

Autofagia en la defense contra el envejecimiento



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Marion Bessin Liver Research Center

Institute for Aging Research



Agradecimientos



Mis padres....

*por tantas
y tantas cosas...*

Agradecimientos



Erwin Knecht



Fred Dice



Departamento de fisiologia

Ximo Roma

Agradecimientos



Fernando Macian



Los verdaderos protagonistas....



Susmita



Eloy



Esperanza



Bindi



Benjamin



Inmaculada



Antonio



Qixheng



Luisa



Julio



Nadia



Luciana



Shuxian



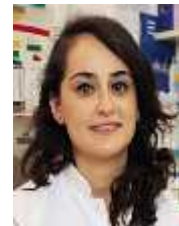
Yves



Phillip



Erika



Kumsal



Ashish



Urmi



Judy



Guy



Marta



Roberta



Esther



Alejandro



Masha



Hiroshi



Lori



Jose



Jaime



Sunandini



Samantha



Jaime



Caroline



Joan

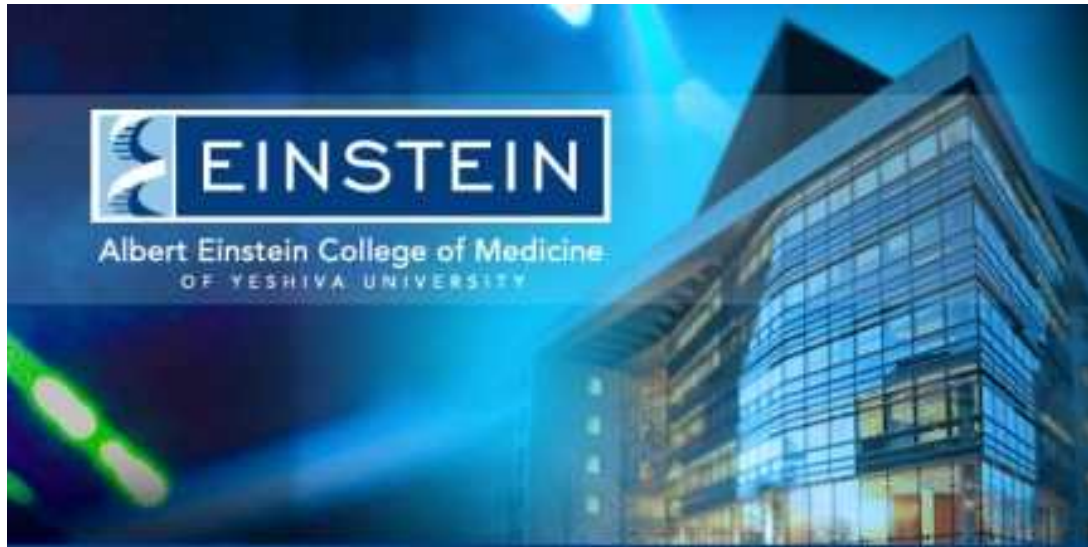


Olatz



Barbara

Autofagia en la defense contra el envejecimiento



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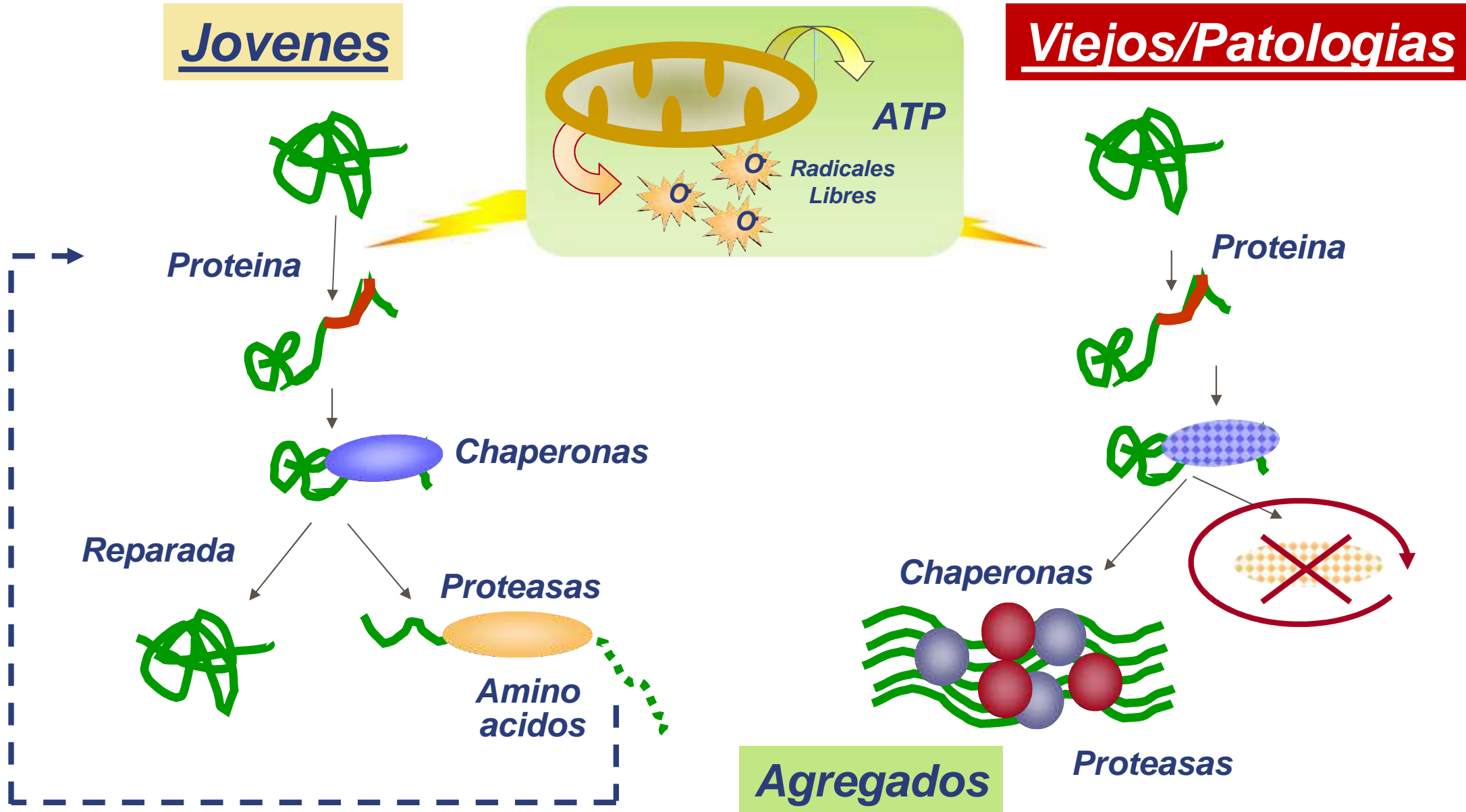
Institute for Aging Research



CONTROL DE CALIDAD CELULAR

Jovenes

Viejos/Patologías



Las células tienen muchos sistemas de limpieza

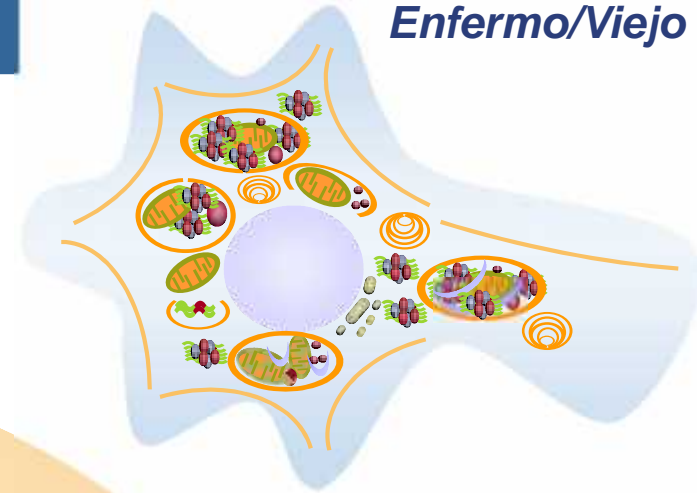
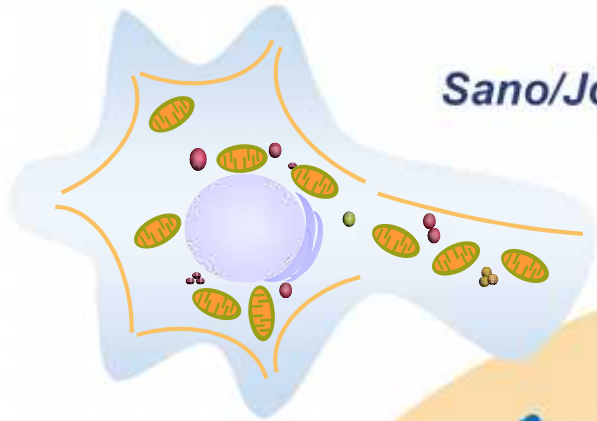
Sano/Joven

Enfermo/Viejo

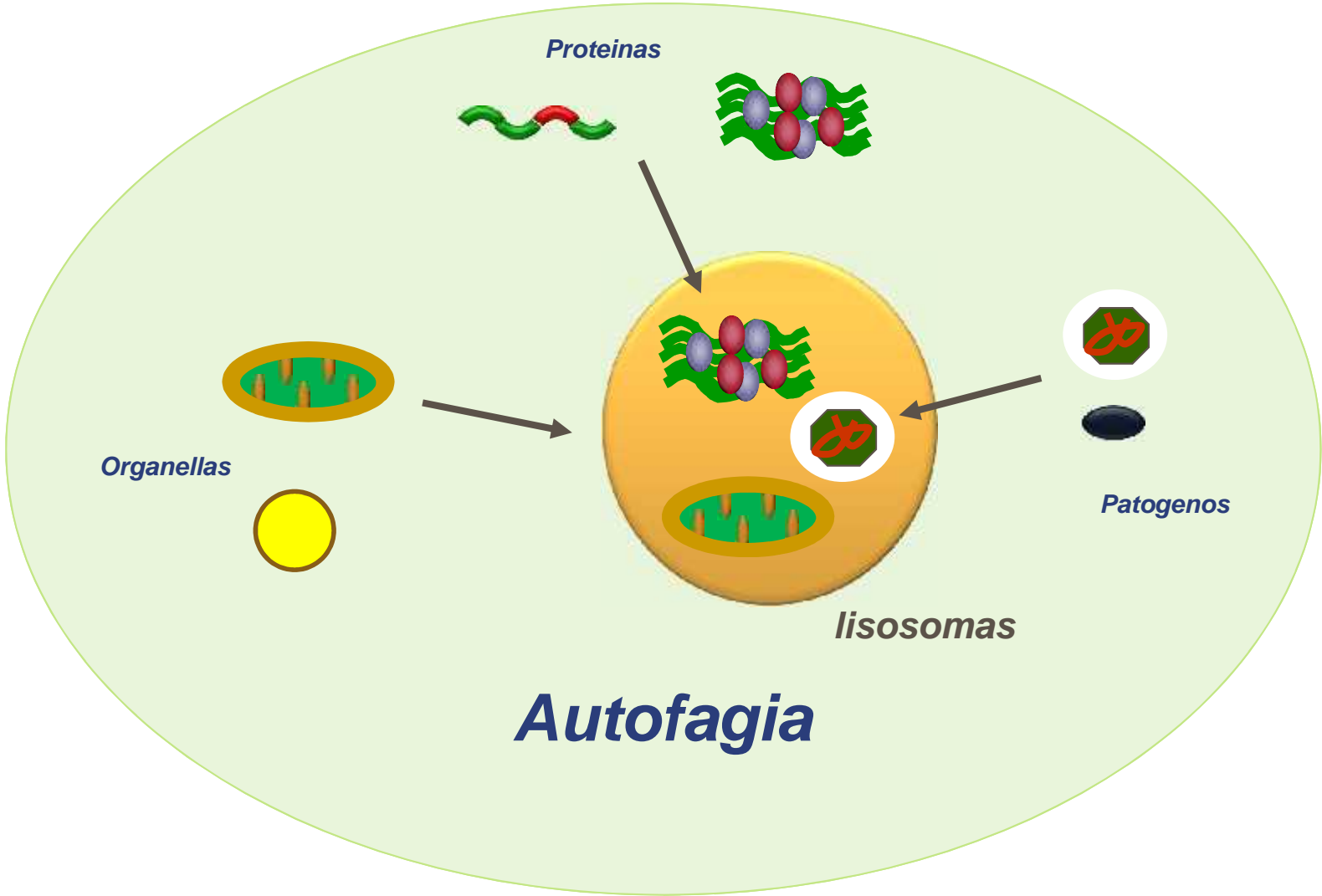
Proteína Normal



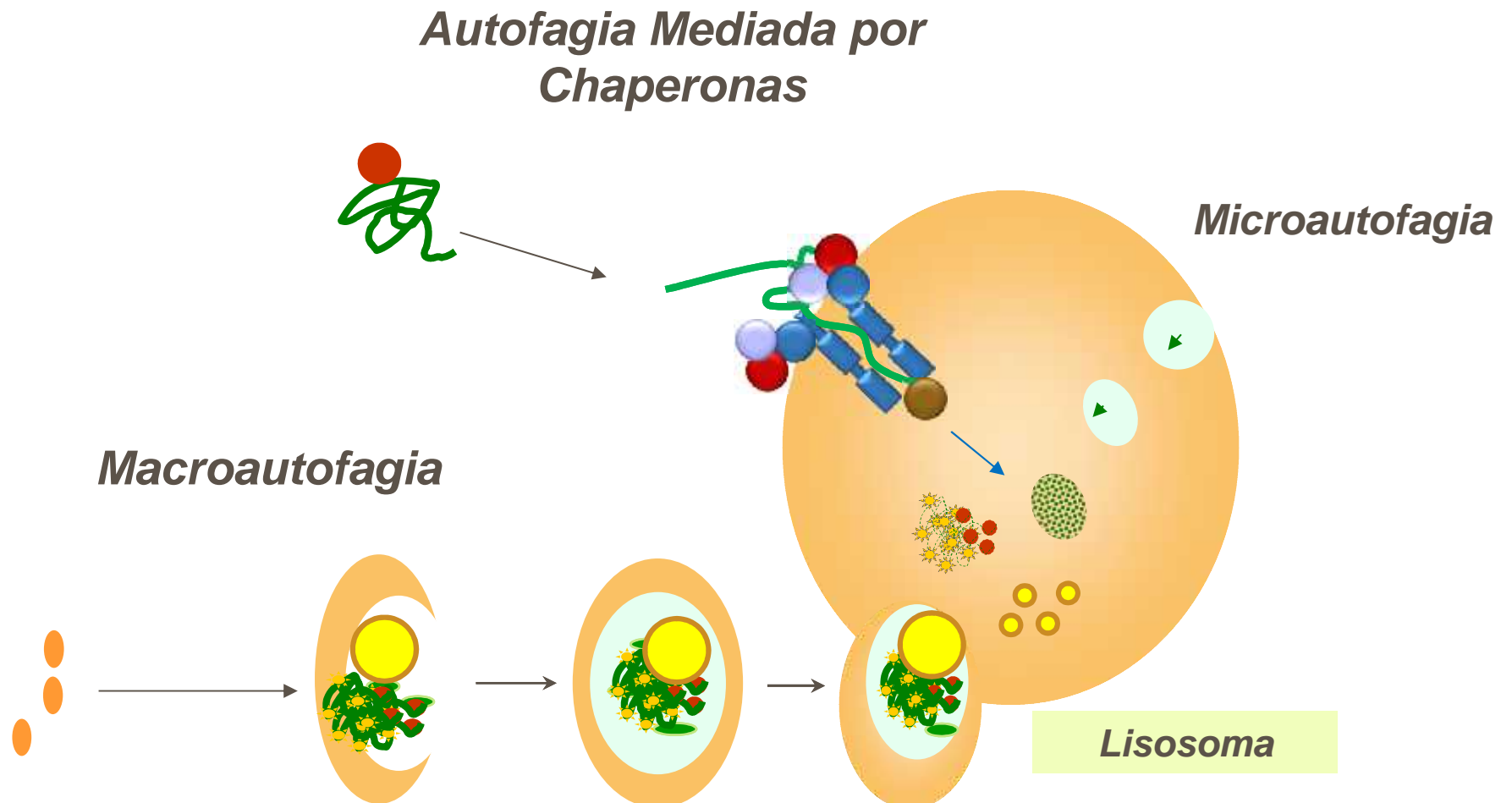
Proteína dañada



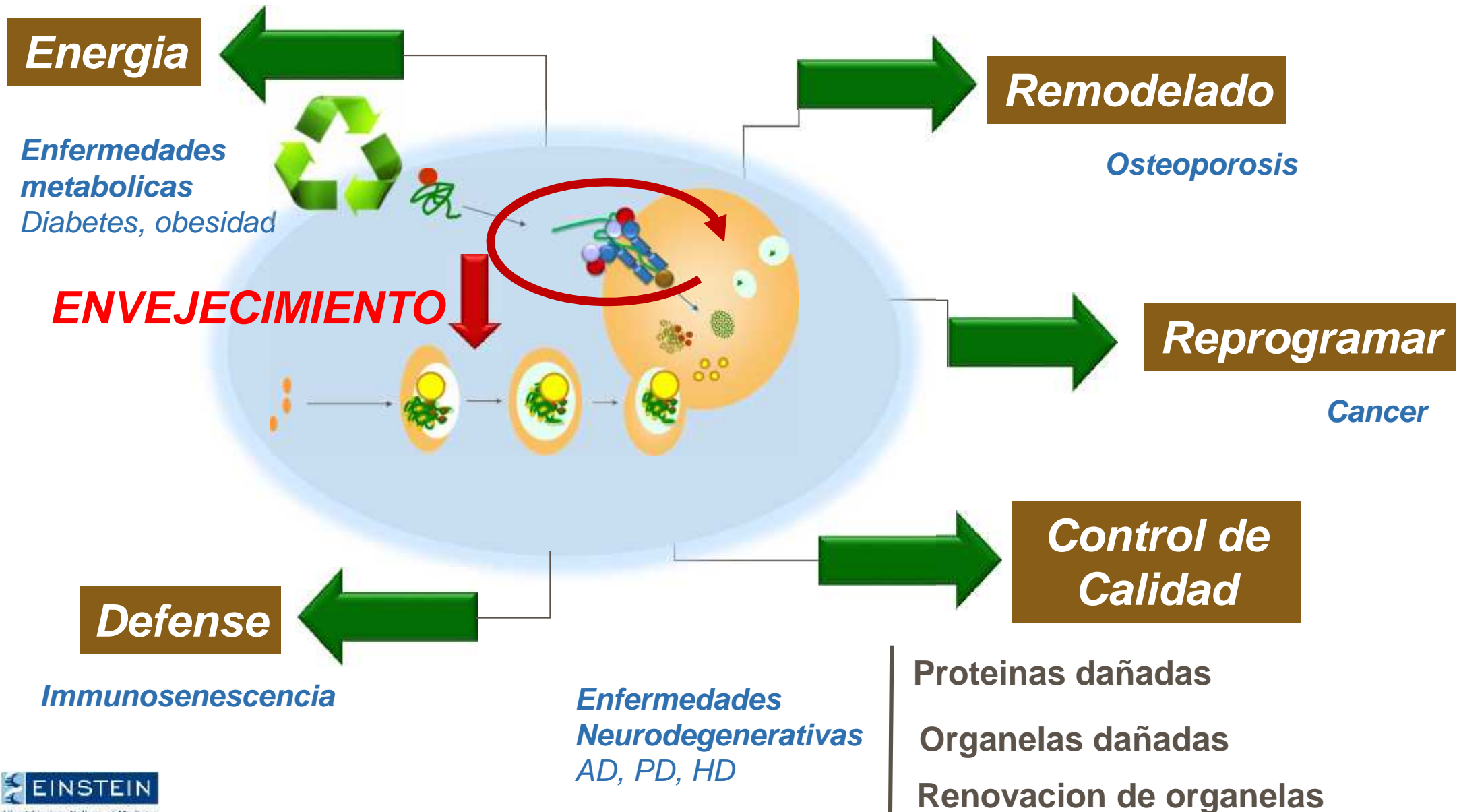
Autofagia



Tipos de Autofagia in Mamíferos



Funciones de la autofagia



Autofagia y el Envejecimiento

1

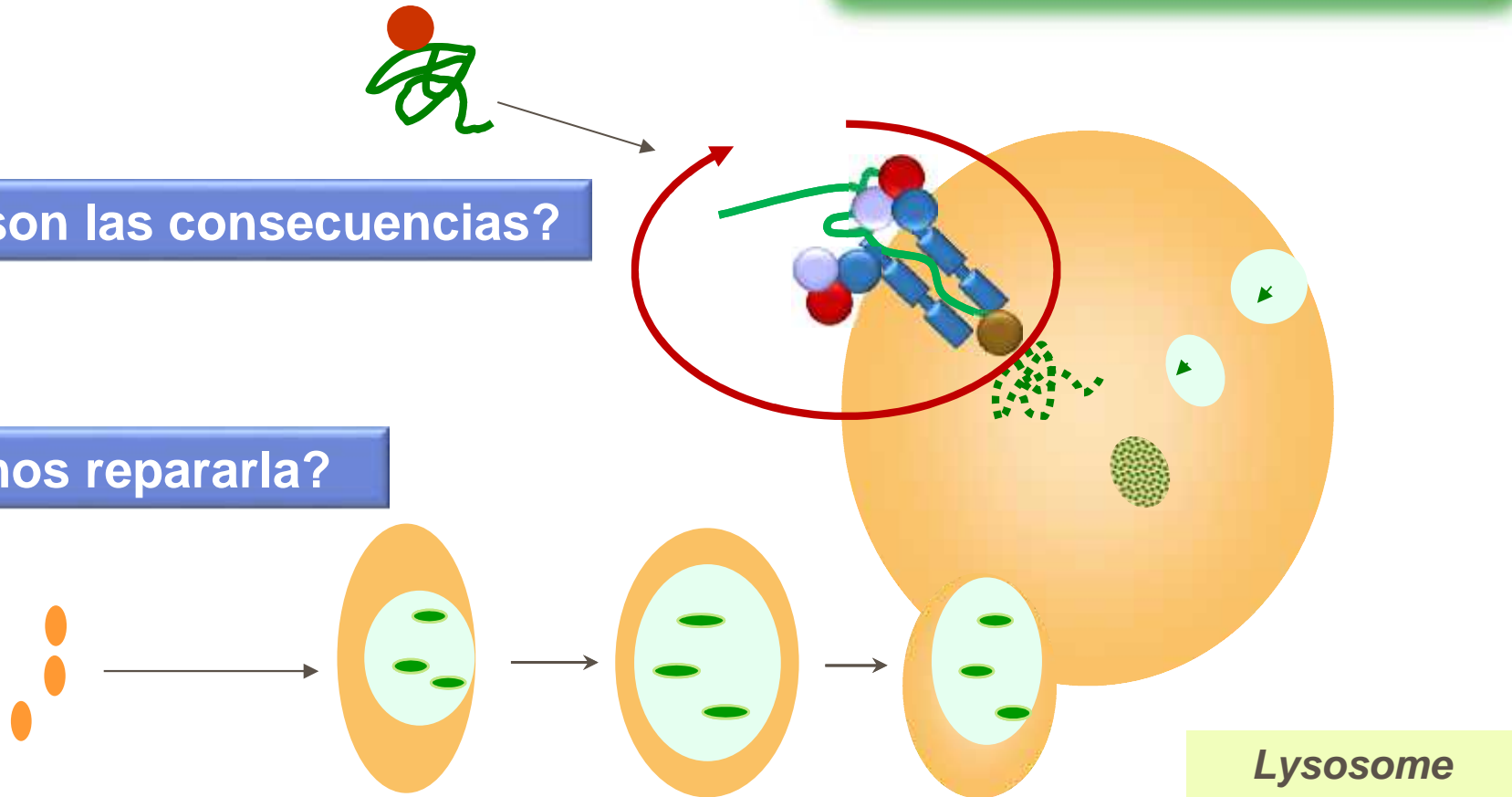
Porque no funciona?

2

Cuales son las consecuencias?

3

Podemos repararla?



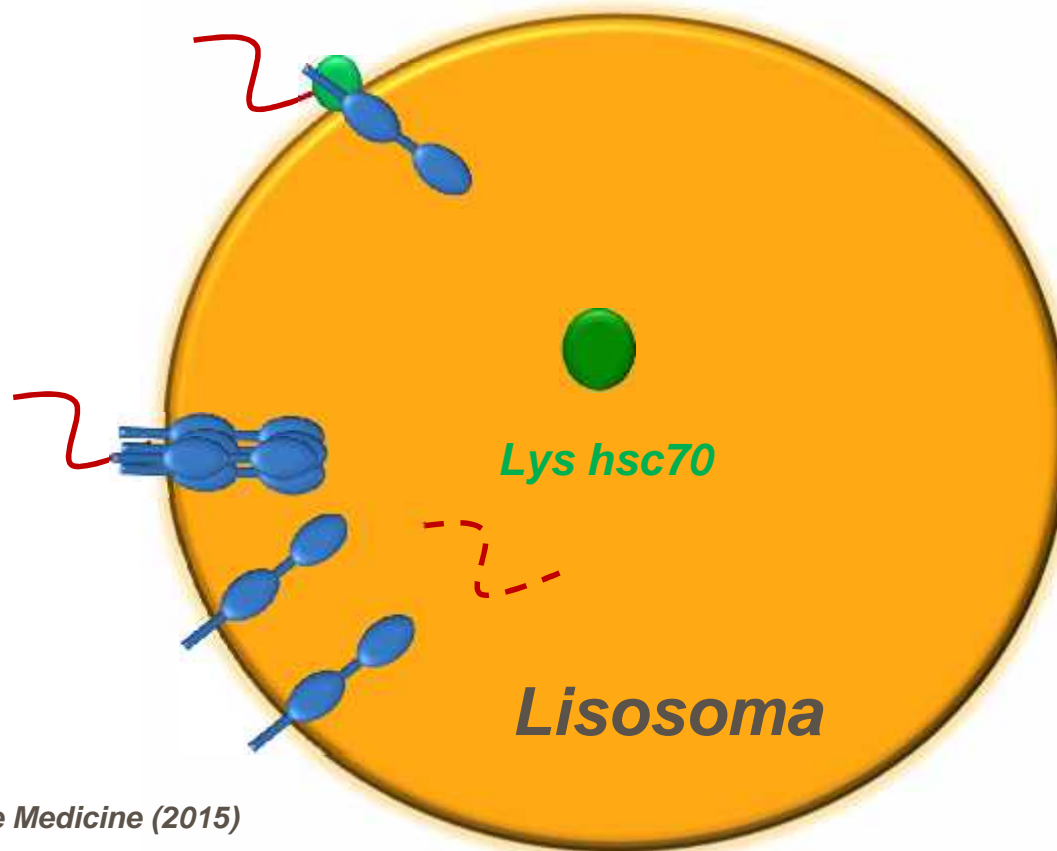
Autofagia mediada por chaperonas (CMA)

Proteina substrato



LAMP-2A

Complejo de translocacion



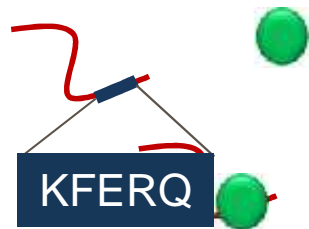
Kaushik and Cuervo, Nature Medicine (2015)

Kaushik and Cuervo, Trends in Cell Biology (2012)

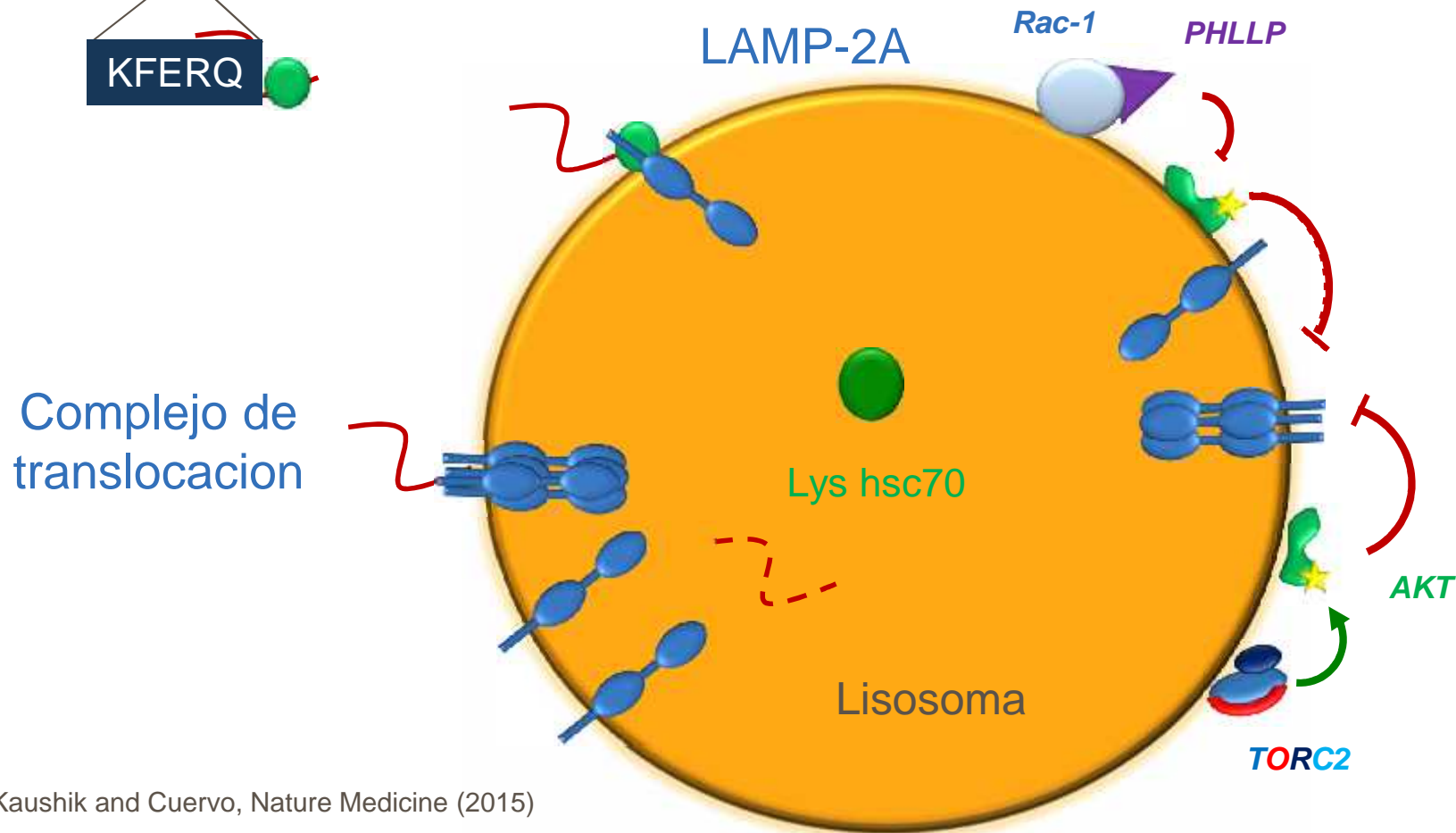
Arias and Cuervo, Current Opinion in Cell Biology (2010)

Autofagia mediada por chaperonas (CMA)

Proteína substrato



Chaperona (hsc70/cochaperones)

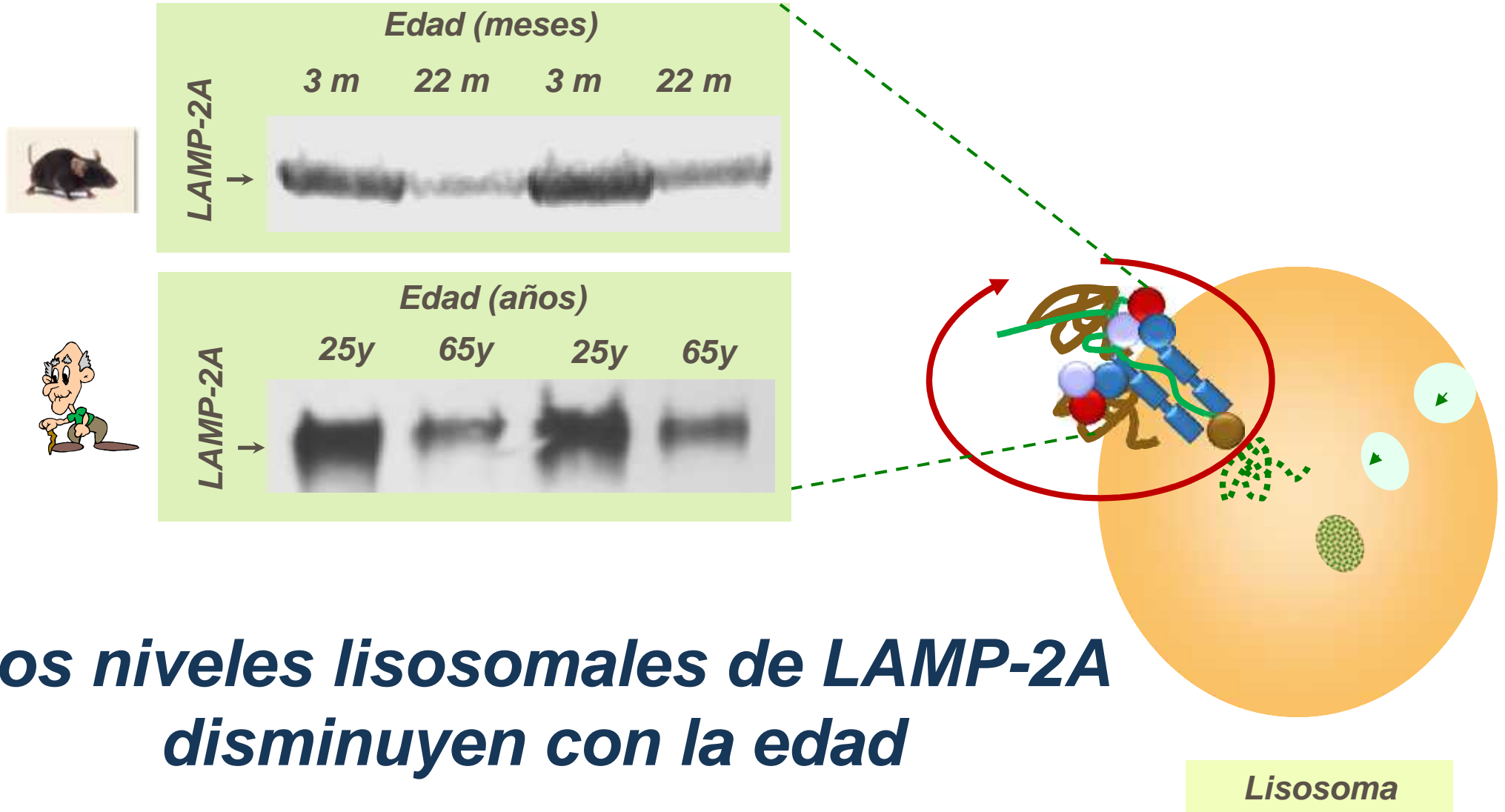


Kaushik and Cuervo, Nature Medicine (2015)

Kaushik and Cuervo, Trends in Cell Biology (2012)

Arias and Cuervo, Current Opinion in Cell Biology (2010)

Fallo funcional de la autofagia en viejos



CMA y neurodegeneracion



Samantha



Benjamin



Esther



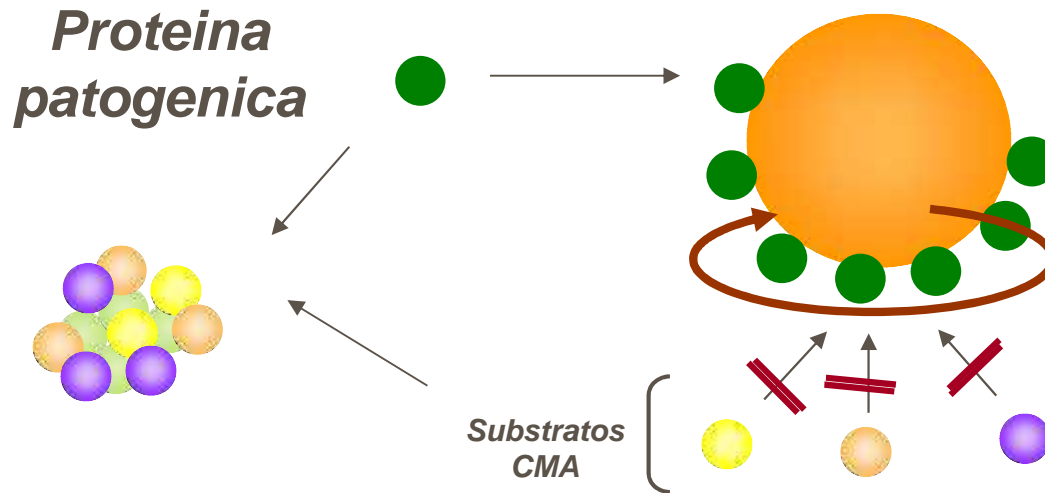
Hiroshi



Inmaculada



Marta



D. Sulzer	P. Lansbury
R. Nixon	E. Mandelkow
H. Ischiropoulos	D. DiMonte
L. Thompson	A. Consiglio/ A. Raya

LRRK2

VPS35

SYN

Enfermedad de Parkinson

TAU

Enfermedad de Alzheimer/Taup.

HTT

Enfermedad de Huntington

Orenstein et al. (2013) *Nat Neurosci*
 Koga et al. (2011) *J. Neurosci*
 Wang et al. (2009) *Hum. Mol. Genetics*
 Martinez-Vicente et al. (2008) *J. Clin. Invest.*
 Mak et al. (2010) *J. Biol. Chem.*
 Cuervo et al. (2004) *Science*

CMA y neurodegeneración



Samantha

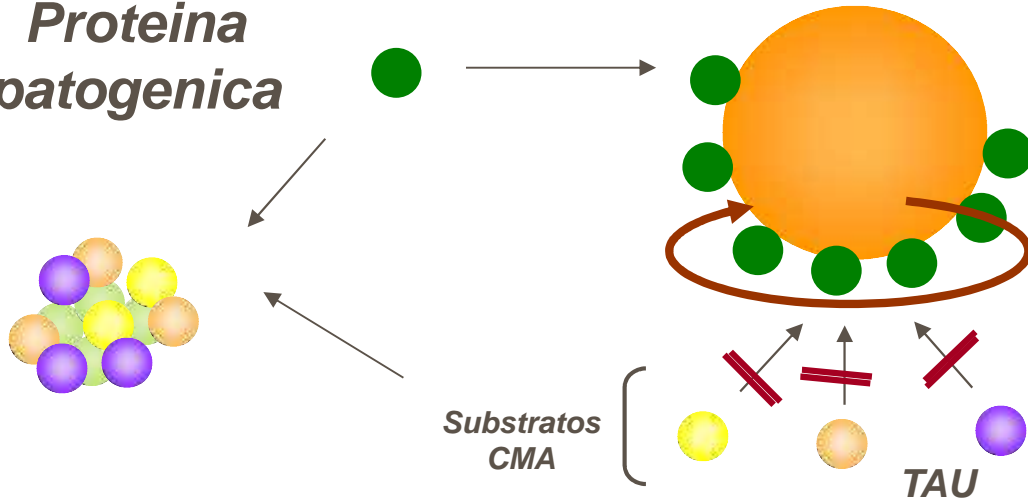


Benjamin



Estrella

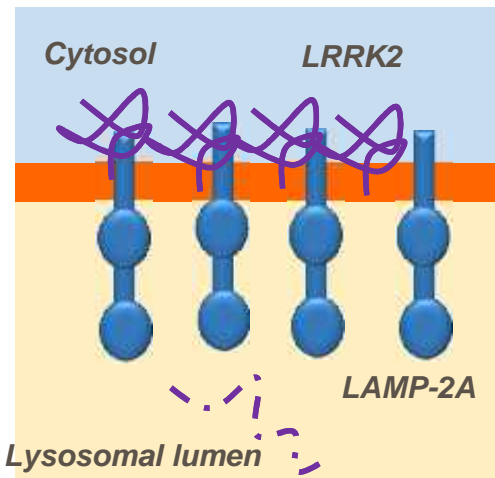
Proteína patogénica



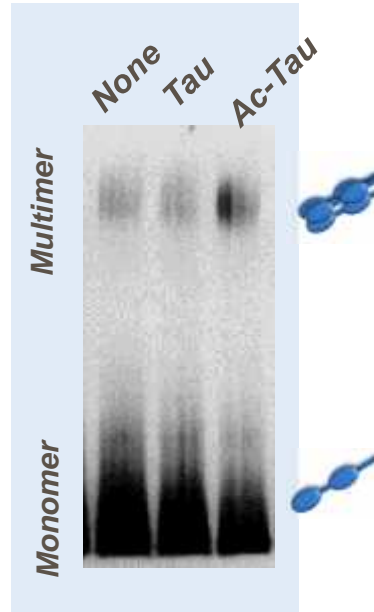
Substratos CMA

TAU

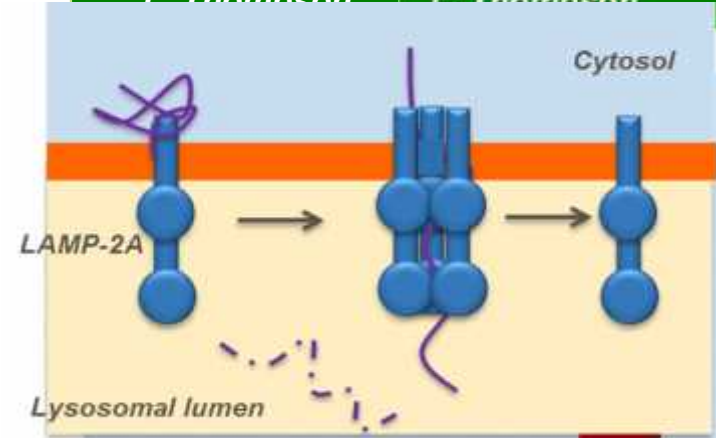
Orenstein et al. (2013) Nat Neurosci



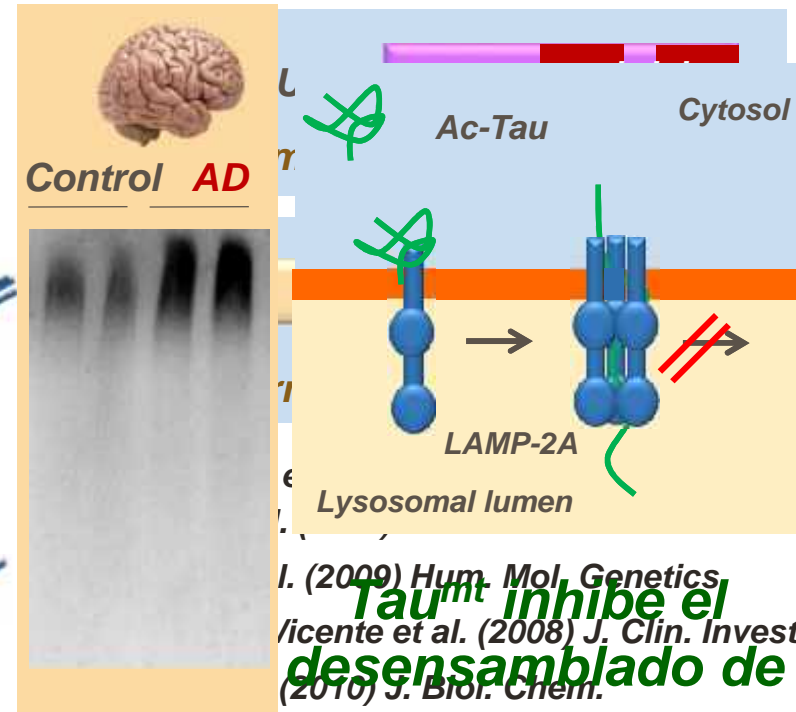
LRRK2^{mt} bloquea la multimerización de L2A



D. Sulzer
P. Lansbury
CONDICIONES NORMALES

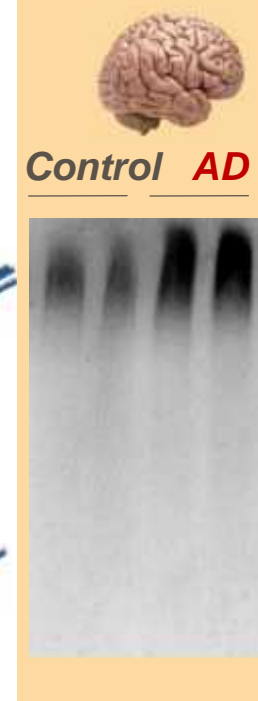
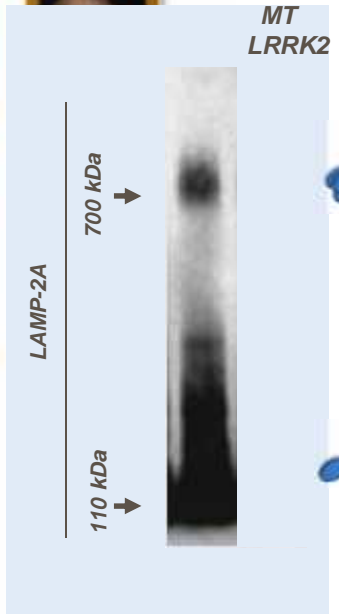


Enfermedad de Parkinson



Tau^{mt} inhibe el desensamblado de L2A

Cuervo et al. (2004) Science



I. (2009) Hum. Mol. Genetics
/icente et al. (2008) J. Clin. Invest.
(2010) J. Biol. Chem.

Autofagia y el Envejecimiento

1

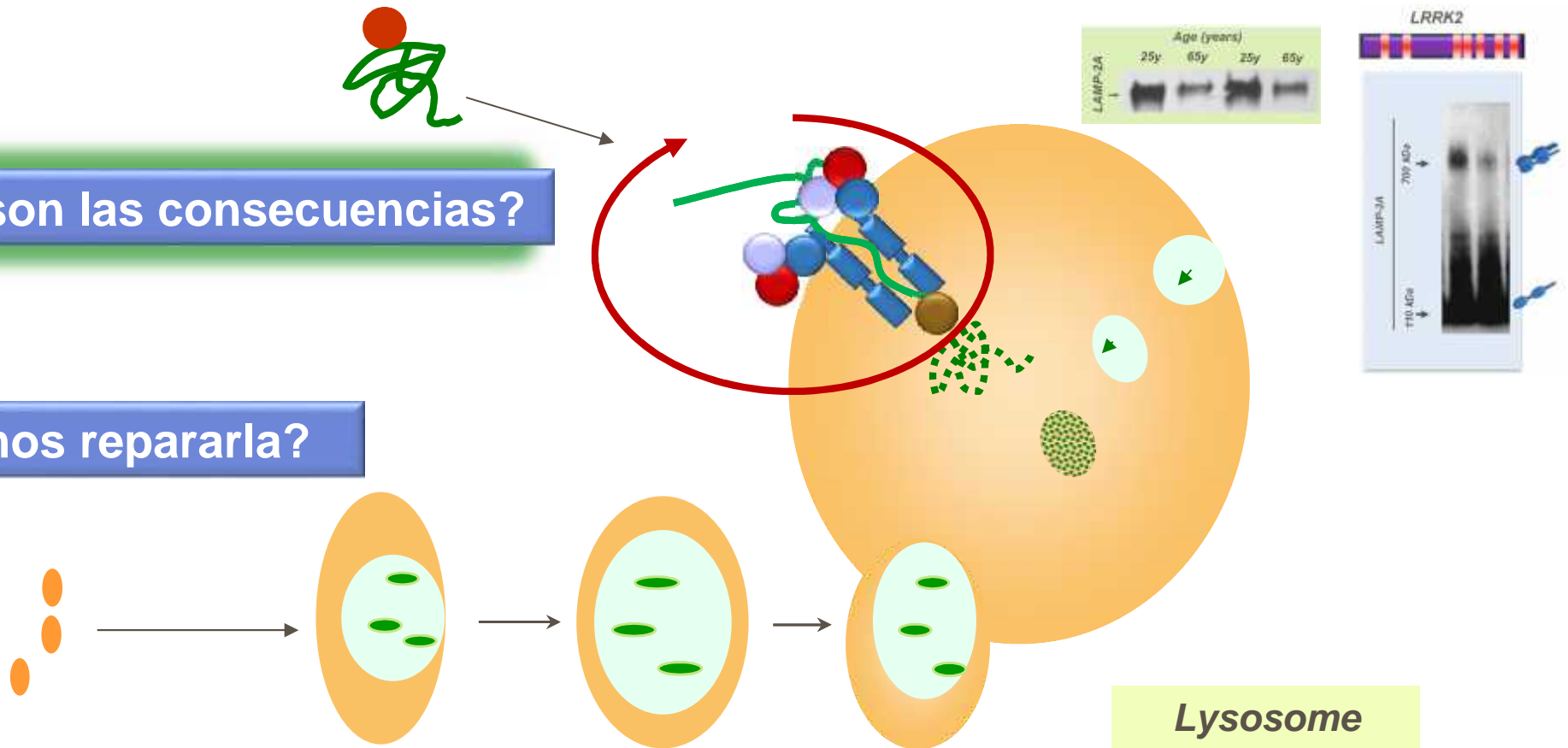
Porque no funciona?

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Cuales son las consecuencias?

3

Podemos repararla?



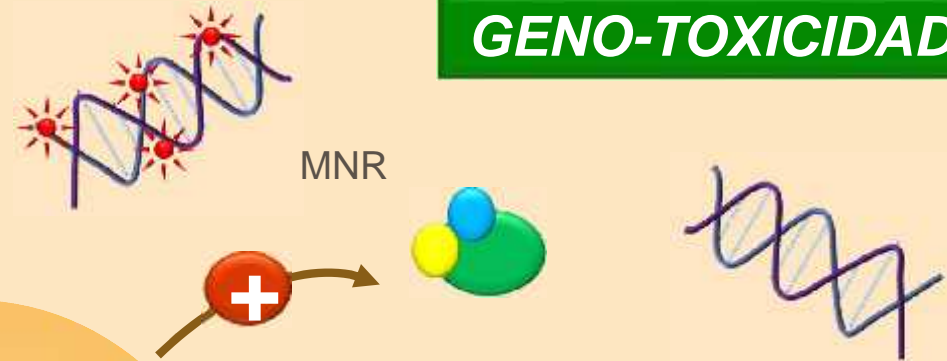
Fisiología de la autofagia mediada por chaperonas

PROTEO-TOXICIDAD



Kiffin et al. Mol Biol Cell (2004)
Cuervo et al. Science (2004)
Zhang and Cuervo, Nat Med (2008)
Martinez-Vicente et al, JCI (2010)
Orenstein et al Nat Neurosci (2013)

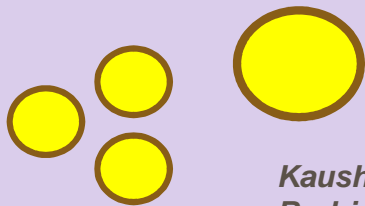
GENO-TOXICIDAD



Park et al Nat Commun (2015)

LIPO-TOXICIDAD

Gotas lipidicas



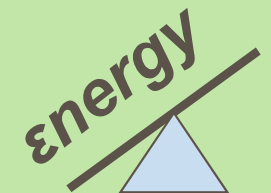
Kaushik et al. J Biol Chem (2008)
Rodriguez et al. PNAS (2012)

Lysosome

ESTRES NUTRICIONAL

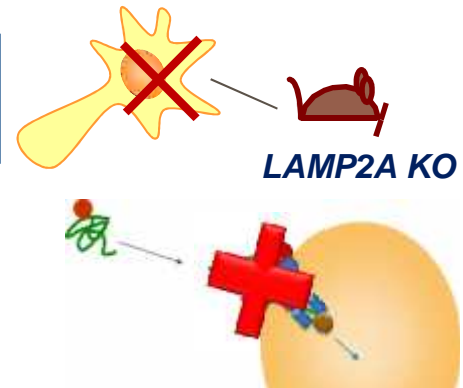
Ayuno prolongado
Metabolismo de la glucose en Cancer

Cuervo et al. Am. J. Physiol (1995)
Cuervo et al. J Biol Chem (1997)
Kon et al. Science Translation (2011)

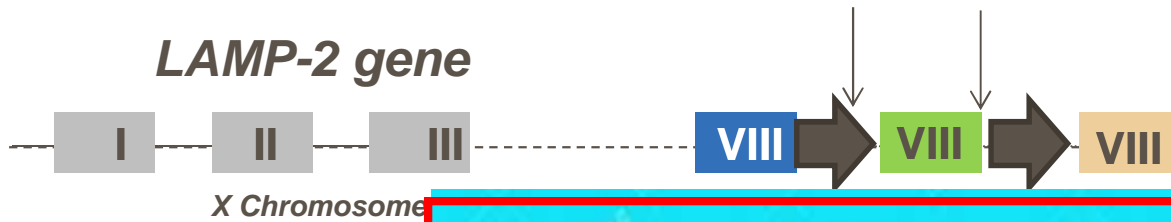


En vivo?

Bloqueo en vivo de CMA



Jaime Schneider



Jaime Schneider



Alb-L2A MICE



Hepatocitos

Bienvenidos a nuestro



Julio Madrigal



LAMP2A^{-/-} MICE



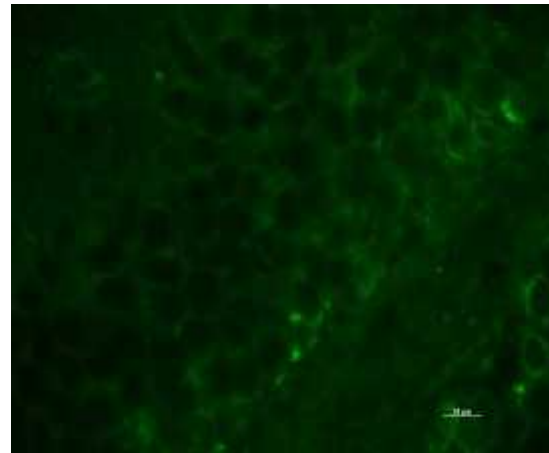
Cuerpo completo

Patología de CMA: Neurodegeneración

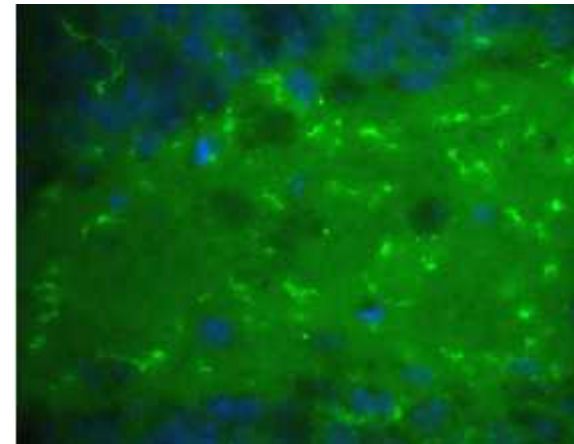
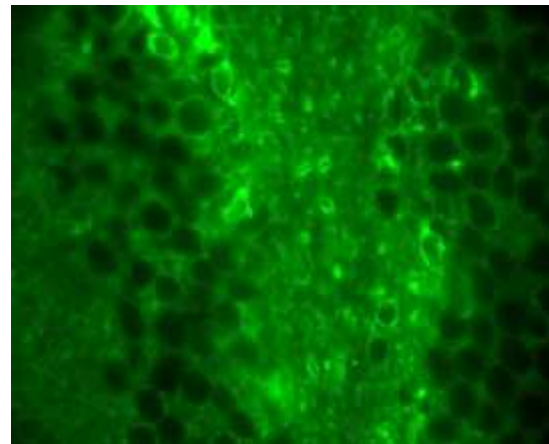
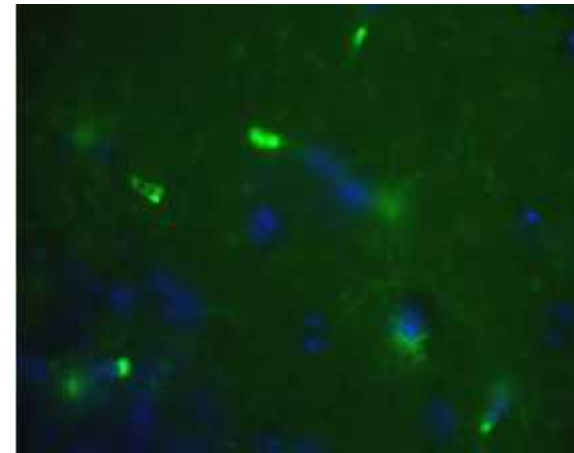
WT



Total tau



Tau Anormal



Perdida de CMA en el cerebro resulta en perdida de proteostasis y neurodegeneracion

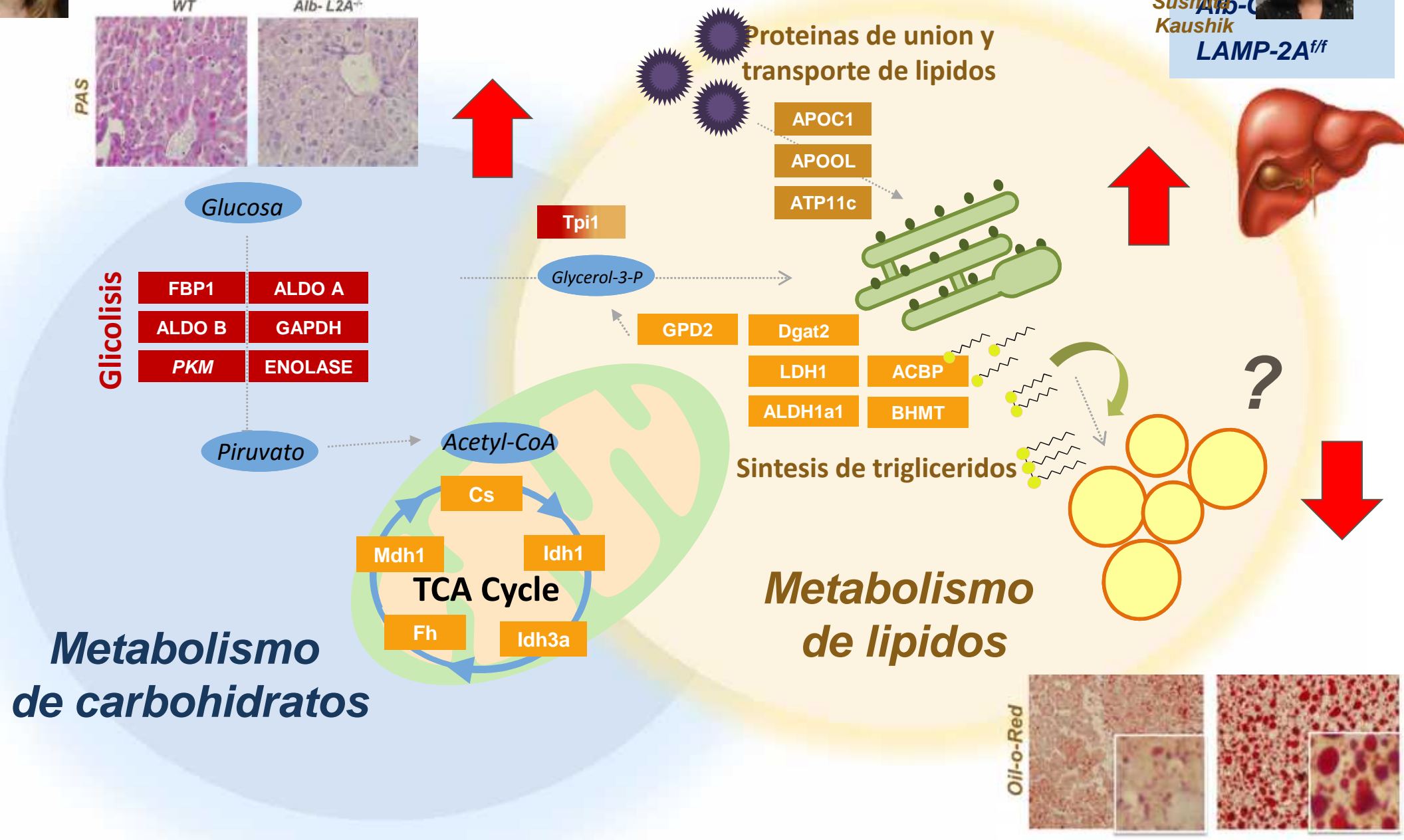
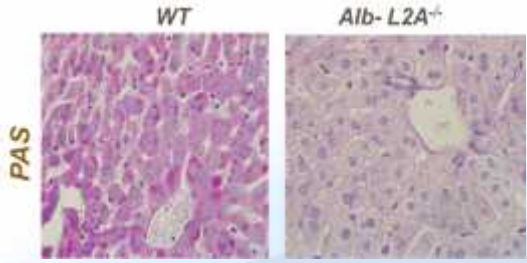


Jaime Schneider

CMA regula el **metabolismo**



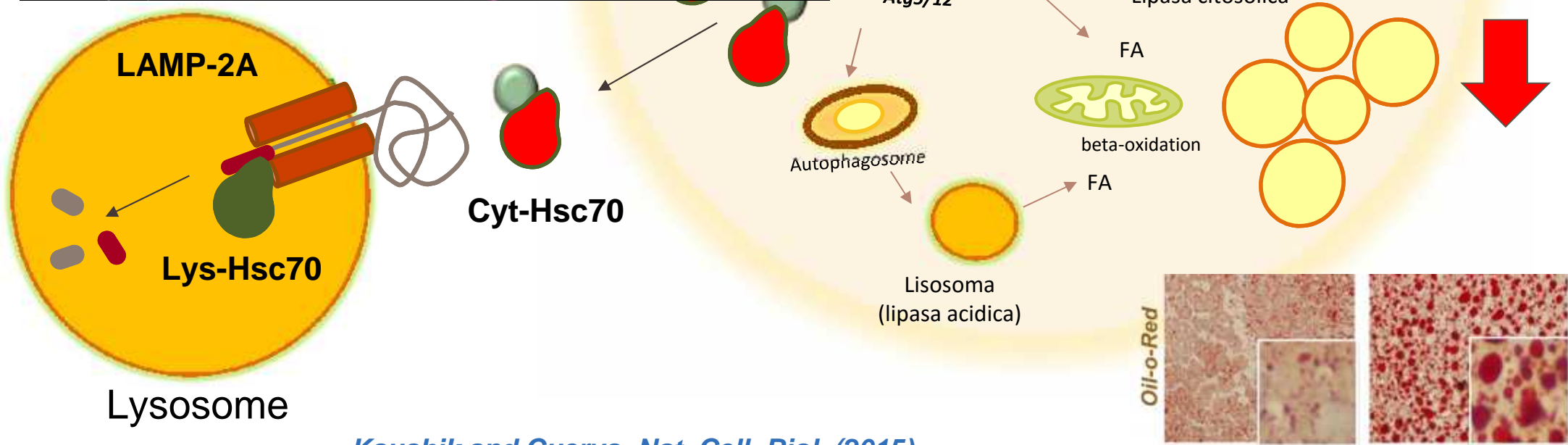
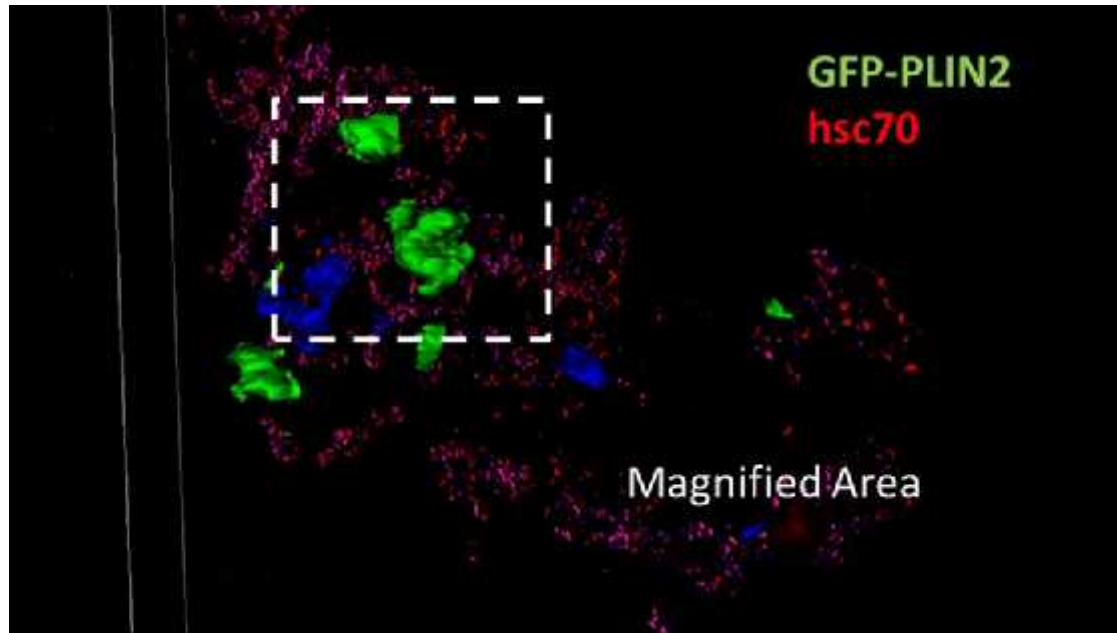
Susmita Kaushik
Alb-C
LAMP-2A^{f/f}



?

Perilipinas – nuevos substrates de CMA

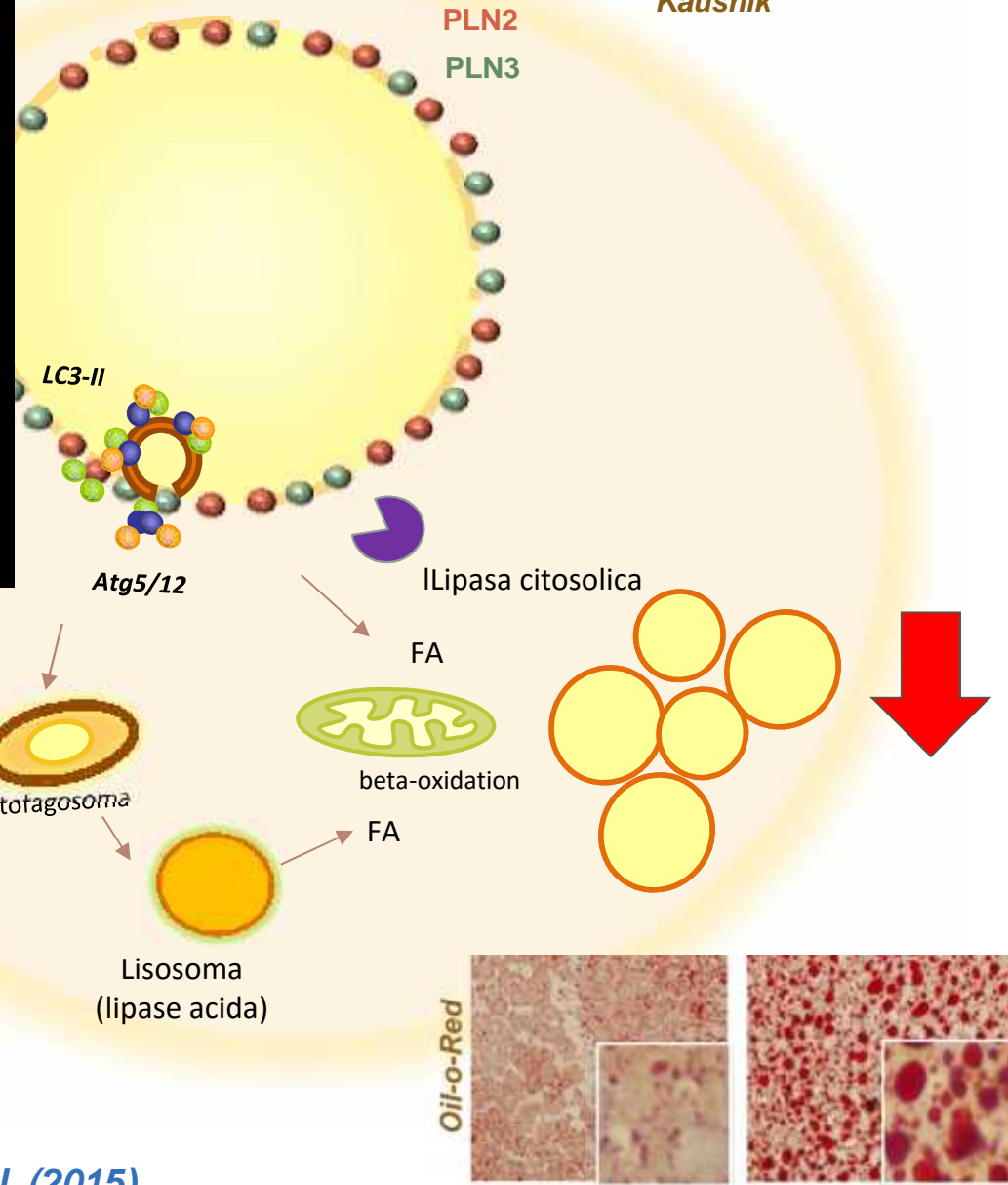
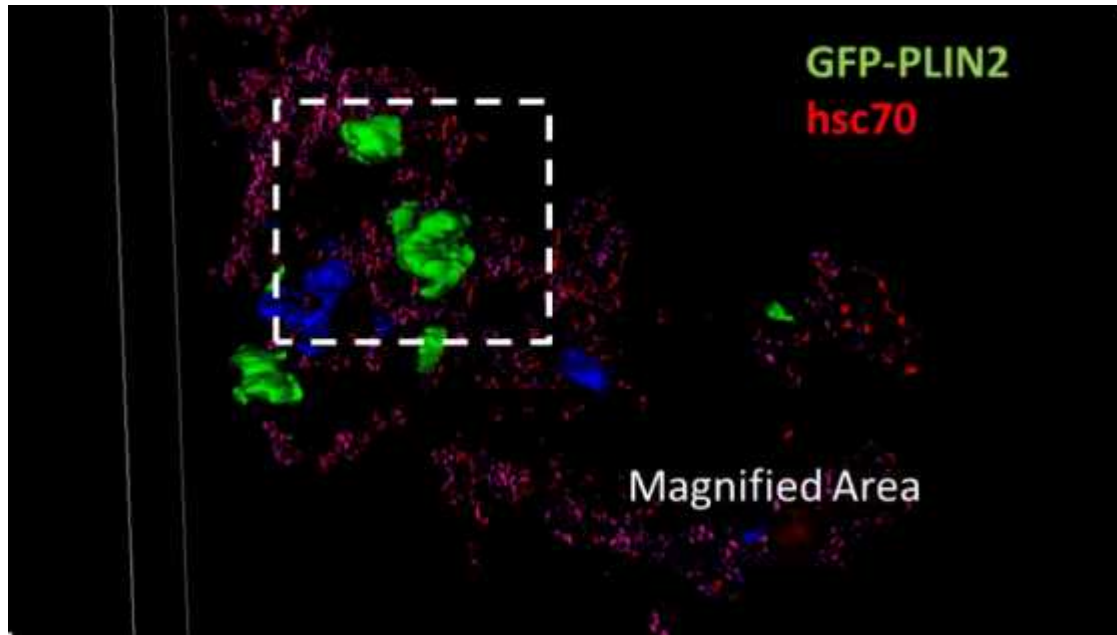
Susmita Kaushik



Kaushik and Cuervo, Nat. Cell. Biol. (2015)

Perilipinas – nuevos substrates de CMA

Susmita Kaushik



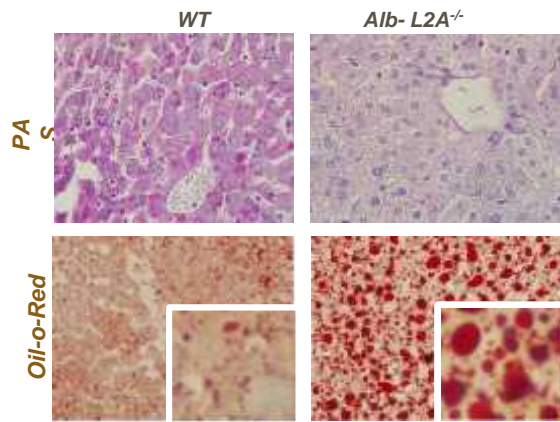
Kaushik and Cuervo, Nat. Cell. Biol. (2015)

CMA en el metabolismo



Julio Madrigal

Anormalias metabolicas locales



Anomalias metabolicas sistemicas

Sindrome metabolico

LAMP2A ^{-/-} MICE

Cuerpo entero

Enfermedad sistematica

WT **L2A KO**
Diabetes

Obesidad

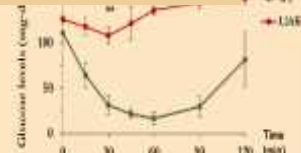
Obesidad

Enfermedades cardiovasculares

Hepato-steatosis

Enfermedad hepatica

Resistencia a la insulina



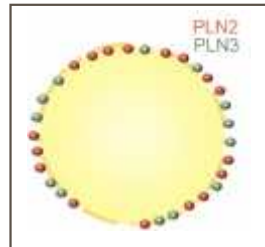
Tejido adiposo

Musculo esqueletico

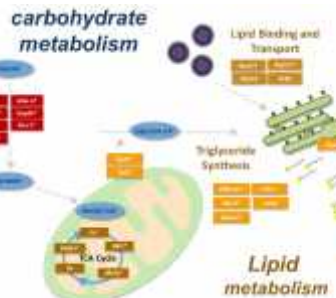
Pancreas

SNC

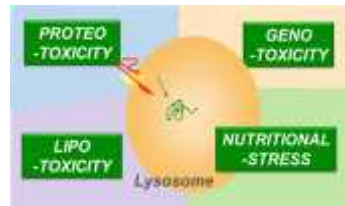
Fallo para eliminar las perilipinas



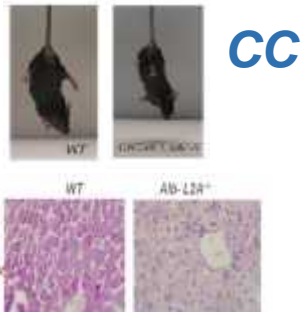
Disregulacion enzimatica



Autofagia y el Envejecimiento



Estres

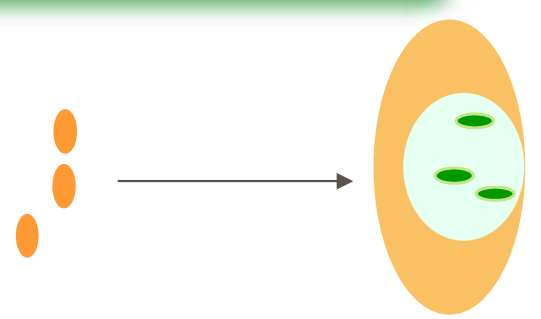
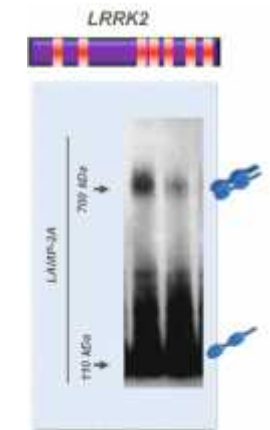
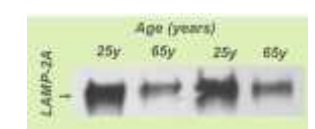
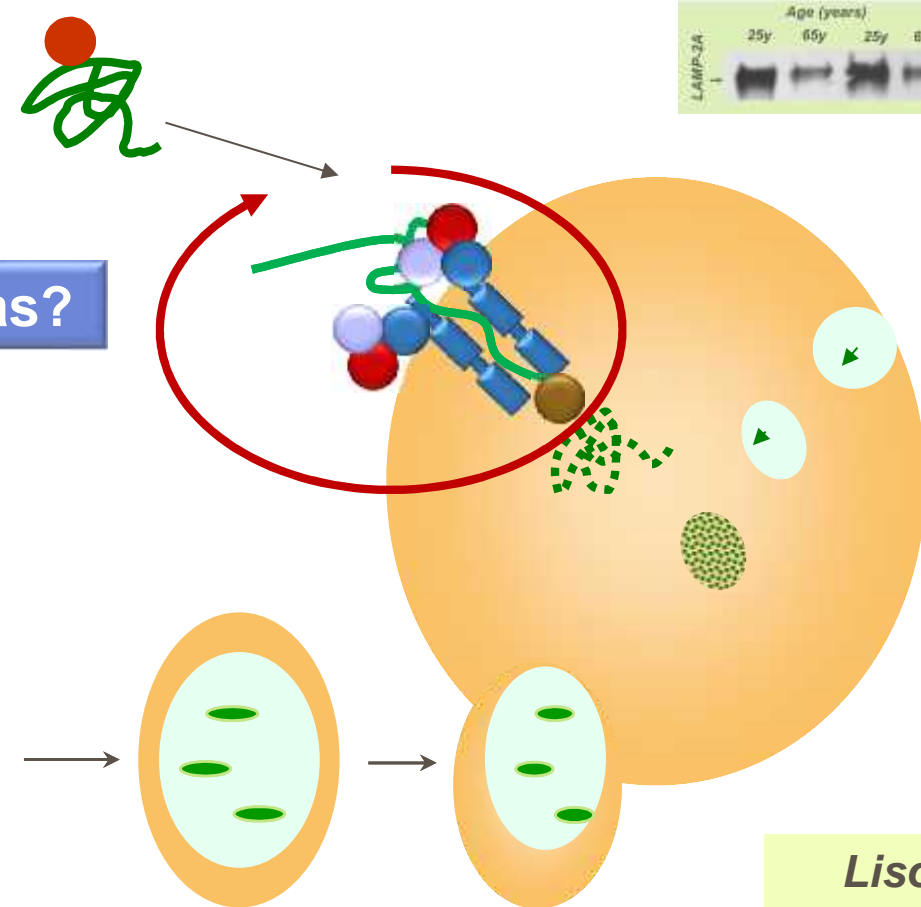


Metabolismo

1 Porque no funciona?

2 Cuales son las consecuencias?

3 Podemos repararla?



Autofagia en Centenarios



Dr. Fernando Macian

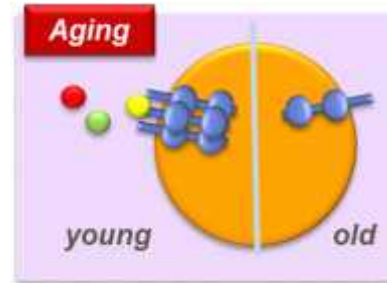


Ignacio Guerrero



Yves Juste

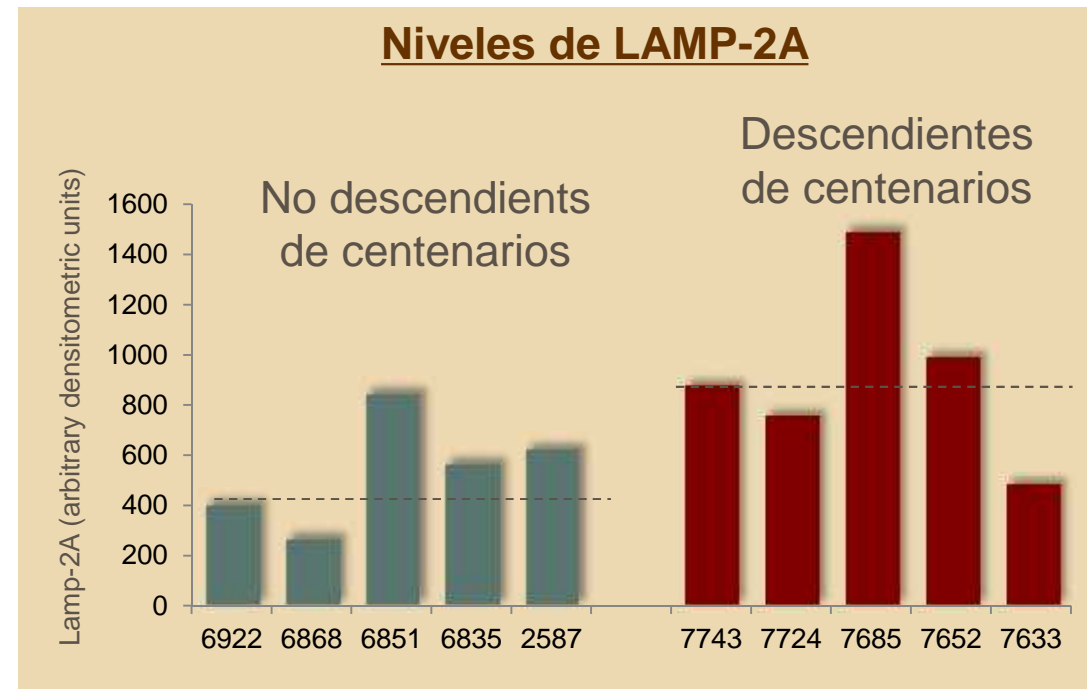
G. Atzmon
N. Barzilai



T cell

Mejor defensa immune

Mejor respuesta de las células T



Centenarios tienen mejor autofagia!



Manteniendo CMA actia!!



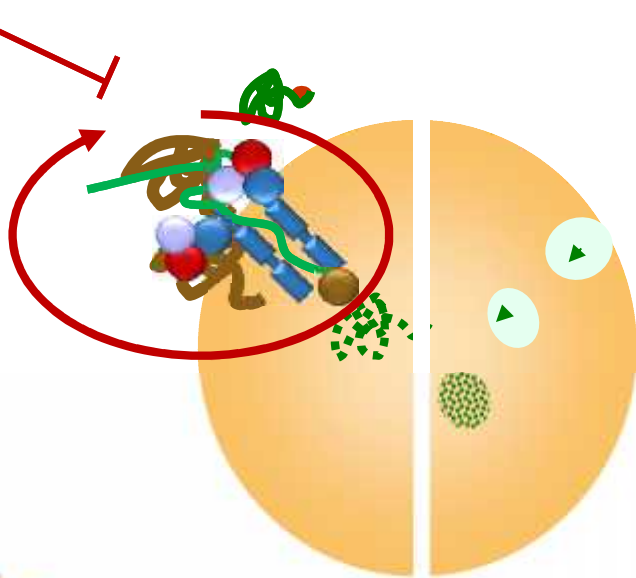
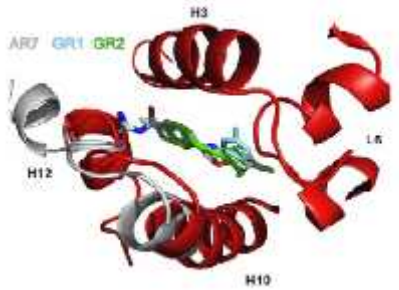
Antonio Diaz

E. Gavathiotis

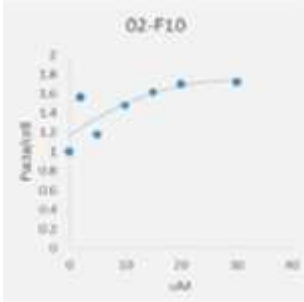
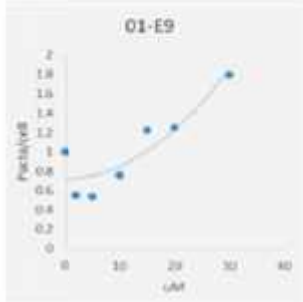
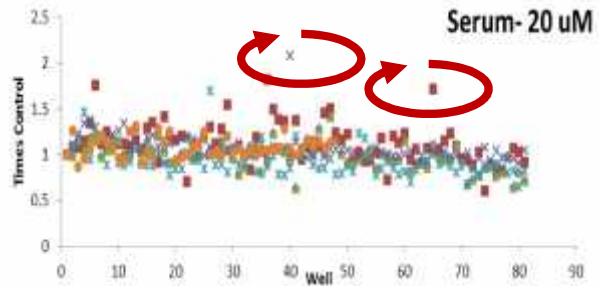
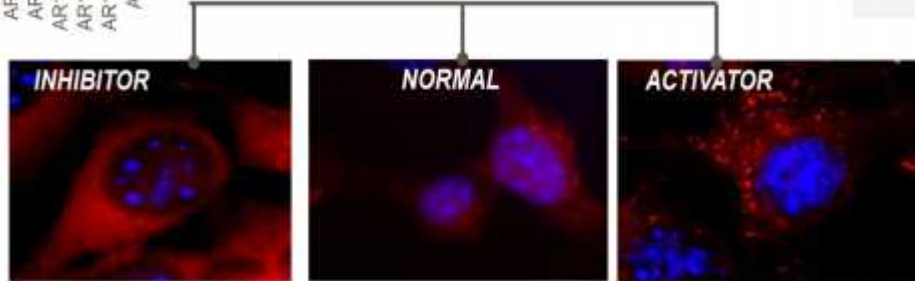
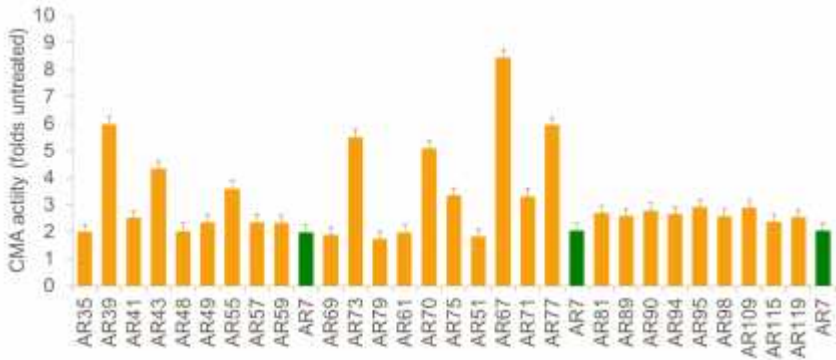
Qisheng Xin

RARa

¿Diana terapeutica?



Anguiano et al. Nat. Chem. Biol. (2013)



Autophagy y el envejecimiento

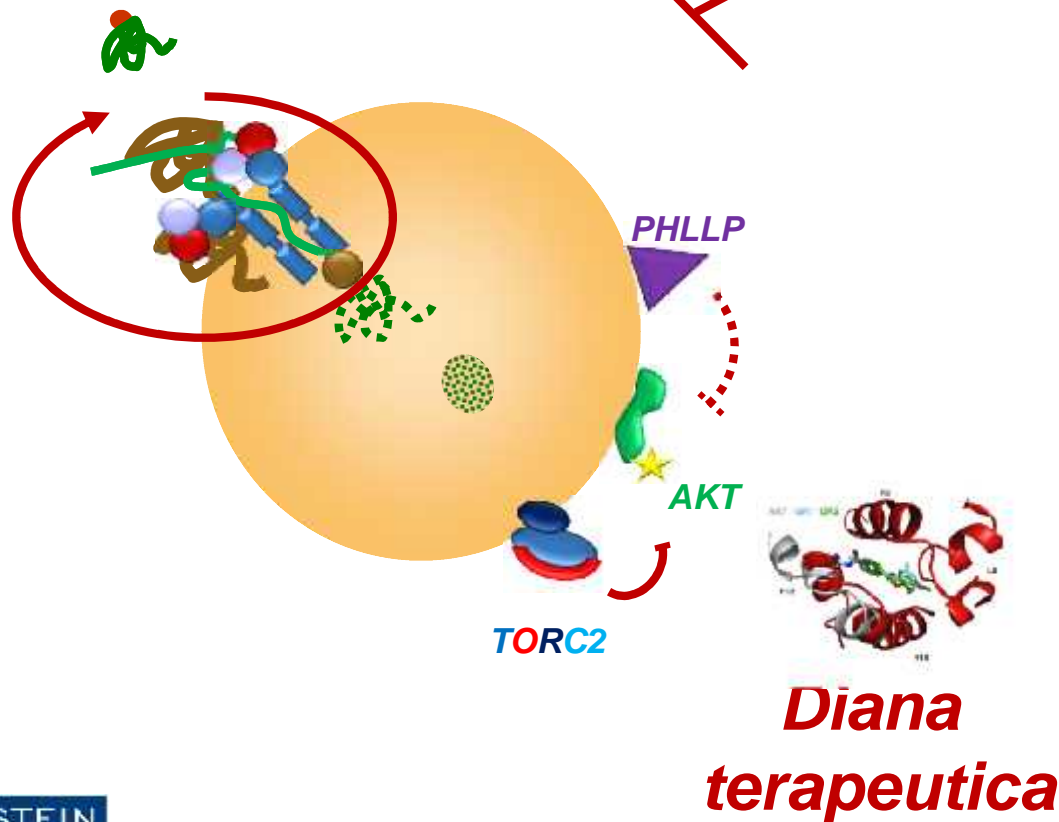
Envejecimiento

Diabetes

Obesidad

Dieta

Proteotoxicidad



Remodelado del Proteoma

Control de Calidad

Energetica

Metabolismo

Lipolisis

Glycolisis

Activacion Programada

Valdor et al. Nature Immunology (2014)

F. Macian

Diferenciacion

Ciclo celular

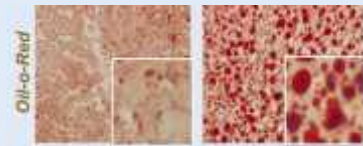
Reparacion DNA



Neurons



Liver



T cell



Acknowledgements

The Cuervo Lab



Current Members

Esperanza Arias
Eloy Bejarano
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Luisa Coletto
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Shuxian Dong
Erika Garay
Luciana Gomes

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Philipp Kirchner
Julio Madrigal
Bindi Patel
Nadia Storm
Inma Tasset
Qisheng Xin

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Urmi Bandyopadhyay
Roberta Kiffin
Maria Kon
Marta Martinez-Vicente
Ashish Massey
Olatz Pampliega
Alejandro Quiroga
Guy Sovak
Lori Spozak

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Jose Rodriguez
Jaime Schneider
Barbara Stiller
Joan Villarroya
Esther Wong
Cong Zhang

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Sheng Zhang (UTSW, TX)
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E+E Mandelkow (Max Plank, GRM)
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Gil De Paolo (Columbia University)
Patrice Codogno (INSERM, Fr)
A. Consiglio / A. Raya (IBUB/CMRB)
Li Gan (Gladstone, SF)
Ander Matute (Biogune)
Francesc Villaroya (U. Barcelona)



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Andreas Jenny
Richard Kitsis
Fernando Macian
B and P Satir
Rajat Singh
David Spray
Yousin Suh
L. Santambrogio
Vlad Verkhusha
Allan Wolkoff

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NIH/NINDS **Rainwaters Foundation**