I. <u>Chemical reactions</u>

The relevant chemical reactions are presented here (molecular species and parameters are defined in the glossary):

$$V_{165} + M_{ECM} \underset{k_{off,V165MECM}}{\overset{k_{on,V165,MECM}}{\rightleftarrows}} V_{165}M_{ECM}$$

$$V_{165} + M_{EBM} \underset{k_{off,V165MEBM}}{\overset{k_{on,V165,MEBM}}{\rightleftarrows}} V_{165}M_{EBM}$$

$$V_{165} + M_{PBM} \underset{k_{off,V165MPBM}}{\overset{k_{on,V165,MPBM}}{\rightleftarrows}} V_{165}M_{PBM}$$

$$V_{165} + R_1 \underset{k_{on,V165,R1}}{\overset{k_{on,V165,R1}}{\rightleftarrows}} V_{165}R_1$$

$$V_{165} + R_2 \underset{k_{off,V165R2}}{\overset{k_{on,V165,R2}}{\rightleftarrows}} V_{165}R_2$$

$$V_{165} + N_1 \underset{k_{off,V165N1}}{\overset{k_{on,V165,N1}}{\rightleftarrows}} V_{165}N_1$$

$$V_{165}N_1 + R_2 \underset{k_{off,V165N1R2}}{\overset{k_{c,V165N1,R2}}{\rightleftarrows}} R_2V_{165}N_1$$

$$V_{165}R_2 + N_1 \underset{k_{off,V165R2N1}}{\overset{k_{c,V165R2,N1}}{\rightleftarrows}} R_2V_{165}N_1$$

$$V_{165} + N_2 \underset{k_{on,V165,N2}}{\overset{k_{on,V165,N2}}{\rightleftarrows}} V_{165}N_2$$

$$V_{165}N_2 + R_2 \underset{k_{off,V165N2R2}}{\overset{k_{c,V165N2,R2}}{\rightleftarrows}} R_2V_{165}N_2$$

$$V_{165}N_2 + R_2 \underset{k_{off,V165R2N2}}{\overset{k_{c,V165R2,N2}}{\rightleftarrows}} R_2V_{165}N_2$$

$$V_{121} + R_1 \underset{k_{off,V121R1}}{\overset{k_{on,V121,R1}}{\rightleftarrows}} V_{121}R_1$$

$$V_{121} + R_2 \underset{k_{off,V121R2}}{\overset{k_{on,V121,R2}}{\rightleftarrows}} V_{121}R_2$$

$$V_{121} + R_1N_1 \underset{k_{off,V121R1}}{\overset{k_{on,V121,R1}}{\rightleftarrows}} V_{121}R_1N_1$$

$$V_{121}R_1 + N_1 \underset{k_{dissoc,R1N1}}{\overset{k_{c,R1,N1}}{\rightleftarrows}} V_{121}R_1N_1$$

$$R_1 + N_1 \underset{k_{dissoc,R1N1}}{\overset{k_{c,R1,N1}}{\rightleftarrows}} R_1N_1$$

$$V_{121} + R_1N_2 \underset{k_{off,V121R1}}{\overset{k_{on,V121,R1}}{\rightleftarrows}} V_{121}R_1N_2$$

$$V_{121}R_1 + N_2 \underset{k_{dissoc,R1N2}}{\overset{k_{c,R1,N2}}{\rightleftarrows}} V_{121}R_1N_2$$

$$R_1 + N_2 \underset{k_{dissoc,R1N2}}{\overset{k_{c,R1,N2}}{\rightleftarrows}} R_1N_2$$

$$V_{165} + A \underset{k_{off,V165A}}{\overset{k_{on,V165,A}}{\rightleftarrows}} V_{165}A$$

$$V_{121} + A \underset{k_{off,V121A}}{\overset{k_{on,V121,A}}{\rightleftarrows}} V_{121}A$$

II. <u>Equations</u>

The complete list of ordinary differential equations is presented below:

A. Interstitial space in normal tissue compartment

$$\begin{aligned}
\frac{d[V_{165}]_N}{dt} = q^N_{V165} &- k^N_{on,V165,MEBM}[V_{165}]_N[M_{EBM}]_N + k^N_{off,V165,MEBM}[V_{165}M_{EBM}]_N \\
&- k^N_{on,V165,MPBM}[V_{165}]_N[M_{PBM}]_N + k^N_{off,V165,MPBM}[V_{165}M_{PBM}]_N \\
&- k^N_{on,V165,MECM}[V_{165}]_N[M_{ECM}]_N + k^N_{off,V165,MECM}[V_{165}M_{ECM}]_N \\
&- k^N_{on,V165,R1}[V_{165}]_N[R_1]_N + k^N_{off,V165R1}[V_{165}R_1]_N \\
&- k^N_{on,V165,R2}[V_{165}]_N[R_2]_N + k^N_{off,V165R2}[V_{165}R_2]_N \\
&- k^N_{on,V165,N1}[V_{165}]_N[N_1]_N + k^N_{off,V164N1}[V_{165}N_1]_N \\
&- k^{N,myo}_{on,V165,N1}[V_{165}]_N[N_1]_{N,myo} + k^{N,myo}_{off,V164N1}[V_{165}N_1]_{N,myo} \\
&- k^N_{on,V165,A}[V_{165}]_N[A]_N + k^N_{off,V164A}[V_{165}A]_N \\
&- \left(\frac{k_L + k^{NB}_{pV}S_{NB}}{U_N}\right)\frac{[V_{165}]_N}{K_{AV,N}} + k^{BN}_{pV}\frac{S_{NB}}{U_N}\frac{U_B}{U_P}[V_{165}]_B
\end{aligned} \tag{S.1}$$

$$\begin{aligned}
\frac{d[V_{121}]_N}{dt} = q^N_{V121} &- k^N_{on,V121,R1}[V_{121}]_N[R_1]_N + k^N_{off,V121R1}[V_{121}R_1]_N \\
&- k^N_{on,V121,R1N1}[V_{121}]_N[R_1N_1]_N + k^N_{off,V121R1N1}[V_{121}R_1N_1]_N \\
&- k^N_{on,V121,R2}[V_{12}]_N[R_2]_N + k^N_{off,V121R2}[V_{121}R_2]_N \\
&- k^N_{on,V121,A}[V_{121}]_N[A]_N + k^N_{off,V121A}[V_{121}A]_N \\
&- \left(\frac{k_L + k^{NB}_{pV}S_{NB}}{U_N}\right)\frac{[V_{121}]_N}{K_{AV,N}} + k^{BN}_{pV}\frac{S_{NB}}{U_N}\frac{U_B}{U_P}[V_{121}]_B
\end{aligned} \tag{S.2}$$

$$\frac{d[M_{EBM}]_N}{dt} = -k_{on,V165,MEBM}^{N}[V_{165}]_N[M_{EBM}]_N + k_{off,V165MEBM}^{N}[V_{165}M_{EBM}]_N \tag{S.3}$$

$$\frac{d[M_{PBM}]_N}{dt} = -k_{on,V165,MPBM}^{N}[V_{165}]_N[M_{PBM}]_N + k_{off,V165MPBM}^{N}[V_{165}M_{PBM}]_N \tag{S.4}$$

$$\frac{d[M_{ECM}]_N}{dt} = -k_{on,V165,MECM}^{N}[V_{165}]_N[M_{ECM}]_N + k_{off,V165MECM}^{N}[V_{165}M_{ECM}]_N \tag{S.5}$$

$$\frac{d[V_{165}M_{EBM}]_N}{dt} = k_{on,V165,MEBM}^{N}[V_{165}]_N[M_{EBM}]_N - k_{off,V165MEBM}^{N}[V_{165}M_{EBM}]_N \tag{S.6}$$

$$\frac{d[V_{165}M_{PBM}]_N}{dt} = k_{on,V165,MPBM}^{N}[V_{165}]_N[M_{PBM}]_N - k_{off,V165MPBM}^{N}[V_{165}M_{PBM}]_N \tag{S.7}$$

$$\frac{d[V_{165}M_{ECM}]_N}{dt} = k_{on,V165,MECM}^{N}[V_{165}]_N[M_{ECM}]_N - k_{off,V165MECM}^{N}[V_{165}M_{ECM}]_N \tag{S.8}$$

$$\begin{aligned}\frac{d[R_1]_N}{dt} = {} & s_{R1}^{N} - k_{int,R1}^{N}[R_1]_N - k_{on,V165,R1}^{N}[V_{165}]_N[R_1]_N + k_{off,V165R1}^{N}[V_{165}R_1]_N \\ & -k_{on,V121,R1}^{N}[V_{121}]_N[R_1]_N + k_{off,V121R1}^{N}[V_{121}R_1]_N \\ & -k_{c,R1,N1}^{N}[N_1]_N[R_1]_N + k_{dissoc,R1N1}^{N}[R_1N_1]_N\end{aligned} \tag{S.9}$$

$$\begin{aligned}\frac{d[R_2]_N}{dt} = {} & s_{R2}^{N} - k_{int,R2}^{N}[R_2]_N - k_{on,V121,R2}^{N}[V_{121}]_N[R_2]_N + k_{off,V120R2}^{N}[V_{121}R_2]_N \\ & -k_{on,V1645R2}^{N}[V_{165}]_N[R_2]_N + k_{off,V165R2}^{N}[V_{165}R_2]_N \\ & -k_{c,V165N1,R2}^{N}[V_{165}N_1]_N[R_2]_N + k_{off,V165N1,R2}^{N}[R_2V_{165}N_1]_N\end{aligned} \tag{S.10}$$

$$\begin{aligned}\frac{d[N_1]_N}{dt} = {} & s_{N1}^{N} - k_{int,N1}^{N}[N_1]_N - k_{c,V121R1,N1}^{N}[V_{121}R_1]_N[N_1]_N + k_{dissoc,R1N1}^{N}[V_{121}R_1N_1]_N \\ & -k_{c,R1,N1}^{N}[N_1]_N[R_1]_N + k_{dissoc,R1N1}^{N}[R_1N_1]_N \\ & -k_{on,V165,N1}^{N}[V_{165}]_N[N_1]_N + k_{off,V165N1}^{N}[V_{165}N_1]_N \\ & -k_{c,V165R2,N1}^{N}[V_{165}R_2]_N[N_1]_N + k_{off,V165R2,N1}^{N}[R_2V_{165}N_1]_N\end{aligned} \tag{S.11}$$

$$\begin{aligned}\frac{d[N_1]_{N,myo}}{dt} = {} & s_{N1}^{N,myo} - k_{\mathrm{int},N1}^{N,myo}[N_1]_{N,myo} \\ & +k_{on,V165,N1}^{N,myo}[V_{165}]_N[N_1]_{N,myo} - k_{off,V165N1}^{N,myo}[V_{165}N_1]_{N,myo}\end{aligned} \tag{S.12}$$

$$\frac{d[V_{165}R_1]_N}{dt} = -k^N_{int,V165R1}[V_{164}R_1]_N + k^N_{on,V165,R1}[V_{165}]_N[R_1]_N - k^N_{off,V165R1}[V_{165}R_1]_N \tag{S.13}$$

$$\frac{d[V_{165}R_2]_N}{dt} = -k^N_{int,V165R2}[V_{165}R_2]_N + k^N_{on,V165,R2}[V_{165}]_N[R_2]_N - k^N_{off,V165R2}[V_{165}R_2]_N \\ -k^N_{c,V165R2,N1}[V_{165}R_2]_N[N_1]_N + k^N_{off,V165R2N1}[R_2V_{165}N_1]_N \tag{S.14}$$

$$\frac{d[V_{165}N_1]_N}{dt} = -k^N_{int,V165N1}[V_{165}N_1]_N + k^N_{on,V165,N1}[V_{165}]_N[N_1]_N - k^N_{off,V165N1}[V_{165}N_1]_N \\ -k^N_{c,V165N1,R2}[V_{165}N_1]_N[R_2]_N + k^N_{off,V165N1R2}[R_2V_{165}N_1]_N \tag{S.15}$$

$$\frac{d[R_2V_{165}N_1]_N}{dt} = -k^N_{int,V165R2N1}[R_2V_{165}N_1]_N \\ +k^N_{c,V165R2,N1}[V_{165}R_2]_N[N_1]_N - k^N_{off,V165R2N1}[R_2V_{165}N_1]_N \\ +k^N_{c,V165N1,R2}[V_{165}N_1]_N[R_2]_N - k^N_{off,V165N1R2}[R_2V_{165}N_1]_N \tag{S.16}$$

$$\frac{d[V_{121}R_1]_N}{dt} = -k^N_{int,V121R1}[V_{121}R_1]_N \\ +k^N_{on,V121,R1}[V_{121}]_N[R_1]_N - k^N_{off,V121R1}[V_{121}R_1]_N \\ -k^N_{c,R1,N1}[V_{121}R_1]_N[N_1]_N + k^N_{dissoc,R1N1}[V_{121}R_1N_1]_N \tag{S.17}$$

$$\frac{d[V_{121}R_2]_N}{dt} = -k^N_{int,V121R2}[V_{121}R_2]_N + k^N_{on,V121,R2}[V_{121}]_N[R_2]_N - k^N_{off,V121R2}[V_{121}R_2]_N \tag{S.18}$$

$$\frac{d[R_1N_1]_N}{dt} = -k^N_{int,R1N1}[R_1N_1]_N \\ +k^N_{c,R1,N1}[R_1]_N[N_1]_N - k^N_{dissoc,R1N1}[R_1N_1]_N \\ -k^N_{on,V121,R1}[V_{121}]_N[R_1N_1]_N + k^N_{off,V121R1}[V_{121}R_1N_1]_N \tag{S.19}$$

$$\frac{d[V_{121}R_1N_1]_N}{dt} = -k^N_{intV121R1N1}[V_{121}R_1N_1]_N \\ +k^N_{c,V121R1,N1}[V_{121}R_1]_N[N_1]_N - k^N_{dissoc,V121N1}[V_{121}R_1N_1]_N \\ +k^N_{on,V121R1N1}[V_{121}]_N[R_1N_1]_N - k^N_{off,V121R1N1}[V_{121}R_1N_1]_N \tag{S.20}$$

$$\frac{d[V_{165}N_1]_{N.myo}}{dt} = -k^{N,myo}_{int,V165N1}[V_{165}N_1]_{N,myo} \\ +k^{N,myo}_{on,V165,N1}[V_{165}]_N[N_1]_{N,myo} - k^{N,myo}_{off,V165N1}[V_{165}N_1]_{N,myo} \tag{S.21}$$

$$\frac{d[A]_N}{dt} = -k^N_{on,V165,A}[V_{165}]_N[A]_N + k^N_{off,V165A}[V_{165}A]_N$$
$$-k^N_{on,V121,A}[V_{121}]_N[A]_N + k^N_{off,V121A}[V_{121}A]_N$$
$$+k^{BN}_{pA}\frac{S_{NB}}{U_N}\frac{U_B}{U_P}[A]_B - \left(\frac{k_L + k^{NB}_{pA}S_{NB}}{U_N}\right)\frac{[A]_N}{K_{AV,N}} \quad \text{(S.22)}$$

$$\frac{d[V_{165}A]_N}{dt} = k^N_{on,V165,A}[V_{165}]_N[A]_N - k^N_{off,V165A}[V_{165}A]_N$$
$$+k^{BN}_{pA}\frac{S_{NB}}{U_N}\frac{U_B}{U_p}[V_{165}A]_B - \left(\frac{k_L + k^{NB}_{pA}S_{NB}}{U_N}\right)\frac{[V_{165}A]_N}{K_{AV,N}} \quad \text{(S.23)}$$

$$\frac{d[V_{121}A]_N}{dt} = k^N_{on,V121,A}[V_{121}]_N[A]_N - k^N_{off,V121A}[V_{121}A]_N$$
$$+k^{BN}_{pA}\frac{S_{NB}}{U_N}\frac{U_B}{U_p}[V_{121}A]_B - \left(\frac{k_L + k^{NB}_{pA}S_{NB}}{U_N}\right)\frac{[V_{121}A]_N}{K_{AV,N}} \quad \text{(S.24)}$$

B. Interstitial space in blood compartment

We denote the luminal receptors and ligand-receptor complexes on endothelial cells (ECs) by the subscript i (i=N for normal ECs; i=T for diseased ECs).

$$\frac{d[V_{165}]_B}{dt} = -c_{V165}[V_{165}]_B - k^B_{on,V165,R1}[V_{165}]_B[R_1]_{B,i} + k^B_{off,V165R1}[V_{165}R_1]_{B,i}$$
$$-k^B_{on,V165,R2}[V_{165}]_B[R_2]_{B,i} + k^B_{off,V165R2}[V_{165}R_2]_{B,i}$$
$$-k^B_{on,V165,N1}[V_{165}]_B[N_1]_{B,i} + k^B_{off,V165N1}[V_{165}N_1]_{B,i} \quad \text{(S.25)}$$
$$-k^B_{on,V165,A}[V_{165}]_B[A]_B + k^B_{off,V165A}[V_{165}A]_B$$
$$-\frac{k^{BN}_{pV}S_{NB}}{U_p}[V_{165}]_B + \left(\frac{k_L + k^{NB}_{pV}S_{NB}}{U_B}\right)\frac{[V_{165}]_N}{K_{AV,N}}$$

$$
\begin{aligned}
\frac{d[V_{121}]_B}{dt} = & -c_{V121}[V_{121}]_B - k^B_{on,V121,R1}[V_{121}]_B[R_1]_{B,i} + k^B_{off,V121R1}[V_{121}R_1]_{B,i} \\
& -k^B_{on,V121,R1N1}[V_{121}]_B[R_1N_1]_{B,i} + k^B_{off,V121R1N1}[V_{121}R_1N_1]_{B,i} \\
& -k^B_{on,V121,R2}[V_{121}]_B[R_2]_{B,i} + k^B_{off,V121R2}[V_{121}R_2]_{B,i} \\
& -k^B_{on,V121,A}[V_{121}]_B[A]_B + k^B_{off,V121A}[V_{121}A]_B \\
& -\frac{k^{BN}_{pV}S_{NB}}{U_p}[V_{121}]_B + \left(\frac{k_L + k^{NB}_{pV}S_{NB}}{U_B}\right)\frac{[V_{121}]_N}{K_{AV,N}}
\end{aligned} \tag{S.26}
$$

$$
\begin{aligned}
\frac{d[R_1]_{B,i}}{dt} = & \; s^B_{R1} - k^B_{int,R1}[R_1]_{B,i} - k^B_{on,V165,R1}\ [V_{164}]_B[R_1]_{B,i} + k^B_{off,V165R1}[V_{165}R_1]_{B,i} \\
& -k^B_{on,V121,R1}[V_{121}]_B[R_1]_{B,i} + k^B_{off,V121R1}[V_{121}R_1]_{B,i} \\
& -k^B_{c,R1,N1}[N_1]_{B,i}[R_1]_{B,i} + k^B_{dissoc,R1N1}[R_NN_1]_{B,i}
\end{aligned} \tag{S.27, S.28}
$$

$$
\begin{aligned}
\frac{d[R_2]_{B,i}}{dt} = & \; s^B_{R2} - k^B_{int,R2}\ [R_2]_{B,i} - k^B_{on,V121,R2}[V_{121}]_B[R_2]_{B,i} + k^B_{off,V121R2}[V_{121}R_2]_{B,i} \\
& -k^B_{on,V165,R2}[V_{165}]_B[R_2]_{B,i} + k^B_{off,V165R2}[V_{165}R_2]_{B,i} \\
& -k^B_{c,V165N1,R2}[V_{165}N_1]_B[R_2]_{B,i} + k^B_{off,V165N1,R2}[R_2V_{165}N_1]_{B,i}
\end{aligned} \tag{S.29, S.30}
$$

$$
\begin{aligned}
\frac{d[N_1]_{B,i}}{dt} = & \; s^B_{N1} - k^B_{int,N1}[N_1]_{B,i} - k^B_{c,V121R1,N1}[V_{121}R_1]_B[N_1]_{B,i} + k^B_{dissoc,R1N1}[V_{121}R_1N_1]_{B,i} \\
& -k^B_{c,R1,N1}[N_1]_{B,i}[R_1]_{B,i} + k^B_{dissoc,R1N1}[R_1N_1]_{B,i} \\
& -k^B_{on,V165,N1}[V_{165}]_B[N_1]_{B,i} + k^B_{off,V165N1}[V_{165}N_1]_{B,i} \\
& -k^B_{c,V165R2,N1}[V_{165}R_2]_{B,i}[N_1]_{B,i} + k^B_{off,V165R2,N1}[R_2V_{165}N_1]_{B,i}
\end{aligned} \tag{S.31, S.32}
$$

$$
\frac{d[V_{165}R_1]_{B,i}}{dt} = -k^B_{int,V165R1}[V_{165}R_1]_{B,i} + k^B_{on,V165,R1}[V_{165}]_B[R_1]_{B,i} - k^B_{off,V165R1}[V_{165}R_1]_{B,i} \tag{S.33, S.34}
$$

$$
\frac{d[V_{165}R_2]_{B,i}}{dt} = -k^B_{int,V165R2}[V_{165}R_2]_{B,i} + k^B_{on,V165,R2}[V_{165}]_B[R_2]_{B,i} - k^B_{off,V165R2}[V_{165}R_2]_{B,i} \tag{S.35, S.36}
$$

$$
\begin{aligned}
\frac{d[V_{165}N_1]_{B,i}}{dt} = & -k^B_{int,V165N1}[V_{165}N_1]_{B,i} + k^B_{on,V165,N1}[V_{165}]_B[N_1]_{B,i} - k^B_{off,V165N1}[V_{165}N_1]_{B,i} \\
& -k^B_{c,V165N1,R2}[V_{165}N_1]_{B,i}[R_2]_{B,i} + k^B_{off,V165N1R2}[R_2V_{165}N_1]_{B,i}
\end{aligned} \tag{S.37, S.38}
$$

$$\frac{d[R_2V_{165}N_1]_{B,i}}{dt} = -k^B_{int,V165R2N1}[R_2V_{165}N_1]_{B,i} + k^B_{c,V165R2,N1}[V_{165}R_2]_{B,i}[N_1]_{B,i} - k^B_{off,V165R2N1}[R_2V_{165}N_1]_{B,i} + k^B_{c,V165N1,R2}[V_{165}N_1]_{B,i}[R_2]_{B,i} - k^B_{off,V165N1R2}[R_2V_{165}N_1]_{B,i} \quad \text{(S.39, S.40)}$$

$$\frac{d[V_{121}R_1]_{B,i}}{dt} = -k^B_{int,V121R1}[V_{121}R_1]_{B,i} + k^B_{on,V121,R1}[V_{121}]_{B,i}[R_1]_{B,i} - k^B_{off,V121R1}[V_{121}R_1]_{B,i} - k^B_{c,R1,N1}[V_{121}R_1]_{B,i}[N_1]_{B,i} + k^B_{dissoc,R1N1}[V_{121}R_1N_1]_{B,i} \quad \text{(S.41, S.42)}$$

$$\frac{d[V_{121}R_2]_{B,i}}{dt} = -k^B_{int,V121R2}[V_{121}R_2]_{B,i} + k^B_{on,V121,R2}[V_{121}]_B[R_2]_{B,i} - k^B_{off,V121R2}[V_{121}R_2]_{B,i} \quad \text{(S.43, S.44)}$$

$$\frac{d[R_1N_1]_{B,i}}{dt} = -k^B_{int,R1N1}[R_1N_1]_{B,i} + k^B_{c,R1,N1}[R_1]_{B,i}[N_1]_{B,i} - k^B_{dissoc,R1N1}[R_1N_1]_{B,i} - k^B_{on,V121,R1}[V_{121}]_B[R_1N_1]_{B,i} + k^B_{off,V121R1}[V_{121}R_1N_1]_{B,i} \quad \text{(S.45, S.46)}$$

$$\frac{d[V_{121}R_1N_1]_{B,i}}{dt} = -k^B_{intV121R1N1}[V_{121}R_1N_1]_{B,i} + k^B_{c,V121R1,N1}[V_{121}R_1]_{B,i}[N_1]_{B,i} - k^B_{dissoc,V121N1}[V_{121}R_1N_1]_{B,i} + k^B_{on,V121R1N1}[V_{121}]_B[R_1N_1]_{B,i} - k^B_{off,V121R1N1}[V_{121}R_1N_1]_{B,i} \quad \text{(S.47, S.48)}$$

$$\frac{d[A]_B}{dt} = q_A - c_A[A]_B - k^B_{on,V165,A}[V_{165}]_B[A]_B + k^B_{off,V165A}[V_{165}A]_B - k^B_{on,V121,A}[V_{121}]_B[A]_B + k^B_{off,V121A}[V_{121}A]_B + k^{BN}_{pA}\frac{S_{NB}}{U_p}[A]_B - \left(\frac{k_L + k^{NB}_{pA}S_{NB}}{U_B}\right)\frac{[A]_N}{K_{AV,N}} \quad \text{(S.49)}$$

$$\frac{d[V_{165}A]_B}{dt} = -c_{V165A}[V_{165}A]_B + k^B_{on,V165,A}[V_{165}]_B[A]_B - k^B_{off,V165A}[V_{165}A]_B - k^{BN}_{pA}\frac{S_{NB}}{U_p}[V_{165}A]_B + \left(\frac{k_L + k^{NB}_{pA}S_{NB}}{U_B}\right)\frac{[V_{165}A]_N}{K_{AV,N}} \quad \text{(S.50)}$$

$$\frac{d[V_{121}A]_B}{dt} = -c_{V121A}[V_{121}A]_B + k^B_{on,V121,A}[V_{121}]_B[A]_B - k^B_{off,V121A}[V_{121}A]_B$$
$$-k^{BN}_{pA}\frac{S_{NB}}{U_p}[V_{121}A]_B + \left(\frac{k_L + k^{NB}_{pA}S_{NB}}{U_B}\right)\frac{[V_{121}A]_N}{K_{AV,N}} \quad \text{(S.51)}$$

C. Interstitial space in tumor compartment

We denote the receptors and ligand-receptor complexes by the subscript *i* (*i*=T for tumor ECs; *i*=*tumor* for tumor cells).

$$\frac{d[V_{165}]_T}{dt} = q^T_{V165} - k^T_{on,V165,MEBM}[V_{165}]_T[M_{EBM}]_T + k^T_{off,V165,MEBM}[V_{165}M_{EBM}]_T$$
$$-k^T_{on,V165,MPBM}[V_{165}]_T[M_{PBM}]_T + k^T_{off,V165,MPBM}[V_{165}M_{PBM}]_T$$
$$-k^T_{on,V165,MECM}[V_{165}]_T[M_{ECM}]_T + k^T_{off,V165,MECM}[V_{165}M_{ECM}]_T$$
$$-k^{T,i}_{on,V165,R1}[V_{165}]_T[R_1]_{T,i} + k^T_{off,V165R1}[V_{165}R_1]_{T,i}$$
$$-k^{T,i}_{on,V165,R2}[V_{165}]_T[R_2]_{T,i} + k^T_{off,V165R2}[V_{165}R_2]_{T,i} \quad \text{(S.52)}$$
$$-k^{T,i}_{on,V165,N1}[V_{165}]_T[N_1]_{T,i} + k^T_{off,V164N1}[V_{165}N_1]_{T,i}$$
$$-k^{T,tumor}_{on,V165,N2}[V_{165}]_T[N_2]_{T,tumor} + k^{T,tumor}_{off,V164N2}[V_{165}N_2]_{T,tumor}$$
$$-k^T_{on,V165,A}[V_{165}]_T[A]_T + k^T_{off,V164A}[V_{165}A]_T$$
$$-\left(\frac{k_L + k^{TB}_{pV}S_{TB}}{U_T}\right)\frac{[V_{165}]_T}{K_{AV,T}} + k^{BT}_{pV}\frac{S_{TB}}{U_T}\frac{U_B}{U_P}[V_{165}]_B$$

$$\frac{d[V_{121}]_T}{dt} = q^T_{V121} - k^T_{on,V121,R1}[V_{121}]_N[R_1]_{N,i} + k^T_{off,V121R1}[V_{121}R_1]_{T,i}$$
$$-k^T_{on,V121,R1N1}[V_{121}]_T[R_1N_1]_{T,i} + k^T_{off,V121R1N1}[V_{121}R_1N_1]_{T,i}$$
$$-k^T_{on,V121,R2}[V_{12}]_T[R_2]_{T,i} + k^T_{off,V121R2}[V_{121}R_2]_{T,i} \quad \text{(S.53)}$$
$$-k^T_{on,V121,A}[V_{121}]_T[A]_T + k^T_{off,V121A}[V_{121}A]_T$$
$$-\left(\frac{k_L + k^{TB}_{pV}S_{TB}}{U_T}\right)\frac{[V_{121}]_T}{K_{AV,T}} + k^{BT}_{pV}\frac{S_{TB}}{U_T}\frac{U_B}{U_P}[V_{121}]_B$$

$$\frac{d[M_{EBM}]_T}{dt} = -k^N_{on,V165,MEBM}[V_{165}]_T[M_{EBM}]_T + k^T_{off,V165MEBM}[V_{165}M_{EBM}]_T \quad \text{(S.54)}$$

$$\frac{d[M_{PBM}]_T}{dt} = -k^T_{on,V165,MPBM}[V_{165}]_T[M_{PBM}]_T + k^T_{off,V165MPBM}[V_{165}M_{PBM}]_T \quad \text{(S.55)}$$

$$\frac{d[M_{ECM}]_T}{dt} = -k^T_{on,V165,MECM}[V_{165}]_T[M_{ECM}]_T + k^T_{off,V165MECM}[V_{165}M_{ECM}]_T \quad \text{(S.56)}$$

$$\frac{d[V_{165}M_{EBM}]_T}{dt} = k^T_{on,V165,MEBM}[V_{165}]_T[M_{EBM}]_T - k^T_{off,V165MEBM}[V_{165}M_{EBM}]_T \quad \text{(S.57)}$$

$$\frac{d[V_{165}M_{PBM}]_T}{dt} = k^T_{on,V165,MPBM}[V_{165}]_T[M_{PBM}]_T - k^T_{off,V165MPBM}[V_{165}M_{PBM}]_T \quad \text{(S.58)}$$

$$\frac{d[V_{165}M_{ECM}]_T}{dt} = k^T_{on,V165,MECM}[V_{165}]_T[M_{ECM}]_T - k^T_{off,V165MECM}[V_{165}M_{ECM}]_T \quad \text{(S.59)}$$

$$\begin{aligned}\frac{d[R_1]_{T,i}}{dt} &= s^T_{R1} - k^T_{int,R1}[R_1]_{T,i} - k^T_{on,V165,R1}[V_{165}]_T[R_1]_{T,i} + k^T_{off,V165R1}[V_{165}R_1]_{T,i} \\ &-k^T_{on,V121,R1}[V_{121}]_T[R_1]_{T,i} + k^T_{off,V121R1}[V_{121}R_1]_{T,i} \\ &-k^T_{c,R1,N1}[N_1]_{T,i}[R_1]_{T,i} + k^T_{dissoc,R1N1}[R_1N_1]_{T,i}\end{aligned} \quad \text{(S.60, S.61)}$$

$$\begin{aligned}\frac{d[R_2]_{T,i}}{dt} &= s^T_{R2} - k^T_{int,R2}[R_2]_{T,i} - k^T_{on,V121,R2}[V_{121}]_T[R_2]_{T,i} + k^T_{off,V120R2}[V_{121}R_2]_{T,i} \\ &-k^T_{on,V1645R2}[V_{165}]_T[R_2]_{T,i} + k^T_{off,V165R2}[V_{165}R_2]_{T,i} \\ &-k^T_{c,V165N1,R2}[V_{165}N_1]_{T,i}[R_2]_{T,i} + k^T_{off,V165N1,R2}[R_2V_{165}N_1]_{T,i}\end{aligned} \quad \text{(S.62, S.63)}$$

$$\begin{aligned}\frac{d[N_1]_{T,i}}{dt} &= s^T_{N1} - k^T_{int,N1}[N_1]_T - k^T_{c,V121R1,N1}[V_{121}R_1]_{T,i}[N_1]_{T,i} + k^T_{dissoc,R1N1}[V_{121}R_1N_1]_{T,i} \\ &-k^T_{c,R1,N1}[N_1]_{T,i}[R_1]_{T,i} + k^T_{dissoc,R1N1}[R_1N_1]_{T,i} \\ &-k^T_{on,V165,N1}[V_{165}]_T[N_1]_{T,i} + k^T_{off,V165N1}[V_{165}N_1]_{T,i} \\ &-k^T_{c,V165R2,N1}[V_{165}R_2]_{T,i}[N_1]_{T,i} + k^T_{off,V165R2,N1}[R_2V_{165}N_1]_{T,i}\end{aligned} \quad \text{(S.64, S.65)}$$

$$\begin{aligned}\frac{d[N_2]_T}{dt} &= s_{N2} - k_{\text{int},N2}[N_2]_T \\ &+k_{on,V165,N2}[V_{165}]_T[N_2]_T - k_{off,V165N2}[V_{165}N_2]_T\end{aligned} \quad \text{(S.66)}$$

$$\frac{d[V_{165}R_1]_{T,i}}{dt} = -k^T_{int,V165R1}[V_{164}R_1]_{T,i} + k^T_{on,V165,R1}[V_{165}]_T[R_1]_{T,i} - k^N_{off,V165R1}[V_{165}R_1]_{T,i} \quad \text{(S.67, S.68)}$$

$$\begin{aligned}\frac{d[V_{165}R_2]_{T,i}}{dt} &= -k^T_{int,V165R2}[V_{165}R_2]_{T,i} + k^T_{on,V165,R2}[V_{165}]_T[R_2]_{T,i} - k^T_{off,V165R2}[V_{165}R_2]_{T,i} \\ &-k^T_{c,V165R2,N1}[V_{165}R_2]_{T,i}[N_1]_{T,i} + k^T_{off,V165R2N1}[R_2V_{165}N_1]_{T,i}\end{aligned} \quad \text{(S.69, S.70)}$$

$$\frac{d[V_{165}N_1]_{T,i}}{dt} = -k^T_{int,V165N1}[V_{165}N_1]_{T,i} + k^T_{on,V165,N1}[V_{165}]_T[N_1]_{T,i} - k^T_{off,V165N1}[V_{165}N_1]_{T,i} - k^T_{c,V165N1,R2}[V_{165}N_1]_{T,i}[R_2]_{T,i} + k^T_{off,V165N1R2}[R_2V_{165}N_1]_{T,i} \quad \text{(S.71, S.72)}$$

$$\frac{d[R_2V_{165}N_1]_{T,i}}{dt} = -k^T_{int,V165R2N1}[R_2V_{165}N_1]_{T,i} + k^T_{c,V165R2,N1}[V_{165}R_2]_{T,i}[N_1]_{T,i} - k^T_{off,V165R2N1}[R_2V_{165}N_1]_{T,i} + k^T_{c,V165N1,R2}[V_{165}N_1]_{T,i}[R_2]_{T,i} - k^T_{off,V165N1R2}[R_2V_{165}N_1]_{T,i} \quad \text{(S.73, S.74)}$$

$$\frac{d[V_{121}R_1]_{T,i}}{dt} = -k^T_{int,V121R1}[V_{121}R_1]_{T,i} + k^T_{on,V121,R1}[V_{121}]_T[R_1]_{T,i} - k^T_{off,V121R1}[V_{121}R_1]_{T,i} - k^T_{c,R1,N1}[V_{121}R_1]_{T,i}[N_1]_{T,i} + k^T_{dissoc,R1N1}[V_{121}R_1N_1]_{T,i} \quad \text{(S.75, S.76)}$$

$$\frac{d[V_{121}R_2]_{T,i}}{dt} = -k^T_{int,V121R2}[V_{121}R_2]_{T,i} + k^T_{on,V121,R2}[V_{121}]_T[R_2]_{T,i} - k^T_{off,V121R2}[V_{121}R_2]_{T,i} \quad \text{(S.77, S.78)}$$

$$\frac{d[V_{121}R_1N_1]_T}{dt} = -k^T_{intV121R1N1}[V_{121}R_1N_1]_{T,i} + k^T_{c,V121R1,N1}[V_{121}R_1]_{T,i}[N_1]_{T,i} - k^T_{dissoc,V121N1}[V_{121}R_1N_1]_{T,i} + k^T_{on,V121R1N1}[V_{121}]_T[R_1N_1]_{T,i} - k^T_{off,V121R1N1}[V_{121}R_1N_1]_{T,i} \quad \text{(S.79, S.80)}$$

$$\frac{d[R_1N_1]_{T,i}}{dt} = -k^T_{int,R1N1}[R_1N_1]_{T,i} + k^T_{c,R1,N1}[R_1]_{T,i}[N_1]_{T,i} - k^T_{dissoc,R1N1}[R_1N_1]_{T,i} - k^T_{on,V121,R1}[V_{121}]_T[R_1N_1]_{T,i} + k^T_{off,V121R1}[V_{121}R_1N_1]_{T,i} \quad \text{(S.81, S.82)}$$

$$\frac{d[V_{165}N_2]_T}{dt} = -k^T_{int,V165N2}[V_{165}N_2]_T + k^T_{on,V165,N2}[V_{165}]_T[N_2]_T - k^T_{off,V165N2}[V_{165}N_2]_T - k^T_{c,V165N2,R2}[V_{165}N_2]_T[R_2]_{T,i} + k^T_{off,V165N2R2}[R_2V_{165}N_2]_T \quad \text{(S.83)}$$

$$\frac{d[R_2V_{165}N_2]_T}{dt} = -k^T_{int,V165R2N2}[R_2V_{165}N_2]_T + k^T_{c,V165R2,N2}[V_{165}R_2]_{T,i}[N_2]_T - k^T_{off,V165R2N2}[R_2V_{165}N_2]_T + k^T_{c,V165N2,R2}[V_{165}N_2]_T[R_2]_{T,i} - k^T_{off,V165N2R2}[R_2V_{165}N_2]_T \quad \text{(S.84)}$$

$$\frac{d[R_1N_2]_T}{dt} = -k^T_{int,R1N1}[R_1N_2]_T + k^T_{c,R1,N2}[R_1]_{T,i}[N_2]_T - k^T_{dissoc,R1N2}[R_1N_2]_T - k^T_{on,V121,R1}[V_{121}]_T[R_1N_2]_T + k^T_{off,V121R1}[V_{121}R_1N_2]_T \tag{S.85}$$

$$\frac{d[V_{121}R_1N_2]_T}{dt} = -k^T_{intV121R1N2}[V_{121}R_1N_2]_T + k^T_{c,V121R1,N2}[V_{121}R_1]_{T,i}[N_2]_T - k^T_{dissoc,V121N2}[V_{121}R_1N_2]_T + k^T_{on,V121R1N2}[V_{121}]_T[R_1N_2]_T - k^T_{off,V121R1N2}[V_{121}R_1N_2]_T \tag{S.86}$$

$$\frac{d[A]_T}{dt} = -k^T_{on,V165,A}[V_{165}]_T[A]_T + k^N_{off,V165A}[V_{165}A]_T - k^T_{on,V121,A}[V_{121}]_T[A]_T + k^N_{off,V121A}[V_{121}A]_T + k^{BT}_{pA}\frac{S_{TB}}{U_T}\frac{U_B}{U_P}[A]_B - \left(\frac{k_L + k^{TB}_{pA}S_{TB}}{U_T}\right)\frac{[A]_T}{K_{AV,T}} \tag{S.87}$$

$$\frac{d[V_{165}A]_T}{dt} = k^T_{on,V165,A}[V_{165}]_T[A]_T - k^N_{off,V165A}[V_{165}A]_T + k^{BT}_{pA}\frac{S_{TB}}{U_T}\frac{U_B}{U_p}[V_{165}A]_B - \left(\frac{k_L + k^{TB}_{pA}S_{TB}}{U_T}\right)\frac{[V_{165}A]_T}{K_{AV,T}} \tag{S.88}$$

$$\frac{d[V_{121}A]_T}{dt} = k^T_{on,V121,A}[V_{121}]_T[A]_T - k^T_{off,V121A}[V_{121}A]_T + k^{BT}_{pA}\frac{S_{TB}}{U_T}\frac{U_B}{U_p}[V_{121}A]_B - \left(\frac{k_L + k^{TB}_{pA}S_{TB}}{U_T}\right)\frac{[V_{121}A]_T}{K_{AV,T}} \tag{S.89}$$

III. Glossary

A. Concentrations

$[V_{121}]$, $[V_{165}]$	Concentration of unbound $VEGF_{121}$ and $VEGF_{165}$
$[M_{ECM}]$, $[M_{EBM}]$, $[M_{PBM}]$	Concentration of VEGF binding sites in the ECM, EBM, and PBM
$[V_{165}M_{ECM}]$, $[V_{165}M_{EBM}]$, $[V_{165}M_{PBM}]$	Concentration of $VEGF_{165}$ bound to the ECM, EBM, and PBM

$[R_1]$, $[R_2]$	Concentration of un-occupiedVEGFR-1 and VEGFR-2 receptor tyrosine kinases
$[N_1]$	Concentration of un-occupied NRP1 co-receptor
$[N_2]$	Concentration of un-occupied NRP2 co-receptor
$[R_1N_1]$	Concentration of the VEGFR1-NRP1 complex
$[R_1N_2]$	Concentration of the VEGFR1-NRP2 complex
$[V_iR_j]$	Concentration of VEGF isoform *i* bound to VEGFR *j*
$[V_iN_1]$	Concentration of VEGF isoform *i* bound to NRP1
$[V_iN_2]$	Concentration of VEGF isoform i bound to NRP2
$[R_2V_{165}N_1]$	Concentration of the VEGFR2-VEGF$_{165}$-NRP1 ternary complex
$[R_2V_{165}N_2]$	Concentration of the VEGFR2-VEGF$_{165}$-NRP2 ternary complex
$[V_{121}R_1N_1]$	Concentration of the VEGF$_{121}$-VEGFR1-NRP1 ternary complex
$[V_{121}R_1N_2]$	Concentration of the VEGF$_{121}$-VEGFR1-NRP2 ternary complex
$[A]$	Concentration of anti-VEGF agent
$[V_iA]$	Concentration of VEGF isoform *i* bound to anti-VEGF agent

B. Geometric parameters

U_i	Volume of compartment *i* (*N*=normal tissue, *B*=blood, *P*=plasma, *T*=tumor)
S_{iB}	Total surface area of endothelial cells at the interface of compartment *i* and blood (*N*=normal tissue, *T*=tumor)
$K_{AV,i}$	Available volume fraction in the tissue, i.e., ratio of available fluid volume to total tissue volume U_i

C. Kinetic parameters

q_{V121}, q_{V165}	Secretion rate of $VEGF_{121}$ and $VEGF_{165}$
q_A	Injection rate of exogenous anti-VEGF agent; q_A = 7.78 mg/min during the infusion time (90 minutes) and q_A = 0 at all other times.
s_R	Insertion rate of receptors into the cell membrane of endothelial cells or myocytes
k_{on}	Kinetic binding rate
k_{off}	Kinetic unbinding rate
k_c	Kinetic coupling rate for receptors
k_{int}	Internalization rate of receptors
k_{pV}^{ij}	Microvascular permeability of VEGF from compartment *i* to compartment *j* (*N*=normal tissue, *B*=blood, *T*=tumor)
k_{pA}^{ij}	Microvascular permeability of anti-VEGF agent and VEGF/anti-VEGF complex from compartment *i* to compartment *j* (*N*=normal tissue, *B*=blood, *T*=tumor)
k_L	Lymphatic drainage rate
c_{V121}, c_{V165}	Rate of plasma clearance of $VEGF_{121}$ and $VEGF_{165}$
c_A, c_{V121A}, c_{V165A}	Rate of plasma clearance of anti-VEGF and VEGF/anti-VEGF complex

IV. Model parameters

Table S1: Whole-body parameters

	Parameter	Value	Unit
Normal	Total volume	61321	cm^3
	Available fluid volume for VEGF	3825	cm^3
Blood	Total volume	5	L
	Available fluid volume for VEGF (plasma)	2.717	L
Tumor	Total volume	33.5	cm^3
	Available fluid volume for VEGF	17.5	cm^3

Table S2: Geometric parameters

	Value (Normal)	Reference	Value (Tumor)	Reference
Cell geometry				
Perimeter of myofiber	222 μm	Calculated in (1)	-	-
Cross-sectional area of myofiber	3000 μm^2	Calculated in (1)	-	-
SMND surface area	1850 μm^2	Calculated in (1)	-	-
Myofiber density	304 per mm^2 tissue	Calculated in (1)	-	-
Tumor cell external diameter	-	-	17 μm	(2)
Surface area of one tumor cell	-	-	997 μm^2	Calculated in (3)
Volume of one tumor cell	-	-	2572 μm^2	Calculated in (3)
Microvessels				
Perimeter of one microvessel	26 μm	Calculated in (1)	43.7 μm	Calculated in (3)
Cross-sectional area of one microvessel	45 μm^2	Calculated in (1)	100.3 μm^2	Calculated in (3)
Average diameter of one microvessel	7.56 μm	Calculated in (1)	10.3 μm	(4)
Endothelial cell thickness	0.5 μm	(5)	0.5 μm	Calculated in (3)
Capillary-myofiber ratio	1.38	(6)	-	-
Capillary density	420 per mm^2 tissue	Calculated in (1)	235 per mm^2 tissue	Calculated in (3)
Surface areas				
Tissue cells	664 cm^2/cm^3 tissue	Calculated in (1)	1534 cm^2/cm^3 tissue	Calculated in (3)
Microvessels	108 cm^2/cm^3 tissue	Calculated in (1)	105 cm^2/cm^3 tissue	Calculated in (3)
Basement membranes (BM)				
Thickness of tissue cell BM	24 nm	(7)	30 nm	Calculated in (3)
Thickness of microvessel BM	43 nm	(7)	50 nm	Calculated in (3)
Volume of parenchymal cell BM	0.00159 cm^3/cm^3 tissue	Calculated in (8)	0.00388 cm^3/cm^3 tissue	Calculated in (8)
of which available to VEGF	0.000307 cm^3/cm^3 tissue	Calculated in (8)	0.002446 cm^3/cm^3 tissue	Calculated in (8)
Volume of microvessel BM	0.00045 cm^3/cm^3 tissue	Calculated in (8)	0.00043 cm^3/cm^3 tissue	Calculated in (8)
of which available to VEGF	0.000087 cm^3/cm^3 tissue	Calculated in (8)	0.00027 cm^3/cm^3 tissue	Calculated in (8)
Volume of extracellular matrix	0.07951 cm^3/cm^3 tissue	Calculated in (8)	0.6062 cm^3/cm^3 tissue	Calculated in (8)
of which available to VEGF	0.061987 cm^3/cm^3 tissue	Calculated in (8)	0.519308 cm^3/cm^3 tissue	Calculated in (8)
Volume fractions				
Interstitial space	0.0816 cm^3/cm^3 tissue	(9, 10)	0.611 cm^3/cm^3 tissue	(11, 12)
of which available to VEGF	0.062381 cm^3/cm^3 tissue	Calculated in (8)	0.522024 cm^3/cm^3 tissue	Calculated in (8)
Microvessels	0.0186 cm^3/cm^3 tissue	Calculated in (1)	0.024 cm^3/cm^3 tissue	Calculated in (3)
of which vascular space	0.0140 cm^3/cm^3 tissue	(13)	0.020 cm^3/cm^3 tissue	Calculated in (3)
Tissue cells	0.8998 cm^3/cm^3 tissue	Calculated in (1)	0.370 cm^3/cm^3 tissue	Calculated in (3)

SMND = skeletal muscle nuclear domain; BM = basement membrane.

Table S3: Kinetic parameters

	Measured parameters			Model parameters			
	Value	Unit	Reference	Value (Normal)	Value (Blood)	Value (Tumor)	Unit
VEGF binding to VEGFR1							
k_{on}	3.0×10^{7}	$M^{-1}s^{-1}$	(3, 8)	4.8×10^{-1}	5.5×10^{-2}	5.8×10^{-2}	$(pmol/cm^3\ tissue)^{-1}s^{-1}$
k_{off}	1.0×10^{-3}	s^{-1}	(3, 8)				
K_d	33	pM	(3, 8)	2.1×10^{-3}	1.8×10^{-2}	1.7×10^{-2}	$pmol/cm^3$ tissue
VEGF binding to VEGFR2							
k_{on}	1.0×10^{7}	$M^{-1}s^{-1}$	(3, 8)	1.6×10^{-1}	1.8×10^{-2}	1.9×10^{-2}	$(pmol/cm^3\ tissue)^{-1}s^{-1}$
k_{off}	1.0×10^{-3}	s^{-1}	(3, 8)				
K_d	100	pM	(3, 8)	6.2×10^{-3}	5.4×10^{-2}	5.2×10^{-2}	$pmol/cm^3$ tissue
$VEGF_{165}$ binding to NRP1							
k_{on}	3.2×10^{6}	$M^{-1}s^{-1}$	(3, 8)	5.1×10^{-2}	5.9×10^{-3}	6.1×10^{-3}	$(pmol/cm^3\ tissue)^{-1}s^{-1}$
k_{off}	1.0×10^{-3}	s^{-1}	(3, 8)				
K_d	312	pM	(3, 8)	2.0×10^{-2}	1.7×10^{-1}	1.6×10^{-1}	$pmol/cm^3$ tissue
$VEGF_{165}$ binding to NRP2							
k_{on}	1.0×10^{6}	$M^{-1}s^{-1}$	(14, 15)	-	-	1.9×10^{-3}	$(pmol/cm^3\ tissue)^{-1}s^{-1}$
k_{off}	1.0×10^{-3}	s^{-1}	(3, 8)				
K_d	1	nM	Calculated	-	-		$pmol/cm^3$ tissue
$VEGF_{165}$ binding to GAGs							
k_{on}	4.2×10^{5}	$M^{-1}s^{-1}$	(3, 8)	6.7×10^{-3}	-	8.0×10^{-4}	$(pmol/cm^3\ tissue)^{-1}s^{-1}$
k_{off}	1.0×10^{-2}	s^{-1}	(3, 8)				
K_d	24	nM	(3, 8)	2.71	-	5.2×10^{-1}	$pmol/cm^3$ tissue
Coupling of NRP1/2 and VEGFR1							
$k_{c\ R1,N}$	1.0×10^{14}	$(mol/cm^2)^{-1}s^{-1}$	(3, 8)	9.3×10^{-1}	9.3×10^{-1}	9.5×10^{-1}	$(pmol/cm^3\ tissue)^{-1}s^{-1}$
$k_{dissoc\ R1,N}$	1.0×10^{-2}	s^{-1}	(3, 8)				
Coupling of NRP1/2 and VEGFR2							
$k_{c\ V165R2,N}$	3.1×10^{13}	$(mol/cm^2)^{-1}s^{-1}$	(3, 8)	2.9×10^{-1}	2.9×10^{-1}	3.0×10^{-1}	$(pmol/cm^3\ tissue)^{-1}s^{-1}$
$k_{off\ V165R2,N}$	1.0×10^{-3}	s^{-1}	(3, 8)				
$k_{c\ V165N,R2}$	1.0×10^{14}	$(mol/cm^2)^{-1}s^{-1}$	(3, 8)	9.3×10^{-1}	9.3×10^{-1}	9.5×10^{-1}	$(pmol/cm^3\ tissue)^{-1}s^{-1}$
$k_{off\ V165N,R2}$	1.0×10^{-3}	s^{-1}	(3, 8)				

	Measured parameters			Model parameters			
	Value	**Unit**	**Reference**	**Value (Normal)**	**Value (Blood)**	**Value (Tumor)**	**Unit**
VEGFR internalization							
$k_{int, R}$	2.8×10^{-4}	s^{-1}	(3, 8)				
$k_{int, C}$	2.80×10^{-4}	s^{-1}	(3, 8)				
VEGF binding to anti-VEGF							
k_{on}	9.20×10^{4}	$M^{-1}s^{-1}$	(16)	1.5×10^{-3}	1.6×10^{-4}	1.8×10^{-4}	$(pmol/cm^3 \text{ tissue})^{-1}s^{-1}$
k_{off}	2.00×10^{-4}	s^{-1}	(16)				
K_d	2.2	nM	(16)	1.4×10^{-1}	1.2	1.1	$pmol/cm^3$ tissue

Conversions to model parameters:
Normal: 6.24×10^{7} ($pmol/cm^3$ tissue)/M and 1.08×10^{14} ($pmol/cm^3$ tissue)/(mol/cm^2 EC)
Blood: 5.43×10^{8} ($pmol/cm^3$ tissue)/M and 1.08×10^{14} ($pmol/cm^3$ tissue)/(mol/cm^2 EC)
Tumor: 5.22×10^{8} ($pmol/cm^3$ tissue)/M and 1.05×10^{14} (pmol/cm3 tissue)/(mol/cm^2 EC)

Table S4: Receptor densities

	Measured parameters		Model parameters	
	Value	**Unit**	**Value**	**Unit**
VEGFR1				
Luminal EC (normal)	550	rec/EC	1.21×10^{-1}	pmol/cm^3 tissue
Abluminal EC (normal)	550	rec/EC	9.86×10^{-3}	pmol/cm^3 tissue
Luminal EC (diseased)	3,750	rec/EC	4.38×10^{-4}	pmol/cm^3 tissue
Abluminal EC (diseased)	3,750	rec/EC	6.54×10^{-2}	pmol/cm^3 tissue
Myocytes	0	rec/myocyte	0	pmol/cm^3 tissue
Tumor cells	1,100	rec/tumor cell	2.81×10^{-1}	pmol/cm^3 tissue
VEGFR2				
Luminal EC (normal)	350	rec/EC	7.70×10^{-2}	pmol/cm^3 tissue
Abluminal EC (normal)	350	rec/EC	6.28×10^{-3}	pmol/cm^3 tissue
Luminal EC (diseased)	300	rec/EC	3.51×10^{-5}	pmol/cm^3 tissue
Abluminal EC (diseased)	300	rec/EC	5.23×10^{-3}	pmol/cm^3 tissue
Myocytes	0	rec/myocyte	0	pmol/cm^3 tissue
Tumor cells	550	rec/tumor cell	1.41×10^{-1}	pmol/cm^3 tissue
NRP1				
Luminal EC (normal)	17,500	rec/EC	3.74	pmol/cm^3 tissue
Abluminal EC (normal)	17,500	rec/EC	3.05×10^{-1}	pmol/cm^3 tissue
Luminal EC (diseased)	20,000[†]	rec/EC	2.34×10^{-3}	pmol/cm^3 tissue
Abluminal EC (diseased)	20,000[†]	rec/EC	3.49×10^{-1}	pmol/cm^3 tissue
Myocytes	34,500	rec/myocyte	2.06	pmol/cm^3 tissue
Tumor cells	39,500	rec/tumor cell	1.01×10^{1}	pmol/cm^3 tissue
NRP2				
Luminal EC (normal)	0	rec/EC	0	pmol/cm^3 tissue
Abluminal EC (normal)	0	rec/EC	0	pmol/cm^3 tissue
Luminal EC (diseased)	0	rec/EC	0	pmol/cm^3 tissue
Abluminal EC (diseased)	0	rec/EC	0	pmol/cm^3 tissue
Myocytes	0	rec/myocyte	0	pmol/cm^3 tissue
Tumor cells	39,500[‡]	rec/tumor cell	1.02×10^{1}	pmol/cm^3 tissue

Receptor quantification from (17, 18). [†] Extrapolated from receptor density on normal ECs, accounting for different cell surface areas. [‡]No NRP2 quantification available; assumed to be the same as NRP1 on tumor cells. Conversions of receptor densities to tissue concentrations:
Abluminal EC receptors (normal): 1.79×10^{-5} (pmol/cm^3 tissue)/(rec/EC); Luminal EC receptors (normal): 2.20×10^{-4} (pmol/cm^3 tissue)/(rec/EC);
Abluminal EC receptors (diseased): 1.74×10^{-5} (pmol/cm^3 tissue)/(rec/EC); Luminal EC receptors (diseased): 1.17×10^{-7} (pmol/cm^3 tissue)/(rec/EC);
Myocyte receptors: 5.96×10^{-5} (pmol/cm^3 tissue)/(rec/myocyte); Myocyte receptor densities are expressed per myonuclear domain;
Tumor receptors: 2.55×10^{-4} (pmol/cm^3 tissue)/(rec/tumor cell)

Table S5: Receptor and matrix binding site densities

	Measured parameter Value	Model parameters Value (Normal)	Value (Tumor)	Unit
Extracellular matrix	0.75 μM	46	389	$pmol/cm^3$ tissue
Microvessel BM	13 μM	1	4	$pmol/cm^3$ tissue
Parenchymal cell BM	13 μM	4	32	$pmol/cm^3$ tissue

BM = basement membrane. VEGF binding sites in the ECM and BMs are based on those volumes:
Normal: 6.2×10^7 ($pmol/cm^3$ tissue)/M(ECM), 8.7×10^4 ($pmol/cm^3$ tissue)/M(EBM), and 3.1×10^5 ($pmol/cm^3$ tissue)/M(PBM).
Tumor: 5.2×10^8 ($pmol/cm^3$ tissue)/M(ECM), 2.7×10^5 ($pmol/cm^3$ tissue)/M(EBM), and 2.4×10^6 ($pmol/cm^3$ tissue)/M(PBM).
M = moles/liter interstitial space; for example, M(EBM) = moles/liter of endothelial basement membrane.

Table S6: Transport parameters

	Value	Reference
VEGF secretion rate		
Normal tissue (92:8 $VEGF_{165}$:$VEGF_{121}$)	0.751 molecules/cell/s	*
Tumor (50:50 $VEGF_{165}$:$VEGF_{121}$)	0.562 molecules/cell/s	(17)
Lymph flow rate	120 mL/h	(19)
Microvascular permeability		
To VEGF in the normal tissue	4.00×10^{-8} cm/s	(8)
To anti-VEGF & VEGF/anti-VEGF complex in the normal tissue	3.00×10^{-8} cm/s	(8)
To VEGF in the tumor	4.00×10^{-7} cm/s	(8)
To anti-VEGF & VEGF/anti-VEGF complex in the tumor	3.00×10^{-7} cm/s	(8)
Clearance		
VEGF	0.0648 min^{-1}	(20)
Anti-VEGF & VEGF/anti-VEGF complex	3.82×10^{-7} min^{-1}	(21)

*Set to achieve ~4.5 pM free VEGF in blood, based on (22).

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