

About CGT Catapult







Part of a **world-leading network** of technology and innovation centres



Provide access to unique technical **facilities** and **expertise** to help adopt, develop and exploit innovations



Bridge the gap between businesses and academic research



Established by Innovate UK as a **not-for profit**, independent centre

It is our vision for the **UK** to be **a global leader** in the development, delivery and commercialisation of cell and gene therapies.

Where businesses can start, grow and confidently develop advanced therapies, delivering them to patients rapidly and effectively.

CGT Catapult Capability:



Accelerate

the commercialisation of innovations from research

Complement

industry and academia with unique technical facilities and expertise

Innovate

in collaboration with academia and industry

Facilitate

operating in UK as a global centre; working with Government, the NHS and international regulators

Development laboratories

- 1200m² purpose built centre
- Analytical characterisation
- Process development
- Viral vector



Manufacturing centre

- 7000m² manufacturing centre designed specifically for cell and gene therapies
- 12 segregated large clean room modules
- Secure supported collaboration model
- Centre of a cell and gene therapy cluster



Cell and gene therapy specialists (>180)

Industrialisation

- Process development
- Analytical development
- Manufacturing systems
- Supply chain

Regulatory and clinical development

- Regulatory
- Non clinical safety
- Clinical delivery
- Programme management

Engagement

- Collaboration formation
- Intellectual property and patent
- Health economics
- Reimbursement

Breaking down industry barriers

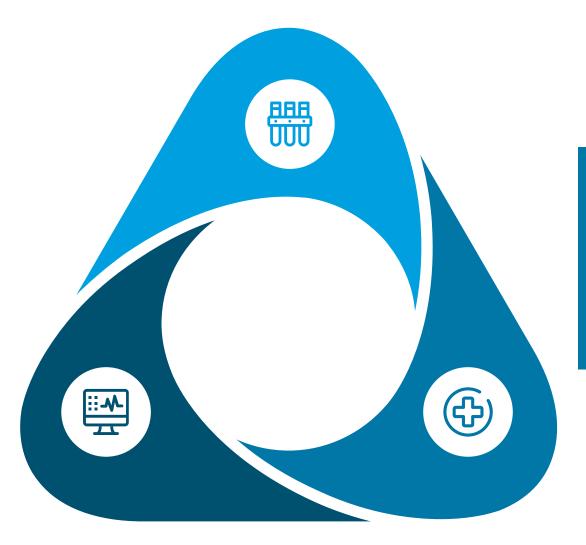


Manufacturing and supply chain

- Ability to scale up cost effective, robust and reliable manufacturing
- Meaningful quality and analytical assays
- Specificity of storage and delivery systems

Health economics

- Uncertainty on reimbursement
- Poorly understood health economics
- Unproven business models



Regulatory and clinical framework

- Uncertain, complex regulatory environment
- Clinical trial site ability to handle live products
- Cautious hospital research committees

Industrialisation



The challenge

Developing a reliable and robust manufacturing process.



How we can help

Identifying ways to lower the costs of manufacturing your product.

Finding innovative ways to make your process more efficient and robust.

Providing methods to accelerate and support clinical trials.

Helping ensure your process and product are controlled and quality compliant.

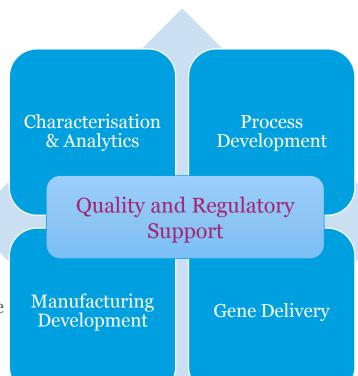
Using tried and tested methods to transfer seamlessly to Good Manufacturing Practice (GMP) manufacturing.

The Industrialisation Team - Our team is your team



- Cell Characterisation
- Potency Assay Development
- In-Process Controls
- Data Mining and Informatics

- GMP Compliance
- GMP Knowledge Base
- CMC
- Documentation



- Design Space
- CPPs for CQAs
- Scale-up / Automation
- Closed Processing
- In-Process Controls
- Process Economics
- Device Design

- Vector Design / Optimisation
- Large Scale production















































Understanding your product



Target Product Profile

Indication, treatment, delivery mode, dose, formulation efficacy, side effects

Quality Target Product Profile

Quality characteristics to ensure safety and efficacy as promised in the label

Critical Quality Attributes

A physical, chemical or biological, property that should be within an appropriate limit, range to ensure product quality

Critical Process Parameters

Process parameter whose variability should be monitored or controlled to ensure the process produces the desired quality

Product Characterisation & Baseline Process

Process Optimisation & Scaling

Process and Analytical Development

Understanding the needs of your stakeholders





Clinic

Investors

Regulators

Manufacturing

Risk to Patient / Product Variations / Failed Manufacture

Not Cost Prohibitive

Safety / Understanding / Control

Design Space / Robust and Reproducible Ease-of-use

Economic/ Commercial Viability

Full Characterisation / GMP Compliance / IPCs

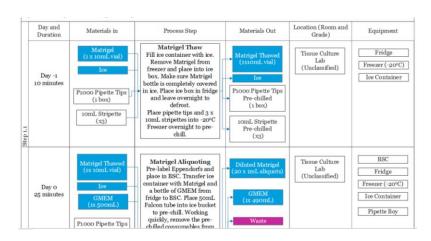
Automation and High-Throughput

Understanding your process

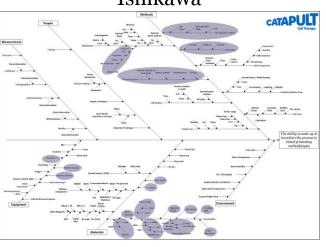


Process Mapping

Areas of process currently undefined

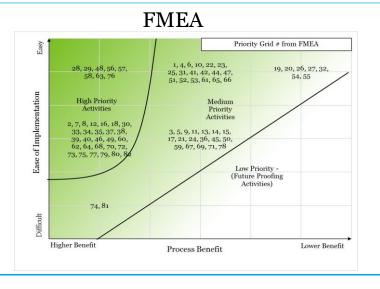


Ishikawa

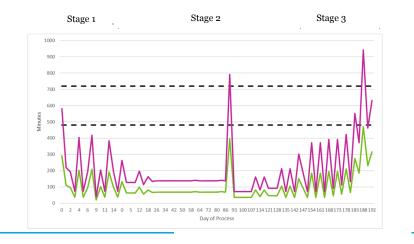


Root Cause of Failure

Risks and Mitigation Strategies



Facility Utilisation and CoGs



Facility Utilisation Profile

Identifying areas of development focus.





Raw Material Supply

(e.g. Adventitious agent Testing/Supply agreements/licensing)



Scalability

Needs of the clinic versus needs of the market / Skilled work-force



Closed Processing

(e.g. Technology Selection/Room grade)



Intermediate / Product Stability

Manufacturing strategy / Clinical population needs



Automation

(e.g. Throughput/accuracy/reproducibility/operator error reduction)



Data Integrity and Storage

(e.g. Electronic Record Keeping and Tracking)



Adaptive Control

(Process robustness and reduced failure rates)



Facility Throughput



Process Control

(e.g. in line analytics / visual observation removal)



Clinical Handling

(Specialised thaw-at-site systems)

Accelerating your program development



Structure

• Structured Development Program to meet Clinical Objectives

- Strategic development appropriate for clinical phase
- Decrease time to pre-clinical & clinical studies
- Focus on high priority areas

Risk

• Reduce the risk of an expensive, failed GMP Manufacture

- Financial Risk Batch losses; Future investment
- Reputational Risk Company; Clinical uptake

• Reduce costs of the Development Program and GMP manufacture

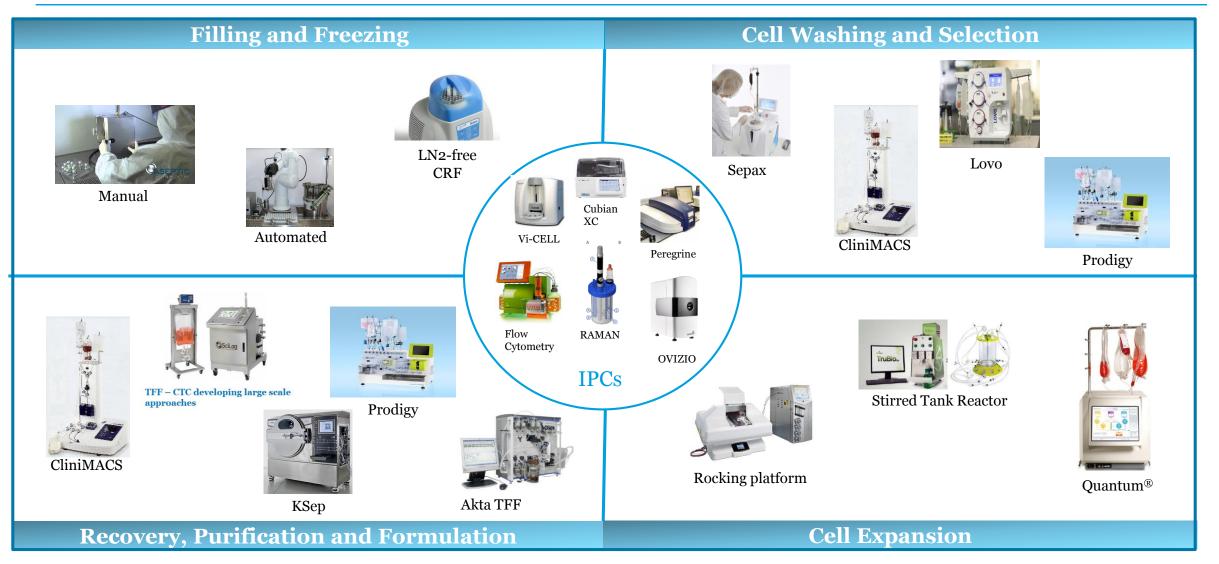
- Decrease CoGs / Increase the probability of achieving the reimbursement price-point
- Dendreon (Provenge) Manufacturing CoGs up to 77% of \$94,000 price tag.
- TiGenix (Chondroselect) Poor uptake in key markets Reimbursement challenges



Industrialisation Team -Supporting Your Development Journey by Leveraging our Assets

Process Development





Analytical Development





High throughput (HTP) flow cytometry 14 colour (extendable to 18)



Medium throughput flow cytometry 8 colour analysis using 3 lases Volumetric analysis



HTP protein array (up to 3840 data point) Fast read time (90 seconds per plate)

Protein



High sensitivity Digital PCR HTP analysis (9216 reactions) Marker screening studies

Molecular

Digital analysis



Low density screening arrays qRT-PCR optimisation/validation Assay transfer to CRO / Manufacture



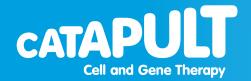
qRT-PCR optimisation/validation Assay transfer to CRO / Manufacture







Automated liquid handling robot Molecular and protein assay set up Assay tech transfer to CRO / Manufacture



Manufacturing
Development Challenges:
Key Factors Shaping the
Field

Maturation of the Field



Yescarta

\$373,000

Strimvelis

€600,000

- (axicabtagene ciloleucel)
- Kite's CAR-T therapy for forms of Diffuse large B-cell lymphoma (DLBCL) in adults. Type of non-Hodgkin lymphoma (NHL).

• GSK's treatment for a very rare disease called ADA-SCID (Severe Combined Immunodeficiency due to Adenosine Deaminase

Kymriah

- (tisagenlecleucel)
- Novaritis's CAR-T therapy for B-cell precursor acute lymphoblastic leukemia (ALL) in children and young adults.

\$475,000

Glybera

deficiency),

- (alipogene tiparvovec)
- UniQure's AAV-based gene therapy to treat the rare inherited disorder lipoprotein lipase deficiency (LPLD)

>€1,000,000

State of Play in the EU – Since Regulation (EC) 2007/1394





- Approved 2015

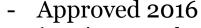


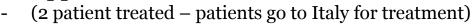
Holoclar





Strimvelis







Zalmoxis

- Approved 2016, Conditional MA



Spherox





Alofisel

- Approved 2018



Yescarta

- Approved 2018



Kymriah

- Approved 2018



Chondroselect

- Voluntary Withdrawal 2016



MACI

- (Reimbursement challenges / Complex Logistics)



Provenge

Approved 2013, Suspended 2014
 (Manufacturing Discontinued)



Glybera

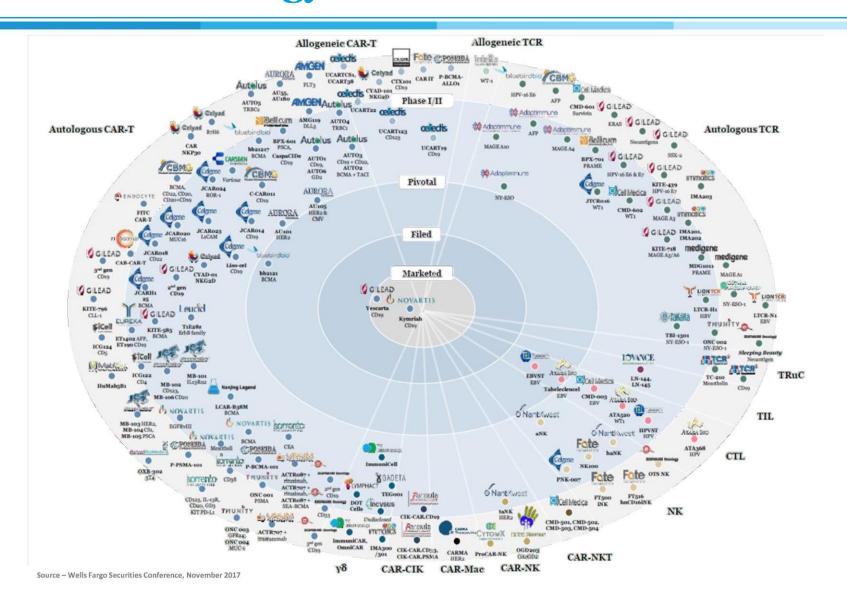
Approved 2013, Withdrawn 2015

(1 patient treated)

Approved 2012, Voluntary Withdrawal 2017

Immuno-Oncology Sector –The Next Generation!



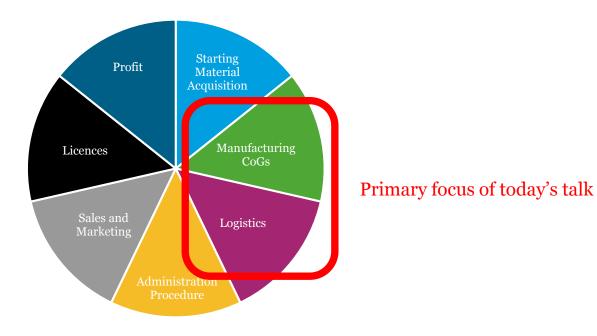


Need to deliver scalable, low cost manufacturing solutions to enable healthcare provider adoption of a diverse portfolio of therapies.

What key factors influence therapy price?



Key Cost Contributors – Product Manufacture and Administration



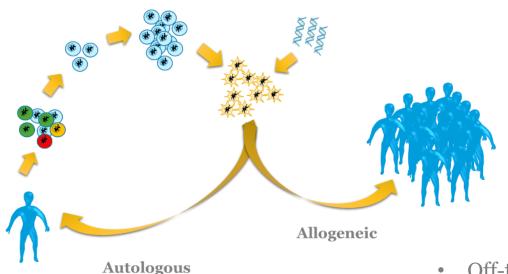
Key Cost Contributors – Perceived / Tangible value to the Healthcare System

- Can be very challenging to define
- What is the true cost (lifetime cost) of a patient to the healthcare system
- How do you engage a patient for their lifetime, especially if they are cured within a year?



Autologous vs Allogeneic – The Concepts





- "Made-to-order"
- Patients own cells are the starting material
- Potential to utilise some blood processing technologies, but lack of technology solutions in general.
- COGs structure is driven by facility throughput capability.

- Off-the-shelf use
- Cell bank based
- Potential to use established biopharma processing technologies
- Scalable COGs structure and spread across multiple doses and therapeutic targets.

Scaling Manufacture



Scale - Out



Autologous

Each reactor contains a single patient's therapy



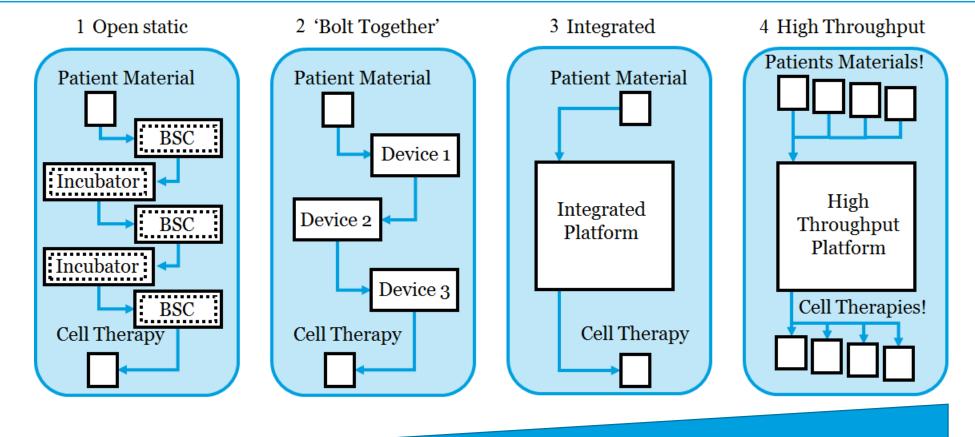


Allogeneic

Each reactor contains enough doses to treat thousands of patients

Automation Strategies for Autologous Therapies





Increasing integration + automation -> increased facility throughput

Increasing integration + automation -> decreasing cost of goods

Example of a "Bolt-Together" Solution

Starting Material



"Bolt-Together" Solutions

Multiple technologies linked together

Each technology is only used for the duration it is required during the process.

Typically analytics are off-line / limited in-line measurements (DO/pH etc).

Still heavily manual in nature – operator is required to move material from system to system

Supports flexibility in process design

Washing and Concentration

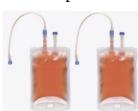




Cell Selection



Cell Expansion



Formulation and Freezing







CGT Catapult Focus - Developing Centralised Control Systems

Example of an "Integrated" Solution

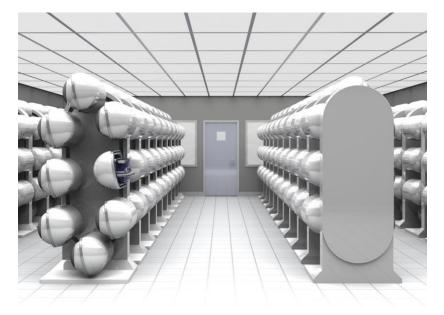


Integrated Solutions

Each reactor contains a single patient's therapy

Each system is "dedicated" for the duration of the process

Typically analytics are off-line / limited in-line measurements (DO/pH etc)



CocoonTM (Octane & Lonza)



Prodigy[®] (Miltenyi)

Example of "High-Throughput" Vision



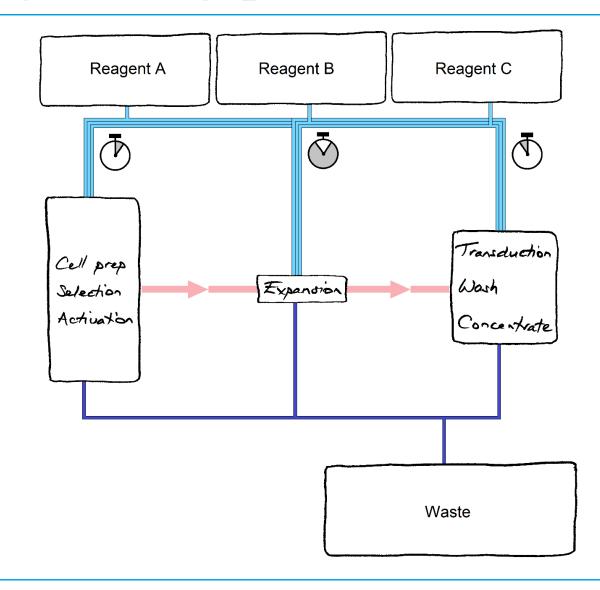
High Throughput Solutions

System is modular in nature allowing segregation of processing bottlenecks.

Each reactor contains a single patient's therapy

Each system is capable of processing multiple patient therapies concurrently.

Analytics are on-line / in-line and feed into decision making algorithms.



CGT Catapult Focus Development of enabling
technologies to support
high-throughput
concepts.



Why do we need a Framework?





"Surely it's just a case of picking up the phone and "voila", next day delivery"

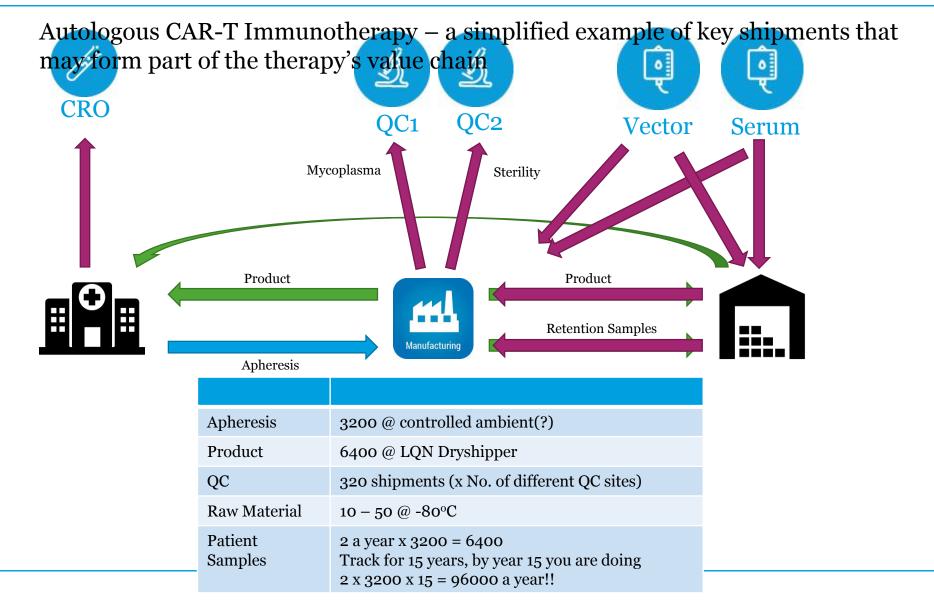
Unfortunately not - the logistics complexity surrounding ATMP manufacture and subsequent connection of final product to patient requires significant planning!

Logistics success will be influenced and impacted by several key stakeholders both internal and external to the therapy developer throughput the development lifecycle.

To be successful, the vision for a commercial logistics strategy needs to be planned early & have quality designed-in from the start.

Logistics – How complex can it be?





Logistics - What could possibly go wrong?







AUTOMATED THERMAL PACKAGING RETURN

STABLE THERMAL PACKAGING

SENSOR + COMMUNICATION EMBEDDED PACKAGING





SECONDARY THERMAL PACKAGING for SITE LOCAL TRANSPORT to BEDSIDE

Logistics - What could possibly go wrong?









CHAIN OF CUSTODY MANAGEMENT



Excursion Statistics

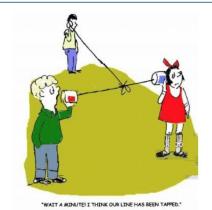
Section

Туре	Value
Low Alarm Threshold (*C)	15.0
Total Time Below	04d 20h 00m 00s
Longest Low Threshold Excursion Event	04d 08h 45m 02s
High Alarm Threshold (°C)	25.0
Total Time Above	00d 00h 00m 00s
Longest High Threshold Excursion Event	00d 00h 00m 00s

Event Type	Time	Duration in Minutes
Excursion Below Threshold	11-Jan-2018 04:13:34 GMT-0700	6,285
Excursion Below Threshold	15-Jan-2018 23:43:40 GMT-0700	675

AUTOMATED DATA ANALYTICS

Unique Challenges Posed by Cell and Gene Therapy Logistics and Packaging



- Manufacturing
- Site
- Patient
- Logistics provider
- Logistics vehicle
- Data integrator
- Qualified person
- To name a few...

REAL TIME SYSTEMS INTEGRATIONS with PARTNERS

Logistics - What could possibly go wrong?





AIRLINE RESTRICTIONS ON COMMUNICATION SYSTEMS



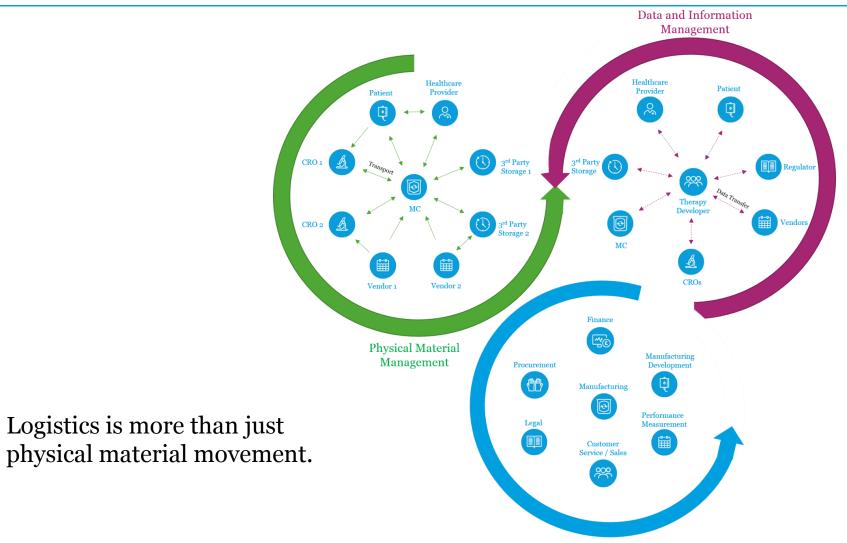
MANAGEMENT of TIME SENSITIVE SHIPMENTS



CLEANLINESS OF PACKAGING

The Key Elements

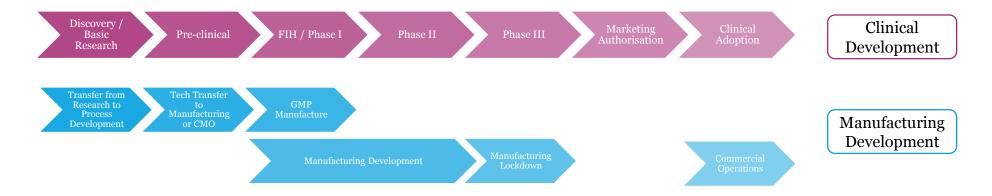




Business Management

When should I start planning?

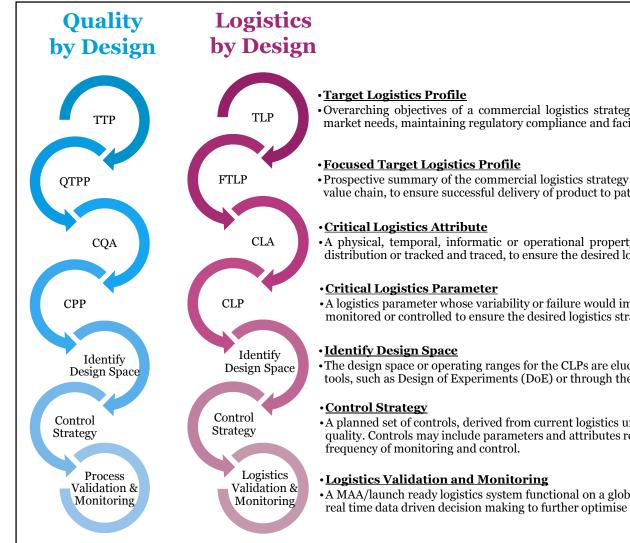




As early as possible – Logistics should have lifecycle management plans similar to clinical and manufacturing development

Logistics by Design – Build in Quality from the Start CATAPU





•Overarching objectives of a commercial logistics strategy with respect to supporting business goals, supplying market needs, maintaining regulatory compliance and facilitating clinical adoption.

• Prospective summary of the commercial logistics strategy traits that need to be achieved for all components of the value chain, to ensure successful delivery of product to patient whilst maintaining chain of custody and identity

• A physical, temporal, informatic or operational property that needs to be within an appropriate limit, range, distribution or tracked and traced, to ensure the desired logistics strategy is fulfilled.

· A logistics parameter whose variability or failure would impact a critical logistics attribute and therefore should be monitored or controlled to ensure the desired logistics strategy is fulfilled.

• The design space or operating ranges for the CLPs are elucidated through practical assessment using supporting tools, such as Design of Experiments (DoE) or through the testing as part of logistics development activities

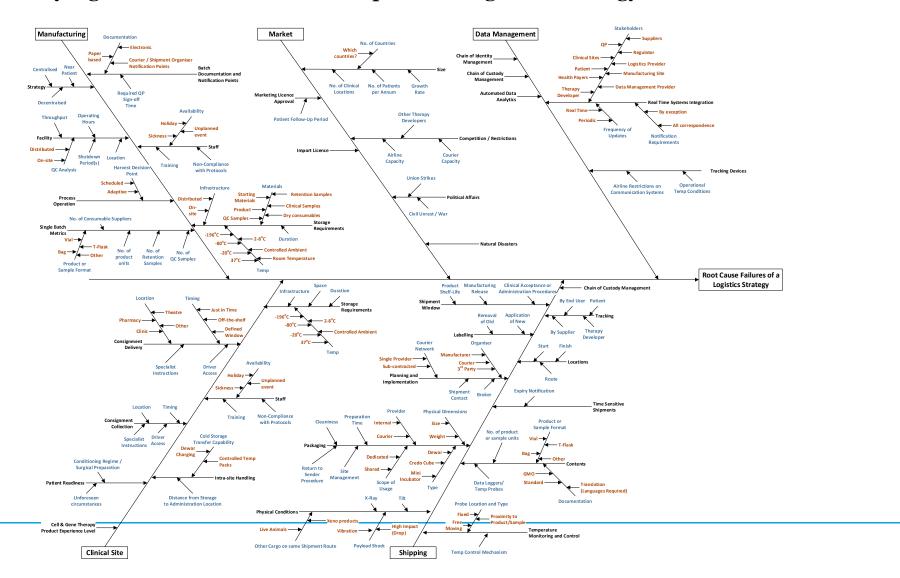
· A planned set of controls, derived from current logistics understanding that ensures service performance and quality. Controls may include parameters and attributes related to physical or informatic characteristics and include

• A MAA/launch ready logistics system functional on a global footprint with regular performance review to support real time data driven decision making to further optimise the logistics undertaking.

Examples of Route Cause Failures

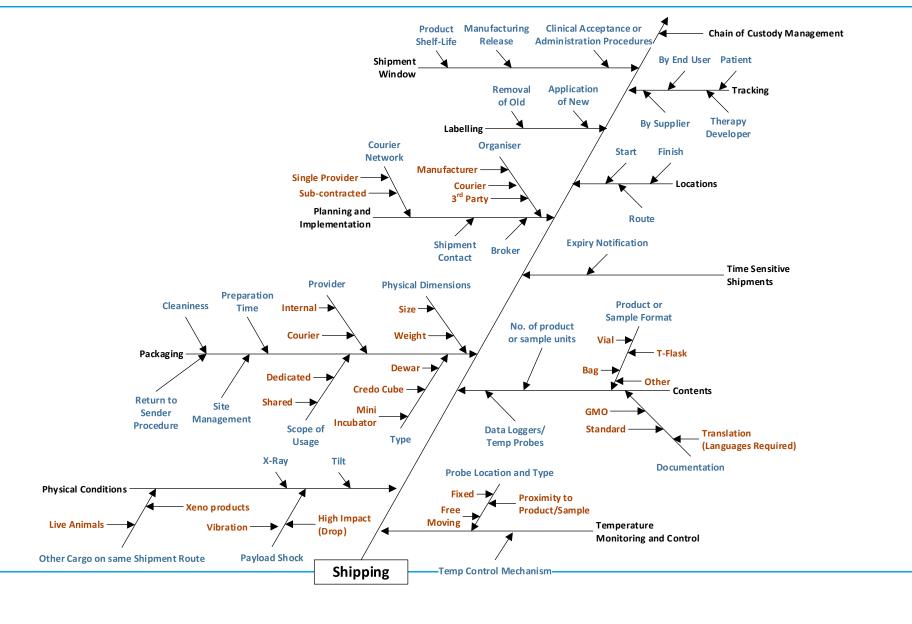


Identifying root cause failures of the planned logistics strategy



Examples of Root Cause Failures

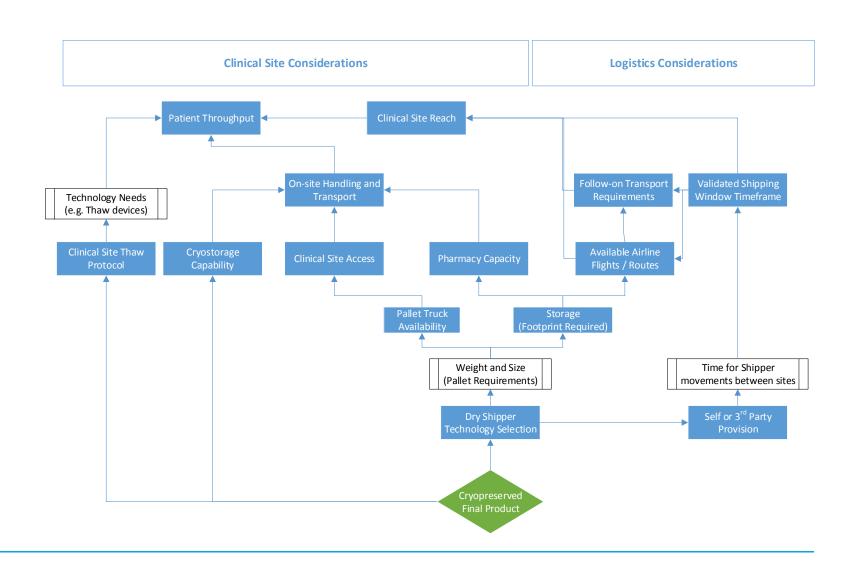




Case Study A: Mapping Complex Networks of Dependencies



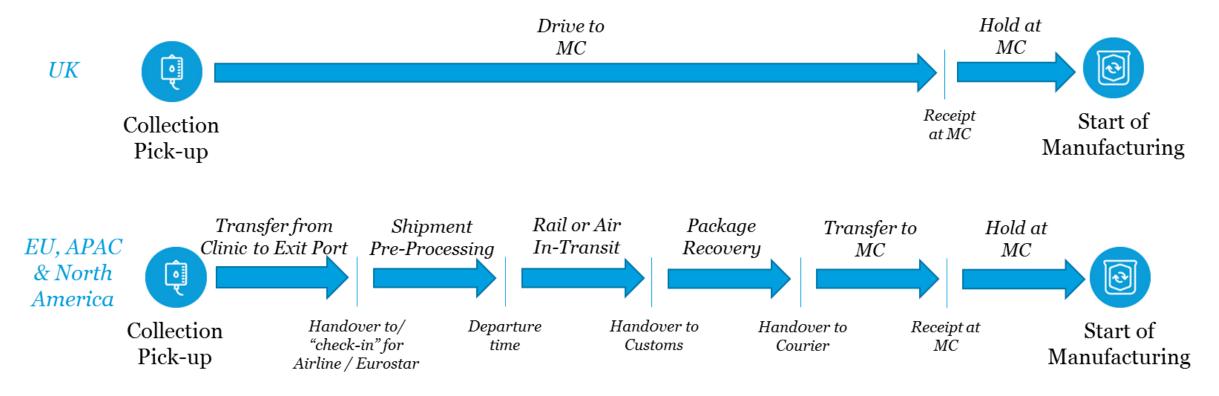
What's the impact of manufacturing or clinical development teams deciding the product should be cryopreserved?



Case Study B: Mapping Shipping Lanes

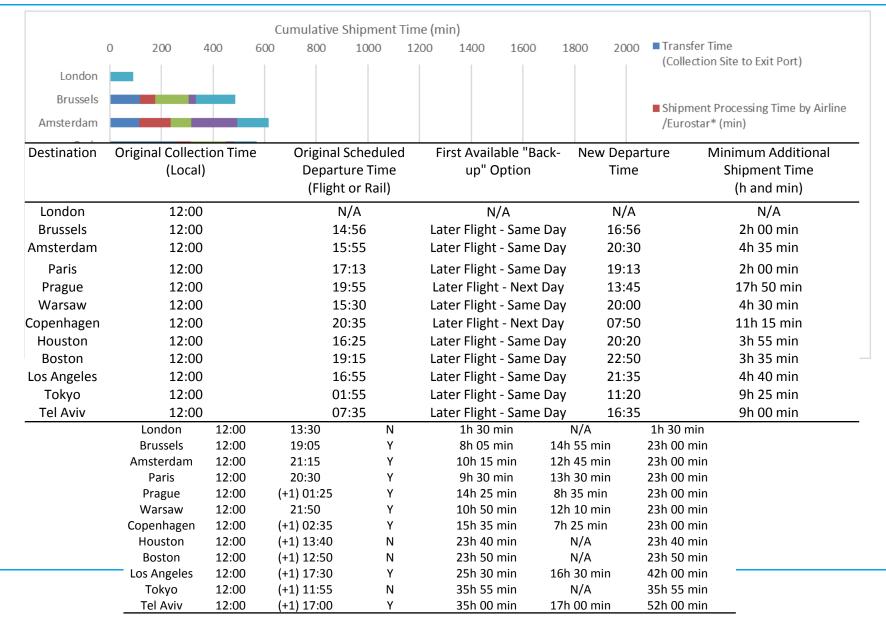


What's the impact on required shipping window / material shelf-life needs as a function of constrained elements within the shipping pathway?



Case Study B: Mapping Shipping Lanes







Cell and Gene Therapy Catapult

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We work with Innovate UK





Delivering on our strategic priorities for autologous therapies







Industrialisation



Analytical development



Process development



Gene delivery systems



Case studies

Developing automated in-process controls for cell and gene therapy manufacturing

Creating characterisation and potency assays

Overcoming challenges in rapid sterility testing

Case studies

Investigating the use of stirred tank bioreactors to scale up

Modelling fluid movement inside bioreactors

Creating an allogenic PSC manufacturing platform

Case studies

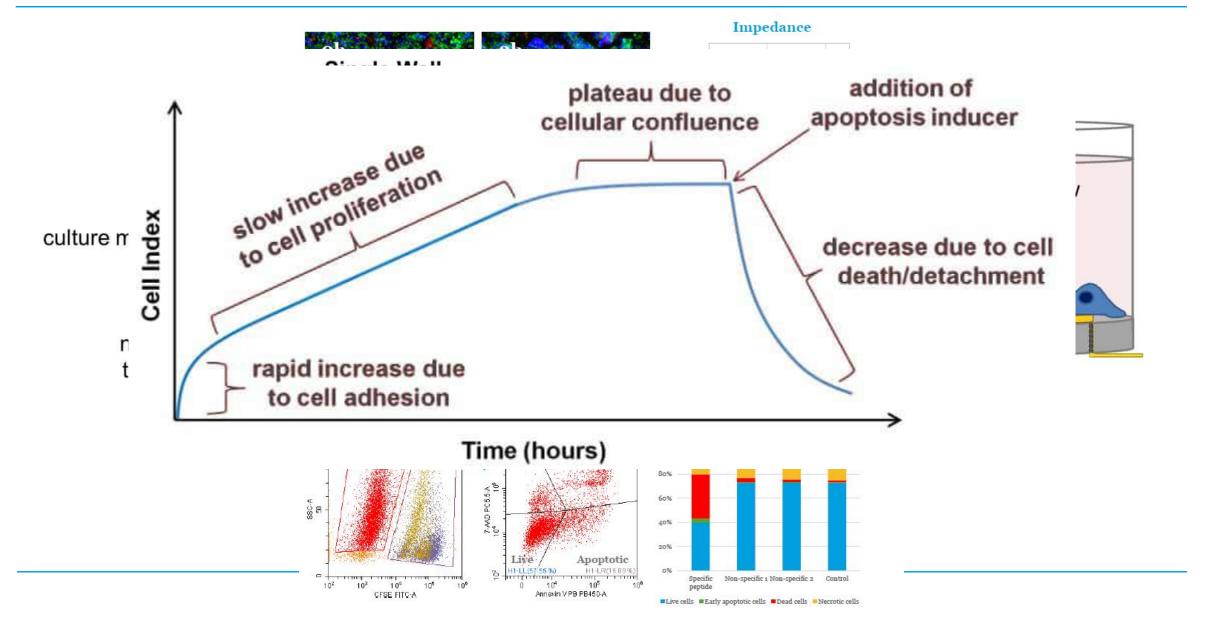
Improving transduction using microfluidic technology

Measuring viral vector using ddPCR

Increasing productivity and quality of lentiviral vectors

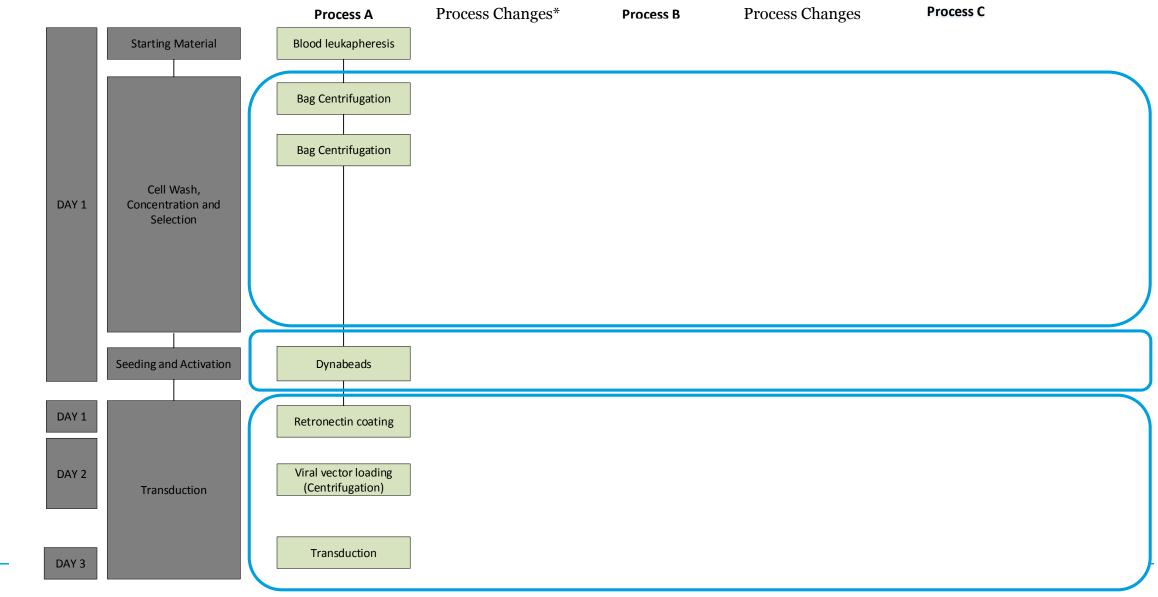
Potency Assay Development for TCR Therapy





Manufacturing Development for a TCR therapy

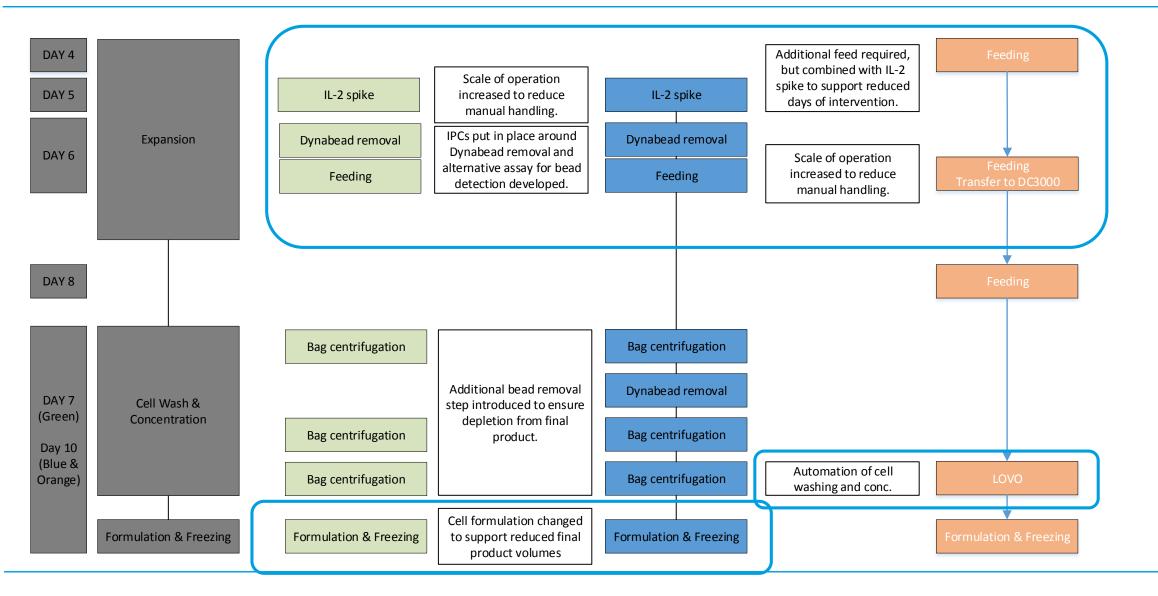


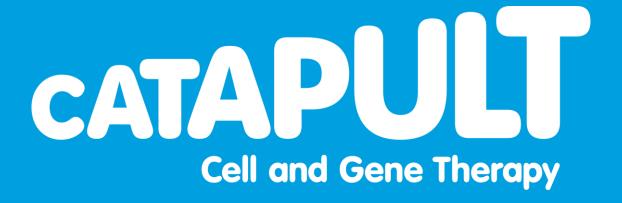


*Changes constrained by on-going clinical trial

Manufacturing Development for a TCR therapy







Cell and Gene Therapy Catapult is committed to ensuring high standards of research integrity and research best practice in the activities we carry out. We subscribe to the principles described in the UK concordat to support research integrity.

Cell and Gene Therapy Catapult is a trading name of Cell Therapy Catapult Limited, registered in England and Wales under company number 07964711, with registered office at 12th Floor Tower Wing, Guy's Hospital, Great Maze Pond, London, SE1 9RT. VAT number 154 4214 33.

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We work with Innovate UK











