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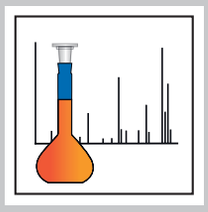

Highlights of Analytical Sciences in Switzerland

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An Introduction to Analytics for Autologous Cell and Gene Therapies

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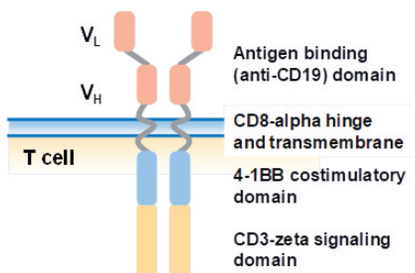
Autologous cell and gene therapies, such as the Chimeric Antigen Receptor Therapy (CAR-T), use the patient's own immune system to fight certain types of cancers. A patient's T cells are reprogrammed with a viral vector to express a transgene receptor, CAR, enabling them to destroy the cancer cells which express a particular antigen: B cells expressing CD19 (Cluster of Differentiation 19).

Leukapheresis material is collected and cryopreserved at the clinical site and then sent to the manufacturing facility where the enrichment and activation is taking place, making use of CD3/CD28 antibody-coated beads before T cell transduction with a lentiviral vector for genetic reprogramming. T cell expansion is the next step before bead removal, formulation and cryopreservation. Then, the cells are shipped back to the clinical site and the administration is taking place. In the patient, the antigen-binding domain recognizes CD19 on B cells. The CD3-zeta signaling domain initiates T cell activation and mediates antitumor activity.

Cell and gene therapy cell processing at the manufacturing site.

The quality control of such a therapy is very specific and 'customized', with biological/molecular methodologies being essential. For Identity testing, a Polymerase Chain Reaction (PCR) based test confirms the presence of the CAR transgene. Safety testing is key, to confirm there is no microbiological contamination and no residual virus DNA in the final product. Tested parameters are: bacterial endotoxins, sterility, mycoplasma, and determination of virus DNA by quantitative PCR. Purity testing includes cellular phenotyping by flow cytometry testing for viable T-cell percentage, transduction efficiency tested by CAR, quantitative PCR and cell viability test. For Impurity testing, residual beads are tested by microscopy, and CD19 B-cells are determined by flow cytometry. For Quantity, the cell count is measured and used together with the purity analysis to calculate viable cell number and dose. Finally, for Potency, CAR-expression by flow cytometry and release of IFNγ in response to CD19-expressing target cells is determined.



Mode of action: CAR-T cells express chimeric antigen receptors. V_L, V_H: light and heavy chain variable domain, respectively.

The laboratories for the execution of quantitative PCR test methods and the rooms for the cell-based assays are to be clearly separated from each other to avoid cross-contamination. Stability is necessary to assure the shelf life of the product. In addition, an important point to consider is the stability of samples and critical analytical reagents in the laboratory.

Cell and gene therapies offer the potential to transform medicine. Analytical tools and technology are key for ensuring the quality of the treatment being produced.

Definitions

T-cell: Type of lymphocyte that develops in the thymus gland.
B-cell: Type of white blood cell of the small lymphocyte subtype.
B-lymphocyte antigen CD19: Transmembrane protein encoded by the gene CD19.
The CD3 protein complex is composed of polypeptide chains. With the T-cell receptor (TCR) and the zeta chain, they form the TCR-CD3 complex, used to activate T lymphocytes.
CD28 is one of the proteins expressed on T cells that provide co-stimulatory signals required for T cell activation.
IFNγ: Dimerized soluble cytokine that is the only member of the type II class of interferons. Interferon-γ is involved in inflammatory processes. It has antiviral, immunostimulating and anti-tumor properties.

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