Manfred Lindau

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After receiving his doctorate from the Technical University of Berlin in 1983, Lindau was a postdoctoral associate at the Max-Planck-Institute for Biophysical Chemistry in Göttingen and at the Free University of Berlin, where he became an assistant professor in 1988. From 1992 through 1997 he was an associate member of the Max-Planck-Institute for Medical Research and taught biophysics at the University of Heidelberg. He joined the faculty at Cornell in 1997. He is active as a consultant in the areas of biophysics, physiology, and cell biology, and is a member of the Biophysical Society and the Society for Neuroscience.

The mechanisms of exocytosis currently represent one of the most exciting topics in cell biology. The process of regulated exocytosis is responsible for release of neurotransmitters and neuropeptides by nerve terminals and endocrine cells, release of enzymes or cytotoxic proteins by granulocytes, release of histamine and other mediators by mast cells, as well as several other secretory processes. During exocytosis the membrane of secretory vesicles fuses with the plasma membrane of the cell, allowing the secretory vesicles to release their contents through the fusion pore. We combine of functional biophysical measurements with molecular biology techniques to elucidate the mechanism of membrane fusion.

Before fusion, vesicles are first tethered at the target membrane. We performed the first measurements of tethering forces applying optical tweezers to manipulate natural secretory granules.

Fusion of vesicles with the plasma membrane increases the plasma membrane area leading to proportional changes of membrane capacitance. In whole-cell patch clamp experiments using chromaffin cells expressing genetically modified proteins capacitance measurements are performed to investigate the dynamics of exocytosis stimulated by photorelease of caged calcium.

The highest resolution to investigate single vesicle fusion events is obtained in measurements of membrane capacitance using capacitance measurements on small membrane patches of living cells. In addition, release of oxidizable substances from single vesicles can be studied by amperometry using a carbon fiber electrode. With these methods we can record the opening of single fusion pores having molecular dimensions and the dynamics of transmitter release during pore opening.

For high throughput we develop microchip devices that will record single vesicle fusion events from hundreds of cells simultaneously.

To relate membrane fusion to molecular events we develop transparent electrochemical detector devices for simultanaous electrochemical detection of fusion and fluorescence imaging of molecular events.

Current Research Project

- Characterization of the biological membrane fusion mechanism in chromaffin cells by biophysical measurements using mutated constructs of the proteins synaptobrevin and SNAP-25
- Investigation of single fusion pore openings pore in chromaffin cells using capacitance measurements and amperometry
- Investigation of the dynamics of exocytosis in whole cell patch clamp capacitance measurements stimulated by flash photolysis of caged calcium
- Development of microfabricated transparent amperometric detector devices to relate fluorescence imaging of molecular events with electrochemical detection of vesicle fusion
- Development of high-throughput microchip devices for electrochemical screening of drugs affecting transmitter release
- Characterization of docking and fusion between secretory granules and between specific components of the exocytotic machinery using optical tweezers and atomic force microscopy

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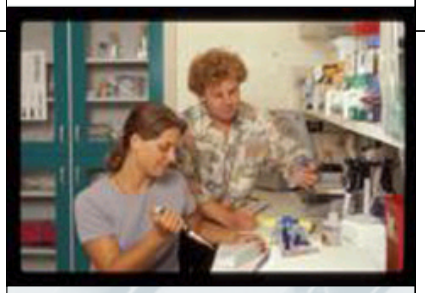
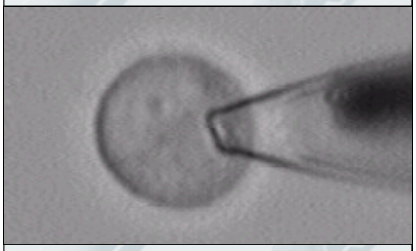


Students in Applied Physics at Cornell University may pursue thesis research in any one of several broad areas, including nanoscience, condensed matter physics, and materials science; optical physics, quantum electronics, and nonlinear optics; biological physics; astrophysics and plasma physics; atomic, molecular, and chemical physics.

Photo by Charles Harrington



Patch pipette entering neuronal cell, example of patch amperometry developed by M. Lindau's research group to study the physical properties of hormonal releasing cells.

Selected Publications

- Fang, Q., K. Berberian, L.W. Gong, I. Hafez, J.B. Sorensen, and M. Lindau. 2008. The role of the C terminus of the SNARE protein SNAP-25 in fusion pore opening and a model for fusion pore mechanics. Proc Natl Acad Sci U S A. 105:15388-92.
- Valero, V., T. Nevian, D. Ho, and M. Lindau. 2008. Tethering forces of secretory granules measured with optical tweezers. Biophys J. 95:4972-8.
- Gong, L.W., G.A. de Toledo, and M. Lindau. 2007. Exocytotic catecholamine release is not associated with cation flux through channels in the vesicle membrane but Na+ influx through the fusion pore. Nat Cell Biol. 9:915-22.
- Hafez, I., K. Kisler, K. Berberian, G. Dernick, V. Valero, M.G. Yong, H.G. Craighead, and M. Lindau. 2005. Electrochemical imaging of fusion pore openings by electrochemical detector arrays. Proc Natl Acad Sci U S A. 102:13879-84.
- Dernick, G., L.W. Gong, L. Tabares, G.A. de Toledo, and M. Lindau. 2005. Patch amperometry: high-resolution measurements of single-vesicle fusion and release. Nat Methods. 2:699-708.
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- Lindau, M., and J.M. Fernandez. 1986. IgE-mediated degranulation of mast cells does not require opening of ion channels. Nature. 319:150-3.

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