Michelson Found Animals Prize & Grants

- History
- What We Learned
- The Future

Linda Rhodes, VMD, PhD
Thomas Conlon, PhD

Michelson Found Animals Foundation

- 501(c)(3) private foundation
- Founded in 2005 by philanthropist Dr. Gary Michelson

Michelson Found Animals Foundation

- Dedicated to developing cost-effective, scalable, sustainable animal welfare business models to save pets and enrich people's lives

Michelson Found Animals Foundation

Found Animals initiatives:

- funding low-cost spay/neuter surgeries
- promoting adoption
- microchip sales
- a free microchip registry service
- Leap Venture Studio, a partnership between Michelson Found Animals, Mars Petcare, and R/GA Ventures is the first dedicated accelerator program for the $100B pet care industry

Mission: To eliminate the euthanasia of healthy, adoptable companion animals and to reduce populations of feral & free-roaming cats & dogs.

Michelson Found Animals Prize & Grants

Launched 2008

Michelson Prize

$25 million for a permanent, single-dose, nonsurgical sterilant for male and female dogs and cats.

Michelson Grants

$50 million in grant funding for promising research in pursuit of a permanent, single-dose, nonsurgical sterilant.

Michelson Prize Criteria

1. Single-dose, permanent, nonsurgical sterilant
2. Safe and effective in male & female dogs & cats
3. Ablates sex steroids and/or their effects
4. Suitable for administration in a field setting
5. Viable pathway to regulatory approval
6. Reasonable manufacturing process and cost

The Michelson Grants

- Proposed research is not required to generate results that will meet all of the Prize criteria.

- Research approaches must represent a potentially significant improvement over existing products.

Bringing New Science

- Neuroscientists
- Oncologists
- Immunologists
- Virologists
- Pharmaceutical chemists
- Molecular biologists
- Reproductive physiologists

Michelson Grants 2008-2018

Funded projects:	37
Grantee publications:	22
Funds committed:	$15.5 million
Funds still available:	$34.5 million

Current Projects

David Baker, PhD
University of Washington

Patricia Donahoe, MD & David Pepin, PhD
Massachusetts General Hospital

Cristina Gobello, MV, DVM, DECAR
National University of La Plata

David Mooney, PhD
Harvard University

Benjamin Renquist, PhD
University of Arizona

Lee Smith, PhD
University of Edinburgh

Grantee Institutions

United States:
Auburn University, Auburn AL
Children's Hospital of Philadelphia, PA
Cornell University, Ithaca NY
Crinetics Pharmaceuticals, La Jolla CA
Harvard University, Cambridge MA
Iowa State University, Ames IA
Massachusetts General Hospital, Boston MA
National Jewish Health, Denver CO
Ohio State University, Columbus OH
Oregon Health & Science University, Portland OR
Scripps Research Institute, Jupiter FL
Southern Illinois University, Carbondale IL
University of Arizona, Tucson AZ
University of California, Berkeley CA
University of Iowa, Iowa City IA
University of Medicine & Dentistry, Piscataway NJ
University of Pennsylvania, Philadelphia PA
University of Virginia, Charlottesville VA
Vaxin Pharmaceuticals, Birmingham AL
Wake Forest University, Winston-Salem NC
Yale University, New Haven CT

Argentina:
National University of La Plata

Australia:
University of Newcastle
University of Western Australia

Canada:
University of Guelph

Netherlands:
University of Utrecht

New Zealand:
University of Auckland

United Kingdom:
University of Edinburgh

Taking the Product to Market

- From proof of concept to regulatory approval in the US
- Manufacturing and distribution to ensure wide availability to reduce pet populations

What Have We Learned?

Early Days: Lots of Ideas

Immunocontraception

Brain

Pituitary Gland

Deslorelin revisited

Gonads

Novel Approaches

Immunocontraception

- Zona pellucida vaccines: Effective, but short term
- GnRH vaccines: Effective in many species, but short term
- Other targets: ?

COULD IT BE DONE BETTER?

Immunocontraception: Novel Vaccine Delivery

Dr. Doug Jones – Iowa State

Bioerodable beads, immune-regulated release of antigen from an implant

Dr. David Putnam – Cornell

Self-boosting outer membrane vesicles with polymeric microparticles

Dr. Michael Munks – Oregon Health and Science Univ.

Using herpes viral vectors to deliver antigens for long-term exposure

Dr. David Mooney – Harvard

Infection mimicking biomaterial scaffolds (in progress)

Immunocontraception: Novel Antigens

Dr. Larry Chamley – Univ. Auckland, NZ

Antigen – sperm reactive protein with anti-sperm antibodies (SPRASA)

Dr. Megan Lloyd – U. Western Australia

Antigen – rat ZP-3 glycoprotein delivered by cytomegalovirus

Dr. Tatiana Samoylova- Auburn University

Phage particles with thousands of copies of GnRH

Dr. Kent Van Kampen – Vaxin, Inc.

Adenovirus vector expressing multiple GnRH copies

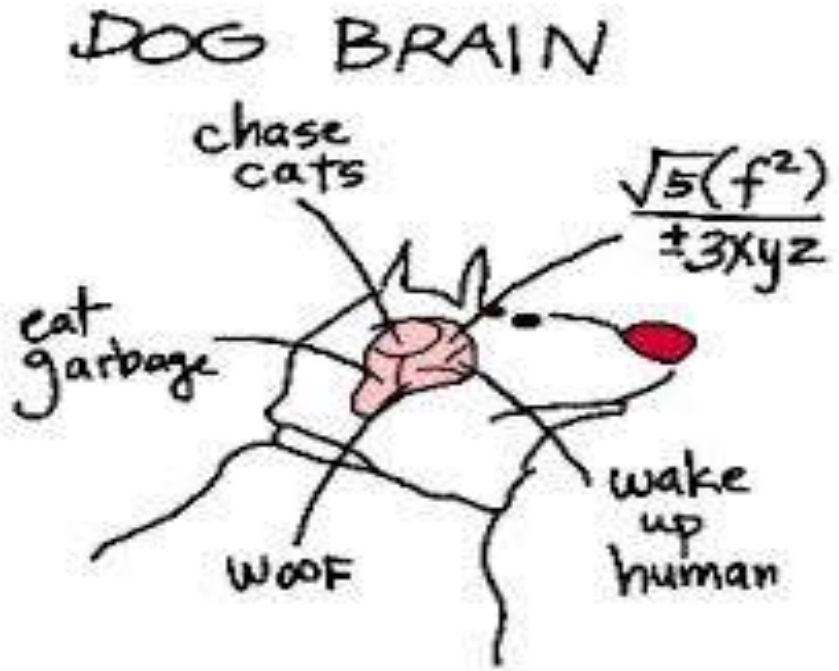
Immunocontraception

Barriers:

- Single shot
- Lifetime immunity

Brain Targets

GnRH Neurons: Master Control of Reproduction



Brain Targets

Dr. Meenakshi Alreja – Yale

Ablate GnRH neurons with kisspeptin-toxin conjugate

Dr. Colin Bishop – Wake Forest Baptist Medical Center

Ablate GnRH neurons using targeted cytotoxic exosomes

Dr. Auke Schaefers-Okkens – Univ. Utrecht

Kisspeptin antagonist to suppress GnRH neurons

Dr. Scott Struthers – Crinetics Pharmaceuticals

Kisspeptin-toxin conjugates caused LH surge, but doesn't kill the neurons

Brain Targets

Dr. Bev Davidson – Children's Hospital, Penn

RNA interference to shut down kisspeptin and neurokinin B in the hypothalamus – couldn't get expression in brain

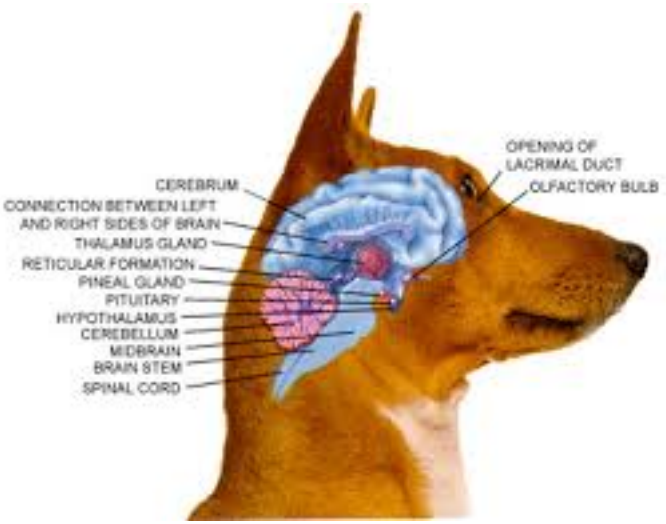
Dr. Sergio Ojeda – Oregon Health and Science Univ.

Developing vectors to specifically home to cat hypothalamic neurons – could not demonstrate targeting

Brain Targets

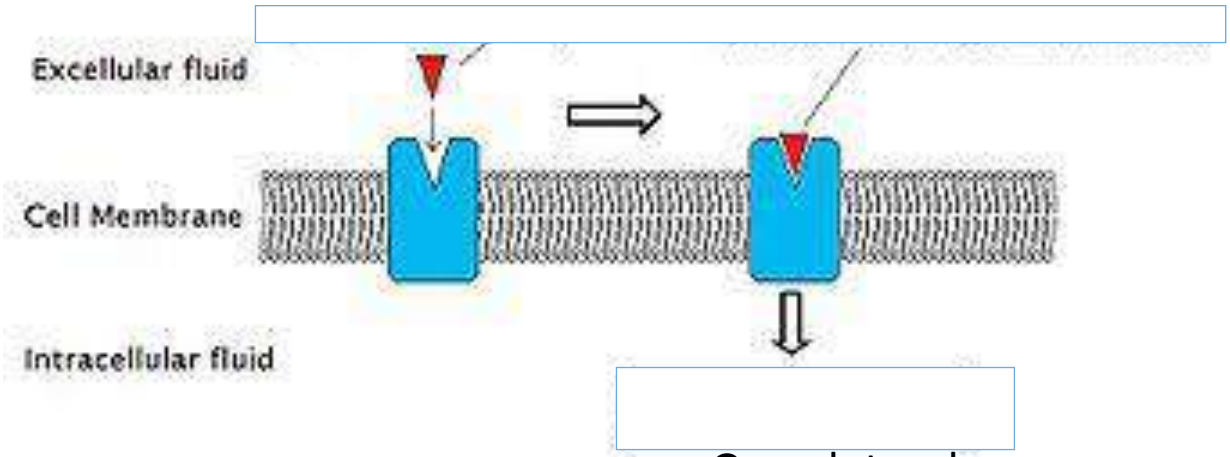
Barriers

- Blood brain barrier
- > 90-95% GnRH neurons need to be inactivated



Pituitary Gonadotrophs

GnRH + Toxin = Dead Gonadotrophs



Pituitary Gonadotrophs

Dr. Tatiana Samoylova – Auburn Univ.

Slow release DNA vaccine against GnRH – receptor to ablate gonadotrophs (immunocontraception in a sense…but with pituitary target)

Dr. Scott Struthers – Crinetics Pharmaceuticals

GnRH-toxin conjugates did not cause ablation

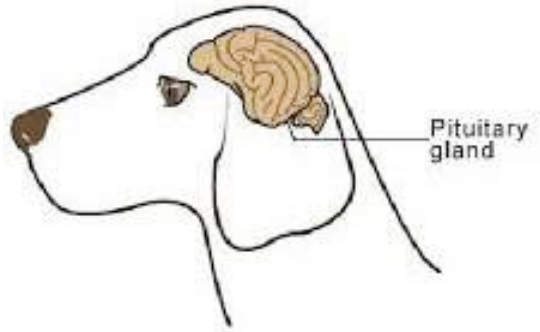
Dr. Ben Renquist – Univ. of Arizona

GnRH-toxin conjugates shown to be inactivated by endosomes (new project in progress to disrupt endosomes)

Pituitary Gonadotrophs

Barriers:

- Resistant to toxin effects
- GnRH receptors may be down-regulated
- Toxins may be inactivated
- Longer exposure than is possible with single shot may be required



Deslorelin Implants

Suprelorin 6 months – 4.7 mg

Suprelorin 12 months – 9.4 mg

Suprelorin 10 years…..?

Deslorelin Implants

Novel Formulation

Dr. John Lannutti – Ohio State Univ.

Electrospun nanofiber formulation of deslorelin – did not release drug in various configurations

Early Administration

Dr. Cristina Gobello – National Univ. of La Plata, Veterinary School

Prepubertal high dose implants in puppies and kittens – significant delay of puberty, but not permanent

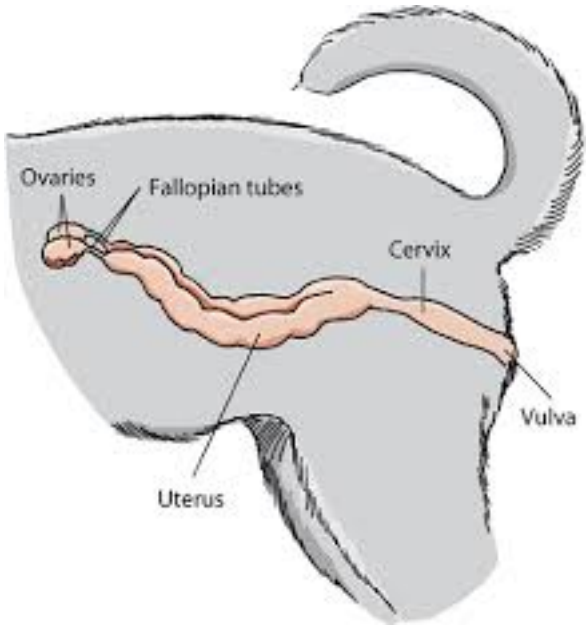
Deslorelin Implants

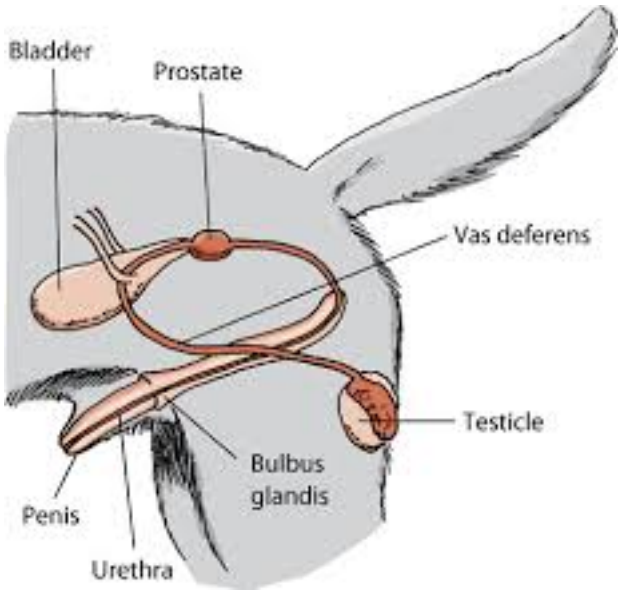
Barrier

Release over 10 years not possible with current technology

Targeting the Gonads

Likely to be effective in only one sex





Targeting the Gonads

Dr. William Ja – Scripps Research Institute

FSH-toxin conjugates for targeting Sertoli and granulosa cells in testes/ovary hard to make, not tested *in viv*o

Dr. Ralph Meyer – PennVet

Inhibition of an enzymatic pathway (PAR) combined with an alkylating agent to kill testicular germ cells (some effect, but reversed in a few months in rodents)

Dr. Prema Narayan – Southern Illinois University

Targeting the LH receptor – no efficacy

Dr. Paul Copeland – Robert Wood Johnson Medical School

Characterize the selenoprotein P testes specific receptor as a potential target

Targeting the Gonads

Dr. George Gerton – Univ. of Pennsylvania

Design superparamagnetic iron-oxide nanoparticles to kill gonadal cells

Dr. John Herr – Univ. of Virginia

Identify peptides that bind oocytes, link to toxin to kill primary oocytes

Dr. Lee Smith – Univ. of Edinburgh

Use of microRNA to inhibit androgen receptor protein in the testes (ongoing)

Dr. John Aitken – Univ. of Newcastle, Australia

Identify new proteins on primary follicles and spermatogonia, couple with cytotoxin, to kill target cells, evaluate alkylated FSH peptides to mediate cell depletion.

Targeting the Gonads

Barriers:

- Approaches for one sex only
- Unproven targets
- Specificity of targets challenging

Novel Approaches

Dr. Jon LaMarre – Univ. of Guelph

Targeting piRNA and endo-siRNA pathways important in meiosis in oocytes and also in spermatogonia – not tested *in vivo*

Dr. George Bentley – Univ. of California, Berkley

Over-expression of a novel gonadotropin inhibitory hormone using a viral vector

Next Steps….

Gene Delivery

Viral vector

Deliver relevant gene

Lifetime expression

Lifetime effectiveness single shot?

What is a Viral Vector?

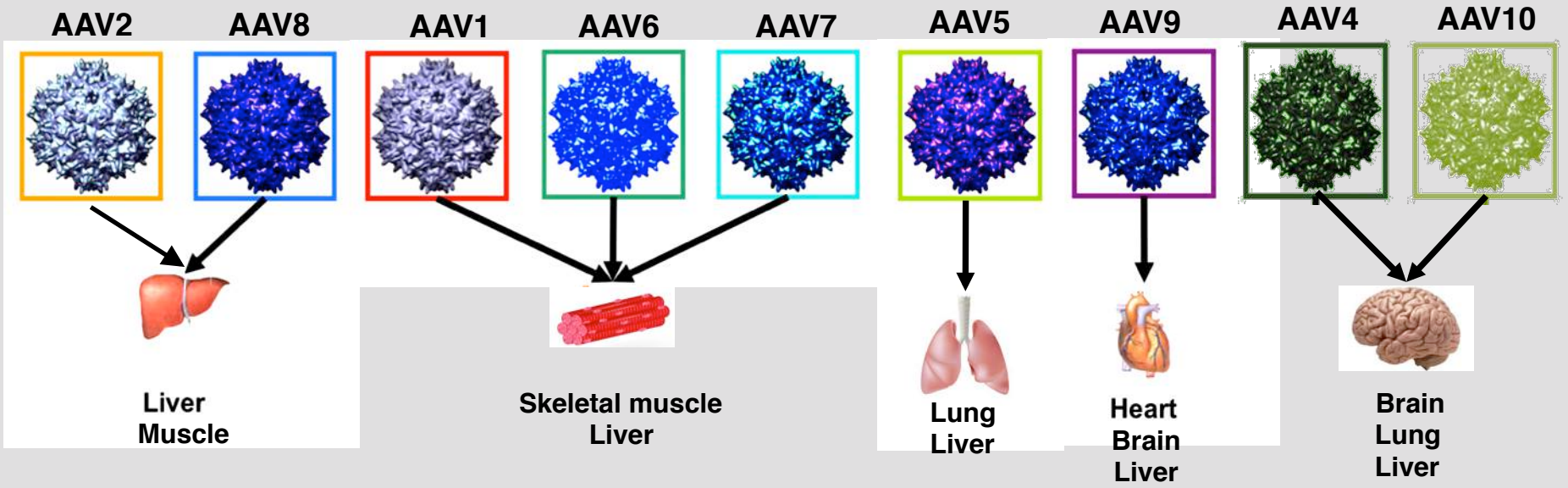
AAV: Adeno-associated virus

Small virus of single stranded DNA

Recombinant AAV: No viral genes, contains therapeutic gene

Establishes in tissues (liver, muscle) and the therapeutic gene is then expressed

Tissue-tropism of AAV serotype vectors



Gene Therapy in Humans

- 728 Phase I US trials (>2,000 worldwide)
- 178 Phase II US trials (279 worldwide)
- 20 Phase III US trials (59 worldwide)
  - 100% are either *ex vivo* hematopoietic or cancer related
- 2 Phase IV US trials
  - Both using Adenovirus expressing p53 tumor suppressor

2017: Two gene therapy drugs have been approved in the USA

Gene Therapy in Animals

Disease	Species Breed	Treatment	Vector	Target Organ
Muscle Weakness "Old Age"	Canine	Anti-myostatin	AAV	Liver
Congenital achromatopsia "Color Blindness"	Canine	Blue-cone opsin	AAV	Retina
Malignant tumors	Canine,Feline Equus	Telomerase	Lentivirus/ Herpes	intra- tumor
Osteosarcoma	Canine	Interleukin-2	Lipid	Lung/bone
Pulmonary Metastatic Cancer	Canine	Interleukin-2	Lipid	Lung
Glanzmann Thrombasthenia (GT)	Canine Great Pyrenees	integrin αIIB	Lentivirus	ex-vivo HSC

Gene Delivery for Contraception

Patent applications for delivering GnRH antibody via viral vector:

- James Wilson (U Penn)
- Bruce Hay (Cal Tech)

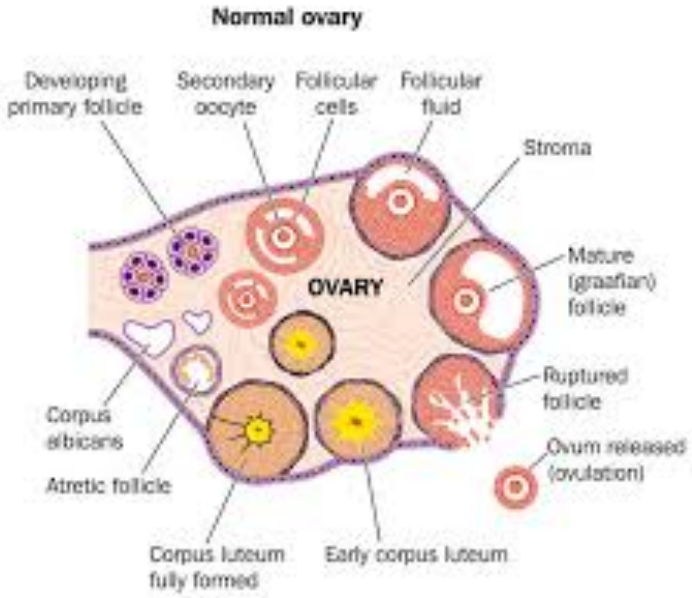
Published proof-of-concept research:

Li J, et al., Vectored antibody gene delivery mediates long-term contraception. Current Biology 25, R811–R826, October 5, 2015.

Gene Delivery for Contraception

Delivery of Mullerian Inhibiting Substance via AAV vector

Block of follicular development



The Future?

Gene delivery offers the potential of single shot lifetime effectiveness

Progress in human medicine will pave the way for animal applications

Gene Delivery is Making an Impact

- Video