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CLiB – a novel cardiolipin-binder isolated via data-driven and *in vitro* screening

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Abstract:

Cardiolipin, the mitochondria marker lipid, is crucially involved in stabilizing the inner mitochondrial membrane and is vital for the activity of mitochondrial proteins and protein complexes. Directly targeting cardiolipin by a chemical-biology approach and thereby altering the cellular concentration of “available” cardiolipin eventually allows to systematically study the dependence of cellular processes on cardiolipin availability. In the present study, physics-based coarse-grained free energy calculations allowed us to identify the physical and chemical properties indicative of cardiolipin selectivity and to apply these to screen a compound database for putative cardiolipin-binders. The membrane binding properties of the 22 most promising molecules identified in the *in silico* approach were screened *in vitro*, using model membrane systems finally resulting in the identification of a single molecule, CLiB (CardioLipin-Binder). CLiB clearly affects respiration of cardiolipin-containing intact bacterial cells as well as of isolated mitochondria. Thus, the structure and function of mitochondrial membranes and membrane proteins might be (indirectly) targeted and controlled by CLiB for basic research and, potentially, also for therapeutic purposes.

Keywords: CLiB, mitochondria, cellular processes, putative cardiolipin-binders, respiration, membrane proteins