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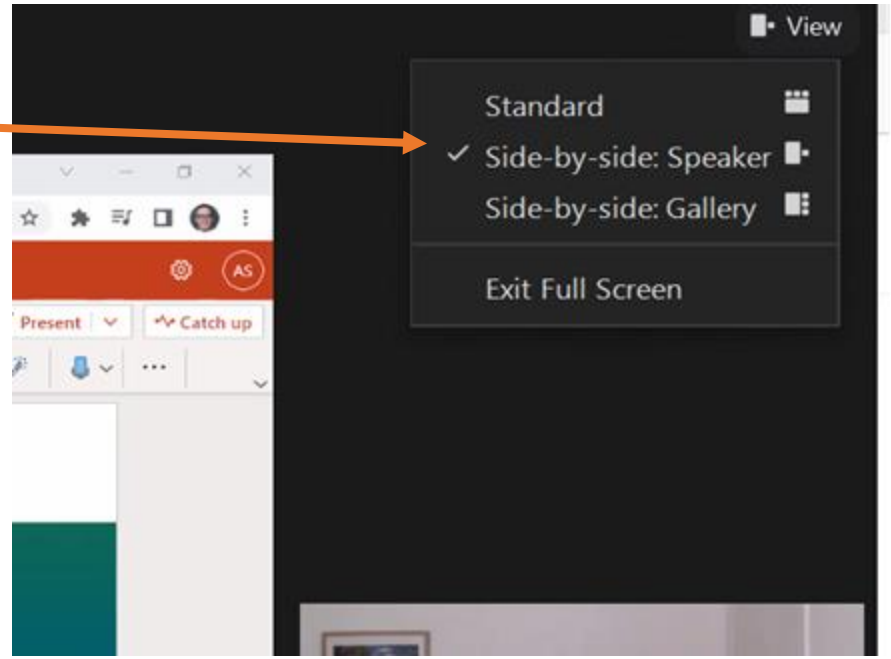

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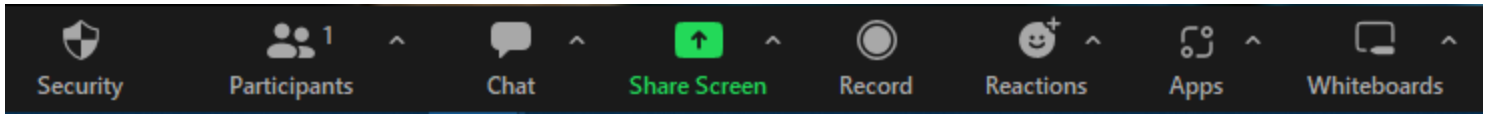

GLOBAL CLINICAL SUPPLIES GROUP

Current challenges in Cell and Gene Therapy

Asia-Pacific Clinical Supplies Webinar Series

27 JUL 2023, 2PM (1400) SGT

Today's Agenda

- GCSG - Who are we and what do we do?
- 1st Speaker: Regulation of cell and gene therapies in Australia by Dr. George Vuckovic (TGA)
- 2nd Speaker: Manufacturing and Regulatory Challenges of Allogeneic Cell Therapies by Harsha Gupta (Cynata)
- 3rd Speaker: Logistical Challenges in CGT Clinical Trials by Manfred Seow (IQVIA)
- Panel Discussion: Challenges in CGT (TGA, IQVIA, Cynata, Marken)
- Post Webinar Survey
- Upcoming GCSG Events

GCSG – Who Are We

- Member-run
- Not-for-profit
- Dedicated to clinical supplies
- Membership for professionals involved in all aspects of the clinical supply chain
- Our first conference was held in 1988
- Global presence
- Largest clinical supplies organization in the world!

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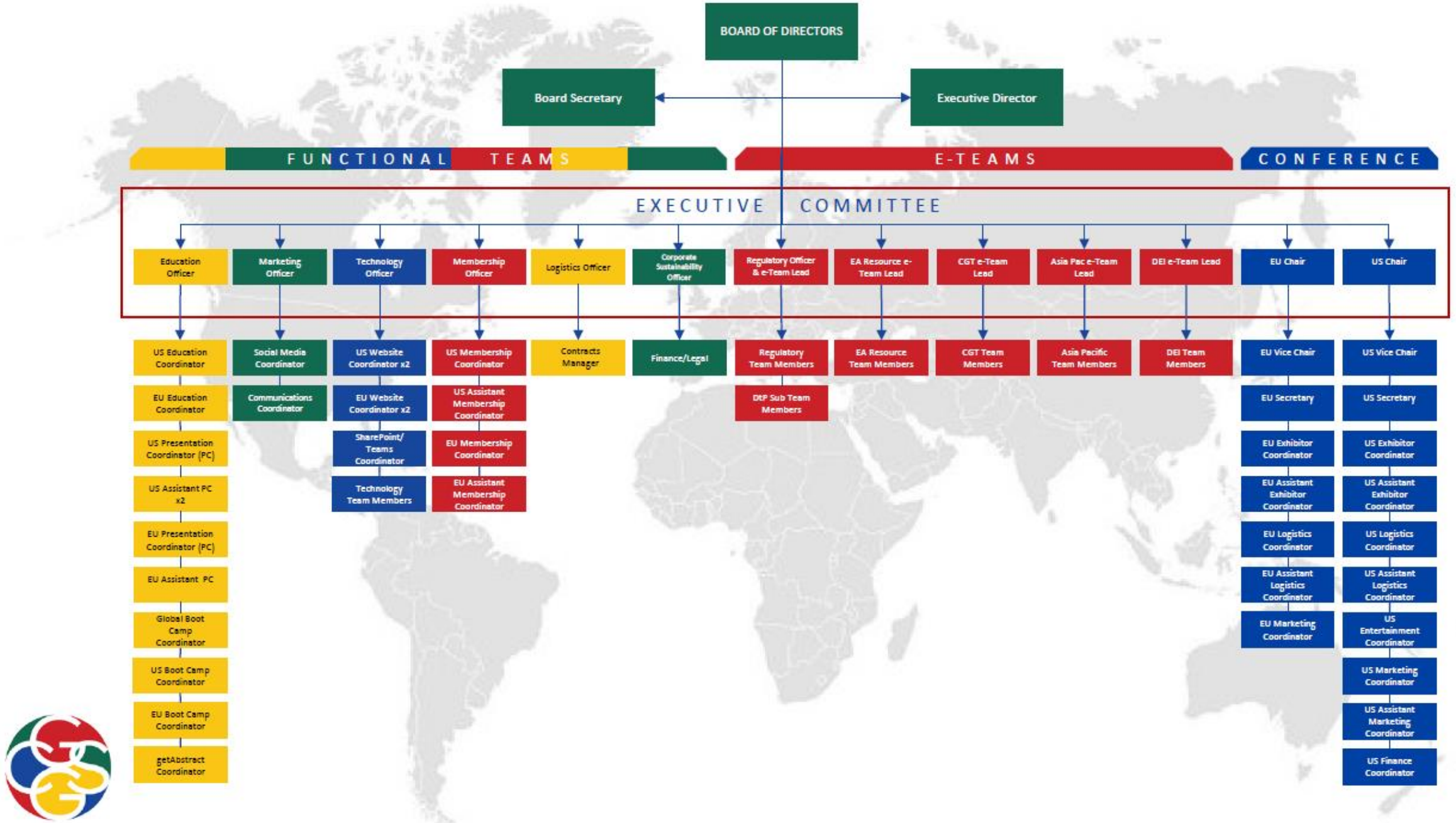
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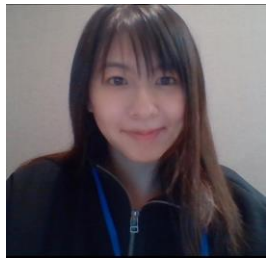
Richard Rossi - Lead

Global Cold Chain & Strategic Projects Director

(CRYOPDP, Australia)



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Arishma Narayan

Senior Quality Manager

(Akesa, Australia)

Puvi Bala

Global Comparator Services Manager

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Mervin Sulistyo

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Country Director - Japan

(4G Clinical, Japan)

Celin Ong

VP, Cell and Gene APAC

(Marken, Singapore)

Philip Gregory

Managing Director, China

(Inceptua CTS, China)

GCSG – Our Aim

- Provide a forum for open discussion
- Share knowledge and industry best practices
- Educate those who are new to our industry
- Provide solutions to problems
- Networking!

Dr George Vuckovic

Assistant Secretary of the Scientific Evaluation Branch (SEB)

- Assistant Secretary of the SEB at the Therapeutic Goods Administration
- SEB approves applications to market biologicals and generic medicines and evaluates the quality of biological medicines, gene therapy products and the infectious disease safety of therapeutic goods
- Held senior positions with the Commonwealth Department of Health, and IP Australia
- PhD in organic chemistry from the ANU

Regulation of cell and gene therapies in Australia

Regulation of cell and gene therapies in Australia

George Vuckovic
Assistant Secretary
Scientific Evaluation Branch
Department of Health and Aged Care, TGA

GCSG APAC 2023

Overview

- Regulatory pathways for Cell and Gene therapy products in Australia
- Available regulatory pathways
- Priority Pathway for Biologicals
- Export-Only Pathway for Biologicals

Biological and Biological Medicines

Biological

- ✓tissue-based products
- ✓cell-based products
- ✓immunotherapy products containing human cells
- ✓autologous human cells and tissue products (including stem cells)
- ✓**gene-modified cell therapies**

Biological Medicines (prescription medicines)

- ✓vaccines (that do not contain viable human cells)
- ✓recombinant products
- ✓plasma derived products (or that contain plasma derived products)
- ✓**gene-therapy vectors alone**

Regulatory Pathways for Gene therapy products

Type of gene therapy	Example	Regulatory pathway	Further information
Ex vivo (gene is delivered to cells outside of the body, which are then transferred back into the body)	CAR-T cells (human cells)	Class 4 biological	Australian regulatory guidelines for biologicals (ARGB)
In vivo (gene is transferred to cells inside the patient's body)	Adeno-associated virus	Prescription medicine	Australian Regulatory Guidelines for Prescription Medicines (ARGPM)

GMP Pathways for Gene therapy products

Product type	Example Regulatory pathway	Further information
Gene therapy vector	GMP clearance pathway (API) MRA pathways available	Manufacturing therapeutic goods
Biological product (human cells and tissues)	GMP certificate for manufacturing site (GMP clearance for Sponsor) This includes sites that conduct donor testing and release testing of biological product	Manufacturing biologicals Australian code of good manufacturing practice for human blood and blood components, human tissues and human cellular therapy products

Pathways and provisions for Cell and Gene Therapy products

Pathway	Biological	Medicine
Standard review pathway	Yes	Yes
Priority review pathway	**Yes***	Yes
Orphan status	No	Yes
Provisional review pathway	No	Yes
Comparable Overseas Regulator (COR)	No	Yes
Export-only pathway	**Consultation complete**	Yes

Priority Pathway for Biologicals

New pathway active November 2022

- New pathway aligned with Priority Pathways for Prescription Medicines and Medical Devices
- Introduction of Priority Pathway for Biologicals was a key recommendation in submissions made to the House of Representative Inquiry (process for approval of new drugs and novel medical technologies in Australia) and from a TGA-commissioned MTPconnect report into regulatory framework for gene, cell and tissue therapies in Australia

- Sponsors must first obtain a Priority Determination for their product
  - Determination applies to one product for one therapeutic indication or intended use
  - Determination fee applies (currently $13,971)
- Once a Priority Determination has been obtained, Sponsors have six months to submit their Priority Inclusion application (evaluation of dossier)

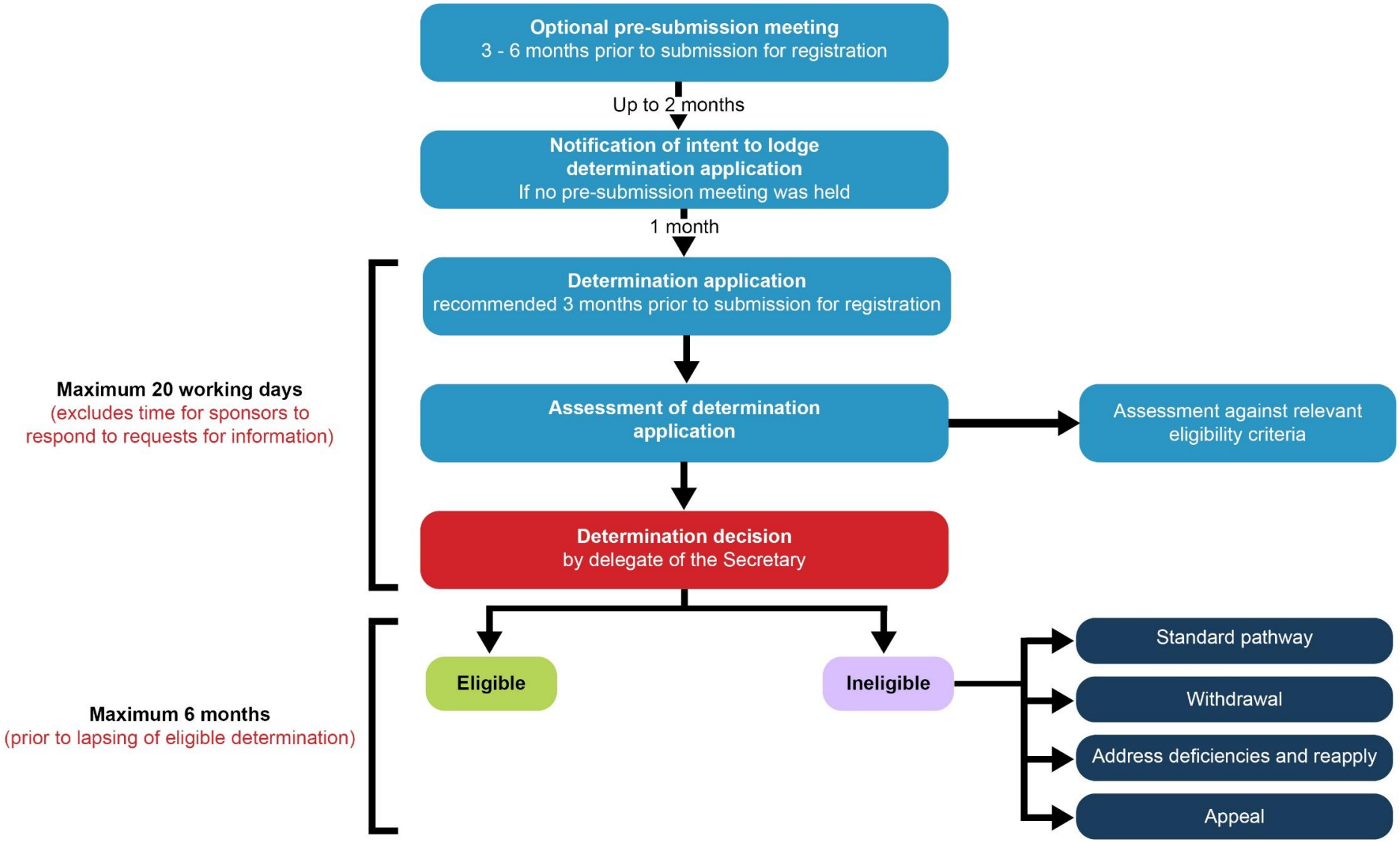
TGA Website:
Priority review pathway for biologicals

Criteria for Priority Determination

Criteria for accepting an application under a priority pathway considered similar pathways followed by the pathways implemented for both prescription medicines and medical devices

- Criterion 1 – New biological or new use
    - the biological is either a new Class 2, 3 or 4 biological for entry in ARTG or an already registered biological with a new intended use / therapeutic indication
- Criterion 2 – Life-threatening disease or seriously debilitating condition
    - the biological is to be used for treatment, prevention or diagnosis of a life threatening or seriously debilitating condition (as described by the TGA)
- Criterion 3 – Fulfils an unmet clinical need or clinically significant improvement over already approved therapeutic goods
    - No therapeutic goods that are intended to treat, prevent or diagnose the condition are entered on or included in the ARTG; or
    - there is substantial evidence demonstrating that the biological provides a clinically significant improvement in the safety or efficacy of the treatment, prevention or diagnosis of the condition compared to therapeutic goods already included in the ARTG
- Criterion 4 – Major therapeutic advantage
    - there is substantial evidence demonstrating that the biological provides a major therapeutic advance

Priority Determination Process

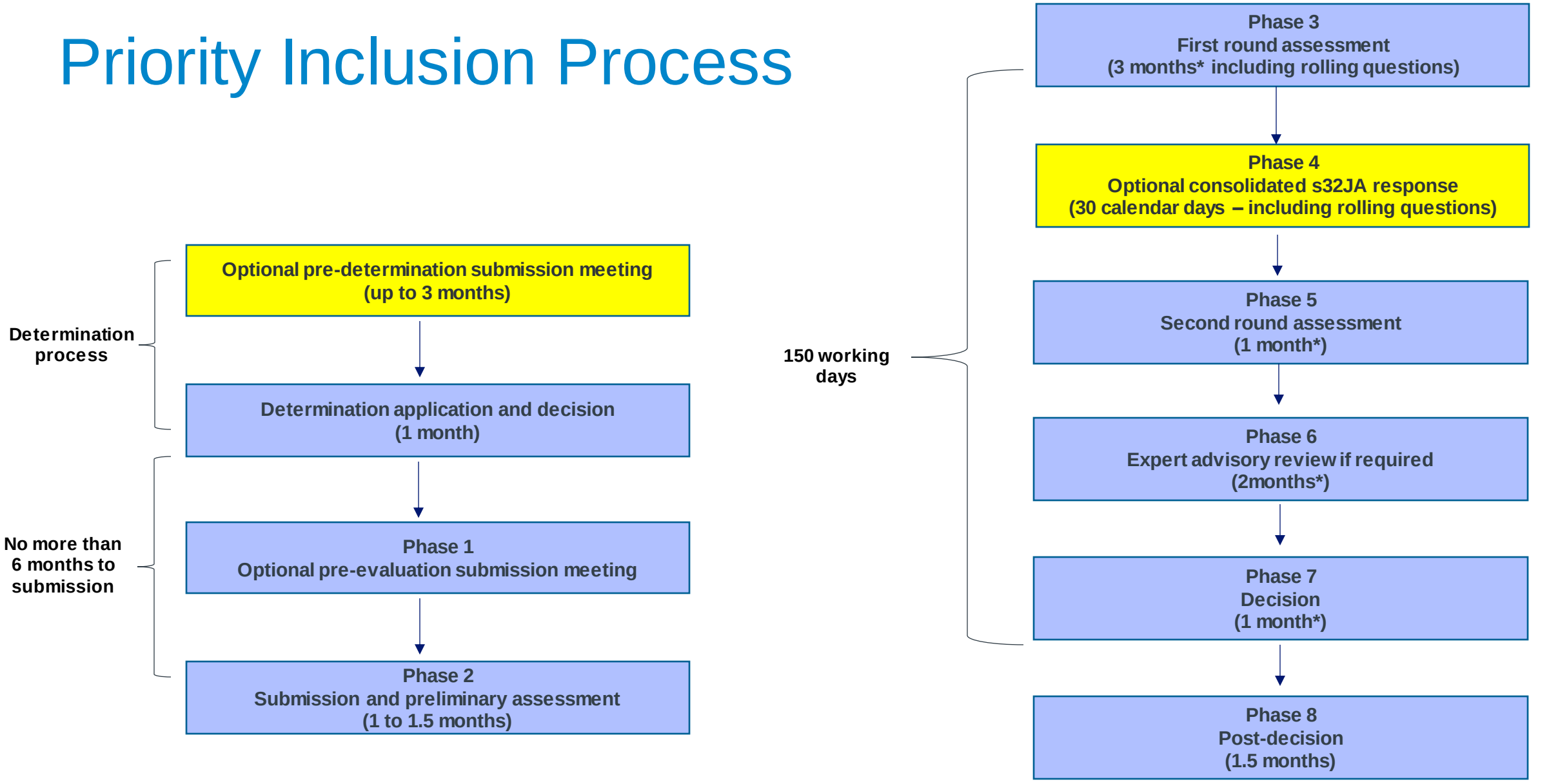


Priority Inclusion Process

- Priority Inclusion Pathway has a target timeframe of 150 working days
  - Compared to 255 WD for Standard Pathway
  - Slightly higher evaluation fees (~5% increase)
  - Dossier requirements for quality/safety/efficacy the same

- Rolling questions during the evaluation phase - if responses obtained by the end of the first round, stop clock will not be applied, and the evaluation can proceed to the next phase.
- Exit criteria – return to Standard Pathway
  - failure to respond to our requests for additional information as part of a formal s32JA request within 30 calendar days
  - identification of significant safety concerns that require further assessment
  - submission of unsolicited or more extensive data than what is required during evaluation (excluding the provision of new safety related data, which you must bring to our attention)
  - you are unlikely to meet the Good Manufacturing Practice (GMP) requirements for inclusion (that is, obtaining either an Australian manufacturing licence or GMP certification by 150 WD).

Priority Inclusion Process



*Timelines are indicative only and may vary on case by case basis

Export only pathway for biologicals

- Therapeutic Goods legislation currently provides a registration pathway for export only medicines and medical devices, however, no such pathway is available for export only biologicals.
- Currently, biologicals manufactured in Australia can be exported but they are not allowed to differ from biologicals included in the ARTG.
    - This means that ‘export only’ biologicals cannot have different indications, release specifications, or labels to the product approved by the TGA
    - This puts extra regulatory burden on the sponsors as importing country may have different requirements
- Public consultation was conducted in Nov-Dec 2021 and respondents showed general support for creation of a dedicated pathway to allow for the export only biologicals that are manufactured in but not supplied in Australia.

Proposed pathway for export only biologicals

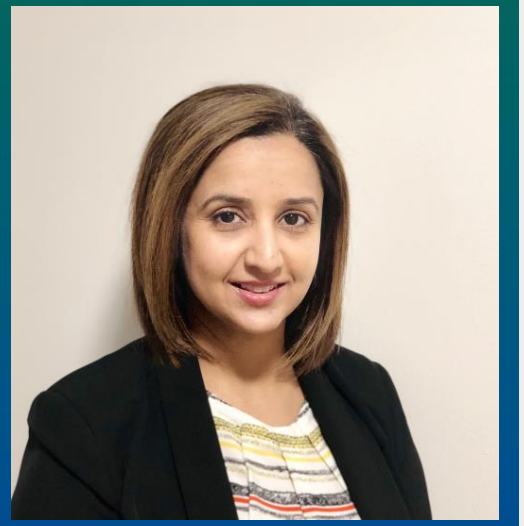
- The TGA proposed a dedicated pathway for inclusion of export only biologicals in the ARTG to the Government.
- Objective of this pathway is to :
  - minimise regulatory burden on biologicals that are for export only
  - bring the biologicals framework into alignment with how other export only therapeutic products are regulated by the TGA.
- The introduction of new pathway is to allow for **a new class** of biologicals in the ARTG for the export only biologicals.
    - Export only biologicals will not be subject to pre-market assessment.
      - All manufacturing sites will require GMP certification
      - There is no formal evaluation. However, the Sponsor must certify that they are meeting the requirements of the legislation.
    - there will be a reduced regulatory and financial burden on the sponsors.
    - aligned with the medicines and medical devices pathways
- The proposed policy position has been approved by the Government and necessary amendments are being made to the legislation for making this provision.

Website references

TGA website	www.tga.gov.au
Australian regulatory guidelines for biologicals (ARGB)	https://www.tga.gov.au/publication/australian-regulatory-guidelines-biologicals-argb
Australian Regulatory Guidelines for Prescription Medicines (ARGPM)	https://www.tga.gov.au/publication/australian-regulatory-guidelines-prescription-medicines-argpm
Manufacturing therapeutic goods	https://www.tga.gov.au/manufacturing-therapeutic-goods
Manufacturing biologicals	https://www.tga.gov.au/manufacturing-biologicals
Australian code of good manufacturing practice for human blood and blood components, human tissues and human cellular therapy products	https://www.tga.gov.au/publication/australian-code-good-manufacturing-practice-human-blood-and-blood-components-human-tissues-and-human-cellular-therapy-products
Priority review pathway for biologicals	https://www.tga.gov.au/how-we-regulate/supply-therapeutic-good/supply-biological/application-process-supplying-biological/priority-review-pathway-biologicals

Questions?

www.tga.gov.au



Harsha Gupta

Senior Manager for Manufacturing and Process Development, Cynata Therapeutics

- Over 10 years experience in GMP and cell therapies (both autologous and allogeneic)
- Background includes manufacturing, operations as well as regulatory affairs and quality
- Has the experience of working in the US and Australia
- Currently undertaking Masters in GMP

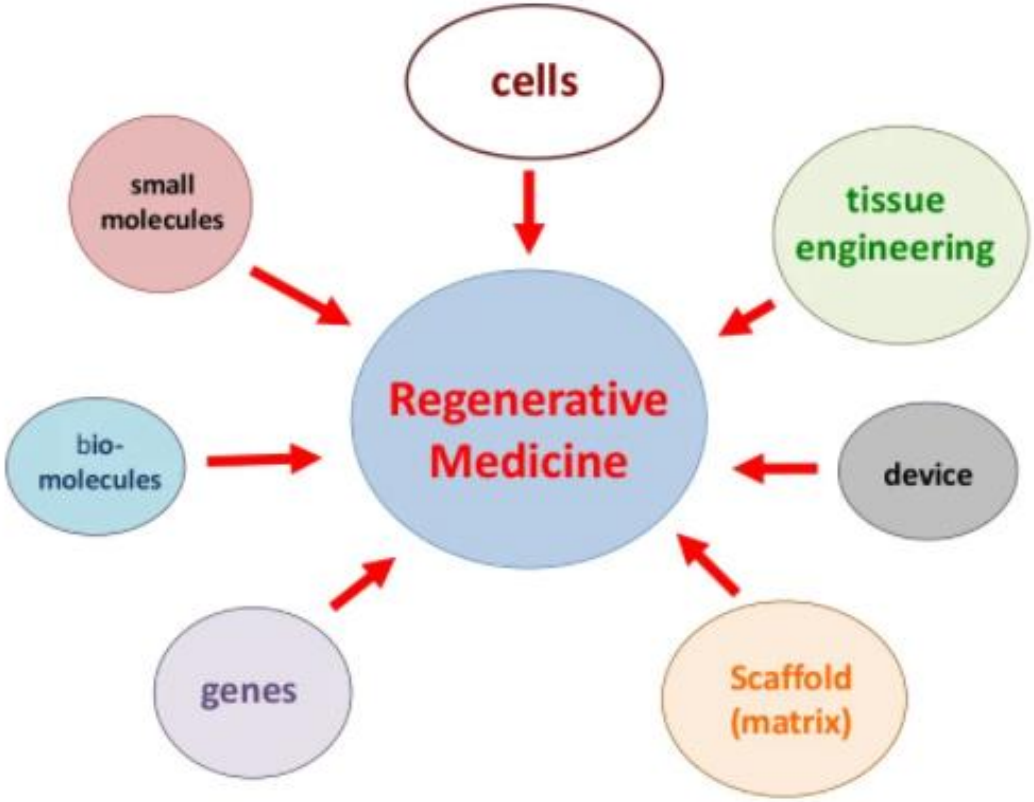
Manufacturing and Regulatory Challenges of Allogeneic Cell Therapies

Session Agenda

- Introduction to Cell and Gene Therapies - Autologous vs Allogeneic
- Manufacturing Challenges
- Regulatory Challenges
- Q&A

Regenerative Therapies:

- Cell therapies:
  - Cells and cellular products
- Tissue engineering:
  - Bio-scaffolds
  - Bio-molecules
- Gene therapies:
  - Gene augmentation therapy
  - Gene inhibition therapy
  - Removal/destruction of specific cells

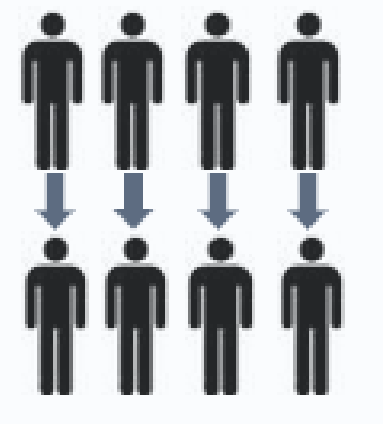


What is Cellular Therapy?

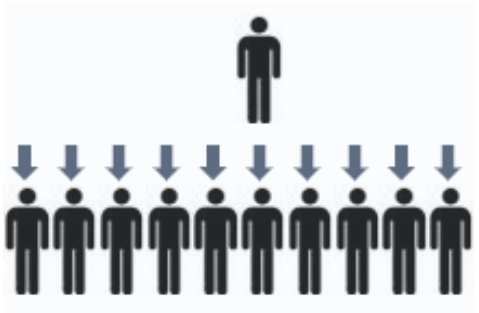
- Cellular therapy (CT) is the *transplantation of human cells to replace or repair damaged tissue and/or cells*.
- As new technologies are emerging, innovative products and therapies are being developed using a variety of cell types to treat a spectrum of diseases and conditions.
- Successful treatment to a spectrum of past untreatable and rare diseases

Types of Cell Therapies:

- Autologous:
  - Manufactured as a single lot from the cells received/acquired from the patient being treated
  - Examples: chondrocyte implantation, tenocyte implantation

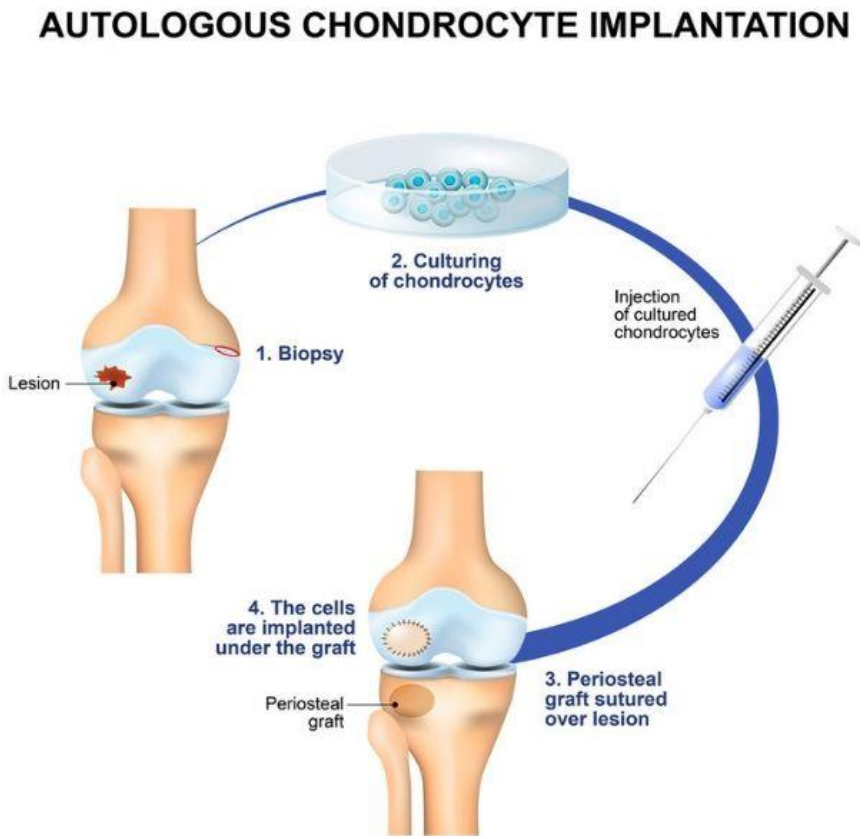


- Allogeneic:
  - Manufactured in large batches from unrelated donor tissues
  - Universal Donor
  - Examples: Stem cells such as Mesenchymal stem cells (MSCs)



Autologous Cell Therapy:

- Most common is Autologous Chondrocyte Implantation (ACI) wherein the patient's own healthy cartilage cells, chondrocytes, are used to treat damaged articular cartilage through regeneration.
- It was first introduced in 1987 and is used worldwide.
- Also uses a tissue engineering graft/scaffold along with autologous chondrocytes
- FDA approved MACI by Vericel (USA) and TGA approved Ortho-ACI by Orthocell (AUS)

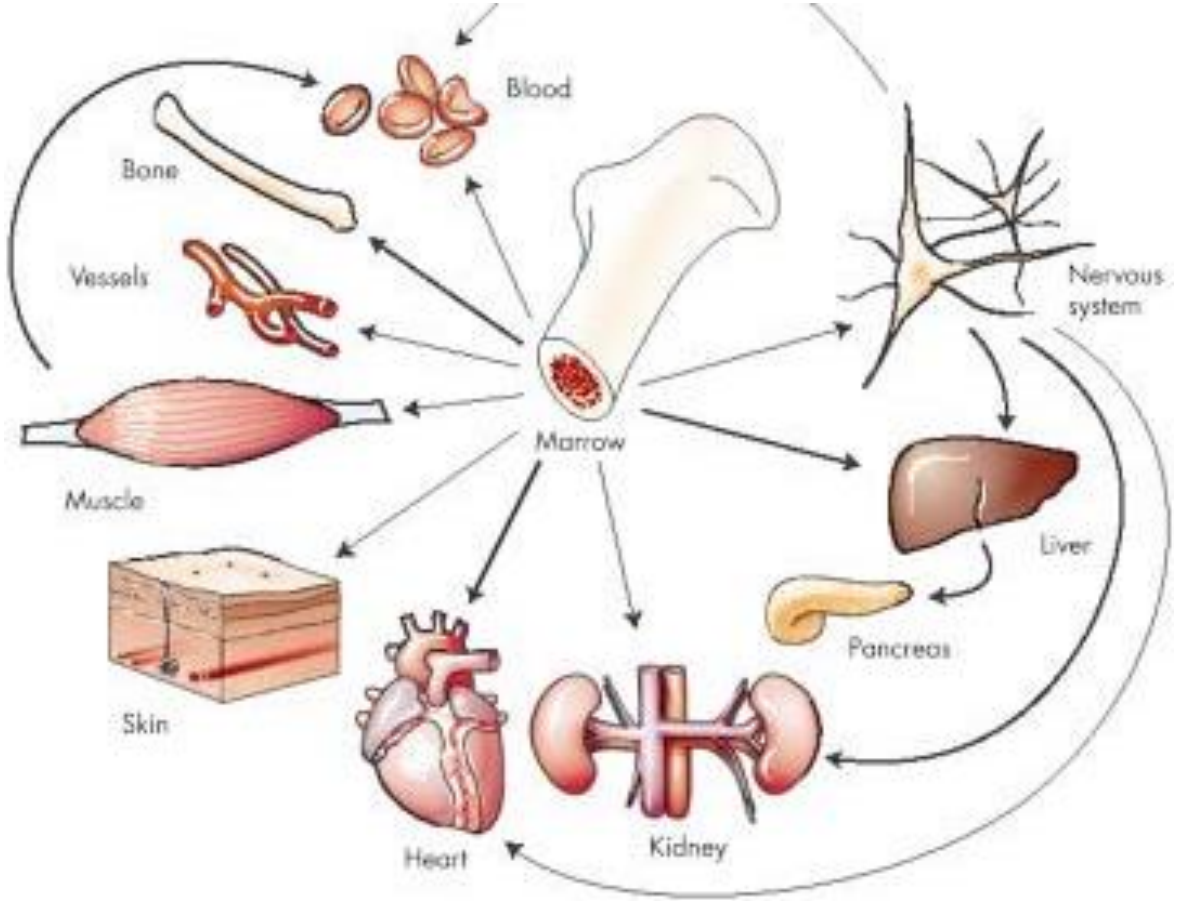


Source: https://hartfordsportsorthopedics.com/autologous-chondrocyte-implantation-aci-carticel-south-windsor-enfield-glastonbury-ct/

Allogeneic – Stem Cells:

- Promoting the *repair response of diseased, dysfunctional or injured tissue*
- Potential for self-renewal and can be differentiated into different cell types.
- Stem cells can be of different types based on whether they can produce single or different cell types:
  - Unipotent: produces only one cell type
  - Multipotent: produces many cell types
  - Pluripotent: produces all three germ layers namely, ectoderm, endoderm and mesoderm
  - Totipotent: produces all cell types

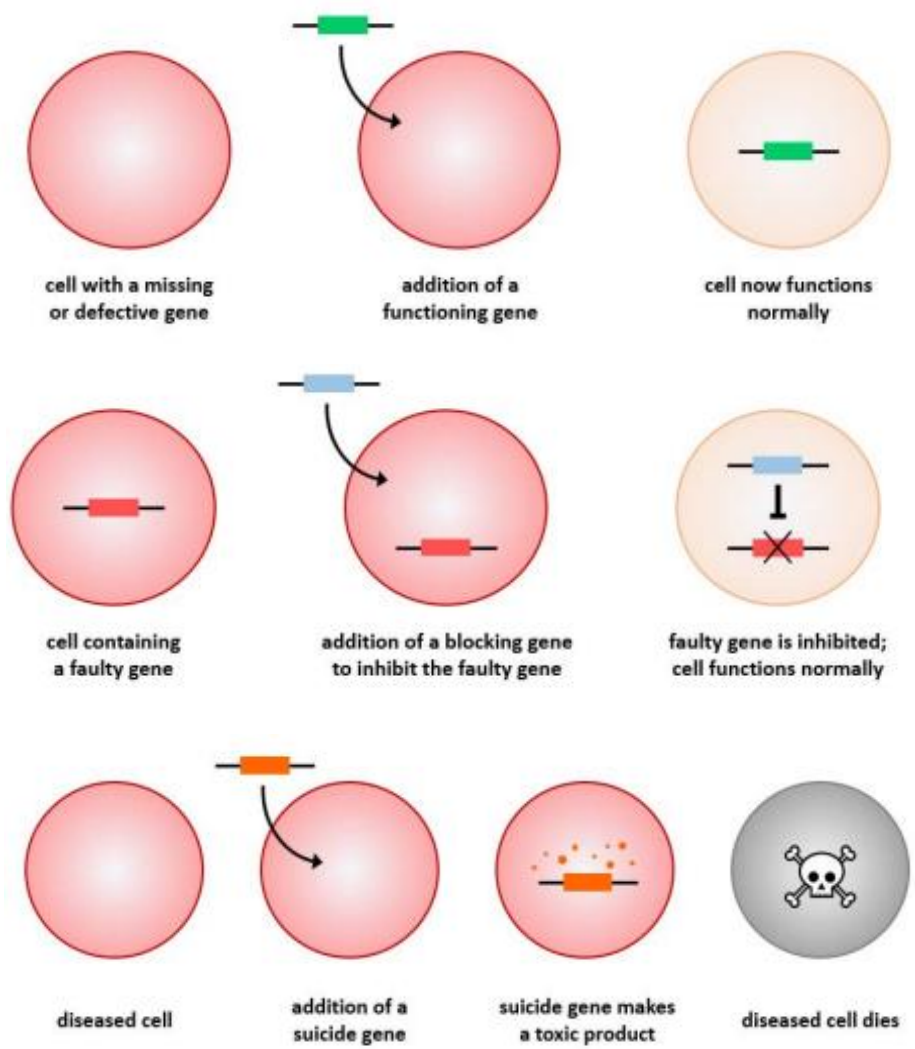
Possible pathways of adult stem cells differentiation



Source:
https://www.researchgate.net/figure/Possible-pathways-of-differentiation-in-adult-stem-cells-Reprinted-with-permission-from_fig2_10829956

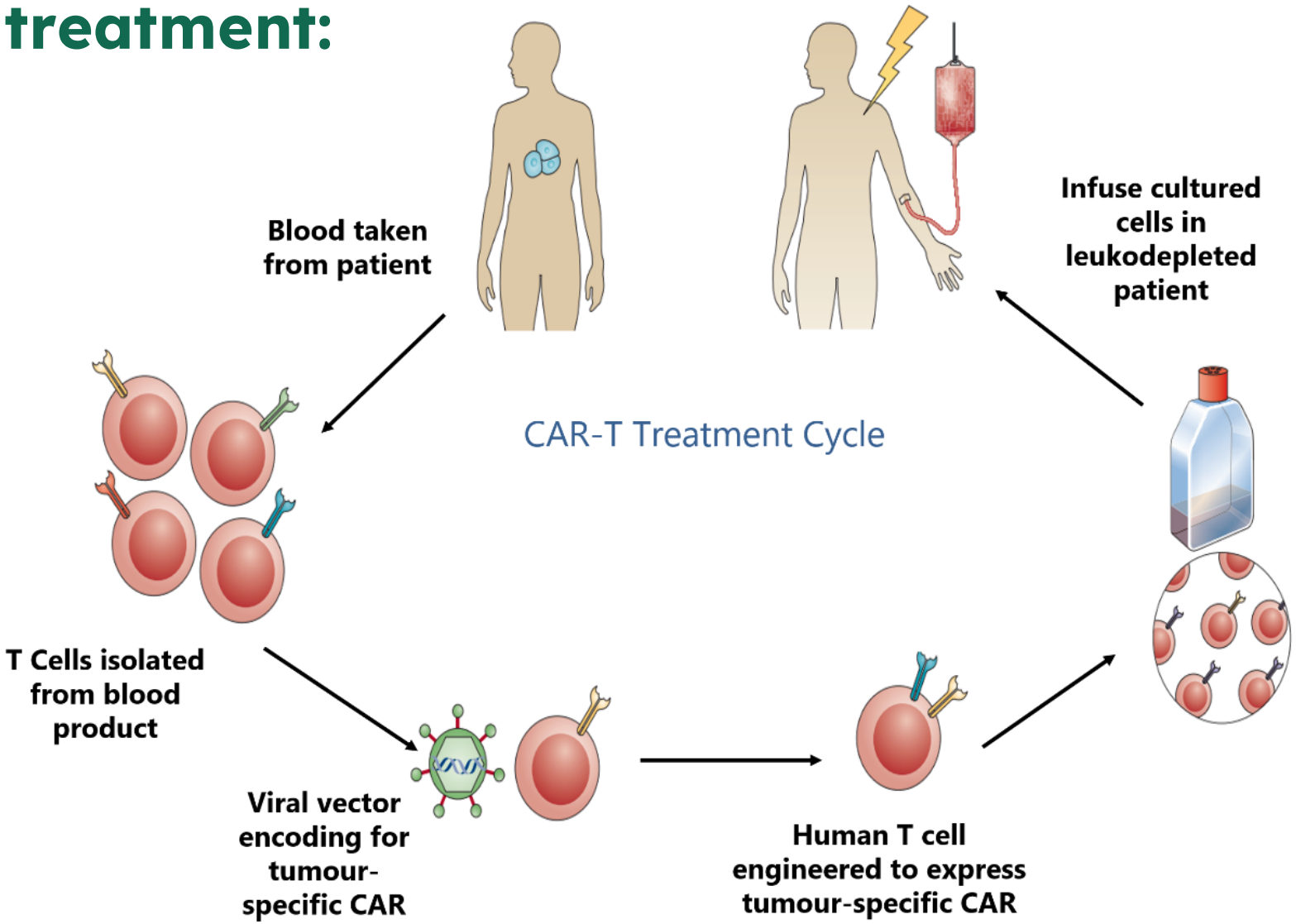
Gene Therapy:

- Gene Augmentation:
- Gene inhibition:
- Gene destruction:



Source:
http://www.kidsresearch.org.au/sites/default/files/Intro%20to%20Advanced%20Therapeutics.pdf

CAR-T treatment:

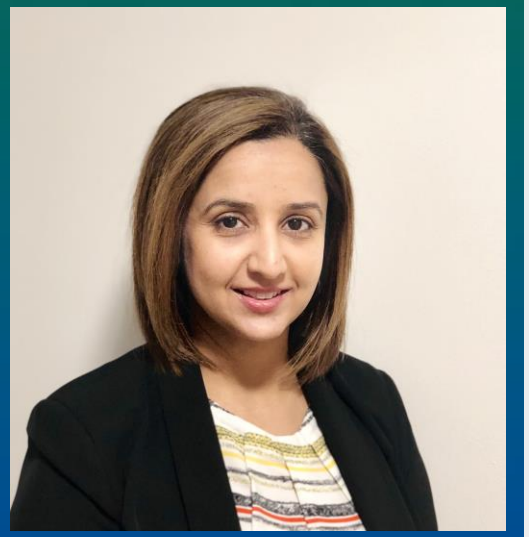


Manufacturing Challenges:

- Appropriate starting material and raw materials
- Feasibility of current production scale
- Master and Working Cell banks
- Storage and logistics
- Commercial Viability
- Cost

Regulatory Challenges:

- Rapid Cell and Gene Therapy Development – Regulation v Therapies
- Different jurisdictional expectations
- Potency assays



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- Currently undertaking Masters in GMP

Questions?

Manfred Seow

Cell and Gene Therapy Strategy Director, IQVIA

- Leads and coordinates IQVIA's multi-disciplinary CGT Centre of Excellence in APAC region
- Prior to that, led the Clinical R&D BD activities in South East Asia, Australia and South Korea
- CGT SME, clinical and operational expertise to develop innovative, data-driven, and patient-centered solution for CGT clinical trials
- Based in Singapore

Logistical Challenges in CGT Clinical Trials

Session Agenda

- Overview of the Cell and Gene Therapy Landscape
- Introduction to Cell and Gene Therapies - Autologous vs Allogeneic
- Why is CGT Logistics Critical?
- What are Some of the Challenges faced by Various Stakeholders?

Landscape of Cell & Gene Therapies

2,220+

Number of CAGT Clinical Trials

There are currently more than 2,220 ongoing clinical trials globally across multiple indications, with oncology leading the pack.

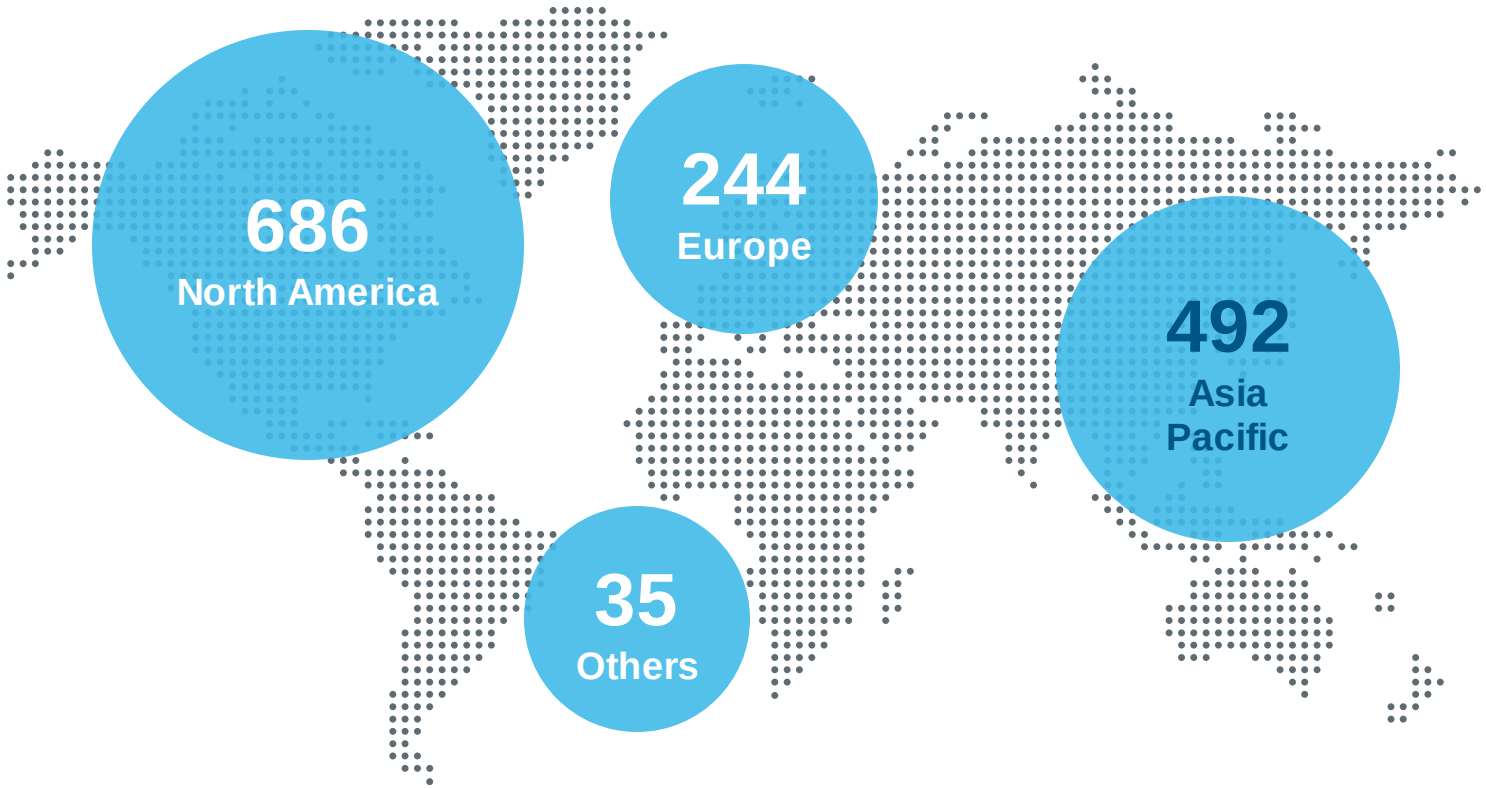
~$12B

Total Global Financing in 2022

Across 478 deals globally

Source: Alliance for Regenerative Medicine – Sector Snapshot, April 2023: A New Vision report;

Cell, Gene and Tissue Based Developers Globally



1,457

Total gene, cell and tissue-based therapeutic developers globally, Y2022

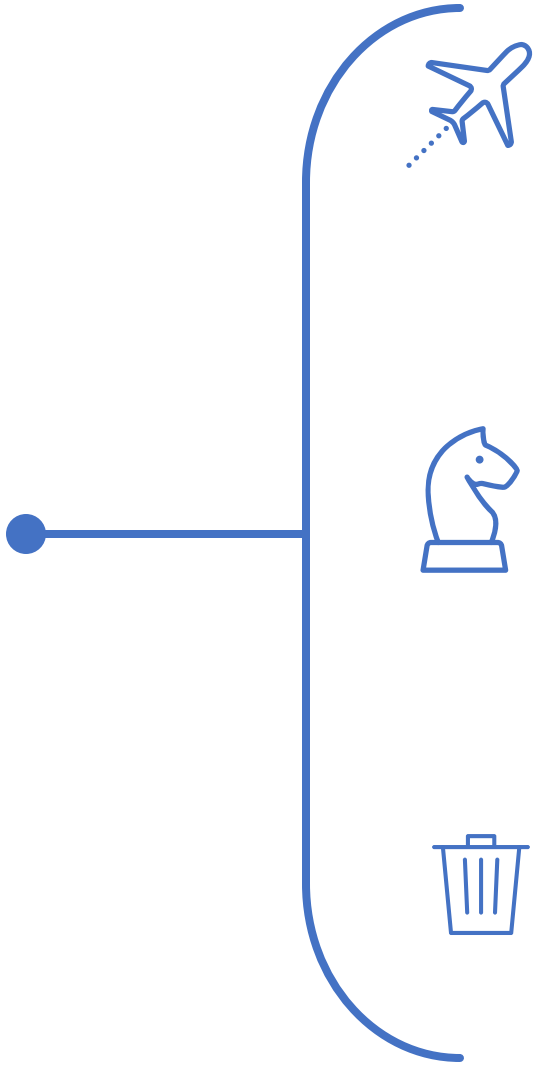
Increase of ~11% YOY, from 1,308 in Y2021

*With **~33% of the players** in the **Asia Pacific Region***

Source: Alliance for Regenerative Medicine – Sector Snapshot, April 2023: A New Vision report;

What is Logistics?

CGT Logistics



Concerns the flow of materials from the point of origin to the final destination.

Involves many activities such as: make-or-buy decisions, supplier selection, purchase order contracts, transportation, material handling, production, packaging, warehousing, inventory storage, picking and packing, security throughout, and delivery.

Responsible for the proper disposing of any waste in the total process, and to abide by all ecological and regulatory requirements.

Extracted from: Elements of Manufacturing, Distribution and Logistics – Thomopoulos, Springer (2016)

What is Gene Therapy?

- Broadly, gene therapy is the use of genetic material in the treatment or prevention of disease
- The transferred genetic material changes how a single protein or group of proteins is produced by the cell
- Gene therapy can be used to reduce levels of a disease-causing version of a protein, increase production of disease-fighting proteins, or to produce new/modified proteins

Adapted from: American Society of Gene + Cell Therapy – Gene and Cell Therapy FAQ - https://asgct.org/education/more-resources/gene-and-cell-therapy-faqs

What is Cell Therapy?

- Cell therapy is the transfer of intact, live cells into a patient to help lessen or cure a disease
- The cells may originate from the patient (autologous cells) or a donor (allogeneic cells)
- The cells used in cell therapy can be classified by their potential to transform into different cell types
- Pluripotent cells can transform into any cell type in the body and multipotent cells can transform into other cell types, but their repertoire is more limited than that of pluripotent cells
- Differentiated or primary cells are of a fixed type
- The type of cells administered depends on the treatment

Adapted from: American Society of Gene + Cell Therapy – Gene and Cell Therapy FAQ - https://asgct.org/education/more-resources/gene-and-cell-therapy-faqs

What is the Difference between Gene Therapy and Cell Therapy?

- **Gene therapy** involves the transfer of genetic material, usually in a carrier or vector, and the uptake of the gene into the appropriate cells of the body
- **Cell therapy** involves the transfer of cells with the relevant function into the patient
- Some protocols utilize both gene therapy and cell therapy. In this case, stem cells are isolated from the patient, genetically modified in tissue culture to express a new gene, expanded to sufficient numbers, and then returned to the patient

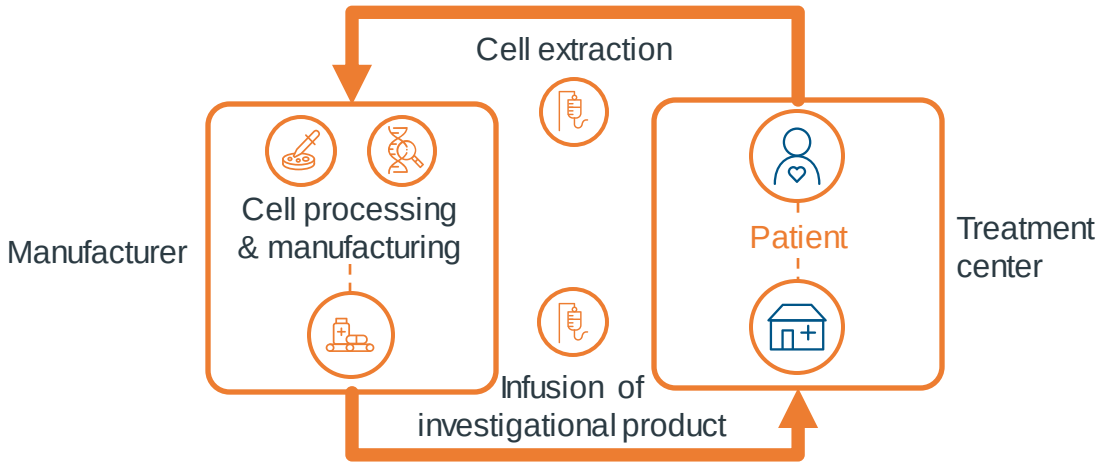
Adapted from: American Society of Gene + Cell Therapy – Gene and Cell Therapy FAQ - https://asgct.org/education/more-resources/gene-and-cell-therapy-faqs

Autologous vs Allogeneic Cell Therapies

Autologous

Autologous therapies are "**personalized"**, and requires an **agile supply chain**, since there is **both supply (of starting materials) and demand (of patients) uncertainty**.

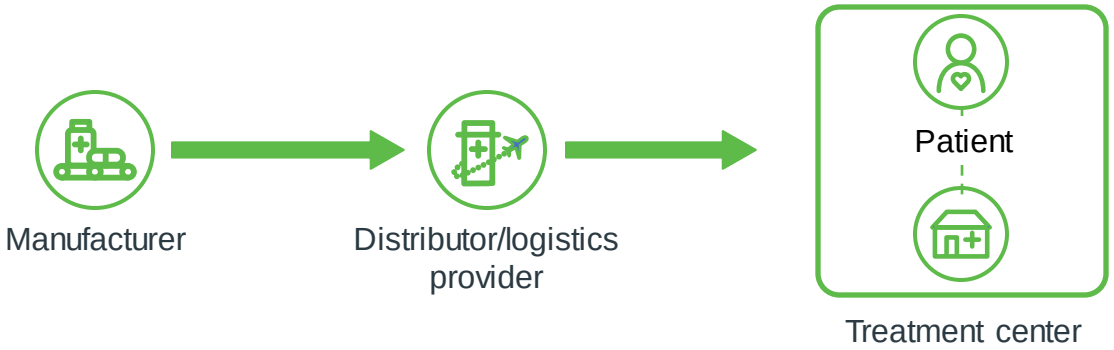
Autologous therapies have a **circular supply chain,** as the patient's cells are required to be sourced (as starting materials), so that manufacturing can take place, before returning the manufactured IP for infusion to the same patient.



Allogeneic

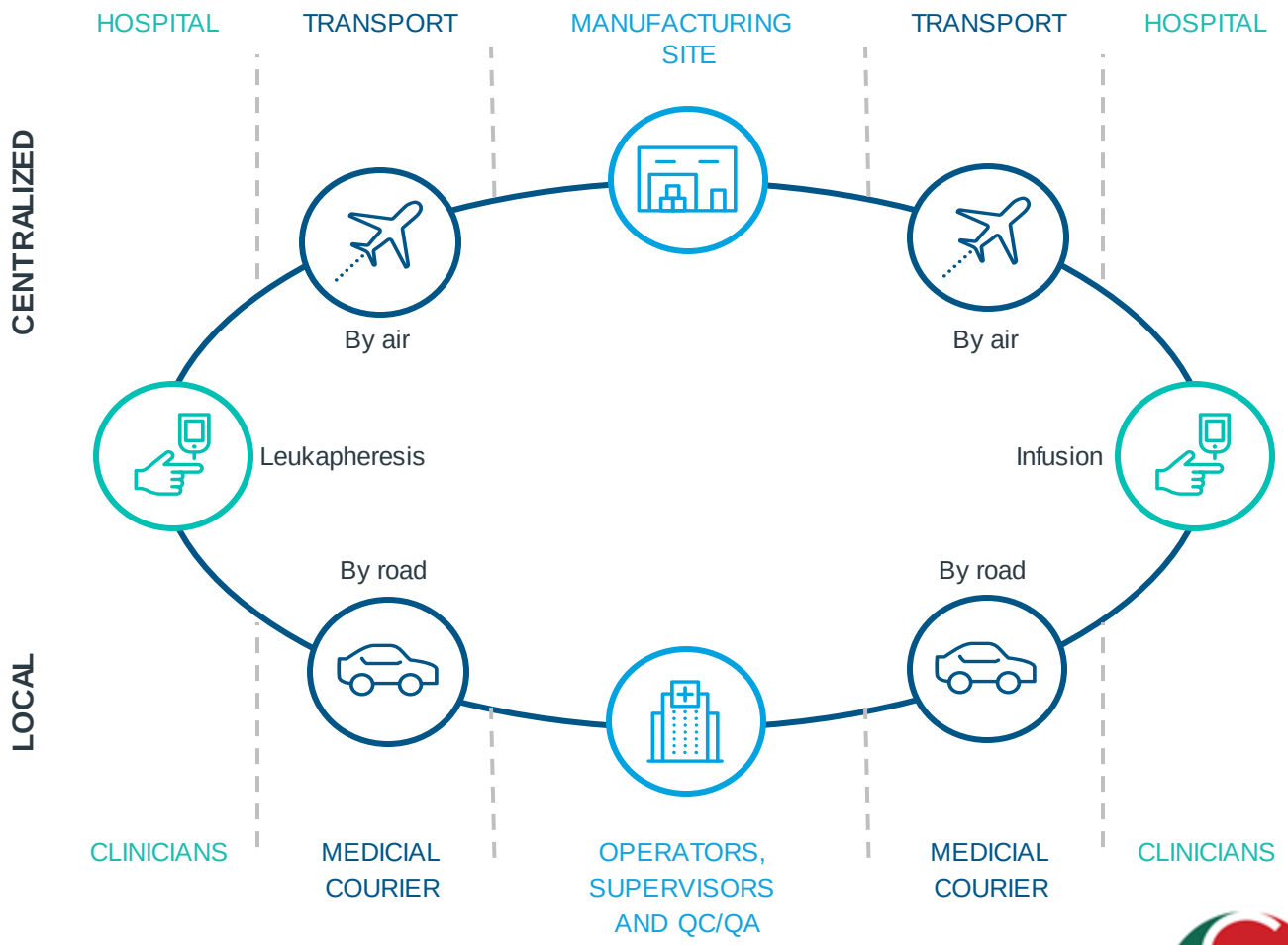
Allogeneic therapies are considered "**off the shelf"**, and may be **manufactured in advance**, **storing it centrally** or at hubs. Human leukocyte antigen (HLA) matched allogeneic cell therapy supply chains can add some complexity.

Allogeneic therapies typically have a **linear supply chain**, which is similar to that of conventional pharmaceuticals.



Why is CGT Logistics Critical?

- **Autologous therapies** - made from a patient's own cells, require highly controlled storage, labelling, custody, packaging, and shipping requirements.
- Typically, there are only 24 to 48 hours (Unless there is a satellite facility to process the cellular materials.) to take the patient's cellular material and transport it to the manufacturing facility to be processed.
- The personalized nature of autologous therapies makes **chain of identity** ("who the patient is") and **chain of custody** ("who has it") vital to patient safety from collection to manufacture to administration – "vein to vein".
- In an autologous cell therapy, the ***process is the product***.



Adapted from Cost analysis of vein-to-vein CAR T-cell therapy: automated manufacturing and supply chain, Lopes et. al (June 2020)

What are some of the Logistical Challenges?

Pharma, Academia and CDMO

- Synchronization of all activities from vein to vein
- Chain of Identity, Chain of Custody, Chain of Condition
- Scalability as trial progresses into global studies and commercialization

Research Sites and CRO

- Patient scheduling for leukapheresis and infusions
- Management of contractors and integration of platforms (i.e.: integration with EDC, IVRS, CDMO, tracking platforms of Supply Chain Partners)

Supply Chain / Clinical Logistics

- Time and temperature sensitive packages that needs to be shipped across clinical sites, manufacturing plants and across borders.
- Import & Export Regulations / Custom Clearance
- Availability of flights / road transportation and proximity to international airports

Conclusion

The Process is the Product

Work out the process / logistics flow with all stakeholders (patients, clients, CDMO, CRO, sites / hospitals, logistics partner, etc), backups included!

A chain is only as strong as its the weakest link! Make sure everyone understands what is needed to be done to ensure success.

Practice makes Perfect

Conduct end to end dry runs, to identify and eliminate any potential issues of the supply chain.

Plan Ahead for Success

Supply Chain Standardization / Optimization / Value Stream Mapping; Lessons and experiences learnt will be used to optimize supply chain in subsequent trials – “more trial sites”, as well as during commercialization

Manfred Seow

Cell and Gene Therapy Strategy Director, IQVIA

- Leads and coordinates IQVIA's multi-disciplinary CGT Centre of Excellence in APAC region
- Prior to that, led the Clinical R&D BD activities in South East Asia, Australia and South Korea
- CGT SME, clinical and operational expertise to develop innovative, data-driven, and patient-centered solution for CGT clinical trials
- Based in Singapore

Questions?

A

Panel Discussion on Challenges in CGT

Our Panellists

Dr George Vuckovic

Assistant Secretary, Scientific Evaluation Branch, TGA

Manfred Seow

Cell and Gene Therapy Strategy Director

IQVIA

Celin Ong

VP, Cell and Gene APAC

Marken, Singapore

Harsha Gupta

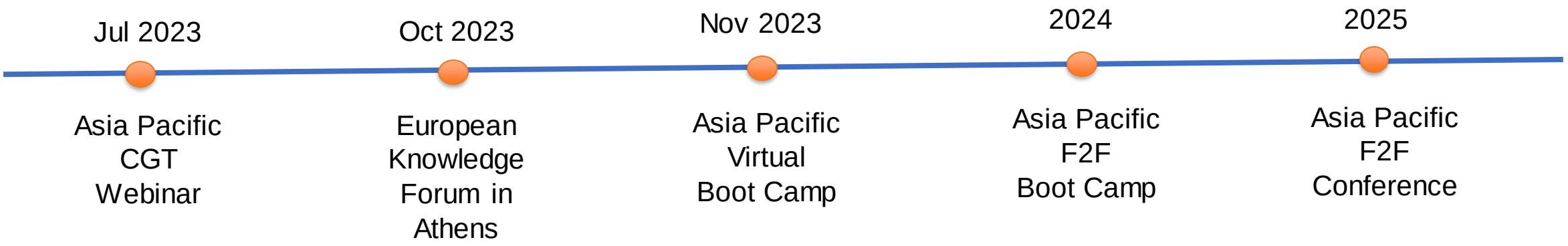
Senior Manager for Manufacturing and Process Development

Cynata Therapeutics

POST WEBINAR SURVEY

Upcoming Events..

Our next GCSG Asia Pacific event is the Introduction to Clinical Supplies Virtual Bootcamp in early November 2023.



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In Closing…

- Thank you for your attendance, questions, comments and feedback
- Please share your experience with your managers and colleagues
- GCSG website www.mygcsg.com
- Consider volunteering
- Job Board https://mygcsg.com/jobs/
- Contact: asiapac@mygcsg.com

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