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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normally used in gene therapy studies because they can fuse with uninfected cells. This 'bystander effect' means that not all cells need be transduced with the therapeutic genes to cause significant cell death.

Lymphomas are a diverse group of cancers affecting the lymphatic system. Approximately 63,600 new cases occur in the USA each year, mostly of the non-Hodgkins form, the incidence of which appears to be rising. Non-Hodgkins lymphomas are classified as either indolent or aggressive. The standard treatment is radiotherapy and/or chemotherapy, and options for those who fail to respond include bone marrow transplant and monoclonal antibody therapy. Currently, 40–50% of patients will die within five years.

MV is ideal for treating lymphoma because the lymphatic system is one of its major replication sites. In the Mayo study[1], a series of experiments was carried out with aggressive and indolent lymphoma cell lines, both *in vitro* and injected into the flanks of severe combined immunodeficient (SCID) mice. Cells infected with MV-Ed were destroyed by lysis *in vitro* and the formation of multinucleated giant cells was observed. Furthermore, infected cells failed to grow into tumours when implanted in mice, in contrast to uninfected controls.

In another experiment, mice with large, established xenografts of either indolent or aggressive lymphoma were given ten daily injections of MV–lacZ (MV-Ed modified with a β-galactosidase reporter gene) directly into the tumour. Both tumour types progressed more slowly than untreated controls or those given inactivated MV–lacZ. Indeed, some tumours showed substantial, and in some cases sustained, regression. Because lymphoma is a systemic disease, another group of ten mice with established aggressive-type lymphomas were given four doses of intravenous MV. Significantly, this halted tumour progression, and the recovery of replicating MV from the tumours suggests that this effect was a result of MV vaccination.

Most adults are immune to MV, and so a mouse model of MV immunity was developed. Tumours in these mice showed the same response to injected MV therapy as the SCID mice, demonstrating that immunity is not an obstacle to this method of viral delivery. However, systemic delivery in immune mice was not attempted. The team also showed that MV infection could induce the expression of immunostimulatory heat-shock proteins *in vitro*, suggesting that it increased the immunogenicity of the lymphoma cells.

Ongoing research

It is not clear exactly how cells are killed by replicating MV (as opposed to FMG constructs), but H and F expression might be part of the mechanism. 'This study is proof-of-principle that measles virus can be oncolytic in human lymphomas *in vivo*,' says lead researcher Adele Fielding. 'The most important next step is to get data in immunocompetent models. So we are currently developing such models and have opened a Phase I human clinical trial.'

A major issue to be addressed, however, is virus delivery. Direct injection into the tumour produced limited viral spread, although this might be because of the mixture of murine and human cells in the model tumours. 'Ultimately, to treat a disease like lymphoma we will probably have to pursue a systemic approach,' says Fielding. 'The fact that all patients are likely to be immune to measles virus should add to the safety of the approach but will mean we have to confront the presence of neutralizing antibodies. This might mean pre-infecting peripheral lymphocytes *ex vivo* and then administering the virus inside the lymphocytes.' Some progress has also been made in targeting virus entry to specific cell-types.

David Linch, Chairman of the National Cancer Research Fund Network Lymphoma Study Group in the UK, notes that there is enthusiasm for various approaches to augment the immune response against lymphoma cells. He describes the Mayo results as encouraging. 'The issues to be resolved are whether proliferating cell-line models are representative of primary tumours, and whether systemic administration of virus will be efficacious in an immunized individual with intact cellular and humoral immunity,' he comments. 'The results of further studies will be awaited with great interest.'

Researchers at the Mayo Clinic are now studying the use of MV against several other cancers.

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