BIOGRAPHICAL SKETCH

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NAME: Anne C. Hart

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POSITION TITLE: Professor, Brown University

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
Michigan State University (E. Lansing, MI)	B.S.	1983-1985	Biochemistry
Univ. of California, Los Angeles (CA)	Ph.D.	1987-1992	Neuroscience
Mass. General Hospital (Boston, MA)	-	1993-1996	-

A. Personal Statement

My research focuses on fundamental problems in neuroscience using the powerful tools available in the nematode *C. elegans*. I collaborate extensively with researchers using other experimental approaches. Currently, my group works in two distinct scientific fields. In the first, we work to delineate conserved molecular mechanisms involved in sleep. In the second, we work to understand the pathological mechanisms underlying neurodegenerative disease. I have extensive experience in combining invertebrate genetic approaches with cellular and molecular analyses. I played a major role in identification/analysis of the *Drosophila sevenless* tyrosine receptor ligand as a graduate student (mentor Dr. S.L. Zipursky) and of the first *C. elegans* AMPA-class glutamate receptor as a post-doctoral fellow (mentor Dr. J.M. Kaplan). As an independent lab head, my contributions include identification of over 30 new *C. elegans* neuropeptide genes, delineating roles for Notch signaling in adult animals during stress response, demonstrating that Notch signaling regulates sleep, developing microfluidic multi-worm sleep assays, and demonstrating dramatic conservation of genes required for sleep between *Drosophila* and *C. elegans.* Additionally, in the field of neurodegeneration, my group generated the first explicit model of neurodegenerative disease in *C. elegans* almost 20 years ago by creating a *C. elegans* model for Huntington's disease polyglutamine toxicity. We now also work on Spinal Muscular Atrophy, Amyotrophic Lateral Sclerosis, and Frontal Temporal Dementia, aiming to understand why neurons degenerate in these diseases

B. Positions and Honors

1993-1996 Postdoctoral Research Fellow in Molecular Biology; Mass. General Hospital and
Postdoctoral Research Fellow in Genetics; Harvard Medical School; Boston, MA
1996-2005 Assistant Professor, Dept. of Pathology, Harvard Medical School, Boston, MA
1996-2006 Assistant Geneticist in Medicine, Mass. General Hospital, Boston, MA
1996-2009 Affiliate Professor in Neuroscience, Harvard Medical School, Boston, MA
2006-2009 Associate Geneticist in Medicine, Mass. General Hospital, Boston, MA
2005-2009 Associate Professor, Dept. of Pathology, Harvard Medical School, Boston, MA
2009-2011 Associate Professor, Department of Neuroscience, Brown University, Providence, RI
Affiliate of Center for Cancer Research, Mass. General Hospital, Boston, MA
2011- Professor, Department of Neuroscience, Brown University, Providence, RI

Awards and Other Professional Activities (last 10 years)
2007-2019 PLoS One Academic Editor

2008-2013 MBL Neural Systems and Behavior course, Resident faculty
2008-date Invertebrate Neuroscience Editorial Board
2009 Organizing Committee, International Notch and International *C. elegans* Meetings
2009-2018 Science Council Member, Marine Biological Laboratories
2010 Organizing Committee, *C. elegans* Neuroscience meeting
2012-2014 Okinawa Institute of Science & Technology, Developmental Neurobiology course, resident faculty
2014 Co-organizer, *C. elegans* Neuroscience meeting
2013-date Editor, "Disease models and drug discovery" section, WormBook
2013-2016 Director Brown-NIH Graduate Partnership Program and Co-Director Neuroscience Graduate Program, Brown University
2015-2020 Organizing officer, WormBoard
2016 Dean's Award for Excellence in Graduate and/or Postdoctoral Teaching and Mentoring
2016-date Adjunct Ryan Research Professor of Neuroscience, University of Rhode Island
2017-date Director Neuroscience Graduate Program, Brown University (on sabbatical AY2019)
2017-2019 Assistant Chair, Department of Neuroscience, Brown University
2018-date PLoS Genetics Academic Editor
2018-2021 Programming Committee Member, Society for Neuroscience Meeting

C. Contributions to Science

1) Established first explicit models of human neurodegenerative disease in *C. elegans*
Faber PW, Alter J, McDonald ME and Hart AC 1999 Polyglutamine-mediated dysfunction and apoptotic death of a *C. elegans* sensory neuron. **PNAS** (Track II) 96:179-184 PMCID: PMC15113

Summary: There was considerable skepticism that invertebrate models could be used to study human neurodegenerative disease. This is one of three papers, published within months of each other, establishing for the first time, explicit models of human neurodegenerative disease in invertebrates. This paper founded an entire community of *C. elegans* researchers explicitly studying human disease. Papers from the Bonini and Zipursky labs established similar precedents for *Drosophila*. Work from my group on polyglutamine toxicity lead to identification of genetic modifiers (Faber *et al*, 2002 PNAS) and other relevant pathways, including HDACs (Bates, *et al*, 2006 J of Neurosci), autophagy (Jia, *et al*, 2006 Autophagy; Jeong, *et al*, 2009 Cell), and metabolism (Varma, *et al*, 2006 Nat Chem Bio; Varma, *et al*, 2007 PNAS). After the *C. elegans* genome was sequenced, we shifted to studying motor neuron diseases in *C. elegans.* Currently, we focus on SMA (Contribution to Science #4), as well as knock-in models of ALS (Baskoylu, et al, 2018 *PLoS Genetic*s and others in preparation) and other neurodegenerative diseases (*i.e.* Sorkac, *et al,* 2016).

2) Mechanisms underlying sensory response, including identification of novel neuropeptides
Nathoo AN, Moeller RA, Westlund BA, and Hart AC 2001. Identification of *neuropeptide-like protein* gene families in *Caenorhabditis elegans* and other species. **PNAS** 98:14000-14005. (Track II) PMCID: PMC61156

Summary: This paper established, for the first time, the unsuspected existence of numerous, diverse *C. elegans* neuropeptides. Until this point, finding neuropeptides required biochemical approaches. Previous work had established the existence of *C. elegans* FMRFamide neuropeptide genes, but no other *C. elegans* neuropeptide genes had been identified. By searching for cDNA sequences in the public databases with sequence motifs characteristics of neuropeptide precursor proteins, we identified *C. elegans* genes encoding non-FMRFamide neuropeptides. None of these genes had been previous identified, some genes encoded neuropeptides conserved in other species, and some genes defined new neuropeptide families. Subsequent work has confirmed that many of these neuropeptides are functionally relevant and demonstrated that these neuropeptides regulate behavior and immune response.

This work was part of a long-term project, focused on understanding the signaling pathways that mediate and modulate response to sensory stimuli. My work in this area includes discovery of *C. elegans* AMPA receptors (Hart, *et al*, 1995 Nature) as a post-doctoral fellow and work from my group includes delineation of roles for GRKs (Fukuto, *et al*, 2004 Neuron), RGS proteins (Ferkey, *et al*, 2007 Neuron), serotonin (Chao, *et al*, 2004 PNAS), Notch (Chao *et al*, 2005 PNAS), PKC-1 (Hyde, *et al*, 2010 Genes Brains Behav) and others.

3) Identification of Notch co-ligands and demonstrating their roles in developmental signaling
Komatsu H, Chao MC, Larkins-Ford J, Corkins ME, Somers GA, Tucey T, Dionne HM, White JQ, Wani K, Boxem M, Hart AC OSM-11 facilitates LIN-12 Notch signaling during *C. elegans* vulval development 2008 **PLoS Biology** 6(8):e196. PMID: 18700817

Summary: This paper reports the identification of a new family of Notch ligands in *C. elegans*, establishes their role in development, and confirms that functional human orthologs exist. Notch signaling is deeply conserved across species; this pathway has many essential roles, including critical roles in cell fate specification, cancer, and stem cell proliferation. Previous work had established that that DSL ligands (Delta, Serrate and LAG-1 ligands) from humans and flies bind to and activate Notch receptors. However, *C. elegans* DSL ligands are tiny compared to DSL ligands in humans and *Drosophila.* Here, we reported that functional *C. elegans* Notch ligands are actually bipartite: a *C. elegans* DSL ligand and a DOS co-ligand, like OSM-11, work in combination to activate Notch receptors. My group established this in the context of *C. elegans* vulval development, a well-established system requiring LIN-12 Notch receptor signaling. We also demonstrated that DLK1 is the mammalian ortholog of *C. elegans* OSM-11 and that both DSL ligands and OSM-11 co-ligands bind to Notch receptor extracellular domains. Subsequent work established that these proteins act as Notch receptor co-ligands in behavioral contexts (see #5 below) and also lead to a series of papers on stress and sirtuins, in the context of aging and metabolism (Walker, *et al*, 2010 Genes & Dev; Moroz *et al*, 2014 Aging Cell; Anderson *et al*, 2016, Mech Ageing Dev).

4) Established utility of *C. elegans* as model for SMA and identification of genetic modifiers
Dimitriadi M, Sleigh JN, Walker AK, Chang HC-H, Sen A, Kalloo G, Harris J, Barsby T, Walsh MB, Satterlee JS, Li C, Van Vactor D, Artavanis-Tsakonas S, Hart AC 2010 Conserved genes act as modifiers of invertebrate SMN loss of function defects. **PLoS Genetics** 6(10): e1001172 PMCID: PMC2965752

Summary: Despite the relatively high incidence of Spinal Muscular Atrophy (SMA) in humans, it remains unclear why motor neurons die when levels of the SMN protein drop. Building on our experience with invertebrate models of disease, we undertook a genome-wide RNAi screen to identify genes and pathways pertinent to SMA. This screen was carried out in parallel with a collaborative genome-wide screen in *Drosophila* (Chang *et al* 2008 PLOS ONE). In Dimitriadi, *et al*, we identified genes that are modifiers in both invertebrate species. This strategy likely defines the genes and pathways in any species critical to neuronal function and survival when SMN levels drop. Examination of the short list of conserved modifier genes suggested that both RNA processing and endocytic pathways are critical modifiers of SMA, and that there are functional connections between these pathways. Interestingly, this short list included Ataxin2 and Profilin as likely "genes of interest in motorneuron disease" before familial ALS alleles in these genes were found in patients. Additionally, this paper implicated endocytic pathways as defective in SMA before numerous genes in vesicular trafficking pathways were identified in ALS and FTD patients. Delineating the connections between these pathways will be critical to understand neurodegenerative disease and my group is actively pursuing this line of research with publications including Dimitriadi, *et al*, 2013 J of Neurosci; Kwon, *et al*, 2013 Mol Bio Cell; O'Hern *et al* 2017 eLife and others in preparation.

5) Demonstrated conserved genes regulate sleep across species, including the Notch pathway,
Chao MC, Singh K, Somers GA, Komatsu H, Corkins ME, Larkins-Ford J, Tucey T, Dionne HM, Walsh MB, Beaumont EK, Hart DP, Lockery S, Hart AC 2011 *C. elegans* Notch signaling regulates adult chemosensory response and larval molting quiescence. **Current Biology** 21(10):825-34 PMID: 21549604

Summary: This paper established for the first time that Notch signaling regulates sleep and arousal thresholds during sleep. Additionally, this paper demonstrates that environmental stress in adult *C. elegans* impacts Notch signaling globally and, thereby, modulates response to sensory stimuli. This publication also established the microfluidic techniques that are currently the "gold standard" in the *C. elegans* field for accurately monitoring sleep. In 2008, Dr. D. Raizen's group lab established that *C. elegans* have a sleep-like state, based on behavioral criteria. Our publication here was temporally coordinated with a simultaneous paper from the Dr. P. Shaw, which demonstrated a role for Notch in *Drosophila* sleep and learning. My group extended these studies and established that virtually all pathways regulating sleep are conserved between *C. elegans* and *Drosophila* (Singh, *et al*, 2014 Sleep). We continue to examine mechanisms and molecular pathways underlying sleep (Fry *et al*, 2016 Genetics, Huang, *et al* Sleep, 2017, and others). Given the deep conservation of genes and signaling pathways across animal species in other paradigms, we expect these genes and pathways to regulate mammalian sleep.

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