



## Ninth World Congress on Inflammation – Overnight Report 3

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Reported by Vicki L Mason, Thomson Reuters, London, UK Email: [vicki.mason@thomsonreuters.com](mailto:vicki.mason@thomsonreuters.com)

*This report contains highlights from Wednesday's poster session.*

### SA-13353: a potential anti-inflammatory and immunomodulatory agent

Transient receptor potential vanilloid 1 (TRPV1), which is activated by capsaicin, has a predominant function in the integration of afferent noxious signals generated by inflammatory mediators. Santen Pharmaceutical's Fumio Tsuji presented data from studies of SA-13353, a TRPV1 agonist, in murine models of acute and chronic inflammation. In C57BL/6 mice, SA-13353 (30 mg/kg po) augmented IL-10 production and inhibited LPS-induced TNF-alpha and IL-1beta production to a greater extent than capsaicin (30 mg/kg po). SA-13353 had no effect in TRPV1-knockout mice. In a murine sepsis model, the compound (30 mg/kg po) reduced lethality more than capsaicin at the same dose. Histological analysis and mRNA expression levels demonstrated that the development of arthritis in human TNF-alpha transgenic mice was reduced by SA-13353 (30 mg/kg po qd). Furthermore, clinical signs and histopathological changes associated with experimental autoimmune encephalomyelitis (EAE) were attenuated by the compound at 30 mg/kg and decreased cytokine production was observed in the EAE model following SA-13353 administration.

### POL-6014 inhibits HNE-induced ALI in mice

Elastin, which imparts structural stability to the lung, is hydrolyzed by human neutrophil elastase (HNE), a 29-kDa serine protease. HNE plays a role in the secretion of pro-inflammatory mediators and mucus, and it is thought to participate in the development of emphysema. Vincent Lagente (Universite de Rennes) described data from a study comparing the local effects of the neutrophil elastase (NE) inhibitors POL-6014 (Polyphor) and sivelestat (Elaspol) on HNE-induced acute lung injury (ALI) in mice. POL-6014 (0.05 to 5 mg/kg) or sivelestat (1 and 5 mg/kg) were administered intranasally to anesthetized C57BL/6J mice 15 min before the intranasal injection of HNE (25 microl, 1 ml/kg). Following HNE administration (4 h), cell composition, hemoglobin (Hb) levels and the activity of IL-6, KC/chemokine (C-X-C motif) ligand 1 (CXCL1) and matrix metalloproteinase 9 were analyzed in bronchoalveolar lavage (BAL) and myeloperoxidase (MPO) in tissue. A dose-dependent reduction of all parameters was observed for POL-6014; 0.5 mg/kg caused maximal reductions of neutrophil influx (41.8 %), Hb (0.071 g/dl), IL-6 (209.6 pg/ml) and KC/CXCL1 (693.8 pg/ml). Comparable inhibition was observed for 5 mg/kg sivelestat and 0.5 mg/kg POL-6014. From these findings, it was suggested that POL-6014 may prove effective in the treatment of NE-associated lung diseases.

### OPL-CCL2-LPM - mechanism of action studies

The pathology of many inflammatory disorders is dependent on the modulation of monocytes/macrophages via the chemokine (C-C motif) ligand 2 (CCL2)/C-C motif chemokine receptor (CCR2) axis. Osprey Pharmaceuticals is developing a therapeutic approach to this which involves the use of a CCR2-targeting fusion protein to eliminate these cells. OPL-CCL2-LPM is a leukocyte population modulator (LPM), comprising a human CCL2 fused to a modified SA1 subunit from *Shigella dysenteriae* holotoxin. SA1 is a ribosome-inactivating protein (RIP), which depurinates ribosomes, arresting protein synthesis and subsequently causing cell death. John R McDonald from the developing company presented results from binding, internalization and cytotoxicity characterization studies. Fluorescence-activated cell sorting and competition binding studies demonstrated that OPL-CCL2-LPM binds to CCR2 in THP-1 monocytic cells and human, rat and monkey peripheral blood mononuclear cells. Using confocal microscopy, it was shown that the compound is rapidly internalized by monocytes. In an in vitro protein synthesis assay, OPL-CCL2-LPM had a RIP IC50 value in the range of 12 to 30 pM and in a cell viability assay it was shown to be cytotoxic to monocytes. It has also been found that the compound is efficacious in animal models of nephritis and EAE. No side effects were reported in these models or in monkey and rat toxicology studies. At the time of presentation, a phase Ib safety trial was ongoing in IgA nephropathy patients.

### Update on Array BioPharma compounds

ARRY-872, a potent and highly selective inhibitor of the receptor tyrosine kinases TrkA (IC50 = 6.5 nM), TrkB (IC50 = 8.1 nM) and TrkC (IC50 = 10.6 nM), is being investigated by Array BioPharma for the potential treatment

of pain. Data demonstrating the compound's analgesic effects in models of inflammatory pain were presented by Kevin Koch from the developing company. Plasma protein binding for the compound has been shown to be 60 to 80% in preclinical species and 70% in humans; it also had IC50 values of greater than 10 microM for hERG and greater than 25 microM for CYP inhibition (seven major isoforms). Genotoxicity testing has shown that ARRY-872 is non-mutagenic and non-clastogenic. At 10, 30 and 100 mg/kg, the compound demonstrated good oral exposure in rats, and brain levels were low following oral dosing, which shows that efficacy is peripherally mediated. In complete Freund's adjuvant (CFA)-naive rats, ARRY-872 (30 mg/kg bid for 8 days) had no effect on thermal latency. In a chronic inflammatory pain model (CFA intraplantar injection, day 1), ARRY-872 (30 mg/kg bid, oral gavage, days 5 to 16) produced sustained inhibition of mechanical allodynia. In this model, the compound was more effective than an anti-nerve growth factor antibody (ip injection, 3.0 mg/kg, day 5). In a CFA-induced rat model of inflammatory pain, ARRY-872 (30 mg/kg) completely reversed hyperalgesia when dosed therapeutically and prophylactically; furthermore, it demonstrated equivalent or superior efficacy to a standard NSAIDs. At the time of presentation, Array BioPharm was planning to progress ARRY-872 into regulated safety assessments and clinical trials.

James D Winkler, also from Array BioPharma, considered the role of MEK in rheumatoid arthritis (RA) by reviewing clinical and preclinical data obtained for the selective and potent MEK inhibitor ARRY-162 (ARRY-438162). MEK inhibitors employ numerous mechanisms, including inhibition of cytokine production (IL-1beta, TNF-alpha, IL-6), ERK phosphorylation and the subsequent blocking of proliferative and destructive responses in the joint, including osteoclast differentiation and bone resorption. Strong inhibition of inflammation and bone destruction has been demonstrated by ARRY-162 preclinically; it has demonstrated efficacy as a single agent in both collagen-induced arthritis and adjuvant-induced arthritis models. When administered in combination with standard-of-care agents, such as NSAIDs, TNF inhibitors and methotrexate, ARRY-162 shows additive efficacious activity. When administered in the clinic, positive pharmacokinetics are shown by ARRY-162, with exposure increasing dose-proportionally. Preliminary evidence of decreased disease activity was demonstrated when ARRY-162 was administered to stable RA patients being treated with methotrexate. In clinical trials to date, no serious adverse events have resulted from ARRY-162 treatment and it has been well tolerated. Top line results are expected in August 2009 from a 12-week, randomized, multicenter, double-blind, phase II trial in patients with active RA, despite methotrexate treatment, comparing placebo and ARRY-162 (10 mg bid, 20 mg bid, 40 mg qd).

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