

## Unveiling the Role of a Lipophilic, Thermoresponsive Pnipam-based Stabilizer in Enhancing the Chemotherapeutic Activity of Lipid Nanoparticles

Arianna Balestri<sup>1</sup>, Barbara Lonetti<sup>2</sup>, Costanza Montis<sup>1</sup>, Debora Berti<sup>1</sup>

<sup>1</sup> Department of Chemistry “Ugo Schiff” (DICUS) & Consorzio Sistemi a Grande Interfase (CSGI), University of Florence, Florence, Italy

<sup>2</sup> Laboratoire Softmat, Université de Toulouse, Toulouse, France

Lipid-based nanocarriers are widely explored in nanomedicine due to their biocompatibility and structural similarity to biological membranes. Their therapeutic performance strongly depends on the stabilizing agents used to provide colloidal stability and control interactions with biological membranes. In this study, we developed a novel class of PNIPAM-based lipid nanoparticles stabilized by a lipophilic and thermoresponsive block copolymer poly(N,N-dimethylacrylamide)-poly(N-isopropylacrylamide) (PDMA-b-PNIPAM), to enhance drug delivery efficiency. To assess these effects, we performed a series of biophysical and cell-based analyses, including confocal laser scanning microscopy (CLSM), flow cytometry, and scanning electron microscopy (SEM), to evaluate nanoparticle uptake and chemotherapeutic efficacy in human cancer cells. Our results demonstrate that the PNIPAM-based stabilizer plays a key role in enhancing both cellular internalization and the cytotoxic activity of the encapsulated anticancer drug camptothecin (CPT), suggesting an improved interaction with cellular membranes. These findings provide deeper insight into the role of polymeric stabilizers in modulating the bio-nano interface and support the potential of PNIPAM-stabilized cubosomes as promising nanocarriers for chemotherapeutic applications.