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NWRC Research Areas: Population Management/Reproductive Control

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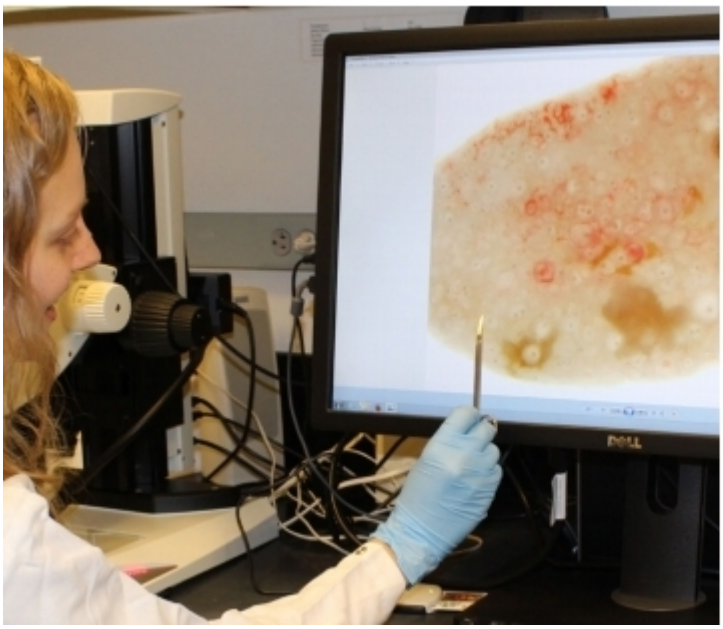

Our scientists are evaluating, developing, and assessing agents and technologies designed to control wildlife populations.

Research on reproductive control of overabundant animal populations, particularly those inhabiting urban or suburban settings (e.g., deer, Canada geese, monk parakeets, various rodents), is a high priority within the Wildlife Services Program.

Traditional methods of population control, such as regulated harvest by licensed hunters, often are impractical or illegal in these areas.

The National Wildlife Research Center has been active in the development and testing of wildlife contraceptive agents since 1992. Research has shown that, to be an effective and useful wildlife contraceptive, a compound should have the following characteristics:

- be safe for the target animal,
- be free of undesirable side effects,
- not affect nontarget species adversely,
- not cause treated food animals to become unsafe for human consumption,
- cause little or no negative social effect on target animals, and
- induce complete and long-lasting infertility that, ideally, is reversible.

Many compounds have been tested at NWRC, including some that were highly effective in sterilizing wild mammals and birds. However, because some of these materials could not meet the criteria listed above, their use was precluded in many management situations. Currently, two vaccines, the porcine zona pellucida (PZP) vaccine and the gonadotropin-releasing hormone (GnRH) vaccine, GonaCon™,as well as diazacon (a drug originally developed to lower cholesterol), are showing great promise for use in animal contraception.

Project Goals and Objectives

Development of Injectable and Oral Contraceptive Technologies and Their Assessment for Wildlife Population and Disease Management

Goal: To develop injectable and oral contraceptives to manage overabundant wildlife populations and reduce the spread of zoonotic diseases.

Objectives:

1. Develop oral and nasal delivery systems for GnRH reproductive inhibitors.
2. Develop and improve rapid GnRH antibody assays.
3. Conduct research to adapt and incorporate GonaCon into wildlife disease control methods.
4. Reduce injection site reactions of GonaCon
5. Determine field efficacy of GonaCon in wildlife species.
6. Determine the effect of health status on the immunological response to GonaCon.
7. Develop methods to minimize nontarget and secondary risks associated with DiazaCon.
8. Develop spatially explicit models to determine constraints on use of reproductive control methods for targeted wildlife population management.
9. Identify and develop new compounds as potential oral wildlife contraceptives.

Publications

- Population Management and Reproductive Control
- Solutions Through Science: Wildlife Contraceptives (665.07 KB) (Brochure)

Expand All

GonaCon™

Introduction

In fall, as day length decreases, reproductive systems in many mammalian species that occupy temperate habitats 'turn on.' Testosterone levels rise in males, and females begin estrous cycling ('going into heat'). Gonadotropin-releasing hormone (GnRH) is part of a pathway that signals the body to produce sex hormones. GnRH is produced by the hypothalamus, a major organ in the brain. Without GnRH, very little estrogen, progesterone, or testosterone are made.

The aim of a GnRH vaccine is to bind to or 'tie up' the GnRH produced within an animal's body so that it does not trigger reproduction. The vaccine induces the body to make antibodies against its own GnRH. To do this, GnRH is synthesized and hooked to a foreign protein. This new material (called a conjugate because it is made up of two components) looks like a giant new molecule that the animal's immune system has never encountered. As a result, when the GnRH vaccine is injected into the animal's body, the body's immune response neutralizes the hormone's function, resulting in infertility in both males and females.

As part of its program to develop tools for managing populations of overabundant wildlife species, NWRC scientists have developed a new GnRH immunocontraceptive vaccine (named GonaCon™) that shows great promise as a wildlife infertility agent. (See GnRH Immunocontraception Technical Discussion)

Two major obstacles had to be overcome during the development of this vaccine. First, a new adjuvant had to be developed (an adjuvant is a compound that improves the immune response, causing higher levels of antibodies). A replacement for the commonly used Freund's adjuvant was needed because the U.S. Food and Drug Administration (FDA) objected to its use in wild animals. Accordingly, NWRC scientists developed a new adjuvant (called AdjuVac™) that is more effective than Freund's adjuvant but lacks the negative side effects. (See Adjuvant Development Technical Discussion)

The second major obstacle to the development of a new immunocontraceptive vaccine for wildlife was the need for a single-dose contraceptive, because of the impracticality of capturing free-ranging wild animals twice to vaccinate them. Previous contraceptive vaccines required at least two injections (an initial dose followed by a booster dose). Although it was originally developed as a two-injection contraceptive treatment, NWRC's GnRH (gonadotropin-releasing hormone) vaccine was subsequently tested in a single-injection form that is much more practical as a field delivery system. Development of the single-injection vaccine was possible only because of the creation of AdjuVac™ adjuvant.

The usefulness of a single-shot immunocontraceptive vaccine depends, among other things, on the duration of the contraceptive effect that the vaccine produces. The combination of AdjuVac™ adjuvant and NWRC's GnRH conjugate produces a much longer-lasting contraceptive effect than was produced by earlier efforts that

combined Freund's adjuvant with the (same) GnRH conjugate. (See Conjugate Design Technical Discussion)

Pen and Field Studies of GonaCon™

Recent studies with free-ranging California ground squirrels, captive Norway rats, domestic and feral swine, wild horses, and white-tailed deer have demonstrated the efficacy of the single-shot GnRH vaccine as a contraceptive agent. Infertility among treated female swine and white-tailed deer, for example, has lasted up to five years without requiring a booster vaccination.

Recent studies have examined the practicality of administering GonaCon™ to free-ranging white-tailed deer as well as the efficacy, toxicity, and safety of the vaccine. Field studies in Maryland and New Jersey evaluated the efficacy of GonaCon™ as a contraceptive agent for free-ranging female white-tailed deer. In Maryland, an overpopulated deer herd on a completely fenced site was initially reduced in density by Wildlife Services sharpshooters at the request of property owners. Once the population size was reduced to a level that could be supported by the available habitat, contraception was applied to adult females. Forty-three does were captured, marked, and released at their capture sites during July 2004. Of those does, 28 were injected with GonaCon™ vaccine, and 15 were maintained as unvaccinated control animals. Data show the vaccine to be 88 percent effective the first year and 47 percent effective the second year in treated deer.

In July 2005, a similar field study involving another 28 deer was started in Morris County, NJ, that showed 67 percent effectiveness the first year and 48 percent effectiveness the second year. NWRC scientists collaborated on this study with White Buffalo, Inc., a non-profit, Connecticut-based research organization dedicated to conserving ecosystems through wildlife population control.

NWRC also collaborated with Pennsylvania State University to conduct studies required by EPA on the toxicity and safety of GonaCon™ in captive deer. Responses of treated and control groups of deer were compared via blood and tissue analyses. Data showed no differences between treatment and control groups.

EPA Registration of GonaCon™

In 2006, the regulatory authority for contraceptives for wildlife and feral animals was moved from the U.S. Food and Drug Administration to the U.S. Environmental Protection Agency (EPA).

GonaCon™ is not yet commercially available. USDA plans to submit data to the EPA in early 2009 to support a registration for the use of GonaCon™ in managing white-tailed deer populations, with registration being granted between 12-18 months following submission. NWRC scientists anticipate that GonaCon™ will be registered by the EPA as a 'Restricted Use' product, probably for use by state or federal wildlife or natural resource management personnel or persons working under their authority. Once the initial registration is granted, it is likely that NWRC will pursue the registration for other species, such as prairie dogs, ground squirrels, feral swine and feral dogs.

Advantages of GnRH

NWRC scientists are hopeful that the GnRH vaccine will soon be approved for use for wildlife fertility control. GnRH vaccines have an advantage over PZP because they prevent eggs from being released from the ovaries, thereby eliminating estrus and some undesirable behaviors (e.g., bucks chasing does across roads) associated with it. In addition, GnRH vaccine has promise for reducing or eliminating certain undesirable behaviors in companion animals. For example, fighting, scent-marking, caterwauling, and wandering by cats, and unruly behavior in horses, could be reduced by GnRH vaccine because the vaccine indirectly blocks the production of sex hormones (e.g., estrogen and testosterone) which contribute to the expression of such behaviors.

The single-shot, multi-year GonaCon™ vaccine will be a useful technique for the management of certain enclosed or urban/suburban wildlife populations, such as deer. GonaCon™ still has limitations, however, especially the need to capture and inject each animal.

GnRH Immunocontraception (Technical Discussion)

Control of Reproduction by GnRH

(NWRC publications on GnRH)

Gonadotropin-releasing hormone, which is produced in the hypothalamus at the base of the brain, controls the release of the pituitary gonadotropins LH (luteinizing hormone) and FSH (follicle-stimulating hormone). These gonadotropins regulate hormones that drive sperm production in males and follicular development and ovulation in females. Excitation of the GnRH neurons results in the release of stored GnRH peptide from its secretory granules in the hypothalamus. After it diffuses into the surrounding capillary blood, the GnRH travels via the hypophysial portal system to the anterior pituitary, where it diffuses from the capillaries and binds to and activates the LH and FSH gonadotrophs. This activation causes the release of stored gonadotropins, which diffuse back through the capillaries into the bloodstream. The gonadotropins then travel to and activate the reproductive organs, resulting in steroid synthesis and normal sexual activity.

GnRH Immunocontraception

The GnRH vaccine stimulates the production and release of GnRH-specific antibody from the B-cell into the bloodsteam. The antibody circulates throughout the body, and when it reaches the capillary region of the hypothalamus, it comes into contact with GnRH that has diffused into the capillaries after being produced in the hypothalamus. Binding of GnRH to the specific antibody forms large immune-complexes that travel down the hypophysial stalk. Because of their large size, however, the immune-complexes are unable to diffuse out of the blood at the pituitary capillaries. Instead, they remain in the venous blood and leave the pituitary without stimulating the release of LH and FSH. Without the LH and FSH that normally stimulate the synthesis of steroids in the reproductive organs, animals of both sexes remain in an asexual, non-reproductive state. As long as there is sufficient antibody to bind all GnRH circulating in the hypothalamic/pituitary portal system, all sexual activity will be suspended and animals will remain non-reproductive.

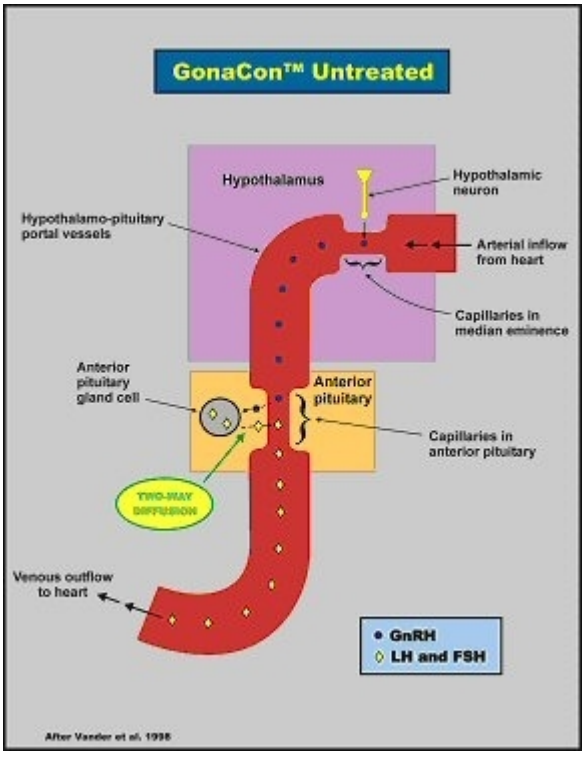

Diagram of gonadotropins pathway untreated with GonaCon

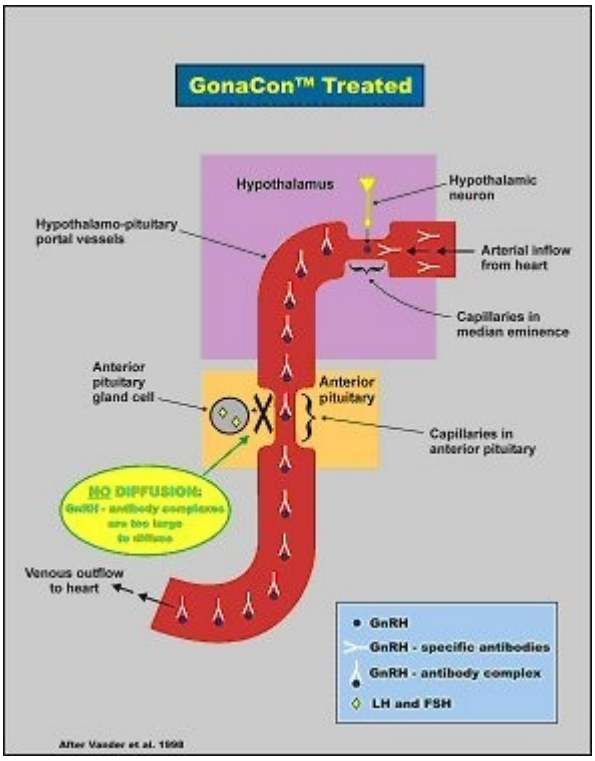

Diagram of gonadotropins pathway treated with GonaCon

Adjuvant Development (Technical Discussion)

AdjuVac™ Research

A typical disease vaccine primes the immune system to be on the alert for an infection caused by organisms with properties similar to those of the vaccine. Antibodies to the disease may be few in number or absent until the infection occurs. The infection then serves as a booster that stimulates an immediate immune response, protecting the vaccinated animal. For an immunocontraceptive vaccine to be effective, however, it must continually produce a high contraceptive antibody titer, so the booster effect must come from a different, non-disease mechanism—the adjuvant.

NWRC has modified and tested a USDA-approved Johne's vaccine called Mycopar™. Mycopar™ is approved for use in food animals by APHIS. The new adjuvant, which NWRC scientists have named AdjuVac™, contains a small quantity of M. avium, a common, generally nonpathogenic bacterium found in many species of domesticated and wild animals. NWRC scientists are testing AdjuVac™ in numerous wildlife species and it appears to be an effective adjuvant for contraceptive vaccines. The GnRH vaccine GonaCon/AdjuVac™, developed by NWRC, has a USDA/APHIS patent-pending status.

The success of the single-injection GonaCon™ contraceptive vaccine is due to the unique design of the GnRH/mollusk conjugate in combination with NWRC's newly developed adjuvant, AdjuVac™. Scientists at NWRC have spent 12 years developing the single-injection GonaCon™ vaccine, which will not be available commercially until it receives EPA approval. The adjuvant portion of the vaccine, however, is available to immunologists and biomedical researchers at a very reasonable price. Scientists are convinced that this adjuvant, which can only be used for research animals, will improve the immune response of almost any antigen.

For pricing and additional information about AdjuVac™ adjuvant, please contact:

USDA Pocatello Supply Depot
238 East Dillon
Pocatello, Idaho 83201
Telephone: 208-236-6920

Conjugate Design (Technical Discussion)

As part of its program to develop contraceptive tools to aid in the management of overabundant wildlife populations, the NWRC has developed a single-injection GnRH immunocontraceptive vaccine called GonaCon™. GonaCon™ has been tested and shown to provide contraceptive effects lasting up to five years in many overabundant species, including white-tailed deer, domestic and feral pigs, bison, wild horses, cats, dogs and California ground squirrels.

The GnRH vaccine generally provides a longer-lasting contraceptive effect in females than in males, probably because the females' demand for GnRH antibody is cyclic, in contrast to the males' constant demand. GonaCon™ contains a GnRH peptide conjugated to KLH combined with AdjuVac™, an adjuvant also developed at NWRC.

The GnRH Vaccine Conjugate Design Developed at NWRC

A single-shot vaccine that provides a multi-year contraceptive effect requires:

1. optimization of the vaccine structural design,
2. optimization of the dose for each target species,
3. use of the best adjuvant available, and
4. development of a delivery system that will protect the injected antigen from rapid destruction by the animal's immune system.

Multiple-shot vaccines are much less demanding with regard to optimal vaccine design.

The design of the GnRH vaccine mimics the repetitive epitopes found in many pathogens. An epitope is the part of a macromolecule that is recognized by the immune system, specifically by antibodies, B cells, or T cells. Pathogenic viruses and bacteria typically exhibit rigid, highly-organized, highly-repetitive protein epitopes. High epitope density in a highly-organized, repetitive arrangement is important in ß-cell responsiveness. Although ß cells are unresponsive to repetitive epitopes that are poorly organized, repetitive epitopes of proper spacing can stimulate multiple surface receptors of similar spacing. The repetitive epitope pattern permits a cross-linking activation of ß-cell receptors, providing an extremely strong, long-lasting

immune response. Mimicry of the repetitive nature of pathogen epitopes is an important aspect of the KLH-GnRH conjugate design. The GnRH peptide, which is analogous to the repetitive epitope, was designed to ensure consistent alignment of the peptide when coupled to the KLH carrier.

Nicarbazin

Nicarbazin may offer a way to limit Canada goose populations. It is a compound traditionally used on broiler chickens to prevent the disease coccidiosis, but decreased egg production and hatching rates occur as side effects. It appears that one mechanism by which nicarbazin exerts its effect on reduced viability of eggs is by causing disruption of the yolk membrane, allowing the yolk and albumin to flow together and creating conditions under which the embryo cannot develop.

Bait development followed the identification of nicarbazin as a promising avian infertility agent. Any nicarbazin bait must have the following characteristics:

- Highly palatable to Canada geese so that they continue to consume bait even when the grass “greens” in the spring, which typically coincides with the start of the breeding season
- Able to stand up to harsh conditions, such as heat, cold, or precipitation, in the field without breaking down.
- Right size, color, etc. to help minimize consumption by nontarget species, such as songbirds and mammals.
- Able to reduce egg-laying but not eliminate it, as laying eggs will keep the female Canada goose incubating the nest instead of re-nesting in an area where she would not continue to consume the contraceptive bait.
- Contain a high enough concentration of nicarbazin required to affect hatchability, even with the reduced drug absorption seen in Canada geese

OvoControl-G® is a semi-soft, wheat-based, extruded bread bait developed by Innolytics, LLC (Long Valley, NJ). OvoControl-G® bait is now registered with the U.S. Environmental Protection Agency as a reproductive inhibitor for use in Canada geese. Because nicarbazin is now registered, current work under this project primarily involves education and outreach.

Diazacon

Diazacon (20,25 diazacholesterol) is a cholesterol mimic that inhibits cholesterol production and blocks steroid hormone formation. The compound was originally developed by the G.D. Searle Co. for use as a cholesterol-reducing agent in humans. Although the drug was successful in reducing cholesterol levels, its use was discontinued because of side effects.

Diazacon was later studied as a reproductive inhibitor for use in control of pest birds. It was thought that since eggs contain cholesterol, lowering cholesterol might inhibit reproduction. More importantly, 20,25 diazacholesterol may have the ability to block production of hormones necessary for reproduction such as estrogen, progesterone, and testosterone.

Tests showed 20,25 diazacosterol to be effective in reducing reproduction in pigeons, blackbirds, starlings, and sparrows. The product was subsequently registered for pigeon population control under the tradename Ornitrol. In some instances, good results were seen, in others, results were less than optimal. One problem with pigeons is that they breed year-round (especially in warm climates). Long-term treatment with high doses of Ornitrol not only became expensive but sometimes muscle tremors developed in the birds.

Diazacon has the same hormone-inhibiting effect in mammals as in birds and has been shown to limit reproduction in different types of rats. The most promising uses of diazacon would logically be in animals (birds or mammals) that have a limited breeding season. Animals in areas where increased population is a problem could be treated prior to the breeding season without the need to treat throughout the year.

Avian Infertility

To date, diazacon has been studied in Japanese quail, ring-necked doves, and brown-headed cowbirds. Studies have shown significant differences in absorption and effectiveness of diazacon among bird species studied. In Japanese quail, diazacon effectively lowered cholesterol and reproductive hormone production in both sexes for several months following treatment. In female Japanese quail, egg-laying, fertility, and hatchability of eggs decreased significantly after one week of

treatment and remained significantly reduced for several months. In ring-necked doves, cholesterol levels were significantly reduced for several months after treatment. Studies in brown-headed cowbirds showed a significant reduction in cholesterol, although subsequent studies are needed to determine the optimal dose and how long the effect lasts. Currently, diazacon absorption and effectiveness are being studied in American crows and in waterfowl.

A Preliminary Field Trial of Diazacon Use in Prairie Dogs

A small study was undertaken to test whether diazacon would be effective in prairie dogs. Due to delays in obtaining the proper permits, treatment began later than planned. Even so, the average number of young as a proportion of adults at treated sites compared to control sites was reduced by about 59%. These results suggest that, at least in animals with a single breeding season, diazacon has potential for use as a fertility control agent.

Porcine Zona Pellucida (PZP)

The National Wildlife Research Center and various cooperators have conducted immunocontraceptive research with porcine zona pellucida (PZP) for several years. Species tested in this research include the white-tailed deer (*Odocoileus virginianu*s) and the coyote (*Canis latrans*).

The zona pellucida is a membrane that coats the egg. Sperm must bind to and penetrate the zona pellucida to fertilize the egg. Immunizing an animal with zona pellucida from pigs causes the production of antibodies that bind to the host's zona pellucida and prevent fertilization of the egg. Females successfully immunized with PZP will cycle and ovulate normally but will not conceive.

The PZP vaccine is a highly effective contraceptive, but unfortunately it causes multiple estrous cycles in female deer. These multiple cycles and the recurrent sexual activity (and deer movements) associated with them may increase deer-vehicle collisions and other deer-human conflicts. The PZP vaccine does not seem to cause multiple estrous cycles in other species on which it has been tested, and it may prove to be a highly useful infertility agent for other wildlife.

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