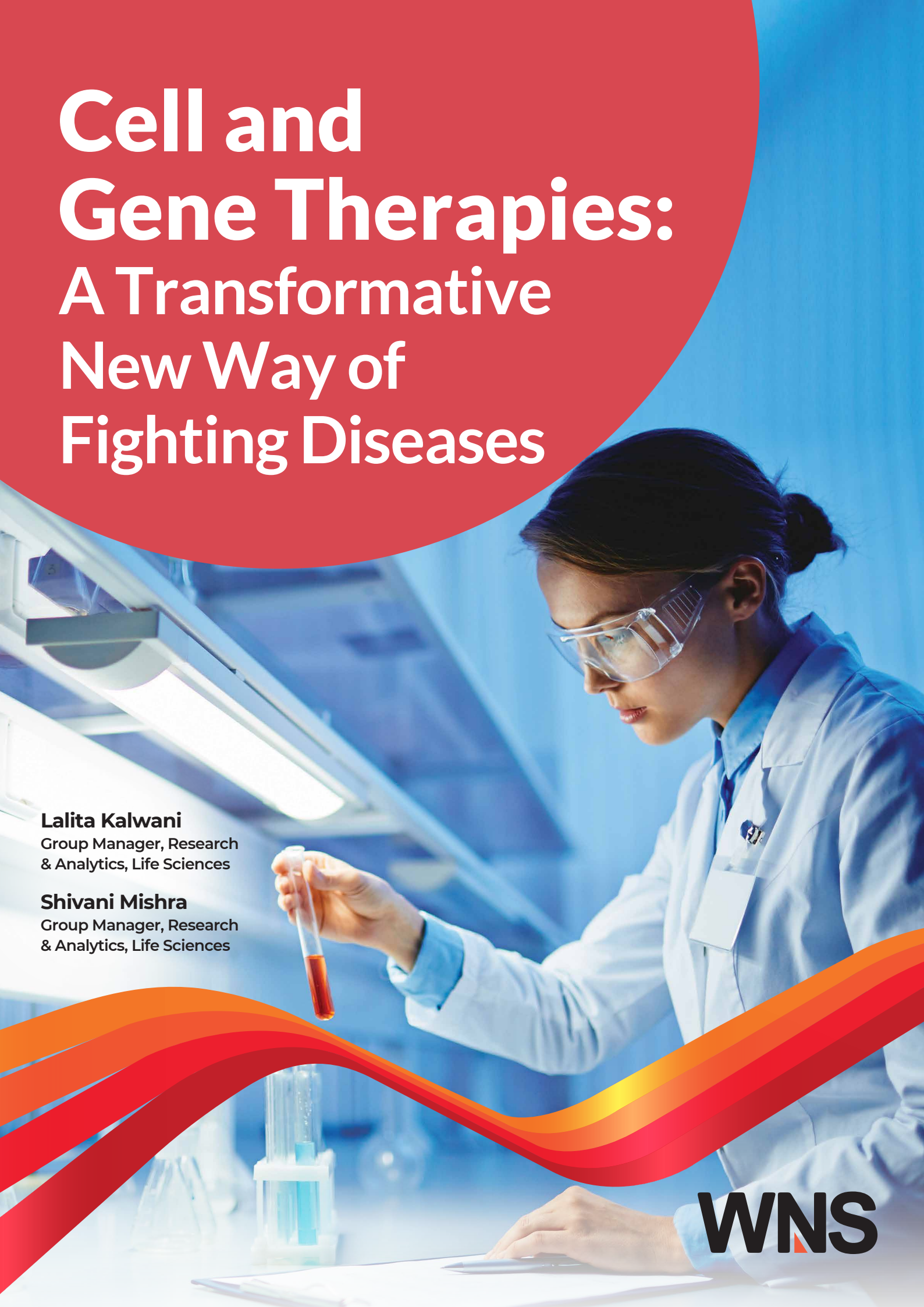
Cell and Gene Therapies: A Transformative New Way of Fighting Diseases



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According to forecasts by Evaluate Pharma, the market for Cell and Gene Therapies (CGT) is expected to reach USD 45 Billion by 2026, rising at a CAGR of 63 percent over 2021-2026. This rapid global expansion is being fueled by the increasing prevalence of chronic diseases, a favorable regulatory environment, technological advancements, and a rise in R&D funding. Worldwide, there are around 2,400 ongoing clinical trials in CGTs and the FDA anticipates Investigational New Drug (IND) approvals for over 200 CGTs by 2025 – that is, some 10-20 CGT approvals every year.

Cell and gene therapies are thus at the very center of healthcare innovation and among the fastest growing therapeutic modalities. CGTs use the body's own systems – either the cellular immune system or the repair and replace mechanisms for defective/missing genes – to restore health. This offers an astounding curative potential in the treatment of cancers, chronic and rare genetic disorders, ophthalmologic conditions and neuro-degenerative disorders, to name just a few.

Furthermore, CGTs require a considerably reduced frequency of administration compared to other therapies. Often, a one-time administration is sufficient. This provides a distinct advantage over currently available treatment options in improving both the overall quality and length of a patient's life.
There are however concerns on CGTs' long-term efficacy and safety, which warrant more scientific and clinical research. These include immunogenicity concerns such as Cytokine Release Syndrome (CRS) and CAR-related Encephalopathy Syndrome (CRES). Other challenges around CGTs include high cost of therapy, complex manufacturing operations, enabling patient access, tapping and managing supply chains, and developing a network of Health Care Providers (HCPs).

Most drug developers find it challenging to keep track of the rapid clinical, regulatory and market changes in this sector. Third-party knowledge providers are thus rising up to help developers navigate the complex landscape of CGTs. The trend shows that they can provide end-to-end consultation and support, from early development planning through clinical trials and regulatory hurdles to post-marketing follow-up strategies. Collaborating with proactive knowledge-providers, who can provide customizable and digitally integrated platform solutions, has become the need of the hour for evolving the CGT business without straining budgets and in-house resources.

Advances in Next-generation Cell Therapies

Cell therapies involve the transfer of modified cells into a patient's body to grow, replace or repair damaged tissue to treat a disease. In the process, a specific set of cells is collected from the human body, re-engineered and then re-injected into the patient.

Figure: Types of Cell Therapies, with Examples

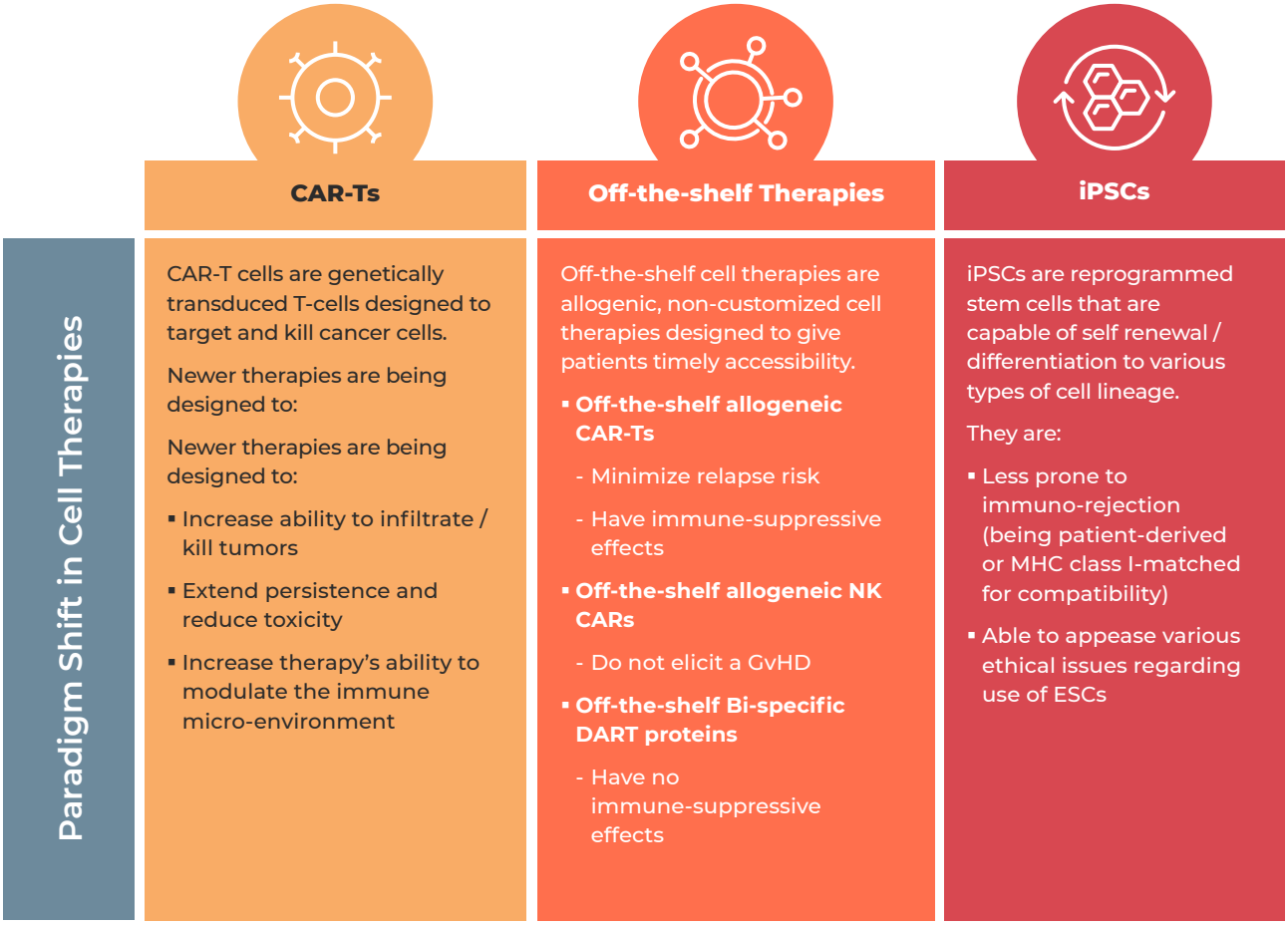
Based on Source	Based on Cell Type		Combination Therapies
	Stem Cell Therapies	Non Stem Cell Therapies	
Autologous Cells derived from a patient's own cells; FCR001 (Talaris / induce immune tolerance transplant / Ph II)	**Immune Adult Stem Cells (ASCs)** ▪ **Hematopoietic stem cells (HSCs):** ALLOCORD (St. Louis Cord Blood Bank / hematopoietic progenitor stem cell transplant) ▪ **Skin stem cells (SSCs):** HOLOCLAR (Holostem / limbal stem cell deficiency)	**Immune cells** ▪ **Dendritic cells (DCs):** Sipuleucel-T (Dendreon / prostate cancer) ▪ **Natural killer (NK) cells:** GSK 794 (GSK / Advanced Round Cell Liposarcoma / Ph II)	**Multicellular Therapies** Therapies containing at least two stem cell and / or non-stem cell types cultured from isolated cells. ▪ **Keratinocytes + Fibroblasts:** GINTUIT (Organogenesis / Mucogingival) ▪ iPSC + NK cells: iPSC-derived NK Cell Program (Fate therapeutics / AML)
Allogenic Cells derived from donor cells: Kymriah (Novartis / ALL, DLBCL)	**Pluripotent stem cells (PSCs)** ▪ **Embryonic stem cells (ESCs):** ESC derived Retinal Pigment Epithelium Cells (Regenerative Patch Technologies / Dry AMD / Ph I/II) ▪ **Induced pluripotent stem cells (iPSCs):** iPSC derived cardiomyocytes (Help Therapeutics / CHF / Ph I) ▪ **Epiblast stem cells (EpiSCs):** CHIR99021 – a GSK 3β inhibitor (USC)	**Non-Immune cells** ▪ **Chondrocytes:** Spherox (CO.DON AG / cartilage defects) ▪ **Pancreatic islet cells:** VX-880 (Vertex / T1D / Ph I / II) ▪ **Fibroblasts:** LAVIV (Fibrocell Science / nasolabial fold)	**Immune CAR-T cells in combination with other therapies** ▪ **Bi-specific T-cell engagers (BiTEs)** – Blincyto / blinatumomab – a CD19*CD3 T-Cell Engager (Amgen, ALL) ▪ **Trispecific killer cell engagers (TriKEs)** – GTB-3550 CD16*IL-15*CD33 (GT Biopharma / AML, MDS / Ph I)
	Cancer stem cell (CSCs) ▪ Magrolimab (anti-CD47 mAb) ▪ CIRMTUZUMAB (anti- ROR1 mAb)	**Adoptive cell therapies** ▪ **Chimeric antigen receptor CAR-T cells:** Kymriah (Novartis / ALL, DLBCL) ▪ **Tumor-specific T-cell receptor (TCR):** mbIL-15 TCR Program (Alaunos / solid tumors / Ph I) ▪ **Tumor-infiltrating lymphocytes (TILs):** ITIL-168 (Instil Bio / melanoma / Ph II)	

Among different cell therapies, CAR-Ts are the most advanced technology reaping commercial success. They are largely generated using autologous T-cells, which face lower immunological rejection (or GvHD) than allogenic therapies. However, allogeneic cell therapies offer more potential when it comes to cost effectiveness, ready availability and higher quality of end product. Thus, the trend in clinical development is shifting towards allogenic therapies with their greater off-the-shelf advantage.

It bears repeating that both types of therapies are associated with certain levels of risk for toxicity-related events such as CRS and CRES, along with a lack of response or reduced efficacy over time.

This is where iPSCs show potential. Induced pluripotent stem cells (or iPSCs) are harvested from the tissue of the patient who needs the transplant. This removes the possibility of immune rejection and also allays ethical concerns around donors. Currently, iPSCs are being explored as a theraputic option for neurological diseases, heart diseases and blood diorders.

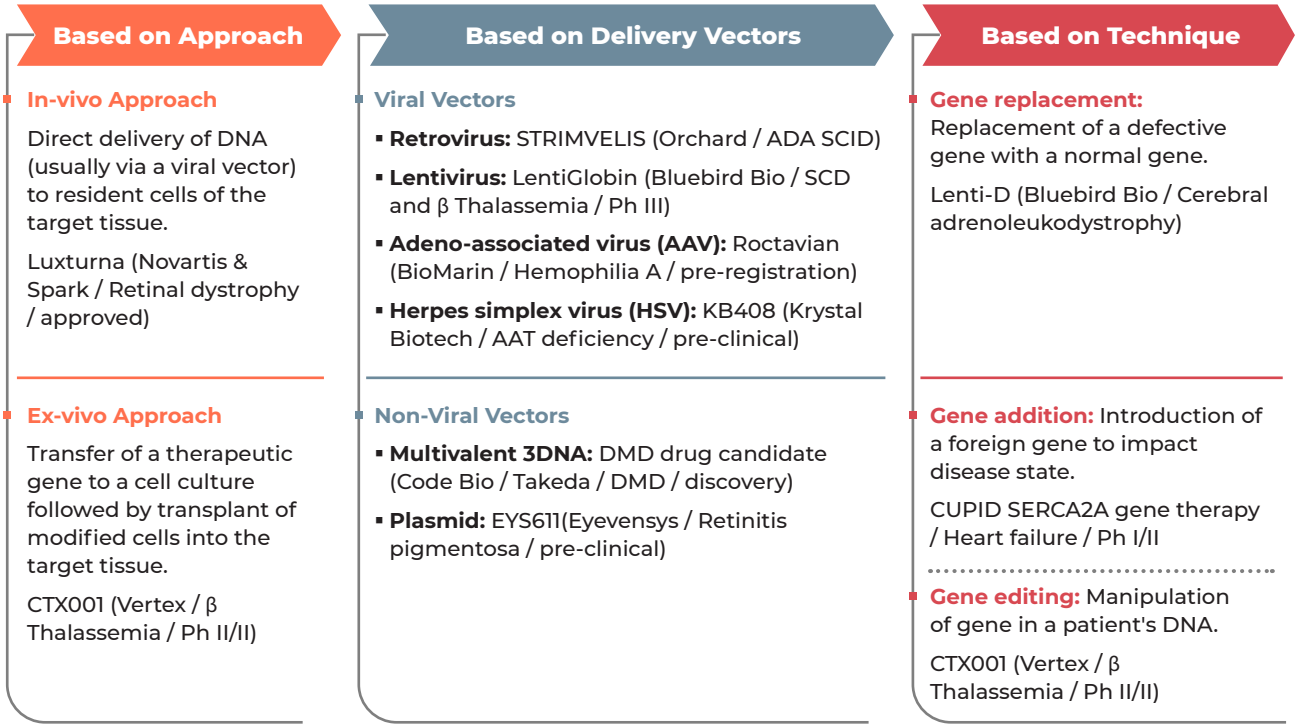
Figure: Emerging Technologies in Cell Therapies



Advancements in Gene Therapies

As the name suggests, gene therapy involves the introduction, removal or change in genetic material to treat a disease.

Figure: Types of Gene Therapies with Examples



Viruses are the most widely used vector for gene therapy due to their intrinsic flexibility and the efficiency with which they deliver the gene. AAV vectors dominate the delivery modality space owing to their well-characterized tissue selectivity. On the other hand, Lentivirus Vectors (LVs) offer advantages due to their ability to transduce non-dividing cells, permanently transform target cell genome and allow stable, long-term transgene expression. LVs have shown potential in the treatment of primary immunodeficiency diseases, hemoglobinopathies, B-cell leukemia and neurodegenerative diseases.

The trend in gene therapies is advancing towards more customizable gene editing. Recent developments include CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats), which is a new targeted approach for DNA repair/replacement with the ability to modify multiple genes at the same time.

Other gene-editing tools that work by cutting specific sequences of DNA include Zinc-finger Nucleases (ZFNs) and Transcription Activator-like Effector Nucleases (TALEN). Thanks to being cost-effective and efficacious, CRISPR is more extensively used for gene editing than ZFNs and TALENs. CRISPR is, however, linked to off-target effects. Notably, all three techniques suffer from constraints in targeting, imperfect specificity and gene-targeting. Several strategies are being worked upon to reduce the off-target effects, including biased or unbiased off-target detection, cytosine or adenine base editing, prime editing, dCas9, Cas9 paired nickase, ribonucleoprotein (RNP) delivery and truncated gRNAs.

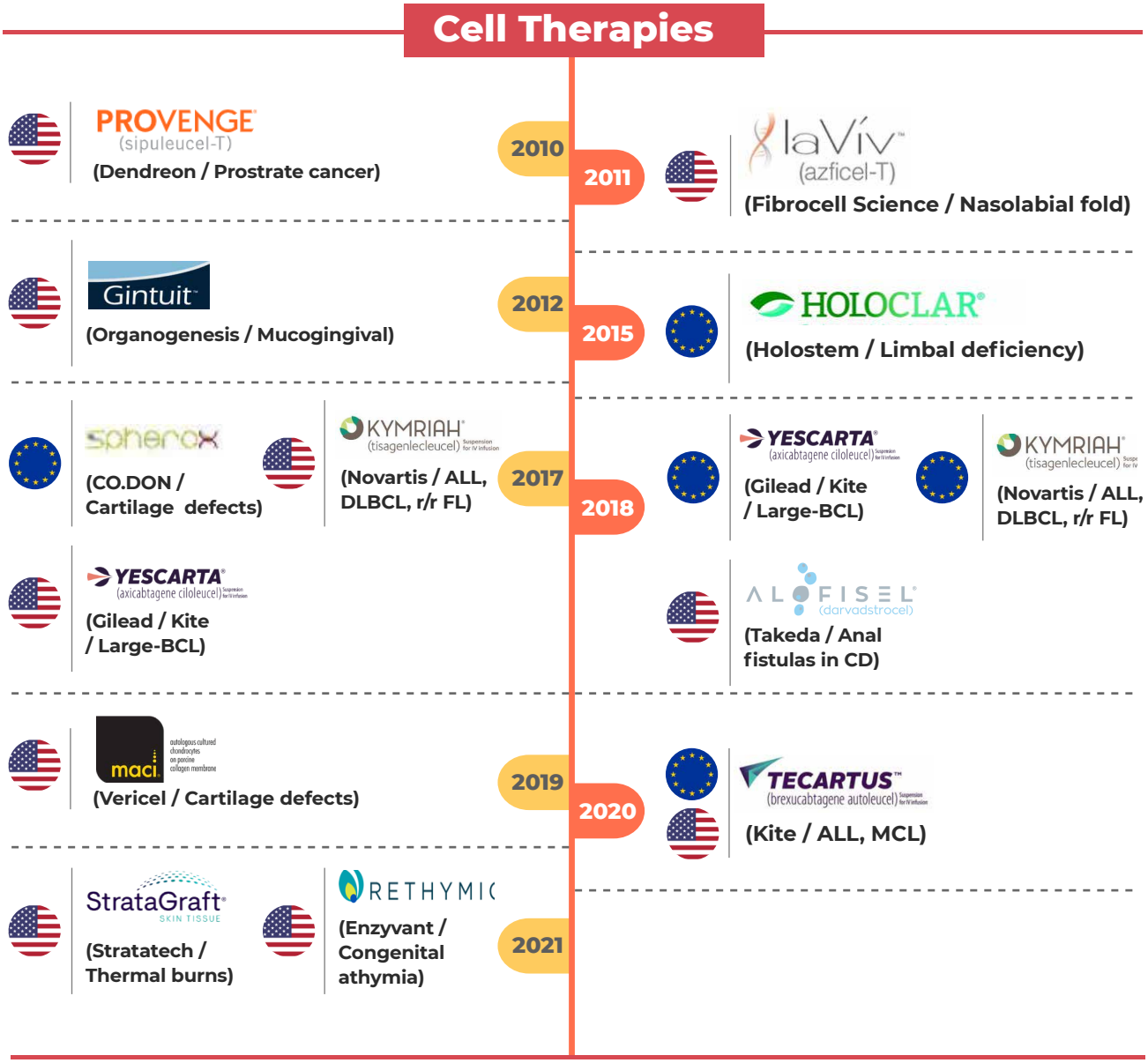
Figure: Emerging Technologies in Gene Editing

ZFN (Zinc-finger Nucleases)	TALEN (Transcription Activator-like Effector Nucleases)	CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)
ZFNs facilitate targeted editing of the genome using a FokI nuclease, which creates **double-strand breaks** by recognizing a **specific trinucleotide** sequence	TALENs enable targeted editing of the genome using a FokI nuclease, which creates **double-strand DNA breaks** by recognizing a **single nucleotide or a sequence**	CRISPR targets genome editing through Cas9-mediated **single/double DNA breaks** using sgRNA and tracrRNA for base pairing and **a protospacer adjacent motif (PAM) sequence** to recognize target DNA
Difficult to target non-G-rich sites with ZFN's	5' targeted base must be a T for each TALEN monomer	Targeted site must precede a PAM sequence

Key Players in Cell and Gene Therapies

The CGT market is concentrated around rare genetic disorders and hematological malignancies / lymphomas. The big players in this field are, notably, Gilead, Novartis, Roche (Spark), BMS and Janssen. Since the approval of CAR-T cell therapies (Kymriah and Yescarta for DLBCL in 2017), several developers have been expanding their focus to other hematological malignancies. They are also looking to develop advanced and next-gen options for recently approved genetically modified cell therapies for lymphomas (e.g. Juno Therapeutics' Breyanzi®, BMS' Abecma and J&J's Carvykti). The figure below gives an overview of currently approved CGTs in the US and EU.

Figure: Approved CGTs in the US and EU



Note: Gene therapy includes genetically modified cell therapies

Gene Therapies

2016

Strimvelis®
(GSK / Orchard / ADA-SCID)

2017

LUXTURNA™ voretigene neparvovec-rzyl
(Novartis / Spark / Retinal dystrophy)

2018

LUXTURNA™ voretigene neparvovec-rzyl
(Novartis / Spark / Retinal dystrophy)

2019

zynteglo™
(Bluebird Bio / β Thalassaemia)

zolgensma® (onasemnogene abeparvovec-xioi)
(Novartis / SMA)

2020

zolgensma® (onasemnogene abeparvovec-xioi)
(Novartis / SMA)

libmeldy™ (atidarsagene autotemcel)
(Novartis / SMA)

2021

Abecma® (idecabtagene vicleucel)
(BMS / Multiple Myeloma)

Breyanzi®
(Juno Therapeutics / Large BCL)

2022

Breyanzi®
(Juno Therapeutics / DLBCL/PMBCL / FL3B)

CARVYKTI™ (ciltacabtagene autoleucel)
(Janssen / Multiple Myeloma)

skysona™
Bluebird Bio / CALD

zynteglo™
Bluebird Bio / β Thalassemia

Note: Gene therapy includes genetically modified cell therapies

The commercial success of CAR-Ts is impacted by its reimbursement, pricing and market access challenges in both the US and EU markets. Bluebird Bio's Zynteglo (gene therapy for β thalassemia) was granted conditional approval in 2019 but was withdrawn in 2021 from the EU market due to reimbursement challenges. This was approved by the FDA on August 17, 2022. With the right strategic partner, developers can accelerate clinical development and ensure commercial success by tailoring their clinical, regulatory, and market access strategic needs.

Evolving Trends in Clinical Development

While hematological malignancies have reigned over the CGT space for decades, clinical development is beginning to shift towards rare chronic genetic disorders, ophthalmologic conditions and neuro-degenerative disorders. Emerging novel therapies are also implementing advanced technological solutions to improve the effectiveness and lower the risks associated with CGTs.

CAR-Ts and combinations of technologies to enhance potency and targeting

The bispecific γδ T-cell engager, being developed by Lava Therapeutics for antibody targeting Vγ9Vδ2 on γδ T-cells and EGFR on tumors cells, demonstrated strong activation of Vγ9Vδ2 T cells and cytotoxic lysis of tumor cells in a mouse xenograft model.

Delivering genetic material to cells / targets

Donated cells are now being modified in such a way that they are not recognized as foreign material by the immune system.

Development of control switches for targeted delivery

Autolus Therapeutics is developing Tunable CAR-T cell therapy for tetracycline mediated disruption of protein-protein interaction.

[Tunable receptors can turn on and off with the delivery of a small molecule and use Boolean combinations of and/or/not receptors, or modular targeting receptors.]

Incorporation of biomarker profiles and AI to CGT

This will aid in correlative studies analysis as well as product and process development and will be used to help determine which patients may benefit from advanced therapies.

Utility and safety of various gene-editing platforms

Such platforms can knock out checkpoint receptors on immune cells that tumors utilize to turn-off immune responses e.g. AAV–Cpf1 developed by Yale University can integrate CAR into TCRα constant chain (TRAC) and knock out PD-1 to turn off immune responses.

New paradigm of decentralized clinical trial solutions

New start-ups, such as Jeeva Informatics Solutions, are emerging with AI-based digital solutions for the management of decentralized GT trials. This is going to aggregate the entire clinical trial processes virtually, thus accelerating their speed and save time.

The design considerations for CGT clinical trials often differ from those of other pharmaceutical products in terms of trial design, clinical endpoints, long-term follow-up and CMC requirements. To minimize regulatory setbacks, developers are engaging with regulators from early phase of development to devise effective clinical trial designs, enabling accelerated approval and adequate post-market confirmatory studies. Regulatory bodies in the US and EU have issued several guidelines for preclinical testing, product development and clinical trial design.

Advanced therapeutic modalities like CGTs require special regulatory focus and a strong partner with deep expertise in all aspects of clinical and regulatory framework to facilitate smooth regulatory submissions and thereby reduce time-to-market.

Figure: Key Features of CGTs that Influence Clinical Trial Design

Biological Activity	Immunogenicity	Invasive Procedures	Endpoints Assessment	Sample Size
▪ Possibility of prolonged biological activity, after even a single administration of CGTs - Results in prolonged AEs including CRS ▪ Long-term follow-up studies are continued even after approval ▪ Up to 5 years for studies using AAV vectors and up to 15 years for integrating vectors and genome-editing products	▪ High potential for inducing immunogenicity and other non-targeted effects ▪ Cell therapy: tumor formation, migration to non-target sites ▪ Gene therapy: immune response to vectors, insertional mutagenesis	▪ Need for relatively invasive procedures (sometimes involving devices) for administration of certain types of CGT products ▪ Associated procedural risks	▪ Certain endpoints such as MTD are relatively straightforward for small molecules ▪ However, considerations are more complex and wide-ranging, and starting doses are often small ▪ Use of biomarkers, surrogate and intermediate endpoints are being considered for accelerated approval of CGTs E.g., factor VIII activity is considered as surrogate endpoint for hemophilia vs ABR (traditional endpoint)	▪ CGTs are often developed for rare diseases, hence large RCTs are not feasible ▪ Consolidating the phase I, II, and III processes into phase I, phase II/III, and post-approval trials is becoming common

Conclusion

We believe CGTs are likely to play a key role in enabling a paradigm shift from current treatment options. Given the recent advances in the clinical development of next generation CGTs, we see their substantial upside potential. Although initial drug approvals have focused on relatively small patient groups, oncology indications and rare diseases, a robust CGT pipeline is steadily moving towards trials in non-oncology indications and other therapeutic areas.

CAR-T dominates cell therapy, but the approved therapies are restricted to heme malignancies. Emerging Adoptive Cell Therapies (ACTs) and off-the-shelf therapies are gaining momentum owing to improved persistence and enhanced effectiveness with ACTs and quick patient access with off-the-shelf therapies.

Gene therapies offer the clear advantage of a one-time treatment with disease curing potential. However, they are linked to many risks including off-target effects and lack of durability of response. The recent development of genome editing technologies, including ZFNs, TALENs and CRISPR have substantially improved the ability to make precise alterations in genomes to correct or introduce genetic modification for treating diseases that are refractory to traditional therapies.

It is becoming imperative for companies developing CGTs to plan clinical trial designs in discussion with regulatory bodies and generate robust long-term efficacy and safety clinical trial data to speed up the regulatory approvals process. Robust data would also support HTA assessment, thereby enabling early market access.

If CGTs have to succeed, then pharmaceutical companies need to closely work with regulatory agencies, manufacturing groups, suppliers, payer organizations and healthcare systems. All these stakeholders must work together to accelerate and streamline the development process of CGTs, thereby reducing the time-to-market for these potential curative treatment options.

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