Protective role of sphingomyelin in eye lens membrane against oxidative stress during aging

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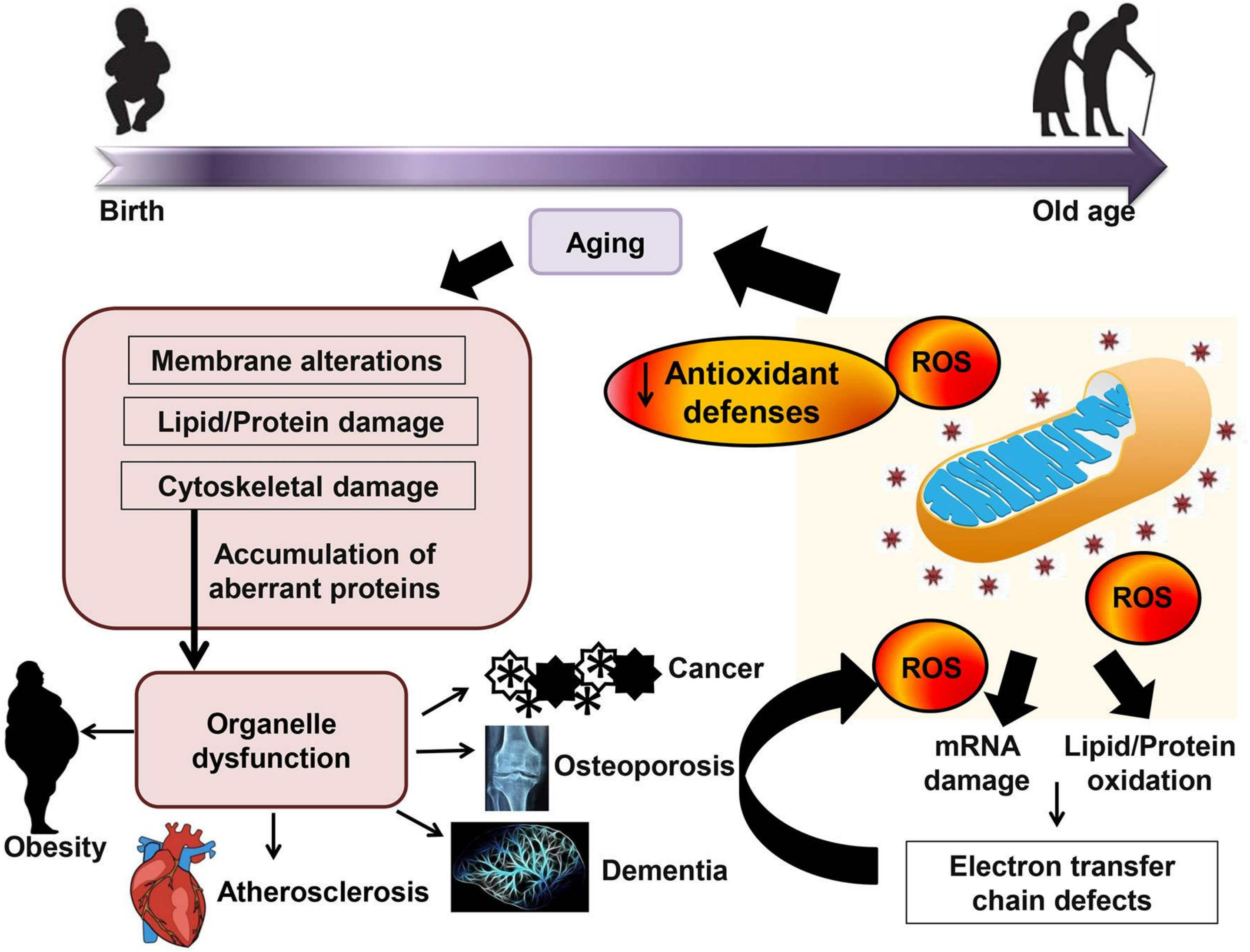
Oxidative stress and aging

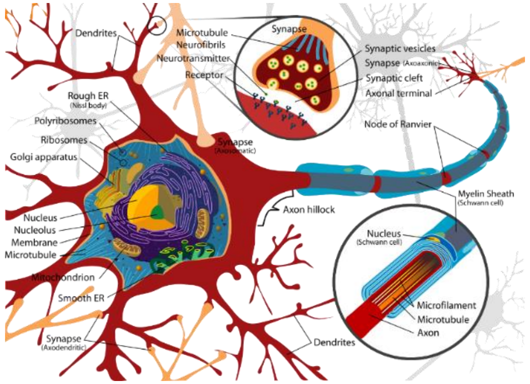


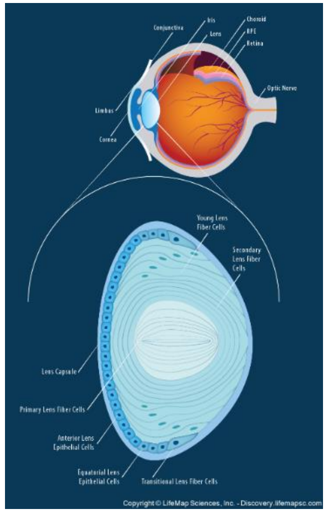
Tan L. B., et al. Frontiers in Pharmacology (2018)

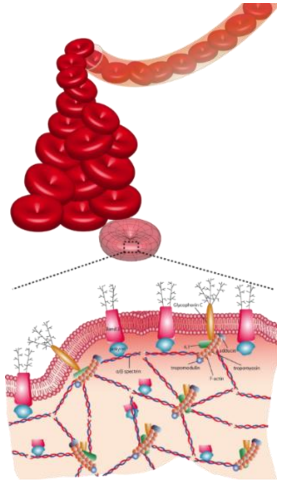
Sphingolipid

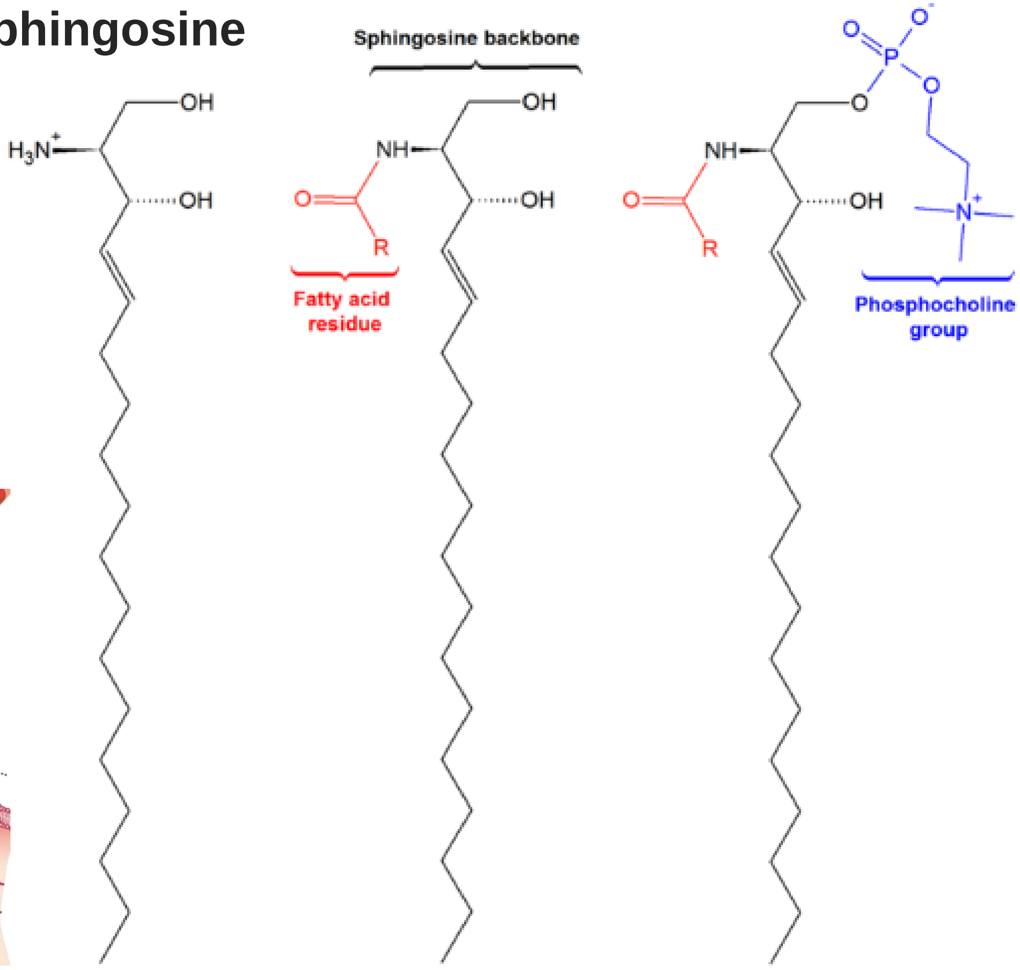
Sphingolipid: Sphingomyelin (SM), Ceramide, and Sphingosine

- In Human, SM represents ~85% of all sphingolipids
- Higher ratio of SM is found in the cell membrane of RBC, Nerve cell axons, and eye lens.





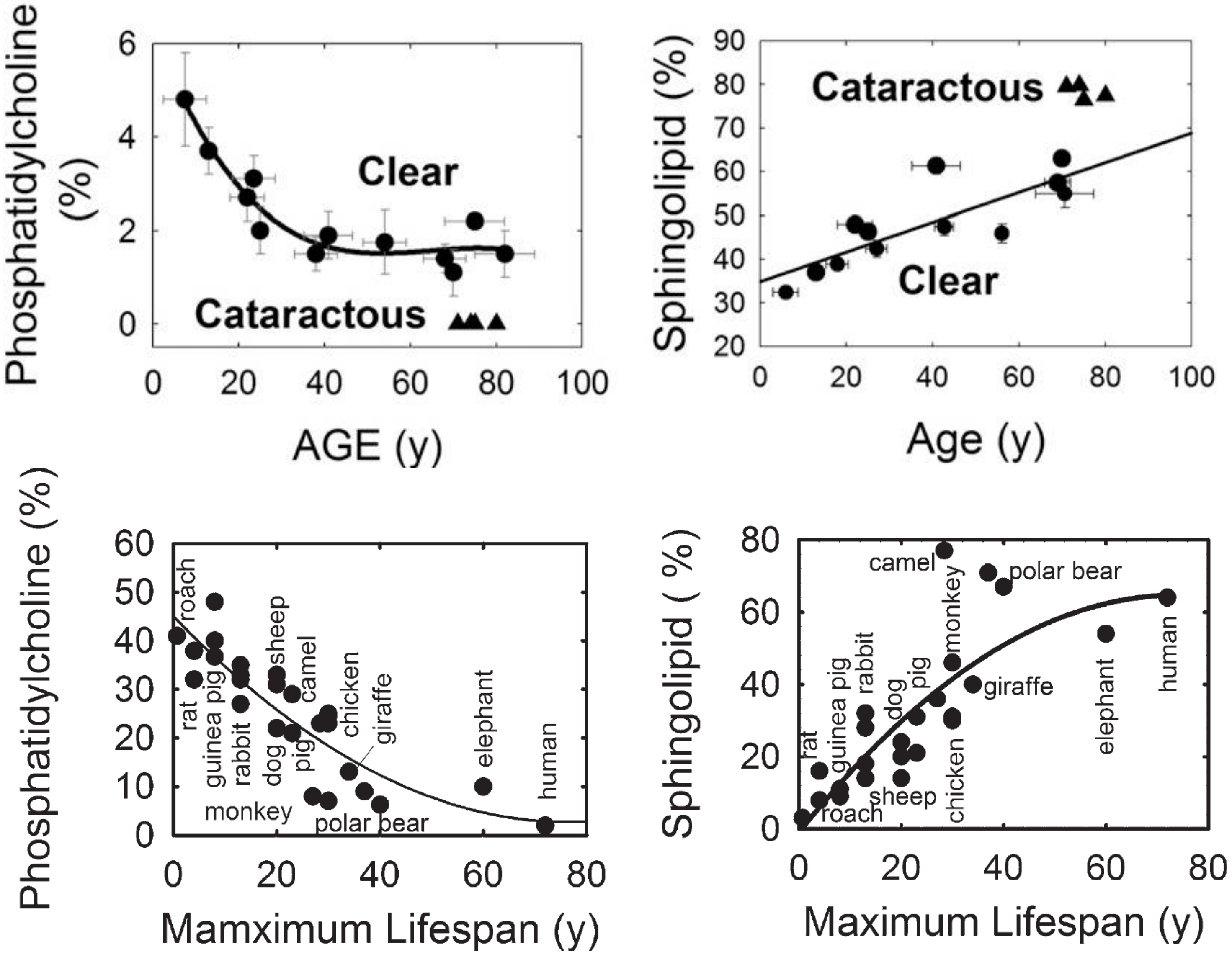




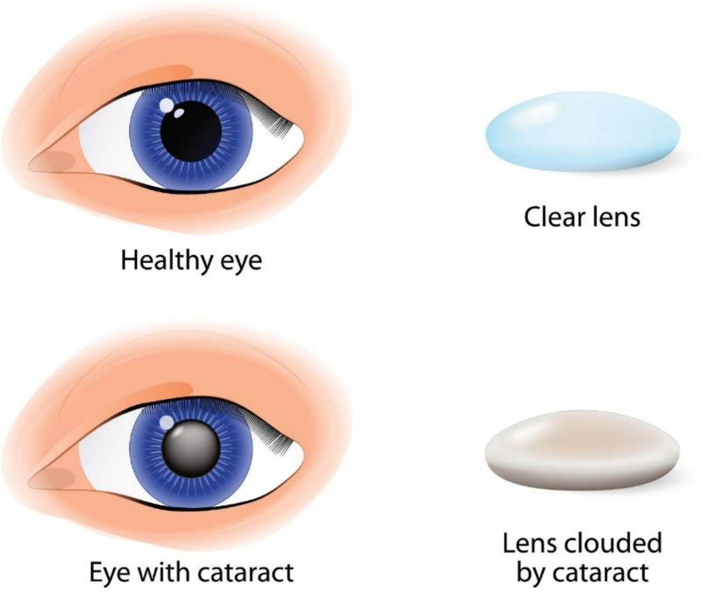
Sphingosine A Ceramide A Sphingomyelin

Ramstedt. B., et al. FEBS Letters, 2002

Mammalian Eye Lens Phospholipid Changes with Age



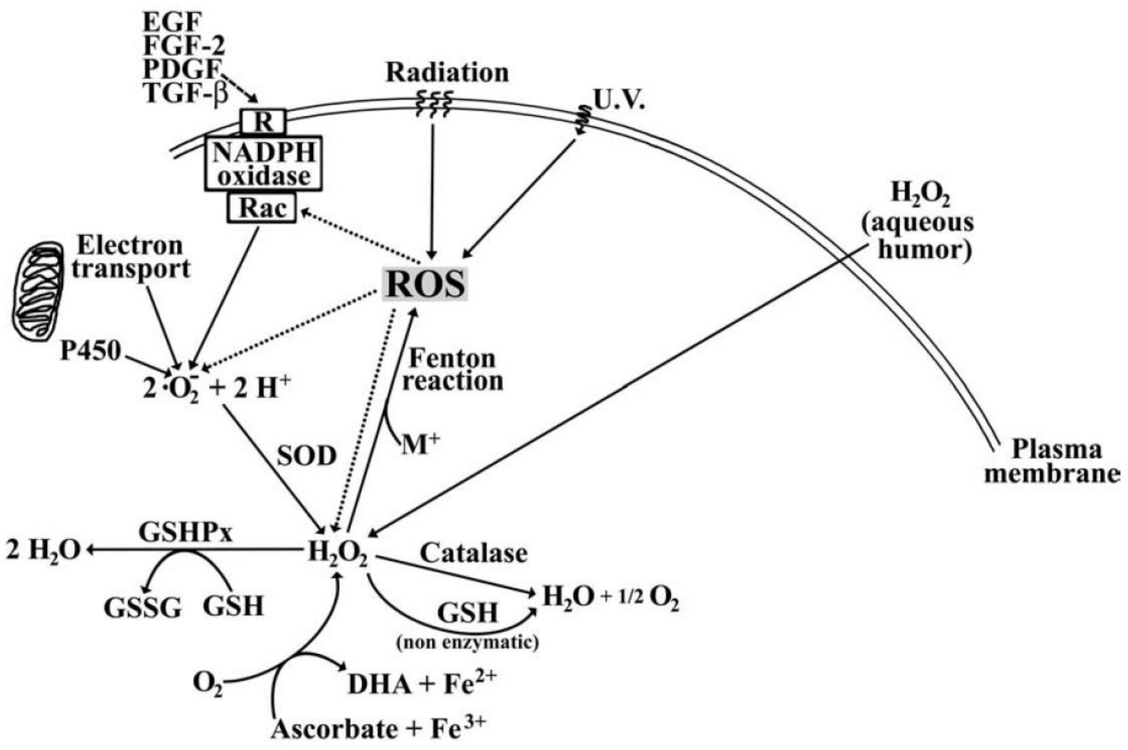
Cataracts, as an age-related disease, can result from oxidative damage in the eye lens membrane.



https://www.katzmaneyes.com/services/cataract-surgery

Borchman M and Yappert M. C. Journal of Lipid Research (2010)

Pathways for generation of ROS in the eye



ROS: ${}^{\bullet}OH$, ${}^{\bullet}O_2^-$, and H_2O_2

Antioxidants: nonenzymatic (ascorbate, GSH, free UV filters, enzymatic (SOD, Catalase, GSH peroxidase)

Hypothesis

⬇

Aging

⬇

Oxidative damage due to less antioxidant activity in the eye

⬇

Increasing the ratio of SM in membrane

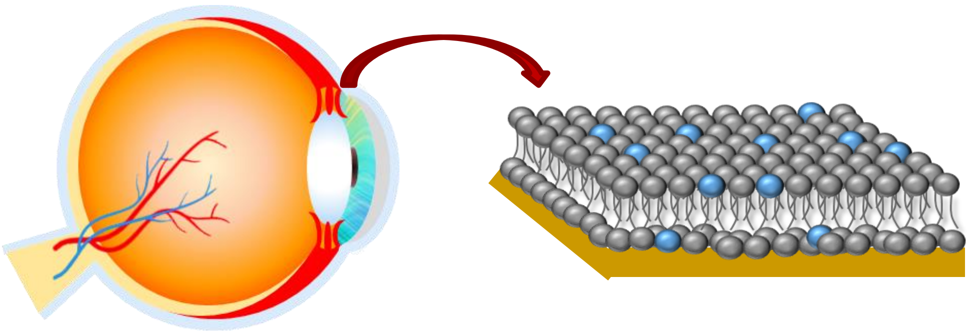
⬇

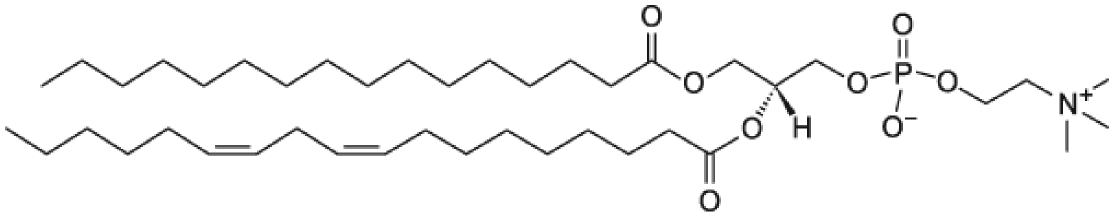
SM Protect the membrane against ROS through increasing the membrane order and stiffness

Berthoud. V. M., et al. ANTIOXIDANTS & REDOX SIGNALING (2009)

Aim of the project

- Increasing the ratio of the SM in eye lens membrane: Why?
- Can SM protect lipid bilayer against oxidative damage?





PLPC: 16:0-18:2 PC

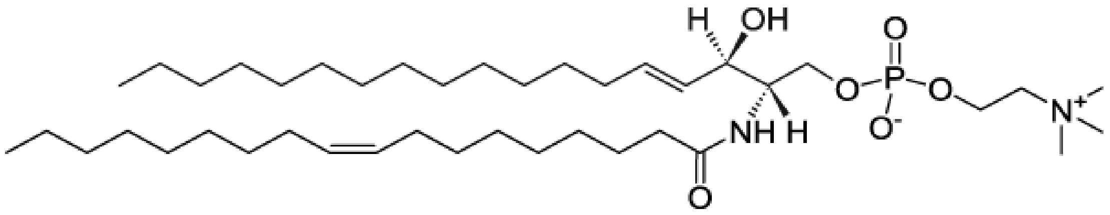
1-palmitoyl-2-linoleoyl-sn-glycero-3-phosphocholine

Model eye lens membranes

PLPC

PLPC:SM (3:1) (Young lens membrane)

PLPC:SM (1:3) (Old lens membrane)



18:1 SM (d18:1/18:1(9Z))

N-oleoyl-D-erythro-sphingosylphosphorylcholine (SM)

Cold physical plasma (CPP)

Medical applications:

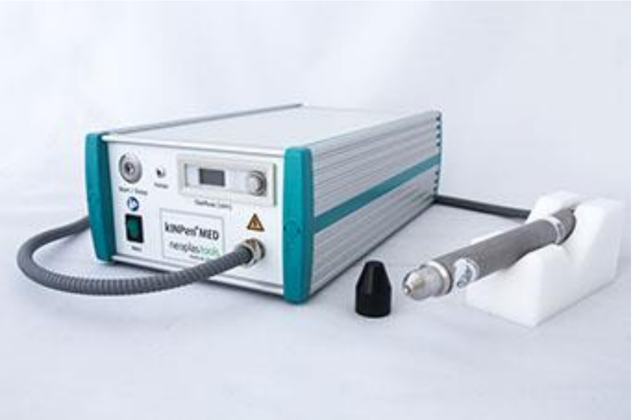
- Wound healing

- Cancer treatments

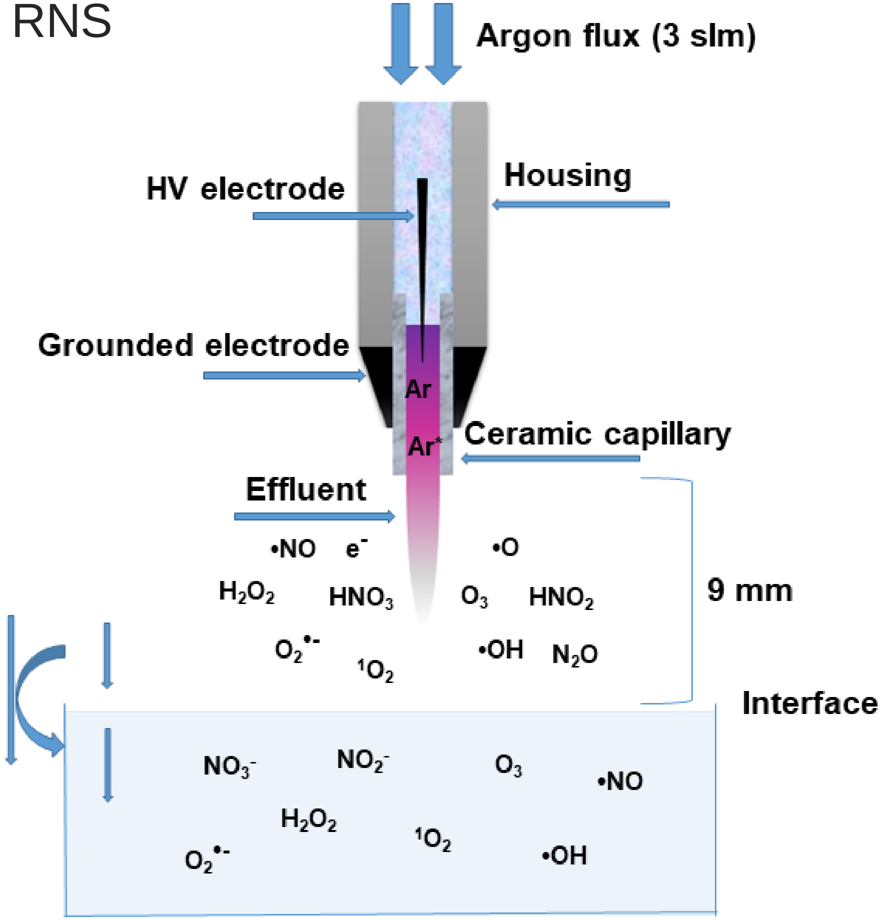
Fundamental research:

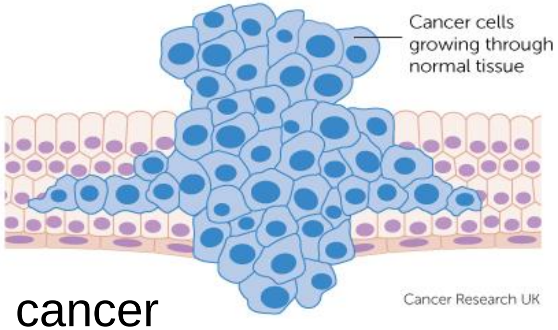
Source of production of ROS and RNS

chronic / infected wounds



kINPen®





cancer

CPP-derived reactive species: mimic the main reactive species in the eye such as $^{\bullet}OH$, $^{\bullet}O_2^-$, and H_2O_2, especially during cataract formation.

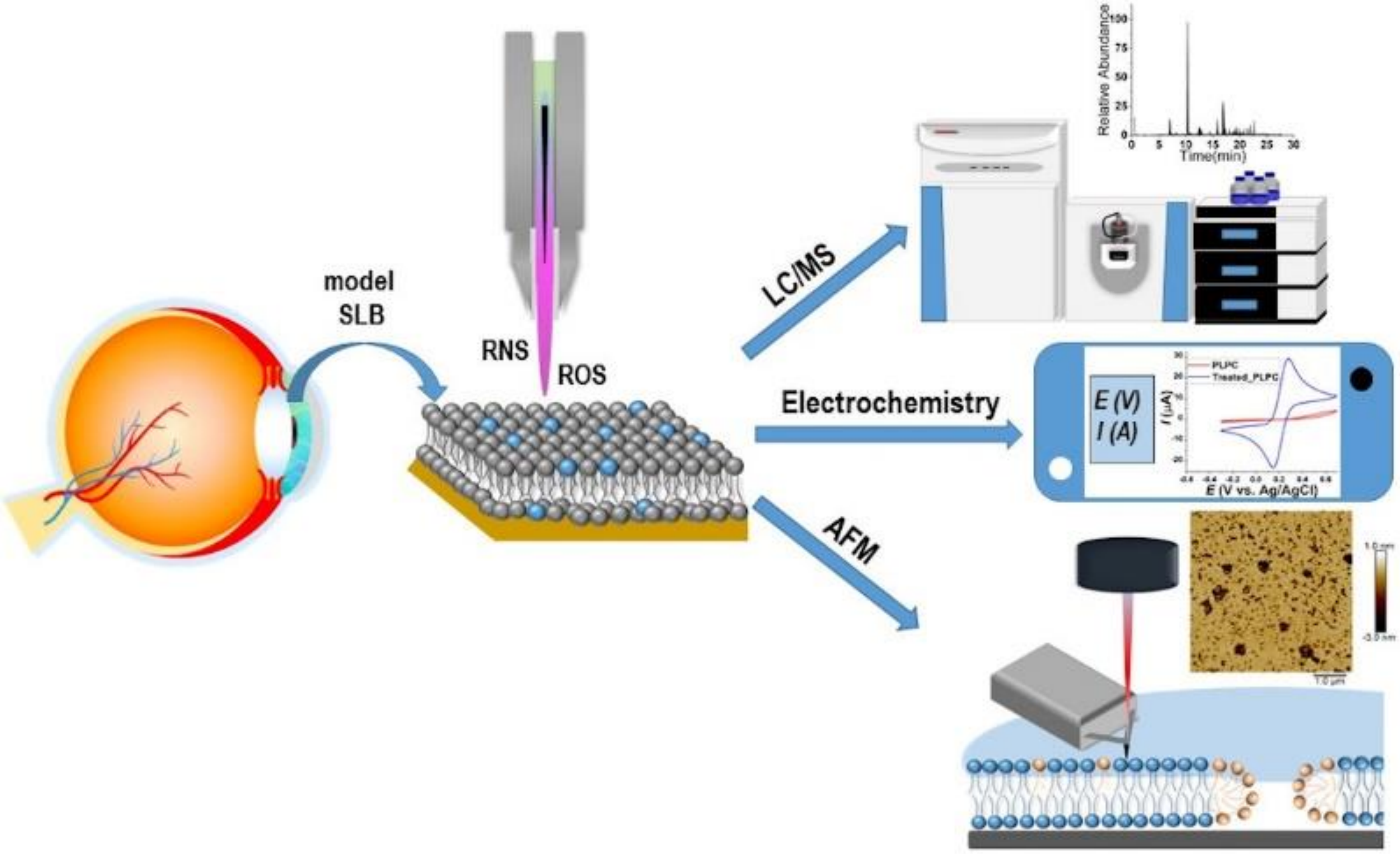
Reuter, S., et al. Journal of Physics D-Applied Physics (2018)

VON Woedtke, T., et al. In Vivo (2019)

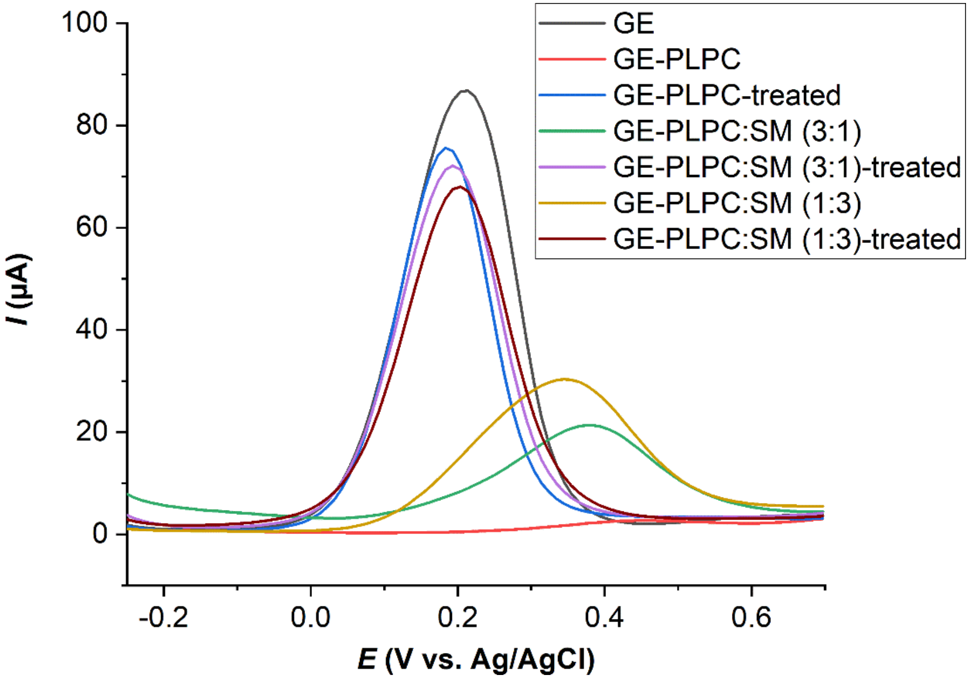
INP FROM IDEA TO PROTOTYPE

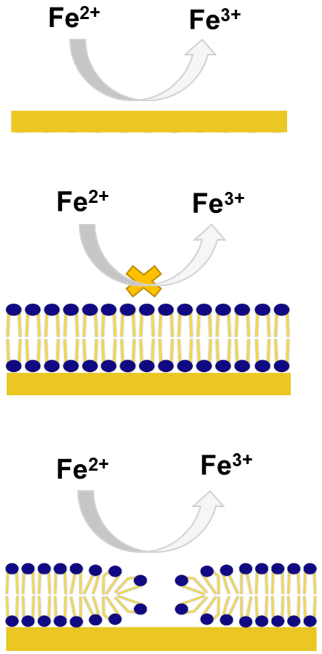
Workflow

plasmatis Plasma plus Cell

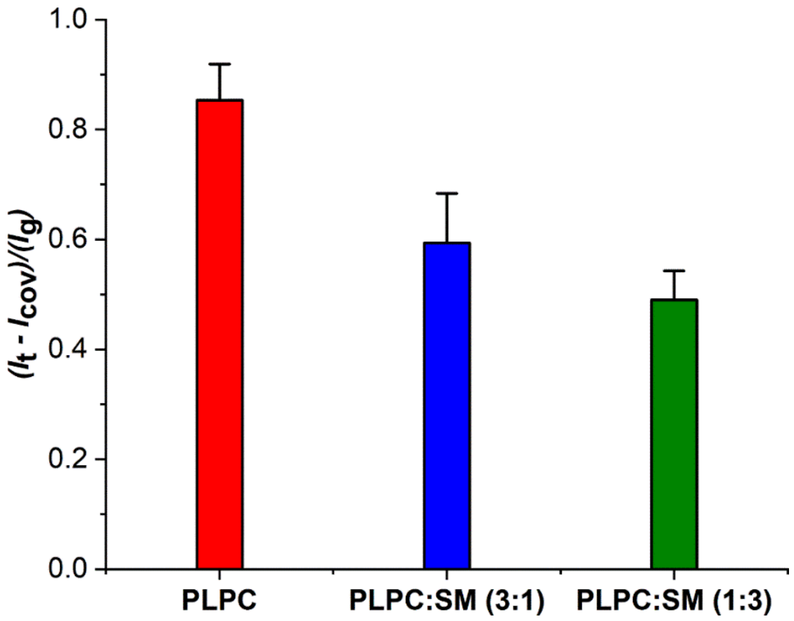


Effect of ROS on model eye lens membranes: Electrochemistry





$$A = (I_t - I_{cov})/I_g$$

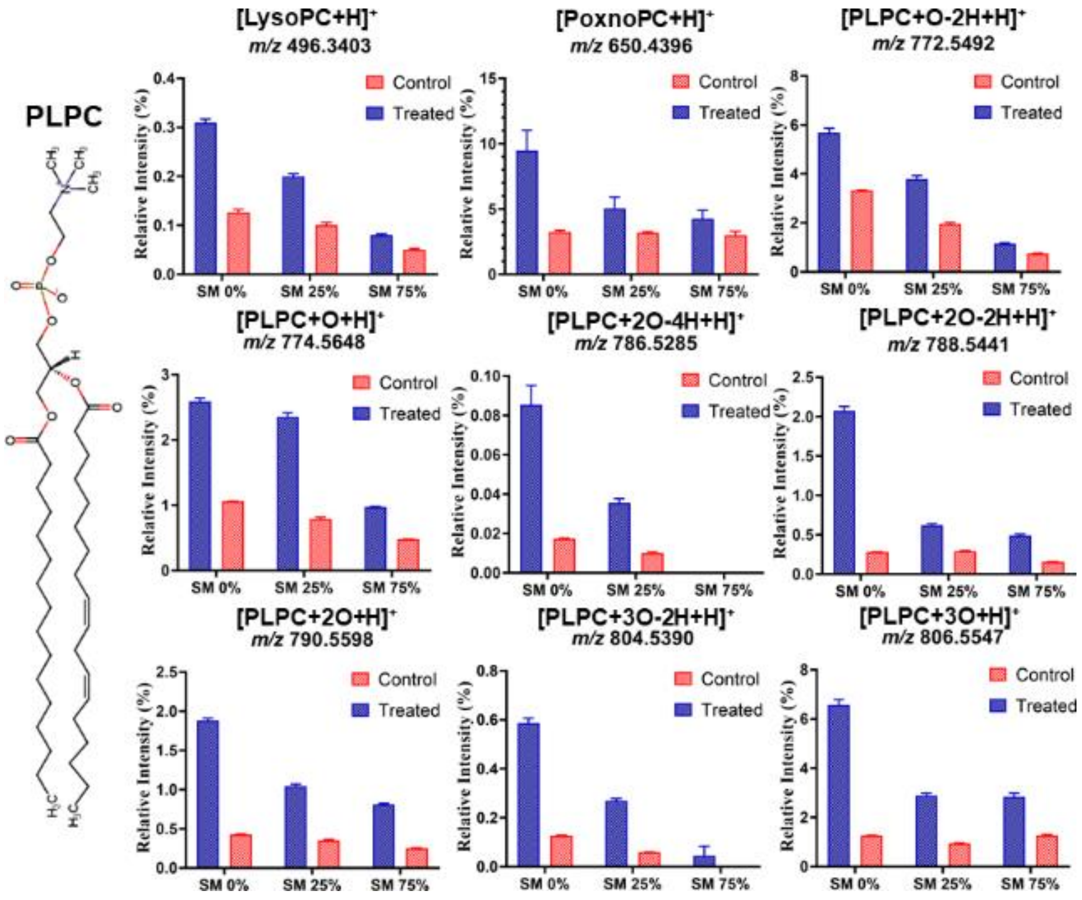


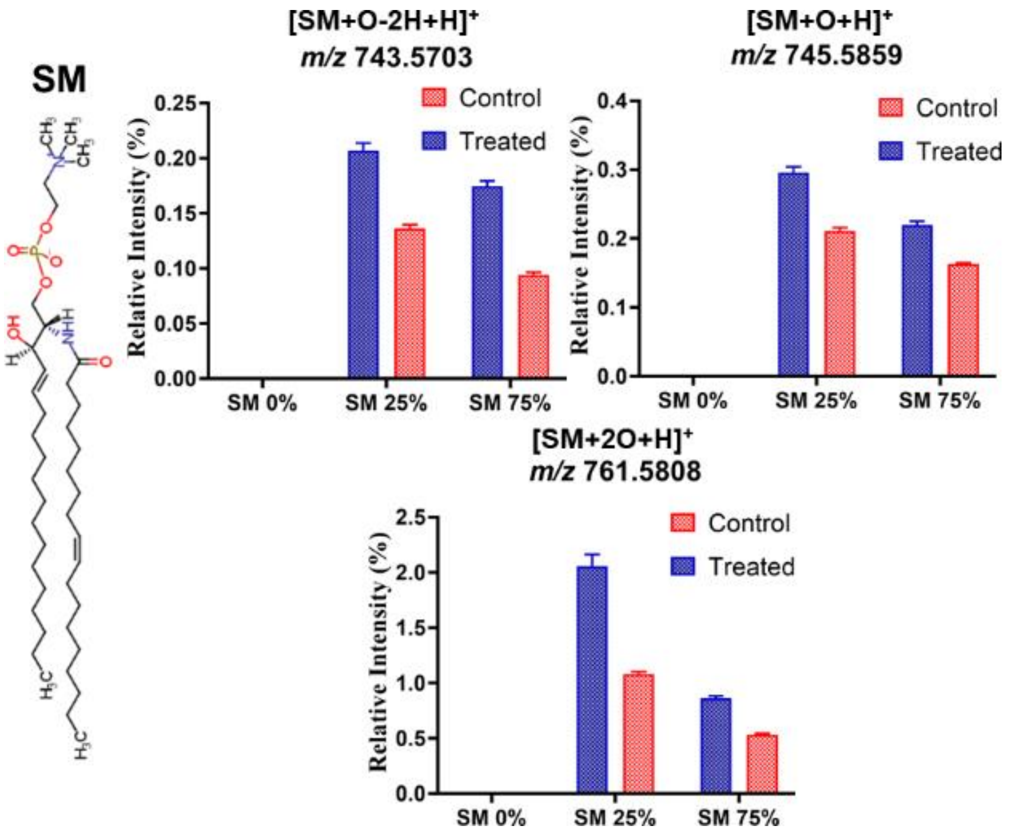
$$\%\ \text{Protective effect} = [(A_{PLPC} - A_{PLPC:SM})/A_{PLPC}] \times 100$$

The electrochemical results indicated a protective effect of 30% and 42% in presence of 25% and 75% SM in lipid bilayer, respectively

Ravandeh, et al. *Biomolecules*, 2020

Effect of ROS on model eye lens membranes: Mass spectrometry





The protective effect increased with SM fraction: 29% and 46% for lipid bilayers with 25% and 75% SM, respectively.

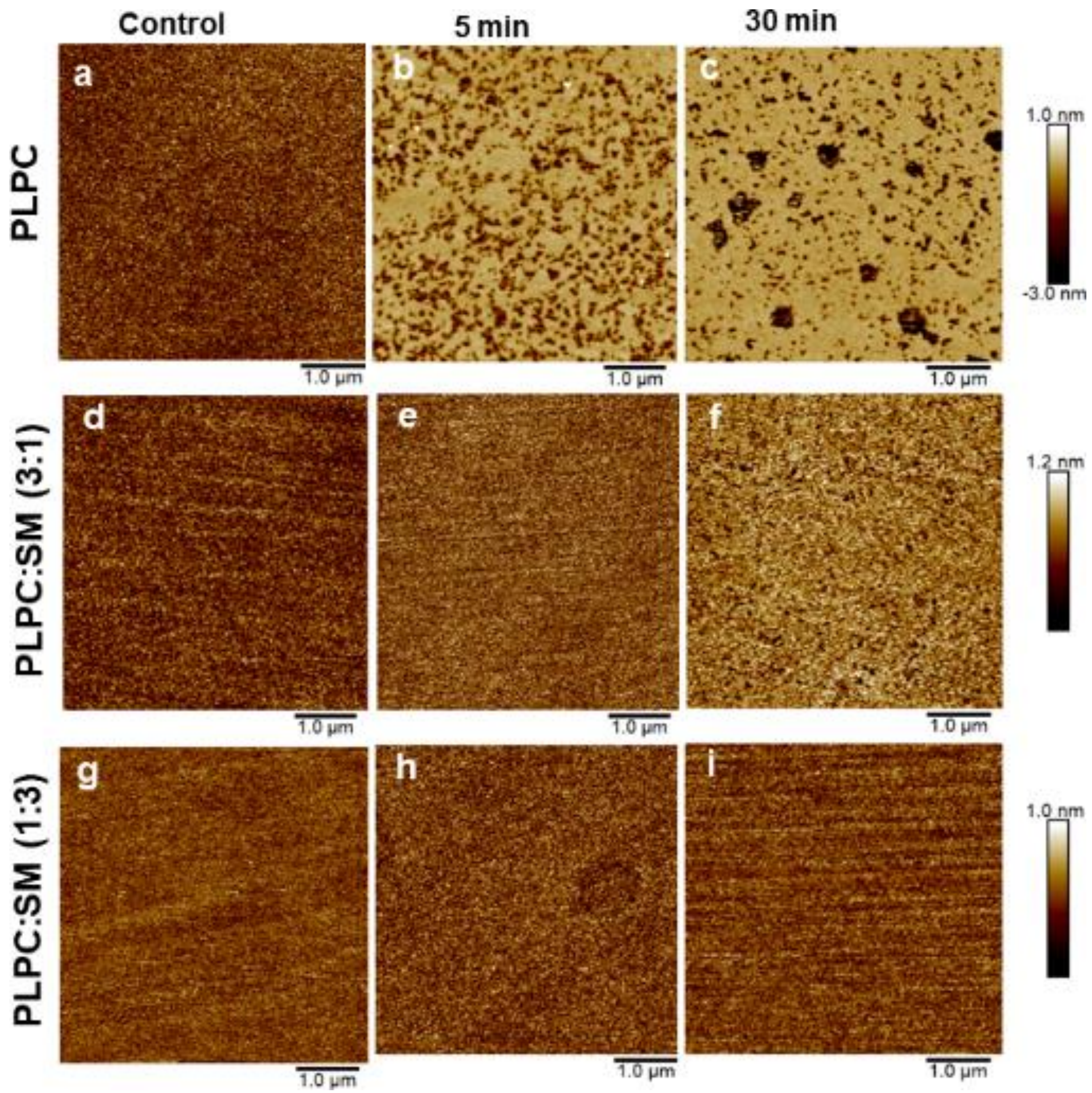
Ravandeh, et al. *Biomolecules*, 2020

Effect of ROS on model eye lens membranes: Atomic force microscopy

- **Mass spectrometry:** PLPC was substantially more oxidized by plasma-derived ROS than SM.

- **AFM imaging of SLB:** changes in the membranes physical structure and morphology

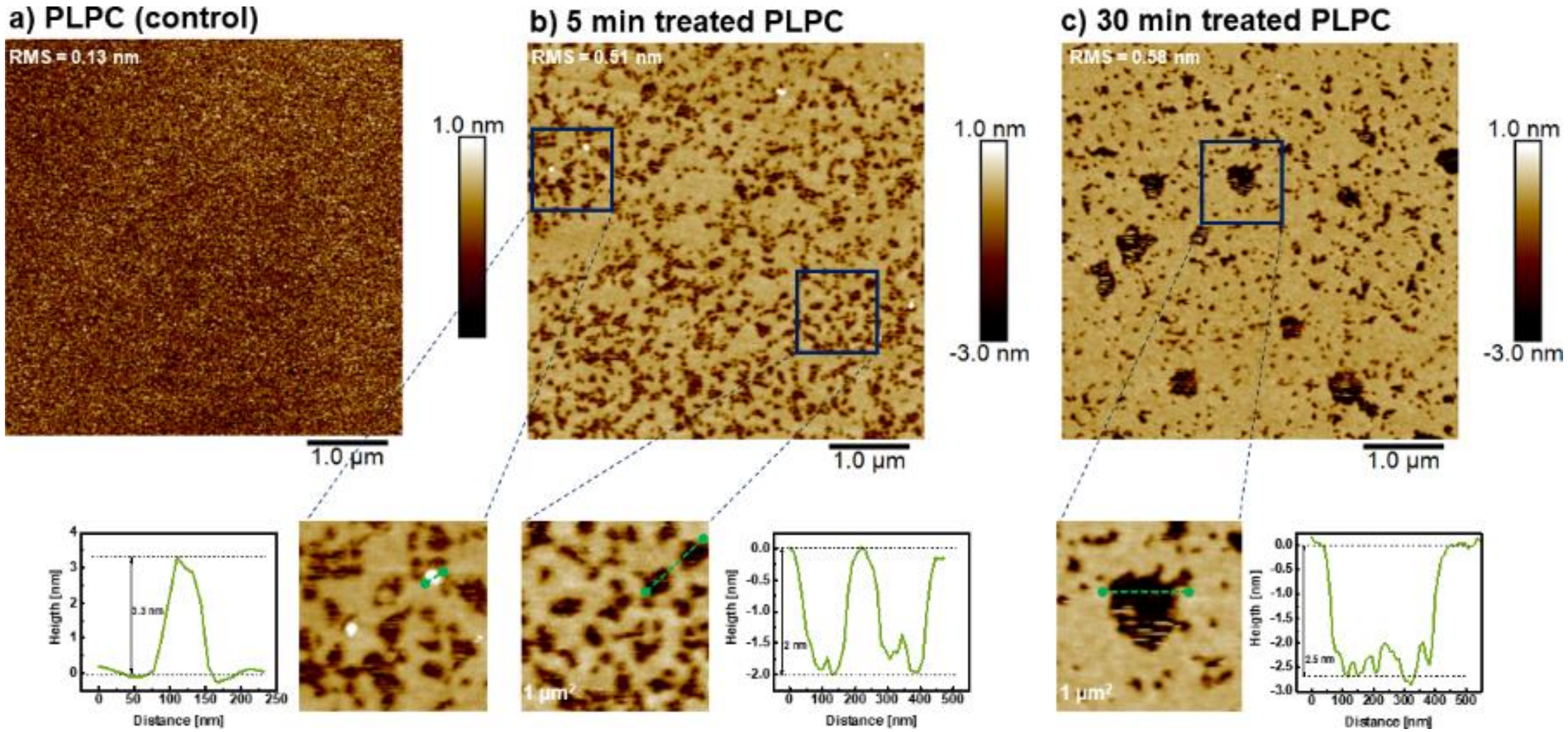
The AFM results confirm the simulation study of Annemie Bogaerts' group that a large amount of lipid aldehyde should be formed to create a pore in the membrane

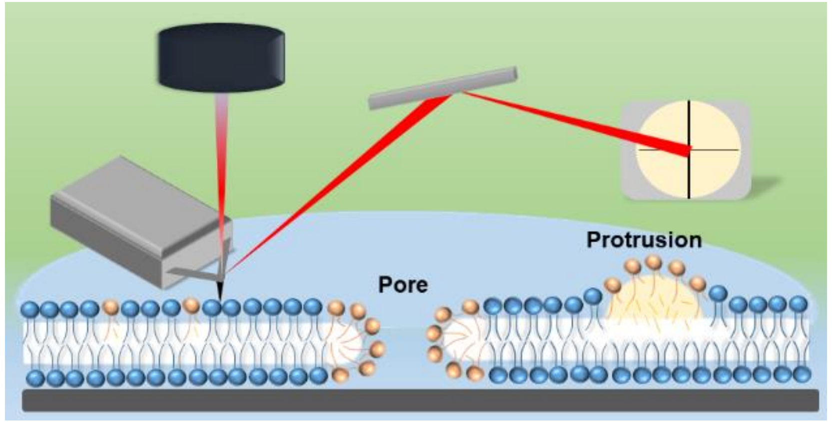


Ravandeh, et al. *Biomolecules*, 2020

Van der Paal, J., et al. Chemical Science (2016)

Effect of ROS on model eye lens membranes: Atomic force microscopy





Conclusion and outlook

- The protective role of a higher fraction of SM in a model eye lens cell membrane against oxidative stress was studied on a macroscopic (by electrochemistry), molecular (by HR-mass spectrometry), and on nm (by AFM) level.
- The dependence of membrane protection on SM fraction is consistent with the idea about the molecular mechanisms which the aging eye increased SM to keep lens transparency and to protect the eye against penetration of reactive species and oxidative stress.
- High amount of lipid aldehydes in a model membrane is necessary for pore formation.

Outlook

- **The role of SM in the function of transmembrane proteins and ion channels in model human eye lens membrane will be the subject of future investigations.**

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