Supplemental material

Mathematical solution of coupled mass-transfer, pharmacokinetic equations

The concentration of biomarker (ZsGreen) in a mouse is given by balances on ZsGreen concentration in the tumor, C_T, and the plasma, C_P.

$$V_T \frac{dC_T}{dt} = \dot{m} C_B V_T - kv V_T (C_T - C_P) \tag{3}$$

$$V_P \frac{dC_P}{dt} = kv V_T (C_T - C_P) - K_e C_P V_p \tag{4}$$

In these equations C_T and C_P are dependent on tumor volume, V_T, the rate of ZsGreen production per bacterium, $\dot{m}$, the tumor bacterial density, C_B, the plasma volume, V_p, the plasma clearance rate, K_e, and the composite mass transfer coefficient, kv. The initial conditions, when $t = 0$, are $C_T(0) = C_P(0) = 0$. These equations have simplified, non-dimensional forms.

$$\frac{d\bar{C}_T}{d\bar{t}} = \alpha - \bar{C}_T + \bar{C}_P \tag{S1}$$

$$\frac{d\bar{C}_P}{d\bar{t}} = \varphi \bar{C}_T - (\varphi + \beta)\bar{C}_P \tag{S2}$$

The concentrations were scaled by the minimum concentration detected in the plasma, C_0, so that $\bar{C}_T = C_T/C_0$ and $\bar{C}_P = C_P/C_0$. The value of C_0 does not affect the result and is arbitrary. Time was scaled by the rate of mass transfer, $\bar{t} = kvt$. The three new parameters are dimensionless biomarker production, α, dimensionless tumor volume, φ, and dimensionless clearance, β.

$$\alpha = \frac{\dot{m} C_B}{C_0 kv} \qquad \varphi = \frac{V_T}{V_P} \qquad \beta = \frac{K_e}{kv} \tag{S3}$$

The two differential equations (Eqns. S1 and S2) were rearranged into a single inhomogeneous second-order equation that describes the concentration of ZsGreen in the plasma.

$$\frac{d^2\bar{C}_P}{d\bar{t}^2} + (\varphi + \beta + 1)\frac{d\bar{C}_P}{d\bar{t}} + \beta \bar{C}_P = \alpha\varphi \tag{S4}$$

This equation has an analytical solution.

$$\bar{C}_P = \frac{\alpha\varphi}{\beta\gamma}\left[(q - \gamma)e^{q\bar{t}} - q e^{(q-\gamma)\bar{t}} + \gamma\right] \tag{S5}$$

Three parameters were introduced to simplify the notation.

$$p = \varphi + \beta + 1 \qquad q = (\gamma - \mathrm{p})/2 \qquad \gamma = \sqrt{p^2 - 4\beta} \tag{S6}$$

The biomarker concentration in the tumor, $\bar{C}_T$, is dependent on $\bar{C}_P$ and $d\bar{C}_P/d\bar{t}$.

$$\bar{C}_T = \frac{1}{\varphi}\left[\frac{d\bar{C}_P}{d\bar{t}} + (\varphi + \beta)\bar{C}_P\right] \tag{S7}$$

$$\frac{d\bar{C}_P}{d\bar{t}} = \frac{\alpha\varphi}{\gamma}\left[e^{(q-\gamma)\bar{t}} - e^{q\bar{t}}\right] \tag{S8}$$

Number of bacteria in normal tissue

The number of bacteria in normal tissue was determined from the rate of ZsGreen production by tissue, P, and the plasma concentration of ZsGreen in control, tumor-free mice, C_{tf}. It was assumed that the production rate per bacterium was equal in tumors and normal tissue. The production of ZsGreen by tumors or tissues was linearly proportional to time (with constant A) because $C_T \gg C_P$.

$$P = A \cdot t \tag{S9}$$

The units of A are $fg \cdot CFU^{-1} \cdot h^{-2}$. Accumulation of ZsGreen in the plasma was the result of production in tissue minus systemic clearance.

$$V_P \frac{dC_P}{dt} = P\, N_B - K_e C_P V_p \tag{S10}$$

Here N_B is the number of bacteria in normal tissue. This equation has a simplified, non-dimensional form.

$$\frac{d\bar{C}_P}{d\bar{t}} + \bar{C}_P = B\,\bar{t} \qquad B = \frac{A\,N_B}{V_p\,C_0\,{K_e}^2} \qquad \bar{C}_P = C_P/C_{tf} \qquad \bar{t} = K_e\,t \tag{S11}$$

The analytical solution of this relation gives the plasma concentration as a function of time in mice without tumors.

$$\bar{C}_P = B\left(\bar{t} + e^{-\bar{t}} - 1\right) \tag{S12}$$

At 72 hours, B was calculated based on $\bar{C}_P = 1$ ($C_P = C_{tf}$). Using a constant value for A, N_B was determined from B.

Mouse weight as a function of time

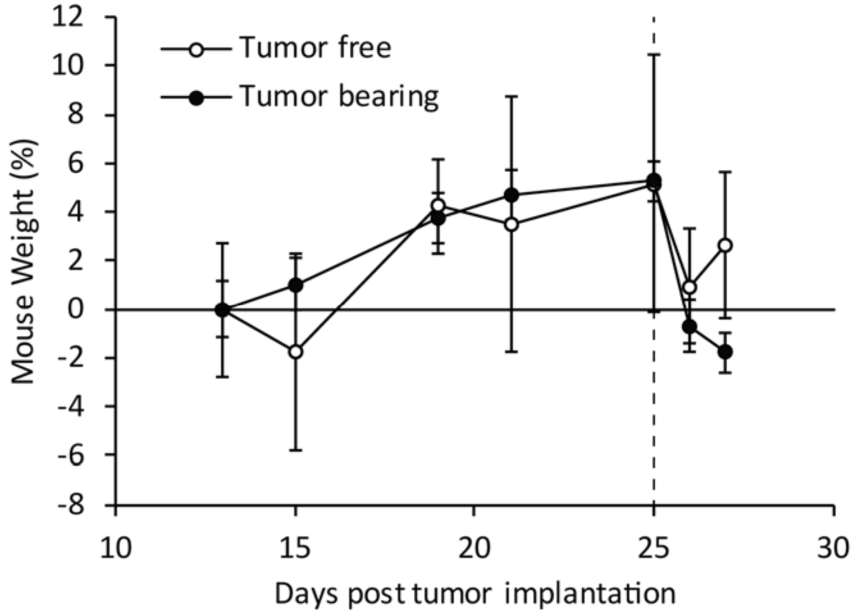

Figure S1. Mouse weight after injection of fluorophore-releasing bacteria. Weights were measured over time after tumor implantation and after bacterial injection on day 25. Weights are represented as a percentage of the weight on day 13 (19.95 and 19.34 g for tumor-free and tumor-bearing mice, respectively).