Animal &
Plant Health
Agency

Developing and delivering oral contraceptives to mammals with an emphasis on the Grey Squirrel

Project Proposal & Summary

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Summary

This is a proposal to move the existing fertility control science to the point that a strategy for the British grey squirrel is available and ready for manufacture.

The research, which would be expected to last 5 years, will involve using existing and proven US developed contraceptives and marrying them with existing leading edge British technology which would allow these contraceptives to be delivered orally. In parallel a species specific hopper will be designed, based on existing and proven designs for warfarin hoppers and form part of the overall fully licensed end research product.

The research will be carried out by the National Wildlife Management Centre, which is part of the Animal & Plant Health Agency unit based outside York.

The research will be directly useful where other species are concerned, notably in the UK for the badger and wild boar. The research would also put APHA in a strong position to win further international contracts for similar studies.

This project will cost £980,000 over the 5 year period.

Background

Fertility control is widely advocated as a safe, effective and publicly supported alternative to lethal control. Single-dose injectable immunocontraceptives, based on vaccines that generate an immune response to proteins essential for reproduction, are increasingly used for wildlife management. For instance, a single dose of the injectable immunocontraceptive vaccine GonaCon, which targets the gonadotropin releasing hormone (GnRH), can induce infertility (in both sexes) for several years in many wildlife species.
In contexts where capture, injection and release are not feasible or economically viable, the availability of oral contraceptives would multiply the breadth of field applications, particularly as species-specific oral delivery systems already exist for some potential target species.

Defra-funded projects demonstrated that a novel GnRH-based compound, tested as a putative oral contraceptive vaccine, generated an immune response in laboratory rats and reduced fertility in some animals. This was the world's first ever demonstration that an animal's immune system can be triggered by oral administration of an immunocontraceptive vaccine. This project builds on that

breakthrough. This project will also explore whether a novel oral contraceptive, registered in 2016 in the US to control rodents, can be effective in grey squirrels, thus widening the spectrum of tools available to reduce overabundant wildlife populations.

Aims

The overall aim of the project is to develop an oral contraceptive to control fertility in wild animals and to optimise the delivery of this contraceptive in the field. Specific objectives of this project are:

1. Identify a formulation of a carrier mechanism to deliver an immunocontraceptive vaccine orally;
2. Test a minimum of two formulations of putative oral contraceptive vaccines to induce infertility in a model species;
3. Identify the contraceptive dose, the number of doses and the frequency of dosing to induce infertility for at least one year in a model species;
4. Develop a bait to deliver oral contraceptive vaccine to a model species;
5. Test effectiveness, longevity and potential side effects of at least two oral contraceptives in at least one target species, including the grey squirrel, in captivity trials;
6. Develop a bait to deliver oral contraceptives to at least one target species including the grey squirrel;
7. Test the effectiveness and longevity of effect of at least one oral contraceptive in pilot field trials with at least one target species including the grey squirrel;
8. Refine species-specific methods to deliver oral contraceptives to wildlife for at least one target species including the grey squirrel;
9. Test bait uptake in pilot field trials, with baits containing placebo contraceptives, to quantify the proportion of the target population consuming baits.
10. Liaise with the Veterinary Medicine Directorate (or relevant authority) to discuss the data required to compile the registration package that will allow a finalized oral contraceptive and species specific delivery mechanism to be manufactured for at least one target species including the grey squirrel.

Expected benefits

- An effective, safe, long-lasting oral contraceptive is identified that can be delivered to the required proportion of the target population, thus revolutionising wildlife management
- The non-specificity of the oral contraceptive will increase the number of field applications for managing other species, both in the UK and in Europe
- Oral contraceptives could be used for wild boar, for which species-specific feeders already exist
- Oral contraception would work synergistically with disease vaccination, thus providing a novel approach to resolving the issue of the European badger as a wildlife reservoir of bTB.

Project Cost : £ 980.000

The majority of the funding will cover staff time; the remaining funding will cover consumables and contribution by collaborators such as Sporomex that will provide the formulation technology, the US National Wildlife Research Center that will provide the immunocontraceptive vaccine and SenesTech that produces ContraPest.

Project Lifetime: 5 years.

Scientific Appendix

Further Background

Defra-funded projects demonstrated that a novel GnRH-based compound, tested as a putative oral contraceptive vaccine, generated an immune response in laboratory rats and reduced fertility in some animals. This was the first ever demonstration that an animal's immune system can be triggered by oral administration of an immunocontraceptive vaccine. Building on these results, novel formulations are required to develop an oral vaccine that elicits a substantially greater and more persistent immune response. A promising approach is an encapsulation technology patented by the UK company Sporomex Ltd. and based on pollen grains and spore shells. Pollen grains and spores are emptied of their internal genetic material to obtain sporopollenin exine capsules (SPECs). These capsules can be filled with a variety of drugs to improve the bioavailability and absorption of the drug. Inexpensive and available in a range of sizes, SPECs have been successfully used to encapsulate fats, vitamins, enzymes, flavours, hormones and several other pharmaceuticals. In particular, SPECs have proven successful for the delivery of *in vivo* vaccines. When fed to laboratory mice, SPECs filled with a model vaccine elicited an immune response that lasted for up to 7 months, thus offering a putative mechanism for long-lasting oral vaccination.

Among other oral contraceptives currently being developed, one of the most promising is *ContraPest*, a drug registered in 2016 in the USA as an oral contraceptive for rodents. *ContraPest* acts by accelerating the natural depletion of ovarian follicles (egg structures), thus rendering females infertile. In males, this drug causes a marked reduction in the ability to fertilize eggs and often induces complete sterility. This approach could be extended to other target species in the UK, as an alternative or complementary drug to oral immunocontraceptives.

Developing safe, effective and relatively long-lasting oral contraceptives is the first step for the non-lethal control of overabundant wildlife populations. Another key step is assessing how these contraceptives can be delivered to a sufficient proportion of the target population so that fertility control can reduce significantly population size. Therefore a study aimed at testing/refining oral contraceptives will also address the practical aspects of delivering these drugs to the target species.

Methods

The laboratory rat will be used as a model species, offering efficient study design with limited individual variation under controlled conditions, and the ability to make direct comparisons to previous trials. The grey squirrel will be used as model target species.

Initial laboratory trials will determine whether encapsulation of the vaccine into SECs of two different plant species has been successful. The efficiency of encapsulation will be verified by assaying the release of the vaccine by liquid chromatography–mass spectrometry (LCMS) and scanning electron microscopy (SEM) of the loaded SECs surfaces and by freeze-cracking open the SECs to view the chamber contents and inner surface.

Animal trials will test the effectiveness of encapsulation with SPECs from different plant species and the effect of using a polymer (i.e. Eudragit) to co-encapsulate a minimum of two SPECs-formulated putative oral contraceptive vaccines. The effectiveness of vaccination will be measured by i. quantification of serum anti-GnRH antibody titres; ii. reduced diameter of uterine horns indicating reduced fertility; iii. reproductive output (i.e. number of females giving birth and litter

size). The most effective contraceptive will be selected for further trials where dose, number of doses and the frequency of dosing will be tested to induce infertility for at least one year in the model species.

Subsequent trials will be focused on offering rats the most effective formulation in a liquid or solid bait base previously tested for palatability. Further captive trials will test the same bait for a target species, such as the grey squirrel, and assess the effectiveness of the dosing schedule developed for rats on the reproductive output of squirrels. In parallel, captive trials will also test the effectiveness, dosing schedule and longevity of infertility of *ContraPest*. Pilot field trials in areas with a high density of grey squirrels will be conducted with the most effective oral contraceptive. Pilot field trials will also be conducted to quantify the proportion of grey squirrels consuming baits containing placebo contraceptives.

As several objectives depend on successful completion of the previous ones, review points will be planned into the project to discuss with the customer progress against milestones.

Project Staffing

The Project Lead will be Dr Giovanna Massei who sits on the US-based Botstiber International Institute for Wildlife Fertility Control and on the European Group for Zoo Animal Contraception and has more than 12 years of experience of this area. The breakthroughs referred to above arose out of projects that she was either leading or participating as to as lead scientist. She has been at APHA for 19 years and she is now leading a team of 14 staff.

The species specific delivery mechanism work will be led by Dr Julie Lane who is the lead for all trap licensing in the UK. Dr Lane has more than 20 years of experience in this area, developed whilst working for APHA and she is the Deputy Head of the National Wildlife Management Centre.