Research Highlights
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Leucine zipper peptide functional liposomal carriers enhances drug uptake in solid tumors

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Evaluation of: Al-Ahmady ZS, Al-Jamal WT, Bossche JV *et al.* Lipid–peptide vesicle nanoscale hybrids for triggered drug release by mild hyperthermia *in vitro* and *in vivo*. *ACS Nano* 6(10), 9335–9346 (2012).

Nanomedical constructs for cancer therapy have been the focus of many research groups since the late 1990s. Improvements in chemotherapeutic drugs bioavailability, tunable pharmacokinetics, enhanced efficacy, combined with reduced toxicity and fewer side-effects are important motivations in nano-oncology. Many nanoconstructs exploit the enhanced permeation and retention effect that allows macromolecular drug carriers to passively accumulate at tumor sites and increase the local chemotherapeutic concentration in the tumor tissue. A multitude of publications have showcased such effects, both in animal studies and patients. However, retarded release of the drug component from the delivery system may still limit the effective dose that is released at the tumor site, resulting in nonoptimal treatment effects. The group of Kostarelos has recently developed a novel temperature-sensitive liposomal (TSL) drug delivery system that can be formulated to allow for rapid drug release upon an external cue. The researchers constructed their TSL system to have a leucine zipper peptide sequence attached to the lipid bilayer. The leucine zipper is able to form super-helix coiled-coil aggregates through α-helix self-assembly at low temperatures that dissociate at temperatures exceeding approximately 40°C. Mild hypothermia will open a zipper in the lipid bilayer and accelerate the release of the drug cargo via diffusion.

These TSL constructs were characterized both via *in vitro* and *in vivo* experiments. Unlike most release studies in the literature, the TSL constructs were evaluated for their chemotherapeutic (doxorubicin [DOX]) release kinetics in mouse serum to better mimic physiological conditions. Both improved drug retention and improved serum stability compared with lysolipid-containing temperature-sensitive liposomes was found for the leucine zipper temperature-sensitive liposomes. An *in vivo* study was performed with ^{14}C-tagged DOX, depicting increased blood circulation of ^{14}C-DOX formulated in temperature-sensitive liposomes compared with common liposomes. After subjecting the animals to hyperthermia at 43°C, a threefold increase in DOX accumulation in the tumor was found for the TSL carriers 24 h after injection compared with lysolipid-containing TSL carriers.

This work demonstrated the potential of creating more stable liposomal drug delivery systems beyond the sterically stabilized polyethylene glycolylated liposomal constructs that are used clinically today. The Kostarelos group has shown that by engineering lipid–peptide chimeras, liposomal constructs with both increased serum stability, extended circulation time and bioresponsiveness upon external cues can be achieved, and we hope to see further studies on their efficacy and tumor inhibition ability in the future.

Financial & competing interests disclosure

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Future Medicine part of fsg

Enhanced localization of magnetic nanoparticles with implantable magnets

Evaluation of: Fu A, Wilson RJ, Smith BR *et al.* Fluorescent magnetic nanoparticles for magnetically enhanced cancer imaging and targeting in living subjects. *ACS Nano* 6(8), 6862–6896 (2012).

Since the concept of the magic bullet approach was postulated by Paul Erlich in the 1920s [1], the dream of tissue-selective and localized therapy of tumors has been a vision of many researchers. Magnetic attraction represents one such potential technique to localize nanomedical constructs to the diseased site *in vivo*. Early studies were published in the mid-1960s [2] and early theranostic systems with paramagnetic particles as carrier of drugs in the mid-1990s [3]. Magnetic targeting is an appealing concept but in practice the large magnetic field necessary to localize nanoparticles (NPs) to deeply residing tumors, especially in large animals or humans, is still problematic and limits the utilization to superficial tissue localization. The group of Gambhir addresses this issue by combining an external permanent magnet and a Ni-based magnetic micromesh that can be placed directly onto a tumor or in its proximity to generate a sufficient magnetic field gradient to localize even very small supraparamagentic NPs. This is visualized via fluorescent labeling of the NPs. Magnetic-guided ligand-mediated targeting of angiogenic vessels with RGD-peptides linked to these NPs was demonstrated to have an effect on tumor regression compared with scrambled peptides in an *in vivo* setting in limited numbers of animals.

Further preclinical developments are of course necessary, but the research group has proposed the development of biodegradable magnetic meshes for implantation. Naturally, this is a very appealing concept for magnetic targeting to tumors, especially for inoperable brain tumors that, unlike most cancers, cannot be removed by surgical regression.

References

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Sustained ocular drug delivery utilizing dendrimer-based hydrogels

Evaluation of: Yang H, Tyagi P, Kadam RS, Holden CA, Kompella UB. Hybrid dendrimer hydrogel/PLGA nanoparticle platform sustains drug delivery for one week and antiglaucoma effects for four days following one-time topical administration. *ACS Nano* 6(9), 7595–7606 (2012).

Eye drop administration of antiglaucoma drugs is by far the most convenient administration route and practical for patients. However, antiglaucoma drugs in the form of eye drops usually require daily administration due to the low bioavailability and short duration of drug activity. The numerous daily administrations of these drugs is a significant problem for the patient, especially for the elderly population. In this study, Yang and coworkers designed a hybrid poly(amidoamine) dendrimer hydrogel/poly(lactic-*co*-glycolic acid) nanoparticle platform for simultaneous co-delivery of two antiglaucoma drugs, brimonidine and timolol maleate. Compared with control dosage forms, one eye drop of this aqueous formulation maintained higher concentrations of drugs up to 1 week in ocular tissues of adult rabbits, and the hybrid poly(amidoamine) dendrimer hydrogel/poly(lactic-*co*-glycolic acid) nanoparticle formulation sustained an effective reduction of intraocular pressure for 4 days. *In vitro* results demonstrated that the cellular uptake of poly(lactic-*co*-glycolic acid) nanoparticles was increased by aid of the dendrimer hydrogel (due to increased mucoadhesive properties from the poly(amidoamine) dendrimer), and the ophthalmic drugs were slowly released over a period of 1 month. Furthermore, this platform did not induce ocular inflammation, and ocular histological analysis did not reveal any pathological changes. The results demonstrated that this hybrid platform could prolong precorneal residence time, enhance drug bioavailability and sustain the antiglaucoma effect. This study suggests that new formulations offering extended drug delivery kinetics may improve long-term patient compliance due to much lower dosing frequency.