BIOGRAPHICAL SKETCH

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NAME: Russell T. Hepple

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

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
University of Saskatchewan, CAN	BSc	05/1988	Physiology
University of Toronto, CAN	MSc	12/1991	Physiology
University of Toronto, CAN	PhD	04/1996	Physiology
University of California San Diego, La Jolla, CA USA	Postdoc	10/1999	Physiology

A. Personal Statement

My lab has been involved with muscle research for more than 20 years. A driving philosophy has been to evolve our technical expertise to meet the needs of the new questions our results are raising. This has allowed us to make a number of first discoveries related to aging muscle. Our journey started by focusing on how aging was impacting skeletal muscle aerobic capacity and the physiological factors involved (e.g., convective oxygen delivery, capillarization, mitochondrial oxidative capacity). We first showed that aging muscle demonstrates a deficit in aerobic function even when provided with a similar convective oxygen delivery (Hepple et al. J Appl Physiol. 2003). We then showed that the structural capacity for oxygen flux determined by the capillaries was maintained in relative excess of the mitochondrial oxidative capacity in aged muscle (Hepple & Vogell, J Appl Physiol. 2004), which implicated a key role for the mitochondrion in the decline of muscle aerobic function. We subsequently showed that these changes in aging muscle were not immutable because life-long caloric restriction could completely prevent the >50% decline in muscle aerobic function in advanced age and this was associated with superior mitochondrial function (Hepple et al. FASEB J. 2005). These profound benefits of caloric restriction were associated with a relative preservation of a master regulator of mitochondrial biogenesis, PGC-1a (Baker et al. J Gerontol Biol Med Sci. 2006; Hepple et al. Rejuv Res. 2006) and better maintained proteostasis through the proteasome pathway (Hepple et al. Am J Physiol Regul Integr Compar Physiol. 2008). We subsequently showed that in contrast to the remarkable benefits of life-long caloric restriction for skeletal muscle in advanced age, initiating exercise training early in the aging process could not prevent the dramatic declines in muscle mass, contractility and aerobic function in advanced age, and this was due in part to a failure of exercise to induce PGC-1a in advanced age (Betik et al. Am J Physiol Regul Compar Physiol. 2009; Thomas et al. Exp Gerontol. 2010). Unexpectedly, exercise training exacerbated some aspects of muscle aging, including the severity of atrophy and oxidative damage (Thomas et al. Exp Gerontol. 2010), despite improving survival and attenuating cardiomyocyte replacement-fibrosis (Wright et al. Exp Gerontol. 2014).

In the context of aging muscle atrophy, we showed that upregulation of a mitochondrial-mediated apoptotic pathway tracked the progression of muscle atrophy with aging (Baker and Hepple, Exp Gerontol. 2006). In contrast to the widely held view that slow twitch muscle is more resilient to aging, we also showed that slow muscle exhibits severe atrophy and contractile impairment in advanced age (Carter et al. Exp Gerontol. 2010), that slow muscle fibers exhibit a similarly severe degree of atrophy in advanced age as fast twitch muscle fibers (Purves-Smith et al. Exp Gerontol. 2012), and that this has likely been obscured in previous studies by technical issues with fiber typing of aged muscle (Purves-Smith et al. Ex Sport Sci Rev.

2014). Several of these findings contradicted widely held views and thus have had a significant impact on the field. This is demonstrated not only by their high rate of citation but by their continued citation years after publication. In this respect, our most important contributions have arguably been in the context of mitochondrial function, where we have shown that mitochondrial function assessment is profoundly affected by mechanical isolation of organelles (Picard et al. PLoS One 2011), and can lead to not only an exaggerated impact of aging but also spurious findings related to the impact of aging on specific aspects of mitochondrial function (Picard et al. Aging Cell 2010). We also showed that denervation of muscle fibers is a primary driver of the acceleration of muscle atrophy in advanced age (Rowan et al. PLoS One, 2012), and that denervation becomes an important modulator of mitochondrial function changes in advanced age in octogenarian men (Spendiff et al. J Physiol. 2016) and women (Sonjak et al. J Gerontol Biol Med Sci. 2019). We also provided the first evidence that mitochondria are sensitized to permeability transition in aging human muscle and this causes myonuclear translocation of mitochondrial-derived pro-apoptotic factors (Gouspillou et al. FASEB J. 2014; cited 107 times). Thus, we have developed an exceptionally strong foundation of knowledge about skeletal muscle, with particularly important contributions to muscle atrophy in advanced age and the role of mitochondria therein.

Key publications include:

1. M. Picard, D. Ritchie, K.J. Wright, M.M. Thomas, S.L. Rowan, T. Taivassalo, and **R.T. Hepple.** Mitochondrial Functional Impairment with Aging is Exaggerated in Isolated Mitochondria compared to Permeabilized Myofibers. *Aging Cell* 9(6): 1032-1046, 2010. PMID: 20849523
2. G. Gouspillou, N. Sgarioto, S. Kapchinsky, F.M. Purves-Smith, B. Norris, C. Pion, S. Barbat-Artigas, F. Lemieux, T. Taivassalo, J.A. Morais, M. Aubertin-Leuhedre, and **R.T. Hepple**. Increased sensitivity to mitochondrial permeability transition and myonuclear translocation of endonuclease G in atrophied muscle of physically active older men. *The FASEB Journal* 28(4): 1621-33, 2014.
3. Spendiff et al. Denervation drives mitochondrial dysfunction in skeletal muscle of octogenarians. *The Journal of Physiology* 594.24: 7361-79, 2016;
4. V. Sonjak, K.J. Jacob, S. Spendiff, M. Vuda, A. Perez, K. Miguez, F.C. Minozzo, C. Spake, J.A. Morais, and **R.T. Hepple**. Reduced Mitochondrial Content, Elevated ROS, and Modulation by Denervation in Skeletal Muscle of Pre-frail/Frail Elderly Women. *Journals of Gerontology Biological and Medical Sciences.* 2019.

B. Positions and Honors

Positions and Employment

2017- Professor, Dept. Physical Therapy, University of Florida
2017- Professor, Dept. of Physiology & Functional Genomics, University of Florida
2017- Adjunct Professor, Dept. of Medicine, McGill University
2015-16 Professor, Dept. Kinesiology & Physical Education, Dept. of Medicine, McGill University
2012-16 Director, McGill Research Centre for Physical Activity & Health
2011-15 Associate Professor, Dept. Kinesiology & Physical Education, Dept. of Medicine, McGill University
2005-10 Associate Professor, Faculty of Kinesiology, Faculty of Medicine, University of Calgary
1999-2005 Assistant Professor, Faculty of Kinesiology, Faculty of Medicine, University of Calgary

Awards

2014&15 Nesbitt-McMaster Award for Excellence in Medicine and Surgery, Research Institute of the McGill University Health Centre
2013-14 Fonds de Recherche Quebec Sante Chercheur Boursiers Senior
2007-10 Alberta Heritage Foundation for Medical Research Senior Scholar
2003 Canadian Institutes of Health Research Special Recognition Award (for topped ranked applicant in the CIHR Open Grant competition from the field of Aging Research)
2003-08 Canadian Institutes of Health Research New Investigator Award
2002-07 Heart & Stroke Foundation of Canada New Investigator Award (declined 2003-07 portion)

Other Experience and Professional Memberships

2018- Reviewing Editor for *The Journal of Physiology*
2018- The Physiological Society member
2015- Society on Sarcopenia, Cachexia and Muscle Wasting Disorders member

2014-15 NIH Common Fund working group exploring needs and opportunities on “Molecular Mechanisms Whereby Physical Activity Prevents Disease and Improves Health Outcomes”, resulting in the Common Fund Molecular Transducers of Physical Activity funding opportunities. Co-Chair of Mitochondria/Energetics Subgroup (with B. Goodpaster)
2007-10 Canadian Institutes of Health Research, Institute Advisory Board Member, Institute of Aging
2000- American Physiological Society member
2002-10 Gerontological Society of America member

C. Contributions to Science

1. Aging skeletal muscle exhibits an impairment in aerobic capacity, independent of a reduction in convective oxygen delivery, and is associated with impaired mitochondrial function (Hagen et al. *J Gerontol Biol Sci.* 2004). This decline in muscle aerobic function and mitochondrial function can be completely prevented by long-term caloric restriction (Hepple et al. *FASEB J.* 2005), but not long-term endurance exercise training (Betik et al. *Am J Physiol* 2009);
    a. J.L. Hagen, D.J. Krause, D.J. Baker, M. Fu, M.A. Tarnopolsky, and **R.T. Hepple**. Skeletal muscle aging in F344BN F1-hybrid rats: I. Mitochondrial dysfunction contributes to the age-associated reduction in VO_{2max}. *Journals of Gerontology Biological Sciences* 59A(11): 1099-1110, 2004. PMID: 15602055
    b. **R.T. Hepple**, D.J. Baker, J.J. Kaczor and D.J. Krause. Long-term caloric restriction abrogates the age-related decline in skeletal muscle aerobic function. *The FASEB Journal* 19(10): 1320-1322, 2005. PMID: 15955841
    c. D.J. Baker, A.C. Betik, D.J. Krause, and **R.T. Hepple**. No decline in skeletal muscle oxidative capacity with aging in long-term caloric restricted rats: effects are independent of mtDNA integrity. *Journals of Gerontology Biological Sci*ences 61A: 675-684, 2006. PMID: 16870628
    d. A.C. Betik, M.M. Thomas, K.J. Wright, C.D. Riel and **R.T. Hepple**. Exercise training from late middle age to senescence does not attenuate the declines in skeletal muscle aerobic function. *American Journal of Physiology Regulatory Integrative and Comparative Physiology* 297(3): R744-755, 2009. PMID: 19571205

2. The traditional approach of mechanically isolating mitochondria from skeletal muscle to study their function dramatically alters not only mitochondrial reticular structure, but also potentiates mitochondrial ROS emission and sensitivity to permeability transition relative to a preparation where mitochondrial structure is preserved (saponin-permeabilized myofibers) (Picard et al. *PLoS One* 2011). Similarly, the magnitude and nature of mitochondrial dysfunction in aging skeletal muscle is highly dependent upon the method used to interrogate the function, where an *in situ* method that preserves mitochondrial structure and permits representation of all mitochondria (saponin-permeabilized myofibers) reveals considerably smaller changes with aging than are seen with mechanically isolated mitochondria (Picard et al. *Aging Cell* 2010). Some of these changes in mitochondrial function in humans can be prevented by maintaining a high level of physical activity (Gouspillou et al. *FASEB J.* 2014) and are exacerbated in those who are very sedentary (Spendiff et al. *J Physiol.* 2016).
    a. M. Picard, D. Ritchie, K.J. Wright, M.M. Thomas, S.L. Rowan, T. Taivassalo, and **R.T. Hepple.** Mitochondrial Functional Impairment with Aging is Exaggerated in Isolated Mitochondria compared to Permeabilized Myofibers. *Aging Cell* 9(6): 1032-1046, 2010. PMID: 20849523
    b. M. Picard, T. Taivassalo, D. Ritchie, K.J. Wright, M.M. Thomas, C. Romestaing, and **R.T. Hepple.** Mitochondrial Structure and Function are Disrupted by Standard Isolation Methods. *PLoS One* 6(3): e18317, 2011. PMID: 21512578
    c. G. Gouspillou, N. Sgarioto, S. Kapchinsky, F.M. Purves-Smith, B. Norris, C. Pion, S. Barbat-Artigas, F. Lemieux, T. Taivassalo, J.A. Morais, M. Aubertin-Leuhedre, and **R.T. Hepple**. Increased sensitivity to mitochondrial permeability transition and myonuclear translocation of endonuclease G in atrophied muscle of physically active older men. *The FASEB Journal* 28(4): 1621-33, 2014. PMID: 24371120
    d. S. Spendiff, M. Vuda, S. Aare, T. Gove, G. Gouspillou, S. Kapchinsky, J. Morais, C. Pilon, M. Aubertin-Leuhedre, S. Hettwer, T. Taivassalo and **R.T. Hepple**. Denervation Drives Mitochondrial Dysfunction in Skeletal Muscle of Octogenarians. *The Journal of Physiology* 594.24: 7361-7379, 2016. PMID: 27619626

3. Denervation is the primary cause of muscle fiber atrophy in advanced age, and the accumulation of persistently denervated muscle fibers parallels the accelerating phase of muscle atrophy in both slow and fast twitch muscles, where denervated muscle fibers exhibit an up-regulation of the proteolytic machinery and muscles generally exhibit an up-regulation of micro-RNAs that are predicted to target neurotrophin genes involved in promoting reinnervation (Rowan et al. *PLoS One* 2012; Purves-Smith et al. *Exp Gerontol.* 2012; Aare et al. *Skeletal Muscle* 2016). Furthermore, mitochondrial dysfunction in advanced age reflects in part changes that originate in persistently denervated muscle fibers, suggesting the mitochondrion may not be an appropriate therapeutic target when muscle atrophy becomes severe and clinically relevant (Spendiff et al. *J Physiol.* 2016);
    a. S.L. Rowan, K.A. Rygiel, F.M. Purves-Smith, N.M. Solbak, D.M. Turnbull and **R.T. Hepple**. Denervation Causes Fiber Atrophy and Myosin Heavy Chain Co-expression in Senescent Skeletal Muscle. *PLoS One* 7(1): e29082, 2012. PMID: 22235261
    b. F.M. Purves-Smith, N.M. Solbak, S.L. Rowan, and **R.T. Hepple**. Severe Atrophy of Slow Fibers in Aging Muscle is Concealed by MHC Co-expression. *Experimental Gerontology* 47(12): 913-918, 2012. PMID: 22884852
    c. S. Aare, S. Spendiff, M. Vuda, D. Elkrief, A. Perez, Q.Wu, D. Mayaki, S.N. Hussain, S. Hettwer, and **R.T. Hepple**. Failed Reinnervation in Aging Skeletal Muscle. *Skeletal Muscle* Sept. 1; 6(1): 29, 2016. PMID: 27588166
    d. S. Spendiff, M. Vuda, S. Aare, T. Gove, G. Gouspillou, S. Kapchinsky, J. Morais, C. Pilon, M. Aubertin-Leuhedre, S. Hettwer, T. Taivassalo and **R.T. Hepple**. Denervation Drives Mitochondrial Dysfunction in Skeletal Muscle of Octogenarians. *The Journal of Physiology* 594.24: 7361-7379, 2016. PMID: 27619626

4. Skeletal muscle of patients with the smoking-related disease COPD exhibits a deficit in mitochondrial respiratory function, and reduction in mtDNA copy number, and in muscle fibers exhibiting a high burden of mtDNA mutations and severe oxidative impairment there is a blunted mitochondrial biogenesis response characterized by both reduced Tfam abundance and Tfam function (less mitochondria for a given Tfam level) (Konokhova et al. *Skeletal Muscle* 2016). Furthermore, these deficits in mitochondrial respiratory function are only partially restored by traditional cycle endurance training and not at all by eccentric cycle training (MacMillan et al. *Frontiers in Physiology* 2017). Finally, our most recent data shows that COPD patients who exhibit low muscle mass have a much higher abundance of persistently denervated muscle fibers accompanied by a failed reinnervation transcriptional response. Data from a smoking mouse model suggests denervation in COPD patients is likely precipitated by years of smoking based upon a smoke-induced degeneration of the neuromuscular junction (Kapchinsky et al. *J Physiol.* 2018).
    a. Y. Konokhova, S. Spendiff, N. MacMillan, S. Kapchinsky, C. Pilon, M. Aubertin-Leuhedre, J. Morais, R.T. Jagoe, **R.T. Hepple**, and T. Taivassalo. Failed upregulation of TFAM protein and mtDNA copy number in oxidatively deficient single fibers of chronic obstructive pulmonary disease locomotor muscle. *Skeletal Muscle* 18[6]: 10, 2016. PMID: 26893822
    b. N.J. MacMillan, S. Kapchinsky, Y. Konokhova, G. Gouspillou, R. de Souza Sena, R.T. Jagoe, J. Baril, T.E. Carver, R.E. Andersen, R. Richard, H. Perrault, J. Bourbeau, **R.T. Hepple**, and T. Taivassalo. Eccentric Ergometer Training Promotes Locomotor Strength but Not Mitochondrial Adaptation in Patients with Severe Chronic Obstructive Pulmonary Disease. *Frontiers in Physiology* 8: 114, 2017. PMID: 28316572
    c. S. Kapchinsky, M. Vuda, K. Miguez, D. Elkrief, A. Rico de Souza, C.J. Baglole, S. Aare, N.J. MacMillan, J. Baril, P. Rozakis, V. Sonjak, C. Pion, M. Aubertin-Leheudre, J.A. Morais, R.T. Jagoe, J. Bourbeau, T. Taivassalo, **R.T. Hepple**. Smoke-induced neuromuscular junction degeneration precedes the fiber type shift and atrophy in COPD. *The Journal of Physiology* 596.14: 2865-81, 2018. PMID: 29663403

A full list of my publications can be found on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=hepple+rt

D. Additional Information: Research Support

ONGOING Research Support

NIH R01 AG059416 (Cummings) 06/2018-11/2023
Study of Muscle, Mobility and Aging (SOMMA)
Goals: Determine the role played by muscle properties in longitudinal changes in mobility disability.
Role: Co-PI.

Florida Health James and Esther King Biomedical Research Program (Ryan/Hepple) 07/2020-06/2023
The role of the aryl hydrocarbon receptor in tobacco smoke-induced adverse muscle impact.
Goals: To identify the role of the aryl hydrocarbon receptor in the muscle atrophy, mitochondrial impairment, and neuromuscular junction degeneration induced by chronic tobacco smoke exposure.
Role: Co-PI.

NIH/NIA/Pepper Center OAIC Pilot Grant R01 AG059416 (Pahor, Hepple) 04/2019-03/2021
Identification of novel circulating factors affecting skeletal muscle mass and function in advanced age.
Goals: Identify proteins circulating in blood that predict the degree to which muscle mass and function are preserved in advanced age.
Role: PI on Pilot grant.

Sutter Health (Hepple) 01/2019-12/2019
Characterizing the transcriptome of very small muscle fibers in aging skeletal muscle.
Goals: To use laser capture to permit extraction of RNA from select populations of muscle fibers in aging muscle to gain insight into the mechanisms causing selective atrophy of muscle fibers.
Role: PI

R01 HL149704 (Ryan) 12/01/2019 – 11/30/2024
NIH/NHLBI
Molecular mechanism regulating peripheral arterial disease pathobiology in chronic kidney disease
The goal is this project is to investigate the molecular pathways that cause worsening PAD pathology in the presence of chronic kidney disease.
Role: Co-Investigator

COMPLETED Research Support IN LAST 5 YEARS

Canadian Institutes of Health Research, Operating Grant MOP 125986 (Hepple) 03/2013-02/2018
Mechanisms of Motor Unit Protection by Exercise Training in Aging Muscle
Goals: Identify novel mechanisms by which exercise training could protect the aging motor unit (motoneuron plus innervated muscle fibers).
Role: PI.

Canadian Institutes of Health Research, Operating Grant MOP 119583 (Hepple) 03/2012-02/2017
Relationship between Denervation, Mitochondrial Dysfunction, and Muscle Atrophy in Sarcopenia
Goals: Identify cause-versus-effect relationships between the accumulation of persistently denervated muscle fibers and mitochondrial dysfunction in aging muscle.
Role: PI.