BIOGRAPHICAL SKETCH

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NAME: William M. Armstead, Ph.D.

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

POSITION TITLE: Research 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)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Pennsylvania, Philadelphia, PA	B.A.	O5/79	Biochemistry
Tulane University, New Orleans, LA	M.S.	05/83	Pharmacology
Tulane University, New Orleans, LA	Ph.D.	05/85	Pharmacology
Tulane University, New Orleans, LA	Post-Doc	05/86	Pharmacology
University of Tennessee, Memphis, TN	Post-Doc	05/88	Physiology

A. Personal Statement

My expertise and research interests are in the control of the cerebral circulation in physiologic and pathologic conditions, such as stroke and traumatic brain injury. I have taken a bidirectional approach wherein the clinical observations have informed the study design of basic science animal work, yielding data which influence and optimize better therapeutic interventions in CNS pathology; a bedside to bench and back again study.

B. Positions and Honors

Positions and Employment

1988-1990 Instructor, Dept of Physiology and Biophysics, University of Tennessee, Memphis, TN
1990-1992 Assistant Professor, Dept of Physiology and Biophysics, U of Tennessee, Memphis, TN
1992-1999 Assistant Professor, Depts of Anesthesia and Pharmacology, U of Pennsylvania; Department of Anesthesiology & Critical Care Medicine, The Children's Hospital of Philadelphia
1999-2009 Research Associate Professor, Depts of Anesthesia and Pharmacology, U of Pennsylvania
2009-present Research Professor, Depts of Anesthesiology and Critical Care, Pharmacology, U of Penn
2014-present Research Professor, Dept of Systems Pharmacology and Translational Therapeutics,U of Penn

Other Experience and Professional Memberships

1992- Member, American Physiological Society
1992- Member, American Society of Pharmacology and Experimental Therapeutics
1992- Member, Neurotrauma Society
1992- Member, Int. Society of Cerebral Blood Flow and Metabolism
1998-2010 Editorial Board, Microcirculation
2001-2005 Chartered Member, AHA National Brain 2 Study Section
2002-2013 Executive Board, ASPET Cardiovascular Division
2002-2010 Member, ASPET CV Division Student/Post Doc Best Abstract Award Committee
2006-2012 Editorial Board, American Journal of Physiology: Heart and Circulatory Physiology
2007-2011 Chartered Member, Veterans Administration Neurobiology C Study Section
2008-2009 Ad Hoc Member, NIH ANIE Study Section

2008-2009 Member, AHA Region II Brain Study Section
2009-2011 Member, AHA Region I Brain Study Section
2010-2013 Chair, Experimental Methods Section, AHA/ASA Int. Stroke Conf Planning Committee
2012-2014 Co-Chair, AHA Brain 1 Study Section
2014- Member, Board of Directors Soc for Neuroscience in Anesthesiology and Critical Care
2014- Chair, Research Committee Soc for Neuroscience in Anesthesiology and Critical Care
2014-2016 Chair, AHA Brain 1 Study Section
2016-2016 Member, Study section, Neuron, Network for European Funding for Neuroscience Research: External Insults to the nervous system. Madrid
2017-2017 Member, NINDS Special Emphasis Panel ZNS1 SRB-M (02)
2017-2017 Member, JPC-6/ CCCRP PTCRA Combat Casualty Care and TBI panel
2018-2018 Member, ZRG1 ETTN-C(10) Small Business: Clinical Neurophysiology, Devices panel

Honors

1979 Phi Lambda Upsilon
1987 Sigma Xi
1994 Established Investigator Award of AHA
2003 Fellow, Cardiovascular Section of the American Physiological Society
2003 Fellow, Stroke Council of the AHA

C. Contribution to Science

Pubmed link: https://www.ncbi.nlm.nih.gov/pubmed?otool=upennlib&db=PubMed&term=armstead+W
215 publications

1. Establishment of the pig as a more human-like model of TBI and stroke to study the role of the neurovascular unit in outcome post insult.

Although several rodent models of TBI have been described, all have the disadvantage of not permitting repeated measurements of systemic physiological variables and regional cerebral blood flow (CBF) because of the small size of the subjects. Additionally, rodents have a lissencephalic brain containing more grey than white matter. In contrast, pigs have a gyrencepahalic brain that contains substantial white matter similar to humans, which is more sensitive to ischemic damage than grey matter. A number of neuroprotectants identified in preclinical rodent stroke and TBI studies have yielded disappointing results when entered into clinical trials. We speculate that the reason for failure may rest on these drugs being primarily grey matter protective owing to the greater amount of grey compared to white matter in the rodent. I am acknowledged as an expert in the study of cerebral hemodynamics in the pig and, in the context of the neurovascular unit, how changes in cerebral autoregulation and cerebral hemodynamics dynamically modulate neuronal cell integrity to contribute to ultimate outcome after stroke and TBI. In our clinical studies, impairment of autoregulation following TBI appears linked to Glasgow Coma Scale (GCS), with greater autoregulatory impairment associated with worse GCS. From a basic science standpoint, investigation of neuronal cell integrity in hippocampal areas CA1 and CA3 can serve as a surrogate for GCS.

a. Bohman LE, Riley J, Milovanova TN, Sanborn MR, Thom SR, Armstead WM. Microparticles impair hypotensive cerebrovasodilation and cause hippocampal neuronal cell injury after traumatic brain injury. J Neurotrauma 33: 169-174, 2016. PMCID: PMC4722602
b. Armstead WM, Riley J, Yarovoi S, Cines DB, Smith DH, Higazi AAR. tPA-S481A prevents neurotoxicity of endogenous tPA in traumatic brain injury. J Neurotrauma 29: 1794-1802, 2012. PMCID: PMC3360893
c. Armstead WM, Ganguly K, Kiessling JW, Chen XH, Smith DH, Higazi AAR, Cines DB, Bdeir K, Zaitsev S, Muzykantov VR. RBC-coupled tPA prevents impairment of cerebral vasodilatory responses and tissue injury in pediatric cerebral hypoxia/ischemia through inhibition of ERK MAPK. J Cereb Blood Flow Metab, 29: 1463-1474, 2009. PMCID: PMC2719676
d. Armstead WM, T Nassar, S Akkawi, DH Smith, XH Chen, DB Cines, and AAR Higazi. Neutralizing the neurotoxic effects of exogenous and endogenous tPA. Nature Neuroscience 9: 1150-1155, 2006.

2. Bidirectional Translational Research. **Role of age and sex in outcome after TBI.**

Clinical and preclinical studies are typically carried out separately with little contemporaneous cross talk. Over the last 10 years, I have collaborated and co-authored 22 studies with Dr. Monica Vavilala (UW, Seattle). Clinically, Dr. Vavilala has observed that after TBI, the younger and male have worse outcomes than the older and female patients. These clinical studies have informed our basic science studies where we have made similar observations in pigs. Use of a pig model allows us to conduct mechanistically driven studies, many of which are ethically constrained in deployment in the human. However, results derived from the piglet studies can inform and improve therapeutic approach in brain injured children. Our approach therefore is one of bedside to bench and back again. The Armstead/Vavilala team is uniquely positioned to seamlessly investigate pig and human TBI in parallel pre-clinical and clinical studies.

a. Armstead WM, Riley J, Vavilala MS. Sex and age differences in epinephrine mechanisms and outcomes after brain injury. J Neurotrauma 34: 1666-1675, 2017. PMCID: PMC5397223
b. Armstead WM, Riley J, Vavilala MS. K channel impairment determines sex and age differences in epinephrine-mediated outcomes after brain injury. J Neurosci Res 95:1917-1926, 2017.PMCID: PMC5561463
c. Curvello V, Hekierski H, Riley J, Vavilala M, Armstead WM. Sex and age differences in phenylephrine mechanisms and outcomes after piglet brain injury. Ped Res 82: 108-113, 2017. PMCID: PMC5509507
d. Curvello V, Hekierski H, Pastor P, Vavilala M, Armstead, WM. Dopamine protects cerebral autoregulation and prevents hippocampal necrosis after traumatic brain injury via block of ERK MAPK in juvenile pigs. Brain Res 1670: 118-124, 2017. PMCID: PMC5538381.

3. Development of a photothrombotic model of stroke in the pig that will allow for conductance of longitudinal studies.

Photothrombosis in pigs offers the advantage of an animal with a gyrencephalic brain containing substantial white matter, which is more sensitive to ischemic damage, similar to humans. A seminal paper described a piglet photothrombotic model of pediatric stroke (Stroke 8: 1932, 2007). However, the method employed involved an invasive retro-orbital surgical approach to expose the middle cerebral artery to induce thrombosis, limiting the ability to perform longitudinal outcome studies. Our recent studies producing photothrombosis through a small craniotomy of the piglet head have pioneered an approach that allows us to perform survival surgery and longitudinally track CBF for several weeks post injury in a more human-like species, an innovative approach needed to identify new pre-clinical paradigms for treatment of stroke.

a. Armstead WM, Ganguly K, Riley J, Zaitsev S, Cines DB, Higazi AAR, Muzykantov VR. RBC-coupled tPA prevents whereas tPA aggravates JNK MAPK mediated impairment of ATP and Ca sensitive K channel mediated cerebrovasodilation after cerebral photothrombosis. Translational Stroke Research 3: 114-121, 2012. PMCID: PMC3619434
b. Armstead WM, Ganguly K, Riley J, Kiessling JW, Cines DB, Higazi AAR, Zaitsev S, Muzykantov VR. RBC-coupled tPA prevents impairment of cerebral vasodilatory responses through inhibition of JNK and potentiation of p38 MAPK after cerebral photothrombosis in the newborn pig. Ped Crit Care Med 12:369-375, 2011. PMCID: PMC3681424
c. Armstead WM, Riley J, Kiessling JW, Cines DB, Higazi AAR. Novel plasminogen activator inhibitor-1 derived peptide protects against impairment of cerebrovasodilation after photothrombosis through inhibition of JNK MAPK. Am J Physiol, 299: R480-R485, 2010 PMCID: PMC2928614

4. Novel approaches towards increasing benefit/risk ratio for the use of tPA in treatment of acute ischemic stroke

The thrombolytic agent tissue-type plasminogen activator (tPA) remains the only approved treatment for ischemic stroke. However, its brief therapeutic window and high incidence of post-treatment complications, have constrained clinical use of tPA to approximately 5-8% of patients eligible for such therapy. We have used 3 types of approaches in studies designed to increase benefit/risk ratio of tPA. In the first, we have administered a novel plasminogen activator inhibitor -1 derived peptide that is fibrinolytic but lacks ability to activate tPA mediated signaling. Results of these studies show protection of autoregulation and prevention of impairment of cerebral hemodynamics post insult. In the second approach we have administered RBC coupled tPA with the idea that such coupling will confine the tPA to the vasculature and limit penetration into brain tissue where tPA may enhance neuronal cell toxicity post stroke. In the third, we propose that tPA exacerbates an uncoupling of CBF from neuronal metabolism that occurs in stroke by aggravating pre-existing over-activity

of N-methyl-D-aspartate receptors (NMDA-Rs) that occurs post stroke. Wild type (wt) tPA, given in a clinically relevant timeframe after stroke in the pig, disrupts CBF autoregulation by impairing vasodilation. Although the NMDA-R antagonist MK 801 protects against cerebral dysregulation after stroke, its toxicity limits usage in humans indicating the need for novel approaches. In ongoing studies, we focus on the contribution of NMDA-Rs to the toxicity of tPA administered after stroke and ask whether this can be mitigated without loss of fibrinolytic activity. To do so, we take advantage of our finding that deletion of the "docking site" in tPA prevents its binding and activation of NMDA-Rs. We constructed a variant, tPA-$K^{296}A/H^{297}A/R^{298}A/R^{299}A$, that prevents the enzyme from binding to NMDA-Rs but fully maintains its fibrinolytic activity. Data from recent studies indicates that this tPA variant limits neuronal cell loss and prevents hemodynamic impairment after stroke.

a. Armstead WM, Hekierski H, Pastor, Yarovoi S, Higazai AAR, Cines DB. Release of IL-6 after stroke contributes to impaired cerebral autoregulation and hippocampal neuronal necrosis through NMDA receptor activation and upregulation of ET-1 and JNK. Transl Stroke Research 2018 Feb 23 doi:10.1007/s12975-018 0617Z [Epub ahead of print]
b. Armstead WM, Hekierski H, Yarovoi S, Higazi AAR, Cines DB. tPA-$A^{296-299}$ prevents impairment of cerebral autoregulation and necrosis of hippocampal neurons after stroke by inhibiting upregulation of ET-1. J of Neuroscience Research 96:128-137, 2017.
c. Armstead WM, Riley J, Yarovoi S, Higazi AAR, Cines DB. tPA-$A^{296-299}$ prevents impairment of cerebral autoregulation after Stroke through LRP dependent increase in cAMP and p38. Stroke 47: 2096-2102, 2016. PMCID: PMC4961526
d. Armstead WM, Ganguly K, Riley J, Zaitsev S, Cines DB, Higazi AAR, Muzykantov VR. RBC-coupled tPA prevents whereas tPA aggravates JNK MAPK mediated impairment of ATP and Ca sensitive K channel mediated cerebrovasodilation after cerebral photothrombosis. Translational Stroke Research 3: 114-121, 2012. PMCID: PMC3619434

D. Research Support

Ongoing Research Support

R01 NS 090998 (Armstead) 9/1/15-8/31/20
NIH/NINDS
Pressor choice influences protection of autoregulation in brain injury
The major goal of this project is to characterize the role of pressor choice in cerebral hemodynamic and histopathologic outcome after brain injury in pigs as a function of age and sex.

Mallinckrodt Grant-in Aid (Armstead) 3/13/17-3/12/18; NCE 7/31/18
Inhaled nitric oxide and brain outcomes after pediatric traumatic brain injury
The project will characterize and develop nitric oxide as a putative neuroprotectant after TBI.

R21NS095321 Vavilala (PI) 9/21/15-9/20/18 (NCE)
The purpose is to examine the role of vasoactive agents on cerebral outcomes in pediatric TBI

2R56NS077773-05A1 (Robinson) 7/1/17-6/30/18
Astroglial glutamate transporters calcium and mitochondria
This project will characterize the role of glutamate transporters in outcome after stroke

Pending Research Support

RO1 NS 090998 Administrative Supplement (Armstead) 6/1/18-5/31/19
NIH/NINDS
Pressor choice influences protection of autoregulation in brain injury
In this proposal we hypothesize that vasoactive agents differentially influence the relationship between cardiac function and protection of autoregulation after TBI and that these differences are attributable to age- and sex-dependent modulation of cerebral and systemic inflammatory mediators and catecholamines.

R01 HL143806 (Muzykantov) 7/1/18-6/30/23
NHLBI
Vascular delivery of nanocarriers by erythrocytes
This application proposes to define the mechanism and enable translation of nanocarriers loading onto red blood cell and the transfer to and localization in recipient cells, and the effect of drug delivery by red blood cell-hitchhiking.

RO1NS106693 (Robinson) 9/1/18-8/31/23

NIH/NINDS

Astroglial glutamate transporters, calcium and mitochondria

This project will characterize the role of glutamate transporters in outcome after stroke