BIOGRAPHICAL SKETCH

NAME: Friedlander, Robert

eRA COMMONS USER NAME (agency login): rmf123

POSITION TITLE: Professor and Chairman, Department of Neurological Surgery

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
Brandeis University, Boston, MA	BA	05/1987	Biochemistry
Brandeis University, Boston, MA	MA	05/1987	Biochemistry
Harvard Medical School, Boston, MA	MD	06/1991	Medicine

A. Personal Statement

My major research interests lie in the study of the mechanistic pathways of neurodegeneration. My laboratory was the first to demonstrate a functional role of the caspase cell death family in ALS and HD. We were first to slow disease progression and delay mortality in ALS and HD mice. My current H-index is 56 with 16,547 total citations. As an indicator of the impact of our work, our 8 highest cited publications have been cited 7,980 times.

A major focus of our research has been to identify the mechanism by which mutant huntingtin (mHtt) mediates cell dysfunction, cell death and disease progression. As a result of these studies, my laboratory has identified melatonin as a neuroprotective chemical that acts specifically through a mitochondrial-mediated action. In our efforts to discover this action, we have generated data showing that neuronal melatonin synthesis takes place in the mitochondria. Given the importance of melatonin as a mitochondrial antioxidant, my laboratory is now focused on defining mechanisms of neuronal melatonin synthesis in the mitochondria. **Thus, the major goal of this proposal is to delineate the mechanisms controlling MT1 signaling in the mitochondria.**

B. Positions and Honors

Positions and Employment

1997 - 1998	Instructor of Neurosurgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA
1998 - 1999	Instructor of Neurosurgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA
2001 - 2008	Associate Professor of Neurosurgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA
2007 - 2010	Vice Chairman, Department of Neurosurgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA
2008 - 2010	Professor, Department of Neurological Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA
2010 -	Professor and Chairman, Department of Neurological Surgery, University of Pittsburgh School of Medicine and UPMC, Pittsburgh, PA
2015 -	Co-Director of the UPMC Neurological Institute, UPMC, Pittsburgh, PA

Other Experience and Professional Memberships

1994 - 1996	National Fellowship Training Award, NIH
1996 - 1997	Fellowship Award, American Brain Tumor Association
2000 - 2000	NSD-B study section, Ad Hoc member, NIH/NINDS
2001 - 2005	NSD-A study section, Member, NIH/NINDS
2003 - 2003	Scientific Advisory Committee, Children's Hospital of Boston
2003 - 2003	ZRG1 BSCT (10B) study section, Ad Hoc member, NIH/NINDS
2003 - 2008	Executive Committee, Congress of Neurological Surgeons
2004 - 2004	UDOL Center Review Special Panel, NIH/NINDS
2005 - 2005	UDOL Center Review Special Panel, NIH/NINDS
2006 - 2006	NSD-A study section, Ad Hoc member, NIH/NINDS

2008 - 2012	Advisor Council, NIH/NINDS
2008 - 2012	Clinical Trials Subcommittee, NIH/NINDS Advisory Council
2008 - 2012	Fellowships and Training Subcommittee, NIH/NINDS Advisory Council
2008 - 2012	Basic Science Subcommittee, NIH/NINDS Advisory Council
2013 - 2014	Chair, Joint Section of Cerebrovascular Surgery
2019	NINDS Board of Scientific Councilors

Honors

1998	Annual Resident Award, Congress of Neurological Surgeons
1999	Joint Section of Cerebrovascular Surgery, Bayer Cerebrovascular Award
2002	International Charcot Award for ALS Research, Motor Neurone Disease Association
2006	Elected Member, American Socity for Clinical Investigation (ASCI)
2006	Elected Member, American Academy of Neurological Surgeons
2008	Elected Member, Society of Neurological Surgeons
2012	Elected Member, Association of American Physicians (AAP)
2012	WINN Prize, Society of Neurological Surgeons
2018	Elected Member, National Academy of Medicine (NAM)

C. Contribution to Science

1. **Demonstrated a functional role of the caspase family in HD:** We were first to slow disease progression and mortality in an HD mouse model. We demonstrated caspase activation in HD human striatum and mouse brain. Inhibiting caspase activity resulted in delay of disease onset and mortality. Furthermore, we demonstrated a sequential activation of caspase-1, mitochondrial cell death pathways culmunating with caspase-3 activation. Additionally, we demonstrated that huntingtin is a functional caspase-3 inhibitor. Most recently, we demonstrated that mutant huntingtin inhibits mitochondrial protein import. This is detected early (i.e. presymptomatic) in vivo and appears to be a critical mechanism by which mutant huntingtin induces mitochondrial dysfunction and neuronal death.
    a. Ona VO, Li M, Vonsattel JP, Andrews LJ, Khan SQ, Chung WM, Frey AS, Menon AS, Li XJ, Stieg PE, Yuan J, Penney JB, Young AB, Cha JH, **Friedlander RM**. Inhibition of caspase-1 slows disease progression in a mouse model of Huntington's disease. **Nature.** 1999 May 20;399(6733):263-7. PubMed PMID: 10353249.
    b. Zhang Y, Leavitt BR, van Raamsdonk JM, Dragatsis I, Goldowitz D, MacDonald ME, Hayden MR, **Friedlander RM**. Huntingtin inhibits caspase-3 activation. **EMBO J**. 2006 Dec 13;25(24):5896-906. PubMed PMID: 17124493; PubMed Central PMCID: PMC1698892.
    c. Yano H, Baranov SV, Baranova OV, Kim J, Pan Y, Yablonska S, Carlisle DL, Ferrante RJ, Kim AH, **Friedlander RM**. Inhibition of mitochondrial protein import by mutant huntingtin. **Nat Neurosci.** 2014 Jun;17(6):822-31. PubMed PMID: 24836077; PubMed Central PMCID: PMC4174557.
    d. Baranov SV, Baranova OV, Yablonska S, Suofu Y, Vazquez AL, Kozai TDY, Cui XT, Ferrando LM, Larkin TM, Tyurina YY, Kagan VE, Carlisle DL, Kristal BS, **Friedlander RM**. Mitochondria modulate programmed neuritic retraction. **Proc Natl Acad Sci U S A**. 2019 Jan 8;116(2):650-659. doi: 10.1073/pnas.1811021116. Epub 2018 Dec 24. PubMed PMID: 30584104; PubMed Central PMCID: PMC6329959.

2. **Demonstrated a functional role of the caspase family in ALS:** We were first to slow disease progression and mortality in an ALS mouse model. We accomplished this by crossing an ALS transgenic mouse with a transgenic mouse we generated specifically expressing a caspase-1 dominant negative transgene in neurons. We extended this work, by then demonstrating that we could also delay disease progression by chronic intraventricular infusion of a peptide caspase inhibitor. A debate in the field was whether caspase-1 was expressed in neurons. We demonstrated neuronal active caspase-1 expression.
    a. **Friedlander RM**, Brown RH, Gagliardini V, Wang J, Yuan J. Inhibition of ICE slows ALS in mice. **Nature.** 1997 Jul 3;388(6637):31. PubMed PMID: 9214497.
    b. Li M, Ona VO, Chen M, Kaul M, Tenneti L, Zhang X, Stieg PE, Lipton SA, **Friedlander RM**. Functional role and therapeutic implications of neuronal caspase-1 and -3 in a mouse model of traumatic spinal

cord injury. **Neuroscience.** 2000;99(2):333-42. PubMed PMID: 10938439.

c. Zhang W, Narayanan M, **Friedlander RM**. Additive neuroprotective effects of minocycline with creatine in a mouse model of ALS. **Ann Neurol.** 2003 Feb;53(2):267-70. PubMed PMID: 12557297.

d. Zhang Y, Cook A, Kim J, Baranov SV, Jiang J, Smith K, Cormier K, Bennett E, Browser RP, Day AL, Carlisle DL, Ferrante RJ, Wang X, **Friedlander RM**. Melatonin inhibits the caspase-1/cytochrome c/caspase-3 cell death pathway, inhibits MT1 receptor loss and delays disease progression in a mouse model of amyotrophic lateral sclerosis. **Neurobiol Dis.** 2013 Jul;55:26-35. PubMed PMID: 23537713; PubMed Central PMCID: PMC3652329.

3. **Demonstrated that melatonin is neuroprotective in stroke, HD and ALS by inhibiting mitochondrial cytochrome c release**. Performing an NINDS sponsored screen searching for inhibitors of cytochrome c release, we identified melatonin as a potent hit. Others and we have demonstrated melatonin to be protective in a number of neurological diseases. Its mechanism of action has been disputed. We, for the first time found melatonin receptors in brain mitochondria. We demonstrated that melatonin-mediated neuroprotection is dependent on melatonin binding to its receptor. Furthermore, in HD there is a loss of melatonin and melatonin receptor, suggesting a functional consequence of the loss of this critical axis in neurodegeneration.

   a. Wang X, Zhu S, Pei Z, Drozda M, Stavrovskaya IG, Del Signore SJ, Cormier K, Shimony EM, Wang H, Ferrante RJ, Kristal BS, **Friedlander RM**. Inhibitors of cytochrome c release with therapeutic potential for Huntington's disease. **J Neurosci**. 2008 Sep 17;28(38):9473-85. PubMed PMID: 18799679; PubMed Central PMCID: PMC2632939.

   b. Wang X, Sirianni A, Pei Z, Cormier K, Smith K, Jiang J, Zhou S, Wang H, Zhao R, Yano H, Kim JE, Li W, Kristal BS, Ferrante RJ, **Friedlander RM**. The melatonin MT1 receptor axis modulates mutant Huntingtin-mediated toxicity. **J Neurosci.** 2011 Oct 12;31(41):14496-507. PubMed PMID: 21994366; PubMed Central PMCID: PMC3213696.

   c. Zhang Y, Cook A, Kim J, Baranov SV, Jiang J, Smith K, Cormier K, Bennett E, Browser RP, Day AL, Carlisle DL, Ferrante RJ, Wang X, **Friedlander RM**. Melatonin inhibits the caspase-1/cytochrome c/caspase-3 cell death pathway, inhibits MT1 receptor loss and delays disease progression in a mouse model of amyotrophic lateral sclerosis. **Neurobiol Dis.** 2013 Jul;55:26-35. PubMed PMID: 23537713; PubMed Central PMCID: PMC3652329.

   d. Suofu Y, Li W, Jean-Alphonse FG, Jia J, Khattar NK, Li J, Baranov SV, Leronni D, Mihalik AC, He Y, Cecon E, Wehbi VL, Kim J, Heath BE, Baranova OV, Wang X, Gable MJ, Kretz ES, Di Benedetto G, Lezon TR, Ferrando LM, Larkin TM, Sullivan M, Yablonska S, Wang J, Minnigh MB, Guillaumet G, Suzenet F, Richardson RM, Poloyac SM, Stolz DB, Jockers R, Witt-Enderby PA, Carlisle DL, Vilardaga JP, **Friedlander RM**. Dual role of mitochondria in producing melatonin and driving GPCR signaling to block cytochrome c release. **Proc Natl Acad Sci U S A**. 2017 Sep 5. pii:201705768. doi: 10.1073/pnas.1705768114. [Epub ahead of print] PubMed PMID: 28874589.

4. **Defining a role for caspase-1 in neuronal cell death and in cerebral ischemia.** Dr. Yuan's laboratory had demonstrated that CrmA, a viral protein which inhibits caspase-1, could inhibit trophic factor deprivation-mediated death of sensory neurons. Building upon these results, I evaluated the role of downstream signals from caspase-1 in cell death. We demonstrated that in situations of cellular stress, mature IL-1β (the product of caspase-1 activation) in a paracrine fashion stimulated the process of cell death. Given the clear role of caspase-1 in cell death, and particularly neuronal cell death, we evaluated whether caspase-1 was activated following cerebral ischemia, as well as evaluated whether caspase-1 inhibition (via transgenic manipulation or pharmacologically) would ameliorate ischemic injury. This resulted in two seminal publications, where for the first time we demonstrated caspase activation in a neurological disease, and that caspase-1 inhibition reduced ischemic injury in vivo. This work laid the foundation to delineate a functional role of caspases in neurological diseases. The last listed publication (from my own lab) demonstrates the mechanism by which caspase-1 mediates neuronal cell death in ischemia.

   a. **Friedlander RM**, Gagliardini V, Rotello RJ, Yuan J. Functional role of interleukin 1 beta (IL-1 beta) in IL-1 beta-converting enzyme-mediated apoptosis. **J Exp Med.** 1996 Aug 1;184(2):717-24. PubMed PMID: 8760825; PubMed Central PMCID: PMC2192702.

   b. **Friedlander RM**, Gagliardini V, Hara H, Fink KB, Li W, MacDonald G, Fishman MC, Greenberg AH, Moskowitz MA, Yuan J. Expression of a dominant negative mutant of interleukin-1 beta converting

enzyme in transgenic mice prevents neuronal cell death induced by trophic factor withdrawal and ischemic brain injury. **J Exp Med**. 1997 Mar 3;185(5):933-40. PubMed PMID: 9120399; PubMed Central PMCID: PMC2196165.

c. Hara H, **Friedlander RM**, Gagliardini V, Ayata C, Fink K, Huang Z, Shimizu-Sasamata M, Yuan J, Moskowitz MA. Inhibition of interleukin 1beta converting enzyme family proteases reduces ischemic and excitotoxic neuronal damage. **Proc Natl Acad Sci U S A**. 1997 Mar 4;94(5):2007-12. PubMed PMID: 9050895; PubMed Central PMCID: PMC20033.

d. Zhang WH, Wang X, Narayanan M, Zhang Y, Huo C, Reed JC, **Friedlander RM**. Fundamental role of the Rip2/caspase-1 pathway in hypoxia and ischemia-induced neuronal cell death. **Proc Natl Acad Sci U S A.** 2003 Dec 23;100(26):16012-7. PubMed PMID: 14663141; PubMed Central PMCID: PMC307684.

5. **Demonstrated that minocycline is neuroprotective in HD and ALS, and delineated its mechanism of action.** Minocycline has been independently demonstrated by a broad number of international laboratories as a neuroprotective drug. We were the first to demonstrate its effect in HD, ALS and traumatic brain injury. We found that minocycline is concentrated in mitochondria and is a potent inhibitor of mitochondrial stress-mediated release of cytochrome c. Mitochondrial cytochrome c release is a key commitment step in the triggering of the caspase cell death cascade. Several clinical trials have taken place based on these findings. Although most of the human trials have not demonstrated efficacy, a human spinal cord injury trial has demonstrated promising findings.

   a. Chen M, Ona VO, Li M, Ferrante RJ, Fink KB, Zhu S, Bian J, Guo L, Farrell LA, Hersch SM, Hobbs W, Vonsattel JP, Cha JH, **Friedlander RM**. Minocycline inhibits caspase-1 and caspase-3 expression and delays mortality in a transgenic mouse model of Huntington disease. **Nat Med.** 2000 Jul;6(7):797-801. PubMed PMID: 10888929.

   b. Sanchez Mejia RO, Ona VO, Li M, **Friedlander RM**. Minocycline reduces traumatic brain injury-mediated caspase-1 activation, tissue damage, and neurological dysfunction. **Neurosurgery.** 2001 Jun;48(6):1393-9; discussion 1399-401. PubMed PMID: 11383749.

   c. Zhu S, Stavrovskaya IG, Drozda M, Kim BY, Ona V, Li M, Sarang S, Liu AS, Hartley DM, Wu DC, Gullans S, Ferrante RJ, Przedborski S, Kristal BS, **Friedlander RM**. Minocycline inhibits cytochrome c release and delays progression of amyotrophic lateral sclerosis in mice. **Nature.** 2002 May 2;417(6884):74-8. PubMed PMID: 11986668.

   d. Wang X, Zhu S, Drozda M, Zhang W, Stavrovskaya IG, Cattaneo E, Ferrante RJ, Kristal BS, **Friedlander RM**. Minocycline inhibits caspase-independent and -dependent mitochondrial cell death pathways in models of Huntington's disease. **Proc Natl Acad Sci U S A.** 2003 Sep 2;100(18):10483-7. PubMed PMID: 12930891; PubMed Central PMCID: PMC193587.

Selected Research Publications:
http://www.ncbi.nlm.nih.gov/myncbi/1B5wTXgScd55s/bibliography/47992491/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

R01SN100743-01A1 (Friedlander) 7/1/18 6/30/23 1.80 Calendar
National Institutes of Health
Melatonin biosynthesis in neuronal mitochondria
The goals of this grant are to provide a novel foundation for understanding the protective action of melatonin on neurons and open a new research avenue for mitochondrial melatonin pharmacology and biology. This project specificall focuses on the mitochondrial melatonin synthesis pathway, the mechanisms that regulate this pathway, and the fate and function of mitochondrially-synthesized melatonin.
Overlap: None

1R01 NR014221 (Hravnack) 2/5/14-3/31/19 0.84 Calendar
National Institutes of Health
Developing Goal Directed Perfusion Therapy in SAH Neurocardiac Injury

Our study goal is to develop perfusion goal-directed therapeutic recommendations for SAHMI patients based upon the optimal perfusion parameters associated with better patient functional outcomes. This innovative approach will enable nurses to apply targeted perfusion therapy to improve outcomes and reduce aSAH burden on patients, the care system, and society. There are no funds available for laboratory research associated with this grant. Role: Co-Investigator
Overlap: There is no overlap.

1R01NS089688 (Cui) 7/1/15-6/30/20 0.96 Calendar
National Institutes of Health
Inhibition of Neural Electrode-mediated Inflammation and Neuronal Cell Death
In this project, we will compare the neural recording performance of microelectrode arrays implanted in caspase-1 knockout vs. the wild type mice. This proposal will uncover the molecular and cellular mechanisms contributing to neural recording performance. Role: Co-Investigator
Overlap:There is no overlap.

Completed Research Support (past 3 years)

2000/01/01-2015/04/30 5R01NS039324, NIH/NINDS Robert Friedlander, MD (PI)
Modulation of Caspase Pathways in Huntington's Disease
Our experimental agenda investigates several molecular pathways that modulate the rate at which Huntington's disease progresses. We are most interested in caspase-1, an enzyme that stimulates neuronal death during HD. We will use methods of mouse genetics and molecular biology to determine what proteins modulate caspase-1, what molecular events ensue from its activation, and how these physiological changes affect HD. Role: PI

2012/02/15-2017/01/31 1R01NS077748, NIH/NINDS Robert Friedlander, MD (PI)
Functional Role of Micro RNA's in Huntington's Disease Pathogenesis
This grant examines the ability of certain miRs to regulate apoptosis in Huntington's Disease in vitro and in vivo. In addition, the project determines if manipulation of these miRs using specific agonists and antagonists can inhibit neuronal apoptosis and thus inhibit progression of the disease. Role: PI

Institutional (Fernandez-Miranda, Friedlander) 4/1/14-6/30/18 0.12 Calendar
University of Pittsburgh Brain Institute 5,000 (effort only for Friedlander)
High-Definition Fiber Tractography (HDFT)
This grant is funded from the University of Pittsburgh Brain Institute (UPBI) to support High-Definition Fiber Tractography (HDFT) research in the Department of Neurological Surgery, including projects in the Fiber Tractography Laboratory, the Neuroanotomy of Fiber Tracts, Presurgical Assessment of Fiber Tracts and Surgical Planning, Fiber Tract Integrity and Damage Progression in Neurodegenerative Disorders, and the Language Connectivity Pathways.