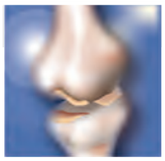
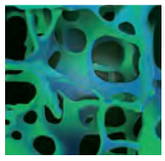


Bulletin Board

Novel molecule discovered to combat dysfunctional immune response

Researchers from the Eastern Virginia Medical School and Children's Hospital of The King's Daughters (VA, USA) have successfully isolated a molecule that can shut down a dysfunctional immune response that destroys joints in rheumatoid arthritis patients.

The molecule, which is small enough to be used as a drug, is a modified peptide known as E23A, and was extracted from a large protein shell of a common virus frequently responsible for childhood diarrhea. In addition to its potential use in combating joint destruction in rheumatoid arthritis patients, the molecule could also help prevent deadly hemorrhagic shock and organ rejection, which also stem from the same faulty immune response.

> "Being able to pharmacologically modulate the complement system could have a huge impact on the practice of medicine, potentially saving the lives of victims of hemorrhagic shock, heart attack patients and even infants who have suffered prolonged hypoxia."

The breakthrough comes almost 5 years after initial experimentation, whereby the shell of a virus that causes childhood diarrhea was inserted into a petri dish primed to measure complement system response, leading to a complete stop in the complement reaction.

Neel Krishna, one of the researchers involved in the investigation comments, "This puts us in a position to move rapidly from *in vitro* testing to *in vivo* testing. Being able to pharmacologically modulate the complement system could have a huge impact on the practice of medicine, potentially saving the lives of victims of hemorrhagic shock, heart attack patients and even infants who have suffered prolonged hypoxia. It could also have a significant impact on treating a wide range of autoimmune and inflammatory diseases."

The complement system developed over millions of years when the deadliest threat to organisms was infectious diseases and is virtually identical across the immune systems of all life forms possessing it.

Earlier research demonstrated that introducing purified, recombinant human astrovirus coat protein, responsible for childhood diarrhea, inhibited the activation of the classical and lectin pathways of complement, responsible for destroying damaged cells, but did not affect the pathway that offers protection from invading pathogens. The protein shell, however, consisted of 787 amino acids, which is too large to be considered as a viable therapeutic option. The new modified peptide, isolated by testing smaller fragments of the coat protein, functions by competitively inhibiting the binding of wild-type coat protein to C1q and, thus, prevents activation of the pathway. It is only 30 amino acids long and has even been shown to be more effective than the original protein. At this size, E23A becomes a feasible candidate for investigation *in vitro* and offers the potential of being developed into a therapeutic drug for the treatment of autoimmune and inflammatory diseases.

"*In vitro* testing is a significant step toward developing a drug that can be used therapeutically," concluded Krishna.

The isolation of E23A is a major step forward in its clinical application, as it has been demonstrated to have a powerful effect on the complement system, at a size small enough to be used a therapeutic drug.

Source: Gronemus JQ, Hair PS, Crawford KB, Nyalwidhe JO, Cunnion KM, Krishna NK: Potent inhibition of the classical pathway of complement by a novel C1q-binding peptide derived from the human astrovirus coat protein. *Mol. Immunol.* (2010) (Epub ahead of print).

in the news...

Subset of necrotizing myopathy patients found with previously unrecorded autoantibodies

A team at Johns Hopkins University (MD, USA) have uncovered a subset of necrotizing myopathy patients expressing an autoantibody with a novel specificity. The breakthrough could represent a valuable discovery for patients who could potentially now benefit from immunosuppressive therapy.

Only patients with immune-mediated myopathies are suitable for immunosuppressive therapies, as opposed to those with other necrotizing myopathies such as muscular dystrophies. A paucity of highly specific clinical evaluations and diagnostic tests has led to cases of inappropriate treatment where immune-mediated myopathies have not been distinguished from the other forms of the disease. The results of the recent publication highlight an antibody that could provide a therapeutic and a diagnostic target for further investigation.

The study used muscle biopsies from 225 patients diagnosed with necrotizing myopathies. Patients were selected if the cause of their myopathy was not well defined, and muscle biopsies were screened for novel autoantibodies. Unique autoantibody specificity against 200 and 100-kd proteins (anti-200/100 autoantibodies) was identified in 16 patients.

The authors tested sera from patients expressing anti-200/100 autoantibody against signal recognition peptide subunits and found that there was no reaction, and sera from patients with anti-recognition peptide autoantibodies did not recognize proteins with molecular weights of 200 or 100 kd. This places those expressing the novel anti-200/100 autoantibodies in an immunologically distinct subgroup to other myopathies, in which patients tested with immunosuppressive therapies gave a positive response.

"We have identified a group of patients with a necrotizing myopathy and a novel anti-200/100 autoantibody specificity," said Andrew Mammen, lead author of the study. "All of the patients responded to immunosuppression, and many experienced a flare of weakness when this treatment was tapered, which supports our hypothesis that this is an immune-mediated myopathy."

The researchers concluded that a novel subset of patients had been identified who could be considered for immunosuppressive treatment. This will hopefully benefit a population of sufferers of this debilitating disorder.

Source: Christopher-Stine L, Casciola-Rosen LA, Hong G, Chung T, Corse AM, Mammen AL: A novel autoantibody recognizing 200-kd and 100-kd proteins is associated with an immune-mediated necrotizing myopathy. *Arthritis Rheum.* 62, 2757–2766 (2010).

in brief...

Sprouty1 is a critical regulatory switch of mesenchymal stem cell lineage allocation. Urs S, Venkatesh D, Tang Y *et al. FASEB J.* 24(9), 3264–3273 (2010).

A new protein has been discovered, dubbed 'Sprouty', which appears to be responsible for regulating body fat and bone mass. The study investigated two groups of transgenic mice, one group with the Sprouty gene deleted in cells that develop into fat and bone, and one group of mice with high expression of Sprouty in these cell types. The results showed that mice with the genetic deletion of Sprouty had increased body fat and bone loss, similar to that observed in osteoporosis, while mice with higher expression levels of Sprouty were leaner than normal, with an increased bone mass. The new discovery will help improve the understanding of how body fat and bone mass is regulated and may, in turn, offer a potential new target for treating conditions such as osteoporosis. "Our study provides insight into the regulation of bone mass and body fat. Therefore, future application of this knowledge may help treat common conditions such as bone loss and obesity," said Lucy Liaw, coauthor of the study from the Maine Medical Center Research Institute.

Physical function improvements and relief from fatigue and pain are associated with increased productivity at work and at home in rheumatoid arthritis patients treated with certolizumab pegol. Hazes JM, Taylor P, Strand V, Purcaru O, Coteur G, Mease P. *Rheumatology (Oxford)* 49(10), 1900–1910 (2010).

The association between improvements in physical function, patient productivity, fatigue and pain relief was investigated in two clinical trials, involving rheumatoid arthritis (RA) patients treated with a combination of certolizumab pegol (CZP) and methotrexate. The majority of RA patients become work disabled within 10 years of onset, thus successful treatment of the disease would provide significant benefits to both patients and the wider society. The odds for patients treated with CZP achieving improvements in minimal clinically important differences were five-times higher for pain and two- to three-times higher for physical function and fatigue, compared with the control groups. Responders to the treatment reported significantly greater work and home productivity compared with nonresponders, as well as reduced interference of RA with their work productivity. The results, therefore, suggest a clear association between treatment with CZP and an improvement in physical function, productivity, and fatigue and pain relief in patients with RA.

About the Bulletin Board

The Bulletin Board highlights some of the most important events and research in the field of rheumatology. If you have newsworthy information, please contact: Christine Forder, Commissioning Editor, International Journal of Clinical Rheumatology, Future Medicine Ltd, Unitec House, 2 Albert Place, London N3 1QB, UK
Tel.: +44 (0)20 8371 6090;
Fax: +44 (0)20 8343 2313;
c.forder@futuremedicine.com

Acupuncture no better than placebo in treating osteoarthritis of the knee

Researchers at The University of Texas MD Anderson Cancer Center have demonstrated that patients with osteoarthritis of the knee treated with traditional Chinese acupuncture did not experience a greater benefit than those treated with sham acupuncture (placebo).

Osteoarthritis is the most common form of arthritis and affects approximately 27 million people in the USA aged 25 years and older. Symptoms include pain, stiffness and swelling of the joints, and many patients look for alternative treatment options to help relieve them. Acupuncture has become an increasingly popular practice for the treatment of a range of ailments and a survey by the National Center for Complementary and Alternative Medicine estimated that approximately 3.1 million adults in the USA had used the treatment in 2006.

The study involved 455 patients with osteoarthritis of the knee, as well as 72 healthy controls and compared the efficacy of traditional Chinese acupuncture with sham acupuncture as a treatment option. In addition, the acupuncturists were trained to interact with patients in either a high expectations style, suggesting that acupuncture is often very successful in treating osteoarthritis, or a neutral expectations style, suggesting it may or may not work for them.

The results showed that there was no statistically significantly difference between patients in the traditional Chinese acupuncture group and the sham group, with joint-specific multidimensional assessment of pain (J-MAP) scores at -1.1 and -1.0, respectively, with the control group scoring -0.1.

"We found a small, but significant effect on pain and satisfaction with treatment, demonstrating a placebo effect related to the clinician's communications style. The improvement in pain and satisfaction suggests that the benefits of acupuncture may be partially mediated through placebo effects related to the behavior of the acupuncturist," comments Maria Suarez-Almazor, one of the investigating researchers at the MD Anderson Cancer Center.

Source: Suarez-Almazor ME, Looney C, Liu Y *et al.*: A randomized controlled trial of acupuncture for osteoarthritis of the knee: effects of patient–provider communication. *Arthritis Care Res. (Hoboken)* 62(9), 1229–1236 (2010).

New MRI technique may help in the diagnosis of osteoarthritis in the knee

A research team from New York University (USA) has described a new method of using MRI to examine sodium ions in the knee joint that may have important implications in diagnosing osteoarthritis. The technique developed by the team is noninvasive and utilises the presence of sodium ions in cartilage in the knee joint.

It has been described previously that the concentration of sodium ions within the body can be used to locate glycosaminogycans (GAGs) in cartilage. GAGs are important molecules that are a component of connective tissue and it is known that a decrease in GAGs can indicate the start of osteoarthritis. However, existing MRI techniques for monitoring GAG concentration do suffer from limitations; they cannot be used to map the concentration of GAGs directly and contrast agents are frequently required to locate the concentrations of GAGs.

Techniques have been developed previously to measure sodium ions in the cartilage at the University of Pennsylvania and Stanford University; however, these techniques are not able to successfully identify the sodium ions in different areas of the knee joint; it is necessary for them to differentiate between sodium ions in the knee cartilage and ions in the synovial fluid and joint effusion. The New York University team has aimed to solve this problem by differentiating between the properties of the sodium ions in the two environments, resulting in a new method that is capable of obtaining images showing sodium signals that only appear from areas of the knee with cartilage tissue.

The researchers are hopeful that the newly developed technique can be used to noninvasively diagnose osteoarthritis in its early stages.

Source: New York University: www.nyu.edu

Positive results with extended-release tapentadol in chronic osteoarthritis knee pain trial

Pivotal Phase III trial results published in *Clinical Drug Investigation* in August have shown safety and efficacy benefit from using Tapentadol (Nucynta®; Johnson and Johnson, NJ, USA) in the treatment of moderate-to-severe chronic osteoarthritis knee pain.

Although the exact mechanism of tapentadol is not known, it acts centrally and has a dual action by working on both ascending and descending pain pathways. By combining both opioid and nonopioid activity, this novel analgesic is used for several pain indications. It is hoped that this extended-release formulation will hold some promise in the field of rheumatology-related pain relief.

The trial randomized 1023 patients in a 1:1:1 ratio to receive twice-daily, controlled, adjustable, oral doses of extended-release tapentadol (100–250 mg), controlled-release oxycodone HCl (20–50 mg) or placebo during a 15-week double-blind treatment period. Demographic and baseline characteristics were fairly well balanced across the treatment groups.

The first group compared tapenatdol to placebo using patient-reported outcomes at weeks 5 and 9 of the maintenance period and then at the end of the study. Patients rated daily pain intensity on an 11-point scale from which averages were taken. Tapentadol ER significantly reduced average pain intensity between baseline and week 12 of the maintenance period versus placebo (least squares mean difference: -0.7; 95% CI:-1.04 to -0.33), and throughout the maintenance period (least squares mean difference: -0.7; 95% CI: -1.00 to -0.33). The rate of treatment-emergent adverse events in the treatment group was 19.2%, whereas in the placebo group it was 6.5%, including a higher incidence of gastrointestinal adverse events in the treatment compared with placebo groups.

"We are pleased that the study indicates that tapentadol ER may be effective in the treatment of moderate to severe osteoarthritis knee pain, and that a low number of patients discontinued the study due to gastrointestinal side effects," commented Bruce Moskovitz, Therapeutic Area Leader for Pain, Ortho-McNeil Janssen Scientific Affairs.

The study was conducted as part of Johnson and Johnson's submission of the extended-release tapentadol formulation to the US FDA for regulatory approval, from which a decision has not yet emerged.

Source: Johnson & Johnson: www.jnj.com/connect/news/all/Pivotal-Phase-3-Study-Compares-Tapentadol-Extended-Release-Tablets-to-Placebo-in-Patients-with-Chronic-Osteoarthritis-Knee-Pain