Commentary

Stem Cell INVESTIGATION

Chimeric antigen receptor (CAR)-directed adoptive immunotherapy: a new era in targeted cancer therapy

Yamei Chen[1,2], **Delong Liu**[1,3]

[1]Division of Hematology/Oncology, Department of Medicine, New York Medical College, Valhalla, New York 10595, USA; [2]Department of Hematology, Xiamen Zhongshan Hospital, Xiamen University, Xiamen 361001, China; [3]Institute of Hematology, Henan Tumor Hospital, Zhengzhou University, Zhengzhou 450003, China

Correspondence to: Delong Liu, MD, PhD, Distinguished Professor. Henan Tumor Hospital, Zhengzhou University, Zhengzhou 450003, China. Email: delong_liu@nymc.edu.

Abstract: As a result of the recent advances in molecular immunology, virology, genetics, and cell processing, chimeric antigen receptor (CAR)-directed cancer therapy has finally arrived for clinical application. CAR-directed adoptive immunotherapy represents a novel form of gene therapy, cellular therapy, and immunotherapy, a combination of three in one. Early phase clinical trial was reported in patients with refractory chronic lymphoid leukemia with 17p deletion. Accompanying the cytokine storm and tumor lysis syndrome was the shocking disappearance of the leukemia cells refractory to chemotherapy and monoclonal antibodies. CAR therapy was reproduced in both children and adults with refractory acute lymphoid leukemia. The CAR technology is being explored for solid tumor therapy, such as glioma. Close to 30 clinical trials are underway in the related fields (www.clinicaltrials.gov). Further improvement in gene targeting, cell expansion, delivery constructs (such as using Sleeping Beauty or Piggyback transposons) will undoubtedly enhance clinical utility. It is foreseeable that CAR-engineered T cell therapy will bring targeted cancer therapy into a new era.

Keywords: Chimeric antigen receptor (CAR); adoptive immunotherapy; T cell immunotherapy

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There have been ongoing attempts on using gene therapy, cellular therapy, and immunotherapy for cancer. Humanized monoclonal antibodies have been widely used for targeted therapy of leukemia, lymphoma, and solid tumors. Translation of gene and immune-targeted cellular therapy to clinical application has been painstakingly slow. As a result of the recent advances in molecular immunology, virology, genetics, and cell processing, chimeric antigen receptor (CAR)-directed cancer therapy has finally arrived for clinical application. CAR-directed adoptive immunotherapy represents a novel form of gene therapy, cellular therapy, and immunotherapy, a combination of three in one. Recently, CAR-engineered T lymphocytes have been successfully used to treat patients with refractory lymphoid leukemias.

The major hurdle in immune-targeted cellular therapy has been the MHC restriction, limited cell dose due to the lack of *in vivo* expansion, and difficulty of long-term maintenance of the engineered cells *in vivo*. In addition, portability of the technology for wide clinical application is a classical problem. CAR technology bypasses the MHC restriction by using the antigen binding site of a specific monoclonal antibody and the T cell receptor signaling machinery, thereby allowing transduction of a specific T cell activation signal directly into the engineered cytotoxic T cells. Built into the CAR cassette is also a sequence that facilitates T cell expansion *in vivo*. Packaging of the CAR cassette into a pseudo-lentivirus on one hand ensures the efficient and safe delivery into the genome of T cells, the technology, on the other hand, makes it easily portable for therapy of different cancer types and other diseases, as well as to many hospitals.

Early phase clinical trial was first reported in patients

with refractory chronic lymphoid leukemia with 17p deletion (1). Accompanying the cytokine storm and tumor lysis syndrome was the shocking disappearance of the leukemia cells refractory to chemotherapy and monoclonal antibodies. CAR therapy was reproduced in both children and adults with refractory acute lymphoid leukemia (2,3). The CAR technology is being explored for solid tumor therapy, such as glioma (4,5). Close to 30 clinical trials are underway in the related fields (www.clinicaltrials.gov). Further improvement in gene targeting, cell expansion, delivery constructs (such as using Sleeping Beauty or Piggyback transposons) will undoubtedly enhance clinical utility (5). It is foreseeable that CAR-engineered T cell therapy will bring targeted cancer therapy into a new era.

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Footnote

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