Supplemental Information

The chemical reactions as well as the equations relevant in our model are presented here. For further information on the choice of parameter values, we invite the reader to look at (1) and (2). The concentrations are noted in brackets (see glossary below).

a. Chemical reactions

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

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

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

$$V_{165} + R_1 \underset{k_{off,V165R1}}{\overset{k_{on,V165,R1}}{\rightleftharpoons}} V_{165}R_1$$

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

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

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

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

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

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

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

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

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

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

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

b. interstitial space (normal tissue and tumor compartments only)

We denote the tissue compartment by the subscript i (i=N for the normal tissue compartment; i=T for the tumor compartment).

$$\frac{d\left[M_{EBM}\right]_i}{dt} = -k_{on,V165,MEBM}\left[V_{165}\right]_i\left[M_{EBM}\right]_i + k_{off,V165MEBM}\left[V_{165}M_{EBM}\right]_i \quad \text{(S.1)}$$

$$\frac{d\left[M_{ECM}\right]_i}{dt} = -k_{on,V165,MECM}\left[V_{165}\right]_i\left[M_{ECM}\right]_i + k_{off,V165MECM}\left[V_{165}M_{ECM}\right]_i \quad \text{(S.2)}$$

$$\frac{d\left[M_{PBM}\right]_i}{dt} = -k_{on,V165,MPBM}\left[V_{165}\right]_i\left[M_{PBM}\right]_i + k_{off,V165MPBM}\left[V_{165}M_{PBM}\right]_i \quad \text{(S.3)}$$

$$\frac{d\left[V_{165}M_{EBM}\right]_i}{dt} = k_{on,V165,MEBM}\left[V_{165}\right]_i\left[M_{EBM}\right]_i - k_{off,V165MEBM}\left[V_{165}M_{EBM}\right]_i \quad \text{(S.4)}$$

$$\frac{d\left[V_{165}M_{ECM}\right]_i}{dt} = k_{on,V165,MECM}\left[V_{165}\right]_i\left[M_{ECM}\right]_i - k_{off,V165MECM}\left[V_{165}M_{ECM}\right]_i \quad \text{(S.5)}$$

$$\frac{d\left[V_{165}M_{PBM}\right]_i}{dt} = k_{on,V165,MPBM}\left[V_{165}\right]_i\left[M_{PBM}\right]_i - k_{off,V165MPBM}\left[V_{165}M_{PBM}\right]_i \quad \text{(S.6)}$$

c. cell surface (normal tissue and tumor compartments only)

$$\begin{aligned}\frac{d\left[R_1\right]_i}{dt} = {} & s_{R1,i} - k_{\text{int},R1}\left[R_1\right]_i - k_{on,V165,R1}\left[V_{165}\right]_i\left[R_1\right]_i + k_{off,V165R1}\left[V_{165}R_1\right]_i \\ & - k_{on,V121,R1}\left[V_{121}\right]_i\left[R_1\right]_i + k_{off,V121R1}\left[V_{121}R_1\right]_i \\ & - k_{c,R1,N1}\left[N_1\right]_i\left[R_1\right]_i + k_{dissoc,R1N1}\left[R_1N_1\right]_i\end{aligned} \quad \text{(S.7)}$$

$$\begin{aligned}\frac{d\left[R_2\right]_i}{dt} = {} & s_{R2,i} - k_{\text{int},R2}\left[R_2\right]_i - k_{on,V121,R2}\left[V_{121}\right]_i\left[R_2\right]_i + k_{off,V121R2}\left[V_{121}R_2\right]_i \\ & - k_{on,V165,R2}\left[V_{165}\right]_i\left[R_2\right]_i + k_{off,V165R2}\left[V_{165}R_2\right]_i \\ & - k_{c,V165N1,R2}\left[V_{165}N_1\right]_i\left[R_2\right]_i + k_{off,V165N1,R2}\left[R_2V_{165}N_1\right]_i\end{aligned} \quad \text{(S.8)}$$

$$\frac{d[N_1]_i}{dt} = s_{N1,i} - k_{\text{int},N1}[N_1]_i - k_{c,V121R1,N1}[V_{121}R_1]_i[N_1]_i + k_{dissoc,R1N1}[V_{121}R_1N_1]_i - k_{c,R1,N1}[N_1]_i[R_1]_i + k_{dissoc,R1N1}[R_1N_1]_i - k_{on,V165,N1}[V_{165}]_i[N_1]_i + k_{off,V165N1}[V_{165}N_1]_i - k_{c,V165R2,N1}[V_{165}R_2]_i[N_1]_i + k_{off,V165R2,N1}[R_2V_{165}N_1]_i \quad \text{(S.9)}$$

$$\frac{d[V_{121}R_1]_i}{dt} = -k_{\text{int},V121R1}[V_{121}R_1]_i + k_{on,V121,R1}[V_{121}]_i[R_1]_i - k_{off,V121R1}[V_{121}R_1]_i - k_{c,R1,N1}[V_{121}R_1]_i[N_1]_i + k_{dissoc,R1N1}[V_{121}R_1N_1]_i \quad \text{(S.10)}$$

$$\frac{d[V_{121}R_2]_i}{dt} = -k_{\text{int},V121R2}[V_{121}R_2]_i + k_{on,V121,R2}[V_{121}]_i[R_2]_i - k_{off,V121R2}[V_{121}R_2]_i \quad \text{(S.11)}$$

$$\frac{d[V_{165}R_1]_i}{dt} = -k_{\text{int},V165R1}[V_{165}R_1]_i + k_{on,V165,R1}[V_{165}]_i[R_1]_i - k_{off,V165R1}[V_{165}R_1]_i \quad \text{(S.12)}$$

$$\frac{d[V_{165}R_2]_i}{dt} = -k_{\text{int},V165R2}[V_{165}R_2]_i + k_{on,V165,R2}[V_{165}]_i[R_2]_i - k_{off,V165R2}[V_{165}R_2]_i - k_{c,V165R2,N1}[V_{165}R_2]_i[N_1]_i + k_{off,V165R2,N1}[R_2V_{165}N_1]_i \quad \text{(S.13)}$$

$$\frac{d[V_{165}N_1]_i}{dt} = -k_{\text{int},V165N1}[V_{165}N_1]_i + k_{on,V165,N1}[V_{165}]_i[N_1]_i - k_{off,V165N1}[V_{165}N_1]_i - k_{c,V165N1,R2}[V_{165}N_1]_i[R_2]_i + k_{off,V165N1,R2}[R_2V_{165}N_1]_i \quad \text{(S.14)}$$

$$\frac{d[R_2V_{165}N_1]_i}{dt} = -k_{\text{int},V165R2N1}[R_2V_{165}N_1]_i + k_{c,V165R2,N1}[V_{165}R_2]_i[N_1]_i - k_{off,V165R2,N1}[R_2V_{165}N_1]_i + k_{c,V165N1,R2}[V_{165}N_1]_i[R_2]_i - k_{off,V165N1,R2}[R_2V_{165}N_1]_i \quad \text{(S.15)}$$

$$\frac{d[V_{121}R_1N_1]_i}{dt} = -k_{\text{int},V121R1N1}[V_{121}R_1N_1]_i + k_{c,V121R1,N1}[V_{121}R_1]_i[N_1]_i - k_{dissoc,V121N1}[V_{121}R_1N_1]_i + k_{on,V121,R1N1}[V_{121}]_i[R_1N_1]_i - k_{off,V121R1N1}[V_{121}R_1N_1]_i \quad \text{(S.16)}$$

$$\frac{d[R_1N_1]_i}{dt} = -k_{\text{int},R1N1}[R_1N_1]_i + k_{c,R1,N1}[N_1]_i[R_1]_i - k_{dissoc,R1N1}[R_1N_1]_i - k_{on,V121,R1}[V_{121}]_i[R_1N_1]_i + k_{off,V121R1}[V_{121}R_1N_1]_i \quad \text{(S.17)}$$

d. ligands in the tissue compartments

We denote the blood compartment by the subscript *B*.

$$\begin{aligned}\frac{d[V_{121}]_N}{dt} &= q^N_{V121} - k_{on,V121,R1}[V_{121}]_N[R_1]_N + k_{off,V121R1}[V_{121}R_1]_N \\ &- k_{on,V121,R1N1}[V_{121}]_N[R_1N_1]_N + k_{off,V121R1N1}[V_{121}R_1N_1]_N \\ &- k_{on,V121,R2}[V_{121}]_N[R_2]_N + k_{off,V121R2}[V_{121}R_2]_N \\ &- \left(\frac{k_L + k^{NB}_{pV}S_{NB}}{U_N}\right)\frac{[V_{121}]_N}{K_{AV,N}} + k^{BN}_{pV}\frac{S_{NB}}{U_N}\frac{U_B}{U_p}[V_{121}]_B\end{aligned} \tag{S.18}$$

The equation includes the secretion of the VEGF_{121} isoform by parenchymal cells (q^N_{V121}), binding to its receptors (secondth to seventh term on the right hand side of the equation (S.18)), and intravasation and extravasation of the ligand. Note that, due to closed pores and inaccessible spaces, free diffusible VEGF is constrained in the "available interstitial fluid volume" $U_{AV} = K_{AV}\,U$, where K_{AV} is the available volume fraction.

Similarly, the equation governing VEGF_{165} is:

$$\begin{aligned}\frac{d[V_{165}]_N}{dt} &= q^N_{V165} - k_{on,V165,MEBM}[V_{165}]_N[M_{EBM}]_N + k_{off,V165,MEBM}[V_{165}M_{EBM}]_N \\ &- k_{on,V165,MECM}[V_{165}]_N[M_{ECM}]_N + k_{off,V165MECM}[V_{165}M_{ECM}]_N \\ &- k_{on,V165,MPBM}[V_{165}]_N[M_{PBM}]_N + k_{off,V165MPBM}[V_{165}M_{PBM}]_N \\ &- k_{on,V165,R1}[V_{165}]_N[R_1]_N + k_{off,V165R1}[V_{165}R_1]_N - k_{on,V165,R2}[V_{165}]_N[R_2]_N \\ &+ k_{off,V165R2}[V_{165}R_2]_N - k_{on,V165,N1}[V_{165}]_N[N_1]_N + k_{off,V165N1}[V_{165}N_1]_N \\ &- \left(\frac{k_L + k^{NB}_{pV}S_{NB}}{U_N}\right)\frac{[V_{165}]_N}{K_{AV,N}} + k^{BN}_{pV}\frac{S_{NB}}{U_N}\frac{U_B}{U_p}[V_{165}]_B\end{aligned} \tag{S.19}$$

In the tumor microenvironment, the lymphatics are thought not to function properly because the interstitial fluid pressure is elevated. To illustrate this property, we set the lymph flow rate k_L to zero in the compartment. Therefore, in the tumor compartment, the equations (S.18) and (S.19) become:

$$\frac{d[V_{121}]_T}{dt} = q^T_{V121} - k_{on,V121,R1}[V_{121}]_T[R_1]_T + k_{off,V121R1}[V_{121}R_1]_T$$
$$- k_{on,V121,R1N1}[V_{121}]_T[R_1N_1]_T + k_{off,V121R1N1}[V_{121}R_1N_1]_T$$
$$- k_{on,V121,R2}[V_{121}]_T[R_2]_T + k_{off,V121R2}[V_{121}R_2]_T$$
$$- k^{TB}_{pV}\frac{S_{TB}}{U_T}\frac{[V_{121}]_T}{K_{AV,T}} + k^{BT}_{pV}\frac{S_{TB}}{U_T}\frac{U_B}{U_p}[V_{121}]_T \quad \text{(S.20)}$$

$$\frac{d[V_{165}]_T}{dt} = q^T_{V165} - k_{on,V165,MEBM}[V_{165}]_T[M_{EBM}]_T + k_{off,V165,MEBM}[V_{165}M_{EBM}]_T$$
$$- k_{on,V165,MECM}[V_{165}]_T[M_{ECM}]_T + k_{off,V165MECM}[V_{165}M_{ECM}]_T$$
$$- k_{on,V165,MPBM}[V_{165}]_T[M_{PBM}]_T + k_{off,V165MPBM}[V_{165}M_{PBM}]_T$$
$$- k_{on,V165,R1}[V_{165}]_T[R_1]_T + k_{off,V165R1}[V_{165}R_1]_T - k_{on,V165,R2}[V_{165}]_T[R_2]_T \quad \text{(S.21)}$$
$$+ k_{off,V165R2}[V_{165}R_2]_T - k_{on,V165,N1}[V_{165}]_T[N_1]_T + k_{off,V165N1}[V_{165}N_1]_T$$
$$- k^{TB}_{pV}\frac{S_{TB}}{U_T}\frac{[V_{165}]_T}{K_{AV,T}} + k^{BT}_{pV}\frac{S_{TB}}{U_T}\frac{U_B}{U_p}[V_{165}]_B$$

e. ligands in the blood compartment

$$\frac{d[V_{121}]_B}{dt} = -c_{V121}[V_{121}]_B - k^{BN}_{pV}\frac{S_{NB}}{U_p}[V_{121}]_B + \left(\frac{k_L + k^{NB}_{pV}S_{NB}}{U_B}\right)\frac{[V_{121}]_N}{K_{AV,N}}$$
$$- k^{BT}_{pV}\frac{S_{TB}}{U_p}[V_{121}]_B + k^{TB}_{pV}\frac{S_{TB}}{U_B}\frac{[V_{121}]_T}{K_{AV,T}} \quad \text{(S.22)}$$

$$\frac{d[V_{165}]_B}{dt} = -c_{V165}[V_{165}]_B - k^{BN}_{pV}\frac{S_{NB}}{U_p}[V_{165}]_B + \left(\frac{k_L + k^{NB}_{pV}S_{NB}}{U_B}\right)\frac{[V_{165}]_N}{K_{AV,N}}$$
$$- k^{BT}_{pV}\frac{S_{TB}}{U_p}[V_{165}]_B + k^{TB}_{pV}\frac{S_{TB}}{U_B}\frac{[V_{165}]_T}{K_{AV,T}} \quad \text{(S.23)}$$

where c_V represents the clearance of VEGF from the blood.

f. anti-VEGF agent and modification of the equations

The available interstitial fluid volumes for the anti-VEGF agent and its complex with VEGF are taken to be the same as that of VEGF. The presence of the anti-VEGF alters the equations governing the VEGF isoforms, i.e., equations (S.18-S.23). These equations become:

$$\begin{aligned}\frac{d\left[V_{121}\right]_N}{dt} &= q_{V121}^{N} - k_{on,V121,R1}\left[V_{121}\right]_N\left[R_1\right]_N + k_{off,V121R1}\left[V_{121}R_1\right]_N \\ &- k_{on,V121,R1N1}\left[V_{121}\right]_N\left[R_1N_1\right]_N + k_{off,V121R1N1}\left[V_{121}R_1N_1\right]_N \\ &- k_{on,V121,R2}\left[V_{121}\right]_N\left[R_2\right]_N + k_{off,V121R2}\left[V_{121}R_2\right]_N \\ &- k_{on,V121,A}\left[V_{121}\right]_N\left[A\right]_N + k_{off,V121A}\left[V_{121}A\right]_N \\ &- \left(\frac{k_L + k_{pV}^{NB}S_{NB}}{U_N}\right)\frac{\left[V_{121}\right]_N}{K_{AV,N}} + k_{pV}^{BN}\frac{S_{NB}}{U_N}\frac{U_B}{U_p}\left[V_{121}\right]_B\end{aligned} \tag{S.24}$$

$$\begin{aligned}\frac{d\left[V_{165}\right]_N}{dt} &= q_{V165}^{N} - k_{on,V165,MEBM}\left[V_{165}\right]_N\left[M_{EBM}\right]_N + k_{off,V165,MEBM}\left[V_{165}M_{EBM}\right]_N \\ &- k_{on,V165,MECM}\left[V_{165}\right]_N\left[M_{ECM}\right]_N + k_{off,V165MECM}\left[V_{165}M_{ECM}\right]_N \\ &- k_{on,V165,MPBM}\left[V_{165}\right]_N\left[M_{PBM}\right]_N + k_{off,V165MPBM}\left[V_{165}M_{PBM}\right]_N \\ &- k_{on,V165,R1}\left[V_{165}\right]_N\left[R_1\right]_N + k_{off,V165R1}\left[V_{165}R_1\right]_N - k_{on,V165,R2}\left[V_{165}\right]_N\left[R_2\right]_N \\ &+ k_{off,V165R2}\left[V_{165}R_2\right]_N - k_{on,V165,N1}\left[V_{165}\right]_N\left[N_1\right]_N + k_{off,V165N1}\left[V_{165}N_1\right]_N \\ &- k_{on,V121,A}\left[V_{165}\right]_N\left[A\right]_N + k_{off,V165A}\left[V_{165}A\right]_N \\ &- \left(\frac{k_L + k_{pV}^{NB}S_{NB}}{U_N}\right)\frac{\left[V_{165}\right]_N}{K_{AV,N}} + k_{pV}^{BN}\frac{S_{NB}}{U_N}\frac{U_B}{U_p}\left[V_{165}\right]_B\end{aligned} \tag{S.25}$$

$$\begin{aligned}\frac{d\left[V_{121}\right]_T}{dt} &= q_{V121}^{T} - k_{on,V121,R1}\left[V_{121}\right]_T\left[R_1\right]_T + k_{off,V121R1}\left[V_{121}R_1\right]_T \\ &- k_{on,V121,R1N1}\left[V_{121}\right]_T\left[R_1N_1\right]_T + k_{off,V121R1N1}\left[V_{121}R_1N_1\right]_T \\ &- k_{on,V121,R2}\left[V_{121}\right]_T\left[R_2\right]_T + k_{off,V121R2}\left[V_{121}R_2\right]_T \\ &- k_{on,V121,A}\left[V_{121}\right]_T\left[A\right]_T + k_{off,V121A}\left[V_{121}A\right]_T \\ &- k_{pV}^{TB}\frac{S_{TB}}{U_T}\frac{\left[V_{121}\right]_T}{K_{AV,T}} + k_{pV}^{BT}\frac{S_{TB}}{U_T}\frac{U_B}{U_p}\left[V_{121}\right]_T\end{aligned} \tag{S.26}$$

$$\frac{d[V_{165}]_T}{dt} = q^T_{V165} - k_{on,V165,MEBM}[V_{165}]_T[M_{EBM}]_T + k_{off,V165,MEBM}[V_{165}M_{EBM}]_T$$
$$- k_{on,V165,MECM}[V_{165}]_T[M_{ECM}]_T + k_{off,V165MECM}[V_{165}M_{ECM}]_T$$
$$- k_{on,V165,MPBM}[V_{165}]_T[M_{PBM}]_T + k_{off,V165MPBM}[V_{165}M_{PBM}]_T$$
$$- k_{on,V165,R1}[V_{165}]_T[R_1]_T + k_{off,V165R1}[V_{165}R_1]_T - k_{on,V165,R2}[V_{165}]_T[R_2]_T \quad \text{(S.27)}$$
$$+ k_{off,V165R2}[V_{165}R_2]_T - k_{on,V165,N1}[V_{165}]_T[N_1]_T + k_{off,V165N1}[V_{165}N_1]_T$$
$$- k_{on,V121,A}[V_{165}]_T[A]_T + k_{off,V165A}[V_{165}A]_T$$
$$- k^{TB}_{pV}\frac{S_{TB}}{U_T}\frac{[V_{165}]_T}{K_{AV,T}} + k^{BT}_{pV}\frac{S_{TB}}{U_T}\frac{U_B}{U_p}[V_{165}]_B$$

$$\frac{d[V_{121}]_B}{dt} = -c_{V121}[V_{121}]_B - k^{BN}_{pV}\frac{S_{NB}}{U_p}[V_{121}]_B + \left(\frac{k_L + k^{NB}_{pV}S_{NB}}{U_B}\right)\frac{[V_{121}]_N}{K_{AV,N}}$$
$$- k^{BT}_{pV}\frac{S_{TB}}{U_p}[V_{121}]_B + k^{TB}_{pV}\frac{S_{TB}}{U_B}\frac{[V_{121}]_T}{K_{AV,T}} \quad \text{(S.28)}$$
$$- k_{on,V121,A}[V_{121}]_B[A]_B + k_{off,V121A}[V_{121}A]_B$$

$$\frac{d[V_{165}]_B}{dt} = -c_{V165}[V_{165}]_B - k^{BN}_{pV}\frac{S_{NB}}{U_p}[V_{165}]_B + \left(\frac{k_L + k^{NB}_{pV}S_{NB}}{U_B}\right)\frac{[V_{165}]_N}{K_{AV,N}}$$
$$- k^{BT}_{pV}\frac{S_{TB}}{U_p}[V_{165}]_B + k^{TB}_{pV}\frac{S_{TB}}{U_B}\frac{[V_{165}]_T}{K_{AV,T}} \quad \text{(S.29)}$$
$$- k_{on,V165,A}[V_{165}]_B[A]_B + k_{off,V165A}[V_{165}A]_B$$

The inclusion of the anti-VEGF agent also introduces new equations in the plasma, in the normal tissue, and in the tumor compartments:

$$\frac{d[A]_N}{dt} = -k_{on,V121,A}[V_{121}]_N[A]_N + k_{off,V121A}[V_{121}A]_N - k_{on,V121,A}[V_{165}]_N[A]_N$$
$$+ k_{off,V121A}[V_{165}A]_N - \left(\frac{k_L + k^{NB}_{pV}S_{NB}}{U_N}\right)\frac{[A]_N}{K_{AV,N}} + k^{BN}_{pV}\frac{S_{NB}}{U_N}\frac{U_B}{U_p}[A]_B \quad \text{(S.30)}$$

$$\frac{d[A]_T}{dt} = -k_{on,V121,A}[V_{121}]_T[A]_T + k_{off,V121A}[V_{121}A]_T - k_{on,V121,A}[V_{165}]_T[A]_T + k_{off,V121A}[V_{165}A]_T - k_{pV}^{TB}\frac{S_{TB}}{U_T}\frac{[A]_T}{K_{AV,T}} + k_{pV}^{BT}\frac{S_{TB}}{U_T}\frac{U_B}{U_p}[A]_B \tag{S.31}$$

$$\frac{d[V_{121}A]_N}{dt} = k_{on,V121,A}[V_{121}]_N[A]_N - k_{off,V121A}[V_{121}A]_N - \left(\frac{k_L + k_{pV}^{NB}S_{NB}}{U_N}\right)\frac{[V_{121}A]_N}{K_{AV,N}} + k_{pV}^{BN}\frac{S_{NB}}{U_N}\frac{U_B}{U_p}[V_{121}A]_B \tag{S.32}$$

$$\frac{d[V_{121}A]_T}{dt} = k_{on,V121,A}[V_{121}]_T[A]_T - k_{off,V121A}[V_{121}A]_T - k_{pV}^{TB}\frac{S_{TB}}{U_T}\frac{[V_{121}A]_T}{K_{AV,T}} + k_{pV}^{BT}\frac{S_{TB}}{U_T}\frac{U_B}{U_p}[V_{121}A]_B \tag{S.33}$$

$$\frac{d[V_{165}A]_N}{dt} = k_{on,V165,A}[V_{165}]_N[A]_N - k_{off,V165A}[V_{165}A]_N - \left(\frac{k_L + k_{pV}^{NB}S_{NB}}{U_N}\right)\frac{[V_{165}A]_N}{K_{AV,N}} + k_{pV}^{BN}\frac{S_{NB}}{U_N}\frac{U_B}{U_p}[V_{165}A]_B \tag{S.34}$$

$$\frac{d[V_{165}A]_T}{dt} = k_{on,V165,A}[V_{165}]_T[A]_T - k_{off,V165A}[V_{165}A]_T - k_{pV}^{TB}\frac{S_{TB}}{U_T}\frac{[V_{165}A]_T}{K_{AV,T}} + k_{pV}^{BT}\frac{S_{TB}}{U_T}\frac{U_B}{U_p}[V_{165}A]_B \tag{S.35}$$

$$\begin{aligned}\frac{d[A]_B}{dt} = {} & q_A - c_A[A]_B - k_{pV}^{BN}\frac{S_{NB}}{U_p}[A]_B + \left(\frac{k_L + k_{pV}^{NB}S_{NB}}{U_B}\right)\frac{[A]_N}{K_{AV,N}} \\ & - k_{pV}^{BT}\frac{S_{TB}}{U_p}[A]_B + k_{pV}^{TB}\frac{S_{TB}}{U_B}\frac{[A]_T}{K_{AV,T}} \\ & - k_{on,V121,A}[V_{121}]_B[A]_B + k_{off,V121A}[V_{121}A]_B \\ & - k_{on,V121,A}[V_{165}]_B[A]_B + k_{off,V165A}[V_{165}A]_B\end{aligned} \tag{S.36}$$

$$\begin{aligned}\frac{d\left[V_{121}A\right]_B}{dt} &= q_{V121A} - c_{V121A}\left[V_{121}A\right]_B - k_{pV}^{BN}\frac{S_{NB}}{U_p}\left[V_{121}A\right]_B + \left(\frac{k_L + k_{pV}^{NB}S_{NB}}{U_B}\right)\frac{\left[V_{121}A\right]_N}{K_{AV,N}} \\ &- k_{pV}^{BT}\frac{S_{TB}}{U_p}\left[V_{121}A\right]_B + k_{pV}^{TB}\frac{S_{TB}}{U_B}\frac{\left[V_{121}A\right]_T}{K_{AV,T}} \\ &+ k_{on,V121,A}\left[V_{121}\right]_B\left[A\right]_B - k_{off,V121A}\left[V_{121}A\right]_B\end{aligned} \tag{S.37}$$

$$\begin{aligned}\frac{d\left[V_{165}A\right]_B}{dt} &= q_{V165A} - c_{V165A}\left[V_{165}A\right]_B - k_{pV}^{BN}\frac{S_{NB}}{U_p}\left[V_{165}A\right]_B + \left(\frac{k_L + k_{pV}^{NB}S_{NB}}{U_B}\right)\frac{\left[V_{165}A\right]_N}{K_{AV,N}} \\ &- k_{pV}^{BT}\frac{S_{TB}}{U_p}\left[V_{165}A\right]_B + k_{pV}^{TB}\frac{S_{TB}}{U_B}\frac{\left[V_{165}A\right]_T}{K_{AV,T}} \\ &+ k_{on,V165,A}\left[V_{165}\right]_B\left[A\right]_B - k_{off,V165A}\left[V_{165}A\right]_B\end{aligned} \tag{S.38}$$

GLOSSARY

Concentrations and densities

$[M_{ECM}]$, $[M_{EBM}]$, $[M_{PBM}]$	Density of VEGF binding sites in the ECM, EBM and PBM
$[V_{121}]$, $[V_{165}]$	Concentration of unbound $VEGF_{121}$ and $VEGF_{165}$ in the available interstitial fluid
$[R_1]$, $[R_2]$	Density of the unoccupied receptor tyrosine kinases VEGFR1 and VEGFR2
$[N_1]$	Density of the unoccupied co-receptor (NRP1)
$[R_1N_1]$	Density of the VEGFR1/NRP1 complex
$[V_iR_j]$	Concentration of VEGF isoform *i* bound to VEGF receptor $VEGFR_j$
$[V_iN_1]$	Concentration of VEGF isoform *i* bound to co-receptor NRP1
$[R_2V_{165}N_1]$	Concentration of ternary complex VEGFR2/$VEGF_{165}$/NRP1
$[V_{121}R_1N_1]$	Concentration of ternary complex $VEGF_{121}$/VEGFR1/NRP1
$[A]$	Concentration of anti-VEGF agent
$[VA]$	Concentration of VEGF/anti-VEGF complex

Kinetic parameters

q_{V121}, q_{V165}	Secretion rate of $VEGF_{121}$ and $VEGF_{165}$
q_A	Injection rate of the anti-VEGF agent
s_R	Rate at which the receptors are inserted into the cell membrane
k_{on}	Kinetic rate for binding

k_c	Kinetic rate for receptor coupling
k_{off}	Kinetic rate for unbinding
k_{int}	Internalization rate of the receptors
k_{pV}^{ij}	Microvascular permeability k_p for VEGF (noted as V) from compartment i to j (N = tissue; B = blood)
k_L	Lymph flow rate
c_{V121}, c_{V165}	Clearance of $VEGF_{121}$ and $VEGF_{165}$ from the blood
c_A, c_{V121A}, c_{V165A}	Clearance from the blood of anti-VEGF, of its complex formed when binding to $VEGF_{121}$ isoform, and of its complex formed when binding to $VEGF_{165}$ isoform

Geometric parameters

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

FIGURE LEGENDS

Figure S1. Anti-VEGF concentration profiles following the intravenous injection of an anti-VEGF agent.

A-B. Single injection (10 mg/kg), **C-D.** Daily injection of 1 mg/kg for 10 days (metronomic therapy). Solid line: normal tissue; dashed line: blood; dotted line: tumor.

Figure S2. VEGF/anti-VEGF concentration profiles following the intravenous injection of an anti-VEGF agent.

A-B. Single injection (10 mg/kg), **C-D.** Daily injection of 1 mg/kg for 10 days (metronomic therapy). Solid line: normal tissue; dashed line: blood; dotted line: tumor. This also illustrates the total VEGF concentration profiles following the intravenous injection of an anti-VEGF agent.

Figure S3. VEGF distribution profiles in normal, blood and tumor tissues.

Concentrations of VEGF bound to the anti-VEGF agent, free, bound to the receptors and sequestered in the extracellular matrix. From top to bottom: normal tissue, blood, tumor. Solid line: VEGF bound to anti-VEGF; dotted line: VEGF bound to the extracellular matrix; dashed line: VEGF bound to receptors; dashed-dotted line: unbound VEGF.

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