Development, validation, and application of DNA methylation libraries for inference of cell-types and phenotypes

Brock Christensen PhD, Dartmouth College; Karl Kelsey MD, Brown University; Devin Koestler PhD, University of Kansas Medical Center; John Wiencke PhD UCSF

Project Overview

• Develop, validate, and apply differential DNA methylation libraries to exposures/phenotypes
• We will pursue DNA methylation: our expertise includes relevant statistical and bioinformatics methods development as well as immunology, exposure biology, and medicine
• We propose to extend, adapt, and apply a suite of DNA methylation-based approaches we have developed to identify epigenetic signatures of interest

Teaming Overview and Objectives

• Our team (listed above) has worked together for >10 yrs on statistical and informatics methods for genome-scale DNA methylation to develop new methods and biomarkers
• Original constrained projection method for inferring immune cell types from DNA methylation and subsequent validations, methods advances, and applications
• Methylation arrays, next-generation sequencing, and single cell sequencing
• We seek integrated platform and device development expertise from collaborators
• We have access to samples from multiple molecular epidemiologic investigations of cancer; cases and controls, including detailed viral exposures data for some

Impact

• With teaming partners on the platform/device side, we expect to develop a point-of-contact platform for targeted epigenetic characterization
• The impact will include:
  • Advancements in the sensitivity of DNA methylation measures, and related statistical and informatics methods to identify exposure-related epigenetic characteristics
  • Point-of-care applications for DNA methylation based immunophenotyping tests and analyses with broad impact for health care systems

Experience example: Improving cell mixture deconvolution by identifying optimal DNA methylation libraries (IDOL)

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Project Overview

- Organs-on-Chips allow human biology to be accurately emulated using living human cells – the Chips establish microengineered environments that control the biology that drives function
- We propose to adapt our platform for epigenetics studies incorporating rich biological complexity not possible with other cell systems
- Platform will be designed to identify epigenetic signatures in various sample types, e.g., immune cells, cfDNA, and biopsies
- We plan to integrate our expertise in Organ-Chip development, instrumentation, and software with partners’ clinical and WMD expertise

Teaming Overview and Objectives

- Emulate team is world leading in the development and use of Organ-Chip systems, including associated analytics and clinically relevant endpoints
- Technology has been proven predictive of in vivo biology and has successfully captured human toxicity and potential biomarkers
- Commercialized Chip and instrument platform provides high-quality data with sufficient capacity and robustness in a plug-and-play format
- Seeking partners with access to suitable clinical samples, WMD expertise, and point-of-care diagnostics development

Impact

- Success will yield a platform for epigenetic signature discovery broadly useful for developing new diagnostics and forensics across civilian and defense needs
- As a high-content approach able to incorporate many tissue types, the platform should allow discovery of signatures across different analytic methods and sample types
- Commercialization strategy and user-centric design will ensure that developed technology will maximize impact in government and commercial arenas

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PROJECT OVERVIEW

• PROSPER HAS IDENTIFIED EPIGENETIC SIGNATURES FOR NUTRITIONAL STATUS, PHYSICAL FITNESS, MENTAL STRESS AND AGING.

• WE USE A LOW-COST PROPRIETARY ASSAY IN COMBINATION WITH ADVANCED BIOINFORMATICS.

• THESE SAME CAPABILITIES CAN BE APPLIED TO, AND BE SYNERGISTIC WITH, THE ECHO GOALS

TEAMING OVERVIEW AND OBJECTIVES

EXISTING TEAM MEMBERS AND PARTNERS

JANET TOMIYAMA PH.D. - PROFESSOR OF PSYCHOLOGY AT UCLA. DIRECTOR OF DIETING, STRESS AND HEALTH LAB AT UCLA. EXPERT IN STRESS BIOLOGY.

STEVE YOUNG, M.D. - Distingushed Professor of Medicine & Human Genetics at UCLA. Expert in Epigenetics and Human Disease.

BRETT DOLEZAL, PH.D. - ASSOCIATE PROFESSOR AT UCLA SCHOOL OF MEDICINE AND DEPARTMENT OF PHYSIOLOGY. EXPERT IN PHYSICAL CONDITIONING.

MICHAEL IRWIN, MD - COUSINS DISTINGUISHED PROFESSOR AND DIRECTOR OF UCLA MINDFULNESS AND AWARENESS CENTER. EXPERT IN MENTAL STRESS AND NEUROIMMUNOLOGY.

KURT HONG, MD, PH.D. - EXECUTIVE DIRECTOR OF USC CENTER FOR CLINICAL NUTRITION AND APPLIED HEALTH RESEARCH. EXPERT IN HUMAN NUTRITION AND DISEASE.

JAKE LUSIS, PH.D - PROFESSOR IN THE DEPARTMENTS OF MICROBIOLOGY AND MEDICINE AT UCLA. EXPERT IN EPIGENETICS, HEREDITY, CHROMATIN BIOLOGY.

MATTEO PELLEGRINI, PH.D. - PROFESSOR IN THE DEPARTMENT OF MOLECULAR, CELL, AND DEVELOPMENTAL BIOLOGY AT UCLA. EXPERT IN EPIGENETICS, BIOINFORMATICS AND AGING.

• SEEKING COLLABORATORS IN:
  • DNA SEQUENCING/DEVICE DEVELOPMENT
  • ARTIFICIAL INTELLIGENCE
  • MORE EFFICIENT SIGNATURE DEVELOPMENT?...LET’S TALK…

IMPACT

• WE ANTICIPATE DISCOVERING NEW EPIALLELES AND COMBINATIONS OF EPIALLELES THAT ARE DIAGNOSTIC OF THE ECHO GOALS

• APPLICATIONS WILL EXTEND BEYOND THE ECHO GOALS TO DTC CONSUMER TESTING AND HEALTHCARE DIAGNOSTICS.

• WE BELIEVE OUR APPROACH CAN ENABLE LOWER COST AND INCREASED ACCURACY

• TECHNOLOGY WILL BE TRANSITIONED TO USE WITH A DEVICE DEVELOPER

CONTACT INFORMATION – RWPHD@GMAIL.COM – (805) 807-1721
**Teaming Overview and Objectives**

- Enhance our existing platform to:
  - Support development of new algorithms for processing epigenetic data
  - Accept data and metadata from field sensors
  - Share data with the Intelligence Community
  - Map sensor data
- Experienced with embedded systems, GPU computing, and secure protocols for data transport and sharing
- 2 ½ years working with the BTO on data sharing projects

**Impact**

- Fast system for analyzing data
- Improve security for airlines, trains, borders, roads
- Track WMD movement
- Add to existing hardware vice making a standalone device
- Target product to military and public safety
- Identify victims of WMD

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Erich Izdepski, CTO, BTS Software Solutions

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