BIOGRAPHICAL SKETCH

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NAME	POSITION TITLE
Twiss, Jeffery L.	Professor, Department Head
eRA COMMONS USER NAME (credential, e.g., agency login)	
JTWISS	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
College of Charleston, Charleston, SC	B.A.	05/84	Chemistry
Medical Univ. of South Carolina, Charleston, SC	M.D.	05/90	Medicine
Medical Univ. of South Carolina, Charleston, SC	Ph.D.	05/92	Molec.& Cell. Biol.
Stanford University, Stanford, California	Resident/ Fellow	07/94	Anatomic Pathology/ Neuropathology
Stanford University, Stanford, California	Post-doc	06/96	Neurobiology

A. Personal Statement

During my post-doctoral work, I stumbled onto the field of translational regulation while studying the signal transduction of neurite regeneration (Twiss & Shooter, 1995). Shortly thereafter, in my own lab we discovered that some of the translation was occurring directly in regenerating neurites and axons. I continued down this line of investigation as my group grew. Our early work was considered as 'heretical' at peer review by NIH study sections, so it took me quite some time to get the early work published (Twiss et al., 2000; Zheng et al., 2001) and funded (R01-NS041596). After proving that protein synthesis occurs in this subcellular compartment, my lab began to address the mechanisms of RNA transport and localized translation, determining which mRNAs localize, and asking what their protein products do for the axon. Moving back to the East Coast in 2002 allowed me to decrease my clinical load substantially and focus more efforts on my research. I believe that we have advanced the field of axonal protein synthesis as we have developed techniques for analyses of axonal constituents at increasingly higher sensitivities. Our lab was the first to conclusively show that mammalian neurons retain the capacity for axonal protein synthesis into adulthood (Zheng et al., 2001). We specifically developed a method for isolation of axons to purity for molecular, biochemical and morphological analyses. We have successfully used this unique culture method for proteomics and transcriptomics to determine what proteins are synthesized in DRG axons, showing that hundreds of different mRNAs localize into mammalian axons and that their transport is regulated by extracellular stimuli (Willis et al., 2005 & 2007). We have developed live cell imaging and colocalization methodologies to dissect axonal transport and localized translational mechanisms with precise spatial and temporal resolution (Willis et al., 2007; Yudin et al., 2008; Vuppalanchi et al., 2010). In work currently under review, we show the importance of localized protein synthesis for axonal regeneration in vivo and prove that this is through transport and localized translation of multiple mRNA cargos for the RNA binding protein ZBP1. Additional studies under review address the translational control of chaperone protein mRNAs in axons. These methods used in these emerging stories have enabled us to identify RNA elements for axonal mRNAs beyond Importin β1 proposed here that will be an invaluable methodological and reagent resource for the experimental plan proposed here.

B. Positions and Honors

Positions and Employment

2009-present Professor of Biology, Drexel University, Philadelphia, PA.
2009-present Head of Biology Department, Drexel University, Philadelphia, PA.
2008-2009 Principal Research Scientist, Nemours Biomedical Research, Wilmington, DE.
2005-2009 Director, Center for Translational Neurobiology, Nemours Biomed. Res., Wilmington, DE.
2004-2009 Associate Professor, Dept. of Pediatrics, Thomas Jefferson Medical School, Philadelphia, PA.
2002-2008 Senior Research Scientist, Nemours Biomed. Res., Wilmington, DE.

2002-2009 Director, Histotechnology Core Laboratory, Nemours Biomed. Res., Alfred I. duPont Hospital for Children, Wilmington, DE.
1996-2002 Assistant Professor, Dept. Pathology and Lab. Med, UCLA, Los Angeles, CA.
1994-1996 Acting Assistant Professor, Dept. Pathology, Stanford Univ. Medical Center, Stanford, CA.
1992-1996 Research Fellow, Dept. Neurobiology, Stanford Univ. Medical School, Stanford, CA.
1993-1994 Chief Resident in Autopsy Pathology, Dept. Pathology, Stanford Univ. Medical Center, Stanford, CA.
1991-1993 Fellowship in Neuropathology, Dept. Pathology, Stanford Univ. Medical Center, Stanford, CA.
1990-1991 Resident in Anatomic Pathology, Dept. Pathology, Stanford Univ. Medical Center, Stanford, CA.

Other Experience

Medical Staff, Stanford University Hospital, 1994-1996.
Medical Staff, UCLA Hospital, 1996-2002.
Medical Staff, Alfred I. duPont Hospital for Children, 2002-2009.
Institutional Animal Care and Use Committee, Nemours Biomedical Research, 2002-2009.
Research Advisory Board, Shriners Hospitals for Children, 2005-2007.
External Advisory Board, Neuroscience Graduate Program, Delaware State Univ., 2006-present.
External Advisory Committee, NSF IGERT, University of Delaware, 2006-2008.
Research Advisory Council, Shriners Hospitals for Children, 2007-present.
Promotions Criteria Committee (Chair), Nemours Biomedical Research, 2008-2009.
External Advisory Board, NIH COBRE "Molecular Design Of Advanced Biomaterials", University of Delaware, 2009-present.
Editorial Board, Molecular and Cellular Proteomics, 2010-present.

Honors

NIH-NINDS Clinical Investigator Development Award (K08-NS01706), 1993.
Faculty Career Development Award, 1997-1998.
Frontiers of Science Faculty Research Development Award, UCLA School of Medicine, 1997.
STOP Cancer Award, Jonnson Cancer Center, UCLA, 1997.

C. Selected Peer-reviewed Publications

Joint publications with the other co-P.I.'s in the present application are marked with **

Most relevant to the current application

1) D.E. Willis, K-W. Li, J-Q. Zheng, A. Smit, T.K. Kelly, T. Merianda, J. Sylvester, J. van Minnen, and **J.L. Twiss**. (2005). *Differential transport and local translation of cytoskeletal, injury-response, and neurodegeneration protein mRNAs in axons.* J Neurosci. 25:778-791. [PMID: 15673657]

2) D.E. Willis, E. van Niekerk, Y. Sasaki, T.T. Merianda, G.G. Williams, M. Kendall, G.J. Bassell, and **J.L. Twiss**. (2007). *Extracellular stimuli specifically regulate localization of individual neuronal mRNAs.* J. Cell Biology 178:965-80. [PMID: 17785519]

3) E. van Niekerk, J.H. Chang, D.E. Willis, K. Reumann, T. Heise, and **J.L. Twiss.** *Sumoylation in axons triggers retrograde transport of the RNA binding protein La*. PNAS 104:12913-12918. [PMID: 17646655]

4) J-Q Zheng, T.K. Kelly, B. Chang, S. Ryazantsev, A.K. Rajasekaran, K.C. Martin, and **J.L. Twiss**. (2001). *A functional role for intra-axonal protein synthesis during axonal regeneration from adult sensory neurons*. J Neurosci 21:9291-303. [PMID: 11717363

5) D. Vuppalanchi, J. Coleman, S. Yoo, T.T. Merianda, A.G. Yadhati, J. Hossain, A. Blesch, D.E. Willis, and **J.L. Twiss**. (2010). *Conserved 3'UTR sequences direct subcellular localization of chaperone protein mRNAs in neurons.* J Biol Chem. 285:18025-38. [PMID: 20308067]

Additional recent publications of importance to the field (in chronological order)

1) **J.L. Twiss** and E.M. Shooter. (1995). *NGF promotes Neurite Regeneration in PC12 Cells by Translational Control.* J Neurochem 64:550-7. [PMID: 7830047]

2) **J.L. Twiss**, D.S. Smith, B. Chang, and E.M. Shooter. (2000). *Translation of ribosomal protein L4 is required for rapid neurite regeneration.* Neurobiol Dis 7:416-28. [PMID: 10964612]

3) R. Molteni, J.Q. Zheng, Z. Ying, and F. Gomez-Pinilla, and **J.L. Twiss**. (2004). *Exercise increases the regenerative potential of sensory neurons.* PNAS 101:8473-8. [PMID: 15159540]

4) ** S. Hanz, E. Perlson, D. Willis, J-Q. Zheng, M. Kohler, J. van Minnen, A. Sabbon, J.J. Huerta, M. Koltzenberg, **J.L. Twiss**, and M. Fainzilber. (2003). *Axoplasmic importins enable retrograde injury signaling in lesioned nerve*. Neuron 40:1095-104. [PMID: 14687545]

5) ** M. Fainzilber and **J.L. Twiss**. (2006). *Tracking in the Wlds - the hunting of the SIRT and the luring of the Draper.* Neuron 50:819-21. [PMID: 16772165]

6) ** D. Yudin, S. Hanz, S. Yoo, E. Iavnilovitch, D.E. Willis, T. Gradus, Y. Segal-Ruder, K. Ben-Yaakov, M. Hieda, Y. Yoneda, **J.L. Twiss**, and M. Fainzilber (2008). *Localized regulation of axonal RanGTPase controls retrograde injury signaling in peripheral nerve.* Neuron 59:241-252. [PMID: 18667152]

7) T.T. Merianda, A. Lin, J. Lam, D. Vuppalanchi, D.E. Willis, N. Karin, C.E. Holt, and **J.L. Twiss**. (2009). *A functional equivalent of endoplasmic reticulum and Golgi in axons for secretion of locally synthesized proteins.* Mol Cell Neurosci 40:128-42. [PMID: 19022387]

8) T. Ma, A. Campana, P. Lange, H.-H. Lee, K. Banerjee, J.B. Bryson, L. Mahishi, S. Alam, R. Giger, S. Barnes, S. Morris, D.E. Willis, **J.L Twiss**, M. Filbin, and R. Ratan. (2010). *A large scale chemical screen for regulators of the arginase 1 promoter identifies the soy isoflavone, daidzein as a clinically approved, small molecule that can promote neuronal protection or regeneration via a cAMP-independent pathway.* J Neurosci 30:739-48. [PMID: 20071539]

9) ** C.J. Donnelly, M. Fainzilber, and **J.L. Twiss**. (2010). *Subcellular communication through RNA transport and localized protein synthesis.* Traffic *in press*: doi: 10.1111/j.1399-0004.2010.01118.x.

D. Research Support Ongoing Research Support

Ongoing Research Support

R01-NS041596-09 (Twiss)
NIH/NINDS
Molecular determinants of RNA transport 4/01-6/11
The major goal of this grant is to dissect RNA transport and translational control elements for axonal mRNAs focusing on growth associated transcripts (calreticulin, neurtin/cgp15, nmp35 and amphoterin) that the PI's lab identified as showing axonal localization in injury-conditioned DRG cultures.
Role: PI
Overlap: There is thematic overlap with current application since some of the RNA elements uncovered in these studies may be utilized in the studies proposed in Aim 4 (e.g., amphoterin mRNA shows constitutive transport into axons but the 60 nucleotide localization motif at beginning of its 3'UTR shares no homology with importin β1 stem-loop outlined here). There is no budgetary or expeirmental overlap.

P116 (Twiss)
IFP/IRP - Internationale Stiftung für Forschung in Paraplegie 5/10-4/12
Integration of injury response through axonal mRNA transport
The major goal of this work is to determine links between injury-induced transcription and axonal mRNA transport, both in peripheral and central branches of DRG neurons.
Role: PI
Overlap: NONE

MCB-1020970
NSF
Assebly of neuronal ribosomes 9/10-8/14
The goal of this award is to determine if axonal RP mRNAs are translated, if their products are added to the ribosome in axons, and if this addition modifies ribosome function.
Role: PI
Overlap: NONE.

P20-RR020173-07 (Shaffer)
NIH/NCRR 9/04-8/15
Center for Pediatric Research (COBRE

The major goal of this center grant proposal is to develop a research center to increase infrastructure and faculty competitiveness for pediatric research in the state of Delaware, an IDEA state [Twiss serves as a faculty mentor on this award].
Role: Faculty mentor for Target Investigators.
Overlap: NONE

Completed Research Support

1 RO1 NS049041-01 (Twiss)
NIH/NINDS 7/06-2/11
Regulation of axonal protein synthesis
The objective of this grant is to determine how growth-promoting and growth-inhibiting stimuli regulate the specificity of axonal protein synthesis using a combination of high throughput proteomics and molecular based approaches to profile acute alterations in axonal mRNA and protein content. *Note: this award does not include any RNA element analyses or live cell imaging approaches that are included in the present proposal.*
Role: PI

TB2-0602-2 (Twiss)
Christopher Reeve Paralysis Fnd. 1/07-6/09
RNA transport in regenerating axons.
The aims of this award are to i.) map out *cis*-elements for RNA transport of neuritin and amphoterin mRNAs, and, ii.) determine how modulating axonal levels of the RNA chaperone La alters axonal regeneration.
Role: PI

R01-NS045729-02 (S.T. Carmichael)
NIH/NINDS 9/04-9/08
Mechanisms of Axonal Sprouting after Stroke
The major goal of the subcontract to J Twiss is to determine efficacy and dosage for agents to block the CNS extracellular matrix inhibition of axonal outgrowth using primary neuronal cultures. The objective of the overall grant is to determine how axonal sprouting can be facilitated after stroke.
Role: Co-investigator.

unnumbered award (Twiss)
Adelson Program in Neural Repair and Rehabilitation. 7/06-12/08
Kinetics of local protein synthesis in regenerating axons.
The objective of this was to use ribonomics and in silico methods for axonal RNA motif discovery.
Role: PI

2003-208 (M. Fainzilber)
US-Israel Binational Science Foundation 9/04-8/08
Local axonal translation in long range retrograde signaling in neurons.
The major objective of this collaborative grant is to explore the role of axonal protein synthesis in generating retrograde signaling complexes.
Role: Co-investigator (US Partner)

R01-NS41596 (Twiss)
NIH/NINDS 4/01-3/08
Dynamic regulation of translation during nerve regeneration.
The major goal of this grant is to study the identify and characterize mRNAs whose translation is temporally or spatially regulated during nerve regeneration.
Role: PI

R21-NS045880 (Twiss)
NIH/NINDS 3/03-2/06
Neuronal mRNA transport and local translation analysis
The major goal of this grant is to generate a transgenic mouse model to analyze PNS mRNA transport.
Role: PI