Dan Cassel

Back in 1997

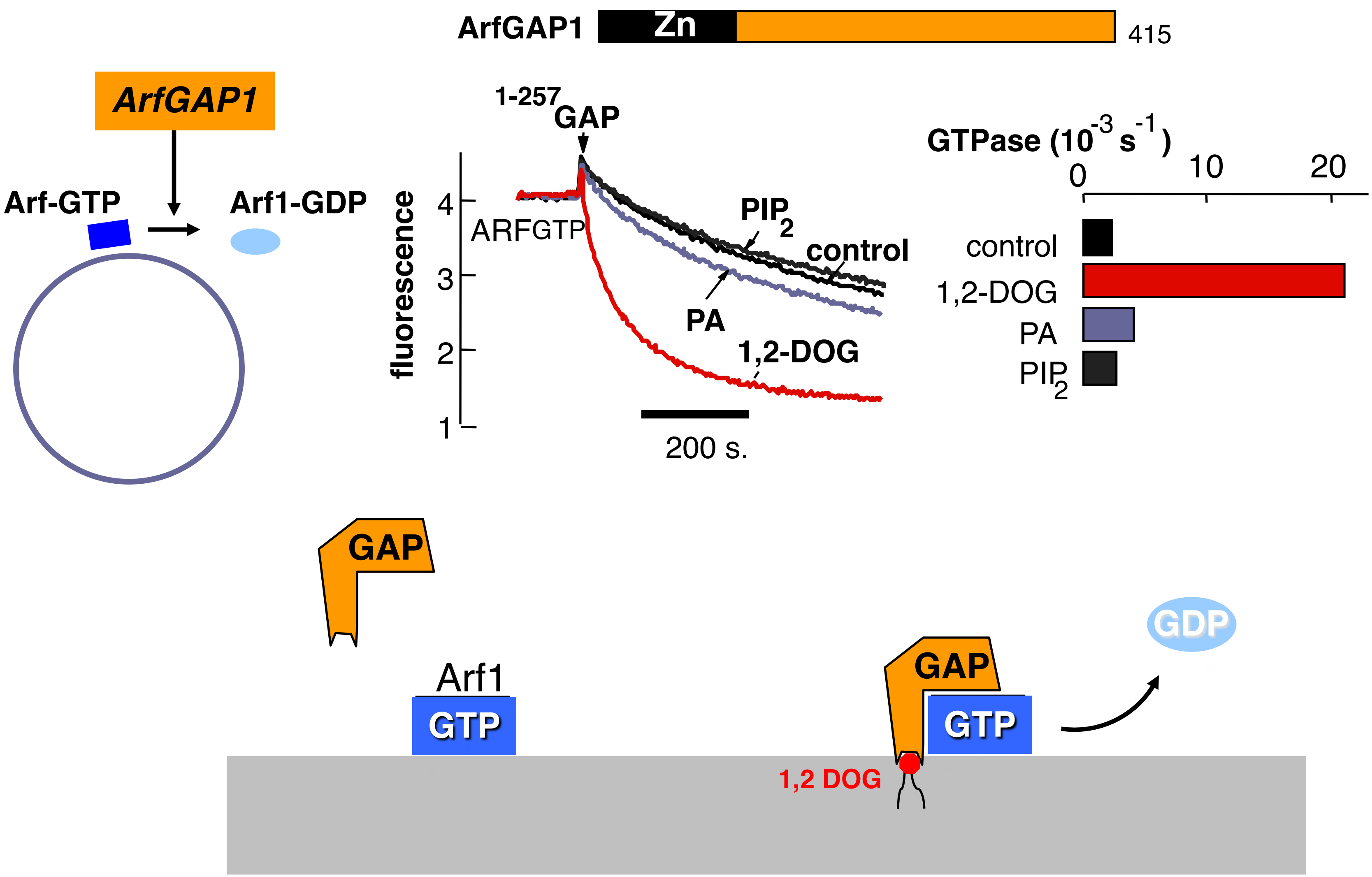
Marc Chabre

The ARF1 GTPase-Activating Protein: Zinc Finger Motif and Golgi Complex Localization

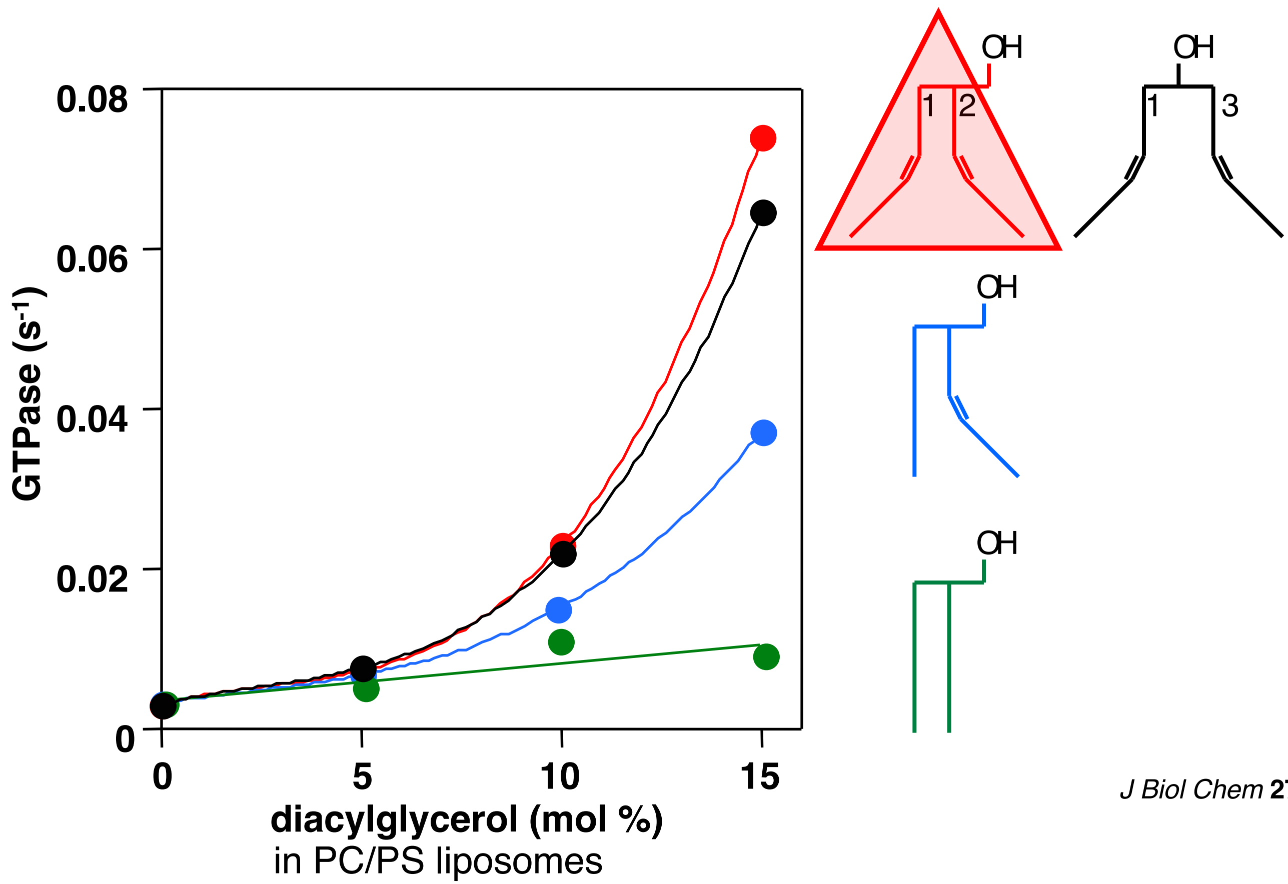
Edna Cukierman, Irit Huber, Miriam Rotman, Dan Cassel*

SCIENCE • VOL. 270 • 22 DECEMBER 1995

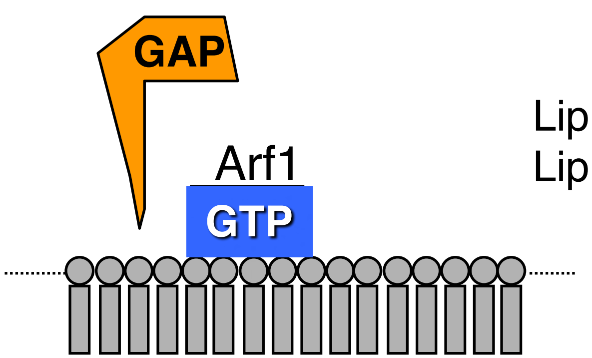
The starting point



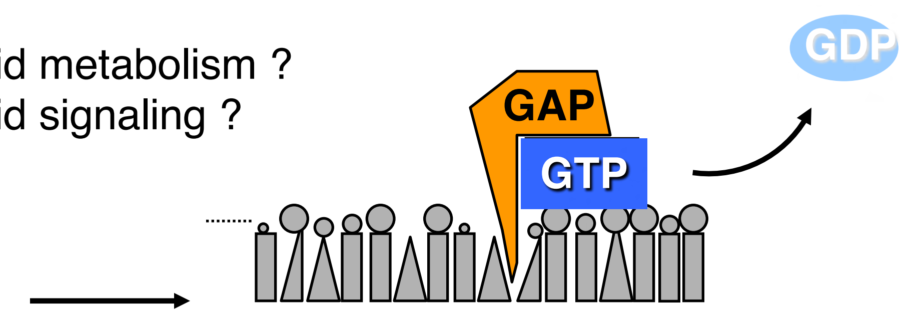
Specific or non specific ?



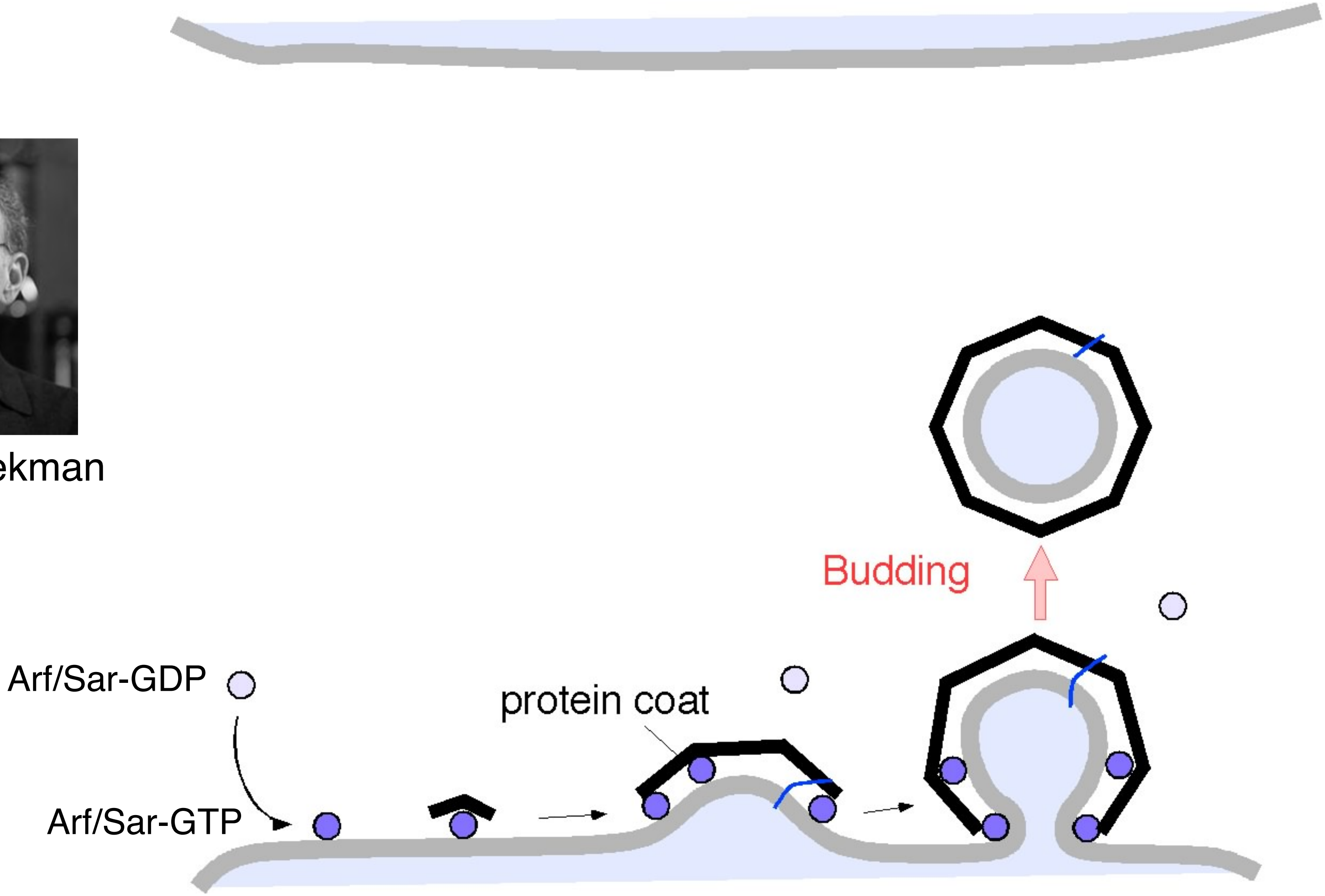
J Biol Chem **272**, *30848*



Lipid metabolism ?
Lipid signaling ?

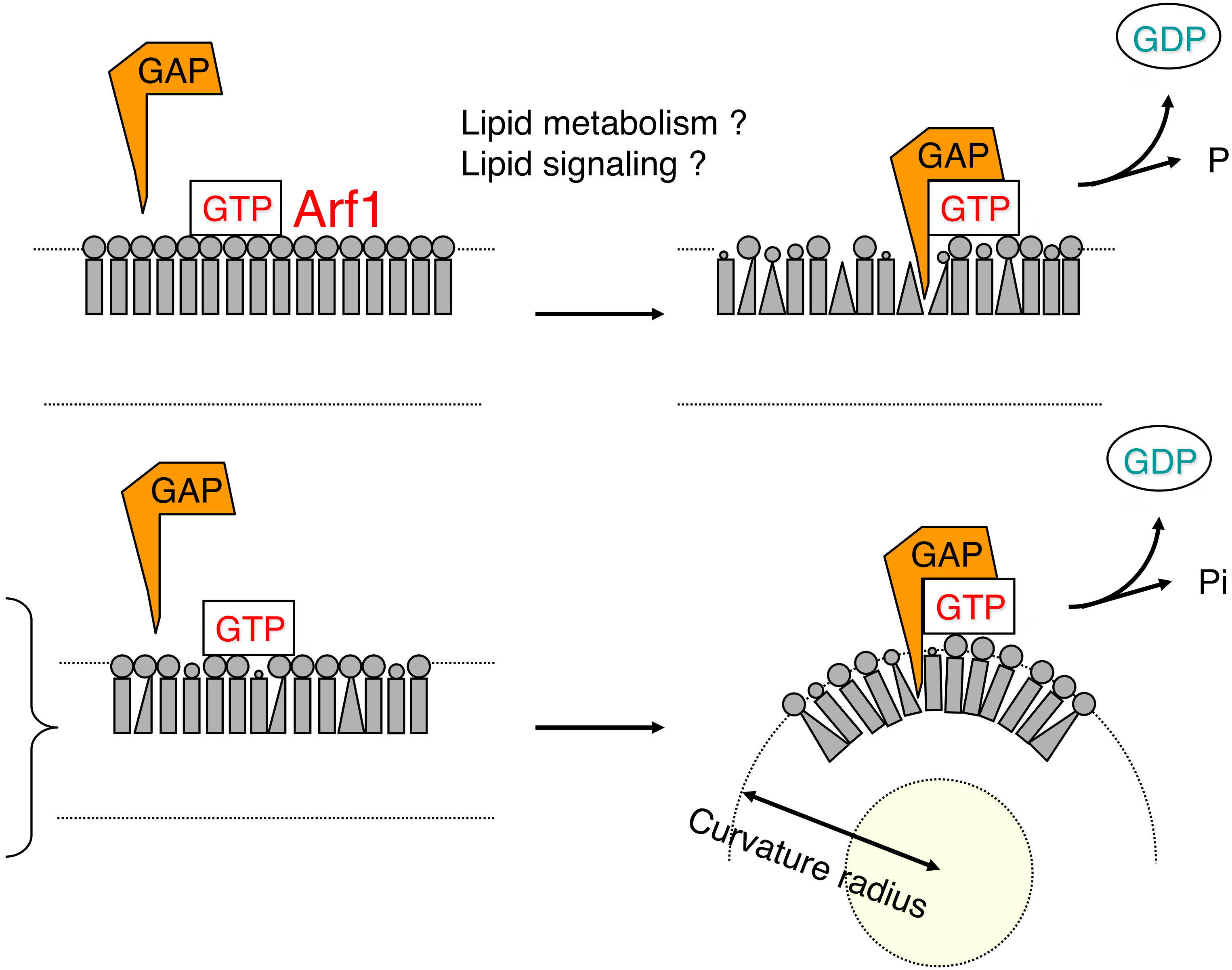


Randy Schekman

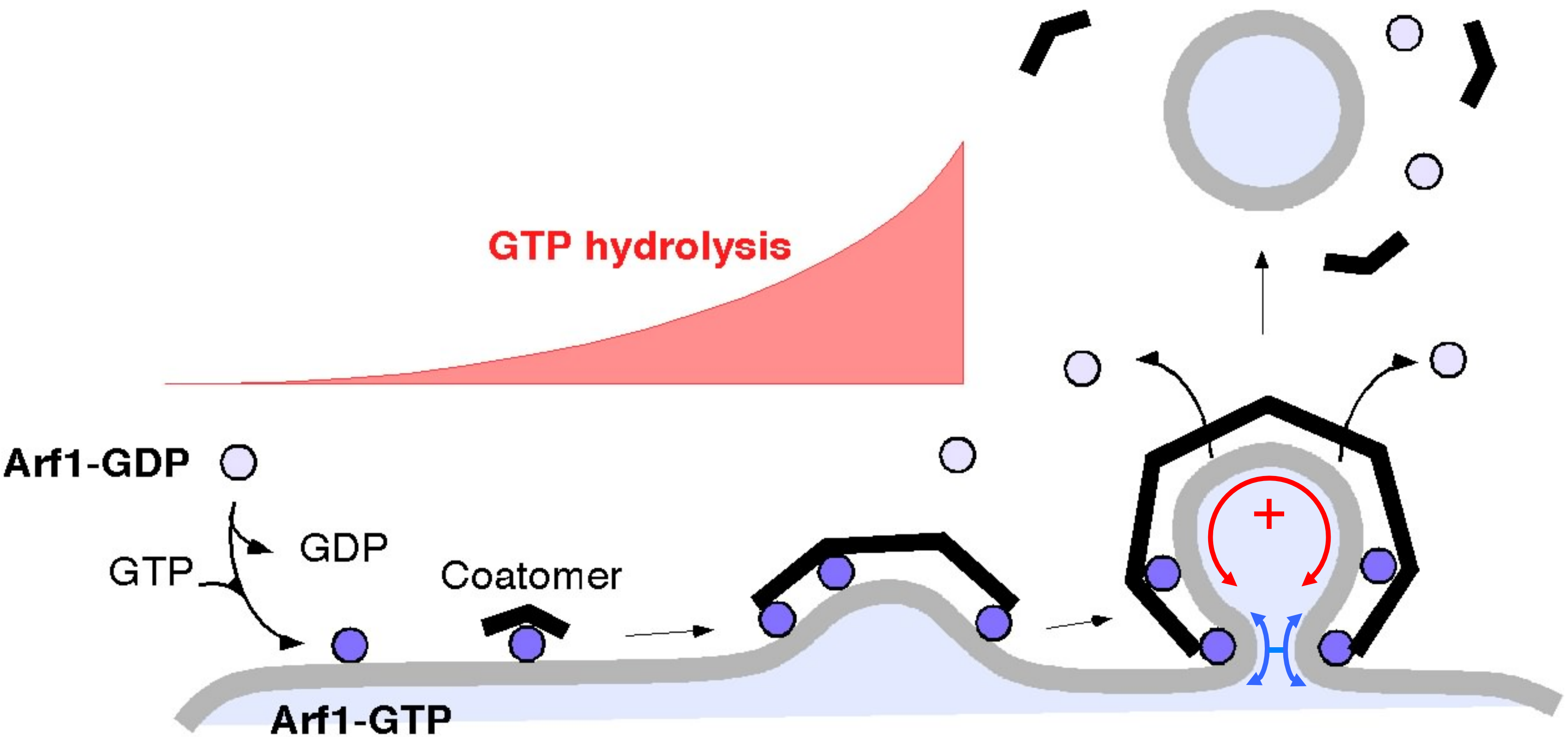


Idea?

PC: 50 %
PE: 19
PS: 5
PI: 10
Chol: 16

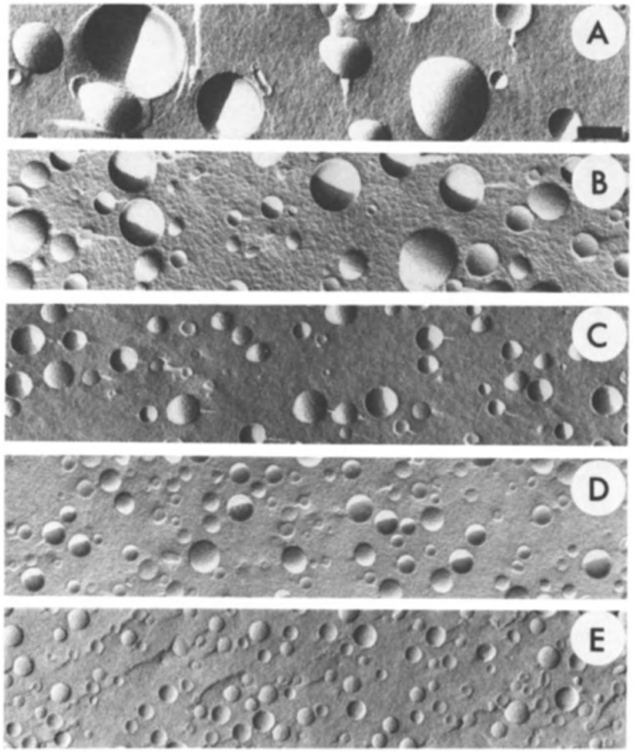


Spatial and temporal organization of GTP hydrolysis in the COPI coat



Preparing liposomes by extrusion

Preparing liposomes by extrusion



400

200

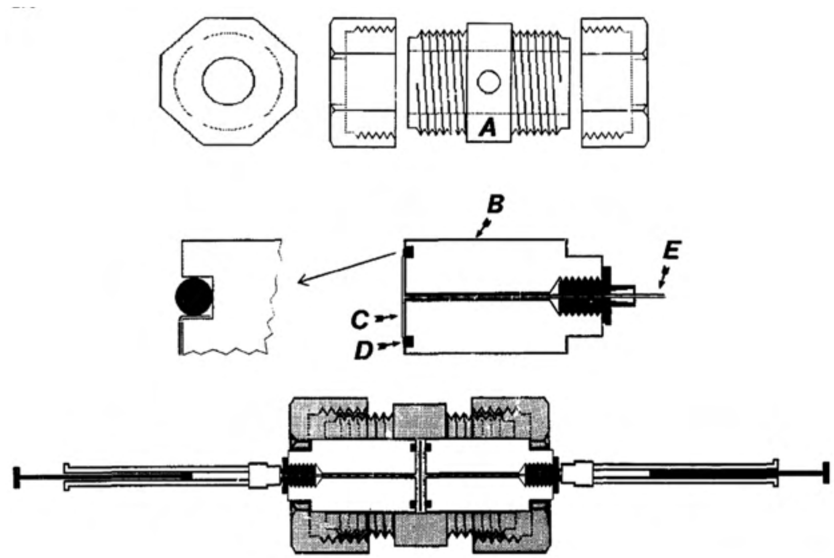
100

50

30

Pore size (nm)

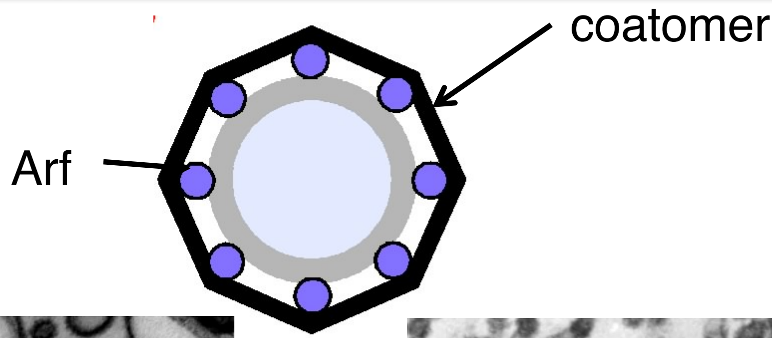
Mayer, L. D., Hope, M. J. & Cullis, P. R. Vesicles of variable sizes produced by a rapid extrusion procedure. *Biochim. Biophys. Acta* **858,** 161–168 (1986).

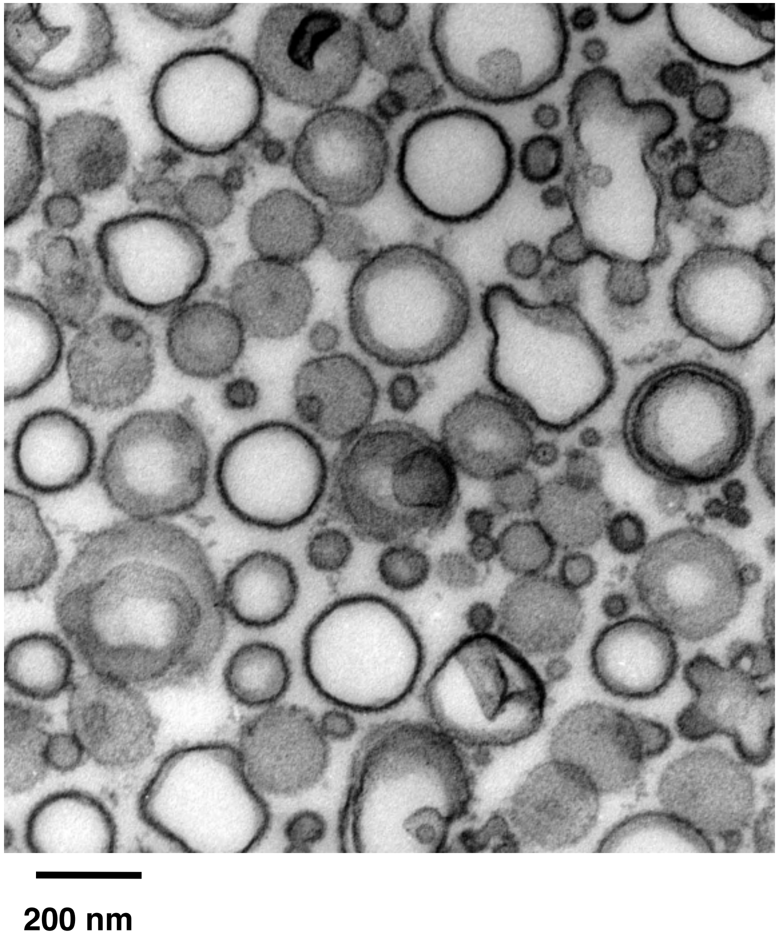


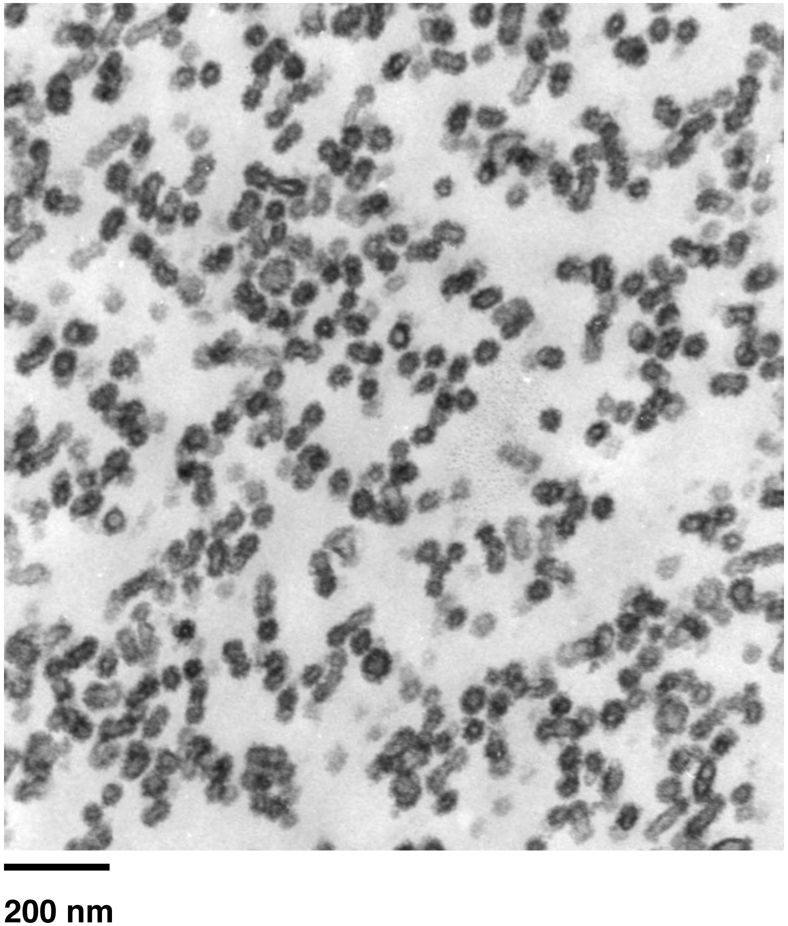
MacDonald, R. C. *et al.* Small-volume extrusion apparatus for preparation of large, unilamellar vesicles. *Biochim. Biophys. Acta* **1061,** 297–303 (1991).

https://avantilipids.com/divisions/equipment-products

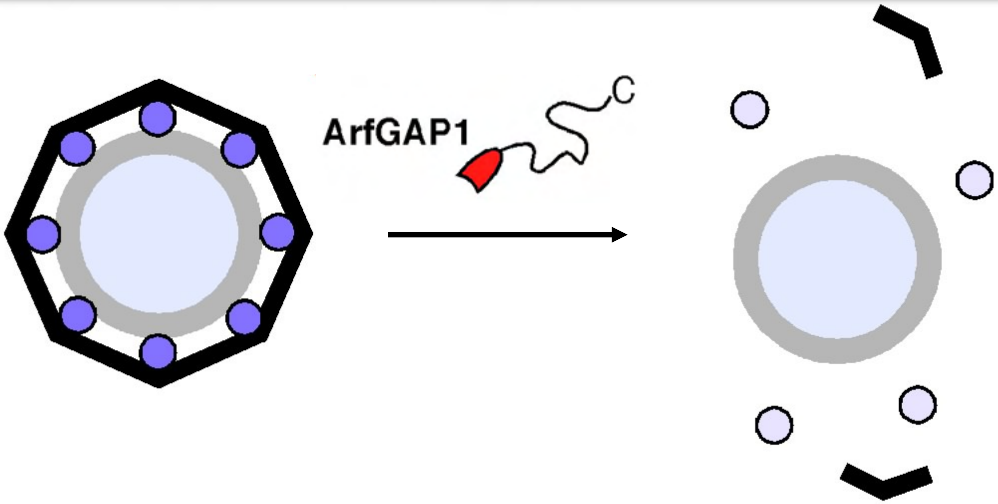
Reconstitution of the COPI coat

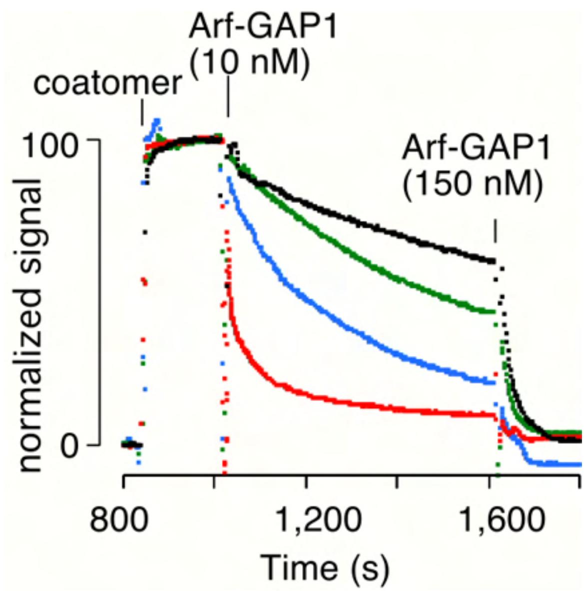


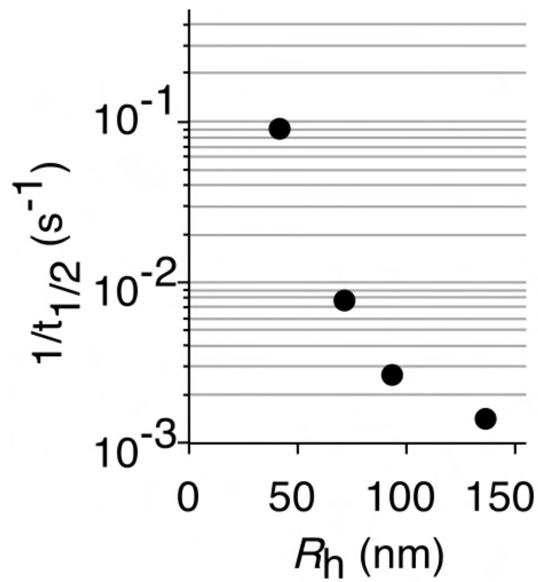




ArfGAP1 is hypersensitive to membrane curvature

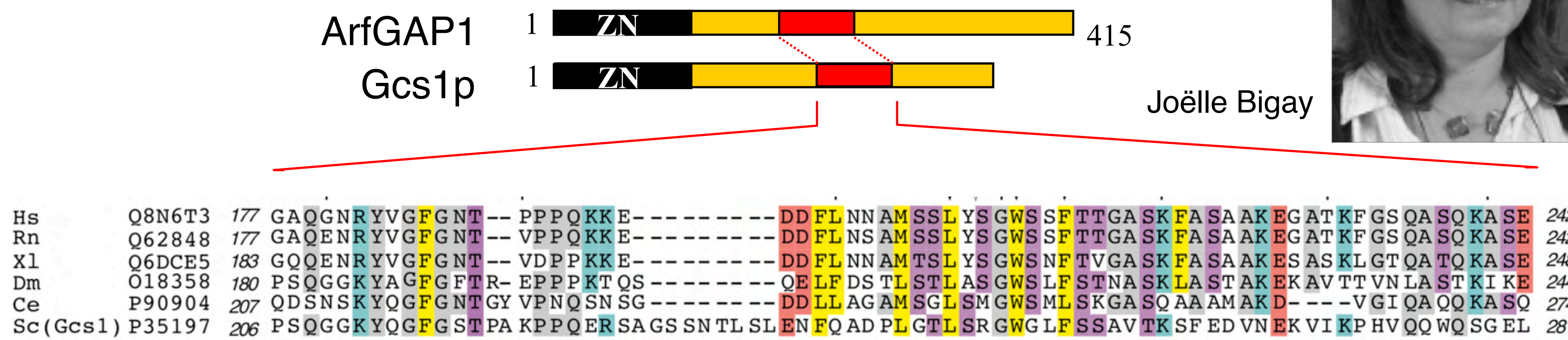






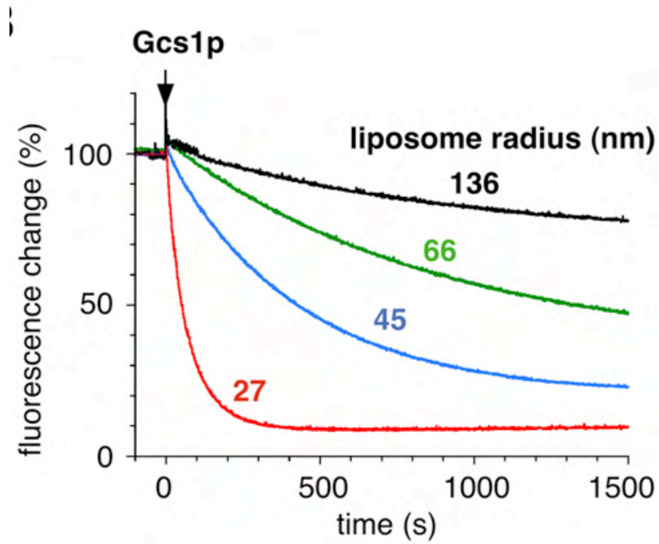
Bigay et al. *Nature* **426**, 563-566 (2003)

Where is the sensor ?



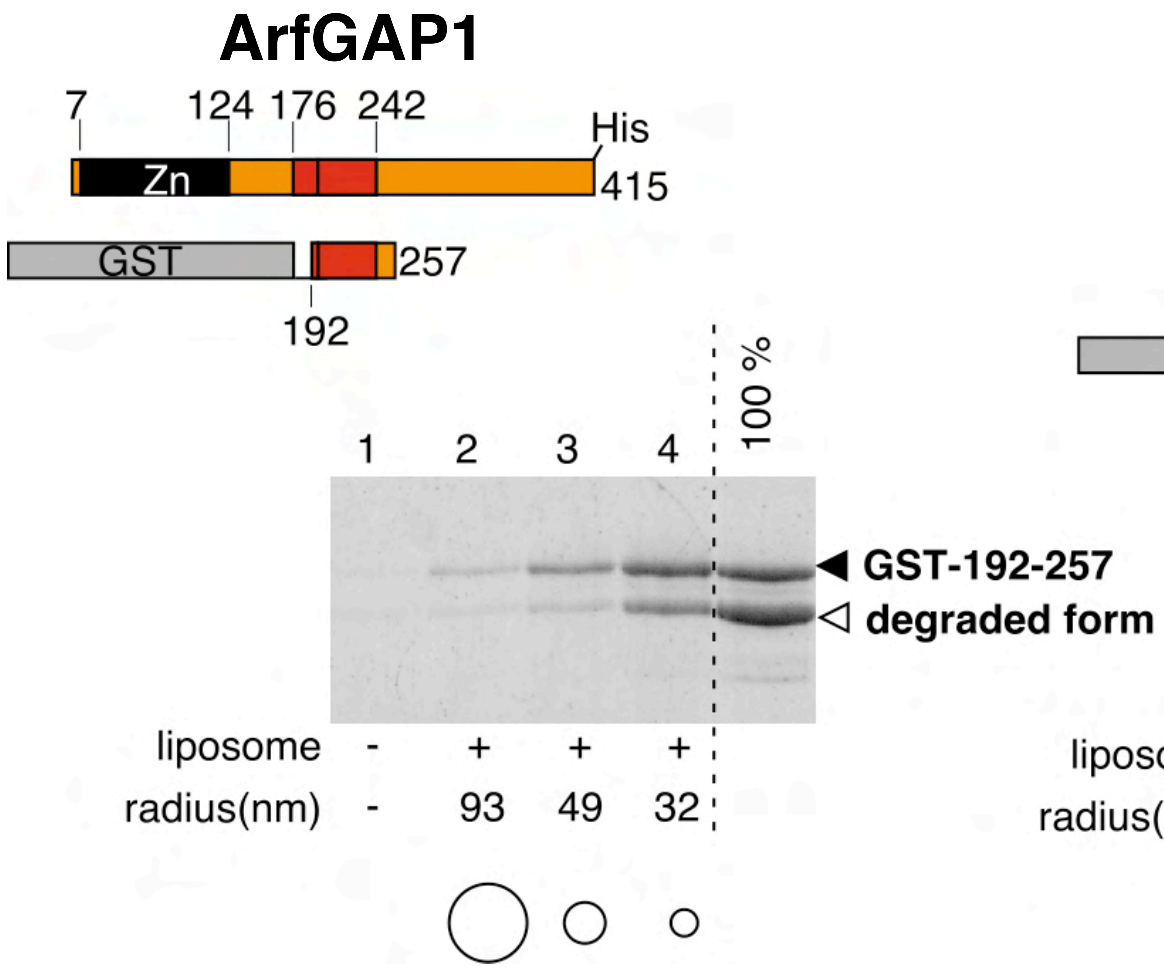
Joëlle Bigay

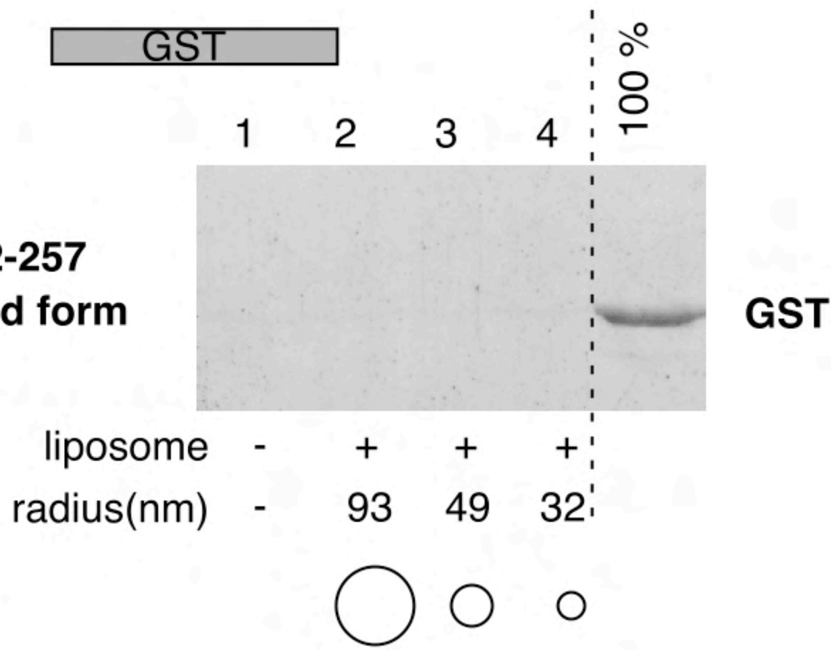
GAP assay



Bigay et al. *Embo J* **24**, 2244 (2005)

Where is the sensor ?

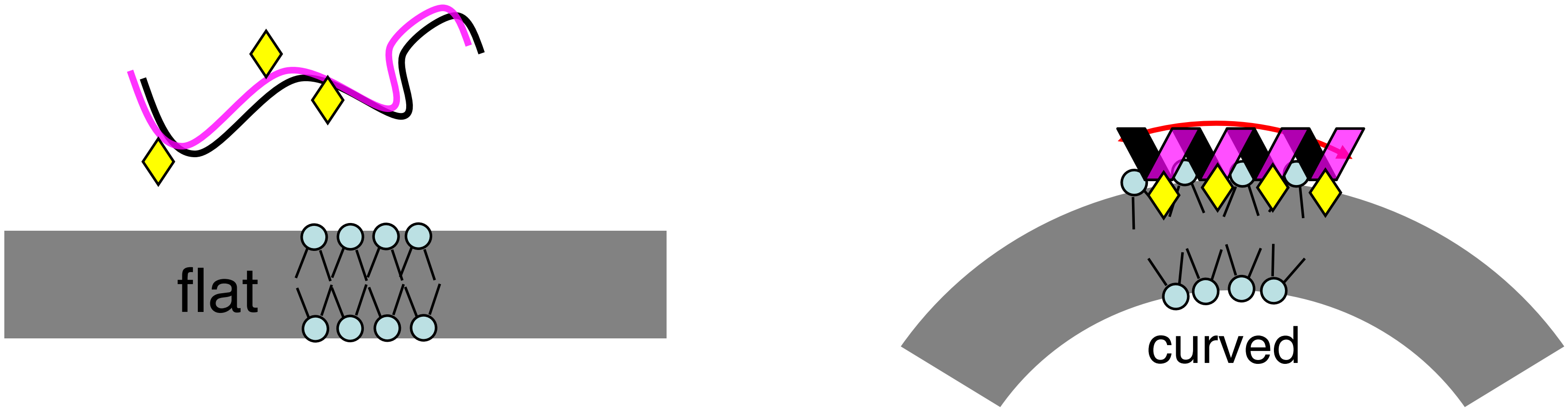




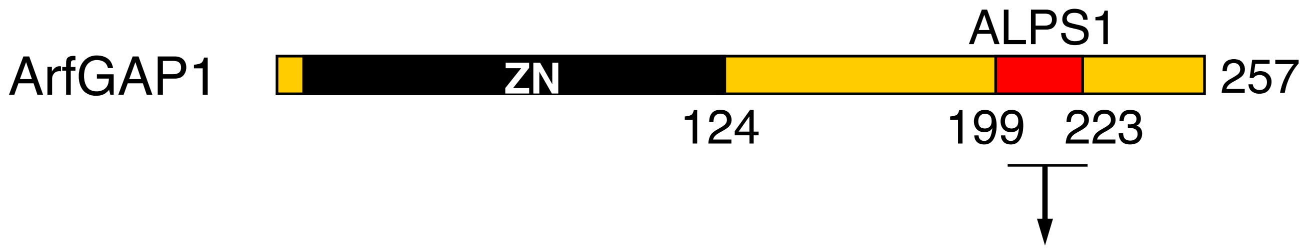
Bigay et al. *Embo J* **24**, 2244 (2005)

How the ALPS motif senses membrane curvature

ALPS motif

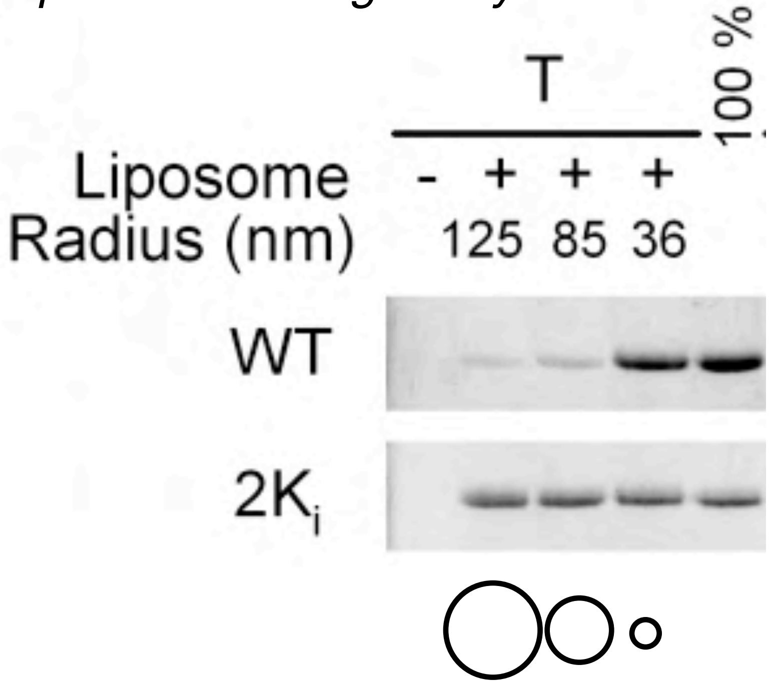


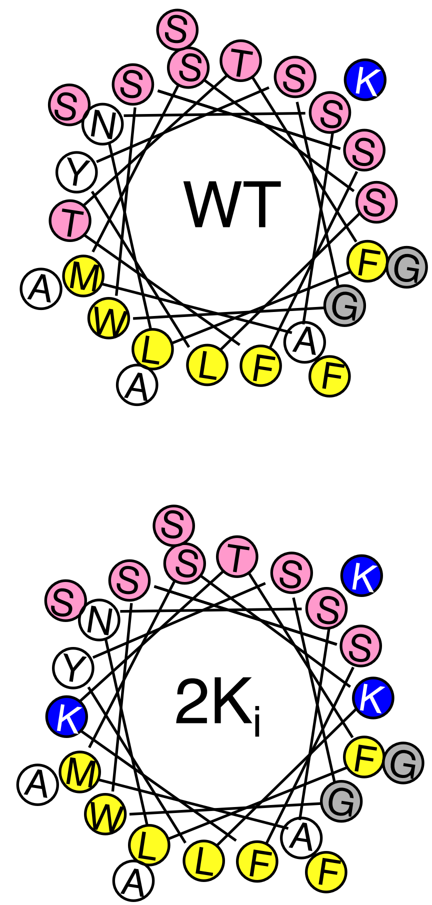
A peculiar amphipathic helix



Guillaume Drin

Liposome binding assay





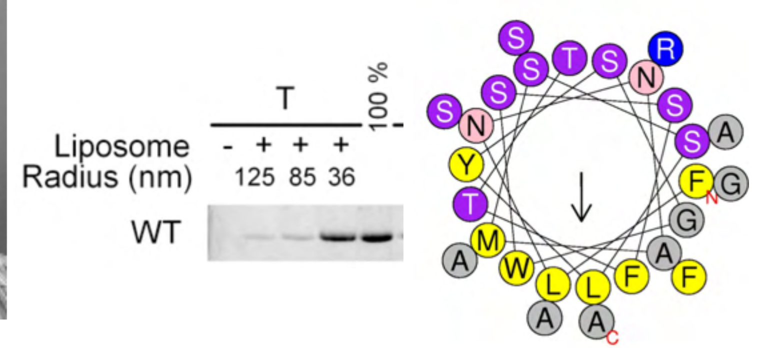
•*Drin et al.Nature Struct & Mol Biol 2007*)

Looking for new ALPS motifs

ArfGAP1 415

FLNNAMSSLYSGWSSFTTGASRFASAA

Romain Gautier



GMAP-210

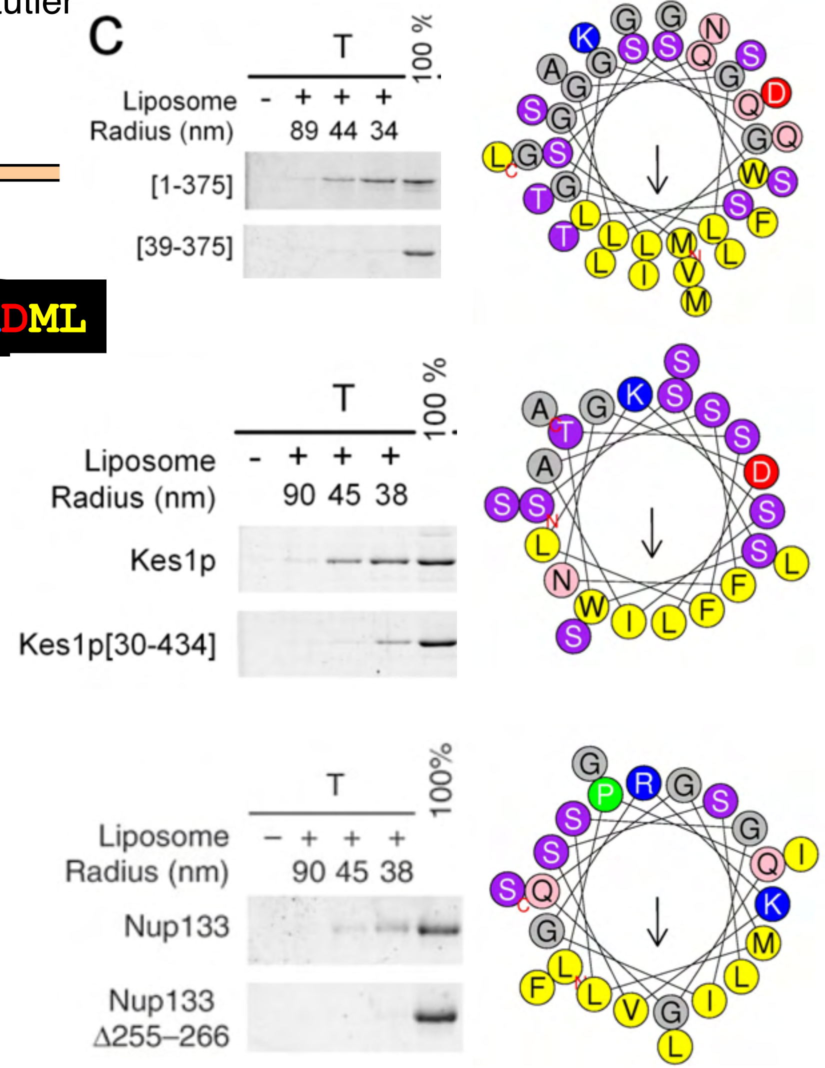
MSSWLGGLGSGLGQSLGQVGGSLASLTGQISNFTKDML

Kes1 434

SSSWTSFLKSIASFNGDLSSLSA

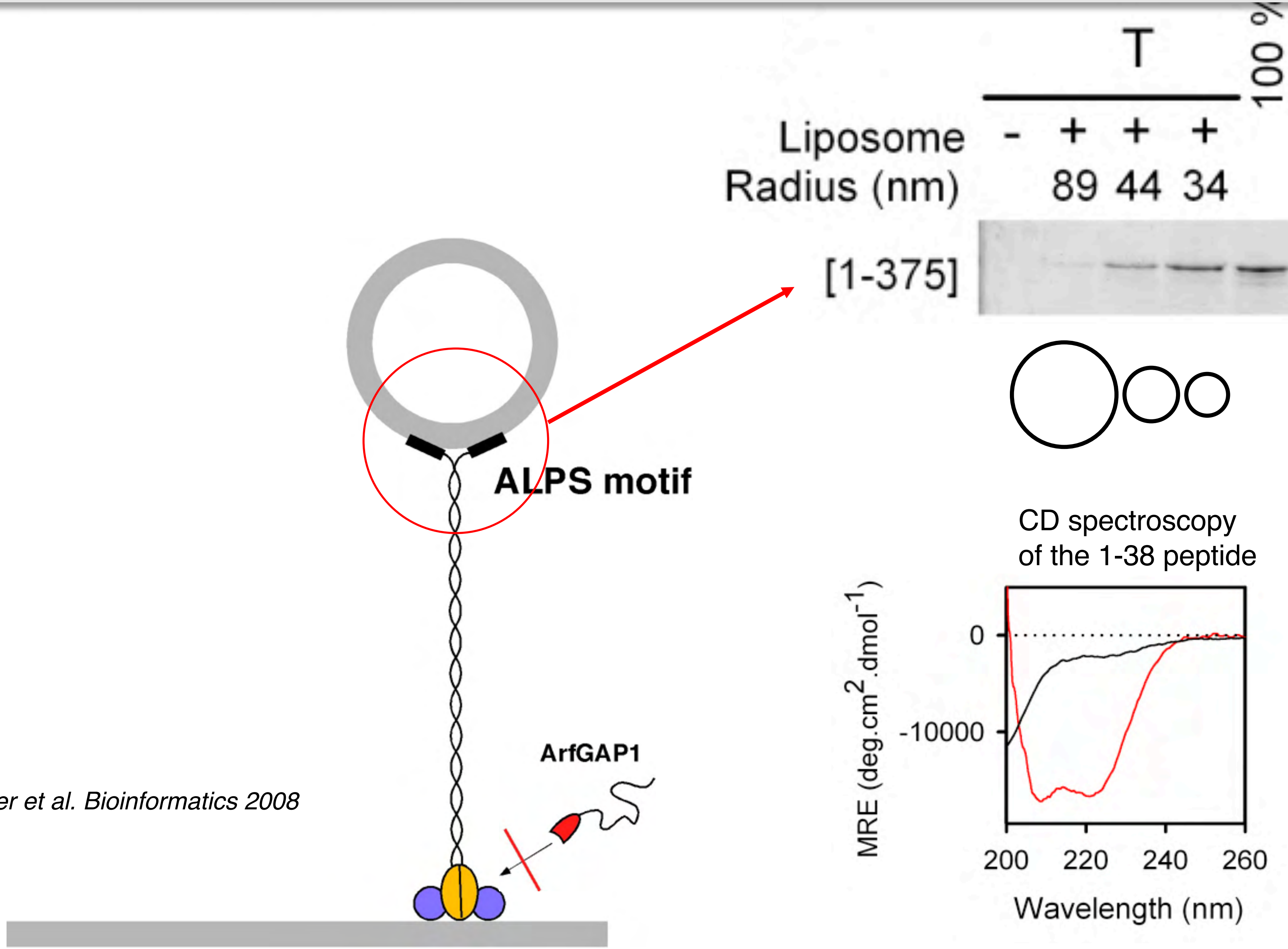
Nup133 1156

LPQGQGMLSGIGRKVSSLFGILS



Gautier et al. Bioinformatics 2008

An ALPS motif at the end of a string

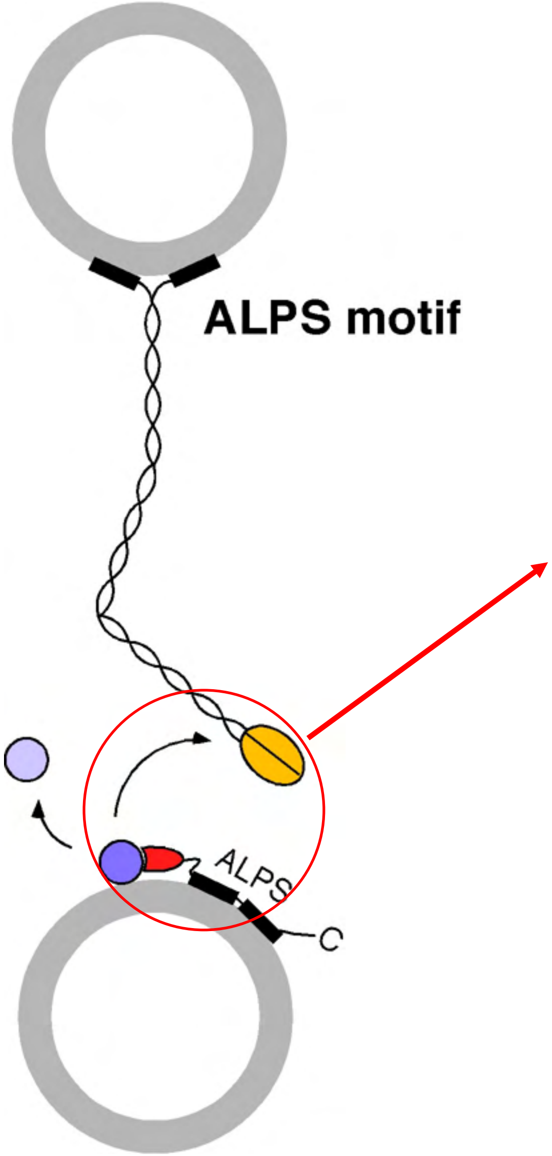


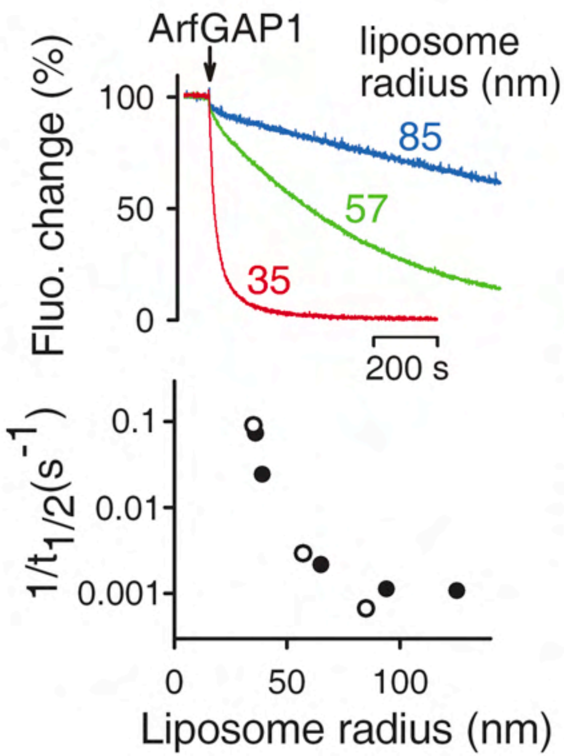
Gautier et al. Bioinformatics 2008

Drin et al.Nat. Struct & Mol Biol 2007

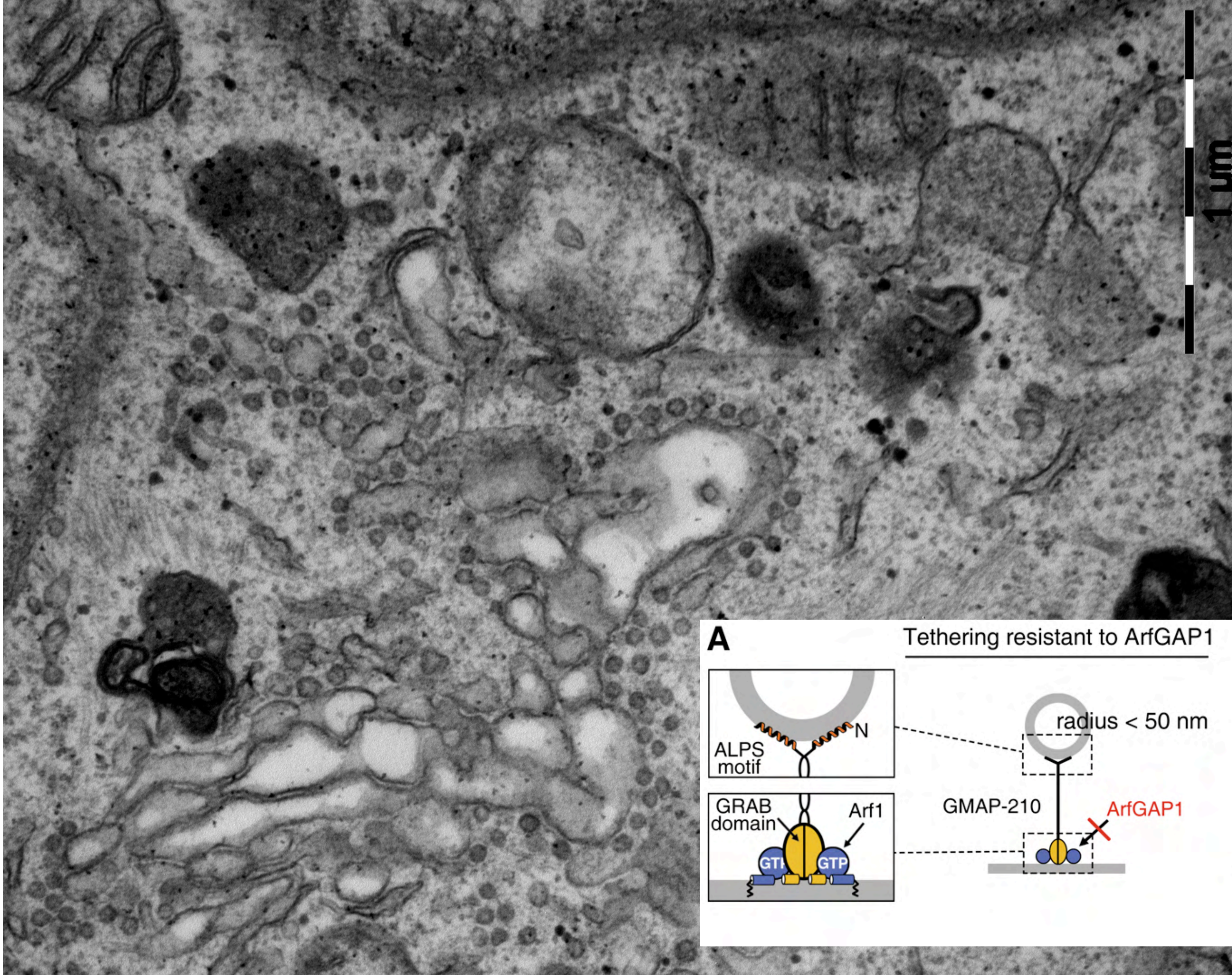
Dual control by membrane curvature ?

Vincent Morello



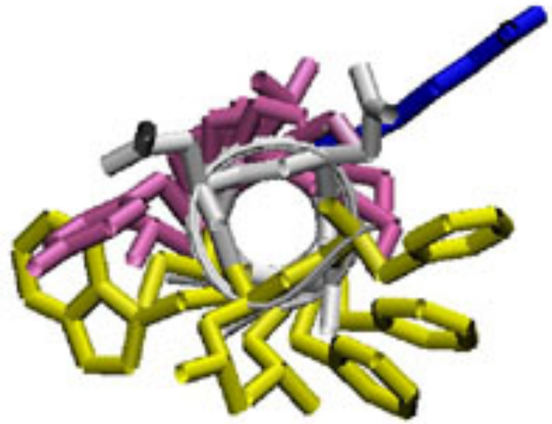


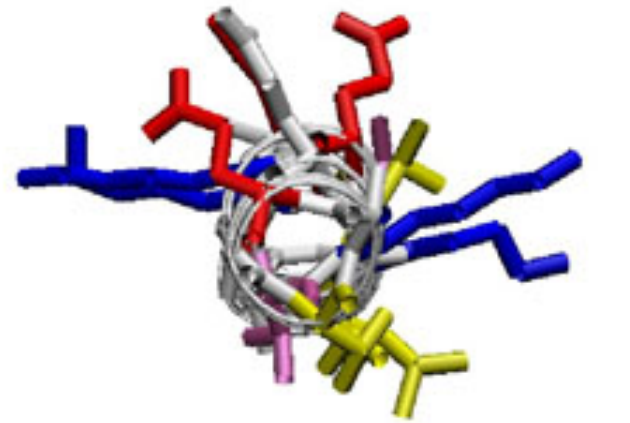
Drin, Morello et al. Science 2008

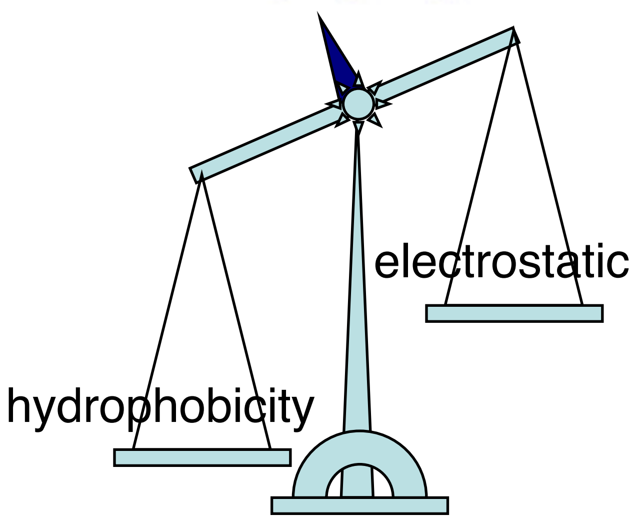

1 µm
A
Tethering resistant to ArfGAP1
N
ALPS
motif
GRAB
domain
Arf1
GTP
radius < 50 nm
GMAP-210
ArfGAP1

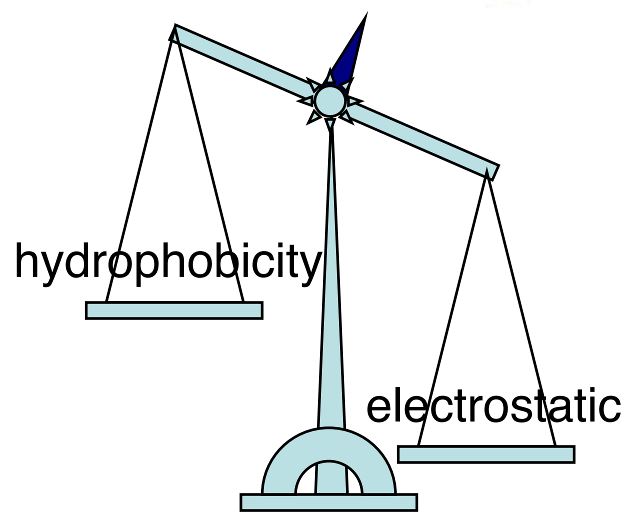
ALPS and α-synuclein: yin and yang

Davidson, W.S., A. Jonas, D.F. Clayton, and J.M. George. 1998. Stabilization of alpha-synuclein secondary structure upon binding to synthetic membranes. J. Biol. Chem. 273:9443–9449.

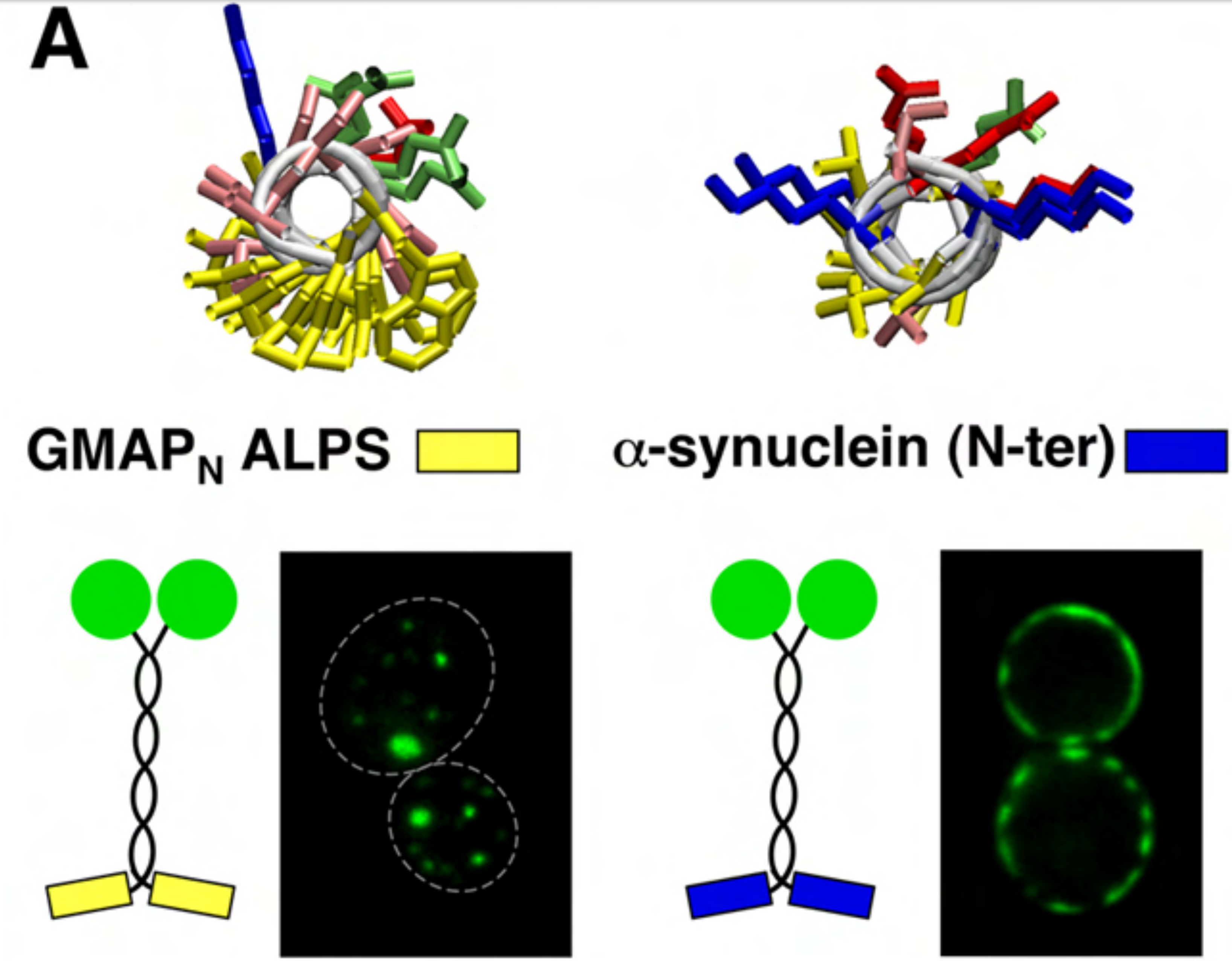




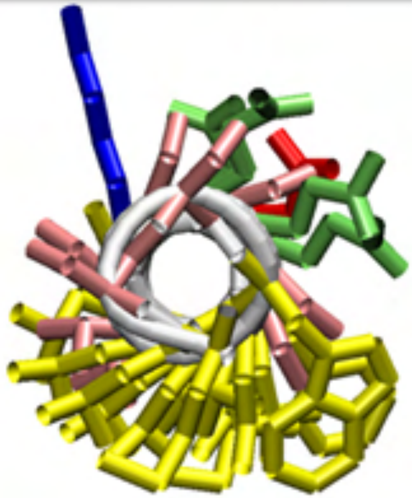


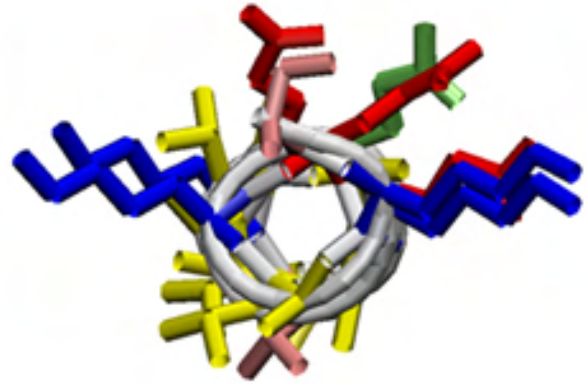


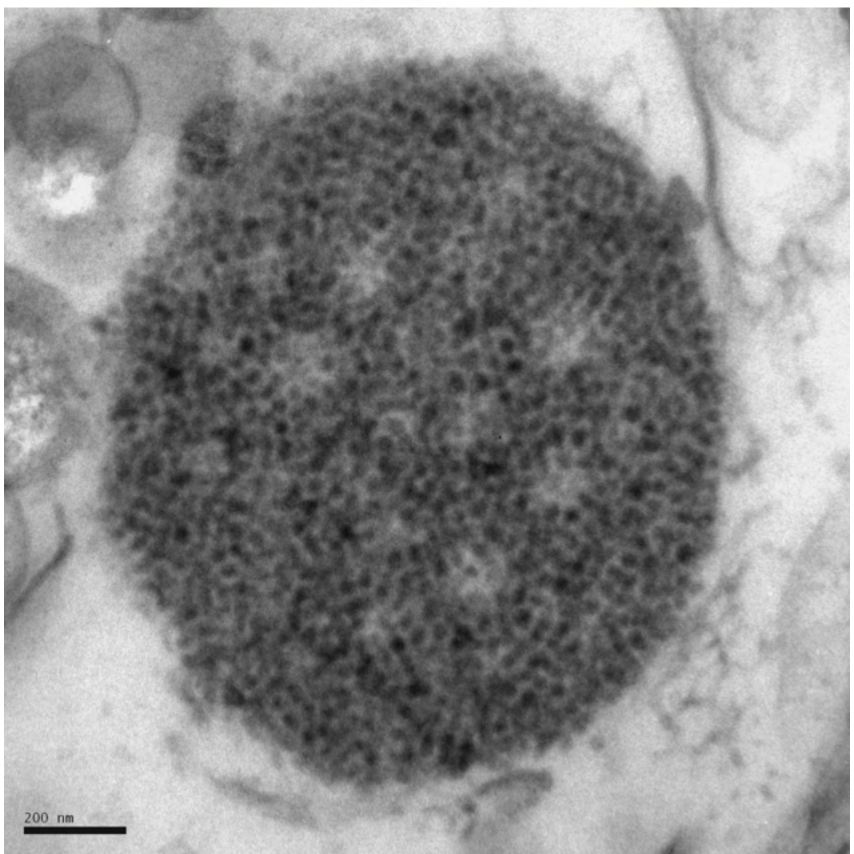
GMAP$_N$ and α-synuclein in yeast cells: contrasting localization

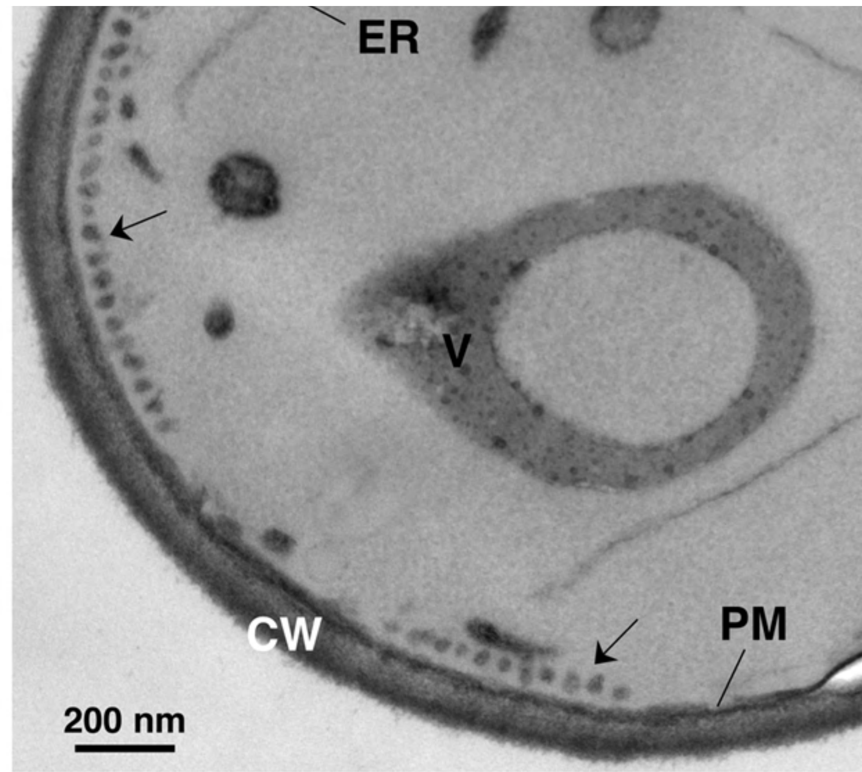


GMAP$_N$ and α-synuclein in yeast cells: contrasting localization

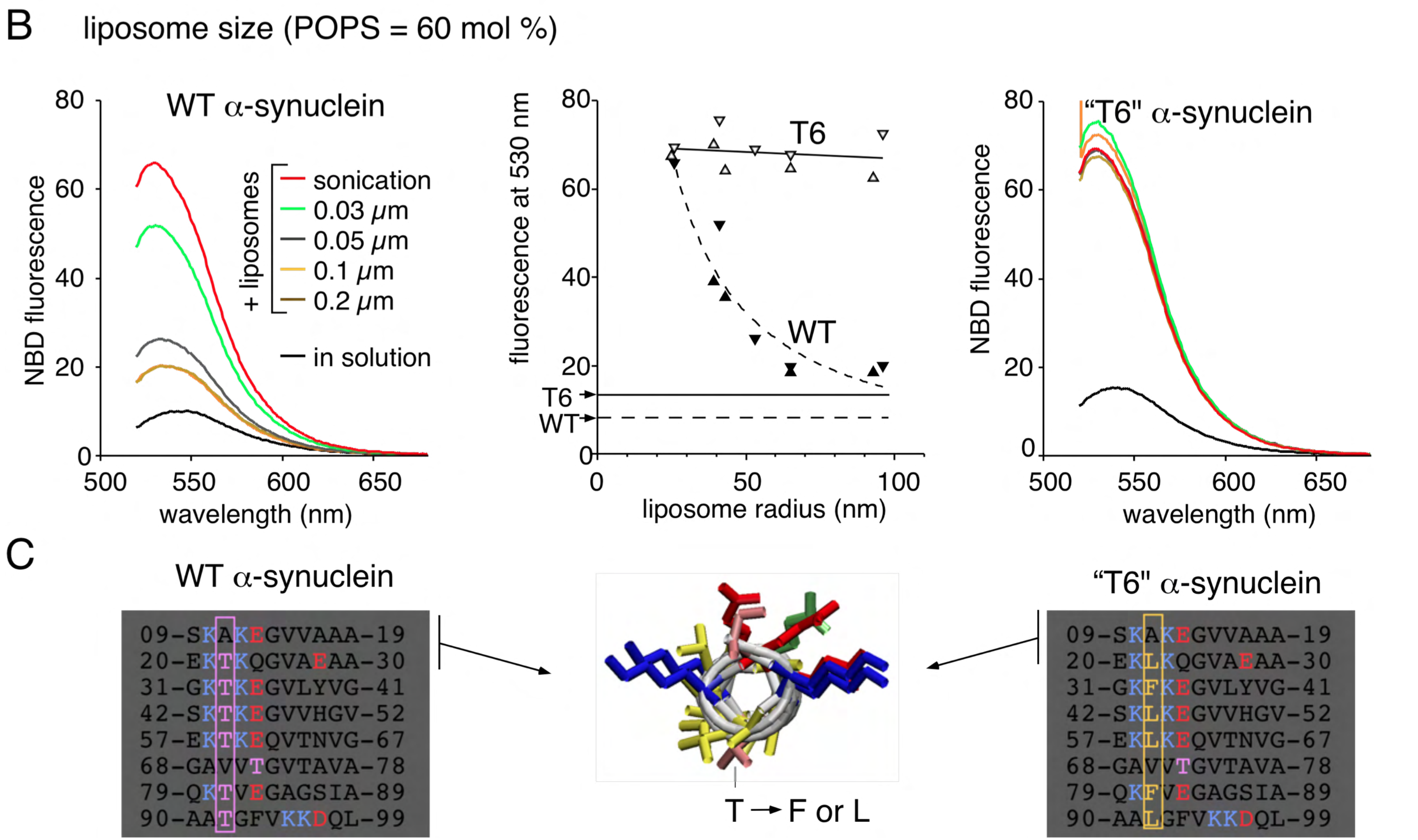




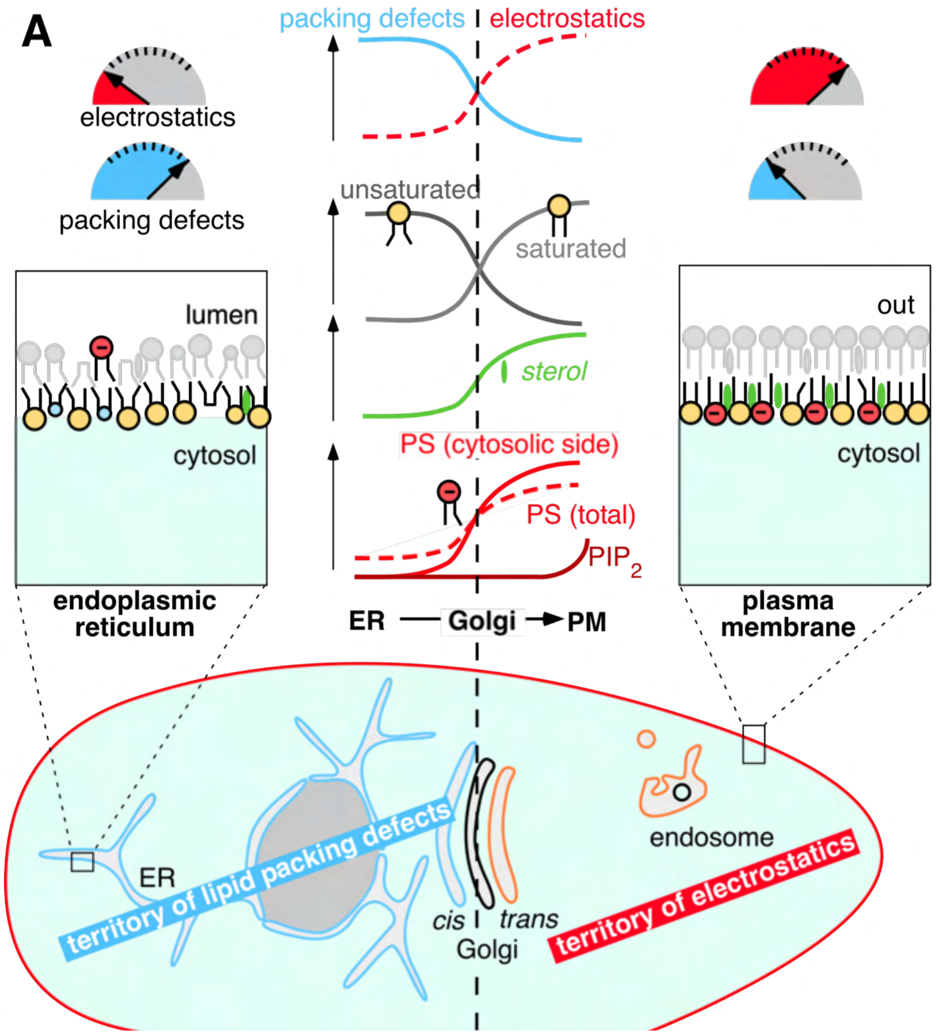




GMAP$_N$ and α-synuclein on liposomes: contrasting sensitivities to charges and packing

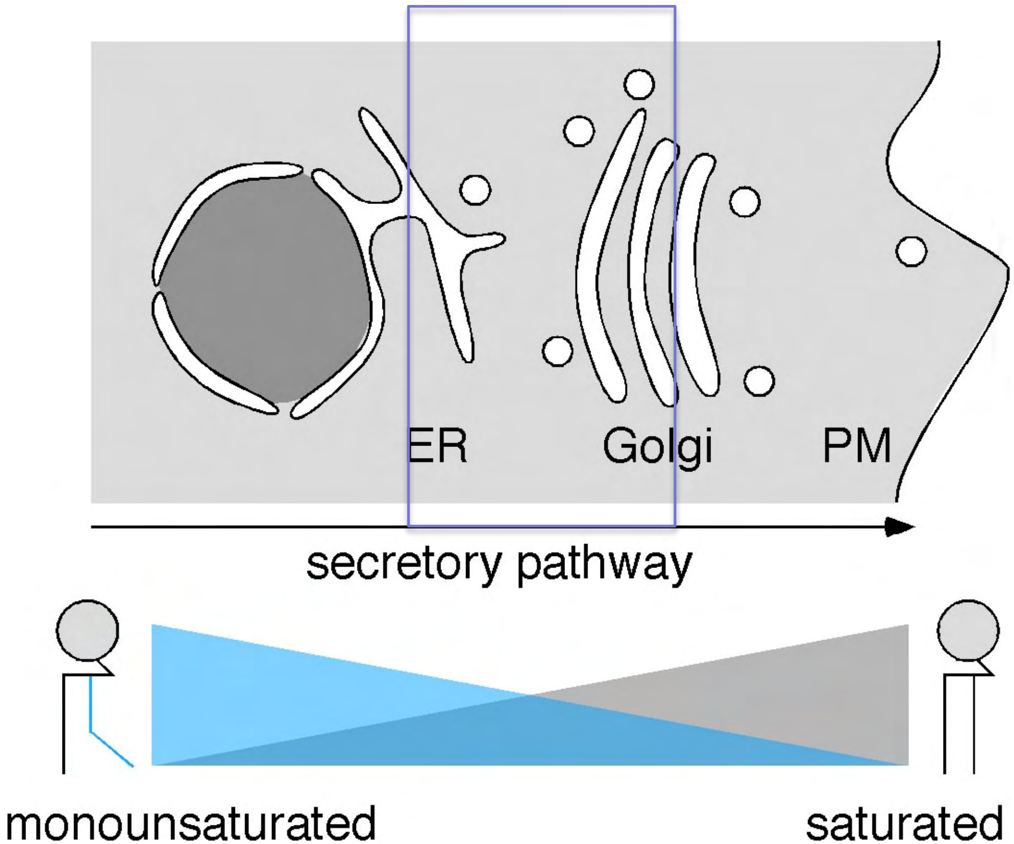


Two main membrane territories



Bigay Antonny Dev Cell 2012

ALPS territory: curvature and lipid monounsaturation



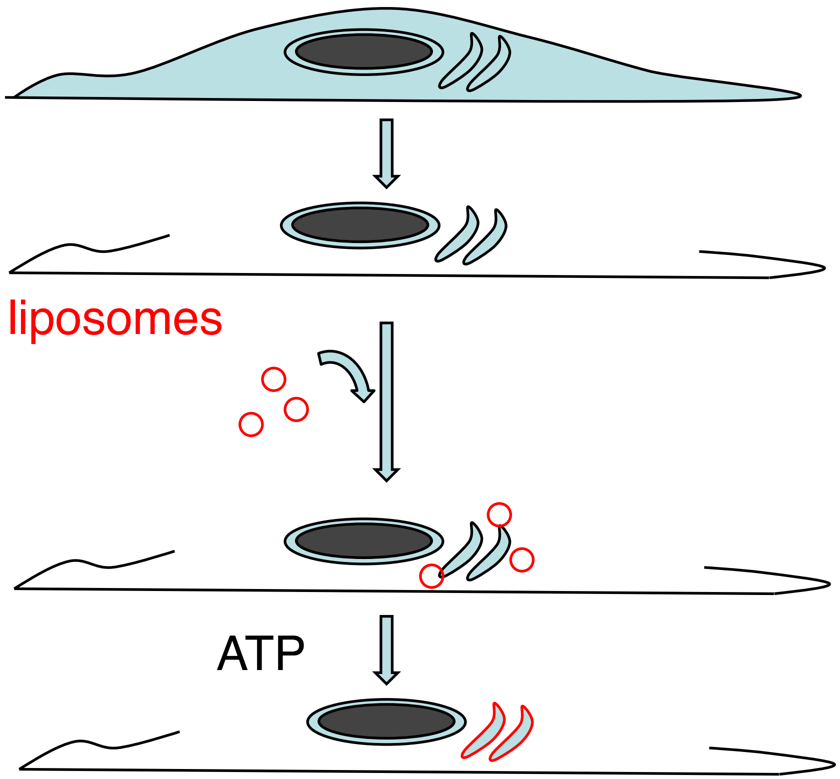
A forgotten paper

Cell, Vol. 55, 797–805, December 2, 1988, Copyright © 1988 by Cell Press

ATP-Dependent Fusion of Liposomes with the Golgi Apparatus of Perforated Cells

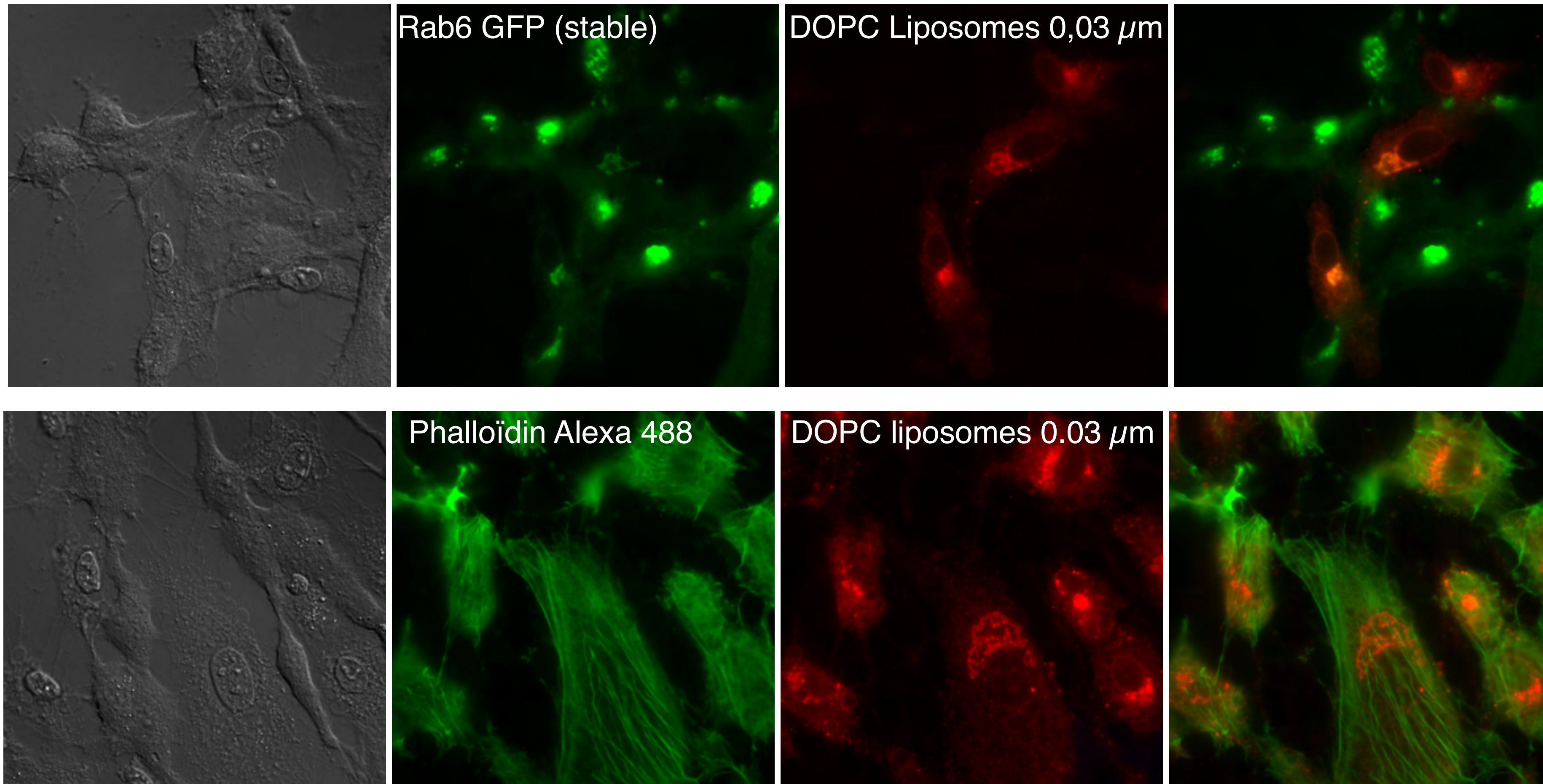
Toshihide Kobayashi and Richard E. Pagano
Department of Embryology
Carnegie Institution of Washington
Baltimore, Maryland 21210

that ER-to-Golgi transport vesicles are approximately 60 nm in diameter (Nowack et al., 1987); ER-to-Golgi transport vesicles in human hepatoma cells appear to be very light in density (Lodish et al., 1987); and Golgi transport vesicles do not contain clathrin (Orci et al., 1986).



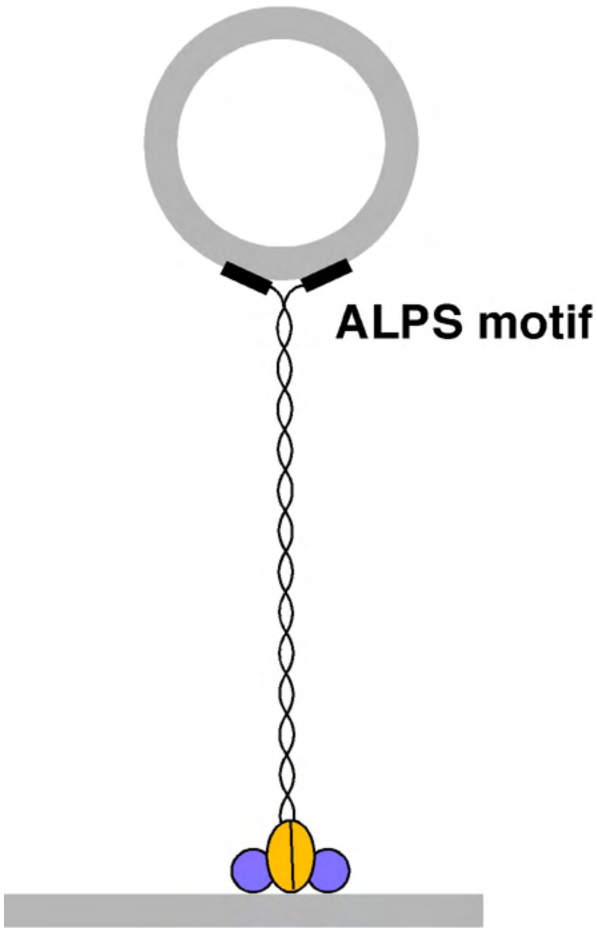
The Kobayashi Pagano experiment…30 years later

Maud de Saint-Jean

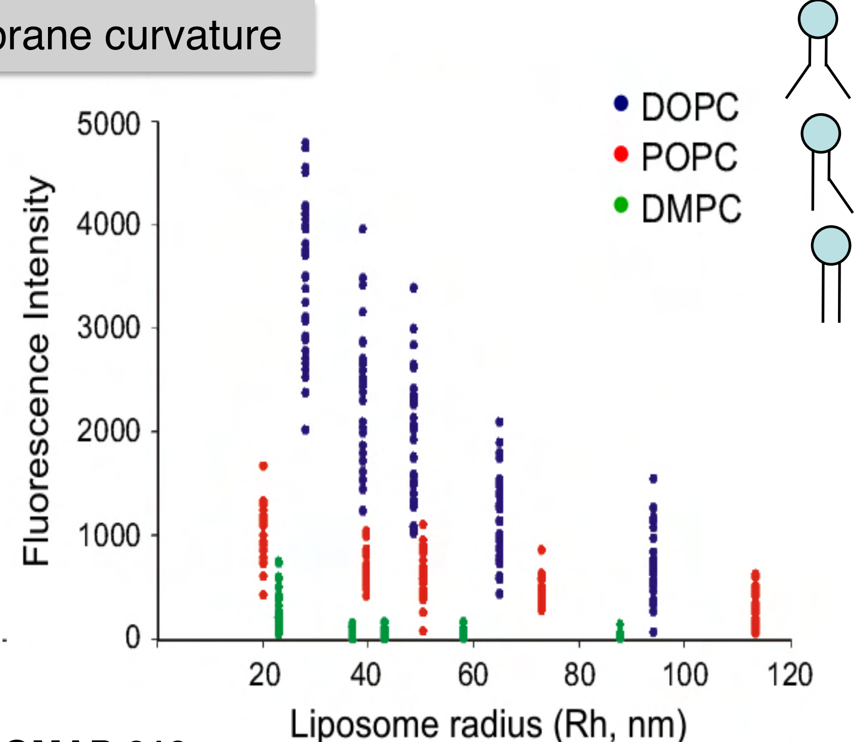


Retinal pigment epithelial cells

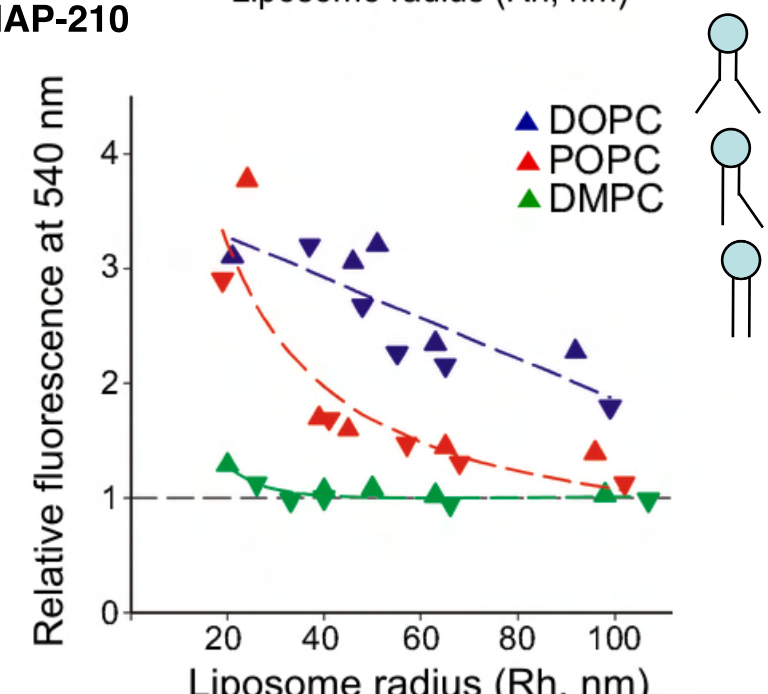
Cumulative effects of lipid unsaturation and membrane curvature



perforated cells

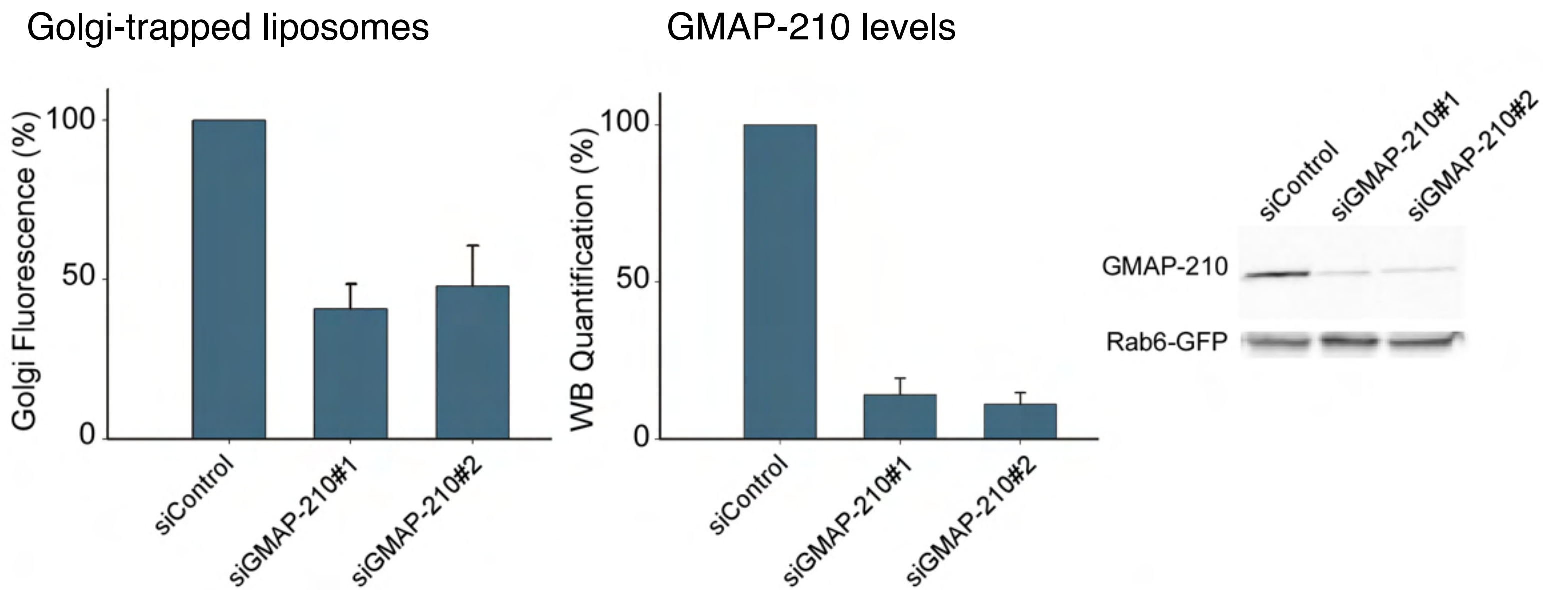


purified GMAP-210



Magdelaine et al. *eLife* (2016)

Knocking down GMAP-210 by siRNA

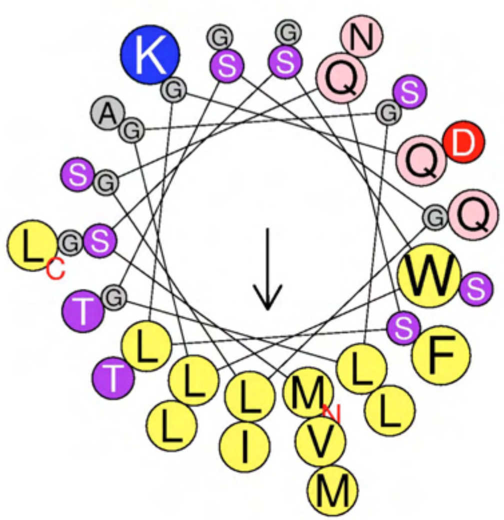


Magdelaine et al. *eLife* (2016)

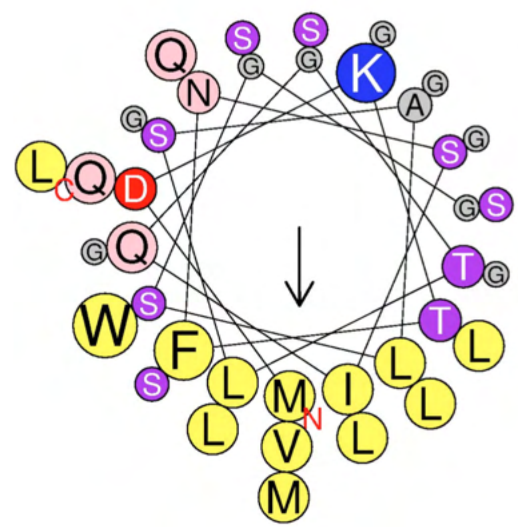
Inversion of the ALPS sequence : to rule out specific interactions

```
ALPS (GMAP-210)    : 1-MSSWLGGLGSGLGQSLGQVGGSLASLTGQISNFTKDML-38
                       =          =    = = =    =          ==
invALPS (GMAP-210) : 1-MDKTFNSIQGTLSALSGGVQGLSQGLSGLGGLWSSML-38
```

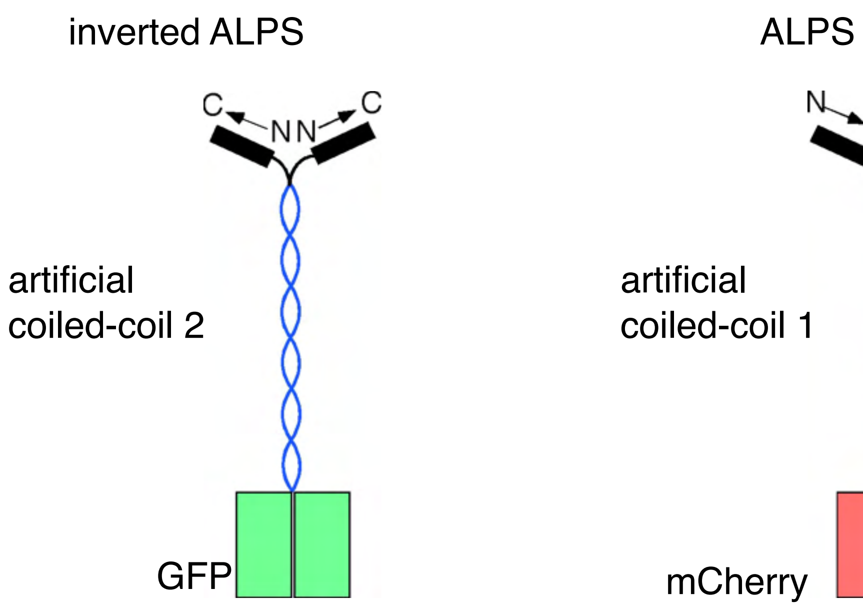
ALPS

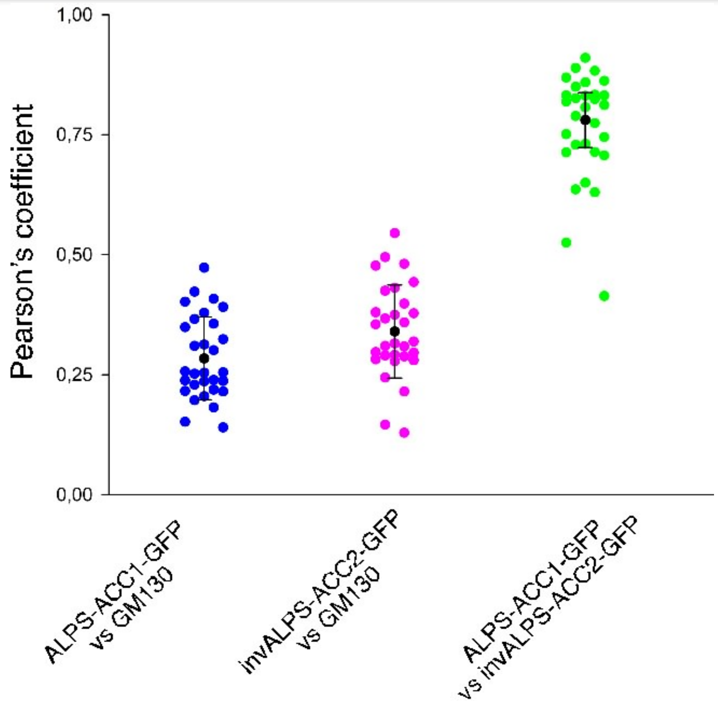


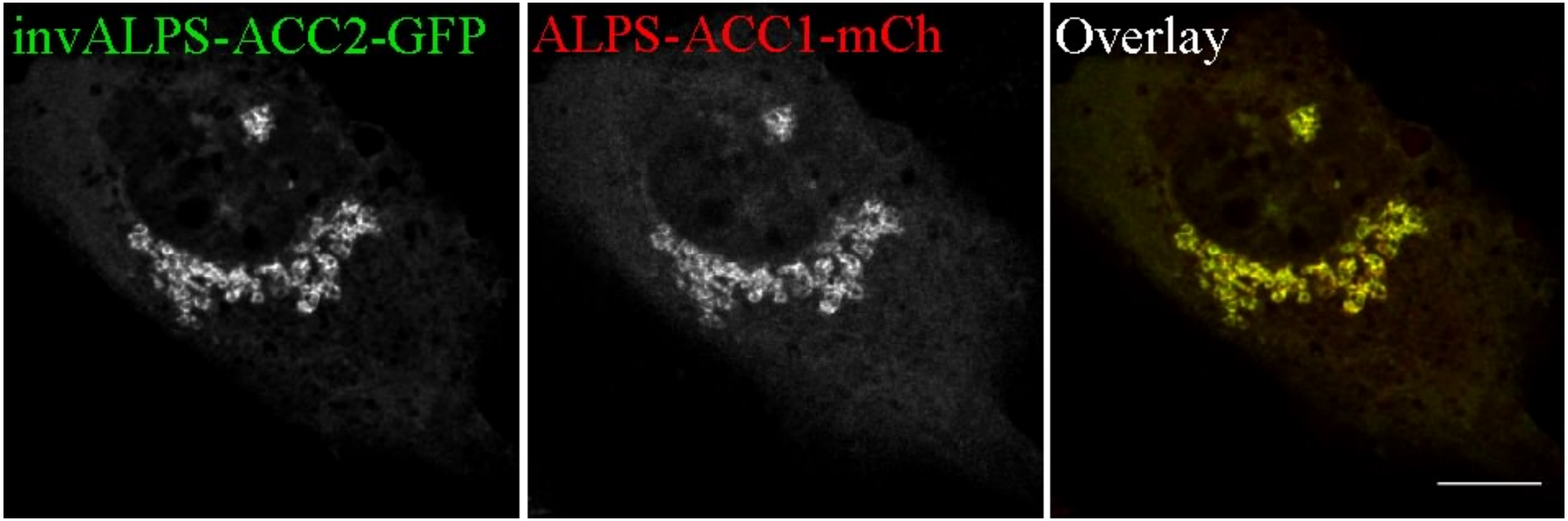
invALPS



Inversion of the ALPS sequence : to rule out specific interactions

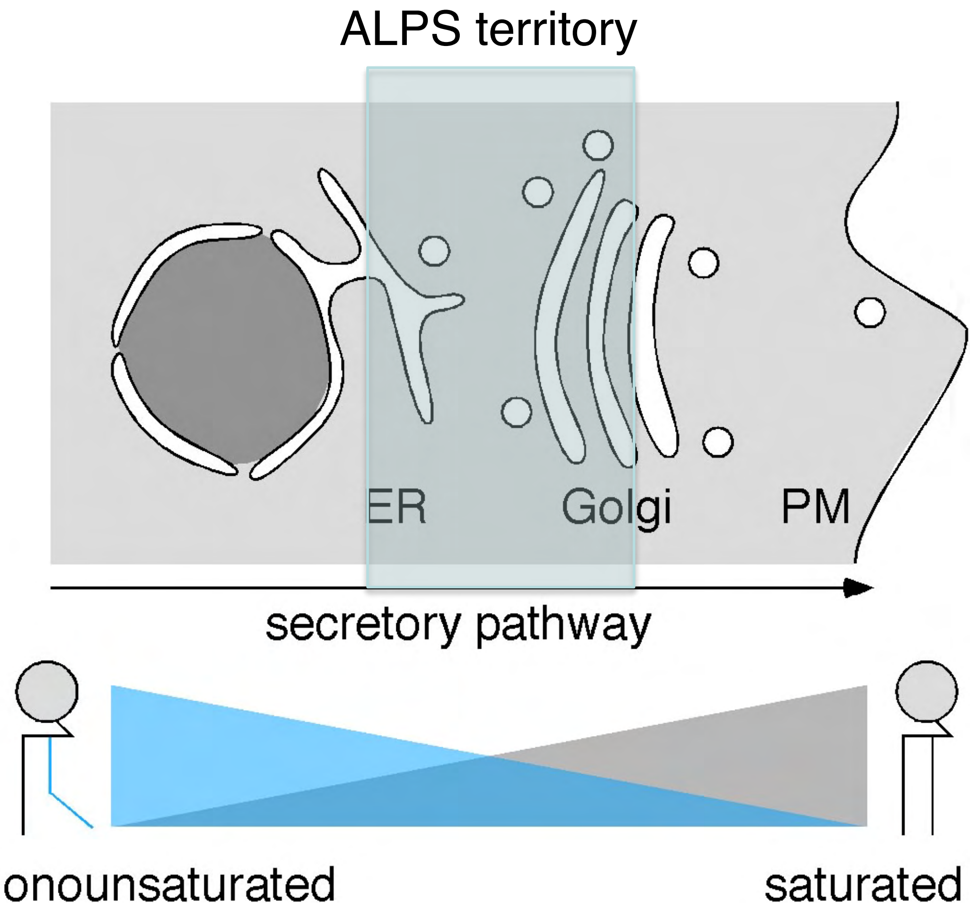




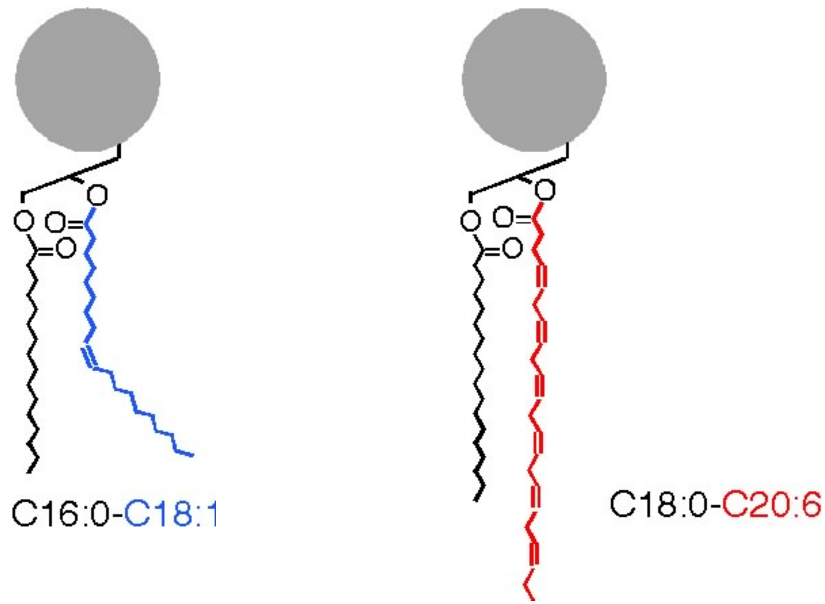


The advantage of a monotonous sequence

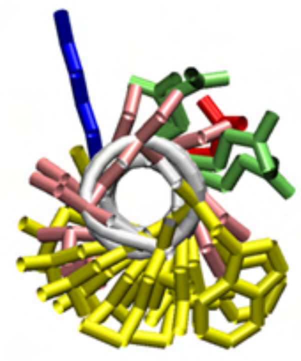
MSSWLGGLGSGLGQSLGQVGGSLASLTGQISNFTKDML

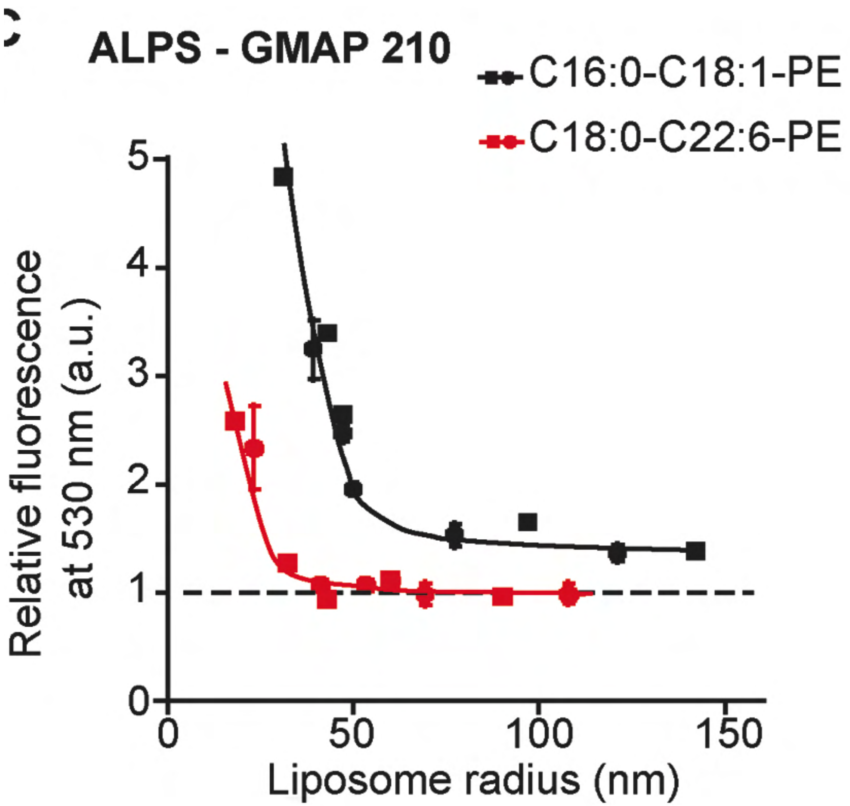


How do polyunsaturated phospholipids behave as regards to lipid packing?



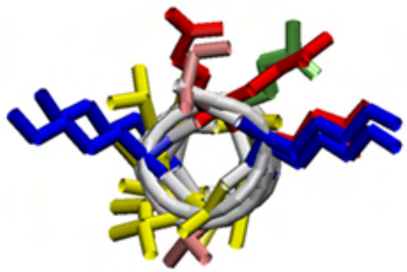
How do polyunsaturated phospholipids compare to monounsaturated phospholipids ?

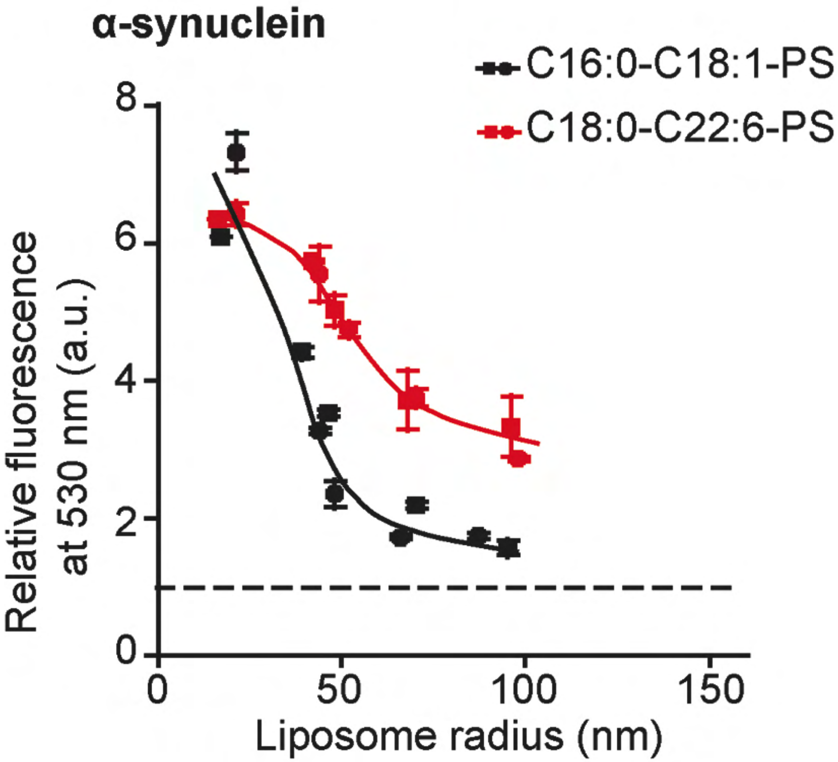


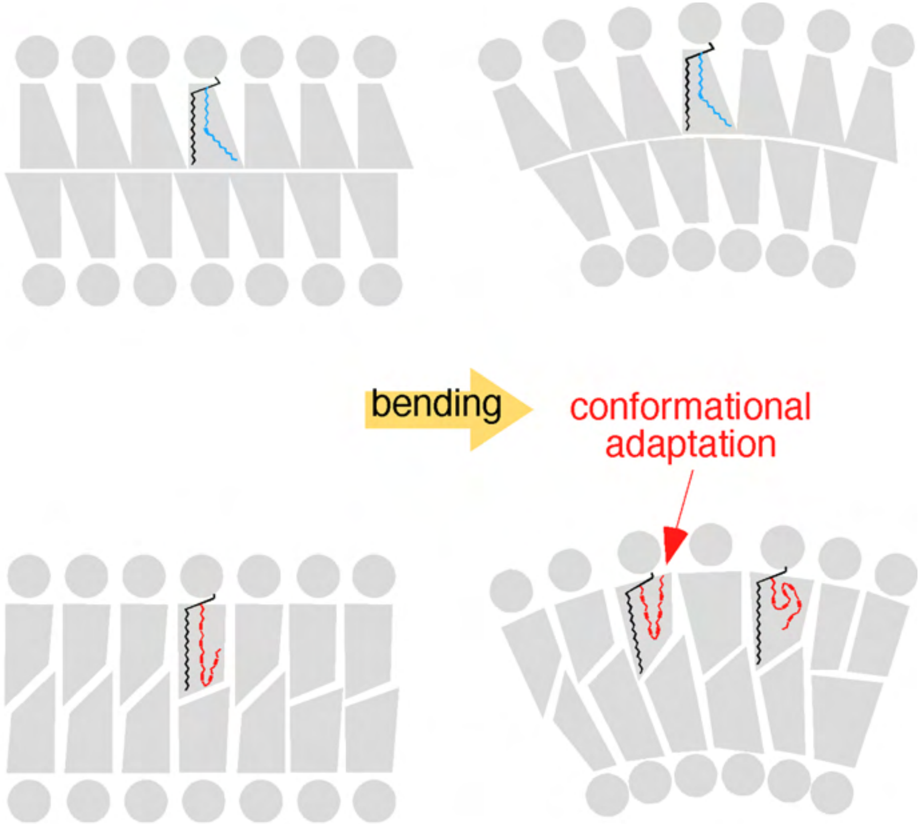


Pinot et al. *Science* (2014

How do polyunsaturated phospholipids compare to monounsaturated phospholipids ?



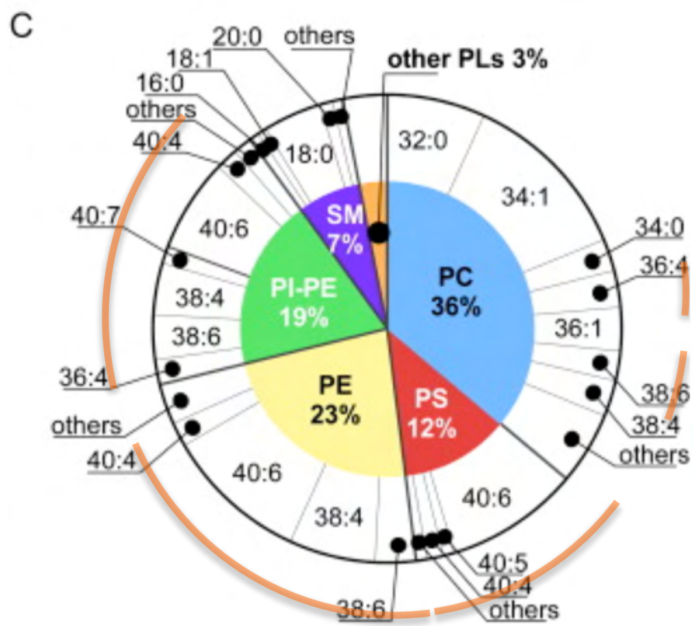


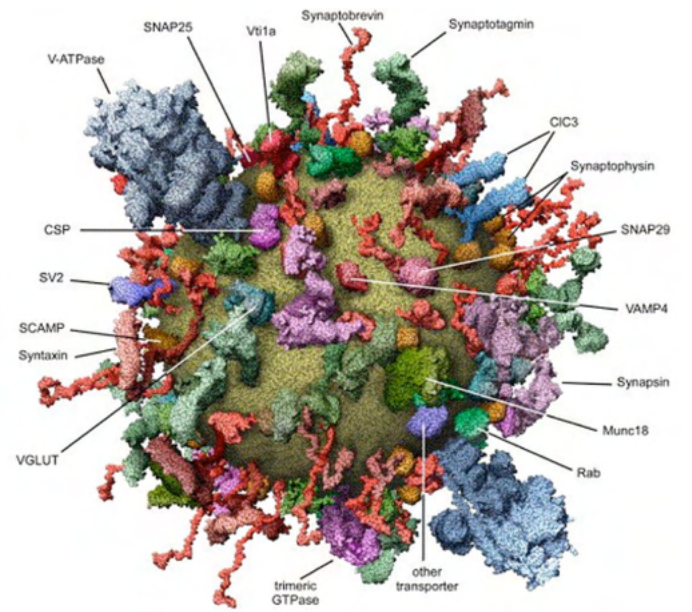


Pinot et al. *Science* (2014)

Synaptic vesicles are very rich in polyunsaturated phospholipids

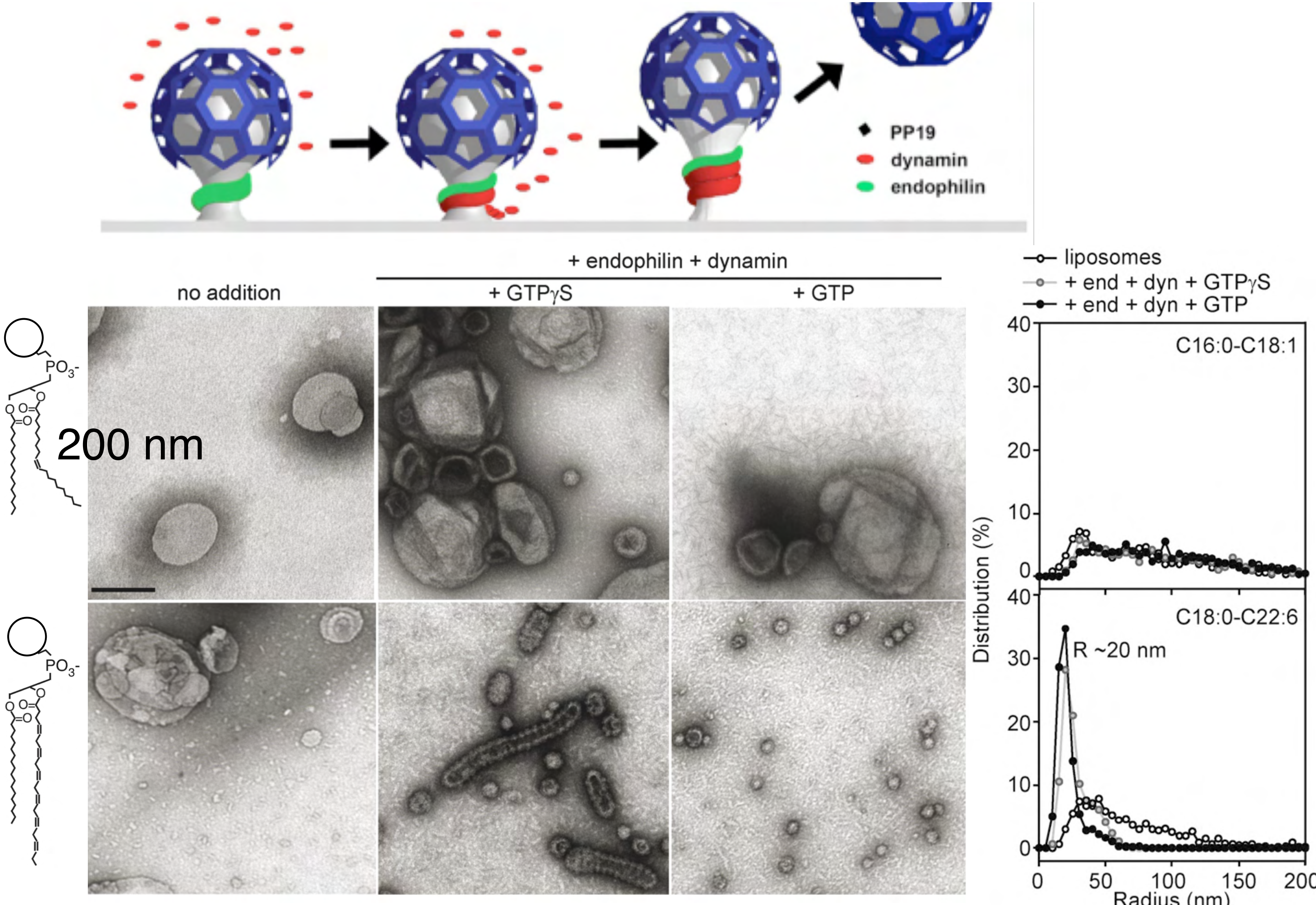
Quantitative analysis of the lipids of synaptic vesicles





Takamori S, et al
Cell. 2006 Nov 17;127(4):831-46.

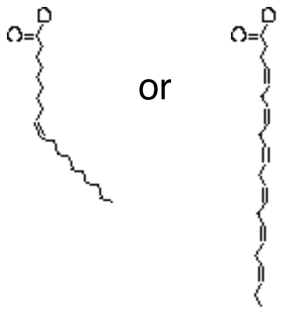
Polyunsaturated lipids and membrane deformation and fission



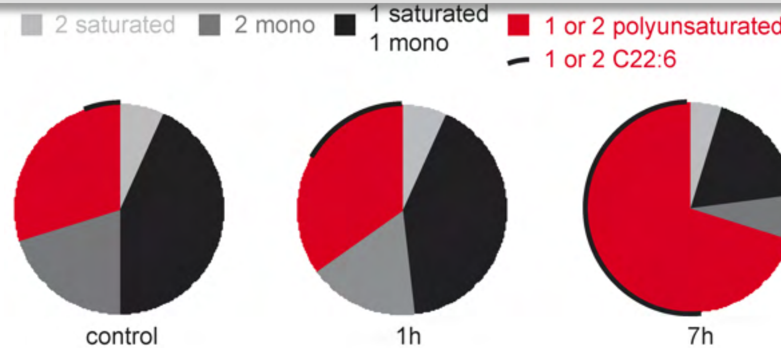
Pinot et al. *Science* (2014)

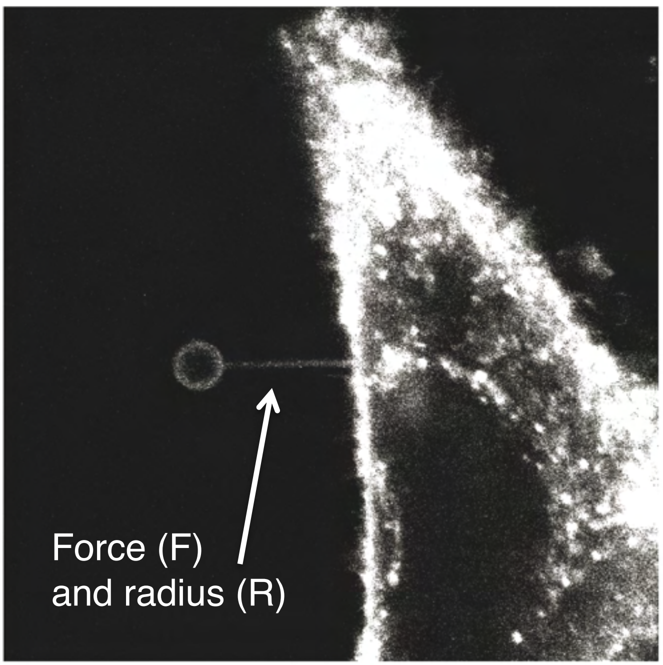
Plasma membrane mechanical properties

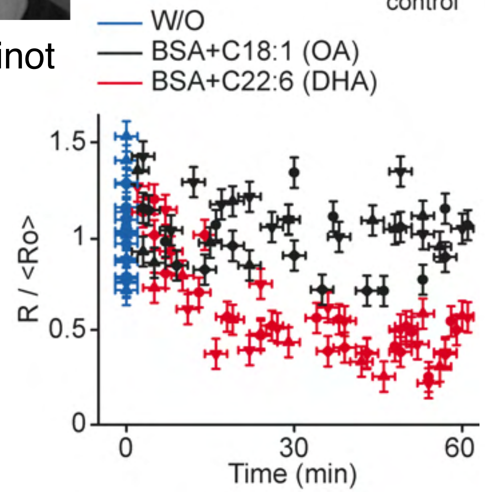
C18:1 or C22:6

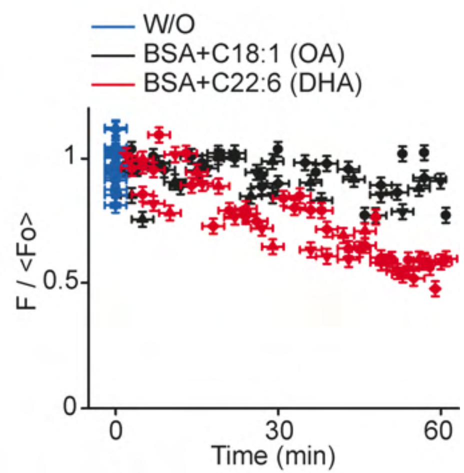


Mathieu Pinot

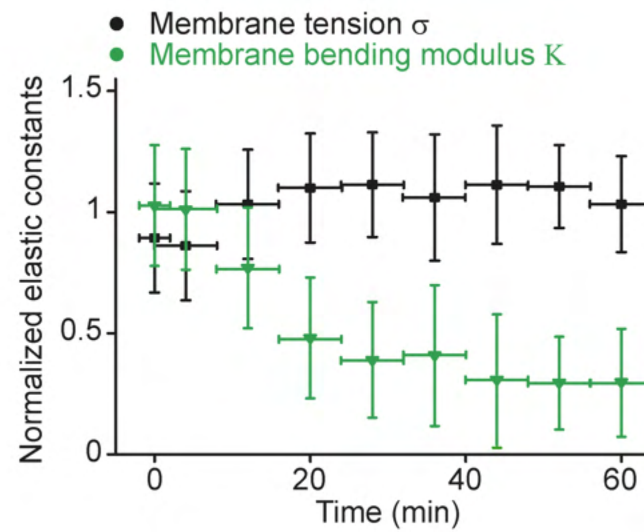






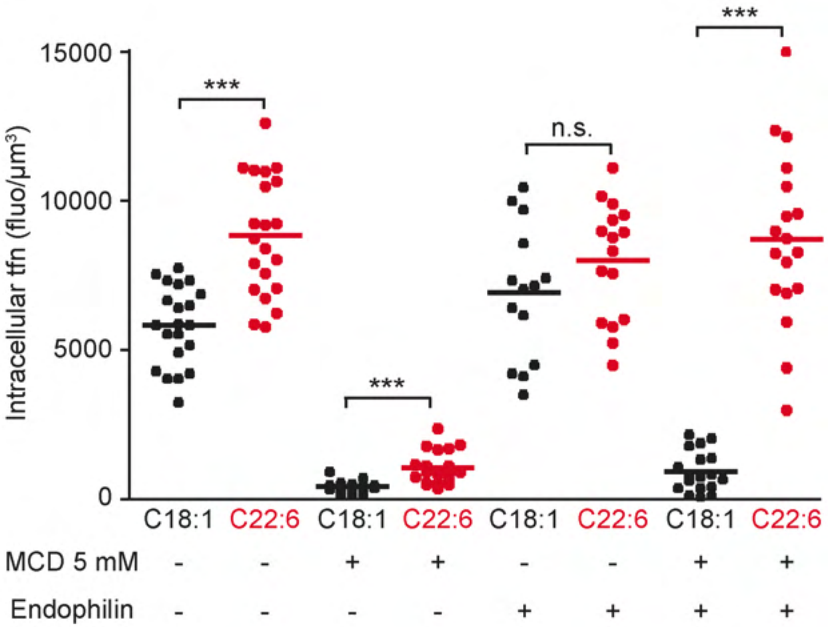


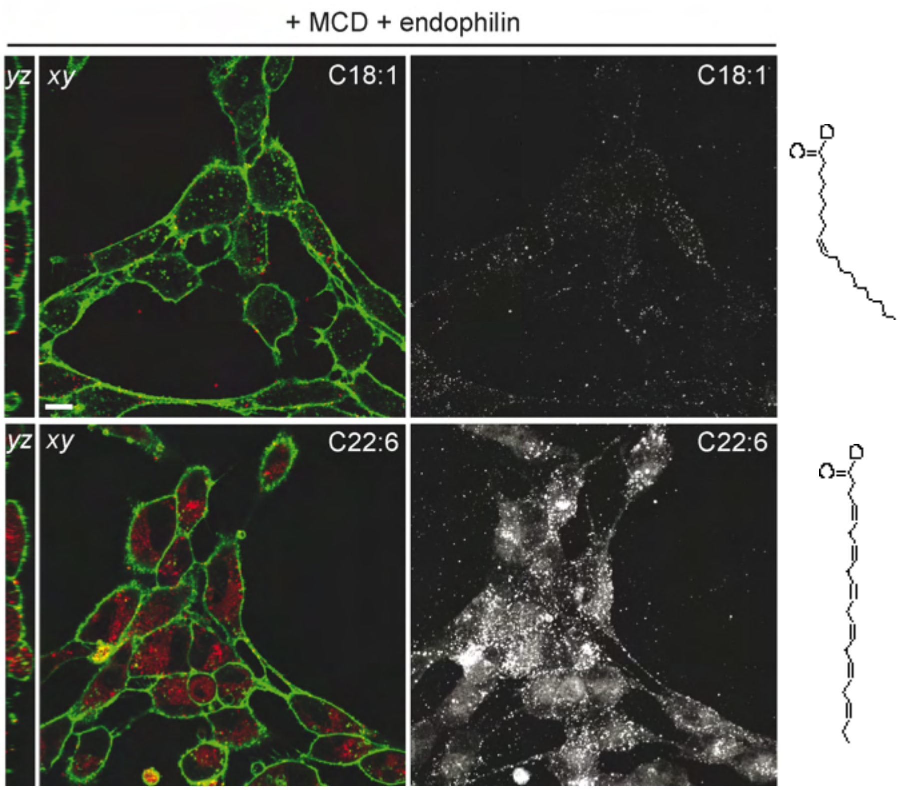
$\kappa = FR/2\pi$ $\sigma = F/(4\pi R)$



Pinot et al. *Science* (2014)

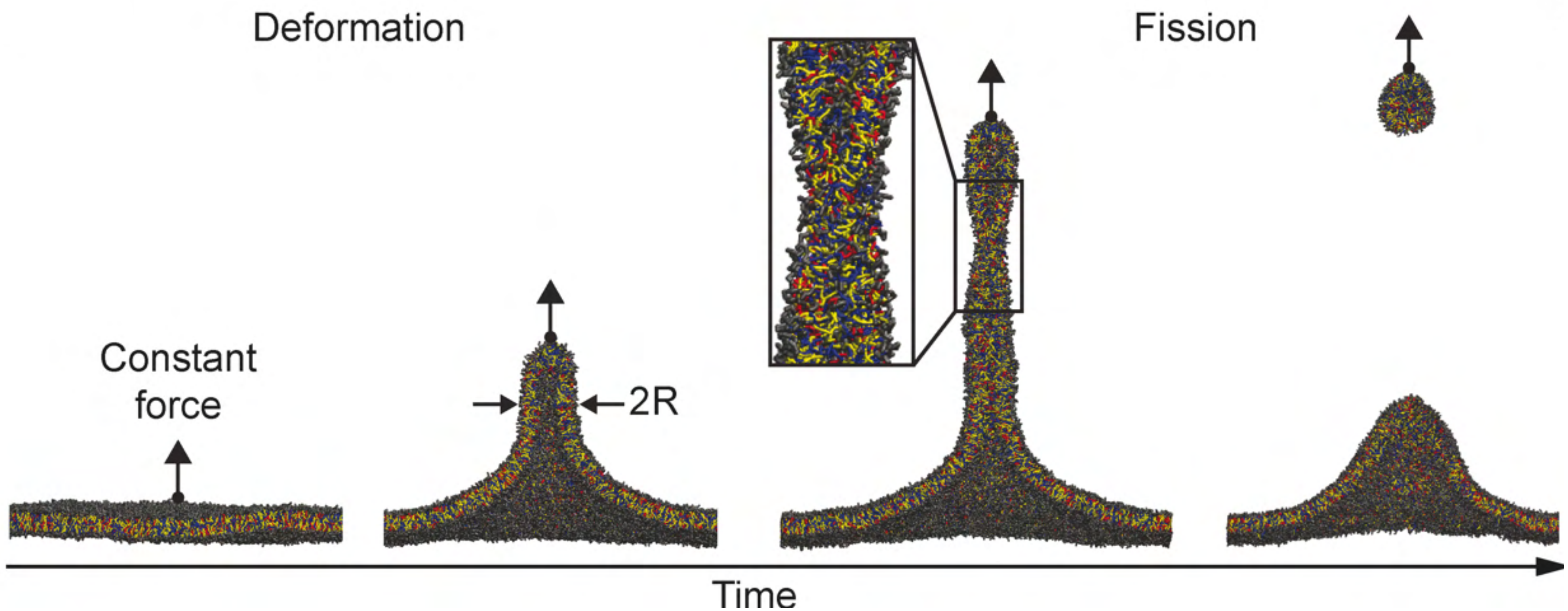
Hélène Barelli



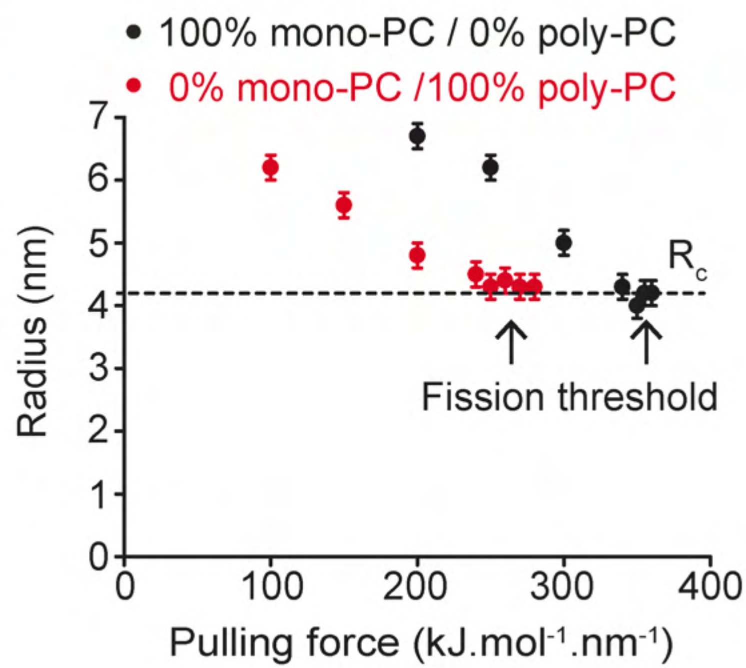


Pinot et al. *Science* (2014)

Molecular dynamics simulations



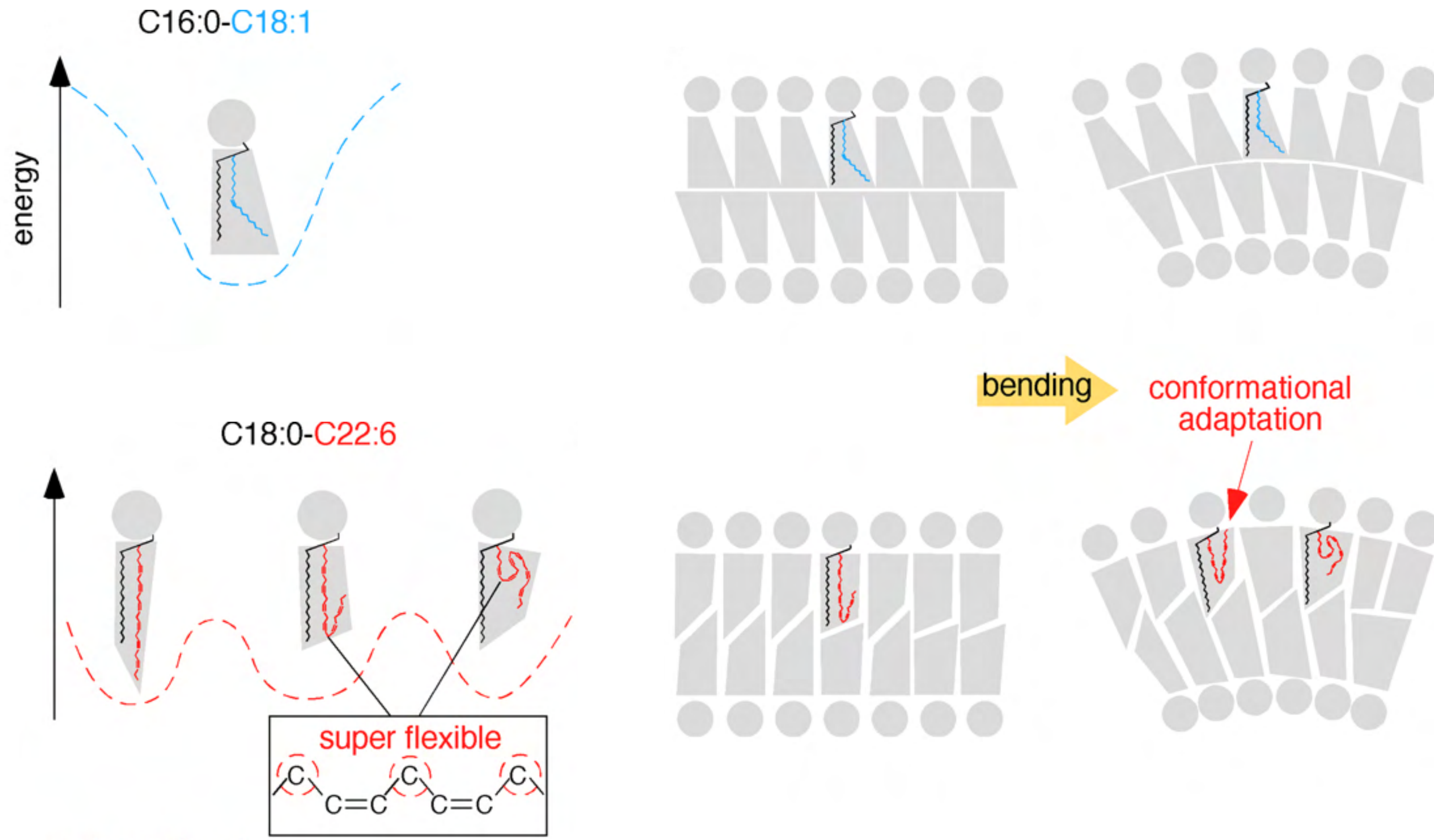
Romain Gautier



Stefano Vanni

Pinot et al. *Science* (2014)

Polyunsaturatated phospholipids are contortionists



Antonny et al *Trends in Cell Biol* 2015

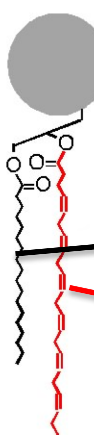
A striking feature of brain lipids as found in 1968

Positional distribution of fatty acids in glycerophosphatides of bovine gray matter

HYAKUJI YABUUCHI* and JOHN S. O'BRIEN

Department of Pathology, University of Southern California School of Medicine, Los Angeles, California 90033

JOURNAL OF LIPID RESEARCH VOLUME 9, 1968 65



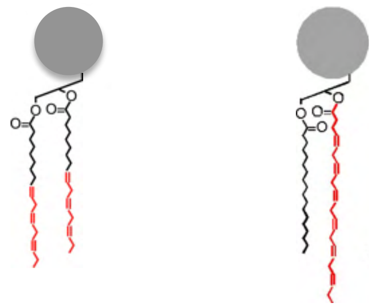
C18:0-C20:6

TABLE 1 FATTY ACIDS OF ETHANOLAMINE GLYCEROPHOSPHATIDES

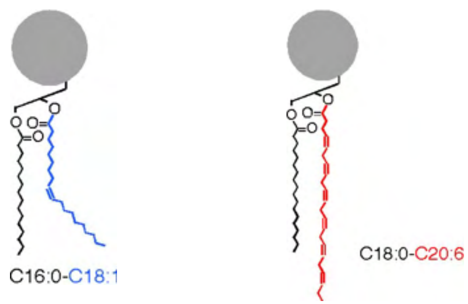
	1-FA	2-FA	Total	Expected
14:0	0.8	0.2	0.3	0.4
15:0	1.0		0.5	0.3
16:0	17.5	3.6	8.4	8.3
16:1	1.6	0.6	0.8	0.9
17:0	1.8		0.2	0.6
18:0	65.0	3.4	28.5	24.4
18:1	12.3	12.6	13.2	12.5
18:2		0.2	0.2	0.1
20:1		0.6	0.2	0.4
20:4		20.5	13.2	13.6
22:5ω6		12.4	6.7	8.2
22:5ω3		1.5	0.5	1.1
22:6		44.4	27.3	29.2
Polyunsaturates		79.0	47.9	52.2

Two fundamental properties of biological membranes

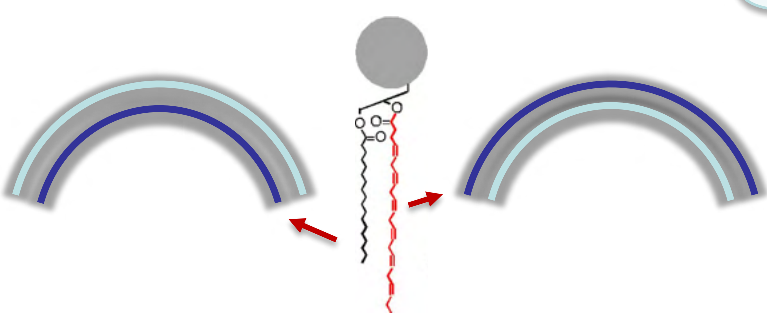
I. Acyl chain asymmetry

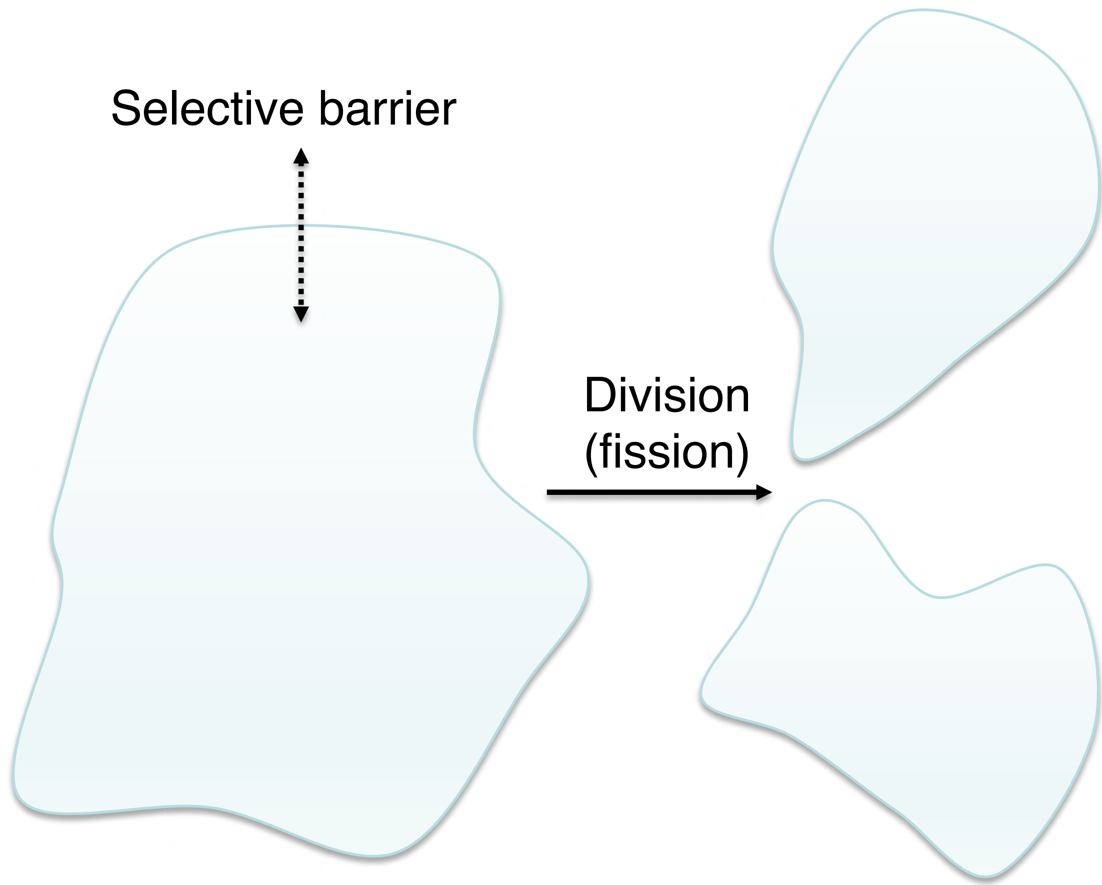


II. Degree of unsaturation

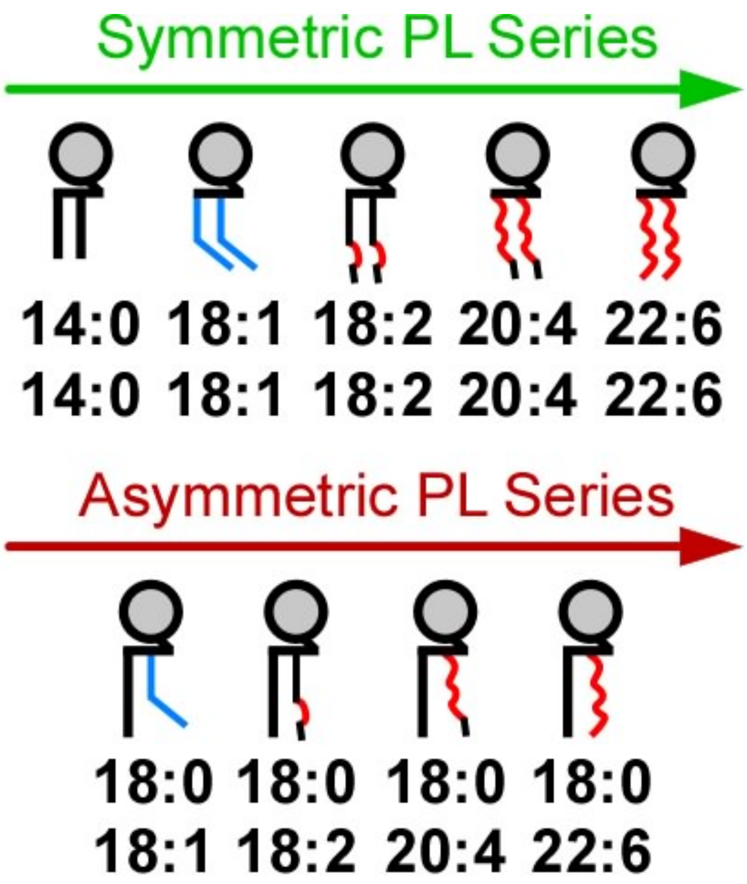


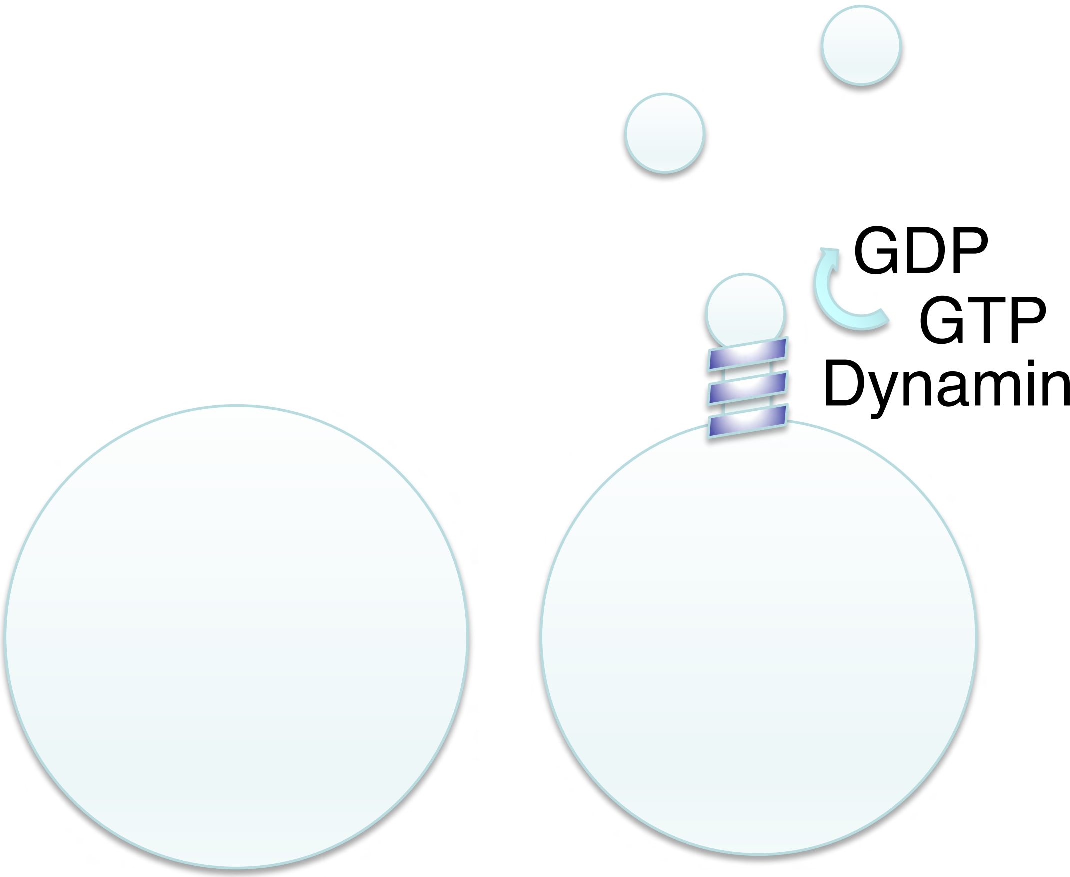
III. Leaflet distribution



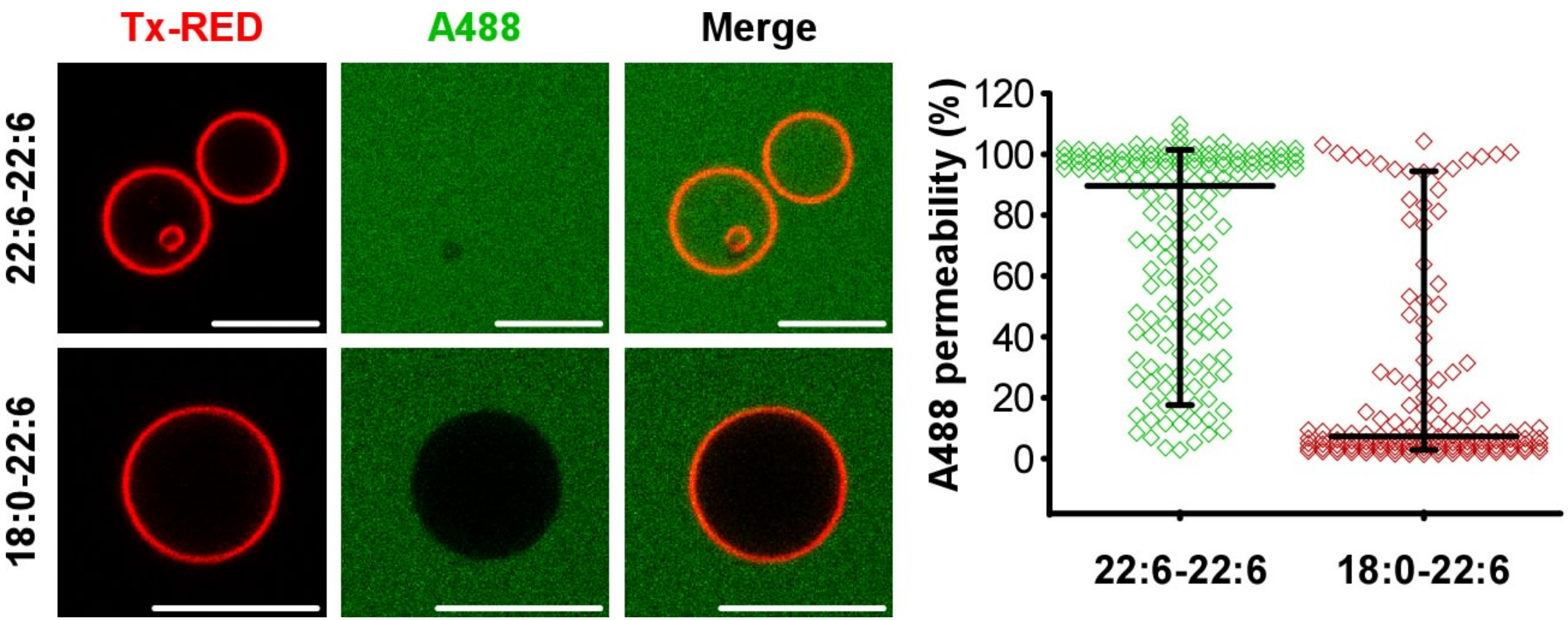


A systematic study

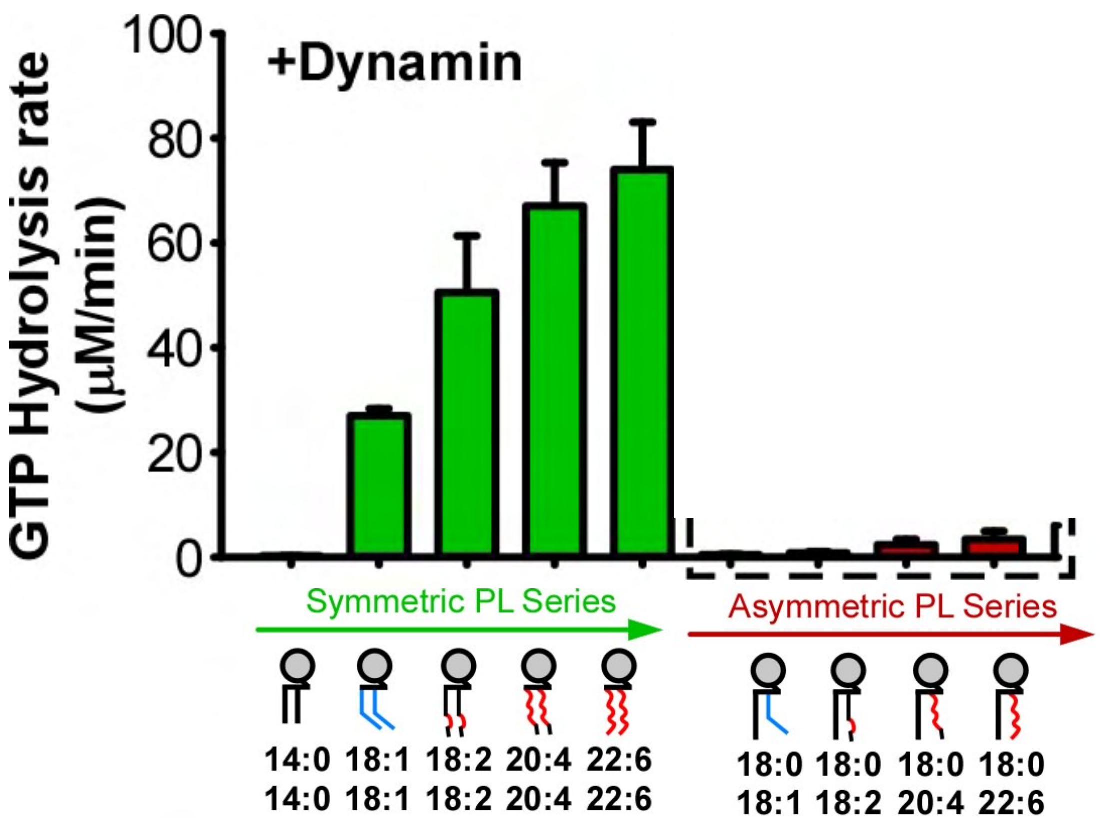




Membranes with symmetric polyunsaturated PLs are leaky to a large solute (≈ 700 Da)

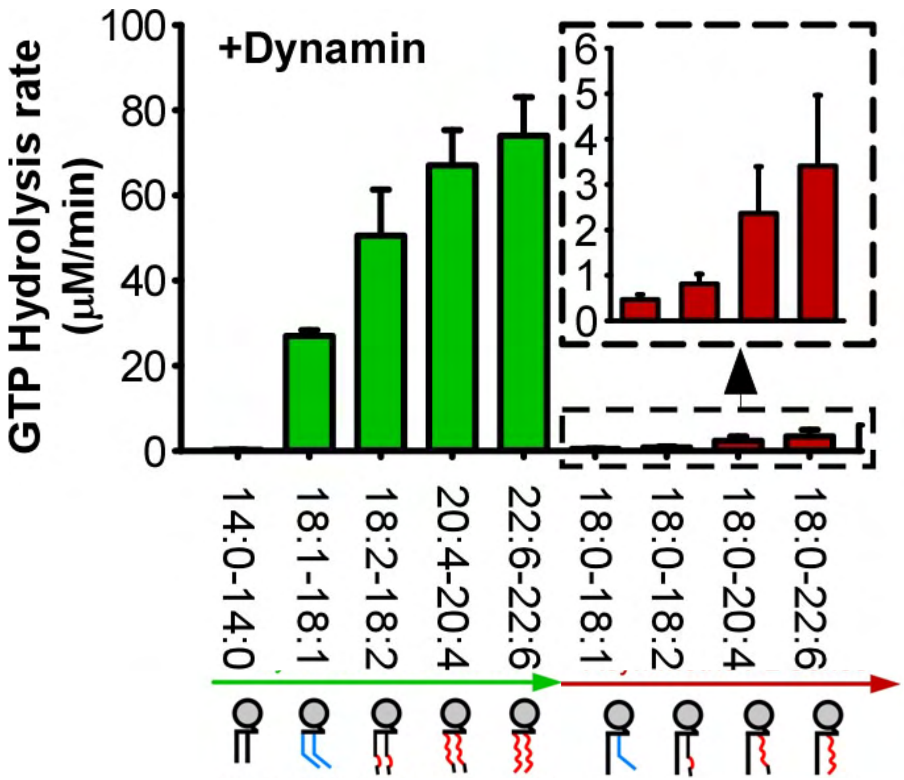


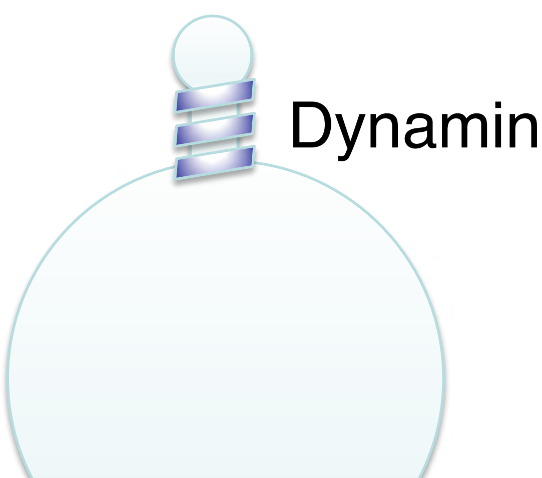
Dramatic effect of acyl chain symmetry

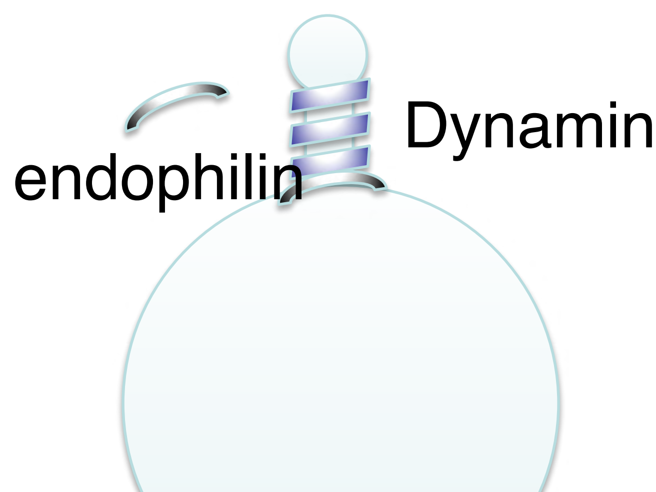


Manni MM, Tiberti M *et al.* Acyl chain asymmetry and polyunsaturation of brain phospholipids facilitate membrane vesiculation without leakage. *eLife* **7,** (2018).

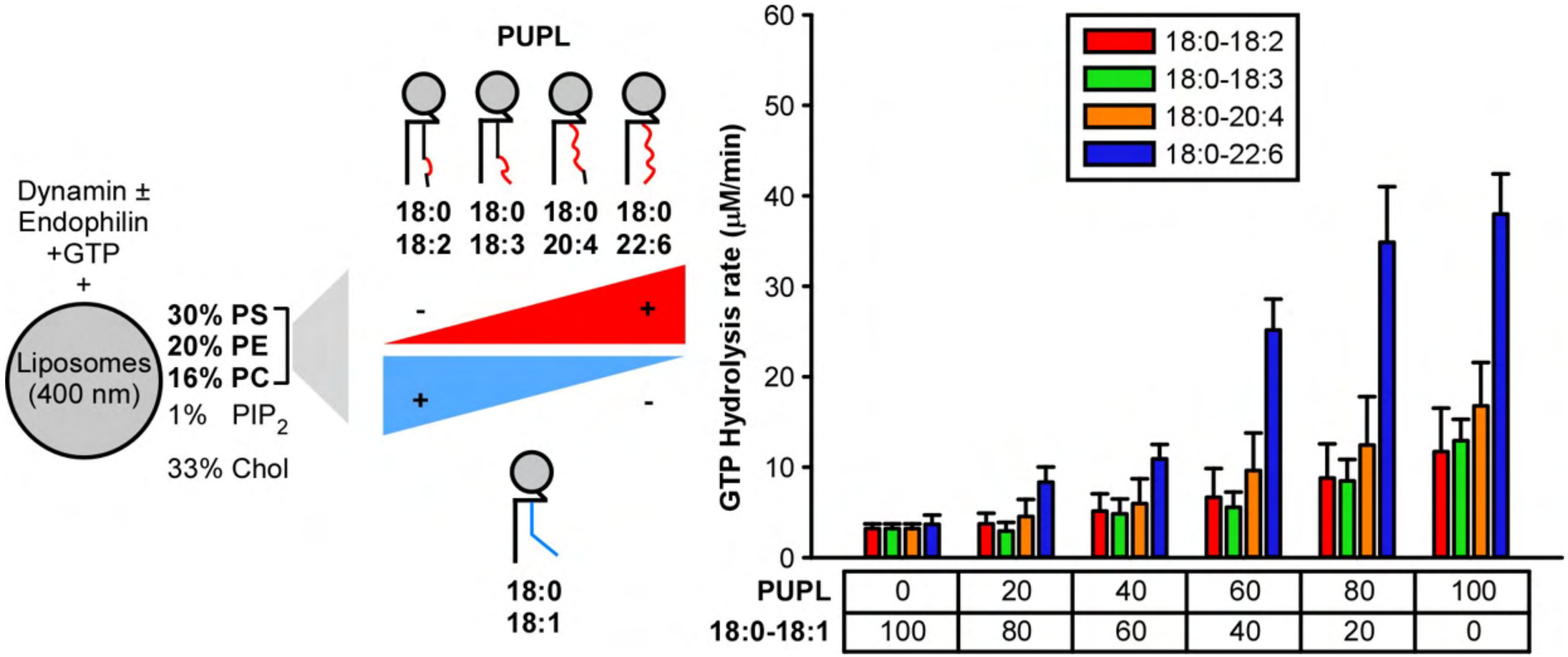
Membranes with asymmetric polyunsaturated PLs provide a compromise







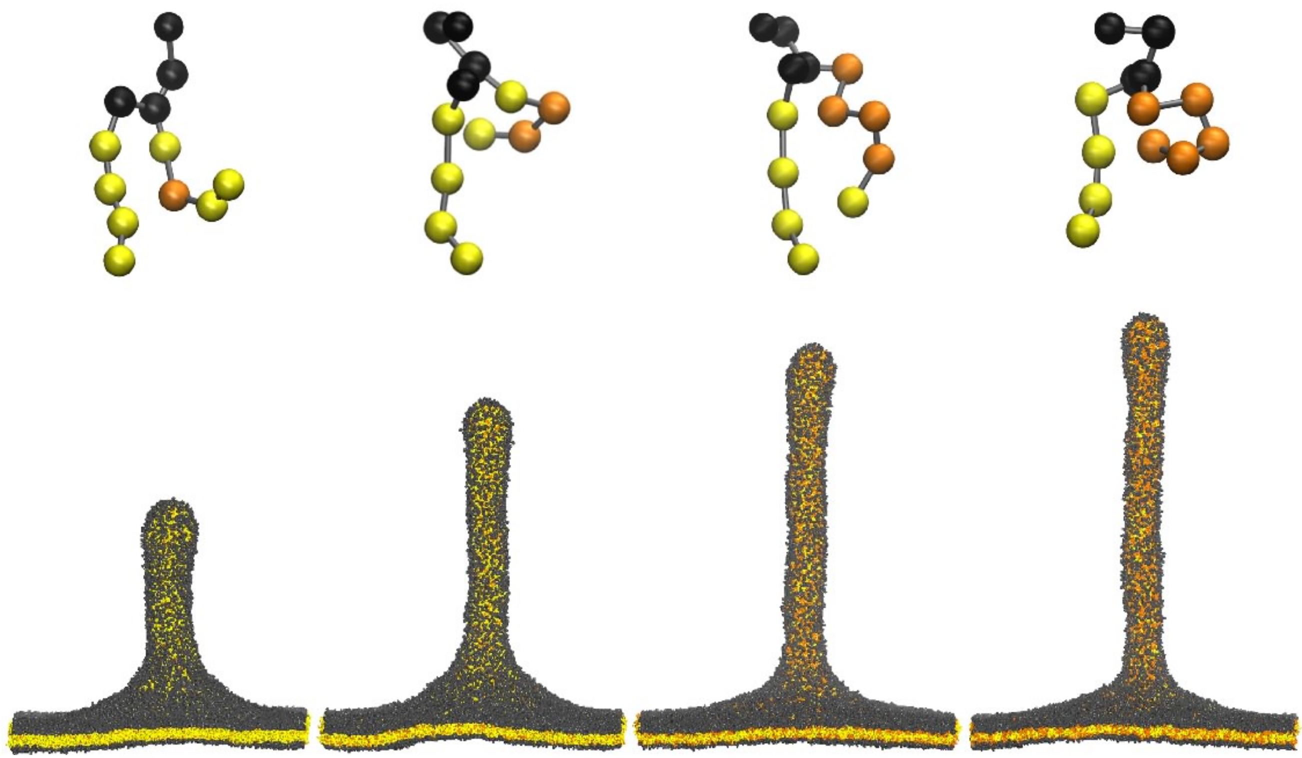
DHA (C22:6) surpasses all other polyunsaturated acyl chains



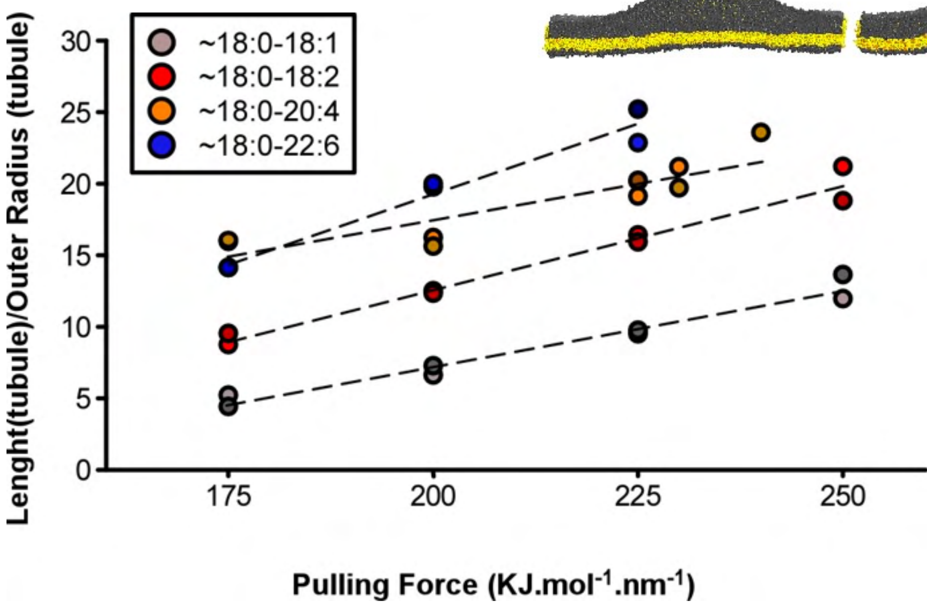
0 ns

A coarse-grained approach

~18:0-18:1 ~18:0-18:2 ~18:0-20:4 ~18:0-22:6

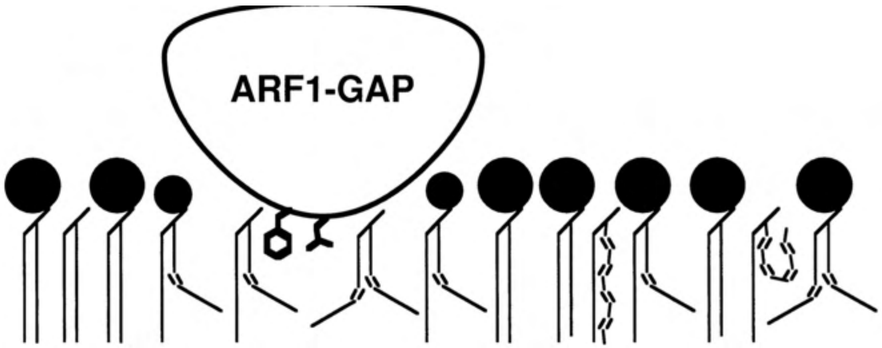


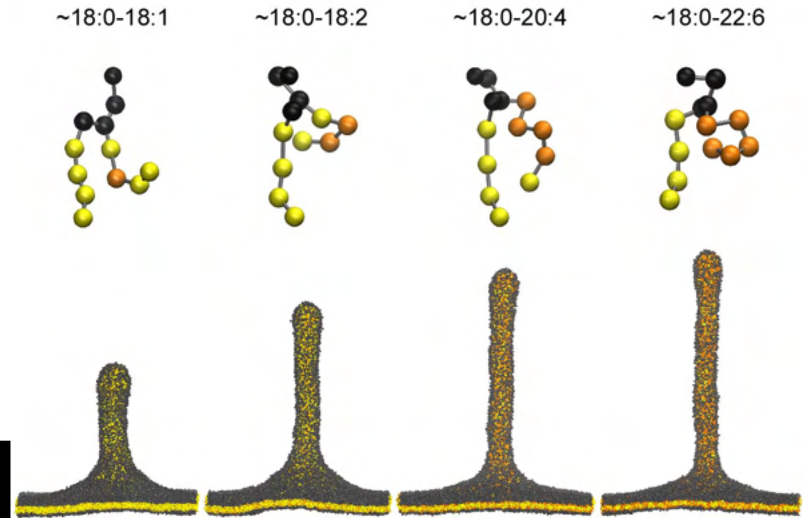
$$E_b = \pi K_b L/R$$



Marion Tiberti

Phospholipid unsaturation, membrane curvature, and cell organelle dynamics





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