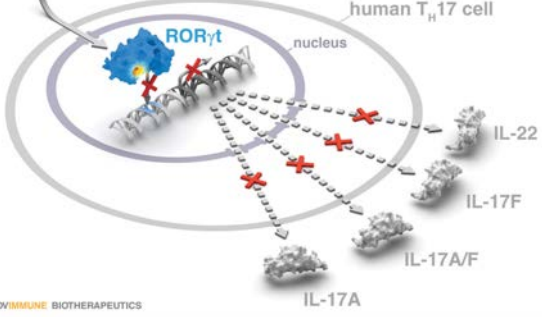
ROR Gamma Inhibitor Tested in Lupus Model

New preclinical research targeting a key receptor thought to be involved in the pathogenesis of systemic lupus erythematosus has shown promising results in a mouse model of the disease, according to results of a study that will be presented this afternoon.

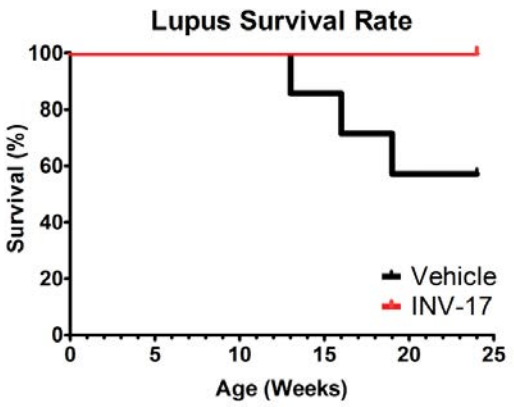
In the study, mice that received an oral small-molecule modulator of retinoic acid receptor-related orphan receptor (ROR) gamma (t) had markedly better survival and significantly less proteinuria, compared with a vehicle control group.

"This is the first study demonstrating the preclinical proof of concept efficacy of targeting ROR gamma in an animal lupus model with an oral-based small-molecule drug," said Dr. Anderson Gaweco, President and Chief Executive Officer of Innovimmune Biotherapeutics Inc., which sponsored the study and is developing the INV-17 RORgt inverse agonist. The results "highlight the importance of targeting T helper 17 [TH17] cells and blocking production of several TH17 cytokines concurrently by singly switching off ROR gamma activity through small-molecule drug modulation," he added in an interview before his presentation.



Patients with systemic lupus erythematosus and lupus nephritis currently have limited treatment options and face substantial side effects from treatment. But research indicates that targeting TH17 cells and their associated interleukin (IL)-17A and IL-17F cytokines, which are key to the pathogenesis of several autoimmune diseases including systemic lupus erythematosus and lupus nephritis, might be worthwhile. Mice and human patients with worsening lupus have increased TH17 cytokine expression, and the RORgt nuclear hormone receptor is a central regulator of TH17 cellular differentiation, function, and cytokine production, Dr. Gaweco and his colleagues noted.

For their study, the researchers randomised 11 lupus-prone MRL/*lpr* mice with proteinuria scores of more than 2 on a 0-3 scale to 6 weeks of either oral INV-17 at a dose of 2 mg/kg or to vehicle control. All of the mice in the treatment group were still alive at age 25 weeks, compared with 57% of the control group. (See graph above.) After 11 days of treatment, mice that received INV-17 agent had a significantly lower mean proteinuria score than did control animals that received the vehicle (1.25 vs. 2.17; $P = .03$), as well as a lower mean proteinuria area under the curve (AUC) score (17.3 vs. 22.1, respectively). The treatment group did not have obvious adverse effects and maintained optimal (grade 3) body condition scores.



The efficacy data "highlights the importance of blocking ROR gamma, as it is the key control switch of TH17 cytokine production, which has been critically implicated in the pathogenesis of lupus," Dr. Gaweco said. Targeting the ROR gamma nuclear hormone receptor makes sense because it inhibits not only IL-17A, but also the TH17 cytokines IL-17F, IL-21, and IL-22, he added. Accordingly, anti-IL-17A and anti-IL17R agents have shown modest efficacy in other autoimmune animal models, he noted.

So far, the INV-17 small-molecule portfolio of RORgt inverse agonists are the only ROR gamma inhibitors in development to show preclinical efficacy in mouse models of rheumatoid arthritis and multiple sclerosis as well as lupus, Dr. Gaweco noted. Researchers are planning investigational new drug-enabling studies of INV-17 for several autoimmune disease indications, and hope to begin first-in-human studies in 2016, he said.

Dr. Gaweco and his colleagues are employees of Innovimmune Biotherapeutics Inc, the maker of the agent and study sponsor.

Basic and Translational Science Session
New players in lupus
Thursday 13:45–15:15
Room 10 I

Mitochondria Reveal Insights Into Dermatomyositis Muscle

Research from France is the first to link innate immunity, reactive oxygen species, mitochondria, and muscle impairment in dermatomyositis.

"Although dermatomyositis [DM] is an autoimmune disease, our findings emphasize that muscle impairment involves mechanisms upstream of adaptive immunity and suggest that reactive oxygen species [ROS] and mitochondria might participate in an auto-amplification of muscle inflammation in DM," said lead author Dr. Alain Meyer from the Muscular Diseases Reference Center at the University Hospital of Strasbourg.

The findings also put mitochondria at a crossroad between metabolic and innate immune processes in DM muscle, said Dr. Meyer, who will be presenting his findings at a PReS Session on Thursday afternoon.

Dermatomyositis has been linked to high type I interferon (IFN-I) signaling in skeletal muscle, which is thought to play a pivotal role in muscle inflammation and impairment. However, the mechanisms by which muscle dysfunction occurs are unknown.


Dr. Meyer

The research team used morphological, molecular, and functional studies to assess the link between inflammation, ROS, and mitochondrial dysfunctions in early, untreated DM patients, cell systems, and a mouse model of autoimmune myositis.

The study included 10 early and untreated DM patients who were compared with controls. Mouse C2C12 cells were exposed to IFN-beta in the presence and the absence of N-acetylcysteine, a potent ROS scavenger. Aerobic capacity was recorded in patients, and muscle strength was evaluated in a mouse model.

During his talk, Dr. Meyer will take delegates through the research team's findings. Overall, he says the results highlight that skeletal muscle in patients with dermatomyositis has mitochondrial dysfunction and high ROS production. In muscle samples from the patients, electron microscopy revealed numerous mitochondrial abnormalities, and oxidative enzymes in the samples exhibited abnormal histochemical staining. These samples also had about a 40% reduction in oxygen consumption, which correlated with patients' maximal aerobic capacities on a cycle ergometer, while at the same time showing an increase in hydrogen peroxide production. Muscle samples from the patients also showed an up-regulated cluster of transcripts of genes encoding proteins involved in inflammatory responses (especially IFN-I induced genes) and another cluster of down-regulated transcripts of genes encoding proteins involved in mitochondrial integrity and functions, the researchers reported.

"We also show that interferon-beta-induced ROS impairs mitochondrial respiration and that ROS participate in muscle weakness and inflammation" in a mouse model of autoimmune myositis, Dr. Meyer said.

The findings highlight that focusing on ROS and mitochondria may open new avenues for the comprehension of the disease, as well as the management of patients, he concluded.

PReS Session
Dermatomyositis I
Thursday 13:45-15:15
Room 10 B