BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow this format for each person. (See attached sample.) **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Felice Elefant eRA commons user name- ELEFANT1	Associate Professor

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
George Washington University, D.C.	B.S.	06/1987	Biology/Zoology
Hofstra University, NY	M.A.	09/1989	Biology
Temple University, PA	Ph.D.	12/1997	Biology
University of Pennsylvania, PA	Post-doc.	08/2002	Epigenetics

A. Personal Statement.

My research program is focused on understanding the epigenetic neural gene control mechanisms that govern regulation of higher order brain function *via* chromatin packaging control in neurons. I have a long standing interest in chromatin biology and a demonstrated track record in studying epigenetic-based mechanisms underlying neural gene control in the brain. During my training as a post-doctoral fellow in the Department of Genetics, University of Pennsylvania, I carried out NIH NRSA funded research focused on exploring epigenetic-based mechanisms underlying locus control region (LCR) function in long-range gene activation of the human growth hormone (hGH) gene locus. Using various transgenic hGH mouse models, I was the first to discover that recruitment of histone acetyltransferase (HAT) activity to the hGH LCR is crucial for its action in hGH gene control in the pituitary. Since starting my independent laboratory in 2003, my research program has expanded to focus on understanding the role(s) of specific HATs in higher order brain function and cognitive disorders. Impairment of epigenetic gene control mechanisms in the brain involving reduced levels of histone acetylation causes significant cognitive deficits that are a debilitating hallmark of most neurodegenerative disorders, including Alzheimer's disease (AD). Nevertheless, the HATS that generate these neuroepigenetic marks and their mechanisms of action remain largely unclear. Insight into HAT based mechanisms underlying cognition and neuropathology was facilitated by published studies from my laboratory on Tip60 neural HAT function. We generated a robust Tip60;APP *Drosophila* model system that enables us to modulate Tip60 HAT levels in neural circuits of choice under AD associated amyloid precursor protein (APP) neurodegenerative conditions, *in vivo*. Its use led to our exciting discovery that Tip60 is critical for cognitive processes based on its role in neural epigenetic gene control and remarkably, protects multiple cognitive neural circuits impaired in the brain during early AD associated neurodegenerative progression. Further, our recent studies indicate that Tip60 HAT function is impaired in the human AD hippocampus. Our findings have laid a solid groundwork for our current proposal and our **goal** for this project is to identify the mechanisms underlying Tip60 HAT action in neuroprotective gene control using fly and mouse AD models and to determine how these Tip60 epigenetic processes go awry in the brains of human AD patients. My expertise and proven track record in the complementing areas of epigenetic mechanisms of neural gene control and *Drosophila* developmental genetics, and my in depth training and experience using chromatin-based technology on human brain primary tissue and transgenic mouse brain models make myself and my laboratory uniquely well poised to successfully carry out these studies.

(a) Zhu, X., Singh, N., Donnelly, C., Boimel, P. & **Elefant, F***. 2007. The cloning and characterization of the histone acetyltransferase human homolog Dmel\TIP60 in Drosophila melanogaster: Dmel\TIP60 is essential for multicellular development. *Genetics* 175, 1229-40. PMID 17179074; PMCID: 1840084 *Editorially Featured as Issue Highlight.*

(b) Johnson, A., Sarthi, J., Pirooznia, S., Ruebe, B., and **Elefant, F*.** 2013. Increasing Tip60 HAT levels rescues axonal defects and associated behavioral defects in a *Drosophila* Alzheimer's disease model. *Journal of Neuroscience*. 17:7535-47. PMID: 23616558; PMCID: 3711104 *Featured as a 'Key Research Article' in "Psychology Progress".*

(c) Xu S, Wilf R, Menon T, Panikker P, Sarthi J, **Elefant F***. 2014. Epigenetic control of learning and memory in Drosophila by Tip60 HAT action. *Genetics* 4:1571-86. PMID: 25326235; PMCID: PMC4256772 *Editorially featured on cover as Issue Highlight.*

(d) Panikker, P., Xu, S., Beaver, M., Ahktar, S, **Elefant, F*.** 2018. Restoring Tip60 HAT/HDAC2 balance in the neurodegenerative brain relieves epigenetic transcriptional repression and reinstates cognition, *Journal of Neuroscience*, Apr 13. pii: 2840-17. Featured in *Newsweek*, Drexel NOW, US Against Alzheimer's, The Space Nation, News Medical Life Sciences, Tech & Science, Science Daily.

B. Positions and Honors.

Positions and Employment

1990-1992	***Research Associate*.** Department of Virology and Antibody Engineering, MedImmune Inc., Gaithersburg, MD
1992-1997	***Ph.D. student.*** Department of Biology, Temple University, Philadelphia, PA
1992-1997	***Teaching Fellow*.** Department of Biology, Temple University, Philadelphia, PA
1997-1999	***Howard Hughes Medical Institute Postdoctoral Fellow*.** Howard Hughes Medical Institute (HHMI), University of Pennsylvania, Philadelphia, PA
1999-2002	***NIH Postdoctoral Fellow.* (NRSA F32-HD-08471)** Departments of Genetics and Medicine, University of Pennsylvania, Philadelphia, PA
2001	***Instructor*.** Department of Medicine, University of Pennsylvania, Philadelphia, PA
2002-2008	***Assistant Professor*.** Department of Biology, Drexel University, Philadelphia, PA
2009-present	**Associate Professor; Co-Associate Department Head (2013).** Department of Biology, Drexel University, Philadelphia, PA
2016-present	**Associate Professor**, Molecular and Cell Biology & Genetics (MCBG) Program, Drexel University College of Medicine, Philadelphia, PA
2017-present	**Director; Graduate Program**, Department of Biology, Drexel University, Phildelphia, PA

Honors and Fellowships

1999-2002	NIH/NIDDK: National Research Service Award (NRSA)
2000	First place poster award and Travel Award, 4th International Conference on Growth Hormone Research Society, Goteborg, Sweden
2004-2006	NIH/NICHD: R03 Award; 1.8 percentile
2005	Dean's award: Graduate student research, Drexel University
2009	STAR student Mentor Award, Drexel University
2010	Doctoral Student "Most Promise" Award, Drexel CoAS
2011	Co-Chair & Speaker, Neuro-Talk 2011, Dalian, China
2012	*Genetics* paper editorially featured on cover as *"Issue Highlight"*
2013	*J. of Neuroscience* paper: 'Key Research Article' in "*Psychology Progress".*
2014	Invited Key Speaker; EpiCongress-London Meeting, London, England.
2014	*Genetics* paper editorially featured on cover as *"Issue Highlight"*
2015	Oral presentation; Epigenetics and Chromatin Session, Annual *Drosophila* Conference, Chicago, IL
2015	Invited Speaker; EpiCongress-Boston Meeting, Boston, MA
2016	Mary Howett Award for Undergraduate Research, Drexel University, Mentor
2017	Oral presentation, Annual *Drosophila* Conference, San Diego, CA
2018	Speaker, Neuroepigenetics International Conference, Cancun, Mexico
2018	International Travel Award, Drexel University, Philadelphia, PA, 10104
2018-2019	Executive Leadership in Academic Technology and Engineering (ELATE) Fellow

Professional Memberships and Activities:

1997-2005	Endocrine Society: member
2000-2003	Growth Hormone Research Society: member

2005-present	American Association for the Advancement of Science: member
2006-present	Genetics Society of America: member
2007-present	Ad hoc reviewer (PloS ONE, Molecular & Cellular Biology, Developmental Biology Journal of Neuroscience, BioEssays, JBM, Neuroscience, J. Neuroscience)
2008-present	University of Pennsylvania Epigenetics Program Member
2011-present	Ad hoc study section member, Italian Ministries of Health
2011	Study section member, Human Cognition Enhancement Program, Drexel U.
2012-present	Editorial Board, *Journal of Molecular Cloning & Genetic Recombination*
2012-2014	National Editorial Board for the Proceedings of National Conferences for Undergraduate Research
2012	Ad hoc study section member, MRC Neurosciences and Mental Health
2012	Ad hoc study section member, NIH NICHD Developmental Biology Subcmt.
2012	Ad hoc study section member, NIH NDPR Neural Differentiation, Plasticity, and Regeneration
2012	Ad hoc study section member, Drexel CURE Formula Grant
2013	Grant reviewer, Hungarian Scientific Research Fund (OKTA)
2013	Ad hoc study section member, NIH NCF Neurogenesis & Cell Fate
2013	Ad hoc study section member, NIH CMBG Cellular & Molecular Biology of Glia
2014-2016	Study section member, Clinical &Translational Research Institute, Drexel U.
2014	Grant reviewer, Netherlands Org. for Health Research & Development
2014	Editorial Board, Advances in Alzheimer's Disease journal
2015	Co-Chair; Epigenetics and Chromatin Session, Annual *Drosophila* Conference
2016	Study Section Member, Commonwealth Universal Research Enhancement (CURE) Program Drexel College of Medicine
2016	Ad hoc Grant reviewer, Israel Science Foundation (ISF)
2016	Ad hoc Grant reviewer, National Science Foundation (NSF)
2017	Ad hoc Grant reviewer, NIH/NIGMS special emphasis panel P20 COBRE
2018	Ad Hoc Grant reviewer, Special Emphasis Panel; Current topics in AD

C. Contributions to Science:

1. ***Molecular Chaperone Proteins.*** My doctoral research and earlier publications focused on exploring a developmental role for the endoplasmic HSC3 and cytoplasmic HSC4 molecular chaperone proteins that function in assembly/folding of macromolecules using *Drosophila* as our model system. As one of the first researchers to utilize the targeted GAL4 system in flies, I screened and characterized a collection of 400 GAL4 enhancer trap lines for useful expression patterns. Using this GAL4 system, I generated unique transgenic flies containing GAL4 responsive wild-type or dominant negative HSC3 and HSC4 genes and targeted their expression to a variety of tissues in the fly. Our results demonstrated that Hsc3 and Hsc4 proteins are each essential for multicellular development and utilize an ATPase hydrolysis dependent cycling mechanism for target protein binding and release during the protein folding process. Importantly, these chaperone fly lines were also utilized by many other research groups and revealed for the first time that induction of molecular chaperone proteins can effectively rescue misfolded protein neurodegenerative disorders modeled in *Drosophila*. As such, the HSC3 and HSC4 molecular chaperone fly lines I generated are still utilized as a powerful tool by numerous laboratories world wide to explore mechanisms underlying the therapeutic role of chaperones in an array of protein misfolding neurological disorders.

(a) Manseau, L., Baradaran, A., Brower, D., Budhu, A., **Elefant, F.,** Phan, H., Philip,A., Yang, M., Glover, D., Kaiser, K., Palter, K.B., Selleck, S. 1997. GAL4 enhancer traps expressed in the embryo, larval brain, imaginal discs, and ovary of *Drosophila*. *Developmental Dynamics* 209: 310-322. PMID: 9215645
(b) Mehta, A.S., Rubin, D,M., **Elefant, F.,** Palter, K.B. 1997. *Drosophila melanogaster HSC4* proteins. In *Guidebook to Molecular Chaperones and Protein Folding Catalysts*, ed. M.J. Gething. Oxford University Press. pg. 42-45.
(c) Elefant, F. and Palter, K.B. 1999. Tissue-specific expression of dominant negative mutant *Drosophila HSC70* causes developmental defects and lethality. *Mol. Biol. Cell* 10: 2101-2117 PMID: 10397752; PMIC: 25422

2. ***Human Growth Hormone LCR.*** As a postdoctoral researcher at the University of Pennsylvania, my research and publications focused on exploring epigenetic-based mechanisms underlying locus control region (LCR) function in long-range gene activation of the human growth hormone (hGH) gene locus using transgenic mouse models and human pituitary primary tissue. During the late 1990's, the idea that histone acetylation was critical for LCR function in chromatin organization was slowly gaining recognition, however methods to test this concept in primary tissues *in vivo* were only just beginning to emerge. As the first researcher to adapt chromatin immunoprecipitation (ChIP) for use in primary human and mouse brain tissue, I was the first to discover that recruitment of histone acetyltransferase activity to the hGH LCR and subsequent acetylation spread LCR wide is crucial for its action in hGH gene control in the pituitary. My findings also provided compelling evidence supporting a new model that tissue specific patterns of histone acetylation contribute to LCR action and hGH gene activation in the pituitary and placenta.

(a) Elefant, F., Cooke, N.E., Liebhaber, S.A. 2000(a). Targeted recruitment of histone acetyltransferase activity to a locus control region. *JBC* 275: 13827-13834. PMID: 10788505
(b) Elefant, F., Su, Y., Liebhaber, S.A., and Cooke, N.E. 2000(b). Patterns of histone acetylation suggest dual pathways for gene activation by a bifunctional locus control region. *EMBO J.* 19: 6814-6822. PMID: 11118216; PMIC: 305892
(c) Ho, Y., **Elefant, F.,** Cooke, N.E., and Liebhaber, S.A. 2002. A defined locus control region determinant links chromatin domain acetylation with long-range gene activation. *Molecular Cell*. 9: 291-302. PMID: 11864603 *Highlighted in Daily University Science News, Penn Medicine News*
(d) Ho, Y., **Elefant, F.**, Cooke, N.E., and Liebhaber, S.A. 2006. Locus control region transcription is required for long range gene activation. *Mol. Cell.* 23: 365-375. PMID: 16885026; PMIC: *Highlighted in Scientist Live, Penn.Medicine News, Medical News today, Bio.com, Drexel Link*

3. ***A neuroprotective role for Tip60 HAT action in cognitive function.*** Since starting my independent laboratory in 2003, my research program has been focused on understanding the epigenetic neural gene control mechanisms that govern regulation of higher order brain function *via* chromatin packaging control in neurons. Impairment of epigenetic gene control mechanisms in the brain involving reduced levels of histone acetylation causes significant cognitive deficits that are a debilitating hallmark of most neurodegenerative disorders, including Alzheimer's disease (AD). Nevertheless, the specific HATs that generate these neuroepigenetic marks and their mechanisms of action in neural epigenetic gene control in the brain remain largely unknown. Insight into HAT based mechanisms underlying cognition and neuropathology was facilitated by published studies from my laboratory on Tip60 neural HAT function. Tip60 is the second highest expressed HAT of the 18 HATs in mammalian adult brain. Yet before our studies, a causative role for Tip60 in cognitive neural function was unknown. We generated a robust Tip60;APP *Drosophila* model system that enables us to modulate Tip60 HAT levels in neural circuits of choice under AD associated amyloid precursor protein (APP) neurodegenerative conditions, *in vivo*. Its use led to our recent exciting discovery and compendium of publications demonstrating that Tip60 is critical for cognitive processes based on its role in neural epigenetic gene control and remarkably, protects multiple cognitive neural circuits impaired in the brain during early AD associated neurodegenerative progression.

(a) Pirooznia, S.[+] and **Elefant , F***. 2013. Targeting Specific HATs for Neurodegenerative Disease Treatment: Translating Basic Biology to Therapeutic Possibilities. Frontiers in Cellular Neuroscience. 7:30. doi: 10.3389/fncel.2013.00030. Epub 2013 Mar 28.18. *Editorially featured as one of top viewed reviews 2013.*
(b) Johnson, A., Sarthi, J., Pirooznia, S., Ruebe, B., and **Elefant, F*.** 2013. Increasing Tip60 HAT levels rescues axonal defects and associated behavioral defects in a *Drosophila* Alzheimer's disease model. *Journal of Neuroscience*. 17:7535-47. PMID: 23616558; PMCID: 3711104 *Featured as a 'Key Research Article' in "Psychology Progress".*
(c) Xu, S., Wilf, R., Menon, T., Panikker, P., Sarthi, J., **Elefant F***. 2014. Epigenetic control of learning and memory in *Drosophila* by Tip60 HAT action. *Genetics* 4:1571-86. PMID: 25326235; PMCID: PMC4256772 *Editorially featured on cover as Issue Highlight.*
(d) Xu, S.[+], Panikker, P.[+], Iqbal, S.[#], **Elefant, F*.** 2016. Tip60 HAT action mediates environmental enrichment induced cognitive restoration. PloS ONE, 11(7);e0159623
(e) Panikker, P., Xu, S., Beaver, M., Ahktar, S, **Elefant, F*.** 2018. Restoring Tip60 HAT/HDAC2 balance in the neurodegenerative brain relieves epigenetic transcriptional repression and reinstates cognition, *Journal*

of Neuroscience, 2018 Apr 13. pii: 2840-17. Featured in **Newsweek**, Drexel NOW, US Against Alzheimer's, The Space Nation, News Medical Life Sciences, Tech & Science, Science Daily.

4. ***Tip60 and APP in sleep.*** Our investigation of Tip60 and APP in higher order brain function opened a new line of investigation for us that focus on a role for Tip60 in sleep. Sleep disturbances are common in neurodegenerative disease such as AD. Unfortunately, how AD is mechanistically linked with interference of the body's natural sleep rhythms remained unclear. Our studies provide compelling evidence that sleep disruption associated with AD is in part, driven by epigenetic changes mediated by Tip60.

(a) Pirooznia, K.., J., Chieu, K., Chan, M., Zimmerman, J and **Elefant, F.*** 2012 Tip60 and APP mediate axonal growth and PDF levels in *Drosophila* clock neurons to regulate sleep. *Genetics* 4:1327-45. PMID: 22982579; PMCID: PMC3512142 *Editorially featured on cover as Issue Highlight.*
(b) Pirooznia, S., and **Elefant, F*.** 2013. A HAT for sleep? – Epigenetic regulation of sleep by Tip60 in *Drosophila*. *Invited "Extra Views" Fly.* 2:99-104. PMID: 23572111;PMCID: PMC3732338
(c) "An Alzheimer's Cure- with Fruit Flies" 2013 *Exel*: Drexel University Research Magazine exelmagazine.org/article/an-alzheimers-cure-for-fruit-flies
(d) "Sleepy Flies Help Understand Alzheimer's Brains" 2014. *Inside Science TV* Video News segment, http://www.insidescience.org/content/sleepy-flies-help-understand-alzheimers-brains/1534

Complete List of Published Work in MyBibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/1BcYdxvdWplkx/bibliography/48036479/public/?sort=date&direction=ascending

D. Research Support.

Current Research Support

8/1/2017- 4/20/2022
R01 NS095799, National Institute of Neurological Disorders and Stroke (NINDS)
Mechanisms underlying Tip60 HAT action in neuroprotection of cognitive function.
Role: PI
Determine how Tip60 epigenetic processes go awry in the Alzheimer's disease brain.

3/2017-6/2018
Commonwealth Universal Research Enhancement (CURE) Program Grant, Pennsylvania Dept. of Health
Effects of GSK3β on the prefrontal dopamine system
Determine epigenetic mechanisms underlying GSK3β control in prefrontal dopamine system. Role: Co-I

Completed Research Support (past 5 years)

1/2015-12/2015
Commonwealth Universal Research Enhancement (CURE) Program Grant, Pennsylvania Dept. of Health
Metabolic Control of neurogenesis via histone acetyltransferase Tip60
To elucidate modulation of metabolic pathways by Tip60 during neurogenesis. Role: Co-Investigator

9/2008-7/31/2013; no cost extension ended 7/31/2015
R01 HD057939-01A1, National Institute of Child Health and Development (NICHD)
Tip60 and APP in Neuronal Development
Role: PI
Identify Tip60/APP controlled neuronal circuits and target genes during early neurogenesis.