Metabolomics

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GBS724: Advanced Topics in Metabolomics

Metabolomics in Models of Cardiovascular Disease

Wednesday, March 9, 2016

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Assistant Professor
Division of Molecular and Cellular Pathology

JDRF IMPROVING LIVES. CURING TYPE 1 DIABETES.

NIH National Heart, Lung, and Blood Institute

ARW

Presenter Disclosure Information

Adam R. Wende, Ph.D.

Metabolomics in Models of Cardiovascular Disease

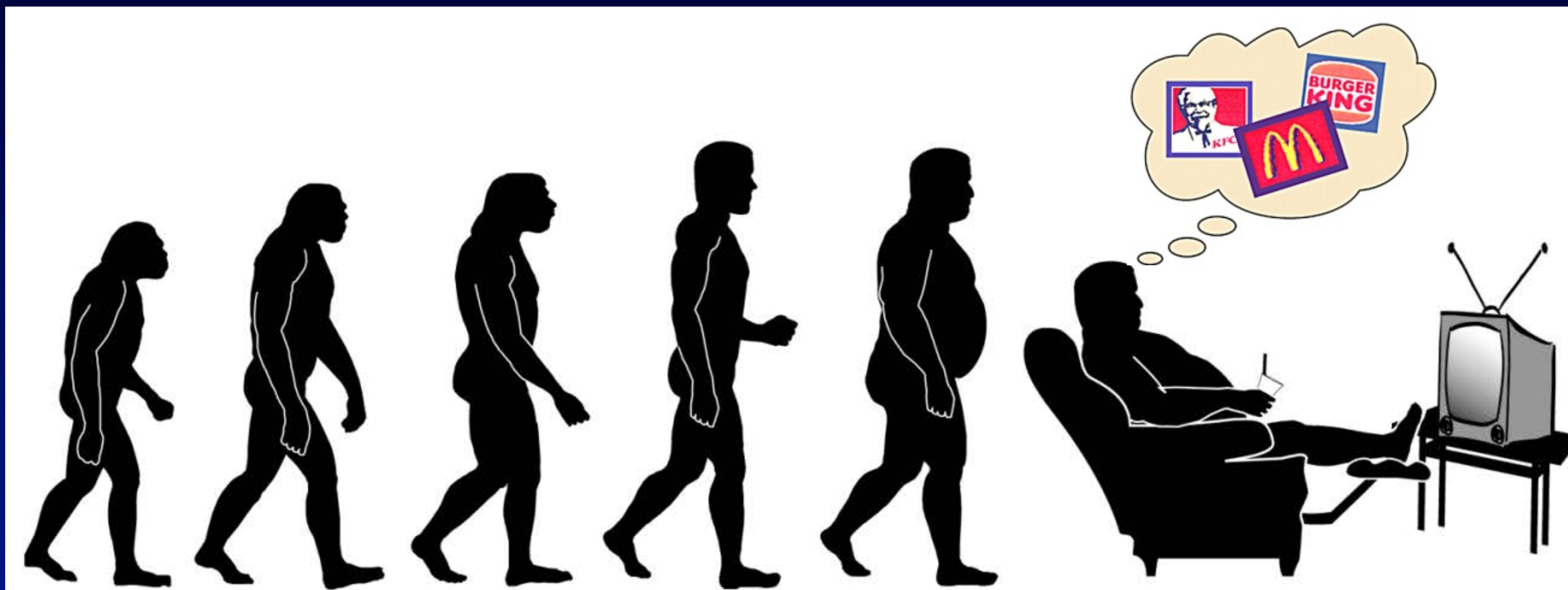
FINANCIAL DISCLOSURE:
None

UNLABELED/UNAPPROVED USES DISCLOSURE:
None

Outline

- Define the question and model to determine the connection between metabolism and diabetic heart disease.
- Identify the molecular mechanisms by which glucose directly alters molecular function using systems biology.
  - Transcriptomics
  - Proteomics
  - Metabolomics
  - Epigenetics (e.g. methylomics)

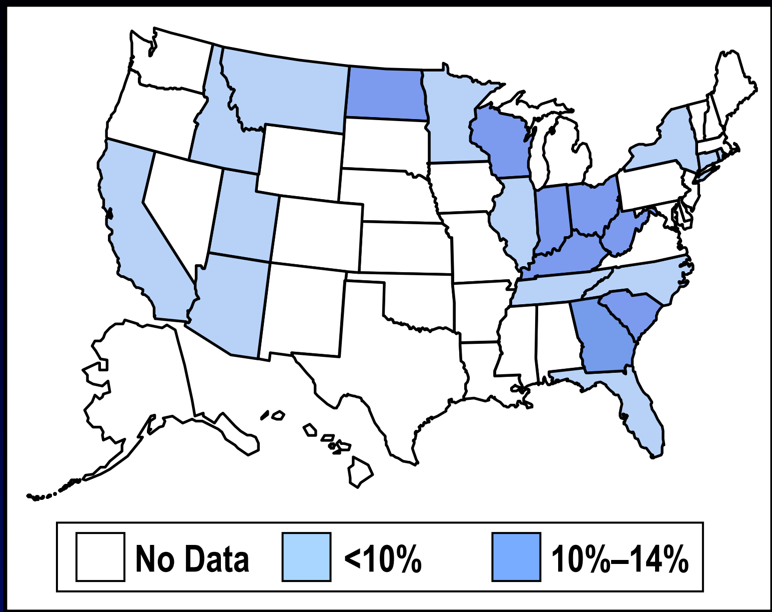
Obesity, Metabolic Syndrome, Diabetes, and Heart Failure



← 2.5 million years → ← 50 years →

From: Roger Unger - UTSW

1985 – Obesity



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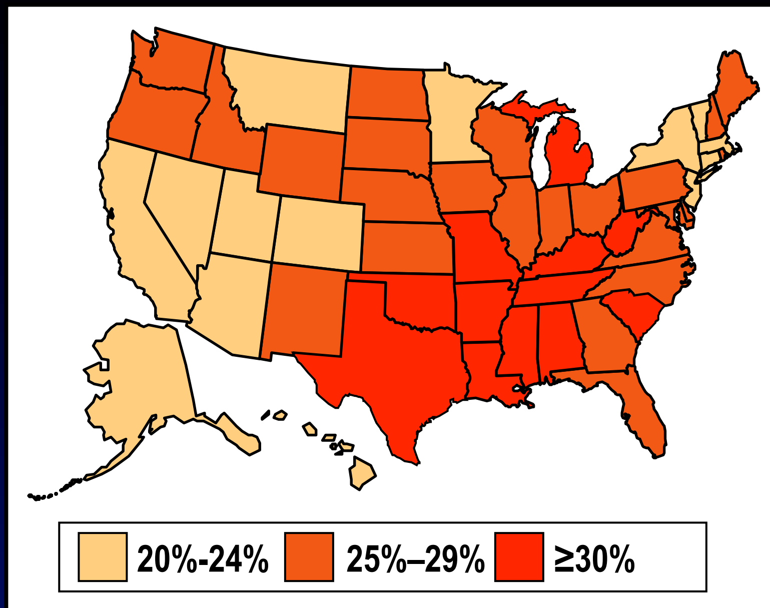
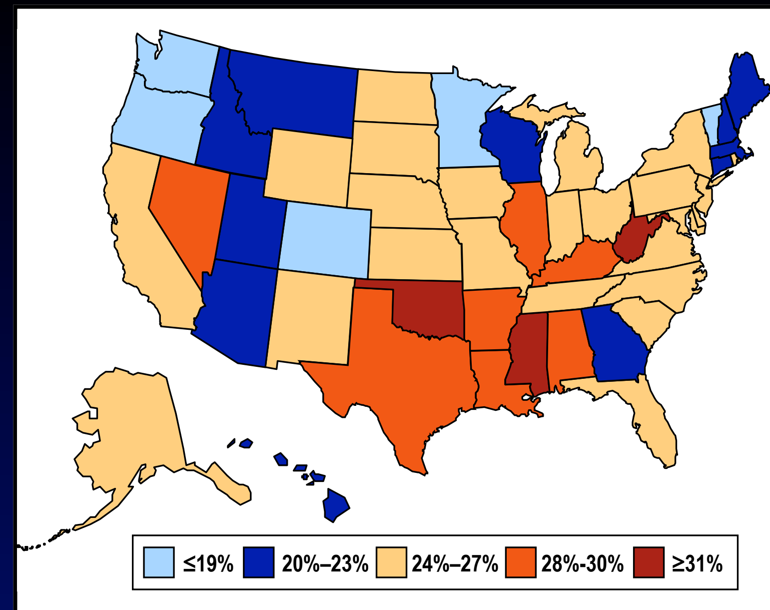
www.cdc.gov/diabetes/statistics and www.cdc.gov/mmwr

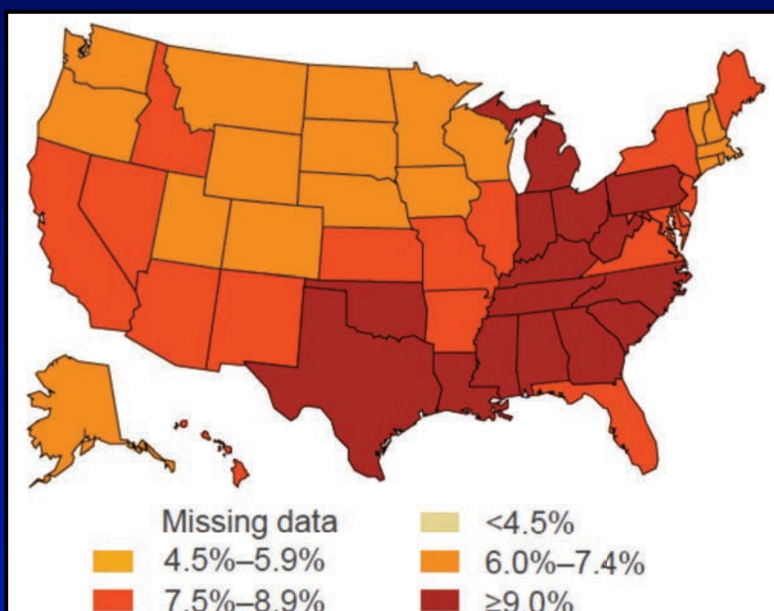
2010 – Obesity



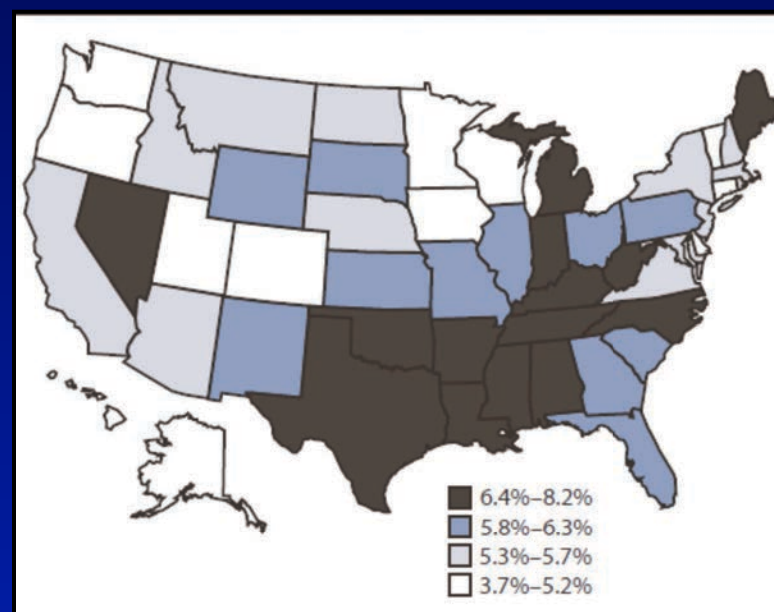
2010 – Physical Inactivity



2010 – Diabetes

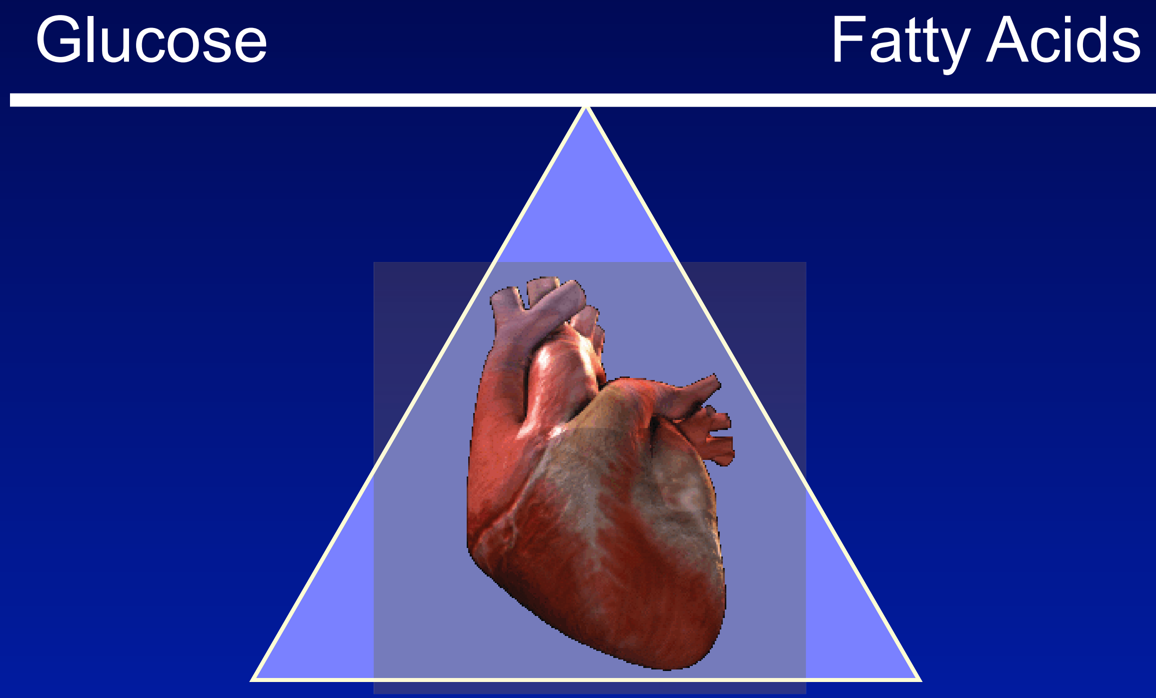


2010 – Heart Disease



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

Maintaining Cardiac Function Through Metabolic Substrate Balance



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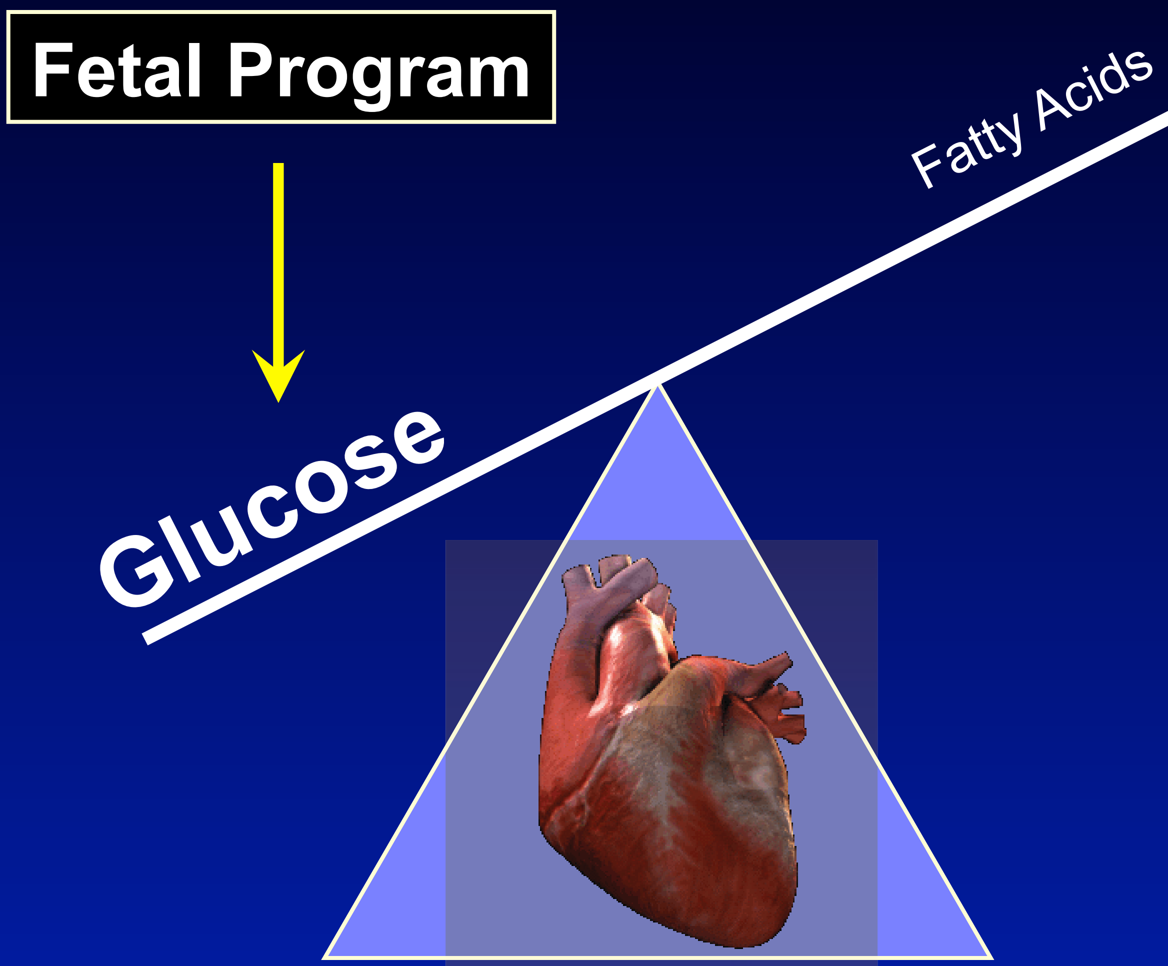
Maintaining Cardiac Function Through Metabolic Substrate Balance



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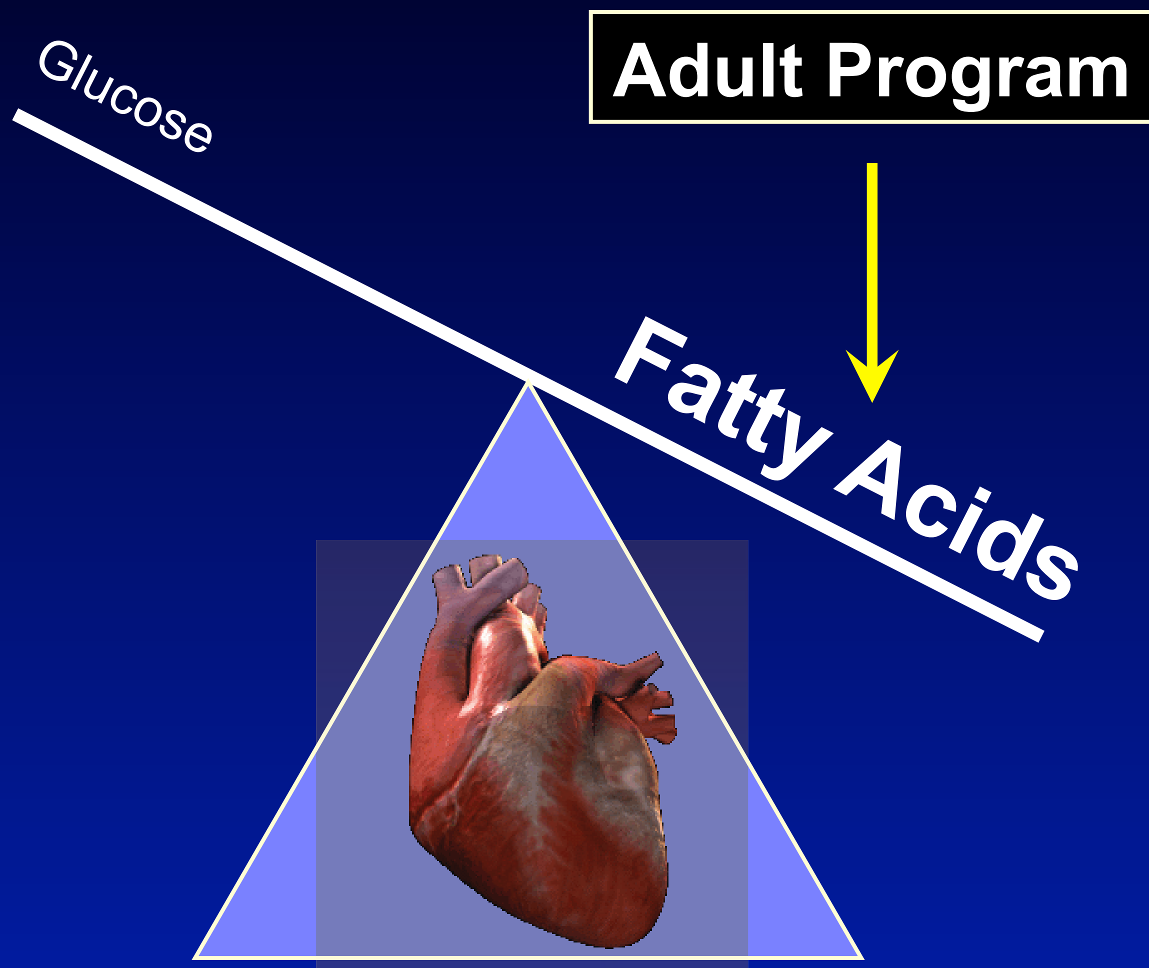
Maintaining Cardiac Function Through Metabolic Substrate Balance



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Maintaining Cardiac Function Through Metabolic Substrate Balance

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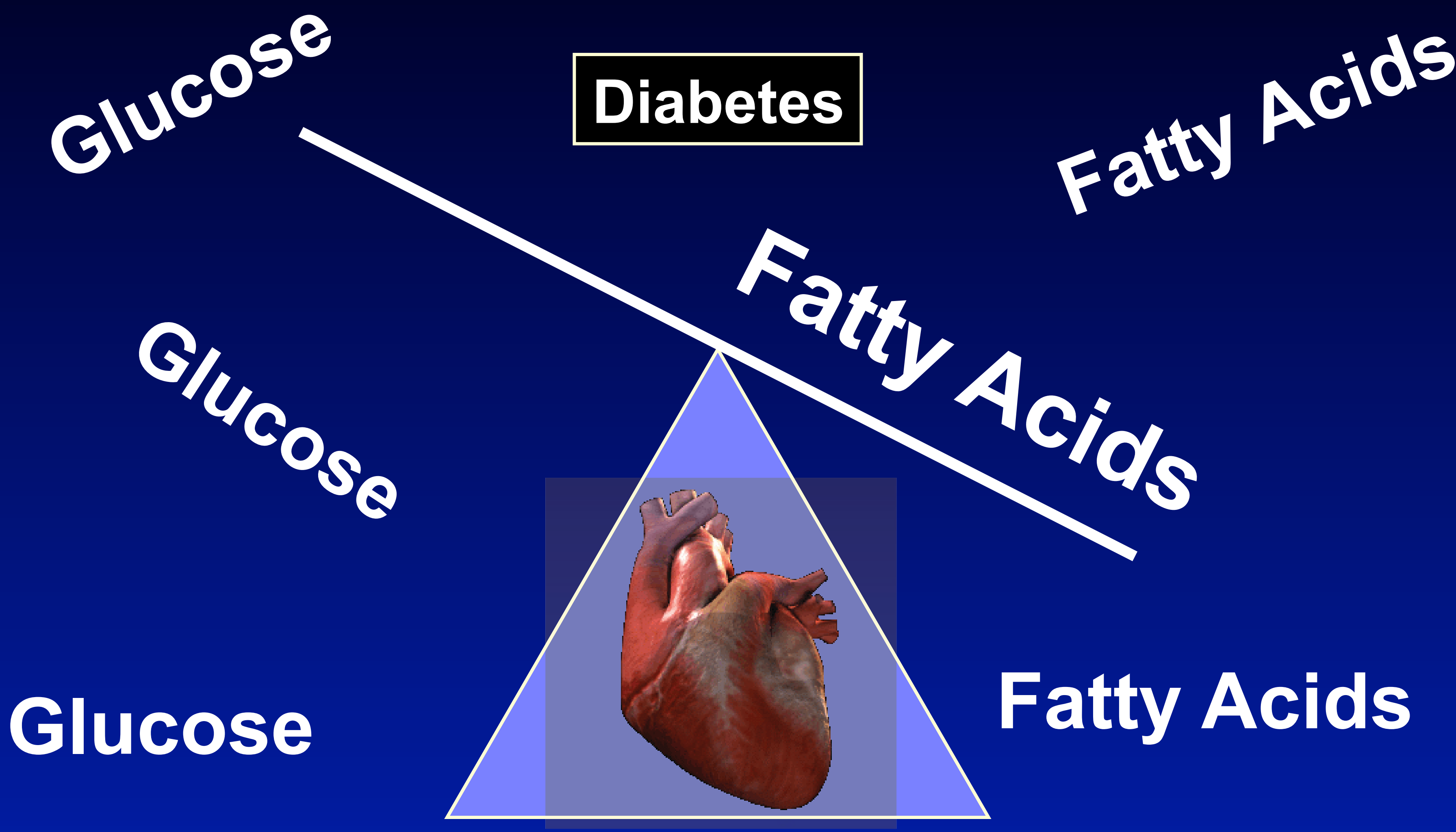
Maintaining Cardiac Function Through Metabolic Substrate Balance



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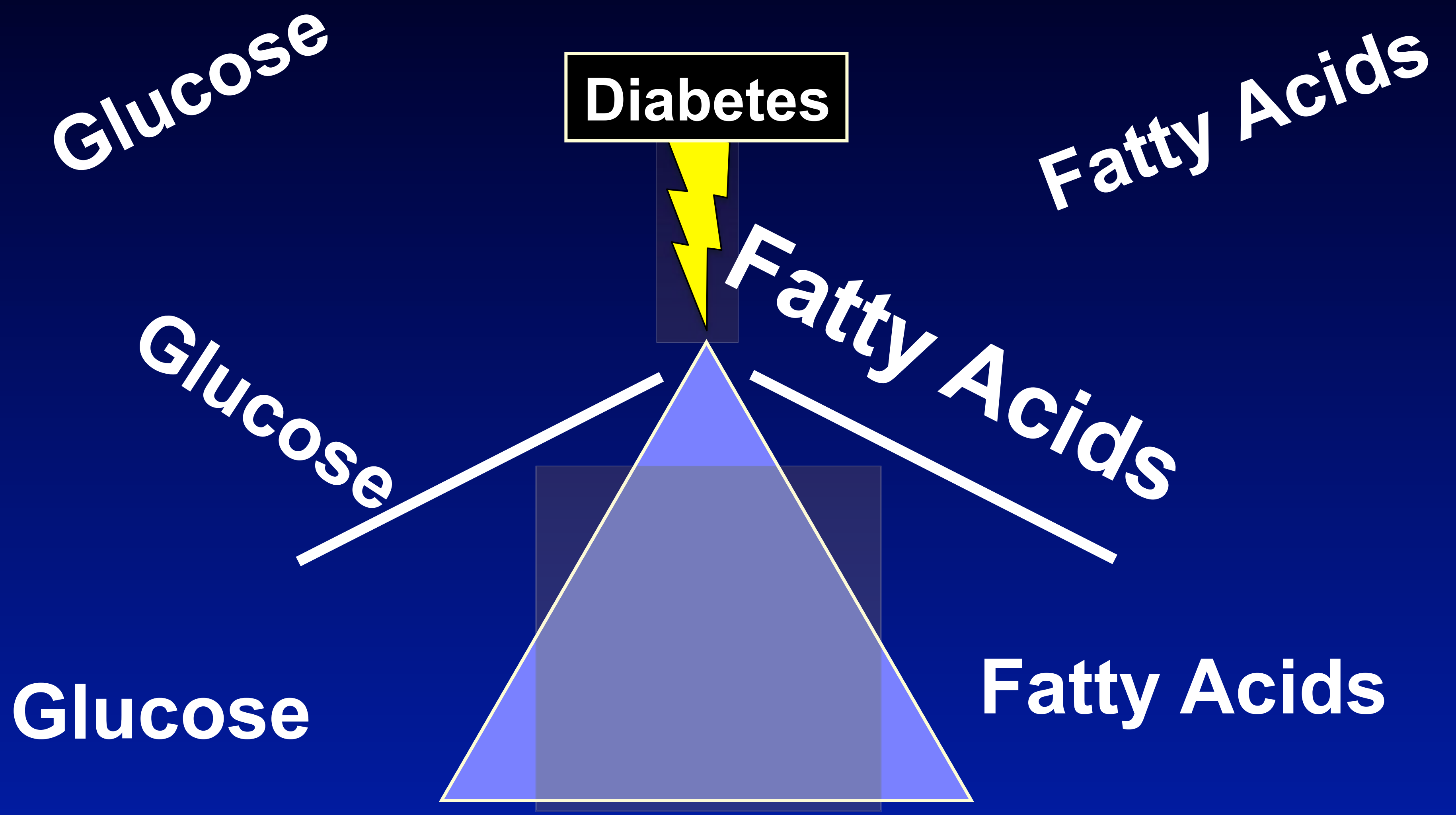
Maintaining Cardiac Function Through Metabolic Substrate Balance



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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.

lactate usage and a slight decline in that of pyruvate. There is no change in utilization of 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 of diabetes is not clear. Anesthesia, which was used in the dogs, may have played some part.

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

Metabolic Substrate Utilization in the Heart

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

	MVO_2	Glucose Metabolism	Fatty Acid Metabolism
Aging	↑	↑	↓
Female sex	↑	↓	↑
Obesity	↑	—	↑
Diabetes, types 1 and 2	—↑	↓	↑
Hypertension: LV hypertrophy	—	↑	↓
Dilated cardiomyopathy	—	↑	↓
Ischemia	↓	↑	↓

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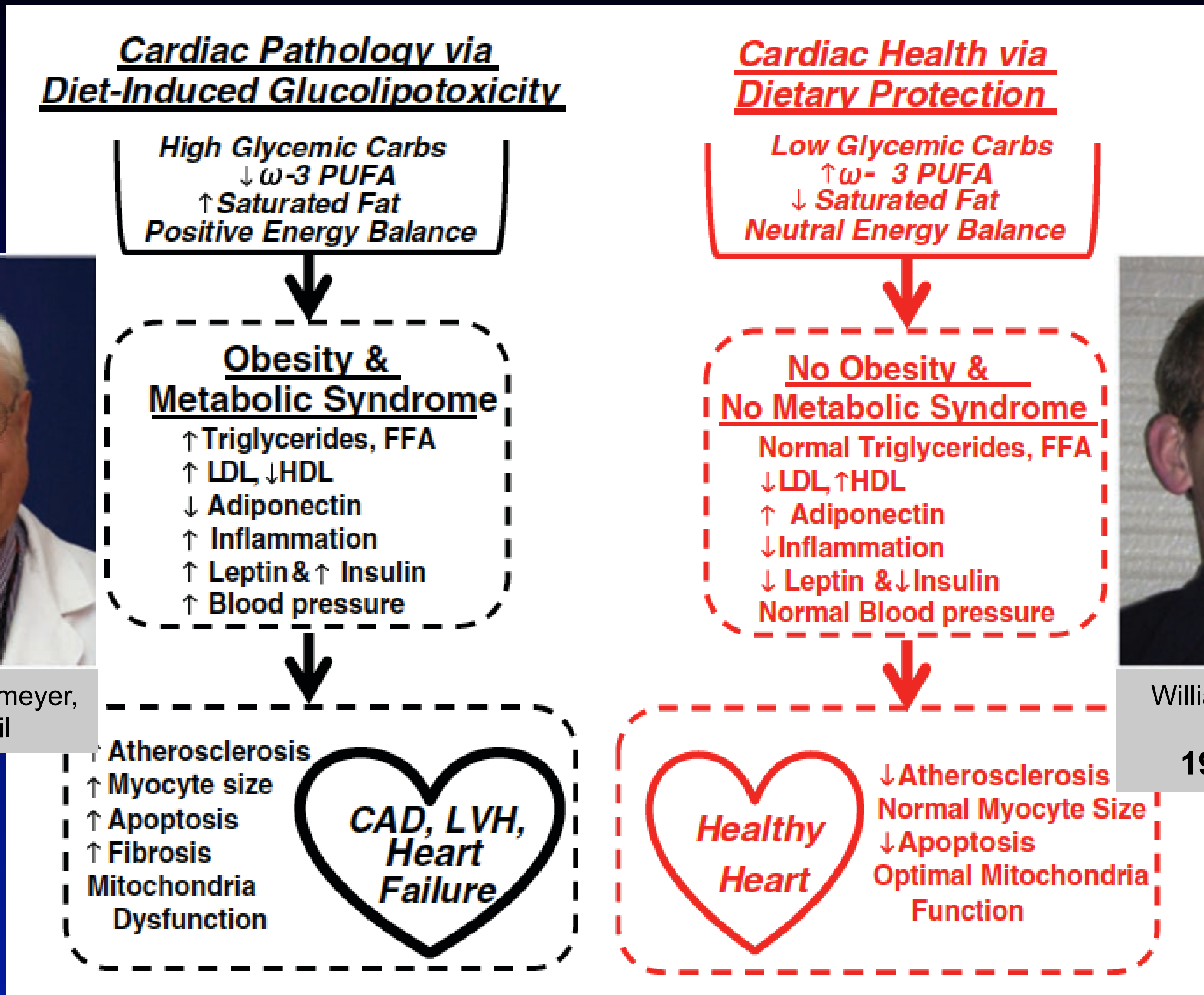
Peterson and Gropler **2010** *Circ Cardiovasc Imaging* 3:211

Point/Counterpoint - The Right Balance?

Heinrich Taegtmeyer, MD, DPhil



William C. Stanley, PhD
1957 - 2013

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Taegtmeyer and Stanley **2011** *J Mol Cell Cardiol* 50(1):2

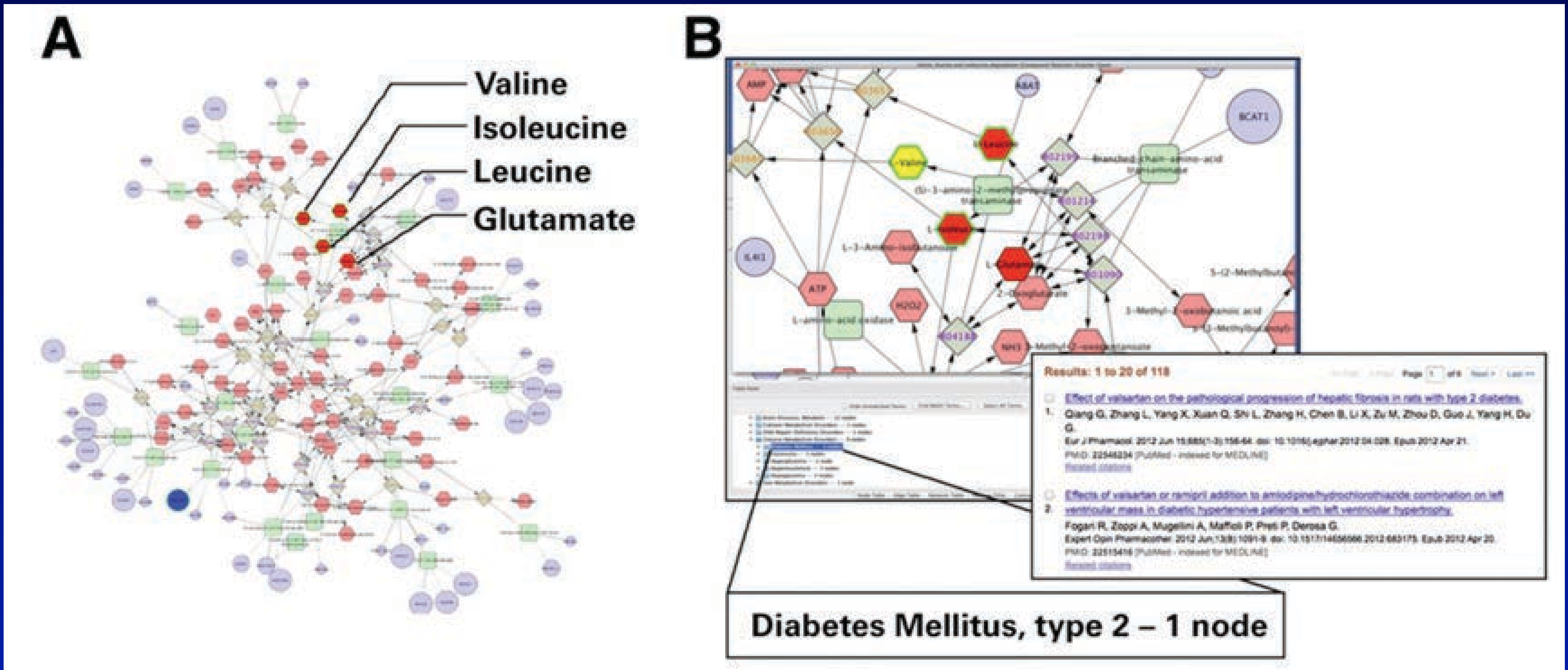
Diabetes and Metabolomics

Diabetes. 2015 Mar;64(3):718-732.

Metabolomics and Diabetes: Analytical and Computational Approaches.

Sas KM[1], Karnovsky A[2], Michailidis G[3], Pennathur S[4].

Metabolomics is an integral part for understanding disease processes … information garnered in the biomarker investigations, future research should shed more light on disease pathogenesis and explore new treatment options.



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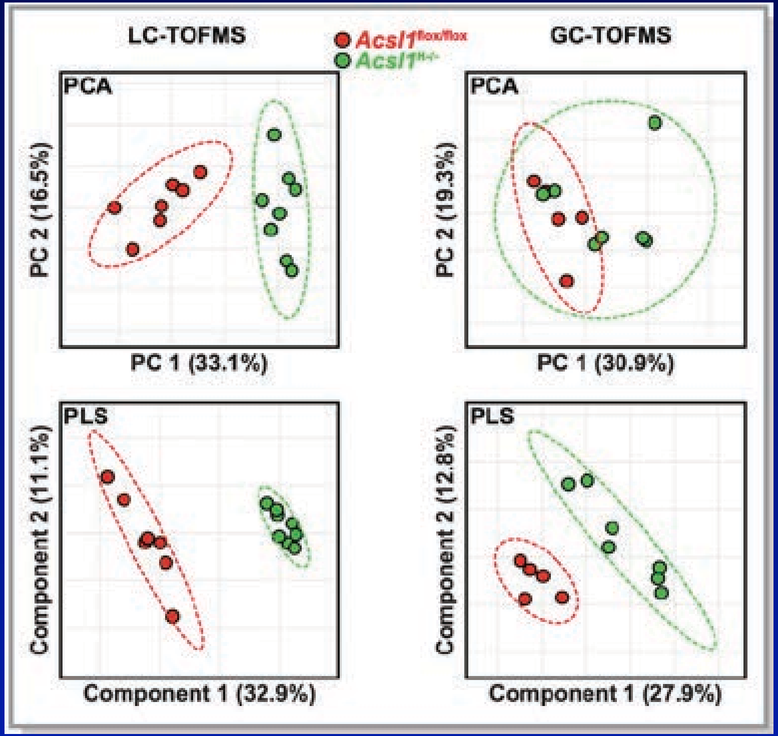
Heart failure and substrate switching

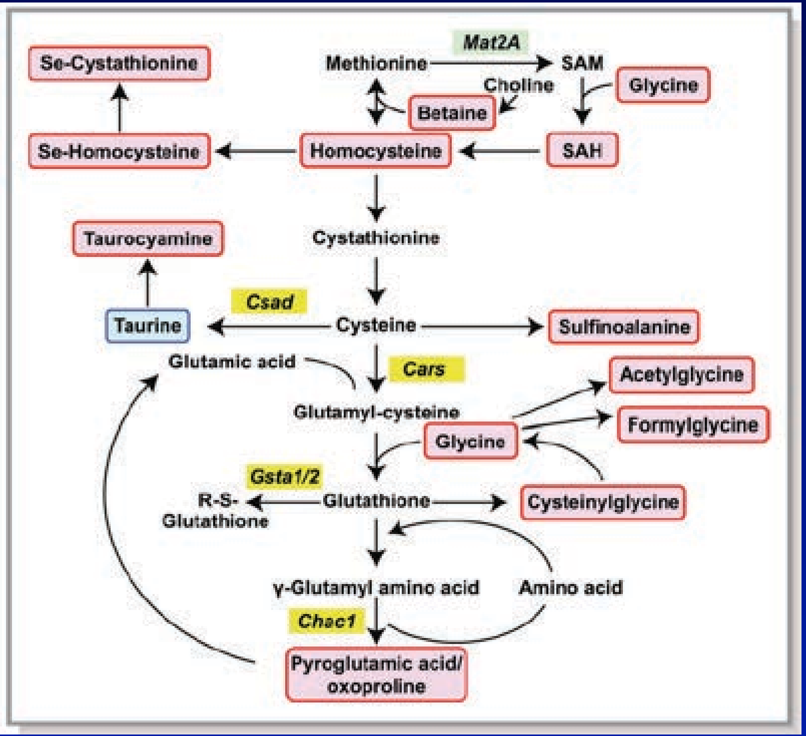
J Am Heart Assoc. 2015 Feb 24;4(2). pii: e001136. doi: 10.1161/JAHA.114.001136.

Cardiac energy dependence on glucose increases metabolites related to glutathione and activates metabolic genes controlled by mechanistic target of rapamycin.

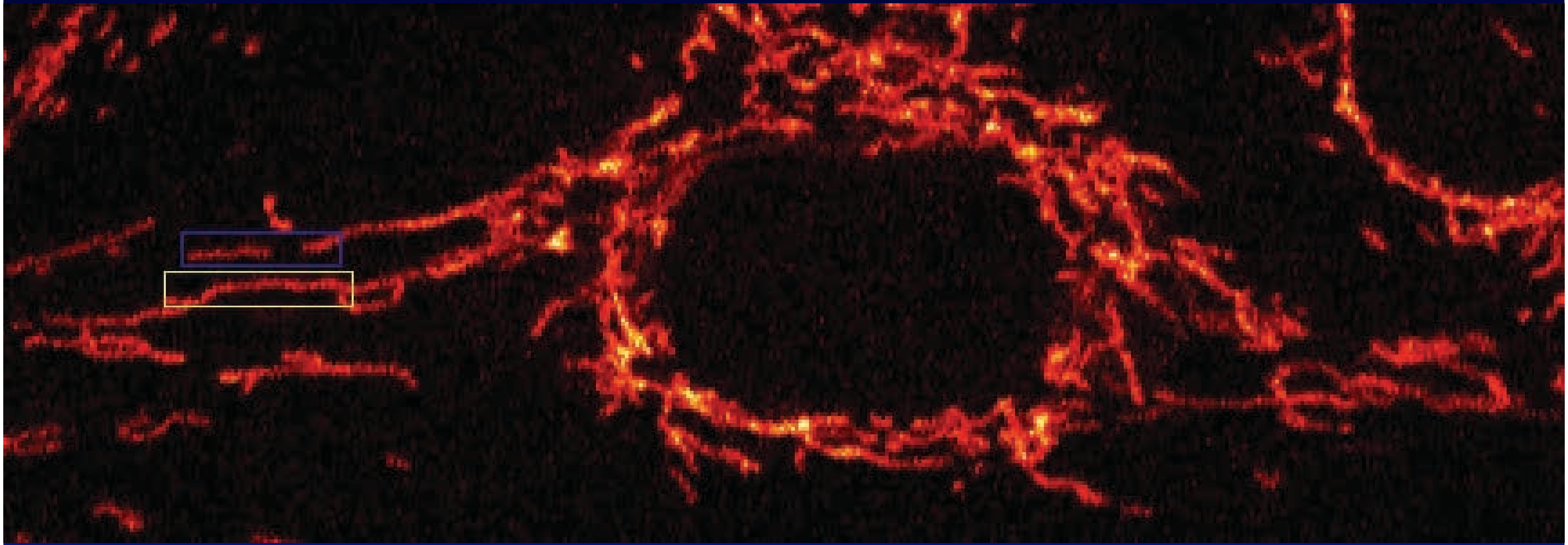
Schisler JC[1], Grevengoed TJ[2], Pascual F[2], Cooper DE[2], Ellis JM[2], Paul DS[2], Willis MS[3], Patterson C[1], Jia W[4], Coleman RA[2].

The hypertrophy, oxidative stress, and metabolic changes that occur within the heart when glucose supplants FA as a major energy source suggest that substrate switching to glucose is not entirely benign.





Mitochondria – a Dynamic Network



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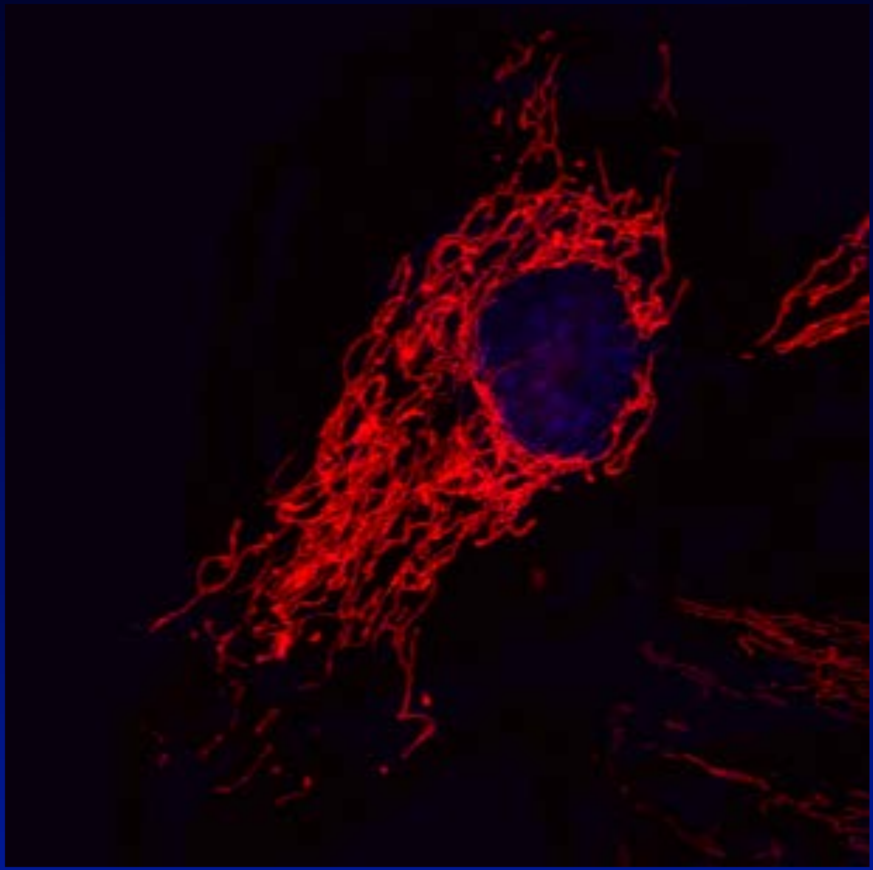
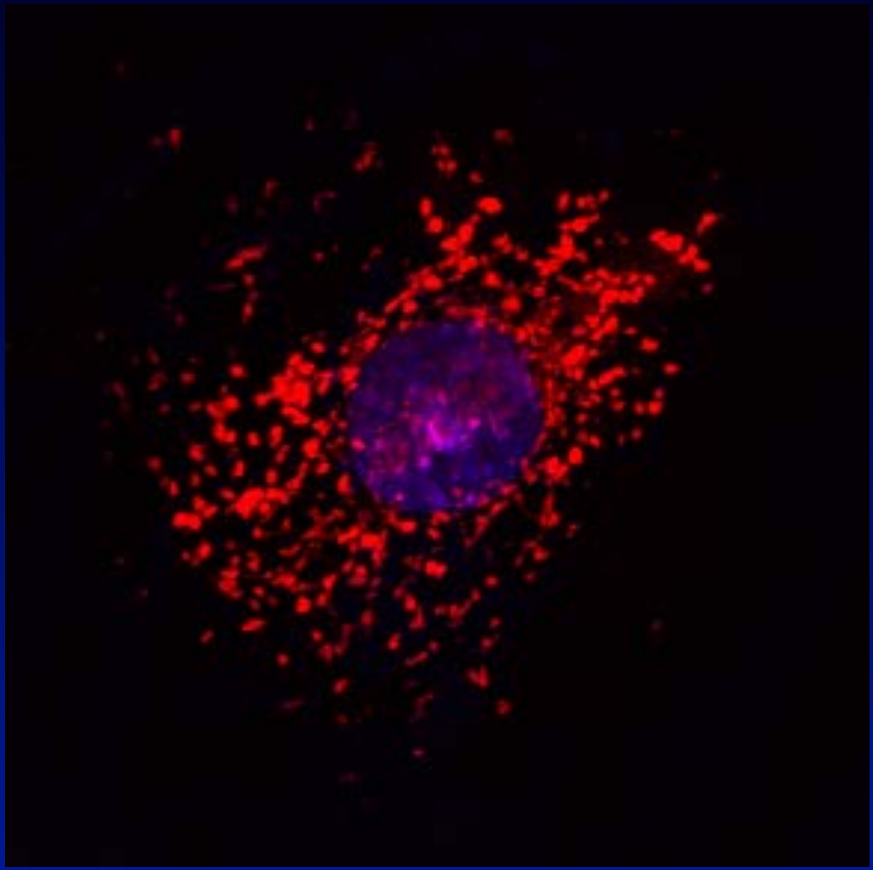
Fan … Brooks **2010** *Free Radic Biol Med* 49(11):1646

Mitochondria – too much fat

Serum



Serum + 500 µM Palmitate



Adapted from Heiko Bugger

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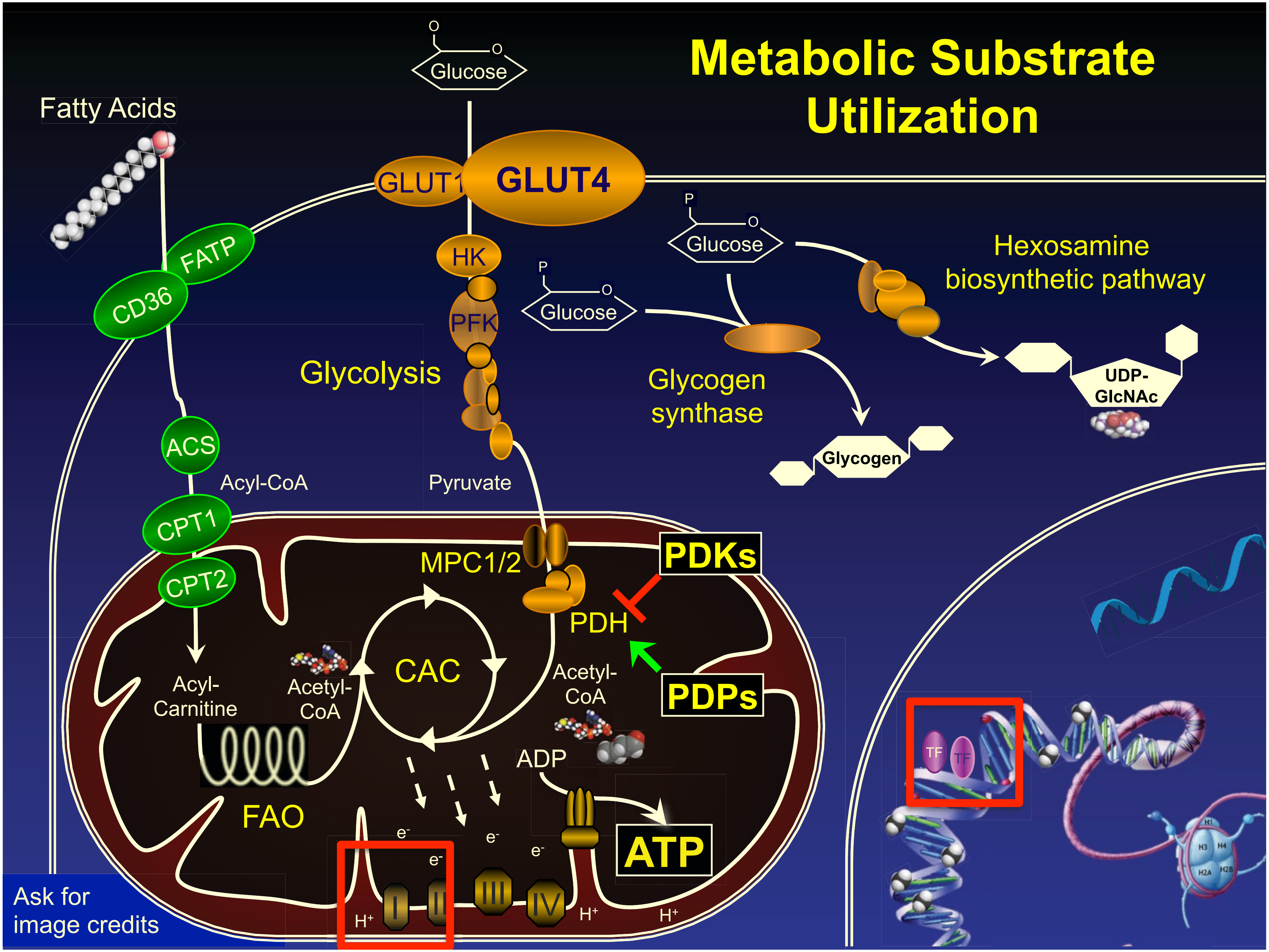

Metabolic Substrate Utilization
Fatty Acids
Glucose
GLUT1
GLUT4
FATP
CD36
HK
PFK
Glycolysis
Glucose
Glucose
Hexosamine biosynthetic pathway
Glycogen synthase
UDP-GlcNAc
Glycogen
ACS
Acyl-CoA
Pyruvate
CPT1
CPT2
MPC1/2
PDKs
PDH
PDPs
Acyl-Carnitine
Acetyl-CoA
CAC
Acetyl-CoA
ADP
FAO
ATP
TF
TF
I
II
III
IV
H+
H+
H+
e-
e-
e-
e-
P
P
O
O
O
O
H1
H3
H4
H2A
H2B
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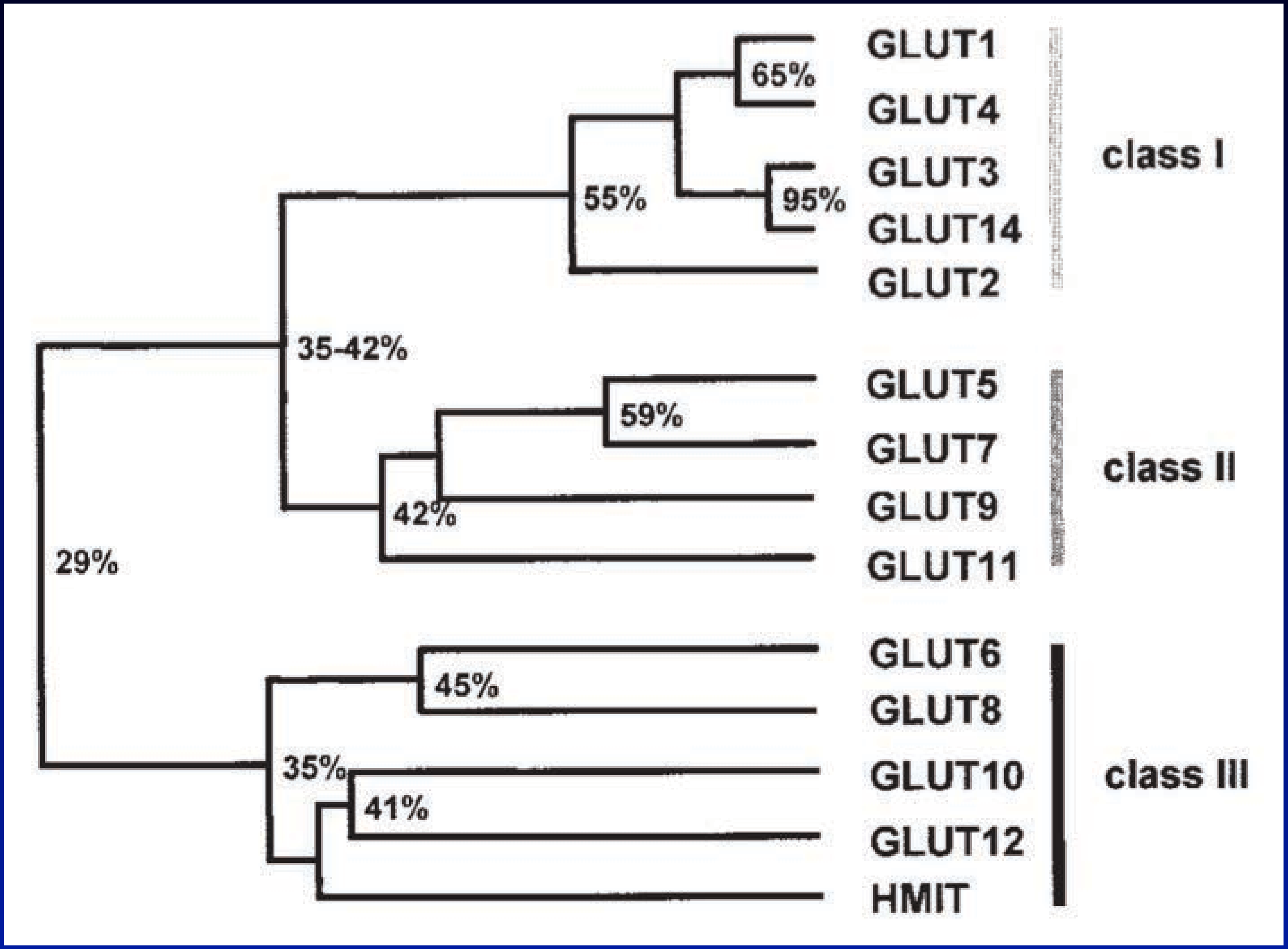
Facilitative Glucose Transporters: GLUTs
"Solute Carrier Family, SLC2A"



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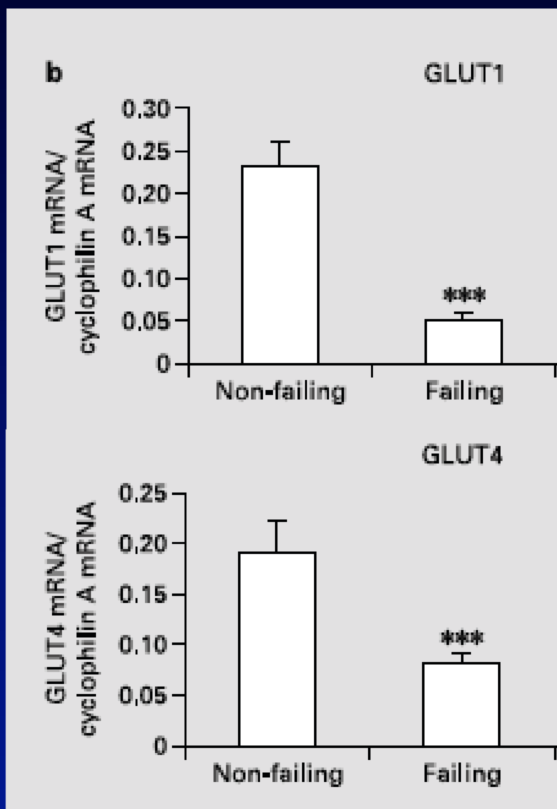
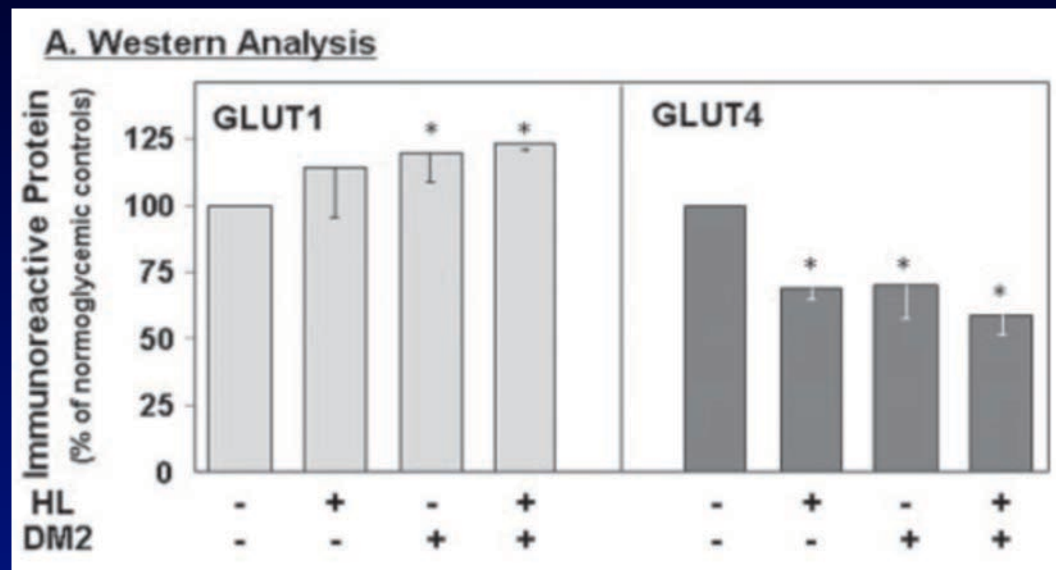
Scheepers … Schurmann **2004** *J Parenter Enteral Nutr* 28:364

Changes in Human Heart GLUT Levels

RNA
Human heart failure



Protein
Human heart diabetes



Biopsies obtained during coronary bypass surgery
HL = hyperlipidemia
DM2 = diabetes mellitus type 2

Razeghi … Taegtmeyer **2002** *Cardiology* 280(41):34786

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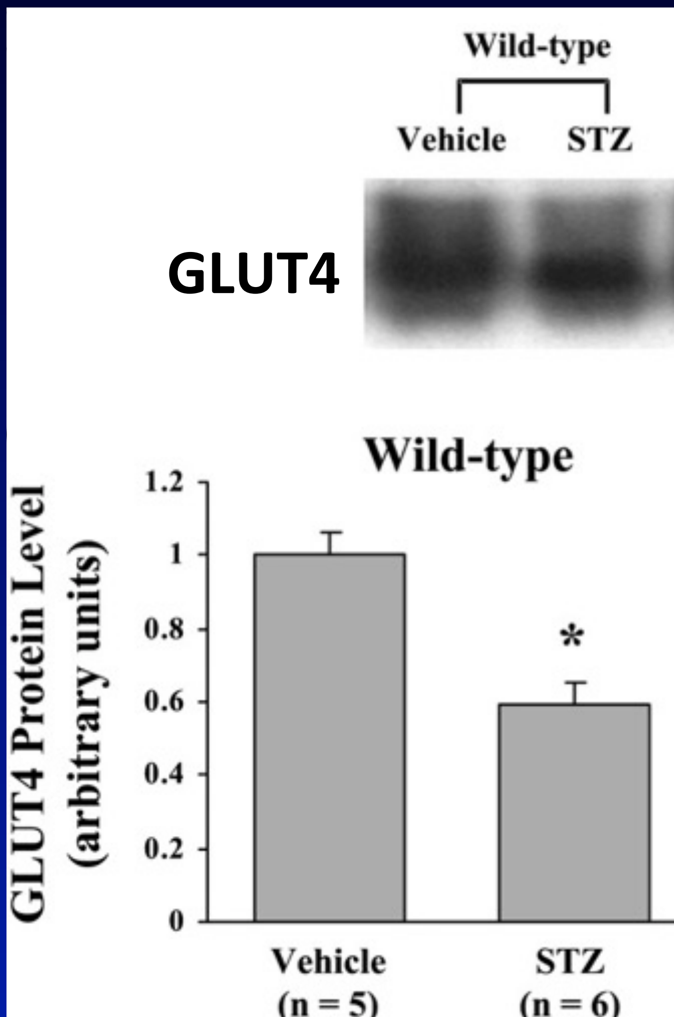
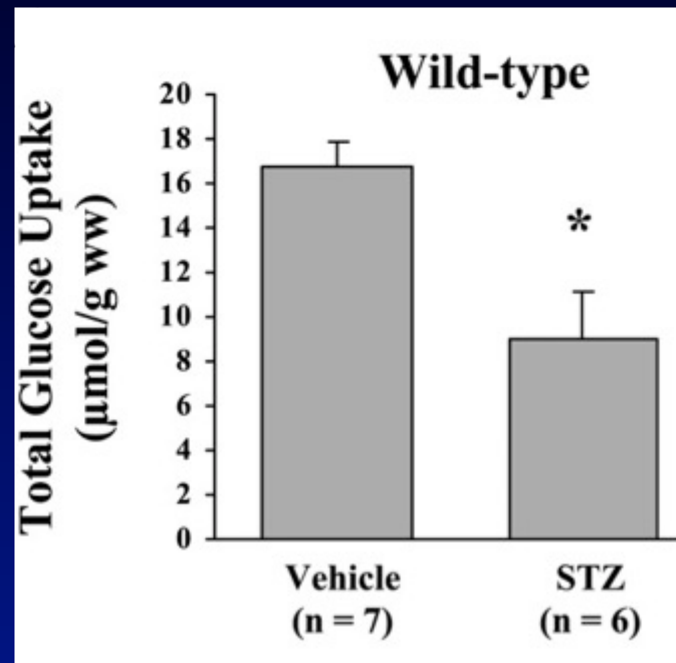
Armoni … Karnieli **2005** *J Biol Chem* 280(41):34786

Glucose Utilization and Rodent Models of Type 1 Diabetes

Protein
Diabetic Mouse Heart



Glucose Uptake
Diabetic Mouse Heart



Panagia … Clarke **2005** *Am J Physiol 288:H2677*

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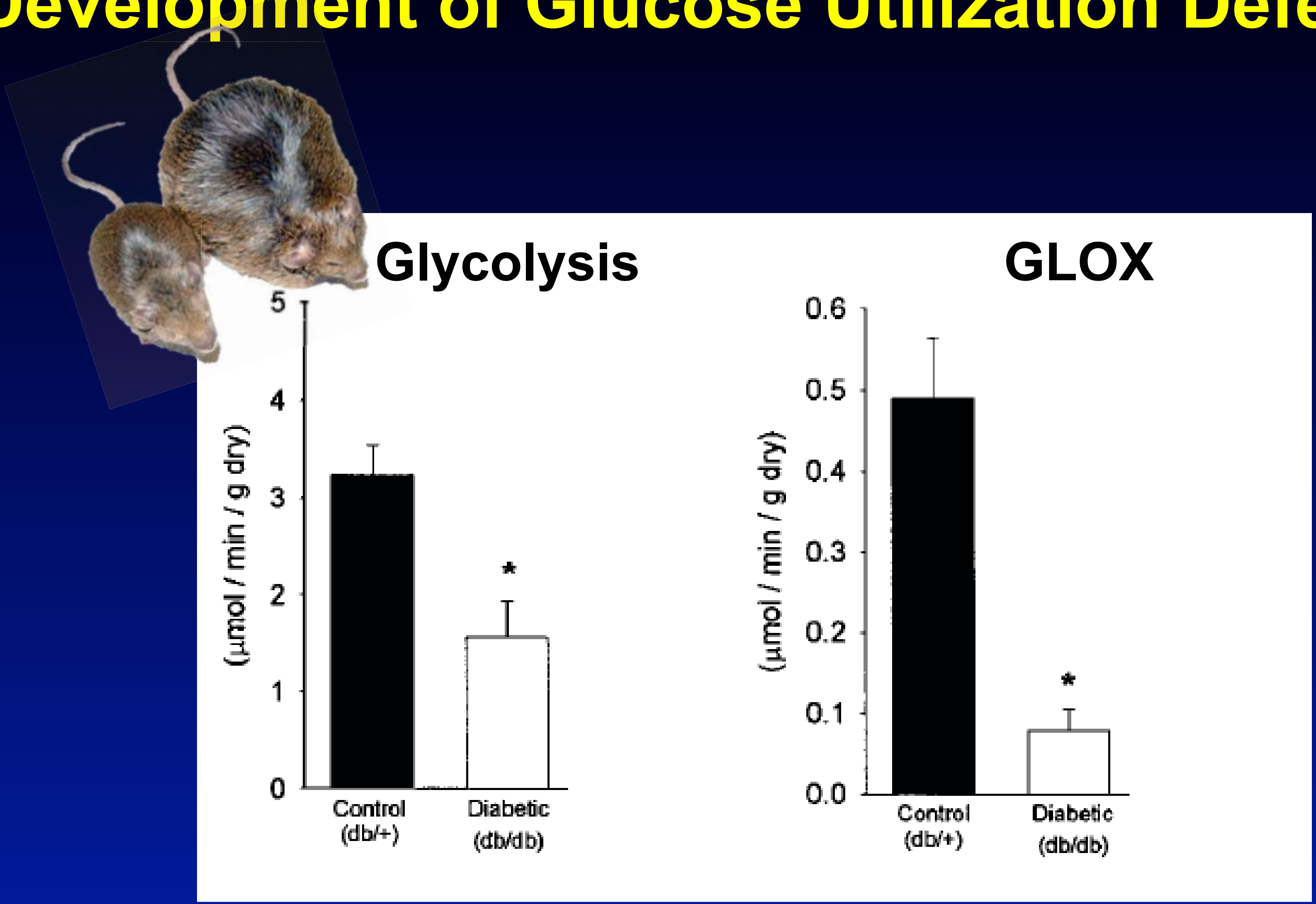
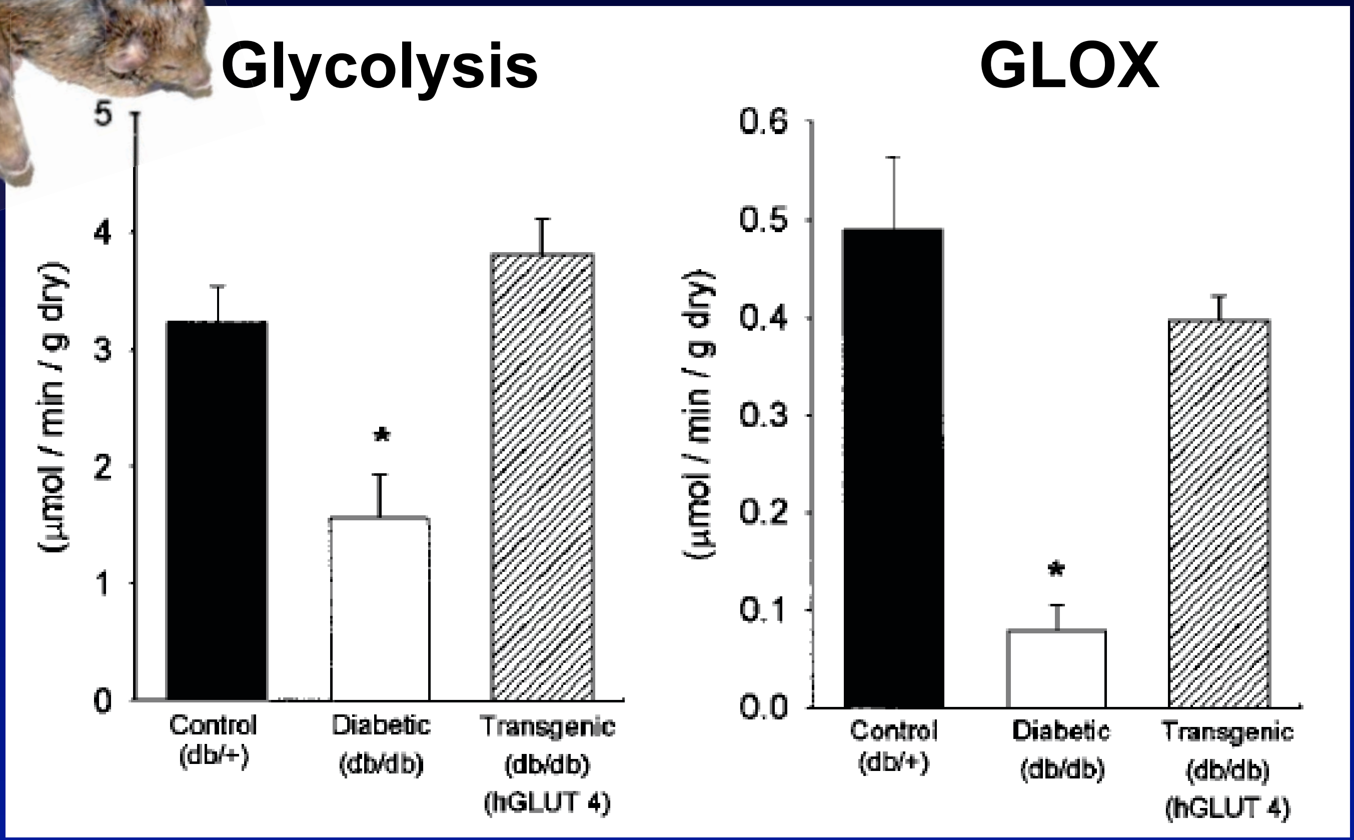
Constitutive GLUT4 Expression Prevents Development of Glucose Utilization Defects



Belke … Severson **2000** *Am J Physiol* 279:E1104

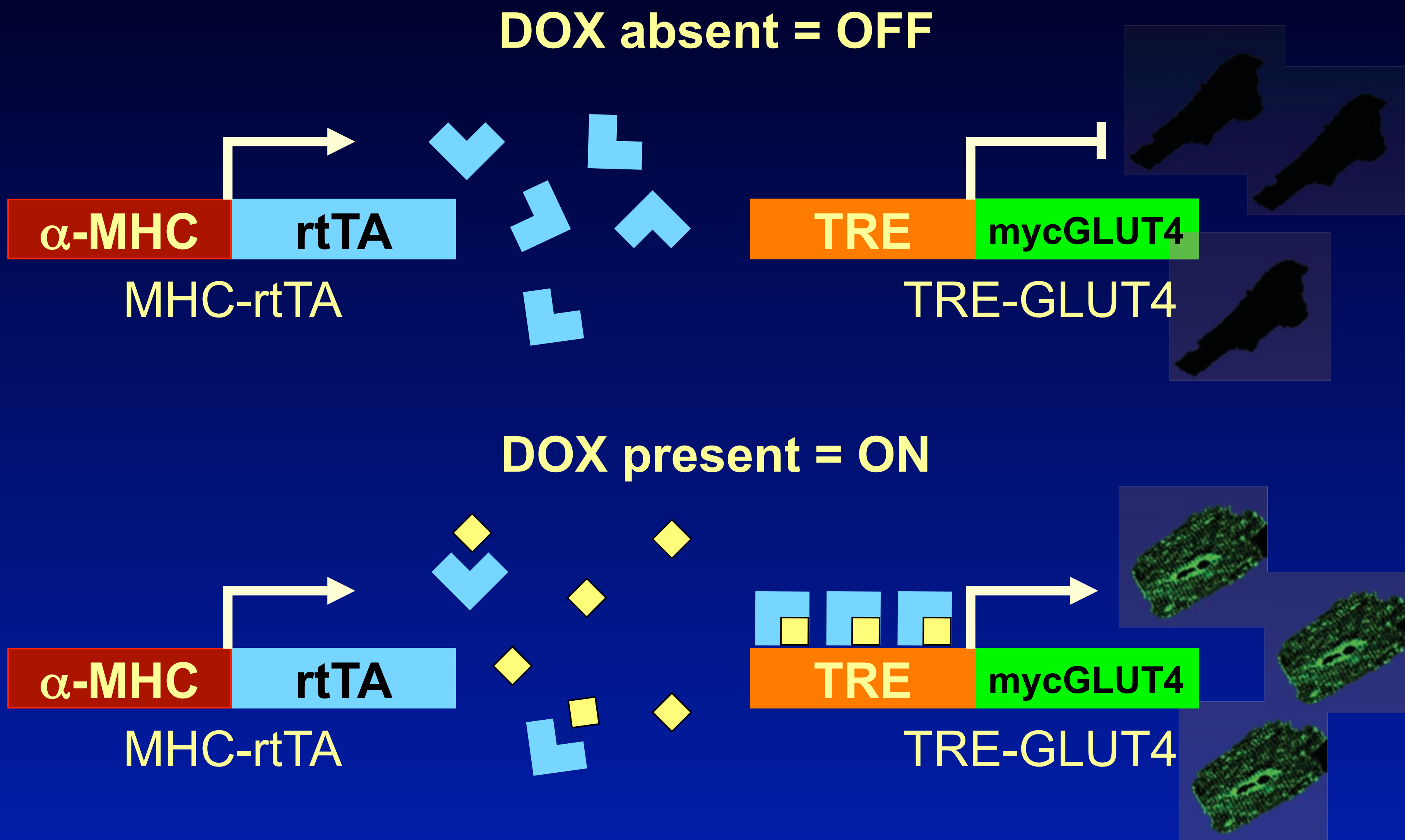
Constitutive GLUT4 Expression Prevents Development of Glucose Utilization Defects



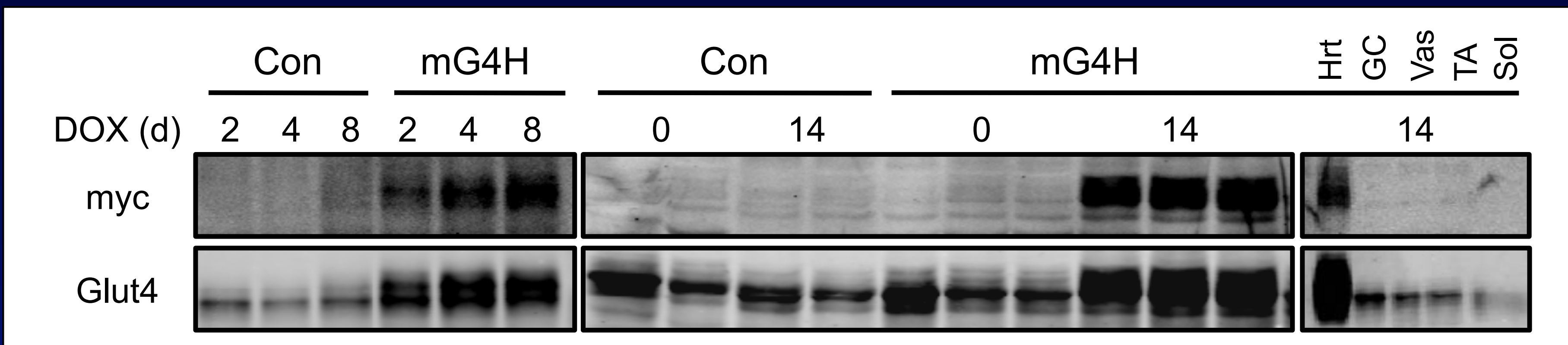
Belke … Severson **2000** *Am J Physiol* 279:E1104

Question: Is the change in cardiac metabolic substrate flexibility adaptive or maladaptive?

Inducible Cardiomyocyte-Specific GLUT4 Expression (mG4H)



mG4H Mice Exhibit Inducible Cardiac-Specific Expression of GLUT4



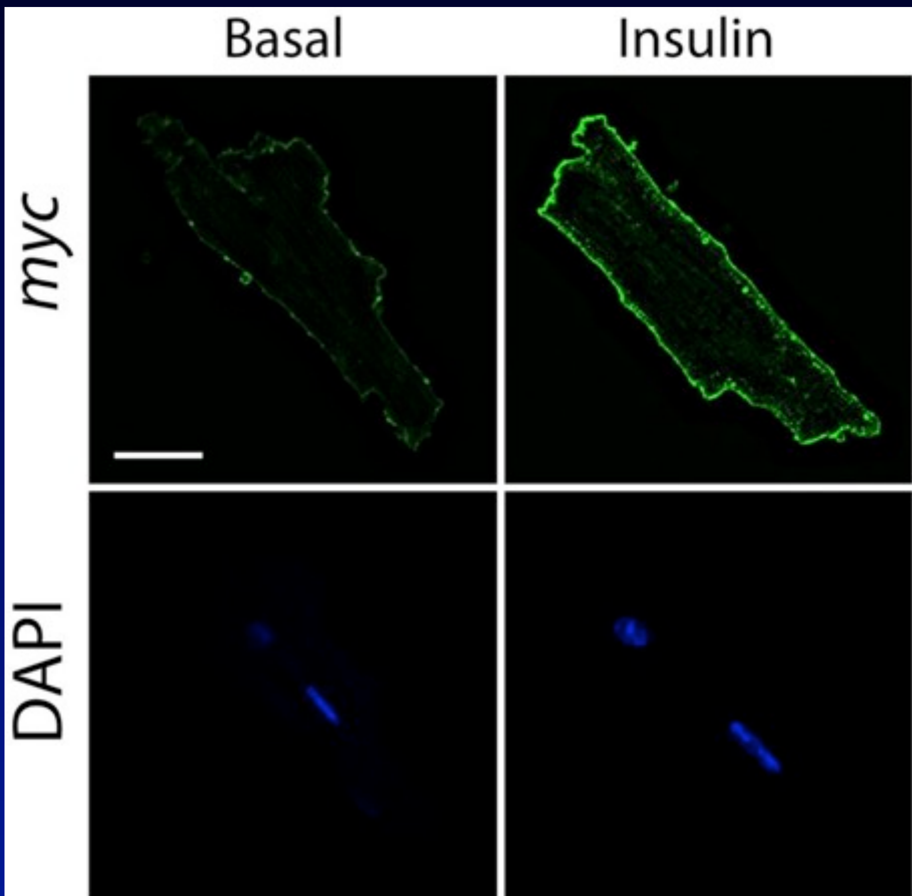
Hrt = Heart
GC = Gastrocnemius
Vas = Vastus lateralis

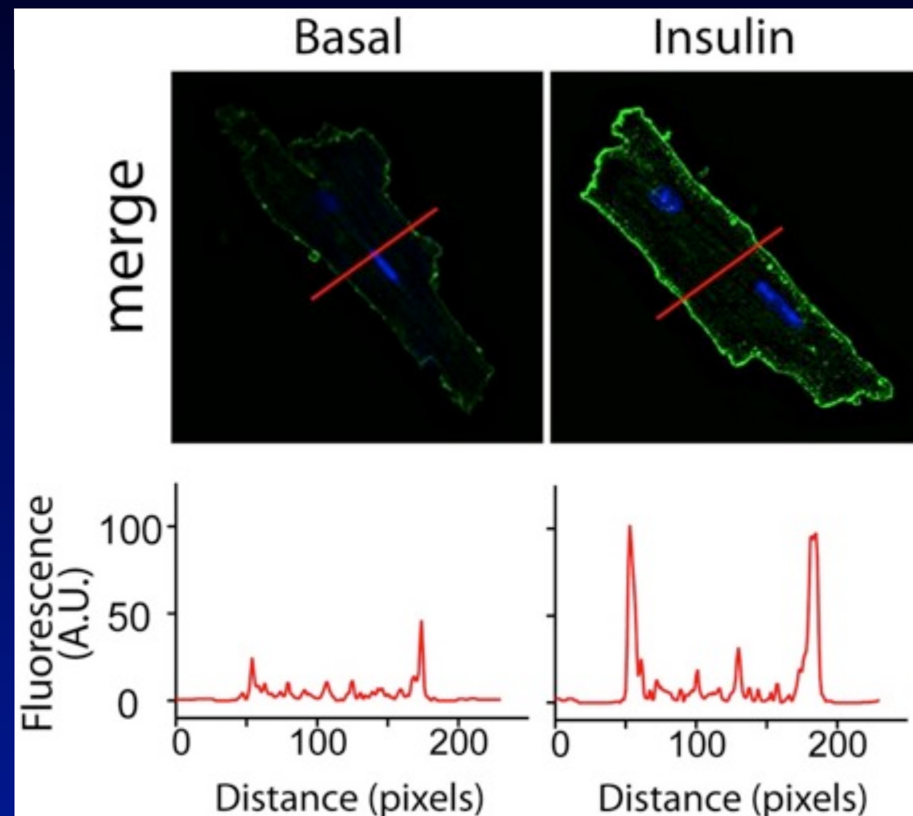
TA = Tibialis anterior
Sol = Soleus

5-fold

5-fold Heart

Insulin-induced GLUT4 Vesicle Fusion and Exofacial Myc-Epitope Exposure

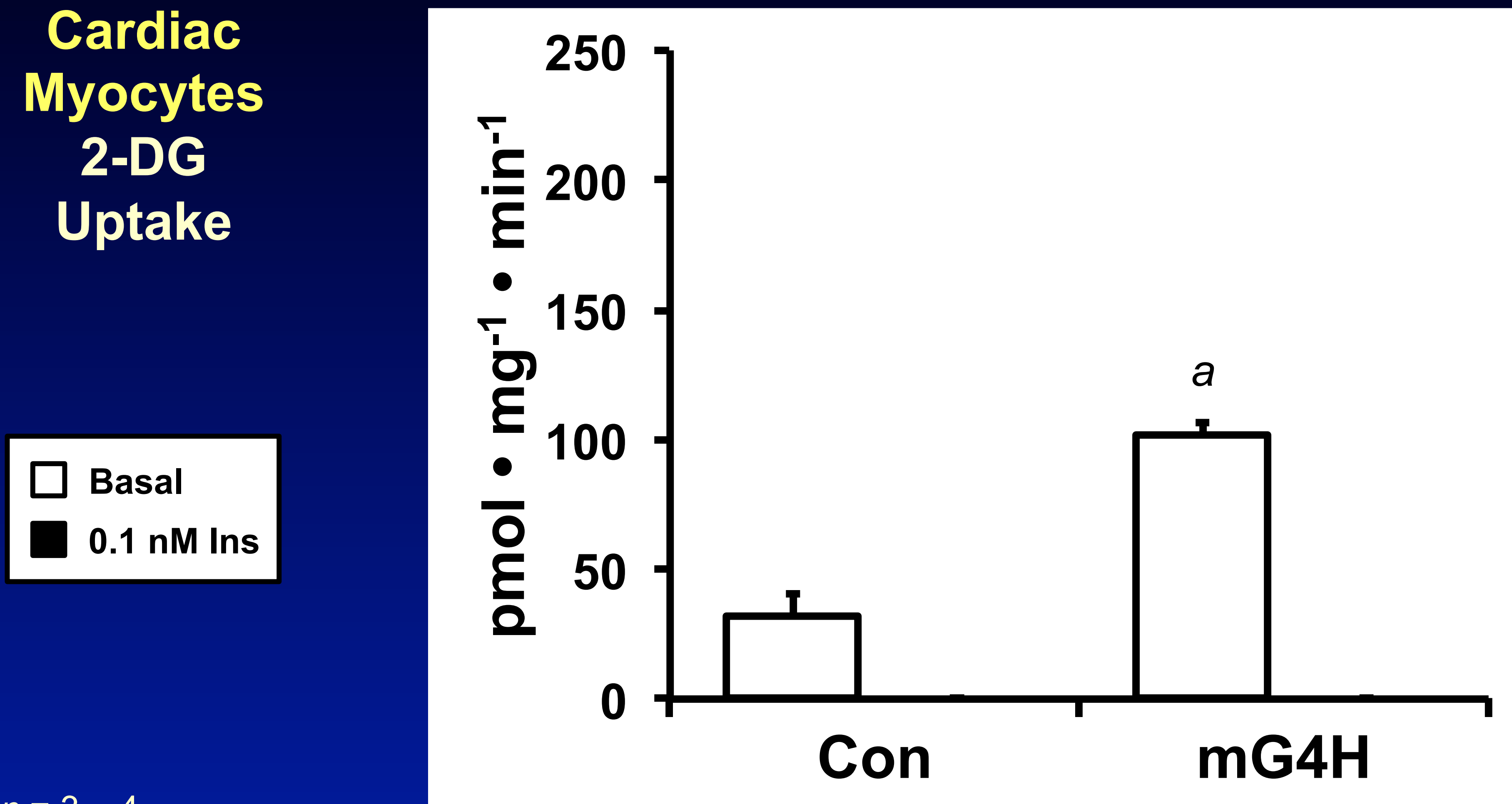




Ariel Contreras-Ferrat
Wende … Abel *in prep*

GLUT4 Induction Increases Basal and Insulin-Stimulated Glucose Uptake

Cardiac Myocytes 2-DG Uptake

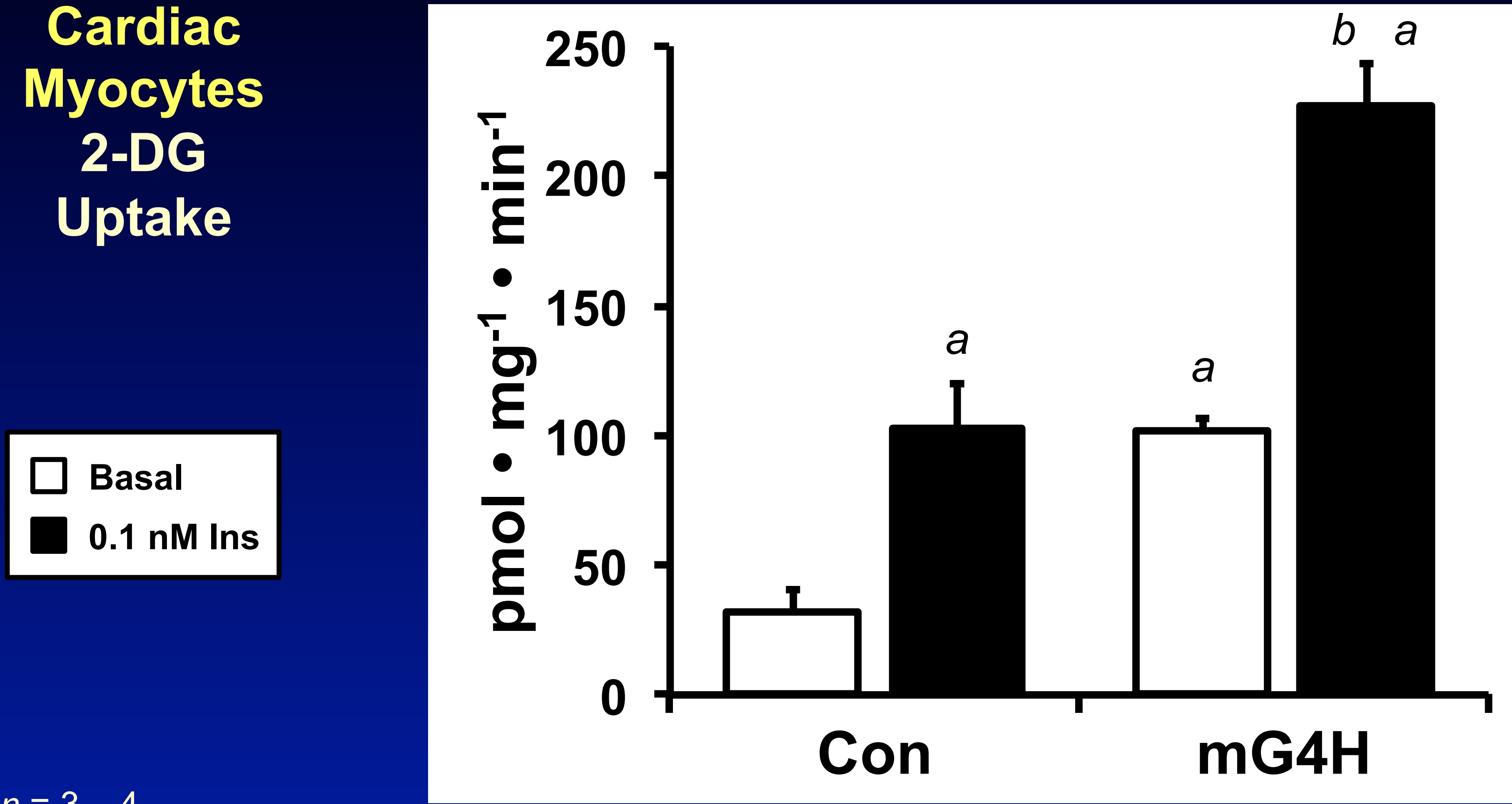


n = 3 – 4
[a] P < 0.01 vs. Con-Basal
[b] P < 0.001 vs. All

Renata O. Pereira
Wende … Abel *in prep*

GLUT4 Induction Increases Basal and Insulin-Stimulated Glucose Uptake

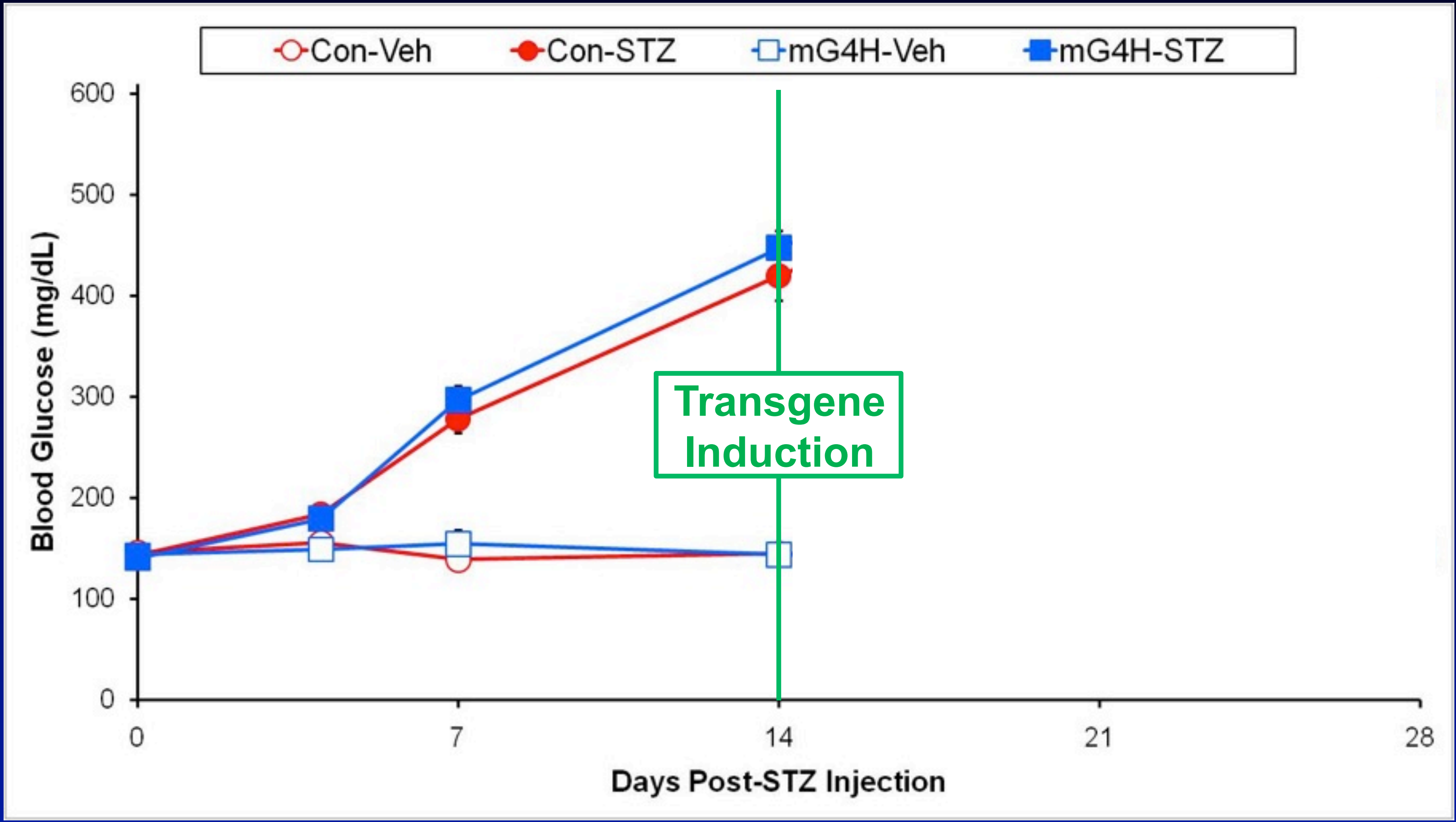
Cardiac Myocytes 2-DG Uptake



n = 3 – 4
[a] P < 0.01 vs. Con-Basal
[b] P < 0.001 vs. All

Renata O. Pereira
Wende … Abel *in prep*

Streptozotocin (STZ)-Induced Hyperglycemia is Not Altered by Transgene Induction



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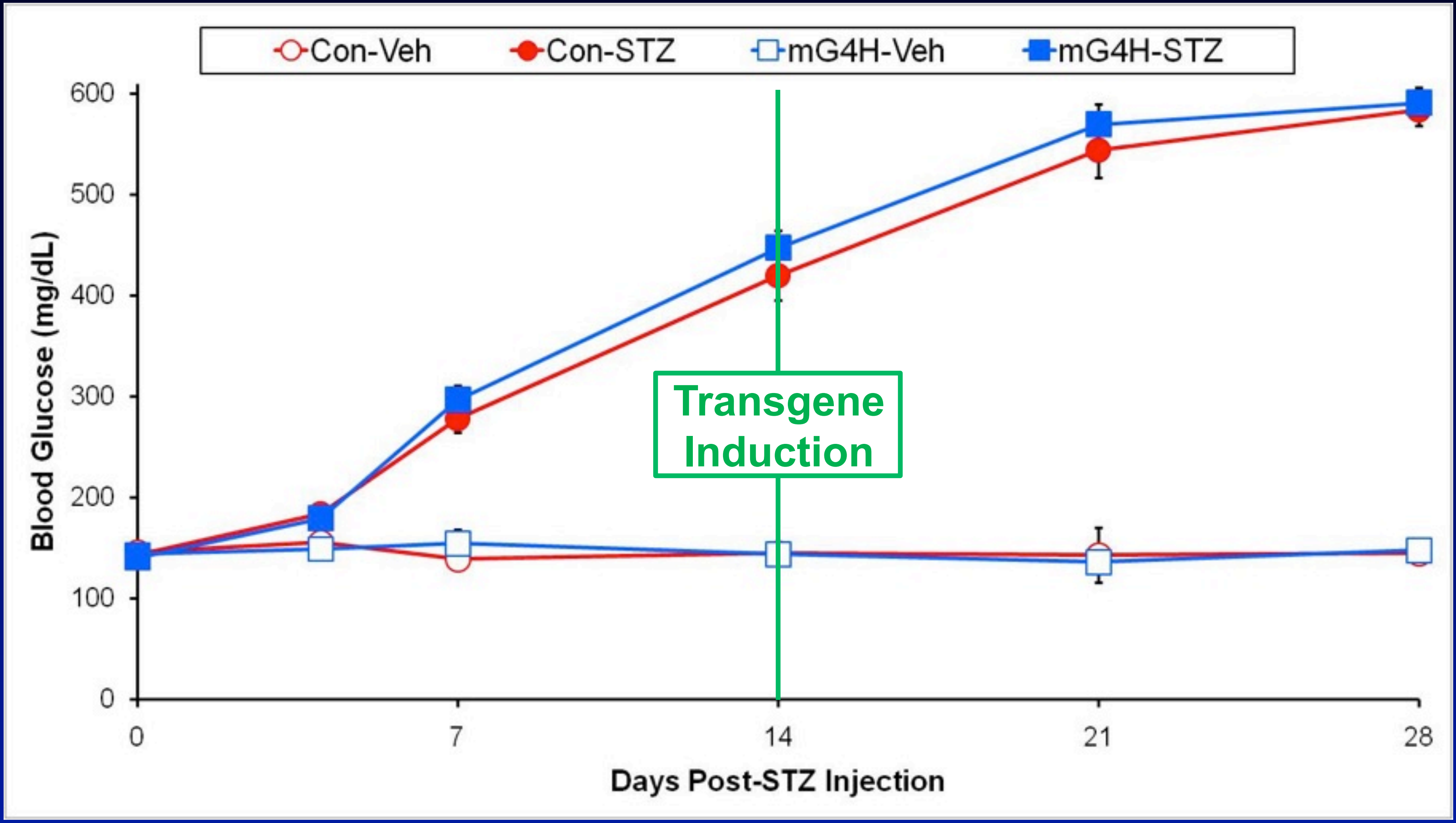
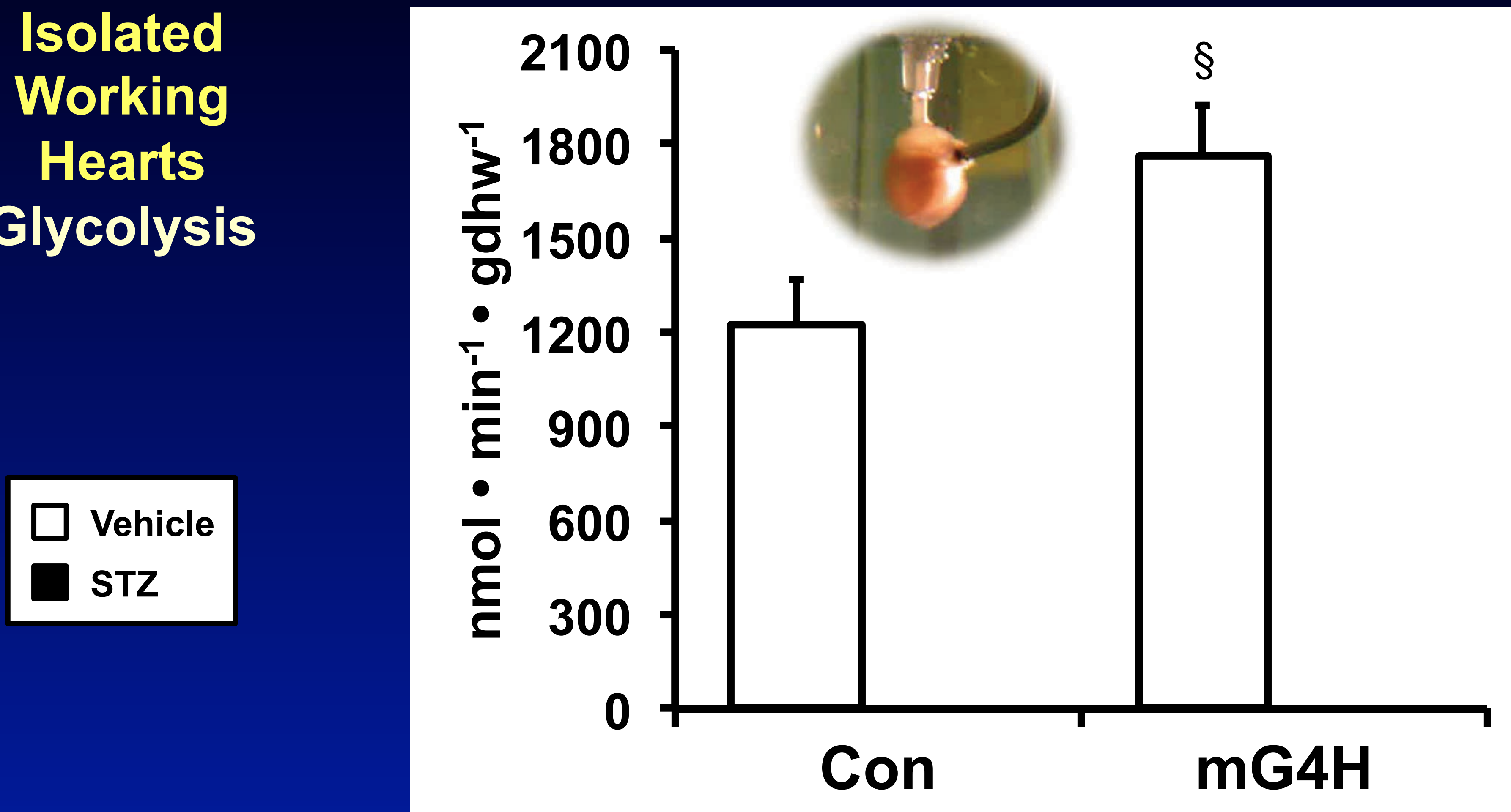


GLUT4 Induction Increases Glycolysis and Rescues Diabetic Cardiac Glycolytic Defects

Isolated Working Hearts Glycolysis



n = 6 – 10
§ P < 0.01 vs. Con

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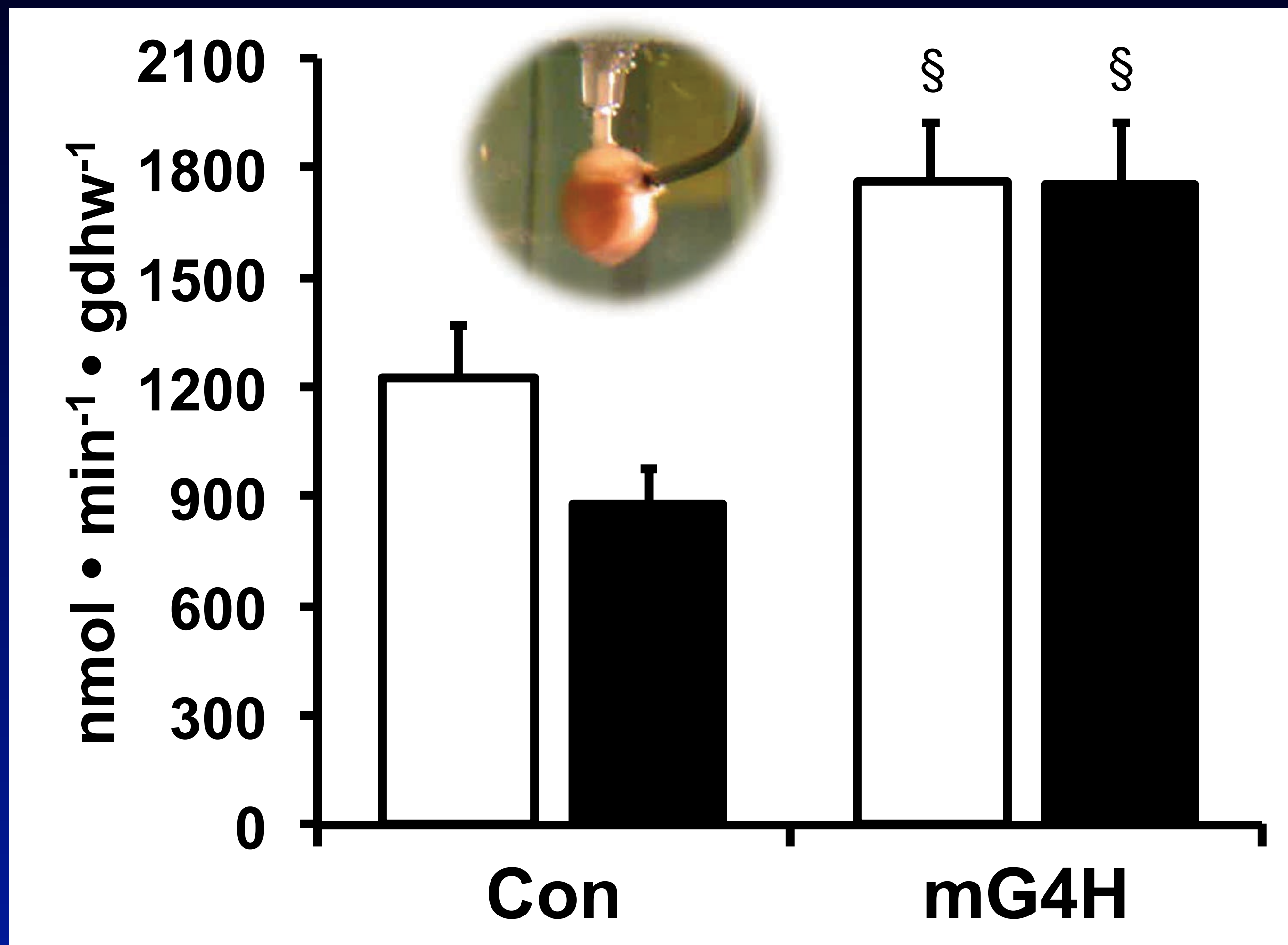
Joseph Tuinei
Wende … Abel *in prep*

GLUT4 Induction Increases Glycolysis and Rescues Diabetic Cardiac Glycolytic Defects

Isolated Working Hearts Glycolysis



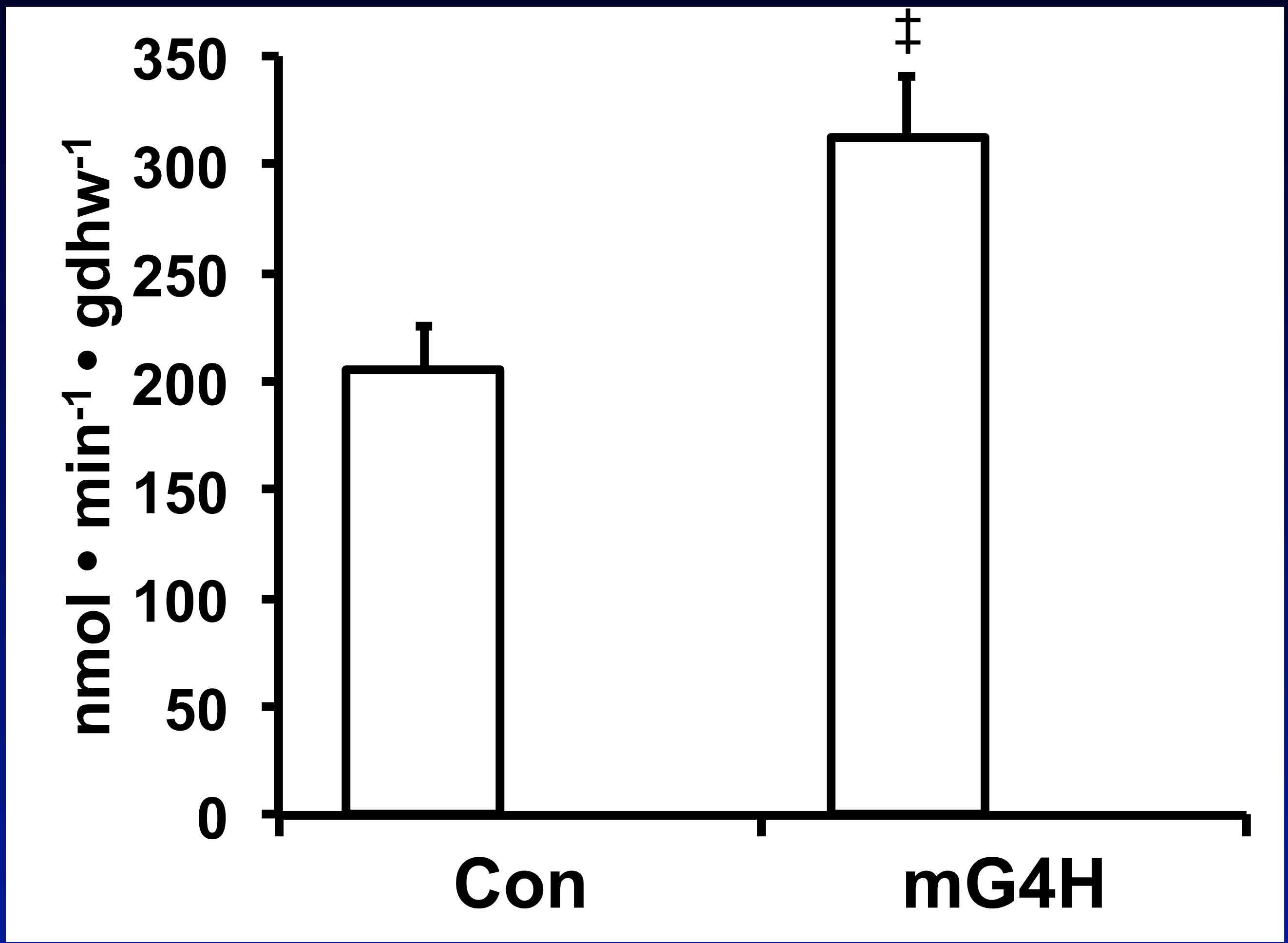
Vehicle
STZ

n = 6 – 10
§ $P < 0.01$ vs. Con
ARW

Joseph Tuinei
Wende … Abel *in prep*

GLUT4 Induction Increases GLOX but Accelerates Diabetic Cardiac GLOX Defects

Isolated Working Hearts Glucose Oxidation (GLOX)



Vehicle

STZ

n = 6 – 10

‡ P < 0.001 vs. All

* P < 0.01 vs. Veh

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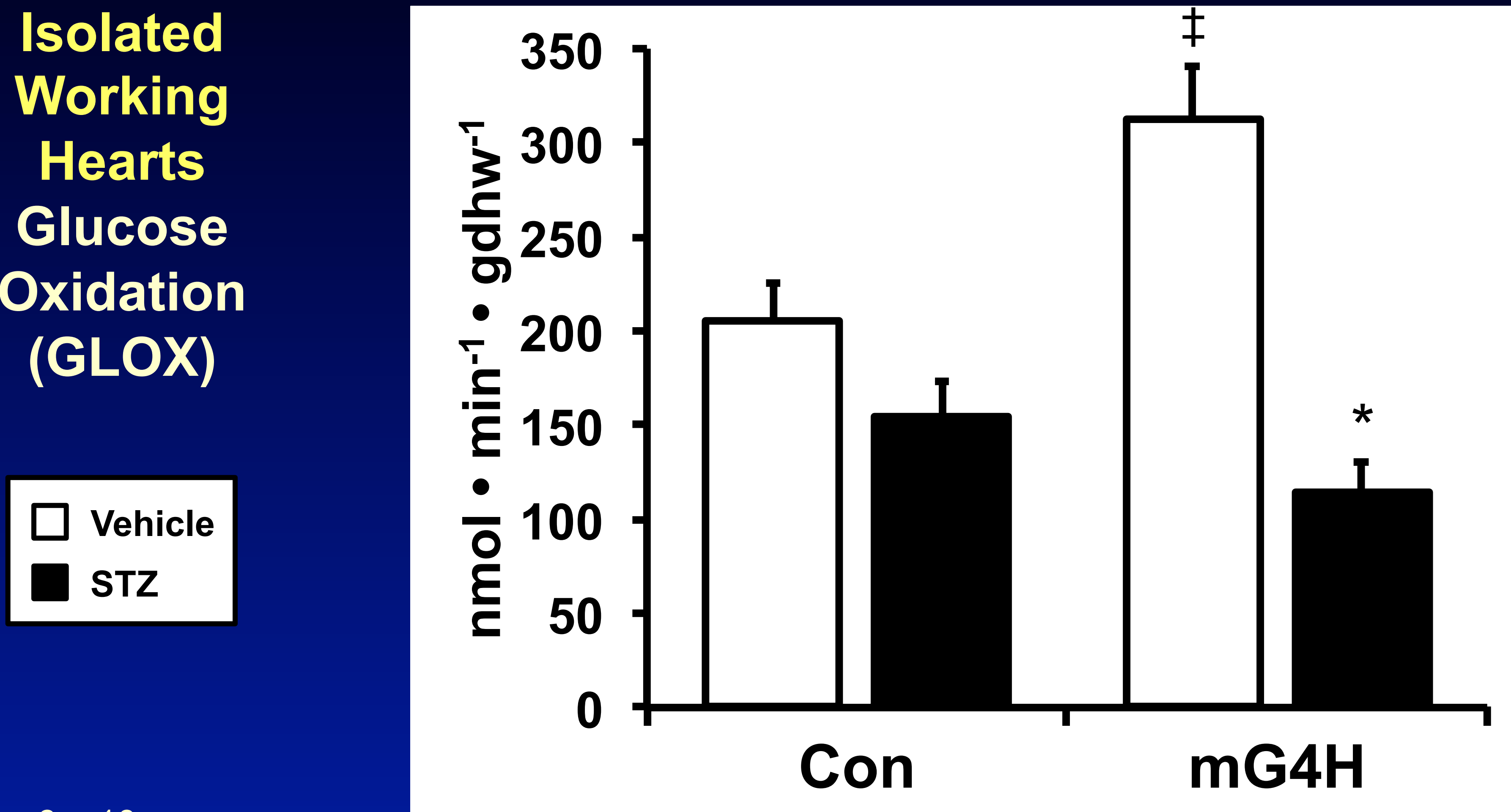
Joseph Tuinei

Wende … Abel *in prep*

GLUT4 Induction Increases GLOX but Accelerates Diabetic Cardiac GLOX Defects

Isolated Working Hearts Glucose Oxidation (GLOX)



n = 6 – 10
‡ P < 0.001 vs. All
* P < 0.01 vs. Veh

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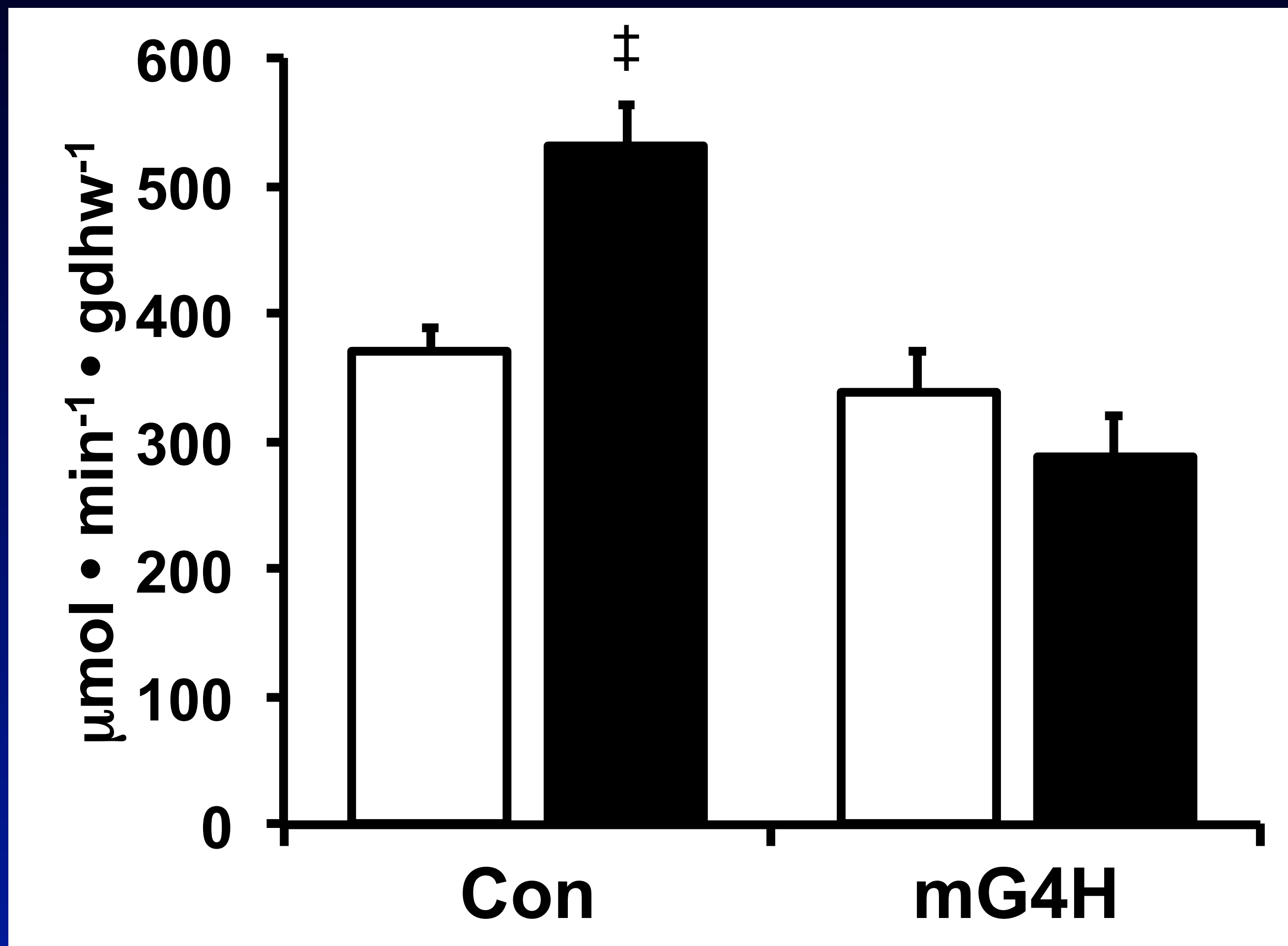
Joseph Tuinei
Wende … Abel *in prep*

GLUT4 Induction Prevents Increased Cardiac POX in Diabetes

Isolated Working Hearts Palmitate Oxidation (POX)



Vehicle
STZ

n = 5 – 13
‡ P < 0.001 vs. All
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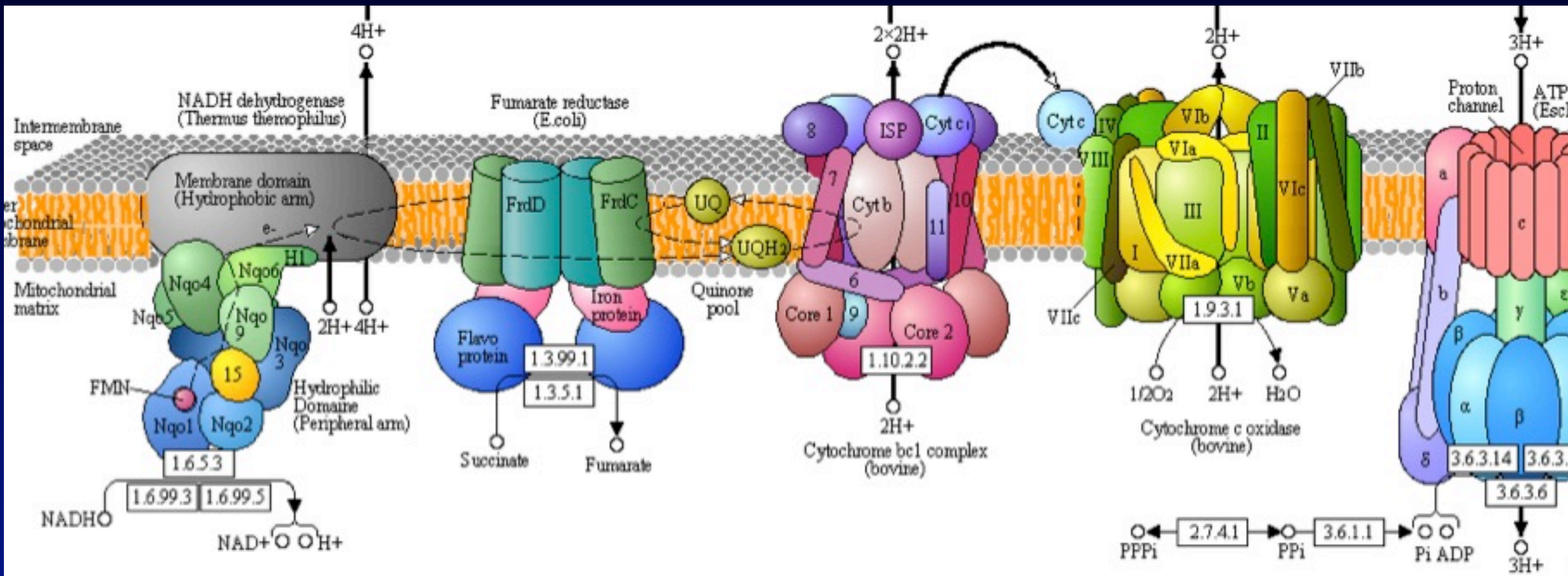
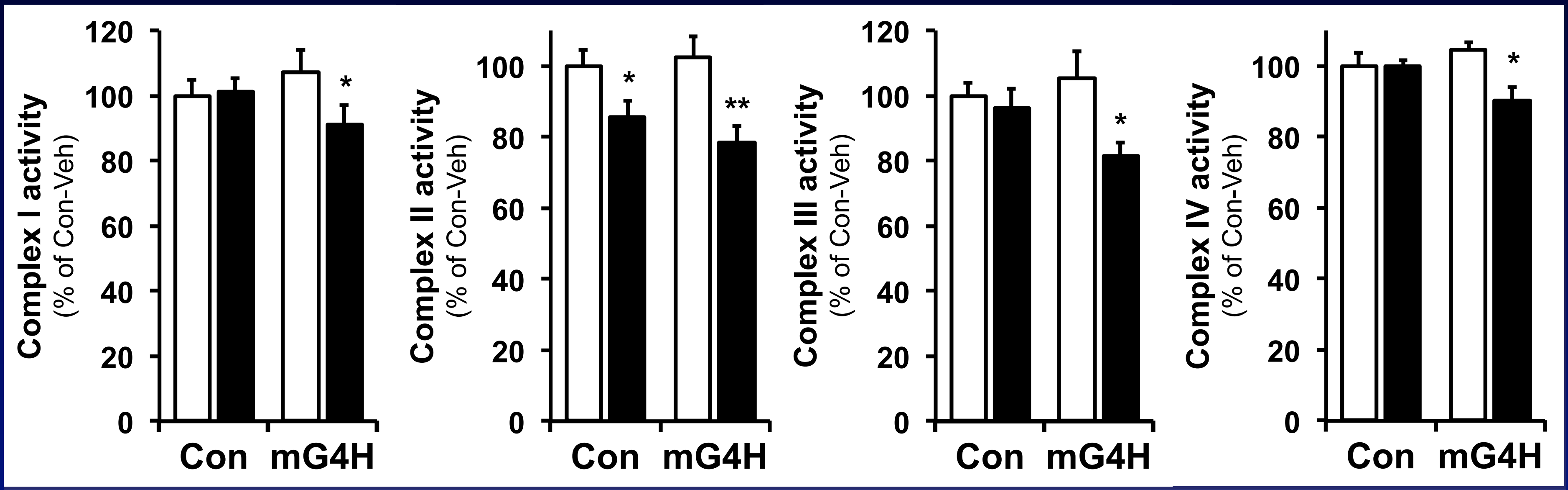
Joseph Tuinei
Wende … Abel *in prep*

Oxidative Phosphorylation



www.genome.jp/kegg/pathway.html

GLUT4 Induction Accelerates Development of Mitochondrial Dysfunction



n = 3 – 4
* P < 0.05
ARW

Oleh Khalimonchuk
Wende … Abel *in prep*

Conclusion – Part 1

In the context of diabetes, enhancing glucose delivery by expression of GLUT4 accelerates the progression of mitochondrial dysfunction.

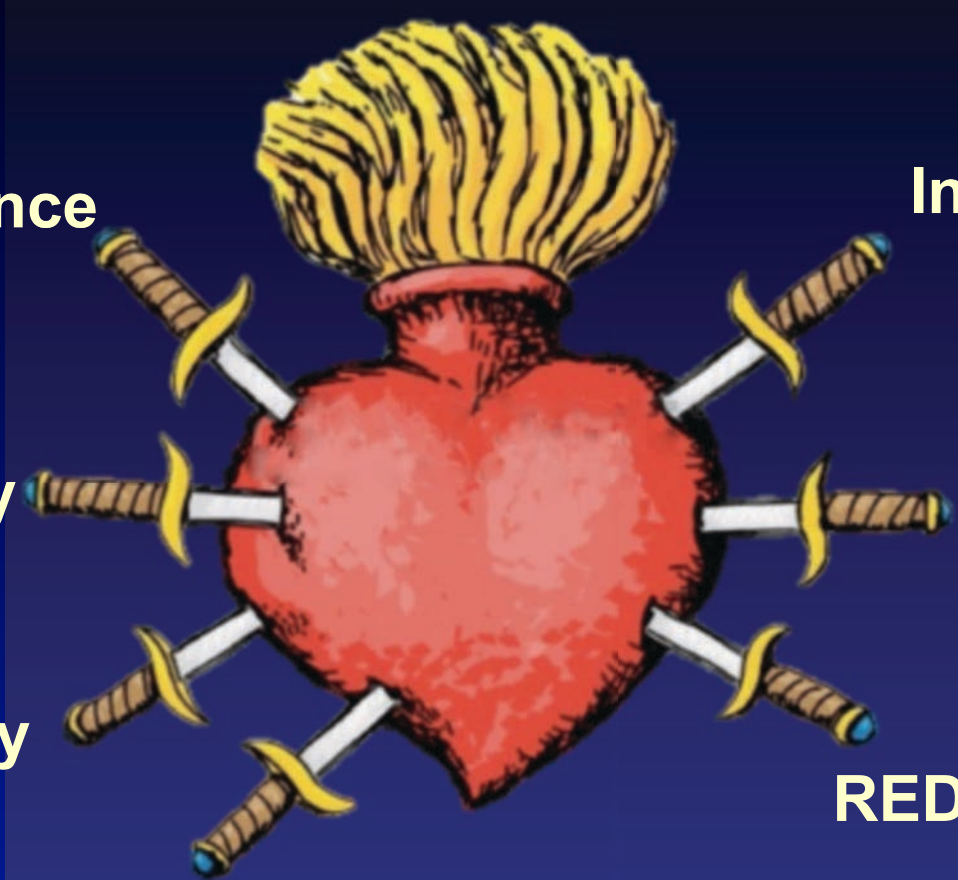
Diabetic Cardiomyopathy
"Death by a Thousand Cuts…"

Insulin resistance

Inflammation

Lipotoxicity

ER stress



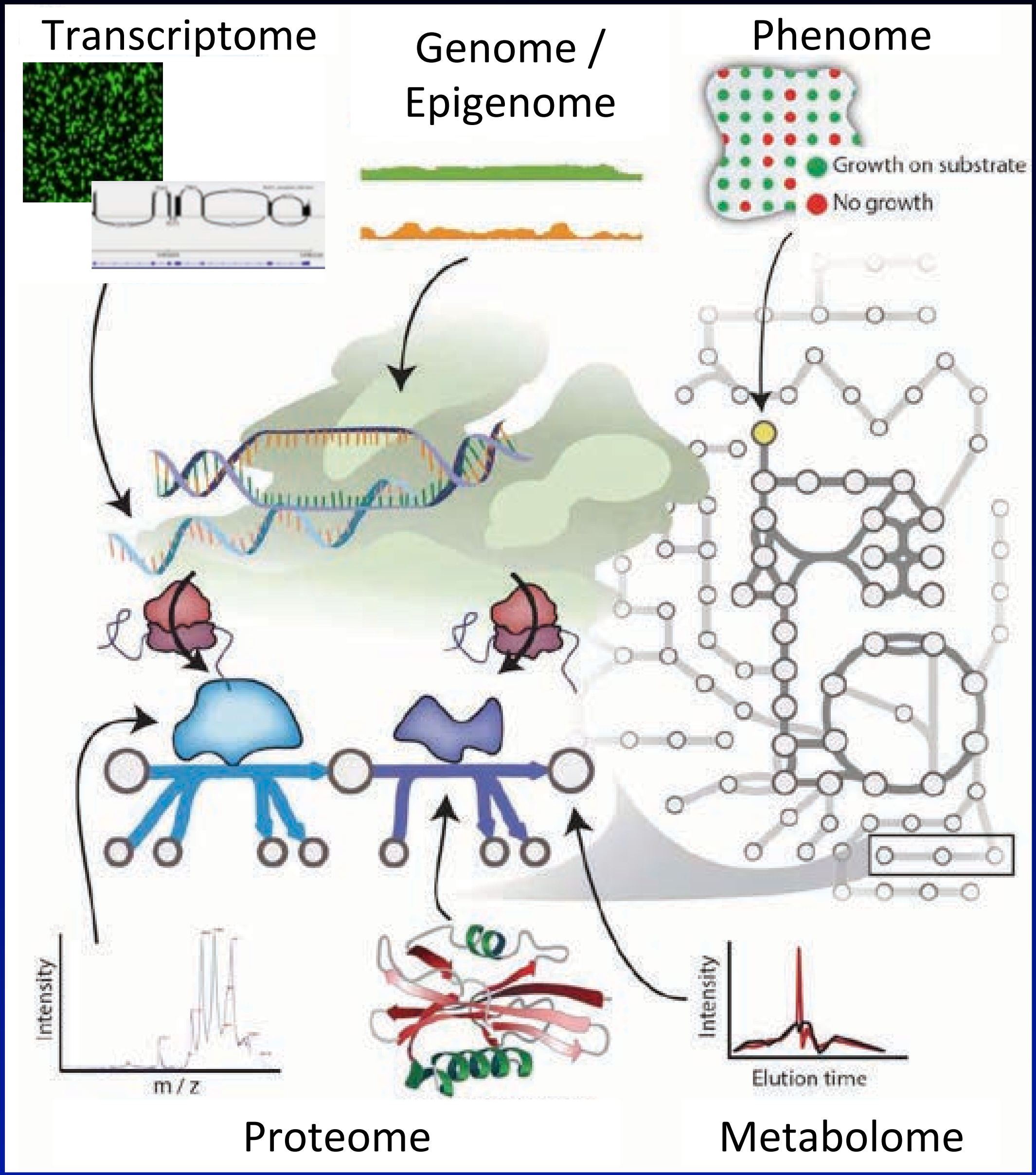
Glucotoxicity

REDOX Imbalance

Mitochondrial dysfunction

Adapted from Wende, Symons, and Abel **2012** *Curr Hypertens Rep* 14(6):517

Systems Biology



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.

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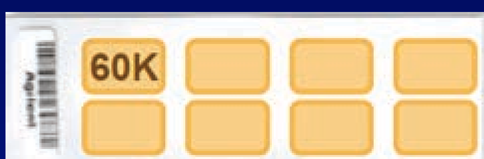
Adapted from Lewis and Abdel-Haleem **2013** *Front Physiol* 4:237

Transcriptomic Analysis Using the Agilent SurePrint G3 60K Microarray



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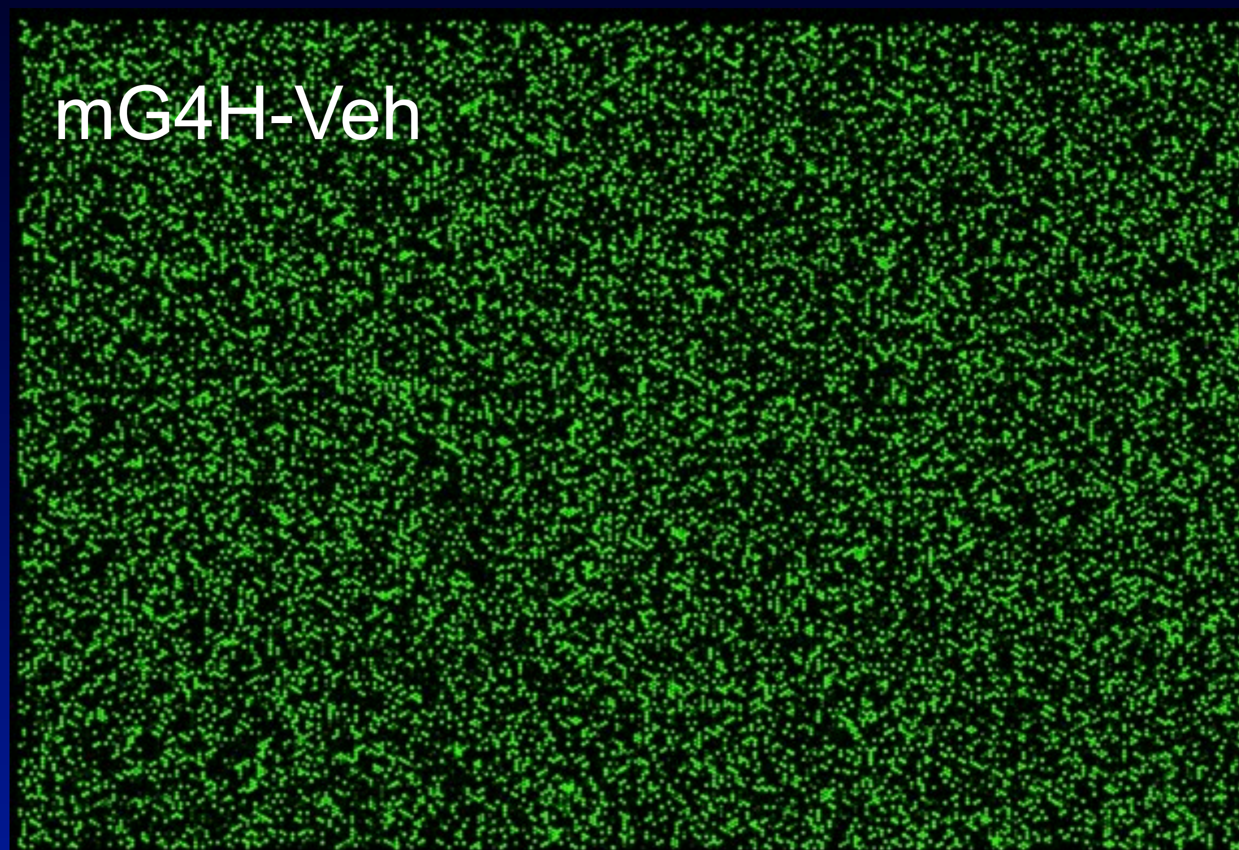

Microarray and Bioinformatic cores – Brian Dalley and Brett Milash
Wende … Abel *in prep*

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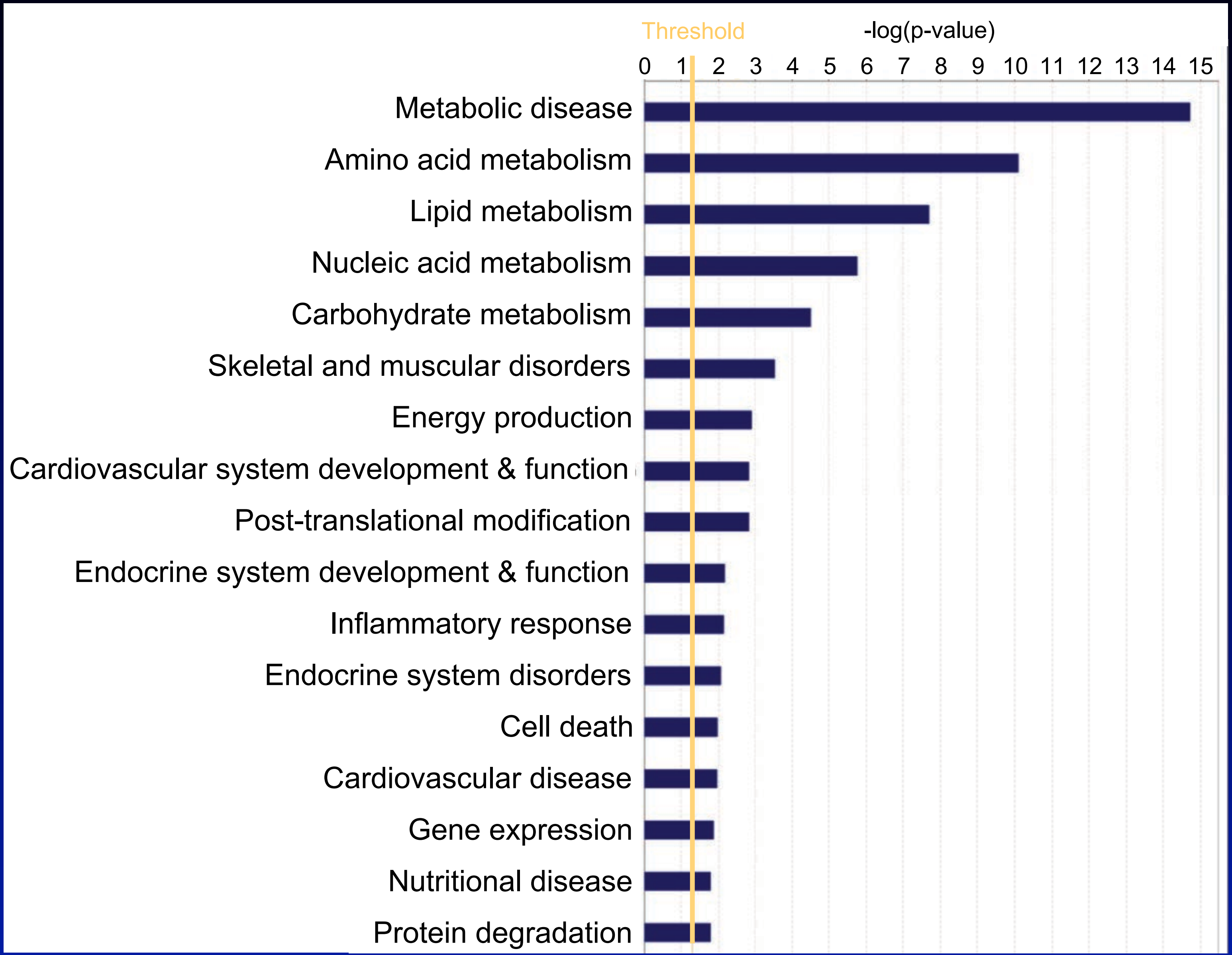
Pathway Analysis of Microarray



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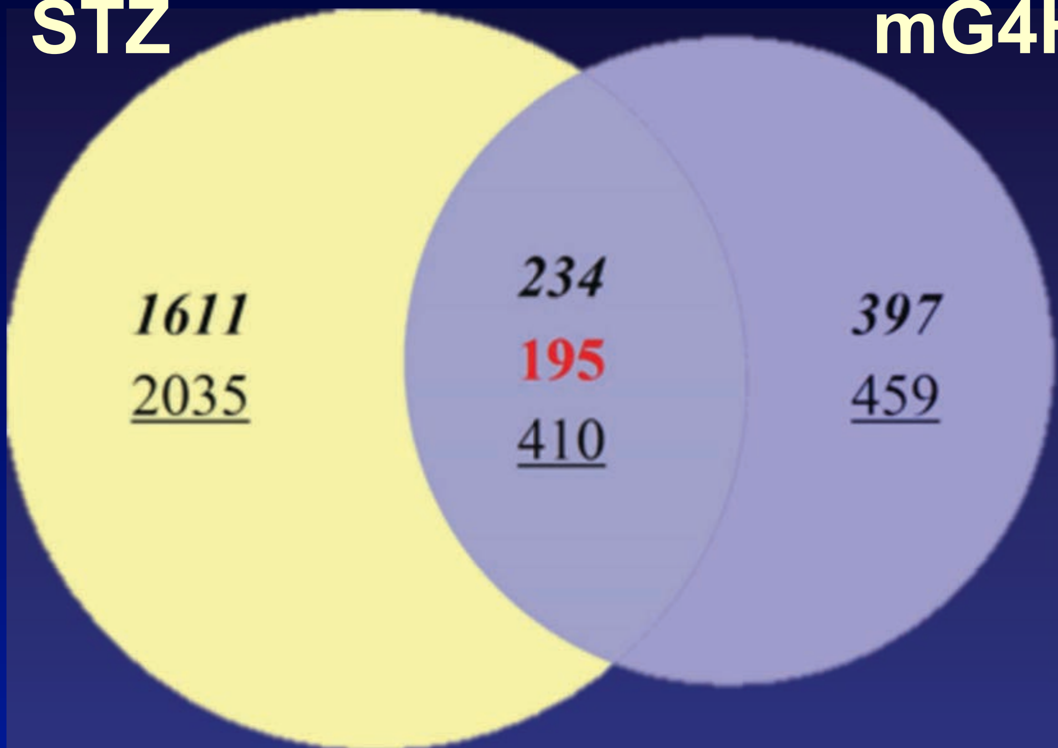
Wende … Abel *in prep*

Glucose Regulated Gene Expression

Mouse STZ

Mouse mG4H



0 *= up-regulated*
0 = contra-regulated
0 = down-regulated

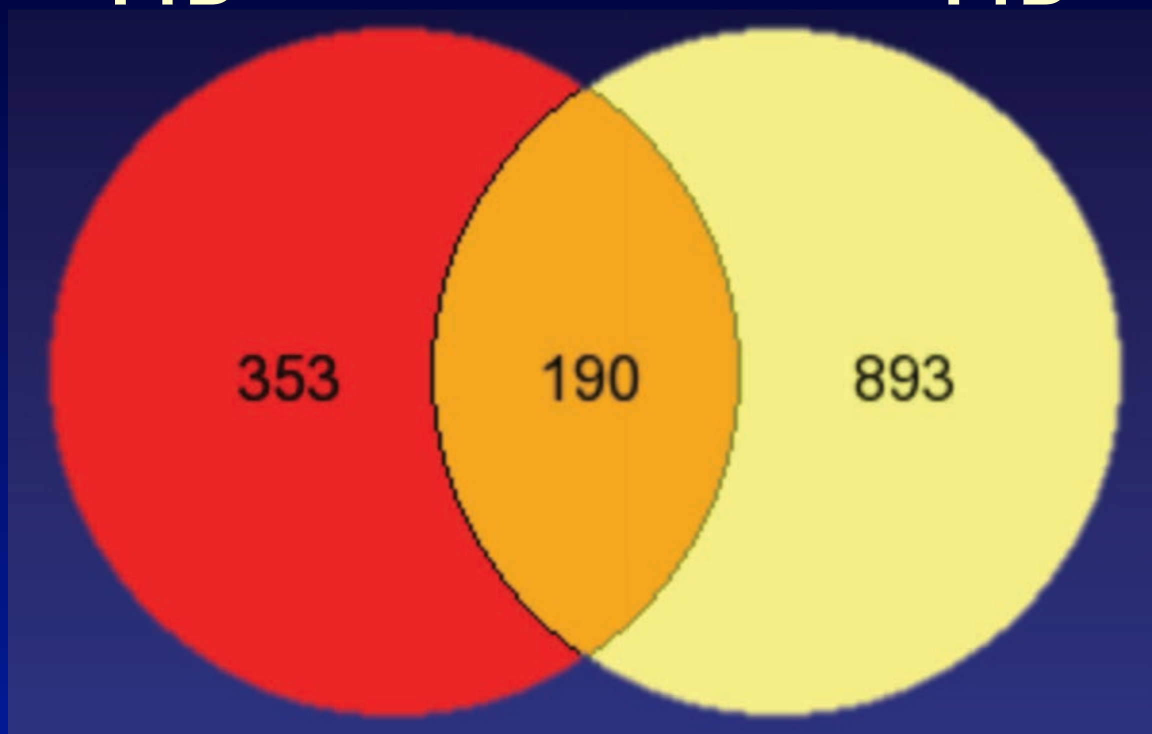
ARW

Wende, unpublished

Species Conservation of Gene Expression Changes in Diabetes

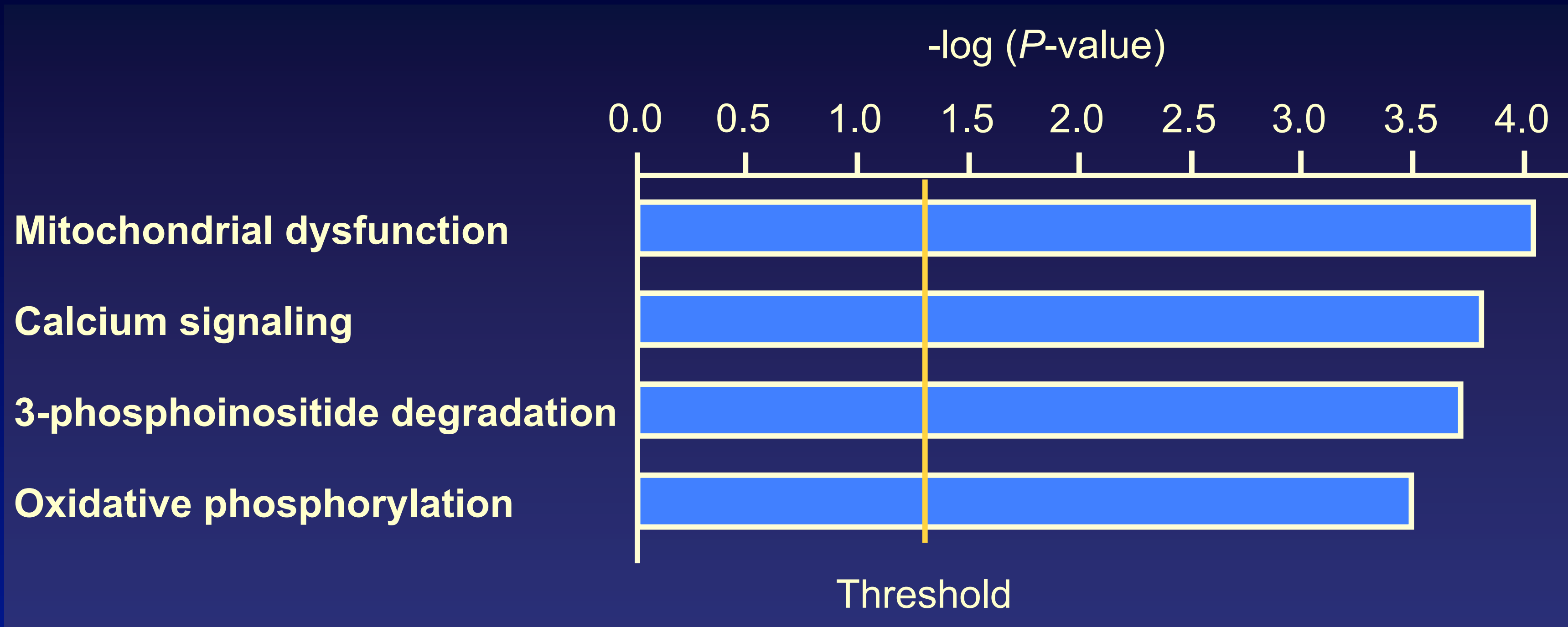
Human T1D

Mouse T1D



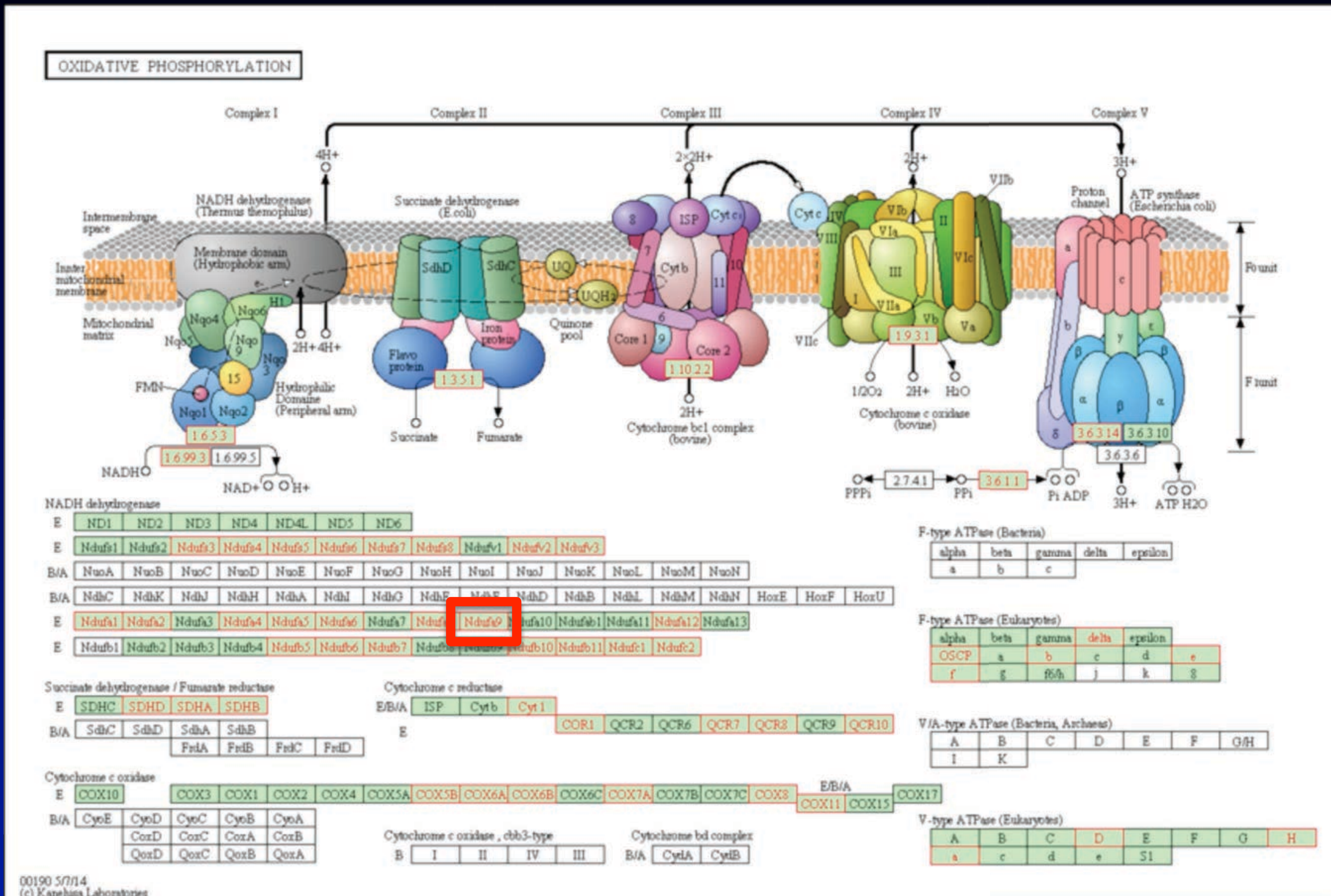
Drakos … Wende, unpublished

Species Conservation of Gene Expression Changes in Diabetes



Drakos … Wende, unpublished

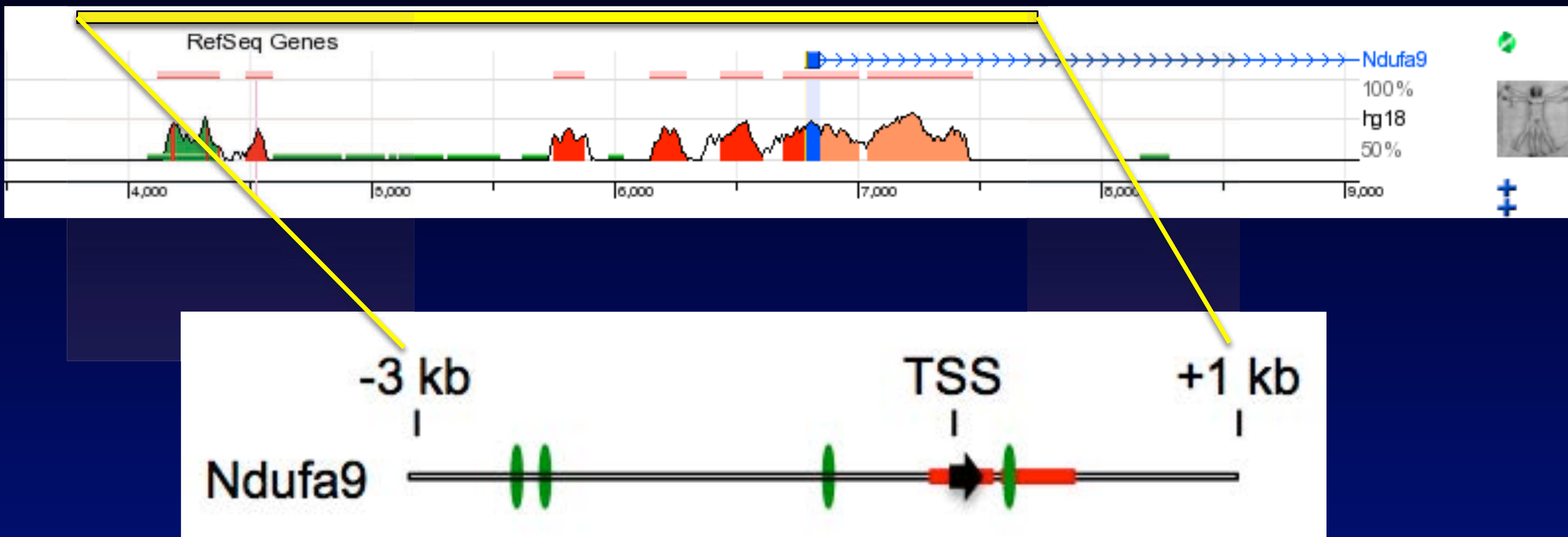
Oxidative Phosphorylation

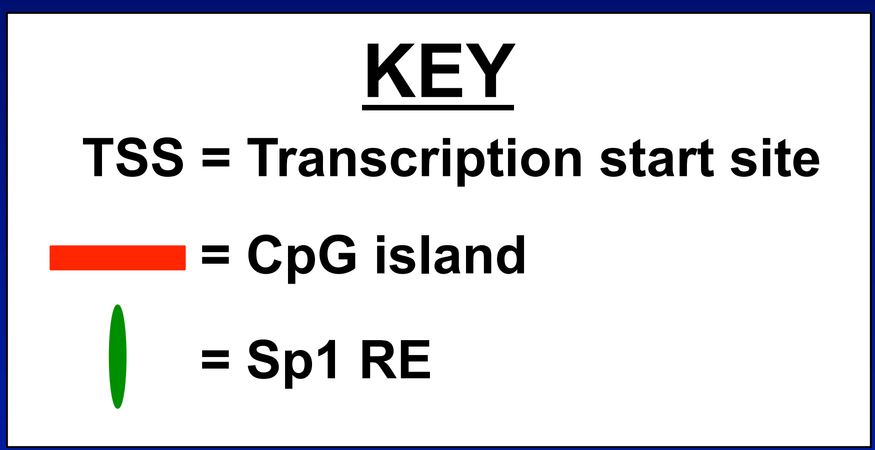


ARW

GeneSifter using KEGG

Ndufa9 Gene Promoter Structure



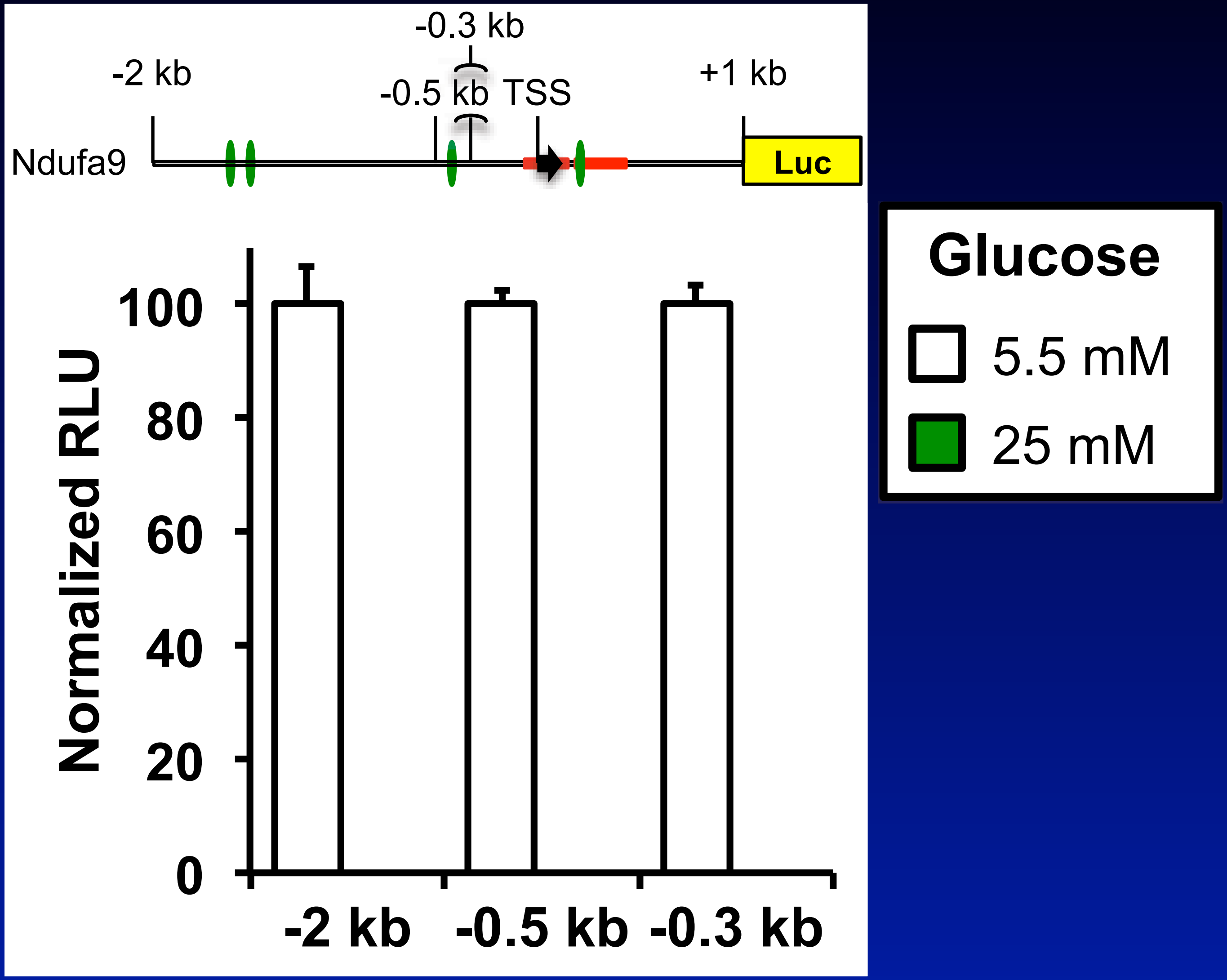


ARW

http://ecrbrowser.dcode.org

Ndufa9 Gene Promoter Mapping

Transient Transfection Promoter Activity



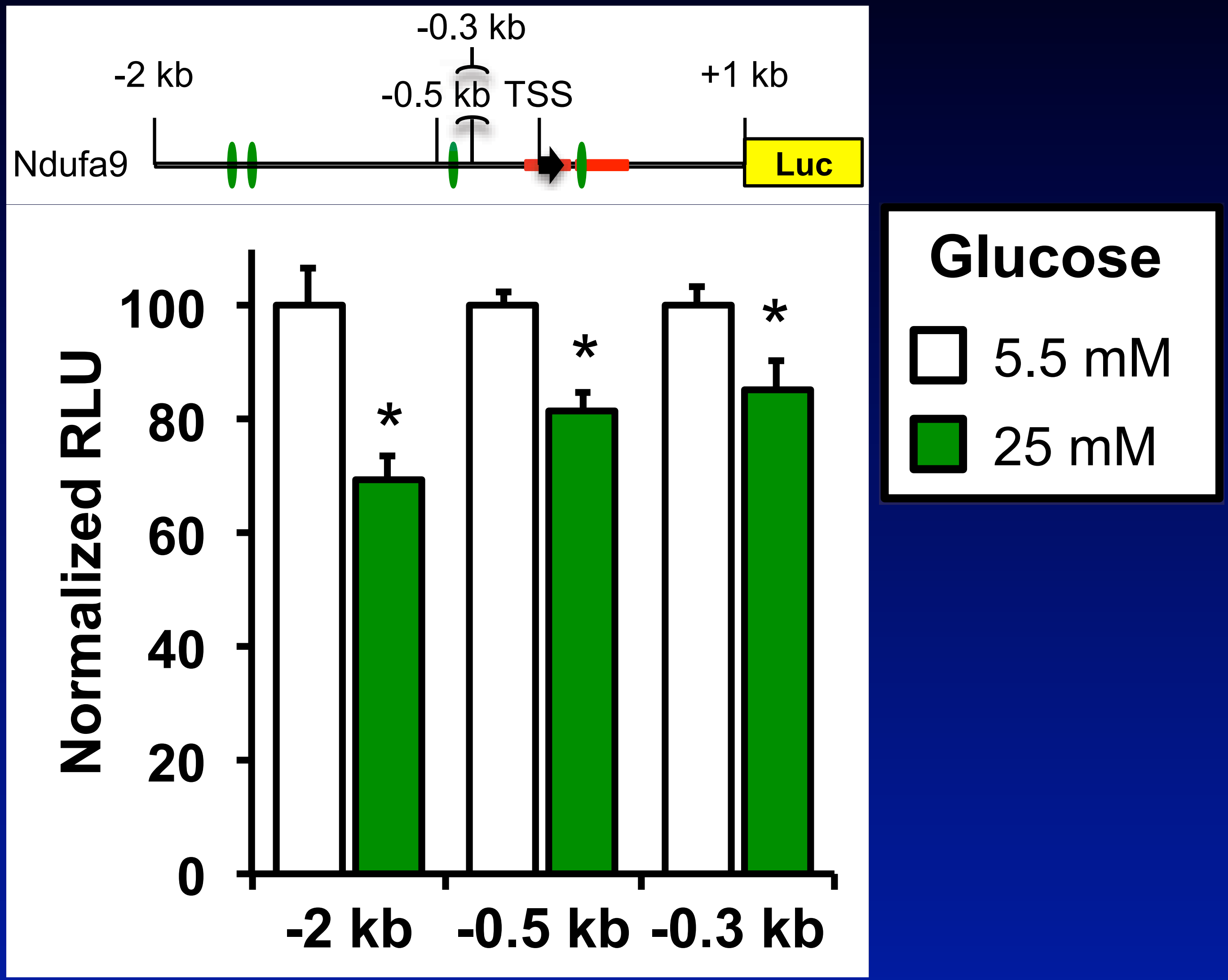
C_2C_{12} Myotubes
n = 9
* P < 0.05

ARW

Wende … Abel *in prep*

Ndufa9 Gene Promoter Mapping

Transient Transfection Promoter Activity



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Ndufa9 Gene Promoter Mapping

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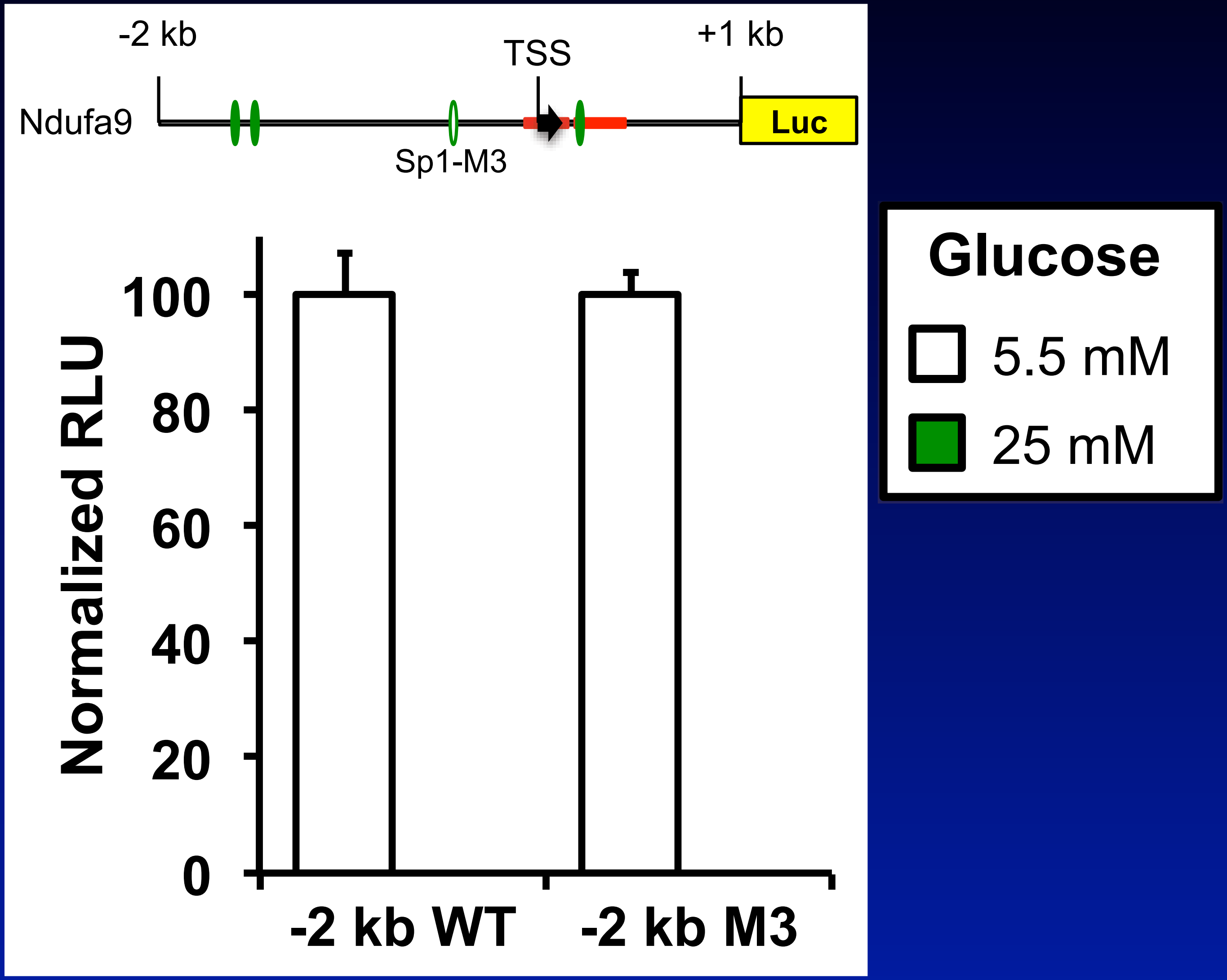

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Ndufa9 Gene Promoter Mapping

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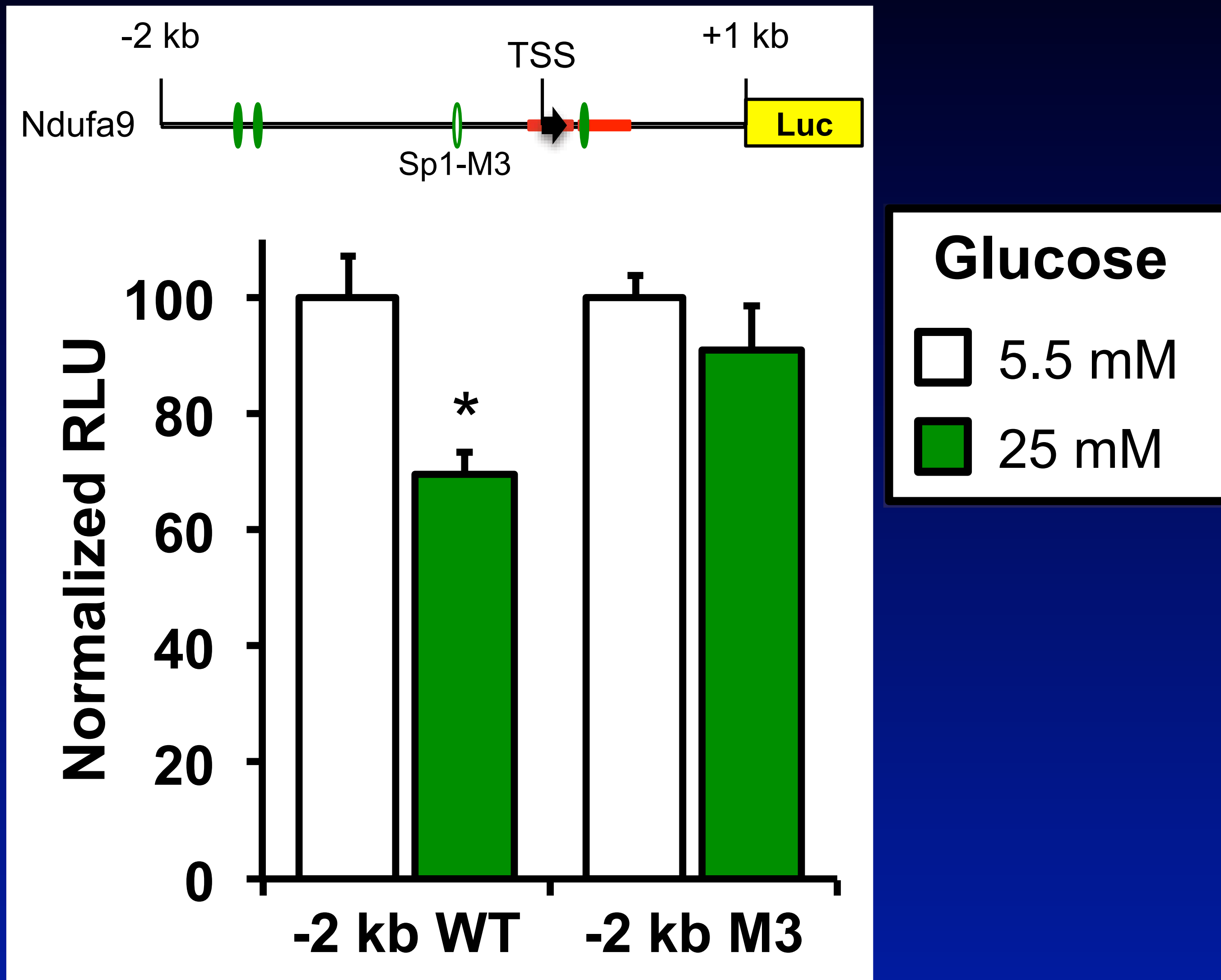

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ARW

Wende … Abel *in prep*

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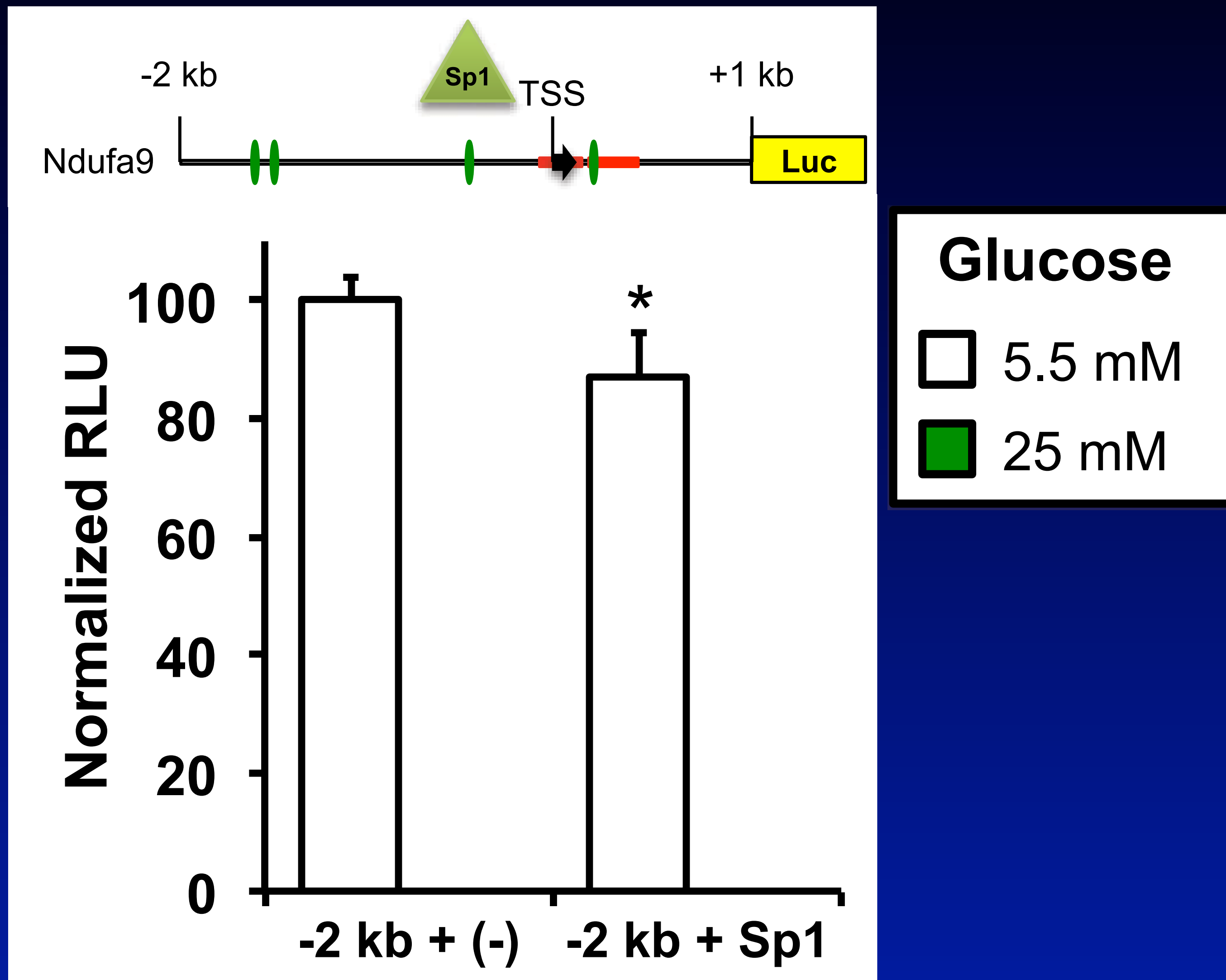

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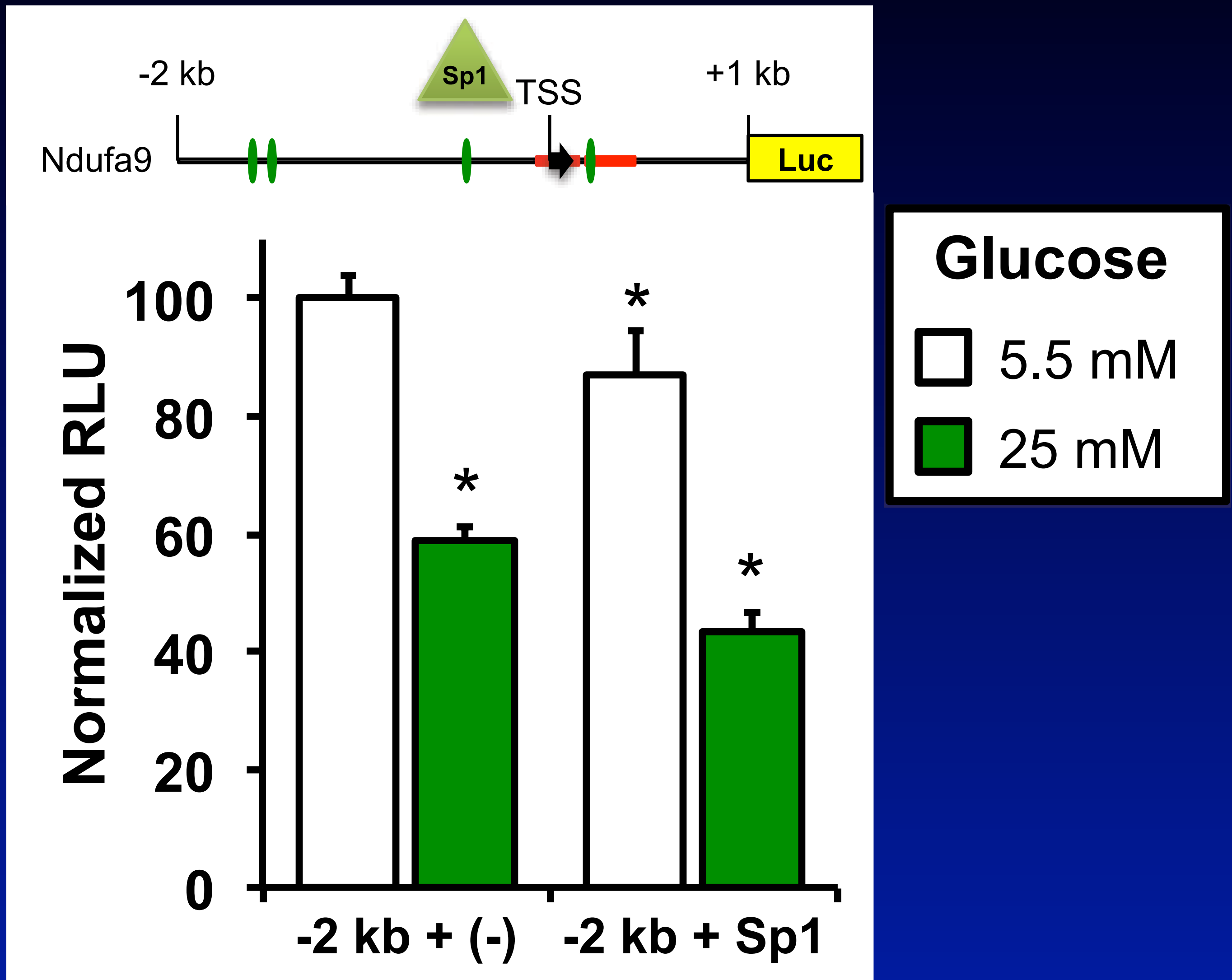
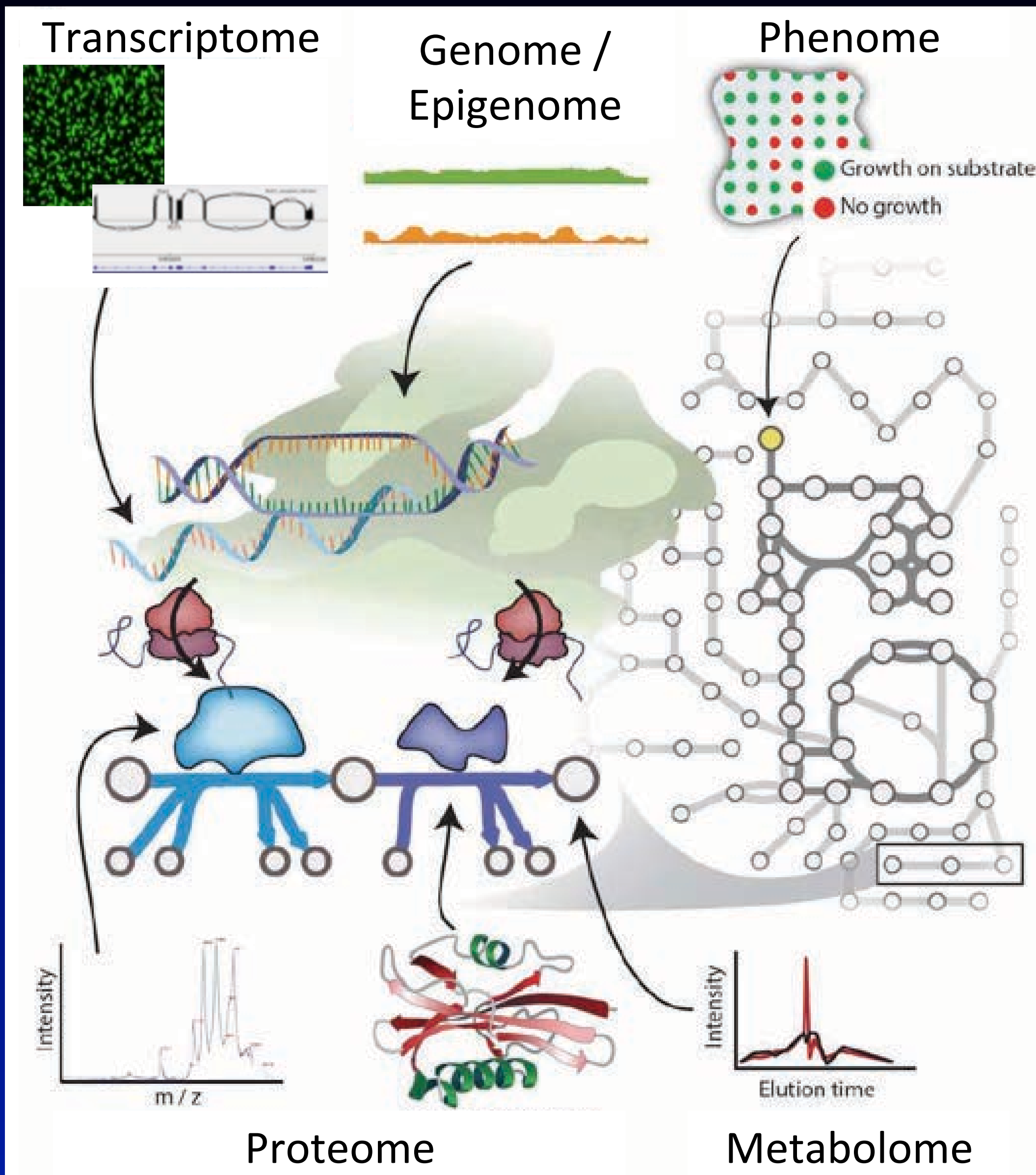


C_2C_{12} Myotubes
n = 9
* P < 0.05

ARW

Wende … Abel *in prep*

Systems Biology



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.

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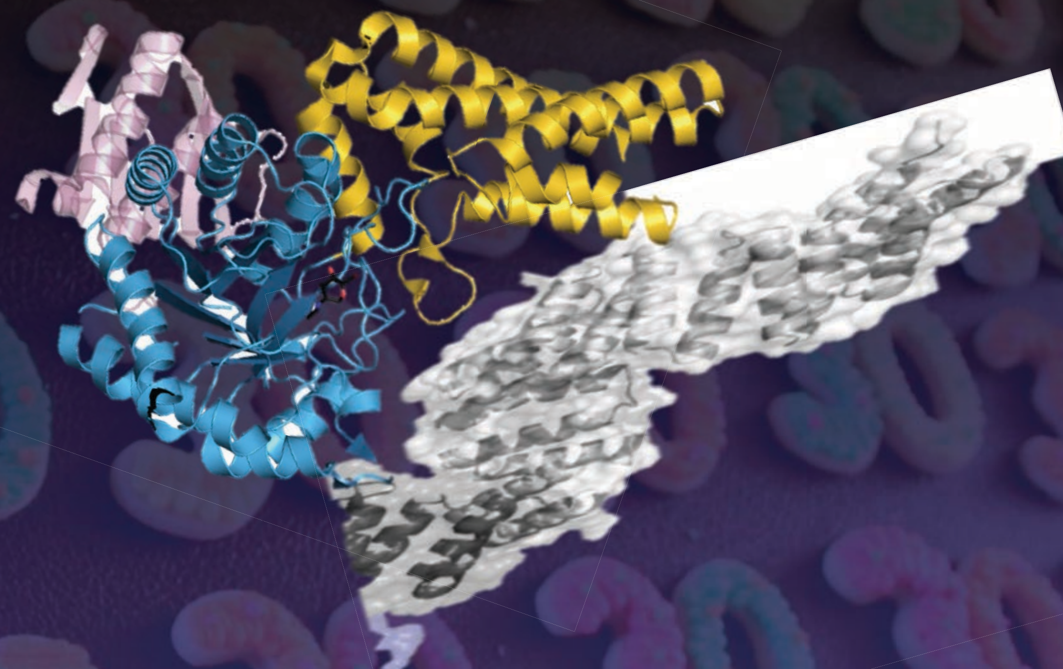
Genome / Epigenome

Southerns, sequencing,
GenBank, ENCODE,
ChIP-seq, bsDNA-seq, etc.

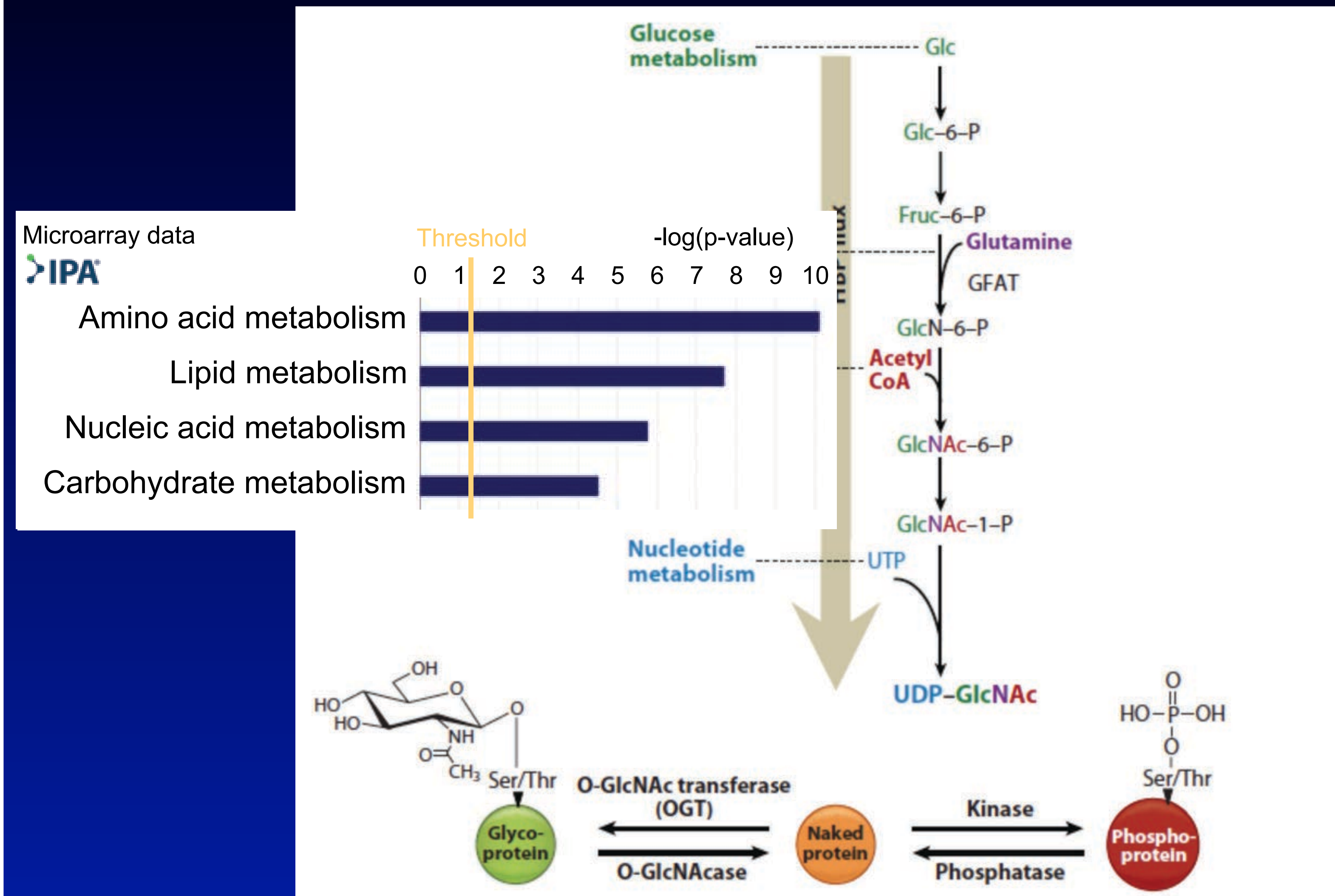
ARW

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

O-GlcNAcylation

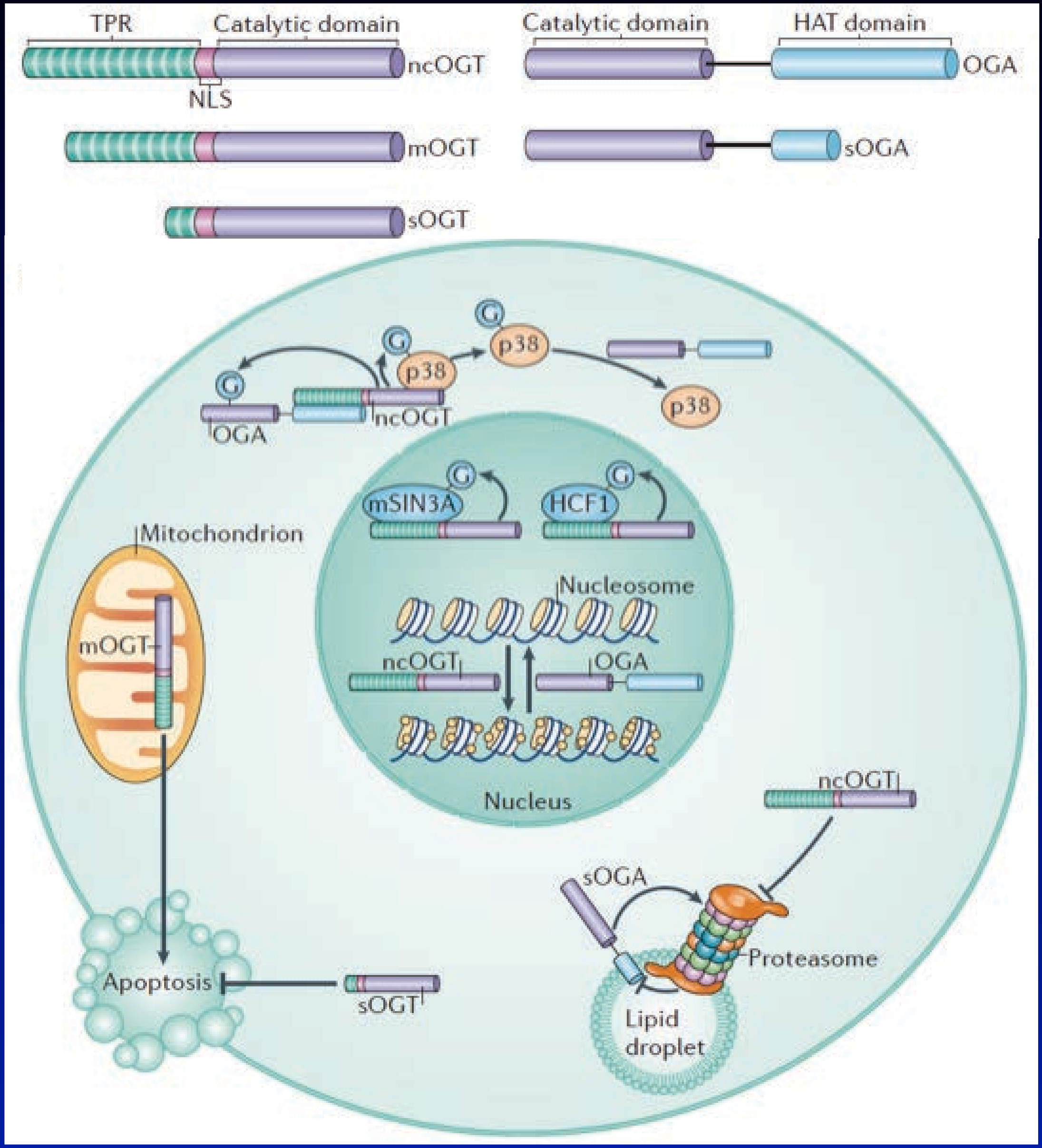


Metabolic Integration: Protein *O*-GlcNAcylation



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

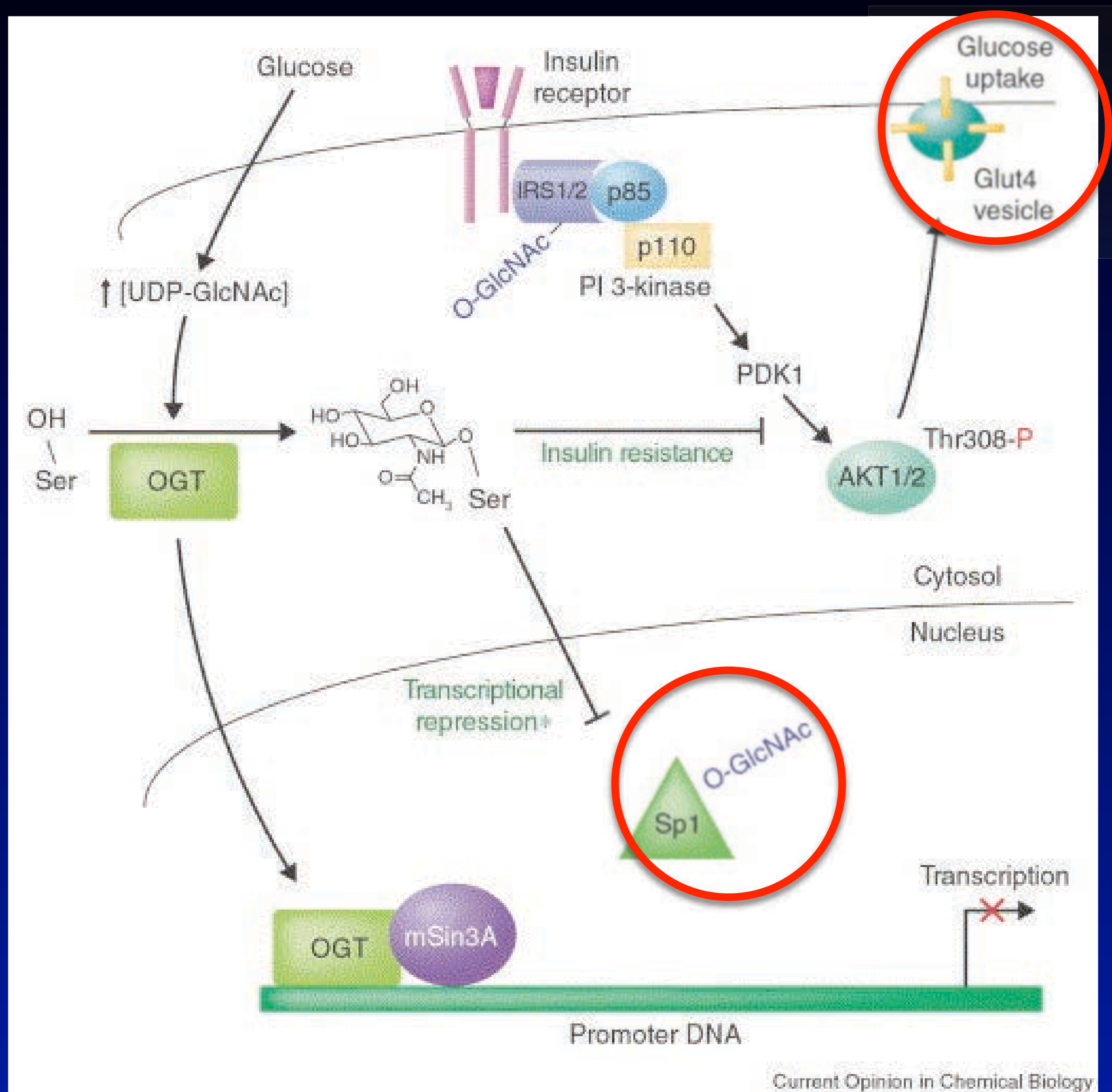
O-GlcNAc Cycling



ARW

Hanover … Love **2012** *Nat Rev Mol Cell Biol* 13(5):312

GlcNAc Regulation of Sp1

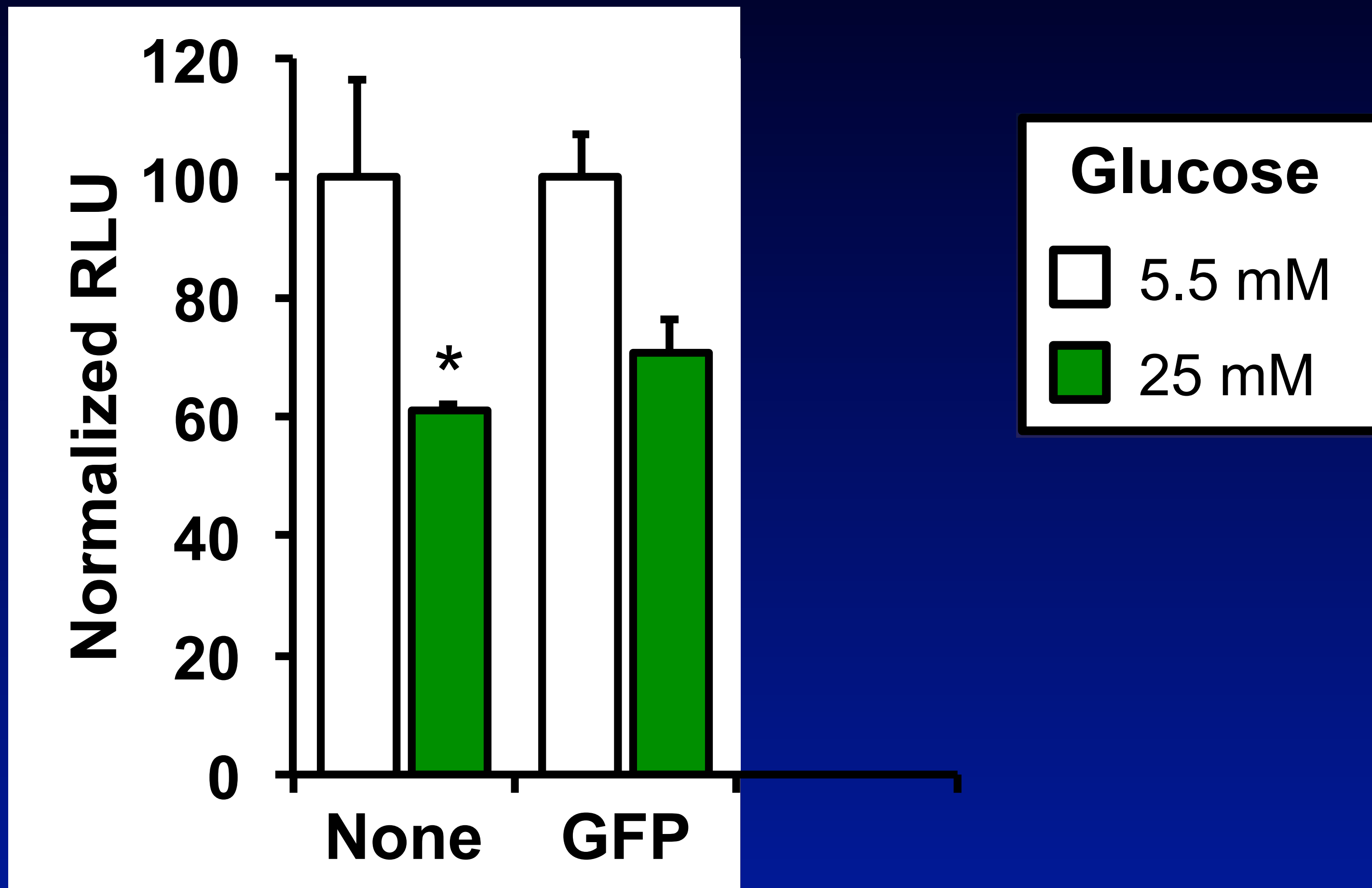


ARW

Vosseller … Hart **2002** *Curr Opin Chem Biol* 6(6):851

GlcNAcylation Regulates *Ndufa9* Gene Expression

Transient Transfection Promoter Activity

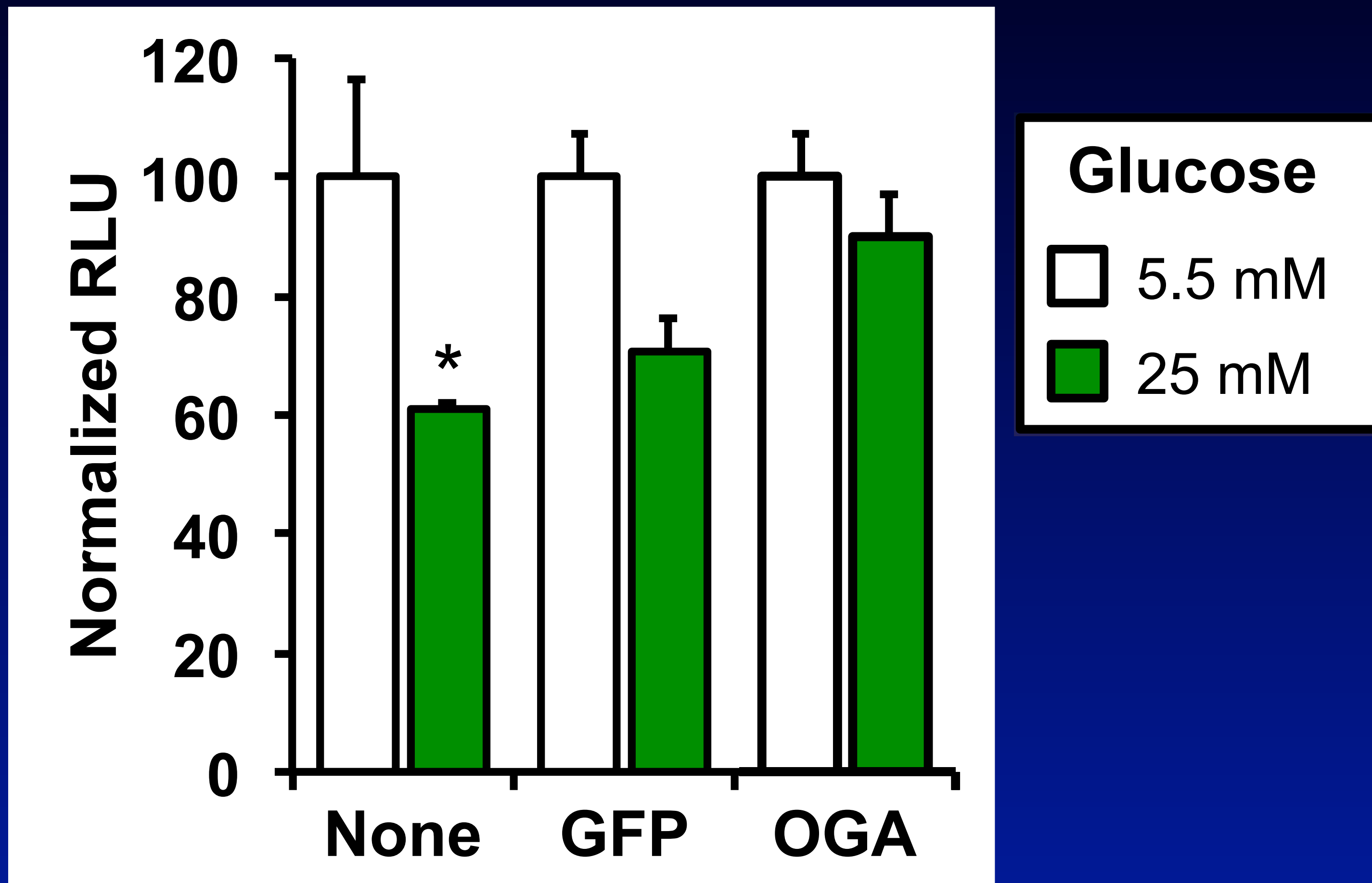


C_2C_{12} Myotubes
$n = 3$
* $P < 0.05$
ARW

Li Wang
Wende … Abel *in prep*

GlcNAcylation Regulates *Ndufa9* Gene Expression

Transient Transfection Promoter Activity



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ARW

Li Wang
Wende … Abel *in prep*

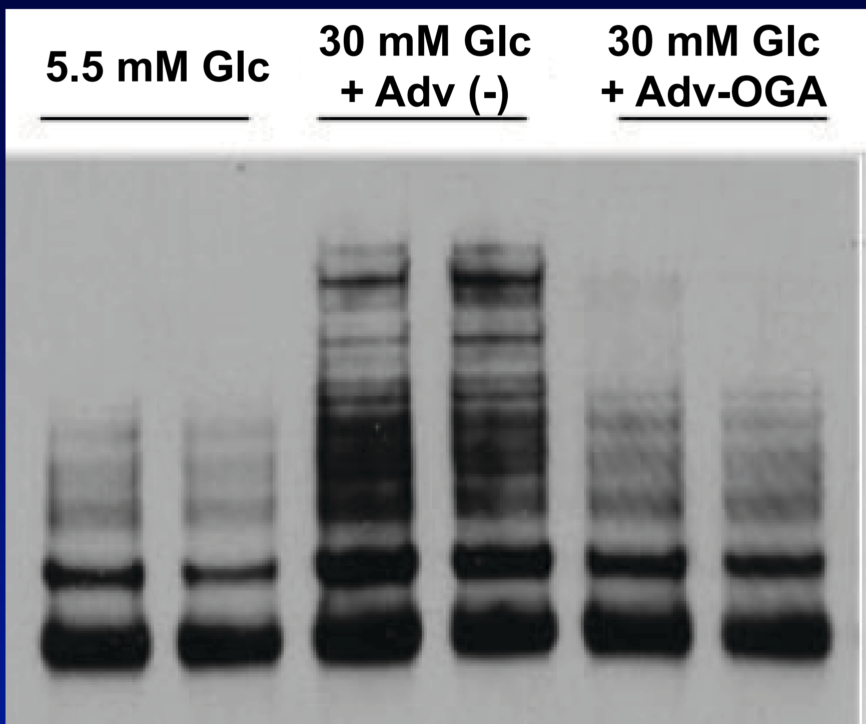
Conclusion – Part 2

Enhanced glucose delivery regulates oxidative capacity via transcriptional mechanisms including GlcNAcylation of transcription factors.

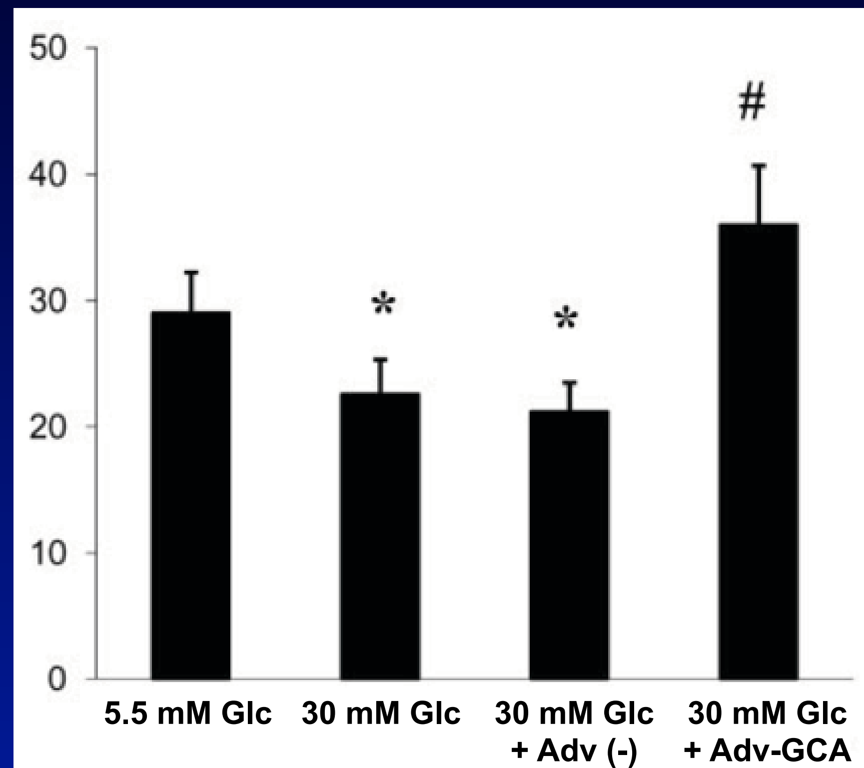
ARW

Mitochondrial Protein *O*-GlcNAcylation and Neonatal Cardiomyocyte Metabolic Function

Mitochondrial Protein
O-GlcNAcylation



Complex I Activity



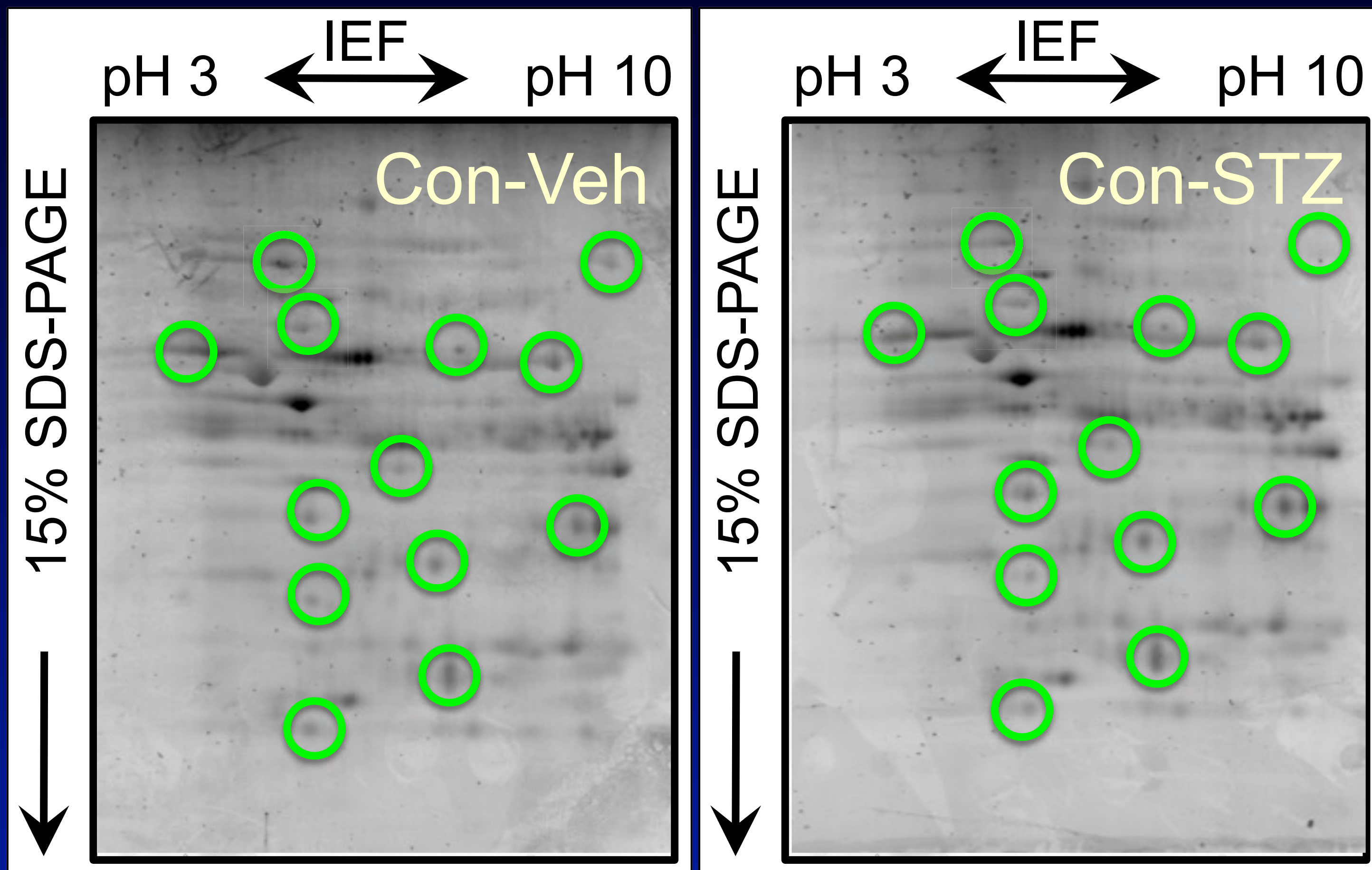
O-GlcNAcylation of NDUFA9

ARW

Hu … Dillmann **2009** *J Biol Chem* 284(1):547

GLUT4 Induction Alters the Cardiac Mitochondrial Glycoproteome

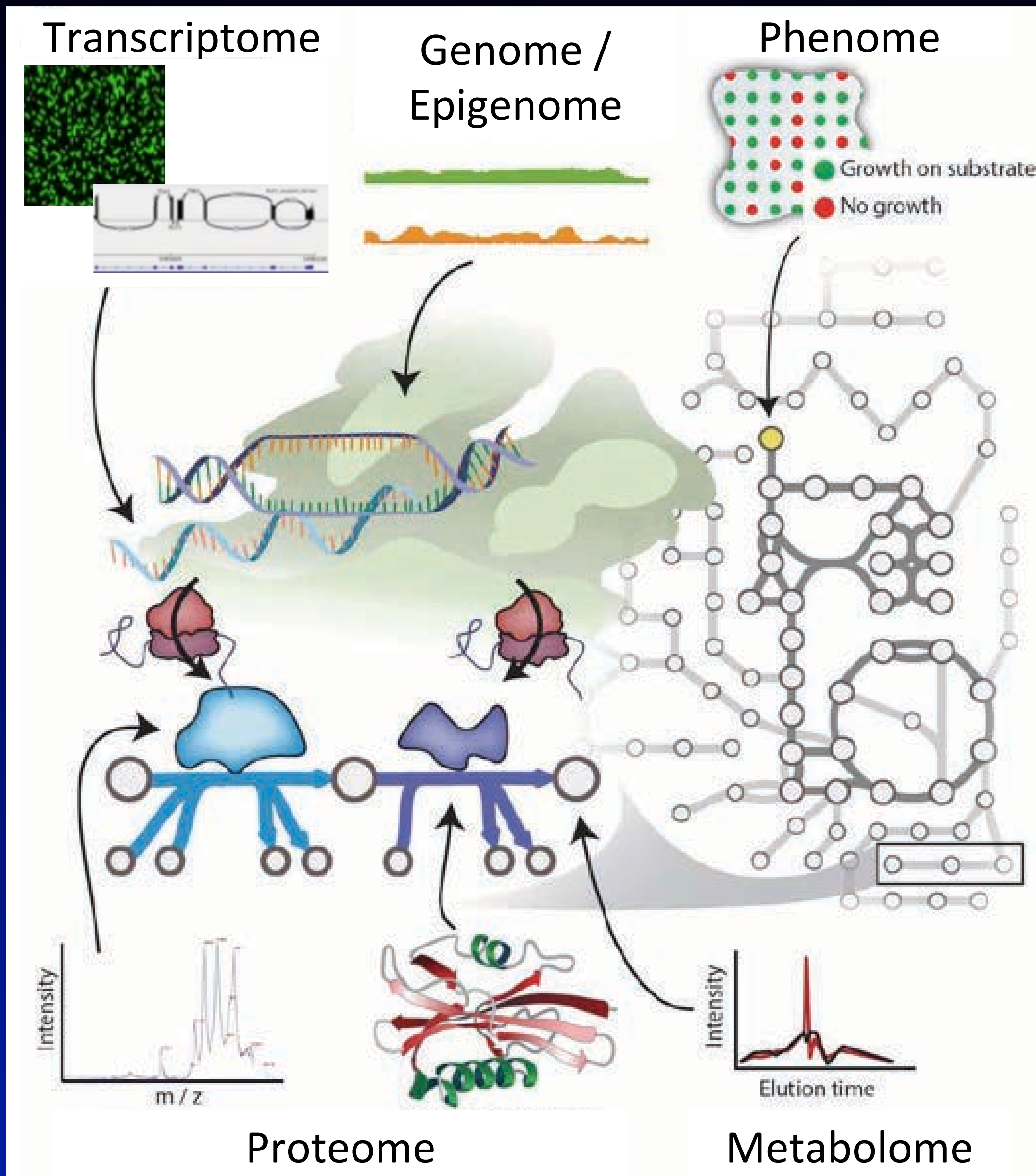
Isolated Mitochondria 2D-PAGE Pro-Q Emerald



Hansjörg Schwertz
Wende, unpublished

ARW

Systems Biology



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

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

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

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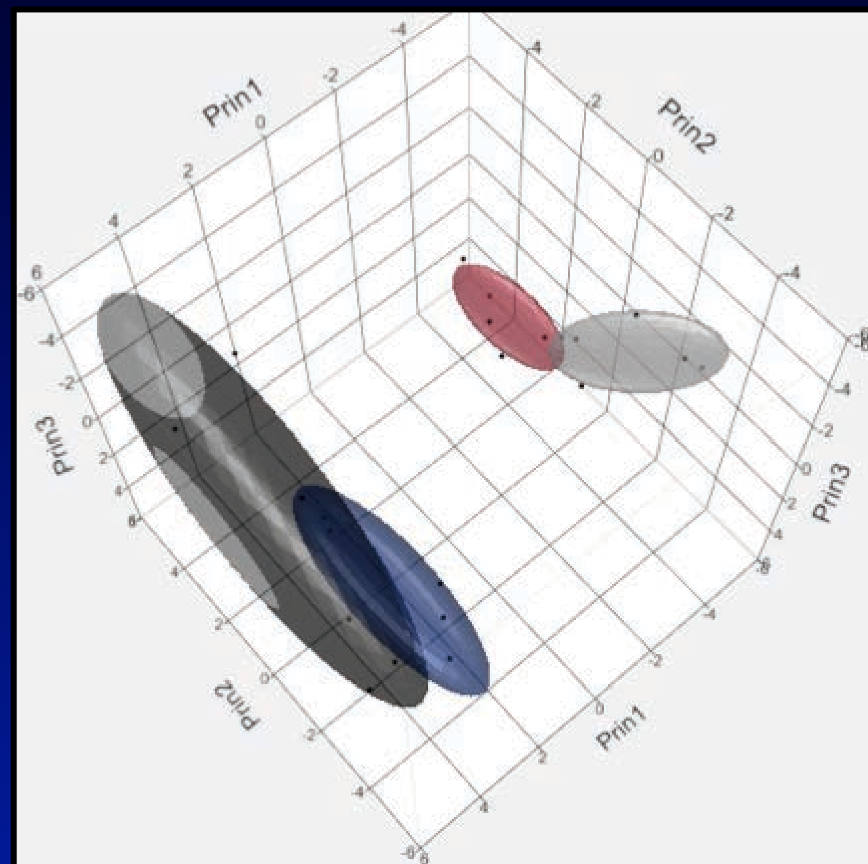
ARW

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

Metabolomic Signatures of Diabetic Heart Disease

3D – PCA



KEY

- Con-Veh
- Con-STZ
- mG4H-Veh
- mG4H-STZ

Studies on Myocardial Metabolism*

IV. Myocardial Metabolism in Diabetes

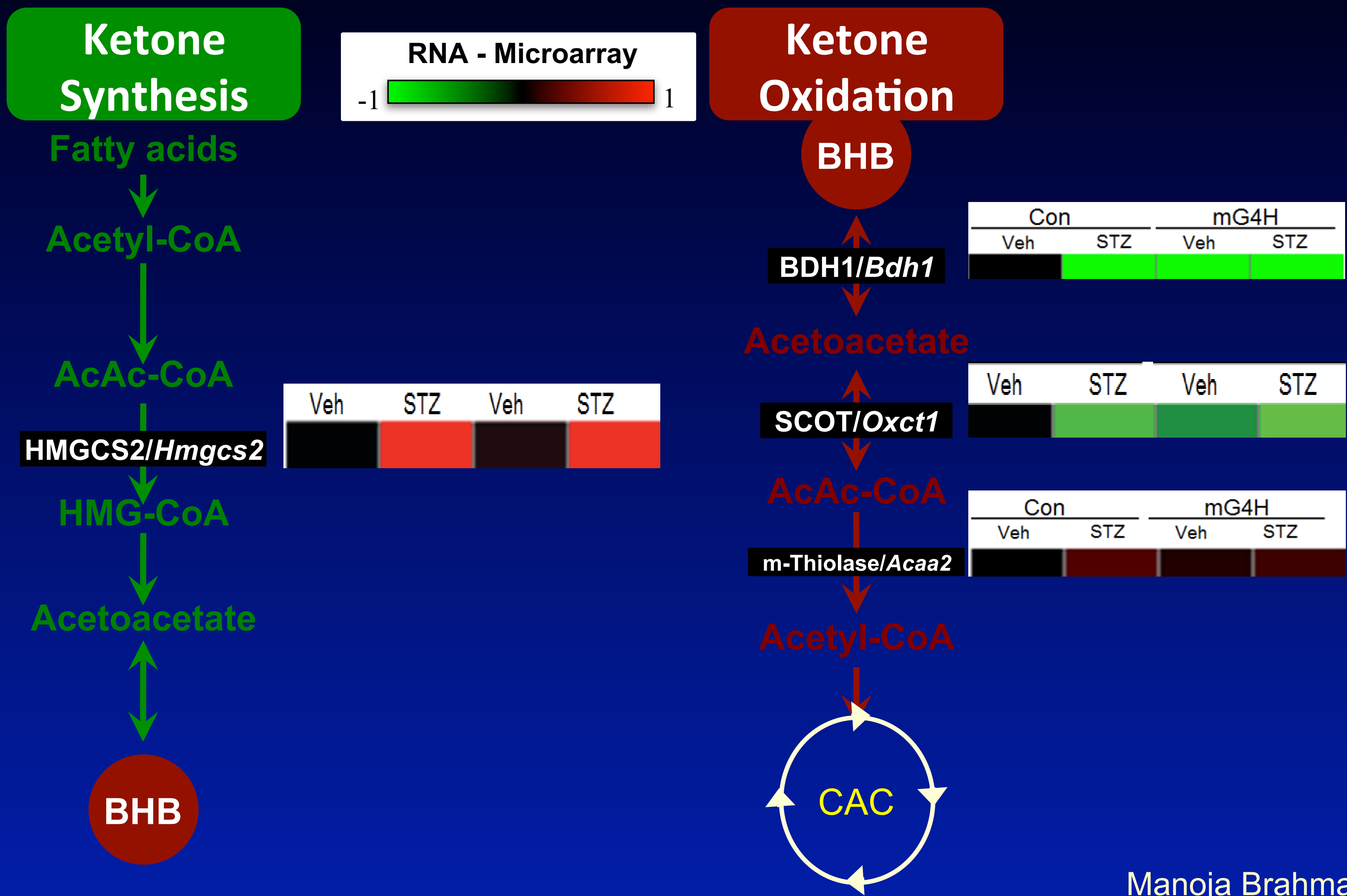
I. Ungar, M.D., M. Gilbert, M.D., A. Siegel, M.S., J. M. Blain, M.D. *and* R. J. Bing, M.D.
Birmingham, Alabama

lactate usage and a slight decline in that of pyruvate. There is no change in utilization of 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 of diabetes is not clear. Anesthesia, which was used in the dogs, may have played some part.

ARW

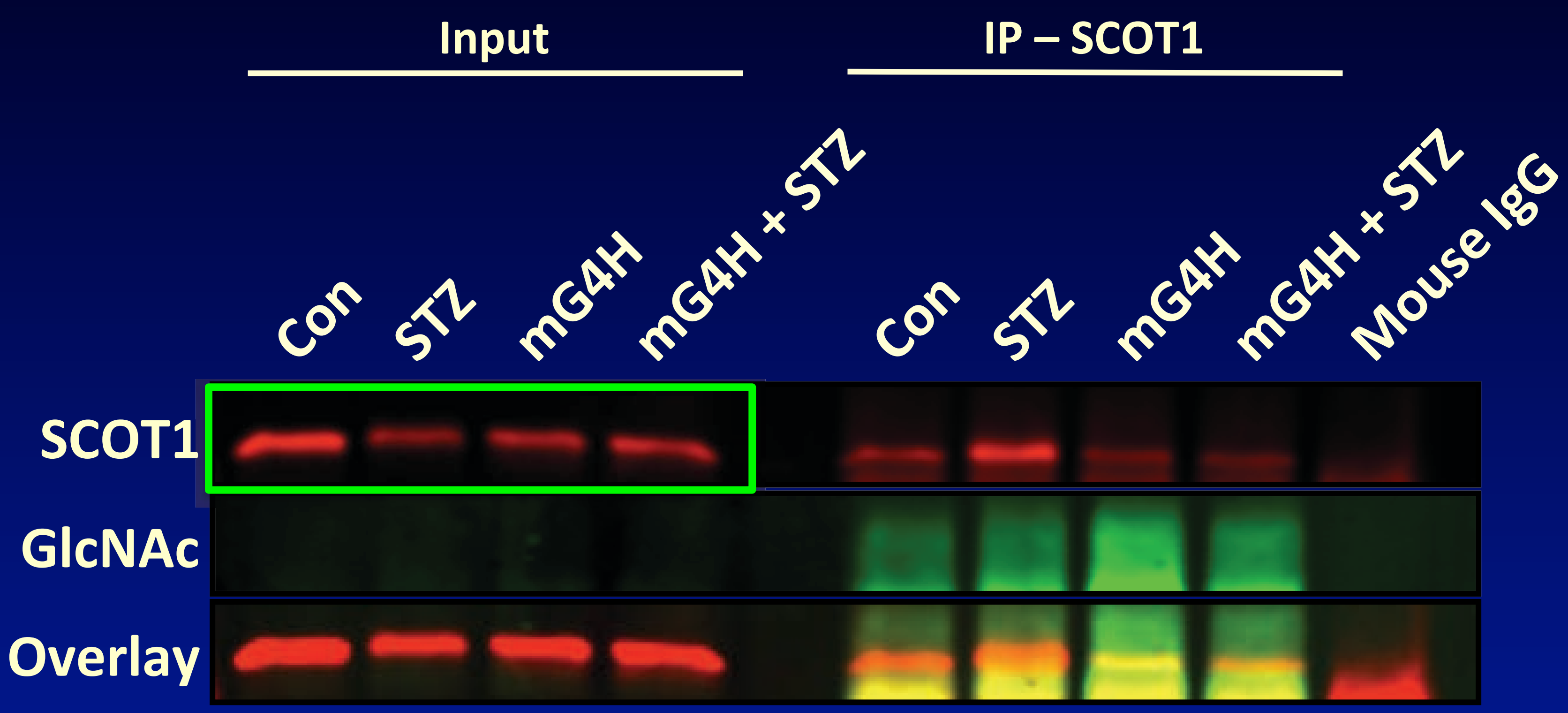
Ungar … Bing **1955** *Am J Med* 18(3):385

GLUT4 Induction Alters Cardiac Ketone Utilization Genes



Manoja Brahma

GLUT4 Induction Alters Cardiac Ketone Protein GlcNAcylation



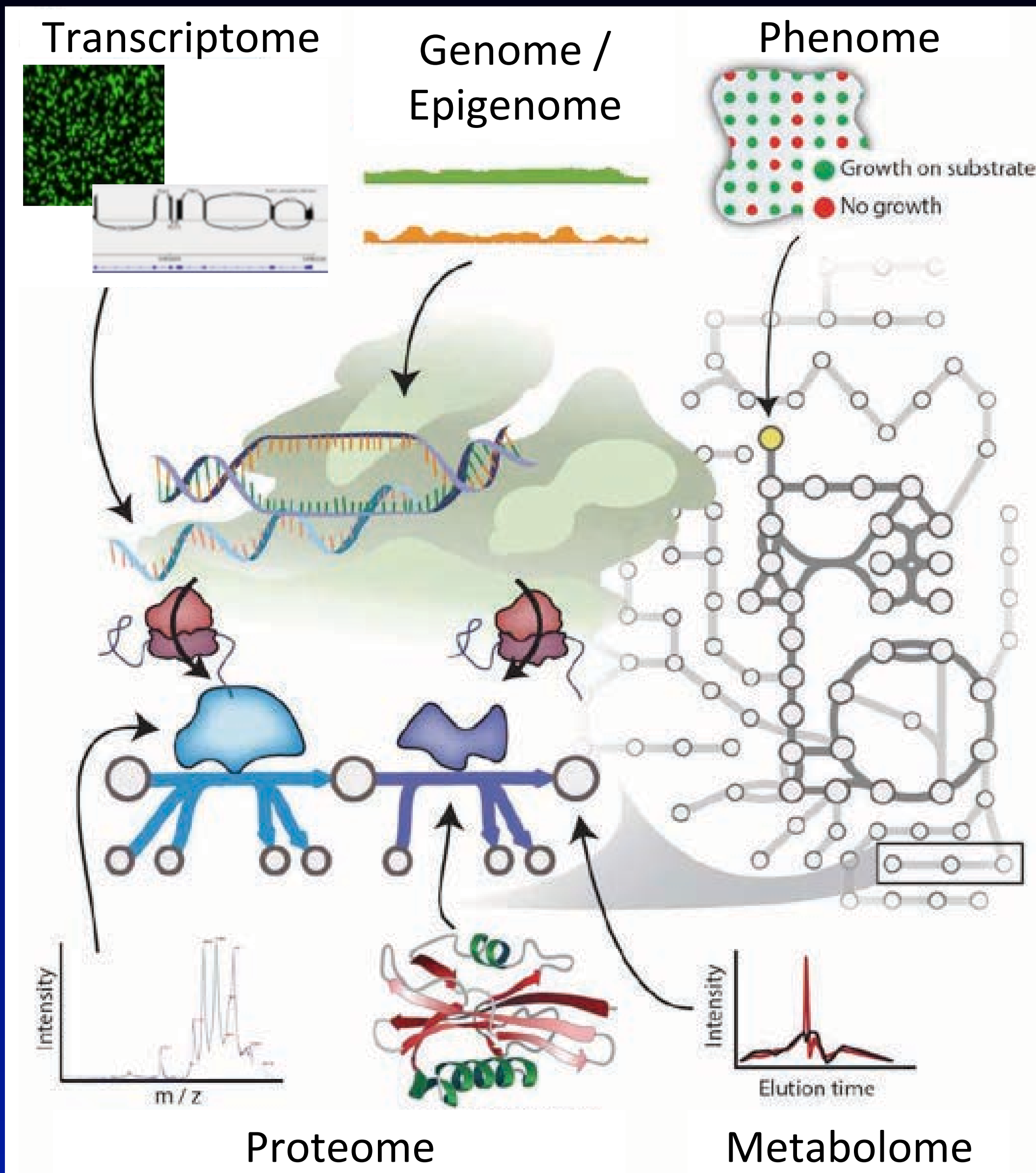
Manoja Brahma

Conclusion – Part 3

Enhanced cardiac glucose delivery alters metabolic flux through other pathways and regulates the mitochondrial proteome via *O*-GlcNAcylation.

ARW

Systems Biology



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Genome / Epigenome
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ARW

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

From Human to Mouse and Back Again

ARW

Broad Institute Communications

Role of Epigenetics in Gene Expression

ARW

Epigenetics - Programming

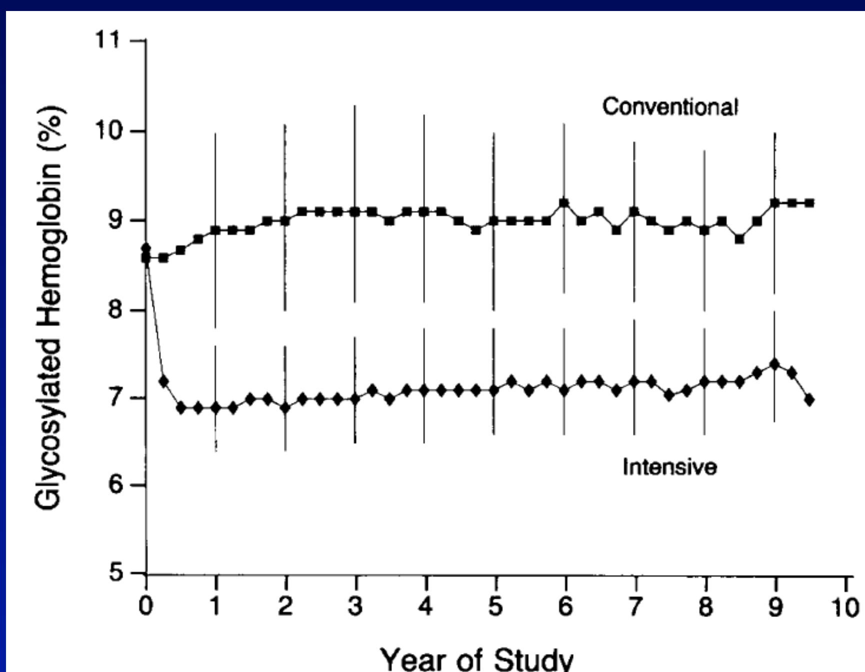
DCCT: Diabetes Control and Complications Trial

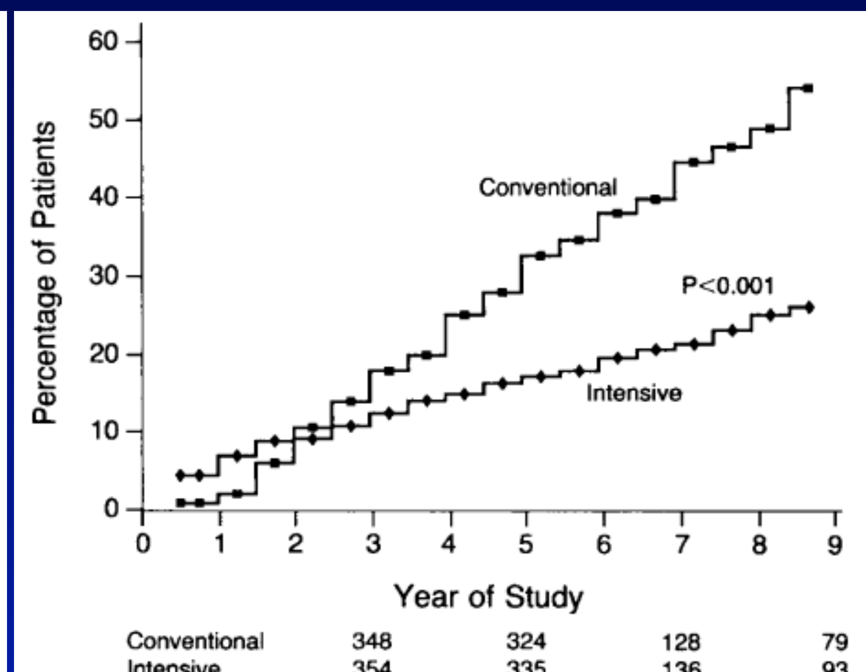
The New England
Journal of Medicine

Volume 329 SEPTEMBER 30, 1993 Number 14

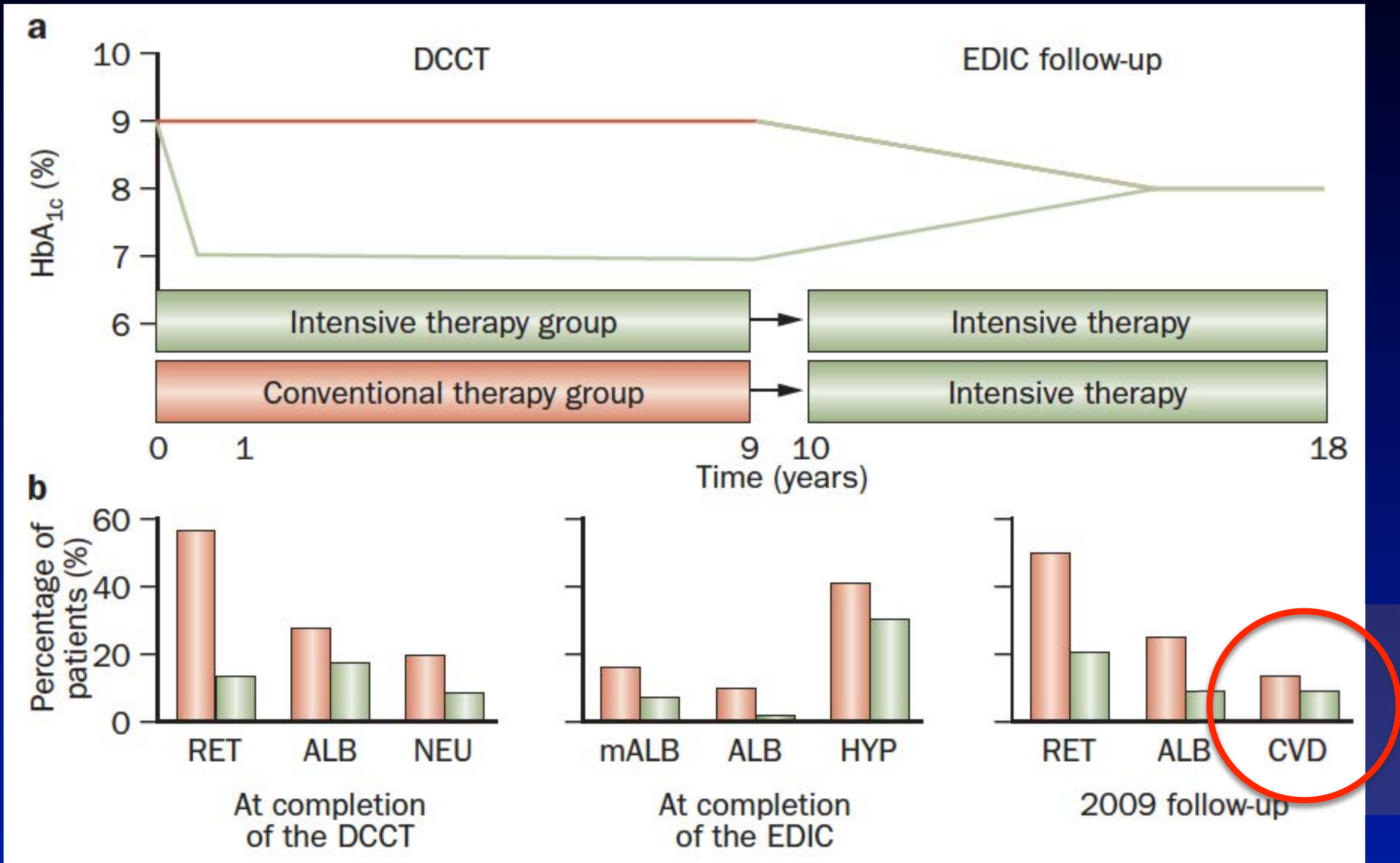
THE EFFECT OF INTENSIVE TREATMENT OF DIABETES ON THE DEVELOPMENT AND PROGRESSION OF LONG-TERM COMPLICATIONS IN INSULIN-DEPENDENT DIABETES MELLITUS

The Diabetes Control and Complications Trial Research Group*





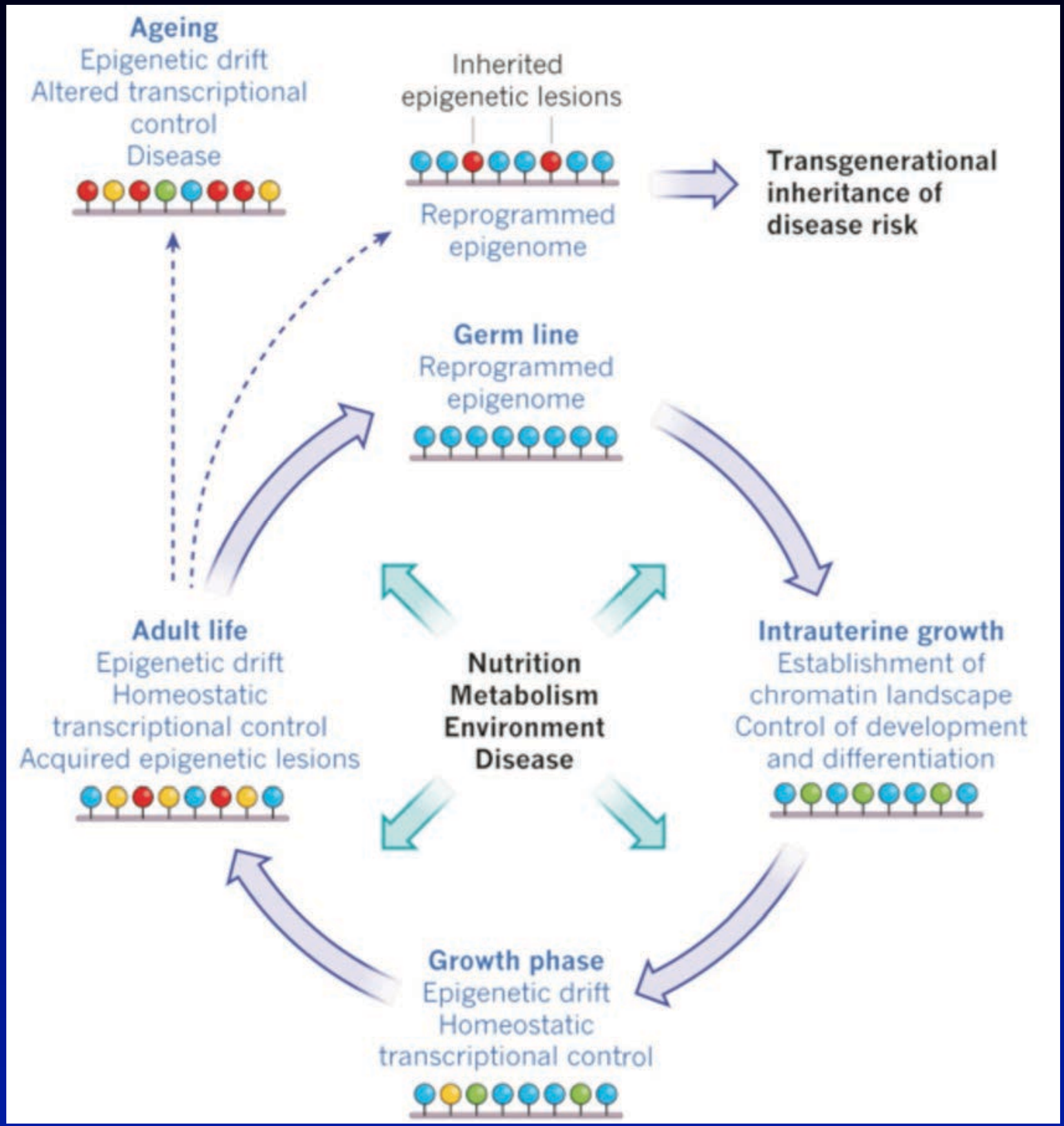
Epigenetics - Memory
EDIC: Epidemiology of Diabetes Interventions Trial



ARW

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

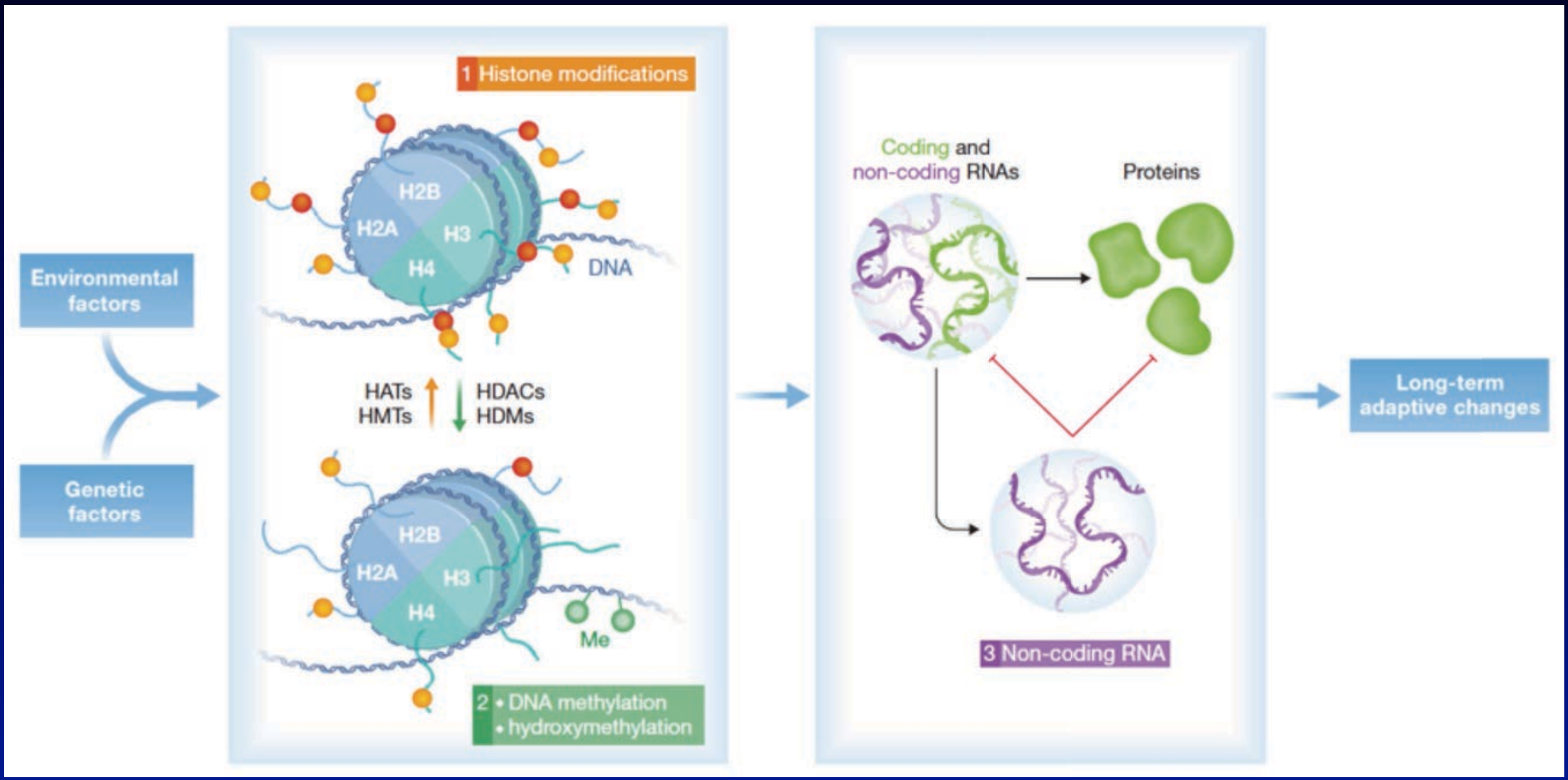
Epigenetics: Transgenerational and Drift



ARW

Gut and Verdin **2013** *Nature* 502:489

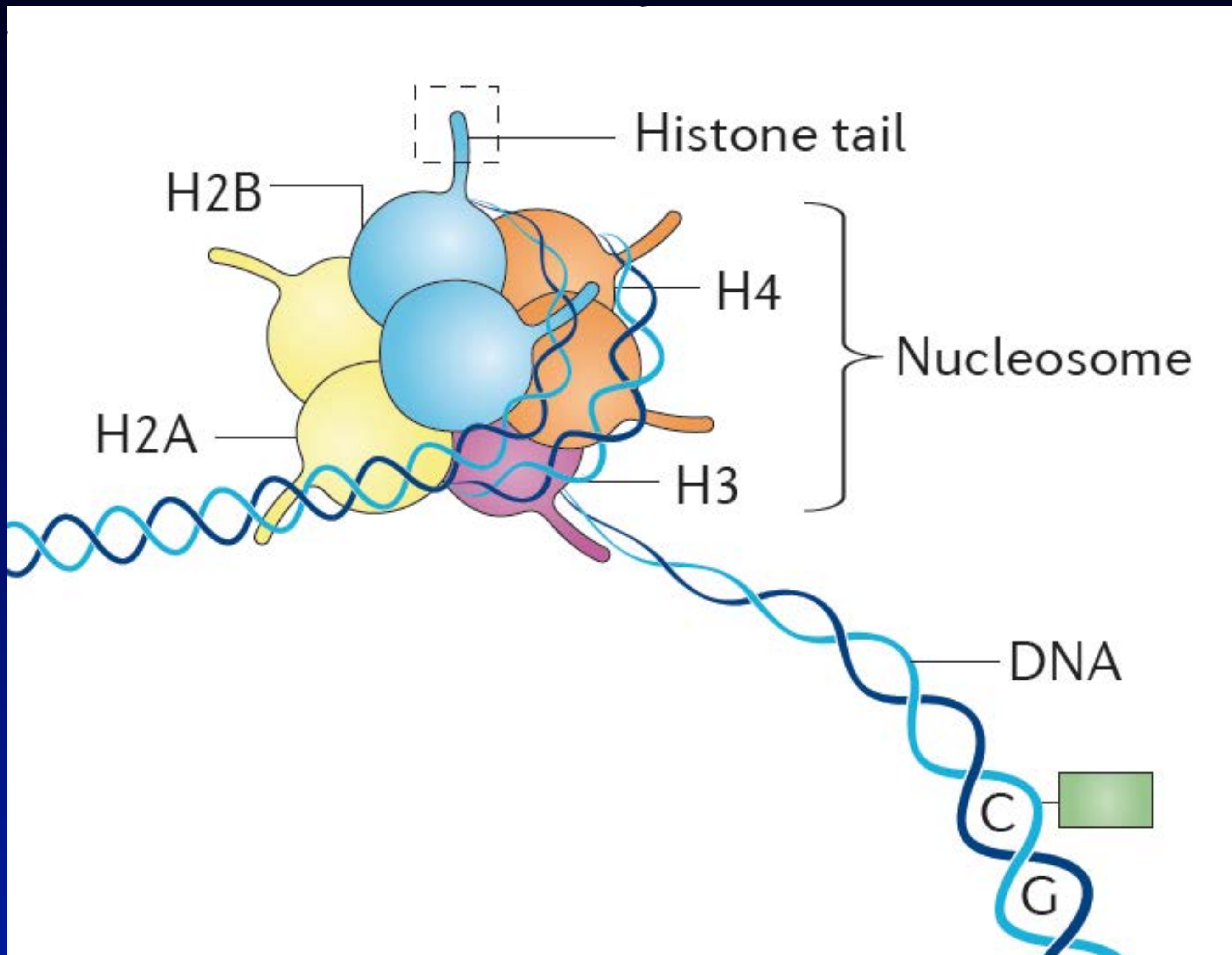
Epigenetic Code



ARW

Fischer **2014** *EMBO J* 33(9):945:489

Chromatin Regulation



ARW

Gräff and Tsai **2013** *Nat Rev Neurosci* 14(2):97

How do metabolites fit in?

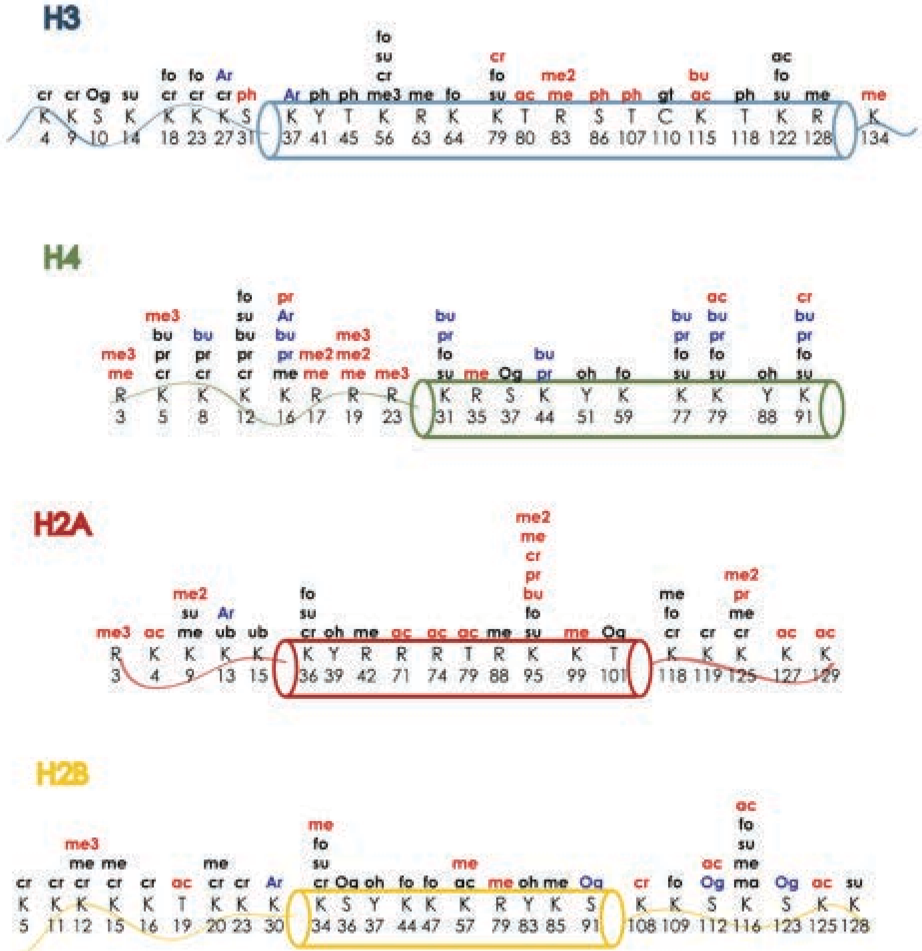
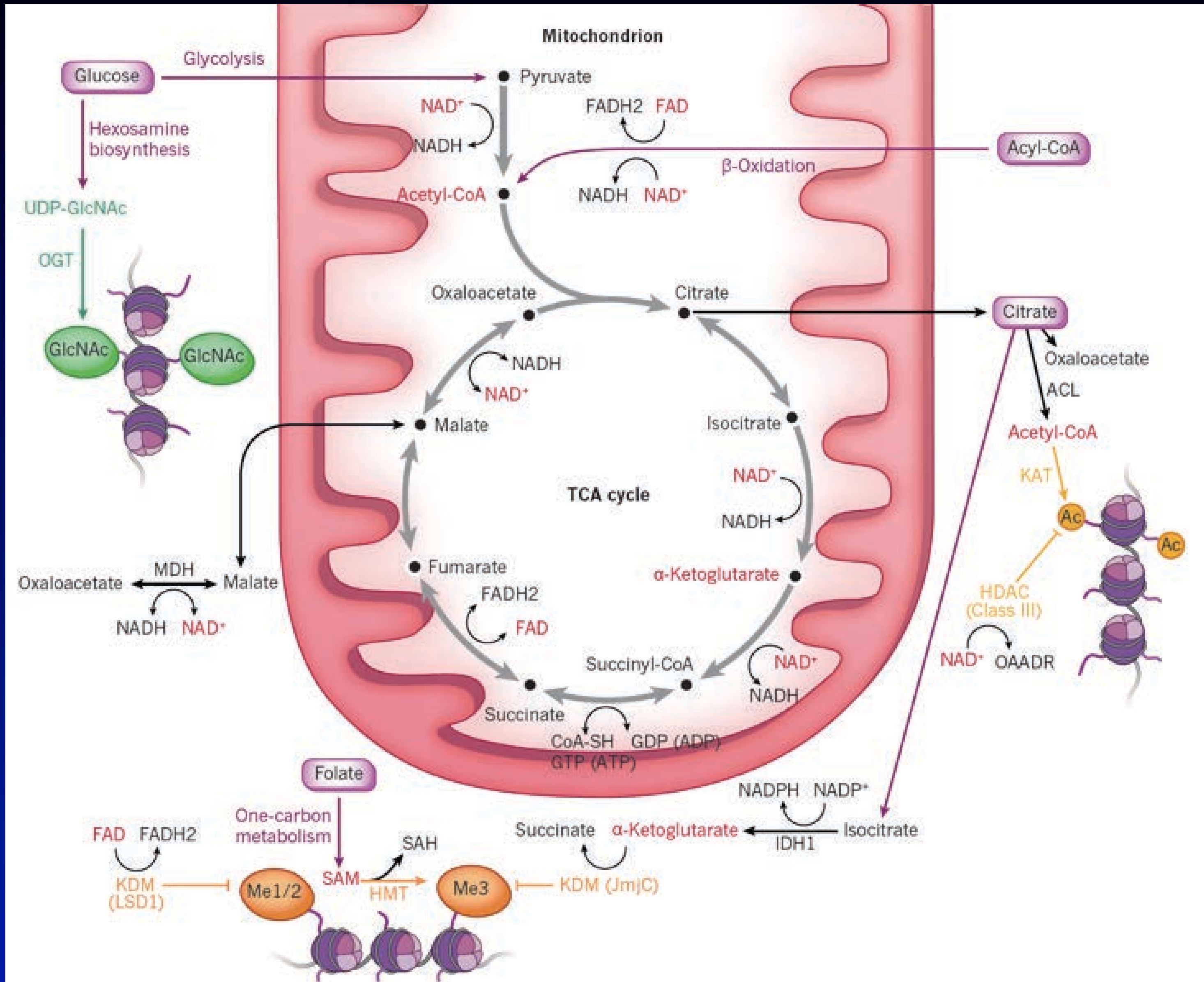


Figure 1 Recently identified modifications on the core histones. Black, modifications found *in vivo* in human; red, modifications found in mouse brain; blue, modifications found *in vitro*. ac, acetylation; Ar, ADP-ribosylation; bu, butyrylation; cr, crotonylation; fo, formylation; gt, glutathionylation; ma, malonylation; me, methylation; Og, O-glcNAcylation; oh, hydroxylation; pr, propionylation; su, succinylation; ph, phosphonylation; ub, ubiquitination.

ARW

Arnaudo … Garcia **2013** *Epigenetics Chromatin* 6(1):24

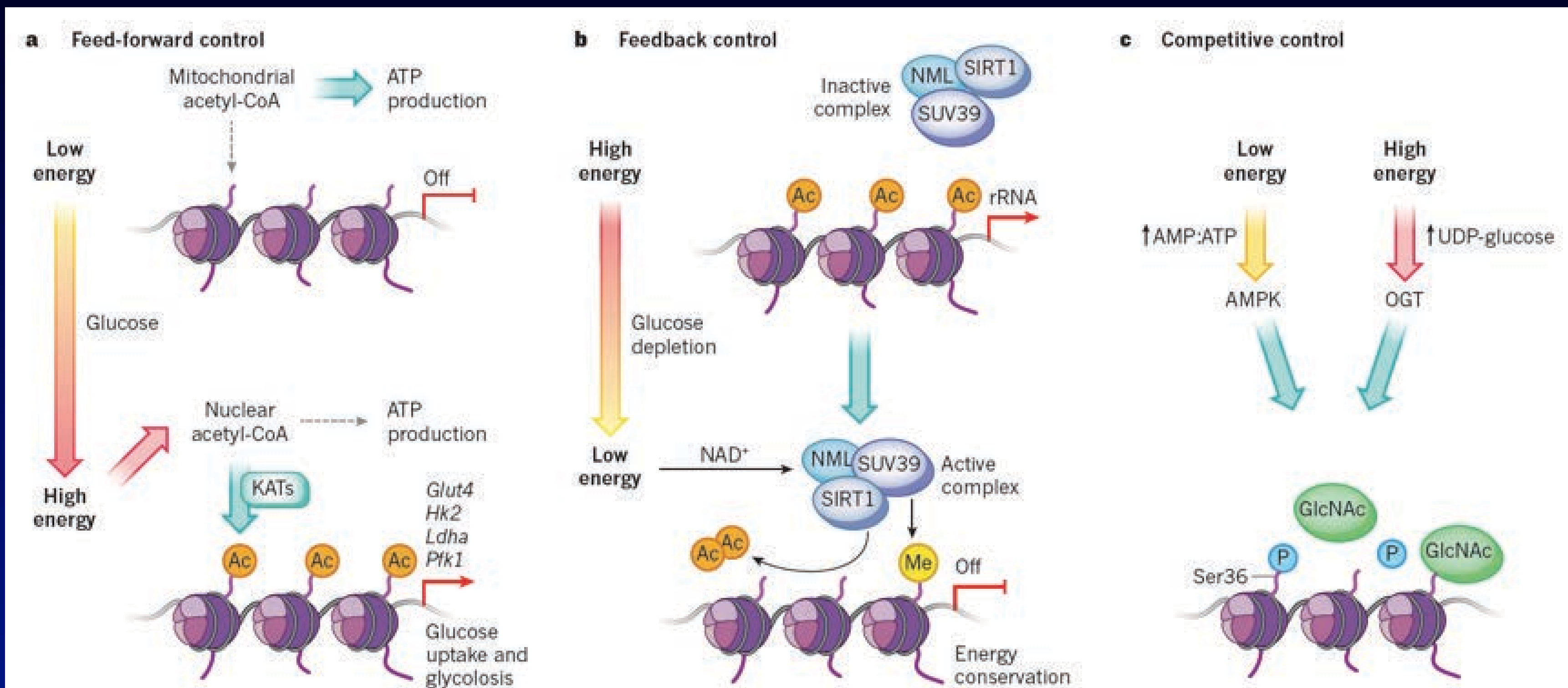
Metabolite Signaling to Chromatin



Gut and Verdin **2013** *Nature* 502:489

ARW

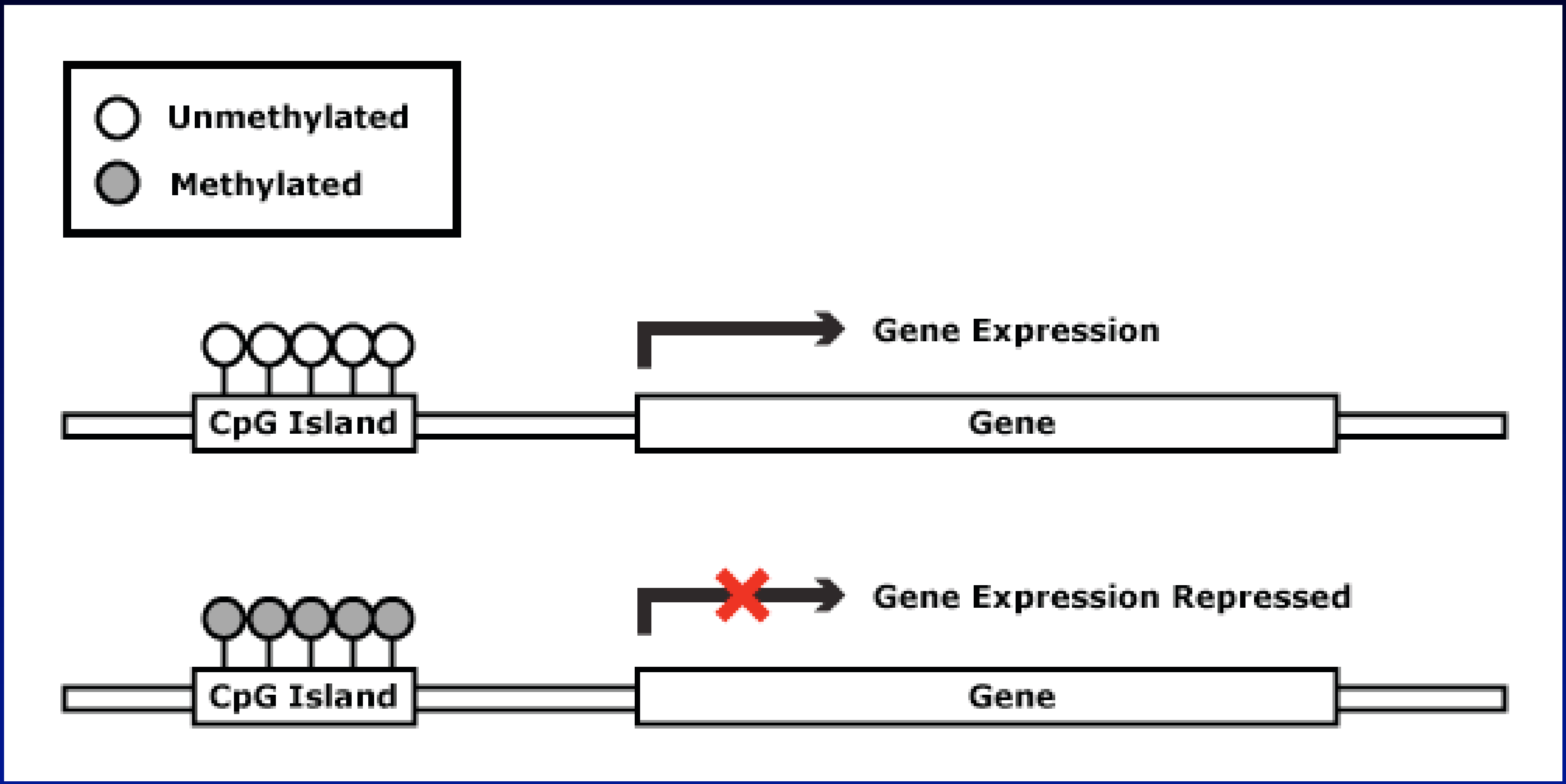
How does GlcNAc fit in?



ARW

Gut and Verdin **2013** *Nature* 502(7472):489

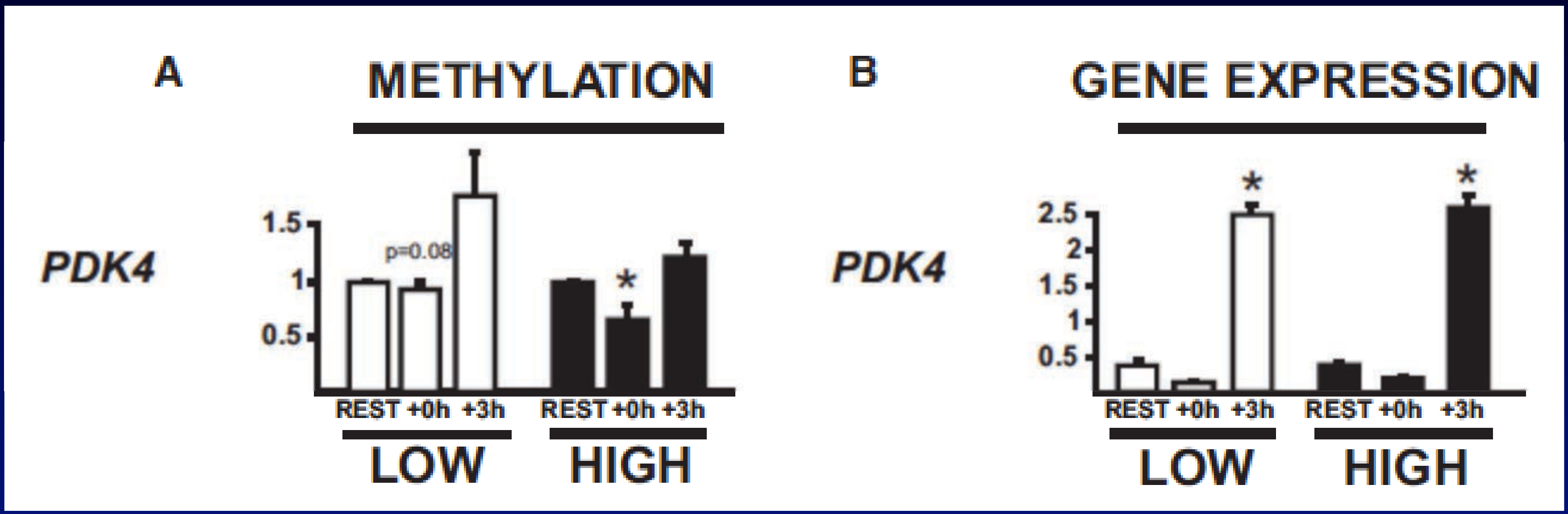
DNA Methylation 101



ARW

ucsf.edu

Exercise Alters DNA Methylation of Key Metabolic Genes



Low = 40% VO_{2peak} High = 80% VO_{2peak}

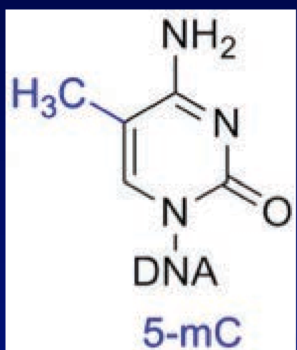
Subjects fasted overnight and then consumed a high carbohydrate diet 4 hr prior to exercise.

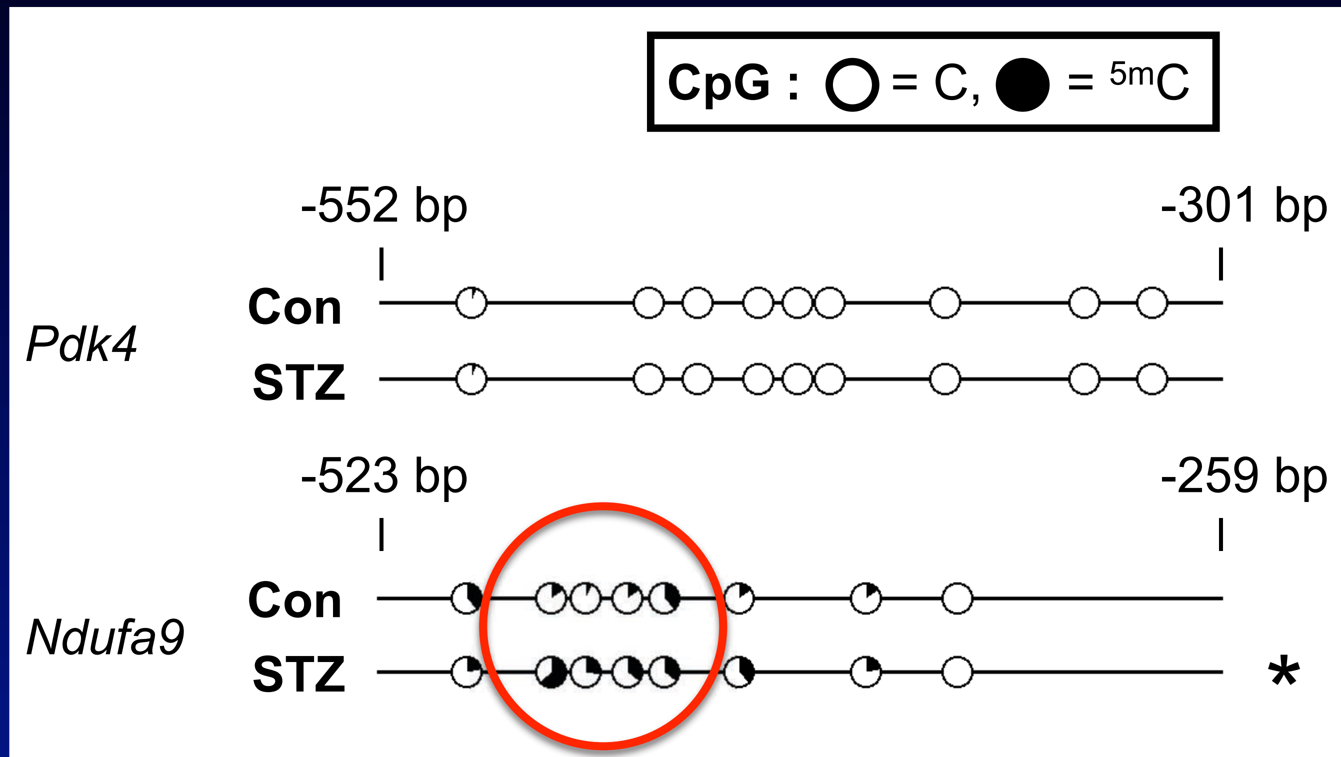
ARW

Barres and Zierath **2012** *Cell Metab* 15:405

Diabetes Regulated Cardiac DNA Methylation

Targeted bsDNA-seq 5-mCpG





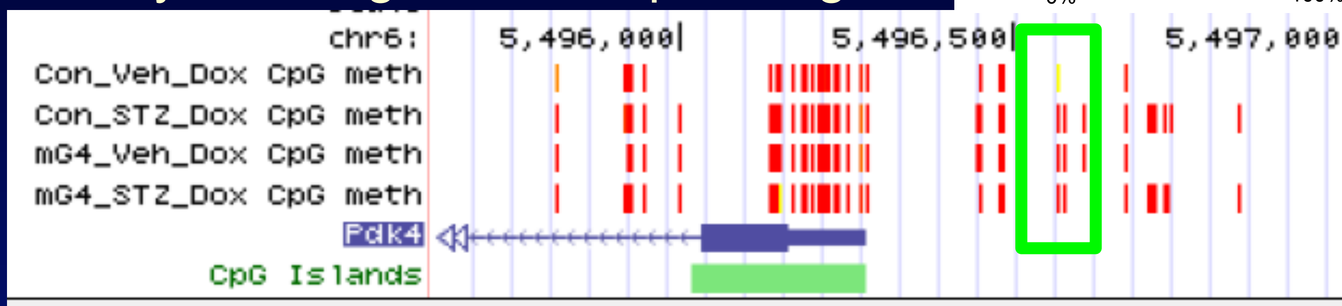
Heart, LV
$n = 10$
* $P < 0.05$
ARW

Wende, unpublished

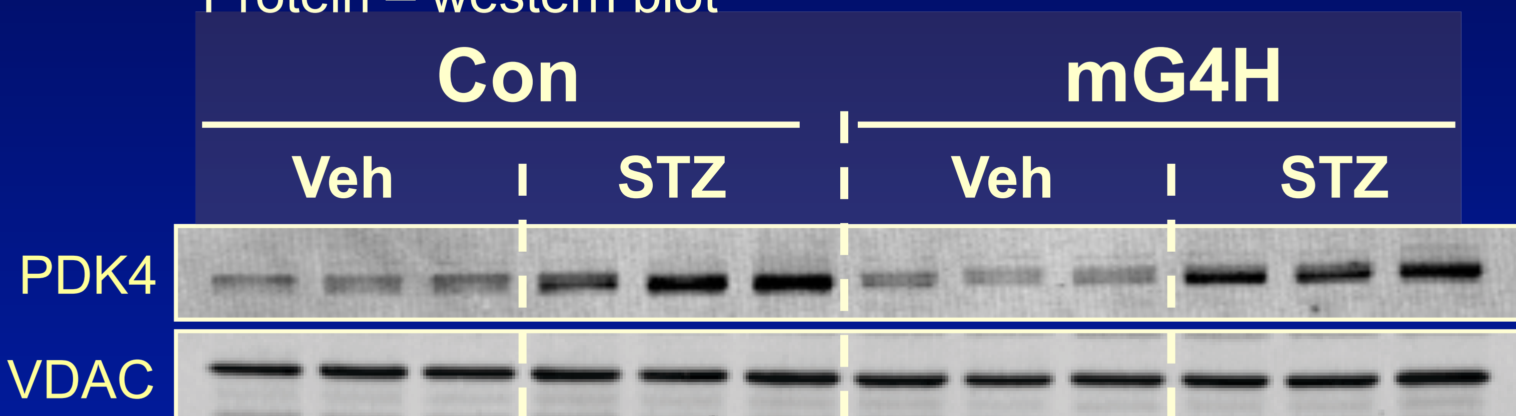
Methylation and Expression

RNA – microarray

Methylation – genome sequencing



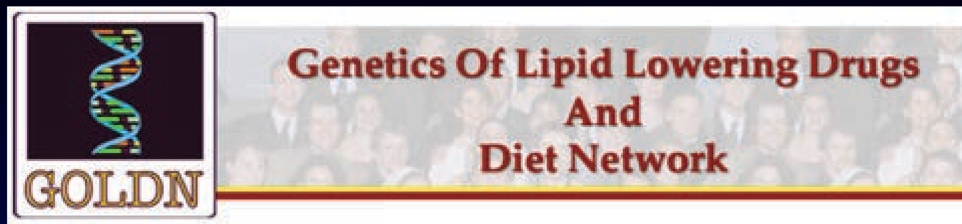
Protein – western blot



GeneSifter and Zymo/UCSC Genome Browser

ARW

Other Human/Mouse Comparisons



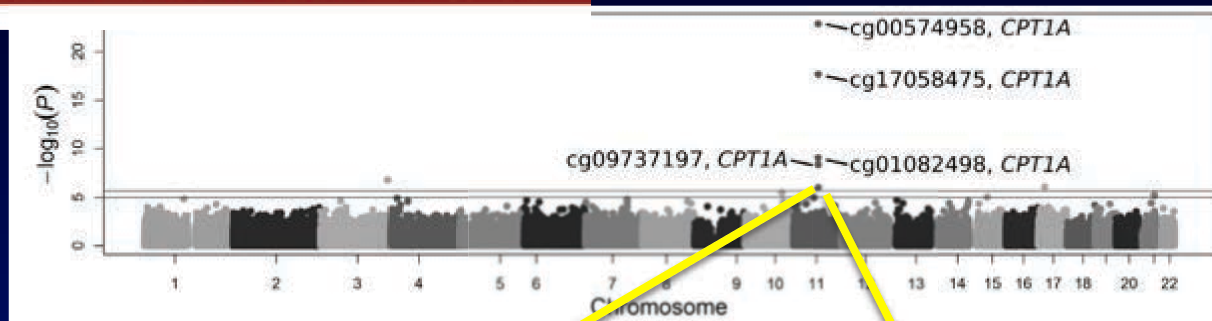


Figure 2. Epigenome-wide association Manhattan plot for VLDL-C in the discovery dataset (n=991). VLDL-C indicates very-low-density lipoprotein cholesterol.

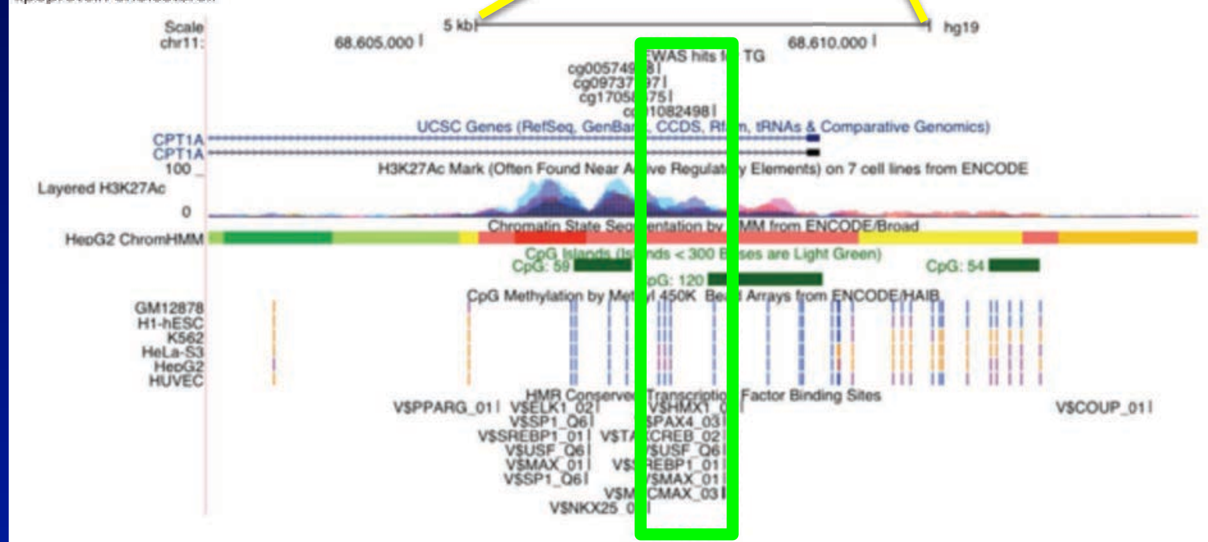


Figure 3. ENCODE annotation of the promoter region and intron 1 of *CPT1A*. Top CpGs for TG are positioned within the gene along with CpG islands, cell line chromatin state (ChromHMM), cell line methylation at CpG sites on the Methyl450 Beadchip according to Hudson Alpha Institute for Biotechnology (HAIB; note blue, purple, and orange highlights correspond to low, medium and high methylation state, respectively), and HMR conserved transcription factor binding sites. CpG indicates cytosine-(phosphate)-guanine; and TG, triglyceride.

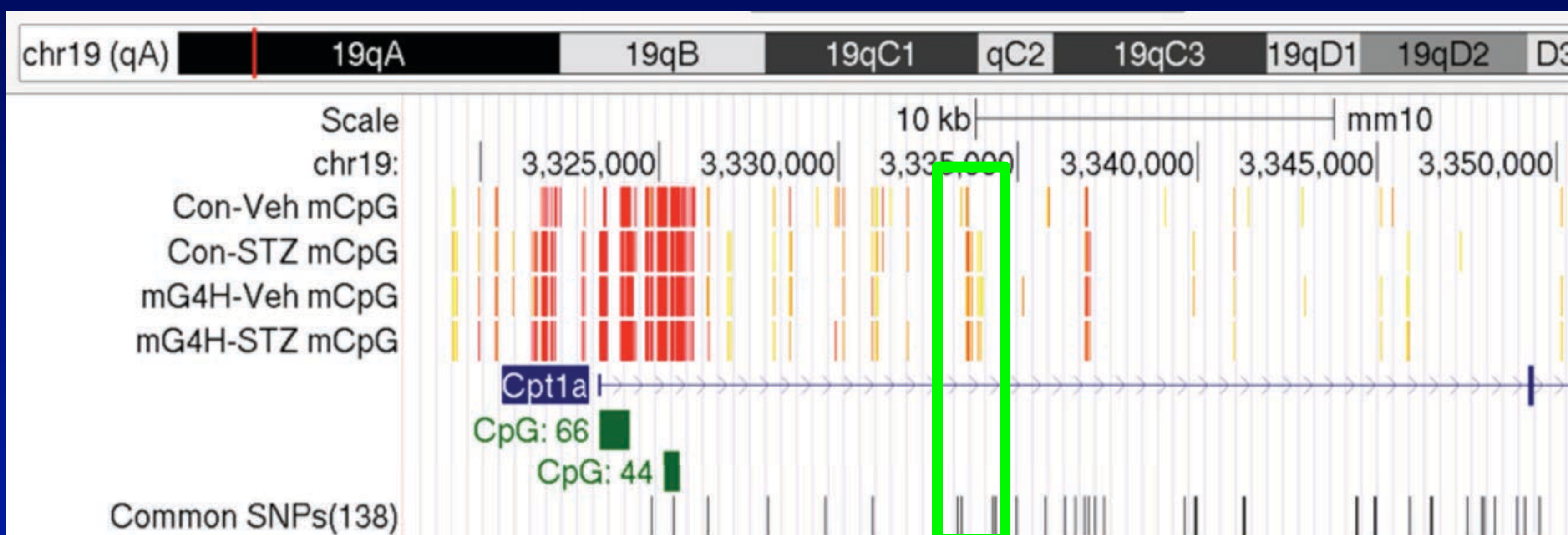
Irvin … Arnett **2014** *Circulation* 130:565

ARW

Other Human/Mouse Comparisons

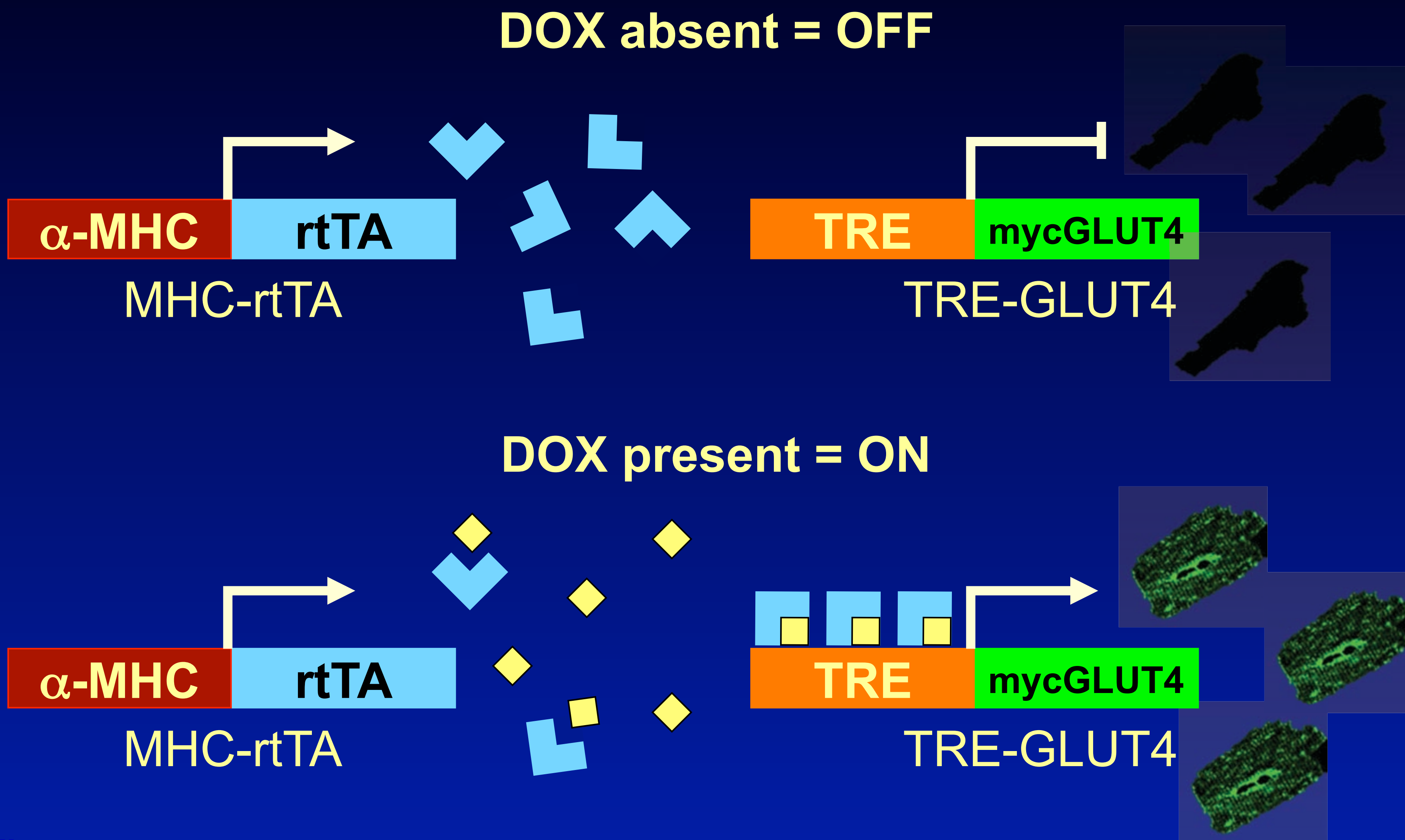
Mouse
Gene Expression

Mouse
DNA Methylation



Wende, unpublished

Where Does Glycemic Memory Fit In?



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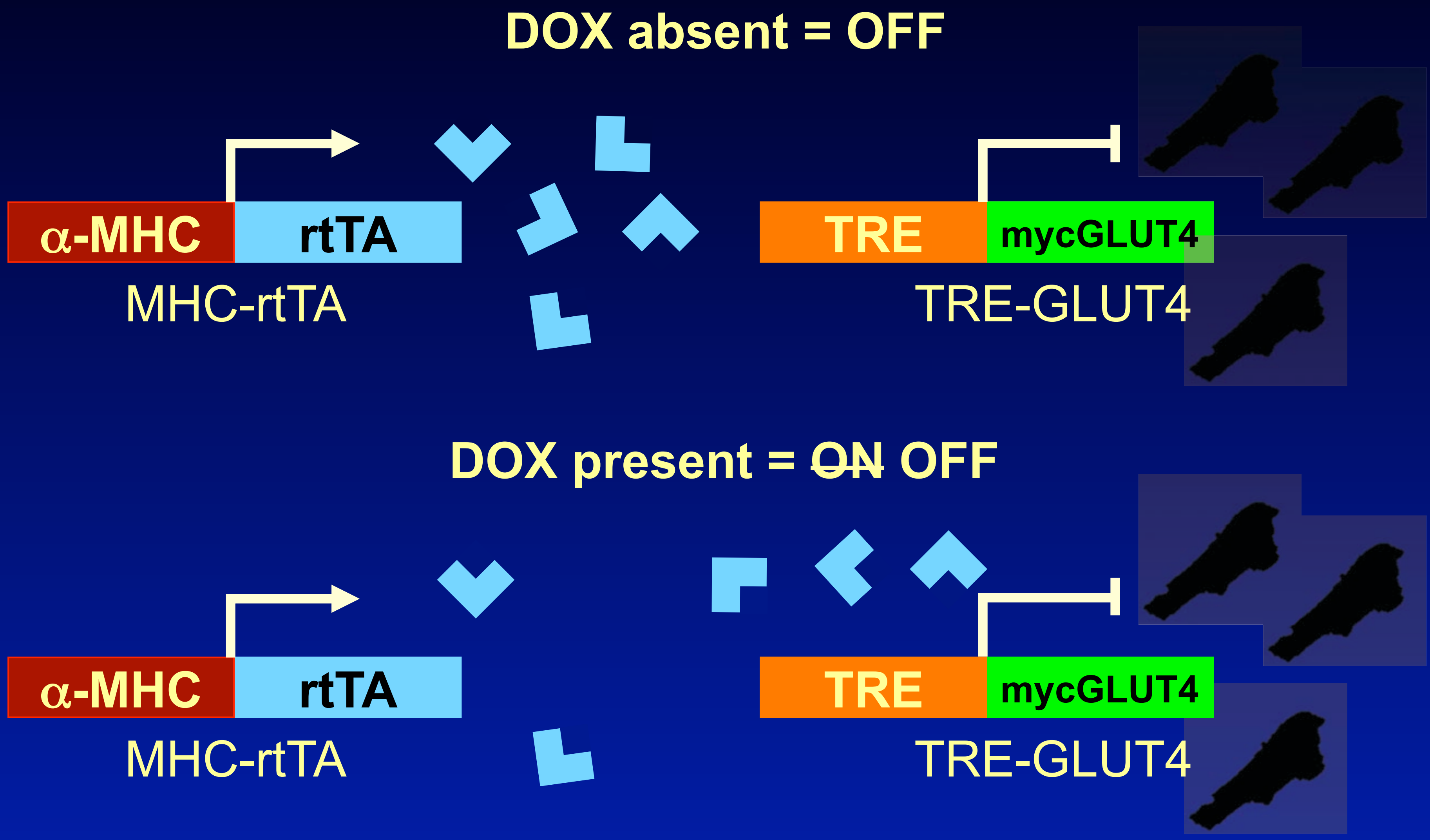
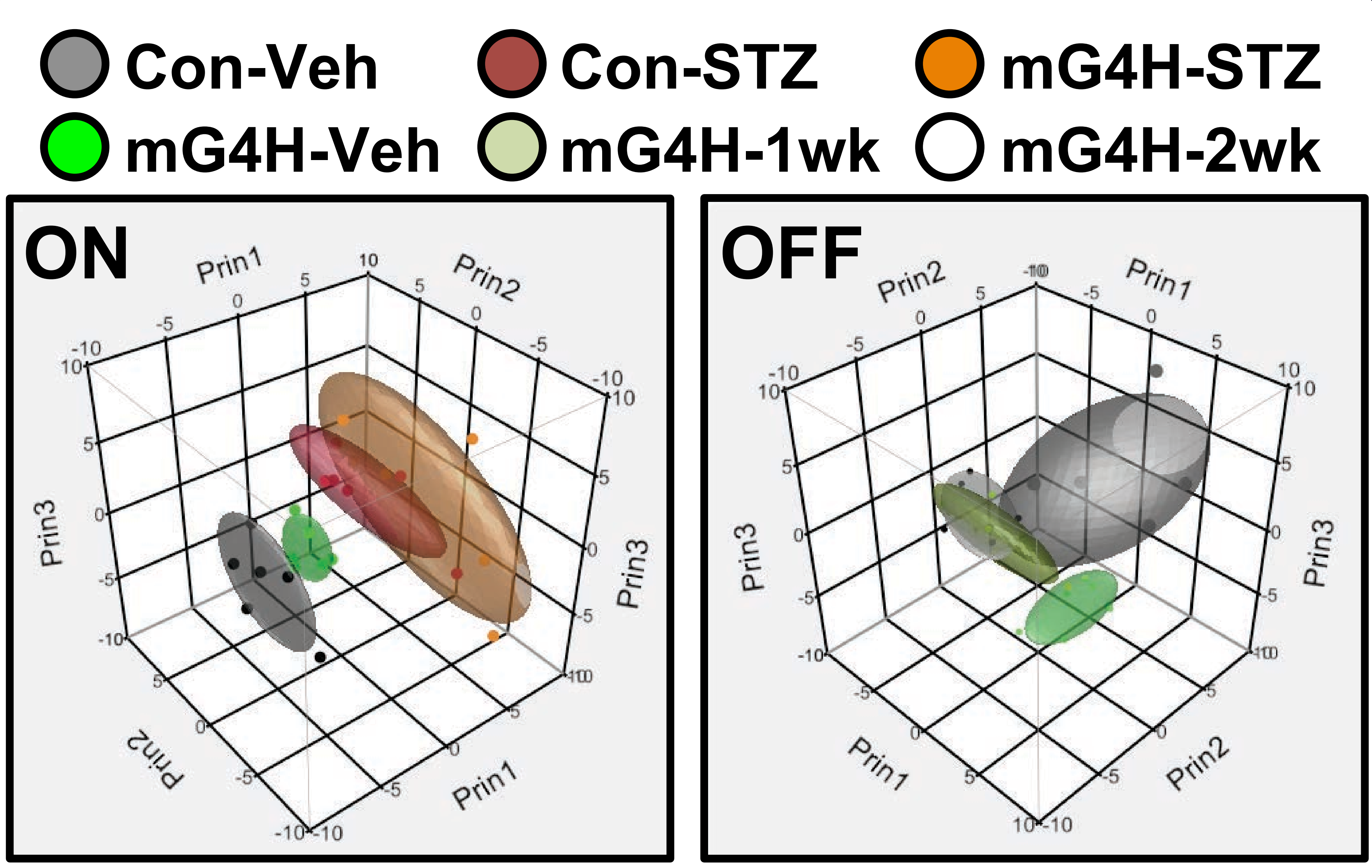


ARW

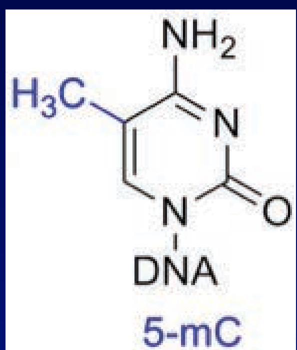
Metabolomics

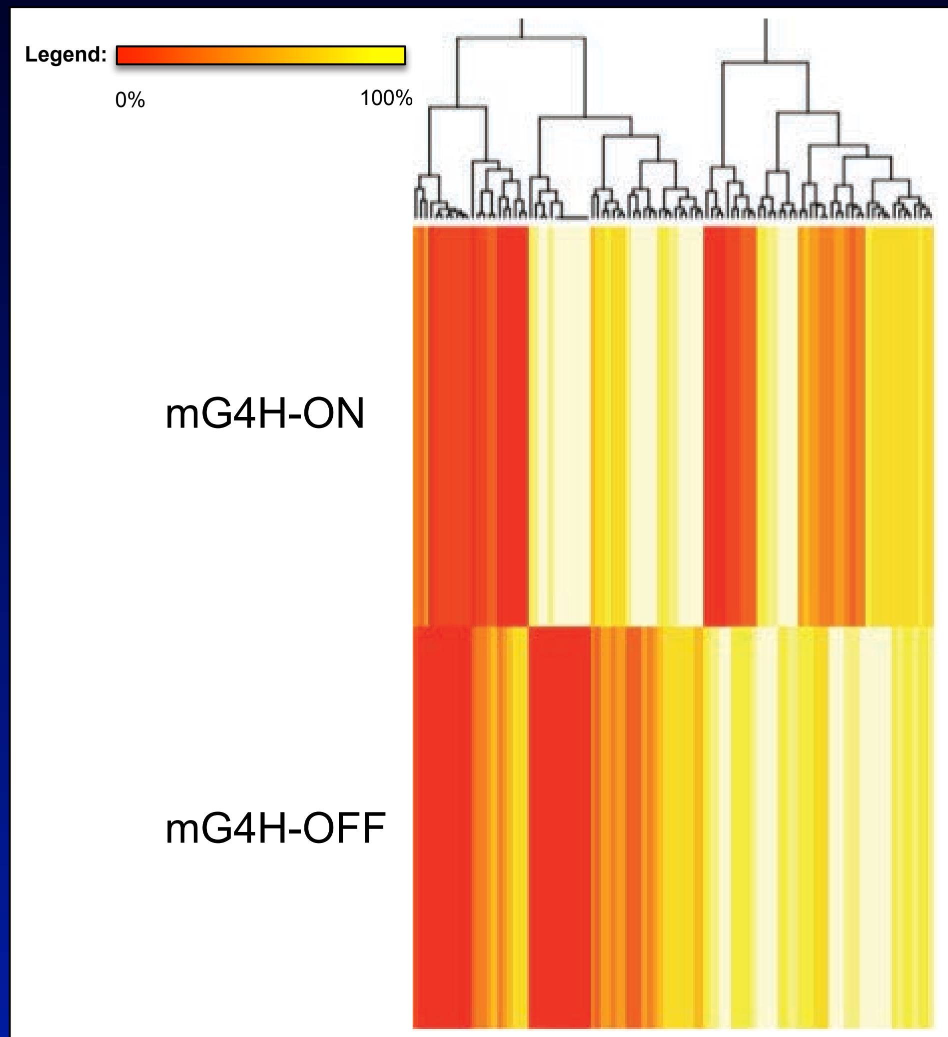


Wende, unpublished

Glucose Cycling Alters Epigenetic Programming

Genomewide bsDNA-seq 5-mCpG



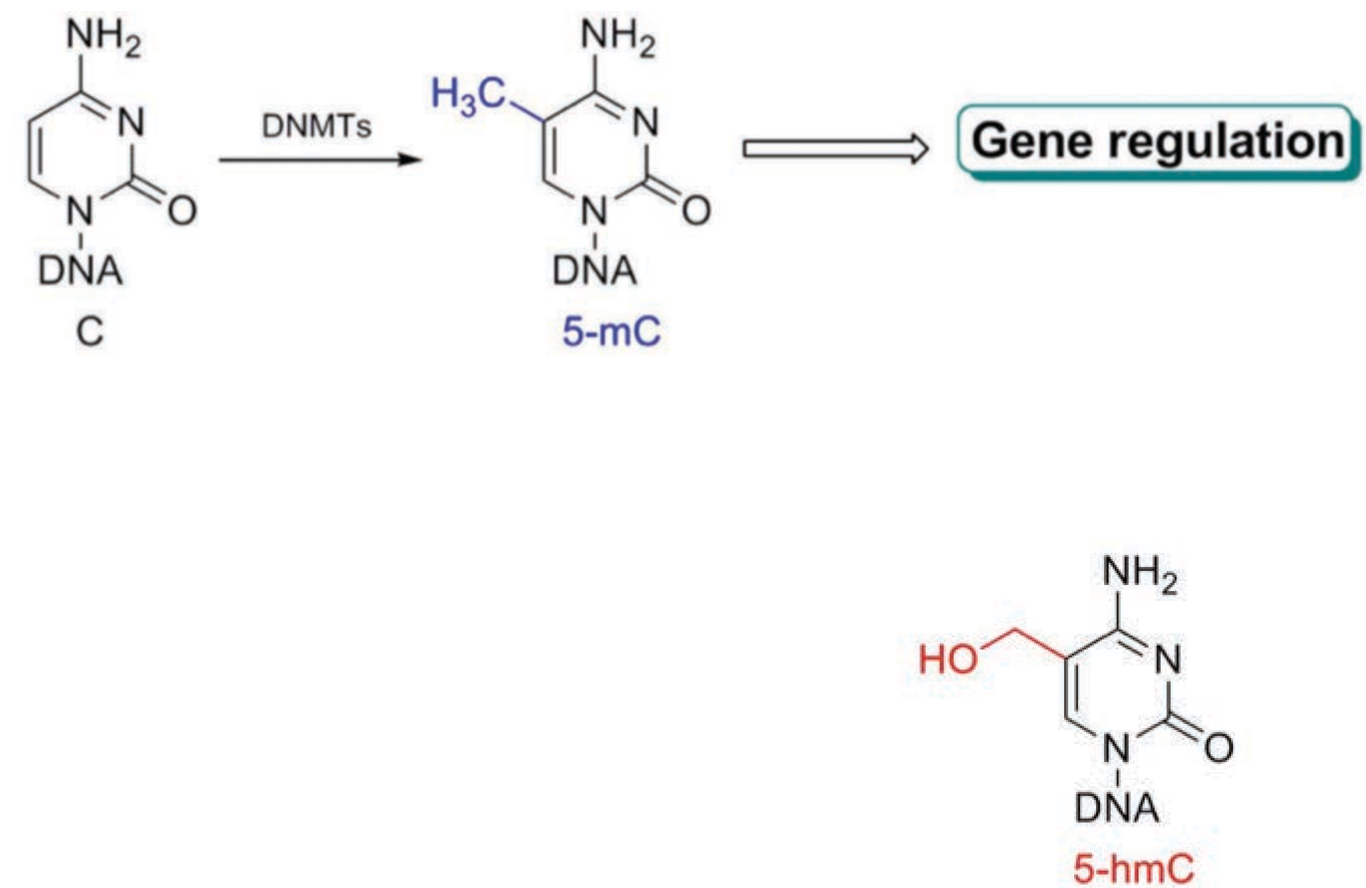


Heart, LV

ARW

Zymo Research
Wende, unpublished

Background

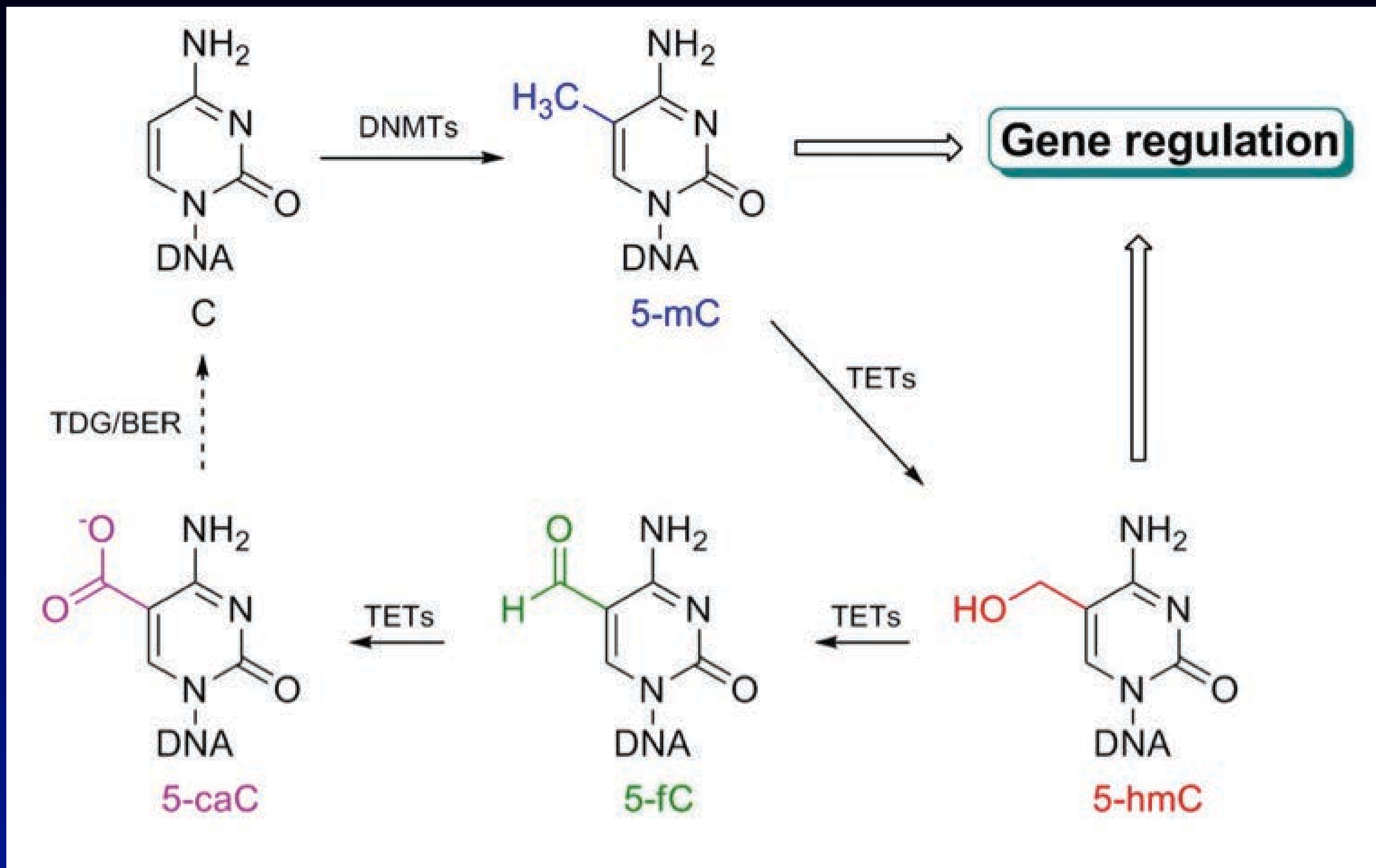


5-hmC

Wyatt and Cohen **1952** *Nature* 170(4338):1072

http://chemistry.uchicago.edu/faculty/faculty/person/member/chuan-he.html

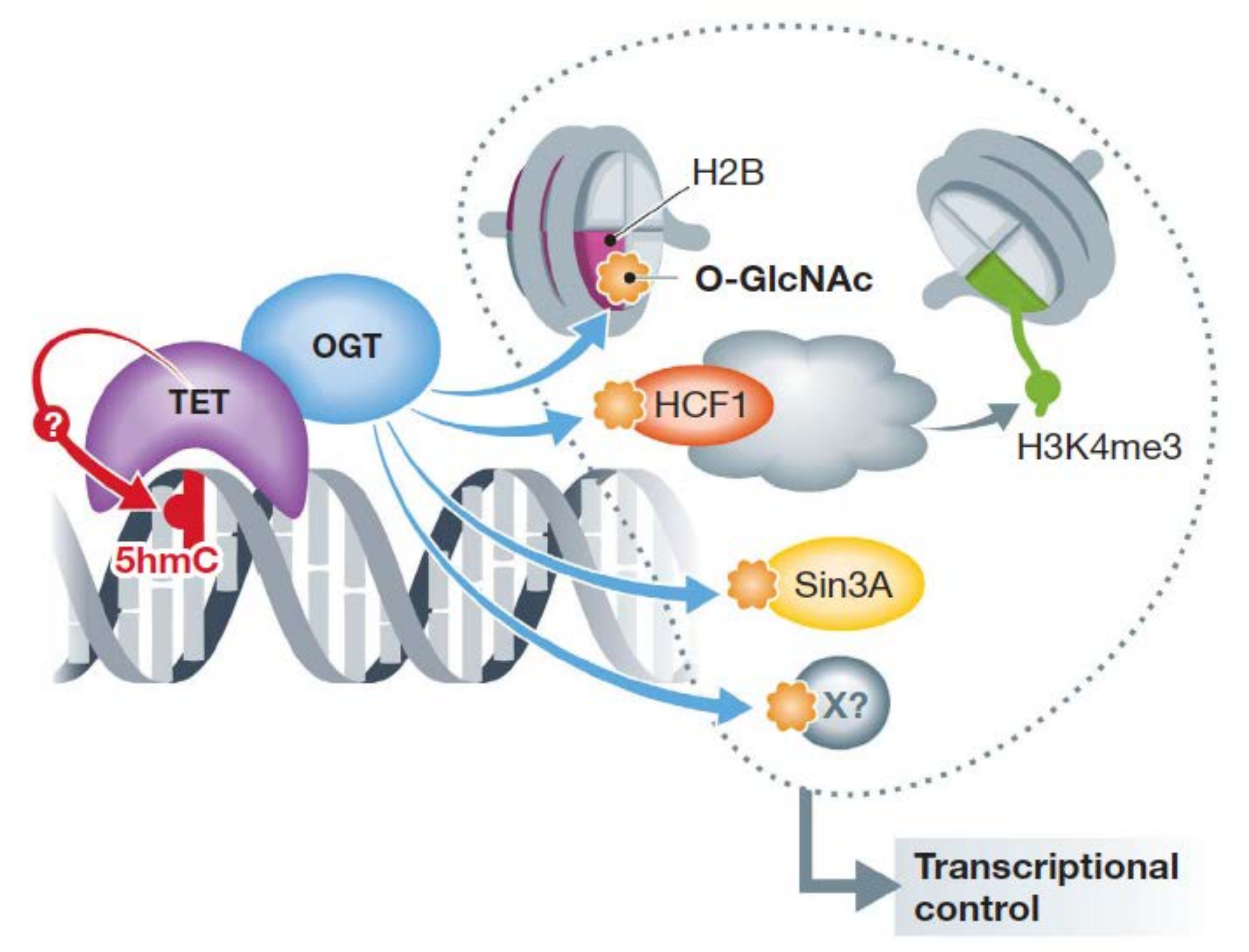
Background



5-hmC
Wyatt and Cohen **1952** *Nature* 170(4338):1072
Kriaucioni and Heintz **2009** *Science* 324(5929):929
Tahiliani … Rao **2009** *Science* 324(5929):930

http://chemistry.uchicago.edu/faculty/faculty/person/member/chuan-he.html

How does GlcNAc fit in?



ARW

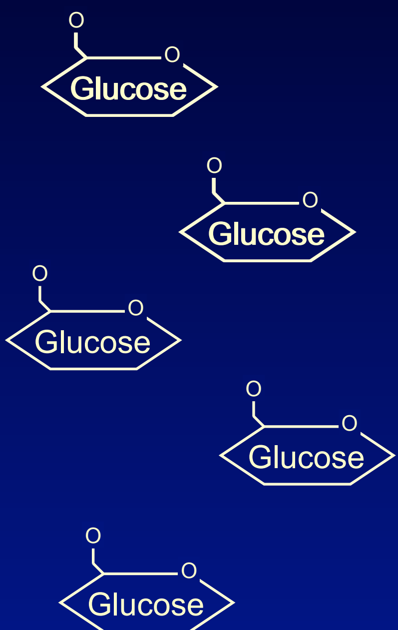
Mariappa … Aalten **2013** *EMBO J* 32:612

Conclusion – Part 4

Cellular glucose fluctuations regulates the epigenome via histone modifications and controlling the machinery for DNA methylation.

ARW

Sugar Gumming Up the Works



ARW

giphy.com

Sugar Gumming Up the Works

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Overall Summary

Using combined methylomics, transcriptomics, proteomics, and metabolomics we have begun to define the mechanism of glucotoxicity.

ARW

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K99R00 HL111322
R00 HL111322-S1

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