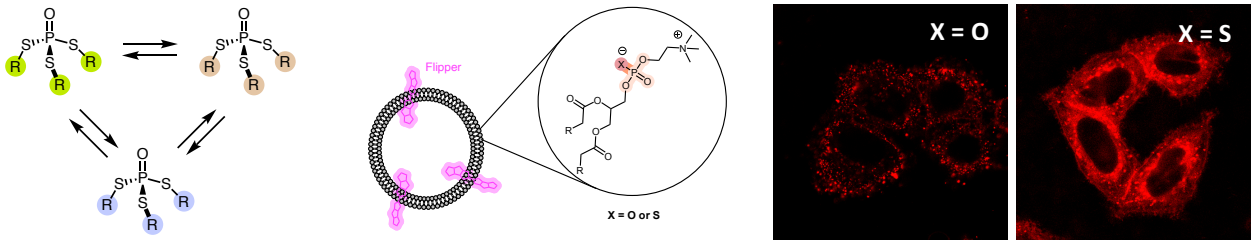
Dynamic Phosphorothioates for Thiol-Mediated Uptake

Jules, Bouffard

Jules.Bouffard@unige.ch

Dynamic covalent chemistry (DCC)[1] relies on reversible covalent bonds that break and reform under equilibrium control, enabling molecular systems to self-correct, reorganize, and adapt to their environment. DCC can be strategically exploited to enable cellular uptake, an enduring challenge in chemical biology. In particular, we focus on thiol-mediated uptake (TMU), which relies on a dynamic exchange cascade with cysteine-rich transmembrane proteins to access the intracellular space[2]. While already established for antimony, bismuth, and arsenic[3], phosphorus was left as the only pnictogen never considered as a dynamic center due to its perceived stability. We recently introduced higher phosphorothioates as fully dynamic P(V) exchange centers capable of fast, reversible thiolate-mediated cascades in organic solvents, aqueous micelles, and living cells[4]. These systems undergo sequential single, double, and triple substitutions with kinetics governed by pH, nucleophilicity, and Hammett-controlled electrophilicity, effectively enabling "molecular walking" along chemical gradients. Their compatibility with cellular TMU networks was validated through potent inhibition of established TMU transporters. Although higher phosphorothioates were limited as TMU substrates because they require three dynamic bonds, single phosphorothioate units can act as pseudo-thiolates to drive the uptake of oligonucleotides[5]. Extending this concept, we showed that replacing a single oxygen atom in phospholipid headgroups dramatically enhances liposome uptake via TMU. Finally, mechanosensitive membrane probes such as Flipper allow us to characterize liposome order, dynamics, and entry pathways with high precision, establishing them as powerful tools to study both natural and synthetic liposomal uptake[6].



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