BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: WATTERS, JYOTI

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

POSITION TITLE: Professor

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)	END DATE MM/YYYY	FIELD OF STUDY
University of Arizona, Tucson, AZ	BS	05/1990	Microbiology/Immunology
University of Washington, Seattle, WA	PHD	07/1997	Pharmacology
University of Wisconsin-Madison, Madison, WI	Postdoctoral Fellow	07/2001	With Prof. Jack Gorski, Biochemistry
University of Wisconsin-Madison, Madison, WI	Postdoctoral Fellow	04/2002	With Prof. Paul Bertics, Biomolecular Chemistry

A. Personal Statement

The overall goal of my research program is to investigate the cellular and molecular mechanisms regulating microglial phenotype and function as they contribute to neural pathology and recovery in chronic neuroinflammatory disorders. We have particular interest in understanding how microglial reprogramming during fetal development impacts CNS development and function later in life. Our observations of behavioral deficits in male offspring of mothers exposed to a model of gestational sleep disordered breathing, and the neuronal spine and network studies currently underway are the first of their kind in this model, and accordingly, they have immense clinical significance with the growing incidence of mothers with sleep disordered breathing during pregnancy and the negative outcomes on their offspring during development. My research expertise involves the study of signal transduction and gene transcriptional mechanisms in microglia. I have a broad background in neuroimmunology and pharmacology with specific training and expertise in kinase signaling mechanisms and regulation of gene transcription by innate immune receptors (purinergic and TLR4). Our recent evidence implicates a critical role for epigenetic processes (e.g. histone demethylation and microRNAs) in the mechanisms employed by maternal sleep disordered breathing on microglial reprogramming during fetal development. We also utilize RNA-Seq, ChIP-Seq and 10X Genomics approaches to study the mechanisms whereby microglia contribute to sexual dimorphisms in neurobehavioral outcomes and the roles they play in neuronal spine morphology and subsequent neuroplasticity in different CNS regions. We have developed powerful and novel flow cytometry and cell sorting tools with which to study specific microglial phenotypic populations *in vivo*, from which nucleic acids (DNA, mRNA and miRNAs) can be isolated for subsequent transcriptional regulation studies and Next-Gen sequencing approaches. These investigations are complemented by biochemical signaling studies in primary cultures, electrophysiological approaches to assess neuroplasticity *in situ*, and rodent behavioral assays to test cognitive function. I actively train graduate, post-doctoral and undergraduate students, and I teach both professional veterinary medicine and graduate level courses. I also serve on the mentoring committees of junior faculty, for several of whom I am an official mentor on NIH pathway to independence awards.

1. Kiernan EA, Wang T, Vanderplow AM, Cherukuri S, Cahill ME, Watters, JJ Neonatal Intermittent Hypoxia Induces Lasting Sex-Specific Augmentation of Rat Microglial Cytokine Expression. Front. Immunol. 2019 Jul; 10:1479. PubMed PMID: 31333645; PubMed Central PMCID: PMC6615134.

2. Johnson SM, Randhawa KS, Epstein JJ, Gustafson E, Hocker AD, Huxtable AG, Baker TL, Watters JJ. Gestational intermittent hypoxia increases susceptibility to neuroinflammation and alters respiratory motor control in neonatal rats. Respir Physiol Neurobiol. 2017 Nov 22;PubMed PMID: 29174411.

3. Dougherty BJ, Kopp ES, Watters JJ. Nongenomic Actions of 17-β Estradiol Restore Respiratory Neuroplasticity in Young Ovariectomized Female Rats. J Neurosci. 2017 Jul 12;37(28):6648-6660. PubMed PMID: 28592693; PubMed Central PMCID: PMC5508255.
4. Smith SM, Kimyon RS, Watters JJ. Cell-type-specific Jumonji histone demethylase gene expression in the healthy rat CNS: detection by a novel flow cytometry method. ASN Neuro. 2014 May 27;6(3):193-207. PubMed PMID: 24735454; PubMed Central PMCID: PMC4034710.

B. Positions and Honors

Positions and Employment

1990 - 1992	Research Technologist, University of Washington, Seattle, WA
1992 - 1997	Graduate Student with Prof. Daniel Dorsa, University of Washington, Seattle, WA
1998 - 2001	Postdoctoral Fellow with Prof. Jack Gorski, University of Wisconsin, Madison, WI
1999 - 2002	Postdoctoral Fellow with Prof. Paul Bertics, University of Wisconsin-Madison, Madison, WI
2002 - 2009	Assistant Professor, University of Wisconsin-Madison, Madison, WI
2009 - 2016	Associate Professor, University of Wisconsin-Madison, Madison, WI
2016 -	Professor, University of Wisconsin-Madison, Madison, WI
2019 -	Associate Chair, Faculty Development, Department of Comparative Biosciences

Other Experience and Professional Memberships

1993 -	Member, American Society for the Advancement of Science
1994 -	Member, Society for Neuroscience
1998 -	Member, Endocrine Society
2002 -	Member, Women in Neuroscience
2005 -	Member, American Society for Neurochemistry
2012 -	Member, American Physiological Society
2014 -	Member, Wisconsin American Veterinary Medical Association

Honors

1990	B.S. Cum Laude With Honors, University of Arizona
1993 - 1996	NIH Pre-doctoral Trainee, University of Washington
1999	Young Investigator Travel Award, Endocrine Society
1999 - 2001	NIH NRSA Recipient, National Cancer Institutes
2002	New Investigator Travel Award, Endocrine Society
2002	New Investigator Travel Award, Women in Endocrinology
2003	New Investigator Travel Award, Society for Women's Health Research
2006	Inaugurated Member, International Biography Center, Cambridge, England
2008	Inaugurated Member, Honors Edition, Who's Who Among Executives and Professionals
2014	Vilas Early-Mid Career Investigator Award, University of Wisconsin-Madison
2015	Vilas Life Cycle Award, University of Wisconsin-Madison

C. Contribution to Science

1. Mechanisms of microglial activation by intermittent hypoxia (IH), a highly clinically relevant disorder to multiple neurodegenerative, traumatic and genetic neural diseases, is a major area of research accomplishment. We have shown that microglia contribute early on to neuroinflammation in IH disease pathology, but they change their activities later, away from being pro-inflammatory towards a more neurosupportive role that involves epigenetic changes in their activities, involving alterations in miRNA expression and histone modifications. We also find that their early pro-inflammatory activities (after only a single night of IH) interferes with the expression of an important form of neural plasticity in the respiratory motor control system.

a. Kiernan EA, Wang T, Vanderplow AM, Cherukuri S, Cahill ME, Watters, JJ Neonatal Intermittent Hypoxia Induces Lasting Sex-Specific Augmentation of Rat Microglial Cytokine Expression. Front. Immunol. 2019 Jul; 10:1479. PubMed PMID: 31333645; PubMed Central PMCID: PMC6615134.

b. Johnson SM, Randhawa KS, Epstein JJ, Gustafson E, Hocker AD, Huxtable AG, Baker TL, Watters JJ. Gestational intermittent hypoxia increases susceptibility to neuroinflammation and alters respiratory motor control in neonatal rats. Respir Physiol Neurobiol. 2018 Oct; 256:128-142. PubMed PMID: 29174411; PubMed Central PMCID: PMC5963968.

c. Kiernan EA, Smith SM, Mitchell GS, Watters JJ. Mechanisms of microglial activation in models of inflammation and hypoxia: Implications for chronic intermittent hypoxia. J Physiol. 2016 Mar 15;594(6):1563-77. PubMed PMID: 26890698; PubMed Central PMCID: PMC4799985.

d. Huxtable AG, Smith SM, Peterson TJ, Watters JJ, Mitchell GS. Intermittent Hypoxia-Induced Spinal Inflammation Impairs Respiratory Motor Plasticity by a Spinal p38 MAP Kinase-Dependent Mechanism. J Neurosci. 2015 Apr 29;35(17):6871-80. PubMed PMID: 25926462; PubMed Central PMCID: PMC4412901.

2. Another area of accomplishment is studying signal transduction mechanisms in microglia, with a focus on mechanisms of purinergic P2X receptor- and Toll-like receptor 4-mediated regulation of gene transcription.

a. Curet MA, Watters JJ. P2Y14 receptor activation decreases interleukin-6 production and glioma GL261 cell proliferation in microglial transwell cultures. J Neurooncol. 2018 Mar;137(1):23-31. PubMed PMID: 29189936; PubMed Central PMCID: PMC5823742.

b. Crain JM, Watters JJ. Microglial P2 Purinergic Receptor and Immunomodulatory Gene Transcripts Vary By Region, Sex, and Age in the Healthy Mouse CNS. Transcr Open Access. 2015 Dec;3(2)PubMed PMID: 26949719; PubMed Central PMCID: PMC4777314.

c. Smith SM, Mitchell GS, Friedle SA, Sibigtroth CM, Vinit S, Watters JJ. Hypoxia Attenuates Purinergic P2X Receptor-Induced Inflammatory Gene Expression in Brainstem Microglia. Hypoxia (Auckl). 2013 Aug 6;2013(1)PubMed PMID: 24377098; PubMed Central PMCID: PMC3873144.

d. Smith SM, Friedle SA, Watters JJ. Chronic intermittent hypoxia exerts CNS region-specific effects on rat microglial inflammatory and TLR4 gene expression. PLoS One. 2013;8(12):e81584. PubMed PMID: 24324707; PubMed Central PMCID: PMC3852519.

3. A major research focus over the last several years has been to develop experimental methodologies to better enable studies of microglia in vivo. Immunohistochemical and morphologic assessments are not sufficient for many of the experimental questions we ask. Thus, we have developed powerful and novel flow cytometry and immunomagnetic cell sorting tools with which to study specific microglial phenotypic populations in vivo, from which nucleic acids (DNA, mRNA and non-coding long and miRNAs) can be isolated for subsequent epigenetic and transcriptional gene regulation studies. The latter can be done efficiently from cells that have been fixed and permeabilized, representing a major advance in the field.

a. Smith SM, Kimyon RS, Watters JJ. Cell-type-specific Jumonji histone demethylase gene expression in the healthy rat CNS: detection by a novel flow cytometry method. ASN Neuro. 2014 May 27;6(3):193-207. PubMed PMID: 24735454; PubMed Central PMCID: PMC4034710.

b. Nikodemova M, Watters JJ. Efficient isolation of live microglia with preserved phenotypes from adult mouse brain. J Neuroinflammation. 2012 Jun 28;9:147. PubMed PMID: 22742584; PubMed Central PMCID: PMC3418565.

c. Nikodemova M, Watters JJ. Outbred ICR/CD1 mice display more severe neuroinflammation mediated by microglial TLR4/CD14 activation than inbred C57Bl/6 mice. Neuroscience. 2011 Sep 8;190:67-74. PubMed PMID: 21683771; PubMed Central PMCID: PMC3156380.

d. Crain JM, Nikodemova M, Watters JJ. Expression of P2 nucleotide receptors varies with age and sex in murine brain microglia. J Neuroinflammation. 2009 Aug 25;6:24. PubMed PMID: 19706184; PubMed Central PMCID: PMC2744668.

4. Understanding heterogeneic function of microglial populations both in the healthy and injured, adult and developing/aging brain has also been a long-standing focus of our research. The role of estrogen receptor

signaling, and mechanisms involved in the control of microglial numbers and function during development is of primary interest. Recently, our observation that optogenetic patterns of blue light could control inflammatory gene expression in non-transgenic microglia has led to the idea that optogenetics, in the absence of exogenously expressed rhodopsins, may be used therapeutically (patent pending).

a. Cheng KP, Kiernan EA, Eliceiri KW, Williams JC, Watters JJ. Blue Light Modulates Murine Microglial Gene Expression in the Absence of Optogenetic Protein Expression. Sci Rep. 2016 Feb 17;6:21172. PubMed PMID: 26883795; PubMed Central PMCID: PMC4756664.
b. Nikodemova M, Kimyon RS, De I, Small AL, Collier LS, Watters JJ. Microglial numbers attain adult levels after undergoing a rapid decrease in cell number in the third postnatal week. J Neuroimmunol. 2015 Jan 15;278:280-8. PubMed PMID: 25468773; PubMed Central PMCID: PMC4297717.
c. De I, Nikodemova M, Steffen MD, Sokn E, Maklakova VI, Watters JJ, Collier LS. CSF1 overexpression has pleiotropic effects on microglia in vivo. Glia. 2014 Dec;62(12):1955-67. PubMed PMID: 25042473; PubMed Central PMCID: PMC4205273.
d. Nikodemova M, Small AL, Smith SM, Mitchell GS, Watters JJ. Spinal but not cortical microglia acquire an atypical phenotype with high VEGF, galectin-3 and osteopontin, and blunted inflammatory responses in ALS rats. Neurobiol Dis. 2014 Sep;69:43-53. PubMed PMID: 24269728; PubMed Central PMCID: PMC4079765.

5. Another area of research accomplishment has been in the field of non-genomic estrogen receptor signaling. Our work was the first to demonstrate the presence of membrane estrogen-receptors in CNS cells, and that their activation could promote the transcription of genes lacking canonical estrogen-response elements.

a. Dougherty BJ, Kopp ES, Watters JJ. Nongenomic Actions of 17-β Estradiol Restore Respiratory Neuroplasticity in Young Ovariectomized Female Rats. J Neurosci. 2017 Jul 12;37(28):6648-6660. PubMed PMID: 28592693; PubMed Central PMCID: PMC5508255.
b. Watters JJ, Chun TY, Kim YN, Bertics PJ, Gorski J. Estrogen modulation of prolactin gene expression requires an intact mitogen-activated protein kinase signal transduction pathway in cultured rat pituitary cells. Mol Endocrinol. 2000 Nov;14(11):1872-81. PubMed PMID: 11075818.
c. Watters JJ, Dorsa DM. Transcriptional effects of estrogen on neuronal neurotensin gene expression involve cAMP/protein kinase A-dependent signaling mechanisms. J Neurosci. 1998 Sep 1;18(17):6672-80. PubMed PMID: 9712639.
d. Watters JJ, Campbell JS, Cunningham MJ, Krebs EG, Dorsa DM. Rapid membrane effects of steroids in neuroblastoma cells: effects of estrogen on mitogen activated protein kinase signalling cascade and c-fos immediate early gene transcription. Endocrinology. 1997 Sep;138(9):4030-3. PubMed PMID: 9275096.

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

Ongoing Research Support

R01 NS085226, National Institutes of Health, NINDS
WATTERS,JYOTI (PI) 07/01/2015-06/30/2020
Regulation of microglial plasticity by TLR4 and microRNAs
The major goal of this project is to investigate the mechanisms whereby TLR4-dependent miRNAs regulate transition of microglial phenotype from pro-inflammatory to reparative in a chronic neuroinflammatory disorder (chronic intermittent hypoxia).
Role: PI

NIH R01HL141249 (Subaward PI: WATTERS,JYOTI J) 04/01/2018 – 03/31/2023
THE UNIVERSITY OF OREGON
Title: Neonatal inflammation impairs control of breathing
Role: Co-Investigator (Huxtable PI)

Major Goals: The major goal of this project is to dissect the cellular mechanisms whereby acute pathogen-induced inflammation early in postnatal life impairs adult respiratory neuroplasticity. Alterations in the spinal microglial transcriptome in adults previously exposed to early neonatal inflammation will be assessed.

UW2020 (MPIs: BAKER, TRACY L and WATTERS, JYOTI J) 05/01/2018 – 04/30/2020
UW-MADISON PILOT FUNDING
Title: Maternal Breathing Dysfunction During
Pregnancy Increases Risk for Psychiatric Disorders
in Her Offspring: A Paradigm-Shifting Concept
Role: Multi-Principal Investigator
Major goals: The goals of this project are to identify underlying molecular and cellular mechanisms of cognitive impairment in juvenile and adult offspring of mothers with sleep disordered breathing during pregnancy. Epigenetic-regulated reductions in microglial phagocytosis and disrupted synaptic pruning will be investigated.

NIH R01HL142752 (MPIs: WATTERS,JYOTI J and BAKER,TRACY L)
DHHS, PHS, NATIONAL INSTITUTES OF HEALTH 11/01/2018 – 10/31/2023
Title: Fetal reprogramming by gestational intermittent hypoxia
impairs respiratory neuromotor control in adult offspring
Role: Principal Investigator
Major goals: The major goals of this project are to identify underlying molecular and cellular mechanisms that impair respiratory neuroplasticity in adult offspring of mothers with sleep disordered breathing during pregnancy. The role of epigenetic alterations in skewing spinal microglial activities to the chronically inflammatory state, and testing various treatment options to reverse the effects of the fetal reprogramming in adults will be investigated.

NIH R01EY029809 (Subaward PI: WATTERS,JYOTI J) 04/01/2019 – 03/31/2023
THE OHIO STATE UNIVERSITY
Title: Master epigenetic regulators and retinal degenerative disease
Role: Co-Investigator (Guo, PI)
Major Goals: The major goal of this project is to understand how BET proteins function in microglial activation and retinal degeneration in a mouse model of degenerative retinopathy. Various members of this family of proteins will be manipulated in vivo and in vitro in order to understand their contributions to retinal disease, and identify whether their pharmacologic targeting will be therapeutically

OVERLAP NONE