Magnetoliposomes for Sequential Controlled Release

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The design of efficient and non-toxic drug delivery systems (DDS) that selectively release therapeutic or diagnostic payloads to their biological target in a controlled way is one of the main objectives of nanomedicine [1]. The simultaneous or sequential delivery of therapeutic active principles to the same site of action is particularly challenging. Self-assembled architectures, made of different building blocks, each providing a specific functionality to the final construct combine a facile synthetic route with a high tunability and structural control. For the first time we provide proof-of-principle of a DDS made of (i) liposomes, providing a fully biocompatible lipid scaffold suitable to host both hydrophobic and hydrophilic drugs [2]; (ii) a double stranded DNA zipper conjugated with a cholesteryl unit that spontaneously insert in the lipid membrane and (iii) hydrophobic and hydrophilic superparamagnetic iron oxide nanoparticles (SPIONs) embedded inside the lipid membrane of liposomes or connected to the DNA zipper, respectively. Upon the application of an alternating magnetic field (AMF), SPIONs can trigger, through thermal activation, the release of DNA or of the liposomal payload, depending on the frequency and the application time of the field, as proved by steady-state and time-resolved fluorescence studies. This unique feature, here presented for the first time, is due to the different localization of the two kinds of SPIONS within the construct and demonstrates the feasibility of a multifunctional DDS, built-up from self-assembly of biocompatible building blocks. Even if additional experiments are needed to determine the stability and leakage characteristics in serum and *in vivo*, this contribution shows for the first time an easily self-assembled build-up system for the sequential or simultaneous release of different therapeutics, which would be paramount to handle diseases that requires a multifaced approach addressing both causal and symptomatic features of the pathology [3].

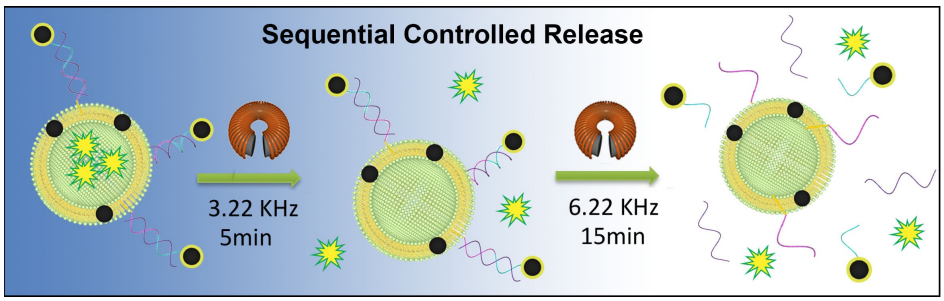

Figure 1 Representative scheme of the DDS functionality for sequential controlled release: the application of a 3.22 KHz AMF for short times is sufficient to provoke the release of the hydrophilic drug contained in the aqueous pool of magnetoliposomes. Subsequently, the application of a 6.22 KHz AMF for longer times allows reaching the DNA melting temperature and the release of the *staple* therapeutic oligonucleotide**.**

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[1] Spsford, K.E. *et al*, *Chem. Rev.* **113,** 1904–2074 (2013).
[2] Allen, T. M. & Cullis, P.R. , *Adv. Drug Deliv. Rev.* **65,** 36–48 (2013).
[3] Wirtz, S. & Neurath, M. F. *Gene Ther.* **10,** 854–860 (2003), Teo, P. Y., Cheng *e tal, Adv. Drug Deliv. Rev.* **98,** 41–63 (2016).