BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: James M Ervasti

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

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 Minnesota, St. Paul, MN	B.S.	1979-83	Biochemistry
University of Minnesota, St. Paul, MN	Ph.D.	1984-89	Biochemistry
University of Iowa, Iowa City, IA	Postdoc.	1989-92	Physiology

A. Personal Statement

For more than 35 years, I have studied the protein biochemistry, cell biology and physiology of the cytoskeleton with emphasis on Duchenne muscular dystrophy. As a postdoctoral fellow in the laboratory of Dr. Kevin Campbell, I first defined the proteins comprising the dystrophin-glycoprotein complex in 12 peer-reviewed publications. I became independent upon moving to the University of Wisconsin in 1992 where I was promoted to the rank of Associate Professor with tenure in 1997 and to Professor in 2002. In 2006, I was recruited to the Department of Biochemistry, Molecular Biology & Biophysics and Muscular Dystrophy Center at UMN where I am currently the Research Director for the UMN Muscular Dystrophy Center and Co-Director of the Minnesota Muscle T32 Training Grant. My research program is focused on the biochemistry of muscular dystrophies involving dystrophin and associated proteins. My lab integrates biochemical, biophysical and structural analyses of dystrophin and its homologue utrophin with *in vivo* assessments of their function in genetically-engineered mouse models. We defined the interaction of dystrophin with actin filaments and its contribution to costamere architecture of skeletal muscle. We identified a function for dystrophin in organizing the microtubule lattice of skeletal muscle and generated new animal models and reagents to further elucidate the pathomechanism of Duchenne muscular dystrophy, other myopathies, and progressive deafness. Of more than 10,760 research studies published on dystrophin, I co-authored three of the ten most-cited. I have directed research projects that have been continuously funded by multiple extramural sources since 1993. I have trained 9 postdoctoral scientists, served as thesis advisor for 21 doctoral students and provided research opportunities for over 40 undergraduate students. Of my 27 past trainees, all but 4 remain in scientific research with 2 of the 4 exceptions working in advanced science education at the high school level. The mean time to PhD for my past graduate trainees is 4.9 years (n = 19) with co-authorship on a mean of 4 publications per trainee. Thus, my group is fully capable to carry out the experiments proposed in this new application for funding.

Ongoing projects that I would like to highlight include:

T32 AR007612-21
Thomas, Lowe and Ervasti (MPI)
05/01/2002 – 04/30/2027
Minnesota Muscle Training Program

R01 AR042423-28
Ervasti (PI)
07/15/1994 – 07/31/2026
Cytoskeletal Interactions of Dystrophin

R01 AR049899-19
Ervasti (PI)
02/01/2005 – 02/28/2026
Costamere Defects in Muscular Dystrophies

Sarepta Therapeutics
Ervasti and Muretta (MPI)
07/01/2023 – 06/30/2025
Structural and molecular determinants of micro-Dystrophin stability and efficacy

B. Positions, Scientific Appointments and Honors

Positions and Employment

2011-Present	Research Director, University of Minnesota Paul and Sheila Wellstone MD Center.
2006-Present	Professor, Department of Biochemistry, Molecular Biology & Biophysics, University of Minnesota.
2002- 2006	Professor, Department of Physiology, University of Wisconsin.
1997- 2002	Associate Professor, Department of Physiology, University of Wisconsin.
1992- 1997	Assistant Professor, Department of Physiology, University of Wisconsin.
1989-1992	Postdoctoral Fellow, Department of Physiology and Biophysics, University of Iowa.
1985- 1989	Graduate Research Assistant, Department of Biochemistry, University of Minnesota.

Other Experience

2018-	Consultant, Sarepeta Therapeutics
2014-2019	Consultant, Solid Biosciences, LLC
2013-	Editorial Board, Journal of Neuromuscular Disorders
2012-	Board of Consulting Editors, Journal of Clinical Investigation
2011-	Editorial Board, PLoS One
2007-2009	MDA Scientific Advisory Committee Ad hoc member
2005-2009	Member, Skeletal Muscle and Exercise Physiology Study Section
2003, 2004	Special Committee for Muscular Dystrophy Cooperative Research Centers (NINDS)
2001-2006	Editorial Board, Journal of Biological Chemistry
1998-2001	Member, Molecular, Cellular and Developmental Neuroscience Study Section 1

Honors

2014	Leon Poliachik Humanitarian Award, Muscular Dystrophy Association
2013-	Paul and Sheila Wellstone Muscular Dystrophy Center Distinguished Scholar
1997	UW Career Development Award, Howard Hughes Medical Institute
1996-2001	KO2 Career Development Award, National Institutes of Health
1996	American Heart Association Established Investigator (declined)
1991-1992	Carl M. Pearson Fellow of the Muscular Dystrophy Association
1990-1991	Muscular Dystrophy Association Postdoctoral Fellowship
1989-1990	National Institute of Neurological Disorders and Stroke Postdoctoral Fellowship

C. Contribution to Science

1. As a postdoctoral fellow in the laboratory of Dr. Kevin Campbell at the University of Iowa, I first defined the protein composition and membrane organization of the dystrophin-glycoprotein complex (DGC), which is disrupted in many forms of human muscular dystrophy. In 12 peer-reviewed publications, I defined all the core subunits in the DGC, characterized each subunit as peripheral or integral to the sarcolemma, demonstrated a high affinity interaction between laminin and extensively glycosylated α-dystroglycan, and actin-binding activity in purified DGC. Three of the following four publications are among the 10 most cited research studies on dystrophin with 1141 to 1151 citations:

a. **Ervasti, J.M.**, Ohlendieck, K., Kahl, S.D., Gaver, M.G. and Campbell, K.P. (1990) Deficiency of a glycoprotein component of the dystrophin complex in dystrophic muscle. *Nature* 345: 315-319. PMID: 2188135. **(856 citations)**

b. **Ervasti, J.M.** and Campbell, K.P. (1991) Membrane organization of the dystrophin-glycoprotein complex. *Cell* 66:1121-1132. PMID: 1913804. **(1142 citations)**

c. Ibraghimov-Beskrovnaya, O., **Ervasti, J.M.**, Leveille, C.J., Slaughter, C.A., Sernett, S.K. and Campbell, K.P. (1992) Primary structure of the 43 and 156 kilodalton dystrophin-associated glycoproteins linking dystrophin to the extracellular matrix. *Nature* 355: 696-702. PMID: 1741056. **(1141 citations)**

d. **Ervasti, J.M.** and Campbell, K.P. (1993) A role for the dystrophin-glycoprotein complex as a transmembrane linker between laminin and actin. *J. Cell Biol.* 122: 809-823. PMID: 8349731 **(1151 citations)**

2. My first contributions to science as an independent investigator were to demonstrate: i) that dystrophin functions as a monomer in the DGC to bind laterally along an actin filament through the concerted actions of two distinct and spatially separated actin binding sites, ii) that dystrophin is necessary for strong mechanical coupling between the sarcolemma and costameric actin filaments, iii) that utrophin can substitute for dystrophin in coupling costameric actin filaments to the sarcolemma when transgenically overexpressed in *mdx* skeletal muscle, iv) and that utrophin binds actin filaments with similar affinity as dystrophin but through distinct modes of contact. Several of these advances were made possible by methods that we pioneered to express and purify biochemical amounts of full-length recombinant dystrophin and utrophin.

a. Rybakova, I.N., Amann, K.J. and **Ervasti, J.M.** (1996) A new model for the interaction of dystrophin with F-actin. *J. Cell Biol.* 135: 661-672. PMCID: PMC2121071

b. Rybakova, I.N., Patel, J.R. and **Ervasti, J.M.** (2000) The dystrophin complex forms a mechanically strong link between the sarcolemma and costameric actin. *J. Cell Biol*. 150:1209-1214. PMCID: PMC2175263

c. Rybakova, I.N., Patel, J.R., Yurchenco, P.D., Davies, K.E. and **Ervasti, J.M.** (2002) Utrophin binds laterally along actin filaments and can couple costameric actin with sarcolemma when overexpressed in dystrophin-deficient muscle. *Mol. Biol. Cell* 13:1512-1521. PMCID: PMC111123

d. Rybakova, I.N., Humston, J.L., Sonnemann, K.J. and **Ervasti, J.M.** (2006) Dystrophin and utrophin bind actin filaments through distinct modes of contact. *J. Biol. Chem.* 281:9996-10001. PMID: 16478721

3. The non-muscle β- and γ-cytoplasmic actin isoforms differ from each other by only 4 amino acids. Using new isoform-specific reagents and conditional knock-out mouse lines developed by my group during the course of our muscular dystrophy studies, we identified both the redundant and non-overlapping functions of β- and γ-actin in mouse embryonic development, developing and adult skeletal muscle, neurons of the CNS and PNS, and in auditory hair cells of the inner ear.

a. Sonnemann, K.J., Fitzsimons, D.P., Patel, J.R., Liu, Y.W., Schneider, M.F., Moss, R.L. and **Ervasti, J.M.** (2006) Cytoplasmic γ-actin is not required for skeletal muscle development but its absence leads to a progressive myopathy. *Dev. Cell* 11:387-397. PMID: 16950128

b. Prins, K.W., Call, J.A., Lowe, D.A and **Ervasti, J.M.** (2011) Quadriceps myopathy caused by skeletal muscle specific ablation of β_{cyto}-actin. *J. Cell Sci.* 124:951-957. PMCID: PMC3048892

c. Patrinostro, X., Roy, P., Lindsay, A., Chamberlain, C.M., Sundby, L.J., Starker, C.G., Voytas, D.F., **Ervasti, J.M.** and Perrin, B.J. (2018) Essential Nucleotide- and Protein-Dependent Functions of *Actb*/β-Actin. *Proc Natl. Acad. Sci. USA* 115:7973-7978. PMCID: PMC6077724

d. Olthoff, J.T., Lindsay, A., Abo-Zahrah, R., Baltgalvis, K.A., Patrinostro, X., Belanto, J.J., Yu, D.-Y., Perrin, B.J., Garry, D.J., Rodney, G.G., Lowe, D.A. and **Ervasti, J.M.** (2018) Loss of peroxiredoxin-2 exacerbates eccentric contraction-induced force loss in dystrophin-deficient muscle. *Nat. Commun.* 9:5104. PMCID: PMC6269445

4. We have defined how dystrophin and utrophin differ in their intrinsic thermal stabilities *in vitro* and how the stability of dystrophin is compromised by missense mutations and therapeutically-relevant internal sequence deletions both *in vitro*, in cultured muscle cells, and in new mouse models. Most recently, we have transitioned to using single molecule force spectroscopy (AFM) to perform the first mechanical characterization of single utrophin molecules.

a. Talsness, D.M., Belanto, J.J. and **Ervasti J.M.** (2015) Disease-proportional proteasomal degradation of missense dystrophins. *Proc Natl. Acad. Sci. USA* 112:12414-12419. PMCID: PMC4603481

b. McCourt, J.M., Talsness, D.M., Lindsay, A., Arpke, R., Chatterton, P., Nelson, D.M., Chamberlain, C.M., Olthoff, J.T., Belanto, J.J., McCourt, P., Kyba, M., Lowe, D.A. and **Ervasti, J.M.** (2018) Mouse models of two missense mutations in actin binding domain 1 of dystrophin associated with Duchenne or Becker muscular dystrophy. *Hum. Mol. Genet.* 27:451-462. PMCID: PMC5886145

c. Rajaganapathy, S., McCourt, J.L., Ghosal, S., Lindsay, A., McCourt, P.M., Lowe, D.A., **Ervasti, J.M.** and Salapaka, M.V. (2019) Distinct mechanical properties in homologous spectrin-like repeats of utrophin. *Sci. Rep.* 9:5210. PMCID: PMC6435810

d. Ramirez, M.P., Rajaganapathy, S., Hagerty, A.R., Hua, C., Baxter, G.C., Vavra, J., Gordon, W.R., Muretta, J.M., Salapaka, M.V. and **Ervasti, J.M.** (2023). Phosphorylation alters the mechanical stiffness of a model fragment of the dystrophin homologue utrophin. *J. Biol. Chem.* 299:102847. PMCID: PMC9922815

5. We have demonstrated that dystrophin can bind directly to microtubules *in vitro* and is necessary *in vivo* to organize subsarcolemmal microtubules into a rectilinear lattice. We have also demonstrated that utrophin can neither bind microtubules *in vitro*, nor can it rescue subsarcolemmal microtubule lattice organization when transgenically overexpressed in dystrophin-deficient *mdx* mice. Our study of transgenic *mdx* mice expressing five different miniaturized dystrophin constructs has demonstrated that three therapeutically relevant micro-dystrophins do not fully restore subsarcolemmal microtubule lattice organization.

a. Prins, K.W., Humston, J.M., Mehta, A., Tate, V., Ralston, E. and **Ervasti, J.M.** (2009) Dystrophin is a microtubule-associated protein *J. Cell Biol.* 186:363-369. PMCID: PMC2728405

b. Belanto, J.J., Mader, T., Eckhoff, M., Strandjord, D.M., Banks, G.B., Gardner, M.K., Lowe, D.A. and **Ervasti J.M.** (2014) Microtubule Binding Distinguishes Dystrophin from Utrophin. *Proc Natl. Acad. Sci. USA* 111:5723-5728. PMCID: PMC3992671

c. Nelson, D.M., Lindsay, A., Judge, L.M., Duan, D., Chamberlain, J.S., Lowe, D.A. and **Ervasti, J.M.** (2018) Variable rescue of microtubule and physiological phenotypes in *mdx* muscle expressing different miniaturized dystrophins. *Hum. Mol. Genet*. 27:2090-2100. PMCID: PMC5985723

d. Nelson, D.M., Fasbender, E.K., Jakubiak, M.C., Lindsay, A., Lowe, D.A. and **Ervasti, J.M.** (2020) Rapid, redox-mediated mechanical susceptibility of the cortical microtubule lattice in skeletal muscle. *Redox Biol.* 37: 101730. DOI: 10.1016/j.redox.2020.101730 PMID: 33002761 PMCID: PMC7527753.

Complete List of Publications in MyBibliography:

https://www.ncbi.nlm.nih.gov/sites/myncbi/james m.ervasti.1/bibliography/40493807/public/?sort=date&direction=descending