Development of Synthetic Transmembrane Phosphate Transporters

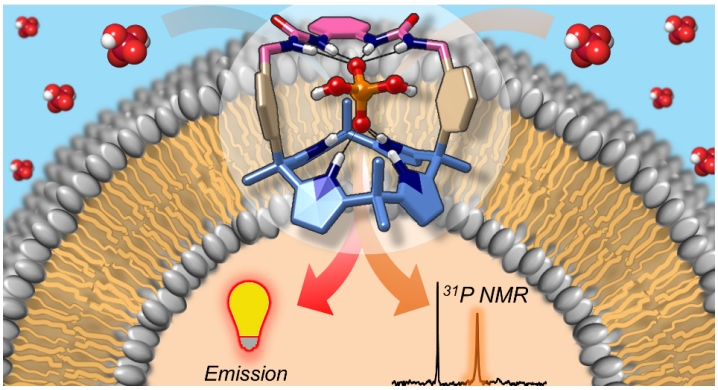
Karolis Norvaisa,[1] Alessio Cataldo,[1] Lau Halgreen,[1] Samantha E. Bodman,[2]
Kristin Bartik,[1] Stephen J. Butler,[2] Hennie Valkenier[1]

[1]Engineering of Molecular NanoSystems (EMNS), Brussels, Belgium; [2]Loughborough University, Department of Chemistry, Loughborough, UK.

Email: karolis.norvaisa@ulb.be

Phosphates and phosphorylated compounds play crucial roles in many biological processes, such as energy transfer in metabolism and enzymatic activity. Because phosphates are anionic and highly hydrophilic, they cannot spontaneously diffuse through cell membranes or lipid bilayers. At the cellular level, transport proteins are essential for moving various charged molecules across cell membranes.[1] While methods exist to purify and reconstitute these transport proteins, along with new assays to track their activity,[2] phosphate carrier proteins still face challenges related to stability and efficient delivery to cell membranes. As an alternative strategy, synthetic compounds can act as mobile carriers or channels in the membrane, typically for transporting chloride as potential therapeutic applications against cystic fibrosis. [3,4]

Until recently, no synthetic transporters for inorganic phosphate were reported. However, in this report, we show a first synthetic carrier based on strapped calix[4]pyrrole scaffold that allows the extraction of strongly hydrated $H_2PO_4^-$ into the lipid bilayer.[5] The deliverable transporter shields negative charges from the lipophilic bilayer interior and transfers inorganic phosphate through the membrane. Phosphate transport was monitored by emission spectroscopy using an encapsulated phosphate sensitive europium(III) probe.[6] Furthermore, ^{31}P-NMR spectroscopy was used to confirm and identify the transported phosphate species.



[1] Hernando, N.; Gagnon, K.; Lederer, E.; *Physiol. Rev.*, **2021**, *101*, 1–35.
[2] Majd, H.; King, M. S.; Palmer, S. M.; Smith, A. C.; Elbourne, L. D.; Paulsen, I. T.; *eLife*, **2018**, *7*, e38821.
[3] Forster, I. C.; Hernando, N.; Biber, J.; Murer, H.; *Mol. Aspects Med.*, **2013**, *34*, 386–395.
[4] Davis, J. T.; Gale, P. A.; Quesada, R.; *Chem. Soc. Rev.*, **2020**, *49*, 6056–6086
[5] Cataldo, A.; Norvaisa, K; Halgreen, L; Bodman, S. E.; Bartik, K.; Butler, S. J.; Valkenier, H.; *J. Am. Chem. Soc.* **2023**, *145*, 16310.
[6] Bodman, S. E.; Breen, C.; Plasser, F.; Butler, S. J.; *Org. Chem. Front.*, **2022**, *9*, 5494.