Thomas Walz, Ph.D.

PROFESSOR, LABORATORY OF MOLECULAR ELECTRON MICROSCOPY

Walz is interested in processes that involve biological membranes. His recent research has focused on how the membrane environment affects the structure and function of membrane proteins, in particular bacterial mechanosensitive channels and the T-cell receptor. He applies cryo-electron microscopy to image macromolecular complexes and membrane proteins, and complements structural results with functional studies and molecular dynamics simulations.

Biological membranes surround cells and cellular compartments, and have to relay signals and allow cargo transport. They also catalyze reactions and mediate all interactions cells have with their environment and with other cells. These functions are performed by proteins embedded in the membranes, and the exploding number of structures determined for membrane proteins reveal how they can carry out their activities. However, most of this structural work is being conducted on isolated membrane proteins in solution, without the lipid bilayer that is the native environment of a membrane protein. Meanwhile, cellular membranes contain thousands of different lipids. It is increasingly being recognized that this diversity in lipid composition, in addition to the physicochemical characteristics of the membrane, such as hydrophobic thickness, curvature and tension, affect most membrane processes as well as many aspects of the embedded membrane proteins.

Walz is broadly interested in processes related to cellular membranes, and much of his current work focuses on exploring how the lipid environment affects the structure and function of membrane proteins. The lab's approach is to combine single-particle cryo-electron microscopy with nanodisc technology, a biochemical tool that makes it possible to explore the structure and function of membrane proteins in the context of custom-designed lipid bilayers.

Nanodiscs are small patches of lipid bilayer stabilized by a scaffold protein that recreate the native environment of a membrane protein and many of its associated characteristics—something that cannot be achieved by detergents, which are traditionally used to prepare membrane proteins for electron microscopy. The Walz group uses nanodiscs to explore steric constraints the membrane imposes on membrane processes and to understand the effect of the lipid environment on the conformation of the embedded membrane proteins. Additionally, they use nanodiscs to visualize lipid-induced conformational changes in membrane proteins, asking, for example, why a membrane is needed to keep the T-cell receptor in its resting state and how membrane tension opens mechanosensitive channels. Structural studies that exploit the latest advances in cryo-EM are combined with functional studies using patch-clamp electrophysiology and molecular dynamics simulations.

The lab also collaborates with other groups to investigate the structure and function of macromolecular complexes. Most recently, they have been collaborating with the de Lange lab to determine the structure of the CST–Polα/primase complex and to elucidate how it is recruited and regulated at human telomeres.

Walz's earlier work includes the use of electron crystallography to determine the structure of the archetypal water channel, aquaporin-1, and as an approach to study how membrane proteins interact with their annular lipids.

EDUCATION

Diploma in biophysics, 1992
Ph.D. in biophysics, 1996
Biozentrum, University of Basel

POSTDOC

University of Sheffield, 1996–1999

POSITIONS

Assistant Professor, 1999–2004
Associate Professor, 2004–2006
Professor, 2007–2015
Harvard Medical School

Professor, 2015–
The Rockefeller University

Investigator, 2008–2015
Howard Hughes Medical Institute

AWARDS

Genzyme Award for Outstanding Achievement in Biomedical Sciences, 2004

SELECTED PUBLICATIONS

Notti, R.Q. et al. The resting and ligand-bound states of the membrane-embedded human T-cell receptor-CD3 complex. *bioRxiv* (2024).

Cai, S.W. et al. POT1 recruits and regulates CST-Polα/primase at human telomeres. *Cell* 187, 3638–3651 (2024)

Yang, S. et al. Dynamic HIV-1 spike motion creates vulnerability for its membrane-bound tripod to antibody attack. *Nat Commun* 13, 6393 (2022).

Notti, R.Q. et al. Native-like environments afford novel mechanistic insights into membrane proteins. *Trends Biochem. Sci.* 47, 561–569 (2022).

Zhang, Y. et al. Visualization of the mechanosensitive ion channel MscS under membrane tension. *Nature* 590, 509–514 (2021).