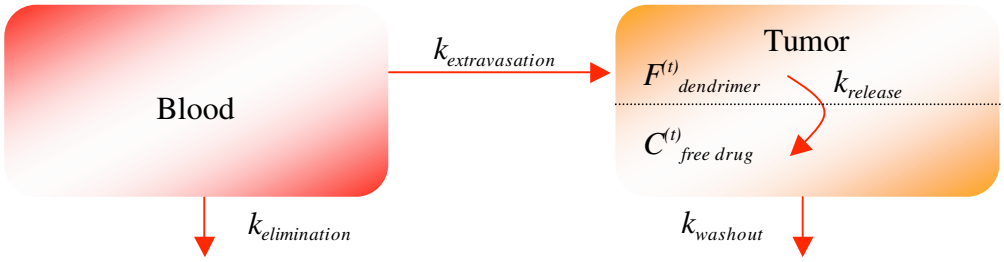
Supplementary Discussion

The effects of dendrimer pharmacokinetics and drug release rate on drug concentration in a tumor.

Similar to other high molecular weight polymers and nanoparticulates, dendrimers exhibit tumor targeting based upon a combination of their long circulation time within the central blood compartment and their small size compared to the pores in the leaky vasculature within tumors. In order to deliver a drug to the tumor, the dendrimer must first accumulate within the tumor. The following pharmacokinetic model can describe this system:



The fraction of the dendrimer that can accumulate in a given tumor, $F^{(t)}_{dendrimer}$, can be easily solved using a mass balance as the following equation:

$$F^{(t)}_{dendrimer} = \frac{\left(1 - e^{(-k_{elimination} - k_{extravasation})t}\right)}{\left(\frac{k_{elimination}}{k_{extravasation}} + 1\right)} \qquad \text{Eq. 1}$$

The $k_{extravasation}$ is the rate constant for deposition of dendrimers into the tumor and the $k_{elimination}$ is the rate constant for the clearance of dendrimers from the blood via the liver, spleen, and kidney. Note that the extravasation is unidirectional and for this model is assumed to be much faster than the clearance of dendrimer from the tumor. Also note that it

is assumed that the concentration of free drug is so low in the blood that negligible amounts can penetrate into the tumor. Lastly, the free drug eliminates directly from the tumor via surrounding lymph and blood and is not tracked after leaving the tumor.

Using Eq. 1, it is possible to model how much of the drug remains bound to the dendrimer in the tumor by multiplying this by an exponentially decreasing term with a first order rate constant. Thus, the following equation estimates the fraction of total drug remaining bound to the dendrimer.

$$F^{(t)}_{drug\_on\_dendrimer} = e^{-k_{release}t} F^{(t)}_{dendrimer} = e^{-k_{release}t} \frac{\left(1 - e^{(-k_{elimination} - k_{extravasation})t}\right)}{\left(\frac{k_{elimination}}{k_{extravasation}} + 1\right)} \qquad \text{Eq. 2}$$

Now we wish to express the concentration of the active form of a drug released from a dendrimer within the tumor. We express this as a concentration, $C^{(t)}_{free\ drug}$, within the tumor of interest according to the following mass balance differential equation:

$$\frac{dN^{(t)}_{freedrug}}{dt} = k_{release} Dose F^{(t)}_{drug\_on\_dendrimer} - k_{washout} N^{(t)}_{freedrug} \qquad \text{Eq. 3}$$

Dividing by the mass of the tumor, m_t, and rearranging we obtain the concentration of drug in the tumor.

$$\frac{dC^{(t)}_{freedrug}}{dt} + k_{washout} C^{(t)}_{freedrug} = k_{release} \frac{Dose}{m_t} F^{(t)}_{drug\_on\_dendrime} \qquad \text{Eq. 4}$$

The above first order differential equation can be solved by multiplying by the integrating factor $\rho = e^{k_{washout}t}$, giving the following equation:

$$e^{k_{washout}t}\frac{dC^{(t)}_{freedrug}}{dt} + k_{washout}e^{k_{washout}t}C^{(t)}_{freedrug} = k_{release}\frac{Dose}{m_t}e^{k_{washout}t}F^{(t)}_{drug\_on\_dendrime}$$ Eq. 5

Therefore,

$$D\left[e^{k_{washout}t}C^{(t)}_{freedrug}\right] = k_{release}\frac{Dose}{m_t}e^{k_{washout}t}F^{(t)}_{drug\_on\_dendrime}$$ Eq. 6

By inserting Eq. 2 into the above equation, letting $\beta = k_{elimination} + k_{extravasation} + k_{release}$, and integrating we obtain:

$$e^{k_{washout}t}C^{(t)}_{freedrug} = \frac{Dosek_{release}}{m_t\left(\frac{k_{elimination}}{k_{extravasation}}+1\right)}\int\left(e^{k_{washout}-k_{release}t} - e^{(k_{washout}-\beta)t}\right)dt$$ Eq. 7

Solving the integral and dividing by the $k_{washout}$ exponential term we obtain the solution for the concentration of free drug in the tumor:

$$C^{(t)}_{freedrug} = \frac{Dosek_{release}}{m_t\left(\frac{k_{elimination}}{k_{extravasation}}+1\right)}\left[\frac{e^{-k_{release}t}}{k_{washout}-k_{release}} - \frac{e^{-\beta t}}{k_{washout}-\beta} + C_1e^{-k_{washout}t}\right]$$ Eq. 8

By inserting the initial condition $C^{(0)}_{free\ drug} = 0$ we solve for the constant C_1 and obtain the complete solution:

$$C^{(t)}_{freedrug} = \frac{Dosek_{release}}{m_t\left(\frac{k_{elimination}}{k_{extravasation}}+1\right)}\left[\frac{e^{-k_{release}t}}{k_{washout}-k_{release}} - \frac{e^{-\beta t}}{k_{washout}-\beta} + \left(\frac{1}{k_{washout}-\beta} - \frac{1}{k_{washout}-k_{release}}\right)e^{-k_{washout}t}\right]$$ Eq. 9