BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Deneen, Benjamin

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

POSITION TITLE: Associate 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 California Davis, Davis, CA	BS	06/1997	Genetics
University of California Los Angeles, Los Angeles, CA	Ph.D.	12/2002	Cancer Biology
California Institute of Technology, Pasadena, CA	Fellowship	12/2008	Developmental Neuroscience

A. Personal Statement

My laboratory studies the molecular and cellular mechanisms that control the generation and differentiation of glial cells. While glia constitute roughly 70-80% of the CNS, the transcriptional mechanisms that control their development and diversity remain poorly defined. We have identified a family of transcription factors (the Nuclear Factor I family or NFI) that control the specification of glial cell identity in the embryonic spinal cord. Using the induction of NFI genes at the onset of gliogenesis as a starting point, my laboratory has begun to unravel the upstream and downstream mechanisms that encompass NFI gene function during this crucial developmental interval. Another focal point of my laboratory is the translation of the molecular mechanisms that control glial fate determination to neurological disease. We have found that NFI genes and several of their critical target genes are expressed in human gliomas and human white matter injury (Multiple Sclerosis) and directly contribute to the associated pathology of these diseases in animal models. Therefore the goal of my research program is identify novel paradigms controlling gliogenesis and apply these principles to the study of neurological disease.

B. Positions and Honors

Positions and Employment

2003 – 2008 Postdoctoral Scholar in Biology, California Institute of Technology, Pasadena, CA.
Division of Biology, HHMI Laboratory of Dr. David Anderson

2009 -- 2013 Assistant Professor, Baylor College of Medicine, Houston, TX.
Department of Neuroscience, Center for Cell and Gene Therapy

2014 – current Associate Professor, Baylor College of Medicine, Houston, TX
Department of Neuroscience, Center for Cell and Gene Therapy

Honors

2010 V Scholar Award, V Foundation for Cancer Research
2011 Sontag Foundation Distinguished Scientist Award
2015 Michael E. DeBakey Excellence in Research Award

C. Contributions to Science

1. **Developmental Gliogenesis:** During my post-doctoral studies and the formative stages of my independent career, I tackled the major question of transcriptional control of developmental gliogenesis. These questions arose after it was found that glial-associated fly homologues did not have the same roles in the mammalian CNS. Using existing mouse tools, I developed novel *in vivo* temporal coding and direct embryonic transplantation approaches to define glial-specific expression profiles and their associated cell fates in the embryonic spinal cord. In parallel, I implemented the first chick-shRNAi system to systematically test the role of candidate factors in gliogenesis *in vivo*. Together, these studies identified the NFI-family of transcription factors, and were the first to identify the transcription factors that control the specification of glial cell identity from neural stem cells *in vivo*. The biology surrounding NFI family genes during developmental gliogenesis and the systems I developed to study these genes has fueled much of the early work from my lab. These studies have resulted in the identification of Sox9 as a key regulator of NFIA induction and collaborator in regulating glial-specific gene programs that drive patterning and early gliogenesis in the embryonic spinal cord.

a. **Deneen B**, Ho R, Lukaszewicz A, Hochstim CJ, Gronostajski RM, Anderson DJ. (2006) The transcription factor NFIA controls the onset of gliogenesis in the developing spinal cord. *Neuron* 52:953-68. PMID: 17178400
b. Hochstim CJ, **Deneen B**, Zhou Q, Anderson DJ (2008) The spinal cord contains positionally distinct astrocyte subtypes whose identities are specified by a homeodomain transcriptional code. *Cell* 133:510-522. PMID: 18455991
c. Lee HK and **Deneen B** (2012) Daam2 is required for dorsal patterning via modulation of canonical Wnt signaling in the developing spinal cord. *Developmental Cell* 22(1):183-196. PMID: 22227309 ***Highlighted in Faculty of 1000*
d. Kang P, Lee HK, Glasgow S, Finley M, Donti T, Gaber ZB, Graham BH, Foster AE, Novitch BG, Gronostajski RM, and **Deneen B** (2012) Sox9 and NFIA coordinate a transcriptional regulatory cascade during the initiation of gliogenesis. *Neuron* 74(1):79-94. PMID: 22500632 ***Highlighted in Faculty of 1000*

2. **Mechanisms Underlying White Matter Injury and Repair:** In addition to cancer, developmental mechanisms also play critical roles in tissue regeneration. Given my longstanding interest in gliogenesis, I expanded my research program into white matter injury and repair. My initial studies in this area uncovered that NFIA plays a key role in suppressing oligodendrocyte differentiation during development and after white matter injury (WMI). Moreover, we characterized NFIA expression in human WMI, showing for the first time that NFIA plays a key role in CNS injury. Next we applied to these principles of WMI to a novel modifier of the Wnt pathway we recently identified, Daam2 (also see section 1). Using a series of developmental and injury models, spanning chick, mouse and human, we identified a novel regulatory pathway for Wnt signaling between Daam2-PIP5K that suppresses repair after WMI. Our developmental and injury studies suggested a pharmacological strategy for stimulating repair after WMI, application of which promoted remyelination after injury. These studies were the first to describe the role of Daam2-PIP5K in both Wnt signaling and oligodendrocyte development, and point to a new therapeutic strategy for repairing WMI.

a. Fancy SF, Glasgow S, Finley M, Rowitch DH, and **Deneen B** (2012) Evidence that NFIA inhibits repair after white matter injury. *Annals of Neurology* 72(2):224-233. PMID: 22807310
b. **Deneen B**. and Gallo, V. (2014) Glial Development: The Crossroads of Regeneration and Repair in the CNS. *Neuron*, 83:283-308. PMID: 25033178
c. Lee HK, Chaboub LS, Zhu W, Zollinger D, Rasband MN, Fancy SF, and **Deneen B**. (2015) Daam2-PIP5K is a novel regulatory pathway for Wnt signaling and therapeutic target for remyelination in the CNS. *Neuron* 85(6): 1227-1243. PMID: 25754822 ***Highlighted in Faculty of 1000*
d. Lee HK, Laug D, Zhu W, Patel JM, Ung K, Arenkiel BR, Fancy SF, Mohila CM, and **Deneen B.** (2015) Apcdd1 stimulates oligodendrocyte differentiation after white matter injury. *Glia* 63(8): 1320-1329. PMID: 25946682

3. **The Intersection of Development and Tumor Biology:** Contemporary views regard tumorigenesis as a convergence of genetic mutation and developmental context. This perspective was reinforced during my graduate studies on the pediatric cancer Ewing's Sarcoma, where I studied the EWS/FLI1 translocation and identified its developmental relationship with the $p16^{Ink4a/ARF}$ tumor suppressor pathway. Towards the end of my post-doctoral studies, I characterized the expression of NFI-family genes in glioma. Since then, my laboratory has focused on the biology of NFI-family genes in glioma, identifying a novel microRNA circuit that regulates NFIA expression in glioma and contributes to tumorigenesis. These studies are the first characterization of NFIA function in glioma. In parallel, we developed a new mouse model of glioma and found that NFIA can interconvert distinct glioma subtypes, providing the first evidence that transcriptional regulators of glial fate oversee the generation of diverse glioma sub-types. Taken more broadly, these findings reveal a new logic to the convergence between development and cancer, where sub-lineage specific developmental relationships oversee the generation of associated tumor sub-types.

a. **Deneen B**, Denny CT. (2001) Loss of p16 pathways stabilizes EWS/FLI1 expression and complements EWS/FLI1 mediated transformation. *Oncogene* 20:6731-41. PMID: 11709708
b. Song H-R, Gonzalez-Gomez I, Suh GS, Commins DL, Sposto R, Ji L, Gilles FH, **Deneen B*** and Erdreich-Epstein A***** (2010) Nuclear Factor I A is expressed in astrocytomas and is associated with improved progression-free survival. *Neuro-Oncology* 12(2):122-32. PMID: 20150379
***Equal Contribution**
c. Glasgow S, Laug D, Brawley V, Zhang Z, Corder A, Yin Z , Wong STC, Li XN, Foster AE, Ahmed A, and **Deneen B**. (2013) The miR223-NFIA Axis Regulates Glial Precursor Proliferation and Tumorigenesis in the CNS. *Journal of Neuroscience* 33(33):13560-13568. PMID: 23946414 ***Featured in Science "Editors Choice" http://www.sciencemag.org/content/341/6150/1044.4.short***
d. Glasgow S, Zhu W, Stolt CC, Huang TW, Chen F, LoTurco JJ, Neul JL, Wegner M, Mohila CM, and **Deneen B.** (2014) Mutual Antagonism Between Sox10 and NFIA Regulates Diversification of Glial Lineages and Glioma Sub-Types. *Nature Neuroscience* 17(10): 1322-1329. PMID:25151262

For a Complete list of my Published Work (27 total publications):
http://www.ncbi.nlm.nih.gov/pubmed/?term=deneen+b

D. Research Support

Active

R01-NS071153 7/01/10 – 6/30/19
Mechanisms governing Nuclear Factor I gene induction and function during the initiation of gliogenesis.
Role: PI
In these studies we will identify the upstream regulators of NFI genes during the initation of gliogenesis and a subset of their target genes, using the embryonic chick spinal cord as our experimental model system.

1RF-AG054111 7/01/16 – 6/30/21
Decoding the role of diverse astrocyte populations in aging and AD
Role: co-PI
In these studies we will examine how diverse astrocyte subpopulations evolve during aging and contribute to the pathogenesis of Alzheimer's disease.

R21-NS093145 7/01/16 – 6/30/18
Developing novel therapeutic approaches for white matter injury in the neonatal brain
Role: PI
In these studies we will test a set of novel small compounds for their ability to stimulate repair after neonatal white matter injury

R21-NS089366 4/01/15 – 3/31/17
The nature of astrocyte heterogeneity in RTT
Role: PI
In these studies we will explore the cellular and molecular heterogeneity of astrocytes from normal and RTT mouse models.

Cancer Prevention Research Institute of Texas 5/1/15 – 4/30/19
Role: PI
Personalized Functionalization of Pediatric High Grade Glioma
The goal of these studies is to perform functional genomics on patient-specific mutation cohorts in a newly developed mouse model of PHGG. These studies will decode driver and passenger relationships amongst patient specific mutation sets, guiding personalized approaches to therapeutics.

Cancer Prevention Research Institute of Texas 3/1/16 – 2/28/19
Role: PI
Decoding Cellular Heterogeneity of Malignant Glioma
The goal of this project is to interrogate the cellular heterogeneity of malignant glioma and to functionally characterize distinct cell compartments, understanding both diverse functions of these populations and the underlying developmental mechanisms that control their genesis

National Multiple Sclerosis Society 10/01/15 – 09/30/18
The role of NFIA in reactive astrocytes after white matter injury in the spinal cord
Role: PI
In this study we will examine how a gene called NFIA contributes to the production of reactive astrocytes after white matter injury in the adult spinal cord, and ultimately how manipulating its associated biology can be used to stimulate repair after demyelinating injuries in the adult CNS.

<u>Completed</u>
V Foundation 09/01/10 – 08/31/14 NCE
Delineating the role of nuclear factor I-A in the generation
of glioblastoma multiforme: Linking glial fate determination and tumorigenesis
Role: PI
Upon completion, these studies will represent the first demonstration of a role for NFIA in GBM formation and provide a mechanistic platform that can be used to develop therapies to target the GBM-TSC through glial specific developmental pathways.

Simmons Foundation CRF (Arenkiel) 03/01/13 – 03/01/14
Uncovering Roles for Astrocytes at Central
Nervous System Synapses
Role: Co-PI
The goal of this project is to delineate the role of astrocytes and their heterogeneity towards synapse formation in the olfactory bulb.

The Sontag Foundation 10/01/11 – 09/30/15
Molecular control of astrocyte precursor migration.
Role: PI
Identification and functional analysis of NFIA target genes that control the migration of astrocyte precursors during development and tumorigenesis.