

Regulation of Systemic Energy Balance and Glucose Homeostasis by Protein-Tyrosine Phosphatase 1B

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Associate Professor

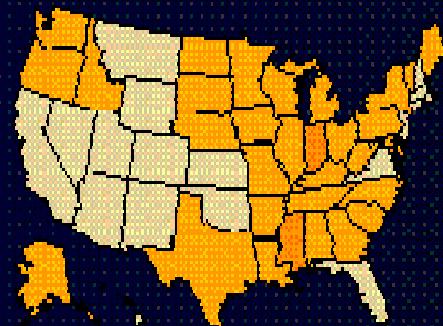


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UNIVERSITY OF CALIFORNIA

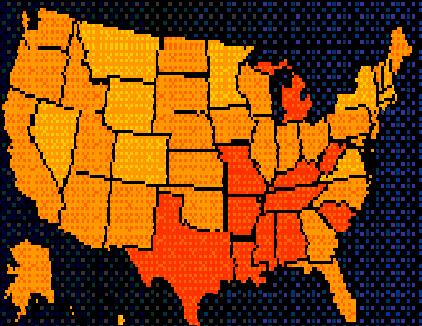
Diagnosed Obesity and Diabetes for Adults aged ≥ 20 years in United States

Obesity (BMI ≥ 30 kg/m 2)

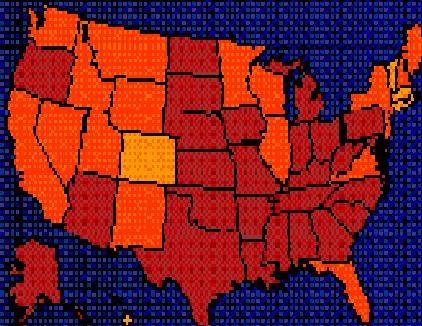
1994



2000

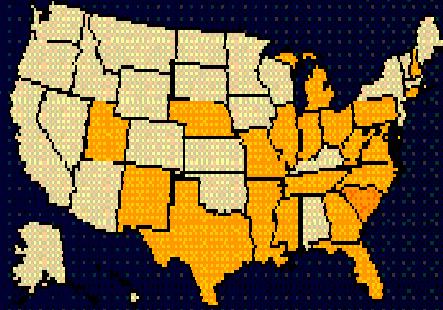


2007

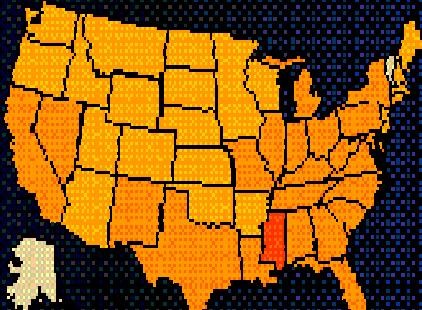


Diabetes

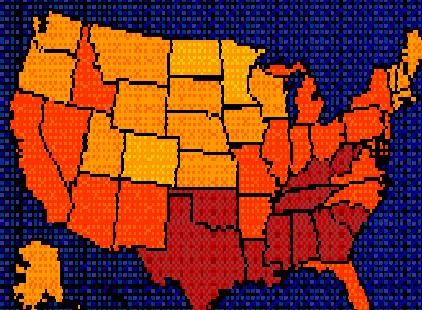
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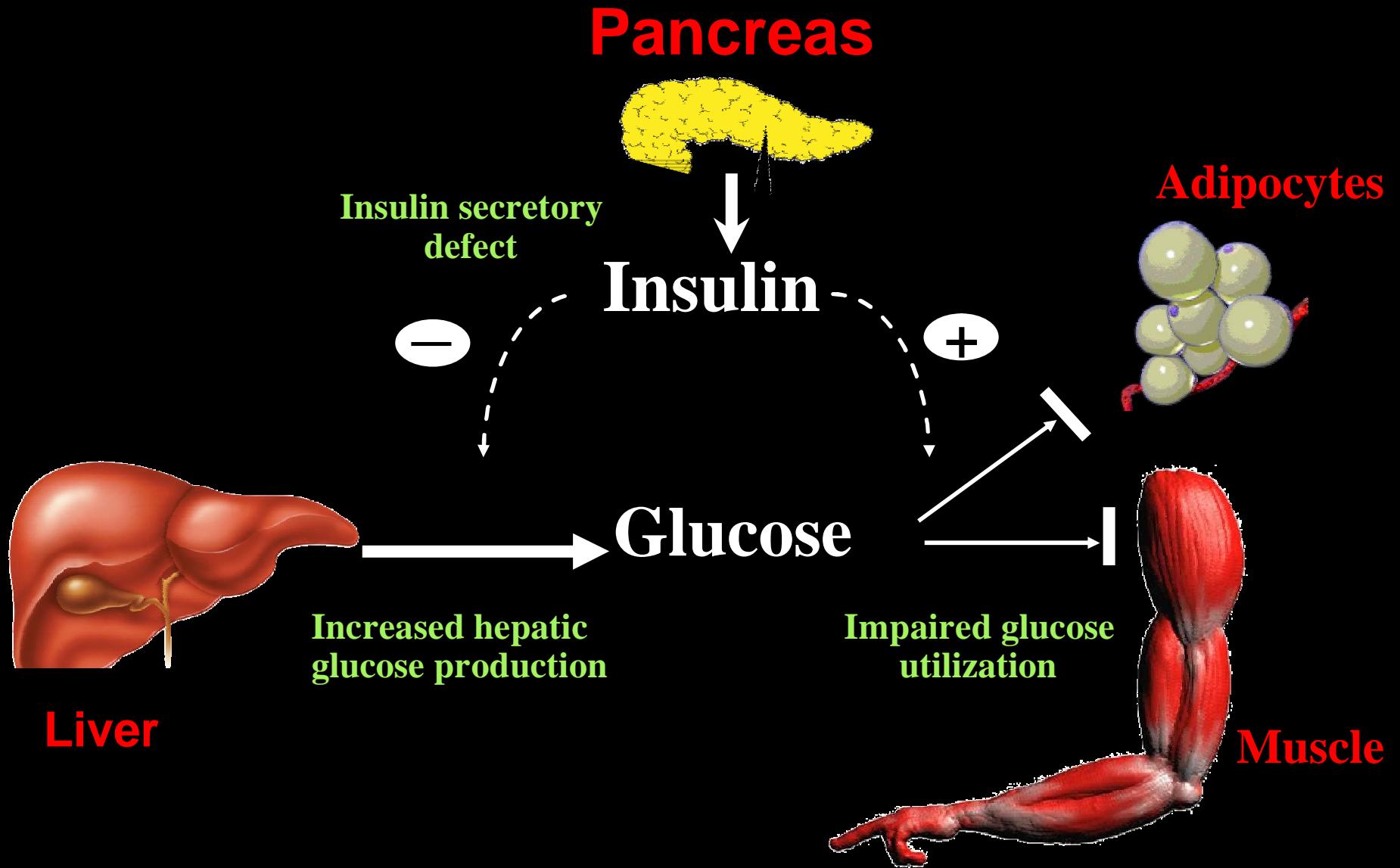


The Obesity Epidemic Has Reached America's Pets



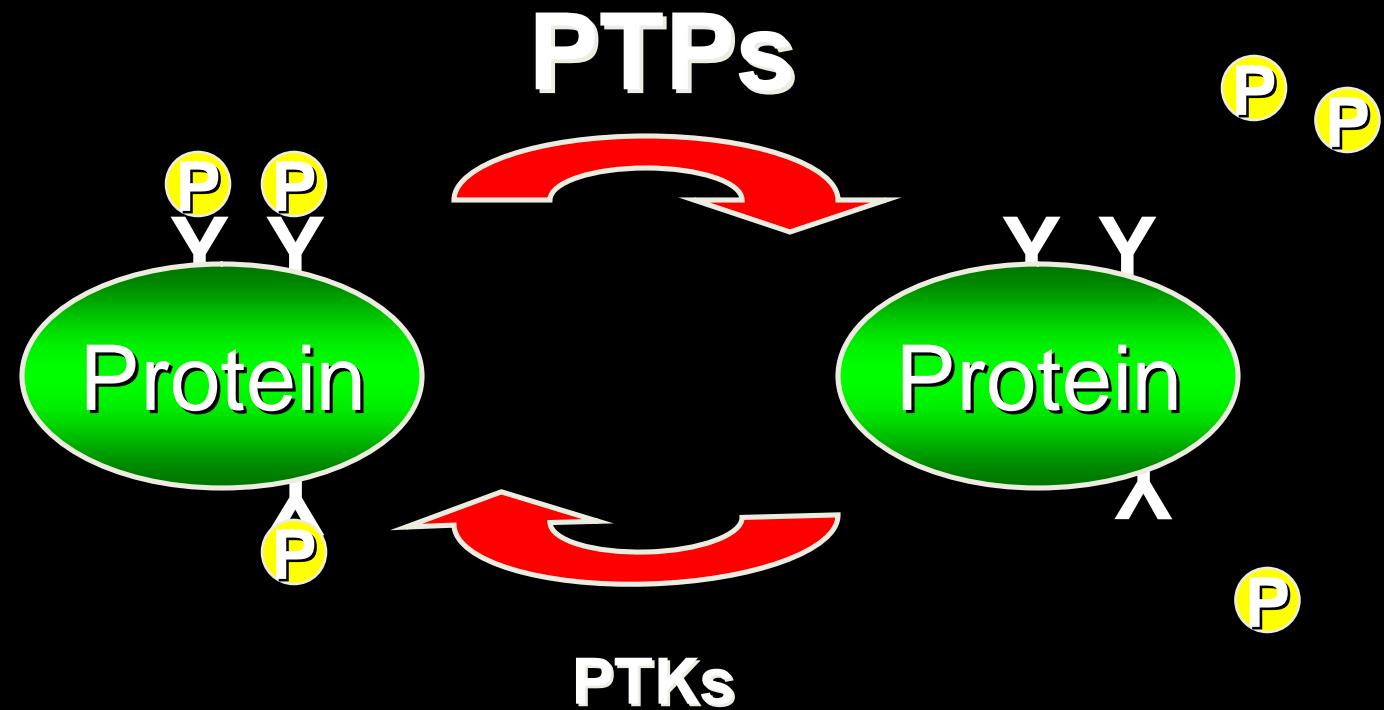
A 28 pound cat!!

System Regulation of Glucose

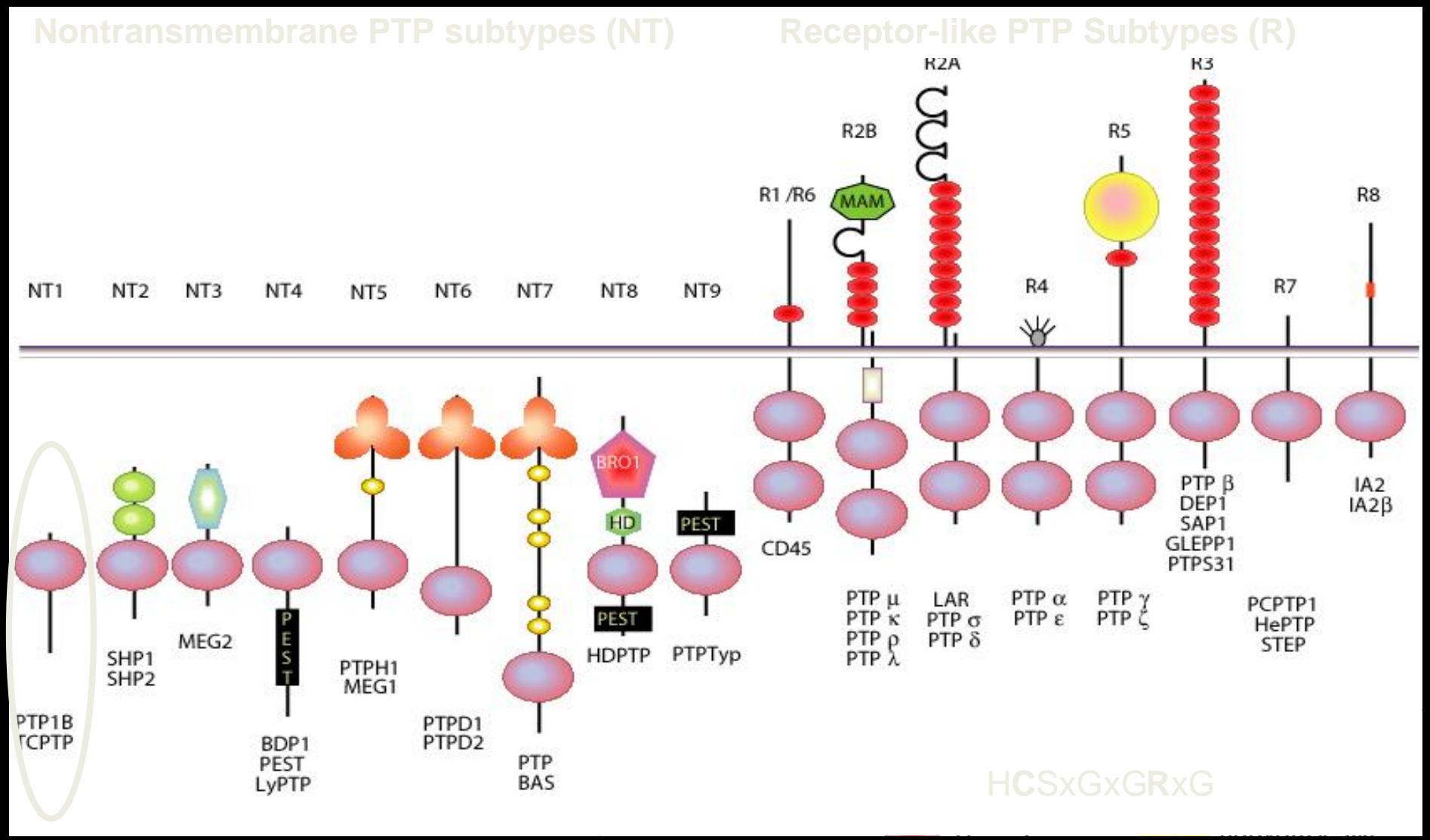


**Understand the Role of Cell Signaling, in
Particular, Tyrosine Phosphorylation in the
Pathogenesis of Metabolic Diseases**

Phosphorylation is reversible



The Classical Protein-Tyrosine Phosphatase (PTP) Family



Protein-Tyrosine Phosphatase 1B (PTP1B)

Is ubiquitously expressed, including all insulin-responsive tissues

Generate PTP1B knockout (KO) mice (protein no longer expressed)

- PTP1B KO mice are insulin-sensitive, and have increased insulin receptor (IR) phosphorylation (Elchebly *et al*, 1999 and Klaman *et al*, 2000)
- PTP1B KO mice are lean and resistant to diet-induced obesity (Elchebly *et al*, 1999 and Klaman *et al*, 2000)



PTP1B Inhibition for Treatment of Metabolic Diseases

- No obvious apparent side effects observed thus far, making PTP1B a good target for treating obesity and diabetes in humans
- Companies are competing to generate a readily bio-available, PTP1B-specific inhibitor

Need to know the SITES and MECHANISMS of PTP1B action

Approach

**Genetically-engineered mice to achieve tissue-specific
deletion of PTP1B**

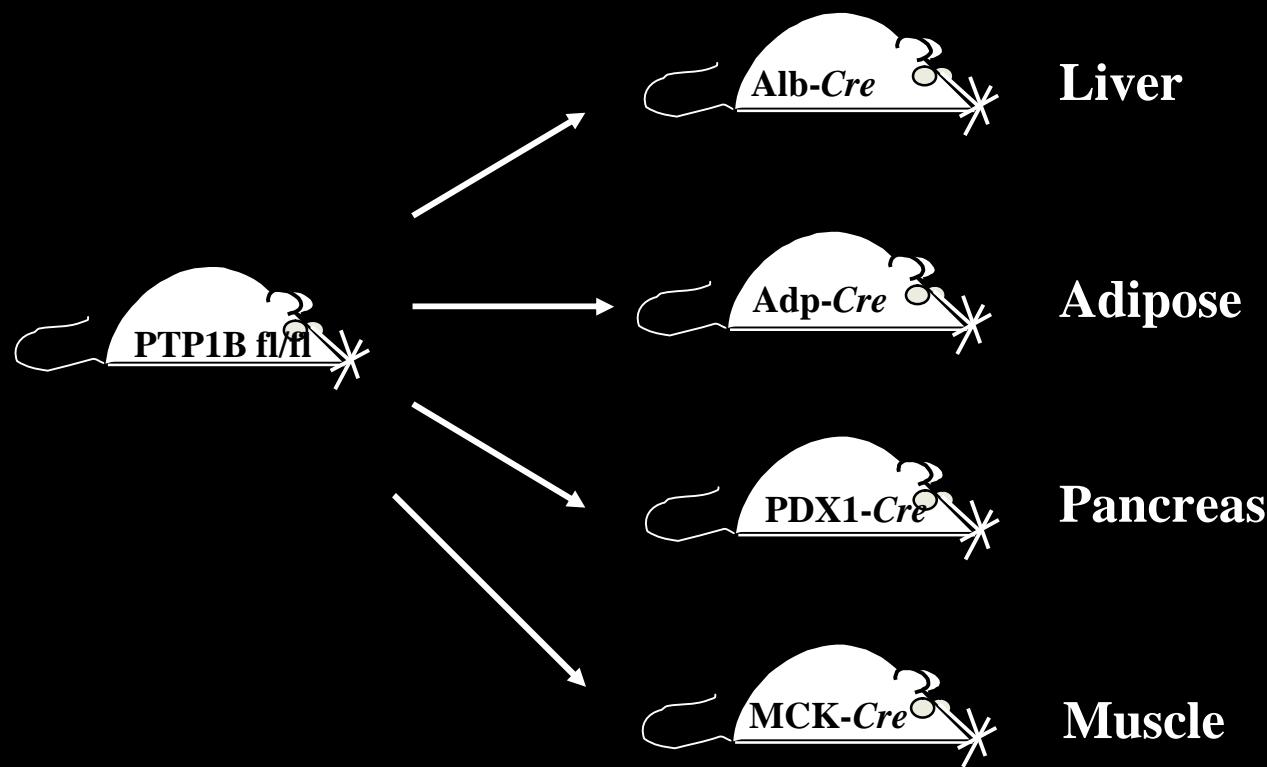
**Quantitative cellular imaging to dissect the mechanism
of PTP1B action**

Approach

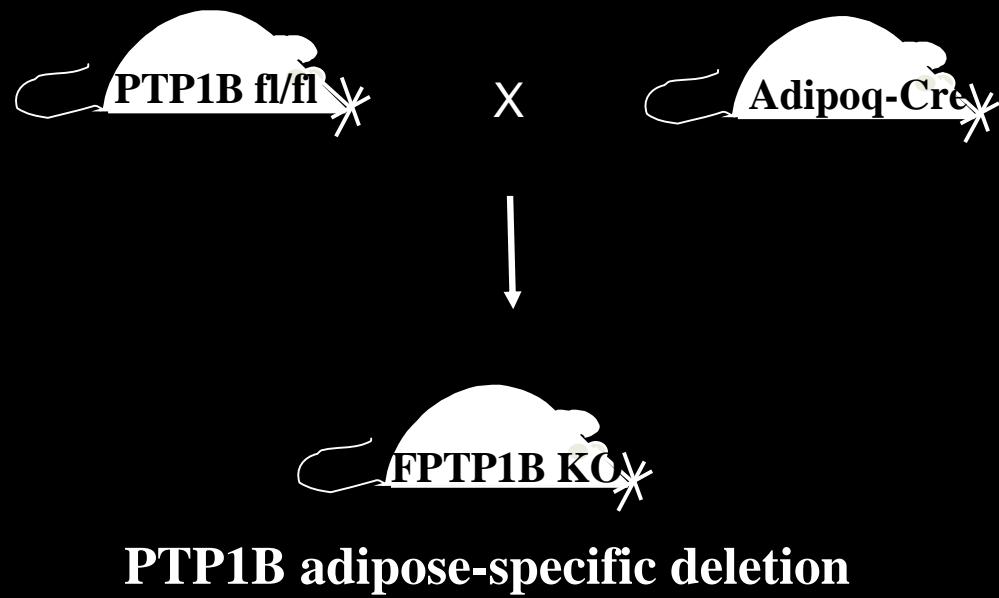
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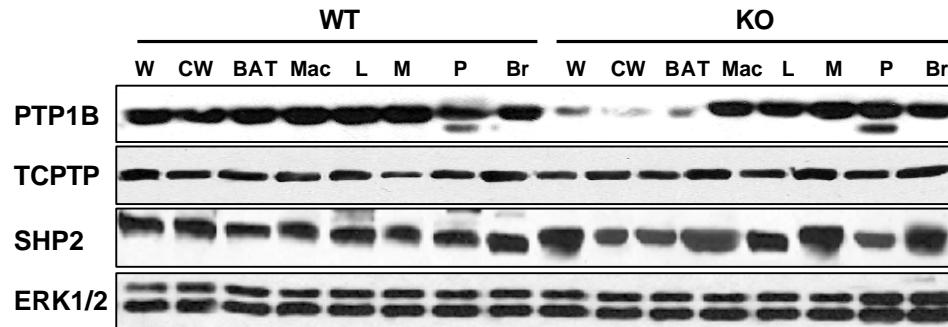
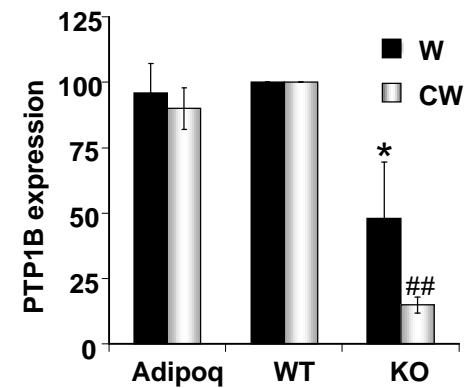
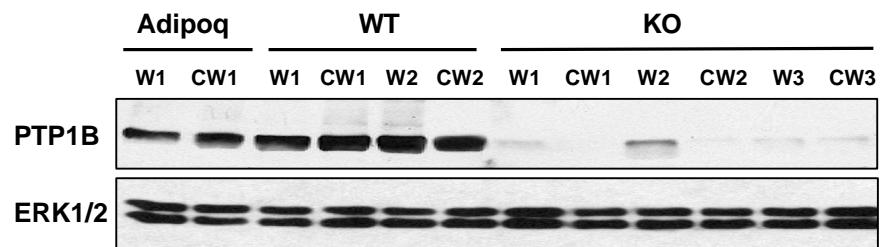
Tissue-Specific Deletion of PTP1B



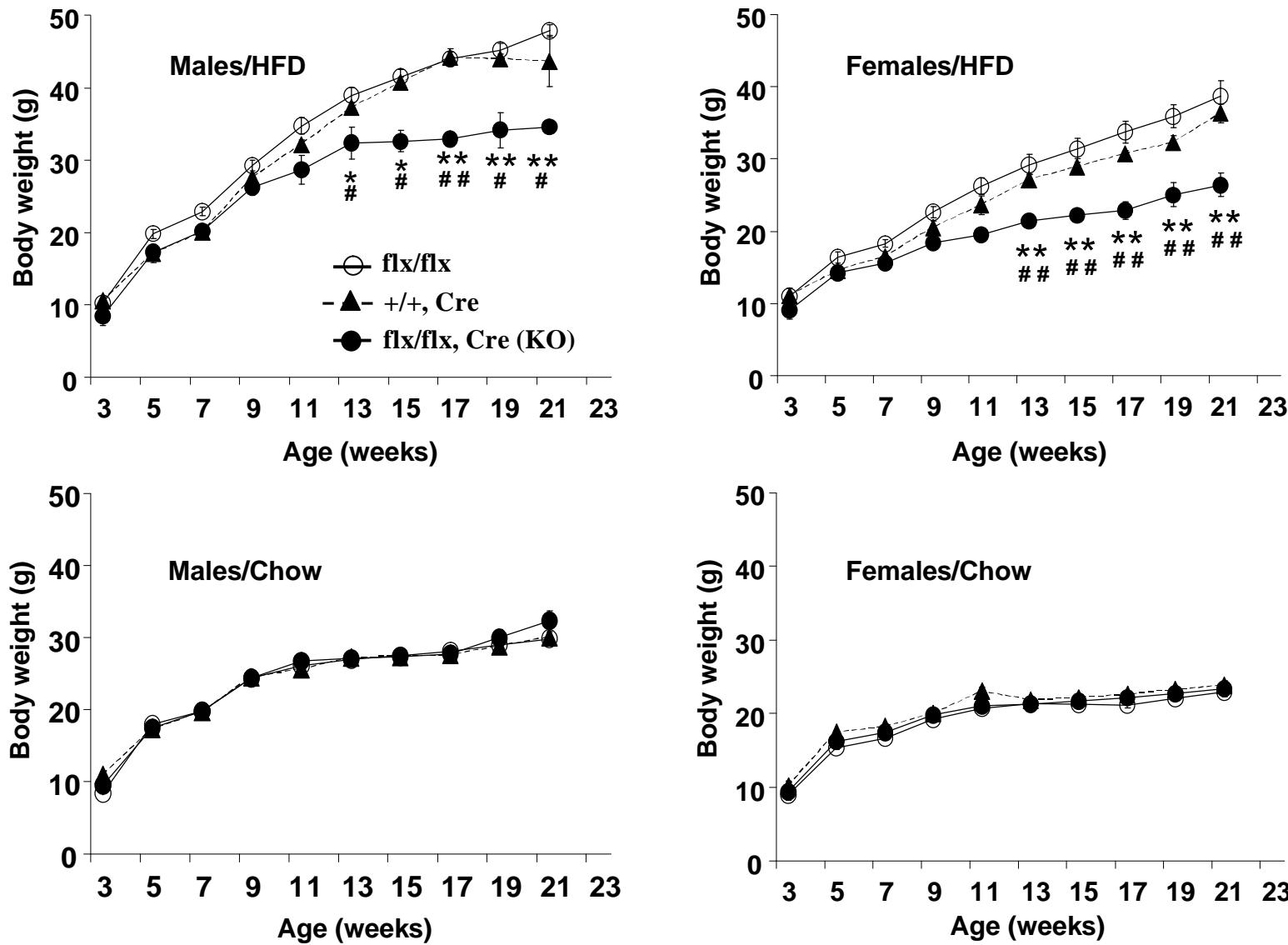
Generation of Adipose-Specific PTP1B Knockout Mice using *Adipoq*-Cre



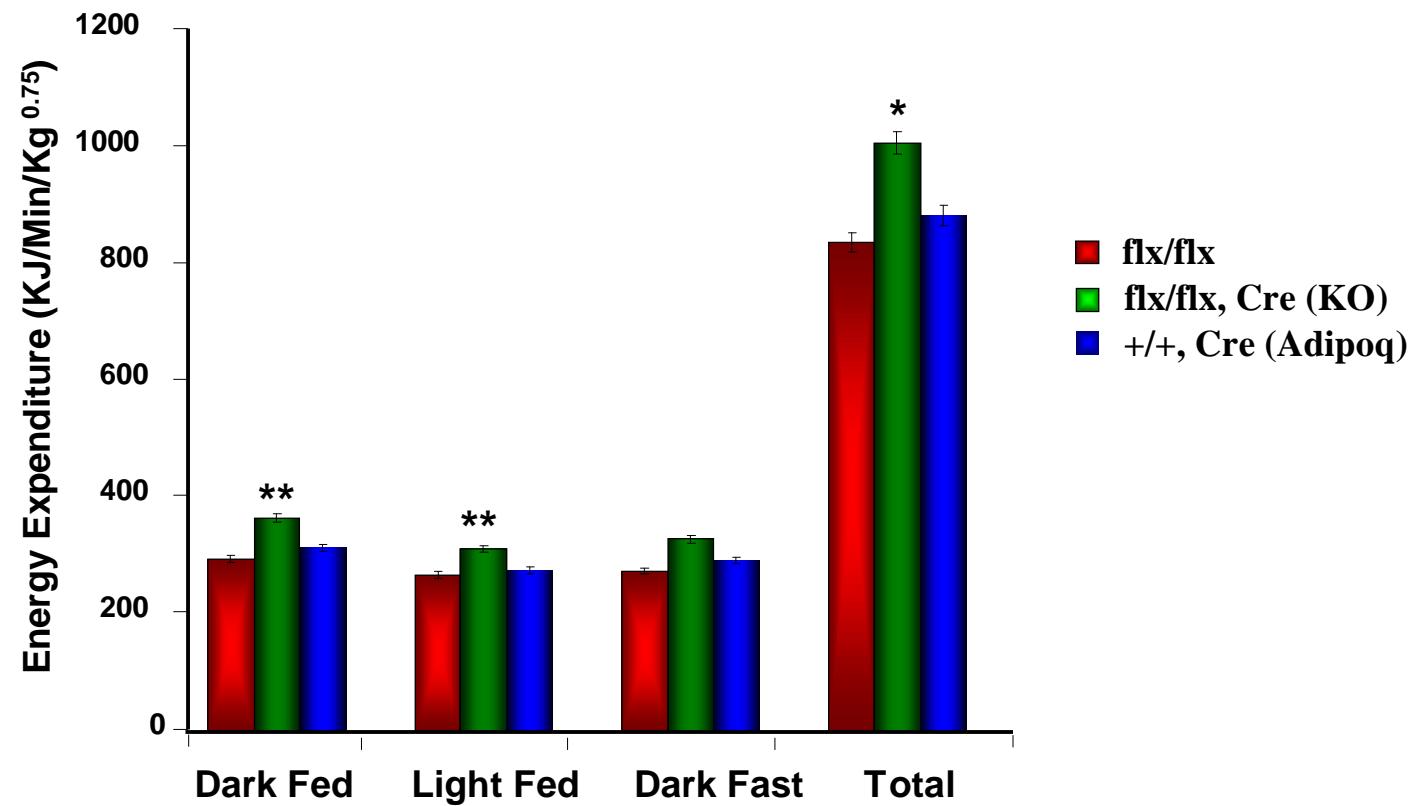
Efficient and Specific Deletion of PTP1B in Adipose Tissue



Resistance to HFD-Induced Obesity in adipose PTP1B KO Mice



Increased Energy Expenditure in Adipose PTP1B KO Mice

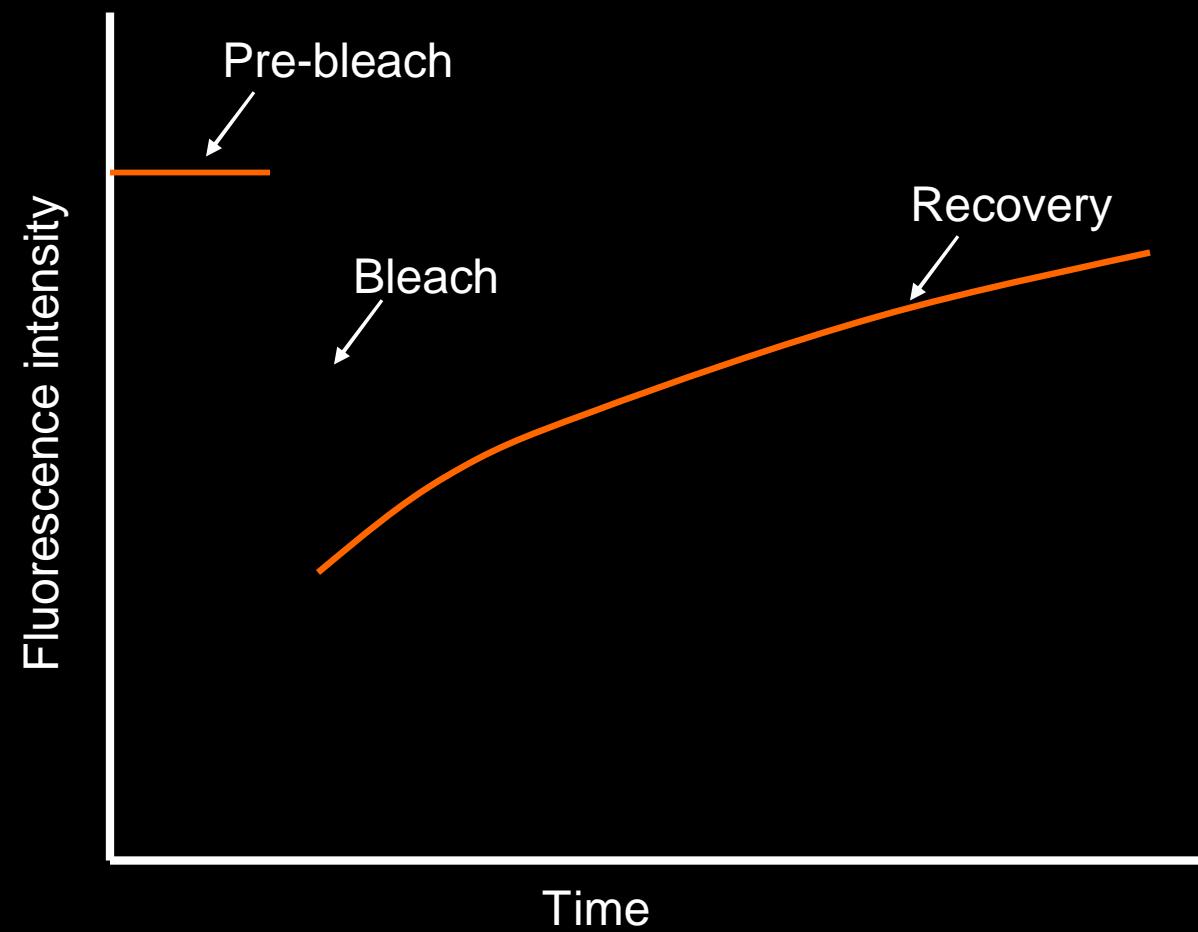
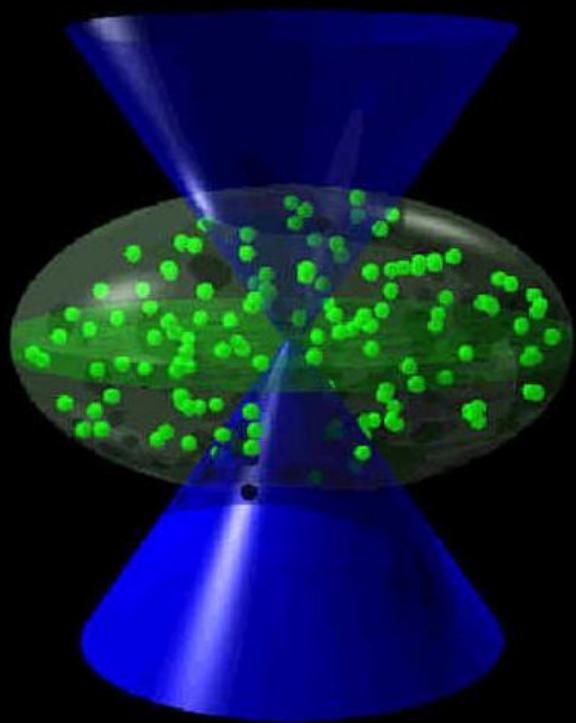


Approach

**Genetically-engineered mice to achieve tissue-specific
deletion of PTP1B**

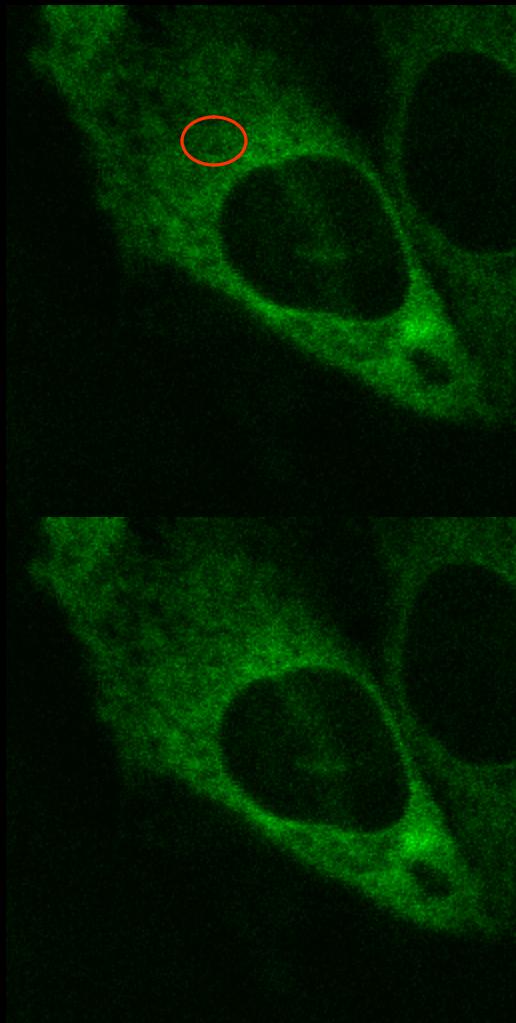
**Quantitative cellular imaging to dissect the mechanism
of PTP1B action**

Fluorescence Recovery After Photobleaching (FRAP)

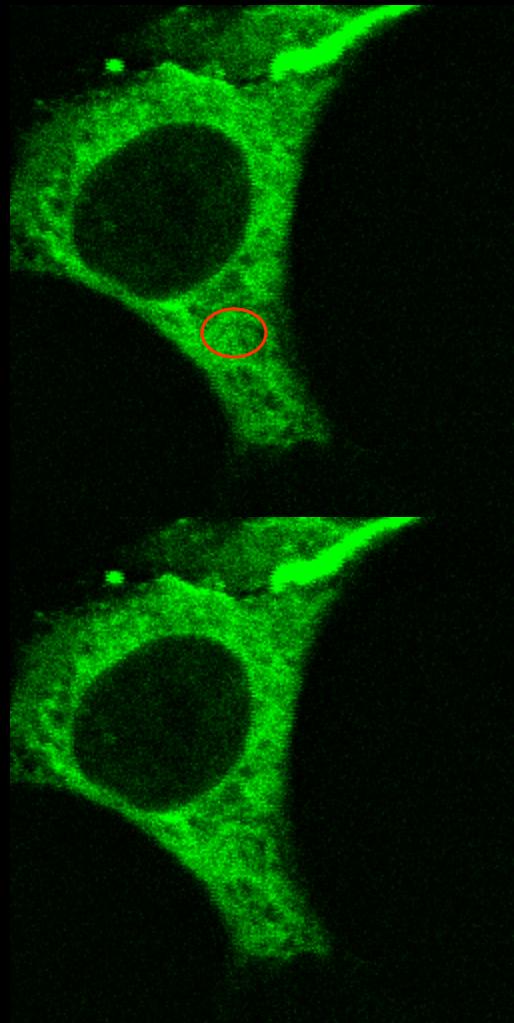


Dynamics of Cellular PTP1B Mobility

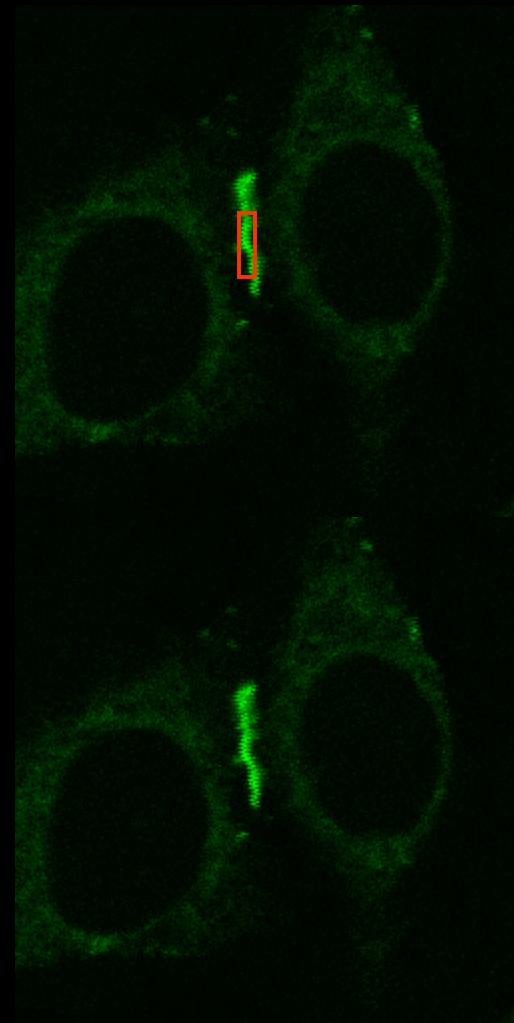
PTP1B WT (ER)



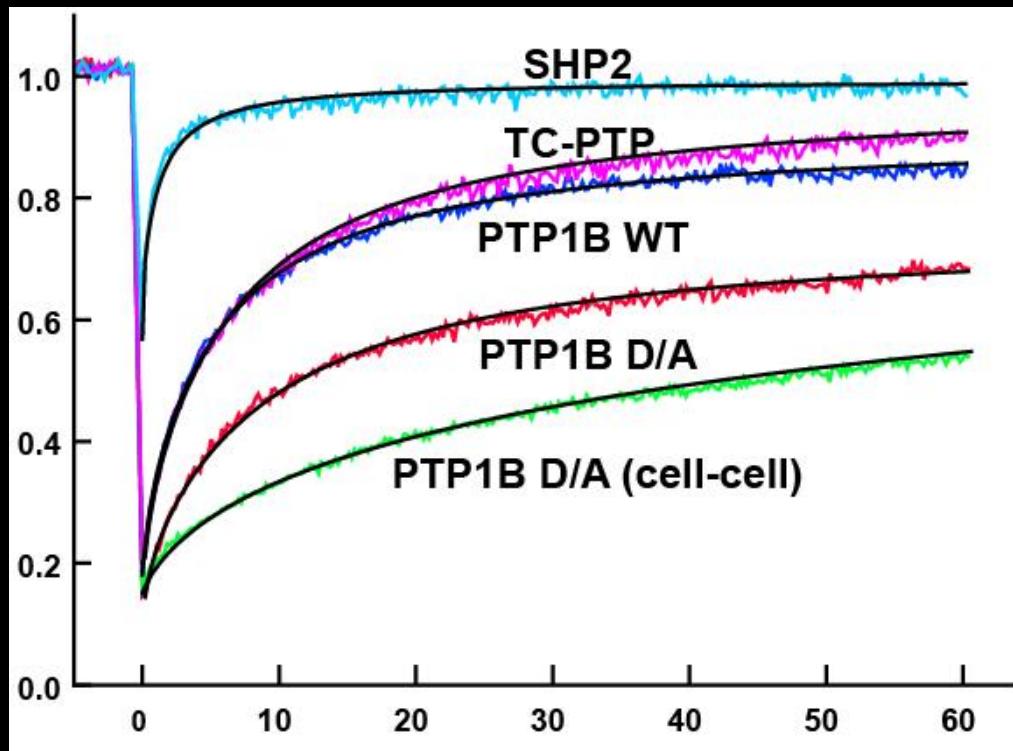
PTP1B D/A (ER)



PTP1B D/A (Cell-Cell)



Quantitative Determination of PTP1B Mobility Using FRAP



WT ER, $D_{\text{eff}} = 0.20 \text{ mm}^2 \text{ s}^{-1}$

D/A ER, $D_{\text{eff}} = 0.07 \text{ mm}^2 \text{ s}^{-1}$

D/A cell-cell

(D_{eff} : Effective diffusion)

Recovery consistent with:

- 1) Rapid turnover (<10 sec)
- 2) Replenishment from ER pool
- 3) No significant “tight binding” fraction

Summary

Adipose-specific PTP1B deletion leads to decreased adiposity and resistance to high fat diet-induced obesity

This is due to increased energy expenditure in adipose PTP1B deficient mice

Cellular imaging identifies the endoplasmic reticulum and cell-cell contact as major cites of PTP1B action in the cell

Conclusion

Tissue-specific deletion and cell biology approaches are necessary to decipher the sites and mechanisms of PTP1B action

This is important for developing drugs that targets PTP1B at the correct site(s)

Future Studies

Investigate the role of PTP1B in other tissues and its mechanism of action at these sites

Investigate the role of other members of PTP superfamily as potential targets to treat obesity and diabetes

Examine regulation of PTP activity by nutrients and diets

Acknowledgements



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