REQUIRED FORMAT FOR LETTERS OF INTENT,
MICHELSON GRANTS IN REPRODUCTIVE BIOLOGY

THIS IS A SAMPLE LOI FOR A FICTIONAL PROPOSAL

Use professional letterhead with your complete mailing address, email & phone number.

Use ¾ inch margins and 11 point Arial or Helvetica Font. Do not exceed 2 pages.

Date

Program Manager
Michelson Grants in Reproductive Biology
Found Animals Foundation
Post Office Box 66370
Los Angeles, CA 90066

Dear Sir or Madam,

This is a Letter of Intent, seeking funding for a proposal entitled: "**Destruction of Hypophyseal GnRH Receptors Using Intravenous Kryptonite: Proof of Concept Study in Mice**" from the Found Animals Foundation. This is anticipated to be a three-year study, conducted in our laboratory and at the animal care facilities of our collaborator, Dr. Jane Doe, at the University of ABCDE.

Proposed approach for developing a single-dose nonsurgical sterilant:
We propose to conjugate kryptonite to a carrier peptide identified by phage panning that will be linked to gonadotropin releasing hormone (GnRH). When administered intravenously, the conjugate will home to the anterior pituitary and selectively bind to and ablate the gonadotrophs, leading to permanent sterility. As GnRH is evolutionarily conserved in both male and female mammals, this treatment, if effective in mice, is hypothesized to be a candidate for a "universal sterilant" in the Foundation's target species. Following proof of concept in mice we plan to submit a later proposal to test the product in male and female dogs and cats.

The rationale for proposing this approach:
In work published from our laboratory (Doe J: *J Irreprod Res*, *33*:12-26, 2007) we showed that kryptonite can be administered intravenously and is selectively toxic to pituitary basophils via inhibition of the glutathione-methyl-peroxidase pathway. We are aware that cells expressing GnRH receptors are present in other body tissues, and that the proposed treatment has the potential of harming non-target cells; however, since non-target cells express the receptor at concentrations and binding affinities more than 1000X lower than in the pituitary, we hypothesize that this treatment will not be harmful to non-target tissues. Simpson and colleagues (*J Irreprod Res, 27*:55-61, 2001) have demonstrated successful use of kryptonite linked to a carrier peptide and corticotropin releasing hormone in chemically ablating ACTH-secreting pituitary adenomas in the dog.

An overview of required research (budget estimates not required):
We propose a three-year study with general objectives of (i) identification and concentration of appropriate homing peptides from the murine hypophysis, using phage panning, (ii) chemical construction of the kryptonite/peptide/GnRH conjugate using techniques in use in our laboratory, (iii) dose titration of the conjugate in mice, first using an *in vitro* cell line expressing the GnRH receptor, and (iv) intravenous administration of the optimal dose, 2X dose and control dose of the conjugate to post-puberal mice, with subsequent safety/efficacy monitoring in a lifetime (18 month) study.

Work on this project could be initiated in our laboratory on receipt of funding.

The investigators confirm that we have reviewed the required resources prior to submission of this letter of intent.

Sincerely,

Principal Investigator, PhD
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Co-Investigator, PhD (if applicable)
co-inv@emailaddress.com