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**Tuesday, March 2, 2021 at 1:50 p.m. (EST)**

A novel and customizable approach for the highly-multiplexed identification and validation of DNA methylation changes in complex human disorders

## **Guest speaker: Jörg Tost, Ph.D.**

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### **Abstract:**

Epigenetics has attracted great interest over the last decade and, driven by technological advances, a large number of DNA methylation changes have been characterized in a variety of diseases. Technologies such as whole genome bisulfite sequencing (WGBS) allow for the comprehensive analysis of the 29M CpGs in the human genome. Since WGBS remains cost-prohibitive for many labs, the analysis of large cohorts is currently performed using standardized microarrays, which can analyze up to 840,000 CpGs (i.e., <3 % of all CpGs), leaving most of the methylome unexplored. Targeted bisulfite sequencing approaches are commonly based either on the enrichment of a large number of loci through hybridization with specific probes (capture) or by PCR amplification. However, increasing the enrichment multiplexity has been difficult due to limitations in both multiplex primer design and PCR chemistry.

Here we present a novel type of assay that enables the targeted and customizable analysis of several thousand

CpGs simultaneously, based on extension of a large pool of locus-specific primers followed by a limited amplification with a universal forward primer and the locus-specific reverse primer. For proof-of-principle, we designed a panel targeting 404 CpGs with 697 primers and covering 2,981 CpGs. Using different cell lines, we found consistently between 96% to 98% of these nearly 3,000 CpGs to be covered with more than 10 reads. Correlation with 450K BeadChip and WGBS data showed very high correlation ( $R > 0.90$ ). Results were highly reproducible between replicates and independent of the starting amount. We also adapted this assay to the analysis of hydroxymethylation, for the analysis of neuron-specific hydroxymethylation previously analyzed by WGBS. Our data show that this highly multiplexed assay for targeted methylation analysis is a well-suited and flexible tool for the simultaneous validation of DNA methylation changes in thousands of CpGs in large cohorts of individuals.



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