

**Title:** Physiologically-based pharmacokinetic modelling of dendrimer nanoparticles to unravel structure – PK parameters relationships

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**Background and Objectives:** Nanoparticles (NPs) have been developed for over two decades in order to improve the pharmacokinetic (PK) profile of drugs and to target specific tissues. The diversity of NPs in terms of structures and properties results in specific PK behaviors. Physiologically-based pharmacokinetic (PBPK) modeling is a powerful tool to predict PK of NPs by integrating parameters describing physiological and biological processes, as well as physicochemical parameters. This approach will allow to better understand the impact of NPs characteristics on the *in vivo* disposition. In the current work, a theoretical PBPK model was developed for gallium-68 radiolabeled-dendrimers to better understand the link between their physicochemical characteristics and their PK properties.

**Methods:** A PBPK model tailored to NPs (nanoPBPK) was developed using R software (4.2.2), including a specific compartmental structure based on the current understanding<sup>1-3</sup> of the PK of NPs. When available, parameter values from the literature were used in the equations. Experimental *in vivo* data previously obtained for seven formulations of dendrimers varying in the length of the alkyl chain, fluorination and presence of RGD, and developed by CINaM and CERIMED<sup>4</sup>, were used for model evaluation and refinement. The data consisted in blood samples (n=6) and PET images (n=6) collected at 9 and 12 time points respectively after intravenous injection in healthy mice. A semi-mechanistic population PK analysis<sup>5</sup> of the data allowed to decipher renal and hepatic clearances as well as partition coefficient values which were integrated in the PBPK model. NPs-specific parameters highly influencing concentrations of dendrimers over time in plasma and organs were identified, allowing to establish relationships between NPs properties and their PK.

**Results:** A nanoPBPK model with both renal and hepatic clearance was built, which included mononuclear phagocyte system sub-compartments for organs such as lungs, spleen and liver. A permeability-limited model was used to describe distribution in tissues. The *a priori* nanoPBPK model well described the evolution of concentrations of dendrimers in plasma and tissues. Partition coefficient and permeability coefficient were found to be the most influential parameters. The parameters were refined in the PBPK model to obtain more accurate predictions, linking structural characteristics of dendrimers to their PK.

**Conclusions:** The PBPK model provided a good description of the experimental data and a breakthrough mechanistic insight into the processes involved in the distribution and elimination of dendrimers. The current work allowed to bridge NPs structural properties with biological properties and *in vivo* behavior. The next step will be the extension of the PBPK model to non-dendrimeric nanoparticle types, such as lipid nanocapsules, in order to provide a generic tool to guide the design of future innovative NPs.

**References:**

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