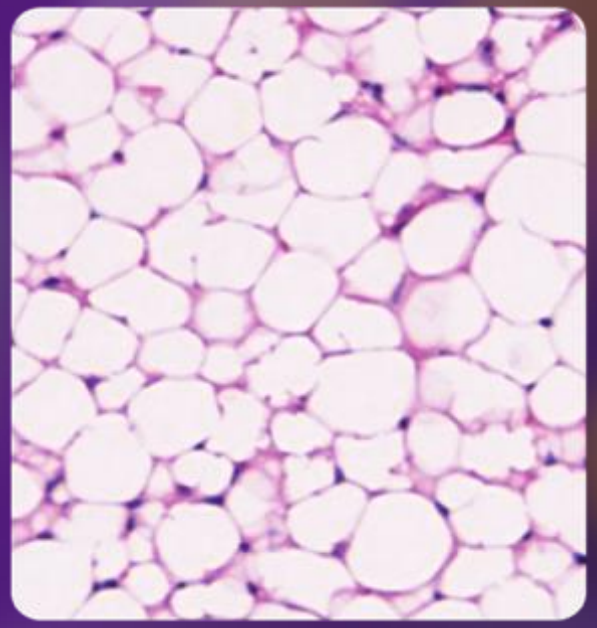
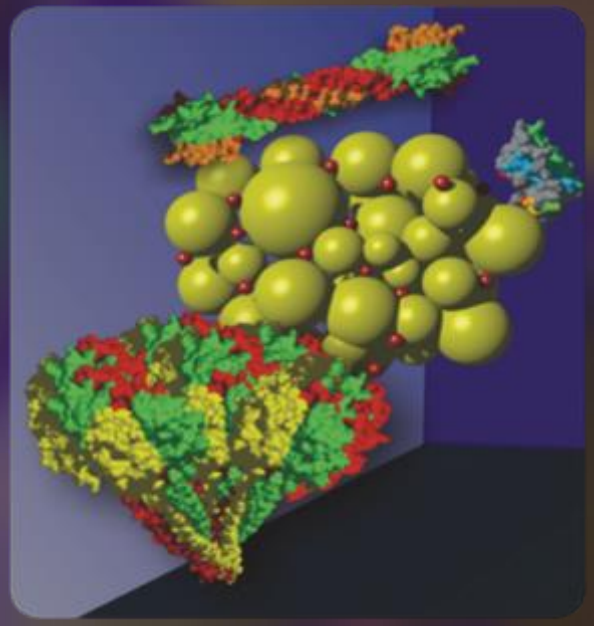
20TH WCIRDC CELEBRATION – A TRIBUTE TO GERALD REAVEN

Adipocytes and Insulin Resistance





20th World Congress on Insulin Resistance WCIRDC Los Angeles

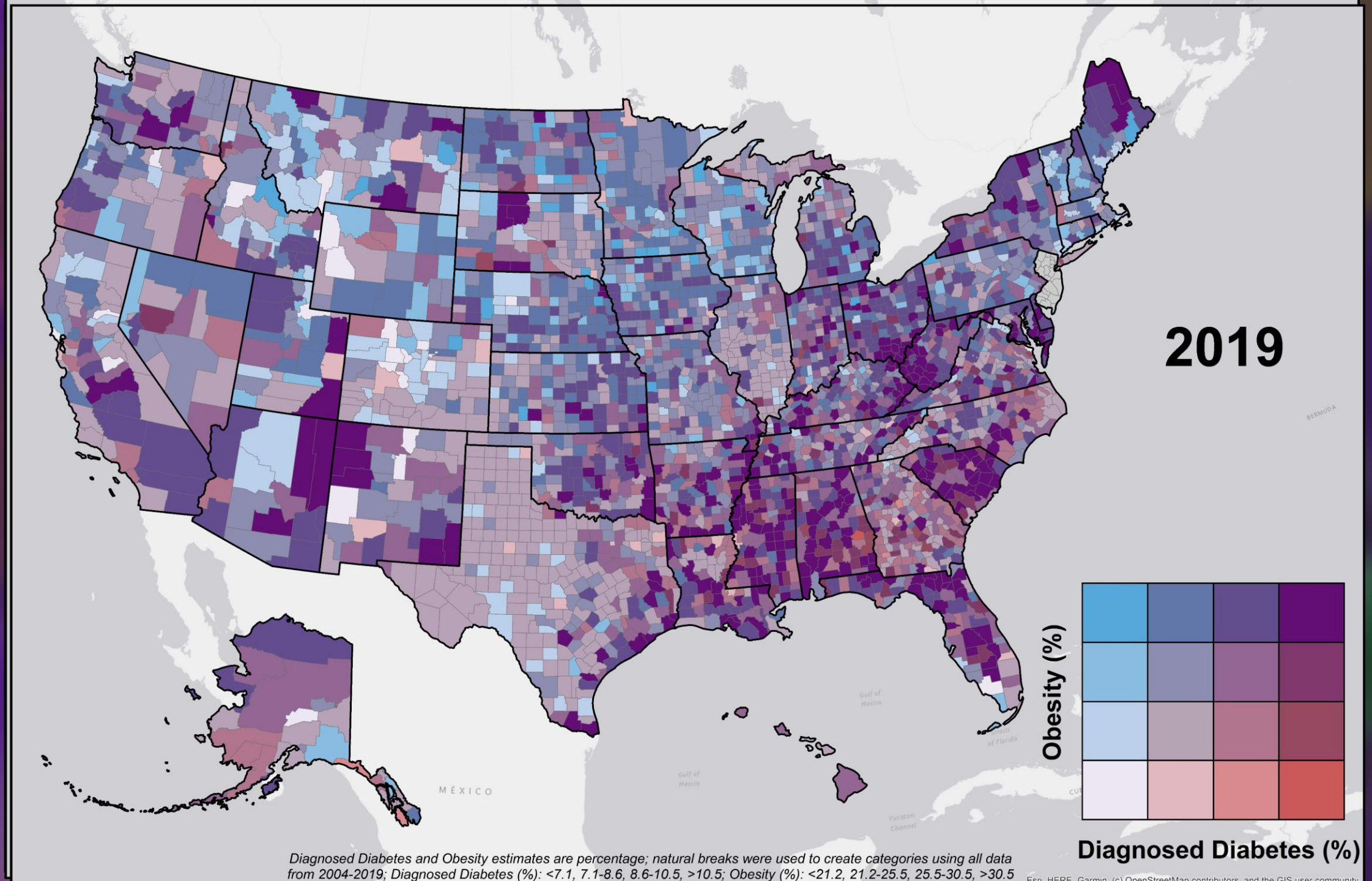
December 1st, 2022

Philipp E. Scherer, PhD

Touchstone Diabetes Center

University of Texas Southwestern Medical Center Dallas, Texas


HOLLYWOOD



Diagnosed Diabetes and Obesity estimates are percentage; natural breaks were used to create categories using all data from 2004-2019; Diagnosed Diabetes (%): <7.1, 7.1-8.6, 8.6-10.5, >10.5; Obesity (%): <21.2, 21.2-25.5, 25.5-30.5, >30.5

Metabolism

Heart

Pancreatic α and β cells

Liver

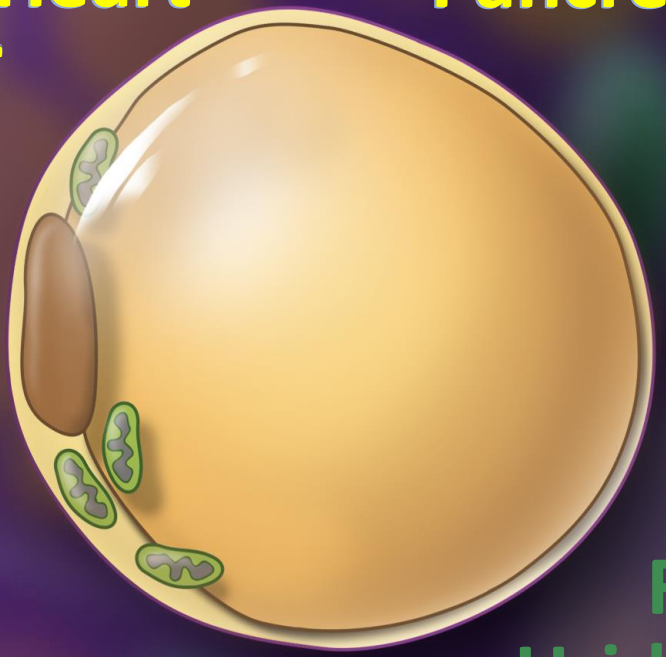
Kidney

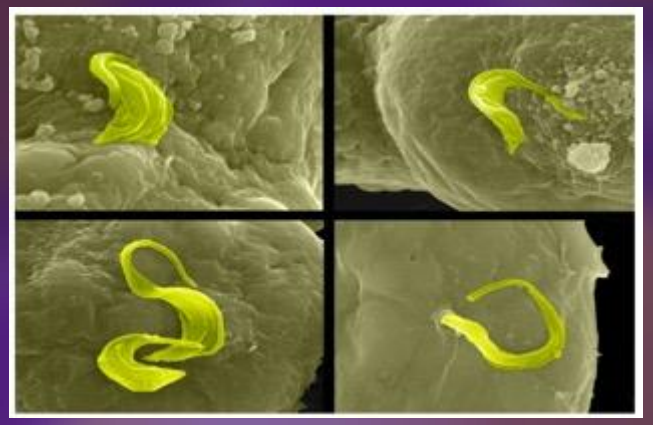
Muscle

Vascular

Endothelium

Brain





Angiogenic Factors

Growth Factors

Cytokines

ECM Modulators

FFAs

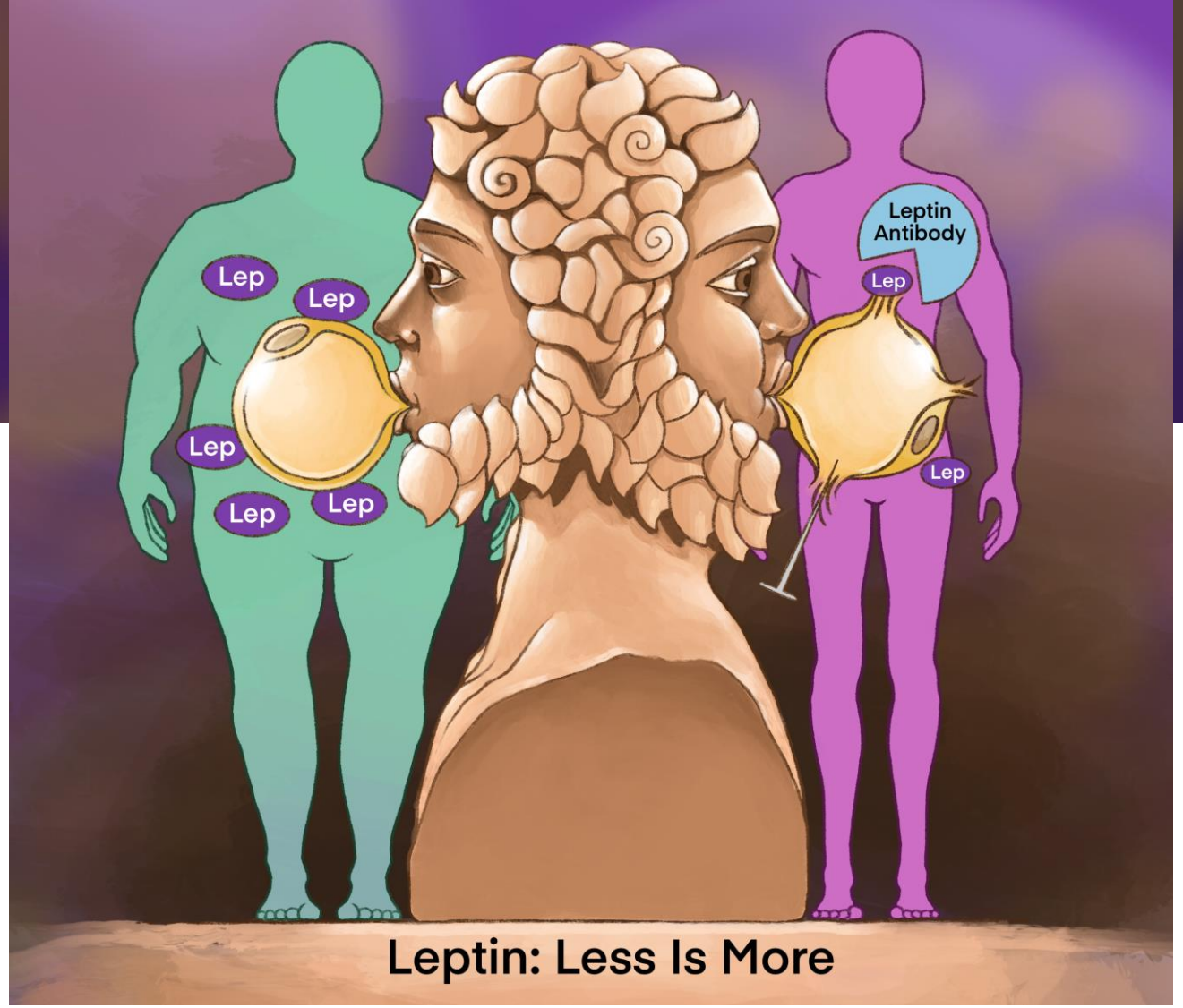
Uridine

Tumor Cell Interactions

Infectious Disease

Diabetes Volume 69, May 2020

Leptin: Less Is More

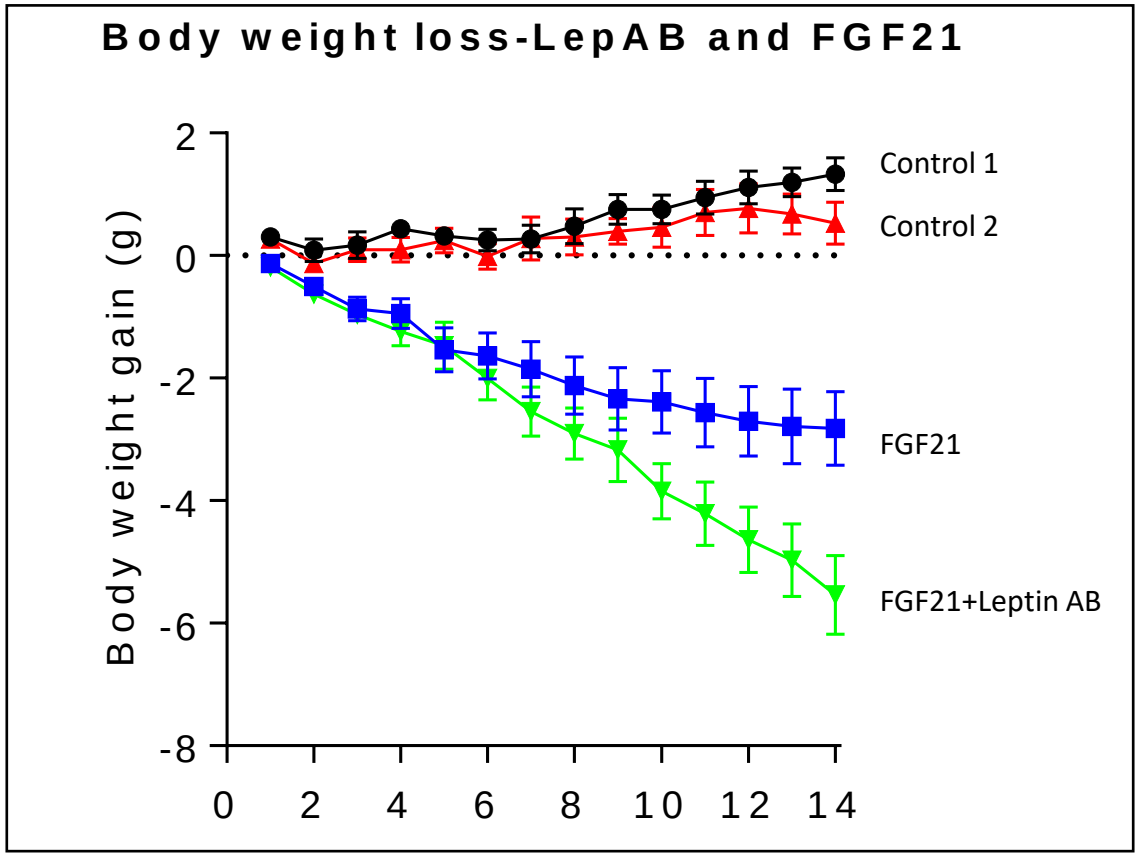


Leptin: Less Is More

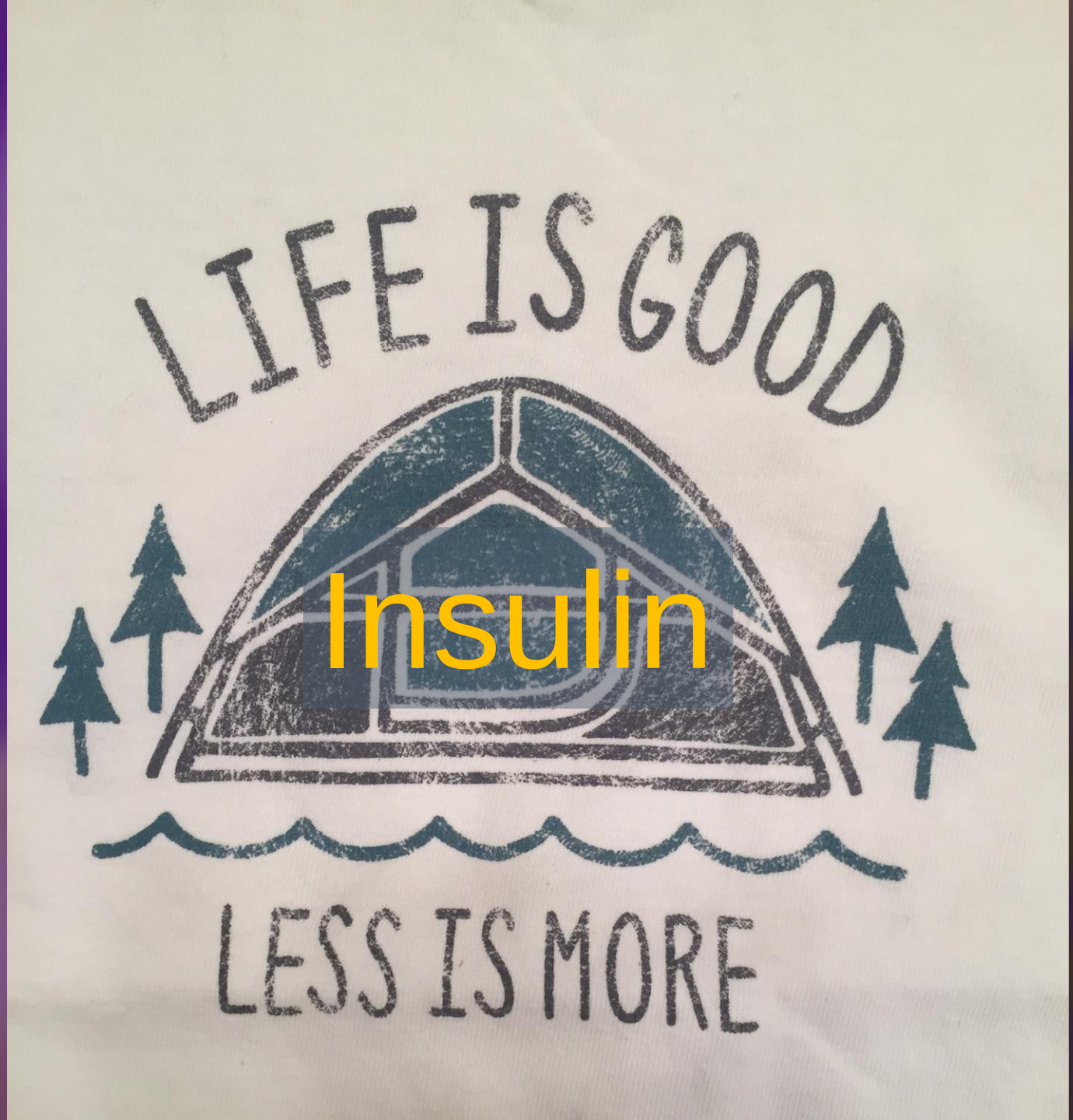
Shangang Zhao,[1] Christine M. Kusminski,[1] Joel K. Elmquist,[2] and Philipp E. Scherer[1]

Diabetes 2020;69:823–829 | https://doi.org/10.2337/dbi19-0018

The synergistic effects of leptin lowering and FGF21 on body weight




LIFE IS GOOD
Leptin
LESS IS MORE

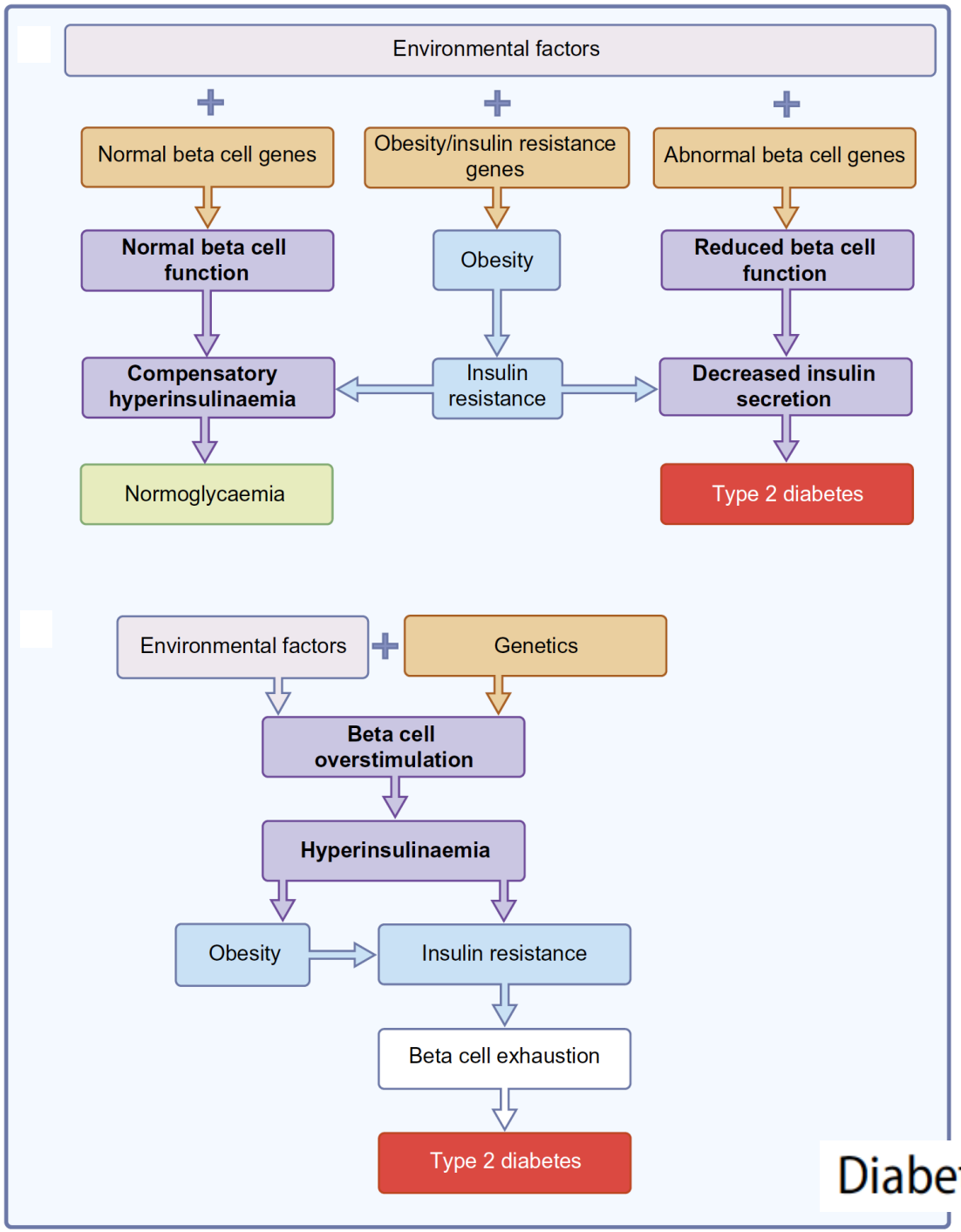

LIFE IS GOOD
Insulin
LESS IS MORE

Diabetologia (2020) 63:2007–2021
https://doi.org/10.1007/s00125-020-05245-x

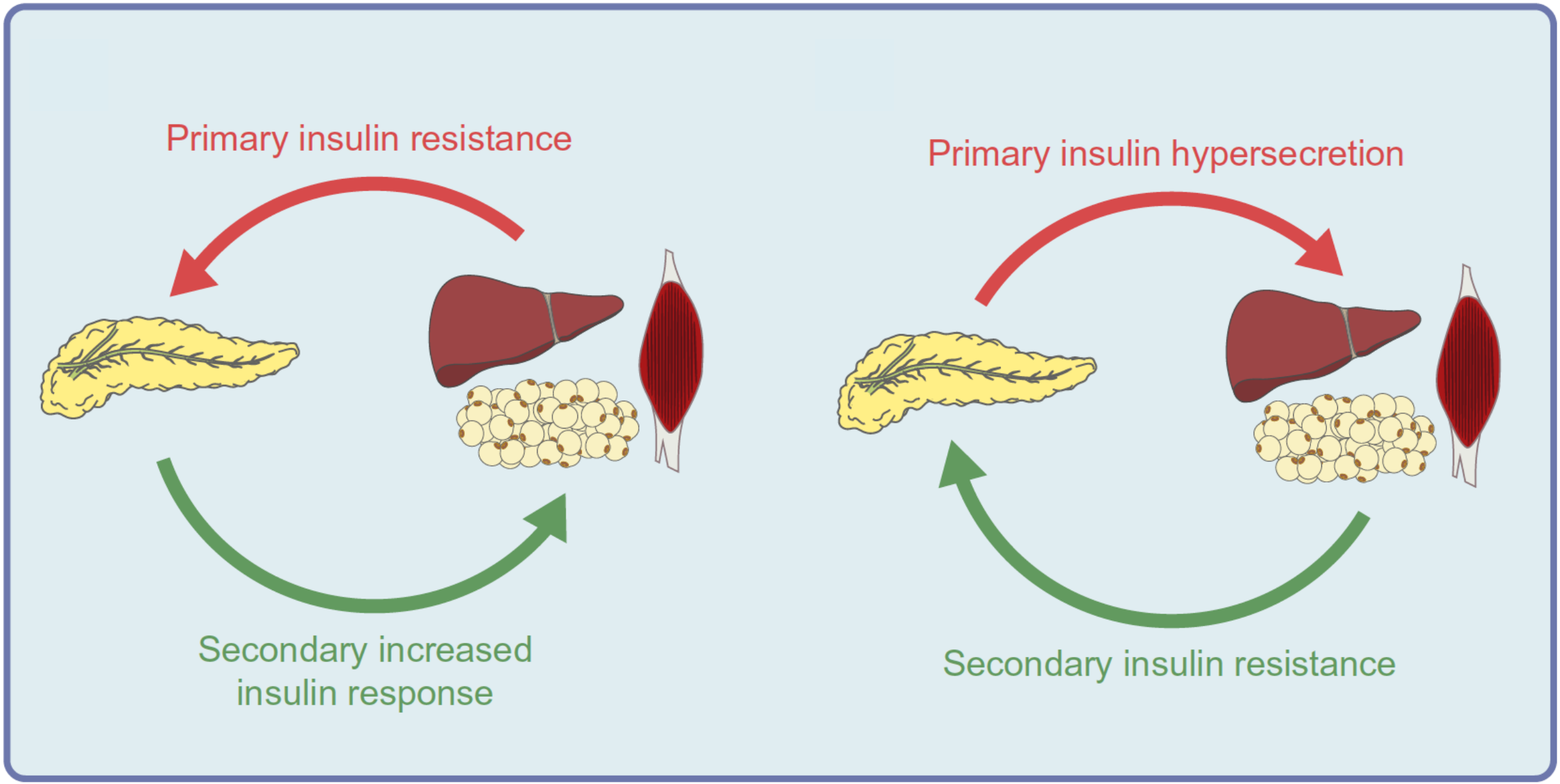
REVIEW

Early beta cell dysfunction vs insulin hypersecretion as the primary event in the pathogenesis of dysglycaemia

Nathalie Esser [1,2] · Kristina M. Utzschneider [1,2] · Steven E. Kahn [1,2]



Diabetologia (2020) 63:2007–2021



Diabetologia (2020) 63:2007–2021

Obesity Is Associated With Increased Basal and Postprandial β-Cell Insulin Secretion Even in the Absence of Insulin Resistance

Stephan van Vliet,[1,2] Han-Chow E. Koh,[1] Bruce W. Patterson,[1] Mihoko Yoshino,[1] Richard LaForest,[3] Robert J. Gropler,[3] Samuel Klein,[1] and Bettina Mittendorfer[1]

Diabetes 2020;69:2112–2119 | https://doi.org/10.2337/db20-0377

Diabetes Volume 69, October 2020

Making the ligand rate limiting

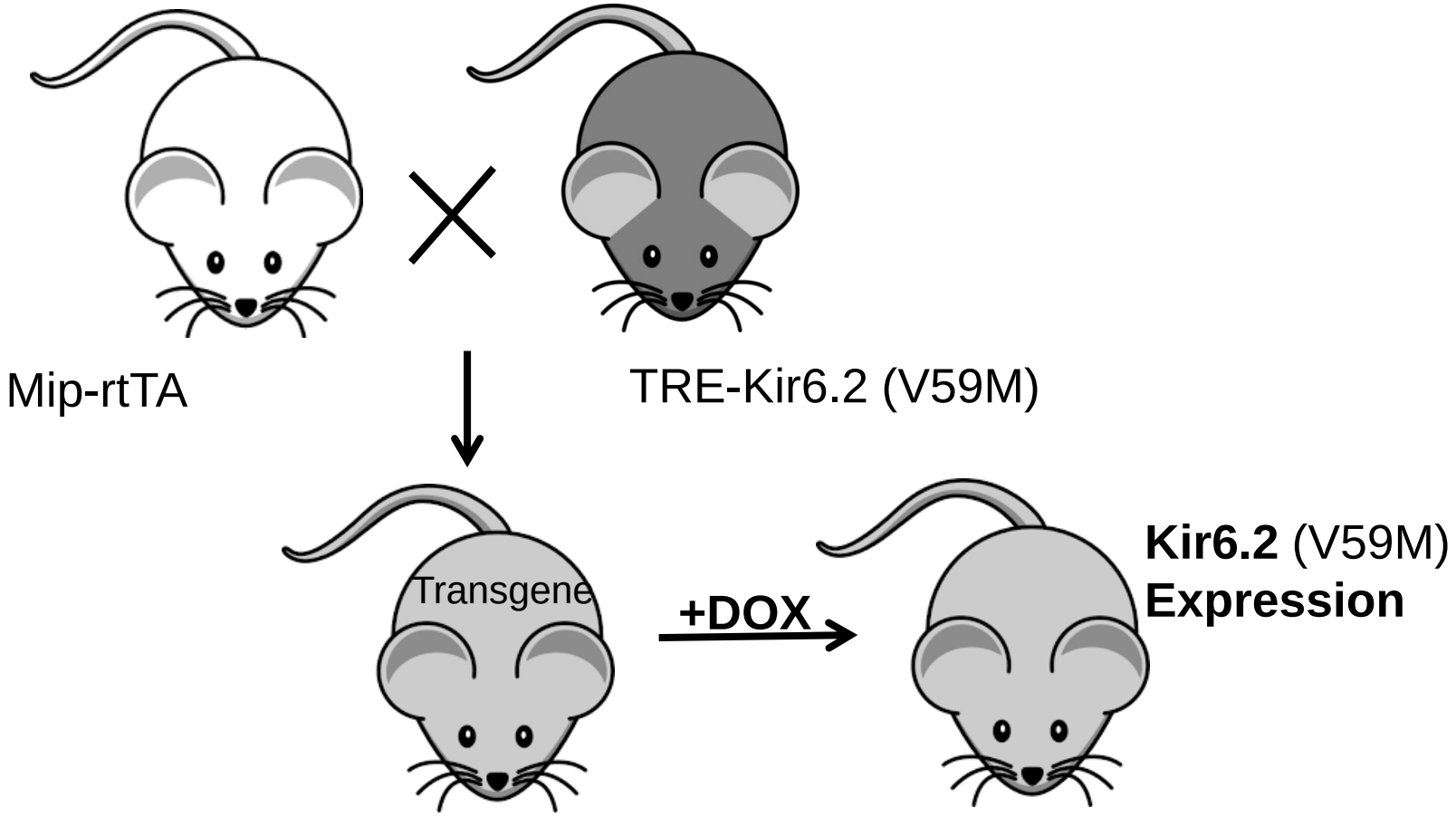
Relevant for Insulin?

V59M gain-of-function mutation in Kir 6.2

- Gain-of-function mutations in the gene encoding the ATP-sensitive K+ (KATP) channel subunits Kir6.2 (KCNJ11)
- Glucose metabolism stimulates insulin secretion from pancreatic β-cells by closing KATP channels, causing plasma membrane depolarization
- Gain of function mutations keep the KATP channel open, thus making β-cells always hyperpolarized and unable to secrete insulin in response to glucose stimulation.

Transgenic Mouse Strategy

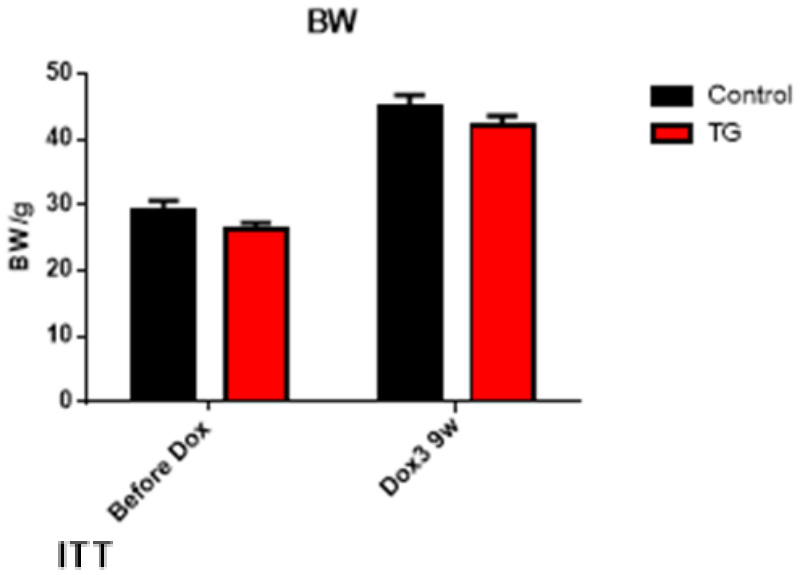
Kir6.2 the pancreatic beta cell KATP channel that is involved in regulation of insulin secretion

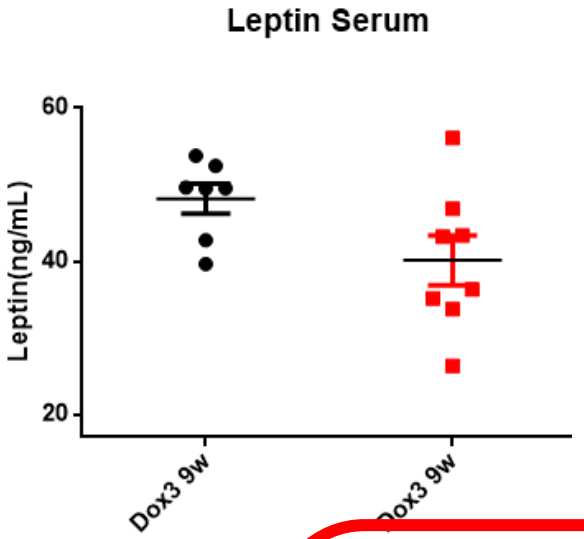


beta cell specific rtTA/TRE-Transgene expression

Kir6.2 Female

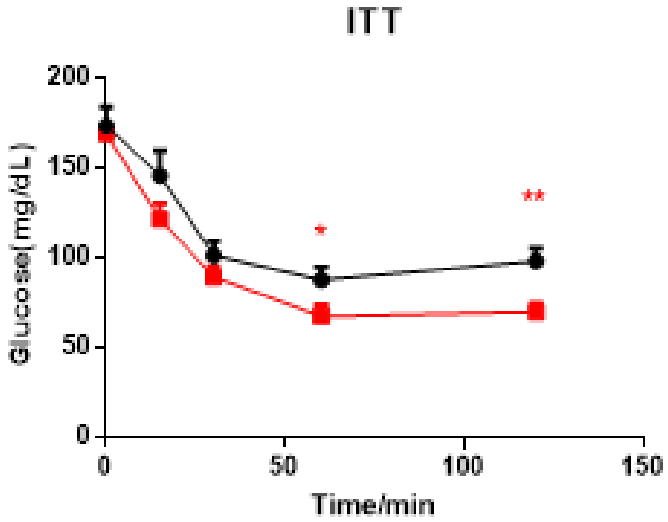
Partial insulin deficiency improves insulin sensitivity

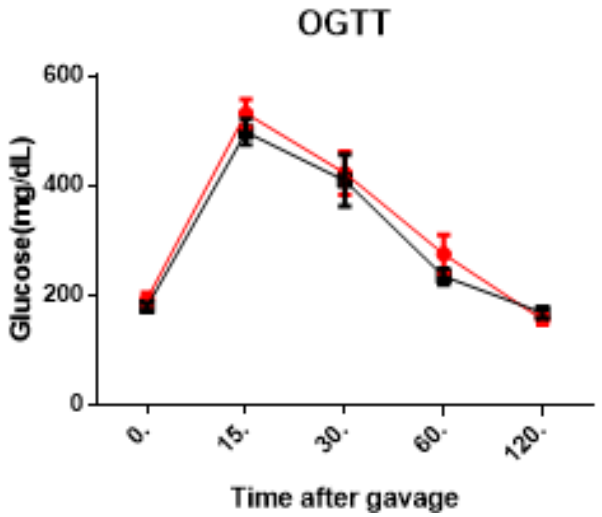


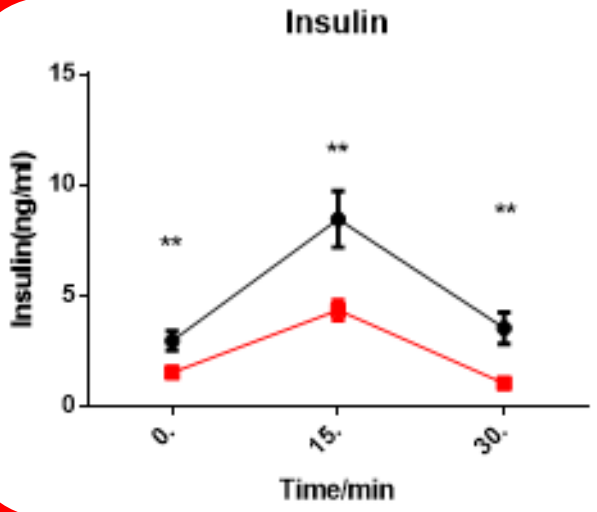


9 weeks HFD DOX 3 FEMALE

SLIGHTLY LOWER LEPTIN LEVELS

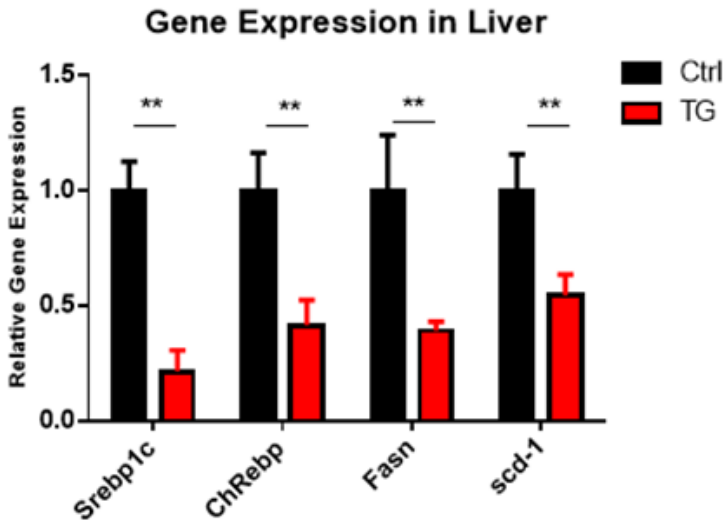






Improving insulin sensitivity reduces liver steatosis

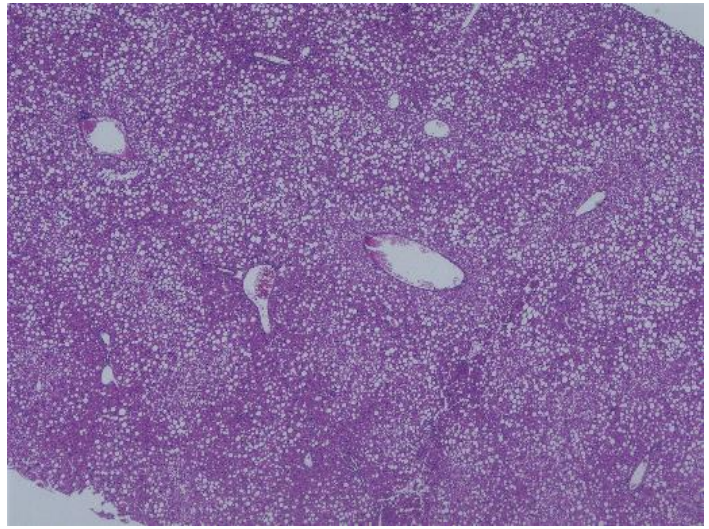
Kir6.2 Female



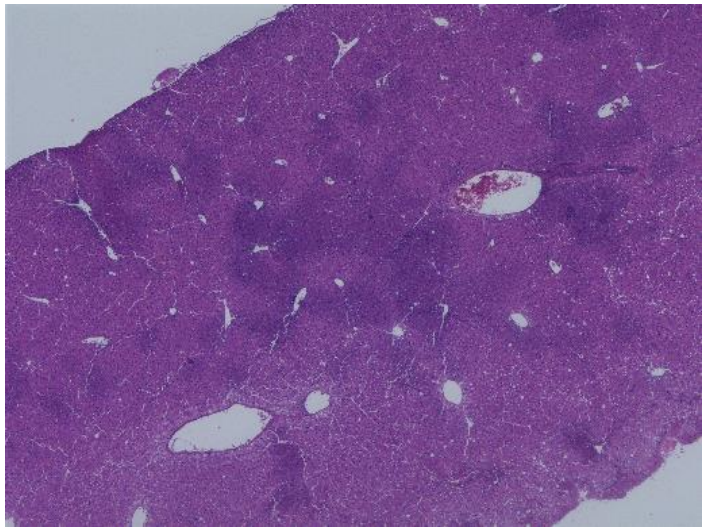
9 weeks HFD DOX 3
FEMALE

Liver Histology

Control

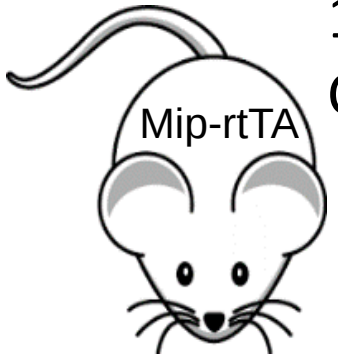


TG



Lower circulating insulin levels protect against diet-induced obesity

Kir6.2 Male

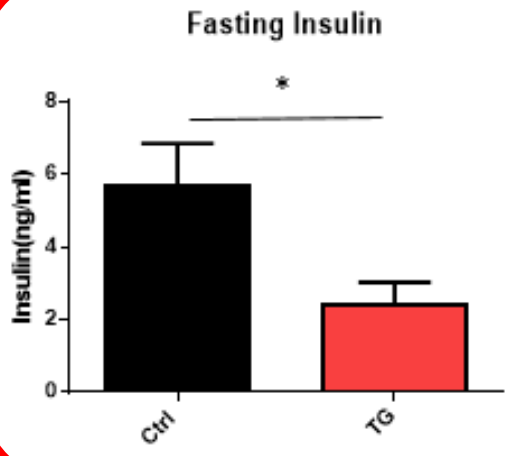


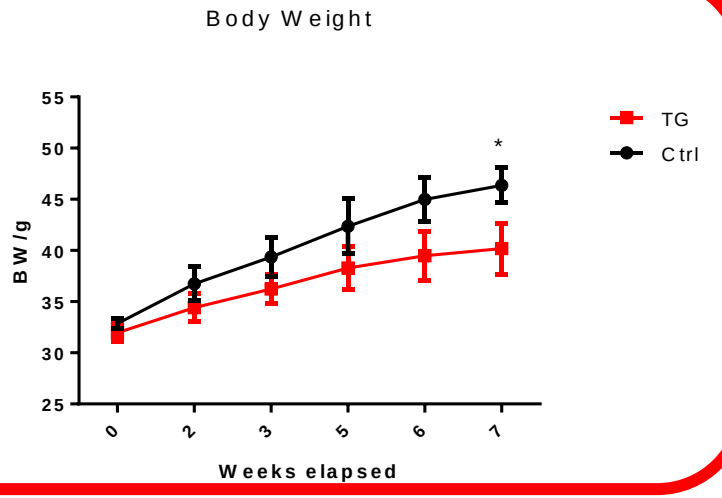
16 weeks old
Control or TG

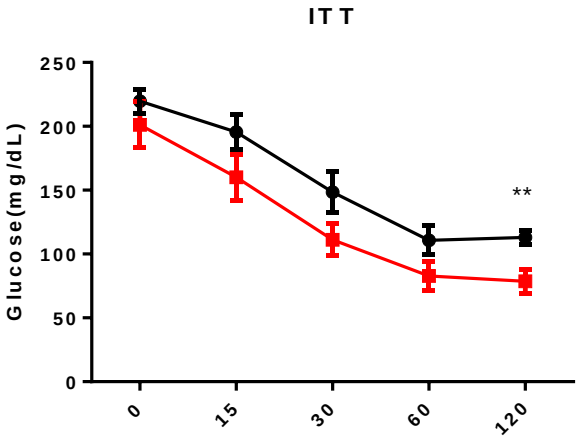
HFD

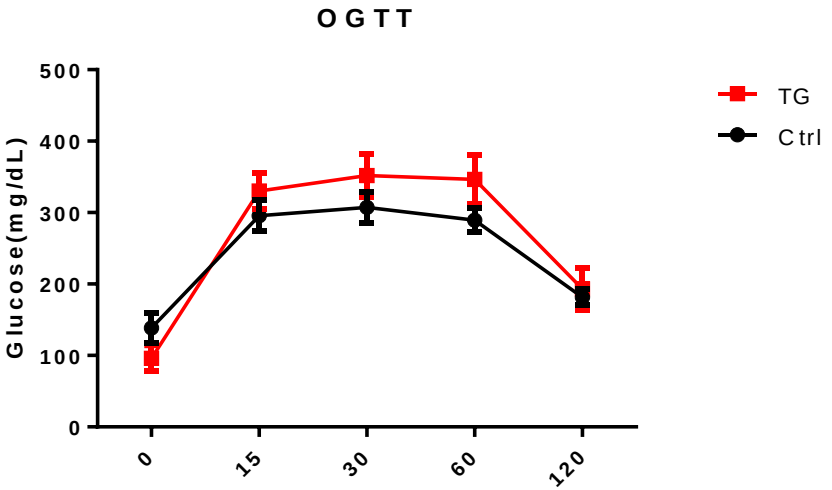
Dox1.5

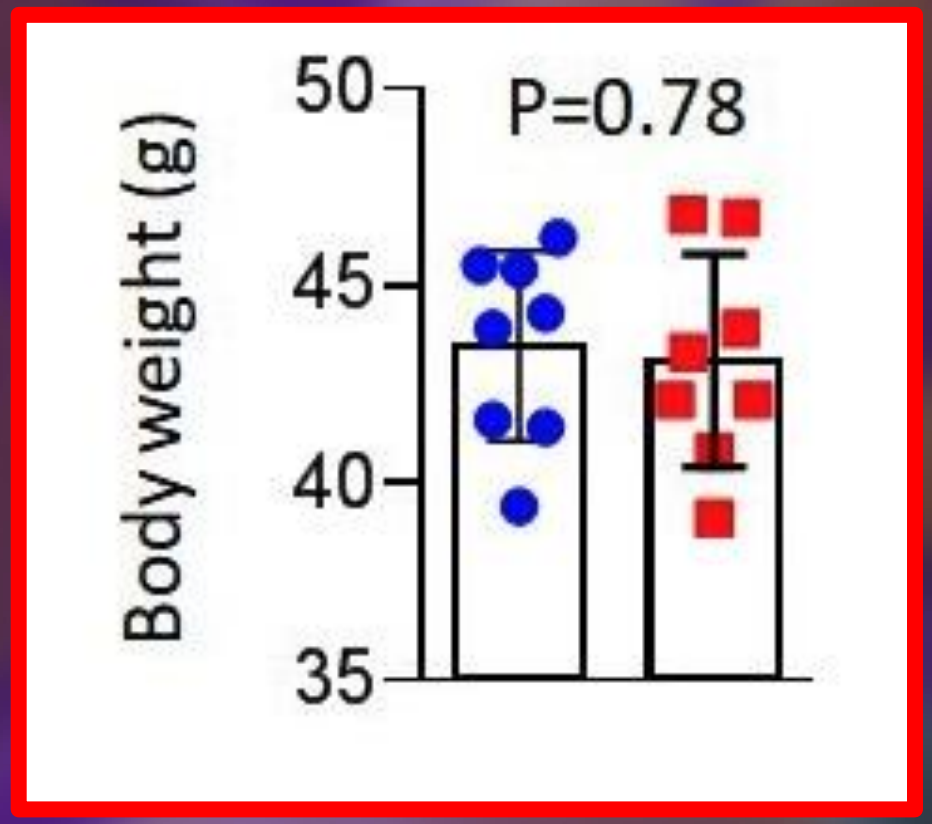
7 WEEKS HFD

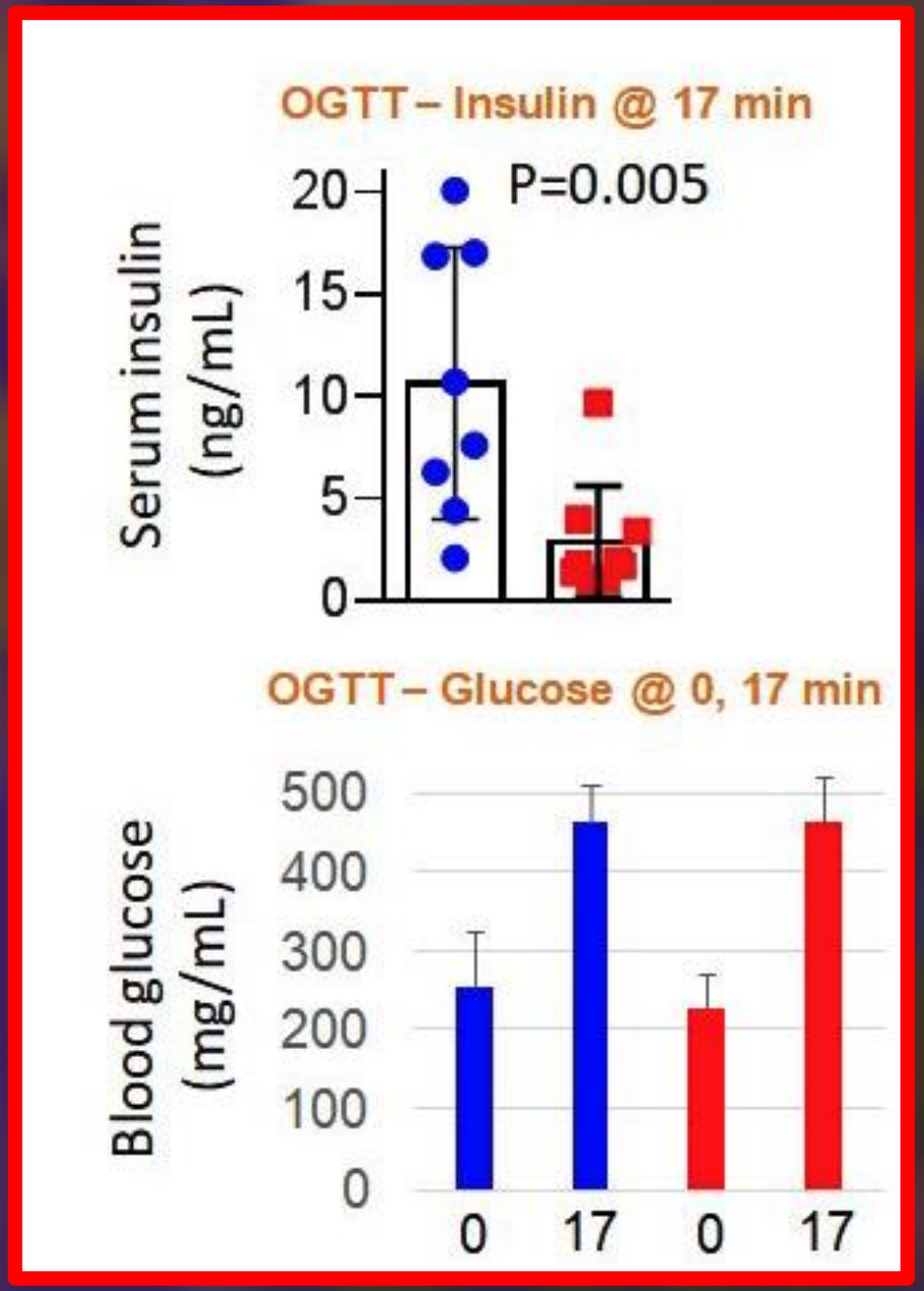




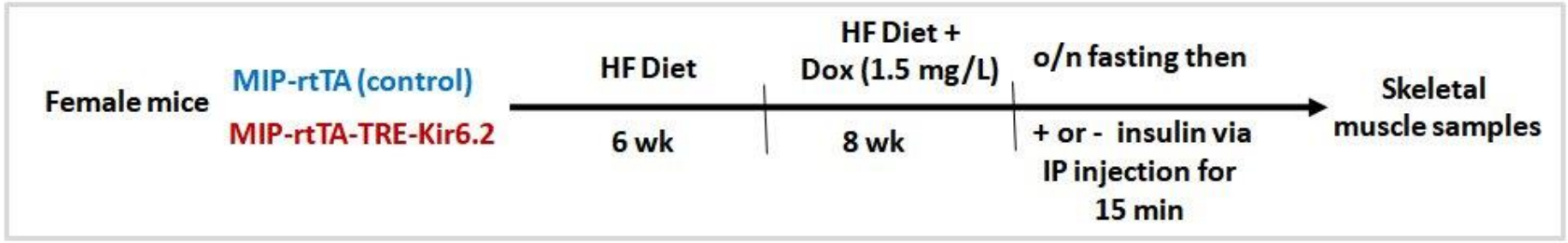




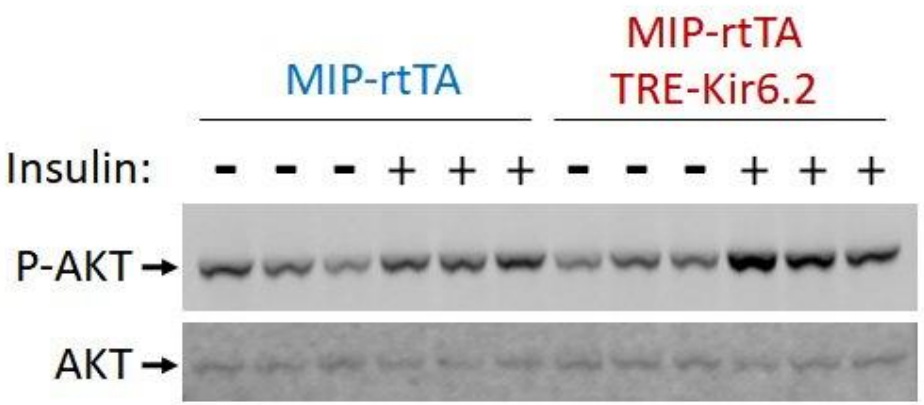

Body weight (g)
50
45
40
35
P=0.78

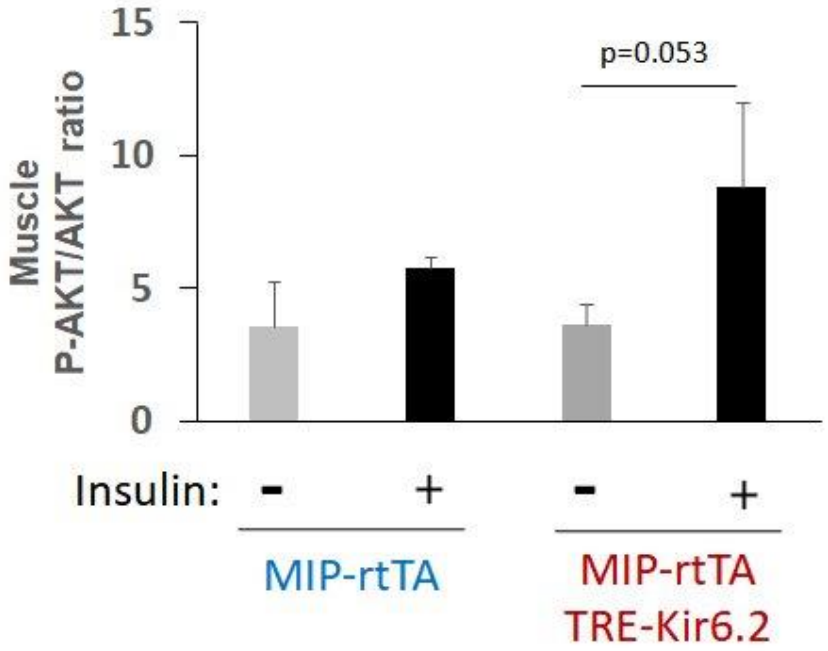

OGTT – Insulin @ 17 min
Serum insulin (ng/mL)
20
15
10
5
0
P=0.005
OGTT – Glucose @ 0, 17 min
Blood glucose (mg/mL)
500
400
300
200
100
0
0
17
0
17

Exogenous insulin-induced AKT phosphorylation in mouse skeletal muscle



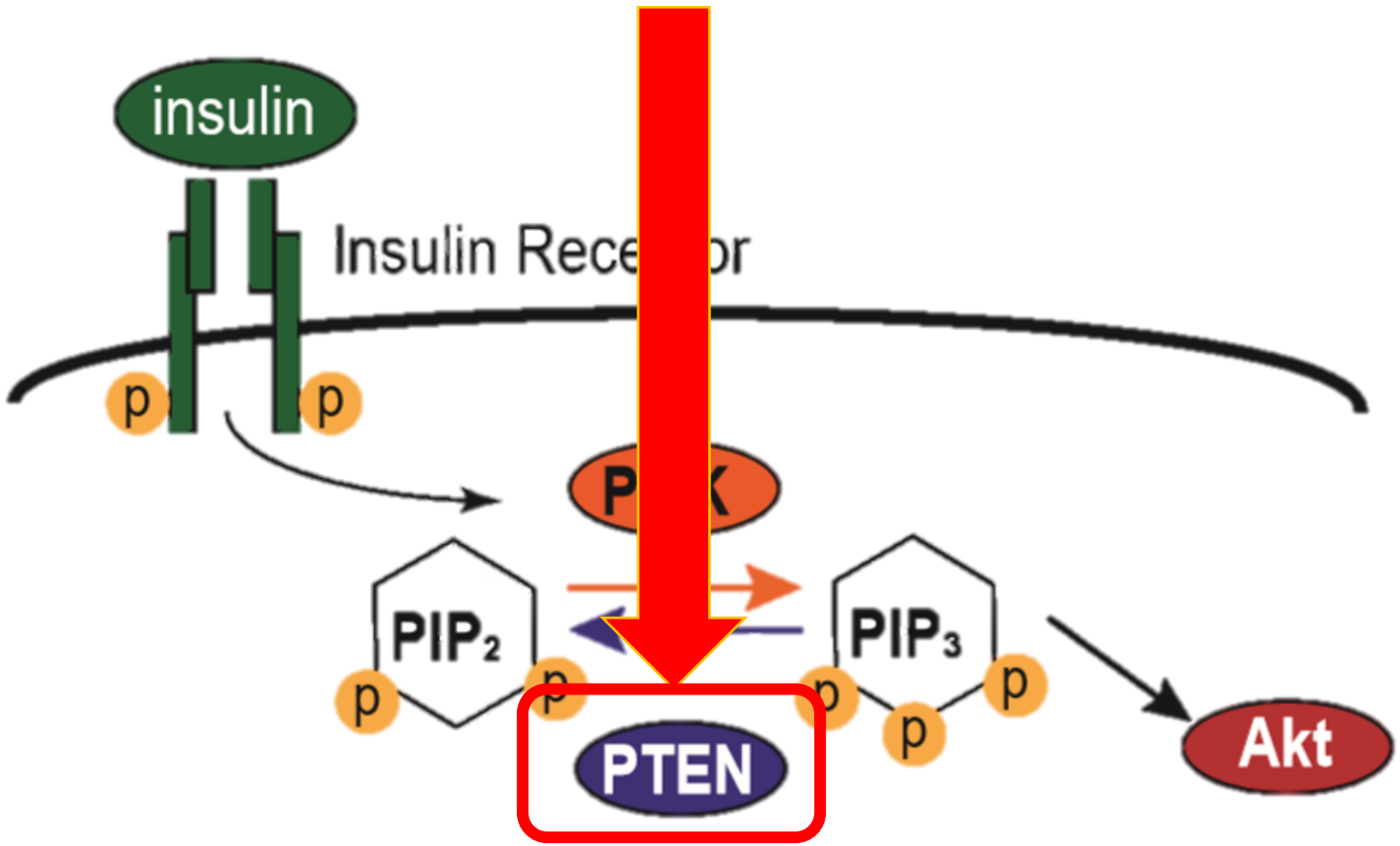
P-AKT Immunoblotting Analysis





Selective Manipulation of Insulin Sensitivity at the Level of Peripheral Target Tissues

PTEN as a Modulator of Insulin Signaling in Adipose Tissue



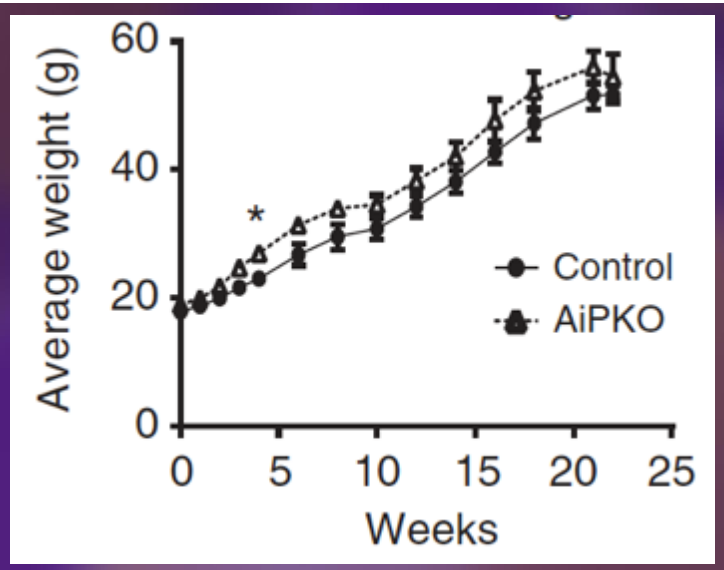
ARTICLE

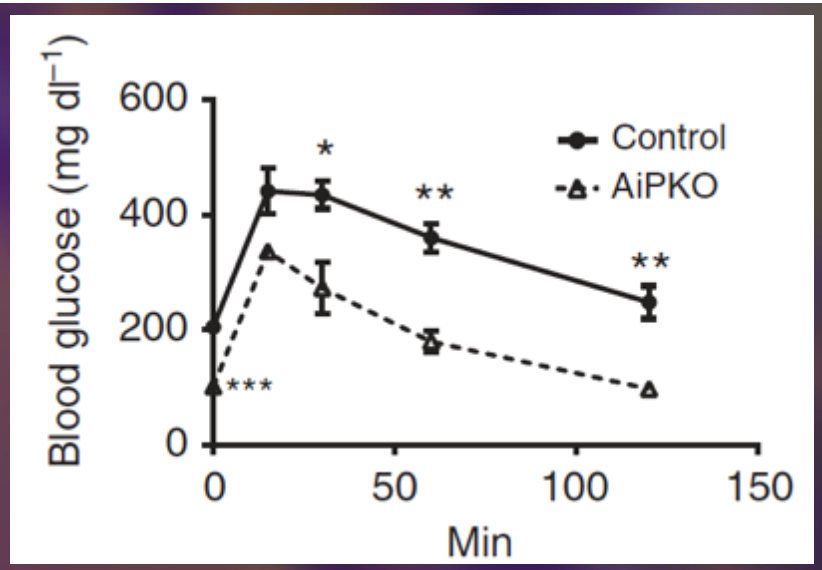
Received 1 Mar 2015 | Accepted 23 Jun 2015 | Published 5 Aug 2015

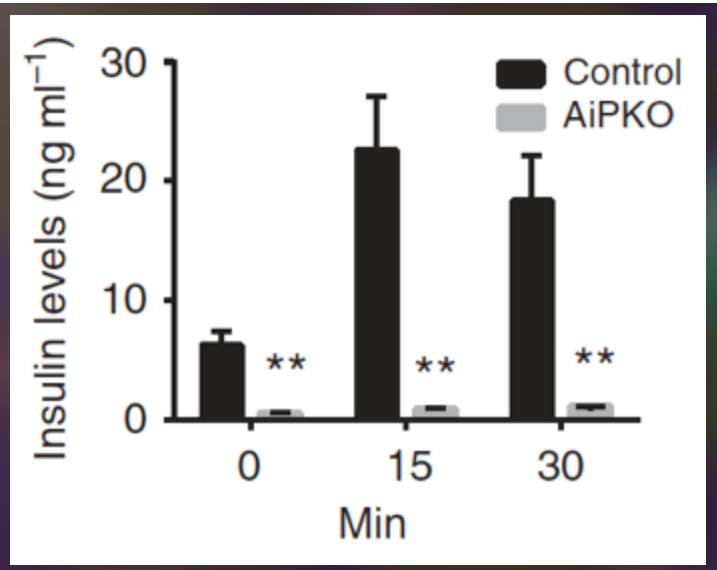
DOI: 10.1038/ncomms8906 OPEN

Selective enhancement of insulin sensitivity in the mature adipocyte is sufficient for systemic metabolic improvements

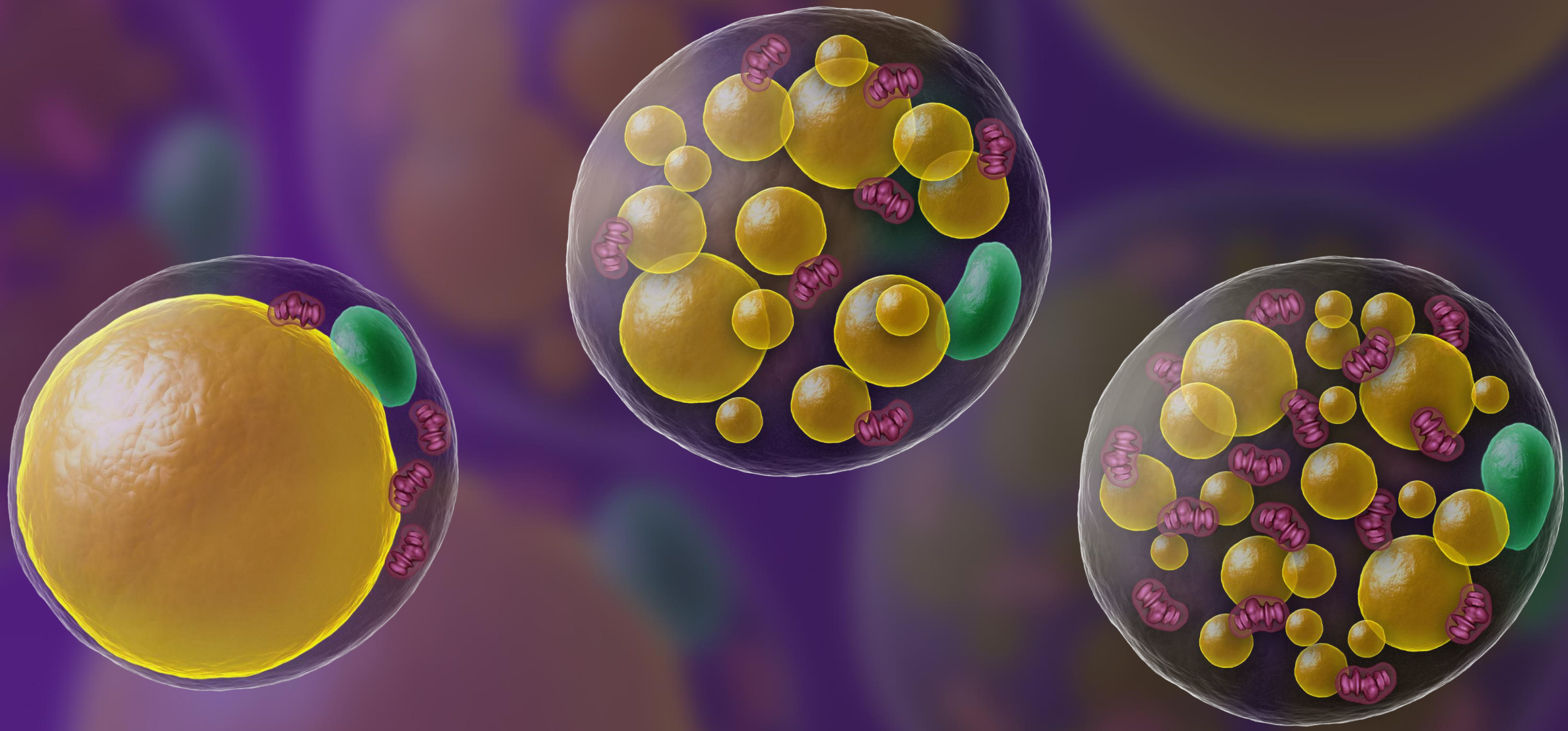
Thomas S. Morley[1], Jonathan Y. Xia[1] & Philipp E. Scherer[1,2]





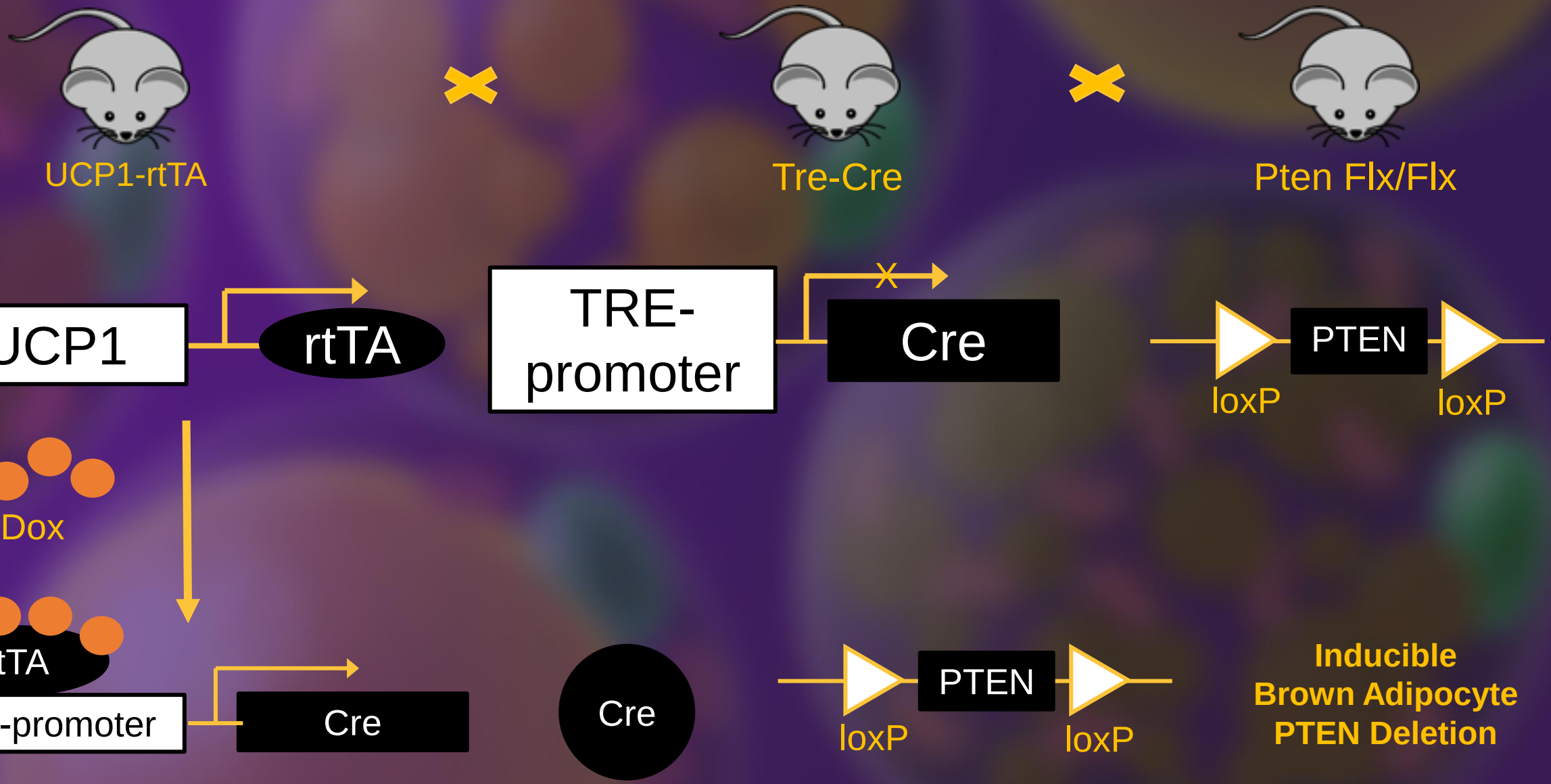


The Brown Adipocyte

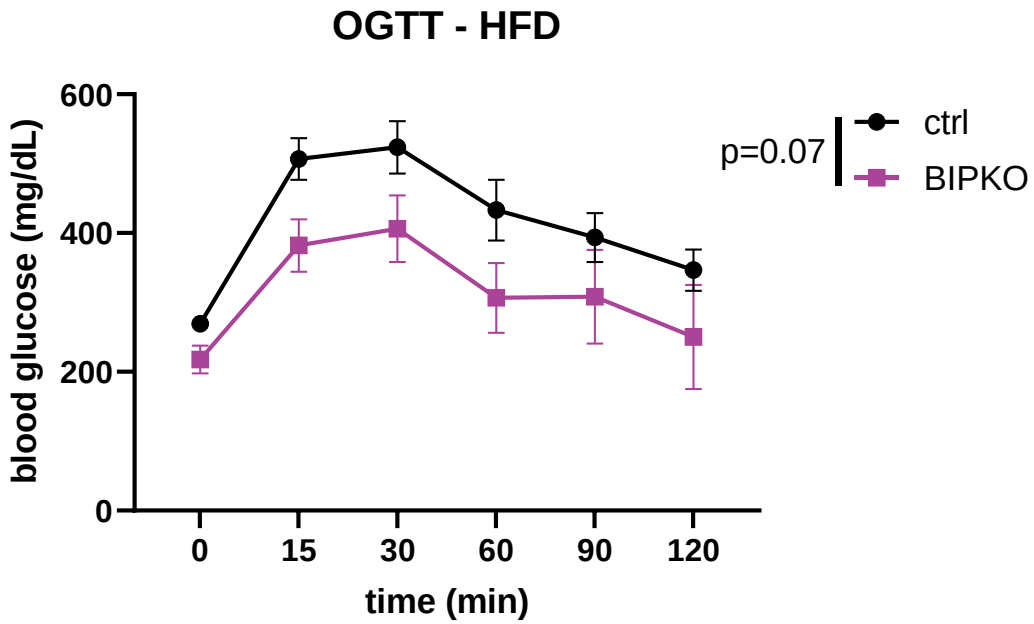


The “BIPKO” Mouse

“Brown/beige adipose Inducible PTEN KO”



Insulin sensitization of BAT causes global glucose tolerance and insulin sensitivity



TRE-ePTEN: a hyperactive PTEN

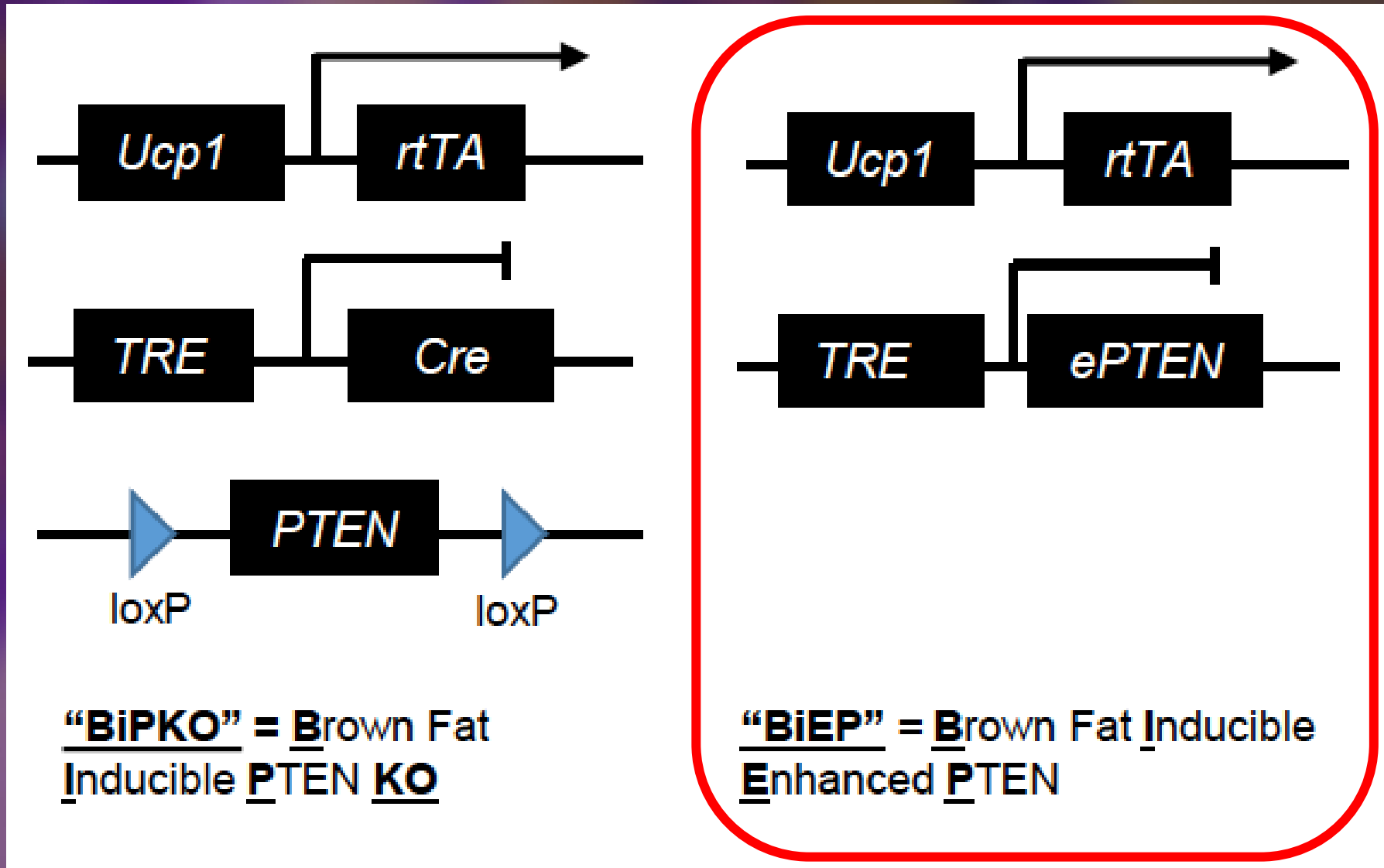
- PTEN is a PI(3,4)P2 3-phosphatase

- We generated ***TRE*-ePTEN** mice, which in combination with the appropriate tissue-specific promoter-rtTA mouse, allows us to overexpress PTEN in any target tissue.

- ePTEN is a potent mutant version of PTEN in which we introduced six point mutations (“enhanced PTEN or ePTEN”)

Nguyen et al., Proc Natl Acad Sci U S A. 2014;111(26):E2684-93

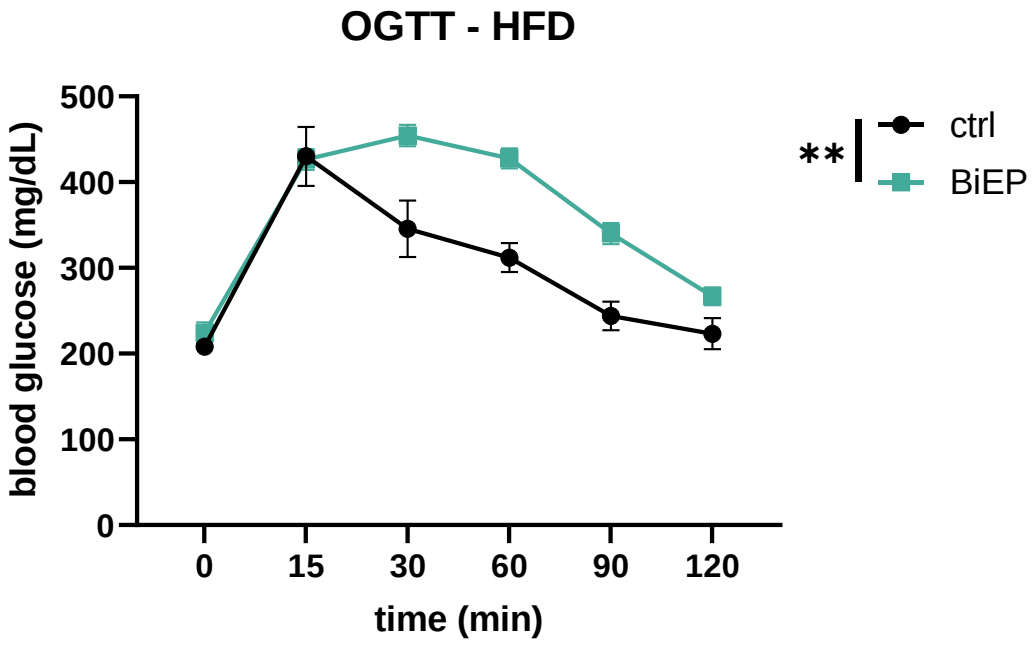
Manipulating Insulin Signaling Trough PTEN

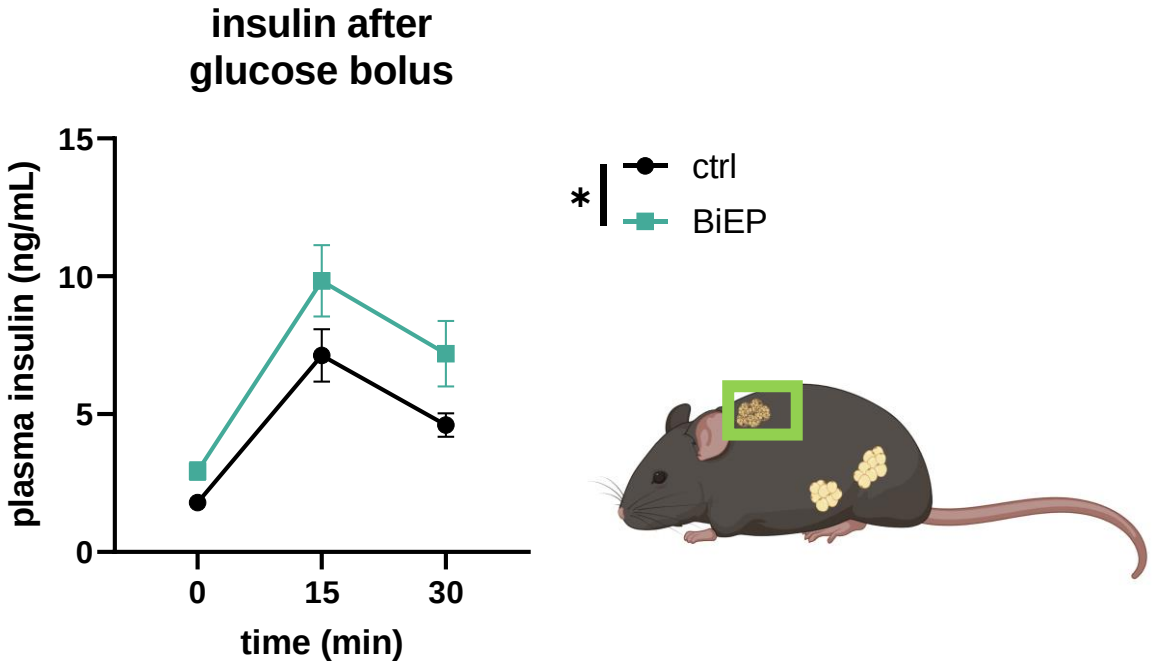


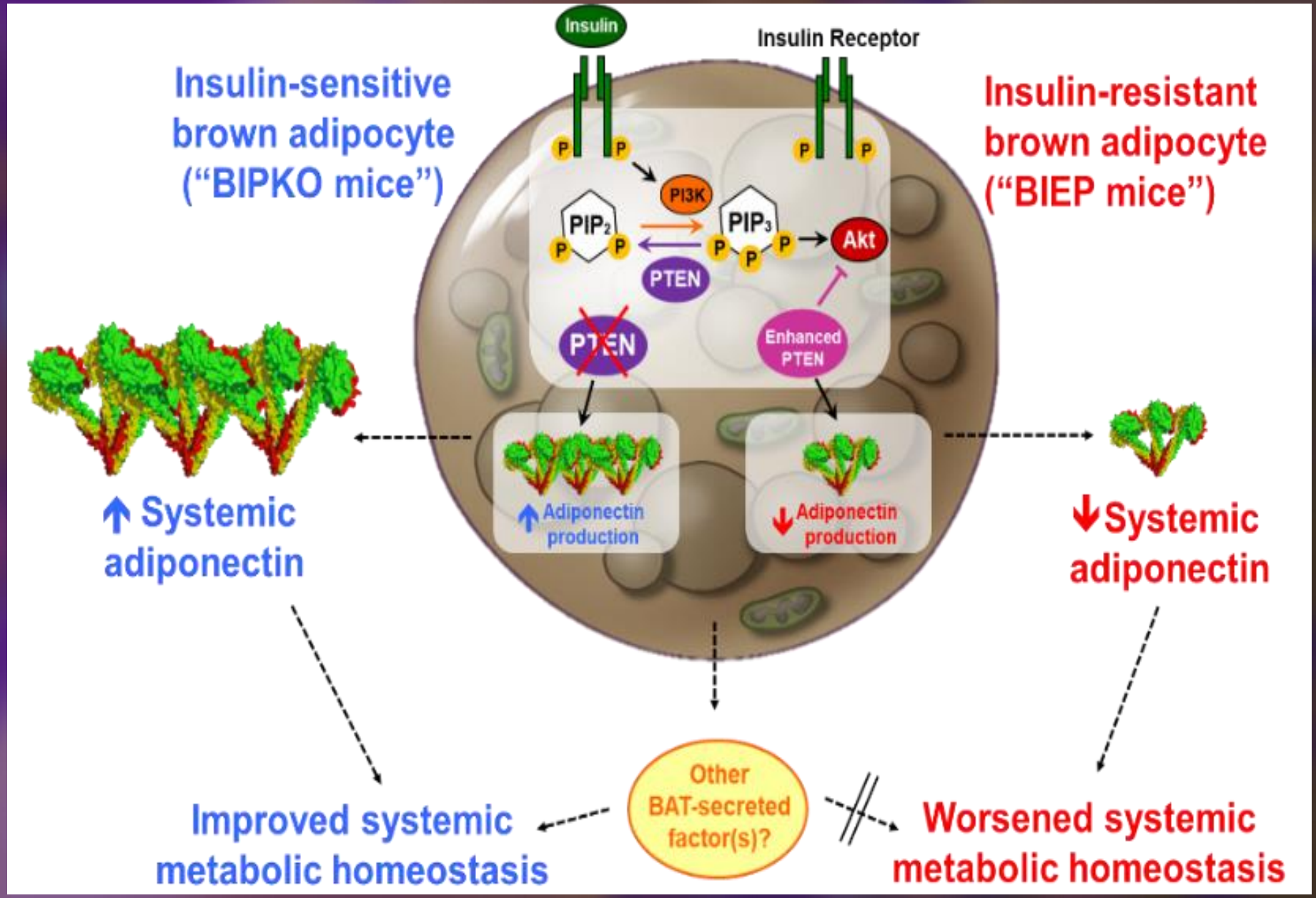
"BiPKO" = Brown Fat Inducible PTEN KO

"BiEP" = Brown Fat Inducible Enhanced PTEN

Insulin desensitization of BAT causes global glucose intolerance and insulin resistance

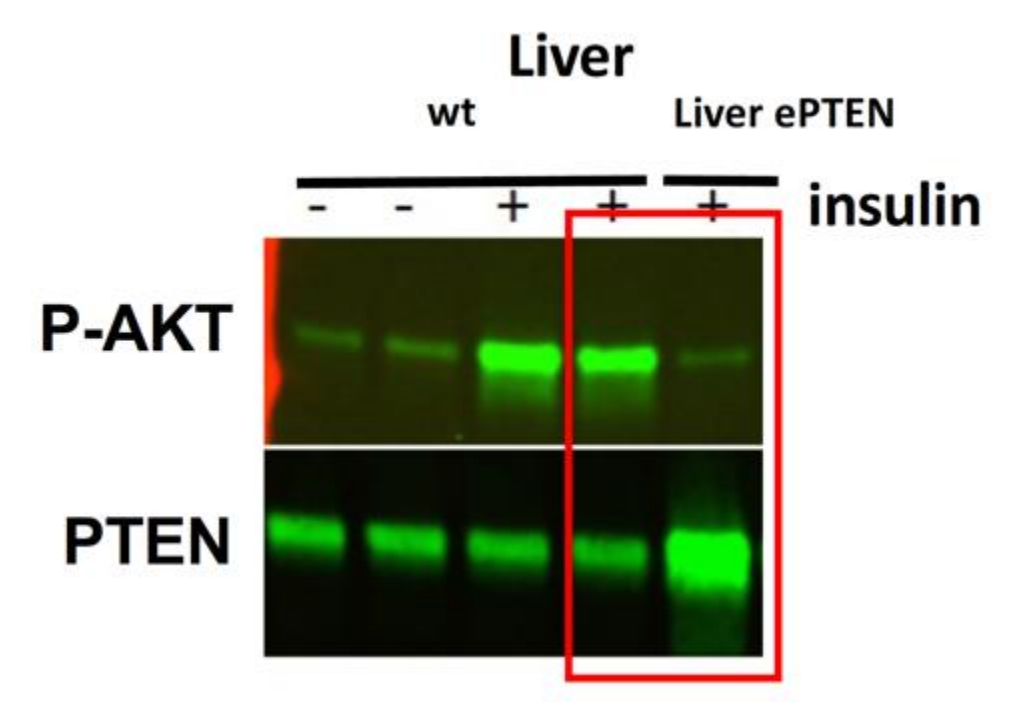


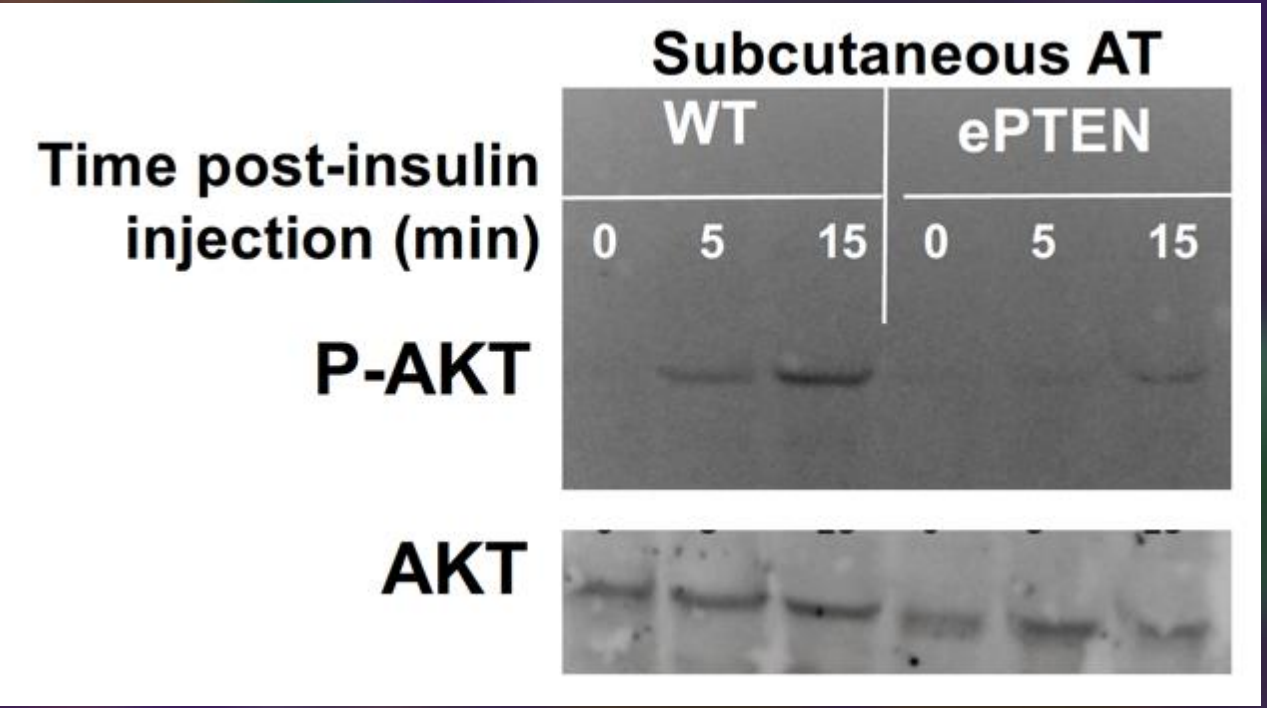



Insulin
Insulin Receptor
Insulin-sensitive brown adipocyte ("BIPKO mice")
Insulin-resistant brown adipocyte ("BIEP mice")
P
PI3K
PIP2
PIP3
Akt
PTEN
PTEN
Enhanced PTEN
↑ Systemic adiponectin
↑ Adiponectin production
↓ Adiponectin production
↓ Systemic adiponectin
Other BAT-secreted factor(s)?
Improved systemic metabolic homeostasis
Worsened systemic metabolic homeostasis

TRE-ePTEN in the Liver

Insulin Resistance "Spills Over"



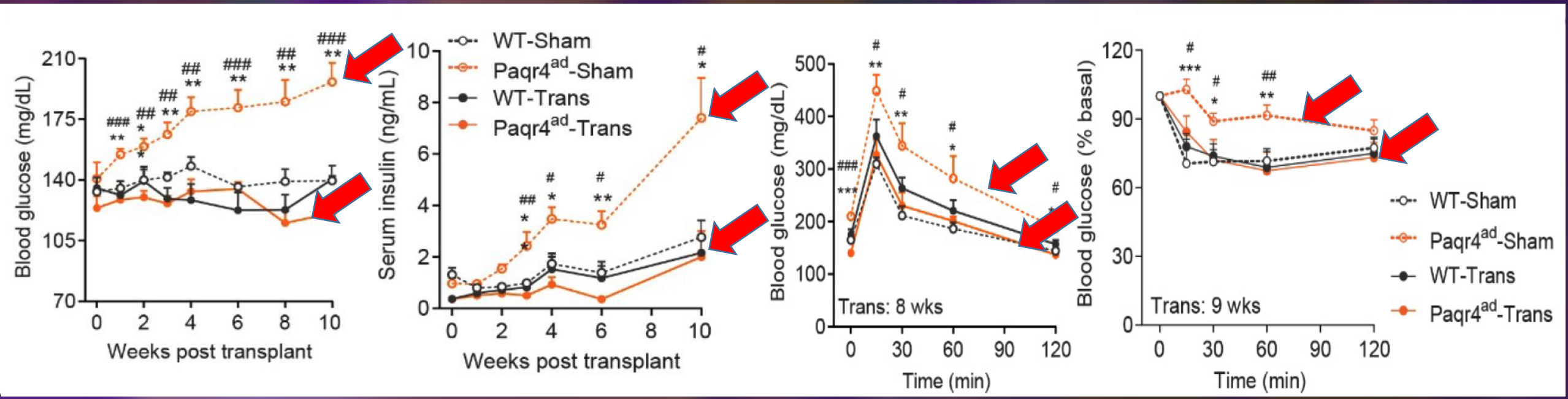


Even small amounts of transplanted dysfunctional adipose tissue can negatively impact systemic insulin sensitivity

Even small amounts of transplanted insulin sensitive adipose tissue can positively impact systemic insulin sensitivity

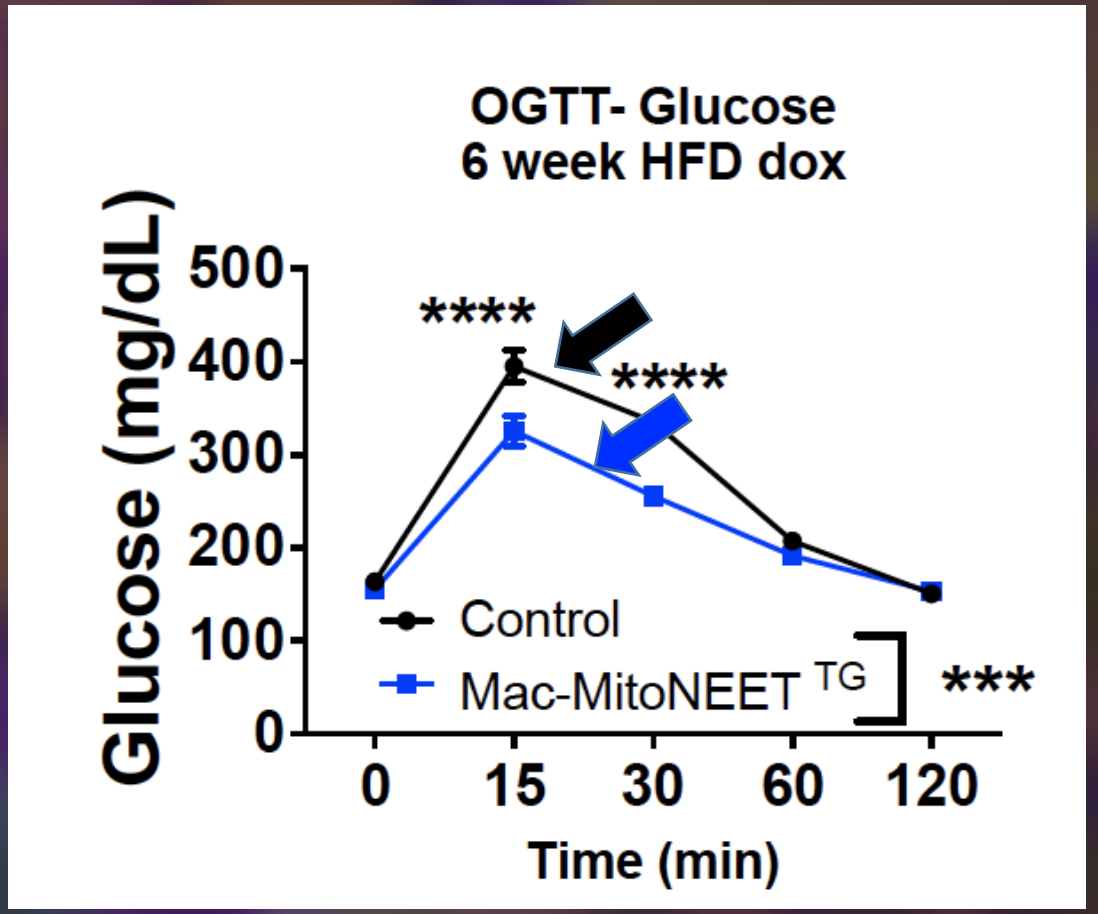
Even small amounts of transplanted insulin sensitive adipose tissue can positively impact systemic insulin sensitivity

Improved Glycemia **Improved Insulin** **Improved OGTT** **Improved ITT**



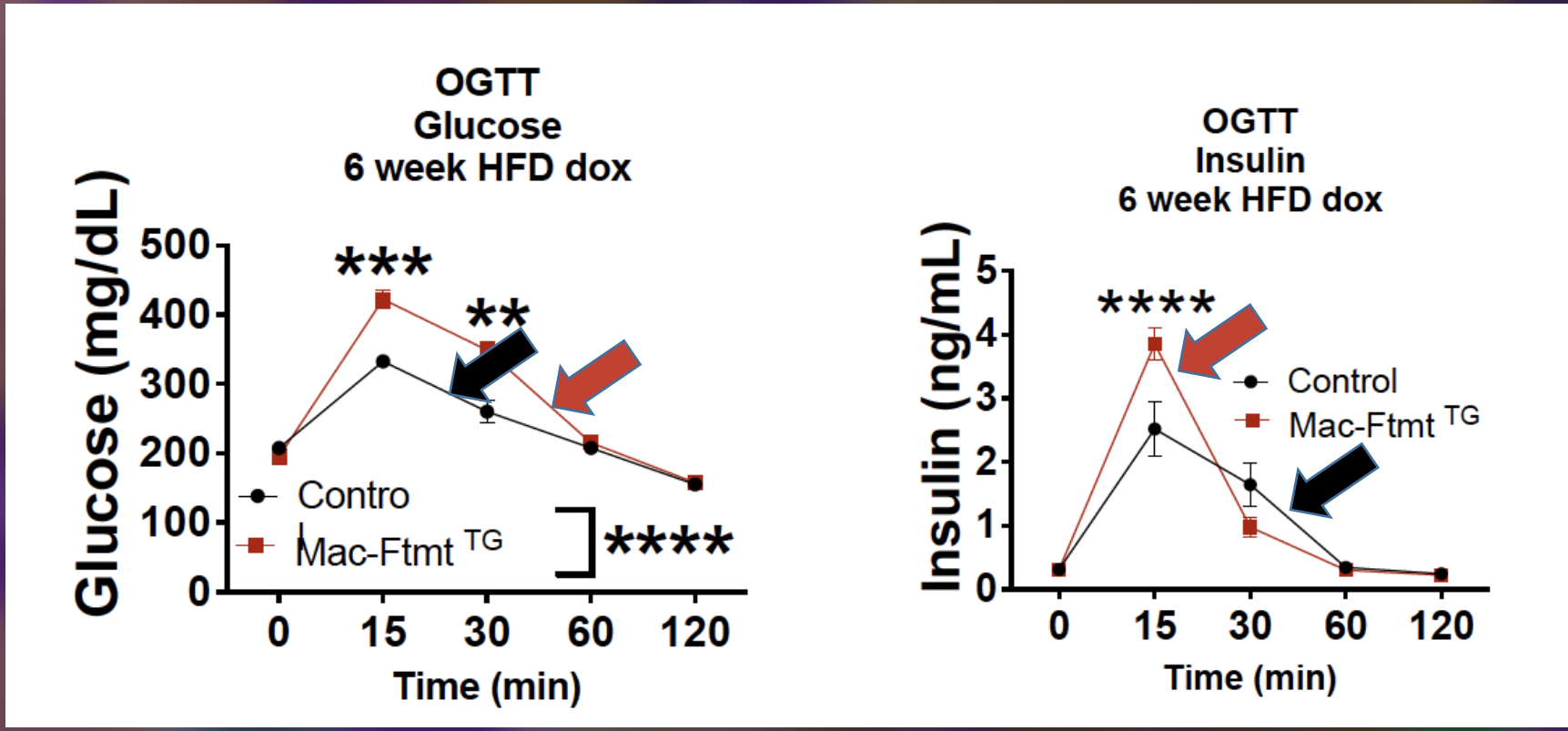
Zhu and Scherer, in revision

Metabolically favorable phenotype can be transplanted!



Joffin, Gliniak et al., Nature Metabolism, 2022, Nov;4(11):1474-1494

Metabolically unfavorable phenotype can be transplanted!



Joffin, Gliniak et al., Nature Metabolism, 2022, Nov;4(11):1474-1494

Bottom Line:

Hyperinsulinemia triggers insulin resistance even in the absence of hyperglycemia

Adipocyte/Adipose Tissue is the central player in systemic insulin sensitivity

Touchstone Diabetes Center
UT SOUTHWESTERN MEDICAL CENTER

60 years NIDDK National Institute of Diabetes and Digestive and Kidney Diseases
60 Years of Advancing Research to Improve Health
Research supported by NIDDK

American Diabetes Association.

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Christy Gliniak
Chao Li, Nancy Sun

Christine Kusminski

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