Workshop Session

Cellular Therapy Operational Considerations

Dean Bradley

Quality Assurance & Quality Control Manager, Newcastle Cellular Therapies Facility, Newcastle University

Northern Alliance
Advanced Therapies Treatment Centre

Cellular Therapy Operational Considerations

DEAN BRADLEY

Cellular Therapies

- Processing
  - Routine
  - Specialist
- Clinical Trials
- Manufacture
- Storage
- Regulation's
  - MHRA
  - HTA
  - JACIE

Accreditation

- Human Tissue Authority (HTA) for Human Application
  - Collection
  - Processing (Process Preparation Dossier – PPD)
  - Storage
  - Shipping (Export?)
- FACT-JACIE (The Foundation for the Accreditation of Cellular Therapy and the Joint Accreditation Committee – ISCT and EBMT)
  - Immune Effector Cells (IEC)

Starting Material

- Relevant Materials (Human Tissue Act 2004)
  - The fundamental concept of relevant material is that if a sample is known to contain even a single cell that has come from a human body, then the sample should be classified as relevant material.

- HTA licensing for those working with ATMPs
  - Where an organisation is involved in the procurement and testing of human tissues or cells, which are to be used in the manufacture of an ATMP, these activities must be carried out under an HTA Human Application licence which covers these activities.

Storage Requirements

- Why Nitrogen?
  - Cell activity effectively stops at -135°C
  - Mechanical ultra low temp only achieve at best -140°C and -135°C
- Vapour Phase Liquid Nitrogen
  - Vapour phase that forms above/outside liquid phase nitrogen -135 to -190°c
  - Safety and ease of access then immersion
- SPC:
  - store and transport below -120°C, e.g. in a container for cryogenic storage (Dewar) in the vapour phase of liquid nitrogen.
  - Bags must be stored in the vapour phase of liquid nitrogen (≤ -150c) and it must remain frozen until the patient is ready for treatment to assure viable live autologous cells are administered to the patient.
  - Store in the original protective envelope (Tyvek) containing the cassette protecting the infusion bag

To Overwrap or not to Overwrap?

- Contamination Issues
  - Liquid nitrogen not only serves as a refrigerant, but like water, can also act as a vehicle for the transmission of viruses, bacteria, fungi, and cells.
    - Infective viruses were found in liquid nitrogen and thus should be treated as a biohazard (Schafer et al., 1976)
    - Bone marrow and stems cells harvested from patients undergoing cytotoxic treatment became contaminated with Hepatitis B virus (HBV) as a result of storage in liquid nitrogen and caused a HBV outbreak (Tedder et al., 1995). Of the six patients afflicted, human DNA, Hepatitis B surface antigen A, and HBV DNA matching those patients were found in the liquid nitrogen. The interesting observation is that DNA from the patients, and thus presumably their cells, was found in the liquid nitrogen indicating that contaminants move both in and out of the storage containers.
    - A follow-up study to this HBV outbreak confirmed the human and HBV sources by DNA sequence analysis (Hawkins et al., 1996).
    - Foutain et al. (1997) conducted a survey of fungal and bacterial contamination of liquid nitrogen freezers used to store hematopoietic stem cells. Of the 583 cultures tested, 1.2% were found to be contaminated by microorganisms.
  - Changes:
    - Licenced products not overwrapped
      - Reluctance to allow overwrap by manufacturer
      - Reluctance to store products without overwrap

Vapour Phase

- No nitrogen inside the vessel (Jacketed)
- Stable for > 7days
- Dedicated storage box
- Fully automated
  - Fill
  - Temperature
  - Alarms -150°c
- Changes:
  - Alarms -155°c
  - Impact –
    - more frequent fills
    - Increased LN usage
    - More fill alarms

Cryopreservation

- Controlled rate freezing of stem cells: the importance of profiles.
  - Cell are preserved at cryogenic temperatures; typically -80 °C or -196 °C.
  - Biological activity is slowed or stopped at these ultra-low temperatures.
  - The controlled-rate freezer is used to get the cells down to the cryopreservation temperature without damage.

- Over 10 years experience using freezing profile
- 1000 cryopreserved units/year
- Engraftment ≥99%

Cryopreservation 2

- Changes:
- Bespoke freezing profile
  - Second controlled rate freezer
  - HTA PPD
    - Validation of the freezing programme
    - Validation of cell viability pre cryo and post thaw

Shipping

- Transport vessels (Dry shipper)
  - Stable for >7days
  - Temperature monitoring
  - Alarm -135°c
- Changes
  - Alarm -150°c

Cell Tracking

- Advanced therapy supply chain
  - Currently 2 products = 2 systems
- The Future
  - Does 40 products = 40 systems?

Regulatory

- Medicine
  - Medicines Act
  - Pharmacy Governance
- Changes:
  - Reconstitution (thaw) under the “supervision” of a pharmacist

Resources

- 550 staff hours incurred before patient 1
  - Audit
  - Training
  - Documentation
  - QMS/Change implementation

Cost Implications

- £42000 Incurred before patient 1
  - Training
  - Infrastructure

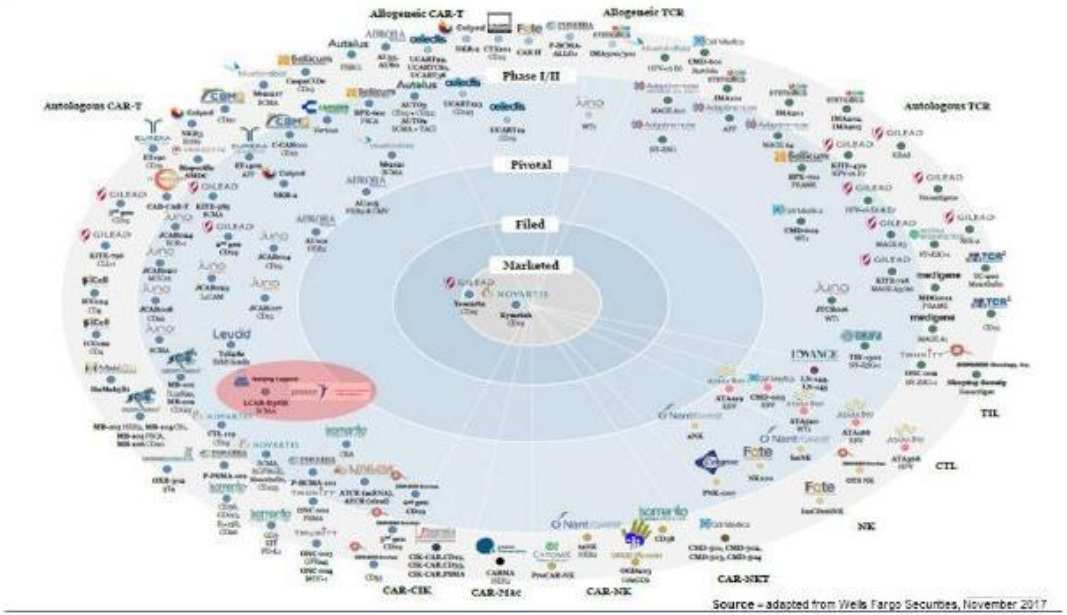
Discussion

- Sustainability?
- JACIE accreditation/NHS England
  - Standardised approach/best practice
- Infrastructure
- Capacity

The Future

Competitive Landscape

Adoptive Cellular Therapy Landscape: predominant focus on CAR technology, then TCR



Source – adapted from Wells Fargo Securities, November 2017

Adaptimmune

Questions