Defining Microbial Control Strategies for cell-free and cell-based Individualized ATMPs

Cell & Gene Therapy Products (CGTP): Manufacturing, Quality and Regulatory Considerations
June 27-29, 2023, Bethesda

Friedrich von Wintzingerode, QC Lead iNeST, Roche-Genentech

Overview

1. How are individualized (make-to-order) ATMPs different from off-the-shelf ATMP’s?
2. Regulatory background
3. Microbiological testing: be thoughtful and keep it simple
    1. Mapping the autogene cevumeran End-to-End Process
    2. Mapping an autologous T cell manufacturing process
4. The importance of raw material control
5. Specific considerations for media fill/APS for cell therapies

Personalized vs individualized medicine

Personalized medicine

Finding the right drug on the shelf to treat the patient

versus

Individualized medicine

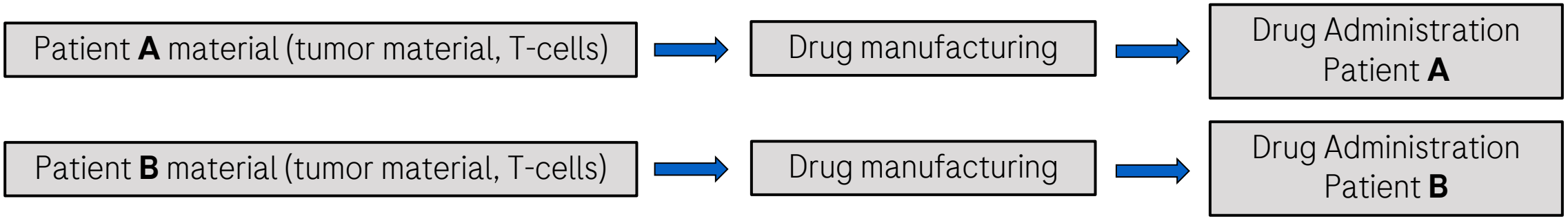
Creating the right drug to treat the patient

Dr. Peter Marks, FDA

How are individualized ATMPs different from off-the-shelf ATMPs?

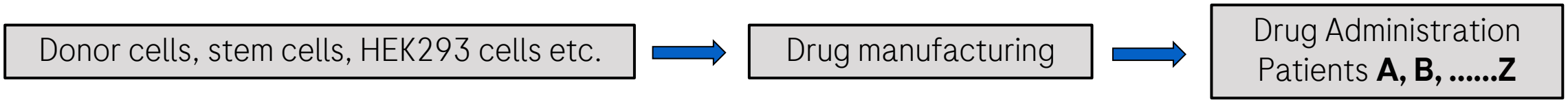
Individualized ATMPs, e.g.

- cell-free mRNA-based individualized, therapeutic cancer vaccines
- autologous T cell therapies



Off-the-shelf ATMPs, e.g.

- allogeneic cell therapies
- viral vector induced in-vivo gene therapies



How are individualized ATMP's different from off-the-shelf ATMPs?

Individualized, patient-specific ATMPs have a unique risk profile

Risk description	Impact individualized ATMPs	Impact off-the-shelf ATMP's
Viral or microbial contamination of donor material	**Cell-free mRNA-based individualized therapy** • Not relevant	**Allogeneic T cell therapy** • Major impact, donor material is not acceptable
	Autologous T cell therapy • Low impact, if contamination is intrinsic	**Viral vector induced in-vivo gene therapies** • Not relevant
Viral or microbial contamination of other raw materials	**Cell-free mRNA-based individualized therapy** • Medium impact since contaminated raw material batch is only used for a limited number of patients • Low risk of viral contamination	**Allogeneic cell therapy** • Major impact, contamination potentially impacts hundreds or even thousands of patients
	Autologous T cell therapy • Medium impact since contaminated raw material batch is only used for a limited number of patients	**Viral vector induced in-vivo gene therapies** • Major impact, contamination potentially impacts hundreds or even thousands of patients
Viral or microbial contamination of product	• Low impact, since each product batch is only affecting one patient • There are targeted treatment options	• Major impact, contamination potentially impacts hundreds or even thousands of patients

Regulatory background

- So far health authorities have not published guidelines specific to **microbiological** topics for ATMP's
- However, EMA has stated that certain Ph. Eur. microbiological monographs apply to ATMP's
  - *Sterility, Chapter 2.6.1*
  - *Mycoplasmas, Chapter 2.6.7*
  - *Bacterial Endotoxins, Chapter 2.6.14*
  - *Nucleic Acid Amplification Techniques, Chapter 2.6.21*
  - *Microbiological Control of Cellular Products, Chapter 2.6.27*
  - *Alternative Methods for Control of Microbiological Quality, Chapter 5.1.6*
- In addition, the following guidelines can be relevant for ATMP manufacturing
  - *Human cells, Tissues, and Cellular and Tissue-based products*, subpart C - Donor Eligibility, 21CFR1271
  - *Additional Standards for Human Blood and Blood Products*, 21CFR640
  - *Raw Materials of Biological Origin for the Production of Cell-based and Gene Therapy Medicinal Products*, Ph. Eur. 5.2.12.

Microbiological testing: be thoughtful and keep it simple

- Individualized ATMP's have tight turn-around-time (TAT) requirements to ensure timely drug administration to patients.
- This requires the following selection criteria for micro methods:
  1. **Scientifically sound**
     - The method must be properly validated and follow industry standards
  2. **Short hands-on time**
     - Short, simple workflows decrease the risk of errors during method execution
  3. **Reliable**
     - The method should have a low false positive rate and low system suitability failures to avoid time consuming investigations
  4. **Flexible execution**
     - It is preferable for micro methods to be executable 6-7 days per week to avoid delays to QC testing and batch release

Microbiological testing: be thoughtful and keep it simple

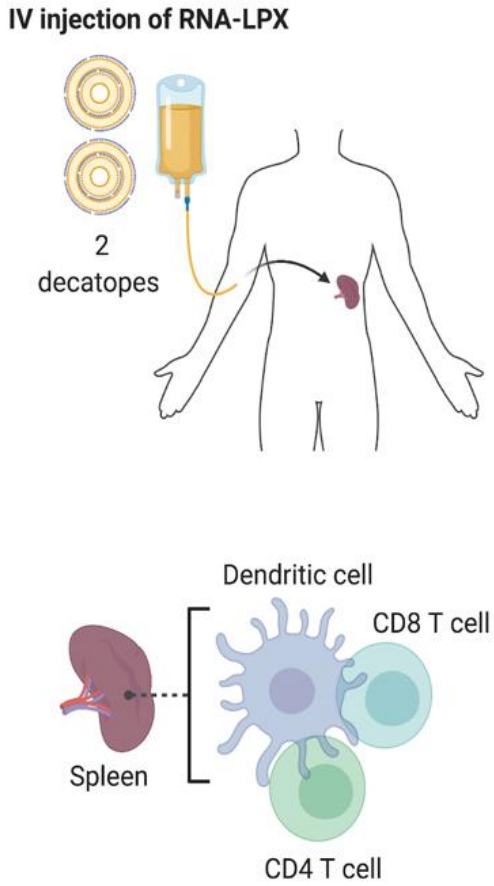
Compendial micro methods usually meet all of the aforementioned criteria, which makes them methods of choice for individualized ATMP's

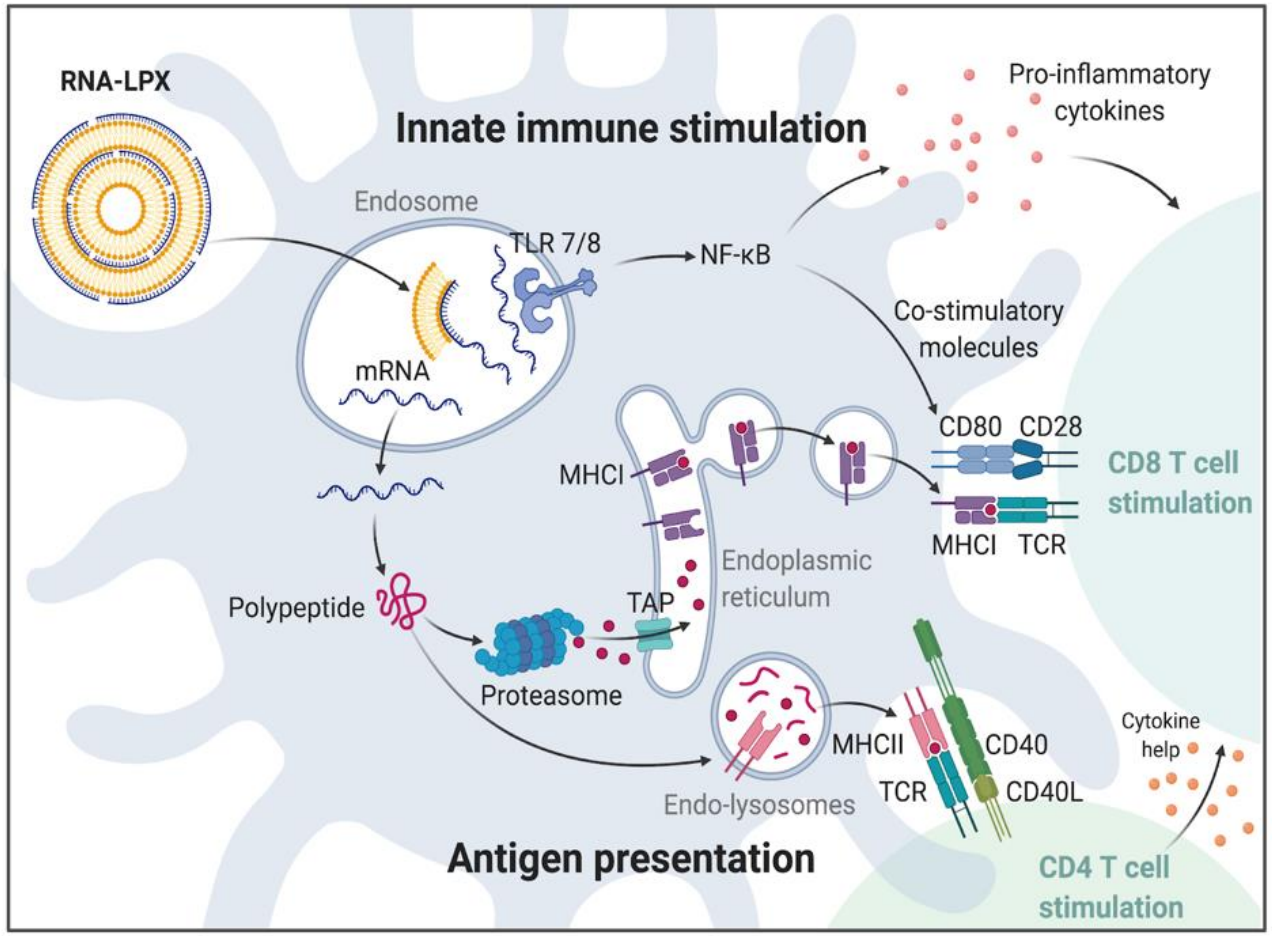
Exceptions

- Careful mapping of manufacturing process and analytical workflow reveals that compendial time-to-results (TTR) negatively impact manufacturing TAT
  - Example:
    - Sterility testing per USP<71>/Ph.Eur. 2.6.1 for Drug Product release -> 14 days TTR
    - Potency testing for Drug Product release -> 8 days TTR
    - Implementation of a rapid sterility test with 7-8 days TTR will help reducing manufacturing TAT
- Compendial test has very long TTR and robust alternative assays are available
  - Example:
    - Mycoplasma testing per Ph.Eur. 2.6.7 -> 28 days TTR
    - Mycoplasma PCR -> 1-2 days TTR

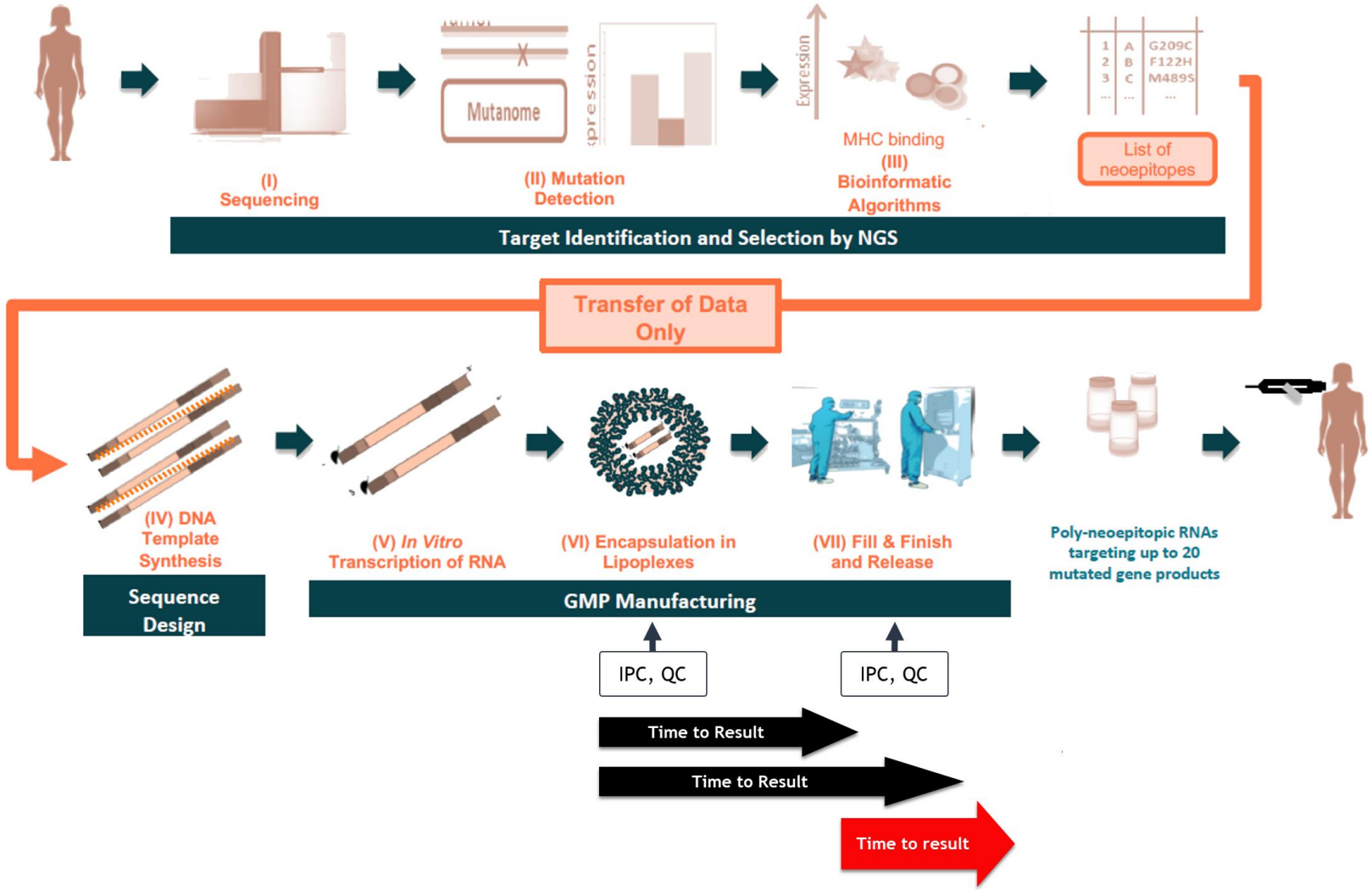
Autogene cevumeran: Delivery and mechanism of action

Autogene cevumeran is in partnership with BioNTech

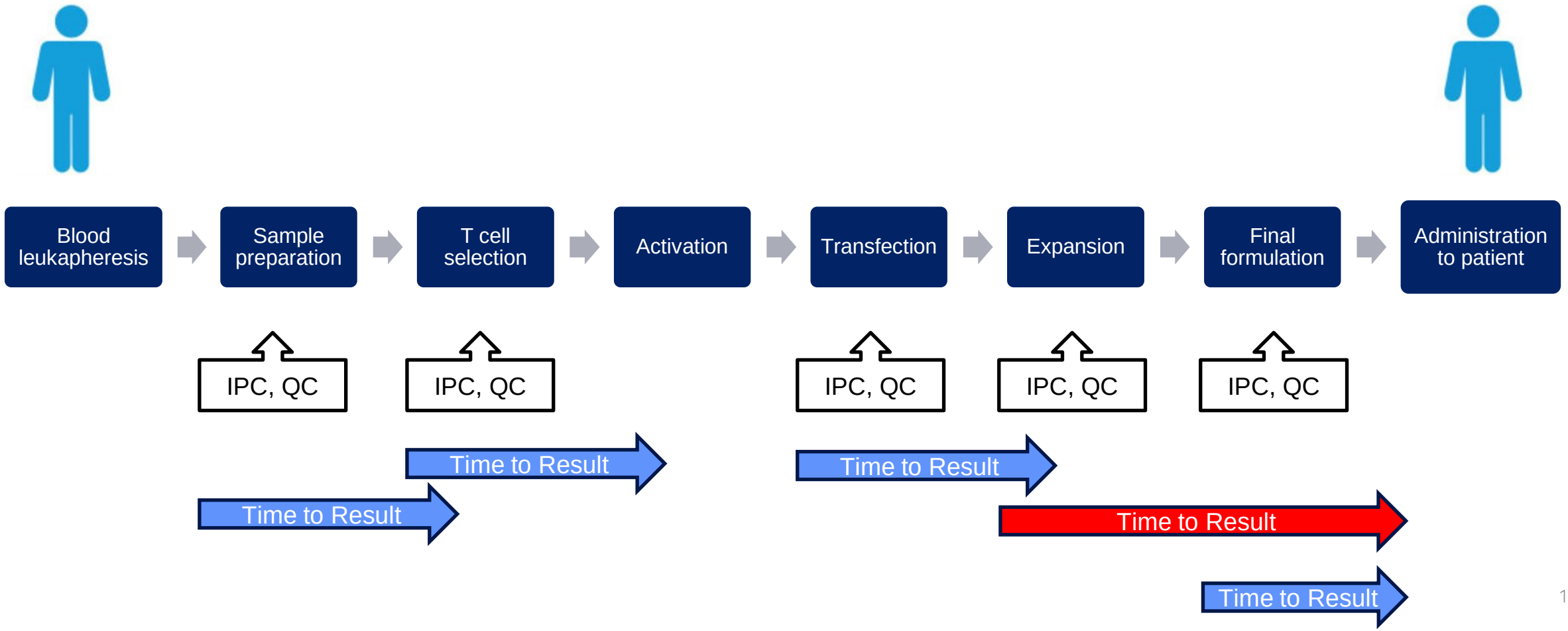




Mapping the autogene cevumeran End-to-End Process



Mapping an autologous T cell manufacturing process



The importance of raw material control

ATMP raw materials are different from raw materials used for traditional drug manufacturing in many ways and pose unique challenges

- ATMP raw materials are often
  - Animal derived
  - Non monographed
  - Not manufactured for GMP applications (e.g., R&D grade)
  - Single sourced

- ATMP material supplier/vendors are often
  - Small, specialized companies with roots in academia
  - Without a GMP quality system

The importance of raw material control

For many ATMP manufacturing processes tight microbial and viral control of raw materials is necessary to ensure manufacturing success

- Cell therapies are E2E aseptic processes without any terminal sterilization step for Drug Product
  - ➢Raw materials added to the process should not increase the risk of microbial or viral contaminations

For individualized ATMP's proper raw material testing can help simplifying the analytical control strategy (by reducing in-process control sampling) and improve manufacturing TAT

- Less testing on product batch level
  - ➢Each test is potentially TAT-critical (e.g., system suitability failure, OOS etc)
- More testing on raw material level
  - ➢Raw material batches are not patient/batch specific -> testing is not TAT critical

Specific considerations for media fill/aseptic process simulation for cell therapies

- ATMP Media fill/aseptic process simulation protocols are often more complex compared to traditional drugs
  - Cell therapy manufacturing is an E2E aseptic process
  - Complex manual operations
- Autologous T cell therapy manufacturing can use starting material from patients which is not sterile (intrinsic microbial contamination). Therefore APS mainly assess the risk of extrinsic contamination (from operational interventions).
- Special operator's qualification programs should be in place (operator APS)

Doing now what patients need next