evaluation Checklist

F-CL-20.00-2 Request for Processing Order (Autologous Product for CAR T-cell Manufacturing)

F-001 CTL Activity Log”

F-561a Autologous Product Description and Quality Certificate

X. APPROVAL BODY

See protocol.

Procedure #

RCTL 026