

**GONADOTROPH AND GNRH NEURON TARGETED APPROACHES FOR NONSURGICAL
STERILIZATION OF CATS AND DOGS**

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Surgical sterilization has been the mainstay of dog and cat population control. However, the associated costs, technical skills required, recovery time and facilities involved, have limited its wider application especially in developing countries. An ideal non-surgical sterilant that is safe, effective, permanent, administered as a single injection, and capable of being inexpensively manufactured could have a significant impact on the world-wide dog and cat overpopulation problem. Appropriate secretion of gonadotropins (LH and FSH) by pituitary gonadotrophic cells is critical for the maintenance of reproductive capacity in mammals. Loss of function of these cells mimics surgical castration in both loss of reproductive capacity and loss of gonadal steroids, including the associated undesirable behavioral effects in companion animals.

Gonadotropin secretion is dependent upon pituitary stimulation by gonadotropin-releasing hormone (GnRH). GnRH secretion is in turn dependent upon a second hypothalamic cell type secreting the peptides kisspeptin, neurokinin B, and dynorphin. First generation GnRH-linked cytotoxins selectively targeted to kill gonadotrophic cells have been explored by others, but the only available longer term study in male dogs showed serum testosterone recovered after 8 months, indicating recovery of reproductive function. The mechanism of this recovery is unknown. Therefore, suitable agents targeting these cells have yet to be developed and significant mechanistic questions remain to be answered to validate the approach. Efforts to target ablation of GnRH neurons have not yet been reported. With support of the Michelson Prize and Grants program administered by the Found Animals Foundation, we are developing strategies for targeted ablation of both of these cell types. In one approach we are exploring the use of small molecule GnRH antagonists linked to various cytoactive agents as improved gonadotroph specific toxins. We are also exploring the use of kisspeptin receptor toxins for GnRH neuron ablation. These approaches for ablation of the hypothalamic and pituitary cells controlling the reproductive endocrine axis, may provide a novel method for nonsurgical sterilization of cats and dogs.