Vectorized photosensitizers to target, detect and destroy peritoneal carcinomatosis while activating the immune system

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Photodynamic therapy or PDT, is a minimally invasive technique which relies on three essential elements: the light, a photosensitizer (PS) and oxygen. After illumination by a light of an appropriate wavelength, the PS is excited from the ground state (PS_0) to the triplet state ($^3PS^*$) and then reacts with molecular oxygen present in the medium to form reactive oxygen species (ROS), such as singlet oxygen $^1O_2$, which are toxic species for cancer cells and conducting to the destruction of these latter.[1]

The aim of our project is to develop a targeted PDT treatment of peritoneal carcinomatosis from ovarian cancer. Despite a conventional treatment about 60% of women relapse[2] from ovarian cancer and this high recurrence rate is mainly due to the presence of residual microscopic residue that remains at the end of the surgery and are not visible by the naked eye of the surgeon.

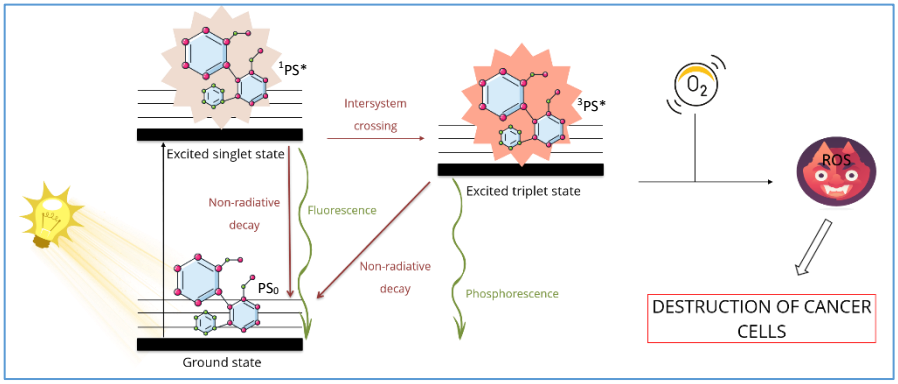

Figure 1. *Principle of photodynamic therapy.*

For this purpose, in order to specifically target the tumoral microscopic residues, we are developing a new targeted PS which result from the coupling between a PS and folic acid (FA) molecule, *via* a PEG spacer. This new PS specifically targets the α isoform of the FA receptor (FRα) which is overexpressed on different cancer cell types, including ovarian cancer cells[3]. Moreover, its low expression by healthy cells and tissues allows a specific targeting. But some stability issues due to the photodecomposition of FA molecule were observed[4]. Therefore, based on molecular docking studies, FA analogues with a potentially high affinity to FRα should be developed.

A first FA analog was synthesized and coupled with pyropheophorbide a. The final product was obtained after 10 synthesis steps and with an overall yield of 2%. The study of its photophysical properties was performed and showed similarity with those of free pyropheophorbide a. The first biological analyses showed no dark toxicity of this new FA analog for various ovarian cancer cell lines and a strong photocytotoxicity with 100 % cell death 24 h after PDT (concentration of 9 µM, with 5 min illumination, 672 nm, 10 mW/cm^2).

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