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OMICS International has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.

An metabolomic approach to identify the endogenous substrate of OCT1

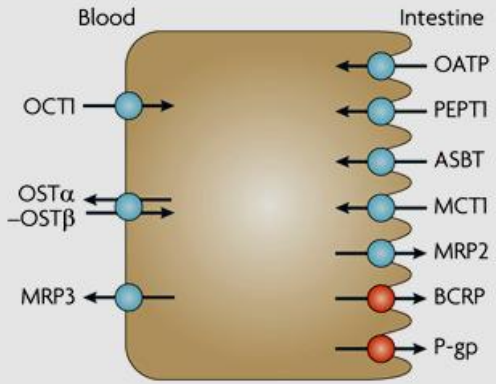
Ligong Chen, Ph.D.

Department of Pharmacology and Pharmaceutical Sciences
School of Medicine

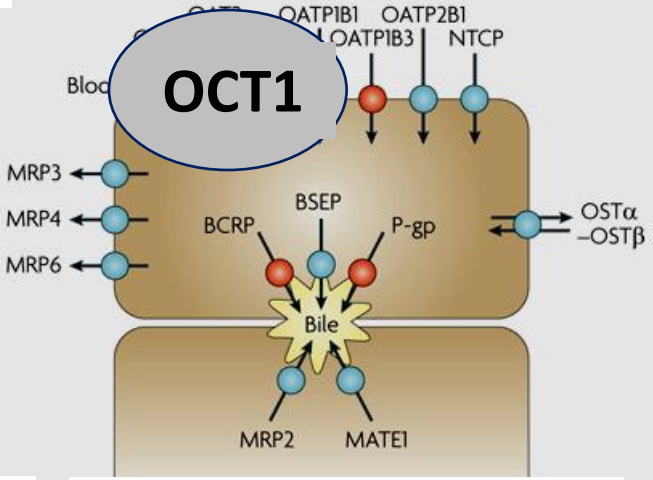
April. 28th, 2015

Transporters Play Critical Roles in Drug and Nutrients A.D.M.E .

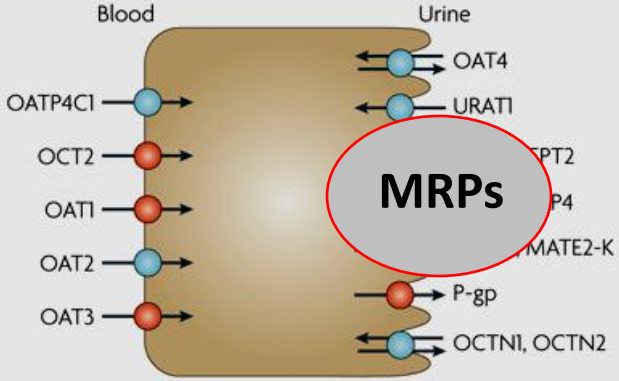
Intestinal epithelia



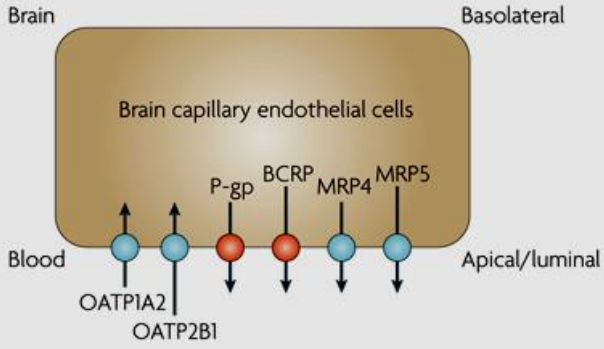
Hepatocyte



Kidney proximal tubules



Blood-brain barrier



Nature Reviews | Drug Discovery

Currently Utilized SLC-drug Targets

Depression,epilepsy,addiction

SLC6 family (TC:2.A.22,APC)

SLC6A1,SLC6A2,

SLC6A4,SLC6A3 (SSRI)

Movement disorders, psychiatric disorders, addiction

SLC18 family (TC:2.A.1,MFS)

SLC18A2

Epilepsy

SLC22 related (MFS)

SV2A

Uricosuresis,gout

SLC22 family (TC:2.A.1.19,MFS)

SLC22A6(OAT1)

Diuresis

SLC12 family (TC:2.A.30)

SLC12A1,SLC12A2,

SLC12A3,SLC12A4

SLC12A5 (NKCC)

Antiosteoporotic,antineoplastic

SLC25 family (TC:2.A.29,MC)

SLC25A4,SLC12A5,SLC12A6

Anti-diabetes

SLC5A2 (Canagflozin)

The List is Increasing……..

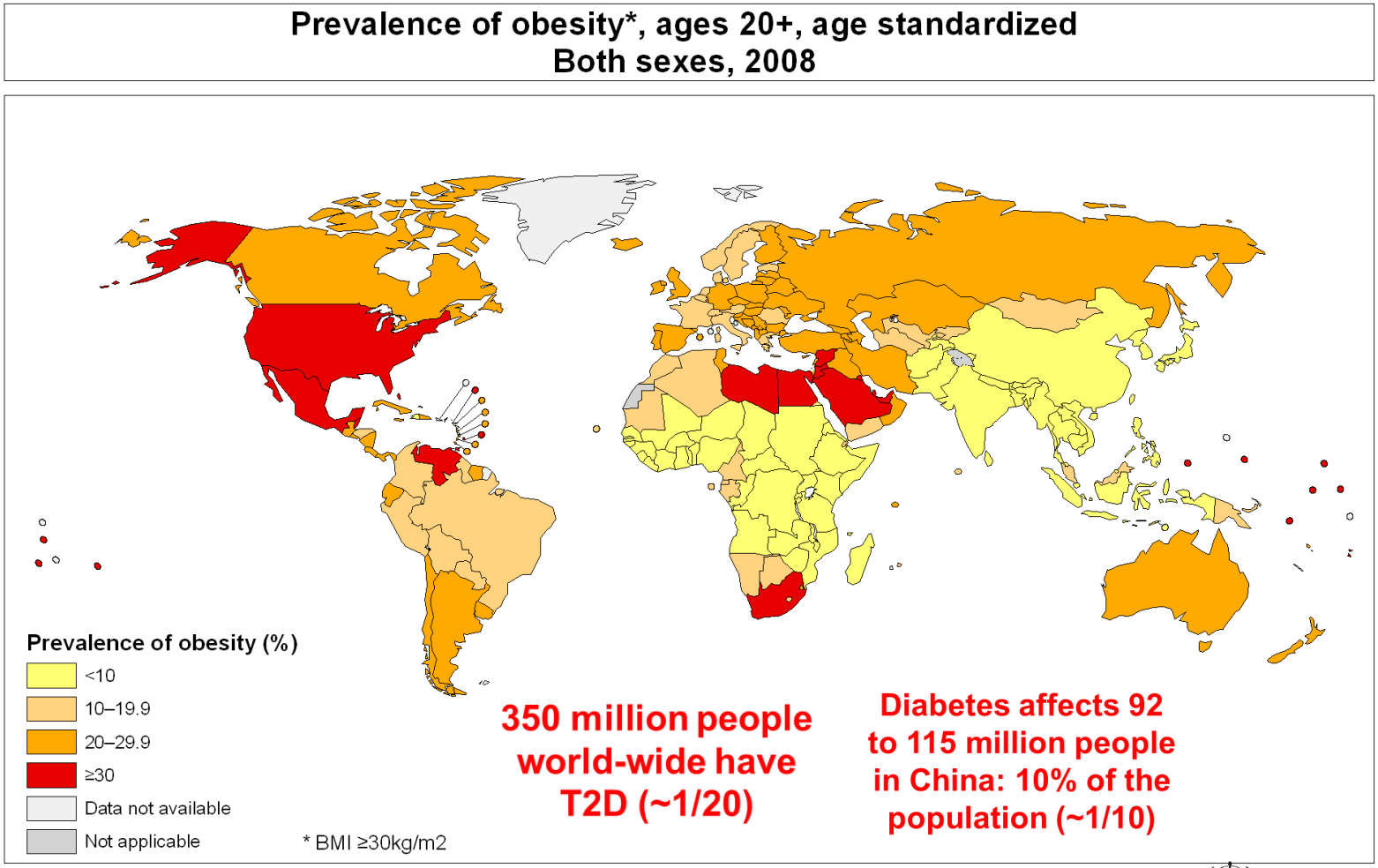
Transporter as Important Disease Susceptible Genes in GWAS

- SLC24A4 for Alzheimer's Disease
- SLC39A6 for Breast/pancreatic cancer/esophageal squamous-cell carcinoma
- SLC16A9 in Metabolic disease
- SLC6A20 in Hyperglycinuria, and iminoglycinuria
- SLC7A9 in Chronic kidney disease
- SLC22A3 in Prostate cancer/heart diease
- SLC2A9 in Gout: Urate acid disease
- SLC1A1 in Pancreatic disease
- SLC30A8 in Diabetes
- SLC22A12 in Gout: Urate acid disease
- SLC45A2 in Melonoma
- SLC17A8 in Lung Cancer Han Chinese
- SLC2A13 in Parkinson's Disease
- SLC6A4 in Schizophrenia

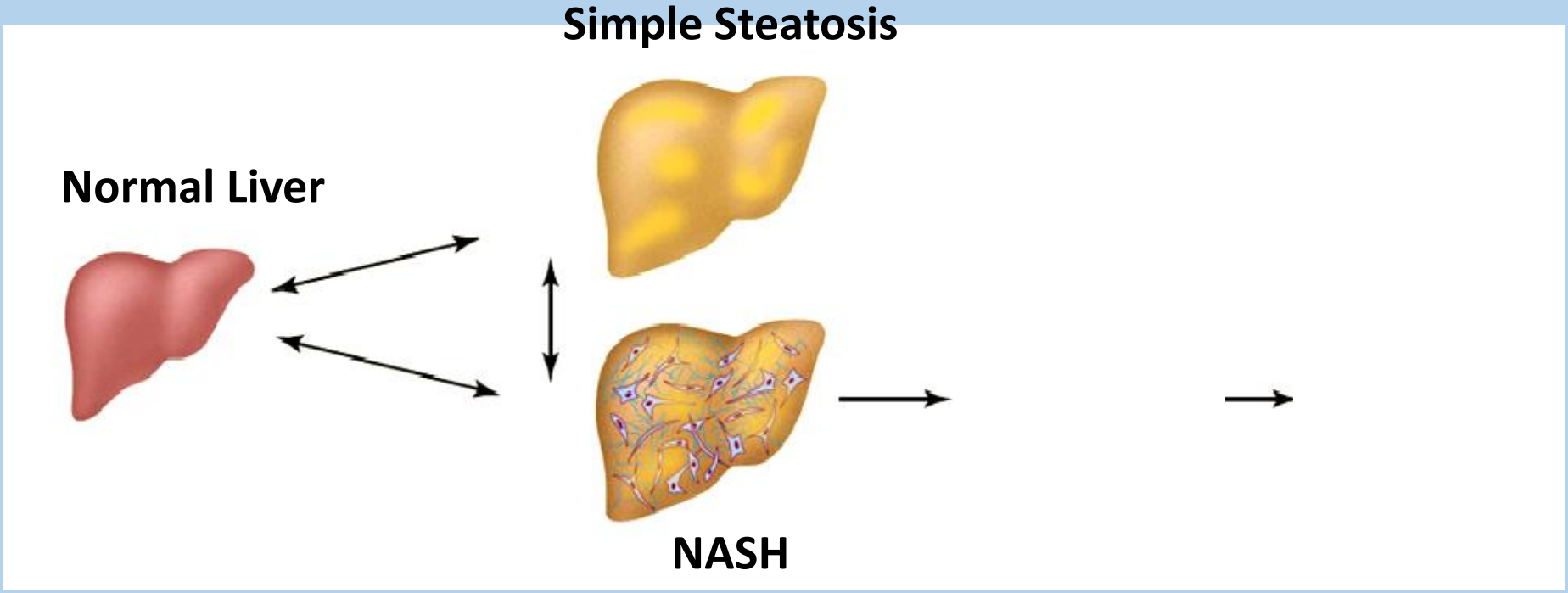
…….

"HOT" Therapeutic Targets

Obesity and Diabetes Rising in the world: How a Rare Disease Becomes a Modern "Pandemic"?



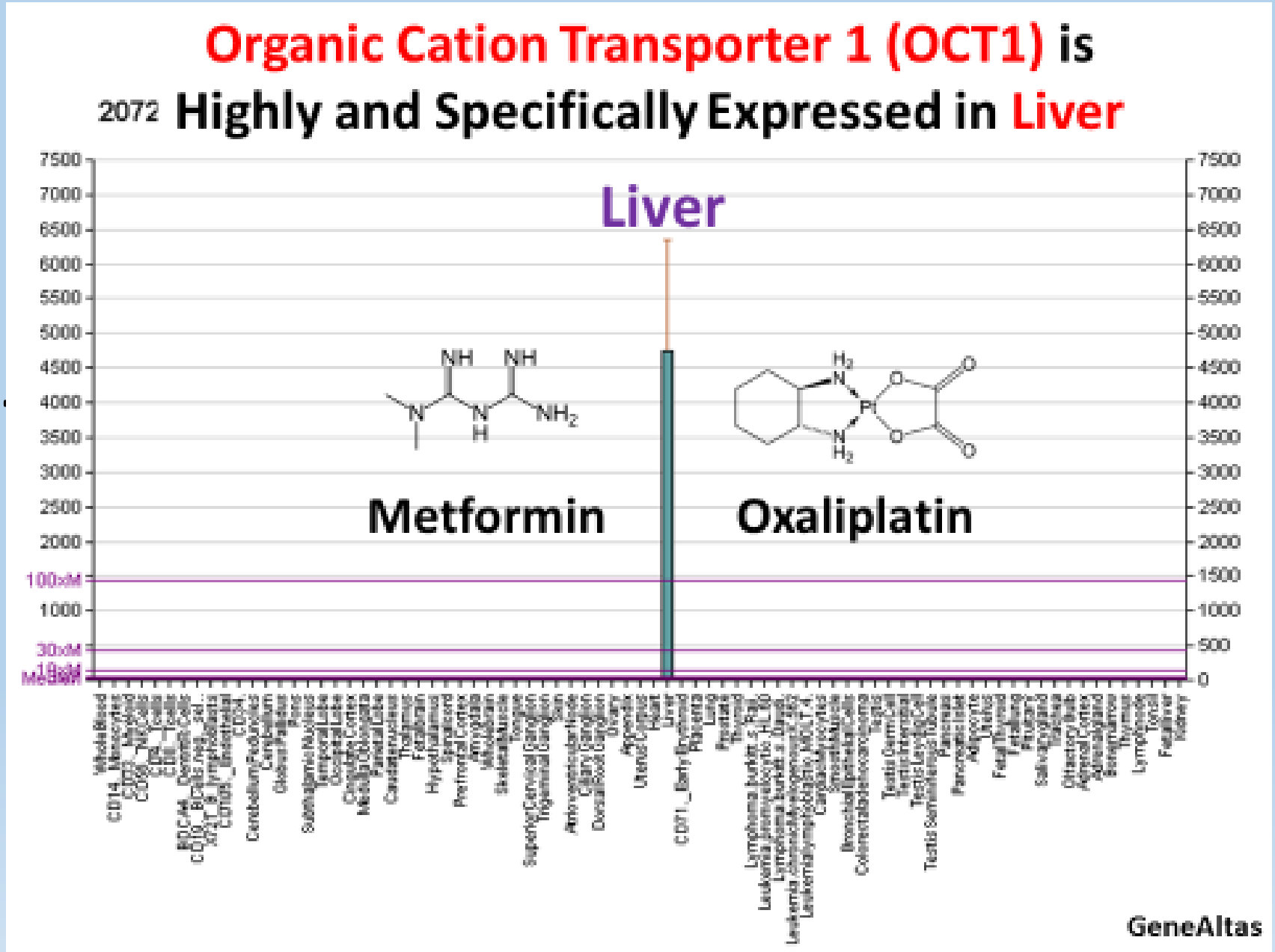
Nonalcoholic steatohepatitis(NASH) disease affects 35% of adults and an increasing number of children



Currently, there is no effective treatment on fatty liver

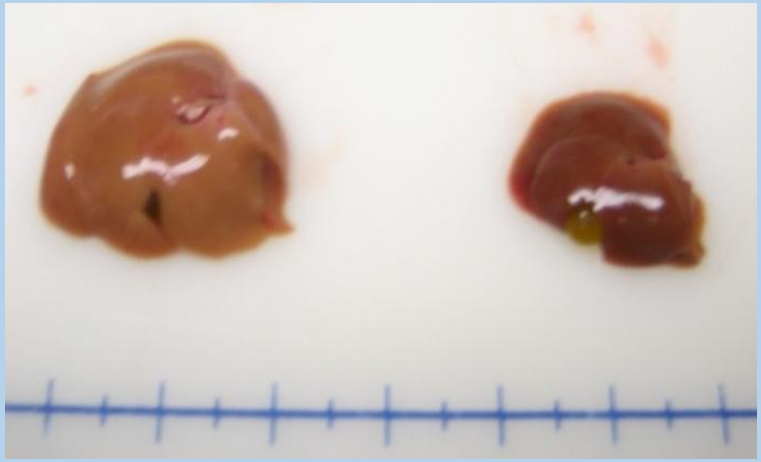
Science, 2011

Major Transporters Expressed in Liver



What **Phenotypes** do we see from the mouse studies?

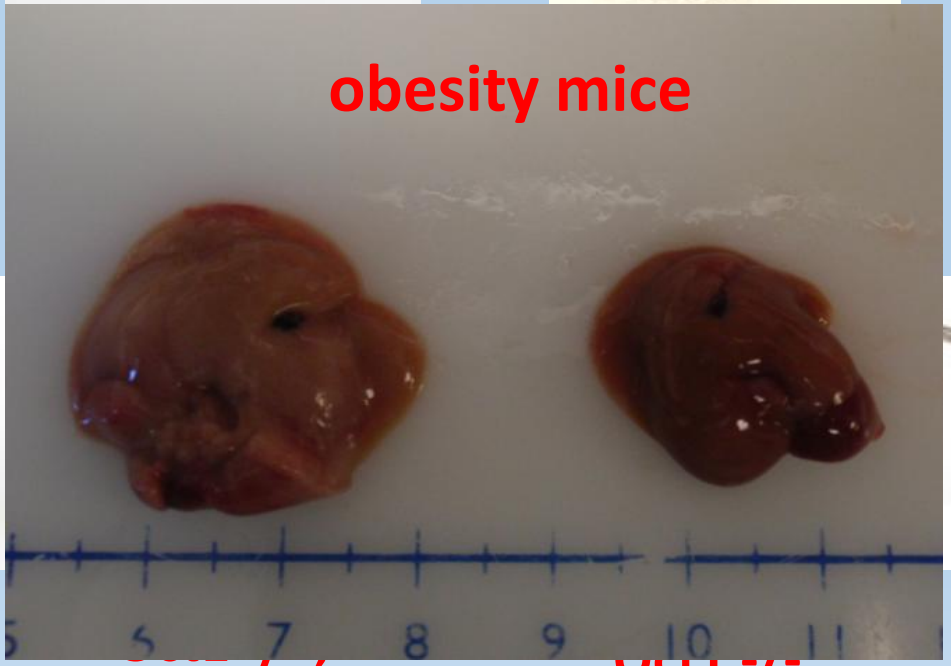
Oct1+/+ **Oct1-/-**



Lean mice

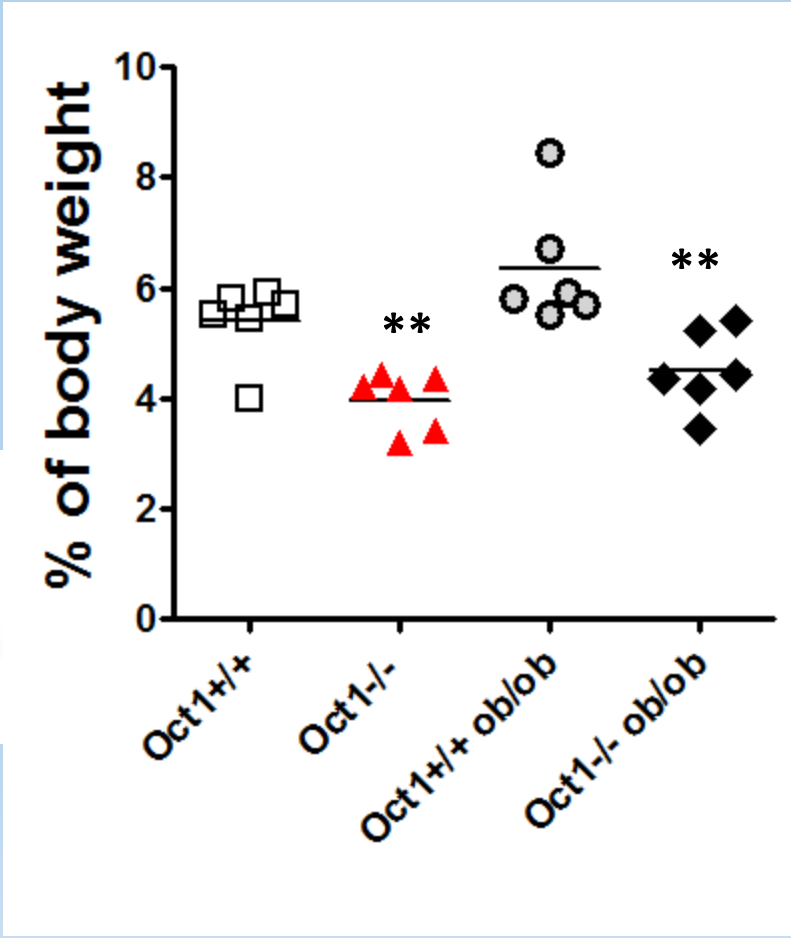
When crossed with Ob/Ob mice (**obesity mice**), the liver size is more **apparently reduced** in KO mice

X

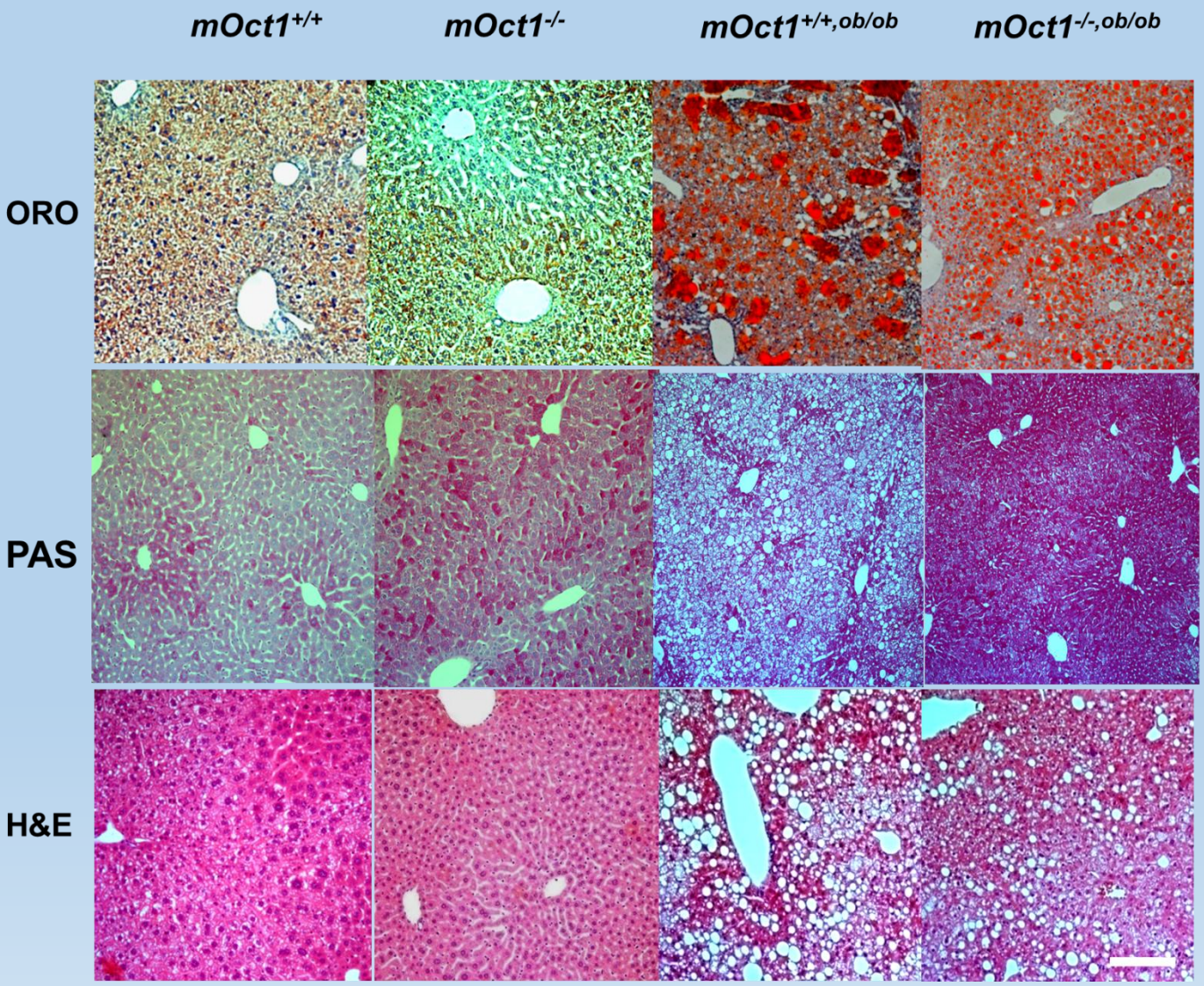


ob/ob

ob/ob

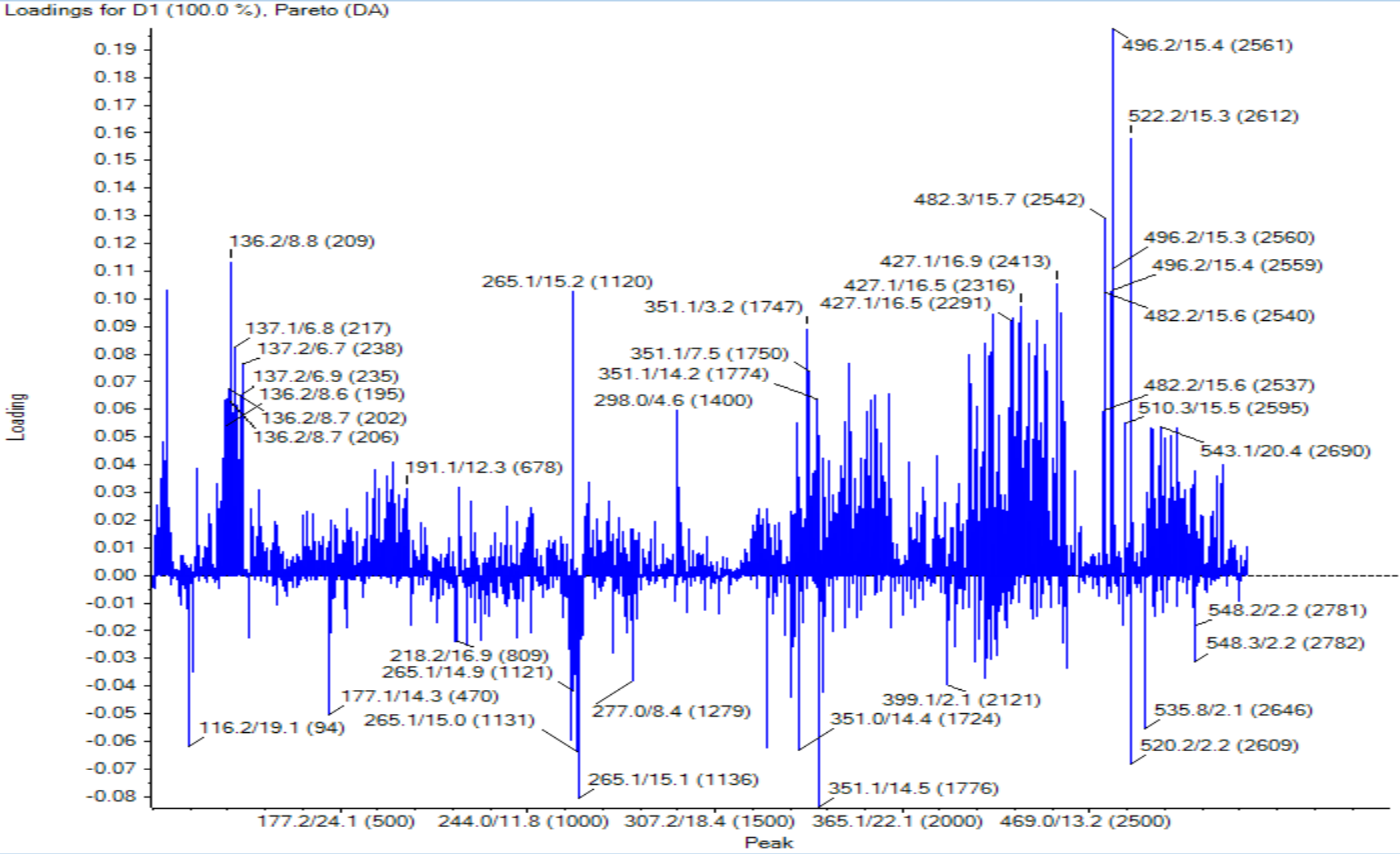


OCT1 knockout mice showed less fat accumulation but higher glycogen in liver than WT

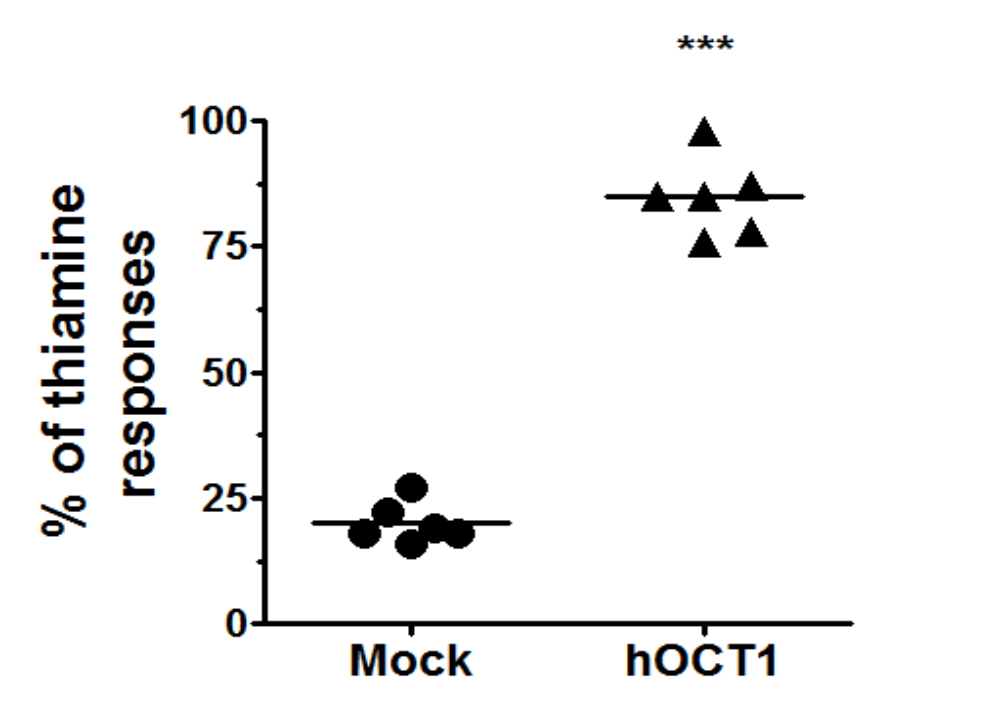


Chen Lab

What's the endogenous substrate of OCT1?

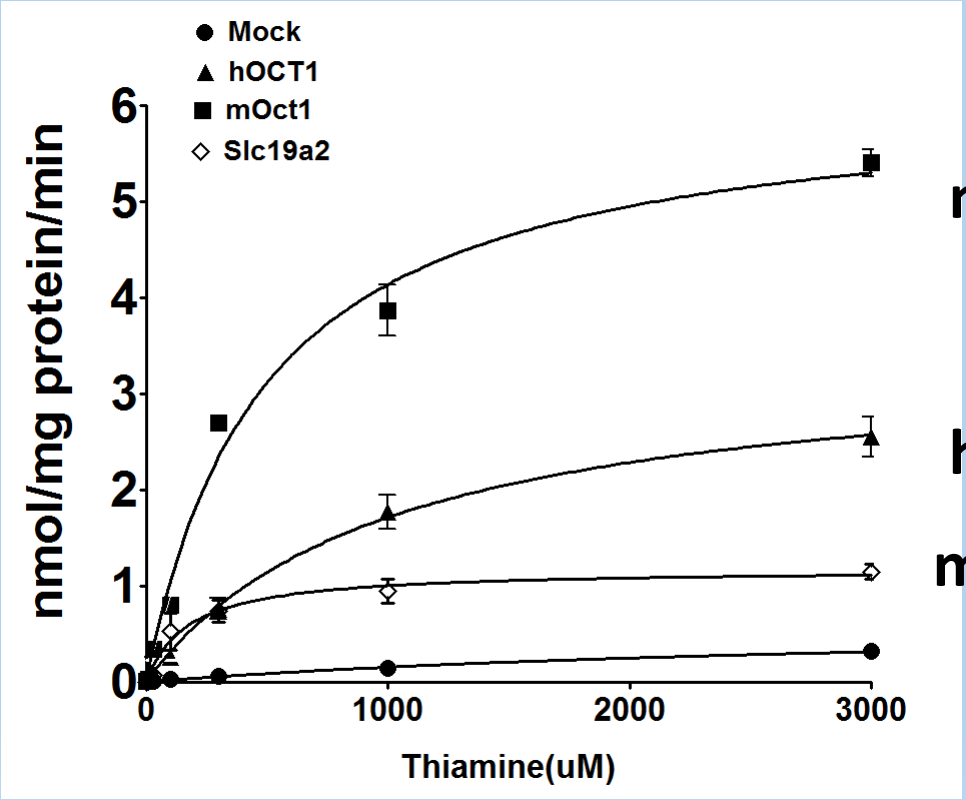


Thiamine (Vitamin B1) is one of the metabolites accumulated highly in HEK293-hOCT1



265.1 / 15.1
m/z / R.T.

OCT1 is high capacity but low affinity thiamine transporter



mOct1

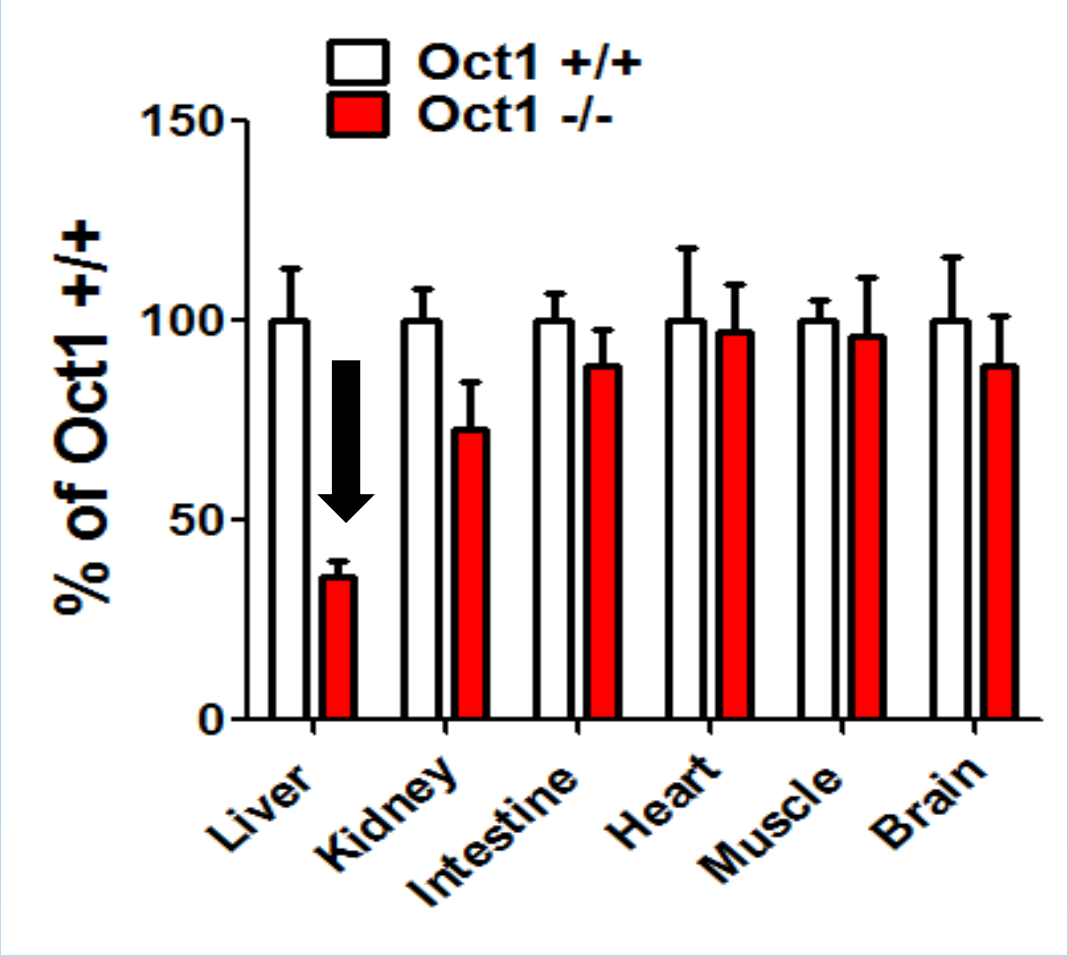
hOCT1

mTHTR1

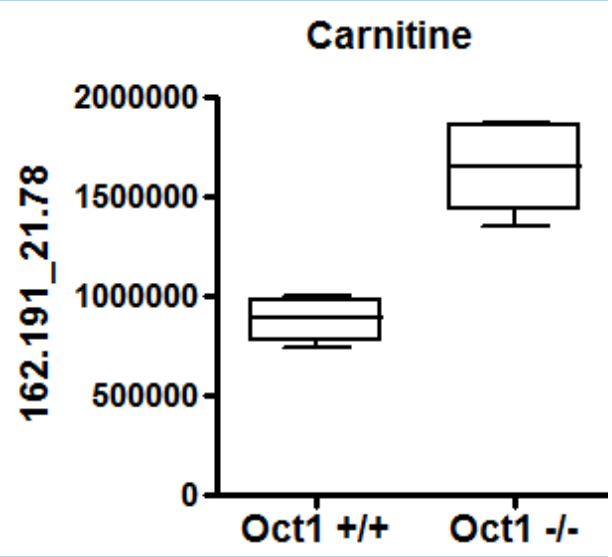
Control

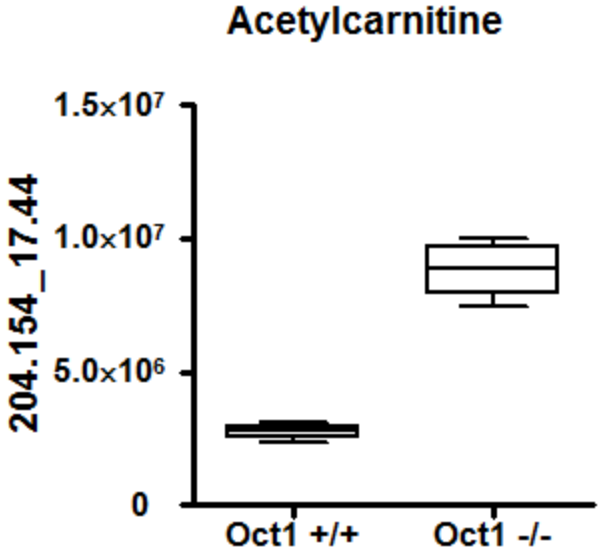
Kinetics

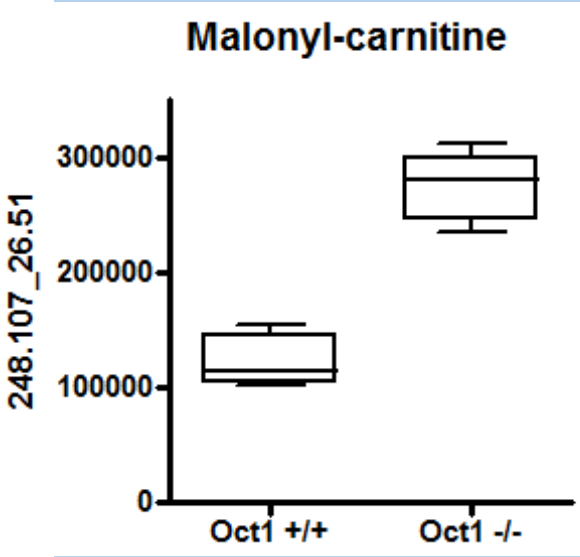
Oct1$^{-/-}$ mice has decreased thiamine distribution in liver



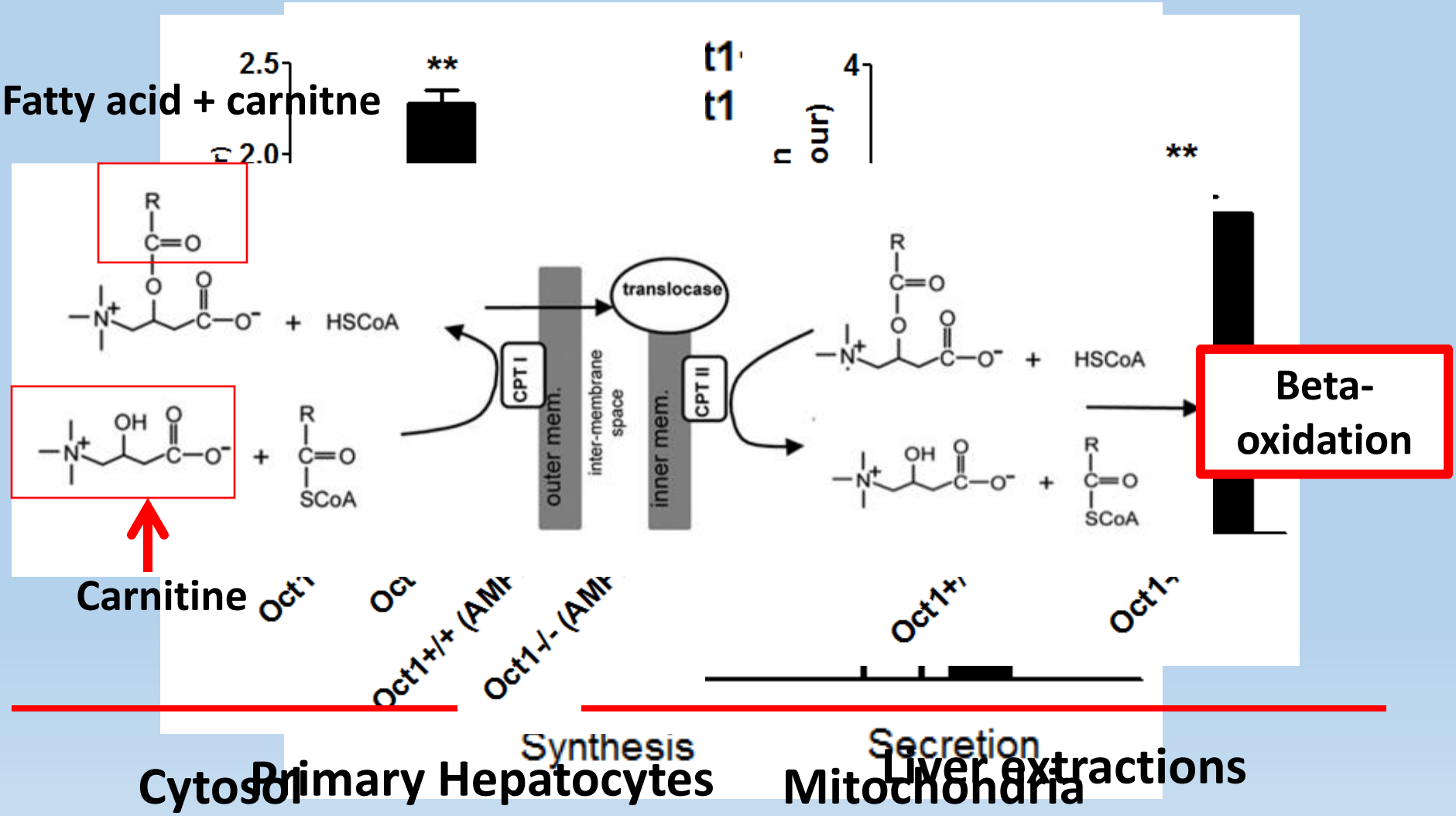
Carnitine and its derivatives are the most **significant metabolites** elevated in KO mice liver







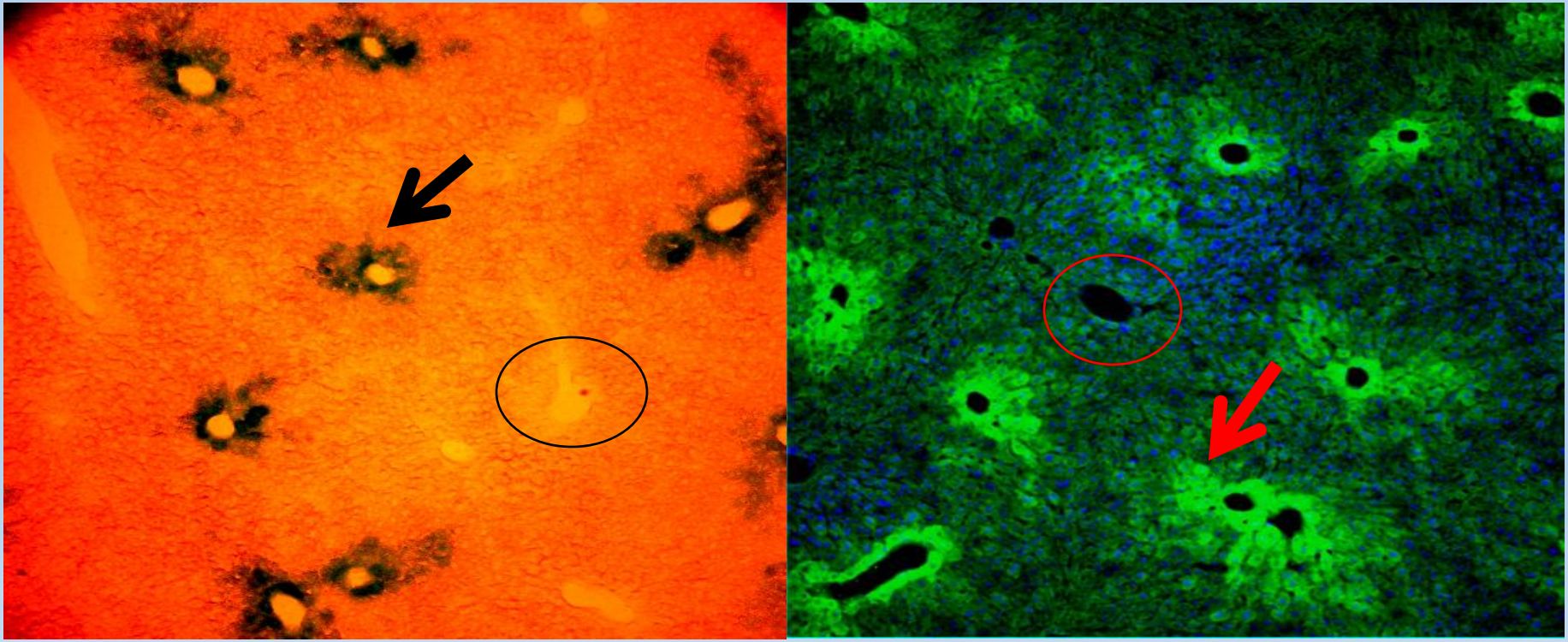
Fatty acid **β-oxidation rate** is higher in Oct1 KO mice but lower fatty acid **synthesis rate**



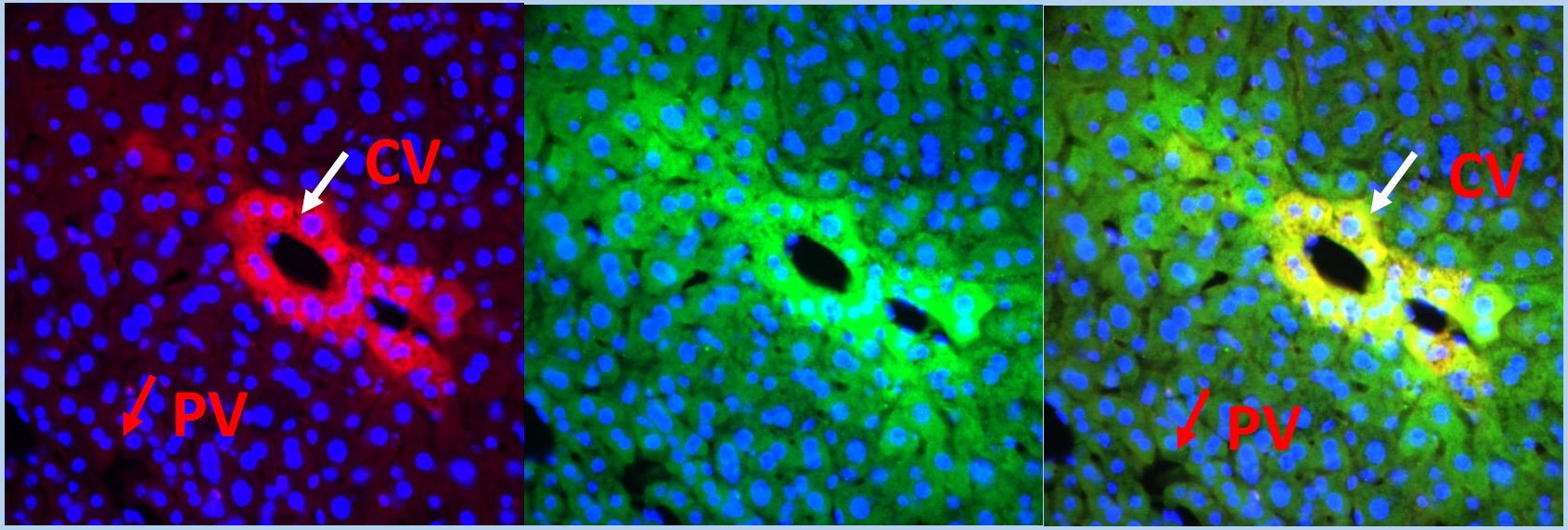
Location, Location……

X-gal staining

Anti-beta Galactosidase



OCT1 only expressed in the hepatocytes around central vein



Glutamine synthetase

β-Galactosidase

Merge

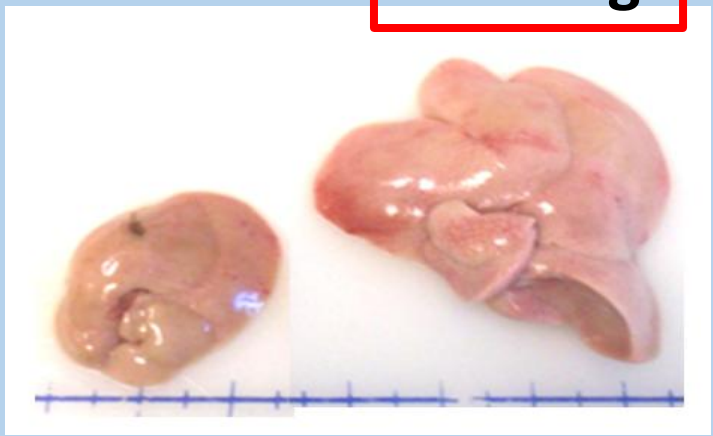
The enlarged liver from human transgenic mice - magnetic resonance imaging (MRI) of liver fat content

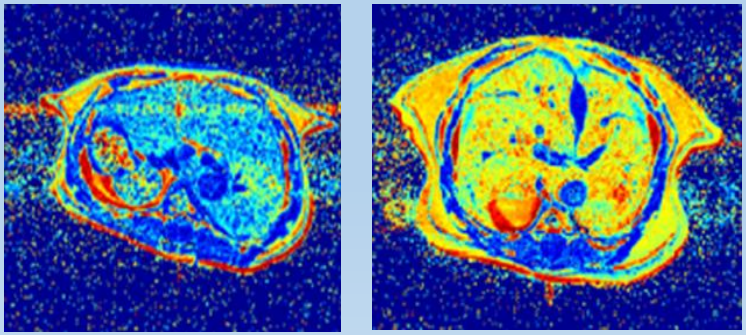
1.96 g

Oct1 +/+

Oct1 +/+, hOCT1tg

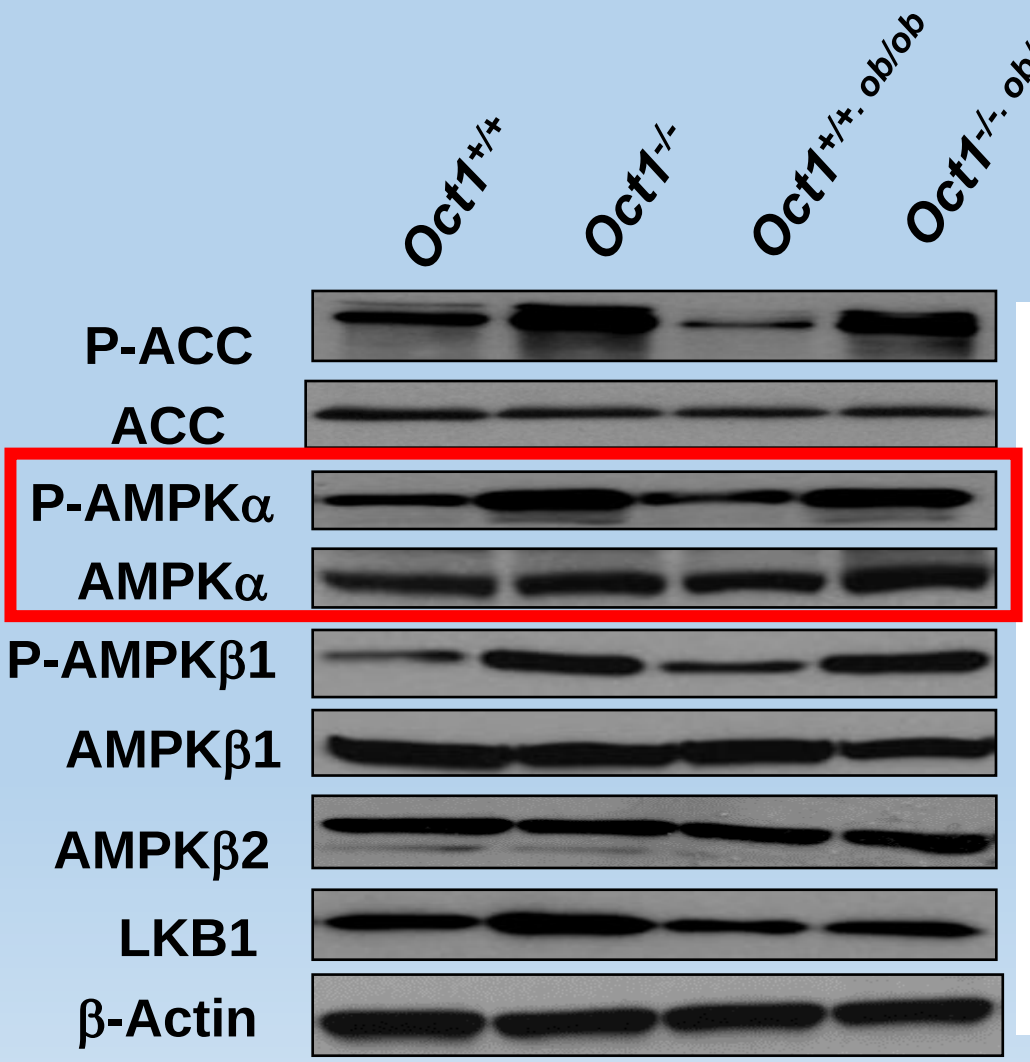
5.13g

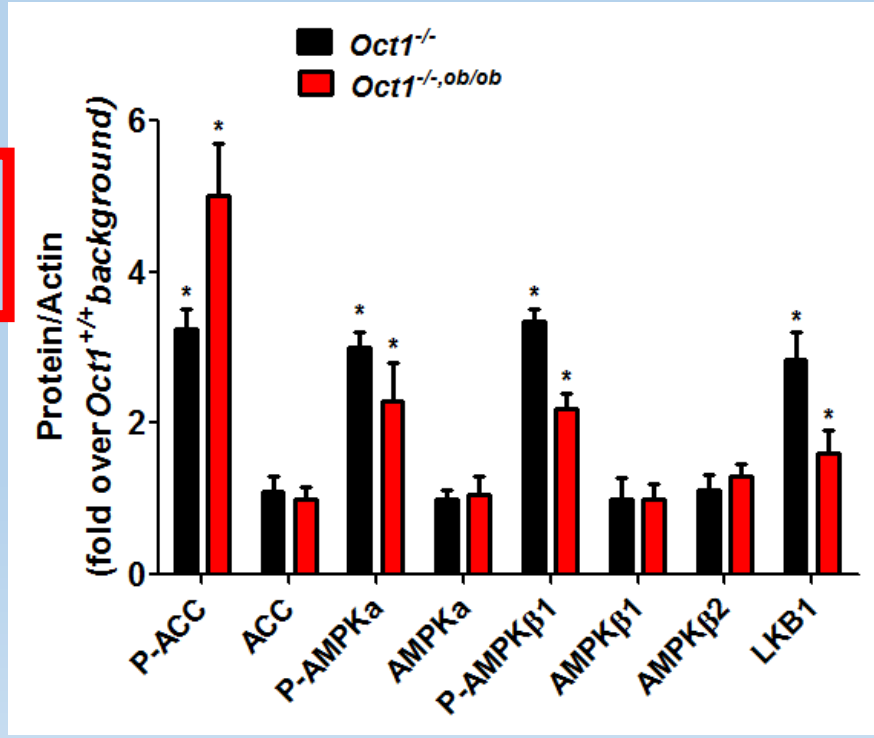




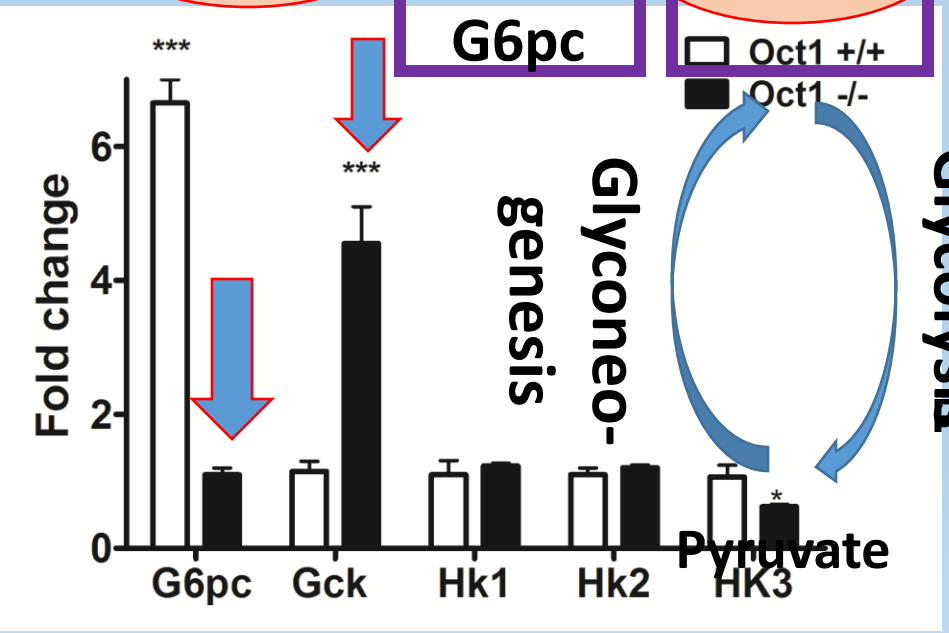
The non-invasive method to monitor the fat amount in living animal.

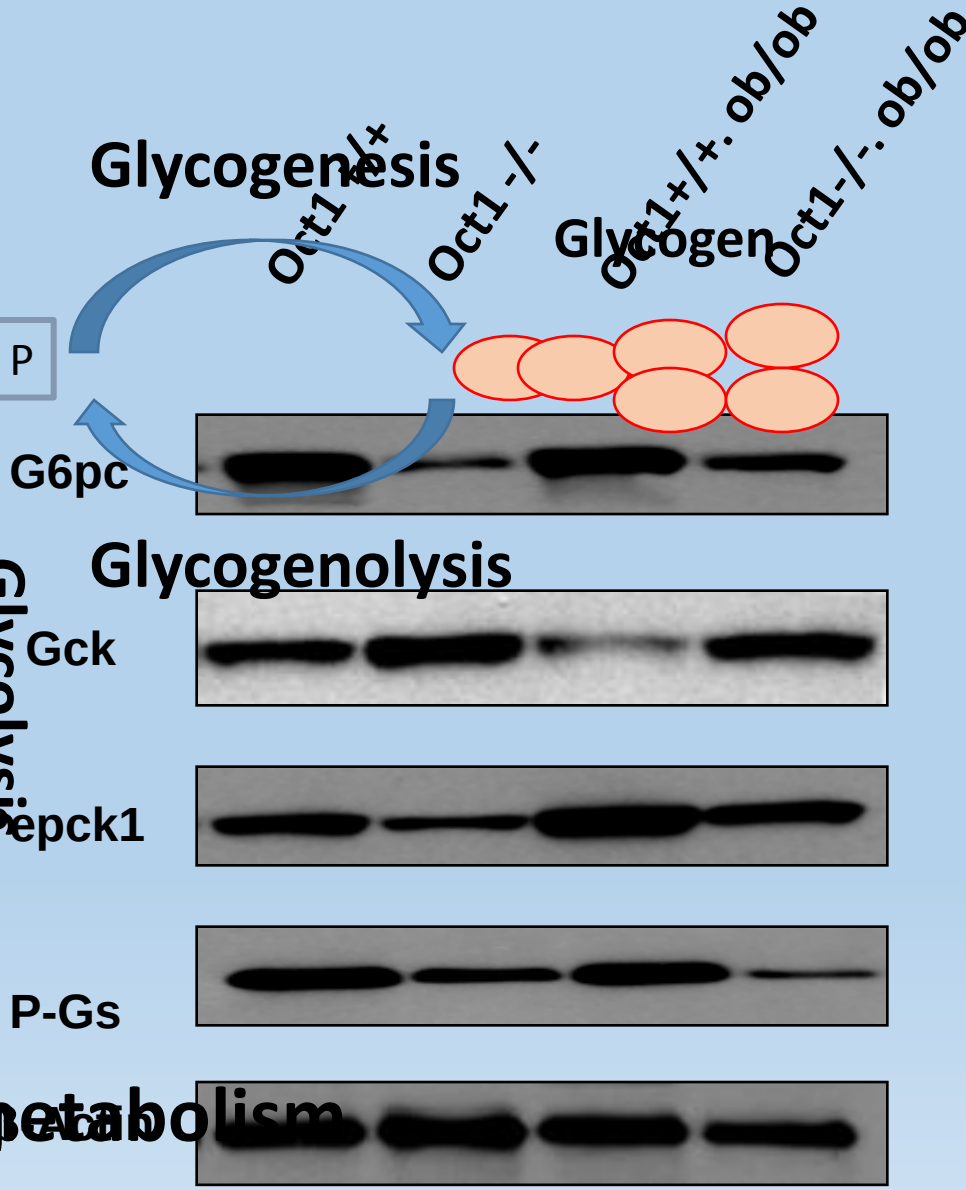
OCT1 activates the P-AMPK to inhibit the fatty acid synthesis





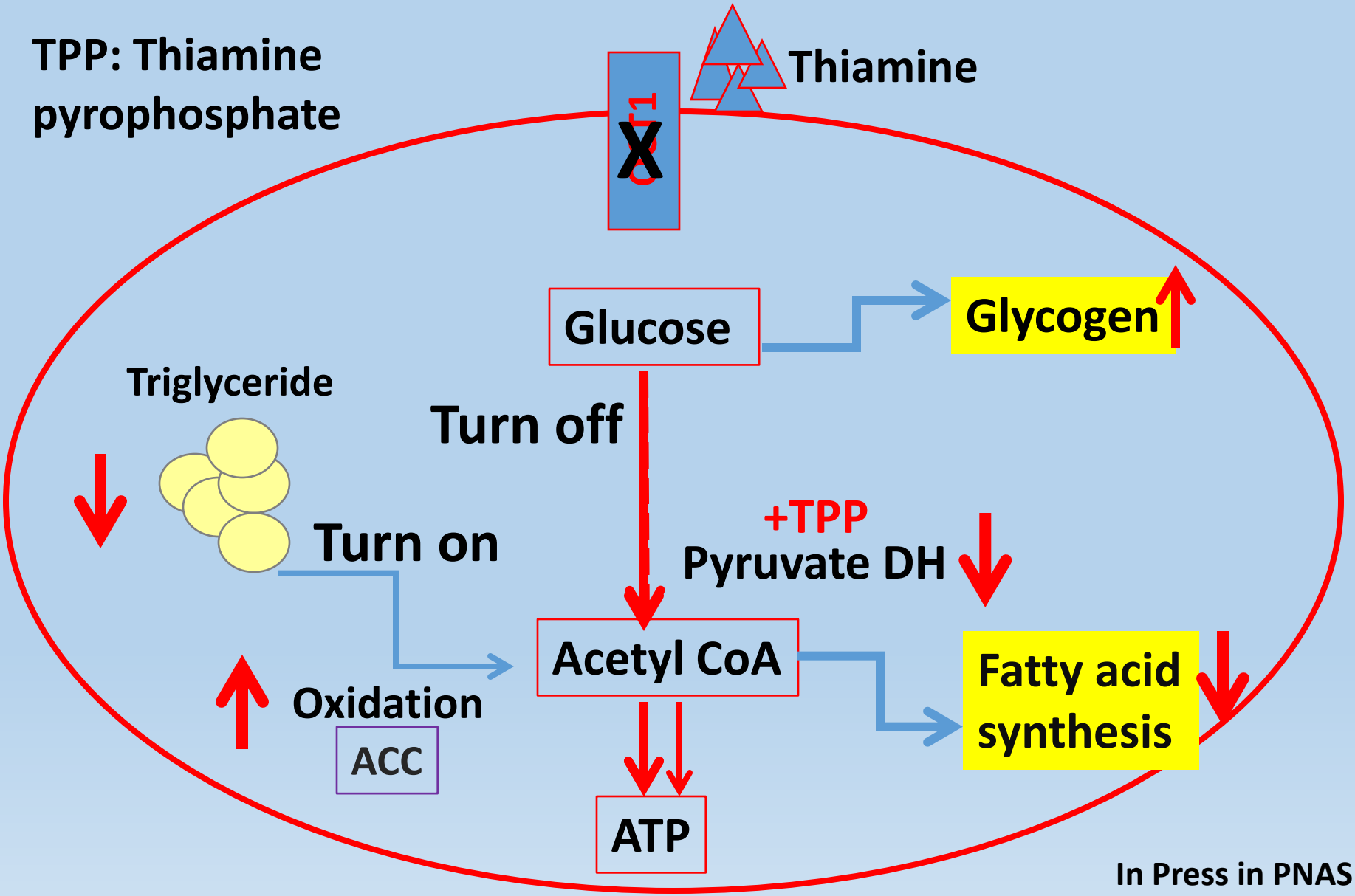
The glycogenesis pathways:





Glucose metabolism

The OCT1--The molecular Switch (分子开关) of energy



In Press in PNAS

In the news……

Science Highlights our Discovery……

METABOLIC DISEASE

A vitamin's dark side in liver disease

Too much of a good thing can be bad for the liver. Chen *et al.* find that mice with high levels of thiamine (vitamin B_1) in their livers develop fatty liver disease, a metabolic disorder that affects one-third of adults in the United States. A protein called organic cation transporter 1 (OCT1) carries dietary thiamine into the liver. When the researchers deleted the *Oct1* gene in mice or fed mice a diet low in thiamine, the mice did not develop the disease. OCT1 also carries the diabetes drug metformin into the liver, which might explain why metformin decreases symptoms of fatty liver disease: By competing with thiamine for OCT1, metformin reduces the amount of dietary thiamine that reaches the liver. — PAK

Proc. Natl. Acad. Sci. U.S.A. 10.1073/pnas.1314939111 (2014).

Science, July 2014

F1000 Prime Wrote the Commentary…..

FM

Meenakshisundaram Ananthanarayanan

F1000 Gastroenterology & Hepatology

Yale University School of Medicine, New Haven, CT, USA.

FOLLOW

INTERESTING HYPOTHESIS | NEW FINDING | NOVEL DRUG TARGET

DOI: 10.3410/f.718467698.793496687

I selected this article because of its demonstration of the relationship of a hepatic cation transporter (organic cation transporter 1 [OCT1]) to steatosis. OCT1 is a transporter known to be involved in the uptake of the anti-diabetic drug metformin. The authors used Oct1-null and Oct1-transgenic mouse models to show that loss of Oct1 and overexpression of Oct1 result in resistance and susceptibility to hepatic steatosis, respectively. The mechanism of this is mediated by the endogenous substrate for Oct1, which is thiamine. Low levels of thiamine due to Oct1 loss (in Oct1-null mice) or inhibition by metformin results in increased activation of AMPK phosphorylation. This leads to increased acetyl CoA carboxylase phosphorylation, leading to decreased fatty acid synthesis and fewer triglycerides in the liver. Opposite results are obtained in Oct1 transgenic mice overexpressing the transporter. In my opinion, this is the first article describing a relationship between a hepatic membrane transporter and the energy sensor AMPK and lipid synthesis.

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- Xinbin Zhao

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Dr. Daniel Nomura in UC Berkeley
Dr. Yueming Li in MSKCC
Dr. Hao Fan in ASTAR
Dr. Avner Schlesinger in Mount Sinai
Wonderful Colleagues in THU

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