

Summary of the ESMO fellowship project “Translational research concerning the molecular biology of lung cancer”

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During my ESMO fellowship at the Institut Gustave Roussy in Paris, France, from October 2005 to November 2006, I had the opportunity to work on a project of translational research concerning the molecular biology of lung cancer under the surveillance of two distinguished scientists, Dr. Pierre Fouret, Professor of Pathology at the University Paris VI (Pierre et Marie Curie) and Dr. Jean-Charles Soria, Professor of Medicine at the University Paris XI (Paris Sud). At the same time, I had also the opportunity to obtain a Master’s degree in translational research in Oncology from the University of Paris XI. Our project was inspired by the observation that there is a significant proportion of female non-smokers among lung adenocarcinoma patients, which implies a distinct pathogenetic mechanism of lung carcinogenesis in this subset of patients. Nevertheless, the molecular characteristics of neoplastic transformation in non-smokers have not yet been adequately elucidated. The aim of our study was to identify the specific molecular profile that differentiates lung oncogenesis in non-smokers from smokers by studying the expression of the most important biological markers interfering in critical intracellular signaling cascades.

To accomplish this project, we used immunohistochemical evaluation of potent downstream effectors of cytoplasmic and nuclear signaling transduction including Extracellular signal-Regulated Kinase (ERK), c-jun terminal Kinase (JNK), P38 Mitogen Activated Protein Kinase (P38), Signal Transducer and Activator of Transcription 3 (STAT3) and Protein Kinase B (PKB or AKT) and one marker of DNA repair (Excision Repair Complement Complex one or ERCC1) were performed using tissue micro-array technology in surgical specimens from 188 chemo-naïve patients with operable lung adenocarcinoma. Differences between smokers and non-smokers were recorded and the specific expression profiles were correlated with corresponding clinical parameters in order to assess the prognostic value of each marker. We found that P38 and JNK are significantly over expressed in non-smokers compared to smokers ($p < 0.001$ and $p = 0.012$ respectively). P38 and STAT3 are predictive of overall survival in unvaried but not in

multivariate analysis. ERK expression may serve as an independent prognostic factor of disease free survival in lung adenocarcinoma patients. According to these results we concluded that a particular molecular profile of biological markers, characterized by increased Mitogen Activated Protein Kinase (MAPK) activity can be identified in non-smokers with lung adenocarcinoma. These findings further support the hypothesis that this subset of patients may harbor additional molecular abnormalities that can provoke neoplastic transformation even in the absence of the carcinogenic effects of smoking. Better comprehension of the distinct biological entities among lung cancer patients may help identify potential new molecular targets for a more selective and “sophisticated” therapeutic strategy.