

BIOGRAPHICAL SKETCH

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NAME Festoff, Barry W. <hr/> eRA COMMONS USER NAME (credential, e.g., agency login) BFESTOFF	POSITION TITLE Professor, Neurology, Physiology, Pharmacology University of Kansas Medical Center; Chief Scientific Officer, pHLOGISTIX LLC		
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
University of Florida, Gainesville, FL Univ. of Miami School of Medicine, Miami, FL Duke University Medical Center, Durham, NC Duke University Medical Center, Durham, NC	BA MD	1962 1966 1966-1967 1967-1969	Political Science MEDICINE (Intern) Medicine Postdoc Fellow, Molec Neurobiology

A. Personal Statement: The Therapeutics and Companion Diagnostics Divisions of the newly-formed neurobiotechnology company pHLOGISTIX LLC seek to accurately diagnose mild traumatic brain injury (mTBI) and to reduce neuroinflammation and improve functional outcomes in CNS trauma, preventing late sequelae such as Alzheimer's disease (AD) and chronic traumatic encephalopathy (CTE). As a discovery company we emphasize translation from animal models to humans and need validated biomarkers as companion diagnostics. For this AD biomarkers project we will utilize mouse AD transgenic models with or without controlled cortical impact (CCI)/traumatic brain injury (TBI) taking both plasma DNA and plasma proteomics approaches. We emphasize mitochondrial DNA (mtDNA) and protein markers and will compare mouse samples with the well-characterized plasma proteome ADNI dataset in this proposal. The overall goal of the proposed research is to provide a validated panel of nucleic acid and protein biomarkers in a novel analytic approach to allow identification of preclinical AD while still at the preclinical stage of mild cognitive impairment (MCI) or prior to TBI permitting us to initiate treatment before permanent sequelae result.

This companion diagnostic approach dovetails with our biotherapeutics efforts that emphasize cytoprotection with fragments of thrombomodulin (TM) and synthetic gene-derived fusion proteins with TM and other anti-inflammatory biologics. These translational studies underscore the evolutionary nexus between coagulation and inflammation in the CNS that have already been shown for peripheral tissues. The Company focuses on their potential for drug discovery in CNS injury, as well as in ischemic, neurodegenerative and other neurologic diseases.

B. Positions and Honors

- 1969-71: Resident, Neurology, Univ of Miami-Jackson Mem. Hospital, Miami, FL
- 1971-73: Clinical Associate, Medical Neurology Branch, NINDS, NIH, Bethesda, MD
- 1973-76: Assoc Investigator, Medical Neurology Branch, NINDS, NIH, Bethesda, MD
- 1976-: Assoc. Prof., Professor (1980) and Vice-Chair (1976-89), Dept of Neurology, Univ of Kansas Medical Center, Kansas City, KS (KUMC)
- 1976-85: Chief, Neurology Service, VA Medical Center, Kansas City, MO (KCVAMC)
- 1976-2010: Director, Neurobiology Research Laboratory, KCVAMC
- 1985-92: Medical Investigator, National VA Career Development Award, KCVAMC
- 1992-2010: Staff Neurologist, KCVAMC
- 1998-: Professor, Department of Pharmacology, Toxicology & Therapeutics, KUMC
- 2004-: Professor, Department of Molecular and Integrative Physiology, KUMC
- 2010- President and CEO; Chief Scientific Officer, pHLOGISTIX LLC

Professional Memberships:

Society for Neuroscience; American Academy of Neurology, Active Member (1975), Fellow (1982); American Neurological Association (1980); Federation of American Scientists; American Association for Advancement of Science; American Society for Neurochemistry (Publ./Education Comm. 1989-91); International Society for Neurochemistry; Sigma Xi (Charter member, UKMC); American Federation of Clinical Research; American Society of Biological Chemists (1980); Medical Society of London; American Association of University

Professors; American Society for Clinical Investigation ("Young Turks", 1984; Emeritus); Neurotrauma Society; International Society of Developmental Neuroscience; American Society for Neurorehabilitation (Charter certificate); *Professeur de l'Académie des Sciences Française*;

Honors (2002-2009): *Chaire et Professeur de l'Académie des Sciences Française*; *Chercheur Associé*, CNRS and INSERM, U 153, Paris, FR; Ed Board, Synapse; Chair, Extravascular Effects of Thrombin, FASEB Summer Res Conf, Copper Mountain, CO; Chair, Neurobiol and Beyond, FASEB Summer Res Conf, Thrombin and Vascular Med, Saxton's River, VT; Symp. Speaker, Proteases and the Nervous System, Amer Soc of Neurochem, Denver; *Chercheur Associé, Poste Vert*, ERS 5644 du CNRS, *Université de Montpellier II*; Elected, Hall of Fame, Univ of Miami Med School; Invited speaker, Fondation Ipsen, Symp on Protein Aggregation in Neurodegeneration, Paris, FR; Organizer and invited speaker, Congress on Neuroprotection and Neurorepair, Magdeburg, Germany; Invited speaker, Transglutaminases and Neurodegeneration, Amer Soc Neurochem.; Faculty Sr. Res Award, KUMC: Session Chair, Invited Speaker, PARs in Neurodegeneration, Pain and Neurotrauma, Amer Soc for Neurochem; INSERM Unit 289, *Hôpital de la Salpêtrière*, Paris, France: Invited speaker, Thrombin/PAR signaling in neurons and glial cells and proinflammatory responses to CNS injury, Euroglia 2003: VI Euro Meeting on Glial Cell Function in Health and Disease, Berlin, Germany: Scientific Advisory Comm, Western ALS; Amer Soc Neurorehab Program Comm.; Visiting Professor, Neuropathology, Columbia P&S, NYC; Visiting Prof. Neurotrauma, Oxford Univ., Oxford, UK

C. Selected peer-reviewed publications (most recent and relevant from more than 150)

- Beecher, K.L., Andersen, T.T., Fenton, J.W., 2nd, and Festoff, B.W. 1994. Thrombin receptor peptides induce shape change in neonatal murine astrocytes in culture. *Journal of neuroscience research* 37:108-115. <http://www.ncbi.nlm.nih.gov/pubmed/8145298>
- Houenou, L.J., Turner, P.L., Li, L., Oppenheim, R.W., and Festoff, B.W. 1995. A serine protease inhibitor, protease nexin I, rescues motoneurons from naturally occurring and axotomy-induced cell death. *Proceedings of the National Academy of Sciences of the United States of America* 92:895-899.
- Smirnova, I.V., Ma, J.Y., Citron, B.A., Ratzlaff, K.T., Gregory, E.J., Akaaboune, M., and Festoff, B.W. 1996. Neural thrombin and protease nexin I kinetics after murine peripheral nerve injury. *Journal of neurochemistry* 67:2188-2199. <http://www.ncbi.nlm.nih.gov/pubmed/8863530>
- Zoubine, M.N., Ma, J.Y., Smirnova, I.V., Citron, B.A., and Festoff, B.W. 1996. A molecular mechanism for synapse elimination: novel inhibition of locally generated thrombin delays synapse loss in neonatal mouse muscle. *Developmental biology* 179:447-457. <http://www.ncbi.nlm.nih.gov/pubmed/8903359>
- Pindon, A., Hantai, D., Jandrot-Perrus, M., and Festoff, B.W. 1997. Novel expression and localization of active thrombomodulin on the surface of mouse brain astrocytes. *Glia* 19:259-268.
- Smirnova, I.V., Zhang, S.X., Citron, B.A., Arnold, P.M., and Festoff, B.W. 1998. Thrombin is an extracellular signal that activates intracellular death protease pathways inducing apoptosis in model motor neurons. *Journal of neurobiology* 36:64-80. <http://www.ncbi.nlm.nih.gov/pubmed/9658339>
- Smirnova, I.V., Vamos, S., Wiegmann, T., Citron, B.A., Arnold, P.M., and Festoff, B.W. 1998. Calcium mobilization and protease-activated receptor cleavage after thrombin stimulation in motor neurons. *J Mol Neurosci* 10:31-44. <http://www.ncbi.nlm.nih.gov/pubmed/9589368>
- Smirnova, I.V., Citron, B.A., Arnold, P.M., Zhang, S.X., and Festoff, B.W. 1998. Characterization of apoptosis in a motor neuron cell line. *Spine (Phila Pa 1976)* 23:151-158. <http://www.ncbi.nlm.nih.gov/pubmed/9474719>
- Citron, B.A., Smirnova, I.V., Arnold, P.M., and Festoff, B.W. 2000. Upregulation of neurotoxic serine proteases, prothrombin, and protease-activated receptor 1 early after spinal cord injury. *J Neurotrauma* 17:1191-1203. <http://www.ncbi.nlm.nih.gov/pubmed/11186232>
<http://www.ncbi.nlm.nih.gov/pubmed/7846074>
- Festoff, B.W., Ameenuddin, S., Santacruz, K., Morser, J., Suo, Z., Arnold, P.M., Stricker, K.E., and Citron, B.A. 2004. Neuroprotective effects of recombinant thrombomodulin in controlled contusion spinal cord injury implicates thrombin signaling. *J Neurotrauma* 21:907-922. <http://www.ncbi.nlm.nih.gov/pubmed/15307903>
- Suo, Z., Wu, M., Citron, B.A., Gao, C., and Festoff, B.W. 2003. Persistent protease-activated receptor 4 signaling mediates thrombin-induced microglial activation. *The Journal of biological chemistry* 278:31177-31183. <http://www.ncbi.nlm.nih.gov/pubmed/12775717>
<http://www.ncbi.nlm.nih.gov/pubmed/9063732>

Program Director/Principal Investigator (Last, First, Middle): Festoff, Barry W.

- Suo, Z., Citron, B.A., and Festoff, B.W. 2004. Thrombin: a potential proinflammatory mediator in neurotrauma and neurodegenerative disorders. *Current drug targets. Inflammation and allergy* 3:105-114. <http://www.ncbi.nlm.nih.gov/pubmed/15032647>
- Suo, Z., Wu, M., Ameenuddin, S., Anderson, H.E., Zoloty, J.E., Citron, B.A., Andrade-Gordon, P., and Festoff, B.W. 2002. Participation of protease-activated receptor-1 in thrombin-induced microglial activation. *Journal of neurochemistry* 80:655-666. <http://www.ncbi.nlm.nih.gov/pubmed/11841573>
- Suo, Z., Wu, M., Citron, B.A., Palazzo, R.E., and Festoff, B.W. 2003. Rapid tau aggregation and delayed hippocampal neuronal death induced by persistent thrombin signaling. *The Journal of biological chemistry* 278:37681-37689. <http://www.ncbi.nlm.nih.gov/pubmed/12821672>
- Suo, Z., Wu, M., Citron, B.A., Wong, G.T., and Festoff, B.W. 2004. Abnormality of G-protein-coupled receptor kinases at prodromal and early stages of Alzheimer's disease: an association with early beta-amyloid accumulation. *J Neurosci* 24:3444-3452. <http://www.ncbi.nlm.nih.gov/pubmed/15056724>
- Snyder, H., Mensah, K., Hsu, C., Hashimoto, M., Surgucheva, I.G., Festoff, B., Surguchov, A., Masliah, E., Matouschek, A., and Wolozin, B. 2005. beta-Synuclein reduces proteasomal inhibition by alpha-synuclein but not gamma-synuclein. *J Biol Chem* 280:7562-7569. <http://www.ncbi.nlm.nih.gov/pubmed/15591046>
- Citron, B.A., Zoloty, J.E., Suo, Z., and Festoff, B.W. 2005. Tissue transglutaminase during mouse central nervous system development: lack of alternative RNA processing and implications for its role(s) in murine models of neurotrauma and neurodegeneration. *Brain Res Mol Brain Res* 135:122-133. <http://www.ncbi.nlm.nih.gov/pubmed/15857675>
- Bilgen, M., Al-Hafez, B., Berman, N.E., and Festoff, B.W. 2005. Magnetic resonance imaging of mouse spinal cord. *Magn Reson Med* 54:1226-1231. <http://www.ncbi.nlm.nih.gov/pubmed/16206177>
- Festoff, B.W., Ameenuddin, S., Arnold, P.M., Wong, A., Santacruz, K.S., and Citron, B.A. 2006. Minocycline neuroprotects, reduces microgliosis, and inhibits caspase protease expression early after spinal cord injury. *J Neurochem* 97:1314-1326. <http://www.ncbi.nlm.nih.gov/pubmed/16638021>
- Farooque, M., Suo, Z., Arnold, P.M., Wulser, M.J., Chou, C.T., Vancura, R.W., Fowler, S., and Festoff, B.W. 2006. Gender-related differences in recovery of locomotor function after spinal cord injury in mice. *Spinal Cord* 44:182-187. <http://www.ncbi.nlm.nih.gov/pubmed/16130019>
- Suo, Z., Cox, A.A., Bartelli, N., Rasul, I., Festoff, B.W., Premont, R.T., and Arendash, G.W. 2007. GRK5 deficiency leads to early Alzheimer-like pathology and working memory impairment. *Neurobiol Aging* 28:1873-1888. <http://www.ncbi.nlm.nih.gov/pubmed/17011668>
- Bilgen, M., Al-Hafez, B., Alrefae, T., He, Y.Y., Smirnova, I.V., Aldur, M.M., and Festoff, B.W. 2007. Longitudinal magnetic resonance imaging of spinal cord injury in mouse: changes in signal patterns associated with the inflammatory response. *Magn Reson Imaging* 25:657-664. <http://www.ncbi.nlm.nih.gov/pubmed/17540277>
- Citron, B.A., Arnold, P.M., Haynes, N.G., Ameenuddin, S., Farooque, M., Santacruz, K., and Festoff, B.W. 2008. Neuroprotective effects of caspase-3 inhibition on functional recovery and tissue sparing after acute spinal cord injury. *Spine (Phila Pa 1976)* 33:2269-2277. <http://www.ncbi.nlm.nih.gov/pubmed/18827691>
- González-Pérez, P., Cirulli, E.T., Drory, V.E., Dabby, R., Nisipeanu, P., Carasso, R.L., Sadeh, M., Fox, A., Festoff, B.W., Sapp, P.C., McKenna-Yasek, D., Goldstein, D.B., Brown, Jr., R.H., Blumen, S.C.: Novel mutation in VCP gene causes atypical amyotrophic lateral sclerosis. *Neurology* (in press).
- Festoff, B.W., Li, C-Y, Woodhams, B., Lynch, S.: Soluble thrombomodulin levels in plasma of multiple sclerosis patients and their implication. *J Neurol Sci.* 323: 61-65. <http://www.ncbi.nlm.nih.gov/pubmed/22967748>
- Vogeti, S., Chou, C-T, Conway, E.M. and Festoff, B.W.: Role of thrombomodulin's lectin-like domain in recovery after spinal cord injury in mice. *Neurobiol. Dis.* (in press)

D. Research Support

Ongoing Research Support:

Festoff, Barry W. (PI) 08/15/11-08/14/12
Kansas Bioscience Authority (\$100,000), "P-O-C Studies of TM in TBI"

Completed Research Support:

Festoff, Barry W. (PI) 06/01/07-05/31/10
Bryon Riesch Paralysis Foundation:
"Novel therapeutic approaches to SCI: siRNA and thrombin Signaling"
Festoff, Barry W. (PI) 07/01/07-06/30/10

Program Director/Principal Investigator (Last, First, Middle): Festoff, Barry W.

Morton Cure Paralysis Foundation

"HMGB1, a proinflammatory cytokine in spinal cord injury: "Friend or Foe"

Festoff, Barry W. (PI) 07/01/07–06/30/09

Wings for Life Spinal Cord Research Foundation -- Individual Research Grant Application.

"SCI translational treatment with siRNA for proteinase-activated receptors"

Festoff, Barry W. (PI) 04/01/04 – 03/31/09

Department of Veterans Affairs/VA Merit Review

"Injury, neuronal hypoxia and thrombin signaling: Adaptation or death?"

Bilgen, Mehmet (PI) 09/01/06-08/31/08

Festoff, Barry W. (Co-I)

National Institutes of Health (R21 NS054019-01A1)

"Vascular plasticity in Injured Spinal Cord-Investigations using MRI"