BIOGRAPHICAL SKETCH

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NAME: Marshall, John

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POSITION TITLE: Professor of Medical Science

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 Nottingham, England	B.Sc.	1983	Biochemistry
Toronto University, Canada	M.Sc.	1985	Medical Genetics
Cambridge University, England	Ph.D.	1989	Mol. Neurobiology

A. Personal Statement

I hold the position of full Professor of Medical Science at Brown University in the Department of Molecular Biology, Cell Biology & Biochemistry. I have a broad background in pharmacology, with specific training in molecular biology and physiology techniques studying BDNF signal transduction pathways using pharmacological reagents, electrophysiological (slice and patch clamping), and biochemical techniques. We study memory and behavior in rodent models of autism and depression. The goal of the proposed research is to develop a novel effective therapeutic intervention using Syn3, a novel cyclic-peptide immunomodulator, to treat traumatic brain injury. Our proposed studies will examine and confirm the beneficial neuroprotective effects of Syn3. As PI or co-Investigator on several university- and NIH-funded grants, I laid the groundwork for the proposed research by characterizing and demonstrating the potential of novel peptidomimetic compounds for the treatment of neurological disorders.

B. Positions, Scientific Appointments, and Honors

2005-present Professor of Medical Science, Brown University
1998-2005 Associate Professor, Brown University
1997-present Adjunct Professor, Cornell University
1995-1998 Upjohn Assistant Professor of Pharmacology, Brown University
1992-1994 Associate Research Scientist, Pharmacology Dept., Yale University
1989-1992 Postdoctoral fellow, Pharmacology Dept., Yale University

Scientific Appointments
1989-Present Member, Society for Neuroscience

Honors
1995-1998 Upjohn Assistant Professor of Pharmacology
1993-1994 American Heart Fellow
1990 European Young Neuroscientist Investigator Award.

Patents

1. Syn3 Patent Application in February 2021 (Number: 62909396).
2. Cyclic-GluR6 analogs, methods of treatment and use. Filing date: May, 2012. Therapeutic treatment of neurological insult such as stroke, traumatic brain injury, epilepsy as well as for pain and neurodegenerative disease. Patent No. 9403876

3. Long term potentiation with cyclic-GluR6 analogs. Filing date: February, 2012. This invention employs a composition that facilitates the induction of long-term potentiation (LTP). It is believed that LTP is the cellular manifestation of learning and memory. LTP failure is implicated in Angelman Syndrome. Patent No. US 8,673,857 B2.
4. Poly-arginine derivatives for enhancing Brain-derived neurotrophic factor to mitigate neurological disorders. Filing Date: January 5, 2022. New International Patent Application No. PCT/US2022/011283 Priority: US Provisional Appl. No. 63/134,059 filed January 5, 2021.

C. Contributions to Science

1. My early publications focused on the function of ionotropic glutamate receptors, focusing on kainate receptors. It is well documented that pathologies associated with brain damage result from glutamate excitotoxicity, mediated by activation of ionotropic glutamate receptors (NMDA and Kainate/AMPA). Over the last 10 years my lab has focused on translational research on traumatic brain injury (TBI), gaining significant experience with rodent models of TBI. We focus on the mechanisms underlying the brain inflammatory response and on therapies directed to limit post-traumatic neuroinflammation and injury. I initiated clinical studies on cyclic peptide drugs targeting brain-derived neurotrophic factor, which has been shown to be neuroprotective, and our group reported a PSD-95/PDZ-binding cyclic peptide (CN2097) that augments brain-derived neurotrophic factor-induced pro-survival signaling. Our research also identified that the cationic arginine-rich peptide, C-R(7), was sufficient to mediate protection via a mitochondrial targeting mechanism.

Marshall J, Zhou XZ, Chen G, Yang SQ, Li Y, Wang Y, Zhang ZQ, Jiang Q, Birnbaumer L, Cao C. Antidepression action of BDNF requires and is mimicked by Gαi1/3 expression in the hippocampus. Proc Natl Acad Sci U S A. 2018 Mar 5. pii: 201722493. doi: 10.1073/pnas.1722493115. [Epub ahead of print] PMID: 29507199.

Marshall, J, Szmydynger-Chodobska J, Rioult-Pedotti MS, Lau K, Chin AT, Kotla SKR, Tiwari RK, Parang K, Threlkeld SW, Chodobski A (2017) TrkB-enhancer facilitates functional recovery after traumatic brain injury. Sci Rep 7:10995.

Marshall, J., Wong, KY., Parang, K., Tiwari, R., Spaller, MR., Rupasinghe, CN., Berberoglu, ED., Zhao, X Sinkler, C., Liu, J., Lee, I., Huttemann, M and Dennis J. Goebel, DJ. Inhibition of NMDA-induced retinal neuronal death by polyarginine peptides is linked to the attenuation of stress-induced hyperpolarization of the inner mitochondrial membrane potential J Biol Chem. **290**, 22030-48 (2015).

2. My lab also focuses on Angelman syndrome (AS), an autism-spectrum disorder, in which BDNF signaling is impaired. We found that CN2097 (and our next generation compound Syn3) restored LTP and learning in an AS mouse model that is anticipated to lead to a new treatment for this disorder.

Cao, C., Rioult-Pedotti, M.S., Migani, P., Yu, C.J., Tiwari, R., Parang, K., Spaller, M.R., Goebel, D.J. & Marshall, J. Impairment of TrkB-PSD-95 Signaling in Angelman Syndrome. *PLoS Biol* **11**, e1001478 (2013).

Cao, C., Huang, X., Han, Y., Wan, Y., Birnbaumer, L., Feng, GS., Marshall, J., Jiang, M and Chu, W.M (2009). Requirement of Gai1 and Gai3 for activation of the Akt/mTORC1 pathway by epidermal growth factor. Science Signal. 2(68):ra17.

Jeyifous,O., Waites, Specht, CG., Fujisawa, S; Schubert, M., Lin, EI., Marshall, J., Aoki, C; de Silva,T., Montgomery, JM., Garner, CC; and Green WN. (2009) SAP97 and CASK mediate sorting of NMDA receptors through a previously unknown secretory pathway. Nature Neuroscience 12, 1011-1019.

3. In recent studies my lab has begun testing our compounds for the treatment of major depression disorder. Aberrant brain-derived neurotrophic factor (BDNF) signaling has been proposed to underlie the pathophysiology of major depressive disorder and Syn3 produces rapid (within hours) antidepressant effects**.** I served as the primary investigator or co-investigator in all of these studies.

Marshall J, Zhou XZ, Chen G, Yang SQ, Li Y, Wang Y, Zhang ZQ, Jiang Q, Birnbaumer L, Cao C. Antidepression action of BDNF requires and is mimicked by Gαi1/3 expression in the hippocampus. Proc Natl Acad Sci U S A. 2018 Mar 5. pii: 201722493. doi: 10.1073/pnas.1722493115. PMID: 29507199.

4. In addition to the contributions described above, my lab has focused on IGF-1 (insulin-like growth factor-1) modulation of neuronal L-type calcium channels and their role in neuroprotection. We demonstrated that the CaV1.3-induced regulation of pCREB arose through Shank interactions with CaV1.3. These studies highlight that the neuroprotective mechanism of growth factors is through an elevation of $Ca2^{+}$ which activates signaling pathways that promote survival.

Gao, L., L.A.C. Blair, G.D. Salinas, L.A. Needleman and J. Marshall. (2006). IGF-1-modulation of CaV1.3 calcium channels depends on Ca^{+2} release from IP_3-senstitive stores and CaMKII-phosphorylation of the alpha1 subunit EF hand. J.Neurosci. 26, 6259-68.

Marshall J, Dolan BM, Garcia EP, Sathe S, Tang X, Mao Z, Blair L.A.C. (2003) Calcium channel and NMDA receptor activity differentially regulate nuclear C/EBP levels to control neuronal survival. *Neuron* **39**: 625-629.

Bence. K.K., Blair, L.A.C., and J. Marshall. (2000) Potentiation of neuronal L calcium channels by IGF-1 requires phosphorylation of the a1 subunit on a specific tyrosine residue. *Neuron* 27, 121-131.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/john.marshall.3/bibliography/45517118/public/?sort=date&direction=ascending