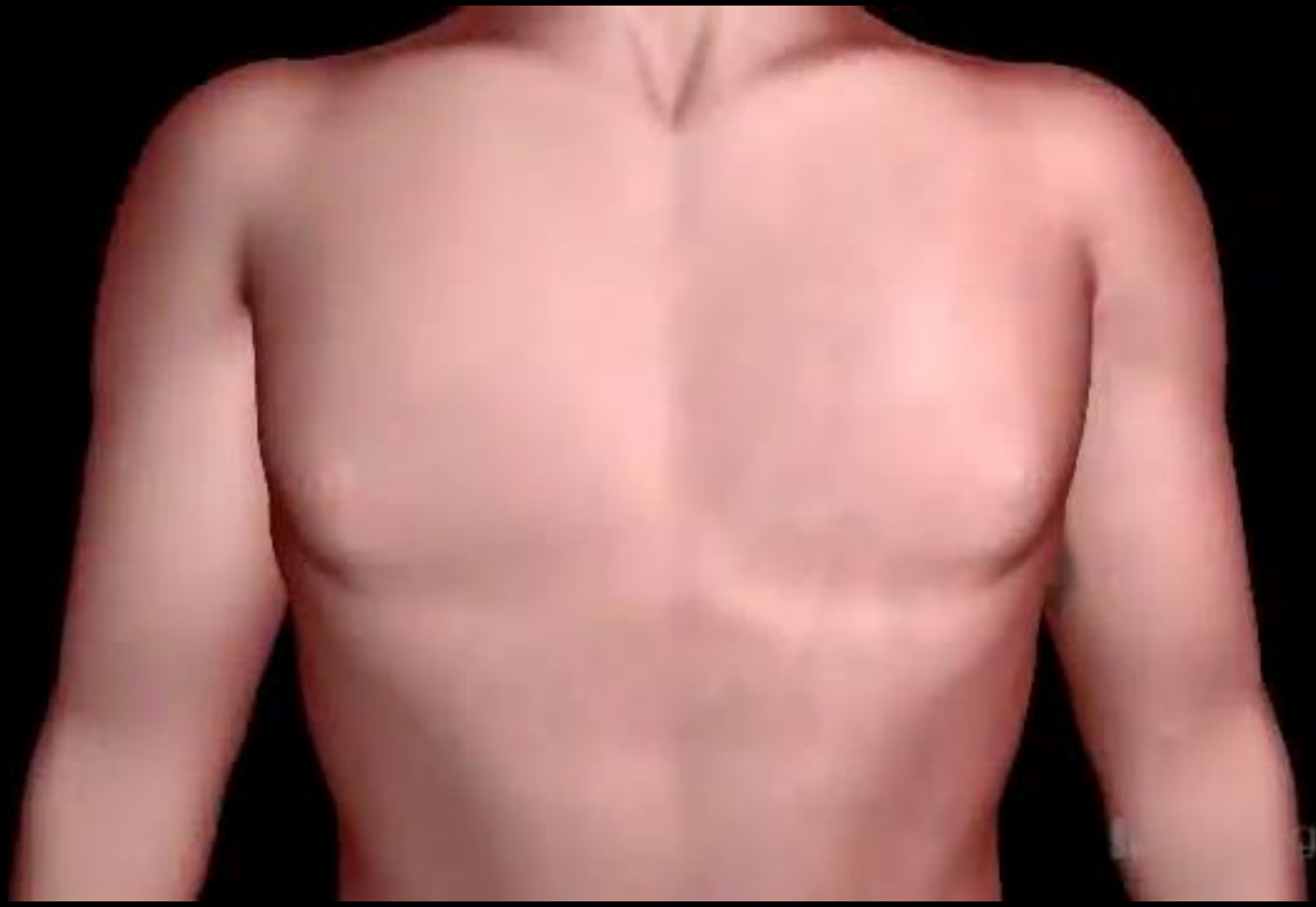
Cellular membrane dynamics and cancer

Harald Stenmark
Institute for Cancer Research, Oslo University Hospital
Centre for Cancer Cell Reprogramming, University of Oslo

Iceland Liechtenstein Norway grants
Norway grants
RO-NO-2019-0601: MEDYCONAI

What is cancer?



Animation from Cancer.Net

Cancer: Cells gone bad

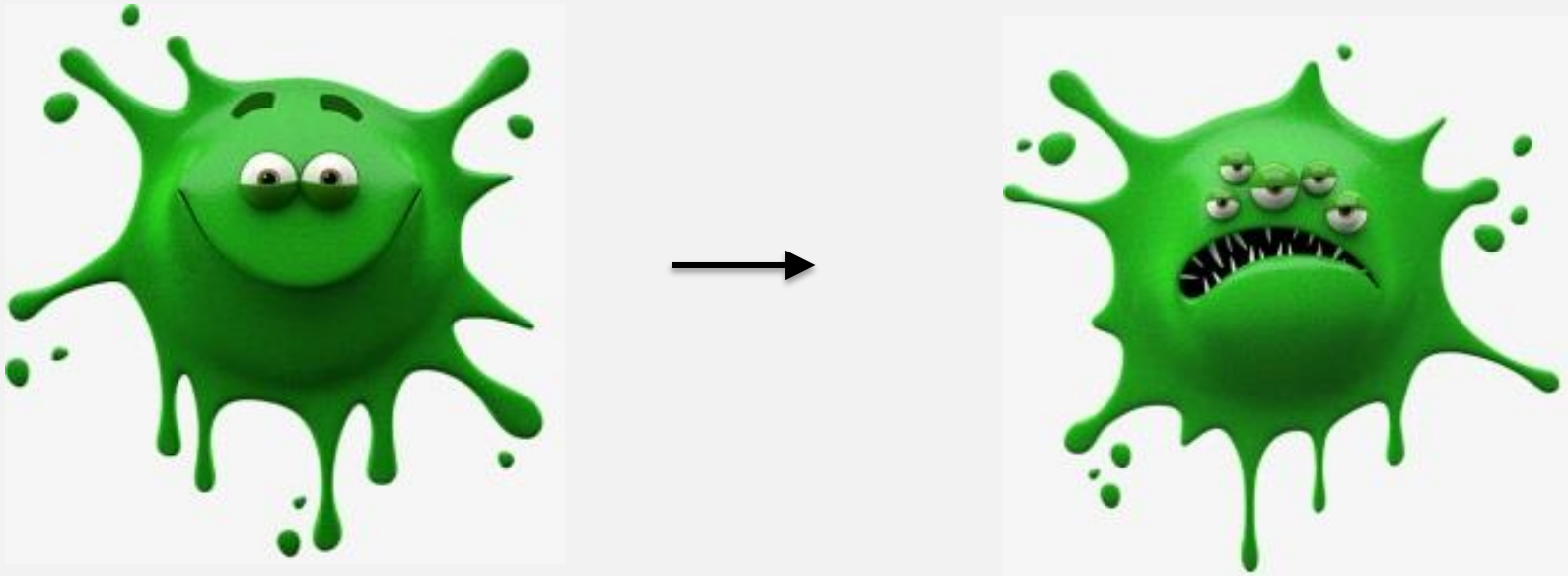
Normal cell

Cancer cell

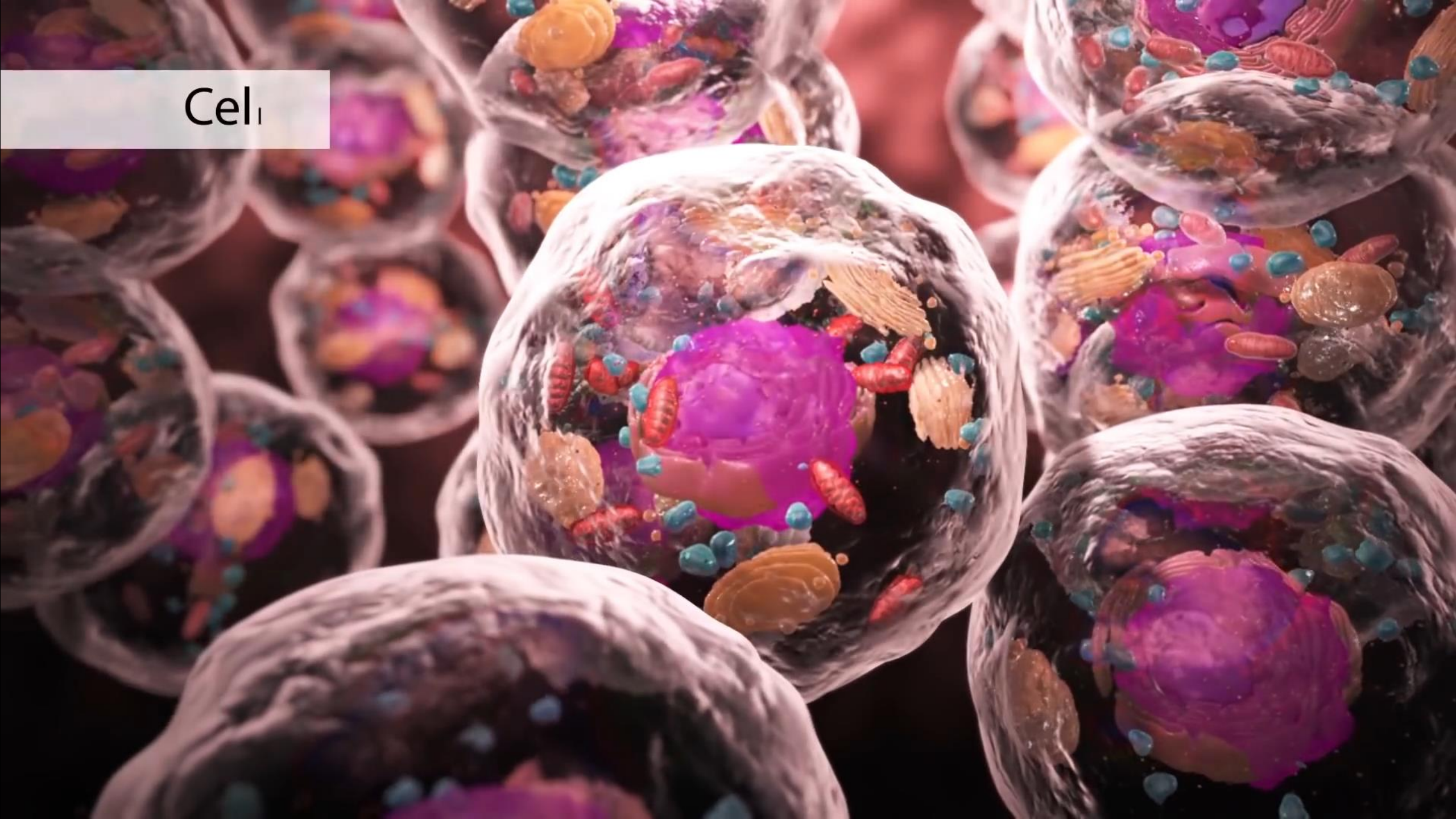
Hallmarks of cancer cells

- Uncontrolled proliferation
- Uncontrolled growth
- Sustained life span
- Invasive
- Escape killing by immune system

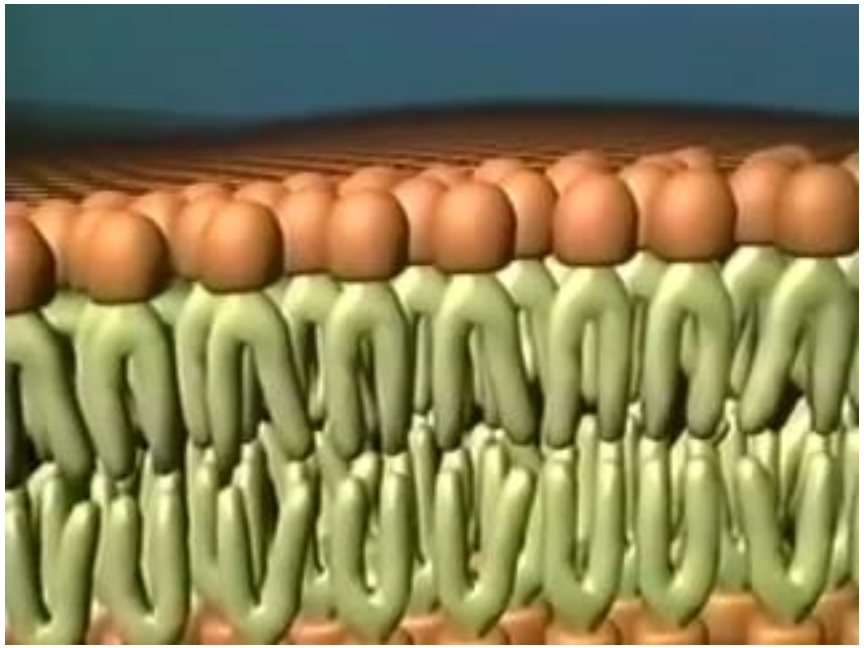
How are normal cells transformed into cancer cells?



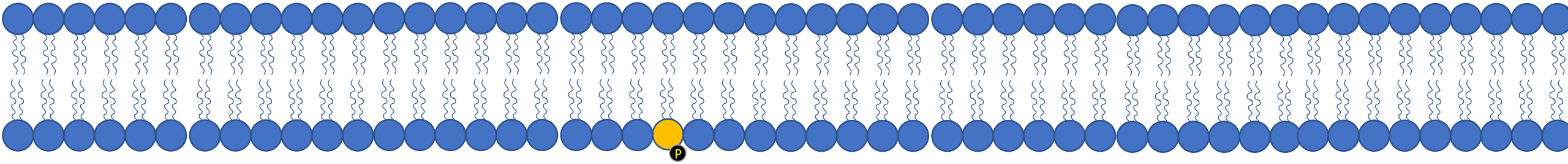
- Changes in DNA (mutations)
- Uncontrolled signalling
- Changes in cellular membranes


Cel

Protein recruitment to membranes

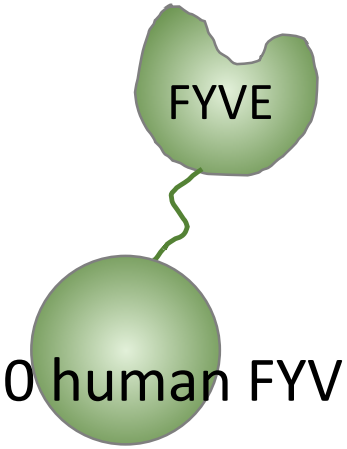


The lipid PI3P recruits FYVE domain proteins to membranes



PI3P

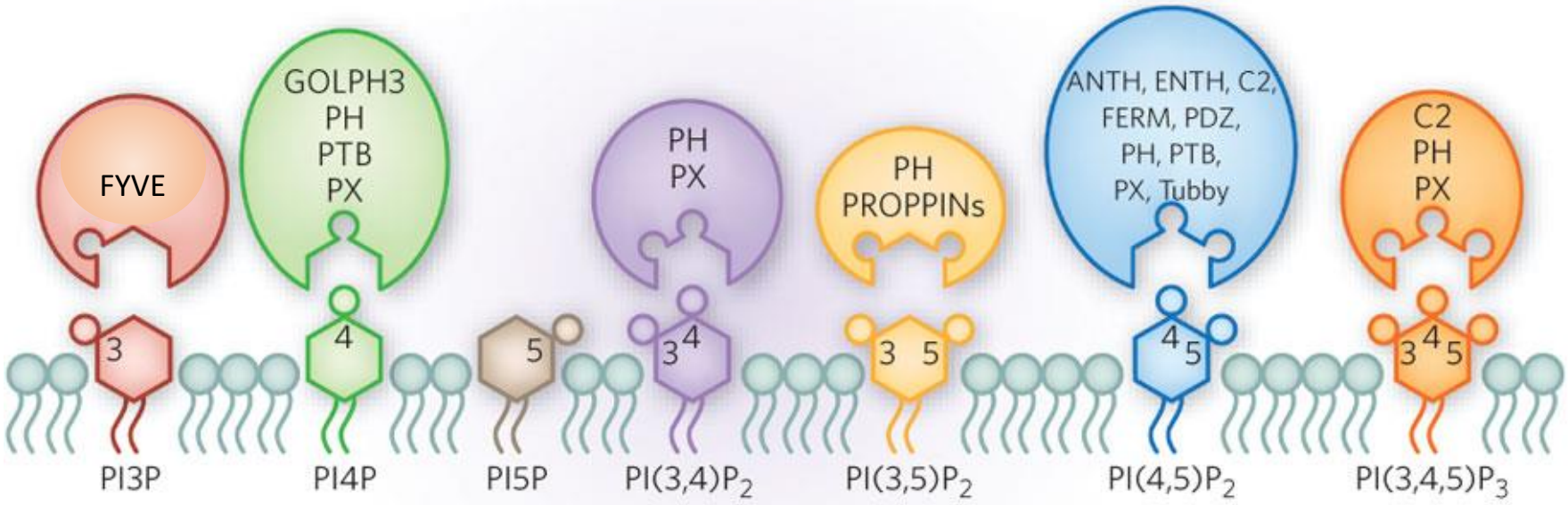
Fab1
YOTB
Vac1
EEA1



30 human FYVE domain-containing proteins: All bind PI3P

Gaullier et al.
Nature, 1998

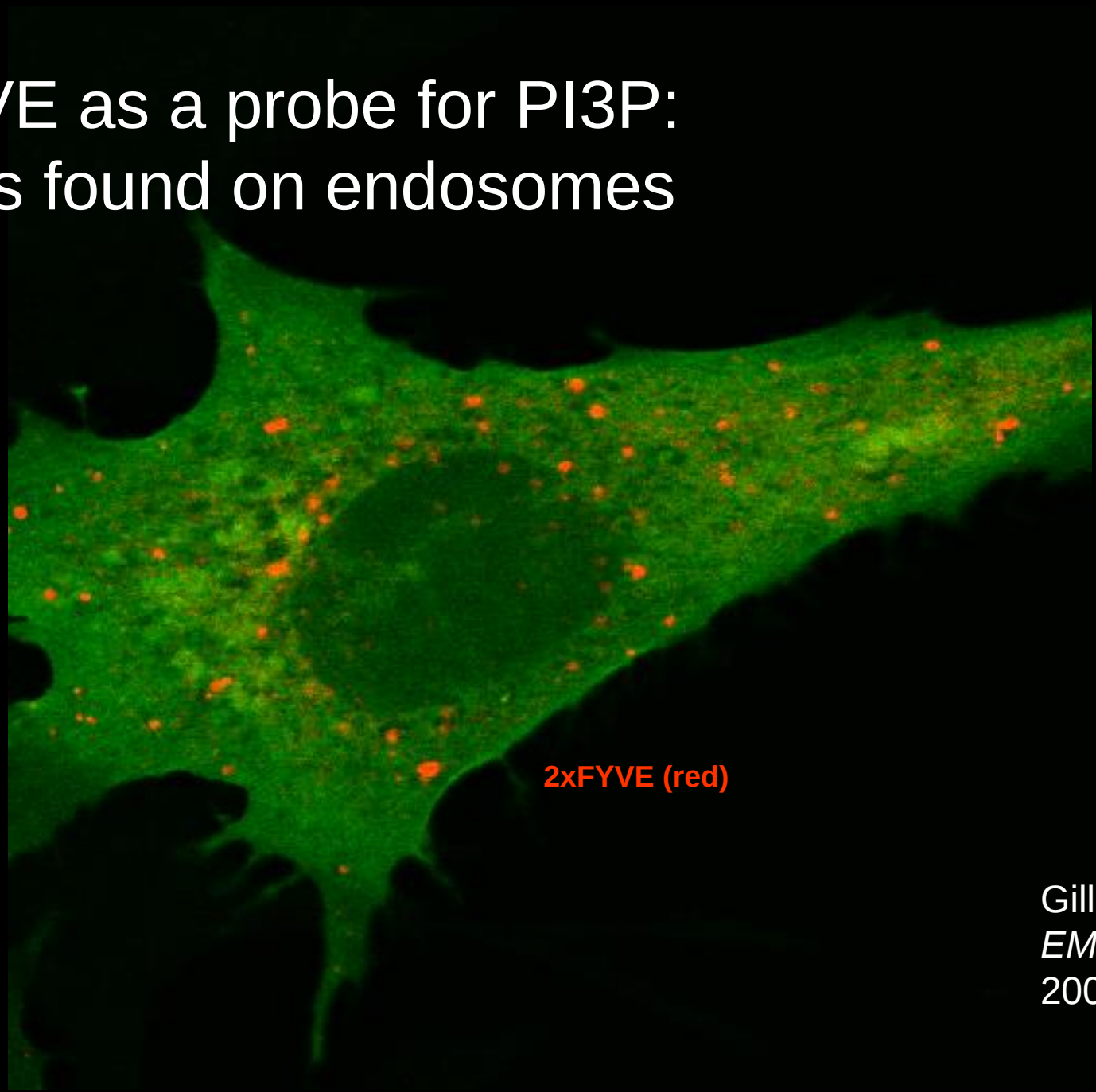
Lipid-binding proteins decode the phosphoinositide code and translate it to cellular responses



Kutateladze (2010)

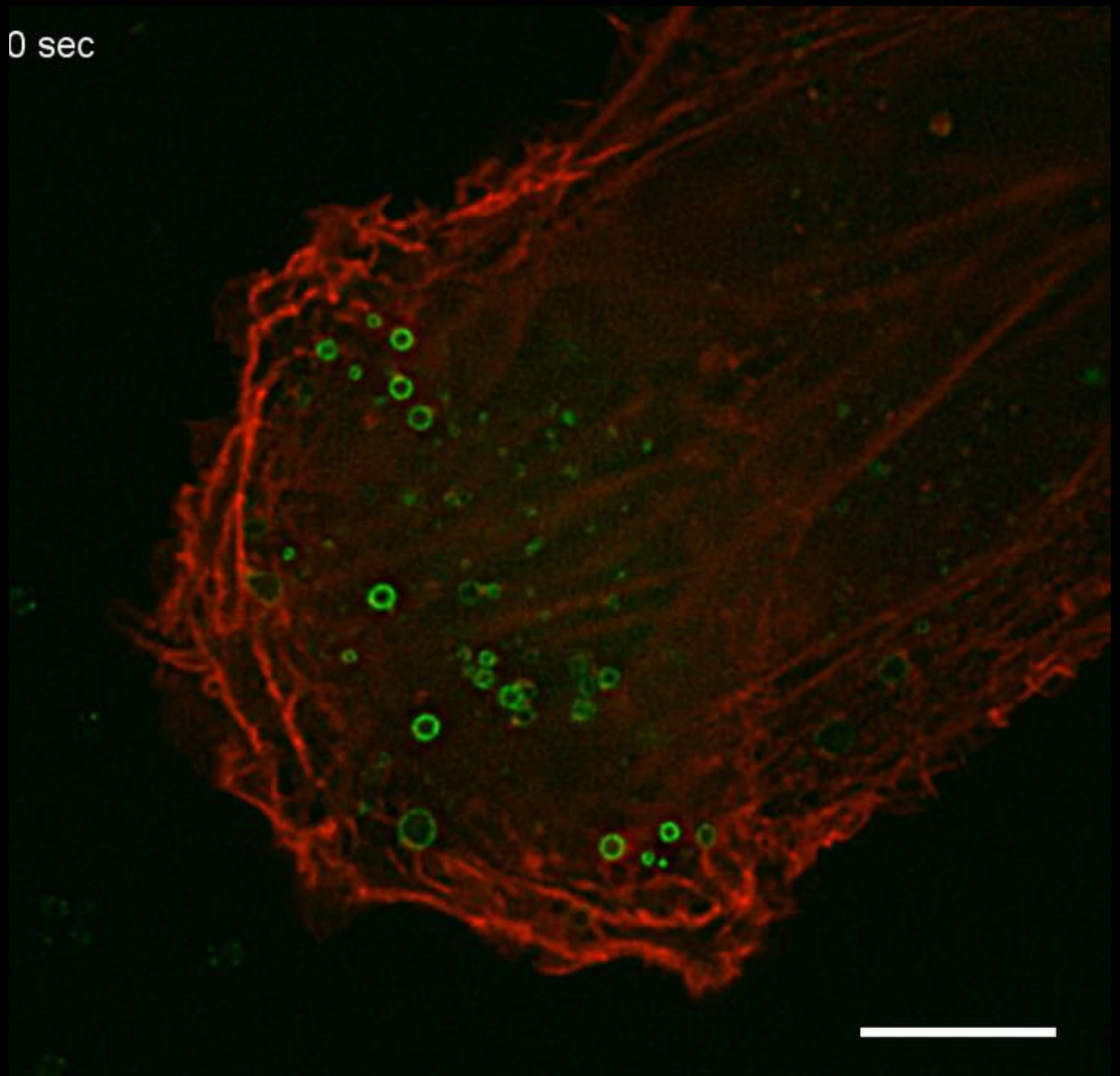
2xFYVE as a probe for PI3P: PI3P is found on endosomes

2xFYVE



Gillooly et al.
EMBO Journal
2000

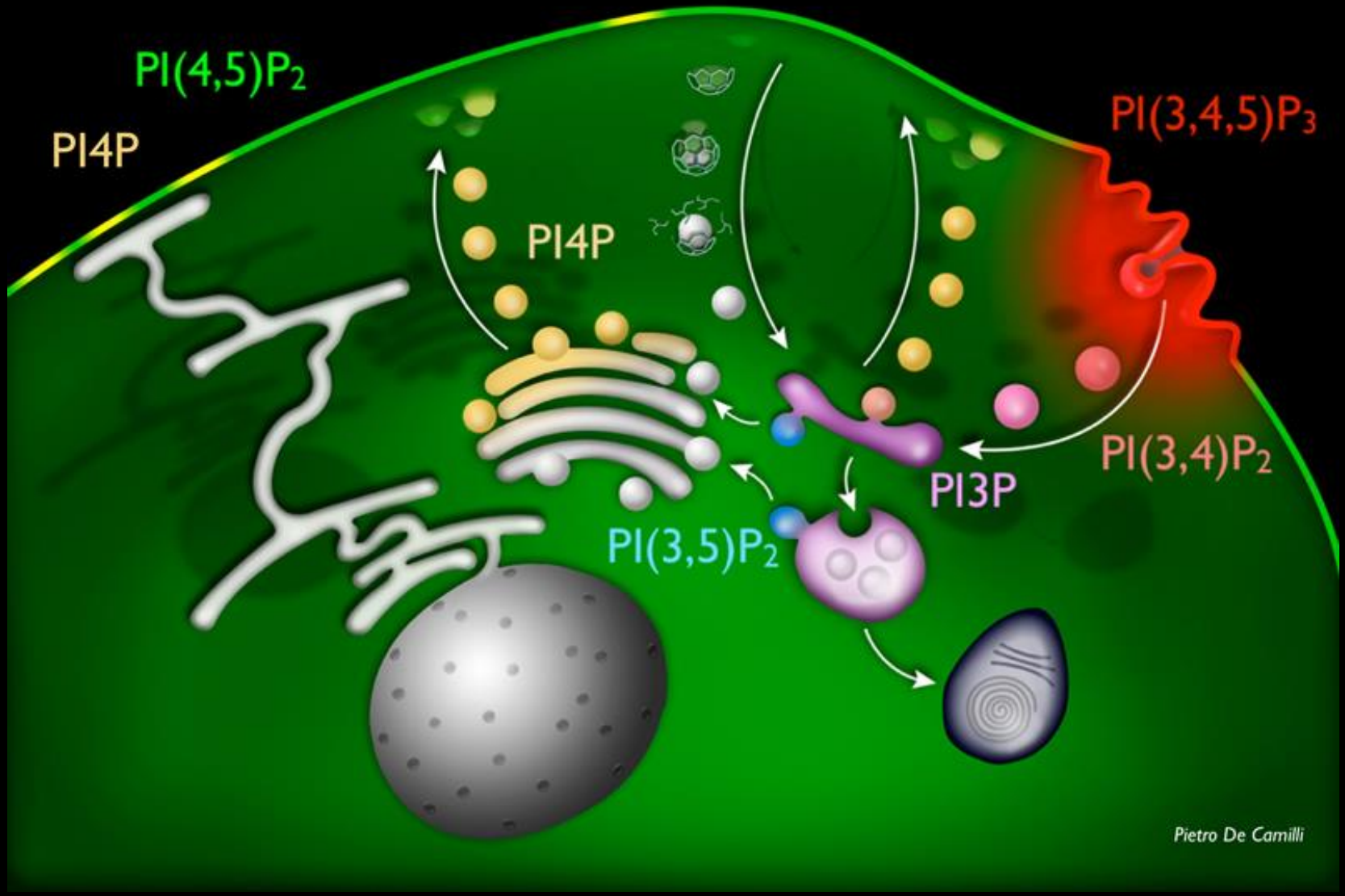
PI3P on endosomes



Actin
2xFYVE

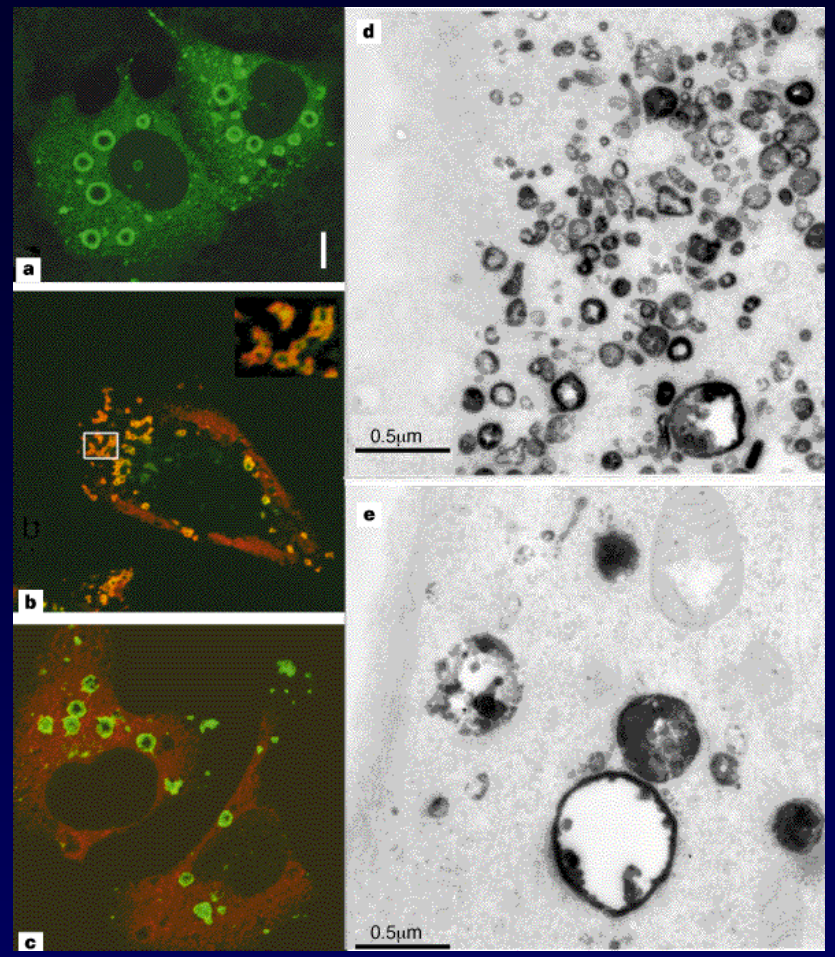
Schink et al.
Nature Comm. 2021

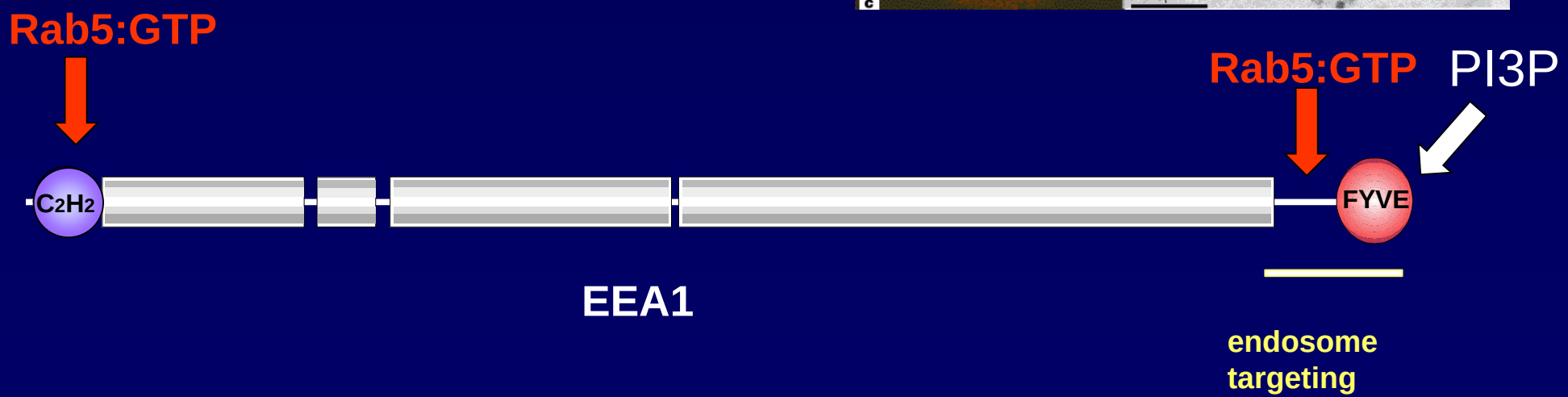
A phosphoinositide code for cellular membranes



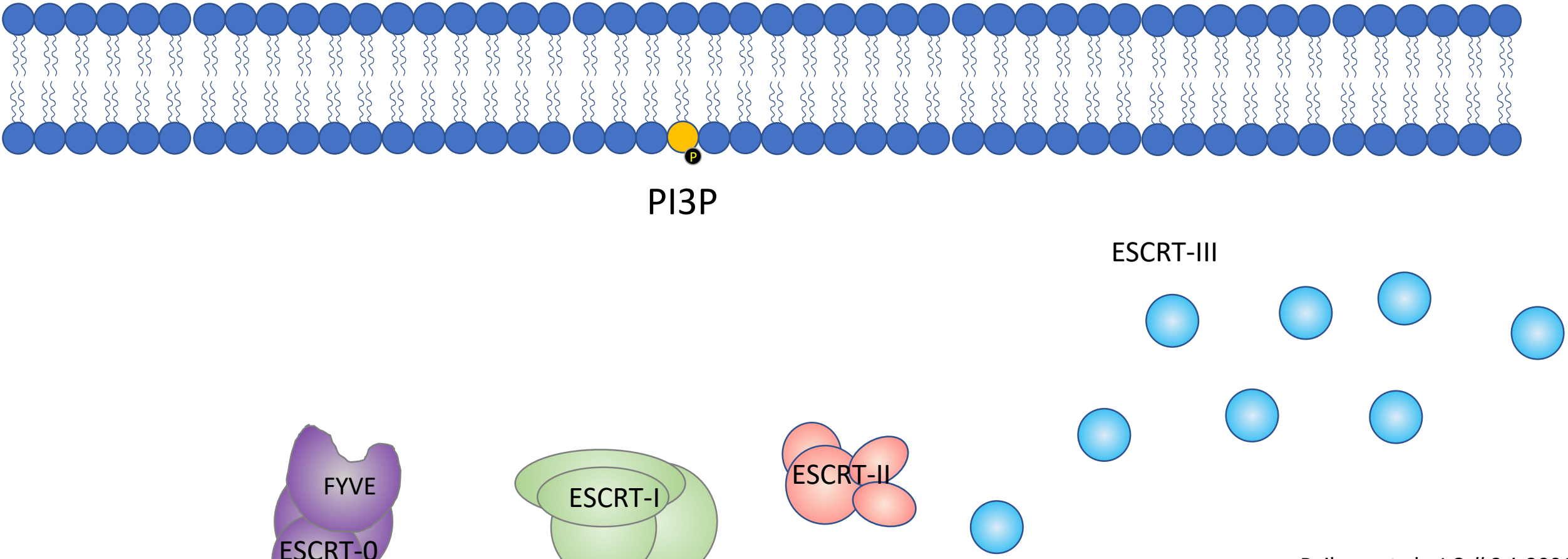
EEA1 mediates Endosome fusion

Simonsen et al.
Nature, 1998



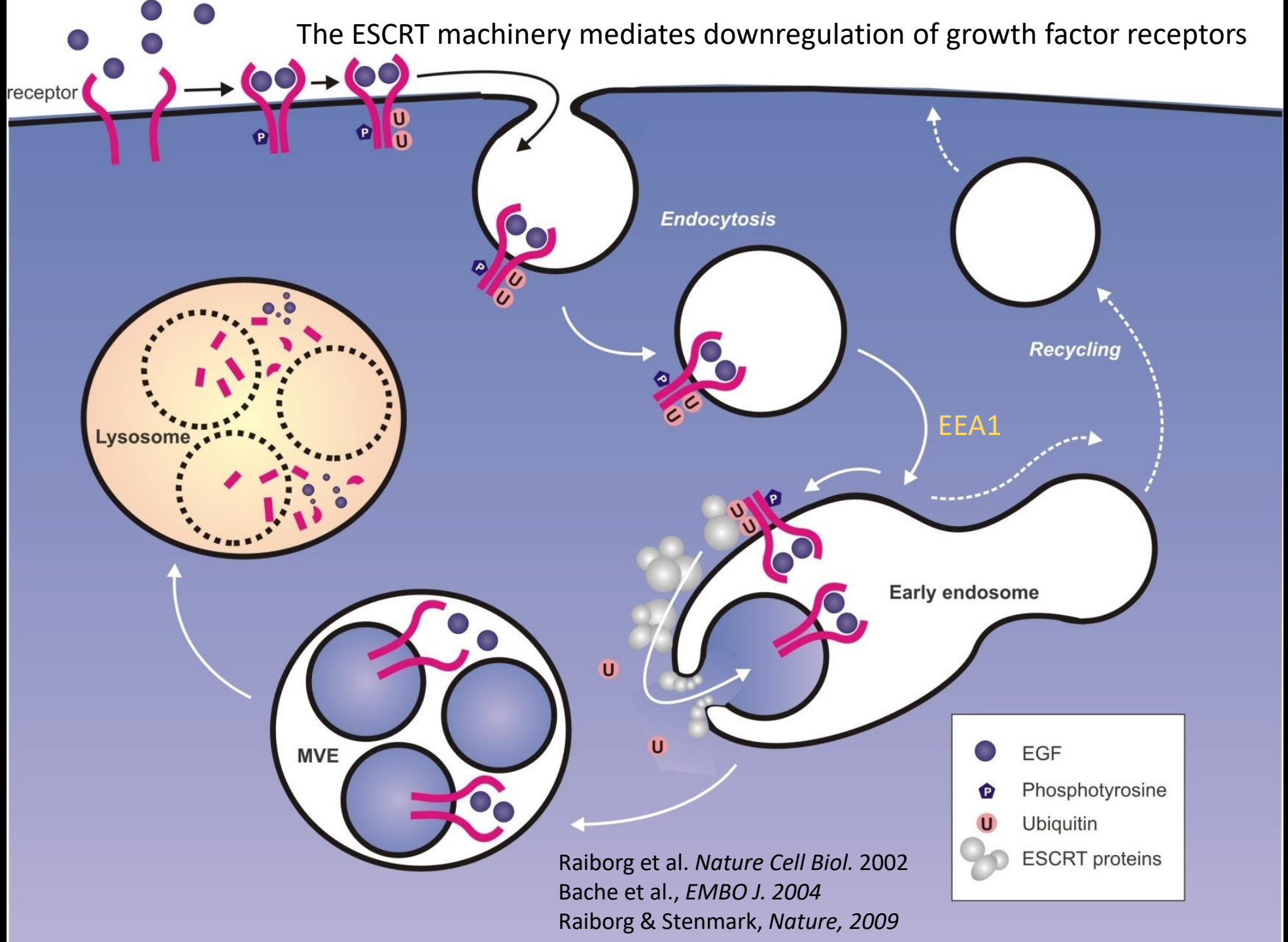


The ESCRT protein machinery is recruited to membranes by PI3P

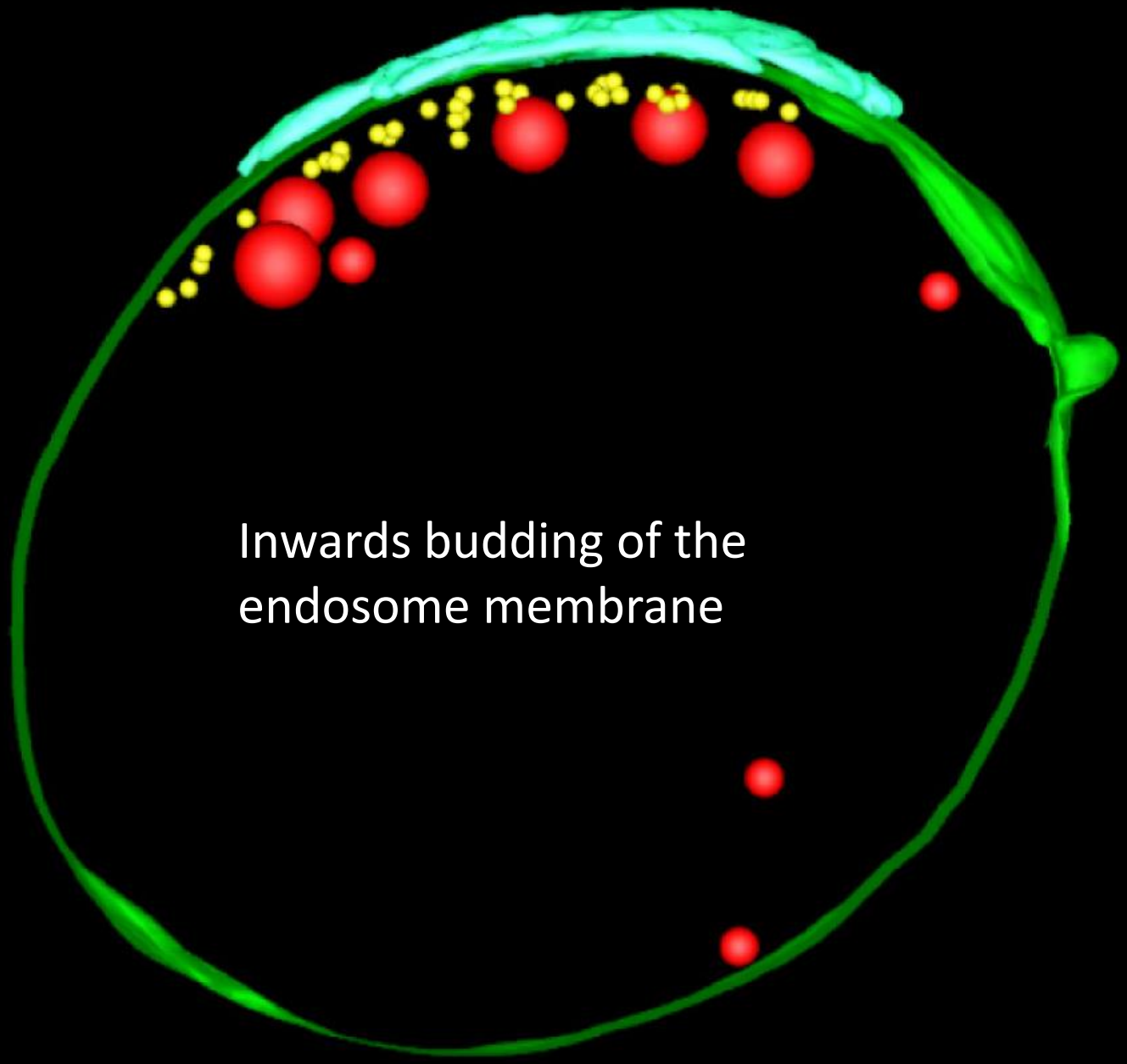


Raiborg et al., *J.Cell Sci.* 2001
Raiborg et al., *EMBO J.* 2002
Bache et al. *J.Biol.Chem.* 2003
Bache et al., *J.Cell Biol.* 2003

The ESCRT machinery mediates downregulation of growth factor receptors

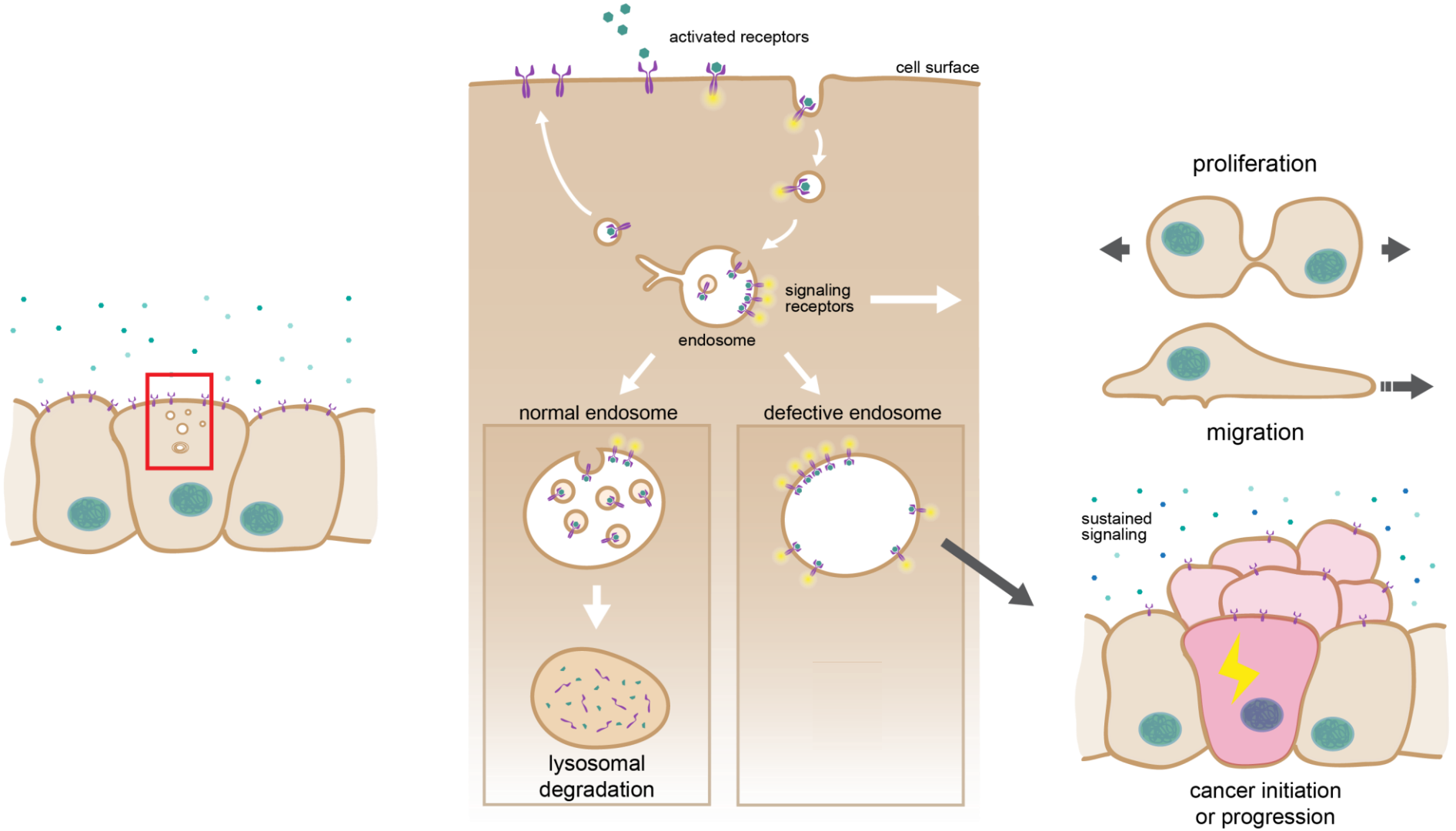


Raiborg et al. *Nature Cell Biol.* 2002
Bache et al., *EMBO J. 2004*
Raiborg & Stenmark, *Nature, 2009*

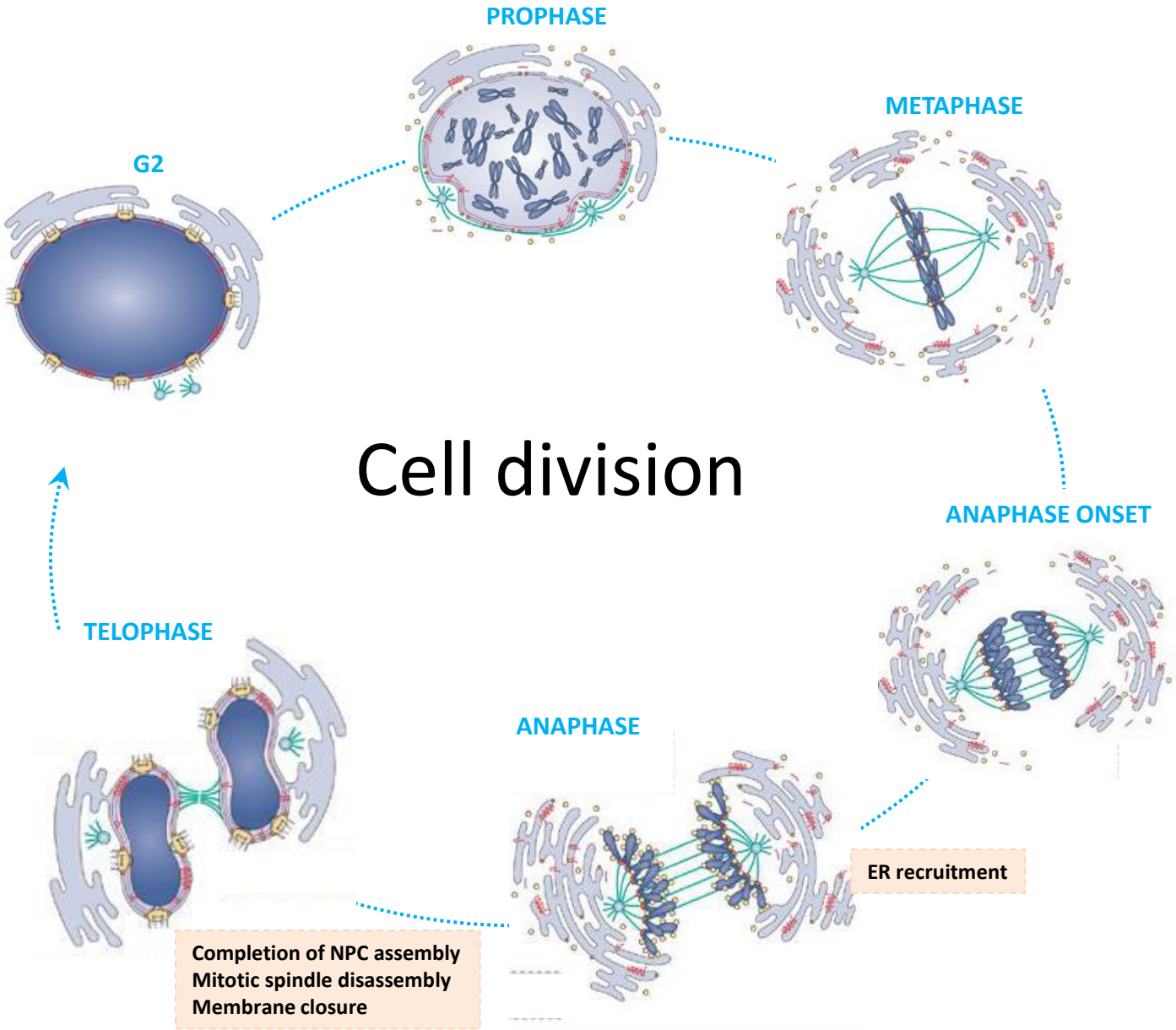


Wenzel et al
Nature Comm. 2019

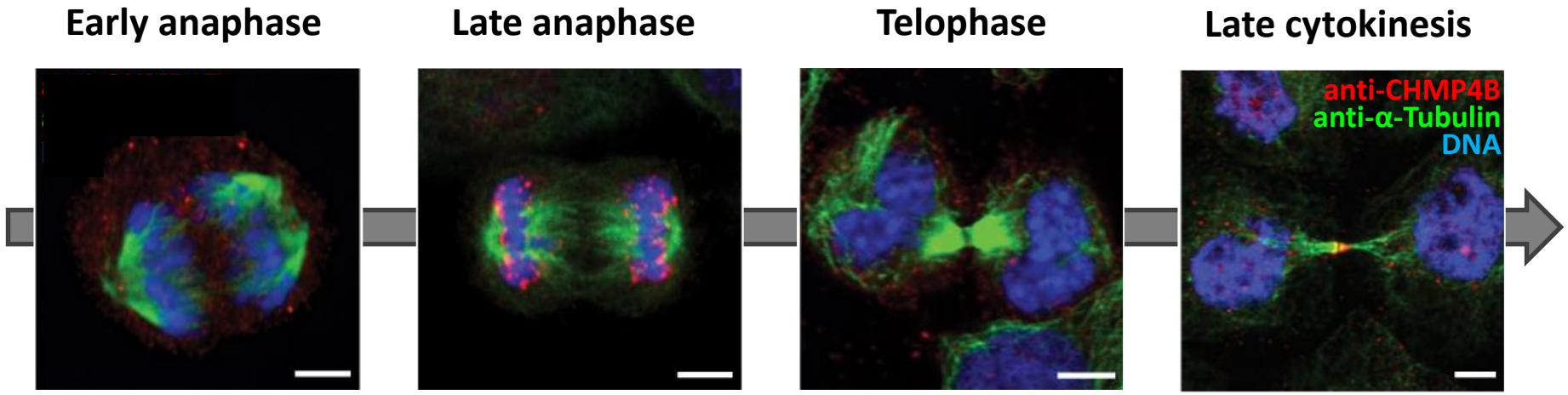
Defective ESCRT activity can cause cancer progression

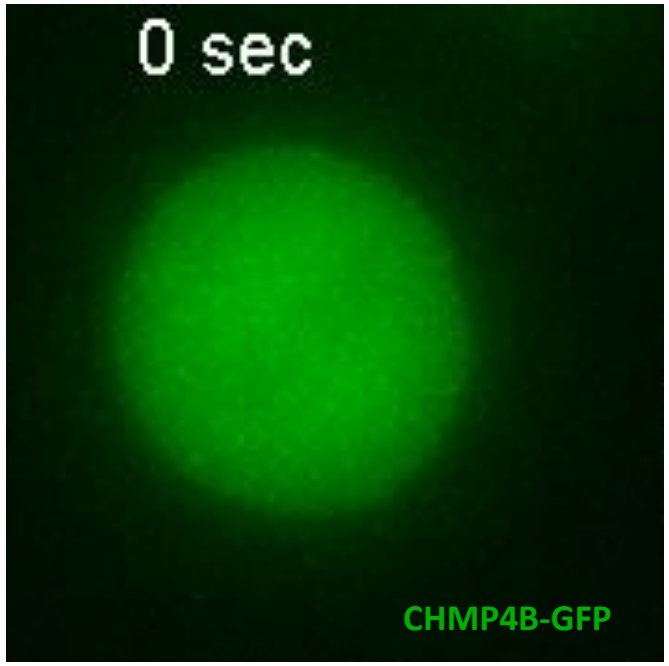


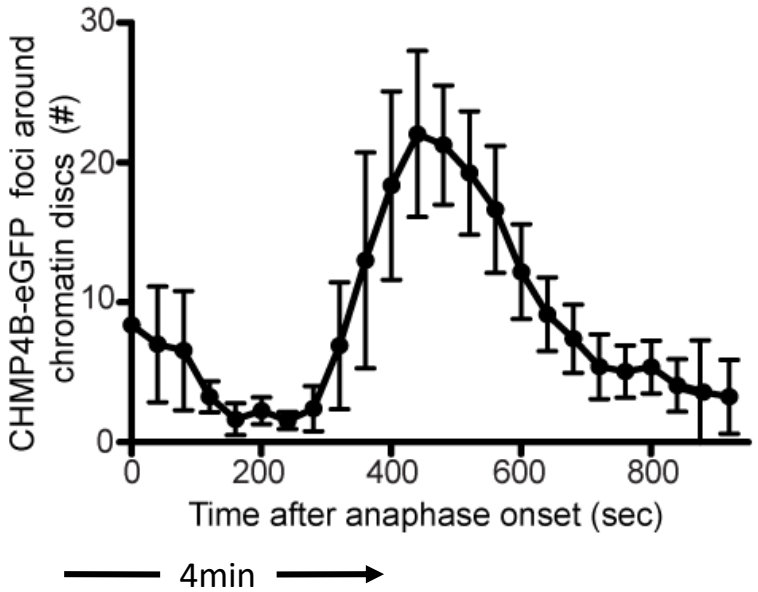
Cell division



ESCRT-III transiently localizes at chromatin discs during late anaphase

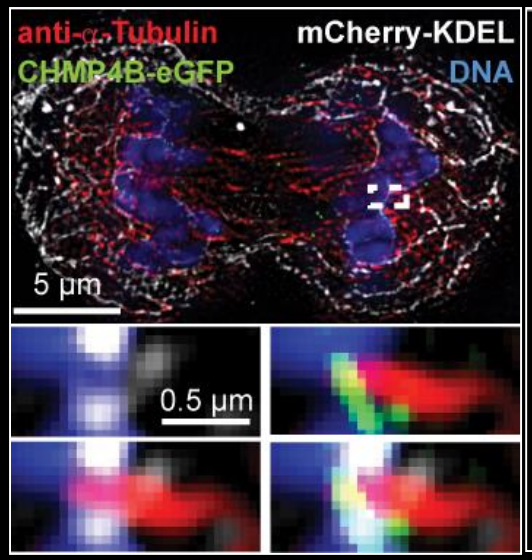


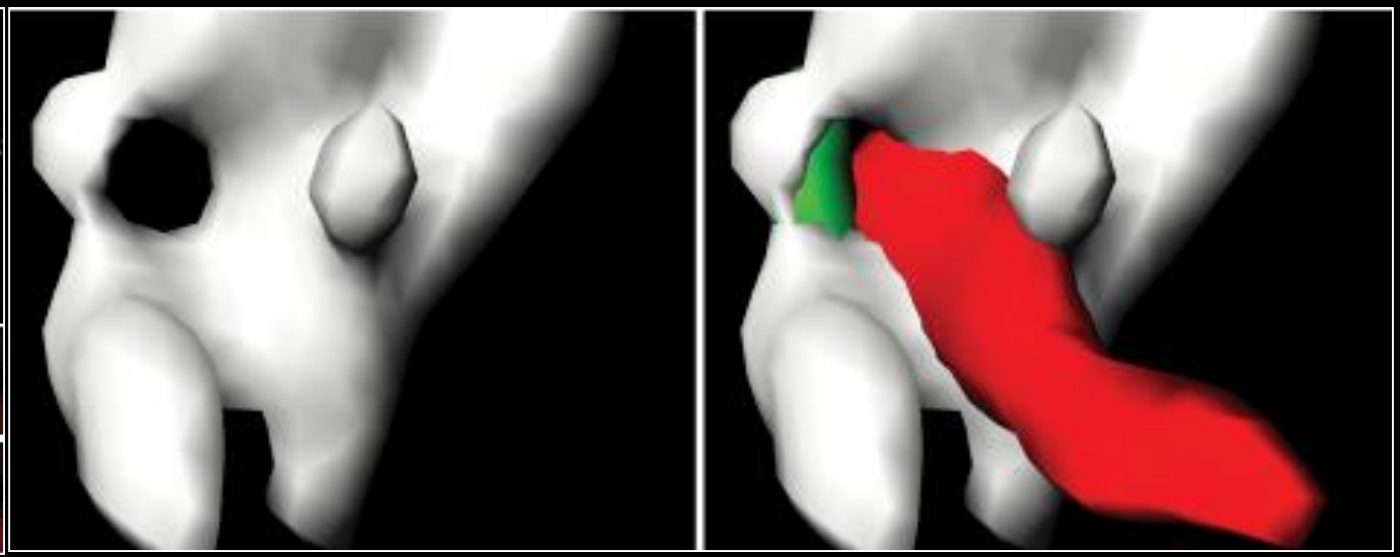


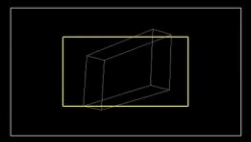


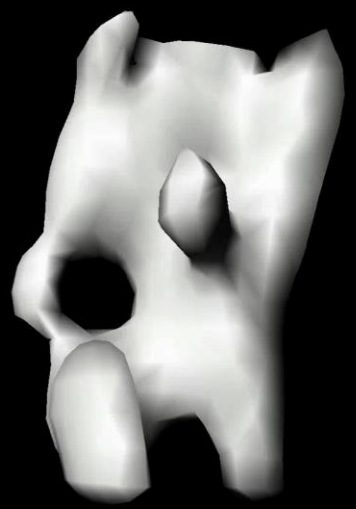
Marina Vietri

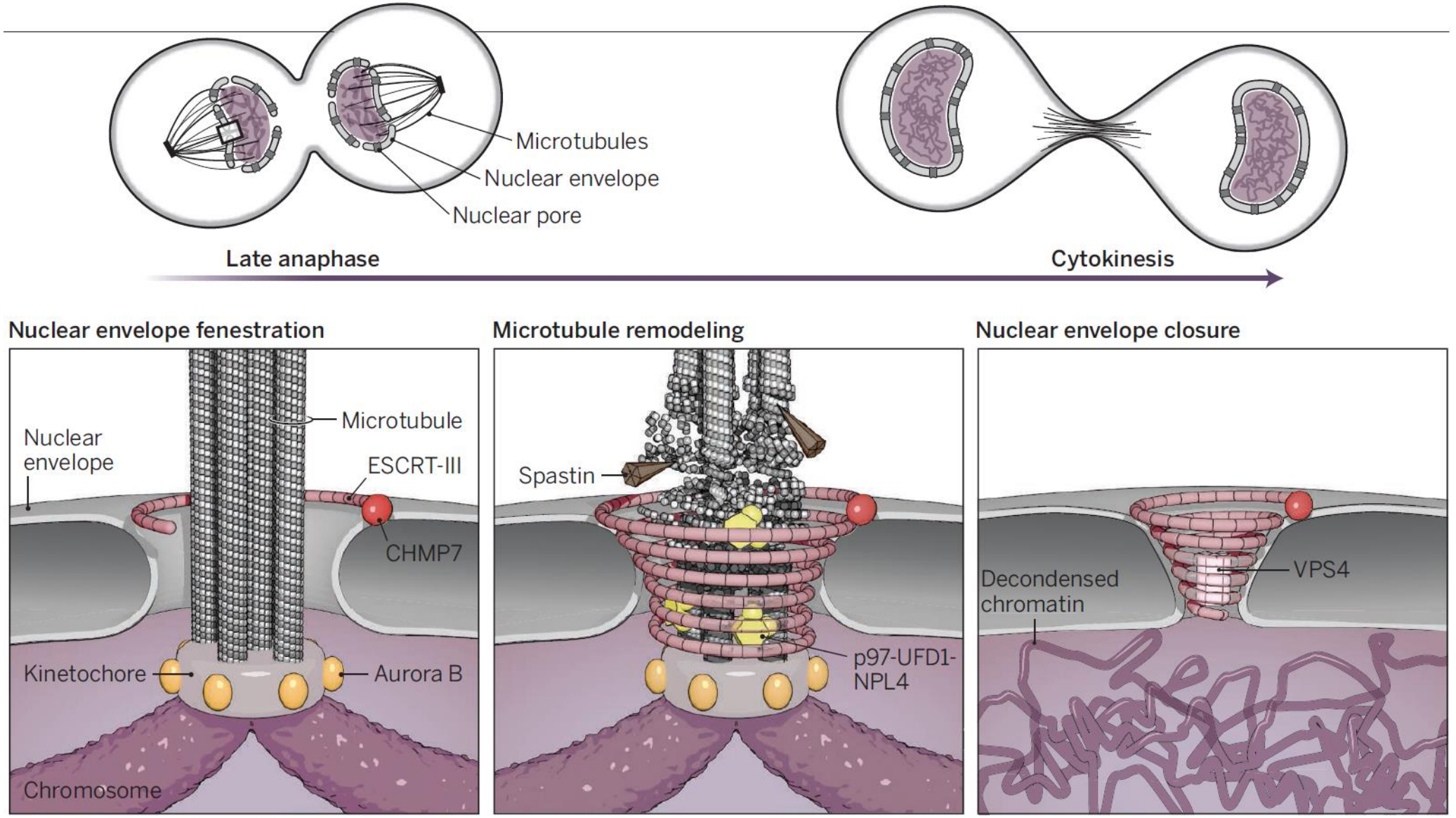
ESCRT-III is recruited where the reforming NE engulfs spindle MTs









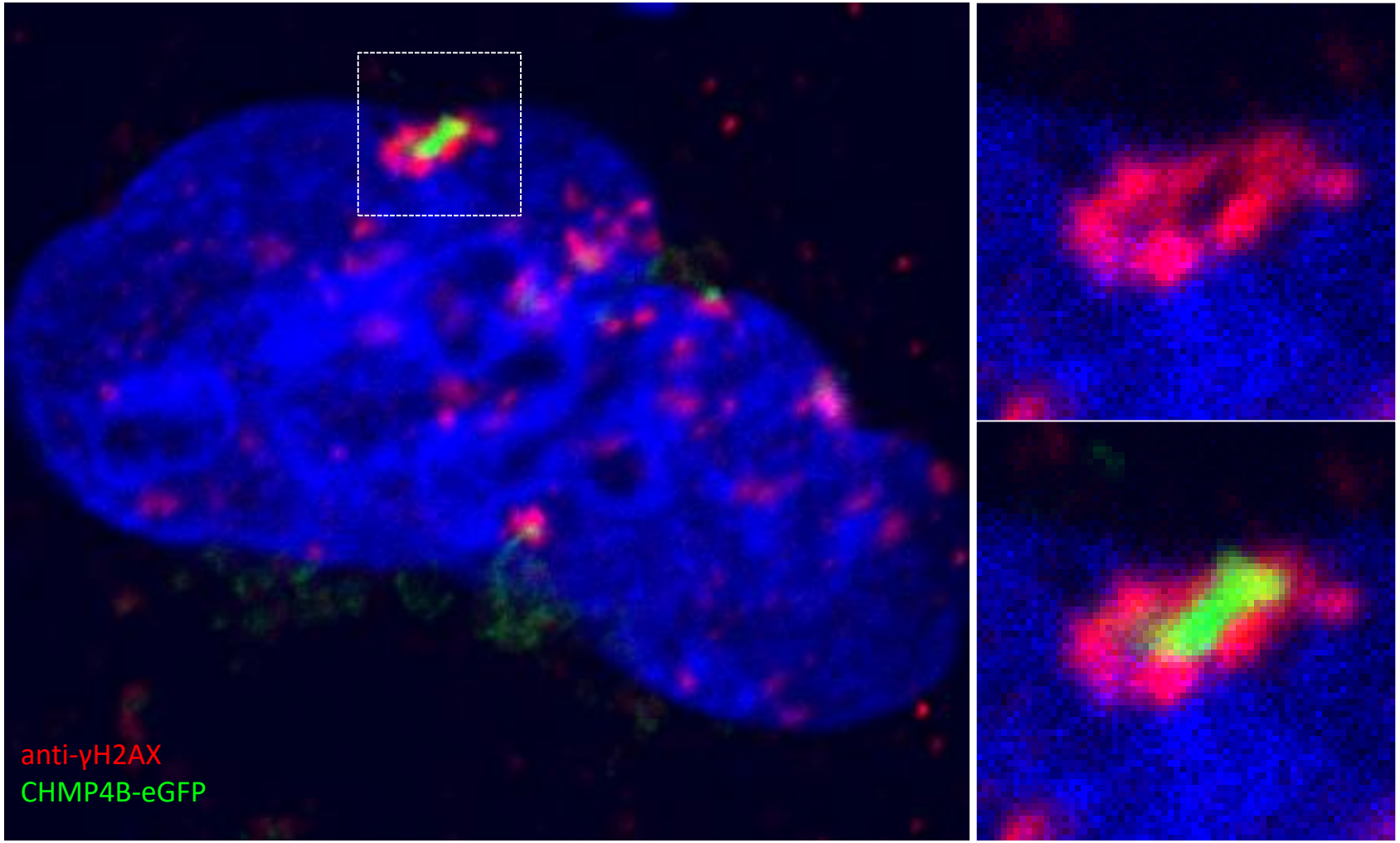


From «Perspective» in *Science*, 2015, by Sundquist and Ullman

Vietri et al., *Nature* 2015

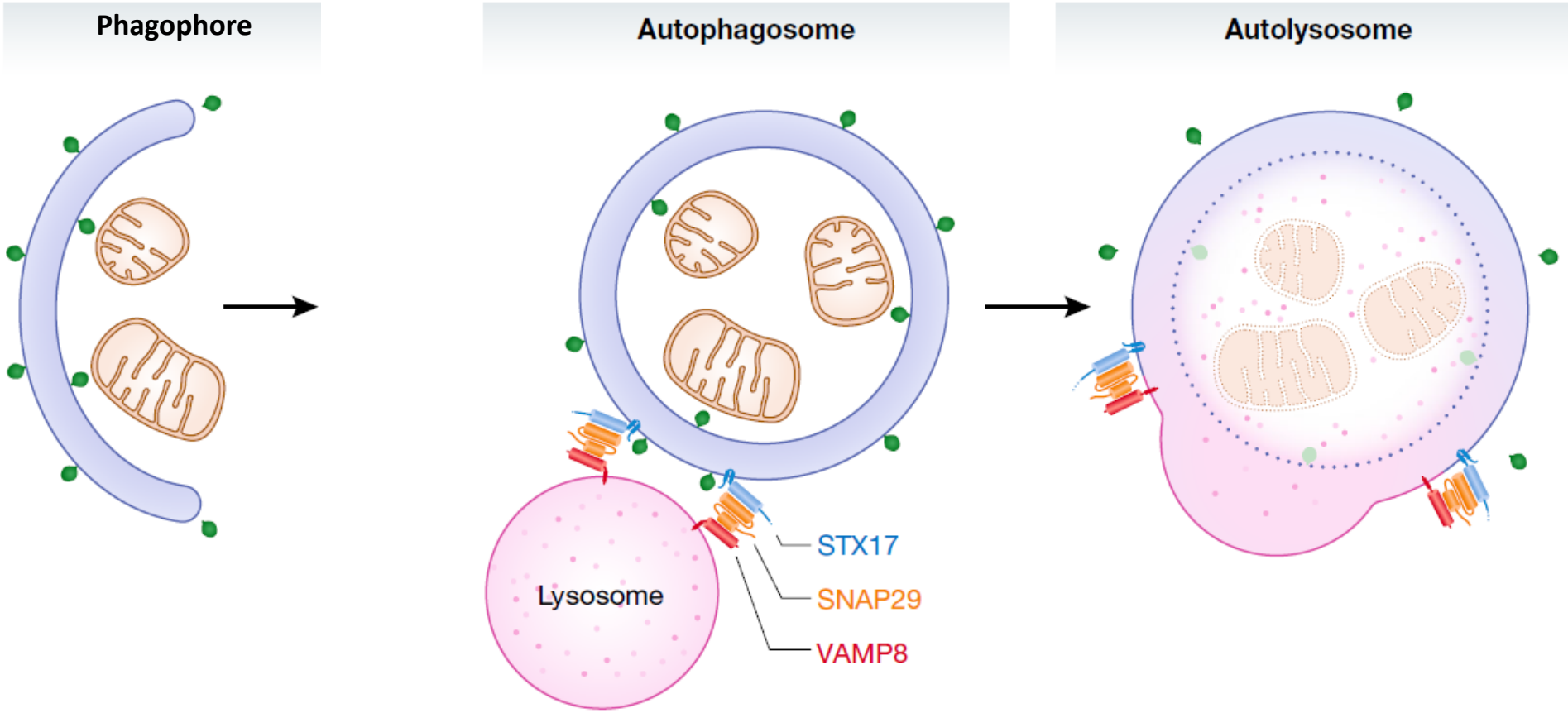
DNA damage in ESCRT-III depleted cells

CHMP2A siRNA

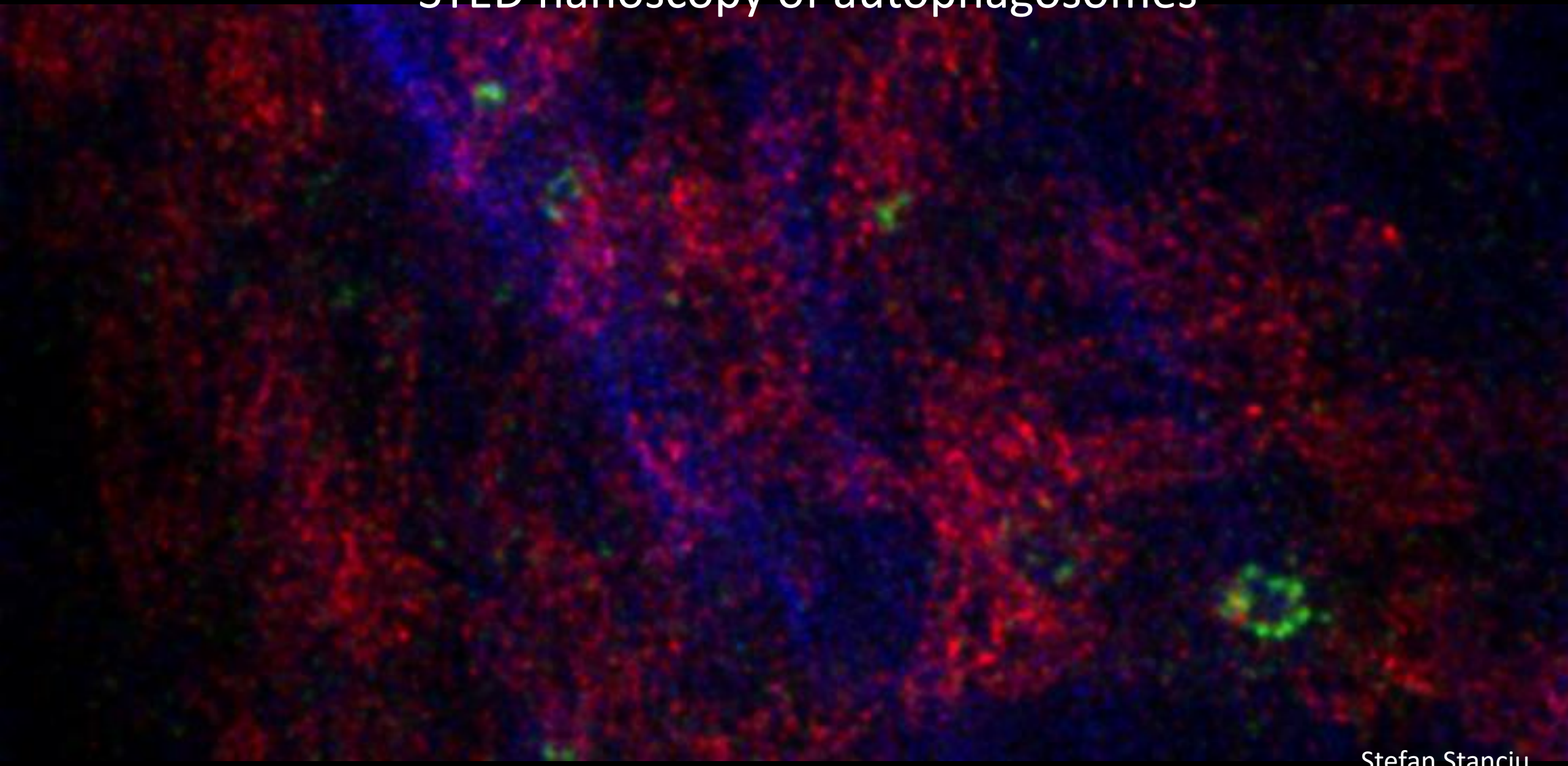


Vietri et al.,
Nature 2015

Autophagy – self-eating

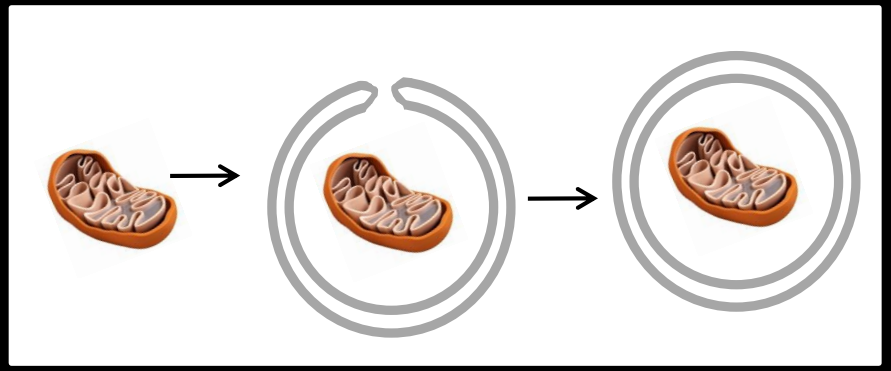


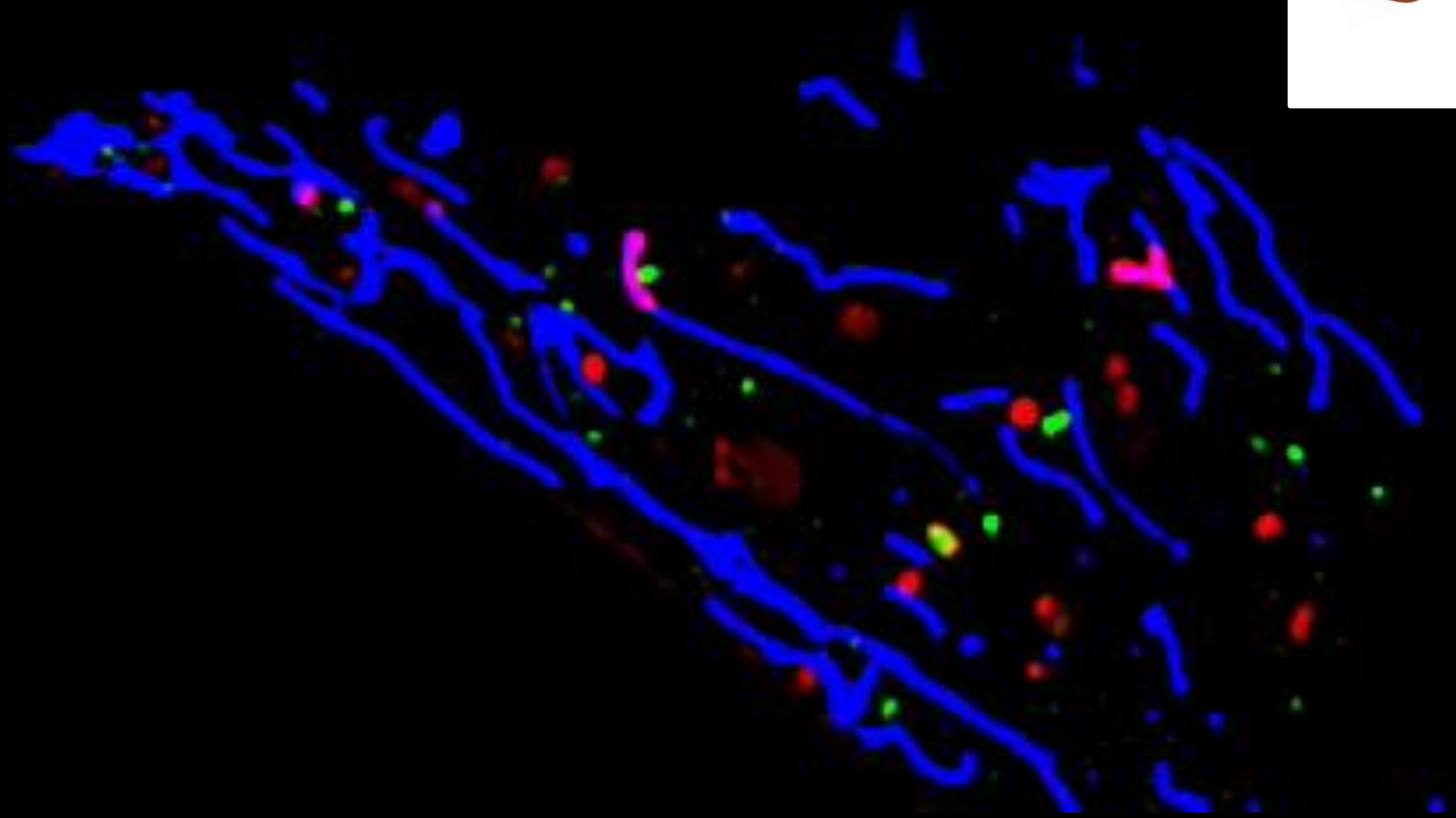
STED nanoscopy of autophagosomes



Stefan Stanciu

ESCRTs in mitophagy

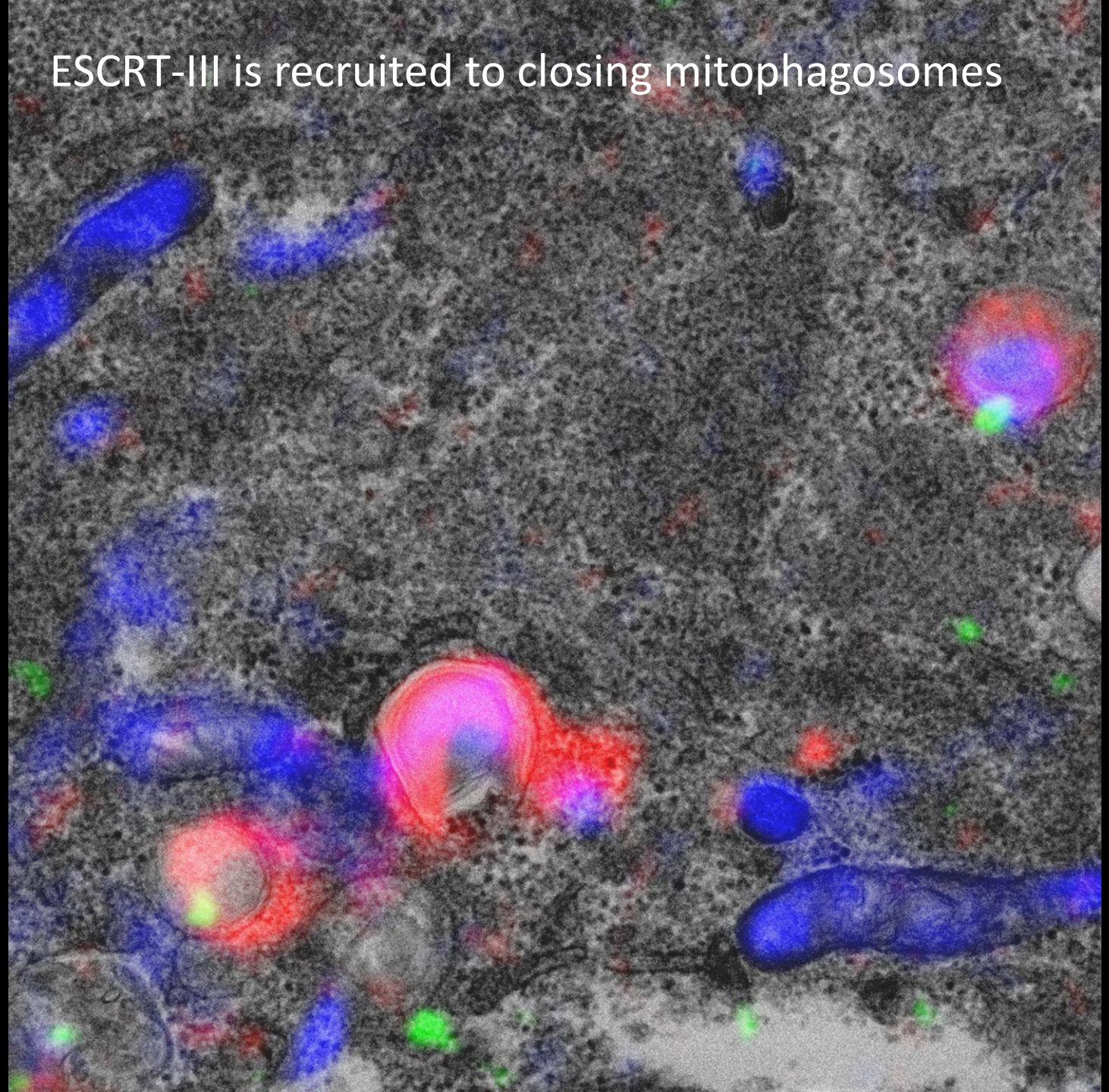




Mitochondria
ESCRT-III
Autophagosome

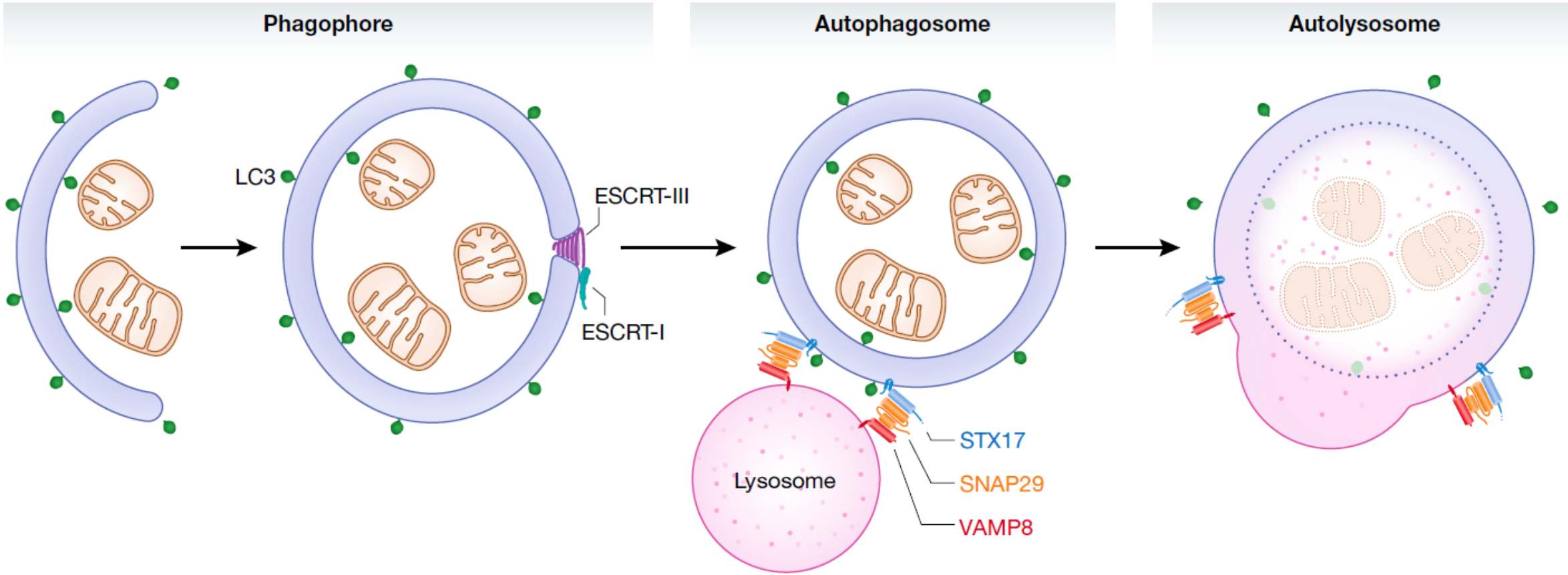
Yan Zhen

ESCRT-III is recruited to closing mitophagosomes



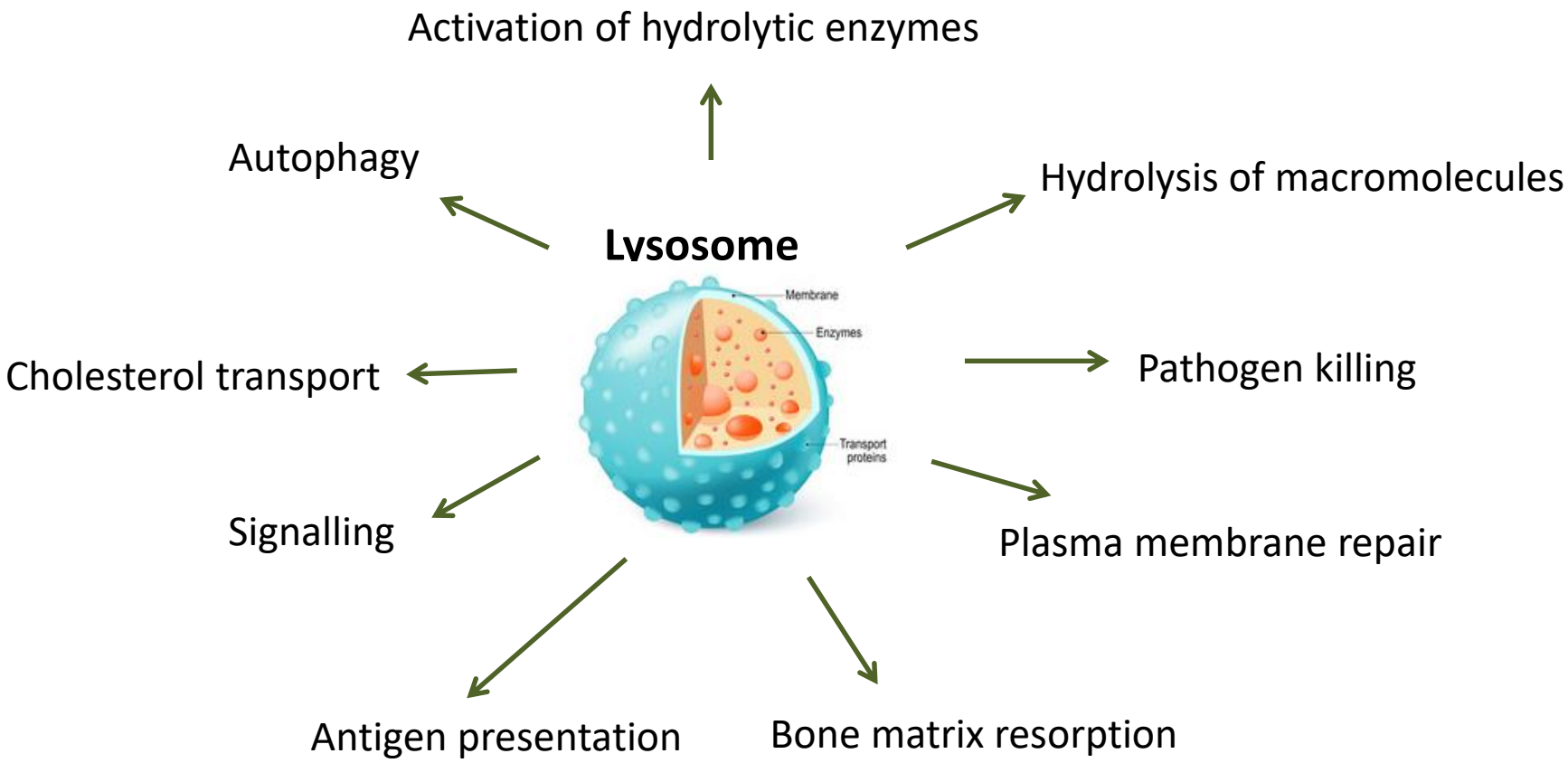
Zhen et al.
Autophagy, 2020

Sealing of the autophagosome

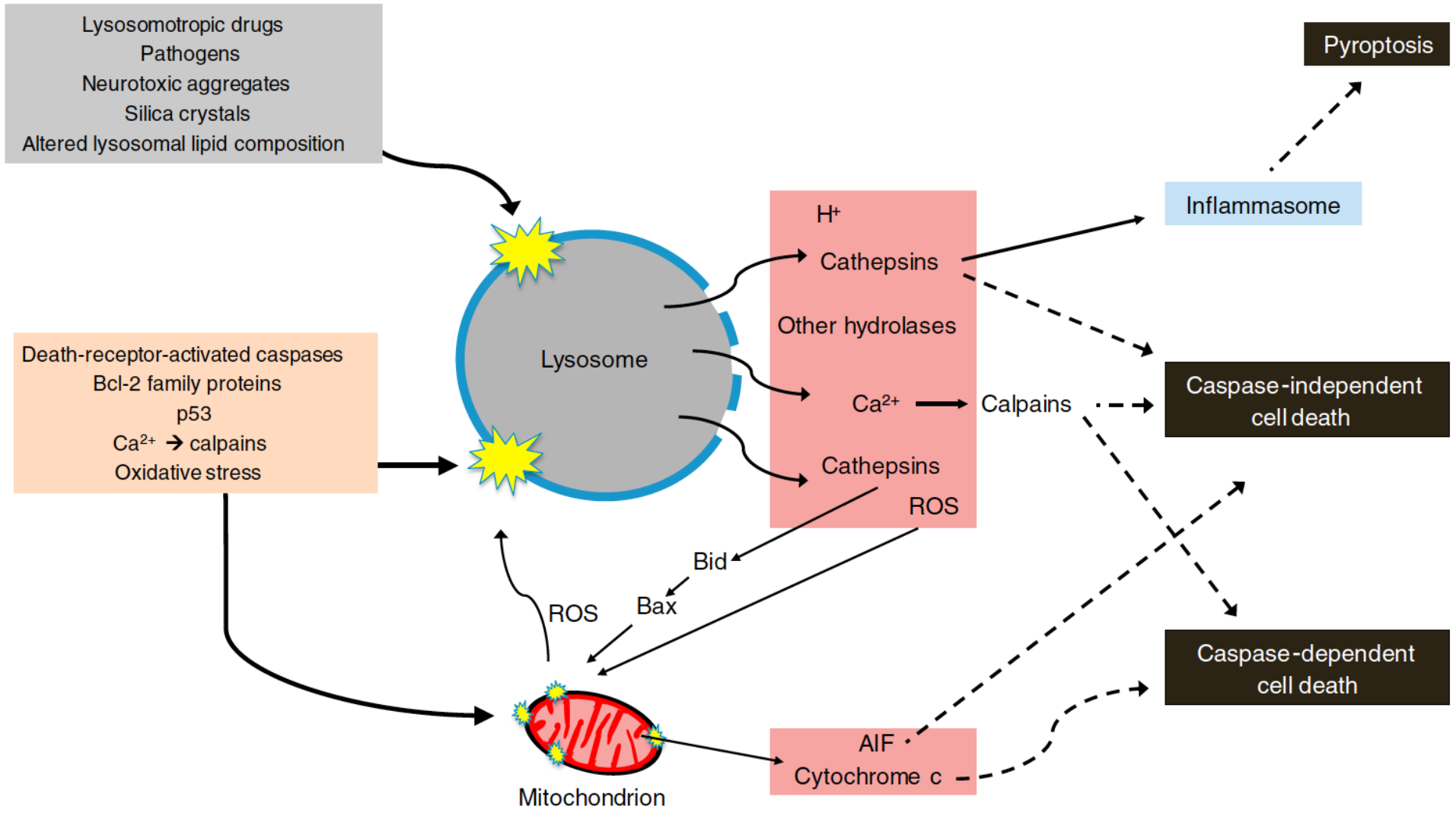


Zhen et al.,
Autophagy 2020

The lysosome has many functions



Lysosomal damage activates cell death

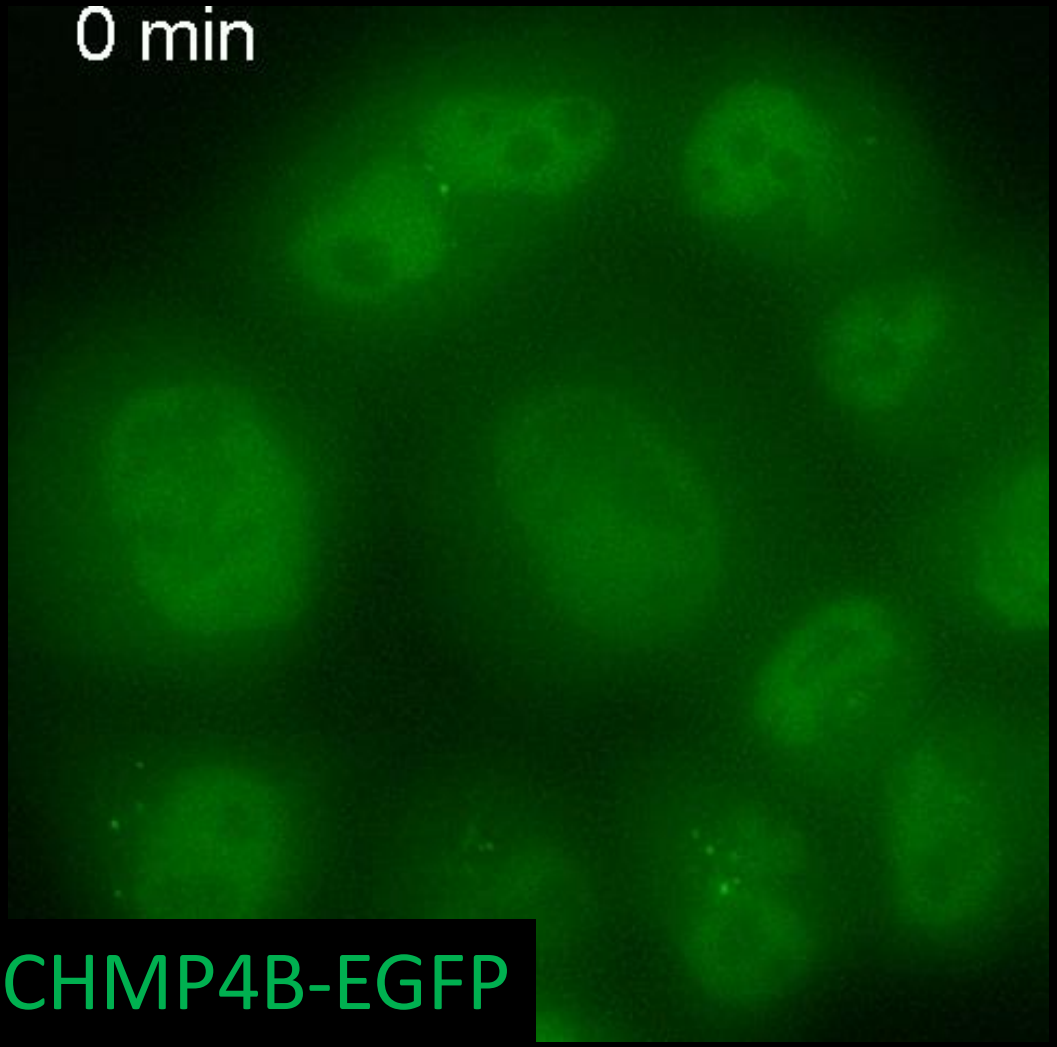


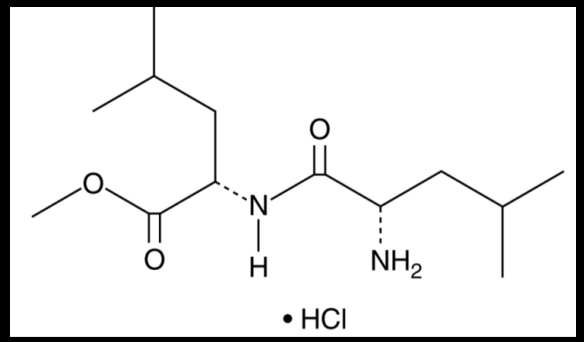
Papadopoulos and Mayer, 2017

Cancer cell lysosomes are vulnerable to damage

Potential for anti-cancer therapy!

Lysosome damage causes accumulation of ESCRT-III on lysosomes

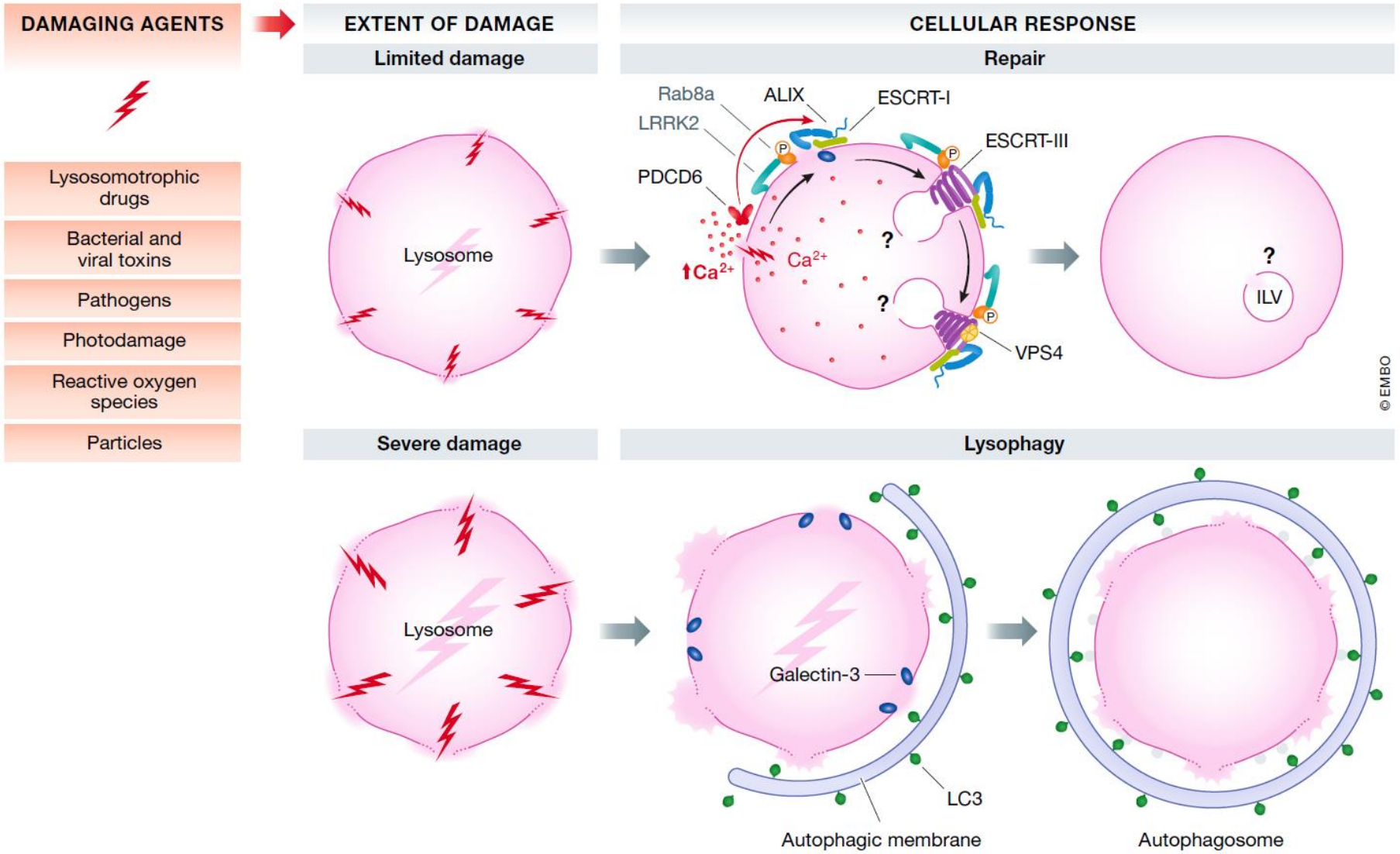




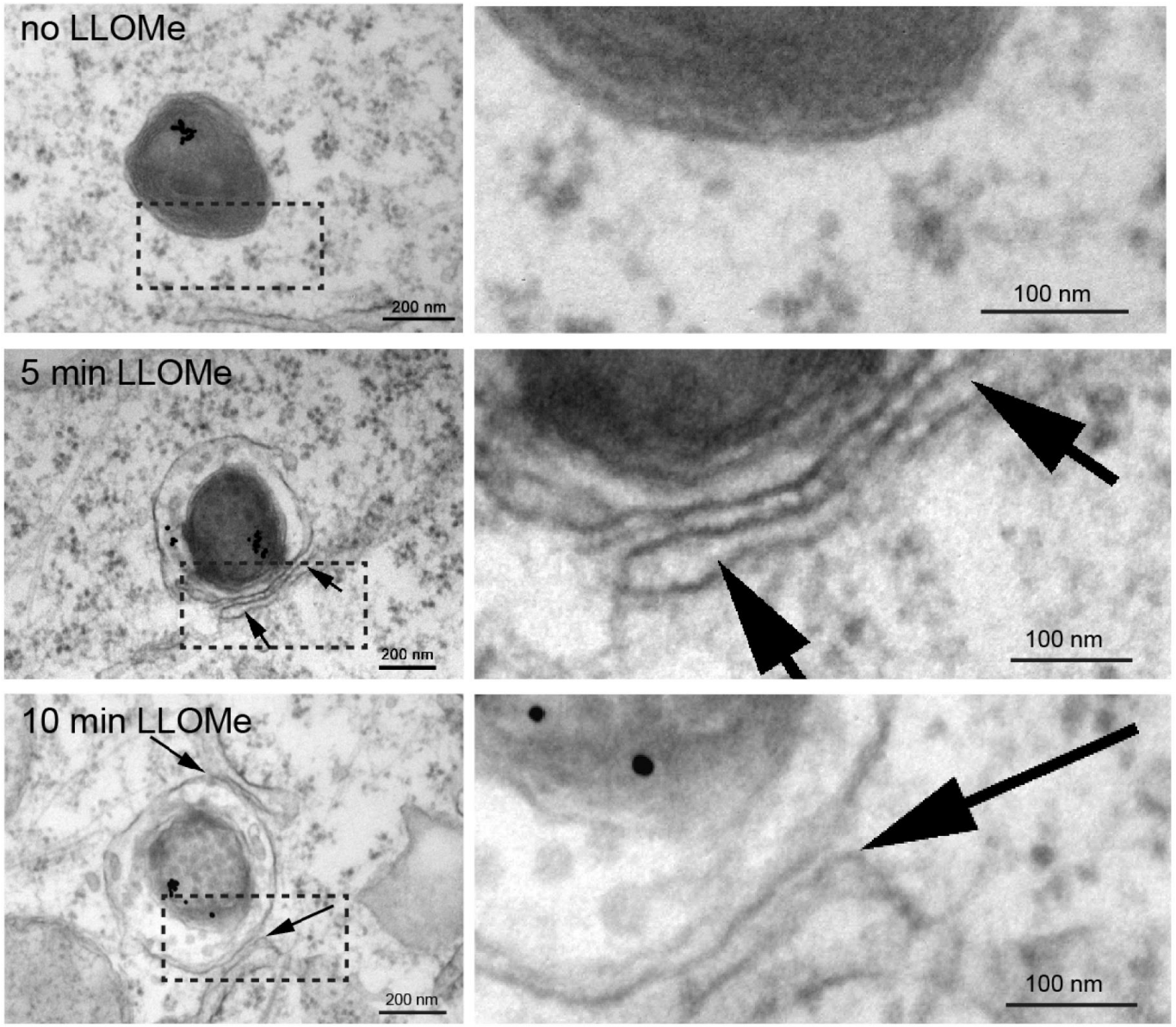
LLOMe, a compound that causes rapid and reversible lysosome damage

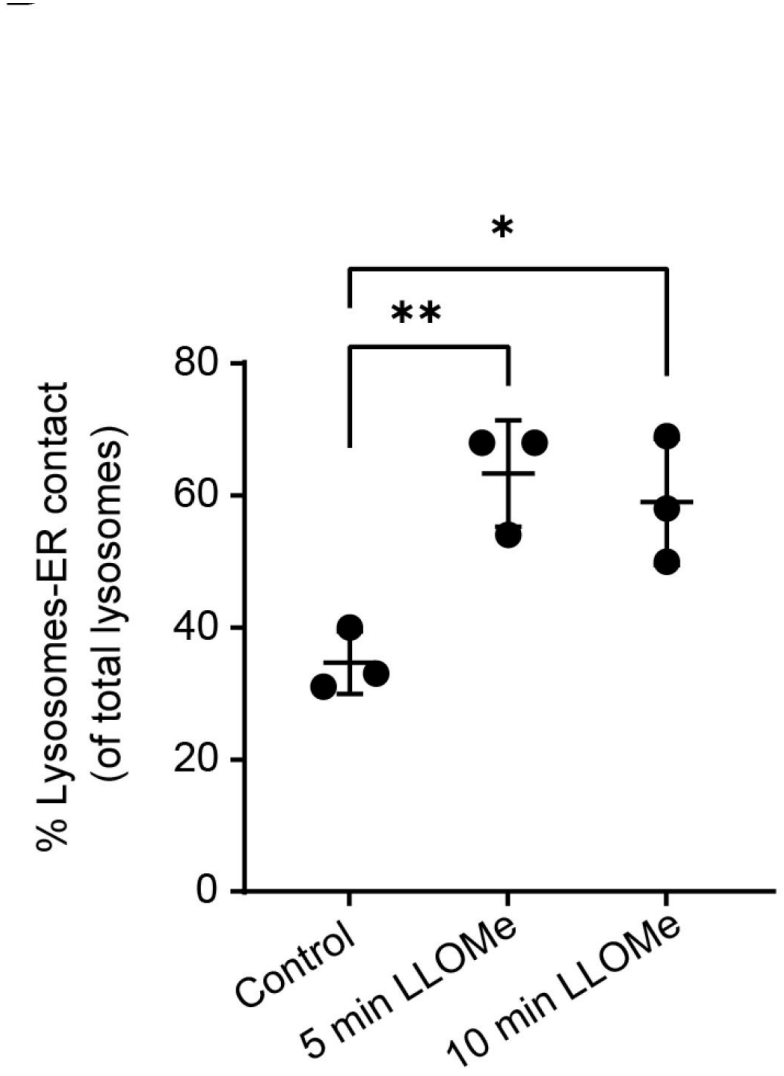
Radulovic et al.
EMBO J. 2018

Lysosome repair



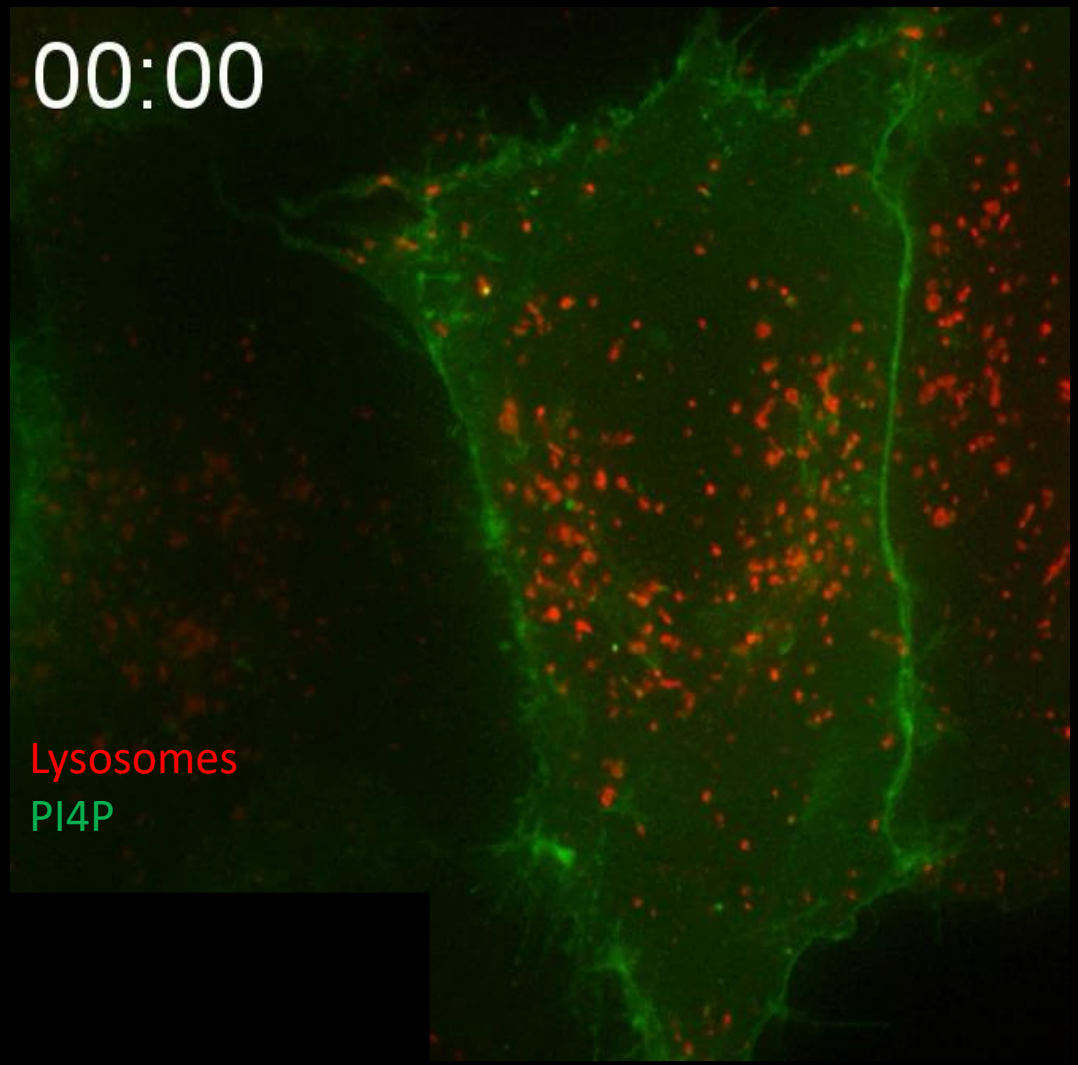
Increased lysosome-ER contacts rapidly after lysosome damage





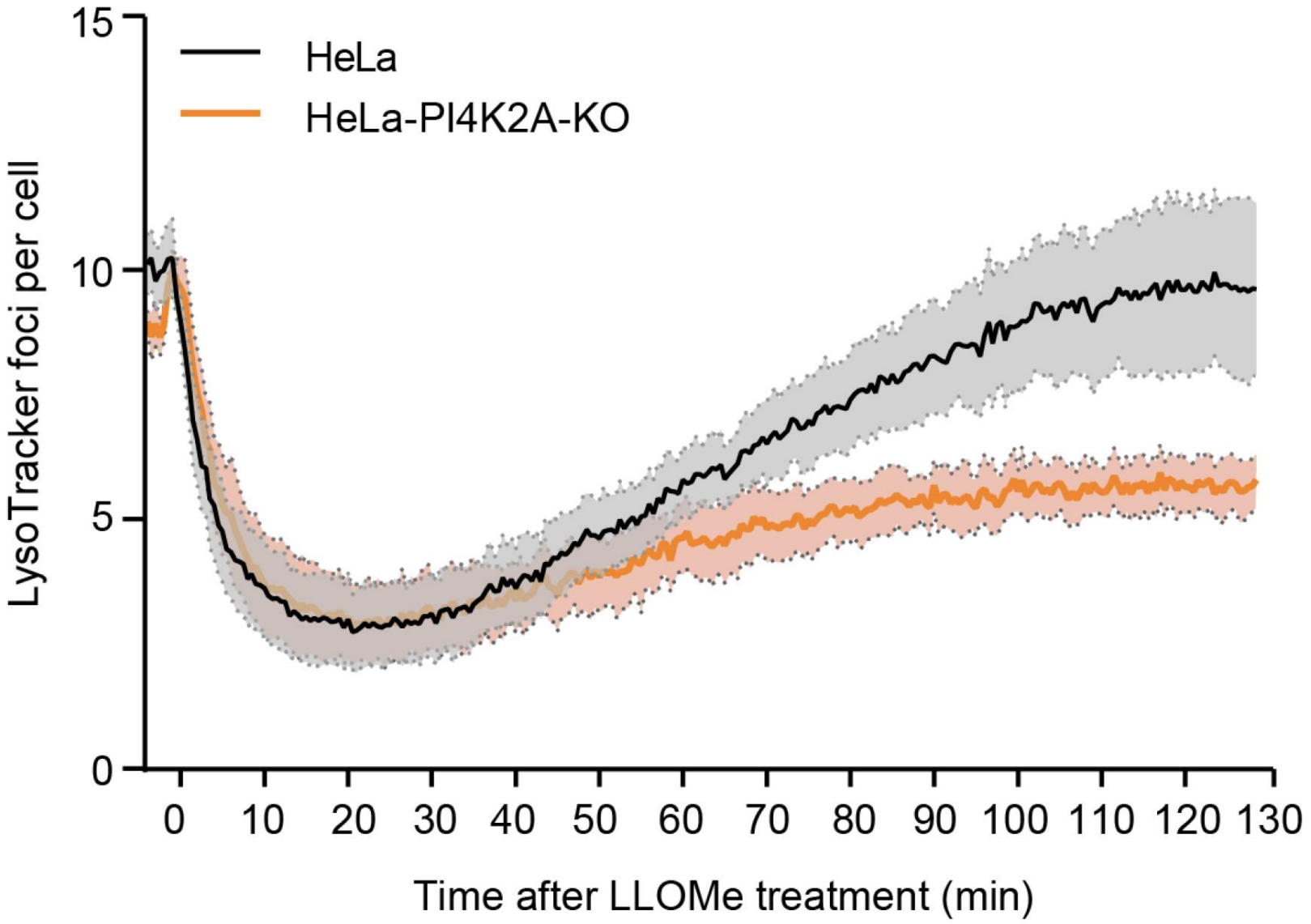
Radulovic et al.
EMBO J. 2022

PI4P is rapidly formed on lysosomes upon damage



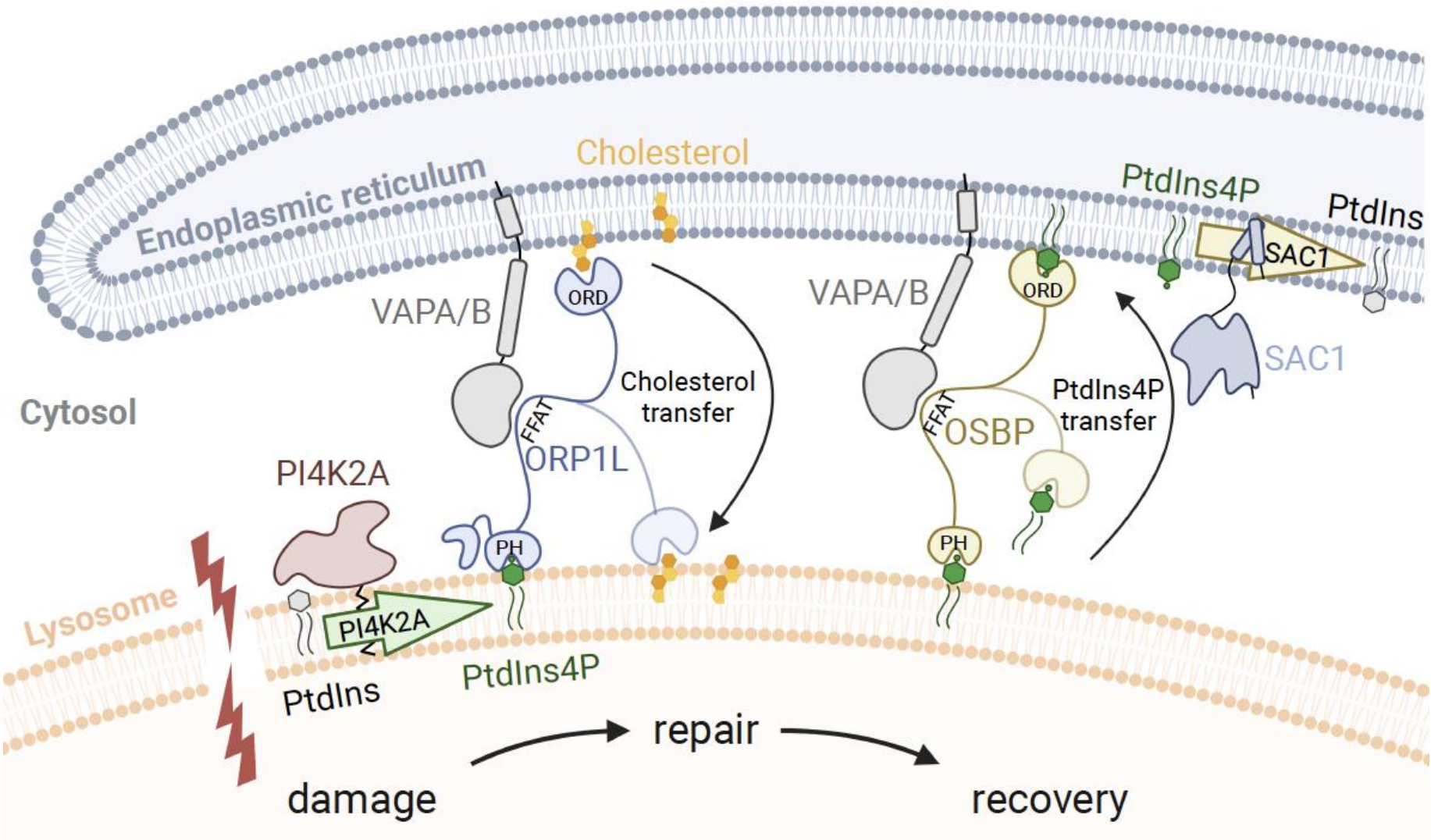
Radulovic et al.
EMBO J. 2022

PI4P is required for repair of damaged lysosomes



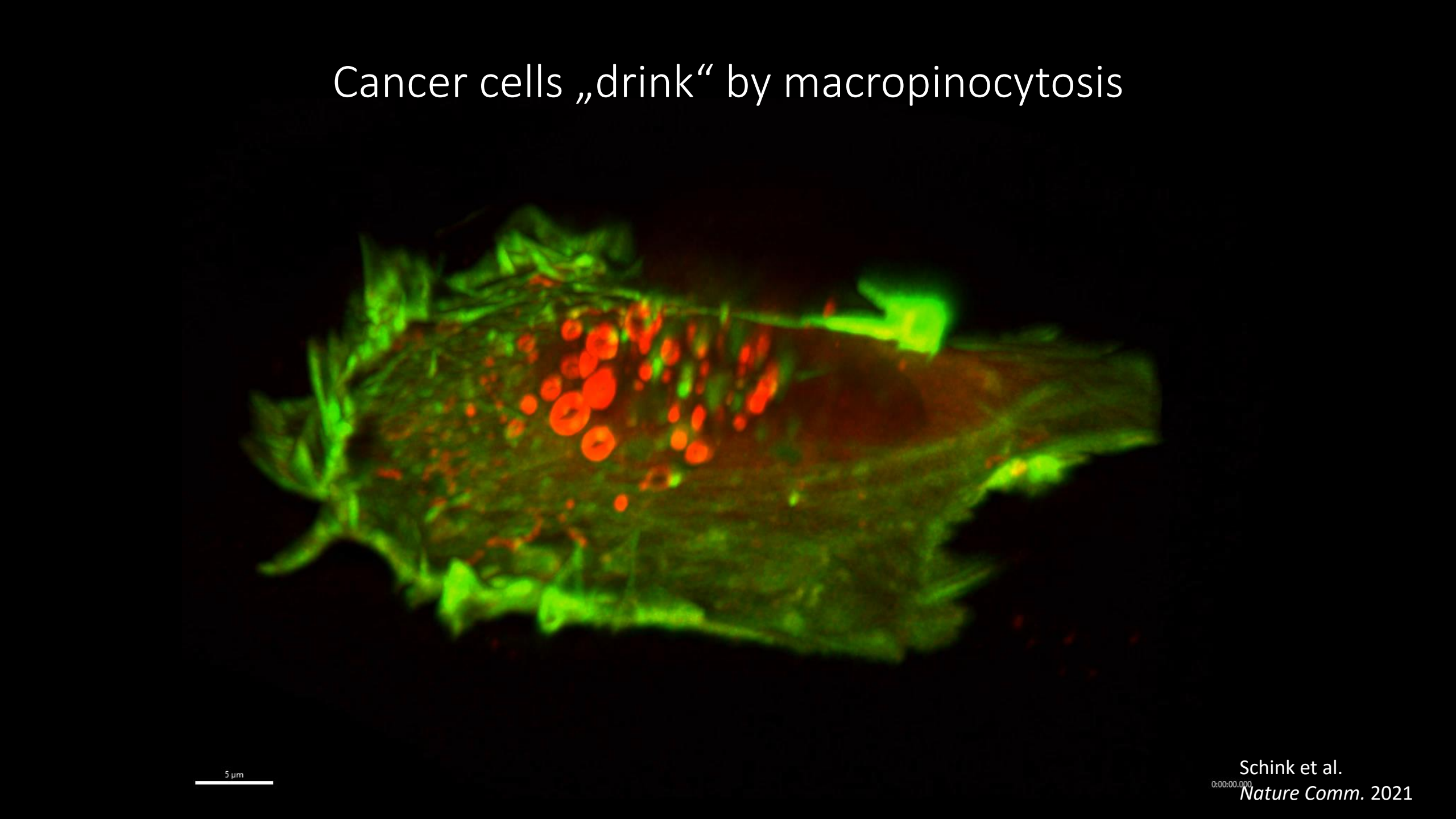
Radulovic et al.
EMBO J. 2022

Cholesterol transfer to lysosomes in response to membrane damage



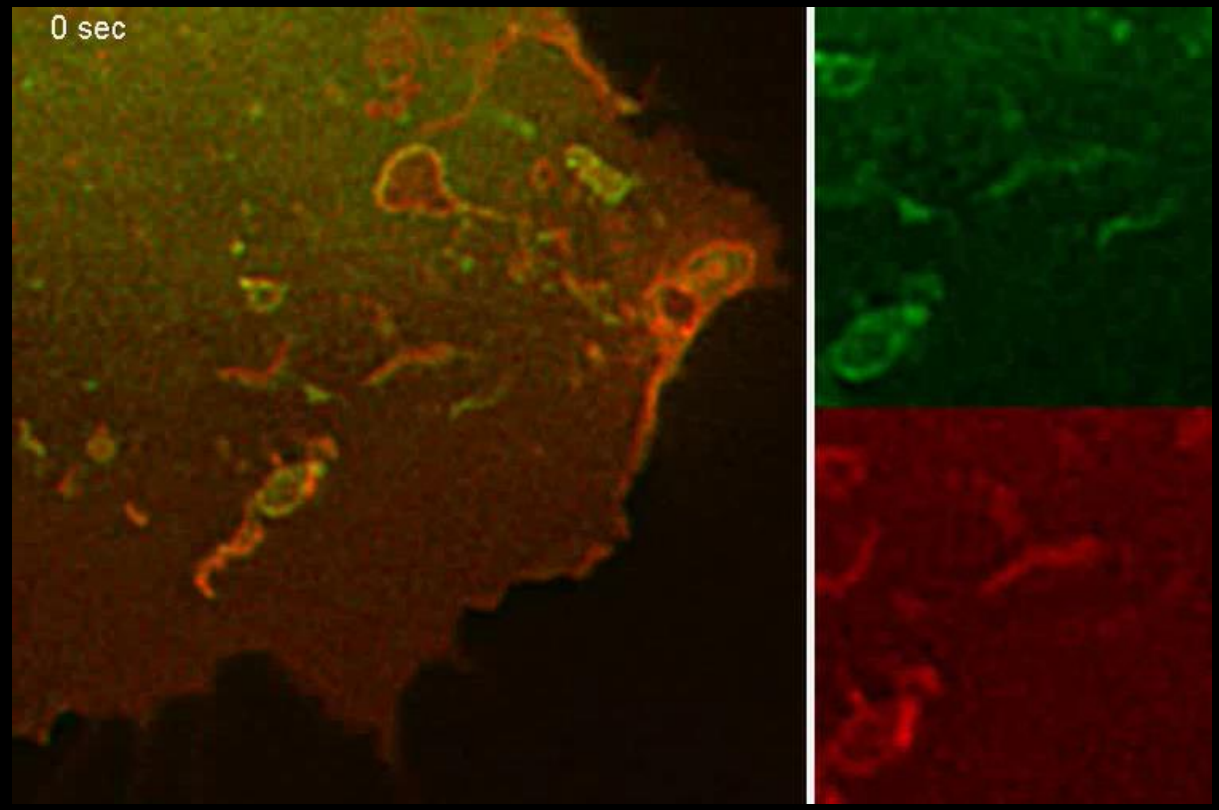
Radulovic et al.
EMBO J. 2022

Cancer cells „drink“ by macropinocytosis



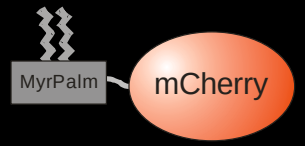
Schink et al.
Nature Comm. 2021

The PI3P binding protein Phafin2 localises to forming macropinosomes



Phafin2

Plasma membrane
(MyrPalm-mCherry)

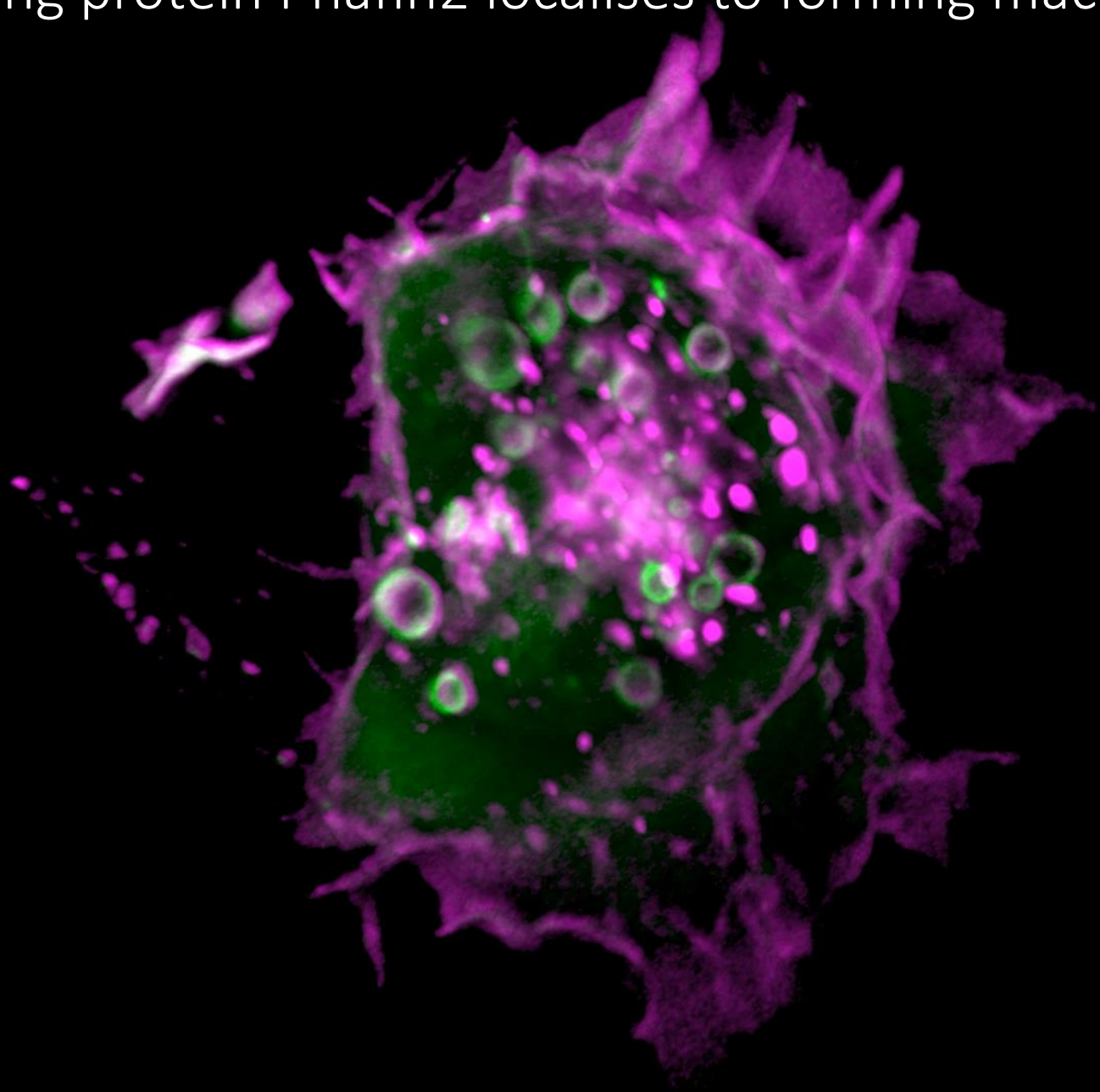


Schink et al.
Nature Comm. 2021

The PI3P binding protein Phafin2 localises to forming macropinosomes

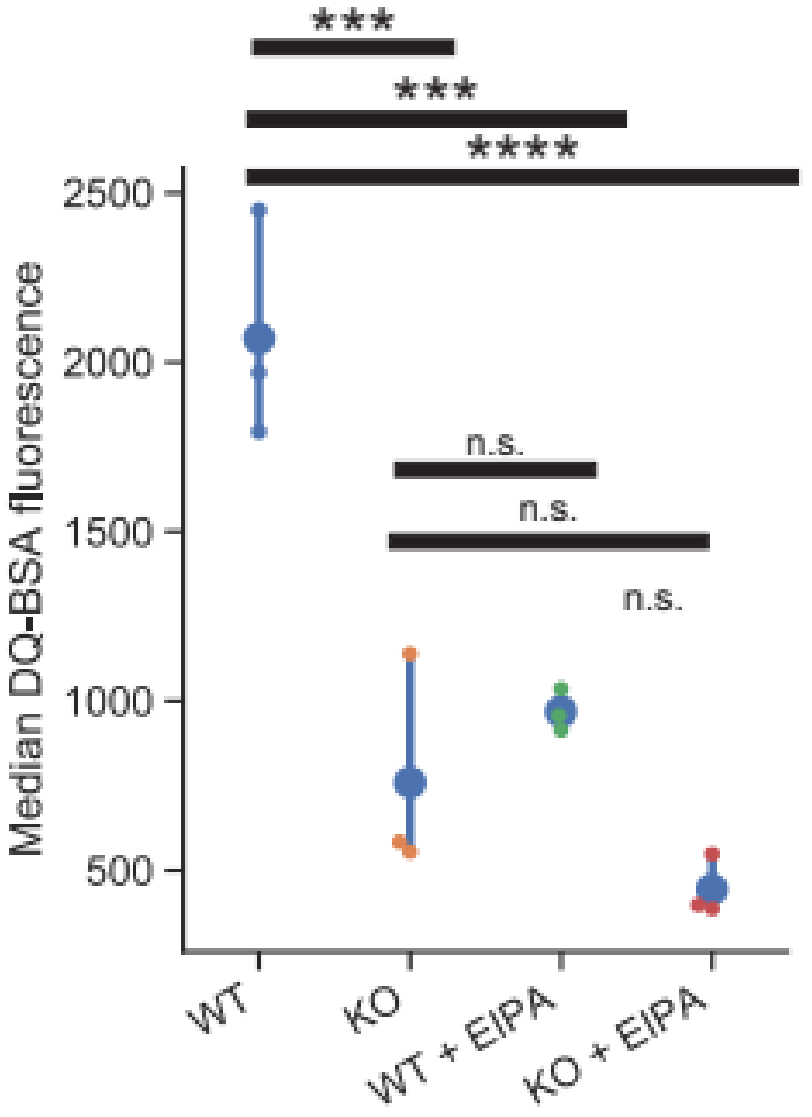
MyrPalm

Phafin2

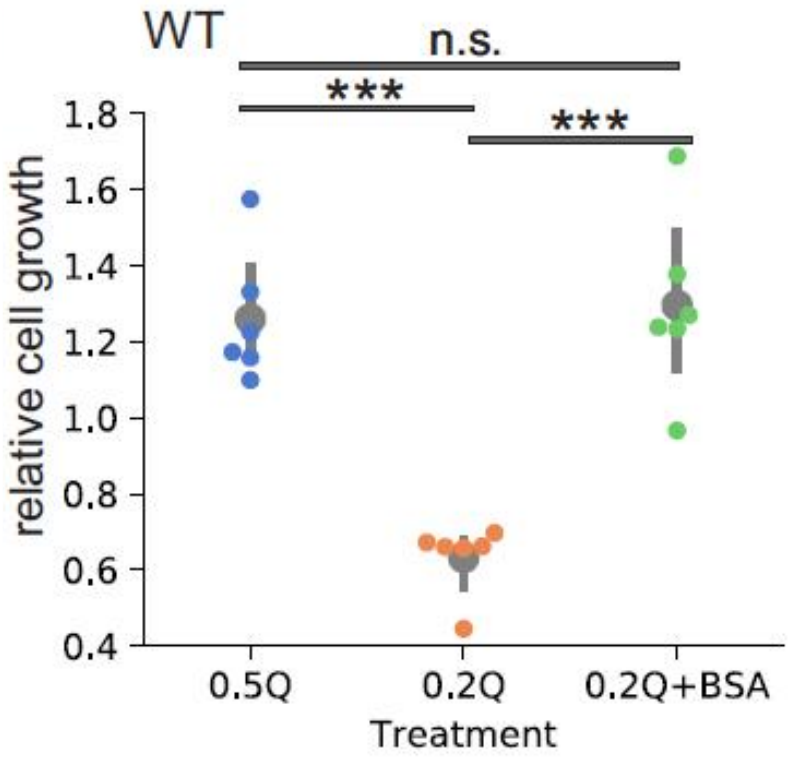


Schink et al.
Nature Comm. 2021

Phafin2 knockout in pancreatic cancer cells inhibits uptake of albumin

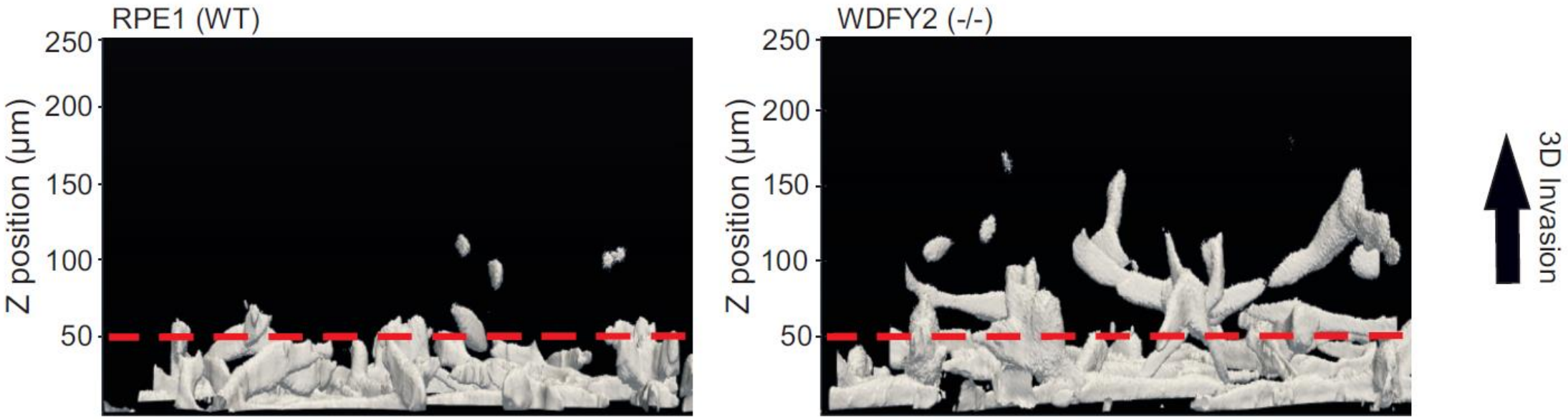


Phafin2 mediates albumin-dependent survival of pancreatic cancer cells under conditions of low glutamine (Q) availability



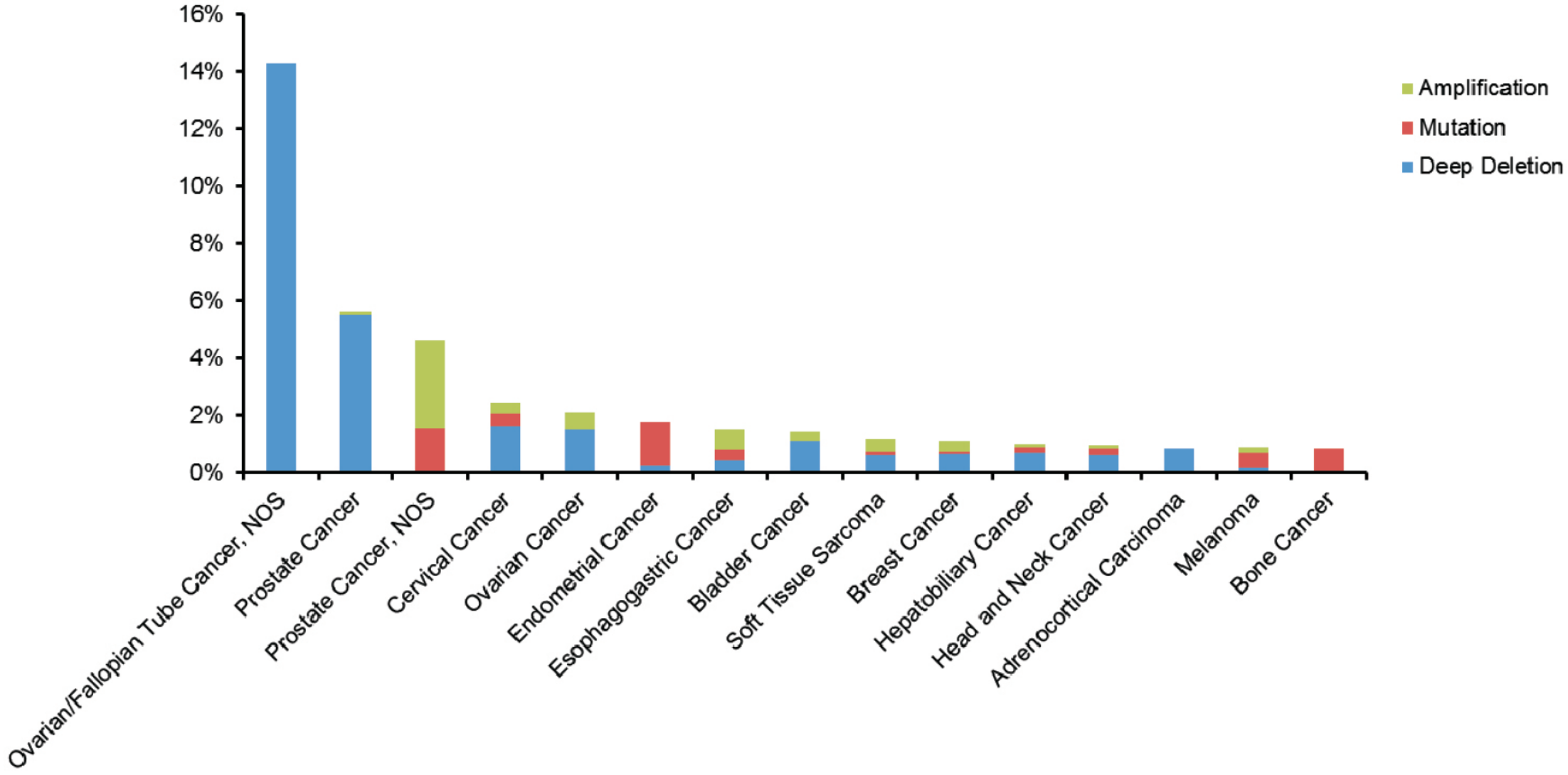
Schink et al.
Nature Comm. 2021

Knockout of the FYVE domain protein WDFY2 causes RPE1 cells to become invasive

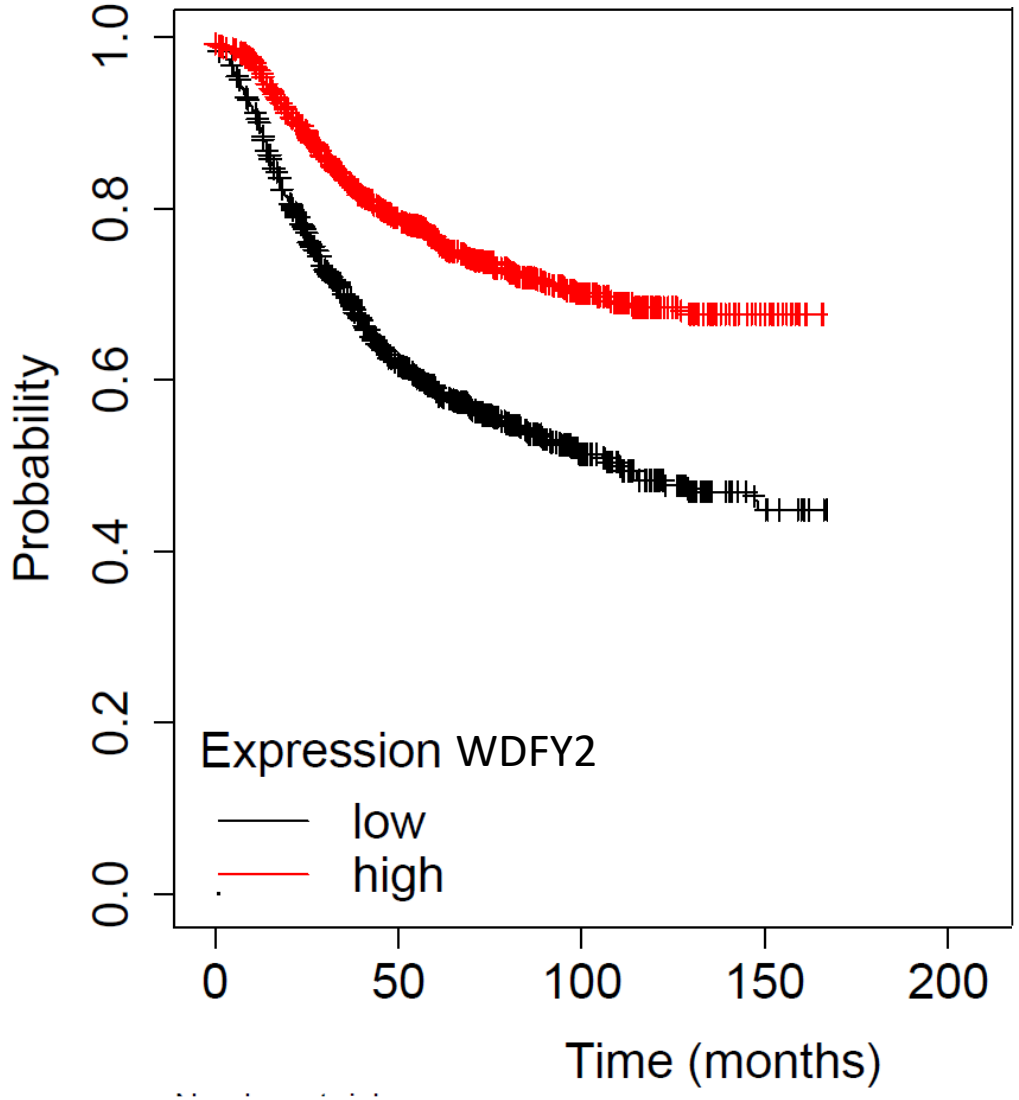


Sneeggen et al.
Nature Comm. 2019

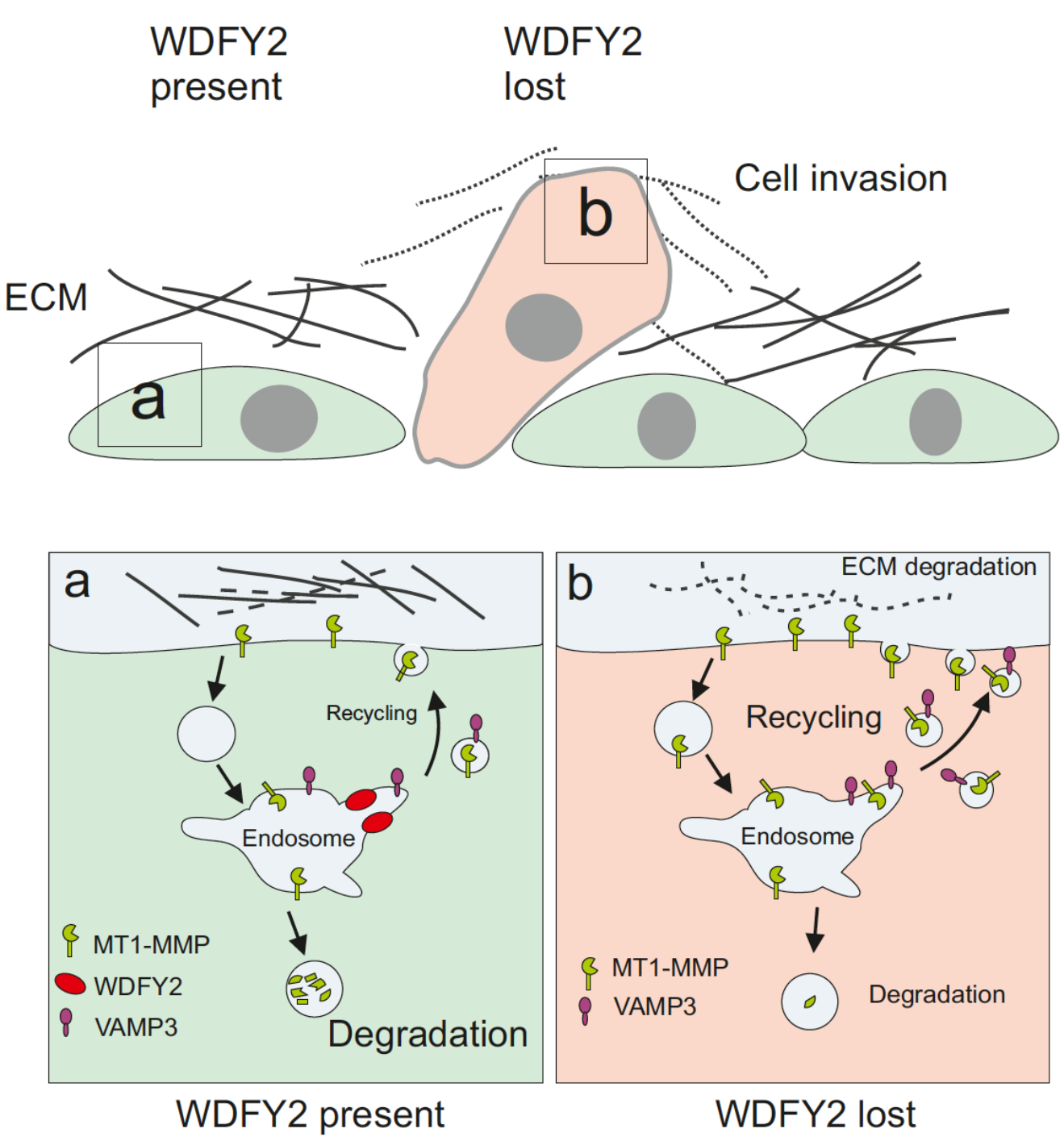
WDFY2 is frequently deleted in cancers



Low expression of WDFY2 in breast cancer is associated with poor prognosis

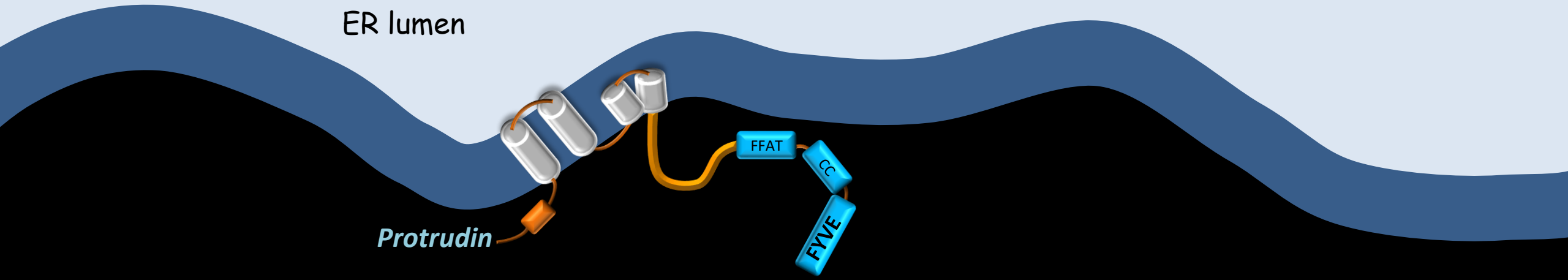


Kaplan-Meier plotter

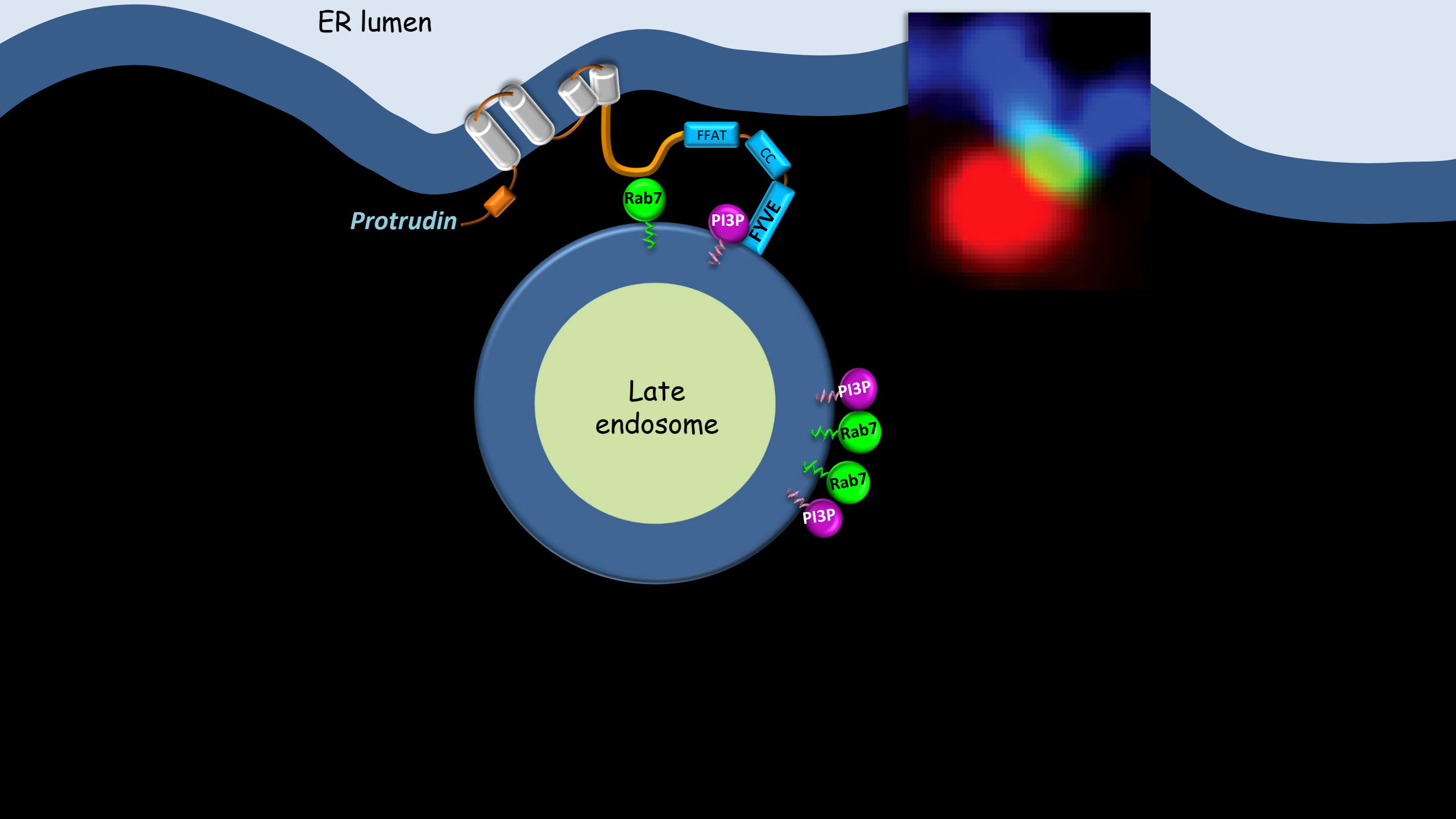


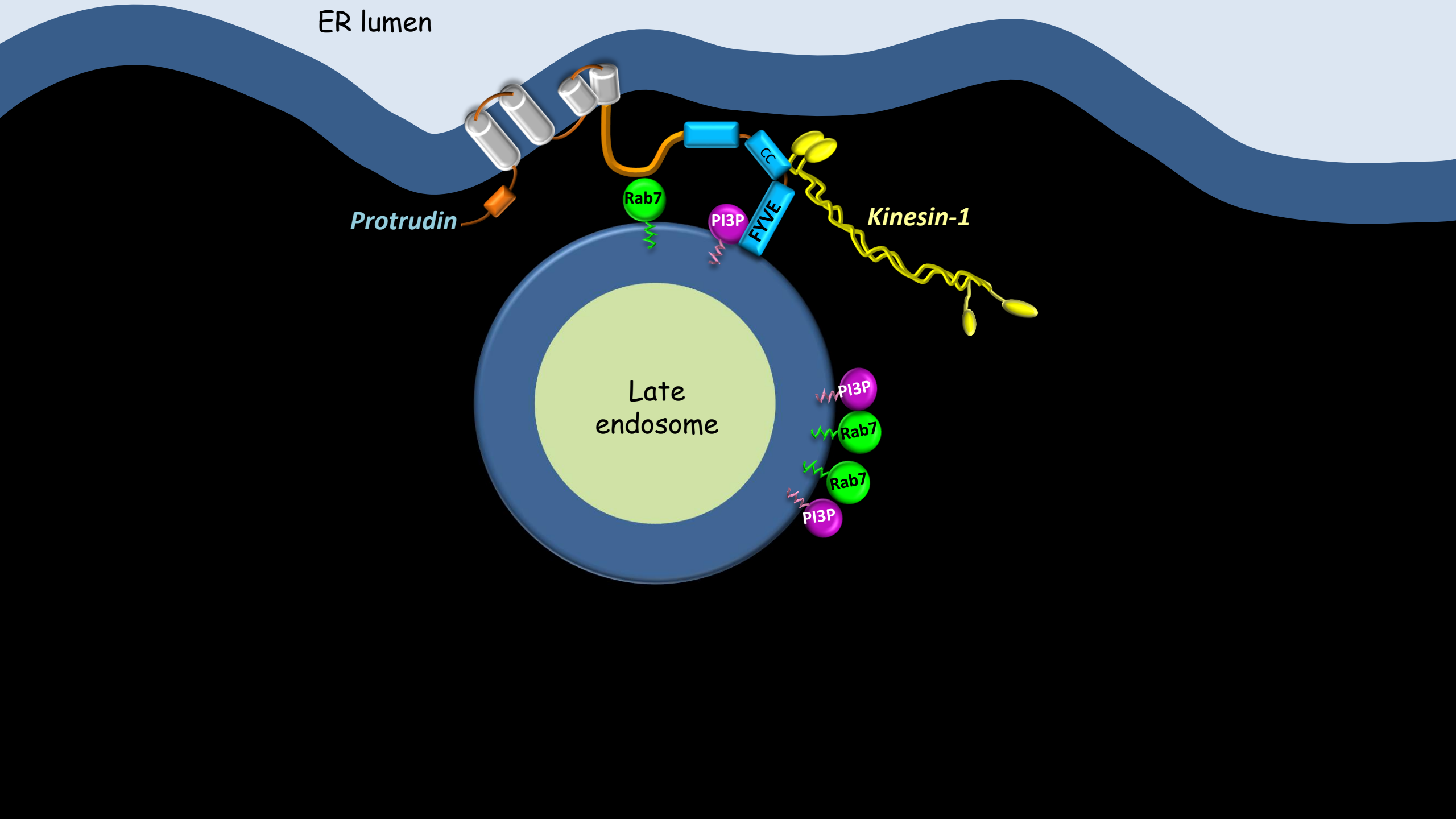
Tumour suppression by WDFY2, a protein that negatively regulates recycling of a matrix metalloprotease

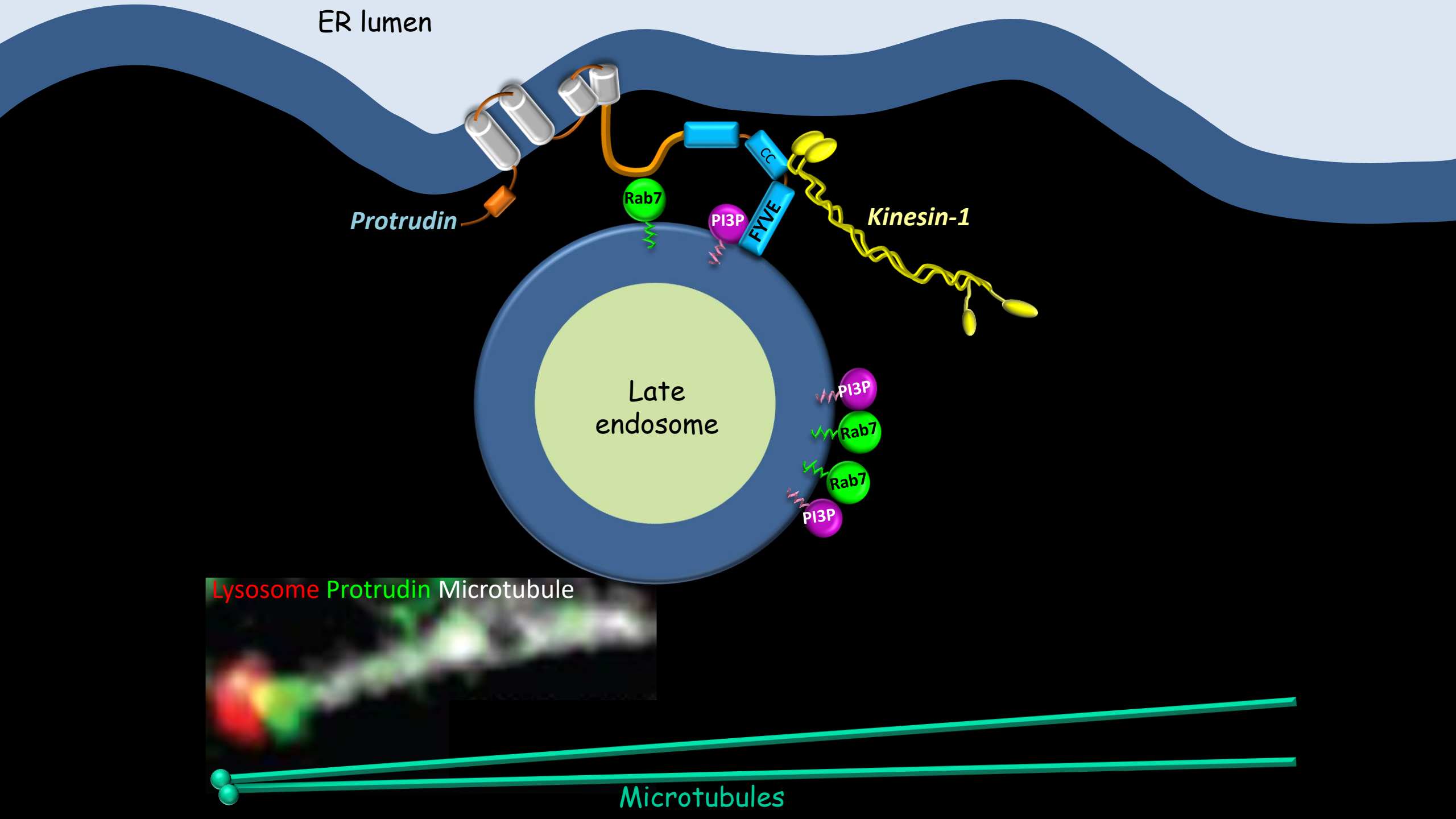
Sneeggen et al.
Nature Comm., 2019

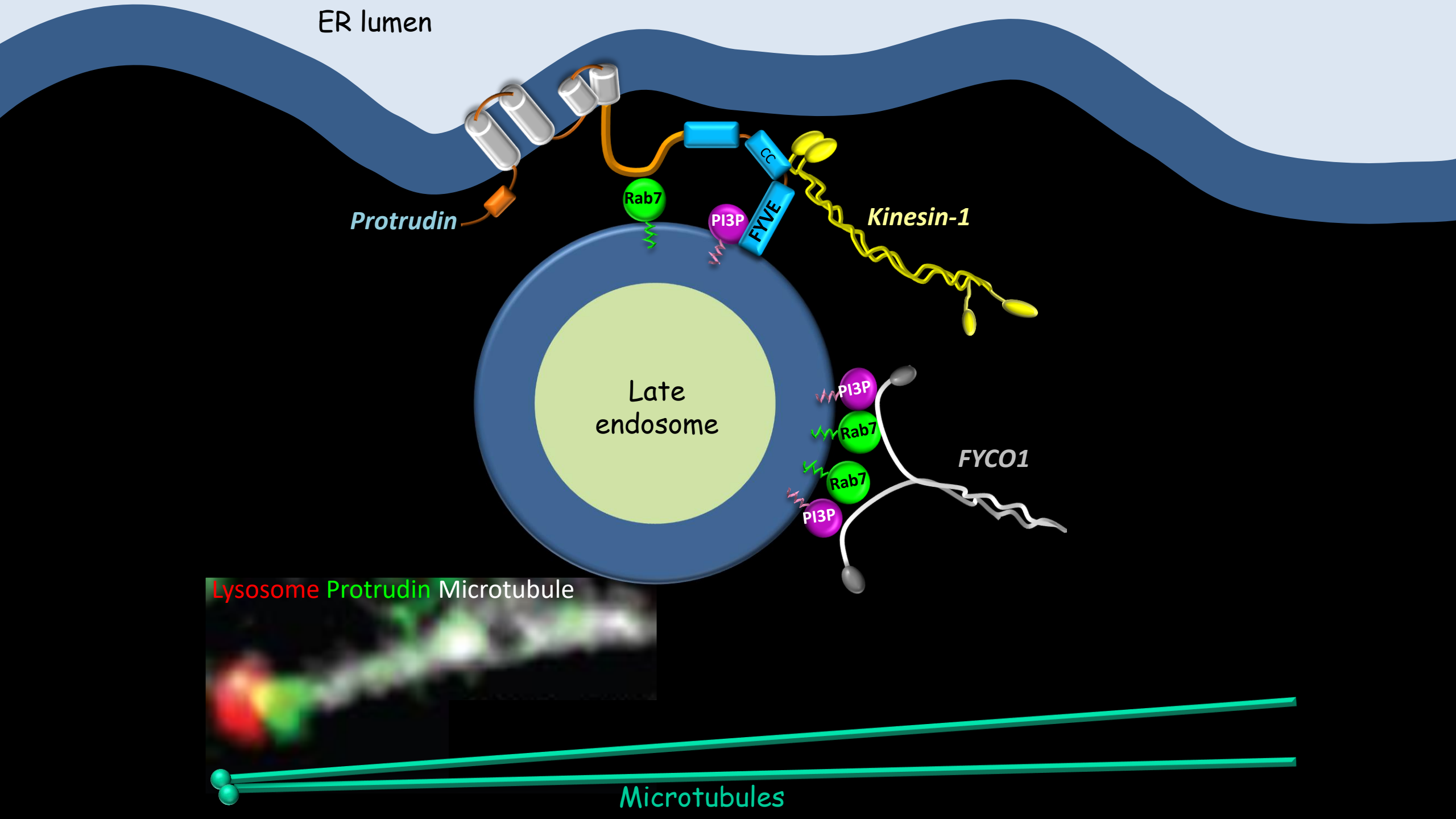


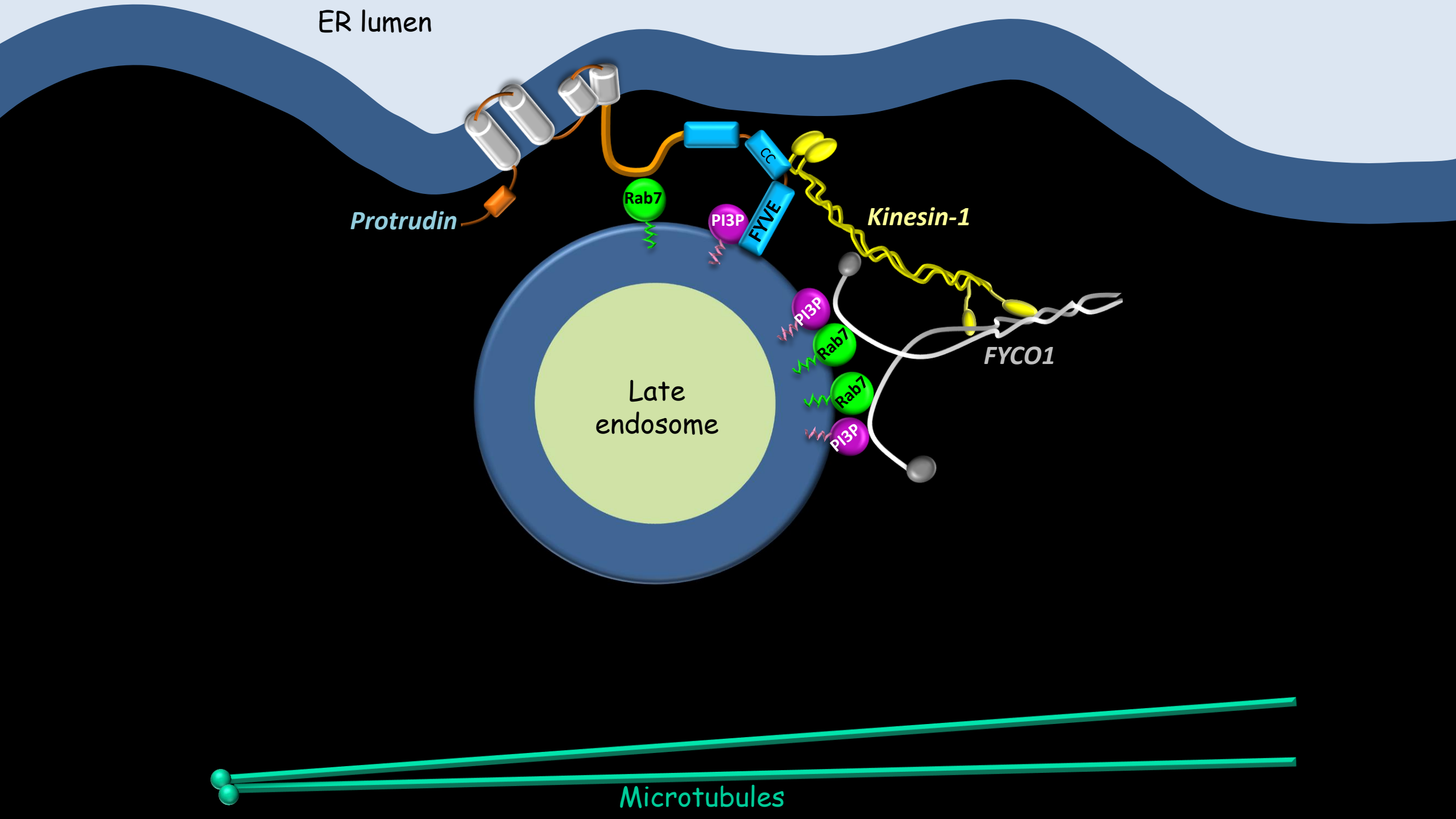
Protrudin, a FYVE domain protein in the endoplasmic reticulum (ER) membrane

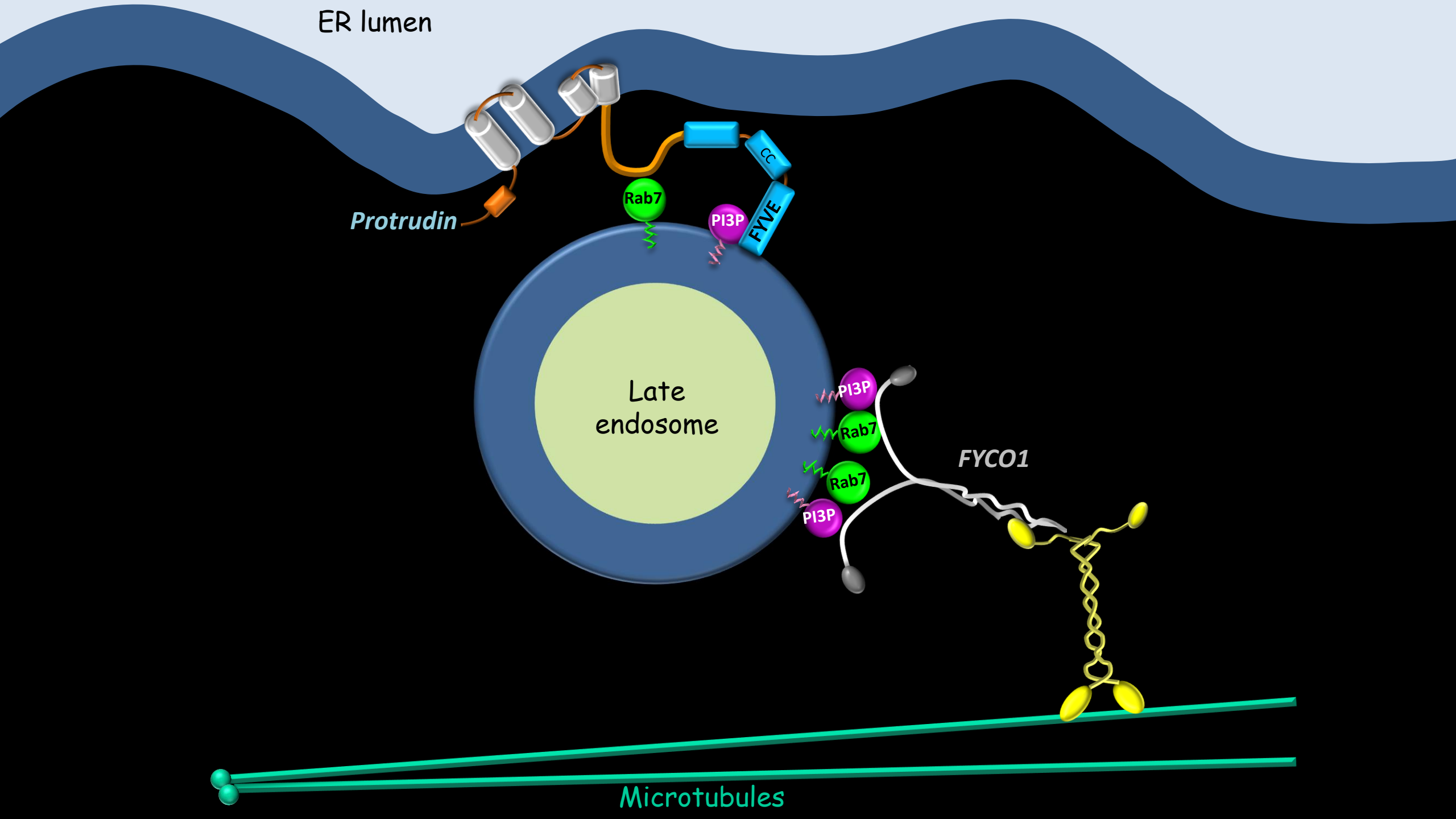

ER lumen
FFAT
CC
Rab7
PI3P
FYVE
Protrudin
Late endosome
PI3P
Rab7
Rab7
PI3P

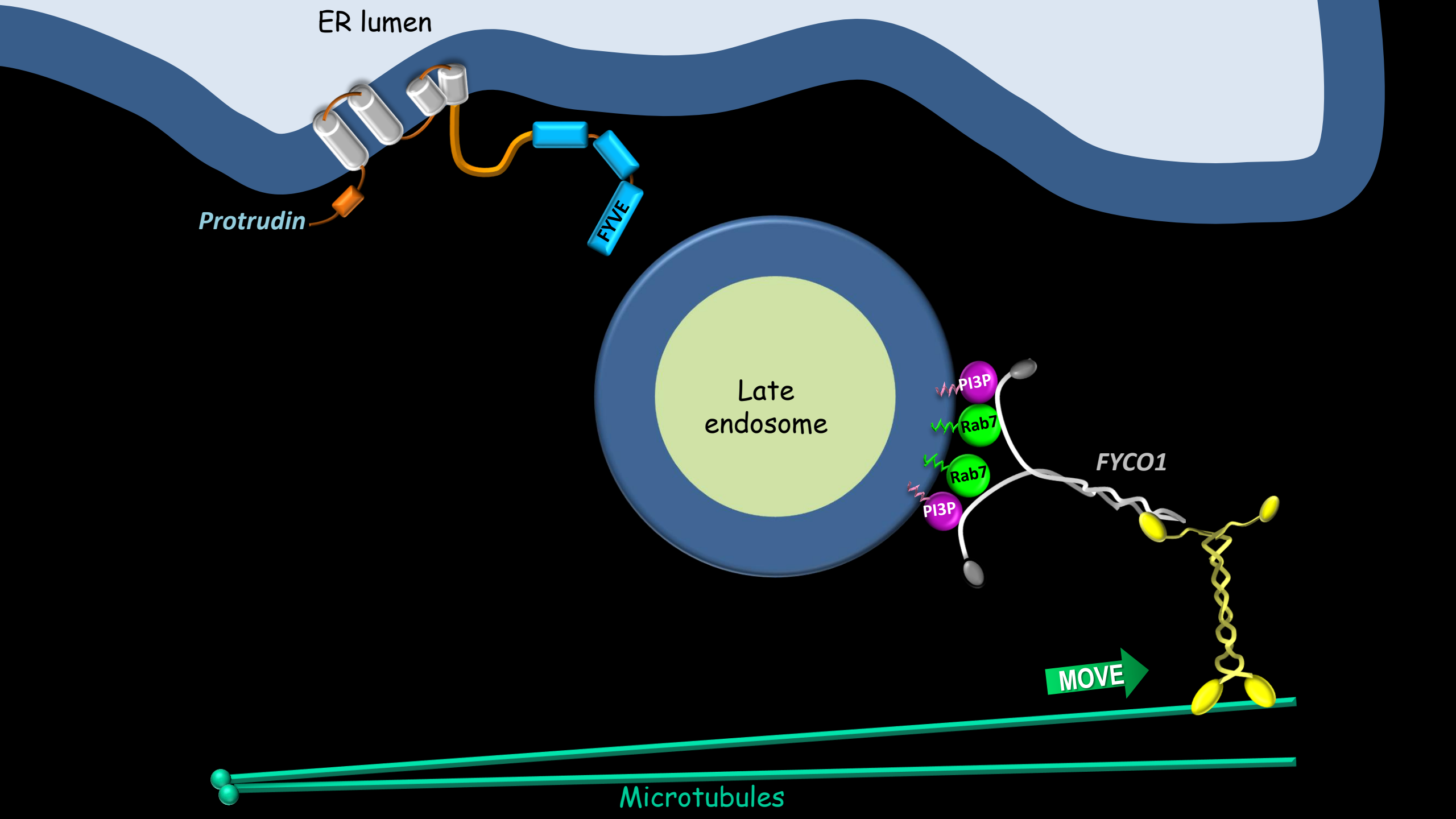

ER lumen
Protrudin
Rab7
PI3P
FYVE
CC
Kinesin-1
Late endosome
PI3P
Rab7
Rab7
PI3P


ER lumen
Protrudin
Rab7
PI3P
FYVE
CC
Kinesin-1
Late endosome
PI3P
Rab7
Rab7
PI3P
Lysosome Protrudin Microtubule
Microtubules

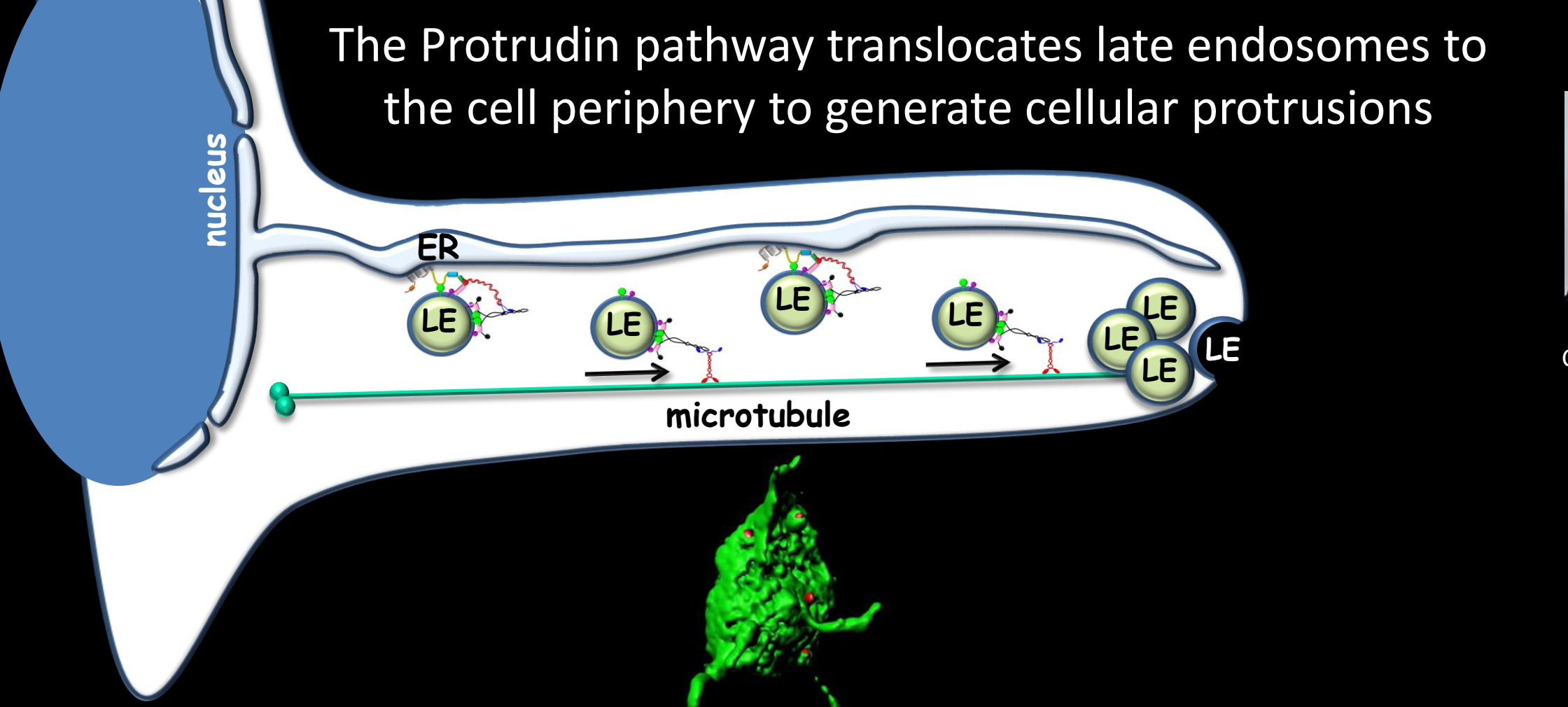

ER lumen
Protrudin
Rab7
PI3P
FYVE
CC
Kinesin-1
Late endosome
PI3P
Rab7
Rab7
PI3P
FYCO1
Lysosome Protrudin Microtubule
Microtubules


ER lumen
Protrudin
Rab7
PI3P
FYVE
CC
Kinesin-1
FYCO1
PI3P
Rab7
Rab7
PI3P
Late endosome
Microtubules

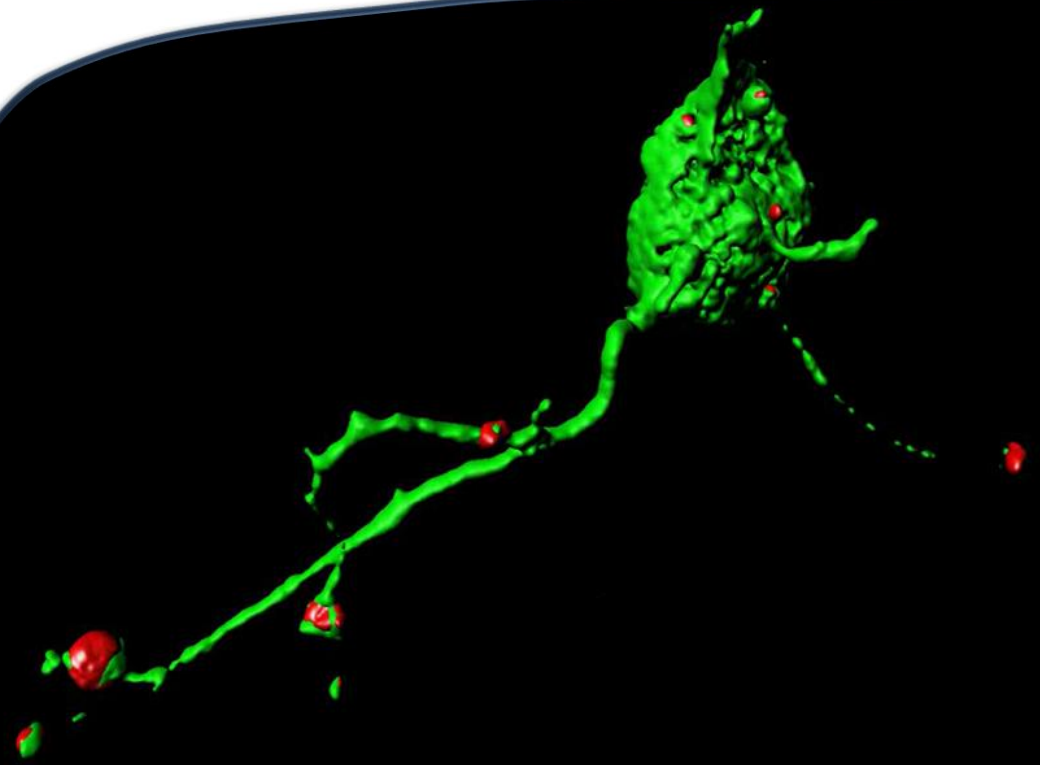

ER lumen
Protrudin
Rab7
PI3P
FYVE
CC
Late endosome
PI3P
Rab7
Rab7
PI3P
FYCO1
Microtubules


ER lumen
Protrudin
FYVE
Late endosome
PI3P
Rab7
Rab7
PI3P
FYCO1
MOVE
Microtubules

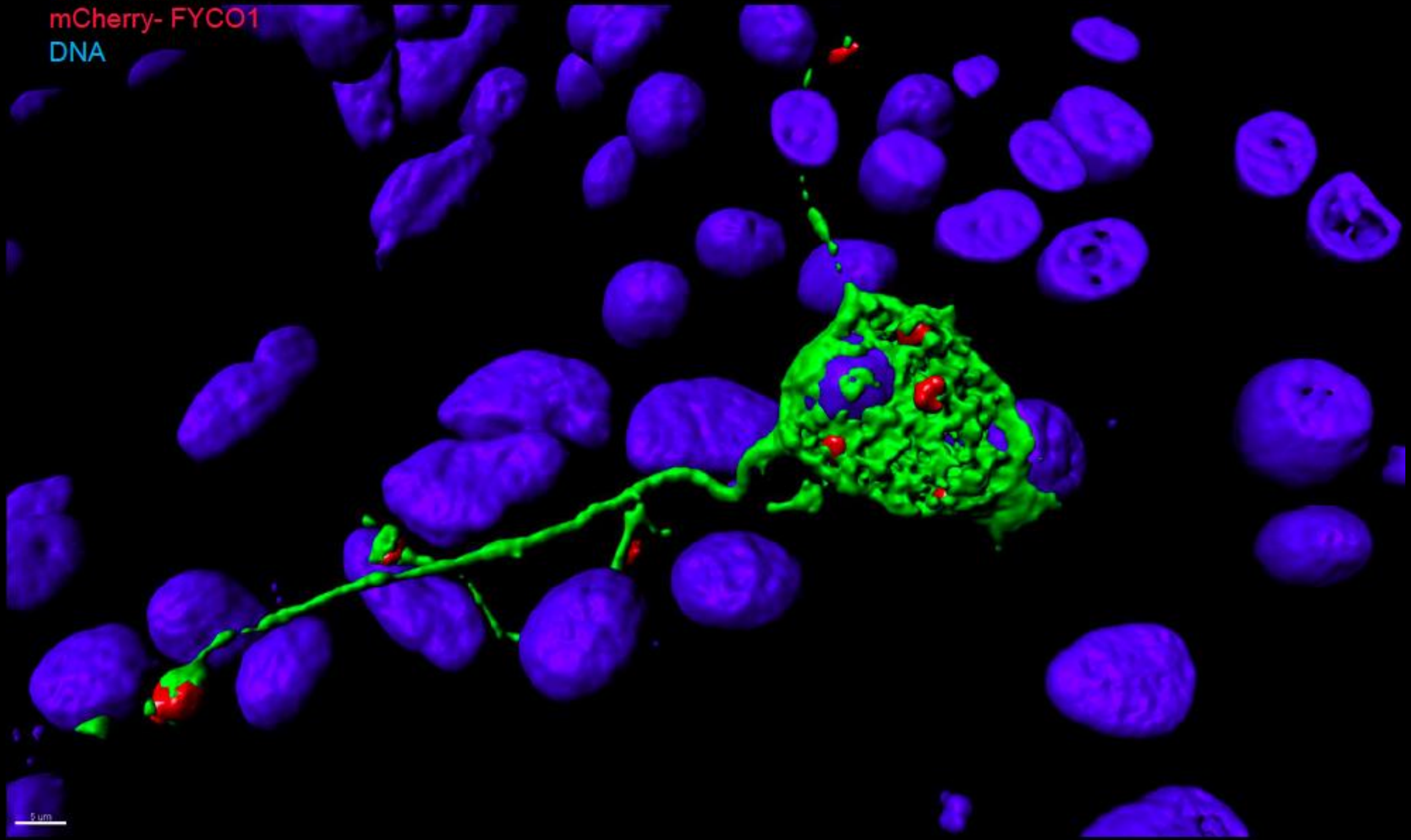
The Protrudin pathway translocates late endosomes to the cell periphery to generate cellular protrusions



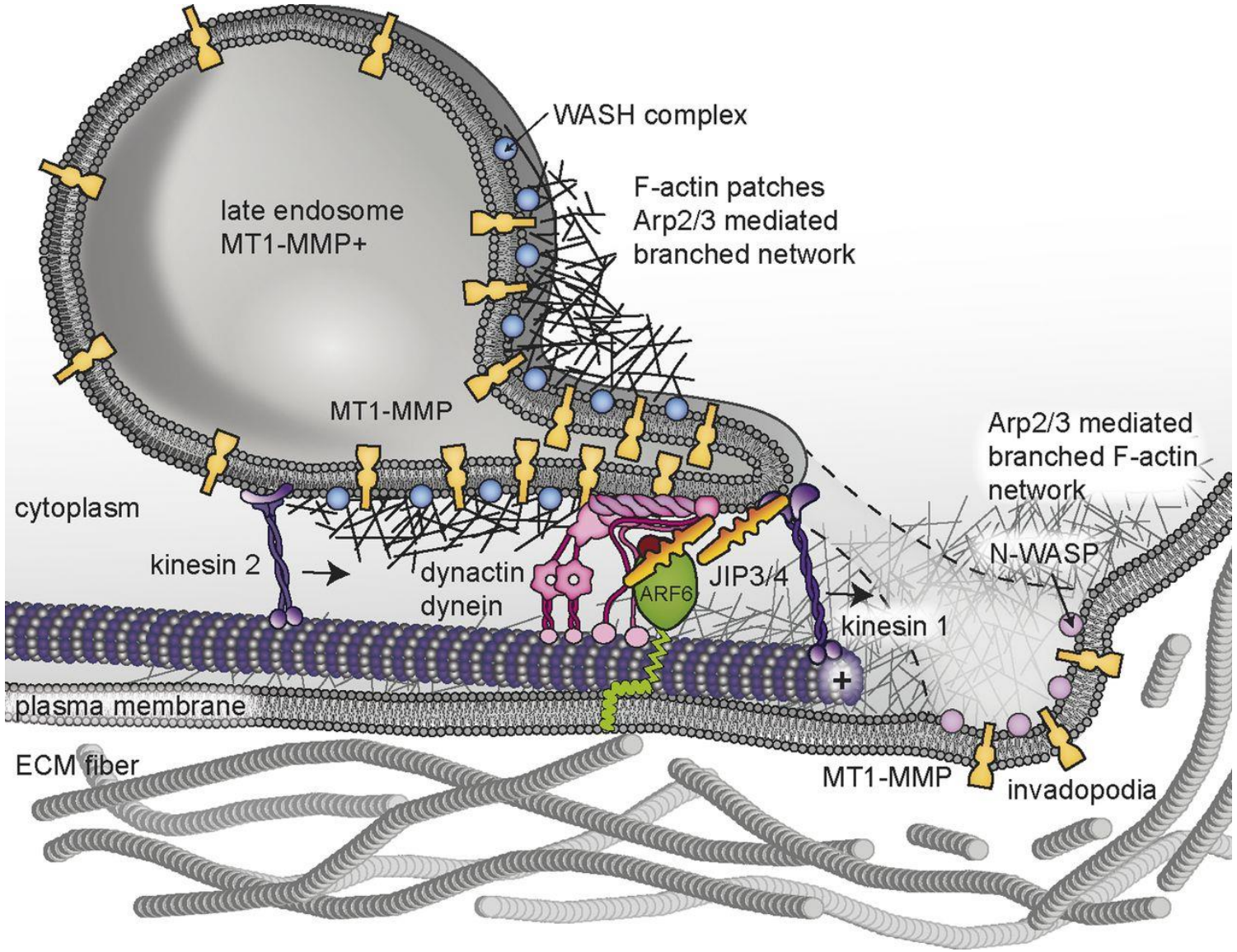
Camilla Raiborg



Raiborg et al., *Nature* 2015

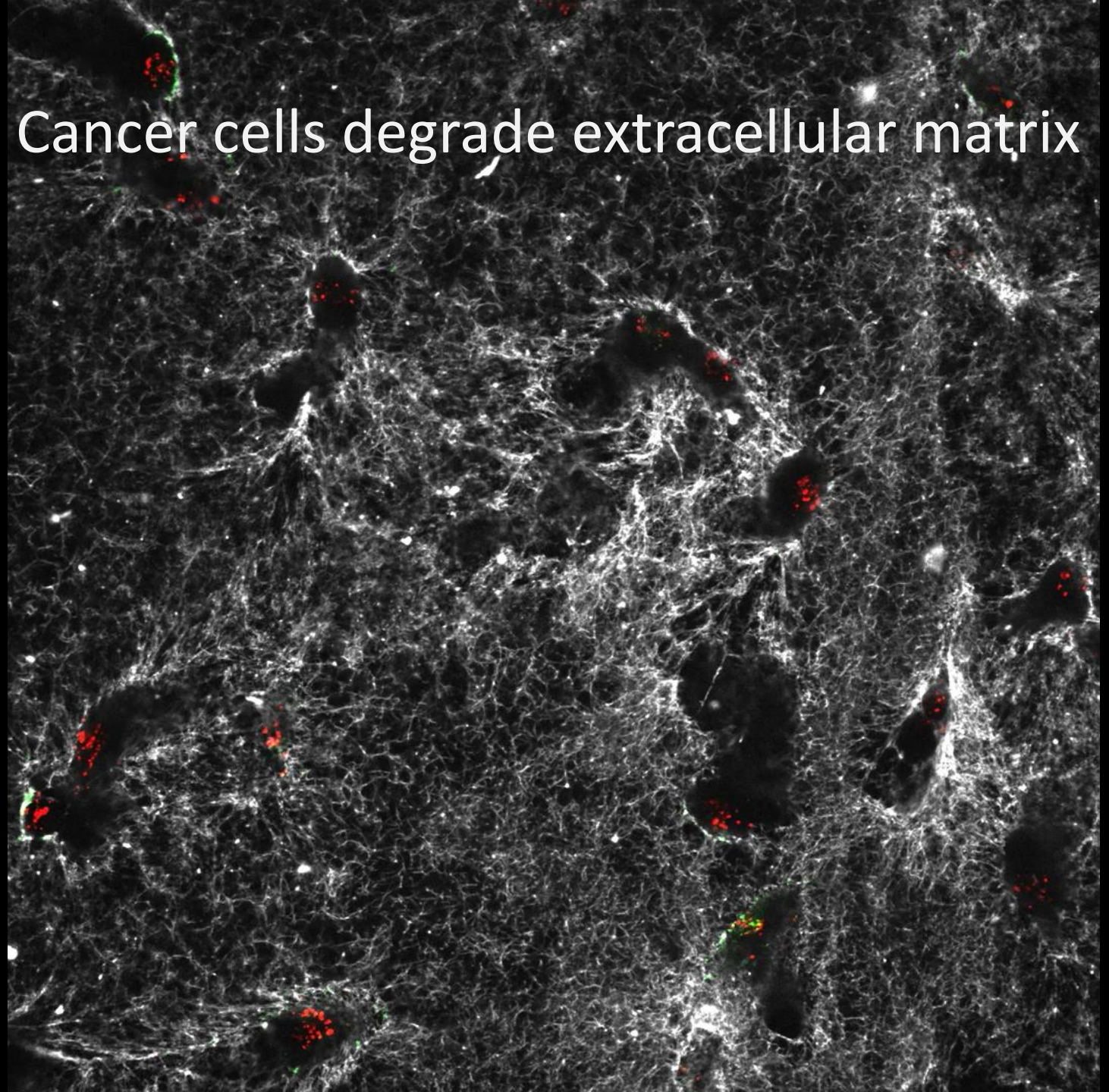

GFP-Protrudin
mCherry- FYCO1
DNA
5 um

Cancer cells use invadopodia to break through extracellular matrix

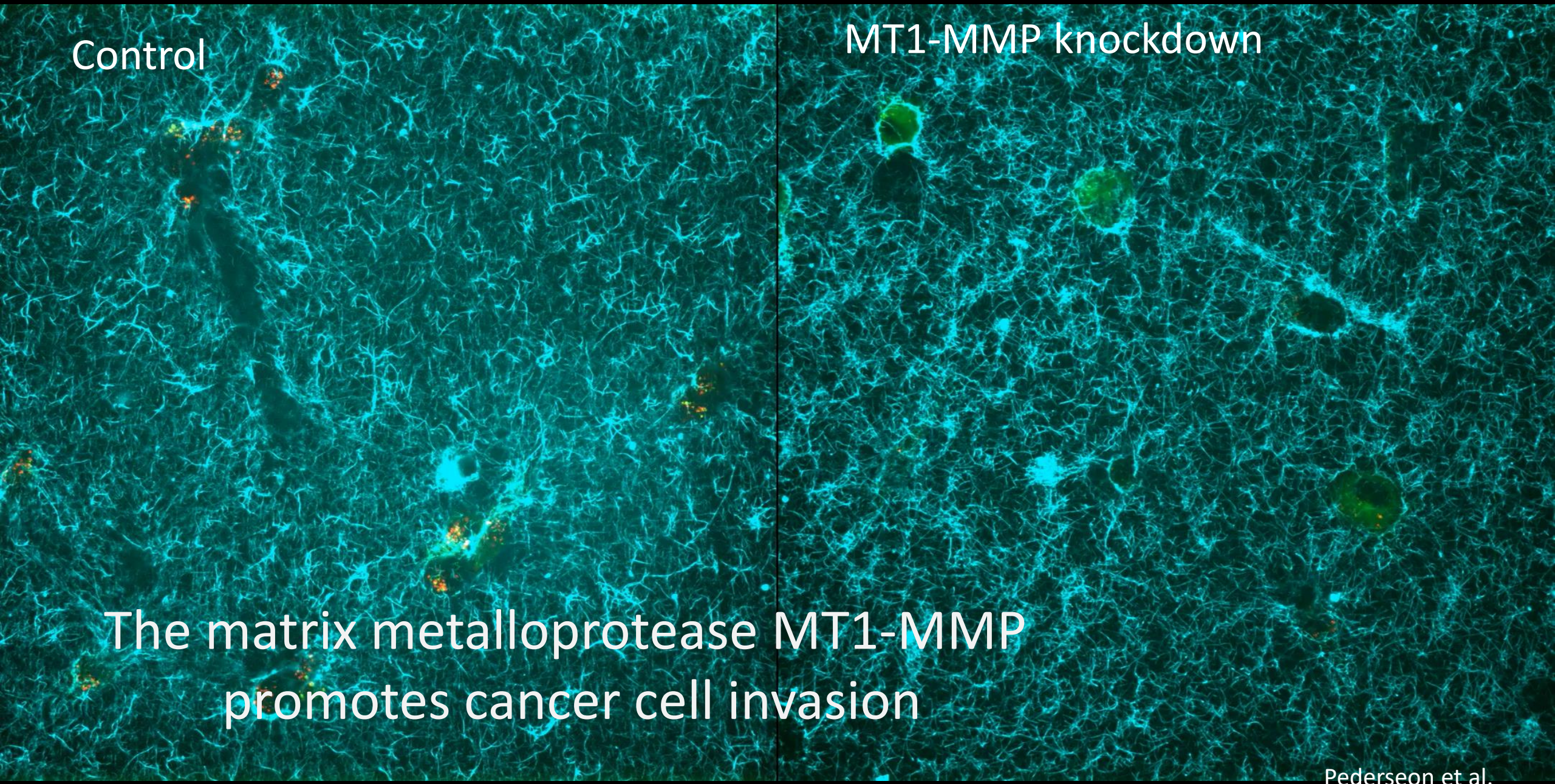


Linder,
JCB, 2015

Cancer cells degrade extracellular matrix



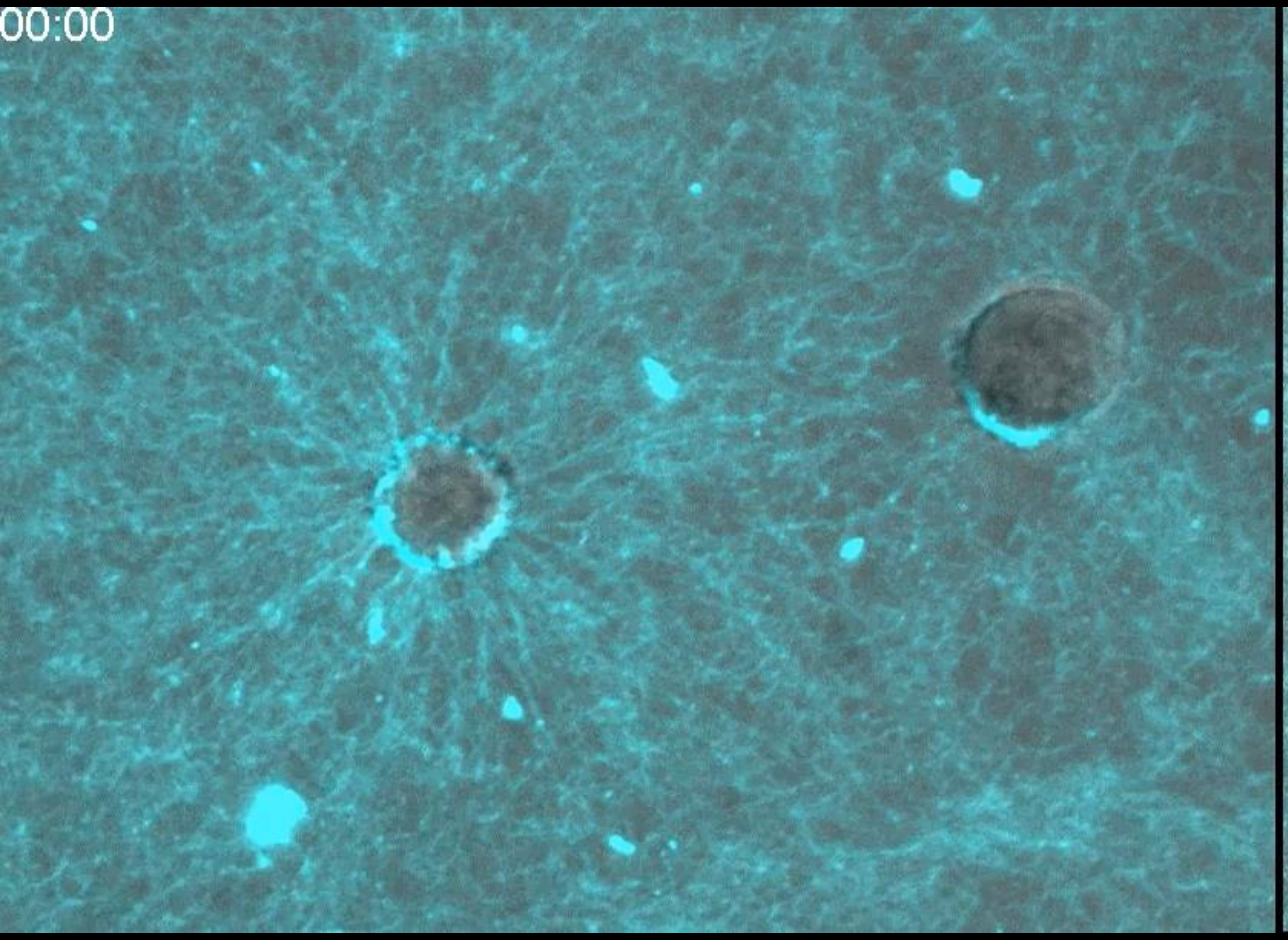
Pederseon et al.
J. Cell Biol. 2020



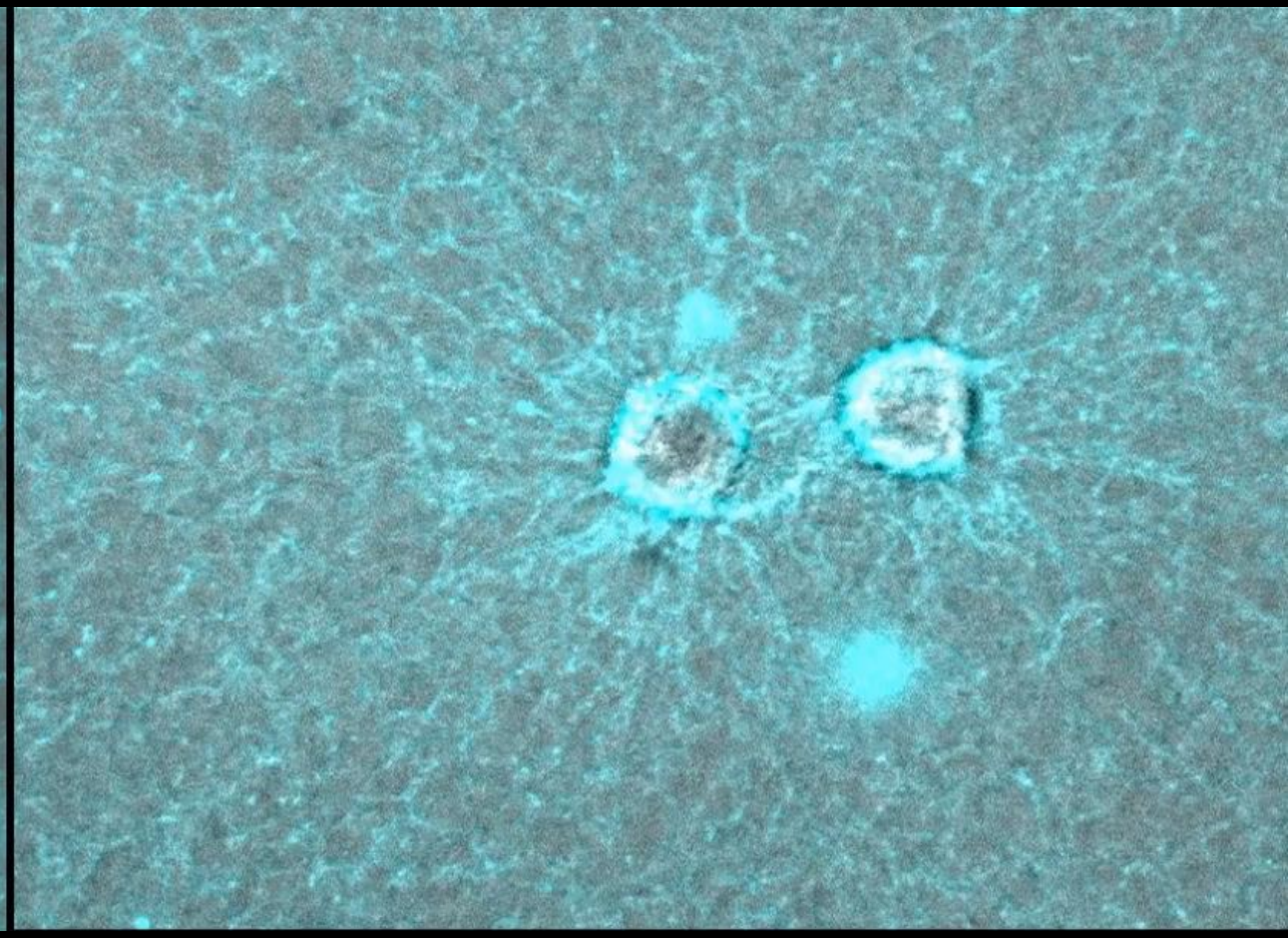
The matrix metalloprotease MT1-MMP promotes cancer cell invasion

Pederseon et al.
J. Cell Biol. 2020

Protrudin is important for cancer cell invasion



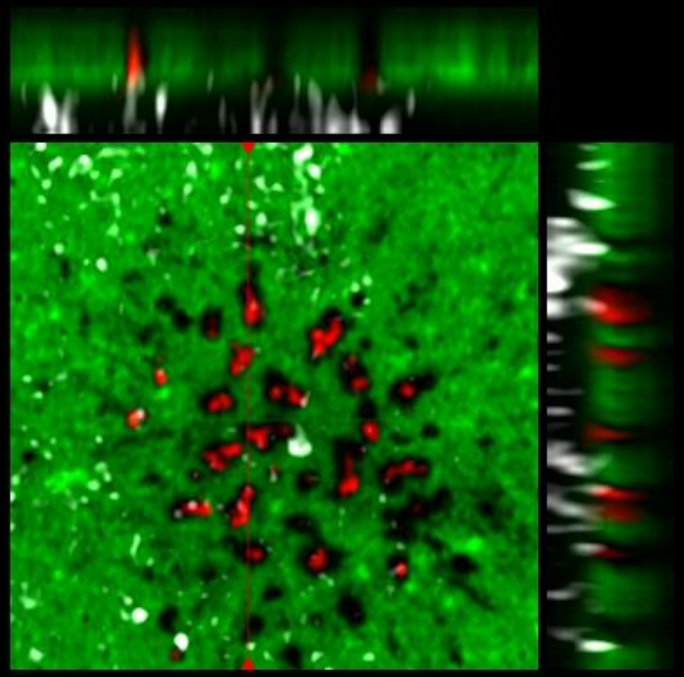
Breast cancer cells lacking Protrudin

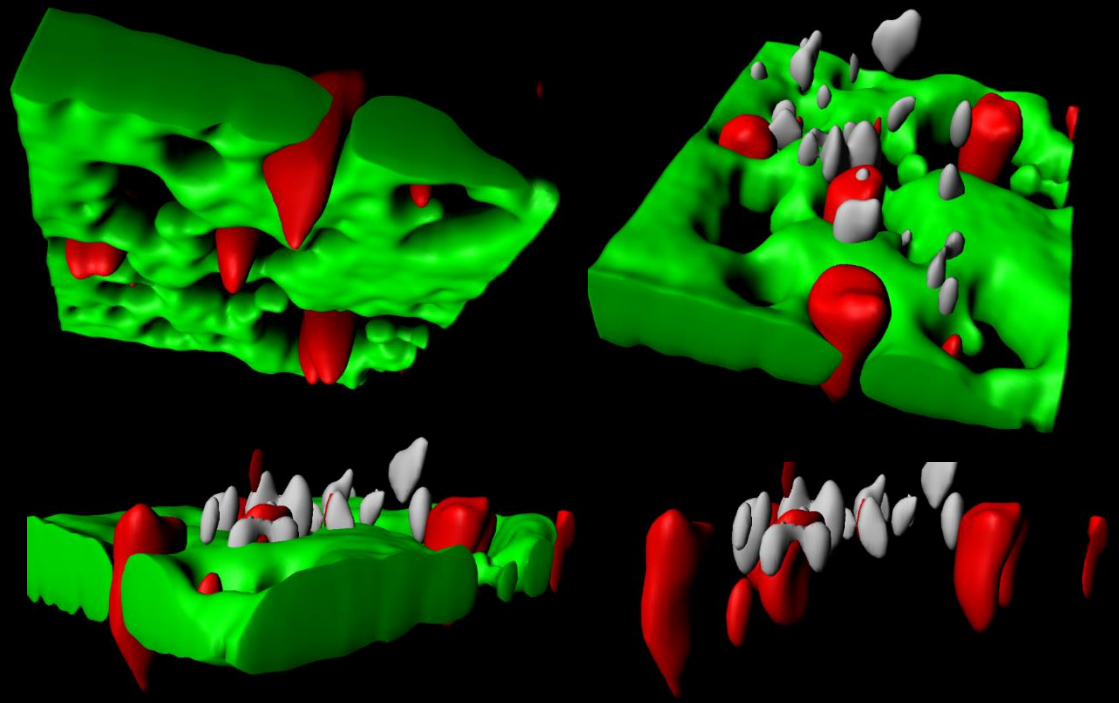


Control breast cancer cells

Pedersen et al.
J. Cell Biol. 2020

Endosomes localize close to invadopodia

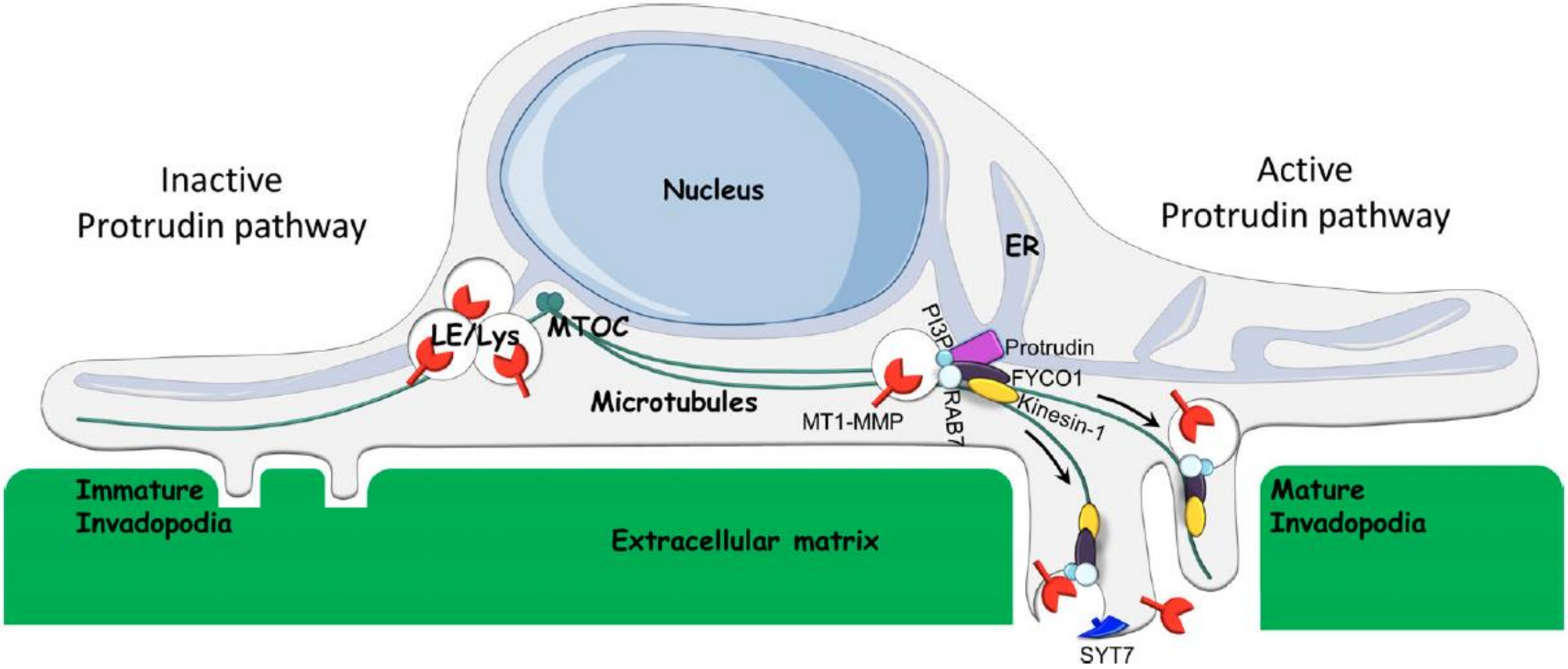




Endosomes
Invadopodia
Gelatin

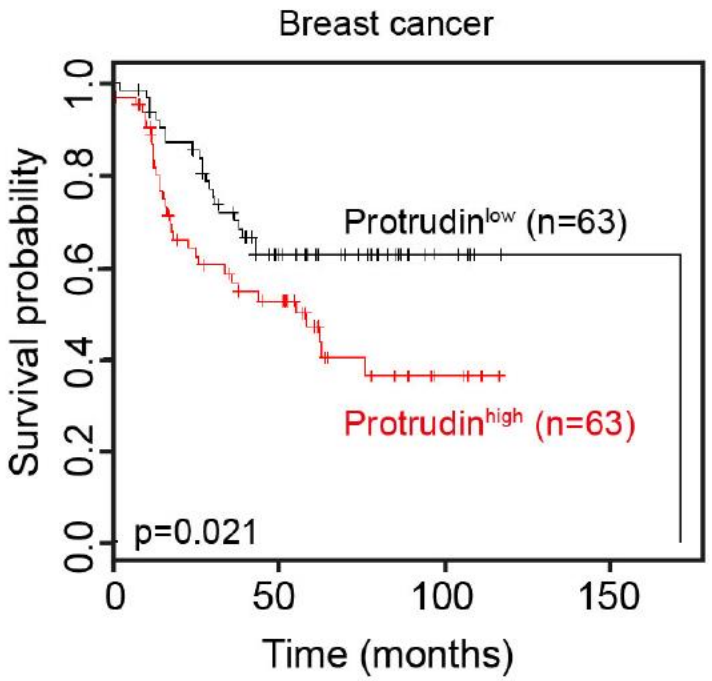
Pedersen et al.
J. Cell Biol. 2020

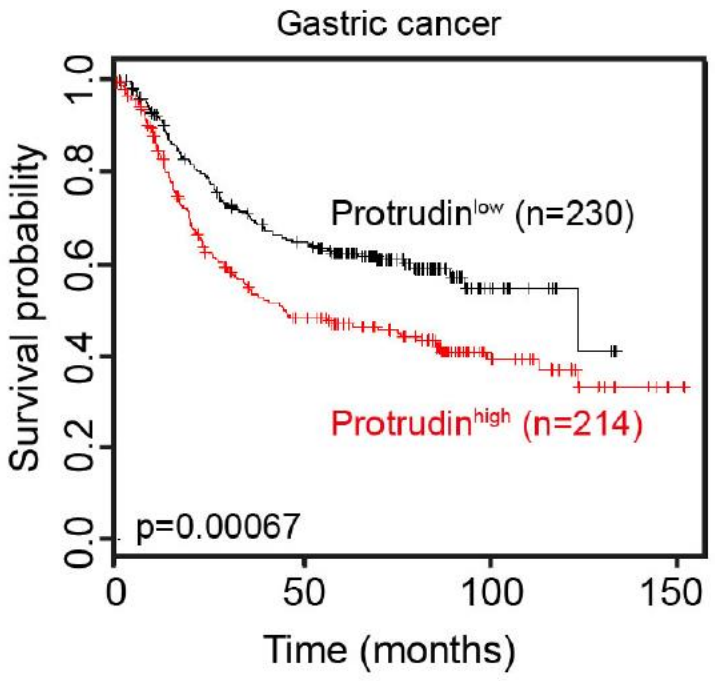
Protrudin mediates exocytosis of the metalloprotease MT1-MMP to promote cancer cell invasion

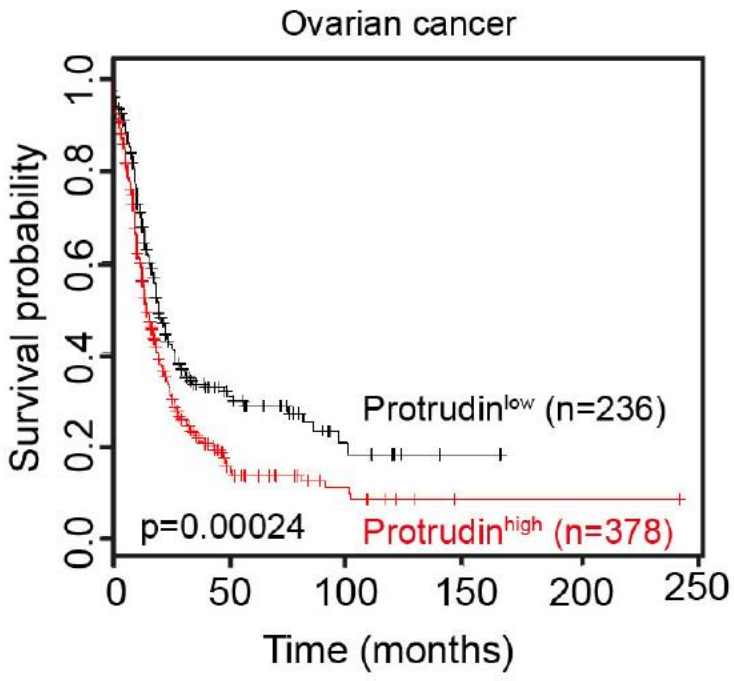


Pedersen et al., *J. Cell Biol.* 2020

High Protrudin levels are associated with poor prognosis in cancers

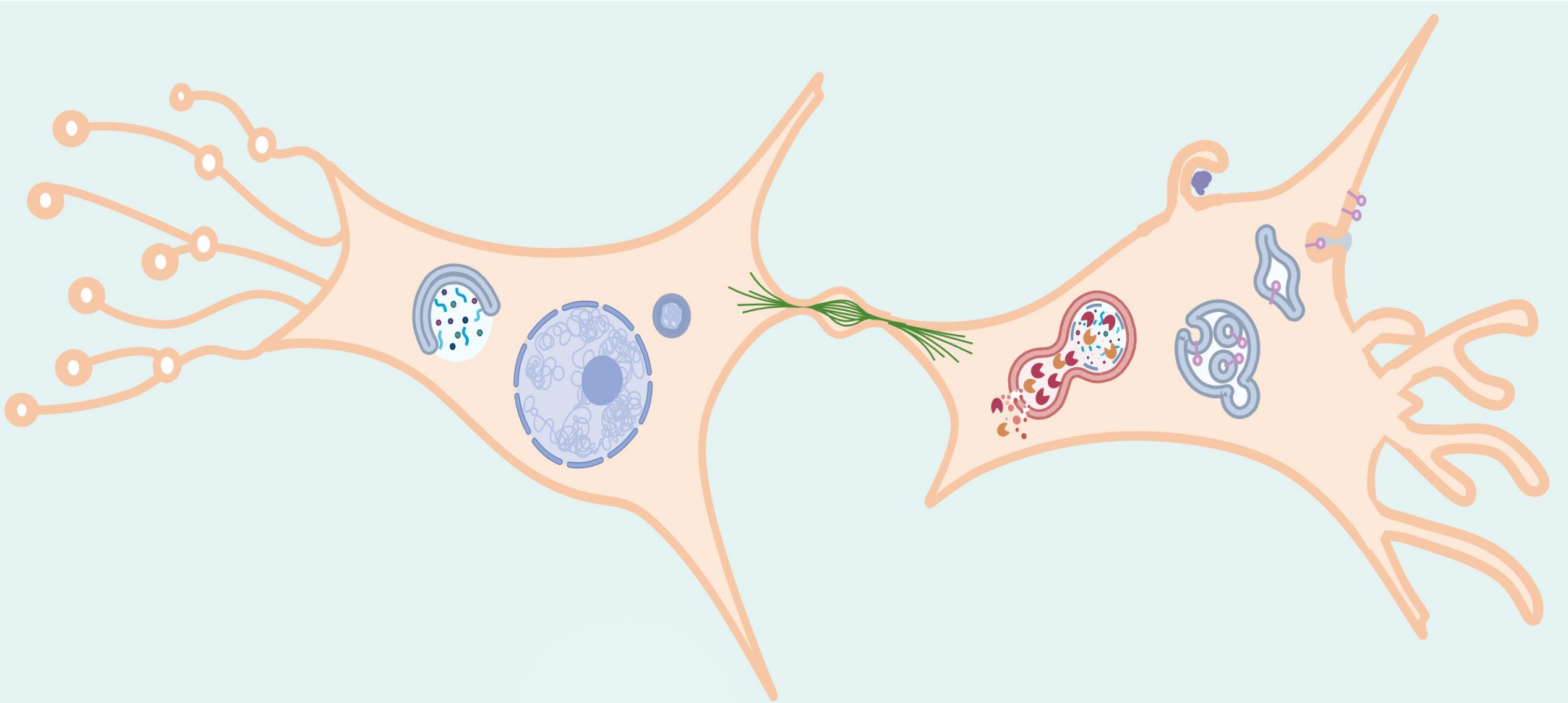


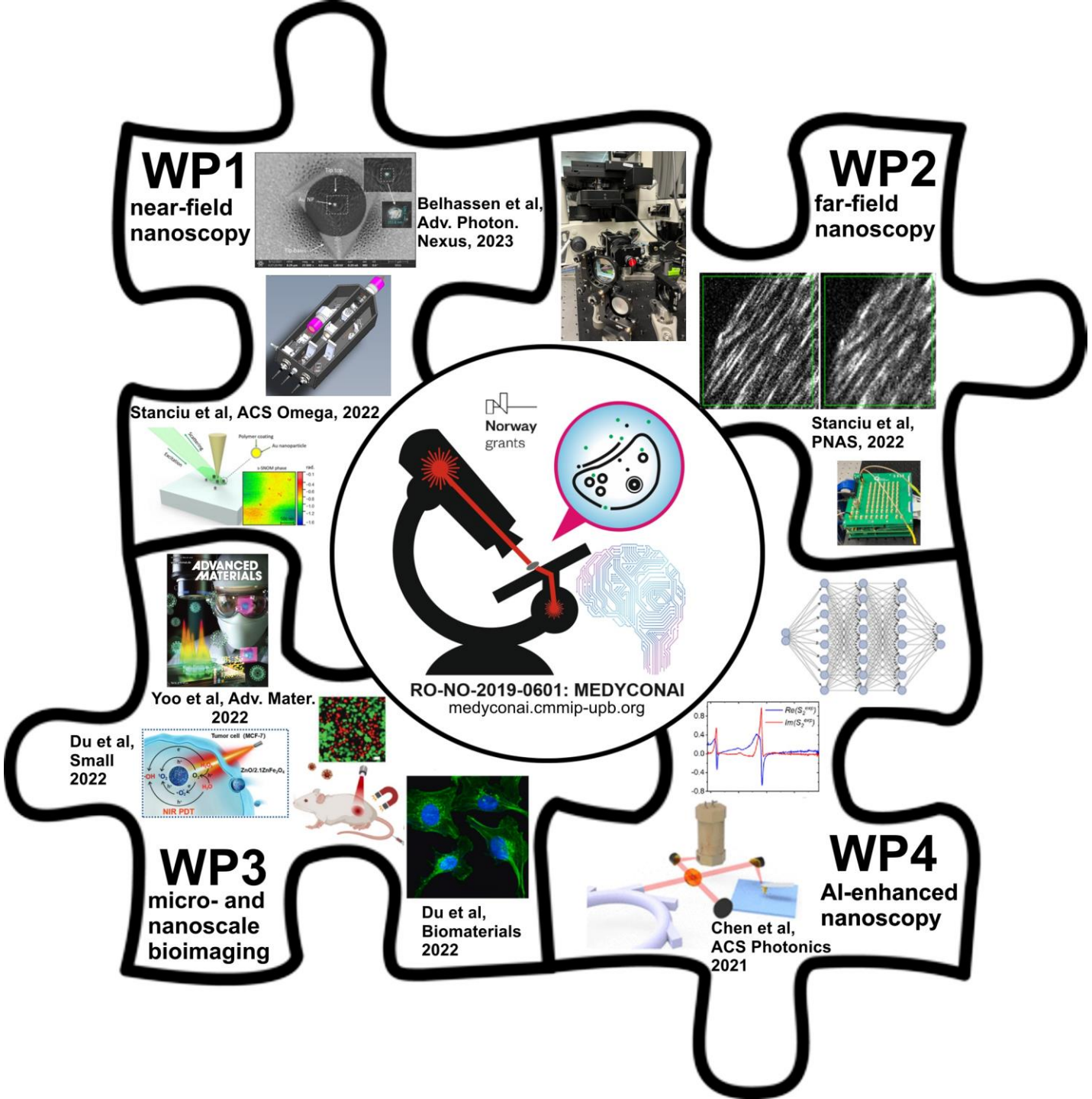




Pedersen et al., *J. Cell Biol.* 2020

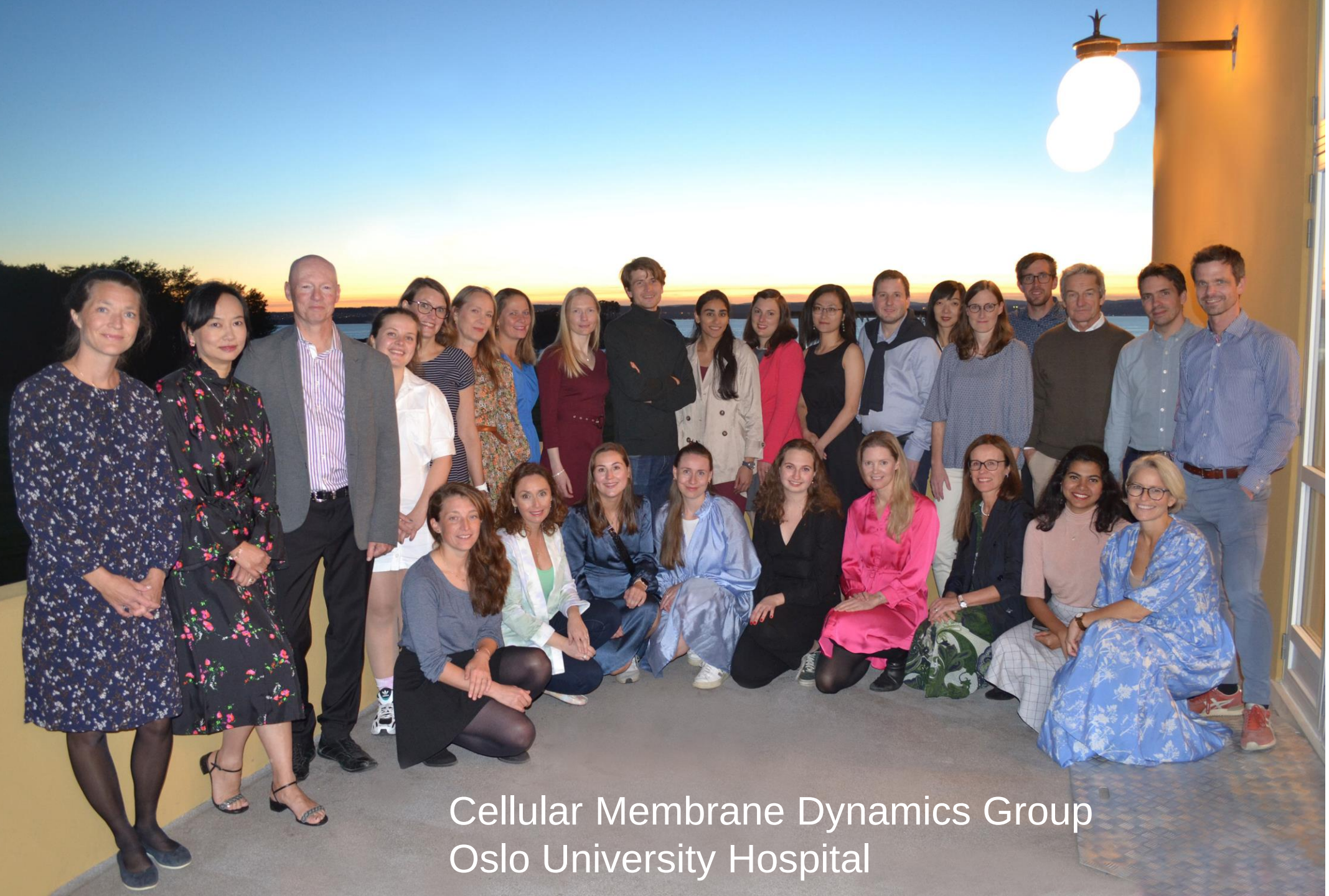
Cellular membrane dynamics and cancer





Stefan Stanciu

The MEDYCONAI project: Nanoscopy in studies of cancer cell membranes



KREFTFORENINGEN

Senter for fremragende forskning
Norges forskningsråd

Oslo universitetssykehus

HELSE SØR-ØST

Iceland Liechtenstein Norway grants
Norway grants

Forskningsrådet
The Research Council of Norway

RO-NO-2019-0601: MEDYCONAI

erc

Centre for Cancer Cell Reprogramming

UiO : CanCell
University of Oslo

Thank you!