3rd Annual Workshop on Metabolomics

Integration of Biology and the Metabolome: Breaking Barriers Across Disciplines

Monday, June 15, 2015

Adam R. Wende, Ph.D.

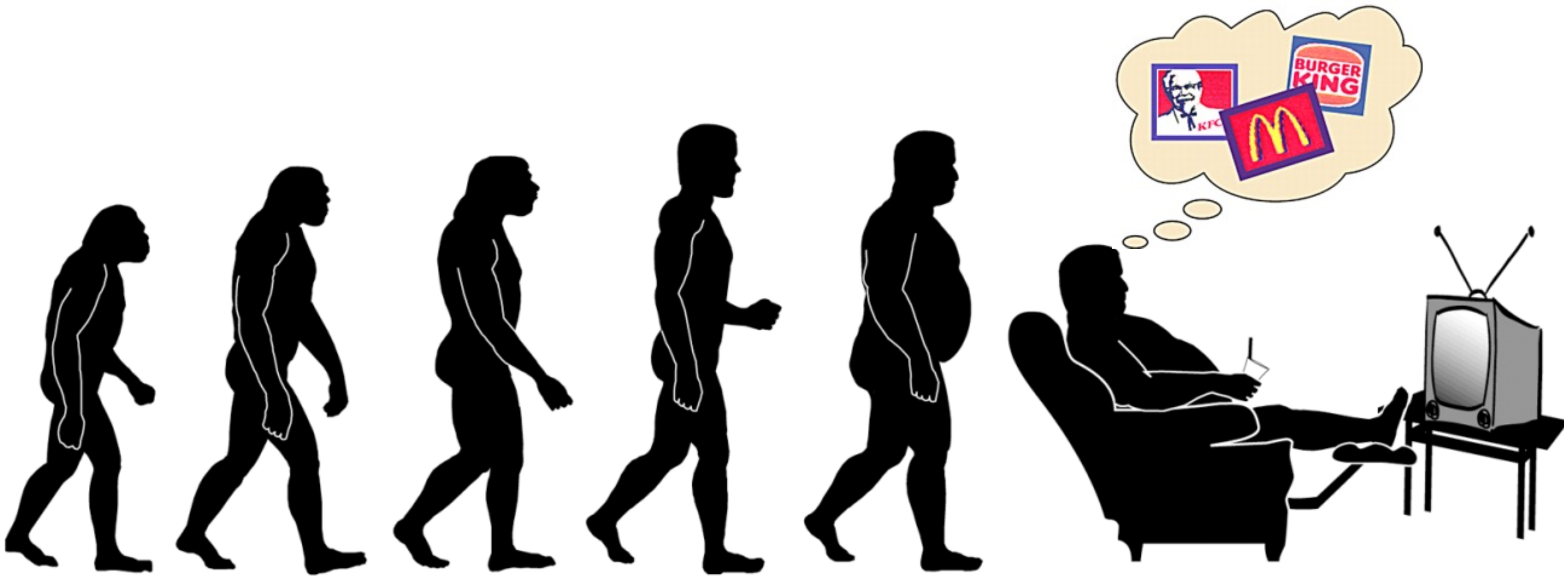
Assistant Professor
Molecular and Cellular Pathology
Department of Pathology

Metabolomics

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Knowledge that will change your world

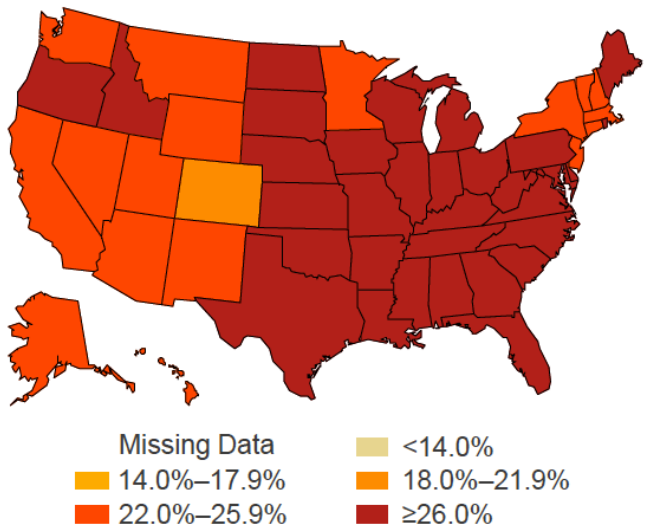
Defining the Problem



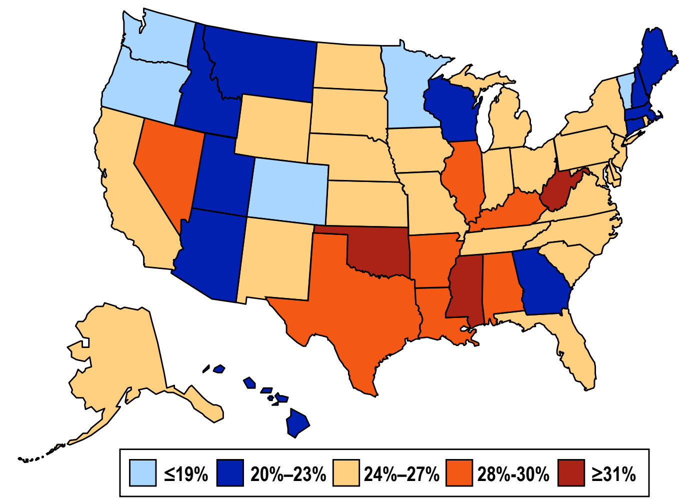
2.5 million years ⟵⟶ 50 years

From: Roger Unger - UTSW

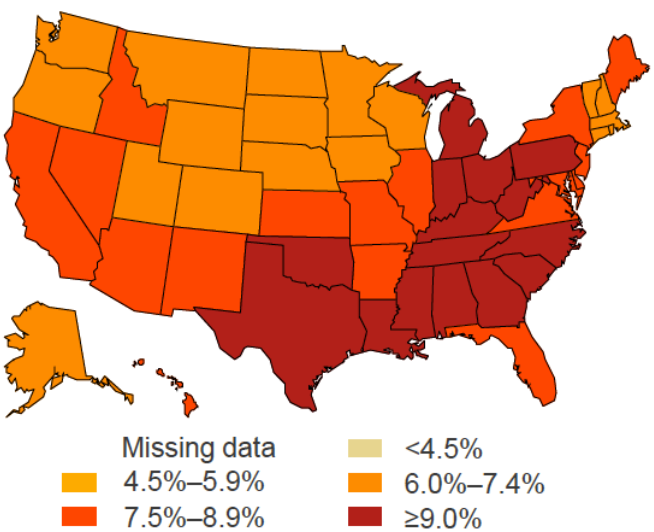
2010 – Obesity



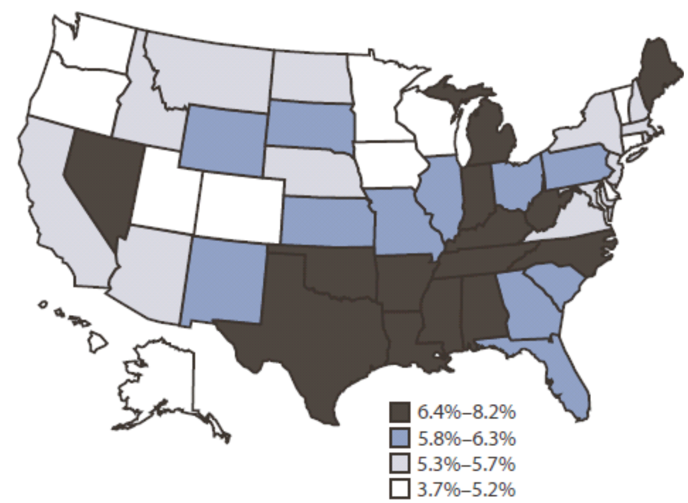
2010 – Physical Inactivity



2010 – Diabetes



2010 – Heart Disease



www.cdc.gov/diabetes/statistics and www.cdc.gov/mmwr

Cardiac Metabolic Substrate Utilization

Table 2. Brief Overview of Myocardial Metabolism in Physiological and Pathophysiological Conditions

	MV_{O_2}	Glucose Metabolism	Fatty Acid Metabolism
Aging	↑	↑	↓
Female sex	↑	↓	↑
Obesity	↑	—	↑
Diabetes, types 1 and 2	—↑	↓	↑
Hypertension: LV hypertrophy	—	↑	↓
Dilated cardiomyopathy	—	↑	↓
Ischemia	↓	↑	↓

Peterson and Gropler **2010** *Circ Cardiovasc Imaging* 3:211

Cardiac Metabolic Substrate Utilization

Studies on Myocardial Metabolism*

IV. Myocardial Metabolism in Diabetes

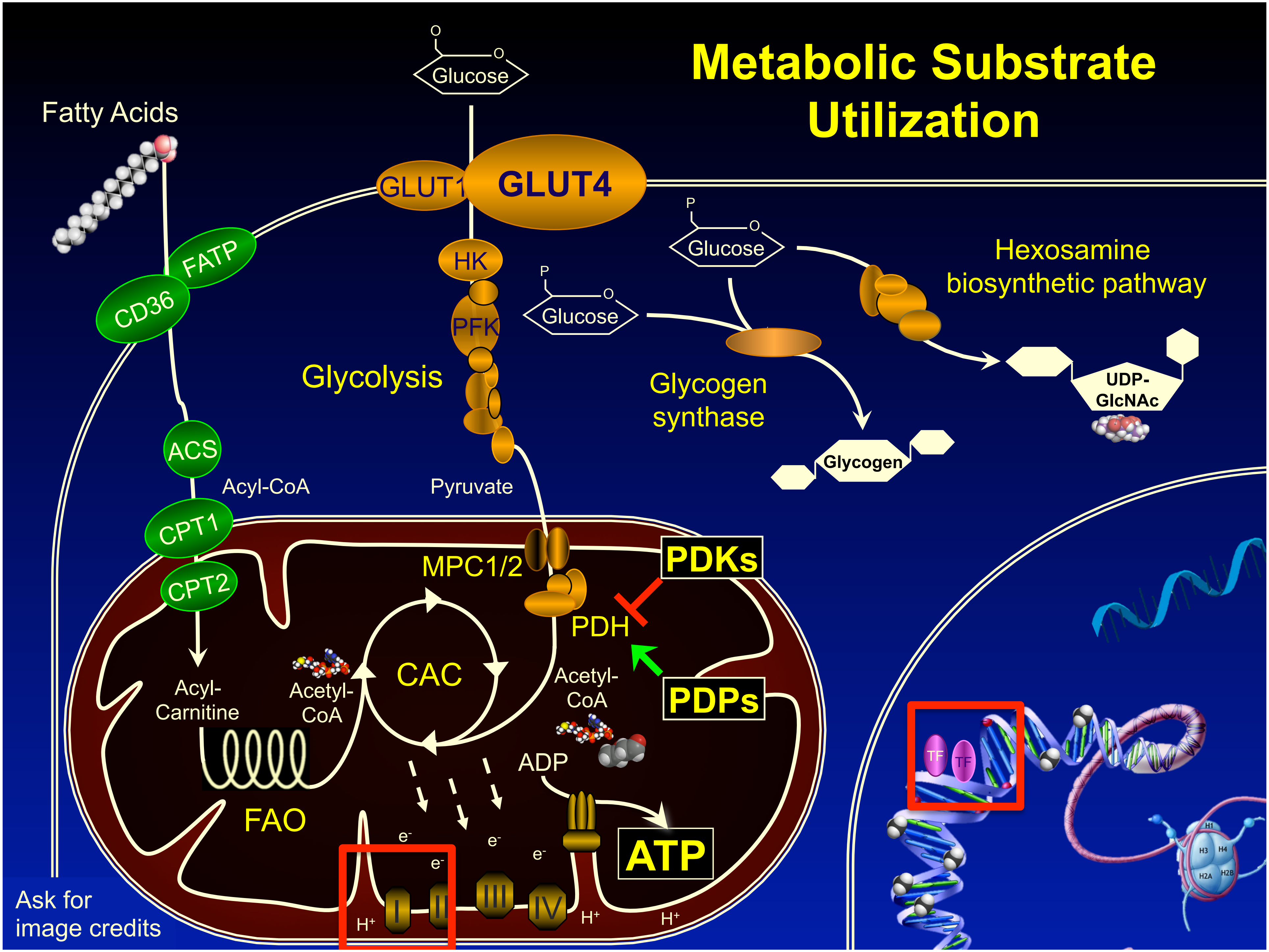
I. Ungar, M.D., M. Gilbert, M.D., A. Siegel, M.S., J. M. Blain, M.D. *and* R. J. Bing, M.D.

* From the Department of Medicine and Physiology, University of Alabama Medical Center, Birmingham, Ala.
Work supported by the U. S. Public Health Service Grant No. H-1129(CS), The Life Insurance Medical Research Fund and the American Heart Association.

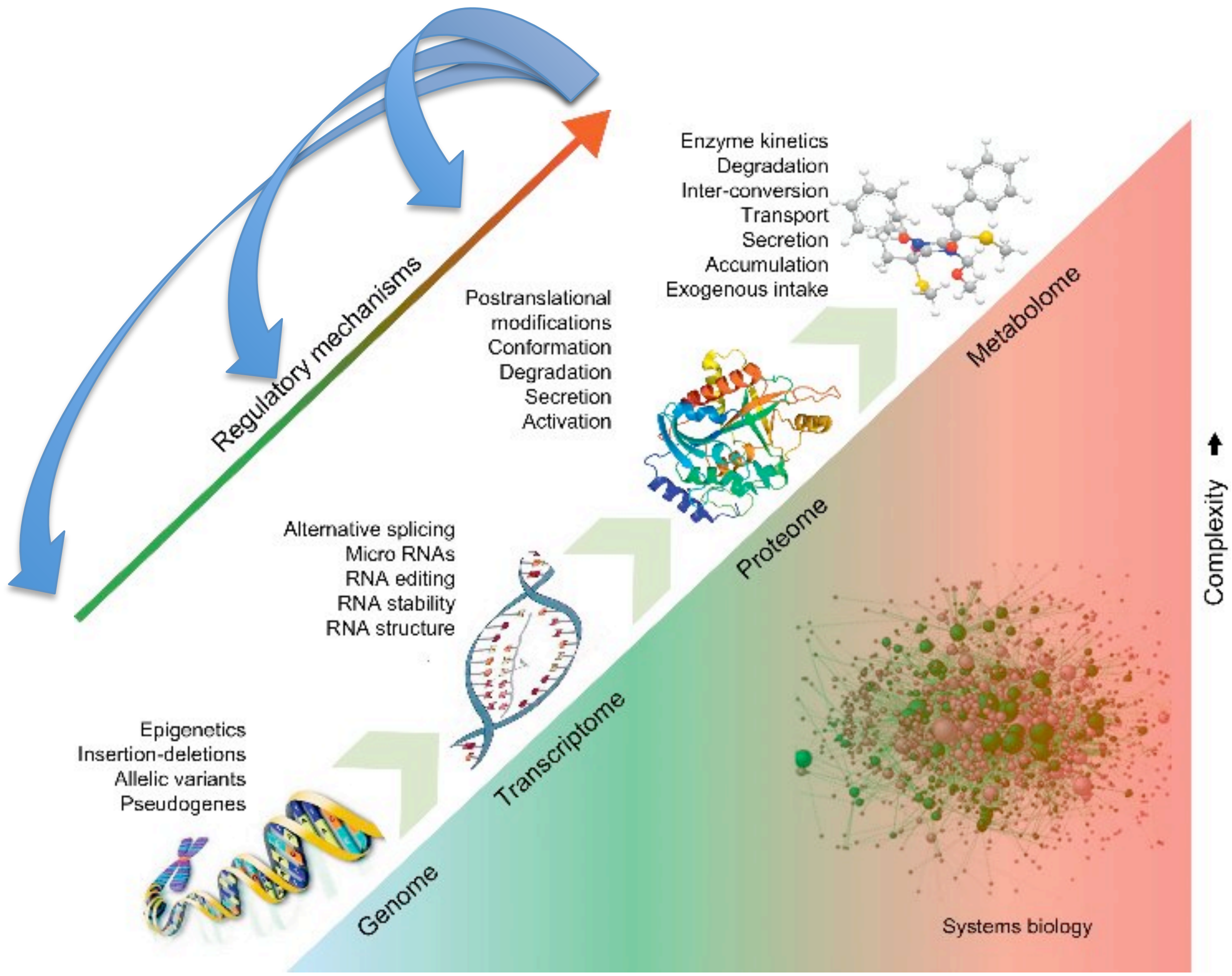
UAB founded in 1969

amino acids by the heart in both species. Myocardial glucose consumption is reduced in dog and man relative to the elevation in blood glucose concentration. The myocardial usage of ketones is slightly increased in diabetic hearts of patients and significantly elevated in the dog. The main difference concerns the utilization of fatty acids; this is significantly increased in the human heart but is unchanged in the dog. Whether this is due to a species difference or to differences in type and severity

Ungar … Bing 1955 *Am J Med* 18(3):385

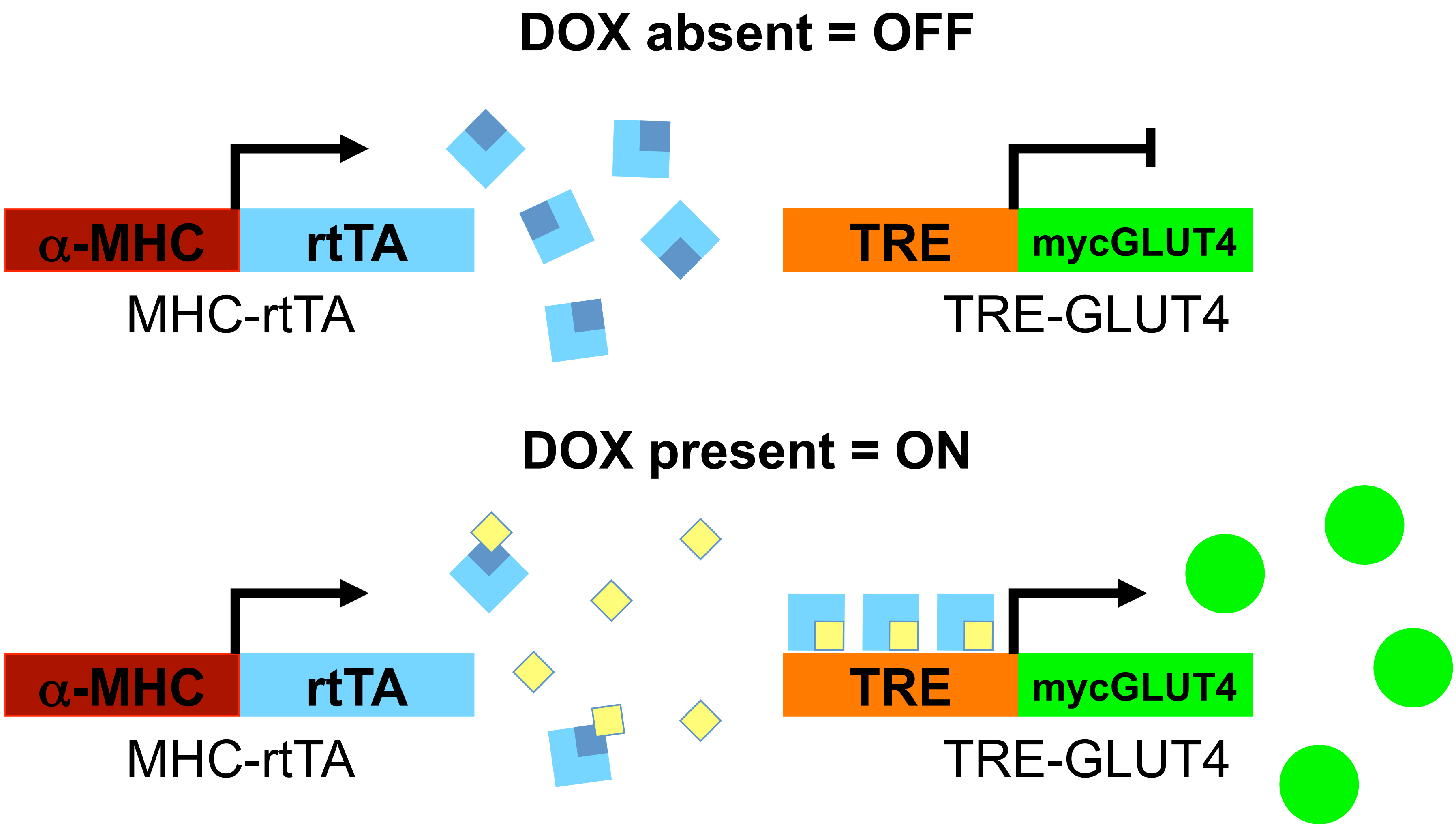

Metabolic Substrate Utilization
Fatty Acids
Glucose
GLUT1
GLUT4
FATP
CD36
HK
PFK
Glycolysis
Glucose
Glucose
Hexosamine biosynthetic pathway
UDP-GlcNAc
Glycogen synthase
Glycogen
ACS
Acyl-CoA
Pyruvate
CPT1
CPT2
MPC1/2
PDKs
PDH
PDPs
CAC
Acyl-Carnitine
Acetyl-CoA
Acetyl-CoA
FAO
ADP
ATP
e-
e-
e-
e-
I
II
III
IV
H+
H+
H+
TF
TF
H1
H3
H4
H2A
H2B
Ask for image credits

Defining the Mechanism



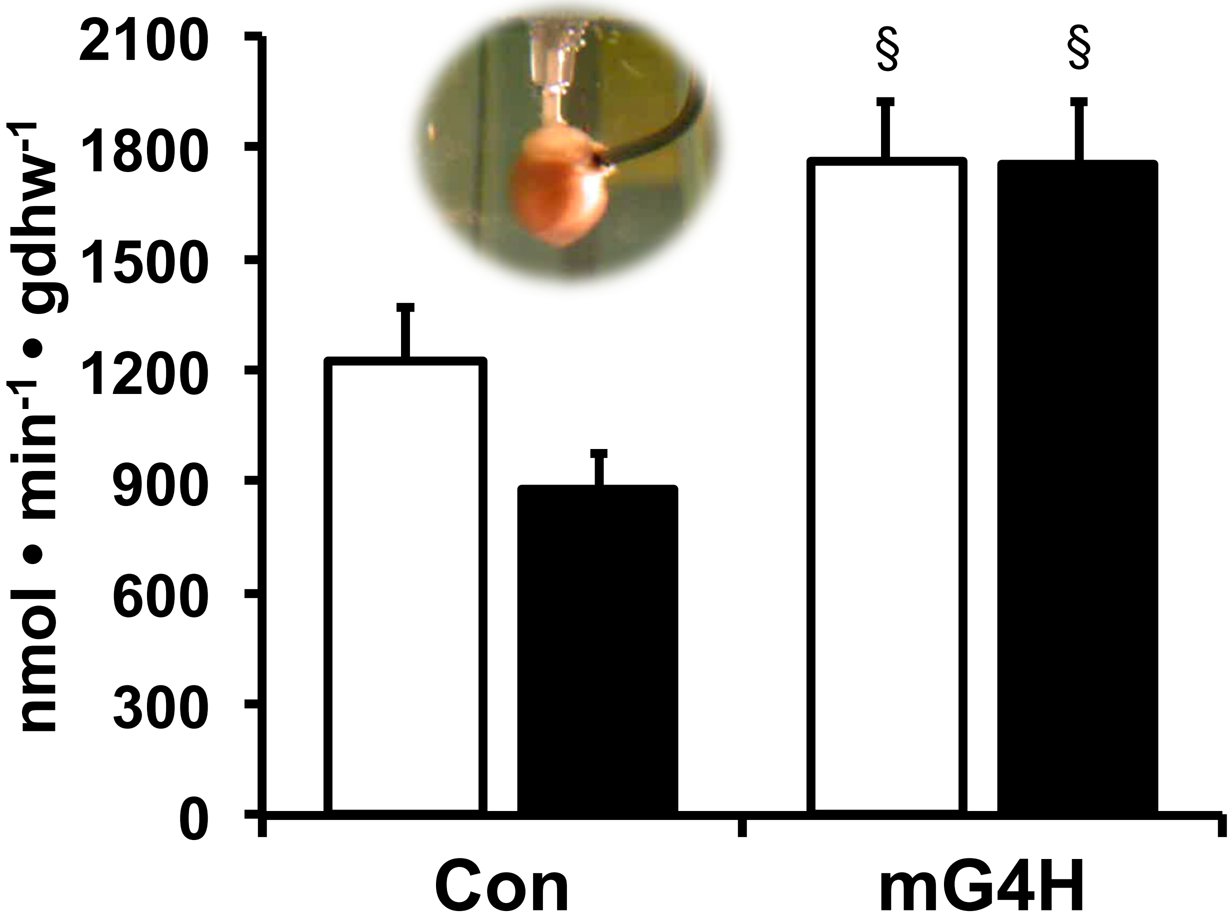
Barallobre-Barreiro … Mayr **2013** *Rev Esp Cardiol* 66:657

Model Development



GLUT4 Induction Increases Glycolysis and Rescues Diabetic Cardiac Glycolytic Defects

Isolated Working Hearts Glycolysis

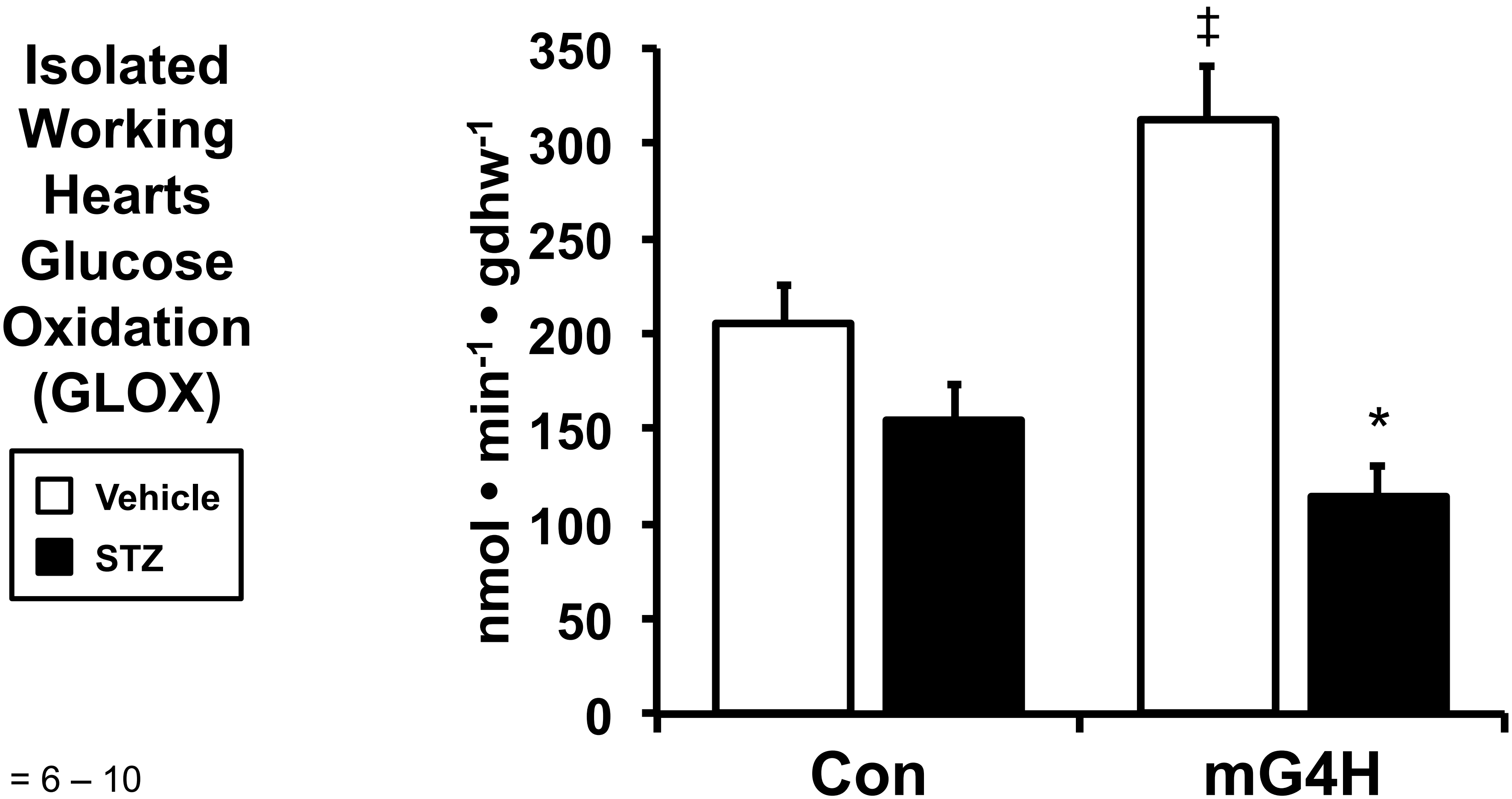


Vehicle
STZ

n = 6 – 10
§ $P < 0.01$ vs. Con

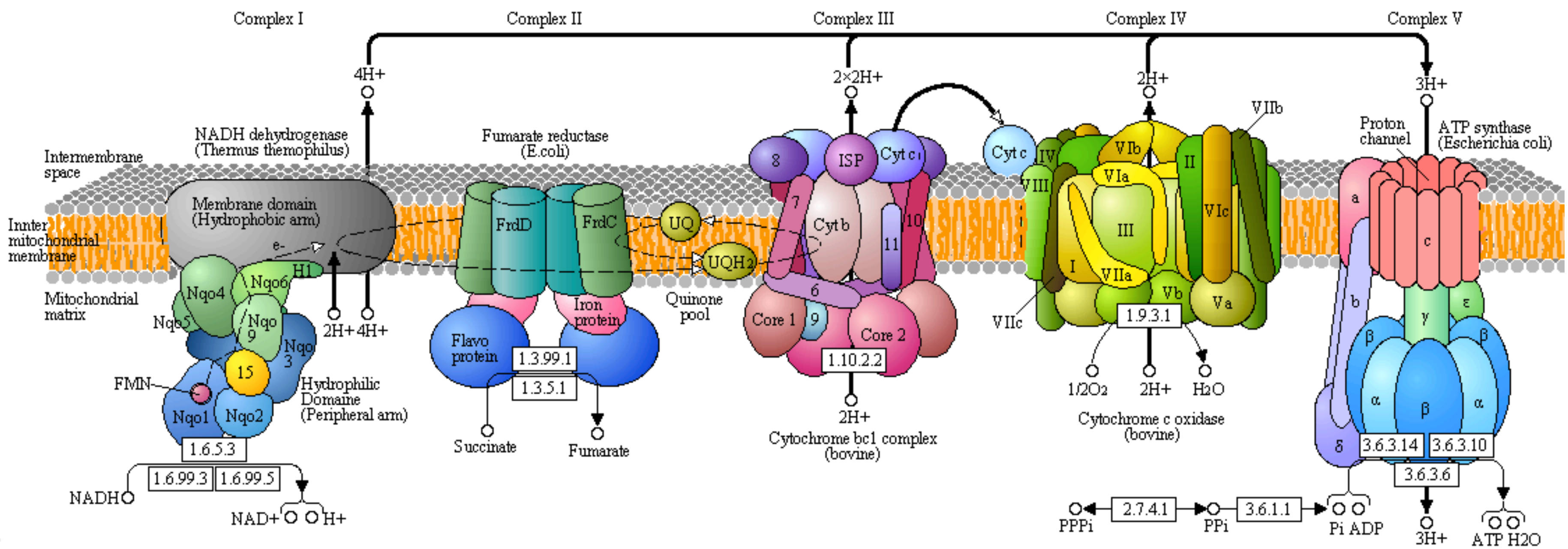
GLUT4 Induction Increases GLOX but Accelerates Diabetic Cardiac GLOX Defects

Isolated Working Hearts Glucose Oxidation (GLOX)



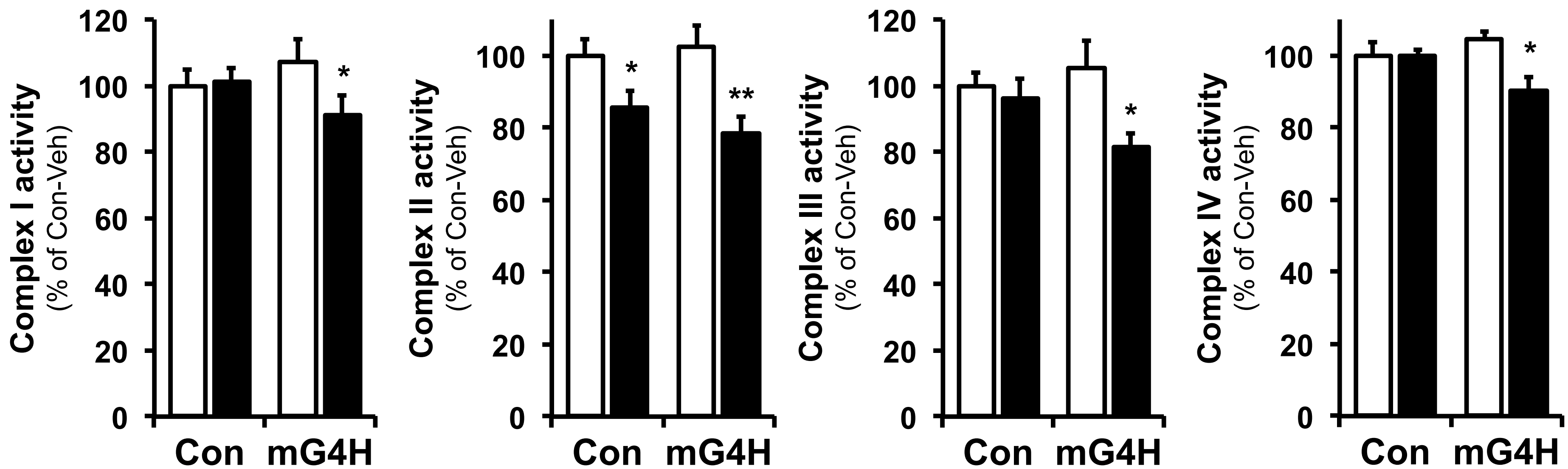
n = 6 – 10
§ P < 0.01 vs. Con

Oxidative Phosphorylation



www.genome.jp/kegg/pathway.html

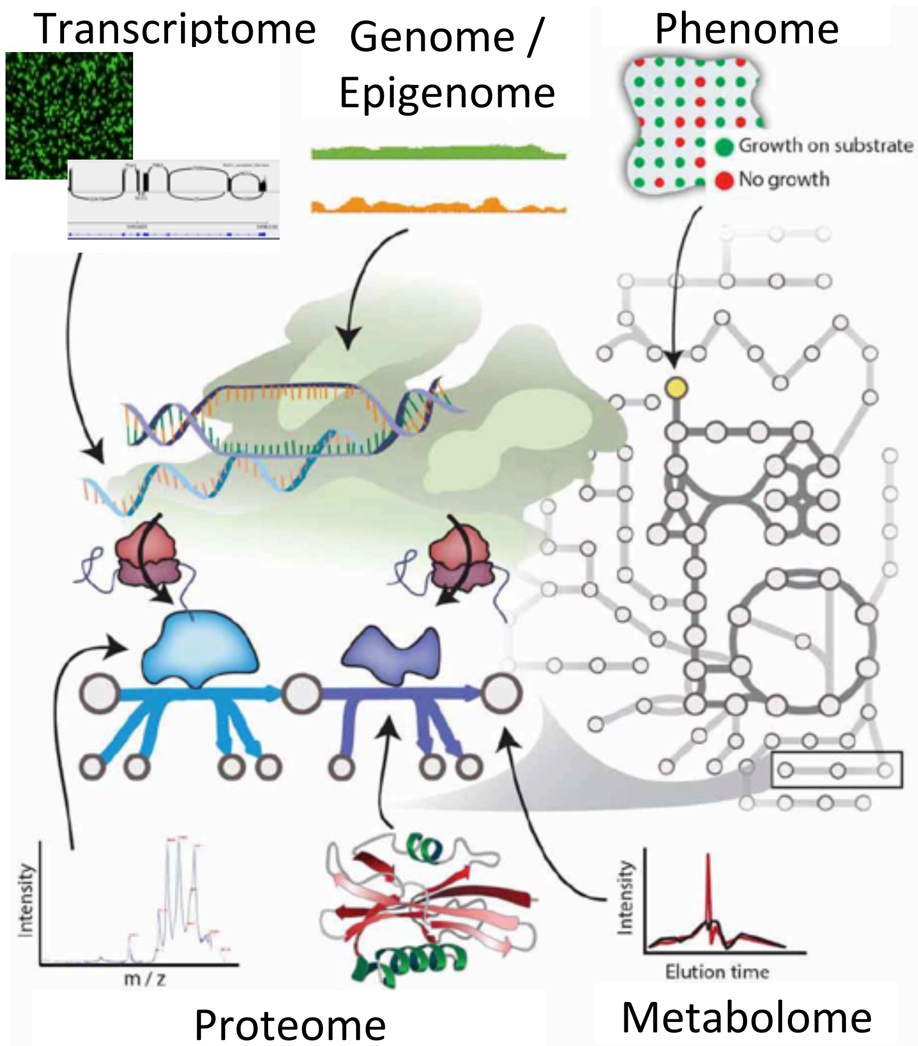
GLUT4 Induction Accelerates Development of Mitochondrial Dysfunction



n = 3 – 4
* $P < 0.05$

Oleh Khalimonchuk
Wende … Abel *in prep*

Systems Biology of the Diabetic Heart



Phenome
Obesity, diabetes, heart failure, BHI, etc.

Transcriptome
Northerns, qPCR, microarray
RNA-seq, miR, lncRNA, etc.

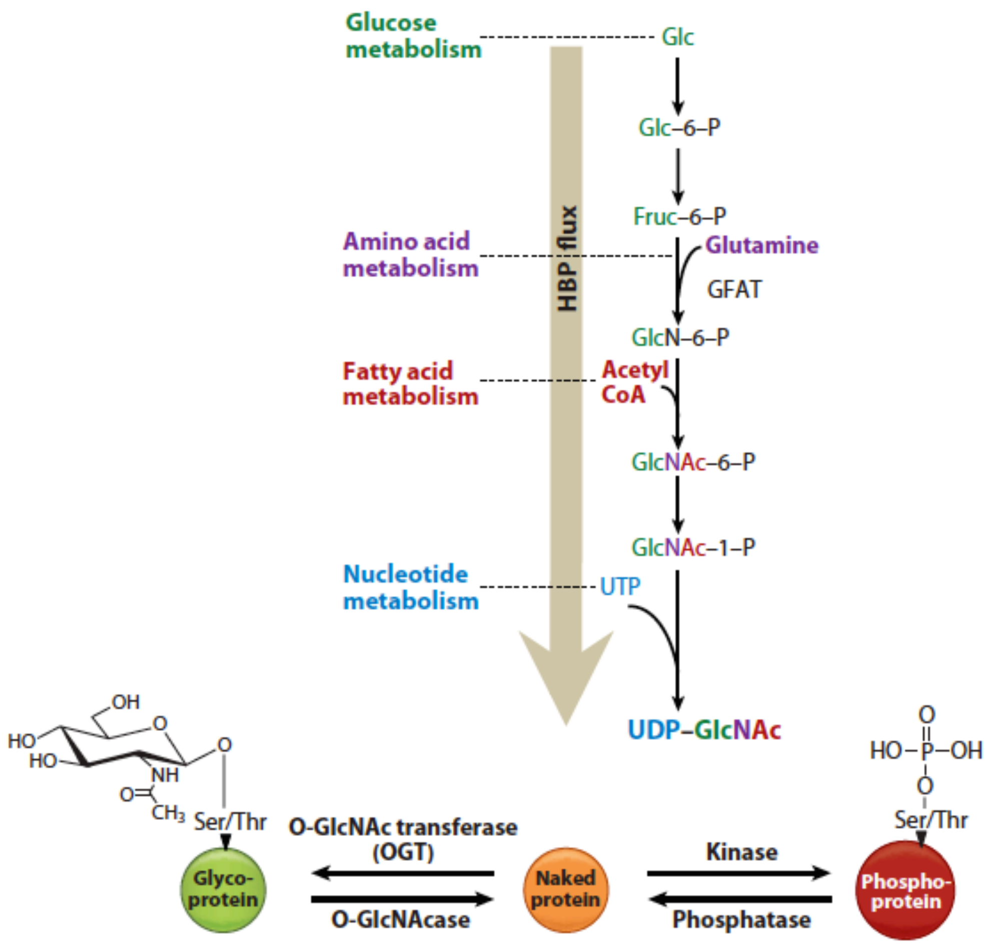
Proteome
Mass spec, western blot, Co-IP, IHC, PTMs, etc.

Metabolome
Glucometer, ELISA, GC-MS, HPLC, NMR, fluxomics, etc.

Genome / Epigenome
Southerns, sequencing, GenBank, ENCODE, ChIP-seq, bsDNA-seq, etc.

Adapted from Lewis and Abdel-Haleem **2013** *Front Physiol* 4:237

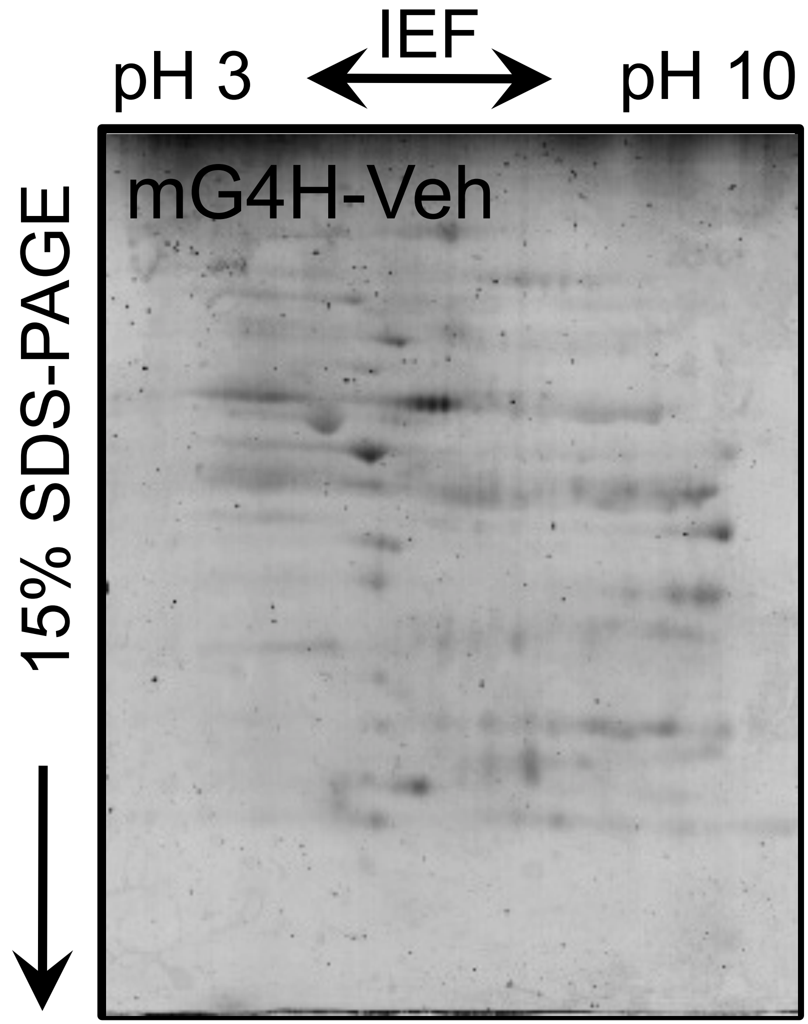
Metabolism, Bringing the System Together



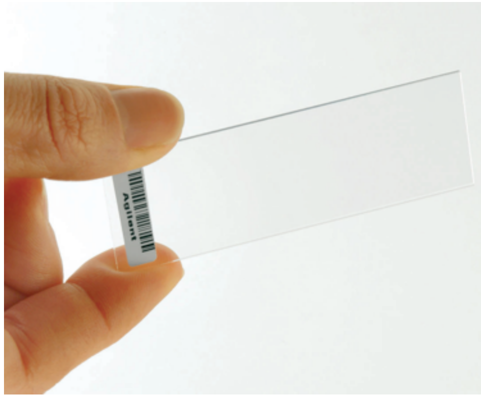
Hart … Lagerlof 2011 *Annu Rev Biochem* 80:825

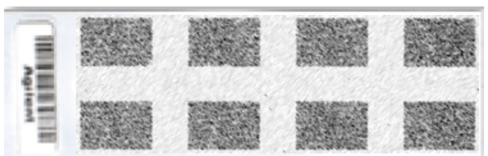
Metabolite Modification of the Proteome

Isolated Mitochondria
2D-PAGE
Pro-Q
Emerald

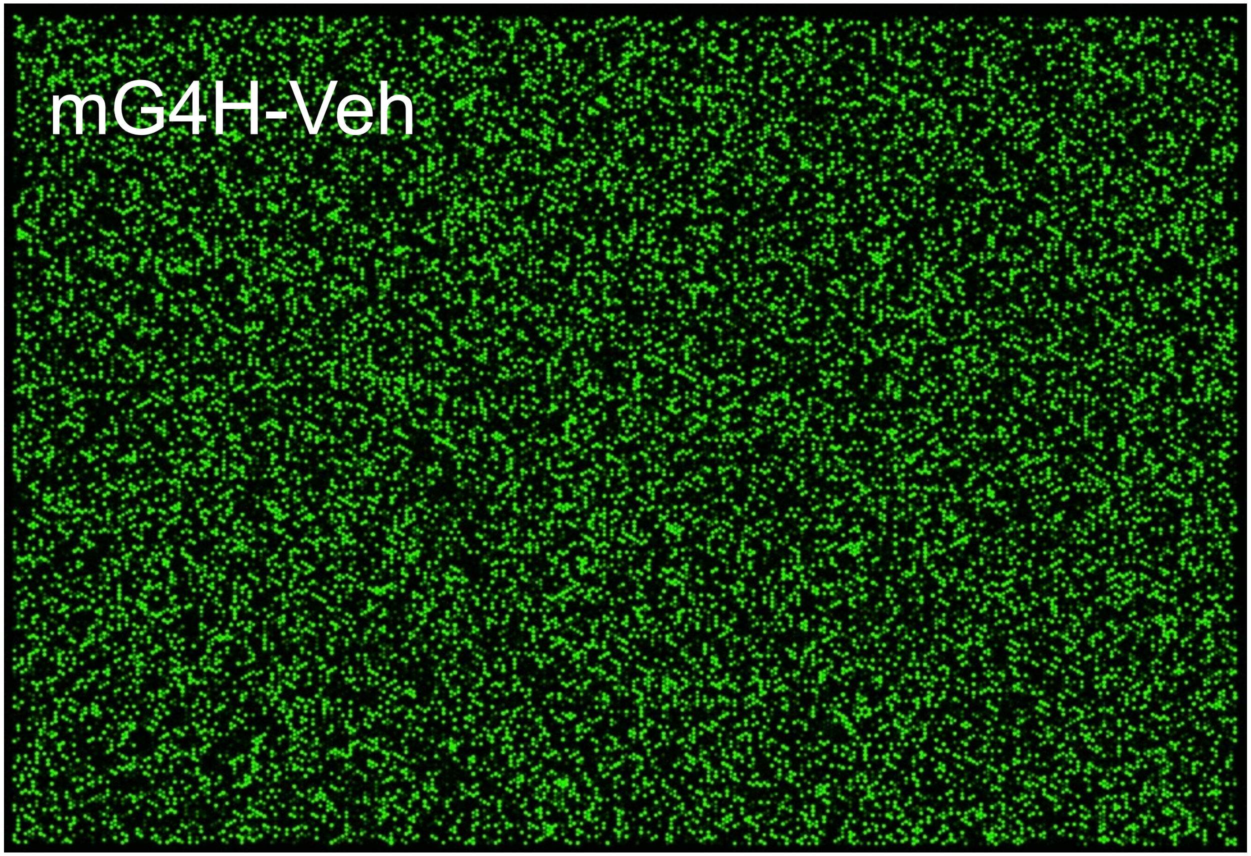


Metabolite Modification of the Transcriptome





181.9 MB



Metabolomics

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Knowledge that will change your world

pathway analysis of Microarray

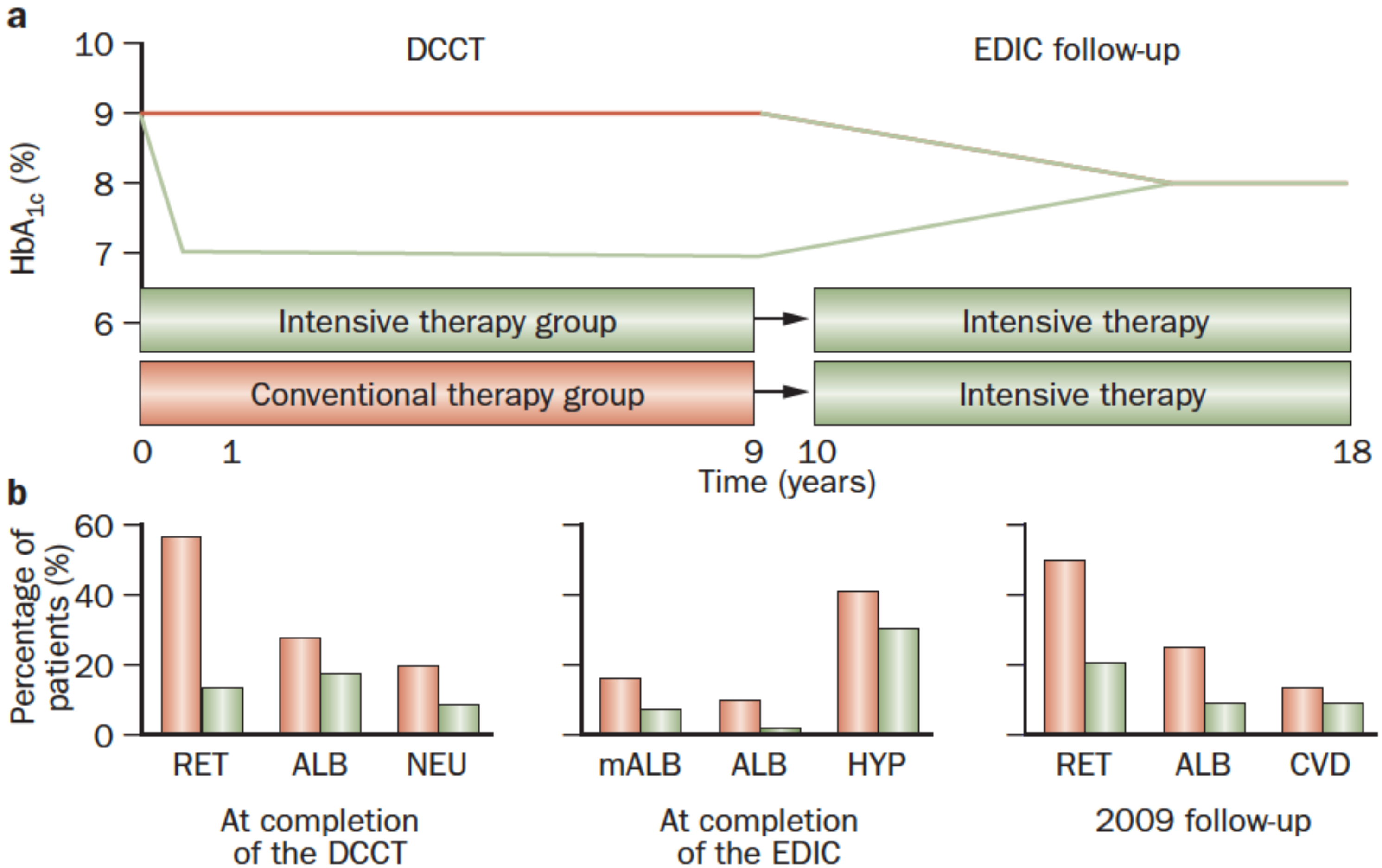
Microarray
2-way
ANOVA

Pathway	List	Genes	z-score
Metabolic pathways	**194**	**1085**	**5.42**
Focal adhesion	35	190	2.30
Insulin signaling pathway	**27**	**135**	**2.49**
Axon guidance	25	127	2.30
PPAR signaling pathway	**22**	**76**	**4.20**
Chagas disease	21	102	2.33
Hematopoietic cell lineage	21	83	3.39
Peroxisome	21	78	3.72
Dilated cardiomyopathy	**20**	**86**	**2.88**
Hypetrophic cardiomyopathy	**20**	**83**	**3.06**
Arrhythmogenlc right ventrlcular cardiomyopathy	19	71	3.50
ECM-receptor interaction	19	79	2.97
Glycolysis / Gluconeogenesis	**19**	**68**	**3.72**
Pyrimldine metabolism	19	95	2.08
Valine, leucine and isoleucine degradation	18	47	5.21
Metabolism of xenobiotjcs by cytochrome P450	16	64	2.90
Leishmaniasis	15	64	2.53
Glutathione metabolism	14	53	2.95
p53 signaling pathway	14	66	2.02
Arginine and proline metabolism	13	52	2.61
Graft-versus-host disease	13	49	2.85
Lysine degradation	13	41	3.60
Type II diabetes mellitus	**13**	**47**	**3.03**
Fatty acid metabolism	**12**	**46**	**2.68**
Type I diabetes mellitus	**12**	**53**	**2.12**

From Human to Mouse and Back Again…

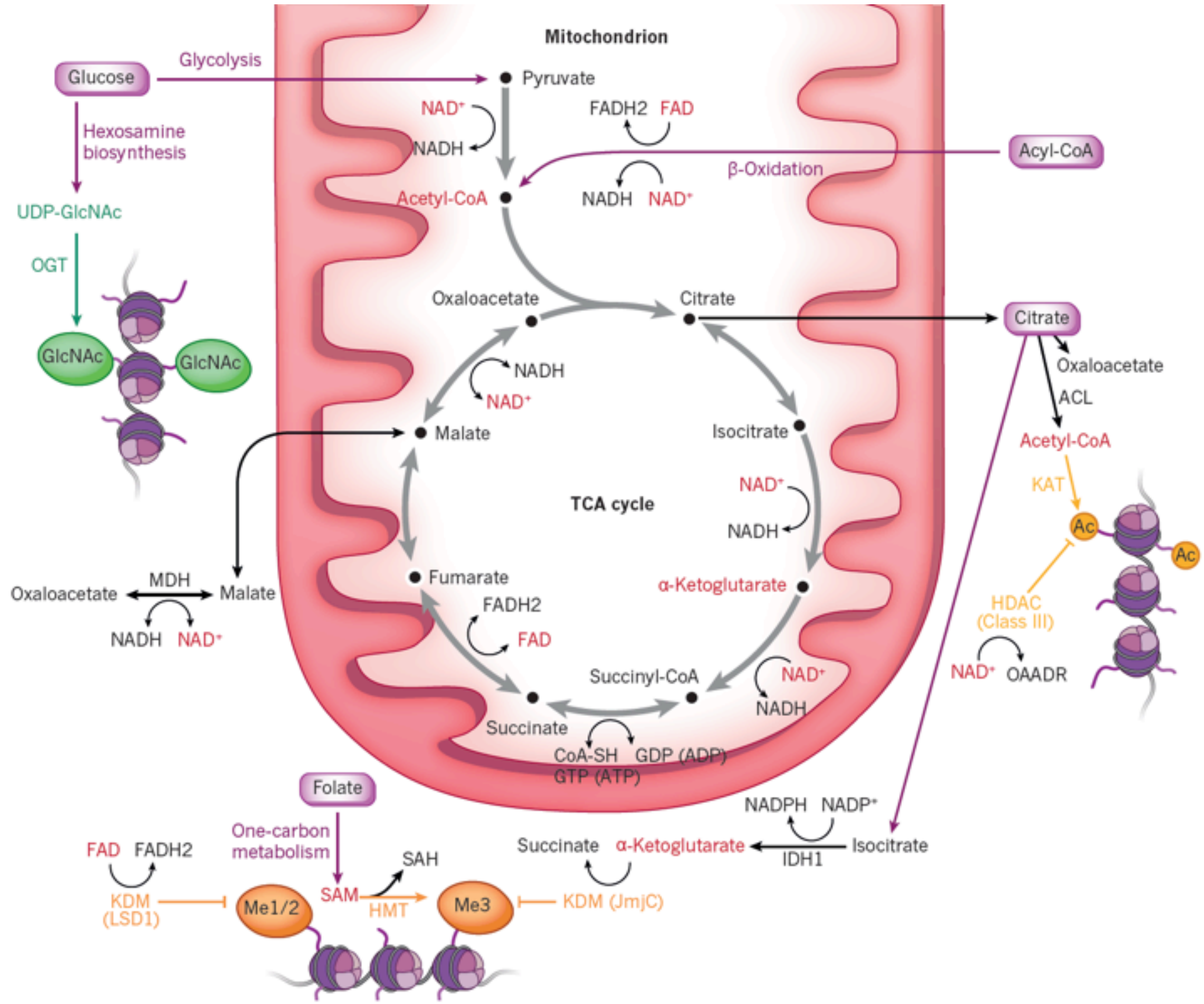
Broad Institute Communications

Epigenetics - Memory
EDIC: Epidemiology of Diabetes Interventions Trial



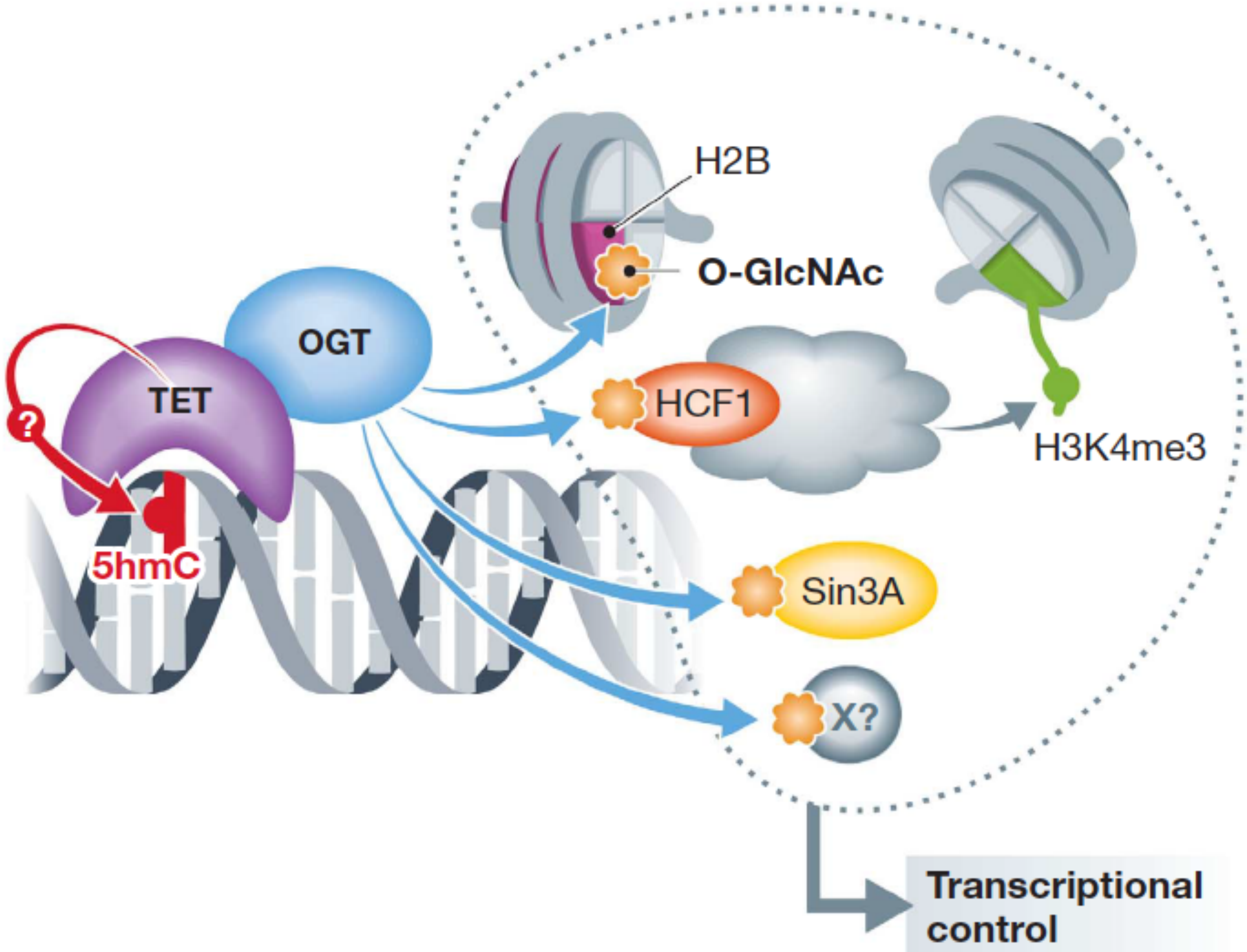
Pirola … El-Osta 2010 Nat Rev Endocrinol 6(12):665

Metabolite Signaling to Epigenetics



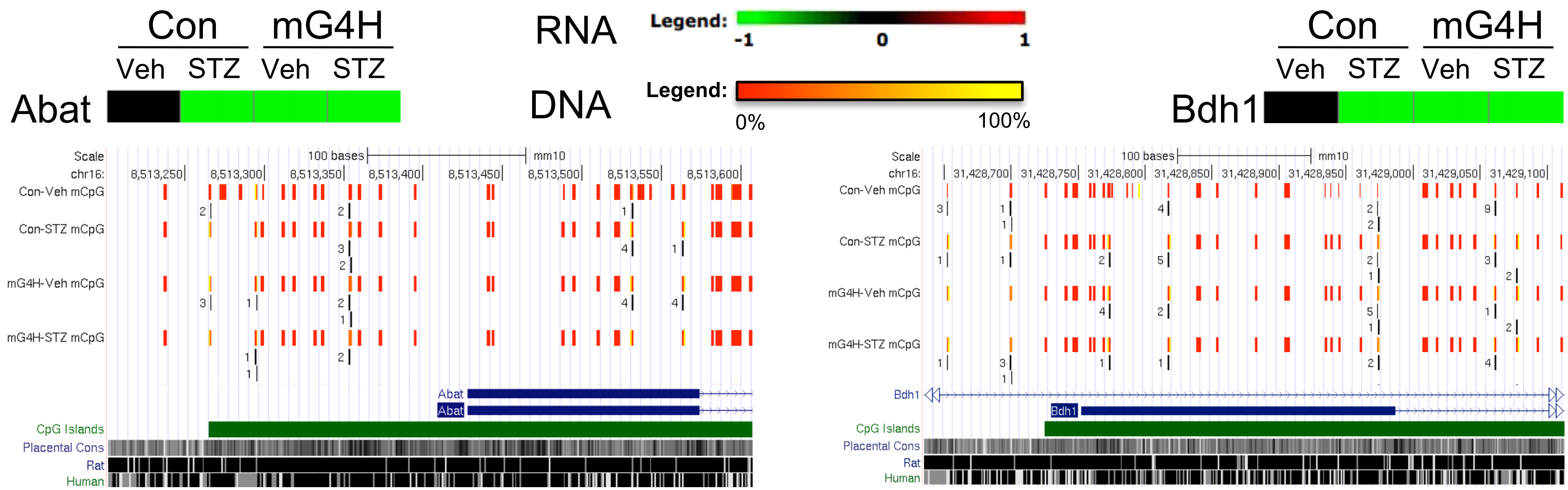
Gut and Verdin 2013 Nature 502:489

How does GlcNAc fit in?



Mariappa … Aalten **2013** *EMBO J* 32:612

Metabolite Modification of the Methylome



Human/Mouse Comparisons

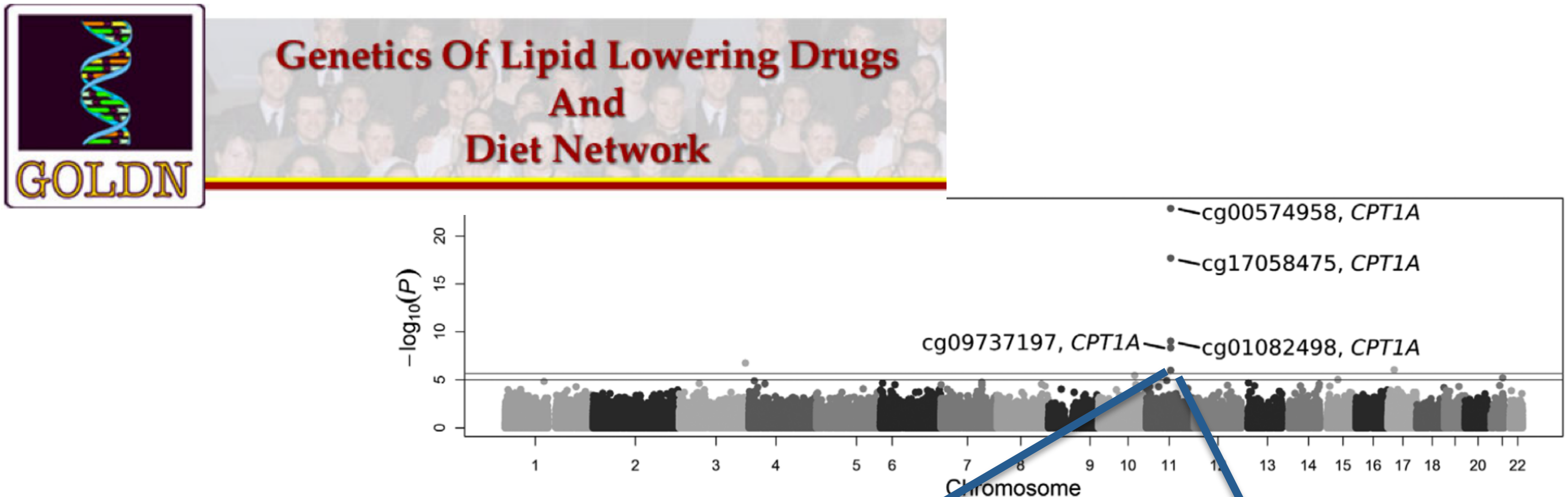
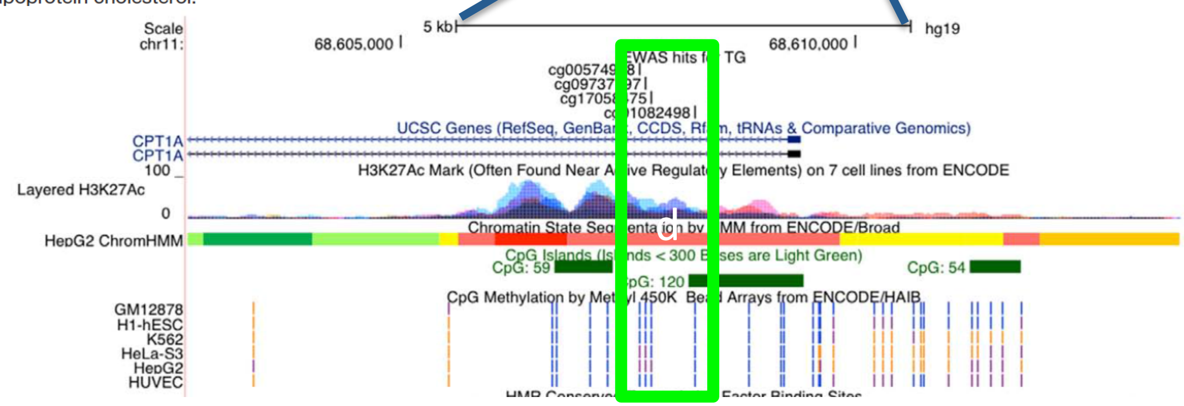


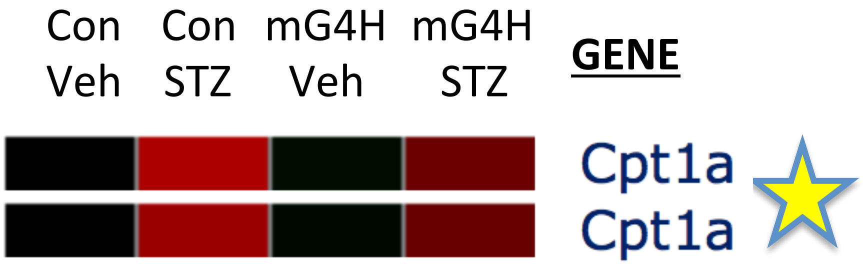
Figure 2. Epigenome-wide association Manhattan plot for VLDL-C in the discovery dataset (n=991). VLDL-C indicates very-low-density lipoprotein cholesterol.



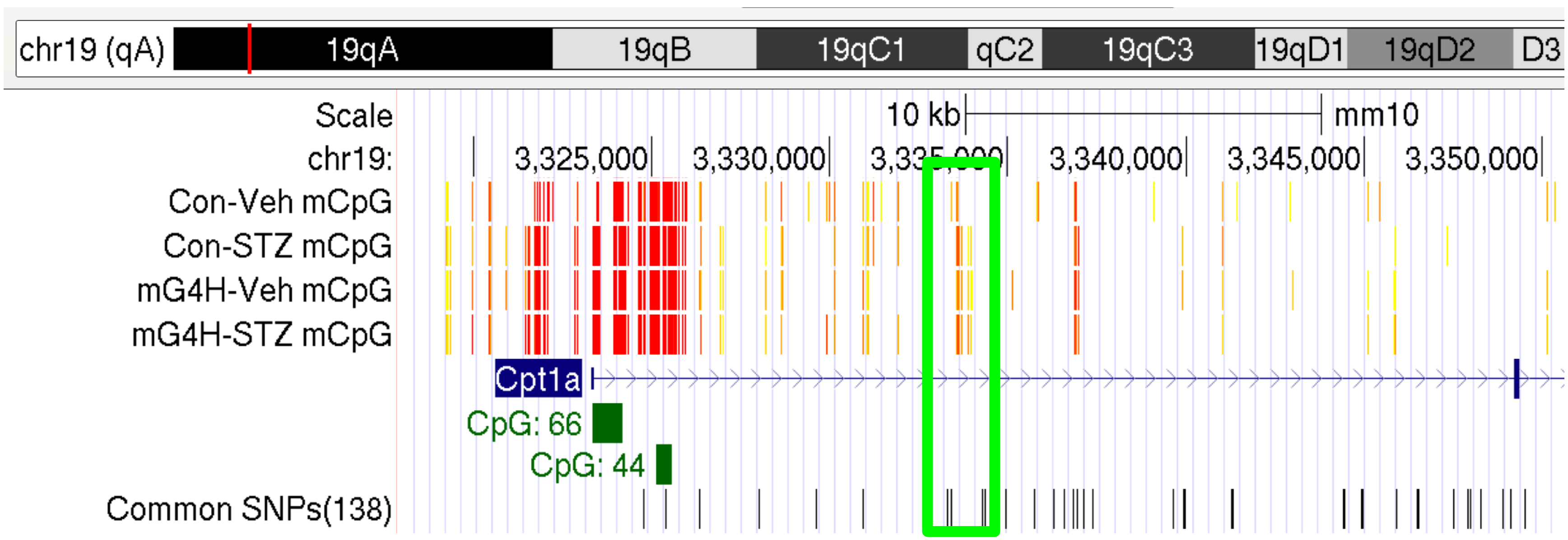
Irvin … Arnett 2014 Circulation 130:565

Human/Mouse Comparisons

Mouse
Gene Expression

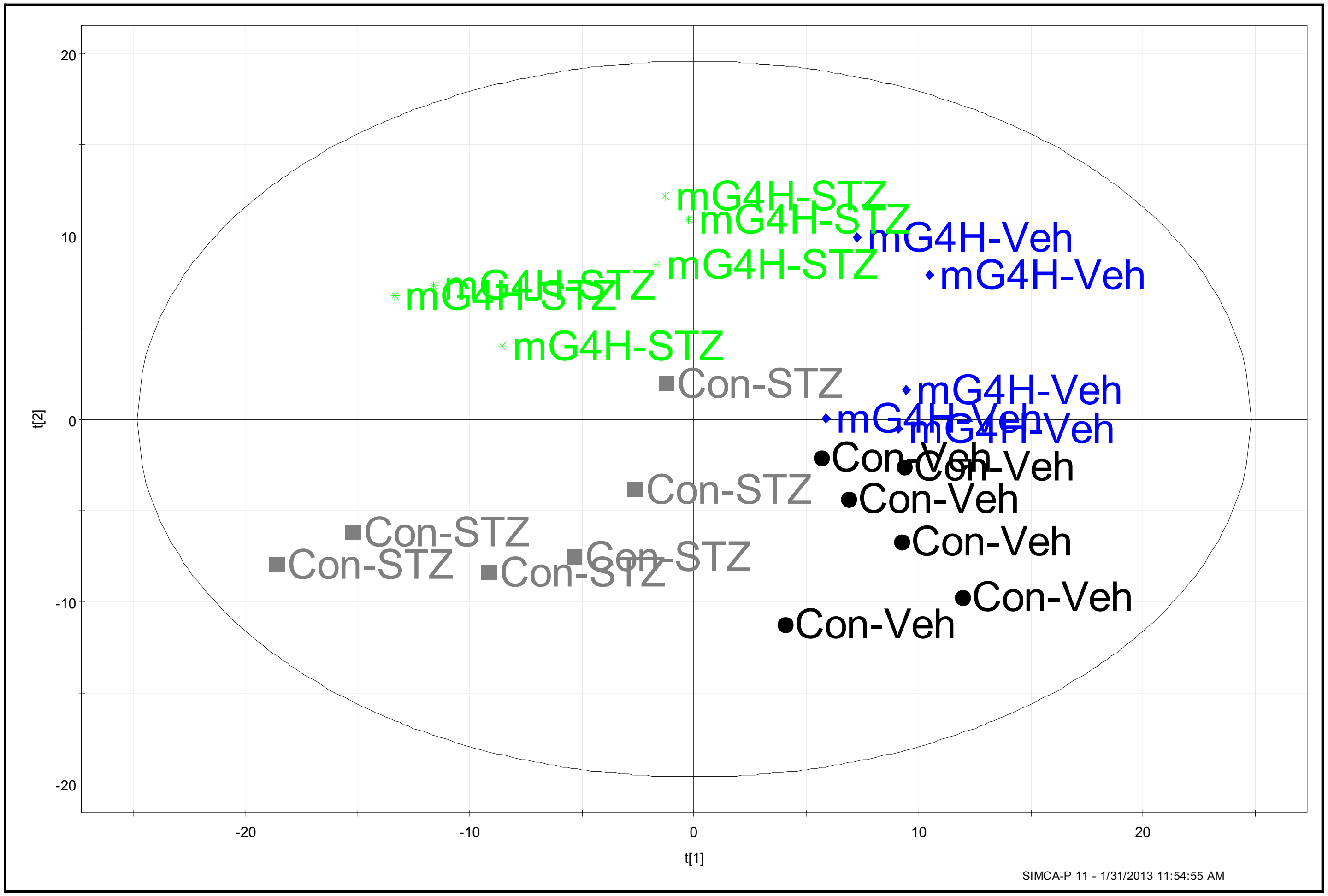


Mouse
DNA Methylation

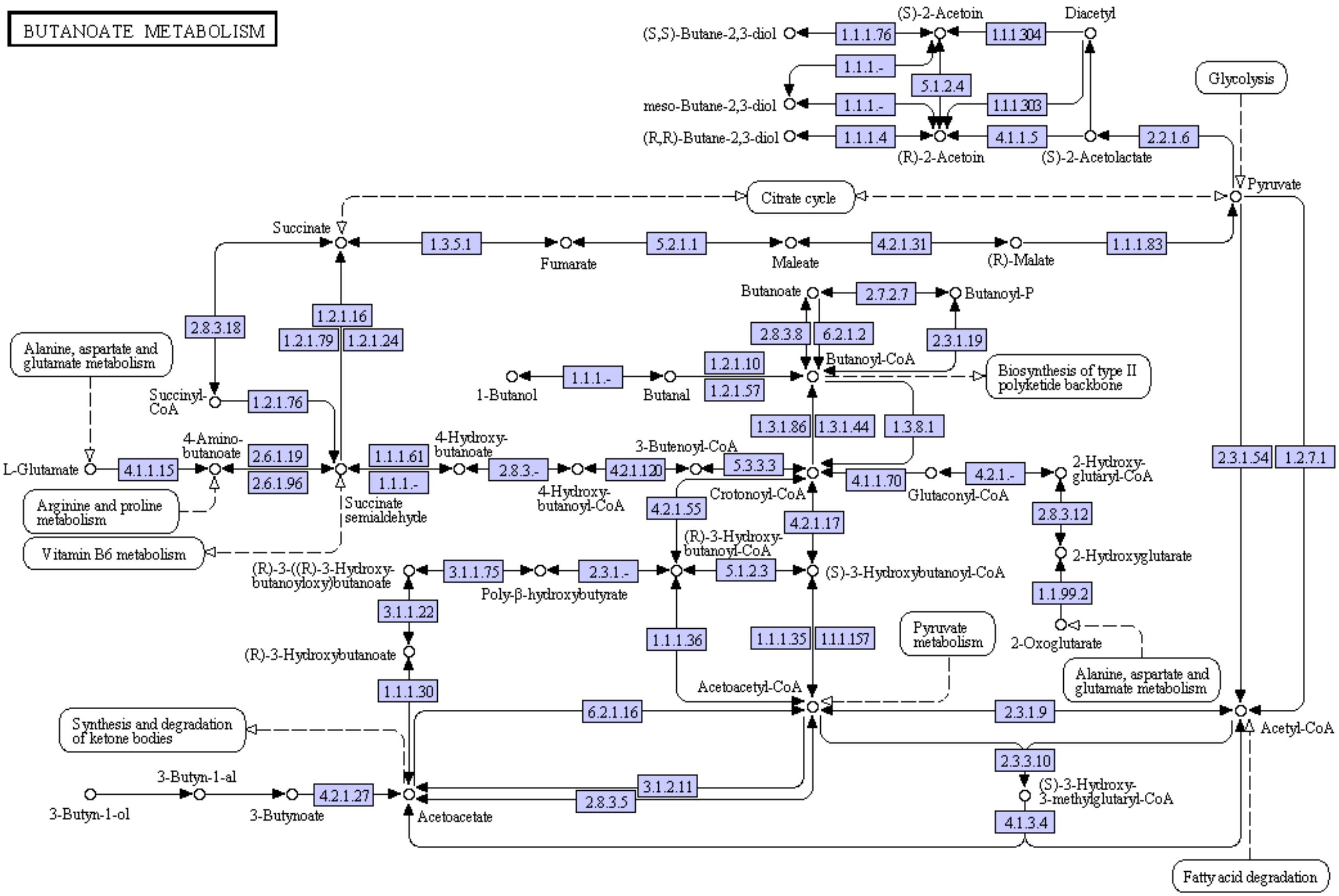


Wende, unpublished

Metabolite Modification of the Metabolome



Metabolite Modification of the Metabolome



Acknowledgements

Wende Lab

Manoja Brahma – Postdoc
Mark C. McCrory – Manager
Brenna G. Nye – Undergrad
Mark Pepin – MSTP
Lamario J Williams – Undergrad

E. Dale Abel – Utah to Iowa

John C. Schell – MD/PhD student
Joseph Tuinei – Industry

Hansjörg Schwertz – GU, Germany

UAB Collaborators

Steve Barnes – Metabolomics
John C. Chatham – GlcNAc
David Crossman – Genomics/Informatics
Farah D. Lubin – Epigenetics

Zymo Research

Keith Booher – DNA methylation
Hunter Chung –Informatics

U of U Cores

James Cox – Metabolomics
Brett Milash – Genomics/Informatics
Krishna Parsawar – Proteomics

JDRF IMPROVING LIVES. CURING TYPE 1 DIABETES.
JDRF 51002608

UAB
Molecular & Cellular Pathology
Redox Biology
Diabetes Center
Cardiovascular Center

National Heart Lung and Blood Institute
People Science Health
R00 HL111322

Metabolomics

UAB THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Knowledge that will change your world