



Inflammation 2007 - Eighth World Congress (Part III) - OVERNIGHT REPORT

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The role of long-lived plasma cells

Andreas Radbruch (Director of the German Rheumatism Research Center) began the penultimate day with a plenary lecture on long-lived plasma cells that was described as "an elegant talk" by the session chair. B-cells have long been known to play an important role in inflammation, and indeed long-lived plasma cells can survive conventional immunosuppressive treatments. The translocation of plasmablasts, the progenitors of plasma cells, from the spleen to the bone marrow was also discussed. These cells express CXCR3 and CXCR4 and, unlike the plasma cells, can migrate in response to the chemokine ligands for these receptors. Various survival factors, including CXCL12 (the CXCR4 ligand), IL-6 and TNF, synergize to form niches in the bone marrow and lymphoid tissue where the plasma cells can survive indefinitely. These niches are limited, however, and the plasma cells face direct competition from plasmablasts, which are attracted by chemokines such as CXCL12 and can migrate into the niches and displace the plasma cells, which then die in the absence of the survival factors. Dr Radbruch estimated that there are between 1000 and 10,000 specificities of memory plasma cells, with approximately ten being added each year and displacing existing ones. This displacement can also explain the elimination of plasma cells at the end of an immune response. Chemokines such as CXCL9, 10 and 11 (the CXCR3 ligands) expressed in inflamed tissue draw in plasmablasts, which enable them to survive as plasma cells, but at the expense of their ability to migrate. Once the inflammation is resolved, there are no survival factors left to maintain the plasma cells, which die without them. Plasmablast and long-lived plasma cells can also contribute to autoimmunity, for example, they are seen in large numbers during flares of systemic lupus erythematosus (SLE) and they have been shown to contribute to pathogenesis in the NZB/W murine SLE model. Dr Radbruch concluded his presentation by suggesting that the long-lived plasma cell could provide a new therapy target for autoantibody-driven inflammation and allergy, and ways to do this could include inhibiting their migration, giving immunosuppressives at the time of exposure, or culling their numbers with anti-thymocyte globulin.

EP-80317 shows promise in a lung injury model

Sylvie Marleau (Universite de Montreal, Canada) reported data on the efficacy of Europeptides' EP-80317, a CD36 receptor-specific hexarelin analog, in ischemia/reperfusion-induced remote lung injury in apoE^{-/-} mice. The animals received 300 microg/kg of subcutaneous EP-80317 daily for 2 weeks prior to 30 min of hindlimb ischemia, followed by reperfusion for 180 min. EP-80317 reduced both lung leukocyte accumulation and opsonized zymosan-induced blood chemiluminescence (ROS release) by 56% compared to control. These effects were abrogated when performed in apoE^{-/-}/CD36^{-/-} mice. Intestinal leukocyte accumulation was reduced by 55% by EP-80317, and a second compound from the program, EP-80318 (also dosed at 300 microg/kg), had a similarly potent effect as EP-80317 on lung leukocyte accumulation. EP-80317, which is also being developed for atherosclerosis and hypercholesterolemia, has previously been shown to reduce aortic fatty streak lesions in apoE^{-/-} mice fed a high fat, high cholesterol diet for 12 weeks. HDL cholesterol was increased and oxidized-LDL-induced peritoneal macrophage accumulation was reduced.

Anthera's A-002 reduces atherosclerosis in mice

Preclinical atherosclerosis model data generated by Eli Lilly on secretory PLA2 inhibitor A-002 (LY-333013) were discussed by Anthera's Colin Hislop and colleagues. Anthera licensed the drug from Lilly and Shionogi in September 2006 [688686]. In apoE^{-/-} mice fed a high fat and high cholesterol diet for 16 weeks, A-002 (30 or 90 mg/kg bid by oral gavage) reduced total cholesterol after 1 month, although the effects were not dose- or time-dependent. Atherosclerotic plaque formation was reduced by 40% and plaque area was halved. Although triglyceride levels tended towards an increase over time, this was not deemed to be clinically significant. In an accelerated atherosclerosis model using apoE^{-/-} mice on angiotensin II and a high fat diet for 4 weeks, A-002 (30 mg/kg bid) halved plaque area, and aneurysms were not observed in any of the 16 drug-treated mice, but were seen in 5 of the 20 untreated animals.

Anthera began a phase II trial of A-002 in 200 patients with stable coronary artery disease caused by atherosclerosis in April 2007. The primary endpoint of the US and European PLASMA study is change in secretory PLA2 levels and activity, and secondary endpoints include changes in lipid and biochemical parameters, LDL and HDL subclasses and inflammatory markers, including C-reactive protein, ICAM-1, VCAM-1, TNF and MCP-1. Anthera plans to complete

enrollment "by the end of this week", with data expected in September or October 2007. The PLASMA study is designed to provide the basis for phase III cardiovascular disease trials, which will use either an anatomical or an outcomes model.

Novel soft topical immunosuppressants

Array BioPharma's development of topical 'soft' cyclosporin A (CsA) derivatives, designed to avoid the systemic exposure-induced cancer risk associated with long-term use of traditional topical versions of the drug, was discussed by Laurence Burgess (Director, Medicinal Chemistry at Array). These soft drugs are so called because they are engineered, via medicinal chemistry, to be effective upon local delivery, but upon systemic exposure they are rapidly inactivated by metabolic pathways. Efficacy was restored to inactive analogs using metabolically labile modifications in order to achieve this aim. Four immunosuppressive CsA analogs were produced, from one of which two further analogs were derived. These were then tested in a rat delayed-type hypersensitivity model, in which animals were treated with drug just prior to, and after oxazolone ear challenge on day 7 after initial priming on day 0. Results showed that the soft CsA compounds decreased ear weight.

Anti-IL-31 antibody tested in murine dermatitis model

Oystein Grimstad (Institute of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology) presented preclinical data on an anti-IL-31 antibody showing mixed results in a murine dermatitis model. Dr Grimstad's presentation featured research from part of the IL-13 collaboration ongoing between Zymogenetics, Novo Nordisk, Neurocrine Biosciences and Merck Serono. In July 2004, Zymogenetics published data showing that severe pruritis, alopecia and skin lesions were seen in transgenic mice overexpressing IL-31, and that IL-31 levels were increased in tissues from animals with airway hypersensitivity. In February 2006, work funded by Serono Pharma and carried out at the Heinrich-Heine-University, demonstrated in vitro that IL-31 mRNA was upregulated in skin biopsies from human pruritic atopic dermatitis lesions, but not from non-pruritic psoriasis lesions [806328]. In the current study, NC/Nga atopic dermatitis mice were treated with the rat-anti-mouse IL-31 antibody (10 mg/kg ip) every 5 days for 7 weeks. The antibody failed to affect histopathology, immunohistochemistry, serum IgE and IL-13, dermatitis or body weight over the 7 weeks, but scratching was reduced between days 22 to 43. Dr Grimstad suggested the lack of effect could have been due to the formation of antibodies against the anti-IL-31 agent, an increase in the importance of other mediators, or a shift in the Th1/Th2 T-cell balance towards a more Th1 phenotype.

Merck Serono's PI3K inhibitors effective in inflammation models

The use of the oral PI3K gamma inhibitor AS-605858 in murine inflammation models was discussed by Christoph Ladel (Merck Serono and the University of Torino). The compound has an IC₅₀ value of 3.4 nM against PI3K gamma, cellular activity of 40 nM for AKT phosphorylation and 2 microM for chemotaxis, more than 80% oral bioavailability and a half-life in mice of 3 h. It was assessed in the innate immune response irritant contact dermatitis (ICD) model, and the T-cell-dependent contact hypersensitivity (CHS) model, and was shown to have a dose-dependent therapeutic effect on some of the parameters measured, with others being inhibited at all doses tested (0.1, 0.3, 1 and 3 mg/kg). The effective doses of the drug were 0.3 mg/kg once-daily and 1 mg/kg twice-daily in the two models, respectively. In the ICD model, ear thickness, PMN recruitment, and MPO, IL-12p70, IL-10 and TNF alpha were reduced. In the CHS model, the drug reduced ear thickness, MPO and infiltration. There was a non-significant trend towards a reduction in IFN-gamma, TNF-alpha and IL-6.

In a poster featuring the same drug, Merck Serono's Vittoria Ardissona described the mechanism of action of AS-605858 in arthritic mice. The drug (15 mg/kg bid for 8 days) reduced clinical and histopathological arthritis features and abrogated disease-induced elevations in AKT phosphorylation. AS-605858 did not affect T-cell counts, although NK cells, memory T-cells and regulatory T-cells were significantly reduced, and B-cell count was moderately, but non-significantly, decreased.

According to previously reported and published data, AS-605240, another compound from this program, suppressed joint inflammation and cartilage damage in a murine collagen-induced arthritis model, and reduced glomerulonephritis and prolonged life span in a mouse model of systemic lupus.