OMB No. 0925-0001/0002 (Rev. 08/12 Approved Through 8/31/2015)

BIOGRAPHICAL SKETCH

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NAME: Slobodan M. Todorovic

eRA COMMONS USER NAME (credential, e.g., agency login): ST9DNIH

POSITION TITLE: Professor of Anesthesiology

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 |
| --- | --- | --- | --- |
| University of Belgrade School of Medicine | MD | 1982 | Medicine |
| University of Illinois in Chicago | PhD | 1990 | Pharmacology |
| Northwestern University in ChicagoWashington University in St. Louis | internshipresidency | 19921996 | MedicineNeurology/Anesthesiology |
| Washington University in St. Louis | post-doc | 2000 | Anesthesiology/Psychiatry |
|  |  |  |  |

**A.** **Personal Statement**. I am a practicing anesthesiologist physician-scientist with my main research interest in pharmacology and physiology of voltage-gated calcium channels. My PhD thesis mentor Dr. Edmund G. Anderson and post-doc mentors Dr. Christopher J. Lingle and Charles F. Zorumski have trained me in the fields of classic neuropharmacology, membrane biophysics and synaptic physiology, respectively. As a post-doc at Washington University in St. Louis,MO I have published two seminal papers in the fields of neuroscience introducing for the first time T-type channels to the field of pain research (***Neuron*, 2001, 31:75-85**) and deciphering cellular mechanisms of anesthesia with nitrous oxide (***Nature Medicine*, 1998, 4(4): 460-463**). I have also initiated at Washington University my fruitful collaboration with Dr. Douglas Covey who introduced me to the field of neuroactive steroids. I continued this line of research as an independent clinician-scientist at University of Virginia and more recently at UC Denver with my main research interest in pharmacology and physiology of voltage-gated calcium channels in cellular mechanisms of anesthesia and analgesia. My unique niche is that in my lab we use *in vitro* recordings from peripheral sensory neurons, spinal cord and brain as well as *in vivo* studies to decipher effects of anesthetics and analgesics at the cellular and system levels. I have maintained a funded NIH sponsored program since 2000 by obtaining Mentored Clinical Scientist K08 Award, two R21 grants and five R01 grants. *My most significant contribution to science has been discovering the role of T-type calcium channels in pain transmission*. I have seen this field develop from the culture dish and whole animals into a several clinical trials during recent years.

Calcium channels are of considerable interest to me as an anesthesiologist since these channels are targets for clinically used drugs widely used in human medicine like anesthetics, analgesics and antiepileptics. Understanding how these drugs affect neuronal circuitry in the brain is clearly relevant to anesthesiology but also to neurology, pediatrics, psychiatry, surgery and medicine. My long-term goal is to discover novel and safer pharmacological agents that can be used as analgesic, antiepileptics or anesthetic agents in human medicine. My short-term goal within the time frame of the present grant application is to learn how general anesthetics affect neuronal excitability in the thalamus in young rats. I am specifically interested in learning how new anesthetic molecules like neuroactive steroids affect function of thalamocortical circuitry. I believe that I am well qualified to lead research efforts as a Principal Investigator in this grant application as I am a practicing anesthesiologist and I have been involved with electrophysiological studies of ion channels and synaptic transmission for the last 20+ years as evidenced by my extensive publication record in this area of research. Some of the most relevant publications showing overall scope of my scientific work are as follow.

1. Todorovic,S.M. and Lingle, C.J. Pharmacological properties of T-type Ca2+ current in adult rat sensory neurons: Effects of anticonvulsant and anesthetic agents*.* ***J Neurophysiol*** 1998, 79:240-252 *This study established that different classes of general anesthetics, anticonvulsants and analgesics inhibit native CaV3.2 T-currents at clinically relevant concentrations.*
2. Todorovic, S.M., Jevtovic-Todorovic, V., Meyenburg, A., Mennerick, S., Perez-Reyes, E., Romano, C., Olney J.W. and Zorumski C.F. Redox modulation of T-type calcium channels in rat peripheral nociceptors. ***Neuron***2001, 31:75-85. This was *the first study that described the role of T-channels in nociception*.
3. Jacus MO, Uebele VN, Renger JJ and Todorovic SM. Presynaptic CaV3.2 channels regulate excitatory neurotransmission in nociceptive dorsal horn neurons. ***J Neurosci*** 2012, 32(27):9374-82. PMCID: PMC 3398424. *This study was first to establish the importance of CaV3.2 T-currents on excitatory synaptic transmission in nociceptive dorsal horn neurons. Recommended by Faculty 1000.*
4. Rose KE, Lunardi N, Boscolo A, Dong X, Erisir A, Jevtovic-Todorovic V, Todorovic SM. Immunohistological demonstration of CaV3.2 T-type voltage-gated calcium channel expression in soma of dorsal root ganglion neurons and peripheral axons of rat and mouse.***Neuroscience*** 2013, 250:263-274. *This is the first paper to demonstrate expression of CaV3.2 channels in peripheral nerves and nociceptive nerve endings using confocal and electron microscopy.*

**B. Positions and Employment:**

1980 – 1982 Demonstrator, Dept. of Medicinal Chemistry, Univ. of Belgrade, Serbia

1982 - 1983 Internship, General Hospital, Pancevo, Serbia

1983 - 1984 Physician, Military Service, Serbia

1984 - 1986 Resident, Dept. of Neurology, Univ. of Belgrade, Serbia

1986 - 1990 Teaching Assistant, Dept. of Pharmacology, Univ. of Illinois, Chicago, Illinois

1990 - 1991 Postdoctoral Research Assoc., Dept. of Pharmacology, Univ. of Illinois, Chicago, Illinois

1991 - 1992 Internship, Dept. of Internal Medicine, Northwestern Univ., Chicago, Illinois

1992 - 1993 Resident, Dept. of Neurology, Barnes Hospital, St. Louis, Missouri

1993 - 1996 Resident, Dept. of Anesthesiology, Barnes Hospital, St. Louis, Missouri

1996 - 2000 Instructor, Dept. of Anesthesiology, Washington Univ., St. Louis, Missouri

2000 - 2001 Assistant Professor on Tenure Track, Dept. of Anesthesiology, Washington Univ., St. Louis, MO

2001 - 2005 Associate Professor on Tenure Track, Dept. of Anesthesiology, UVA, Charlottesville, VA

2005- 2008 Associate Professor with Tenure, Dept. of Anesthesiology, UVA, Charlottesville, VA

2006- 2008 Associate Professor of Neuroscience, UVA, Charlottesville, VA

2008- 2015 Professor of Anesthesiology and Neuroscience, UVA, Charlottesville, VA

2016- present Professor with Tenure in the Department of Anesthesiology, University of Colorado School of Medicine, Anschutz Medical Campus, Aurora, CO

**Honors and Awards:**

1999 – 2001 The FAER/Abbott New Investigator Award, Foundation for Anesthesia Education and Research, The American Society of Anesthesiologists.

2000 – 2005 Research Career Development Award (K-08), NIH/NIDA, Mentor Charles F. Zorumski

2005-present Ad-hoc reviewer for DOD, VA, NIH CNNT and NIH SCS neuroscience study sections

2015- present Regular member of NTRC study section of NIH

**C. Contributions to Science**

1**.** After graduating from Medical School in Belgrade, SerbiaI came to the United States in 1986 to pursue a graduate program in Pharmacology at the University of Illinois in Chicago. There, under the guidance of my advisor and chairman of Pharmacology, Edmund G. Anderson, Ph.D., I developed an isolated dorsal root ganglion (DRG) preparation as a model to study the pharmacology of serotonin receptors in rat sensory neurons. I became proficient at techniques used in the electrophysiology laboratory, such as current-clamp intracellular recording with a sharp electrode *in-vitro*. My thesis work in Dr. Anderson’s laboratory has been presented in 5 major publications and several abstracts. This work introduced me to the field of **neuropharmacology** and pain processing and established a foundation for the future preclinical studies of the role of different subtypes of serotonin receptors in pain processing.

1. Todorovic, S.M. and Anderson, E.G. 5-HT2 and 5-HT3 receptors mediate two distinct depolarizing responses in rat dorsal root ganglion neurons. ***Brain Res*** 1990, 511:71-79
2. Todorovic, S.M. and Anderson, E.G. Pharmacological characterization of 5-HT2 and 5-HT3 receptors in rat DRG neurons. ***J Pharm Exp Ther*** 1990, 254:109-115
3. Todorovic, S.M. and Anderson, E.G. Serotonin preferentially hyperpolarizes capsaicin-sensitive C-type sensory neurons by activating 5-HT1A receptors. ***Brain Res*** 1992, 585:212-218.
4. Todorovic, S.M., Scroggs,R.S. and Anderson, E.G. Cationic modulation of 5-HT2 and 5-HT3 receptors in rat sensory neurons: The role of K+, Ca2+ and Mg2*+.* ***Brain Res*** 1997, 765:291-300

2. Upon completing graduate school, I did a one-year medicine internship at Northwestern University Medical School in Chicago, then moved to Washington University Medical School (WUMS) in Saint Louis to do one year of residency in Neurology and 3 years of residency in Anesthesiology. As a resident, I developed a strong interest in two major areas of neuroscience research: **the molecular and cellular mechanisms of anesthesia and analgesia**. WUMS was a good place to be for a physician-scientist embarking on an academic career and having such research interests. I had design studies dealing with the mechanisms of action of common general anesthetics including isoflurane and nitrous oxide (laughing gas, N2O). These findings greatly contributed to a better understanding of this frequently used anesthetic, analgesic, and drug of abuse. I served as the primary investigator or co-investigator on all of these studies.

1. Jevtovic-Todorovic,V., Todorovic, S.M., Mennerick,S., Powell,S., Dikranian,K., Benshoff, N., Zorumski,C.F. and Olney, J.W. Nitrous oxide (laughing gas) is an NMDA antagonist, neuroprotectant and neurotoxin*.* ***Nature Medicine*** 1998, 4(4): 460-463. *This article was first describing NMDA receptors as molecular targets for nitrous oxide anesthesia and neurotoxicity. The study was widely publicized in scientific literature.*
2. Todorovic, S.M., Jevtovic-Todorovic, V., Mennerick, S., Perez-Reyes, E. and Zorumski, C.F. Cav3.2 channel is a molecular substrate for inhibition of T-type calcium currents in rat sensory neurons by nitrous oxide.***Mol Pharmacol*** 2001, 60: 603-610
3. Joksovic PM, Weiergraber M, Lee WY, Struck H, Schneider T and Todorovic SM. Isoflurane-sensitive presynaptic R-type calcium channels contribute to inhibitory synaptic transmission in the rat thalamus. ***J Neurosci*** 2009, 29(5):1434-1445. PMCID: PMC2659547.
4. DiGruccio MR, Joksimovic S, Joksovic PM, Lunardi N, Salajegheh R, Jevtovic-Todorovic V, Beenhakker M, Goodkin HP, Todorovic SM. Hyperexcitability of thalamocortical networks after exposure to general anesthesia during brain development. ***J Neurosci*** 2015, 35(4):1481-92. PMCID: PMC4308595

3. In 2001 my wife, Vesna Jevtovic-Todorovic, MD, PhD, MBA and I were recruited to the Department of Anesthesiology at the University of Virginia (UVA) School of Medicine. There, as an Associate Professor in Anesthesiology and physician-scientist, I started my own independent research career. This was an exciting time, since UVA has an excellent Neuroscience Graduate Program that encompasses more than 70 laboratories and prominent scientists in the field of ion channels. I have continued my exciting research on the role of **redox modulation of Cav3.2 channels in nociception** that I initiated with my seminal paper (*Neuron*, 2001). My studies have firmly established the pro-nociceptive role of Cav3.2 channels and currently several pharmaceutical companies are sponsoring clinical phase 2 trials of the role of T-channel blockers in treating pain disorders. I served as the primary investigator an all of these studies.

1. Nelson M.T., Joksovic P.M., Perez-Reyes E. and Todorovic S.M. The endogenous redox agent L-cysteine induces T-type Ca2+ channel-dependent sensitization of a novel subpopulation of rat peripheral nociceptors. ***J Neurosci*** 2005, 25(38):8766-75. *This article was highlighted among other articles published in this issue.*
2. Nelson MT, Woo J, Kang H-W, Barrett PQ, Vitko J, Perez-Reyes E, Lee J-H, Shin H-S, and Todorovic SM. Reducing agents sensitize C-type nociceptors by relieving high-affinity zinc inhibition of T-type calcium channels. ***J Neurosci*** 2007, 27(31):8250–8260
3. Lee WY, Orestes P, Latham J, Naik AK, Nelson MT, Vitko I, Perez-Reyes E, Jevtovic-Todorovic V and Todorovic SM. Molecular mechanisms of lipoic acid modulation of T-type calcium channels in pain pathway. ***J Neurosci*** 2009, 29(30):9500-9509. PMCID: PMC3073510.
4. Nelson MT, Joksovic PM, Su, P, Kang H-W, Van Deusen A, Baumgart JP, David LS, Snutch TP,Barrett PQ, Zorumski CF, Lee J-H, Perez-Reyes E, and Todorovic SM. Molecular mechanisms of subtype-specific inhibition of neuronal T-type calcium channels by ascorbate. ***J Neurosci***2007, 14;27(46):12577-83. *Highlighted in Science, Editor’s choice: N. R. Gough, Vitamin C as Neuronal Modulator.* Sci. STKE***2007****, tw424 (2007).*

4. I also initiated at University of Virginia the studies to investigate the role of plasticity of CaV3.2 channels in pain pathways in animal models of Type 1 and Type 2 **painful diabetic neuropathy**. Our studies have firmly established that up-regulation of CaV3.2 channels in pain pathway contribute to the painful symptoms of peripheral diabetic neuropathy. This is important since all currently available therapies for painful diabetic neuropathy are either inconsistently effective or associated with serious side effects. Hence, T-channel inhibitors and modulators may be new therapies for this difficult to teat medical condition. I served as the primary investigator or co-investigator on all of these studies.

a. Jagodic MM, Pathirathna S, Nelson MT, Mancuso S, Joksovic PM, Rosenberg ER, Bayliss DA, JevtovicTodorovic V and Todorovic SM. Cell-specific alterations of T-type calcium current in painful diabetic neuropathy enhance excitability of sensory neurons.***J Neurosci*** 2007, 27(12):3305-3316.

b. Messinger RB, Naik AK, Jagodic MM, Nelson MT, Lee WY, Choe WJ, Orestes P, Latham, JR, Todorovic SM and Jevtovic-Todorovic V. In-vivo silencing of the Cav3.2 T-type calcium channels in sensory neurons alleviates hyperalgesia in rats with streptozocin-induced diabetic neuropathy. ***Pain*** 2009, 145(1-2):184-195. PMCID: PMC2735619

c. Latham JR, Pathirathna S, Jagodic MM, Choe WJ, Levin ME, Nelson MT, Yong Lee W, Krishnan K, Covey DF, Todorovic SM, Jevtovic-Todorovic V. Selective T-type calcium channel blockade alleviates hyperalgesia in ob/ob mice. ***Diabetes*** 2009, 58(11):2656-65. PMCID: PMC2768156

d. Orestes P, Osuru HP, McIntire WE, Jacus MO, Salajegheh R, Jagodic MM, Choe W, Lee J, Lee SS, Rose KE, Poiro N, Digruccio MR, Krishnan K, Covey DF, Lee JH, Barrett PQ, Jevtovic-Todorovic V, Todorovic SM. Reversal of neuropathic pain by targeting glycosylation of CaV3.2 T-type calcium channels. ***Diabetes*** 2013, 62:3828-3838. PMCID: PMC3806612. *This article was accompanied with commentary: “Location, location, location: Is the pain of diabetic neuropathy generated by hyperactive sensory neurons?” Nigel A. Calcutt, Diabetes, 62:3658-3660.*

5. In addition to the contributions described above, years of formal collaboration with Dr. Vesna Jevtovic-Todorovic, Dr. Lingle, Dr. Zorumski and Dr. Douglas F. Covey at Washington University and University of Virginia resulted in several publications on **neuroactive steroids** as novel blockers of T-type calcium channels and cellular mechanisms of analgesia in both acute pain and chronic neuropathic pain resulting from the sciatic nerve injury. I served as the primary investigator or co-investigator on all of these studies.

1. Todorovic, S.M., Prakriya, M., Nakashima, Y.M., Nillson, K.R., Han,M., Zorumski,C.F., Covey,D.F. and Lingle, C.J. Enantioselective blockade of T-type Ca2+ current in adult rat sensory neurons by a steroid that lacks GABA-modulatory activity. ***Mol Pharmacol*** 1998, 54:918-927
2. Todorovic, S.M., Pathirathna, S., Brimelow, B.C., M.M. Jagodic, S-H, Ko, Jiang, X., Nilsson, K.R., Mennerick, S., Zorumski, C.F., Covey, D.F. and Jevtovic-Todorovic, V. 5-reduced neuroactive steroids are novel voltage-dependent blockers of T-type Ca2+ channels in rat sensory neurons *in vitro* and potent peripheral analgesics *in vivo.* ***Mol Pharmacol***2004, 66(5): 1223-1235
3. Pathirathna S, Todorovic SM, Covey DF and Jevtovic-Todorovic,V. Novel 5-reduced neuroactive steroids induce peripheral thermal anti-nociception in rats with neuropathic pain. ***Pain*** 2005, 117(3): 326-339
4. Ayoola C, Hwang SM, Hong SJ, Rose KE, Boyd C, Bozic N, Park JY, Osuru HP, DiGruccio MR, Covey DF, Jevtovic-Todorovic V, Todorovic SM. Inhibition of CaV3.2 T-type calcium channels in peripheral sensory neurons contributes to analgesic properties of epipregnanolone. ***Psychopharmacology*** *(****Berl)*** 2014, 231(17):3503-15.

Complete List of Published Work in My Bibliography:

**http://www.ncbi.nlm.nih.gov/pubmed/?term=todorovic+sm**

**D. Research Support:**

ONGOING

**1R01 GM102525-01A1 Todorovic SM (PI)** 01/01/2014-11/30/2018 (NCE period)

NIH/NIGMS

“Effects of anesthetics on thalamic signaling”

The main goal of this project is to study plasticity of thalamic neurons after exposure of young rats to general anesthesia.

**1R01 NS091353-01A1 Todorovic SM, Jevtovic-Todorovic V (MPI)** 06/01/2016-05/31/2021

NIH/NINDS

 “Molecular mechanisms of glycosylation of Cav3.2 channels in pain pathway”

The main goal of this project is to study plasticity of sensory neurons using animal models of Type 1 and Type 2 painful diabetic neuropathy.

 **R01 GM118197-10: Jevtovic-Todorovic V (PI)** 03/01/2005-12/31/2019

 NIH/NICHD

 “Anesthesia-Induced Developmental Neurotoxicity”.

The main goal of this project is to study the mechanism of anesthesia-induced neurotoxicity in the developing brain of several mammalian species.

Role: Todorovic SM (Co-Investigator), since 12/2010

 **R01 GM1237476-01: Todorovic SM, Jevtovic-Todorovic V (MPI)** 09/01/2017-05/31/2021

 NIH/NIGMS

 “Novel neurosteroid anesthetics and perioperative analgesia”.

The main goal of this project is to study the mechanism of analgesia in perioperative period using novel neurosteroids that target voltage-gated calcium channels.

COMPLETED

**R21 DA-034448-01A1: Todorovic, SM (PI)** 04/01/2013-06/30/2015

NIH/NIDA

**“**The role of trace metals and T-channels in pain”

This grant will study the role of selective modulation of T-type voltage-gated calcium channels and their role in enhanced excitability of neurons in pain pathways.

 **March of Dimes National Award: Jevtovic-Todorovic, V (PI)** 06/01/2014-05/31/2017

 March of Dimes Foundation, Todorovic, SM (Co-Investigator)

 “Anesthesia-induced risks of cognitive impairment during early stages of development: mechanism and prevention”.

 The main goal is to investigate the role of mitochondrial protector, PPX in prevention of anesthesia-induced cognitive development.

 **R21 HD080281-01A1: Jevtovic-Todorovic, V (PI)** 04/01/2015-03/31/2017

 NIH/NICHD Todorovic, SM (Co-Investigator)

 “Anesthesia impairs developmental axon pruning and functional neuronal networks”

This proposal examines the effects of an early exposure to general anesthesia on the developing hippocampus structures.