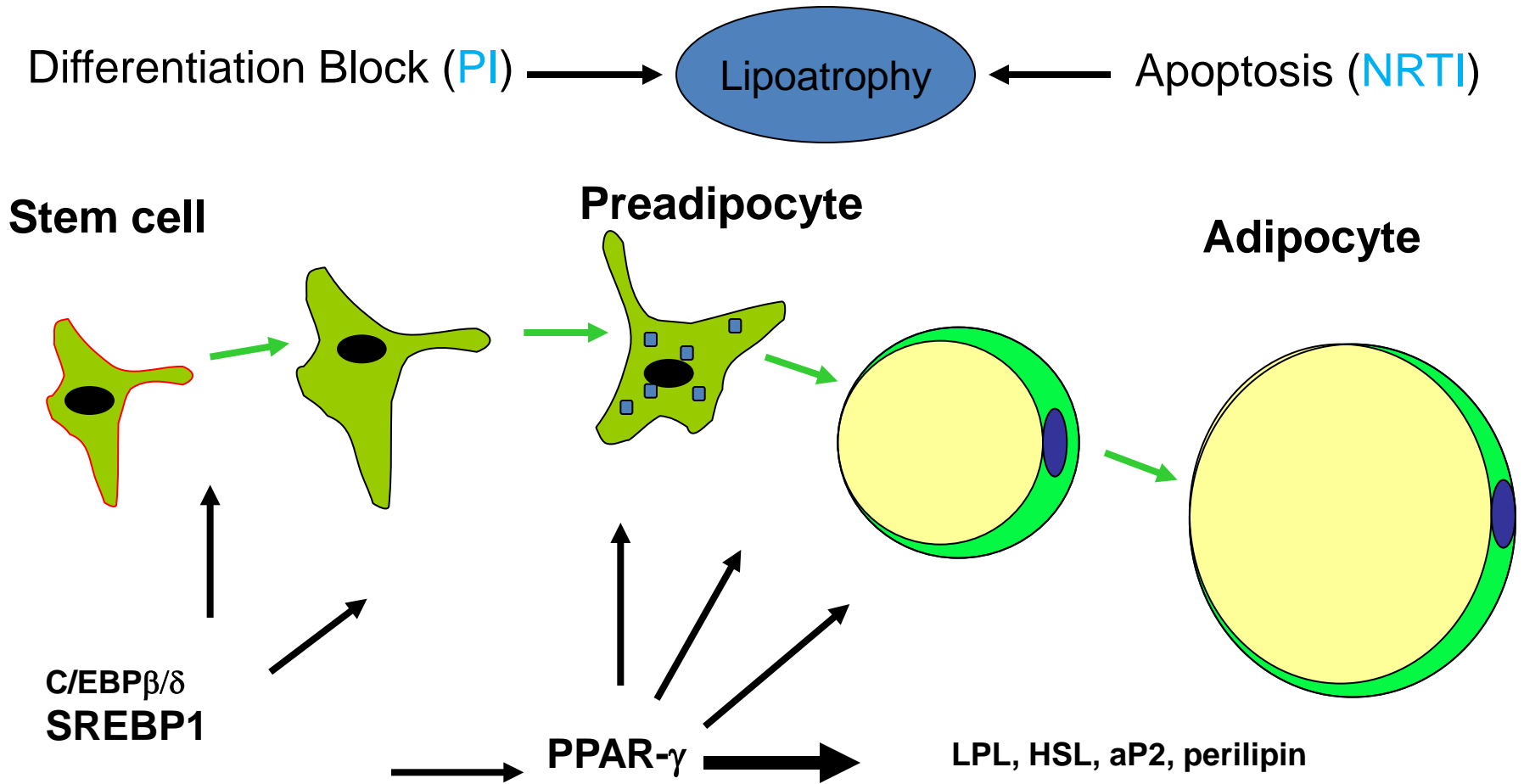


# **HIV VPR alters fat metabolism**

Dorothy E Lewis PhD/Ashok Balasubramanyam MD

# Old Dogma for HIV associated lipodystrophy



**BUT**, happens **without** ART and in Elite suppressors—**COULD HIV CAUSE????**

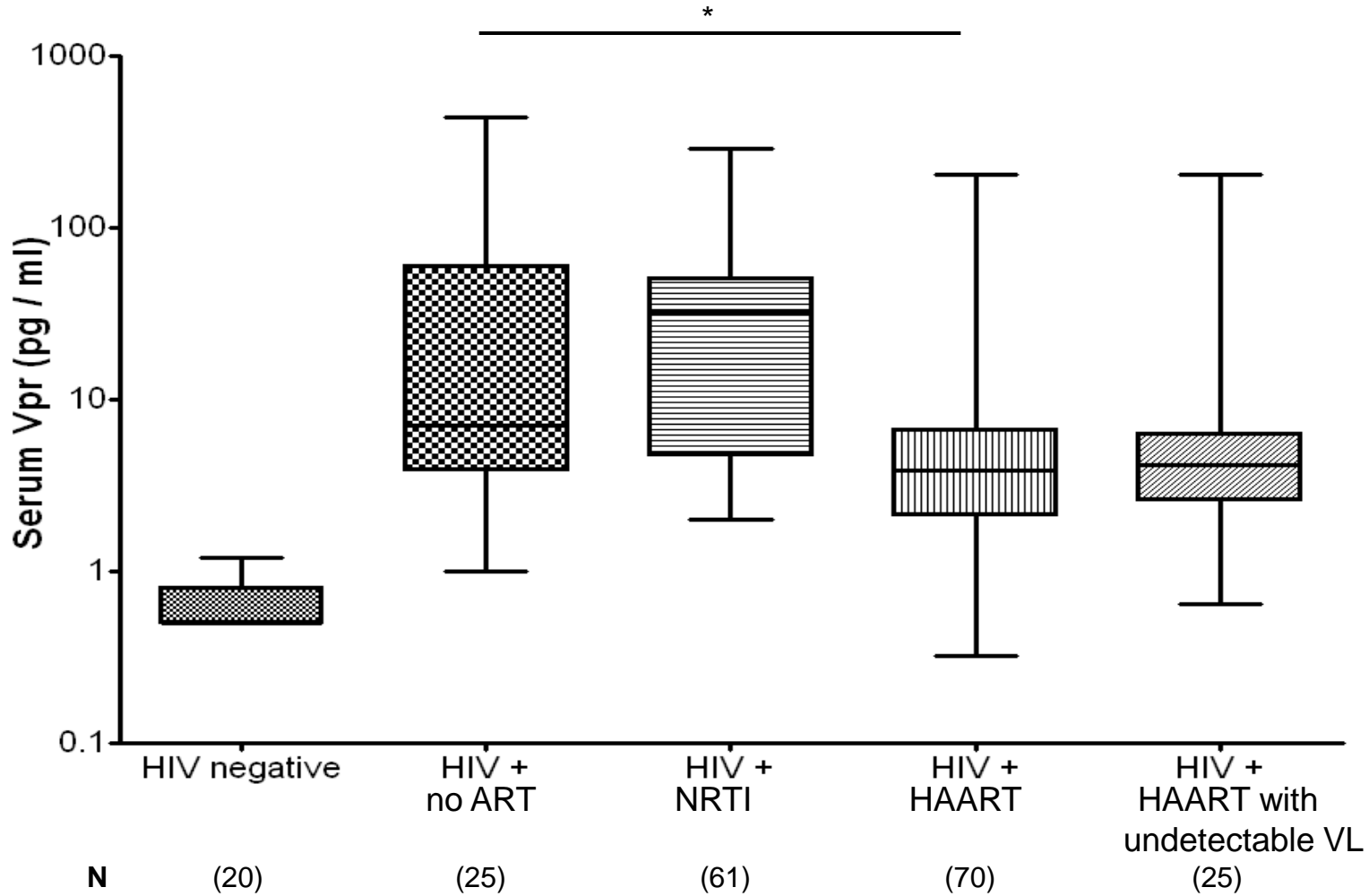
# Metabolic features of HIV (2018)

- Less lipoatrophy
- Less severe dyslipidemia
- More generalized obesity
- Dysglycemia, CVD, osteoporosis, NAFLD

# Could there be a direct viral cause?

- VPR in virally suppressed people
- VPR is systemic and circulates
- VPR acts without whole virus

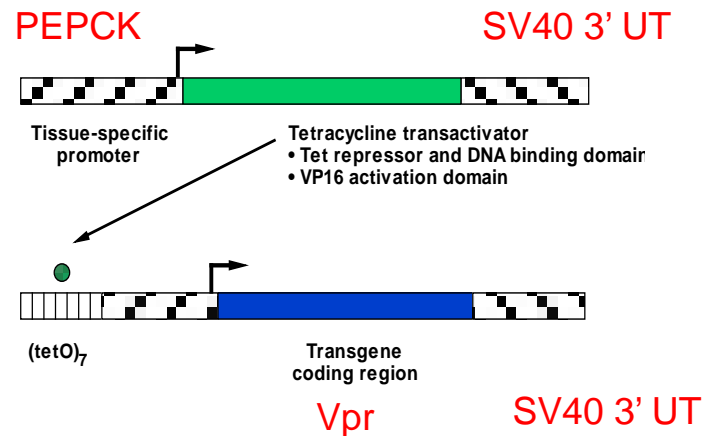
# Vpr in virally suppressed patients (Immunoaffinity Capillary Electrophoresis)



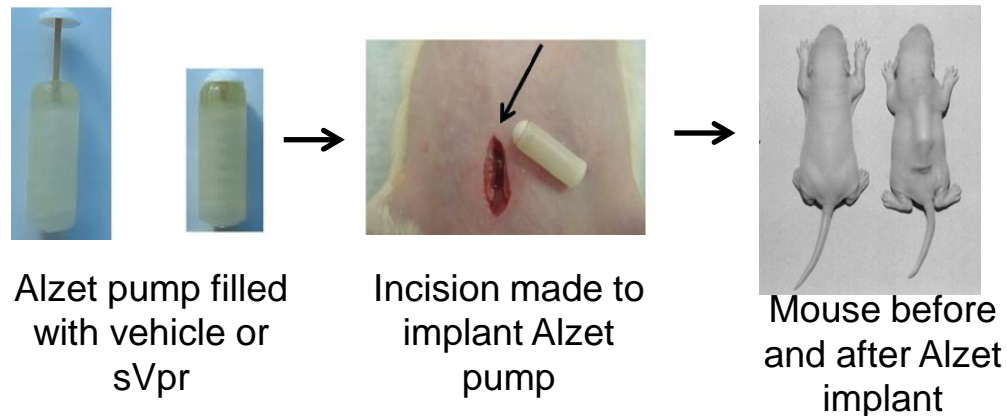
# Mouse Models to study Vpr effects

## A. Vpr-Transgenic Model

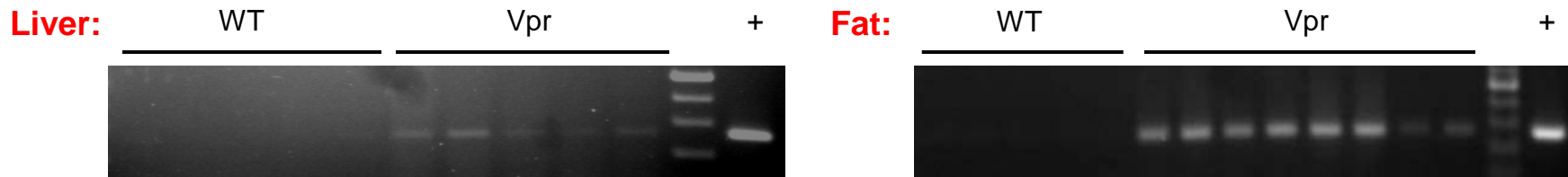
Inducible expression of Vpr in liver and fat



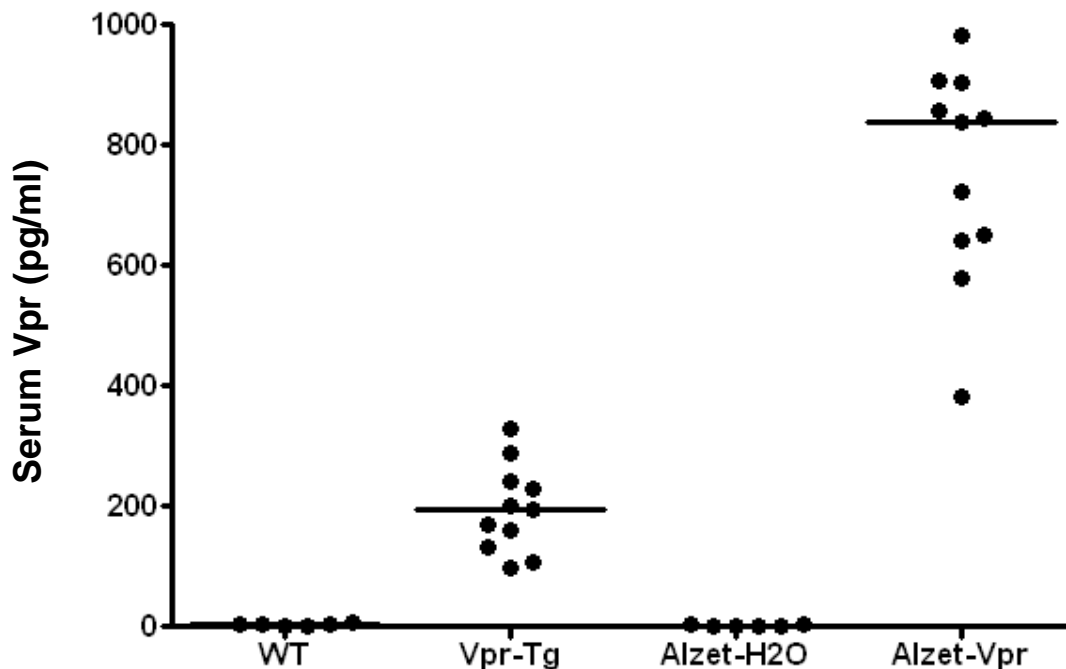
## B. Circulating Vpr Model (sVpr treatment)



# Vpr mRNA Expression in Liver and Adipose Tissues of Vpr-Tg Mice

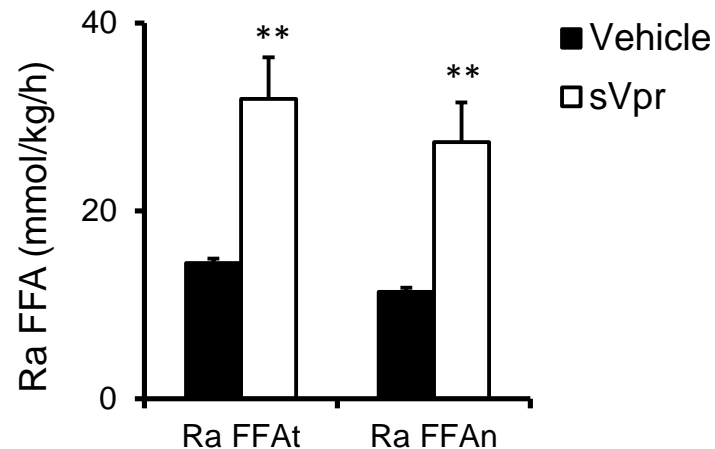
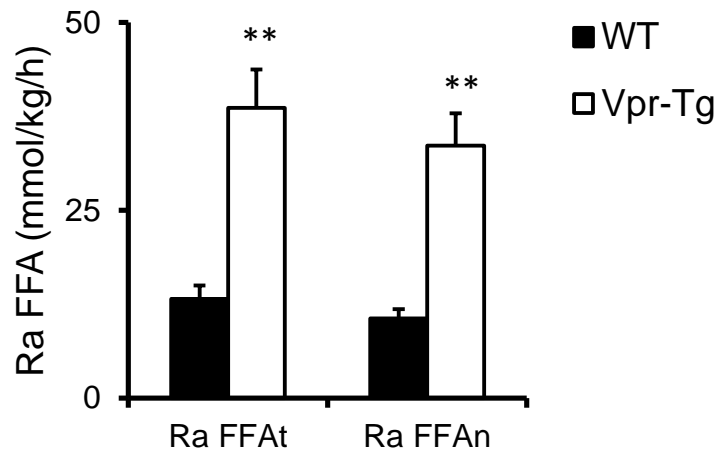


## Vpr Expressed in Liver and Adipose Tissues Also Circulates in the Blood of Vpr-Tg Mice

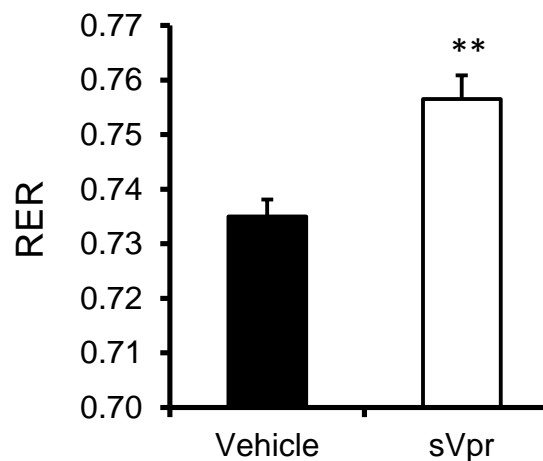
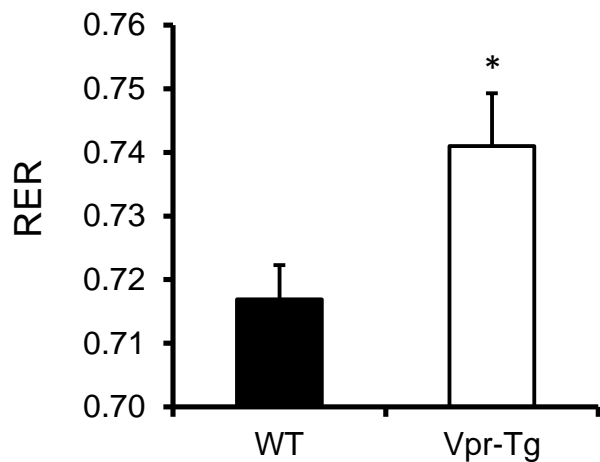


# Vpr Increases Lipolysis and Blunts Fat Oxidation

## Increased lipolysis



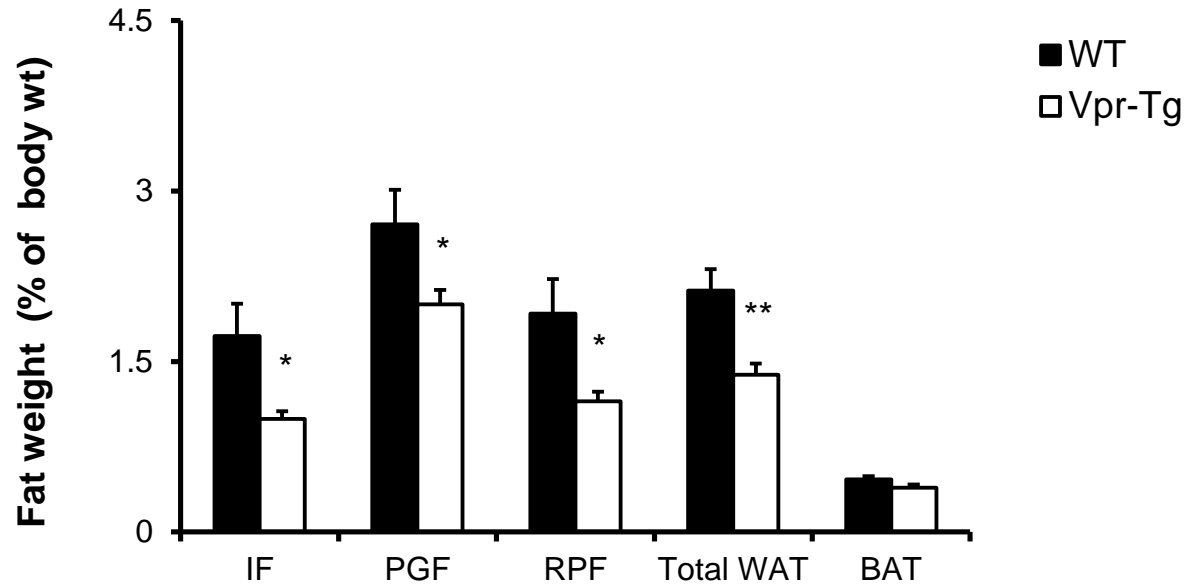
## Blunted fat oxidation during fast



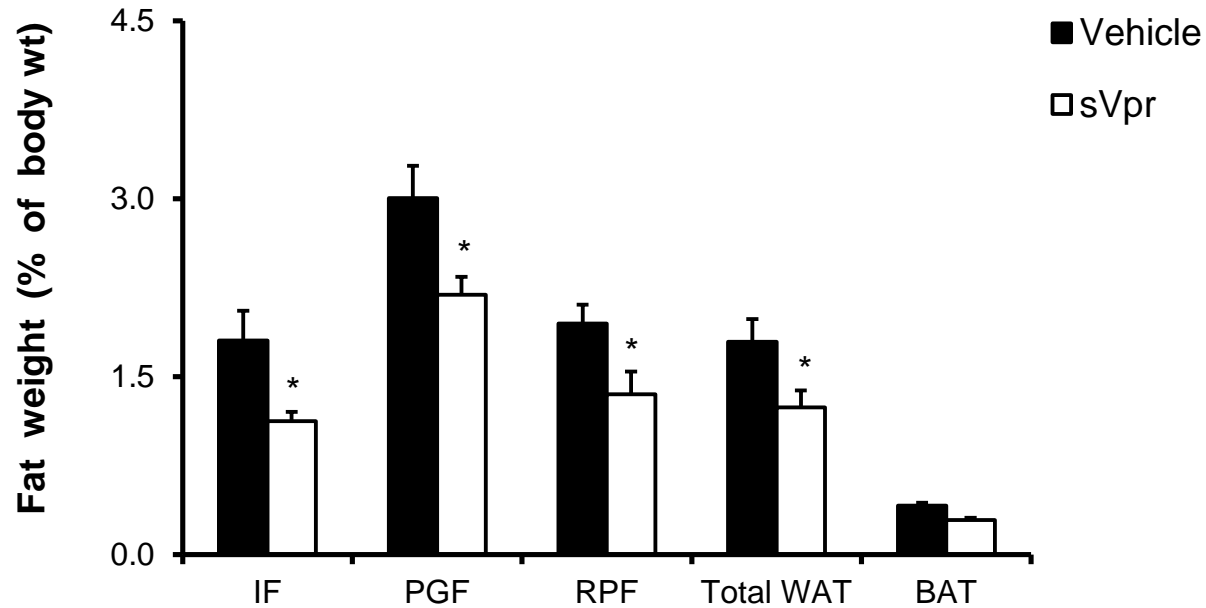


# Vpr Decreases Fat Mass

Vpr-Tg

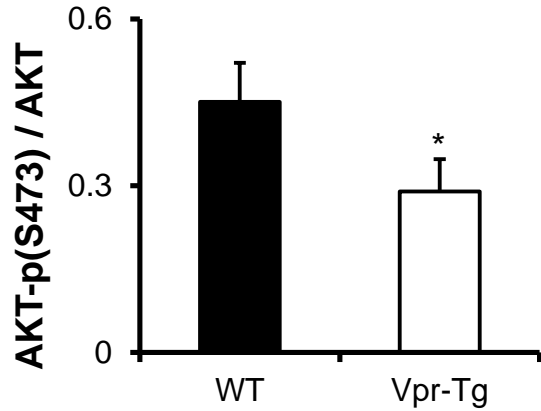
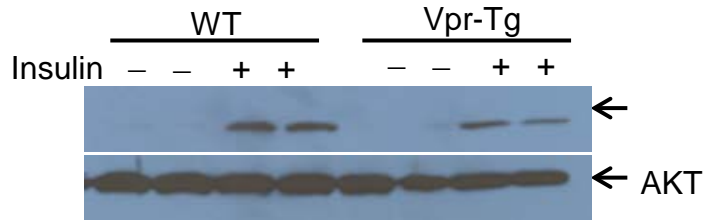


sVpr-treated

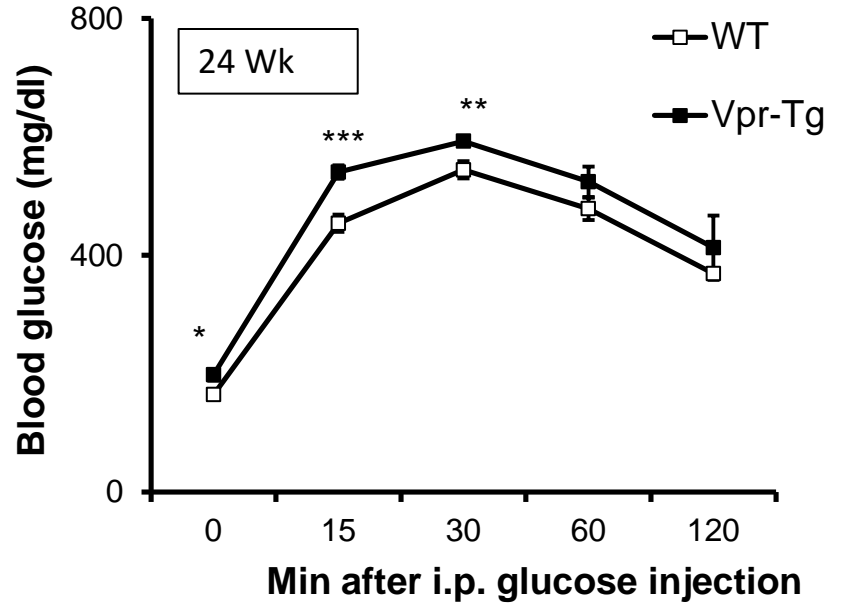


# Vpr Causes Modest Insulin Resistance

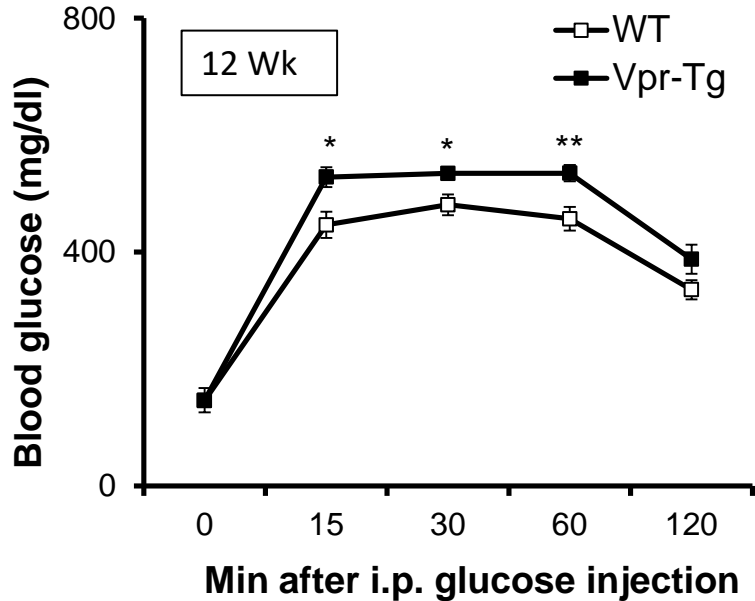
**A.**



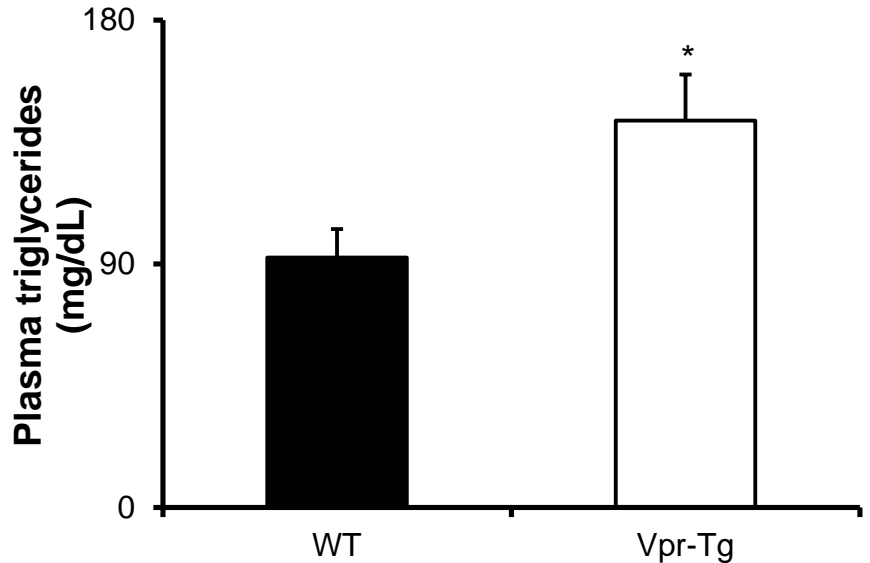
**C.**



**B.**



**D.**

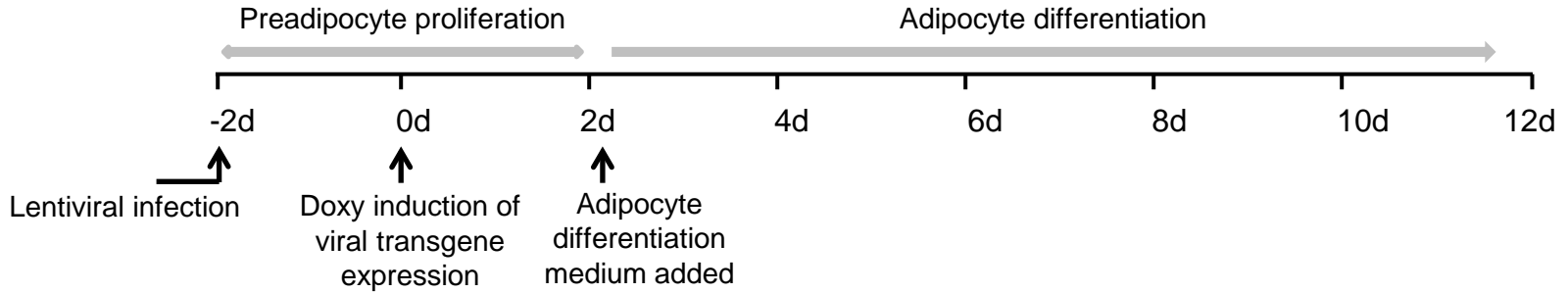


# VPR Mechanisms

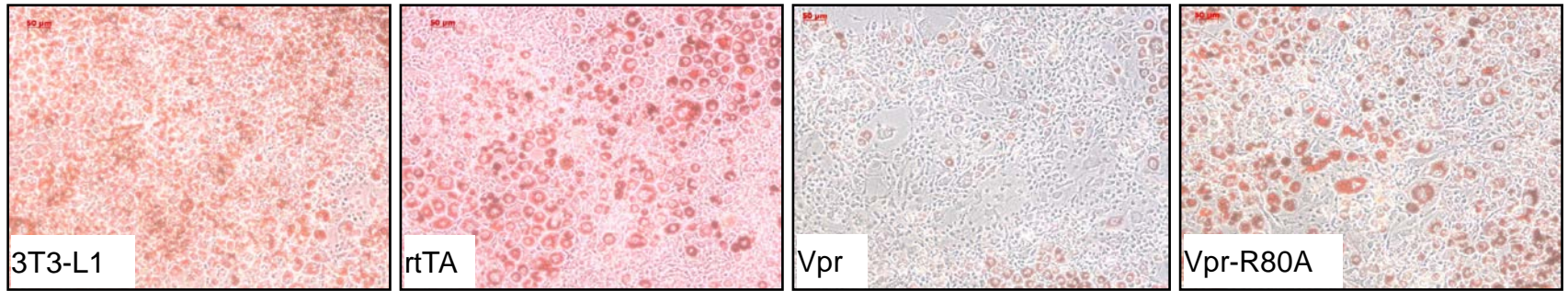
- VPR acts on adipocyte differentiation
- VPR acts on adipocyte function
- Lentiviral VPR in cultured adipocytes

# Vpr Blocks Differentiation of Preadipocytes

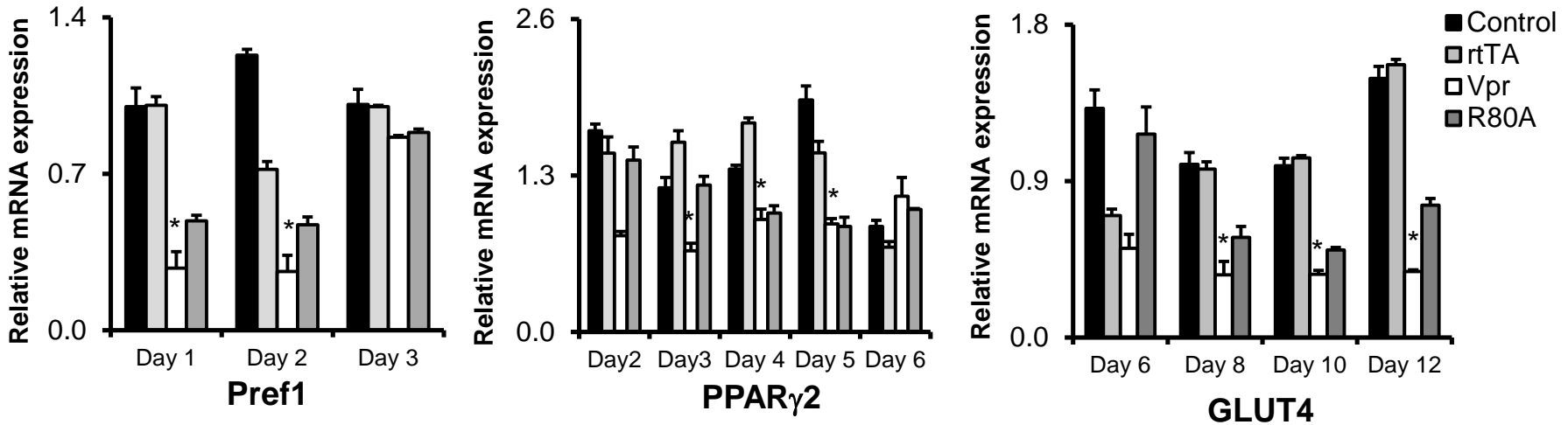
## Early expression of Vpr



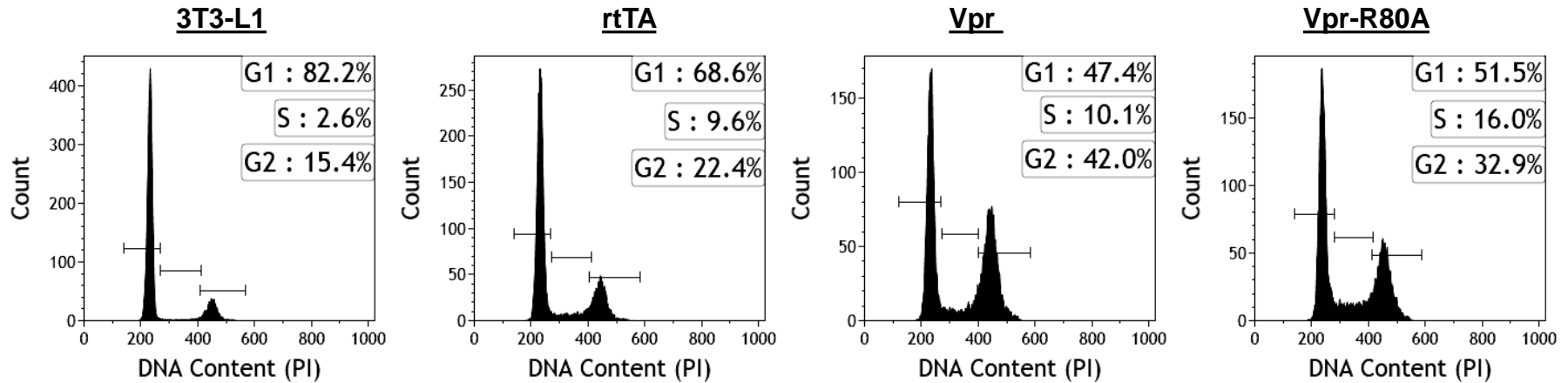
**A.**



**B.**

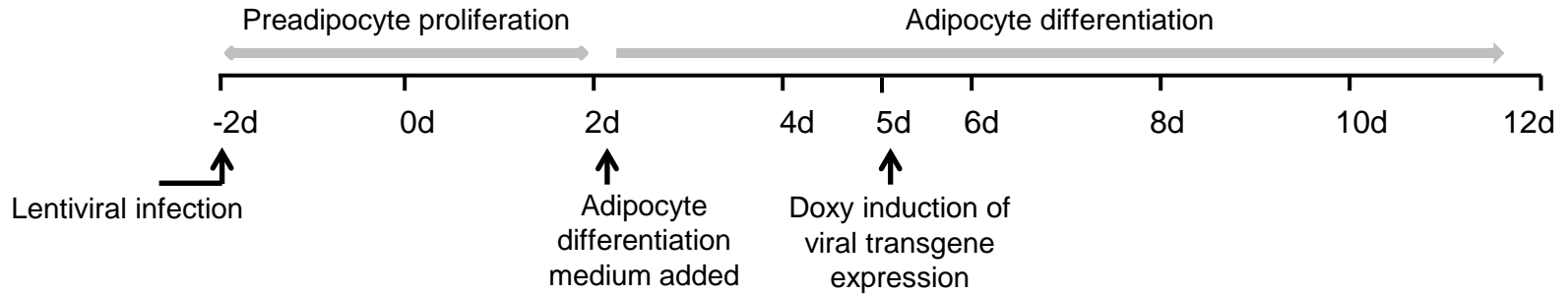


# Vpr Inhibits Preadipocyte Differentiation By blocking Cell Cycle

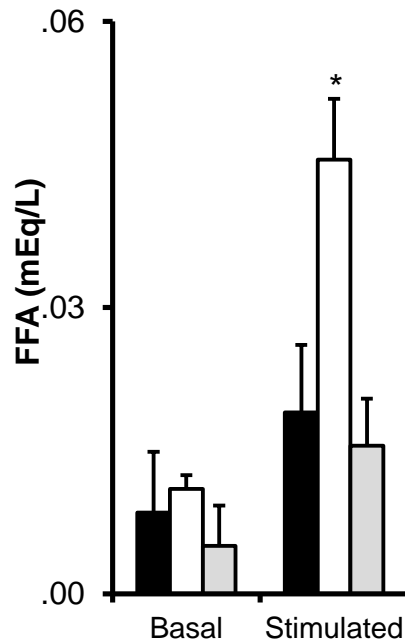


# Vpr Increases Lipolysis in Mature Adipocytes

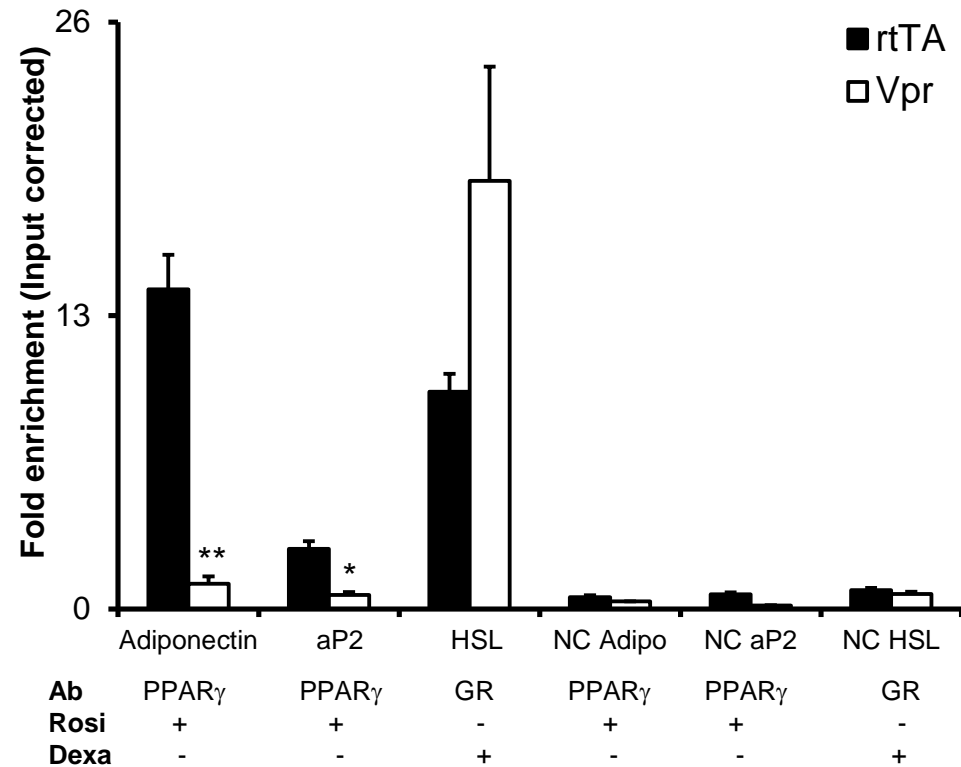
## Late expression of Vpr



**A.**



**B.**



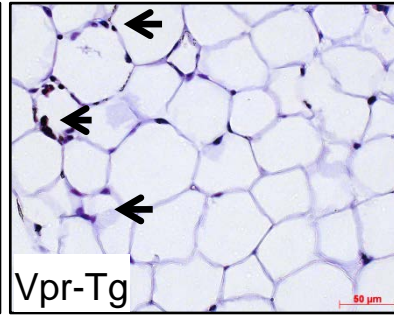
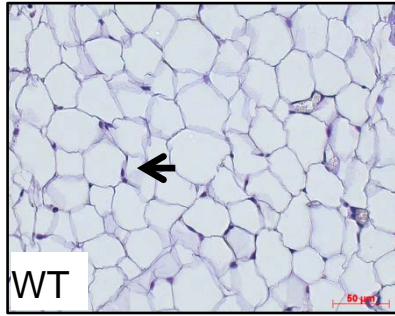
Ab	PPAR $\gamma$	PPAR $\gamma$	GR	PPAR $\gamma$	PPAR $\gamma$	GR
Rosi	+	+	-	+	+	-
Dexa	-	-	+	-	-	+

# VPR mechanisms

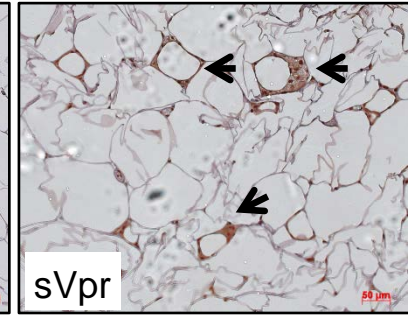
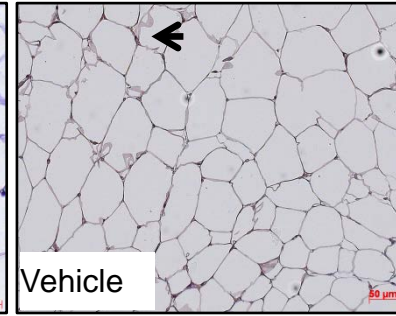
- VPR inhibits adipocyte differentiation
- VPR increases lipolysis in adipocytes
- What are other consequences????

# Macrophage Infiltration in Fat of Vpr Mice

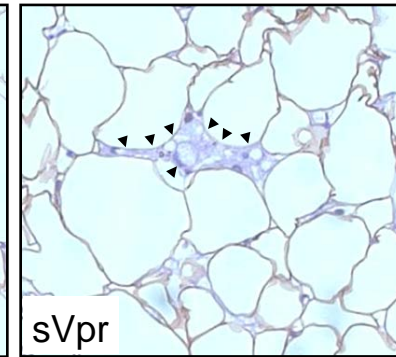
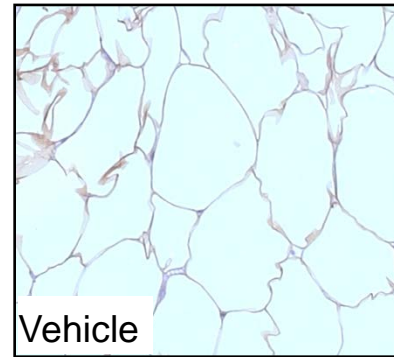
**A.**



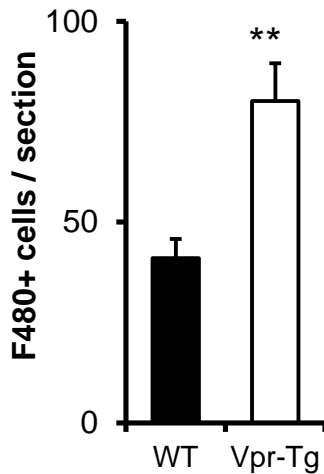
**B.**



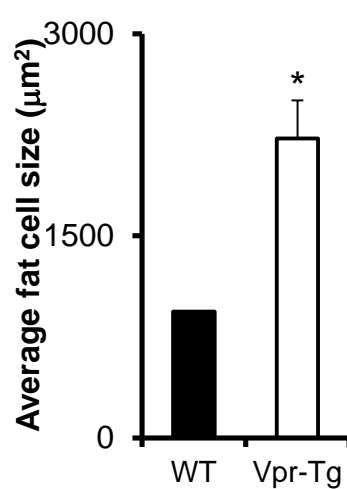
**C.**



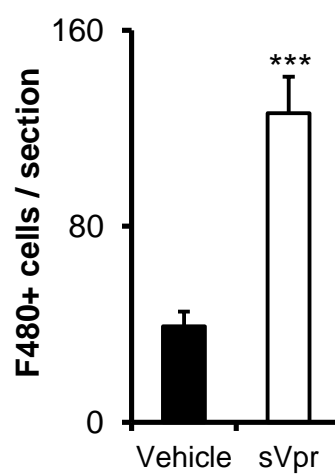
**D.**



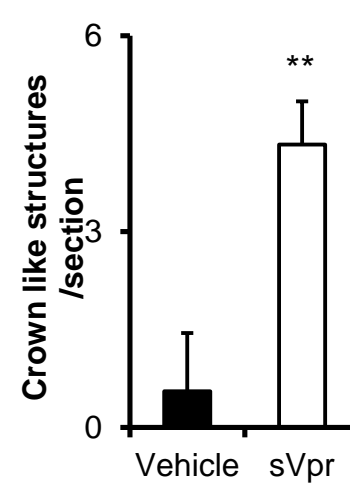
**E.**



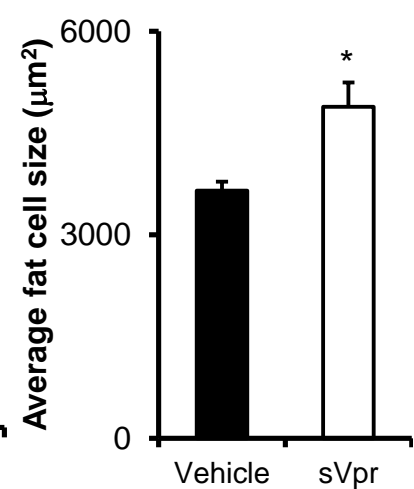
**F.**



**G.**



**H.**





# HIV infection in fat

- HIV/SIV infected immune cells in adipose\*
- HIV is infectious but not much transcription
- HIV VPR could have direct effect in vivo

\*

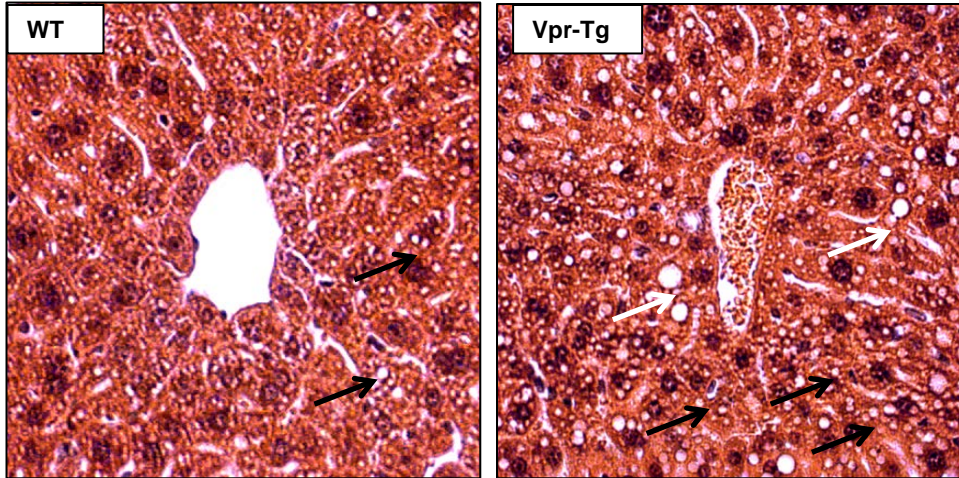
Couturier et al AIDS 2015, Couturier et al Retrovirology 2016

# Other consequences of VPR?

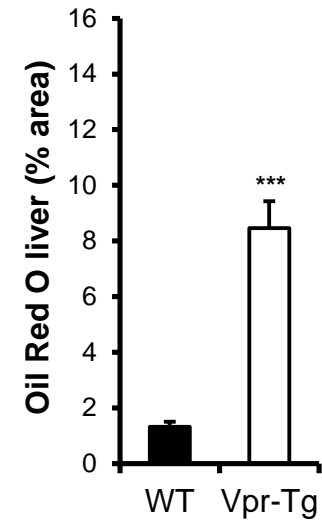
- VPR expressed from transgene in adipose and liver from PEPCK promoter
- Is there an effect on liver fat metabolism??

# HIV VPR causes NASH

A

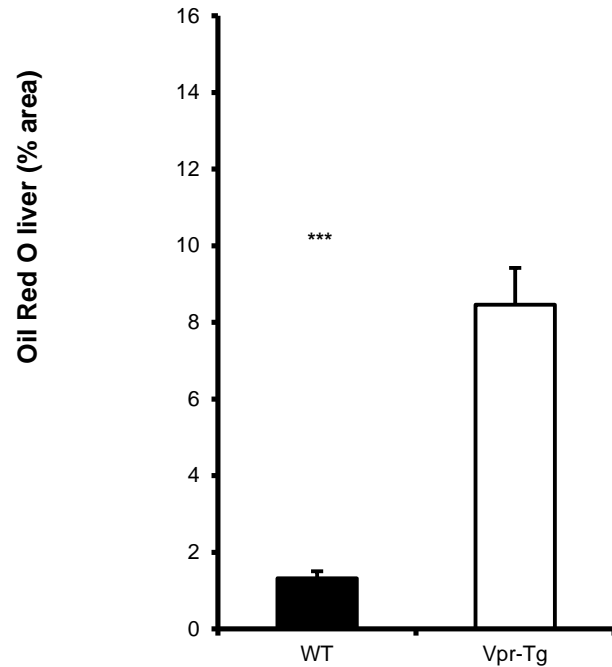


B

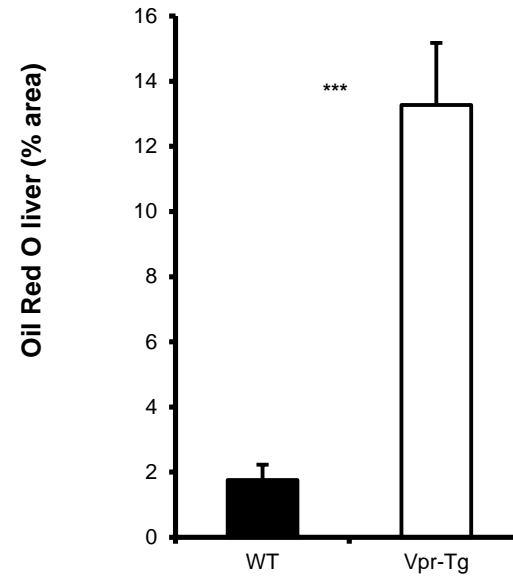


# VPR increases lipid storage

14 weeks



28 weeks



# VPR increases liver weight and TGs

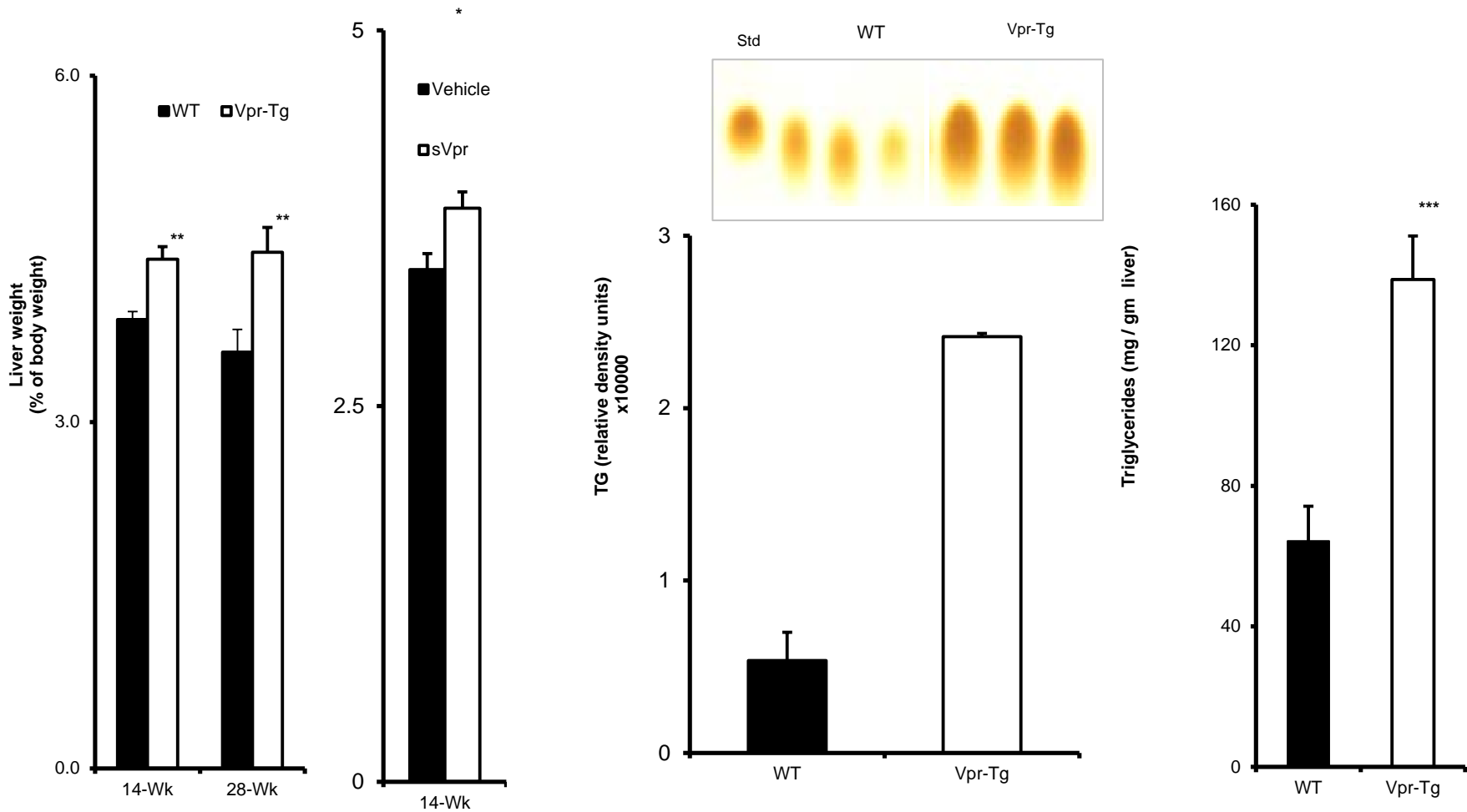
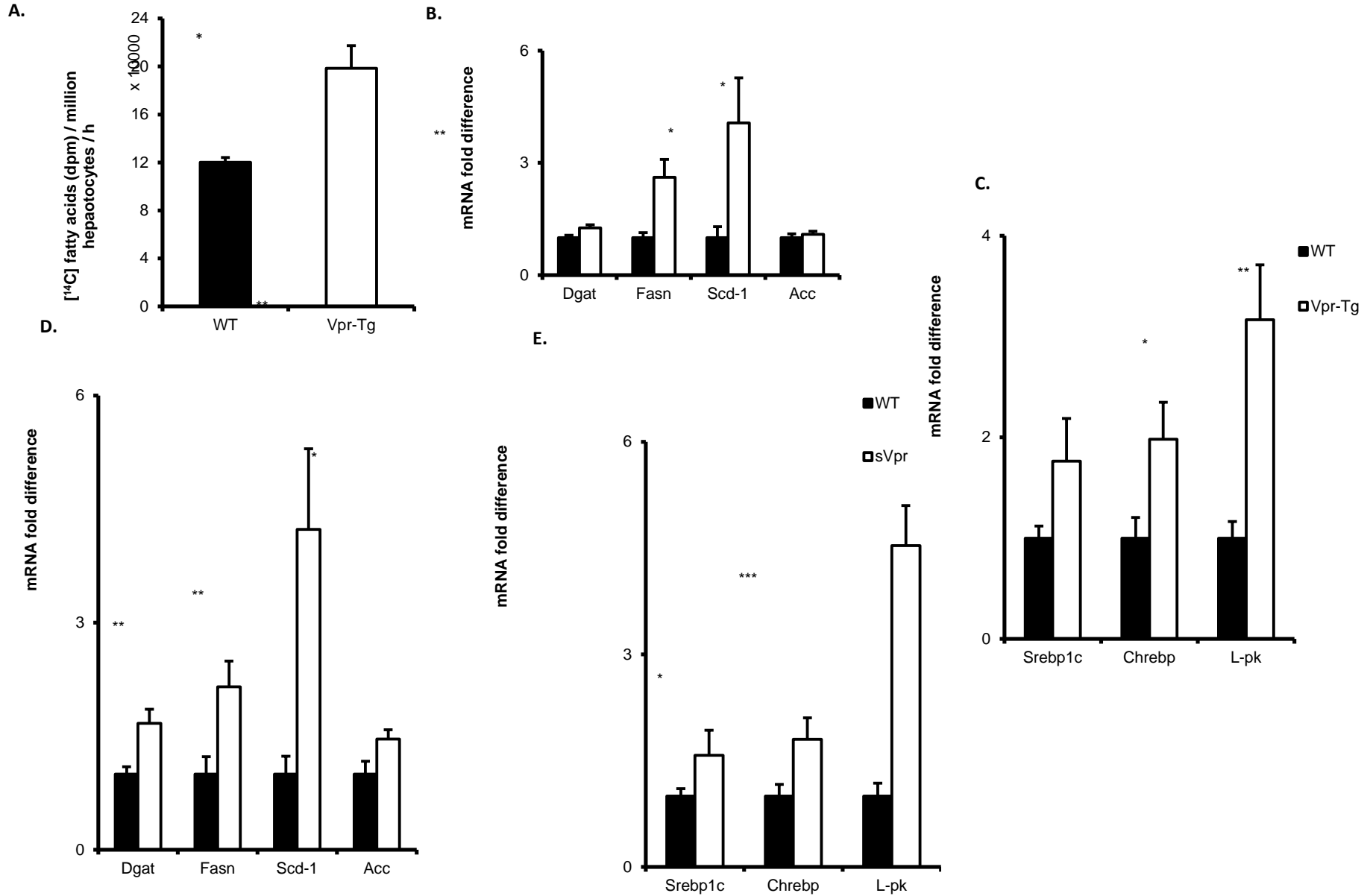


Figure 1

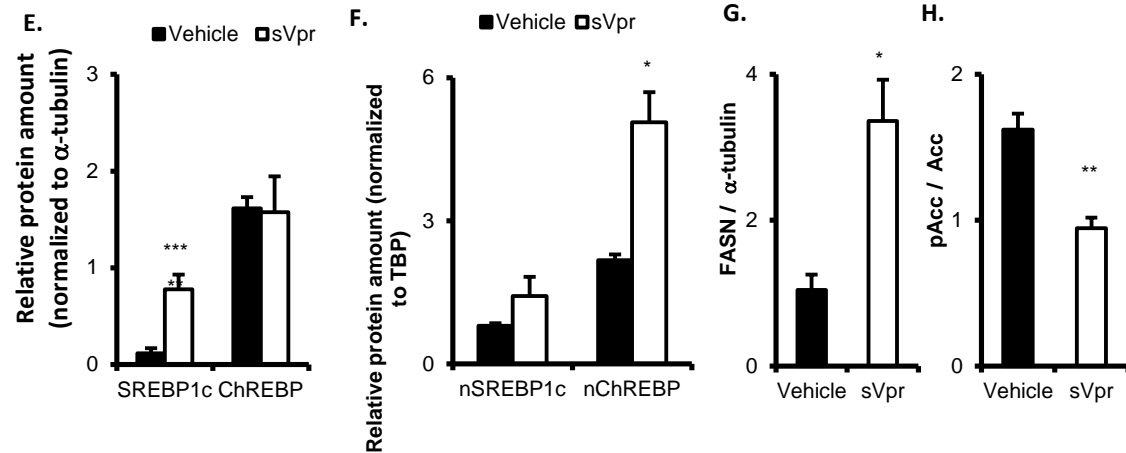
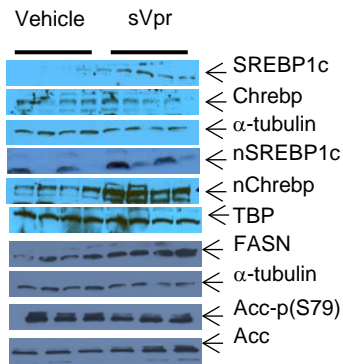
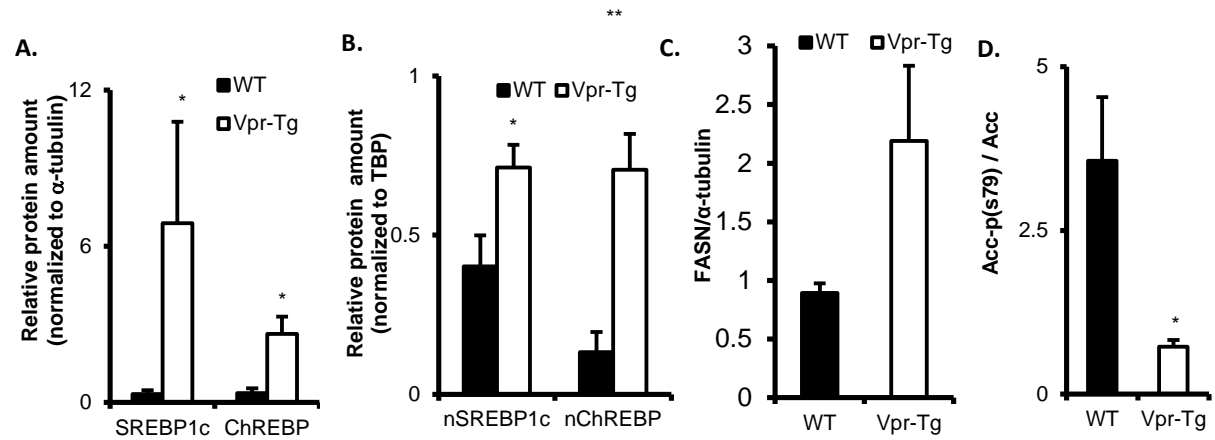
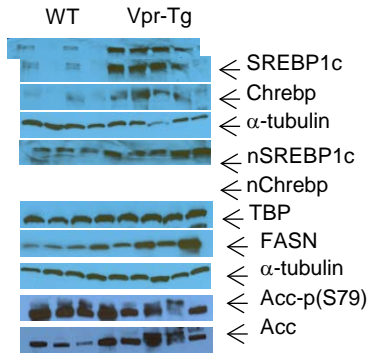
# Liver function enzymes in VPR mice

	WT $\pm$ SE (n=10)	Vpr $\pm$ SE (n=14)	P
TG (mg/dL)	87.56 $\pm$ 6.04	120.05 $\pm$ 13.21	0.03
ALT (IU/L)	47.70 $\pm$ 6.87	67.85 $\pm$ 9.99	0.12
AST (IU/L)	96.40 $\pm$ 13.6	136.56 $\pm$ 11.2	0.03
Alk Phos (IU/L)	26.58 $\pm$ 2.67	40.38 $\pm$ 5.05	0.03
Total Bilirubin (mg/dl)	1.09 $\pm$ 0.13	2.11 $\pm$ 0.29	0.01

# Vpr Increases Hepatic Lipogenesis

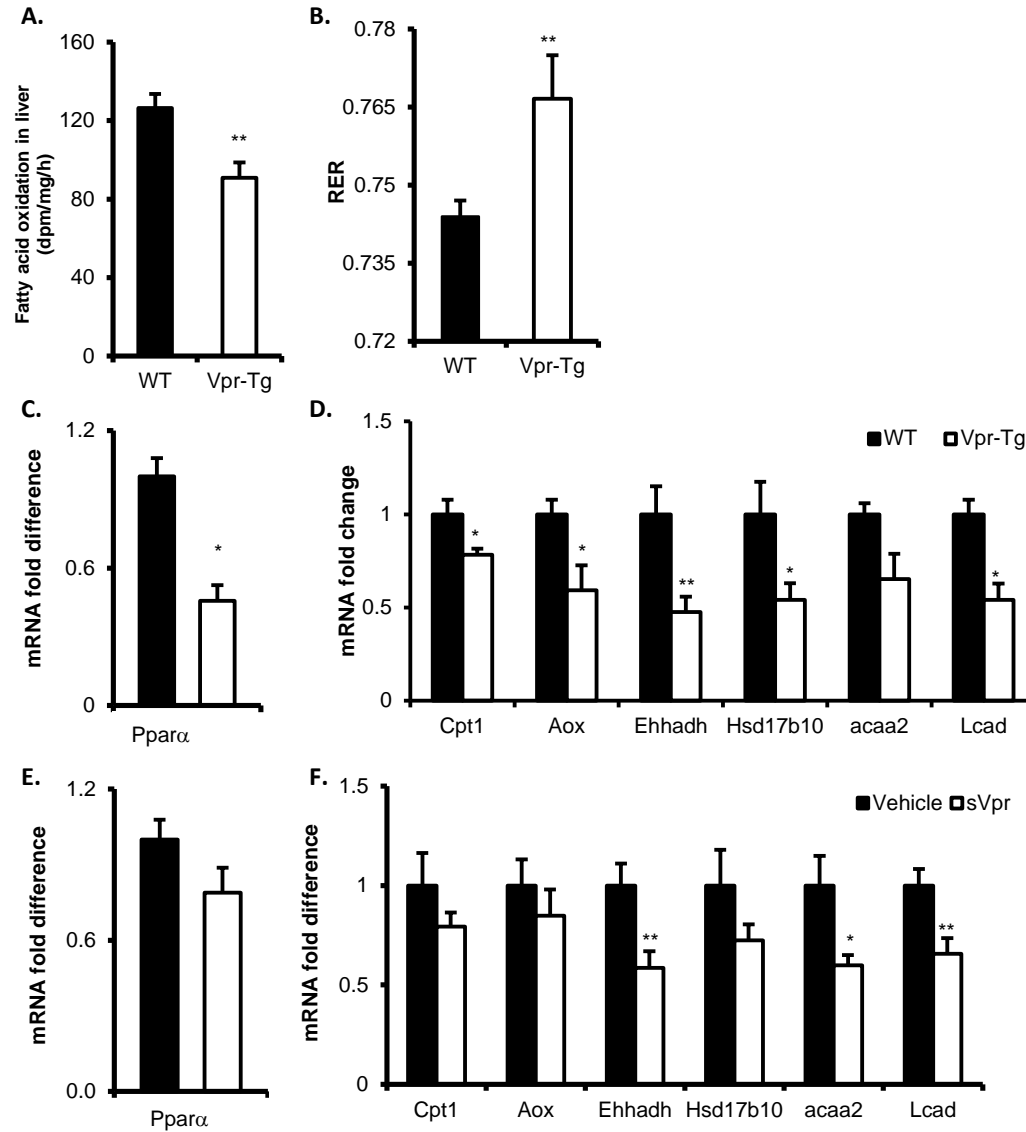


# Vpr increases proteins associated with liver lipogenesis

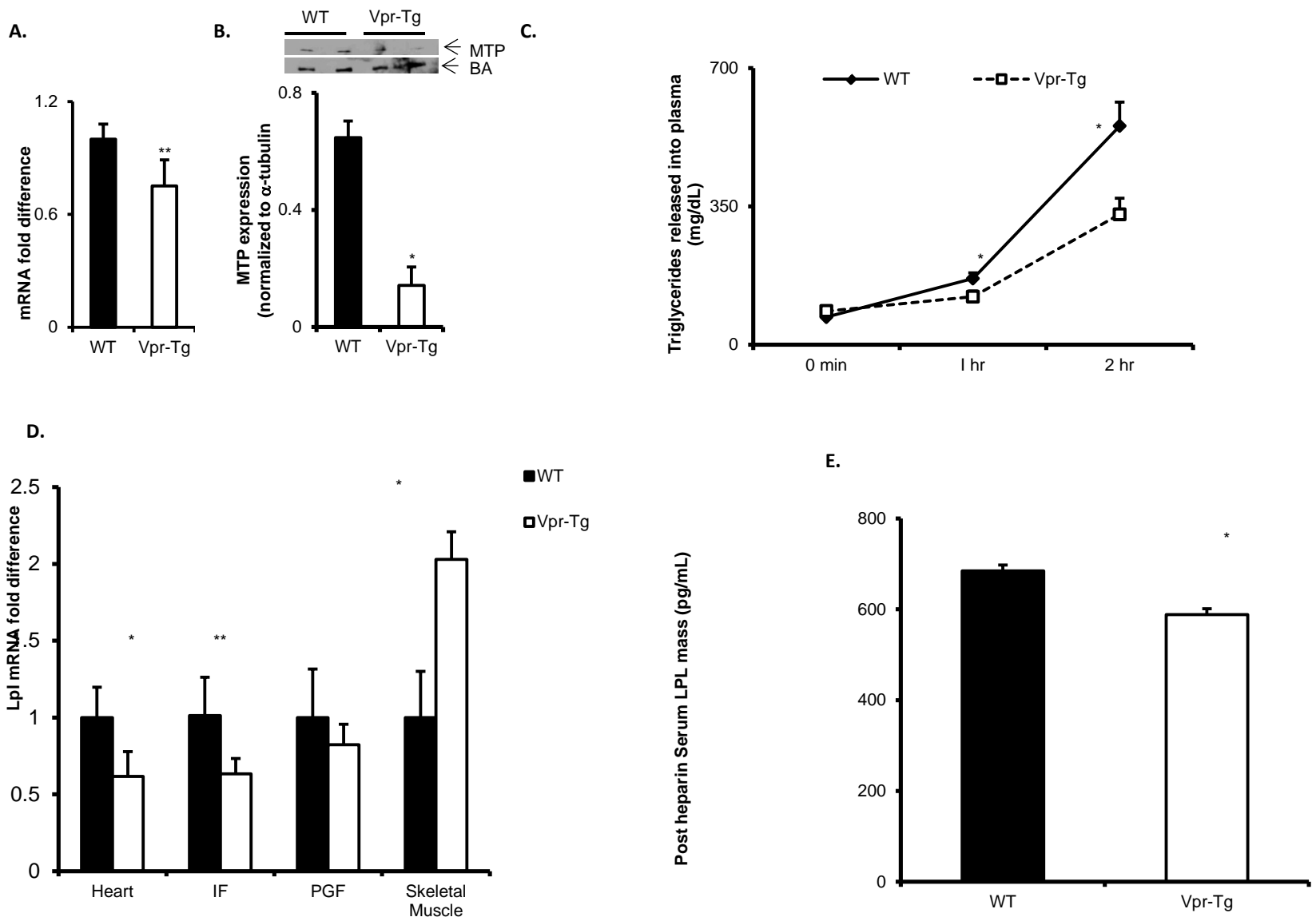




# Vpr Blunts Hepatic Fat Oxidation



# Vpr Inhibits Hepatic VLDL-TG Export



# Do these Vpr Mouse Models Explain Adipose / Liver Metabolic defects in HIV+ Humans?

	Vpr Mice	HIV+ Humans
Lipolysis	↑	↑
Fat oxidation	↓	↓
Fat mass	↓	↓
Fatty liver	↑	↑
FGF21	↑	↑
<b>SAT “beiging”</b>	<b>+</b>	<b>+</b>
<b>Circulating Vpr without intact HIV</b>	<b>+</b>	<b>+</b>

Koch's Postulates?

# CREDITS

## Expression / Function Studies:

**Neeti Agarwal**

**Dinakar Iyer**

**Toni Oplt**

**Sanjeet Patel**

Jeffrey Kopp

Ulrich Schubert

Terry Phillips

Tomoshige Kino

## Human Samples:

**Maria Rodriguez-Barradas**

## Adipose HIV Reservoir

**Dorothy Lewis**

**Jacob Couturier**

Sara Cromer

## Human / Mouse Metabolic Studies:

**R. V. Sekhar**

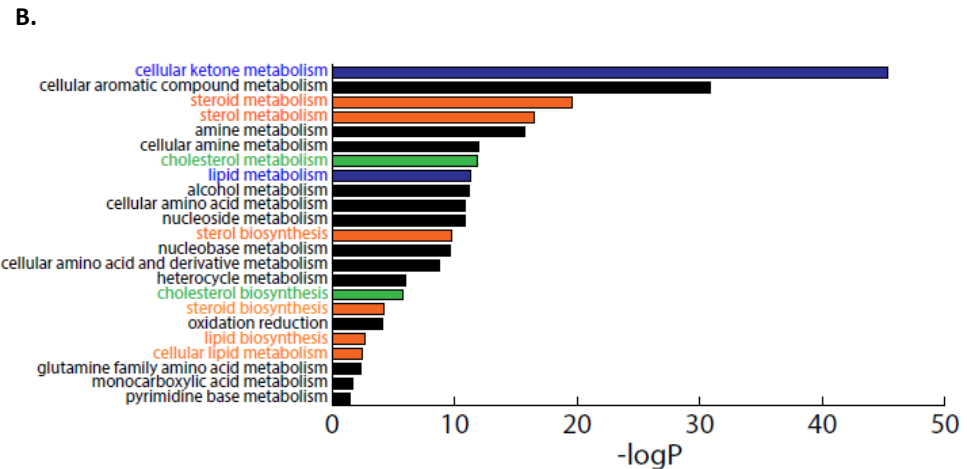
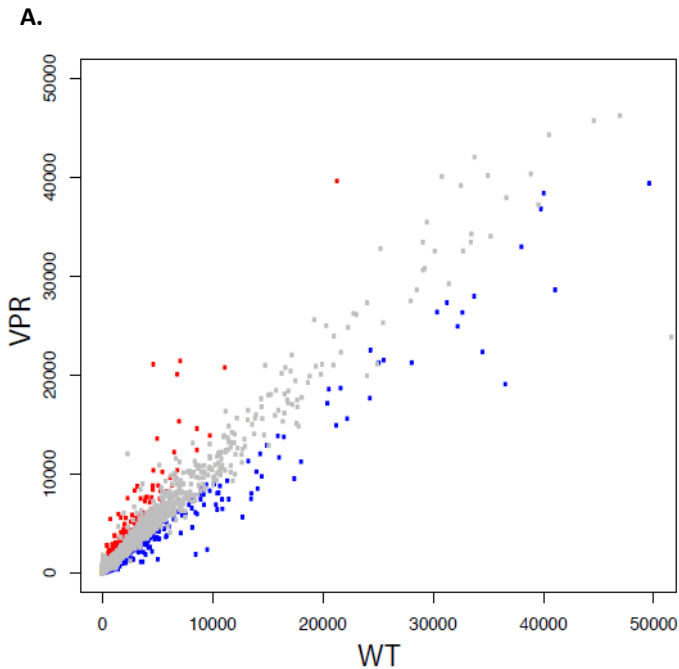
**Farook Jahoor**

Sue Samson

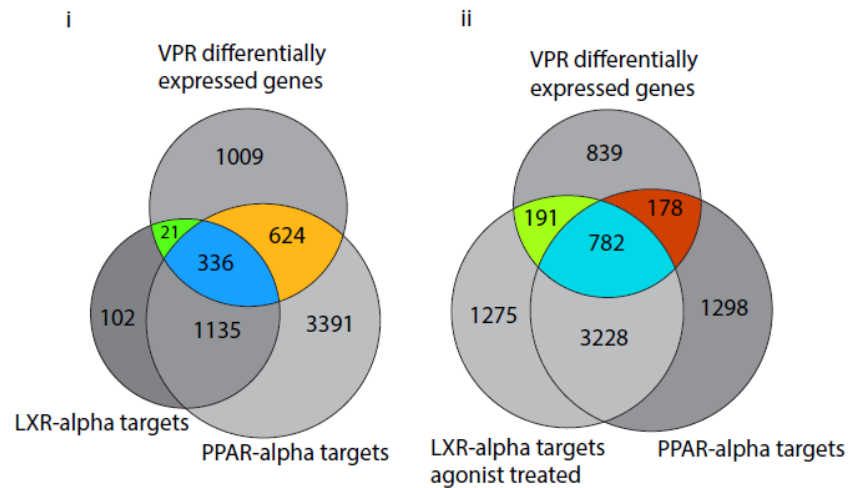
Sanjeet Patel

Jordan Lake

# Vpr Associates With Hepatic Genes Involved in Lipid and Sterol Metabolism



**C.**



# Vpr Coactivates LXR

