OMB No. 3145-0279 (Expiration Date 10/31/2026)

NIH BIOGRAPHICAL SKETCH COMMON FORM

Name: Hansen, Malene

Persistent Identifier (PID) of the Senior/Key Person: https://orcid.org/0000-0002-6828-8640

Position Title: CSO and Professor

Organization and Location: Buck Institute for Research on Aging, Novato, California, United States

PROFESSIONAL PREPARATION

INSTITUTION AND LOCATION	DEGREE	Start Date	Completion Date	FIELD OF STUDY
University of California, San Francisco, San Francisco, California, United States	Postdoctoral Fellow	10/2001	06/2007	Genetics of Aging
Copenhagen University, Copenhagen, Not Applicable, N/A, Denmark	DOCTOR OF PHILOSOPHY	04/1998	09/2001	Molecular Biology
Copenhagen University, Copenhagen, Not Applicable, N/A, Denmark	Master of Science (MS)	09/1994	03/1998	Biochemistry/Cell Biology

Appointments and Positions

2021 - present	CSO and Professor, Buck Institute for Research on Aging, Novato, California, United States
2024 - present	Co-Organizer, Cold Spring Harbor Laboratory conference on Proteostasis, Cold Spring Harbor, New York, United States
2023 - present	External Advisory Committee, Nathan Shock Center, University of Washington, Seattle, Washington, United States
2023 - present	Scientific Advisory Board Member, Glenn Foundation for Medical Research, Santa Barbara, California, United States
2022 - present	Scientific Advisory Board Member, Institute for Molecular Biology, Mainz, Not Applicable, N/A, Germany
2022 - present	Scientific Advisory Board Member, Nathan Shock Center, University of Alabama, Birmingham, Alabama, United States
2022 - present	Co-Director and Steering Committee Member, NIH R13 AG059431 Summer Training Course in Experimental Aging Research, Novato, California, United States
2022 - present	Member, Academy of Health & Lifespan Research, Boston, Massachusetts, United States
2021 - present	External Advisory Committee, Autophagy, Inflammation, and Metabolism (AIM) Center, Albuquerque, New Mexico, United States
2021 - present	Admin Core Leader, NIH U54 AG075934 Cellular Senescence Network, Human Tissue Mapping Center, Buck Institute for Research on Aging, Novato, California, United States
2021 - present	Adjunct Professor, University of Southern California, Los Angeles, California, United States
2020 - present	Co-Founder & Mentoring Committee Member, Women in Autophagy - Beth Levine's Legacy Network, Novato, California, United States

Products

Products Closely Related to the Proposed Project

1. Yang Y, Arnold ML, Lange CM, Sun LH, Broussalian M, Doroodian S, Ebata H, Choy EH, Poon K, Moreno TM, Singh A, Driscoll M, Kumsta C, Hansen M. Autophagy protein ATG-16.2 and its WD40 domain mediate the beneficial effects of inhibiting early-acting autophagy genes in C. elegans neurons. Nat Aging. 2024 Feb;4(2):198-212. PubMed Central PMCID: PMC11022750.
2. Tan EP, Lyang N, Doroodian S, Sanz-Martinez P, Xu J, Zaretski S, Nieto-Torres JL, Ebata H, Lim SHY, Hou WC, Clay KJ, Yoon L, Massey LA, Rhoades D, Garza D, Johnson KA, To A, Ambaye L, Bentley EP, Petrascheck M, Stolz A, Kelly JW, Hansen M. Autophagy activator AA-20 improves proteostasis and extends Caenorhabditis elegans lifespan. Proc Natl Acad Sci U S A. 2025 Aug 12;122(32):e2423455122. PubMed Central PMCID: PMC12358921.

3. Nieto-Torres JL, Shanahan SL, Chassefeyre R, Chaiamarit T, Zaretski S, Landeras-Bueno S, Verhelle A, Encalada SE, Hansen M. LC3B phosphorylation regulates FYCO1 binding and directional transport of autophagosomes. Curr Biol. 2021 Aug 9;31(15):3440-3449.e7. PubMed Central PMCID: PMC8439105.
4. Wilkinson DS, Jariwala JS, Anderson E, Mitra K, Meisenhelder J, Chang JT, Ideker T, Hunter T, Nizet V, Dillin A, Hansen M. Phosphorylation of LC3 by the Hippo kinases STK3/STK4 is essential for autophagy. Mol Cell. 2015 Jan 8;57(1):55-68. PubMed Central PMCID: PMC4373083.
5. Kumsta C, Chang JT, Lee R, Tan EP, Yang Y, Loureiro R, Choy EH, Lim SHY, Saez I, Springhorn A, Hoppe T, Vilchez D, Hansen M. The autophagy receptor p62/SQST-1 promotes proteostasis and longevity in C. elegans by inducing autophagy. Nat Commun. 2019 Dec 11;10(1):5648. PubMed Central PMCID: PMC6906454.

Other Significant Products Highlighting Contributions to Science

1. Gelino S, Chang JT, Kumsta C, She X, Davis A, Nguyen C, Panowski S, Hansen M. Intestinal Autophagy Improves Healthspan and Longevity in C. elegans during Dietary Restriction. PLoS Genet. 2016 Jul;12(7):e1006135. PubMed Central PMCID: PMC4945006.
2. Chang JT, Kumsta C, Hellman AB, Adams LM, Hansen M. Spatiotemporal regulation of autophagy during Caenorhabditis elegans aging. Elife. 2017 Jul 4;6 PubMed Central PMCID: PMC5496740.
3. Egan DF, Shackelford DB, Mihaylova MM, Gelino S, Kohnz RA, Mair W, Vasquez DS, Joshi A, Gwinn DM, Taylor R, Asara JM, Fitzpatrick J, Dillin A, Viollet B, Kundu M, Hansen M, Shaw RJ. Phosphorylation of ULK1 (hATG1) by AMP-activated protein kinase connects energy sensing to mitophagy. Science. 2011 Jan 28;331(6016):456-61. PubMed Central PMCID: PMC3030664.
4. Hansen M, Hsu AL, Dillin A, Kenyon C. New genes tied to endocrine, metabolic, and dietary regulation of lifespan from a Caenorhabditis elegans genomic RNAi screen. PLoS Genet. 2005 Jul;1(1):119-28. PubMed Central PMCID: PMC1183531.
5. Lapierre LR, De Magalhaes Filho CD, McQuary PR, Chu CC, Visvikis O, Chang JT, Gelino S, Ong B, Davis AE, Irazoqui JE, Dillin A, Hansen M. The TFEB orthologue HLH-30 regulates autophagy and modulates longevity in Caenorhabditis elegans. Nat Commun. 2013;4:2267. PubMed Central PMCID: PMC3866206.

Certification:

I certify that the information provided is current, accurate, and complete. This includes, but is not limited to, information related to current, pending, and other support (both foreign and domestic) as defined in 42 U.S.C. § 6605.

In accordance with Section 10632 of the CHIPS and Science Act of 2022 (42 U.S.C. § 19232), each individual identified as a senior/key person must certify that they are not a party to a malign foreign talent recruitment program.

Research Security Training Requirement for Federal Award Personnel: In accordance with Section 10634 of the CHIPS and Science Act of 2022 (42 U.S.C. § 19234), each individual identified as a senior/key person must certify that they have completed the requisite research security training that meets the requirements specified in Item 2 of Important Notice No. 149 within 12 months prior to proposal submission.

Misrepresentations and/or omissions may be subject to prosecution and liability pursuant to, but not limited to, 18 U.S.C. §§287, 1001, 1031 and 31 U.S.C. §§3729-3733 and 3802.

Certified by Hansen, Malene in SciENcv on 2026-05-21 23:27:38

NIH BIOGRAPHICAL SKETCH SUPPLEMENT

Name: Hansen, Malene

Persistent Identifier (PID) of the Senior/Key Person: https://orcid.org/0000-0002-6828-8640

Position Title: CSO and Professor

Organization and Location: Buck Institute for Research on Aging, Novato, California, United States

Personal Statement

Our laboratory is a leading research group investigating links between the cellular recycling process of autophagy and organismal aging. Our research is significant because autophagy plays critical roles in numerous diseases, many of which are age-related. The lab's research, using the short-lived and genetically tractable model organism *C. elegans* as well as mammalian cell culture systems, has resulted in multiple high-profile publications describing novel molecular mechanisms of autophagy regulation with relevance to aging and disease. Our lab has also provided many powerful assays and tools for monitoring the autophagy process in adult *C. elegans* during the ~15 years it was located at the Sanford Burnham Prebys Medical Discovery Institute (SBP) in La Jolla, CA, and subsequently from Aug. 2021, when I moved to the Buck Institute for Research on Aging as Chief Scientific Officer. I have been recognized by the 2021 Irving Wright Award of Distinction from the American Federation for Aging Research for my research and community efforts in the aging research field.

In addition to our research, I am an active member of the aging and autophagy research communities; e.g., I co-chaired the Cold Spring Harbor Laboratory (CSHL) Meeting on Mechanisms of Aging from 2014-2018, and I am currently a co-organizer of the CSHL meeting on Proteostasis. I frequently peer-review for scientific journals, and I have served as chair of the NIH study section CMAD. Moreover, I am strongly committed to mentoring junior scientists to pursue future careers in autophagy and aging research. At SBP, I served as Associate Dean for Student Affairs for its accredited Graduate School of Biological Sciences, as well as Faculty Advisor for Postdoctoral Training for the institute's ~120 postdocs. In the latter capacity, I offered several professional- and career-development courses to trainees in San Diego and beyond. At Buck, I similarly work to enhance education and training of the next generation of aging and autophagy researchers, including as co-director of the NIA summer training course. I am the proud recipient of the 2017 Mentor of the Year Award from the National Postdoctoral Association.

It is my distinct pleasure to be part of the proposed NIH R25 application, considering my commitment to foster the next generation of research in the aging research space.

Funded projects that I would like to highlight include:

5 R01 AG038664-12 (Hansen, PI) 02/28/22-11/30/27
Regulation of the Autophagy Pathway with Age and in Long-lived Animals

5 R01 AG072791-03 (Hansen, PI) 08/15/21-04/03/27
Role of Selective Autophagy in Organismal Health

5 R01AG082824-02 (Zhou, PI; Hansen, Co-PI) 08/01/23-06/30/28
Novel mitochondria-to-lysosome crosstalk contributes to lysosomal dysfunction during aging

Honors

2024	Bennett Cohen Award, University of Michigan Medical School
2021	Irving Wright Award of Distinction, American Federation for Aging Research
2017	2017 Mentor Award, National Postdoctoral Association Garnett-Powers & Associates, Inc.
2014	Julie Martin Mid-Career Award, American Federation for Aging Research
2011	Glenn Award for Research in Biological Mechanisms of Aging, Glenn Foundation for Medical Research
2008	New Scholar in Aging Award, Ellison Foundation
2005	Senior Postdoctoral Fellowship, American Foundation of Aging Research
2003	Postdoctoral Fellowship, Danish Medical Research Council

2002 Postdoctoral Fellowship, Danish Natural Sciences Research COuncil
1991 Aspiring Researcher Prize, Novo Nordisk, Denmark

Contributions to Science

1. **Novel Longevity Determinants**

   My early research as a postdoctoral fellow in Dr. Cynthia Kenyon's lab at UCSF aimed at identifying novel genes with roles in longevity. This task had long been complicated by the difficulty of isolating genetic mutants with aging phenotypes from classical mutagenesis screens since aging is intrinsically a population phenotype. However, this limitation was greatly helped by the establishment of genome-wide RNAi libraries in *C. elegans*. Together with my collaborators Drs. Andrew Dillin and Allen Hsu, I carried out the first unbiased, genome-wide RNAi longevity screen to identify new genes affecting *C. elegans* lifespan (Hansen et al., PLOS Genetics, 2005; the Ruvkun lab simultaneously carried out a similar screen, using the Ahringer RNAi library).

   My independent lab at SBP investigated several of these novel genes when it started at the end of 2007, including the oncogene integrin-linked kinase (ILK). Together with Dr. Rolf Bodmer, we found that ILK has conserved functions in longevity and stress resistance in *C. elegans* and in *Drosophila*; in the latter, ILK plays an important role in age-related heart function.

   During my postdoctoral training, I also conducted other reporter RNAi screens to identify new longevity genes, which led to the discovery that inhibition of mRNA translation can extend *C. elegans* lifespan. At SBP, we subsequently reported on the underlying mechanisms of this conserved longevity paradigm by studying S6K in collaboration with Dr. Brian Kennedy. Taken together, these studies identified several novel and conserved longevity genes along with their mechanistic regulation and highlight genetic targets that may function as entry points to better understand age-related disorders.

2. **Role of Macro-autophagy in Aging**

   Following the discovery that mRNA translation influences aging, I became interested in cellular processes regulated by the nutrient sensor mTOR. Although autophagy was known to be induced by stresses such as nutrient deprivation, a direct role for autophagy in lifespan extension from dietary restriction (DR) had not been demonstrated when I began studying this as a postdoc. I showed that macroautophagy (hereafter autophagy) is regulated by DR in *C. elegans* and autophagy genes are required for the long lifespan in dietary-restricted animals.

   At SBP, we demonstrated that this relationship broadly applies across longevity paradigms, including germline-less animals. Using this model, we proposed that autophagy may influence aging through lipophagy, the autophagic turnover of lipids. We also identified the helix–loop–helix transcription factor HLH-30, the *C. elegans* ortholog of TFEB, as a conserved regulator of autophagy required for lifespan extension in multiple autophagy-dependent longevity paradigms (Lapierre et al., Nat Comm, 2013). Our later work examined tissue-specific roles of autophagy, including autonomous and non-autonomous functions in the intestine during DR (Gelino et al., PLOS Genetics, 2016). We also performed a comprehensive spatiotemporal analysis of autophagy in a live organism, revealing an age-dependent decline and distinct tissue-specific contributions in different long-lived mutants (Chang et al., Elife, 2017).

   More recently, we investigated selective autophagy in *C. elegans* aging and found that the autophagy receptor p62/SQSTM1, is sufficient to drive autophagy, improve proteostasis, and extend lifespan (Kumsta et al., Nat Comm, 2019). Moreover, we have initiated efforts to identify new pharmacological approaches to induce autophagy in beneficial manners (Tan et al., PNAS, 2025). Together, these studies establish autophagy, including selective autophagy, as a central promoter of organismal health- and lifespan.

3. **Novel Regulators of Autophagy**

   While studying the role of autophagy in aging, we have made significant progress in understanding the underlying regulatory mechanisms of autophagy. These experiments, carried out at SBP, have highlighted an emerging role for transcriptional regulation of autophagy and identified the several transcription factors, including HLH-30/TFEB Lapierre et al., Nat Comm, 2013). Moreover, our studies have increased our understanding of post-translational mechanisms of autophagy regulation. For example, our study in collaboration with Dr. Reuben Shaw (Salk Institute) showed that the energy sensor AMP-activated kinase (AMPK) plays a conserved role in regulating autophagy; we carried out all the *C. elegans* analyses for this study (Egan et al., Science, 2011).

In later lines of research, now also employing mammalian cell cultures in addition to *C. elegans*, we discovered that the Hippo kinases STK3/STK4 are conserved regulators of autophagy, and that mammalian STK3/STK4 regulate autophagy by a novel mechanism involving direct phosphorylation of the essential autophagy protein LC3B/ATG8. Notably, this phosphorylation of LC3B was found playing a crucial role in immunity by our collaborators in Dr. Victor Nizet's lab at UCSD (Wilkinson et al., Mol Cell, 2015). In follow-up work, we showed that LC3B phosphorylation dictates directional transport of vesicles in the cell, a key event in the autophagy process and other LC3-related processes (Nieto-Torres et al., Curr Biol, 2021). Taken together, our studies have provided new mechanistic insights into the regulation of autophagy by providing information about novel regulators and mechanisms that may prove useful in developing future treatments for age-related diseases.

4. **Non-Canonical Roles for Autophagy Genes in Aging**

Our latest research interests, developed at SBP and continued at the Buck Institute, focuses on novel, non-canonical functions for autophagy genes. While investigating the role of neuronal knockdown for autophagy genes in wild-type animals, we surprisingly discovered that inhibition of early-acting autophagy genes extends the lifespan and improves neuronal protein aggregation by a mechanism involving the autophagy protein ATG-16.2 and its highly conserved WD40 domain. Together with our long-term collaborators in Dr. Monica Driscoll's lab at Rutger's University, we linked these phenotypes to an increased neuronal biogenesis of exophers, a very large vesicle which can facilitate extrusion of aggregated proteins (Yang et al., Nat Aging, 2024). Our studies indicate a cell-intrinsic role for neuronal ATG-16.2 in exopher formation, a process that has remained undefined molecularly, and linked exopher formation, as well as non-canonical autophagy gene functions to longer lifespan for the first time.
Currently, we are actively investigating if exophers may constitute 'non-canonical' autophagy vesicles, which are characterized by ATG16-mediated conjugation of the autophagy protein ATG8 proteins to single membranes, as reviewed recently by us. Moreover, we are interested in determining if/how non-canonical functions for autophagy genes may more broadly contribute to aging in both cellular and organismal aging.

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