Supplementary Information

S1. Plasma AUC correlates with total drug released

Below we show that the area-under-the-curve (AUC) of TSL-encpasulated drug concentration in systemic plasma, calculated during hyperthermia, correlates with total amount of drug released. In the following equations, the units are listed in square brackets.

The amount of encapsulated (liposomal) drug entering the tumor (µg drug per mL tumor per second) is:

$$\acute{Q}_{Lip}{}^{T}\left[\tfrac{\mu g}{sec}\right] = c_{p\_Lip}{}^{S} \cdot F_{p}{}^{T} \cdot V^{T} \quad \text{(Equation S1)}$$

We assume TSL release can be approximated by a linear function (Figure 7). Then, the fraction of encapsulated drug released (R) while TSL pass through the tumor capillaries depends on release time t_{rel} and tissue transit time (TT):

$$R = \frac{TT}{t_{rel}} \quad ; [t_{rel} > TT]$$

$$R = 1 \quad ; [t_{rel} < TT] \qquad \text{(Equation S2)}$$

E.g., if the TSL release time is twice as long as the transit time, 50% of the encapsulated drug would be released.

The amount of drug released within the tumor (µg drug per second) is then:

$$\acute{Q}_{Drug}{}^{T}\left[\tfrac{\mu g}{sec}\right] = R \cdot c_{p\_Lip}{}^{S} \cdot F_{p}{}^{T} \cdot V^{T} \qquad \text{(Equation S3)}$$

Assuming a hyperthermia duration t_{heat}, then the total amount of drug released within the tumor (µg drug) is:

$$Q_{Drug}{}^{T}[\mu g] = R \cdot c_{p\_Lip}{}^{S} \cdot t_{heat} \cdot F_{p}{}^{T} \cdot V^{T} \qquad \text{(Equation S4)}$$

Until now, we assumed that the systemic plasma concentration of liposomal drug ($c_{\text{P\_Lip}}{}^{S}$) is constant. If we now assume that this concentration varies with time ($c_{\text{P\_Lip}}{}^{S}(t)$), then the term '$c_{\text{P\_Lip}}{}^{S}{\cdot}t_{\text{heat}}$' in Equation S4 becomes an integral. If we assume heating starts at time t_0, obtain:

$$Q_{Drug}{}^{T}[\mu g] = F_{p}{}^{T} \cdot V^{T} \cdot R \cdot \int_{t_0}^{t_0+t_{heat}} c_{p_{Lip}}{}^{S}(t)\,\mathrm{dt} \quad \text{(Equation S5)}$$

The integral in equation S5 is the area-under-the-curve (AUC) of the systemic plasma concentration of TSL-encapsulated drug, calculated during hyperthermia. I.e., the total amount of drug released in the tumor during hyperthermia ($Q_{\text{Drug}}{}^{T}$) correlates with this AUC. In addition, the amount of drug released depends on R, which depends on the TSL formulation and temperature.

Table 1. List of variables and parameters used in Equation S1-S5.

Variable/Parameter [Units]	Description
$c_{\text{P\_Lip}}{}^{S}$ [µg/mL]	TSL-encpasulated drug concentration in systemic plasma
V^{T} [mL]	Tumor volume
t_{rel} [sec]	TSL release time (see Figure 7)
TT [sec]	Tumor transit time (time required for plasma to pass through tumor capillaries, see Figure 4)
R []	Fraction of TSL-encapsulated drug released
$Q'_{\text{Drug}}{}^{T}$ [µg/sec]	Amount of drug released in tumor per second
$Q'_{\text{Drug}}{}^{T}$ [µg]	Total amount of drug released in tumor during hyperthermia
t_{heat} [sec]	Hyperthermia duration
t_0 [sec]	Time when hyperthermia starts

S2. Reviewed nanoparticle publications

For comparison between TSL and other nanoparticle formulations in terms of tumor uptake (Figure 3), we used a prior review that compared 117 studies on nanoparticle formulations between 2005-2015 [1], and added TSL studies within that same time period. In addition, we performed a literature search between 2016-2022 to include newer nanoparticles as well in our comparison, using the same search criteria and normalization methods as in Wilhelm et al. [1]. Specifically, Using GoogleScholar and SciFinder search engines, combinations of keywords such as nanoparticles, biodistribution, quantitative, %ID, and thermosensitive liposomes were searched in English-language, peer-reviewed journals between 2016-2022. Studies not directly reporting quantitative information such as tumor drug uptake as percent injected dose within specific time periods (%ID/g) or where the tumor AUC could not be calculated by reported details (e.g., injected dose, µg drug per g tumor; for volumes, 1 mL tumor was considered as 1.2g) were not included. Total tumor AUCs for concentrations (C, %ID/g) and time (t, in hours) were calculated by the linear trapezoid method:

$$AUC = \sum_{i=1}^{n}(0.5\,(C_i + C_{i-1}) \cdot (t_i - t_{i-1})) \quad \text{(Equation S6)}$$

Total %ID/g was then normalized by dividing the AUC by the study's reported period of biodistribution measurements in hours. Table 2 lists the prior studies that were considered in addition to the 117 prior studies reviewed by Wilhelm et al [1].

Table 2. Prior studies with passive, active and triggered nanoparticles between 2016-2022 were reviewed, as well as TSL studies. Tumor uptake was normalized as described by Wilhelm et al [1]. Studies where 'Type' is succeeded by an asterisk (*) indicate that tumor drug uptake was measured only at a single time point. Typically, the tumor uptake AUC (Equation S6) underestimated true AUC in these studies since tumor concentration is assumed zero immediately after the measured time point.

Year	Material	Type	Tumor uptake [%ID/g]	Drug	Ref
2007	liposomes	TSL*	12.8	doxorubicin	[2]
2010	liposomes	TSL*	4.5	doxorubicin	[3]
2010	liposomes	TSL*	9.6	doxorubicin	[3]
2010	liposomes	TSL*	10	doxorubicin	[3]
2010	liposomes	TSL*	14.8	doxorubicin	[3]
2010	liposomes	TSL*	19	doxorubicin	[3]
2011	liposomes	TSL*	15	doxorubicin	[4]
2011	liposomes	TSL*	6.6	doxorubicin	[4]
2013	liposomes	TSL*	37.5	gemcitabine	[5]
2014	liposomes	TSL*	0.9	cisplatin	[6]
2016	gold hybrid	triggered	7.5	doxorubicin	[7]
2016	polymer (iron-PEG)	active	6	doxorubicin	[7]
2016	hybrid (bismuth-PDA)	triggered	4.6	doxorubicin	[8]
2016	lipid-polymer (PLGA)	active	1.1	doxorubicin	[9]
2016	polymer (PLGA)	passive	2.6	emodin	[10]
2016	polymer (HPMA)	passive	7.9	doxorubicin	[11]
2016	polymer (heparin-deoxycholate)	passive	1.2	doxorubicin	[12]

2016	polymer (PEG-PDTC)	active	2.6	doxorubicin	[13]
2016	lipid-polymer hybrid	passive	0.8	doxorubicin	[14]
2016	polymer (inulin)	active	5.0	epirubicin	[15]
2016	polymer (PCSSL)	triggered	3.6	doxorubicin	[16]
2016	polymer (PEG)	passive	0.9	paclitaxel	[17]
2016	lipid-polymer (zinc)	passive	4.6	cisplatin, siRNA	[18]
2016	polymer (chitosan)	active	1.3	siRNA	[19]
2016	folate-cobalt	active	1.3	doxorubicin	[20]
2017	liposomes	TSL*	0.8	cisplatin	[21]
2017	iron oxide	passive	6.6	enzymes	[22]
2017	silica-lipid	triggered	11.2	doxorubicin	[23]
2017	copper hybrid	active	8.9	artesunate	[24]
2017	polymer (chitosan)	triggered	3.5	doxorubicin	[25]
2017	silica	passive	1.0	doxorubicin, miRNA	[26]
2017	silica-liposome	passive	6.1	doxorubicin, cytokine	[27]
2017	polymer (PLys-PGlu-PEG-PCL)	passive	1.3	cabazitaxel	[28]
2017	polymer (PLGA)	passive	0.47	garcinol	[29]
2017	polymer (POEA)	triggered	11.4	doxorubicin	[30]
2017	polymer (PEG-CM cellulose)	passive	4.2	podophyllotoxin	[31]
2017	polymer (PLGA-PEG)	triggered	0.8	paclitaxel	[32]
2017	polymer (heparin)	active	2.6	cisplatin	[33]
2017	polymer (PEG)	triggered	11.2	doxorubicin	[34]
2017	polymer (PLGA-PEG)	passive	3.6	vincristine	[35]
2017	polymer (PEG-TMCC)	passive	1.0	docetaxel	[36]
2017	silica-polydopamine	triggered	14.6	doxorubicin	[37]
2017	hybrid (gold-manganese-PLGA)	triggered	1.2	docetaxel	[38]
2017	polymer (chitosan)	active	2.4	paclitaxel	[39]
2017	polymer (POEA)	triggered	7.6	doxorubicin	[40]
2018	iron oxide-silica	active	13.6	epirubicin	[41]
2018	polymer (PEG-PLGA)	active	3.7	curcumin	[42]
2018	iron oxide-silica	triggered	22.4	doxorubicin	[43]
2018	nanocrystal (albumin)	passive	1.0	paclitaxel	[44]
2018	silica hybrid-copper	triggered	4.6	doxorubicin	[45]

Year	Material	Type	Size	Drug	Ref.
2018	silica	triggered *	2.6	doxorubicin	[46]
2018	protein (albumin)	active	6.1	paclitaxel	[47]
2018	liposomes	active	2.1	doxorubicin	[48]
2018	gold-silica	triggered *	4.3	doxorubicin	[49]
2018	polymer (polyrotaxane)	active	3.75	paclitaxel	[50]
2019	liposomes	TSL*	12.4	doxorubicin	[51]
2019	liposomes	TSL*	11.0	doxorubicin	[52]
2019	polymer (oleyl hyaluronic acid)	passive	1.7	doxorubicin	[53]
2019	hybrid (polymer-liposome)	passive	0.9	oxaliplatin	[54]
2019	Iron acetylacetonate	active*	1.5	*18F	[55]
2019	polymer (PEG-MPE-BzMA)	triggered	4.4	camptothecin	[56]
2019	gold	active*	3.8	cisplatin	[57]
2019	hybrid (lipid-PLGA)	passive*	6	docetaxel	[58]
2019	liposomes	active	11.8	doxorubicin	[59]
2019	hybrid (HMPB-PVP)	triggered	0.8	doxorubicin	[60]
2019	polymer (PLGA)	active*	0.18	doxorubicin	[61]
2020	polymer (PEG)	triggered	1.4	paclitaxel	[62]
2020	polymer (PLGA)	active*	3.9	Epigallo-catechin-3-gallate	[63]
2020	gold	active*	4.5	-	[64]
2020	polymer (PEG-PLA)	passive	2.5	cabazitaxel	[65]
2020	hybrid (gold-polysiloxane)	passive	1.4	radiosensitizer	[66]
2020	polymer (PCD)	passive*	4	enzymes	[67]
2020	liposomes	active*	20	oxaliplatin	[68]
2020	liposomes	active	3.8	radionuclide	[69]
2020	polymer (PDMA)	triggered *	5.6	camptothecin	[70]
2020	polymer (hyaluronan)	triggered *	7.3	7-ethyl-10 hydroxy-camptothecin	[71]
2020	liposomes	triggered *	0.3	In-111 (radionuclide)	[72]
2020	polymer (PAMAM)	triggered	7.9	cisplatin	[73]
2020	gold-silver colloid	passive	1.6	gold-silver	[74]
2021	liposomes	TSL	13.5	idarubicin	[75]
2021	liposomes	TSL	3.5	doxorubicin	[75]

2021	polymer (PAMAM)	triggered	11.6	gefitinib	[76]
2021	polymer (PRES)	passive*	0.85	paclitaxel	[77]
2021	liposomes	active	3.5	radioisotopes	[78]
2021	gold	triggered	16.7	methotrexate	[79]
2021	nanocrystal colloid (vaterite)	passive*	11.0	porphyrazine	[80]
2021	gold	triggered	6.7	doxorubicin	[81]
2022	liposomes	TSL	8.0	doxorubicin	[82]
2022	liposomes	triggered	3.5	doxorubicin	[83]
2022	hybrid (polymer-iron-calcium carbonate)	triggered*	2.25	cisplatin	[84]

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