cell therapies

GMP challenges in cellular therapy products

Gerry McKiernan, Quality Manager

cell therapies

Agenda

Cellular Therapy:

- Landscape
- GMP Challenges
- Future

Winner Nobel Prize in Physiology or Medicine 2012 (iPSCs)

Yamanaka invented cell time machine

NOBEL WINNER Breakthrough technique is transforming research

By Erin Allday Published 4:57 pm PDT, Tuesday, October 16, 2012

CSN Time Machine®

STEM CELL THERAPY

Dr. Berman talks about his research in fat stem cells.

OVERVIEW OF DR. BERMAN'S STEM CELL THERAPY

ADULT (NON EMBRYONIC) MESENCHYMAL STEM CELLS

Most people (doctors included) believe that stem cell therapy is still several years away from being available to the public. However, since 2010, in association with my partner, urologist Elliot Lander, MD, FACS, we have been conducting stem cell deployment as part of an ongoing investigative project collecting data on thousands of treated patients. After several successful outcomes in the orthopedic arena that I obtained in collaboration with orthopedic surgeon, Dr. Tom Grogan, Elliot and I formed the California Stem Cell Treatment Center followed a year later by the Cell Surgical Network – the world's largest network of stem cell physicians utilizing technology we developed with renown Korean plastic surgeon, Dr. Lee Hee Young. We currently teach doctors from the USA and worldwide our techniques using the CSN Time Machine® to effectively harvest and process fat into stromal vascular fraction (SVF) rich in stem cells. Starting with a 10 minute mini-liposuction painlessly done under local anesthesia, this 1 ½ hour process has yielded results that have been successfully recapitulated all over the world. Currently, there are about 100 CSN centers in the US and many more throughout the world, including dozens in China in association with our partners, RE Stem Biotech.

CAR-T Cell Potential

Rapid and sustained response to Chimeric Antigen Receptor T cell therapy in double hit diffuse large B cell lymphoma

Abhinav Deol | Joseph Uberti

Department of Oncology, Wayne State University/Karmanos Cancer Institute, Detroit, Michigan

Correspondence
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Email: deola@karmanos.org

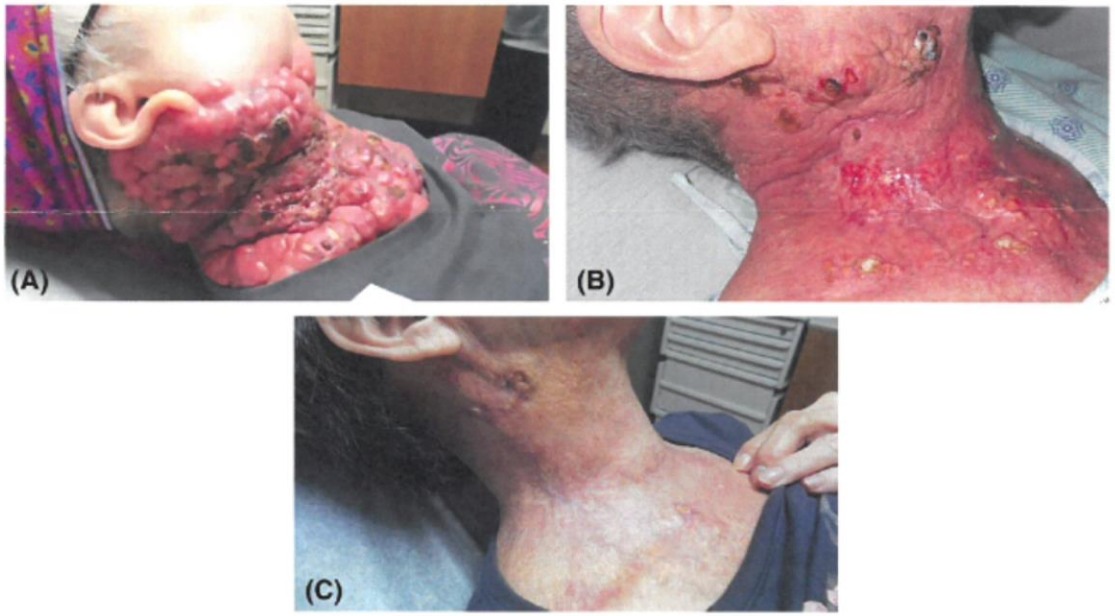
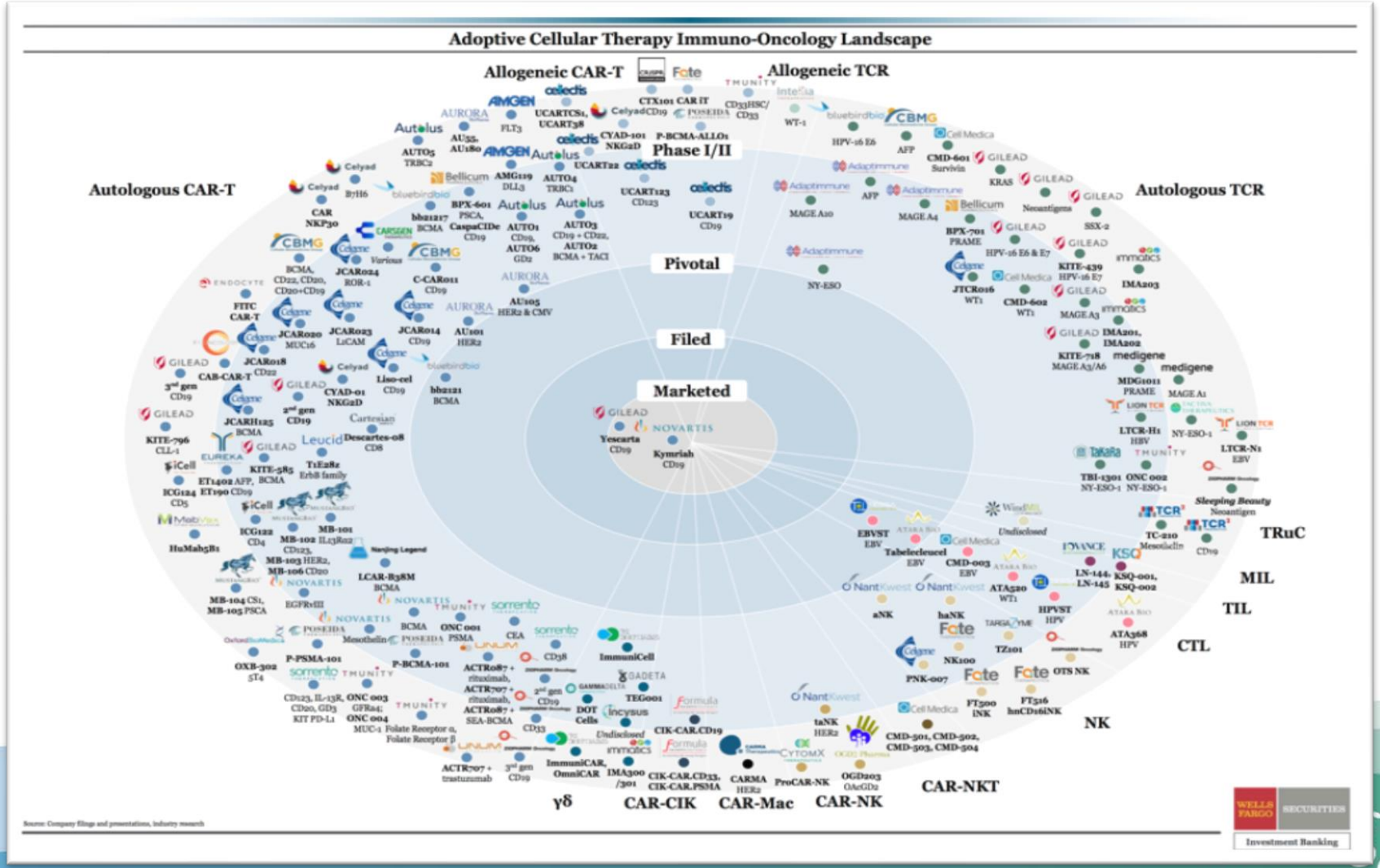


IMAGE 1 (A) Baseline disease status at the time of initiation of lymphodepleting chemotherapy. (B) Disease status 10 days after infusion of CAR T cell therapy. (C) Disease status at day 60 post infusion of CAR T cells

T-Cell Activity 2018

291 CAR-T products in development, 161 in trials



Cell Therapies PTY LTD

- Independent CDMO with PeterMac as shareholder
- In operation for 15 years
- 10 Grade B cleanrooms and associated storage and lab space
- Administered various TGA licences on behalf of clients in the past
- Currently hold generic licences for T-Cell manufacture, clinical trials and commercial supply (1st in Australia)

Licence to Manufacture Therapeutic Goods – Part 1

Licence Number:

MI-2015-LI-10786-1

Granted to:

Cell Therapies Pty Ltd
ABN: 15 100 285 916

Manufacturing Site Address:

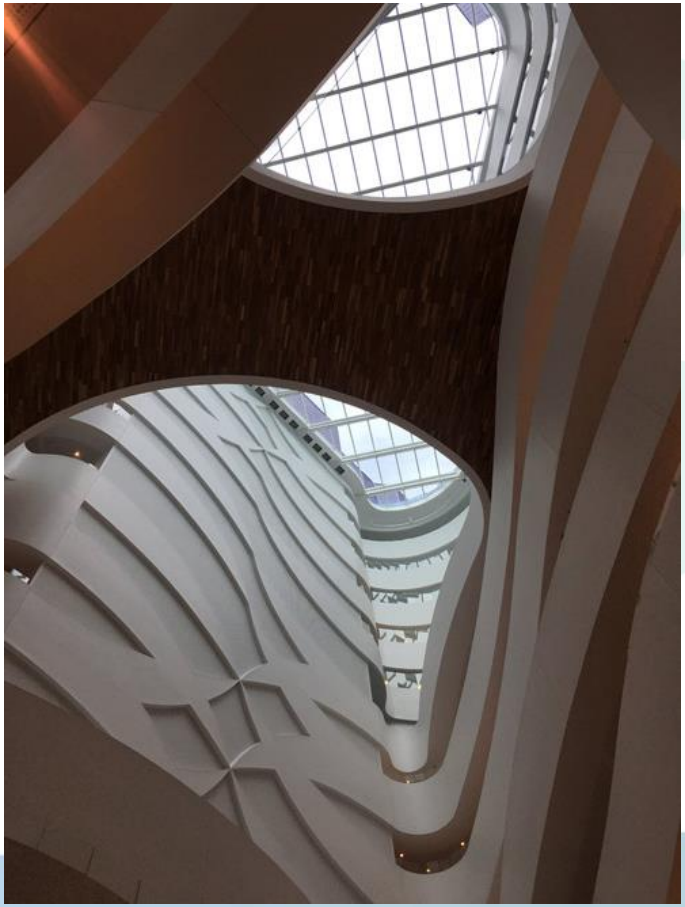
Ground Floor (Room 00-1.037), Levels 3, 4, 9 and 13
305 Grattan Street
Melbourne VIC 3000

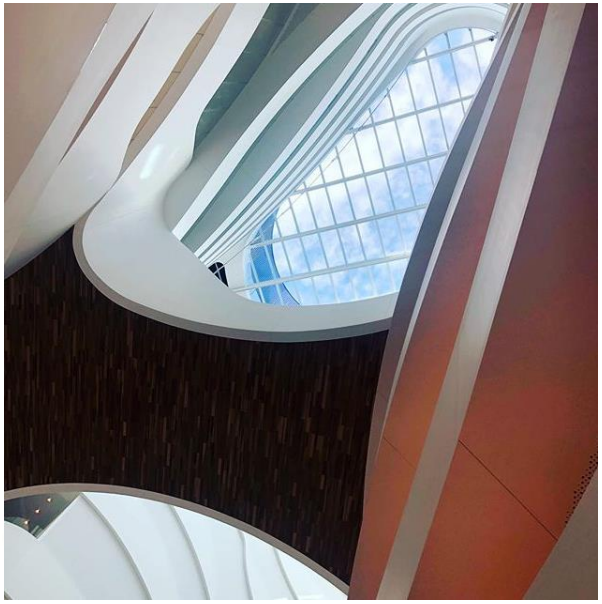
The manufacturer above is hereby authorised under section 38 of the *Therapeutic Goods Act 1989* to carry out the following steps in the manufacture of therapeutic goods at the manufacturing site address specified above.

Manufacturing Type	Sterility	Product Code	Manufacturing Step
Cellular	Manufactured Aseptically	Therapeutic Goods for Clinical Trials - T-Cells	Collection Processing Storage on site Release for supply
Cellular	Manufactured Aseptically	T-Cells	Collection Processing Storage on site Release for supply
Testing Laboratory - Blood Tissue Cellular	Not applicable	Not applicable	Testing Immunobiological Cell Count and Viability Flow Cytometry Product Microbial Contamination Testing
Testing Laboratory	Not applicable	Not applicable	Testing Physical

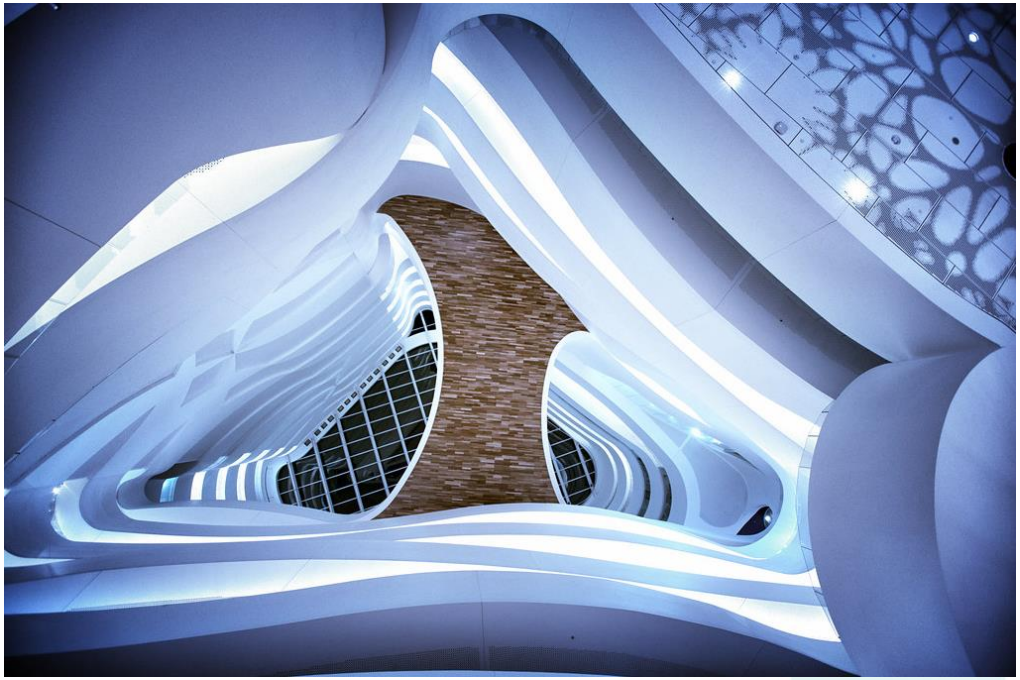
Located on Level 9, Peter MacCallum Cancer Centre (VCCC)

Peter Mac

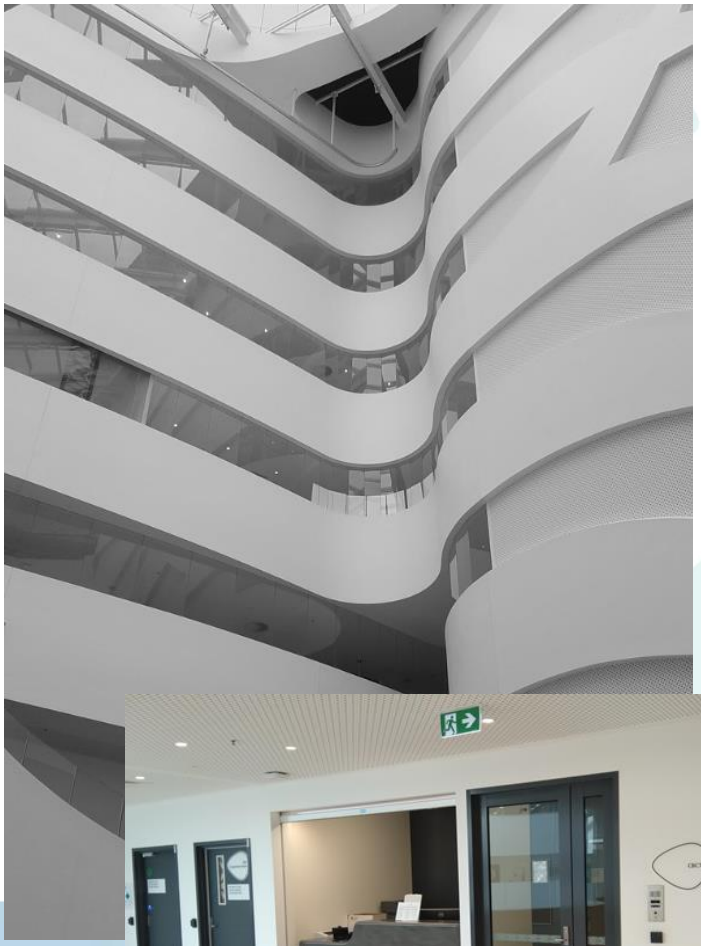


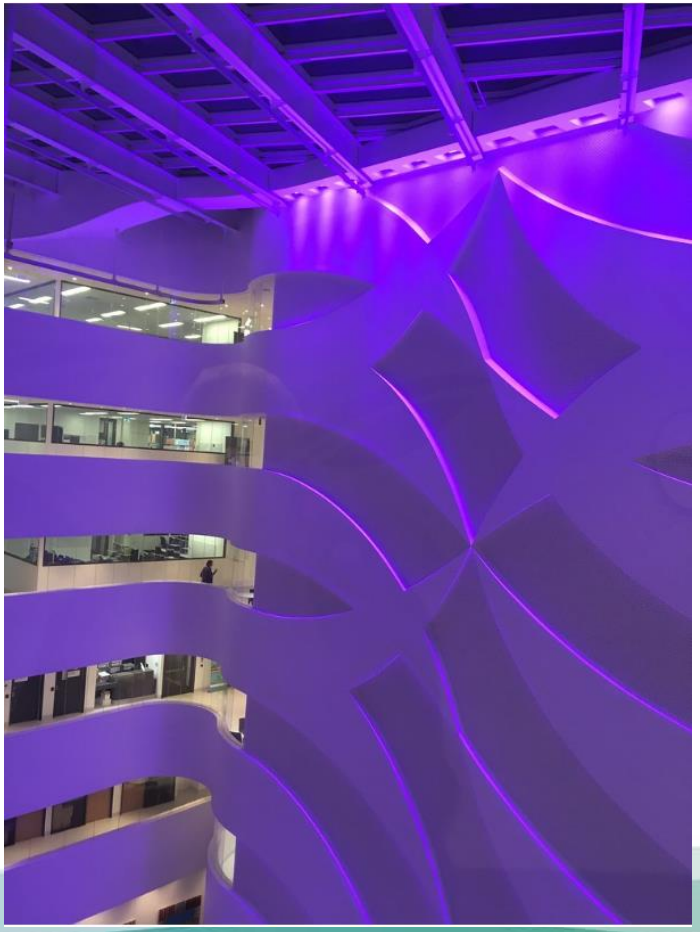


PeterMac



PeterMac

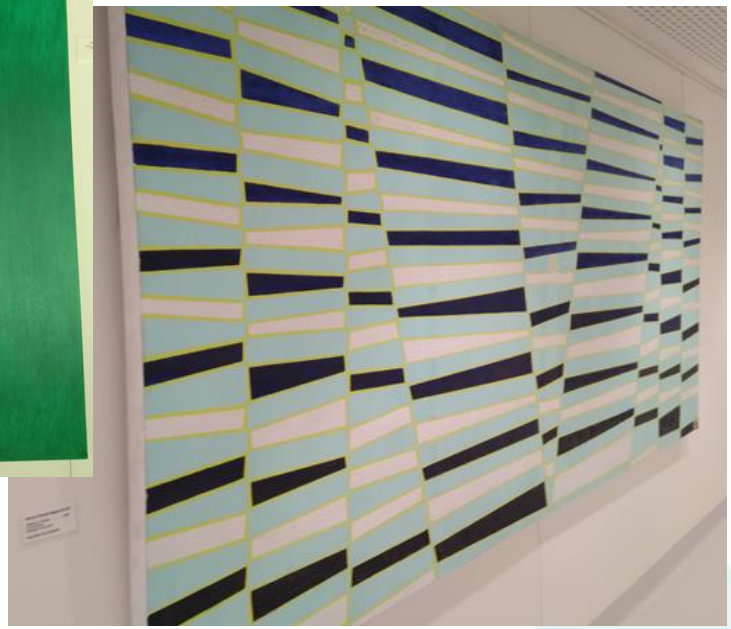


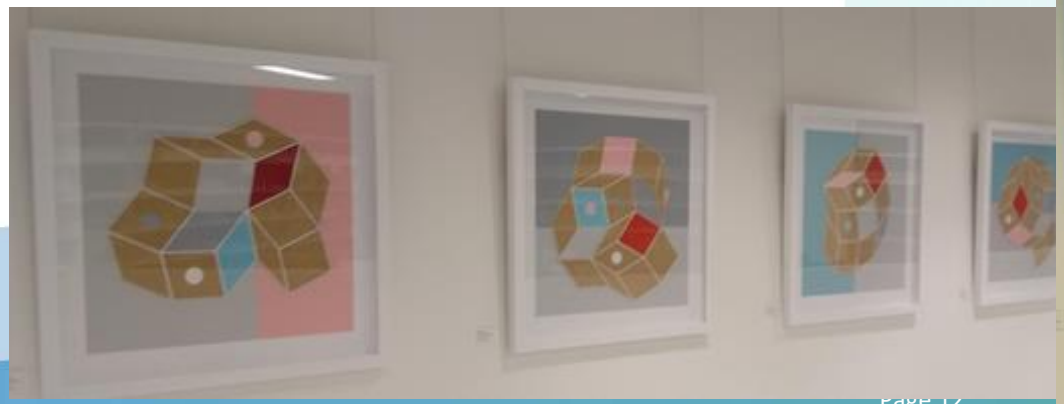


3 December
2019

cell therapies

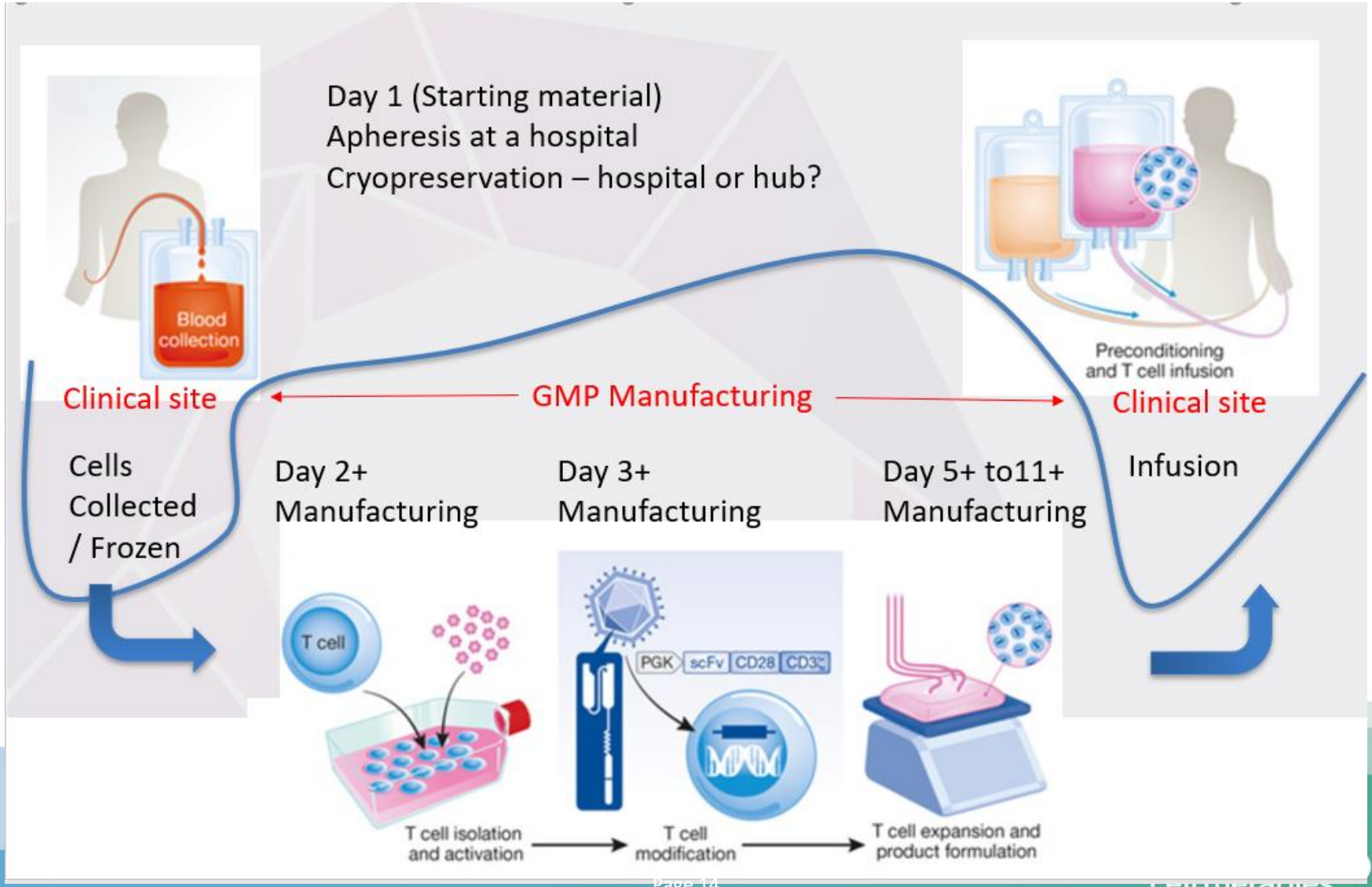
PeterMac - The Art Gallery





PeterMac - The Art Gallery

Autologous CAR T-cell therapy process



Typical supplier qualification strategy

- Identify reputable supplier
- GMP Accreditation
- History of supply
- Other products on the market

Typical supplier qualification strategy

Hospital apheresis units

- GMP Accreditation (exists but rare) ✘
- History of supply ✘
- Supply of other products ✘

Typical starting material strategy

External supplier assessment:

- Technically competency of staff
- Training / GMP training
- Equipment / validation
- Document control / archiving
- QC testing lab
- Facility – structure, waste, cleaning, cross contamination
- QMS systems - Dev., CC., CAPA, Risk Management
- Materials management / status labelling
- Supplier qualification
- Quality independent from production

Typical starting material strategy

Hospital apheresis units:

- Technically competency of staff ✓
- Training / GMP training ✓
- Equipment / validation ✓
- Document control / archiving ✓
- QC testing lab ✓
- Facility – structure, waste, cleaning, cross contamination ✓
- QMS systems - Dev., CC., CAPA, Risk Management ✗
- Materials management / status labelling ✗
- Supplier qualification ✗
- Quality independent from production ✗

Typical starting material strategy

- **Hospital apheresis units**
- Technically competency of staff ✓
- Training / GMP training ✓
- Equipment / validation ✓
- Document control / archiving ✓
- QC testing lab ✓
- Facility – structure, waste, cleaning, cross contamination ✓
- QMS systems - Dev., CC., CAPA, Risk Management ✗
- Materials management / status labelling ✗
- Supplier qualification ✗
- Quality independent from production ✗

Critical deficiencies to meet GMP requirements

Quality in apheresis hospital units

- Hospitals already run quality systems, however these are solely focussed on the patient
- There is little to no understanding of product quality or GMP within the clinical setting
- Absence of manufacturing process understanding

Clinical vs Manufacturing Quality focus

- Clinical priority:
  - Patient safety is paramount
  - Maximum patient access
  - Wide product specification to allow for patient factors

- Manufacturing priority:
  - Low process variability
  - Tight product specification
  - Quality oversight

Why is quality overlay so important in apheresis?

- Most critical but difficult to control starting material
- A cited cause of manufacturing failure

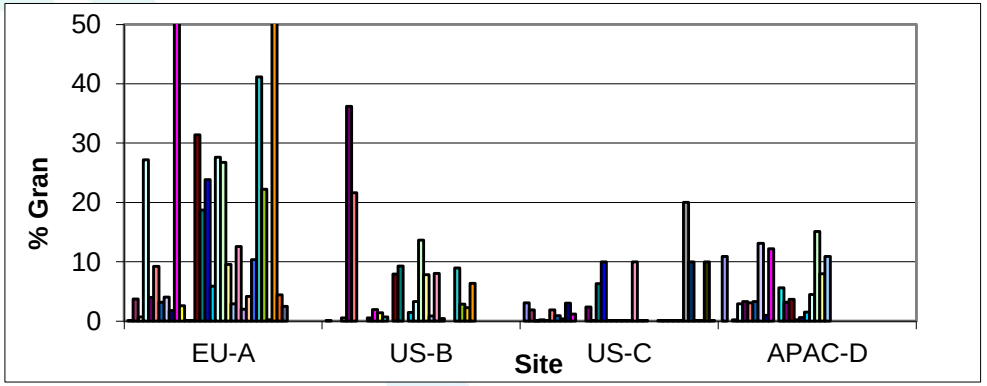
Apheresis variability & manufacturing drives product variability

- **What manufacturing wants**
- *T-cells*: collection efficiency, minimise undesirable impurities
- *Collection efficiency for CD3*

Other factors to consider

- Impact of specialised requirements on standard unit operations
- Ability/willingness to collect additional data
- Characterising variability and impact on manufacturing

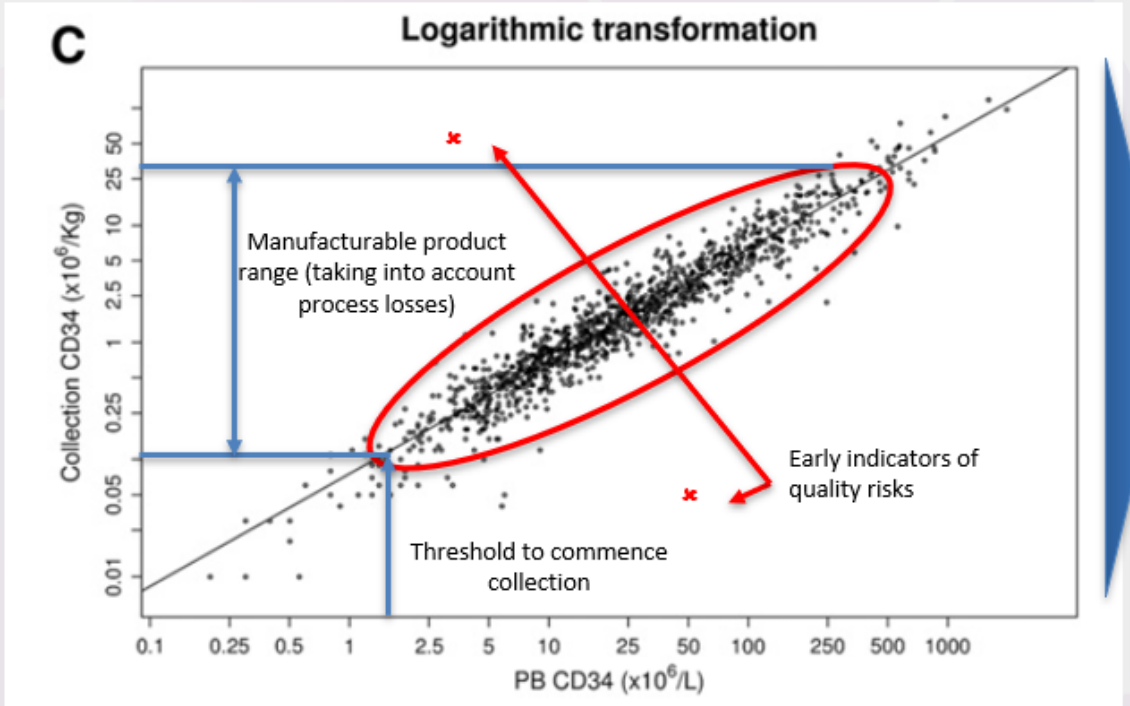
Granulocyte contamination: peripheral blood apheresis



Cryoprotectant variability

Cryomedium content DMSO plus	Number of EU sites (n=14)	Number of JP sites (n=4)
HSA + heparin + N.S.	2	
HSA + N.S.	2	
ACD-A	2	
HES/ Voluven	2	
Plasmalyte + HSA + ACD-A	1	4
HSA + ACD-A	1	
Plasmalyte + HSA + HES	1	
Cryostor 10	1	
Serum + N.S.	1	
MEM	1	

Cell therapy products are often variable



Variable dose for autologous product

- Is the product the same from each donor?
- How many donors do you need?
- How many are there?

Collection Process and Variables

- Multiple sources of variability and risk (Inter-collection centre):
- High donor variability, especially when the patient is un-mobilised
  - Bone marrow function
  - Procedure tolerance
  - Venous access
- Moderate operator variability GMP-
  - Knowledge and experience, particularly for specialised collections – tweaking?
  - Collection efficiency and product purity
  - Equipment
- Microbial contamination risks from skin

Collection Process and Variables

- Multiple sources of variability and risk (Intra-collection centres):

- Multiple collection centres
  - Variable equipment makes used for collection
  - Variable consumables
  - Multiple cryopreservation labs
  - Differing cryoprotectants and control rate freezer models
  - Multiple quality systems
  - Highly complex logistics, inexperienced logistics personnel

Cell Therapies / Peter Mac Model

Apheresis unit managed as a manufacturing facility

- CTPL QMS oversees apheresis and cryopreservation in hospital
- GMP trained clinical staff
- Full equipment/process validation
- Full GMP QMS operating within apheresis unit
- GMP compliant collection facility, including HVAC
- Full records traceability
- Full materials and supplier control
- Quality separate from Manufacturing (clinical collection) org structure
- Dedicated Quality resource embedded within apheresis unit
- Product Quality unit independent from hospital Quality unit
- Clear delineation of responsibility for product and patient
- Weekly/quarterly Quality review meetings which include clinical staff

Outcome:

PeterMac first hospital approved in Australia for Kymirah for treatment of DLBCL

Alternative Model

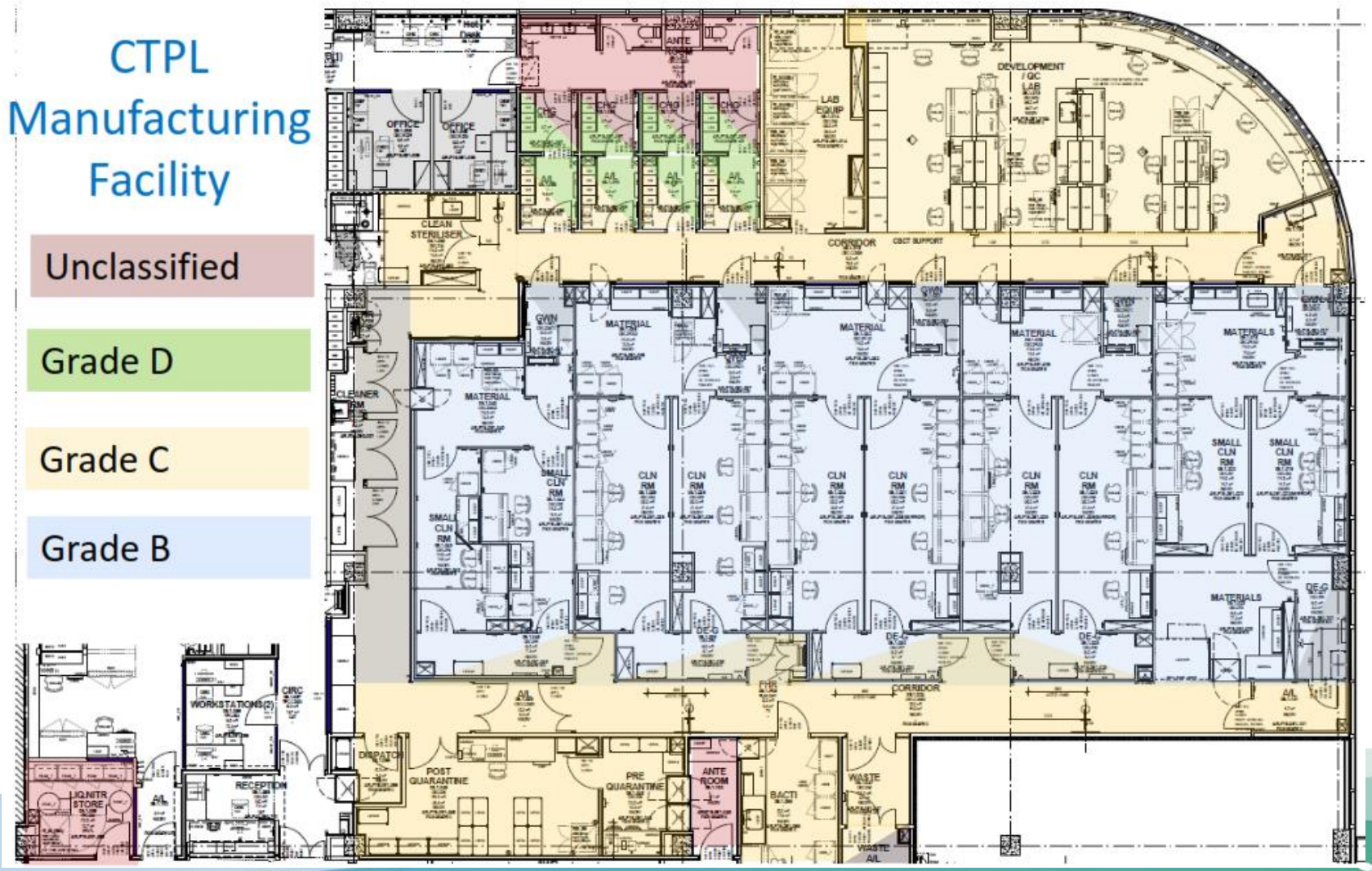
Risk Evaluation and Mitigation Strategy (REMS)

- Typical manufacturer / supplier model
- Moves burden from regulator to manufacturer
- Allows manufacturer to apply own quality standards over each collection facility

Issues:

- Apheresis units audit fatigue
- High risk for error due to competing Quality requirements from different manufacturers

GMP - Good Aseptic Practice



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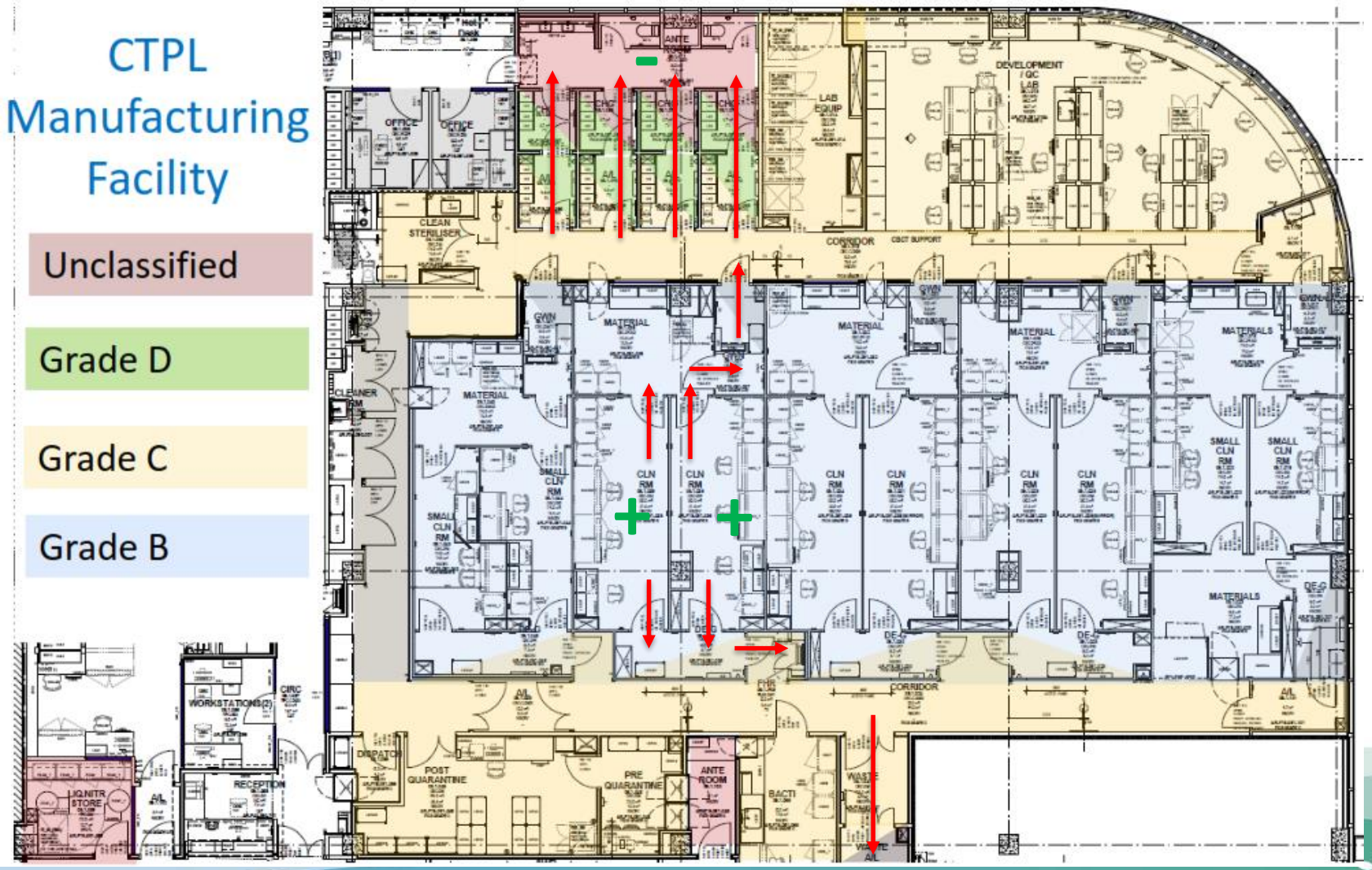
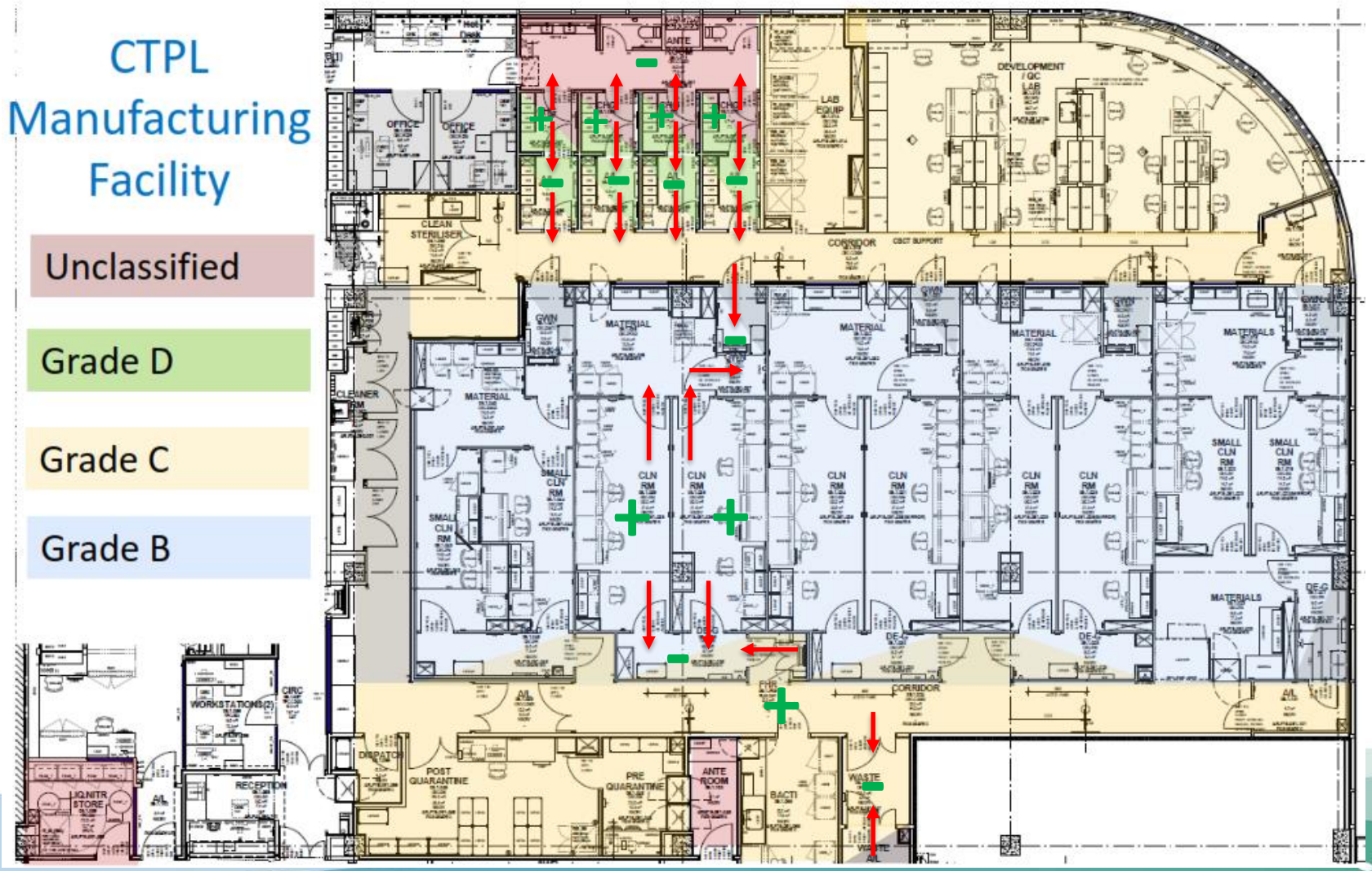
GMP - Good Aseptic Practice



GMP - Good Aseptic Practice



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GMP - Process Validation

Expected	Actual	Solution
Tightly controlled process parameters	Large process variables, large specifications e.g. - Transduction efficiency: >5% (10-35%) - Vector Copy Number: 1 – 3 - Cell viability >70? >80? >90% >10? - Impurity profiles, different batch to batch. Exacerbated by unmet clinical need.	Justification in clinical trial or product registration
Tight specification for starting material	Large process variables in starting material	None, accepted as process variable
High quality starting material	Starting material of variable quality e.g. cell viability, high levels of debris, cells impacted by various patient treatment regimes - 'happy' cells	None, accepted as process variable
Material used in validation replicates those intended to be used in released product	Ethical issues around collecting patient material	Using healthy donor collections as surrogate

GMP - QC of Final Product

Expected	Actual	Solution
Tightly defined QC test methods, no opportunity for operators to manipulate data	Due to patient to patient variability, cell scatter changes for each batch. Difficult to define generic flow cytometry gating protocols	Lock method, audit trails and procedures in place on gating changes
Full safety testing of product prior to release e.g. - replication competent testing for vectors by cell culture - sterility testing - particulate visual inspection	- Cell culture testing takes 10 weeks in the US. Patient will expire prior to release of product - Cell culture sterility test takes 2 weeks, patient may expire - Not possible to perform to opaque nature of cell based products	TGA approval to release prior to testing. Approval for alternative test methods e.g. qPCR or rapid microbial testing (BacT). Validate process for particles.

GMP - Release of Final Product

Expected	Actual	Solution
Full testing of product prior to release	Limited test results, including safety tests. Especially applicable to fresh release products	TGA approval. Take additional safety tests earlier in the process. Monitor and ensure other risk controls are operational e.g. aseptic qualification, staff culture. Conduct post release testing.
Rejection of product not meeting specification	Allowed if treating clinician determines that the benefit of administration outweighs the risk	Procedure in place to allow for transfer of responsibility for release to clinician.

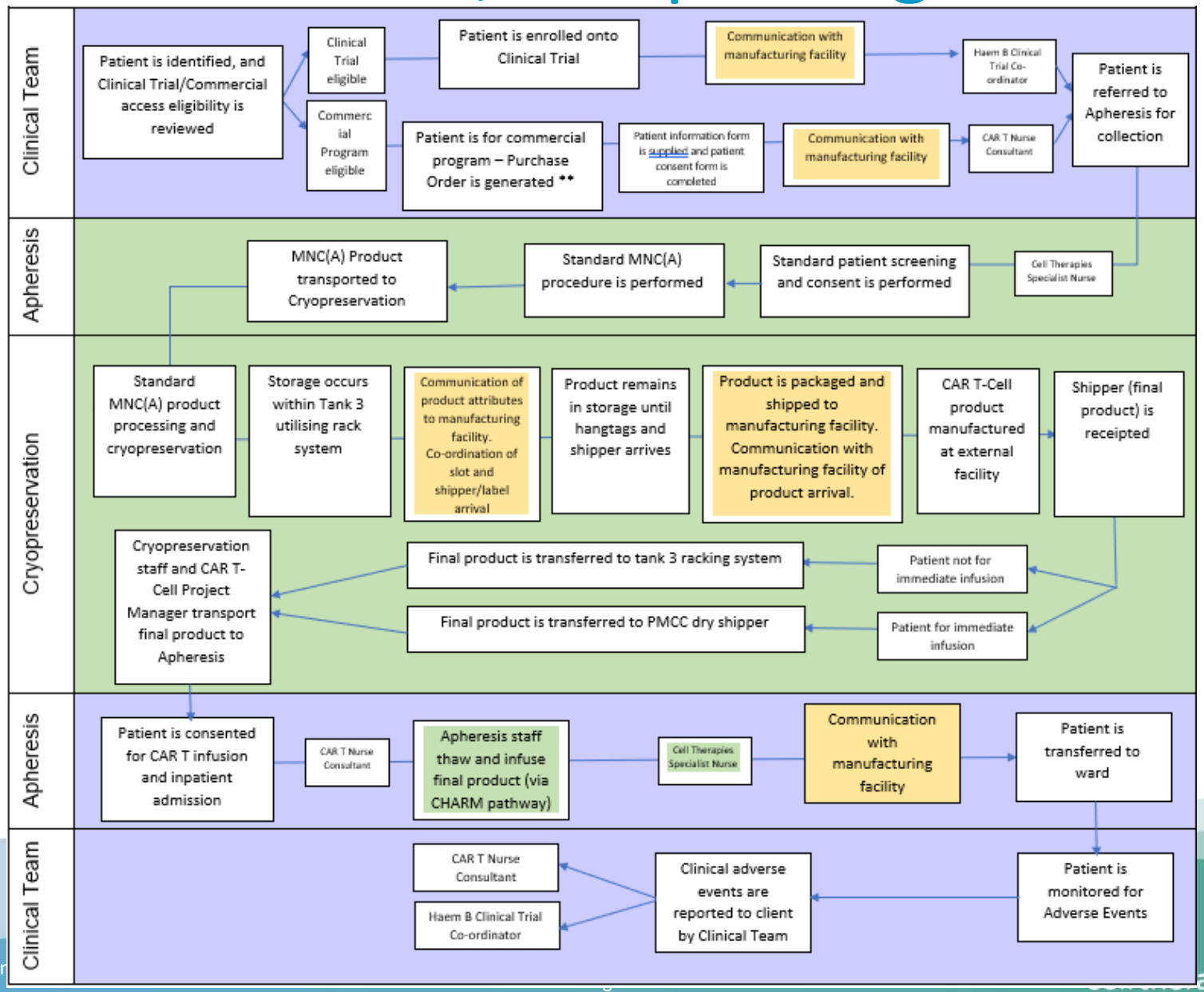
GMP - Post release

Expected	Actual	Solution
Product remains integral and efficacious until administered to patient	Compliance but with difficulties to be managed: - Product needs to shipped at <140^{o}C - Shipper tipping over during transport - Loss of data monitoring during shipping - Shipper not maintaining temp - Shipper getting stuck at customs	- Quality agreements with transport couriers - Only using couriers with guaranteed slots on flights - Only using couriers with preapproved customs clearance - Shippers with networked remote monitoring - Shippers with tilt sensors

GMP - Post release

Expected	Actual	Solution
Product remains integral and efficacious until administered to patient	- Difficulties in storage of product at point of infusion - Difficulties in management of thawing of product: - water bath vs automated - over heating of product - extended time since thawing	- Storage considerations reviewed as part of site selection, responsibility for storage defined, pharmacy or ward? - Quality agreement in place with hospital - Extensive training of clinical staff - Escalation pathway to manufacturer for deviations during administration (especially applicable during commercial phase)

CAR-T cell, complex logistics



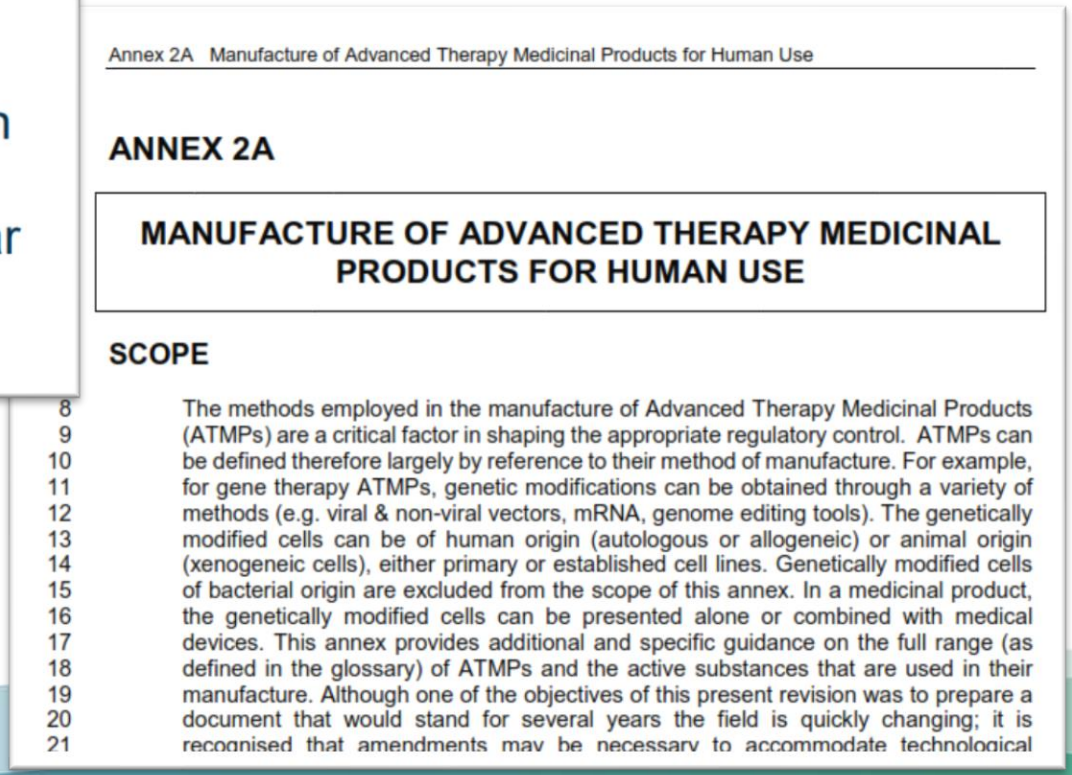
Future – Code Change

TGA to move to PIC/S Annex 2a?

Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Code of Good Manufacturing Practice for human blood and blood components, human tissues and human cellular therapy products

Version 1.0 April 2013



Annex 2A Manufacture of Advanced Therapy Medicinal Products for Human Use

ANNEX 2A

MANUFACTURE OF ADVANCED THERAPY MEDICINAL PRODUCTS FOR HUMAN USE

SCOPE

The methods employed in the manufacture of Advanced Therapy Medicinal Products (ATMPs) are a critical factor in shaping the appropriate regulatory control. ATMPs can be defined therefore largely by reference to their method of manufacture. For example, for gene therapy ATMPs, genetic modifications can be obtained through a variety of methods (e.g. viral & non-viral vectors, mRNA, genome editing tools). The genetically modified cells can be of human origin (autologous or allogeneic) or animal origin (xenogeneic cells), either primary or established cell lines. Genetically modified cells of bacterial origin are excluded from the scope of this annex. In a medicinal product, the genetically modified cells can be presented alone or combined with medical devices. This annex provides additional and specific guidance on the full range (as defined in the glossary) of ATMPs and the active substances that are used in their manufacture. Although one of the objectives of this present revision was to prepare a document that would stand for several years the field is quickly changing; it is recognised that amendments may be necessary to accommodate technological

National Centre of Excellence in Cellular Immunotherapy

- A **$105 million** co-investment from the Australian government, CTPL & Peter Mac Foundation
  - **New Manufacturing Capacity**
  - Commitment to build 1700 m^2 additional commercial manufacturing capacity at Peter Mac to support clinical and commercial CAR-T cell therapies for Australian patients
  - **Increased Clinical Capabilities**
  - Create a new 14 bed/chair clinical unit focused on cellular immunotherapy treatments
  - **Increased trials activity**
  - Additional clinical and pre-clinical research resources to support new treatment candidates, and for eligible Australian projects, to fund CTPL manufacturing for Pilot/Phase 1 studies

thank you

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