BIOGRAPHICAL SKETCH

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NAME: Bruce D. Carter

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POSITION TITLE: Professor of Biochemistry

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
Alma College, Alma, MI	B.S.	1982-86	Biology/Chemistry
University of Michigan, Ann Arbor, MI	Ph.D.	1986-92	Biological Chemistry
Max Planck Inst. for Psychiatry, Munich, Germany	Postdoc	1993-96	Neurobiology
Cornell Univ. Med. School, New York, NY	Postdoc	1996-97	Neurobiology

A. Personal Statement

I have been involved in neuroscience research for over 20 years and have been a faculty member carrying out research in the area of developmental neurobiology since 1997. The major focus of my research is understanding the signaling mechanisms regulating the development of the mammalian nervous system. Specifically, we study the molecular mechanisms regulating neuronal apoptosis and myelin formation in the developing peripheral nervous system (PNS) using cellular, biochemical and genetic approaches. In addition, we recently began investigating the mechanisms by which apoptotic neurons are cleared in the developing PNS. I have also been involved in training graduate students since 1997 and 8 of my students, including 1 MSTP, have successfully completed their PhD and 3 others are currently in the lab. I have also trained 9 postdoctoral fellows and there are currently 2 in the lab. In addition, I have served on or am serving on PhD thesis committees for 39 students and I have mentored numerous undergraduates (over 20) and medical students. I also teach in several graduate and medical school courses and am currently the Director of Graduate Studies for the Neuroscience Program. I have also been a member of the Faculty Advisory Committee for Vanderbilt's MSTP program for 10 years and have served as a faculty advisor for the Goodpasture MSTP Advising College for the last 5 years.

B. Positions and Honors

1986-1992 Graduate Student Research Assistant with Dr. Fedor Medzihradsky, Dept. Biological Chemistry, University of Michigan, Ann Arbor, MI

1993-1996 Postdoctoral Fellow with Dr. Yves-Alain Barde, Dept. Neurobiochem., Max Planck Institute for Psychiatry, Munich, Germany

1996-1997 Postdoctoral Fellow with Dr. Moses V. Chao, Dept. of Cell Biology and Anatomy, Cornell University Medical College, New York, NY

1997 -2003 Assistant Professor, Dept. Biochemistry, Center for Mol. Neurosci., Vanderbilt Univ. Med. School, Nashville, TN

2003- 2007 Associate Professor, Dept. Biochemistry, Center for Mol. Neurosci., Vanderbilt Univ. Med. School, Nashville, TN

2007 -present Professor, Dept. Biochemistry, Center for Mol. Neurosci., Vanderbilt Univ. Med. School, Nashville, TN

2014-present Associate Director for Education and Training, Vanderbilt Brain Inst., Vanderbilt Univ. Med. School, Nashville, TN

Honors/Awards

Alma College Outstanding Senior Chemist Award, 1986; American Chemical Society Midland Section Award, 1986; University of Michigan Regents Fellowship, 1986-88; Rackham Predoctoral Fellowship, 1989-91; Associate Member, Sigma Xi Scientific Honor Society, 1992; NIH NRSA Postdoctoral Fellowship, 1997; National Alliance for Research on Schizophrenia and Depression Young Investigator Award, 1998-00.
Fellow, American Association for the Advancement of Science, 2011-present
Distinguished Graduate Lectureship, Dept. Biol. Chem., Univ. Michigan Med. School, 2013

Memberships/ Professional Activities

Member, American Assoc. for the Advancement of Science, Society for Neuroscience, International Society for Developmental Neuroscience, American Society for Biochemistry and Molecular Biology, Middle TN Chapter of the Society for Neuroscience.
Ad hoc reviewer, NIH, NINDS/JDF, RFA on diabetic neuropathy, 2000.
Member, National Multiple Sclerosis Society Review Board, 2013-present.
Ad hoc reviewer for NINDS Study Sections MDCN6, 2002; ZRG1 NOMD-A, 2006, 2013; NOMD, 2010, 2012 ZRG1 MDCN-N(02)S, 2011, ZRG1 IMM-G (02)M, 2012.
Ad hoc reviewer for National Parkinson's Disease Foundation, 2004.
Ad hoc reviewer for Wellcome Trust, Spinal Cord Research Foundation, Alberta Heritage Foundation, Alzheimer's Association.
Ad hoc reviewer for J. Biol. Chem., J. Neurosci., Exp. Cell Res., Cell Death Diff., J. Cell Biol., Glia, J. Neurochem., J. Neurosci. Res., J. Neurobiol., Proc. Natl. Acad. Sci. USA., EMBO J., Mol. Cell. Neurosci., Cell Death & Dis., Cell Stem Cell, Nat. Comm., eLife, Neuron, Nat. Neurosci., Neuron
Editorial Board member, Journal Biological Chemistry, 2007-2013.
Graduate Faculty Assembly Delegate, 2001-present
Medical Scientist Training Program Executive Council, 2001-present
Faculty Search Committee, 2000; 2001 (co-chair); 2002 (chair); 2004 (chair). 2006 (chair)
Search Committee for Vanderbilt Brain Institute Director, 2007.
Interdisciplinary Graduate Program Curriculum Committee, 2009-present.
Center for Cellular and Molecular Neuroscience Website Design Committee, 2009
Center for Molecular Neuroscience Cores Advisory Committee 2010-2012
Scientific Advisory Board, Tyratech, 2009
Vanderbilt Brain Institute Steering Committee, 2011
Neuroscience Program Curriculum Committee, 2008-present, Chair, 2011-present
President-Elect, Middle Tennessee Chapter of the Society for Neuroscience, 2011-2013
Vanderbilt Kennedy Center, Membership Committee, 2012-present
American Society for Neurochemistry Programming Committee, 2014.

C. Contributions to Science

(full list of citations available at: http://www.ncbi.nlm.nih.gov/sites/myncbi/1VUraTnT9it5i/bibliography/40724194/public/?sort=date&direction=descending *)*

1. As a postdoctoral fellow, I demonstrated that **the p75 neurotrophin receptor is a signaling receptor**. At the time, p75 was widely considered a nonsignaling receptor that simply functions to present neurotrophins to members of the Trk family of tyrosine kinase receptors. I found that p75 activates the transcription factor NF-kB (Carter et al., 1996). This finding drew much attention to the p75 receptor and initiated a series of studies on its function, carried out by multiple labs. Together with Patrizia Casaccia-Bonnefil, I then went on to discover that p75 could induce programmed cell death (Casaccia-Bonnefil et al., 1996), which was very surprising for a neurotrophin receptor. Since then, the p75 neurotrophin receptor has become the focus of many studies examining the mechanisms of cell death in the developing nervous system, in neurodegenerative conditions, and following nerve injury. Activation of p75 has a paradoxical function, being able to promote apoptosis in some contexts, yet being pro-survival in others. I have continued to investigate

the mechanisms by which p75 mediates its many effects, primarily using developing sympathetic neurons as a model system. My research group demonstrated that the E3 ubiquitin ligase, TNF receptor associated factor 6 (TRAF6) (Yeiser et al., 2004) and the novel DNA binding protein, Neurotrophin receptor interacting factor (NRIF) (Linggi et al., 2005) are two intracellular signaling molecules essential for p75 apoptotic signaling.

Carter, B.D., Kaltschmidt, C., Kaltschmidt, B., Offenhauser, N., Bohm-Matthaei, R., Baeuerle, P. and Y.A. Barde. Activation of NFkB by Nerve Growth Factor through the neurotrophin receptor p75. *Science,* 272:542-545, 1996.

Casaccia-Bonnefil, P., Carter, B. D., Dobrowsky, R. T. and M. V. Chao. Nerve growth factor-mediated cell death of mature oligodendrocytes through the p75 neurotrophin receptor. *Nature,* 383:716-719, 1996.
Yeiser, E.C., Rutkoski, N.J., Naito, A., Inoue, J. and Carter. B.D. Neurotrophin signaling through the p75 receptor is deficient in *traf6-/-* mice. *J. Neurosci*. 24: 10521-10529, 2004.

Yeiser, E.C., Rutkoski, N.J., Naito, A., Inoue, J. and Carter. B.D. Neurotrophin signaling through the p75 receptor is deficient in *traf6-/-* mice. *J. Neurosci*. 24: 10521-10529, 2004.

Linggi, M.S., Burke, T.L., Williams, B.B., Harrington, A.W., Kraemer, R., Hempstead, B.L., Yoon, S.O. and Carter, B.D. NRIF is an essential mediator of apoptotic signaling by the p75 neurotrophin receptor. *J Biol Chem.* 280: 13801-8, 2005.

2. In the process of exploring **the signaling mechanisms activated by the p75 neurotrophin receptor**, we elucidated a novel pathway from the receptor directly to the nucleus. We found that p75 activates the stress kinase JNK, which then promotes the proteolytic cleavage of the receptor in the extracellular domain by the metalloprotease ADAM17, followed by cleavage in the transmembrane domain by the gamma-secretase complex (Kenchappa et al., 2010). The cleavage of the receptor liberates the intracellular domain of the receptor, thereby facilitating nuclear translocation of the transcription factor NRIF, which is required for the apoptotic signal (Kenchappa et al., 2006). Shuttling of NRIF into the nucleus also requires the E3 ubiquitin ligase TRAF6. We demonstrated that NRIF and TRAF6 directly associate (Gentry et al., 2004) and TRAF6 attaches a lysine 63-linked ubiquitin chain to NRIF, which is necessary for nuclear translocation and, subsequently, apoptosis (Geetha et al., 2005). This was one of the first examples of a K63 ubiquitin chain being utilized as a nuclear translocation signal.

Geetha, T., Kenchappa, R., Wooten, M.W. and Carter, B.D. Nuclear shuttling of the p75 neurotrophin receptor interacting factor NRIF is regulated by TRAF6-dependent K63-polyubiquitination. *EMBO J* 24:3859-68. 2005.

Gentry, J.J., Rutkoski, N.J., Burke, T. and Carter, B.D. A functional interaction between the p75 neurotrophin receptor interacting factors, TRAF6 and NRIF. *J Biol Chem*. 279:16646-16656. 2004.

Kenchappa, R., Zampieri, N., Chao, M.V., Barker, P.A., Teng, H.K., Hempstead, B.L. and Carter, B.D. Ligand dependent cleavage of the p75 neurotrophin receptor is necessary for NRIF nuclear translocation and apoptosis in sympathetic neurons. *Neuron* 50:219-232. 2006.

Kenchappa, R.S., Tep, C., Korade, Z., Urra, S., Bronfman, F.S., Yoon, S.O. and Carter, B.D. P75NTR mediated apoptosis in sympathetic neurons involves a biphasic activation of JNK and up regulation of TACE/ADAM17. *J. Biol. Chem.,* 285(26):20358-68. 2010. (PMC2888447)

3. My research group has also been investigating the **mechanisms regulating Schwann cell differentiation** into a myelinating phenotype. Myelin, produced by Schwann cells in the periphery and oligodendrocytes in the CNS, ensheaths axons and allows for the rapid conduction of electrical signals, acts as a protective barrier for axons, regulates regeneration and provides trophic support for neurons. The molecular mechanisms regulating this process are not well understood. Several years ago, we made the discovery that activation of the transcription factor NF-kB in Schwann cells is critical for their differentiation into a myelinating phenotype (Nickols et al., 2003). We found that the growth factor neuregulin I, type 3, which is expressed on axons and required for myelin formation, was the signal responsible for stimulating

NF-kB (Limpert & Carter, 2010). The activation of NF-kB in Schwann cells also required phosphorylation of the p65 subunit of NF-kB by protein kinase A (PKA) and this was necessary for the formation of myelin (Yoon et al., 2008). This finding was particularly interesting since the PKA activator cAMP has long been known to promote Schwann cell differentiation. We went on to demonstrate that NF-kB associates with the chromatin remodeling complex BRG1 during Schwann cell differentiation and localizes to the promoter of the pro-myelinating transcription factor SOX10 (Limpert et al., 2013). Furthermore, genetic deletion of BRG1 selectively in Schwann cells resulted in severe demyelination due to the Schwann cells arresting at a precursor stage (Limpert et al., 2013).

Nickols, J., Valentine, W., Kanwal, S. and Carter B. D. Activation of NF-kB in Schwann cells is required for peripheral myelin formation. *Nature Neurosci*., 6:161-167, 2003.

Yoon, C., Korade, Z. and Carter, B.D. Phosphorylation of the p65 subunit of NF-kB in Schwann cells is required for myelin formation. *J. Neurosci.,* 28:3738-3746. 2008.

Limpert, A. and Carter, B.D. Axonal neuregulin 1 type III activates NF-kB in Schwann cells during myelin formation. *J. Biol. Chem.,* 285(22):16614-22. 2010. (PMC2878070)

Limpert, A., Bai, S., Narayan, M., Wu, J., Yoon, S.O., Carter*, B.D. and Lu*, Q.R. The BRG1/SMARCA4 chromatin remodeling complex is required for peripheral myelination. *J. Neurosci*. 33(6):2388-97. 2013. (PMC3711599). *co-corresponding authors.

4. We recently made the interesting discovery that **apoptotic neurons in the peripheral nervous system are phagocytosed by glial progenitor cells**, not macrophages (Wu et al., 2009). Even under conditions of enhanced apoptosis due to deletion of a neurotrophin, the glial precursors were the primary phagocytes. We also identified a novel engulfment receptor, named Jedi1, which is homologous to the phagocytic receptors CED1, in C. elegans, and Draper, in Drosophila. Surprisingly, until his finding, the mechanisms by which the apoptotic neurons are cleared in the periphery were unknown despite the fact that neuronal apoptosis was first described in the dorsal root ganglia some 70 years ago. These neuronal corpses must be efficiently cleared in order to avoid an inflammatory response. In fact, improper clearance of apoptotic cells is thought to contribute to autoimmune diseases such as systemic lupus erythrematosus. We have been investigating the mechanisms of Jedi1 signal transduction and demonstrated that this receptor promotes engulfment through recruitment of the tyrosine kinase Syk (Sheib et al., 2012). In addition, we found that Jedi1 also associates with the adaptor protein GULP (CED6 in nematodes) and this interaction is required for Jedi1-mediated engulfment (Sullivan et al., 2014). Although CED6 was known to be required for phagocytosis in C. elegans and Drosophila, its mechanism of action had yet to be determined. We demonstrated that GULP recruits clathrin heavy chain, which promotes the formation of an actin complex. Phagocytosis had generally been considered to be a clathrin independent process, due to the size limitation of a typical clathrin coated vesicle and the much larger size of an internalized apoptotic bodies. This was the first report to identify a direct role for mammalian clathrin in the phagocytosis of apoptotic cells.

Wu, H.-H., Bellmunt, E., Venegas, V., Burkert, C., Scheib, J.L., Reichardt L.F., Zhou, Z., Farinas, I. and Carter, B.D. Satellite Glial Cell Precursors Clear Neuronal Corpses during Dorsal Root Ganglia Development via Two Novel Engulfment Receptors, MEGF10 and Jedi-1. *Nature Neurosci.,* 12:1534-1541. 2009. (PMC2834222).

Scheib, J.L., Sullivan, C.S. and Carter, B.D. Jedi-1 and MEGF10 signal engulfment of apoptotic neurons through the tyrosine kinase Syk. *J. Neurosci*., 32(38):13022-31. 2012. (PMC3464495)

Sullivan, C.S., Scheib, J.L., Ma, Z., Dang, R.P., Schafer, J.M., Hickman, F.E., Brodsky, F.M., Ravichandran, K.S. and Carter, B.D. The adaptor protein GULP promotes Jedi-1-mediated phagocytosis through a clathrin-dependent mechanism. *Mol Biol Cell* 25(12):1925-1936. 2014. (PMC4055271)

D. Research Support (for the last three years)

ONGOING:

RO1 NS38220, (Carter) 9/01/2011-8/31/2015
NIH/NINDS
Mechanisms of neurotrophin signaling through the p75 receptor.
The goals of this project are to determine the role of NRIF, a protein that binds to the p75 neurotrophin receptor, in p75 signaling and to evaluate the functional significance of the interaction between NRIF and another p75 binding protein, TRAF6.

COMPLETED:
RO1 R01NS064278-01A1, (Carter) 7/01/09-6/30/14.
NIH/NINDS
Mechanisms of apoptotic neuron clearance in the peripheral nervous system
The goal of this study is to elucidate the cellular and molecular mechanisms underlying the phagocytosis of apoptotic neurons in the developing peripheral nervous system. We hypothesize that the phagocytosis of dead DRG neurons during embryogenesis by satellite cells involves two mammalian homologs of CED-1, MEGF10 and Jedi.

R01NS058815-01A2, (coPIs: Carter, Sanders, CR) 04/01/2010 – 03/31/2013
NIH/NINDS
Structure, Folding, and Misfolding of PMP22
The goals of this project are to elucidate the molecular biophysical nature of the perturbations made by Charcot-Marie Tooth Disease-associated mutations to the structure, stability and folding of PMP22.