ERNDIM Symposium 2025

Cell trafficking and autophagy in neurometabolic disorders

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Universitat Abat Oliba-CEU

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CEU Universitat
Abat Oliba | Barcelona

What is

CELL TRAFFICKING

Process of signals and metabolites exchange between cellular compartments.

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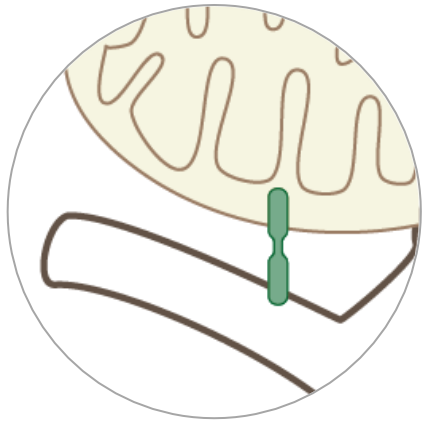
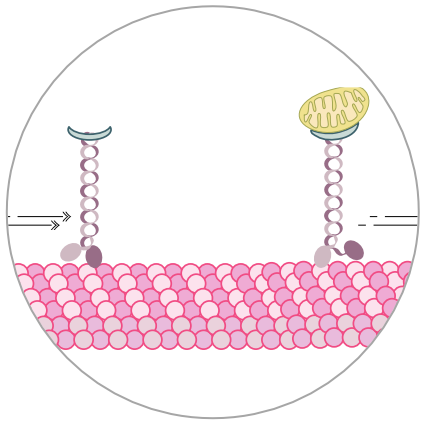
MEMBRANE TRAFFICKING

Traditional vesicular trafficking

AUTOPHAGY



MEMBRANE CONTACT SITES

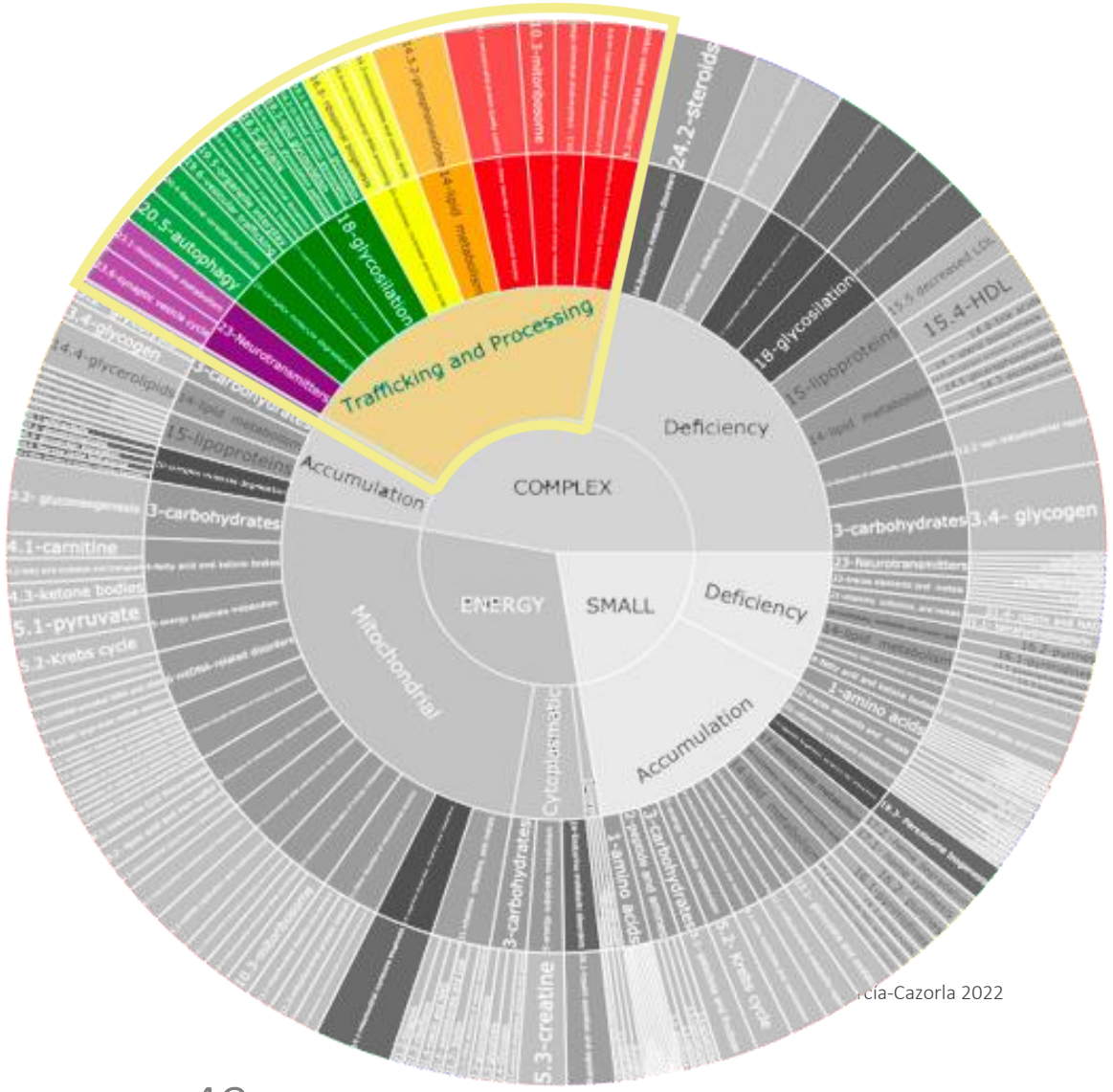


CYTOSKELETAL TRANSPORT

What is

CELL TRAFFICKING

Process of signals and metabolites exchange between cellular compartments.



García-Cazorla 2022

49 genes (2011) → >370 genes (2024)

One of the largest categories in the IMD

What is

CELL TRAFFICKING

Process of signals and metabolites exchange between cellular compartments.

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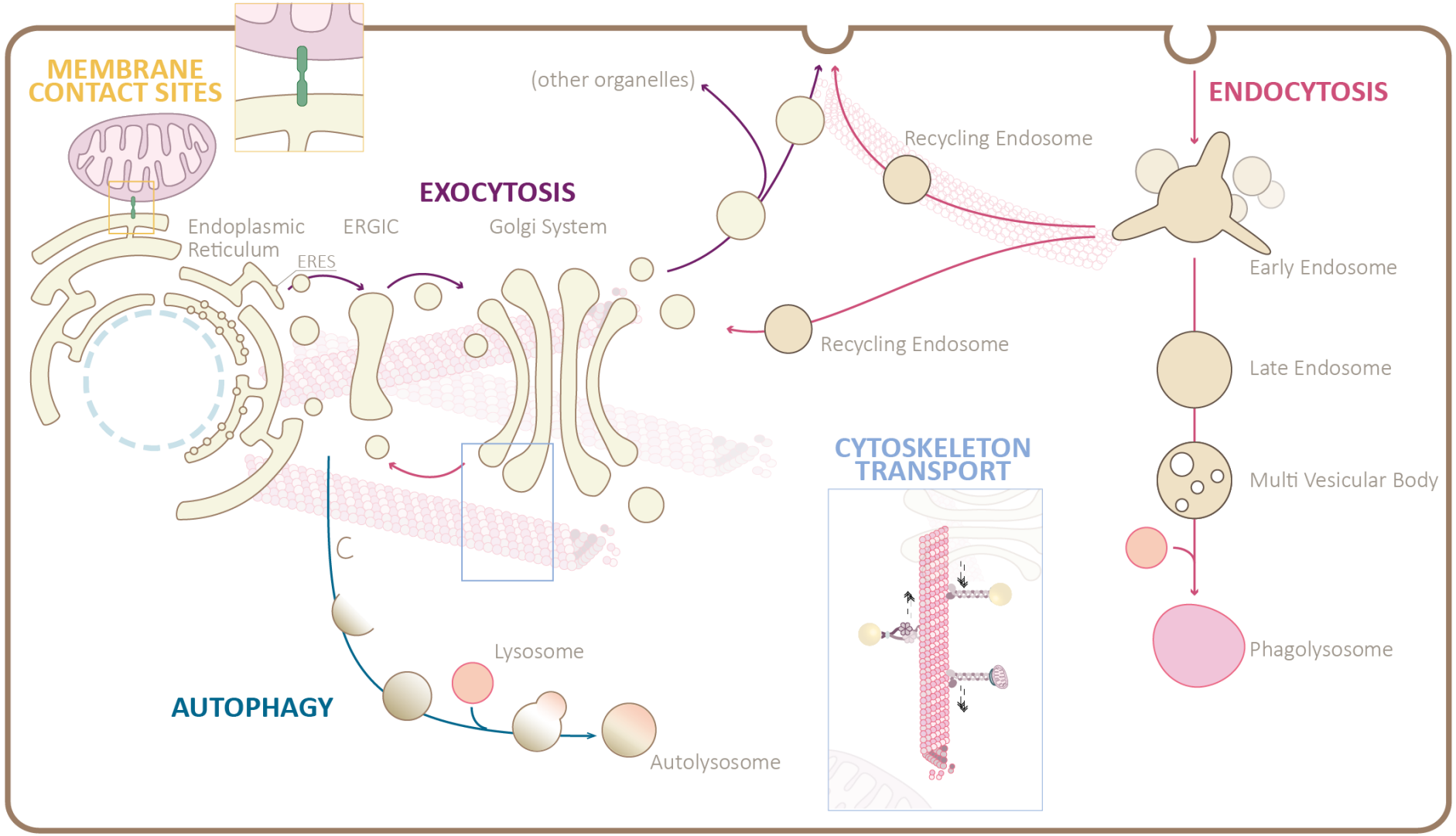
All processes are interrelated



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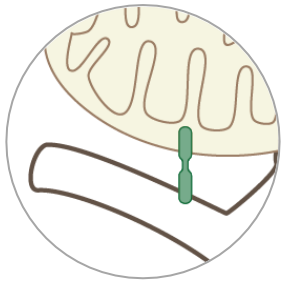

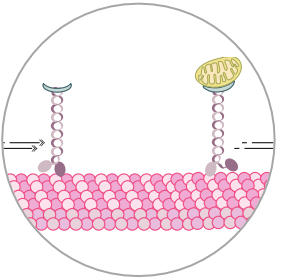

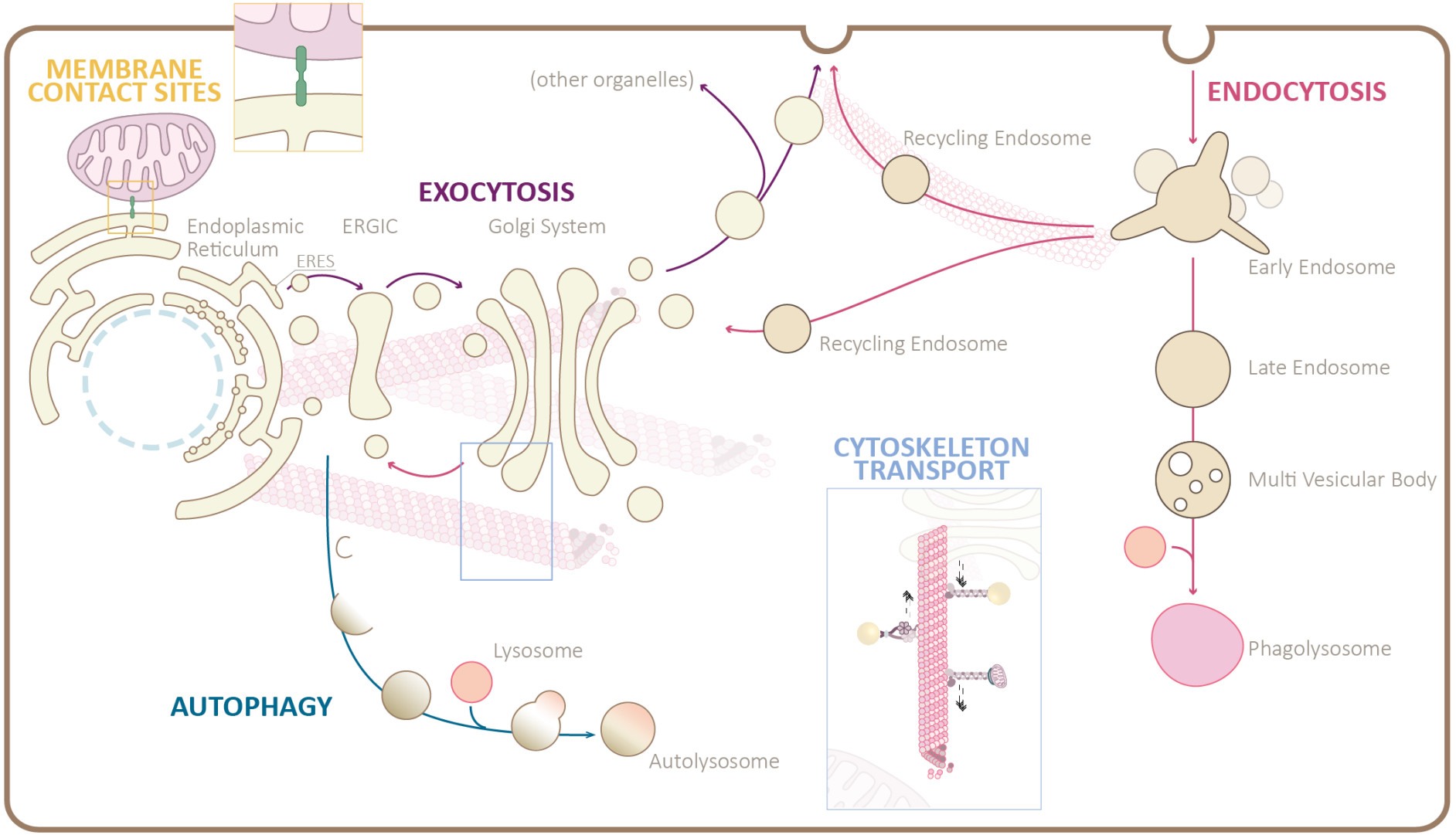

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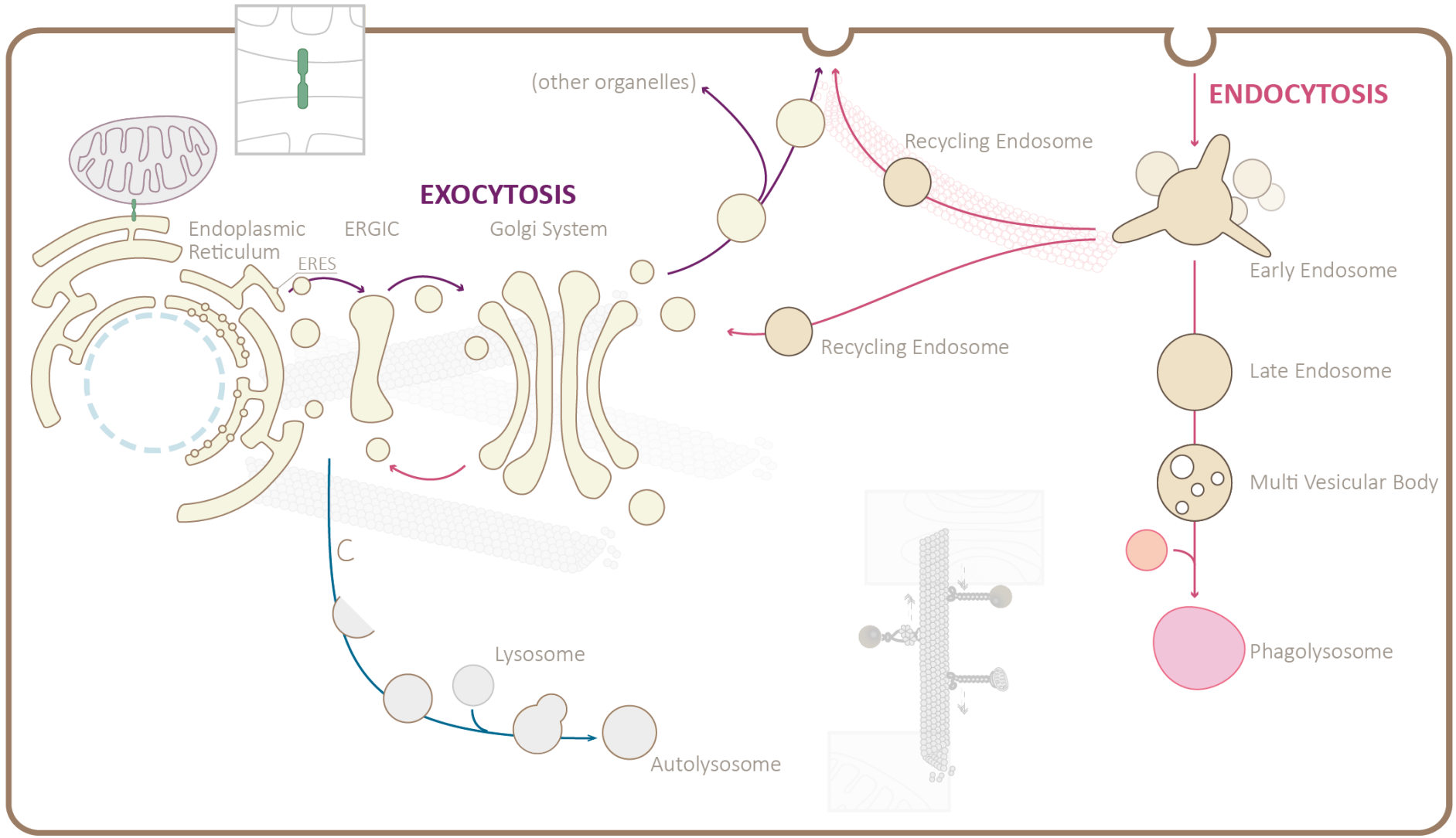
MEMBRANE TRAFFICKING



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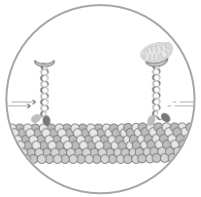
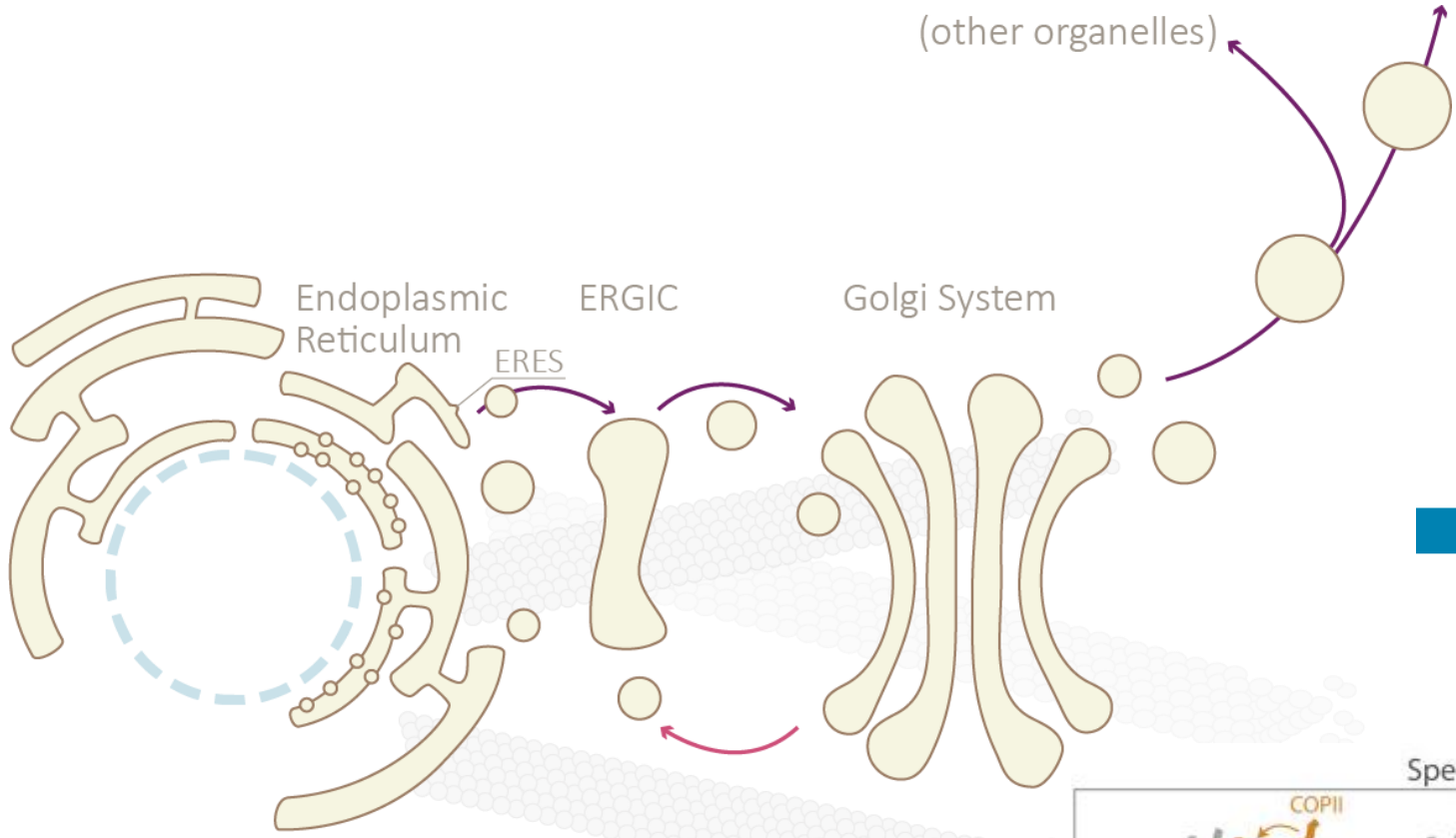


EXOCYTOSIS

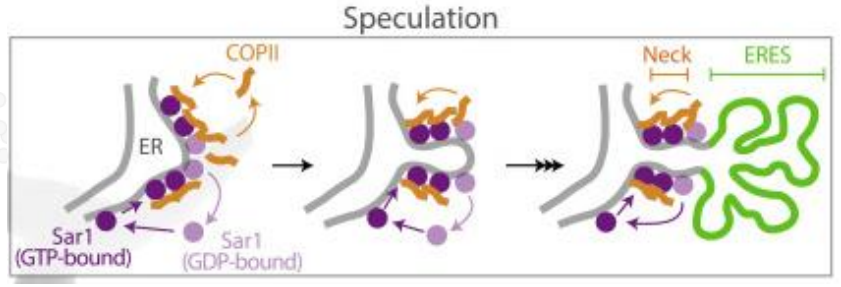
Movement OUTSIDE from the cell.
Secretory pathway and membrane proteins



CellPress

Article

ER-to-Golgi protein delivery through an interwoven, tubular network extending from ER



Weigel, Cell 2021

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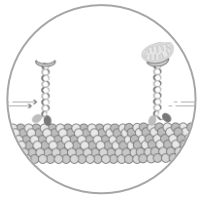

EXOCYTOSIS

Movement OUTSIDE from the cell.
Secretory pathway and membrane proteins

(other organelles)

ER – Golgi defects mutations affecting

Early onset	Congenital-postnatal µcephaly + ID	TRAPP
	NDD, adquired µcephaly + muscle	TANGO2, TRAPP
Late onset	Motor dysfunction	TANGO2

Endoplasmic Reticulum ERGIC Golgi System ERES

Received: 18 December 2018 | Revised: 15 June 2019 | Accepted: 3 July 2019
DOI: 10.1002/jimd.12149
Received: 15 July 2021 | Revised: 21 September 2021 | Accepted: 29 September 2021
DOI: 10.1002/ajmg.a.62543
AMERICAN JOURNAL OF

scientific reports

Check for updates

OPEN

Mitochondrial dysfunction associated with TANGO2 deficiency

Paige Heiman[1], Al-Walid Mohsen[1,2], Anuradha Karunanidhi[1], Claudette St Croix[3], Simon Watkins[3], Erik Koppes[1], Richard Haas[4], Jerry Vockley[1,2] & Lina Ghaloul-Gonzalez[1,2]✉

Scientific Reports | (2022) 12:3045

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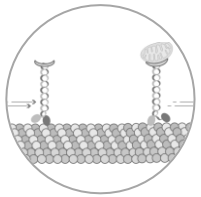
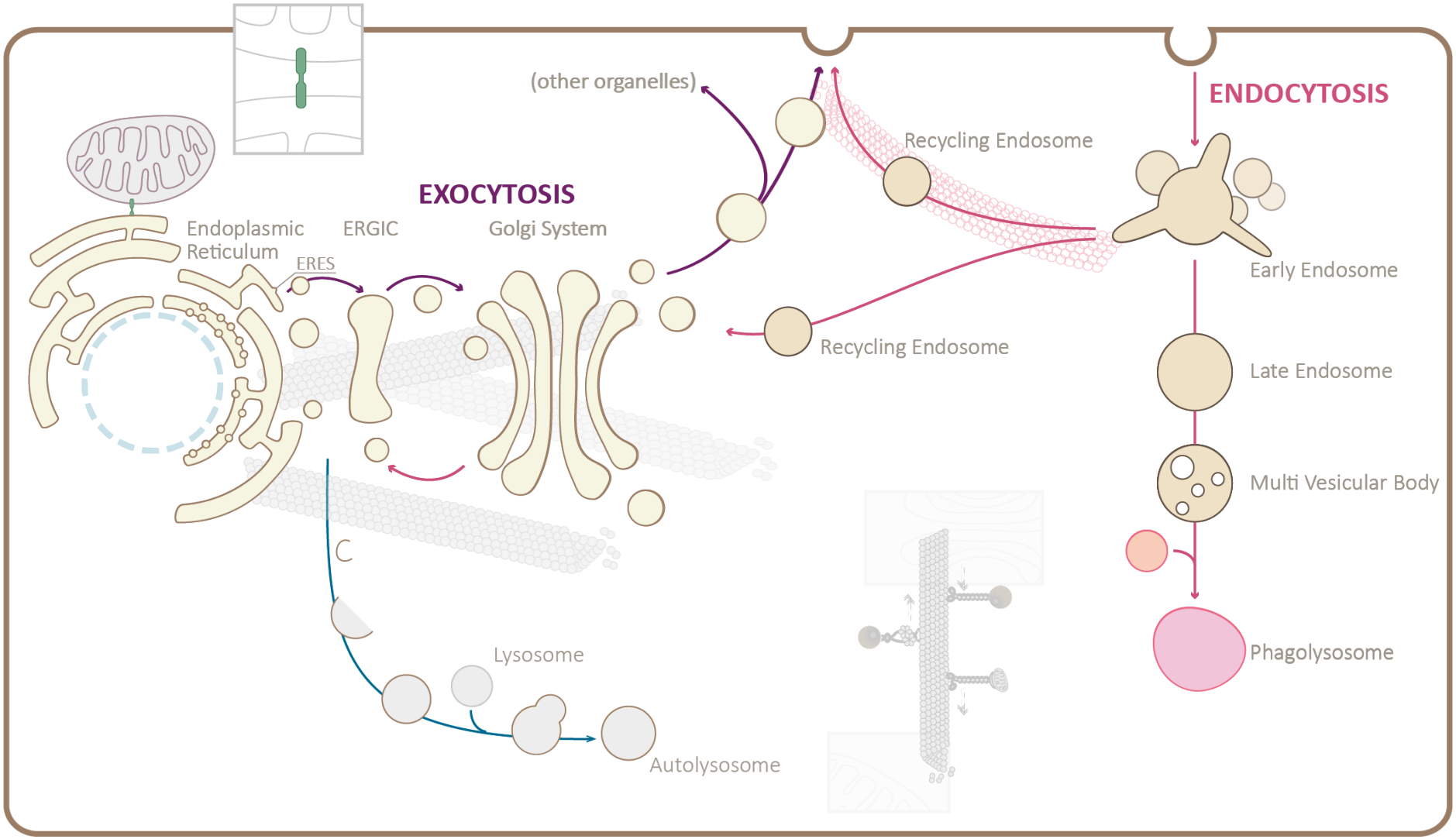
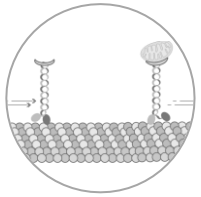
UNIVERSITAT DE BARCELONA

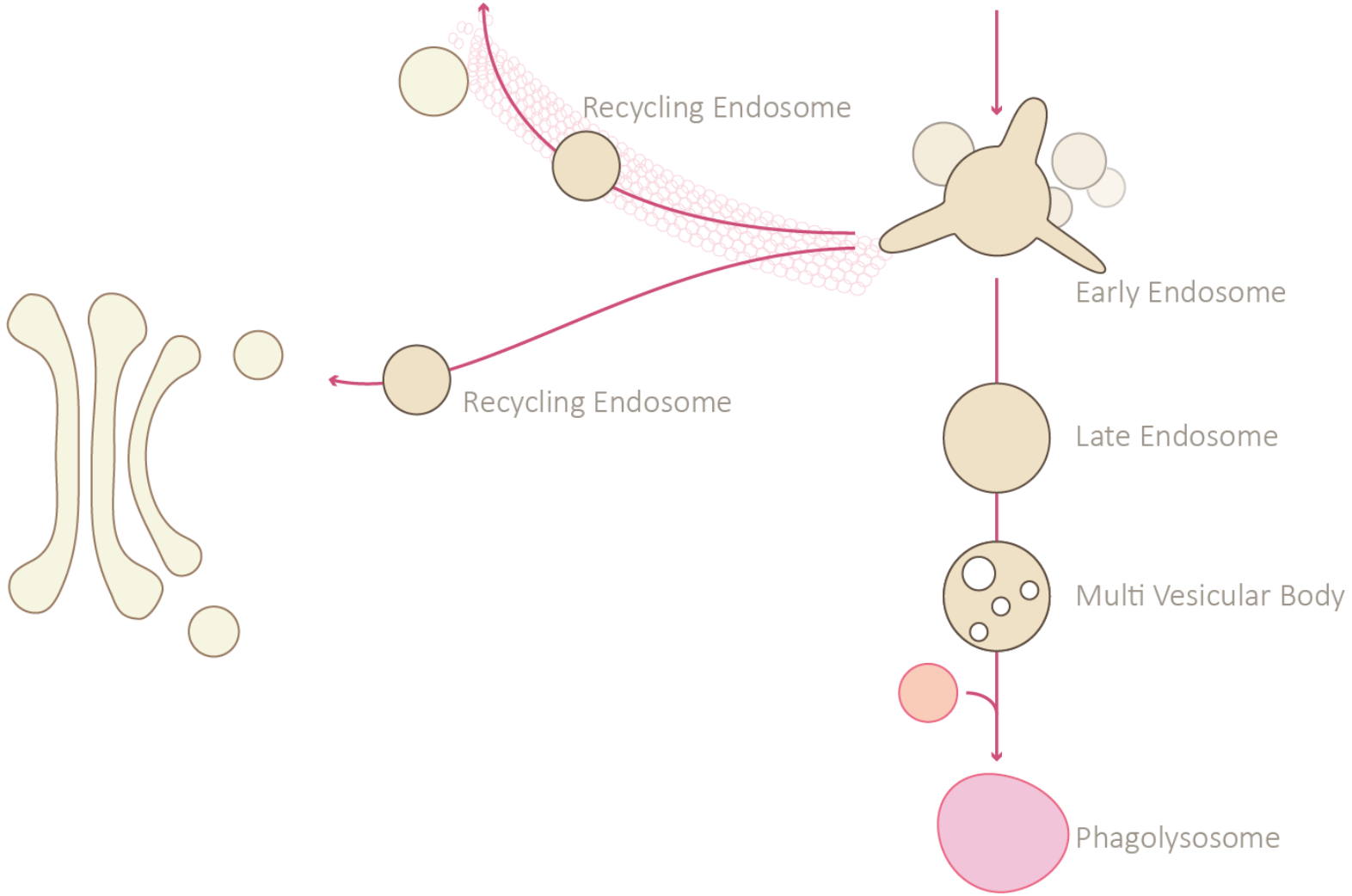






ENDOCYTOSIS

Movement INSIDE to the cell.
Secretory pathway and membrane proteins



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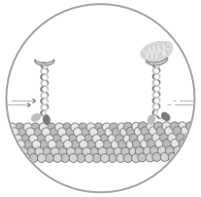

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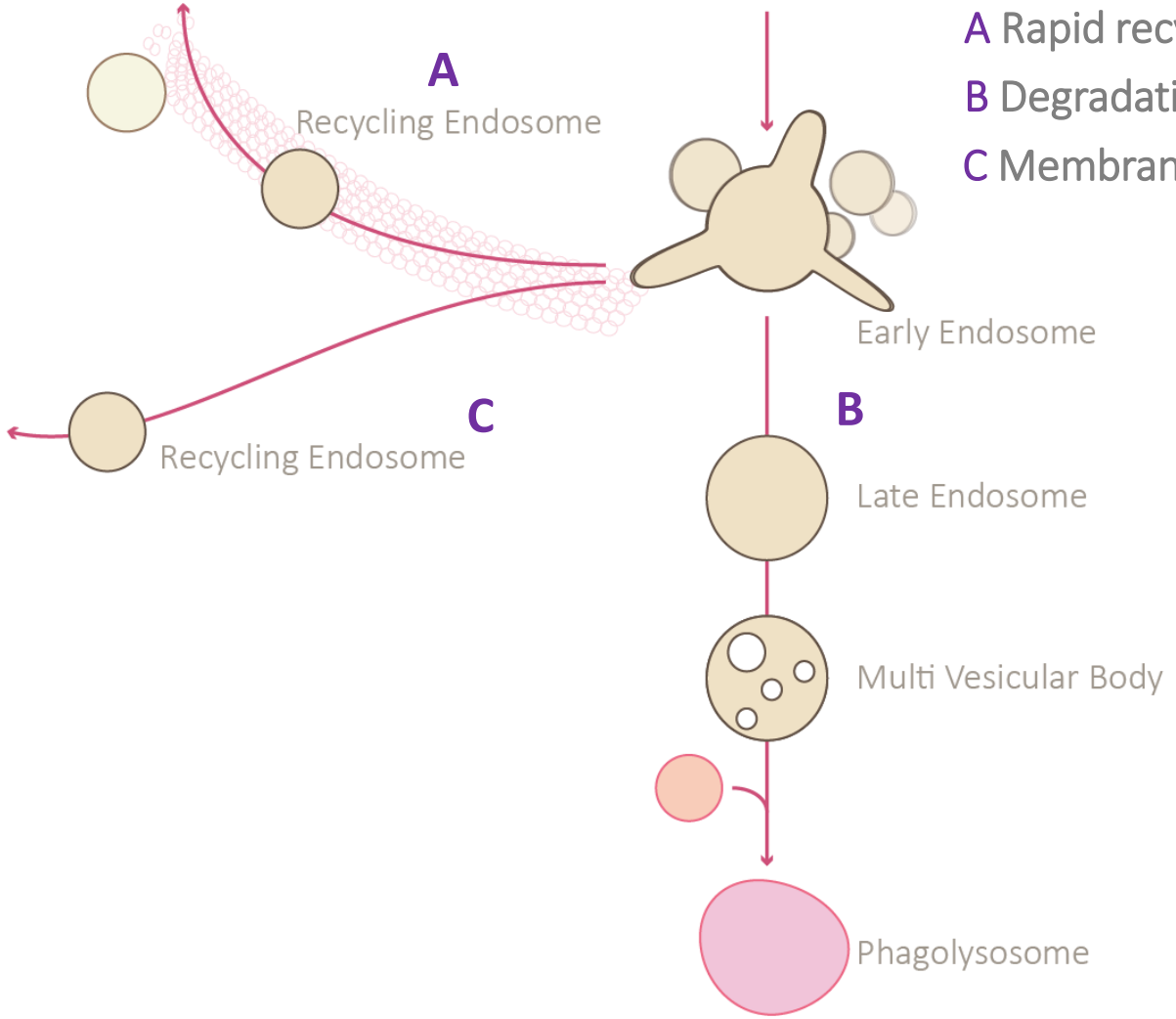

A Rapid recycling

B Degradation via autophagy

C Membrane receptors recycling

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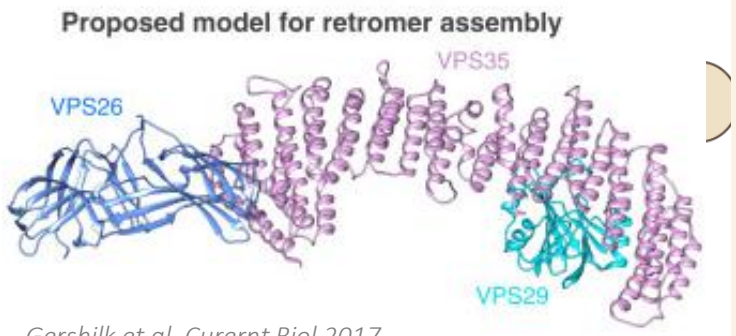
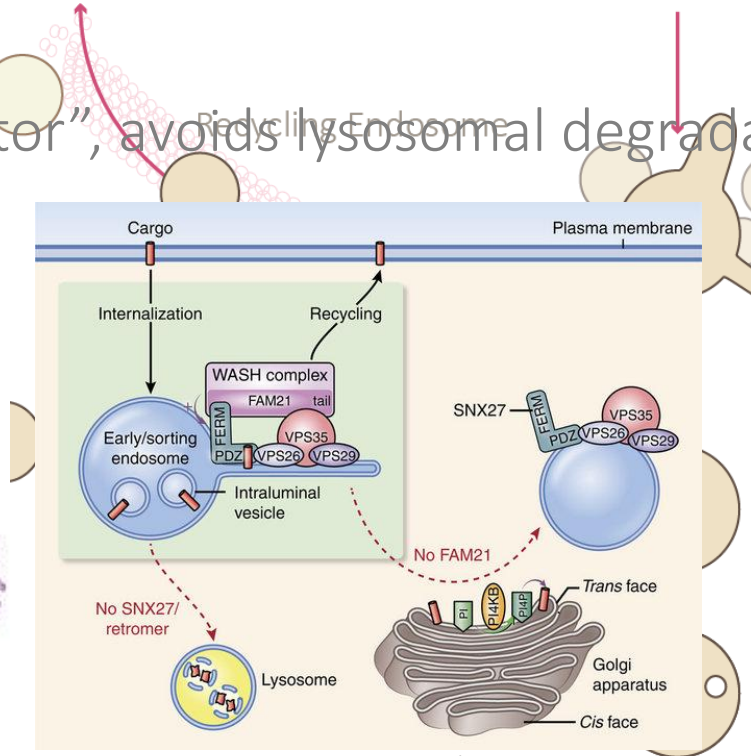
ENDOCYTOSIS

Movement INSIDE to the cell.
Secretory pathway and membrane proteins

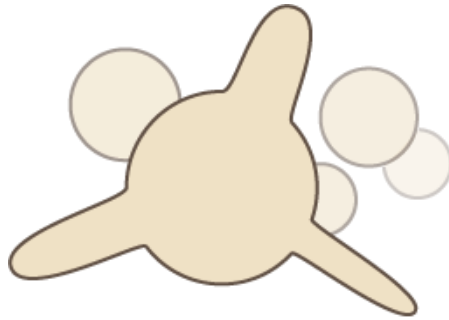
RETROMER: "Master regulator", avoids lysosomal degradation



Gershilk et al, Curernt Biol 2017.



Lee et al, Nature Comm 2016.



Early Endosome

Late Endosome

Multi Vesicular Body

Phagolysosome

1- Endosome recruits retromer
2- Cargo binds retromer via SNX27
3- Membrane deformation via SNX-BAR
4- Tubulation SNX-BAR + Actin + WASH complex

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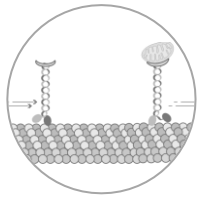
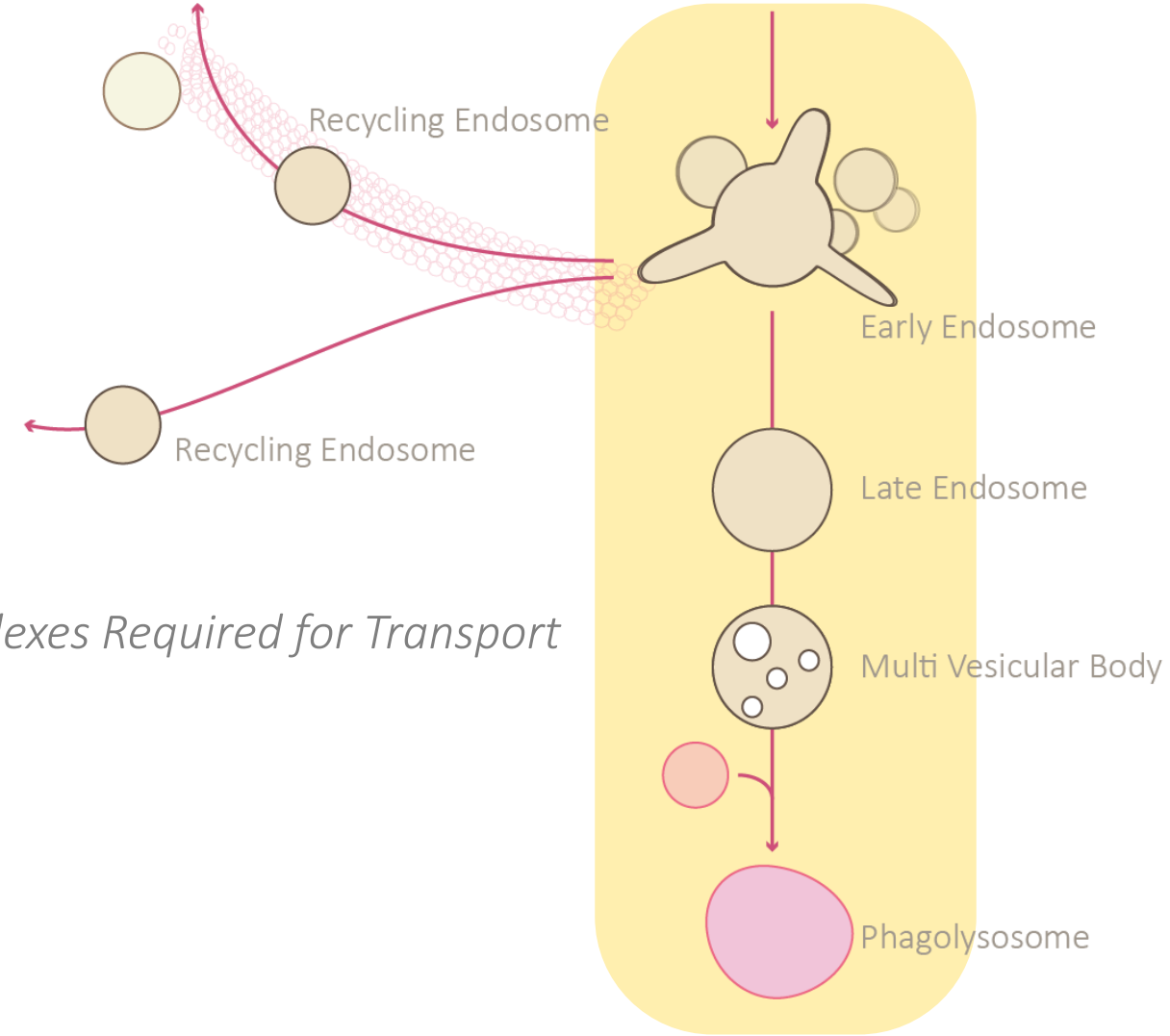
ENDOCYTOSIS

Movement INSIDE to the cell.
Secretory pathway and membrane proteins





Endosomal Sorting Complexes Required for Transport
(ESCRTs)

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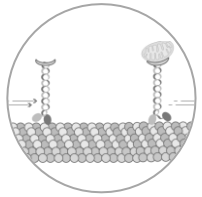
ENDOCYTOSIS

Movement INSIDE to the cell.
Secretory pathway and membrane proteins



Golgi - endoseomes defects

Complex early-onset encephalopathies that may associate with multisistemic involvement

SLC9A6

Late endosome - lysosome defects

- Neonatal seizures — ATP6A2
- Complex multisystemic — SNAP29
- Peripheral neuropathy — RAB7
- Lysosome biogenesis defects — Lowe syndrome
- HOPSANDs (*HOPS Associated Neurological Disorders*)

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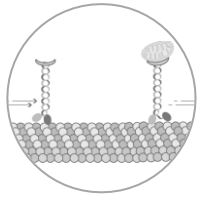
ENDOCYTOSIS

Movement INSIDE to the cell.
Secretory pathway and membrane proteins



Golgi - endoseomes defects

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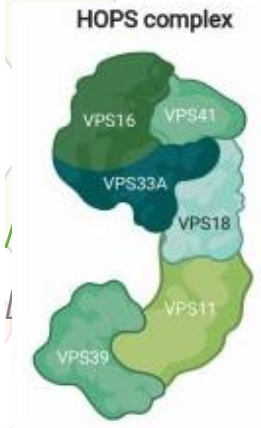
Late endosome - lysosome defects

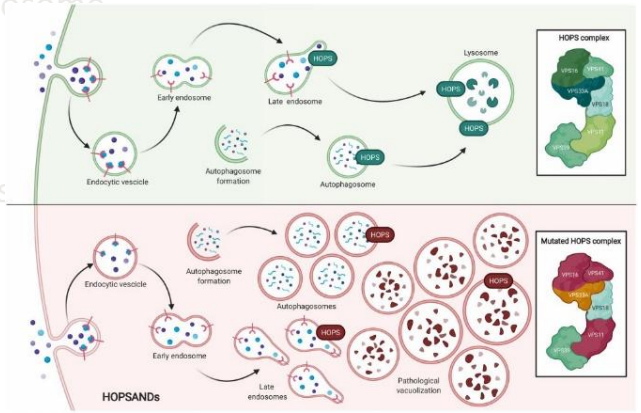
doi:10.1093/brain/awab161 BRAIN 2021: 144; 2610–2615 | 2610

BRAIN UPDATE

HOPS-associated neurological disorders (HOPSANDs): linking endolysosomal dysfunction to the pathogenesis of dystonia

Edoardo Monfrini,[1,2] Michael Zech,[3,4] Dora Steel,[5,6] Manju A. Kurian,[5,6] Juliane Winkelmann[3,4,7,8] and Alessio Di Fonzo[2]





Recycling Endosome

Early Endosome

Recycling Endosome

Phagolysosome

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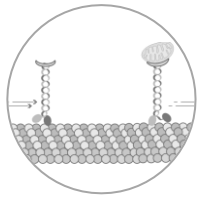

AUTOPHAGY

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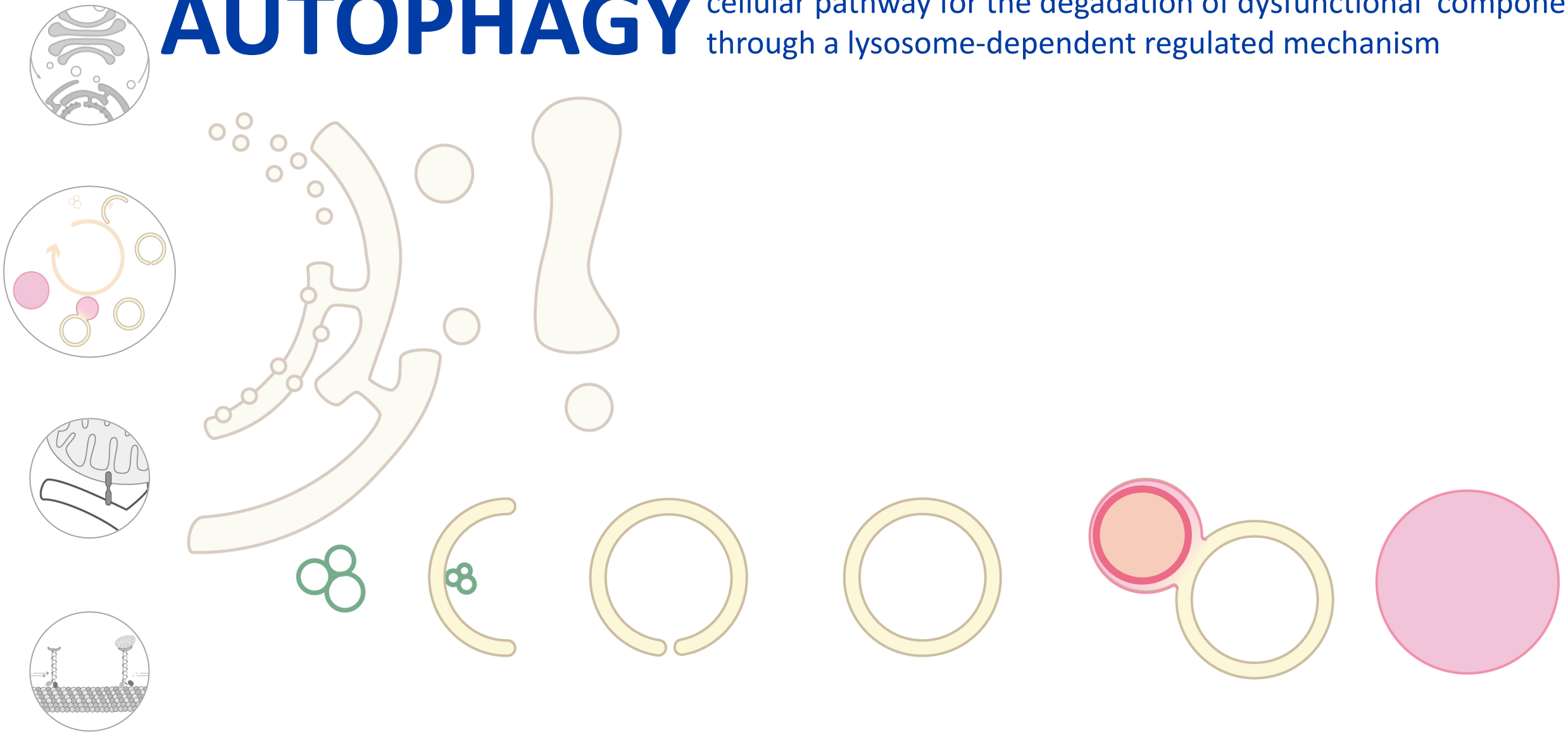
AUTOPHAGY

cellular pathway for the degadation of dysfunctional components through a lysosome-dependent regulated mechanism



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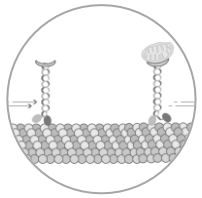


endocytosis +
cell trafficking

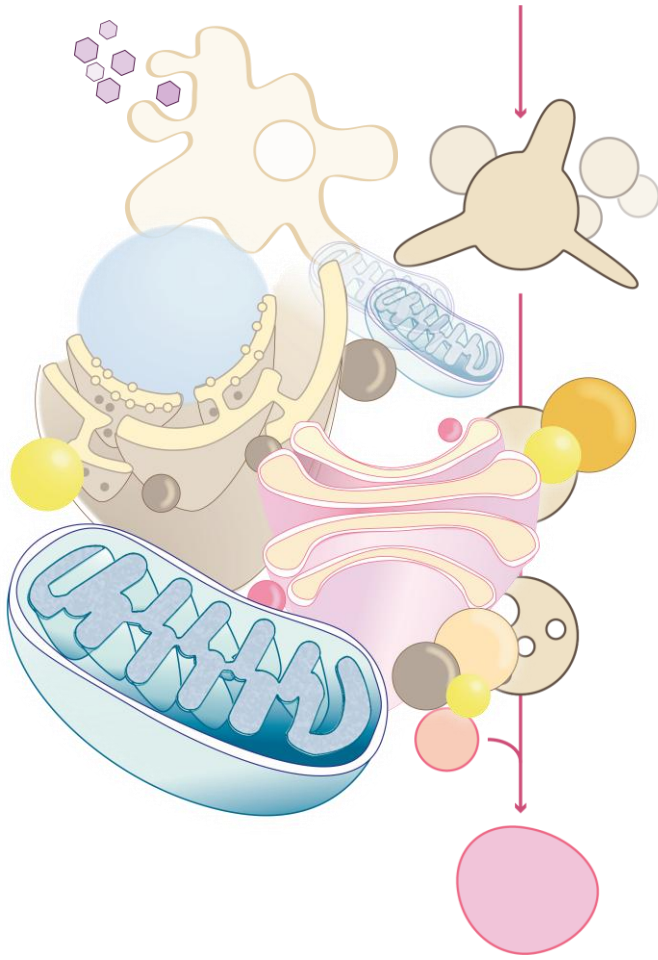
inter-organelle
communication

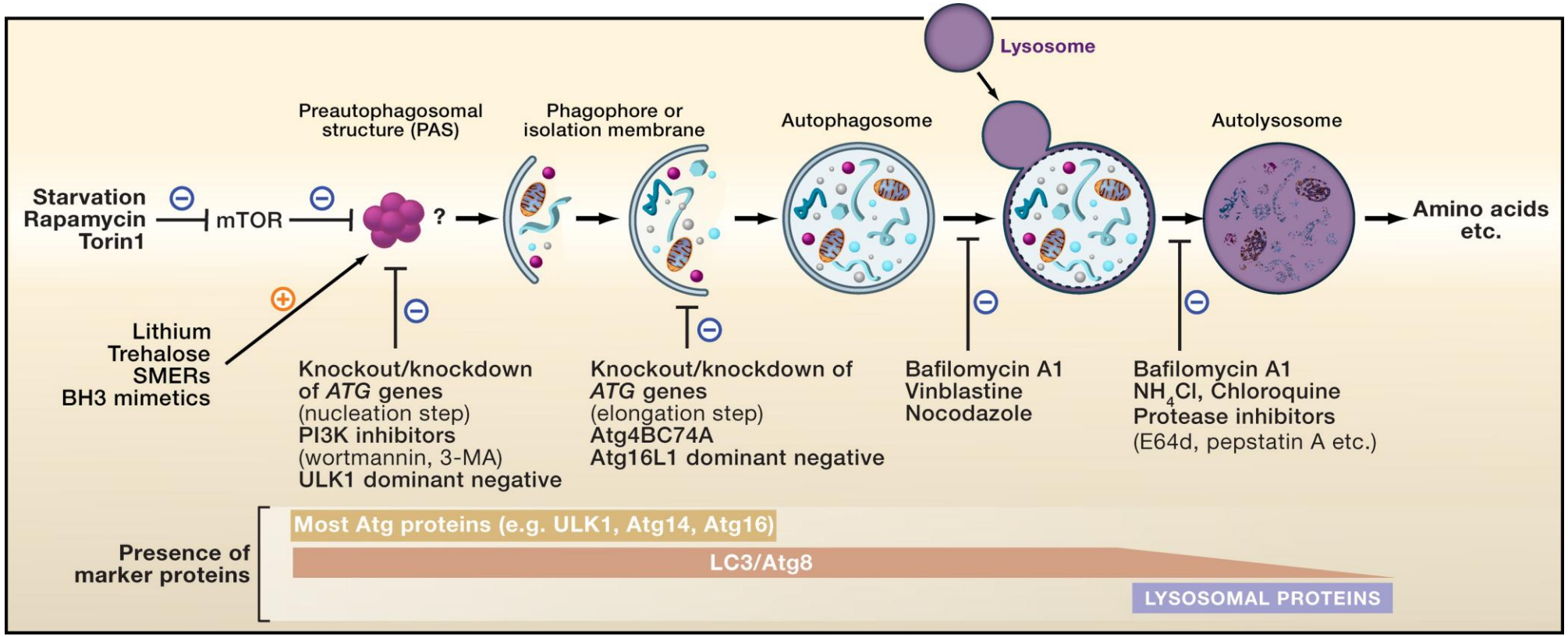
metabolism

immunologic
processes

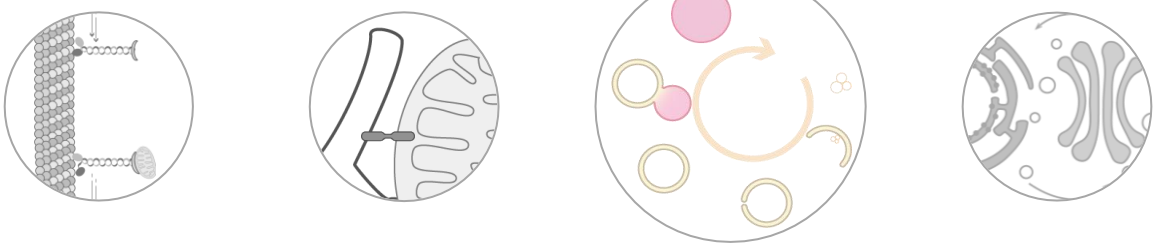
cell signaling

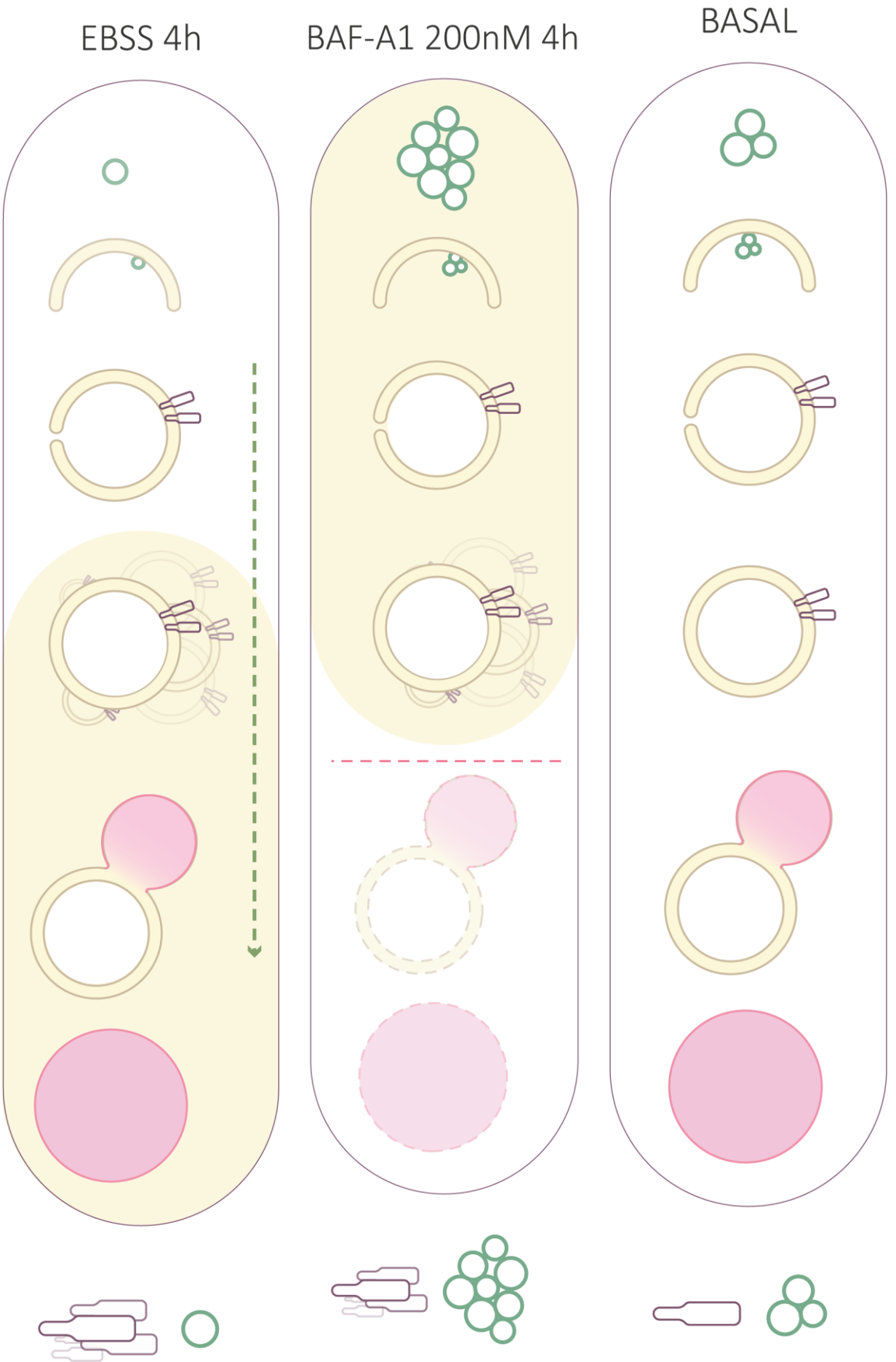
LYSOSOME:
a cellular hub





Noboru Mizushima, et al. Methods in Mammalian Autophagy Research, *Cell*, 2010




EBSS 4h
BAF-A1 200nM 4h
BASAL

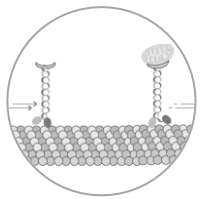
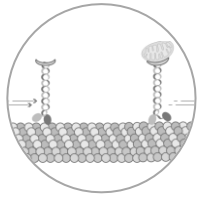


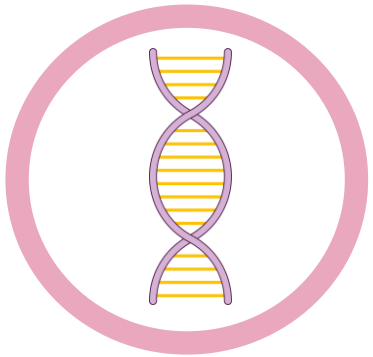
Table 2 | **Human diseases linked to autophagy and clinical translation**

Disease	Mechanism	Compounds
Autophagy activation in neurodegenerative diseases		
Alzheimer disease	mTOR inhibition (via 5-HT_6R activation)	AVN-211; Lu AE58054 (idalopirdine); SB-742457
	Inhibition of AKT–mTOR pathway	rAAV/Aβ vaccine
	ACAT1 inhibition	F12511
	mTOR inhibition	Rapamycin, latrepirdine and metformin
	AMPK activation	Resveratrol and resveratrol-like small molecules
	Lysosomal acidification	Nicotinamide
	GSK3β and IMPase inhibition	Lithium
	Unclear mechanism	Berberine
	MTMR14 (autophagy inhibitor) inhibition	AUTEN-67
Parkinson disease	NRF2 activation	DMF
	TFEB activation	Curcumin analogue
	Beclin 1 complex activation	*BECN1* gene transfer
	TFEB regulation	*TFEB* gene
	Beclin 1 activation	Dual GLP-1–GIP receptor agonists
ALS	Unclear mechanism	Berberine
Huntington disease	MTMR14 inhibition	AUTEN-67
	mTOR inhibition	Rapamycin
	Unclear mechanism	Berberine



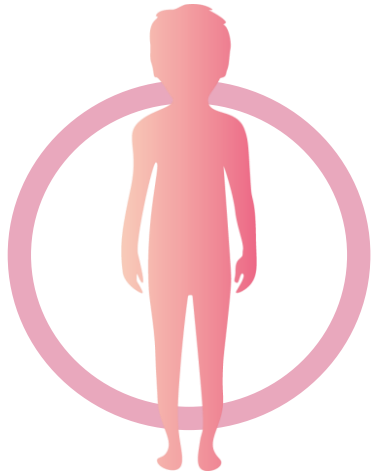
AUTOPHAGY DEFECTS AS **PRIMARY CAUSE OF THE DISEASE**

Beta-propeller Protein-Associated Neurodegeneration (BPAN)



Caused by mutations in *WDR45*

Neurodegenerative metabolic disease



Bi-phasic clinical course

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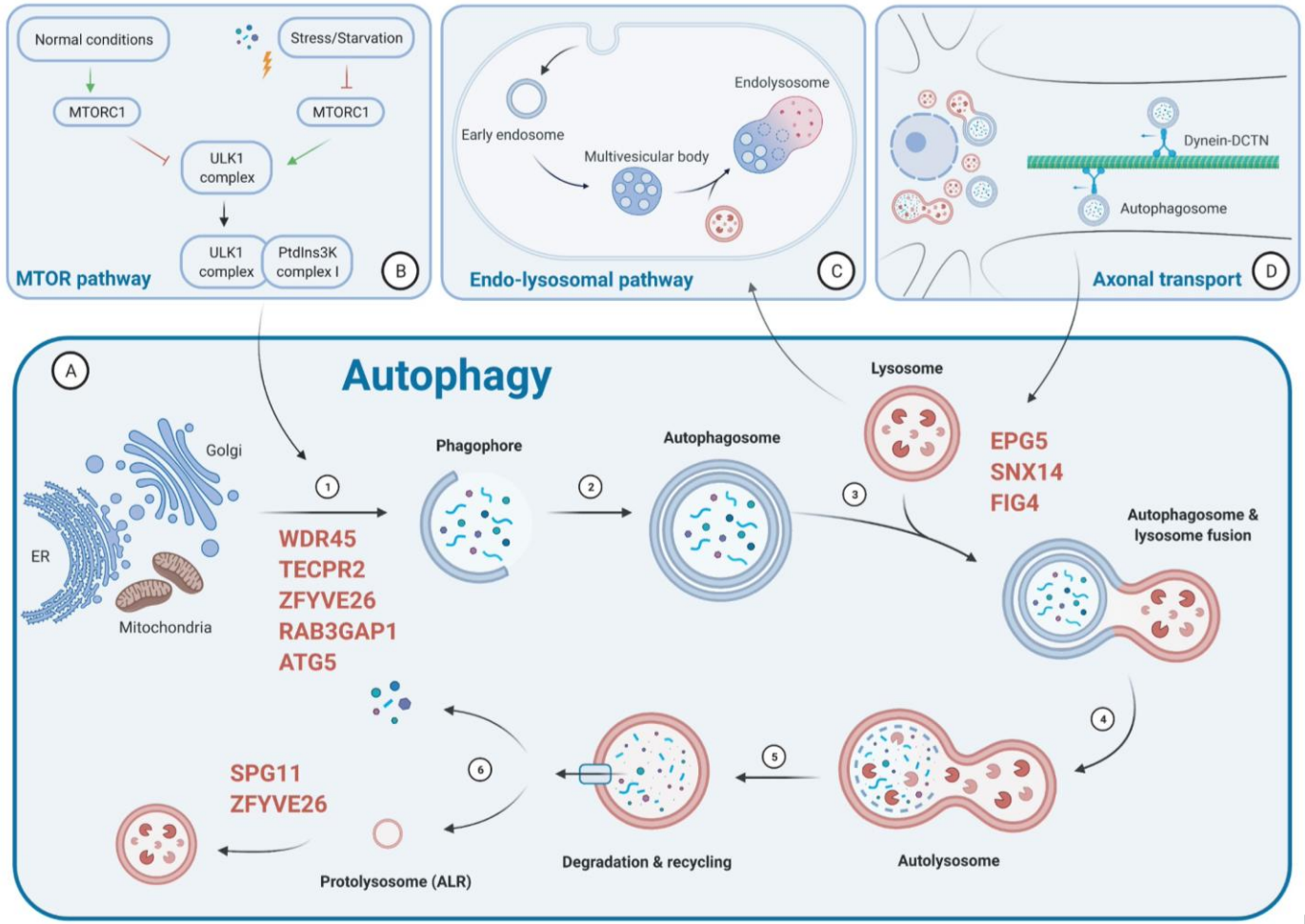
AUTOPHAGY DEFECTS AS **PRIMARY CAUSE OF THE DISEASE**



Deneubourg et al., Autophagy 2022

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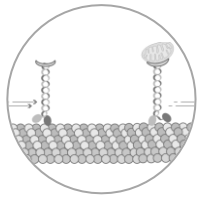

AUTOPHAGY DEFECTS AS **UNDERLYING ELEMENTS OF PATHOPHYS.**

doi:10.1093/brain/awab161 BRAIN 2021: 144; 2610–2615 | 2610

BRAIN
UPDATE

HOPS-associated neurological disorders (HOPSANDs): linking endolysosomal dysfunction to the pathogenesis of dystonia

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Article

SOURCE DATA | TRANSPARENT PROCESS | OPEN ACCESS | CHECK FOR UPDATES

EMBO Molecular Medicine

Unraveling autophagic imbalances and therapeutic insights in Mecp2-deficient models

Alessandro Esposito[1✉], Tommaso Seri[1], Martina Breccia[2], Marzia Indrigo[1], Giuseppina De Rocco[1,2], Francesca Nuzzolillo[3], Vanna Denti[4], Francesca Pappacena[1], Gaia Tartaglione[1], Simone Serrao[4], Giuseppe Paglia[4], Luca Murru[5], Stefano de Pretis[6], Jean-Michel Cioni[1], Nicoletta Landsberger[1,2], Fabrizia Claudia Guarnieri[1,5✉] & Michela Palmieri[1,3✉]

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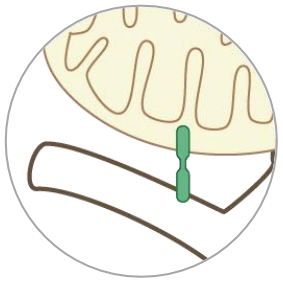
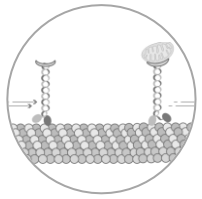
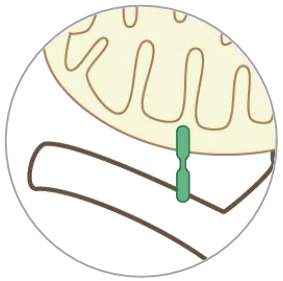
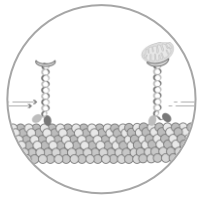




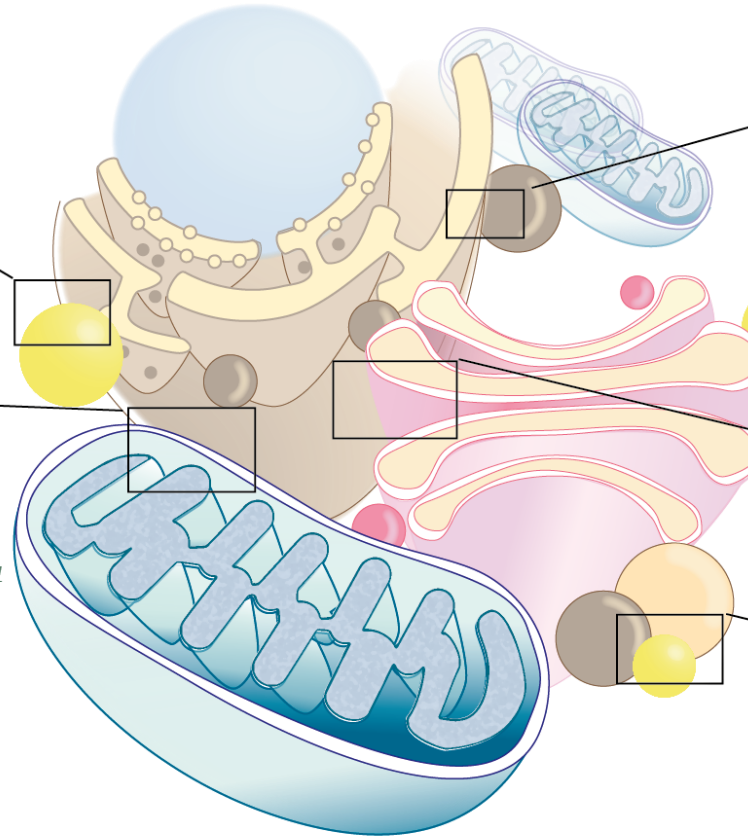
MEMBRANE CONTACT SITES

Not membrane trafficking strictly, but crucial for communcation





MEMBRANE CONTACT SITES



ER-Lipid droplet:
-Spastic Paraparesis *BSCL2* (Seipin) (*), *REEP1* and *ATL1* (Atlas-tin-1)

ER-Mitochondria
-Amyotrophyc Lateral Sclerosis: *TARDBP*, alpha1 receptor, VAPB, *SigR1*
-Alzheimer's Disease: Presenilin, alpha-synuclein
-Spastic Paraparesis: *REEP1*, *SigR1*
-Chorea-Acanthocytosis: *VPS13A*
-CMT: *MFN2*, alpha-synuclein
-GM1 gangliosidosis
-Parkinson's Disease: *VDAC1*
-Epileptic encephalopathy: *PACS2*

ER-Endosome:
-Parkinson Disease: *VPS13C*

Lipid droplet-peroxisomes
-Spastic Paraparesis: Spastin (*SPAST*), *ABCD1* (ATP-binding cassette sub-family D member 1)

ER-Golgi (TGN):
-Amyotrophyc Lateral Sclerosis: *VAPB*
-Intellectual disability: *CERT1*

Endosome-Lysosome-Lipid droplet:

VPS13A and VPS13C bind to the ER, tethering it to mitochondria (VPS13A), to late endosome/ lysosomes (VPS13C) and to lipid droplets (both VPS13A and VPS13C).

Choreoacanthocytosis: *VPS13A*
Parkinson's Disease: *VPS13C*

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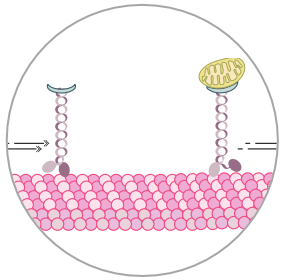

TRANSPORT ALONG THE CYTOSKELETON

Not an IMD *per se*, but probably will fall in the category in the future

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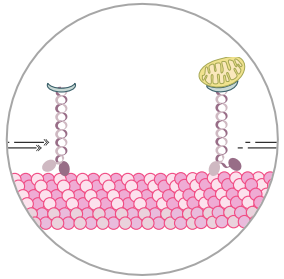
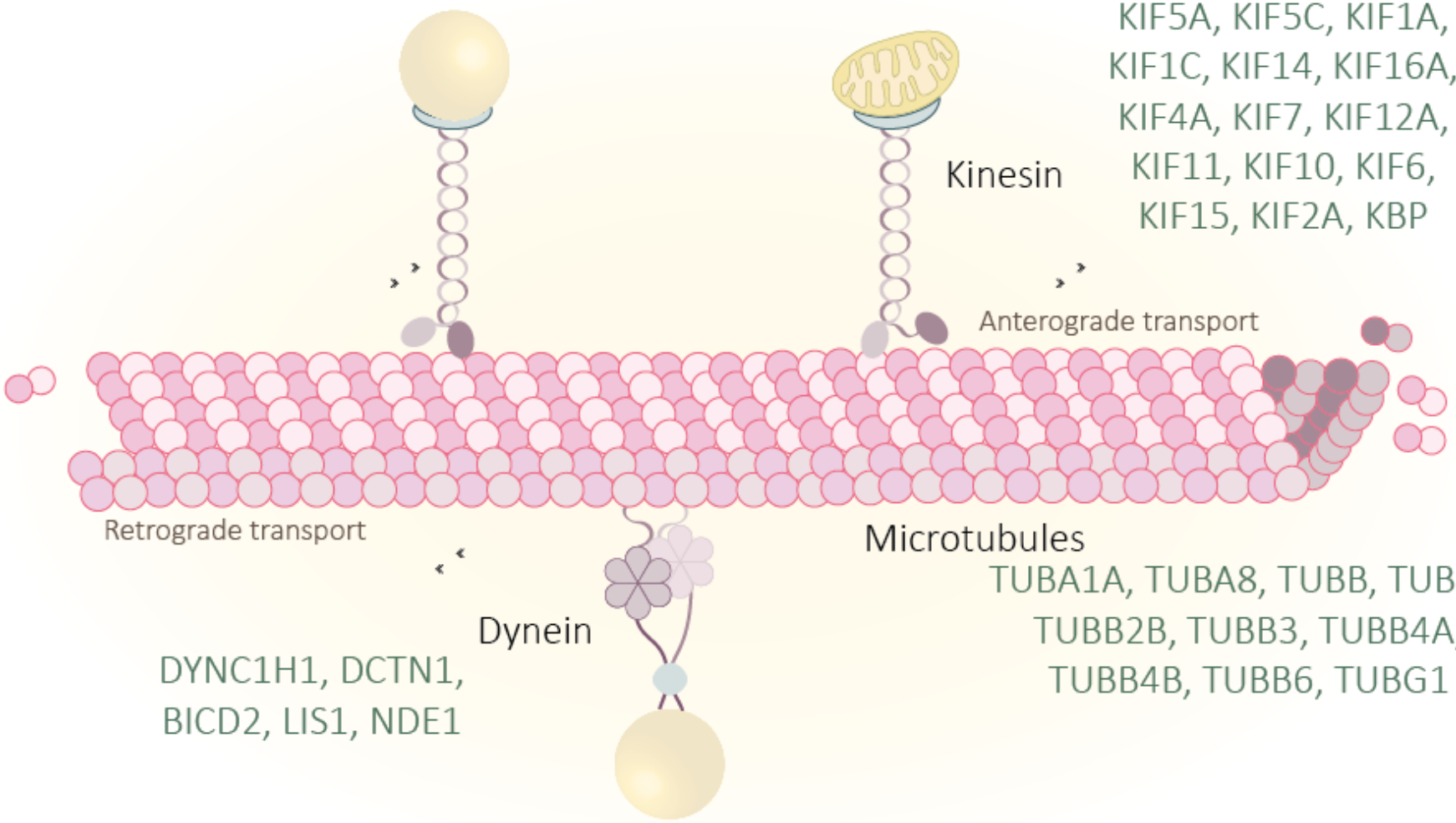
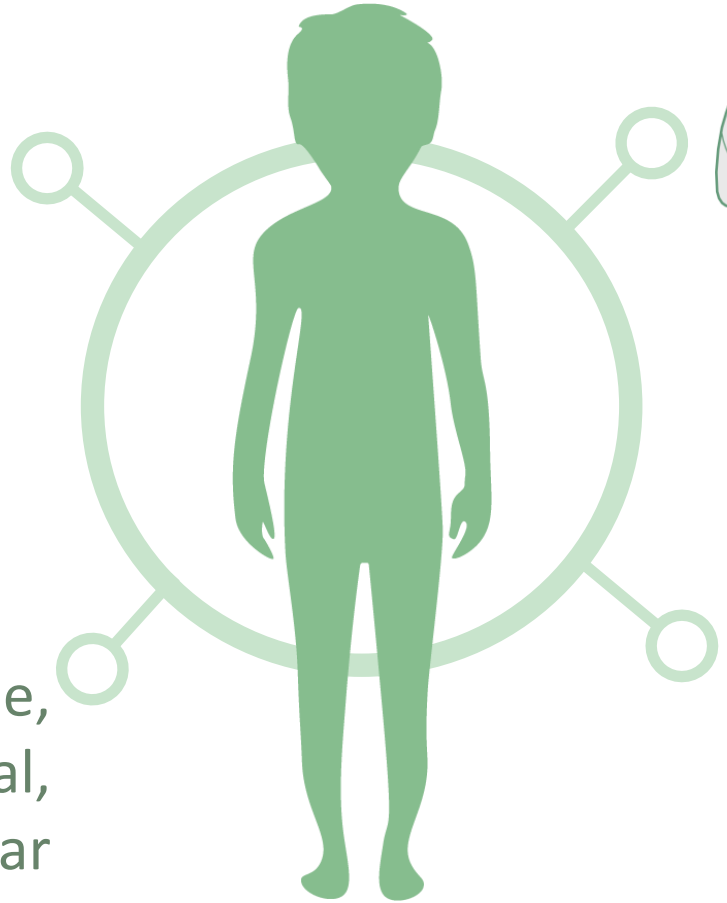


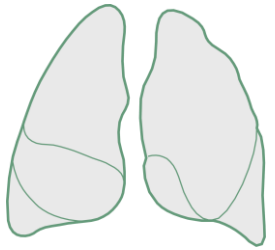
TRANSPORT ALONG THE CYTOSKELETON



Nervous system

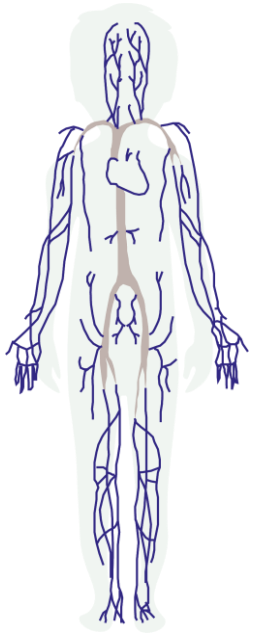
CNS development
Neuronal homeostasis
Synaptic communication





Respiratory system

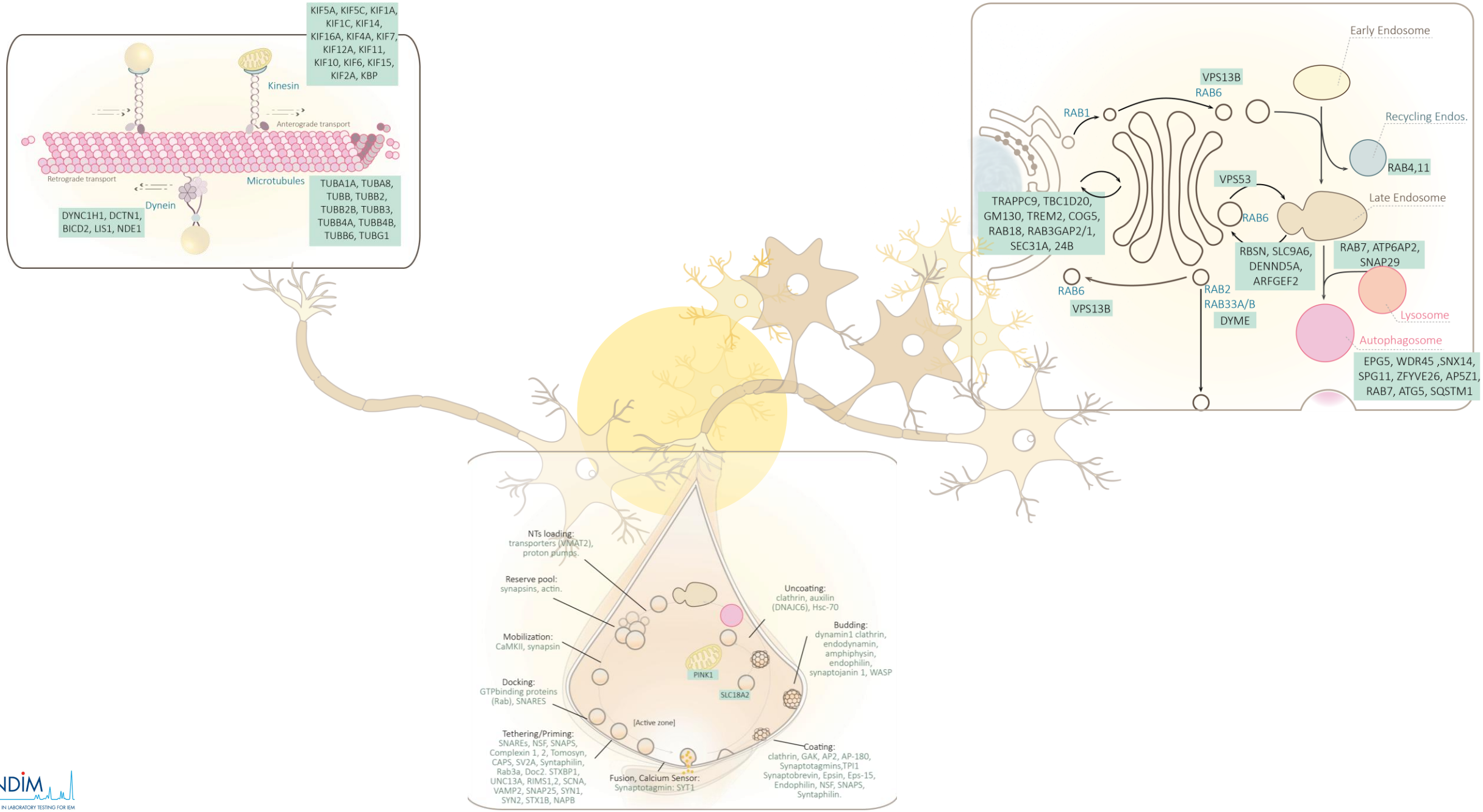
Mucociliary clearance



Blood + immune system

Haematopoiesis
Cytokine release
Pathogen removal

Endocrine, musculoskeletal, cardiovascular ....



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CELL TRAFFICKING

Cell trafficking is essential for cell function and represents a growing disease category

All cell trafficking processes are interconnected

Studying the cellular basis of cell trafficking is critical to understand their pathophysiology and define new treatments

Autophagy is a promising therapeutic target for these and other disorders

ERNDIM Symposium 2025

Cell trafficking and autophagy in neurometabolic disorders

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