Volume 60 • Supplement 1 • June 2011

INFLAMMATION Research

OFFICIAL JOURNAL OF

The International Association of Inflammation Societies

The European Histamine Research Society

Book of Abstracts

10th World Congress on Inflammation

June 25–29, 2011
Palais des Congrès, Paris, France

Springer

P-446
AQX-1125, A FIRST-IN-CLASS CLINICAL-STAGE SHIP1 ACTIVATOR SMALL MOLECULE FOR THE TREATMENT OF PULMONARY DISEASES: SUPPRESSION OF CHEMOTAXIS IN VITRO AND EFFICACY IN RODENT MODELS OF ASTHMA AND COPD IN VIVO

C. Szabo[1,], L. F. MacKenzie[1], G. R. Stenton[1], P. Tam[1], J. L. Cross[1], C. Harwig[1], J. Raymond[1], J. Toews[1], D. Chernoff[1], T. MacRury[1]*

[1]Aquinox, Richmond, Canada

Pharmacological modulation of the phosphoinositide 3-kinase (PI3K)/Akt pathway is emerging as a means to control inflammatory disorders. The SH2-containing inositol-5′-phosphatase 1 (SHIP1) metabolizes PI[3,4,5]P3 to PI[3,4]P2. SHIP1-deficient mice exhibit a marked degree of inflammatory cell recruitment into the lung, leading to pulmonary inflammation. Pharmacological, allosteric activation of SHIP1 exerts anti-inflammatory effects (Ong et al., Blood, 2008). Here we overview the biological effects of AQX-1125, a small molecule SHIP1 activator, a current clinical development candidate. AQX-1125 induced a concentration-dependent increase in the catalytic activity of human recombinant SHIP1 enzyme. AQX-1125 suppressed Akt phosphorylation in SHIP1-proficient MOLT-4 cells, but not in SHIP1-deficient Jurkat cells. AQX-1125 inhibited degranulation of wild-type bone marrow-derived mast cells, but not of SHIP1-deficient cells. As phosphoinositide signaling plays a key role in cytokinesis, the effect of AQX-1125 was tested on leukocyte chemotaxis. AQX-1125 was found to be a nanomolar, a pan-selective inhibitor of leukocyte chemotaxis. AQX-1125 exhibited high oral bioavailability (>80%) and long terminal half-life (>5 h) in rodents and dogs, and yielded high concentrations in the lung. AQX-1125 exerted anti-inflammatory effects and reduced inflammatory cell infiltration into the BAL in a rat ovalbumin-mediated airway inflammation model, in a rat pulmonary inflammation model induced by LPS, and in a mouse model of cigarette smoke-induced airway inflammation. AQX-1125 markedly reduced the production of multiple chemokines/cytokines in the lung. Thus, SHIP1 activation may have utility for the treatment of respiratory disorders such as chronic obstructive pulmonary disease and asthma. The first-in-class SHIP1 activator AQX-1125 demonstrates ideal drug-like properties and has recently entered Phase I clinical testing.

Disclosure of interest: C. Szabo Consultant/Speaker's bureau/Advisory activities with: Aquinox; employee of: Aquinox; stock ownership or royalties of: Aquinox. L. MacKenzie employee of: Aquinox, stock ownership or royalties of: Aquinox, G. Stenton employee of: Aquinox, stock ownership or royalties of: Aquinox, P. Tam employee of: Aquinox, stock ownership or royalties of: Aquinox, J. Cross Grant/research support from: Aquinox, C. Harwig employee of: Aquinox, stock ownership or royalties of: Aquinox, J. Raymond: none declared, J. Toews employee of: Aquinox, D. Chernoff Consultant/Speaker's bureau/advisory activities with: Aquinox, stock ownership or royalties of: Aquinox, T. MacRury employee of: Aquinox, stock ownership or royalties of: Aquinox

P-447
USE OF NEW COLLAGEN DEPOSITION AS NOVEL READ-OUT IN BLEOMYCIN-INDUCED LUNG FIBROSIS

M. E. Blaauboer[1,2], R. Hanemaaijer[1], S. Turner[3], M. van Erk[1], R. Stoop[1,]*

[1]TNO, Leiden, [2]ACTA, Amsterdam, Netherlands, [3]Kinemed, Emeryville, United States

The bleomycin-induced pulmonary fibrosis model in the mouse is the most common model to investigate potential new therapies for idiopathic pulmonary fibrosis (IPF). The main read-outs used to quantify the severity of fibrosis are based on the amount of collagen deposition (either measured using histological sections or by biochemical assay). However, this becomes a problem when the model is run using a therapeutic treatment protocol in which treatment is only started after fibrosis has been allowed to establish. Since the production of collagen (the main component of fibrous tissue) already starts during in the initial inflammatory phase, the window for measuring effects of new compounds is much smaller in the therapeutic protocol versus preventive treatment. In this study, we investigated the kinetics of collagen deposition during bleomycin-induced lung fibrosis in C57Bl/6 mice using deuterated water (D_2O) to label newly formed collagen synthesis. Furthermore, we used whole gene array analysis in combination with the ToxProfiler software to differentiate between the different pathways induced during fibrosis. Array analysis showed that inflammatory processes were maximal during the first week of disease, while extracellular matrix related pathways were maximal during the second and third week after induction, after which they slowly returned to base line levels. The new collagen assay showed that during the first week already substantial collagen formation took place, despite strong upregulation of inflammatory processes. The production of collagen was further upregulated during the second and third week, after which collagen synthesis returned to pre-induction levels. This high level of collagen synthesis during the first week explains the difficulties in obtaining sufficient window during therapeutic treatment.

Disclosure of interest: None declared.

P-448
COMMD1 AND CSN5: TWO ANTI-INFLAMMATORY PROTEINS IN THE CONTEXT OF CYSTIC FIBROSIS?

A. De Becdelievre[1,2,3,], A. Aissat[1,2], L. Drévillon[1], A. Hinzpeter[1], A. Tarze[1], P. Fanen[1,3]*

[1]U955, INSERM, [2]Faculté de Médecine, UPEC, [3]Service de Génétique, AP-HP, GH Mondor-Chenevier, Créteil, France

Cystic fibrosis (CF) is an autosomal recessive disease caused by mutations in the *CFTR* gene, which encodes an epithelial anion channel. Morbidity is mainly due to the lung disease, characterized by a chronic neutrophilic inflammation. Deregulation of inflammatory pathways is observed in the airways of CF patients, as evidenced by an