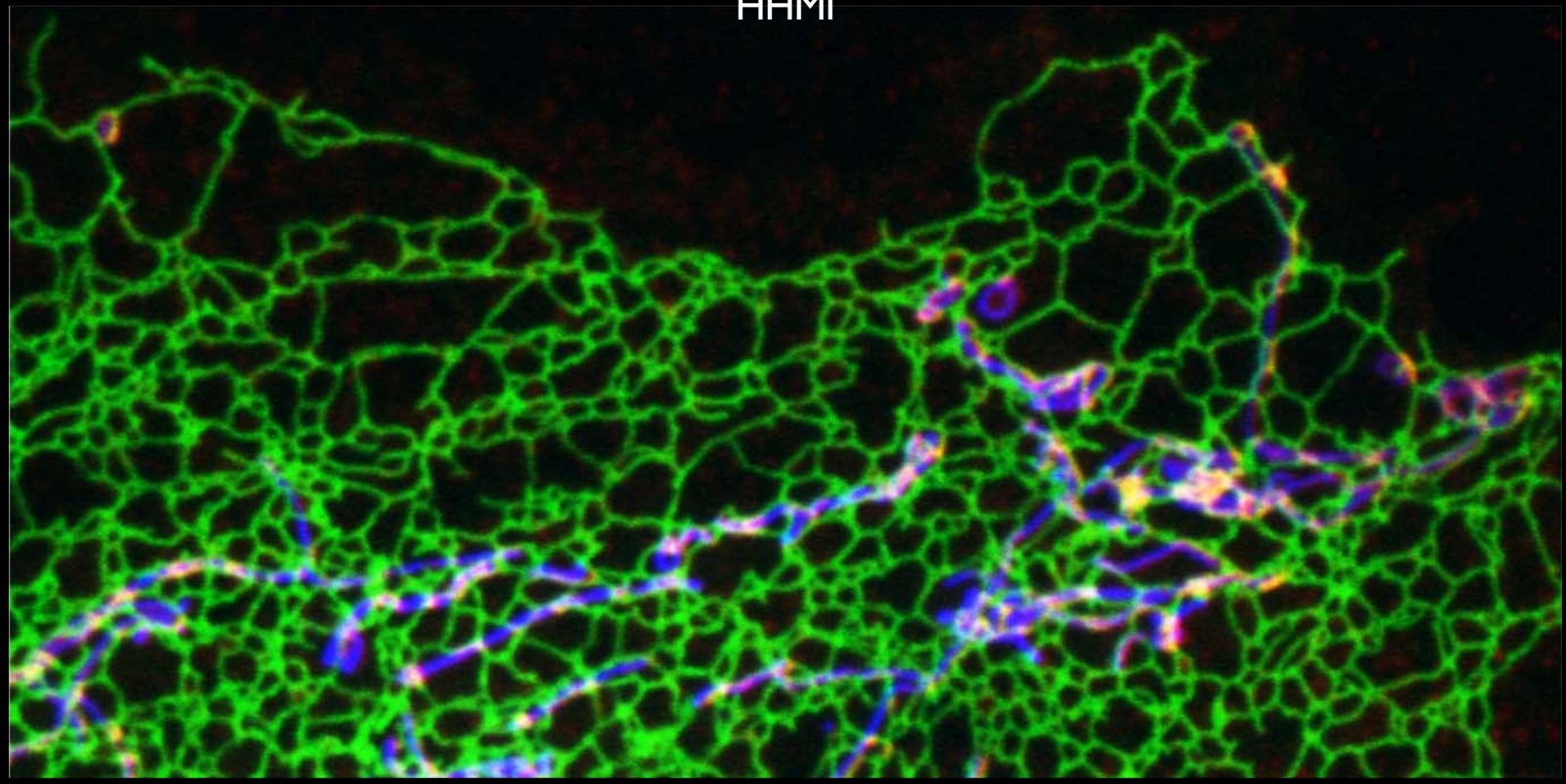
Lipid Transport at Membrane Contact Sites

Pietro De Camilli

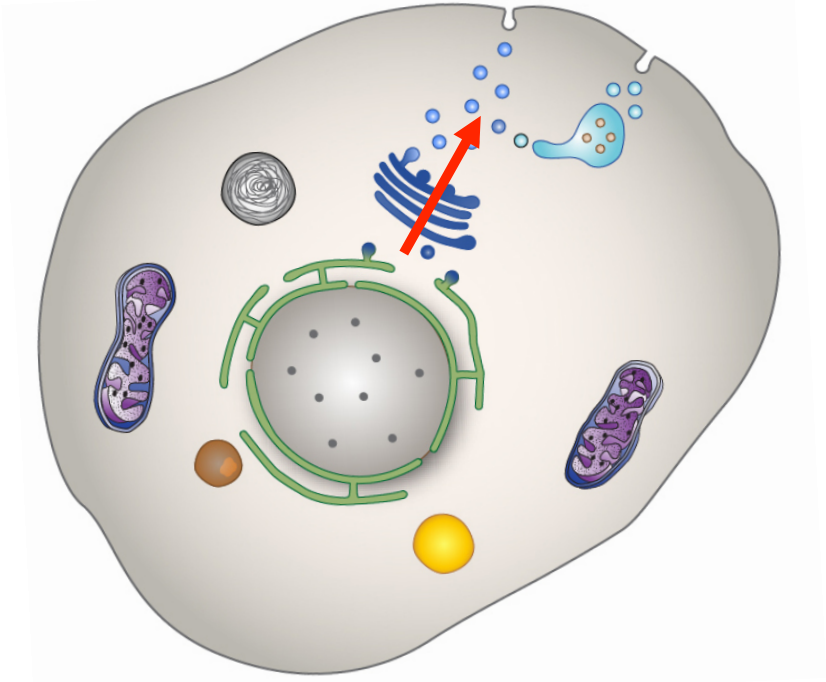
Departments of Neuroscience and Cell Biology
&
HHMI



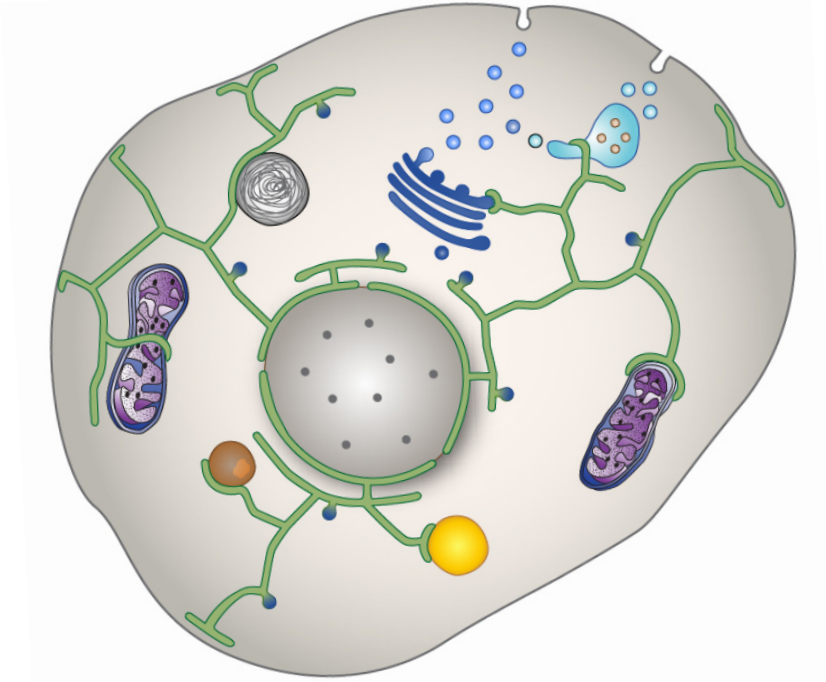
Yale NIDA Neuroproteomic Center
Yale University
May 1st 2019

Eukaryotic cell

Most membrane lipids are synthesized in the ER

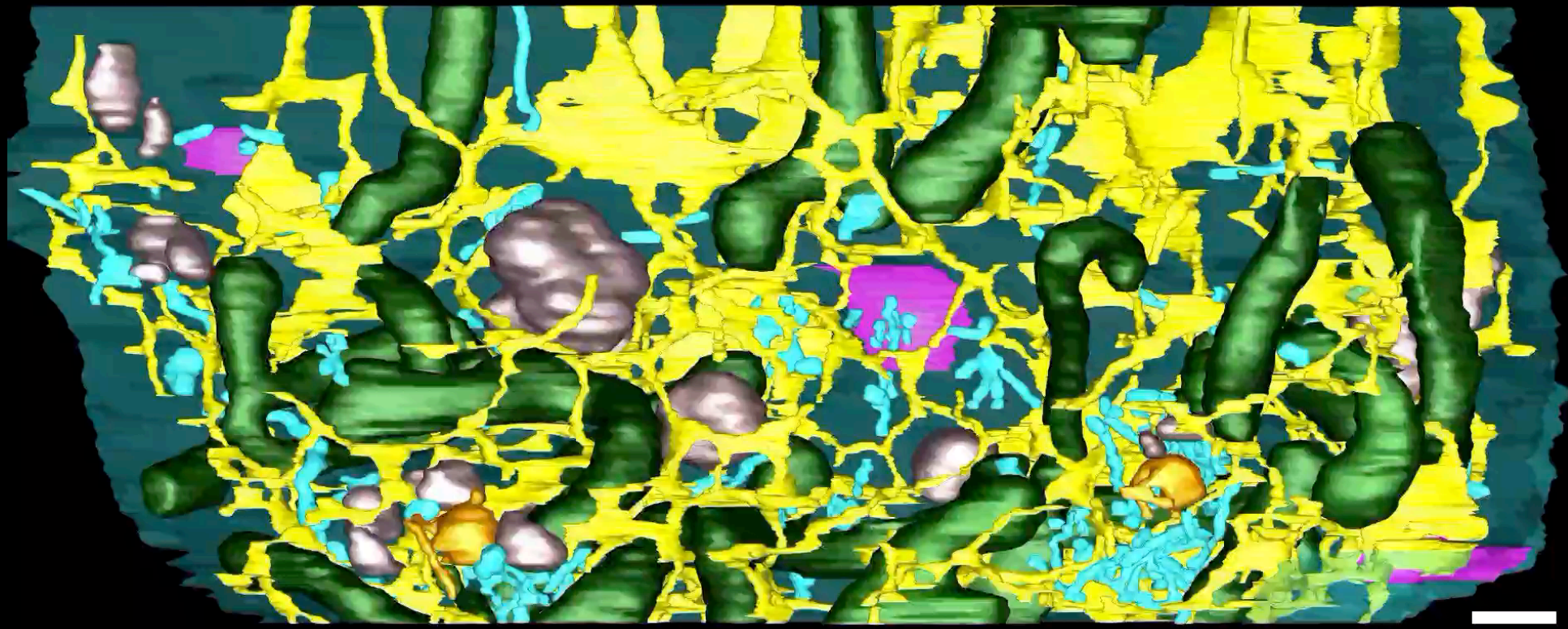


The ER makes contacts with all other membranous organelles



The ER make contacts with all other membranous organelles

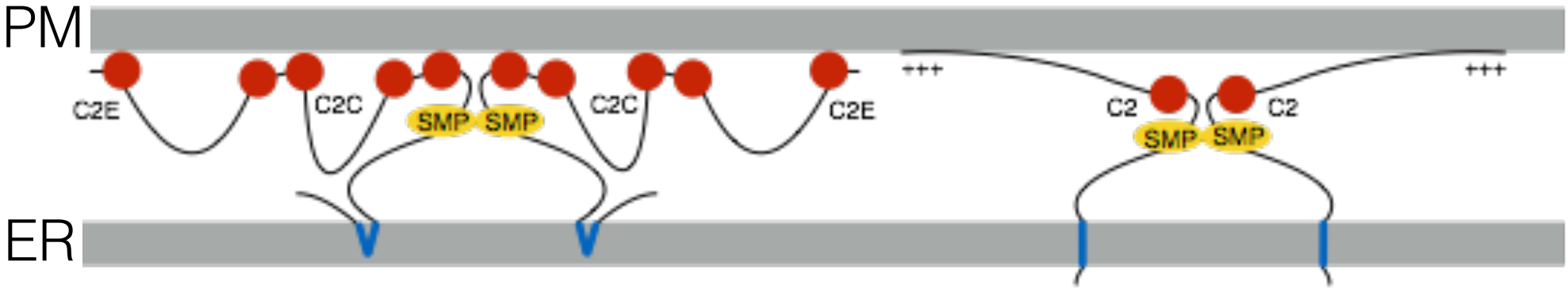
Reconstruction of the ER (yellow) and other membranes
in a neuronal cell body (from FIB-SEM data)



Wu …& De Camilli PNAS 2017

Some proteins that transport lipids at membrane contact sites have SMP domains

ER – plasma membrane contacts



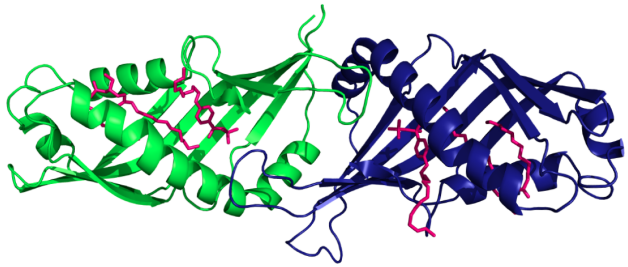
Extended synaptotagmins

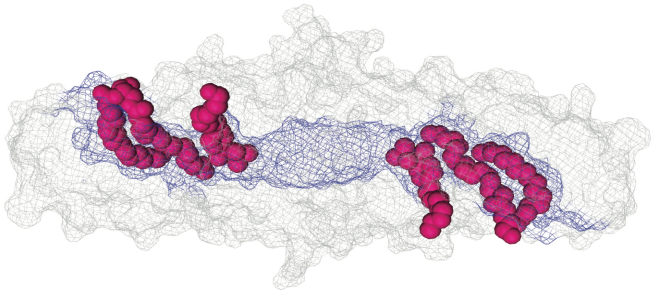
TMEM24 & C2CD2

Giordano et al. Cell 2013
Schauder et al. Nature 2014
Fernandez-Busnadiego et al. PNAS 2015
Idevall-Hagren et al. EMBO J 2015
Saheki et al. NCB 2016
Bian et al. EMBO 2017

Lees et al. Science 2017

SMP domain
(from E-Syt2)





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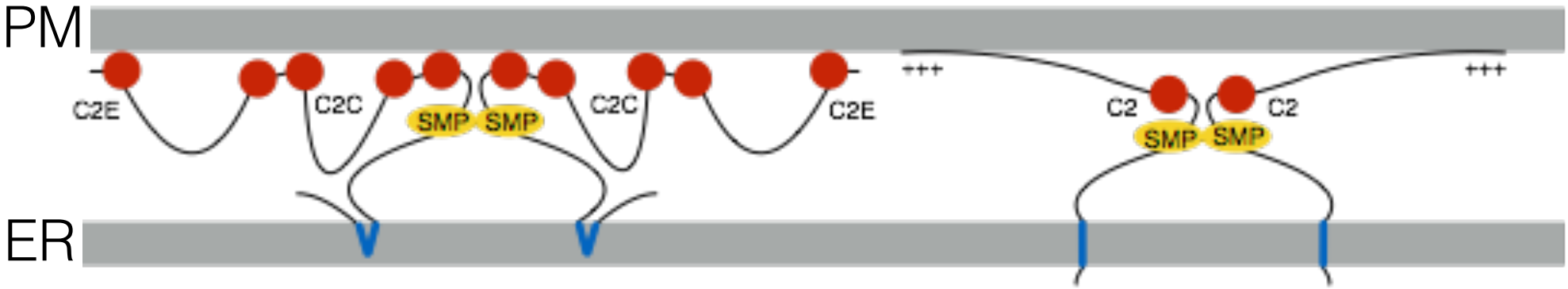

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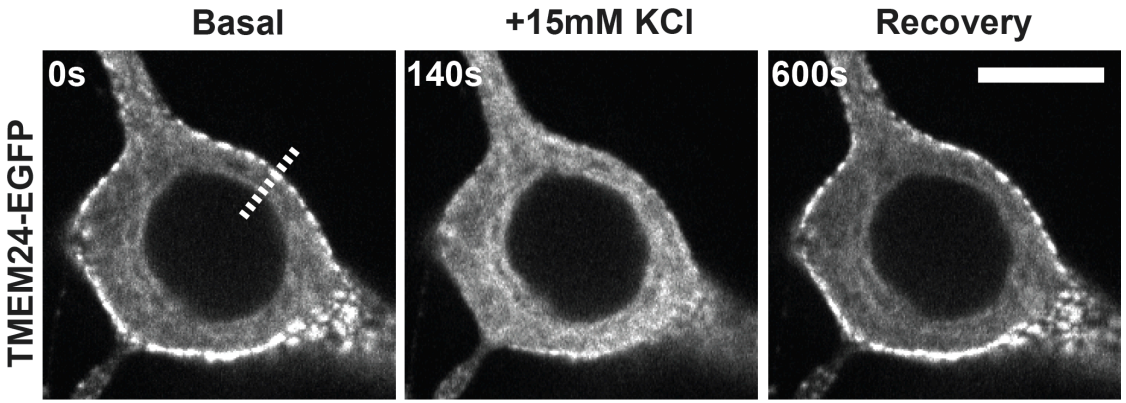
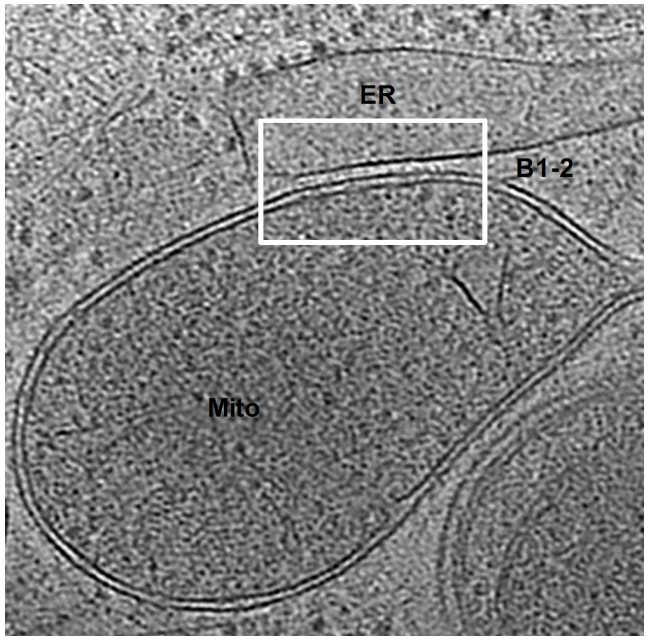


Lees et al. Science 2017

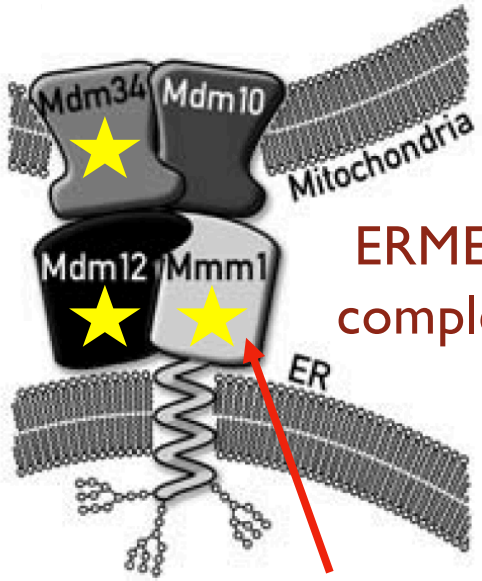
ER - mitochondria contacts

The heterotetrameric **ERMES complex** mediates lipid transport at these contacts in yeast. Three of its components (yellow stars) contain SMP domains



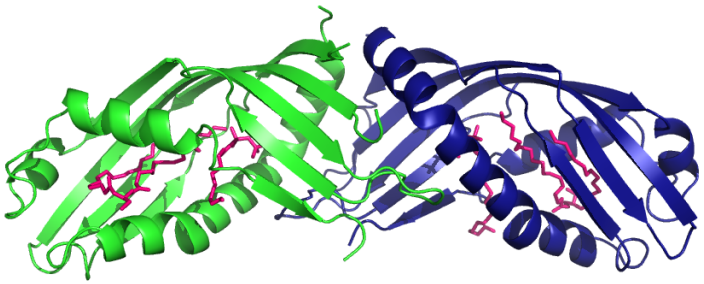
Xia Li & Jun Liu (Yale West Campus)

The ERMES complex is not present in metazoa

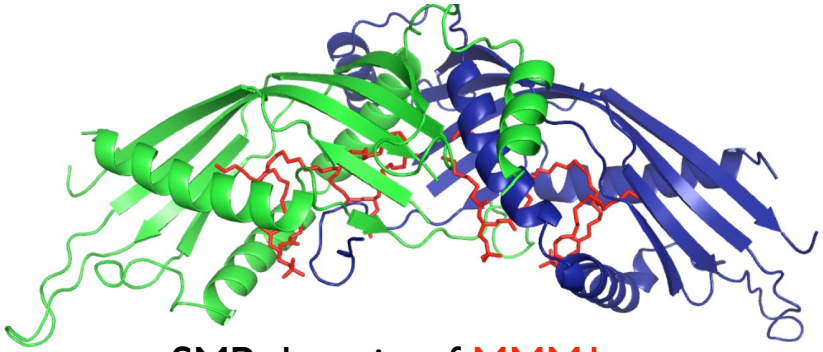


ERMES complex

Kornmann et al. Science 2009



SMP domain of **E-syt2**



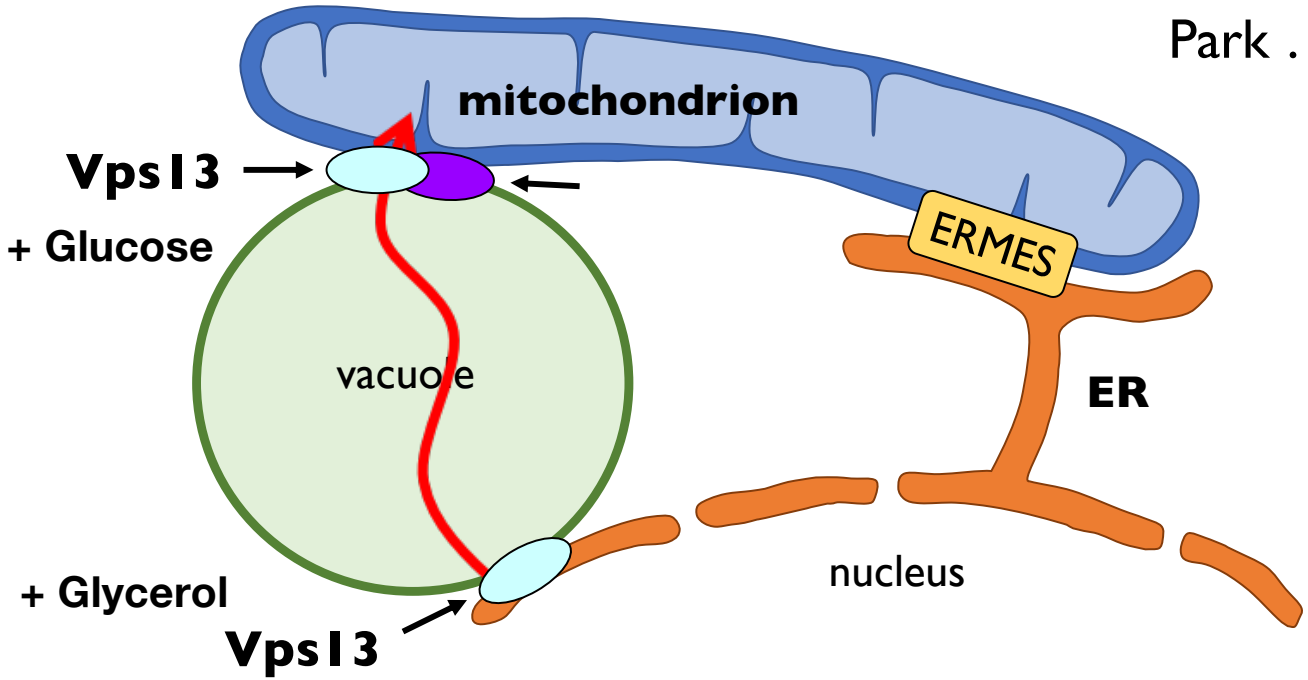
SMP domain of MMM1

Jeong et al. PNAS 2017

ERMES deficiency in yeast can be bypassed by dominant mutations in Vps13

Lang … & Kornmann, JCB 2015

Park … & Neiman, MBoC 2016



Yeast VPS13 is localized at contacts between the vacuole and either the ER or mitochondria, suggesting a bypass route for lipid transport between the ER and mitochondria via the vacuole

Since ERMES is not present in metazoans, could VPS13 perform some of the functions of ERMES?

Four VPS13 genes in mammals

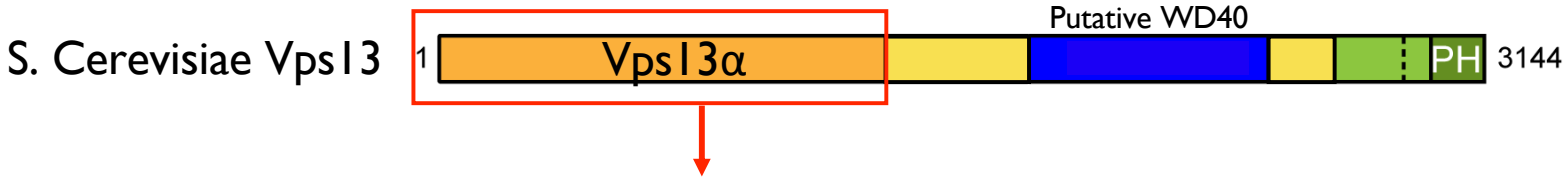
Mutations cause neurological diseases

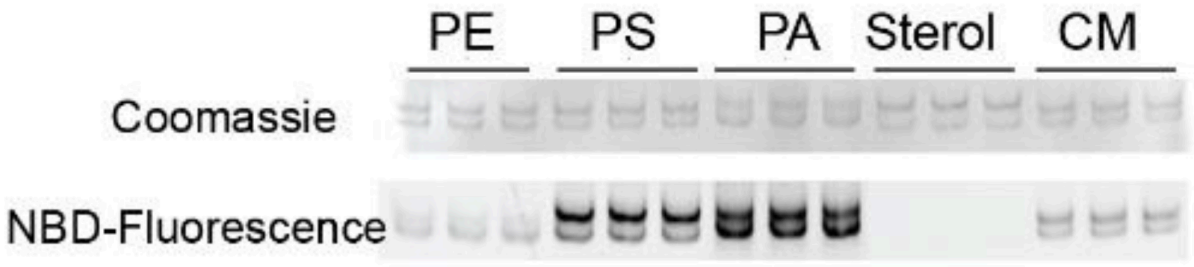
- **VPS13A - Chorea-Acanthocytosis** (Rampoldi…Monaco, Nat Genet. 2001; Ueno…Sano, Nat Genet. 2001)
- **VPS13B - Cohen Syndrome** (Kolehmainen..Lehesjoki, Am J Hum Genet. 2003)
- **VPS13C - Early-Onset Parkinson's Disease** (Lesage et al, Am J Hum Genet. 2016; Schormair et al. Clin. Genet. 2018)
- **VPS13D - Ataxia with Spasticity** (Seong et al. Ann. Neurol. 2018)
  - Childhood Movement Disorders (Gauthier et al. Ann. Neurol. 2018)

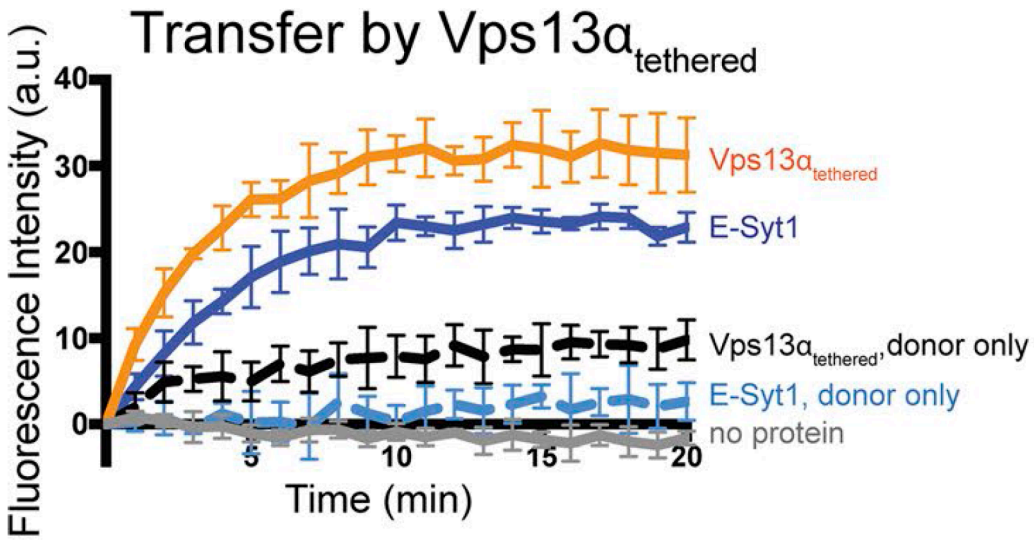
Is VPS13 a lipid transport protein ?

Collaboration with the Reinisch lab

VPS13 can harbor and transport lipids



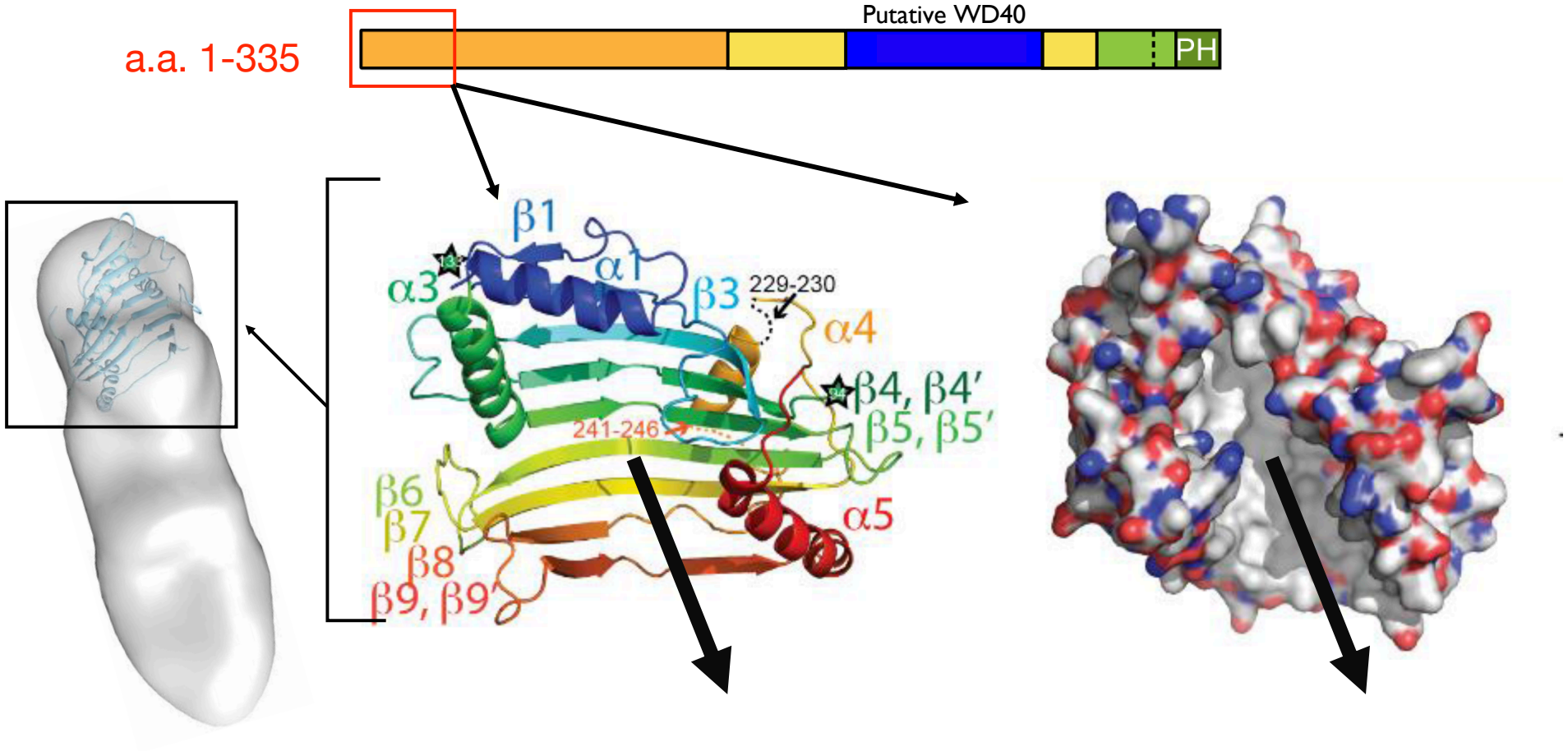




Kumar, Leonzino et al. JCB 2018

The N-terminal portion of VPS13 contains hydrophobic cavity

from *Chaetomium thermophilum*



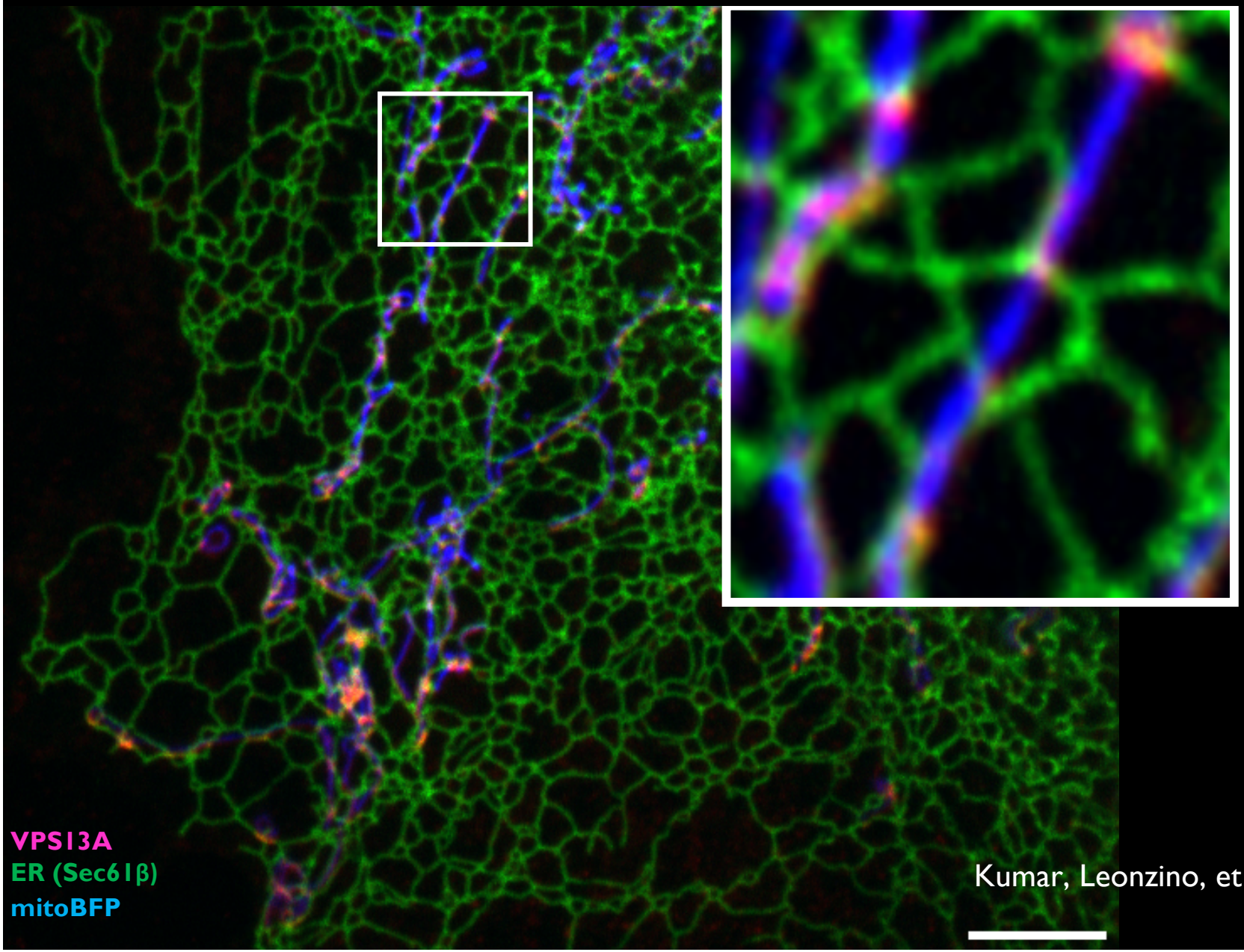
EM and bioinformatic analyses predict (hypothesis) that the entire N-terminal region may be represented by an elongated rod with a cavity running along its length

Kumar, Leonzino et al. JCB 2018

Where do mammalian VPS13 isoforms achieve their lipid transport function ?

VPS13A localizes at ER - mitochondria contacts

Cos-7 cells

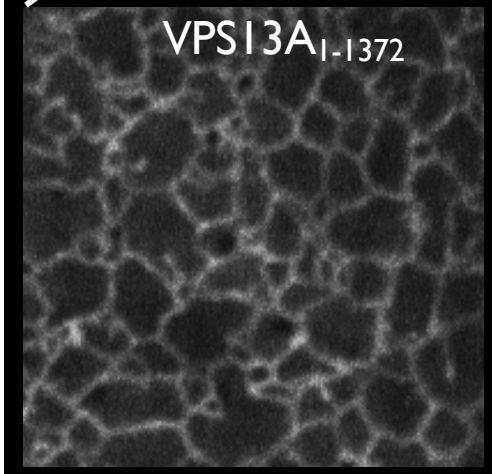


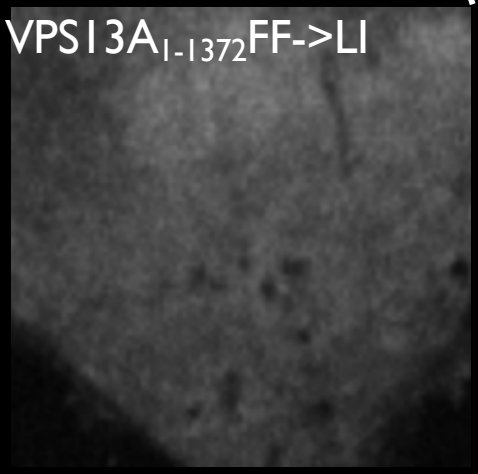
VPS13A
ER (Sec61β)
mitoBFP

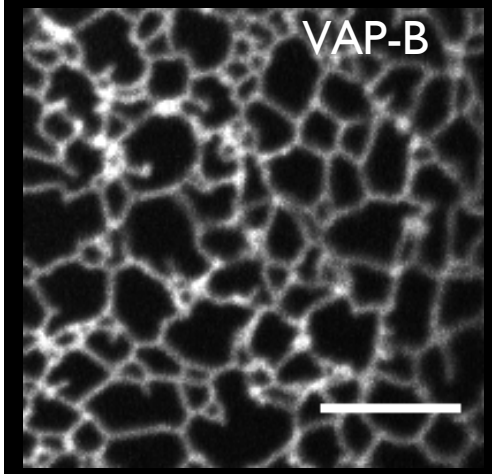
Kumar, Leonzino, et el., 2018 *JCB*

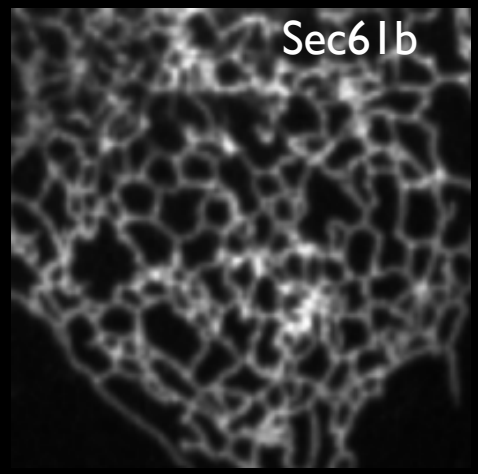
VPS13A tethering domains

FFAT motif for binding to the ER protein VAP

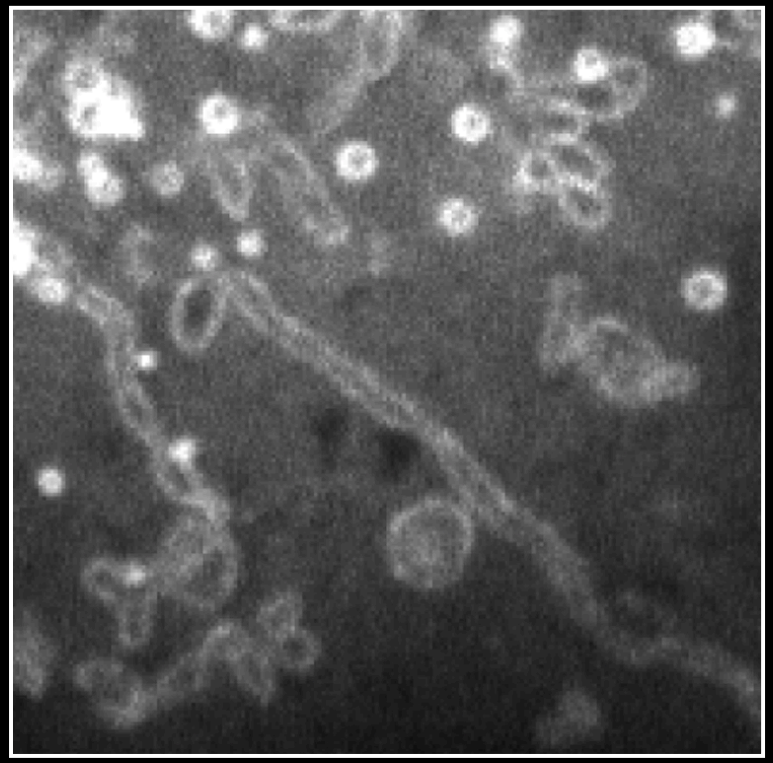






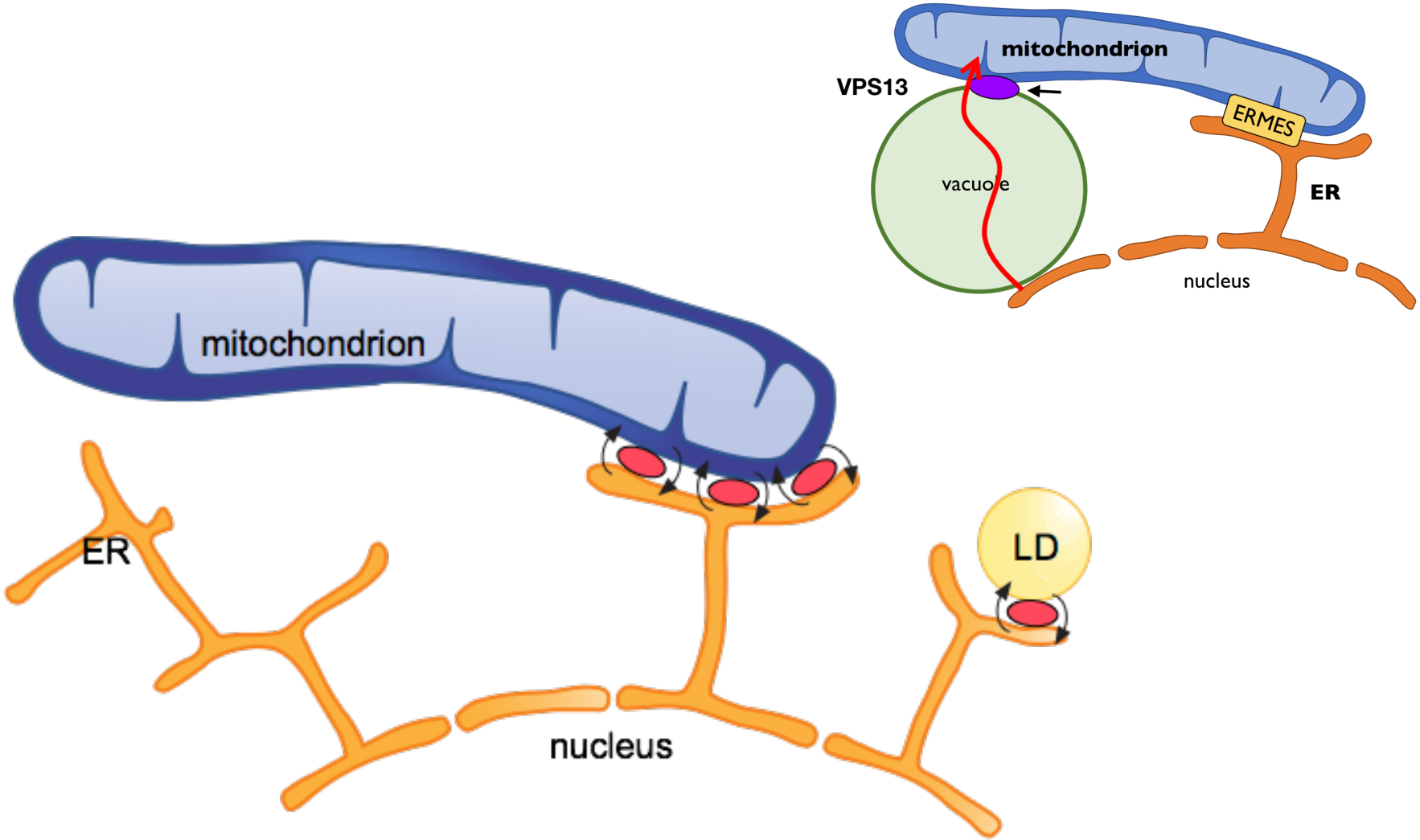


VPS13A2750-3174



Kumar, Leonzino, et el., 2018 *JCB*

VPS13A is localized at contacts of the ER with mitochondria and with lipid droplets



Marianna Leonzino

What about VPS13C?

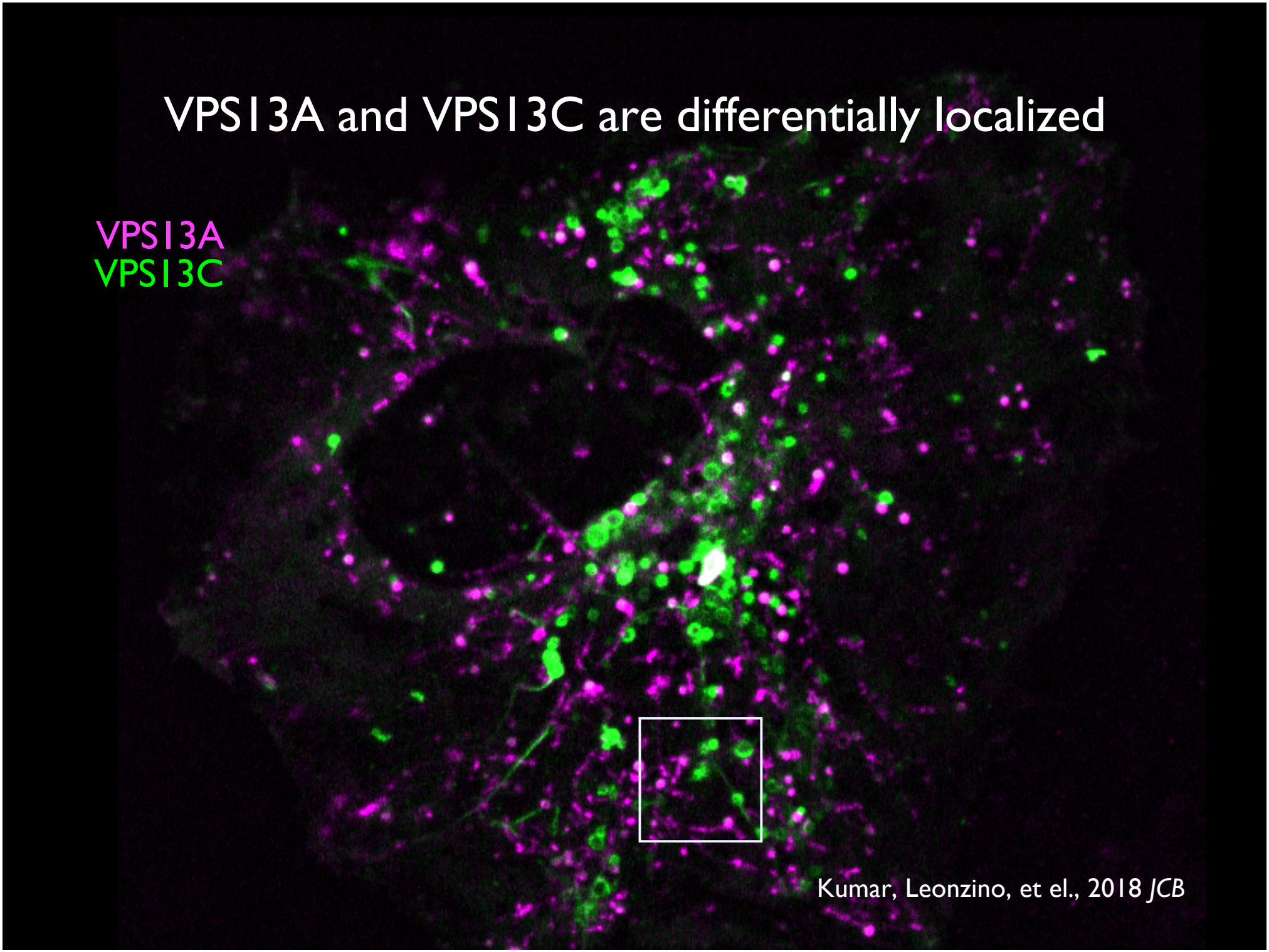
Loss of VPS13C Function in Autosomal-Recessive Parkinsonism Causes Mitochondrial Dysfunction and Increases PINK1/Parkin-Dependent Mitophagy

Lesage et al. The American Journal of Human Genetics 2016

- **Chorea-Acanthocytosis**

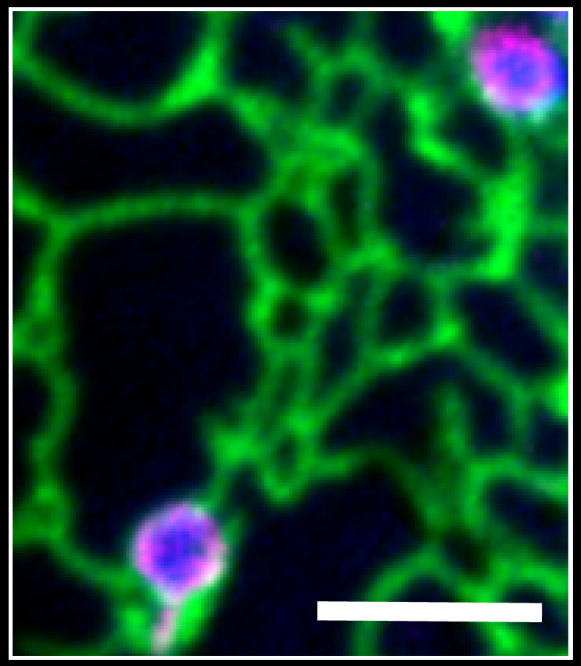
- **Parkinson**

VPS13A and VPS13C are differentially localized

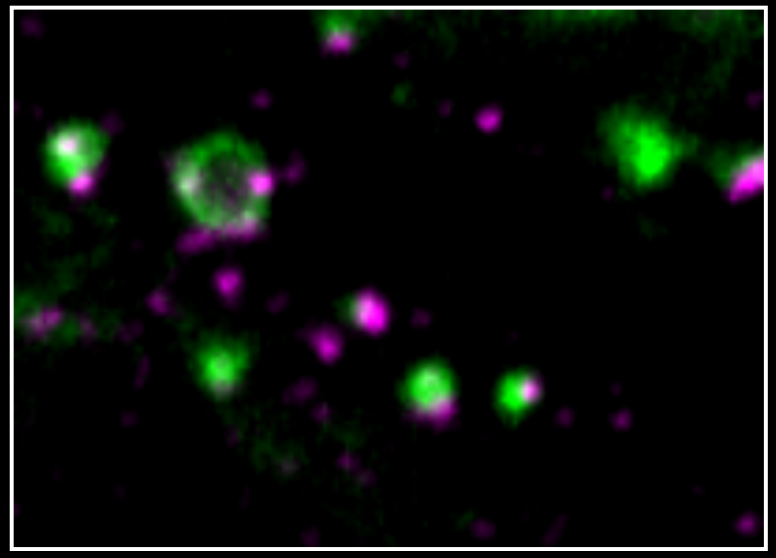


VPS13C localizes at ER - late endosomes/ysosomes contacts

VPS13C
Sec61β
Dextran



HA epitope Knock-in at
the endogenous
VPS13AC locus

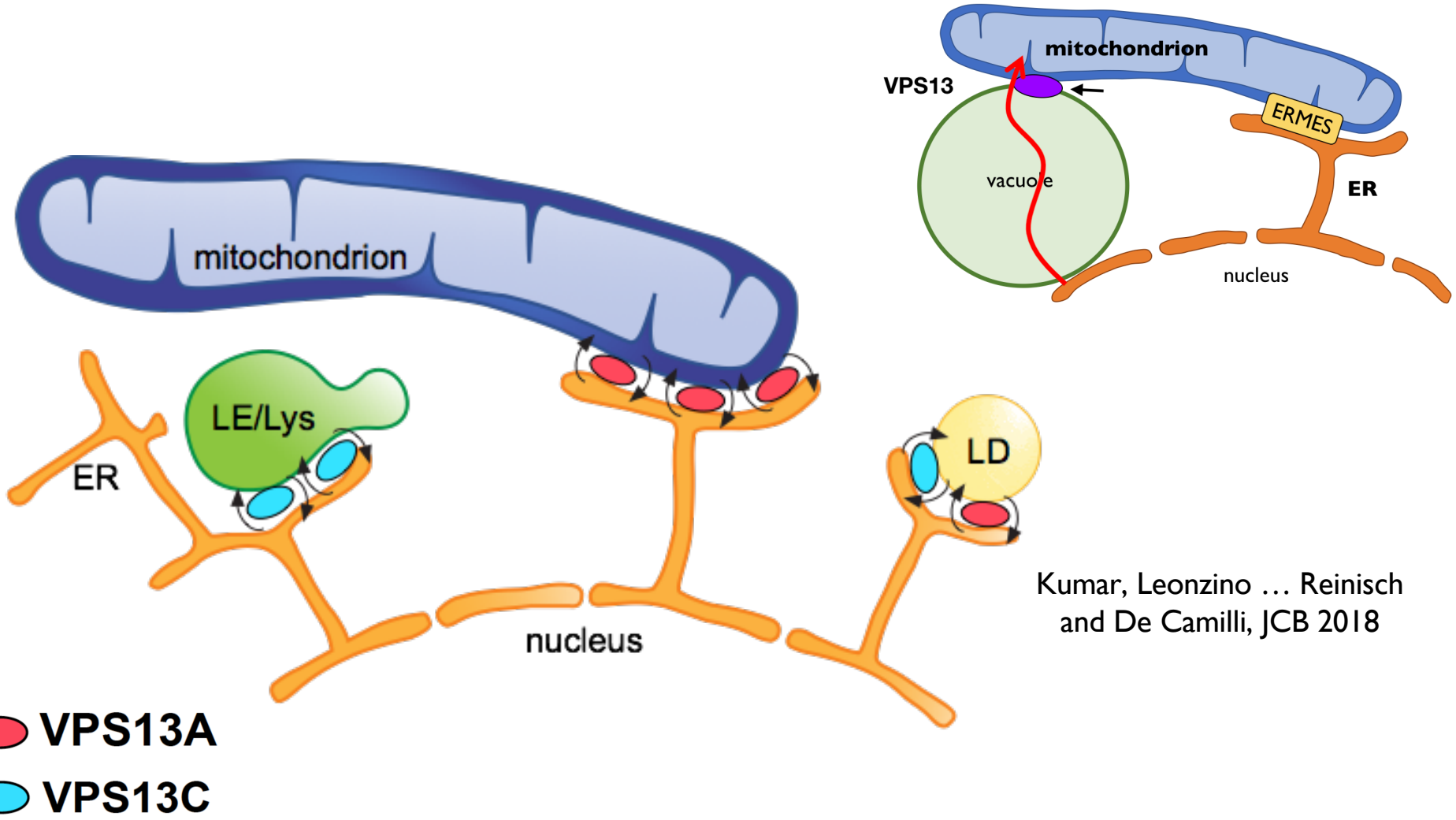


HA-Endogenous VPS13C
Rab7

Kumar, Leonzino, et el., 2018 *JCB*

VPS13A and VPS13C

Organelle tethering proteins with lipid transport properties and with distinct subcellular localizations

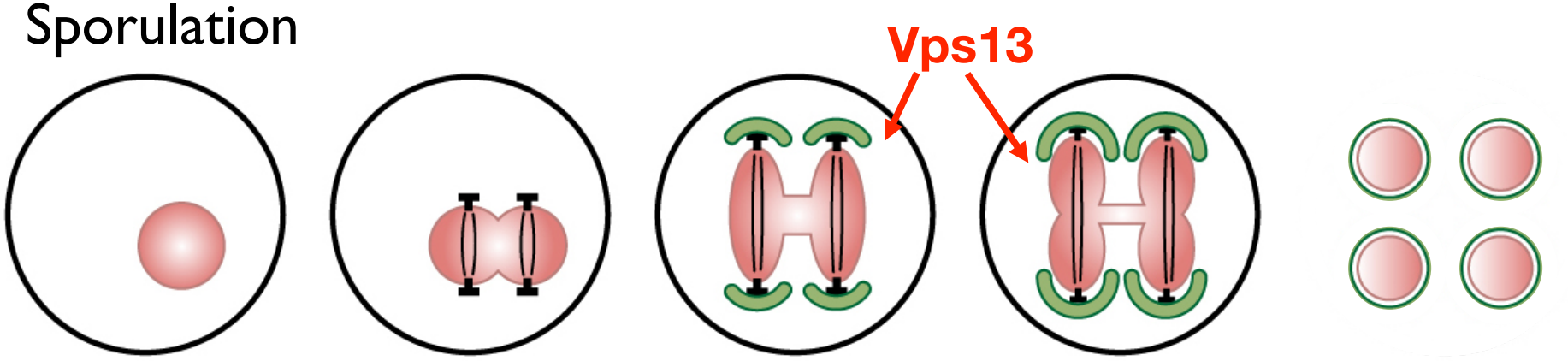


Kumar, Leonzino … Reinisch and De Camilli, JCB 2018

Vps13 is implicated in membrane growth in yeast

Needed for the growth of the sporulation membrane

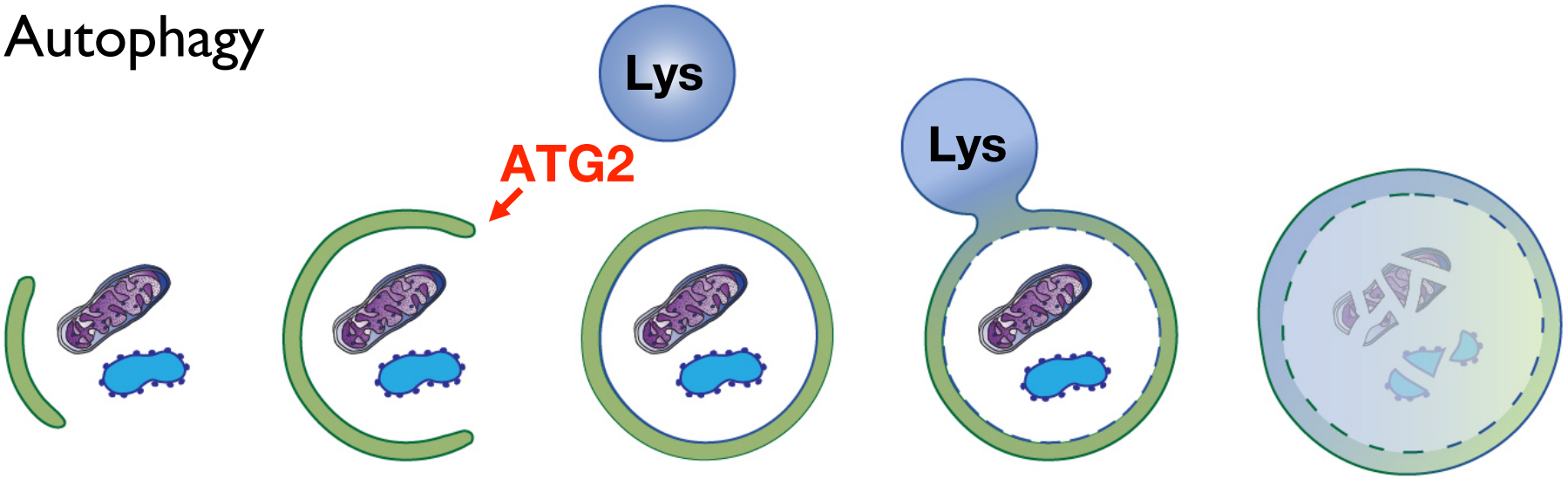
Sporulation



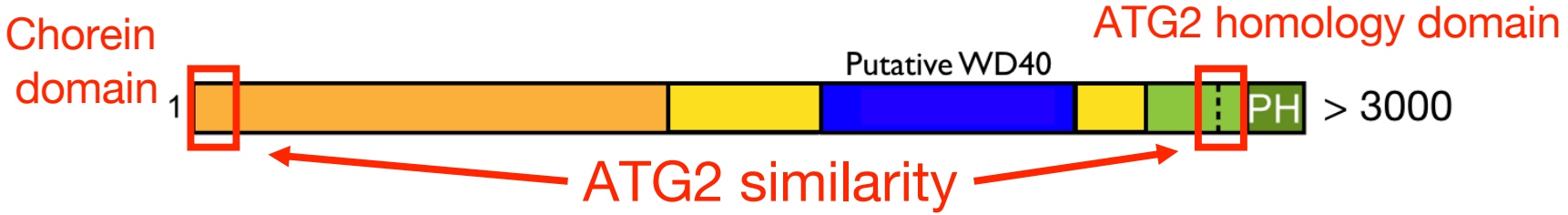
Autophagy is a another process that, like sporulation, implies membrane growth

Growth of the autophagic membrane requires ATG2

Autophagy



Vps13 has a.a. similarity to ATG2

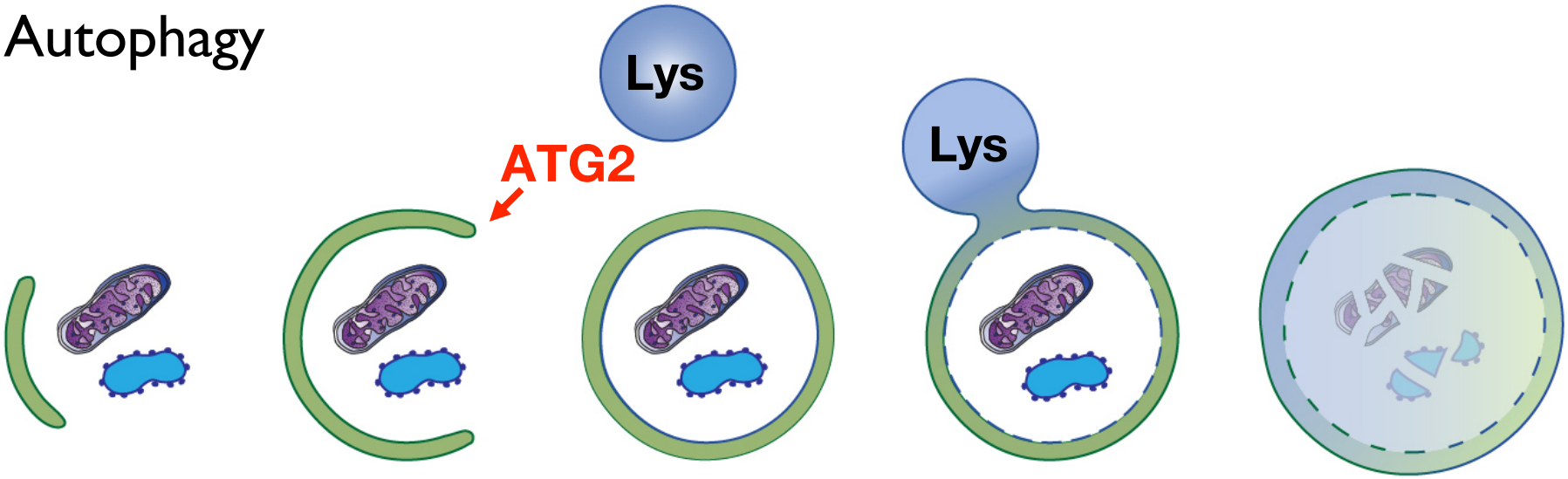


Atg2 is involved in contacts between the endoplasmic reticulum and the autophagic membrane

Gomez-Sanchez, Rose … Ungermann & Reggiori, *J. Cell Biol. 2018*

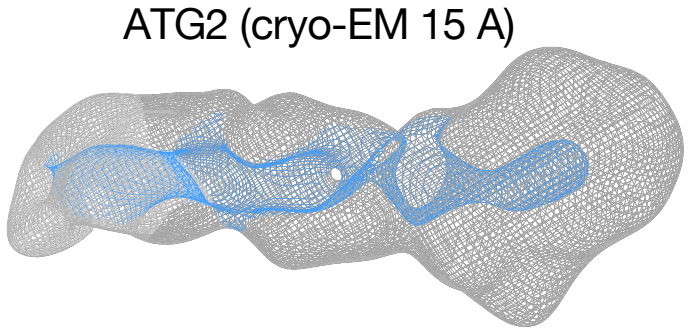
Kotani … & Nakatogawa, *PNAS* 2018

Autophagy

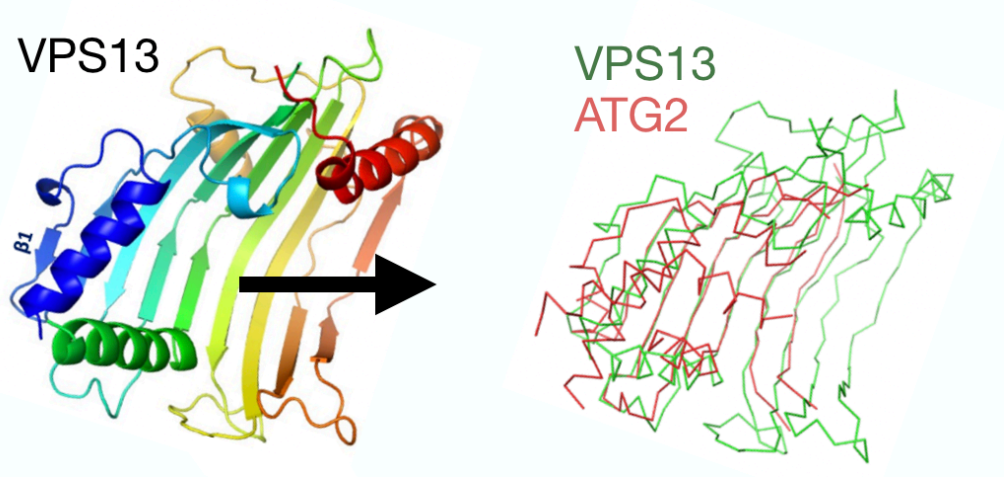


Recent studies have confirmed the structural similarity of VPS13 to ATG2

ATG2 transports lipids to promote autophagosome biogenesis
Valverde et al. J. Cell Biol. 2019



ATG2 mediates direct lipid transfer between membranes for autophagosome formation
Osawa et al. Nature Struct Biol. 2019



Summary on VPS13

- VPS13 joins the family of lipid transport proteins
- Abnormal lipid transport may be responsible for diseases due to VPS13 mutations
- VPS13 proteins function as conduits for the transport of lipids between different organelles, including lipid droplets
- Different VPS13 paralogs have different functions
- VPS13A may account for the lack of the ERMES complex in metazoan cells
- ATG2 is also likely to be a lipid transport protein

Future directions

To elucidate

- structure, mechanisms, energetics and regulation
- physiological importance (distinct and overlapping functions)
- mechanisms of disease

Thanks to:

My laboratory

Collaborators

Karin Reinisch
(Yale)
- Nikit Kumar
- Florian Horenkamp
- Josh Lees
- PeiQi Li

Harald Hess
(HHMI/Janelia)
- Shan Xu
- Ken Hayworth