

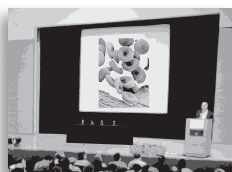


Immunotherapy

NEWS



CONFERENCE SCENES



Clinical trial shows sublingual immunotherapy to be effective for treatment of children with grass pollen allergy

A new study, published in the *Journal of Allergic and Clinical Immunology*, has reported that high-dose sublingual immunotherapy (SLIT) can effectively reduce allergic symptoms and medication use in allergic rhinoconjunctivitis. The authors state in their publication that their findings support the use of SLIT as a viable alternative to subcutaneous immunotherapy and could be particularly effective in the treatment of children.

SLIT administered as drops or tablets placed under the tongue has been shown to be a successful treatment strategy in adults. This study aimed to take this research further by implementing a randomized, double-blind, placebo-controlled study to investigate the safety and efficacy of high-dose SLIT in children allergic to grass pollen. Following a baseline seasonal observation, 207 children aged between 4 and 12 years suffering from grass pollen allergic rhinitis/rhinoconjunctivitis with or without bronchial asthma were enrolled into the study. The subjects then received either high-dose grass pollen SLIT or placebo between January and August. The children receiving SLIT were administered up to four drops a day

(3600–4800 µg) of an aqueous grass solution containing equal extracts from six species of grass. These were: *Dactylis glomerata*, *Festuca pratensis*, *Holcus lanatus*, *Lolium perenne*, *Phleum pratense* and *Poa pratensis*. The investigators determined the primary end point to be the change in the area under the curve of the symptom-medication score from the baseline season to the first season after the start of treatment. Secondary outcomes were well-days, responders, immunological changes and safety.

“The effects on allergen-specific antibodies was well tolerated, safe and appears to be a valid treatment strategy for children allergic to grass pollen.”

The mean change under the curve was significantly greater for the SLIT group when compared with the placebo group: -212.5 (SLIT) versus -97.8 (placebo). The symptom-medication score for rhinoconjunctivitis and separated symptom and medication scores were also statistically different between the treatment and placebo groups. Changes in the levels of allergen-specific IgE and IgG were also observed, indicating a significant immunologic effect. Importantly, the authors also found that the SLIT treatment was well tolerated and no serious side effects were apparent. More well days were reported in the treatment group, as well as more responders compared with the placebo group.

The authors write that the findings confirm that their SLIT preparation is beneficial to children suffering from





grass pollen allergic rhinitis, reducing symptoms and medication use. The effects on allergen-specific antibodies was well tolerated, safe and appears to be a valid treatment strategy for children allergic to grass pollen. The authors commented on the value of their clinical trial in the paper: “Such standardized studies in the pediatric population are considered necessary and will allow researchers to compare different results and to build more appropriate meta-analyses with more reliable conclusions

about SLIT efficacy and safety in allergic children.”

– Written by Jonathan Wilkinson

Source: Wahn U, Klimek L, Ploszczuk A et al. High-dose sublingual immunotherapy with single-dose aqueous grass pollen extract in children is effective and safe: a double-blind, placebo-controlled study. *J. Allergy Clin. Immunol.* doi:10.1016/j.jaci.2012.06.047 (2012) (Epub ahead of print).

Cytotoxic T lymphocyte response may predict HIV-1 disease progression

Investigators from the Multi-Center AIDS Cohort Study (MACS) at the UCLA AIDS institute (CA, USA) have published findings that may explain HIV to AIDS progression variation amongst individuals. One of the major discussion points in AIDS research is why some HIV-positive patients take more than a decade for AIDS to develop, if at all. The reported average time between HIV infection and AIDS in the absence of retroviral treatment is thought to be around 10 years. However, some individuals develop AIDS within 2 years of infection, while others can remain free of AIDS for more than 20 years. The authors of this latest study believe that the answer may be a killer T-cell response that occurs in the early stages of HIV infection and targets an epitope of an HIV protein.

“Cytotoxic T lymphocyte responses in the early stages of HIV infection are thought to be important in the long-term rate of disease progression.”

B57 is associated with slow disease progression after HIV infection. However, heterozygotes result in a number of different outcomes, including rapid progression. Catherine Brennan, the study’s lead author explained: “Since the hope for a vaccine is that it would elicit immune control, the thought has been that understanding how B57 protection works would yield helpful lessons and principles for vaccine design. There have

been a lot of efforts to understand how the immune response to HIV in B57 carriers is superior to the response in non-B57 carriers, but it has been hard to nail anything down conclusively.” Cytotoxic T lymphocyte (CTL) responses in the early stages of HIV infection are thought to be important in the long-term rate of disease progression. Despite this however, few data on early CTL responses of slow progressors currently exist.

The investigators used the MACS to retrospectively examine the early HIV-1-specific CTL responses of 14 B57-positive individuals whose time of disease development ranged from 3.5 years to more than 25 years post-infection. Beth Jamieson, the study’s principal investigator emphasized the importance of the MACS in this research: “What made this kind of study possible for us is the MACS, which is an incredible longitudinal study. The MACS has been freezing blood samples every 6 months since 1984 from thousands of men either at risk of HIV infection or already infected. The size and duration of the study, along with the careful documentation of participant health and stewardship of frozen samples, allowed us to recover blood samples taken shortly after HIV infection from HLA-B57 carriers with known infection dates and known long-term outcomes. This allowed us to correlate early immune responses with long-term outcomes.”

It was found that in general a greater breadth of targeting of epitopes from structural proteins such as Gag, as well as highly conserved epitopes from any HIV-1 protein, correlated with longer disease progression. The single elite controller in the study cohort was an outlier on several correlations of CTL targeting and time until disease. When targeting of individual epitopes was analyzed, it was found that early CTL response to the IW9 epitope of Gag correlated with delayed progression to disease.

“...it was found that early CTL response to the IW9 epitope of Gag correlated with delayed progression to disease.”

Although the small study sample is an obvious limitation to the study, Jamieson explained the significance of the results: “We found that those who targeted the IW9 epitope early in infection had significantly longer times until onset of AIDS than those who did not. The finding that targeting of IW9 seems to be important is novel, as this epitope had been overlooked in many earlier studies of B57 and HIV. This work, although not powered by a large cohort and necessarily exploratory in nature, does suggest that the role of IW9 targeting in B57-mediated protection merits closer attention. Understanding the detailed mechanisms by which B57 is associated with slow progression to disease will

reveal underlying principles of immune control of HIV-1, which is critical for the development of rational vaccine design strategies.”

– Written by Jonathan Wilkinson

Sources: Brennan CA, Ibarondo FJ, Sugar CA et al. *Early HLA-B*57-restricted CD8⁺ lymphocyte responses predict HIV-1 disease progression*. J. Virol. 86(19), 10505–10516 (2012); UCLA Newsroom: <http://newsroom.ucla.edu/portal/ucla/researchers-identify-possible-238685.aspx>



New generation of drugs may treat diverse array of allergic/inflammatory diseases

Research lead by Saul Yedgar, professor at Hebrew University-Hadassah Medical School (Jerusalem, Israel) and Chief Scientific Officer and co-founder at Morria Biopharmaceuticals Plc (London, UK), has developed a new generation of drugs that safely and effectively treat a diverse array of allergic and inflammatory diseases, including sepsis, inflammatory bowel diseases, asthma and CNS inflammation.

Allergic and inflammatory diseases affect vast numbers of people worldwide, and are currently a major focus for pharmaceutical companies. Currently, the most common drugs to treat these diseases are steroids. Although these are potent, they are also associated with severe side effects such as weight gain, increased blood pressure, diabetes, glaucoma, cataracts, bone fragility, depression and psychosis. As a result, for many years there have been great efforts focused on the discovery of nonsteroidal alternative anti-inflammatory drugs. Unfortunately, many of these are not as potent as steroids, can be costly and have their own side effects. Therefore, there is a need for further treatments for allergic and inflammatory diseases.

Inflammatory and allergic diseases present a highly diverse range of symptoms; however, many of them share certain

biochemical mechanisms. Thus, these mechanisms are a prime target for the development of broadly effective drugs. A key mechanism among these is the action of an enzyme family called phospholipase A₂, which initiates the production of a cascade of proinflammatory mediators, such as eicosanoids, involved in the induction of inflammatory diseases.

“...MFAIDs were shown to be safe and efficient in treating contact dermatitis when incorporated into skin cream, and allergic rhinitis when administered as a nasal spray. These results appear promising...”

Yedgar and his colleagues have devised a novel synthetic generation of drugs that control phospholipase A₂ activity and the subsequent cascade of proinflammatory mediators, thereby providing multifunctional, anti-inflammatory drugs (MFAIDs).

In animal models, MFAIDs have shown an excellent safety and efficacy profile when treating a diverse array of conditions including sepsis, inflammatory bowel diseases, asthma and CNS inflammation. This was shown using a variety of methods of administration, including oral, rectal, intravenous, inhaled and injected.

In addition, in two clinical studies, MFAIDs were shown to be safe and efficient in treating contact dermatitis when incorporated into skin cream, and allergic rhinitis when administered as a nasal spray. These results appear promising for the future of MFAIDs.

Yedgar has been awarded the Kaye Innovation Award at the Hebrew University for his work on MFAIDs.

The technology has been licensed to Morria Biopharmaceuticals Plc, which is currently developing these drugs to treat inflammatory diseases of the airways (hayfever and cystic fibrosis), the skin (eczema), the eye (conjunctivitis) and the gut (colitis and Crohn's disease).

– Written by Jonny Patience

Sources: Dan P, Rosenblat G, Yedgar S. *Phospholipase A₂ activities in skin physiology and pathology*. Eur. J. Pharmacol. 691(1–3), 1–8 (2012); Morria Biopharmaceuticals press release: www.morria.com/press_relases.html; Yedgar S. *A novel class of multi-functional anti-inflammatory drugs (MFAIDs) for the treatment of inflammatory/allergic diseases*: <http://cc.cfu.org/docs/IMRIC/Kaye-Awards-2012-IMRIC-1-SY.pdf>

Super antibody may have the potential to both prevent and cure flu

A breakthrough may have been made in the battle against flu viruses. Scientists from The Scripps Research Institute (CA, USA)

and Sea Lane Biotechnologies (CA, USA) have been investigating the co-crystal structure of a human antibody that is

thought to have the power to neutralize a broad range of flu viruses. They report that the key structure most flu viruses



use to attach to healthy host cells, which was previously thought to be too small for antibodies to latch on to, can be recognized and targeted by the apparatus of this immune protein.

For the study, Sea Lane Biotechnologies created a ‘comprehensive flu library’ of billions of antibodies. Bone marrow was sourced both locally and internationally from individuals who were known to have been exposed to certain strains of flu. Many new flu-specific antibodies with the ability to bind to proteins from a range of dangerous influenza A viruses were identified, including the C05 antibody, which has demonstrated unique flu neutralizing capabilities.

Researchers observed that C05 protected cells from infection by flu viruses *in vitro*, and *in vivo* prevented infection in mice despite exposure to lethal influenza A viruses. The C05 antibody also demonstrated remarkable results

post-infection, rescuing 100% of mice when administered as many as three days after a flu infection had begun.

C05 acts by specifically recognizing and blocking the receptor binding site (RBS) of the flu virus that mediates the attachment of the flu virus to host cells. The RBS is relatively exposed to the immune system, but was thought to be too small for an antibody to ‘grab’. To get a good grip on the RBS, an antibody generally also has to grab the surrounding structures, which can differ significantly between strains of the virus. Therefore, antibodies designed for specific strains can become redundant if the strain mutates.

“It is hoped that C05, and maybe even more potent antibodies, could be used as therapies for severe flu infections.”

“This is why universal flu vaccine strategies in recent years have been focused more on the hemagglutinin stem than on the head,” explained Damian Ekiert, researcher at the University of California (CA, USA) and first author of the paper. His team found that C05 avoided the hypervariable structure around the RBS,

instead reaching in and grabbing the RBS with an elongated protein loop. C05 has two of these loops, one on each arm, and appears to be most effective when using both loops on separate RBSs. As the RBS has a very similar structure in most flu strains, C05 is thought to be effective against a broad range of influenza A viruses.

It is hoped that C05, and maybe even more potent antibodies, could be used as therapies for severe flu infections. A vaccine that could elicit antibodies such as these in humans could change our relationship with influenza. Lawrence Horowitz, CEO of Sea Lane Biotechnologies, concluded that “If we can figure out how to induce this sort of antibody in a vaccine, we would have something that’s very useful.”

– Written by Sophie Breeze

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Sources: Ekiert DC, Kashyap AK, Steel J et al. Cross-neutralization of influenza A viruses mediated by a single antibody loop. *Nature* 489(7417), 526–532 (2012); Flu antibody’s ‘one-handed grab’ may boost effort toward universal vaccine, new therapies: www.scripps.edu/news/press/2012/20120916wilson.html

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