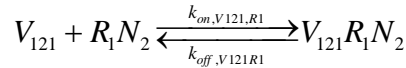
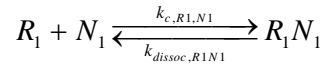
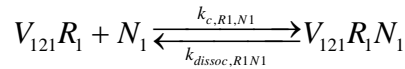
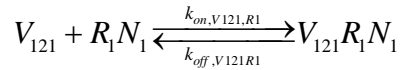
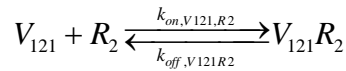
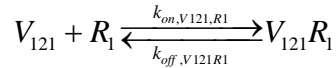
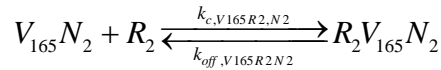
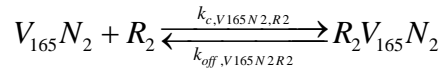
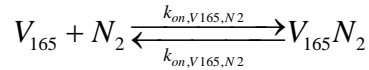
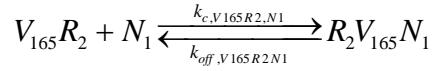
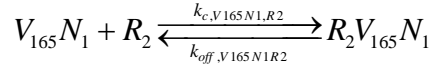
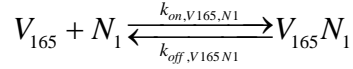
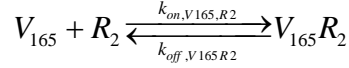
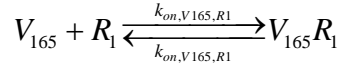
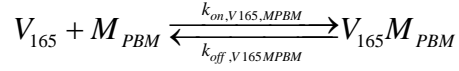
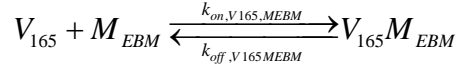
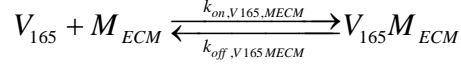
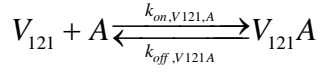
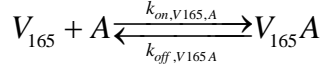
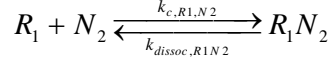
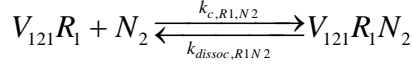


## I. Chemical reactions

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





## II. Equations

The complete list of ordinary differential equations is presented below:

### A. Interstitial space in normal tissue compartment

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

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

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

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

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

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

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

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

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

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

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

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

$$\frac{d[V_{165}R_1]_N}{dt} = -k_{int,V165R1}^N[V_{164}R_1]_N + k_{on,V165,R1}^N[V_{165}]_N[R_1]_N - k_{off,V165R1}^N[V_{165}R_1]_N \quad (S.13)$$

$$\begin{aligned} \frac{d[V_{165}R_2]_N}{dt} &= -k_{int,V165R2}^N[V_{165}R_2]_N + k_{on,V165,R2}^N[V_{165}]_N[R_2]_N - k_{off,V165R2}^N[V_{165}R_2]_N \\ &\quad - k_{c,V165R2,N1}^N[V_{165}R_2]_N[N_1]_N + k_{off,V165R2N1}^N[R_2V_{165}N_1]_N \end{aligned} \quad (S.14)$$

$$\begin{aligned} \frac{d[V_{165}N_1]_N}{dt} &= -k_{int,V165N1}^N[V_{165}N_1]_N + k_{on,V165,N1}^N[V_{165}]_N[N_1]_N - k_{off,V165N1}^N[V_{165}N_1]_N \\ &\quad - k_{c,V165N1,R2}^N[V_{165}N_1]_N[R_2]_N + k_{off,V165N1R2}^N[R_2V_{165}N_1]_N \end{aligned} \quad (S.15)$$

$$\begin{aligned} \frac{d[R_2V_{165}N_1]_N}{dt} &= -k_{int,V165R2N1}^N[R_2V_{165}N_1]_N \\ &\quad + k_{c,V165R2,N1}^N[V_{165}R_2]_N[N_1]_N - k_{off,V165R2N1}^N[R_2V_{165}N_1]_N \\ &\quad + k_{c,V165N1,R2}^N[V_{165}N_1]_N[R_2]_N - k_{off,V165N1R2}^N[R_2V_{165}N_1]_N \end{aligned} \quad (S.16)$$

$$\begin{aligned} \frac{d[V_{121}R_1]_N}{dt} &= -k_{int,V121R1}^N[V_{121}R_1]_N \\ &\quad + k_{on,V121,R1}^N[V_{121}]_N[R_1]_N - k_{off,V121R1}^N[V_{121}R_1]_N \\ &\quad - k_{c,R1,N1}^N[V_{121}R_1]_N[N_1]_N + k_{dissoc,R1N1}^N[V_{121}R_1N_1]_N \end{aligned} \quad (S.17)$$

$$\frac{d[V_{121}R_2]_N}{dt} = -k_{int,V121R2}^N[V_{121}R_2]_N + k_{on,V121,R2}^N[V_{121}]_N[R_2]_N - k_{off,V121R2}^N[V_{121}R_2]_N \quad (S.18)$$

$$\begin{aligned} \frac{d[R_1N_1]_N}{dt} &= -k_{int,R1N1}^N[R_1N_1]_N \\ &\quad + k_{c,R1,N1}^N[R_1]_N[N_1]_N - k_{dissoc,R1N1}^N[R_1N_1]_N \\ &\quad - k_{on,V121,R1}^N[V_{121}]_N[R_1N_1]_N + k_{off,V121R1}^N[V_{121}R_1N_1]_N \end{aligned} \quad (S.19)$$

$$\begin{aligned} \frac{d[V_{121}R_1N_1]_N}{dt} &= -k_{int,V121R1N1}^N[V_{121}R_1N_1]_N \\ &\quad + k_{c,V121R1,N1}^N[V_{121}R_1]_N[N_1]_N - k_{dissoc,V121N1}^N[V_{121}R_1N_1]_N \\ &\quad + k_{on,V121R1N1}^N[V_{121}]_N[R_1N_1]_N - k_{off,V121R1N1}^N[V_{121}R_1N_1]_N \end{aligned} \quad (S.20)$$

$$\begin{aligned} \frac{d[V_{165}N_1]_{N,myo}}{dt} &= -k_{int,V165N1}^{N,myo}[V_{165}N_1]_{N,myo} \\ &\quad + k_{on,V165,N1}^{N,myo}[V_{165}]_{N,myo}[N_1]_{N,myo} - k_{off,V165N1}^{N,myo}[V_{165}N_1]_{N,myo} \end{aligned} \quad (S.21)$$

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

$$\begin{aligned}
\frac{d[V_{165}A]_N}{dt} = & k_{on,V165,A}^N [V_{165}]_N [A]_N - k_{off,V165A}^N [V_{165}A]_N \\
& + k_{pA}^{BN} \frac{S_{NB}}{U_N} \frac{U_B}{U_P} [V_{165}A]_B - \left( \frac{k_L + k_{pA}^{NB} S_{NB}}{U_N} \right) \frac{[V_{165}A]_N}{K_{AV,N}}
\end{aligned} \tag{S.23}$$

$$\begin{aligned}
\frac{d[V_{121}A]_N}{dt} = & k_{on,V121,A}^N [V_{121}]_N [A]_N - k_{off,V121A}^N [V_{121}A]_N \\
& + k_{pA}^{BN} \frac{S_{NB}}{U_N} \frac{U_B}{U_P} [V_{121}A]_B - \left( \frac{k_L + k_{pA}^{NB} S_{NB}}{U_N} \right) \frac{[V_{121}A]_N}{K_{AV,N}}
\end{aligned} \tag{S.24}$$

## 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).

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

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

$$\begin{aligned}
\frac{d[R_1]_{B,i}}{dt} = & s_{R1}^B - k_{int,R1}^B [R_1]_{B,i} - k_{on,V165,R1}^B [V_{164}]_B [R_1]_{B,i} + k_{off,V165R1}^B [V_{165}R_1]_{B,i} \\
& - k_{on,V121,R1}^B [V_{121}]_B [R_1]_{B,i} + k_{off,V121R1}^B [V_{121}R_1]_{B,i} \\
& - k_{c,R1,N1}^B [N_1]_{B,i} [R_1]_{B,i} + k_{dissoc,R1N1}^B [R_1N_1]_{B,i}
\end{aligned} \tag{S.27, S.28}$$

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

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

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

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

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

$$\begin{aligned}
\frac{d[R_2 V_{165} N_1]_{B,i}}{dt} &= -k_{int,V165R2N1}^B [R_2 V_{165} N_1]_{B,i} \\
&+ k_{c,V165R2,N1}^B [V_{165} R_2]_{B,i} [N_1]_{B,i} - k_{off,V165R2N1}^B [R_2 V_{165} N_1]_{B,i} \\
&+ k_{c,V165N1,R2}^B [V_{165} N_1]_{B,i} [R_2]_{B,i} - k_{off,V165N1R2}^B [R_2 V_{165} N_1]_{B,i}
\end{aligned} \tag{S.39, S.40}$$

$$\begin{aligned}
\frac{d[V_{121} R_1]_{B,i}}{dt} &= -k_{int,V121R1}^B [V_{121} R_1]_{B,i} \\
&+ k_{on,V121,R1}^B [V_{121}]_{B,i} [R_1]_{B,i} - k_{off,V121R1}^B [V_{121} R_1]_{B,i} \\
&- k_{c,R1,N1}^B [V_{121} R_1]_{B,i} [N_1]_{B,i} + k_{dissoc,R1N1}^B [V_{121} R_1 N_1]_{B,i}
\end{aligned} \tag{S.41, S.42}$$

$$\frac{d[V_{121} R_2]_{B,i}}{dt} = -k_{int,V121R2}^B [V_{121} R_2]_{B,i} + k_{on,V121,R2}^B [V_{121}]_B [R_2]_{B,i} - k_{off,V121R2}^B [V_{121} R_2]_{B,i} \tag{S.43, S.44}$$

$$\begin{aligned}
\frac{d[R_1 N_1]_{B,i}}{dt} &= -k_{int,R1N1}^B [R_1 N_1]_{B,i} \\
&+ k_{c,R1,N1}^B [R_1]_{B,i} [N_1]_{B,i} - k_{dissoc,R1N1}^B [R_1 N_1]_{B,i} \\
&- k_{on,V121,R1}^B [V_{121}]_B [R_1 N_1]_{B,i} + k_{off,V121R1}^B [V_{121} R_1 N_1]_{B,i}
\end{aligned} \tag{S.45, S.46}$$

$$\begin{aligned}
\frac{d[V_{121} R_1 N_1]_{B,i}}{dt} &= -k_{intV121R1N1}^B [V_{121} R_1 N_1]_{B,i} \\
&+ k_{c,V121R1,N1}^B [V_{121} R_1]_{B,i} [N_1]_{B,i} - k_{dissoc,V121N1}^B [V_{121} R_1 N_1]_{B,i} \\
&+ k_{on,V121R1N1}^B [V_{121}]_B [R_1 N_1]_{B,i} - k_{off,V121R1N1}^B [V_{121} R_1 N_1]_{B,i}
\end{aligned} \tag{S.47, S.48}$$

$$\begin{aligned}
\frac{d[A]_B}{dt} &= q_A - c_A [A]_B - k_{on,V165,A}^B [V_{165}]_B [A]_B + k_{off,V165A}^B [V_{165} A]_B \\
&- k_{on,V121,A}^B [V_{121}]_B [A]_B + k_{off,V121A}^B [V_{121} A]_B \\
&+ k_{pA}^{BN} \frac{S_{NB}}{U_p} [A]_B - \left( \frac{k_L + k_{pA}^{NB} S_{NB}}{U_B} \right) \frac{[A]_N}{K_{AV,N}}
\end{aligned} \tag{S.49}$$

$$\begin{aligned}
\frac{d[V_{165} A]_B}{dt} &= -c_{V165A} [V_{165} A]_B + k_{on,V165,A}^B [V_{165}]_B [A]_B - k_{off,V165A}^B [V_{165} A]_B \\
&- k_{pA}^{BN} \frac{S_{NB}}{U_p} [V_{165} A]_B + \left( \frac{k_L + k_{pA}^{NB} S_{NB}}{U_B} \right) \frac{[V_{165} A]_N}{K_{AV,N}}
\end{aligned} \tag{S.50}$$

$$\begin{aligned}
\frac{d[V_{121}A]_B}{dt} &= -c_{V121A}[V_{121}A]_B + k_{on,V121,A}^B[V_{121}]_B[A]_B - k_{off,V121A}^B[V_{121}A]_B \\
&\quad - k_{pA}^{BN} \frac{S_{NB}}{U_p}[V_{121}A]_B + \left( \frac{k_L + k_{pA}^{NB} S_{NB}}{U_B} \right) \frac{[V_{121}A]_N}{K_{AV,N}}
\end{aligned} \tag{S.51}$$

### 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).

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

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

$$\frac{d[M_{EBM}]_T}{dt} = -k_{on,V165,MEBM}^N [V_{165}]_T [M_{EBM}]_T + k_{off,V165MEBM}^T [V_{165}M_{EBM}]_T \tag{S.54}$$

$$\frac{d[M_{PBM}]_T}{dt} = -k_{on,V165,MPBM}^T [V_{165}]_T [M_{PBM}]_T + k_{off,V165MPBM}^T [V_{165}M_{PBM}]_T \tag{S.55}$$



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

$$\begin{aligned}
\frac{d[V_{165} A]_T}{dt} &= k_{on,V165,A}^T [V_{165}]_T [A]_T - k_{off,V165A}^N [V_{165} A]_T \\
&+ k_{pA}^{BT} \frac{S_{TB}}{U_T} \frac{U_B}{U_P} [V_{165} A]_B - \left( \frac{k_L + k_{pA}^{TB} S_{TB}}{U_T} \right) \frac{[V_{165} A]_T}{K_{AV,T}}
\end{aligned} \tag{S.88}$$

$$\begin{aligned}
\frac{d[V_{121} A]_T}{dt} &= k_{on,V121,A}^T [V_{121}]_T [A]_T - k_{off,V121A}^N [V_{121} A]_T \\
&+ k_{pA}^{BT} \frac{S_{TB}}{U_T} \frac{U_B}{U_P} [V_{121} A]_B - \left( \frac{k_L + k_{pA}^{TB} S_{TB}}{U_T} \right) \frac{[V_{121} A]_T}{K_{AV,T}}
\end{aligned} \tag{S.89}$$

### III. Glossary

#### A. Concentrations

$[V_{121}], [V_{165}]$	Concentration of unbound VEGF <sub>121</sub> and VEGF <sub>165</sub>
$[M_{ECM}], [M_{EBM}], [M_{PBM}]$	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 <sub>165</sub> bound to the ECM, EBM, and PBM

$[R_1], [R_2]$	Concentration of un-occupied VEGFR-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 <sub>165</sub> -NRP1 ternary complex
$[R_2V_{165}N_2]$	Concentration of the VEGFR2-VEGF <sub>165</sub> -NRP2 ternary complex
$[V_{121}R_1N_1]$	Concentration of the VEGF <sub>121</sub> -VEGFR1-NRP1 ternary complex
$[V_{121}R_1N_2]$	Concentration of the VEGF <sub>121</sub> -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 <sub>121</sub> and VEGF <sub>165</sub>
$q_A$	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 <sub>121</sub> and VEGF <sub>165</sub>
$c_A, c_{V121A}, c_{V165A}$	Rate of plasma clearance of anti-VEGF and VEGF/anti-VEGF complex

#### IV. Model parameters

**Table S1: Whole-body parameters**

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

**Table S2: Geometric parameters**

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

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

**Table S3: Kinetic parameters**

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



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

Conversions to model parameters:

Normal:  $6.24 \times 10^7$  (pmol/cm<sup>3</sup> tissue)/M and  $1.08 \times 10^{14}$  (pmol/cm<sup>3</sup> tissue)/(mol/cm<sup>2</sup> EC)

Blood:  $5.43 \times 10^8$  (pmol/cm<sup>3</sup> tissue)/M and  $1.08 \times 10^{14}$  (pmol/cm<sup>3</sup> tissue)/(mol/cm<sup>2</sup> EC)

Tumor:  $5.22 \times 10^8$  (pmol/cm<sup>3</sup> tissue)/M and  $1.05 \times 10^{14}$  (pmol/cm<sup>3</sup> tissue)/(mol/cm<sup>2</sup> EC)

**Table S4: Receptor densities**

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

Receptor quantification from (17, 18). <sup>†</sup> Extrapolated from receptor density on normal ECs, accounting for different cell surface areas. <sup>‡</sup>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):  $1.79 \times 10^{-5}$  (pmol/cm<sup>3</sup> tissue)/(rec/EC); Luminal EC receptors (normal):  $2.20 \times 10^{-4}$  (pmol/cm<sup>3</sup> tissue)/(rec/EC);

Abluminal EC receptors (diseased):  $1.74 \times 10^{-5}$  (pmol/cm<sup>3</sup> tissue)/(rec/EC); Luminal EC receptors (diseased):  $1.17 \times 10^{-7}$  (pmol/cm<sup>3</sup> tissue)/(rec/EC);

Myocyte receptors:  $5.96 \times 10^{-5}$  (pmol/cm<sup>3</sup> tissue)/(rec/myocyte); Myocyte receptor densities are expressed per myonuclear domain;

Tumor receptors:  $2.55 \times 10^{-4}$  (pmol/cm<sup>3</sup> tissue)/(rec/tumor cell)

**Table S5: Receptor and matrix binding site densities**

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

BM = basement membrane. VEGF binding sites in the ECM and BMs are based on those volumes:

Normal:  $6.2 \times 10^7$  ( $\text{pmol}/\text{cm}^3$  tissue)/M(ECM),  $8.7 \times 10^4$  ( $\text{pmol}/\text{cm}^3$  tissue)/M(EBM), and  $3.1 \times 10^5$  ( $\text{pmol}/\text{cm}^3$  tissue)/M(PBM).

Tumor:  $5.2 \times 10^8$  ( $\text{pmol}/\text{cm}^3$  tissue)/M(ECM),  $2.7 \times 10^5$  ( $\text{pmol}/\text{cm}^3$  tissue)/M(EBM), and  $2.4 \times 10^6$  ( $\text{pmol}/\text{cm}^3$  tissue)/M(PBM).

M = moles/liter interstitial space; for example, M(EBM) = moles/liter of endothelial basement membrane.

**Table S6: Transport parameters**

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

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

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