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

NIH BIOGRAPHICAL SKETCH COMMON FORM

Name: Kirchhausen, Tomas

Persistent Identifier (PID) of the Senior/Key Person: https://orcid.org/0000-0003-0559-893X

Position Title: Senior Investigator, Professor of Cell Biology

Organization and Location: Boston Children's Hospital, Boston, Massachusetts, United States

PROFESSIONAL PREPARATION

INSTITUTION AND LOCATION	DEGREE	Start Date	Completion Date	FIELD OF STUDY
Harvard Medical School, Boston, Massachusetts, United States	Postdoctoral Fellow	09/1979	12/1985	Biochemistry
The University of Chicago, Chicago, Illinois, United States	Postdoctoral Fellow	02/1978	09/1979	Biochemistry
Instituto Venezolano de Investigaciones Cientificas, Miranda, Not Applicable, N/A, Venezuela	Doctor of Philosophy (PHD)	06/1975	06/1977	Biophysics and Physiology
Universidad Peruana Cayetano Heredia, Lima, Not Applicable, N/A, Peru	Master of Science (MS)	06/1973	06/1975	Biophysics
Instituto Venezolano de Investigaciones Cientificas, Miranda, Not Applicable, N/A, Venezuela	Master of Science (MS)	06/1973	06/1975	Biophysics
Universidad Peruana Cayetano Heredia, Lima, Not Applicable, N/A, Peru	Bachelor of Science (BS)	04/1969	04/1972	Biology

Appointments and Positions

2012 - present	Senior Investigator, Professor of Cell Biology, Boston Children's Hospital, Boston, Massachusetts, United States
2016 - 2019	Visiting Scientist, Janelia Research Campus, HHMI, Ashburn, Virginia, United States
2013 - present	Springer Family Professor of Pediatrics, Harvard Medical School, Boston, Massachusetts, United States
2012 - present	Professor, Department of Pediatrics, Harvard Medical School, Boston, Massachusetts, United States
2012 - present	Senior Investigator, Program in Cellular and Molecular Medicine (PCMM) at Boston Children’s Hospital, Boston, Massachusetts, United States
2009 - 2015	HMS Director, Harvard-Portugal Program in Translational Research and Medical Education, Boston, Massachusetts, United States
2007 - 2012	Executive Faculty Committee, Immune Disease Institute, Boston, Massachusetts, United States
2006 - 2012	Chair IT Committee, Immune Disease Institute, Boston, Massachusetts, United States
1999 - present	Professor, Department of Cell Biology, Harvard Medical School, Boston, Massachusetts, United States
1999 - 2012	Senior Investigator, Immune Disease Institute, Boston, Massachusetts, United States
1993 - 1999	Associate Professor, Department of Cell Biology, Harvard Medical School, Boston, Massachusetts, United States
1992 - 1999	Investigator, The Center for Blood Research, Inc., Boston, Massachusetts, United States
1991 - 1993	Associate Professor of Anatomy and Cellular Biology, Harvard Medical School, Boston, Massachusetts, United States
1986 - 1991	Assistant Professor of Anatomy and Cellular Biology, Harvard Medical School, Boston, Massachusetts, United States
1984 - 1985	1984-1985 Assistant Head Tutor, Biochemical Sciences, Harvard University, Cambridge, Massachusetts, United States
1982 - 1985	Research Associate in Biochemistry, Harvard University, Cambridge, Massachusetts, United States
1981 - 1982	Postdoctoral, Department of Biochemistry and Molecular Biology, Harvard University, Cambridge, Massachusetts, United States

1980 - present Tutor in Biochemical Sciences, Harvard University, Cambridge, Massachusetts, United States

Products

Products Closely Related to the Proposed Project

1. Sanyal A, Scanavachi G, Somerville E, Saminathan A, Nair A, Bango Da Cunha Correia RF, Aylan B, Sitarska E, Oikonomou A, Hatzakis NS, Kirchhausen T. Neuronal constitutive endolysosomal perforations enable α-synuclein aggregation by internalized PFFs. J Cell Biol. 2025 Feb 3;224(2) PubMed Central PMCID: PMC11665449.
2. Sanyal A, Scanavachi G, Somerville E, Aylan B, Costa-Filho JI, Brooks F, Dickson JR, Hyman BT, Kirchhausen T. Tau seeding in neurons enabled by transient endolysosomal perforations are confined within endolysosomes. bioRxiv. 2025 Nov 3; PubMed Central PMCID: PMC12637672.
3. Nair A, Nair A, Stock P, Jain A, Somerville E, Sanyal A, Costa-Filho JI, Kirchhausen T. Close-up of vesicular ER exit sites by volume electron imaging using FIB-SEM. J Cell Biol. 2026 Jan 5;225(1) PubMed PMID: 41171079; NIHMSID: NIHMS2172049.
4. Gallusser B, Maltese G, Di Caprio G, Vadakkan TJ, Sanyal A, Somerville E, Sahasrabudhe M, O'Connor J, Weigert M, Kirchhausen T. Deep neural network automated segmentation of cellular structures in volume electron microscopy. J Cell Biol. 2023 Feb 6;222(2) PubMed Central PMCID: PMC9728137.

Other Significant Products Highlighting Contributions to Science

1. Gao R, Asano SM, Upadhyayula S, Pisarev I, Milkie DE, Liu TL, Singh V, Graves A, Huynh GH, Zhao Y, Bogovic J, Colonell J, Ott CM, Zugates C, Tappan S, Rodriguez A, Mosaliganti KR, Sheu SH, Pasolli HA, Pang S, Xu CS, Megason SG, Hess H, Lippincott-Schwartz J, Hantman A, Rubin GM, Kirchhausen T, Saalfeld S, Aso Y, Boyden ES, Betzig E. Cortical column and whole-brain imaging with molecular contrast and nanoscale resolution. Science. 2019 Jan 18;363(6424) PubMed Central PMCID: PMC6481610.
2. Hoffman DP, Shtengel G, Xu CS, Campbell KR, Freeman M, Wang L, Milkie DE, Pasolli HA, Iyer N, Bogovic JA, Stabley DR, Shirinifard A, Pang S, Peale D, Schaefer K, Pomp W, Chang CL, Lippincott-Schwartz J, Kirchhausen T, Solecki DJ, Betzig E, Hess HF. Correlative three-dimensional super-resolution and block-face electron microscopy of whole vitreously frozen cells. Science. 2020 Jan 17;367(6475) PubMed Central PMCID: PMC7339343.
3. Aguet F, Upadhyayula S, Gaudin R, Chou YY, Cocucci E, He K, Chen BC, Mosaliganti K, Pasham M, Skillern W, Legant WR, Liu TL, Findlay G, Marino E, Danuser G, Megason S, Betzig E, Kirchhausen T. Membrane dynamics of dividing cells imaged by lattice light-sheet microscopy. Mol Biol Cell. 2016 Nov 7;27(22):3418-3435. PubMed Central PMCID: PMC5221578.
4. He K, Marsland R III, Upadhyayula S, Song E, Dang S, Capraro BR, Wang W, Skillern W, Gaudin R, Ma M, Kirchhausen T. Dynamics of phosphoinositide conversion in clathrin-mediated endocytic traffic. Nature. 2017 Dec 21;552(7685):410-414. PubMed Central PMCID: PMC6263037.

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 Kirchhausen, Tomas in SciENcv on 2026-05-07 10:16:50

NIH BIOGRAPHICAL SKETCH SUPPLEMENT

Name: Kirchhausen, Tomas

Persistent Identifier (PID) of the Senior/Key Person: https://orcid.org/0000-0003-0559-893X

Position Title: Senior Investigator, Professor of Cell Biology

Organization and Location: Boston Children's Hospital, Boston, Massachusetts, United States

Personal Statement

Our research examines the mechanisms that mediate and regulate cellular membrane remodeling. We study intracellular vesicular trafficking and organelle architecture, with emphasis on interactions between endosomes and lysosomes and the cytosol; fusion and fission in the endosomal system; formation and resolution of perforations in endolysosomal limiting membranes; intraluminal vesicle formation in endosomes; regulation of cell size and endoplasmic reticulum organization during cell division; post-mitotic nuclear pore complex assembly; cell-cell communication during development; and interactions between viruses and host cells. Throughout this work, we have used emerging technologies to connect molecular structure with dynamics in living cells, from molecular cloning and X-ray crystallography to single-molecule biophysics, electron cryomicroscopy, and advanced live-cell imaging coupled with machine-learning methods.

Over the past three decades, our work has helped define molecular mechanisms of clathrin-mediated sorting, the principal pathway for receptor-mediated endocytosis, synaptic membrane recycling, and a route of entry used by many viral and bacterial pathogens. We have clarified the structure, interactions, and assembly-disassembly cycle of clathrin and its associated proteins. We determined the first atomic-resolution X-ray structures of clathrin and AP-1. Using cryo-EM, we visualized the complete clathrin coat at subnanometer resolution, defined triskelion architecture and lattice packing, and characterized ATP-dependent uncoating by auxilin and Hsc70. Related structural studies showed how β-arrestins and adaptor proteins engage clathrin, linked clathrin machinery to noncanonical Wnt signaling, and helped define how internalized non-enveloped viruses escape vesicular confinement to reach the cytosol during early stages of infection.

We now combine high-resolution molecular analysis with live-cell imaging to define the dynamic mechanisms that govern membrane remodeling in physiology and disease. Using lattice light-sheet microscopy and adaptive-optics lattice light-sheet microscopy in cultured cells, organoids, and tissues, we have observed transient perforations in endosomal membranes and linked these events to the initiation of amyloid-seeded aggregation in neurons, with implications for Parkinson’s disease and Alzheimer’s disease. We complement dynamic imaging with large-scale three-dimensional focused ion beam-scanning electron microscopy, which provides label-free volumetric visualization from organelle to cellular scales. These approaches generate large four-dimensional datasets that we analyze with computational methods, including deep-learning-based approaches for segmentation, quantitation, and modeling.

Our research program provides both the intellectual setting and the technical resources for training graduate students and postdoctoral fellows. I aim to create an environment in which trainees can develop ideas independently, receive sustained critical feedback, and pursue new directions while learning to work collaboratively. I emphasize rigor in experimental design, record keeping, and data analysis. I have extensive experience teaching and organizing graduate-level courses at Harvard Medical School, MIT, and in international settings. I have chaired or co-chaired Gordon Research Conferences and other scientific meetings, and I co-founded the Harvard-Portugal Program, which I directed for seven years.

Honors

2025	Fellow, American Academy of Arts and Sciences
2023	Fellow, American Academy of Microbiology
2017	EMBO Keynote Lecture, FEBS – EMBO Advance Lecture Course in Molecular Architecture Dynamics and Function of Biomembranes
2017	Honorary Member, Associazione di Biologia Cellulare e del Differenziamento, Italy
2016	Honorary Professor, University of Hong Kong
2016	Academia Nacional de Ciencias (Peru), Académico Correspondiente
2015	EMBO Keynote Lecture, Systems Biology of Infection
2015	Speaker of the year, Netherlands Society for Biochemistry and Molecular Biology

2014	Elected Associated Member , EMBO
2013	Doctor Honoris Causa, Universidad Ricardo Palma, Peru
2013	Springer Family Professor of Pediatrics, Harvard Medical School
2008	Fellow, AAAS
2002	Honorary Professor, Universidad Peruana Cayetano Heredia, Peru
1999	Master Arts (Honorary), Cell Biology, Harvard University
1986 - 1991	Established Investigator Award, American Heart Association

Contributions to Science

1. Molecular architecture of clathrin coats and mechanism of uncoating (1981-)
   Through studies extending over three decades, we defined the structure and interactions of clathrin and many of its associated proteins and the assembly and uncoating mechanisms for clathrin coats. Highlights: clathrin heavy-chain sequence -- at the time, the longest protein sequence derived by cDNA cloning; high-resolution crystal structures of a large N-terminal fragment of clathrin and its complex with a "clathrin box" peptide, of the core of the AP-1 adaptor complex, and of a complex between Disheveled and the □2 subunit of the AP-2 adaptor complex; sub nanometer structure of a clathrin coat (22MDa) by cryo-EM, yielding a complete molecular model for clathrin at 8 Å resolution; cryo-EM structure of a clathrin coat with bound auxilin and Hsc70. Structure of clathrin coat with bound Hsc70 and auxilin: mechanism of Hsc70-facilitated disassembly. EMBO J (2010)] and subsequent in vitro and in vivo single-molecule total internal reflection fluorescence (TIRF) microscopy studies of uncoating [He, K. et al. Dynamics of phosphoinositide conversion in clathrin-mediated endocytic traffic. Nature (2017)].

2. Live-cell imaging (2004-)
   Building on the biochemical and structural discoveries outlined above, we analyzed mechanisms of coated-vesicle formation in living cells, applying emerging technologies in fluorescence microscopy and live-cell imaging. Our use of spinning disc confocal microscopy led to the following description of molecular events in clathrin-mediated endocytosis: coated pits nucleate at the plasma membrane and grow by steady addition of clathrin triskelions; Hsc70-mediated uncoating follows promptly upon dynamin-induced membrane scission; arrival of auxilin, the clathrin specific, J-domain co-chaperone for Hsc70, determines the timing of this event; clathrin assembly ordinarily provides the principal driving force for membrane invagination, but at high membrane tension or with very elongated cargo, actin polymerization is also required. When our TIRF microscopy technology had reached the level of single-molecule counting, we showed that coated-pit initiation proceeds by coordinated arrival of clathrin and the AP2 adaptor complex, the latter recruited by interaction with PtdIns (3,4)P2, and that accessory proteins are then essential for sustained growth, and that a single rung of a dynamin tube is sufficient for coated pit neck scission. Our most recent findings follow our keen and long-standing interests on studies focusing on mechanisms of cell-cell interactions in the context of Notch-Delta signaling, and of cell host / virus interactions taking advantage of our advance optical imaging capabilities using LLSM.

3. Frontier optical-imaging modalities using LLSM (2015-)
   After initial use at Janelia Research Campus of LLSM to resolve coated-vesicle formation at dorsal and ventral cell surfaces. Asymmetric formation of coated pits on dorsal and ventral surfaces at the leading edges of motile cells and on protrusions of immobile cells. MBoC (2016), we built a second-generation LLSM with guidance from Betzig's team. Our published work with this instrument, in continuous use since July 2014, includes reexamination of clathrin-coat assembly dynamics in 45 cells and ~250,000 AP-2 traces, requiring MATLAB development and 3D cmeAnalysis [Aguet, F. et al. Membrane dynamics of dividing cells imaged by lattice light-sheet microscopy. Mol. Biol. Cell (2016)]; studies of lipid-droplet maturation; studies of ESCRT assembly in yeast. Recruitment dynamics of ESCRT-III and Vps4 to endosomes and implications for reverse membrane budding. With Janet Shaw, we showed that mitochondrial position shapes local energy gradients. We developed phosphoinositide sensors and showed that a cascade of molecular conversions, enabled by separation of a clathrin-coated vesicle from its parent membrane, including accumulation of PtdIns(3)P or PtdIns(4)P and PtdIns(3,4)P2, brings about auxilin arrival and triggers uncoating [He, K. et al. Dynamics of phosphoinositide conversion in clathrin-mediated endocytic traffic. Nature (2017)]. We used LLSM to show that inherited nuclear-pore substructure templates post-mitotic nuclear-pore assembly and FIB-SEM to show that these templating subassemblies (octamers of the outer-ring building blocks) are "stored" in fenestrated mitotic ER.

4. Since August 2016, we have closely collaborated with Eric Betzig to develop AO-LLSM and use it for live visualization of multicellular structures. Our initial studies focused on quantitative tracking of endocytic coated pits and vesicles in muscle and brain cells, visualizing migrating lymphocytes and cancer cells, measuring cell area and volume during division, and tracing axonal growth in various systems, including zebrafish embryos.
   Combined with expansion microscopy, we visualized the Drosophila brain interactome at ~70 nm resolution [Gao, R. et al. Cortical column and whole-brain imaging with molecular contrast and nanoscale resolution. Science (2019)]. With help and advice from Betzig, we built an AO-LLSM system at Janelia, which we then transfer to our lab has been fully functional since April 2021.

   Starting with collaborations with Betzig and Harald Hess, we contributed to nanoscale 3D visualization of endosomes using super-resolution microscopy of high-pressure frozen cells coupled with FIB-SEM [Hoffman, D. P. et al. Correlative three-dimensional super-resolution and block-face electron microscopy of whole vitreously frozen cells. Science 367 (2020)]. Since 2018, we have independently handled in our lab sample preparation using high-pressure freezing and FIB-SEM imaging [Nair et al. Close-up of vesicular ER exit sites by volume electron imaging using FIB-SEM.JCB (2025); Sanyal, A. et al. Neuronal constitutive endolysosomal perforations enable α-synuclein aggregation by internalized PFFs. JCB (2025); Sanyal, A. et al. Tau seeding in neurons enabled by transient endolysosomal perforations are confined within endolysosomes. BioRxiv (2026); Gallusser, B. et al. Deep neural network automated segmentation of cellular structures in volume electron microscopy. JCB (2022)]

5. Deep learning in object recognition (2022-)
   We have built a high-capacity computing infrastructure with GPU and CPU clusters, enabling the development of deep-learning pipelines to automatically analyze 3D images from FIB-SEM Gallusser, B. et al. Deep neural network automated segmentation of cellular structures in volume electron microscopy and fluorescence microscopy SpatialDINO: A Self-Supervised 3D Vision Transformer that enables Segmentation and Tracking in Crowded Cellular Environments. These imaging tools, available to the community, facilitate denoising and automated segmentation of intracellular structures, from ER, Golgi, and mitochondria to clathrin-coated pits, caveolae, and nuclear pores.

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