Invitation to review a manuscript for Clinical Epigenetics - CLEP-D-15-00158R2

From: **Clinical Epigenetics Editorial Office** (em@editorialmanager.com)
Sent: Thu 1/28/16 10:14 PM
To: Shicheng Guo (shicheng.guo@hotmail.com)

CLEP-D-15-00158R2
Genome-wide analysis of DNA methylation and gene expression defines molecular characteristics of Crohn's disease-associated fibrosis
Tammy Sadler; Jeffrey M Bhasin; Yaomin Xu; Jill Barnholz-Sloan; Yanwen Chen; Angela H Ting; Eleni Stylianou, Ph.D.
Clinical Epigenetics

Dear Dr. Guo,

I would like to invite you to review the manuscript above which has been submitted to Clinical Epigenetics. Further details including the full abstract can be found at the end of this email.

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Thank you for your time, and I look forward to hearing from you.

Best wishes,

Ahihiro Umezawa
Clinical Epigenetics
http://www.clinicalepigeneticsjournal.com/

CLEP-D-15-00158R2
Research
Genome-wide analysis of DNA methylation and gene expression defines molecular characteristics of Crohn's disease-associated fibrosis
Clinical Epigenetics

Abstract: Background: Fibrosis of the intestine is a common and poorly understood complication of Crohn's disease (CD) characterized by excessive deposition of extracellular matrix and accompanied by narrowing and obstruction of the gut lumen. Defining the molecular characteristics of this fibrotic disorder is a vital step in the development of specific prediction, prevention and treatment strategies. Previous epigenetic studies indicate that alterations in DNA methylation could explain the mechanism by which mesenchymal cells adopt the requisite pro-fibrotic phenotype that promotes fibrosis progression. However, to date, genome-wide analysis of the DNA methylome of any type of human fibrosis is lacking. We employed an unbiased approach using deep sequencing to define the DNA methylome and transcriptome of purified fibrotic human intestinal fibroblasts (HIF) from the colons of patients with fibrostenotic CD.

Results: When compared with normal fibroblasts, we found that the majority of differential DNA methylation was within introns, intergenic regions and not associated with CpG islands. Only a low percentage occurred in the promoters and exons of genes. Integration of the DNA methylome and transcriptome identified regions in three genes that inversely correlated with gene expression: WNT2B and two eicosanoid synthesis pathway enzymes (prostacyclin synthase and prostaglandin D2 synthase). These findings were independently validated by RT-PCR and bisulfite sequencing. Network analysis of the data also identified candidate molecular interactions relevant to fibrosis pathology.

Conclusions: Our definition of a genome-wide fibrosis-specific DNA methylome provides new gene networks and epigenetic states by which to understand mechanisms of pathological gene expression that lead to fibrosis. Our data also provide a basis for development of new

fibrosis-specific therapies, as genes dysregulated in fibrotic Crohn's disease, following functional validation, can serve as new therapeutic targets.