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Title: Molecular profiling of lung squamous carcinogenesis

Dr. Celine 27062 Mascaux celinejmmascaux@gmail.com MD [1,2,3], Dr. Jennifer 27106 Beane jbeane77@gmail.com [1], Kahkeshan 27107 Hijazi kahkshan@bu.edu [1], Geraldine 27108 Anthoine g.anthoine@gmail.com [2], Dr. Karen 27109 Willard-Gallo kwillard@ulb.ac.be [2], Dr. Annick 27119 Haller annick.wittersheim@wanadoo.fr MD [2], Dr. Vincent 27165 Ninane Vincent_NINANE@stpierre-bru.be MD [4], Prof. Arsène 27169 Burny arsene.burny@guest.ulg.ac.be [2], Prof. Avrum 27170 Spira avspira@gmail.com MD [1] and Prof. Jean-Paul 27175 Sculier sculier@bordet.be MD [2]. [1] Section of Computational Medicine, Department of Medicine, Boston University School of Medicine, Boston, MA, United States ; [2] Department of Intensive Care and Thoracic Oncology, Jules Bordet Institute, Centre Des Tumeurs De L'Université Libre De Bruxelles, Brussels, Belgium ; [3] Deparment of Medical Oncology, Princess Margaret Cancer Center, University of Toronto, Toronto, ON, Canada and [4] Department of Pulmonology, CHU St Pierre, Brussels, Belgium .

Body: Molecular profiling of from pre-invasive bronchial lesions may identify promising new biomarkers for early detection and targets for chemoprevention/treatment of lung cancer. mRNA expression was analyzed (Agilent microarrays) from fresh frozen human bronchial biopsies (N=122, 77 patients) at successive morphological stages of lung squamous carcinogenesis. Modules of co-expressed genes were identified among the 7739 stage associated genes, selected using a linear mixed-effects model adjusting for smoking status, gender and history of cancer as fixed effects and patient as a random effect, Genes expression alterations were grouped based on their behavior across 4 successive molecular steps. Four different gene-expression patterns were observed: gene modules primarily up-regulated among the early or late steps, up-regulated in a linearly across the 4 steps, as well as down- then up-regulated (biphasic). Modules that changed in the early step were characterized by genes involved in cell function/maintenance, cell growth/proliferation and cell-to-cell signaling. Modules with linear up-regulation included genes involved in cell cycle, cellular assembly, DNA replication/repair. At the later stages, the transition to high-grade dysplasia, the most significant gene expression changes included immune/inflammatory response genes. These data provide a platform for future in depth investigation into the precise molecular mechanisms and pathways involved in lung carcinogenesis. The significant modification of inflammatory/immune response genes in association with high-grade lesions suggests a critical role of the surrounding microenvironment at this critical stage of carcinogenesis and raises the possibility of new chemopreventive approaches.