



Crinetics
Pharmaceuticals

Gonadotroph and GnRH Neuron Targeted Approaches for Nonsurgical Sterilization of Cats and Dogs

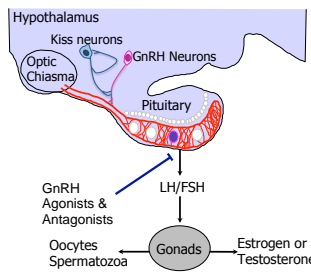
5th International Symposium on Non-Surgical Contraceptive Methods of Pet Population Control
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Neuropeptide Receptor Targeted Therapeutics for the Treatment of Endocrine Diseases and Cancers

The Hypothalamic-Pituitary-Gonadal (HPG) Endocrine Axis

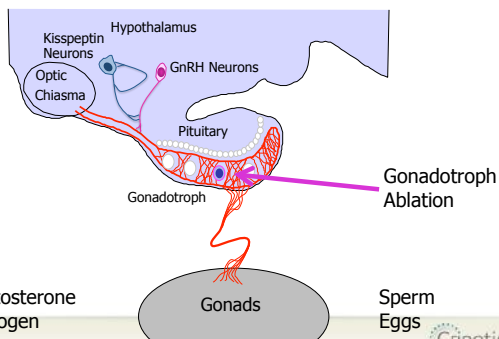


GnRH Therapeutics

- *Breast/Prostate Cancer*: eliminate gonadal steroids
- *Endometriosis/Fibroids*: Prevent high mid-cycle estrogens
- *Infertility*: Prevent premature LH surge
- *Precocious Puberty*: block LH/FSH pulsatility




Sterilization Strategies



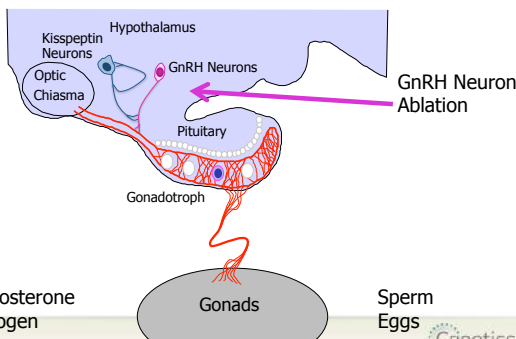
Gonadotroph Ablation

Testosterone Estrogen

Sperm Eggs




Sterilization Strategies

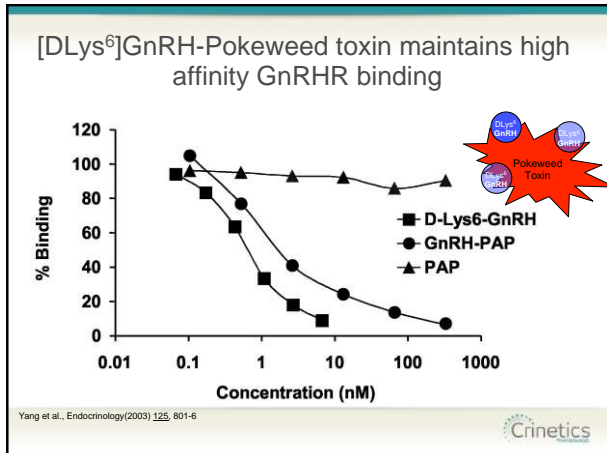
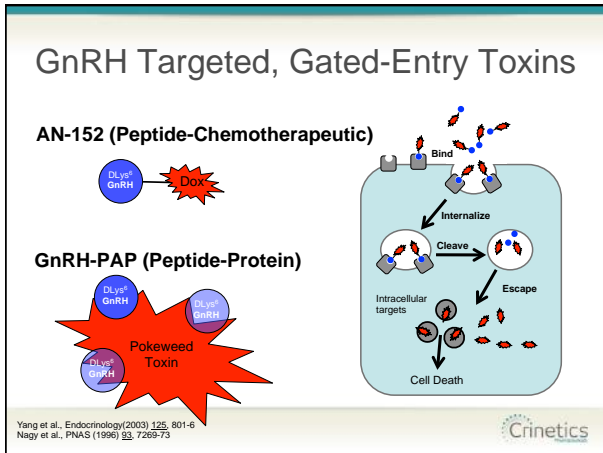
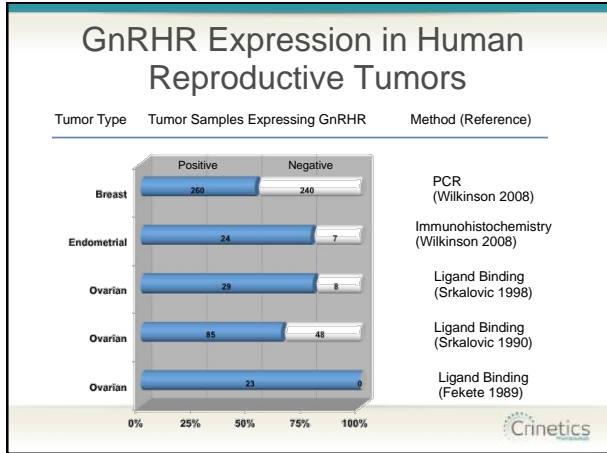
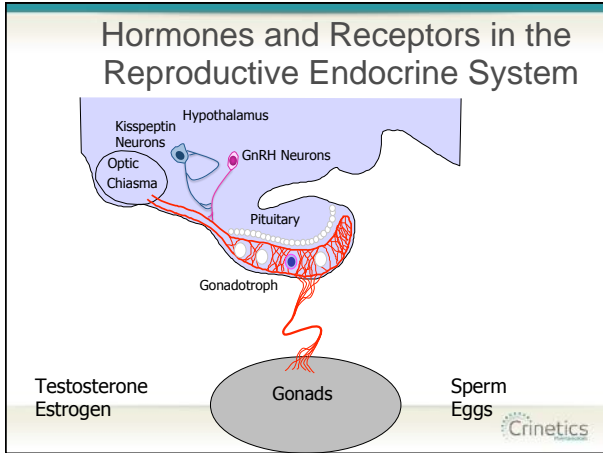


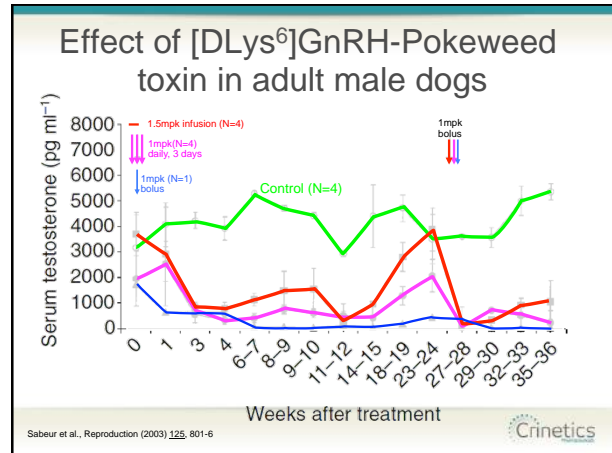
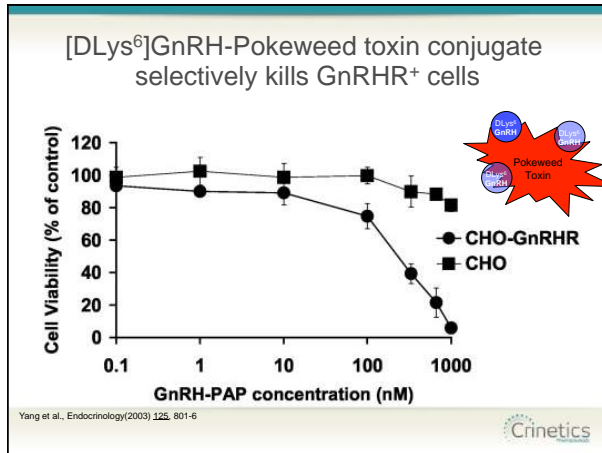
GnRH Neuron Ablation

Testosterone Estrogen

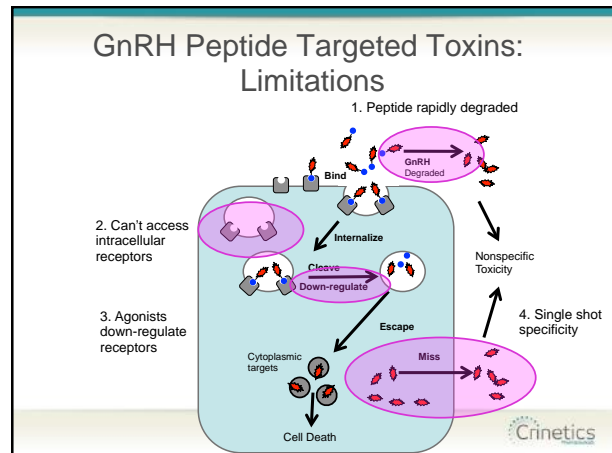
Sperm Eggs





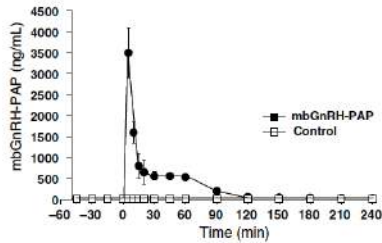


- ## Unanswered Questions
- Were gonadotrophs ablated?
 - Time course more consistent with GnRH immunization.
 - Why did reproductive function return?
 - If gonadotrophs were killed, do they regenerate?
 - What limits efficacy of first generation GnRH-toxins?



Pharmacokinetics of [DLys⁶]GnRH-Pokeweed toxin in sheep

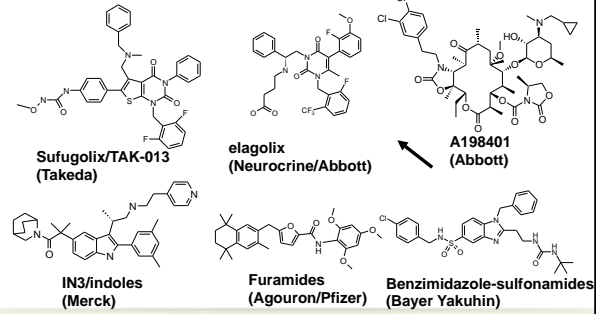
Rapid degradation of DLys⁶[GnRH]-PAP conjugates in sheep



Yang et al. Am J Repro Immunol (2006) 55, p208

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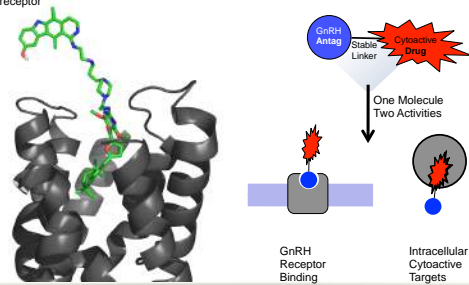
Orally available, small molecule GnRH antagonists



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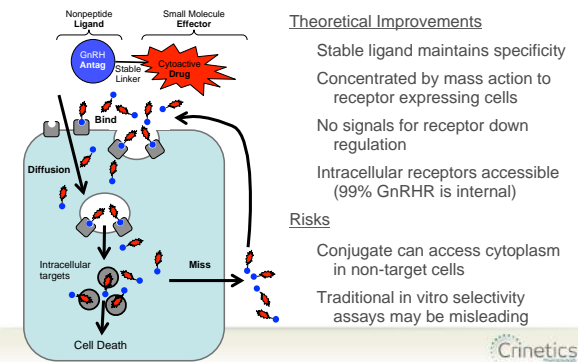
Hypothesis: Stably linked, small molecule GnRH antagonist conjugates

Nonpeptide GnRH antagonist bound to the GnRH receptor

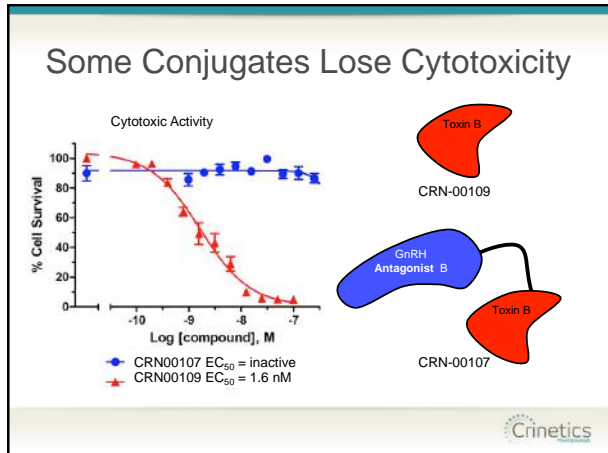
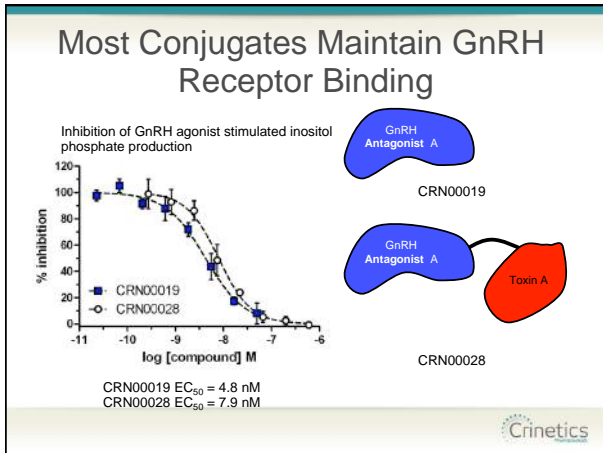
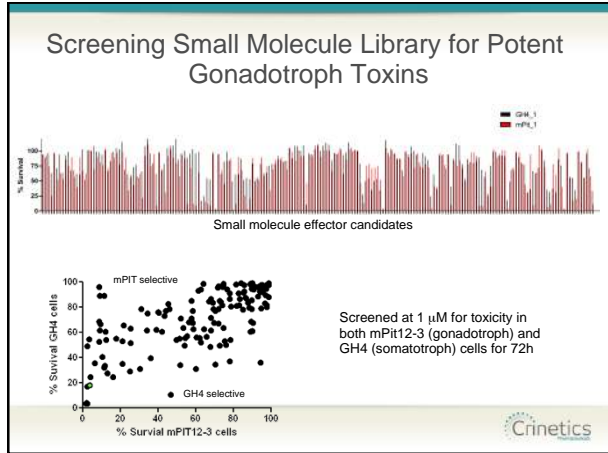
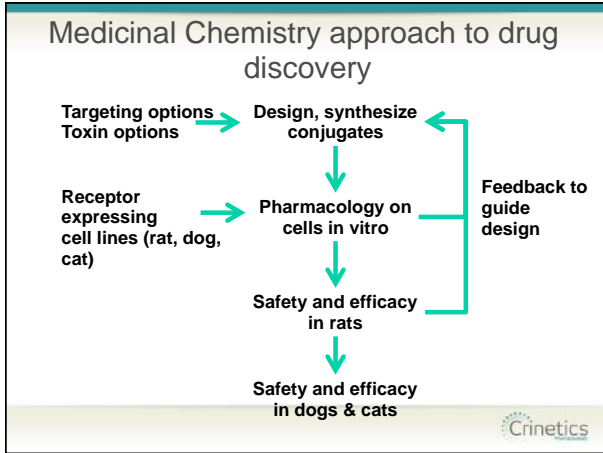


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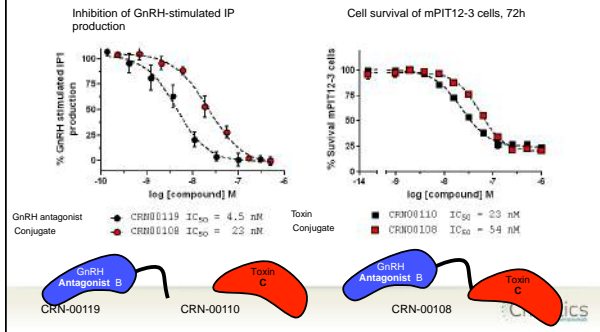
“Concentrate and Kill” model



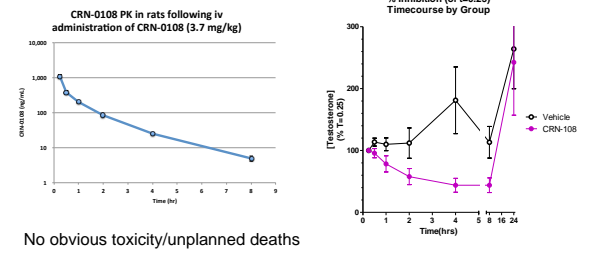
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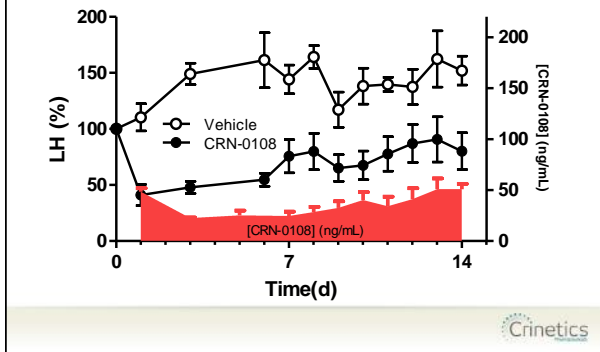
CRN-0108 Is Both a Potent GnRHR Antagonist and Toxin



Effects of single dose CRN-0108 in intact male rats



Effects of 14-day infusion of CRN-0108 in castrate rats



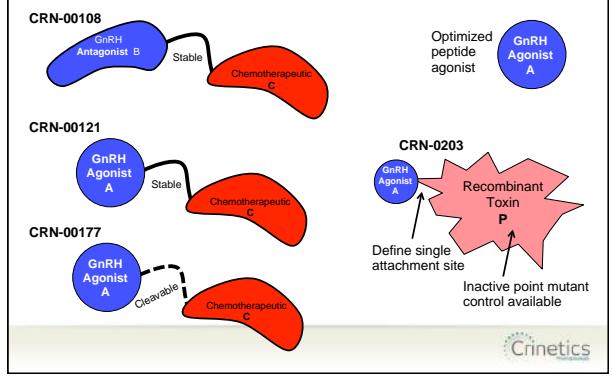
Conclusions so far

- Small molecule GnRH antagonists can be used to target GnRHR expressing cells
- Multiple small molecule toxins can be targeted without loss of cytotoxic activity
 - Impaired cytoplasmic access is a common issue
- CRN-0108: Occupies GnRH receptors in vivo with minimal gonadotroph cytotoxicity
 - Insufficient intracellular delivery in vivo?
 - Ineffective toxin for quiescent eutopic gonadotroph?

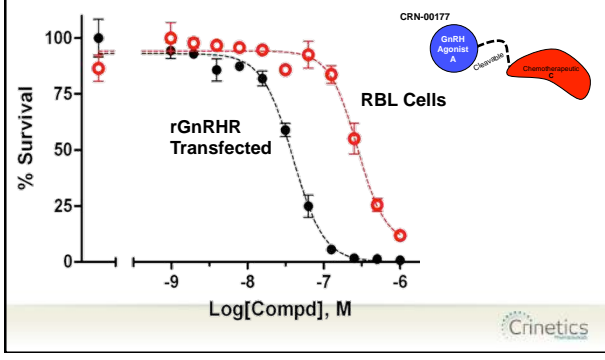
Questions

- Are GnRH agonists more effective for intracellular delivery of small molecule cytotoxins?
- Are there more effective toxins for quiescent eutopic gonadotrophs?

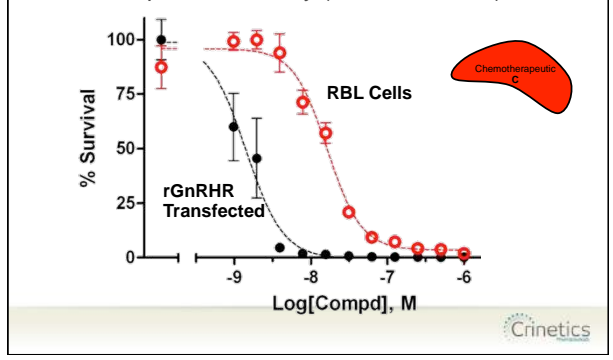
Next Steps: *Controls and more controls*



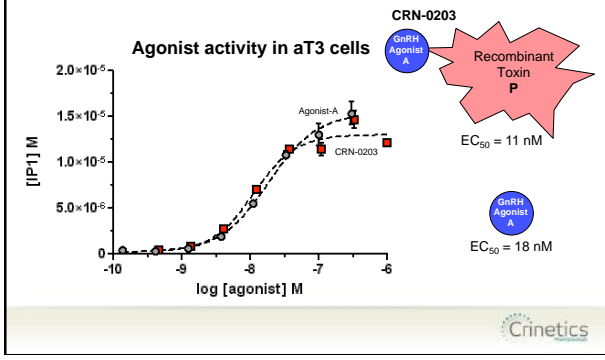
CRN-177 appears to be selective for GnRHR expressing cells



Comparing transfected to untransfected cells is inappropriate for determining GnRHR receptor dependent toxicity (for some toxins)



Second generation GnRH agonist targeted protein toxins



Acknowledgements



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