BIOGRAPHICAL SKETCH

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NAME: Ross, Sarah

eRA COMMONS USER NAME: ross_sa

POSITION TITLE: Associate Professor, Department of Neurobiology

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of Western Ontario, London, Canada	BS (Hons)	1991 - 1995	Physiology
University of Michigan, Ann Arbor, MI	PhD	1995 - 2001	Physiology (Ormond MacDougald)
Harvard Medical School, Boston, MA	Post-doc	2002 - 2011	Neurobiology (Michael Greenberg)

A. Personal Statement

I am an Associate Professor at the University of Pittsburgh Medical School in the Department of Neurobiology and the Pittsburgh Center for Pain Research. My lab is focused on dissecting the neural circuits of pain and itch using a combination of molecular approaches, electrophysiology and behavior. I am very committed to the mentorship of Ruby Holland, and I believe that my lab will be an outstanding environment for her PhD training as an MSTP student, thereby preparing her for a successful career as a physician scientist in the field of pain. In support of this idea, I have a growing track record of successful trainees, funded grants, and strong publications.

A new direction for my lab is the dissection of descending circuits from the RVM. For the last year, we have been successfully targeting this region of the brain with viruses to manipulate neurons therein, and thus I have no concerns about the feasability of Ruby's project. Moreover, we have very recently (in the last few months) acquired and validated the MOR-cre allele (from Richard Palmiter), which will allow us to dissect the role of MOR-expressing RVM neurons in a new way. I am very excited about Ruby's proposal — to focus on a specific type of MOR-expressing RVM neurons that project to the spinal cord. These are putative ON-cells which are proposed to facilitate pain. Now, Ruby will be able to visualize these cells and manipulate their activity. Since no one has ever selectively activated ON-cells in the context of pain behaviors, Ruby's experiments have the potential to provide important new insight into the function and circuitry of descending modulation.

B. Positions and Honors

Positions and Employment

2011 – 2017 Assistant Professor, Department of Neurobiology and Pittsburgh Center for Pain Research, University of Pittsburgh, Pittsburgh, PA
2012 – Secondary Appointment, Department of Anesthesiology
2016 – Secondary Appointment, Department of Clinical and Translational Science
2018 – Associate Professor, Department of Neurobiology and Pittsburgh Center for Pain Research

Other Experience and Professional Memberships

2011 – Member, American Pain Society
2011 – Member, International Federation for the Study of Itch
2013 Co-organizer, 7th World Congress on Itch
2014 Ad hoc reviewer, Wellcome Trust
2015 – Member, International Association for the Study of Pain
2015 – Member, Society for Neuroscience
2015 Ad hoc reviewer, ETS Zurich Research Grants
2015 – Member, Rita Allen Review Committee

2016	Add hoc reviewer, NIH (NIDCR)
2016 – 2017	Member, Interagency Pain Research Coordinating Committee (IPRCC)
2016 –	Editorial board member, *Pain*
2016 –	Editorial board member, *Itch*
2018 –	Co-chair, basic science SIG (American Pain Society)
2019 –	Co-chair, itch SIG (International Association for the Study of Pain)
2019 –	Co-organizer, Keystone Conference (Somatosensation: From Detection to Perception)

Honors

1996	Henry Caulkins Scholarship, University of Michigan
1997	Henry Caulkins Scholarship, University of Michigan
1997	Susan Lipschutz Award for Women Graduate Students, University of Michigan
1997	NSERC Predoc Award, The Natural Sciences and Engineering Research Council of Canada
1997	Outstanding Graduate Teaching Award, University of Michigan
1998	Henry Caulkins Scholarship, University of Michigan
2000	Henry Caulkins Scholarship, University of Michigan
2000	Rackham Predoctoral Training Award, University of Michigan
2002	Distinguished Dissertation Award, University of Michigan
2002	CIHR post-doctoral award (declined), Canadian Institute of Health Sciences
2002	Jane Coffin Childs Fellowship, Jane Coffin Childs Foundation
2007	Career Development Fellowship, Harvard Medical School
2007	William Randolph Hearst Award, Harvard Medical School
2012	Rita Allen Foundation Pain Scholar, Rita Allen Foundation
2012	Whitehall Award, Whitehall Foundation
2017	Mallinckrodt Scholar Finalist (1 of 4)

C. Contribution to Science

Complete List of Published Work in Google Scholar (42 publications; h-index 24; >8000 citations): https://scholar.google.com/citations?user=ILpDSFYAAAAJ&hl=en

1. **Functional circuitry of the dorsal horn** My research program is aimed at understanding the neural basis of somatosensory integration. In particular, we use molecular genetic, electrophysiological and behavioral experiments to analyze neural circuits in the spinal dorsal horn. Recently, we provided key evidence showing that B5-I neurons are a population of spinal inhibitory interneurons that function to inhibit itch. We found that B5-I neurons release the kappa opioid dynorphin, and our experiments revealed that kappa opioids modulate itch tone bidirectionally at the level of the spinal cord (*Neuron 82: 573*). We also investigated which afferents respond to dynorphin by characterizing the sensory neurons that express the kappa opioid receptor *(Neuron, 99: 1274).*

   Since mice lacking B5-I neurons mice develop neuropathic itch, these mice provided us with an opportunity to test novel therapeutic treatments for this condition. Working in collaboration with Allan Basbaum, we found that neuropathic itch can be treated by restoring inhibition via spinal cord transplantation of inhibitory interneurons. These findings illustrate the utility of a cell-based therapy to ameliorate severe neuropathic itch (*JCI 124: 3612*). We have also collaborated with Qiufu Ma and Martyn Goulding to study the role of dynorphin-expressing in mechanical sensation. These studies revealed that dynorphin-expressing inhibitory interneurons are involved in the gating of mechanical pain (*Cell 159: 1417*).

   a. Kardon AP, Polgár E, Hachisuka J, Snyder LM, Cameron D, Savage S, Cai X, Karnup S, Fan CR, Hemenway GM, Bernard CS, Schwartz ES, Nagase H, Schwarzer C, Watanabe M, Furuta T, Kaneko T, Koerber HR, Todd AJ*, **Ross SE***. (2014) Dynorphin acts as a neuromodulator to inhibit itch in the dorsal horn of the spinal cord. *Neuron*. 82(3):573-86. PMC4022838

   b. Snyder, L. M., M. C. Chiang, E. Loeza-Alcocer, Y. Omori, J. Hachisuka, T. D. Sheahan, J. R. Gale, P. C. Adelman, E. I. Sypek, S. A. Fulton, R. L. Friedman, M. C. Wright, M. G. Duque, Y. S. Lee, Z. Hu, H. Huang, X. Cai, K. A. Meerschaert, V. Nagarajan, T. Hirai, G. Scherrer, D. H. Kaplan, F. Porreca, B. M. Davis, M. S. Gold, H. R. Koerber and S. E. Ross (2018). "Kappa Opioid Receptor Distribution and Function in Primary Afferents." *Neuron* **99**(6): 1274-1288 PMID30236284

c. Braz JM, Juarez-Salinas D, **Ross SE**, Basbaum AI. (2014) Transplant restoration of spinal cord inhibitory controls ameliorates neuropathic itch. *J Clin Invest*. 124(8):3612-6. PMC4109547

d. Duan B, Cheng L, Bourane S, Britz O, Padilla C, Garcia-Campmany L, Krashes M, Knowlton W, Velasquez T, Ren X, **Ross SE**, Lowell BB, Wang Y, Goulding M, Ma Q. (2014) Identification of spinal circuits transmitting and gating mechanical pain. *Cell*.159(6):1417-32 PMC4258511

2. **Developed novel approaches and created novel genetic tools to study spinal circuitry** We spent several years developing a novel preparation that enables us to ask questions about spinal circuitry that were previously elusive. In our new preparation, the lumbar spinal cord, saphenous nerve, and hindpaw skin are dissected in continuum, allowing us to record from spinal projection neurons while we provide natural stimulation to the skin and optogenetic manipulation of spinal interneurons (*eLIFE*, e22866).

   In parallel to these efforts, we have generated a series of novel genetic tools that allow us to dissect spinal circuits by giving us access to specific cell types. In particular, we generated three new knockin alleles: a *Bhlhb5-flpo* knockin mouse, so that we could use intersectional genetic strategies to target B5-I neurons (*Dev. Biol. 414:149*), a *KOR-cre* knockin mouse, in order to visualize and manipulate the cells that express KOR (*Genesis, 54:29*), and a *NK1R-creER* mouse, to give us a genetic handle on spinal projection neurons (*Genesis 54:593*). These alleles have now been described and made freely available to others.

   a. Hachisuka J, Baumbauer, KM, Omori Y, Snyder LM, Koerber HR*, **Ross SE*** (2016) Semi-intact ex vivo approach to investigate spinal somatosensory circuits. *eLife,* 5: e22866. PMC5214752

   b. Cai X, Kardon AP, Snyder LM, Kuzirian MS, Minestro S, de Souza L, Rubio ME, Maricich SM, **Ross SE***. (2016) Bhlhb5::flpo allele uncovers a requirement for Bhlhb5 for the development of the dorsal cochlear nucleus. *Dev Biol.* 414(2):149-60. PMC4930277

   c. Cai X, Huang H, Kuzirian MS, Snyder LM, Matsushita M, Lee MC, Ferguson C, Homanics GE, Barth AL, **Ross SE***. (2016) Generation of a KOR-Cre knockin mouse strain to study cells involved in kappa opioid signaling. *Genesis.* 54(1):29-37. PMC4747253

   d. Huang H, Kuzirian MS, Cai X, Snyder LM, Cohen J, Kaplan DH and **Ross SE*** (2016) Generation of a NK1R-CreER Knockin Mouse Strain to Study Cells Involved in Neurokinin 1 Receptor Signaling. *Genesis.* 54(11):593-611. PMC5241089

3. **Somatosensory Integration: current and future directions** A main focus of my lab is to understand how neural circuits integrate somatosensory information, particularly pain and itch. Recently, we took an optogenetic approach to study the neural circuit basis for wind-up, which is one mechanism through which sensory input is amplified in the spinal cord. Our studies reveal that a specific population of excitatory neurons (defined genetically using the *Nts-cre* allele) are necessary and sufficient for wind-up (*Pain*, in press). These findings suggest that wind-up is mediated through a polysynaptic circuit of spinal interneurons. A second (and often under-appreciated are where somatosensory integration occurs is the skin, which communicates to sensory neurons. Our work revealed that optogenetic activation of keratinocytes is sufficient to excite primary afferents whereas optogenetic inhibition of keratinocytes reduces primary afferent excitability. These findings suggest that the skin is in constant communication with sensory neurons, where it plays a key role in the modulation of sensory input (*eLIFE* 4: e09674). We also continue to test the latest tools and technologies, providing insight into both their utility and limitations (*J. Neurosci 36:107690*). Finally, we are working to develop new and better ways to analyze mouse behavior. For instance, we recently devised a new method that takes advantage of the fact that scratching is a stereotyped behavior that is audible. Thus, we developed an approach that uses supervised learning to extract scratching behavior from acoustic recordings (*PLoS One **12**(7)*). This approach will provide an inexpensive and scalable means to quantify itch in a mouse's home cage over extended periods of time.

   a. Hachisuka J, Omori Y, Chiang MC, Gold MS, Koerber HR* and **Ross SE*** (2018) Wind-up in lamina I spinoparabrachial neurons: a role for reverberatory circuits. *Pain* 159(8): 1484-1493 PMC6053328

   b. Baumbauer KM, DeBerry JJ, Adelman PC, Miller RH, Hachisuka J, Lee KH, **Ross SE**, Koerber HR, Davis BM, Albers KM. (2015) Keratinocytes can modulate and directly initiate nociceptive responses *eLIFE* 4:e09674. PMC4576133

   c. Saloman JL, Scheff NN, Snyder LM, **Ross SE**, Davis BM and Gold MS. (2016) Gi-DREADD expression in peripheral nerves produces ligand-dependent analgesia, as well as ligand-independent functional changes in sensory neurons. *J Neurosci.* 36(42):10769-81. PMC5083007

d. Elliot P, G'Sell M, Snyder LM, **Ross SE**, Ventura V. (2017). Automated acoustic detection of mouse scratching *PLoS One* ***12****(7): e0179662.* PMC5497976

4. **Neural Development: Bhlhb5 and Prdm8 form an obligate repressor complex.** As a postdoctoral fellow in Dr. Mike Greenberg's laboratory, I studied the function of transcription factors in neural development and function, with a particular focus on members of the Atonal superfamily *(Neuron 39: 13; Science 303: 2011).* Towards this end, I generated a number of knockout and knock-in mice for the transcription factors *Bhlhb4* and *Bhlhb5*.

   This work led to the discovery Bhlhb5 forms a repressor complex with the PR/SET domain protein, Prdm8 *(Neuron 73: 292*). I found that Bhlhb5 binds to sequence-specific DNA elements and then recruits Prdm8, which mediates the repression of target genes. This interaction is critical for repressor function since mice lacking either Bhlhb5 or Prdm8 have strikingly similar cellular and behavioral phenotypes, including axonal mis-targeting by neurons of the dorsal telencephalon and abnormal itch behavior. I also discovered that Cadherin-11 functions as target of the Prdm8/Bhlhb5 repressor complex that must be repressed for proper neural circuit formation to occur. These findings suggest that Prdm8 is an obligate partner of Bhlhb5, forming a repressor complex that directs neural circuit assembly in part through the precise regulation of Cadherin-11.

   One of the key functions of the Bhlhb5/Prdm8 repressor complex is for the survival of B5-I neurons, a subtype of spinal inhibitory interneuron that is required normal itch sensation (*Neuron* 65: 886). This discovery became the foundation for the initial studies as I began my own research program at the University of Pittsburgh.

   a. **Ross SE**, Greenberg ME, Stiles CD. Basic helix-loop-helix factors in cortical development. *Neuron*. 2003 39(1):13-25. PMID: 12848929

   b. Brunet A, Sweeney LB, Sturgill JF, Chua KF, Greer PL, Lin Y, Tran H, **Ross SE**, Mostoslavsky R, Cohen HY, Hu LS, Cheng HL, Jedrychowski MP, Gygi SP, Sinclair DA, Alt FW, Greenberg ME. (2004) Stress-dependent regulation of FOXO transcription factors by the SIRT1 deacetylase. *Science*. 303(5666):2011-5. PMID: 14976264

   c. **Ross SE**, McCord AE, Jung C, Atan D, Mok SI, Hemberg M, Kim TK, Salogiannis J, Hu L, Cohen S, Lin Y, Harrar D, McInnes RR, Greenberg ME. (2012) Bhlhb5 and Prdm8 form a repressor complex involved in neuronal circuit assembly. *Neuron*. 73(2):292-303. PMC3269007

   d. **Ross SE**, Mardinly AR, McCord AE, Zurawski J, Cohen S, Jung C, Hu L, Mok SI, Shah A, Savner EM, Tolias C, Corfas R, Chen S, Inquimbert P, Xu Y, McInnes RR, Rice FL, Corfas G, Ma Q, Woolf CJ, Greenberg ME. (2010) Loss of inhibitory interneurons in the dorsal spinal cord and elevated itch in Bhlhb5 mutant mice. *Neuron*. 65(6):886-98. PMC2856621

5. **Cell Fate Decisions: Wnt signaling blocks adipogenesis** As a graduate student in Dr. Ormond MacDougald's laboratory, I explored how individual cells respond to their environment by investigating molecular mechanisms through which extracellular factors regulate lineage specification of multipotent progenitors. My work led to the discovery that Wnt signaling acts as a determination switch, regulating the cell fate decision between fat cells and muscle cells *(Science, 289: 950)*, and I identified some of the transcriptional targets that mediate this developmental switch *(Mol. Cell. Biol. 22: 5989)*. In a separate line of investigation, I discovered that the transcription factor C/EBPα (which is mutated in acute myeloid leukemia) is regulated through phosphorylation in response to extracellular growth factors *(Mol. Cell. Biol. 19: 8433*). In addition, I showed that ERK-mediated phosphorylation inhibits C/EBPα function and thereby blocks the differentiation of blood cell progenitors into granulocytes *(Mol. Cell. Biol. 24: 675)*. Thus, my graduate studies uncovered two important molecular mechanisms through which extracellular signals regulate cell fate.

   a. **Ross SE,** Erickson RL, Hemati N, MacDougald OA. (1999) Glycogen synthase kinase 3 is an insulin-regulated C/EBPalpha kinase. *Mol Cell Biol*. (12):8433-41. PMC84944

   b. **Ross SE**, Hemati N, Longo KA, Bennett CN, Lucas PC, Erickson RL, MacDougald OA. (2000) Inhibition of adipogenesis by Wnt signaling. *Science*. 289(5481):950-3. PMID: 10937998

   c. **Ross SE**, Erickson RL, Gerin I, DeRose PM, Bajnok L, Longo KA, Misek DE, Kuick R, Hanash SM, Atkins KB, Andresen SM, Nebb HI, Madsen L, Kristiansen K, MacDougald OA. (2002) Microarray analyses during adipogenesis: understanding the effects of Wnt signaling on adipogenesis and the roles of liver X receptor alpha in adipocyte metabolism. *Mol Cell Biol*. (16):5989-99. PMC133961

d. **Ross SE**, Radomska HS, Wu B, Zhang P, Winnay JN, Bajnok L, Wright WS, Schaufele F, Tenen DG, MacDougald OA. (2004) Phosphorylation of C/EBPalpha inhibits granulopoiesis. *Mol Cell Biol*. 24(2):675-86. PMC343788

D. Research Support

ONGOING RESEARCH SUPPORT

R01 AR063772 07 — Ross (PI) 04/01/18 – 01/31/23 6 calendar months
Investigating the neural circuits of itch

R01 NS096705 03— Koerber (PD/PI) 09/01/16 – 08/31/21 3 calendar months
Molecular genetic dissection of the spinal microcircuits of wind-up (Role: MPI)

R01 EY029323 01— Demb (PI) 09/01/16 – 08/31/21 0.5 calendar months
Molecular genetic dissection of the spinal microcircuits of wind-up (Role: co-PI)

ADRC (Pilot Project) — Ross (PI) 04/01/19 – 03/31/20 0 calendar months
The role of neurovascular dysfunction in the development of Alzheimer's Disease

COMPLETED RESEARCH SUPPORT

CTSI (Pilot project) — Ross (co-PI) 7/1/17 – 6/30/18 0 calendar months
Kappa antagonists to treat pain

AMRF — Ross (PI) 07/01/16 – 06/30/17 0.6 calendar months
Molecular genetic approaches to understand the ontogeny of the dorsal cochlear nucleus

Fight for Sight 07/01/15 – 06/30/16 0.6 calendar months
Intersectional genetic strategies define a large population of monostratified wide-field amacrine cells

CTSI (Pilot project) — Ross (co-PI) 07/01/15 – 06/30/16 0 calendar months
Understanding the amplification of pain

Rita Allen Foundation Award in Pain 09/01/12 – 08/31/15 1.8 calendar months
Investigating the neural circuits of itch and pain

R21 AR064445 — Ross (PI) 4/1/13 – 3/31/15 1.8 calendar months
Using dual intersectional genetics to understand and modulate itch

CMRF (Pilot project) — Ross (PI) 7/1/12 – 6/30/14 0.6 calendar months
Understanding the neural mechanisms of itch

CTSI (Pilot project) — Ross (PI) 7/1/12 – 6/30/13 0 calendar months
Understanding the neural circuits of nociception

Whitehall Research Grant — Ross (PI) 1/1/13 – 12/31/13 2.4 calendar months
Dissecting the neural mechanisms of itch and scratching behavior