## BIOGRAPHICAL SKETCH

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NAME: Walz, Thomas

eRA COMMONS USER NAME (credential, e.g., agency login): TWALZ1

POSITION TITLE: Professor and Head of Laboratory

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 |
|---|---|---|---|
| University of Basel, Switzerland | Diploma | 05/1992 | Biochemistry |
| University of Basel, Switzerland | Ph.D. | 01/1996 | Biophysics |
| University of Sheffield, U. K. | Postdoc | 09/1998 | Electron Microscopy |

**NOTE: The Biographical Sketch may not exceed five pages. Follow the formats and instructions below.**

### A. Personal Statement

I am a molecular electron microscopist who uses single-particle cryo-EM to visualize membrane proteins and macromolecular complexes. Currently, we are using this approach to study complexes that play roles in vesicular transport, chromatin remodeling and telomere maintenance. We also continue to study the structural basis that allows membrane proteins to perform their varied functions, taking advantage of the unique possibilities provided by EM. In particular, we are focusing on single-particle cryo-EM of membrane proteins reconstituted into nanodiscs, with the goal to visualize how lipids regulate the conformation, and thus the function, of membrane proteins. As specialists in single-particle cryo-EM (see reviews below), we also engage in collaborations to help colleagues interested in using this approach to answer their biological questions.


1. Cheng, Y. and Walz, T. (2009) The advent of near-atomic resolution in single-particle electron microscopy. *Annu. Rev. Biochem.* 78: 723-742.
2. Cheng, Y., Grigorieff, N., Penczek, P. A., and Walz, T. (2015) A primer to single-particle cryo-electron microscopy. *Cell* 161: 438-449.
3. De Zorzi, R., Mi, W., Liao, M., and Walz T. (2016) Single-particle electron microscopy in the study of membrane protein structure. *Microscopy* 65: 81-96.


### B. Positions, Scientific Appointments and Honors

**Positions**

2016 – 2022 Visiting Scientist, Biogen, Cambridge, MA
2015 – pres. Professor and Head of Laboratory, The Rockefeller University, New York, NY
2015 – 2017 Visiting Professor, Harvard Medical School, Boston, MA
2008 – 2015 Investigator, Howard Hughes Medical Institute, Harvard Medical School, Boston, MA
2007 – 2015 Professor of Cell Biology, Harvard Medical School, Boston, MA
2004 – 2006 Associate Professor of Cell Biology, Harvard Medical School, Boston, MA
1999 – 2004 Assistant Professor of Cell Biology, Harvard Medical School, Boston, MA
1998 – 1999 Independent Research Fellow, Krebs Institute, University of Sheffield, U.K.

**Scientific Appointments**

2004 – 2006 Member of the Membrane Protein Laboratory, University of Texas Medical Branch Galveston, TX

2004 – 2009 Adjunct Position, Department for Neurobiology and Cell Biology, University of Texas Medical Branch Galveston, TX

2003 – 2015 Founding Member of the Center for Molecular and Cellular Dynamics, Harvard University, Cambridge, MA

2003 – 2015 Member of the Harvard Center for Neurodiscovery, Harvard University, Cambridge, MA

2002 – 2015 Director of the Electron Microscopy Core Facility, Harvard Medical School, Boston, MA

2000 – 2015 Member of the Harvard Program in Biophysics, Harvard University, Cambridge, MA

1999 – 2003 Member of the Harvard Center for Structural Biology, Harvard University, Cambridge, MA

**Honors**

2013 Distinguished Visitor Lecture, EMBL, Heidelberg, Germany

2013 Keynote Lecture: The Notch Meeting VII, Athens Greece

2013 Invited Speaker, Symposium on the Occasion of the Inauguration of the new EM facility at University of Zurich, Switzerland

2012&2014 Harvard Medical School Excellence in Tutoring Award from the Academy at Harvard

2012 Plenary Lecture: Annual Meeting of the Israel Society for Microscopy, Ben-Gurion University, Beer Sheva, Israel

2012 Keynote Lecture, Boehringer Ingelheim Fonds International Titisee Conferences “Lipids as Organizers of Cell Membranes”, Titisee, Germany

2011 Invited Speaker, Biozentrum 40-Year Jubilee Symposium, University of Basel, Switzerland

2009 Biozentrum Lecture, University of Basel, Basel, Switzerland

2008 Invited Speaker, Dean’s Scientific Research Symposium, Case Western Reserve University School of Medicine, Cleveland, OH

2007 Invited Speaker, 1st LMB Graduate Symposium “From Molecules to Systems” MRC-LMB, Cambridge, U.K. (organized by the graduate students)

2006 Invited Speaker, Symposium in celebration of the 45th anniversary of Cinvestav “The Biological Chemistry of Macromolecules: Frontiers in Structural Biochemistry”, Mexico City

2004 Award for Outstanding Achievement in Biomedical Sciences (Sponsored by Genzyme)

2003 Invited Speaker, Milestone Symposium “Molecular Architecture and Cellular Function” in celebration of the inauguration of the New Research Building, Harvard Medical School, Boston, MA

1998 – 1999 Award of a David Phillips Research Fellowship from the Biotechnology and Biological Sciences Research Council (BBSRC)

1998 Fellowship Award from the Swiss National Foundation for Scientific Research

1996 – 1998 Fellowship Award from the European Molecular Biology Organization (EMBO)

## C. Contribution to Science

1. I have always been interested in the structure and function of aquaporins (AQPs). I was involved in determining the first AQP structure, AQP1, by electron crystallography. We then determined the structure of the lens-specific water channel AQP0 first at 3 Å resolution, revealing the channel in the closed state, and then at 1.9 Å, the highest resolution structure determined by EM at the time. The structure revealed the water molecules in the channel and the annular lipids surrounding the protein. We also determined a projection structure of mammalian AQP9, an aquaglyceroporin with unusually broad substrate specificity, and I contributed to the structure determination of AQP4, the main water channel expressed in the brain.
   a. Murata, K., Mitsuoka, K., Hirai, T., Walz, T., Agre, P., Heymann, J. B., Engel, A., and Fujiyoshi, Y. (2000) Structural determinants of water permeation through aquaporin-1. *Nature* 407: 599-605.

b. Gonen, T., Sliz, P., Kistler, J., Cheng, Y. and Walz, T. (2004) Aquaporin-0 membrane junctions reveal the structure of a closed water pore. *Nature* 2004 429: 193-197.

c. Gonen, T., Cheng, Y., Sliz, P., Hiroaki, Y., Fujiyoshi, Y., Harrison, S. C. and Walz, T. (2005) Lipid-protein interactions in double-layered two-dimensional AQP0 crystals. *Nature* 438: 569-570.

d. Viadiu, H., Gonen, T. and Walz T. (2007) Projection map of aquaporin-9 at 7 Å resolution. *J. Mol. Biol.* 367: 80-88.

2. Continuing on from our structure of AQP0 in the lipid DMPC, we began a series of studies designed at systematically investigating the factors that govern lipid–protein interactions. We have determined structures of AQP0 in a variety of lipid bilayers and combine these studies with molecular dynamics simulations. This work is aimed to build a foundation to understand how membrane proteins and annular lipids adapt to each other and affect each other. We are currently particularly interested in understanding how cholesterol and sphingolipids organize proteins into membrane microdomains and how phosphatidyl-inositol lipids affect AQP function.

   a. Hite, R. K., Gonen, T., Harrison, S. C. and Walz, T. (2008) Interactions of lipids with aquaporin-0 and other membrane proteins. *Pflugers Arch.* 456: 651-661. PMC2682226

   b. Hite, R. K., Li, Z., and Walz, T. (2010) Principles of membrane protein interactions with annular lipids deduced from aquaporin-0 2D crystals. *EMBO J.* 29: 1652-1658. PMC2876970

   c. Aponte-Santamaría, C., Briones, R., Schenk, A. D., Walz, T. and de Groot, B. L. (2012) Molecular driving forces defining lipid positions around aquaporin-0. *Proc. Natl. Acad. Sci. U. S. A.* 109: 9887-9892. PMC3382485

   d. Hite, R. K., Chiu, P. L., Schuller, J. M. and Walz, T. (2015) Effect of lipid head groups on double-layered two-dimensional crystals formed by aquaporin-0. *PLoS One* 10: e0117371. PMC4311914

3. Recently we have focused on different ways to stabilize membrane proteins in a more native environment. We have explored the use of peptidiscs, which are well suited for studies focused on the membrane proteins themselves, and nanodiscs, which provide a native membrane environment and make it possible to study the effect of specific lipids and membrane characteristics on the membrane proteins.

   a. Mi, W., Li, Y., Yoon, S. H., Ernst, R. K., Walz, T and Liao. M. (2017) Structural basis of MsbA-mediated lipopolysaccharide transport. *Nature* 549: 233-237. PMC5759761.

   b. Gutmann, T., Kim, K. H., Grzybek, M., Walz, T. and Coskun, Ü. (2018) Visualization of ligand-induced transmembrane signaling in the full-length human insulin receptor. *J. Cell Biol.* 217: 1643-1649. PMC5940312

   c. Angiulli, G., Dhupar, H. S., Suzuki, H., Wason, I. S., Duong Van Hoa, F. and Walz, T. (2020) New approach for membrane protein reconstitution into peptidiscs and basis for their adaptability to different proteins. *Elife* 9: e53530. PMC7053995

   d. Zhang, Y., Daday, C., Gu, R.-X., Cox, C. D., Martinac, B., de Groot, B. and Walz, T. (2021) Visualization of the mechanosensitive ion channel MscS under membrane tension. *Nature* 590: 509-514. PMC in progress.

4. We have contributed to our understanding of the structural organization, and the mechanism underlying ligand binding and, if applicable, signal transduction of numerous cell-surface receptors. In particular, we established the conformational rearrangements that underlie outside-in and inside-out signaling of integrins. We also elucidated the structure of receptors in the nervous and the immune systems and numerous cytokine receptors.

   a. Takagi, J., Petre, B. M., Walz, T. and Springer, T. A. (2002) Global conformational rearrangements in integrin extracellular domains in outside-in and inside-out signaling. *Cell* 110: 599-611.

   b. Takagi, J., Strokovich, K., Springer, T. A. and Walz, T. (2003) Structure of integrin $\alpha_5\beta_1$ in complex with fibronectin. *EMBO J.* 22: 4607-4615.

   c. Cheng, Y., Zak, O., Aisen, P., Harrison, S. C. and Walz, T. (2004) Structure of the human transferrin receptor-transferrin complex. *Cell* 116 (4): 565-576.

   d. Skiniotis, G., Boulanger, M. J., Garcia, K. C. and Walz, T. (2005) Signaling conformations of the tall cytokine receptor gp130 when complexed with IL-6 and IL-6 receptor. *Nat. Struct. Mol. Biol.* 12: 545-551.

5. We worked on the structural characterization of vesicular coats, generating a pseudo-atomic model of the clathrin cage. Using electron tomography, we also visualized *in vivo* assembled clathrin-coated vesicles, revealing the clathrin lattice architectures. We expanded our work to multisubunit tethering complexes that are thought to function as crucial organizers of membrane trafficking. We have already determined the subunit organization and Rab GTPase binding sites for several MTCs, providing some understanding of commonalities and differences in different tethering processes. Most recently, we have been working on the structure of the BBSome and how it shuttles cargo GPCRs across the ciliary transition zone.
   a. Fotin, A., Cheng, Y., Sliz, P., Grigorieff, N., Harrison, S. C., Kirchhausen, T. and Walz, T. (2004) Molecular model for a complete clathrin lattice from electron cryomicroscopy. *Nature* 432: 573-579.
   b. Tan, D., Cai, Y., Wang, J., Zhang, J., Menon, S., Chou, H. T., Ferro-Novick, S., Reinisch, K. M. and Walz T. (2013) The EM structure of the TRAPPIII complex leads to the identification of a requirement for COPII vesicles on the macroautophagy pathway. *Proc. Natl. Acad. Sci. U. S. A.* 110: 19432-19437. PMC3845172
   c. Chou, H. T., Apelt, L., Farrell, D. P., White, S. R., Woodsmith, J., Svetlov, V., Goldstein, J. S., Nager, A. R., Li, Z., Muller, J., Dollfus, H., Nudler, E., Stelzl, U., DiMaio, F., Nachury, M. V. and Walz, T. (2019) The molecular architecture of native BBSome obtained by an integrated structural approach. *Structure* 27: 1384-1394. PMC6726506
   d. Yang, S., Bahl, K., Chou, H. T., Woodsmith, J., Stelzl, U., Walz, T. and Nachury, M. V. (2020) Near-atomic structures of the BBSome reveal the basis for BBSome activation and binding to GPCR cargoes. *Elife* 9: e55954. PMC7311171

**Complete List of Published Work in MyBibliography:**
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