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In situ targeted activation of an anticancer agent using ultrasound-triggered release of composite droplets

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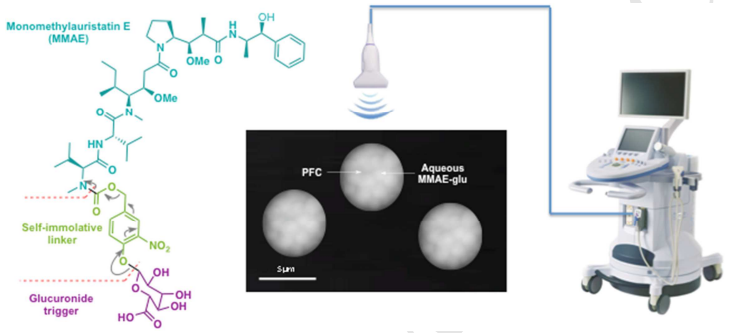

ABSTRACT: The efficiency of a drug is usually highly dependent on the way it is administered or delivered. As such, targeted-therapy, which requires conceiving drug-delivery vehicles that will change their state from a relatively stable structure with a very slow leak-rate to an unstable structure with a fast release, clearly improves the pharmacokinetics, the absorption, the distribution, the metabolism and the therapeutic index of a given drug. In this context, we have developed a particularly effective double stimuli-responsive drug-delivery method allowing an ultrasound-induced release of a monomethylauristatin E-glucuronide prodrug and its subsequent activation by a β-glucuronidase. This led to an increase of cytotoxicity of about 80% on cancer cells.

1. Introduction

The development of 'smart' carriers programmed for the localized delivery of highly cytotoxic drugs in response to extracorporeal physical stimuli offers promises for cancer chemotherapy [1-3]. Such systems are indeed designed to release most, if not all, the administered drug dose directly at the tumor site thereby avoiding any undesired toxicity in healthy tissues. To date, several stimuli-triggered release methods have been reported in the literature; these include ultrasound-activated structures [4,5], especially microbubbles [6-10] or thermosensitive liposomes [11-16]. Considering that ultrasound benefit from their high spatial (millimeter) and temporal (microsecond) resolution, their depth of penetration (up to 10 cm) and their ubiquity in hospitals worldwide [17], they represent a method of choice for achieving optimal spatial- and temporal-controlled release in the context of drug delivery. Within this framework, we previously demonstrated that ultrasound-sensitive perfluorocarbon (PFC) composite droplets injected systemically could transport large payload of fluorescein and deliver their content *in vivo* using a clinical ultrasound scanner with a millimetric resolution [18,19]. This strategy was also used by Fabiilli and co-workers to carry and release chlorambucil, a lipophilic chemotherapeutic [20], and thrombin, a serine protease used in the treatment of pseudoaneurysms [21]. More recently, Fabiilli *et al*. also reported the biodistribution of such composite droplets of perfluorocarbon (6 µm or less in diameter) in rats [22]. While this technology appeared very useful for internal tattooing of tissues, the slow leakage of the encapsulated compound observed from un-induced droplets appeared as a potential drawback to envision the adaptation of this concept to the delivery of highly toxic anticancer agents. Since the problem of unspecific release is inherent to all the carriers developed so far [23], we herein propose to evaluate a new generation of ultrasound-sensitive drug delivery systems based on the encapsulation, within ultrasound-sensitive perfluorocarbon composite droplets, of a none/less active drug precursor instead of the parent drug. Indeed, by specifically manufacturing the active agent within the ultrasound focus, not only would we be able to exclusively limit its activity within the zone delineated on the imaging scanner, but we would also limit any undesired side effects, which could occur downstream.

In order to evaluate the feasibility of this new drug delivery concept, we previously demonstrated that we were able to trigger a spontaneous reaction with a high spatial and temporal control [24]. A first proof of concept was achieved by promoting a Cu-free click reaction using a single ultrasound pulse specifically within the focus of a transducer (0.6 mm in width) and within a time frame of less than 3 ms. Since these acoustic