BIOGRAPHICAL SKETCH

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NAME: Andrew Dillin

eRA COMMONS USER NAME (credential, e.g., agency login): andydillin

POSITION TITLE: Professor

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)*	Start Date MM/YYYY	Completion Date MM/YYYY	FIELD OF STUDY
UNIVERSITY OF NEVADA	BS	09/1989	09/1993	BIOCHEMISTRY
UNIVERSITY OF CALIFORNIA	PHD	07/1993	07/1998	GENETICS
UCSF – POST-DOC	NA	09/1998	09/2002	GENETICS

A. Personal Statement

My research interest in mitochondrial function and dysfunction in the aging process was launched when I was conducting postdoctoral work with Dr. Cynthia Kenyon at UC San Francisco. In 2002, we reported that inhibiting activity of the electron transport chain and ATP synthase with RNA interference during development in C. elegans extended adult lifespan. It suggests a regulatory system in developing animals that monitors mitochondrial activity early in life and, in response, establishes rates of respiration, behavior, and aging that persist during adulthood. Since its conception, my own lab has been working with a diligent and focused devotion to understand the relationship between organelles, stress responses, and aging. Our work on mitochondrial proteostasis began over a decade ago and now encompasses the knowledge gained from the work of many talented current and former lab members. Since 2002, my lab has housed over 13 PhD thesis students, 6 of which are currently in the lab. Within this group, over 50% are women, 2 are URMs and one was a lineman for the University of California's football team. To say the least, this is a diverse group. Peppered in with the thesis students have been a cadre of rotation students, approaching 30 total, and we have an internal program in my lab that supports 10 undergraduate students/year. While I advise all of the students individually, I am aided by the large number of post-docs. Since 2002, my lab has fostered the creation and development of 16 independent labs from places such as Harvard, UTSW, MRC, Penn and host of other institutions, one of which is led by a former post-doc that is female and handicapped. I currently have 9 post-docs in the lab, 5 of which are women.

As a group leader, I have always encouraged my postdocs and graduate students to explore new areas of biology and reach out of their collective comfort zone. This approach has allowed my laboratory to make seminal discoveries in many areas, including protein homeostasis, HSF-1 activity, insulin/IGF1 signaling, ER, and mitochondrial biology. In summary, I have demonstrated both a strong record of creative scientific achievements and preparing students and postdocs for the next level of their respective careers. We strive to use every useful biological tool available to us, and when the expertise is not present in the lab, we actively collaborate to get the job done and done right.

B. Positions and Employment

1990-1991 Undergraduate Student with Dr. Jeff Seemann, University of Nevada. Regulation of RUBISCO in the spinach plant.
1991-1993 Undergraduate Student with Dr. Ardythe McCracken, University of Nevada. ER associated protein degradation.
1993-1998 Graduate Student with Dr. Jasper Rine, University of California, Berkeley. Studies of transcriptional repression, regulation of replication initiation and mitosis in yeast.
1998-2002 Postdoctoral Fellow with Dr. Cynthia Kenyon, University of California, San Francisco, Determinants of longevity in the nematode *Caenorhabditis elegans.*
2002-2007 Assistant Professor, The Salk Institute for Biological Studies, Molecular and Cell Biology Laboratory La Jolla, CA
2007-2011 Associate Professor, The Salk Institute for Biological Studies, Molecular and Cell Biology Laboratory, La Jolla, CA
2007-2012 Adjunct Associate Professor, University of California, San Diego, CA
2008-present Investigator, Howard Hughes Medical Institute
2009-2012 Director, Glenn Center for Aging Research at the Salk Institute
2011-2012 Professor, The Salk Institute for Biological Studies, Molecular and Cell Biology Laboratory, La Jolla, CA
2012-present Professor, University of California at Berkeley, Molecular and Cell Biology Department

C. Contributions to Science

1. Communication of mitochondrial stress. The PI discovered that mitochondrial stress in one tissue can be communicated to distal, unaffected tissue to ensure longevity and health. Within these discoveries, the hypothesis of a mitokine molecule that travels from perturbed neurons to the periphery was put forth. Serotonin has been shown to be an important mediator of this event, along with several chromatin modifiers in both the sending and receiving cells.

   Berendzen KM, Durieux J, Shao LW, Tian Y, Kim HE, Wolff S, Liu Y, **Dillin** A. Neuroendocrine Coordination of Mitochondrial Stress Signaling and Proteostasis. Cell. 2016 Sep 8;166(6):1553-1563. PMID: 27610575

   Merkwirth C., Jovaisaite V., Durieux J., Matilainen O., Jordan S.D., Quiros P.M., Steffen K.K., Williams, E.G., Mouchiroud L., Uhlein S.N., Murillo V., Wolff S., Shaw R.J., Auwerx J*, and Dillin A.G.* A conserved class of histone demethylases regulate mitochondrial stress-induced longevity. Cell. 2016 May 19;165(5):1209-23. PMID: 27133168

   Tian Y, Garcia G, Bian Q, Steffen KK, Joe L, Wolff S, Meyer BJ, **Dillin** A. Mitochondrial Stress Induces Chromatin Reorganization to Promote Longevity and UPR(mt). Cell. 2016 May 19;165(5):1197-208. PMID: 27133166

   Durieux, J. Wolff, S. & Dillin A. (2011). The cell non-autonomous nature of electron transport chain-mediated longevity. Cell, 144(1), 79-91. PMCID: PMC3062502.

   Dillin A, Hsu AL, Arantes-Oliveira N, Lehrer-Graiwer J, Hsin H, Fraser AG, Kamath RS, Ahringer J, Kenyon C. Rates of behavior and aging specified by mitochondrial function during development. Science. 2002;298(5602):2398-401. PMID: 12471266.

2. Made the fundamental discovery that protein stress in one cell's organelles can be communicated to distal cells yet to undergo proteotoxic stress. Dillin has shown that damage in the mitochondrial proteome of nerve cells can be communicated to distal cells, using a signal he termed the mitokine. Important papers for this discovery are found above. In Addition to the mitokine hypothesis, Dillin found a similar system for the communication of stress within the endoplasmic reticulum and by cytoplasmic heat shock transcription factor HSF-1.

Taylor, R. & Dillin, A. (2013). XBP-1 is a cell-nonautonomous regulator of stress resistance and longevity. Cell,153(7), 1435-47. PMCID: PMC4771415.

Douglas, P, Baird N, Simic M, Uhlein S, McCormick M, Kennedy B, Dillin A. Heterotypic Signals from Neural HSF-1 Separate Thermotolerance from Logevity. Cell Reports 12, 1196–1204 August 18, 2015. PMID: 26257177

Daniele JR, Higuchi-Sanabria R, Durieux J, Monshietehadi S, Ramachandran V, Tronnes SU, Kelet N, Sanchez M, Metcalf MG, Garcia G, Frankino PA, Benitez C, Zeng M, Esping DJ, Joe L, Dillin A. UPR_{ER} promotes lipophagy independent of chaperones to extend life span. Sci Adv. 2020 Jan 1;6(1)

Frakes AE, Metcalf MG, Tronnes SU, Bar-Ziv R, Durieux J, Gildea HK, Kandahari N, Monshietehadi S, Dillin A. Four glial cells regulate ER stress resistance and longevity via neuropeptide signaling in *C. elegans*. Science. 2020 Jan 24;367(6476):436-440. PMID: 31974253

3. The first report in which of an aging pathway was altered to combat an age related neurodegenerative disease. While Dillin first reported the effects of IGF-1 signalling on Aβ toxicity in worms, he later demonstrated that his findings were conserved in a mouse model for Alzheimer's Disease (AD), opening up a novel pathways that can be targeted by therapeutics in an attempt to treat this devastating disease. This work also provided the first experimental evidence that formation of Aβ plaques from toxic Aβ oligomers is a protective event along the course of Alzheimer's Disease progression. This work was initially met with scepticism by the Alzheimer's field, as his results suggested that oligomers of Aβ acted as a more toxic species, while plaques alternatively could provide a protective value in the disease progression *in vivo*. Since his discovery, however, this body of work has become well accepted by nearly all of those who study protein-misfolding diseases. This work was first described in the worm and later confirmed in the mouse by Dillin; more recently, others have confirmed these findings using patient brains. More recently, Dillin has expanded out his findings to show that HSF-1 plays multiple roles beyond just the upregulation of chaperones, and instead works to protect the cell by mediating cytoskeletal health during aging.

   Cohen, E., Bieschke, J., Perciavalle, R., M., Kelly, J. W. & Dillin, A. (2006). Opposing activities protect against age-onset proteotoxicity. Science, 313(5793),1604-1610. PMID: 16902091

   Cohen, E. Paulsson, J.F., Blinder, P., Burstyn-Cohen, T., Du, P., Estepa, G., Adame, A., Pham, H.M., Holzenberger, M., Kelly, J.W., Masliah, E. & Dillin, A. (2009). Reduced IGF-1 Signaling Delays Age Associated Proteotoxicity in Mice. Cell, 139(6),1157-69. PMCID: PMC3017511.

   Baird NA, Douglas PM, Simic MS, Grant AR, Moresco JJ, Wolff SC, Yates JR 3rd, Manning G, Dillin A.(2014). HSF-1-mediated cytoskeletal integrity determines thermotolerance and life span. Science, 346(6207), 360-3. PMID: 25324391

4. Identification of the first factor essential and specific for diet restriction induced longevity. Since the first discovery of diet restriction mediated longevity reported by McCay in 1929, the aging field has long searched for the underlying genetic requirements of this process. In a string of Nature papers Dillin reported and characterized conserved components of the genetic pathway required for this phenomenon. Dillin is thus accredited with the discovery of the genetics behind the diet restriction pathway. The pathway he discovered in worms has subsequently been shown to play a role in the regulation of glucose homeostasis, insulin secretion, hepatic triglyceride synthesis, fatty acid transport, and IGF-1 signalling, in adult, mammalian cells.

   Panowski, S., Wolff, S., Aguilaniu, H. & Dillin, A. (2007). PHA-4/Foxa mediates diet-restriction-induced longevity of C. elegans. Nature, 447(7144), 550-556. PMID: 17476212

Mair, W., Morantte, I., Rodrigues, A.P.C., Manning, G., Montminy, M., Shaw, RJ., Dillin, A. (2011) CRTC-1 couples energy homeostasis to longevity. Nature, Feb; 470(7334):404-8. PMCID:21331044.

Carrano, A., Liu, Z., Dillin, A. & Hunter, T. (2009). A conserved ubiquitination pathway determines longevity in response to diet restriction. Nature, 16(7253), 369-399. PMCID: PMC2746748.

5. First identified that mice lacking TRPV1 pain receptors are long-lived, displaying a youthful metabolic profile at old age. Dillin then found evidence that levels of the secreted peptide CGRP were negatively associated with metabolic health during aging. These data suggest that ablation of select pain sensory receptors or the inhibition of CGRP is associated with increased metabolic health and control longevity.

   Riera CE, Huising MO, Follett P, Leblanc M, Halloran J, Van Andel R, de Magalhaes Filho CD, Merkwirth C, Dillin A. (2014) TRPV1 pain receptors regulate longevity and metabolism by neuropeptide signaling. Cell. 2014 May 22;157(5):1023-36. PMID: 24855942

6. Made the discovery that one of the by-products of longevity is an increased proteasome activity and "stemness" in somatic cells upon a block in reproduction. The somatic cells of worms without a germline are capable of mounting an enhanced defence against proteotoxic stressors such as those found in Huntington's Disease. Mammalian embryonic stem cells also exhibit a similar heightened level of proteostasis that is determined by the activity of its proteasome.

   Vilchez D, Morantte I, Liu Z, Douglas PM, Merkwirth C, Rodrigues AP, Manning G, & Dillin A. (2012). RPN-6 determines C. elegans longevity under proteotoxic stress conditions. Nature, 489(7415), 263-8. PMID: 22922647

   Vilchez D, Boyer L, Morantte I, Lutz, M, Merkwirth C, Joyce D, Spencer B, Page L, Masliah E, Berggren WT, Gage FH, and Dillin A. Increased proteasome activity in human embryonic stem cells is regulated by PSMD11. Nature. 2012: 489(7415):304-8. PMID: 22972301.

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

R01ES021667 (Dillin, PI) 03/01/2012-06/30/2022
NIH
Distal Mitochondrial Signaling in a Multicellular Organism
The major goal of this project is to perform research on how mitochondrial stress in one cell type can be communicated to a distal cell type.
Role: PI

R01AG055891 (Dillin, PI) 04/01/2017-03/31/2022
NIH/NIA
The Collapse of Proteostasis during Aging is Mediated by Cytoskeletal Actin Functions
The major goal of this project is to perform research towards the cytoskeleton's role in maintaining the overall health of the cell
Role: PI

R37AG024365 (Dillin, PI) 09/01/2004-03/31/2021
NIH/NIA
The Perception of Mitochondrial Stress in Receiving Cells
The major goal of this project is to determine how distal tissues can sense mitochondrial stress in other tissues, and how their own form and function might change in response to distal mitochondrial signaling.
Role: PI

R01 AG059566 (Dillin, PI) 7/15/2018 – 3/31/2023

NIH/NIA
Glial Regulation of Longevity Through a Transcellular Unfolded Protein Response. The major goal of this project is to pinpoint the origin and identity of the glial cell non-autonomous signal and to uncover the mechanism by which the signal is perceived in distal tissues.
Role: PI

-- (Dillin, PI) 09/01/2008-08/31/2024
Howard Hughes Medical Institute
Molecular Pathways of Aging
The major goal of this project is to perform high risk, innovative research towards the understanding of aging and age-related diseases.
Role: PI

Completed Research Support

R01AG042679 (Dillin, PI) 03/15/2013-02/28/2019
NIH/NIA
The Cell Non-Autonomous Nature of UPR Signaling
The major goal of this project is to discover how the UPR within the endoplasmic reticulum with neurons can communicate with distal tissues to increase the chance of survivorship as the organism ages.
Role: PI

RB5-06974 (Dillin, PI) 03/01/2014-02/28/2017
California Institute for Regenerative Medicine
A Requirement for Protein Homeostasis in the Mediation of Stem Cell Health
The major goal of this project is to understand the behaviors and regulation of UPR and stress responses in stem cells.
Role: PI

R01 ES021667 (Dillin, PI) 10/19/2012-12/31/2016
NIH/NIA
Distal Mitochondrial Signaling in a Multicellular Organism
The major goal of this project is to discover how mitochondria within the nervous system can communicate a signal that will ensure the survival of an animal under conditions of stress.
Role: PI

R01 AG027463 (Dillin, PI) 07/01/2008-06/30/2014
NIH/NIA
Genetic Regulation of the Response to Dietary Restriction
The major goal of this project is to understand the molecular mechanism by which a core-signaling pathway that responds to and integrates an organism's response to reduced caloric intake, perceives and interprets the environmental signals that ultimately result in increased longevity. [Funds shared by two investigators.]
Role: PI

P01 AG031097 (Kelly, PI) 02/01/2009-01/31/2014
NIH/NIA
Molecular Mechanisms Linking Aging, Abeta Proteotoxicity, and Neurodegeneration
The major goal of Project 3, Age-Associated Neuroprotection by Insulin/IGF-1 Signaling: From Worm to Mouse, is to investigate the molecular mechanisms that prevent proteotoxicity during early life that become compromised with age.
Role: PI, Project 3