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Session 6: Regenerative medicine
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Controlled Delivery of Reactive Sulfur Species for Stimulating Angiogenesis

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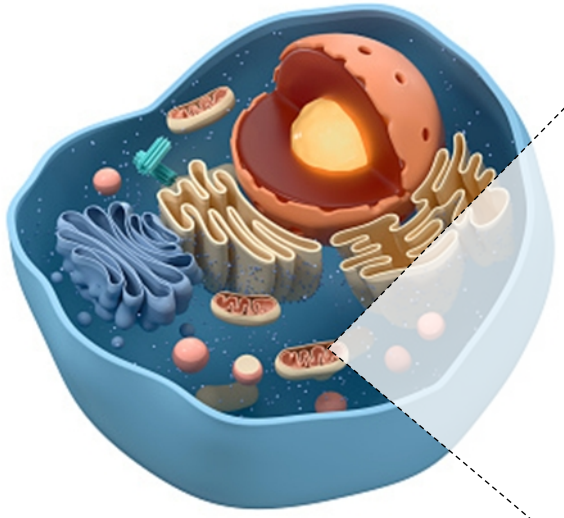
Small reactive species: Redox signaling regulators in the body



Reactive oxygen species (ROS)

H_2O_2, $\cdot O_2^-$, $\cdot OH$ …

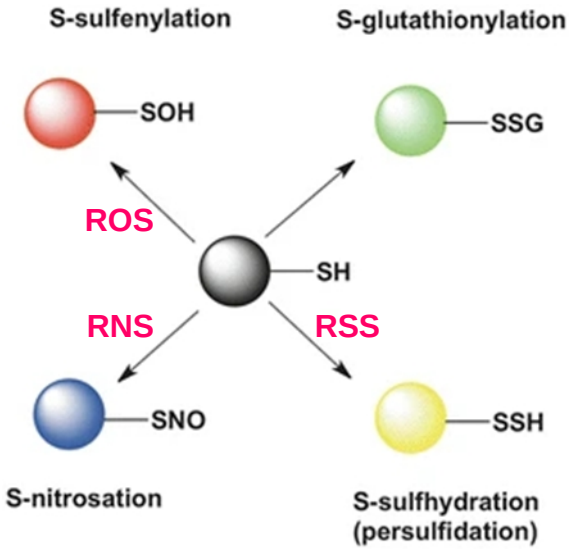
Reactive nitrogen species (RNS)

NO, $ONOO^-$, N_2O_3 …

Reactive sulfur species (RSS)

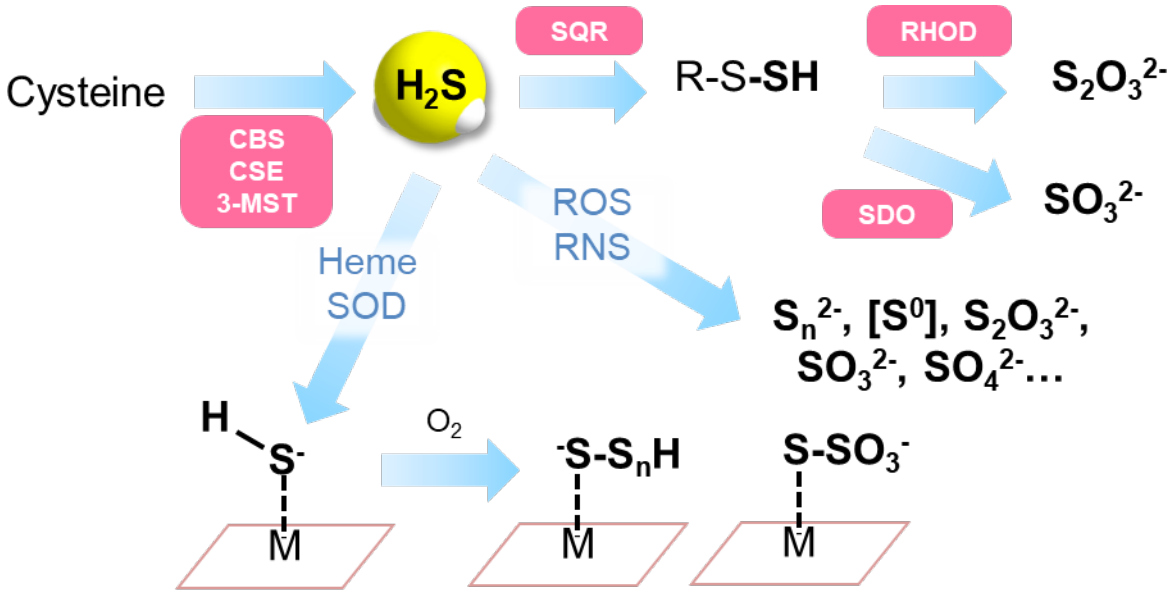
H_2S, H_2S_n, RSS_nH, $S_2O_3^{2-}$…

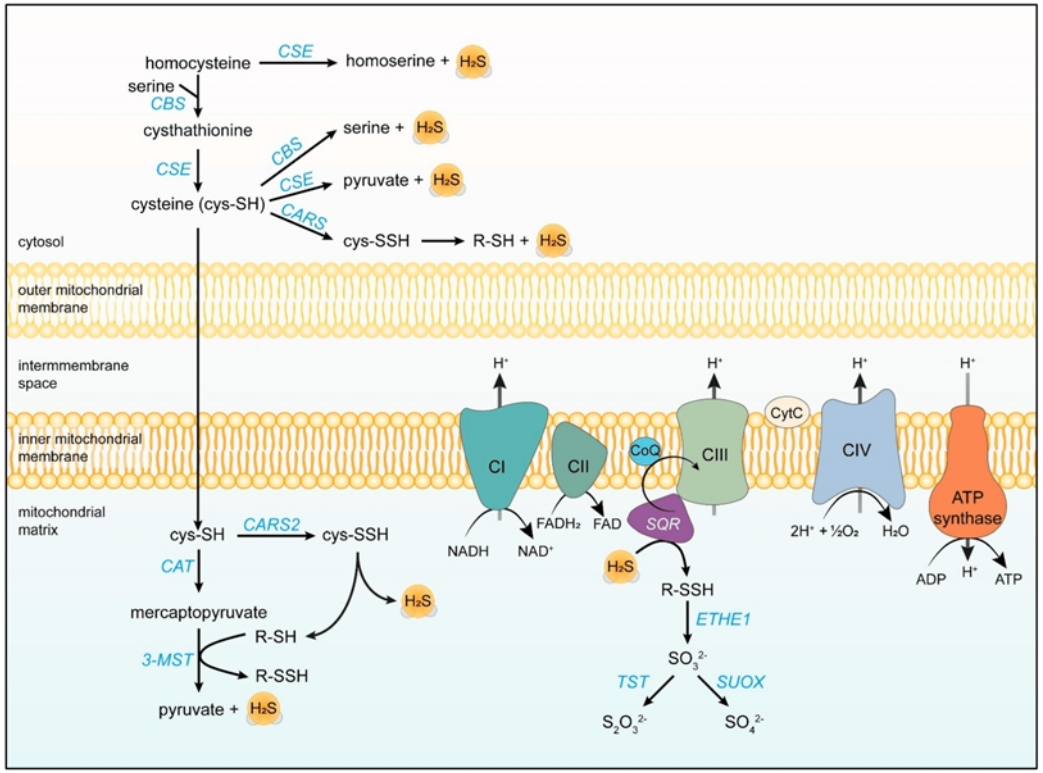
Post-translational modification of proteins



ROS, RNS and RSS are small reactive molecules that are produced endogenously in cells and regulate cellular redox signaling.

Reactive Sulfur Species (RSS)

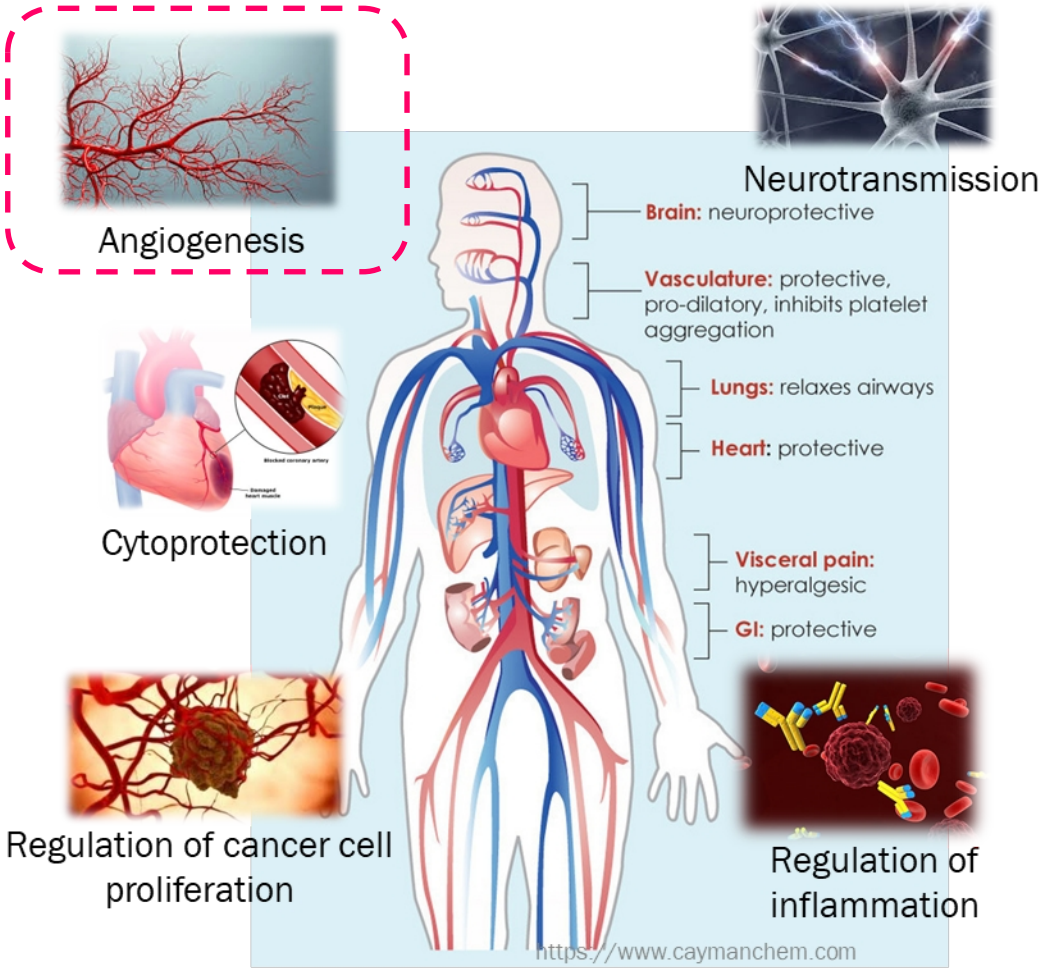




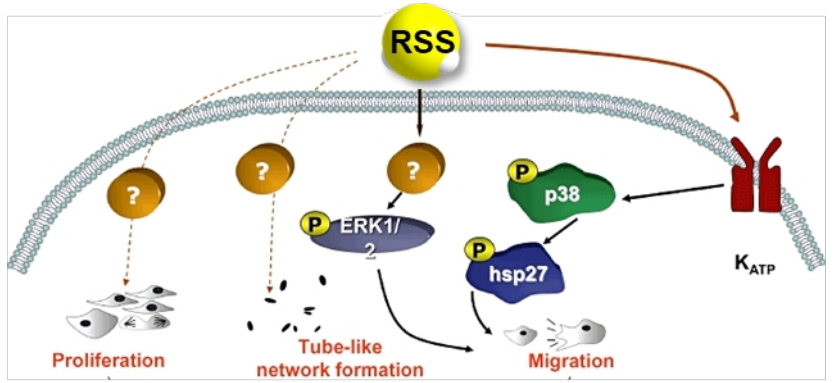
H_2S is generated in cells through cysteine metabolism and oxidized to a series of sulfur species such as per/polysulfides via enzymatic and non-enzymatic processes.

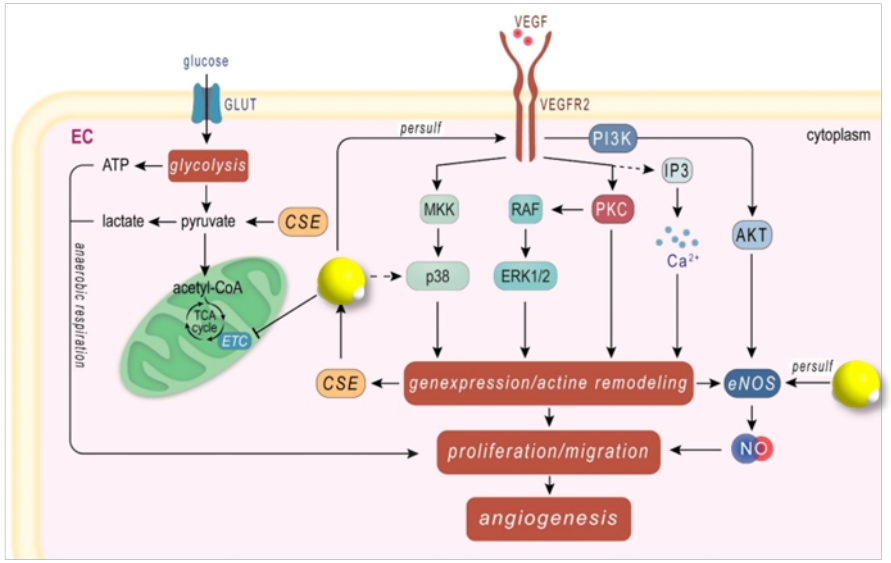
Lin *et al.*, *Chemical Society Reviews* 2015, 44 (14), 4596-4618.
Bechelli et al., *Int. J. Mol. Sci.* 2023, 24(12), 9955

RSS biology



Proangiogenic activity of RSS



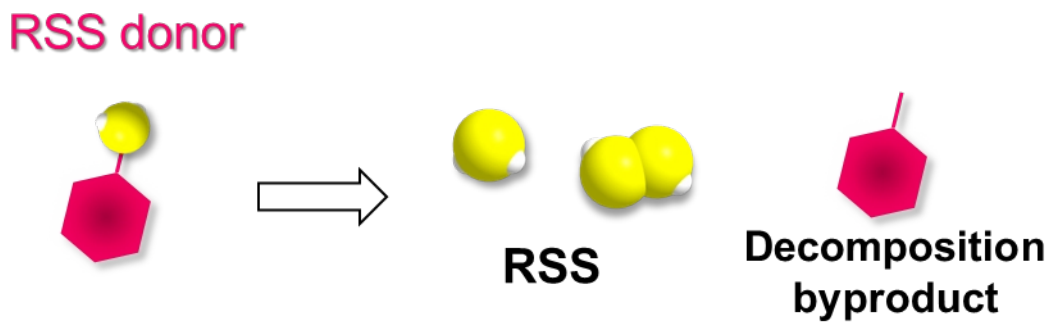


Paul *et al.*, *Nat. Rev. Mol. Cell. Biol.* (2012) 13, 499. Szabó *et al.*, *J. Br J Pharmacol.* (2011) 164, 853.
Kajimura *et al.*, *Antioxidant & Redox Signaling* (2010) 13, 157, J. Furne *et al.*, *Am J Physiol Regul Integr Comp Physiol* (2008) 295, R1479, Bechelli et al., *Int. J. Mol. Sci.* 2023,

Challenges in therapeutic applications of RSS

- Inherent instability, short half-lives in the body
- Time- and dose-dependent biological activities
- Complex sulfur biochemistry

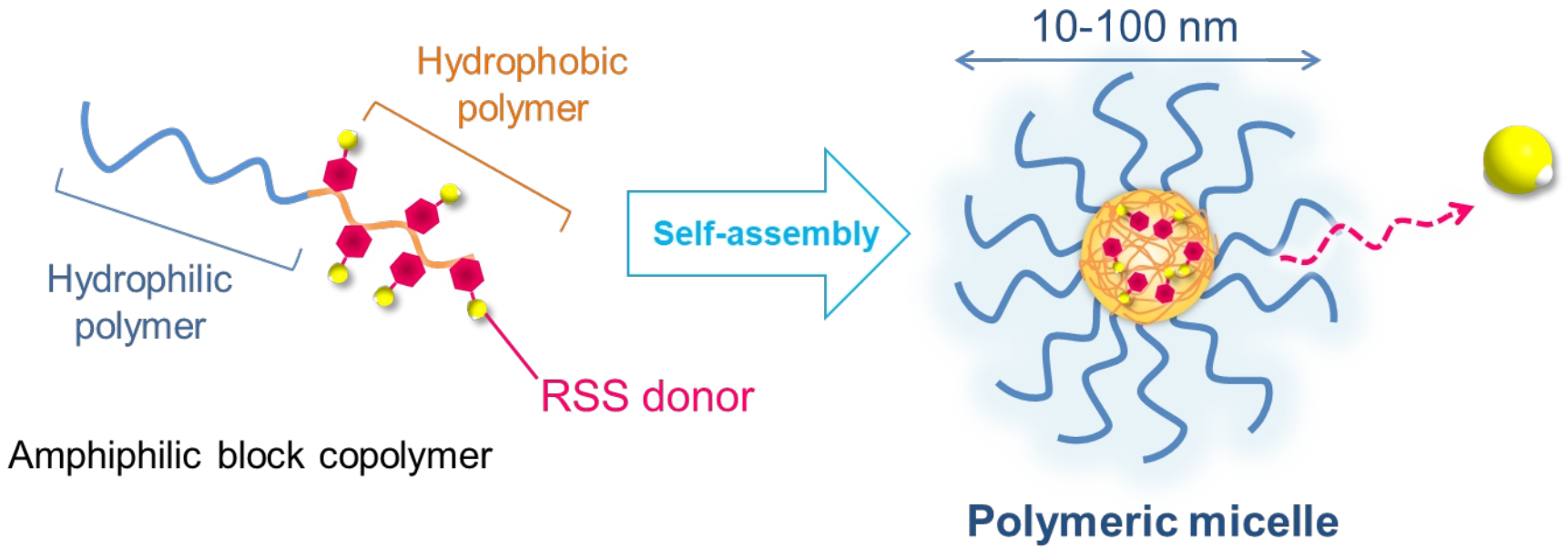
Common Approach: Small donor molecules



Limitations

- Fast and uncontrolled rate of RSS release
- Side effects caused by the donor compounds and/or decomposition byproducts
- Poorly controlled pharmacokinetics

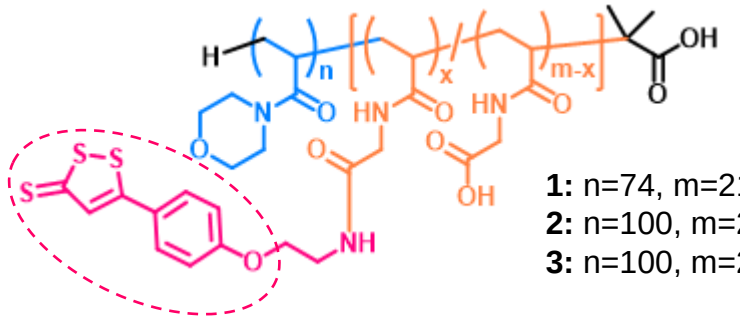
Our approach: Polymeric micelles for controlled release of RSS



- Sustained/controlled RSS release by optimizing micelle core design
- Inhibition of side effects caused by the donor molecules
- Improved solubility and stability of RSS donors
- Modulating interaction with cells and biological systems

van der Vlies et al., *Advanced Healthcare Materials*, (2023)12 (6), 2201836. Chen et al. , *Polymer Chemistry*, (2020), 11, 4454-4463, Takatani-Nakase et al., *Molecular BioSystems*, (2017), 13, 1705-1708. van der Vlies et al., *Bioconjugate Chemistry*, (2016) 27 (6), 1500-1508. Hasegawa et al., *Medicinal Chemistry Communications*, (2015), 6 273-276.

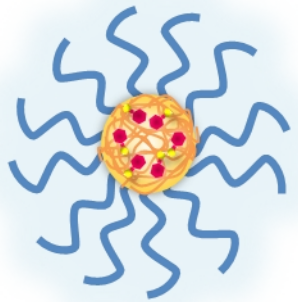
Controlled H_2S release from the polymeric micelles



H_2S donor (ADT)

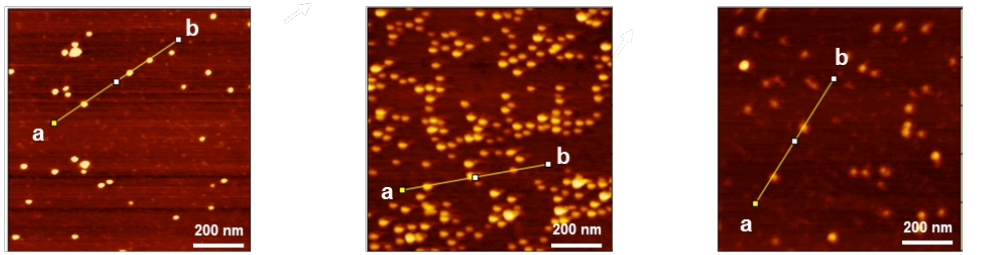
Hydrophobic

Self-assembly



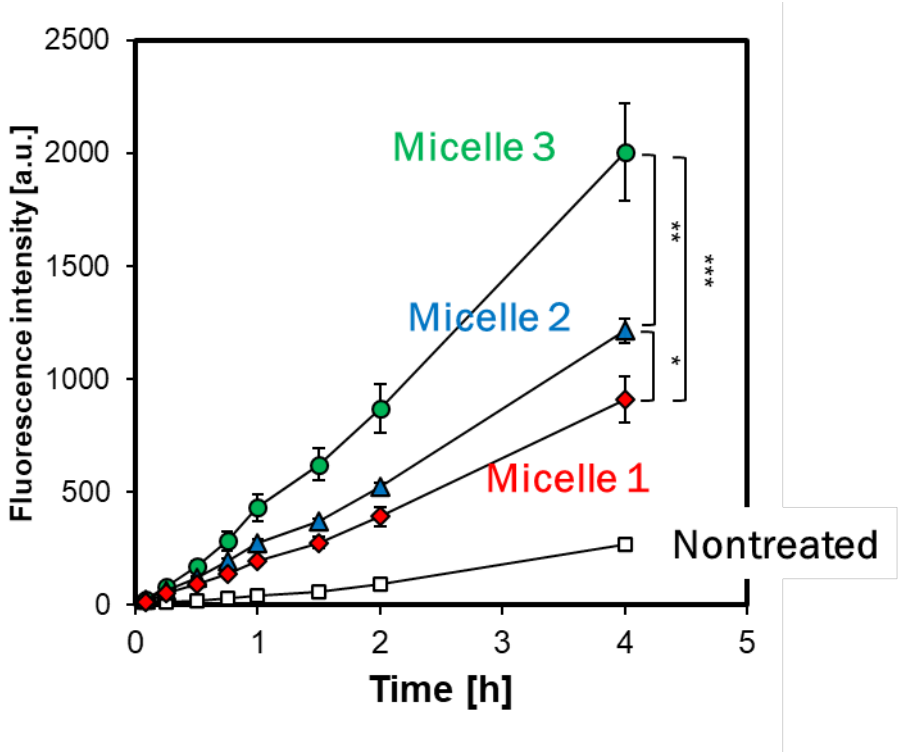
1: n=74, m=21, x=21
2: n=100, m=21, x=18
3: n=100, m=21, x=12

Micelle 1 | Micelle 2 | Micelle 3



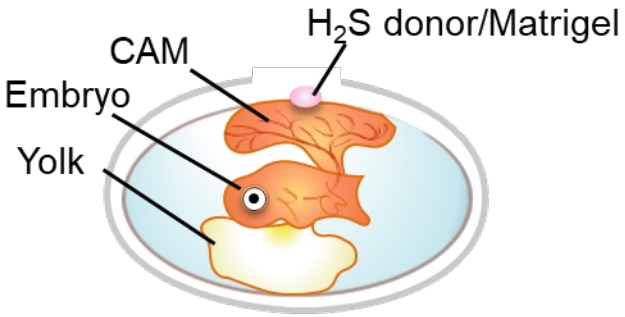
Rigid core ⟷ Flexible core

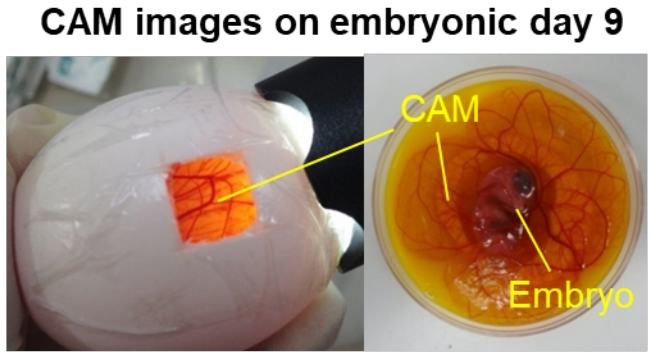
H_2S release in human umbilical vein endothelial

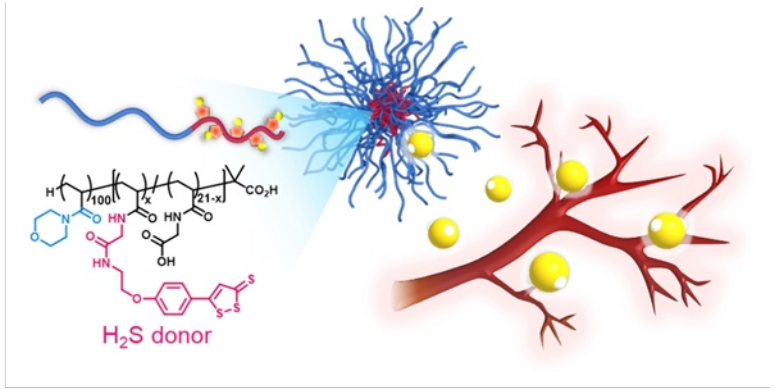


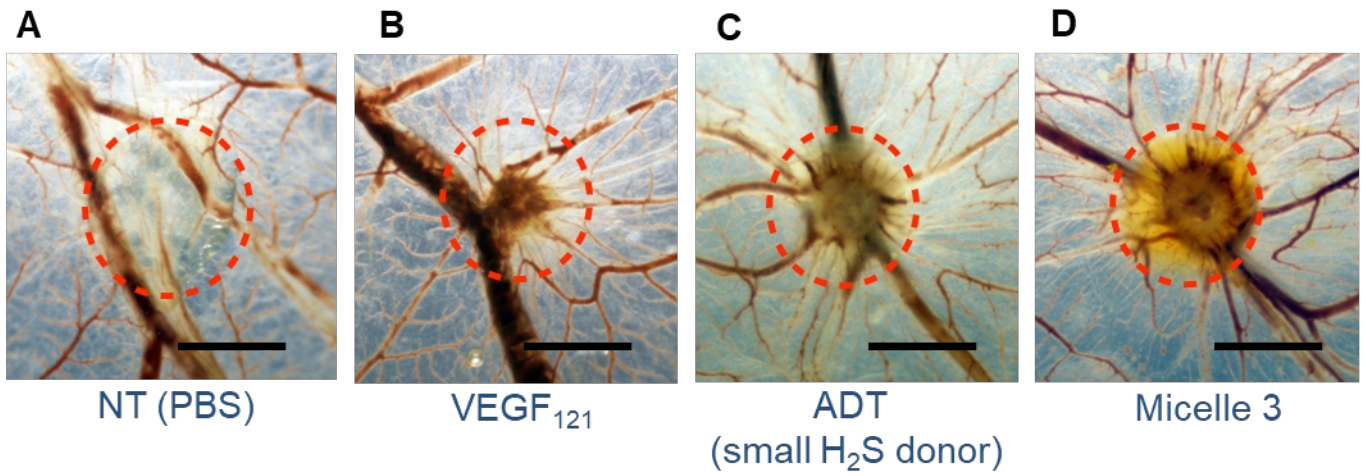
Chen *et al*., Polym. Chem. (2020) 11, 4454.

Proangiogenic activity of the H_2S donor micelles









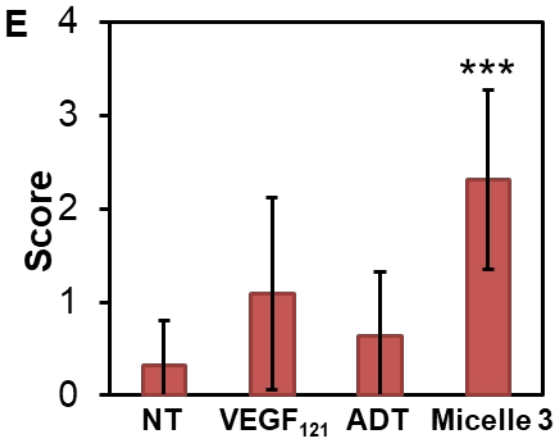
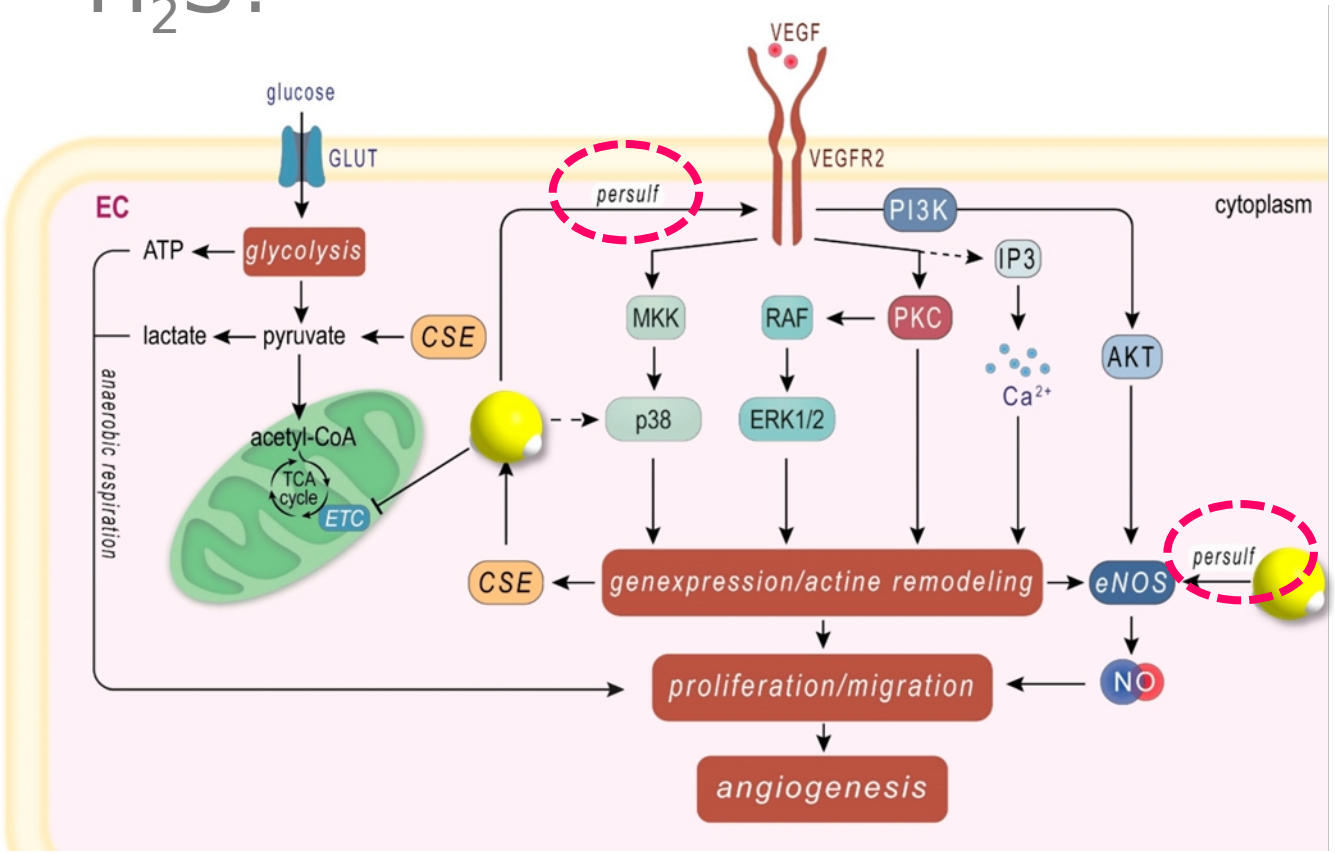


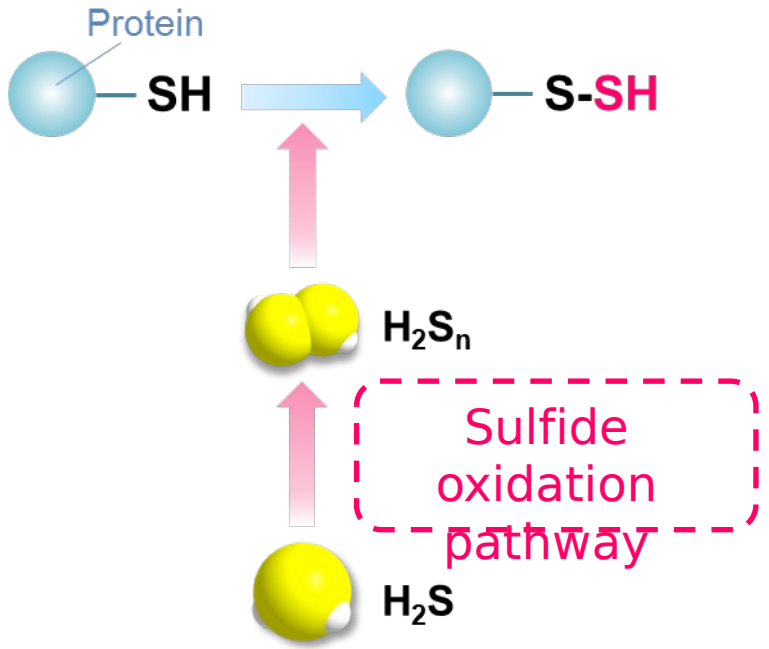
Figure. Blood vessel structure of the CAMs treated with growth factor reduced Matrigel containing (A) PBS (NT), (B) $VEGF_{121}$ (11 μg/mL), (C) ADT (0.58 mM) and (D) Micelle 3 (0.58 mM ADT moieties). The samples were placed on the CAM on embryonic day 9. On day 11, the CAMs were fixed, took out from eggs and observed using macro zoom microscope. Scale bar: 2 mm. (E) Semi-quantitative scoring. *** p<0.001 versus NT, n=8-10.

Chen *et al*., Polym. Chem. (2020) 11, 4454.

Can we further boost the proangiogenic activity of H_2S?



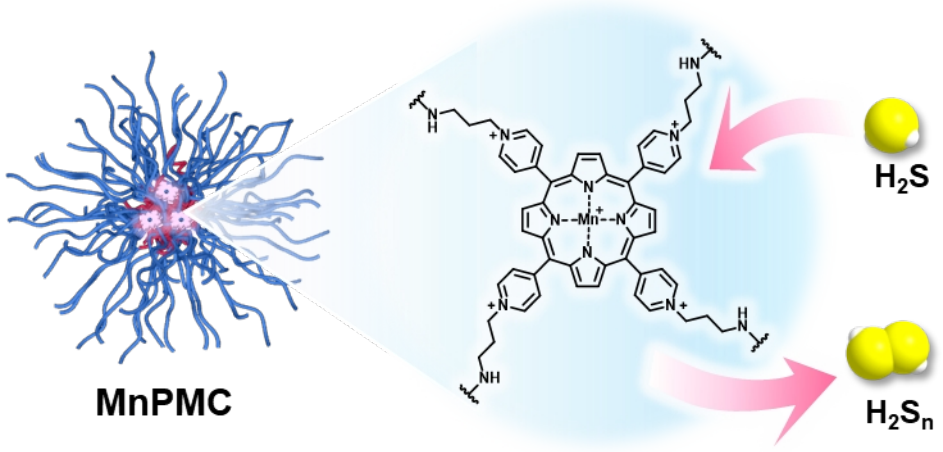
Protein persulfhydration



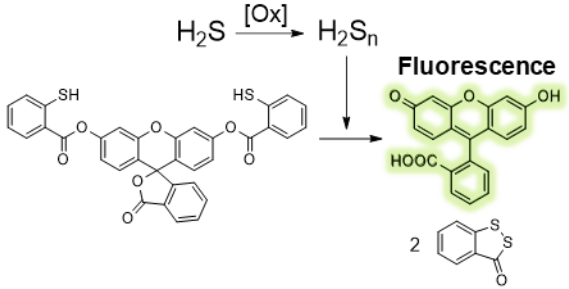
Can we increase conversion of H_2S to H_2S_n?

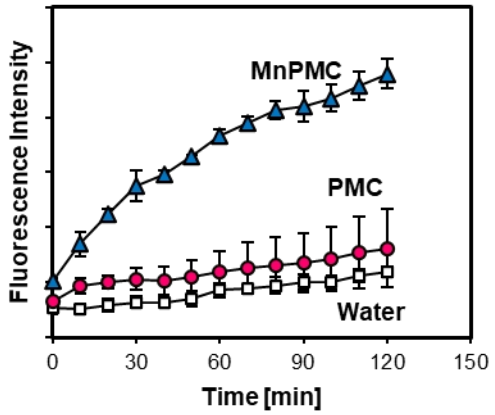
Bechelli et al., *Int. J. Mol. Sci.* 2023, 24(12), 9955

Per/polysulfide delivery by catalytic polymeric micelle system

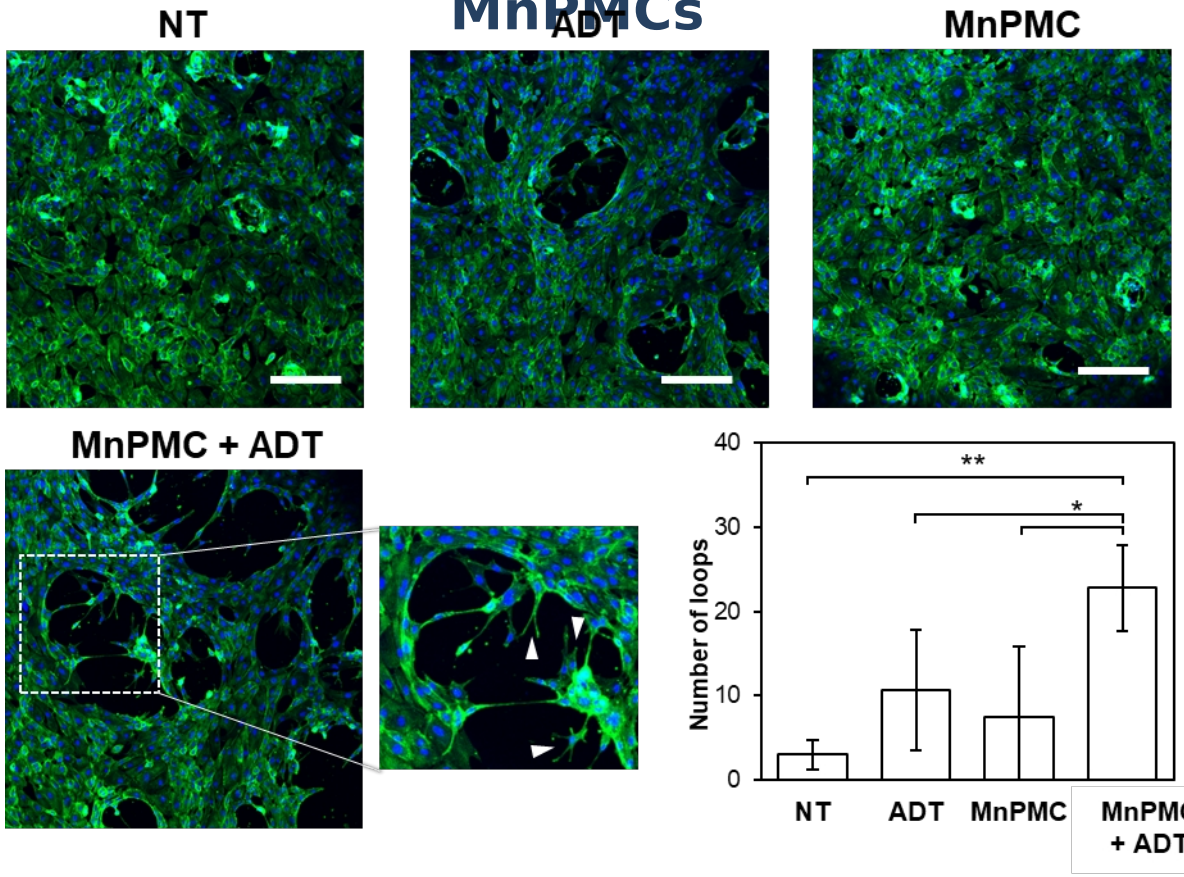


H_2S oxidation by MnPMCs





Proangiogenic activity of MnPMCs



*** ADT: Small H_2S donor**

Kemper *et al*., Adv. Healthc. Mater. 2302429. *in press*. Doi: 10.1002/adhm.202302429.

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