

FcRn-Mediated IgG Kinetics: Parameterization of an FcRn Submodel Within a Physiologically Based Pharmacokinetic Model

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In recent years FcRn (neonatal Fc Receptor) has been shown to play a major role in IgG kinetics. Expressed within endothelial cells lining the microvasculature of muscle, skin, and liver, FcRn rescues IgG from an intracellular lysosomal degradation pathway by binding to the Fc region of the immunoglobulin molecule and recycling it back into plasma. This mechanism of Fc-mediated IgG regulation has generated much excitement in the therapeutic monoclonal antibody (mAb) research community, since FcRn binding sites within therapeutic mAbs could conceivably be manipulated in order to improve drug efficacy. Examples of such drugs are Rituxan and Herceptin, used to treat B-cell lymphomas and certain types of breast cancer, respectively. Based on a previously published model, we have constructed a novel mathematical description of the FcRn mechanism in the context of a larger physiologically based pharmacokinetic model describing mAb flux through blood and major organs (fig. 1 & 2). Unknown model parameters, including FcRn submodel parameters, were successfully fit to biodistribution data of anti-CEA mAbs (cT84.66) in tumor bearing nude mice, resulting in a superior fit of model to data than previously seen. Subsequent to the parameterization process, the model was successfully used to *predict* the biodistribution of cT84.66 F(ab')₂ fragments, which cannot interact with FcRn due to the lack of a mAb Fc region. This model has several major, potential uses: *a)* aid in the design of therapeutic mAbs and other Fc-conjugated protein-based therapeutics by simulating the pharmacokinetic effect of attenuating or augmenting FcRn affinity of the drug; *b)* maximize drug efficacy by optimizing patient dosing schedules; requires scaling of model parameters from animal to human; *c)* optimize dosing for imaging purposes; maximize tumor-background ratio.

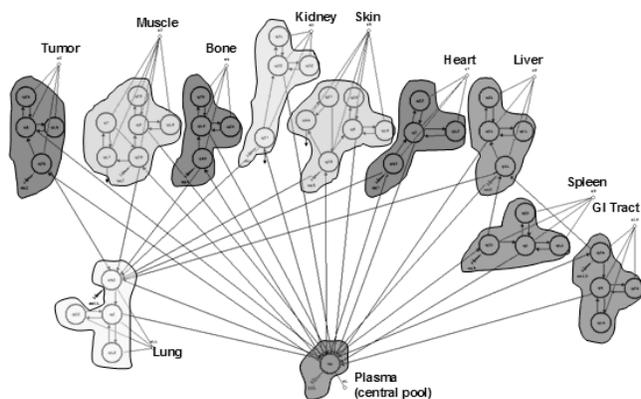


Figure 1. Schematic representation of the physiologically-based pharmacokinetic model.

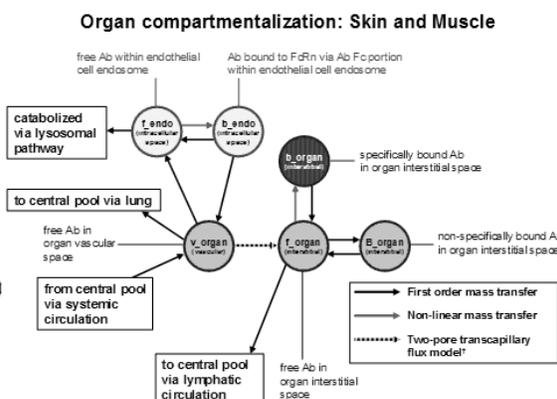


Figure 2. Schematic representation of organ pool composition; skin and muscle, each containing an FcRn submodel.

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