GENETICALLY ENGINEERED MOUSE MODEL USED AS AN ALTERNATIVE SCREENING METHOD FOR EVALUATING P-GLYCOPROTEIN SUBSTRATE TOXICITY IN AVERMECTIN-SENSITIVE DOGS

Technology Summary

A pitfall to avermectins is central nervous system (CNS) toxicities in herding dogs. As a result, all new avermectins must be tested in a "Collie Safety Study" to determine the degree of CNS toxicity. The toxicity is due to a 4 base pair mutation in the ATP-binding cassette, sub-family B member 1 (ABCB1) gene. This gene encodes for the P-glycoprotein (P-gp) that affects absorption, distribution, and elimination of certain drugs.

Researchers at FDA have developed an alternate animal model that includes two transgenic mouse models, one containing the mutant form of the canine ABCB1 gene (Yancy 1 line) and the other containing the canine wild-type gene (Yancy 2 line). The paired mouse system can be utilized to assess the safety of avermectins and other canine drugs by determining the toxicity to canines with the mutated form of the ABCB1 gene. Ivermectin, a derivative of the avermectin family of heartworm drugs used to treat and control parasitic infections, was used to verify this mouse model. This technology will enhance the population predictions derived from clinical safety data and serve to reduce the use of dogs in avermectin derivative safety studies that are part of the Investigational New Animal Drug (INAD) approval process.

Potential Commercial Applications

- Drug screening technology to assess the toxicity of canine drugs to canines with the mutated form of the ABCB1 gene.

Competitive Advantages

- Use as an alternative in vivo model to canines for assessment of drug safety in the presence of the ABCB1 mutation.

Development Stage: In vivo data available

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Publications:

- Myers, MJ. et. al. Impact of ABCB1 genotype in Collies on the pharmacokinetics of R- and S-fexofenadine. J Vet Pharmacol Ther. 2018 Dec;41(6):805-814.PMID: 30020547
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- Identification of potential biomarkers of P-glycoprotein substrate neurotoxicity in transgenic mice expressing the mutated canine ABCB1 gene. Am J Vet Res. 2014 Dec;75(12):1104-10. PMID: 25419811
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- Orzechowski K, et al., Neurotoxic effects of ivermectin administration in genetically engineered mice with targeted insertion of the mutated canine ABCB1 gene. Am J Vet Res. 2012 Sep;73(9):1477-84. PMID: 22924731

Product Area: Research materials, mouse model

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