Pacific Northwest
NATIONAL LABORATORY

PNNL-32284

Glucuronidase Function in Clinical Samples

CRADA 539 (PNNL 79104)

November 2021

Aaron Wright

Enzymetrics Bioscience, Inc.

U.S. DEPARTMENT OF ENERGY

Prepared for the U.S. Department of Energy
under Contract DE-AC05-76RL01830

DISCLAIMER

PACIFIC NORTHWEST NATIONAL LABORATORY
operated by
BATTELLE
for the
UNITED STATES DEPARTMENT OF ENERGY
under Contract DE-AC05-76RL01830

Printed in the United States of America

Available to DOE and DOE contractors from the
Office of Scientific and Technical Information,
P.O. Box 62, Oak Ridge, TN 37831-0062;
ph: (865) 576-8401
fax: (865) 576-5728
email: reports@adonis.osti.gov

Available to the public from the National Technical Information Service
5301 Shawnee Rd., Alexandria, VA 22312
ph: (800) 553-NTIS (6847)
email: orders@ntis.gov <https://www.ntis.gov/about>
Online ordering: http://www.ntis.gov

PNNL-32284

Glucuronidase Function in Clinical Samples

CRADA 539 (PNNL 79104)

Abstract

November 2021

Aaron Wright

Prepared for
the U.S. Department of Energy
under Contract DE-AC05-76RL01830

Pacific Northwest National Laboratory
Richland, Washington 99354

Abstract

The purpose of this CRADA is to expand upon the work previously performed through CRADA No. PNNL/381. As explained in the previous CRADA, Glucuronidase enzymes are important for contributing to enterohepatic recycling of numerous therapeutic drug compounds, resulting in impaired or prolonged drug activity. Further, other pathways within the gut, such as bile acid metabolism through the action of bile salt hydrolase enzymes (BSH), have shown to impact both the development of colon cancers and impact recovery. Adapting the activity-based protein profiling (ABPP) technologies developed at PNNL to a microtiter plate-based chemical probe assay was the first step in demonstrating the clinical usability of the technology. With assay proof-of-concept complete through CRADA No. PNNL/381, clinical cohort testing using the developed assay is the next step towards commercialization of this technology.

Some chemotherapeutic agents are mediated by gut-produced microbiota through enterohepatic circulation. For example, irinotecan, the first line treatment for many colon and other cancers, can be recycled into a patient's system through gut microbiota produced glucuronidase enzymes. A significant percentage of patients subjected to irinotecan treatment experience dose-limiting diarrhea and gastric distress that limits treatment options and delays effective intervention. Relatedly, bile salt hydrolases modify ratios of bile acids in the gut, which alter nutrient and pharmaceutical uptake by the intestines and impact patient response to treatment. Coupled together these gut-mediated disorders can significantly decrease patient outcomes.

In this project, we propose to investigate a clinical cohort of samples from colon cancer patients to better understand gut microbiome activities surrounding microbiota produced glucuronidases to aid clinician decisions and enhance therapeutic intervention. Our project will measure glucuronidase activity of individual patients and compare this activity to a variety of factors, including patient medical history, treatment response, and overall outcomes. Data will be compared with metagenomic, metabolomic, and proteomic analyses to fully defined the entire gut microbiome space and correlate results with the glucuronidase activity. Resultant analysis is expected to provide actionable information to direct decision making towards therapeutic intervention.

Pacific Northwest National Laboratory

902 Battelle Boulevard
P.O. Box 999
Richland, WA 99354
1-888-375-PNNL (7665)

www.pnnl.gov