Supplemental Materials for

A novel integrated pharmacokinetic-pharmacodynamic model to evaluate combination therapy and determine in vivo synergism

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This document includes:

Supplementary Methods.

**Figure S1.** Simulated Dox and Sor concentration versus time curves in mice treated with multiple doses of Dox and Sor.

**Figure S2.** Verification of the PK-PD Model D developed in this study.

**Figure S3.** Inhibition of tumor growth (%) by various doses of Dox and Sor combinations, as predicted by the new PK-PD Model D.

**Table S1.** PD parameters estimated by fitting the hypothetical tumor growth data to the conventional Model C1 and C2 as well as new Model D.

*MATLAB files are available on line.*
Supplementary Methods.

In the current PK/PD model for combination therapy (Model C in Fig. 1C), all parameters are defined as reported [20-21]. However, the interaction factor ($\psi$) may be assigned to either drug, leading to two possibilities, Model C1 and Model C2. Corresponding differential equations are shown below, where $\psi$ is the interaction factor that has been utilized to assess synergism in all previous studies.

\[
\frac{dx_1}{dt} = \frac{2L_0L_1x_1^2}{(L_1+L_0x_1)^3} - \left[\psi_A \cdot k_{2A} \cdot C_A + k_{2B} \cdot C_B\right] \cdot x_1 \quad (S1)
\]

\[
\frac{dx_1}{dt} = \frac{2L_0L_1x_1^2}{(L_1+L_0x_1)^3} - \left[k_{2A} \cdot C_A + \psi_B \cdot k_{2B} \cdot C_B\right] \cdot x_1 \quad (S2)
\]

In Equation S3, the respective $k_2$ (e.g., $k_{2A}$ and $k_{2B}$) and C ($C_A$ and $C_B$) are utilized for Dox and Sor, respectively, while other parameters are same.

\[
\frac{dx_2}{dt} = k_{2A} \cdot C_A \cdot x_1 - k_1' \cdot x_2 \quad \text{or} \quad \frac{dx_2}{dt} = k_{2B} \cdot C_B \cdot x_1 - k_1' \cdot x_2 \quad (S3)
\]

Equations for $\frac{dx_3}{dt}$ and $\frac{dx_4}{dt}$ are the same as Equations 17-21 described in the main text.

\[
\frac{dx_3}{dt} = k_1' \cdot x_2 - k_1' \cdot x_3 \quad (17)
\]

\[
\frac{dx_4}{dt} = k_1' \cdot x_3 - k_1' \cdot x_4 \quad (18)
\]

\[
w = x_1 + x_2 + x_3 + x_4 \quad (19)
\]

\[
x_2(0) = x_3(0) = x_4(0) = 0 \quad (20)
\]

\[
x_1(0) = w_0 \quad (21)
\]
Supplementary Figure S1. Simulated Dox (A) and Sor (B) concentration versus time curves in mice treated with multiple doses of Dox and Sor.
Supplementary Figure S2. **Verification** of the PK-PD Model D developed in this study by using test set data of combination therapy (n = 2). **A**, Visual inspection of the observed and simulated tumor progression profiles. **B**, Linear regression of observed versus simulated data, as well as Pearson correlation values.
Supplementary Figure S3. Inhibition of tumor growth (%) by various doses of Dox and Sor combinations, as predicted by the new PK-PD Model D. Dox and Sor doses were compared to their corresponding experimental doses (set as 1).
Supplementary Table S1. PD parameters estimated by fitting the hypothetical tumor growth data (Fig. 5) from mice treated with the same dose combination (Dox+Sor) to Model C1, C2 and D, respectively. CI values were also calculated for individual cases.

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</table>

Calculated parameter

| CI [-] | 3.66 | 1.53 | 1.13 | 0.691 | 0.290 |

$w_0$, initial tumor volume prior to administration; $k'_1$, transient rate constant; $\alpha$, contribution factor of Dox; $\beta$, contribution factor of Sor; CI, combination index.