EXPLORATORY ASSESSMENT OF NOVEL FLUORINATED *STAR* PLA: PRELIMINARY INSIGHTS IN *IN VITRO* CANCER CELL CULTURES

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Osteosarcoma (OS) poses a significant challenge in terms of treatment efficacy, despite extensive efforts from medical clinicians and researchers. This is partly due to the rapid clearance or non-specific binding of current therapeutic agents used in OS treatment. Consequently, there is an urgent need for novel therapeutic strategies to address these limitations.

FINE project (Italian MUR PRIN 2022) aims to address this need by designing and developing novel fluorinated dendrimers based on amphiphilic copolymers. These dendrimers will possess controllable functionalities, including pH-sensitive hydrazone units, and a high content of chemically equivalent fluorine atoms. The final goal is to create novel pH-responsive drug nanocarriers and ^{19}F-MRI nanoprobes (NanoDenFluo) for the management of osteosarcoma.

A first synthesis of a fluorinated three-armed *star* PLA (star PLA-Flu) was performed by sequentially combining a Ring Opening Polymerization (ROP) of L-lactide, using glycerol as the core, with an anionic ROP (AROP) of a selected epoxy-fluorinated monomer.

The AROP was catalyzed by tetrameric phosphazene base tBuP4, the only organic base successfully employed with alcohols as initiating systems for the polymerization of epoxides.

The biological performance of *star* PLA-Flu was evaluated on standard 2D cancer cell cultures, including MG63, SAOS2, and U2-OS cell lines, as well as the healthy cell model hFOB 1.19. Cytotoxicity, apoptosis, autophagy, and ROS production were assessed to determine if star PLA-Flu affects cellular behaviour. Additionally, cellular uptake and intracellular localization of star PLA-Flu were examined using fluorescence microscopy.

The preliminary results demonstrate that the *star* PLA-Flu is easily internalised by the cells without compromising the cellular behaviour.

The promising results obtained in terms of cytocompatibility, and cellular behaviours of the proposed system will drive the synthesis of the final NanoDenFluo. The best formulation will be validated in a more predictive 3D scaffold-based osteosarcoma model, recapitulating in detail the complexity of the cancer tissue *in vivo* and reducing the limitation of the standard *in vitro* 2D culture systems.

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