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Brenda Griffin

Scott-Ritchey Research Center

Baker Henry

Scott-Ritchey Research Center

Welles Elizabeth

Auburn University

Lowell Miller

USDA/APHIS/WS National Wildlife Research Center

Kathleen Fagerstone

USDA/APHIS/WS National Wildlife Research Center

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RESPONSE OF DOGS TO A GNRH-KLH CONJUGATE CONTRACEPTIVE VACCINE ADJUVANTED WITH ADJUVAC®

Brenda Griffin¹, Henry Baker¹, Elizabeth Welles², Lowell Miller³
and Kathleen Fagerstone³.

Scott-Ritchey Research Center¹, Department of Pathobiology², College of Veterinary
Medicine, Auburn University, AL. USDA/APHIS/WS National Wildlife Research
Center³, Ft. Collins, CO.

An urgent need exists worldwide to sterilize millions of dogs in order to prevent their unintentional reproduction and continuation and exacerbation of their surplus and associated welfare issues. Non-surgical methods of sterilization have the potential to increase the number of dogs sterilized since they may be faster and more widely available than surgical methods. The goals of this project were to demonstrate the feasibility and efficacy of immunizing dogs against gonadotropin releasing hormone using a GnRH-keyhole limpet hemocyanin conjugate antigen adjuvanted with Adjuvac® (which contains *M. avium*). This vaccine construct and adjuvant have been developed by the National Wildlife Research Center (patent pending). A single administration of this vaccine has been shown to provide long term suppression of reproductive hormones and function in rodents, deer, pigs, horses and bison.

Three healthy adult male beagles, ranging in age from 2-4 years, were immunized with a single IM injection of 400 micrograms (0.5ml) GnRH-KLH with Adjuvac® in the right rear limb. This study was limited to male dogs. Breeding soundness and fertility were assessed biweekly for 1 year using five parameters: serum anti-GnRH antibody concentrations, serum testosterone concentrations, testicular size (based on caliper measurements), prostate size (based on digital rectal palpation and ultrasound imaging), and semen analysis (by manual ejaculation, including assessment of libido, semen concentration, motility and morphology). Blood samples were collected weekly for 8 weeks, then biweekly, and assays were performed in batch. Anti-GnRH antibody concentrations were measured using a modified radioimmunoassay with results expressed as a percent of a hyperimmunized rabbit control. Testosterone concentrations were determined using a solid phase I¹²⁵ radioimmunoassay (Diagnostic Products Corp., Los Angeles, CA) which was validated for canine sera based on spiking recovery, dilutional parallelism and measurement of intra- and inter-assay coefficients of variation (<10%). After 1 year, dogs were anesthetized and surgically castrated. Histopathology of the testes was performed. Hematology and serum biochemistries were performed prior to vaccination and castration. Following surgical recovery, the dogs were adopted to homes.

Two/three dogs developed rapid and robust anti-GnRH responses within 3-4 weeks of immunization (>65% by week 4, peaking at >90% and gradually declining to <50% by the end of the study). Infertility was achieved in these 2 dogs (based on undetectable testosterone concentrations and azoospermia) for approximately 14 weeks, after which time they rapidly recovered. After approximately 8 additional weeks, 1 of these 2 dogs experienced a second suppression, which lasted approximately 14 additional weeks before recovery. One three dogs developed only a modest anti-GnRH response rising

gradually to a peak of 60% by week 9 post-vaccination and gradually declining to <10% by week 27). This dog experienced only a brief period of oligospermia. All 3 dogs maintained excellent libido throughout the study period, even during periods of suppression during which the dogs had “dry” ejaculates. Motility and morphology of sperm and testicular and prostatic size correlated with serum testosterone and semen concentrations. All 3 dogs experienced severe injection site reactions within days following administration of the vaccine, characterized by massive swelling, pain, lameness, inflammation, necrosis, rupture and drainage of inflammatory exudate (based on cytology). Two/three dogs required treatment with oral antibiotics for secondary bacterial infection for weeks to months because the persistent inflammatory response resulted in a chronic open wound. Although the injection site reactions reduced in size, they persisted throughout the duration of the study in all 3 dogs. The remaining tissue was surgically removed and evaluated histopathologically at the time of castration. Baseline and week 52 hematology and serum biochemistries were normal in all dogs. Histopathology of the testes revealed normal seminiferous tubules with active spermatogenesis. Histopathology of the vaccine-site reactions revealed marked chronic mononuclear inflammation. We conclude that a single injection of this vaccine formulation is neither safe (due to the severe local reactions), nor effective at inducing long term suppression of reproductive function in dogs.

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