Supplementary Information

Drug Transport Kinetics of Intravascular Triggered Drug Delivery Systems

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Fig. S1. Schematic depicting the interplay between three categories: physiology/biology, drug delivery system (DDS), and drug. The terms in each box are often used to describe or characterize each category. The terms adjacent to each arrow highlight the transport properties that are influenced by the interplay between two categories. For example, the plasma half-life, permeability, and clearance of a DDS depend on the interaction between the physiology/biology and the DDS. Depending on the state of the drug (i.e. DDS-associated or free), the transport properties may be different (e.g. half-life). Stimuli may be used to change the transport kinetics by changing the drug state from DDS-associated to free. Note, this is not a complete list.
Fig. S2. *In vivo* fluorescence linearity. Intravascular fluorescence was compared to plasma concentration quantified from blood samples at various time points after administration of unencapsulated dye (data in Fig. S5).

Fig. S3. Intravital image processing overview. a Fluorescence images (920x920 μm FOV) with TSL-encapsulated carboxyfluorescein (green) dye, before and after 10 min heating. b Segmented vasculature network. c Mean intra- and extravascular fluorescence intensity.

Fig. S4. Pharmacokinetic (PK) model for PK parameter calculation. A two-compartment model was used for calculation of clearance and distribution parameters for free (unencapsulated) dye.
**Fig. S5. Plasma clearance.** Clearance of free (unencapsulated) carboxyfluorescein (CF) dye, measured at 5 different doses. Error bars indicated standard deviation (n=3 animals at each dose/time point).

We normalized the plasma concentration data (Fig. S5) for each dose relative to the first time point at 2 min (Fig. S6). Subsequently, a bi-exponential fit (Equ. 7) was made (Fig. S7) from which the distribution and clearance rate constants were calculated (Equ. 8).

**Fig. S6. Normalized clearance data.** Clearance and distribution rate constants were calculated based on normalized clearance data. Shown is normalized data for 5 doses, and average based on data from Fig. S5.
Fig. S7. Biexponential fit to clearance data. Normalized mean plasma concentration (average of 5 doses from Fig. S6) (x markers), and fitted bi-exponential curve from Eqn. 7 ($R^2=0.99$), with following parameters: $C_0=1.363; \alpha=0.4407; \lambda_1=0.02832; \lambda_2=0.2903$.

Fig. S8. IV-DDS release kinetics. a We assumed zero-order release kinetics for IV-DDS as shown on the graph, with release time ($t_{rel}$) indicating time required for complete release. b For IV-DDS with non-zero-order release kinetics, release time ($t_{rel}$) can be approximated if release kinetics is approximately linear up to the transit time ($TT$; in our tumor model, $TT=5\text{ s}$). The estimated release time ($t_{rel}$) is where the linear approximation intersects with 100% release. This approximation is adequate since release from IV-DDS only occurs during transit of the tumor region (i.e. up to the transit time ($TT$)). After that, IV-DDS return to systemic circulation without further release. We used this approximation to estimate release time ($t_{rel}$) for sTSL and fTSL (see Fig. S10-12; Table S3).
Fig. S9. Schematic of computational model. Model parameters are indicated in red, and model variables are indicated in green (see Table 3 and Table S2 for parameter and variable descriptions).

Table S1. Comparison of in vivo studies and computer model. Error values are calculated relative to experimental in vivo results for both the studies with unencapsulated (free) drug, and the studies with thermosensitive liposomes (TSL).

| Parameter [units] | In vivo | Computer model | Error of computer model | Parameter description |
|-------------------|---------|----------------|-------------------------|-----------------------|
| **Free drug studies** | | | | |
| $C_{0\text{,peak}}$ [μg/ml] | 5.4 ± 0.3 | 5.7 | 0.3 (4.0%) | Peak EES concentration |
| $\text{AUC } C_{0}$ [μg/ml*min] | 56.9 | 58.2 | 1.3 (2.4%) | AUC of EES concentration |
| $C_{0}(t)$ [μg/ml] | - | - | 0.2 (3.8%)* | Mean absolute error of $C_{0}(t)$, t=0…20 min (Normalized error (%)) |
| **TSL studies** | | | | |
| $C_{\text{plateau,TSL}}$ [μg/ml] | 25.9 ± 5.8 | 18.2 | 7.6 (29.5%) | Plateau EES concentration |
| $\text{AUC } C_{0\text{,TSL}}$ [μg/ml*min] | 192.5 | 135.6 | 56.8 (29.5%) | AUC of EES concentration |
| $\text{err}_{\text{TSL}}$ [μg/ml] | - | - | 4.0 (14.9%)* | Mean absolute error of $C_{0}(t)$, t=0…20 min (Normalized error (%)) |
| $C_{\text{plateau,TSL}}$ [μg/ml] | 2.5 ± 1.4 | 2.5 | 0.03 (1.4%) | Plateau EES concentration |
| $\text{AUC } C_{0\text{,TSL}}$ [μg/ml*min] | 36.8 | 17.3 | 19.4 (52.9%) | AUC of EES concentration |
| $\text{err}_{\text{TSL}}$ [μg/ml] | - | - | 1.2 (48.4%)* | Mean absolute error of $C_{0}(t)$, t=0…20 min (Normalized error (%)) |

* Normalized mean absolute error (%)
Table S2. Parameters used in computational model.

| Parameter | Value | Parameter description | Parameter source |
|-----------|-------|-----------------------|------------------|
| $Hct^S$ [1] | 0.45  | Systemic Hematocrit  | 1                |
| $Hct^MV$ [1] | 0.19 | Hematocrit inside tumor microvasculature | 2                |
| $v_v$ [1] | 0.29  | Tumor blood volume fraction (imaging window) | Intravital Imaging |
| $v_p^T$ [1] | 0.16 | Tumor plasma volume fraction (whole tumor) | $v_p^T = v_v(1-Hct^S)$ |
| $v_e$ [1] | 0.71  | Tumor extravascular volume fraction (imaging window) | Intravital Imaging |
| $k_{av}$ [1] | 0.39 | Available volume fraction in extravascular space (for unencapsulated dye) | Intravital Imaging |
| $v_{e,av}$ [1] | 0.28 | Available extravascular tumor volume fraction | $v_{e,av} = k_{av} * v_e$ |
| $t_{rel}$ [s] | 8.2 (fTSL) | IV-DDS release time at 42ºC | In vitro measurement |
| $TT$ [s] | 5.0   | Tissue transit time of tumor segment | Intravital Imaging |
| $V_p^S$ [μL] | 1120 | Systemic plasma volume (=IV-DDS volume of distribution) | Calculated based on animal weight (20 g) 3 |
| $VT$ [μL] | 10    | Tumor volume | Measured in animals |
| $V_p^T$ [μL] | 0.16 | Tumor plasma volume | $V_p^T = VT * v_p^T$ |
| $ID$ [μg] | 60    | Injected dose of IV-DDS encapsulated drug (based on 20 g animal weight, and a dose of 8 μmol/kg) | Defined |
| $PS$ [1/s] | 0.012 | Vascular permeability-surface area product ($P$ represents the apparent permeability rather than true vascular permeability) | Intravital Imaging |
| $F_p$ [mL/(mL*s)] | 0.047 | Tumor plasma perfusion rate (imaging window) | Intravital Imaging |
| $V_D$ [mL] | 8.99 | Initial volume of distribution for unencapsulated drug (Peak plasma concentration=([Injected Dose]/$V_D$) | Serial blood sampling |
| $k_p$ [s$^{-1}$] | 1.29 * 10$^{-3}$ | Transport rate constant, tissue -> plasma | Serial blood sampling |
| $k_t$ [s$^{-1}$] | 0.90 * 10$^{-3}$ | Transport rate constant, tissue -> plasma | Serial blood sampling |
| $k_e$ [s$^{-1}$] | 0.80 * 10$^{-3}$ | Elimination rate constant | Serial blood sampling |

Fig. S10. TSL release kinetics and stability in fetal calve serum (FCS). a Release kinetics of fast (fTSL) and slow releasing TSL (sTSL) at 42ºC, over 10 min. b Encapsulation stability of fTSL and sTSL at 37ºC, over 60 min.
**Fig. S11. fTSL release kinetics.** Shown during first 4 seconds for temperatures of 38 to 42°C. Linear approximation is indicated as black line, and release time was calculated based on the slope of this linear approximation ($t_{rel}=1/R$, where $R$ is the slope of the linear approximation).
**Fig. S12.** sTSL release kinetics. Shown during first 10 seconds for temperatures of 38 to 40°C, and for first 4 seconds for 41 and 42°C. Linear approximation is indicated as black line, and release time was calculated based on the slope of this linear approximation ($t_{rel}=1/R$, where $R$ is the slope of the linear approximation).

**Table S3.** Release time in sec for fTSL and sTSL for temperatures from 38 to 42°C.

| Temperature [°C] | fTSL release time ($t_{rel}$) [s] | sTSL release time ($t_{rel}$) [s] |
|------------------|----------------------------------|----------------------------------|
| 38               | 104.9                            | 2857.1                           |
| 39               | 86.7                             | 2409.6                           |
| 40               | 43.9                             | 466.2                            |
| 41               | 11.9                             | 96.1                             |
| 42               | 8.2                              | 63.0                             |
**Global sensitivity analysis**

We performed global sensitivity analyses based on the computer model parameter variability indicated in Table S4, both for unencapsulated drug and for thermosensitive liposomes (TSL). We calculated (1) main effects, which indicate the contribution of an individual parameter on output variance, and (2) total effects, which indicate both the individual contribution of a parameter and its interactions with other parameters on output variance. As output we considered the root-mean-square error (RMSE) of the tumor interstitial (EES) concentration calculated over 20 min, in comparison to the reference EES concentration based on the parameter means (Equ. 19).

The results for unencapsulated drug suggest that the variability in tumor drug uptake is primarily dependent on pharmacokinetic parameter variation, i.e. mainly affected by systemic distribution and elimination (Fig. S13). In contrast, for TSL the pharmacokinetic parameters have little impact. Tumor drug uptake variability for TSL (i.e. IV-DDS) is primarily dependent on the variability of tumor transport parameters (transit time ($TT$), permeability-surface area product ($PS$)), and on TSL release time ($t_{rel}$)(Fig. S14). These three parameters are also present in the two indices (release index ($R.I.$), permeability index ($P.I.$)) that have been identified as dictating tumor drug uptake, providing additional evidence for the relevance of these indices.

*Table S4 Parameters and parameter variability used in uncertainty and sensitivity analyses.* The mean value and variability (standard deviation) are indicated for each parameter based on our *in vivo* data.

| Parameter [Units] | Value             | Parameter description                                                      | Parameter source                        |
|-------------------|-------------------|---------------------------------------------------------------------------|-----------------------------------------|
| $v_o$ [1]         | 0.23 ± 0.07       | Tumor plasma volume fraction (imaging window)                             | Intravital Imaging                     |
| $v_e$ [1]         | 0.71 ± 0.09       | Tumor extravascular volume fraction (imaging window)                      | Intravital Imaging                     |
| $k_{av}$ [1]      | 0.39 ± 0.13       | Available volume fraction in extravascular space (for unencapsulated dye) | Intravital Imaging                     |
| $v_{e,av}$ [1]    | 0.28 ± 0.13       | Available extravascular tumor volume fraction (28% of extravascular volume is available to dye for distribution) | $v_{e,av} = k_{av} \cdot v_e$          |
| $v_p^T$ [1]       | 0.16 ± 0.05       | Tumor plasma volume fraction (whole tumor)                                | Calculated (see Table S2)              |
| $t_{rel}$ [s]     | 8.2 ± 0.8         | IV-DDS release time at 42°C (TSL)                                        | *In vitro* measurement                 |
| $TT$ [s]          | 5.0 ± 0.5         | Tissue transit time of tumor segment                                      | Intravital Imaging                     |
| $V_p^S$ [μL]      | 1120 ± 16         | Systemic plasma volume (=IV-DDS volume of distribution)                   | Calculated based on animal weight (20 g)³ |
| $VT$ [μL]         | 10 ± 1            | Tumor volume                                                              | Measured in animals                    |
| $V_p^F$ [μL]      | 0.30 ± 0.02       | Tumor plasma volume                                                       | Intravital Imaging                     |
| $PS$ [1/s]        | 0.012 ± 0.005     | Vascular permeability-surface area product ($P$ represents the apparent permeability rather than true vascular permeability) |                                          |
| $F_p$ [mL/(mL*s)] | 0.047 ± 0.02      | Tumor plasma perfusion rate (imaging window)                              | $F_p = v_p^F/TT$                       |
| $V_0$ [mL]        | 8.99 ± 0.58       | Initial volume of distribution for unencapsulated drug                    | Serial blood sampling                  |
| $k_0$ [s⁻¹]      | 1.29 ± 0.52 × 10⁻³| Transport rate constant, tissue -> plasma                                 | Serial blood sampling                  |
| $k_t$ [s⁻¹]      | 0.90 ± 0.22 × 10⁻³| Transport rate constant, tissue -> plasma                                 | Serial blood sampling                  |
| $k_e$ [s⁻¹]      | 0.80 ± 0.30 × 10⁻³| Elimination rate constant                                                 | Serial blood sampling                  |

* For the parameters indicated, no experimental data was available to estimate variability and we assumed a standard deviation equal to 10% of the mean.

** These parameters can be derived from other parameters in this table, and were therefore not explicitly included in the sensitivity analysis.
Fig. S13. Global sensitivity analysis results for computational model of unencapsulated drug. Parameters are listed at the bottom. “Main Effect” indicates the first-order effect of a parameter, and “Total Effect” includes the first-order effect as well as interaction effects with any other parameter(s) (of any order). Colored bars indicate bounds for each effect. The output variability is primarily dictated by the pharmacokinetic parameters describing distribution and elimination of free drug ($k_p$, $k_e$, $V_D$).

Fig. S14. Global sensitivity analysis results for computational model of IV-DDS encapsulated drug (fTSL). Parameters are listed at the bottom. “Main Effect” indicates the first-order effect of a parameter, and “Total Effect” includes the first-order effect as well as interaction effects with any other parameter(s) (of any order). Colored bars indicate bounds for each effect. The output variability is primarily dictated by two tumor transport parameters (permeability-surface area product ($PS$), tumor transit time ($TT$)), and by IV-DDS release time ($t_{rel}$).
Table S5. Hepatic first-pass extraction fraction (EF) for common chemotherapy agents. The ratio $PS/F_p$ was calculated from $EF$ based on Eq. 1. $EF$ in tumors may differ from the hepatic $EF$ indicated here, but is usually not available due to the difficulty in measuring tumor $EF$.

| Agent       | Hepatic Extraction Fraction (EF) | Ratio $PS/F_p$ |
|-------------|-----------------------------------|----------------|
| FUDR        | 0.94-0.99                         | 2.8-4.6        |
| Paclitaxel  | 0.95                              | 3.0            |
| Gemcitabine | 0.55-0.89                         | 0.8-2.2        |
| Doxorubicin | 0.4-0.5                           | 0.5-0.7        |
| Oxiplatin   | 0.5                               | 0.6            |
| 5-FU        | 0.3-0.4                           | 0.4-0.5        |
| Cisplatin   | 0.24-0.27                         | 0.3            |
| Mitomycin C | 0.1-0.2                           | 0.1-0.2        |

Table S6. Characterization of thermosensitive liposomes. Both sTSL and fTSL were analyzed by dynamic light scattering (DLS).

| Liposome formulation | Size (nm) ± PDI | Polydispersity index (PDI) ± SD | Zeta potential (mV) ± SD | Loading efficiency (%) ± SD |
|----------------------|-----------------|---------------------------------|--------------------------|-----------------------------|
| sTSL                 | 83.0 ± 1.1      | 0.054 ± 0.017                   | -11.30 ± 1.79            | 3.37 ± 0.44                 |
| fTSL                 | 82.8 ± 3.6      | 0.045 ± 0.016                   | -12.56 ± 2.11            | 3.18 ± 0.37                 |

Fig. S15. Tissue transit time calculation example. Upper panels show intravital images (921 x 921 μm) following bolus administration of free carboxyfluorescein (CF) dye after 4 s, 12 s, and 20 s. Lower graph shows the corresponding intravascular signal $I(t)$ during the first 30 s. The transit time ($TT$) of this tissue segment was calculated by deconvolution of $I(t)$ as described in the methods, and $TT=4.6$ s for this dataset.
Supplementary Note 2

Computer model considering varying release times due to recirculation of IV-DDS

We created an extended computer model where we implemented the consideration of multiple IV-DDS populations, depending on whether IV-DDS had already passed through the tumor. However, this extended model is only applicable for the simplified case of IV-DDS having a constant release time (e.g. assuming a constant temperature throughout triggered release if thermosensitive liposomes (TSL) are used). The issue of multiple passes is relevant for IV-DDS that do not conform perfectly to 0th order release kinetics under certain conditions, such as the fTSL and sTSL employed here (see Fig. S10). In such a case, if an IV-DDS passes the tumor a second time, the release time will be different from the first time. We assumed the specific release kinetics of our example IV-DDS (fTSL and sTSL), and as mentioned assumed a simplified case where release times and temperature are constant during the release duration. This assumption considerably simplifies the model, since then each IV-DDS population that passed through the tumor a certain number of times has the same release time assigned – i.e. resulting in a very limited number of IV-DDS populations that need to be considered, rather than an infinite number of populations as would be required for a generalized model. This approach takes advantage of the fact that all IV-DDS that passed through the tumor once release the same amount of drug; the same is true for IV-DDS passing through the tumor a second and third time. IV-DDS with more than three passes were ignored, as they represent <<0.01% of all IV-DDS based on our model results. Each of these three IV-DDS populations was assigned a specific release time based on our experimental data, where we measured release time of fast releasing (fTSL) and slow releasing thermosensitive liposomes (sTSL) at 42°C. We determined the release time as described above, but now measured three release times, for liposomes that had passed through the tumor zero, once, or twice, respectively. Accordingly, we made a linear fit to the TSL release data (1) during the first 5 s (=tumor transit time, i.e. the time a liposomes would spend in the tumor during a single pass), (2) from 5-10 s, (3) and from 10-15 s (Table S7).

**Table S7.** Release time for fTSL and sTSL at 42°C, with 0, 1 and 2 prior passes through the tumor.

| Prior tumor passes | fTSL release time \((t_{rel})\) [s] | sTSL release time \((t_{rel})\) [s] |
|--------------------|----------------------------------|----------------------------------|
| 0                  | 8.2                             | 63.0                             |
| 1                  | 38.0                            | 47.5                             |
| 2                  | 94.3                            | 43.5                             |

We added the following equations, where we represent IV-DDS populations individually that passed the tumor already zero, one, or two times (as mentioned, IV-DDS entering with >2 prior passes represent <<0.01% of all IV-DDS, and were ignored):

\[
\frac{dc_{p,DDS_0}^S(t)}{dt} = - \frac{V_p^T}{V_p^S} \frac{F_p}{v_p} c_{p,DDS_0}^S(t) \quad \text{(Equ. S1)}
\]

\[
\frac{dc_{p,DDS_1}^S(t)}{dt} = \frac{V_p^T}{V_p^S} \frac{F_p}{v_p} \left( c_{p,DDS_0}^S(t) - c_{p,DDS_1}^S(t) \right) \quad \text{(Equ. S2)}
\]

\[
\frac{dc_{p,DDS_2}^S(t)}{dt} = \frac{V_p^T}{V_p^S} \frac{F_p}{v_p} \left( c_{p,DDS_1}^S(t) - c_{p,DDS_2}^S(t) \right) \quad \text{(Equ. S3)}
\]
As mentioned, for IV-DDS release, each IV-DDS population was considered with its specific release time, and Equ. 9 and Equ. 10 were modified accordingly to consider all three IV-DDS populations from Equ. S1-S3. We performed a simulation where we assumed that the tumor was instantaneously heated to 42°C, and remained at 42°C for 6.6 min. This scenario represents a worst case relative to our experimental conditions, where temperature slowly approached 42°C (where release is fastest), and remained between 41-42°C for only 6.6 min (Fig. 4a). Note that below 41°C, release is very slow (Fig. S11), and no significant tumor drug accumulation occurs until tumor temperature reaches 41°C (Fig. 4a,c).

Figure S15 shows the results for the standard model compared to the model considering multiple passes. The reduced release from fTSL that pass through the tumor a 2nd or 3rd time manifests as lower concentrations in tumor plasma ($c_p^T$) and tumor interstitium ($c_e^T$) (Fig. S15b). The error due to neglecting multiple passes was however small, with 2.7% mean error for fTSL, and with 0.9% mean error for sTSL (Table S8).

The volume ratio of tumor plasma (where drug release from IV-DDS occurs) to systemic plasma (which serves as reservoir of IV-DDS-encapsulated drug) in the model was ~700:1, which is based off a mouse tumor with a volume of 10 μL. For comparison, to achieve this same ratio in a human patient would require a human tumor of >6 cm diameter. I.e. the consideration of the varying release time due to recirculation of IV-DDS can be neglected not only here, but also for most human tumors since the plasma volume where drug release from IV-DDS is triggered is very small compared to the systemic plasma volume.

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**Fig. S16. Computer model comparison: with vs. without consideration of multiple passes of fTSL through tumor.**

fTSL were simulated with triggered release duration of 6.6 min. a Drug concentrations based on standard model as used in the manuscript, and b based on the revised model considering multiple passes of fTSL. c Fraction of encapsulated drug based on standard model. d Total fTSL-encapsulated drug, and separately indicated fTSL populations with 0, 1, and 2 prior passes through the tumor, based on model considering multiple passes of fTSL. After 10 min, 94.6% of total encapsulated drug remained in systemic circulation, with 10.0% of fTSL having passed the tumor once, and 0.6% of fTSL having passed the tumor twice. a and b show tumor plasma concentration ($c_p^T$) and tumor interstitial concentration ($c_e^T$). All concentrations in a and b are plotted relative to the maximum possible concentration ($C_{max}$).
Table S8. Errors due to ignoring multiple passes of IV-DDS, shown for fTSL and sTSL. Errors are based on comparing the default model used in the main text to the model considering multiple passes of IV-DDS through the tumor.

|                          | fTSL          | sTSL          |
|--------------------------|---------------|---------------|
| error $c_0^T$ plateau [μg/ml] | 0.5 (2.5%)    | 0.05 (1.9%)   |
| mean error $c_e^T$ [μg/ml]     | 0.5 (2.7%)    | 0.02 (0.9%)   |
| error AUC($c_e^T$) [μg/ml*min] | 5.1 (4.1%)    | 0.2 (1.4%)    |
Supplementary References

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