OMB No. 0925-0001 and 0925-0002 (Rev. 09/17 Approved Through 03/31/2020)

BIOGRAPHICAL SKETCH

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NAME: Fletcher A. White, M.S., Ph.D.

eRA COMMONS USER NAME (credential, e.g., agency login): fwhite1

POSITION TITLE: Professor, Anesthesia and Pharmacology and Research Career Scientist, VAMC

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 DateMM/YYYY | FIELD OF STUDY |
| --- | --- | --- | --- |
| Baldwin-Wallace College, Berea, OH | Bachelors | 06/1985 | Psychology |
| Medical College of Ohio, Toledo, OH | Masters | 06/1989 | Pathology |
| Medical College of Ohio, Toledo, OH | Doctorate | 06/1994 | Neurobiology |
| Washington University, St. Louis, MO(Mentor: William D. Snider) | Postdoctoral | 1994-1998 | Developmental  Neurobiology |
| Massachusetts General Hospital/Harvard Medical School, Boston, MA (Mentor: Clifford J. Woolf) | Postdoctoral | 1998-1999 | Neurobiology of Peripheral Nerve Injury |

**A. Personal Statement**

 I am a medical school-trained neuroscientist involved in both pre-clinical and clinical research studies for nearly 30 years. My laboratory has published over 90 papers in peer-reviewed journals. The focus of my pre-clinical research career includes the role of neurotrophins during neurodevelopment/apoptosis in sensory ganglia (NGF/TrkA & NT3/TrkC), axon guidance molecules during development of the peripheral nervous system (semaphorins). We were the first to recognize the role of neuronal chemokines/receptors in neuropathic pain rodent models (CCL2/CCR2, CCL5/CCR5 and CXCL12/CXCR4). Central to the current R01 proposal has been my more recent work on the influence of toll-like receptor-4 (TLR4) following oxaliplatin chemotherapy, peripheral nerve injury and opioid-induced hyperalgesia together with non-endotoxin TLR4 agonists including oxaliplatin, the opiate metabolite morphine-3 glucuronide (M3G), and high mobility group box- 1 (HMGB1). Several publications utilize proven TLR4 inhibitor and decoy peptides. A number of our published observations from these basic laboratory studies have been instrumental in the translation to the clinic of new therapeutic uses for existing drugs which appear to modify the influence of neuronal TLR4 signaling on voltage-gated sodium channels.

The translational impact of the aforementioned basic research studies has focused on the combination of FDA-approved non-narcotic drugs in combination with opioids to improve pain management and reduce opioid consumption. To this end, I have partnered with medical faculty members of the Simon Family Cancer Center at Indiana University, and the Roudebush Veterans Administration Medical Center in Indianapolis to move a number of these concepts from bench to bedside. These interventional studies include (i) a safety toxicity trial on the effects of oxcarbazepine in combination with morphine for chemotherapy-induced peripheral neuropathy (NCT02078089); (ii) the use of lacosamide as an adjunct to opioids for pain control due to hip arthroplasty (NCT02342977); and (iii) adjuvant use of lacosamide in combination with opioids for bone cancer pain control in multiple myeloma patients.

The current application builds logically on my prior unpublished/published peer-reviewed studies with opiates/opioids and rodent behavior, the reknown imaging expertise of Dr. Xiaoming Jin (and co-author), the internationally-known methamphetamine expert, Dr. Bryan Yamamoto, the presence of the Alzheimer's Disease Precision Models Center (MODEL-AD) state-of-the-art behavioral core facility run by Dr. Dave Mckinzie and my longtime affiliation with Dr. Edward Campbell.

Ed and I were members of the same department at Loyola University School of Medicine in Chicago and have managed to stay in touch due to both a common interest in neuroinflammation and my participation on the dissertation committee of a MD/PhD student. Much of the success of our ongoing collaborations can be measured by the inclusion of the Caspase-1 Biosensor (inflammasome mouse) in a jointly awarded State of Indiana grant in 2019 on traumatic brain injury and neuroinflammation (White, Jin and Campbell). For the current proposal, I will be directly involved in all the in vivo aspects of this proposal. The following publications are relevant to the proposed studies.

1) Due MR, Piekarz AD, Wilson NM, Feldman P, Ripsch, MS, Khanna R, **White FA**. Neuroexcitatory effects of morphine-3-glucuronide are dependent on Toll-like receptor 4 signaling. ***Journal of Neuroinflammation***, Aug 16;9(1):200, 2012. PMID: 22898544.

2) Allette, YM, Due MR, Wilson SM, Feldman P, Ripsch MS, Khanna R, **White FA**. Identification of a functional interaction of HMGB1 with Receptor for Advanced Glycation End-products in a model of neuropathic pain.

***Brain Behavior and Immunity***, Nov; 42:169-77, 2014. PMID:25014009

3) Due MR, Yang XF, Allette YM, Randolph AL, Ripsch MR, Dustrude ET, Wilson SM, Khanna R, **White FA**. Carbamazepine potentiates the effectiveness of morphine in a rodent model of neuropathic pain.

**PLoS1**, Sep 15;9(9):e107399, 2014. PMID: 25221944

4) Allette YM, Kim Y, Smith JA, Randolph AL, Ripsch MS, **White FA**. Decoy peptide targeted to Toll-IL-1R domain inhibits LPS and TLR4-active metabolite morphine-3 glucuronide sensitization of sensory neurons.

***Scientific Reports***, Jun 16;7(1):3741, 2017. PMID: 28623271

**B. Positions and Honors**

* 1. Associate Research Scientist, Neurology & Anesthesiology, Yale University School of Medicine

2002-2008 Assistant Professor, Cell Biology, Neurobiology and Anatomy, Loyola University of Chicago,

2003-2008 Assistant Professor, Anesthesiology, Loyola University of Chicago

2003-2009 Investigator, Neuroscience Institute, Loyola University of Chicago

2007-2009 Director, Anesthesiology Research Laboratory, Loyola University of Chicago,

2008-2009 Associate Professor, Cell Biology, Neurobiology & Anatomy and Anesthesiology, Loyola University of Chicago

2008-present Associate Member, Children’s Memorial Hospital Research Center

2009-present Professor of Anesthesia, Indiana University School of Medicine (IUSOM)

2009-2017 Vice Chair for Research, Anesthesia, IUSOM

2010-present Director, Anesthesia Research Fellowship

2009-present Professor, Department of Pharmacology, IUSOM

2009-present Primary Investigator, Stark Neuroscience Institute, IUSOM

2009-present Primary Investigator, IU Spinal Cord and Brain Injury Research Group, Stark Neuroscience Institute, IUSOM

2009-2017 Lecturer, Physiology, Loyola University of Chicago

2010-present Member, Center for Immunobiology, IUSOM

2011-2016 Research Scientist, RL Roudebush VA, Indianapolis, IN

2016-present Research Career Scientist, RL Roudebush VA, Indianapolis, IN

2012-present Professor, Department of Cell Biology/Anatomy, IUSOM

2013-present Full Member, IU Simon Cancer Center, IUSOM

2017-present Executive Committee, Stark Neuroscience Research Institute

2018-present Chairman, University Awards Committee

**Federal Study Section Review Panels** since 2016

2016 NIH/NINDS, IFCN4/SCS study section, ad hoc

2016 MRMC (US Army), Clinical and Rehabilitative Medicine

2016 MRMC (US Army), Combat Casualty Care

2016 -present NIH/NCI, ZCA, SEP, NCI Provocative Questions-PQ9, regular member

2017 NIH/NINDS, ETTN (13), Small Business: Neuroscience Assay and Diagnostics, ad hoc

2017 VA SPIRE Grants, RR&D, ad hoc

2017 -present NIH/NINDS ZRG1 ETTN (11) Small Business: Drug Discovery for Aging, Neuropsychiatric

 and Neurologic Disorders, regular member

2017 -present NIH/NCI, ZCA, NCI Provocative Questions-PQ12, regular member

2018 NIH/NINDS, ZRG1 MDCN-E (50) NIH Blueprint for Neuroscience Research

2018 NIH/NCCIH ZAT1 National Center for Complementary and Integrative Health, SEP

2018 CDMRP (Dept of Defense), Applied Pain Research

2019 NIH/NINDS Acute to Chronic Pain Signatures (A2CPS) for Omics Data Generation and Data Integration Centers

2019 NIH/NCATS, ZTR1-TC-7-01, HEAL Initiative Review

2019 NIH/NCCIH, ZAT1-AJT-10, Training Grant Proposals

2019 P2RMIS Defense Medical Research, Pain Management

2019 NIH/NCI, ZCA1-RPRB-6-O2

2019 Department of Veterans Affairs RRD8 – Career Development Panel

2019 Technical Expert, Helping End Addiction Long-term (HEAL) collaboration proposals, ad-hoc

**Honors**

1989 Barrels Fellowship, International Brain Research Organization, Phoenix, AZ

1995,1996 T32 Research Training Grant Award, Sensory Physiology and Biophysics, St. Louis, MO

2000 Gordon Research Conference Fellowship, Neurotrophic Factors, Newport, RI

2001 Christopher Reeve Paralysis Foundation Postdoctoral Fellowship, New Haven, CT

2002 Gordon Research Conference Fellowship, Neural Development, Newport, RI

2002 Illinois Excellence in Academic Medicine Award, Illinois Department of Public Health

2009 V.K. Stoelting, Endowed Chair, Indiana University School of Medicine, Indianapolis, IN

2015 7th Annual Veterans Administration Scientific Symposium,1stPlace, Outcome-Oriented Research

 **C. Chronological Contribution to Science**

**I.)** One foci of my research program explored the role of chemotactic cytokines (chemokines)on the injured adult peripheral nervous system. My laboratory published several papers in internationally-recognized journals on the topic of chemokines and neuropathic pain including a seminal paper ([White et al., 2005](#_ENREF_12)) and invited review ([White et al., 2007](#_ENREF_9)) in the *Proceedings of the National Academy of Science* on the influence of chemokine monocyte chemoattractant protein-1 (MCP-1/CCL2) on neuronal CCR2. Our results demonstrated that MCP-1 and CCR2, participated in neural signal processing which contributes to sustained excitability of primary afferent neurons ([Bhangoo et al., 2007a](#_ENREF_2)). In addition, we also implicated another chemokine, stromal-derived factor 1 alpha (SDF1a; aka CXCL12) acting via the chemokine receptor CXCR4, as a central feature of HIV-1 induced distal symmetrical polyneuropathy ([Bhangoo et al., 2007b](#_ENREF_3)) and opioid-induced hyperalgesia (Wilson et al., 2011). The role of chemokine signaling, and chronic lower back pain continues to be a clinical topic of interest in my laboratory. To this end, we are currently analyzing clinical samples of cerebrospinal fluid derived from chronic lower back pain patients for the present of these pronociceptive factors.

-This work has been supported by grants from the Veterans Administration and NIH/NINDS.

1) **White FA**, Sun J, Waters SM, Ma C, Ren D, Ripsch M, Steflik J, Cortright DN, Lamotte RH, Miller RJ (2005) Excitatory monocyte chemoattractant protein-1 signaling is up-regulated in sensory neurons after chronic compression of the dorsal root ganglion. ***Proc Natl Acad Sci U S A*** 102:14092-14097. *Cited 298 times*. PMID:16174730

2) Bhangoo S, Ren D, Miller RJ, Henry KJ, Lineswala J, Hamdouchi C, Li B, Monahan PE, Chan DM, Ripsch MS, **White FA** (2007a) Delayed functional expression of neuronal chemokine receptors following focal nerve demyelination in the rat: a mechanism for the development of chronic sensitization of peripheral nociceptors. ***Mol Pain*** 3:38. *Cited 153 times*. PMID:18076762

3) Bhangoo SK, Ren D, Miller RJ, Chan DM, Ripsch MS, Weiss C, McGinnis C, **White FA** (2007b) CXCR4 chemokine receptor signaling mediates pain hypersensitivity in association with antiretroviral toxic neuropathy. ***Brain Behav Immun*** 21:581-591. *Cited 126 times*. PMID:17292584

4) Wilson NM, Jung H, Ripsch MS, Miller RJ, White FA (2011) CXCR4 signaling mediates morphine-induced tactile hyperalgesia.***Brain Behavior and Immunity***, 25(3):565-73. *Cited 73 times*. PMID:21193025

**II.)** A prominent receptor that is known to modulate chemokine/receptor expression in non-neural cells is toll-like receptor 4 (TLR4). Recent observations from my laboratory demonstrate that small and medium diameter sensory neurons derived from the lumbar DRG exhibit functional toll-like receptor 4 (**TLR4**) ([Due et al., 2012](#_ENREF_4)). More importantly, activation of neuronal TLR4 by either bacterial endotoxin or the morphine-3-glucuronide (M3G) serves to increase the current density for the voltage-gated sodium channels (NaV) NaV1.6, 1.7 and 1.9 but not 1.8 ([Due et al., 2012](#_ENREF_4)). These observations paved the way for a potential therapeutic use of opioids/opiates in combination with the anti-epileptic drug (AED), carbamazepine (CBZ), which is known to inhibit several NaV currents as a combinational treatment for neuropathic pain and opioid-sparing effects in the clinic ([Due et al., 2014](#_ENREF_5)). Based on this pre-clinical research we believe that neuronal TLR4 activation and increased NaV current is central to opioid-induced hyperalgesia.

-This work has been supported by grants from the Veterans Administration, NIH/NIDA and State of Indiana Department of Health

1) Due MR, Piekarz AD, Wilson N, Feldman P, Ripsch MS, Chavez S, Yin H, Khanna R, **White FA** (2012) Neuroexcitatory effects of morphine-3-glucuronide are dependent on Toll-like receptor 4 signaling. ***J Neuroinflammation*** 9:200*. Cited 60 times*. PMID: 22898544

2) Allette YM, Kim Y, Smith JA, Randolph AL, Ripsch MS, **White FA**. (2017) Targeting neuronal signaling by TLR4 Toll/IL-1 receptor domain-derived decoy peptides therapeutically disrupts nociceptive signaling. ***Scientific Reports,*** Jun 16;7(1):3741. *Cited 11 times* PMID: 28623271

3) Chen X, Liu D, Zhou D, Si Y, Stamatkin CW, Ghozayel MD, Ripsch MS, Obukhov AG\*, Meroueh S\*, **White FA**\*. (2018) Small-molecule CaVα1⋅CaVβ antagonist suppresses neuronal voltage-gated calcium-channel trafficking. ***Proc Natl Acad Sci USA***, Nov 6;115(45):E10566-E10575. PMID:30355767 \* Shared senior authorship.

**III.)** We have not restricted our studies to the exogenous sources of TLR4 agonists as it is known that assorted damage-associated molecular proteins (**DAMPs**) activate TLR4 and elicit neuronal excitability ([Feldman et al., 2012](#_ENREF_6)). One prototypical DAMP in particular, high mobility group box-1 (**HMGB1**) is now known to excite neurons through a receptor-mediated process that can involve either TLR4 (disulphide state of HMGB1) or the receptor for advanced glycation end-products (all-thiol HMGB1) ([Allette et al., 2014](#_ENREF_1)). We have reason to believe that the release of these DAMPs following injury, disease or cancer lead to chronic inflammatory conditions in the rodent and possibly in the clinical patient. Based on these published observations we are now examining tissue samples (blood, CSF and stool samples) derived from individuals admitted to Neuro-ICU for TBI or ICU for polytrauma to determine biomarkers which may be indicative of morbidity and mortality.

-This work has been supported by grants from the NIH/NIDDK, NIH/NINDS and State of Indiana Department of Health.

1) Feldman P, Due MR, Ripsch MS, Khanna R, **White FA** (2012) The persistent release of HMGB1 contributes to tactile hyperalgesia in a rodent model of neuropathic pain. ***Journal of Neuroinflammation*** 9:180.*Cited by 63*. PMID:22824385

2) Allette YM, Due MR, Wilson SM, Feldman P, Ripsch MS, Khanna R, **White FA** (2014) Identification of a functional interaction of HMGB1 with Receptor for Advanced Glycation End-products in a model of neuropathic pain. ***Brain Behav Immun*** 42:169-177. *Cited by 37* PMID:25014009

3) Hiasa M, Okui T, Allette YM, Ripsch MS, Sun-Wada GH, Wakabayashi H, Roodman GD, **White FA**, Yoneda T. (2017) Bone pain induced by multiple myeloma is reduced by targeting V-ATPase and ASIC3. ***Cancer Research***, Mar 15:77(6), 1283-1295. *Cited by 7* PMID: 28254863

**IV.)** Based on our pre-clinical observations we are now examining tissue samples (blood and CSF) derived from psychiatric patients with established pain conditions; and individuals admitted to Level 1 trauma center Emergency Departments or Methodist Hospital Intensive Care Unit for mild TBI plus polytrauma or polytrauma alone to determine biomarkers which may be indicative of morbidity and mortality.

-This work has been supported by grants from the Department of Defense and State of Indiana Department of Health.

1) Weber D, Allette YM, Wilkes DS, White FA. The HMGB1-RAGE Inflammatory Pathway: Implications for Brain Injury Induced Pulmonary Dysfunction. ***Antioxid & Redox Signal***, Special Forum Issue on DAMP-driven Immunopathology, accepted March 3, 2015 *Cited by 19* PMID: 25751601

2) McKinley TO, Lei Z, Kalbas Y, **White FA**, Shi Z, Wu F, Xu ZC, Rodgers RB (2018) Blood purification by nonselective hemoadsorption prevents death after traumatic brain injury and hemorrhagic shock in rats. ***J Trauma Acute Care Surg***, Dec;85(6):1063-1071. PMID: 30211852

3) Carey C, Saxe J, **White FA**, Naugle KM (2019) An exploratory study of endogenous pain modulatory function in patients following mild traumatic brain injury.

***Pain Medicine***, PMID: 30938813

4) Niculescu AB, Le-Niculescu H, Levey D,Roseberry K, Soe KC, Rogers J, Khan F, **White FA** (2019) Towards precision medicine for pain: diagnostic biomarkers and repurposed drugs. ***Molecular Psychiatry***, Feb 12 PMID:30755720

**Complete List of Published Work in MyBibliography:** <https://www.ncbi.nlm.nih.gov/sites/myncbi/fletcher.white.1/bibliography/40234758/public/?sort=date&direction=descending>

**D. Additional Information: Research Support and/or Scholastic Performance**

**Current Funding**

**1)** PRMRP, W81XWH-18-1-0433 9/1/18-8/31/21

Chronic headache due to mild traumatic brain injury in adults: Alterations of brain function, central sensitization and inflammatory processes.

Goal: Correlate quantitative sensory testing and biomarkers in individuals with concussion.

**Role: PI**

OVERLAP: None.

**2)** NIH/NINDS R01NS102415 9/1/18-8/31/23

The role of cell-specific TLR-4 signaling in oxaliplatin-induced peripheral neuropathy

Goal: Determine the molecular mechanisms associated with oxaliplatin-induced peripheral neuropathy in rodents.

**Role: PI**

OVERLAP: None

**3)** Indiana Spinal Cord and Brain Injury Grant Program 7/1/19-6/30/20

Title: Sensitization of sensory neuron subpopulations by Toll-like receptor 4 after chronic spinal cord injury

Goal: Neurophysiological attributes associated with TLR4-bearing sensory neurons after spinal cord injury.

**Role: PI**

OVERLAP: None

**4)** Indiana Spinal Cord and Brain Injury Grant Program 7/1/18-6/30/20

Pain Modulatory Systems in Chronic Post-Traumatic Headache (PTH)

Goal: The overall aim of this prospective pilot study is to evaluate whether pain modulatory profiles predict the intensity and frequency of chronic post-traumatic headaches in mild traumatic brain injury adult and adolescent patients.

**Role: Co-PI**

OVERLAP: None

**5)** Indiana Spinal Cord and Brain Injury Grant Program 7/1/18- 6/30/20

Impact of the adiopocyte secretome on anxiety behavior in a rodent model of closed head injury.

Goal: Determine the degree to which adiopocyte secretome diminish behavioral sequela post-injury.

**Role: PI**

OVERLAP: None

**Completed Support in last 5 years**

**1)** VA MERIT BLR&D (1I01BX001860) 3/1/14-12/30/18

Chemokine signaling in the transition from acute to chronic pain.

Goal: Determine the role of chemokines in the transition to chronic pain following nerve injury

**Role: PI**

**2)** NIH/NIDA (R01 NS089509) 7/1/14-6/30/18

Homeostatic plasticity in the control of neuropathic pain

Goal: Use advanced research techniques (optogenetics) to test a highly innovative and unconventional hypothesis on the mechanism and control of neuropathic pain.

Role: Co-I (**PI**, **Xiaoming Jin**)

**3)** NIH/NIDDK (RO1 DK100905) 9/1/13- 5/31/16

The role of DAMPS in painful bladder syndrome

Goal: Demonstrate the contribution of DAMPs in a rodent model of painful bladder syndrome

**Role: PI**