LATE-BREAKING ABSTRACTS PRESENTED AT SCIENTIFIC SESSIONS AAAAI 62ND ANNUAL MEETING MARCH 3-7, 2006

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Late Breaking Abstracts: Basic Sciences

LB1 Pharmacological Inhibition of Leukotrienes in an Animal Model of Bleomycin-Induced Lung Fibrosis: Role of the Cysteinyl and B4 Leukotrienes

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RATIONALE: Leukotrienes are increased locally in idiopathic pulmonary fibrosis. Furthermore, a role for 5-lipoxygenase products has been thoroughly characterized in the animal bleomycin model of lung fibrosis by using different gene knock-out settings.

In the present study, we investigated the efficacy of pharmacological inhibition of leukotrienes activity in the development of bleomycin-induced lung injury by comparing the responses in wild-type mice with mice treated with zileuton, a 5-lipoxygenase inhibitor and MK-571, a cysleukotrienes receptor antagonist.

METHODS: Mice were subjected to intra-tracheal administration of bleomycin or saline and were assigned to receive either MK-571 at 1 mg/Kg, zileuton at 50 mg/Kg or saline by means of mini-osmotic pump implanted subcutaneously. One week after fibrosis induction, BAL cell counts, lung histology with Masson's trichrome and immunohistochemical analysis for myeloperoxidase, IL-1 and TNF-α were performed.

RESULTS: Following bleomycin administration both MK-571 and zileuton treated mice exhibited a reduced degree of lung damage and inflammation when compared to WT mice as shown by the reduction of: (i) loss of body weight, (ii) mortality rate, (iii) lung infiltration by neutrophils (myeloperoxidase activity, BAL total and differential cell counts), (iv) lung edema, (v) histological evidence of lung injury and collagen deposition, (vi) lung myeloperoxidase, IL-1 and TNF-α staining.

CONCLUSIONS: This is the first study showing that the pharmacological inhibition of leukotrienes activity can suppress bleomycin-induced lung injury in mice. Thus, these two drug classes already in clinical use for asthma therapy might now be meaningfully trialed for the treatment of idiopathic pulmonary fibrosis, a disease that still represents a major challenge to medical treatment.

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Late Breaking Abstracts: Basic Sciences

LB2 Blocking Intrapulmonary Activation of Complement Cascade on the Development of Airway Hyperresponsiveness: Utility In Sight?

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RATIONALE: Intrapulmonary activation of the complement cascade plays a crucial role in the pathogenesis of asthma. Treatment with an anti-C5 monoclonal antibody (mAb) has profound therapeutic effects in a rodent model of asthma.

METHODS: Intrapulmonary activation of complement cascade was blocked by nebulization of an anti-mouse C5 mAb in animals with severe established airway inflammation. Efficacy of anti-C5 treatment on the development of airway responses to aerosol challenges of methacholine was compared with that of corticosteroid treatment.

RESULTS: Anti-mouse C5 mAb as well as a humanized anti-human C5 mAb can be successfully nebulized with common Jet-Air nebulizers with aerodynamic characteristics suitable for aerosol delivery to lower airways. Antibody retains its activity and integrity after nebulization with a mass median aerodynamic diameter less than 2.6μm for both antibodies. Repeated chronic aerosol administrations of anti-mouse C5 mAb did not cause detectable changes of airways in normal animals. Nebulization of anti-mouse C5 mAb achieved intrapulmonary C5 inhibition without inhibiting C5 activity systemically and had a therapeutic efficacy on the development of airway responses similar to that of corticosteroid treatment in animals. Blocking the generation of both C5a and C5b-9 is required to improve functions of lower airways and ameliorate airway inflammation, both of which regulate intrapulmonary inflammatory cascade by their powerful chemotactic and cell activation activities. Finally, combination therapy with corticosteroid demonstrated significantly enhanced efficacy, due to the unique anti-inflammatory properties of intrapulmonary C5 inhibition.

CONCLUSIONS: Blocking intrapulmonary activation of C5 is a potential clinical approach for treating patients with asthma.

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Late Breaking Abstracts: Basic Sciences

LB3 Activation of the High Affinity Receptor for IgE on Human Oral Langerhans Cells Leads to the Induction of Tolerogenic Mechanisms

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RATIONALE: The oral mucosa represents an immune privileged organ with a high threshold for the manifestation of allergic reactions despite a high frequency of allergen contact. This peculiarity leads the assumption of tolerance induction sustaining the immunological balance within the oral mucosa. Most likely Dendritic cells as antigen presenting cells are crucial for the maintenance of oral tolerance mechanisms. We could show recently that human oral Langerhans Cells (oLC) constitutively express the high affinity receptor for IgE (FcepsilonRI) enabling these cells to bind applied allergen via surface bound IgE. So we investigated whether FcepsilonRI on oLC might be involved in mechanisms leading to tolerance induction.

METHODS: Human oLC were isolated from fresh oral mucosal tissue by trypsinization.

RESULTS: We could show that activation of FcepsilonRI on oLC increased the production on tolerogenic cytokines such as IL-10 and TGF-beta1 leading to decreased proliferation of T cells. Furthermore, activation of FcepsilonRI on oLC enhanced the production of chemokines involved in the recruitment of T regulatory cells (Tregs) such as TARC/CCL17 and MDC/CCL22 leading to an increase of Tregs migration in vitro. In addition, preactivation of Tregs with FcepsilonRI activated oLC enhanced the suppressive activity of Tregs.

CONCLUSIONS: Our data leads to the suggestion that FcepsilonRI on oLC might by critically involved in immunological mechanisms leading to tolerance induction toward allergens and bacteria within the oral mucosa by production of tolerogenic cytokines and the recruitment of Tregs.