Center for Molecular Epidemiology at Dartmouth

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GEISEL SCHOOL OF MEDICINE AT DARTMOUTH

July 15, 2014

Dr. Maria Jamela Revilleza
Scientific Program Analyst
NIGMS
mrevilleza@NIGMS.NIH.GOV

Re: NIGMS Science Advance New Publication / Scientific News; Center for Molecular Epidemiology (P20GM104416)

Dear Dr. Revilleza,

We are writing to inform you that the research reported in the following publications was supported in part by an Institutional Development Award (IDeA) from the National Institute of General Medical Sciences of the National Institutes of Health under grant number P20GM104416 (PI, Margaret Karagas):

Ung M, Ma X, Johnson KC, Christensen BC, Cheng C. Effect of estrogen receptor alpha binding on functional DNA methylation in breast cancer. Epigenetics. 2014 Apr 1;9(4):523-32. PMID: 24434785 [PMC in process]

Selvakumar P, Owens TA, David JM, Thomas GV, Petrelli NJ, Christensen BC, Lakshmikuttyamma A, Rajasekaran AK. Epigenetic silencing of Na,K-ATPase β 1 subunit gene ATP1B1 by methylation in clear renal cell carcinoma. Epigenetics. 2014 Apr 1;9(4):579-86. PMID: 24452105 [PMC in process]

Project Title: Center for Molecular Epidemiology at Dartmouth, Project 1: "Early Risk Factor Related Epigenetic Alterations in Breast Cancer Pathogenesis" (Project Leader: Dr. Brock Christensen)

Institution and State: Dartmouth College, New Hampshire

PI Name: Dr. Margaret R. Karagas (Center PI/Director)

Background:
Ung et al., *Epigenetics* manuscript
Epigenetic modifications introduce an additional layer of regulation that drastically expands the instructional capability of the human genome. The regulatory consequences of DNA methylation is context dependent; it can induce, enhance, and suppress gene expression, or have no effect on gene regulation. Therefore, it is essential to account for the genomic location of its occurrence and the protein factors it associates with to improve our understanding of its function and effects.

Selvakumar et al., *Epigenetics* manuscript
The Na,K-ATPase or sodium pump carries out the coupled extrusion of Na(+) and uptake of K(+) across the plasma membranes of cells of most higher eukaryotes. We have shown earlier that Na,K-ATPase-β 1 (NaK-β) protein levels are highly reduced in poorly differentiated kidney carcinoma cells in culture and in patients' tumor samples. The mechanism(s) regulating the expression of NaK-β in tumor tissues has yet to be explored. We hypothesized that DNA methylation plays a role in silencing the NaK-β gene (ATP1B1) expression in kidney cancers.

Advance:
In Ung et al. we reported evidence for a relation of DNA methylation at estrogen receptor binding sites with estrogen receptor activity. In addition, there were several transcription factors including FOXA1, GATA1 and SUZ12 that were related with breast cancer based on the methylation status of their estrogen receptor binding sites in tumor samples. Together, these results provide new insights into the interplay between estrogen receptor activity and epigenetic regulation in breast cancer.

In Selvakumar et al. we elucidated DNA methylation as a regulator of gene expression for *ATP1B1*, a coupled sodium/potassium pump that is highly expressed in kidney cells. In addition, we demonstrated and confirmed that *ATP1B1* expression is silenced by DNA methylation in renal cell carcinoma.

How NIGMS Grant Enabled Advance: Funds from the NIGMS Grant partially funded the study co-author Dr. Brock Christensen**.**

Public Health Impact Statement:
Ung et al. leveraged and integrated multiple publicly available data sets to inform genome wide function and regulation of estrogen receptor alpha in breast cancer that may aid in the development of targeted therapies in a precision medicine setting.

Selvakumar et al. further confirms the tumor suppressive role of *ATP1B1* in renal cell carcinoma and demonstrates a mechanism of its aberrant silencing that is potentially reversible using approved chemotherapeutic agents.

NIH Director's theme(s) relevance*:
Ung et al. addresses estrogen receptor gene regulation in breast cancer, the most common non-keratinocyte cancer in women.

Selvakumar et al. addresses the regulation and therapeutic targeting of a key tumor suppressor gene in kidney cancer.

Grant Support:
Ung et al., *Epigenetics* manuscript
This research was supported by an American Cancer Society Research Grant, #IRG-82-003-27 (C.C.), and by P20GM104416 (B.C.C.).

Selvakumar et al., *Epigenetics* manuscript
This research was supported by NIH grants DK56216 (A.K.R.), P20GM103464 (T.S.), P20GM104416 (B.C.C.), and the Nemours Foundation.

Publication Citation and Link (if applicable):
http://www.ncbi.nlm.nih.gov/pubmed/?term=24434785
http://www.ncbi.nlm.nih.gov/pubmed/?term=24452105[uid]

Key Words:
Ung et al.: transcription factor, DNase I hypersensitivity, estrogen receptor alpha, breast cancer, differential methylation, differential gene expression, ChIP-seq

Selvakumar et al.: epigenetics, DNA methylation, renal cell carcinoma, Na,K-ATPase, ATP1B1

NIGMS Point of Contact: Margaret R. Karagas (Margaret.R.Karagas@dartmouth.edu)

I am currently serving on the National Academies of Sciences committee to evaluate EPA's Integrated Risk Information System (IRIS) on inorganic arsenic (http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=18594). I also recently received the Squires endowed chair at Dartmouth (http://geiselmed.dartmouth.edu/news/2014/karagas-appointed-to-squires-professorship/).

Please let me know if you would like any additional information.

Sincerely,

Margaret R. Karagas, PhD
PI/Director, Center for Molecular Epidemiology at Dartmouth
Professor and Section Head, Biostatistics and Epidemiology
Vice Chair, Department of Community and Family Medicine
Geisel School of Medicine at Dartmouth

Cc: Dr. Yanping Liu (liuyanp@mail.nih.gov)