A Novel Pathway that Regulates Body Fat and Insulin Signaling in Mice

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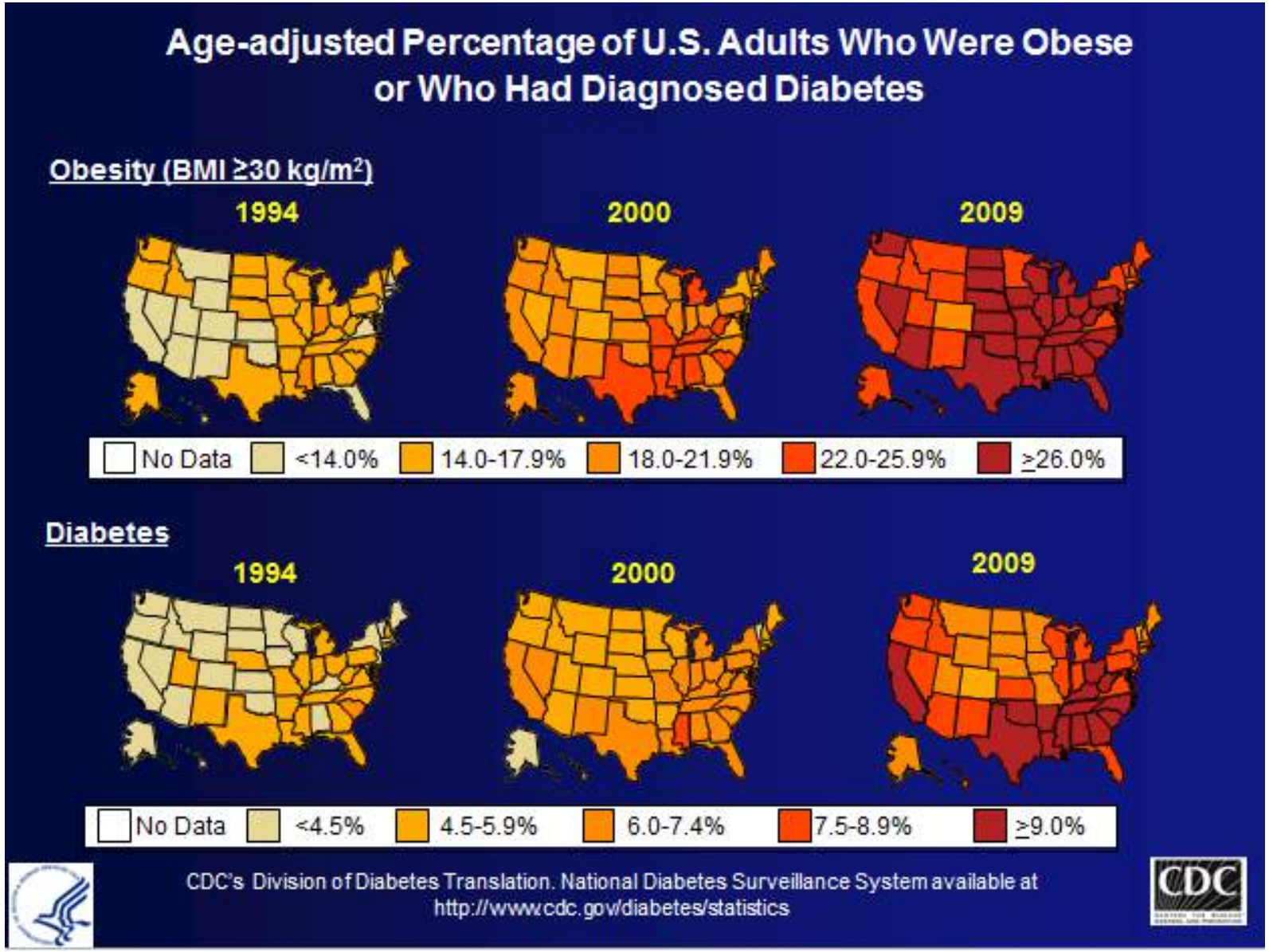
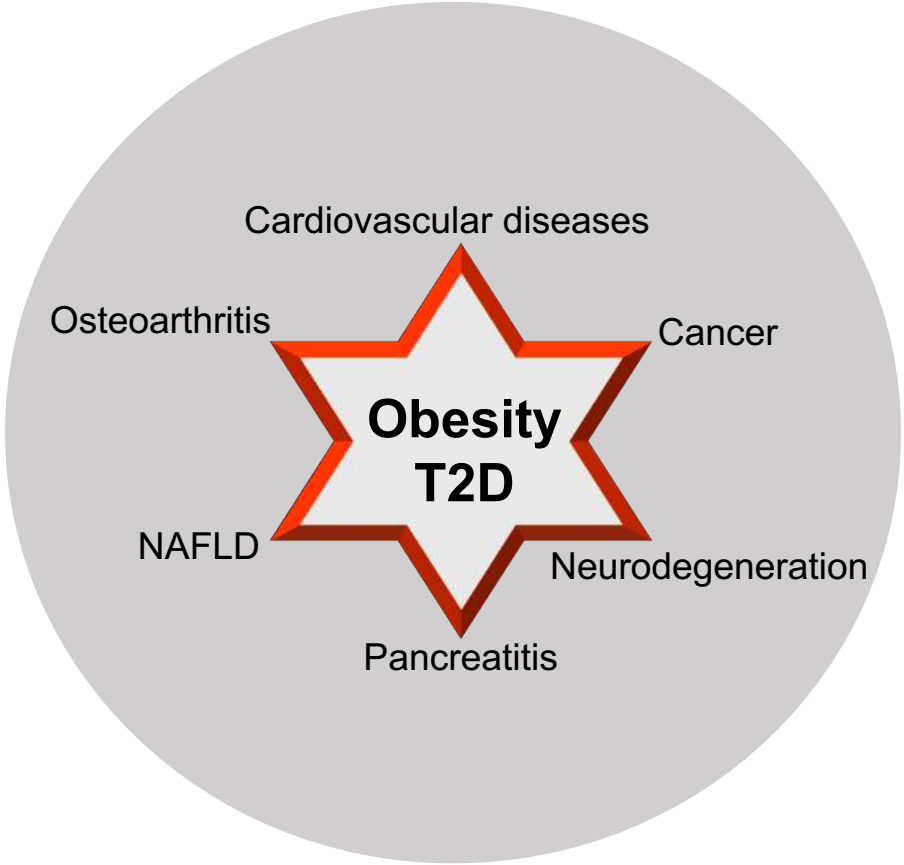
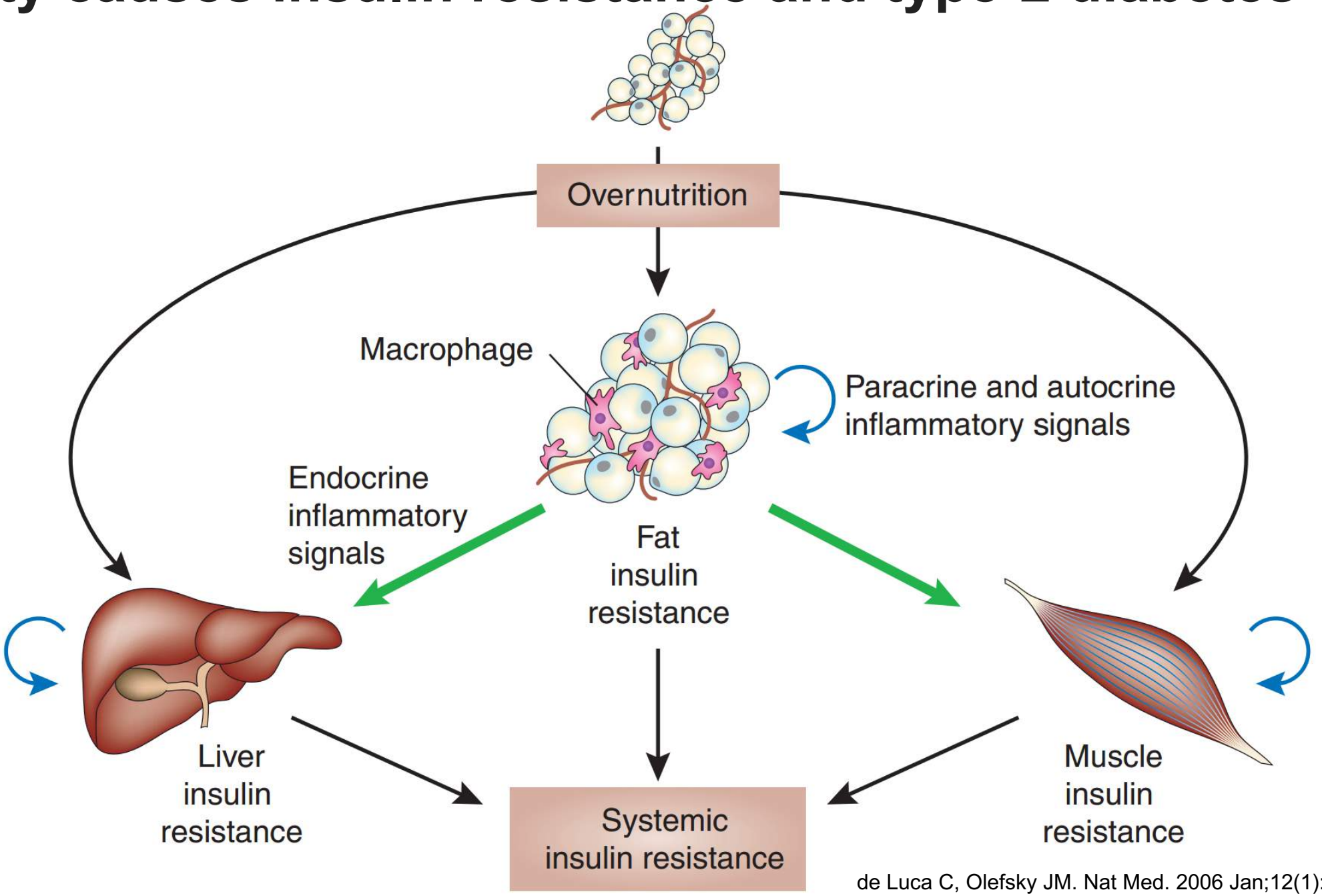
Obesity and type-2 diabetes are serious health concerns





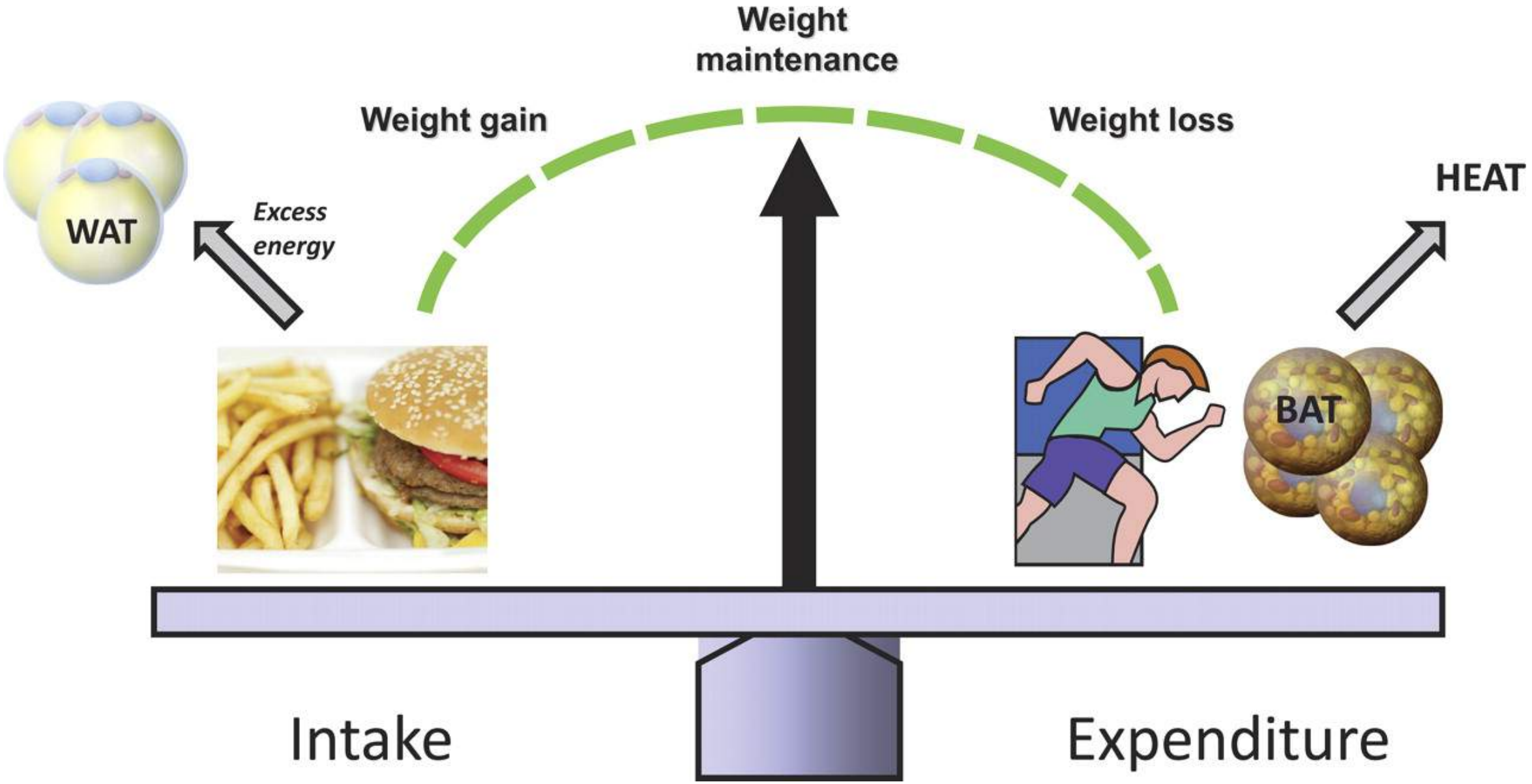
Chakraborty model slide, 2017.

Obesity causes insulin resistance and type-2 diabetes



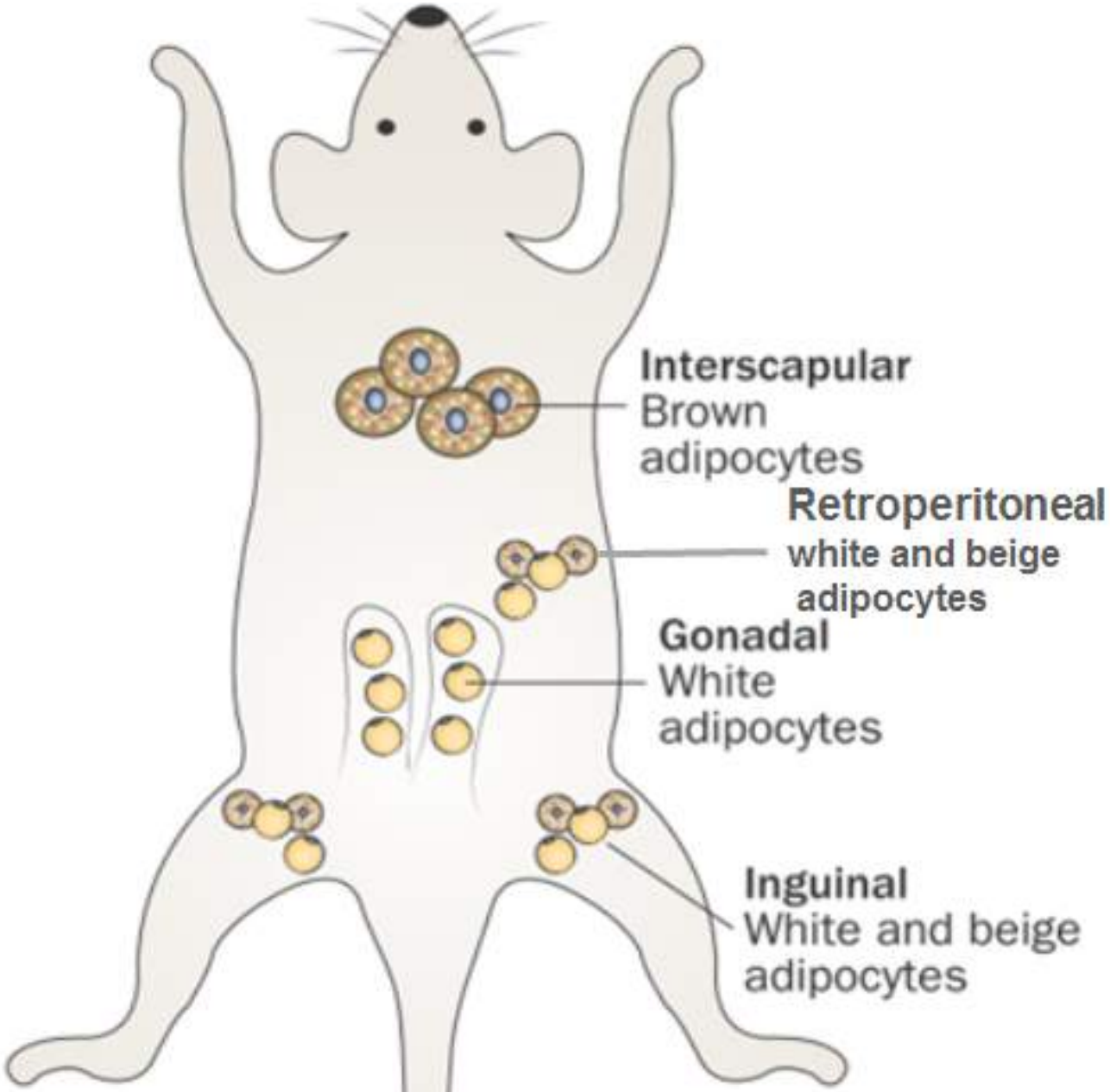
de Luca C, Olefsky JM. Nat Med. 2006 Jan;12(1):41-2; discussion 42.

Energy homeostasis

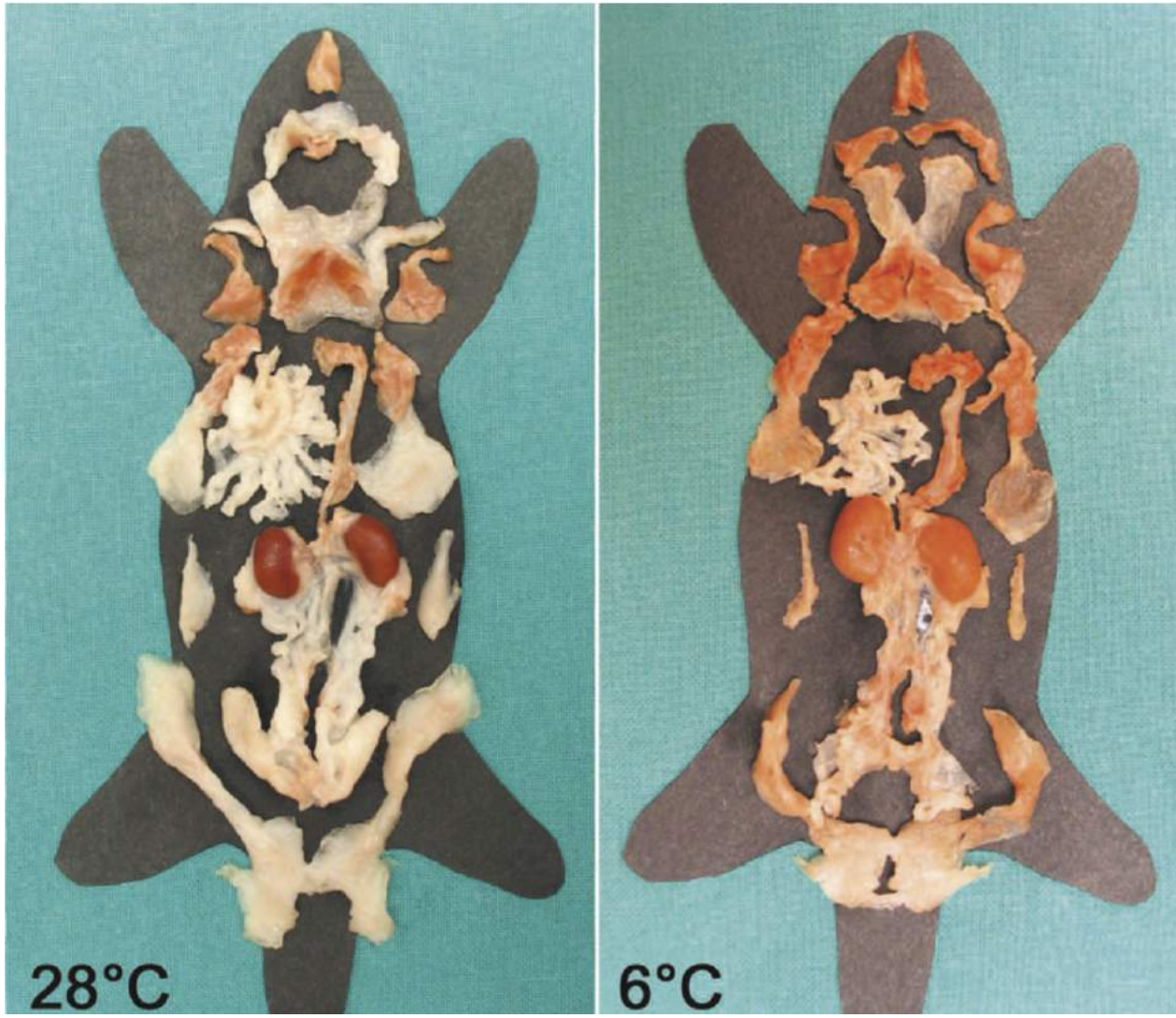


Seale and Lazar. Diabetes. 2009, 58, 1482-4.

Adipocytes: White, brown and beige (brown-like)



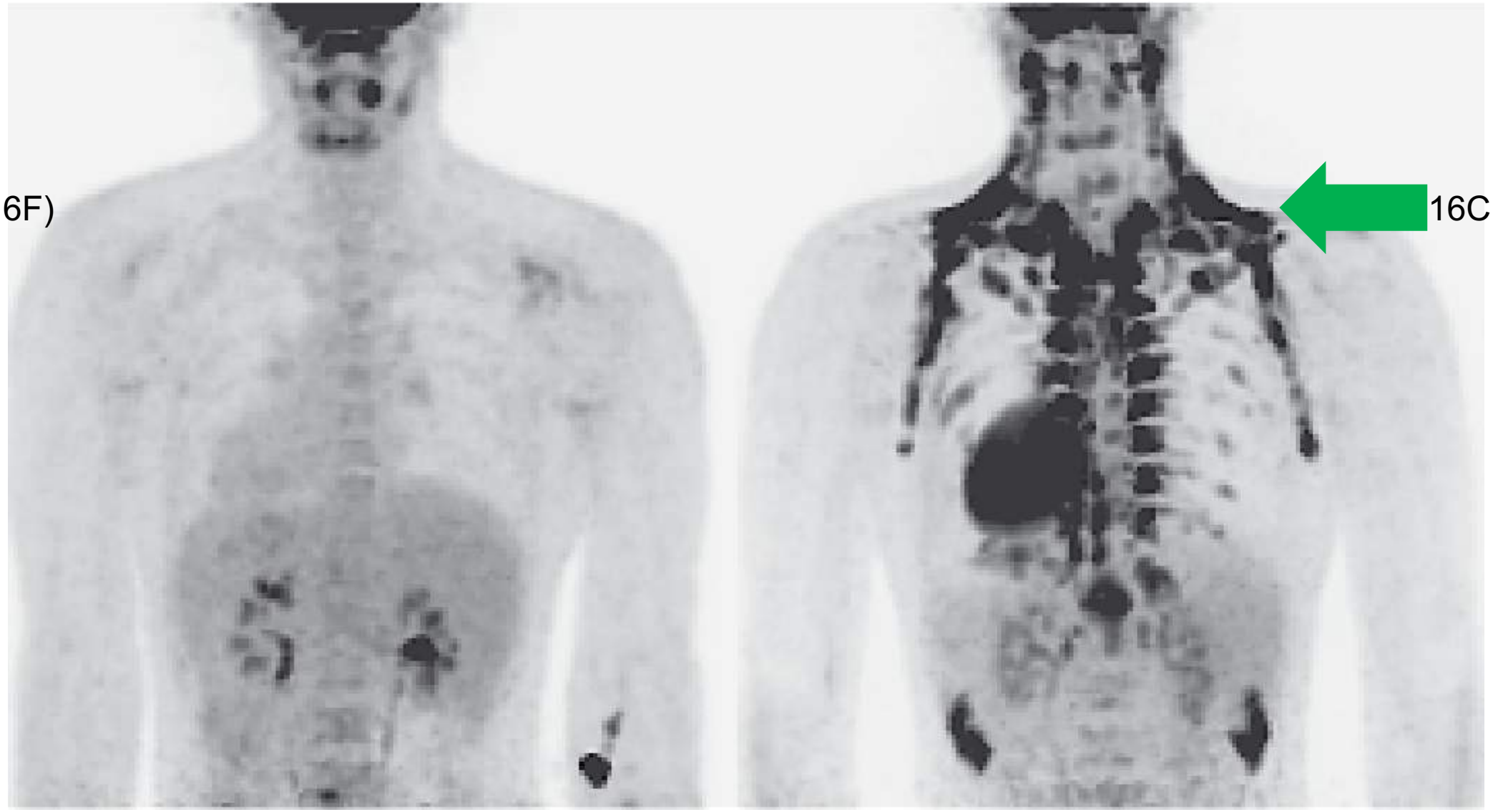
Modified from Bartelt and Heeren. Nat Rev Endocrinol. 2014, 10, 24-36. Review.



Cinti S. Am J Physiol Endocrinol Metab. 2009, 297, :E977-86. Review.

Cold-induced brown/beige adipocytes reduces body fat and enhances insulin sensitivity in humans

22C (71.6F)

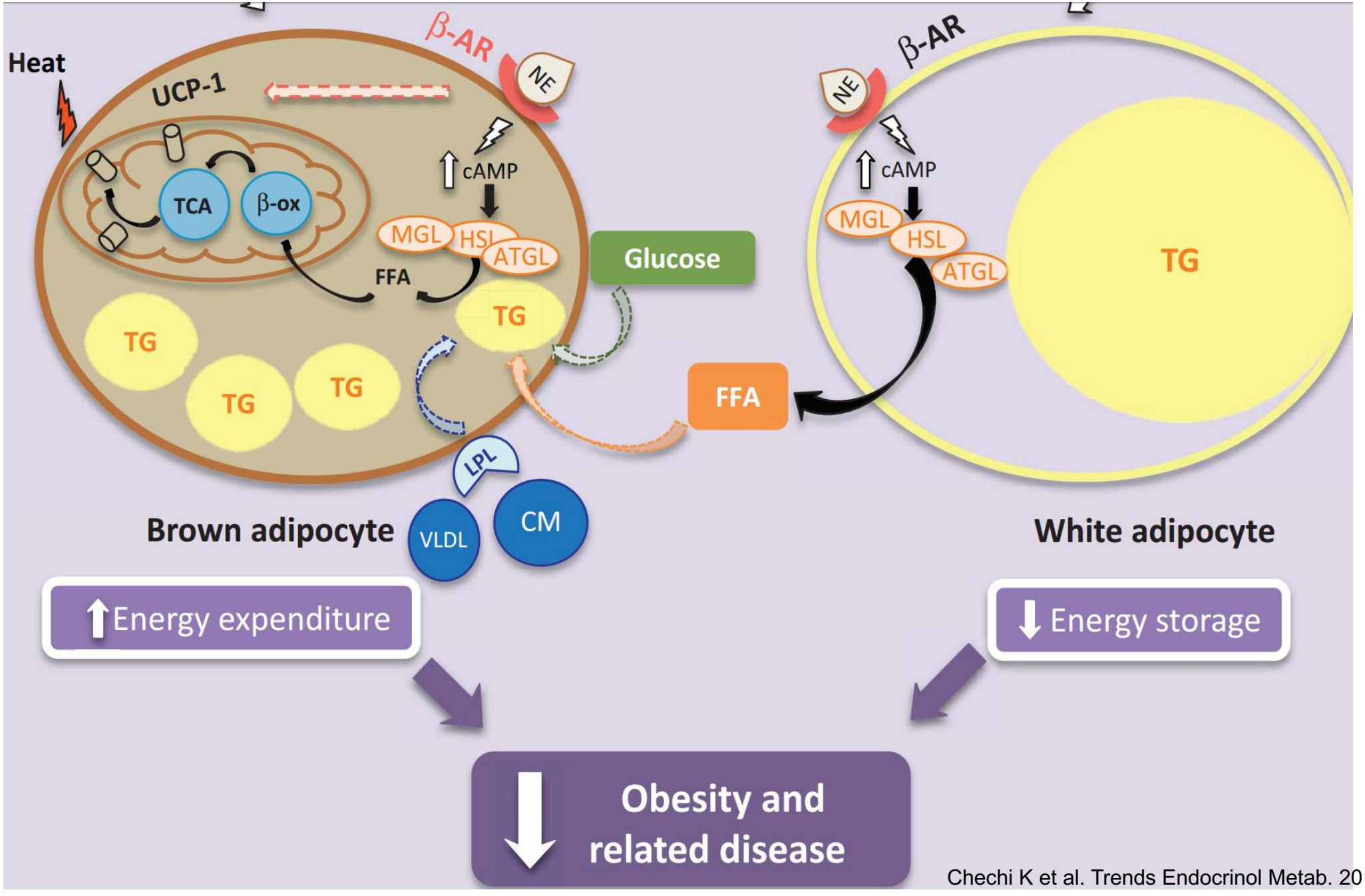


16C (60.8F; 4h)

24 healthy men (10 lower than 25 and 14 higher than 25 BMI). Brown-adipose-tissue activity was observed in 23 of the 24 subjects during cold exposure.

van Marken Lichtenbelt et al. N Engl J Med. 2009, 360, 1500-8.

White and brown/beige adipocytes coordinate to maintain energy homeostasis



Chechi K et al. Trends Endocrinol Metab. 2013, 24, 408-20.

A complete understanding of adipocyte (cell) biology is lacking

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Communication

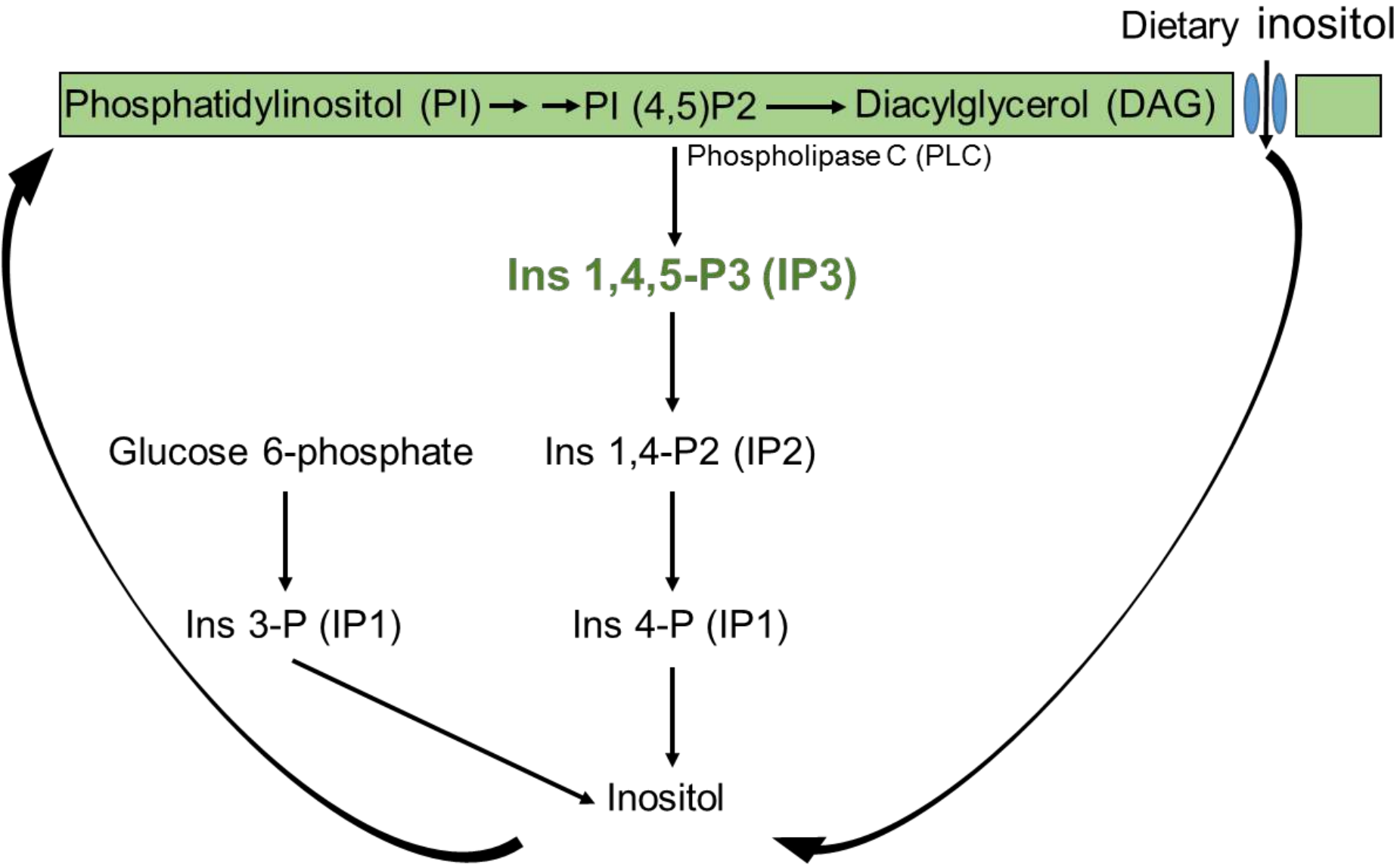
Proteins of Unknown Function in the Protein Data Bank (PDB): An Inventory of True Uncharacterized Proteins and Computational Tools for Their Analysis

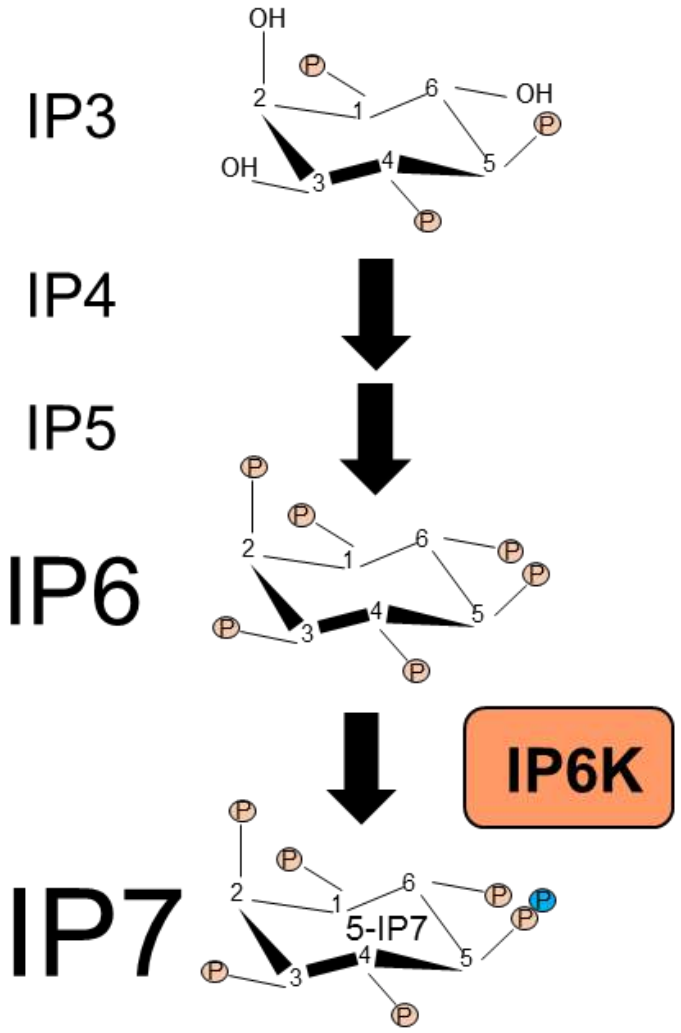
Nurul Nadzirin and Mohd Firdaus-Raih *

Uncharacterized protein data acquisition from PDB	2549
UniProtKB equivalent search	1681
Sequence similarity search (Blast)	1303
Fold similarity search (Dali)	1084

Nadzirin N, Firdaus-Raih M. Int J Mol Sci. 2012 Oct 8;13(10):12761-72.

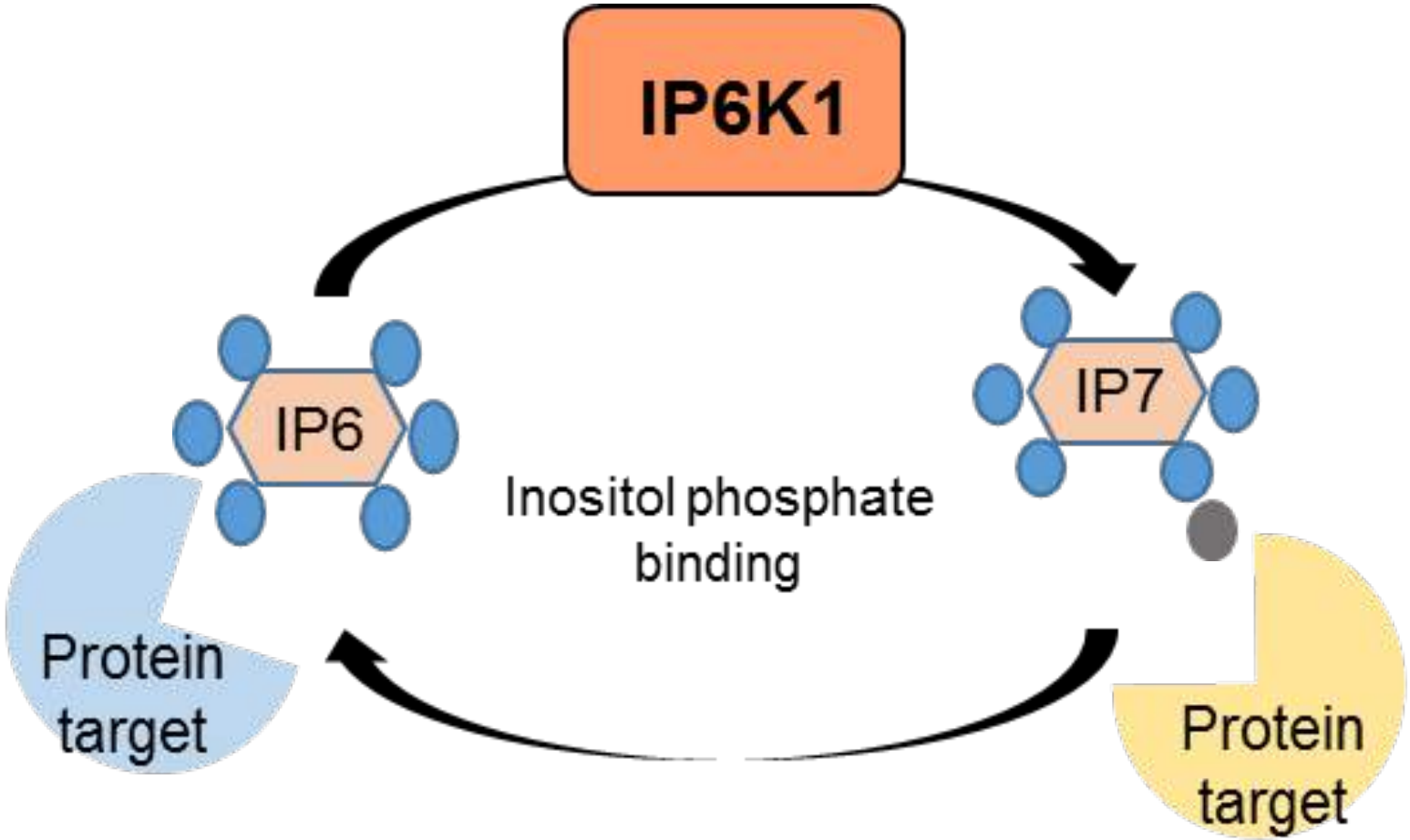
Myo-inositol and its derivatives in mammals





Chakraborty model slide, 2017.

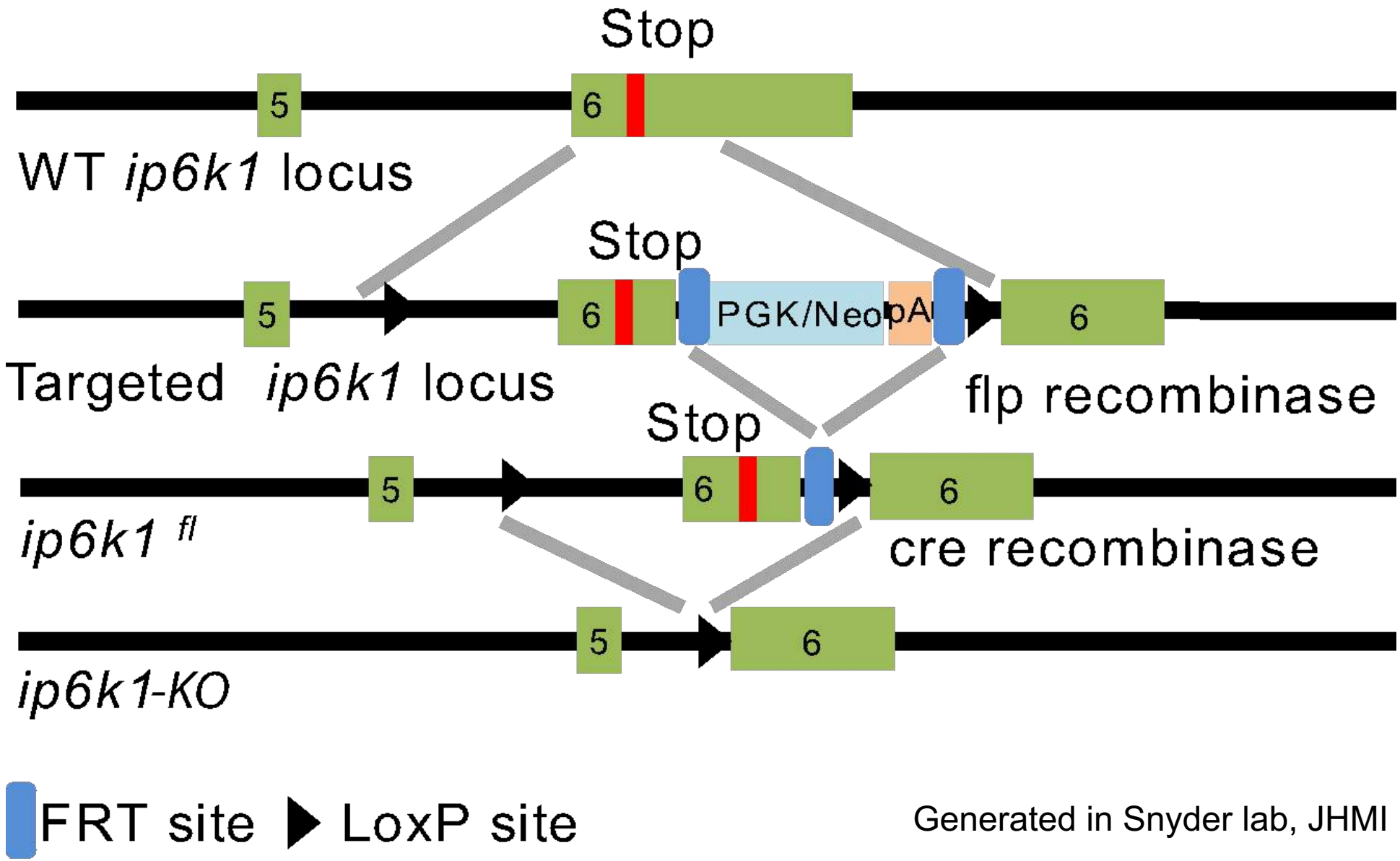
IP6K1 inhibits proteins that stimulate energy expenditure and insulin signaling



IP6K1 /5-IP7 promotes weight gain and insulin resistance

Chakraborty model slide, 2017.

Generation of whole-body *IP6K1* knockout (IP6K1-KO) mice

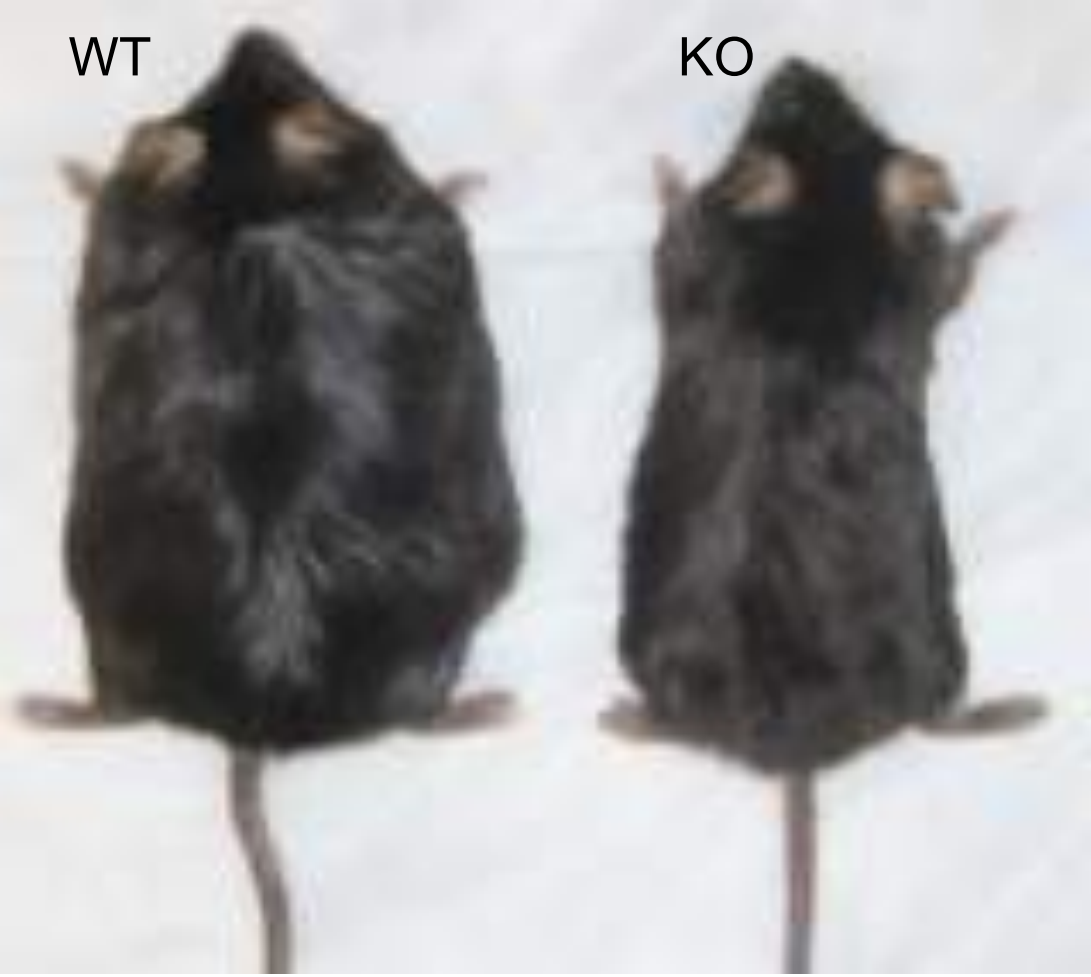


Generated in Snyder lab, JHMI

Breeding with mice that express the Cre recombinase under the control of the phosphoglycerate kinase 1 promoter in all tissues.

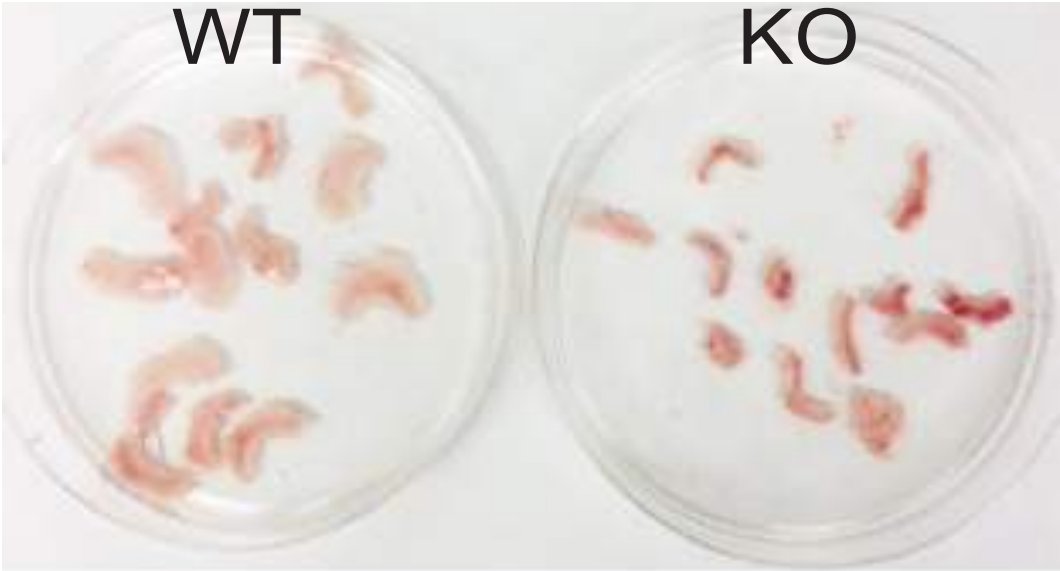
Whole-body *IP6K1* deletion protects mice from high fat diet induced obesity and insulin resistance

High fat diet (HFD: 60% Kcal fat): to 8-wks old mice for 8-wks.



Chakraborty et al. *Cell.* 2010, 143, 897-910.

White adipose tissue of global IP6K1-KO mice appears brown



Ambient temperature: 23 degree

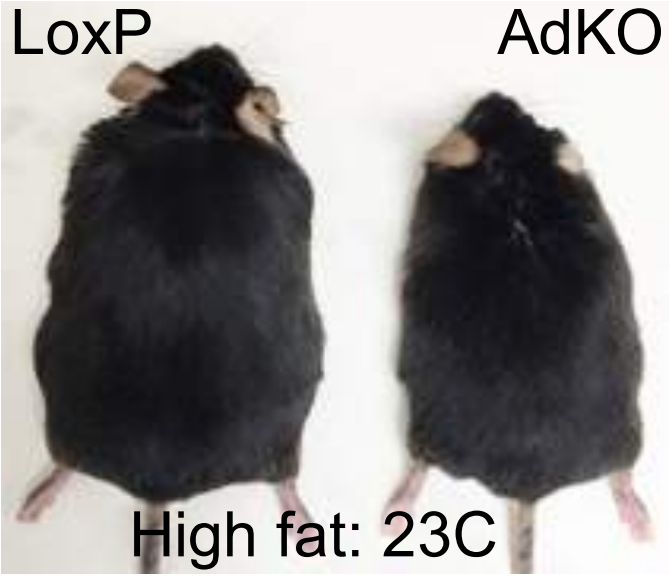
Chow; IWAT

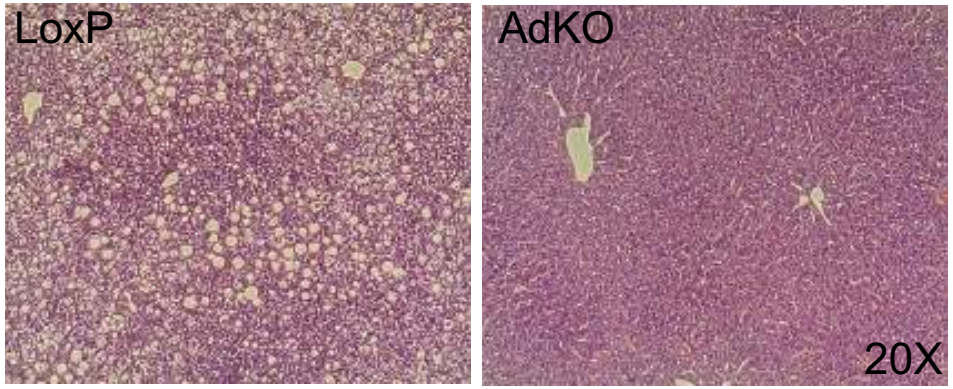
Inguinal white adipose tissue (IWAT)

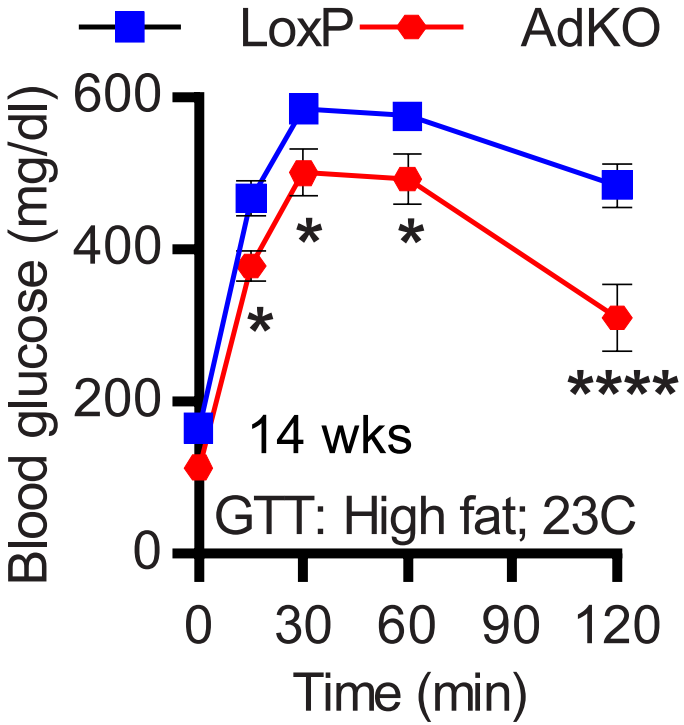
Zhu et al. *Mol. Metab.* (2017), 6, 73-85.

Generation of adipocyte-specific IP6K1-KO (ADKO) Mice

AdKO mice are also protected from obesity and insulin resistance





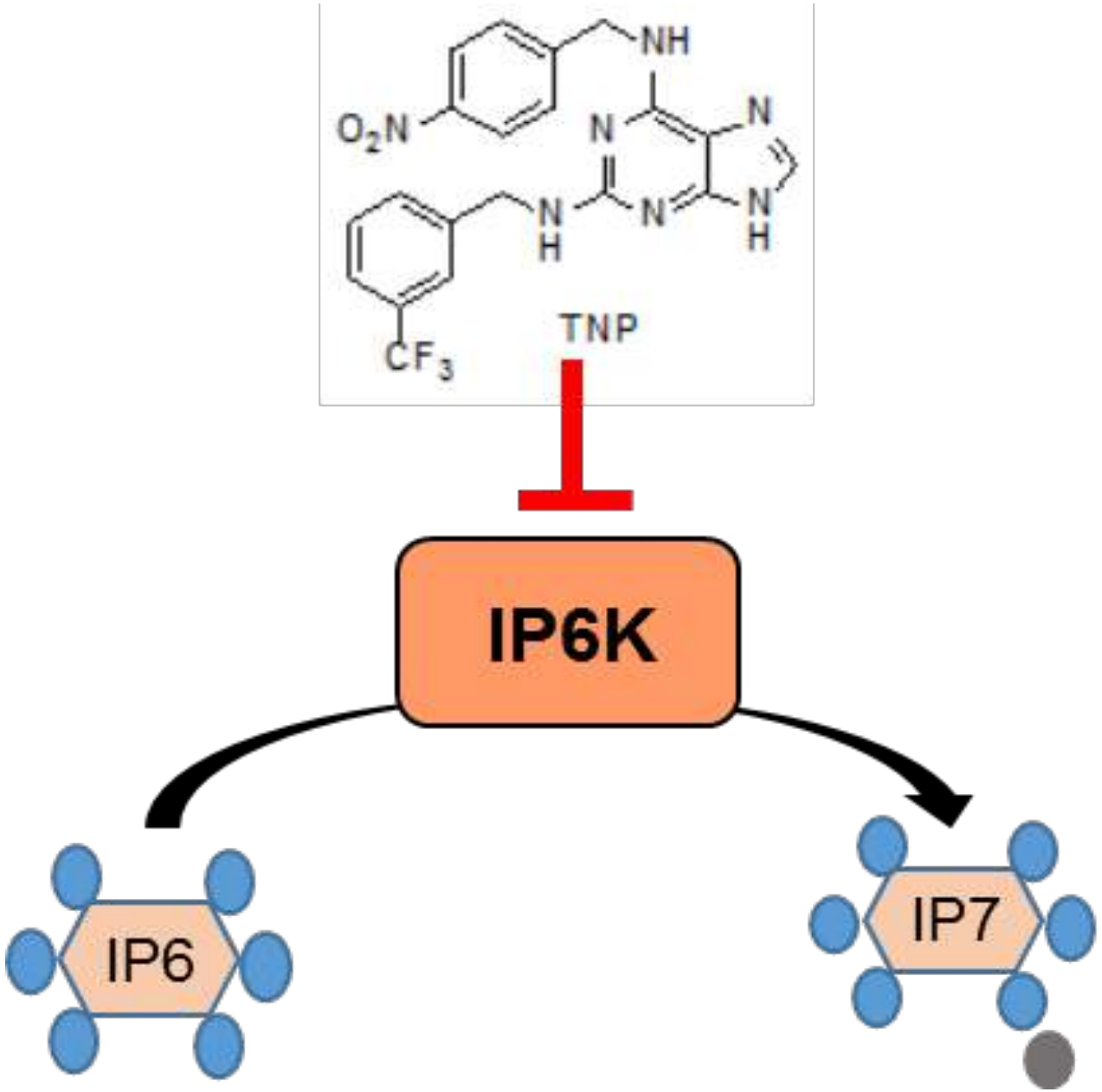


IP6K1: A genetic target in obesity and diabetes

Is IP6K1 a pharmacologic target in obesity and diabetes?

Zhu et al. *J. Clin. Invest.* (2016), 126, 4273-4288.

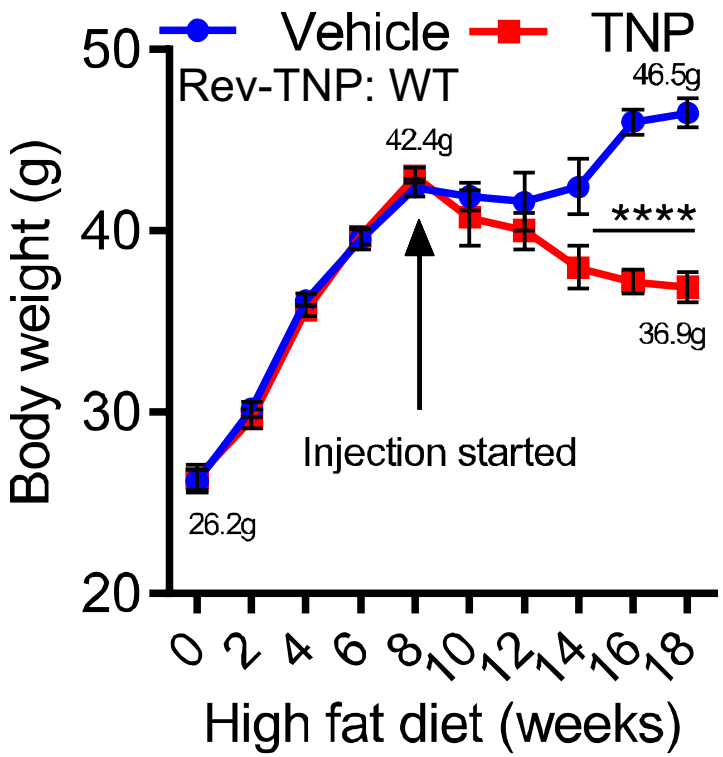
IP6K1: A pharmacologic target in obesity and diabetes?

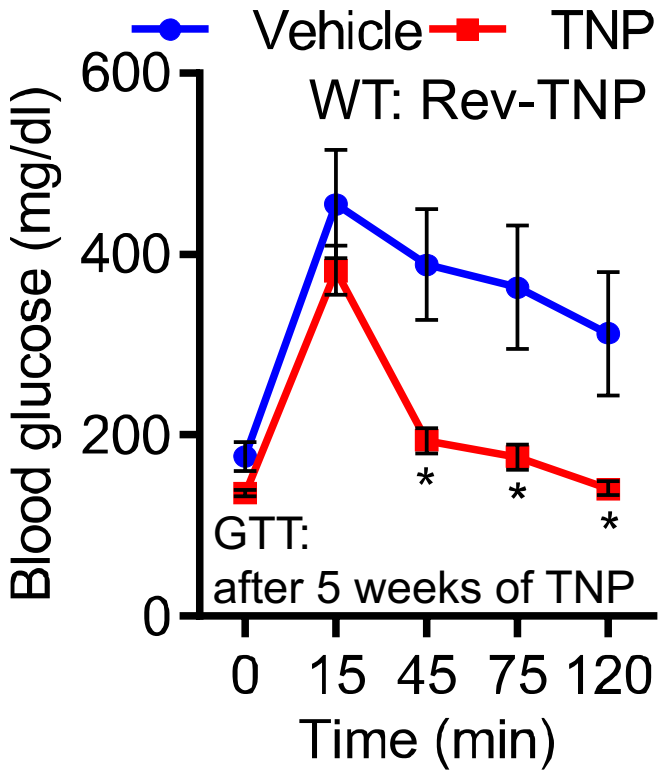


Padmanabhan et al. JBC, 2009, 284, 10571-82.

Pharmacologic inhibition of IP6Ks ameliorates obesity and insulin resistance in mice

*TNP dose: 10 mg/kg daily (i.p.) for 10-weeks in DIO mice.





Ghoshal et al. *Mol Metab.* 2016, 5, 903-17.

Summary

IP6K1-KO mouse is a novel anti-obesity/anti-diabetic mouse model.

IP6K1 inhibits energy expenditure in the adipose tissue, by reducing adipocyte browning.

IP6K1 promotes diet (and age) induced insulin resistance.

Pharmacologic inhibition of IP6Ks ameliorate diet induced obesity and insulin resistance.

Inositol Pyrophosphates Inhibit Akt Signaling, Thereby Regulating Insulin Sensitivity and Weight Gain

Cell

Anutosh Chakraborty,[1] Michael A. Koldobskiy,[1] Nicholas T. Bello,[2] Micah Maxwell,[1] James J. Potter,[3] Krishna R. Juluri,[1] David Maag,[1] Seyun Kim,[1] Alex S. Huang,[1] Megan J. Dailey,[2] Masoumeh Saleh,[1] Adele M. Snowman,[1] Timothy H. Moran,[2] Esteban Mezey,[3] and Solomon H. Snyder[1,2,4,*]
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[2]Department of Psychiatry and Behavioral Sciences
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[4]Department of Pharmacology and Molecular Sciences
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DOI 10.1016/j.cell.2010.11.032

TNP [N2-(m-Trifluorobenzyl), N6-(p-nitrobenzyl) purine] ameliorates diet induced obesity and insulin resistance *via* inhibition of the IP6K1 pathway

MOLECULAR METABOLISM

Sarbani Ghoshal[1], Qingzhang Zhu[1], Alice Asteian[2,5], Hua Lin[2], Haifei Xu[3], Glen Ernst[4], James C. Barrow[4], Baoji Xu[3], Michael D. Cameron[2], Theodore M. Kamenecka[2], Anutosh Chakraborty[1,*]

The Journal of Clinical Investigation

RESEARCH ARTICLE

Adipocyte-specific deletion of *Ip6k1* reduces diet-induced obesity by enhancing AMPK-mediated thermogenesis

Qingzhang Zhu,[1] Sarbani Ghoshal,[1] Ana Rodrigues,[1] Su Gao,[1] Alice Asterian,[2] Theodore M. Kamenecka,[2] James C. Barrow,[3] and Anutosh Chakraborty[1]

[1]Department of Metabolism and Aging, The Scripps Research Institute, Jupiter, Florida, USA. [2]Department of Molecular Therapeutics, The Scripps Research Institute, Jupiter, Florida, USA.

[3]Drug Discovery Division, Lieber Institute for Brain Development, Baltimore, Maryland, USA.

Global IP6K1 deletion enhances temperature modulated energy expenditure which reduces carbohydrate and fat induced weight gain

MOLECULAR METABOLISM

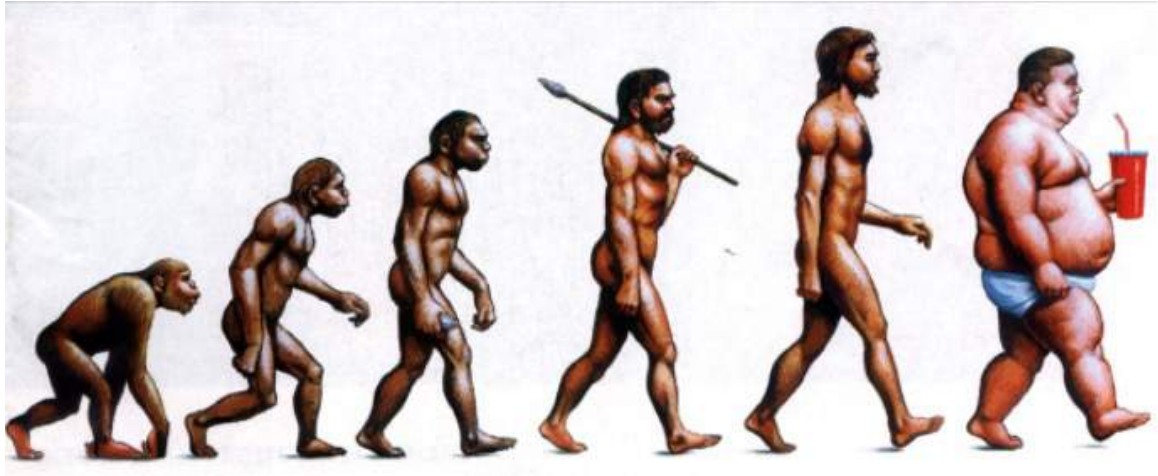
Qingzhang Zhu[1], Sarbani Ghoshal[1], Richa Tyagi[2], Anutosh Chakraborty[1,*]

Science Signaling

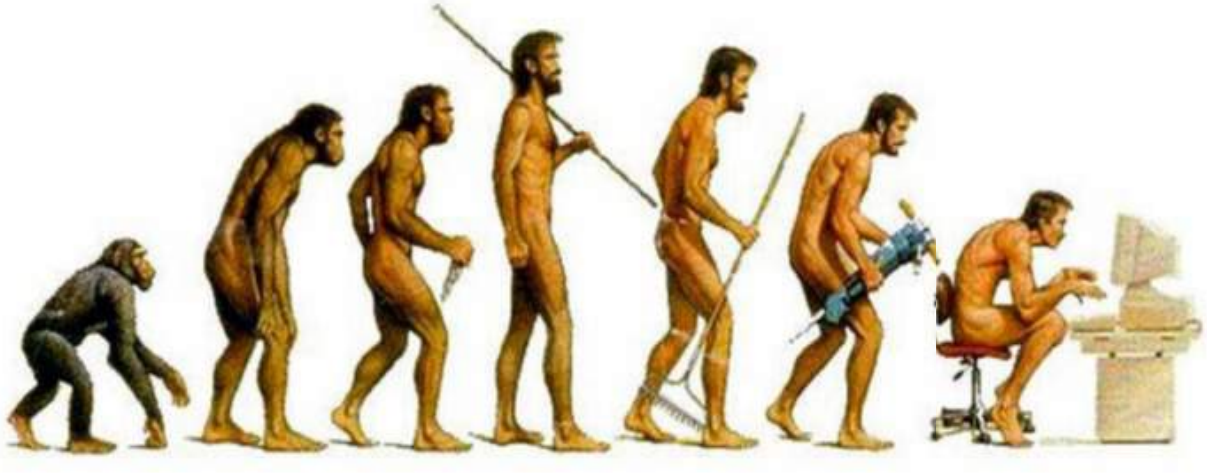
AAAS

` **Inositol Pyrophosphates as Mammalian Cell Signals**
Anutosh Chakraborty, Seyun Kim and Solomon H. Snyder (30 August 2011)
Science Signaling **4** (188), re1. [DOI: 10.1126/scisignal.2001958]

Obesity and T2D are diseases of modern era

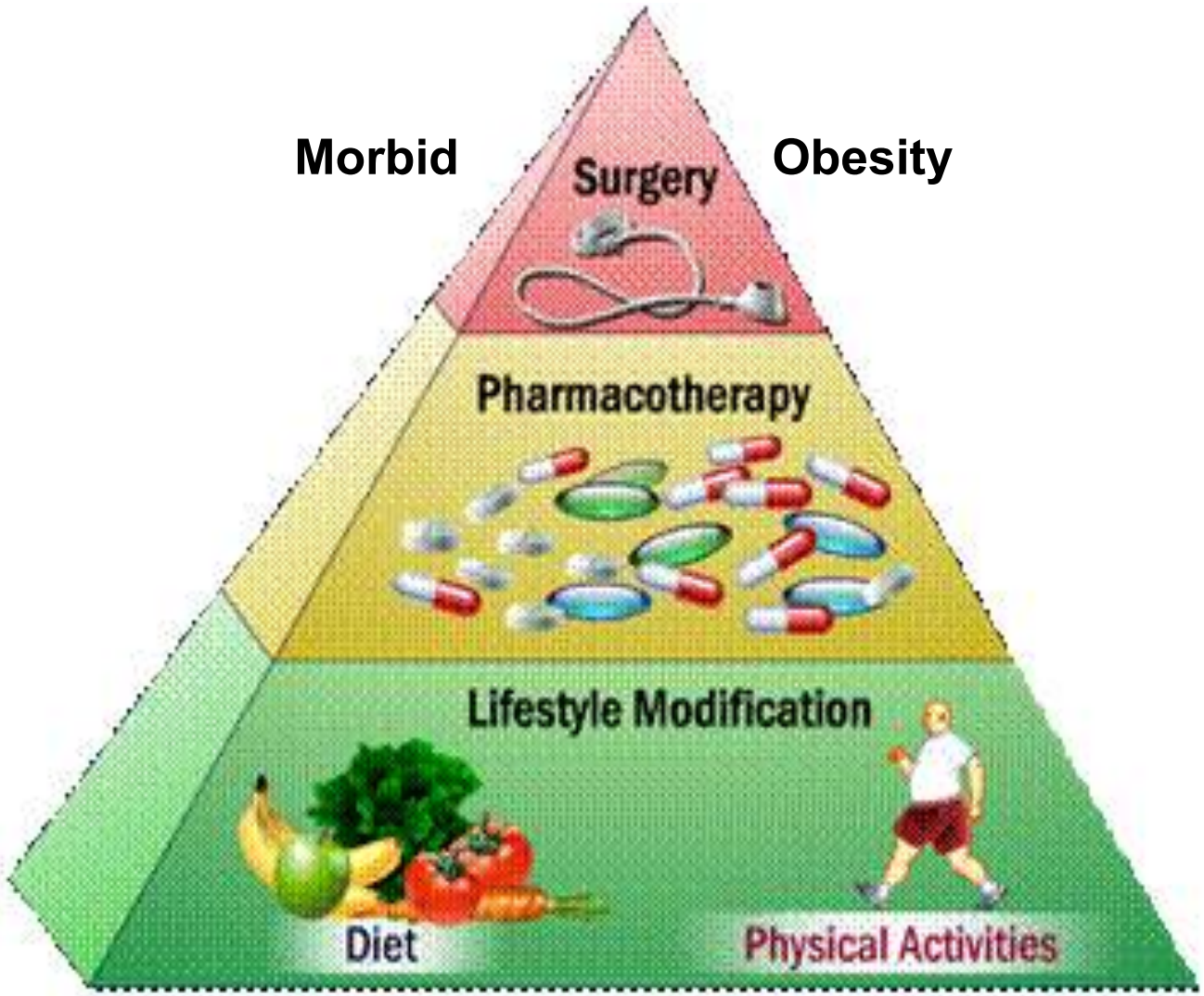


http://innerwestcrossfit.com/2011/07/tuesday-19711/evolution-of-obesity/



http://www.badgeronline.co.uk/the-stone-age-recipe/

Lifestyle management is essential, yet at times, not sufficient to treat obesity

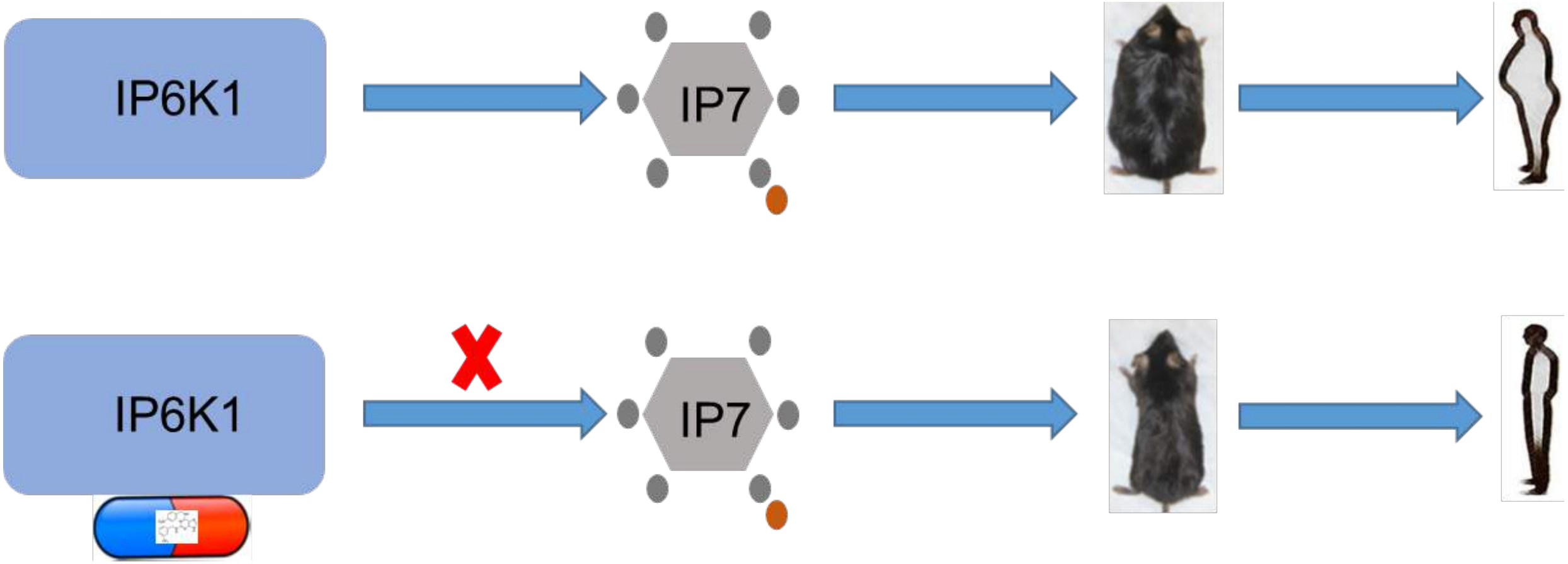


http://www.drsharma.ca/obesity-what-do-doctors-advise-patients-about-losing-weight.html

$3.7 billion is projected for a safe and effective anti-obesity drug.

Rodgers RJ et al. Disease Models and Mechanisms, 2012, 5, 621-626. Review.

Pharmacologic targeting of IP6K1 is expected to ameliorate obesity and diabetes in human subjects



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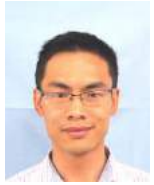
Patrick Griffin

Roy Smith

Andrew Butler

Department of Molecular Medicine



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NIDDK
NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

R01DK103746

Thank you!