Cancer vaccine for CML shows promise

Vaccines have long been seen as a potentially attractive option for treating cancer. Now a group targeting a peptide that plays a key role in CML think they may be onto a winner.

An Italian team of researchers has shown for the first time that a vaccine against a BCR-ABL-derived peptide can provoke a clinical response in patients with chronic myelogenous leukaemia (CML). Results from the 16-patient study of the vaccine, named CML-VAX100, were published in the *Lancet* (19 February 2005, p 657).

The target peptide, p120, is key to the pathology of CML as it is the product of the fusion gene, BCR-ABL, that forms with the characteristic Philadelphia chromosome mutation.

No company has directly expressed an interest in the vaccine to lead investigator Monica Bocchia of Siena University, whose team shares patent rights with US investigators. She said companies were welcome to talk to her about the possibility of developing the product, but the team was determined to go ahead with a Phase III trial even without commercial support, particularly as the vaccine is not difficult to manufacture. She would be approaching Italian co-operative groups about the study using CML-VAX100 plus imatinib versus imatinib alone.

Although Novartis's BCR-ABL tyrosine kinase inhibitor, Glivec (imatinib), has revolutionised CML treatment, there is still a lot of work going on to further refine therapy. Patients with chronic phase CML tend to have a rapid response to the treatment – they can achieve a complete cytogenetic response within six to 12 months – but molecular remissions are rare. "The eradication of residual disease (and possibly the cure) without bone marrow transplantation still seems a difficult goal for a tyrosine kinase inhibitor approach alone," note the study authors.

Very effective

In the *Lancet* study, CMLVAX100 was "very effective" in inducing a specific immune response say the authors – 70% of patients had a positive delayed-type hypersensitivity reaction and most generated a CD4 proliferative response. In an accompanying commentary (p 631), Saswati Chatterjee and K Wong of the City of Hope National Medical Center in California say it is "reassuring" that antigen-specific responses were generated in the trial.

Ten patients started the trial after 12 months of imatinib treatment, while six patients started after six months of treatment with interferon.

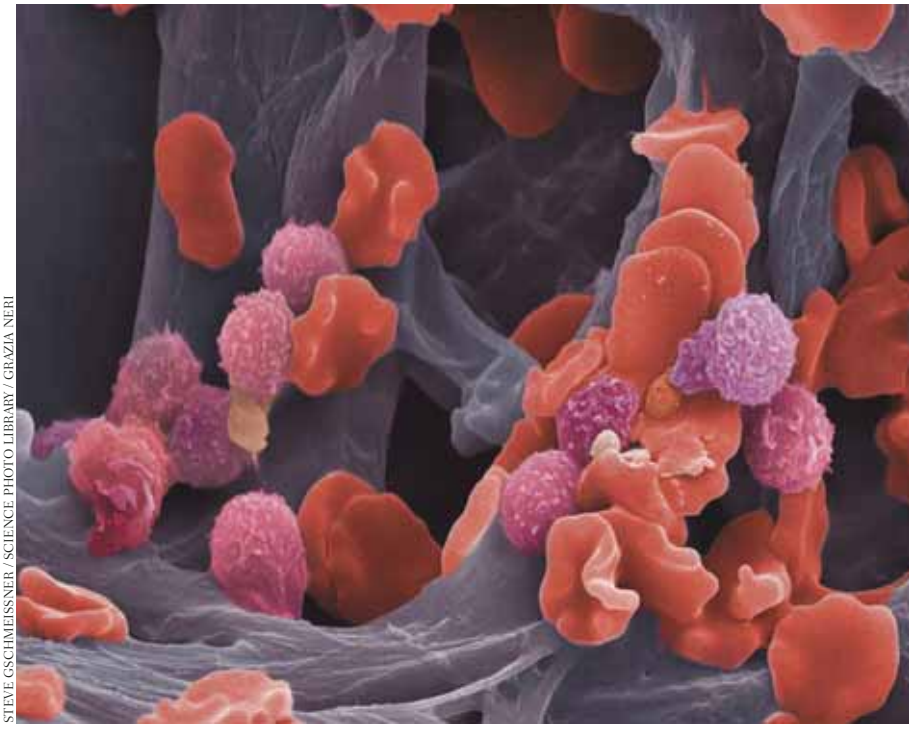
In the imatinib group, in which all patients had stable cytogenetic disease (median duration 10 months) at the start of the trial, apart from one with stable complete cytogenetic remission, all patients had improved cytogenetic responses after six vaccinations over 11 weeks. Five patients reached complete cytogenetic remission with three of these having undetectable levels of mRNA transcript from the BCR-ABL gene.

In the interferon group, in which patients had a median of 17 months stable residual disease before the study, all but one patient had improved cytogenetic responses and two reached complete cytogenetic remission. The degree of reduction in residual disease across the study seemed to correlate with the level of delayed-type hypersensitivity reaction.

All the patients received granulocyte-macrophage colony-stimulating factor (GM-CSF) and QS-21 as immune adjuvants. Wong and Chatterjee point out that, in previous studies, GM-CSF alone has increased the rate of cytogenetic remission in CML patients, but the dose was higher, so GM-CSF was unlikely to account for the success of Bocchia's trial.

Future option

CMLVAX100 is certainly a potential therapeutic option for CML in order to reduce residual disease and increase the number of patients who achieve a molecular response, the authors believe. Although the trial was not controlled, the speed of



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The proportion of patients reaching undetectable transcript levels contrasts with data on imatinib

response and the fact that three imatinib patients had undetectable transcripts make it likely that the vaccine had an effect on the patients in the study, said Bocchia.

The proportion of patients reaching undetectable transcript levels in a "very short period" contrasts with recent data on imatinib. A new molecular analysis of the IRIS study* showed that only 4% of patients in complete cytogenetic remission after imatinib treatment had undetectable transcripts, while this figure rose to 30% in patients with an early cytogenetic response.

Wong and Chatterjee say the development of vaccines against BCR-ABL or other CML-specific antigens appears to be a "reasonable avenue for further investigation" given the early promise of efficacy, ease of administration and lack of toxicity. However, they caution that there have been many disappointments in the history of work on tumour vaccines for CML, comparing the progress of development to the labours of Sisyphus.

The Phase II study with CML-VAX100 has now expanded to 22 patients. As well as plans to take the product into randomised Phase III trials, Bocchia's team is working on another vaccine. CMLVAX100 is suitable for the 60% of CML patients whose disease is characterised by the b3a2 break in the BCR gene; the new vaccine will tackle the remaining 40% of patients with b2a2 disease.

The emergence of imatinib resistance supports the development of new strategies to treat the disease, says the commentary. Novartis and rival Bristol-Myers Squibb have certainly realised this. Both are working on candidates for Glivec-resistant CML, and other companies are focusing on drugs to counter the problem in another of Glivec's indications, gastrointestinal stromal tumours. One company working to develop a commercial CML vaccine is Antigenics. It is studying a personalised cancer vaccine, AG-858, in Phase II studies.

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**The IRIS study (International Randomized IFN vs ST1571) is the largest CML Phase III study ever conducted. It compared the effects of interferon vs imatinib (Glivec) in 1106 CML patients treated at 117 centres in 16 countries*