Macrophage entrapped silica coated superparamagnetic iron oxide particles for controlled drug release in a 3D cancer model

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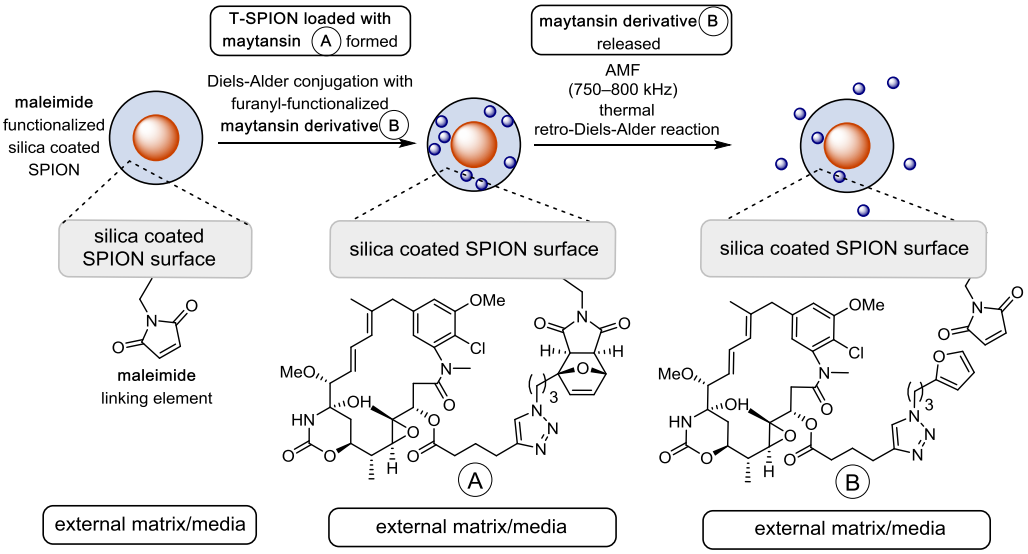
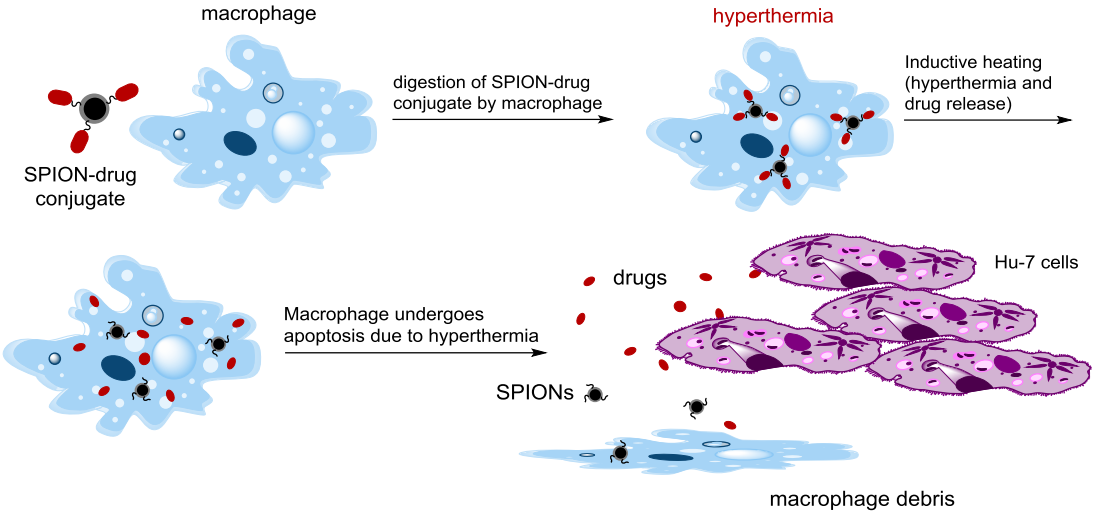
Targeted delivery of drugs is a major challenge in treatment of diverse diseases. Systemically administered drugs demand high doses and are accompanied by poor selectivity and side effects on non-target cells. In a joint research programme between LNQE, BMWZ at Leibniz Universität Hannover and the Helmholtzzentrum für Infektionsforschung (HZI) in Braunschweig we recently introduced a new principle for targeted drug delivery. It is based on macrophages as transporters for nanoparticle-coupled drugs as well as controlled release of drugs by hyperthermia mediated disruption of the cargo cells and simultaneous deliberation of nanoparticle-linked drugs. Hyperthermia is induced by an alternating electromagnetic field (AMF) that induces heat from silica-coated superparamagnetic iron oxide nanoparticles (SPIONs) (Figure 1)

Figure 1: Concept of drug delease from SPIONs by hyperthermia.



We demonstrated the proof-of-principle of controlled release by the simultaneous disruption of the cargo macrophages and the controlled, AMF induced release of a toxin, which was covalently linked to silica-coated SPIONs via a thermo-sensitive linker (Figure 2). Cells that had not been loaded with SPIONs remain unaffected. Moreover, in a 3D co-culture model we demonstrate specific killing of associated tumor cells when employing a ratio as low as 1:40 (SPION-loaded macrophage : tumor cells). Overall, our results demonstrate that AMF-induced drug release from macrophage-entrapped nanoparticles is tightly controlled and may be an attractive novel strategy for targeted drug release.

Figure 2. Macrophages as cargo systems for SPION-drug conjugates (see figure 1 for details), concept for externally induced drug relase. The hyperthermia leads to cell death of macrophages and cleavage of toxin ansamitocin followed by elimination of liver tumor cells (Hu-7).



Using an in vitro tumor model we found elimination of tumors which sets the stage for extending these studies to in vivo investigations.

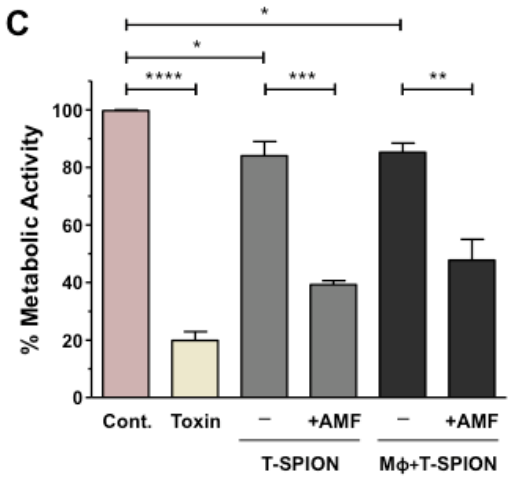


Figure 3:
Induced cell death by AMF-mediated release of an ansamitocin derivative from a nanostructured superparamagnetic iron oxide particle after takeup by macrophages.

Reference (LNQE and BMWZ are acknowledged): S. Ullah, K. Seidel, S. Türkkan, D. P. Warwas, T. Dubich, M. Rhode, H. Hauser, P. Behrens, A. Kirschning, M. Köster, D. Wirth*, Macrophage entrapped silica coated superparamagnetic iron oxide particles for controlled drug release in a 3D cancer model, *J. Contr. Release*, **2019**, *294*, 327-336. DOI: 10.1016/j.jconrel.2018.12.040