

Modeling the effects of photo-activated drugs in a biological membrane model by molecular dynamics simulations

DELOVA Anastasiia^A, **LOSANTOS Raul**^B, **MONARI Antonio**^A

A) ITODYS, Université Paris Cité and CNRS, F-75006 Paris, France.

B) Universidad de La Rioja, Departamento de Química, Centro de Investigación en Síntesis Química, 26006 Logroño, Spain.

anastasiia.delova@u-paris.fr

This study presents a comprehensive analysis of the interactions between photo-induced molecular switches and model lipid bilayers, alongside the molecular dynamics of the IgV domain of TIM-3 protein with lipid membranes, through advanced molecular modeling and simulation techniques. We explore the effects of a cyclocurcumin derivative, a potential agent for light-activated chemotherapy, on lipid bilayers mimicking cell membranes¹. Utilizing classical molecular dynamics and enhanced sampling simulations via the coupling of ABF and Metadynamics (meta-eABF) to determine free energy profiles for the penetration of the switch in the membranes, we investigate the chromophore's interaction and penetration into membranes composed of 1,2-dipalmitoyl-sn-glycero-3-phosphatidylcholine (DPPC) and a complex mixture of DPPC, DOPC lipids and cholesterol. Our findings reveal concentration-dependent interactions with DPPC membranes and modulation of structural parameters through E/Z photoisomerization of cyclocurcumin derivative, offering insights into non-oxygen dependent therapies for hypoxic tumors². In the more complex membrane, we showed that the cyclocurcumin derivative interacted differently, causing less profound damages and changes in the lipid bilayer³. However, for both membrane models we confirmed that the structural parameters of the bilayer are differently affected by two isomers, and hence can be modulated through photoswitching, offering interesting perspectives for future applications (Fig.1).

Furthermore, we characterize the interaction of the IgV domain of TIM-3 protein with a model lipid membrane, demonstrating stable yet dynamic complexes facilitated by phosphatidylserine-containing POPS lipids and Ca²⁺ ion. Enhanced sampling MD simulations highlight the thermodynamically favorable insertion of phosphatidylserine into the IgV binding pocket, suggesting mechanisms for modulating TIM-3 activity⁴. This study not only elucidates the molecular basis of lipid-protein interactions but also provides a foundation for future immunotherapy strategies targeting the TIM-3 pathway in cancer treatment.

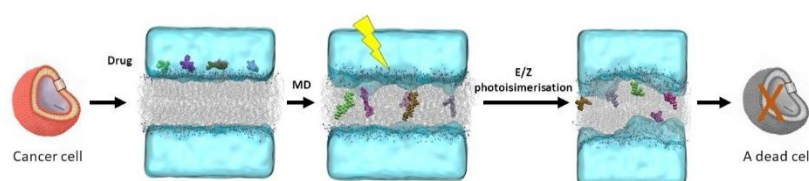


Figure 1. Schematic representation of the cell destruction process as a result of a cyclocurcumin derivative photoisomerization

¹ J. Pecourneau, R. Losantos, A. Delova, Y. Bernhard, S. Parant, M. Mourer, A. Monari, A. Pasc “Biomimetic Photo-Switches Softening Model Lipid Membranes”, *Langmuir*, 2022

² A. Delova, R. Losantos, J. Pecourneau, “Perturbation of Lipid Bilayers by Biomimetic Photoswitches Based on Cyclocurcumin”, *JCIM*, 2022

³ A. Delova, R. Losantos, J. Pecourneau, M. Mourer, A. Pasc, A. Monari, “Modelling the effects of E/Z photoisomerization of a cyclocurcumin analogue on the properties of cellular lipid membranes”, *PCCP*, 2023

⁴ A. Delova, A. Pasc, A. Monari, “Interaction of the Immune System TIM-3 Protein with a Model Cellular Membrane Containing Phosphatidyl-Serine Lipids”, *Chemistry A European Journal*, 2024

Keywords: cyclocurcumin, TIM-3, phosphatidylserine, molecular dynamics, photoisomerization, lipid membranes