Martin Weber et al., J Mol Biomark Diagn 2015, 6:4
http://dx.doi.org/10.4172/2155-9929.C1.025

OMICS International
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6th International Conference on
Biomarkers & Clinical Research
August 31-September 02, 2015 Toronto, Canada

DNA methylation biomarkers for lung cancer: From tissue based discovery to cell free DNA methylation testing

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Disease-specific alterations of DNA methylation patterns are frequently found in cancer and are currently considered to be suitable biomarkers. These alterations are optimal biomarkers for early detection and disease monitoring when detectable in cell-free DNA. We have developed a multiplexed methyl sensitive restriction enzyme (MSRE) qPCR protocol allowing up to 96 parallel qPCR reactions out of 400µl patient's plasma. The method was applied on 1) a panel of 35 methylation markers discovered in lung tissue by a targeted DNA methylation micro-array and 2) 63 candidate markers derived form genome wide methylation analyses using Illumina-Methylation450K-Beadchip. To test the feasibility for differential diagnosis via cell free DNA methylation testing, multivariate classification using MSRE qPCR data from marker panel 1) enabled differentiation of Lung cancer (n=348; Adeno-Ca: n=100, Squamous cell-Ca: n=100, Small cell-Ca: n=100, and Large cell Ca: n=48) versus cancer-free controls (n=332) with an AUC of 0.81-0.91 depending on the lung cancer entity. Using panel 2) a total of 204 serum and plasma samples (lung cancer, n=33; fibrotic Interstitial lung disease - ILD, n=68; COPD, n=42; healthy, n=61) were tested. ROC analysis revealed an AUC of 0.91 for lung cancer, 0.815 for fibrotic ILD, 0.73 for COPD, and 0.828 for all diseases versus healthy controls. Additionally a set of independent cancer and normal samples could be classified on basis of the top 4 markers (HOXD10, PAX9, PTPRN2 and STAG3) showing an AUC 0.85. Based on 2 discovery studies lung-cancer biomarkers suitable for minimal invasive diagnostics using multiplexed DNA methylation measurement from 10ng circulating cfDNA have been defined. Both marker-sets and the MSRE qPCR approach will be the basis for further validation to improve minimal invasive diagnostics. Moreover, this study confirms that our strategy is suitable for qualifying tissue derived DNA-methylation markers for liquid biopsy testing.

Biography

Martin Weber has completed his PhD at the Center for Molecular Biology (ZMBH) in Heidelberg/Germany. He then served in different positions at QIAGEN GmbH (Hilden/Germany) for more than 17 years, heading the corporate research and innovation group in his last position at the company. Since 2012 he is the Head of the Molecular Diagnostics business unit at AIT Austrian Institute of Technology, the biggest non-university research institute in Austria. He has published more than 20 papers and patent applications.

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