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Cellular therapies: Day by day, all the way

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ABSTRACT

Tremendous effort and knowledge have elucidated a new era of 'cellular therapy,' also called "live" or "living" drugs. There are currently thousands of active clinical trials that are ongoing, seeking hope for incurable conditions thanks to the increased accessibility and reliability of gene editing and cellular reprogramming. Accomplishments in various adoptive T cell immunotherapies and chimeric antigen receptor (CART) T cell therapies oriented researchers to the field. Cellular therapies are believed to be the next generation of curative therapeutics in many ways, the classification and nomenclature for these applications have not yet reached a consensus. Trends in recent years are moving towards making tissues and cell processes only in centers with production permits. It is quite promising that competent authorities have increased licensing activities of tissue and cell establishments in their countries, under good practice (GxP) rules, and preclinical and clinical trials involving cell-based therapies have led to significant investments. Despite the initiatives undertaken and the large budgets that have been allocated, only limited success has been achieved in cellular therapy compared to conventional drug development. Cost, and cost effectiveness, are important issues for these novel therapies to meet unmet clinical needs, and there are still many scientific, translational, commercializational, and ethical questions that do not have answers. The main objectives of this review is to underline the current position of cellular therapies in research, highlight the timely topic of immunotherapy and chimeric antigen receptor (CAR) T-cell treatment, and compile information related to regulations and marketing of cellular therapeutic approaches worldwide.

1. Introduction

The motto of cellular therapy is best described by Paracelsus, a 16th century physician, as 'similis similibus curantur' (likes are cured by likes) [1]. The cornerstones of cellular studies emerged after the discovery of cells as the building blocks of life following the invention of the microscope, the first observations of cell proliferation and differentiation, and the understanding that different blood cells come from a primary cell. 'Cell therapy', 'cellular therapy', 'cellular immunotherapy' or 'regenerative medicine' refer to the administration of living cells for various purposes, including the destruction of unwanted cells, therapeutic purposes, or repairs to establish normal function. Manipulating cells in different ways in vivo has moved the field toward in situ cellular therapy, mostly following a set of gene therapy strategies that modify the expression of an individual's genes. The classification and nomenclature for these applications have not yet reached a consensus. It would be preferable for studies to be structured uniformly to enable them to focus on achieving success rather than redefining their terms.

The first cell therapy application in medical history was the intravenous transfusion of whole blood from a donor to a recipient following the identification of human blood groups [2,3]. Irradiation-induced damage to bone marrow led to bone marrow transplantation studies after first being considered during World War II. The first allogeneic hematopoietic stem cell transplantation (HSCT) was pioneered and reported by E. Donnall Thomas in 1957 [4]. Since then, the field has evolved; today, both autologous and allogeneic HSCT are standards of care that have expanded worldwide. The discovery of the existence of differentiable cells from different tissue lines in hematopoietic stem cell products, the discovery of embryonic stem cells from the blastocyst, and the possibility of reprogramming gave this field new excitement and motivation [5]. Although embryonic stem cell trials raised expectations quite high, immune rejection, differentiation problems for desired cell types, and ethical issues led to a decline in the clinical translation of ESC research [6]. These factors ultimately led to the Nobel-winning invention of induced pluripotent stem cells (iPSCs). Takahashi and Yamanaka transferred a limited number of genes to reprogram an adult

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somatic cell to an embryonic-like state [7]. More sophisticated and controlled studies started taking place after in vivo and *ex vivo* gene therapy became involved in the field. Numerous studies have been conducted on mesenchymal stem cells derived from different sources, genetically modified T-cells and autologous stem cells, adult stem cells from different tissues, pluripotent stem cells, and immunocompetent cells isolated from peripheral cancers. Significant advancements in controlling the developmental, morphological and physiological properties of stem cells have given rise to the field of tissue engineering. Currently, the field of tissue engineering which goals to generate tissues and organs to be used for regeneration, replacement, or reconstruction can not be considered apart from cellular therapies.

Application of chimeric antigen receptor T cell (CAR T cell) therapy in hematological malignancies is a huge step forward in the field of cellular therapy; more than 200 clinical trials have been launched worldwide since invention. Preclinical and clinical trials involving cell-based therapies have led to significant investments. Despite the initiatives undertaken and the large budgets that have been allocated, only limited numbers of patients involved in trials and success is controversial compared to conventional drug development. Ethical and regulatory issues apply to scientists across various national health systems. The main objectives of this review are to underline the current position of cellular therapies in research and regulation, highlight the timely topics of immunotherapy and CAR T-cell treatment, compile information related to cellular therapeutic approaches worldwide, and to discuss what our role as scientists should be in developing strategies to better govern product development. In doing so, we aim to gather a large set of information under a comprehensive study to make it easier to understand the complex evolution of cellular therapies.

2. Cell-based therapeutic approaches

Today, two main categories of cell-based therapy are recognized for treatments: autologous and allogeneic stem cell therapies. Autologous stem cells (i.e., the host's cells) offer safer treatment because they avoid the problems of tissue rejection and requiring immunosuppressant drugs [8]. Stem cells are studied in a variety of diseases, including neurological, cardiological, orthopedical diseases, cancer research, eye and ear disorders; their classification may address their therapeutic indication or cell type [9–12]. Researchers also developed a classification system based on the underlying technologies in order to find solutions for manufacturing and regulatory issues. The methodology/technology approach mirrors the subdivisions of Advanced Therapy Medicinal Products (ATMP) in EU classification which shown in Table 1 [12].

Adult stem cells and progenitors are promising, or have already proven successful, in tissues that show high regenerative potential, such as bone or bone marrow [13]. The therapeutic effect was demonstrated as paracrine in less-regenerative organs such as the brain and the heart. On the other hand, mesenchymal stromal cells (MSCs) are characterized by their plasticity, differentiating into bone, fat and cartilage; their ability to modulate the immune system; and their functions in repairing tissue and exerting anti-fibrotic activity [14]. Unknowns in genome engineering and insufficiently addressed modes of cell delivery still limit experiments in the stem cell field [15,16]. Indeed, iPSC research has expanded in recent years after the development of technologies for efficient and safe genetic engineering, as well as expansion and differentiation in a clinical setting [17,18] The breakthrough step in genome editing was the development of engineered nucleases including zinc finger nucleases (ZFNs), TALENs (transcription activator-like effector nucleases), and CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9) to correct disease-specific mutations [19].

Current trials are mostly focused on transplanting pluripotent stem cell based products to treat macular degeneration. In Japan, two patients are already enrolled in a clinical trial for transplantation of autologous iPSC-derived retinal cells; one patient was successfully treated without serious complications or unexpected proliferation [20]. Industry-sponsored clinical trials based on human ESCs for spinal cord injury have also been initiated [21]. Although the long-term results are still pending, no evidence of significant change in neurological function has been reported [22]. There are also clinical trials registered for treating diabetes by applying ESC-derived beta cells and transplanting hESC-derived progenitors for severe heart failure [23,24].

Cellular products are still too young to be considered as standardized therapies [25,26]. Therefore, it is important to establish the efficacy, safety and quality of these applications with pre-clinical and clinical studies [27]. There are numerous examples of cellular therapies marketed in the United States of America (USA) and the European Union (EU) [28,29]. Some examples are listed in Table 2. There are potential risks related to specific grafts and their function, the application procedure, and the organ to be treated. For instance, Allocord®, Clevecord®, Hemacord® and Ducord® have boxed warnings in their package inserts regarding fatal infusion reactions, graft vs host disease (GVHD), engraftment syndrome, and graft failure [30–33]. Holoclar® is associated with the risk of blepharitis [34]. Imlygic® is associated with the risk of spread of herpes infection in patients with severely impaired immune system [35]. Strimvelis® is associated with the risk of anemia, aplastic anemia, hepatitis, thrombocytopenia, Guillain-Barré syndrome [36]. Zalmoxis® is associated with the risk of acute GVHD [37].

If there is a potential effect that has been shown to be at least an animal study, an application can be applied to a patient in a desperate

Table 1
Cell-based therapy technology classification (Adapted from Mount et al.[12]).

Technology	Cells/Materials of use	Purpose
Somatic cell technology	HSC, MSC, Tumor infiltrationg lymphocytes, chondrocytes, skin stem cells, viral reconstitution T cells, dendritic cells, regulatory T cells	Administration of specific cell product for specific therapeutic treatment without further technological input
Immortalized cell lines	Neuronal stem cell line CTX	Derived from fetal cortical brain tissue, CTX can be used for stroke
Ex vivo gene modification of cells using viral vector technologies	T cells, HSC, MSC	Genetically modify the cells to target and activate them to effect selectively
In vivo gene modification of cells using viral vector technologies	T cells, HSC, MSC	Introduction of genetic material into the human body by viral vectors
Genome editing technologies (TALEN, ZFNs, meganucleases, CRISPR-Cas9 systems)	Many different cells	Target genes for different theurapeutic approaches
Cell plasticity technologies	Mouse and human induced IPS	Unlimited supply of cells for treatment
Three dimensional technologies	Hyaluronic acid, bone substitutes, alginate-encapsulated islets, Biomaterial scaffolds, smart biomaterials	Support cell viability, induction of cell differentiation, provision of a substrate for cell growth and support for tissue regeneration

HSC: Hematopoietic Stem Cells, IPS: Induced pluripotent stem cell, MSC: Mesenchymal stem cells.