Final Examination of

Melissa A. Goddard

For the Degree of

DOCTOR OF PHILOSOPHY

COMMITTEE IN CHARGE

David Bowton, MD, FCCP, FCCM, Chairperson

Martin K. Childers, DO, Ph.D., Advisor

Valerie Kelly, PhD

Rob Grange, PhD

George Christ, PhD

Anthony Marsh, PhD

David Mack, PhD

WF Bio-Tech Place - Auditorium
April 27, 2015
12:00 p.m.
PROFESSOR(S) IN CHARGE OF RESEARCH
Martin K. Childers, DO, PhD

FIELDS OF GRADUATE STUDY
Major Subject:
Physiology and Pharmacology

SUMMARY OF DISSERTATION

THE EFFECTS OF GENE REPLACEMENT THERAPY ON RESPIRATORY AND GAIT FUNCTION IN A CANINE MODEL OF X-LINKED MYOTUBULAR MYOPATHY

X-linked myotubular myopathy (XLMTM) is a fatal pediatric disease caused by a deficiency of the protein myotubularin due to mutation of the MTM1 gene on the X chromosome. Affected boys experience profound skeletal muscle weakness and are typically ventilator and wheelchair dependent, with respiratory failure as the leading cause of death. A potential gene therapy has being developed where AAV8 mediates MTM1 replacement. A naturally-occurring canine model of the disease displays a phenotype similar to that seen in patients, including markedly reduced survival, and decreased strength and function in the muscles of the limbs and respiratory system. XLMTM dogs were treated once with AAV8 containing a full length canine MTM1 cDNA under a muscle-specific desmin promoter by three different routes of administration—local intramuscular injection of the hindlimb, isolated perfusion of the hindlimb and systemically. Systemic treatment was carried out at three different doses to determine the minimum effective dose for full preservation of function. Respiratory function and ambulation was measured in these dogs and compared to untreated and normal true control littermates over time. XLMTM dogs treated intramuscularly show improvement only at the site of injection, with no improvement in gait or respiration. However, dogs treated by isolated limb perfusion are able to maintain normal ambulation and respiratory function and continue to survive well after treatment. For dogs treated systemically, mid- and high-dose treatment is associated with maintained respiratory function and continued survival, while measures remain subnormal in low-dose treated dogs. Similarly, ambulation in mid- and high-dose treated dogs approaches normal measures, while low-dose treated dogs more closely resemble their untreated littermates. Outcome measures in the dog sensitive to changes due to the disease or treatment were also identified, including stride velocity and length, peak inspiratory flow and inspiratory time, which could be useful in the translation of this potential treatment for XLMTM to the clinic.
SCHOLASTIC VITAE

EDUCATION

2015  Ph.D., Integrated Physiology and Pharmacology, Wake Forest University, Winston-Salem, NC

2004  B.S., Molecular Biology and Genetics, University of Guelph, Guelph ON Canada

AWARDS

2014  Travel Award, American Society for Gene and Cell Therapy

2014  Outstanding Poster Award, American Society for Gene and Cell Therapy

2013  Travel Award, American Society for Gene and Cell Therapy

2001-2004  National Development Scholarship (Barbados)

Professional Memberships

2015- Current  American Society of Cell Biology

2014- Current  American Heart Association

2012- 2015  American Society of Gene and Cell Therapy
PUBLICATIONS

Manuscripts


Abstracts

1. Buj-Bello A; Holder M; Grange RW; Lawlor MW; Masurier C; Poulard K; Poppante K; Guan X; Goddard M; Burlingame E; Mitchell E; Barber J; Furtth ME; Moullier P; Beggs AH; Childers MK. Intramuscular delivery of AAV8-MTM1 rescues severe weakness and atrophy of targeted muscles in a canine model of X-linked myotubular myopathy. Treat NMD Conference (2011)(Poster)

2. Goddard M; Smith B; Byrne B; Mitchell E; Grange RW; Childers MK. In vivo measures of respiratory function in a canine model of X-linked myotubular myopathy provide endpoints for clinical translation. Treat NMD Conference (2011)(Poster)

