WBMT Graft Processing Workshop

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Graft Processing

- Integral part of the transplant programme
- Specialised manpower and equipment: ?cost factored into transplant calculation
- Minimal to advanced extensive processing
- Stem cell sources: BM vs PBSC vs Cord
- Essential parameter in determining engraftment; graft versus host disease; immune reconstitution; relapse
Main functions:

- Overseeing the safe receipt/handling of donor stem cells
- Defining the product: its quality and characteristics----Francesco Lanza
- any manipulation required for the transplant---- Francesco Lanza
- Safe delivery back to the hospital/patient including infectious diseases
- quality assurance
Minimal Requirements and Essential Features for Setting up a Stem Cell Processing Laboratory.

- **Thomas Leemhuis**
  - Carolyn Keever-Taylor
  - Takanori Teshima,
  - Christian Chabannon,
  - Ali Bazarbachi

- **Douglas Padley**
  - Dietger Niederwieser
  - Francesco Lanza,
  - Paul Szabolcs,
  - Mickey BC Koh

- On behalf of the Graft Processing Subcommittee of the Worldwide Network for Blood and Bone Marrow Transplantation (WBMT).
Scope of Talk

- Physical Layout and considerations
- Equipment/reagents and personnel needed
- Range of Processing Services offered
- Guidance documents and resources
Key Considerations

- Access to reliable electricity supply
- Minimally Manipulated Products in support of a transplant programme: not Haplo-identical or advanced cell processing
- Improvements will be made as additional resources become available and as volume and scope of clinical transplant services increase
Physical Considerations

- Does every transplant programme require a processing lab?
- Does centralising reduce costs and make best use of manpower?
- Number of centres; transplant numbers; distances from lab to centres
- Hospital based vs involvement of the Transfusion Service
- Examples of processing labs in the UK and Singapore
Strengths of Transfusion Laboratories and Blood Banks

• Harvesting and handling of apheresis and cellular products
• Quality systems with a focus on “processes”
• Product safety focus including stringent donor testing
• Multidisciplinary: technologists, similar staff training; microbiologists
• Back-up power supplies
Scope of Talk

- Physical Layout and considerations
- **Equipment/reagents and personnel needed**
- Range of Processing Services offered
- Guidance documents and resources
Equipment/Reagents

- Reliable Maintenance and Availability
- Qualification/validation and monitoring of equipment/reagents
- -70°C product storage in mechanical freezers vs liquid nitrogen: length of storage and viability
- Back up/Contingency: all need for JACIE!
Important Considerations

- Qualified staff and Training programmes
- How many lab staff are needed: minimum of 2
- to limit each workstation and each staff member to the processing of one product at a time
- Quality systems
- Quarantine
Clinical Focus

- Representation at Clinical Transplant Meetings
- Correlation with engraftment data and clinical outcomes (CD₃⁴; TNC; viability; microbiology)
- Assurance that the clinical outcomes match the reliability of processing
- Apheresis /processing/ staff /equipment all contribute
- Threshold of $2\times 10^6$ CD₃⁴/kg and a desirable $5\times 10^6$ CD₃⁴/kg
# Required Equipment:

## Dedicated:

<table>
<thead>
<tr>
<th>Equipment</th>
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</thead>
<tbody>
<tr>
<td>Biosafety Cabinet</td>
<td>Refrigerator</td>
<td>Balance (Scale)</td>
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<tr>
<td>Water bath</td>
<td>Centrifuge</td>
<td>Freezer (≤ -70°C)</td>
</tr>
<tr>
<td>Hematology Analyzer</td>
<td>Tubing sealer</td>
<td>Personal computer</td>
</tr>
<tr>
<td>Plasma Extractor</td>
<td>SCD</td>
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<tr>
<td>Pipette Aid</td>
<td>Hemostats</td>
<td>Tubing stripper</td>
</tr>
<tr>
<td>Cryo-transporter</td>
<td>Micropipettes</td>
<td>Label printer</td>
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</tbody>
</table>

## Shared:

<table>
<thead>
<tr>
<th>Equipment</th>
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<tbody>
<tr>
<td>Hematology Analyzer</td>
<td>Flow Cytometer</td>
<td>Micro Lab</td>
</tr>
<tr>
<td>Microscope</td>
<td>LN$_2$ Freezer</td>
<td>Reference Thermometer</td>
</tr>
</tbody>
</table>
Scope of Talk

- Physical Layout and considerations
- Equipment/reagents and personnel needed
- **Range of Processing Services offered**
- Guidance documents
Auto vs Allo

- **Autologous:** freezing capacity and secure storage for the stem cell graft. Largely PBSC based with higher mobilisation failure

- **Allogeneic:** red blood cell (RBC) and plasma depletion services and be prepared to thaw and infuse cord blood products. DLIs

- Is Autologous processing more challenging?

- Allo products if given fresh actually needs less doing than auto except for plasma/red cell depletion in ABO mismatched transplants. If PBSC-only plasma depletion and this often not mandatory
What else to be considered

- Post thaw viability
- Sterility testing
- Non conforming product
- Bedside vs lab thawing
- Adverse effects
- Registry of all facilities processing stem cells
- Cell Therapy for regenerative medicine and its knock on effects
Key partners in Cell Processing / Therapy Organisations

- AABB
- ISCT
- ISBT
- WBMT: FAQs and email
- CTCLAG
- AHCTA
- FACT/JACIE
Discussion

- Transplant programmes and graft processing labs: relationship
- Qualified manpower and training: twinning?
- How should one start? Auto vs Allo. The cell processing perspective
- Costs for running a cell processing lab
- Access to equipment/maintenance, reliability of power and qualified staff. Freezing capacity
- Advanced cell processing
AIDE-MEMOIRE
for National Health Authorities*

Tissue and cell transplantation represent essential and rapidly developing therapies in modern healthcare. It is the responsibility of national health authorities to ensure that the needs of patients are met with a supply of safe tissues and cells of appropriate and consistent quality. A nationally supported legislative framework which defines consent requirements and supports donation and a regulatory system which authorises tissue and cell banks are prerequisites to achieving this goal. Donation and transplantation activities should be organised in a transparent way with the provision of adequate information and data to enable the public to make informed choices.

Tissue and cell transplantation carry risks of disease transmission. Viruses (including HIV, hepatitis B and C), bacteria, fungi, parasites
General flowchart of cell & tissues used for therapy from source to final usage

1. **Cell or Tissue Donor**
   - Screening of donors, including for infections
   - Informed consent
   - Further manipulation of cells

2. **Extraction of cell or tissue**
   - Cold chain, prevention against infection & contamination

3. **Cells & tissue transported to laboratories for processing**
   - In laboratories; etc
   - By technicians
   - Using machines/ laboratory procedures

4. **Processed cell & tissue stored**
   - In cell & tissue banks; etc
   - By technicians
   - Using machines/ laboratory procedures

5. **Distribution of cell & tissue**
   - Cold chain, prevention against infection & contamination
   - Screening of recipients

6. **Implanted, transfused back into donor (autologous)**
   - Monitoring for short and long term adverse effects
   - Traceability back to donor

7. **Implanted, transfused into persons other than donor (allogenic)**
   - Product recall system

8. **Screening of recipients**
   - In patients in healthcare institution & in community
   - By healthcare institution/laboratories;

9. **Informed consent**
   - In healthcare institution; By licensed personnel (exception - extraction of blood)

10. **Monitoring for short and long term adverse effects**

11. **Product recall system**

Transport. Import/Export and Regulatory Issues

- Labelling and Cold Chain Transport
- **Country Regulations.**
- Traceability of Stem Cell donations
- Infectious Disease Testing
- Required environment for cell processing
Dealing with cell therapy tourism
United States

• Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) regulated by US Food & Drug Administration

• HCT/Ps that meet ALL of the following criteria = “361” products
  – Minimally manipulated
  – Intended for homologous use
  – Not combined with drug or device
  – No systemic effect or not dependent on metabolic activity for primary function
  ❖ No pre-market approval
  ❖ Comply with Tissue Rules, including tissue establishment registration

• Other HCT/Ps = “351” products
  – Comply with Tissue Rules
  – Regulated as biologics or device (IND/BLA, IDE/PMA/510K)
Cell Therapy: Potential

Potential Patients (USA)

- Cardiovascular Diseases: 58M
- Autoimmune Diseases: 30M
- Diabetes: 16M
- Cancer: 10M
- Osteoporosis: 8M
- Neurologic Diseases
- Burn Injuries
- Birth Defects

Science 2000;287;1423
2011

- US$1.53 billion
- US$2.72 billion
- US$1.12 billion

Total: US$5.37 billion

2016

- US$2.82 billion
- US$4.65 billion
- US$1.41 billion

Total: US$8.88 billion

Nature Reviews | Drug Discovery
<table>
<thead>
<tr>
<th>Attribute</th>
<th>Test Method</th>
<th>Specification</th>
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<tbody>
<tr>
<td>Donor Screening</td>
<td>Summary of Records; Donor Eligibility Form</td>
<td>Donor Eligible</td>
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<tr>
<td>Infectious Disease Testing</td>
<td>Certified Laboratory</td>
<td>Negative (exclusive of CMV)</td>
</tr>
<tr>
<td>Infusion Volume</td>
<td>Measurement</td>
<td>≤20mL / Kg / Infusion</td>
</tr>
<tr>
<td>DMSO Volume</td>
<td>Calculation</td>
<td>≤ 1mL / Kg / Day</td>
</tr>
<tr>
<td>Total Nucleated Cell (TNC) Count</td>
<td>Automated Cell Counter</td>
<td>As Measured</td>
</tr>
<tr>
<td>RBC content (if ABO incompatible)</td>
<td>Automated Cell Counter</td>
<td>≤20mL-30mL /Adult Infusion</td>
</tr>
<tr>
<td>CD34+ Cell Count</td>
<td>Flow Cytometry</td>
<td>≥ 2 x 10^6 / kg</td>
</tr>
<tr>
<td>CD3+ Cell Count (if allogeneic)</td>
<td>Flow Cytometry</td>
<td>As measured</td>
</tr>
<tr>
<td>Viability (pre-freeze)</td>
<td>Flow Cytometry</td>
<td>≥ 80%</td>
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<tr>
<td>Sterility</td>
<td>Bacterial Culture</td>
<td>No Growth</td>
</tr>
<tr>
<td>Sterility</td>
<td>Fungal Culture</td>
<td>No Growth</td>
</tr>
<tr>
<td>Final Product Labeling</td>
<td>Observation</td>
<td>Labeled Correctly</td>
</tr>
</tbody>
</table>