Self-assembled amphiphilic random copolymers as drug delivery system for highly hydrophobic anticancer Combretastatin A4

E. Martinelli, E. Guazzelli Author's
[1]*Università di Pisa - Department of Chemistry and Industrial Chemistry, Pisa, Italy*

Solvophobic interactions in amphiphilic random copolymers may lead to the formation of unimer micelles in selective solvents, typically water, through single-chain folding. These unimer micelles fall in the larger category of the so-called single-chain nanoparticles (SCNPs) and feature an extremely small size range (1–20 nm). A tailored synthesis and in-depth characterization of size, shape, and conformation of these materials might drive their future exploitation in environmental chemistry, industrial catalysis, biomedicine and drug delivery.[1,2]

In this work, PEGMAx-*co*-FAy copolymers were synthesized using ARGET-ATRP. Complementary techniques, including small angle X-ray scattering (SAXS) and dynamic light scattering were used to study the self-assembly behavior in water and different organic solvents. In particular, the SAXS studies confirmed the formation of compact-globular single-chain self-folded thermoresponsive unimer micelles in water, which generally presented small hydrodynamic diameters (D_h < 10 nm) as a result of the folding of the hydrophobic perfluorohexylethyl acrylate counits, and a cloud point temperature (T_{cp}) easily tunable by the copolymer structure in terms of composition and side-chain length of the hydrophilic component.[3] As a proof of concept, the formed hydrophobic nanocavities were used to encapsulate Combretastatin A-4 (CA-4), an active but poorly water-soluble anticancer drug.[4] The cellular internalization of the unimer micelles was studied with copolymers tagged with fluorescein O-methacrylate, in biodistribution assays. Cytotoxicity tests toward different cell lines demonstrated the effectiveness of the anticancer drug when encapsulated.

Acknowledgments
This work was supported by the Italian MUR (PRIN 2022 BIOCOMMON, CUP I53D23004120006, under the responsibility of E. Martinelli)

References

[1] Single-Chain Polymer Nanoparticles; Pomposo, J.A., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, **2017**; ISBN 9783527806386.
[2]Terashima, T. Controlled Self-Assembly of Amphiphilic Random Copolymers into Folded Micelles and Nanostructure Materials. J. Oleo Sci. 2020, 2020, 1–10.
[3] Guazzelli E., Masotti E., Kriechbaum M., Uhlig F., Galli G., Martinelli E., **2022**, *Macromol Chem Phys*, DOI: 10.1002/macp.202200360
[4] Calosi M., Guazzelli E., Braccini S., Lessi M., Bellina F., Galli G., Martinelli E., **2022**, *Polymers*, 14 (4), 774, DOI: 10.3390/polym14040774