Multi-omics links IL-6 trans-signalling with neutrophil extracellular trap formation and *Haemophilus* infection in COPD

Sofia Winslow[1], Lina Odqvist[2], Sarah Diver[3], Rebecca Riise[2], Suado Abdillahi[2], Cecilia Wingren[2], Helena Lindmark[4], Annika Wellner[5], Sofia Lundin[1], Linda Yrlid[2], Elisabeth Ax[1,6], Ratko Djukanovic[7], Sriram Sridhar[8], Andrew Higham[9], Dave Singh[9], Thomas Southworth[9], Christopher E. Brightling[3], Henric K. Olsson[1] and Zala Jevnikar[1]

[1]Translational Science and Experimental Medicine, Research and Early Development, Respiratory and Immunology, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden. [2]Bioscience COPD/IPF, Research and Early Development, Respiratory and Immunology, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden. [3]Dept of Respiratory Science, Institute for Lung Health, NIHR Leicester Biomedical Research Centre, University of Leicester and University Hospitals of Leicester NHS Trust, Leicester, UK. [4]Discovery Sciences, R&D, AstraZeneca, Gothenburg, Sweden. [5]Medicinal Chemistry, Research and Early Development, Respiratory and Immunology, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden. [6]Krefting Research Centre, Institute of Medicine at the Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden. [7]NIHR Southampton Respiratory Biomedical Research Unit, Clinical and Experimental Sciences and Human Development and Health, University of Southampton, Southampton, UK. [8]Oncology Bioinformatics, Translational Science, Early Oncology, Oncology R&D, AstraZeneca, Gaithersburg, MD, USA. [9]The University of Manchester Division of Infection, Immunity and Respiratory Medicine, School of Biological Sciences, Faculty of Biology, Medicine and Health, Manchester Academic Health Science Centre, The University of Manchester and University Hospital of South Manchester, NHS Foundation Trust, Manchester, UK.

Corresponding author: Zala Jevnikar (Zala.JevnikarRojnik@astrazeneca.com)

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Lung IL-6 trans-signalling driven by *Haemophilus influenzae*-induced NETosis is a pathological feature of COPD patients with chronic *Haemophilus* infection, stable neutrophilic inflammation and uncontrolled disease https://bit.ly/30vhgD5

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Abstract

Background: Interleukin (IL)-6 trans-signalling (IL-6TS) is emerging as a pathogenic mechanism in chronic respiratory diseases; however, the drivers of IL-6TS in the airways and the phenotypic characteristic of patients with increased IL-6TS pathway activation remain poorly understood.

Objective: Our aim was to identify and characterise COPD patients with increased airway IL-6TS and to elucidate the biological drivers of IL-6TS pathway activation.

Methods: We used an IL-6TS-specific sputum biomarker profile (soluble IL-6 receptor (sIL-6R), IL-6, IL-1β, IL-8, macrophage inflammatory protein-1β) to stratify sputum data from patients with COPD (n=74; Biomarkers to Target Antibiotic and Systemic Corticosteroid Therapy in COPD Exacerbation (BEAT-COPD)) by hierarchical clustering. The IL-6TS signature was related to clinical characteristics and sputum microbiome profiles. The induction of neutrophil extracellular trap formation (NETosis) and IL-6TS by *Haemophilus influenzae* were studied in human neutrophils.

Results: Hierarchical clustering revealed an IL-6TS-high subset (n=24) of COPD patients, who shared phenotypic traits with an IL-6TS-high subset previously identified in asthma. The subset was characterised by increased sputum cell counts (p=0.0001), persistent sputum neutrophilia (p=0.0004), reduced quality of life (Chronic Respiratory Questionnaire total score; p=0.008), and increased levels of pro-inflammatory mediators and matrix metalloproteinases in sputum. IL-6TS-high COPD patients showed an increase in Proteobacteria, with *Haemophilus* as the dominating genus. NETosis induced by *H. influenzae* was identified as a potential mechanism for increased sIL-6R levels. This was supported by a significant positive correlation between sIL-6R and NETosis markers in bronchoalveolar lavage fluid from COPD patients.

Conclusion: IL-6TS pathway activation due to chronic colonisation with *Haemophilus* may be an important disease driver in a subset of COPD patients.