*Review Article*

# An overview on cell-based therapy: Unique perspective for cancer management

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**Abstract**

Cell-based immunotherapy is currently one of the most exciting developments in the fight against cancer, and to date, cellular therapies have been approved for people with certain blood cancers, but the cell therapy for solid tumors has yet to achieve that same milestone. Solid tumors comprise about 90% of all cancer diagnoses, thereby indicating more research on cell therapy technology as well as scalable production that could expand this treatment to the larger number of people with cancer. Cell therapy uses the living cells as a drug to treat disease, and when used to treat cancer, cell therapy takes advantage of the immune system's intrinsic ability to seek out and destroy abnormal cells in the body. Developing cell therapies to attack cancer cells for solid tumors, to persist in the body and overcome tumor's ability to hide from the immune system, has been notoriously difficult. With the technologies available, cell therapy is very expensive and difficult to produce in scalable quantities.

***Keywords*:** Cell-based therapy, virtues, cancer management, regulatory aspects

## Introduction

Functional nanomaterials carry great promise to overcome delivery challenges related to conventional drug administration in cancer therapy, and have been designed to conquer the physiological barriers at several scales to improve biodistribution, targeting specific cells, enhancing accumulation in tumor microenvironment (TME) and influencing intracellular trafficking (Kuncic, 2015; Anselmo and Mitragotri, 2016). However, heterogeneity among cancer types and diffusion-limited transport in tumors keep the expectations from nanoparticle (NP) drug carriers greatly unfulfilled (Jain and Stylianopoulos, 2010; Dewhirst and Secomb, 2017; Stefan et al., 2016). Dormant cells present in the deeper parts of the tumor significantly contribute to the drug resistance as well as clinical relapse, and hence, such cells are hard to reach by systemically administered therapeutics and also external radiotherapy becomes less effective in poorly oxygenated tumor core (Combes et al., 2020; Zhou et al., 2018).Interest has grown to exploit the biological agents with ability to migrate actively to tumors, due to the difficulties faced in drug delivery (Schmidt et al., 2020; Ngandeu Neubi et al., 2018). Some types of cell are naturally armed with the encoded onboard sensing which permit them to follow the signals of cancer environment, and their tumor homing can be enhanced via intercellular communication (Yoo et al., 2011; Fliervoet and Mastrobattista 2016). As soon as tumor site is reached, innate toxicity and co-delivered drugs or toxins secreted on-site can initiate the therapeutic response, and these features allow cells to be recast as programmable living vehicles carrying a potential for contributing towards the ultimate goal of cancer treatment i.e. selective and complete eradication of cancer cells with minimal off-target effects (Forbes, 2010). Along with a few strains of bacteria and immune cells, some types of prokaryotic as well as eukaryotic cells have been identified as the potential candidates for cell-based cancer therapy (Bush et al., 2021; Hosseinidoust et al., 2016). Bacteria are able to penetrate deeply into the tumor at tissue level, owing to their own flagellar propulsion for the motility (Alapan et al., 2019).

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Presently, diverse tools and techniques of synthetic biology have made it possible to engineer the bacteria for cancer therapy along with the specific and safe functionality. Additionally, stem cells with their significant contribution to tissue regeneration, are also capable of homing to the tumor sites (Sieow et al., 2021; Lutz et al., 2019; Reagan and Kaplan, 2011). Low-immunogenicity further facilitates their exploitation for the applications in drug delivery. Furthermore, mesenchymal stem cells (MSCs) modulate immune response in damaged tissue thereby motivating the reengineering of these multipotent cells (Bush et al., 2021; Kusuma et al., 2020). Platelets are another type of cell, functioning as an intelligent cell-based delivery system and circulating in blood with no biological machinery for reproduction and active migration. However, their close interactions with tumor cells, whether in primary tumors, circulating tumor cells (CTCs) or in metastases, have made them attractive candidates for drug delivery, and their potential in vascular integrity as well as immunomodulation is linked with their selective activation in presence of cancer and their blood-borne nature improves drug pharmacokinetics with the minimal immunogenicity (Gay and Felding-Habermann, 2011; Buergy et al., 2012; Huong et al., 2019). Additionally, natural killer (NK) cell, a specialized immune effector cell, plays critical role in immune activation against abnormal cells. Different from the T cell activation, NK cell activation is usually governed by the interaction of NK receptors with the target cells, independent of antigen processing, and due to relatively unsophisticated signals for activation, NK cell has significantly gained attention in cancer immunotherapy. Many efforts are emerging to develop and engineer NK cell-based cancer immunotherapy (Barros-Becker et al., 2017).

**Virtues of cell-based therapy**

Cell-based therapies are accompanying new era of drug delivery wherein unique attributes of different cells (immune cells, stem cells, NK cells, and platelets) and bacteria are leveraged to overcome the current limitations in cancer therapy. By implementing onboard sensing, intercellular communication and autonomous motion, these cells can achieve tumor homing. Moreover, their innate features offer modification and augmentation via genetic reprogramming, and when used as drug carriers, they can act as controlled delivery depots by improving pharmacokinetic profiles of their payload. Moreover, external signals including magnetic fields and light have also been used to boost tumor homing as well as therapeutic efficacy, by assisting chemotaxis and guiding cells to the tumor sites (Amulic et al., 2012). By modifying cell membrane, higher specificity in the TME for cancer cells has been achieved. Synthetic biology helps to provide therapeutic vectors that are capable of multifaceted responses to wide variety of disease signatures, and specifically it has offered the means to increase specificity and safety by producing attenuated strains, allowing spatiotemporally controlled release and integrating further sensing or targeting functionalities (Tecchio et al., 2014). Current efforts for chimeric antigen receptor (CAR)-T cells are focused on the development of autonomous, feedback circuits triggering downregulation in response to the toxicity indications, and for bacteria, using attenuated auxotrophic mutants has shown promise in mitigating unintended immunogenicity. Consequently, such prevention-based strategies can improve the safety as well as therapeutic potential of these living systems (Hidalgo et al., 2007).

By considering exclusive features of each cell-based system, their complementary therapeutic actions could be envisioned in the context of combination therapy. Immune cells infiltrate the well-oxygenated rim whereas platelets exhibit unique targeting to CTCs, and combining engineered bacteria for local release as well as CAR-T cells with enhanced specificity, could potentially provide a successful treatment of primary tumors which can be complemented by platelet-mediated recognition and eradication of intravasated cancer cells. Additionally, micro- or nanoagents mediating external stimuli application, can be included as a part of therapy in the delivered payload (Moore et al., 1995; Constantin et al., 2000; Maas et al., 2018).

**Key requirement for cell-based therapy**

Identification of molecules that are found predominantly, or only on cancer cells, is a key requirement for cell-based therapy (Jamieson et al., 2012). The lack of cancer-specific molecules marking solid tumors has been a major obstacle in bringing the cell therapy to large population with cancer, and this is mainly challenging for childhood cancers as tumor cells and healthy cells share many of the same molecular tags in children (Katoh et al., 2013). Having cancer-specific surface protein library in hand, researchers can effectively explore how to target solid tumor cells. While cell-based therapy is a promising area of research, there are more challenges to overcome, and further research is required to identify who will benefit the most from cell therapy, and how to make a cancer more vulnerable to such treatments (Davies et al., 2013).

**Current scenario**

Cell-based immunotherapy is currently one of the most exciting developments in the fight against cancer, and to date, cellular therapies have been approved for people with certain blood cancers, but the cell therapy for solid tumors has yet to achieve that same milestone. Solid tumors are comprising about 90% of all cancer diagnoses, thereby

indicating more research on cell therapy technology as well as scalable production that could expand this treatment to the larger number of people with cancer (Zhou et al., 2020). Cell therapy uses the living cells as a drug to treat disease, and when used to treat cancer, cell therapy takes advantage of the immune system's intrinsic ability to seek out and destroy abnormal cells in the body. This approach is also known as immune cell therapy and adoptive cell therapy.

However, they all refer to the same type of cancer treatment (Abraham et al., 2010). Specialized immune cells are either engineered for recognizing the unique tags on an individual's cancer or selectively isolated from a patient's tumor for growing them in a large number in the laboratory and then given back to the patient through intravenous infusion (Qian et al., 2011; Halama et al., 2016). Developing cell therapies to attack cancer cells for solid tumors, to persist in the body and overcome tumor's ability to hide from the immune system, has been notoriously difficult. With the technologies available, cell therapy is very expensive and difficult to produce in scalable quantities (Nakatsumi et al., 2017; Manome et al., 1995; Lu and Kang, 2009).

**Regulatory and clinical aspect of cell-based therapy**

It is important for manufacturers, researchers and clinicians to be aware of the FDA's regulatory guidance on cell therapy products. Human cells, tissues, and cellular and tissue-based products (HCT/P) are defined by the FDA under the Title 21 of the Code of Federal Regulations (CFR) Part 1271.3(d) as "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient." Several examples falling under this definition include epithelial cells on a synthetic matrix and manipulated autologous chondrocytes. If the therapy does not meet the definition of HCT/P in 21 CFR 1271.3(d) such as blood components/derivatives, the regulations in 21 CFR Part 1271 do not apply (US, 2020).

The cancer therapy has been evolved from the systemic targeting of tumors via chemotherapy or radiotherapy to a more targeted approach through novel biologic treatments including oncolytic viruses, monoclonal antibodies, and cell therapy (such as antigen presenting cell (APC)-based anticancer vaccines and CAR-T cells). Along with the commercial cell therapy products, a multitude of cell therapies have been investigated for cancer treatment, and although several examples are already clinically used or being tested in clinical trials, limitations must be overcome to unleash the full potential of cell-based therapies. Incomplete eradication of cancer cells occurs due to inadequate infiltration, resulting mostly from heterogeneity of tumors at both cellular and tissue level. Safety concerns, particularly in case of CAR-T cells and bacteria, necessitate further study of their tolerance *in vivo*. Another critical aspect in cell-based therapies is to develop effective means for upscaling the production of cells using good manufacturing practice (GMP) principles (Bonapace et al., 2014; Zugazagoitia et al., 2016; Long et al., 2016).

**Conclusion**

With crucial ongoing efforts addressing the safety as well as efficacy of living intelligent therapeutics and with an assistance of all the available tools related to cell-based therapeutics, great advancements in cancer treatment seem to be on the horizon, and the indications are also expected to include infectious diseases, organ transplantation, and autoimmune diseases. It can be expected that, along with the technological advances, the foundations of cell-based therapies will be extended in the future.

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**Authors Contribution**

All Authors have contributed equally.

**Conflict of Interests**

Author declares no conflict of interests.

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