BIOGRAPHICAL SKETCH

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NAME: HAYWARD, LAWRENCE J

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POSITION TITLE: Professor of Neurology

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)	END DATE MM/YYYY	FIELD OF STUDY
Washington University, St. Louis, MO	BS	05/1982	Electrical Engineering
Baylor College of Medicine, Houston, TX	PhD	05/1987	Neuroscience
Baylor College of Medicine, Houston, TX	MD	02/1989	Medicine
Baylor College of Medicine, Houston, TX	Resident	02/1990	Medical Intern
Massachusetts General Hospital, Boston, MA	Resident	06/1993	Neurology
Massachusetts General Hospital, Boston, MA	Fellow	06/1997	Neuromuscular

A. Personal Statement

I am a physician-scientist and Director of the Neuromuscular Division at the University of Massachusetts Chan Medical School with experience over the past 25 years investigating molecular mechanisms of neuromuscular diseases, primarily amyotrophic lateral sclerosis (ALS), facioscapulohumeral muscular dystrophy (FSHD), and periodic paralysis. My background includes clinical neurology, neuromuscular medicine, and specific expertise in neuroscience, muscle biology, ion channel physiology, mouse models, single-cell RNAseq, and phenotypic screening relevant to the design of targeted therapies for these conditions. At UMass Chan, I participate in a highly collaborative scientific community with research strengths in neurodegenerative and neuromuscular diseases, RNA biology and therapeutics, chemical biology and screening, and gene editing and delivery approaches. As a board-certified neurologist, I direct the multidisciplinary facioscapulohumeral muscular dystrophy (FSHD) clinic at UMass Chan, teach residents weekly in the neuromuscular clinic, and I attend on the neurology inpatient services for 6-8 weeks per year.

The UMass Chan Wellstone Cooperative Research Center for FSHD maintains a repository of frozen primary muscle biopsies from FSHD patients and unaffected first-degree relatives. These include pairs of both deltoid (less affected) and biceps (more affected) muscles from affected individuals and controls comprising 56 families. From these biopsies, we have also isolated primary myogenic cells and selected immortalized iPSCs to establish cellular and xenograft FSHD models. I interact closely with the New England Chapter of the FSHD Society and reach out to local providers serving underrepresented groups in our community to bring services to FSHD patients and to communicate recent advances in research. I lead an IRB-approved FSHD biomarker study to engage patients in the donation of DNA and tissue samples for research. I serve as the site P.I. for the Phase 2b and Phase 3 clinical trials of losmapimod in FSHD and as the P.I. for the PROPEL gene therapy study for adrenomyeloneuropathy. In the lab, I have gained expertise in single-cell RNAseq analyses and collaborate closely with our Wellstone group to characterize cellular models of FSHD. My relevant publications in the FSHD field include:

1. Ghasemi M, Emerson CP Jr, Hayward LJ. Outcome Measures in Facioscapulohumeral Muscular Dystrophy Clinical Trials. Cells. 2022 Feb 16;11(4) PubMed Central PMCID: PMC8870318.
2. Guo D, Daman K, Chen JJ, Shi MJ, Yan J, Matijasevic Z, Rickard AM, Bennett MH, Kiselyov A, Zhou H, Bang AG, Wagner KR, Maehr R, King OD, Hayward LJ, Emerson CP Jr. iMyoblasts for ex vivo and in vivo investigations of human myogenesis and disease modeling. Elife. 2022 Jan 25;11 PubMed Central PMCID: PMC8789283.

3. Jagannathan S, de Greef JC, Hayward LJ, Yokomori K, Gabellini D, Mul K, Sacconi S, Arjomand J, Kinoshita J, Harper SQ. Meeting report: the 2021 FSHD International Research Congress. Skelet Muscle. 2022 Jan 17;12(1):1. PubMed Central PMCID: PMC8762812.

I am deeply committed to education, training, and mentoring. I regularly contribute to teaching in medical and graduate school courses. In my lab, I have directly supervised 5 MD/PhD students, 14 PhD students, 2 MD students, and 10 undergraduate students. The latter have included students from disadvantaged backgrounds accepted into the Summer Undergraduate Research Program (SURP) at UMMS. In the graduate program, I have served on 38 qualifying exam committees and 21 thesis research advisory committees. I have been a mentor for 5 postdoctoral fellows in my lab, 3 of whom obtained positions in academia, and one in industry. I currently serve as a longitudinal faculty mentor for 13 MD/PhD students in the Blackstone House at UMass Chan and have also served as a mentor for the UMass Chan Junior Faculty Development Program (JFDP).

I look forward to continuing to serve as a mentor and thesis advisor for MD-PhD students. I strongly support an approach to mentoring that includes structured mentor training, mentoring contracts, Individual Development Plans (IDPs), and a commitment to the guidelines for thesis project selection for students that is assessed through the instrument presented in Appendix S.4.15 of this application.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2023 -	Ad hoc reviewer, Muscular Dystrophy UK (London)
2022 -	Director, Neuromuscular Division, UMMS/UMMMC
2021 -	Member, Neuromuscular Study Group
2021 -	Co-Director, UMMS Wellstone Muscular Dystrophy Cooperative Research Center for FSHD
2020 -	MD/PhD Program Faculty Mentor, UMMS
2018 -	Member, World Muscle Society
2017 -	Reviewer, Research Advisory Committee, Muscular Dystrophy Association
2017 -	Director, Facioscapulohumeral Muscular Dystrophy Clinic, UMMS/UMMMC, Worcester, MA
2016 -	Member, UMMS Wellstone Muscular Dystrophy Cooperative Research Center for FSHD
2012 - 2014	Ad hoc reviewer, ALS Association
2010 -	Professor of Neurology, UMMS/UMMMC, Worcester, MA
2008 -	Ad hoc reviewer, Motor Neurone Disease Association and MRC
2006 - 2012	Ad hoc reviewer, Scientific Advisory Committee, Muscular Dystrophy Association
2004 - 2021	Ad hoc reviewer, Special Emphasis Panels: ZNS1 SRB-E, BDCN-F11, NRSA CDRC, NLM G13, BDCN-N03, ZRG1 BST-J, NIH
2004 - 2007	Ad hoc reviewer, Telethon Foundation for Biomedical Research
2004 - 2006	Ad hoc reviewer, Neurobiology-E Merit Review Panel, Veterans Administration
2003 - 2016	Reviewer and Board Member, ALS Therapy Alliance
2003 - 2010	Associate Professor of Neurology, UMMS/UMMMC, Worcester, MA
2000 - 2003	Assistant Professor of Neurology, University of Massachusetts Chan Medical School (UMMS), UMass-Memorial Medical Center (UMMMC), Worcester, MA
1997 - 2000	Instructor of Neurology, Harvard Medical School, Boston, MA
1997 - 2000	Assistant in Neurology, Massachusetts General Hospital, Boston, MA
1995 -	Diplomate in Neurology #41929, American Board of Psychiatry and Neurology
1995 - 2006	Member, Biophysical Society
1992 -	MA Physician License, MA Board of Registration in Medicine
1991 -	Member, American Academy of Neurology
1985 -	Member, Society for Neuroscience

Honors

2022	MD/PhD Program Award for Outstanding MD/PhD Program Mentor, UMMS
2017	Dean's Award for Outstanding Contribution to Curricular Development, UMMS

2013 Lou Gehrig Humanitarian Award, Muscular Dystrophy Association, Worcester chapter
2007 Morton H. Sigel Award for ALS Research, Worcester Foundation
2001 Biomedical Research Award, Worcester Foundation
1995 S. Weir Mitchell Award for Research in Neurology, American Academy of Neurology
1994 Postdoctoral Fellowship for Physicians, Howard Hughes Medical Institute
1988 Sigma Xi Ph.D. Dissertation Excellence Award, 1st place, Texas Medical Center chapter
1982 Eta Kappa Nu and Tau Beta Pi Engineering Honor Societies, Washington University
1982 Medical Scientist Training Program Fellowship, Baylor College of Medicine
1978 Alexander S. Langsdorf Fellowship, Washington University (full merit scholarship)

C. Contribution to Science

1. **Contractile protein gene regulation during skeletal muscle development.** My early work in the laboratory of Robert J. Schwartz first revealed the sequential switching of actin gene transcripts during avian myogenesis in vivo and established substantial differences compared to actin gene regulation in cultured muscle cells. This highlighted the importance of the tissue environment upon isoform transitions during differentiation, which remains highly relevant today for understanding the phenotypes of iPSC-derived cellular models. Recently, in collaboration with Charles Emerson's group, I have characterized single-cell gene expression in iPSC-derived myoblasts from individuals with FSHD.

    a. Hayward LJ, Zhu YY, Schwartz RJ. Cellular localization of muscle and nonmuscle actin mRNAs in chicken primary myogenic cultures: the induction of alpha-skeletal actin mRNA is regulated independently of alpha-cardiac actin gene expression. J Cell Biol. 1988 Jun;106(6):2077-86. PubMed Central PMCID: PMC2115141.
    b. Hayward LJ, Schwartz RJ. Sequential expression of chicken actin genes during myogenesis. J Cell Biol. 1986 Apr;102(4):1485-93. PubMed Central PMCID: PMC2114155.
    c. Bergsma D, Hayward L, Grichnick J, Schwartz R. Molecular Biology of Muscle Development. Fischman DA, Nadal-Ginard B, Siddiqui MAQ, editors. New York: Alan R. Liss, Inc.; 1986. Regulation of actin gene expression during chicken myogenesis; p.531-46.

2. **Biophysical properties of myotonic and paralytic sodium channel mutants.** Defective ion channels can produce episodic "channelopathy" phenotypes that include life-threatening arrhythmias, epilepsy, movement disorders, or altered muscle excitability. As an HHMI postdoctoral fellow in the laboratories of Robert H. Brown, Jr. and Stephen Cannon, I identified functional electrophysiological defects in mutant skeletal muscle sodium channels that cause periodic paralysis and related myotonic disorders. My findings revealed abnormally persistent sodium currents, altered channel activation, and impaired fast or slow inactivation caused by mutants that can produce either mild depolarization (which leads to repetitive firing and muscle stiffness) or severe depolarization (which causes paralysis by inactivating the majority of normal sodium channels). For this body of work, I received the S. Weir Mitchell award for research in neuroscience from the American Academy of Neurology.

    a. Hayward LJ. Channelopathies of the Nervous System. Rose MR, Griggs RC, editors. Oxford: Butterworth-Heinemann; 2001. Techniques for assessing ion channel function in vitro; p.49-63.
    b. Hayward LJ, Sandoval GM, Cannon SC. Defective slow inactivation of sodium channels contributes to familial periodic paralysis. Neurology. 1999 Apr 22;52(7):1447-53. PubMed PMID: 10227633.
    c. Hayward LJ, Brown RH Jr, Cannon SC. Slow inactivation differs among mutant Na channels associated with myotonia and periodic paralysis. Biophys J. 1997 Mar;72(3):1204-19. PubMed Central PMCID: PMC1184504.
    d. Hayward LJ, Brown RH Jr, Cannon SC. Inactivation defects caused by myotonia-associated mutations in the sodium channel III-IV linker. J Gen Physiol. 1996 May;107(5):559-76. PubMed Central PMCID: PMC2217015.

3. **Misfolding of mutant Cu,Zn superoxide dismutase (SOD1) variants in ALS.** I investigated biophysical and structural properties of 14 SOD1 mutants to provide the first comprehensive analysis of these purified

variants in terms of metal ion coordination, specific activity, and thermal and proteolytic stability. With NIH R01 support, my group showed that the ALS mutants shared an increased vulnerability to disulfide bond reduction both in vitro and in vivo and that they exposed aberrant hydrophobic surfaces under cellular reducing conditions. Additional collaborative studies employed our purified SOD1 mutants to identify specific structural perturbations caused by the mutants, and we reported in 2009 that impaired metal binding increases the population of misfolded SOD1 thought to trigger neuronal toxicity. Our findings drove interest in understanding aberrant interactions resulting from conformationally altered SOD1s during folding or after oxidative damage.

a. Tiwari A, Liba A, Sohn SH, Seetharaman SV, Bilsel O, Matthews CR, Hart PJ, Valentine JS, Hayward LJ. Metal deficiency increases aberrant hydrophobicity of mutant superoxide dismutases that cause amyotrophic lateral sclerosis. J Biol Chem. 2009 Oct 2;284(40):27746-58. PubMed Central PMCID: PMC2785702.
b. Tiwari A, Xu Z, Hayward LJ. Aberrantly increased hydrophobicity shared by mutants of Cu,Zn-superoxide dismutase in familial amyotrophic lateral sclerosis. J Biol Chem. 2005 Aug 19;280(33):29771-9. PubMed PMID: 15958382.
c. Tiwari A, Hayward LJ. Familial amyotrophic lateral sclerosis mutants of copper/zinc superoxide dismutase are susceptible to disulfide reduction. J Biol Chem. 2003 Feb 21;278(8):5984-92. PubMed PMID: 12458194.
d. Hayward LJ, Rodriguez JA, Kim JW, Tiwari A, Goto JJ, Cabelli DE, Valentine JS, Brown RH Jr. Decreased metallation and activity in subsets of mutant superoxide dismutases associated with familial amyotrophic lateral sclerosis. J Biol Chem. 2002 May 3;277(18):15923-31. PubMed PMID: 11854284.

4. **Targeted mouse models and therapy for hyperkalemic periodic paralysis (HyperKPP).** Through MDA and NIH K08 support, I established and characterized the first knock-in mouse model of HyperKPP ($Na_V1.4$ mutant M1592V) that reproduces many features of the disease, including myotonia, potassium-sensitive weakness, and the development of a slowly progressive vacuolar myopathy. In collaboration with Torben Clausen's lab we showed that acute stimulation of Na+/K+ pumps can dramatically restore contractile function in mutant muscles. With Jean-Marc Renaud's group, we showed that resistant mutant muscles, such as the diaphragm, compensate for a high burden of Na+ influx by increasing Na+/K+ pump activity and can generate greater force despite membrane depolarization. Ongoing studies have provided insights that may help identify novel therapeutic targets for preventing attacks of weakness and chronic myopathy in HyperKPP.

a. Uwera F, Ammar T, McRae C, Hayward L, Renaud J. Lower Ca2+ enhances the K+-induced force depression in normal and HyperKPP mouse muscles. Journal of General Physiology. 2020 July 06; 152(7):-. Available from: https://rupress.org/jgp/article/doi/10.1085/jgp.201912511/151656/Lower-Ca2-enhances-the-Kinduced-force-depression DOI: 10.1085/jgp.201912511
b. Ammar T, Lin W, Higgins A, Hayward LJ, Renaud JM. Understanding the physiology of the asymptomatic diaphragm of the M1592V hyperkalemic periodic paralysis mouse. J Gen Physiol. 2015 Dec;146(6):509-25. PubMed Central PMCID: PMC4664826.
c. Clausen T, Nielsen OB, Clausen JD, Pedersen TH, Hayward LJ. Na+,K+-pump stimulation improves contractility in isolated muscles of mice with hyperkalemic periodic paralysis. J Gen Physiol. 2011 Jul;138(1):117-30. PubMed Central PMCID: PMC3135321.
d. Hayward LJ, Kim JS, Lee MY, Zhou H, Kim JW, Misra K, Salajegheh M, Wu FF, Matsuda C, Reid V, Cros D, Hoffman EP, Renaud JM, Cannon SC, Brown RH Jr. Targeted mutation of mouse skeletal muscle sodium channel produces myotonia and potassium-sensitive weakness. J Clin Invest. 2008 Apr;118(4):1437-49. PubMed Central PMCID: PMC2260907.

5. **Understanding neurodegeneration and identifying possible therapeutic targets.** The mechanisms by which mutant genes linked to RNA metabolism (e.g. TDP43 and FUS) cause ALS are not clearly understood. My lab established cellular, zebrafish, and mouse models of FUS-mediated ALS and was among the first to show that FUS mutants can aberrantly localize to the cytoplasm and be recruited into stress granules. We participated in collaborative studies to i) identify modulators of FUS toxicity using a yeast genetic screen, ii) show loss of protein arginine methyltransferase 1 (PRMT1) function linked to

cytoplasmic accumulation of FUS mutants in motor neurons, and iii) quantify altered protein synthesis in a FUS model. These studies suggest that mutant FUS expression may perturb cellular homeostasis via both gain and loss of function mechanisms to which motor neurons are vulnerable.

a. Tibshirani M, Tradewell ML, Mattina KR, Minotti S, Yang W, Zhou H, Strong MJ, Hayward LJ, Durham HD. Cytoplasmic sequestration of FUS/TLS associated with ALS alters histone marks through loss of nuclear protein arginine methyltransferase 1. Hum Mol Genet. 2015 Feb 1;24(3):773-86. PubMed Central PMCID: PMC4291251.
b. Convertini P, Zhang J, de la Grange P, Hayward LJ, Zhu H, Stamm S. Genome wide array analysis indicates that an amyotrophic lateral sclerosis mutation of FUS causes an early increase of CAMK2N2 in vitro. Biochim Biophys Acta. 2013 Aug;1832(8):1129-35. PubMed Central PMCID: PMC3679306.
c. Ju S, Tardiff DF, Han H, Divya K, Zhong Q, Maquat LE, Bosco DA, Hayward LJ, Brown RH Jr, Lindquist S, Ringe D, Petsko GA. A yeast model of FUS/TLS-dependent cytotoxicity. PLoS Biol. 2011 Apr;9(4):e1001052. PubMed Central PMCID: PMC3082520.
d. Bosco DA, Lemay N, Ko HK, Zhou H, Burke C, Kwiatkowski TJ Jr, Sapp P, McKenna-Yasek D, Brown RH Jr, Hayward LJ. Mutant FUS proteins that cause amyotrophic lateral sclerosis incorporate into stress granules. Hum Mol Genet. 2010 Nov 1;19(21):4160-75. PubMed Central PMCID: PMC2981014.

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/lawrence.hayward.1/bibliography/public/