REVIEW ARTICLE

# Next Generation Stem Cells and their Implications in Cancer Therapy

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## Abstract

Stem cells have been implicated for decades in the treatment of hematological malignancies. These cells when isolated from the bone marrow, adipose tissue, or foetal tissue are deemed as the *first generation* of stem cells. The turn of the century saw the discovery of the *second generation* of stem cells such as the human Embryonic Stem Cells (hESCs) and induced Pluripotent Stem Cells (iPSCs).

Advances in gene editing technology, in the past decade, have stimulated the rise of *next-generation* stem cells. Recent studies exploit the tumour tropism, multi-lineage differentiation, and auto-renewal capability of stem cells, and combine it with molecular biology techniques, to create potent anti-cancer therapies. Stem cells have been modified to have low immunogenicity and are thus being used as 'trojan horses' for the targeted, intra-tumoral delivery of anti-cancer drugs.

Presented here is a review on the techniques employed in the creation of the next generation of stem cells and their applications in anti-cancer drug delivery and immunotherapy.

**Keywords:** Tumor Tropism, Stem Cells, iPSCs, Next Generation Stem Cells, MSCs, Drug Delivery, Gene editing, Immunotherapy

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## Introduction

Stem cells can be defined as biological units capable of self-renewal, and multi-lineage differentiation[1]. These cells have extensive therapeutic potential as well as applications in tissue repair and regeneration[2].

Based on their source stem cells can be classified as embryonic, foetal, or adult stem cells[1]. Adult stem cells include Haematopoietic Stem Cells (HSCs), Mesenchymal Stem Cells (MSCs), and differentiated somatic cells that can be re-engineered to produce induced Pluripotent Stem Cells (iPSCs)[2].

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**Stem Cells and Oncology:** In the field of Oncology, naturally occurring haematopoietic stem cells, isolated from the bone marrow, have been used for decades in the treatment of blood cancer[3]. Research into the genetics of Human Leukocyte Antigen (HLA) has directly lead to improved donor selection, thus enabling routine use of HSCs in the clinic[4]. Now greater than 50,000 bone marrow transplants occur annually across the globe[5].

**Mesenchymal Stem cells:** offer ease of isolation due to their countless sources including bone marrow, adipose tissue, umbilical cord blood, and dental pulp among others[6]. No MSC therapy has yet been approved for cancer treatment. However, there are 25 clinical trials currently underway globally to explore the therapeutic potential of MSCs in oncology[7].

While HSCs and MSCs are multipotent - able to differentiate into specific cell lineages, iPSCs are pluripotent and can potentially form any cell of the human body[8]. Somatic cells are re-engineered using only four transcription factors, namely Oct3/4, Sox2, c-Myc, and Klf4, to exhibit embryonic stem cell-like properties[9]. IPSCs have enormous potential in cancer immunotherapy due to their long retention, self-renewal, and multi-lineage differentiation capabilities. Some key clinical trials on the applications of iPSCs and MSCs in cancer treatment are shown in Table 1.

**Next Generation Stem Cells:** Recent advancements in gene editing technology such as CRISPR are giving rise to a new generation of stem cells. Such gene-edited stem cells can escape immune recognition, possess antigenic specificity, and execute cytotoxicity. They do so while still retaining the longer retention times and *tumour trophic* properties of stem cells.

Tumour Tropism is a key ability of stem cells, allowing them to home to primary and metastatic tumour locations, and also cross the blood-brain barrier[10]. This property is being utilized for the *targetted delivery of anticancer agents*[11]. These anti-cancer agents include prodrug-converting enzymes, apoptosis-inducing factors, oncolytic viruses, etc[2]. Delivery of therapeutic agents such as Interferons, immune checkpoint inhibitors, and iPSC-derived cytotoxic cells is also influenced by this inherent

**Table-1:** Stem Cells based Clinical Trials for Cancer Therapy.

| S. No. | Therapy | Study | Antigen Specificity | Disease | Stage of Development | Reference |
|---|---|---|---|---|---|---|
| **iPSC Derived Therapies** | | | | | | |
| 1 | CNTY-101 (CAR iNK) | ELiPSE-1 | CD-19 | R/R B-cell malignancy | Phase 1 | NCT05336409 |
| 2 | 4G7-CARD T cells | CARD | CD19 | Relapsed B-cell malignancy | Phase 1 | NCT02893189 |
| 3 | FT576 (iNK) | FT576-101 | BCMA | R/R Multiple Myeloma | Phase 1 | NCT05182073 |
| 4 | FT516 (iNK) | Intraperitoneal FATE | B7-H3 | Ovarian Cancer | Phase 1 | NCT04630769 |
| 5 | FT500 (iNK) | FT 500-101 | | Advanced Solid Tumours | Phase 1 | NCT03841110 |
| **MSC Derived Therapies** | | | | | | |
| 6 | MSC expressing TRAIL | TACTICAL | Lung Cancer | Metastatic NSCLC | Phase I/II | NCT03298763 |
| 7 | AloCelyvir (MSCs carrying Icovir-5 -oncolytic adenovirus) | PULSE-UM | pRB | Metastatic Uveal Melanoma | Phase I/II | NCT05047276 |
| 8 | MSC11FCD (suicide gene-cytosine deaminase-CD) | MSC11FCD-GBM | Glioblastoma | Recurrent Glioblastoma | Phase 1 | NCT04657315 |
| 9 | MSC-DNX-2401 (oncolytic adenovirus) | MSC-DNX-2401 | Brain cancer | Recurrent High-Grade Glioma | Phase 1 | NCT03896568 |
| 10 | Descartes-25 (MSC secreted bispecific antibody and IL-12) | Descartes-25 | BCMA, Secrete IL-12 | R/R Multiple Myeloma | Phase I/IIa | NCT05113342 |

**anti-B-cell maturation antigen (BCMA)*

property of stem cells.

A hurdle in the transplantation of stem cells is their genetic instability and tumourigenicity[12]. Cell therapy products have a prolonged half-life, thus it is essential to ensure patient safety before entering clinical trials. The incorporation of a suicide gene has shown selective destruction and elimination of these cells upon in-vivo activation[13]. The most common suicide genes used in cellular therapies are Herpes-simplex- virus thymidine-kinase (HSV-TK), and inducible-caspase-9 (iCas9)[14].

**Tools to Create Next-Generation Stem Cells:** Stem cells are modified in-vitro or enhanced safety, efficacy, and for specific clinical applications.

The gene editing methods currently being used for creating next-generation stem cells include the use of viral vectors such as lentiviral vectors derived from Human Immunodeficiency Virus[15], specific endonucleases such as transcription activator-like effectors nucleases (TALENs), zinc finger nucleases (ZFNs), and clustered regularly interspaced short palindromic repeat (CRISPR)/CRISPR-associated system 9 (CRISPR-Cas9)[16].

Apart from gene editing, the use of bio-orthogonal chemistry can be employed for the creation of next-generation stem cells. This implies cell surface modification using copper-free click chemistry for targetted delivery of anti-cancer drugs[17].

**Viral Vectors:** Lentiviral vectors have been exploited as efficient vehicles for targetted gene delivery. This is due to their capacity to integrate large DNA segments and to transduce both dividing and nondividing cells[18]. CAR T-cell therapies generated using lentiviral vectors have gained significant clinical success leading to the FDA approval of tisagenlecleucel (Kymriah, Novartis) for the treatment of B-cell acute lymphoblastic leukaemia (B-ALL)[15]. Third-generation lentiviral vectors use innovative safety features to eliminate the risk of generating replication-competent viruses in-vivo. This includes the deletion of 3′ Long Terminal Repeat (LTR) region to create self-inactivating viruses[19], and the use of split-genome design to create non-functional recombinants[20].

**Endonucleases:** Endonucleases cause gene alterations by generating double-stranded breaks (DSBs) in the target DNA, These DSBs can be repaired by either one of the two cellular repair mechanisms namely: homology-directed repair (HDR) and nonhomologous end-joining (NHEJ)[21]. This results in DNA integration or gene disruptions, respectively as shown in Figure 1. The

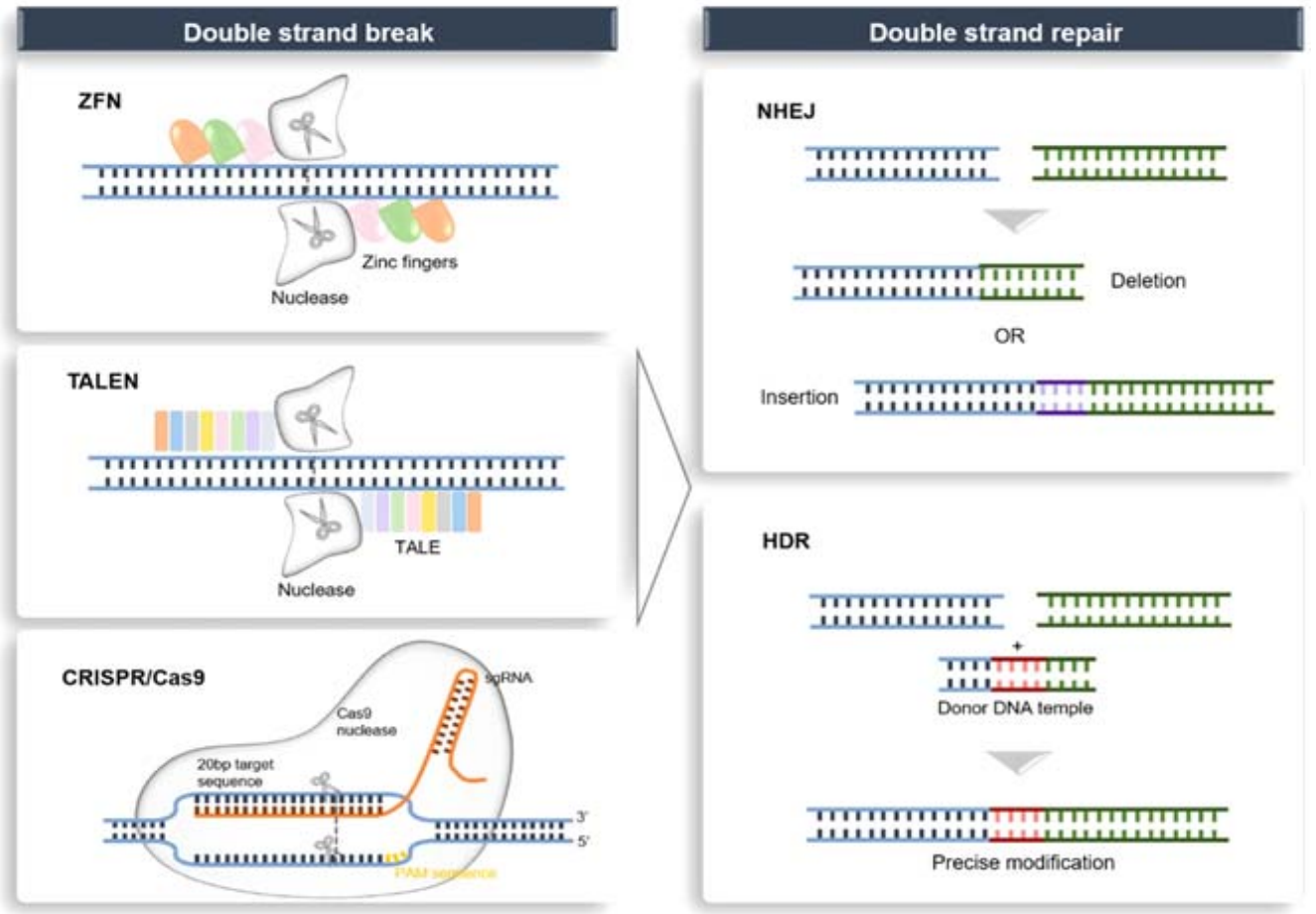


**Figure-1:** Endonucleases used in gene editing and their corresponding repair mechanisms. (NHEJ: Non-Homologous End Joining, HDR: Homology Directed Repair). Taken from (21).

commonly used endonucleases for targeted gene editing are elucidated below:

- Zinc Finger Nucleases (ZFNs) were used in the early days of gene editing. They required the generation of specialised proteins with sequence-specific DNA-binding domains, connected to a non-specific nuclease for targeted DNA cleavage[22].

- Transcription Activator-Like Effector Nucleases (TALENs) are a class of DNA-binding proteins isolated from the bacteria *Xanthomonas* and can cleave any target DNA sequence with high frequency[23]. They bind to DNA via a central domain made up of tandem repeats and thus require the creation of artificial effectors with new specificities for each successfully targeted cell[24].

- CRISPR-Cas9, Clustered regularly interspaced short palindromic repeat (CRISPR)-associated 9 (Cas9) nuclease is a part of the bacterial adaptive immune system and was first explored as a gene editing platform in 2013[25, 26]. It functions by modifying the genome of eukaryotic cells through DNA cleavage, targeted through specific RNA molecules.

CRISPR/Cas9 technology applications include genomic sequence correction or alteration, epigenetic, and transcriptional modifications[21]. This technology improves upon the other nucleases by providing a simple, efficient, and fast method of gene editing in-vivo.

A potential disadvantage of CRISPR-Cas9 technology is the probability of having off-target effects[27], it is thus essential to detect such unintended alterations using efficient methodologies such as DISCOVER-Seq (Discovery of In Situ Cas Off-targets and VERification by Sequencing) technique[28].

**Click chemistry:** Click chemistry enables stem cell-based drug delivery by facilitating a reaction between azide-coated cells and a cyclooctyne such as dibenzocyclooctyne (DBCO)[17]. In a pre-clinical study on animal models of Acute Myeloid Leukaemia Hu et al. showed that azide-coated HSCs can be conjugated to

DBCO-coated platelets bearing anti-programmed death-1 (PD-1) antibody for intra-tumoural delivery of this checkpoint inhibitor. The system of targeted drug delivery halted tumour growth, improved survival time, and prevented cancer recurrence[29].

**Applications of next-generation stem cells:** The applications of next-generation stem cells in cancer therapy continue to evolve as newer methodologies are discovered to increase their efficacy, safety, and therapeutic potential. Currently investigated therapeutic and drug delivery applications of next-generation stem cells in oncology are elucidated below:

**Antigen-specific stem cell therapy:** The stimulation of the body's immune system to fight cancer has resulted in remarkable benefits in the treatment of haematological malignancies. This therapy relies on the principle of adoptive immunity to generate cancer-specific cytotoxic T-cells namely Chimeric Antigen Receptor T (CAR-T) cells. This led to the approval of Kymriah, CD19-specific CAR-T cells, by The Food and Drug Association (FDA) in 2017[30].

**Table-2:** FDA-approved CAR-T therapies for haematological malignancies [31].

| S. No. | FDA-approved CAR-T therapies | Company | Disease |
|---|---|---|---|
| 1 | Abecma (idecabtagene vicleucel) | Celgene Corporation | MM |
| 2 | Breyanzi (lisocabtagene maraleucel) | Juno Therapeutics | B-Cell Lymphoma |
| 3 | Kymriah (tisagenlecleucel) | Novartis Pharma | B-ALL, B-Cell Lymphoma |
| 4 | Tecartus (brexucabtagene autoleucel) | Kite Pharma | MCL |
| 5 | Yescarta (axicabtagene ciloleucel) | Kite Pharma | B-Cell Lymphoma, FL |

Legend: MM: Multiple Myeloma, B-ALL: B-cell precursor acute lymphoblastic leukemia, MCL: Mantle Cell Lymphoma, FL: Follicular Lymphoma

The FDA has now approved 5 CAR-T therapies for blood cancers as listed in Table 2.

The use of stem cells to generate CAR-T cells helps elongate the in-vivo retention time of these cellular therapies and has the potential to generate off-the-shelf allogenic CAR-T cells. Since the first experiment combining iPSC and CAR-T technology was conducted in 2013[32] the field has seen great interest from scientists across the globe.

The technology has evolved to include iPSC-induced Natural Killer (NK) cells and Macrophages. Zhang et al. described the *ex-vivo* production of induced Pluripotent stem cells derived, CAR-expressing macrophage cells (CAR-iMac). The use of stem cells to generate these macrophages provides an unlimited supply of cells. The lentiviral transfer of CAR genes into iMacs makes them antigen-dependent. The cells still maintain macrophage functions like the secretion of cytokines, pro-inflammatory M1 state polarization, tumour cell phagocytosis, and *in vivo* anticancer cell activity[33]

**ALLOGENEIC / Off-the-Shelf Therapies:** The use of autologous CAR-T cells can cost a patient precious time, be labour intensive, and be expensive. This is due to the production of individual cell therapy products for each patient. Hence there is a significant shift in moving toward allogeneic cellular therapies.

In a pre-clinical study on ovarian cancer, it was observed that NK cells are cytotoxic to tumour cells and virally infected cells without stimulation by the human leukocyte antigen (HLA). Using iPSCs to generate antigen-specific NK cells enhances their long-term survival and proliferation both in vitro and in-vivo. CARs labeled with NK cell activation domains such as NKG2D improve the therapy's anti-tumour efficacy against solid tumours. Such iPSC-derived CAR-NK cells have been shown to inhibit tumour growth and prolong survival in a xenograft model of ovarian cancer[34].

Similarly, Woan et al. have demonstrated the successful use of iPSC-induced NK cells in pre-clinical studies on xenograft models of Acute Myeloid Leukaemia (AML) and Multiple Myeloma (MM). These NK cells termed iADAPT, can persist in-vivo without exogenous cytokine administration, have enhanced antitumour function, and can be combined with other chemotherapy regimens[35].

Their enhanced safety profiles due to low neurotoxicity, less incidence of Graft vs Host Disease (GvHD), and Cytokine Release Syndrome (CRS), along with their allogenic use make iPSC CAR-NK cells attractive alternatives to CAR-T cells for future cellular therapies in Cancer.

**Stems Cells in Anti-Cancer Drug Delivery:** Mesenchymal Stem cells due to their tumour trophic properties are being utilized for the delivery of anti-cancer agents, as shown in Figure 2. These cells have low immunogenicity and less incidence of tumourigenicity, thus are safe for administration[36]. Low immunogenicity warrants their use as allogenic drug delivery vehicles for cancer immunotherapy.

MSCs can be isolated from adipose tissue, bone marrow, or iPSCs. They express chemokine receptors such as

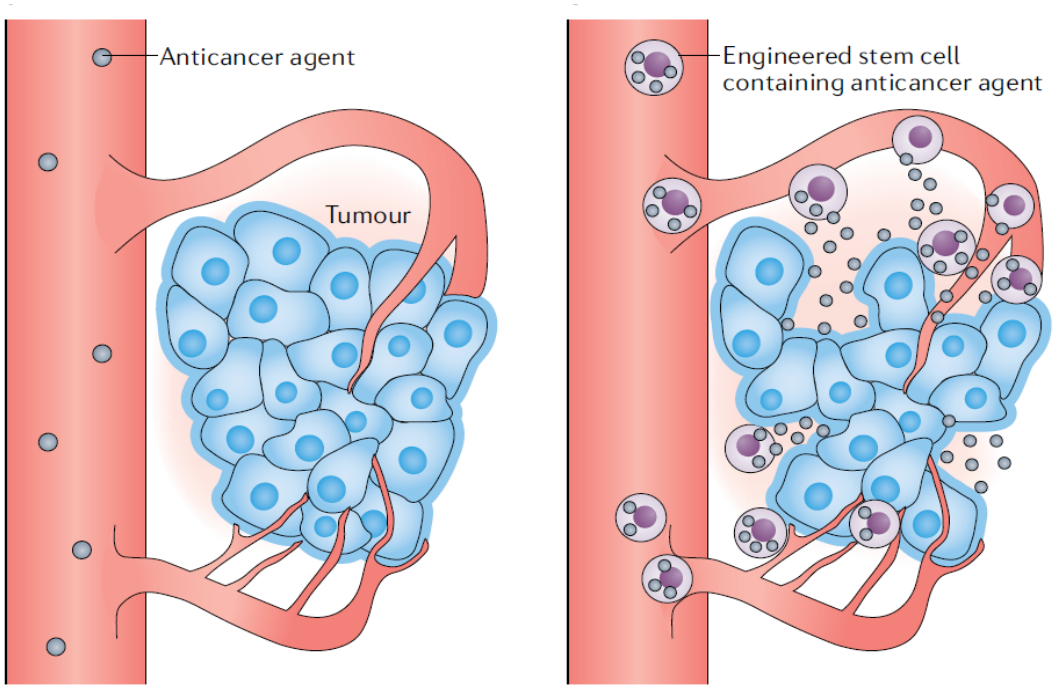


**Figure-2:** Tumor tropism of stem cells enables intra-tumoral delivery of anti-cancer agents[2].

CCR-1, CXCR-4, and CXCR-7[37] which enable their trafficking to primary and metastatic tumour sites that secrete the corresponding chemokines.

*Oncolytic viruses* (OVs) infect, replicate in and destroy cancer cells. They initiate an anti-tumour immune response leading to tumour cell death. OVs however are immunogenic and lack tumour tropism[38]. MSCs are being used as efficient carriers of OVs to tumour sites. They confer the OVs systemic protection from neutralizing immune responses and allow viral replication in-vivo.

MSCs are also used for the delivery of *anti-cancer drug encapsulated nanoparticles* (NP). These NPs are conjugated to the surface of MSCs using methods such as copper-free click chemistry[39] and Avidin Biotin Complex (ABC). In a pre-clinical study on murine colon adenocarcinoma, MSCs were loaded with doxorubicin liposomes (DOX-Lips) using the ABC method. The therapy suppressed tumour proliferation and growth in a lung metastasis mouse model[40].

*Exosomes* derived from MSCs are also being explored in the realm of anti-cancer drug delivery. Exosomes are highly biocompatible, non-toxic, and less immunogenic when compared to nanoparticles or liposomes. Their ability to cross biological barriers makes them ideally suited for intracellular drug delivery[41, 42].

In pre-clinical studies on a xenograft model of bladder cancer, Liu et. al.[43] demonstrated the successful deployment of exosomes from Adipose-Derived Mesenchymal Stem Cells (ADSCs), for the delivery of tumour-suppressor micro-RNA (miR-138-5p). Penetration of tumour tissue by these exosomes resulted in in-vivo suppression of tumour growth and proliferation[43].

## Conclusion

Stem cells possess tremendous potential for the creation of anti-cancer therapies and targetted drug delivery. MSCs serve as excellent delivery vehicles for oncolytic viruses and cytolytic agents, while iPSC-based therapies such as CAR-NK, and iMac cells offer new hope for the treatment of non-responsive tumours.

Treatment issues such as the off-target effects of CRISPR, gene-editing, and tumourigenicity of iPSCs, are being addressed using novel detection techniques and the deployment of suicide genes. Similarly, the development of off-the-shelf, allogenic stem cell therapies, will help save precious time, costs, and enable improved drug quality control. Further exploration into the domain of next-generation stem cells can help create more targetted, efficacious, and long-term therapies in the defense against cancer.

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