Proceedings of the 8th International Symposium on Canine and Feline Reproduction

ISCFR

June 22-25, 2016
Paris, France

In a joint meeting with the XIX EVSSAR Congress

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Gene therapy with Mullerian inhibiting substance as a female dog and cat contraceptive with lifetime suppression of fertility

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Mullerian Inhibiting Substance (MIS) is a paracrine hormone secreted by granulosa cells of early growing follicles which maintains follicular homeostasis by exerting negative feedback on the recruitment of new primordial follicle into the growing pool. To evaluate the contraceptive potential of exogenous MIS in vivo, we engineered a novel peptide analog of MIS with a modified Leader sequence and a Q425R substitution in its activating C-terminal cleavage site, called LR-MIS (1). This highly secreted and cleaved LR-MIS transgene was introduced into an AAV9 gene therapy vector, which can infect muscle cells and confer lifetime expression of a therapeutic protein at high levels (2). When female mice were treated with a single injection of 3E11 particles of AAV9-LR-MIS we observed a complete block of folliculogenesis at the primordial follicle stage, with no detectable growing preantral, antral follicle, or corpus luteum 39 days after administration. Mice subsequently stopped cycling as evidenced by vaginal cytology and were completely infertile when continuously paired with proven male breeders for up to a year. This inhibitory effect could be seen with doses as low as 1E11 particles per mouse. Evaluation of a panel of clinical toxicology blood markers including ALT/AST, CK, amylase and examination of vital organ cytology and general wellness indicated that LR-MIS was very well tolerated during continuous stable expression for up to a year. The favorable safety profile was predicted by the limited expression of the MIS receptor (MISR2) and the comparatively high circulating levels of MIS in prepubescent males. The dramatic effect of AAV9-LRMIS on the ovaries of mice and their fertility predicts that MIS will be an ideal permanent contraceptive for cats and dogs with limited long-term side effects thanks to its high level of specificity to the gonads.
