



Lipid droplet assembly: From nucleation to budding

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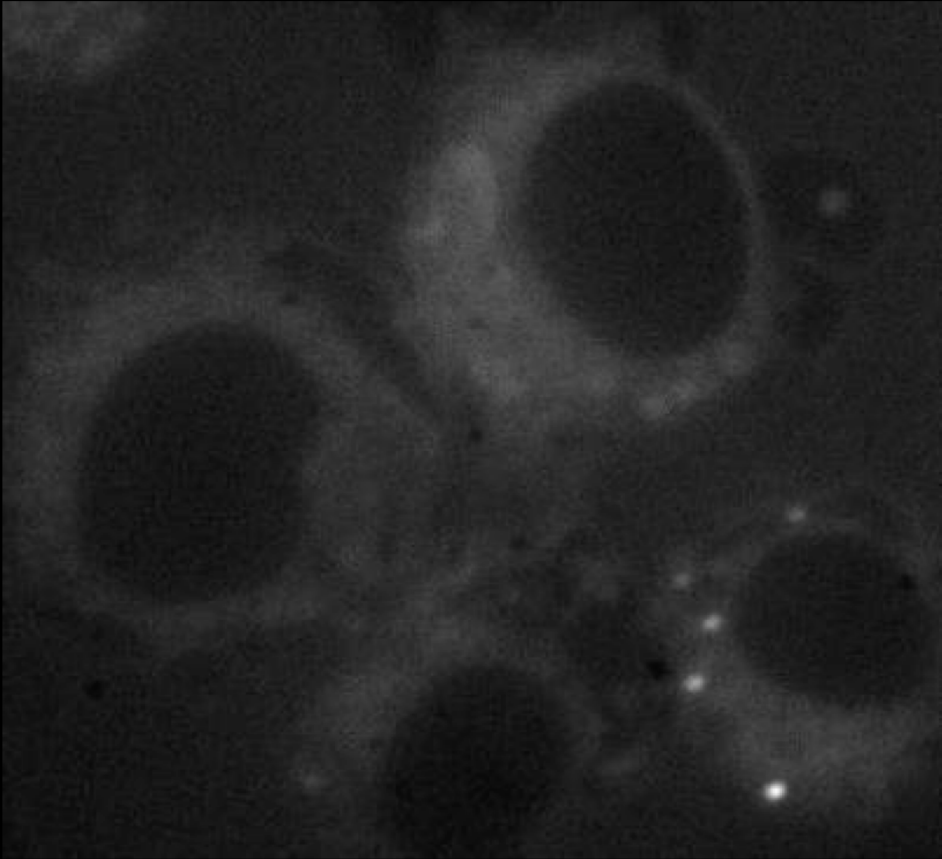
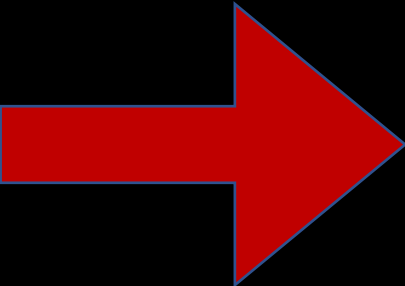
Laboratoire de Physique



Lipid Droplets form in energy excess or stress conditions

excess energy stored

INTAKE

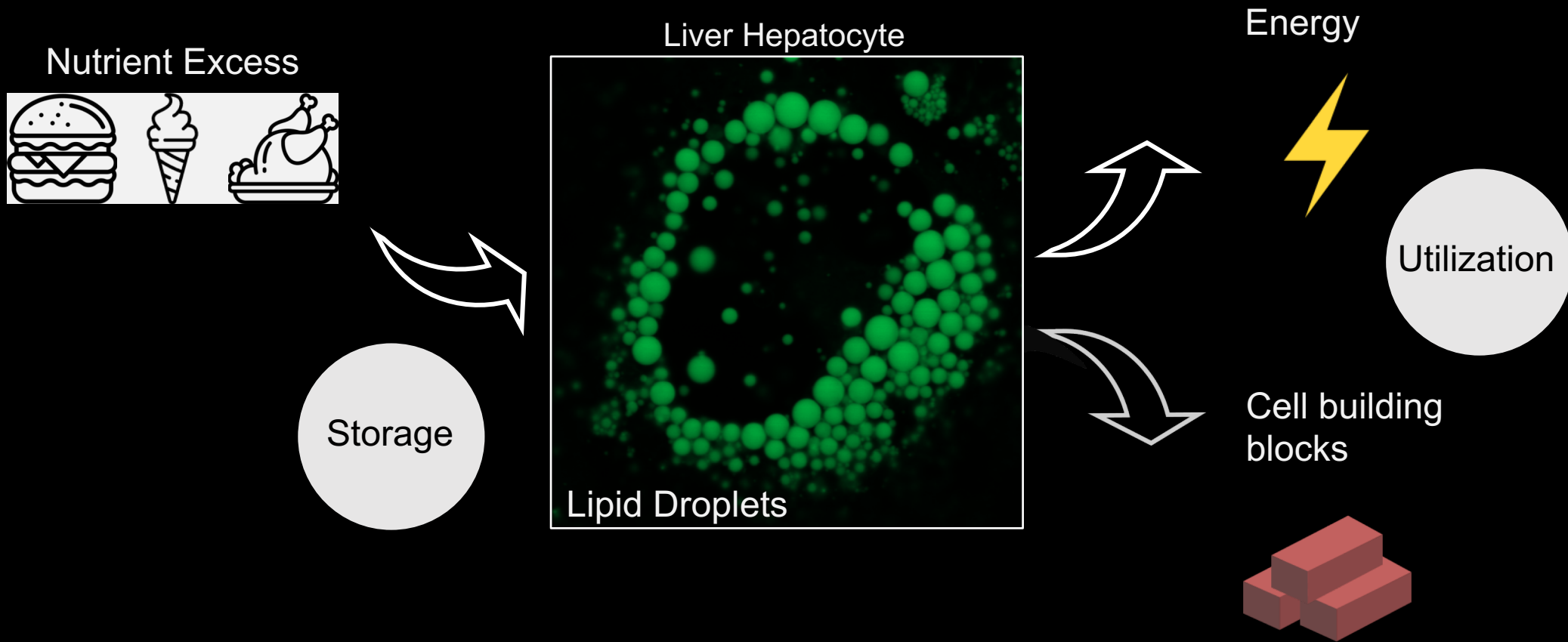


EXPENDITURE

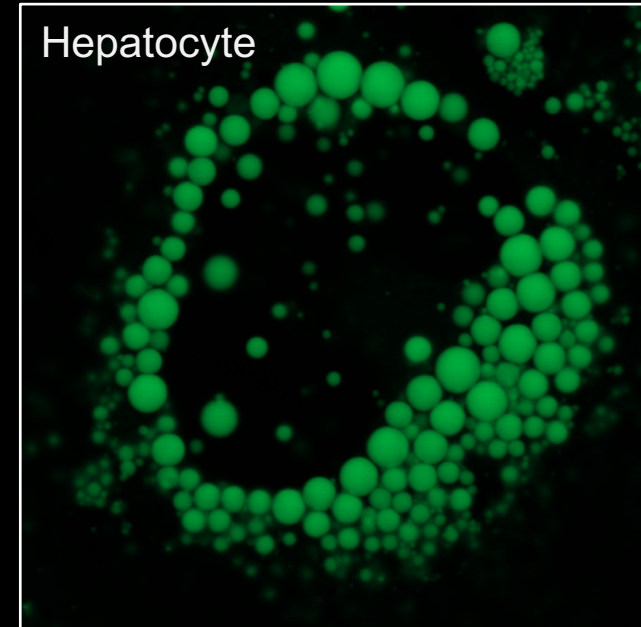
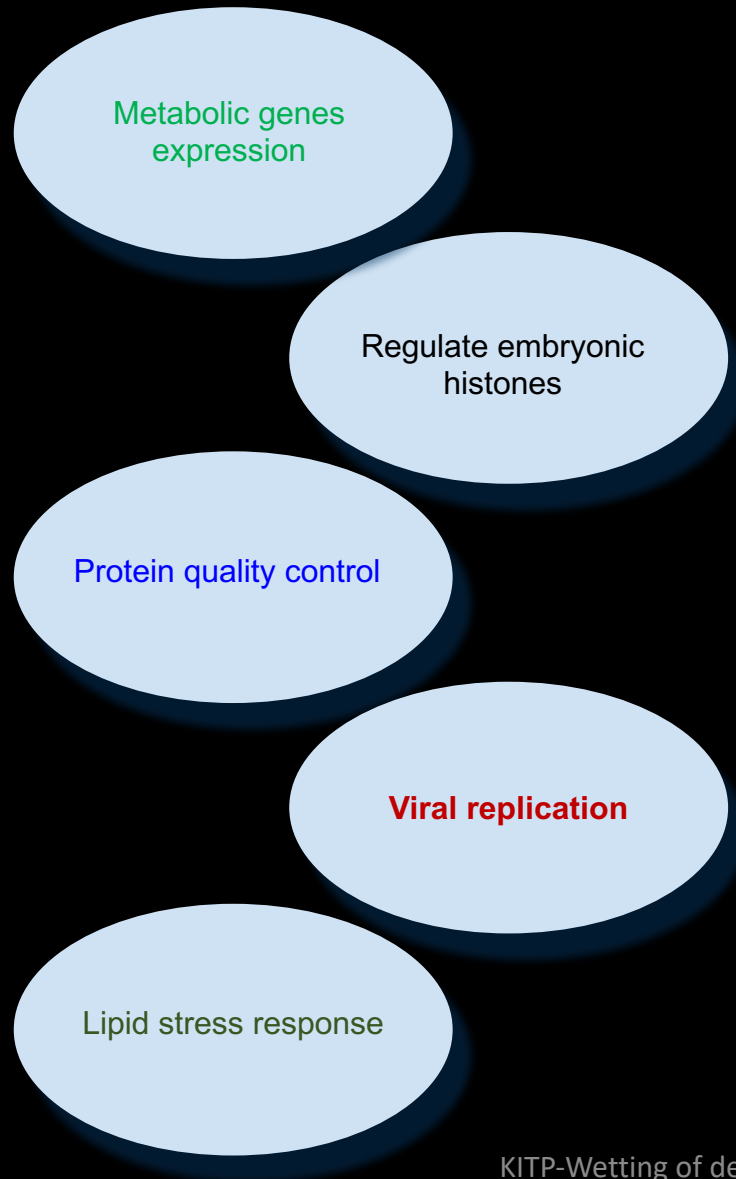


Lipid Droplets

Lipid droplets are at the nexus of cellular energy metabolism

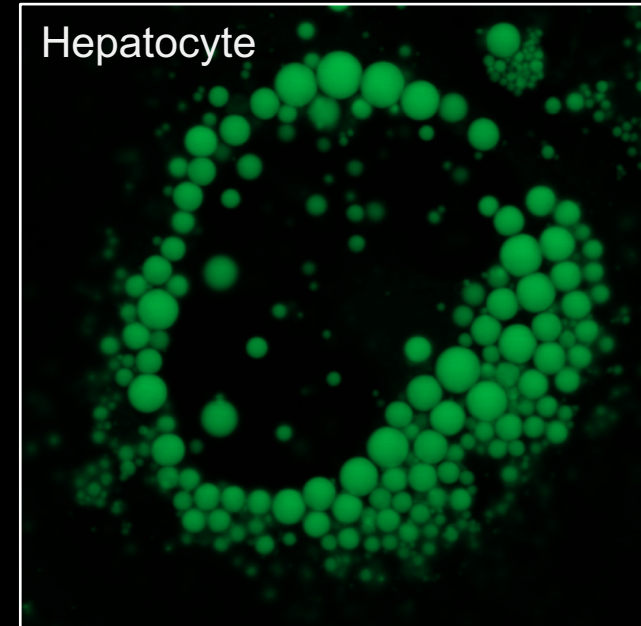
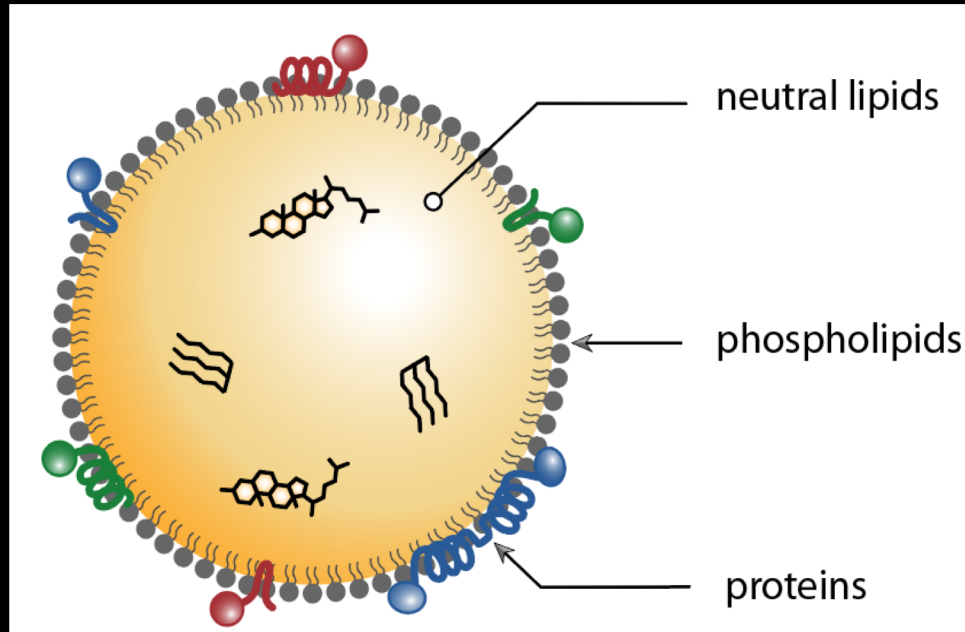


Lipid droplets have several non-metabolic functions

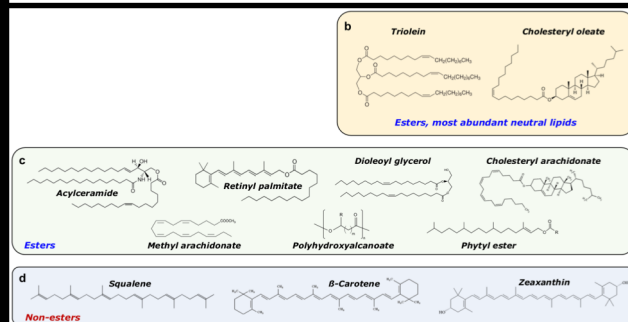


Cellular Lipid Droplets

Lipid droplet structure



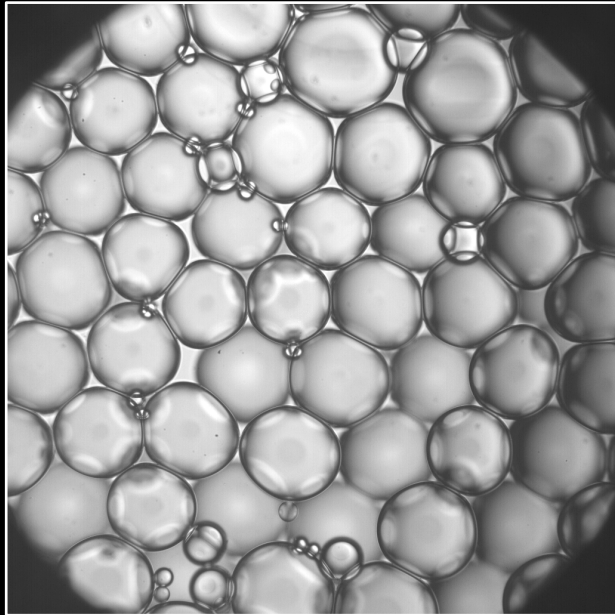
Cellular Lipid Droplets



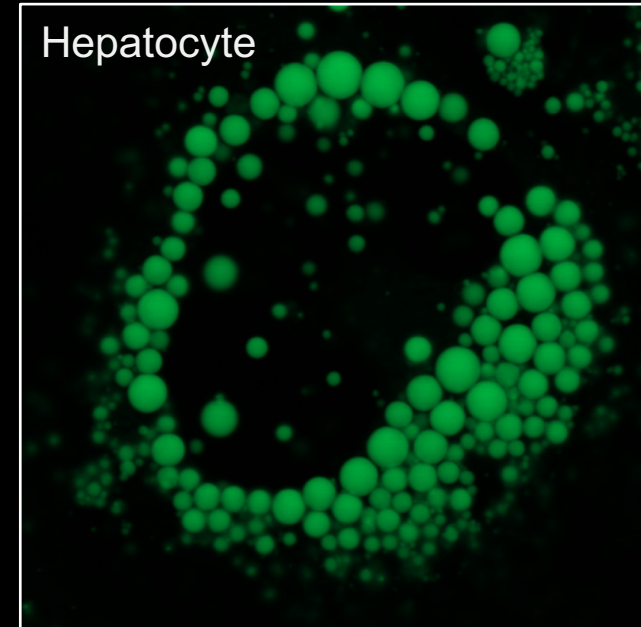
Thiam & Ikonen TCB 2020

KITP-Wetting of deformable sheets, June 17th 2021

Lipid droplets are intracellular emulsion droplets



Artificial Oil Droplets



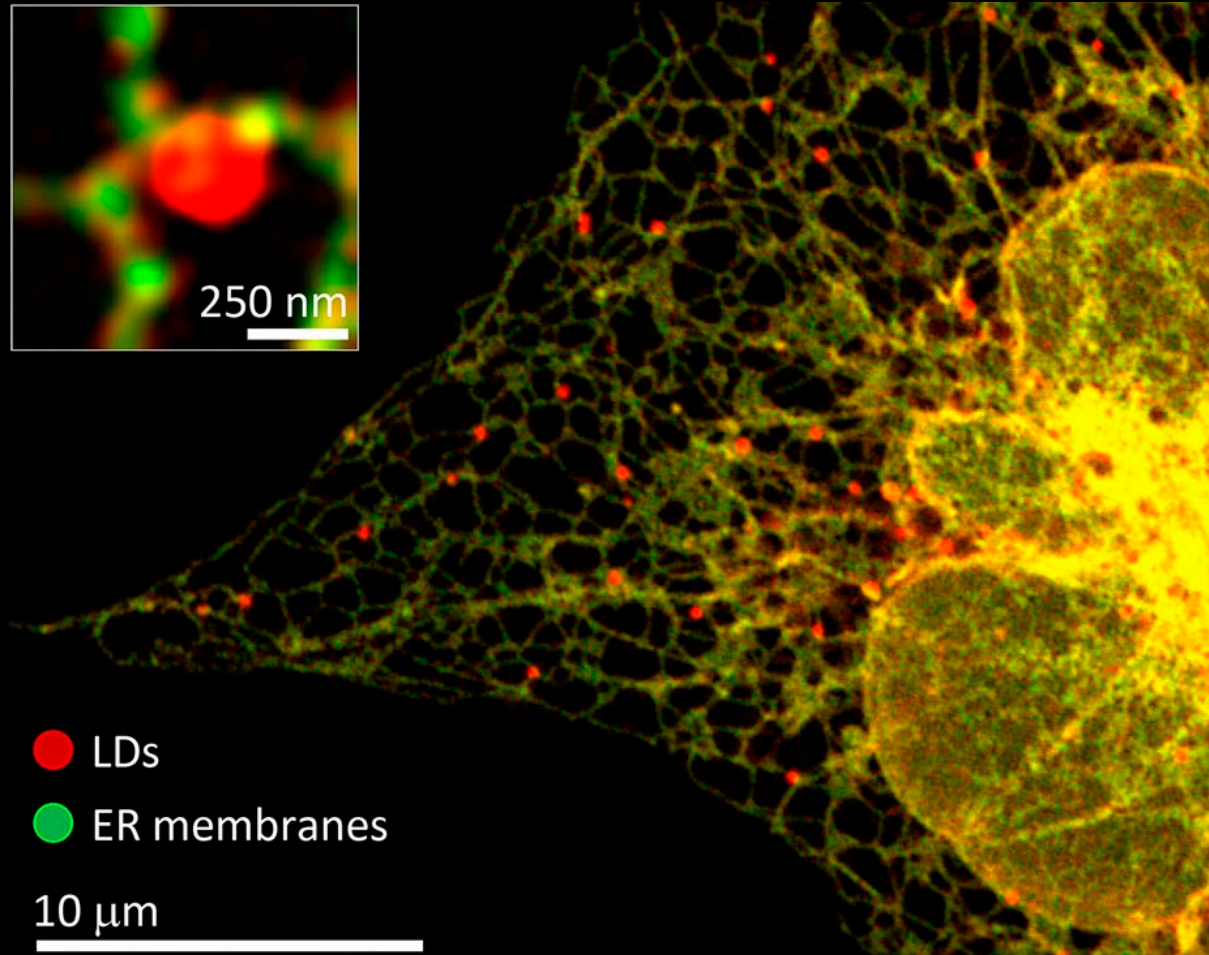
Cellular Lipid Droplets



Virtually all organisms make droplets

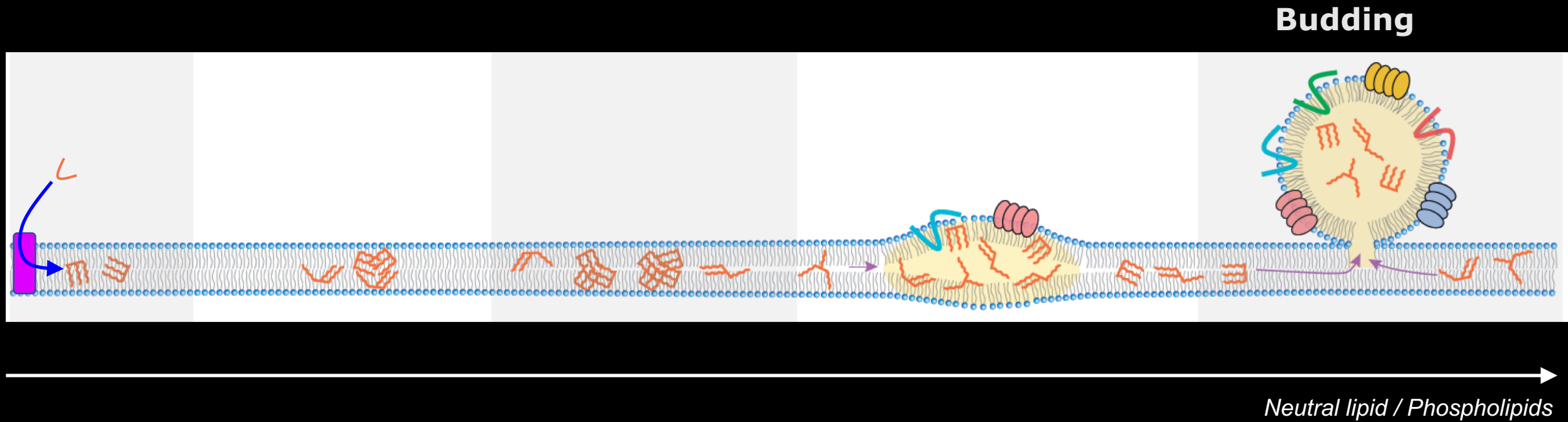
How lipid droplets form is being thoroughly prospected

Lipid droplets form at the endoplasmic reticulum



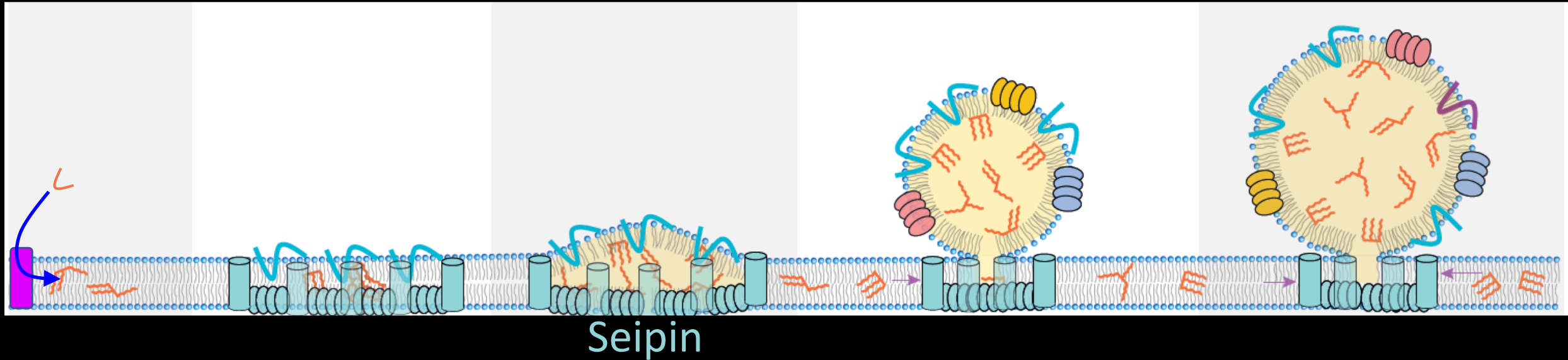
Pol et al. 2014 JCB

Lipid droplets likely assemble by a phase separation process



Thiam & Ikonen TCB 2020
Thiam & Foret BBA, MCBL, 2016

Seipin controls lipid droplet biogenesis



Salo et al. Dev Cell 2019
Chung et al. , Dev Cell 2019
Santinho et al. Curr Biol 2020
...
Prasana et al. Plos Biol 2021,
Zoni et al. PNAS 2021

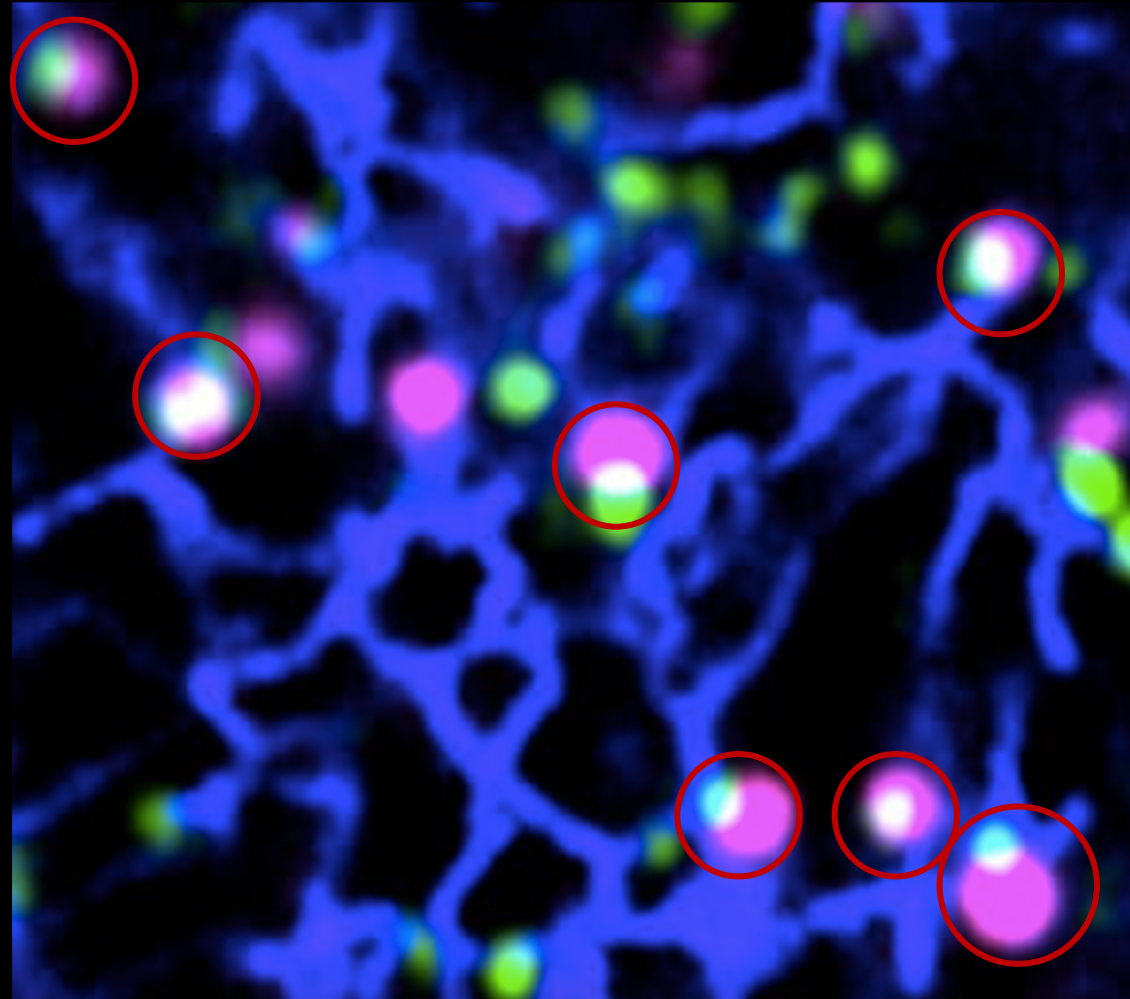
Thiam & Ikonen TCB 2020
Thiam & Foret BBA, MCBL, 2016

Seipin is at the junction of LDs and the ER

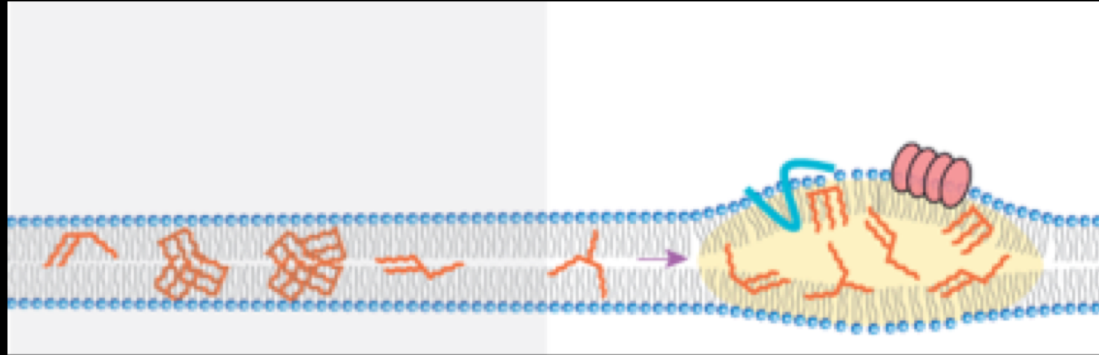
Seipin

Endoplasmic reticulum

Lipid droplet

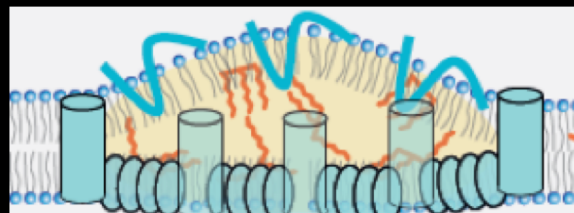


Salo et al. 2019, Dev cell



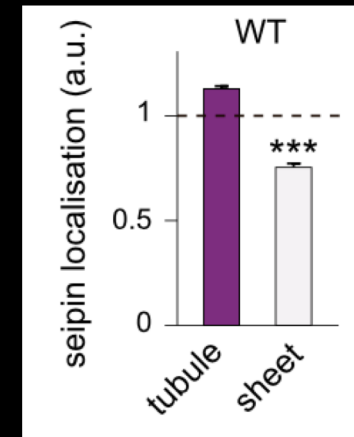
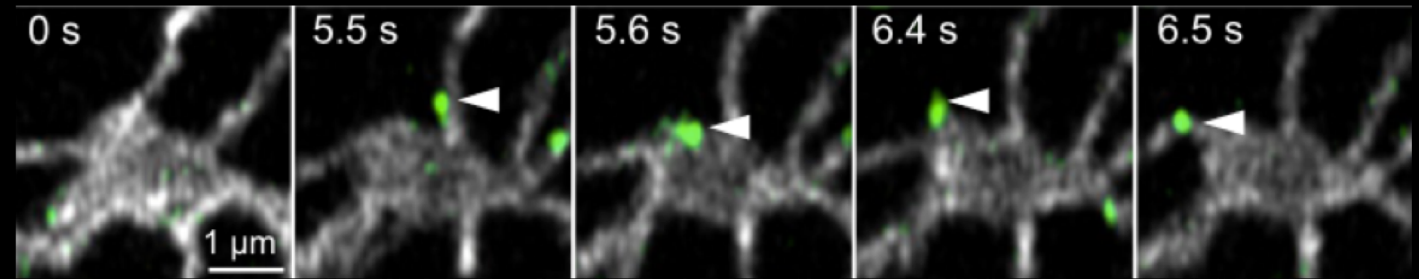
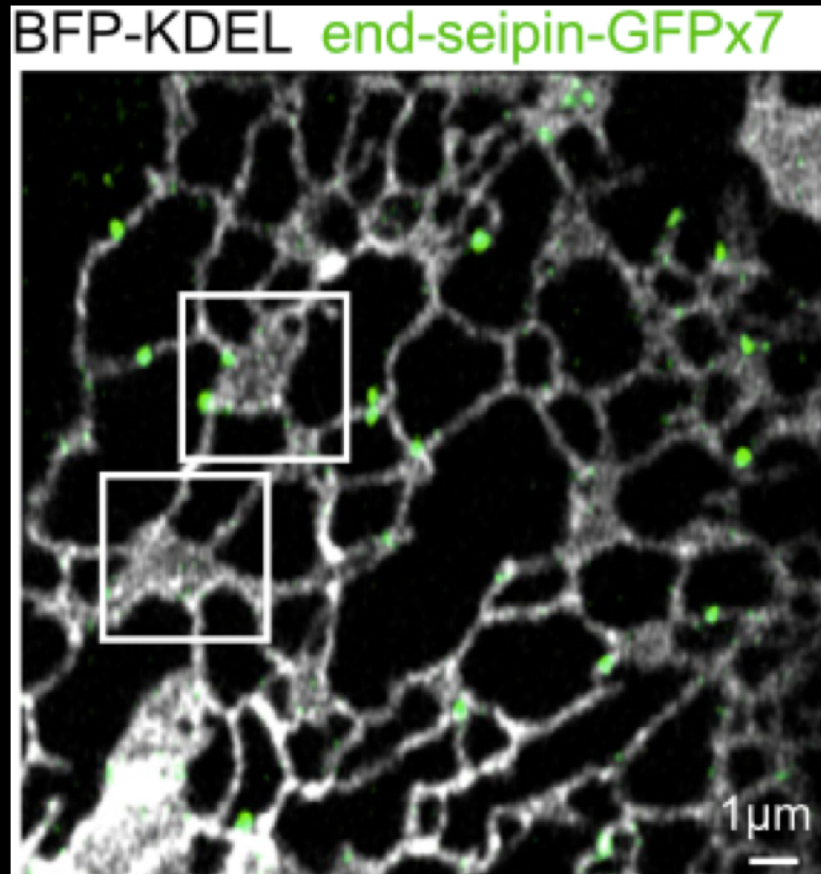
How is the phase transition triggered ?

Lipid droplets appear on tubules



Seipin

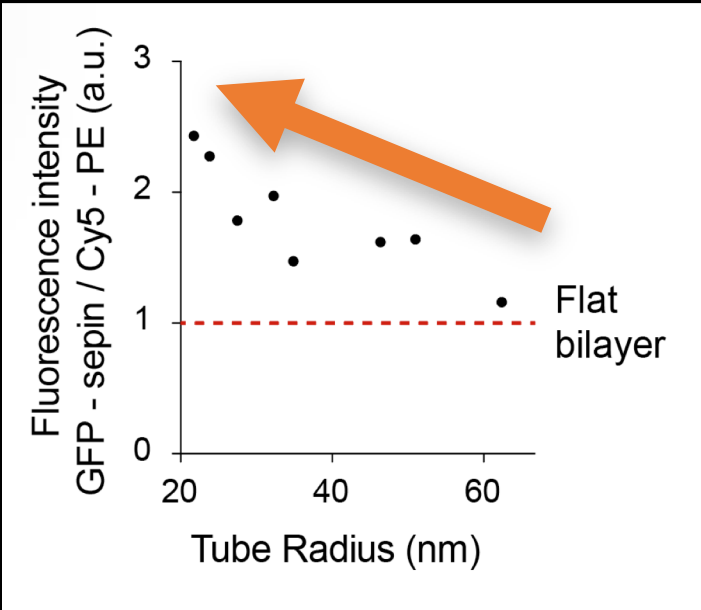
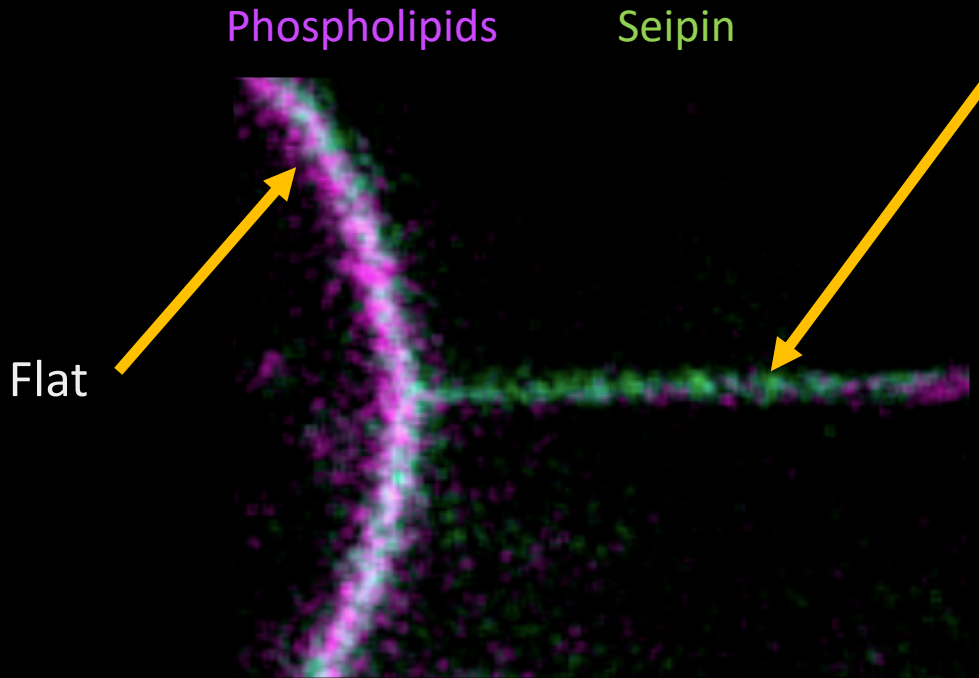
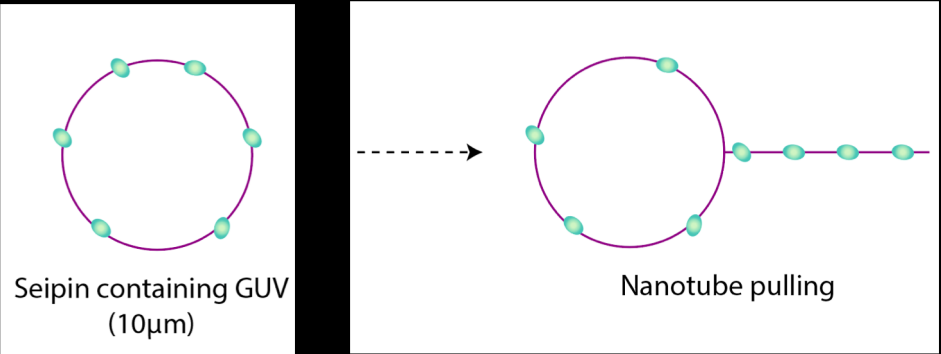
Seipin freely diffuses at the ER bilayer prior LDs form



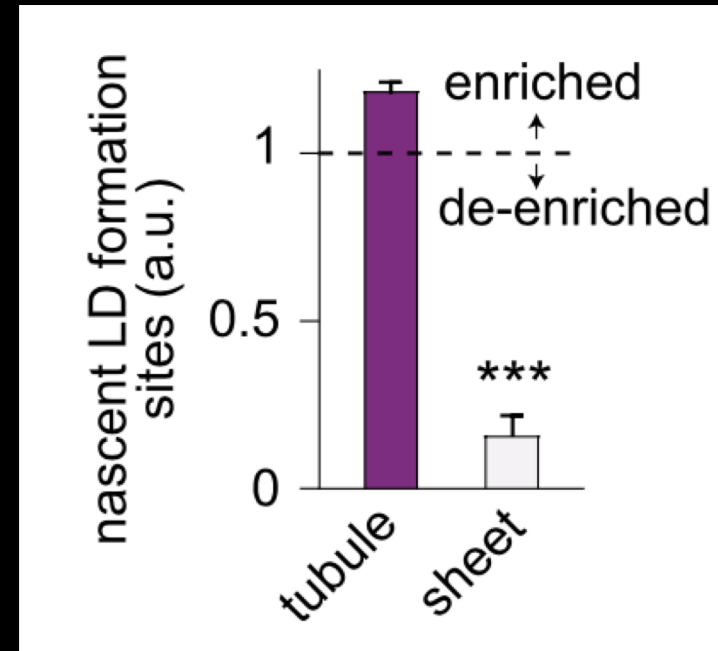
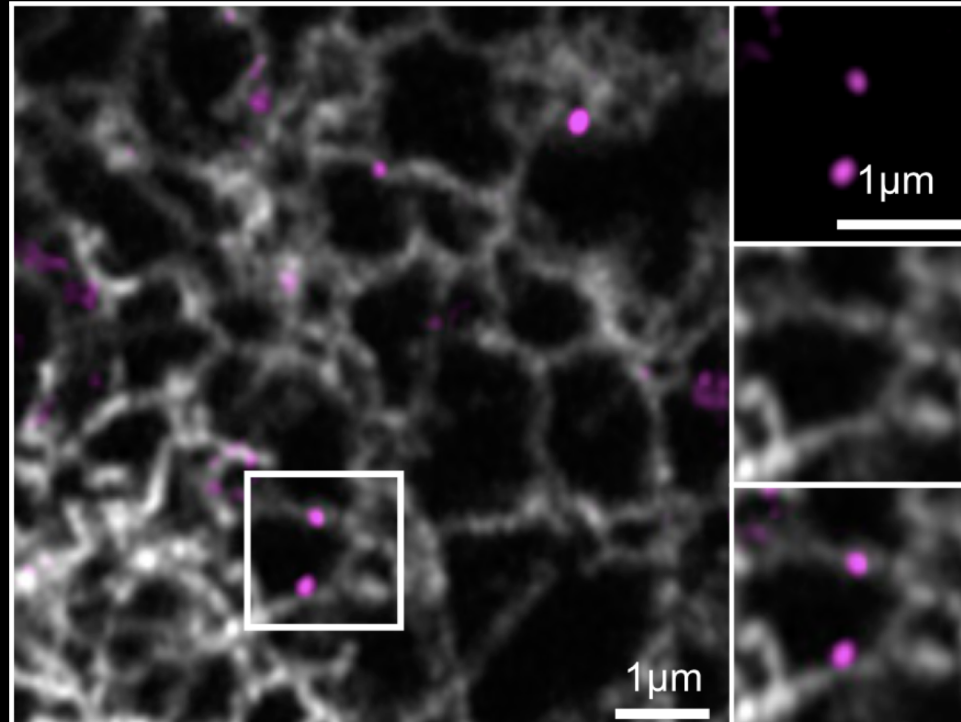
Santinho 2020, Curr Bio

V. Salo, E. Ikonen

Seipin is enriched in tubules by curvature



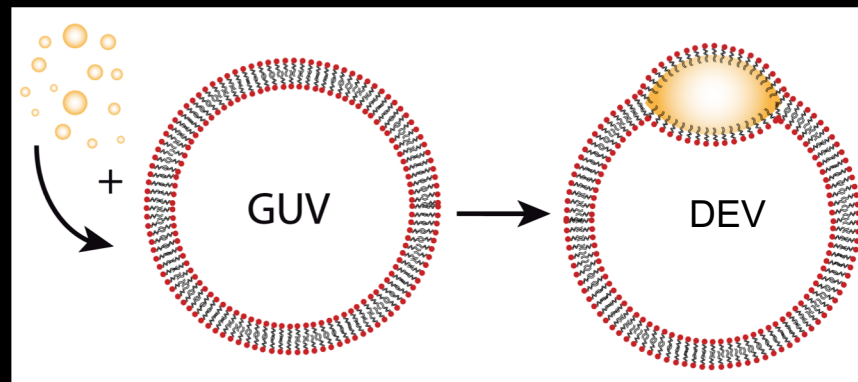
Lipid droplets **still** nucleate at tubules without seipin



Is curvature favoring the neutral lipid condensation?

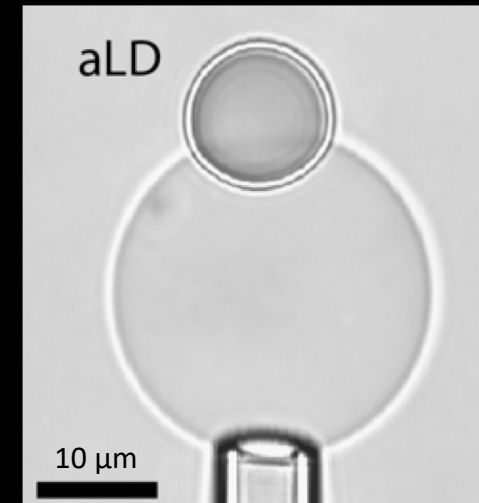
DEVs reproduce droplet-bilayer contiguity

Artificial LDs

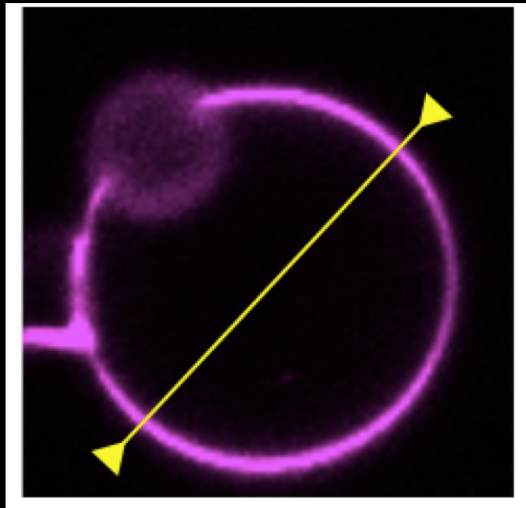


Giant Unilamellar
Vesicle (GUV)

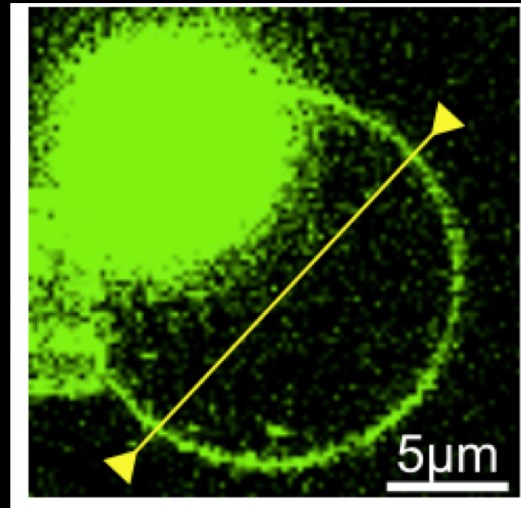
Droplet Embedded
Vesicle (DEV)



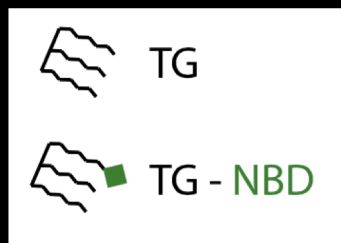
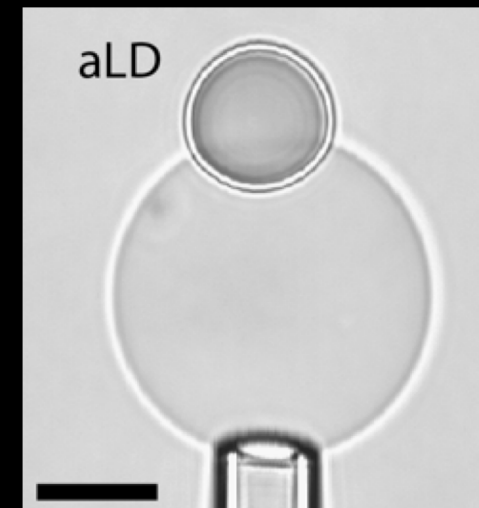
The neutral lipids equilibrate between the bilayer and the droplet



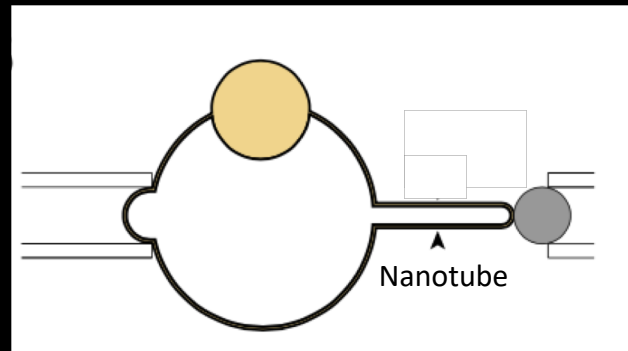
Phospholipids



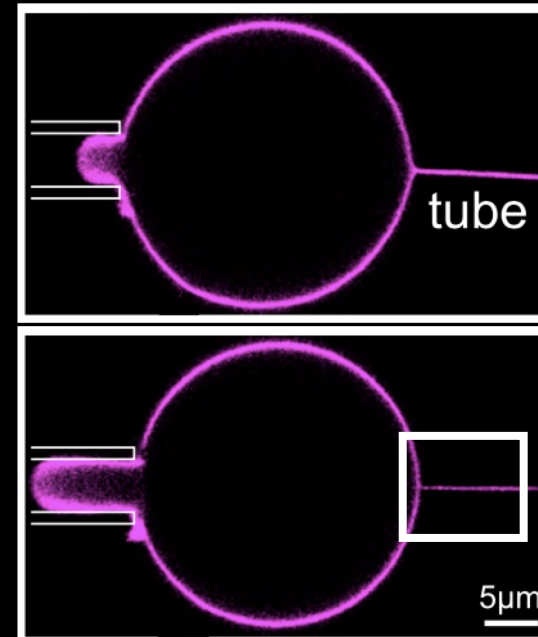
Oil



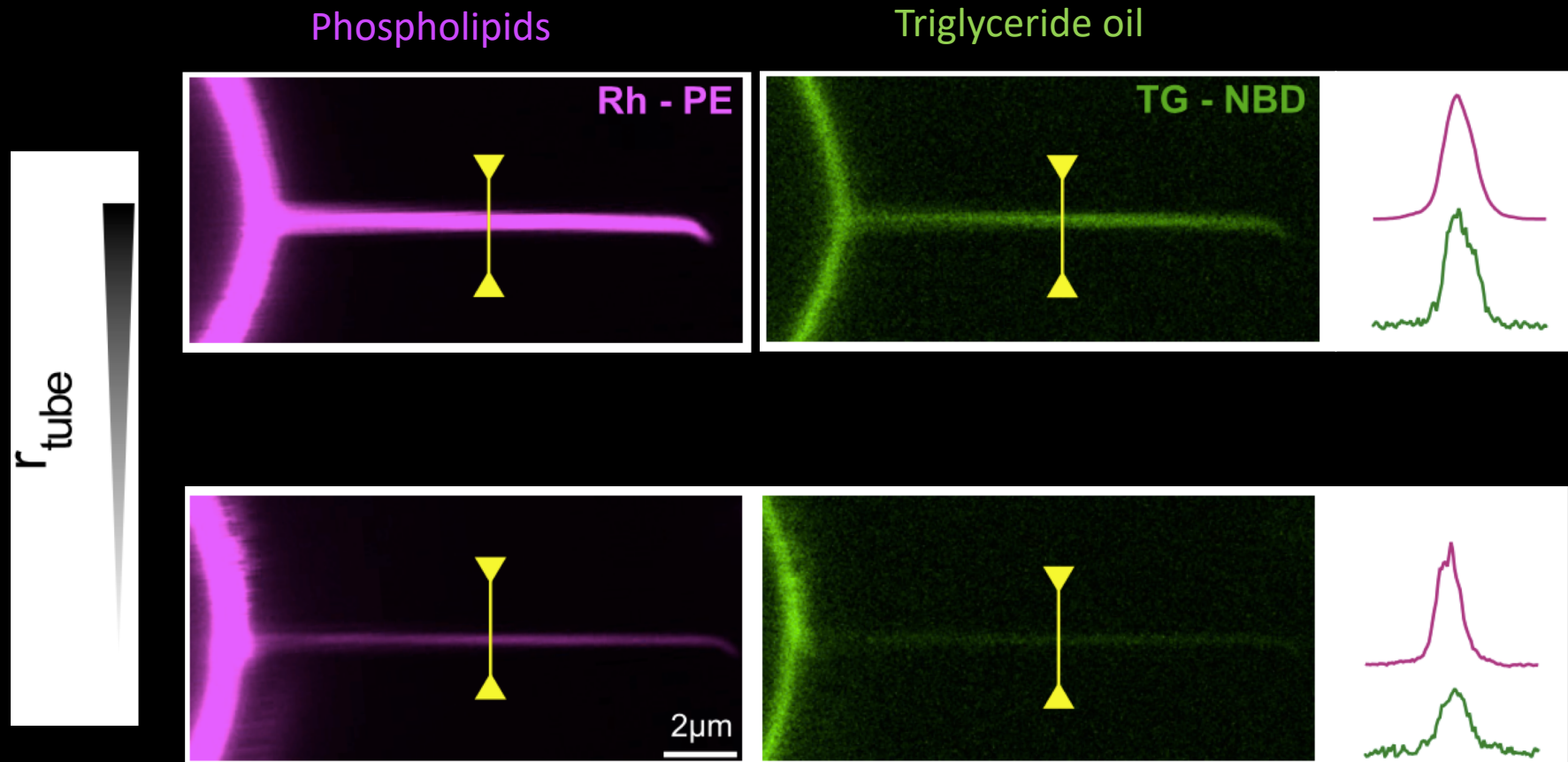
Tubules can be pulled out of DEVs



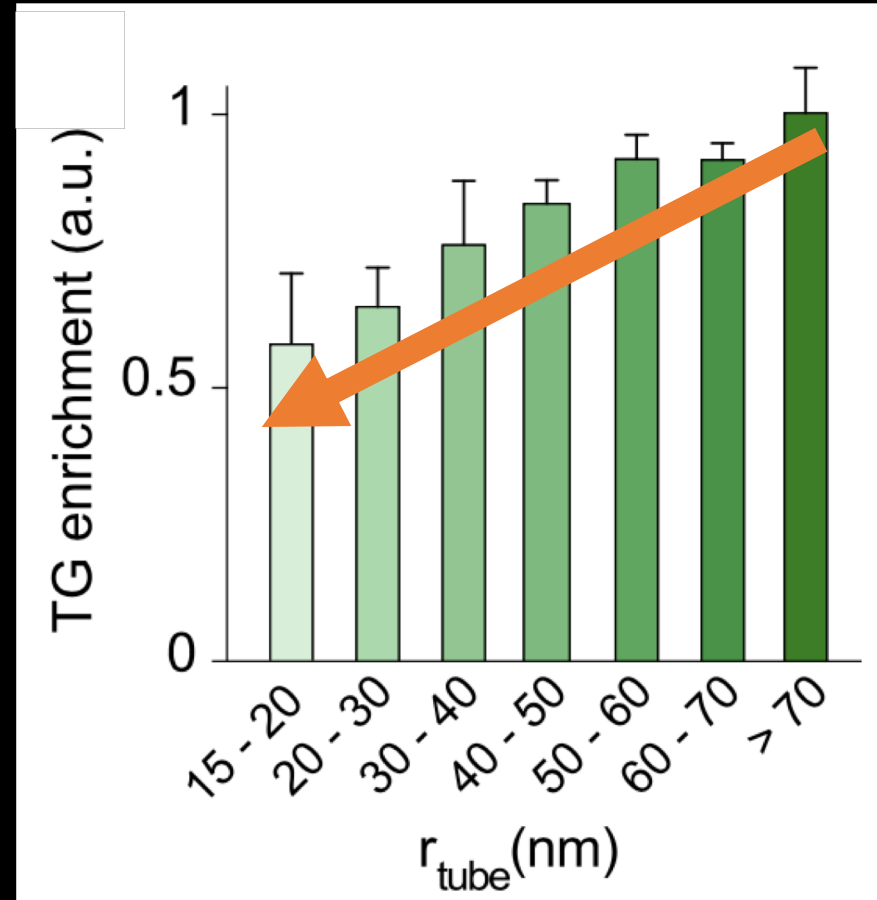
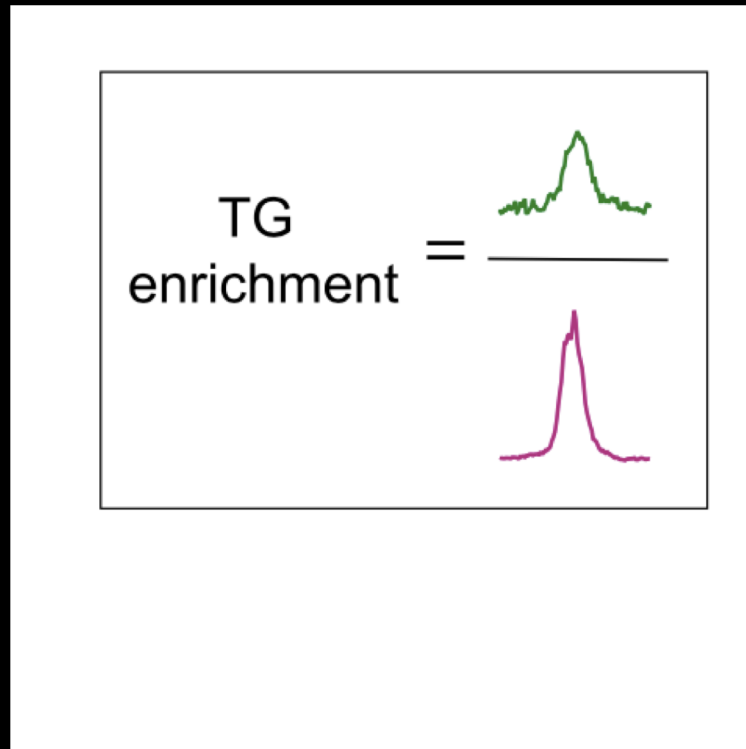
Phospholipids



Determining the impact of curvature on the neutral lipid level



Triglycerides are excluded from tubules by curvature

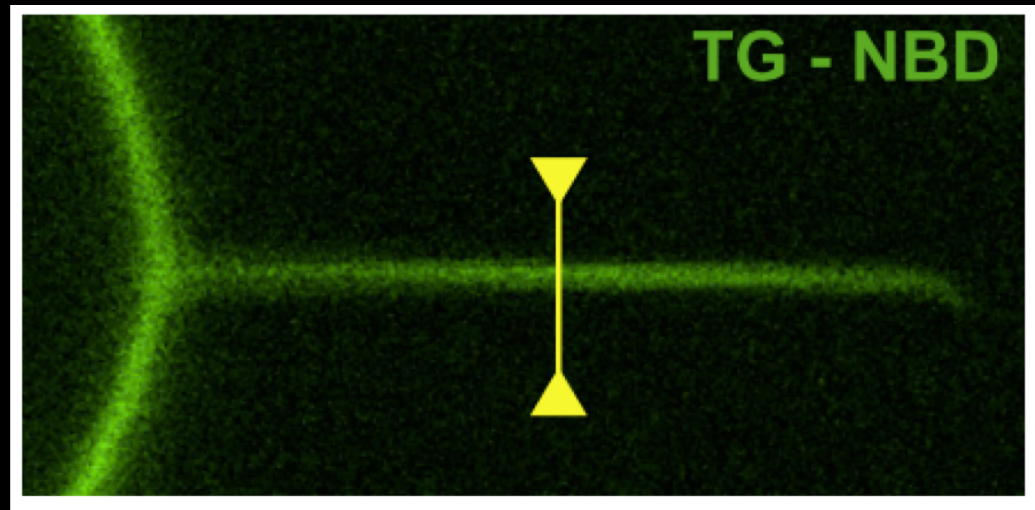


Determining the impact of curvature on the neutral lipid level

Triglyceride oil

Flat

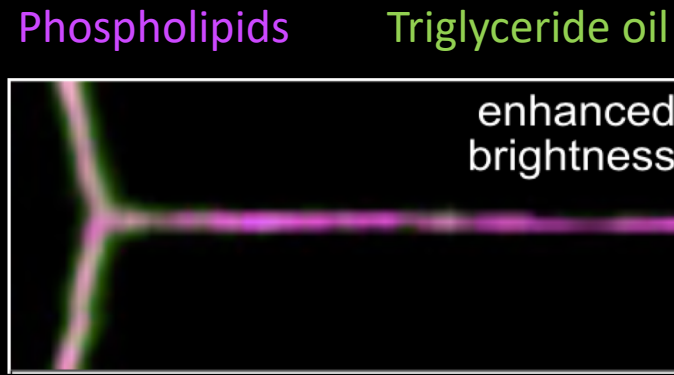
Low chemical
potential



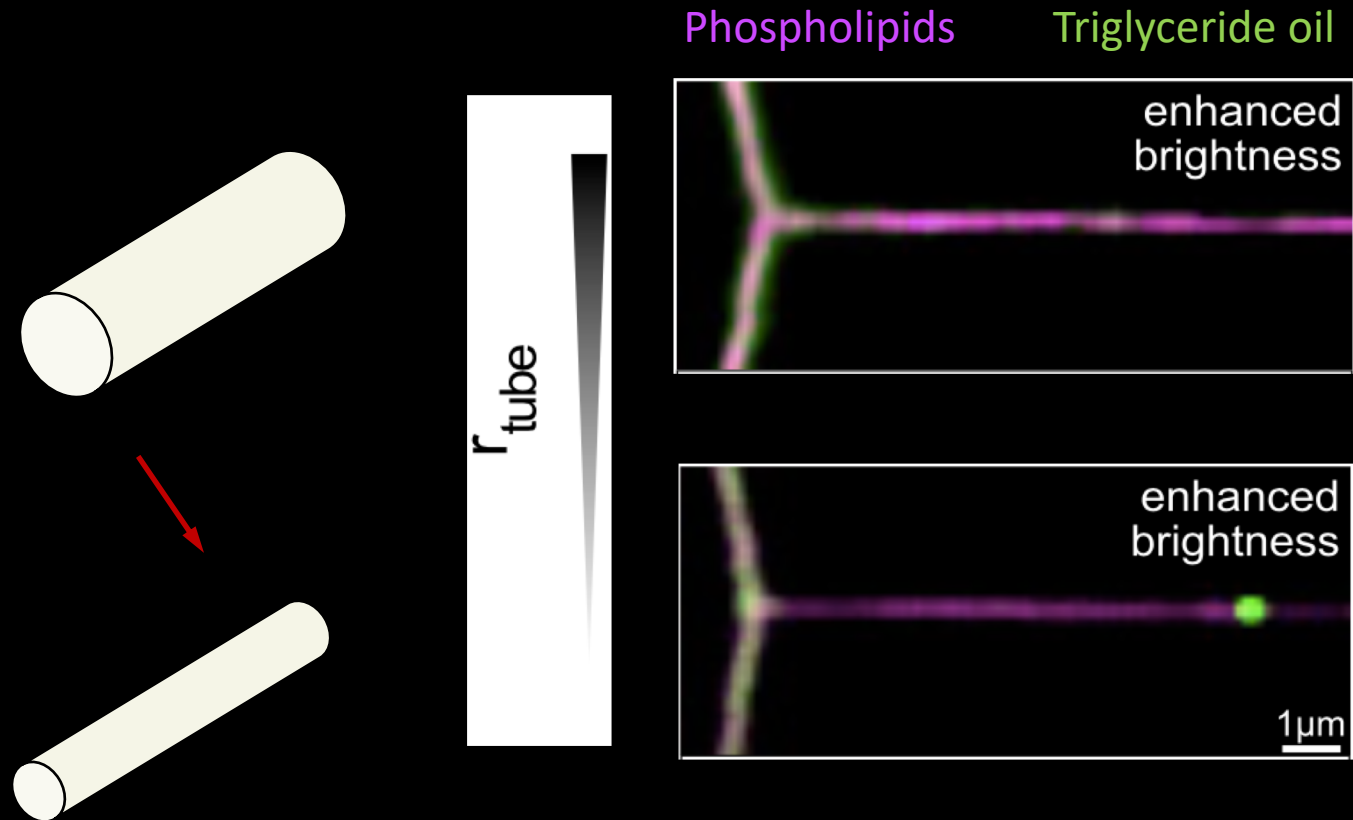
Curved

High chemical
potential

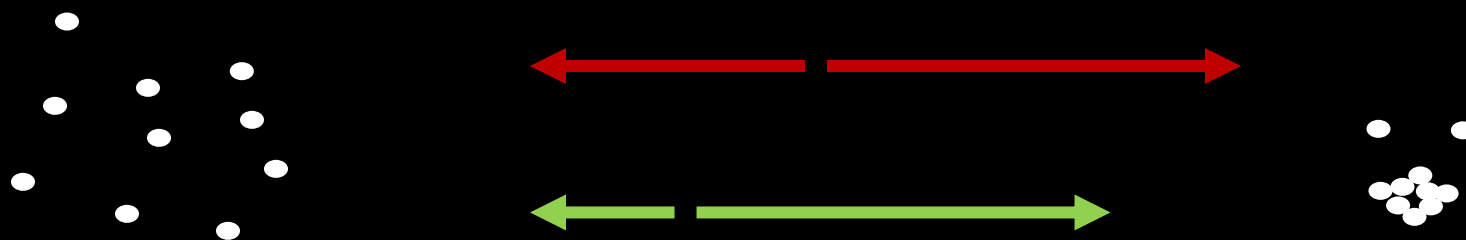
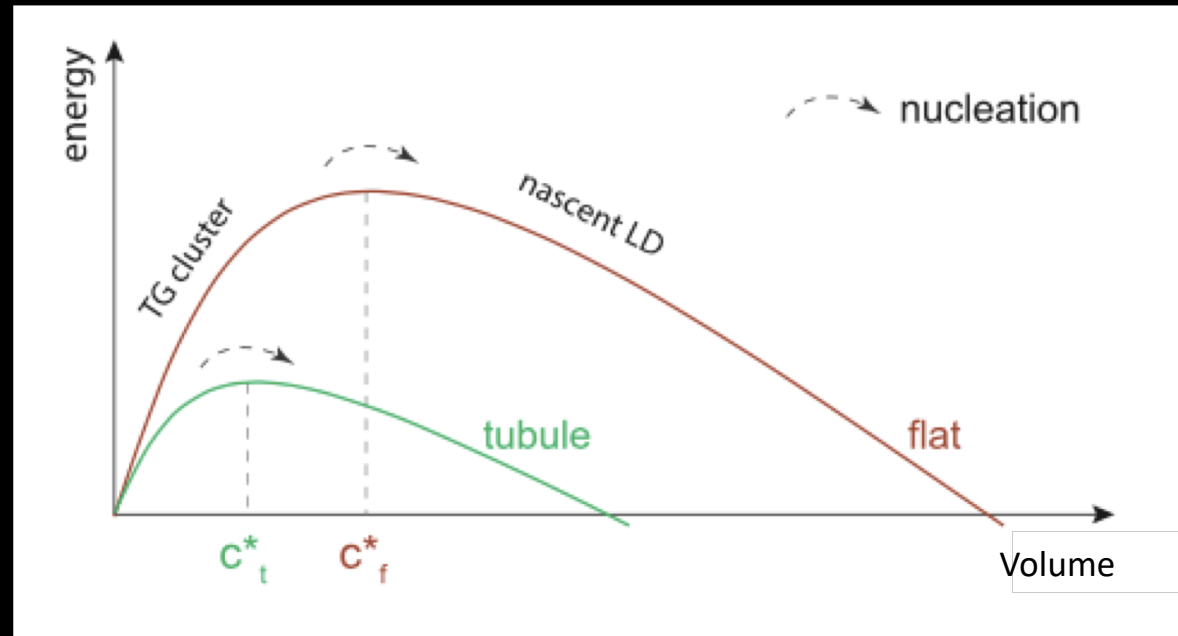
TGs remain independent in tubules connected to flat membranes



Triglycerides condense in tubules upon a rapid radius decrease

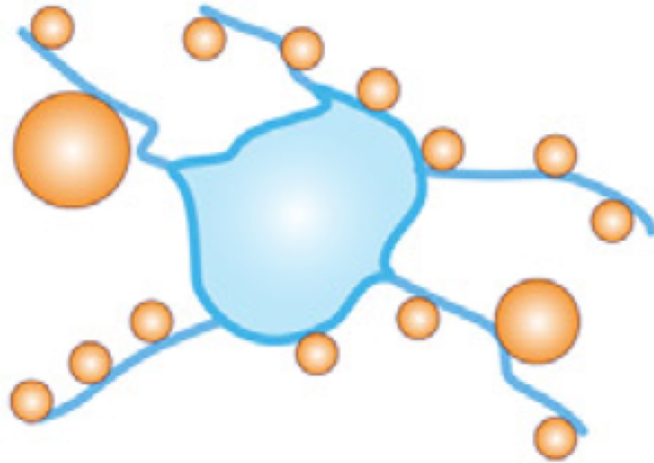


Basic principles of phase separation phenomena applied to LDs

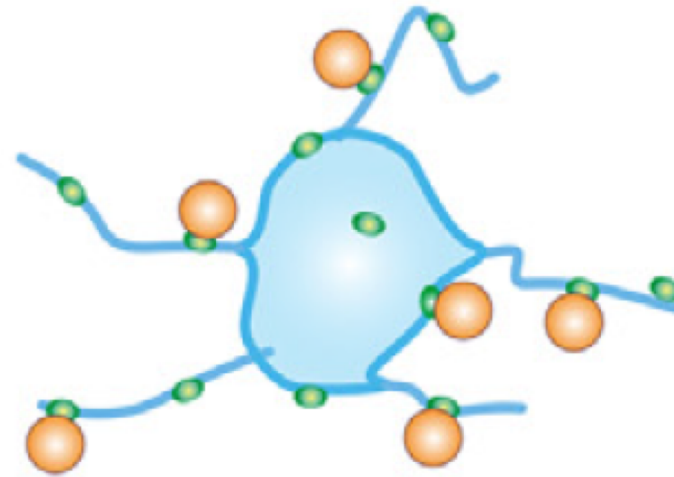


Working model

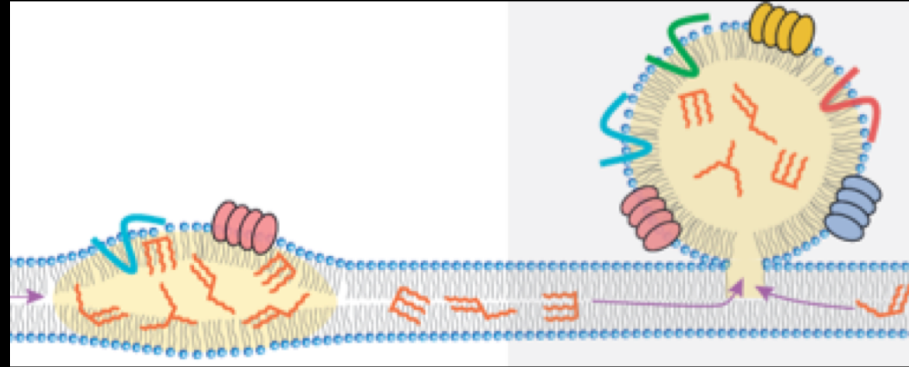
Lipid droplet nucleation events



- Seipin

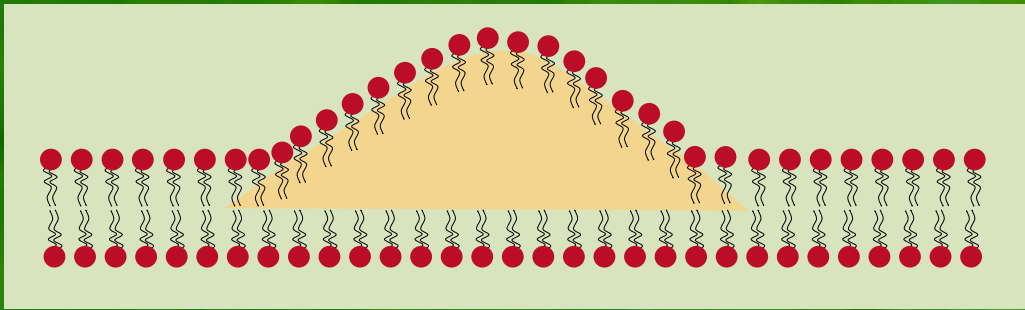


+ Seipin

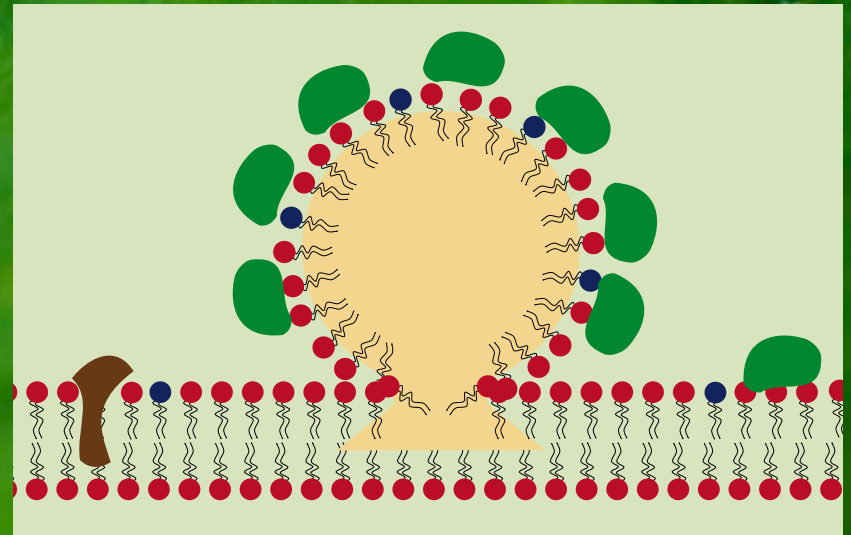


How do Lipid droplets bud off ?

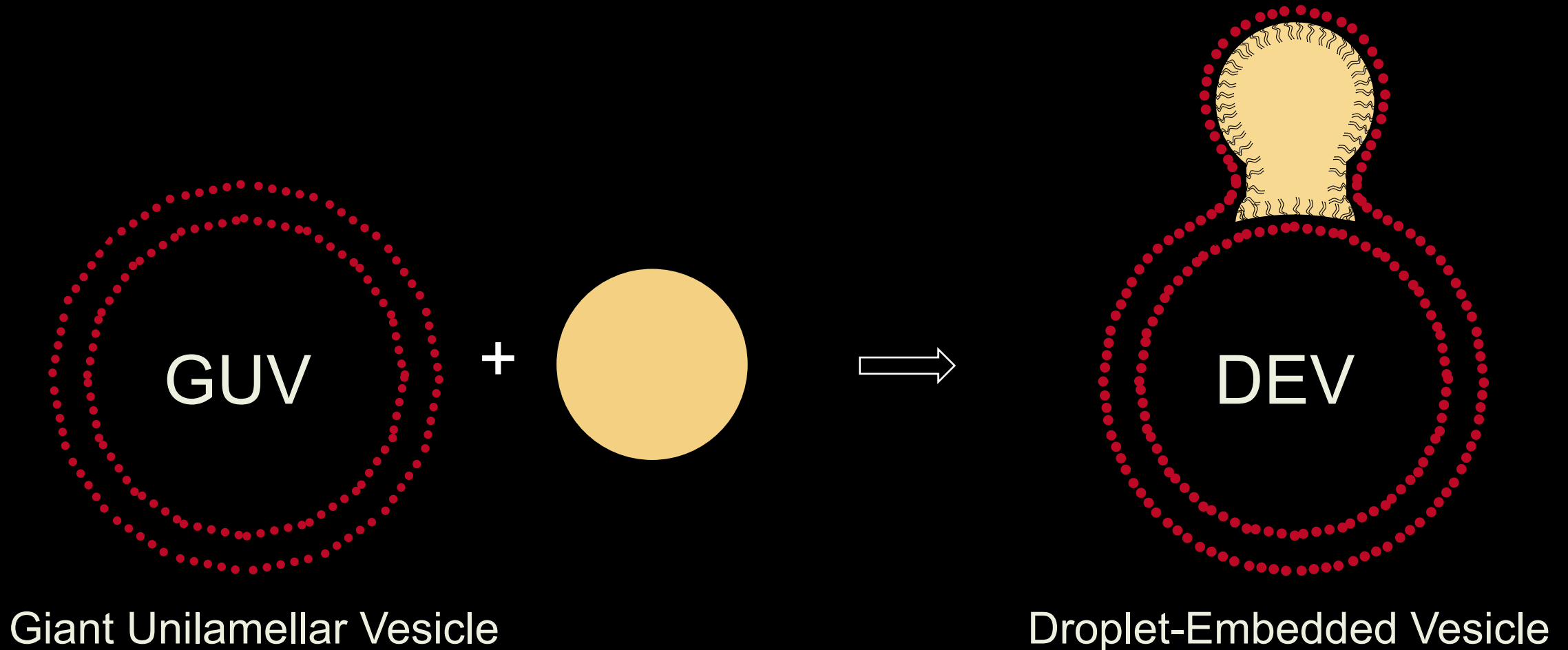




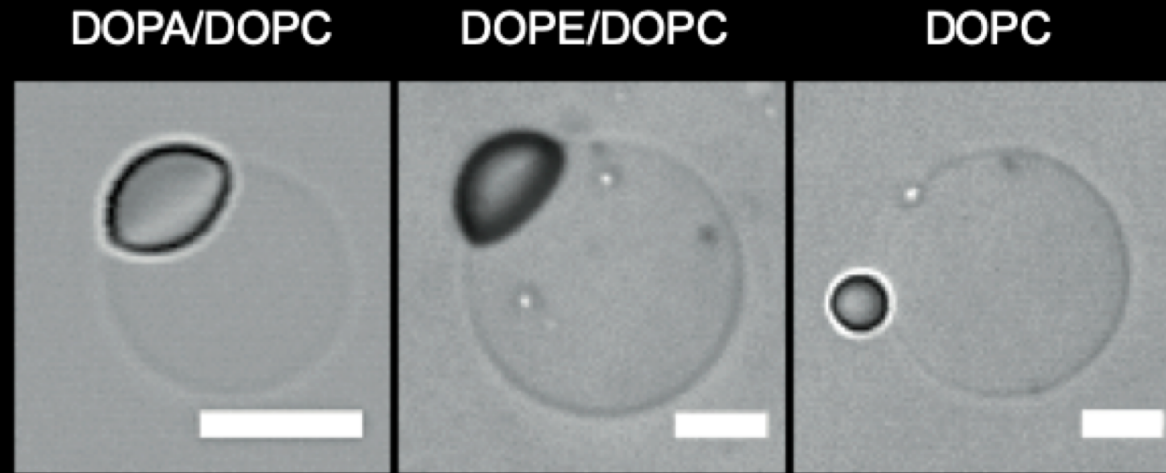
$$r \sim (\kappa/\gamma)^{1/2} > 30 \text{ nm}$$



Reconstitution of lipid droplet budding topology

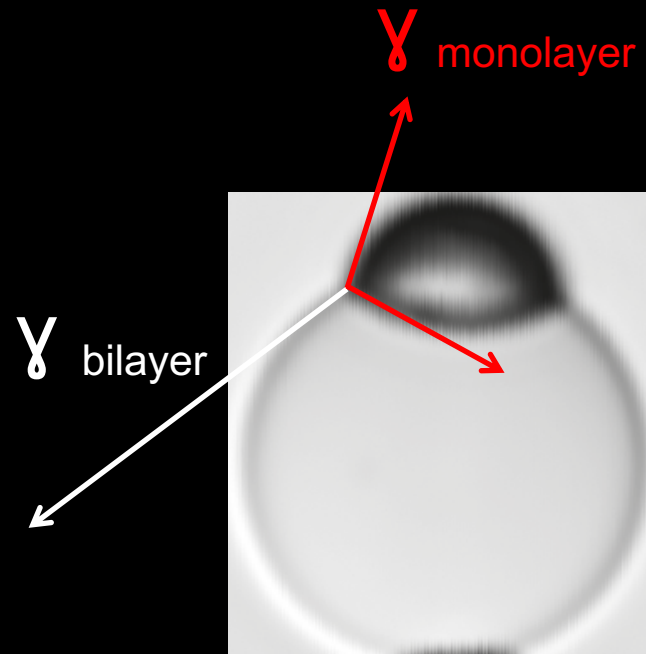


Droplets have different shapes depending on the phospholipid type



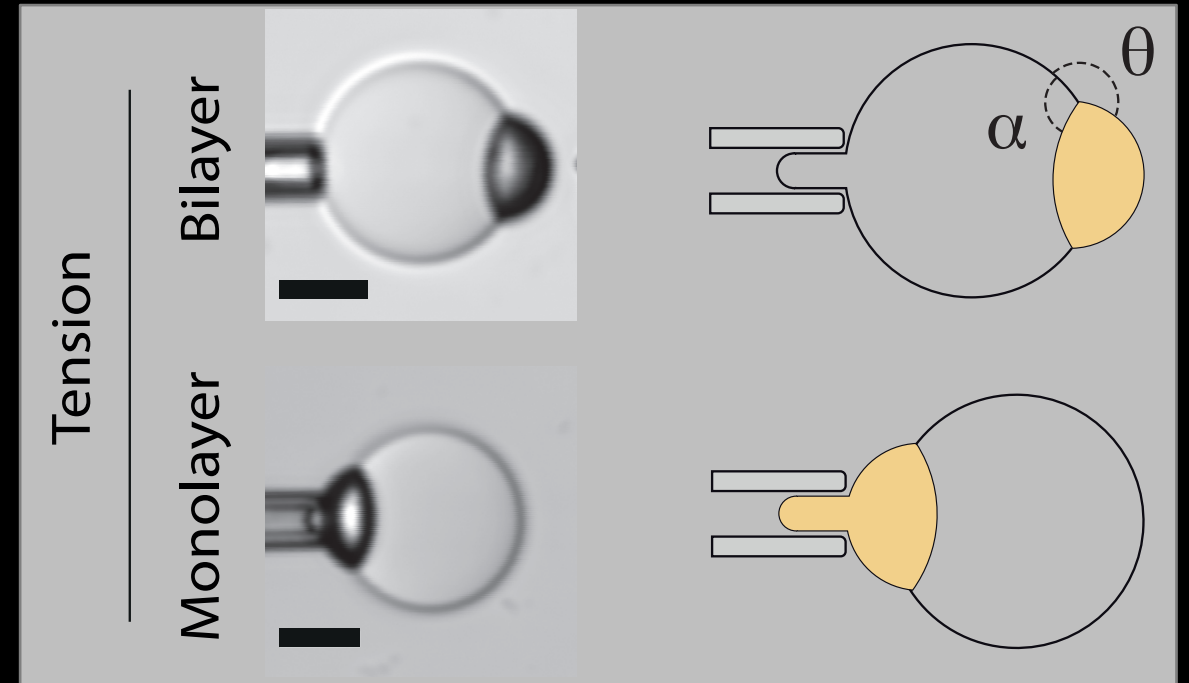
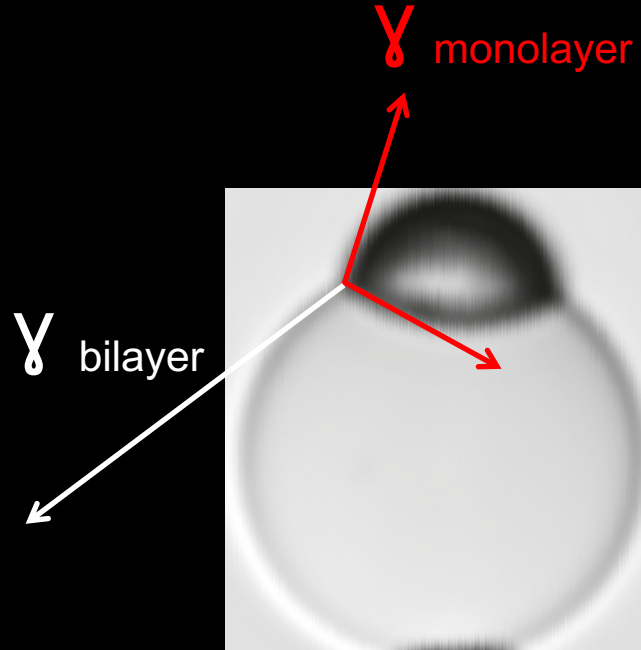
Ben M'barek et al. Dev Cell 2017

Tension interplay at the droplet edge



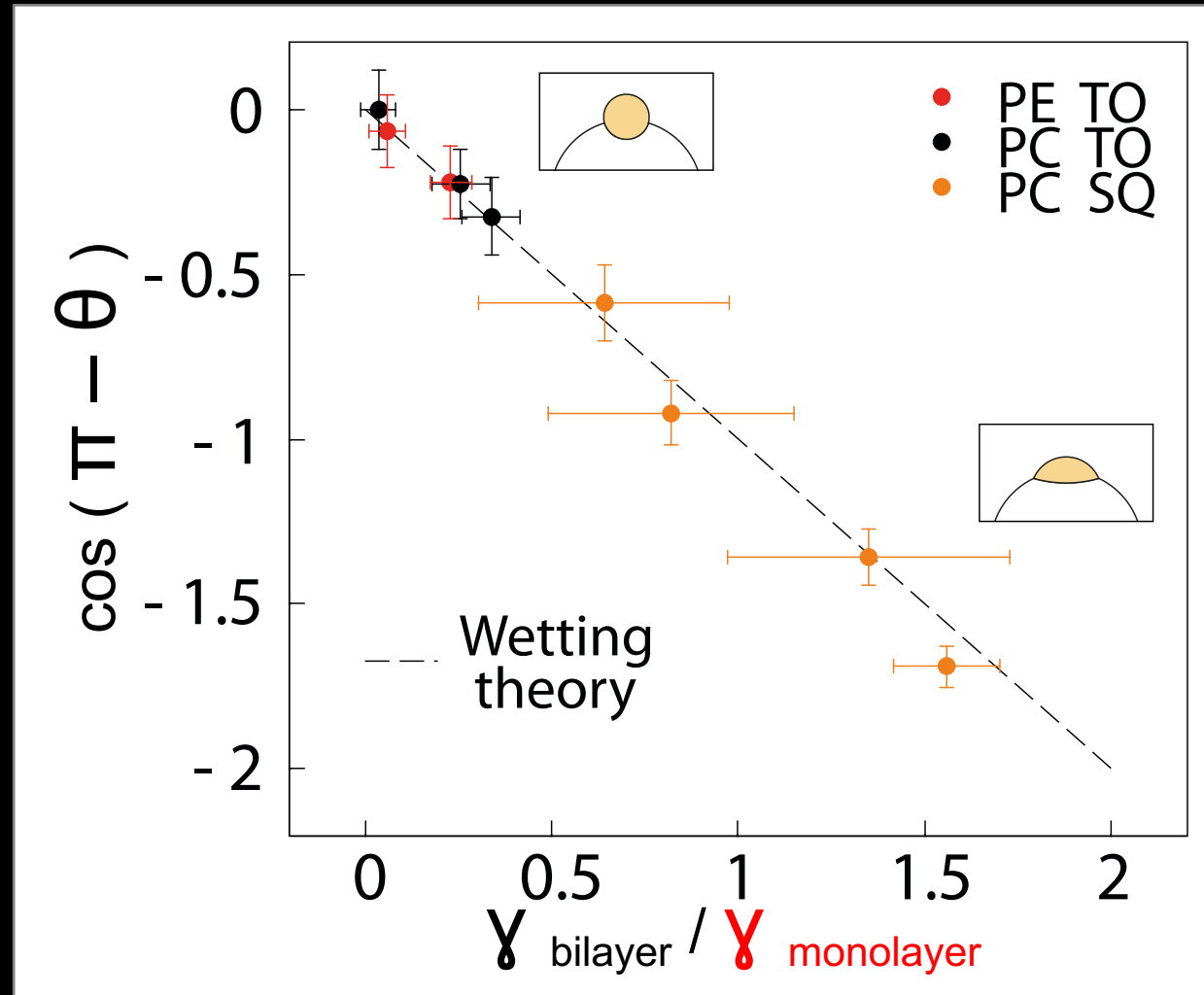
$$\gamma_{\text{bilayer}} = 2 * \gamma_{\text{monolayer}} \cos(\pi - \theta)$$

Tension interplay at the droplet edge



$$\gamma_{\text{bilayer}} = 2 * \gamma_{\text{monolayer}} \cos(\pi - \theta)$$

Experiments follow the Young-Dupré equation

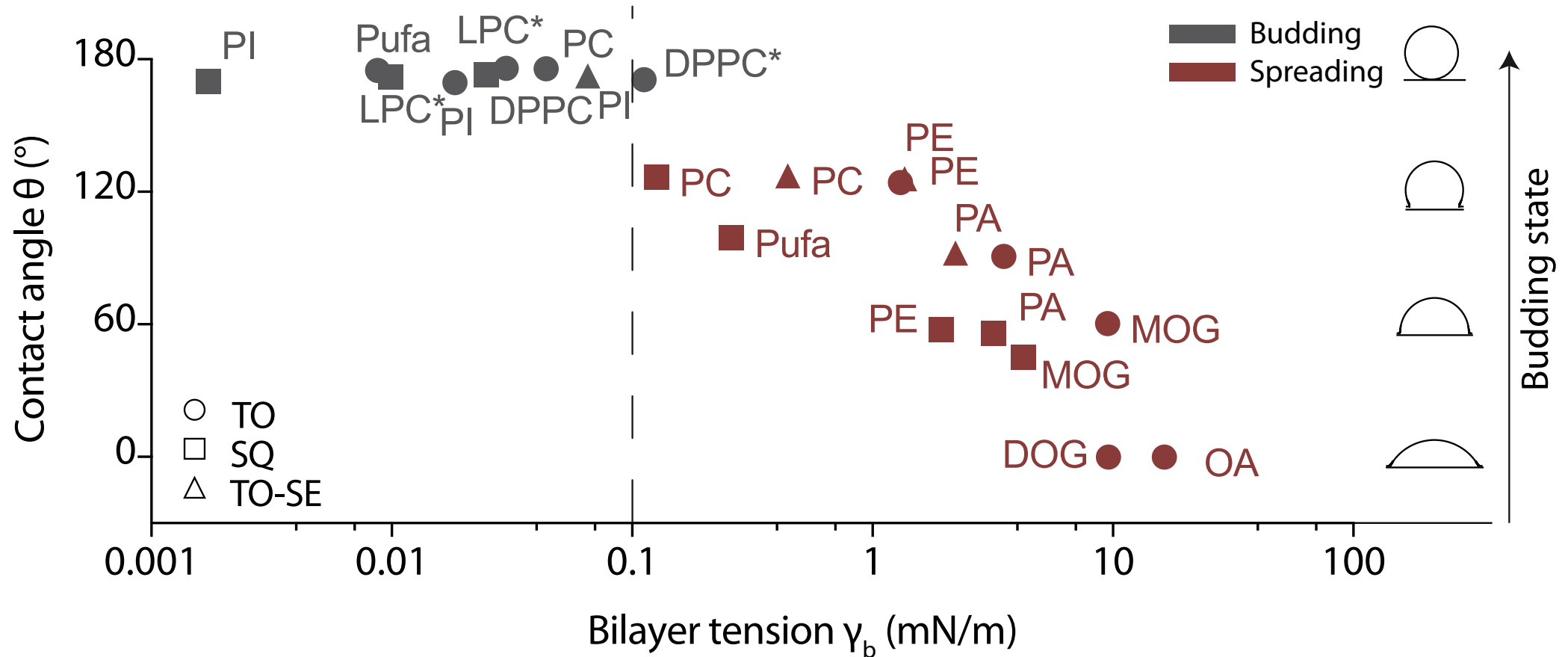


$$\gamma_{\text{bilayer}} = 2 * \gamma_{\text{monolayer}} \cos(\pi - \theta)$$

Budding essentially requires low bilayer tensions

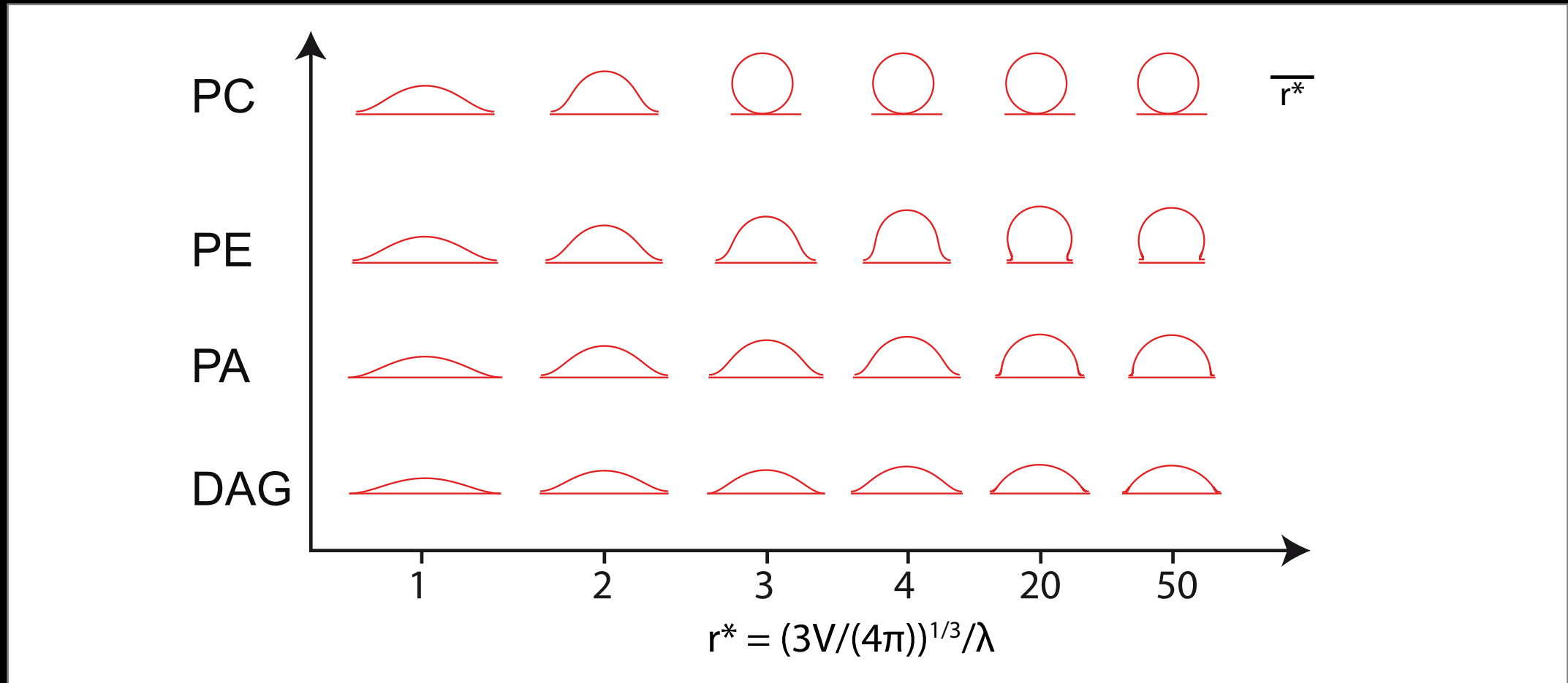
(Data from droplet interface bilayers)

□ Triolein oil ○ Sterol ester oil △ Squalene oil

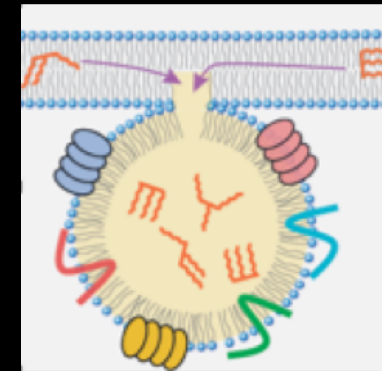
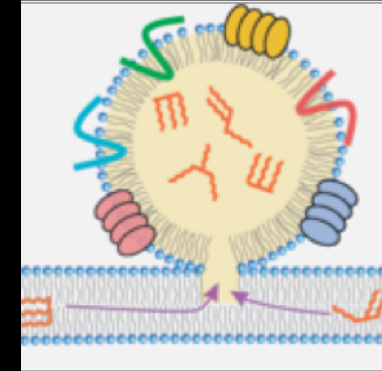
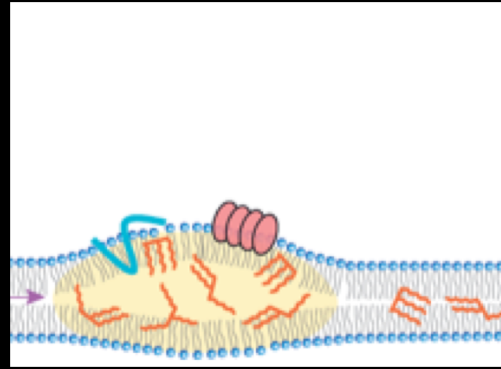


Ben M'barek et al. Dev Cell 2017

Numerical predictions of the droplet shape evolution during droplet formation

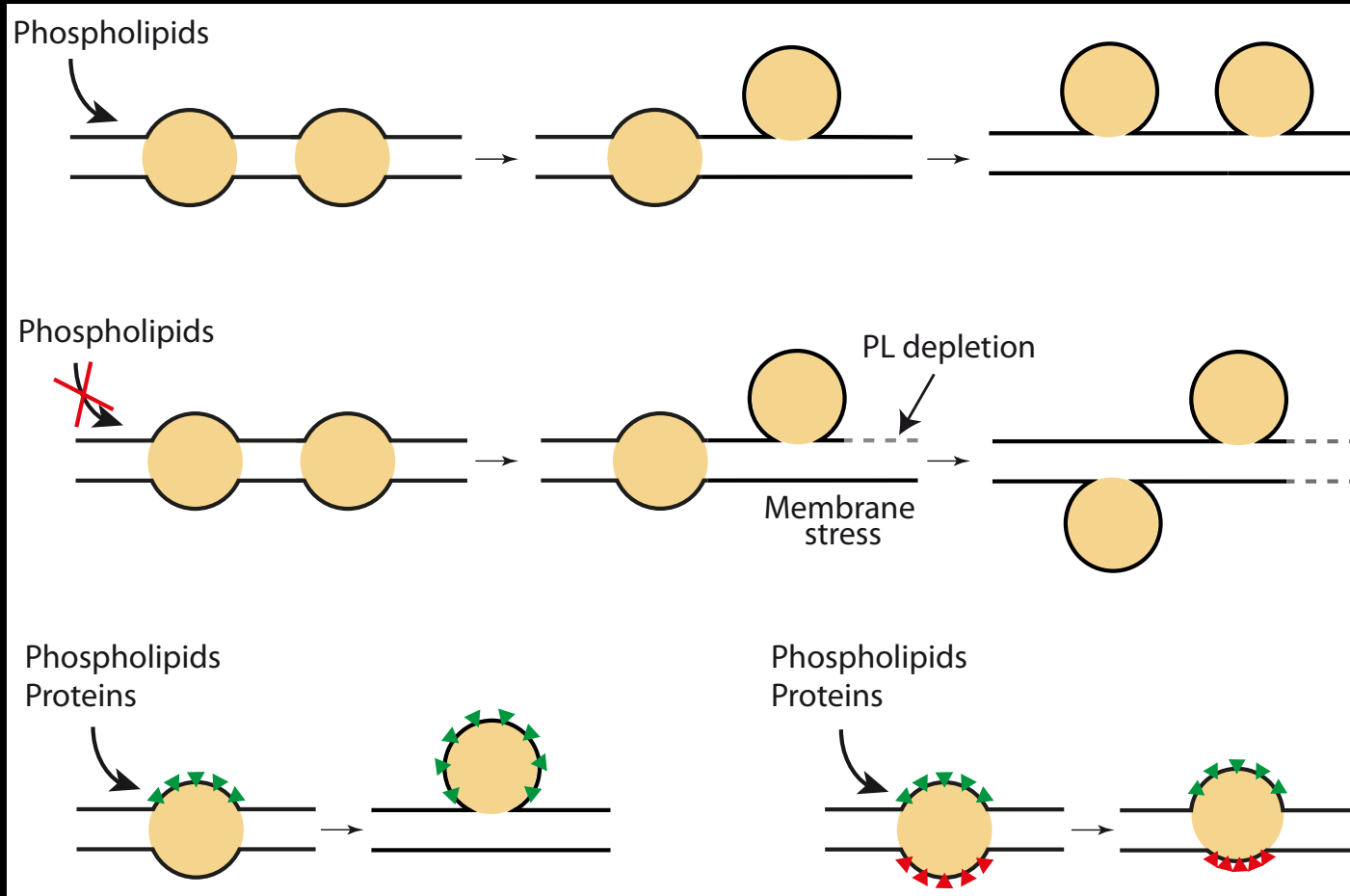


Lipid droplets directionally emerge

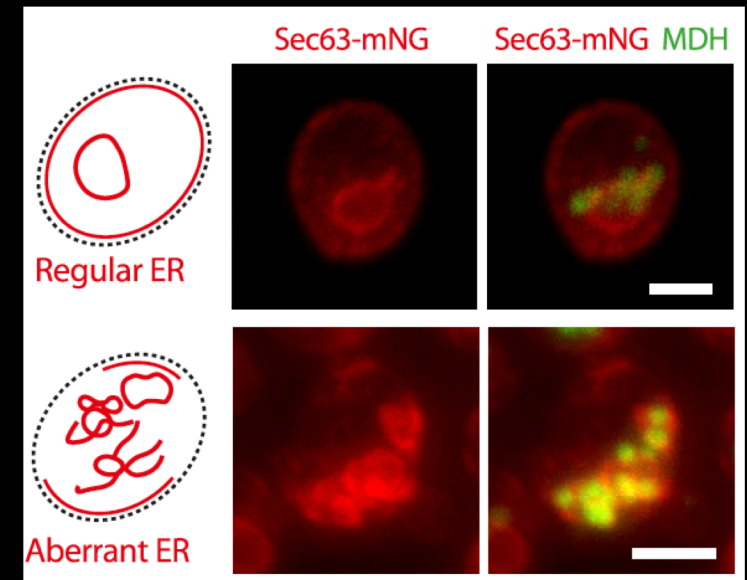
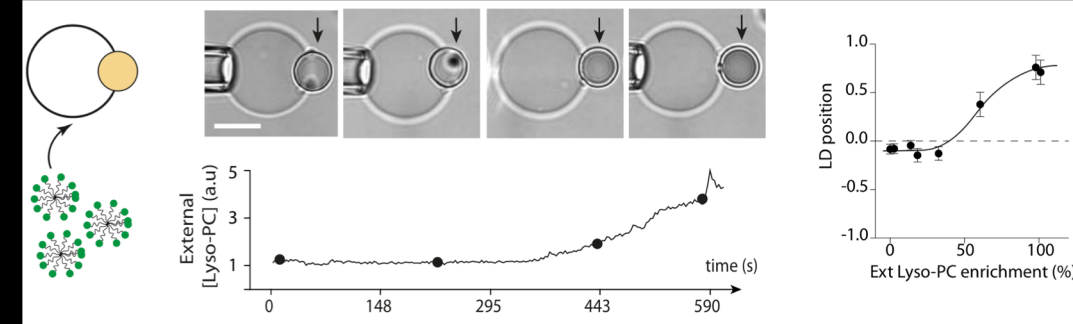
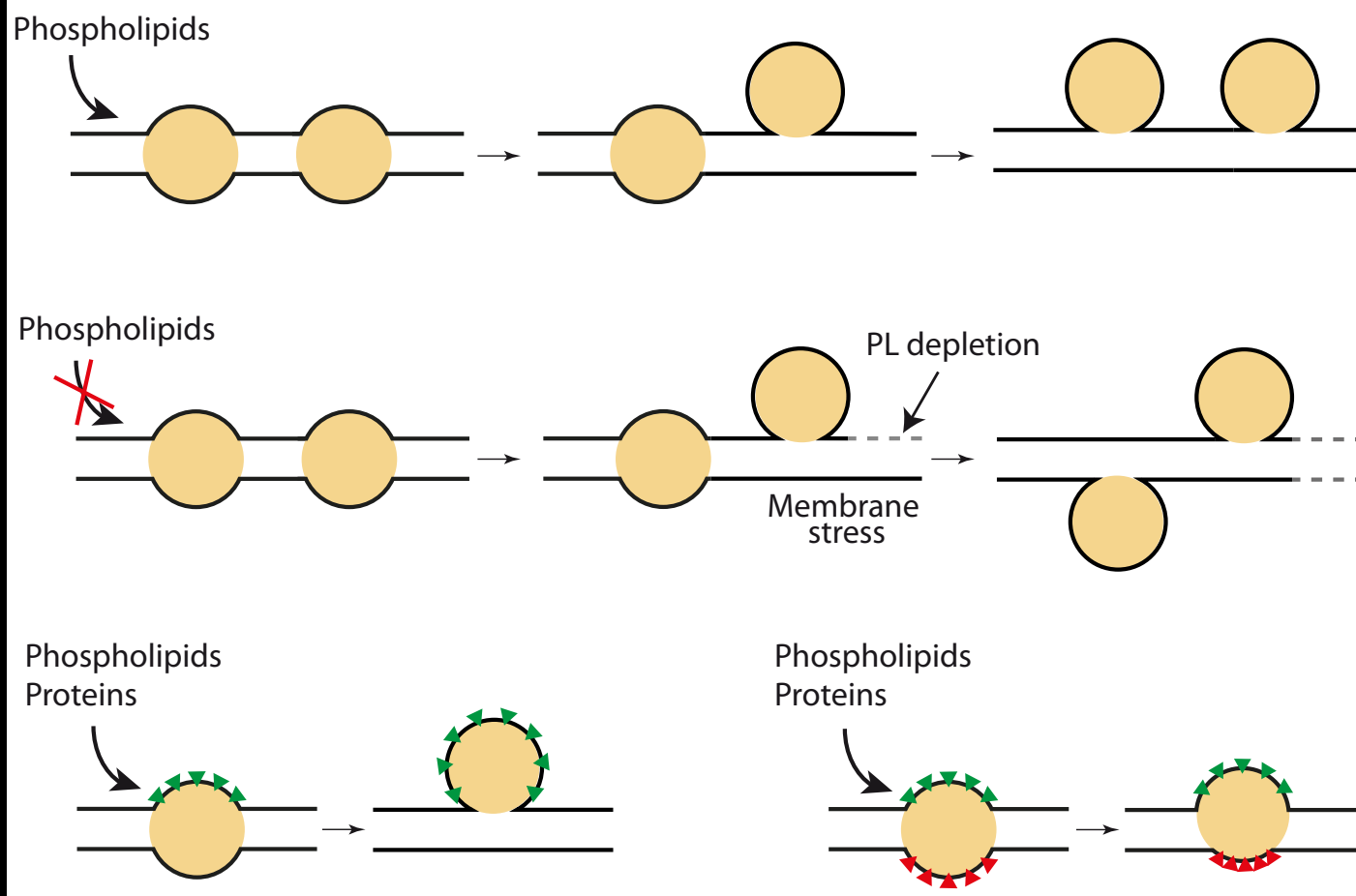


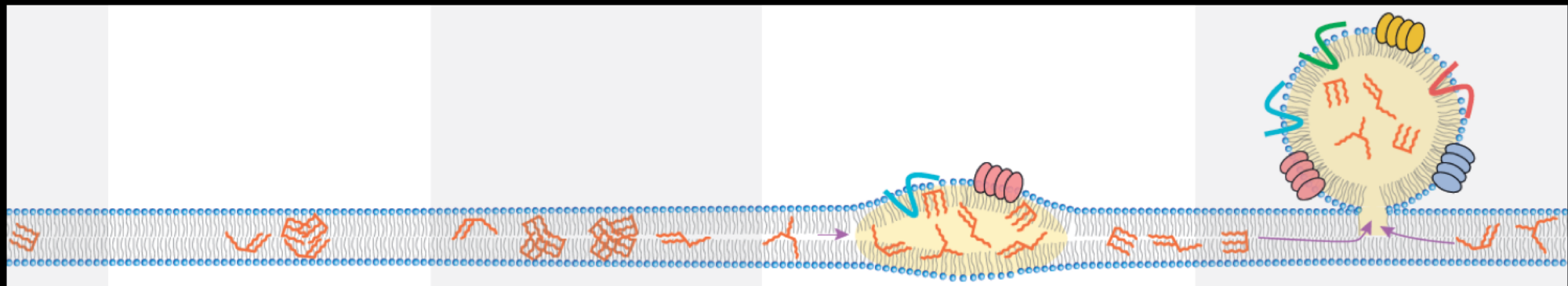
How the budding direction is determined ?

A supply of materials is necessary for directionality and ER homeostasis

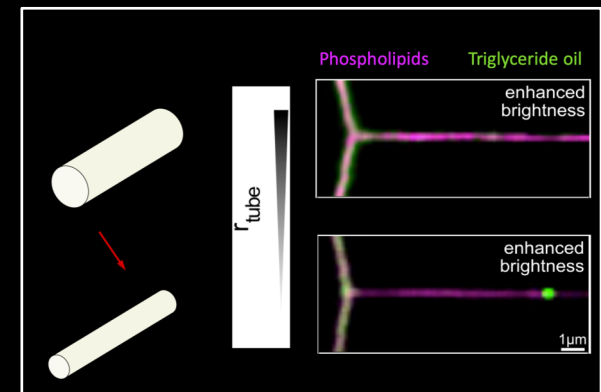
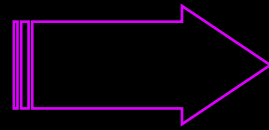
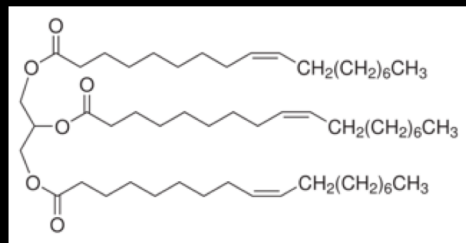


A supply of materials is necessary for directionality and ER homeostasis

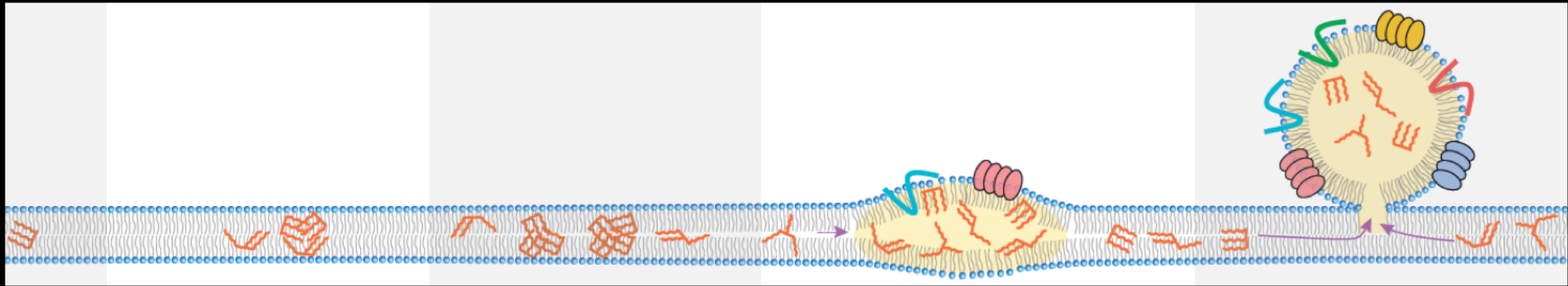




Triglycerides



How does curvature promote **TG LD nucleation** ?



- Triglycerides \neq ce ?
- Cholesteryl esters
- Impact of curvature on **chemical potential** ?
- How does **seipin** modulate ER membrane properties ?
Does it hold a curvature inducing capacity ?

- Fission

- Does the **bilayer/monolayer rigidity** play on the nucleation and budding steps.
- What is the rigidity of a phospholipid monolayer at an oil/water interface (not of microemulsions)