

BIOGRAPHICAL SKETCH

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NAME Natalia Shirokova		POSITION TITLE Associate Professor	
eRA COMMONS USER NAME (credential, e.g., agency login) nshirokova			
EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)			
INSTITUTION AND LOCATION	DEGREE (if applicable)	MM/YY	FIELD OF STUDY
MPhTI, Moscow, USSR Bogomoletz Institute of Physiology, Kiev, Ukraine Rush University Medical School, Chicago, USA	MS PhD Post-Doc	1987 1991 1991-1996	Molecular/Chem. Physics Physiology&Biophysics Physiology

A. Personal Statement.

The overall goal of the present proposal is to established cellular mechanisms leading to deterioration of cardiac functions in muscular dystrophy. Specifically, we plan to examine if and to what extent dysregulation of connexin43 expression contributes to hallmark features of dystrophyc cardiomyopathy: impaired Ca^{2+} homeostasis and oxidative stress. A variety of electrophysiological, imaging and biochemical techniques will be employed to achieve our goals. I have a strong scientific background in muscle research. Over last ten years I expanded my studies from the skeletal muscle excitation contraction coupling to cardiac cellular physiology and metabolism. I have a specific training in key techniques that will be used in this application. My research as of independent investigator was (is) funded by several agencies, such as NIH, AHA and MDA. This application is a logical continuation of our current work on skeletal and cardiac phenotypes of muscular dystrophy. We build up a great team of collaborators from different department of our medical school, which include Drs. D. Fraidenraich, and J. Cortreras. Each team member has a unique scientific and technical expertise, which would greatly benefit our studies. Overall, I believe that we have experience, expertise and motivation necessary to carry out this project.

B. Positions and Honors.**Positions and Employment**

- 1987-1990: Aspirant MPhTI in the Bogomoletz Institute of Physiology, Kiev, Ukraine (Advisor: Dr. P.Kostyuk).
- 1990-1997: Research Associate of the Department of General Physiology of the Nervous System, Bogomoletz Institute of Physiology, Kiev, Ukraine.
- 1991-1996: Research Associate in the Department Molecular Biophysics and Physiology, Rush University, Chicago, IL, USA (Advisor: Dr. E. Rios).
- 1996-2000: Assistant Professor (non-tenure track) in the Department Molecular Biophysics and Physiology, Rush University, Chicago, IL, USA.
- 2000-2009: Assistant Professor (tenure track) in the Department of Pharmacology and Physiology, UMDNJ-New Jersey Medical School, Newark, NJ, USA.
- 2009-date: Associate Professor with tenure in the Department of Pharmacology and Physiology, UMDNJ-New Jersey Medical School, Newark, NJ, USA.

Other experience and Professional Memberships

- 1991-date Biophysical Society
- 1994-date Society of General Physiologists
- 1991-date Referral work for American Journal of Physiology (Cell Physiol.), Biophysical Journal, Journal of Physiology (London), Journal of General Physiology, Cell Calcium, Journal of Biological

Program Director/Principal Investigator (Last, First, Middle):

Chemistry, European Heart Journal, Cardiovascular Research, Journal of Cellular and Molecular Cardiology, Cell Biochemistry and Biophysics, PlosONE

Honors

1985 MS with the Highest Honor, MPhTI.
1997-1998 Fellowship under the NIH Training Program

C. Trainees

Alena Isaeva, Postdoctoral Fellow, 1/4/01 - 11/29/03
Vyacheslav Shkryl, Postdoctoral Fellow, 8/1/03 - 12/31/2003
Taras Blashkiv, Postdoctoral Fellow, 01/2005 -12/2005
Adriano Martins, Postdoctoral Fellow, 03/2006 - 08/2009
Eva Polakova, Postdoctoral Fellow, 12/2007 - 9/2011
Krisztina Pocsai, Postdoctoral Fellow, 02/2009 - 10/2011
Sergiy Kyrychenko, Postdoctoral Fellow, 03/2010 – 05/2014
Victoria Kyrychenko, Postdoctoral Fellow, 03/2011 – 05/2014
Radoslav Janicek, Postdoctoral Fellow, 10/2013 - 01/2015
Myriam Bard, Postdoctoral Fellow, 09/2013 – 08/2015
Chifei Kang, Ph.D. Graduate Student, 09/2012 – 02/2017

D. Selected Peer-reviewed Publications

Most relevant to the current application

1. J.P. Gonzalez, J. Ramachandran, E. Himelman, M.A. Badr, C. Kang, J. Nuet, N. Fefelova, L.-H. Xie, **N. Shirokova***, J.E. Contreras* and D. Fraidenraich*. Normalization of connexin 43 protein levels prevents cellular and functional signs of dystrophic cardiomyopathy in mice. *Journal of Neuromuscular Disorders* **28**:361-372, 2018. *Corresponding authors. PMID: 9477453.
2. A.S. Martins, V.M. Shkryl, M.C. Nowycky and **N. Shirokova**. Reactive oxygen species contribute to Ca²⁺ signals produced by osmotic stress in mouse skeletal muscle fibres. *Journal of Physiology* **586**:197-210, 2007. PMCID: PMC2375568.
3. W.J. Durham, P. Aracena-Parks, C. Long, A.E. Rossi, S.A. Goonasekera, S. Boncompagni, D.L. Galvan, C.P. Gilman, M. Baker, **N. Shirokova**, F. Protasi, R. Dirksen and S.L. Hamilton. RyR1 S-Nitrosylation underlies environmental heat stroke and sudden death in Y522S RyR1 knock-in mice. *Cell*, **133**: 53-65, 2008. PMCID: PMC2366094.
4. C. Jung, A.S. Martins, E. Niggli and **N. Shirokova**. Dystrophic cardiomyopathy: amplification of cellular damage by Ca²⁺ signalling and reactive oxygen species-generating pathways. *Cardiovascular Research* **77**: 766-773, 2008.
5. V.M. Shkryl, A.S. Martins, N.D. Ullrich, M.C. Nowycky, E. Niggli and **N. Shirokova**. Reciprocal amplification of ROS and Ca²⁺ signals in stressed *mdx* dystrophic skeletal muscle fibers. *Pflugers Archive* **458**: 915-928, 2009
6. M. Fanchaouy, E. Polakova, C. Jung, J. Ogradnik, **N. Shirokova** and E. Niggli. Pathways of abnormal stress-induced Ca²⁺ influx into dystrophic *mdx* cardiomyocytes. *Cell Calcium* **46**:114-121, 2009. PMCID: PMC2745084.
7. N.D. Ullrich, M. Fanchaouy, K. Gusev, **N. Shirokova** and E. Niggli. Hypersensitivity of excitation-contraction coupling in dystrophic *mdx* mouse cardiomyocytes. *American Journal of Physiology* **297**:H1992-2003, 2009.

8. S. Kyrychenko, E. Poláková, C. Kang, K. Pocsai, N.D. Ullrich, E. Niggli and N. Shirokova. Hierarchical accumulations of Ryr posttranslational modifications drive disease progression in dystrophic cardiomyopathy. *Cardiovascular Research*, **97**:666-675, 2013. PMID: PMC3583259
9. N. Shirokova and E. Niggli. Cardiac Phenotype of Duchenne Muscular Dystrophy: Insights from Cellular Studies. *Journal Molecular and Cellular Cardiology* **58**:217-224, 2013. PMID: PMC3615054.

Additional recent publications of importance to the field (in chronological order)

10. R.Shirokov, R.Levis, N.Shirokova and E. Ríos. Two classes of gating current from L-type Ca channels in guinea pig ventricular myocyte. *Journal of General Physiology* **99**: 863-895, 1993. PMID: PMC2216624.
11. R.Shirokov, R.Levis, N.Shirokova and E. Ríos. Calcium dependent inactivation of cardiac L-type calcium channels does not involve their voltage sensor. *Journal of General Physiology* **102**: 1005-1030, 1993. PMID: PMC2229185.
12. N.Shirokova, G.Pizarro and E. Ríos. A damped oscillation in the intramembrane charge movement and calcium release flux of frog skeletal muscle fibers. *Journal of General Physiology* **104**: 449-477, 1994. PMID: PMC2229223.
13. N. Shirokova, A.Gonzalez, J.Ma, R.Shirokov and E. Ríos. Properties and roles of an intramembrane charge mobilized at high voltages in skeletal muscle. *Journal of Physiology* **486**: 385-400, 1995. PMID: PMC1156529.
14. N.Shirokova, J.Garcia, G.Pizarro and E. Ríos. Ca²⁺ release from the sarcoplasmic reticulum compared in amphibian and mammalian skeletal muscle. *Journal of General Physiology* **107**: 1-18, 1996. PMID: PMC2219250.
15. N. Shirokova and E. Ríos. Caffeine enhances intramembraneous charge movement in skeletal muscle by increasing cytoplasmic Ca²⁺ concentration. *Journal of Physiology* **493**: 341-356, 1996. PMID: PMC1158921.
16. N.Shirokova and E. Ríos. Activation of Ca²⁺ release by caffeine and voltage in frog skeletal muscle. *Journal of Physiology* **493**: 317-339, 1996. PMID: PMC1158920.
17. G.Pizarro, N Shirokova, A.Tsugorka and E. Ríos. Quantal release of calcium in skeletal muscle. *Journal of Physiology* **501**: 289-303, 1997. PMID: PMC1159477.
18. N Shirokova and E. Ríos. Small event Ca²⁺ release. A probable precursor of Ca²⁺ sparks in frog skeletal muscle. *Journal of Physiology* **501**: 3-11, 1997. PMID: PMC1159568.
19. H. Cheng, L.S. Song, N.Shirokova, A. González, E.G. Lakatta, E. Ríos and M.D. Stern. Amplitude distribution of calcium sparks in confocal Images. Theory and studies with an automatic detection method. *Biophysical Journal* **76**: 606-17, 1999. PMID: PMC1300067.
20. N. Shirokova, J. Garcia and E. Ríos. Local calcium release in mammalian skeletal muscle. *Journals of Physiology* **512**: 377-384, 1998. PMID: PMC2231212.
21. N.Shirokova, A. González, W.G. Kirsch, E. Ríos, G. Pizarro, M.D. Stern and H. Cheng. Calcium sparks: release packets of uncertain origin and fundamental role *Journal of General Physiology* **113**: 377-384, 1999. PMID: PMC2222897.
22. E.Ríos, M.D. Stern, A.González, G.Pizarro and N.Shirokova. Calcium release flux underlying Ca²⁺ sparks in frog skeletal muscle. *Journal of General Physiology* **114**: 31-48, 1999. PMID: PMC2229636.
23. N. Shirokova, R. Shirokov, D. Rossi, A. González, W.G.Kirsch, J. García, V.Sorrentino and E. Ríos. Spatially segregated control of Ca²⁺ release in developing skeletal muscle. *Journal of Physiology* **521**: 483-495, 1999. PMID: PMC2269670.
24. A.González, A., W.G.Kirsch, N.Shirokova, G.Pizarro, M.D.Stern and E. Ríos. The spark and its ember. Separately gated local components of Ca²⁺ release in skeletal muscle. *Journal of General Physiology* **115**: 139-157, 2000. PMID: PMC2217200.
25. A.González, W.G.Kirsch, N.Shirokova, G.Pizarro, G.Brum, I.N.Pessah, M.D.Stern, H.Cheng and E. Ríos. Involvement of multiple intracellular release channels in calcium sparks of muscle. *PNAS* **97**: 4380-4385, 2000. PMID: PMC18250.
26. G. Brum, A. González, J. Rengifo, N. Shirokova, and E. Ríos. Fast imaging in two dimensions resolves extensive sources of Ca²⁺ sparks in frog skeletal muscle *Journal of Physiology* **528**: 419-433, 2000. PMID: PMC2270146.

28. E. Ríos, N. Shirokova, W.G. Kirsch, G. Pizarro, M.D. Stern, H. Cheng, and A. González. A preferred amplitude of calcium sparks in skeletal muscle. *Biophysical Journal* **80**: 169-183, 2001. PMID: PMC1301224.
29. E.V. Isaeva and N. Shirokova. Metabolic regulation of Ca²⁺ release in permeabilized mammalian skeletal muscle fibres. *Journal of Physiology* **547**:453-462, 2003. PMID: PMC2342647.
30. E.V. Isaeva, V.M. Shkryl and N. Shirokova. Mitochondrial redox state and Ca²⁺ sparks in permeabilized mammalian skeletal muscle. *Journal of Physiology* **565**:855-872, 2005. PMID: PMC1464560.
31. V.M. Shkryl and N. Shirokova. Transfer and tunneling of Ca²⁺ from sarcoplasmic reticulum to mitochondria in skeletal muscle. *Journal of Biological Chemistry* **281**: 1547-1554, 2006
32. E.V. Isaeva, V.M. Shkryl and N. Shirokova. Ca²⁺ sparks – SOS signals of struggling muscle. *Physiology News* **62**: 27-28, 2006.
33. E. Niggli and N. Shirokova. A guide to sparkology: The taxonomy of elementary cellular Ca²⁺ signaling events. *Cell Calcium* **42**: 379-387, 2007.
34. N. Shirokova and E. Niggli. Studies of RyR functions in situ. *Methods*, **46**: 183-193, 2008.
35. E.Niggli, N.D. Ullrich, D. Gutierrez, S. Kyrychenko, E. Poláková and N. Shirokova. Posttranslational modifications of cardiac ryanodine receptors: Ca²⁺ signaling and EC-coupling. *Biochemical Biophysical Acta* **1833**: 866-875, 2013. PMID: PMC3548064.
36. A. Tjondrokoesoemo, N. Li, Z. Pan, C.J. Ferrante, M. Brotto, N. Shirokova, J. Ma, N. Weisleder. P3R1 activates RyR1 to mediate Ca²⁺ sparks signaling in adult mammalian skeletal muscle. *Journal of Biochemical Chemistry* **288**:2103-2109, 2013. PMID: PMC3554882.
37. N. Shirokova and E. Niggli. Cardiac Phenotype of Duchenne Muscular Dystrophy: Insights from Cellular Studies. *Journal of Molecular and Cellular Cardiology* **58**:217-224, 2013. PMID: PMC3615054.
38. V. Kyrychenko, E. Poláková, R. Yanichek and N. Shirokova. Mitochondrial dysfunctions during progression of dystrophic cardiomyopathy. *Cell Calcium* **58**:186-195, 2015. PMID: PMC4501876.
39. J.P. Gonzalez, S. Kyrychenko, V. Kyrychenko, J.S. Schneider, C.J. Granier, E. Himelman, K.C. Lahey, Q. Zhao, G. Yehia, Y.X. Tao, M. Bhaumik, N. Shirokova and D. Fraidenraich. (2016). Small Fractions of Muscular Dystrophy Embryonic Stem Cells Yield Severe Cardiac and Skeletal Muscle Defects in Adult Mouse Chimeras. *Stem Cells* **35**: 597-610, 2016. PMID: 27734557.
40. C. Kang, M.A. Badr, V. Kyrychenko, E.-L. Eskelinen, and N. Shirokova. Deficit in PINK1/PARKIN-mediated mitochondrial autophagy at late stages of dystrophic cardiomyopathy. (2018). *Cardiovascular Research* **114**:90-102. PMID: PMC5852524

E. Research Support

Ongoing Research Support

R01 HL141170 Fraidenraich (PI), Contreras (PI), Shirokova (PI) 09/01/2018-06/30/22
“Connexin 43: a new player in Duchenne muscular dystrophy-cardiomyopathy”
The goal is identify role of Cx43 remodeling in DMD.

Completed Research Support

R01 HL093342 Shirokova (PI) 04/01/11-02/29/15

“Cardiac dystrophy: cellular mechanisms”

The goal of this project is to identify intracellular feedback mechanisms contributing to the damage of dystrophic cardiomyocytes.

Role: PI

R01 AR053933 Shirokova (PI) 09/01/2008-08/31/2013

“Mitochondria and Calcium Signaling in Skeletal Muscle”

The main goal is to examine how mitochondria regulate intracellular calcium signaling in healthy and diseased skeletal muscle.

Role: PI

Swiss Foundation for Research on Muscle Diseases Research Grant

01/01/2009-08/31/2011

