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Peptide vaccines for myeloid leukaemias

Tao Dao MD, PhD
Senior Research Scientist

David A. Scheinberg* MD, PhD
Chairman
Molecular Pharmacology & Chemistry Program, Leukemia Service, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA

The development of cancer vaccines directed against myeloid leukaemias has been a research area of intense interest in the past decade. Both human studies in vitro and mouse models in vivo have demonstrated that leukaemia-associated antigens (LAAs), such as the fusion protein BCR-ABL, Wilms' tumour protein and proteinase 3, may serve as effective targets for cellular immunotherapy. Peptide-based vaccines are able to induce cytotoxic T-lymphocyte responses that kill leukaemia cells. Based on these results, pilot clinical trials have been initiated in chronic and acute myeloid leukaemia and other haematological malignancies, which include vaccination of patients with synthetic peptides derived from these LAAs. Results from these trials show that peptide vaccines are able to induce immune responses that are sometimes associated with clinical benefit. These early clinical results are promising and provide valuable information for future improvement of the vaccines. This chapter will focus mainly on discussing the preclinical studies of peptide vaccines in human systems, the results from clinical trials and the future prospects for vaccine therapy for myeloid leukaemia.

Key words: myeloid leukaemia; vaccine; peptide; WT1; BCR-ABL; PR1; RHAMM-R3.

The development of tumour vaccines that elicit cytotoxic T-lymphocyte (CTL) responses directed against malignant cells has been a major goal for cancer immunotherapy. Leukaemia-associated antigens (LAAs) have been identified that potentially allow for selective immunological targeting and elimination of leukaemia cells. Many LAAs are not membrane proteins and therefore are not targets for antibody therapies. However, these LAAs may be processed and presented on the cell surface as 9–10-mer peptides that can be recognized by CTLs in the context of human leukocyte antigen (HLA) class I molecules.[1,2]

* Corresponding author. Tel.: +1 646 888 2190; Fax: +1 646 422 0296.
E-mail address: d-scheinberg@ski.mskcc.org (D.A. Scheinberg).

Allogenic bone marrow transplant (BMT) is an effective therapy for chronic and acute myeloid leukaemia (CML and AML) due to the presence of a graft-versus-disease effect mediated by alloreactive effector cells.[3,4] Donor lymphocyte infusion in relapsed leukaemia after allogenic BMT has also provided clear evidence that donor-derived T cells are capable of eliminating leukaemia cells. The high relapse rate of T-cell-depleted transplantation has further demonstrated the important role of T cells in eradicating leukaemia.[5–7] This graft-versus-leukaemia (GVL) effect has been attributed to the response of donor T cells to major or minor histocompatibility complex (MHC) molecules expressed by recipient-derived cells.[8–12] A component of the GVL effect may be the more specific targeting of leukaemia cells through the recognition of LAAs expressed by these cells.

Unfortunately, donor T cells also recognize allogeneic targets expressed by host non-haematopoietic elements, resulting in manifestations of graft-versus-host disease, which remains a major cause of transplant-related mortality.[8,13] An ideal therapeutic strategy would be the development of leukaemia vaccines that could educate host immune effector cells to target leukaemia cells selectively, while sparing normal cells via the generation of functionally potent leukaemia-specific cytotoxic T cells.

In this context, the identification of LAAs has made a therapeutic approach based on targeting specific antigens a real possibility. These include the BCR-ABL fusion protein, Wilms' tumour protein (WT1) and proteinase 3. Most LAAs are either self-antigens that are overexpressed in leukaemia cells or abnormal fusion proteins resulting from chromosome translocations, and serve as relatively leukaemia-specific targets for CTL responses.[14,15] Immunotherapy targeting these LAAs using a number of different approaches, including DNA vaccines, protein-based vaccines, and cellular- or dendritic cell (DC)-based vaccines, has opened promising new therapeutic avenues.[16–18]

Preclinical studies have shown that peptide vaccines derived from the WT1 protein, protenase-3, hyaluronic-acid-mediated motility (RHAMM) and the fusion protein BCR-ABL are able to induce CTL responses against leukaemia cells.[19–23] Subsequently, these peptide vaccines have been tested in clinical trials on patients with CML, AML and myelodysplastic syndrome (MDS). The preliminary results from these trials show that peptide vaccines are able to induce specific T-cell responses that are associated with clinical responses in some patients.[24–33] This chapter will focus on reviewing the preclinical studies, preliminary results from clinical trials and the prospects for using peptide vaccines against myeloid leukaemias.

PEPTIDE VACCINES THAT TARGET THE BCR-ABL FUSION PROTEIN

CML is a haematological progenitor cell disorder characterized by the presence of the Philadelphia (Ph1) chromosome in leukaemia cells. *Ph1* represents a translocation in which the *ABL* gene on chromosome 9q34 has moved to *BCR* on chromosome 22q11, forming the *BCR-ABL* chimeric gene. In CML, the second or third exon of the *BCR* gene is usually spliced into the second exon of the *ABL* gene, creating B2A2 or B3A2 transcripts. When translated, B2A2 or B3A2 mRNA each generate a 210-kDa BCR-ABL protein. The BCR-ABL fusion protein shows tyrosine kinase activity and is essential and sufficient for leukaemia transformation. The junctional sequences of BCR-ABL are only expressed in leukaemia cells, and are therefore an ideal tumour-specific target for the immunotherapy of CML patients.[24,34] Peptides spanning the BCR-ABL breakpoint for both MHC class I and class II have been shown to induce peptide-specific T-cell responses in preclinical studies and clinical trials.