BIOGRAPHICAL SKETCH

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NAME: **Hansen, Malene**

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

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

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
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 ~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 the NIA summer training course. I am the proud recipient of the 2017 Mentor of the Year Award from the National Postdoctoral Association.

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

Citations:

1. Y. Yang, M.L. Arnold, E. Choy, C. Lange, K. Poon, M. Broussalian, L-H. Sun, T. Moreno, A. Singh, M. Driscoll, C. Kumsta and M. Hansen, *Autophagy protein ATG-16.2 and its WD40 domain mediate the*

beneficial effects of inhibiting early-acting autophagy genes in C. elegans neurons, **Nature Aging,** 2024 Feb; 4 (2): 198-212. PMCID: PMC11022750.

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. 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.

B. Positions, Scientific Appointments, and Honors

Professional Experience

April 2024	Co-organizer of Cold Spring Harbor Lab's conference on Proteostasis, NY
2023-Present	Member, External Advisory Committee, Nathan Shock Center University of Washington, Seattle, Washington
2023-Present	Member, Scientific Advisory Board, Glenn Foundation for Medical Research
2022-Present	Member, Scientific Advisory Board, Institute for Molecular Biology, Mainz, Germany
2022-Present	Member, External Advisory Board, University of Alabama's Nathan Shock Center
2022-Present	Member, Steering Committee, NIH R13 AG059431 Summer training Course in Experimental Aging Research
2021-Preseent	Member, External Advisory Committee, Autophagy, Inflammation, and Metabolism (AIM) Center, New Mexico
2021-Present	Admin Core-leader NIH U54 AG075934 Cellular Senescence Network, Human Tissue Mapping center at the Buck Institute
2021-Present	Co- Director, Glenn Center for Biology of Aging Research at the Buck Institute
2021-Present	Professor & Chief Scientific Officer, Buck Institute for Research on Aging, Novato, CA
2021-Present	Adjunct Professor, University of Southern California, Leonard Davis School of Gerontology
2021-Present	Chair, External Advisory Board, San Diego Nathan Shock Center
2021-Present	Member, External Advisory Committee, Autophagy, Inflammation, and Metabolism Center, University of New Mexico
2021-Present	Adjunct Professor, Sanford Burnham Prebys (SBP) Medical Discovery Institute, La Jolla, CA
2021	Member, Academy for Health & Lifespan Research
2020-2021	Core Leader for Research Development Core, San Diego Nathan Shock Center
2020-2021	Professor, SBP Medical Discovery Institute, La Jolla, CA (till August 2021)
2020-2021	Chair, Cellular and Molecular Mechanisms of Aging and Development (CMAD)
2017-2020	Standing Member, NIH Study Section, CMAD
2016-2021	Faculty Advisor, Postdoctoral Training, SBP Medical Discovery Institute, La Jolla, CA
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, 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, Copenhagen (CPH) University, Denmark (DK)
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, CPH University, DK
1991-1994	Trainee/Research Technician at Novo Nordisk A/S, DK

Honors

2024	Recipient of the Bennett Cohen Award, University of Michigan Medical School
2023	NIH/R01 5-year research grant (co-PI)
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 (with P. Adams and N. Cosford, SBP)
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 years
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, La Jolla, CA
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 years
2003-2005	Postdoctoral Fellowship, Danish Medical Research Council, DK, 2 years
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	Inaugural recipient of Novo Nordisk A/S "Aspiring Researcher" Prize
1991	Number-one graduating high-school student in DK (Køge Gymnasium)

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 limitation was greatly helped by the discovery of RNA interference (RNAi) and the establishment of genome-wide RNAi libraries in *C. elegans*. Together with my collaborators Drs. Andrew Dillin and Ao-Lin Allen Hsu, 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, original RNAi library from the Ahringer lab). We investigated several of these novel genes in my lab at the Sanford-Burnham-Prebys Medical Discovery Institute (SBP), including the oncogene integrin-linked kinase (ILK). Together with Dr. Rolf Bodmer at SBP, 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 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. At SBP, we subsequently reported on the underlying mechanisms of this conserved longevity paradigm by studying the ribosomal kinase S6K in collaboration with Dr. Brian Kennedy at the Buck Institute for Research on Aging. 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.

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 Macro-autophagy in Aging

Following the discovery of a role for mRNA translation in organismal aging during my postdoc studies, I became more broadly interested in cellular processes regulated by the nutrient sensor mTOR. 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. I showed that macroautophagy (hereafter referred to as autophagy) is modulated by dietary restriction in *C. elegans,* and autophagy genes are required for lifespan extension observed in dietary- restricted animals. At SBP, 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 later studies have focused on understanding autophagy in tissue-specific contexts, e.g., we have reported on autonomous and non-autonomous roles for autophagy in the intestine of dietary-restricted animals. To this end, we carried out the first comprehensive spatiotemporal analysis of autophagy in a live organism, showing an age-dependent decrease in autophagy, along with studies on how long-lived germline-less vs. insulin/IGF-1 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 ongoing efforts of screening for novel receptors of autophagy, we have found that p62/SQSTM1, the first described autophagy receptor in metazoans with specificity for ubiquitinated cargo, is sufficient to drive autophagy to promote proteostasis and extend longevity. Taken together, our investigations have established a central role for autophagy in organismal aging, and suggest that autophagy induction, possibly in a selective fashion, may improve the healthspan 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. 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. PMCID: PMC6906454.

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 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; we carried out all the *C. elegans* analyses for this study. In a later line of research, 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. In follow-up work, we were able to show that LC3B phosphorylation dictates directional transport of

vesicles in the cell, a key event in the autophagy process and other LC3-related processes. 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.

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.

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 exopher biogenesis. As first shown by the Driscoll lab in 2017, neurons but also other tissues and other organisms can extrude exophers, a very large vesicle which can include aggregated proteins. We hypothesize that exophers may constitute so called 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. 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.

1. Y. Yang, M.L. Arnold, E. Choy, C. Lange, K. Poon, M. Broussalian, L-H. Sun, T. Moreno, A. Singh, M. Driscoll, C. Kumsta and M. Hansen, Autophagy protein ATG-16.2 and its WD40 domain mediate the beneficial effects of inhibiting early-acting autophagy genes in *C. elegans* neurons, Nature Aging, 2024 Feb; 4 (2): 198-212. PMID: 38177330.
2. L-H. Sun, C. Lange, M. Hansen and C. Kumsta. Neuronal waste management: New roles for autophagy genes in the extrusion of protein aggregates and in longevity. **Autophagy**, 2024, Mar 6:1-3. doi: 10.1080/15548627.2024.2322420, PMID: 38411179.
3. J.L. Nieto-Torres, S. Zaretski, T. Liu, P. Adams, M. Hansen, *Post-translation modifications of ATG8 proteins: an emerging mechanism of autophagy control*. **Journal of Cell Science**, 2023 Aug 15;136(16):jcs259725. doi: 10.1242/jcs.259725. Epub 2023 Aug 15. PMID: 37589340.
4. JL Nieto-Torres, AM Leidal, J. Debnath, and M. Hansen, Beyond autophagy: the expanding roles of ATG8 proteins, **Trends in Biochemical Sciences**, 2021, Feb. 5, doi: 10.1016/j.tibs.2021.01.004, PMID: 33558127.

Complete List of Published Work in My Bibliography (78 citations):

https://www.ncbi.nlm.nih.gov/sites/myncbi/malene.hansen.1/bibliography/41554582/public/