EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Quality development considerations - Regulatory perspective

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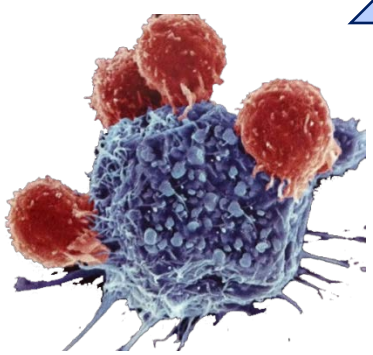
Genetically modified, cell-based cancer immunotherapies

GOAL modify immune cells to attack and clear tumor cells

APPROACH CAR-T –cells, TCRs, NKs / TANKs, TRUCKS,….

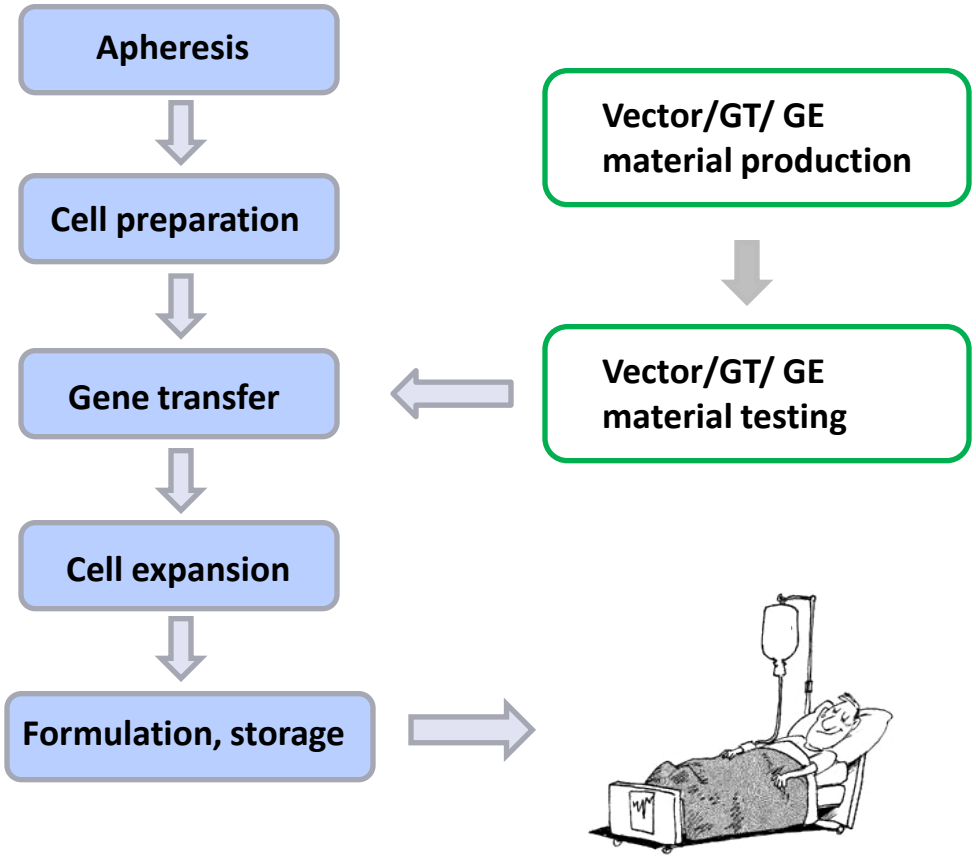
MEANS viral vectors, plasmids, gene editing

STATUS several products in clinical studies, but new technologies evolve fast



FUTURE more and more complex products, multiple modifications, off the shelf/allogeneic products safety switches, inductors, in vivo GE?

Cell-based cancer immunotherapies (GTMPs!)



Quality needs to be built-in within every step of the manufacturing process!

Apheresis

- window for collection and information on pre-treatments + possible impact on the cellular starting material
- donor testing, autologous vs. allogeneic
- method of cell collection → should collection systems be standardised or validate multiple approaches?
- acceptance criteria for the apheresis preparation
- controlled transportation to the manufacturing site;

Cell preparation

- which cells

- cell isolation (PBMCs) and enrichment, choice of the method

- activation of the cells required for signalling and transduction

- issues related to scale-up and automisation → comparability

→ suitable, specific markers to control the cell type
→ **product-related impurities, variability**
→ quality specifications for the cells
→ impurities, **e.g.** removal of beads - **impact on the quality of the product**
→ critical in-process parameters to be identified early on

- direct genetic manipulation or cryopreservation for later use

Vector/ GT/GE material production and testing

- Considerations for the ‘therapeutic sequence’ must be justified
- Starting material considerations
- cell bank/viral seed qualifications
- gene editing technologies: off-target effects
- viral safety and microbiological purity of starting and raw materials;
- release testing for vectors- including identity, titer, potency, purity

Gene transfer

- transduction, electroporation, gene editing…
- generation of control cells e.g. for microbiological purity testing?
- transduction / gene editing efficiency,
- need to demonstrate the genetic modification(s) are correct and overall genetic stability
- check persistence and genetic stability in patients

Cell expansion

- multiple expansion methods available, including specific process for gene-edited cells
- culture conditions and quality of the biological raw materials
- time in culture (max PDLs) to be justified based on product quality
- expansion process to be defined and validated

Formulation, storage

- formulation should not change the safety and efficacy of the product
- specific formulation studies may be needed for longer storage period
- quality and number of cells after storage
- considerations for frozen cells

Specific issues concerning the manufacturing process

- GMP and aseptic processing (GMP guideline for ATMPs)
- Vector Quality (draft Gene Therapy guideline)
- quality of critical raw materials (Ph.Eur. General text on biological raw materials for production of cell and gene therapy products)
- ability of the process to give clinically meaningful cell numbers
- mitigation of variability/consistency, validation of the process → limits for variability
- process changes and comparability

Quality control

- control strategy to be planned early on taking into consideration the limitations, but also all quality attributes that need to be controlled

- level of characterization to define QC tests

- impurities (product/process-related), purity and number of the intended cell type, viability; microbiological purity

- identity testing

- potency testing

- stability testing

- suitability of analytical methods and validation of key assays

Potency testing

- should follow mode of action;
  simple e.g. marker-based assays can be accepted for release provided that a more thorough assay package is available for process validation & comparability testing

- functional, cell-based assays challenging, if require materials from the donor for the assay (e.g. to demonstrate cytotoxicity)

- one option would be to have a functional (PoC) assay for characterisation (with 1-2 donor cells) and use it to correlate other methods → need a negative control to compare to the activation caused by external factors (cytokines, aAPCs…)

- possible release/comparability methods could be based on cell-surface markers, expression of the CAR-construct, substances secreted by the activated T-cells,…

- sensitivity (to detect subpotent batches) and specificity

Comparability testing

- where changes made to the production process, materials, etc. could lead to clinically significant changes in the final product

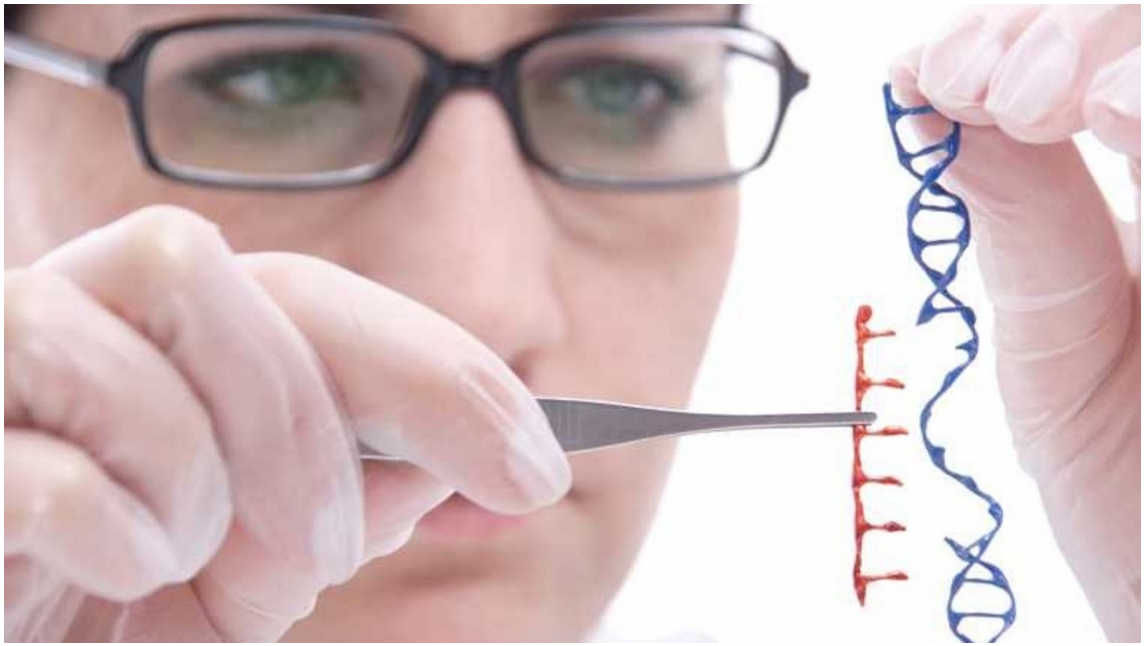
- critical parameters

- level of testing (release + characterisation), stability testing

- when would quality data alone be sufficient to demonstrate comparability of cells

Points for discussion

- apheresis: how to mitigate variability?
  should collection systems be standardised?
- cell bank/viral seed qualifications: control cells e.g. for microbiological purity testing?
- QC and release criteria, potency testing
- how to demonstrate comparability?
- Requirements for viral vector and finished medicinal product analysis regarding integration and specificity



Thank you for your attention!