Predicting monoclonal antibody pharmacokinetics following subcutaneous administration via whole-body physiologically-based modeling

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Supplementary Material

The supplementary material below includes the list of model equations. See Table 3 in the manuscript for definition of parameters and variables.

Lung

Vascular space

$$\begin{aligned} V_{vasc}^{Lung} \bullet \frac{dCIgG_{vasc}^{Lung}}{dt} &= Q^{Lung} \bullet CIgG^{Plasma} - (Q^{Lung} - L^{Lung}) \bullet CIgG_{vasc}^{Lung} \\ &- CL_{pino}^{Lung} \bullet CIgG_{vasc}^{Lung} + fIgG_{recyc} \bullet CL_{pino}^{Lung} \bullet CIgFc_{recyc}^{Lung} \\ &- PS_L^{Lung} \bullet (CIgG_{vasc}^{Lung} - CIgG_{inter}^{Lung}) \bullet \frac{Pe_L}{e^{Pe_L} - 1} - PS_S^{Lung} \bullet (CIgG_{vasc}^{Lung} - CIgG_{inter}^{Lung}) \bullet \frac{Pe_S}{e^{Pe_S} - 1} \\ &- J_L^{Lung} \bullet (1 - \sigma_L) \bullet CIgG_{vasc}^{Lung} - J_S^{Lung} \bullet (1 - \sigma_S) \bullet CIgG_{vasc}^{Lung} \end{aligned} \tag{1}$$

$$\begin{aligned} V_{vasc}^{Lung} \bullet \frac{dCmAb_{vasc}^{Lung}}{dt} &= Q^{Lung} \bullet CmAb^{Plasma} - (Q^{Lung} - L^{Lung}) \bullet CmAb_{vasc}^{Lung} \\ &- S_{pino} \bullet CL_{pino}^{Lung} \bullet CmAb_{vasc}^{Lung} + S_{pino} \bullet fIgG_{recyc} \bullet CL_{pino}^{Lung} \bullet CmAbFc_{recyc}^{Lung} \\ &- S_{diff-conv} \bullet PS_L^{Lung} \bullet (CmAb_{vasc}^{Lung} - CmAb_{inter}^{Lung}) \bullet \frac{Pe_L}{e^{Pe_L} - 1} - S_{diff-conv} \bullet PS_S^{Lung} \bullet (CmAb_{vasc}^{Lung} - CmAb_{inter}^{Lung}) \bullet \frac{Pe_S}{e^{Pe_S} - 1} \\ &- S_{diff-conv} \bullet J_L^{Lung} \bullet (1 - \sigma_L) \bullet CmAb_{vasc}^{Lung} - S_{diff-conv} \bullet J_S^{Lung} \bullet (1 - \sigma_S) \bullet CmAb_{vasc}^{Lung} \end{aligned} \tag{2}$$

Vascular Endothelial Cell Endosomal Space Sub-compartment 1 (pH=7.4)

$$\begin{aligned} \frac{dCIgG_{7.4}^{Lung}}{dt} &= (CL_{pino}^{Lung} \bullet CIgG_{vasc}^{Lung} + CL_{pino}^{Lung} \bullet CIgG_{inter}^{Lung}) / V_{endo,sub}^{Lung} \\ &+ k_{off}^{7.4} \bullet CIgFc_{7.4}^{Lung} - k_{on}^{7.4} \bullet CIgG_{7.4}^{Lung} \bullet CFcRn_{7.4}^{Lung} - \frac{1}{\tau} \bullet CIgG_{7.4}^{Lung} \end{aligned} \tag{3}$$

$$\frac{dCIgFc_{7.4}^{Lung}}{dt} = k_{on}^{7.4} \bullet CIgG_{7.4}^{Lung} \bullet CFcRn_{7.4}^{Lung} - k_{off}^{7.4} \bullet CIgFc_{7.4}^{Lung} - \frac{1}{\tau} \bullet CIgFc_{7.4}^{Lung} \tag{4}$$

$$\frac{dCmAb_{7.4}^{Lung}}{dt} = (S_{pino} \bullet CL_{pino}^{Lung} \bullet CmAb_{vasc}^{Lung} + S_{pino} \bullet CL_{pino}^{Lung} \bullet CmAb_{inter}^{Lung}) / V_{endo,sub}^{Lung}$$
$$+ k_{off}^{7.4} \bullet CmAbFc_{7.4}^{Lung} - k_{on}^{7.4} \bullet CmAb_{7.4}^{Lung} \bullet CFcRn_{7.4}^{Lung} - \frac{1}{\tau} \bullet CmAb_{7.4}^{Lung} \quad (5)$$

$$\frac{dCmAbFc_{7.4}^{Lung}}{dt} = k_{on}^{7.4} \bullet CmAb_{7.4}^{Lung} \bullet CFcRn_{7.4}^{Lung} - k_{off}^{7.4} \bullet CmAbFc_{7.4}^{Lung} - \frac{1}{\tau} \bullet CmAbFc_{7.4}^{Lung} \quad (6)$$

The concentration of the FcRn receptor in this first endosomal sub-compartment ($CFcRn_{pH\,7.4}^{Lung}$) is assumed to be constant [1].

Vascular Endothelial Cell Endosomal Space Sub-compartment 2 (pH=7.0)

$$\frac{dCIgG_{7.0}^{Lung}}{dt} = k_{off}^{7.0} \bullet CIgFc_{7.0}^{Lung} - k_{on}^{7.0} \bullet CIgG_{7.0}^{Lung} \bullet CFcRn_{7.0}^{Lung} + \frac{1}{\tau} \bullet (CIgG_{7.4}^{Lung} - CIgG_{7.0}^{Lung}) \quad (7)$$

$$\frac{dCIgFc_{7.0}^{Lung}}{dt} = k_{on}^{7.0} \bullet CIgG_{7.0}^{Lung} \bullet CFcRn_{7.0}^{Lung} - k_{off}^{7.0} \bullet CIgFc_{7.0}^{Lung} + \frac{1}{\tau} \bullet (CIgFc_{7.4}^{Lung} - CIgFc_{7.0}^{Lung}) \quad (8)$$

$$\frac{dCmAb_{7.0}^{Lung}}{dt} = k_{off}^{7.0} \bullet CmAbFc_{7.0}^{Lung} - k_{on}^{7.0} \bullet CmAb_{7.0}^{Lung} \bullet CFcRn_{7.0}^{Lung} + \frac{1}{\tau} \bullet (CmAb_{7.4}^{Lung} - CmAb_{7.0}^{Lung}) \quad (9)$$

$$\frac{dCmAbFc_{7.0}^{Lung}}{dt} = k_{on}^{7.0} \bullet CmAb_{7.0}^{Lung} \bullet CFcRn_{7.0}^{Lung} - k_{off}^{7.0} \bullet CmAbFc_{7.0}^{Lung} + \frac{1}{\tau} \bullet (CmAbFc_{7.4}^{Lung} - CmAbFc_{7.0}^{Lung}) \quad (10)$$

$$\frac{dCFcRn_{pH7.0}^{Lung}}{dt} = k_{off}^{7.0} \bullet CIgFc_{7.0}^{Lung} - k_{on}^{7.0} \bullet CIgG_{7.0}^{Lung} \bullet CFcRn_{7.0}^{Lung}$$
$$+ k_{off}^{7.0} \bullet CmAbFc_{7.0}^{Lung} - k_{on}^{7.0} \bullet CmAb_{7.0}^{Lung} \bullet CFcRn_{7.0}^{Lung} \quad (11)$$
$$+ \frac{1}{\tau} \bullet (CFcRn_{pH7.4}^{Lung} - CFcRn_{pH7.0}^{Lung})$$

The differential equations of sub-compartments 3 (pH=6.5) are similar to those of sub-compartment 2.

Vascular Endothelial Cell Endosomal Space Sub-compartment 4 (pH=6.0)

$$\frac{dCIgG_{6.0}^{Lung}}{dt} = k_{off}^{6.0} \bullet CIgFc_{6.0}^{Lung} - k_{on}^{6.0} \bullet CIgG_{6.0}^{Lung} \bullet CFcRn_{6.0}^{Lung} + \frac{1}{\tau} \bullet (CIgG_{6.5}^{Lung} - CIgG_{6.0}^{Lung}) \quad (12)$$

$$\frac{dCIgFc_{6.0}^{Lung}}{dt} = k_{on}^{6.0} \bullet CIgG_{6.0}^{Lung} \bullet CFcRn_{6.0}^{Lung} - k_{off}^{6.0} \bullet CIgFc_{6.0}^{Lung} + \frac{1}{\tau} \bullet (CIgFc_{6.5}^{Lung} - CIgFc_{6.0}^{Lung}) \quad (13)$$

$$\frac{dCmAb_{6.0}^{Lung}}{dt} = k_{off}^{6.0} \bullet CmAbFc_{6.0}^{Lung} - k_{on}^{6.0} \bullet CmAb_{6.0}^{Lung} \bullet CFcRn_{6.0}^{Lung} + \frac{1}{\tau} \bullet (CmAb_{6.5}^{Lung} - CmAb_{6.0}^{Lung}) \quad (14)$$

$$\frac{dCmAbFc_{6.0}^{Lung}}{dt} = k_{on}^{6.0} \bullet CmAb_{6.0}^{Lung} \bullet CFcRn_{6.0}^{Lung} - k_{off}^{6.0} \bullet CmAbFc_{6.0}^{Lung} + \frac{1}{\tau} \bullet (CmAbFc_{6.5}^{Lung} - CmAbFc_{6.0}^{Lung}) \quad (15)$$

$$\begin{aligned} \frac{dCFcRn_{pH\,6.0}^{Lung}}{dt} &= k_{off}^{6.0} \bullet CIgFc_{6.0}^{Lung} - k_{on}^{6.0} \bullet CIgG_{6.0}^{Lung} \bullet CFcRn_{6.0}^{Lung} \\ &+ k_{off}^{6.0} \bullet CmAbFc_{6.0}^{Lung} - k_{on}^{6.0} \bullet CmAb_{6.0}^{Lung} \bullet CFcRn_{6.0}^{Lung} \\ &+ \frac{1}{\tau} \bullet (CFcRn_{pH\,6.5}^{Lung} - CFcRn_{pH\,6.0}^{Lung}) \end{aligned} \quad (16)$$

Vascular Endothelial Cell Recycling Endosomal Space (pH=6.0)

$$\frac{dCIgFc_{recyc}^{Lung}}{dt} = \frac{1}{\tau} \bullet CIgFc_{6.0}^{Lung} - CL_{pino}^{Lung} \bullet CIgFc_{recyc}^{Lung} / V_{endo,sub}^{Lung} \quad (17)$$

$$\frac{dCmAbFc_{recyc}^{Lung}}{dt} = \frac{1}{\tau} \bullet CmAbFc_{6.0}^{Lung} - S_{pino} \bullet CL_{pino}^{Lung} \bullet CmAbFc_{recyc}^{Lung} / V_{endo,sub}^{Lung} \quad (18)$$

Interstitial Space

$$V_{inter}^{Lung}\frac{dCIgG_{inter}^{Lung}}{dt}=(1-fIgG_{recyc})\bullet CL_{pino}^{Lung}\bullet CIgFc_{recyc}^{Lung}-CL_{pino}^{Lung}\bullet CIgG_{inter}^{Lung}-(1-\sigma)\bullet L^{Lung}\bullet CIgG_{inter}^{Lung}$$
$$+PS_L^{Lung}\bullet(CIgG_{vasc}^{Lung}-CIgG_{inter}^{Lung})\bullet\frac{Pe_L}{e^{Pe_L}-1}+PS_S^{Lung}\bullet(CIgG_{vasc}^{Lung}-CIgG_{inter}^{Lung})\bullet\frac{Pe_S}{e^{Pe_S}-1}$$
$$+J_L^{Lung}\bullet(1-\sigma_L)\bullet CIgG_{vasc}^{Lung}+J_S^{Lung}\bullet(1-\sigma_S)\bullet CIgG_{vasc}^{Lung} \quad (19)$$

$$V_{inter}^{Lung}\frac{dCmAb_{inter}^{Lung}}{dt}=S_{pino}\bullet(1-FR)\bullet CL_{pino}^{Lung}\bullet CmAbFc_{recyc}^{Lung}-S_{pino}\bullet CL_{pino}^{Lung}\bullet CmAb_{inter}^{Lung}-(1-\sigma)\bullet L^{Lung}\bullet CmAb_{inter}^{Lung}$$
$$+S_{diff-conv}\bullet PS_L^{Lung}\bullet(CmAb_{vasc}^{Lung}-CmAb_{inter}^{Lung})\bullet\frac{Pe_L}{e^{Pe_L}-1}+S_{diff-conv}\bullet PS_S^{Lung}\bullet(CmAb_{vasc}^{Lung}-CmAb_{inter}^{Lung})\bullet\frac{Pe_S}{e^{Pe_S}-1}$$
$$+S_{diff-conv}\bullet J_L^{Lung}\bullet(1-\sigma_L)\bullet CmAb_{vasc}^{Lung}+S_{diff-conv}\bullet J_S^{Lung}\bullet(1-\sigma_S)\bullet CmAb_{vasc}^{Lung} \quad (20)$$

<u>Liver</u>

Vascular space

$$V_{vasc}^{Liver}\frac{dCIgG_{vasc}^{Liver}}{dt}=(Q^{GI}-L^{GI})\bullet CIgG_{vasc}^{Liver}-(Q^{Spleen}-L^{Spleen})\bullet CIgG_{vasc}^{Spleen}$$
$$-(Q^{Liver}-L^{Liver})\bullet CIgG_{vasc}^{Liver}+(Q^{Liver}-Q^{GI}-Q^{Spleen}+L^{GI}+L^{Spleen})\bullet CIgG_{vasc}^{Lung}$$
$$+fIgG_{recyc}\bullet CL_{pino}^{Liver}\bullet CIgFc_{recyc}^{Liver}-CL_{pino}^{Liver}\bullet CIgG_{vasc}^{Liver} \quad (21)$$
$$-PS_L^{Liver}\bullet(CIgG_{vasc}^{Liver}-CIgG_{inter}^{Liver})\bullet\frac{Pe_L}{e^{Pe_L}-1}-PS_S^{Liver}\bullet(CIgG_{vasc}^{Liver}-CIgG_{inter}^{Liver})\bullet\frac{Pe_S}{e^{Pe_S}-1}$$
$$-J_L^{Liver}\bullet(1-\sigma_L)\bullet CIgG_{vasc}^{Liver}-J_S^{Liver}\bullet(1-\sigma_S)\bullet CIgG_{vasc}^{Liver}$$

$$V_{vasc}^{Liver}\frac{dCmAb_{vasc}^{Liver}}{dt}=(Q^{GI}-L^{GI})\bullet CmAb_{vasc}^{Liver}-(Q^{Spleen}-L^{Spleen})\bullet CmAb_{vasc}^{Spleen}$$
$$-(Q^{Liver}-L^{Liver})\bullet CmAb_{vasc}^{Liver}+(Q^{Liver}-Q^{GI}-Q^{Spleen}+L^{GI}+L^{Spleen})\bullet CmAb_{vasc}^{Lung}$$
$$-S_{pino}\bullet CL_{pino}^{Liver}\bullet CmAb_{vasc}^{Liver}+S_{pino}\bullet fIgG_{recyc}\bullet CL_{pino}^{Liver}\bullet CmAbFc_{recyc}^{Liver} \quad (22)$$
$$-S_{diff-conv}\bullet PS_L^{Liver}\bullet(CmAb_{vasc}^{Liver}-CmAb_{inter}^{Liver})\bullet\frac{Pe_L}{e^{Pe_L}-1}-S_{diff-conv}\bullet PS_S^{Liver}\bullet(CmAb_{vasc}^{Liver}-CmAb_{inter}^{Liver})\bullet\frac{Pe_S}{e^{Pe_S}-1}$$
$$-S_{diff-conv}\bullet J_L^{Liver}\bullet(1-\sigma_L)\bullet CmAb_{vasc}^{Liver}-S_{diff-conv}\bullet J_S^{Liver}\bullet(1-\sigma_S)\bullet CmAb_{vasc}^{Liver}$$

The differential equations for the vascular endothelial cell endosomal space and interstitial space are similar to those of lung.

Other organs

Vascular space

$$
\begin{aligned}
&V_{vasc}^{Organ}\frac{dCIgG_{vasc}^{Organ}}{dt}=Q^{Organ}\bullet CIgG_{vasc}^{Organ}-(Q^{Organ}-L^{Organ})\bullet CIgG_{vasc}^{Organ}\\
&-CL_{pino}^{Organ}\bullet CIgG_{vasc}^{Organ}+fIgG_{recyc}\bullet CL_{pino}^{Organ}\bullet CIgFc_{recyc}^{Organ}\\
&-PS_{L}^{Organ}\bullet(CIgG_{vasc}^{Organ}-CIgG_{inter}^{Organ})\bullet\frac{Pe_L}{e^{Pe_L}-1}-PS_{S}^{Organ}\bullet(CIgG_{vasc}^{Organ}-CIgG_{inter}^{Organ})\bullet\frac{Pe_S}{e^{Pe_S}-1}\\
&-J_{L}^{Organ}\bullet(1-\sigma_L)\bullet CIgG_{vasc}^{Organ}-J_{S}^{Organ}\bullet(1-\sigma_S)\bullet CIgG_{vasc}^{Organ}
\end{aligned}
\tag{23}
$$

$$
\begin{aligned}
&V_{vasc}^{Organ}\frac{dCmAb_{vasc}^{Organ}}{dt}=Q^{Organ}\bullet CmAb_{vasc}^{Organ}-(Q^{Organ}-L^{Organ})\bullet CmAb_{vasc}^{Organ}\\
&-S_{pino}\bullet CL_{pino}^{Organ}\bullet CmAb_{vasc}^{Organ}+S_{pino}\bullet fIgG_{recyc}\bullet CL_{pino}^{Organ}\bullet CmAbFc_{recyc}^{Organ}\\
&-S_{diff-conv}\bullet PS_{L}^{Organ}\bullet(CmAb_{vasc}^{Organ}-CmAb_{inter}^{Organ})\bullet\frac{Pe_L}{e^{Pe_L}-1}-S_{diff-conv}\bullet PS_{S}^{Organ}\bullet(CmAb_{vasc}^{Organ}-CmAb_{inter}^{Organ})\bullet\frac{Pe_S}{e^{Pe_S}-1}\\
&-S_{diff-conv}\bullet J_{L}^{Organ}\bullet(1-\sigma_L)\bullet CmAb_{vasc}^{Organ}-S_{diff-conv}\bullet J_{S}^{Organ}\bullet(1-\sigma_S)\bullet CmAb_{vasc}^{Organ}
\end{aligned}
\tag{24}
$$

The differential equations for the vascular endothelial cell endosomal space and interstitial space are similar to those of lung.

References

1. Li T, Balthasar JP (2019) Application of Physiologically Based Pharmacokinetic Modeling to Predict the Effects of FcRn Inhibitors in Mice, Rats, and Monkeys. J Pharm Sci 108:701–713. https://doi.org/10.1016/j.xphs.2018.10.065