BIOGRAPHICAL SKETCH

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NAME: LaDora V. Thompson

eRA COMMONS USER NAME (credential, e.g., agency login): THOMP067

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Marquette University, Milwaukee, WI	BS	05/1984	Physical Therapy
Marquette University, Milwaukee, WI	PhD	05/1991	Muscle Physiology
Marquette University, Milwaukee, WI	Post doc	06/1993	Cellular Physiology
Smith College, Northampton, NH		1995	Molecular Biology

A. Personal Statement

Since my introduction to older adults as a child growing up in a midwestern small farm community, I have been motivated to make a difference not only in the individuals I cared for as a physical therapist, but to advance and further the scientific basis for geriatric physical therapy practice. Encountering the irreversible effects of aging during clinical practice has further impressed upon me the importance of prevention as a means of helping people live longer with preserved quality of life. Early exposure to basic scientists, who through their impactful research changed the landscape of skeletal muscle physiology, motivated me to change course during my clinical practice to pursue doctoral training in muscle physiology. Since the initiation of my own independent research program I have been involved in aging research and professional associations associated with aging. Indeed, throughout my entire scientific career! Recently, I was recruited to Boston University as the inaugural Travis M. Roy Endowed Professor in Rehabilitation Sciences. My research laboratory is focused on aging, frailty and muscle. Normal aging is associated with a decline in muscle function. The underlying mechanisms responsible for the decline in function are only partially identified. My research laboratory was one of the first laboratories to fully characterize, at the single fiber level, age-related contractility (impaired contraction velocity and weakness). These studies were followed by seminal investigations demonstrating structural and post-translational modifications of myosin, which explain muscle weakness. We clearly demonstrate that it is possible to rescue age-related slowing of contraction by over-expressing a key regulatory protein, myosin light chain 3f. Recently, my research team developed the *first pre-clinical mouse physical frailty phenotype*, which is modeled from the Fried's human frailty phenotype. Using this mouse physical frailty phenotype we are able to identify the onset, prevalence and risk of mortality. This mouse physical frailty phenotype will be the basis for investigating underlying mechanisms contributing to the onset of frailty and in the future to identify meaningful interventions. Indeed, a true preclinical model, reverse translation! This area of research is truly translational, bringing community to the bedside to the bench and back. Collectively, my research team has expertise in muscle and single skeletal fiber physiology, biochemistry, molecular biology, proteomics, and behavioral testing.

In the current R01 proposal, we investigate the "onset of frailty" in the lifespan of mice, a critical time point. The proposed studies are logical extensions of my previous work demonstrating the validity of using the mouse physical frailty phenotype to identify frailty onset, progression, and mortality risk. Most importantly, the proposal takes advantage of the expertise of my colleague, Dr. Brown-Borg (aging models, genetics of longevity) to delve into an unexplored area, the link between frailty, inflammaging, and muscle dysfunction. This is the beginning of a new collaboration, the research methodology is in place, and the results will provide the foundation/premise for future investigations.

Key papers between Drs. Brown-Borg and Thompson:

1. Chen, C-N, Brown-Borg, H.M., Rakoczy, S.G. and **L.V. Thompson**. Muscle disuse: adaptation of antioxidant systems is age-dependent. *J Gerontol A Biol Sci Med Sci***.** 63(5): 461-466, 2008. PMID: 18511748
2. Chen, C-N, Brown-Borg, H., Rakoczy, S.G., Ferrington, D.A., and **L.V. Thompson**. Aging impairs the expression of glutamate cysteine ligase catalytic subunit in soleus muscle under stress. *J Gerontol A Biol Sci Med Sci*. 65(2):129-37, 2010. PMID: 20018823
3. Romanick, M., **Thompson, L.V.**, and H.M. Brown-Borg. Murine models of atrophy, cachexia, and sarcopenia in skeletal muscle. *Biochim Biophys Acta*, 2013 Mar 20. Doi:pii:S0925-4439(13)00085-0. 10.1016.

B. Positions and Honors

Positions and Employment

1993-1999	Assistant Professor of Physical Medicine and Rehabilitation, University of Minnesota
1993-1999	Assistant Professor of Physiology, University of Minnesota
1999-2008	Associate Professor of Physical Medicine and Rehabilitation, University of Minnesota
1999-2008	Associate Professor of Physiology, University of Minnesota
2008-2016	Full Professor of Physical Medicine and Rehabilitation, University of Minnesota
2008-2016	Full Professor of Physiology, University of Minnesota
2012-2013	Interim Director of the Physical Therapy Program, University of Minnesota
2013-2016	Director of the Physical Therapy Program, University of Minnesota
2016-2019	Professor & Chair of the Department of PT & AT, Boston University
2019-	Professor of Physical Therapy, Boston University

Honors

1988-1989, Marquette University Fellowship; **1987-1991**, Foundation for PT Doctoral Scholarships; **1989-1991**, AHA Predoctoral Fellowship; **1992-1993**, NASA Postdoc Fellowship; **1994**, University of MN Candidate for the National Brookdale Fellowship on Aging; **1994-2001**, AHA Grant-In-Aid;**1997-1999**, Foundation for PT Grant Award; **2000-2001**, Fesler-Lampert Chair in Aging Studies; **2000-2001**, NIA-R03 Award (R03 AG018156); **2001-2014**, NIA-R01 Award (R01 AG017768); **2003-2008**, NIA-K02 Career Award, Independent Scientist Award (K02 AG021626); **2005**, Keynote Speaker COBRAF Brazil; **2006**, Gordon Research Conference Vice-Chair, Biology of Aging; **2006**, Keynote Speaker: University of Constance, Germany; **2007**, Gordon Research Conference Co-Chair, Biology of Aging (R13 AG030289); **2008-2016**, NIA-T32 Award, PI/Director (T32 AG029796). **2010-2013**, University of Minnesota: Women's Faculty Cabinet and Senate Research Committee; 2**011-2013,** American Aging Association: President-Elect and President (R13 AG044134); **2011-2014,** GSA BS Secretary/Treasurer; **2011**, GSA Fellow; **2015,** Gordon Research Conference (Oxidative Stress and Disease) Vice-Chair; **2017**, Gordon Research Conference (Oxidative Stress and Disease, R13 AG055293) Co-Chair. **2016- present**, Inaugural Travis M. Roy Endowed Professor.

C. Contributions to Science

Single skeletal muscle fiber contractile dysfunction with aging

My initial studies fully characterized the changes in contractile function at the single cell level, across the lifespan of the rat. One critical finding showed that fibers from aged rats generated ~20% lower maximum force without changes in the ATPase activity. This result indicated a decrease in the energetic efficiency, a partial uncoupling between ATPase activity and force generation during contraction in aged muscle. Under unloaded shortening conditions in the same muscle, aging resulted in a 16% decrease in the myofibrillar ATPase activity and a similar decrease in the shortening velocity. These data suggested that changing actin-myosin interactions contribute to age-related inhibition of contractility. In order to investigate age-related changes in actin-myosin interaction, I pursued biochemical experiments on purified actin and myosin from young adult and aged rats. These experiments showed a decrease in two parameters of the actomyosin ATPase, V_{max} and K_m. Subsequent mixing of actin and myosin from young adult and old muscle in four combinations showed that the age-related decrease in V_{max} was primarily due to age-related changes in myosin. However, the age-related decrease in K_m is due to changes in both proteins, as actin from young adult rats attenuated the age-related decrease in K_m for myosin from old rats. The data from these experiments suggests that changes in actin, together with changes in myosin, are involved in the molecular mechanism of age-related deterioration of muscle contractility.

1. **Thompson L.V.** and Brown, M.B. Age-related changes in contractile properties of single skeletal fibers from the soleus muscle. *J Appl Physiol,* 86(3):881-886, 1999.
2. Lowe, DA, Thomas, D.D., and **L.V. Thompson**. Force generation, but not myosin ATPase activity, declines with age in rat muscle fibers. *Am J Physiol Cell Physiol* 283:187-192, 2002.

3. Prochniewicz, E, Thomas, D.D., and **L.V. Thompson**. Age-related decline in actomyosin function. *Journals of Gerontology*, 60(4):425-43, 2005.
4. Graber, T.G., Kim, J.H., Grange, R.W., McLoon, L.K., and **L.V. Thompson**, C57BL/6 Lifespan Study: Age-related declines in muscle power production and contractile velocity, *AGE*, June;37(3):9773. Doi:10.1007/s11357-9773-1. Epub 2015 Apr 17 PMID: 25893911

Myosin structure changes with aging

As noted above, both the physiological fiber studies and the biochemical protein studies implicate myosin. Thus, I hypothesized that the age-related decline in single skeletal muscle fiber force-generating capacity was due to structural changes in myosin. In order to investigate age-induced structural changes in myosin, a biophysical experimental approach was used. Electron paramagnetic resonance (EPR) is a high-resolution spectroscopic method which, in combination with site-specific spin labeling of Cys_{707} of myosin, detects changes in the structure of myosin associated with relaxation and contraction of muscle fibers. Specifically, EPR can be used to determine quantitatively the fraction of myosin molecules in the weak- and strong-binding structural states. Using EPR, Dr. Thompson showed that the age-related 24% - 27% decrease in the specific force was associated with 24% - 30% decrease in the fraction of myosin heads in the strong-binding, force-generating structural state. In other words, there were structural changes in myosin with age.

1. Lowe, D.A., Surek, J.T., Thomas, D.D., and **Thompson, L.V.** Electron paramagnetic resonance reveals age-related myosin structural changes in rat skeletal muscle fibers. *Am. J. Physiol.,*280 (3):C540-547,2001.
2. **Thompson, L.V.,** Lowe, D.A., Ferrington, D.A., and Thomas, D.D. Electron paramagnetic resonance: a high-resolution tool for muscle physiology. *Exercise and Sport Sciences Reviews*, 29:3-6, 2001.
3. Lowe, D.A., Warren, G.L., Snow, L.M., **Thompson, L.V.** and D. D. Thomas. Muscle activity and aging affect myosin structural distribution and force generation in rat fibers. *J Appl Physiol*, 96(2): 498-506, 2004.
4. **Thompson, L.V.,** Durand, D., Fugere, N.A., Ferrington, D.A. Myosin and actin expression and oxidation in aging muscle. *J Appl Physiol* (July 13, 2006). doi:10.1152/japplphysiol.00426.2006.

Skeletal muscle protein damage occurs with aging

Oxidative stress is thought to play a significant role in sarcopenia by modifying key amino acids leading to a loss of key skeletal muscle protein structure and function. Thus, I concentrated my efforts on determining whether the decline in force-generating capacity was due, in part, to changes in the structure of myosin resulting from post-translational modifications. Selective markers of oxidative damage, such as carbonylation, nitration, formation of 4-hydroxy-2-nonenal (HNE) adducts, glycation and oxidation of cysteines were evaluated using a variety of biochemical, proteomic and mass spectrometry approaches. In one approach, this hypothesis was pursued by isolating the individual proteins, myosin and actin, and determining the reactive cysteines. An age-related decrease in cysteine content was detected in myosin, but the cysteine content of actin was unaffected by age. Another possible explanation of age-related inhibitory effects on contractile function is glycation. In another approach, I detected 3-nitrotyrosine and HNE-adducts in both actin and myosin, but in both cases the level of modification was similar in myosin and actin from young adult and old rats. Although this finding did not implicate accumulation of these two oxidative stress markers (oxidative stress theory of aging), it did not eliminate other site-specific modifications of key amino acids which are critical for function. Lastly, carbonylation, the irreversible production of carbonyl groups to proteins, through direct and indirect oxidation of amino acid side-chains and amino termini by reactive oxygen species generated in cells. The level of damage increases almost exponentially with age. In a broad proteomics approach (a protocol using biotin hydrazide and avidin-affinity chromatography, multiplex iTRAQ labeling, and pulsed Q dissociation on a modified linear ion trap (LTQ)S mass spectrometer) carbonylated proteins were identified and quantitated. The results found over 240 modified proteins within skeletal muscle mitochondria, predominantly involved in oxidative phosphorylation. These experimental approaches will be used in the current proposal to investigate post-translational modifications in the masseter muscle with age and periodontal disease.

1. Fugere, N.A., Ferrington, D.A. and **L.V. Thompson.** Protein nitration with aging in the rat semimembranosus and soleus muscles. *Journals of Gerontology*, 61(8):806-12, 2006.
2. Meany, D., Xie, H., **Thompson, L.V.**, Arriaga, E.A., and Griffin, T.J. Identification of carbonylated proteins from enriched rat skeletal muscle mitochondria using affinity chromatography-stable isotope labeling and tandem mass spectrometry. *Proteomics* 7:1150-1163, 2007.
3. Prochniewicz, E, Lowe, D.A., Spakowicz,D., Higgins, L., O'Conor, K., **Thompson, L.V.**, Ferrington, D.A., and D.D. Thomas. Functional, structural and chemical effects of hydrogen peroxide oxidation of muscle fibers: an *in vitro* model of muscle aging. *American Journal of Physiology, Cell*, 294: C613-C626, 2008.

4. Feng, J., Navratil, M., **Thompson, L.V**., and E.A. Arriaga. Principal component analysis reveals age- and muscle-type related differences in protein carbonyl profiles of muscle mitochondria. *J Gerontol A Biol Sci Med Sci*. 63(12):1277-88, 2008.

Overexpression of myosin light chain 3 rescues age-related slowing of contraction

Although the above elegant studies point to myosin and actin as key players in age-related muscle weakness, the reported age-induced changes in calcium sensitivity and contraction velocity cannot be explained by post-translational modifications of myosin or myosin heavy chain isoform switching. Thus, I investigated myosin light chains (MLC_{1f} and MLC_{3f}), which modulate velocity of the cross-bridges. We reported, for the first time, that it is possible to rescue the slowing of muscle contraction with aging by over expressing MLC_{3f} protein in the individual skeletal muscle cells. This comprehensive study used multiple approaches (e.g., molecular biology, proteomics, and single fiber physiology) to successfully identify the important role of MLC3f. Because increasing MLC_{3f} content via recombinant adenovirus (rAd)- MLC_{3f} DNA injection rescues the age-related decline in contractile velocity, we tested the hypothesis that increasing MLC_{3f} protein content would attenuate the deterioration in velocity following non-weight bearing conditions (e.g., hindlimb unloading) in MHC type IIB fibers.

1. Kim JH, Torgerud WS, Mosser KH, Hirai H, Watanabe S, Asakura A, and **Thompson LV**. Myosin light chain 3f attenuates age-induced decline in contractile velocity in MHC type II single muscle fibers. *Aging Cell* 11: 203-212, 2012.
2. Zhong, S. and **L.V. Thompson.** The roles of myosin ATPase activity and myosin light chain content in the slowing of type II fibers with hindlimb unweighting. *Am. J. Physiol.- Cell.* 2007 May 9; [Epub ahead of print] PMID: 17494635.
3. Jong-Hee Kim, Ted G. Graber, Haiming Liu, Shuichi Watanabe, Atsushi Asakura, and **LaDora V. Thompson** Protecting against Non-Weight Bearing-Induced Decline in Contractile Velocity in MHC type IIB Muscle Fibers: Myosin Light Chain 3F.
4. Kim, J.H. and **L.V. Thompson**, Non-weightbearing-induced muscle weakness: the role of myosin quantity and quality in MHC type II fibers. Am J Physiol Cell Physiol. 2014 Jul 15;307(2):C190-4. doi: 10.1152/ajpcell.00076.2014. Epub 2014 May 14. PMID: 24829495

Frailty and the mouse frailty phenotype

We completed a comprehensive evaluation of animal physical performance, muscle contractility, protein expression, and developed two frailty assessment tools (neuromuscular healthspan scoring system, frailty phenotype) using the C57BL/6 mouse model. *This mouse physical frailty phenotype was a first*! The frailty phenotype parallels and reverse-translates the 'human' frailty assessment tools (Fried Frailty Phenotype). In a subset of mice receiving wheel-running exercise, we found: (i) when comparing young (6-8 mo) and elderly (28-30 mo) mice, grip strength and endurance performance is lower in the elderly. (ii) When wheel-running exercise is performed daily for 4 weeks, endurance performance is significantly improved in the elderly such that it matches the young. (iii) The young mice voluntarily run more than the elderly. (iv) Myosin Heavy Chain composition shifts do not appear to be responsible for this improvement in performance. (v) Whole muscle contractility (e.g., force production) as well as cross-sectional area of the soleus muscle was improved by the exercise in the young mice only.

We recently completed three feasibility studies focused on investigating frailty across the lifespan in both male and female C57BL/6 mice. The mouse physical frailty phenotype, which includes body weight, walking speed, strength, endurance and physical activity, is able to identify the onset, prevalence and risk of mortality. The onset of frailty occurs earlier in the lifespan, the prevalence of frailty increases across the lifespan, and frailty accurately predicts mortality. Collectively, frail mice lack resilience; in that, multiple tissue/organ systems may deteriorate at an accelerated rate and ultimately lead to early mortality when compared to non-frail mice. Identifying the onset and prevalence of frailty, in addition to predicting mortality, has potential to yield information about several aging processes.

1. Baumann, C.W., Kwak, D., and **L.V. Thompson,** Sex-specific components of frailty in C57BL/6 mice. *Aging*, (Albany NY). 2019, Jul 29;11(14):5206-5214. doi: 10.18632/aging.102114. PMID: 31355774
2. Kwak, D., Baumann, C.W., and **L.V. Thompson**, Identifying characteristics of frailty in female mice using a phenotype assessment tool. *Journals of Gerontology, A Biol Sci Med Sci.,* 2019, Apr 8. pii: glz092. doi: 10.1093/gerona/glz092. PMID: 30958526
3. Baumann, C.W., Kwak, D., and **L.V. Thompson**, Assessing onset, prevalence and survival in mice using a frailty phenotype. *Aging*, (Albany NY). 2018 Dec 18. doi: 10.18632/aging.101692. [Epub ahead of print] PMID: 30562163

4. Graber TG, Ferguson-Stegall L, Liu H, **Thompson LV**. Voluntary aerobic exercise reverses frailty in old mice. *J Gerontol A Biol Sci Med Sci. 2015* Sep;70(9):1045-58. doi: 10.1093/gerona/glu163. Epub 2014 Sep 30. PMID: 25271307

https://www.ncbi.nlm.nih.gov/pubmed/?term=thompson+lv

D. Additional Information: Research Support and/or Scholastic Performance

ACTIVE

Travis M. Roy Endowed Professorship (PI: Thompson)
Travis M. Roy Endowment for Research, 2016 – present

R56 AG067724-01 (MPI: Thompson, Brown-Borg) NIH/NIA
Frailty: Prediction of Onset and Progression
Goals/Responsibilities: The goal is to examine underlying characteristics of frailty in robust, nonfrail and frail mice.
2020 – 2021

K07 AG072124-01 (PI: Thompson) NIH/NIA
Academic Leadership Award: The Translational Rehabilitation in Geroscience Initiative
Goals/Responsibilities: The goal of this project is to enhance early stage translational research.
2021 – 2026

R03 AG067983-01 (Danny Roh, MD, PhD) NIH/NIA
Role of Senescence in the Impaired Wound Healing of Aging
Goals/Responsibilities: GEMSSTAR Mentor
2020 – 2022

Boston University
Research Laboratory Recruitment and Start-up Funds
2016 - present

Completed Research Support

R01 AG20866 (Arriaga) NIH/NIA
Quantitating Mitophagy in Skeletal Muscle Models
Goals/Responsibilities: In this study we were developing instrumentation to analyze individual mitochondria.
04/15/02 – 03/31/21

T32 AG029796 (Thompson/Ferrington) NIH/NIA
Training Grant: Functional Proteomics of Aging
Goals/Responsibilities: This is a training grant to develop leaders in the field of biology of aging. Dr. Thompson was one of the inaugural Co-Director on this training grant prior to leaving University of Minnesota.
05/01/08 – 04/30/23

National Research Foundation of Korea (PI: Kim, Thompson) #01176098
Global Research Network, A pre-clinical approach for the enhancement of quality of life in patients with DMD
Goals/Responsibilities: The goal was to assess the effectiveness of a selective immunoproteasome inhibitor MDX mice. Dr. Thompson provided proteasome expertise.
09/01/16 – 08/31/19