OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 09/30/2024)

BIOGRAPHICAL SKETCH

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NAME: White, Fletcher A.

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

POSITION TITLE: Vergil K. Stoelting Chair of Anesthesia, Professor of Anesthesia, Pharmacology, Indiana University School of Medicine; Research Career Scientist, Richard L. Roudebush VA Medical Center

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 | BA | 6/1985 | Psychology |
| Medical College of Ohio, Toledo, OH | MS | 6/1989 | Pathology |
| Medical College of Ohio, Toledo, OH | PhD | 6/1994 | Neurobiology |
| Washington University, St. Louis, MO | Postdoctoral Fellow | 1/1998 | Developmental Neurobiology |
| Massachusetts General Hospital/Harvard Medical School, Boston, MA | Postdoctoral Fellow | 11/1999 | 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 pre-clinical research career foci includes the effect on early nerve injury on peptidergic (CGRP/SP/Galanin) and non-peptidergic (IB4) neurons in the trigeminal ganglia, role of neurotrophins during neurodevelopment/apoptosis in sensory ganglia (NGF/TrkA, NT3/TrkC, BAX), axon guidance molecules during development of the peripheral nervous system (SEMA3A/6A). My work in numerous rodent models of chronic pain states examines the role of chemokines/receptors in adult (CCL2/CCR2, CCL5/CCR5 and CXCL12/CXCR4), toll-like receptor-4 (TLR4), TRPA1, voltage-gated ion channels (NaV1.6/1.7, CaV2.2) and a damage-associated molecular pattern protein and their cognate receptors (HMGB1/RAGE/TLR4). Models of behavioral pain states include peripheral and central nervous system injury, and painful neuropathy due to HIV and chemotherapy drugs. Several of these studies have been instrumental in the discovery of both novel small molecule inhibitors and new therapeutic uses for existing drugs. More recent research includes the study of mild traumatic brain injury on neuroinflammation in aged mice.

 A number of my pre-clinical observations have been translated into clinical observational and interventional research studies. My clinical observational studies include biomarkers of (i) patients with mild traumatic brain injury who develop post-traumatic headache; (ii) patients with polytrauma alone or in combination with mild to moderate traumatic brain injury, (iii) patients with spinal cord injury suffering with neuropathic pain and (iv) a high-risk patient group for co-morbid pain disorders and increased perception of pain; psychiatric patients. My interventional studies focus on the combination of FDA-approved non-narcotic drugs with opioids to improve pain management and reduce opioid consumption. Manuscripts from these projects have been published in peer-reviewed publications including *Neuron*, *PNAS, Nature Medicine, Molecular Psychiatry, Cancer Research, Journal of Neuroscience, Pain, Journal of Neuroinflammation, and Brain Behavior and Immunity.*

My history of training students for careers in biomedical careers is extensive and includes high school and college underrepresented STEM students, graduate students and postdoctoral fellows. I have also participated in training 8 MD/PhDs, and 27 physicians during residency and fellowship. My students to date at Indiana University have been supported by the NSF Louis Stokes Alliances for Minority Participation; the IU Simon Cancer Center Future Scientists Program; the IU MedNeuro Undergraduate Summer Scientific Research Program; The Indiana University-Purdue University Indianapolis (IUPUI) Graduate Preparation for the Biomedical and Behavioral Sciences (IPREP, funded by NIH R25), Indiana University MD/PhD Outreach Program, Student Research Program in Academic Medicine; and the Foundation for Anesthesia Education and Research (FAER) Summer Fellowship program. I will continue to mentor for these programs as long as I am part of the active faculty at IU School of Medicine.

Ongoing and recently completed projects that I would like to highlight include:

CP220068 - Department of Defense - Chronic Pain Management Research Program

White (PI)

1/24 to 12/28

The Prevalence of Neuropathic Pain Pathophysiology Associated with Ankle Fracture

-Clinical observational study of the etiology of ankle fracture associated neuropathic pain

R01AR083130 - NIAMS

White (PI/PD Multi PI)

7/24 to 6/29

Novel treatments of fracture repair and bone pain

-Pre-clinical study of fracture-associated neuropathic pain

I01RX004297 – Department of Veterans Affairs

White (PI)

7/01/23 to 6/30/27

Novel treatments of chronic pain due to repetitive mild traumatic brain injury

-Pre-clinical mechanism study of the impact of mTBI on aged mice

R01DK132709

White PI (Co-PI; Fogel)

5/22-4/26

Safety, tolerability, and dose limiting toxicity of lacosamide in patients with painful chronic pancreatitis

-Clinical intervention safety study

R01NS102415

White (PI)

9/18 to 6/23 (NCE)

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

-Pre-clinical mechanism study of chemotherapeutic-induced painful peripheral neuropathy

W81XWH-18-1-0433 DOD - Peer Reviewed Medical Research Program

White (PI)

9/18 to 8/23

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

-Clinical observational study of the etiology of mild traumatic brain injury associated headache

Recent Publications from White lab:

1. Talley S, Nguyen T, Van Ye L, Valiauga R, DeCarlo J, Mustafa J, Cook B, **White FA**, Campbell EM. Characterization of age-associated inflammasome activation reveals tissue specific differences in transcriptional and post-translational inflammatory responses. ***Immunity and Ageing***. 2024 Sep 10;21(1):60 PMID: 39256821
2. Nguyen T, Nguyen N, Cochran AG, Smith JA, Al-Juboori M, Brumett AM, Saxena S, Talley S, Campbell EM, Obukhov AG, **White FA**. Repeated Closed-Head Mild Traumatic Brain Injury Induced Inflammation is Associated with Nociceptive Sensitization. ***Journal of Neuroinflammation*** 2023 Aug 27;20(1):196. PMID: 37635235
3. Smith JA, Nguyen T, Karnik S, Davis BC, Al-Juboori MH, Kacena MA, Obukhov AG, **White FA**. Repeated Mild Traumatic Brain Injury in Mice Elicits Long Term Innate Immune Cell Alterations in Blood, Spleen, and Brain. ***Journal of Neuroimmunology***, 2023 May 16;380:578106. PMID: 37245410
4. Smith JA, Nguyen T, Davis BC, Lahiri DK, Hato T, Obukhov AG, White FA. Propranolol treatment during repetitive mild traumatic brain injuries induces transcriptomic changes in the bone marrow of mice. ***Frontiers of Neuroscience*** 2023 Sep 12;17:1219941.

**PMID: 37817806**

1. Niculescu AB Le-Niculescu H, Levey DF, Soe KC, Roseberry K, Khan F, Jones TJ, Judd S, McCormick MA, Williams A, Kurian S, **White FA**. Towards Precision Medicine for Pain: Diagnostic Biomarkers, Pharmacogenomics, and Repurposed Drugs. ***Molecular Psychiatry*** Apr;24(4):501-522, 2019

PMID:**30755720**

**B. Positions, Scientific Appointments and Honors**

**Positions**

2024 - present Chairman, Biomedical Research Committee, IUSM

2018 - present Chairman, Awards Committee, IUSM

2017 - present Executive Committee, Stark Neuroscience Research Institute

2011 - present Research Scientist, Roudebush Veterans Hospital, Indianapolis, IN

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

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

 Institute, IUSM

2009 - present Primary Investigator, Stark Neuroscience Institute, IUSM

2009 - present Professor, Department of Pharmacology, IUSM

2009 - present Vice Chair, Anesthesia, IUSM

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

2002 - 2009 Associate Professor, Cell Biology, Neurobiology & Anatomy, Loyola University of Chicago

1999 - 2002 Associate Research Scientist, Neurology & Anesthesiology, Yale University School of

 Medicine

**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 Depart of VA Scientific Symposium, First Place, Outcome-Oriented Research

**Patents (awarded**)

2018 US Patent #WO2018001973A1 Pyrazolylacypyrazoline Compounds and Method for Treating Pain

**Editorial Boards: Associate Editor, Frontiers in Pain Research (2020-present); Scientific Reports (2023-present)**

**Scientific Review Boards:** 2004-present American Federation of Aging Research, National Scientific Advisory Council

**Professional Activities:** (since 2015)

NIH/NINDS, IFCN4/SCS study section, (2015, 2016), ZRG1 MDCN-E (50) NIH Blueprint for Neuroscience Research (2018), Acute to Chronic Pain Signatures (A2CPS) for Omics Data Generation and Data Integration Centers ETTN P70 U54 (2019), Technical Expert, Helping End Addiction Long-term (HEAL) collaboration proposals (2019), ZRG1 IFCN-J NINDS Special Emphasis Panel (2022), ZNS1 SRB-G (51) NINDS Special Emphasis Panel (2022); NIH/NIDA, ZRG1 AARR-C (2015), NIH/NCCIH ZAT1 National Center for Complementary and Integrative Health, SEP (2018), ZAT1-AJT-10, (2019); NIH/NCATS, ZTR1-TC-7-01, HEAL Initiative Review (2019); NIH/NCI, ZCA, SEP, NCI Provocative Questions-PQ9 (2016-2020), NIH/NCI, ZCA1-RPRB-6-O2 (2019); NIH/NINDS ZRG1 ETTN (11) Small Business: Drug Discovery for Aging, Neuropsychiatric and Neurologic Disorders (2017-2022); NIH/NIGMS Musculoskeletal Rehabilitation Sciences (2020); VA MERIT RR&D (2015, 2017, 2019-2022); CDMRP/Dept of Defense (Applied Pain Research 2015; Combat Casualty Care - 2016, Pain Management - 2019); Pennsylvania Traumatic Brain Injury Review Group (2022), Swiss National Science Foundation (SNSF), AO Davos (2021, 2022) NIH/NIGMS ZRG1 MBBC-G (2023), NIH/NNDS ZNS1 SRB K (2023); NIH/NINDS NST-4 Study Section (2024) Ad Hoc Reviewer for ~40 journals.

 **C. Contributions to Science**

**Total publications 115, Citations>9245, H-factor 51, i10 index 88*)***.

1. 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) and invited review (White et al., 2007) 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). 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) 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 was 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 422 times*. PMID:16174730.
2. 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 Behavior and Immunity* 21:581-591**. *Cited 164times*. PMID:17292584.
3. 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 95 times*. PMID:21193025.

2. 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). 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). 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). Based on this pre-clinical research we believe that neuronal TLR4 activation and increased NaV current is central to opioid-induced hyperalgesia.

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

a. 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 117 times*. PMID: 22898544.

b. Allette YM, Kim Y, Smith JA, Randolph AL, Ripsch MS, **White FA**. (2017) 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***. *Cited 16 times* PMID: 28623271.

c. 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 U S A, Nov 6;115(45):E10566-E10575***. *Cited 26 times* PMID: 30355767. \* Shared senior authorship.

**3.** 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). 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). 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 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.

a. 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 129*. PMID:22824385

b. 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 95* PMID:25014009

c. Ping X, Chai Z, Wang WM, Cungen M, **White FA**, Jin X (2021) Blocking receptor for advanced glycation end-products (RAGE) or toll like receptor 4 (TLR4) prevents posttraumatic epileptogenesis in mice. ***Epilepsia***, 2021 Sep 18. doi: 10.1111/epi.17069. *Cited by 5* PMID: 34535891

**4.** An important area of study for our group has been the study of repetitive head injury-induced pain which degrades quality of life in Veterans and civilian populations alike. The lack of both an understanding of traumatic pain states and effective therapeutics enhance the disability produced by this condition. Central to our pre-clinical studies have been understanding the response of the innate immune system following trauma. Using a **luciferase reporter of caspase-1 biosensor mouse**, evaluation of specific cell types associated with sites of inflammation and responses by the central nervous system provides us with greater understanding mTBI-associated pain state.

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

1. Smith JA, Nguyen T, Karnik S, Davis BC, Al-Juboori MH, Kacena MA, Obukhov AG, **White FA** (2023) Repeated Mild Traumatic Brain Injury in Mice Elicits Long Term Innate Immune Cell Alterations in Blood, Spleen, and Brain. ***Journal of Neuroimmunology***, May 16;380:578106. PMID: 37245410
2. Nguyen T, Nguyen N, Cochran AG, Smith JA, Al-Juboori M, Brumett AM, Saxena S, Talley S, Campbell EM, Obukhov AG, **White FA** (2023) Repeated Closed-Head Mild Traumatic Brain Injury Induced Inflammation is Associated with Nociceptive Sensitization. ***Journal of Neuroinflammation*** Aug 27;20(1):196. PMID: 37635235
3. Talley S, Nguyen T, Ye LV, Valiauga R, DeCarlo J, Mustafa J, Cook B, **White FA**, Campbell EM. Characterization of age associated inflammasome activation reveals tissue specific differences in transcriptional and post-translational inflammatory responses. ***Immunity and Ageing*** 2024 Sep 10;21(1):60. doi: 10.1186/s12979-024-00462-z. PMID: 39256821

**5.** 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.

 a. Chen X, Taylor-Nguyen N, Riley AM, Herring, BP, **White FA**, ***Obukhov AG***. (2019) The TRPC6 inhibitor, larixyl acetate, is effective in protecting against traumatic brain injury-induced systemic endothelial dysfunction. ***J Neuroinflammation***Jan 31;16(1):21. *Cited by 16* PMID: 30704505

 b. Naugle KM Carey C, Saxe J, **White FA** (2020) The role of deficient pain modulatory systems in the development of subacute and chronic post-traumatic headaches following mild traumatic brain injury: An exploratory study. ***Journal of Headache and Pain***, Dec 3;21(1):138*. Cited by 17* PMID: 33272206

 c. Naugle KM, Corrona S, Smith JA, Nguyen T, Saxe J, **White FA** (2021) Physical activity behavior in the first month following mild traumatic brain injury is associated with physiological and psychological risk factors for chronic pain. ***Pain Reports***, Oct 29;6(4):e969. *Cited by 6* PMID: 34765852

d. Naugle KM, Nguyen T, Smith JA, Saxe J, **White FA** (2023) Racial differences in pain-related outcomes

following mild traumatic brain injury. ***Journal of Neurotrauma***, Aug;40(15-16):1671-1683. PMID: **36565020**

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

https://www.ncbi.nlm.nih.gov/myncbi/fletcher.white.3/bibliography/public/