Title: Up-regulation of EGFR gene family in COPD patients: Correlation with airway obstruction

Dr. Eirini 17399 Neofytou niniof@gmail.com 1, Mr. Aristotelis 17400 Anagnostis niniof@gmail.com MD 2, Dr. Nikolaos 17401 Soulitzis niniof@gmail.com 1, Mr. Dimitris 17402 Kampas niniof@gmail.com 1, Mr. Ioannis 30731 Tzortzakis tzortzaki@med.uoc.gr 2, Mrs. Despoina 17403 Demitzaki tzortzaki@med.uoc.gr MD 3, Prof. Dr Eleni 17404 Tzortzaki tzortzaki@med.uoc.gr MD 1,2 and Prof. Dr Nikolaos 17406 Siafakas siafak@med.uoc.gr MD 1,2. 1 Laboratory of Molecular and Cellular Pulmonology, Medical School, University of Crete, Heraklion, Heraklion, Crete, Greece ; 2 Department of Thoracic Medicine, University Hospital of Heraklion, Heraklion, Crete, Greece and 3 Department of Anaesthesiology, University Hospital of Heraklion, Heraklion, Crete, Greece.

Body: Background: Growth factors receptors mediate a variety of cellular responses to the environment. Specifically, exposure of lung epithelium to oxidative stress induced by cigarette smoke stimulates aberrant Epidermal Growth Factor Receptor (ERBB) family activation. Aim: As a part of a genome-wide microarray screening analysis, this study’s objective was to evaluate the expression of ERBB1-4 receptors in smokers with or without COPD. Methods: Lung tissue samples from selected patients were subjected to microarray analysis, and confirmed by Quantitative Real-Time PCR in 45 male subjects: A) 20 COPD patients (GOLD stage II), B) 15 non-COPD smokers and C) 10 non-smokers. Results: Microarray data analysis revealed that ERBB receptors were elevated, from 1.62-fold to 2.45-fold, in COPD patients compared to non-COPD smokers (p<0.01). Real-Time qPCR verified that COPD patients had higher ERBB1-3 expression levels compared to non-COPD smokers (P_{ERBB1}<0.001; P_{ERBB2}=0.003; P_{ERBB3}=0.003) and non-smokers (P_{ERBB1}=0.019; P_{ERBB2}=0.005; P_{ERBB3}=0.011). On the other hand, ERBB4 mRNA levels gradually increased from non-smokers (0.74±0.19) to non-COPD smokers (1.11±0.05) to COPD patients (1.57±0.28), and were correlated with the degree of airflow obstruction (P_{FEV1}<0.001). Conclusions: These data suggest that ERBB1-3 overexpression is possibly related to COPD pathogenesis and not to smoking exposure, while the gradual increase of ERBB4 expression could indicate a direct link between ERBB4 and disease severity.