VECTORIZED PHOTOSENSITIZERS TO TARGET, DETECT AND DESTROY PERITONEAL CARCINOMATOSIS WHILE ACTIVATING THE IMMUNE SYSTEM

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Despite conventional treatment combining maximal cytoreduction surgery with the use of platinum-based chemotherapy, 60% of women with ovarian cancer relapse[1]. One hypothesis is that this high rate of recurrence is strongly related to the presence of microscopic residue at the end of surgery. Therefore, it is important to specifically detect and treat these microscopic peritoneal metastases after gross cytoreduction surgery.

As part of this strategy, the use of photodynamic therapy (PDT) would be a promising approach. Indeed, this minimally invasive technique relies on the activation by illumination of a photosensitizer specifically targeting cancer cells in the presence of oxygen, resulting in the production of reactive oxygen species toxic to these cells and inducing their death, such as singlet oxygen $^1O_2$. PDT is then based on the synthesis of an effective photosensitizer, which will preferentially bind to cancer cells to avoid any accumulation in healthy cells and tissues which can induce adverse effects including high photosensitivity, and which is also capable of producing reactive oxygen species to induce cancer cell death.[2] For this, to improve the specificity of PS for ovarian cancer cells, one of the strategies would be to develop addressing molecules that would specifically target cancer cells via membrane receptors overexpressed on their surface. Among these receptors, the alpha isoform of the folate receptor seems to be a very promising target, as it is overexpressed by several types of cancer cells[3] while being very weakly expressed by healthy cells and tissues.

In 2020, our research team published biological results on the use of a new photosensitizer (pyropheophorbide *a* - polyethylene glycol - folic acid) targeting the folic acid receptor overexpressed by ovarian cancer cells[4]. The latter combines pyropheophorbide *a* with folic acid. However, stability problems for folic acid have been revealed. Thus, the objective of our research work is to design new stable folic acid analogs and/or antifolates which would be able to bind specifically folate receptor overexpressed by ovarian cancer cell, thereby obtaining the necessary selectivity for the application of PDT. The best FA analogue(s) candidate(s) will be coupled to photosensitizers for targeted PDT treatment.

A first folic acid analogue was synthesized and coupled with pyropheophorbide *a*. The final product was obtained after 10 syntheses steps. The study of its photophysical properties was performed and showed promising properties such as fluorescence and singlet oxygen quantum yield of ΦF=0.26 and $\Phi\Delta$=0.41 respectively in ethanol.

The first biological analyses were carried out by Léa BOIDIN in the ONCOTHAI laboratory. Biological tests were performed on three different ovarian cancer cell lines (OVCAR3, SKOV3 and HT1080). No dark toxicity was generated by this new PS and its efficiency in PDT was put in evidence by the induction of cell death at a concentration of 9 µM after 5 minutes of illumination.

References

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