BIOGRAPHICAL SKETCH

NAME: **Malene Hansen**

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

POSITION TITLE: **Professor and Chief Scientific Officer**

EDUCATION/TRAINING:

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	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	Postdoc	07/2007	Genetics of Aging

A. 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 last 14 years, where it was located at the Sanford Burnham Prebys Medical Discovery Institute (SBP) in La Jolla, CA. In August 2021, I moved to the Buck Institute of Aging Research, where we are establishing a new research group.

In addition to our lab's research efforts, for which I was recently recognized by the 2021 Irving Wright Award of Distinction from the American Federation for Aging Research, I am an active member of the aging and autophagy research communities. For example, I co-chaired the Cold Spring Harbor Meeting on Mechanisms of Aging from 2014-2018 and the 2020 Keystone Aging Meeting; I also co-chair the 2022 Gordon Research Conference on Autophagy. I frequently peer-review for high-profile journals, and I previously served as chair for the NIH study section CMAD.

Last but not least, I am strongly committed to mentoring junior scientists to pursue future careers in autophagy and aging research. As specific examples, I helped the first graduate student and the first postdoctoral fellow in my laboratory obtain independent funding from the NIH (F31 and K99 awards, respectively), and I have since mentored several other recipients of K99 awards. Moreover, at SBP, I previously served as Associate Dean for Student Affairs as well as Faculty Advisor for Postdoctoral Training for the institute's ~150 postdocs. In the latter capacity, I offered several professional- and career-development courses to trainees in San Diego and beyond. For these mentoring efforts, I am the proud recipient of the 2017 Mentor of the Year Award from the National Postdoctoral Association.

2R01 AG038664-11 (Hansen, PI) 02/15/22-11/31/26
Regulation of the Autophagy Pathway with Age and in Long-lived Animals
The goal of this project is to investigate the role of autophagy with age and in long-lived *C. elegans* mutants.

1R01 AG072791-01 (Hansen, PI) 08/15/21-04/30/26
Role of Selective Autophagy in Organismal Health
The goal of this project is to investigate a novel longevity role for the selective autophagy receptor p62/SQSTM1 in *C. elegans*.

BIG20016 (Hansen, PI) 07/01/20-06/30/23
American Foundation for Aging Research
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. 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**.** PMCID: PMC6906454.
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.

Positions, Scientific Appointments, and Honors

Professional Experience

2021-present	Professor & Chief Scientific Officer, Buck Institute for Research on Aging, Novato, CA
2020-2021	Core Leader for Research Development Core, San Diego Nathan Shock Center
2020-2021	Professor, SBP Medical Discovery Institute, La Jolla, CA (thru August 2021)
2017-2021	Chair, Cellular and Molecular Mechanisms of Aging and Development (CMAD)
2017-2021	Standing Member, NIH Study Section, CMAD
2016-2021	Faculty Advisor, Postdoctoral Training, SBP Medical Discovery Institute, La Jolla, CA
2015	Review Editor, *Frontiers in Endocrinology*
2015-present	Editorial Board Member, *Frontiers in Cellular Biochemistry*
2014-present	Editorial Board Member *npj Aging and Mechanisms of Disease*
2014-2021	Associate Dean for Student Affairs, SBP Medical Discovery Institute, La Jolla, CA
2014-2018	Co-organizer of Cold Spring Harbor Lab's conference on Mechanisms of Aging, NY
2013	Guest Editor, *PLOS Genetics*
2013-2017	Associate Professor, SBP Medical Discovery Institute, La Jolla, CA
2012-present	Member of Faculty 1000, Aging Section
2012	Co-organizer, *C. elegans* topic meeting on aging etc., Madison, WI
2011-present	Review Editor, *Frontiers in Genetics of Aging*
2011-present	NIH Ad-Hoc Study Section & Special Emphasis Panel Reviewer
2007-present	Reviewer, *Science, Nature-, Cell-, PLOS journals, PNAS, Autophagy, Aging Cell,* etc.
2007-2013	Assistant Professor, Sanford Burnham Prebys (SBP) Medical Discovery Inst., La Jolla, CA
2001-2002	Scientific Advisor, Oregon Museum of Science and Industry
2001-2007	Postdoctoral Fellow, University of California, San Francisco, CA (Advisor: Prof. C. Kenyon)
2001	Visiting Graduate Student, University of Illinois, Urbana-Champaign, IL
2001	Visiting Graduate Student, The Scripps Research Institute, La Jolla, CA
2000	Visiting Graduate Student, University of North Carolina at Chapel Hill, NC
1998-2001	Ph.D. Student, CPH University
1998-1999	Ph.D. Student Representative, President's Graduate Student Council, CPH University
1996	Visiting Cand. Scient. Student, University of North Carolina at Chapel Hill, NC
1996	Cand. Scient. Student Representative, Faculty of Science, CPH University, DK
1991-1998	Cand. Scient. (M.Sc.) Student, Copenhagen (CPH) University, DK
1991-1994	Trainee/Research Technician at Novo Nordisk A/S, Denmark (DK)

Honors

2021	Irving Wright Award of Distinction, American Federation for Aging Research
2021, 2022	Two NIH/R01 5-year research grants
2019	Larry L. Hillblom Foundation Research Network grant
2017	2017 Mentor Award, National Postdoctoral Association Garnett-Powers & Associates, Inc.
2016	Two NIH/R01 4-5-year research grants
2014	American Federation of Aging Research Julie Martin Mid-Career Award, 4-year
2011	Glenn Award for Research in Biological Mechanisms of Aging, 1-year
2011	Two NIH/R01 5-year research grants

2010	American Federation of Aging Research 1-year Research Grant
2008, 2010	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*
2008-2012	Ellison Foundation 4-year New Scholar in Aging Award
2005-2007	Ellison senior postdoctoral fellowship, American Federation of Aging Research, 2-year
2003-2005	Postdoctoral fellowship, Danish Medical Research Council, DK, 2-year
2002	Postdoctoral fellowship, Danish Natural Sciences Research Council, DK, 1-year
2001	Tuition scholarship to participate in *C. elegans* course, Cold Spring Harbor Lab, NY
1997	Cand. scient. scholarship, Danish Cancer Society, DK
1996-2000	Travel scholarships from misc. Danish foundations for visits to U.S. labs/meetings
1996	Cand. scient. (M.Sc) Scholarship, Novo Nordisk A/S, DK
1991	Novo Nordisk A/S "Aspiring Researcher" Prize
1991	Number-one graduating high-school student in Denmark (DK) (Køge Gymnasium)

B. Contributions to Science

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 work, I conducted other reporter RNAi screens to identify new 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.

1. 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.
2. 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.
3. 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
4. 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.

1. 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.
2. 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.
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/eLife.18459. PMID: 28675140; PMCID: PMC5496740.
4. 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. PMCID: PMC6906454.

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 LC3B. Notably, this phosphorylation of LC3B was found by our collaborators in Dr. Victor Nizet's lab at UCSD to play a crucial role in immunity. Interestingly, LC3B phosphorylation dictates directional transport of vesicles in the cell, a key event in the autophagy process. 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.

1. 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.
2. 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.
3. 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.
4. J. L. Nieto-Torres, S-L. Shanahan, R. Chassefeyre, T. Chaiamarit, S. Zaretski, S. Landeras-Bueno, A.Verhelle, S. E. Encalada, M. Hansen, *LC3B phosphorylation regulates FYCO1 binding and directional transport of autophagosomes.* **Current Biology**, 2021, Jun 15;S0960-9822(21)00750-8. PMCID: PMC8439105.

5. 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 MyBibliography (66 citations):
https://www.ncbi.nlm.nih.gov/sites/myncbi/malene.hansen.1/bibliography/41554582/public/