Transfusion Involvement in Cellular Therapies, Tissue Immunology

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Introduction

- Blood Services currently play a vital role in Transfusion Medicine
- Core competencies include:
  - Adherence to standards and best practice for the collection, processing, testing and storage of blood products,
  - Research experience
- Are ideally situated to:
  - Manufacture human derived cell culture supplements for use in expansion of human cell therapy products
  - Establish banks for other types of cells and tissues of human origin
  - Harvest cells/tissue for further manipulation and re-infusion
  - Perform state of the art tissue immunology testing for transplantation programmes

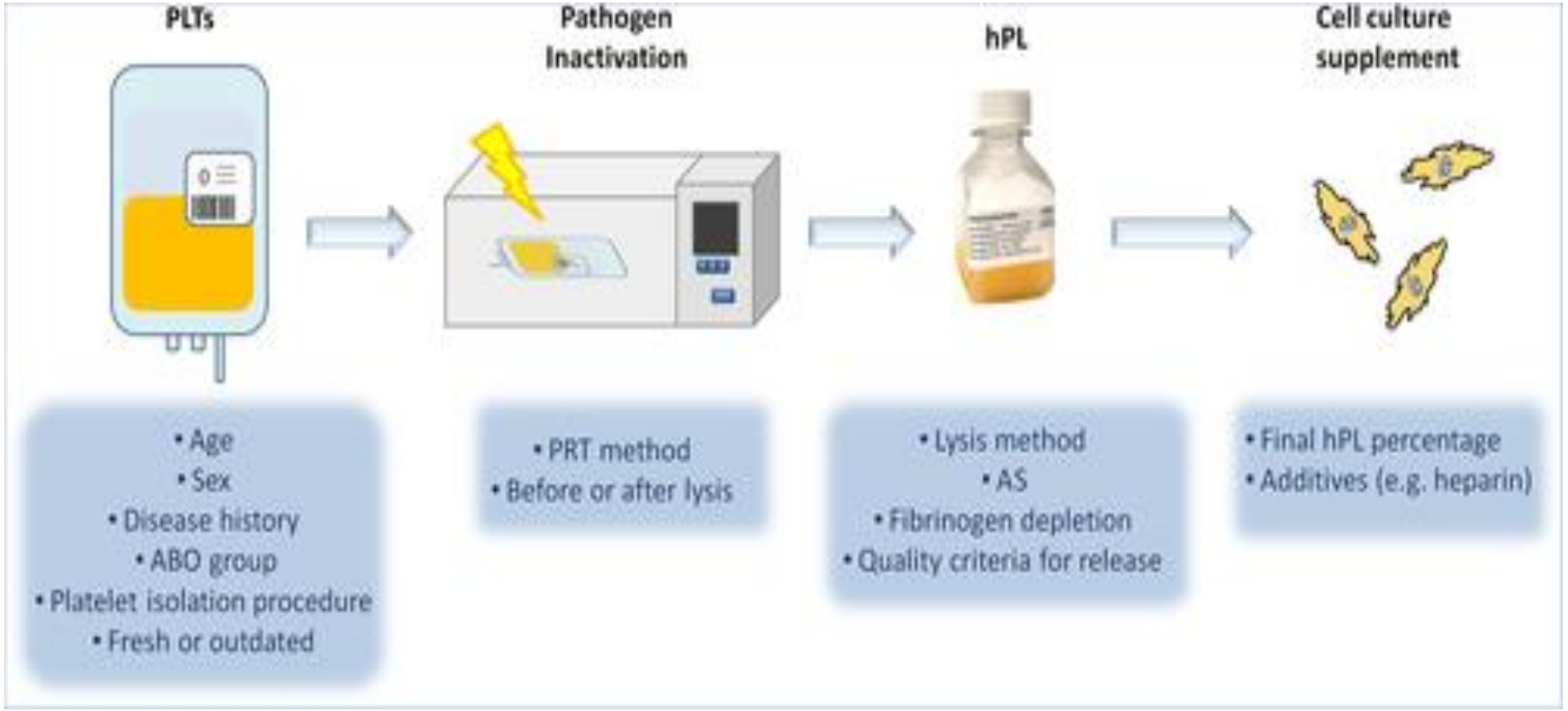
Human Platelet Lysates (hPL's)

- Cellular therapeutics are increasingly being investigated to treat cancer, organ degeneration, or (auto)immune diseases
- Cells such as mesenchymal stromal cells (MSCs) need to be expanded after collection and before they can be used for patient care
- Increased demand for their large-scale, high-quality production globally.
  - Currently, foetal bovine serum (FBS) is the most widely used growth factor supplement
  - Many challenges exist with scaling up FBS to meet demand (ethical, regulatory and quality related)
  - Human platelet lysate (hPL) has been identified as a human derived growth supplement that can be used to replace FBS
  - hPL is a cell-free, protein rich fluid produced from lysed or activated platelet concentrates. It is rich in growth factors and other cell growth promoting biomolecules important for wound healing and tissue repair

hPL's (Continued)

- Recently expired platelets used
- SANBS has an excess of 600 000 buffy coats rich in platelets that are discarded annually
  - Starting material already exists to prepare hPL's
- No risks of cross-species immune reactions nor transmissions of animal pathogens.
- hPL shown to be more effective in hastening cell growth.
- hPL can support greater proliferation of MSCs compared to FBS (demonstrated by a number of studies)
- SANBS is exploring options for manufacture hPL's

Process Followed for Preparation of Human Platelet Lysates



Transfusion, August 2019

Serum Eye Drops (Autologous)

- Used to treat severe dry eye syndrome
- Autologous serum eye drops have a composition that more closely resembles natural tears.
- Patient donates a unit of blood which is tested for infectious markers.
- Unit is allowed to clot, processed with addition of saline (approximately 1:4 ratio) with end product having about 20% of serum
- Packaged into tubing, segmented and frozen
- Patient then uses one segment a day
- SANBS currently makes this product

Umbilical Cord Blood Banking

- Entails preserving the stem cells found in the blood of the umbilical cord and placenta after birth
- The process involves collection, processing , testing and storage.
- Cells are used today to treat haematological diseases such as leukaemia but also increasingly in regenerative medicine
- Many Transfusion Services have well established Cord Blood Banks which are mostly “Public Banks” with anonymous donors
- Private Cord Blood Banks also in various Countries

Umbilical Cord Blood Stem Cells

- The advantages of cord blood stem cells for transplantation include:
  - Immediate availability of cells,
  - Absence of risk to the donor,
  - Lower risk of graft-versus-host disease and
  - A lower need for donor-recipient HLA compatibility.
  - Can be stored frozen for long periods
- A limiting factor is the low number of hematopoietic stem cells
- Recent focus has also been on the use of cord blood cells in hypoxic brain injury, including cerebral palsy and autism

Human Milk Banks

- Similar selection and testing processes for blood donation:
  - Potential donors provide blood samples which are tested for infectious disease markers such as HIV, Hepatitis B and C, syphilis and human T-cell lymphotropic virus (HTLV).
  - Exclusion factors include anyone who smokes or uses tobacco products, uses recreational drugs, has a recent tattoo or piercing, takes certain medications or has had a blood transfusion within the past 6 months
- Typically donations from up to three donors are pooled, pasteurised and tested for sterility
- Transfusion Centres are well placed to manage the milk banks of the infectious disease testing

Faecal Microbiota Transplantation

- Involves the transfer of the full spectrum of microbiota stool from a healthy screened donor to a recipient
  - The aim is to normalise the perturbed gut microbiome associated with *Clostridioides difficile,*"
  - *C. difficile* is among the most common hospital-acquired infections among adults
    - Almost half a million cases diagnosed every year in USA.
  - Usually treated with antibiotics, however patients with recurrent infections are eligible for faecal microbiota transplant
    - Has a clinical cure rate between 80-90%, depending on the mode of delivery

Ref: AABB

Transfusion Involvement in Faecal Microbiota Banking

- Voluntary or paid donors recruited
- Undergo rigorous selection and testing process prior to being enrolled on the programme
  - In one New York programme donors undergo 18 stool laboratory investigations and 14 serology screen tests
  - Only 3% of applicants are accepted as stool donors
- Once donated, samples are mixed with an inert cryo-preservative, filtered with micro filters to remove fibre, homogenized and stored at minus 80 degrees Celsius.
- In Denmark the material is packaged into capsules and taken orally

Chimeric Antigen Receptor (CAR) T cells

- Are an autologous cell therapy product which is genetically manipulated, ex vivo expanded, and induces T cell mediated kill of targeted cancer cells.
- Two CAR T cell formulations were licensed in the US and one in Europe in late 2018 and other licenses are expected in 2019
- At least 200 clinical trials using CAR T cells are currently listed within clinicaltrials@gov
- Process of manufacture requires harvesting of cells, processing and expansion in a laboratory and re-infusion

Ref:AABB

CAR T Cell Production

- GMP-grade production of CAR T cell therapies includes
  - apheresis of low-density mononuclear cells,
  - Monocyte depletion by density gradient separations,
  - T cell enrichments,
  - transduction with the CAR using viral vectors,
  - T cell activation and expansion using anti-CD3/antiCD28 stimulation in the presence of interleukin-2.
  - Expansion periods range from one to three weeks followed by re-infusion
- The Clinical Apheresis departments of Blood Services are well placed to collect and re-infuse the cells.

Clinical Apheresis

- Therapeutic plasma exchange (TPE) is offered mainly for Acquired thrombotic thrombocytopenia purpura (aTTP) patients
  - Can improve survival from less than 10% to greater than 80%.
  - Entails patients plasma removal to lower specific auto-antibodies and this is followed by donor plasma replacement
- Autologous and Allogeneic Haematopoietic Stem Cells harvesting, storage and re-infusion for patients with haematological malignancies
  - Done by Blood Services for a number of years
- Potential for harvesting cells from patients selected for CAR T cell therapy
- Harvesting of specific cells for other emerging novel therapies

HLA Testing

- Blood Services have been involved for more than 3 decades in providing HLA typing for transplantation programmes
  - Significant advances in technology and testing methods over the past few years
- SANBS and other blood services keep up with latest technology to ensure the appropriate level of service is provided to our stakeholders

Thank You