SESSION OVERVIEW

Dr. Stephen Boyle

Session presenters were Dr. Kathleen Fagerstone, Dr. Julie Levy, Dr. Gary Killian, Dr. Brij Saxena, Dr. Jay Kirkpatrick, Dr. Chris Hardy, and Dr. S.K. Gupta (see separate documents for individual presenters' materials).

The immune system of animals is a complex collection of cells that allow the clearance of foreign materials (produced outside of the animal) that have entered across the physical barrier presented by the skin or mucus membranes. One of the major arms of the immune system involves the ability of certain cells to produce antibodies that interact with the foreign materials (termed "antigens") and cause them to be targeted for destruction. These antibodies circulate in the blood and other body fluids and can last for a long time. In addition, once these antibody-producing cells have been activated, they create a memory cell line, which produces antibodies much quicker if the antigen is subsequently encountered. When these antigens are specifically introduced by injection to create an immunization, they are called vaccines. Traditional vaccines are components extracted from disease-causing pathogens. The immune response is characterized by the production of specific antibodies and/or cells that recognize many of the components of the vaccine and therefore the pathogen. The net result is rapid buildup of antibodies and cells that result in the destruction of the pathogen.

Normally, the immune system will not recognize the materials that make up the animal's body (self); this is a recognition of self-components that prevents the immune system from destroying the animal. There are ways, however, to make the immune system recognize self-components as antigens and cause the antibodies to interfere with their function or target them for destruction; this is a type of autoimmunity. This type of recognition is the basis for contraceptive vaccine technology. Specifically, components of the reproductive system – e.g., hormones, egg or sperm proteins – are administered in a manner that induces a type of autoimmunity resulting from the production of antibodies that interfere with the function of the reproductive system. For example, if antibodies recognize the surface components of an egg, they can prevent the binding of sperm and thus inhibit fertilization. Similarly, if antibodies recognize the reproductive hormones in the blood, they cause infertility as the result of decreasing the hormone's availability to stimulate the production of sperm and/or eggs in the testes and ovaries, respectively.

In the contraceptive vaccine session, seven speakers, as well as several poster sessions, presented materials dealing with the induction of immune responses to each of the following:

- Zona pellucida (ZP) – a coating of the mammalian egg
- A hormone-type molecule that is a hybrid protein consisting of luteinizing hormone (LH) and chorionic gonadotropin hormone (CG)

- Master reproductive hormone, gonadotrophin-releasing hormone (GnRH)
- The protein that makes up the receptor for luteinizing hormone

In the case of the hybrid antigen, CG::LH, this protein was shown to be antigenic in immunized mice and correlated to a suppression of serum progesterone levels in the blood. No follow-up studies showing the ability of this vaccine to inhibit fertility were presented and, as such, this vaccine falls into the "under development" category.

In the case of ZP, although no efficacy has been shown to date for its use as contraceptive vaccines for cats and limited efficacy has been demonstrated in dogs, three presentations were made. One speaker reviewed the 30-year history underlying the use of ZP as a contraceptive antigen in a wide variety of vertebrates, excluding the cat. The great lesson learned from the use of ZP was that its efficacy as a contraceptive antigen was greatly influenced by the purity of the antigen as well as the target animal species receiving the antigen. Both of these factors will greatly influence the ability of ZP to induce a contraceptive effect. No insights were provided as to why ZP does not induce infertility in cats.

A second speaker reviewed the development of virally vectored ZP vaccines for use in mice and foxes. The recombinant canine herpes virus expressing ZP remains to be rigorously tested in foxes and feral/wild dogs. This effort has been supported by the Australian government for the last ten years to help control non-indigenous species. We learned that because of a government decision, the immunocontraceptive program in Australia will be severely curtailed beginning in 2007 and the virally vectored contraceptive vaccine for canines will not be tested.

A third speaker presented data showing that ZP derived from dogs and combined with the protective components of the rabies virus induced about 50% of the immunized dogs to become infertile. Although larger studies need to be performed, this vaccine holds the promise of being able to not only prevent rabies but simultaneously decrease fertility in the feral dog, which is a principal reservoir of this life-threatening disease.

In the case of the GnRH vaccines, the speakers presented a somewhat more encouraging future for their application to a variety of vertebrates, including cats and dogs. The USDA has begun the product registration process for the single-shot GonaCon™ immuno-contraceptive vaccine developed by the Wildlife Service's National Wildlife Research Center and initiated over 10 years ago. This vaccine was originally developed for controlling the population of white-tailed deer but has been shown to induce high GnRH antibodies and prevent pregnancy in several species following a single dose: deer, wild rats, squirrels, cats, dogs, domestic and feral pigs, rabbits, coyotes, wild horses, and bison.

Studies with a small number of cats over the past three years have shown that approximately 75% of females are contracepted for at least 30 months given a single dose of the vaccine. An unexpected side effect of this treatment is that two years after initial vaccination, cats developed granulomas at the injection site, which raises questions about

the safety of this approach that will need to be addressed. In order for the efficacy of contraception to be optimized for a single-shot vaccine, additional research is necessary on adjuvant formulation with a larger number of cats.

Just as encouraging is the decision by the Food and Drug Administration (via the Center for Veterinary Medicine) to transfer its product registration for contraception in wildlife and feral animals to the Environmental Protection Agency; this should make it somewhat less onerous for products that will need registration for application in feral cats and dogs. A poster presentation demonstrated that it was possible to genetically engineer a feline herpes virus (FHV) and have it express a GnRH multimer fused to a known adjuvant protein. This product holds the possibility of being able to be used in the field, as FHV only infects cats. The vaccine is being tested on both mice and cats for its ability to induce antibodies and infertility.

Although the GonaCon vaccine for cervids is in its final stage of development and beginning registration, all of the other approaches mentioned above, particularly those for use in dogs and cats, are in the research stage, and will require additional work before a product can be tested and registered for widespread use.

The idea of using the immune system of the dog or cat to prevent the maturation or interaction of the egg and sperm is not new. What is needed is the ability to test these products on a larger scale and in a cost-effective manner. One idea that is being studied to facilitate this testing is an exploration with the National Institutes of Health of the creation of a no-kill, national testing facility for the non-surgical contraception of cats and dogs. The rationale here is to demonstrate the need for such testing as a means to reduce the numbers of feral dogs and cats, as they are some of the principal disease reservoirs for a variety of human diseases, including rabies.