AAV-Vectored Generation of GnRH-Binding Immunoglobulins for Non-Surgical Sterilization of Domestic Cats

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Gonadotropin Releasing Hormone (GnRH) is required for both gametogenesis and sex-steroid production. It is considered the master regulator of reproduction, and as such, is an attractive candidate for non-surgical sterilization studies. Empirically, GnRH has been targeted with immunocontraceptives that vaccinate an animal against endogenous GnRH. The major drawback to this approach is the transitory nature of the contraceptive effects. Thus, a critical need still exists to develop a non-surgical sterilant that can persist throughout the life of the animal without requiring a booster vaccination. Previous research in the mouse demonstrated that a high affinity anti-GnRH monoclonal antibody (SMI41) expressed in a recombinant adeno-associated viral (AAV) vector was both safe and effective in producing long-term infertility in males and females (Li et al. 2015. Curr. Biol. 25: R820-22). The objective of this study was to determine if AAV2/8 vectored expression of SMI41 could induce long-term infertility in the domestic cat (*Felis silvestris catus*). Three female cats received $3.4x10^{13}$ viral particles via an intramuscular injection of the caudal thigh muscles. SMI41 titer levels were determined using an in-house developed ELISA. Fecal hormone monitoring of estradiol (E2) and progesterone (P4) metabolites was used to assess three time periods: pre-treatment (4 months before injection), treatment (day 7–day 30), and post-treatment (month 1–month 6). Consistent among the three cats, there were no injection site reactions, adverse events, or off-target effects of the construct throughout the six month post-injection observation period. All three cats had detectable SDMI41 antibody titer before injection (9.7±6.3µg/ml). Titer levels peaked approximately seven days after injection (19.4±3.5µg/ml) and returned to baseline by one month post-injection (11.9±6.4µg/ml). Both E2 and P4 concentrations trended slightly lower during the treatment period, but neither reduction was significant (E2-treatment: 98.4 ng/g dried feces, E2-pre: 106.2, E2-post: 129.1, p=0.4065; P4-treatment: 18957.9, P4-pre: 24168.7, P4-post: 21935.0, p=0.0914). In the mouse, threshold titer level to produce infertility was 200ug/ml. Cat titer levels were well below that value and this likely explains the lack of ovarian suppression. Preliminary tests showed the cats were producing antibodies against the framework of SMI41. In conclusion, we were able to express a functional GnRH antibody in the cat using a recombinant AAV-vectored approach without comprising the safety or welfare of the animals. However, due to the suspected immunogenicity of the anti-GnRH antibody, the threshold titer level to inhibit ovarian cyclicity could not be achieved. Funded by the Joanie Bernard Foundation and CalTech.