Title: mRNA biomarker screening in pulmonary tumors showing neuroendocrine differentiation

Body: Neuroendocrine tumors of the lung comprise more than 25% of all lung tumors. Typical and atypical carcinoids, large cell neuroendocrine and small cell neuroendocrine carcinomas belong to this subgroup of lung cancer. Until now most of the neuroendocrine tumors exhibit poor survival rates due to a lack of treatment strategies, diagnostic, prognostic and predictive biomarkers. The aim of this study is to identify key biomarkers that could help to overcome these limitations. 201 patients with lung tumors with neuroendocrine differentiation were chosen for the study. 80 patients with diagnostically verified entity were used for NanoString nCounter expression analysis with a custom CodeSet. A total of 91 genes were investigated targeting genes of SOX signaling, MET, MTOR signaling, angiogenesis, apoptosis, neuroendocrine differentiation, folate synthesis, DNA-repair, cell cycle regulation, tumormileu and miscellaneous. Statistical analysis was done using the R statistical program. CDK6, CDKN2A, CHGA, FOLR1, SOX4, SYP and TYMS exhibited most significant values for tumor type and grade. Additional 28 genes correlated significantly with tumor grade and 41 with tumor type. Highly significant correlations were found for PAX6 regarding overall survival. GABBR2, OCT4 and PCDHB9 were found to be most significant for progression free survival. Additional significant correlations were found for tyrosine kinase inhibitor targets, TNM-staging, tumor size and further tumor characteristics. Expression analysis of distinct neuroendocrine tumor entities exhibited several significant biomarkers that could enhance tumor subgroup classification, treatment strategies, prediction and prognosis in routine clinical settings.