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Title: Development of a physiologically-based pharmacokinetic model to understand and predict the disposition of gallium-68 radiolabeled-dendrimers *in vivo*

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Introduction/Objectives: In the past twenty years, numerous diverse nanoparticles (NPs) have been designed in order to improve the pharmacokinetic (PK) profile of drugs and to target specific tissues. However, the multi-functionalities and specific properties of NPs result in challenges to understand the mechanisms driving their PK behavior. Physiologically-based pharmacokinetic (PBPK) modeling is a powerful tool to better understand and predict PK of NPs as well as the impact of their properties on the *in vivo* disposition. PBPK models integrate generic parameters describing physiological processes, physicochemical parameters and mixed parameters including biological processes. To date, few PBPK models tailored to NPs (nanoPBPK) have been reported, usually lacking crucial biological processes such as opsonization or the role of the mononuclear phagocyte system (MPS)¹⁻³ in distribution and elimination of NPs. In addition, influential parameters are often estimated *a posteriori* to fit the experimental data, making it difficult to predict the PK. In the current work, a PBPK model was developed to describe the pharmacokinetics and biodistribution of gallium-68 radiolabeled-dendrimers. The most influential parameters were identified by a sensitivity analysis and measured *in vitro* when possible.

Methods: A theoretical PBPK model tailored to NPs was built using R software (4.2.2), with a specific compartmental structure based on the current understanding 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^{4,5}, were used for model evaluation and refinement. The data consisted in blood samples (n=6) and PET images (n=6) collected at 12 time points after intravenous injection in mice. A previous semi-mechanistic population PK analysis of the data allowed to decipher renal and hepatic clearances as well as partition coefficient values to be fed in the PBPK model. A sensitivity analysis was carried out to identify NPs-specific parameters that highly influenced dendrimers distribution (specifically concentrations over time in organs and plasma) and for which accurate values were consequently needed.

Results: A PBPK model with both renal and hepatic clearance was built, which included MPS sub-compartments for organs such as lungs, spleen and liver. A permeability-limited model was used to describe distribution in tissues. The PBPK model well described dendrimer biodistributions in plasma and tissues in mice. The non-fitted *a priori* PBPK model well described the evolution of concentrations of dendrimers in plasma and tissues. Opsonization and permeability coefficient were found to be the most influential parameters. Permeability was measured on Caco-2 cells, while opsonization would be indirectly quantified based on the complement system activation. The parameters were updated 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. The current work allowed to bridge NPs structural properties with *in vitro* biological properties and *in vivo* behavior, and provides a breakthrough mechanistic insight into the processes involved in the distribution and elimination of dendrimers. The next step will be the extension of the PBPK model to non-dendrimer nanoparticle types, in order to provide a generic tool to guide the design of future innovative NPs.

References:

- [1] Yuan, D.; He, H.; Wu, Y.; Fan, J.; Cao, Y. Physiologically Based Pharmacokinetic Modeling of Nanoparticles. *J. Pharm. Sci.* **2019**, *108* (1), 58–72.
- [2] Utembe, W.; Clewell, H.; Sanabria, N.; Doganis, P.; Gulumian, M. Current Approaches and Techniques in Physiologically Based Pharmacokinetic (PBPK) Modelling of Nanomaterials. *Nanomaterials* **2020**, *10* (7), 1267.
- [3] Kutumova, E. O.; Akberdin, I. R.; Kiselev, I. N.; Sharipov, R. N.; Egorova, V. S.; Syrocheva, A. O.; Parodi, A.; Zamyatnin, A. A.; Kolpakov, F. A. Physiologically Based Pharmacokinetic Modeling of Nanoparticle Biodistribution: A Review of Existing Models, Simulation Software, and Data Analysis Tools. *Int. J. Mol. Sci.* **2022**, *23* (20), 12560.
- [4] Garrigue, P.; Tang, J.; Ding, L.; Bouhleb, A.; Tintaru, A.; Laurini, E.; Huang, Y.; Lyu, Z.; Zhang, M.; Fernandez, S.; Balasse, L.; Lan, W.; Mas, E.; Marson, D.; Weng, Y.; Liu, X.; Giorgio, S.; Iovanna, J.; Pricl, S.; Guillet, B.; Peng, L. Self-Assembling Supramolecular Dendrimer Nanosystem for PET Imaging of Tumors. *Proc. Natl. Acad. Sci.* **2018**, *115* (45), 11454–11459.
- [5] Ding, L.; Lyu, Z.; Louis, B.; Tintaru, A.; Laurini, E.; Marson, D.; Zhang, M.; Shao, W.; Jiang, Y.; Bouhleb, A.; Balasse, L.; Garrigue, P.; Mas, E.; Giorgio, S.; Iovanna, J.; Huang, Y.; Pricl, S.; Guillet, B.; Peng, L. Surface Charge of Supramolecular Nanosystems for In Vivo Biodistribution: A MicroSPECT/CT Imaging Study. *Small* **2020**, *16* (37), 2003290.