BIOGRAPHICAL SKETCH

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NAME: Onifer, Stephen M.

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

POSITION TITLE: Associate Professor of Neuroscience

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
Lock Haven State College, Lock Haven, PA	B.S.	8/1976	Biology
Indiana University, School of Medicine, Indianapolis, IN	Ph.D.	3/1991	Physiology & Biophysics
University of Miami, School of Medicine, Miami, FL	Post-Doc	9/1994	Neuroscience

A. Personal Statement

Critical to improving the clinical efficacy of spinal manipulative therapy (SMT) is basic science research of hypothesized neurobiological mechanisms using simulated SMT techniques and pain models. Motivated by this, we found short-term alleviation of rat nociceptive behaviors in popular models of chronic neuropathic[a] and persistent[b] peripheral pain following administration of low velocity variable amplitude non-thrust spinal manipulation (LVVA-SM) at a lumbar vertebra using a custom-made device. These findings being similar to those from clinical research led us to propose for a funded NIH/NCCIH-funded R15 project to characterize LVVA-SM-induced anti-allodynia in the neuropathic pain model and then leverage a multidisciplinary collaboration to determine whether this is mediated by endogenous activation of cannabinoid receptors in the spinal cord dorsal horn, the site for integration and modulation of nociceptive input.

My broad basic neuroscience research expertise about central and peripheral nervous systems injury, plasticity, and repair makes me extremely well-suited as Principal Investigator to successfully perform the R15 project. Collectively during my training and independent research, I investigated cellular and pharmacological approaches to enhance the adaptive neural plasticity mechanisms that occur following nervous system trauma. Non-pharmacologic environmental enrichment and task-specific skilled locomotion approaches were also used to affect neural plasticity mechanisms. In particular, as a founding faculty member of the Kentucky Spinal Cord Injury Research Center, my laboratory tested hypotheses about peripheral nerve graft bridges, chondroitin sulfate proteoglycans (CSPG), chondroitinase ABC, rolipram, sensory axon regeneration and collateral sprouting, tactile discrimination, as well as forelimb and hindlimb sensorimotor function recovery after cervical spinal cord injury (SCI). As a faculty member of the Spinal Cord and Brain Injury Research Center, I used my Kentucky Spinal Cord & Head Injury Research Trust grant funding to further test hypotheses about CSPG, chondroitinase ABC, sensory axon collateral sprouting, glutamatergic neurotransmission, tactile discrimination, and forelimb sensorimotor function recovery after cervical SCI. We also evaluated whether combining task-specific forelimb rehabilitation with chondroitinase ABC would enhance the anatomical and behavioral effects of the pharmacological intervention.

My investigations of non-pharmacologic rehabilitation interventions led me to the Palmer Center for Chiropractic Research (PCCR). Here, I am utilizing my basic neuroscience research expertise to identify neurobiological mechanisms of SMT. This required a transition from working in the area of the damaged nervous system, adaptive plasticity mechanisms, and sensorimotor repair to the area of pain, maladaptive plasticity mechanisms, and SMT. The transition also involved setting up a laboratory in a new institution as well as establishing new models and methods. Thus far, an article describing findings from a preliminary study for

the R15 project is in press[a] and an article reporting our initial findings has been published[b]. A collaboration on a project investigating SMT effects on adult rat thalamic neuron electrophysiological responses to noxious stimuli also resulted in a co-authorship of 2 published articles[c,d]. My long-term goal is that my experimental findings about SMT ultimately will be translated to treatments for persons whose physical and mental function, quality of life, and socioeconomic status are devastated by pain.

As a research faculty member, I have mentored 29 graduate, medical, undergraduate, and high school students performing various biomedical research projects. Three graduate students completed thesis projects for their M.D./Ph.D. and M.S. degrees. Five undergraduate students completed projects for Honors in Biology, Honors in Psychology, and Community College Honors programs. The other students did their projects for Independent Work in Biology, Independent Undergraduate Research, Professional Student Mentored Research Scholars, Summer Research Scholars, Young Scientist Summer Research, Summer Research Opportunity, Summer Science Scholars, Math Science and Technology, and Laboratory Internship Programs as well as for laboratory rotations. In addition to their presentations at local meetings, these students were first or co-authors of 12 peer-reviewed articles. These experiences also make me extremely well-suited to successfully meet the goals of the R15 program by providing Palmer College of Chiropractic's students with mentored opportunities to participate in all phases of a biomedical research project about a SMT technique that they are taught and frequently use in clinical practice.

a. Onifer SM, Sozio RS, DiCarlo DM, Li Q, Donahue RR, Taylor BK, Long CR: Spinal manipulative therapy reduces peripheral neuropathic pain in the rat. NeuroReport. In press, 2017.
b. Onifer SM, Reed WR, Sozio RS, Long CR: Anti-nociceptive effects of low velocity variable amplitude spinal manipulation on behavior of adult rats during the formalin test. Evidence-Based Complementary and Alternative Medicine. 2015, 520454, 2015. PMCID: PMC4674607.
c. Reed WR, Cranston JT, Onifer SM, Little JW, Sozio RS: Decreased spontaneous activity and altered evoked nociceptive response of rat thalamic submedius neurons to lumbar vertebra thrust. Experimental Brain Research. 2017.
d. Reed WR, Sozio RS, Pickar JG, Onifer SM: Effect of spinal manipulation thrust duration on trunk mechanical activation thresholds of nociceptive specific lateral thalamic neurons. Journal of Manipulative and Physiological Therapeutics. 37: 552-560, 2014. PMCID: PMC4394198

B. Positions and Honors

Positions and Employment

1994-1998 Instructor, The Miami Project to Cure Paralysis & Dept. of Neurological Surgery, Univ. of Miami, School of Medicine, Miami, FL
1996-1998 Supervisor, The Miami Project to Cure Paralysis Histology & Biochemistry Facilities, Univ. of Miami, School of Medicine, Miami, FL
1997 Visiting Scientist, Department of Neuroscience, Karolinska Institute, Stockholm, Sweden
1998-2001 Research Assistant Professor, Dept. of Neurological Surgery, Univ. of Louisville, School of Medicine, Louisville, KY
2000-2005 Supervisor, Kentucky Spinal Cord Injury Research Center Surgery Facilities, Univ. of Louisville, School of Medicine, Louisville, KY
2001-2005 Assistant Professor, Dept. of Neurological Surgery & Kentucky Spinal Cord Injury Research Ctr., Univ. of Louisville, School of Medicine, Louisville, KY
2001-2005 Secondary Appointment, Dept. of Anatomical Sciences & Neurobiology, Univ. of Louisville, School of Medicine, Louisville, KY
2005-2008 Adjunct Assistant Professor (Gratis), Dept. of Anatomical Sciences & Neurobiology, Univ. of Louisville, School of Medicine, Louisville, KY
2005-2007 Scientist III, Spinal Cord & Brain Injury Research Ctr., Univ. of Kentucky, College of Medicine, Lexington, KY
2005-2013 Supervisor, Spinal Cord & Brain Injury Research Ctr. Animal Surgery, TBI/SCI, & Behavioral Testing Core Facilities, Univ. of Kentucky, College of Medicine, Lexington, KY
2007-2012 Research Assistant Professor, Spinal Cord & Brain Injury Research Ctr., Univ. of Kentucky, College of Medicine, Lexington, KY
2007-2013 Secondary Appointment, Dept. of Anatomy & Neurobiology, Univ. of Kentucky, College of

Medicine, Lexington, KY

2012-2013 Research Associate Professor, Spinal Cord & Brain Injury Research Ctr., Univ. of Kentucky, College of Medicine, Lexington, KY

2013-Present Associate Professor of Neuroscience, Palmer Center for Chiropractic Research, Palmer College of Chiropractic, Davenport, IA

Other Experience and Professional Memberships

1986-Present Society for Neuroscience
1991-1998 Miami Chapter of the Society for Neuroscience, Univ. of Miami, Miami, FL
1997-1998 Member, Institutional Animal Care and Use Committee, Univ. of Miami, Miami, FL
1998-2005 Louisville Chapter of the Society for Neuroscience, Univ. of Louisville, Louisville, KY
1999-2005 Member, Institutional Animal Care and Use Committee, Univ. of Louisville, Louisville, KY
2003-2005 Vice Chair, Institutional Animal Care and Use Committee, Univ. of Louisville, Louisville, KY
2005-2013 Blue Grass Chapter of the Society for Neuroscience, Univ. of Kentucky, Lexington, KY
2008-2013 Kentucky Academy of Science
2010-2013 Treasurer, Blue Grass Chapter of the Society for Neuroscience

Professional Activities (Referee/Reviewer)

Grants NIH/Acute Neural Injury and Epilepsy Study Section (Mail 2013; Ad Hoc 6/2014, 10/2014) Department of Defense, Paralyzed Veterans of America, The Craig H. Neilsen Foundation, Medical Research Council, Wellcome Trust, The Physician's Services Incorporated, Medical Faculty of Heinrich-Heine-University

Journals *Acta Neurobiologiae Experimentalis, European Journal of Neuroscience, Evidence-Based Complementary and Alternative Medicine, Experimental Neurology, Glia, Journal of the American Association for Laboratory Animal Science, Journal of Cerebral Blood Flow and Metabolism, Journal of Neuroscience, Journal of Neuroscience Methods, Journal of Neuroscience Research, Journal of Neurotrauma, Journal of Visualized Experiments, Neurotherapeutics, Neuroscience Letters, Restorative Neurology and Neuroscience, Spine*

Honors

2009: "Friend of the Year", Friends for Michael, Inc. Spinal Cord Injury Organization

C. Contribution to Science

1. **Characterized embryonic neuron and neuronal cell line transplantation for repairing the damaged adult central nervous system.** Neuron loss following central nervous system trauma and disease leads to devastating dysfunctions. My American Heart Association fellowships-funded graduate student thesis project determined the therapeutic potential of lost neuron replacement by intracerebral embryonic tissue transplantation. Following transplantation of embryonic gerbil hippocampal tissue into the adult gerbil hippocampus chronically depleted of CA1 pyramidal neurons by global cerebral ischemia, I observed that transplanted neurons survived, the transplanted tissues were innervated by host cholinergic and serotonergic axons, and that a spatial memory deficit was ameliorated[a]. Part of my post-doctoral research at The Miami Project to Cure Paralysis focused on neuronal cell lines as alternatives to embryonic neurons. I found that the morphological differentiation of a rat raphe-derived, immortalized neuronal cell line was determined by local epigenetic signals following transplantation into the normal adult rat hippocampus or spinal cord[b]. As a Principal Investigator, my laboratory subsequently saw that morphological differentiation of the immortalized neuronal cell line was suppressed following transplantation into the adult rat spinal cord after chronic neuron depletion or neuron denervation[c] possibly by injury- and/or plasticity-related molecules.
   a. Onifer SM, Low WC. Spatial memory deficit resulting from ischemia-induced damage to the hippocampus is ameliorated by intra-hippocampal transplants of fetal hippocampal neurons. Progress in Brain Research, 82:359-366, 1990.
   b. Onifer SM, Whittemore SR, Holets VR. Variable morphological differentiation of a raphé-derived neuronal cell line following transplantation into the adult rat CNS. Experimental Neurology, 122:130-142, 1993.
   c. Onifer SM, Cannon AB, Whittemore SR. Altered differentiation of neural progenitor cells after transplantation into the injured adult rat spinal cord. Cell Transplantation, 6:327-228, 1997.

2. **Developed contusive cervical SCI model for sensory and motor function recovery investigations.** Traumatic spinal cord injuries frequently occur at the cervical segments and are of the contusion type. The resulting tetraplegia is devastating. Therefore, another part of my post-doctoral research focused on developing a clinically relevant adult rat model of contusive cervical SCI and behavior tests to evaluate forelimb function for neurorestorative treatments research. Perhaps due to speculated mortality and morbidity issues, there was only one report of a rat model of contusive cervical SCI at this time and it involved the middle segments[a]. I observed that contusive low cervical SCI produced chronic proximal and distal forelimb dysfunctions that impaired forelimb extension, grip strength, and pellet retrieval[b]. Contusive cervical spinal cord injuries frequently are incomplete and some functions spontaneously recover. As a Principal Investigator, my laboratory used this model to investigate spontaneous recovery of forepaw somatosensory evoked potentials. We found that this was temporally associated with recovery of neural transmission in the appropriate relay of forepaw somatosensory information, the brainstem dorsal column cuneate nucleus,[c] by an unknown mechanism. To determine whether glutamate is involved, I established recording cuneate nucleus glutamate levels with glutamate-sensitive, ceramic microelectrode arrays[d].
   a. Onifer SM, Rabchevsky AG, Scheff SW. Rat models of traumatic spinal cord injury to assess motor recovery. ILAR Journal, 48:385-395, 2007.
   b. Onifer SM, Rodríquez JF, Santiago DI, Benitez JC, Kim DT, Brunschwig J-P, Pacheco JT, Perrone JV, Llorente O, Martinez-Arizala A. Cervical spinal cord injury in the adult rat: Assessment of forelimb dysfunction. Restorative Neurology and Neuroscience, 11:211-223, 1997.
   c. Onifer SM, Nunn CD, Decker JA, Payne BN, Wagoner, MR, Puckett AH, Massey JM, Armstrong J, Kaddumi EG, Fentress KG, Wells MJ, Calloway CC, Schnell JT, Whitaker CM, Burke DA, Hubscher CH. Loss and spontaneous recovery of forelimb evoked potentials in both the adult rat cuneate nucleus and somatosensory cortex following contusive cervical spinal cord injury. Experimental Neurology, 207:238-247, 2007. PMCID: PMC2141689
   d. Onifer SM, Quintero JE, Gerhardt GA: Cutaneous and electrically evoked glutamate signaling in the adult rat somatosensory system. Journal of Neuroscience Methods, 208:146-154, 2012.

3. **Established CSPG digestion as a strategy for functional axon growth in synaptic target sites denervated by SCI.** In addition to alterations in spared neuronal circuitries, axon regeneration and axon collateral sprouting then target neuron reinnervation are processes by which neural transmission and function can recover and be improved following traumatic SCI. Identifying mechanisms and approaches that facilitate these processes is vital to overcoming the overwhelming physical, psychosocial, and financial hardships. Using funding from the American Paralysis Association and the Paralysis Project of America, my laboratory investigated methylprednisolone's potential for promoting motor and sensory axon regeneration then locomotion when multiple peripheral nerve graft bridges across a thoracic spinal cord complete transection were combined with FGF1. Subsequently, my NIH/NINDS RO1 grant and NIH/NCRR/COBRE project funding was used to evaluate functional forelimb sensory fasciculus cuneatus axon regeneration through an extraspinal peripheral nerve graft bridge between the transected cervical spinal cord dorsal columns and the axons' synaptic target site in the brainstem cuneate nucleus. To do so, we confirmed that anatomically complete transection of the cervical spinal cord dorsal columns fasciculus cuneatus abolished forepaw somatosensory evoked potentials and impaired forelimb sensory behavior[a]. Preliminary studies found electrophysiological evidence of modest fasciculus cuneatus axon regeneration through the graft bridge. Anatomical examination revealed that axon growth out of the graft into the cuneate nucleus was slight. Increased CSPG expression occurring at the human and experimental animal traumatic SCI site plays a critical role in axon growth failure. For the first time, we demonstrated that this also takes place at synaptic target sites denervated by SCI. We saw increased CSPG expression within the extracellular matrix and perineuronal nets of the cuneate nucleus following anatomically complete transection of the cervical spinal cord fasciculus cuneatus[b]. We also showed for the first time that functional neural circuitry reconstruction occurs in synaptic target sites when CSPG expression is altered following SCI. We found anatomical and electrophysiological evidence of collateral sprouting by spared forelimb fasciculus cuneatus axons and functional neuron reinnervation within the cuneate nucleus when the bacterial enzyme chondroitinase ABC was administered to it to degrade CSPG following cervical spinal cord dorsal column transection[c]. Importantly, these results indicate that functional reconstruction of neural circuitry after traumatic SCI by axon collateral sprouting and axon regeneration will require approaches that deal with the increased presence of inhibitory molecules in the extracellular matrix at synaptic target sites.

a. Onifer SM, Zhang YP, Burke DA, Brooks DL, Decker JA, McClure NJ, Floyd AR, Hall J, Proffitt BL, Shields CB, Magnuson DSK. Adult rat forelimb dysfunction after dorsal cervical spinal cord injury. Experimental Neurology, 192:25-38, 2005.
b. Massey JM, Amps J, Viapiano MS, Matthews RT, Wagoner MR, Whitaker CM, Alilain W, Yonkof A, Khalyfa A, Cooper NGF, Silver J, Onifer SM. Increased chondroitin sulfate proteoglycan expression in denervated brainstem targets following spinal cord injury creates a barrier to axonal regeneration overcome by chondroitinase ABC and neurotrophin-3. Experimental Neurology, 209:426-445, 2008. PMCID: PMC2270474
c. Massey JM, Hubscher CH, Wagoner MR, Decker JA, Amps J, Silver J, Onifer SM. Chondroitinase ABC digestion of the perineuronal net promotes functional collateral sprouting in the cuneate nucleus following cervical spinal cord injury. Journal of Neuroscience, 26:4406-4414, 2006.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/stephen.onifer.1/bibliography/47721284/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

NIH/NCCIH, 1R15AT009612-01 7/5/17-6/30/20
Role: SM Onifer PI; BK Taylor Co-PI (Univ. of Kentucky); CR Long Co-I
"Antinociceptive Mechanisms of Spinal Manipulative Therapy for Neuropathic Pain"
The goals of this project are to leverage a multidisciplinary collaboration to 1) characterize anti-allodynia produced by our innovative rat model of a frequently used non-thrust spinal manipulative therapy technique (low velocity variable amplitude spinal manipulation) in a well-characterized rat model of chronic peripheral neuropathic pain (spared nerve injury) and to 2) determine whether this anti-allodynia effect is mediated by endogenous activation of cannabinoid receptors in the spinal cord dorsal horn. Additionally, Palmer College of Chiropractic students will be provided opportunities to learn about biomedical research through mentored hands-on participation in the project.

Completed Research Support (last 3 years)

Palmer Center for Chiropractic Research SEED Grant 5/19/16-6/30/17
Role: SM Onifer PI
"Anti-Nociceptive Effects of Spinal Manipulative Therapy on Behavior and Spinal Cord Neurons"
The goal of this project is to test the hypothesis that thoracolumbar spinal cord dorsal horn NMDARs mediate LVVA-SM's anti-nociception in an adult rat model of persistent peripheral pain.

Faculty Resources Support, Palmer Center for Chiropractic Research 10/1/14-5/31/16
Role: SM Onifer PI
"Effects of Spinal Manipulation on Chronic Pain"
The goals of this project were in an adult rat model of chronic neuropathic pain to test the hypotheses that LVVA-SM 1) alleviates allodynia and 2) affects central nervous system neurons' responsiveness.

Faculty Resources Support, Palmer Center for Chiropractic Research 6/1/13-5/31/14
Role: SM Onifer, PI
"Effects of Spinal Manipulation on Pain"
The goals of this project were to test the hypotheses that LVVA-SM 1) has an anti-nociceptive effect in an adult rat model of persistent peripheral pain, the hindpaw formalin test, and 2) activates central nervous system neurons, including those in the thoracolumbar spinal cord dorsal horn.