

Before treatment, the 13 patients were mounting a primarily T helper cell type 2 (Th2) immune response. This is typified by a surplus production of interleukin 10 (IL-10), an immunosuppressive cytokine, and a reduced production of γ -interferon, a cytokine that activates other immune cells. After treatment, this pattern was reversed; IL-10 production fell, γ -interferon production rose, and the pattern of the immune response returned to a more favourable Th1 response. IL-10 is known to inhibit the maturation of dendritic cells and natural killer (NK) cells and, during treatment, as IL-10 fell, there was a demonstrable burst of maturing dendritic cells and NK cells into the circulation. Frincke and colleagues suspect that the effect of HE2000 on dendritic cell maturation could hold the key to the mechanism of action of the drug, and perhaps to fundamental control mechanisms within the immune system itself.

It may be that further research will uncover more about this control process but, in the next year or so, Frincke's team aims to build on the results obtained in this preliminary trial and to concentrate on testing the efficacy of HE2000 more fully.

HE2000 also shows promise in boosting immune response against other infectious diseases that result in a Th2 immune response – including malaria, hepatitis B and C and tuberculosis (TB). Future trials will investigate the efficacy of HE2000 against malaria; this infection does not have the long latency period of HIV/AIDS, and the trial will aim to establish the principle that the upregulation induced by HE2000 can actually fight infection. 'Finding out whether the upregulation of the immune system that is elicited by HE2000 will prevent or improve the outcome of opportunistic infections is a critical next step,' says Thomas Merigan,

Hollis Eden Board member and Director of the Center for AIDS Research, Stanford University (Stanford, CA, USA).

Another strong possibility for the future is combining HE2000 with an AIDS vaccine. 'Much effort has gone into developing potential vaccines, but the problem is that a vaccine cannot effect an immune response in individuals whose immune system is suppressed.' If this suppression could be reversed by HE2000, a combination therapy with a conserved epitope vaccine could be a realistic possibility for an effective therapeutic vaccine rather than a fleeting wisp of hope.

1 K. Senior (1999) New drug makes host cell machinery unavailable to HIV. *Mol. Med. Today* 5, 234–235

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Emerging infectious diseases: a global problem

Four separate reports in a single recent issue of the *New England Journal of Medicine*^{1–4} highlight the need for the global health community to focus its efforts in dealing with emerging infectious diseases: (1) Khean Jin Goh and colleagues¹, from the University of Malaya (Kuala Lumpur, Malaysia), provide clinical details of Nipah virus encephalitis among pig farmers in Malaysia, associated with an outbreak of infection in pigs. Out of 94 cases, 32% of patients died and 15% of survivors suffered residual neurological deficits; (2) Paul Fey and colleagues², from the Nebraska Medical Center (Omaha, NE, USA), describe the case of a child who acquired a ceftriaxone-resistant salmonella infection, most likely from contact with infected cattle; (3) Toni Petrillo and co-workers³, from the Children's Healthcare of Atlanta (Egleston, Atlanta, GA, USA), report on the occurrence of enteritis necroticans in a 12-year-old boy with poorly controlled diabetes mellitus after he consumed pig intestines. This study particularly highlights the increased potential for infectious diseases among people with other conditions, such as cancer, diabetes and other immunosuppressive diseases; and (4) Paolo Aureli and colleagues⁴, from Istituto Superiore di Sanita (Rome, Italy) report on an outbreak of febrile gastroenteritis caused by *Listeria monocytogenes* associated with the consumption of corn.

A 1992 Institute of Medicine report⁵ highlights many reasons for the emergence and re-emergence of these deadly microbes, including societal changes (such as population growth and migration), changes in health care (such as the widespread use of antibiotics), an increasing number of immuno-suppressed patients, the globalization of the food supply and changes in the way food is grown and produced. The report was instrumental in support of the increased capacity of the Centers for Disease Control (CDC) to monitor and respond to the threat of emerging diseases. For the past three years, the CDC have introduced a surveillance system where field workers canvass hospitals and laboratories looking actively for disease. In addition, the CDC have introduced the unexpected death and serious illness project, where intensive care centres and medical examiners report deaths considered to be from infectious diseases which they have failed to identify.

Critics believe that the initiatives of the CDC are still under funded and it is all too easy for emerging diseases to fall through their surveillance nets. 'We still have a system that is fragmented and incomplete,' says Michael T. Osterholm, author of an editorial accompanying the papers in the *New England Journal of Medicine*, and the CEO of Ican Inc. (an internet company providing information on infectious diseases). He cites the example of West Nile disease, the mosquito-borne virus

that struck New York last year. West Nile disease was only identified after one clinic saw two patients. Without such serendipity, they might have missed the disease altogether.

As infectious diseases know no boundaries, experts agree that the only way to tackle the problem is from a global perspective. 'At a global level we do not have much of a surveillance mechanism. New HIVs could be hatching out right now and it would be years before we woke up to them,' says Joshua Lederberg, Nobel prize winner and emeritus professor at the Rockefeller Institute (New York, NY, USA), and principal author of the 1992 Institute of Medicine report.

The WHO, who co-ordinate global health initiatives, face the problem of different countries having different infrastructures, making international schemes difficult to implement. The WHO needs to be invited to investigate emerging diseases and many countries are reluctant to have WHO documenting the poor state of their public health. 'Even with good surveillance systems we will still get major pandemics of new diseases. But there will be more lead time and we will be better equipped to deal with the problem. The result would be a far smaller death toll,' says Professor Lederberg.

The Sandia National Laboratory of the US Department of Energy (Albuquerque, NM, USA) has launched a pilot programme that is hoped might solve the problem of

surveillance by identifying an emerging disease as rapidly as possible, enabling them to contain outbreaks. By definition emerging diseases have no treatment – what is needed is prophylaxis and isolation of infected individuals. The US\$ 50 000 pilot project will be limited, at first, to diseases reported at the University of New Mexico (UNM) Hospital Emergency Room and Urgent Care Center, but the architects say the project could provide a blue print for a scheme that could be implemented both nationally and internationally. ‘The Department of Energy is interested in developing technologies to combat bioterrorism. But if these tools are going to be useful in rare circumstances they are going to need to be applicable on a daily basis with regard to garden variety health concerns,’ says Sandia team leader, Al Zelicoff [Center for National Security and Arms Control (Albuquerque, New Mexico)].

In the project, physicians enter details such as the patient’s age, sex, postcode of their home and work, whether they have travelled recently and whether they are employed in high-risk occupations. The physician is then asked to pick one of six syndromes – an influenza-like syndrome, a syndrome of fever with diarrhoea, fever with skin rash, fever

with mental status changes, hepatitis and one other. The information is sent to a central computer at the New Mexico Department of Health and within minutes, the physician receives a report showing all the cases of the same syndrome reported in the past 30 days, with a map displaying cases according to postcode. ‘We are trying to give physicians the tools to make the diagnosis of a specific disease based on the patient’s presentation as well as all the other patients who have presented with similar symptoms in the same area,’ explains Dr Zelicoff. ‘If you give the physicians this additional information they are often able to go from the syndrome (e.g. cough and runny nose) to a specific diagnosis.’

Dr Zelicoff believes that the biological weapons convention would provide the perfect vehicle to introduce the scheme internationally. The biological weapons convention, which has been in existence for 25 years, forbids countries to stockpile biological materials for weapons use. But inspections of countries thought to be producing material have been farcical as it is all too easy to conceal material. After the Gulf War, a UN special commission inspection of Iraq undertook three dozen inspections that revealed nothing. It was

only after Saddam Hussein’s son-in-law defected, that evidence was gained.

‘What is needed is an international system for monitoring reportable diseases and syndromes that would have the advantage of picking up both emerging diseases and those resulting from biological weapons. The side effect of this system would enhance public health world wide,’ says Dr Zelicoff.

- 1 Goh, K.J. *et al.* (2000) Clinical features of Nipah virus encephalitis among pig farmers in Malaysia. *New Engl. J. Med.* 342, 1229–1235
- 2 Fey, P. *et al.* (2000) Ceftriaxone-resistant salmonella infection acquired by a child from cattle. *New Engl. J. Med.* 342, 1242–1249
- 3 Petrillo, T.M. *et al.* (2000) *Enteritis necroticans* (pigbel) in a diabetic child. *New Engl. J. Med.* 342, 1250–3
- 4 Anreli, P. (2000) An outbreak of febrile gastroenteritis associated with corn contaminated by *Listeria monocytogenes*. *New Engl. J. Med.* 342, 1236–1241
- 5 Lederberg, J. *et al.* (1992) *Emerging infections: microbial threat to health in the United States*. National Academy Press

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Fibronectin fragment accelerates wound healing in diabetic mice

Surgeons are at a loss when faced with wounds that take a very long time to heal. Now, scientists at the University of Michigan (Ann Arbor, MI, USA) have shown that a single topical treatment with a fibronectin fragment, Pro-His-Ser-Arg-Asn (PHSRN), activates wound healing in diabetic mice¹ – a finding that might eventually overcome problems of delayed wound closure.

Plasma fibronectin is a soluble glycoprotein that circulates in the blood and other body fluids. When tissue is damaged, fibronectin at the injury site is cleaved into fragments by the enzymes involved in blood clotting and wound repair. The fragments diffuse outward and bind to fibronectin receptors, integrins, on cells surrounding the damaged tissue, thus stimulating them to invade and repair the injury.

The activity of the PHSRN sequence of fibronectin was discovered in *in vitro* cell-migration studies. The researchers used basement membranes from sea urchin embryos as invasion substrates, which are

naturally serum-free, thus providing ideal circumstances to identify the invasion-inducing sequences of fibronectin. Amidating and acetylating the respective charged termini of the peptide – which helps to mimic the conformation within a polypeptide chain and makes the peptide exoprotease-resistant – increased the wound healing activity of the peptide by 100-fold.

Encouraged by these results, the researchers were curious to see whether the peptide would activate wound healing in living animals. They chose an established model of impaired wound healing, obese diabetic C57BL6/KsJ *db/db* mice. In the experiment, diabetic mice and normal, age-matched littermate controls received small biopsy wounds in the skin of their upper back. The wounds were then treated with either a tiny drop of the activated peptide (0.4 µg µl⁻¹) or of saline. While the saline-treated wounds in the normal animals were covered by skin within 9 days, saline-treated

wounds in diabetic mice took 20–42 days to heal. Treatment with Ac-PHSRN-NH₂ resulted in wound healing within 7–8 days in both normal and diabetic animals.

‘It is as if we eliminated the diabetic defect in re-epithelialization, or covering the wounds with skin, with a single treatment’, says Donna Livant, lead author of the study.

Investigation of sectioned *db/db* wounds showed that treatment with the peptide stimulates keratinocyte and fibroblast invasion of wounds and induces the formation of the prominent fibers associated with wound contraction. ‘The action of the peptide is probably a very rapid event’, explains Livant. ‘We would really like to know what signalling happens downstream of the integrin when it binds the sequence, a fascinating question. We are hoping to begin to work on this question fairly soon.’

Kenneth Yamada at the National Institute of Dental and Craniofacial Research (Bethesda, MD, USA) is puzzled by the