# Ninth World Congress on Inflammation – Overnight Report 1

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## 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, Tadamitsu 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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