Personalized cancer vaccine promises remission

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A personalized, therapeutic vaccine has recently been shown to eliminate cancer in a Phase I clinical study of patients with chronic myelogenous leukaemia (CML) who are also being treated with Gleevec® [1].

Cancer vaccines

Although approaches to manufacturing cancer vaccines vary and include – but are not limited to – the use of whole cells, peptides, genetically modified tumour cells and apoptotic tumour cells, they are all geared toward the same end; namely, to stimulate the host's immune system to respond to antigens characteristic of cancer cells. Pramod Srivastava, Professor of Immunology and Director of the Center for Immunotherapy of Cancer and Infectious Diseases at the University of Connecticut School of Medicine (http://www.uchc.edu), believes 'cancers are as unique as a fingerprint' and, therefore, the approach 'has to be personalized'. Srivastava is also the co-founder of Antigenics (http://www.antigenics.com), the company that develops the research for this vaccine, designated AG858, and for other cancer vaccines based on heat shock protein technology, such as Oncophage.

The Gleevec© club

CML is a cancer of the blood that is characterized by the unchecked proliferation of transformed bone marrow stem cells. It accounts for 15–20% of all adult leukaemias, with a median age of diagnosis of 50 years. Patients with CML usually progress through three phases: chronic, accelerated and blast crisis. Most patients are diagnosed by a routine blood test in the chronic phase wherein many are asymptomatic, but after a few years patients are likely to experience fatigue, weight loss, abdominal distention, bleeding and/or night sweats due to an excess of white blood cells in the peripheral blood and bone marrow. The leukaemic cells of almost all CML patients contain the Philadelphia chromosome (Ph), an acquired mutation that is the result of a reciprocal translocation between chromosomes 9 and 22. Ph encodes the fusion gene, Bcr-Abl whose translated product is a constitutively active tyrosine kinase that drives the growth of the leukaemic cells.

Brian Druker, a medical oncologist at the Oregon Health & Science University Cancer Institute in Portland, Oregon (http://www.ohsu.edu) says, 'CML is one of a handful of diseases where we clearly know that the immune system plays a major role in its treatment.' CML can be cured by bone marrow transplantation but donor availability and patient age limits the number of patients who are eligible [2].

Interferon-α and chemotherapeutic agents are also used to treat CML but since 2001 the treatment of choice has been Gleevec®, a Bcr-Abl tyrosine kinase inhibitor [3]. David Scheinberg, Chairman of the Molecular Pharmacology and Chemistry Program and Chief of the Leukemia Service at Memorial Sloan Kettering Cancer Center (http://www.mskcc.org) whose group has shown that a tumour-specific, Bcr-Abl peptide-derived vaccine can elicit measurable peptide specific T-cell immune responses in CML patients notes; 'While Gleevec® is effective in inducing a cytogenetic remission, nearly all patients are left with minimal residual disease – a state that is ideal for exploring the use of a vaccine to clear the final cells,' [4]. Druker, who was in large part responsible for the development of Gleevec®, adds; 'That's the whole point behind the Antigenics study... if you could figure out a way to get a patient's own immune system to help attack their leukaemia you might have a much more effective treatment by adding it to the available treatments.'

Heat shock-ing discovery

AG858 consists of autologous heat shock protein 70 (HSP70)-peptide complexes purified from the peripheral blood mononuclear cells of CML patients. According to Garo Armen, Chairman and CEO of Antigenics, HSPs have the role of intracellular 'schleppers' by shuttling peptides from one compartment of the cell to another. If the contents of the cell spill into the extracellular environment, during necrosis for example, HSPs send out a danger signal, basically recruiting antigen-presenting cells (APCs), such as dendritic cells (DCs), which internalize the HSP-peptide complexes (Fig. 1). 'There is evidence that when APCs take up HSPs together with the peptides they chaperone, the accompanying peptides are delivered into the antigen-processing pathways, leading to peptide presentation by

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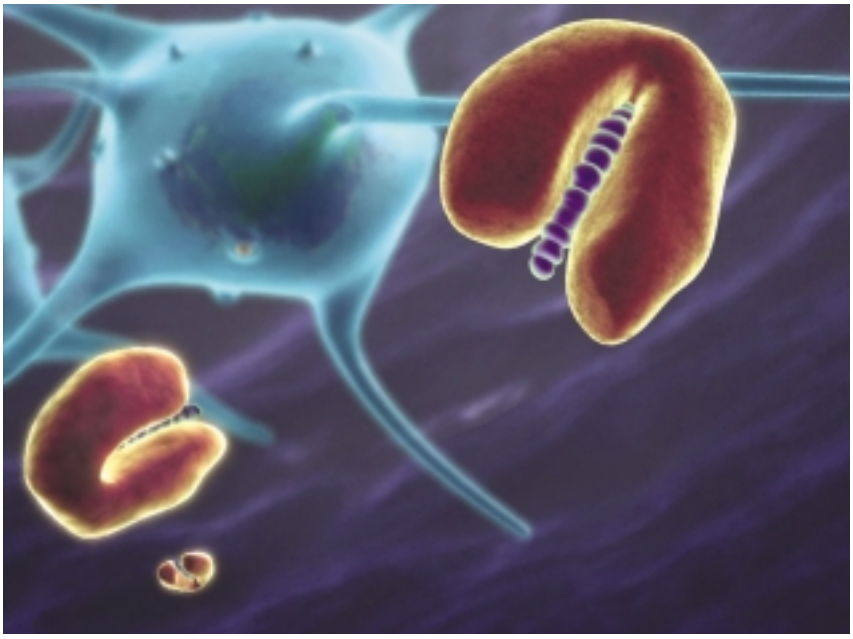

Figure 1. Antigenics' (http://www.antigenics.com) AG858, a personalized vaccine designed to treat chronic myelogenous leukaemia, consists of heat shock protein (HSP)-peptide complexes derived from individual patients' cancerous cells [heat shock proteins are shown in red and are carrying peptides (purple)]. The HSP-peptide complexes bind to and are taken in by the immune system's antigen-presenting cells (APCs), such as dendritic cells (blue cell), at the site of injection. APCs travel to the lymph nodes, where they re-present the antigenic peptides on their surfaces, thereby triggering a cancer-specific immune response. Figure courtesy of Garo Armen, Antigenics.

major histocompatibility complex (MHC) molecules,' explains Emmanuel Katsanis, Associate Professor of Pediatrics and Pathology at the Childrens Research Center, University of Arizona, Tucson (http://www.arizona.edu), who has studied tumour-derived chaperone-rich cell lysate (CRCL) and CRCL-pulsed DCs in a mouse model of CML [5]. When DCs travel to the lymph nodes T cells recognize the antigenic peptides and are specifically activated against cancer cells bearing these peptides [6].

Custom cancer cure?

Armen believes that the antigenic repertoire that is bound to heat shock protein is unique to the source from which the HSP is extracted. But, 'in a disease like CML where there is the same identifiable oncogene and oncoprotein target found in 100% of the cancer cells of the patients, it is possible to target nearly everyone with the disease, with one vaccine,' says Scheinberg. Srivastava argues that one person's cancer is different from another person's because 'as cancer cells divide, there is the generation of random diversity inherent in the process of cell division'.

In the Phase I trial designed to determine the feasibility of making the vaccine, seven out of eight patients experienced cytogenetic remission following a course of eight weekly injections, demonstrating measurable reduction in leukaemic cells. Two patients experienced molecular remission, indicating the elimination of cancer cells. According to Srivastava, 'Molecular remission with Gleevec® is extremely rare,' but because these patients were not necessarily Gleevec® resistant, a large, multicenter Phase II trial of AG858 in formally Gleevec®-resistant patients has begun 'to leave no doubt as to where the activity is coming from,' he says. 'If the magnitude of the response is similar to what we have observed in this trial we should be in good shape.' The investigators hope to see results of the Phase II trial by the middle of 2004.

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