Researchers have carried out the first in-human trial of a tolerizing DNA vaccine for an autoimmune disorders, with promising results

First human trial of DNA-based vaccine to treat multiple sclerosis

A randomized, double-blind, placebo-controlled trial for the treatment of multiple sclerosis (MS) has shown promising results for the target and treatment of the immune system in relapse-remitting and secondary-progressive MS. The disease affects around 85,000 people in the UK and can become quickly debilitating.

The vaccine, currently known as BHT-3009, works by targeting the brain and immune system; areas of the body that are targeted by the disease. The DNA vaccine is a 'naked' strand of human DNA encoding for the human myelin basic protein. In a diseased patient, protective myelin sheaths containing myelin basic protein are targeted by the bodies own immune system and destroyed and eventually the nerve cells beneath the sheaths are also destroyed. This disrupts nerve signaling and causes muscle weakness, visual problems, fatigue and pain.

It is thought that the vaccine works by dampening down the bodies own immune system so the damage to nerves can be lessened. The team led by Amit Bar-oh, from the Montreal Neurological Institute, Canada, tested the vaccine primarily for safety and tolerability. Bar-oh explained, "We have demonstrated in this first, to our knowledge, in-human trial of a DNA vaccine for autoimmune disease that the approach is safe and well-tolerated."

In the study, 30 patients with relapse-remitting and secondary-progressive MS were injected with either the vaccine or a placebo, between 2005 and 2006. The injections were given at 1, 3, 5 and 9 weeks, in doses of 0.5, 1.5 or 3 mg. Some patients were coadministered atorvastation, which was hypothesized to increase the benefit of the vaccine, although no evidence for this has been found in this study. At week 13, patients who received the placebo injection were given four injections of BHT-3009.

The team then investigated outcome measures such as the number and volume of gadolinium-enhanced lesions on magnetic resonance imaging (MRI), relapses, and analysis of antigen-specific immune responses, to asses the effectiveness of the vaccine. MRI scans were observed at 5, 9, 13, 26, 38 and 50 weeks enabling visualization of lesions.

"BHT-3009 was safe and well tolerated, provided favorable trends on brain MRI and produced beneficial antigen-specific immune changes" explained lead author Bar-oh.

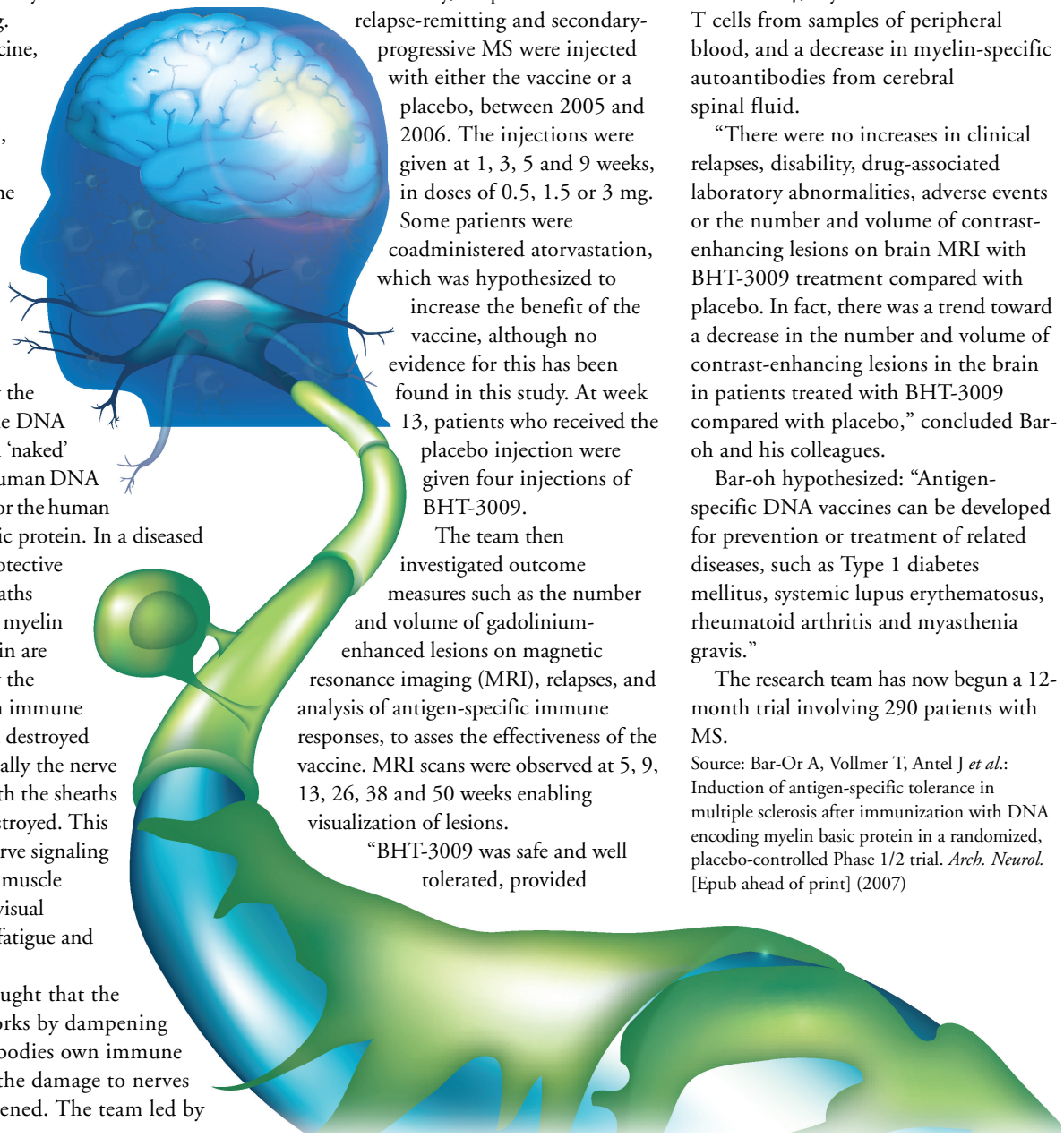
Favorable trends on MRI brain scans were evident along with beneficial antigen-specific immune changes. There was a decrease in proliferation of interferon-γ, myelin-reactive $CD4^+$ T cells from samples of peripheral blood, and a decrease in myelin-specific autoantibodies from cerebral spinal fluid.

"There were no increases in clinical relapses, disability, drug-associated laboratory abnormalities, adverse events or the number and volume of contrast-enhancing lesions on brain MRI with BHT-3009 treatment compared with placebo. In fact, there was a trend toward a decrease in the number and volume of contrast-enhancing lesions in the brain in patients treated with BHT-3009 compared with placebo," concluded Bar-oh and his colleagues.

Bar-oh hypothesized: "Antigen-specific DNA vaccines can be developed for prevention or treatment of related diseases, such as Type 1 diabetes mellitus, systemic lupus erythematosus, rheumatoid arthritis and myasthenia gravis."

The research team has now begun a 12-month trial involving 290 patients with MS.

Source: Bar-Or A, Vollmer T, Antel J *et al.*: Induction of antigen-specific tolerance in multiple sclerosis after immunization with DNA encoding myelin basic protein in a randomized, placebo-controlled Phase 1/2 trial. *Arch. Neurol.* [Epub ahead of print] (2007)



in brief…

Ibandronate is effective in preventing skeletal events in patients with bone metastases from colorectal cancer.

Heras P, Karagiannis S, Kritikos K, Hatzopoulos A, Mitsibounas D: *Eur. J. Cancer Care* 16(6) 539–542 (2007).

Ibandronate has already been shown to be effective in the treatment of bone metastases from breast cancer. A randomized, placebo-controlled trial was conducted to evaluate the efficacy and safety of ibandronate and the relative high-risk complications from bone metastasis of colorectal carcinoma (CRC). Primary efficacy end points included the proportion of patients with skeletal-related events. 73 patients were administered with intravenous ibandronate 6 mg via a 15-min infusion. These patients showed a significant decrease in adverse skeletal events, 39% compared with 78% with placebo. The time until first event was also prolonged to an average of 6 months. Results indicate that ibandronate may be an effective treatment for patients with metastasis bone disease following CRC.

Impact of preventive therapy with nadolol and topiramate on the quality of life of migraine patients.

Garcia-Monco J, Foncea N, Bilbao A, Ruiz de Velasco I, Gomez-Beldarrain M: *Cephalalgia* 27(8), 920–928 (2007).

Topiramate and nadolol are evaluated for their ability to reduce migraine frequency and improve the quality of life (QoL) of the sufferer. Patients aged 16 and over with frequent migraines were selected for 16 weeks of therapy: nadolol or topiramate 40 mg and 100 mg daily. QoL questionnaires (SF-36 and MSQOL) and anxiety and depression scales (HADS) were used to evaluate outcome. SF-36 showed a significant improvement. HADs did not change with therapy, with MSQOL global showing a statistically significant improvement. Preventive therapy with nadolol and topiramate significantly improves QoL, although additional efforts are required to place them in a nearer-to-normal situation compared with the general population.

Outcome of enzyme replacement therapy in patients with Gaucher disease type I. The Romanian experience.

Sido PG, Drugan C, Cret V *et al.*: *J. Inherit. Metab. Dis.* (2007) [Epub ahead of print]

This study outlines the first evaluation of therapeutic responses in patients with Gaucher's disease type 1, when treated with Cerezyme. A total of 24 patients received the replacement enzyme every 2 weeks for at least 18 months. The study showed an overall improvement in the patients and no further progression of bone disease. It is hypothesized that longer treatment periods may result in improved skeletal disease.

Mesalamine linked to cancer protection for high-risk inflammatory bowel disease patients

A study presented at the 72nd Annual scientific meeting of the American College of Gastroenterology has indicated that mesalamine use among patients with inflammatory bowel disease (IBD) decreases the incidence of colorectal cancer when comparing cases and controls.

In the study, 16 patients with IBD and 23 control subjects with similar body mass index, family history of IBD, family history of colorectal cancer and smoking were followed. The patients with ulcerative colitis (UC) who remained free from colorectal cancer, were all using mesalamine. In patients with UC who did develop colorectal cancer, only 76.9% were using mesalamine.

"This finding suggests an association between mesalamine use and reduced risk of colorectal cancer", explained Jeffrey Tang, lead author of the study.

Further studies conducted by the group reveled that doses of mesalamine greater than 5068 g in patients with IBD were associated with an 89% reduction in risk of colorectal cancer, compared with IBD patients matched for other major risk factors.

The authors note that further investigation will be required to confirm the chemoprevention potential of mesalamine. Patients with IBD including UC face a higher than average risk for colorectal cancer. Current guidelines recommend more frequent screening in these individuals.

Source: American College of Gastroenterology Press Release www.acg.gi.org/media/releases/2007am/Colorectal%20Cancer%20Risk%20in%20IBD.pdf

New therapeutic strategy could change the treatment of autoimmune disorders

The use of oral allergens combined with *Lactococcus lactis* (*L.lactis*), a lactic acid bacterium, may pave the way for new strategies in the treatment of autoimmune and allergic disorders.

***L. lactis* is a well-known food bacterium used in the cheesemaking process, and is currently in trials as a treatment for gastroenteritis, with the initial results being described as 'promising'.**

In the treatment of autoimmune disorders it is hoped that *L. lactis* will be successfully used as a delivery vehicle for therapeutic ingredients. Currently scientists have found great difficulty in introducing drugs for treatment into the intestine in an effective manner. The researchers decided to insert the code for a therapeutic protein, ovalbumin (OVA), into the bacterium DNA. So far the *L. lactis* bacterium has been able to successfully produce the OVA protein.

The construct had been tested in mice with an induced allergy to OVA. The mice received OVA-secreting bacteria, which were delivered to the intestine and successfully created OVA-tolerant mice.

This new technique will be developed further for the treatment of other autoimmune disorders. The incidence of immune disorders is increasingly requiring a greater need for more effective treatments with fewer side effects.

Source: Huibregtse IL, Snoeck V, de Creus A *et al.:* Induction of ovalbumin-specific tolerance by oral administration of Lactococcus lactis secreting ovalbumin. *Gastroenterology* 133(2), 517–528 (2007).

Radioactive 'seed' therapy for easier removal of cancerous breast tissue

A new technique for treating breast cancer could aid the surgical removal of cancerous breast tissue.

"The new technique is less invasive for the patient and allows us to be more precise when removing possible breast-cancer tumors"

The new technique is being pioneered by physicians at UT Southwestern Medical Center, Texas, USA and involves the use of a radioactive 'seed' or pellet implanted into suspected tissue mass in the breast to pin-point the location for surgical removal.

The radioactive seed, about the size of a grain of rice, is inserted using a needle, then later detected in surgery to locate the correct mass and to enable the best pathway for removal to be found.

Roshni Rao, a specialist in breast cancer at UT Southwestern, commented, "The new technique is less invasive for the patient and allows us to be more precise when removing possible breast-cancer tumors".

Previous techniques involved using hooks and wires to guide the surgeon to the mass, the entry site for the wire is often distant from an ideal site where a surgeon would prefer to make an incision.

"The seed procedure pinpoints the location of a nonpalpable tumor more accurately than the wire and it is more efficient" Rao said. "The wire method, on the other hand, requires patients to undergo the pre-operative procedure just hours before surgery because if left in longer, the wire could become dislodged".

"The seed procedure pinpoints the location of a nonpalpable tumor more accurately than the wire and it is more efficient."

It is hoped that this new technique will replace existing procedures and is currently being offered at only three hospitals in the USA.

Source: Southwestern Medical centre. Press release http://www8.utsouthwestern.edu/utsw/cda/dept353744/files/415701.html.

Osteoarthritis targeted by new disease-modifying drug

The new research in rats has indicated that oral calcitonin may effectively protect postmenopausal women from the disabling effects of joint destruction.

Calcitonin is an amino acid hormone produced by the thyroid gland and is known to decrease bone deterioration and to increase bone density. Ovariectomized rats, a model that closely resembles human skeletal changes during menopause were used in the study. A total of 50 female rates were used in five study groups: ovariectomy; ovariectomy plus 60-day release estrogen pellet; ovariectomy plus 2.0 mg/kg of salmon calcitonin and 50 mg/kg of 5CNAC, a carrier; ovariectomy, plus 50 mg/kg of 5CNAC without calcitonin; and a sham operation. Blood samples from each group were analyzed for C-telopeptide type II collagen (CTX-II), which is shown to correlate with degradation of cartilage in rats. The rats were also microscopically examined to find evidence of surface erosions of cartilage in the knee joint.

Oral calcitonin may be effective in protecting postmeopausal women form the pain associated with osteoarthritis.

The results showed that the ovariectomized rats had an increase in CTX-II, which indicated an increase in cartilage degradation. After 9 weeks, estrogen therapy effectively worked to counteract the increased levels of CTX-II, whereas the calcitonin group brought levels of CTX-II down to below those in the sham group.

Estrogen and calcitonin also provided protection from surface erosion of knee joint cartilage, with calcitonine preventing erosion completely. The study did reveal that calcitonin had the highest negative impact on weight gain; the rats in the group gained the most out of all. Weight gain is known to increase the amount of erosion on weight baring knee joints.

Furthermore, it is thought that calcitonin activity may not just be limited to prevention of damage, but may also have a therapeutic possibility in the early stages of the disease.

Lead author of the study, Bodil-Cecilie Sondergaard concluded: "Calcitonin treatment may counter the acceleration of cartilage degradation and the related rise of surface erosions, indicating important chondroprotective properties of this drug which need to be explored in upcoming clinical trials".

Source: Sondergaard B-C, Oestergaard S, Christiansen C *et al.*: The effect of oral calcitonin on cartilage turnover and surface erosion in an ovariectomized rat model. *Arthritis Rheum.* 56(8), 2674–2678 (2007).