



REVIEW

Engineered Cell Therapy: A Successful Approach to Treat Cancer

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ABSTRACT

Cancer is the abnormality which happens in the cell cycle, resulting in uncontrolled cell division and is the second largest cause of deaths in the world accounting 13% of all deaths followed by the cardiovascular diseases. Finding a therapeutic solution for cancer is a continuous process. A number of therapeutic approaches like chemotherapy, preventive therapies, radiation and magnetic therapy, adjuvant therapy, Immunotherapy, gene therapy, cell transplantation therapy, Hyperthermia and surgery are under research in order to treat cancer. Targeted therapy is the most preferred way to treat cancer globally and researchers are focusing on the different ways of targeted therapy. Gene therapy with its first approved drug for cancer (Gendicine™) in China revolutionized the cancer drugs but a number of questions in scientific community around the world and its rejection in European and American market raised question marks on its authenticity as cancer drug. Successful clinical trials for mesenchymal stem cell (MSCs) and engineered cells based therapy against cancer emerged the concept of gene and cell therapy for cancer and a number of clinical trials also produced successful results in this case. Engineered cells are new agents of targeted cancer therapy and have been considered by researchers, as a promising therapeutic candidates. Engineered cell therapy (combination of gene and cell therapy) as a part of targeted therapy of cancer may provide a valuable resource. T-Cell engineering has faced successful results, whereas MSC engineering is passing through a transition phase. Successful engineering of MSCs could be a hope for cancer patients in near future.

Keywords: Cancer therapy, stem cell transplantation, cancer statistics, cancer mortality, cancer prevalence

Malignancy always remains a big challenge for life science researchers as being the leading cause of death worldwide. According to the GLOBOCAN 2012 & WHO, 8.2 million people

died (about 13% of all deaths) just because of cancer in 2012 and these deaths are predictable to continue rising, with an estimated 13.1 million deaths in 2030 from which, the majority are caused by lung cancer.

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14.1 million new cancer cases have been diagnosed with a total of 32.6 million living persons with cancer. According to the WHO, Lung cancer has the highest global prevalence. Near about 23/100,000 persons are suffering from lung cancer in the world and 19/100,000 patients are dying of lung cancer every year world-wide. According to American Cancer Society, an estimated 160,340 Americans were expected to die from lung cancer in 2012, accounting for approximately 28 percent of all cancer deaths. Following table shows the top six types of cancer with their prevalence and deaths in numbers (http://globocan.iarc.fr/Pages/fact_sheets_population.aspx).

Table1: Top 6 types of cancers showing prevalence and death rate

Sr. No.	Type of Cancer	Deaths ^{1&2} (Millions)	Prevalence ^{1&2} (Millions)
1	Lung	1.58	1.82
2	Liver	0.74	0.78
3	Stomach	0.72	0.95
4	Colorectal	0.69	1.36
5	Breast	0.52	1.67
6	Prostate	0.30	1.11
World Health Organization ¹ GloboCan Statistics ²			

Cellular malignancy has been described as invasion of cancer cell in its surroundings via different cellular activities like epithelial-mesenchymal transition, cell-cell adhesion, cell-matrix adhesion, cellular and vesicular migration and a number of signalling pathways such as, activation of trimeric-G-proteins, phosphoinositide 3-kinase, src, Rab, Rac and Rho of small GTPases [1].

Recent studies have explained novel cancer mechanisms, i.e. faulty placement of essential enzymes in the ER of cells made them cancerous i.e. initiation of GalNAc-type O-glycosylation [2].

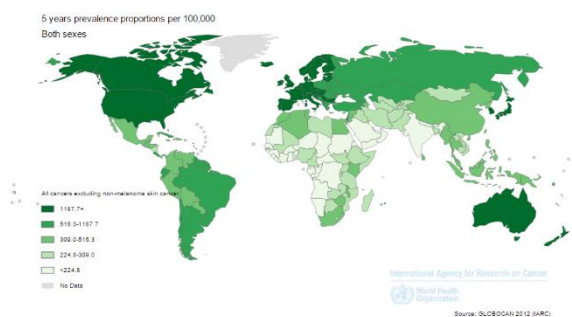


Figure 1a: Prevalence of all types of Cancer (excluding non-melanoma skin cancer) in the world in both, males and females

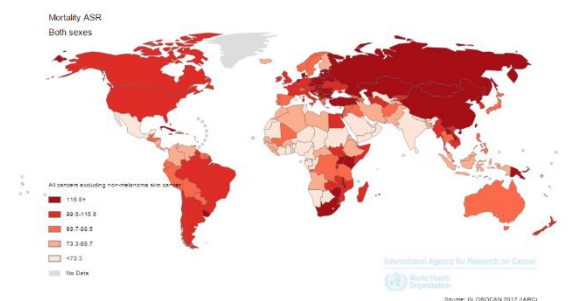


Figure 1b: Mortality of all types of Cancer (excluding non-melanoma skin cancer) in the world, both in males and females per 100,000

Role of the glucose-regulated proteins (GRPs) have also been described as a new agent involve in several cancer initiated functions like control signalling pathways, proliferation, invasion, apoptosis, inflammation and immunity that lead to the organ development, tumorigenesis, metastasis and angiogenesis [3]. For therapeutic purposes, cancer cells have been modified with several anti-proliferative, pro-apoptotic and anti-angiogenic genes targeting different types of cancer [4]. Different approaches including surgical, chemotherapy, radiation therapy, gene therapy, cell therapy have been applied to combat cancer in last three decades [5]. Gene therapy with the invention of Gendicine and Cell therapy for MSCs have shown promising candidates in cell therapy [4, 6]. These therapeutic approaches are facing several challenges and a new approach of combining gene and cell therapy has been introduced[7]. A number of cells including T-cells and stem cells like MSCs have been engineered to overcome these challenges and their clinical trials have shown a remarkable success

in the cell engineered therapy, proposing a cancer therapeutic candidate for near future [8, 9]. A detailed discussion on the numbers of pros and cons of gene therapy, cell therapy and engineered cell therapy is given to discuss the proposed hypothesis that engineered cells may be used as a targeted therapy to treat cancer malignancies.

Gene Therapy for Cancer:

Near about 1331 clinical trials of gene therapy for cancer have been performed since 1989 when the first clinical trial of gene therapy for cancer had been conducted as in table number 1 given below. More than 60% of these clinical trials have been conducted using viral vectors and remaining others were conducted using non-viral vectors. A few trials for naked DNA insertion have also been conducted [10]. In the last decade, gene therapy has seen milestone achievement with the approval of first gene therapy drug (Gendicine™) in China [11]. It was discussed that this may encourage the global researchers for advancement and development in the gene therapy drugs but soon after the announcement of Gendicine™, it receive a huge critical response from the western research community whereas a positive response from the Asian states [12-14]. Commercialization of gene therapeutic for a daily routine practice was proposed in 2013 [15].

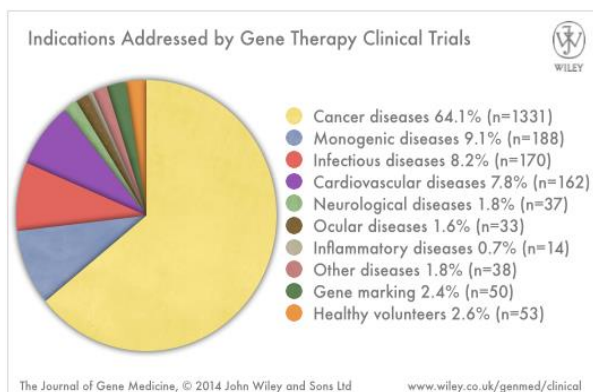


Figure 2: Candidate diseases targeted by Gene Therapy.

Cell Therapy for Cancer:

Cell therapy has been considered as an important therapy to defeat cancer. About 8357 studies are registered on clinical trials that have been completed for cancer using cell therapy whereas more than 12,000 are in process, making it a significant approach to cure cancer (www.clinicaltrials.gov). Stem cell therapies based on mesenchymal stem cells, showed promising and most successful therapeutic approach ever applied for different kinds of cancers modification because of their anticancer potential [16-19]. Mesenchymal stem cells (MSCs) have an enormous potential to be utilized to treat a number of different cancer types because these have inherent tumor-tropic migratory properties, which allows them to serve as vehicles for delivering effective, targeted therapy to isolated tumors and metastatic disease [4]. MSCs inhibit cancer metastasis by regulating the Wnt and Akt signalling pathways which are crucial in cancer regulation [20]. 8 clinical trials out of 206 clinical trials have been conducted on different kind of cancer using MSCs [21]-[22]. Different progenitor cells such as T-cells have also been applied in clinical trials for a variety of cancers, which have produced interesting results [23]. Stem cells like MSCs and progenitor cells like T-cells have been used in clinics with encouraging outcomes for researchers. According to the American Cancer Society (www.cancer.org), stem cells have 3 basic types; Autologous, Allogeneic and Syngeneic. Adult stem cells like MSCs, stromal cells and hematopoietic stem cells are the most preferred cells applied in clinics to target cancer [19, 24, 25]. Engineered cells (engineered stem and progenitor cells) have started a new trend in targeted cancer therapy, in which cells are engineered with cancer targeting agents (TNF, TRAIL etc) and are transplanted using recommended transplantation methodologies for enhanced therapeutic results.

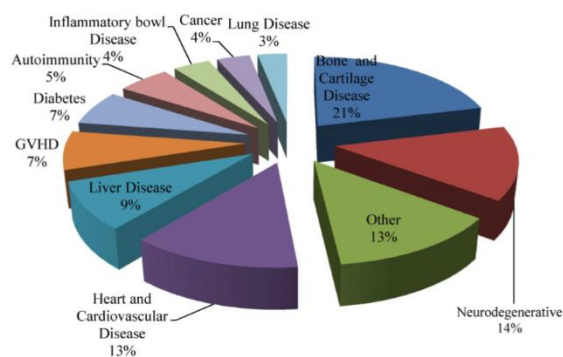


Figure 3: Clinical applications of mesenchymal stem cells (MSCs) for various diseases. Cancer accounts only 4% for all MSCs clinical trials.

Engineered Cell Therapy:

Cell therapy (also known as cytotherapy) is a decades old practice to treat diseases. With the first successful bone marrow transplantation, cell transplantation gain a considerable attention by researchers and clinicians [26]. Currently, cell therapy has been hypothesized to be the third pillar of medicine[27]. With the development and advancement in scientific knowledge, a number of cells have been recommended for therapeutic purposes. Adult stem cells, like mesenchymal stem cells, hematopoietic stem cells, keratinocytes stem cells and progenitor cells like T-cells are being applied in clinics for treatment and research purposes (Ref). Reprogrammed cells, iPSCs have also been proposed, the promising cell therapeutic agents for coming generation [28]. More than 28000 studies are registered on the US registry of clinical trials (www.clinicaltrials.gov) from which Cancer is ranked top being treated by cell therapy. MSCs because of their tumor tropism and T-cells because of their immune response have been applied to treat cancer. The mechanism of tumor tropism is still unknown. MSCs have been engineered to investigate their possible mechanisms involved in tumor tropism and its enhancement to target cancer specifically [20]. This newly developed approach of engineered stem cells (combination of cell and gene therapy)

has revolutionized the research area and a number of progenitor cells have also been engineered to target cancer precisely [29, 30]. MSCs are being engineering to enhance their tumor tropism and T-cell engineering to enhance their identification capabilities of cancer cells and to kill them is an ongoing interested research area.

MSC Engineering:

Pre-clinical and clinical studies have shown that stem cell-based therapies hold tremendous promise for the treatment of human disease. Stem cells like mesenchymal stem cells and hematopoietic stem cells are kind of stem cells that have been transplanted to treat cancer [31]. Their therapeutic efficacy has been achieved via engineering the cells and their therapeutic potential to target cancer has been improved [32]. Tumor-directed migration capacity of MSCs has been enhanced to treat cancer via engineering MSCs as a research on MSC-mediated anticancer strategy. MSCs have also been engineered to express anti-proliferative, pro-apoptotic, anti-angiogenic agents that specifically target different cancer types[4] as these have been considered as an ideal carriers to deliver anticancer agents. A number of cancer-cell oriented migration agents have been carried via engineered MSCs like phosphatase and tensin homolog (PTEN) and their effects on the enhanced migration of stem cells towards cancer cells have been investigated [8, 33], as a part of targeted therapeutic approach.

T-Cell Engineering

It has been known that T-cells perform their specific role in the recognition and killing of tumor cells as there are functional tumor-specific T-cells which perform this job. Their function is limited because of their poor recognition and gradual modulation by cancer cells. The hypothesis that how we can enhance this recognition so that T-cells can avoid modulatory effects of cancer cells, leads to the concept of engineering cancer patients immune system to target cancer in the body. For this purpose, T-cells have been modified with transgenes

encoding T-cell receptors (TCRs) or chimeric antigen receptors (CAR) i.e. 19-28z chimeric antigen receptor specific to the CD19 antigen to enhance T-cells functioning and their specificity in tumor recognition for specific targeted effects [9, 34-36]. Table 2 shows the clinical trials of engineered T-cells to target cancer.

Table 2: Published reports of clinical trials using genetically redirected T-cells for cancer therapy

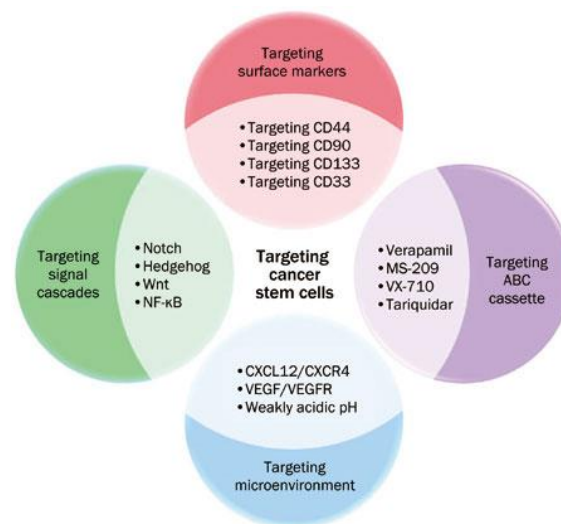
Sr. No.	Type of Cancer in Clinical Trials (CT)	No of patients	Year of CT report	Ref.
1.	AML	4	2013	[37]
2.	Colorectal and breast	27	2002, 2010, 2011	[38-41]
3.	Leukemia and lymphoma	106	2008, 2010, 2011, 2013	[42-48]
4.	Melanoma & sarcoma	142	2006, 2009, 2010, 2011, 2013	[49-55]
5.	Multiple myeloma	11	2012	[56]
6.	Neuroblastoma	25	2007, 2011	[57, 58]
7.	Ovarian	12	2006	[59]
8.	RCC	11	2011	[60, 61]
9.	Prostate	5	2013	[62]

Future Perspectives:

Targeting cancer cells to eradicate cancer malignancies is the hot topic of research in modern medicine or life sciences research. Number of successful clinical trials using MSCs and T-cells indicate their potential in targeted cancer therapy. A few limitations are still observed while targeting cancer malignancies. This limitation may be due to the inadequate knowledge of cancer stem cells (CSCs) residing in almost all types of solid tumors which generate resistance to chemotherapy and radiotherapy and also modulate the transplanted cells. A number of strategies targeting CSCs such as altering the

microenvironment (niches), targeting ABC superfamily, anti-apoptotic factors, detoxifying enzymes, DNA repair enzymes and distinct oncogenic cascades (such as the Wnt/ β -catenin, hedgehog, EGFR and Notch pathways) etc have been observed in last few years[63, 64].

Cancer stem cells (CSCs) have been identified as rare type of malignant T-cells in leukemia, solid tumors etc. which have been considered as the agents involved in cancer initiation, progression, metastasis, recurrence and drug resistance. Discovery and development of CSC-related therapies targeting key molecules involved in controlling CSC populations is currently the new approach for cancer researchers. Targeting circles of CSC populations is given in figure 4.



Source:
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Figure 4: Therapeutic key molecules in targeted cancer stem cell therapy.

It can be concluded that engineering MSCs and T-cells after a sufficient knowledge of CSCs to target cancer cells is a promising field in the treatment of cancer. Studies have shown that these engineered cells secrete cytokines and support immunity against cancer. Genetically modified MSCs and T-cells have provide optimism to researchers to treat leukemia and some common solid tumors. As we have

concluded in this discussion, CSCs are rare but significant populations of cancer cells that their response is creating limitations in cancer therapy. Tumor tropism of MSCs and their failure to cure cancer is may be due to the CSCs populations residing in solid tumors. The modulator effects of CSCs on engineered (stem) cells may answer the limitations in cancer cell therapy.

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Conflict of Interest:

There is no any conflict of interest with any person or organization regarding this manuscript.

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