



# Ninth World Congress on Inflammation – Overnight Report 1

6-10 July 2009, Tokyo, Japan

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

## Introduction

The Ninth World Congress on Inflammation (WCI) is being held in conjunction with the 30th Annual Meeting of the Japanese Society of Inflammation and Regeneration (JSIR), and jointly organized by the Science Council of Japan. It began with an opening ceremony in which the Congress President Kouji Matsushima from the University of Tokyo explained that an enduring goal of inflammation research has been the regeneration of organs that have been impaired by excessive chronic inflammation: consequently, the main theme of the congress is 'Innovative Research of Inflammation, Repair and Regenerative Medicine.' Ian Ahnfelt Ronne from Novo Nordisk and President of the International Association of Inflammation Societies (IAIS), the global umbrella organization of inflammation societies, explained that this was the second time that the WCI was being held in Tokyo and that since the first time in 1997, significant advances have been made in inflammation research. Dr Ahnfelt Ronne thanked Professor Matsushima and his team for putting together a great program of events, which included keynote and special lectures, main morning symposium and society sponsored symposium, in addition to the presentation of over 350 abstracts. The opening ceremony concluded with a message of congratulation from the Japanese Prime Minister Taro Aso, welcoming participants from all over the world and wishing great success for the Congress.

## Chemokine involvement in inflammation

In the Presidential Lecture, Professor Matsushima considered chemokines, presenting a history of their research, their involvement in inflammation and reviewing clinical programs targeting them and their pathways. In 1970, reports were made of leukocyte-derived neutrophil chemotactic activity and monocyte chemotactic activity; however, the molecular properties underlying this were unclear. In 1987 and 1989, respectively, Professor Matsushima and Teizo Yoshimura discovered a neutrophil chemotactic cytokine interleukin 8 (IL8; CXCL8) and a monocyte chemotactic cytokine (CCL2) at the National Cancer Institute, which went a long way to explaining this previously reported activity. Subsequently, over 40 chemotactic cytokines, now known as chemokines, have been identified along with their receptors. It is now known that chemokines play a pivotal role in the migration of all subsets of leukocytes, both in homeostatic and inflammatory conditions. Furthermore, CCR5 and CXCR4 are amongst chemokine receptors identified as co-receptors for HIV infection. As a consequence the chemokine system has become a major target of therapeutic efforts for inflammatory, immune and infectious diseases, and cancer.

Despite pharmaceutical companies having many programs focused on chemokine receptors, there have been relatively few drug approvals in this field. Maraviroc (Celsentri; Selzentry), a CCR5 receptor antagonist fusion inhibitor, has been developed and launched by Pfizer in the US and UK for combination antiretroviral treatment of adults with CCR5-tropic HIV-1 infection. Plerixafor (Mozobil), a CXCR4 inhibitor and hematopoietic stem cell mobilizer, has been developed and launched in the US by Genzyme. Administered via subcutaneous injection, the drug is indicated for use in combination with G-CSF to mobilize stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma and multiple myeloma. Professor Matsushima also referred to a phase I clinical trial, in which patients with adult or peripheral T-cell lymphoma were administered KW-0761 (Kyowa Hakko Kirin), a humanized monoclonal antibody (mAb) against CCR4, once-a-week intravenously for 4 weeks at doses ranging from 0.01 to 1.0 mg/kg. From the study the recommended phase II dose was determined to be 1.0 mg/kg, adverse events were considered to be tolerable and the overall response rate was 31%.

Professor Matsushima finished his presentation by stating that understanding of the mechanisms underlying inflammation and immune response have been furthered by the discovery of chemokines, and novel anti-inflammatory and immune-regulating medicines are anticipated from clinical development targeting the chemokine system.

## IL-6 and Th17

In a keynote lecture, Tadimitsu Kishimoto from Osaka University explained that IL-6 has been shown to have pleiotropic activity in various tissues and cells, and that several chronic inflammatory conditions and hemopoietic malignancies result from its deregulation. Tocilizumab (Actemra) is an injectable humanized anti-IL-6 receptor mAb that is approved in Japan for the treatment of Castleman's disease, rheumatoid arthritis and systemic onset

juvenile idiopathic arthritis. It has been shown to be effective in inflammatory disease that is unresponsive to anti-TNF therapy. Th17 has recently been shown to be a causative factor in the pathogenesis of autoimmune disease, and IL-6 and TGF-beta are necessary for Th17 induction. Professor Kishimoto's group has identified aryl hydrocarbon receptor (Ahr), a transcription factor necessary for Th17 cell induction by IL-6 and TGF-beta. The negative activity of Stat1 and Stat5 in the induction of Th17 cell differentiation is abrogated by Ahr, and its interaction with STAT-1 in macrophages has been shown to negatively regulate LPS-induced inflammatory cytokines production. Data were presented demonstrating that Ahr has distinct functions in T-cells and macrophages: in T-cells it acts as a pro-inflammatory nuclear receptor and in macrophages it inhibits NF-kappaB transcription acting as a negative regulator of inflammation. By determining which cells play a role in which type of inflammation Ahr may become an attractive target for drug development.

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## Ninth World Congress on Inflammation – Overnight Report 2

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### **Bindarit reduces uMCP-1 in lupus nephritis patients**

Preclinical and clinical evidence has amassed to indicate a role for monocyte chemoattractant protein-1 (MCP-1) in kidney injury. It has been shown that MCP-1 gene and protein expression is upregulated following protein overload in renal tubular cells. In addition, urinary MCP-1 (uMCP-1) is proportional to the degree of albuminuria. Bindarit, an indazolic derivative, has been shown to be an inhibitor of MCP-1 production in vitro and in vivo. Findings from a double-blind, placebo-controlled, pilot study of bindarit in patients (Caucasian, n = 22, 19 to 50 years of age, both genders) with active lupus nephritis (WHO classes III to IV), receiving standard methylprednisolone treatment, were presented by Angelina Research Center's Angelo Guglielmotti. Methylprednisolone (1 g iv, alternate days) was administered to patients in the first week of study. In weeks 2 to 24, patients received bindarit (600 mg bid; n = 11) or placebo (n = 11) and oral methylprednisolone (gradually reduced from 40 to 4 mg/day). Primary endpoints were disease remission and time to relapse according to the European Consensus Lupus Activity Measurement (ECLAM) index; secondary endpoints were uMCP-1 and urinary albumin excretion (UAE). At week 8, uMCP-1 was reduced by 29% for bindarit-treated patients; at week 19, the maximum reduction relative to baseline was attained (62%). Relative to baseline, bindarit reduced UAE by 71% at week 24 and uMCP-1 reduction correlated with this. From these results it was suggested that MCP-1 may be a potential therapeutic target for kidney disease and that further clinical trials are merited to investigate bindarit's therapeutic potential.

### **YM-254890 suppresses airway responses in rodents**

YM-254890, a selective decapeptide, is a selective Galpha (q/11) inhibitor. In previous studies, carotid patency status post-thrombolysis was significantly improved by intravenous bolus injection (10 microg/kg); however, systemic blood pressure was decreased in anesthetized rats by 30 microg/kg of the compound. Furthermore, bleeding time was prolonged and systemic blood pressure was decreased in mouse models at three-fold the dose required to produce significant effects on neointima formation and thrombosis. Susumu Tsujimoto (Astellas Pharma) presented findings from studies in spasmogen-induced bronchoconstriction and cigarette smoke (CS)-induced airway inflammation rodent models, which suggested that local administration of YM-254890 may be effective in the treatment of chronic obstructive pulmonary disease (COPD) and asthma. Methacholine (MCh)-induced bronchoconstriction in rats was dose-dependently suppressed by intratracheally administered YM-254890 (ED50 = 0.73 microg/kg). There was no effect on systemic blood pressure or bleeding time at doses of up to 30 microg/kg. Relative to the saline control, MCh-induced bronchoconstriction was significantly inhibited by YM-254890 for 6 h following intratracheal administration. When administered by metered-dose inhalation (0.1%, 1 puff), the compound significantly inhibited MCh-induced bronchoconstriction in rats (30 min post-inhalation). In a leukotriene D4-induced guinea pig model of bronchoconstriction, the compound had an ED50 value of 1.1 microg/kg. In mice experiencing CS-induced airway inflammation, infiltration of neutrophils, eosinophils and lymphocytes in to the airways was significantly suppressed by the intranasal instillation of YM-254890 (10 microg/kg). Furthermore, histological examination of lungs from rats demonstrated that treatment with the compound (0.1%, 3 puffs qd for 7 days) induced alveolar foam cells and inflammatory cells.

### **Pulmonary monocytic inflammation reduced by INCB-3344**

Chronic inflammation of the lung is a principal pathology in patients with COPD. In induced sputum and bronchial biopsies of these patients, macrophages, neutrophils and CD8+ lymphocytes are predominantly elevated. MCP-1, which is known to act via chemokine (C-C motif) receptor 2 (CCR2), has also been shown to be elevated. Boehringer Ingelheim's Silke Hobbie presented data from a study investigating the effect of INCB-3344, a CCR2 antagonist, in two mouse COPD models of pulmonary monocytic inflammation. MCP-1-induced pulmonary monocytic inflammation was completely suppressed by INCB-3344 (ID50 = 22 mg/kg). At 100 mg/kg, the compound reduced CS-induced pulmonary monocytic inflammation by 47% which was comparable to the phosphodiesterase4 (PDE4) inhibitor roflumilast (Daxas; Nycomed) which reduced CS-induced monocytic inflammation in mice by 34% when administered at a human relevant dose of 5 mg/kg. Therefore, it was proposed that CCR2 inhibition may provide an anti-inflammatory therapeutic option for COPD patients.

## **CXCR7 has a pathogenic role in RA**

In rheumatoid arthritis (RA), it is known that interactions between CXCL12 and CXCR4 in the synovium play an important part in the production of inflammatory cytokines, angiogenesis and inflammatory cell recruitment. CXCR7 has recently been determined to be an alternative receptor for CXCL12; it is thought that tumor growth and homing of renal progenitor cells may be promoted by the interaction between these two components. Kaori Watanabe (Tokyo Medical and Dental University) presented findings from a study performed in collaboration with ChemoCentryx, determining the potential pathogenic role of the CXCL12/CXCR7 pathway in RA. In RA synovium, CXCR7 was expressed on endothelial cells; this expression was much weaker in osteoarthritis synovium. In unstimulated human umbilical vein endothelial cells (HUVECs), CXCR7 mRNA was detected and was upregulated by IL-beta stimulation. In IL-beta-stimulated HUVECs, CXCL12 increased CXCR7 expression which was not changed with stimulation by CXCL12 or TNF-alpha alone; stimulation with IL-beta alone downregulated CXCR4 mRNA. CXCL12-induced tube formation was inhibited by the CXCR7 antagonist CCX-733 and the CXCR4 antagonist plerixafor (Mozobil); this also occurred for IL-beta-enhanced CXCL12-induced tube formation. In murine collagen-induced arthritis (CIA), treatment with 10 mg/kg CCX-733 decreased soft tissue swelling scores and significantly lowered destructive changes in bone. Furthermore, the compound had no effect on anticollagen antibody levels. These results suggest that CXCR7 may also have a function in angiogenesis in RA synovium. Therefore, given its role in angiogenesis, CXCR7 may be a potential therapeutic target for RA.

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## Ninth World Congress on Inflammation – Overnight Report 3

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*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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## Ninth World Congress on Inflammation – Overnight Report 4

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### Therapeutic requirements - chemokine receptor antagonists

Thomas J Schall of Chemocentryx gave an engaging keynote lecture in which he stated his belief that a golden age in the development of therapeutic modalities for inflammatory disease is just beginning, and that the chemokine system may be key to this. In the human genome 55 genes have been identified for distinct chemokines. The chemokine system is an attractive drug development target because of its natural selectivity and the knowledge that different chemokines in different tissues are associated with specific diseases. Furthermore, chemokine receptors belong to the seven-transmembrane-spanning GPCR class, which is historically known to be amenable to drug development. It has been hard to predict the therapeutic window for chemokine receptors, with only a small difference existing between non-effective and toxic levels. The A10 value, which is the amount of compound required in 100% serum to reduce migration ten-fold at any concentration of chemokine agonist, is a useful parameter, in addition to binding affinity, when considering chemokine antagonists.

Preclinical data were presented for CCR2 receptor antagonist CCX-140, which is anticipated to commence phase II trials for diabetes shortly. In Yorkshire swine treated with CCX-140 continuously at the A10 value for 28 days following bare metal stent implantation, restenosis was inhibited. This was an extremely healthy response, but the data showed that to be effective a high concentration of compound was required. In a rabbit intra-articular injection model of arthritis, a correlation was observed for CCX-354 (20 mg/kg) administration between consistent therapeutic effect and continuous A10 chemotaxis inhibition in 100% serum. This oral CCR1 antagonist is expected to enter phase II trials for arthritis shortly. The CCR9 antagonist CCX-807 (100 mg/kg bid) caused a maximal decrease in T-cell trafficking to the gut when the A10 value in 100% serum was covered.

Dr Schall described the 'A10 Con-Cov Rule', by which a full biological response can be elicited if a 'few' chemokine receptors remain unoccupied, stressing that most of the receptors must be covered by the drug for the majority of the time for this response to be blocked. This rule is not met by most anti-inflammatory chemokine compounds in clinical development, including CCR2 antagonist MK-0812 (c-6448; Merck), and CCR1 antagonists CP-481715, BX-471 (ZK-811752) and MLNM-3987, for reasons that include insufficient potency and oral absorption, CYP450 inhibition, hERG channel inhibition, excessively fast liver clearance and a lack of selectivity. In the past 15 years, only two antagonists targeting the chemokine system have been approved: maraviroc (Celsentri) and plerixafor (Mozobil), which respectively act at CCR5 and CXCR4.

CCX-282 (CCX282-B; Traficet-EN) is an orally active CCR9 chemokine receptor antagonist under development for the treatment of inflammatory bowel disease (IBD), in particular Crohn's disease (CD), and data from the induction phase of the PROTECT-1 trial of this compound, which involved approximately 120 test sites in 17 countries, were presented. In the induction stage of the trial (12 weeks), 436 subjects were randomized (1.5:1:1:1) to receive placebo twice daily or CCX-282B daily at 250 or 500 mg, or twice daily at 250 mg. At entry to the trial subjects required a CD activity index (CDAI) of greater than or equal to 250 and C-reactive protein (CRP) values of less than 7.5 mg/l. All patients were then treated with 250 mg of the compound twice a day for 4 weeks. Subsequently, CDAI responders ( $\geq$  70-point drop) were randomized to placebo or 250 mg of the compound twice daily for 36 weeks; non-responders discontinued the trial at this time. Finally, a 4-week follow-up period occurred in which no drug was administered. Relative to placebo at 12 weeks, the 500 mg daily CCX-282B treatment demonstrated higher CDAI 70-point ( $p = 0.039$ ) and 100-point ( $p = 0.029$ ) response rates, irrespective of anatomic location, duration or concomitant treatment of CD; the two 250-mg dose regimens showed no difference from placebo. In addition the 500-mg dose demonstrated efficacy in previous non-responders to anti-TNF therapy. The CD endoscopic index of severity was also significantly lower for the CXC-282B-treated group at this dose at 12 weeks relative to placebo ( $p < 0.05$ ), and there was no evidence of toxicity or immunosuppression: this dose was well tolerated. Dr Schall considered that this may be the first large-scale clinical example of therapeutic benefit in an inflammatory disease for a chemokine receptor antagonist.

### Kinase inhibitor design

p38 is implicated in inflammatory responses and disease because of the role it plays in the modulation of TNF-alpha, IL-1beta, IL-6 and COX-2. Array BioPharma's Kevin Koch explained that it is becoming apparent that it also has a role in hematopoietic function and pain. First- and second-generation p38 inhibitors suffer from poor selectivity and

human whole blood (HWB) potency, with clinical adverse events including dizziness, rash, CNS toxicity and elevation of liver enzymes. Using the Delve program, consensus binding regions were identified using computational small fragment docking. An early lead from this effort was AR-190, which had p38 and HWB IC50 values of 60 and 1200 nM, respectively. In mice, this compound inhibited LPS-induced TNF-alpha production by 44% at a 30 mg/kg oral dose. Subsequently, ARRY-797 and ARRY-614 were generated with respective IC50 values of 7 and less than 2 nM for p38, and less than 2 and 14 nM for HWB. In a rat therapeutic model of collagen-induced arthritis (CIA), 10 mg/kg twice-daily treatment with ARRY-797 showed comparable efficacy to etanercept (Enbrel) at the same dose. In a murine bone fracture model, ARRY-797 at 30 mg/kg daily post-fracture reduced spontaneous guarding. This was comparable to the effect seen for celecoxib (Celebrex) at a 4 mg/kg daily dose post-fracture, but unlike celecoxib, there was no inhibition of callous formation. In a clinical post-surgical model of dental pain, ARRY-797 provided pain relief in a dose-dependent manner. ARRY-614 was shown to be effective at alleviating tactile allodynia in the rat breast carcinoma bone pain model MRMT-1, and it also decreased tumor bone destruction at a dose of 30 mg/kg; when this tumor line was grown subcutaneously in vivo, ARRY-614 did not inhibit its growth. ARRY-797 was shown to clinically lower CRP post-surgery, an effect that continued for several days; the decrease in CRP may be indicative of liver enzyme increases being off target. Dr Koch concluded that Array Biopharma has decided that p38 is not a viable target for the treatment of inflammatory disease.

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