ABSTRACTS

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DEVELOPMENT OF NEW STEM CELL-BASED TECHNOLOGIES FOR CARNIVORE REPRODUCTION RESEARCH

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New reproductive technologies based on stem cells offer several potential benefits to both domestic animal and wild carnivore species. Because cats and dogs are important biomedical models of human disease, these new technologies can be used to benefit human health as well. Numerous types of stem cells have been described. For the purposes of this abstract, we shall concentrate on embryonic stem cells (ES cells) and spermatogonial stem cells (SSC), the stem cells of the male germine.

ES cells are pluripotent, meaning that they can differentiate into a wide variety of tissues representing all three embryonic germ layers. They are typically derived from the inner cell mass of blastocysts. Because they can be maintained in culture, they are readily accessible for genomic manipulations, such as the addition, deletion, or alteration of genes. The modified ES cells can be injected into embryos to generate chimeric offspring. Should they contribute to the germline, then they would provide a means to generate transgenic offspring. Currently, there are no published reports of feline ES cells, and only 3 reports of ES-like cells in dogs. None of these have been shown to contribute to the germline in a chimera, which is the “gold standard” for demonstrating true ES cell nature. Recently it has been shown in the mouse and human that somatic cells can become pluripotent by transiently expressing 3-4 specific genes. If this technology could be extended to carnivores, then cells that have the key characteristics of ES cells could be generated from adult tissues of individual patients. This might lay a foundation for the development of stem cell-based regenerative medical therapies that would avoid the issues of immune rejection. The study of inducible pluripotent stem cells is therefore potentially of great clinical interest.

Techniques based on SSC, such as spermatogonial stem cell transplantation and testis xenografting, offer complementary approaches to propagate genetically valuable individual males, even if they should die before producing sperm. These techniques might therefore have application to the conservation of endangered species of carnivores, as well as to biomedical research. Recently, our laboratory has successfully performed spermatogonial stem cell transplantation in the dog, with a recipient dog producing sperm of donor genetic origin. This technique first involves the preparation of the recipient testis; for dogs and cats, typically focal external beam radiation is used to deplete the endogenous germ cells. Next, cells from the donor testis must be individualized and injected into the rete testis of the recipient in a retrograde fashion, so that the donor cells can find and take up their appropriate niche on the basement membrane of the seminiferous tubules. Because the SSC can be transduced in culture prior to injection, spermatogonial stem cell transplantation also offers a method of generating transgenic animals. Testis xenografting is technically easier, involving only the preparation of small pieces of donor testis parenchyma, which are then transplanted into immunodeficient mice. This approach has been used to produce sperm from pre-pubertal testis tissue from both cats and ferrets. However, canine xenografts have not yet supported spermatogenesis, suggesting significant species-specific differences. The functionality of carnivore sperm produced by either method has not been demonstrated, although xenograft- and transplantation-derived sperm of other species have both been used to generate offspring. Such demonstrations represent critical next steps before these stem cell-based technologies can be used to provide the widest scope of research, clinical and conservation benefits in carnivores.