Muscular Dystrophy (MD) Studies on Dogs: Time for a Change?

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ABSTRACT

In 1981, University of Georgia experimenters observed that two littermates—Rusty and Dusty—exhibited signs of Golden Retriever muscular dystrophy (GRMD). This observation initiated decades of deliberate breeding of dogs to be afflicted with this disease marked by the progressive degeneration of skeletal and cardiac muscle. As MD ravages their bodies, dogs experience difficulty walking, eating, swallowing, and breathing. Potential treatments in dogs are assessed using measurements of muscle strength and joint contractures. Clinical milestones such as loss of ambulation and the need for ventilator support are tracked. However, researchers acknowledge that after decades of testing on generations of debilitated dogs, there is still no cure or treatment to reverse the course of MD in humans. We consider the global proliferation of colonies of MD dogs, challenges encountered in using dogs, and promising alternative research methods.

LACK OF TRANSPARENCY

Texas A&M University (TAMU) has been purposefully breeding dogs to have MD. Despite publications and records documenting this, TAMU has attempted to mislead the public:

"*Affected dogs are born with the disease and are not artificially made to be 'sick.'*"– Texas A&M Official Statement

The Humane Society Veterinary Medical Association disagrees that perpetuating this agony is in any way helping dogs. Other experts refute the scientific claim that these experiments help humans suffering from muscular dystrophy:

"*[T]he differences between dogs and humans … make dogs poor surrogates for muscular dystrophy research. Indeed, canine muscular dystrophy research has not led to treatments that cure or target the cause of muscular dystrophy in human children*." -- Narda G. Robinson, D.O., D.V.M., M.S., F.A.A.M.A.

http://www.kagstv.com/news/local/texas-ams-second-response-to-peta-claims/429341935/

MUSCULAR DYSTROPHY

Differences Between Human MD and Canine MD

Indication	Humans	Dogs
Neonatal death	Rare	20-30% of canine DMD puppies
Age at first symptom	2 to 4 years	Birth to 3 months
Growth retardation	Absent	60% of normal by 6 mos.
Ambulation	Lost during early teens	Complete loss absent
Cardiomyopathy	Evident at 16 years	Detectable at 6 months
Neurocognitive symptoms	33% of affected individuals	Not noted
Lifespan	25-33% normal length	50% normal length
Functional orientation	Biped	Quadruped

The Experiences of a Dog in a Canine MD Lab

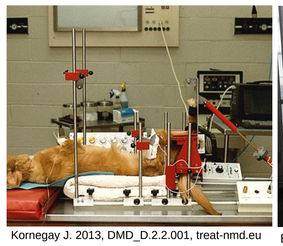
The suffering of dogs bred to have GRMD begins early in life. Symptoms manifest in puppyhood, often requiring specialized care.

Dogs with GRMD experience the following:

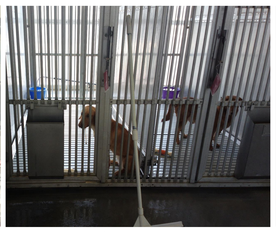
- Inability to suckle
- Stunted growth
- Stiff gait and exercise intolerance
- Cannot open their mouths fully due to spasms of the jaw muscles (trismus)
- Abnormal stance from muscle weakness
- Contracted muscles, causing the spine to curve inward
- Enlarged muscles in the tongue and diaphragm
- Difficulty breathing and swallowing
- Lifetime imprisonment in barren cages, unable to run, play, or even eat properly

For dogs in canine MD laboratories, their suffering is magnified by the invasive and painful tests to which they are subjected, including:

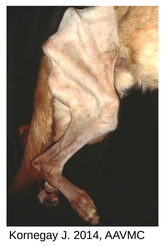
- Repeated surgeries to obtain muscle biopsies and other tissue samples
- The use of mechanical levers to stretch the dogs' muscles until they tear
- Injection of experimental drugs, often with painful and/or lethal side effects
- Delivery of repeated electrical shocks to stimulate muscle contractions



Kornegay J. 2013, DMD_D.2.2.001, treat-nmd.eu



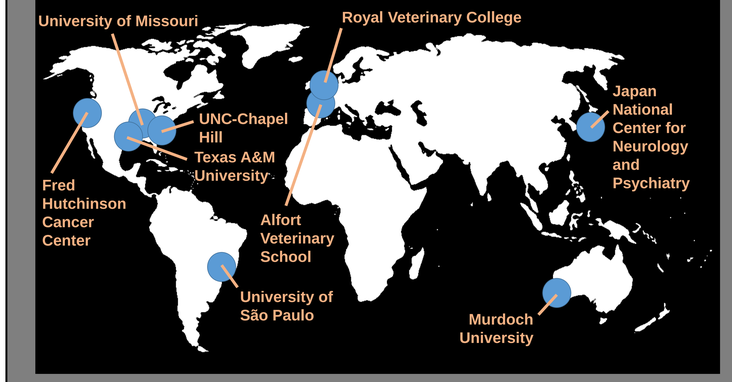
Eyewitness photo from inside TAMU's canine MD lab, given to PETA



Kornegay J. 2014, AAVMC

Dogs that carry the GRMD gene but are asymptomatic are kept as breeding stock. Confined in small kennels for their entire lives, they exhibit stereotypic and abnormal behaviors due to boredom, stress, and anxiety.

PAST AND PRESENT CANINE MD BREEDING COLONIES



DRUG DEVELOPMENT

Translational Problems
(as listed by a canine MD experimenter)

NEUROSCIENCE TEXAS A&M UNIVERSITY

Lost in Translation
(Ergorul and Levin 2013)

- The *Butterfly Effect* (chaotic behavior whereby small differences in the animal model lead to substantial differences in clinical results);
- The *Princess and the Pea* problem based in variability of effect size when progressing from biochemical findings through tissue culture and animal and human studies (the pea does not indent the mattress to the same degree as the princess);
- The *Two Cultures* problem evident in preclinical and clinical research (need for more rigorous experimental design in preclinical studies).

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The Realities of Drug Development

- The success rate for Phase II human clinical trials fell from 28% in 2006-2007 to 18% for 2008-2009 (Arrowsmith 2011).
- Over half (51%) of 108 reported Phase II failures occurred due to insufficient efficacy, even though most drugs were assessed in animal models (Plenge et al. 2013).
- Only 28 of 76 (37%) of *highly-cited* studies that investigated a preventive or therapeutic intervention in an *in vivo* animal model over the 1980-2000 period were replicated in human randomized trials (Hackam and Redelmeier 2006).

Kornegay J. 2014, AAVMC

The Eteplirsen Controversy

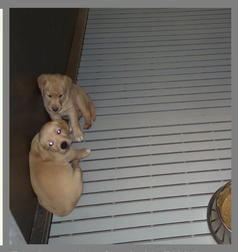
In 2016, a U.S. Food & Drug Administration (FDA) review committee recommended *against* approval for Eteplirsen, an exon-skipping drug which was tested in mice, dogs, and monkeys. Following a 12-person clinical trial, the FDA concluded there was little evidence of Eteplirsen's efficacy, but their recommendation was overruled by director Janet Woodcock after a heartfelt plea from patient advocacy groups.

"*The research history for DMD, and in particular the animal experiments using dogs have been an absolute failure despite several decades of effort. The unwarranted approval of Eteplirsen is a measure of the futility and frustration around the fact that there is nothing to show for all this research*." – John Pippin, M.D., F.A.C.C.

The current standard of care for patients, corticosteroids, is only palliative and has many negative side effects.

2-yr-old normal and affected male

McGreevy JW, et al. 2015, Dis Model Mech, http://creativecommons.org/licenses/by/3.0/



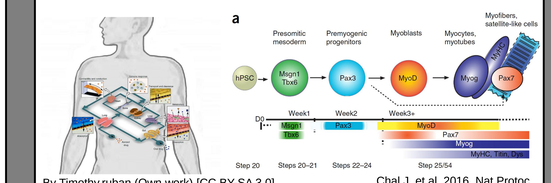
Eyewitness photo from inside TAMU's canine MD lab, given to PETA

Kornegay J, et al. 2014, ILAR J

PEONY: SEE HER STORY BELOW

Nghiem P, et al. 2017, Mamm Genome, http://creativecommons.org/licenses/by/4.0/

ALTERNATIVES



By Timothy.ruban (Own work) [CC BY-SA 3.0]

Chal J, et al. 2016, Nat Protoc

Microfluidics: "Human Muscle-on-a-chip"

- Can be integrated with other organs: cardiac, respiratory systems
- Most accurate representation of human microenvironment
- Potential for personalized medicine
- High-throughput

Stem cell technologies

- Patient-derived induced pluripotent stem cells have a *human* genetic MD background
- Can study early cellular phenotypes of MD
- Adult-human satellite cells can produce muscle progenitors for drug screening, cell therapy, or functional engraftment

PEONY'S STORY

Peony, a golden retriever who was bred to have canine muscular dystrophy, was born on May 19, 2011 at the University of North Carolina (UNC)-Chapel Hill. At UNC, Peony suffered from bouts of intestinal parasites normally associated with poor sanitation and crowding. These infections caused vomiting, nausea, an uncomfortably bloated abdomen, weight loss, decreased energy, and painful, often bloody diarrhea.

Peony was subjected to painful muscle biopsies. One of her incisions became infected, swelling painfully and oozing thick yellow pus. She was already underweight, and her growth was stunted because of the GRMD, but her body condition worsened with the infection and repeated experimentation. In 2012, Peony was transferred to TAMU.

Her enlarged tongue, a symptom of GRMD, made her salivate uncontrollably and she struggled to swallow, breathe and eat.

By the time she was 21 months old, Peony was emaciated, weighing just under 30 pounds. The average weight for healthy female golden retrievers this age is 55 to 70 pounds.

Peony's enlarged tongue, caused by the GRMD, made her salivate uncontrollably, and she had difficulty swallowing, breathing, and eating. She regularly had excessive saliva hanging in long strings of 8 inches or more from her mouth. The drool soaked the fur on her chest and caused a moist skin infection and hair loss.

While at TAMU, Peony, with little fat on her body to regulate body temperature, was hosed down with cold water because employees claimed there was no way to adjust the water temperature. In November 2012, Peony was found lying on her side and unwilling to get up. She was crying out and salivating more than usual. The lead experimenter suggested she could be experiencing heart problems associated with GRMD.

Peony was euthanized on March 3, 2013, two months shy of her second birthday.

https://www.peta.org/features/dog-laboratories-jelly-peony/

CONCLUSION

In a cost/benefit analysis, the negligible information gained through MD experiments on dogs does not outweigh the tremendous suffering experienced by these animals. Funds currently being spent on canine MD research should be reallocated towards human-based methods.