BIOGRAPHICAL SKETCH

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NAME: Seward Brian Rutkove

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

POSITION TITLE: Professor of Neurology, Harvard Medical School

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
Cornell University, Ithaca, NY	BA	05/1985	Chemistry
Columbia University, New York, NY	MD	05/1989	Medicine
St. Joseph Mercy Hospital, Ann Arbor, MI		06/1991	Internal Medicine
Harvard-Longwood Neurology, Boston, MA		06/1994	Neurology
Brigham & Women's Hospital, Boston, MA		06/1995	Neurophysiology

A. Personal Statement

I have been continuously NIH-funded in neuroscience translational research since 2003 and have been deeply involved in the development of novel approaches for assessing neuromuscular disease, including the development of new technologies (electrical impedance myography) and new biomarkers (electrical impedance and novel electrophysiologic markers). I believe my longstanding and dedicated interest in neurophysiology will make me a valuable member of the team that Dr. Wainger is assembling. Specifically, I have detailed knowledge and experience with excitability measures of peripheral nerve, including both large and small fibers, motor and sensory. I have been working with threshold tracking technologies for approximately 12 years and have published on them in both animals and human subjects. Moreover, in earlier work, I was deeply involved in diabetic polyneuropathy studies assessing the impact of temperature on axonal conduction and utilizing temperature metrics as novel approaches for assessing the presence of small fiber polyneuropathy. I look forward to working with Dr. Wainger in his team as I provide input on peripheral clinical neurophysiological aspects of the project and assist as needed to with data analysis and interpretation.

Ongoing and recently completed projects that I would like to highlight include:

NIH R01NS055099
Rutkove (PI)
8/1/2018-7/31/2023
Electrical impedance myography in an animal model

NIH R21NS118434
Rutkove, Halter (PIs)
07/01/2020-5/31/2022
Electrical impedance tomography for the assessment of pulmonary function in neuromuscular disease

Blavantik Family Foundation
Rutkove, PI

07/01/2020-06/30/2024
A neuronal electrical excitability recording system for improved diagnosis and biomarker assessment of the therapeutic impact of drugs in peripheral sensory and pain disorders.

NIH U24 NS107183
Darras, Rutkove (PIs)
7/15/18-6/30/23
Boston Children's Hospital and Beth Israel Deaconess NeuroNEXT Clinical Research Site

NASA 80NSSC19K1598
Rutkove (PI)
10/1/2019-9/30/2022
Approaching gravity as a continuum: musculoskeletal effects of fractional reloading

NASA 80NSSC21K0369
Rutkove (PI)
2/1/2021-1/31/2022
Resveratrol and electrical muscle stimulation as countermeasures to preserve sensorimotor function during a 60-day head-down bedrest protocol

NIH 1KL2TR002542-03
Rutkove, Bredella (PIs)
05/01/2018 – 04/30/2023
Harvard Clinical and Translational Science Center; Institutional Career Development Core

Citations and Patents:

1. Mortreux M, Riveros D, Bouxsein ML, **Rutkove SB**. A Moderate Daily Dose of Resveratrol Mitigates Muscle Deconditioning in a Martian Gravity Analog. Front Physiol. 2019 Jul 18;10:899. doi: 10.3389/fphys.2019.00899. PMID: 31379604; PMCID: PMC6656861.
2. **Rutkove SB**, Narayanaswami P, Berisha V, Liss J, Hahn S, Shelton K, Qi K, Pandeya S, Shefner JM. Improved ALS clinical trials through frequent at-home self-assessment: a proof-of-concept study. Ann Clin Transl Neurol. 2020 Jul;7(7):1148-1157. PMCID: PMC7359124.
3. Nagy JA, DiDonato CJ, **Rutkove SB**, Sanchez B. Permittivity of ex vivo healthy and diseased murine skeletal muscle from 10 kHz to 1 MHz. Sci Data. 2019 Apr 18;6(1):37. PMCID: PMC6472406.
4. US Patent #9,974,463, **Rutkove SB**, Dawson J. A hand-held device for electrical impedance myography, 2018.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments:

2021-	Chairman, Department of Neurology, BIDMC, Harvard Medical School
2018-2021	Associate Director for Investigators and Director Postdoctoral Office, BIDMC
2018-	Co-Director KL2 Grant Program/Harvard Catalyst
2013-21	Associate Editor, Neuromuscular Disease, *Annals of Neurology*
2012-	Professor of Neurology, Harvard Medical School
2003-21	Chief, Division of Neuromuscular Disease, BIDMC
2003-21	Multiple NIH study sections
2002-12	Associate Professor Neurology, Harvard Medical School, Boston, MA
1997-2002	Assistant Professor of Neurology, Harvard Medical School, Boston, MA
1995-97	Instructor in Neurology, Harvard Medical School, Boston, MA
1995-	Neurology Associate, Beth Israel Deaconess Medical Center (BIDMC), Boston MA

Honors:

2021	Innovation Award, American Assoc. of Neuromuscular and Electrodiagnostic Medicine
2019	Herbert P. Schwan International Award in Bioimpedance

2018 New York University, Northwestern University, Dartmouth College, Grand Rounds
2016 Keynote Speaker, Bioengineering Workshop, University of Sydney, Sydney, Australia
2015 Keynote Speaker, European Neurologists to Cure ALS,Dublin, Ireland
2015 Harvard Longwood Neurology Grand Rounds
2014 President's Research Award, Am. Ass. Neuromus. Electrodiagnostic Medicine
2014 Invited Speaker, International Conference of Clinical Neurophysiology, Berlin.
2013 Invited Speaker, University of Missouri
2013 Invited Speaker, Robert Packard Center for ALS research
2013 *IEEE Transactions in Biomedical Engineering*, highlighted work
2012 Grand Rounds, National Institute of Neurological Diseases, NIH
2011-21 Best of Boston Doctor, Neurology, *Boston Magazine*
2011 Winner, Prize4Lifes ALS Biomarker Challenge Prize
2011 *Science,* Newsmaker Article for winning of Biomarker Challenge Prize
2011 Invited speaker, FDA-sponsored Spinal muscular atrophy biomarker workshop
2009 Winner, Prize4Life ALS Biomarker Progress Prize
2008 President's Research Award, Am. Ass. Neuromus. Electrodiagnostic Medicine
2005 Harvard Longwood Neurology Grand Rounds
2002 Runner-up, Best Abstract, American Association of Electrodiagnostic Medicine
1999 Invited Speaker, Myositis Association of America, Annual Meeting
1995 Junior Member Recognition Award, American Association of Electrodiagnostic Medicine
1985 BA, Magna cum laude in chemistry, distinction in all subjects, Cornell University

C. Contributions to Science

My overarching contribution to science has focused on advancing the field of neuromuscular health. While much of my work has included study of several specific neuromuscular diseases, including amyotrophic lateral sclerosis and Duchenne muscular dystrophy, my research efforts have sought broader concepts that cut across many conditions. With a specific attention to technology and biomarker development, I have advanced methodologies, including the concept of applying surface and needle electrical impedance methods and quantitative ultrasound techniques for the assessment of muscle condition. This has led to broader application of improved biomarkers for tracking disease progression and response to therapy in these disorders. In addition, this work has drawn me in other directions, including the assessment of muscle alterations related to simple disuse, including that due to prolonged hospitalization, space flight and also aging-associated change (sarcopenia). Current efforts include a wide variety of studies focused on better measurement of muscle condition, therapeutic interventions to improve outcomes, and an improved understanding of basic mechanisms underlying muscle deterioration and recovery.

<u>Contribution #1: Application of electrical impedance methods for neuromuscular disorder assessment.</u>

Since the late 1990s, I began to study the potential of using electrical impedance methods for the assessment of neuromuscular disease. While the original effort was to find a technology that would be less invasive and more quantitative than standard needle electromyography, it became clear early on that the real value of impedance methods was that they could provide simple outcomes for clinical use, as they reflect basic structural and compositional aspects of muscle. Defining the concept as electrical impedance myography (EIM), I have been able to show that this method can provide a means of giving biopsy-like information on muscle health and tracking disease progression and remission over time. It can serve as a biomarker of therapy effect. Another major benefit of EIM is that it is also able to assess conditions that do not typically impact standard electromyography, such as disuse atrophy or sarcopenic change. Given the technology is very rapid and simple to apply, it can even serve as an at-home biomarker in future clinical trials.

5. **Rutkove SB**, Caress JB, Cartwright MS, et al. Electrical impedance myography as a biomarker to assess ALS progression. Amyotroph Lateral Scler. 2012 Sep;13(5):439-45. PMCID: PMC3422377.
6. Sanchez B, **Rutkove SB**. Electrical Impedance Myography and Its Applications in Neuromuscular Disorders. Neurotherapeutics. 2017 Jan;14(1):107-118. PMCID: PMC5233633.
7. **Rutkove SB**, Kapur K, Zaidman C, Wu JS, Pasternak A, Madabusi L, Yim S, Pacheck A, Szelag H, Harrington T, Darras BT. Electrical impedance myography for assessment of Duchenne muscular dystrophy. Ann Neurol. 2017 Jan 11. PMID: 28076894.

8. **Rutkove SB**, Narayanaswami P, Berisha V, Liss J, Hahn S, Shelton K, Qi K, Pandeya S, Shefner JM. Improved ALS clinical trials through frequent at-home self-assessment: a proof-of-concept study. Ann Clin Transl Neurol. 2020 Jul;7(7):1148-1157. PMCID: PMC7359124.

Contribution #2: Developing a theory and science of impedance assessment of muscle.

Despite the progress in applying EIM to human disease and corresponding animal models, without a firm grasp of the underlying mechanisms of impedance alteration, the technology could have limited application given data interpretation challenges. Thus, in parallel with the clinical research program described above, I have also pursued a program focused on understand the challenging and complex relationship between impedance data and the underlying electrical material properties of muscle. Specifically, we have sought to understand complexities connecting the electrical material properties of muscle (the relative permittivity and conductivity) to specific tissue characteristics, including muscle fibrosis, fat deposition and myofiber atrophy and hypertrophy. As part of this work, we have sought to understand better the anisotropic nature of muscle and how that is impacted in disease states. By using a combination of finite element method and circuit component modeling, we have been able to develop a broader understanding of how basic impedance theory can be applied to the assessment of neuromuscular disorders.

1. Jafarpoor M, Li J, White JK, **Rutkove SB**. Optimizing electrode configuration for electrical impedance measurements of muscle via the finite element method. IEEE Trans Biomed Eng. 2013 May;60(5):1446-52. PMCID: PMC3984469.
2. Li J, Jafarpoor M, Bouxsein M, **Rutkove SB**. Distinguishing neuromuscular disorders based on the passive electrical material properties of muscle. Muscle Nerve. 2015 51:49-55. PMCID: PMC4201890.
3. **Rutkove SB**, Wu JS, Zaidman C, Kapur K, Yim S, Pasternak A, Madabusi L, Szelag H, Harrington T, Li J, Pacheck A, Darras BT. Loss of electrical anisotropy is an unrecognized feature of dystrophic muscle that may serve as a convenient index of disease status. Clin Neurophysiol. 2016 Dec;127(12):3546-3551. Epub 2016 Oct 13. PMCID: PMC5181855.
4. Nagy JA, DiDonato CJ, **Rutkove SB**, Sanchez B. Permittivity of ex vivo healthy and diseased murine skeletal muscle from 10 kHz to 1 MHz. Sci Data. 2019 Apr 18;6(1):37. PMCID: PMC6472406.

Contribution #3: Technology development for neuromuscular disorder evaluation.

Through collaboration with like-minded physicians, engineers and entrepreneurs, I have been developing improved technologies that are now being incorporated into clinical trials and into regular clinical care. A major focus on this has been in the field of impedance technologies, and two companies have been spun out of my work: Myolex, Inc, and Haystack Diagnostics, the former focusing on non-invasive surface-based impedance measurement techniques and the latter on melding standard needle electromyography with needle impedance measurements. Myolex systems are already being used in clinical trials and a new EIM-based product, the Myolex® mScan™, is currently undergoing FDA 510(k) clearance. The concepts have also led to novel systems for evaluating tongue muscle condition at the bedside, and I am an inventor on 5 patents in the field of electrical impedance. In addition to these efforts, we are now working on improving and simplifying electrical excitability testing methods, based on work completed by Hugh Bostock, PhD. This work, which is currently ongoing, promises to advance an unrelated area of neurophysiological assessment.

1. Shefner JM, **Rutkove SB**, Caress JB, Benatar M, David WS, et al. Reducing sample size requirements for future ALS clinical trials with a dedicated electrical impedance myography system. Amyotroph Lateral Scler Frontotemporal Degener. 2018 Sep 28:1-7. PubMed PMID: 30265154.
2. **Rutkove SB**, Kwon H, Guasch M, Wu JS, Sanchez B. Electrical impedance imaging of human muscle at the microscopic scale using a multi-electrode needle device: A simulation study. Clin Neurophysiol. 2018 Aug;129(8):1704-1708. Epub 2018 May 25. PubMed PMID: 29804914.
3. US Patent #9,014,797: Shiffman CA, Aaron R, **Rutkove SB**. Electrical impedance myography
4. US Patent #9,974,463. **Rutkove SB**, Dawson J. A hand-held device for electrical impedance myography.

Contribution #4: Improved understanding of mechanisms of muscle health and dysfunction across the neuromuscular disorder spectrum

The fact that my work embraces many neuromuscular disorders has led to my applying concepts that cut across the neuromuscular disorder spectrum. In fact, my work is increasingly assessing the border zone between health and disease. This has been, in part, supported by substantial NASA funding over the past 5 years. This work has included studying models of microgravity and fractional gravity (as would be observed on the Moon and Mars) and the impact on muscle health. This work also includes relevant applications in the fields of aging

muscle (sarcopenia) and secondary disuse due to injury or prolonged hospitalization. It encompasses not only functional and electrophysiological assessments, but deeper studies investigating histological and molecular alterations. My most recent contributions are increasingly focused on molecular mechanisms of dysfunction and potential approaches for reversing the untoward effects of prolonged disuse, including the use of therapeutics.

1. Mortreux M, Ko FC, Riveros D, Bouxsein ML, **Rutkove SB**. Longitudinal time course of muscle impairments during partial weight-bearing in rats. NPJ Microgravity. 2019 Aug 22;5:20. doi: 10.1038/s41526-019-0080-5. PMID: 31453318; PMCID: PMC6706399.
2. Mortreux M, Riveros D, Bouxsein ML, **Rutkove SB**. A Moderate Daily Dose of Resveratrol Mitigates Muscle Deconditioning in a Martian Gravity Analog. Front Physiol. 2019 Jul 18;10:899. PMID: 31379604; PMCID: PMC6656861.
3. Malkani S, Chin CR, Cekanaviciute E… Costes SV, **Rutkove SB**, Grabham P, Mason CE, Beheshti A. Circulating miRNA Spaceflight Signature Reveals Targets for Countermeasure Development. Cell Rep. 2020 Dec 8;33(10):108448. PMID: 33242410.
4. Hu N, Kim E, Antoury L, Li J, González-Pérez P, **Rutkove SB**, Wheeler TM. Antisense oligonucleotide and adjuvant exercise therapy reverse fatigue in old mice with myotonic dystrophy. Mol Ther Nucleic Acids. 2020 Nov 26;23:393-405. PMID: 33473325; PMCID: PMC7787993.

URL to full list of published research: http://www.ncbi.nlm.nih.gov/pubmed/?term=rutkove