Intestinal lymphatic transport of lipids and drugs scales allometrically from preclinical models to human patients

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Advances in understanding of the role that lymphatics play in diseases such as cancer, inflammatory and metabolic diseases has prompted increasing interest in lymphatic drug delivery[1]. The potential to translate lymphatic delivery strategies into the clinic is however impeded by incomplete understanding of the drivers of lymph uptake and secondly, the inability to quantify or predict lymph uptake in human patients because of the invasive procedures required to collect lymph. The current study aimed to: i) collect intraoperative thoracic lymph from human patients, ii) compare intestinal lymph flow, lipid and drug transport across preclinical species and humans for the first time, and iii) develop models to predict intestinal lymph flow, lipid and drug transport in patients. An intraoperative thoracic lymph duct cannulation method was used in human patients for postoperative serial sampling. Mice, rats, dogs and the patients were administered lipid feed +/- model lipophilic drug (halofantrine or α-tocopherol) at different rates into the intestine, and mesenteric or thoracic lymph was collected. Lymph flow rate, triglyceride (TG) and drug concentrations were measured. Surprisingly, lymph flow rate, TG and drug transport (Fig 1) increased with body weight and scaled allometrically according to the equations: $L = aM^{0.93}$ and $D = bM^{0.3}$ (where L is rate of fluid or lipid transport into lymph (ml/h or mg/h), D is the proportion of the drug dose transported into lymph (% dose), M is the body mass of the animal (kg) and *a* and *b* are constants). The flow rate of blood through the portal vein, and indeed all veins in the body, is also widely reported to scale allometrically with an exponent of 0.75[2]. Thus, the reason that intestinal lymphatic drug uptake increases with species body weight is likely due to the increase in the ratio of lymph:blood flow with size. Overall these data suggest that lymph flow, lipid and drug uptake in humans can be predicted from data in pre-clinical species via allometric scaling and that lymphatic drug uptake is significantly greater (4-5 fold) in humans when compared to small animal species.

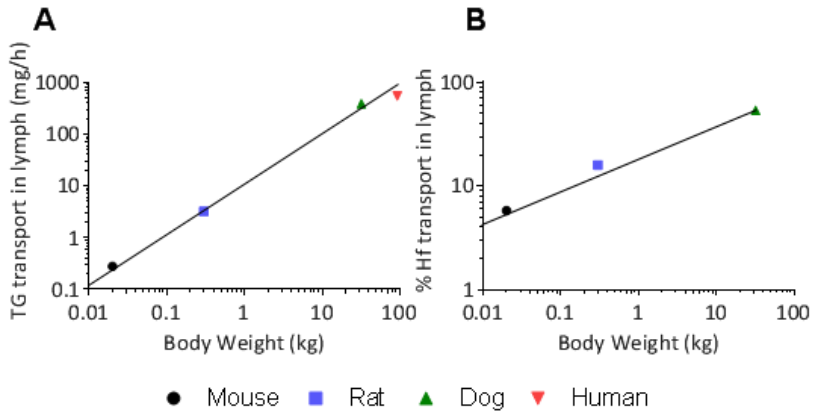

Figure 1: Allometric scaling of (A) TG lymph transport rate (mg/h) and (B) % Hf transport in fasted state versus body weight (kg) across species.

[1] Trevaskis NL et al. *Nat Rev Drug Discov* **2015**, *14*, 781-803.
[2] West GB et al. *Proc Natl Acad Sci USA* **2002**, *99*, 2473-8.

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