



Topic Insights

Cell Therapy: Pharmacological Intervention Enters a Third Era

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1. Introduction

On August 30, 2017, the US Food and Drug Administration (FDA) released a news statement on its website titled “FDA approval brings first gene therapy to the United States” [1]. The article disclosed the use of FDA-approved Kymriah (tisagenlecleucel), a cell-based gene therapy developed by Novartis Pharmaceuticals Corporation, for certain pediatric and young adult patients with refractory or relapse acute lymphoblastic leukemia (ALL). ALL is a cancer of the bone marrow and blood, which progresses quickly and is the most common childhood cancer in the United States. Kymriah, which is a genetically modified autologous T cell immunotherapy, is approved for use in those up to 25 years of age with B cell precursor ALL. The individual patient’s own T cells are genetically modified with a new gene that contains a specific protein (chimeric antigen receptor, CAR) directing the T cells to target and kill leukemia cells with a specific antigen (cluster of differentiation 19, i.e. CD19) on the surface. In fact, Kymriah represents a kind of adoptive cellular immunotherapy using gene-engineered T cells. “We’re entering a new frontier in medical innovation with the ability to reprogram a patient’s own cells to attack a deadly cancer,” said FDA Commissioner Scott Gottlieb, MD. From a historic point of view, cell therapy—or, more accurately, cell-based gene therapy—represents an important marker indicating that pharmacological disease intervention has entered a new era. The first era of disease intervention by drugs was based on chemical medicine, and the second era was based on biological drugs. Now the third era has arrived: cell therapy. This article outlines the historical progress and characteristics of three eras of pharmacological disease intervention, and analyzes the prospects for cell therapy.

2. The three eras of pharmacological disease intervention

Drugs have long been used as a technical means of intervening in the course of a disease in order to achieve a cure. Written between 221 BCE–220 CE, *Huangdi Neijing* (literally the *Inner Canon of Huangdi*) holds 13 prescriptions for the treatment of diseases. Since then, traditional Chinese medicine practitioners have accumulated rich experience in the treatment of human diseases with Chinese medicine. Human use of opium and its natural active ingredient, morphine, also has a 5000-year history [2]. With developments in modern science and technology, the material basis of

the use of this ancient empirical drug has been fully established. This paper puts forward the concept of three eras of pharmacological disease intervention with a focus on the influence of science and technology on historical progress in drug intervention in human disease. Our purpose is to analyze the far-ranging effects of the key technical milestones in each era, and to identify the changing regularity and development trends. It is notable that the relationship between the three eras of pharmacological disease intervention is not one of substitution; rather, it involves superimposition or even mutual reinforcement.

One of the most important historical advances in medicine is the diagnosis of disease, which contributes to medical progress through two disciplines: basic medicine and clinical medicine. According to the 10th revision of the World Health Organization’s International Classification of Diseases (ICD) (ICD-10), there are 2468 major categories of human disease and 19 707 subcategories.

Another important advance in medicine is the use of drug treatment for disease intervention. In 1763, the British cleric Edward Stone extracted salicin from willow bark. In 1899, Bayer AG in Germany introduced the first synthetic chemical drug, aspirin (developed from salicin), to the market, thereby initiating the era of chemical medicine treatment—the first era of pharmacological disease intervention.

2.1. The first era of pharmacological disease intervention: Chemical medicine treatment

The major characteristics of the era of chemical drug therapy are discussed below in terms of demand, technology, and society.

2.1.1. Demand for disease treatment: The driving force for the development and application of chemical drugs

The demand for disease treatment determines the types and varieties of chemical drugs, the concentration and allocation of research and development (R&D) resources, and the direction and focus of application. Changes in the demand for disease treatment also have an impact.

Since the 19th century, and particularly since World War II, improvements in living conditions have greatly improved human health and extended our life expectancy. Healthcare developments, the use of vaccines for large-scale prevention of infectious diseases, and improvements in living conditions have relieved the threat to human health that has long been posed by classic deadly infectious

diseases such as smallpox and the plague. However, infectious diseases such as influenza, tuberculosis, and acquired immunodeficiency syndrome (AIDS) still threaten the health of people in certain countries and regions. Cross-species transmission of microorganisms also threatens the health of people in certain areas by infecting people with avian influenza virus and Ebola virus in the form of emerging and reemerging infectious diseases.

Nevertheless, the extension of human life expectancy has caused the global population to become an aging one. Senescence is a major risk factor in disease. Thus, chronic non-communicable diseases, such as cancer, cardiovascular and cerebrovascular diseases, diabetes, Alzheimer's disease, osteoporosis, obesity, and pain, have gradually become the major threat to human health worldwide. This change in the disease spectrum is affecting the direction and emphasis of the R&D of chemical drugs. More than 2600 chemical entity drugs with different chemical structures are currently available in the world. When combinations of basic molecules, structural modifications, and so forth are included, there are more than 10000 listed drugs [2]. These drugs can be used to treat more than 1100 major categories of human disease. At present, the hottest areas of research and funding include cancer and diabetes, among others [3]. However, it is clear that there has been insufficient investment in the R&D of Alzheimer's disease, pain, schizophrenia, and more, due at least in part to their unclear mechanisms and high R&D business risk.

2.1.2. Technological drug research: Shifting focus from active chemical components to molecular-targeting receptors

The classic drug R&D mode is based on active chemical components. First, a toxin, herb, or other plant material exhibiting a pharmacological effect on laboratory animals is found, and its active chemical component (or components) is separated. Next, its molecular structure is confirmed and a way to synthesize the molecule is identified. Finally, the biological activity of the compound is identified. After that, the molecule can be modified to optimize its structure in order to reduce the dosage and improve the curative effect. Most of the frequently used 433 molecular entities at present were found using the classic drug R&D mode. This mode, which was used in the development of chemical drugs from the early 20th century to the middle of the 20th century, has two major disadvantages: ① The targets of the drug for the molecule or cell are mostly unknown; and ② the process is costly and time consuming due to the strict requirements for a potential drug, which include a large quantity of synthetic compounds and a great deal of animal experimentation.

In fact, receptor theory and quantitative pharmacological analysis methods of drug research have always been associated with the classic drug R&D mode, and gradually became the mainstream of drug R&D by the middle of the 20th century. Receptor theory was first put forward in the early 19th century by the British physiologist John Newport Langley and the German immunologist Paul Ehrlich, and had a great and far-reaching impact on drug development. In 1933, Alfred Joseph Clark put forward the embryonic form of "occupation theory," and in 1956, Robert P. Stephenson introduced the concept of "efficacy" and perfected the theory of receptor occupation. In 1966, Robert Furchgott proposed the concept of "intrinsic efficacy," which separated the effectiveness of the organizational response from the efficacy of the agonist receptor complex; the concept of "relative efficiency" has since been widely used to describe different receptor systems. The two-state theory (1957) and rate theory (1961) further perfected the receptor theory in regards to the opening and closing of the ion channel and the difference in the antagonist and agonist rates, while the study of G protein-coupled receptors developed the receptor theory into the more complex and elaborate tripartite multistate receptor system. In the past few decades, a model with drug molecular

targets at its core has gradually replaced the traditional "black box" model in the R&D of chemical drugs. The importance of receptor theory in the development of chemical drugs is that it causes chemical drugs to be more targeted; active research in receptor theory, along with increased output, is taking place in drug development for cancer and cardiovascular diseases. About 50 kinds of antitumor small-molecule-targeted drugs have been developed for the treatment of cancers; these have good therapeutic effect and fewer side effects than conventional chemotherapy. Although doctors and patients favor these targeted drugs, their costs are high. Due to the difficulty in finding new drug targets, targeting the same molecule or receptor for a novel drug is a universal characteristic in the industry.

2.1.3. Stable growth of the pharmaceutical industry: A balance between strict governmental supervision and control and new high-tech industries

All countries adopt strict regulatory policies and laws for drug R&D. Clinical trials involve the key aspect of supervision, along with a focus on security and effectiveness. High risk is a primary feature of chemical drug development. It is generally believed that the probability of producing a desired compound is 1 in 5000 compounds, while only 10% of tested compounds in clinical trials are approved [2]. As a result, drug R&D has a long cycle and requires a high level of investment. It takes 10–15 years to develop an innovative drug. At the beginning of the 21st century, the total R&D expenditure of an innovative drug required about 800 million USD. That cost rose to about 1 billion by 2013. The R&D of an innovative drug reflects a dependence on high-tech innovation and talents, the need for patent-centric intellectual property rights, and highly specialized personnel support. Therefore, the R&D of an innovative drug is a highly systematic work, and an insurmountable problem in any link of the chain leads to its failure. However, the development of innovative drugs also has a high return: After a new drug is listed, a high income is obtained.

In general, drug R&D is divided between small companies that engage in preclinical research on drugs with the support of venture capital, and big pharmaceutical companies that merge with the former when their clinical trials have good prospects. Bayer's transition from a dyestuff chemical company into a chemical pharmaceutical company 120 years ago started the development of the pharmaceutical industry. The global drug market has expanded rapidly over the past 50 years, with its total market value doubling on average every six years [2]. In 2017, the total sales of the global drug market were 1.128 trillion USD and the annual growth rate was 4.81%. The drug market thus accounted for 1.5% of the global GDP, with the top 15 of the world's pharmaceutical companies accounting for about 50% of the market. Of the global drug market, 40% is located in North America, 22% in EU countries, 20% in China, 8% in Japan, and 10% in other countries.

2.2. The second era of pharmacological disease intervention: Biopharmaceuticals

In 1922, Frederick Grant Banting and Charles Herbert Best at the University of Toronto discovered insulin and used animal-derived insulin to treat diabetic patients, thereby initiating the era of biological drugs. In 1982, Eli Lilly and Company introduced recombinant human insulin, the world's first genetically engineered drug, into the market, thus bringing pharmacological disease intervention into the second era—the biopharmaceutical era, which introduced changes in terms of demand, technology, and society.

2.2.1. Demand: Addressing many refractory diseases

The large-scale application of low-cost, safe, and effective recombinant human insulin has greatly benefited the majority of

diabetic patients. Furthermore, erythropoietin (EPO) can be used for anemia in patients with chronic renal failure, tissue plasminogen activator (tPA) and urokinase can be used to treat myocardial infarction, and growth hormone (GH) can be used in the treatment of dwarfism. Interferon- β is now available for scleroderma, which has had no effective drug treatment for a long time, and antitumor necrosis factor antibody drugs can relieve refractory rheumatoid arthritis (RA). As of June 2016, the US FDA had approved 72 targeted antitumor drugs, including 24 targeted antibody drugs. Antibody drugs targeting immune checkpoints—including the anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody drug ipilimumab of Bristol-Myers Squibb (BMS), the anti-programmed cell death protein 1 (PD-1) antibody drugs pembrolizumab of Merck Sharp & Dohme and nivolumab of BMS, and the anti-programmed death-ligand 1 (PD-L1) antibody drug atezolizumab of Genentech/Roche—have demonstrated good results on solid refractory malignant tumors. These biopharmaceuticals are generally safe and have been shown to have a curative effect, with more than 30% of patients responding [3].

2.2.2. Technology: A clear target

Biopharmaceuticals have clear targets and a clear mechanism of action. Their high selectivity avoids the side effects caused by “off-target” toxicity. Therefore, they are safer than small-molecule chemical drugs. In particular, antibody drugs are highly favored by researchers due to their specificity to antigens.

2.2.3. Society: Monoclonal antibodies as a driving force for the development of biological drugs

Antibody drugs are highly targeted and have little clinical risk of failure. Compared with small-molecule chemical drugs, the development time of an antibody drug is short, the cost is low, and the market is growing rapidly. Therefore, antibody drugs have been the focus of R&D in large pharmaceutical companies as well as in small and medium-sized drug R&D companies, and their prospects are promising.

2.3. The third era of pharmacological disease intervention: Cell therapy

Today, pharmacological disease intervention has entered the third era of cell therapy. First, let us take a look back at the major milestones of this era. When bone marrow transplantation was carried out in the 1980s, T cells were inadvertently discovered to have therapeutic uses. T cells in whole-bone marrow grafts show antitumor activity. However, adoptive T cell transfer (ACT) not only causes a graft antitumor response, but also induces graft-versus-host disease (GVHD) [4]. In view of the side effects of allogeneic T cells, researchers have turned their attention to autologous T cells. In this regard, Steven Rosenberg at the US National Cancer Institute (NCI) is a pioneer in the treatment of cancer with ACT. In 1986, Rosenberg’s team first conducted the autotransfusion of lymphokine-activating killer (LAK) cells with interleukin-2 (IL-2) in the treatment of metastatic tumor patients [5]. High-dose IL-2 injection can result in capillary leak syndrome in patients, which stopped the clinical use of LAK cell infusion. During 1987–1994, Rosenberg’s team conducted a series of studies on tumor-infiltrating lymphocytes (TIL) in the treatment of metastatic melanoma. One study with 88 cases showed an effective rate of 34% [6]. The preparation for TIL is complex, and the polyclonal characteristics of TIL make it difficult to fully reflect its tumor specificity. In 2006, Rosenberg’s team reported for the first time that T cells modified by a T cell receptor (TCR) specific to the tumor-associated melanoma antigen recognized by T cells 1 (MART-1) could be adopted for the treatment of cancer patients [7]. This tumor-specific autologous T cell gene-engineering technique can develop so-called genetically engineered TCR-T cells, in parallel with CAR-T

cell technology. These technologies represent two directions of T cell engineering for cancer treatment. TCR-T cell technology is currently widely studied in clinical trials in the field of solid malignancies. Targeting NY-ESO-1 with TCR-T cells has attracted widespread attention due to its wide anti-tumor spectrum and few toxic side effects. Some scholars hope that this technique can be aimed at the frequent occurrence of mutated antigens during the development of malignant tumors, making the individualized treatment of tumors more specific.

In 1989, Eshhar et al. [8], a group of Israeli scientists, reported for the first time a CAR with antibody specificity. In 2011, June et al. [9] of the University of Pennsylvania reported the use of CAR-T cells for chronic lymphocytic leukemia (CLL) in the treatment of B cell lymphomas in the blood system with CD19 targeting. Multiple laboratories, including those of Sadelain et al. [10] at the Memorial Sloan-Kettering Cancer Center in 2013, Grupp et al. [11] at the University of Pennsylvania in 2014, and Turtle et al. [12] at the Fred Hutchinson Cancer Research Center in 2016, have reported the use of CAR-T cells for ALL; this treatment has yielded a high rate of response (70%–90%) and has had a durable effect.

In August 2017, Novartis launched CAR-T cell technology as a Kymriah product; as the first FDA-approved CAR-T cell technology, this product ushered in a new era of cell therapy application. In October of the same year, the US pharmaceutical company Kite Pharma targeted CD19 CAR-T cell therapy (Yescarta, axicabtagene ciloleucel); the US FDA approved this therapy for second-line therapy or additional rounds of treatment for adults with recurrent or refractory large B cell lymphoma. Despite the risk of serious side effects in the use of CAR-T cell therapy, the US FDA has carefully and conditionally approved this landmark technology.

Changes have also occurred in the demand-related, technological, and social characteristics of pharmacological disease intervention in the era of cell therapy, as represented by CAR-T cell therapy.

2.3.1. Demand: Tackling more complex and refractory diseases

Kymriah is adaptable to refractory or recurrent ALL, and the same is true of Yescarta treatment for large B cell lymphoma. The indications of these treatments are basically failed cases treated by chemotherapy, targeted drugs, and bone marrow transplantation; therefore, Kymriah and Yescarta belong to a second-line or third-line therapy scheme. Ongoing research projects are focusing on refractory Burkitt-like leukemia/lymphoma (BLL) and multiple myeloma. Of course, the validity of the approved CAR-T cell therapy is limited to malignant B cell lymphomas in the blood system. An effective treatment strategy has not yet been found for most malignant tumors involving non-B cell lymphomas in the blood system, or for solid tumors.

2.3.2. Technology: Strategies based on cells as carriers, synthetic gene-expressed proteins, and other key technologies

Technological strategies for pharmacological disease intervention in the third era are supported by the use of cells as drug delivery carriers, synthetic gene-expressed proteins as action molecules, and key technologies from cell engineering, antibody engineering, genetic engineering, and synthetic biology techniques. Cell therapy uses the T cell, which can proliferate *in vitro* as an effector cell. In this way, it solves the problem that most mature normal somatic cells cannot be amplified *in vitro*, and has therefore become a model for the successful application of cell engineering in humans.

Cell infusion and cell therapy efficacy are based on cell engineering. T cells are chosen as effector cells because they can proliferate *in vitro*. CAR-T cell therapy via antibody engineering technology uses monoclonal antibody fragments as targeted molecules for treatment, thus giving full play to the advantage of the

high antigen specificity of monoclonal antibodies. In CAR-T cell technology, a T cell surface receptor gene has been successfully synthesized by means of genetic engineering and synthetic biological techniques; the gene is then transfected into the patient's own T cells by a retrovirus or lentivirus vector *in vitro*. As a result, the extracellular fragment of the CAR-T cell is a specific antibody that can target the antigen on the tumor cells, whereas the intracellular fragment of the cell is comprised of normal molecules that can mediate T cell signal transduction and T cell activation, thus killing the tumor cell. This synthetic CAR can be regarded as an innovative application of drug receptor theory in the 21st century. In this way, cell therapy builds on practical support from genetic engineering and synthetic biology techniques, and receives theoretical support from oncology and tumor immunology.

2.3.3. Society: Government and societal response to the high-risk challenges of new CAR-T cell therapy technologies

CAR-T cell therapy was finally launched, largely due to its use as an effective treatment for refractory cancers. An initial, typical case brought this new technology into prominence. In April 2012, a six-year-old girl named Emily Whitehead, who had ALL, was continuing to get worse after two rounds of chemotherapy. She accepted CAR-T cell therapy from the June's team. The treatment produced a strong side effect on Emily—so much so that she was unconscious at one time. Later, however, she revived and recovered. Subsequent bone marrow examination revealed that her tumor cells had miraculously disappeared. Researchers later discovered that this side effect is mainly caused by cytokine release syndrome (CRS). In 2014, NCI pediatric clinicians in the United States used anti-IL-6 antibodies—a drug for rheumatoid arthritis—to treat CRS, and achieved good results [13]. In a sense, with the positive cooperation of patients and their families, doctors and scientists have engaged in clinical trials in order to continue to carry out innovative exploration based on problem solving. This has been an important scientific and technological factor in the success of CAR-T cell therapy, and has laid a solid foundation for regulatory science. Nevertheless, innovation in government regulation remains a key factor in the success of CAR-T cell therapy.

CAR-T cell therapy targeting the CD19 molecule has been used in the treatment of B cell tumors. Three pharmaceutical companies led this work: a big pharmaceutical company, Novartis, working in cooperation with June's team; a small company, Kite Pharma, working in partnership with Rosenberg's team; and another small pharmaceutical company, Juno Therapeutics, working with Sadelain's team. In 2016, within the JCAR015 clinical trial of the Juno Therapeutics for ALL, five patients died of cerebral edema. In July of the same year, the project ceased carrying out clinical trials, and in March 2017, Juno Therapeutics announced the termination of the JCAR015 project. Although the products of the other two companies were eventually listed, the US FDA took two important measures simultaneously when Kymriah was approved, as CAR-T cells can cause fatal CRS and certain side effects of nervous system toxicity. First, the scope of indications of the anti-IL-6 antibody drug Actemra (tocilizumab) was expanded in the treatment of CRS induced by CAR-T cell therapy. Second, a risk evaluation and mitigation strategy (REMS) for Kymriah products was established that is initiated as required, and includes elements to assure safe use (ETASU). Its procedures also include relevant technical requirements for clinical medical institutions and personnel researchers, in order to ensure that the benefits of the products are greater than the risks. The US FDA granted Kymriah the designations Priority Review and Breakthrough Therapy, thus ensuring that it will not only be listed as soon as possible, but will also involve risk control.

3. Prospects for cell therapy

3.1. Genetic engineering immunocytotherapy development

Genetic engineering immunocytotherapy will be developed in combination with other therapies in a multi-target direction with dynamic targeting, an expanding scope, and function optimization. Cell therapy has been derived from immune T cells for cancer immunotherapy. In the foreseeable future, cell therapy will be further developed in the area of immunotherapy for cancers. Here, the focus will be on targeting malignant solid tumors, in which the selection of the appropriate target is a key factor. This therapeutic strategy may be combined with chemotherapy and targeted therapy in order to attain better results. Considering the polygenic correlation of cancers, multi-targeting may be the design choice for the next generation of genetically engineered immune effector cells. Due to tumor heterogeneity and mutation, dynamic targeting strategies may be required in different treatment phases. In addition, cell therapy will expand in the treatment of diseases. Autoimmune diseases, infections, inflammation, degenerative diseases, and fibrosis may all become new fields for cell therapy [14]. Furthermore, the function of genetically engineered immune cells will be optimized, for example by reducing the release of harmful cytokines and causing cells to live longer *in vivo*.

3.2. Active cell therapy development in intelligence, automation, and facilitation

Active cell therapy is an important starting point for the development of precision medicine. Using cells as carriers results in a comprehensive performance that is much better than those of single-chemical and biological drugs. Cells can achieve intelligent functions, such as directional migration and aggregation, or cell death after the completion of the role, thus driving a certain function at a given stage. The automation of cell production *in vitro* is also a trend. Artificial intelligence and automation can be used to achieve the collection of cells, culture, infusion, and other components of automation, thus replacing manual labor. Cell therapy has made individualized medicine possible, and has become an important starting point for the development of precision medicine.

3.3. Live cell therapy challenges the government regulatory system and brings opportunities for reform and development

The question of whether cell therapy is a technology or a drug has always been a controversial one. If a government regulatory system is drug-based (as it is in most countries), then how can a multi-target continually adjusting treatment regimen be approved and regulated? Perhaps an innovative supply system will vigorously promote the rapid development of cell therapy, and thereby benefit all of humanity.

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