A multifunctional nanoparticle platform for imaging guided therapy of cancer

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Introduction: To overcome the rapid clearance and side effects of systemically injected drugs nanoparticle delivery systems are useful. This is especially true for nanoparticle formulations that can be used for encapsulation and delivery of water insoluble drugs. We developed a new multifunctional platform to deliver therapeutic and diagnostic hydrophobic materials to tumors. This "theranostic" platform is based on an oil-in-water nanoemulsion carrying a hydrophobic glucocorticoid for therapeutic purposes as well as iron oxide nanocrystals and Cy7 dye for diagnostic imaging (Figure 1). In the current study we demonstrate the delivery, accumulation and therapeutic efficacy of our nanoparticle formulation when applied to nude mice with subcutaneous LS174T (human colon carcinoma) tumors.

Figure 1

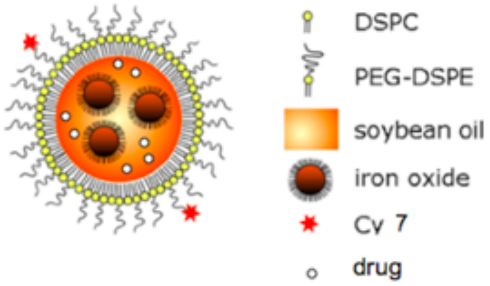
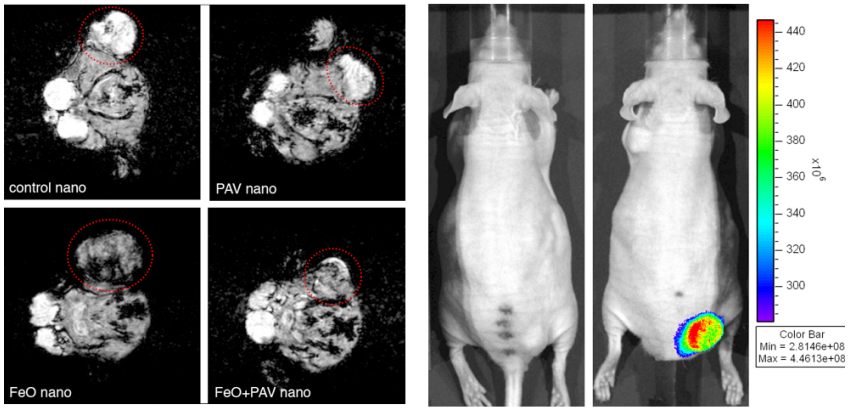


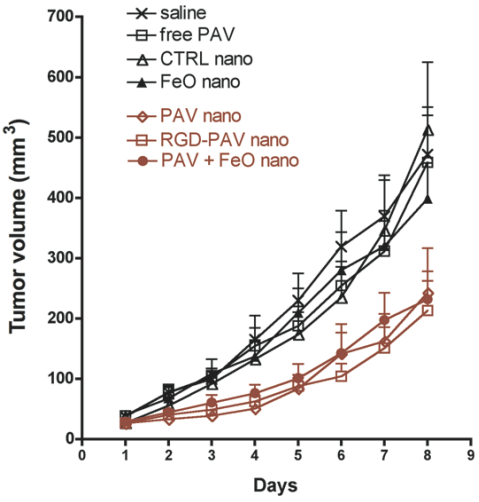
Figure 2



Materials and Methods: The oil-in-water emulsion consisted of a soybean oil core and a lipid corona mixture of DSPC and PEG2000-DSPE (1:1 molar ratio). Oleic acid coated iron oxide nanocrystals (FeO) were included into the oil phase to enable their detection by MRI. The inclusion of Cy7–PEG-DSPE on the surface allowed its detection with NIR fluorescence imaging. Prednisolone acetate valerate (PAV) was included for therapeutic purposes. Some formulations were functionalized with RGD-PEG-DSPE to enable the specific targeting of $\alpha v\beta_3$ expressing endothelial cells.
Swiss nude mice were inoculated with 2 x 10^6 LS174T cells to induce subcutaneous tumors. When tumors were palpable (day 1) mice were iv injected with saline, free PAV, control nanoemulsions (no PAV), PAV loaded nanoemulsions, RGD-PAV loaded nanoemulsions, FeO loaded nanoemulsions or PAV+FeO loaded nanoemulsions. Every mouse received three injections (day 1, 3, 6). The nanoemulsions were dosed at 30 mg Fe/kg and 10 mg PAV/kg. Tumor sizes were recorded daily with a digital caliper. At day 8, mice were imaged on a 3T Philips clinical scanner (FOV 30 x 30 mm^2, 36 slices, TR 150 ms, 8 echoes, TE1 2.7 ms and ΔTE 4.2ms) and the Xenogen IVIS optical imaging system prior to sacrifice.

Results and Discussion: At day 8, MRI was performed on mice injected with PAV loaded nanoemulsions, control nanoemulsions, PAV+FeO loaded nanoemulsions and FeO loaded nanoemulsions. Representative T2*-weighted images are shown in Figure 2A. Tumors of animals injected with control and PAV loaded nanoemulsions appeared bright as compared to surrounding muscle tissue. Tumors of FeO and FeO+PAV loaded nanoemulsion injected mice appeared hypointense, indicative of FeO accumulation in these tumors. The quantitative evaluation of T2*-maps showed a 50% reduction of T2* values in the tumors of animals injected with nanoemulsions containing FeO compared to tumors of mice injected with nanoemulsions that did not contain FeO. The nanoparticle accumulation was corroborated by NIRF imaging in the mice injected with Cy7 coupled nanoemulsions (Figure 2B).
Histology revealed the accumulation of the non-functionalized nanoemulsions in the tumor interstitial space to occur via the enhanced permeability and retention effect, while the RGD peptide functionalized nanoemulsions targeted the angiogenic endothelial cells in tumors due to their affinity for $\alpha v\beta_3$-integrin.
Importantly tumor growth profiles revealed a significant tumor growth inhibition for all the PAV loaded nanoemulsions treated animals as compared to the ones treated with control nanoemulsions, free drug or saline (Figure 3).

Figure 3



Conclusions: In conclusion, this study convincingly demonstrated that our nanoemulsion is a flexible and unique platform that can be employed for imaging guided therapy of cancer. Loading the nanoemulsions with iron oxide nanocrystals, Cy7 dyes and PAV resulted in a combined drug delivery and imaging system. Further biochemical experiments will be performed to clarify the mechanism of action.