**Title:** Krüppel-like zinc finger proteins in end-stage COPD lungs with and without severe alpha1-antitrypsin deficiency

Dr. Rembert 30765 Koczulla koczulla@med.uni-marburg.de MD 2, Dr. Jonigk 30853 Danny Jonigk.Danny@MH-Hannover.de MD 3, Dr. Thomas 30920 Wolf t.wolf@dktz-heidelberg.de 8,6, Dr. Christian 30942 Herr christian.herr@uniklinikum-saarland.de 7, Dr. Sarah 30945 Noeske noeske@med.uni-marburg.de MD 2, Prof. Dr Walter 30953 Klepetko walter.klepetko@meduniwien.ac.at MD 5, Dr. Sabine 30764 Wrenger wrenger.sabine@mh-hannover.de 1, Prof. Dr Claus 30960 Vogelmeier Claus.Vogelmeier@med.uni-marburg.de MD 3, Dr. Nils 30961 von Neuhoff Neuhoff.Nils.von@mh-hannover.de 8, Dr. Heiko 30964 Golpon golpon.heiko@mh-hannover.de MD 1, Dr. Robert 30971 Vosswinkel Robert.Voswinckel@innere.med.uni-giessen.de 4, Prof. Dr Tobias 30974 Welte welte.tobias@mh-hannover.de MD 1 and Prof. Dr Sabina 30766 Janciauskiene Janciauskiene.Sabina@mh-hannover.de 1. 1 Department of Respiratory Medicine, Hanover Medical School, Hanover, Germany; 2 Division of Pulmonary Diseases, Philippus University Marburg, Germany; 3 Institute for Pathology, Hanover Medical School, Hanover, Germany; 4 University of Giessen Lung Center, University Hospital, Giessen, Germany; 5 Division of Thoracic Surgery, Medical University of Vienna, Austria; 6 Department of Theoretical Bioinformatics, German Cancer Research Center DKFZ, Heidelberg, Germany; 7 Department of Internal Medicine V, Pulmonology, Allergology, Respiratory and Environmental Medicine, Saarland University, Homburg/Saar, Germany and 8 Institute of Molecular Pathology, Hanover Medical School, Hanover, Germany.

**Body:** Chronic obstructive pulmonary disease (COPD) is influenced by environmental and genetic factors. An important fraction of COPD cases harbor a major genetic determinant, inherited ZZ (Glu342Lys) α1-antitrypsin deficiency (AATD). Severe, ZZ AATD is associated with a predisposition to early onset, rapidly progressive COPD where emphysema is a major component. We hypothesized that gene expression pattern differs in end-stage COPD with and without AATD. Tissues from explanted lungs of end-stage AATD-related (ZZ, n=3, never treated with AAT augmentation therapy) and “normal” (MM, n=3) COPD were used for microarray gene expression analysis. A total of 162 genes were found to be differentially expressed (p-value ≤ 0.05 and |FC| ≥ 2) between MM and ZZ COPD patients. Of those, 134 gene sets were up-regulated and 28 were down-regulated in ZZ relative to MM lung tissue. A subgroup of genes, zinc finger protein 165, snail homolog 1 (Drosophila), and Krüppel-like transcription factors (KLFs) 4 (gut), 9 and 10, perfectly segregated ZZ and MM COPD patients. The relative expression of KLF 9 and 10 was higher in lung and in liver cirrhosis tissue from ZZ (n=6) compared to MM (n=6) as verified by RT-PCR. Genes associated with COPD or lung function decline generally come from three groups:
protease-antiprotease, oxidant/antioxidant and immune/inflammatory mediators. In this small cohort, we show that end-stage COPD patients with and without AATD can be perfectly grouped by the cluster of the zinc-finger family of transcriptional regulators. Our data provide new insight into the putative difference in the mechanisms involved in COPD development in subjects with and without inherited AATD.