Pharmacokinetic Variability of Long-circulating Nanomaterials: Insights into its Origins and Neglected Importance in Rodent Models

Rodent models fulfill several roles in the preclinical testing of novel nanomaterial-based drug delivery systems, including screening for drug pharmacokinetics, efficacy, toxicity, etc. Since the success of nanomaterial formulations are often judged on their pharmacokinetic uniformity, experimental reproducibility in rodent models is critical. However, in the context of many clinical nanomaterials, significant interpatient pharmacokinetic variability is routinely observed and is believed to significantly contribute to the failure of some nanomedicines in the early clinical phase [1]. Thus, a paradox exists wherein the rodent models and benchmarks/expectations used for evaluating the success of nanomaterials—i.e., consistent and long-circulating pharmacokinetics—are unrepresentative and potentially misleading of behaviors observed in patients.

To address this paradox, our team investigated the origins of pharmacokinetic variability of long-circulating nanomaterials in rodent models from among experimental factors (dose level) and animal model characteristics (sex, weight, strain, pathology). We analysed post hoc the plasma pharmacokinetic profiles of porphyrin-lipid based nanomaterials (Porphysomes) from over 200+ rodent models. Our findings revealed the greatest influences on Porphysome pharmacokinetic variability were dose level, model pathology (e.g., healthy vs tumour-bearing) and sex. Although our analysis was limited from identifying the mechanisms underlying the observed variability, our findings highlight the importance of its consideration for accurately assessing nanomaterial pharmacokinetics and for developing models to predict profiles in patients using rodent datasets.