Molecular Phenotyping in Diabetes, Obesity and Nutrition

Charles Burant, MD, PhD

University of Michigan Health System

Michigan Metabolomics and Obesity Center

NCIBI National Center for Integrative Biomedical Informatics

Center for Computational Medicine and Biology

Burant lab
Mary Treutelaar
Amy Rothberg
Erin Shellman
Andrew Miller
Arun Das
Jinghua Xu
Katie Overmyer
Sydney Bridges

NCIBI/CCMB
Maureen Sartor
Alla Karnovsky
H V Jagadish
Jing Gao
Brian Athey
Jim Cavalcoli

MCRU
Theresa Han-Markey
Bionutrition Support
Metabolic Kitchen

SPH
Alex Tsodikov
Karen Peterson
Ken Resnicow

Pathology
Chris Beecher

MMOC
Arun Das
Nathan Qi
Jane Cao

Internal Medicine
Sub Pennathur
Jaimin Byun

Chemistry
Bob Kennedy
Charles Evans

PM&R
Steve Britton
Lauren Koch

USC
Michael Goran
Tom Buchanan

UCLA
Chris Roberts

Loyola
Richard Cooper
Amy Luke

Wisconsin
Alan Attie

NCIBI

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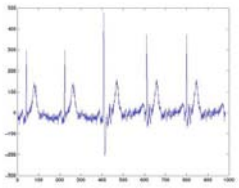
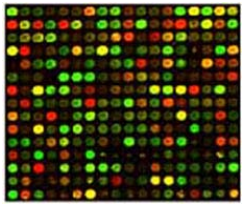


Biological Data



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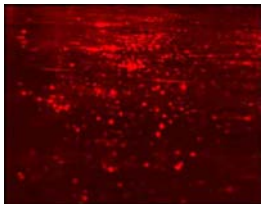
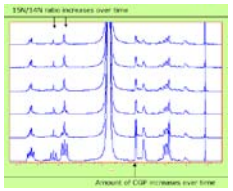
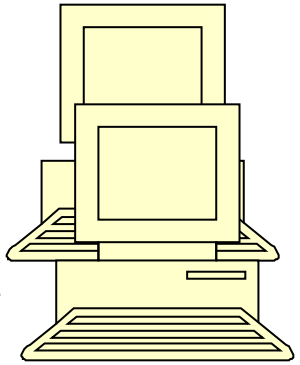
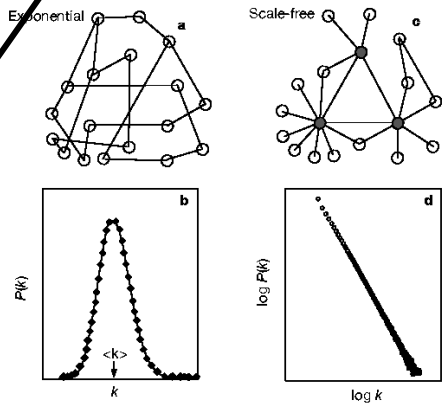


Proteomics



Metabolomics





Predictive Model of the System

Projects

Ongoing

- Using Systems Biology to Understand Islet Adaptation and Failure in a Model of Type 2 Diabetes
- Molecular Determinants of Aerobic Capacity in a Rat Model of the Metabolic Syndrome
- Defining a Biomarker for Macronutrient Intake in Humans

Launching

- Broad and Deep Phenotyping of Individuals Enrolled in the Investigational Weight Management Clinic

Each project has collaborations with NCIBI researchers to develop tools to understand environmental effects on phenotype.

Defining a Personalized Nutritional Intervention

- Nutrients are inescapable environmental substances that have a differential effect on risk for disease
- Study goals
  - Create an unambiguous biomarker signature of short term and long term macronutrient intake
  - Prospectively define macronutrient advice to individuals based on baseline phenotypic characteristics

The Study

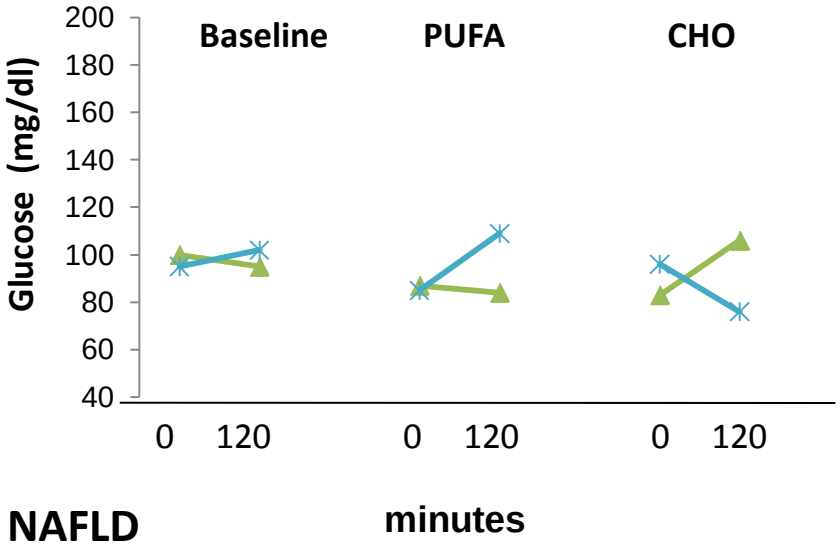
•Period 1, isocaloric, high polyunsaturated fat diets (10-15% protein, 35-50% carbohydrate, 40-50% fat, <10% fat as saturated).

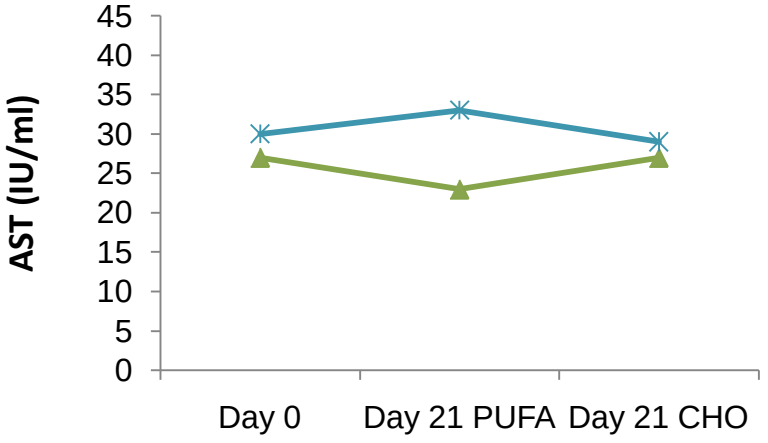
• Period 2, isocaloric, high carbohydrate diet (10-15% protein, 60-70% carbohydrate, 15-30% fat, <10% fat as saturated).

Blood for metabolites and transcripts assessed at baseline and at 2, 7, 21 days of diet.

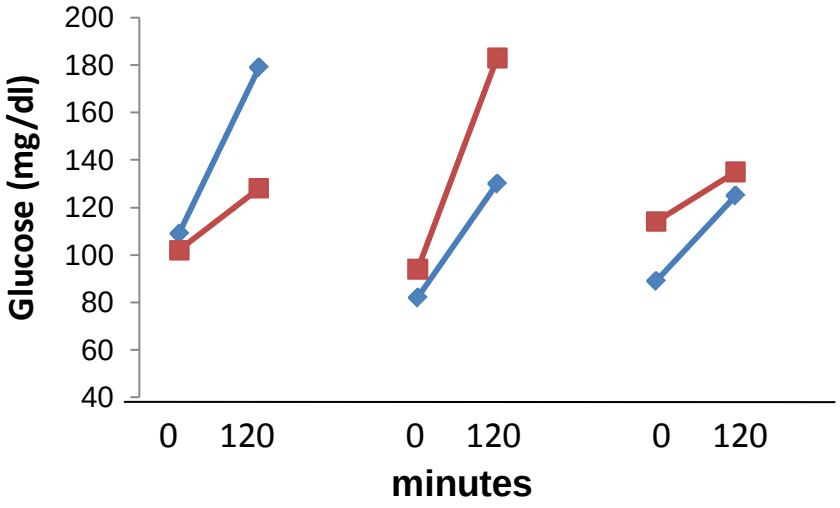
Variable phenotypic response to diet

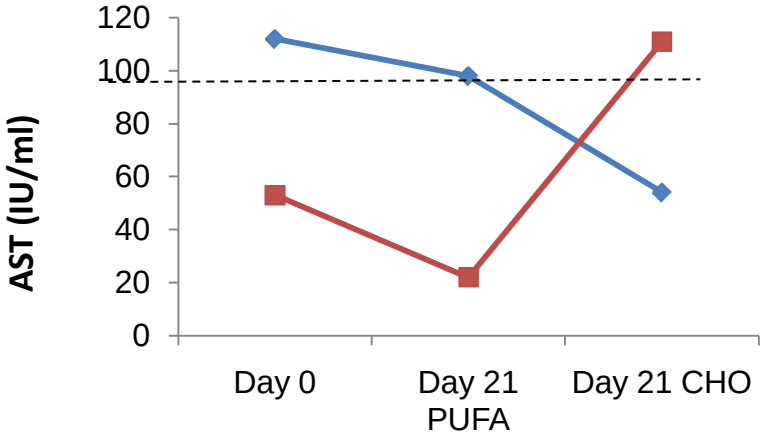
Controls





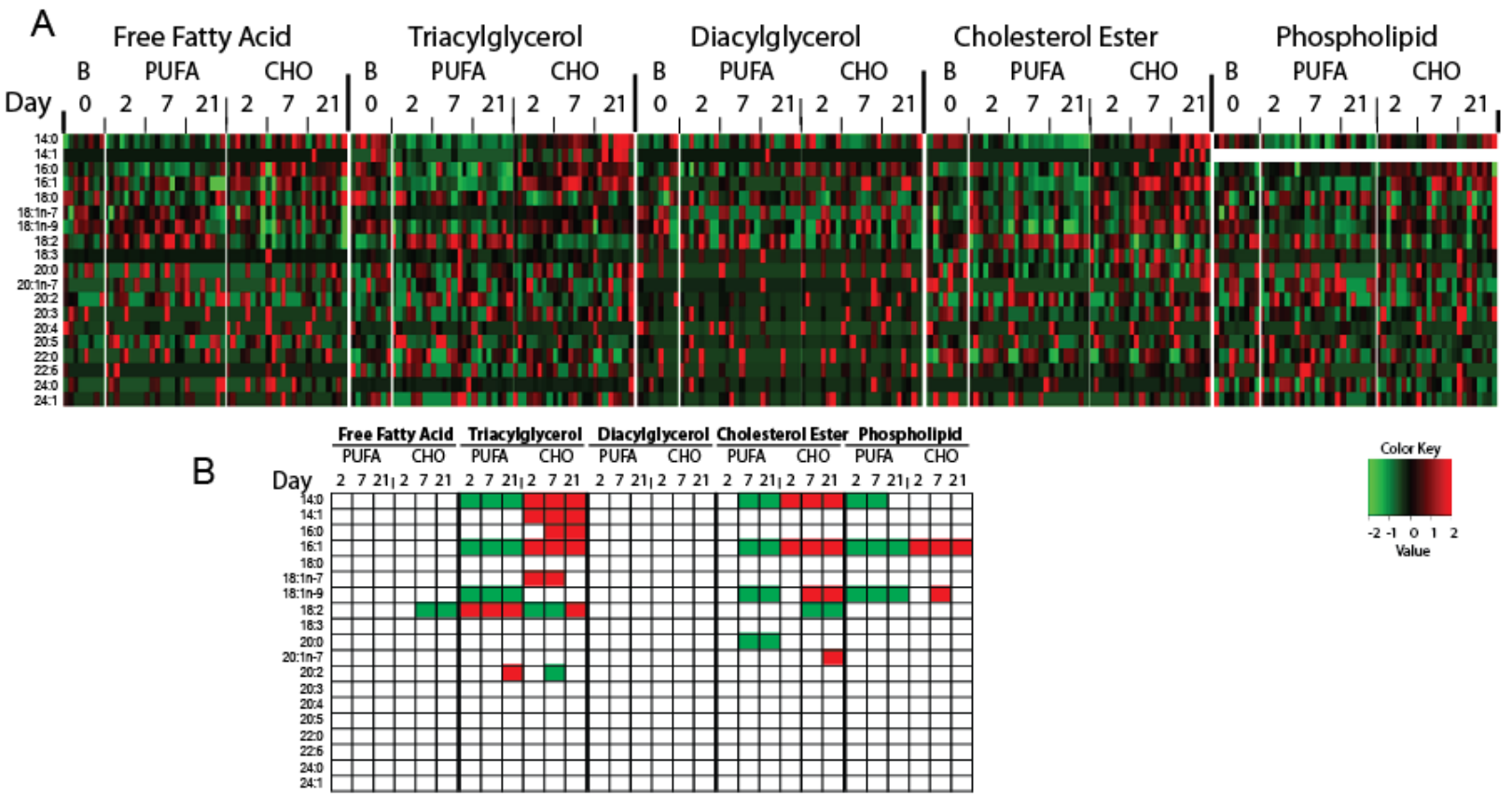
NAFLD





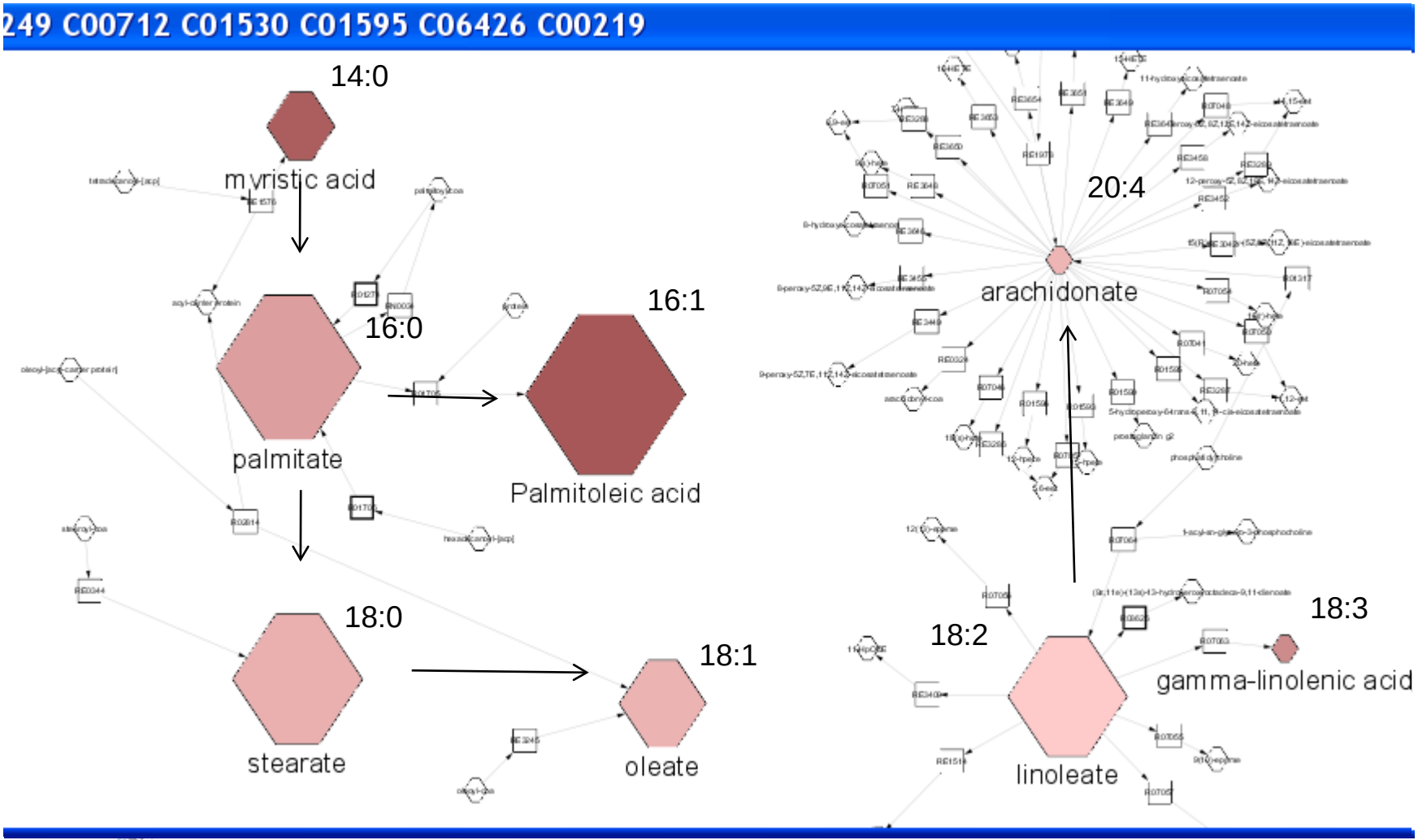
Lipomic assessment of plasma

- Can macronutrient consumption be detected in fatty acid profiles?



METSCAPE

CHO – 21 Day



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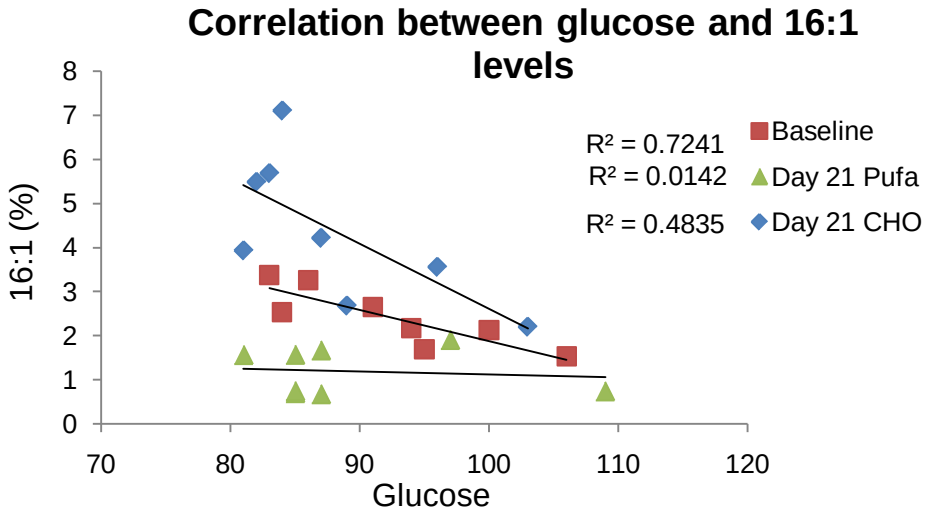
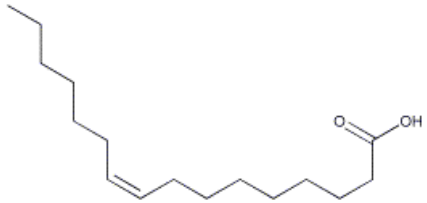
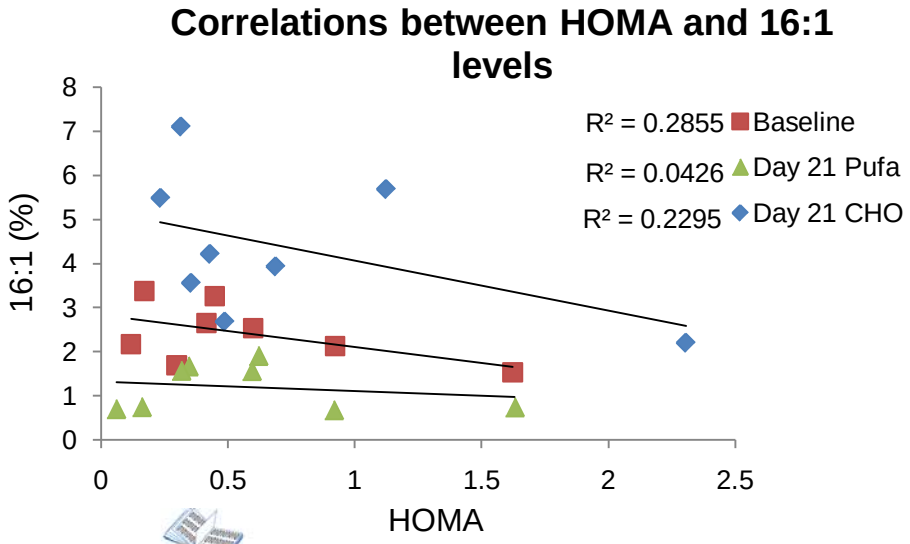
Palmitoleic acid: derived from de novo FA synthesis

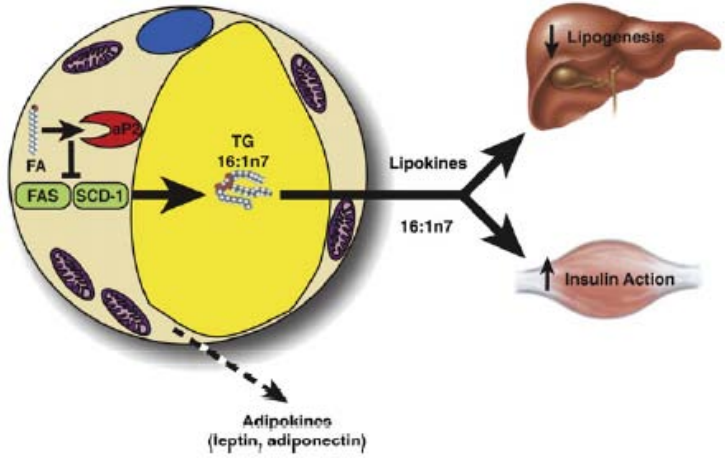






Identification of a Lipokine, a Lipid Hormone Linking Adipose Tissue to Systemic Metabolism

Haiming Cao,[1] Kristin Gerhold,[1,3] Jared R. Mayers,[1] Michelle M. Wiest,[2] Steven M. Watkins,[2] and Gökhan S. Hotamisligil[1]
[1]Department of Genetics and Complex Diseases, Harvard School of Public Health, Boston, MA 02115, USA
[2]Lipomics Technologies, West Sacramento, CA 95691, USA
[3]Present addresses: Department of Molecular and Cell Biology, University of California, Berkeley, Berkeley, CA 94703, USA
*Correspondence: ghotamis@hsph.harvard.edu
DOI 10.1016/j.cell.2008.07.048



The peripheral blood transcriptome dynamically reflects system wide biology: a potential diagnostic tool

CHOONG-CHIN LIEW, JUN MA, HONG-CHANG TANG, RUN ZHENG, and ADAM A. DEMPSEY

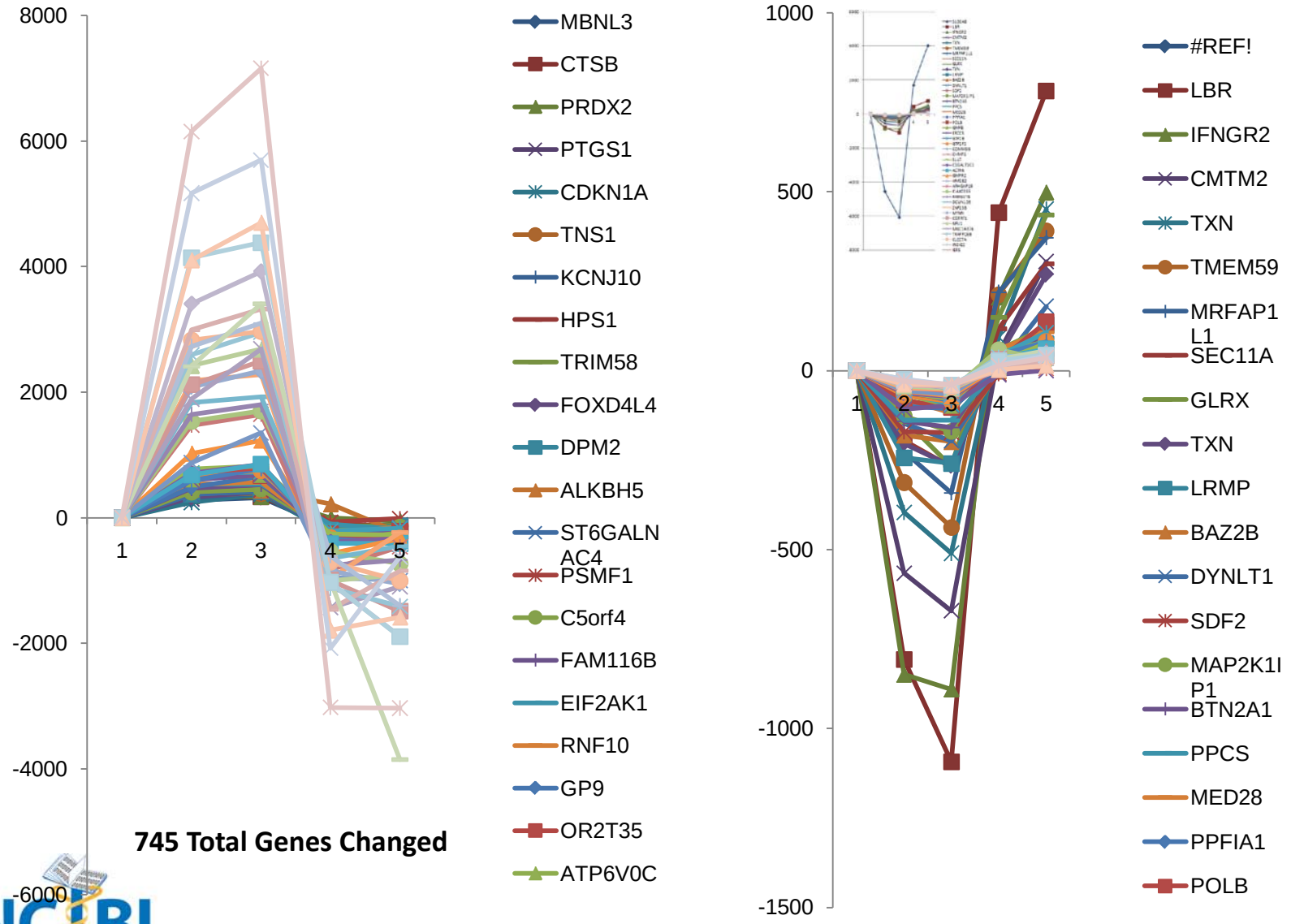
TORONTO, ONTARIO, CANADA AND BOSTON, MASSACHUSETTS

In our genome-wide survey of gene expression in human peripheral blood cells using both an expressed sequence tag (EST) and a microarray hybridization approach, we identified the expression of a large proportion (approximately 80%) of the genes encoded in the human genome. Comparison of the peripheral blood transcriptome with genes expressed in nine different human tissue types revealed that expression of over 80% was shared with any given tissue. We also sought to determine whether those gene transcripts undetected by these methods were also expressed in peripheral blood cells. Using reverse-transcriptase-polymerase chain reaction, we detected additional tissue-specific gene transcripts including beta-myosin heavy chain (heart specific) and insulin (specific to pancreatic islet beta cells), in circulating blood cells. Arguably, the detection of low levels of tissue-specific transcripts could be considered products of "illegitimate" transcription; however, our study also demonstrates that environmental conditions affect the transcriptional regulation of insulin in the peripheral blood. We thus hypothesize that blood cells can act as sentinels of disease and that we could capitalize on this property of blood for the diagnosis/prognosis of disease (the "Sentinel Principle"). Peripheral blood is an ideal surrogate tissue as it is readily obtainable, provides a large biosensor pool in the form of gene transcripts, and response to changes in the macro- and micro-environments is detectable as alterations in the levels of these gene transcripts. (J Lab Clin Med 2006;147:126–132)

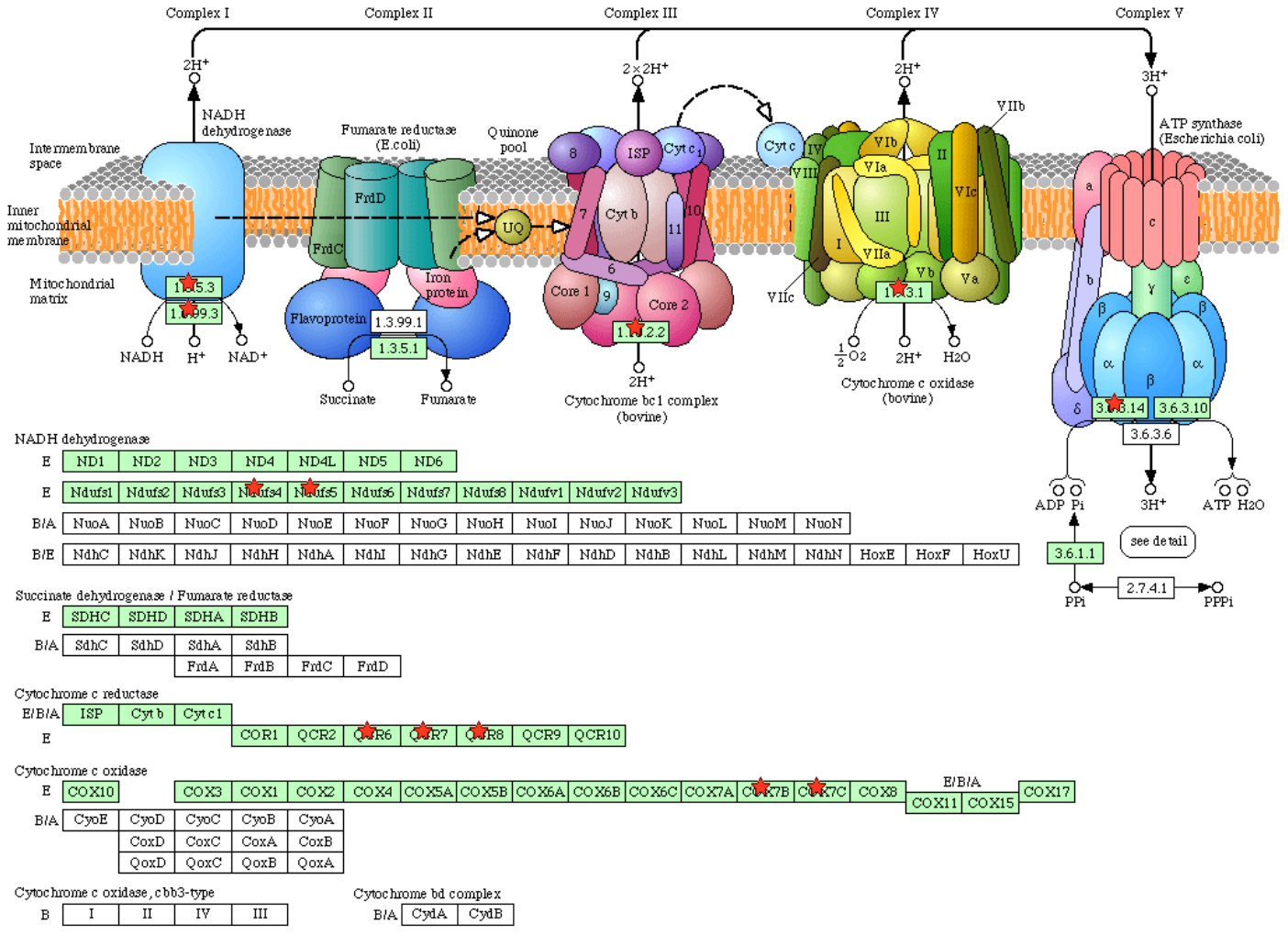
Table I. Genes expressed in peripheral blood cells shared with one of nine human tissues

Tissues	Brain	Colon	Heart	Kidney	Liver	Lung	Prostate	Spleen	Stomach
Number of genes/expressed	13961	13767	12440	13428	13840	15202	11706	13224	10898
Number of co-expressed genes in blood	11428	11360	10472	11166	11490	12301	9955	10892	9408
Percentage of co-expressed genes in blood	81.9%	82.5%	84.2%	83.2%	83.0%	80.9%	83.9%	85.0%	86.3%

Gene changes sorted on PUFA day 21



Down in PUFA; Up in CHO

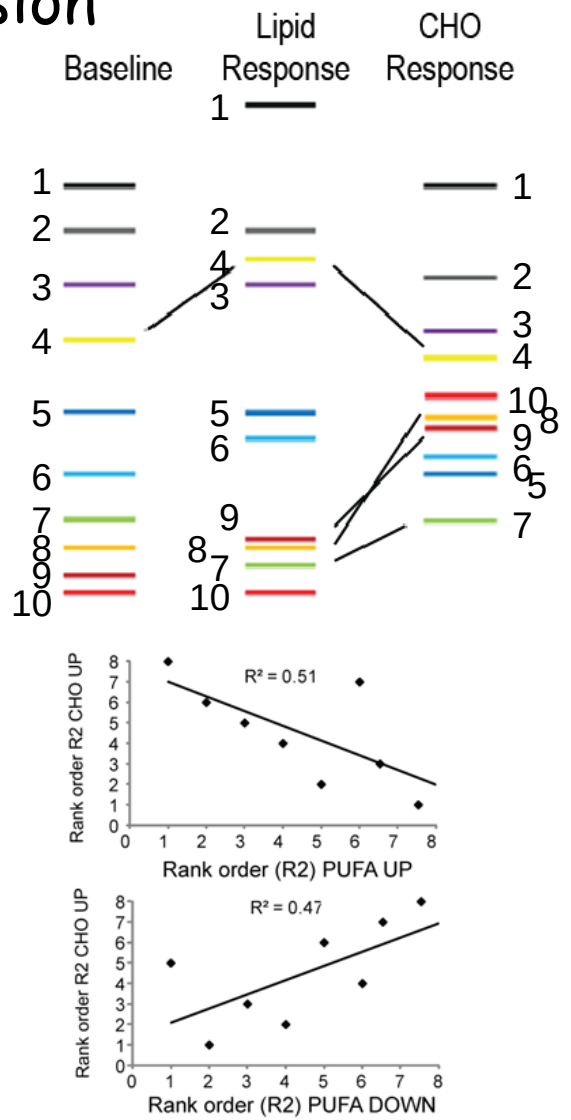


Relatedness mapping to estimate dietary macronutrient Content from gene expression

The relative levels of gene expression within a sample will be dependent on genetic makeup and environment (dietary macronutrients).

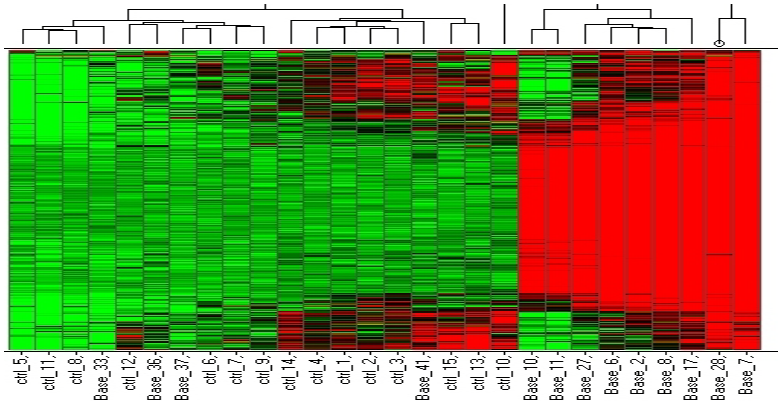
- Identifying the genes that change under experimental dietary conditions will provide a set of dietary 'indicators' that may be relatively dependent on diet
- Assigned a rank-ordered principal value to the most highly expressed genes that were altered in a statistically significant manner in by each diet, either up or down.

- Compare the rank order of 'test' sets with the 'standard' sets developed (essentially the standard curve). Used a nonparametric,
rank-based pattern-matching strategy
based on the Kolmogorov-Smirnov statistic.

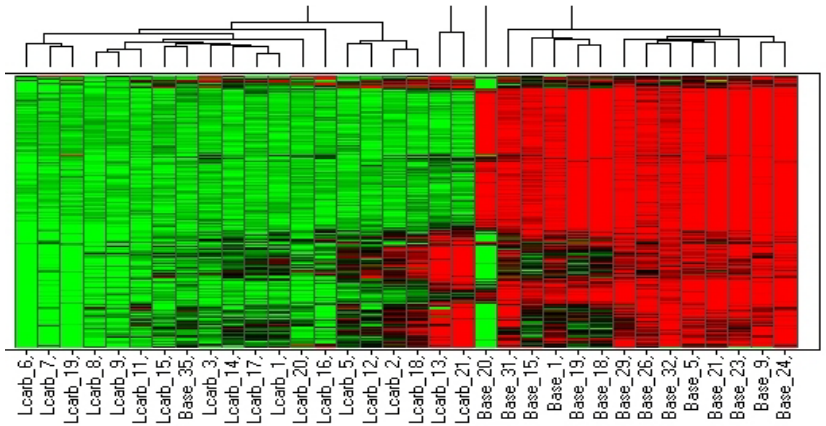


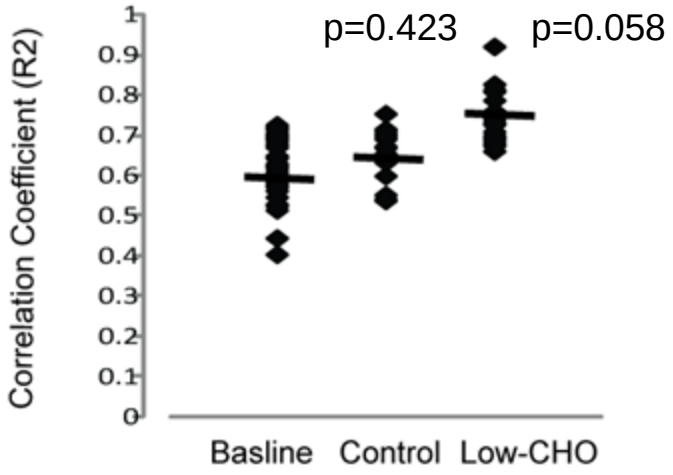
Clustering and Macronutrient Mapping

Control



LCHO





Analytical Hierarchy