

DIABETE ED OBESITÀ

SI PUÒ INVECE
TIRE LA ROTTÀ?



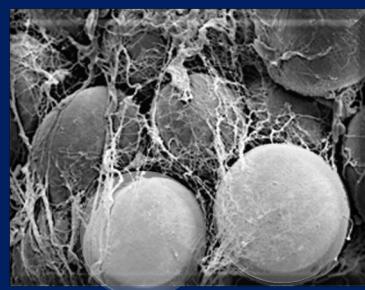
RUOLO DELLA TERMOGENESI ADATTATIVA NELLA PERDITA E RECUPERO DEL PESO



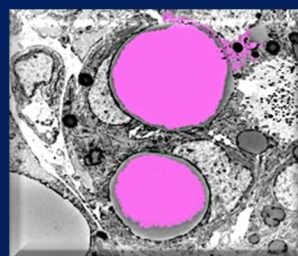
Saverio Cinti MD
Scientific Director of
Obesity Center
Marche Polytechnic University,
Ancona, Italy
Distinguished Emeritus Professor of
Bonn University
Affiliated Professor at Copenhagen
University

saverio.cinti@icloud.com

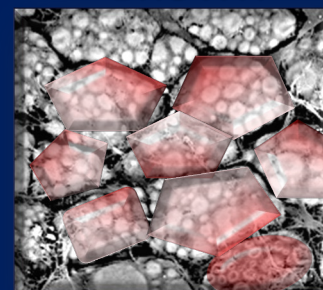
WHITE



PINK



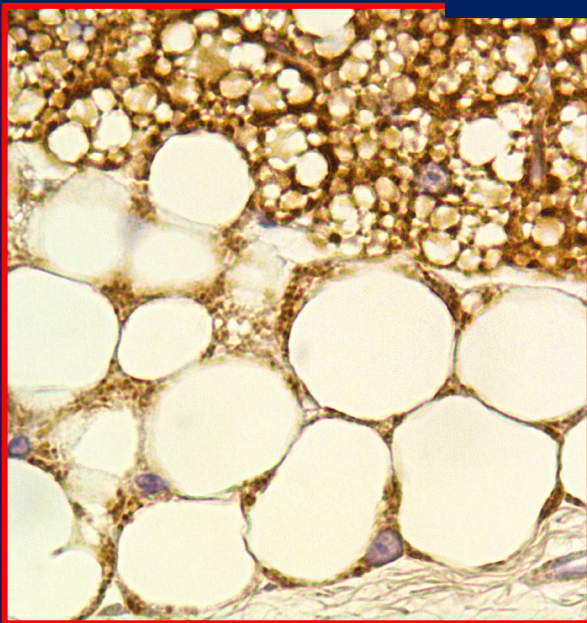
BROWN



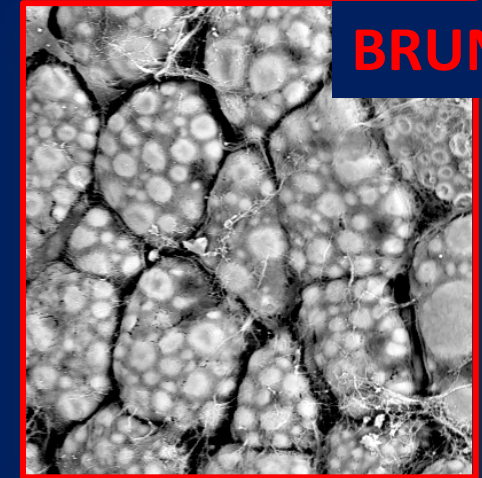
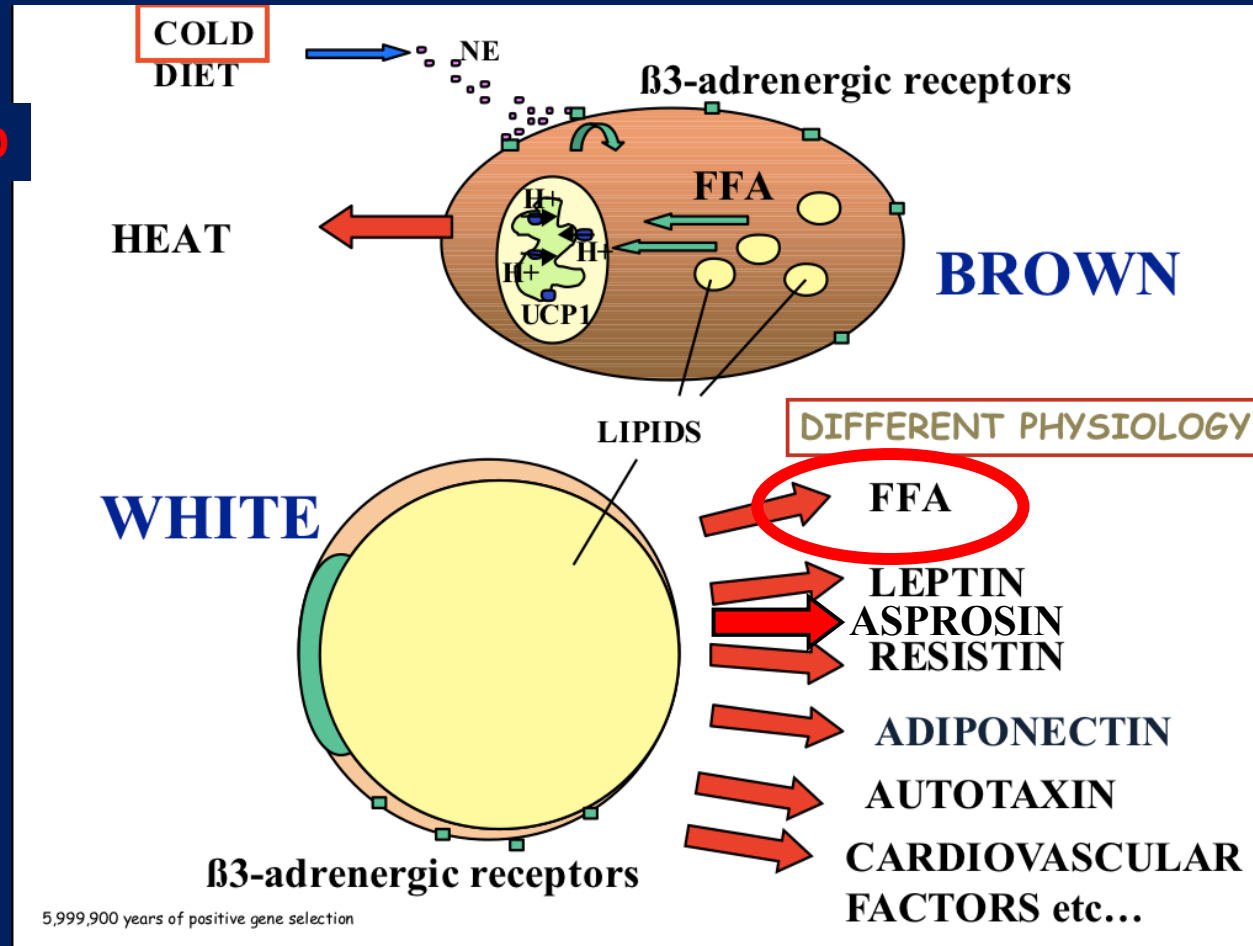
ADIPOCITI

MICROSCOPIA OTTICA

BRUNO

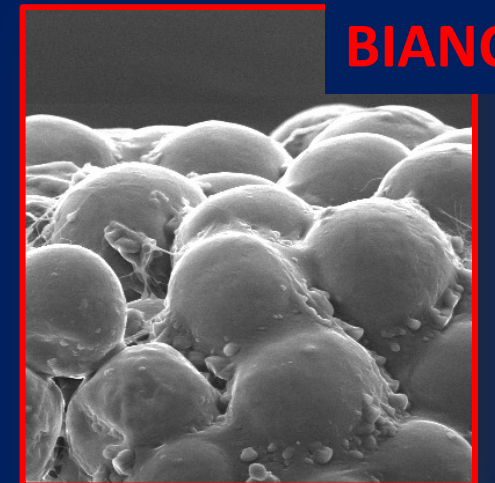


BIANCO



BRUNO

SEM



BIANCO

Cinti S
Obesity, T2 diabetes
and the Adipose Organ
Springer 2018

> Nature. 1994 Dec 1;372(6505):425-32. doi: 10.1038/372425a0.

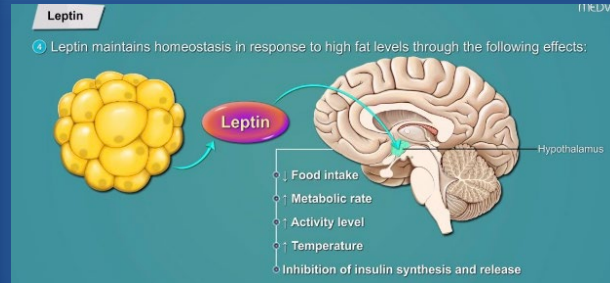
Positional cloning of the mouse obese gene and its human homologue

Y Zhang¹, R Proenca, M Maffei, M Barone, L Leopold, J M Friedman

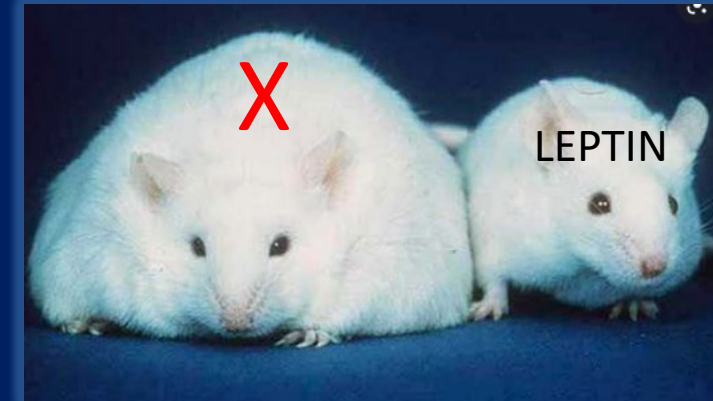
Affiliations + expand

PMID: 7984236 DOI: 10.1038/372425a0

1994

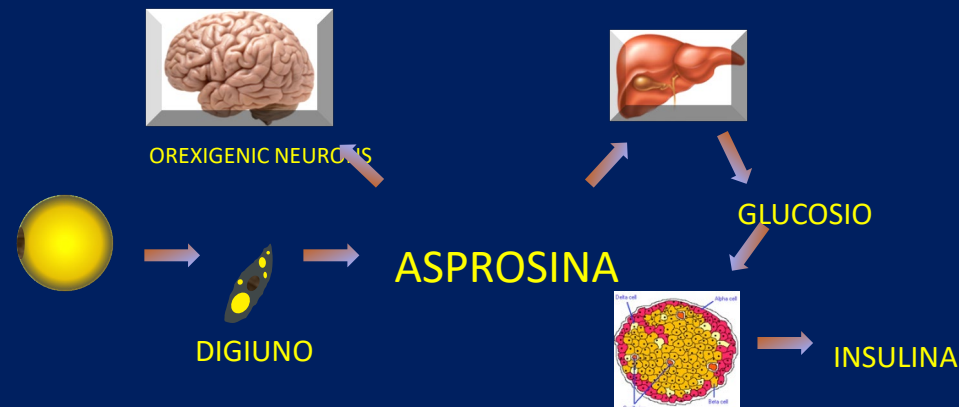


WAT physiology

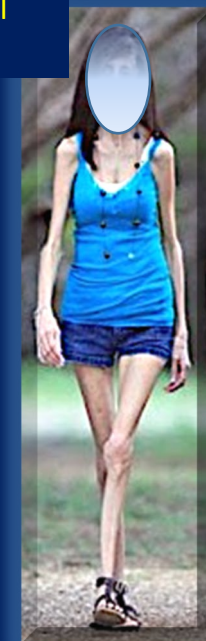


J. FRIEDMAN

2016



LIPODISTROFIA
DOVUTA A
MANCANZA DI
ASPROSIN



Cell. 2016 Apr 21;165(3):566-79. doi: 10.1016/j.cell.2016.02.063. Epub 2016 Apr 14.

Asprosin, a Fasting-Induced Glucogenic Protein Hormone.

Romere C¹, Duerschmid C¹, Bournat J¹, Constable P¹, Jain M², Xia F², Saha PK¹, Del Solar M², LeMaire SA⁵, Coselli JS⁵, Milewicz DM⁶, Sutton VR², Butte NF⁴, Moore DD¹, Chopra AR⁷.

Nat Med. 2017 Dec;23(12):1444-1453. doi: 10.1038/nm.4432. Epub 2017 Nov 6.

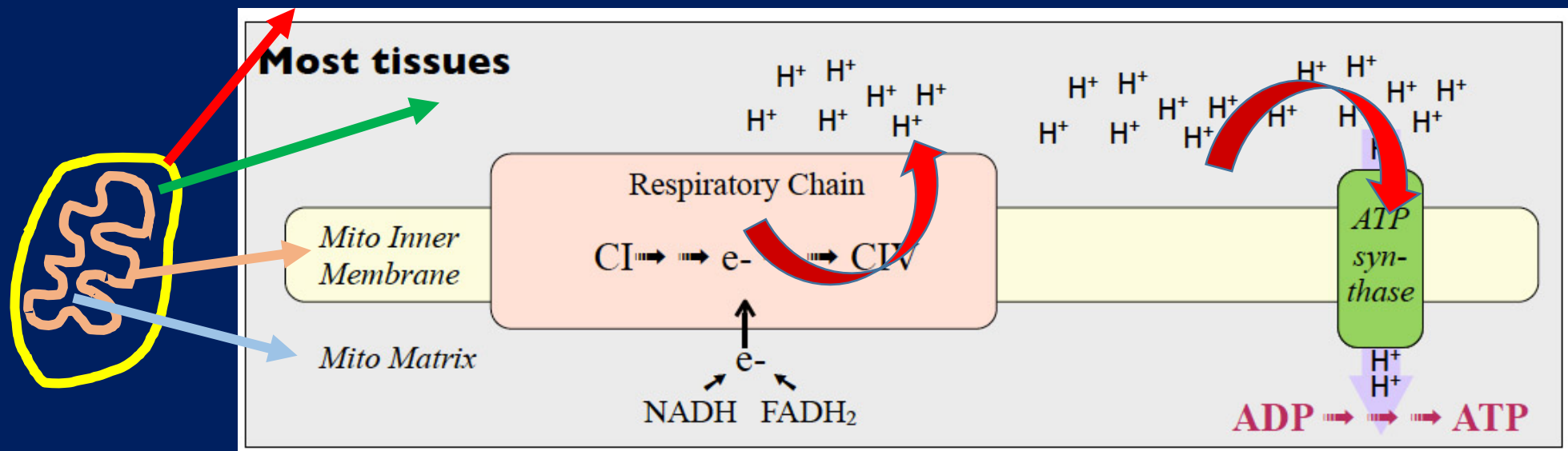
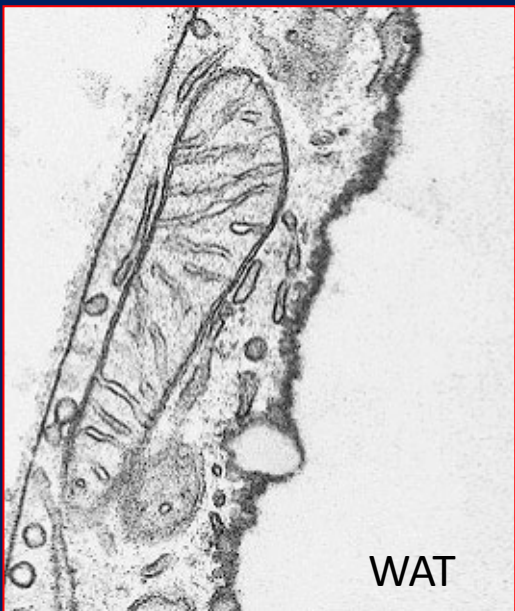
Asprosin is a centrally acting orexigenic hormone.

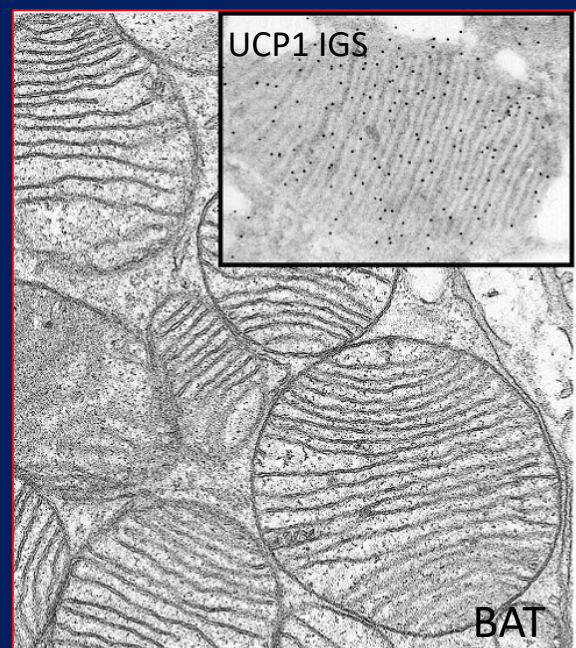
Duerschmid C¹, He Y², Wang C², Li C^{3,4}, Bournat JC¹, Romere C¹, Saha PK¹, Lee DM⁷, Sutton VR⁸, Moore DD¹, Butte NF², Krashes MJ^{3,4}, Xu Y^{1,2}, Chopra AR^{1,8}.



A. CHOPRA

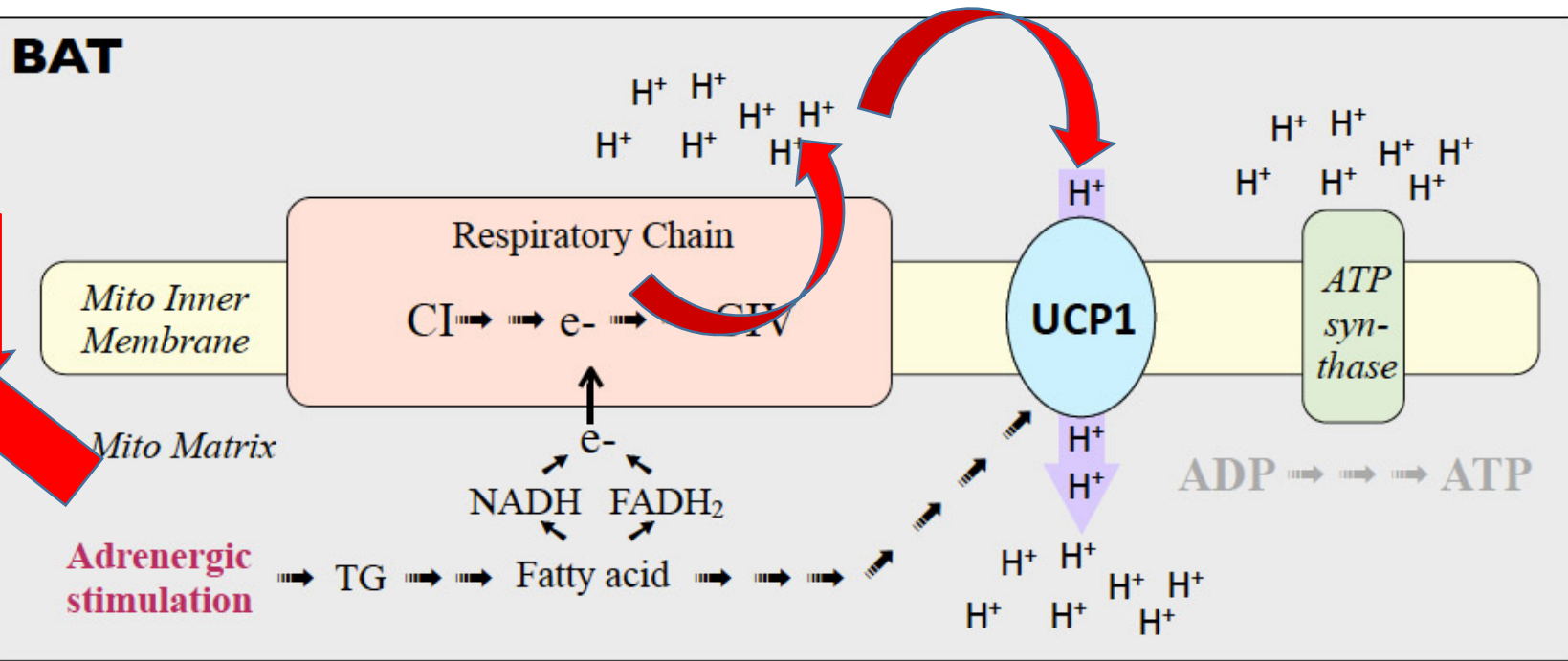
IL TESSUTO ADIPOSO BRUNO (BAT)



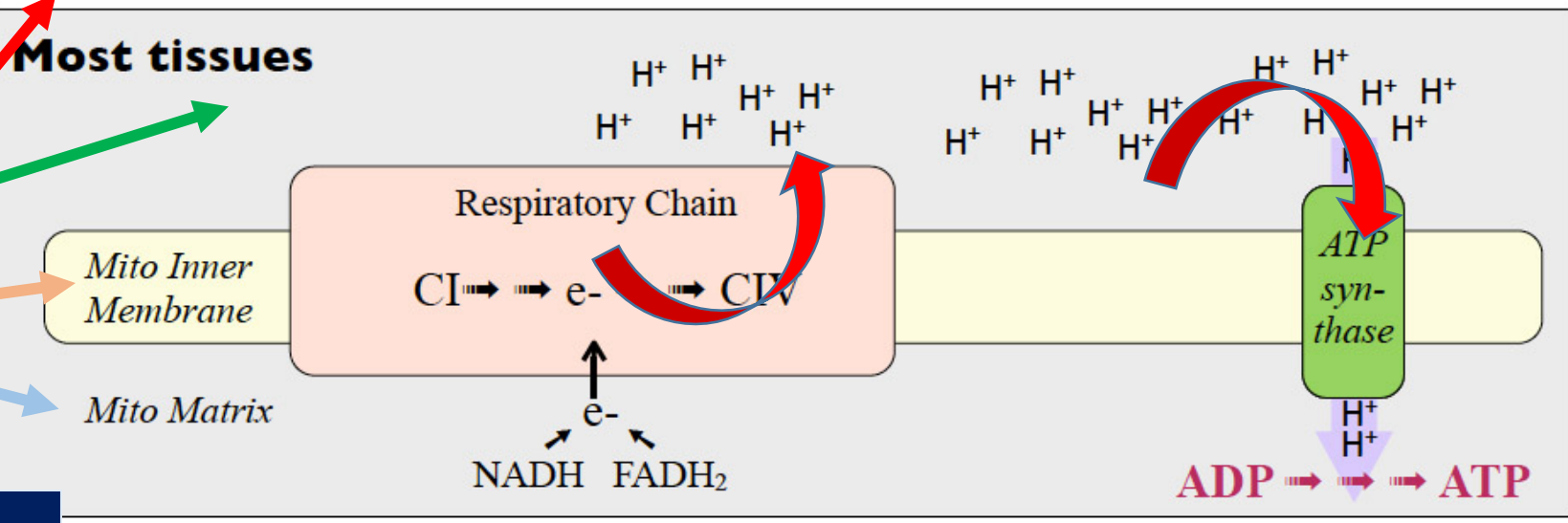


HEAT

BAT



Most tissues

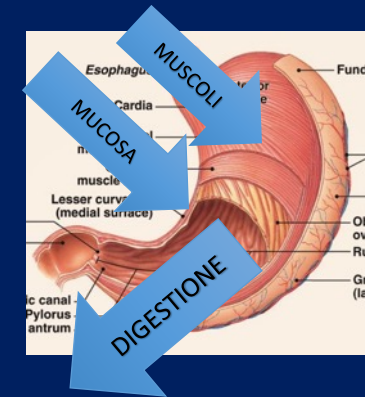


Cinti S
Obesity, T2 diabetes
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Springer 2018

WAT

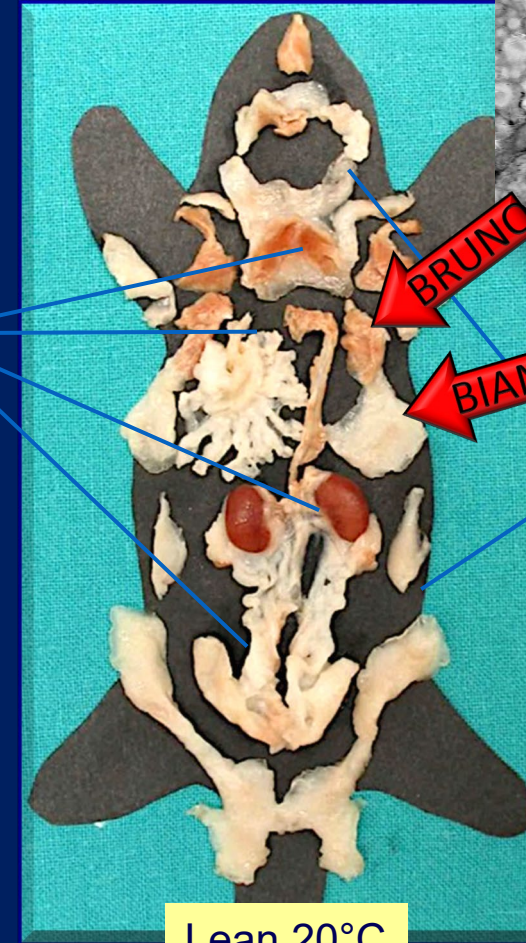
DEFINIZIONE DI ORGANO

STRUTTURA DISSECABILE,
FORMATA DA ALMENO
DUE TESSUTI DIVERSI
RESPONSABILI DI FUNZIONI DIVERSE
E COORDINATE CHE
CONVERGONO PER RAGGIUNGERE
UN SINGOLO RUOLO FINALISTICO

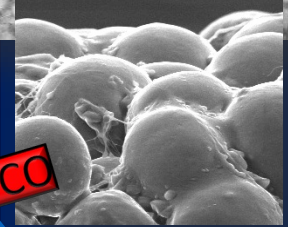
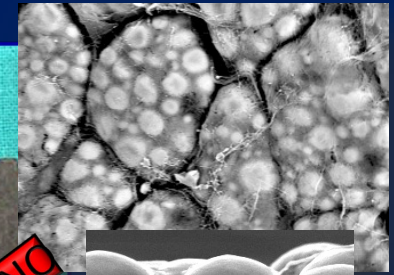


I TESSUTI ADIPOSI FORMANO UN ORGANO DISSECCABILE

visceral



Lean 20°C

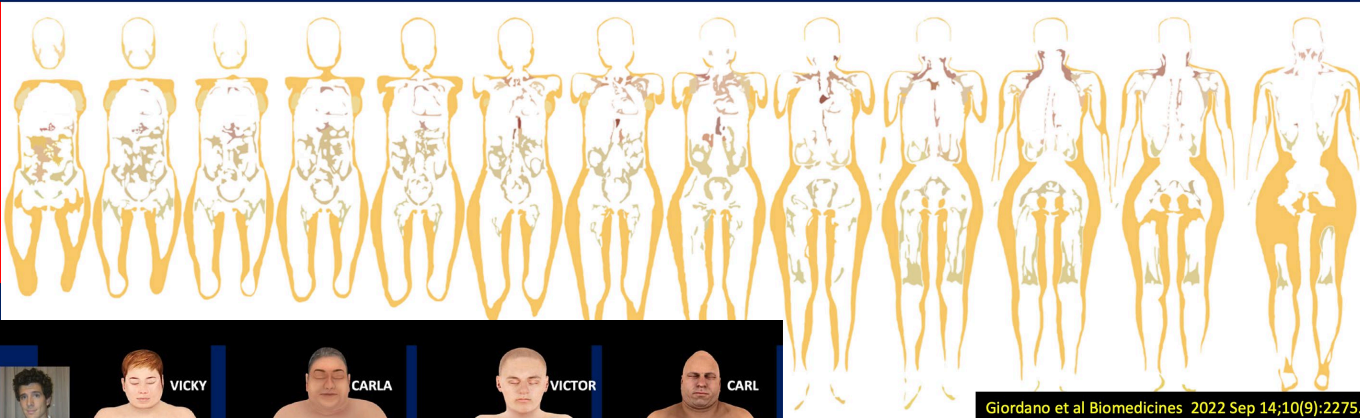
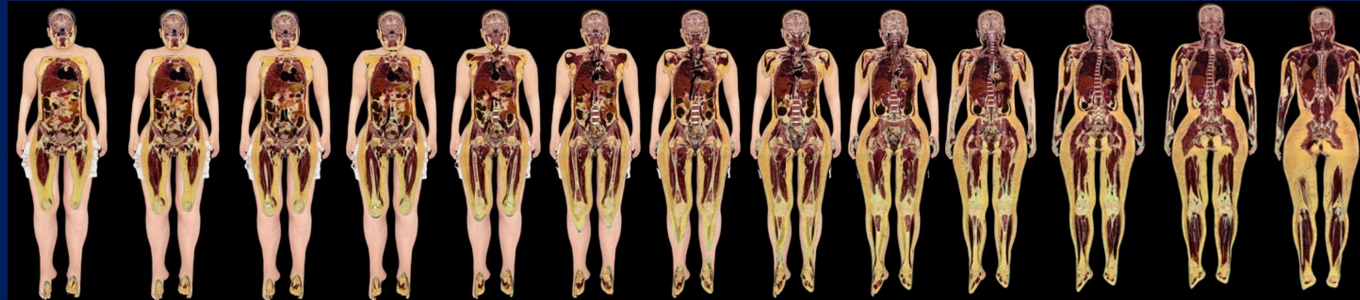


BRUNO

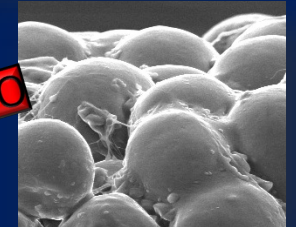
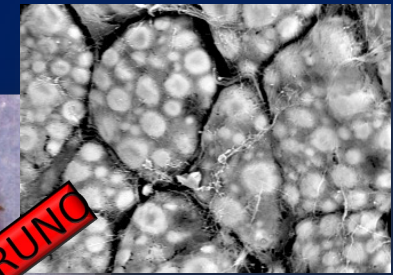
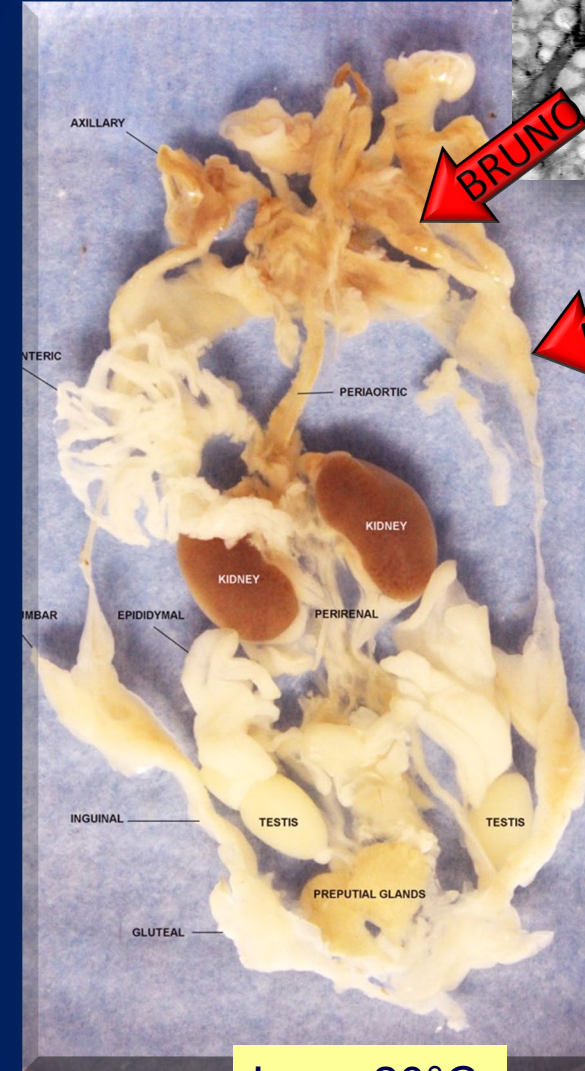
BIANCO

subcutaneous

S. Cinti World Congress on Obesity 1998 PARIS



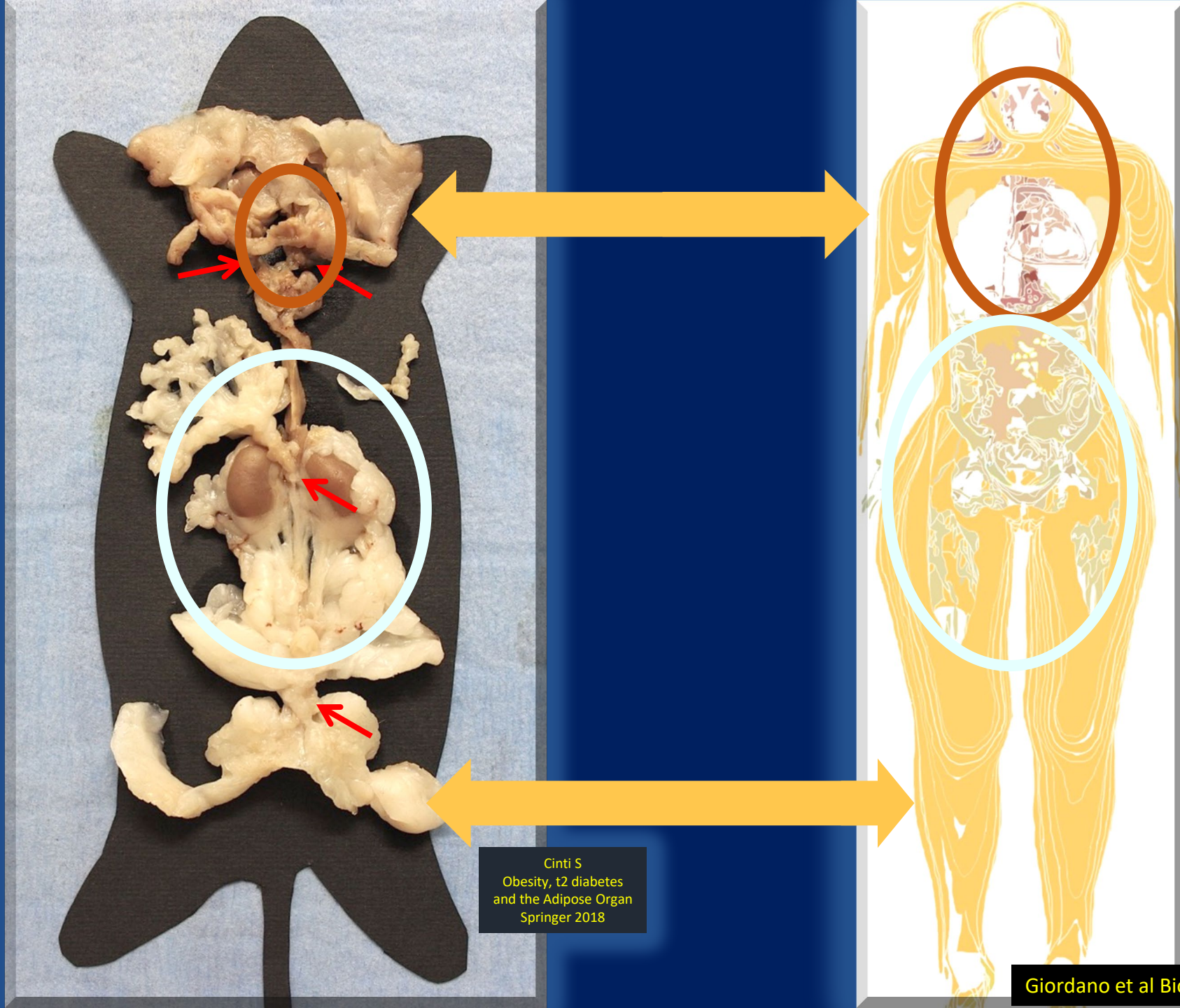
Giordano et al Biomedicines 2022 Sep 14;10(9):2275.



Lean 20°C

Giordano et al Biomedicines 2022 Sep 14

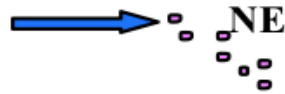
2D



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Springer 2018

Giordano et al Biomedicines 2022 Sep 14;10(9):2275.

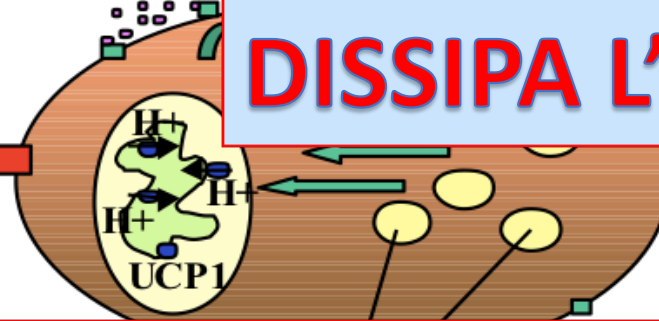
**COLD
DIET**



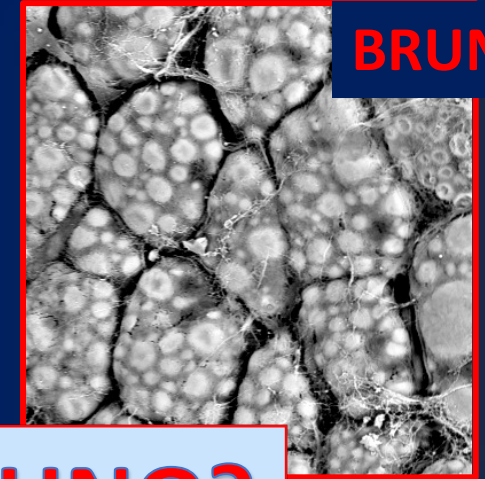
β 3-adrenergic receptors

DISSIPA L'ENERGIA

HEAT



BROWN



BRUNO

QUALE COOPERAZIONE TRA BIANCO E BRUNO?

WHITE

IMMAGAZZINA L'ENERGIA

β 3-adrenergic receptors



FFA



**LEPTIN
ADIPOCTIN**



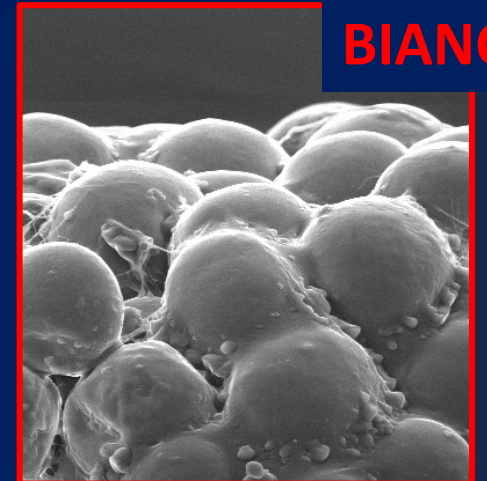
ADIPONECTIN



AUTOTAXIN



**CARDIOVASCULAR
FACTORS etc...**



BIANCO

5,999,900 years of positive gene selection

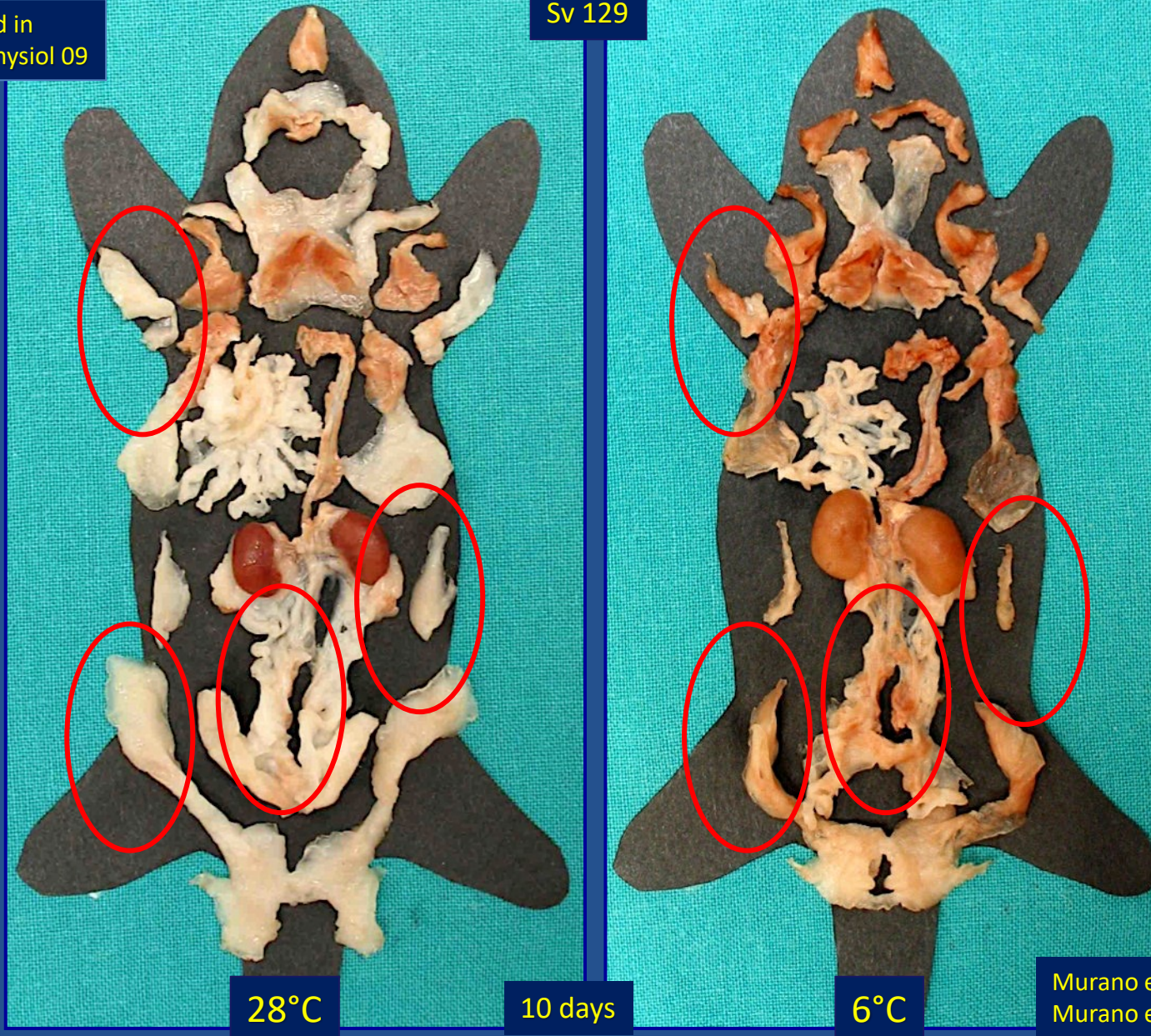
5,999,900 years of positive gene selection

Cinti S
Obesity, t2 diabetes
and the Adipose Organ
Springer 2018

L' ORGANO ADIPOSO E' PLASTICO....

Reviewed in
Cinti S Am J Physiol 09

Sv 129



Murano et al Adipocytes 05
Murano et al J Anatomy 2009

ACCLIMATATI AL CALDO:

12% (B6) vs 53 % (SV129)

$P < 0.007$

ADIPOCITI UCP1+

B6

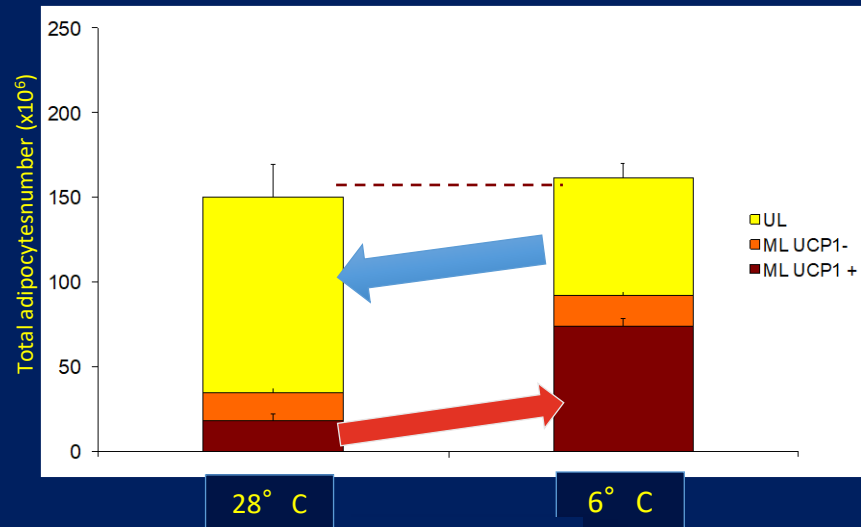
ACCLIMATATI AL FREDDO:

45% (B6) vs 60% (SV129)

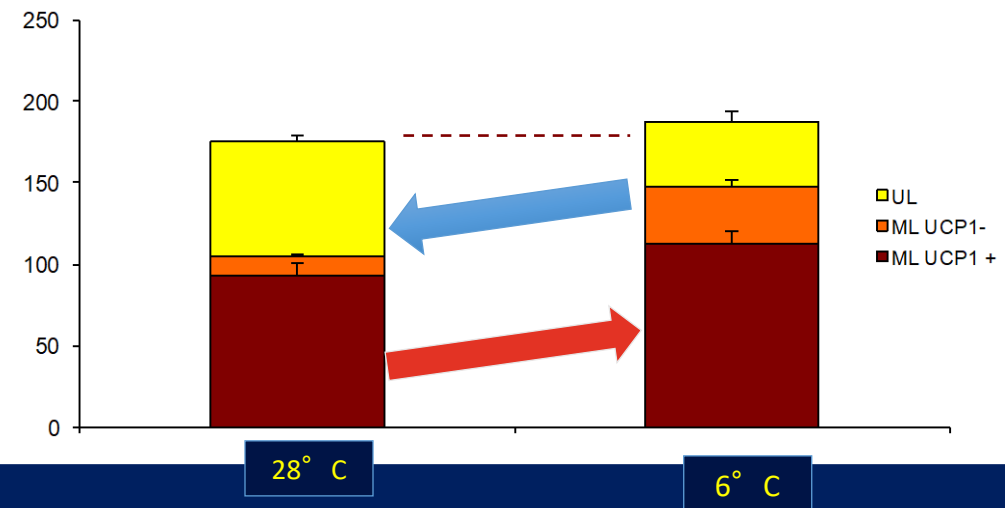
$p < 0.03$

ADIPOCITI UCP1+

SV129



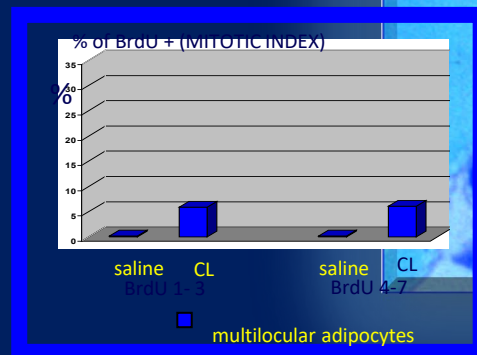
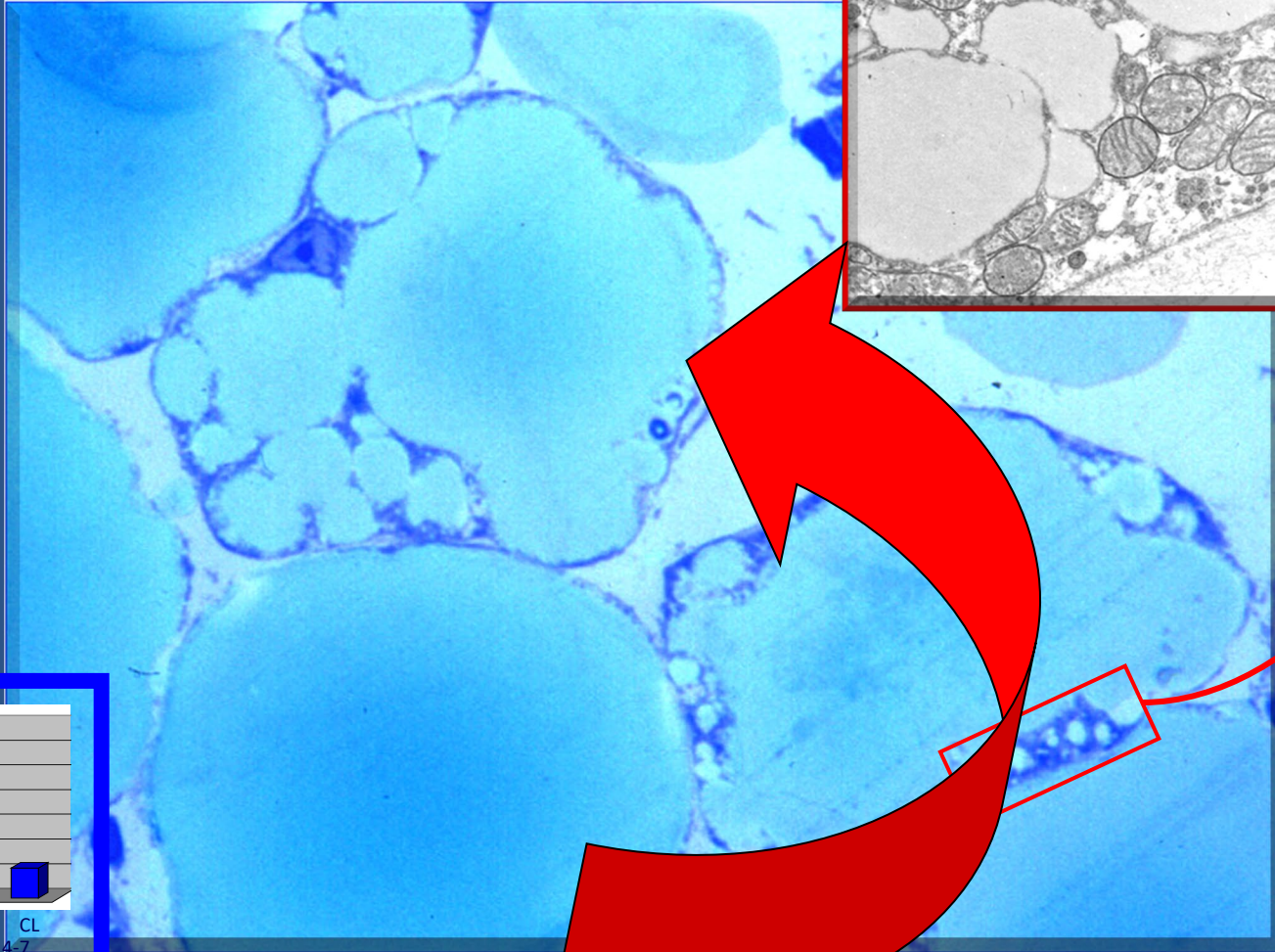
PRONO OBESITA'



RESISTENTE OBESITA'



...QUINDI, GLI ADIPOCITI POSSONO TRANSDIFFERENZIARE



CL 316,243 / 7days – RP 20w₅o rats

Himms-Hagen et al Am J Physiol 2000

The emergence of cold-induced brown adipocytes in mouse white fat depots is determined predominantly by white to brown adipocyte transdifferentiation

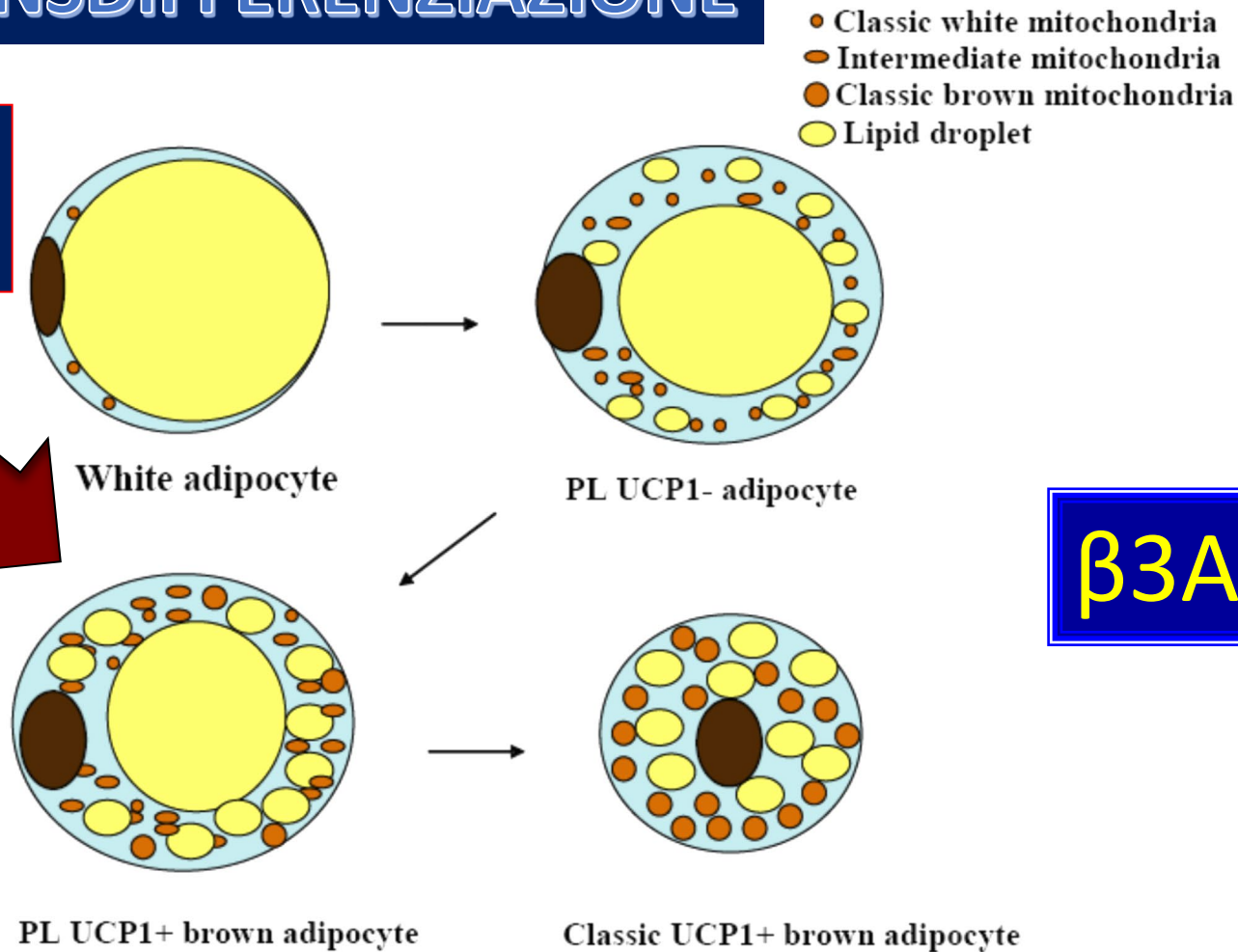
Barbatelli et al Am J Physiol EM. 2010

TRANSDIFFERENZIAZIONE

ADIPOCITI PAUCILOCLULARI UCP1+
SONO MARKERS DI
TRANSDIFFERENZIAZIONE



IHC UCP1



$\beta 3AR$

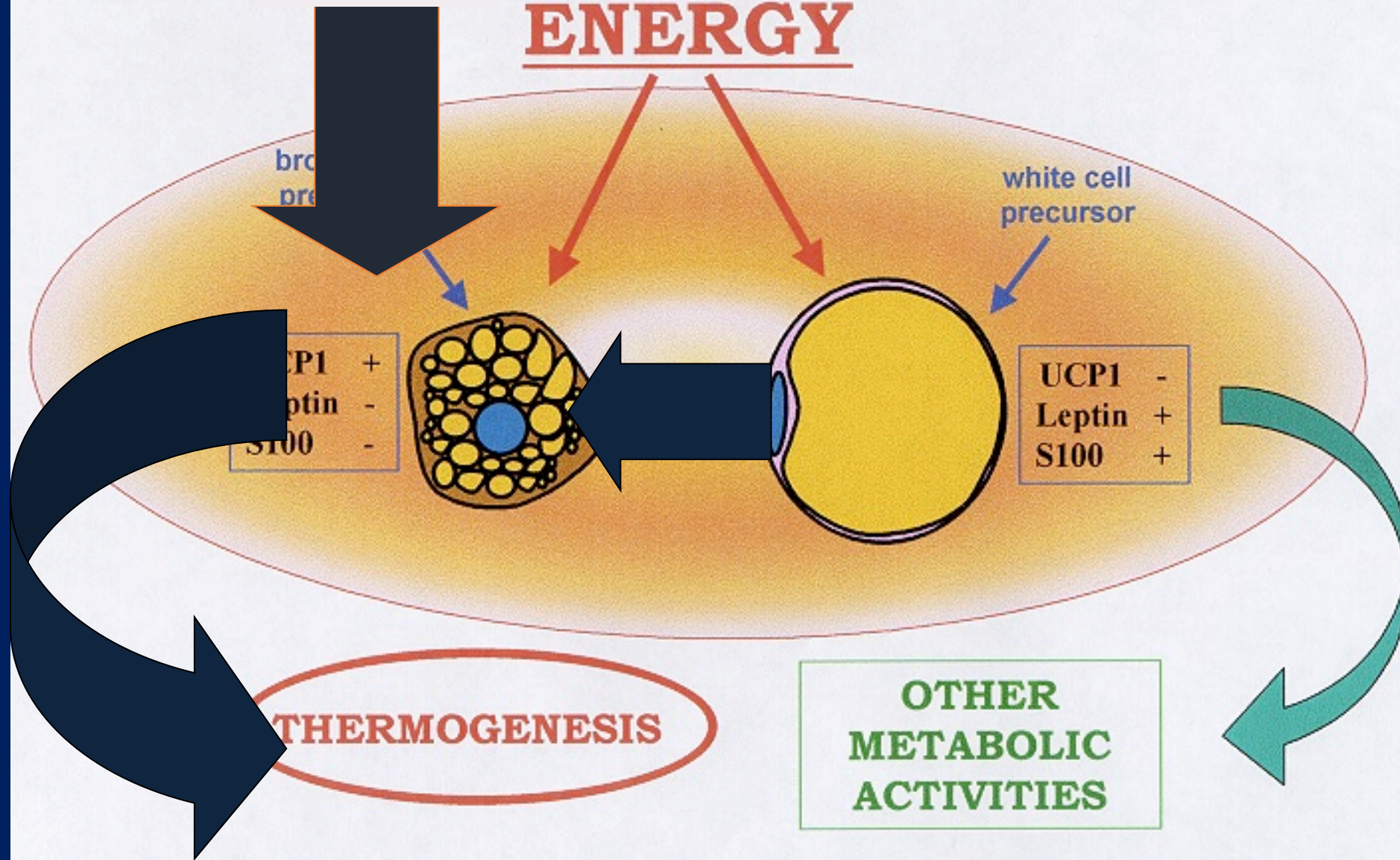
PERCHE' DUE TESSUTI DIVERSI (BIANCO E BRUNO),
CON RUOLI FUNZIONALI DIVERSI,
SONO CONTENUTI NELLO STESSO ORGANO (ORGANO ADIPOSO)?

STRUTTURA DISSECABILE,
FORMATA DA ALMENO
DUE TESSUTI DIVERSI
RESPONSABILI DI FUNZIONI DIVERSE
E COORDINATE CHE
CONVERGONO PER RAGGIUNGERE
UN SINGOLO RUOLO FINALISTICO

FREDDO
CRONICO

THE ADIPOSE ORGAN
S.Cinti 1999

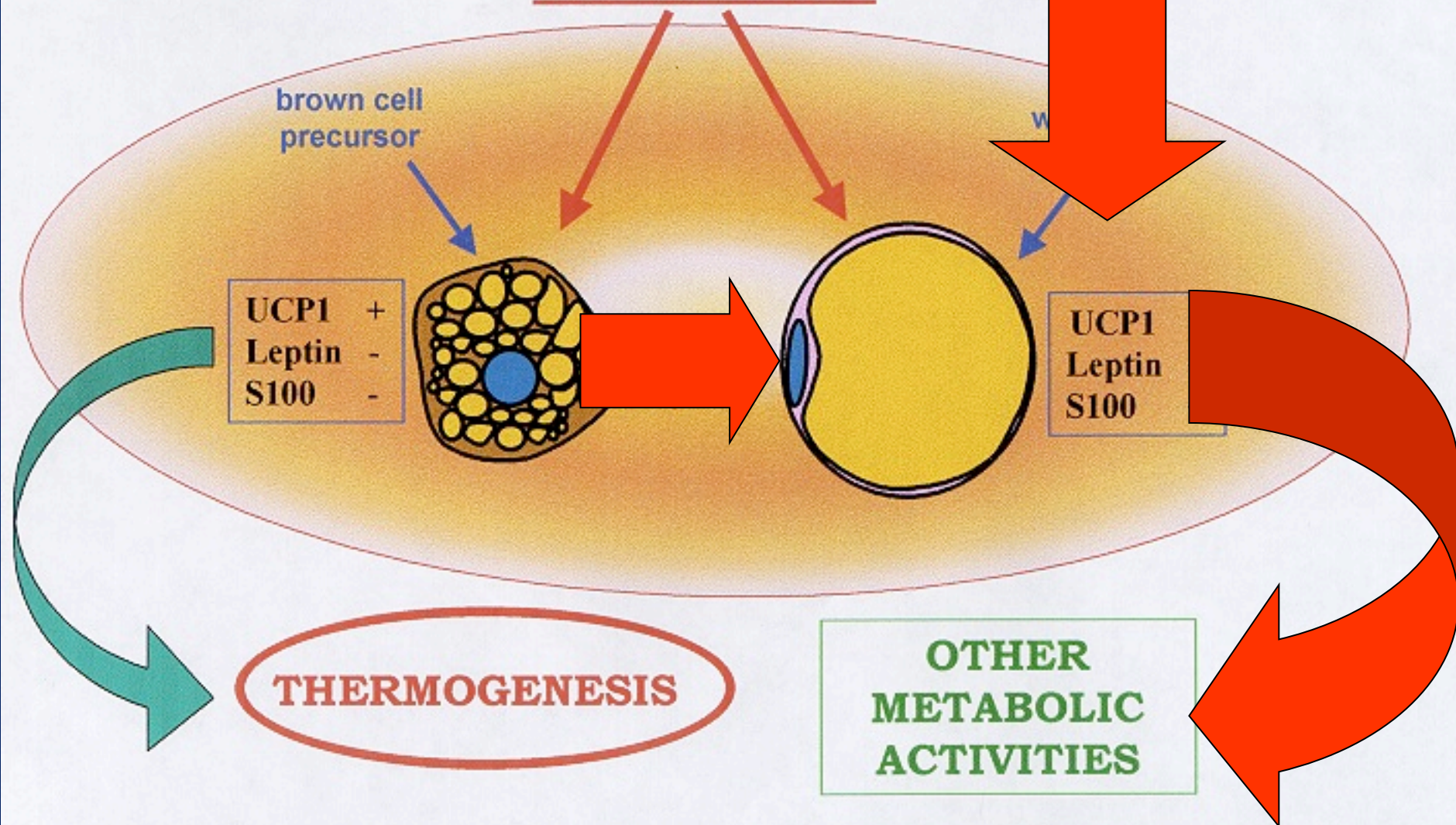
ENERGY



THE ADIPOSE ORGAN
S.Cinti 1999

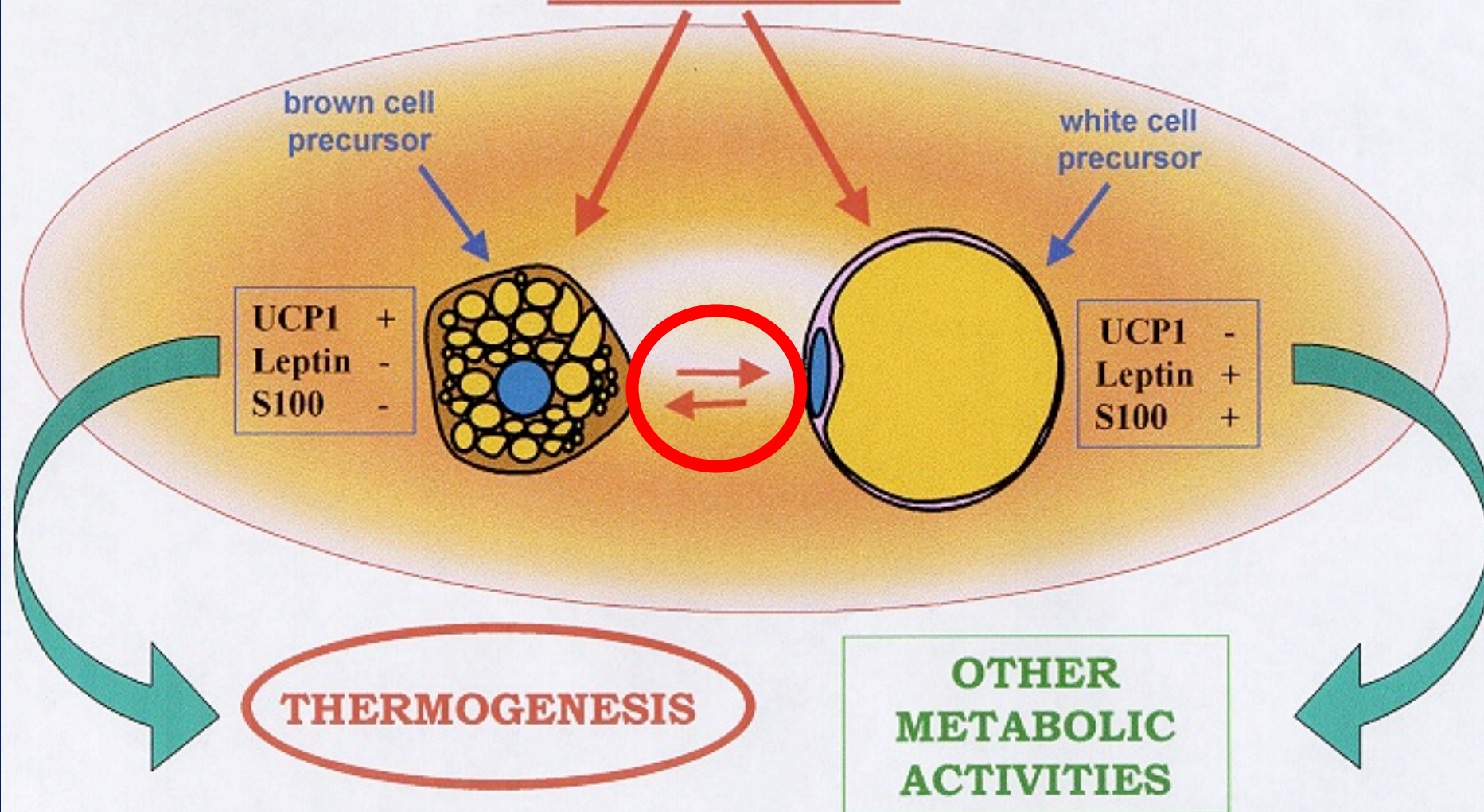
DIETA
OBESOGENA

ENERGY

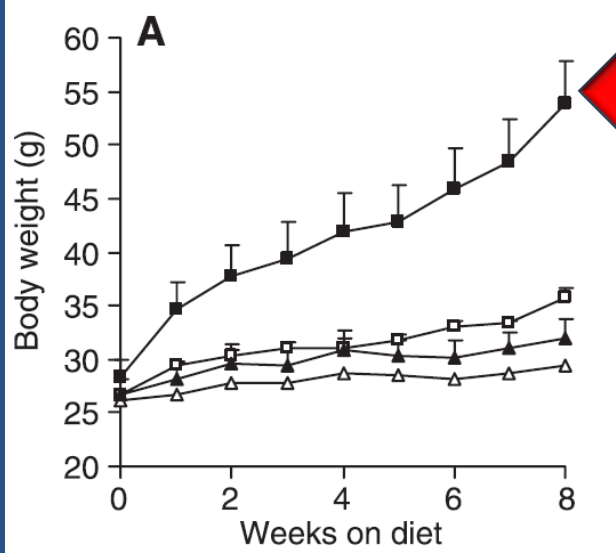


THE ADIPOSE ORGAN
S.Cinti 1999

ENERGY



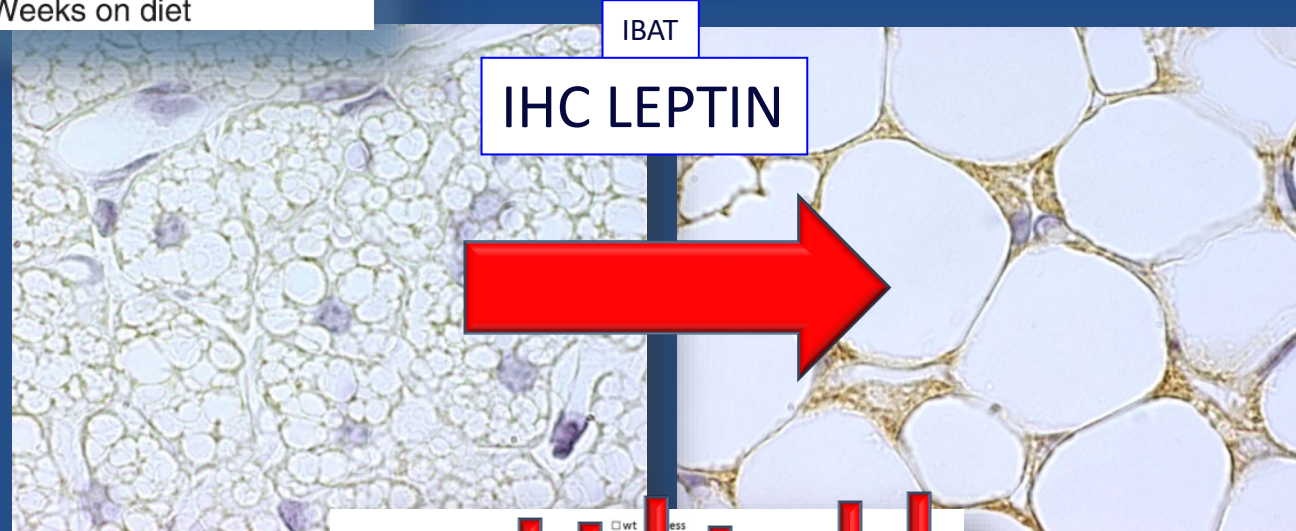
IMPORTANZA CLINICA?



IBAT Ablation Required for Diet-Induced Thermogenesis and Obesity Resistance

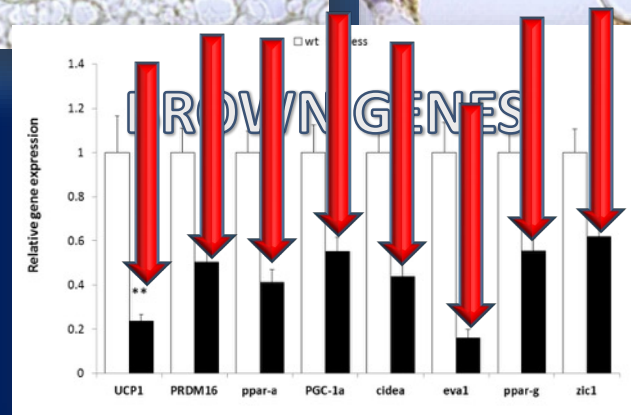
Eric S. Bachman,¹ Harveen Dhillon,¹ Chen-Yu Zhang,¹
Saverio Cinti,² Antonio C. Bianco,³ Brian K. Kobilka,⁴
Bradford B. Lowell^{1*}

Science 02



B. LOWELL

BRUNO IMPORTANTE
PER PREVENIRE L'OBESITA'

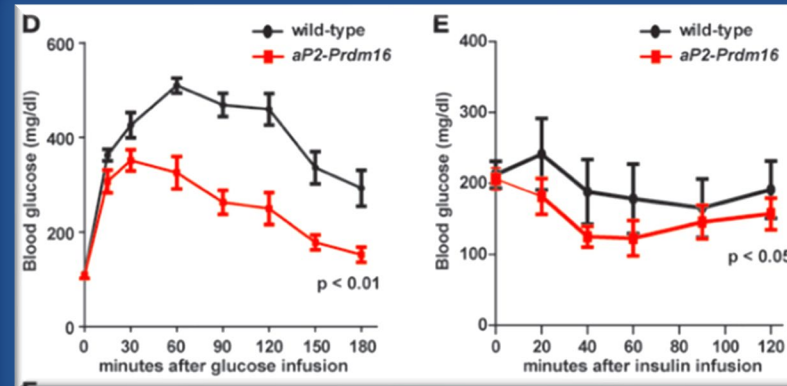
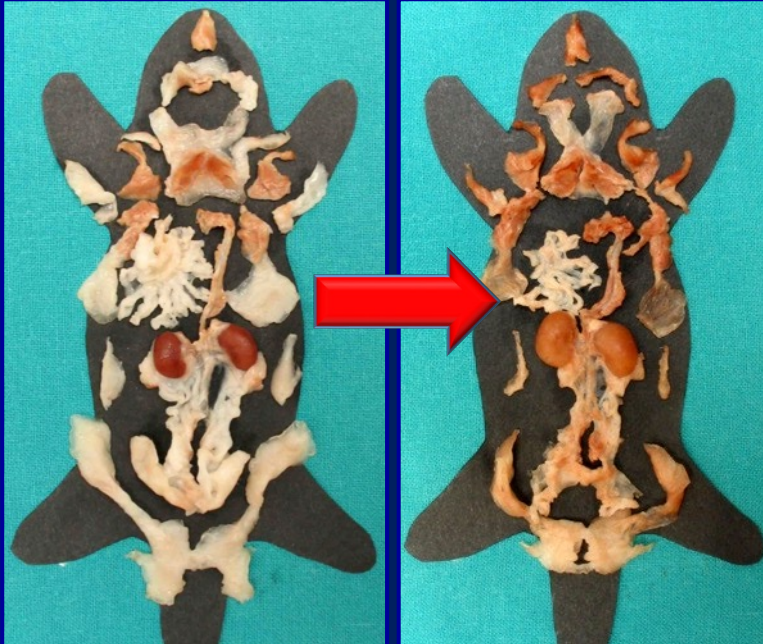


Ravazzoli et al Mol Metab 2016

Prdm16 determines the thermogenic program of subcutaneous white adipose tissue in mice

Patrick Seale,¹ Heather M. Conroe,² Jennifer Estall,² Shingo Kajimura,² Andrea Frontini,³ Jeff Ishibashi,¹ Paul Cohen,² Saverio Cinti,³ and Bruce M. Spiegelman²

J Clin Invest 2011



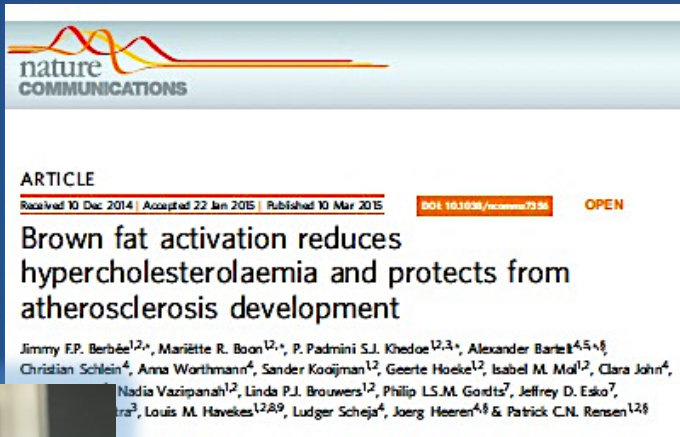
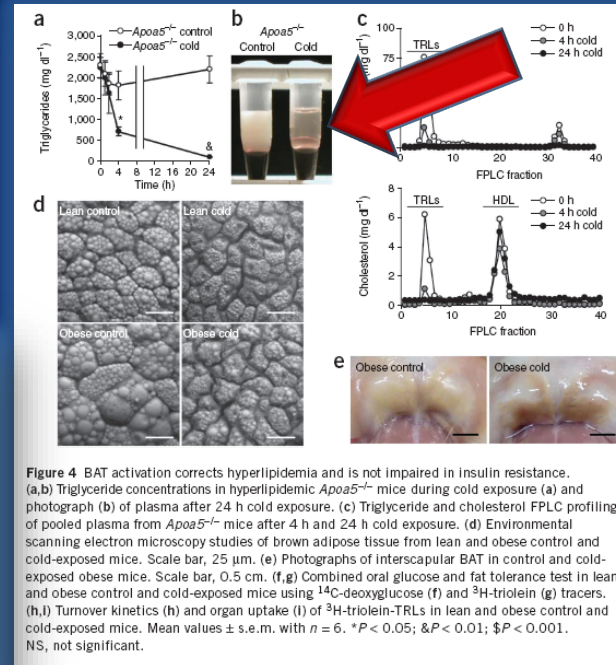
P. SEALE

BRUNO IMPORTANTE PER PREVENIRE IL DIABETE

BRUNO IMPORTANTE PER PREVENIRE L' ATEROSCLEROSI

Brown adipose tissue activity controls triglyceride clearance

Alexander Bartelt et al

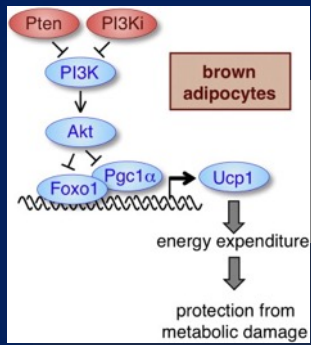


P. RENSEN

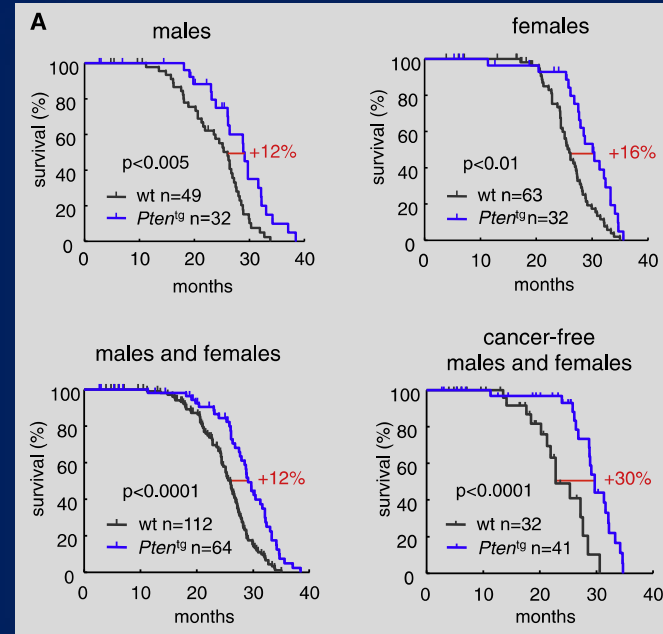
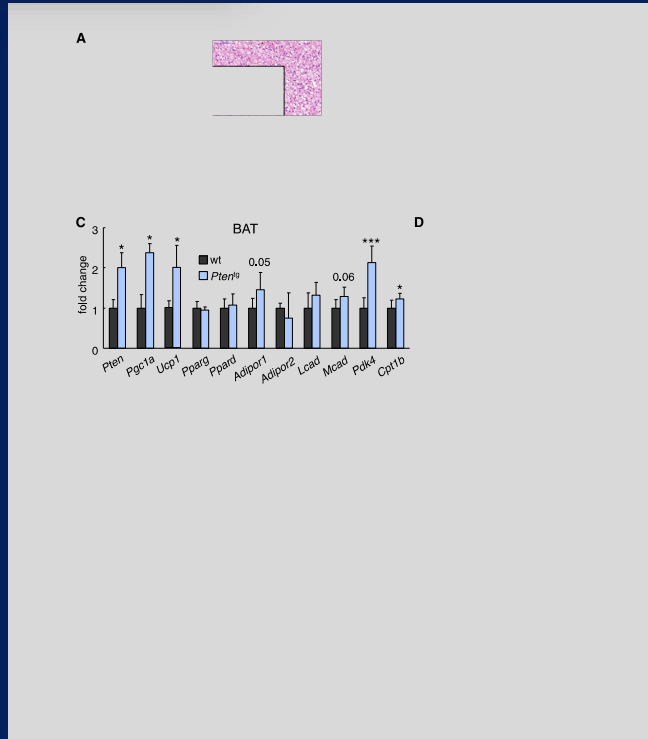


J. HEEREN

FEBRUARY 2011
Nature medicine



Pten Positively Regulates Brown Adipose Function, Energy Expenditure, and Longevity



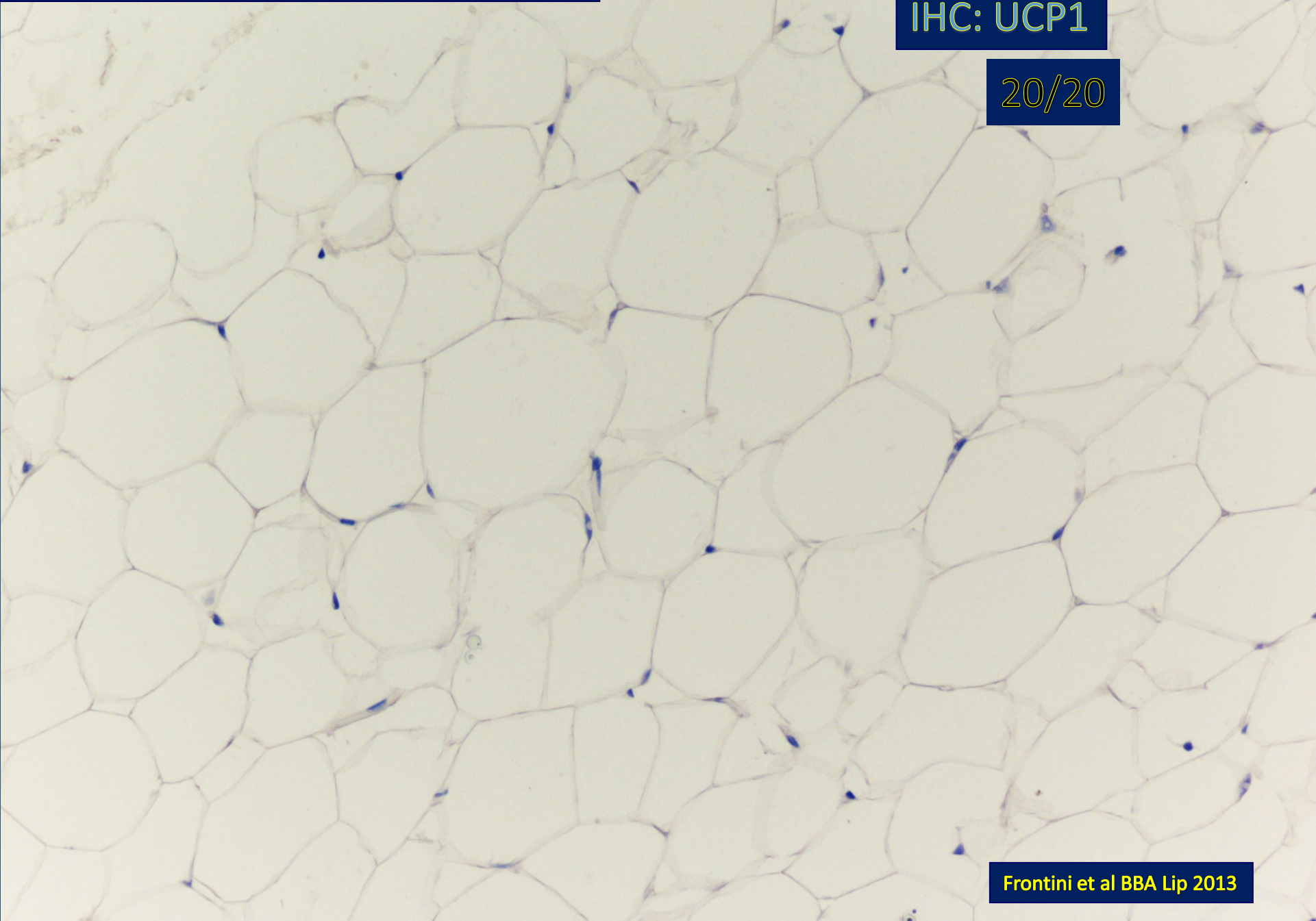
M. SERRANO

TRANSDIFFERENZIAZIONE NEGLI ESSERI UMANI?

Normal human adult omentum

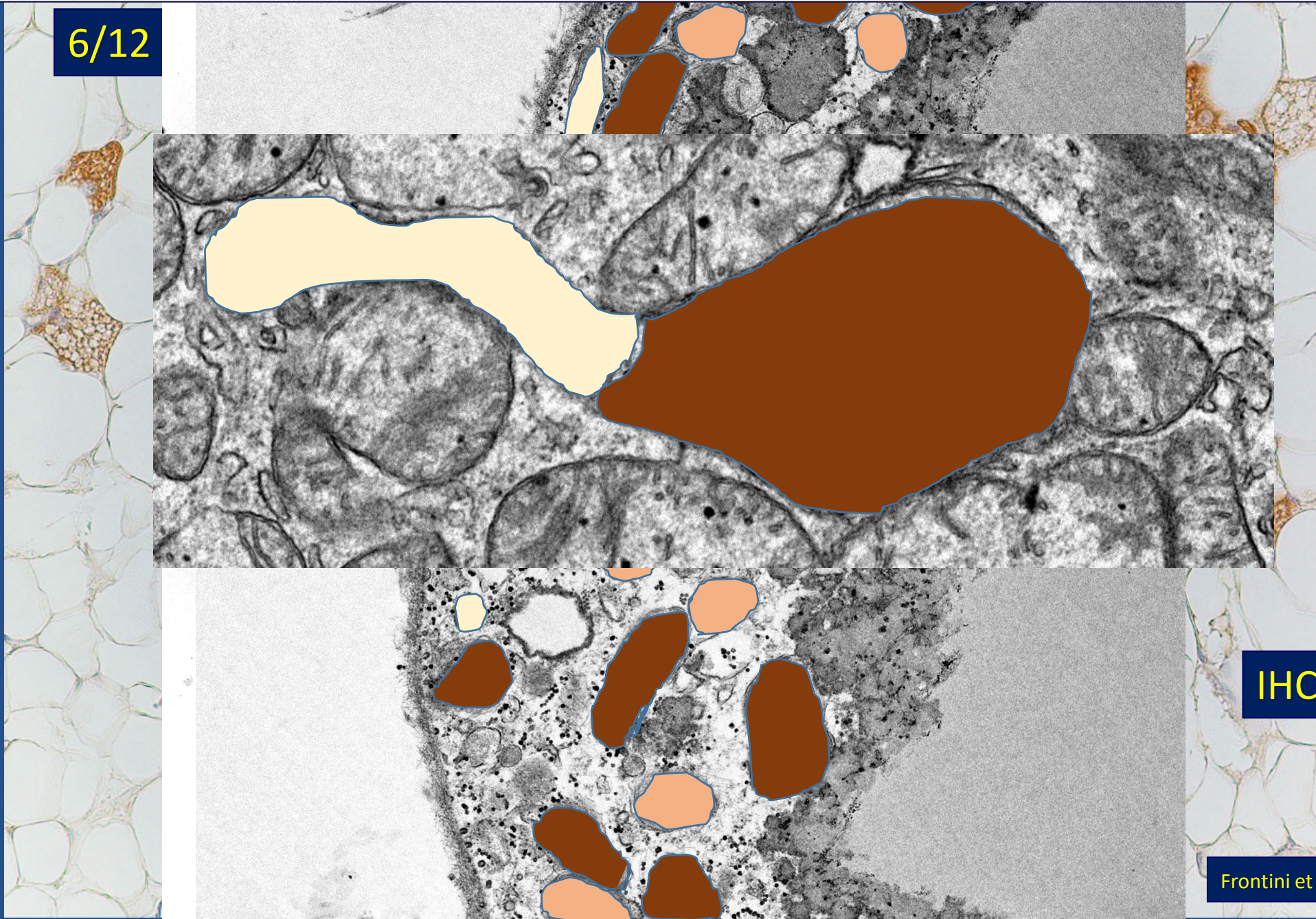
IHC: UCP1

20/20



Omento di uomo adulto con Feocromocitoma (tumore benigno che secerne NE)

6/12



IHC: UCP1

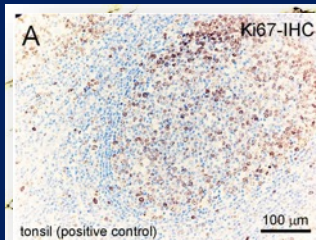
Human adult omentum in Pheocromocytoma



D RICQUIER

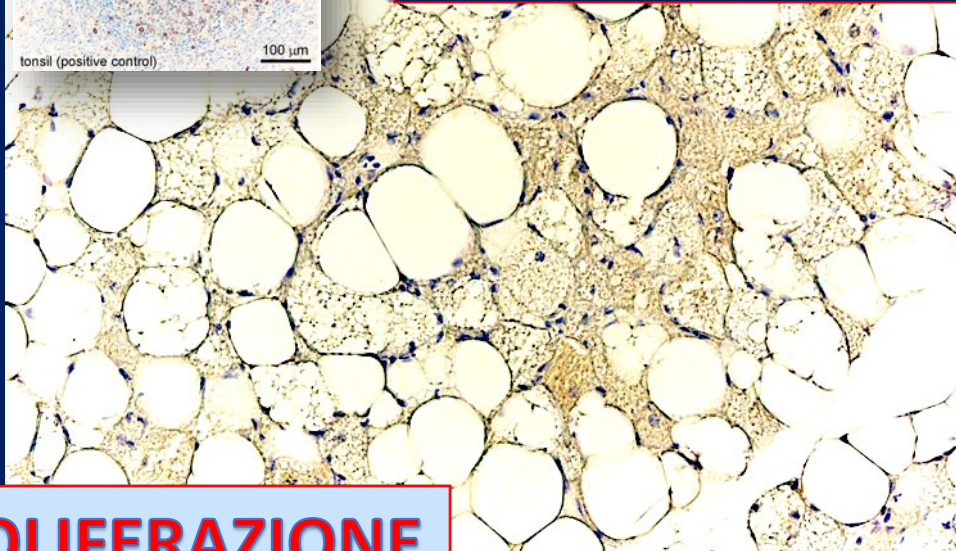


Frontini et al BBA Lip 2013

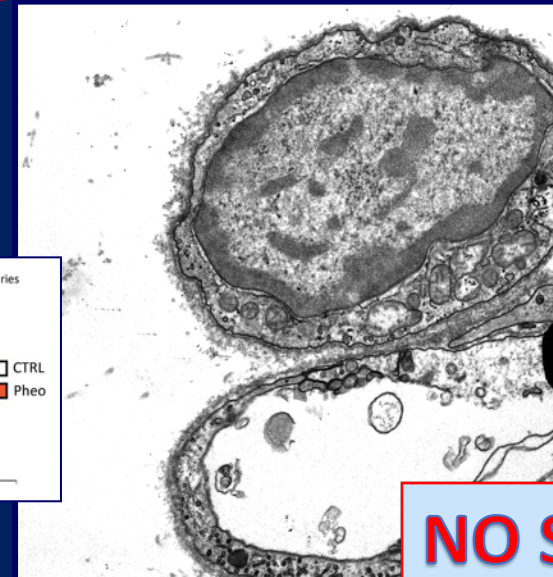
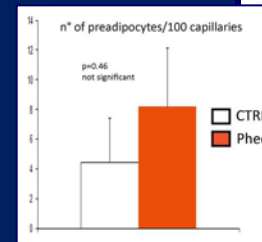


Ki67 IHC

NEO-FORMED BROWN ADIPOCYTES WERE Ki67 NEGATIVE



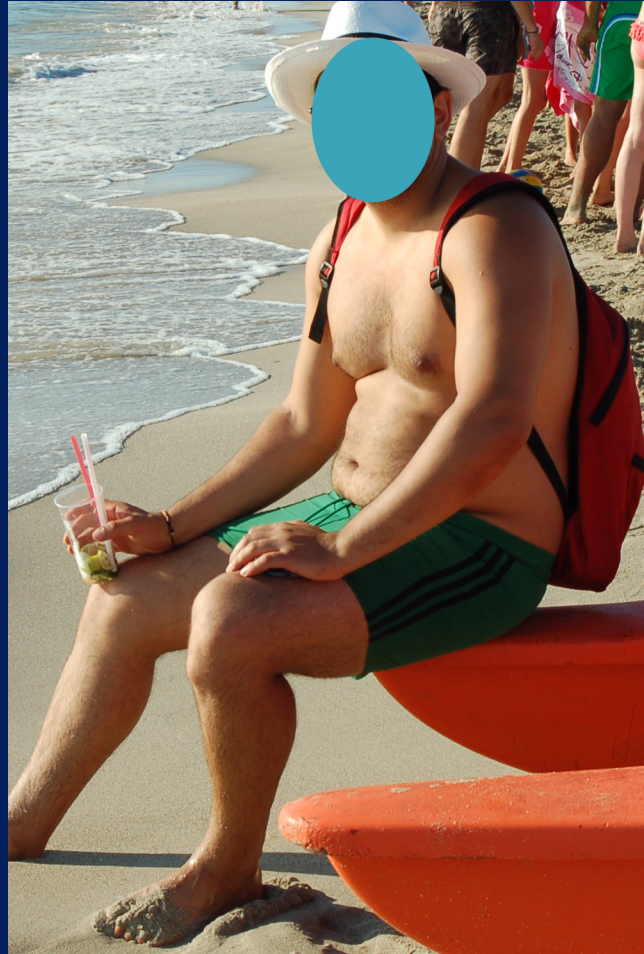
NO PROLIFERAZIONE



NO SVILUPPO

COLD ADAPTATION AND WEIGHT LOSS IN HUMANS

5 months of spontaneous cold exposure without diet restriction



PRE



POST

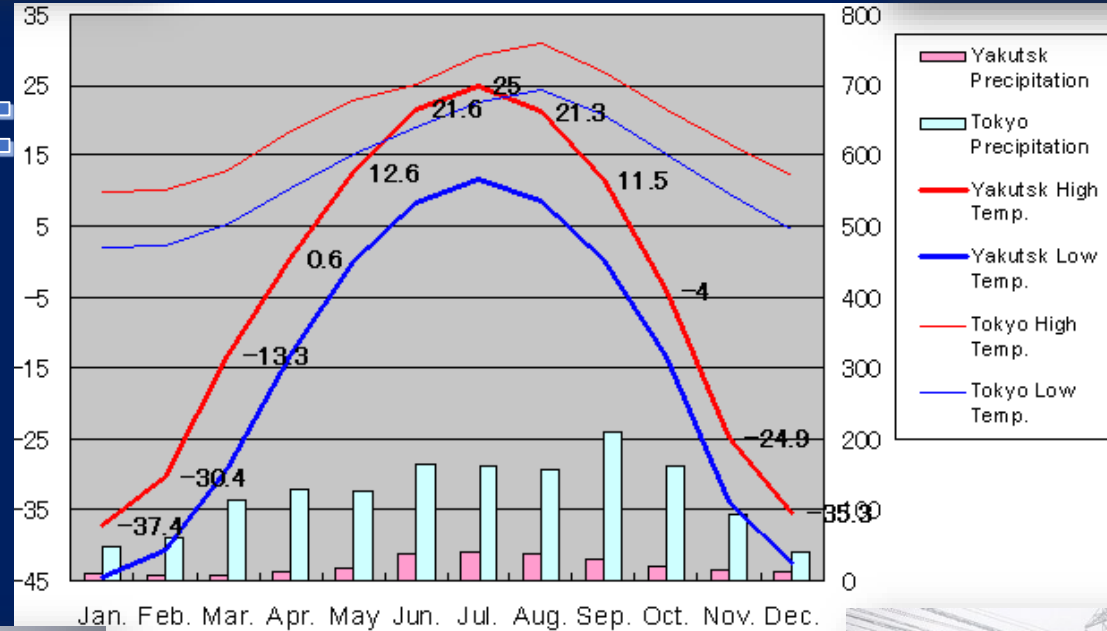
-5KG



Siberia



Record:
-68°C



Media
Annuale:
-10°C

Yakutsk



1° Sept 2014



FEDERAL AGENCY OF THE SCIENTIFIC ORGANIZATIONS
FEDERAL STATE INSTITUTION
«YAKUT SCIENTIFIC CENTER OF COMPLEX MEDICAL PROBLEMS»
THE SIBERIAN BRANCH, THE RUSSIAN ACADEMY OF MEDICAL SCIENCES



Tomskii Mikhail

Director, prof., MD

17:53 91 %

Якутск
Ясно
-50°

Вторник Сегодня -46 -48

Сейчас	13	14	15	16:00	16
☾	☀	☀	☀	☀	☀
-50	-46	-46	-47	Закат	-46

Среда	☁	-43	-47
Четверг	☁	-37	-37
Пятница	❄	-31	-33
Суббота	☁	-29	-32
Воскресенье	☁	-31	-35

Y! 23rd Dec 2014



1° Sept 2014



FEDERAL AGENCY OF THE SCIENTIFIC ORGANIZATIONS
FEDERAL STATE INSTITUTION
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THE SIBERIAN BRANCH, THE RUSSIAN ACADEMY OF MEDICAL SCIENCES



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Вторник Сегодня -46 -48

Сейчас	13	14	15	16:00	16
☾	☀	☀	☀	☀	☀
-50	-46	-46	-47	Закат	-46

Среда	☁	-43	-47
Четверг	☁	-37	-37
Пятница	❄	-31	-33
Суббота	☁	-29	-32
Воскресенье	☁	-31	-35

Y! 23rd Dec 2014

-5Kg

A large proportion of visceral fat of Siberian adult people is formed by multilocular and paucilocular UCP1 immunoreactive adipocytes.

A. Efremova¹, M. Senzacqua², W. Venema², E. Isakov¹, A. Di Vincenzo², M.C. Zingaretti², M. Thomsen¹, A. Giordano² and S. Cinti²

1- Yakut Scientific Center of Complex Medical Problems, Yakutsk, Russia

2-Dpt Experimental and Clinical Medicine, Center of Obesity, University of Ancona (Politecnica delle Marche), Italy

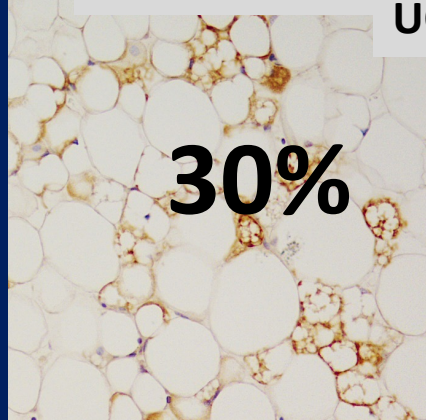
Patient	Age	Sex	Profession	Ethnicity	Cause of death
1	unknown	M	unknown	yakut	trauma
2	56	M	unknown	russian	myocardial infarction, atherosclerosis
3	46	M	trader	uzbek	subarachnoid hemorrhage
4	64	M	pensioneer	russian	myocardial infarction
5	unknown	M	homeless	russian	alcoholic cardiomyopathy
6	30	M	farmer	yakut	pancreatic necrosis
7	46	F	workless	russian	total pancreosclerosis, DIC-syndrome
8	61	F	pensioneer	yakut	unknown
9	42	F	laboratory worker	yakut	subarachnoid hemorrhage
10	55	F	pensioneer	yakut	subarachnoid hemorrhage
11	53	M	pensioneer	russian	hypertrophic cardiomyopathy
12	43	M	janitor	armenian	alcoholism, pneumonia
13	48	F	workless	even	alcoholism, cirrhosis
14	20	M	student	russian	astrocitoma
15	40	M	hunter	yakut	-

AGRAPHENA EFREMOVA
PhD student at Ancona

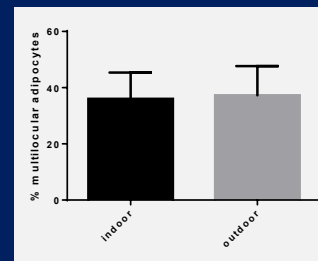
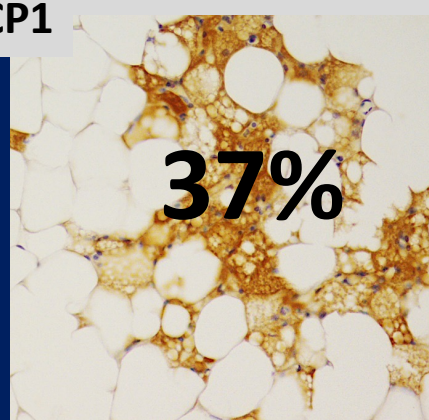


Periaortic adipose tissue

INDOOR

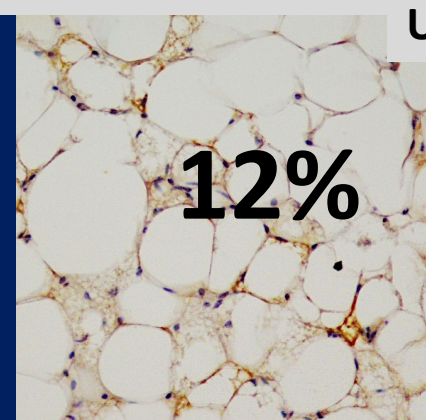


OUTDOOR

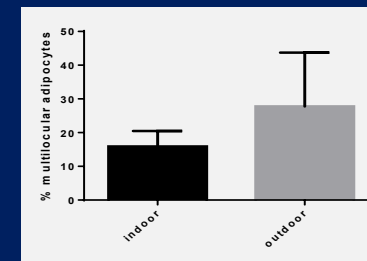
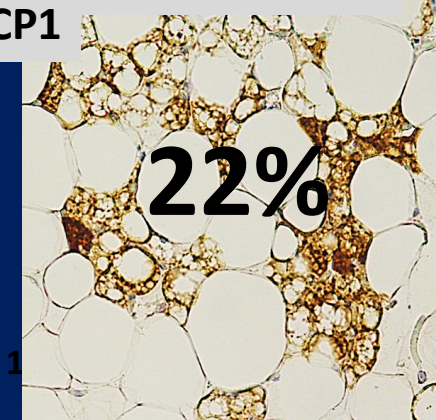


Perirenal adipose tissue

INDOOR



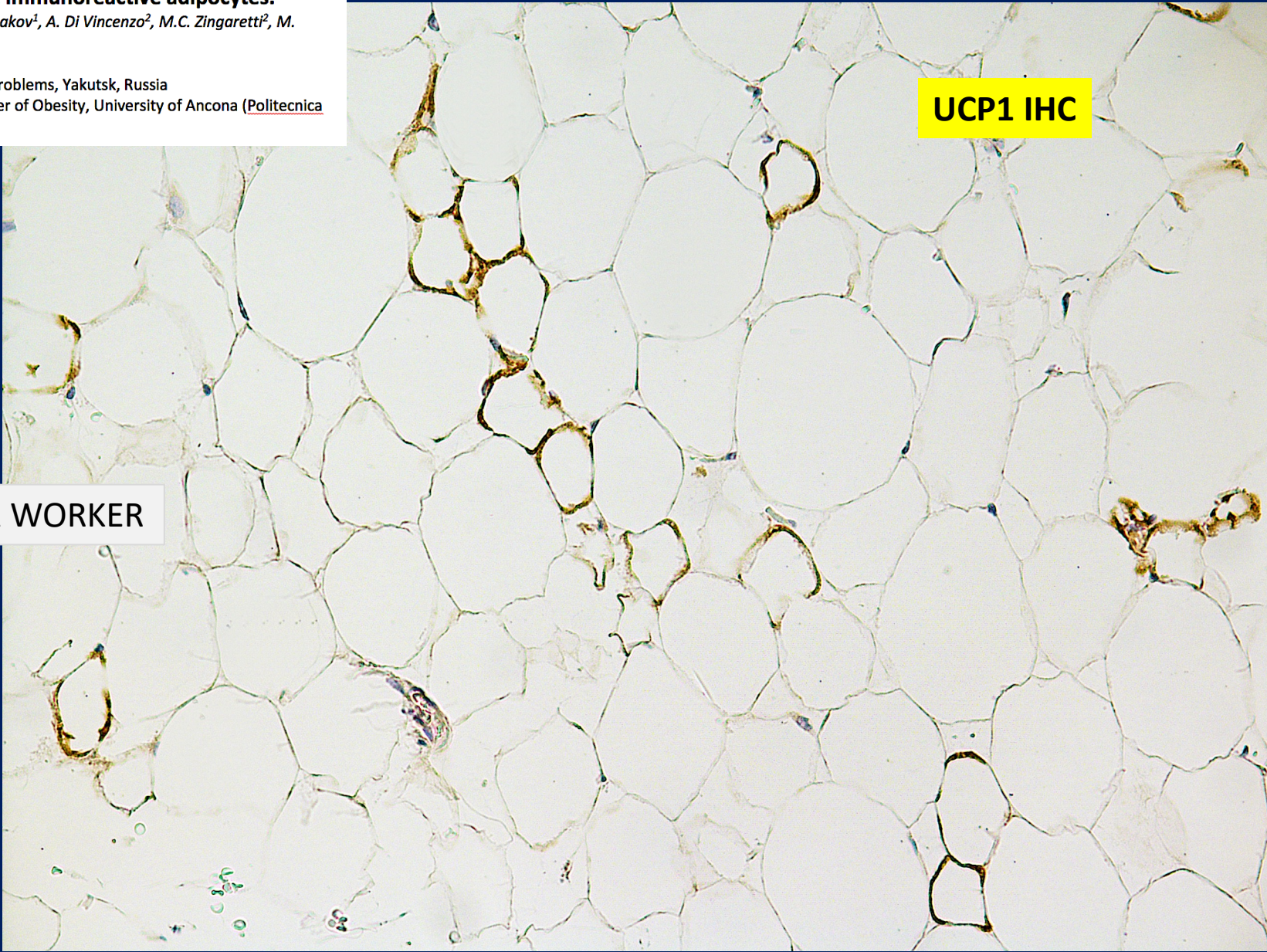
OUTDOOR



A large proportion of visceral fat of Siberian adult people is formed by multilocular and paucilocular UCP1 immunoreactive adipocytes.

A. Efremova¹, M. Senzacqua², W. Venema², E. Isakov¹, A. Di Vincenzo², M.C. Zingaretti², M. Thomsen¹, A. Giordano² and S. Cinti²

1- Yakut Scientific Center of Complex Medical Problems, Yakutsk, Russia
2-Dpt Experimental and Clinical Medicine, Center of Obesity, University of Ancona ([Politecnica delle Marche](#)), Italy



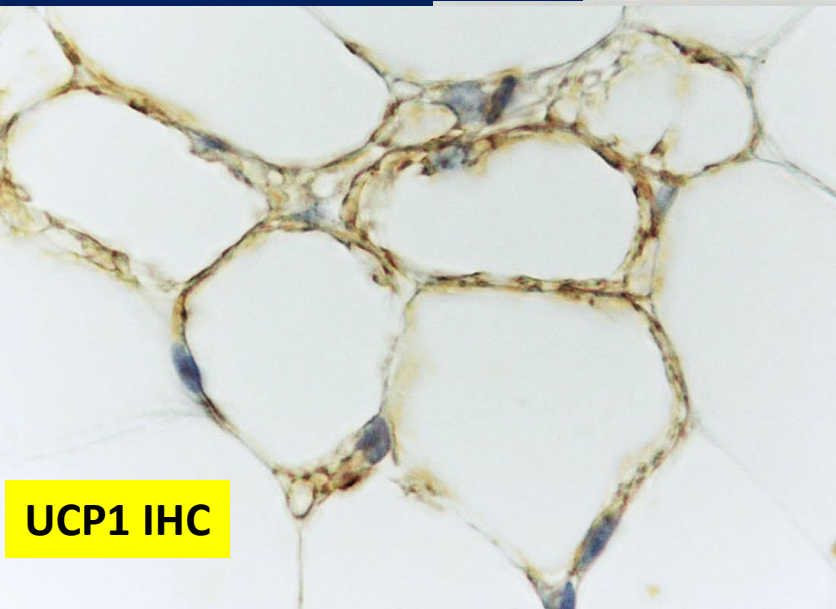
UCP1 IHC

53 YO MAN INDOOR WORKER

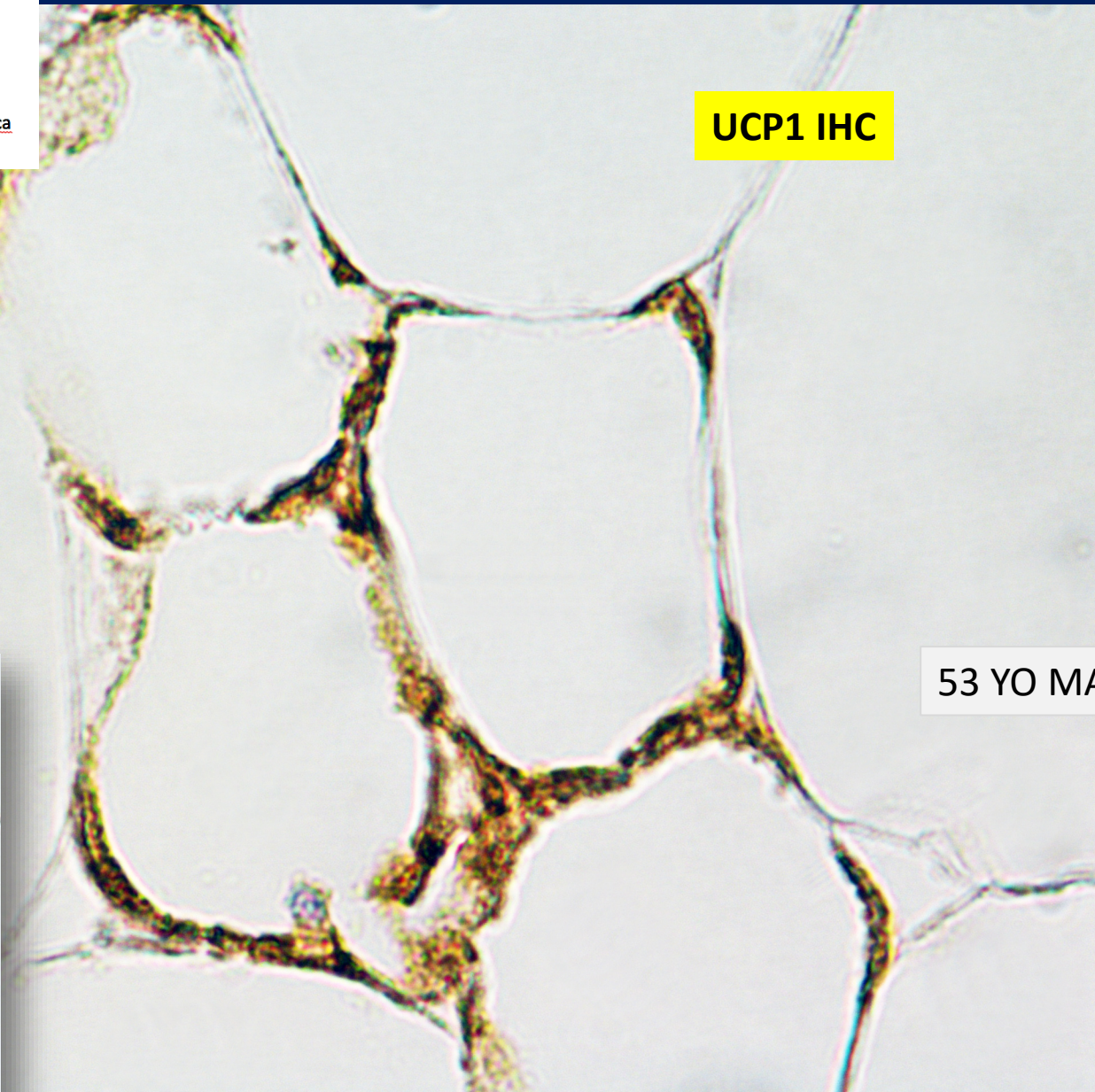
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A. Efremova¹, M. Senzacqua², W. Venema², E. Isakov¹, A. Di Vincenzo², M.C. Zingaretti², M. Thomski¹, A. Giordano² and S. Cinti²

1- Yakut Scientific Center of Complex Medical Problems, Yakutsk, Russia
2-Dpt Experimental and Clinical Medicine, Center of Obesity, University of Ancona ([Politecnica delle Marche](#)), Italy

2h cold exposed mouse



UCP1 IHC



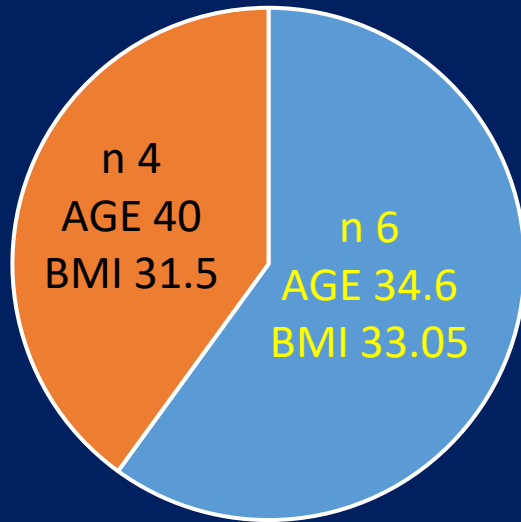
UCP1 IHC

53 YO MAN INDOOR WORKER

CRYOTHERAPY n 15 TREATMENTS

3 min a -130°C x 3 volte/sett

PRELIMINARY RESULTS



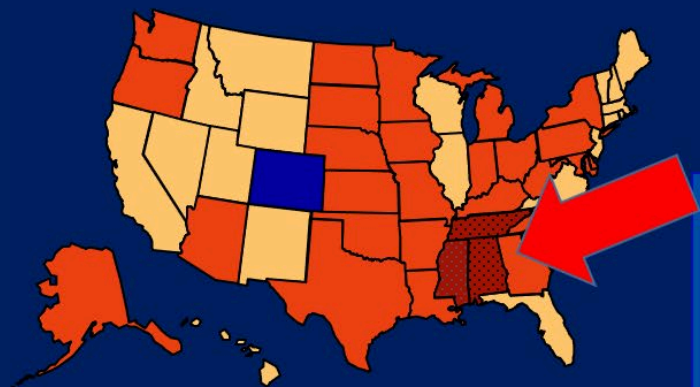
-2.6 Kg FAT = -2.6%
+1.8 Kg LM = +2.6%



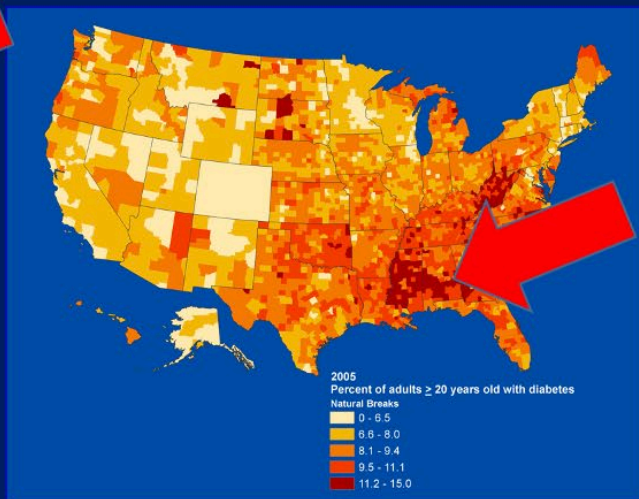
IN COLL DR BONOMI

L' ESPOSIZIONE AL FREDDO E' L'UNICO MODO?

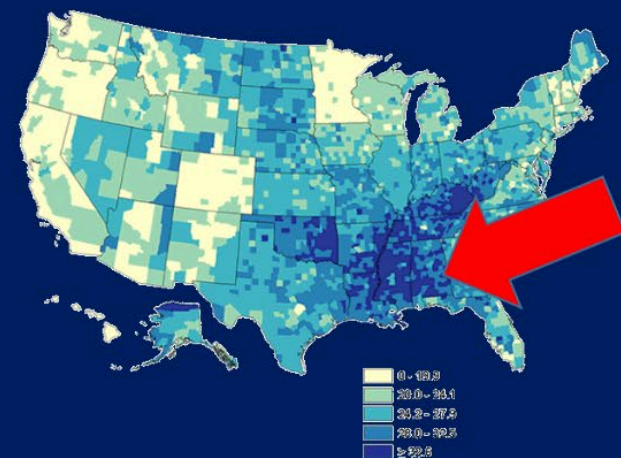




Obesity 2005

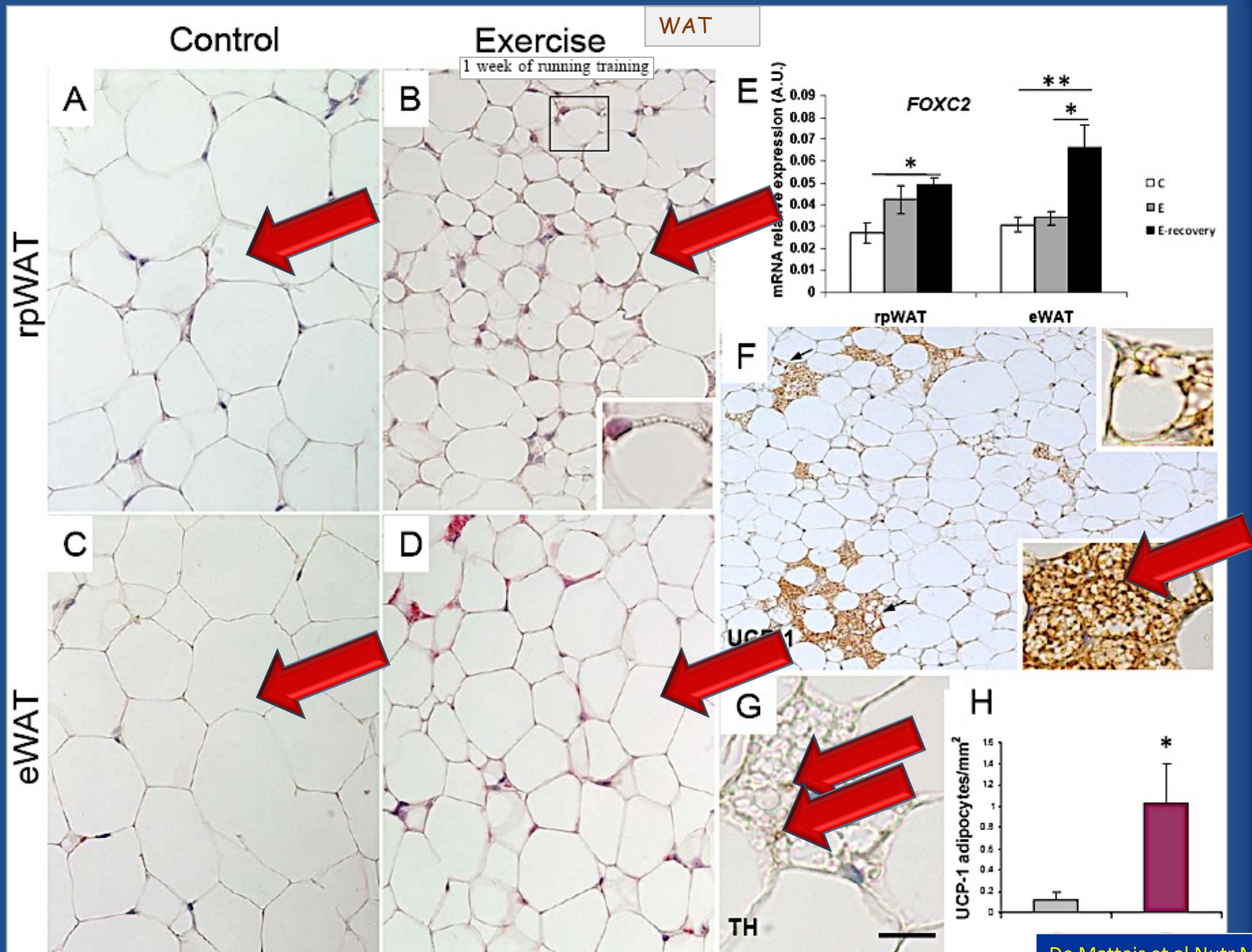


T2 Diabetes 2005



Physical inactivity 2008

ATTIVITA'
FISICA



A PGC1 α -dependent myokine that drives browning of white fat and thermogenesis.

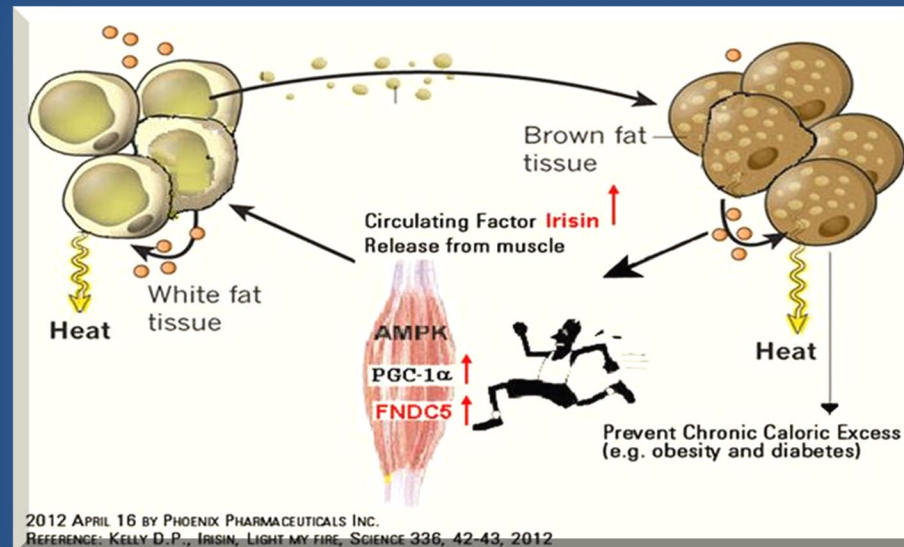
Pontus Boström¹, Jun Wu¹, Mark P. Jedrychowski², Anisha Korde¹, Li Ye¹, James Lo¹, Kyle A. Rasbach¹, Elisabeth Almer Boström³, Shingo Kajimura¹, Maria Cristina Zingaretti⁴, Birgitte F. Vind⁵, Hua Tu⁶, Saverio Cinti⁴, Kurt Højlund⁵, Steven P. Gygi², Bruce M. Spiegelman^{1*}

¹Dana-Farber Cancer Institute and Harvard Medical School, 3 Blackfan Circle, CLS Building, floor 11, Boston, MA, 02115, USA.

²Department of Cell Biology, Harvard Medical School, Boston, MA, 02115, USA.

³Renal Division, Brigham and Women's Hospital, Harvard Medical School

⁴Department of Experimental and Clinical Medicine, Università Politecnica delle Marche, Electron Microscopy Unit-Azienda Ospedali Riuniti, Ancona 60020, Italy



BRUCE SPIEGELMAN
HARVARD UNIVERSITY

irisin
Nature 2012

INTERMITTENT FASTING

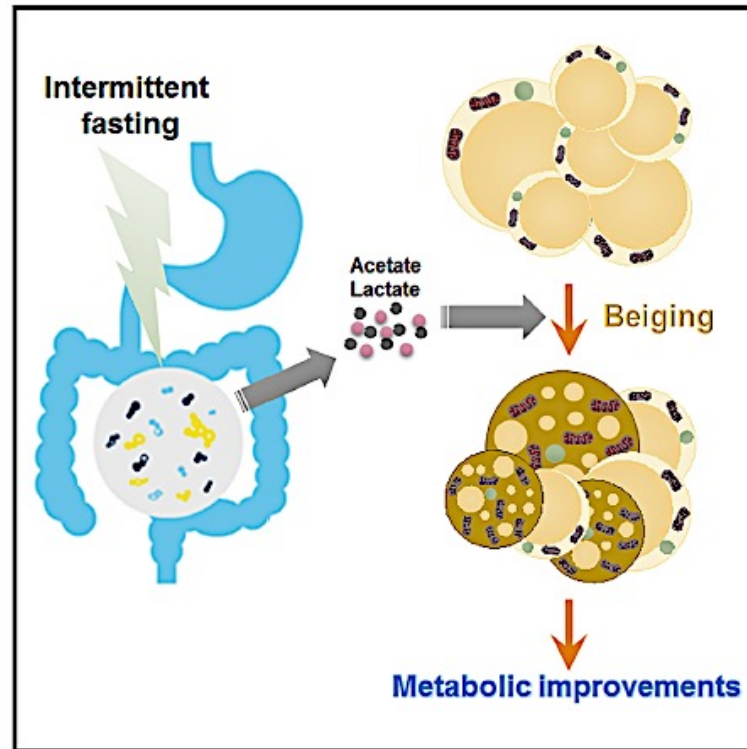
Cell Metabolism

Article

2017

Intermittent Fasting Promotes White Adipose Browning and Decreases Obesity by Shaping the Gut Microbiota

Graphical Abstract



Authors

Guolin Li, Cen Xie, Siyu Lu, ...,
Oksana Gavrilova,
Andrew D. Patterson,
Frank J. Gonzalez

Correspondence

hnsdgl@hunnu.edu.cn (G.L.),
gonzalef@mail.nih.gov (F.J.G.)

In Brief

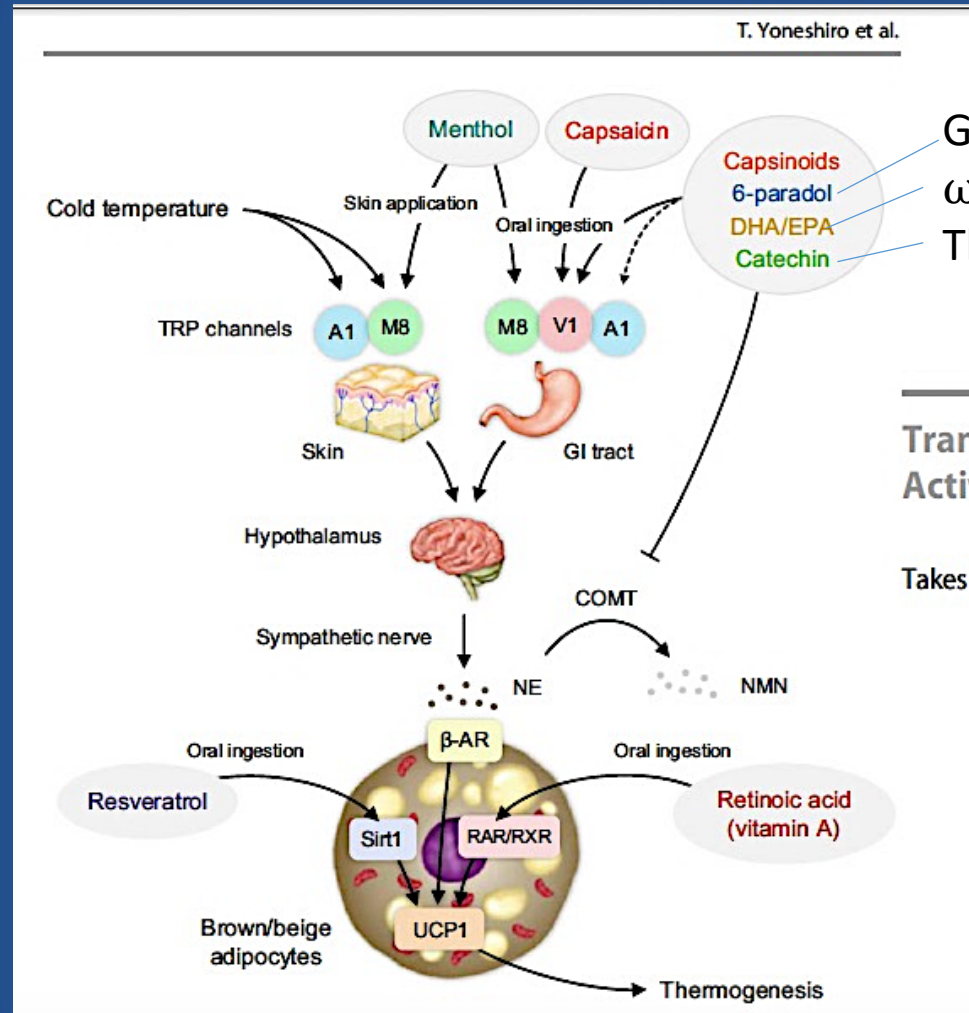
White adipose beiging is a promising therapy for obesity and related metabolic diseases. Here, Li, Xie and colleagues find that an EODF regimen can selectively induce the beiging of white adipose tissue and subsequently ameliorate metabolic disorders in mice. Gut microbiota orchestrate the effects of EODF on beiging and metabolic improvement.

NUTRIENTS

BROWNING FOOD



MASAYUKI SAITO



Guinea pepper and Turmeric
 $\omega 3$
Thé (camelia sinensis)

Translational Aspects of Brown Fat Activation by Food-Derived Stimulants

Takeshi Yoneshiro, Mami Matsushita, and Masayuki Saito

DRUGS

Anti-obesity and antihyperglycemic effects of β 3-adrenoceptor agonists are usually associated with increased density of UCP1-positive brown adipocytes within white adipose depots

Champigny O et al., *Proc Natl Acad Sci USA* **88**, 10774-10777, 1991

Himms-Hagen J et al., *Am J Physiol* **266**, R1371-R1382, 1994

Collins S et al., *Endocrinology* **138**, 405-413, 1997

Ghorbani M & Himms-Hagen J, *Int J Obesity* **21**, 465-475, 1997

Ghorbani M et al., *Biochem Pharmacol* **54**, 121-131, 1997

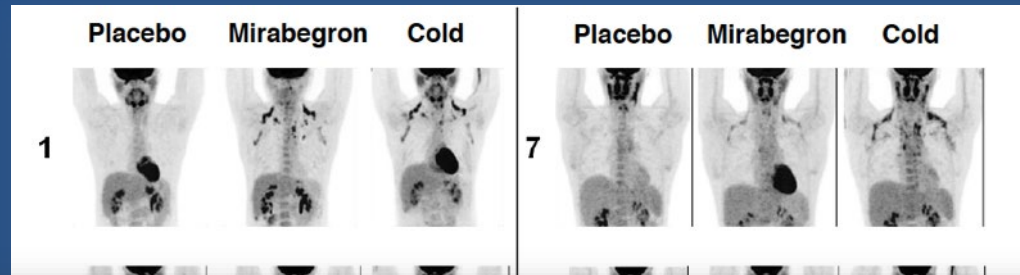
Fisher MH et al., *J Clin Invest* **101**, 2387-2393, 1998

Sasaki N et al., *J Vet Med Sci* **60**, 465-469, 1998

DRUGS



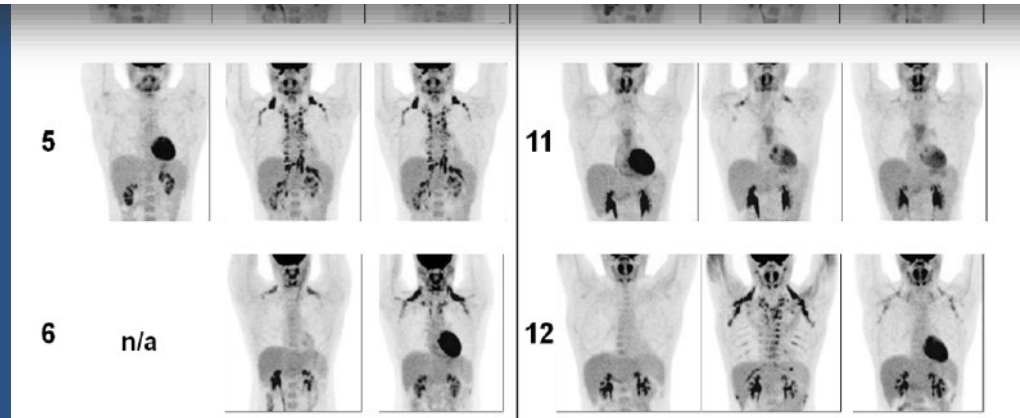
A. CYPRESS



COLD
14°C FOR 2 H



MIRABEGRON
200MG PER OS



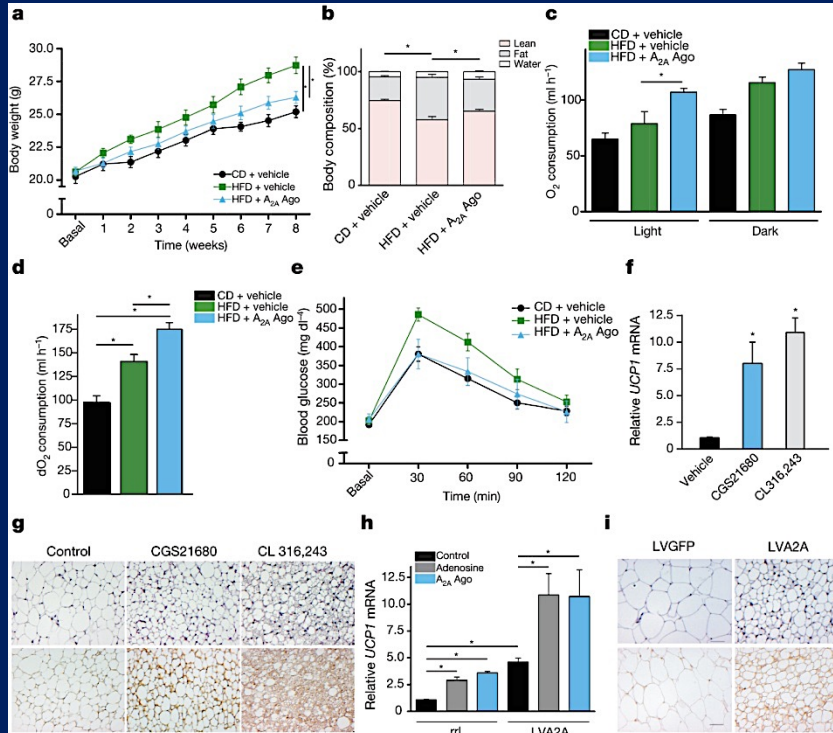
DRUGS

Adenosine activates brown adipose tissue and recruits beige adipocytes via A2A receptors



A PFEIFER

nature



T Gnad et al. *Nature* **2014**, 1-5 (2014) doi:10.1038/nature13816

Original article

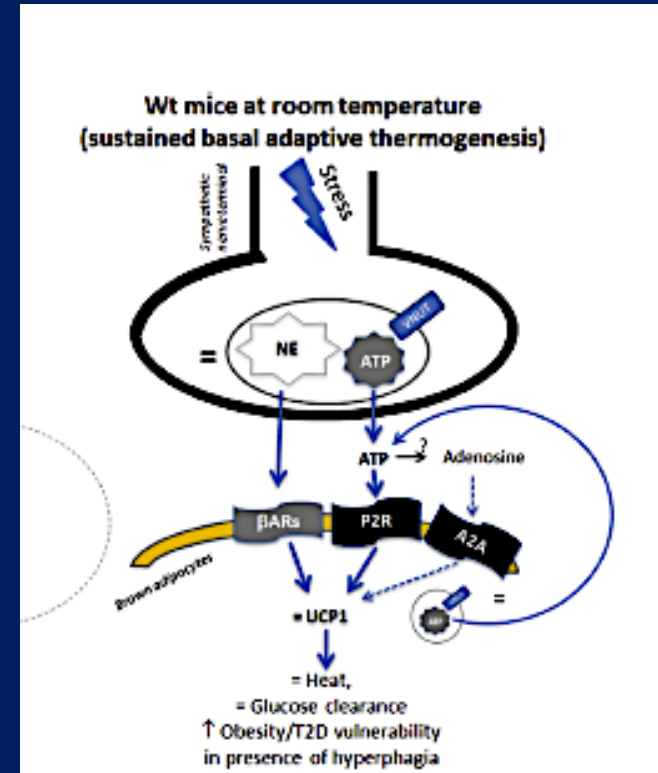
2015

MOLECULAR
METABOLISM



Stress-induced activation of brown adipose tissue prevents obesity in conditions of low adaptive thermogenesis

Maria Razzoli^{1,2}, Andrea Frontini^{2,3}, Allison Gurney^{1,4}, Eleonora Mondini², Cenkut Cubuk², Ulla S. Katz⁴, Cheryl Coro¹, Patrick J. Bolan⁵, Joaquin Dopazo⁶, Antonio Vidal-Puig^{6,7}, Saverio Costi², Alessandro Bartolomucci^{1,2}



A BARTOLOMUCCI

DRUGS

> Mol Metab. 2022 Oct;64:101550. doi: 10.1016/j.molmet.2022.101550. Epub 2022 Jul 31.

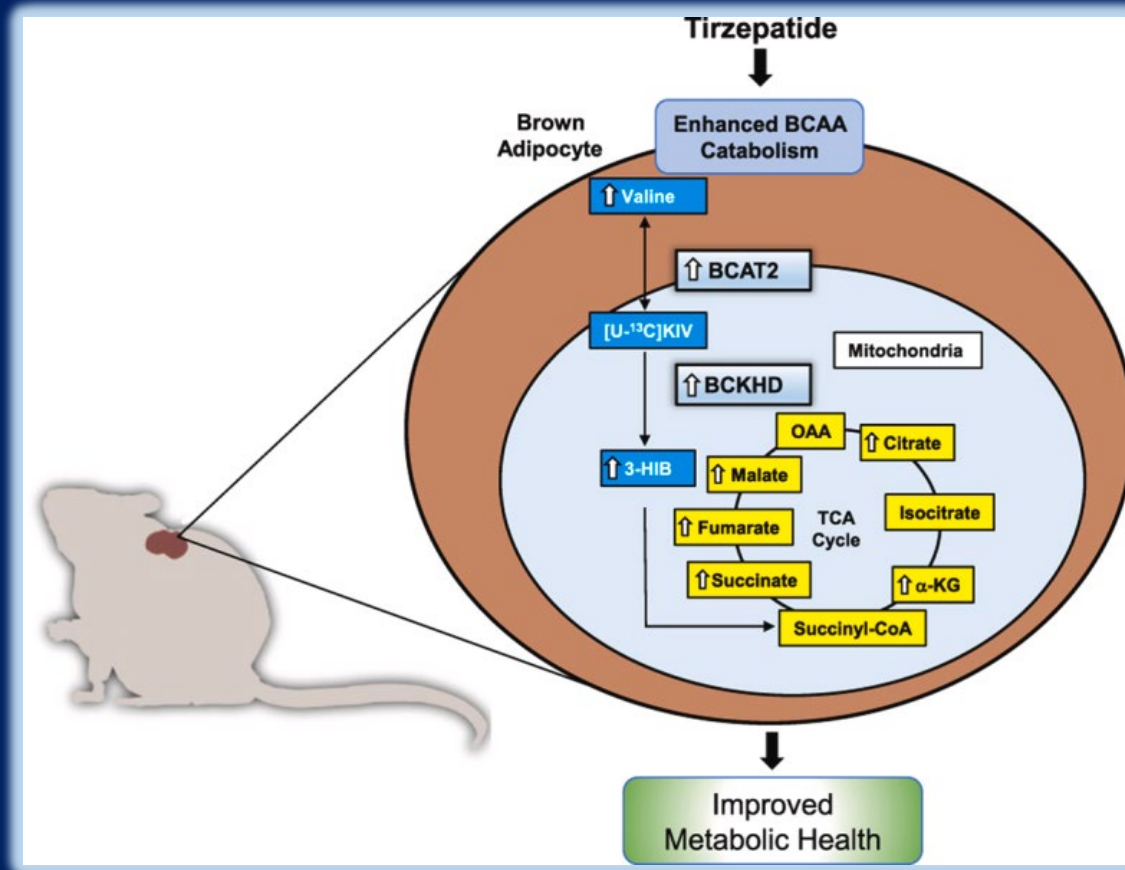
Tirzepatide induces a thermogenic-like amino acid signature in brown adipose tissue

Ricardo J Samms¹, GuoFang Zhang², Wentao He³, Olga Ilkayeva², Brian A Droz⁴, Steven M Bauer⁴, Cynthia Stutsman⁴, Valentina Pirro⁴, Kyla A Collins⁴, Ellen C Furber⁴, Tamer Coskun⁴, Kyle W Sloop⁴, Joseph T Brozinick⁴, Christopher B Newgard⁵

Novel dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist (RA) tirzepatide



C.B. NEWGARD



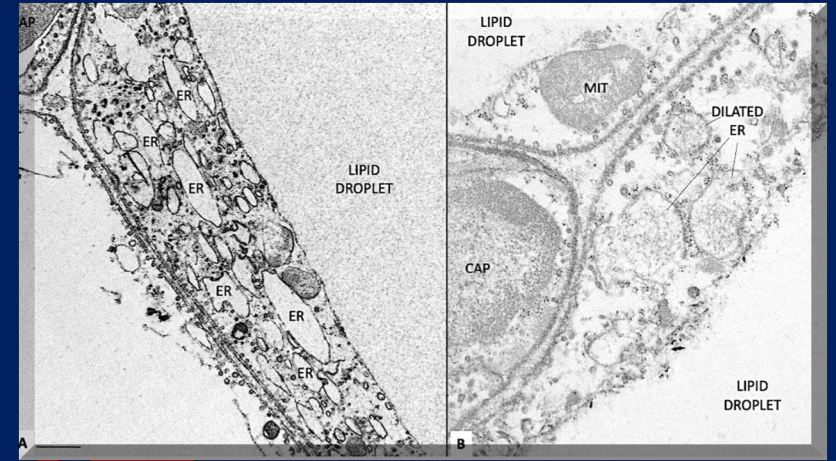
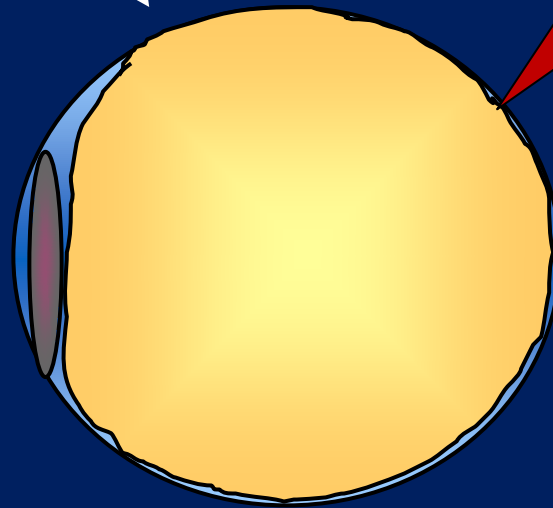
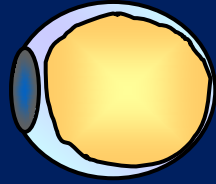
DIABETE-OBESITA'

L'ORGANO ADIPOSO OBESO



Pathogenesis of inflammation and T2 Diabetes

Cinti et al J Lip Res 2005
Murano et al J Lip Res 2008
Giordano et al J Lip Res 2013
Camastra et al Sci Rep 2017
Kotzbeck et al J Lip Res 2018

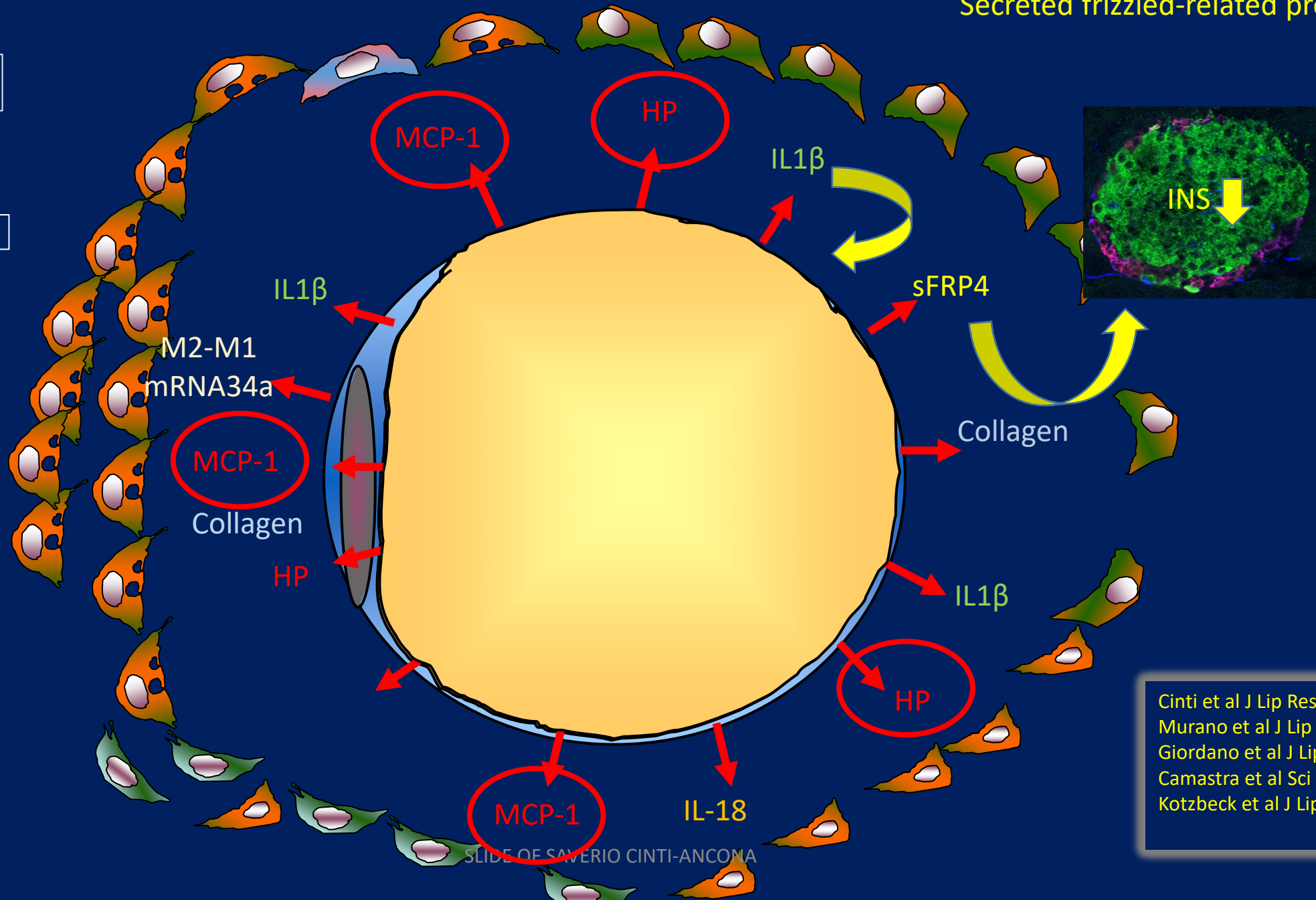


Reviewed in
Cinti S
Antioxidants 2023

M2-M1
mRNA34a
Pan et al JCI 2019

sFRP4
Mahdi et al Cell Metab 2012

Secreted frizzled-related protein 4



Cinti et al J Lip Res 2005
Murano et al J Lip Res 2008
Giordano et al J Lip Res 2013
Camastra et al Sci Rep 2017
Kotzbeck et al J Lip Res 2018

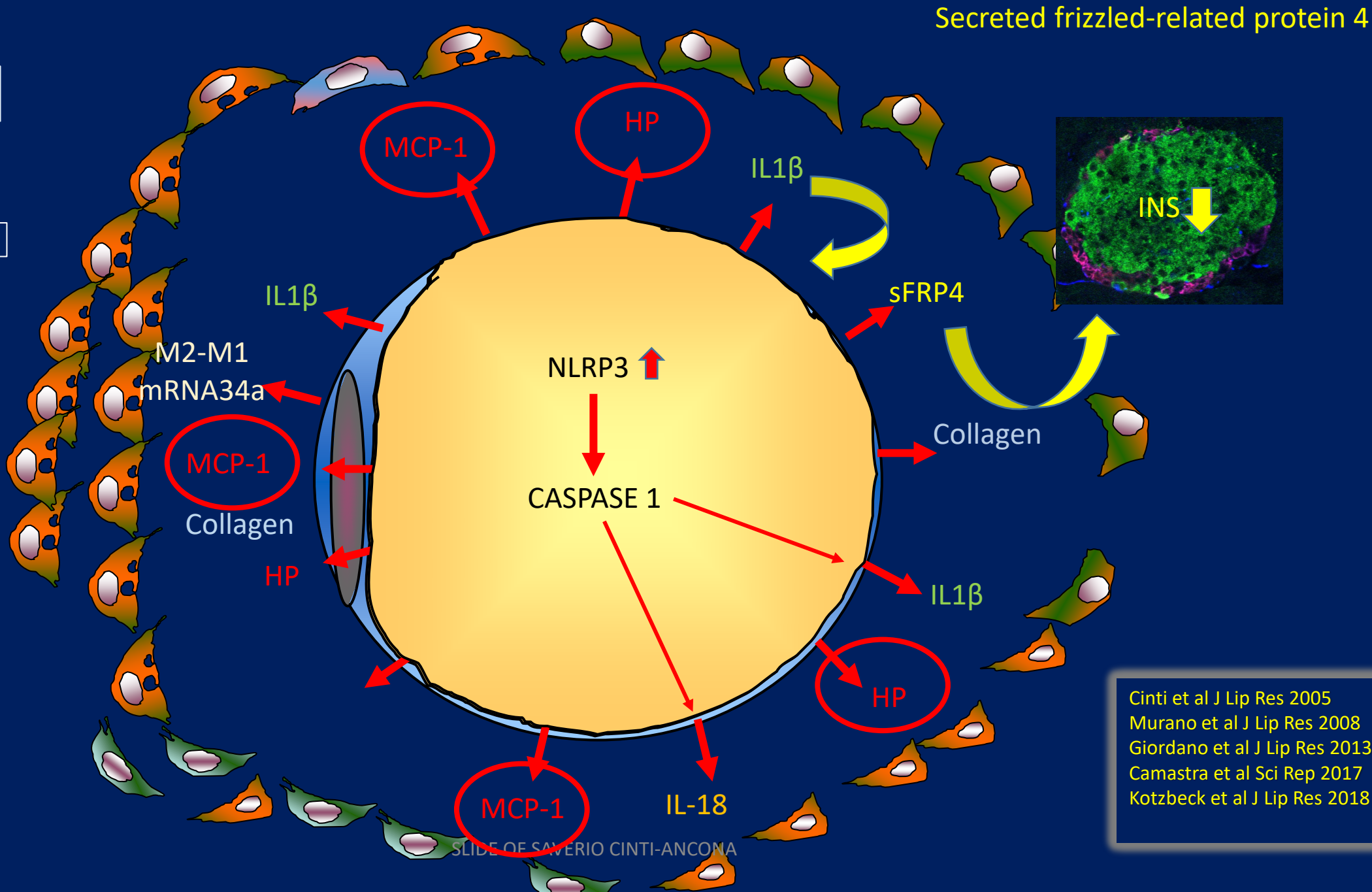
SLIDE OF SAVERIO CINTI-ANCONA

M2-M1
mRNA34a
Pan et al JCI 2019

sFRP4
Mahdi et al Cell Metab 2012

MCP-1
Sartipy et al PNAS 2003

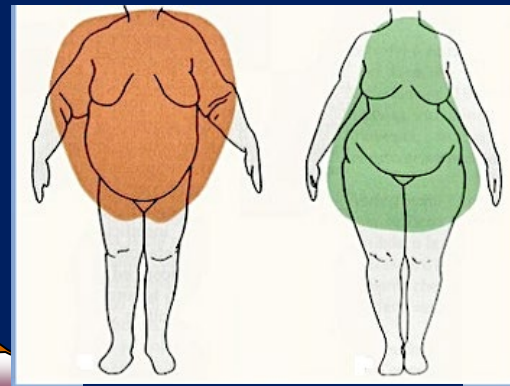
HP Maffei et al End Rev 2016



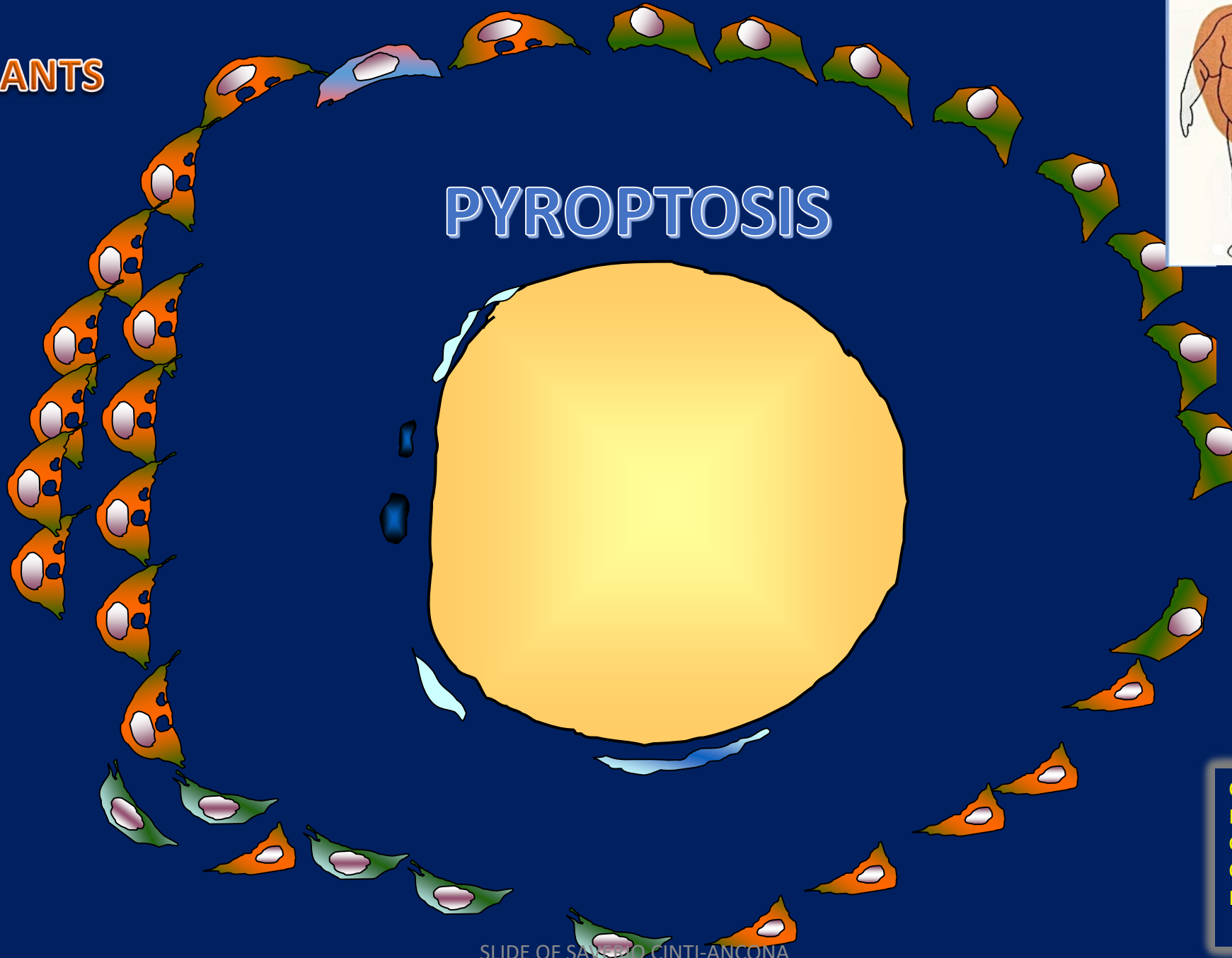
Cinti et al J Lip Res 2005
Murano et al J Lip Res 2008
Giordano et al J Lip Res 2013
Camastra et al Sci Rep 2017
Kotzbeck et al J Lip Res 2018

REMNANTS

PYROPTOSIS

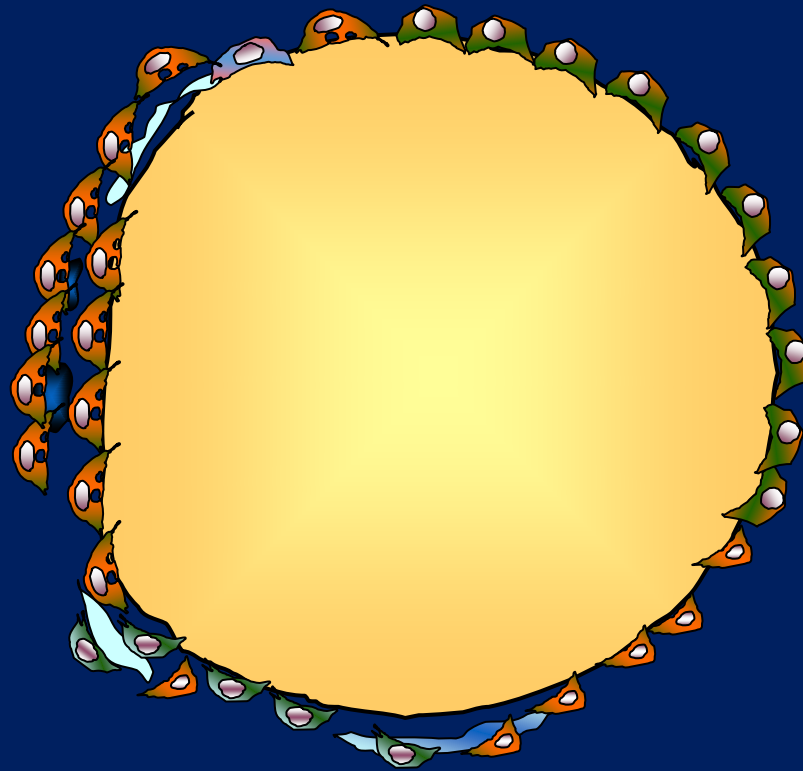
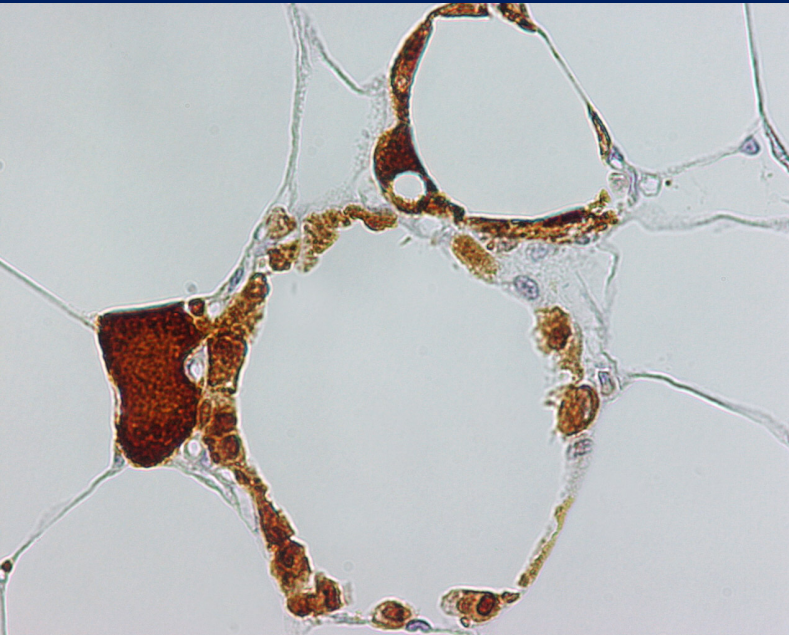


VISCERAL FAT:
LOWER CRITICAL
DEATH SIZE

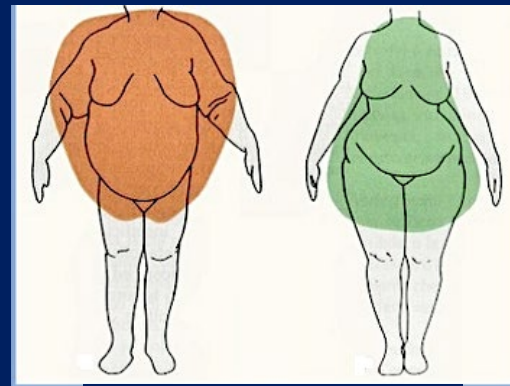


Cinti et al J Lip Res 2005
Murano et al J Lip Res 2008
Giordano et al J Lip Res 2013
Camastra et al Sci Rep 2017
Kotzbeck et al J Lip Res 2018

CLS



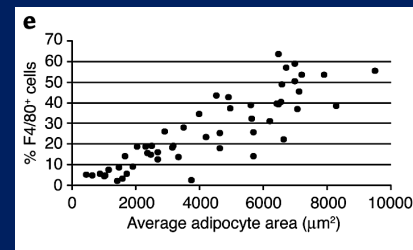
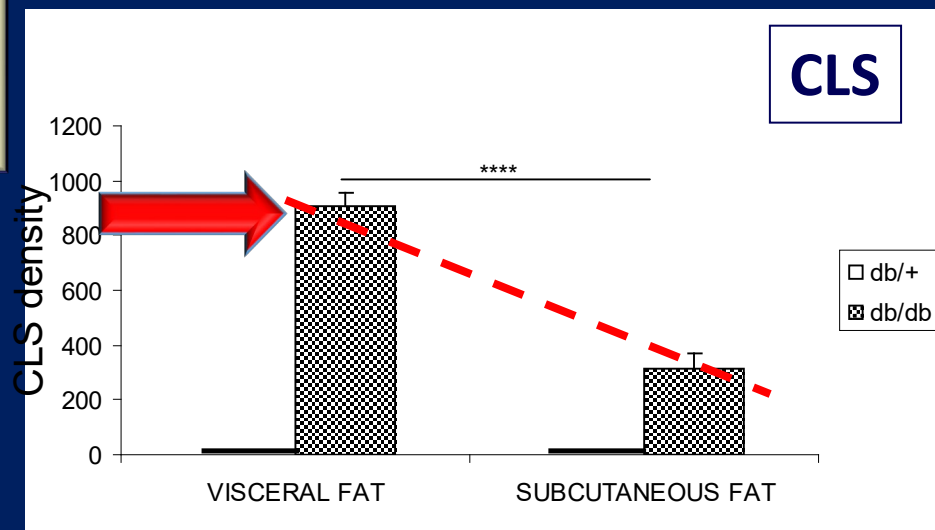
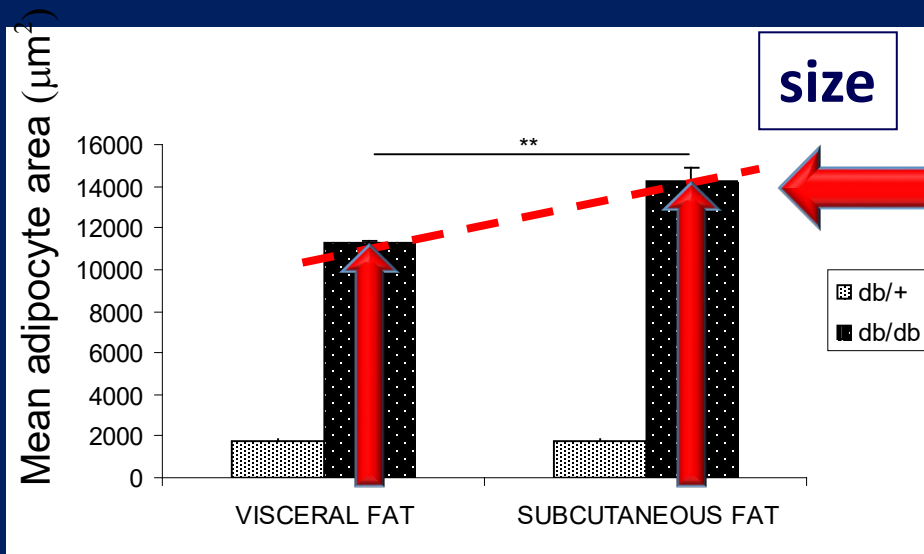
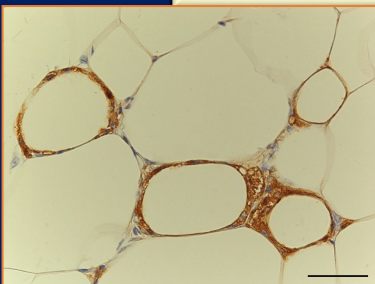
SLIDE OF SAVERIO CINTI-ANCONA



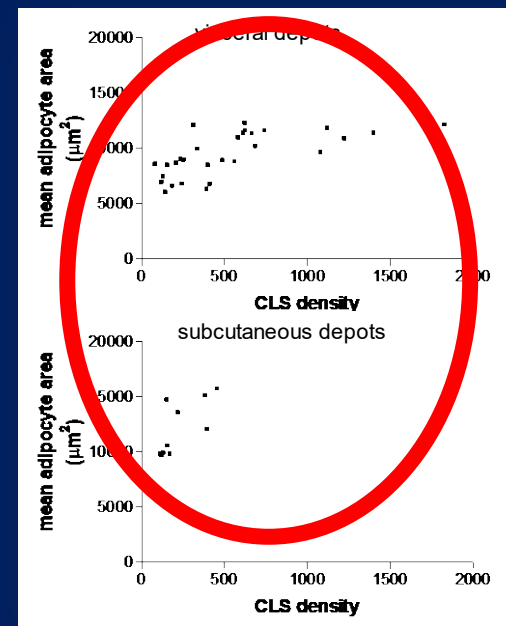
VISCERAL FAT:
LOWER CRITICAL
DEATH SIZE

Cinti et al J Lip Res 2005
Murano et al J Lip Res 2008
Giordano et al J Lip Res 2013
Camastra et al Sci Rep 2017
Kotzbeck et al J Lip Res 2018

**db/db
obese
mice**



Weisberg et al JCI 2003



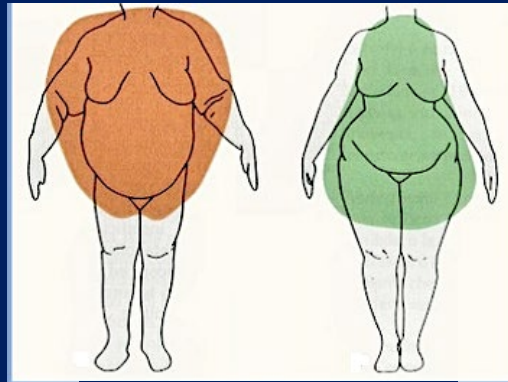
The critical size triggering death (critical death size) is smaller in visceral adipocytes

Murano I et al J Lipid Res 08

Central adiposity and the overweight risk paradox in aging: follow-up of 130,473 UK Biobank participants

Kirsty Bowman,¹ Janice L. Atkins,¹ João Delgado,¹ Katarina Kos,² George A. Kuchel,³ Alessandro Ble,¹ Luigi Ferrucci,⁴ and David Melzer^{1,3}

AM J CLIN NUTR 2017



VISCERAL FAT:
LOWER CRITICAL
DEATH SIZE

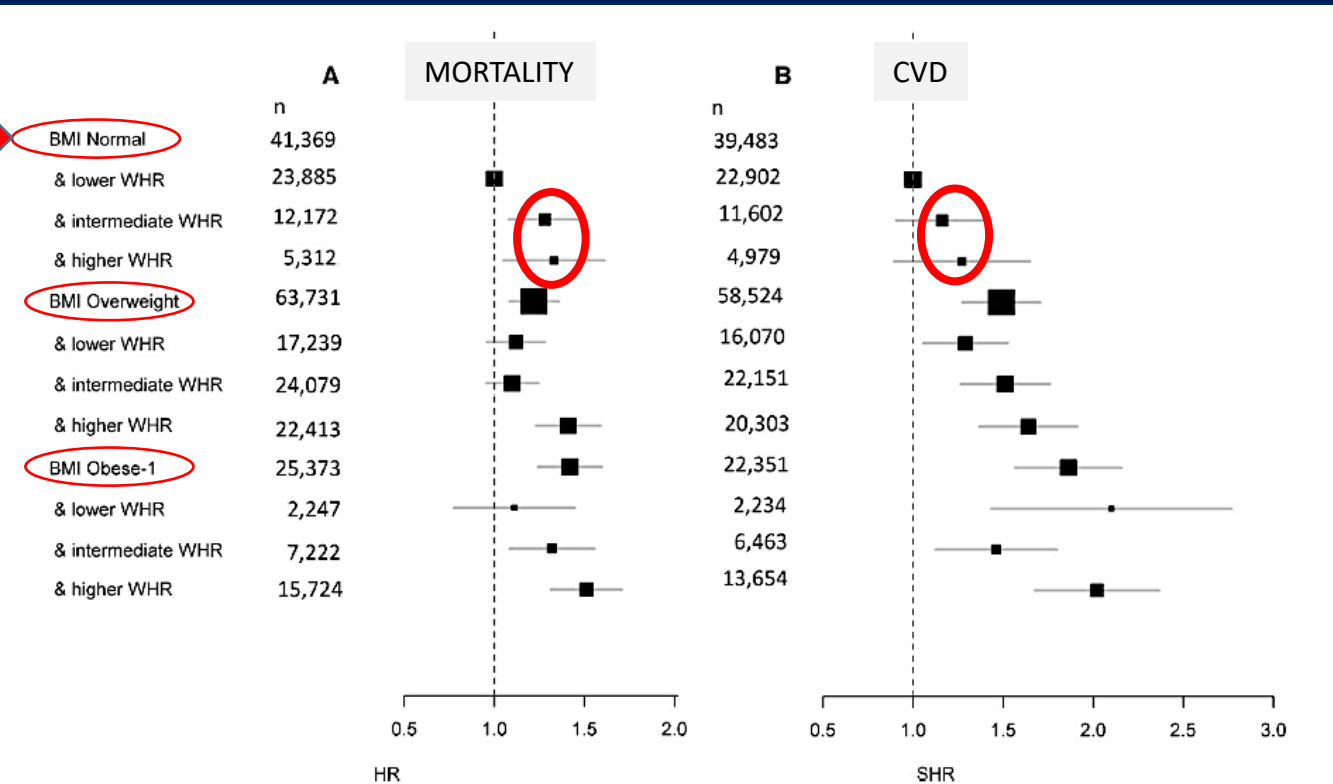
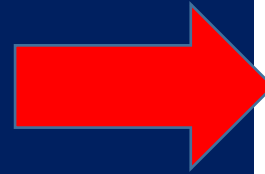
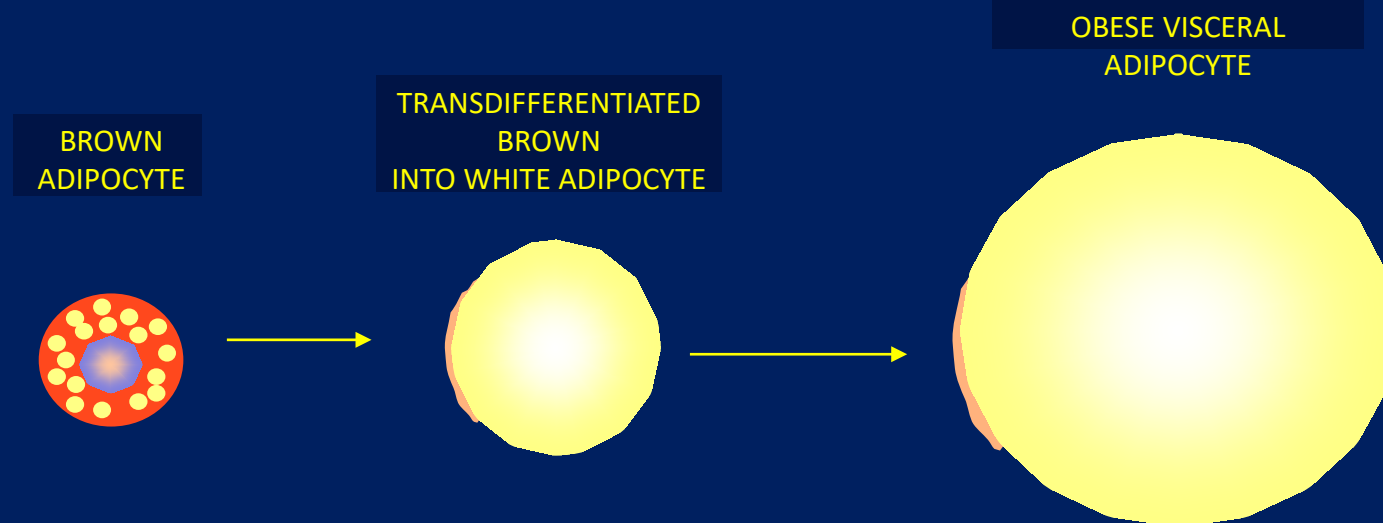
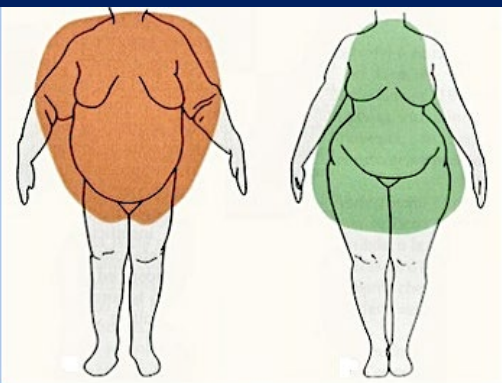
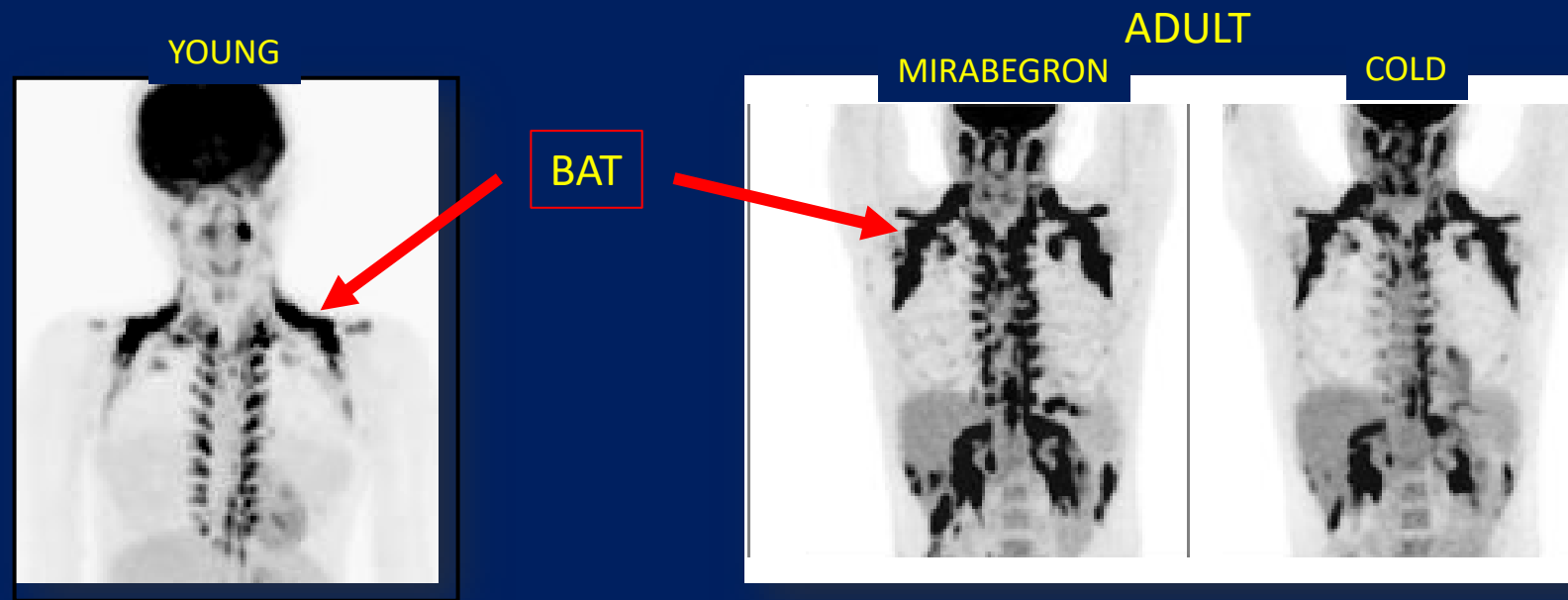
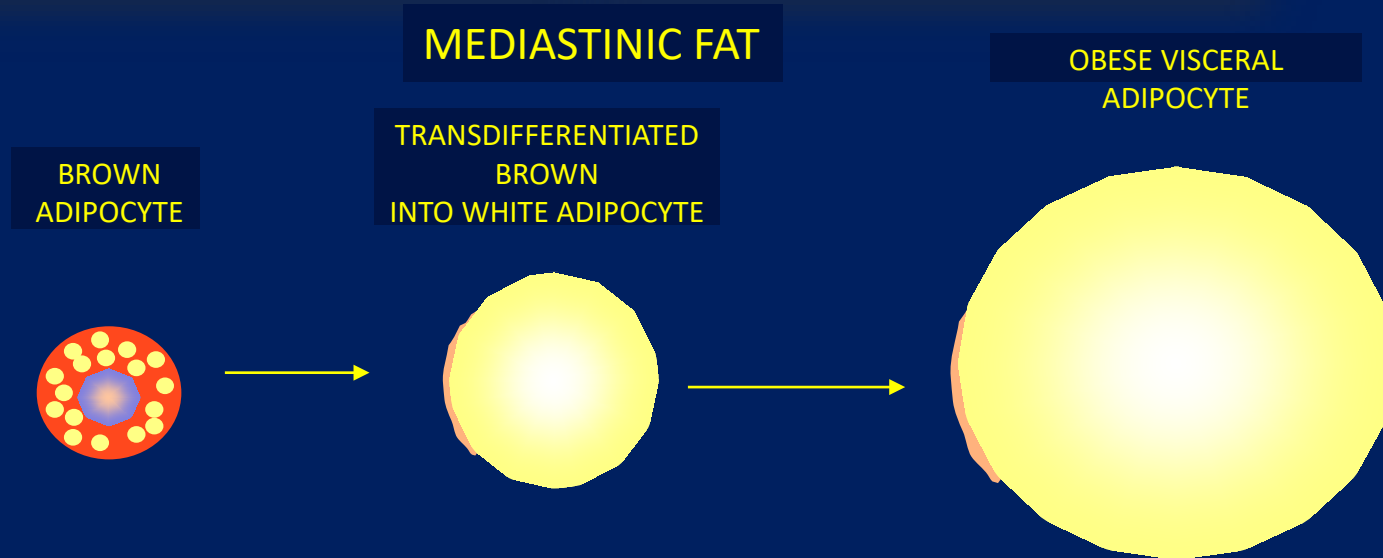
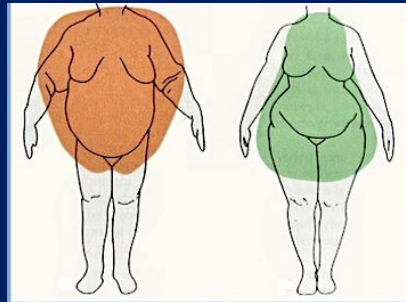
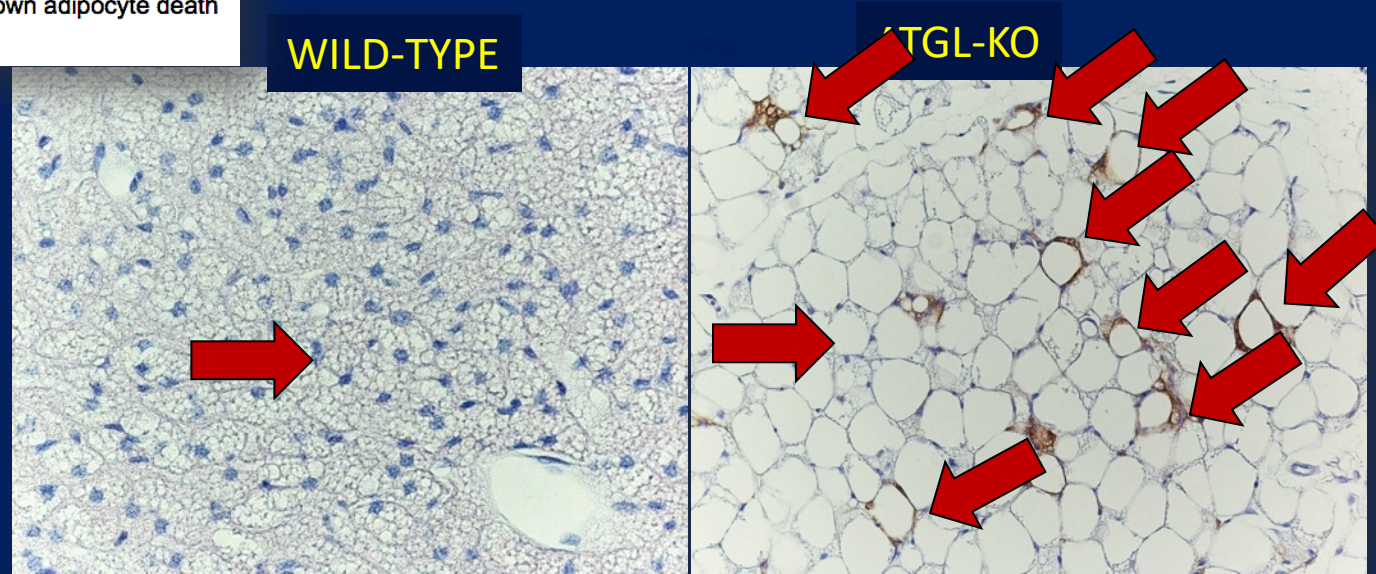


FIGURE 1 Joint association of BMI categories and WHR tertiles with mortality (A) and CAD (B). (A) Joint associations of BMI categories and WHR tertiles with mortality ($n = 130,473$) for “healthier agers” aged 60–69 y from the UK Biobank. (B) Joint associations of BMI categories and WHR tertiles with incident CAD. Previous cases of CAD were excluded ($n = 10,115$). Competing risk models (accounting for mortality) were used for CAD with SHRs reported. Survival models and competing risk models were adjusted for age, sex, smoking history (never or former smoker), alcohol intake, and educational attainment. Healthier agers included current nonsmokers and individuals without recent or disease-associated (e.g., from dementia, heart failure, or cancer) weight loss. The first 2 y of follow-up were excluded. Values are presented as the number of participants within each category reported for mortality and CAD. The reference group comprised individuals with a normal BMI and lower WHR tertile. WHR was categorized by population sex-specific tertiles as follows: lower WHR, <0.91 for men and <0.79 for women; intermediate WHR, 0.91 to <0.96 for men and 0.79 to <0.85 for women; and higher WHR, ≥ 0.96 for men and ≥ 0.85 for women. BMI categories (in kg/m^2) were as follows: normal weight, 18.5 to <25 ; overweight, 25 to <30 ; and class I obesity, 30 to <35 . For BMI groupings for BMI and WHR, see Table 1. CAD, coronary artery disease; Obese-1, class I obesity; SHR, sub-HR; WHR, waist-to-hip ratio.



Brown adipose tissue whitening leads to brown adipocyte death and adipose tissue inflammation^[S]

Kotzbeck P et al J Lip Res 2018



UMANI?

T2 DIABETIC OBESE PATIENTS



S. CAMASTRA

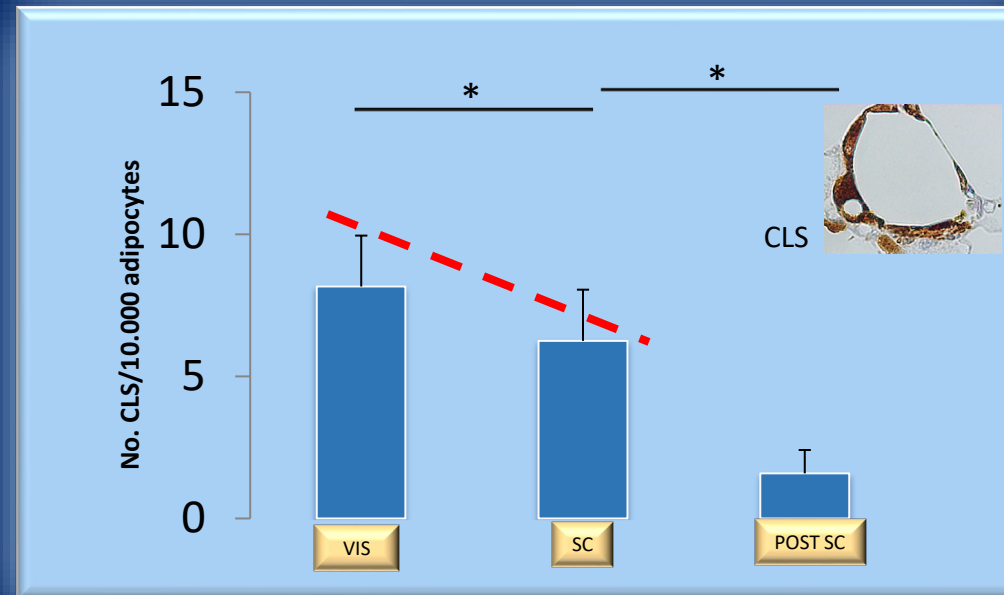
VIS = Omental fat

SC = Subcutaneous fat

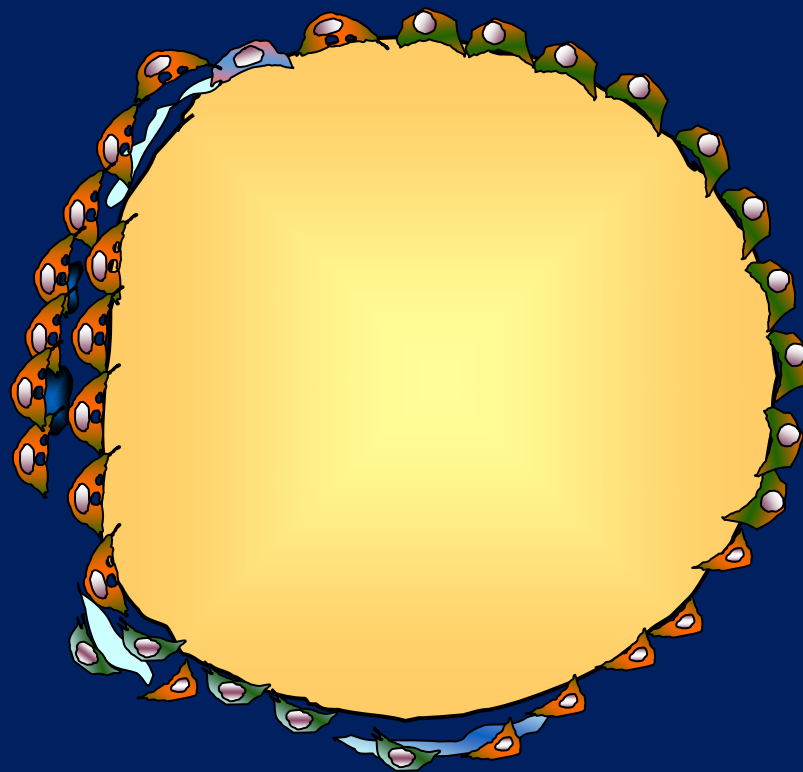
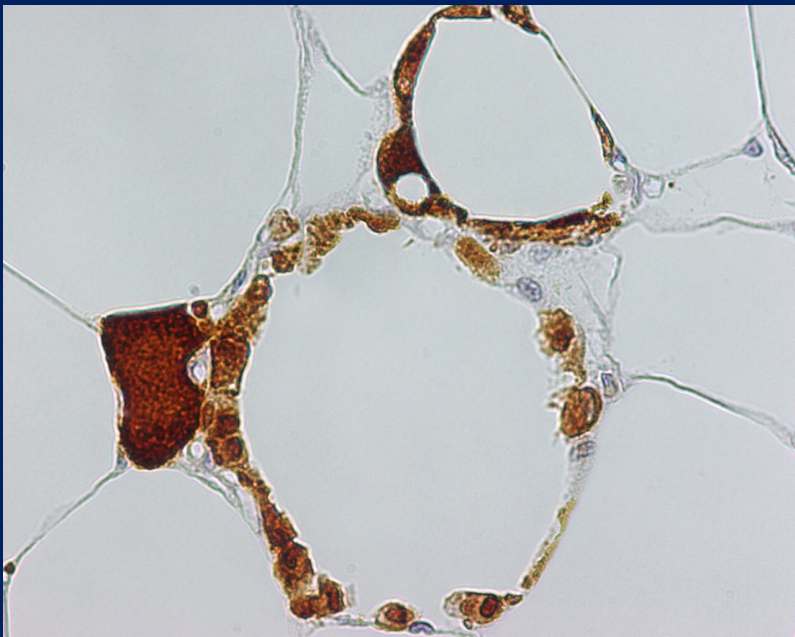
POST SC = Post surgery
subcutaneous fat



E. FERRANNINI



CLS



SLIDE OF SAVERIO CINTI-ANCONA

Cinti et al J Lip Res 2005
Murano et al J Lip Res 2008
Giordano et al J Lip Res 2013
Camastra et al Sci Rep 2017
Kotzbeck et al J Lip Res 2018

Pathogenesis of inflammation and T2 Diabetes

Alzheimer

Cancer

Chronic low grade inflammation

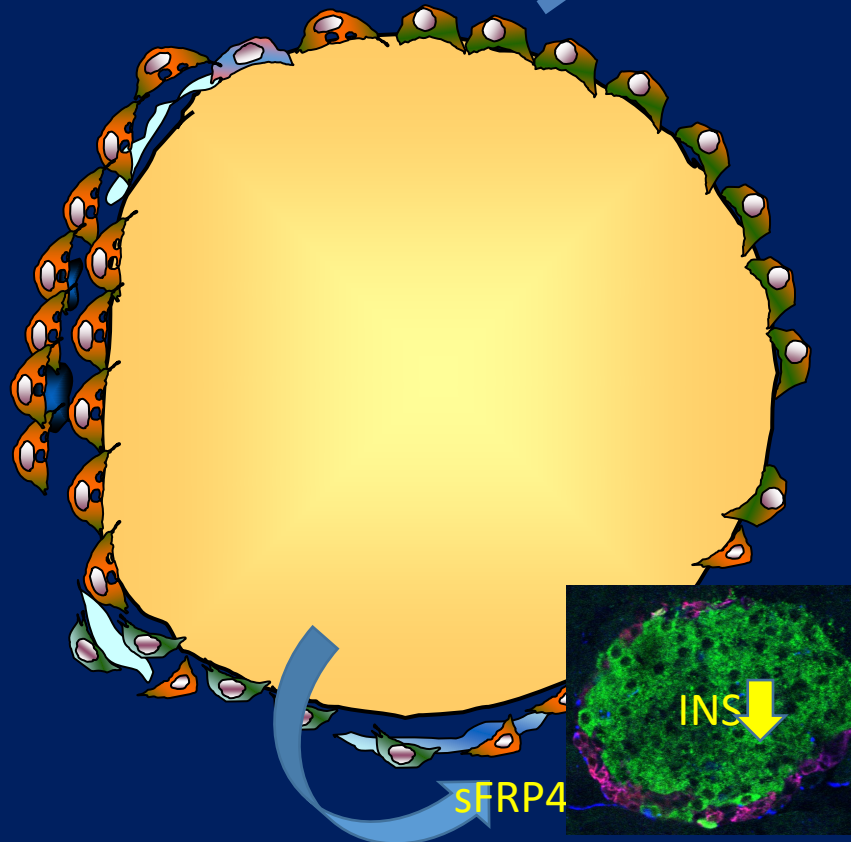
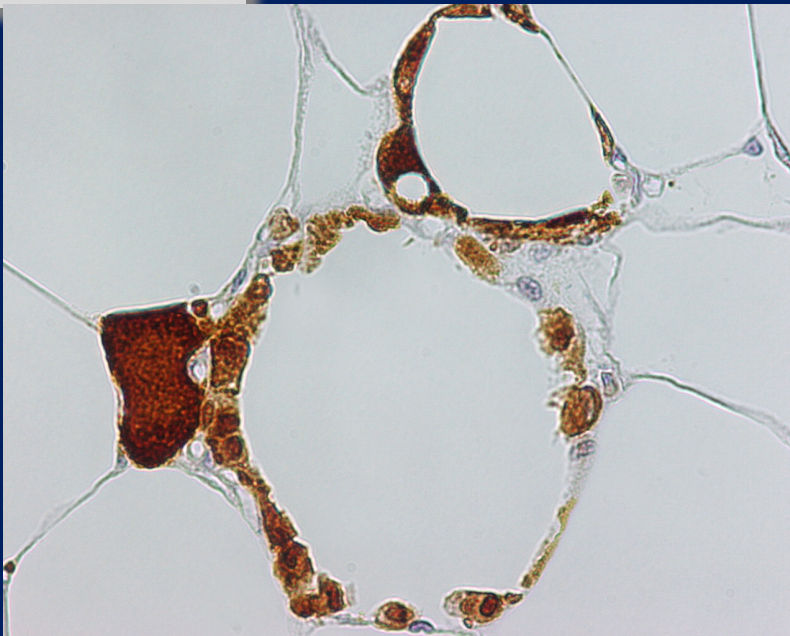
TNF α , IL6...
Resistin
Exosome-MicroRNA

insulin resistance

T2 DIABETES

CLS

Cinti et al J Lip Res 2005
Murano et al J Lip Res 2008
Giordano et al J Lip Res 2013
Camastra et al Sci Rep 2017
Kotzbeck et al J Lip Res 2018



Increased density of innervation in the pancreatic parenchymal nerve fibers of Langerhans of obese mice

I Giannulis¹, E Mondini¹, F Cinti¹, A Fronti², D Accili³, S Cinti⁴

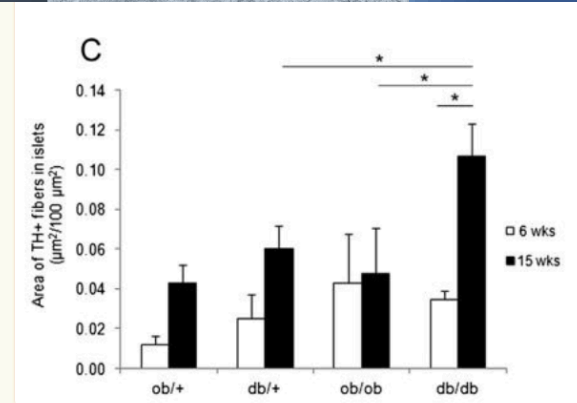
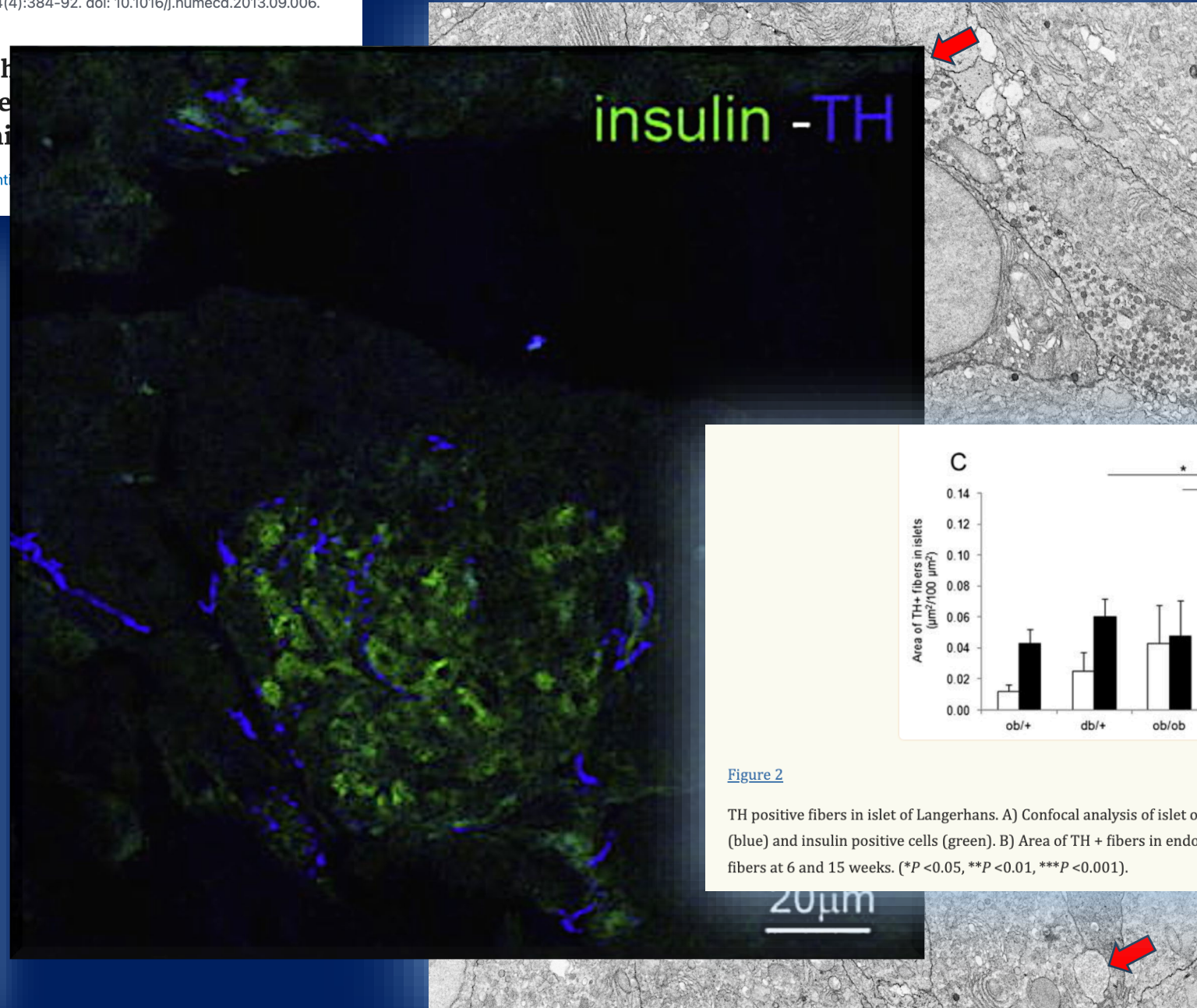
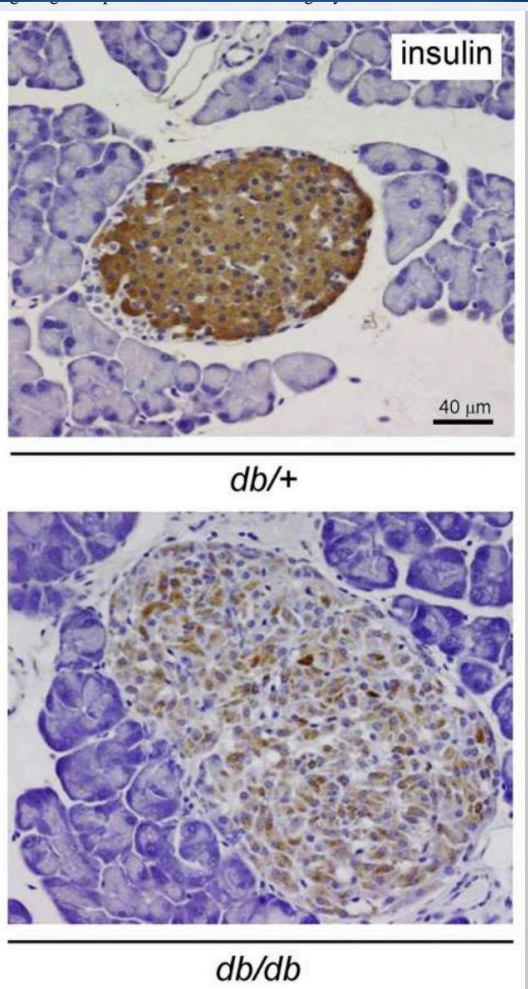
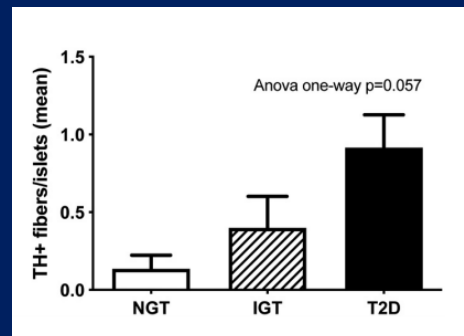
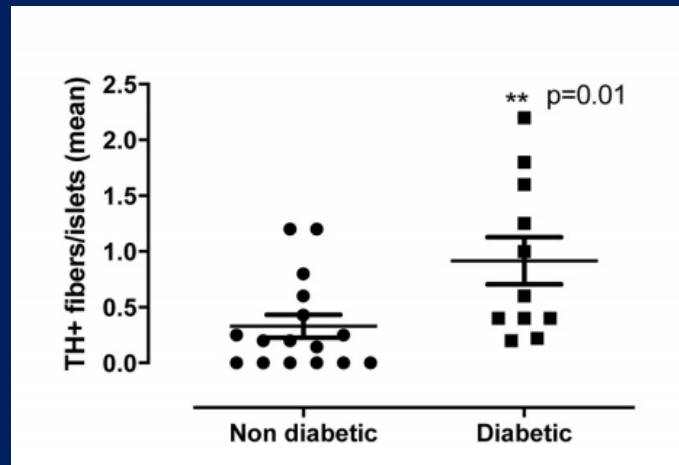


Figure 2

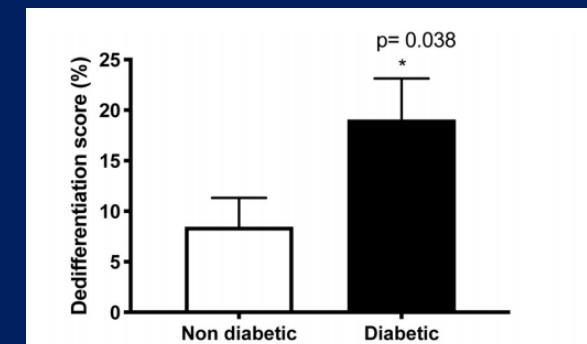
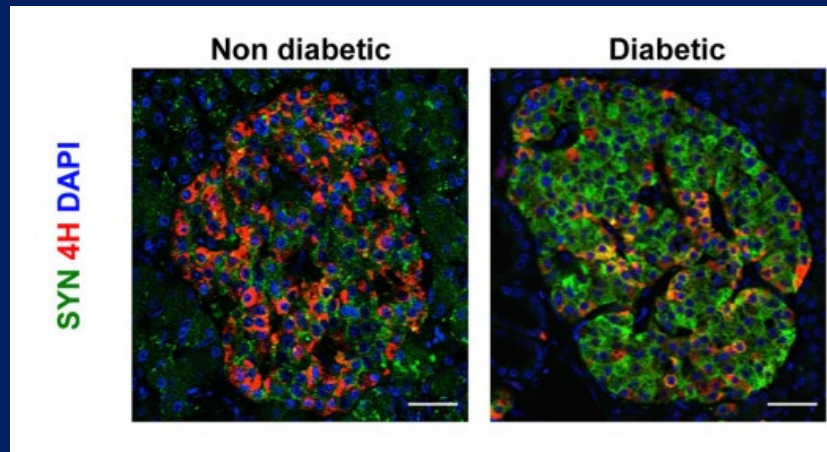
TH positive fibers in islet of Langerhans. A) Confocal analysis of islet of Langerhans in *db/db* mouse. TH + fibers (blue) and insulin positive cells (green). B) Area of TH + fibers in endocrine and exocrine pancreas. C) Area of TH + fibers at 6 and 15 weeks. (* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$).

NORADRENERGIC FIBERS ARE ASSOCIATED WITH BETA-CELL DEDIFFERENTIATION AND IMPAIRED BETA-CELL FUNCTION IN HUMANS

In pancreas of diabetic subjects a **3-fold increase** of noradrenergic fibers has been observed compared to non-diabetic one



Fibers directly relates to the % of dedifferentiated cells within the islets and is associated with worsening β cell function



[Diabetologia](#). 2018; 61(2): 257–264.

Published online 2017 Dec 9. doi: [10.1007/s00125-017-4513-y](https://doi.org/10.1007/s00125-017-4513-y)

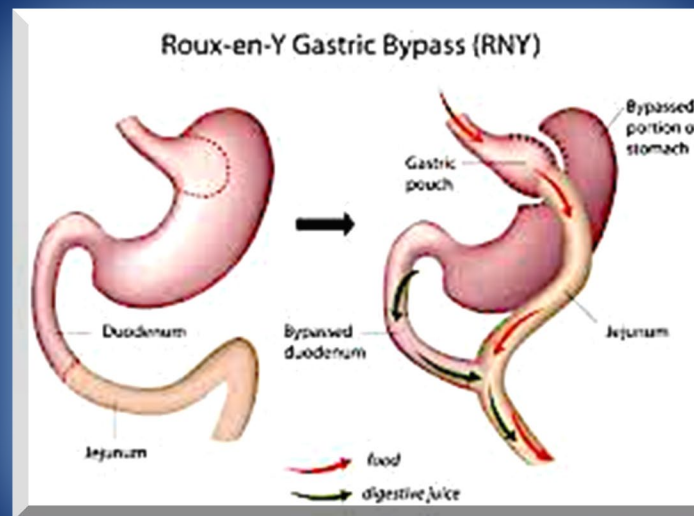
PMCID: PMC6448

PMID: [29224](#)

Metabolic surgery for the treatment of type 2 diabetes in obese individuals

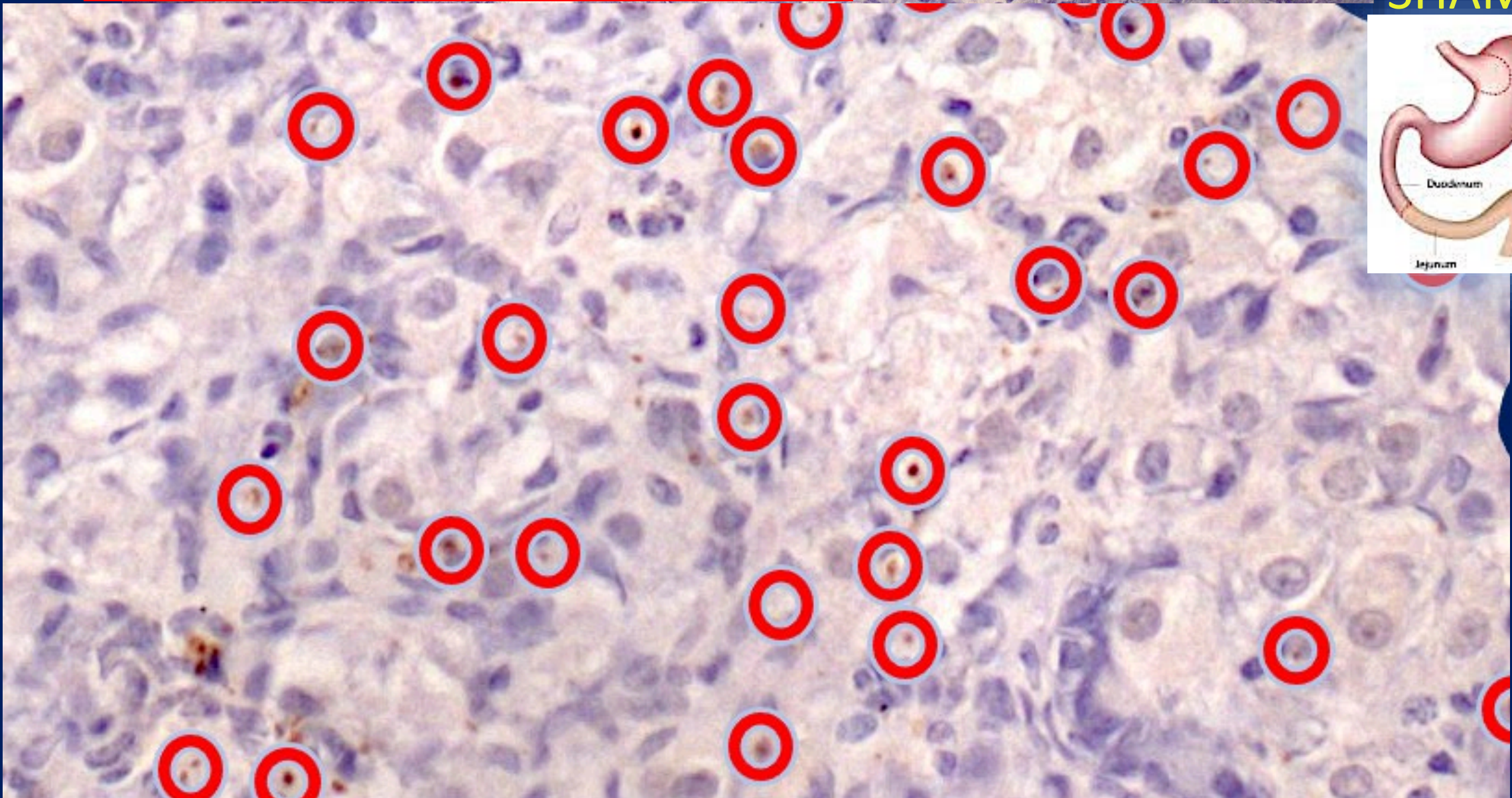
[David E. Cummings](#)^{✉1,2} and [Francesco Rubino](#)^{✉3}

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NORADRENERGIC FIBERS IN SHAM OPERATED OBESE RAT

SHAM



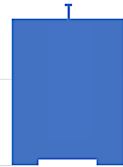
NORADRENERGIC FIBERS IN BY PASS OPERATED OBESE RAT

BY PASS

n TH+ FIBERS/ISLET +SE

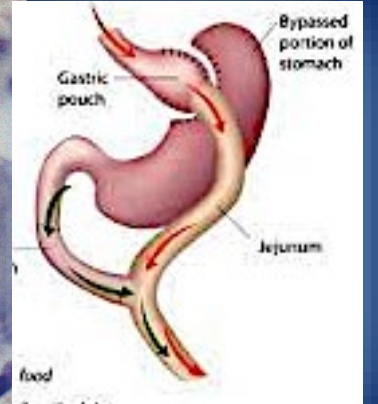
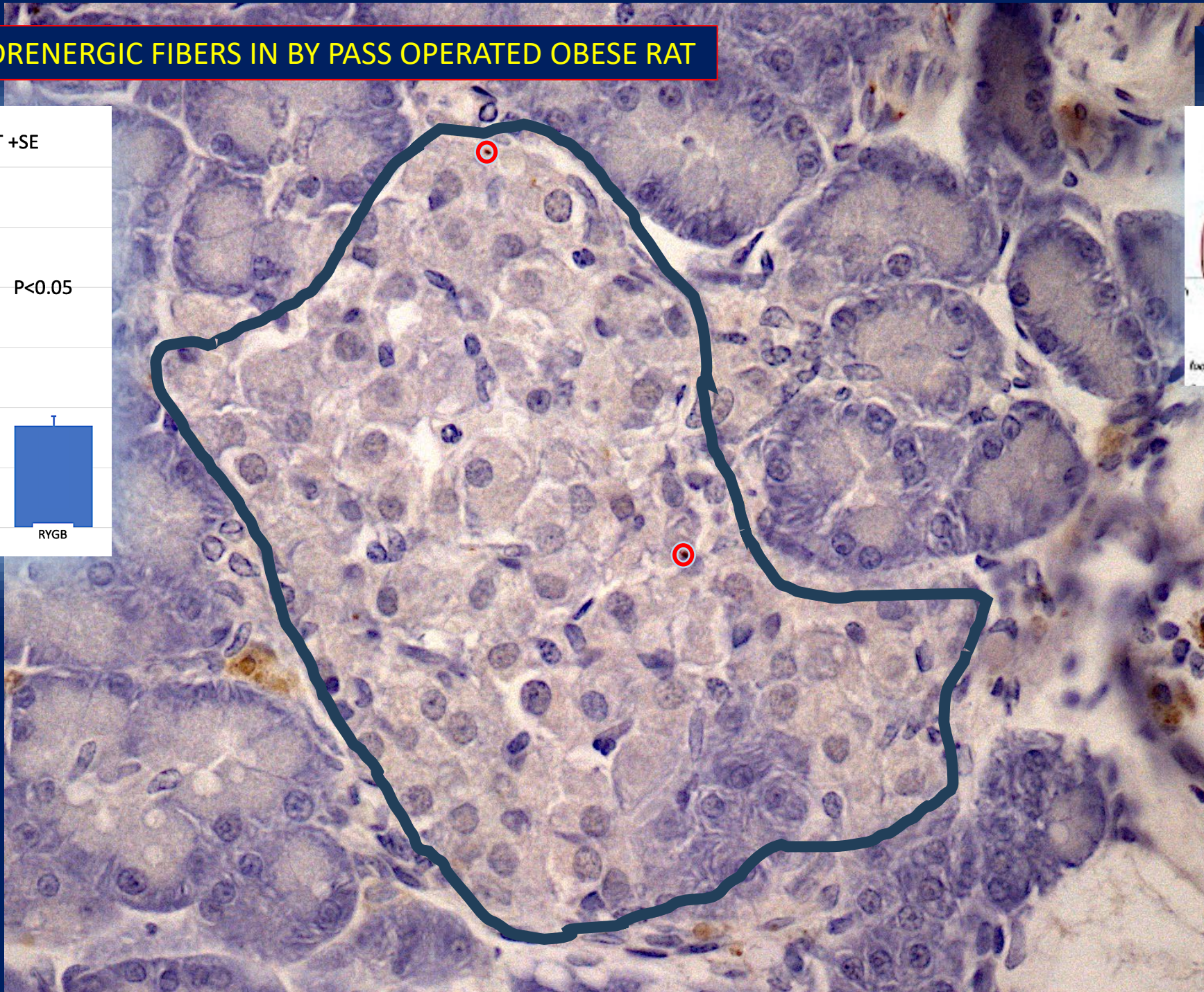


SHAM



RYGB

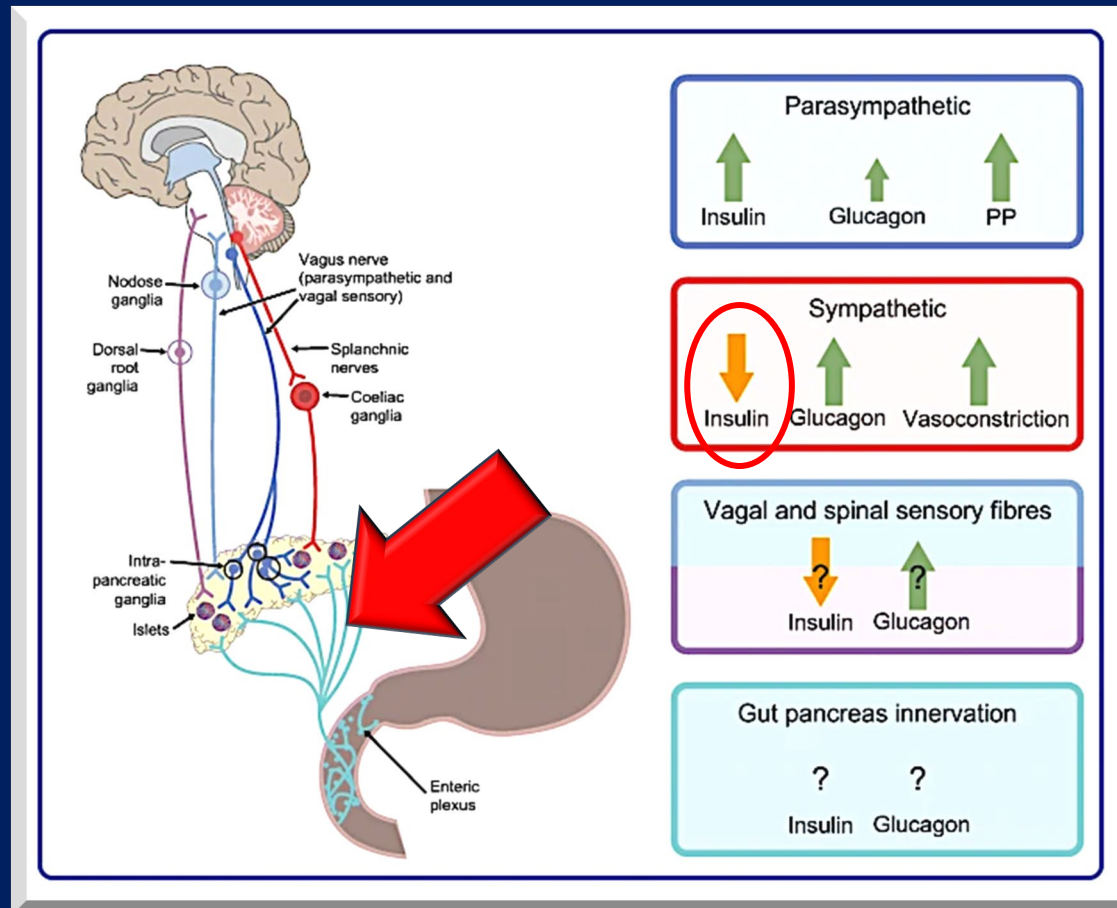
$P < 0.05$



Unravelling innervation of pancreatic islets

[Rollie F. Hampton](#), [Maria Jimenez-Gonzalez](#) & [Sarah A. Stanley](#) [✉](#)

[Diabetologia](#) **65**, 1069–1084 (2022) | [Cite this article](#)



Pathogenesis of inflammation and T2 Diabetes

Alzheimer

Chronic low grade inflammation

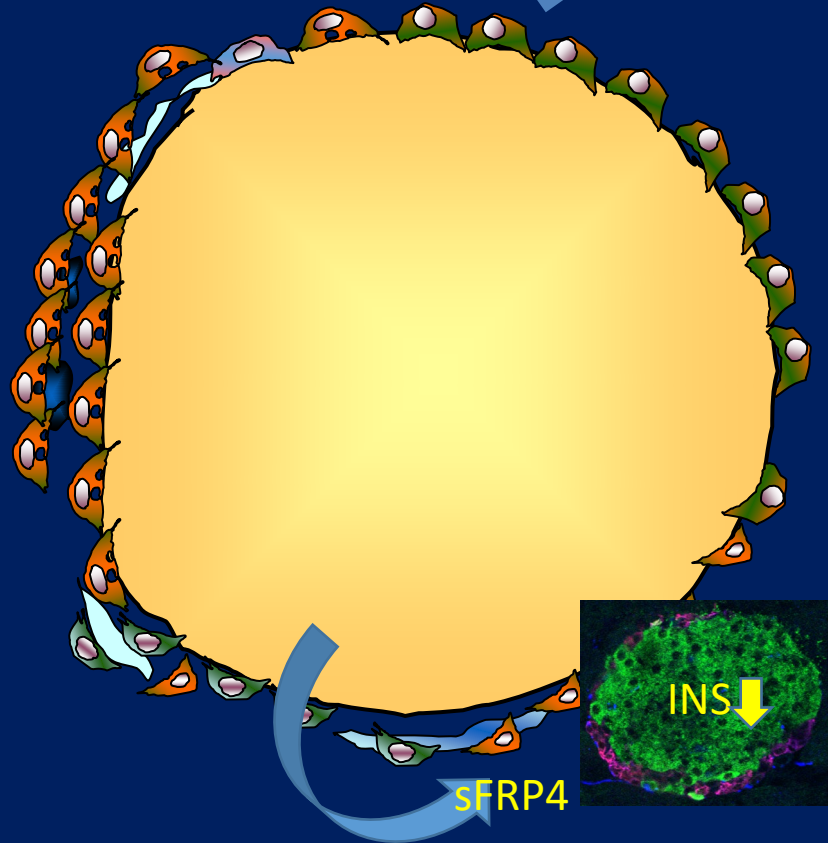
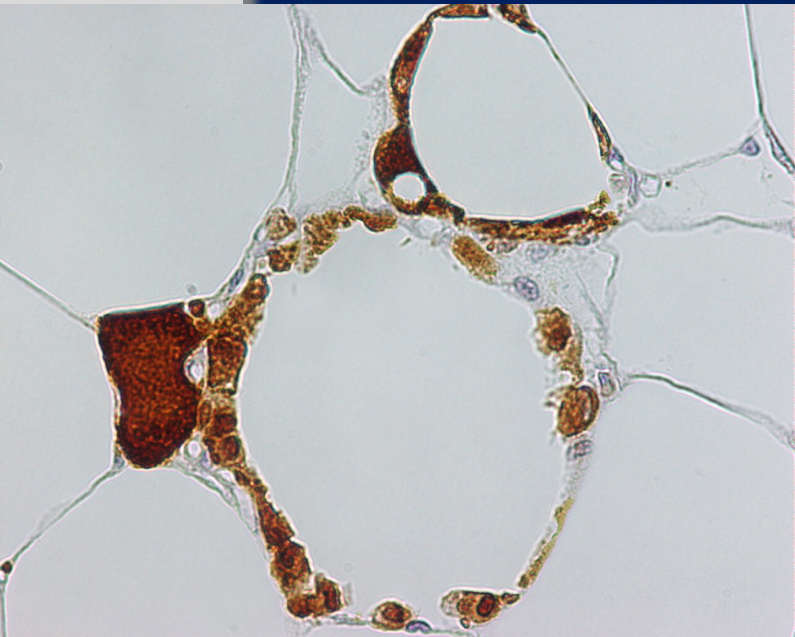
Cancer

TNF α , IL6...
Resistin
Exosome-MicroRNA

insulin resistance

Cinti et al J Lip Res 2005
Murano et al J Lip Res 2008
Giordano et al J Lip Res 2013
Camastra et al Sci Rep 2017
Kotzbeck et al J Lip Res 2018

CLS



> *Nutr Metab Cardiovasc Dis.* 2014 Apr;24(4):384-92. doi: 10.1016/j.numecd.2013.09.006. Epub 2013 Oct 23.
Increased density of inhibitory noradrenergic parenchymal nerve fibers in hypertrophic islets of Langerhans of obese mice
I Giannulis ¹, E Mondini ¹, F Cinti ¹, A Frontini ¹, I Murano ¹, R Barazzoni ², G Barbatelli ¹, D Accili ³, S Cinti ⁴

> *J Clin Endocrinol Metab.* 2016 Mar;101(3):1044-54. doi: 10.1210/jc.2015-2860. Epub 2015 Dec 29.
Evidence of β -Cell Dedifferentiation in Human Type 2 Diabetes
Francesca Cinti ¹, Ryotaro Bouchi ¹, Ja Young Kim-Muller ¹, Yoshiaki Ohmura ¹, P R Sandoval ¹, Matilde Masini ¹, Lorella Marselli ¹, Mara Suleiman ¹, Lloyd E Ratner ¹, Piero Marchetti ¹, Domenico Accili ¹

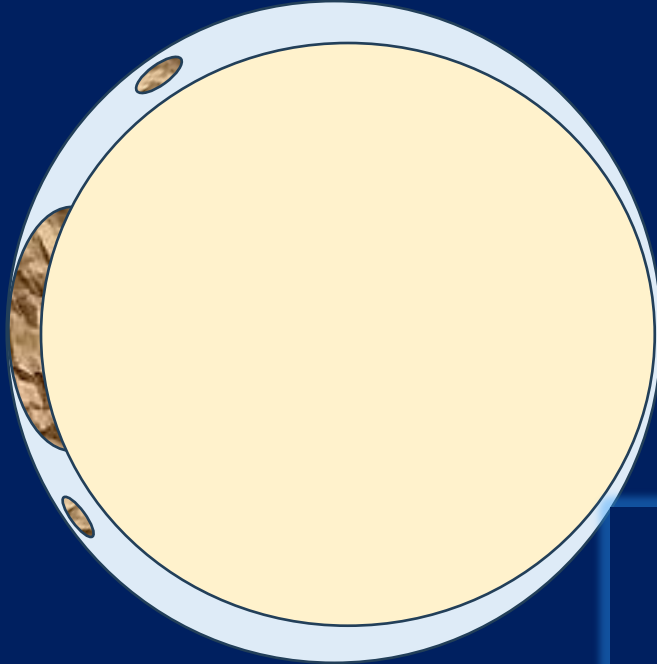
> *Metabolism.* 2021 Jan;114:154414. doi: 10.1016/j.metabol.2020.154414. Epub 2020 Oct 28.
Noradrenergic fibers are associated with beta-cell dedifferentiation and impaired beta-cell function in humans
F Cinti ¹, T Mezza ¹, I Severi ², M Suleiman ³, C M A Cefalo ¹, G P Sorice ¹, S Moffa ¹, F Impronta ¹, G Quero ⁴, S Alfieri ⁴, A Mari ⁵, A Pontecorvi ⁶, L Marselli ³, S Cinti ², P Marchetti ³, A Giaccari ⁷

T2 DIABETES

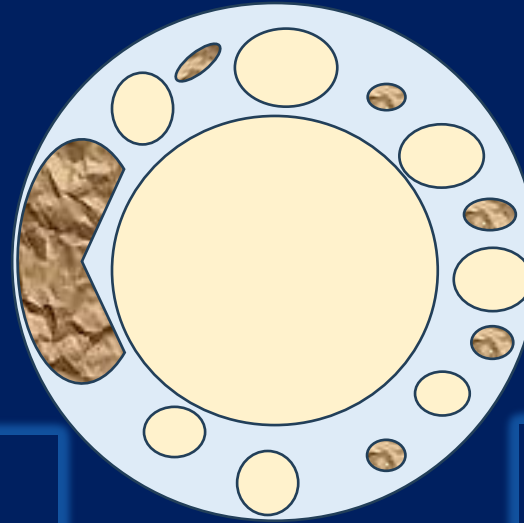
BIANCO

PAUCILOCULARE (BEIGE)

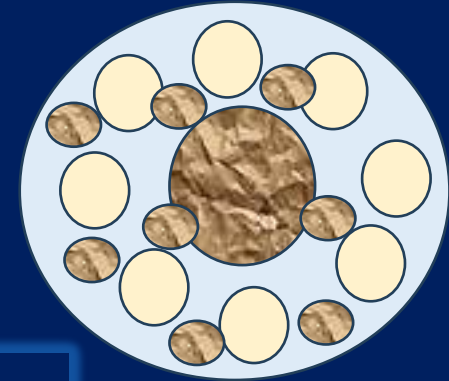
BRUNO



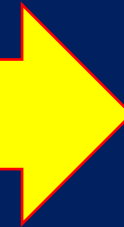
COLD
DRUGS
NUTRIENTS
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COLD
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