WAKE FOREST
UNIVERSITY

GRADUATE SCHOOL *of*
ARTS & SCIENCES

Final Examination of

Melissa A. Goddard

For the Degree of

DOCTOR OF PHILOSOPHY

COMMITTEE IN CHARGE

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Valerie Kelly, PhD

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George Christ, PhD

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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-occuring 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

1. **Goddard MA**, Mitchell EL, Smith BK, Childers MK. Establishing clinical end points of respiratory function in large animals for clinical translation. *Phys Med Rehabil Clin N Am*, 23, 75-94. (2012)
2. Grange RW, Doering J, Mitchell E, Holder MN, Guan X, **Goddard M**, Tegeler C, Beggs AH, Childers MK. Muscle function in a canine model of X-linked myotubular myopathy. *Muscle Nerve*. Oct;46(4):588-91. (2012)
3. Childers MK, Joubert R, Poulard K, Moal C, Grange RW, Doering JA, M. Lawlor MW, Rider BE, Jamet T, Danièle N, Martin S, Rivière C, Soker T, Hammer C, Van Wittenberghe L, Lockard M, Guan X, **Goddard M**, Mitchell E, Barber J, Williams JK, Mack DL, Furth ME, Vignaud A, Masurier C, Mavilio F, Moullier P, Beggs AH and Buj-Bello A, Gene therapy prolongs survival and restores function in murine and canine models of myotubular myopathy. *Sci Transl Med*. 6(220):220ra210. (2014)
4. Smith BK, **Goddard M**, Childers MK. Respiratory assessment in centronuclear myopathies. *Muscle Nerve*. 50(3):315-326. (2014)
5. **Goddard MA**, Burlingame E, Beggs AH, Buj-Bello A, Childers MK, Marsh AP, Kelly VE. Gait characteristics in a canine model of X-linked myotubular myopathy. *J Neurol Sci*. (2014)

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; Furth 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)
3. Smith BK, **Goddard MA**, Childers MK, Byrne BJ. *Clinical Trial Readiness for Gene Replacement to the Diaphragm: Translational Respiratory Endpoints in Ventilator-Dependent Neuromuscular Diseases.* ASGCT (2013)(Poster)
4. Childers MK, Joubert R, Holder MN, Grange RW, Doering J, Lawlor MW, Moal C, Jamet T, Daniele N, Martin S, Riviere C, Poppante K, Soker T, Hammer C, Van Wittenberghe L, **Goddard M**, Mitchell E, Barber J, Furth ME, Vignaud A, Masurier C, Moullier P, Beggs AH, Buj-Bello A. *Intravenous AAV8-MTM1 Prolongs Life and Ameliorates Severe Muscle Pathology in Mouse and Dog Models of X-Linked Myotubular Myopathy.* ASGCT (2013)(Oral Presentation)
5. **Goddard M**, Joubert R, Poulard K, Grange R, Lawlor M, Moal C, Jamet T, Danièle N, Martin S, Rivière C, Hammer C, Van Wittenberghe L, Mitchell E, Vignaud A, Masurier C, Moullier P, Beggs A, Buj-Bello A, Smith B, Byrne B, Childers M. *Respiratory Function in a Canine Model of X-Linked Myotubular Myopathy Following Regional Limb Infusion with Recombinant AAV8-MTM1.* ASGCT (2013)(Oral Presentation)(Travel Award)