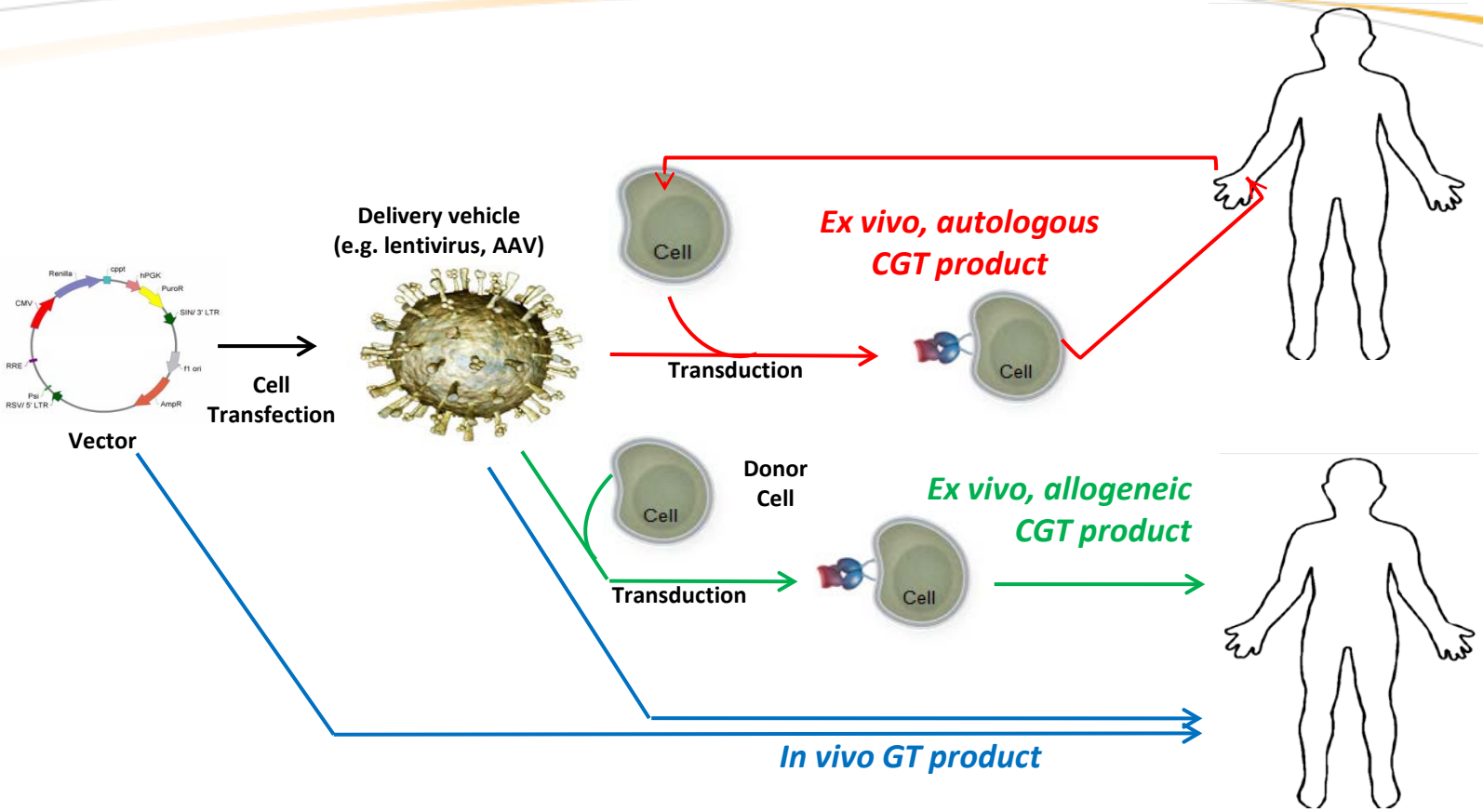
CMC Development and Manufacturing Challenges

Steven Howe, GSK, Cell and Gene Therapy (CGT) Platform

16 Dec 2016

Summary of CGT technologies – GSK View



- ATMPs broader than Gene Therapy. GSK focus has been on Gene Therapy hence the focus of this talk
- Comments, differing points of view on other ATMPs welcome

Partnerships to accelerate growth and build expertise

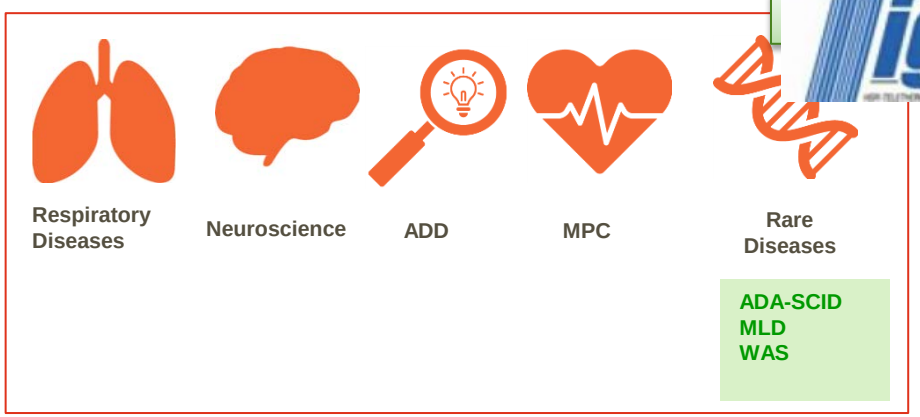
GSK's investment in ex vivo autologous cell platform

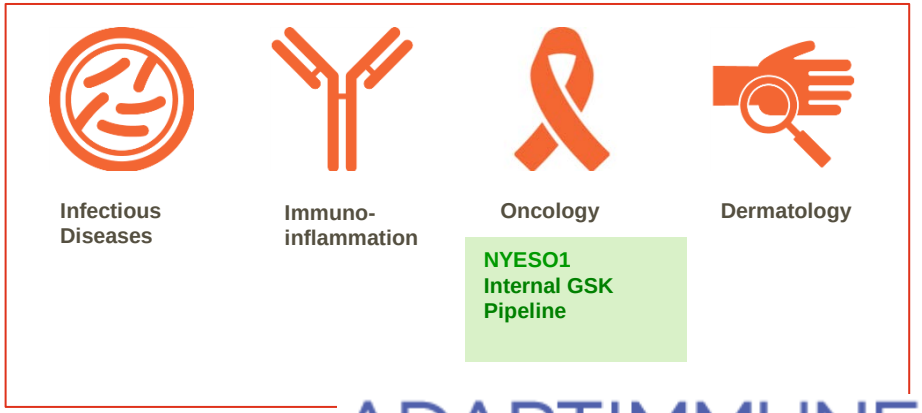
Development and manufacturing collaborations

MOLMED

MACS Miltenyi Biotec

***Ex Vivo* Autologous CGT Pipeline**





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ADAPTIMMUNE
transforming T cell therapy

Promise and Challenge of CGT Medicines

Pipeline

Ex-Vivo Autologous Therapy

Development and Manufacturing Challenges

- Vector Scale-Up - Capacity, Quality, Robustness
  - Current challenge and some suggested future approaches
- Ex-Vivo Cell Processing – Scale out – 1 patient = 1 batch
  - Scale out challenge and proposed future vision
- Change Management – Approach to Comparability
  - Rational approach to comparability
- Analytical- Modernization of analytical tools
- Supply chain – Logistics and Supply Chain

Vector Manufacturing

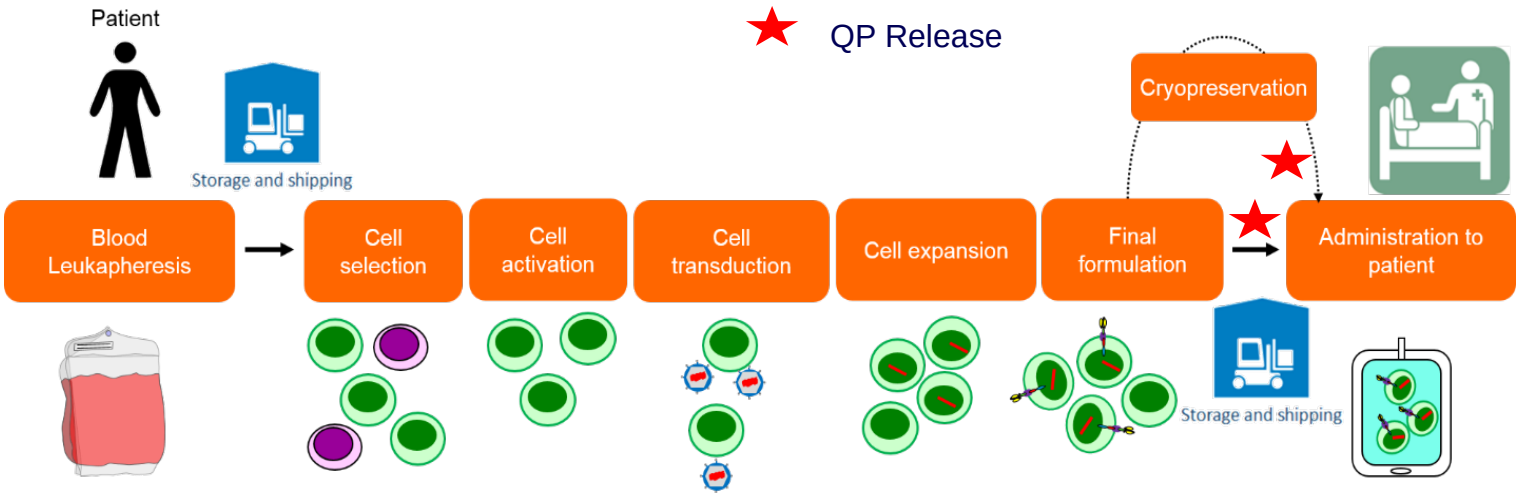
- Adherent cell factory processes
- Operation usually in <100L volumes
- 1 batch can meet the drug product needs for 1 to 10 patients (typically)

Vector Scale Up – Proposed approach

- Fully disposable scalable platform
- Move from adherent culture to suspension
- Move from transient transfection to stable cell line production
- Eliminates the need for ongoing plasmid manufacture
- Important challenges to address, stability of cell line, titer, “true platform”
- Has the potential to transform current processes to meet demands such that 100s and 1000s of doses per batch

Cell Process Scale out

- Current process manual, very often involve open manipulations by highly skilled operators
- Scale out needs significant as patient populations particularly in Oncology could be large

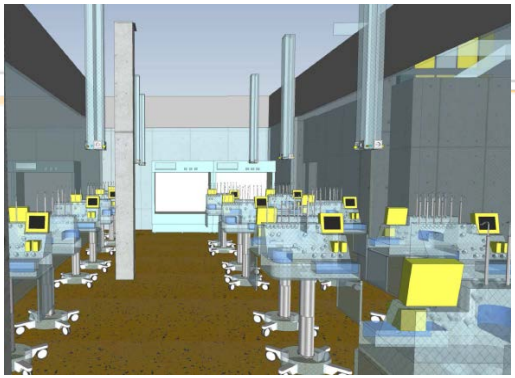


Manufacturing Models

- Centralized
  - Single facility, cells in (Fresh/frozen), drug product out (typically frozen)
  - Controlled operations, minimize product variation, maximize expertise
  - Challenges: practicality for large indications, availability of trained operators, logistical challenges
- De-centralized
  - Regional Hubs
  - True scale out, reduces logistical challenges, better patient access
  - Tech transfer needed, both process and analytics
  - Raw Materials, consumables supply chain

Cell Process Scale out – Future Direction

Bespoke, manual process



Multiple Automated units in a ballroom suite in regional hubs

Fully automated system with integrated QC testing

Current Regional Cell Processing Hubs

'Ballroom' Suites in Regional Hubs with Exact Copy Automation

Cell Processing "In Hospital Solution"

Challenges

Technical	GMP/Regulatory
Fully closed, automated process	QA, QP Release Local?
In-line, in –process analytics	Manufacturing within hospital
Continuous process validation	Robust tracking
Raw Material sourcing/supply	Troubleshooting, deviation management, QMS
Process and product drift over time	

Change Management and Comparability

- Rapid pace of innovation in tools for manufacturing and testing
- Continuous and logical application of these tools will involve management of change and proving comparability
- Approach to comparability that GSK has followed is based on Risk Assessments and general framework provided by ICH Q5E
- Examples based on expected changes in manufacturing

Proposed Changes – An Approach to Address Comparability

Manufacturing Process Component		Process v 1.0	Proposed Process v 2.0	Rationale for Change
Vector Process Case 1	Cell expansion	Adherent	Suspension	• Enable treatment of larger population of patients including some older patients • Improve supply chain robustness
Cell Process Case 2	Cell manipulation	Manual production	Implementation of automation	
	Final product formulation	Fresh product with 4 hour shelf life	Cryopreserved product.	

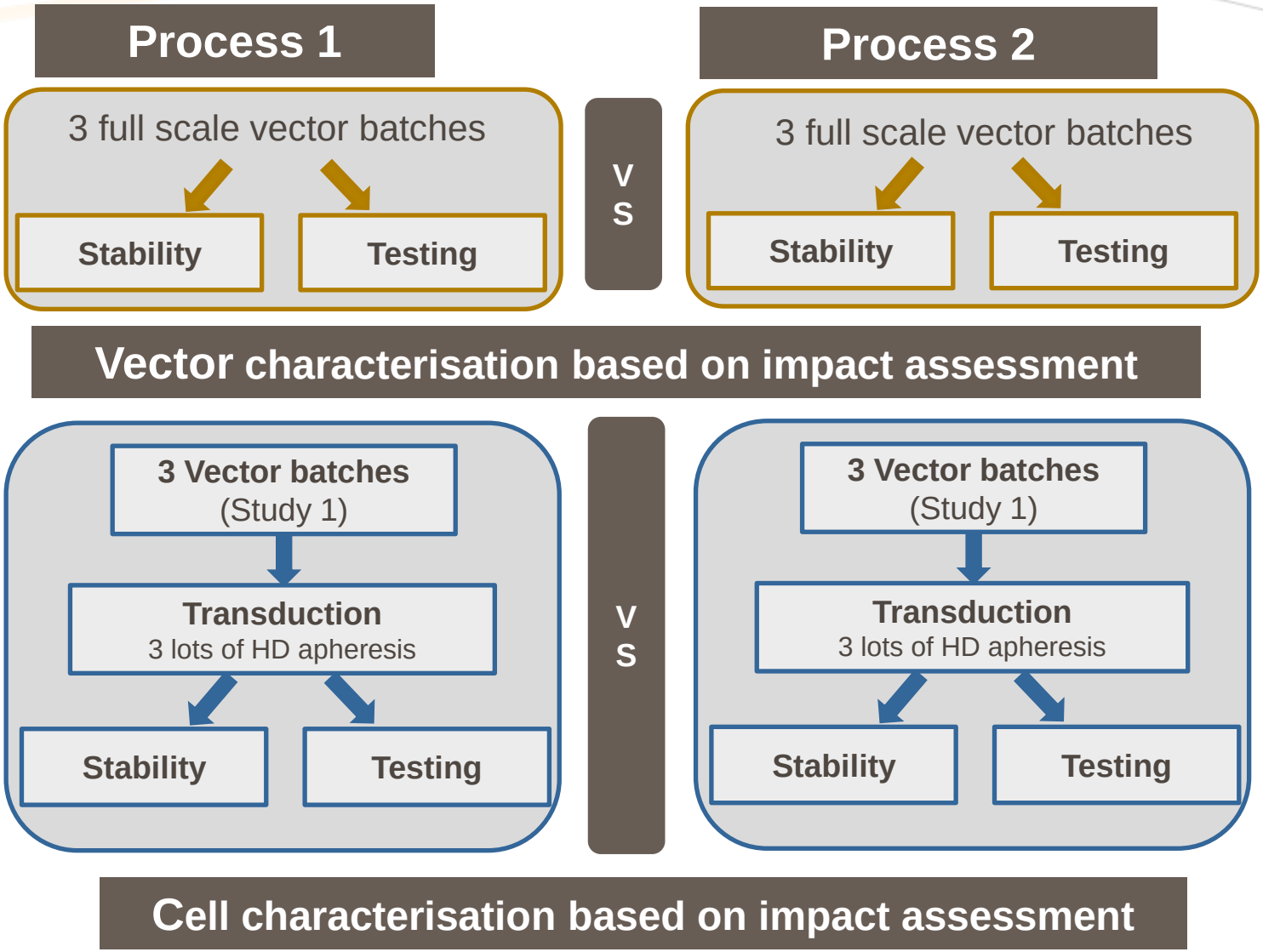
Assess Impact of Vector Process Change

Vector CQAs	Potential Impact
Infectious viral titer	H
Infectivity	H
Transgene sequence	L
Vector Integrity	L
HCP	H
HC DNA	H
Benzonase	L
Microbiological Control	L
mycoplasma	L
endotoxin	L
Adventitious virus	L
Plasmid DNA	M
RCL	L

Cell Product CQAs	Potential Impact
Percent CD34+	L
Vector copy number	H
CD34+ Stem Cell Potential	L
Enzyme Activity	H
Cell Viability (%)	L
Transduction efficiency	H
Endotoxin	L
Mycoplasma	L
Microbiological Control	L
RCL	L
Adventitious virus	L
HCP	H
Plasmid DNA	M
Host Cell DNA	H
Residual cytokines	L

Capture rationale for outputs to be studied

Comparability Study Design



Discussion Points

1. The need for *in vivo* comparability studies
2. Will cell product comparability always be required to support vector process changes?
3. How should in vitro comparability studies be designed when considering manufacturing site changes (e.g. sites in Europe and US)?
    a) Split apheresis between two sites (logistical risks)
    b) How to set acceptance criteria despite inherent variability of starting material? Use (sometimes limited) clinical and development data?
4. What are comparability implications for a true decentralized or in-hospital solution?
5. Need for analytical method comparability (bridging studies) when assays are changed

Summary

- ATMPs have the potential to be transformative medicines
- Current manufacturing paradigms will need substantial innovation in all aspects – Technical, Regulatory, Quality, to supply global demand for these medicines
- Close collaboration between industry, academia, and regulatory agencies needed to bring these transformational medicines to a wider patient population