

TITLE

Mechanistic Investigation of the Pre-Clinical Pharmacokinetics and Interspecies Scaling of PF-05231023, a Fibroblast Growth Factor 21-Antibody Protein Conjugate

Craig Giragossian, Chandra Vage, Jun Li, Kathleen Pelletier, Nicole Piché-Nicholas, Manoj Rajadhyaksha, Jennifer Liras, Alison Logan, Roberto Calle, Yan Weng

Pfizer Inc., Eastern Point Road, Groton, CT (C. G., C. V., J. L., K. P., M. R., A.L.) and Cambridge MA (N.P.N., J. L., R. C., Y. W.)

Supplemental Table 1. Compilation of lymph flow rates from literature and estimated blood/lymph ratios

| Species | Lymph Duct | Lymph Flow Rate mL/h/kg | Blood Flow Rate mL/min/kg | Blood/Lymph Ratio | Reference |
|---------|---------------|-------------------------|---------------------------|-------------------|---|
| Rabbit | Heart | 0.1 | 6.4 | 3840 | Ups J Med Sci (1979) 84, 129-36 |
| Canine | Beating Heart | 0.04 to 0.1 | 5.4 | 4629 | Physiol Rev (1963) 43, 115-213 |
| Rat | Hepatic | 0.4 ± 0.3 | 80 | 12000 | Blood (1950), 5, 177-90 |
| Rat | Hepatic | 0.5 | 80 | 9600 | Am J Physiol (1956) 184, 11-7 |
| Rabbit | Hepatic | 0.26 ± 0.02 | 71 | 16385 | J Clin Chem Clin Biochem (1986) 24, 19-33 |
| Feline | Hepatic | 0.73 ± 0.06 | 27 | 2219 | Quart J Exp Physiol (1956) 41, 318-25 |
| Canine | Hepatic | 0.8 to 1.2 | 40 | 2400 | Physiol Rev (1963) 43, 115-213 |
| Canine | Hepatic | 0.50 ± 0.06 | 40 | 4800 | J Clin Chem Clin Biochem (1986) 24, 19-33 |
| Rat | Intestine | 4.7 ± 1.3 | 30 | 383 | Blood (1950), 5, 177-90 |
| Rat | Intestine | 2.8 ± 0.2 | 30 | 643 | J Clin Chem Clin Biochem (1986) 24, 19-33 |
| Rat | Intestine | 16.3 ± 5.5 | 30 | 110 | Contemp Top Lab Anim Sci (1998) 37, 56-8 |
| Rat | Intestine | 6.6 ± 3.0 | 30 | 273 | J Pharmacol Toxicol Methods (2004) 49, 115-20 |
| Rabbit | Intestine | 1.5 ± 0.1 | 44 | 1760 | J Clin Chem Clin Biochem (1986) 24, 19-33 |
| Feline | Intestine | 1.54 ± 0.10 | 20 | 779 | Quart J Exp Physiol (1956) 41, 318-25 |
| Canine | Intestine | 2.3 ± 0.1 | 22 | 574 | J Clin Chem Clin Biochem (1986) 24, 19-33 |
| Rat | Spleen | 0.32 ± 0.07 | 2.5 | 473 | J Immunol (2010) 184, 4547-56 |
| Canine | Spleen | 0.0075 to 0.03 | 2.5 | 8000 | Physiol Rev (1963) 43, 115-213 |
| Rat | Thoracic | 4.9 ± 3.6 | 80 | 980 | Blood (1950), 5, 177-90 |
| Rat | Thoracic | 4.2 ± 0.2 | 80 | 1143 | J Clin Chem Clin Biochem (1986) 24, 19-33 |
| Rat | Thoracic | 10.7 ± 0.6 | 80 | 449 | J Clin Chem Clin Biochem (1986) 24, 19-33 |
| Rat | Thoracic | 5.0 ± 0.4 | 80 | 960 | J Clin Chem Clin Biochem (1986) 24, 19-33 |
| Rat | Thoracic | 7.6 | 80 | 632 | Microsurgery (2003) 23, 239-245 |
| Rat | Thoracic | 34.5 ± 6.9 | 80 | 139 | J Pharmacol Toxicol Methods (2004) 49, 115-20 |
| Rat | Thoracic | 2.0 to 2.4 | 80 | 2750 | Annals of Surgical Oncology (1996) 3, 329-35 |
| Rabbit | Thoracic | 2.9 ± 0.3 | 71 | 1469 | J Clin Chem Clin Biochem (1986) 24, 19-33 |
| Rabbit | Thoracic | 5.4 ± 0.4 | 71 | 789 | J Clin Chem Clin Biochem (1986) 24, 19-33 |
| Rabbit | Thoracic | 3.2 ± 0.3 | 71 | 1331 | J Clin Chem Clin Biochem (1986) 24, 19-33 |
| Feline | Thoracic | 2.42 ± 0.12 | 27 | 669 | Quart J Exp Physiol (1956) 41, 318-25 |
| Canine | Thoracic | 1.5 ± 0.2 | 31 | 1240 | J Clin Chem Clin Biochem (1986) 24, 19-33 |
| Canine | Thoracic | 3.6 ± 0.4 | 31 | 517 | J Clin Chem Clin Biochem (1986) 24, 19-33 |
| Human | Thoracic | 2.3 ± 1.4 | 20 | 522 | Gut (1974) 15, 903-6 |
| Human | Thoracic | 2.9 ± 1.1 | 20 | 414 | Gut (1974) 15, 903-6 |
| Human | Thoracic | ~0.9 | 20 | 2400 | Gut (1974) 15, 903-6 |
| Human | Thoracic | 5.3 ± 2.8 | 20 | 226 | N Engl J Med (1960) 263, 471-4 |
| Human | Thoracic | 1 to 2 | 20 | 1650 | JOP (2007) 8, 374-99 |
| Human | Thoracic | 0.7 to 1.6 | 20 | 750 | Annals of Surgical Oncology (1996) 3, 329-35 |

Note: liver blood flow rate was conservatively used for thoracic duct

Supplemental Figure 1. Comparison between PBPK model fits and mean 2CMT parameters for a set of human mAbs in rat (n=8), monkey (n=9) and human (n=6). Mean alpha/beta phase half-lives were 6.6/259 hr, 12/225 hr and 29/449 hr in rats, monkeys and humans, respectively.

