What is the exposome?

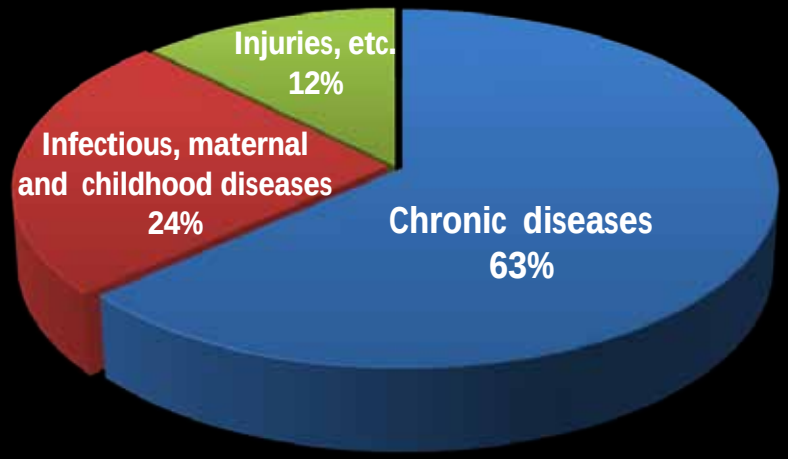
S.M. Rappaport

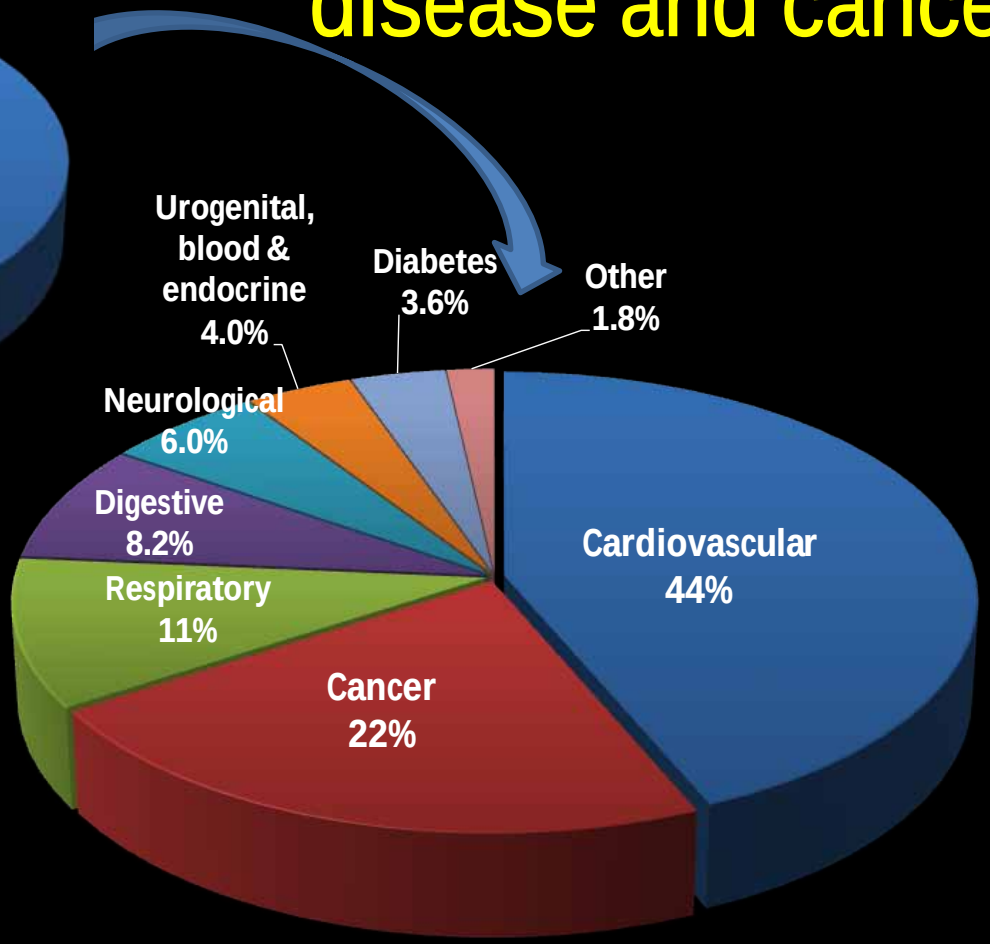
University of California, Berkeley

CEB Center For Exposure Biology

About 2/3 of people die from chronic diseases ...

mostly from heart disease and cancer





Worldwide deaths , 2010 (50M)
(Data from Lozano *et al.*, *Lancet*, 2012)

Are chronic diseases caused by the genes (G) or exposures (E)?

Explained variance of cancer incidence
(Swedish Family-Cancer Database of 10M individuals)

Site	Genetic	Shared exposures	Childhood exposures	Non-shared exposures
Stomach	0.01	0.15	0.13	0.71
Colon	0.13	0.12	0.06	0.69
Rectum	0.12	0.09	0.03	0.75
Lung	0.08	0.09	0.04	0.79
Breast	0.25	0.09	0.06	0.60
Cervix (invasive)	0.22	0.00	0.03	0.75
Cervix (*in situ*)	0.13	0.00	0.13	0.74
Testis	0.25	0.00	0.17	0.58
Kidney	0.08	0.08	0.06	0.78
Bladder	0.07	0.12	0.04	0.77
Melanoma	0.21	0.02	0.08	0.69
Nervous system	0.13	0.05	0.02	0.80
Thyroid	0.53	0.01	0.10	0.36
Endocrine	0.28	0.03	0.11	0.58
Non-Hodgkin's lymphoma	0.10	0.06	0.02	0.83
Leukemia	0.01	0.08	0.04	0.88
Median	***0.13***	***0.07***	***0.06***	***0.75***

K Czene, P Lichtenstein and K Hemminki, Int J Cancer 2002, 99: 260-6

Discovering causes of cancer

- Cancer risks attributable to genetic factors (G) are typically small (<10%)
- Primary causes must be environmental (E) or GxE
  - However, most of the E risks have not been identified
- *What tools are available for identifying G and E causes of cancer?*

Studying genetic factors

SNPs per assay	
1997	1
2001	10
2002	1,000
2004	50,000
2006	500,000
2007	1,000,000
2010	>>1,000,000

Genome-Wide Association Studies (GWAS) performed with 2,000-20,000 samples (2 billion - 20 billion genotypes)

SM Rappaport

Courtesy of E. Lander, MIT/Broad

Studying exposures

Two thirds of studies relied upon subjects to assess their own exposures!

B.K. Armstrong *et al. Principles of Exposure Measurement in Epidemiology,* Oxford Med. Pubs., 1992

Table 2.2 Distribution of the main methods of exposure measurement (one selected from each study) in 564 studies of the aetiology of non-infectious disease published in the *American Journal of Epidemiology* between January 1980 and December 1989

Methods	Distribution (%)
Personal interview	49.1
Face to face	43.0
Telephone	4.1
Unclassifiable type	2.0
Self-administered questionnaire	14.0
By mail	6.4
Under supervision	7.6
Reference to records	22.3
Medical records	7.1
Other records	15.2
Physical or chemical measurements	13.3
On subject	10.8
On environment	2.5
Unclassifiable	1.2

Cancer Epidemiol Biomarkers Prev 2005;14(8). August 2005

Editorial

Complementing the Genome with an "Exposome": The Outstanding Challenge of Environmental Exposure Measurement in Molecular Epidemiology

Christopher Paul Wild

Molecular Epidemiology Unit, Centre for Epidemiology and Biostatistics, Leeds Institute of Genetics, Health and Therapeutics, Faculty of Medicine and Health, University of Leeds, Leeds, United Kingdom

EPIDEMIOLOGY

Environment and Disease Risks

Stephen M. Rappaport and Martyn T. Smith

A new paradigm is needed to assess how a lifetime of exposure to environmental factors affects the risk of developing chronic diseases.

Although the risks of developing chronic diseases are attributed to both genetic and environmental factors, 70 to 90% of disease risks are probably due to differences in environments (*1*–*3*). Yet, epidemiologists increasingly use genome-wide association studies (GWAS) to investigate diseases, while relying on questionnaires to characterize "environmental exposures." This is because GWAS represent the only approach for exploring the totality of any risk factor (genes, in this case) associated with disease prevalence. Moreover, the value of costly genetic information is diminished when inaccurate and imprecise environmental data lead to biased inferences regarding gene-environment interactions (*4*). A more comprehensive and quantitative view of environmental exposure is needed if epidemiologists are to discover the major causes of chronic diseases.

An obstacle to identifying the most important environmental exposures is the fragmentation of epidemiological research along lines defined by different factors. When epidemiologists investigate environmental risks, they tend to concentrate on a particular category of exposures involving air and water pollution, occupation, diet and obesity, stress and behavior, or types of infection. This slicing of the disease pie along parochial lines leads to scientific separation and confuses the definition of "environmental exp... these exposure cate... chronic diseases and... collectively rather th...

To develop a mor... ronmental exposure,... nize that toxic effect...

chemicals that alter critical molecules, cells, and physiological processes inside the body. Thus, it would be reasonable to consider the "environment" as the body's internal chemical environment and "exposures" as the amounts of biologically active chemicals in this internal environment. Under this view, exposures are not restricted to chemicals (toxicants) entering the body from air, water, or food, for example, but also include chemicals produced by inflammation, oxidative stress, lipid peroxidation, infections, gut flora, and other natural processes (*5*, *6*) (see the figure). This internal chemical environment continually fluctuates during life due...

School of Public Health, University of California, Berkeley, CA 94720–7356, USA. E-mail: srappaport@berkeley.edu

EMERGING SCIENCE FOR ENVIRONMENTAL HEALTH DECISIONS

WORKSHOP

The Exposome: A Powerful Approach for Evaluating Environmental Exposures and Their Influences on Human Disease

FEBRUARY 25-26, 2010 . WASHINGTON, DC

THURSDAY, 8:30–5:00, FRIDAY, 8:30-NOON . NAS BUILDING, 2100 C STREET, NW, AUDITORIUM

EMERGING SCIENCE FOR ENVIRONMENTAL HEALTH DECISIONS

AGENDA

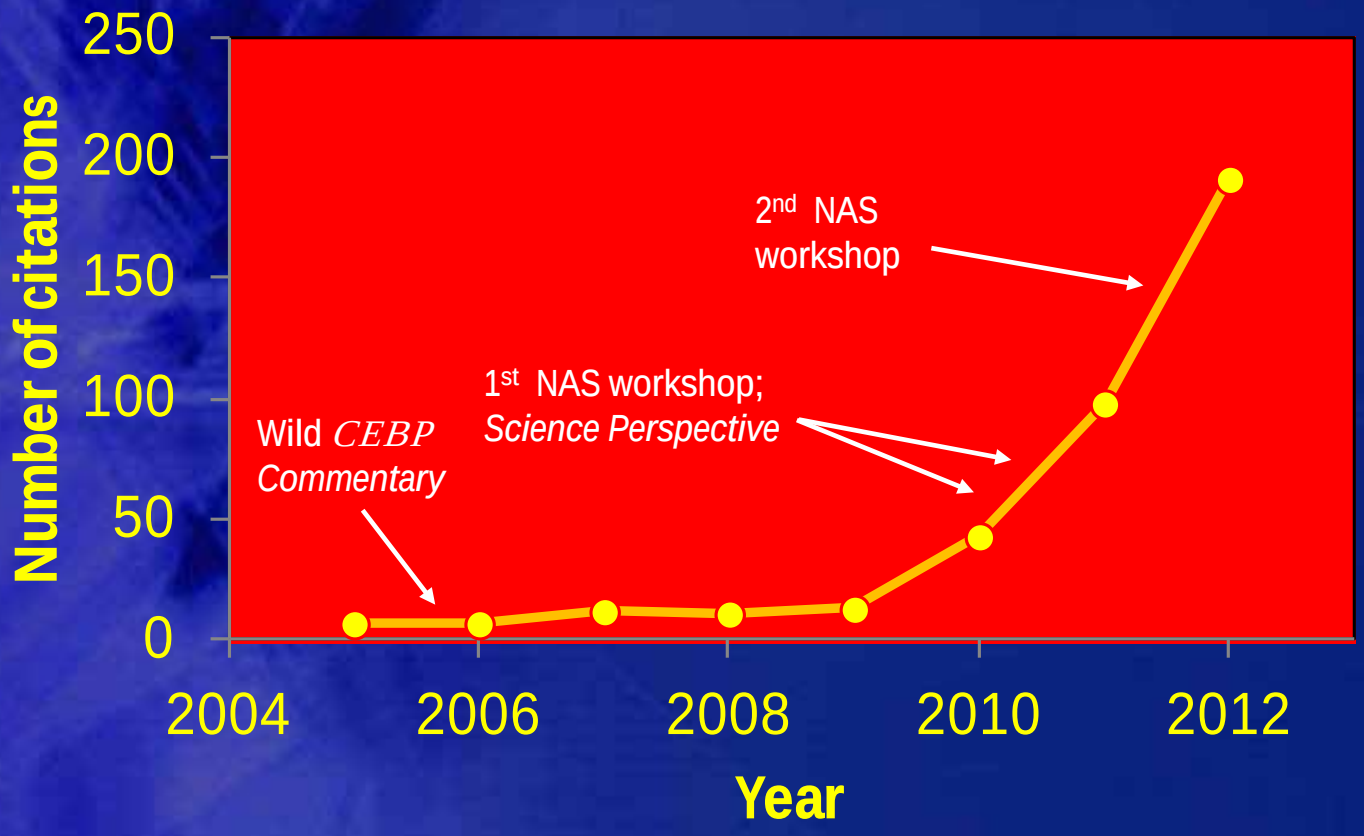
Emerging Technologies for Measuring Individual Exposomes

DECEMBER 8–9, 2011 ▪ THURSDAY, 8:30–5:00, FRIDAY, 8:30–NOON*

HOUSE OF SWEDEN EVENT CENTER, 2900 K STREET, NW, WASHINGTON, DC

THIS WORKSHOP WILL BE WEBCAST.

Scientific citations to ‘exposome’ (Google Scholar)



Capturing *all* exposures

EPIDEMIOLOGY

Environment and Disease Risks

Stephen M. Rappaport and Martyn T. Smith

A new paradigm is needed to assess how a lifetime of exposure to environmental factors affects the risk of developing chronic diseases.

Although the risks of developing chronic diseases are attributed to both genetic and environmental factors, 70 to 90% of disease risks are probably due to differences in environments (*1*–*3*). Yet, epidemiologists increasingly use genome-wide association studies (GWAS) to investigate diseases, while relying on questionnaires to characterize "environmental exposures." This is because GWAS represent the only approach for exploring the totality of any risk factor (genes, in this case) associated with disease prevalence. Moreover, the value of costly genetic information is diminished when inaccurate and imprecise environmental data lead to biased inferences regarding gene-environment interactions (*4*). A more comprehensive and quantitative view of environmental exposure is needed if epidemiologists are to discover the major causes of chronic diseases.

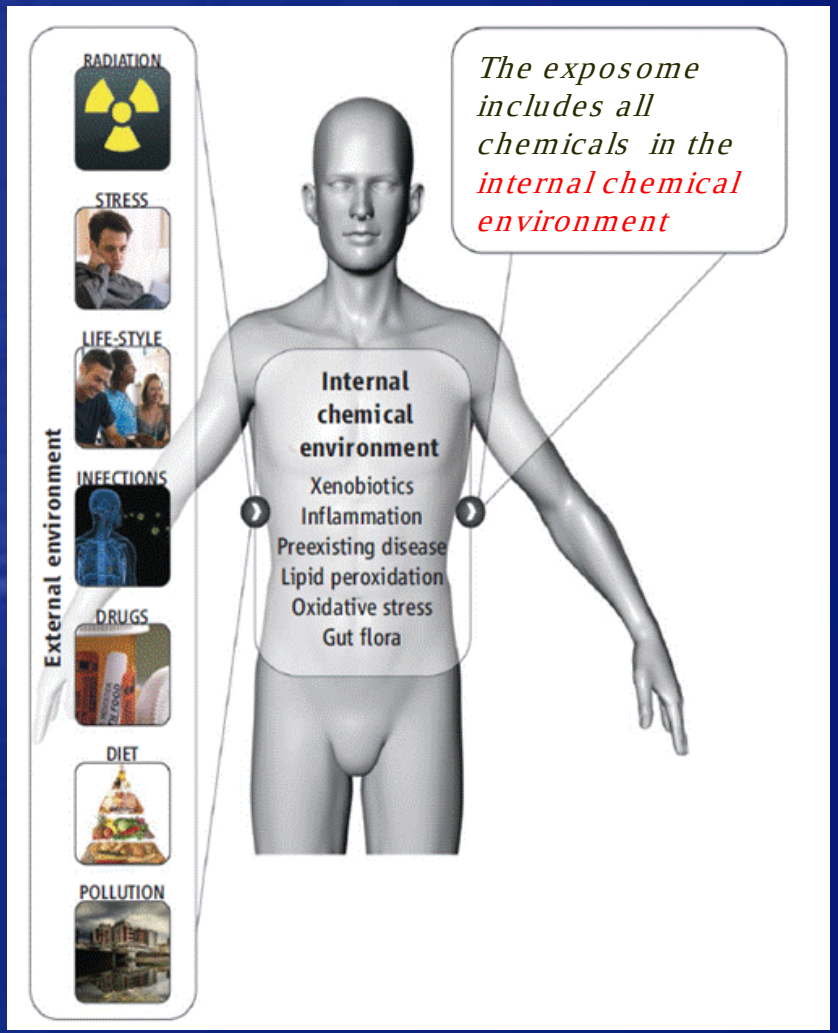
An obstacle to identifying the most important environmental exposures is the fragmentation of epidemiological research along lines defined by different factors. When epidemiologists investigate environmental risks, they tend to concentrate on a particular category of exposures involving air and water pollution, occupation, diet and obesity, stress and behavior, or types of infection. This slicing of the disease pie along parochial lines leads to scientific separation and confuses the definition of "environmental exposures." In fact, all of these exposure categories can contribute to chronic diseases and should be investigated collectively rather than separately.

To develop a more cohesive view of environmental exposure, it is important to recognize that toxic effects are mediated through chemicals that alter critical molecules, cells, and physiological processes inside the body. Thus, it would be reasonable to consider the "environment" as the body's internal chemical environment and "exposures" as the amounts of biologically active chemicals in this internal environment. Under this view, exposures are not restricted to chemicals (toxicants) entering the body from air, water, or food, for example, but also include chemicals produced by inflammation, oxidative stress, lipid peroxidation, infections, gut flora, and other natural processes (*5*, *6*) (see the figure). This internal chemical environment continually fluctuates during life due to changes in external and internal sources, aging, infections, life-style, stress, psychosocial factors, and preexisting diseases.

The term "exposome" refers to the totality of environmental exposures from conception onwards, and has been proposed to be a

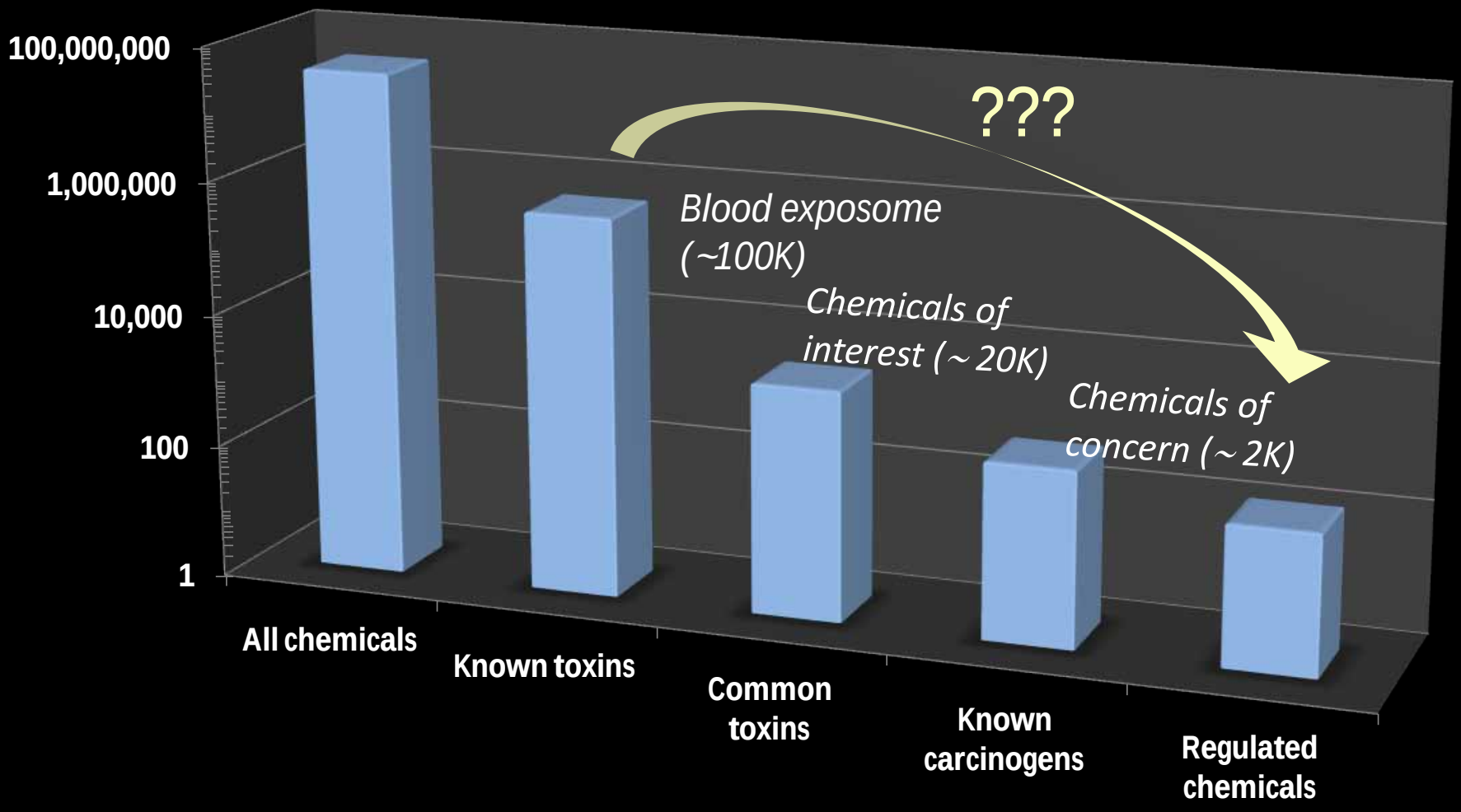
School of Public Health, University of California, Berkeley, CA 94720–7356, USA. E-mail: srappaport@berkeley.edu

Published by AAAS



S.M. Rappaport and M.T. Smith, Science, 2010: 330:460-461

Exposures are chemicals



S. M. Rappaport

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

Julijana Ivanisevic,[†,‡] Zheng-Jiang Zhu,[†,‡] Lars Plate,[§] Ralf Tautenhahn,[†] Stephen Chen,[†] Peter J. O'Brien,[#] Caroline H. Johnson,[†] Michael A. Marletta,[§] Gary J. Patti,[*,∥] and Gary Siuzdak[*,†]

[†]Scripps Center for Metabolomics and Mass Spectrometry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, United States

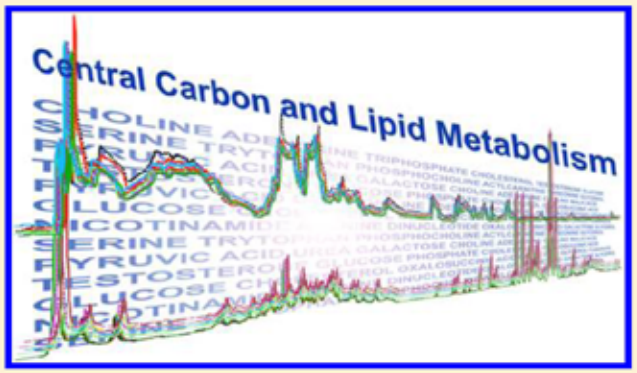
[§]Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, United States

[∥]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

Supporting Information

ABSTRACT: Although the objective of any 'omic science is broad measurement of its constituents, such coverage has been challenging in metabolomics because the metabolome is comprised of a chemically diverse set of small molecules with variable physical properties. While extensive studies have been performed to identify metabolite isolation and separation methods, these strategies introduce bias toward lipophilic or water-soluble metabolites depending on whether reversed-phase (RP) or hydrophilic interaction liquid chromatography (HILIC) is used, respectively. Here we extend our consideration of metabolome isolation and separation procedures to integrate RPLC/MS and HILIC/MS profiling. An amino-propyl-based HILIC/MS method was optimized on the basis of mobile-phase additives and pH, followed by evaluation of reproducibility. When applied to the untargeted study of perturbed bacterial metabolomes, the HILIC method enabled the accurate assessment of key, dysregulated metabolites in central carbon pathways (e.g., amino acids, organic acids, phosphorylated sugars, energy currency metabolites), which could not be retained by RPLC. To demonstrate the value of the integrative approach, bacterial cells, human plasma, and cancer cells were analyzed by combined RPLC/HILIC separation coupled to ESI positive/negative MS detection. The combined approach resulted in the observation of metabolites associated with lipid and central carbon metabolism from a single biological extract, using 80% organic solvent (ACN:MeOH:H_2O 2:2:1). It enabled the detection of more than 30,000 features from each sample type, with the highest number of uniquely detected features by RPLC in ESI positive mode and by HILIC in ESI negative mode. Therefore, we conclude that when time and sample are limited, the maximum amount of biological information related to lipid and central carbon metabolism can be acquired by combining RPLC ESI positive and HILIC ESI negative mode analysis.



More than 30,000 small molecules detected in 0.1 ml (2 drops) of serum

Anal. Chem. 2013, 85, 6876–6884

Exposome-wide association studies (EWAS)

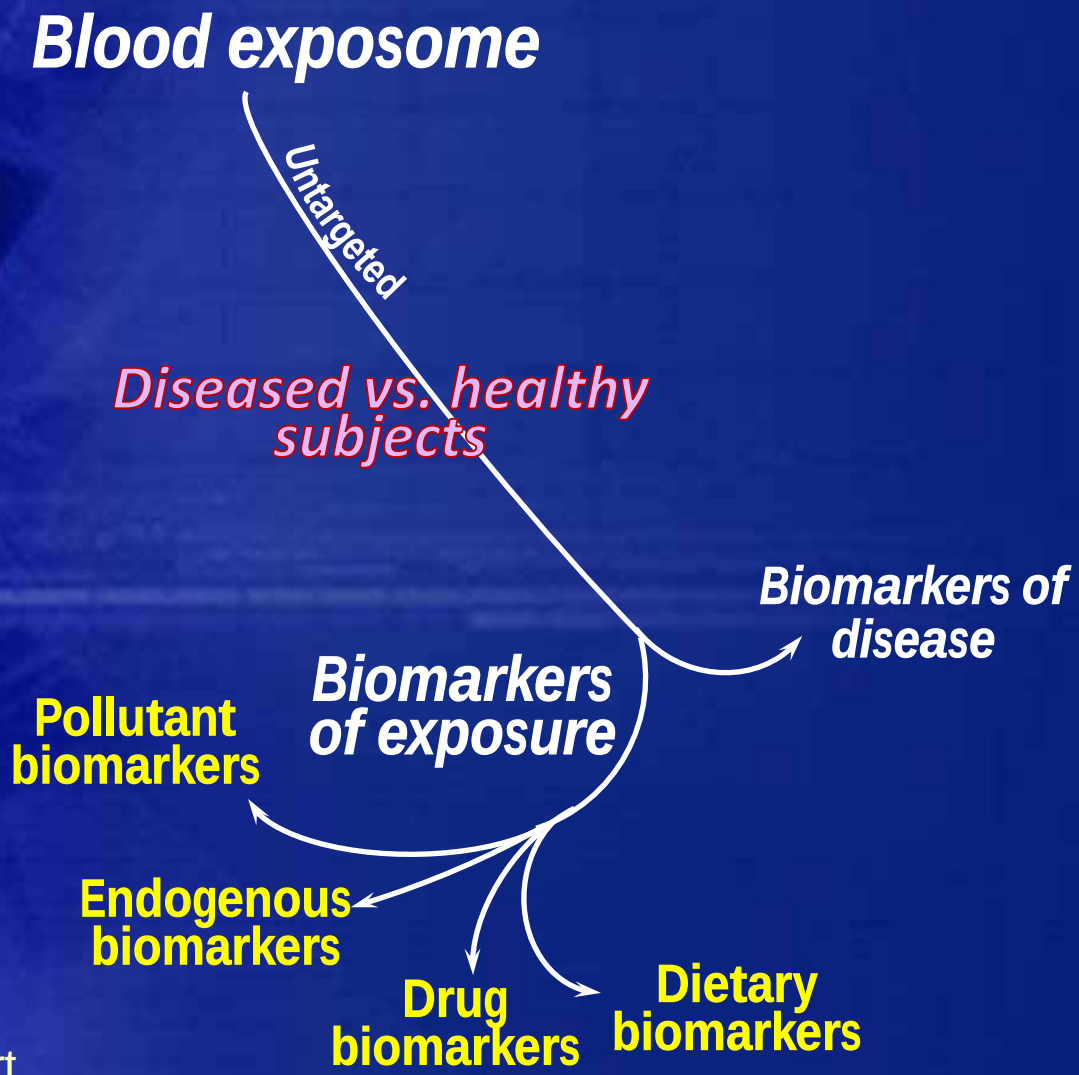
By applying untargeted EWAS to biospecimens from some healthy and diseased subjects, we can discover useful biomarkers

http://www.flickr.com/photos/paulieparker/246707763/

Then we can target useful biomarkers in large populations

S. Rappaport, *Biomarkers*, 2012, 17(6), 48: 3-9

Untargeted EWAS



Based on: S. Rappaport, *Biomarkers*, 2012, 17(6), 48: 3-9

SM Rappaport