2. Car T-Cell Therapy- Science & Technology

Researchers at IIT Bombay addressed a critical challenge in CAR T-cell and other adoptive T-cell transfer (ACT) therapies

T-Cells- Structure, Types and Immunological Role

Origin and Development

T-cells (T-lymphocytes) are a subset of lymphocytes derived from hematopoietic stem cells in the bone marrow. They mature in the thymus gland, which is why they are called "T" cells. During maturation, they undergo positive and negative selection, ensuring they recognize foreign antigens while avoiding self-reactivity (central tolerance).

Major Types of T-Cells

Cytotoxic T-cells ($CD8^+$)

1. Directly kill infected or malignant cells.
2. Release perforin and granzymes to induce apoptosis.
3. Critical in anti-viral and anti-cancer immunity.

Helper T-cells ($CD4^+$)

1. Coordinate immune responses.
2. Activate B-cells (antibody production), macrophages, and cytotoxic T-cells.
3. Subtypes- Th1, Th2, Th17, Tfh depending on cytokine profile.

Regulatory T-cells (Tregs)

1. Suppress immune responses to prevent autoimmunity.
2. Maintain immune homeostasis.

Memory T-cells- Provide long-term immunity after infection or vaccination.

Role in Cancer Immunology- Recognize tumor antigens presented via MHC molecules. Tumors often evade T-cell detection through immune checkpoint pathways (e.g., PD-1/PD-L1). This forms the basis for modern immunotherapies.

CAR T-Cell Therapy – Concept and Mechanism

Definition

CAR-T therapy is a form of adoptive cell transfer immunotherapy in which a patient's T-cells are genetically engineered to express Chimeric Antigen Receptors (CARs) that specifically target cancer cells.

Step-by-Step Procedure

Leukapheresis- T-cells are collected from the patient's blood.

Genetic Engineering- A viral vector (usually lentivirus or retrovirus) inserts a gene encoding CAR.

CAR structure includes-

1. Antigen-binding domain (derived from antibody)
2. Transmembrane domain
3. Intracellular signaling domains (CD3ζ, costimulatory molecules like CD28 or 4-1BB)

Expansion- Engineered T-cells are multiplied in vitro under controlled laboratory conditions.

Reinfusion- Modified CAR-T cells are infused back into the patient after lymphodepletion chemotherapy.

Tumor Targeting- CAR-T cells recognize tumor antigen (e.g., CD19 in B-cell cancers) independent of MHC. Direct cytotoxic destruction of cancer cells.

NexCAR19 – India's Indigenous CAR-T Innovation

Developed by Immuno ACT, incubated at IIT Bombay. NexCAR19 targets CD19 antigen in B-cell malignancies (e.g., acute lymphoblastic leukemia, lymphoma).

It is the world's first humanised CAR-T product, meaning-

1. Reduced immunogenicity.
2. Lower risk of severe immune rejection.

Major breakthrough in India's biotech ecosystem. Significantly reduces cost compared to imported CAR-T therapies (which can cost ₹3–4 crore).

Benefits of CAR-T Cell Therapy

Targeted Precision

1. Selectively attacks tumor cells expressing specific antigens.
2. Minimal off-target toxicity compared to chemotherapy and radiotherapy.

Personalized Medicine

1. Autologous therapy (uses patient's own cells).
2. Tailored to individual cancer profile.

Long-Term Immunological Memory

1. Engineered cells can persist for years.
2. Reduces recurrence risk.

Reduced Overall Treatment Burden

1. Fewer cycles compared to chemotherapy.
2. Potentially shorter long-term hospitalization.

Expanding Therapeutic Frontiers

Research ongoing for-

1. Multiple myeloma
2. Solid tumors (lung, breast, brain cancers)
3. Autoimmune diseases

Indigenous Affordability

1. NexCAR19 enhances accessibility in India.
2. Supports Atmanirbhar Bharat in biotechnology.

Latest Technological Developments

3D Fibrous Scaffold Innovation

Scientists are using **3D fibrous scaffolds** that mimic the natural extracellular matrix.

Advantages-

1. Faster T-cell expansion.
2. More physiologically relevant growth environment.

Cell Recovery Challenge

1. T-cells adhere strongly to scaffolds.
2. Retrieval without damaging functionality is critical.

Recovery Methods Tested

1. Manual flushing – less effective.
2. TrypLE enzyme – harsher, reduced cell viability.
3. **Accutase** – gentler enzyme.

Key Finding

Accutase preserved-

1. Cell viability
2. Cytotoxic potency
3. Immune functionality

Implication

1. Improves reliability and scalability of adoptive T-cell therapies.
2. Potential to reduce production costs.

Disadvantages and Challenges

Severe Side Effects

Cytokine Release Syndrome (CRS)

1. Massive immune activation.
2. Symptoms- Fever, hypotension, organ failure.

Neurotoxicity (ICANS)- Confusion, seizures, cerebral edema.

High Cost and Infrastructure Demand

1. Requires GMP-certified labs.
2. Needs skilled immunologists and hematologists.

Tumor Antigen Escape

1. Cancer cells may lose CD19 expression.
2. Leads to relapse.

Limited Success in Solid Tumors

Challenges include-

1. Tumor microenvironment suppression
2. Poor T-cell infiltration
3. Antigen heterogeneity

Immunosuppression Risks- Increased susceptibility to infections.

Long-Term Monitoring

1. Risk of secondary malignancies.
2. Requires years of follow-up.

Importance for India

1. Reduces dependence on imported biotech products.
2. Strengthens domestic bioeconomy.
3. Promotes advanced research in synthetic biology and gene therapy.
4. Potential to democratize advanced cancer care.

Way Forward

Enhancing Safety

1. Better CRS prediction models.
2. Improved CAR constructs with safety switches.

Expanding Indications

1. Dual-target CARs to prevent antigen escape.
2. Research in solid tumors.

Automation & Cost Reduction

1. Closed-loop manufacturing systems.
2. AI-assisted cell engineering.

CRISPR Integration- Gene-editing to create universal "off-the-shelf" CAR-T cells.

Scaffold Implantation Strategy- Direct implantation of T-cell-loaded scaffolds into tumor sites (future research).

Conclusion

CAR-T cell therapy represents a paradigm shift from conventional cytotoxic oncology to precision immuno-oncology. With innovations like NexCAR19 and 3D scaffold-based cell engineering, India is emerging as a significant player in next-generation cancer therapeutics.

Source- https-//indianexpress.com/article/explained/explained-health/cancer-immunotherapy-t-cells-recovery-10517380/