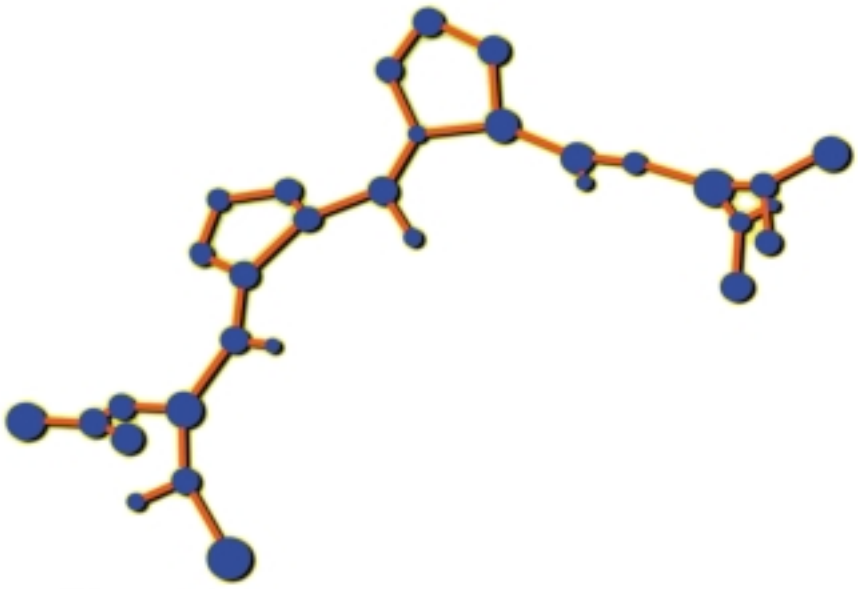


Figure 1. The peptide proline-threonine-threonine-proline (NT13) as it appears in solution. The NMDA-receptor partial agonist is due to enter clinical trials in patients with neuropathic pain. Figure kindly provided by Joseph Moskal (Northwestern University and Nyxis Neurotherapies, Evanston, IL, USA).

made animals acquire the associative learning task faster [5]. Moskal explains: 'Hippocampal lesions in humans and animals cause severe deficits in the ability to transfer information from short- to long-term stores and thus from new memories. In the trace paradigm, a blank 'trace' period intervenes between CS [conditioned stimulus; a warning tone] offset and US [unconditioned stimulus; a gentle puff of air into the eye] onset, which requires the formation of a very short-term memory of the CS in order to successfully predict US onset and perform conditioned responses [eye blink] timed properly to avoid the US.'

Using a gerbil model of ischaemia, the team demonstrated that NT13 given pre-ischaemia or 1–5 hours post-ischaemia had a neuroprotective effect equivalent to that of MK801 (Moskal, J.R. *et al.* Abstract to be presented at the *Society for Neuroscience 32nd Annual Meeting*, 2–7 November 2002, Orlando, FL, USA).

According to Moskal, NT13 can also alleviate neuropathic pain. To test this, the investigators crushed the sciatic nerves of rats to induce mechanical allodynia – a condition in which things that normally do not hurt cause pain. After 13 days, they measured the injured hindpaws' sensitivity to pressure with von Frey hairs (horsehair of increasing diameter). Moskal says that, in this model, '15 min and 60 min after injection, NT13 robustly and statistically reduced neuropathic pain'. Based on these results, the investigators plan to test proof-of-concept later on this year in patients with neuropathic pain.

References

1 Moskal, J.R. *et al.* (2001) The use of antibody engineering to create novel drugs that target *N*-methyl-D-aspartate receptors. *Curr. Drug Targets* 2, 331–345

2 Massieu, L. *et al.* (1998) The role of excitotoxicity and metabolic failure in the pathogenesis of neurological disorders. *Neurobiology* 6, 99–108

3 World Health Organization (2001) World Health Report 2001. Mental health: new understanding, new hope. (http://www.who.int/whr/2001/main/en/index.htm)

4 Thompson, L.T. *et al.* (1992) Hippocampus-dependent learning facilitated by a monoclonal antibody or D-cycloserine. *Nature* 359, 638–641

5 Gamelli, A.E. *et al.* (2001) NT-13 facilitates acquisition of trace eyeblink conditioning in rats. *Society for Neuroscience 31st Annual Meeting*, 10–15 November 2001, San Diego, CA, USA (available online at http://sfn.ScholarOne.com/itin2001)

Peptide provides three-in-one protection

Joanne Clough, joanne.clough@drugdiscoverytoday.com

A newly discovered peptide, derG, has been found to provide 100% protection from infection in a mouse model of malaria infection. These results, a collaboration between CEL-SCI Corporation (Vienna, VA, USA) and the Naval Medical Research Center (NMRC; Silver Spring, MD, USA), were presented at the *Experimental Biology 2002* Meeting (20–24 April 2002, New Orleans, LA, USA). Protection from disease symptoms was also reported with the herpes simplex virus (HSV) skin scarification and tumour models, after administration of this peptide [1].

  PII: S1359-6446(02)02347-4

Malaria

Malaria is a fatal disease caused by the parasite *Plasmodium falciparum*. Other species of *Plasmodium*, although genetically not fatal, can cause severe and debilitating disease. Statistics show that every 30 seconds a child dies from *P. falciparum*, which is endemic in 100 countries. Each year, 300–500 million cases of malaria occur, with an estimated 1.2–2.7 million deaths from the disease (http://www.cdc.gov; http://www.who.int), which is transmitted by the female *Anopheles* mosquito upon taking a blood meal. Symptoms present typically eight days after infection and include fever, headaches and gastrointestinal or respiratory illnesses. *P. falciparum* can induce symptoms up to three months after infection. The malaria parasite has a complex lifecycle in both animals and insects and comprises >5000 genes, many of which are highly polymorphic adding to the challenge of developing an effective malaria vaccine.

Current treatments

The use of mono-therapies of antimalarials is losing its effectiveness because of the increasing resistance of the parasites to these drugs. The quinoline-based antimalarial drugs, which work in part by interfering with the haem polymerization and detoxification process in the host organism, have some occasional side effects. These can include stomach upsets and blurred vision, sunlight sensitivity and neuropsychological symptoms. No single drug is 100% effective in preventing malaria at present. Some newer antimalarial drugs are based on compounds that are derived from an ancient Chinese remedy [2].

The study – all or none

The recent malaria study, conducted at the NMRC by a team led by Yupin Charoenvit, showed 100% protection from infection by sporozoites in one strain of mice (A/J), following the subcutaneous administration, three weeks apart,

of two low doses of the peptide derG. Because the peptide is a modified version of a human sequence (MHC II β chain second domain CD4 binding region) that binds to both human and mouse immune cells, these recent results could have direct applicability to humans, although this peptide has not yet been studied in humans.

Dan Zimmerman, Senior Vice President of Research, Cellular Immunology, at CEL-SCI, said that the results for protection were measured by a total lack of malaria parasites in the bloodstream evaluated for the next two weeks after challenge with the malaria parasite. He continued, 'Not even a small amount of parasites were detected – it was an all or none analysis.' The parasites were assayed by microscopic examination of thin blood smears from mice at 5, 7 and 14 days post sporozoite inoculation. This study was unusual in that it did not involve the administration of the disease antigen. Usually the antigen together with an adjuvant will promote an immune response. However, with derG, administration well in advance of animals being exposed to infection conferred protection against the disease.

The peptide derG came from CEL-SCI's L.E.A.P.S.™ discovery platform where it showed up as a T-cell binding ligand. It is a low molecular weight peptide of 18 amino acids, which is a low cost material to synthesize and can be administered infrequently (weekly, bimonthly or monthly) and at low doses. Various doses were evaluated, ranging from 25 μg to 1.25 μg. It is not yet known what the mechanism-of-action of derG is and what exactly it is acting on in the body, apart from being derived from a peptide with known ability to bind to immune cells.

David Warhurst, a professor at the London School of Hygiene and Tropical Medicine (London, UK), said: 'Immunostimulants such as BCG [3] were reported in the 1970s to protect against malaria infections in mice, and more recently this area has been revisited in primates' [4]. He added, 'This study suggests that if a cheaply-produced immunostimulant could be given safely to populations in endemic areas at intervals, it might serve to reduce malaria transmission. Equally the treatment might be usable as a prophylactic approach for those visiting malarious areas. No doubt, more work needs to be carried out, especially from the safety point of view. Immunostimulation can be a double-edged sword and has not yet found an established role in infectious disease.'

Three in one

Other research conducted by CEL-SCI in collaboration with Northeastern Ohio Universities College of Medicine (NEOUCOM; Rootstown, OH, USA) and Onyvax (St George's Hospital Medical School, London, UK) showed that the peptide derG also protected against HSV and cancer, respectively.

Data were also presented from the team of Kenneth S. Rosenthal from NEOUCOM (as part of the broader study at the *Experimental Biology 2002* meeting), which showed derG treatment protected the mouse from HSV in the skin scarification–zosteriform spread model. Optimal results in delaying the appearance of herpes lesion, and in reducing mortality, were obtained when the derG was administered subcutaneously one day before challenge.

Work conducted at the biotechnology company Onyvax by Mike Whelan showed that derG, when used in the allogeneic melanoma (skin cancer) tumour vaccine model, improved protection

induced by an experimental tumour vaccine alone.

Geert Kersten, CEO of CEL-SCI, said: 'The fact that we were able to see protection without disease antigen in several diseases opens up the possibility that derG could become an inexpensive general immune regulatory drug that protects people from a large number of diseases.' Zimmerman added, 'We did not receive any reports of any adverse side effects [in the animals], such as weight loss or gain, diarrhoea, constipation, coat loss or discoloration, or evidence of neurological effects from any of the three study sites.'

Further treatments

Potential future indications for derG could be protection against other infectious diseases and a treatment for influenza, hepatitis B and C, and allergies. It could also have the potential to enhance protective immunity following vaccination and could eliminate the necessity of booster shots.

Zimmerman added that the next steps are: (1) to optimize for dose; (2) to evaluate in other strains and species for preventive and therapeutic efficacy with appropriate disease models; and (3) large scale ADME/tox studies. He envisaged the peptide going into clinical trials within two to three years.

References

1 Charoenvit, Y. *et al.* (2002) A non-immunogenic small peptide analogue of human MHC II β chain induces protective responses to tumor and infectious challenges. Presented at the *Experimental Biology 2002* meeting, 20–24 April 2002, New Orleans, LA, USA (Poster LB517)

2 Cumming, J.N. *et al.* (1997) Antimalarial activity of artemisinin (qinghaosu) and related trioxanes: mechanism(s) of action. *Adv. Pharmacol.* 37, 253–297

3 Clark, I.A. *et al.* (1976) Protection of mice against *Babesia* and *Plasmodium* with BCG. *Nature* 259, 309–311

4 Puri, S.K. *et al.* (1996) Poly ICLC inhibits *Plasmodium cynomolgi* B malaria infection in rhesus monkeys. *J. Interferon Cytokine Res.* 16, 49–52

Tailoring vaccines to individual lymphomas

Matt Brown, matt.brown@elsevier.com

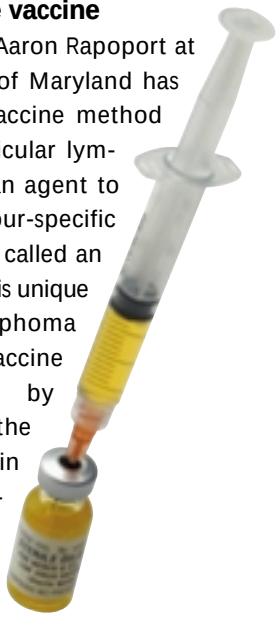
A custom-made vaccine has been developed to combat non-Hodgkin's lymphoma (NHL) that uses a patient's own tumour cells. Researchers at the University of Maryland Greenebaum Cancer Center (Baltimore, MD, USA) are testing the vaccine as part of a Phase III multi-centre study at 25 institutions across North America. The vaccine is particularly targeted at follicular lymphoma, a common and low-grade form of NHL.

Lymphomas: types and treatments

Non-Hodgkin's lymphoma is a term that encompasses a wide variety of diseases. Lymphomas are cancers of the lymphatic system, which filters the blood and protects the body from illness. As the cancer grows, the body accumulates large numbers of non-functioning lymphocytes, which can block and compromise the lymphatic system and rapidly metastasize to other organs. There are two general types of lymphoma: Hodgkin's (named after Thomas Hodgkin, who was the first to recognize this form in 1832) and non-Hodgkin's lymphoma. NHL is much more heterologous, less predictable and can attack more types of lymphatic tissue than Hodgkin's lymphoma can (for a background to the disease see http://www.patientcenters.com/lymphoma/).

One particularly common but lower-risk type of NHL is follicular lymphoma. This disease afflicts mainly middle-aged and elderly people and can readily spread to different parts of the lymphatic system. Most cases are the result of overexpression of the BCL-2 gene, which produces a protein that blocks apoptosis. Current therapies for the disease depend on the extent of the cancer's progress. If the lymphoma is caught early, it can be treated with localized radiotherapy. Treatment is often deferred, however, until symptoms appear. When the disease is more advanced, chemotherapy or whole-body radiation might be necessary. Generally, low-grade follicular cancers are easily treated, but are prone to recur.

A tailor-made vaccine



A team led by Aaron Rapoport at the University of Maryland has developed a vaccine method to combat follicular lymphoma using an agent to target a tumour-specific surface protein called an idiotype, which is unique to every lymphoma patient. The vaccine is developed by conjugating the idiotype protein to an immunogenic carrier protein, keyhole limpet

1359-6446/02/$ – see front matter PII: S1359-6446(02)02351-6