BIOGRAPHICAL SKETCH

NAME:	**Hansen, Malene**
eRA COMMONS USER NAME:	**malenehansen**
POSITION TITLE:	**Professor and Chief Scientific Officer**

EDUCATION/TRAINING:

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
Copenhagen University, Denmark	M.Sc.	03/1998	Biochemistry/Cell Biology
Copenhagen University, Denmark	Ph.D.	09/2001	Molecular Biology
University of California, San Francisco, CA	Postdoc	07/2007	Genetics of Aging

A. PERSONAL STATEMENT

The Hansen lab is focused on elucidating the role and regulation of the cellular recycling process of autophagy in organismal aging. This research is significant since autophagy plays critical roles in numerous diseases, many of which are age-related. The lab's research, using both 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 transcriptional- and post-translational mechanisms of autophagy regulation with relevance to aging and disease. Moreover, the lab has provided many powerful assays and tools for monitoring the autophagy process in adult *C. elegans*.

In addition to these research efforts, Dr. Hansen is an active member of the aging and autophagy research communities. For example, she has co-chaired the Cold Spring Harbor meeting on Mechanisms of Aging from 2014-2018; she was the lead organizer of the 2020 Keystone meeting on aging; and she will co-chair the 2020 (now 2022) Gordon Research Conference on Autophagy. She frequently peer-reviews for many high-profile journals, she is the current chair of the NIH study section CMAD, and she is strongly committed to mentoring junior scientists, and have developed a number of career-development programs to this end. Her mentoring efforts were acknowledged with the 2017 Mentor of the Year Award from the National Postdoctoral Association.

1. M. Hansen, DC. Rubinsztein, and DW Walker. "Autophagy as a promoter of longevity: insights from model organisms". **Nature Reviews Molecular Cell Biology** (2018), Sep;19(9):579-593, doi:10.1038/s41580-018-0033-y. PMCID: PMC6424591.
2. C. Kumsta, JT. Chang, R. Lee, EP. Tan, Y. Yang, R. Loureiro, E. Choy, SHY. Lim, I. Saez, A. Springhorn, T. Hoppe, D. Vilchez, and M. Hansen. "The autophagy receptor p62/SQST-1 promotes proteostasis and longevity in C. elegans by inducing autophagy." **Nature Communications**, 2019 Dec 11;10(1):5648. doi: 10.1038/s41467-019-13540-4. PMID: 31827090**.**
3. JT. Chang, C. Kumsta, A. Hellman, L. Adams, and M. Hansen. "Spatiotemporal regulation of autophagy during *C. elegans* aging", **eLife** (2017);6. doi:10.7554/eLife18459. PMCID:PMC5496740.
4. DS. Wilkinson, JS. Jariwala, E. Anderson, K. Mitra, J. Meisenhelder, JT. Chang, T. Ideker, T. Hunter, V. Nizet, A. Dillin, M. Hansen, "Phosphorylation of LC3 by the Hippo kinases STK3/STK4 is essential for autophagy", **Molecular Cell**, 2015, Jan 8;57(1):55-68. PMCID: PMC4373083.

B. POSITIONS AND HONORS

Positions and Employment

2001-2007	Postdoctoral Fellow, University of California, San Francisco, CA (Advisor: Prof. C. Kenyon).
2007-2013	Assistant Professor, Sanford Burnham Prebys (SBP) Medical Discovery Inst., La Jolla, CA.
2013-2017	Associate Professor, SBP Medical Discovery Institute, La Jolla, CA.
2017-2021	Professor, SBP Medical Discovery Institute, La Jolla, CA
2021-present	Professor & Chief Scientific Officer, Buck Institute for Aging Research, Novato, CA.
2014-2021	Associate Dean for Student Affairs, SBP Medical Discovery Institute, La Jolla, CA.
2016-2021	Faculty Advisor, Postdoctoral Training, SBP Medical Discovery Institute, La Jolla, CA.

2020-2021 Core leader for Research Development Core, San Diego Nathan Shock Center.

Other Experiences and Professional Memberships

1991-1994 Trainee/Research technician at Novo Nordisk A/S, Denmark (DK).
1991-1998 Cand. scient. (M.Sc.) Student, Copenhagen (CPH) University, DK.
1995 Instructor at Copenhagen University, DK.
1996 Cand. scient. student representative, Faculty of Science, CPH University, DK.
1996 Visiting cand. scient. student, University of North Carolina at Chapel Hill, NC.
1998-1999 Ph.D. student representative, President's Graduate Student Council, CPH University.
1998-2001 Ph.D. student, CPH University.
2000 Visiting graduate student, University of North Carolina at Chapel Hill, NC.
2001 Visiting graduate student, The Scripps Research Institute, La Jolla, CA.
2001 Visiting graduate student, University of Illinois, Urbana-Champaign, IL.
2001-2007 Postdoctoral fellow, University of California, San Francisco, CA (Advisor: Prof. C. Kenyon).
2001-2002 Scientific advisor, Oregon Museum of Science and Industry.
2007-present Reviewer for *Science, Nature-, Cell-, PLOS journals, PNAS, Autophagy, Aging Cell,* etc.
2011-present NIH ad-hoc study section reviewer.
2011-present Review editor, *Frontiers in Genetics of Aging.*
2012 Co-organizer of *C. elegans* topic meeting on aging etc., Madison, WI.
2012-present Member of Faculty 1000, Aging section.
2013 Guest editor for *PLOS Genetics.*
2014-present NIH ad-hoc study section reviewer, Special Emphasis Panel (ZRG1).
2014-2018 Co-organizer of Cold Spring Harbor Lab's conference on Mechanisms of Aging, NY.
2014-present Editorial Board member *npj Aging and Mechanisms of Disease.*
2015-present Editorial Board member, *Frontiers in Cellular Biochemistry.*
2015 Review editor, *Frontiers in Endocrinology.*
2017-present Standing member of NIH study section, CMAD.
2020-present Chair, CMAD.

Honors

1991 Number-one graduating High School student in Denmark (DK) (Køge Gymnasium).
1991 Novo Nordisk A/S "Aspiring Researcher" Prize.
1996 Cand. scient. (M.Sc) Scholarship, Novo Nordisk A/S, DK.
1996-2000 Travel scholarships from misc. Danish foundations for visits to U.S. labs/meetings.
1997 Cand. scient. scholarship, Danish Cancer Society, DK.
2001 Tuition scholarship to participate in *C. elegans* course, Cold Spring Harbor Lab, NY.
2002 1-year Postdoctoral fellowship, Danish Natural Sciences Research Council, DK.
2003-2005 2-year Postdoctoral fellowship, Danish Medical Research Council, DK.
2005-2007 2-year Ellison senior postdoctoral fellowship, American Federation of Aging Research.
2008-2012 Ellison Foundation 4-year New Scholar in Aging Award.
2008 Cancer Center Seeding Grant, SBP Medical Discovery Institute.
2008 American Heart Association 4-year Scientist Development Grant – *Declined.*
2008 American Federation of Aging Research 2-year Research Grant – *Declined.*
2010 American Federation of Aging Research 1-year Research Grant.
2010 Cancer Center Seeding Grant, SBP Institute.
2011 Two NIH/R01 5-year research grants.
2011 Glenn Award for Research in Biological Mechanisms of Aging, 1-year.
2014 American Federation of Aging Research Julie Martin Mid-Career Award, 4-year.
2016 Two NIH/R01 4-5-year research grants.
2017 National Postdoctoral Association Garnett-Powers & Associates, Inc. Mentor Award.
2019 Larry L. Hillblom Foundation Research Network grant.

C. CONTRIBUTIONS TO SCIENCE

1. Novel Longevity Determinants

My early research as a postdoctoral fellow 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 obstacle was greatly helped by the discovery of RNAi interference (RNAi) and the establishment of genome-wide RNAi libraries in *C. elegans*. Together with my collaborators Drs. Ao-Lin Allen Hsu and Andrew Dillin, I carried out the first unbiased, genome-wide RNAi longevity screen to identify new genes affecting *C. elegans* lifespan (the Ruvkun lab simultaneously carried out a similar screen, using the same RNAi library from the Ahringer lab). We have investigated several of these novel genes in my own lab, including the oncogene integrin-linked kinase (ILK). Together with Dr. Rolf Bodmer at our institute, we have found that ILK has conserved functions in longevity and stress resistance in *Drosophila*, where ILK plays an important role in age-related heart function. During my postdoctoral research, I conducted other reporter RNAi screens to identify additional longevity genes, which led to the discovery that inhibition of genes with functions in mRNA translation can extend *C. elegans* lifespan. We have subsequently reported on the underlying mechanisms of this conserved longevity paradigm in collaboration with Dr. Brian Kennedy. Taken together, these studies have brought forward several novel and conserved longevity genes, and highlight genetic targets that may function as entry points to better understand age-related disorders.

a. M. Hansen', A-L. Hsu', A. Dillin and C. Kenyon, "New genes tied to Endocrine, Metabolic and Dietary Regulation of Lifespan from a *Caenorhabditis elegans* Genomic RNAi Screen*",* **PLOS Genetics** (2005) Jul 25; 1(1):119-28, PMCID: PMC1183531.

b. M. Hansen, S. Taubert, D. Crawford, N. Libina, S-J. Lee, and C. Kenyon, "Lifespan extension by conditions that inhibit translation in *C. elegans*", **Aging Cell** (2007) Feb; 6(1):95-110. PMID:17266679. DOI:10.1111/j.1474-9726.2006.00267.x

c. C. Kumsta, T.-T. Ching, M. Nishimura, A. E. Davis, S. Gelino, H. H. Catan, X. Yu, C.-C. Chu, B. Ong, S. H. Panowski, N. Baird, R. Bodmer, A.-L. Hsu, M. Hansen, "Integrin-linked kinase modulates longevity and thermotolerance in C. *elegans* through neuronal control of HSF-1", **Aging Cell** (2014) Jan 9; 13(3):419-430. PMCID: PMC4059541**.**

d. PR. McQuary, CY. Liao, JT. Chang, C. Kumsta, X. She, A. Davis, CC. Chu, S. Gelino, RL. Gomez-Amaro, M. Petrascheck, LM. Brill, WC. Ladiges, BK. Kennedy and M. Hansen. "*C. elegans* S6K mutants require a creatine kinase-like effector for lifespan extension", **Cell Reports** (2016) Mar 8;14(9):2059-67. PMCID: PMC4823261.

2. Role of Autophagy in Aging

Following our discovery of a role for mRNA translation in organismal aging, I became more broadly interested in cellular processes regulated by the nutrient sensor TOR. Although the cellular homeostatic process of autophagy was known to be induced by cellular stresses, including dietary restriction, no direct link had been reported at the time I started working on this as a postdoc. Using *C. elegans*, I showed that autophagy is modulated in response to dietary restriction*,* and autophagy genes are required for lifespan extension observed in dietary- restricted animals. In my own lab, we subsequently showed that this relationship exists in all longevity paradigms investigated to date, including in germline-less animals. Using this longevity model, we were the first to propose a potential mechanism for how autophagy could contribute to aging, namely via lipophagy, i.e., turnover of lipids. We also discovered that the helix-loop-helix transcription factor HLH-30, the *C. elegans* ortholog of TFEB, regulates autophagy in a conserved fashion, and is universally required for the long lifespan associated with at least six autophagy-dependent longevity paradigms. Our most recent studies are focused on understanding autophagy in tissue-specific contexts, and we recently reported critical autonomous and non-autonomous roles for autophagy in the intestine of dietary-restricted animals. We also carried out the first comprehensive spatiotemporal analysis of autophagy in a live organism, showing an age-dependent decrease in autophagy, and insights into how long-lived mutants use tissue-specific autophagy to promote lifespan extension. We have also focused intensively on elucidating the role of selective autophagy in aging. In addition to screening for novel receptors of autophagy, we have found that p62/SQSTM1, the first described autophagy receptor with specificity for ubiquitinated cargo, is sufficient to drive autophagy to promote proteostasis and extend longevity. Taken together, these investigations have firmly established a central role for autophagy in organismal aging, and suggest that autophagy induction, possibly in a highly selective fashion, may improve the health of the organism in highly tissue-specific ways.

a. LR. Lapierre, S. Gelino, A. Meléndez, and M. Hansen, "Autophagy and lipid metabolism coordinately modulate lifespan in germline-less *C. elegans*", **Current Biology** (2011) Sep 27; 21(18), 1507–1514 (featured article, selected article for Faculty of 1000). PMCID: PMC3191188.

b. S. Gelino; JT. Chang; C. Kumsta; X. She, A. Davis; C. Nguyen, S. Panowski, and M. Hansen, "Intestinal Autophagy Improves Healthspan and Longevity in *C. elegans* During Dietary Restriction", **PLOS Genetics** (2016) Jul 14;12(7):e1006135. PMCID: PMC4945006.

c. JT. Chang, C. Kumsta, A. Hellman, L. Adams, and M. Hansen. "Spatiotemporal regulation of autophagy during *C. elegans* aging", **eLife**, 2017;6. doi: 10.7554/eLife.18459. PMID: 28675140; PMCID: PMC5496740.

d. C. Kumsta, JT. Chang, R. Lee, EP. Tan, Y. Yang, R. Loureiro, E. Choy, SHY. Lim, I. Saez, A. Springhorn, T. Hoppe, D. Vilchez, and M. Hansen. "The autophagy receptor p62/SQST-1 promotes proteostasis and longevity in C. elegans by inducing autophagy." **Nature Communications**, 2019 Dec 11;10(1):5648. doi: 10.1038/s41467-019-13540-4. PMID: 31827090**.**

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 have highlighted an emerging role for transcriptional regulation of autophagy, and identified the transcription factors PHA-4/FOXA, HLH-30/TFEB, and HSF-1. 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. More recently, 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 LC3. Notably, this phosphorylation of LC3 was found by our collaborators in Dr. Victor Nizet's lab at UCSD to play a crucial role in immunity. We also developed a phospho-specific antibody that will allow us to better monitor the autophagy process in mammalian cells. Taken together, these 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- and autophagy-related diseases.

a. DF. Egan, DB. Shackelford, MM. Mihaylova, S. Gelino, RA. Kohnz, W. Mair, DS. Vasquez, A. Joshi, DM. Gwinn, R. Taylor, JM. Asara, J. Fitzpatrick, A. Dillin, B. Viollet, M., Kundu, M. Hansen, and RJ. Shaw, "Phosphorylation of ULK1 (hATG1) by AMP-activated protein kinase connects energy sensing to miophagy", **Science** (2011) Jan 28;331(6016):456-461. PMCID: PMC3030664.

b. LR. Lapierre, C. Daniel De Magalhaes Filho, PR. McQuary, CC. Chu, O. Visvikis, JT. Chang, S. Gelino, B. Ong, A. Davis, JE. Irazoqui, A. Dillin, and M. Hansen*, "*The TFEB orthologue HLH-30 regulates autophagy and modulates longevity in *Caenorhabditis elegans",* **Nature Communications** (2013) Aug 8; 4:2267. PMCID: PMC3866206.

c. DS. Wilkinson, JS. Jariwala, E. Anderson, K. Mitra, J. Meisenhelder, JT. Chang, T. Ideker, T. Hunter, V. Nizet, A. Dillin, M. Hansen, "Phosphorylation of LC3 by the Hippo kinases STK3/STK4 is essential for autophagy", **Molecular Cell** (2015) Jan 8;57(1):55-68. PMCID: PMC4373083.

d. C. Kumsta, JT. Chang, J. Schmalz, and M. Hansen. *Hormetic heat stress and HSF-1 induce autophagy to improve survival and proteostasis in* C. elegans*,* **Nature Communications** (2017) Feb 15;8:14337. doi: 10.1038/ncomms14337, PMID: 28198373, PMCID: PMC5316864.

Complete List of Published Work in My Bibliography (58 total + 1 pending):
https://www.ncbi.nlm.nih.gov/sites/myncbi/malene.hansen.1/bibliography/41554582/public/?sort=date&d%20irection=ascending

RESEARCH SUPPORT

Ongoing Research Support

R01 AG038664 Hansen (PI) 09/01/2016 – 04/30/2021
NIH/NIA
Title: "Regulation of the Autophagy Process in Organismal Aging"
The goal of this project is to investigate the role of autophagy in long-lived *C. elegans* mutants.

R01 GM117466 Hansen (PI) 09/01/2016 – 03/31/2021 (NCE)
NIH/NIH
Title: "Autophagy Regulation by Hippo Kinases STK3/STK4"
The = goal of this project is to elucidate the molecular mechanism by which STK3/STK4 regulate autophagy via the central autophagy protein Atg8.

2019-A-005-NET Adams (PI) 01/01/2020 – 12/31/2023
Larry L. Hillblom Foundation

Title: “Autophagic Control of the Epigenome in Senescence - From Mechanisms to Senolytics”

The goal of this project is to investigate the mechanisms by which autophagy controls the epigenome and that keep aged and tissue-damaging senescent cells alive, with a view to developing strategies to kill those cells to promote healthy aging and suppress disease, including neurodegeneration.

Role: Co-Investigator

BIG20016 Hansen (PI) 07/01/2020 – 06/30/2023
American Foundation for Aging Research
Title: “Non-canonical functions of autophagy genes in organismal lifespan”

The goal of this proposal is to understand new non-canonical functions for early-acting autophagy genes in *C. elegans* and in mammalian cells.

1 P30 AG068635-01 (PI: Shadel) 07/01/2020 – 06/30/2025
The Salk Institute for Biological Studies/NIH

Title: “San Diego Nathan Shock Center”

This proposal aims to enhance the understanding of the role of cell heterogeneity in the aging process as well as promote career development of researchers with interest in aging research.

Role: Research Development Core Leader

Completed Research Support

Julie Martin Mid-Career Award Hansen (PI) 07/01/2014 – 06/30/2019
American Federation for Aging Research
Title: “Elucidating the Regulatory Network of the Transcription Factor HLH-30/TFEB”
The goal of this research was to identify new genetic and pharmacological regulators of HLH/30/TFEB.
Role: PI

P30 CA030199 Powis (PI) 05/01/2017 - 04/30/2018
NIH/NCI
Cancer Center Seeding/Pilot Grant to M. Hansen
Title: “Novel regulators of the STK3/4-LC3 axis controlling cell proliferation and autophagy”
The goal of this research was to screen regulators of STK3/4 kinases controlling cell proliferation and autophagy.
Role: Pilot-Project PI