Controlled Release for Depot and Implant Technologies, as it Applies to Developing Non-Surgical Alternatives to Sterilize Cats and Dogs

Scientific Think Tank
April 17-19, 2012
Los Angeles, CA

Overview

On April 17-19, 2012, a think tank on the application of controlled release technologies to the delivery of contraceptive agents to cats and dogs was held at the DoubleTree Hotel in Los Angeles, California. The meeting was convened by the Alliance for Contraception in Cats & Dogs (ACC&D), with support from the Found Animals Foundation (FAF), to discuss the potential of depot and implant technologies to control the delivery of chemical, immunological, or biological agents in the search for a non-surgical sterilant for cats and dogs.

The mission of ACC&D is to expedite the successful introduction of non-surgical methods to sterilize cats and dogs and to support the distribution and promotion of these products. ACC&D's motivation is to reduce animal death and suffering worldwide by enhancing the tools available to humane population control programs. Non-surgical approaches are presumed to be less expensive and less labor-intensive options for sterilization, allowing far more animals to be treated quickly and safely. The mission of FAF is to reduce shelter euthanasia in the United States. The establishment of the FAF Michelson Prize and Grants in Reproductive Biology, to fund research into the development of a "safe, effective, and practical non-surgical sterilant for use in cats and dogs," has contributed to an increase in interest in and research toward reaching this goal.

In addition to population control, an attractive aspect of a non-surgical sterilant would be suppression of reproductive hormones resulting in the possible reduction of behaviors such as roaming, spraying, or fighting associated with intact animals that can result in harm to the animal, the spread of infectious disease, and, frequently, in animals being abandoned or returned to shelters.

Previous scientific think tanks organized by ACC&D have focused on population modeling as a tool to guide the design and implementation of contraceptive approaches to best achieve stabilization or reduction of population size, and on gene silencing and immunocontraception as research areas with promise for achieving the goal of a non-surgical sterilant. The immunocontraception think tank in particular raised the question of whether technologies exist that would allow delivery of an agent over an extended period of time, or in multiple discrete doses, with a single injection.

Experts in drug delivery, precision manufacturing, FDA regulatory procedures, and dog and cat reproductive biology were brought together for this think tank focused on controlled release technology. The goal of the think tank was to arrive at an understanding of the state of the art in the areas of controlled release, to discuss how these technologies might be used to deliver potential

non-surgical sterilants, and to gain insight into future technologies on the horizon.

Joyce Briggs, president of ACC&D, described the hoped for outcomes of the Think Tank to include a summary report that would serve as a reference to new and existing researchers in the field of dog and cat contraception.

Attendees

(See www.acc-d.org for bios of participants.)

Note: An asterisk (*) indicates members of the planning committee for this think tank.

Foundation and Nonprofit Representatives:

Joyce Briggs, MS*	President, Alliance for Contraception in Cat & Dogs, Portland, OR
Shirley Johnston, DVM, PhD*	Director of Scientific Research, Found Animals Foundation, Los Angeles, CA

Scientific Panel:

Larry Acquarulo, PhD, CPD	Founder and CEO, Foster Corporation, Putnam, CT
Michael McDonald Crowley, PhD*	President, Theridian Technologies, LLC, Austin, TX
Linda A. Felton, PhD	Chair, Department of Pharmaceutical Sciences and Associate Professor of Pharmaceutics, University of New Mexico College of Pharmacy, Albuquerque, NM
Gary E. Gamerman, MS, JD*	President, Seraphim Life Science Consulting LLC, Vienna, VA
Viraj Mane, PhD	Faculty Research Associate, Institute for Bioscience and Biotechnology Research, University of Maryland, College Park, MD
David Petrick, VMD, JD	The Delta Consortium, Princeton, NJ
Satya Prakash, PhD	Professor, McGill University, Co-Founder and Director, Micropharma, Montreal, Quebec, Canada
Linda Rhodes, VMD, PhD*	CEO, Aratana Therapeutics, Inc., Kansas City, KS

Topics of Discussion

Overview of the Challenge

Joyce Briggs introduced the purpose of the think tank and explained ACC&D's interest in promoting the discovery and introduction of non-surgical alternatives for the sterilization of cats and dogs. She presented background data on dog and cat overpopulation and the challenges presented by reliance on surgical sterilization to control these populations. In United States shelters, 3.5 to 4.5 million dogs and cats are euthanized annually. Though this represents a significant decline since the 1970s when approximately 20 million dogs and cats were euthanized yearly, the number of animals put to death remains unacceptably high and demands a new approach to the control of dog and cat populations.

ACC&D is interested in finding safe and effective alternatives to surgical sterilization for cat and dog populations. Alternatives to surgery could become a key tool for agencies treating homeless populations of cats and dogs seeking adoptive homes, or feral cats through trap, neuter, return (TNR) programs. Other key U.S. markets for non-surgical alternatives include low-income families for whom surgical sterilization is a financial burden, and pet owners opposed to surgery but who do not object to sterilization of their pet.

The decrease in euthanasia rates over the past 40 years is due largely to an increase in sterilization rates. In 2011, approximately 78% of owned dogs and 88% of owned cats were spayed or neutered in the United States. However, only about 5% of the 9 to 90 million un-owned cats in the United States are sterilized, resulting in a large number of kittens entering shelters every year. Thus, in the United States, controlling feral or un-owned cat populations is an important goal.

Worldwide, different priorities direct the control of cat and dog populations. Free-roaming dog populations present a public health risk in many parts of the world, where dog bites are a primary source of human rabies cases. Controlling the owned, community, and stray dog population sizes is difficult in countries where a lack of trained small animal veterinarians and insufficient funding to support their work results in a relatively low percentage of the population receiving surgical sterilization.

Joyce Briggs presented information she gathered on a recent visit to Tianjin, China, where ownership of companion animals is increasing without a concomitant increase in the availability of veterinary services. Indeed, she found little awareness of the benefits of sterilization of pets, and a lack of publicly supported shelters for un-owned animals. The situation in China is similar to that facing many communities. During the same trip she rode the Maglev Train which can go over 200 MPH. Despite the availability of such technology, the average speed of a train in the US is 50 MPH. The reason: the tracks. In the case of cat and dog overpopulation, the "rails" are surgical sterilization; it simply is too expensive and too slow to effectively reach the number of animals required to stabilize or shrink populations on a broad scale with the current technology and infrastructure.

The Goal

Joyce Briggs explained that the ultimate goal of ACC&D is to arrive at a safe and effective sterilant that is effective for life, or a contraceptive that is effective for the reproductive life span of the animal. Average lifespan is estimated to be 3 years in feral cats in the United States, and about the same for community dogs in India, so ACC&D has interest in a contraceptive effective for at least 3 years. It was noted, however, that the focus of this think tank was to be on breakthroughs to essentially sterilize rather than contracept. Ideally, the sterilant would require a single treatment, since for many populations there is little likelihood of a veterinarian or technician seeing an animal more than once. The

treatment will most likely need to be an injection or implant, since oral agents delivered as bait could pose a threat to the environment if they are not specific to the target species and therefore could face major regulatory hurdles. Also, the treatment must be affordable, which is defined differently in different markets, ranging from $1 to $25 or higher.

Shirley Johnston spoke to the interest of FAF in the subject matter of the think tank. To support its mission of reducing shelter euthanasia in the United States, FAF sponsors the Michelson Prize & Grants program: the Michelson Prize of $25 million will be awarded to the first entity to provide the foundation with a low cost, single dose, non-surgical sterilant for use in cats and dogs. Additional funding, up to $50 million, is available in the form of grants to fund research towards the goal of the prize. The winning agent must be safe, effective for at least 10 years, and active in both cats and dogs, and in both males and females. Additionally, the agent must be able to be administered in the field, and must have a viable path to regulatory approval. Ideally, the cost per treatment would be under $5. Fuller details are available at http://michelson.foundanimals.org/michelson-prize.

Therefore, though not identical, the goals and interests of ACC&D and FAF are complimentary, and both organizations see value in collecting and providing information about drug delivery technologies to the biologists researching non-surgical sterilization.

Shirley Johnson outlined the current state of research in the field, as reflected by work currently supported by Michelson grants. Targets for suppression of fertility include suppression or inhibition of gonadotropin-releasing hormone (GnRH), ablation of pituitary gonadotrophs, and ablation or suppression of primordial stem cells within the gonad. Methodologies include gene silencing, immunocontraception (including vaccines against gonadotropin releasing hormone (GnRH) and the zona pellucida), and targeting of cytotoxins to the brain, pituitary gonadotrophs, or gonad. She expressed her particular interest in discussing the applicability of controlled release technologies to increasing the persistence of infertility resulting from GnRH vaccines, since these vaccines are proven effective in multiple species, albeit for short periods of time.

Introductory Discussion

As a starting point, Joyce Briggs pointed out that there are two non-surgical fertility control products currently approved for dogs, Esterilsol™/Zeuterin™ from Ark Sciences, and Suprelorin® from Peptech Animal Health (now a part of Virbac). Esterilsol has regulatory approval in Mexico, Columbia, Bolivia and Panama. The formulation is FDA approved for use in puppies between 3 and 10 months old (previously known as Neutersol®) and expected to launch in the United States later in 2012 under the name Zeuterin™. The product is a solution of zinc gluconate and L-arginine that is injected into each testicle of a male dog.

More closely related to the subject of the think tank, Suprelorin, approved in Australia, New Zealand, and the European Union, is a sustained-release biocompatible implant that releases deslorelin, a GnRH agonist decapeptide, over time. There are two doses marketed, a 4.7 mg implant for 6 months duration and a 9.4 mg implant for 12 months duration. The implant is placed subcutaneously between the shoulder blades and is only approved for use in male dogs. Implants can be repeatedly administered to assure contraception over the lifetime of the male dog.

As a practical consideration, the panel discussed how to recognize whether an animal has been treated. With Esterilsol, a specific tattoo is recommended, positioned on the upper thigh. With trap, neuter and return (TNR) programs of feral cats, removal of the tip of the left ear under sedation is fairly universally done. It was agreed that alongside the development of sterilization technologies, a permanent, obvious, and non-invasive marking system will be needed. In the United States where microchipping is common and most shelters have a scanner, the information could be included on the chip.

The group discussed the percentage of a dog or cat population that would need to be treated in order to stabilize or reduce the population. Shirley Johnston explained that the number of animals that need to be targeted to reduce colony size is not yet known, though a population modeling effort is underway with ACC&D guidance and participation. Older data suggests 70% to 80% of animals in a dog or cat population must be treated to stabilize population size. Joyce Briggs added

that for population control, it is believed that targeting females is more important than males, and modeling will also investigate whether there is an advantage to treating juveniles vs adults.

Gary Gamerman pointed out that the usefulness of an approach will be a combination of ease of delivery and effectiveness of the treatment: a treatment that is effective in 80% of treated animals and is easy to deliver to close to 100% of a population may be preferable to a treatment that is 100% effective but difficult to administer.

Larry Acquarulo stated that it might be possible to deliver an agent over a 10-year period, within physical limitations dependent on how much agent must be delivered, and how large the implant can be based on the site of implantation. Gary Gamerman added that since human implants and intrauterine devices (IUDs) are able to deliver 10 to 20 μg of steroids per day for a period of 5 to 7 years, delivery over a period of 10 years seems feasible if a drug has sufficient potency and stability.

Overview of Extended and Controlled Release Technologies

Linda Felton presented an overview of technologies for controlled drug delivery that are currently available or in development for human or animal applications. Most extended delivery systems incorporate polymers such as polylactides, polyglycolides, poly(lactide-co-glycolide), polyanhydrides, etc, which can be engineered to control properties such as permeability and biodegradation rate.

Implants for drug delivery fall into four general categories: diffusion-controlled implants, erodible matrixes, osmotic pump implants, and electrically driven implants. Injectables for extended delivery include polymer-based microspheres and in situ–forming implant systems. Discussion revolved around examples of each technology, their advantages and disadvantages, and their potential applications.

1. Diffusion-controlled implants

These implants consist of a capsule with a permeable outer membrane or monolithic matrix designed to allow a chemical to diffuse out at a specific rate. Usually the implant is removed when empty. The panel agreed that in many scenarios of un-owned dog and cat sterilization, the implant would likely need to stay in the animal since the animal might not be recaptured to see a veterinarian a second time.

Michael Crowley pointed out drug release from these implants follows Fick's first law of diffusion, and the rate relies on the permeability of the outer membrane or matrix.

Examples:

Vantas® Implant: histrelin acetate (a nonapeptide, MW=1324 g/mol) in a non-biodegradable cylinder 3.5 cm x 3 mm, with 12-month drug release. This implant is used for the treatment of prostate cancer in men.

Norplant Implant: levonorgestrel (a steroidal hormone, MW=312 g/mol) in a silicon capsule. Six capsules, each 3.4 cm x 2.4 mm, are injected under the skin of the upper arm for 5-year drug release. This implant is a contraceptive for women.

Norplant II (Jadelle®): levonorgestrel in a silicone matrix in a silicone rod. Two rods, each 4.3 cm x 2.5 mm, are effective for 3 years. Releases 80 μg per day for first month, decreases to 50 μg per day by the end of 9

months, and levels out at 25-30 μg per day thereafter. This is a contraceptive for women.

Implanon®: etonogestrel (a hormone, MW 324=g/mol) in a single rod, 4 cm x 2 mm, inserted subcutaneously on the inside of a woman's upper arm for drug release over 3 years. This is a contraceptive for women.

Mirena®; levonorgestrel in a silicon matrix and polydimethylsiloxane membrane, released from a reservoir within an IUD. Initially, levonorgestrel is released at a rate of 20 to 22 μg/day. The release rate decreases to about 10 μg per day after 5 years. This is a contraceptive for women.

Gonazon™ implant : azagly-nafarelin (a GnRH agonist decapeptide, MW=1322 g/mol) dispersed throughout a solid matrix consisting of a silicone elastomer, in a rectangular implant 1.4 cm x 3 mm x 1 mm injected subcutaneously in the regions of the umbilicus in dogs. This product is effective for 12 months in female dogs, and approved but not marketed in the EU. It was originally developed by Intervet (now part of Merck Animal Health).

Summary: These are the only drug delivery systems on the market that can deliver drug over multiple years. This technology is compatible with small chemicals and peptides.

2. Erodible matrix implants

These implants consist of a drug blended with a polymer. Over time, the polymer degrades, releasing drug. Formulation, including geometry, can affect rate of drug release. These are the most commonly used of the discussed technologies. With this technology, it can be difficult to attain long-term release; release usually occurs over a period no longer than one year.

Release is pseudo first-order release, with an initial burst followed by a decline, instead of a steady state.

Examples:
Gliadel® wafers: carmustine (an organic compound, MW=214 g/mol) in the polymer polifeprosan 20, implanted directly in the brain after removal of brain tumors. 70% of the drug is released in 3 weeks.

Zoladex® implant: goserelin acetate (a decapeptide, MW=1269 g/mol) in a biodegradable lactide/glycolide polymer system. Injected under the skin of the abdomen with a single-use syringe. Available in two depot formulations to release drug over 1 or 3 months. This drug is used for treatment of prostate and breast cancers and endometriosis in women.

Vitrasert® implant: ganciclovir (an organic compound, MW=255 g/mol) in tablet form, implanted intraocularly. Releases drug over 5 to 8 months, and is used in HIV patients with CMV intra-ocular infections.

Suprelorin implant : deslorelin (a nonapeptide analog of GnRH, MW=1282 g/mol), combined with hydrogenated palm oil, lecithin, and sodium acetate formed in a cylinder 1.2 cm x 2.3 mm (for the 6-month formulation) and placed subcutaneously between the lower neck and lumbar region of dogs, or between the shoulder blades of ferrets. Drug release occurs over 6 (4.7 mg implant) or 12 (9.2 mg implant) months.

Linda Felton noted that in the case of Vitrasert, drug delivery persists longer, most likely because the drug is being delivered locally to where it is needed, so less drug is needed and release rates can be lower than with systemic delivery.

Summary: This technology can release drug over a period of weeks or up to 6 to 12 months. This technology is compatible with small organic compounds and peptides.

3. Osmotic pumps

These implants consist of concentric cylinders: an outer semipermeable membrane containing a salt solution surrounds an impermeable drug reservoir. As fluid enters the outer reservoir, it increases osmotic pressure on the drug-containing reservoir and forces drug out of the delivery portal. Michael Crowley explained that since osmotic systems require moving parts, delivery of low dose drugs can be challenging.

Example:
Viadur®: leuprolide acetate (a nonapeptide, MW=1269 g/mol) in a 4.5 cm x 4 mm titanium alloy reservoir with a

polyurethane rate-controlling membrane, elastomeric piston, polyethylene as a diffusion modulator, and NaCl as osmogen. Inserted subcutaneously, allows 12-month drug release. This drug is used for treatment of prostate cancer in men.

Summary: With osmotic pumps, drug release can occur over at least a year. In theory, delivery could be over a much longer period if used with highly potent, stable, and soluble drugs. This technology is compatible with peptides.

4. Electrically driven pumps

These are technologies that would allow intermittent dosing.

Examples:

MicroCHIPS Inc. recently published a human trial in which 20 doses of teriparatide, a polypeptide, were released once daily over 20 days. The peptide needed to be sealed hermetically within the device, a 30-minute operation was required to implant the device, and the device was removed after 4 months. The same group is currently working to expand the microchips to contain hundreds of doses.

MiniMed Paradigm® Revel™ insulin pump, an external electric Insulin pump that can deliver a constant level of insulin, or adjust insulin release based on signals from a separate glucose sensor.

The panel was very interested in this technology, particularly since it might make it possible to specifically release vaccine doses according to a pre-determined schedule. Concern was expressed regarding expense, due to use of titanium and complicated manufacturing. Polyetheretherketone (PEEK™), a thermoplastic, might be a less expensive alternative to titanium. Michael Crowley stated that a computer chip (NanoMedical Systems) can be manufactured for less than $1, and can be used to control release from a separate capsule.

Questions were also posed regarding whether the reservoir size of a microchip could contain enough antigen/adjuvant (agent) for the vaccination application, whether the device would need to be too large, and if the device could last longer than a year. Michael Crowley stated his belief that the challenge of a longer-term microchip implant would be battery life, as he is not aware of a small microchip battery lasting beyond 5 years. Satya Prakash and Gary Gamerman felt that trying to maintain the stability and activity of an agent for such a long period of time in vivo would be the greater challenge.

Summary: With this technology, drug release can occur over months. This technology may be compatible with peptides.

5. Polymer-based microspheres

These microspheres are biodegradable polymer systems that can be injected intramuscularly (IM) or subcutaneously, and slowly release drug, usually over a period of months. Particle size and polymer choice both affect release rate. Microsphere systems have been commercially successful.

Examples:

Risperdal®: risperidone (organic molecule, MW=410 g/mol) injected IM, and drug delivered over 2 weeks to treat schizophrenia in humans.

Nutropin®: somatropin (growth hormone, a protein with 191 amino acids, MW=22 kDa) encapsulated in poly(D,L-lactic-co-glycolic acid) biodegradable microspheres. Injected subcutaneously with drug release over 2 to 4 weeks for treatment of growth hormone deficiency.

Trelstar® depot: triptorelin pamoate (a decapeptide, MW=1700 g/mol). Injected IM with drug delivery over a

period of up to 6 months, for the treatment of endometriosis in women and of prostate and breast cancers.

Summary: This technology can deliver drug over weeks or months, and is compatible with small chemicals, peptides, and proteins as large as growth hormone (22 kDa).

6. In situ—forming implant systems

These injections contain a mixture that congeals to form a solid, biodegradable implant after injected. Depot formulation can include thermoplastic pastes, cross-linked polymers, or thermally induced gelling systems.

Example:
Eligard® injection: leuprolide acetate (a nonapeptide, MW=1269 g/mol) in suspension for subcutaneous injection. 45 mg injection provides continuous delivery for 6 months for treatment of prostate and breast cancers in humans.

Summary: This technology can deliver drug over months, and is compatible with peptides.

Other delivery technologies discussed included drug-eluting stents used in cardiac surgery, IUDs, and nanoparticles. David Petrick pointed out that sustained-release obtained through depots formulated with an oily base, as opposed to polymers, is traditional technology in animal health. These products generally deliver drug over a period of days rather than months.

Linda Felton emphasized that the final product must be sterile, stable, and easy to use. The pharmacokinetics of the active ingredients is important to the choice of delivery system, whether continuous, intermittent, or one-time dosing is required. Stability on the shelf is important, but with long-term implants, it would be necessary to demonstrate stability of the active agent when the implant is within the animal. She wondered how best to accumulate in vitro data that could be predictive of release performance, before moving to animal experiments. For example, if delivery is needed/expected over five years, is there a way to carry out accelerated testing in vitro to demonstrate stability of the active agent, so you don't have to wait the entire five years?

The panel agreed that stability of the active agent is an important concern. Most drugs lose stability at higher temperature and once solubilized. Steroids are extremely stable in the solid state, while peptide stability is likely sequence dependent, and proteins will need to maintain their correct three-dimensional structure to maintain activity. Larry Acquarulo suggested that blending can improve stability, but maintaining stability over years in vivo might be difficult.

Gary Gamerman added it might also be necessary to demonstrate stability of the device over time, and to characterize how the body might react to the device. It might also be necessary to determine whether the optimal profile of release might vary by species, sex, or maturity of the animal.

Larry Acquarulo noted that capsules of PEEK plastic containing a radioisotope could be implanted at a specific site. Gary Gamerman pointed out that for treatment of female animals, inaccessibility of the ovary probably necessitates systemic as opposed to local delivery of a cytotoxic agent.

The panel agreed that multiple issues regarding the therapy to be delivered would determine the optimal delivery system: size and chemical nature of the agent to be delivered, dose that needs to be delivered, number of doses, and timing of delivery. These would be the focus of the afternoon discussion.

Matching of Delivery Technologies With Agents of Interest

Gary Gamerman served as facilitator during a round table discussion of the application of the drug delivery technologies discussed in the morning session to the objective of non-surgical sterilant development. He outlined the following variables to be considered:

Action of agent

1. Vaccination approach: need initial exposure and maybe later booster exposures

2. Effector approaches: agonist, antagonist – requires continuous delivery
3. Direct chemical assault, targeted to tissue of interest such as germline or gonadotroph, might need a high-potency short-duration dosing

Biology
1. Site of action – getting agent to correct place
2. Animal size – might need to adjust formulation based on animal size
3. Site of delivery – might limit the size of implant or type of agent

Chemistry
1. Molecular size of agent (small molecule, steroid, peptide, aptamer, protein)
2. Stability of agent on shelf and in vivo
3. Potency of agent/dosage needed
4. Profile of delivery needed (single dose, long-term release, pulsatile)

Design of Delivery Technology
1. Physical size of device
2. Type of release profiles available
3. Compatibility with agent
4. Blending polymers to modulate release
5. Performance/therapeutic index

Economy
1. Intellectual property
2. Manufacturability
3. Maturity of technology
4. Hard/soft costs
5. Supply side

The panel agreed that it is difficult to discuss engineering specifically without knowing the nature of the agent to be delivered, and the optimal delivery profile for that agent. Discussion focused generally on matching available technologies to potential agents of interest.

Location of implant:
An implant would most likely be placed under the skin between the shoulder blades of the animal. This is where microchips are generally placed, as is the Suprelorin implant. A relatively large implant can be tolerated in this area since the skin is loose, Linda Rhodes mentioned that another implant, Gonazon, is placed near the umbilicus, due to the shape or rigidity of the implant resulting in migration if placed on the back.

Biological reaction against long-term implants (such as formation of fibrous capsules around the implant), and erosion of an implant back out through the skin, were not considered to be major concerns since these are not observed in microchipped dogs and cats. If fibrous capsule formation were found to be a problem that interfered with drug delivery, the possibility of incorporating a separate agent into the device to combat the formation of such fibrous tissue, analogous to the drug incorporated into cardiac stents, was discussed. The shape of the implant must be designed not to irritate the animal so they will not scratch at the site. Larry Acquarulo suggested memory polymers, which can be warmed, injected, and then will assume the correct shape, such as a coil.

Selection of Delivery Technology Based on Size of Agent:
Michael Crowley and Larry Acquarulo put forward that delivery of a small molecule over an extended period of time up to at least 3-5 years should be possible based on existing products such as Implanon and Norplant. With a stable drug, Gary Gamerman believed that 7 to 10 year or more release should be feasible.

Delivery of larger molecules such as peptides over 20 residues or proteins would be more difficult, since maintaining the stability and activity of a protein over a long period of time in vivo is likely to be more challenging. Microchips were thought by the group to be a promising technology for delivery of proteins, since the protein can be protected from body fluids until the time it is to be released. Michael Crowley discussed a technology from NanoMedical Systems in which a computer chip located at the end of a plastic tube controls release of large

proteins, monoclonal antibodies, from the reservoir, indicating that release systems are feasible for large proteins and monoclonal antibodies. However, maintaining stability in vivo may still be difficult at body temperature.

Formulation of medium-term injections based on oil suspensions or water-oil emulsions can be used with small molecules, but are not likely to be compatible with proteins.

Selection of Delivery Technology Based on Dosing Profile of Agent:

For very long-term delivery over years, the Norplant or Implanon technologies could be a good start. The limitation with these technologies, as explained by Michael Crowley, is their size, which will depend on the carrying capacity of the polymer for the agent of interest.

For first-order delivery over weeks or months, Larry Acquarulo said bioresorbable rods would be effective. These could also be engineered to incorporate an initial burst of agent if needed.

For more complicated delivery patterns, the panel discussed the possibility of mixing multiple technologies, compared with engineering a more complex single device. For example, microspheres containing drug could be injected along with the same drug in solution, allowing for an initial dose and a delayed dose with a single treatment.

David Petrick suggested two formulations, which can be drawn from separate bottles, mixed at the time of injection, and be injected at once. Linda Felton and Satya Prakash agreed this would be the easiest way. Linda Felton pointed out that the best way to vary release rates can be to change the size of the particles, rather than change polymers, so the same formulation in different sizes might be used to achieve different dose times. Larry Acquarulo added that beads can be engineered not to release drug for an extended period of time, up to 2 years. However, Gary Gamerman argued that it would be easier to develop and gain approval for a single formulation than for two formulations to be injected together.

Other technologies discussed for controlled release included self-sealing balloons, which can be injected subcutaneously and then filled with drug. The polymer making up the walls of the balloon could be engineered for different diffusion rates. Viraj Mane suggested injecting microspheres into the balloon, giving two layers of control over release rate or profile

Satya Prakash, Linda Felton and Viraj Mane questioned whether delivery vehicles such as microspheres could be engineered to target specific organs. Viraj Mane pointed out that in situations where the addition of a targeting moiety may mask or hinder the activity of the active agent, targeting the delivery vehicle might be preferable. Gary Gamerman countered that it was easier to engineer the agent to be targeted.

Important Knowledge Gaps Identified in This Session:

- How to formulate a protein delivery system that can maintain stability and activity of the protein over a period of months or years

Delivery Technologies for GnRH Vaccines

The group spent one session specifically considering delivery technologies that could be used with the GnRH vaccine to allow the priming dose and one or more booster doses to be delivered in a single shot.

Linda Rhodes provided an overview of GnRH vaccines, including GonaCon™, a GnRH vaccine approved in the United States for wildlife management, and Improvac®, a GnRH vaccine approved in Australia, New Zealand, and other countries as an agent to prevent boar taint.

GonaCon is an oil-based vaccine approved for use in cervids (white-tailed deer), containing GnRH conjugated to keyhole limpet hemocyanin (KLH) and adjuvanted with a bacterial adjuvant. In a study carried out by Julie Levy at the University of Florida, cats received a single dose of GonaCon after which 93% of the cats remained infertile at 1 year, 73% at 2 years, 53% at 3 years, 40% at 4 years, and 27% at the end of the study at 5 years. Dog studies have not shown an adequate contraceptive effect;

serious injection-site reactions seem to be caused by the adjuvant.

Improvac contains a synthetic GnRH analog coupled to a diphtheria toxoid as a carrier protein. It is administered to male pigs at 8 weeks of age, and again 4 to 6 weeks before slaughter, which usually occurs around 6 months of age. If the second injection is administered 7 to 8 weeks before slaughter, the effect begins to wear off, indicating that in pigs, at least, a single booster does not provide an immunity level sufficient to avoid boar taint for more than 6 weeks. It is formulated in DEAE-dextran adjuvant.

Linda Rhodes also discussed another GnRH vaccine approved for treatment of benign prostate hypertrophy in dogs (sponsored by Pfizer Animal Health). This vaccine, which was on the market only a short time, required an initial injection, a booster at 1 month, and boosters every 6 months thereafter, again speaking to the difficulty of achieving life-long immunity with GnRH vaccines.

Linda Rhodes expressed that for vaccination, it is important that the antigen be given at an interval or in pulses; constant exposure to the antigen can result in tolerance. The optimal interval for doses varies by vaccine and indication. She also emphasized that GnRH vaccine effectiveness rarely reaches 100%, and is lower in populations where animals' immune responses are weakened due to stress, malnourishment, or illness.

The panel questioned at what time interval boosters may be needed in cats and dogs. David Petrick pointed out that such an agent would be considered an immunologic new animal drug as opposed to a USDA animal vaccine, since USDA and FDA do not consider pregnancy a disease condition. For FDA approval, both the size of the window during which a boost is effective, and the ability of the delivery technology to deliver a dose within that window will need to be demonstrated.

Gary Gamerman noted it might be necessary to co-inject a short-acting contraceptive if immediate sterilization is desired, as most vaccines will take several weeks to become effective.

If boosts are required every 6 months for multiple years, then Linda Felton suggested a microchip is the best way to go. Gary Gamerman proposed a non-microchip approach, involving a rod or similar implant with stacked segments to provide multiple doses or exposures to the vaccine. Stabilized vaccine with CpG adjuvant and a water-driven dispersant such as methyl cellulose would be contained within each layer, and between each layer would be an erodible material to provide a time control between exposures. On implantation, the first segment would be rapidly exposed, providing the initial vaccination. A subsequent exposure would occur after erosion of a spacer exposed the next segment, allowing release of the vaccine contained within. Additional exposures would be achieved by the incorporation of additional spacers and vaccine-containing segments. The approach would require that the vaccine be tolerant to reasonable time variance between pulses, since time to erosion of the spacer might vary. An alternative would be to have a two (or more) sided rod with one side set for immediate release, and the other side for a longer time to exposure, either through the top or by wall erosion. Stabilization of the vaccine would be critical for any delayed-release approach.

Viraj Mane suggested administration of systemic vaccine, the prime, concomitantly with implantation of a delayed-release implant to provide a 3- to 6-month boost in burst release format.

However, the only way to determine how many boosts are needed and their optimal timing is to test the vaccine in cats and dogs, and this will require long-term studies.

The panel discussed possible alternative adjuvants. Shirley Johnston recommended a literature review to

determine whether an adjuvant is required in cats and dogs when the antigen is coupled to a large protein. Most vaccines using protein antigens do require adjuvant, but some new vaccine technologies based on viral vectors or virus like particles do not require adjuvants. Saponins, alum, and CpG oligos were suggested as alternative adjuvants. Gary Gamerman felt CpGs were very promising for this application since they activate the immune responses that are needed for GnRH vaccines, have low toxicity, can be synthesized at low cost, are stable and have features relevant for extended formulation.

To answer some questions about GonaCon, the panel spoke by phone with Kathleen Fagerstone of the USDA's National Wildlife Research Center (NWRC), a division of the Animal and Plant Health Inspection Service (APHIS). She explained that the GonaCon formulation is a thick emulsion that acts as a depot, remaining under the skin for a few days to a month after injection and extending the time over which the immune system is exposed to the vaccine. She noted the importance of M. avium (Mycobacterium avium) in the adjuvant for a robust response to a single vaccine dose, and said they had tried to reengineer the vaccine to reduce injection site reactions in dogs. They currently have two formulations developed, with and without M. avium, and expect longer duration with M. avium. With GonaCon, some non-responders are always observed, about 0% to 10% of deer in pens, and about 5% in healthy cats and dogs. In the field with less healthy populations, the number of non-responders increases to 30% to 50%. Kathleen Fagerstone felt a single boost should be enough to achieve a response in almost all animals that had initially responded. Though the GonaCon label for deer recommends a boost at 30 to 60 days, she did not feel the exact timing was crucial.

Important Knowledge Gaps Identified in This Session:

- Optimal number and spacing of boosters, amount of antigen, and age of animal to achieve maximum effectiveness of GnRH vaccine, which will require experiments in the target animal species

- What kind of responder rates can be expected in various populations of dogs and cats (well-kept pets vs feral, malnourished animals)

- Whether adjuvant is necessary in dog and/or cat, and if so, which adjuvant is most effective, and compatibility of adjuvants with delivery systems

- If boosters are required, how tight must be the timing of each boost; for example, if optimal timing for a boost is at 6 months, how wide is the effective window, 5.5 to 6.5 months, or 3 to 9 months? This information will require experiments in the target animal species.

- Can delivery technologies match the width of the effective window; that is, if the window is narrow, is there a technology which can consistently deliver drug within that window?

Delivery Technologies of the Future

A final session was held, focused on the state of the art and future expectations for delivery technologies.

A great deal of interest remained for microchip-based delivery systems, since these promise the ultimate in precise control of dose timing. Larry Acquarulo was also intrigued by the injectable balloon model, which would allow a large volume of liquid agent to be administered, and release to be controlled based on the engineering of the balloon membrane.

Viraj Mane suggested magnetic nanoparticles, currently being studied in thermoablation of tumors, and which might be adapted by this field to destroy other tissues such as gonad. The nanoparticles can be targeted using a ligand, and once in the target tissue, are activated with ultrasound or magnetic fields. Any particles that do not target correctly are not dangerous, since only the ones in the target organ will be activated, and Iron oxide magnetite nanoparticles are well-described as biocompatible and non-toxic. Magnetic nanoparticles could be made field applicable, depending on the expense and portability of the activation technology, would be relatively inexpensive, and have good shelf stability. At the present time, the GE VScan ultrasound device is very portable, about the size of a cell phone, and costs about $4000. There were concerns that the equipment needed might be too expensive, though Viraj Mane pointed out that the cost of ultrasound or magnetic-field activation hardware may be partially offset by the low cost of the nanoparticles themselves. The main

difficulty the panel foresaw with this approach was targeting the activation signal, whether ultrasound or magnetic, specifically to the ovary, especially if incorrectly targeted nanoparticles end up in nearby organs such as kidney or adrenal gland. Overall, the approach was thought to be a favorable one, because it requires only one injection, is safe for the administrator, and requires no follow-up.

Conclusions and Recommendations of the Panel

In conclusion, there was enthusiasm for the potential of extended drug delivery technologies to facilitate the development of a non-surgical, long-term contraceptive drug and/or vaccine, and perhaps a permanent sterilant, for cats and dogs. Though much depends on the active agent selected, the panel felt that for the majority of challenges presented by potential active agents, a delivery technology could most likely be found or developed to allow its delivery. The one exception was delivery of large proteins over the course of multiple years, which was felt to be challenging due to the difficulty of stabilizing proteins in an active conformation under in vivo temperatures. Important factors in design of a potential product include:

- The identity of the agent to be delivered
- The stability of the agent over the time it will be present within the body waiting for release
- The maintenance of activity of the agent over the time it will be present within the body waiting for release
- The delivery profile of the agent, whether a continuous dose over a period of days, weeks, months, or years, or a series of multiple discrete doses over time

If the active agent is a highly potent peptide (up to 20 to 30 amino acids in length) or small molecule, and if the required delivery profile is relatively simple, then multiple technologies already exist that can allow that small molecule to be delivered over a period of weeks, months, or years. In addition to various types of implants, long-lasting injectables such as microspheres or oil- or polymer-based depots, can be used to provide a sustained level of drug over shorter time frames.

If the active agent is a protein or other large molecule, or if multiple, discrete doses are required over a period of months or years, then the engineering becomes more difficult. Two issues arise: fewer technologies are able to accurately deliver a dose after a period of several months or years, and it is more difficult to maintain the stability and activity of a protein or large peptide over a long period.

Recommendations for Future Work

There was enthusiasm for work to collect basic data on using GnRH vaccines in cats and dogs. Knowledge gaps that need to be filled include:

- The optimal formulation of the vaccine for cats and dogs with respect to amount of antigen injected and identity of adjuvant used
- The optimal dosing to achieve long-term contraception: whether a depot formulation to extend the presence of the injected material (as in GonaCon) is important, and whether and how frequent boosts are needed
- Accurate data as to the number of animals who respond to the vaccine, and the persistence of the response under different dosing protocols

There was also enthusiasm for investigation into basic science relevant to delivery of proteins, and to complex delivery profiles:

- Identification of ways to stabilize proteins for long-term storage within an implant in vivo
- Determination of whether implant or microsphere systems can consistently and accurately deliver a discrete dose of drug after several months or even years
- Ability of microchip-type implants to deliver the volumes necessary for vaccine boosts

Finally, the panel agreed that along with development of a very long-acting contraceptive or sterilant, a permanent, obvious, and non-invasive marking system to identify animals that have been treated will be needed.

This Report was prepared by Tamara Golden, PhD, Golden Bioscience Communications, LLC

Special thanks to the Found Animals Foundation for funding this project!

Appendix A. Independent Reviewer Comments: Dr. Karl Malcolm, PhD, Reader in Pharmaceutics, School of Pharmacy, Queen's University of Belfast

Note: Dr. Malcom was unable to participate in the think tank in person but generously agreed to share comments based on the report of the proceedings. These comments, in some cases accompanied by responses from think tank planning committee members Gary E. Gamerman (GEG) and/or Linda Rhodes (LR), follow.

1. The primary focus on the development of depot and implant technologies is justified, since it is unlikely that the other drug delivery technologies discussed during the meeting will be able to achieve the goal of lifetime (multi-year) sterilisation / fertility control from a single application / treatment.

2. Given the clinical success of the contraceptive, progestogen-releasing implantable devices Implanon and Jadelle in humans, it is surprising that these commercially available devices have not yet been tested in cats or dogs. Such a study would provide proof-of-concept, with further iterations to the device design and the steroid compound in order to optimise the regime.
GEG: While the implant technology is suitable, I believe that these agents were said to be unsuitable for the species. LR: Progestagen compounds have been shown to have serious toxicities in both dogs and cats, sometimes at the effective dose. Therefore these compounds are too dangerous to be developed for contraceptives for companion animals.

3. I'm glad to see there is some leeway in the FAF definition of “affordable”! A device costing $1 is highly optimistic, and most likely completely unrealistic. Even a $5 device will be major challenge, given the significantly higher costs of current human implantable devices.
GEG: I believe Mike is referring to the delivery shell, not the API (active pharmaceutical ingredient)-containing finished product. Except for very expensive APIs, $5 is doable. I personally have experience with the human implant above and the ability to make them (finished, out the door) for around $5-7. LR: Cost has to be considered in the context of the current cost to surgically spay/neuter dogs and cats.

4. I note that most of the studies currently being supported by Michelson funding are geared towards identifying targets for suppression of fertility. Although this is a very important aspect of the work, it is only one of many that need to be addressed in order to move forward. Even in the absence of identifiable targets (and active agents), there is considerable merit in performing other studies that help define the nature of an implantable device (e.g. dimensions, safety, release kinetics, etc).
GEG: Agreed, one of the key recommendations/issues identified in by the think tank is that these issues need to be considered and studied (see page 12).

5. Thinking about the Suprelorin implantable device (which releases GnRH decapeptide), it would be interesting to know what aspects of the device design limit its clinical effectiveness to 6 or 12 months. Is it related to limitations in release kinetics of the lipidic medium, the drug loading of the active, to the lipid medium loading, for example? Could the device be re-engineered to provide release for longer periods?
GEG: Agreed, however, I do not know of any similar type of implant that can deliver drug longer than 6-12 months, largely for the points cited.

6. If targeting females is more important than males, another option might be a steroid-releasing vaginal ring device. Similar progestogen-only ring devices are being pursued for women, with the most advanced device providing fertility control for one year. In fact, a one year device is currently marketed in various South American countries for postpartum fertility control (Fertiring, Progering). It would be relatively easy task to rescale such ring devices to fit the dog or cat vagina (much of my own work is performed in macaques and sheep). Also, extending the release beyond one year is possible; for example, we have developed ring devices is my laboratory that release actives continuously for four years, albeit delivery antiretrovirals rather than steroids / steriliants. I suspect the main obstacle here is in identifying a safe and potent active agent that can be effectively released from a ring device.
GEG: This was considered and rejected by the board as not physiologically suitable for dogs and cats.

7. Gary Gamerman's comments on the practicality versus effectiveness of a sterilisation strategy are well made. The HIV microbicide community is also struggling with

this issue, although we would be delighted to achieve a 50% effective strategy!
GEG: Thanks!

8. Larry Acquarulo's comments are also highly relevant. For an implantable device, potency and stability are critical. You need to thinking about actives that are effective at daily release rates in the order of low mcg/day or less. He rightly points out that the size of the device, and thus the loading of the active agent, are critical determinants in the duration of release.
GEG: Agreed. LR: This is the advantage of the GnRH agonist class of drugs- they are active at very low concentrations if administered continuously.

9. Linda Felton's overview of controlled release drug delivery technologies was very helpful, and covered all the bases. I was pleasantly surprised to learn that the Gonazon silicone elastomer implant was capable of providing controlled of the GnRH agonist azagly-nafarelin. Again, it might be possible to re-engineer such a device to provide longer duration of release. For example, the current device appears to be a matrix-type device where the active agent is homogeneously distributed throughout the device, and where daily release rates effectively decrease with time. A modified version containing a non-medicated, rate-controlling membrane might usefully extend the release duration and provide zero-order release kinetics.
GEG: Entirely agree, this was a major board recommendation, except that there is a major clinical gap in knowing the release profile that is need for effectiveness (not just what is used in the current product) as this has a major impact on loading and costs.

10. Note the limited choice of polymeric materials for diffusion controlled release devices - silicone elastomer and the thermoplastic poly(ethylene-co-vinyl acetate) (PEVA). Polyurethane is also beginning to appear on the market.
GEG: Sadly correct.

11. I'm not convinced by the utility of erodible devices for this particular indication. First, the rate of bio-erosion depends primarily on the physiological environment in which the device is placed, which may vary from animal to animal. In other words, release of the active is environment controlled rather than device controlled. Second, the first-order release kinetics are not optimal. Third, the duration of release from these implantable devices is rather limited.
GEG: Agreed.

12. Both the osmotic systems and the electrically driven pumps are a pipe dream for this indication, mostly on account of the high costs. Viadur is now discontinued, but did costs thousands of dollar per device.
GEG: Mike's point is that with modern injection molding in PEEK, the costs are vastly lower than with older, high-precision machined products.

13. Microspheres and depot injections will not provide release beyond several months at best.
GEG: Agreed.

14. Linda Felton asked if it was possible to conduct accelerated stability tests. The answer is "yes"; these types of accelerated storage tests are routinely used in the pharmaceutical industry as part of early stage product development (preformulation, formulation and preclinical studies). For example, based on kinetics of drug degradation at 40oC, rates of degradation at lower temperatures can be determined, based on knowledge of the Arrhenius equation. The comments regarding the relative stability of steroids, peptides and proteins were all correct, including the recognition that solubilised actives are more prone to stability issues. Maintaining the stability of proteins in complex controlled release devices is exceptionally challenging. By comparison, contraceptive steroids are relatively easy to formulate.
GEG: Agreed.

15. Gary Gamerman commented that it might be necessary to characterize how the body might react to the device. The issue would initially be evaluated using placebo devices (no active agent) as part of preliminary safety studies.
GEG: I think how the body reacts to the implant in ways that affect performance might vary by species (and implant location) and other factors.

16. The delivery aspects of the vaccine approach are complicated by the usual requirement for prime-boost regimes. There has been some evidence reported in the literature to show that continuous administration of a vaccine antigen+ adjuvant can lead to successful

vaccination, although you run the risk of inducing immune tolerance. (P.S. Just realized upon further reading that this very point was also noted by Linda Rhodes!).
GEG: Entirely correct.

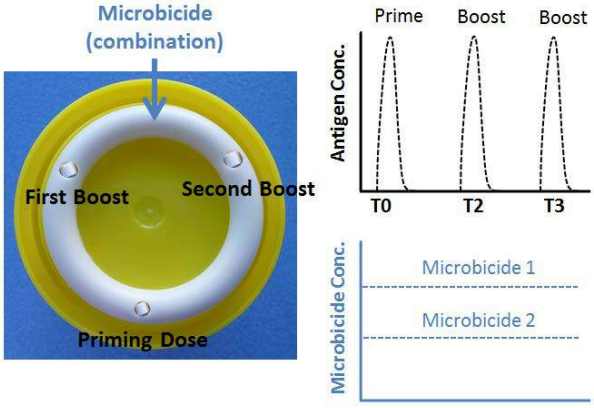
17. The panel noted the difficulty in discussing engineering solutions without knowing the nature of the active agent in advance. I agree - it would be much easier to first select an active agent with demonstrable sterilising / contraceptive activity and then consider the means of delivery the active over long periods.
GEG: Yes.

18. I was encouraged by the comment that the likely location of an implantable device (between the shoulder blades) was suitable for larger sized implants. Again, I think this will be critical in order not to constrain the engineering of such a device and to achieve the required release duration.

19. Michael Crowley and Larry Acquarulo's comment about the possibility of a device releasing a small molecule over 5-10 years are entirely valid, so long as the active is highly potent (ng or low mcg per day) and the pharmacokinetics are appropriate. I have attached a paper we published back in 2005 in which preliminary in vitro release data for dapivirine from a reservoir-type vaginal ring device could be extrapolated such that continuous, zero-order release over 4 years would be entirely practical (Malcom RK, Woolfson AD, Toner CF, Morrow RJ, McCullagh SD. Long-term, controlled release of the HIV microbicide TMC120 from silicone elastomer vaginal rings. *Journal of Antimicrobial Chemotherapy*. 2005. 56:954-956).

20. Michael Crowley's comment about starting with a device similar in construction to Implanon is an excellent suggestion. That's where I would start, too.
GEG: My thoughts as well, this was one of the panel recommendations once the right API is identified.

21. Gary Gamerman commented that it might be necessary to co-inject a short-acting contraceptive with a vaccine in order to cover the time required to for an immunological response to develop. There is much interest in the HIV field in co-administration of a vaccine and a small molecule microbicide; in fact, my group is developing a single vaginal ring device that simultaneously delivers a vaccine/adjuvant combination over up to seven days as well as a small-molecule microbicide. Both agents are simply located in different compartments within the device. In the device we have developed, the vaccine component is located in freeze-dried rods that are inserted into the microbicide-loaded ring body. This approach could also be engineered into an implantable rod type device, like Implanon.



GEG: While a neat concept…a nightmare from production/regulatory, supply chain management, I think.

22. Overall, the successful development of a controlled release implantable device for non-surgical sterilisation of cats / dogs will inevitably require collaborative input from experts across a wide range of scientific disciplines, including (but not limited to) reproductive biology, drug delivery, polymer processing / engineering, device manufacturing, animal testing and regulatory affairs.
GEG: Yes.

Appendix B. Independent Reviewer Comments:
David A. Brake, PhD
BioQuest Associates, LLC

Note: Dr. Brake was unable to participate in the think tank in person but generously agreed to share comments based on the report of the proceedings. These comments, in some cases accompanied by responses from think tank planning committee members Gary E. Gamerman (GEG) and/or Linda Rhodes (LR), follow.

Regarding the groups' conclusion that delivery of larger molecules, such as peptides over 20 residues or proteins, would be more difficult: it is generally recognized that relatively short peptides (e.g., <20 residues) require conjugation to a carrier protein in order be immunogenic or must be displayed in highly repetitive display via other larger molecules (e.g., VLP display). Thus, for the current delivery technologies discussed, immunogenic peptide delivery will be highly challenging.
GEG: Correct. It may not have been clear that we were discussing peptides/proteins with direct effect not as immunization agents, and that while you can do peptides in current elastomers, large proteins have not been successful.

There are newer classes of potent adjuvants for dogs and cats that are considerably safer with regard to injection-site reactions and could be tested in combination with GnRH-KLH.
GEG: Agreed…see discussion on using CpGs.

Completely agree with suggestion by Viraj Mane to co-administer systemic vaccine with a delayed release implant as a highly attractive approach to consider.
GEG: It might be necessary, or even a short-medium term depot to cover fertility until vaccination causes sufficient immune response to contracept. A point I did not consider: any co-administered suppressant cannot be one that causes down expression of the target epitopes or immune effectors that impair vaccination.

There are some other Mycobacterium-based immunostimulants described in the literature that when formulated with GonaCon may provide the required efficacy but are significantly less reactogenic.
GEG: Yes, adjuvanting needs to be explored. The problem with most of the adjuvants of these types is that they are not compatible with an implant and delayed release system I think.

Regarding the injectable balloon model, where (body site) the balloon is administered may increase risk of unintentional mechanical rupture based during periods of high physical activity by dog/cat.
GEG: Agreed, this was more speculation about delivery technologies than proposing as suitable for this application.

How has microchip battery technology evolved over the past 5 years? Is it possible in 2 years that battery life may be 7 or 10 years due to rapid technology evolution?
GEG: This is a power and cost requirements issue (though higher power also poses safety challenges). New generation batteries use energy harvester technologies (convert body heat or movement to power). For the microchip, the low running power requirements (timer and release element watts are less than a pacemaker I expect) might be doable, but battery life is not yet there and not in sight in 2 years. That said, the silicon-air battery is extremely promising on all counts (power density, cell durability life, safety, discharge profile) for this application.

Do PEEK-based electrically driven pumps already exist?
GEG: No reason why not; it is not a far reach as a replacement for most structural plastics, metals and ceramics. Michael Crowley: Yes, there are medical devices made of PEEK with electronic components. Medtronic has a line of products (neurostimulators – Restore, Synchromed, etc) for several conditions that are made of PEEK (and other materials) and have a battery driven pump. They are large and implanted with a line to an exterior bag that feeds the drugs (pain meds, diabetes, etc).

Here are some links if you want to look at them more closely:

http://www.medtronic.com/patients/chronic-pain/device/drug-pumps/our-drug-pumps-for-pain/synchromed-ii/index.htm
http://www.medtronic.com/patients/chronic-pain/device/neurostimulators/our-neurostimulators-for-pain/restore-sensor/index.htm

NanoMedical Systems (NMS) has a PEEK based implant that does not use an electrically driven pump to push the drug out. It works by a powerless computer chip and relies upon diffusion. I am a paid consultant with NMS and discussed their technology during our meeting. Their website is below and the animation of the front page is excellent to describe how the technology works: http://www.nanomedsys.com/

Recommended resources for additional information:
A good review of magnetic nanoparticles:
Mahmoudi et al. Superparamagnetic iron oxide nanoparticles (SPIONs): Development, surface modification and applications in chemotherapy. Adv Drug Rev 2011. 63:24-46.

Controlled release of vaccines:
Masotti A, Ortaggi G.Chitosan micro- and nanospheres: fabrication and applications for drug and DNA delivery. Mini Rev Med Chem. 2009. 9(4):463-9.

Particulate vaccine delivery systems:
De Temmerman ML, et al. Particulate vaccines: on the quest for optimal delivery and immune response. Drug Discov Today. 2011. 16(13-14):569-82.

Newer adjuvants for veterinary species:
Heegaard PM, et al. Adjuvants and delivery systems in veterinary vaccinology: current state and future developments. Arch Virol. 2011. 156(2):183-202.

New mycobacterial adjuvants:
Andersen CA et al. Novel generation mycobacterial adjuvant based on liposome-encapsulated monomycoloyl glycerol from Mycobacterium bovis bacillus Calmette-Guérin. J Immunol. 2009. 15;183(4):2294-302.

Appendix C. Independent Reviewer Comments:
Tridib Kumar Bhowmick, PhD
Postdoctoral Fellow, Silvia Muro lab, Institute for Bioscience and Biotechnology Research and Fischell Department of Bioengineering, University of Maryland, College Park

Note: Dr. Bhowmick was unable to participate in the think tank in person but generously agreed to share comments based on the report of the proceedings. These comments, in some cases accompanied by responses from think tank planning committee members Gary E. Gamerman (GEG) and/or Linda Rhodes (LR), follow.

The points discussed in the report expressed concern regarding the availability of few technologies that are able to accurately deliver a dose and maintain the stability of a protein or peptide for a prolonged time period.

I am in agreement with the other panel members' view of the need for development of a very long-acting contraceptive, and the urgent need for better information on the optimal formulation of a vaccine, optimal dosing information to achieve long-term contraception and acquisition of accurate data as to the number of animals who respond to the vaccine.

I would like to emphasize the following points in addition to the points mentioned in the report:

Overview of Extended and Controlled Release Technologies:
Bio-degradable implants (other than PLGA) - A biodegradable and biocompatible elastomer could be useful for an implant device [e.g. poly(glycerol-sebacate)].
GEG: Possible… I'm not as familiar with this. The problem erodibles have faced is control of release over very long periods and low loading capability

Non-degradable implants:
One method of drug release involves the use of a biocompatible non-degradable polymer (e.g. silicone elastomer).
GEG: Correct, or EVA

For more complicated delivery patterns:
There is a possibility of mixing multiple technologies vs engineering a more complex single device, (combining biocompatible degradable and non-degradable implant device with core and shell morphology).

Possible advantage:
Release of the drug from the delivery systems can be designed by enclosing the drug in a polymer shell or coat where the dissolution of the polymer limits the drug release. After the dissolution of the coating, the drug molecules are liberated and become available for absorption. Release of the drug at a controlled rate can be accomplished by controlling the thickness of the coating.

Possible disadvantage:
For peptides contained in degradable-coated implants, degradation can occur inside the implant while crossing the rate-limiting membrane.

Delivery technologies of the future:
Below are listed some newer technologies not discussed in the report:

Oral controlled release:
GEG: Orals are not suitable for long term delivery thus were not considered

- Multi-porous Oral Drug Absorption System (Elan Corporation, Ireland) is surrounded by a non-disintegrating, timed-release coating, which after coming in contact with gastrointestinal fluid is transformed into a semi-permeable membrane through which the drug diffuses in a rate-limiting manner.

- Multipor technology (Ethical Holdings Plc., UK) consists of a tablet core of an active drug, which is surrounded by a water-insoluble polymer membrane.

- TIMERx (Penwest Pharmaceuticals Co., USA) is a controlled-release drug delivery technology applicable to a broad range of orally administered drugs. This technology is based on an agglomerated hydrophilic matrix. The matrix consists of two pharmaceutically acceptable polysaccharides, locust bean gum and xanthan gum. Interactions between these components in an aqueous environment form a tight gel with a slowly eroding core from which the drug is released at a controlled rate for an extended period of time.

Large-molecule delivery:

- Bio-erodable Enhanced Oral Drug Absorption System (Elan Corporation) is an oral micro-particulate drug delivery technology designed for the delivery of macromolecules and is based on the entrapment of active pharmaceutical entities in a range of submicron sizes within biodegradable polymer matrices.
GEG: See above

- DepoFoam (DepoTech Corporation, USA) drug delivery system consists of microscopic spherical particles composed of hundreds to thousands of non-concentric chambers encapsulating the drug to be delivered.
GEG: A good technology, but like other depots cannot provide delivery for long term. LR: Depo-bupivicaine developed by Pacira using the DepoFoam technology just achieved regulatory approval – the release of bupivacaine is over about 1-3 days.

- DUROS (Alza Corporation) is based on implant technology, which provides an alternative for the delivery of a wide range of therapeutic compounds, including peptides, proteins, and other bioactive macromolecules. These implants are miniature titanium cylinders designed to provide continuous osmotically driven delivery of drugs within the body for up to one year.
GEG: This is Viadur that Mike discussed, good but expensive and not really available, but the fundamental concept is the basis for the other implants considered.

- Localized Drug Absorption System (Elan Corporation) is a novel targeted oral drug delivery technology. This technology utilizes targeting ligands, which specifically bind to certain absorption sites located on the apical surface of the epithelium cells of the human GI tract.
GEG: This is an oral approach

- Oral Mucosal Vaccines (Cortecs International Ltd.) can be administered by mouth and act by presenting the antigen to specialized cells within the intestine that pick up small particles via the Peyer's Patch and can process them into the immune system to stimulate a defensive response at mucosal sites.
GEG: Cortecs failed (I worked on a similar product with other companies). It is a very interesting approach but it has not been shown to be a robust vaccination route. Also use of oral route for a sterilizing vaccine is highly problematic due to human exposure concerns.

- Medipad (Elan Corporation) is a patient friendly system that enables controlled parenteral delivery while minimizing discomfort. This system is designed for the delivery of a broad range of compounds, from small molecules to proteins and peptides.
GEG: Would not be suitable for this application.

Transdermal and topical delivery:
GEG: Like orals, not suitable for species (fur-bearing) and application.

- Dermaflex (Elan Corporation) is a passive transdermal patch employing a hydrogel matrix in which a pharmaceutical compound is incorporated.

- Microsponge systems (Advanced Polymer Systems Inc., USA) are based on microscopic polymer-based microspheres that can bind, suspend, or entrap a wide variety of substances and incorporate them into a formulated product, such as gel, cream, liquid, or powder.

- E-trans (Alza Corporation) is an electro-transport system that uses low-power electric current to control drug administration through intact skin.

Future Work:
I also feel there is a need to collect basic data on using GnRH vaccines in cats and dogs and with all the listed points to fill the knowledge gap regarding formulation, dosing information and accurate dose response data mentioned in the report which ultimately could lead to development of an effective, single-injection, multi-year, contraceptive agent for sterilizing cats and dogs.

Appendix D. Independent Reviewer Comments:
Cory Berkland, PhD
Associate Professor, School of Engineering,
University of Kansas

Note: Dr. Berkland was unable to participate in the think tank in person but generously agreed to share comments based on the report of the proceedings. These comments, in some cases accompanied by responses from think tank planning committee members Gary E. Gamerman (GEG) and/or Linda Rhodes (LR), follow.

I believe that a single administration vaccine approach may be the only way to meet all of these competing goals. I think that is a tall order, technically. In the nearer term, prophylaxis of the female population using hormone implants may be plausible.

GEG: Yes. LR: Yes, but only if by hormone you mean the GnRH agonist molecules like deslorelin. Estrogens and progestational drugs are not safe for dogs and cats for contraception.