Exploring the exposome
Outline

The exposome

- Our vision

Agilent and the exposome

Analytical Methodologies

Summary
Phenotype $\propto G \times E$

The question: what proportion of chronic diseases are caused by genes and/or exposure?

GWAS is stunningly comprehensive

- But has explained relatively little chronic-disease risk

Elaborating the E matrix is less robust

- *de facto* questionnaires, geographic information and limited targeted measurements

E must be explored to understand its contribution
Wild (2005) espoused the exposome:

The sum of “…life-course environmental exposures (including lifestyle factors), from the prenatal period onwards”

Rappaport and Smith (2010) expanded the definition of the exposome to include endogenous chemicals

- a quantity of critical interest to understand the causes of most chronic disease (Rappaport, 2011)

Wild, CP. *Cancer Epidemiol Biomarkers Prev*, 2005
SM Rappaport. *JESEE*, 2011
The exposome

Wild (2005) espoused the exposome: 

“The sum of "...life-course environmental exposures (including lifestyle factors), from the prenatal period onwards”

Gary Miller, Dean Jones (2014)

“The cumulative measure of environmental influences and associated biological responses throughout the lifespan including exposures from the environment, diet, behavior, and endogenous processes”
In our paradigm: the exposome is...

Specific to human biology / health

Chemicals (exposures)

• Roughly 200K circulating in human blood (environment)
  – Dietary chemicals, drugs, reactive electrophiles, metals

Not to be conflated with pollutants in the environment

• People immediately presume air/water when they hear exposome
  – These are ancillary and needed after validation to determine source

Should not be construed as absolute in time and space
Exposome contribution to chronic disease

Artificial sweeteners induce glucose intolerance by altering the gut microbiota

Rappaport and Macherone, Agilent Technical Brief. 2013
The exposome is measured by…

Using state-of-the-art technology to:

• Develop and validate biological markers
• Apply them in human population studies

Applying current omics technologies

• Measure the broader scope of the exposome:
  – Exogenous and endogenous chemicals
• Use of “big data” tools (software)
Characterizing the exposome

Multi-disciplinary, multi-technique collaboration with epidemiologists, social-scientists, chemists, molecular and systems biologists and bioinformaticists…

Disease first

- Inductive – from the individual to the population
- Requires sophisticated bioinformatics

Preferably large prospective longitudinal cohort studies

- Nested case / controls
The exposome

AGILENT STRATEGY
Science first

Symposia and workshops

Research

• Engage key thought leaders and establish collaborations

Literature / application notes
ASMS Workshop

75 attendees
Martyn Smith, David Graham, Skip Kingston

Voted to create exposome interest group in the Society
Agilent exposome events

US

• SETAC:
  – The Exposome: A New Paradigm for Environmental Health and Exposure Sciences to Identify the Causes of Chronic Human Disease
    • Shoji Nakayama, Marc Strynar, Shane Snyder + 5 others
  
• The Hamner Institutes
  – Agilent Emerging Omics Research Tour
    • David Balshaw, James Swenberg, Martyn Smith, Mary McBride
Agilent Collaborative Partnerships

Keys:

• Enthusiastic PI
• Samples on premises and ready for analysis
• Human resources
• Invested and engaged Project Manager
Dr. Steven Rappaport,

a collaborator of Agilent and a prominent advocate of the concept of Exposome.

Offers

- Application & Technical notes
- Webinar reply done by Dr Rappaport some month ago
- MPP/PA promotion
- Deployed in October timeframe
Targeted POPs in blood

In-House pilot Study

• Collaboration with Smith lab (Berkeley) and Imperial College

50 matched case / controls nested from a prospective cohort in West London called LOLIPOP

GC/TQ for POPs in blood

If time and sample volume permits

• will also run GC/QTOF in discovery mode
Exposing the Exposome

Using the Blood Exposome to Discover Causes of Disease

Technical Overview

Introduction

Of the 52.8 million world-wide deaths in 2010, approximately two-thirds were caused by chronic diseases, mainly cardiovascular disease (> 15 million) and cancer (> 7 million) [1]. Thus, it is reasonable to ask whether chronic diseases are attributable to genetic factors, exposures, or some combination of the two. Data compiled by the Swedish Family-Cancer Database indicate that genetic (G) risks for 15 common cancers were 10% or less [2]. This suggests that environmental (E) factors may be responsible. Environmental factors can result from exposures (E) or GxE interactions, and a few nutrients, medications, and other exposures are known to modify disease risk [2].

Despite the relatively small genetic contribution, exquisite tools are available to investigate the exposome.
The exposome

METHODOLOGIES
The exposome is chemicals: small molecules, proteins, foreign DNA, metals, reactive electrophiles, etc.

Measure using EWAS, targeted and semi-targeted methods.


Agilent exposome portfolio
Toward ‘Omic Scale Metabolite Profiling: A Dual Separation–Mass Spectrometry Approach for Coverage of Lipid and Central Carbon Metabolism


†Scripps Center for Metabolomics and Mass Spectrometry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, United States
§Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, United States
‖Departments of Chemistry, Genetics, and Medicine, Washington University, One Brookings Drive, St. Louis, Missouri 63130, United States
#Pfizer Worldwide Research and Development, La Jolla Laboratories, San Diego, California 92121, United States
Two-step strategy

Step 1
- Data-driven EWAS
- Identify biomarkers

Step 2
- Knowledge-driven investigations

Breadth

Depth

- Elucidate:
  - Exposure-response relationships (biochemical epidemiology)
  - Sources of exposure and human kinetics (exposure biology)
  - Mechanisms of action (systems biology)

Reduced exposures

Early diagnosis of diseases

Improved public health

Personalized medical interventions

Rappaport and Macherone, Agilent Technical Brief. 2013
What does the two-phase strategy offer vs. current methodologies?

Provides a link between exposure and disease and insight into disease mechanisms.

The measured end-points represent a composite of exposure response and downstream biological outcome.


Rappaport and Macherone, Agilent Technical Brief. 2013
The exposome

SUMMARY
The exposome

A counterpart to the human genome

- The genome is the unique blueprint of an individual for life
- The exposome is a collection of chemicals of exogenous and endogenous exposures

Integrates technologies / disciplines

- Goes further than any one technology alone

Offers insight into causal and reactive pathways

Establishes:

- Exposure-response relationships (biochemical epidemiology)
- Sources of exposure and human kinetics (exposure biology)
- Mechanisms of action (systems biology)
Future of the exposome…

Transformative research happens once in a generation

- “Exposomic research will find disease causes and should dominate the next generation.” Stephen Morris Rappaport
- "The difficulty lies, not in the new ideas, but in escaping from the old ones." John Maynard Keynes