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Editorial

Cell Therapy: A New Era of Disease Intervention

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Cell therapy has been developing rapidly in recent years, and has brought forward unique perspectives, methods, and means for curing human diseases. Following surgery, chemotherapy, and radiotherapy, cell therapy is known as the "fourth weapon" in malignant tumor treatment. Significant progress has also been made in the use of cell therapy to treat tissue injuries, genetic diseases, and diabetes. In fact, cell therapy is not only a hot topic in experimental and clinical research, but also a target of industry. According to the 2017–2021 report by Technavio, an internationally renowned market research company, the global cell therapy market is expected to grow at a compound annual growth rate of 23.27% between 2017 and 2021, up to 120 billion USD by 2021. Cell therapy technology has provided new solutions for serious diseases such as malignant tumors, and has become the hope of patients fighting a losing battle with disease. In this context, *Engineering*, the official journal of the Chinese Academy of Engineering (CAE), has published a special issue on cell therapy. This issue is composed of eight reviews and treatises on cell therapy that cover different aspects of this field. The editorial board of this special issue is deeply grateful to all the authors, reviewers, and editors who made this special issue possible.

In 2010, Emily Whitehead, a five-year-old patient with acute lymphoblastic leukemia, was the first pediatric patient to receive CD19-directed chimeric antigen receptor-modified (CAR) T cell (CART19) treatment. This treatment, which was jointly provided by the University of Pennsylvania and Novartis, completely cured Emily's disease with a single infusion of CART19s. Eight years later, no relapse has been observed. This breakthrough led to the maturation and fame of CART19 therapy, which was officially made broadly available on the market in 2017, to the benefit of acute lymphoblastic leukemia patients. Many countries around the world, including China, have conducted clinical research on cell therapy at various scales for tumor treatment.

In this special issue, Professor Xiaojun Huang from Peking University Institute of Hematology reports on the results of clinical research using CART19 and the "Beijing Protocol" developed in his department to treat leukemia. Professor Fang Chen of the University of Pennsylvania describes a successful experience with CAR T cell clinical research with his team, and discusses new ideas on T cell basic product development as a cure for cancer.

In addition to CAR T cells, many immune cells such as natural killer (NK) cells, gamma delta ($\gamma\delta$) T cells, and dendritic cells (DCs) are ideal for tumor treatment. Professor Zhigang Tian of the University of Science and Technology of China and Professor Cai Zhang of Shandong University share their findings, discuss current problems in the field, and describe the prospects of NK cell therapy for cancer treatment.

Immune attack plays an important role in killing tumors, and interfering with the immune escape mechanism employed by tumors is also being widely explored. Regulatory T cells (Tregs) are an immune cell subpopulation with immunomodulatory properties, and research has shown that Tregs suppress immune response and facilitate immune escape in the tumor microenvironment. Therefore, ways to control the function and stability of Tregs have become a new focus for tumor immunotherapy. In this issue, Professors Bin Li and Dan Li of Shanghai Jiao Tong University and Professor Hongtao Zhang of the University of Pennsylvania respectively review new ideas in antineoplastic therapy that involve regulating Tregs through checkpoint blockade, function inhibition, specific depletion, and epigenetic modification.

Tregs have also been shown to effectively prevent the occurrence of graft-versus-host disease (GVHD) after bone marrow transplantation. The use of Treg therapy to prevent GVHD was pioneered by Professor Bruce R. Blazar and his team; here, Professor Blazar discusses the current status and difficulties of cell therapy aimed at preventing or treating GVHD and adverse immune responses in patients such as those with autoimmune disease. In China, Professor Ling Lu of Nanjing Medical University, who is taking the lead in the application of Tregs to induce immune tolerance after liver transplantation, has reported on the successful

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achievement of tolerance induction in some patients by means of Treg therapy.

Current statistics show that a great deal of the world's cell therapy research is being conducted in China, which gives China unique advantages in terms of clinical resources in the field of cell research. Therefore, the key issue at present is how supervisory departments can guide this field to make cell therapy more standardized, both scientifically and internationally. With his team, Professor Junzhi Wang, the chief expert in biological product quality control at National Institutes for Food and Drug Control of China, has composed a set of guidelines for the quality control and safety evaluation of cell therapy, including standards for product quality and cell therapy evaluation norms—a work that is partly based on his experience with the World Health Organization. This work provides an important reference for the approval and supervision of units, institutions, and industries that carry out cell therapy product development and research in China.

What changes and trends will cell therapy bring to disease treatment in the future? Professor Wei He of the Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences, and School of Basic Medicine of Peking Union Medical College discusses how Chinese medical innovation has impacted the historical process of drug intervention in disease treatment, including its features and development trend, and cell therapy. Treatment interventions in patients have led to the development of the eras of chemotherapy, biomedicine treatment, and cell therapy. Although cell therapy has demonstrated great advantages in the treatment of leukemia, significant challenges remain in the treatment of other hematologic malignancies, and especially in the treatment of solid tumors, which present an even more complex situation. At the same time, improvements in the curative efficacy of cell therapy are accompanied by obvious toxicity and side effects. The problem of how to expand the indications, increase the efficacy, and improve the safety of cell therapy has not yet been solved. In terms of need, cell therapy mainly focuses on treating complicated and refractory diseases. In terms of technical strategy, the cell is used as a carrier for drug delivery. This technology is supported by the fields of cell engineering, antibody engineering, genetic engineering, and synthetic biology techniques. In future, cell therapy will be integrated with other therapies and will be developed further in order to achieve multi-targeting, dynamic targeting, range expansion, functional optimization, and so forth. Cell therapy will be developed in order to realize intelligence, automation, and convenience, and will become an important means of development for precision medicine.

With the advent of the cell therapy era, what should China do? At present, four domestic problems urgently require solutions: ① Breakthroughs must be achieved in bottlenecks in the core technology; ② a strict supervisory system and approval process must be established; ③ scientific clinical evaluation must be performed; and ④ a successful industrial demonstration must be set up. Regarding the last of these problems, the pilot work of planning the framework and construction of the China Cell Valley (CCV) in Nanjing may provide a demonstration of cell translational research and industrialization for the cell therapy industry in the near future. The CCV is committed to promoting cell research and industrial development in accordance with a concept known as "one union, two wings, and four bodies." Within this concept, the "one union" refers to the cell engineering research institutes within the CCV, while the "two wings" includes the Fund for cell research and innovation, and the other is the Museum of cell and life. The "four bodies" refer to the cell research and development platform, the cell preparation and detection platform, the cell storage platform, and the clinical cell platform. The layout of the CCV permits the realization of centralized supervision, examination, and approval, along with a regional preparation center and clinical cell infusion. It also includes the full support and coordination of governmental departments at all levels, without which it would remain a formality. China's biomedical industry should seize this historic opportunity to become a world leader in cell therapy by making good use of China's current advantages, undertaking the dual management of clinical technology and drugs, propelling the establishment of a cell therapy approval and supervision system, exploring new forms and applications of cell therapy, and thus promoting the development of this new era of disease intervention.