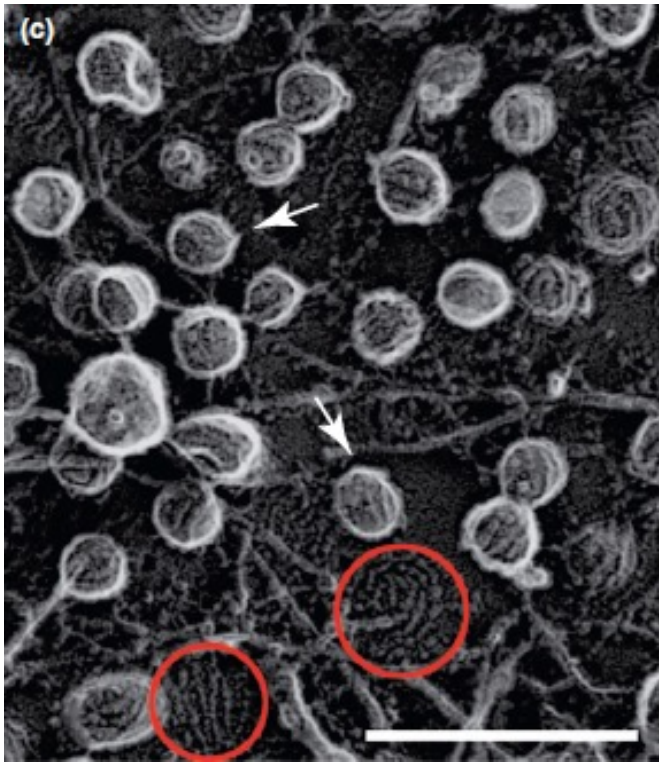


Caveolae: Specialized Plasma Membrane Nanodomains

60-80 nm invaginations
at plasma membrane

(1953 Palade, 1955 Yamada)



(N. Morone)

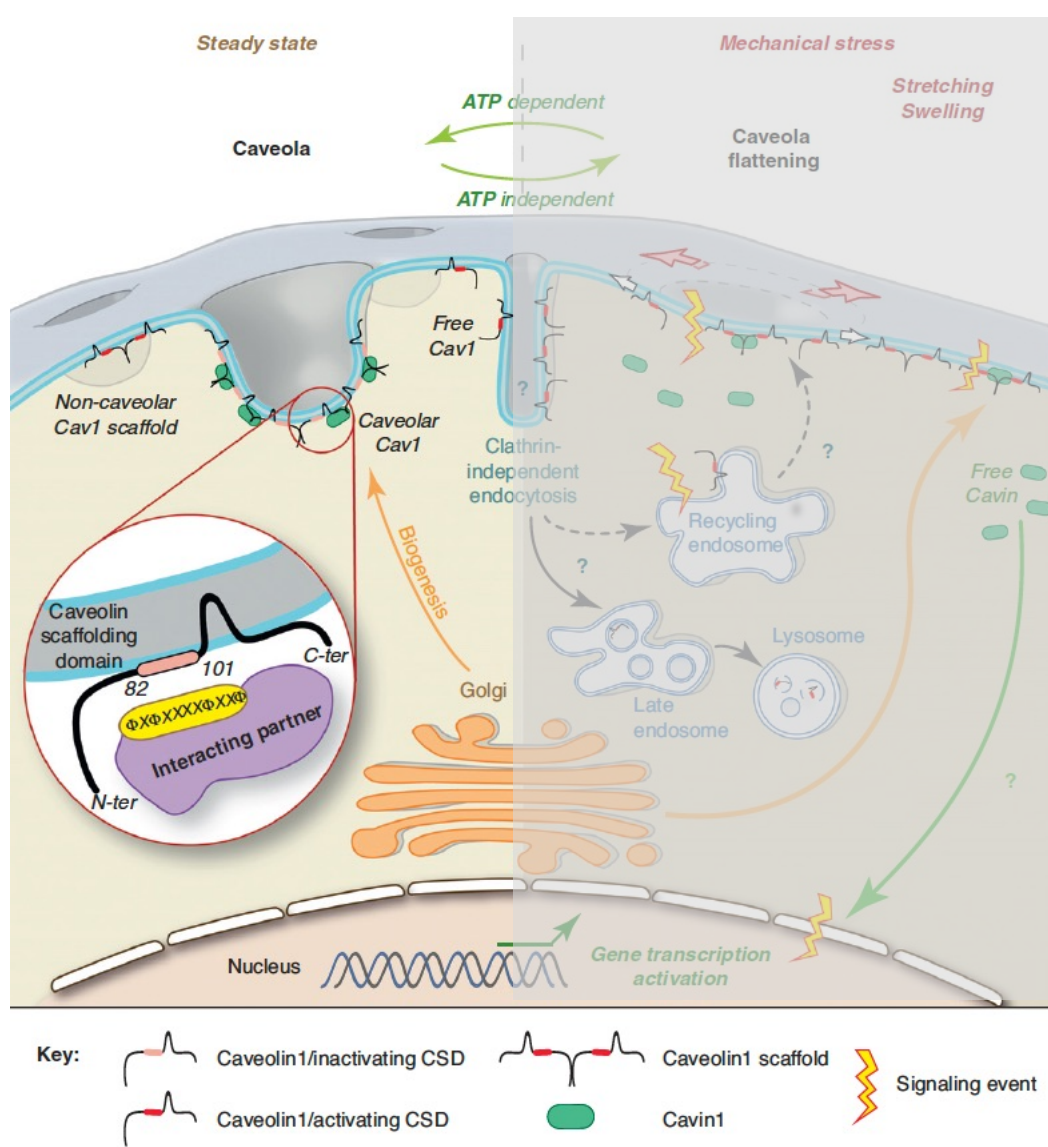
250 nm

Involved in:

- Signalling
- Mechanotransduction
(tension buffering)

P. Nassoy, C. Lamaze *Trends Cell Biol.* (2012)

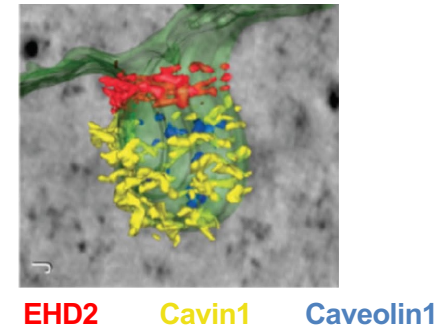
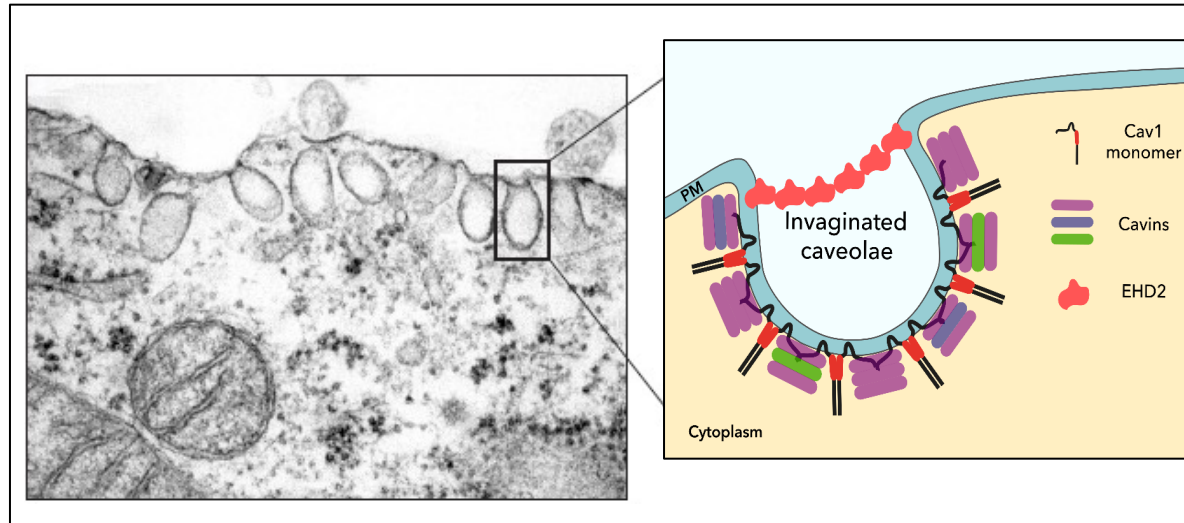
Caveolin = Essential Component of Caveolae



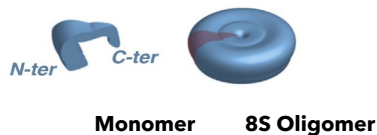
Caveolin

- Oligomerizes at the Golgi
- Transported through vesicles to PM
- Essential component of *Caveolae*

Caveolae: Rich in Sphingolipid (SM) and Cholesterol



- Caveolin (Cav1, Cav2)



Rich in Cholesterol, sphingolipids

Cav1 high affinity for cholesterol

- Cavins (1-4)

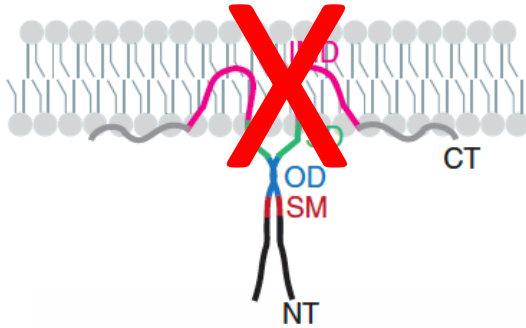


- EHD2



+ Assemble on the *cytosolic* leaflet

Caveolin Structure

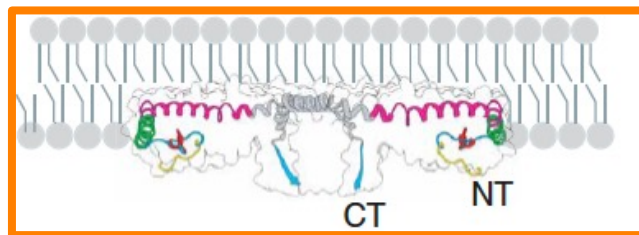
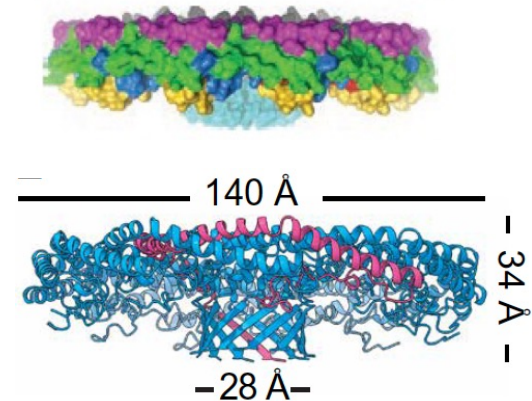
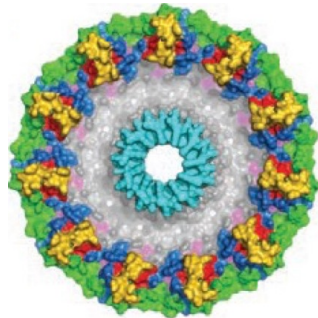
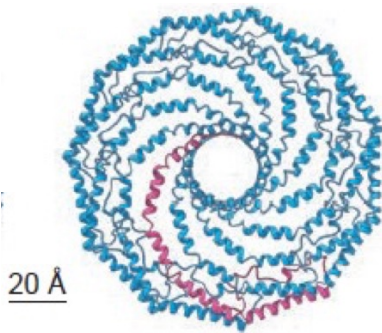


Anne Kenworthy and Melanie Ohi labs

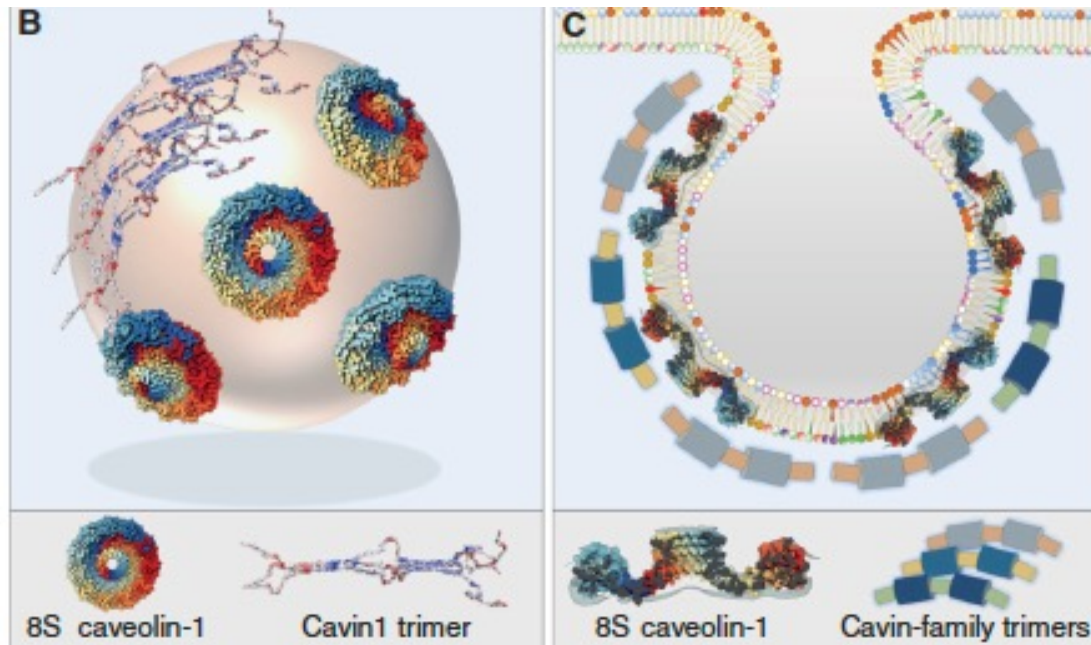
Porta et al, *Sci. Adv.* (2022)

Cryo-EM structure of 8S complex in detergents

3.5Å resolution & 11-fold symmetry



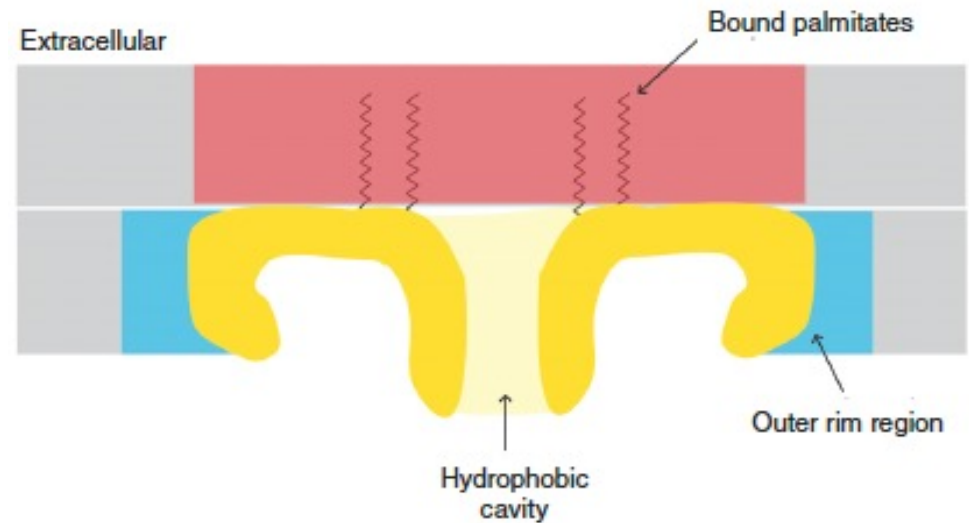
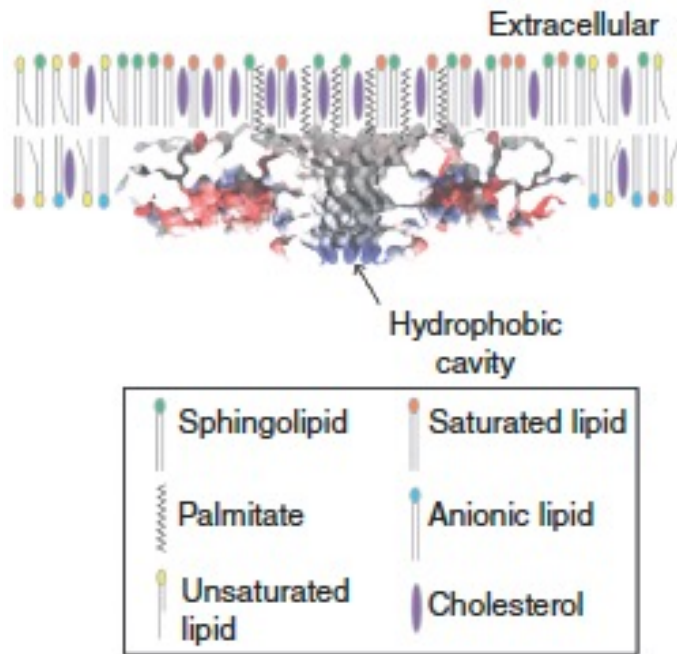
Updated view of caveolae



A. K. Kenworthy.....R. G. Parton *Cold Spring Harb. Perspect. Biol.* (2023)

Putative organization of the lipids around the 8S complex

(Remember that the Plasma membrane is very asymmetric)



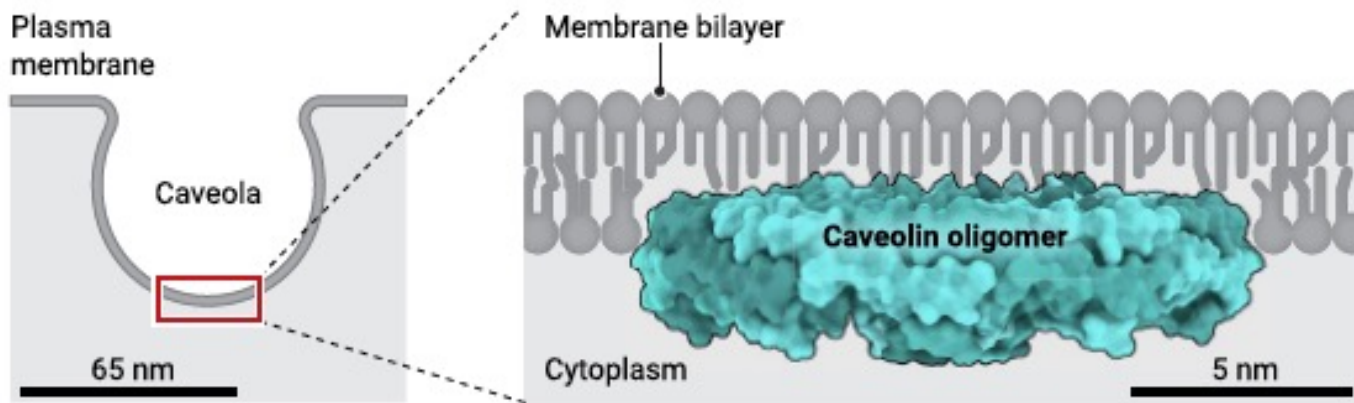
Different lipids in different area

A. K. Kenworthy.....R. G. Parton

B. *Cold Spring Harb. Perspect. Biol.* (2023)

Question:

Does caveolin oligomer bend membranes ? How ?



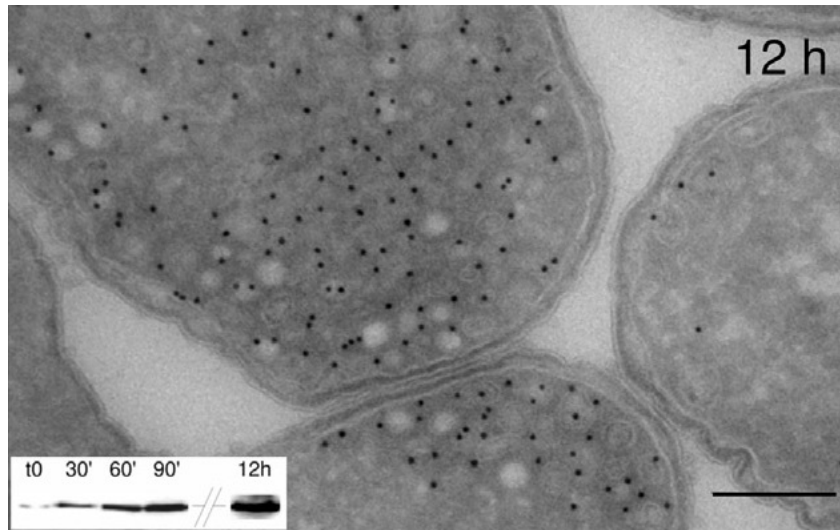
Parton R. *Sci. Adv.* (2022)

Is cavin required to bend membranes?

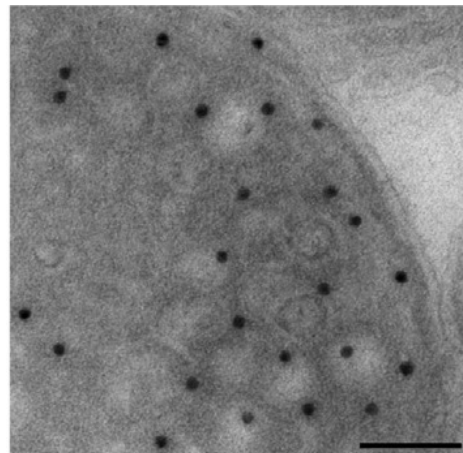
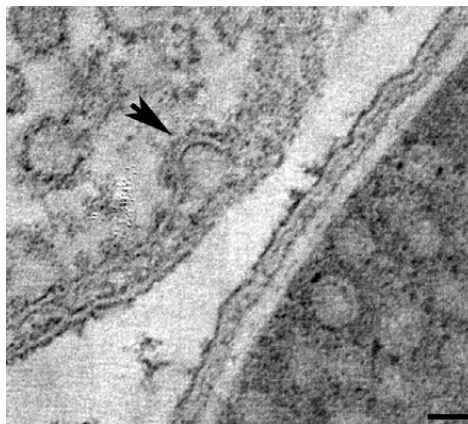
Can caveolin bend membranes on its own?

Caveolin-coated vesicles form when expressed in bacteria

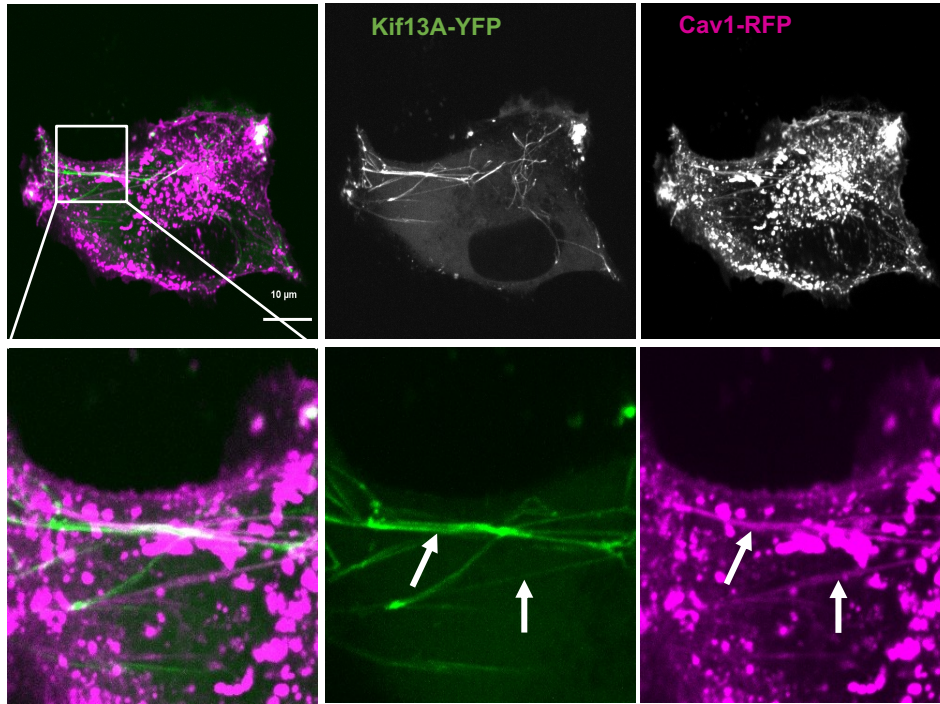
no cavin, no cholesterol



$\varnothing \sim 40 \text{ nm}$



Cav1 present in endosomal tubules in cells

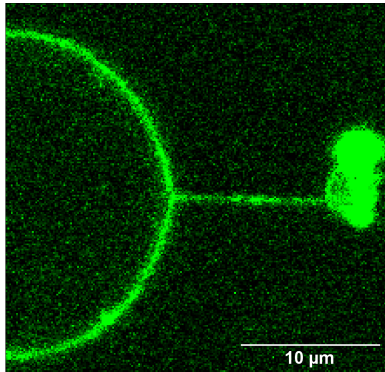


(J. Podkalicka)unpublished

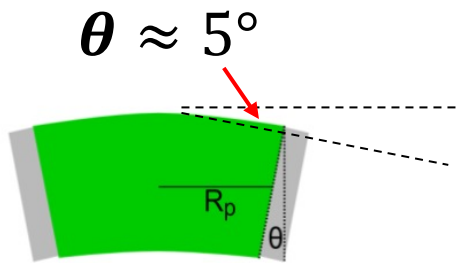
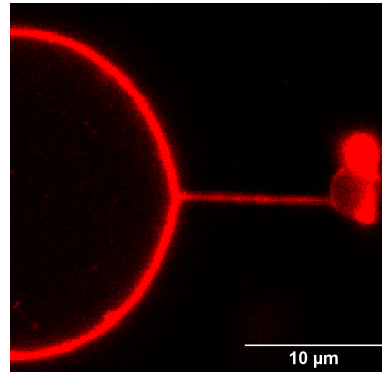
- Cav1 purified and reconstituted in GUVs (Z.Q. Wu) unpublished

Caveolin enriched in nanotubes

Caveolin



Lipid



$$C_p = 1/40 \text{ nm} \quad (R_c = 80 \text{ nm})$$



Caveolin can bend membranes without cavin

But, MECHANISM ????

Questions (Markus Deserno)

1. What supports the idea that these structures insert into a single leaflet?
2. How does caveolin bend membranes eventually? Could membrane asymmetry play a structural role in membrane bending? How could this be approached? List experiments for studying this more precisely.
3. What level of detail do we need to model this? Or more precisely, what known effects require what level of modeling? What presently unknown effects would we have to be wary of?
4. Can you develop a hierarchy of coarse grained models, all the way from atomistic to continuum? Which levels would you use to probe what question?
5. If we have multiple 8S complexes, how would they interact with one another, given how they sit in a membrane?
6. Does the central beta-barrel just “tie up” the wheel in the middle, or does it have a function? Why is it hydrophobic in its interior? Could it be a “portal” that makes the distal membrane leaflet directly accessible from the cytosolic side? Do we know what proteins bind there that could exploit such a gatekeeping function?
7. Could we use Cav-1 8S structures outside their direct biological context as tools in biophysical measurements, or in some bioengineering/biomedical applications?