Current Status of Human Melanoma Vaccines
Can They Control Malignant Melanoma?

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Summary

The characterisation of human melanomas as immunogenic and the observation of spontaneous regression have led to the development of active specific immunotherapy in the form of vaccines for treatment of malignant melanoma. These vaccines have recently been the subject of considerable interest, particularly since the introduction of melanoma antigen cloning, the identification of specific peptide sequences recognised by the immune system, and better understanding of antigen presentation. Today, melanoma vaccines are a significant therapeutic agent in treatment of malignant melanoma. There are many melanoma vaccines that are in clinical trials which have produced very encouraging clinical responses. This review discusses the different forms of melanoma vaccines used in the 1990s and their current status in clinical trials.
An uncommon cancer several decades ago, cutaneous melanoma has increasingly become a significant health risk around the world, particularly in populations from North America, Europe and Australasia. Cutaneous melanoma most frequently occurs in Caucasians and residents of ‘sunbelt’ areas. Although numerous studies have strongly identified the major aetiological agent as ultraviolet light, the incidence of melanoma is increasing more than 5% annually in the United States, faster than most other cancers.[1] The 2 possible major reasons for this increase are the reduction in the ozone layer and the increase in leisure time associated with the modern lifestyle.

The incidence of cutaneous melanoma significantly exceeds the mortality from melanoma. Because of modern medicine, greater public awareness and various screening programmes, small melanoma lesions are often detected early; therefore, the mortality of melanoma fortunately has not kept pace with its incidence. However, melanoma lesions that are not detected early and are allowed to progress can eventually lead to fatal metastatic disease.

At present, the major therapeutic approach to malignant melanoma is surgical removal followed by adjuvant therapy.[2-4] Conventional adjuvant therapies such as radiation and chemotherapy have been moderately effective against this highly aggressive cancer.[2] The melanocyte, the normal counterpart precursor cell of melanoma, is located at the junction of the epidermis and the dermis in the skin and thus is routinely exposed to more solar radiation and chemical carcinogens than any other anatomical site. The melanocyte resists genetic damage by an efficient DNA repair mechanism; however, this repair mechanism may also account for the strong resistance of melanoma to DNA lesion–inducing radiotherapy and chemotherapy.

Active specific immunotherapy is a promising alternative because melanoma can be very immunogenic in humans.[4-9] Interestingly, the melanocyte has some properties similar to antigen-presenting cells such as dendritic and Langerhans cells, which are well known for initiating immune responses.[10] Indeed, the immunogenicity of melanoma has been exploited for several decades and is the premise underlying vaccine therapy.[5,11-18]

A vaccine is one of the most efficacious, safe, nontoxic and economical weapons to prevent disease and to control the spread of disease. Conventional vaccines are a form of immunoprophylaxis given before disease occurrence to afford immunoprotection by generating a strong host immunological memory against a specific antigen.[19,20] The primary aim of vaccination is to activate the adaptive specific immune response, primarily to generate B and T lymphocytes against specific antigen(s) associated with the disease or the disease agent.

A cancer vaccine also requires antigenic targets for an immune response to be focused on. Melanomas can be immunogenic and can activate host immune responses (antigen-specific effector cells and/or antibodies) capable of controlling the disease and causing tumour regression.[4,5,9,18] However, melanoma at the same time can be specifically and nonspecifically immunosuppressive and can evade the host’s immune system.[21-28] The time for which the patient has had melanoma and the tumour burden will also play an important role in how the immune system has been responding to the tumour antigens. These are factors which will play a role in designing an efficacious vaccine. The success of a melanoma vaccine will depend on the:

- system of tumour antigen presentation
- duration of antigen stimulation
- level of antigen expression
- immunogenicity of the epitopes of the antigen
- immunoregulation towards the antigen
- relative homology of the tumour antigen with respect to normal antigens.

Overall, in developing an effective melanoma vaccine, information on the natural history of metastatic melanoma must be well integrated in the vaccine treatment protocol. In this review, we first discuss the tumour antigens that can induce immune responses in humans. We then review the types of melanoma vaccines developed to date and the clinical results if available. Finally, we discuss antigen presentation and delivery systems of melanoma vaccines, since these are important in determining