Cyclodextrin polymers as carriers of three orthogonal therapeutic agents for the innovative combination of chemo- and phototherapies in hypoxic conditions

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Solid cancer cells are often characterized by a low concentration of molecular oxygen (O_2) in the tissues, a condition named hypoxia which activates resistance mechanisms to standard chemotherapy and impairs photodynamic therapy (PDT) relying on the conversion of O_2 into reactive oxygen species (ROS). The H2020 project HypoCyclo aims to develop a nanocarrier combining three therapeutic agents in one platform and overcoming the limitations induced by hypoxic conditions. A biocompatible cyclodextrin polymer forming nanoparticles in water[1] will be loaded with i) a taxane, protecting it and enabling the *in situ* release of the drug; ii) a photosensitizer (PS) allowing PDT; iii) a newly synthesized oxygen releasing agent (ORA) for the supply of O_2 either in its triplet state to feed the PS or as singlet oxygen ($^1O_2$), the most effective ROS. Anthracene and naphthalene endoperoxides have been selected as ORAs and their photocatalyzed synthesis from aromatic substrates has been achieved in the presence of a PS in homogeneous aqueous environment thanks to the use of the cyclodextrin polymer as inert reaction matrix.[2] Co-encapsulation of three agents in the carrier has been achieved in dosage-consistent amounts as confirmed by UV-Vis and emission spectroscopies. Further, the ability of the PS to generate $^1O_2$ and the tendency of the ORA to release O_2 upon thermolysis were unaltered upon complexation in the polymer loading the three components. These preliminary results forecast the use of this polymer as interesting, scalable vessel for the production, carry and delivery of a combination of therapeutic agents.

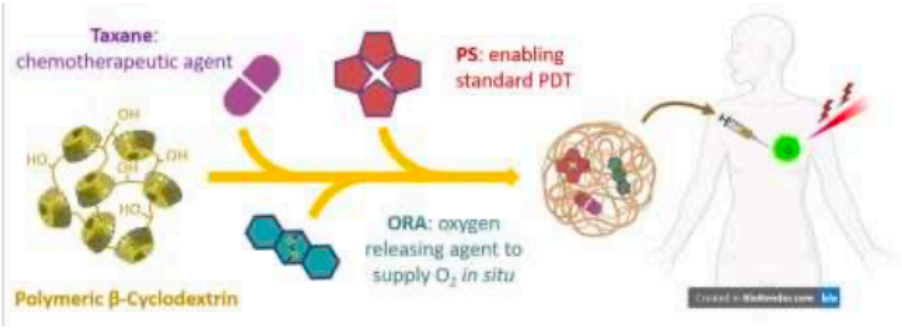

Figure 1. Cartoon representing the strategy for a novel TNBC-targeting combinatorial therapy.

References

1) M. Agnes *et al.*, *Macromol. Biosci.* **2022**, 22, 2200090 DOI: 10.1002/mabi.202200090

2) M. Agnes *et al.*, *Chem. Eur. J.* **2023**, e202300511 DOI: 10.1002/chem.202300511