BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.

NAME	POSITION TITLE
Donald B. DeFranco	Professor
eRA COMMONS USER NAME (credential, e.g., agency login) ddefranco	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Temple University, Philadelphia, PA	B.A.	1972-1976	Biology
Yale University, New Haven, CT	Ph.D.	1977-1981	Molecular Biophysics & Biochemistrv
University of California, San Francisco, CA	Postdoc	1982-1985	Biochemistry

A. Personal Statement

My laboratory has spent nearly 25 years examining the glucocorticoid receptor function focusing predominantly on the mechanisms of glucocorticoid receptor transactivation, interaction with coactivators, subcellular and subnuclear trafficking, interactions with molecular chaperones and processing. Over the years we have utilized various experimental model systems to provide novel mechanistic insights into receptor action. Some of our studies are utilized neuronal cell systems and in particular, we were one of the first to provide direct demonstration of glucocorticoid receptor tethering to a DNA-bound transcription factor of the homeodomain family (i.e. Oct-1) utilizing a cell line of hypothalamic origin. Furthermore, using cells of hippocampal origin we provided one of the first demonstrations of developmentally regulated receptor degradation that is likely to be influenced by a receptor co-chaperone (e.g. CHIP). We have furthermore utilized state of the art molecular approaches (e.g. chromatin immunoprecipitation) to provide insights into receptor interactions with unique coregulator proteins (i.e. Hic-5) on chromatin. In the past few years we have initiated a collaboration with Dr. Paula Monaghan-Nichols, a developmental neurobiologist with expertise in the role of select transcription factors in neural stem cell proliferation, cell cycle transit and differentiation, to expand our analysis of glucocorticoid receptor function to an area of clinical relevance. Clinical studies of postnatal and antenatal glucocorticoid administration and both *in-vivo* and *in-vitro* animal studies suggest that detrimental effects of these hormones on neural function in adults and juveniles may be caused by alterations in the proliferation and differentiation of embryonic neural stem cells. I have been involved in training at various levels having mentored 20 graduate students, 11 postdocs, and 8 clinical fellows. I served as a regular member of the BRT study section for 5 years and reviewed T32 applications in many areas (pharmacology, neurobiology, MSTP, cell and molecular biology, etc) and was the PI of a T32 in Pharmacological Sciences that was renewed during my leadership on its first submission.

B. Positions and Honors

Positions and Employment

1977-1981 Graduate Research Assistant, Laboratory of Dr. Dieter Söll, Department of Molecular Biophysics and Biochemistry, Yale University, New Haven, CT
1982-1985 Postdoctoral Fellow, Laboratory of Dr. Keith Yamamoto, Department of Biochemistry and Biophysics, University of California, San Francisco, CA
1985-1991 Assistant Professor, Department of Biological Sciences, University of Pittsburgh, Pittsburgh, PA
1991- 1996 Associate Professor, Department of Biological Sciences, University of Pittsburgh
1996 – 2000 Professor, Department of Biological Sciences, University of Pittsburgh

1997 - Professor, Department of Neuroscience, University of Pittsburgh (Secondary Appointment)
1998 Acting Chairman, Department of Biological Sciences, University of Pittsburgh
2000 - Professor, Department of Pharmacology & Chemical Biology, University of Pittsburgh School of Medicine
2010 - Vice-Chair of Medical Education, Department of Pharmacology & Chemical Biology, University of Pittsburgh School of Medicine
2014 - Assistant Dean of Medical Student Research, University of Pittsburgh School of Medicine

Other Experience and Professional Memberships

1995- 2008 Editorial Board (1995-2003), Associate Editor (2004-2008), *Molecular Endocrinology*
2009 - 2013 Editor-in-Chief, *Molecular Endocrinology*
1996- 2001 Editorial Board, *Journal of Biological Chemistry* (1996-2001), *Neuroendocrinology* (1997-1999)
2001- 2003 Director, Molecular Biology Section of "Course in Neurobiology", Marine Biological Laboratory, Woods Hole, MA

Honors

1976 Summa cum laude, Honors in Biology, Phi Beta Kappa, N.D. Lane Science Prize
1982-1983 Damon Runyon-Walter Winchell Postdoctoral Fellowship
1986-1989 Basil O'Connor Starter Scholar Award, March of Dimes Foundation
1991-1996 Research Career Development Award, National Cancer Institute

Federal Government Public Advisory Committee Service

1992-1998 Endocrinology Study Section, ad-hoc (1992-1994), full member (1994-1998)
1993-2005 National Institutes of Health Special Emphasis Panels or Site Visits
1. NIDDK Program Project on "Mechanism of Growth Control by Steroids", UTHSC, Galveston, TX (11/93, 03/95), 2. NINDS Special Study Section, "Parkin Protein and Parkinson's Disease" (11/00), 3. NINDS Special Mock Study Section on "Hypothermia and Neuroprotection", University of Alaska-Fairbanks (09/02), 4. Biochemical and Endocrinology Sciences Study Section Special Emphasis Panel on "Reproductive Sciences" (03/03, 11/03), 5. NCI Program Project on "Mechanisms of Prostate Cancer", University of Virginia (06/03, 02/04), 6. NIA Special Emphasis Panel on "Reproductive Hormones and the Brain" (11/05)
2007 Molecular and Cellular Endocrinology Study Section, ad-hoc member
2007- 2013 Biomedical Research and Training (BRT-A) Study Section, full member
2014 NIEHS Intramural Program Site Visit, Ad hoc reviewer

C. Selected peer-reviewed publications

Most Relevant to the current application

1. Levinthal DJ, **DeFranco DB.** (2005) Reversible oxidation of ERK-directed protein phosphatases drives oxidative toxicity in neurons. J. Biol Chem. 280, 5875-5883. PMID: 15579467, PMCID in process
2. Heitzer M.D. and **DeFranco D.B.** (2006) Regulation of androgen induced KGF gene transcription in prostate stromal cells by a cell type-restricted androgen receptor coactivator, Hic-5/ARA55. Cancer Res. 66, 7326-7333. PMID: 16849583, PMCID in process
3. Samarasinghe RA, Di Maio R, Volonte D, Galbiati, F, Lewis M, Romero G, **DeFranco DB** (2011). Non-genomic glucocorticoid receptor action regulates gap junction intercellular communication and neural progenitor cell proliferation. Proc. Natl. Acad. Sci. USA 108, 16657-16662. PMID: 21930911, PMCID: PMC3189065
4. Grubisha, MJ, Cifuentes ME, Hammes, S, **DeFranco DB** (2012). A local paracrine and endocrine network involving TGFβ, Cox-2, ROS and estrogen receptor beta impacts reactive stromal cell regulation of prostate cancer cell motility. Mol. Endocrinol. 26, 940-954. PMCID: PMC3355541
5. Tsiarli MA, Monaghan-Nichols AP, **DeFranco DB** (2013). Differential subcellular localization of the glucocorticoid receptor in distinct neural stem and progenitor populations of the mouse telencephalon *in vivo*. Brain Research 1523, 10-27 (cover article). PMID: 23751362, PMCID: PMC374978

Additional recent publications of importance to the field (in chronological order) (selected from 102 publications)

1. Cummings, C.J., Mancini, M.A., Antalffy, B., **DeFranco, D.B.**, Orr, H.T., and Zoghbi, H.Y. (1998). Chaperone suppression of ataxin-1 aggregation and altered subcellular proteosome localization imply misfolding in SCA1. Nature Genet. 19, 148-154. PMID: 9620770, PMCID in process
2. Xiao, N., Callaway, C.W., Lipinski, C.A., Hicks, S.D., and **DeFranco, D.B.** (1999). Geldanamycin provides post-treatment protection against glutamate-induced oxidative toxicity in a mouse hippocampal cell line. J. Neurochem., 72, 95-101. PMID: 988605, PMCID in process
3. Chandran, U.R., Warren, B.S, Baumann, C.T., Hager, G.L., and **DeFranco D.B.** (1999). The glucocorticoid receptor is tethered to DNA-bound Oct-1 at the mouse GnRH distal negative glucocorticoid response element. J. Biol. Chem. 274, 2372-2378. PMID: 9891005, PMCID in process
4. Liu, J., and **DeFranco, D.B.** (1999). Chromatin recycling of glucocorticoid receptors: Implications for multiple roles of heat shock protein 90. Mol. Endocrinol.13, 355-365. PMID: 10076993, PMCID in process
5. Stanciu, M., Wang, Y., Kentor, R., Burke, N., Watkins, S., Klann, E. Johnson, J. and **DeFranco, D.B.** (2000). Persistent activation of ERKs is a late event that contributes to glutamate-induced oxidative toxicity in a neuronal cell line and primary cortical neuron cultures. J. Biol. Chem. 275, 12200-12206. PMID: 10766856, PMCID in process
6. Jiang H, Nucifora, F., Ross, C.A., and **DeFranco D.B.** (2003). Cell death triggered by polyglutamine-expanded huntingtin in a neuronal cell line is associated with degradation of CREB-binding protein. Human Mol. Genet. 12, 1-12. PMID: 12490527, PMCID in process
7. Kasai, M, Guerrero-Santoro, J, Friedman, R, Leman ES. Getzenberg, RH, and **DeFranco D.B.** (2003). The group 3 LIM domain protein paxillin potentiates androgen receptor transactivation in prostate cancer cell lines. Cancer Research, 63, 4927-4935. PMID: 12941817, PMCID in process
8. Elbi C, Romero G., Walker D., Sullivan W., Toft, D., Hager G.L. and **DeFranco D.B.** (2004). Molecular chaperones function as nuclear mobility factors for steroid receptors. PNAS, USA, 101, 2876-2881. PMID: 14978266, PMCID: PMC365713
9. Sen A, De Castro I, **DeFranco DB**, Deng F-M, Jonathan Melamed, Kapur J, Raj GV, Rossi R, Stephen R Hammes SR (2012). Paxillin regulates prostate cancer proliferation by serving as a liaison between extranuclear kinase signaling and intranuclear transcription. J. Clinical Invest. 122, 2469-2481. PMID: 22684108, PMCID: PMC3386821
10. Indyk JA, Candido-Vitto C, Wolf IM, Venkatarman S, Munor, R, Saladino RA, Witchel, SF, **DeFranco DB** (2013). Altered glucocorticoid signaling in children with critical illness: reduced glucocorticoid receptor protein expression and increased free cortisol concentration. Horm. Res. Pediatr. 79, 169-178. PMID: 23548248, PMCID in process.

D. Research Support

ACTIVE

1. "The Chromatin Landscape of Fetal Hypothalamic Stem Cells"
Principal Investigator: Donald B. DeFranco, Ph.D.
Agency: NIH/NIDDK Type: U24 (DK097746, Year 1): Period 09/17/12 – 08/31/14

The specific aims of this application are: 1) To use global DNase I hypersensitivity (DHS) analysis of fetal hypothalamic neural stem/progenitor cells (NSPCs) to determine whether glucocorticoid (GC) exposure leads to sex-specific, transient or permanent alterations in chromatin landscape. Global DHS analysis will be performed with fetal hypothalamic NSPC cultures derived from male and female embryos to reveal sex-specific differences in GC action. We will also examine NSPC cultures of increasing passages (e.g. P1 vs. P3) during which stem and progenitor cells become progressively lineage restricted as different populations of HT neurons are being specified. 2) To use ChIP-Seq and gene expression microarrays to identify genomic glucocorticoid receptor occupancy and regulated transcripts, respectively, in fetal hypothalamic NSPCs of different sexes and stages of lineage restriction. Biological outcomes that will be assessed in GC treated NSPC cultures at different passages include examination of hormone effects on differentiation.

COMPLETED

1. “Intracellular Mechanisms of Glucocorticoid Action”
Principal Investigator: Donald B. DeFranco, Ph.D.
Agency: NIH/NIDDK
Type: R01 (DK078394, Years 18-23): Period 07/01/07 – 06/30/12

The specific aims of this application are: (1) To identify the pathway of chaperone complex assembly that mediates their activity as steroid receptor nuclear mobility factors, (2) To determine whether molecular chaperones participate in the dynamic exchange of GR and other factors at glucocorticoid response elements (GREs), (3) To determine whether molecular chaperones are required for hormone exchange on nuclear GR.

PENDING

1. “Glucocorticoid Signaling Pathways in Neural Progenitor Cells”
Principal Investigator: Donald B. DeFranco, Ph.D. & AP Monaghan-Nichols, Dual PIs
Agency: NICHD Type: R01: Period 7/01/12 – 06/30/17
This proposal will identify and distinguish the contribution of genomic and nongenomic GC signaling pathways to neuronal specification and function. Cav-1 deficient mice will be used for *in vitro* and *in vivo* studies to isolate novel nongenomic signal mechanisms and to determine their contribution to genomic signaling. Aim 1: To determine and distinguish the short- and long-term consequences of genomic and nongenomic GR signaling pathway on NPC function *in vitro* using NPC cultures derived from embryonic control and Cav-1 deficient mice. Aim 2: To determine the effects of prenatal activation of nongenomic and genomic GR pathways in control and Cav-1 deficient mice on NPC proliferation and differentiation *in vivo*. Aim 3: To determine the contribution of nongenomic GC signaling to the regulation of candidate and genome-wide GR target genes in NPC cultures derived from control and Cav-1 deficient mice.

2. “Estrogen Receptor-beta Signaling in Benign Prostatic Hyperplasia”
Principal Investigator (Project 3): Donald B. DeFranco, Ph.D.
Agency: NIH/NIDDK Type: U54 George M. O’Brien Urology Research Center (Z. Wang, Ph.D., PI)
Period 07/01/14 – 06/30/17

This proposal will examine whether the prostate microenvironment in benign prostatic hyperplasia (BPH) limits the protective effect of estrogen receptor-beta (ERß) by either altering local production of receptor ligands or ERß action on target genes that limit epithelial-mesenchyme transition (EMT) and maintain tissue homeostasis. We hypothesize that the inflammatory drive on BPH derives in part from the inhibition of ERß action. Aim 1 will determine whether ERß limits the progression towards EMT *in vivo* or alters the response of AR to inflammation in wild type and ERß knockout mice. Aim 2 will determine the impact of oxidative stress and inflammatory mediators on ERß target gene expression in immortalized normal prostate epithelial cells and the BPH-1 cell line. Finally, aim 3 will determine whether celecoxib and/or finasteride can alter the ERß signaling pathway or target gene expression in human BPH tissues from a phase II clinical trial.