Computational model of the intra-pulmonary distribution of nanocarriers in a mouse model of spatially heterogeneous ARDS

Model Structure and Parameters

A semi-physiologic model was used to describe the disposition of nanocarriers in healthy and unilateral LPS mice (Figure 1). Briefly, carriers were administered into the central compartment (V_1) and were able to be directly administered from this space by a linear clearance term (CL). Distribution of carriers between the central compartment and the tissue of interest (lung) was governed by a physiologically relevant blood flow rate (Q_{co}). The lung was further subdivided into spaces representing the left lung, superior lobe, and remainder, whose volume and blood flows were described using experimentally measured values to allow for relevant changes between healthy and diseased animals. Target interaction within each lung space was assumed to occur under equilibrium conditions and was governed by the equilibrium dissociation constant (K_D) and the basal target expression (*ICAM, PECAM*). Elimination of carriers via target-mediated processes was assumed to be negligible over the studied time course (e.g. the time required for binding, internalization, degradation, and radiolabel efflux is greater than the time course of the study). In healthy tissues, due to the large size of carriers (~150 nm) relative to endothelial pore sizes (~5 nm) [1], it was assumed that no extravasation of carriers would occur. However, due to increased endothelial permeability in unilateral LPS mice, it was assumed that a fraction of carriers could directly enter the interstitium of the inflamed lobe via convective transport, governed by lymph flow (L), set at 0.2% of plasma flow, consistent with physiologically-based pharmacokinetic (PBPK) models developed for antibody therapeutics [2], and a vascular reflection coefficient (σ_{lu}). Using pore theory calculations described by Levick and Michel [3], the reflection coefficient was calculated for a theoretical pore size of 500 nm, representing a 100-fold increase in pore size, to describe enhanced capillary leak in the unilateral LPS model. When available, parameters were obtained from the literature and fixed to relevant values (Table 1). In order to estimate unknown parameters (CL, V_1, and K_D), the model was fit to blood and lung pharmacokinetic data for PECAM-targeted liposomes in healthy mice.

Model Evaluation

To evaluate the predictive capacity of the model, simulations (with no additional fitting of parameters) were performed in healthy and in unilateral LPS mice to describe the blood and lung distribution of IgG, ICAM-targeted, and PECAM-targeted liposomes. From the simulated values PATH ratios were calculated for all three carriers and compared to observed data.

Sensitivity Analysis

In order to generate hypotheses regarding critical parameters controlling nanocarrier disposition in ARDS, a sensitivity analysis was performed wherein parameters related to non-specific elimination (CL), target expression (*ICAM, PECAM*), hypoxic vasoconstriction (blood flow and vascular volume), and vascular permeability (σ_{lu}) were individually altered 2-fold and PATH ratios were compared to the base parameter values. For example, it was shown experimentally that ICAM expression increased 3.6-fold following LPS administration, so sensitivity was evaluated for 7.2-fold and 1.8-fold increases in this parameter relative to healthy tissue. Fractional changes in PATH ratio from initial values were calculated to determine sensitivity of the model to select parameters.

Figure 1: Semi-physiologic model for nanoparticle distribution in unilateral LPS mice

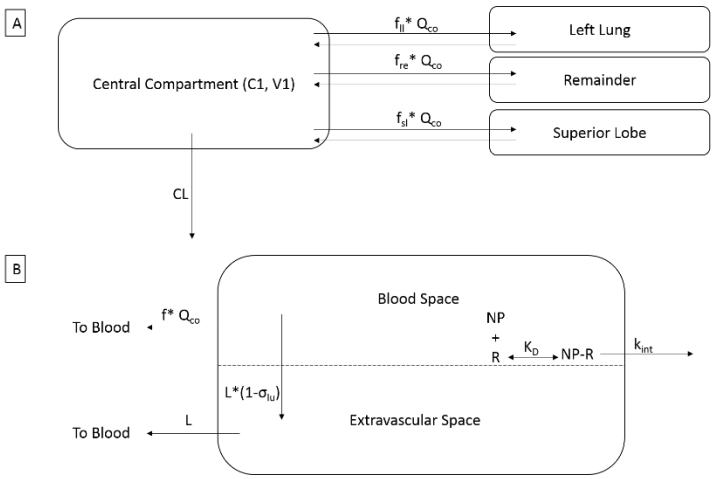


Table 1: Fixed parameters in semi-physiologic model

Parameter	Healthy	ARDS
Q_{co} (mL/min)[a]	10.09	
fQ_{ll}[b]	0.30	0.38
fQ_{sl}[b]	0.19	0.11
fQ_{re}[b]	0.51	
V_{ll} (mL)[b]	0.0474	0.0455
V_{sl} (mL)[b]	0.0259	0.0510
V_{re} (mL)[b]	0.0753	0.0714
Vv_{ll} (mL)[c]	0.0125	0.0158
Vv_{sl} (mL)[c]	0.00685	0.00397
Vv_{re} (mL)[c]	0.0115	0.0189
ICAM (μmoles/mL)[d]	0.00116	0.00417
PECAM (μmoles/mL)[d]	0.000667	0.000400
σ_{lu}	0.000	0.687

[a]Obtained from BioDMET database and scaled to a 25 g mouse (https://pdsl.research.ge.com/)
[b]Obtained from experimental results
[c]Values for healthy animals obtained from BioDMET database and scaled to 25 g mouse, values for ARDS mice obtained by scaling changes with changes in relative blood flow
[d]Values derived from [4]

Model Fitting Results

The model was fit to data for anti-PECAM liposomes administered to healthy mice to obtain estimates of several parameters (CL, V_1, K_D). The model was able to estimate parameters with good confidence and was able to reasonably well characterize the observed data.

Table 2: Final Parameter Estimates

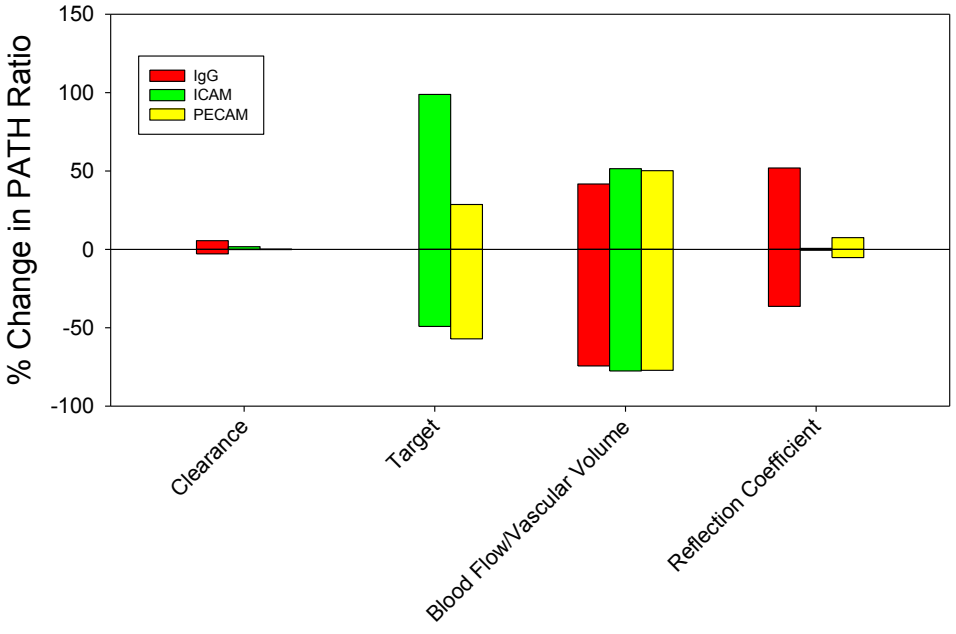
Parameter	**Estimate (CV%)**
CL (mL/minute)	0.0321 (13.4%)
V_1 (mL)	6.80 (8.74%)
K_D (μmoles/mL)[a]	5.54×10^{-6} (13.93%)

[a]K_D represents the affinity of the conjugated antibody molecules for the target, the estimated value is calculated to be 5.54 nM

Model Validation
Simulations were performed with the model to calculate PATH ratios at 30 minutes for IgG, anti-ICAM, and anti-PECAM liposomes using the previously identified parameters. The **model predicted PATH ratios were 2.54, 1.66, and 0.316, for IgG, anti-ICAM, and anti-PECAM liposomes**, respectively. These values are similar to the experimentally measured values, and follow the observed trend of PATH ratios for the various targeting strategies.

Sensitivity Analysis
A sensitivity analysis was performed to assess the dependence of the calculated PATH ratio on select parameters. It is immediately noted that there is minimal sensitivity to clearance, suggesting that the rate of non-specific elimination of a particle does not affect the relative lung distribution between healthy and unilateral LPS mice. However, disease-specific parameters were shown to have an impact on the PATH ratio, as shown by the sensitivity of model-predicted PATH ratios to changes in target expression, blood flow/vascular volume, and the reflection coefficient in inflamed tissue. This allows for a ranking of the relative importance of a given parameter for a specific targeting moiety. Each parameter can be related to a given disease parameter: change in target expression, hypoxic vasoconstriction (blood flow/vascular volume), and capillary leak (reflection coefficient). For untargeted (IgG coated) liposomes, the rank order was (1) capillary leak, (2) hypoxic vasoconstriction, and (3) change in target expression. For ICAM-targeted particles, this order was (1) change in target expression, (2) hypoxic vasoconstriction, and (3) capillary leak. Finally, for PECAM-targeted particles, the rank order was (1) hypoxic vasoconstriction, (2) change in target expression, and (3) capillary leak. The model-predicted dominant mechanism for altered lung distribution for each targeting moiety is in agreement with the hypotheses generated from the experimental data.

Figure 2: Sensitivity of PATH Ratio to Select Parameters



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