

BIOGRAPHICAL SKETCH

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NAME LORI L. ISOM, PH.D.		POSITION TITLE PROFESSOR OF PHARMACOLOGY	
eRA COMMONS USER NAME (credential, e.g., agency login) LLISOM			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
Washington University, St. Louis, MO	A.B.	1982	Chemistry, biology
Vanderbilt University, Nashville, TN	Ph.D.	1987	Pharmacology
University of Washington, Seattle, WA	Postdoctoral	1988-1993	Pharmacology

A. POSITIONS AND HONORS.**POSTDOCTORAL TRAINING**

1988-1993 Senior Fellow in Pharmacology, Univ. of WA, (laboratory of William A. Catterall, Ph.D.),

ACADEMIC APPOINTMENTS

1993-1995 Lecturer in Pharmacology, Univ. of WA

1995-2001 Assistant Professor of Pharmacology, Univ. of MI

2001-2007 Associate Professor of Pharmacology with tenure, Univ. of MI

2007- Professor of Pharmacology, Univ. of MI

2006-2008 Associate Director, Program in Biomedical Sciences, Univ. of MI

2008- Director, Program in Biomedical Sciences, Univ. of MI

2009- Professor of Molecular and Integrative Physiology, Univ. of MI

HONORS AND AWARDS

1983 National Research Service Award to Attend Vanderbilt University

1985 Pharmaceutical Manufacturer's Association Advanced Predoctoral Fellowship

1989-1991 Individual National Research Service Award (5 F32 NS08560)

1991-1992 National Research Service Award Trainee (T32 NS07332-02)

1992-1993 Fellowship, Keck Center for Neurosignaling, University of Washington

Finalist, Burroughs-Wellcome Fund New Investigator Award in the Pharmacological Sciences

1996-1999 Johnson and Johnson Focused Giving Award

Roche Bioscience Award for outstanding poster presentation, Advances in Ion Channel Research Meeting, San Francisco.

2001 American Heart Association Established Investigator Award

2004 Ralph C. Wilson Jr. Medical Research Grant Program Award

2009 Alumni Lecturer, University of Washington Department of Pharmacology

2009 University of Michigan Distinguished Faculty Award

B. SELECTED PEER-REVIEWED PUBLICATIONS (OF 54 TOTAL)

1. Isom, Lori L., DeJongh, K.S., Patton, D.E., Reber, B.F.X., Offord, J., Charbonneau, H., Walsh, K., Goldin, A.L., Catterall, W.A.: Primary Structure and Functional Expression of the β 1 Subunit of the Rat Brain Na⁺ Channel. *Science* 256:839-842, 1992.
2. Isom, Lori L. and Catterall, William A.: Na⁺ channel subunits and Ig domains. *Nature* 383: 307-308, 1996.
3. Xiao, Z.-C., Ragsdale, D.S., Malhotra, J.D., Mattei, L.N., Braun, P.E., Schachner, M., and Isom, L.L. Tenascin-R: a functional modulator of sodium channel β subunits. *J. Biol. Chem.* 274: 26511-26517, 1999. <http://www.jbc.org/cgi/content/full/274/37/26511>
4. Kazen-Gillespie, K.A., Ragsdale, D.S., D'Andrea, M.R., Mattei, L.N., Rogers, K.E., Isom, L.L., Cloning, Localization, and Functional Expression of Sodium Channel β 1A Subunits, *J. Biol. Chem.*, 275: 1079-1088, 2000. <http://www.jbc.org/cgi/content/full/275/2/1079>
5. Malhotra, J.D., Kazen-Gillespie, K., Hortsch, M., and Isom, L.L., Sodium Channel β Subunits mediate Homophilic Cell Adhesion and Recruit Ankyrin to Points of Cell-Cell Contact. *J. Biol. Chem.* 275: 11383-11388, 2000. <http://www.jbc.org/cgi/content/full/275/15/11383>

6. Malhotra, J.D., Chen, C., Rivolta, I., Abriel, H., Malhotra, R., Mattei, L.N., Brosius, F.C., Kass, R.S., and Isom, L.L., Characterization of Sodium Channel α and β subunits in Rat and Mouse Cardiac Myocytes. *Circulation*, 103: 1303-1310, 2001. <http://circ.ahajournals.org/cgi/content/full/103/9/1303>
7. Meadows, L., Malhotra, J.D., Stetzer, A., Isom, L.L., and Ragsdale, D.S., The Intracellular Segment of the Sodium Channel β 1 Subunit is Required for Functional Modulation of Brain Sodium Channels Expressed in a Mammalian Cell Line. *J Neurochem*. 76: 1871-1878, 2001.
8. Kaplan, M.R., Cho, M.-H., Ullian, E.M., Isom, L.L., Levinson, S.R., and Barres, B.A., Differential control of clustering of the sodium channels Nav1.2 and Nav1.6 at developing CNS nodes of Ranvier. *Neuron* 30: 105-119, 2001.
9. Kazarinova-Noyes, K.* , Malhotra, J.D.* , McEwen, D.P.* , Mattei, L.N., Ranscht, B., Levinson, S.R., Schachner, M., Shrager, P.#, Isom, L.L.#, and Xiao, Z.-C.. Contactin/F3/F11 Associates with Na⁺ Channels and Increases their Functional Expression *Equal contribution of authors. #Equal corresponding authors. *J. Neurosci.* 21: 7517-7525, 2001. <http://www.jbc.org/cgi/content/full/277/29/26681>
10. Malhotra, J.D., Koopmann, M.C., Kazen-Gillespie, K.A., Fettman, N., Hortsch, M., and Isom, L.L. Structural Requirements for Interaction of Sodium Channel β 1 Subunits with Ankyrin, *J. Biol. Chem.* 277: 26681-26688, 2002.
11. Chen, C.* , Bharucha, B.* , Chen, Y.* , Westenbroek, R.E., Brown, A., Malhotra, J.D., Jones, D., Avery, C., Gillespie, P.J., III, Kazen-Gillespie, K.A., Saunders, T.L. , Macdonald, R.L., Ransom, B., Scheuer, T., Catterall, W.A., and Isom, L.L., Reduced Sodium Channel Density, Altered Voltage Dependence of Inactivation, and Increased Susceptibility to Seizures in Mice Lacking Sodium Channel β 2 Subunits, *Equal contribution of authors, *Proc. Natl. Acad. Sci. U.S.A.*, 99: 17072-17077, 2002. [PMCID: PMC139271](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC139271/)
12. Meadows, L.S., Malhotra, J., Loukas, A., Thyagarajan, V., Kazen-Gillespie, K.A., Koopmann, M.C., Kriegler, S., Isom, L.L., and Ragsdale, D.S., Functional and Biochemical Analysis of a Sodium Channel β 1 Subunit Mutation Responsible for Generalized Epilepsy with Febrile Seizures Plus Type 1, *J. Neurosci.* 22: 10699-10709, 2002. L. Meadows and J. Malhotra contributed equally to this work. <http://www.jneurosci.org/cgi/content/full/22/24/10699>
13. Aronica, E., Troost, D., Rozemuller, A.J., Yankaya, B., Jansen, G.H., Isom, L.L., and Gorter, J.A., Expression and regulation of voltage-gated sodium channel β 1 protein in human gliosis-associated pathologies, *Acta Neuropathol.* 105: 515-523, 2003.
14. McEwen, D.P., Meadows, L.S., Chen, C., Thyagarajan, V., and Isom, L.L., Sodium channel β 1 subunit-mediated modulation of Na_v1.2 currents and cell surface density is dependent on interactions with contactin and ankyrin, *J. Biol. Chem.* 279: 16044-16049, 2004. <http://www.jbc.org/cgi/content/full/279/16/16044>
15. Chunling Chen, Ruth E. Westenbroek, Xiaorong Xu, Chris A. Edwards, Yuan Chen, Dyke P. McEwen, Heather A. O'Malley, Vandana Bharucha, Laurence S. Meadows, Gabriel A. Knudsen, Thomas L. Saunders, Todd Scheuer, Peter Shrager, William A. Catterall, and Lori L. Isom, Mice lacking sodium channel β 1 subunits display defects in neuronal excitability, sodium channel expression, and nodal architecture, *J. Neurosci.* 24: 4030-4042, 2004. <http://www.jneurosci.org/cgi/content/full/24/16/4030>
16. Malhotra, J.D., Thyagarajan, V., Chen, C. and Isom, L.L., Sodium channel tyrosine-phosphorylated- and nonphosphorylated- β 1 subunits are differentially localized in cardiac myocytes. *J. Biol. Chem.* 279(39): 40748-40754, 2004. <http://www.jbc.org/cgi/content/full/279/39/40748>
17. Spanpanato, J., Kearney, J.A., de Haan, G., Mc Ewen, D. P., Escayg, A., MacDonald, B.T., Levin, S.I., Aradi, I., Soltesz, I., Benna, P., Montalenti, E., Isom, L.L., Goldin, A.L., and Meisler, M.H., A novel GEFS+ mutation in the sodium channel SCN1A identifies a cytoplasmic domain for β subunit interaction, *J. Neurosci.* 24:10022-34 (2004) <http://www.jneurosci.org/cgi/content/full/24/44/10022>
18. Davis, T., Chen, C., and Isom, L.L., Sodium Channel β 1 Subunits Promote Neurite Outgrowth In Cerebellar Granule Neurons, *J. Biol. Chem.* 279: 51424-51432, 2004. <http://www.jbc.org/cgi/content/full/279/49/51424>
19. McEwen, D.P. and Isom, L.L., Heterophilic Interactions of Sodium Channel β 1 Subunits with Axonal and Glial Cell Adhesion Molecules, *J. Biol. Chem.* 279: 52744-52752, 2004. <http://www.jbc.org/cgi/content/full/279/16/16044>
20. Grieco, T.M., Malhotra, J.D., Chen, C. Isom, L.L., Raman, I.M. Open-channel block of sodium channels by the cytoplasmic tail of β 4 mimics resurgent sodium current. *Neuron*, 45: 233-244, 2005.
21. Meadows, L.S. and Isom, L.L., Sodium channels as macromolecular complexes: implications for inherited arrhythmia syndromes, *Cardiovasc Res*, 67:448-58, 2005. <http://cardiovascres.oxfordjournals.org/cgi/content/full/67/3/448>
22. Marie Pertin, Ru-Rong Ji, Temugin Berta, Andrew J. Powel, Nicolas Gilliard, Simon N. Tate, Lori L. Isom, Clifford J. Woolf, Donat R Spahn, Isabelle Decosterd, Upregulation of the voltage-gated sodium channel β 2

- subunit in neuropathic pain models : characterization of expression in injured and non-injured primary sensory neurons. *J. Neurosci.*,25:10970-10980, 2005. <http://www.jneurosci.org/cgi/content/full/25/47/10970>
23. Luis F. Lopez-Santiago, Marie Pertin, Xavier Morisod, Chunling Chen, Shuangsong Hong, John Wiley, Isabelle Decosterd and Lori L. Isom, Sodium channel $\beta 2$ subunits regulate tetrodotoxin-sensitive sodium channels in small dorsal root ganglion neurons and modulate the response to pain, *J. Neurosci.*, 26:7984-94, 2006. <http://www.jneurosci.org/cgi/content/full/26/30/7984>
 24. Fein, Amanda J., Meadows, Laurence S., Chen, Chunling, and Isom, Lori L., Cloning and expression of the zebrafish *SCN1B* ortholog and identification of a species-specific splice variant, *BMC Genomics* 2007 Jul 10;8:226. [PMCID: PMC1965480](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1965480/)
 25. Luis Lopez-Santiago*, Laurence S. Meadows*, Sara J. Ernst, Chunling Chen, Jyoti Dhar Malhotra, Dyke P. McEwen, Audrey Speelman, Jeffrey L. Noebels, Sebastian K.G. Maier, Anatoli N. Lopatin, and Lori L. Isom (* equal contributions), Sodium channel $\beta 1^{-/-}$ mice exhibit prolonged QT and RR intervals, *J Mol Cell Cardiol.* 2007 Nov;43(5):636-47. [PMCID: PMC2099572](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2099572/)
 26. Chunling Chen, Travis L. Dickendesher, Fumitaka Oyama, Haruko Miyazaki, Nobuyuki Nukina, and Lori L. Isom, Floxed Allele for Conditional Inactivation of the Voltage-gated Sodium Channel $\beta 1$ Subunit *Scn1b*, *Genesis* 2007 Sep;45(9):547-53
 27. William J. Brackenbury, Tigwa H. Davis, Chunling Chen, Emily A. Slat, Matthew J. Detrow, Travis L. Dickendesher, Barbara Ranscht, Lori L. Isom, Voltage-gated Na^+ channel beta1 subunit-mediated neurite outgrowth requires Fyn kinase and contributes to postnatal CNS development *in vivo.*, *J. Neurosci.* 2008, Mar 19, 28: 3246-3256. <http://www.jneurosci.org/cgi/content/full/28/12/3246>
 28. Brackenbury, W.J. and Isom, L.L., Voltage-gated Na^+ channels: Potential for β subunits as therapeutic targets, *Expert Opin Ther Targets*, 2008, Sep 12: 1191-203. <http://www.informapharmascience.com/doi/abs/10.1517/14728222.12.9.1191>
 29. Brackenbury WJ, Djamgoz MB, Isom LL., An Emerging Role for Voltage-Gated Na^+ Channels in Cellular Migration: Regulation of Central Nervous System Development and Potentiation of Invasive Cancers. *Neuroscientist.* 2008 Dec;14(6):571-83.
 30. Fein AJ, Wright MA, Slat EA, Ribera AB, Isom LL. *scn1bb*, a zebrafish ortholog of *SCN1B* expressed in excitable and nonexcitable cells, affects motor neuron axon morphology and touch sensitivity. *J Neurosci.* 2008 Nov 19;28(47):12510-22.
 31. O'Malley HA, Shreiner AB, Chen GH, Huffnagle GB, Isom LL. Loss of Na^+ channel beta2 subunits is neuroprotective in a mouse model of multiple sclerosis. *Mol Cell Neurosci.* 2009 Feb;40(2):143-55 PMID: 19013247
 32. William J. Brackenbury, Jeffrey D. Calhoun, Lori L. Isom and Mustafa B. A. Djamgoz A novel adhesion molecule in human breast cancer cells: Voltage-gated Na^+ channel $\beta 1$ subunit, Athina-Myrto Chioni, *Int J Biochem Cell Biol.* 2009 May;41(5):1216-27. PMID: 19041953
 33. Aman, T.K., Grieco-Calub, T.M., Chen,C., Slat, E.A., Isom, L.L., and Raman, I.M., Regulation of persistent Na^+ current by interactions among β subunits of voltage-gated Na^+ channels, *J. Neuroscience* 2009 Feb 18;29(7):2027-42. PMID: 19228957
 34. McEwen DP, Chen C, Meadows LS, Lopez-Santiago L, Isom LL. The voltage-gated Na^+ channel beta3 subunit does not mediate trans homophilic cell adhesion or associate with the cell adhesion molecule contactin. *Neurosci Lett.* 2009 Oct 25;462(3):272-5. Epub 2009 Jul 17. PubMed PMID: 19596049.
 35. Sato PY, Musa H, Coombs W, Guerrero-Serna G, Patiño GA, Taffet SM, Isom LL, Delmar M. Loss of Plakophilin-2 Expression Leads to Decreased Sodium Current and Slower Conduction Velocity in Cultured Cardiac Myocytes. *Circ Res.* 2009 Aug 6. [Epub ahead of print] PubMed PMID: 19661460.
 36. Gustavo A. Patino, Lieve R. F. Claes, Luis F. Lopez-Santiago, Emily A. Slat, Raja S. R. Dondeti, Chunling Chen, Heather A. O'Malley, Charles B. B. Gray, Haruko Miyazaki, Nobuyuki Nukina, Fumitaka Oyama, Peter De Jonghe, and Lori L. Isom. A Functional Null Mutation of *SCN1B* in a Patient with Dravet Syndrome, *J. Neurosci.* 2009;29 10764-10778

C. Research Support

Ongoing Research Support

1RC1NS068684 Meisler (PI)

2009-2011

NIH

Stem Cell Derived Neurons and Inherited Epilepsy

The goal of this project is to develop the induced pluripotent stem cell method to generate excitatory and inhibitory neurons from patient fibroblasts to study the mechanisms of inherited epilepsy.

1R01MH59980 Isom (PI)

04/01/06 to 03/31/11

NIH

Sodium Channel β Subunit Cell Adhesive Interactions.

The goals of this project are to: 1. investigate the mechanism of $\beta 1$ -mediated neurite outgrowth from cerebellar granule neurons. 2. to determine the domains of $\beta 1$ that are required to mediate neurite outgrowth and to

investigate whether deletion of the $\beta 1$ gene results in differences in neurite outgrowth *in vivo* by investigating the migration and neurite extension of corticospinal axons and cerebellar granule cells in $\beta 1^{-/-}$ mice. 3. to test the hypothesis that $\beta 1$ contains a tyrosine-based targeting domain that includes $\beta 1Y181$ and that phosphorylation of this residue results in differential localization of pY $\beta 1$ to ankyrin-independent subcellular domains in neurons.

Role: PI

Partnership for Pediatric Epilepsy Isom (PI) 03/2008 - 03/2010

Role of sodium channel $\beta 1$ subunits in pediatric epilepsy.

The goal of this project is to determine the role of $\beta 1$ subunits in hippocampal GABAergic neurons.

Role: PI

RG 3771A4/3 Isom (PI) 04/01/08-03/31/11

NMSS Research Grant

Role of sodium channel $\beta 2$ subunits in neuroprotection.

The goal of this project is to understand the role of sodium channel $\beta 2$ subunits in axonal sparing in a murine model of Multiple Sclerosis.

Role: PI

University of Michigan Isom (PI) 03/01/09-02/28/10

Multiple Sclerosis Society Collaborative Research Center

Role of sodium channel $\beta 2$ subunits in neuroprotection *in vivo*.

The goal of this project is to develop microRNA vectors that can be used for Scn2b knockdown in spinal cord *in vivo*.

American Epilepsy Society Parent (PI) 01/01/09 - 12/31/09

Novel Method to Study Human Epilepsy Gene Mutations.

The goal of this project is to investigate the mechanism of a novel human mutation causing Dravet Syndrome.

D. COMPLETED PROJECTS IN THE LAST 3 YEARS

Pilot Grant Isom (PI) 07/2006-06/2007

NMSS

Role of sodium channel $\beta 2$ subunits in neuroprotection

The goal of this project was to explore the role of $\beta 2$ in a mouse model of multiple sclerosis.

Role: PI

RG2882 Isom (PI) 04-01-97-03-31-07

National Multiple Sclerosis Society

Molecular Control of Na^+ Channel Density and Localization in Myelinated Axons

The goal of this project was to understand the mechanism of Na^+ channel β subunits in action potential conduction in myelinated axons.

Role: PI

Pfizer Global Research Contract Isom (PI) 06/01/04 – 05/30/06

Pharmacological Evaluation of Anti-Convulsant Drugs on a Panel of Voltage-Gated Sodium Channels

Expressed in Mammalian Cells

The goal of this project was to test novel anti-convulsant drugs on Na^+ channels expressed in transfected cell lines.

Role: PI

R21NS51747-01 Isom (PI) 04-01-2005-03-31-07

NIH

Voltage-gated sodium channel β subunits in zebrafish

The goal of this project was to understand the roles of β subunits in neuronal pathfinding and regulation of Na^+ current in zebrafish.

Role: PI

Wyeth Pharmaceuticals Research Collaboration Isom (PI) 07/2005-07/2007

Function of sodium channel $\beta 4$ subunits in DRG neurons

The goal of this project was to determine the role of $\beta 4$ in modulation of Na^+ current in nociceptive neurons.

Role: PI