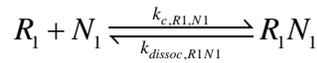
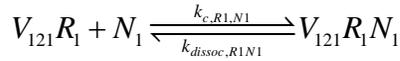
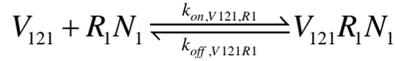
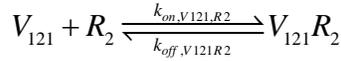
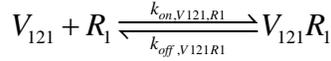
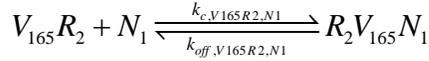
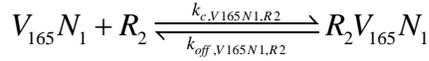
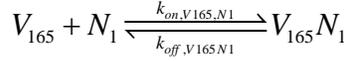
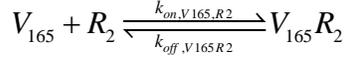
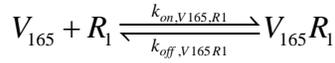
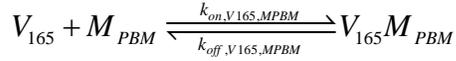
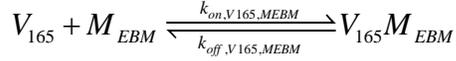
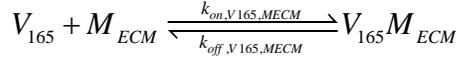


Supplemental Information

We present here the chemical reactions as well as the equations provided from [1]. Note that there is no diseased tissue compartment in the present study. The concentrations are noted in brackets (see glossary below).

a. Chemical reactions



b. interstitial space (tissue compartment only)

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

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

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

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

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

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

c. cell surface (equations valid for both the tissue and the blood compartments)

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

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

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

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

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

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

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

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

$$\begin{aligned}
\frac{d[R_2V_{165}N_1]}{dt} = & -k_{\text{int},V_{165}R_2N_1} [R_2V_{165}N_1] + k_{c,V_{165}R_2,N_1} [V_{165}R_2][N_1] \\
& -k_{\text{off},V_{165}R_2,N_1} [R_2V_{165}N_1] + k_{c,V_{165}N_1,R_2} [V_{165}N_1][R_2] \\
& -k_{\text{off},V_{165}N_1,R_2} [R_2V_{165}N_1]
\end{aligned} \tag{S.15}$$

$$\begin{aligned}
\frac{d[V_{121}R_1N_1]}{dt} = & -k_{\text{int},V_{121}R_1N_1} [V_{121}R_1N_1] + k_{c,V_{121}R_1,N_1} [V_{121}R_1][N_1] \\
& -k_{\text{dissoc},V_{121}N_1} [V_{121}R_1N_1] + k_{\text{on},V_{121},R_1N_1} [V_{121}][R_1N_1] \\
& -k_{\text{off},V_{121}R_1N_1} [V_{121}R_1N_1]
\end{aligned} \tag{S.16}$$

$$\begin{aligned}
\frac{d[R_1N_1]}{dt} = & -k_{\text{int},R_1N_1} [R_1N_1] + k_{c,R_1,N_1} [N_1][R_1] - k_{\text{dissoc},R_1N_1} [R_1N_1] \\
& -k_{\text{on},V_{121},R_1} [V_{121}][R_1N_1] + k_{\text{off},V_{121}R_1} [V_{121}R_1N_1]
\end{aligned} \tag{S.17}$$

d. ligands in the tissue compartment

We denote the tissue compartment by the subscript N .

$$\begin{aligned}
\frac{d[V_{121}]_N}{dt} = & q_{V_{121}}^N - k_{\text{on},V_{121},R_1}^N [V_{121}]_N [R_1]_N + k_{\text{off},V_{121}R_1}^N [V_{121}R_1]_N \\
& -k_{\text{on},V_{121},R_1N_1}^N [V_{121}]_N [R_1N_1]_N + k_{\text{off},V_{121}R_1N_1}^N [V_{121}R_1N_1]_N \\
& -k_{\text{on},V_{121},R_2}^N [V_{121}]_N [R_2]_N + k_{\text{off},V_{121}R_2}^N [V_{121}R_2]_N \\
& -k_{pV}^{NB} \frac{S_{NB}}{U_N} \frac{[V_{121}]_N}{K_{AV,N}} + k_{pV}^{BN} \frac{S_{NB}}{U_N} \frac{U_B}{U_p} [V_{121}]_B
\end{aligned} \tag{S.18}$$

The first term of the equation represents the secretion of the VEGF₁₂₁ isoform by parenchymal cells. The next six terms correspond to the interactions of the VEGF₁₂₁ isoform with its receptors. Finally, the last two terms represent the extravasation and intravasation, respectively, of VEGF₁₂₁. Because of 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. The displacement of VEGF molecules from the compartment i to j follows:

$$U_{AV,i} \frac{d[V_{121}]_{AV,i}}{dt} = -k_{pV}^{ij} S_{ij} [V_{121}]_{AV,i} + k_{pV}^{ji} S_{ij} [V_{121}]_{AV,j} \tag{S.19}$$

which can be re-expressed in terms of $[V_{121}]_j$ by using the relationship $U_{AV,i} [V_{121}]_{AV,i} = U_i [V_{121}]_i$. Note that, for the blood compartment, $U_p = K_{AV,B} U_B$, which means that the volume of plasma is the available fluid volume for VEGF in the blood. Similarly, the equation governing VEGF₁₆₅ is:

$$\begin{aligned}
\frac{d[V_{165}]_N}{dt} = & q_{V165}^N - k_{on,V165,MEBM}^N [V_{165}]_N [M_{EBM}]_N + k_{off,V165,MEBM}^N [V_{165}M_{EBM}]_N \\
& - k_{on,V165,MECM}^N [V_{165}]_N [M_{ECM}]_N + k_{off,V165,MECM}^N [V_{165}M_{ECM}]_N \\
& - k_{on,V165,MPBM}^N [V_{165}]_N [M_{PBM}]_N + k_{off,V165,MPBM}^N [V_{165}M_{PBM}]_N \\
& - k_{on,V165,R1}^N [V_{165}]_N [R_1]_N + k_{off,V165,R1}^N [V_{165}R_1]_N - k_{on,V165,R2}^N [V_{165}]_N [R_2]_N \\
& + k_{off,V165,R2}^N [V_{165}R_2]_N - k_{on,V165,N1}^N [V_{165}]_N [N_1]_N + k_{off,V165,N1}^N [V_{165}N_1]_N \\
& - k_{pV}^{NB} \frac{S_{NB}}{U_N} \frac{[V_{165}]_N}{K_{AV,N}} + k_{pV}^{BN} \frac{S_{NB}}{U_N} \frac{U_B}{U_p} [V_{165}]_B
\end{aligned} \tag{S.20}$$

e. ligands in the blood compartment

We denote the blood compartment by the subscript B .

$$\frac{d[V_{121}]_B}{dt} = -c_{V121} [V_{121}]_B - k_{pV}^{BN} \frac{S_{NB}}{U_p} [V_{121}]_B + k_{pV}^{NB} \frac{S_{NB}}{U_B} \frac{[V_{121}]_N}{K_{AV,N}} \tag{S.21}$$

$$\frac{d[V_{165}]_B}{dt} = -c_{V165} [V_{165}]_B - k_{pV}^{BN} \frac{S_{NB}}{U_p} [V_{165}]_B + k_{pV}^{NB} \frac{S_{NB}}{U_B} \frac{[V_{165}]_N}{K_{AV,N}} \tag{S.22}$$

where c_V represents the clearance of VEGF from the blood.

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
Kinetic parameters	
q_{V121}, q_{V165}	Secretion rate of VEGF ₁₂₁ and VEGF ₁₆₅
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 ($N = \text{tissue}$; $B = \text{blood}$)
c_{V121}, c_{V165}	Clearance of VEGF ₁₂₁ and VEGF ₁₆₅ in the blood
<i>Geometric parameters</i>	
U_i	Volume of the compartment i ($N = \text{tissue}$, $B = \text{blood}$, $p = \text{plasma}$)
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

REFERENCE:

1. Stefanini MO, Wu FT, Mac Gabhann F, Popel AS (2008) A compartment model of VEGF distribution in blood, healthy and diseased tissues. BMC Syst Biol 2: 77.