Magnetic polymer micelles and nano-vesicles for selective cytotoxicity by magnetic hyperthermia and magnetic field-triggered drug release

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Many decades ago, clinicians proposed to destroy cancer cells by their heating with magnetic nanoparticles submitted to radiofrequency alternating magnetic fields (AMF). Since 2011, magnetic fluid hyperthermia is authorized as a complementary therapy of high grade brain cancer in synergy with radiotherapy. However, this utilization of AMF to achieve brain tumor necrosis necessitates stereotaxic injection of a high concentration of magnetic nanoparticles directly into the tumor, as developed at Charité Hospital in Berlin by the MagForce company, and the gain in patient lifetime is only moderate (a few months). In general, translation from laboratory to clinics of *in vitro* or *in vivo* magnetic hyperthermia experimental results is not straightforward due to the difficulty to concentrate magnetic nanoparticles at a localized spot inside a living organism, particularly in human. Therefore many teams work on other ways to use AMF to destroy cancer cells, at much lower iron oxide concentrations not allowing that temperature rises up macroscopically. One strategy named "magneto-chemotherapy" makes use of thermo-sensitive drug nanocarriers, by releasing a chemo-toxic drug in the vicinity of cancer cells by "local" (nanometer scale) heating in the vicinity of thermo-sensitive vectors encapsulating the drug. Magnetic thermo-sensitive copolymer nanovesicles loaded with the anticancer drug doxorubicin illustrate this method as demonstrated *in vitro* on HeLa cells [1]. A series of works recent highlighted the experimental finding that a significant cytotoxicity can also be induced by AMF application without any added drug or macroscopic temperature rise, introducing the concept of "cold hyperthermia", or "intra-lysosomal hyperthermia", since the most often cited mechanism would be the release of reactive oxygen species (ROS) in the cytoplasm provoked by a permeability increase of internal cellular membranes (endosomes) [2-6]. The second part of the talk will present our recent results of *in vitro* AMF-induced cytotoxicity, showing dose-responses on two cell lines (L929 murine fibroblasts and U87 human glioma cells) both with field application time and concentration of magnetic polyion complexation micelles made of arborescent copolymer core and a hydrophilic shell to insure colloidal stability in cell culture media [7].

References

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