

# Bio-Engineered Cell Based Functional Systems as Next Generation for Cancer Therapeutics



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## Abstract

Cell based therapy with enthusiastic capability of intrinsic homing tumor sites with noticeable on-board sensing ability helps to design the way towards the target in fatal as well as intractable disease like cancer. Structurally engineered, these cell-based systems are equipped with sensing functionality which allows them to follow the cues to reach tumor microenvironment, that potentially frames them as advanced ideal candidates in smart cancer therapeutics. The discussed review presents the highlights of all the progress and advancements on the most promising cancer cell-based therapy as targeted theragnostic including genetically engineered materials and techniques in stem cell therapy, CAR-T cell therapy, NK-cell immune therapy, as emerging era on the horizon.

**Keywords:** Cancer cell-based therapy, CAR-T cell therapy, NK-cell immune therapy

## Introduction

Cell based therapy utilizing the programmable living vehicles and their delivery to tumor sites with contribution to communicate with faulty oncogenes in order to defraud the cancer cells as a potential to initiate the therapeutic transgenes. This may show an intrinsic immune response against the proliferating cells, with a potential to emerge as an attractive alternative to traditional resistance developing strategies for cancer targeting[1,2]. The engineered cell-based modalities can harness and mimic the proliferating cells, hence contribute for efficient biodistribution to the target site and orchestrate the complex cellular response to destroy the abnormal cells. Despite of such functionalities, the naturally derived structured tailored materials face series of challenges as discussed below, that require to be addressed[1].

- Robust cell source.
- Maintenance of viability and GRAS state.
- Relative similarity between PK/PD profile of cells and physiologic site.
- Must achieve the predicted therapeutic potency.
- Scalability considering the safety and tumorigenicity profiles of cell-based systems.

The discussion and motive of the perspective begins with landscape of cell based therapies and their advancements comprised of highly focussed CAR-T cell therapy as synthetic biology to encapsulate the CAR in T cells have risen within decades as genetic tools to introduce transgenes inside the cells, that is further highlighted briefly in recent advancement along with successful emergence of stem cells as well as NK cells as genetically engineered structural modules that can not only home and migrate to the tumor sites but also strap the tumor tropism[3,4].

### **Emerging strategies and recently advanced cancer cell-based techniques:**

There are numerous innovations like genome-epigenome editing as computational approach, synthetic biology, that are in recent interest in order to address all the challenges for cell based therapy. When it comes to target the cancer with engineering techniques, genetic mutation based genome-epigenome editing always play a key role to target by utilizing zinc-finger nuclease (ZFNs), transcription activator like effector nuclease (TALENs) and clustered regularly interspaced short palindromic repeats CRISPR-Cas9 system, which knockout the faulty gene, insert the correct gene and mutate the targeted gene to destroy the oncogenes in cancer. Newly derived CRISPR-Cas9 has been a lot in attention due to its practicability and reproducibility to maintain the GRAS state that is one of the challenge as discussed [5]. One such study conducted with CRISPR-Cas9 has been used as endogenous disrupting agent to mutate the resistant T cells against PD-L1 inhibition in order to produce allogenic CAR-T cells with reduced immunogenicity [6]. Also, as it has been proven that the combined strategy is always a better option, one such study as combination of CRISPR-Cas9/ stem cells that is cultured with motif to mutate four colorectal cancer based genes including p53, APC, KRAS and SMAD4 with a detailed screening of mutant cells to work against the cancer[7].

Synthetic biology is an approach to introduce transgenic artificial genes inside the cells via genetic engineering, likewise the incorporation of chimeric antigen receptor CAR gene in T cells has been approached in recent times. Synthetic remote control circuit on CAR activity that follows the cues to sense the surface ligands have been a lot in attention. Synthetic sense response programmable receptor that can sense one surface ligand that enhance the target cell specificity and coupled with CAR to sense second ligand, thereby can autonomously target with no off target delivery and enabling of such Boolean gate response can enhance the uptake with destruction of cell proliferation. Numerous approaches on this like combinatorial model of split, universal and programmable CARs (SUPRA-CARs)[8] as multivalent protein scaffolds have also been constructed to enable the recognition of antigen combinations. Transfection of CAR gene in T cells is such a wide area of research, and still it is on going on fourth as well as fifth generation of CARs to overcome the toxic profiles of previous generations. This also belongs to one of very attractive model comprised of scFvs, single-domain antibodies (sdAbs) and scaffold proteins. One such preclinical study by sommermeyer and smith on scFvsCARs targeting recognized human CD-19 and BCMA specific ligands that is known to be a well-known in multiple myeloma. They reported host immune anti-murine CAR responses to limit the frequent dosing with prolonged persistence, the study priorly begins with genetic engineering of thoroughly screened BCMA clones specific CARs with rapid in-vivo expansion and infusion with T cell to eliminate the immunosuppressive cells. Still their efficiency and efficacy are on stemming trial on research[9].

tumortropic MSC delivery with the immunoapoptotin and HER2. For clinical usage, anti-HER2 antibodies were employed because of HER2 overexpression in many types of tumors such as breast cancer as an approach for tumor tropism, and resulted with synergistic effect of immunoapoptotin engineered MSC, thus provide a motivational design of dual-targeting delivery systems for a wide variety of cancer types [10].

### **Nano-based drug delivery in cancer cell therapy.**

Identification and mutation of cells to correct the faulty genes is always challenging.

In above discussed cases CRISPR-Cas9 with high molecular weight leads to develop difficulty in targeting without a strategized delivery system to not only translocate but limit the off-target delivery as there are three categorized cargos of CRISPR-Cas 9 such as Cas9 endonuclease protein and its complex with sgRNA (RNP), another is mRNA, that is utilized for ex-vivo till date due to lack of stability. Hence to nano-drug delivery can enhance the stability but also improves the PK/PD profiles. Recently advancing technique to deliver Cas9 via engineering exosome vesicular drug delivery, that is explored as microinjection of exosome loaded with Cas9/sgRNA in combination against SKOV3 ovarian cancer to inhibit PARP-1 gene leading to apoptosis. Hybrid exosomes have also been studied and engineered as Cas9-loaded exosomes, likewise many of studies conducted to hybridize the exosome fusion with two cargos with increased loading efficiency as well as transfection of mesenchymal stem cells as study to provide synergistic effect t[11].

NANO-CART is strategy reported to be the alternative to sub optimal single domain CAR-T therapy associated with aggregation problem, also fence off the concern about the immune reflux. NANO-CARs have been explored as VHH (also known as nanobodies) that is better candidate than scFVs, as it quite closely resembled the human clone family of VHH, less immunogenic as variable domain heavy chain lacks the synthetic linker peptides. One study with NANO-CARs that locally secrete VHH-type immune modulators targeting CD47 or PD-L1. Another by Ackaert et al. conducted a study to investigate the possible immunogenicity of two nanobodies that are currently being investigated in Phase II clinical trials, the study reported the biological imaging of nanobodies in breast cancer to be less immunogenic that can be a potential for targeting moieties. Such nanobodies are much similar to human VH, hence a study on NANO-CAR redirected VHH based PSMA expressing genetically engineered cells incorporated that efficiently triggered the anti-tumor activity and tumor cell elimination with upregulation of immune checkpoint inhibition as well as anti-proliferating agents against the cancer [8].

MSCs have highest potential for tumor tropism, in special cases where hypoxic preconditioning is applied that improves the tumor homing as well as migration. In the field of nanotechnology MSCs have been widely explored, a study comprised the increase in expression of chemokine receptor-4 (CXCR-4) that was found to increase the tropism of MSCs via potentially using polymeric nanoparticles complexed with MSCs that shown increase in migration velocity, deep penetration, co-localization within the hypoxic tumor microenvironment [12].

The cell-based therapy can be widely used in membrane coated nanoparticles to reduce the immune reflux-based responses as eye catcher in cancer, that not only reduce the

immunogenicity but also can be biomimetic carrying device for cancer theragnostic. Genetic modification via hybridization, extrusion techniques can be efficiently utilized for surface receptor targeting. Amongst all the discussed merits of membrane coated nanoparticles, fusion of membranes and its incorporation on the surface of synthetic nanoparticles can do wonders in all the challenging situations like immunogenicity, off target delivery, receptor mediated uptake, resistance showing mutations [13]. Variety of delivery systems have been explored till date such as biomimetic RBC membrane coated nanoparticles, nucleic acid coated nanoparticles, immune cell coated nanoparticles, stem cells coated nanoparticles, neutrophil coated nanoparticles as well as platelet membrane coated nanoparticles depending on various sources as demonstrated in figure shown below:

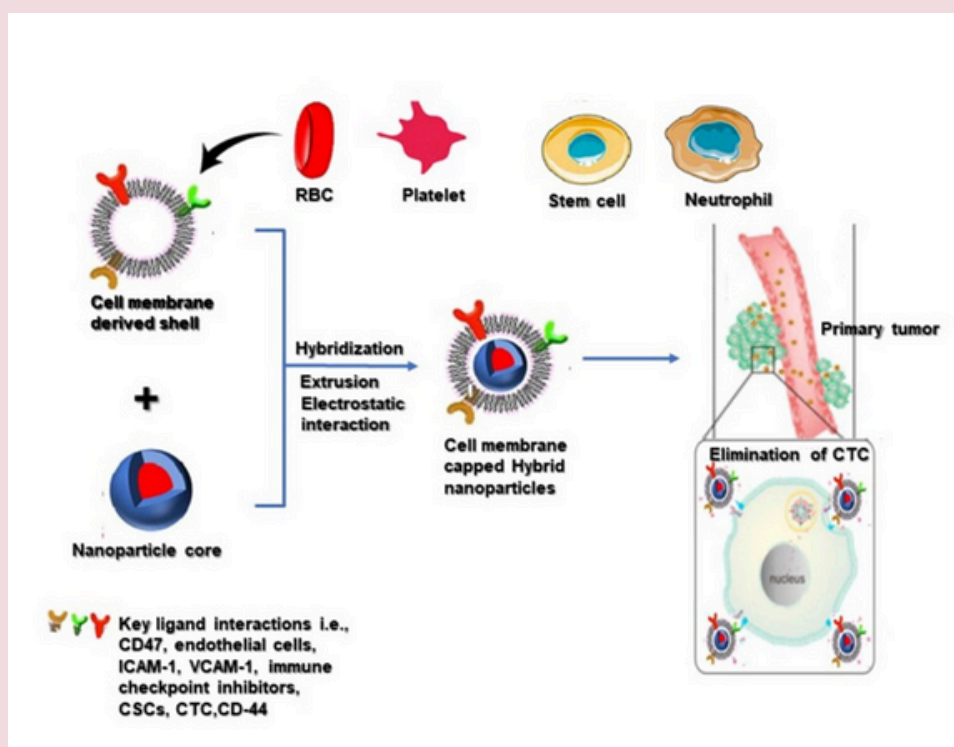


Figure 1 Coated Nanoparticle as a drug delivery system

Natural killing cells (NK cells) are the powerhouse for apoptosis as well as immune surveillance, that is known to secrete variety of cytokines once activated to regulate the immune system, as also to destroy the target cells. One such study on NK cell protein camouflaged nanoparticles as biomimetic tool using photosensitizer for cancer theragnostic by Deng's group demonstrated a successful attempt to produce anti-tumor effect via M1 polarization and cell death by photodynamic therapy (PDT) thus improving the antitumor immune workpiece ratio of the NK-cell membrane [14].

### Conclusion and outlook

Significant importance of genetic engineering strategies as rising in recent advancement highlighted in the review can clarify the vast areas of cell based therapy, clear that it can be a ideal strategy for cancer targeting as well as theragnostic area of research if conducted with motive to overcome the challenges considering the safety, efficacy point of view. We anticipate that these technologies will continue to refine autologous cell therapy pipelines (for example, CAR-T therapy), offering improvements in the mode of action.

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# Fun & frolic – Wordsearch | solution

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R	F	W	X	R	N	W	A	F	C	E	S	W	N	L	C	J	L	M	Y
W	H	T	N	B	T	Y	E	J	F	K	W	A	V	I	E	D	U	Y	J
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HEMGENIX	LUXTURNA	RETHYMIC
STRATAGRAFT	ZYNTEGLO	ZOLGENSMA
TECARTUS	IMLYGIC	GINTUIT