already discussing future strategies with several pharmaceutical companies.

Meanwhile, the fundamental research work continues. The next steps include resolving the known single-gene antibiotic polypeptides to the smallest possible sequence and elucidating the structure of each of these polypeptide antibiotics with their targets. 'These polypeptide antibiotics might be rational design tools for pharmaceutical companies to develop drugs that inhibit essential bacterial enzymes,' predicts Young.

Overcoming resistance

The possibility of developing several new classes of antibiotic is crucial as well as exciting. 'The need to define new targets for antimicrobial agents and to develop innovative strategies is clearly urgent,' says Charles Stratton, Director of Clinical Microbiology, Vanderbilt University School of Medicine (Nashville, TN, USA). In the past decade, the spread of multiple antibiotic resistance has become a major threat to the continued efficacy and use of current antibiotics. Stratton finds the approach of Bernhardt and colleagues of great interest. 'The main advantage of proteins produced by phages is that they target the cell wall, a structure that does not exist in human cells,' he says. He highlights the example of penicillin, the first antibiotic to be discovered. 'Penicillin is a β-lactam antibiotic and, although resistance to it is now a huge problem worldwide, it has proved to be one of the safest antibiotics because it targets peptidoglycan. Bacteriophage proteins that target different steps in cell-wall biosynthesis could be equally safe, but this premise must be proven,' he stresses. However, if it does prove correct, bacteriophages and the proteins they produce could become a major source of new antimicrobial agents.

Young agrees, and points out that phage proteins could have an added attraction: 'In principle, one could easily modify polypeptide antibiotics by changing the encoding DNA sequence. It is also possible to actually select random changes in a polypeptide that would overcome resistance, using the powerful tools of bacterial molecular genetics. But that really is looking into the future,' he concludes.

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Milking nature for Alzheimer's treatment

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A new drug derived from mammals' first-milk could provide an effective new treatment for Alzheimer's disease (AD). An interim report has recommended that ReGen Therapeutics (London, UK) be allowed to progress to the end-point of its 90-patient, multi-centre, double-blind, placebo-controlled clinical study of the efficacy of Colostrinin™ for treating AD.

The international steering committee of the trial, carried out in Poland, found that there were no adverse reactions related to Colostrinin and an encouraging trend of efficacy in patients treated with the drug compared with the placebo group. The committee also recommended that a further 18 patients should be enrolled to increase the statistical power of the trial.

The cost of AD

AD is an increasingly common, progressive neurodegenerative disease for which there is no cure. The disease slowly destroys the brain, impairing cognitive functions such as memory, abstract thinking and language function, and causes other symptoms such as attention deficit, depression, anxiety and agitation. The pharmaceutical industry is, therefore, under pressure to develop therapies for AD, which inflicts substantial emotional and financial costs to families, businesses and governments.

AD neurodegeneration is typified by the presence of amyloid plaques, tau tangles and loss of neurons[1]. The plaques consist of amyloid β (Aβ) deposits, which are formed as a result of the abnormal cleavage of amyloid precursor protein (APP)[2]. Tau tangles are caused by an overproduction of the tau protein[1], which, upon release from the cell, becomes heavily phosphorylated and glycated[3,4], and thus more insoluble. It is thought that both of these pathogenic processes could be a result of oxidative stress[1,3,4].

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Colostrinin and cognition

Colostrinin is a proline-rich polypeptide constituent of colostrum – the milk produced by mammals after giving birth, which provides the newborn with innate immunity against infection. Because of its immunomodulatory properties, studies were undertaken by Josef Lisowski and colleagues (Institute of Immunology and Experimental Therapy, Wroclaw, Poland) to determine whether Colostrinin could be used to correct immune disorders. During these studies, the researchers noticed that volunteers showed improvements in cognitive abilities and mood. This prompted the group to investigate Colostrinin as a potential treatment for AD.

In the past few years, Colostrinin has been found to improve learning and memory in rats[5], and a Colostrinin derivative was shown to retard the progress of AD and delay the loss of long-term memory in aged rats[6]. Furthermore, in 46 AD patients given either 100 μg oral Colostrinin, commercially available selenium supplements or placebo over a one-year trial, eight of 15 Colostrinin-treated patients showed an improvement in the disease, and stabilization of the disease was observed in the remaining seven patients[7] (as measured by mini mental-state examination; MMSE). Importantly, the drug was found to have only a few mild and transient side effects such as anxiety, stimulation, insomnia and tiredness.

Mechanism of action

There are several mechanisms by which Colostrinin might stabilize AD. First, Colostrinin has been shown to induce the secretion of cytokines, such as interferon-γ (IFN-γ)[8] and tumour necrosis factor-α (TNF-α)[9], which have been shown to inhibit amyloid plaque formation[10]. Second, in studies by ReGen, Colostrinin was found to reduce the intracellular oxidation of a fluorescent substrate (fluorescein) as determined by a reduction in fluorescence intensity, demonstrating that Colostrinin is an anti-oxidant that can scavenge free radicals. Third, researchers at ReGen found that in leukocyte cultures, treatment with either whole Colostrinin or its constituent peptides for six days caused increased proliferation and adhesiveness (Fig. 1) when compared with untreated controls. Interestingly, such an increase in proliferation and adhesiveness is essential because AD causes a massive loss of neurons and, therefore, by increasing the adhesiveness of cells it might eventually be possible to reattach neurons and make them function. More importantly, scientists at ReGen demonstrated that Colostrinin, or its constituent peptides, can induce morphological changes: PC12 nerve progenitor cells were found to differentiate after treatment (Fig. 2), into epithelial, fibroblastoid or nerve-type cells.

Marian Kruzel, Senior Scientific Advisor at ReGen, has been studying milk proteins and peptides for a long time. He said: 'I am interested in the whey

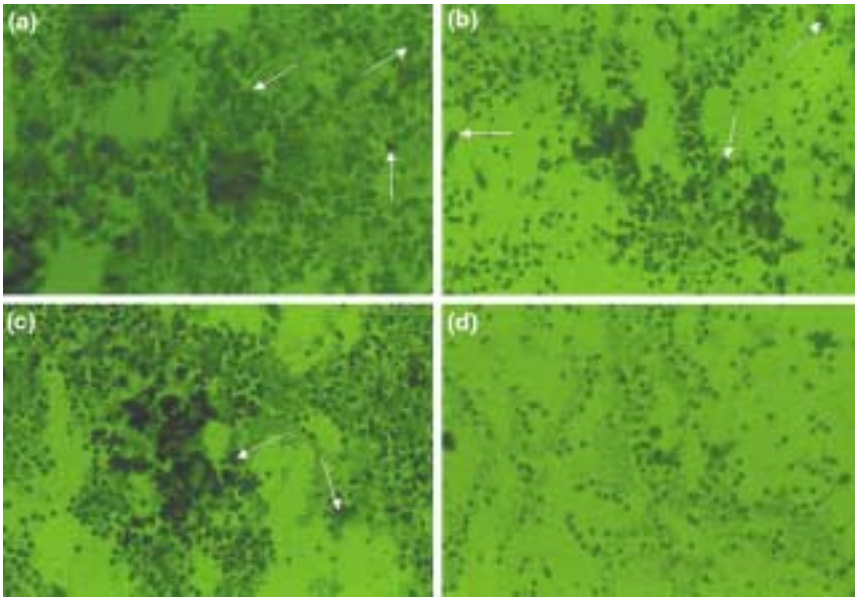

Figure 1. Fluorescence micrograph images of human leukocyte proliferation. Treatment with either whole Colostrinin, or its constituent peptides (referred to here as peptide 2 and peptide 10), for six days, caused increased proliferation and adhesiveness compared with untreated cultures. **(a)** Treatment with peptide 2, **(b)** treatment with Colostrinin, **(c)** treatment with peptide 10, **(d)** negative control. The arrows indicate increased proliferation and regions of cell aggregation (clumping).

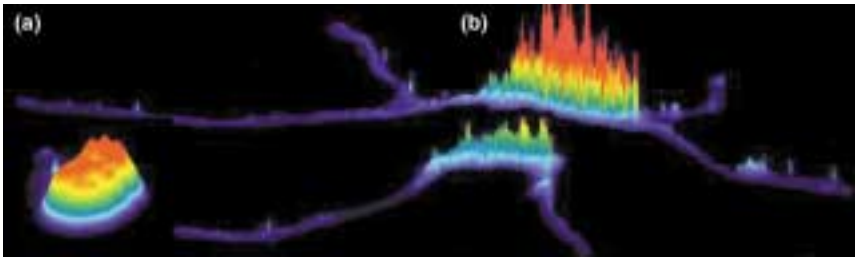

Figure 2. Differentiation of PC12 nerve progenitor cells after treatment with Colostrinin. This three-dimensional fluorescence image shows **(a)** control PC12 cell; and **(b)** a fibroblastoid differentiating cell after treatment with Colostrinin™.

proteins because of their immunomodulatory function in humans and animals. I have established an international network of scientists (France, New Zealand, Poland and USA) working on lactoferrin, one of the major proteins in colostrum and mature milk.' He continued: 'Colostrinin, as a proline-rich polypeptide complex, has its own beauty, because of the variety of biological activities associated with the complex. It is extremely exciting to work with a product that has the potential to treat a variety of, as yet, untreatable disorders.'

ReGen is now recruiting the extra 18 patients required for the second phase of its clinical trial, and now aims to optimize and validate the dosage form and continue to develop the science and intellectual property of Colostrinin-based therapies. Jerzy Georgiades, Chief Scientific Officer at ReGen, revealed that the second phase of the trial might be carried out in Poland in parallel with other European countries, including the UK. He added that the same parameters (mainly MMSE) will be used to evaluate efficacy, but within a larger population.

Kruzel believes that further research into Colostrinin will address its applicability not only to AD, but to other neurodegenerative and neoplastic disorders.

Although ReGen scientists are focusing their research primarily on the treatment of AD, they are also looking to find preventive measures. Kruzel concludes that: 'Nothing is more rewarding than the improvement in patients treated with your experimental drug; we are looking forward to the positive clinical results from our current studies in Poland.'

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Measles vaccine could treat lymphoma

Jo Whelan, Freelance writer

Patients with advanced lymphomas could be treated with measles vaccine in the future. Researchers at the Mayo Clinic (Rochester, MN, USA) have shown that a strain of measles virus used in vaccines causes regression of human lymphoma tumours in immunodeficient mice[1].

The idea that viruses can be used to fight cancer is not new. Sporadic reports have appeared in the literature throughout the past century, but interest intensified in the late 1990s with the advent of gene therapy. Several types of virus have shown promise in preclinical studies, and some clinical studies are already under way. For example, a Phase II trial of intratumoural injections of ONYX-015 (a genetically modified adenovirus) combined with standard chemotherapy drugs to treat recurrent head and neck cancer[2] has shown substantial benefits over chemotherapy alone.

Cytopathic effects

The Mayo team is concentrating on the measles virus (MV), specifically on a live, attenuated vaccine derived from the non-pathogenic Edmonston-B strain (MV-Ed). This has been used worldwide for more than 30 years and is safe and easily available.

Mayo researchers have previously found that cell death can be induced with MV-derived fusogenic membrane-glycoproteins (FMGs) known as F and H. These glycoproteins cause the infected cell to fuse with others to form large, multinucleated bodies that die in a non-apoptotic process involving nuclear fusion[3]. FMGs kill tumour cells more efficiently than suicide genes of the type

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