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Spontaneous Phospholipid Membrane Formation by Chemoselective Ligation Reactions

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Introduction: Phospholipid membranes are employed in numerous practical applications such as the study of protein-membrane interactions, drug-delivery, origin-of-life research, and artificial reactors. While the capability of phospholipids to self-assemble into membranes is well characterized, the *de novo* synthesis and formation of membranes from simple precursors is poorly understood. Therefore, one of the major goals of chemical prebiology is the development of simple and robust methods for the preparation of self-assembling non-natural membranes, that will help understand the fundamental structural, dynamical and biochemical features on which nature builds living systems. Here we describe the use of histidine ligation (HL) to form phospholipids *de novo* [1] from water-soluble starting materials – namely a histidine functionalized lysophospholipid and a water soluble fatty acyl thioester (*Fig.* 1). The resulting phospholipids can spontaneously self-assemble into vesicles that can grow to several microns in diameter. Moreover, the orthogonality, the high reaction rate, and the biocompatibility of this approach are key features that make it a powerful tool for the efficient encapsulation of relevant biomolecules, such as proteins. We foresee future applications of HL membrane assembly in understanding of fundamental chemical mechanisms of origin and early evolution of life, especially in relation to membranes. Such approach will also be useful in bottom-up synthetic biology, molecular self-assembly, and biomimetic chemistry research.

As an ongoing work in our group, we have utilized a similar strategy to ligate an amine-functionalized lysolipid and fatty acyl adenylate to generate phospholipid membranes. We hypothesize that such chemistry played an important role in transitioning from primitive fatty acid based membranes to more sophisticated phospholipid based membranes.

References:

[1] Roberto J Brea[#], Ahanjit Bhattacharya[#], Neal K Devaraj (**2017**) *Synlett* 28(01): 108-112. (# Equally contributing author)

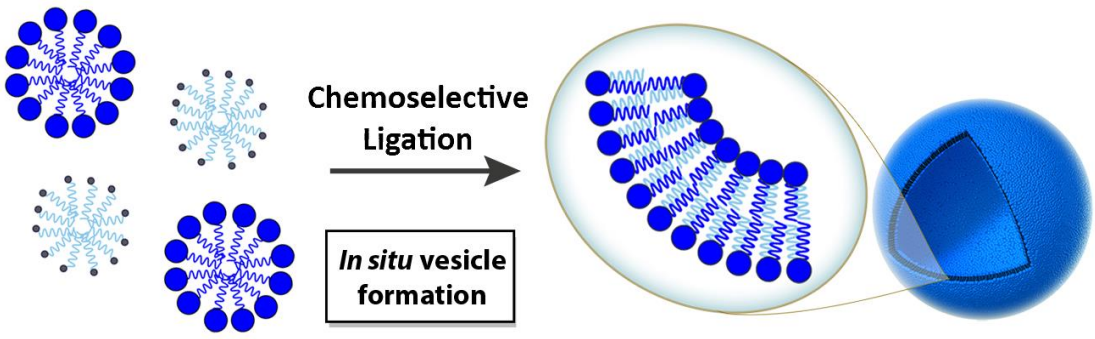

Figure 1 – Formation of membrane forming phospholipids by a chemoselective ligation reaction between non-membrane forming precursors