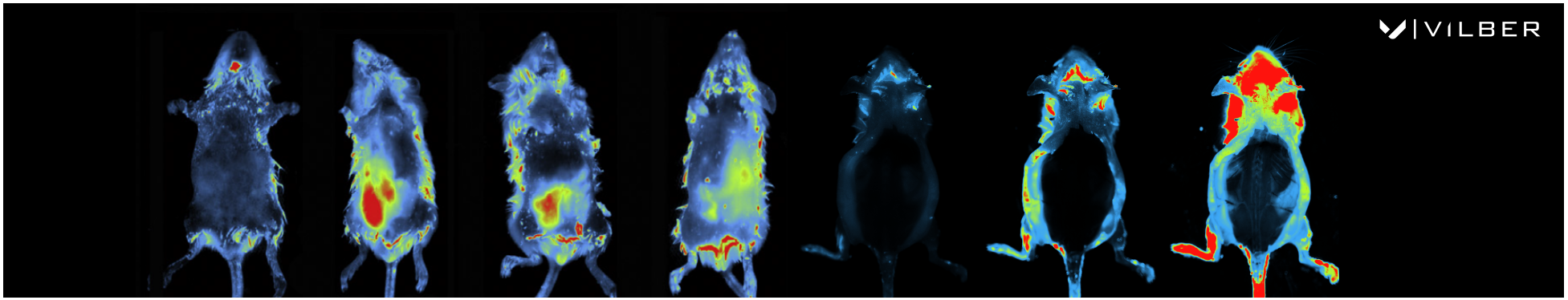

VISUALIZATION OF NANOMEDICINES IN THERAPEUTIC TREATMENTS WITH NEWTON 7.0

AUTHORS

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INTRODUCTION

Gastric cancer (GC) is one of the leading causes of cancer-related death worldwide. Recent advances identified reliable predictive biomarkers such as human epidermal growth factor receptor (HER2), thus introducing molecular targeted drug therapy. GC's HER2-positive, when amplified or over expressed, play an important role in the development and progression of certain aggressive types of breast cancer. Trastuzumab, an anti-HER2 mAb (monoclonal antibody), has been used previously as a targeted therapy for HER2-positive GC. It induces an immune-mediated response that causes internalization and downregulation of HER2 and yields excellent treatment outcomes. Radioimmunotherapy (RIT) is a targeted radioisotope treatment method that uses an antibody as a carrier of therapeutic radioisotopes. The selective targeting of radioisotopes to the tumor using a radiolabeled cancer-specific antibody enables the delivery of a high dose of radiation directly to cancer cells while minimizing the exposure of normal cells. ^{211}At is of particular interest because it emits highly cytotoxic α -particles that can kill a target cell, making it one of the most potent cell-killing agents available. Astatine-211 is therefore particularly suited to the targeted killing of disseminated or micrometastatic solid tumors that are usually resistant.

OBJECTIVE

This study designed a liposomal nanoprimer with specific physico-chemical attributes chosen to favor its liver accumulation. This nanoprimer occupies transiently and physically the liver cells involved in the clearance of nanomedicines, Kupffer cells and Liver Sinusoidal Endothelial Cells (LSEC), to redefine the nanomedicines bioavailability. Furthermore, since a bioavailability increase alone may not be sufficient to improve the treatment's benefit/risk ratio (potential new toxicity, target tissue diffusion or cell uptake), the impact of liposomal nanoprimer on a given nanomedicine efficacy was evaluated.

MATERIAL & METHODS

Liposomes synthesis.

Liposomal nanoprimers were composed of 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine-N-(succinyl) (sodium salt) (SPE) and Chol (50:50, molar ratio). They were synthetized using the thin-film hydration technique and the concentration of phospholipid was determined by colorimetric assay.

Nanoprimer biodistribution study.

All *in vivo* manipulations were performed on adult female mice (NMRI-Fox1nu/Foxn1nu) (Janvier, France) at the Ecole Nationale Veterinaire d'Alfort (Maisons-Alfort, France). For Newton mini biodistribution study, liposomal nanoprimer were loaded with 20nm fluorescent polystyrene nanoparticles. This liposomal nanoprimer was synthetized as described above but including fluorescent polystyrene nanoparticles in the hydration medium. After extrusion process, non-encapsulated polystyrene nanoparticles were removed from loaded liposomal nanoprimer by size exclusion chromatography on a sephacryl S-1000 column. For Newton mini follow up, fluorescently labelled nanoprimer injections (20mM; 10mL/kg) were performed in the tail vein of anesthetized mice (Isofurane (1–5%), oxygen (1–2L/min)). Then animals were immediately placed in dorsal recumbency and imaged with Newton mini (Vilber Lourmat) to perform 2D fluorescent acquisitions (ex: 745nm; em: 820nm) starting 1min after nanoprimer injection, every minute during 1h on whole body. The fluorescence acquisitions were analyzed with the software Newton FT500.

RESULTS

Figure 1. Nanoprimer accumulates specifically and drastically in the liver after intravenous injection.

A 110mM fluorescent labelled nanoprimer solution was intravenously injected in the tail vein of mice at 2ml/kg. Then, fluorescence acquisitions were performed on whole mice during 1 h using Newton Mini (Vilber Lourmat, France).

Fig1. shows preferential accumulation of the liposomal nanoprimer in the liver within the 10 min following intravenous injection in mice, with only a small fraction remaining in the blood. Thus suggesting that a time schedule of 10 min could be used between the injections of nanoprimer and nanomedicine.

Figure 2. Impact of nanoprimer on nanomedicine model bioavailability. Nanoprimer increases nanoparticles systemic bioavailability.

PEG-coated polystyrene (PS) nanoparticles were used as nanomedicine model. 200 nm fluorescent PEG-coated PS nanoparticles were intravenously injected in mice alone, or 10 min after intravenous injection of the liposomal nanoprimer. Immediately after PS nanoparticles injections, whole body fluorescence acquisitions were performed on mice for 1 H, using an *in vivo* imaging device, Newton mini (Vilber Lourmat, France). An increased bioavailability of PS nanoparticles is observed for at least 1 H when administered in the presence of the nanoprimer. This enhanced blood availability is correlated with a lower accumulation of the PS nanoparticles in the liver and the spleen and without a noticeable accumulation in other organs.

CONCLUSION

This study establishes a new strategy to redefine benefit / risk ratio of therapeutic agents by priming the body to receive the treatment, as demonstrated above. The imaging performed with Newton mini (Vilber Lourmat, France) enlightens the ability of the liposomal nanoprimer to increase nanoparticles blood circulation, and also demonstrates the abilities of the Newton mini in imaging nanoparticles and their distribution pattern.