BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2. Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Nancy M. Bonini	Professor of Biology
eRA COMMONS USER NAME nbonini	

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Princeton University, Princeton, NJ	AB	1981	Biology
University of Wisconsin, Madison, WI	PhD	1987	Neuroscience
California Institute of Technology, Pasadena, CA	Postdoc	1988-94	Neuroscience

A. Personal Statement

The research in my laboratory focuses on using the model organism *Drosophila* to reveal insight into genes, mechanisms and risk factors for human brain degenerative disease. In these studies, we use the fly and also human brain tissue with our collaborators. My laboratory pioneered the approach of using the fly to address human brain disease, which has been a popular and impactful application across many laboratories and model organisms. My postdoctoral studies with Dr. Seymour Benzer introduced me to the molecular and genetic power of the fly, as well as the originality in applying *Drosophila* toward questions of relevance to human behavior & brain dysfunction. Since establishing my laboratory in 1994, we developed the fly to study problems of neural degeneration, acute neural injury and aging of the brain. Our initial findings showed that it is possible to model a human degenerative state in this simple model organism with remarkable precision, then "cure" it with the molecular chaperone Hsp70. We have continued establishing and studying various models to reveal novel insight into human brain dysfunction with age through powerful genetic approaches. We have also launched into studies of human disease tissue, and then applied the findings back to the fly for conservation/implications of the discoveries.

My work has received numerous awards, including a David and Lucile Packard Award; John Merck Scholars Award; being named an Investigator of the Howard Hughes Medical Institute; an NIH EUREKA award; an Ellison Senior Scholars Award; an NIH R35 Outstanding Investigator award. My leadership in the field is reflected by election to the board of the Genetics Society of America in 2007, and the National *Drosophila* Board in 2010. I co-organized the Annual *Drosophila* Research Conference in 2008, the Neurobiology of *Drosophila* meeting at Cold Spring Harbor in 2011, and co-organized the 2016 *Drosophila* Research Conference which launched a new meeting format whereby advances in multiple model organisms and their importance to human biology and disease were united in one meeting. I am the Editor of the Annual Reviews of Genetics, and have been elected to the National Academy of Sciences, the National Academy of Medicine, and the American Academy of Arts and Sciences. My record as a scientist with transformative impact is reflected in the original contributions to science that my laboratory has made.

B. Positions & Honors

1981 summer Research Assistant, Princeton University. Advisor: Dr. William G. Quinn.
Research focus: Learning and memory behavior in *Drosophila*.

1981-1987 Graduate Research Assistant, Neurosciences Training Program,

	University of Wisconsin-Madison. Advisor: Dr. David L. Nelson.
	Research focus: regulation of ciliary motility by membrane potential in *Paramecium*.
1983 summer	Cold Spring Harbor Laboratory course, Molecular and Cellular Neurobiology.
1988 summer	Cold Spring Harbor Laboratory course, Neurobiology of *Drosophila*.
1988-1994	Postdoctoral fellow, California Institute of Technology.
	Advisor: Dr. Seymour Benzer.
	Research focus: Molecular genetic control of cell survival in the nervous system.
1994-2000	Assistant Professor, Dept of Biology, University of Pennsylvania
1995-	Member of the David Mahoney Institute for Neurological Sciences
2000-2005	Associate Professor, Dept of Biology, University of Pennsylvania
2000-2013	Investigator, Howard Hughes Medical Institute, University of Pennsylvania
2000-	Adjunct faculty, Department of Neuroscience, Penn School of Medicine
2005-	Professor, Dept of Biology, University of Pennsylvania
2006-2012	Lucille B. Williams Term Professor of Biology, University of Pennsylvania
2008	Cold Spring Harbor Laboratory course, *C elegans*
2009-2014	Member of the Penn Genome Frontiers Institute
2012-	Florence R.C. Murray Professor of Biology, University of Pennsylvania
2012-	Member of the Institute of Regenerative Medicine, Neuroscience Program
2013-	Adjunct Faculty, Cell and Developmental Biology, Penn School of Medicine
2013-	Affiliate Scientist, Lawrence Berkeley National Laboratory, Genome Sciences
2014, 2018	Visiting Scientist, Feb 2014, Jan 2018, Salk Institute, with Dr. Joe Ecker.
2014-	Associate member, Computation and integrative Biology Center, Rutgers University

Honors and Awards

1983 Grass Foundation Fellowship, Cold Spring Harbor Laboratories
1988 Jerzy E. Rose Neuroscience Award, for outstanding PhD thesis, University Wisc-Madison
1989 American Cancer Society national postdoctoral fellowship
1991 American Cancer Society, California Division, postdoctoral fellowship
1995 John Merck Scholars Award in the Biology of Developmental Disabilities in Children
1996 March of Dimes, Basil O'Connor Award
1997 David and Lucile Packard Fellowship for Science and Engineering
1998-2000 Huntington's Disease Society of America, Coalition for the Cure Award
1999-2001 Hereditary Disease Foundation, Cure Huntington's Disease Initiative Award
2000 Selected Investigator of the Howard Hughes Medical Institute in national competition
2001-2002 G. William Fox Corporate Humanitarian Award
2002 Princeton Day School Achievement Award, Princeton, NJ, for outstanding alum achievement
2008 Fidelity Foundation Award
2009 NIH EUREKA award
2009 Ellison Medical Foundation Senior Scholar Award
2012 Elected Fellow of the American Association for the Advancement of Science;
National Academy of Sciences; Institute of Medicine of the National Academy of Sciences
2014 Elected Fellow of the American Academy of Arts and Sciences
2016 NIH R35 Outstanding Investigator award

Federal Government Public Advisory Committee Service:

Ad-hoc member of study sections for the NEI, NINDS, and the NIA
Reviewer for NIH Pioneer Awards and Transformative Grants.
Member of the NINDS Scientific Review Council, 2002-2007
Member of CMND study section (formerly NDBG), 2005-2009
Member and Chair of Study Section MNG, 2016- (Chair since 2018)

Scientific and Review Boards:
Council Member Society for Neuroscience, Philadelphia Chapter, 1995-1997

Coalition for the Cure Steering Committee, Huntington's Disease Society of America, 2001-2003
Medical & Scientific Advisory Committee, Huntington's Disease Society of America, 2004-2008
Coalition Review Committee, Huntington's Disease Society of America, 2004-2008
Grants and Fellowships Review Committee, Huntington's Disease Society of America, 2004-2008
Member, Scientific Advisory Board for the Thomas Hartman Foundation Cold Spring Harbor Laboratory Parkinson's Research Partnership, 2005
Genetics Society of America, Board of Directors, 2007-2009
Scientific Advisory Board member, Genome Espana, Cetegen, Spain, 2007-2010.
National Drosophila Board, 2010-2013
VIB Review Board, Department of Molecular and Developmental Genetics, Belgium 2010
Scientific Review Board, The Telethon Foundation, Rome, Italy, 2012-2016
Scientific Review Board, National Ataxia Foundation, 2011-
Scientific Research Advisory Board, Project A.L.S. 2012-
Advisory Board for the Bloomington *Drosophila* Stock Center, 2012-
Scientific Advisory Board, Glenn Foundation for Medical Research, 2017-

C. Contributions to Science

My contributions to science include the demonstration, by example, that *Drosophila* can be used as a remarkable model for human disease. My laboratory's research has shown how such a model can be used to reveal unique insights into perturbed pathways, increasing our biological understanding and developing a foundation for therapeutics. We have discovered unexpected and novel pathways involved in both disease and normal biology, and have also pioneered the application of *Drosophila* toward understanding of additional important problems in human biology and injury. Our initial study that illustrated that the fly can be used as a model of disease was in collaboration with human geneticists, where we expressed in *Drosophila* the normal and mutant forms of a human neurodegenerative polyQ disease protein. These studies showed that the normal protein had no effect when expressed in the fly, whereas expression of the mutant disease form conferred an effect that recapitulated the essential features of the human disorder within an exceptionally rapid time frame, compared to other *in vivo* models.

These studies served to open this field to many investigators for similar studies with other human degenerative diseases, additional human diseases and fundamental biological problems. These applications are not only in *Drosophila*, but also in other organisms with powerful genetic approaches, including yeast and *C. elegans*. We proved the power of this approach by manipulating the genetics of the organism to reveal insight into the disease process. An initial pathway identified was molecular chaperones, where we showed that upregulation of chaperone activity can powerfully mitigate polyQ disease effects in the fly. This work was then applied to Parkinson's disease where we could also mitigate disease effects through a similar approach, thereby establishing chaperones as strong therapeutic targets in multiple neurodegenerative situations. In the latter, we also showed disruptions in the same pathways in human disease tissue. Thus, we have shown by example how genetic modifier pathways identified and characterized in *Drosophila* can define pathways of great relevance to human disease intervention. In the course of our studies, we have revealed novel roles for microRNAs in the brain with ageing and disease susceptibility, novel modulators of triplet repeat expansion, that the RNA encoding the polyQ disease protein has toxicity beyond the encoded disease protein, among others. My laboratory's success with using *Drosophila* as an *in vivo* model for human neurodegenerative disease has encouraged us to investigate additional processes of importance to human brain disease and health, and additional impacts on disease, including environmental insults and the gut microbiota, and launch into studies of the human brain directly. This success has also led us to generate and publish protocols and examples for others, encouraging this important field and approach. We have also launched into studies directly on the human brain in aging and disease.

1. My laboratory's publication that introduced by example the approach that *Drosophila* could be a remarkable model for human disease is Warrick *et al.* (1998). Since that time, we have also introduced models for other neurodegenerative diseases.

a. Warrick JM, Paulson H, Gray-Board GL, Bui QT, Fischbeck K, Pittman RN, and **Bonini NM** (1998) Expanded polyglutamine protein forms nuclear inclusions and causes neural degeneration in *Drosophila*. Cell 93: 939-949.

2. Our publications that proved the power of the modeling approach and applying that power to the human condition are illustrated by the below publications. These examples include molecular chaperones, new human disease risk factors, and the foundation for therapeutic possibilities.

a. Auluck PK, Chan HYE, Trojanowski JQ, Lee VML and **Bonini NM** (2002) Chaperone Suppression of α-Synuclein Toxicity in a *Drosophila* Model for Parkinson's Disease. Online 1067389. Science 295:865-868.

b. Elden AC^, Kim H-J^, Hart M^, Chen-Plotkin AS^, Johnson BS, Fang X, Armakola M, Geser F, Greene R, Lu MM, Padmanabhan A, Clay D, McCluskey L, Elman L, Juhr D, Gruber PJ, Rub U, Auburger G, Trojanowski JQ, Lee VM-Y, Van Deerlin VM, **Bonini NM*** and Gitler AD* (2010) Ataxin-2 intermediate length polyglutamine expansions are associated with increased risk for ALS. Nature 466: 1069-75. PMC 2965417. ^ co-first authors, *co-senior authors.

c. Kim HJ, Raphael AR, LaDow ES, McGurk L, Weber RA, Trojanowski JQ, Lee VM, Finnkbeiner S, Gitler AD, **Bonini NM** (2014) Therapeutic modulation of eIF2α phosphorylation rescues TDP-43 toxicity in amyotrophic lateral sclerosis disease models. Nat Genet 46:152-160. Epub 2013 Dec 15. PMC3934366.

d. Berson A, Sartoris A, Nativio R, Van Deerlin V, Toledo JB, Porta S, Liu S, Chung CY, Garcia BA, Lee VM, Trojanowski JQ, Johnson FB, Berger SL, **Bonini NM** (2017) TDP-43 promotes neurodegeneration by impairing chromatin remodeling. Curr Biol 27: 3579-3590. PMC5720388.

3. Publications that detail unexpected genetic pathways that modulate disease effects in *Drosophila*, including elucidation of key players in brain ageing, for novel insight:

a. Jung J and **Bonini NM** (2007) CREB-binding Protein Modulates Repeat Instability in a Drosophila Model for PolyQ Disease. Science 315: 1857-1859. Published online 1 March 2007 10.1126/science.1139517. PMC2778376.

b. Li LB, Yu Z, Teng X and **Bonini NM** (2008) RNA toxicity is a component of ataxin-3 degeneration in Drosophila. Nature, 453:1107-11. Epub 2008 Apr 30. PMC2574630.

c. Liu N, Landreh M, Cao K, Abe M, Hendriks GJ, Kennerdell JR, Zhu Y, Wang LS, **Bonini NM** (2012) The microRNA miR-34 modulates ageing and neurodegeneration in *Drosophila*. Nature 482: 519-23. Doi 10.1038/nature 10810. PMC3326599.

d. Burguete AS, Almeida S, Gao FB, Kalb R, Akins MR, **Bonini NM** (2015) GGGGCC microsatellite RNA is neurotically localized, induces branching defects, and perturbs transport granule function. Elife 4:e08881. PMC4758954.

4. Publications that detail how we have investigated additional processes of critical importance to human biology and health, and additional features of disease (such as environmental impacts) on the degenerative process, and protocols to encourage the field:

a. Meulener M, Xu K, Thomson L, Ischiropoulos H and **Bonini NM** (2006) Mutational analysis of DJ-1 in Drosophila implicates functional inactivation by oxidative damage and aging. Proc. Natl. Acad. Sci USA 103: 12517-22. Epub 2006 Aug 7.

b. Fang Y, Soares L, Teng X, Geary M and **Bonini NM** (2012) A novel Drosophila model of nerve injury reveals an essential role of endogenous Nmnat in maintaining axon integrity. Curr Biol 22: 590-595. PMC3347919.

c. Fang Y, Soares L and **Bonini NM** (2013) Design and implementation of in vivo imaging of neural injury responses in the adult *Drosophila* wing. Nat Protocol 8: 810-19. Epub 2013 Mar 28. PMC4032490.

d. Nativio R, Donahue G, Berson A, Lan Y, Amlie-Wolf A, Tuzer F, Toledo JB, Gosai SJ, Gregory BD, Torres C, Trojanowski JQ, Wang LS, Johnson FB, **Bonini NM**, Berger SL. (2018) Dysregulation of the epigenetic landscape of normal aging in Alzheimer's disease. Nat Neurosci 21: 497-505. doi: 10.1038/a41593-018-0101-9. PMC6124498.

Complete list of publications:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1VgfyYHftHKk7/bibliograpahy/44355946/public/?sort=date&direction=descending

D. Research Support

ACTIVE:

National Institutes of Health/NINDS, R35-NS097275 (Bonini, PI) 12/2016-11/2024
Molecular genetic insight into neurodegenerative disease from *Drosophila*
The goals of this grant are to use the power of *Drosophila* to discover molecular insight into modifiers, mechanisms, and risk factors for human neurodegenerative disease, with special focus on ALS.

Robert J. Kleberg, Jr. and Helen C. Kleberg Foundation 9/1/2018- 8/31/21
(Berger, Shelley, and Bonini, co-Principal Investigators)
Epigenetic dysfunction in human Alzheimer's disease
Study of enhancer dysfunction in Alzheimer's disease. There is no overlap with the current project.