The Role of the Graft Processing Laboratory in Stem Cell Transplantation

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Stem Cell Product Life Cycle

• Procurement
• Transport to laboratory
• Processing and testing
• Storage
• Transport to patient bedside
• Administration to patient
Procurement

• Physician request(s) for procurement and processing
  • Scheduling with lab ensures proper staffing
  • Product type and target dose
  • Date of collection
  • Donor and recipient identifiers
    • Allows laboratory to confirm product identity at receipt
  • Donor identified before procurement
  • Product labeled immediately post procurement
    • Unique identifier needed
<table>
<thead>
<tr>
<th><strong>Recipient Mayo Clinic Number</strong></th>
<th><strong>Donor Mayo Clinic Number</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recipient Name</strong></td>
<td><strong>Donor Name</strong></td>
</tr>
<tr>
<td><strong>Recipient Weight</strong> kg</td>
<td><strong>Start Date (Month DD, YYYY)</strong></td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td><strong>Location</strong></td>
</tr>
<tr>
<td>Consented to Cell and Serum Bank - IRB 1087-01</td>
<td>Gonda 10</td>
</tr>
<tr>
<td><strong>On Protocol for BMT</strong></td>
<td><strong>Informed Consent Obtained for Collection</strong></td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Product to be Collected</strong></td>
<td><strong>Target Dose</strong></td>
</tr>
<tr>
<td>HPC-A (RBC)</td>
<td>$10^9$ CD34/kg</td>
</tr>
<tr>
<td>TC-T (DU)</td>
<td>$10^9$ CD3/kg</td>
</tr>
<tr>
<td>HPC-M (BM)</td>
<td>$10^9$ Nucleated Cells/kg</td>
</tr>
<tr>
<td><strong>Cellular Therapy Product</strong></td>
<td></td>
</tr>
<tr>
<td>IRB Number</td>
<td>Protocol Name</td>
</tr>
<tr>
<td><strong>Other (Describe)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Processing Request</strong></td>
<td></td>
</tr>
<tr>
<td>Cryopreserve</td>
<td>RBC Reduction Needed</td>
</tr>
<tr>
<td>Give Fresh</td>
<td>Yes</td>
</tr>
<tr>
<td>Both (Describe)</td>
<td></td>
</tr>
<tr>
<td><strong>Special Processing Request</strong></td>
<td></td>
</tr>
<tr>
<td>Cellular Therapy Product</td>
<td></td>
</tr>
<tr>
<td>IRB Number</td>
<td>Protocol Name</td>
</tr>
<tr>
<td>Other (Describe)</td>
<td></td>
</tr>
<tr>
<td>I authorize Transfusion Medicine personnel to order and collect Infectious disease testing as needed per procedure.</td>
<td>Physician Signature</td>
</tr>
</tbody>
</table>

Sample Product Request
Transportation Within the Hospital

- Product labeled after procurement
- Carried by hand in a cooler or closed container
- No ice or cold packs necessary
- Processing usually begins shortly after product receipt in laboratory
Long Distance Transportation (non-frozen product)

- Usually from unrelated donor
  - Not processed before transport
- Insulated cooler required
  - Ice or Ice packs can be included
- Hand carried by courier instead of shipping company
- Should arrive <48 hours after collection
  - prolonged transport = worse outcomes
Long Distance Transportation (frozen product)

- Usually from cord blood bank
- Shipped in “dry shipper”
  - Liquid nitrogen in absorbent material
- Holds temperature for several days
  - Usually shipped without courier
- Monitor temperature during shipment
Receipt

• Assign or record unique laboratory identifier
• Document date/time of receipt
• Inspect for proper appearance
• Compare label to physician request
• Process per request
Collection Time: 00:40

Unique identifier: Q 26829-3

Expiry date: 06 OCT 31

Blood Type: A

Product Type: TC-T CELLS CRYOPRESERVED

Additives: 30% Normosol-R, 10% DMSO, 10% Plasma, 5u/mL Heparin

Store at <=-120C

Other required phrases and warnings:

- See circular of information for indications, contraindications, cautions and methods of infusion.
- VOLUNTEER DONOR
- Warning: This product may transmit infectious agents. Rx only

Collected and processed by MAYO CLINIC ROCHESTER Transfusion Medicine Rochester, Minnesota 55905

DO NOT USE LEUKOREDUCTION FILTERS and DO NOT IRRADIATE.
ISBT 128

- International Labeling Standard for Cellular Therapies
  - Standardized terminology and numbering system
  - Standardized label format
- Easier international exchange of products
- Being phased in over the next several years
  - Not widely used yet
Cellular Therapy Laboratory Documentation - Product Manufacturing

- Manufacturing record for each product
  - All details of product manufacturing
    - Receipt
    - Testing- tests and results
  - Details of processing
    - Staff involved
    - Materials and reagents used
      - Lot numbers, expiry date
    - Cell counts, volumes, process performed
    - Equipment used for testing and storage
    - Storage conditions
    - Deviations or events
  - Disposition of product
    - Administered, shipped, or discarded
Processing for Fresh Administration

• No processing
  • Perform required testing only
  • Label and distribute for administration

• Red Blood Cell Reduction

• Volume Reduction
Red Blood Cell Reduction

• To remove incompatible red cells
  • Type A, B or AB donor to type O recipient
  • ABO mismatched transplants are not unusual
    • Hemolytic reaction without removing RBC
  • Bone marrow > 300 mL RBC
  • PBSC 10-30 mL
  • Red cells removed by centrifugation or sedimentation in blood bags
    • HES improves process
  • Predictable loss of stem cells (~15-25%)
Volume Reduction

- For pediatric patients
- To remove plasma containing antibodies against recipient rbcs
- Centrifugation in blood bags
- High recovery of stem cells
Cryopreservation

• Autologous transplants

• Some allogeneic transplants
  • Usually for logistic reasons
  • Donor and recipient are not available at the same time or in the same location

• Long term storage of stem cells
Steps of Cryopreservation

• Cell count
• Concentration/volume reduction
• Addition of Cryoprotectant
  • 10% DMSO, Electrolyte solution, plasma
• Freezing
  • Controlled rate or mechanical freezer
  • Controlled rate more expensive + LN2 source
  • Mechanical – shorter term storage
Computer Controlled Freezing

Let product = Chamber
Before start

Need to determine during validation

Latent Heat of fusion

Region I
1°/min

Region II
Supercooling
Then resume
1°/min (some 2-3°)

Region III
Increase Rate to
5-10°/min

Product Temperature

Chamber Temperature

Temperature

Time

End temp may vary from -60 to -100
Storage of Products

- Liquid/Vapor nitrogen tanks
  - -196 C Best for long term storage
    - Less susceptible to power interruptions
- Mechanical Freezer
  - -80 C to -150 C
    - Need back up power supply
- Both methods need back up plan with alternate storage location
Storage of Products

• Temperature monitoring of storage location
  • Continuous recording or regular frequency
• Alarm system to notify of abnormal temperature
• Inventory system to track/locate products
Product Certificate of Analysis

• Document summarizing product details
  • Donor identifier, if applicable
  • Processing
  • Additives
  • Test results all meet specifications
  • Biohazard warnings, if applicable
  • Reviewed by laboratory director prior to administration
Preparation for Administration (frozen products -1)

- Physician request to administer cells
- Locate product in freezer
- Confirm identity of product with physician request
- Ensure proper labeling
- Ensure all required tests are completed
  - Infectious diseases
  - Cell dose
  - Sterility culture of product
Preparation for Administration (frozen products -2)

- Compare product label with recipient identity
- Prepare waterbath
- Thaw product
- Administer product
  - IV infusion
  - No Leukoreduction Filter
Post Administration

- Monitor for adverse events
- Track patient outcome as quality monitor
Process Control and Traceability/Trackability

• A well documented, controlled, reproducible, manufacturing process is the best way to ensure high quality products

• It is critical to document all steps of product manufacturing from procurement to administration
  • To facilitate recalls and lookbacks (Biovigilance)
  • To allow for thorough investigations of adverse events or other outcomes

• Process control and traceability/trackability equals cGMPs

• This is accomplished via Quality Systems
Elements of a Quality System

• Organization, Leadership, and Customer Focus
• Facilities, Work Environment, and Safety
• Human Resources
• Suppliers and Supply Management
• Equipment Management

• Process Management
• Documents, Records, and Information Management
• Nonconforming Events
• Monitoring and Assessment
• Continual Improvement

The laboratory and BMT program should have processes, policies, and procedures addressing each of these topics.