Synthesis, characterization and structure-properties relationship study of molecular and supramolecular systems for sonodynamic therapy applications

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Sonodynamic therapy (SDT) is an alternative strategy that manages malignancies by the generation of cytotoxic factors after the excitation of sono-sensitive agents (SSA) upon ultrasound irradiation [1]. The detailed mechanisms are still unclear but the SDT pathway is based on photodynamic therapy (PDT) concept. Nowadays PDT has been approved as anticancer treatment for particular cases of tumor (i.e. Photofrin for Barrett's esophagus). The main ingredients in this treatment are: sensitizer molecule (non-toxic drug, first ingredient) able to be excited by light (excitation source, second ingredient) absorption; during the relaxation processes reactive oxygen species (ROS, third ingredient) are generated and these radicals start a series of biological events which cause tumor cells death. The differences between PDT and SDT concern mainly the excitation energy source. SDT exploit the thermal effect induced by acoustic cavitation (obtained by ultrasound or shock-waves) rather than light. Harsh conditions generated by acoustic cavitation, promote important physical changes (including thermal excitation) and chemical reactions. As it has been touched on before, the SDT requires the contemporary presence of cavitation and specific molecules able to be excited and able to generate radicals. Many studies indicate as good candidates for this purpose porphyrins derivative [2].

Hence, this project is aimed to synthesize new sono-sensitive agents (porphyrin backbone) in order to enhance the sonodynamic effect and reducing PDT limitations (skin photosensitivity and low penetration of light into the tissue) after linking them onto specific nanosupport (SWCNT, Graphene, nanoparticles, liposome and nanobubbles). In the case of SWCNT, particular high efficiency has been observed thanks to the intrinsic features of that nano hybrid material. Whereas, the encapsulation of *ad-hoc* designed porphyrin derivatives into nanobubble shell turned out in a new US-activated theranostic agent. Moreover, the activity of new SSAs would be enriched by the addition of targeted moiety with the purpose to drive more selectively the SSA to target cells. The SDT efficacy has been evaluated on HT-29 or LS 174 T cell lines and great proliferation reduction come out. Since the synthetic pathway to obtain porphyrin derivatives is often arduous, natural source of porphyrin derivative (Chlorophyll) has been considered and encapsulated on biocompatible nanosystems. *In vitro* tests to investigate the ability to generate radical species as consequence of ultrasound irradiation are ongoing.

[1] a) Rosenthal I, Sostaric JZ, Riesz P, *Ultrasonic Sonochemistry*., **2004**, 11, 349; b) Tachibana K, Feril Jr L, Ikeda-Dantsuji Y, *Ultrasonics*, **2008**, 48, 253; c) Trendowski M, *Cancer and Metastasis Reviews,* **2014**, 33, 143.
[2] Chen H, Zhou X, Gao Y, Zheng B, Tang F and Huang J, Drug Discovery Today, **2014**, 19(4), 502.

Figure. Schematic representation of sensitizer (S) excitation after US irradiation, and consequent ROS generations with tumor cell death