

Curriculum Vitae

Name: Holger Wille
Position: Assistant Adjunct Professor
 Department of Neurology and
 Institute for Neurodegenerative Diseases
 School of Medicine
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Education:

1983 - 1988	Universität Hamburg, Germany	Diplom Biologe (equiv. to MS)
1988 - 1992	Universität Hamburg, Germany	Dr. rer. nat. (Ph.D.)

Employment:

1985 - 1987	Biologische Anstalt Helgoland (Marine Biology Institute of Heligoland), Hamburg, Germany Research Assistant
1987 - 1988	Max-Planck Unit for Structural Molecular Biology, Hamburg, Germany Diploma Student
1988 - 1992	Max-Planck Unit for Structural Molecular Biology, Hamburg, Germany PhD Student
1992 - 1993	Max-Planck Unit for Structural Molecular Biology, Hamburg, Germany Postdoctoral Fellow
1993 - 1996	University of California, San Francisco, Department of Neurology, School of Medicine Postdoctoral Fellow
1996 - present	University of California, San Francisco, Department of Neurology, School of Medicine Assistant Adjunct Professor

Honors and Awards:

1987 - 1988	Basic fellowship of the German National Merit Foundation (Studienstiftung des deutschen Volkes).
1988 - 1990	Ph.D. fellowship of the German National Merit Foundation
1993 - 1994	Postdoctoral fellowship of the Boehringer Ingelheim Fonds, Germany
1994 - 1996	Feodor-Lynen Fellow of the Alexander von Humboldt-Stiftung, Germany

Keywords / Areas of Interest:

Neurodegenerative diseases, prion diseases, Alzheimer's disease, protein folding diseases, amyloid structure, electron microscopy, electron crystallography, image processing, atomic force microscopy, X-ray crystallography, fiber diffraction, polyoxometalates, nanoparticles.

Professional Activities:**Membership in Professional Organizations:**

- 1989 - present Gesellschaft für Biochemie und Molekularbiologie, Germany (German Society for Biochemistry and Molecular Biology)
- 1995 - 2002 Alexander von Humboldt Association of America
- 1996 - present American Society for Cell Biology
- 2002 - present Biophysical Society

Service to Professional Publications:

- 1999 - present *Ad hoc* referee for: Biochimica Biophysica Acta – Proteins and Proteomics, Biophysical Journal, FASEB Journal, Journal of Biological Chemistry, Journal of Molecular Biology, Journal of Structural Biology, Neurobiology of Aging, Proceedings of the National Academy of Sciences U.S.A., Protein Science.

Invited Presentations (talks and seminars):**International:**

- 1993, April European Research Conference “Biophysics of the Cytoskeleton”, Giens, France “Structure and self-assembly of microtubule-associated proteins”.
- 1993, May Maurice E. Müller Institute for High Resolution Electron Microscopy, Biocenter Basel, Switzerland “Electron microscopy of microtubule-associated protein 2c (MAP2c) and tau”.
- 1996, September Fall Meeting of the German Society for Biochemistry and Molecular Biology, Leipzig, Germany “Prion proteins: Structure and Infectivity”.
- 1996, September Max-Planck Unit for Structural Molecular Biology, Hamburg, Germany “Structure and infectivity of prions”.
- 1998, June Institute for Cell Biology and Clinical Neurobiology at the University Hospital Eppendorf, University of Hamburg, Germany “Ultrastructure and infectivity of the scrapie prion protein”.
- 1998, June Max von Pettenkofer-Institute and Genecenter, Ludwig-Maximilians-University Munich, Germany “Ultrastructure and infectivity of the scrapie prion protein”.
- 1999, April The Netherlands Cancer Institute, Amsterdam, The Netherlands “Ultrastructural studies on the scrapie prion protein”.
- 2000, September Max-Planck Unit for Structural Molecular Biology, Hamburg, Germany “What can electron crystallography tell us about the structure of the scrapie prion protein? First insights from projection maps and difference maps”.
- 2002, September The Netherlands Cancer Institute, Amsterdam, The Netherlands “Electron crystallographic analyses on two-dimensional crystals of the scrapie prion protein constrain structural models”.
- 2002, September Institute für Physikalische Biologie, Heinrich Heine Universität, Düsseldorf, Germany “Electron crystallographic analyses on two-dimensional crystals of the scrapie prion protein constrain structural models”.
- 2003, March 30th NIPS International Symposium on Frontiers of Biological Electron Microscopy - Proteins to Supramolecules, Okazaki, Japan “Electron crystallographic analyses on two-dimensional crystals of the scrapie prion protein”.
- 2004, May First International Conference of the European Network of Excellence NeuroPrion; Prion 2004 in Paris, France “A left-handed, parallel beta-helical architecture as a model for the structure of the scrapie prion protein”.
- 2005, July First International ICAM Workshop: Physical, Molecular, and Biological Approaches to Understanding the Role of Protein Aggregation in Neurodegenerative and Systemic Diseases, Lausanne, Switzerland “Electron crystallography of the scrapie prion protein”

- 2005, October International Conference of the European Network of Excellence NeuroPrion; Prion 2005 in Düsseldorf, Germany "Probing the structure of PrP^{Sc} via heavy metal complexes and electron crystallography"
- 2007, February Protein Structure Dynamics Working Group – Satellite meeting at the PrP Canada 2007 Conference, Calgary, Alberta, Canada; Keynote lecture: "Solving the structure of PrP^{Sc} – problems and solutions"

National:

- 2002, February 46th Annual Meeting of the Biophysical Society, San Francisco, California "Structural studies of the scrapie prion protein by electron crystallography".
- 2002, September National Academy of Science, Institute of Medicine Committee on Transmissible Spongiform Encephalopathies: Assessment of Relevant Science, Meeting II, Washington, DC "Electron crystallographic analyses on two-dimensional crystals of the scrapie prion protein".

Regional and Other Invited Presentations:

- 1993, January Center for Molecular Neurobiology, University of Hamburg, Hamburg, Germany "Electron microscopy of microtubule-associated protein 2c (MAP2c) and tau".
- 1998, March 15th Anniversary Meeting of the Boehringer Ingelheim Fonds, Woods Hole, Massachusetts "Ultrastructure and infectivity of the scrapie prion protein".
- 2000, September 3rd North American Meeting of the Boehringer Ingelheim Fonds, Woods Hole, Massachusetts "What can electron crystallography tell us about the structure of the scrapie prion protein? First insights from projection maps and difference maps".
- 2001, April Infectious Agents and Particles Symposium, Texas Woman's University, Denton, Texas "Structure and infectivity of the scrapie prion protein".
- 2002, March Division of Biological Sciences, University of California at Davis, Davis, California "Structure and infectivity of the scrapie prion protein".
- 2002, June FASEB Summer Research Conference on "Amyloid & Other Abnormal Protein Folding Processes", Snowmass Village, Colorado "Electron crystallographic analyses on two-dimensional crystals of the scrapie prion protein constrain structural models".
- 2002, August 2nd International Yeast Prion Symposium, Calistoga, California, "Electron crystallographic analyses on two-dimensional crystals of the scrapie prion protein".
- 2002, September 4th North American Meeting of the Boehringer Ingelheim Fonds, Woods Hole, Massachusetts "Structural studies of the scrapie prion protein by electron crystallography".
- 2004, February Institute for Complex Adaptive Matters, Workshop on Protein Misaggregation: From Biomolecules to Neurodegeneration. Boston, Massachusetts "Structural studies of PrP^{Sc} by electron crystallography".
- 2006, August FiberNet Fiber Diffraction Workshop, Fall Creek Falls, Tennessee "Studying the structure of infectious prions by fiber diffraction"

Government and Other Professional Service:

- 2003 External tenure-track reviewer, National Institutes of Health (1 review)
- 2005 – present Member of the Alberta Prion Research Institute – College of International Review (4 rounds of reviews)
- 2007 – present Member of the Reuters Insight Community of Experts
- 2007 – present Member of the Scientific Committee for the Prion2008 Congress to be held in Madrid, Spain.

University and Public Service:**University Service:**

- 2003 External dissertation reviewer: Heinrich Heine-Universität Düsseldorf, Germany:
Dissertation of Karl-Werner Leffers
- 2005 – present Reviewer for the UC Discovery Biotechnology Grant Review Board (5 review sessions)
- 2008 Chairman of a UC Discovery Biotechnology Grant Review session (Spring 2008)

Public Service:

- 1996 – 2000 Sea Kayaking Instructor with Outdoors Unlimited at Millberry Union, University of California, San Francisco
- 2001 – 2004 Volunteer at the Cheryl Anderson Sorensen Childcare Center, VA Medical Center, San Francisco
- 2003 – 2004 Member and Acting Treasurer, Board of Directors, Cheryl Anderson Sorensen Childcare Center, VA Medical Center, San Francisco
- 2004 – present Assistant Manager for the Video Library, German School of San Francisco
- 2005 – present Assistant Instructor (Black Belt level) at the UCSF, Millberry Union Tae Kwon Do Club
- 2006 – present Member, Board of Directors, German School of San Francisco
- 2008 Science Fair judge, St. Anne's Junior High School, San Francisco

Teaching and Mentoring:**Predoctoral Students supervised:**

<u>Dates</u>	<u>Name</u>	<u>Position</u>	<u>Function</u>	<u>Current position</u>
2000 - 2002	Karl-Werner Leffers	Visiting grad. student	Research supervision	Schwarz Pharma
2002	David Mobley	Rotation student	Supervised lab work	Postdoc, UCSF
2003	Mary Jane Budny	Rotation student	Supervised lab work	Grad. Student, UCSF
2006	Jan Stöhr	Visiting grad. student	Research supervision	
2007 - present	Jay Choi	Grad. student	Mentoring	

(PhD advisor: Fred E. Cohen, Dept. of Cell. and Mol. Pharmacology)

Postdoctoral Fellows supervised:

<u>Dates</u>	<u>Name</u>	<u>Position</u>	<u>Function</u>	<u>Current position</u>
1996 - 2000	Martin Schlumpberger	Postdoctoral fellow	Research supervision	Qiagen
2006 - present	David W. Colby	Postdoctoral fellow	Research supervision	
2007 - present	Silvia C. R. Catharino	Postdoctoral fellow	Research supervision	
	Julian Ollesch	Postdoctoral fellow	Research supervision	
	Maheswaran Shanmugam	Postdoctoral fellow	Research supervision (co-supervision with Jeffrey R. Long from UC Berkeley)	
2008 - present	Jan Stöhr	Postdoctoral fellow	Research supervision	

Informal Teaching:

- 1985 - 1987 Teaching assistant at the Institute of General Botany (Institut für Allgemeine Botanik), Hamburg University, Germany
- 1988 - 1993 Taught students, visiting scientists, and coworkers at the Max-Planck Unit for Structural Molecular Biology how to operate the Philips CM12 electron microscope. Advised on methods of sample preparation, especially negative staining, glycerol spray, and quick freeze deep etch techniques.

- 1993 – present Teach research assistants and coworkers at the University of California, San Francisco, how to prepare samples for electron microscopy. Demonstrate and teach the use of the Jeol JEM 100CX II and Philips Tecnai F20 electron microscopes and how to interpret electron micrographs. Supervise and train co-workers in various other spectroscopical, biophysical, and biochemical methods of analysis.
- 1996 – 2000 Taught basic sea kayaking skills and risk avoidance in formal classes and excursions with Outdoors Unlimited at Millberry Union, University of California, San Francisco.
- 2002 LECTURED UCSF Dep. of Neurological Surgery residents on general biology of prion diseases.
- 2005 – present Assistant Instructor (Black Belt level) at the University of California, San Francisco, Millberry Union - Tae Kwon Do Club

Summary of Teaching Hours:

- 2006 – 2007 500 hours of teaching (including preparation)
 Formal class or course teaching hours: 0
 Informal teaching hours: 400 hours
 Mentoring: 100 hours
- 2007 – 2008 500 hours of teaching (including preparation)
 Formal class or course teaching hours: 0
 Informal teaching hours: 300 hours
 Mentoring: 200 hours
- 2008 – 2009 Total anticipated hours of teaching: 500 hours (as above)

Teaching Narrative:

In the laboratory, I am mentoring and advising younger researchers and research associates in various biophysical and biochemical techniques including electron microscopy, sample preparation for electron microscopy, use of electron microscopes and spectroscopic equipment, and interpretation of electron micrographs. In particular, I am currently supervising and mentoring four postdoctoral fellows and one graduate student all of which are working on structure related projects. Additionally, I am scheduling and overseeing the laboratory meetings, journal clubs, and ethics meetings of the Prusiner laboratory. Furthermore, I am participating and giving presentations at the above mentioned laboratory meetings, journal clubs, and ethics meetings as well as other scientific retreats and review meetings (e.g. Asilomar, Fairchild review meetings etc.). On occasion, I have lectured UCSF medical residents on general biology of prion diseases.

Research and Creative Activities:

Research Awards and Grants:

Current:

Title: Degenerative and dementing diseases of aging 01/01/04-12/31/08
 Agency: NIH NIA PO1 AG02132 (Prusiner)
 Project 1, Title: Toward a structure of PrP^{Sc}
 Role: Co-Principal Investigator

Title: Molecular pathogenesis of age-dependent CNS degeneration 04/01/05-03/31/10
 Agency: NIH NIA PO1 AG10770 (Prusiner)
 Project 3, Title: Structural analysis of synthetic prions
 Role: Co-Principal Investigator

Pending:

Title: Degenerative and dementing diseases of aging 01/01/09-12/31/13
 Agency: NIH NIA PO1 AG02132 (Prusiner)
 Project 1, Title: Interaction of polyoxometalates with prions
 Role: Co-Principal Investigator

Title: Degenerative and dementing diseases of aging 01/01/09-12/31/13
 Agency: NIH NIA PO1 AG02132 (Prusiner)
 Project 2, Title: Structural analysis of prions and related amyloidogenic peptides
 Role: Investigator

Peer Reviewed Publications:

- 1) Siebers, D., Lucu, C., Winkler, A., Dalla Venezia, L., and **Wille, H.** (1986). Active uptake of sodium in the gills of the hyperregulating shore crab *Carcinus maenas*. *Helgoländer Meeresuntersuchungen* 40, 151-160.
- 2) Siebers, D., Lucu, C., Winkler, A., Grammerstorf, U., and **Wille, H.** (1987). Effects of amiloride on sodium chloride transport across isolated perfused gills of shore crabs *Carcinus maenas* acclimated to brackish water. *Comparative Biochemistry and Physiology* 87A, 333-340.
- 3) Hagestedt, T., Lichtenberg, B., **Wille, H.**, Mandelkow, E.-M., and Mandelkow, E. (1989). Tau protein becomes long and stiff upon phosphorylation: Correlation between paracrystalline structure and degree of phosphorylation. *Journal of Cell Biology* 109, 1643-1651.
- 4) Siebers, D., **Wille, H.**, Lucu, C., and Dalla Venezia, L. (1989). Conductive sodium entry in gill cells of the shore crab, *Carcinus maenas*. *Marine Biology* 101, 61-68.
- 5) Nörenberg, U., **Wille, H.**, Wolff, J.M., Frank, R., and Rathjen, F.G. (1992). The chicken neural extracellular matrix molecule restrictin: Similarity with EGF-, fibronectin type III- and fibrinogen-like motifs. *Neuron* 8, 849-863.
- 6) **Wille, H.**, Drewes, G., Biernat, J., Mandelkow, E.-M., and Mandelkow, E. (1992a). Alzheimer-like paired helical filaments and antiparallel dimers formed from microtubule-associated protein tau in vitro. *Journal of Cell Biology* 118, 573-584.
- 7) **Wille, H.**, Mandelkow, E.-M., and Mandelkow, E. (1992b). The juvenile microtubule-associated protein MAP2c is a rod-like molecule that forms antiparallel dimers. *Journal of Biological Chemistry* 267, 10737-10742.
- 8) **Wille, H.**, Mandelkow, E.-M., Dingus, J., Vallee, R.B., Binder, L.I., and Mandelkow, E. (1992c). Domain structure and antiparallel dimers of microtubule-associated protein 2 (MAP2). *Journal of Structural Biology* 108, 49-61.
- 9) Berling, B., **Wille, H.**, Röhl, B., Mandelkow, E.-M., Garner, C., and Mandelkow, E. (1994). Phosphorylation of microtubule-associated proteins MAP2a,b and MAP2c at Ser 136 by proline-directed kinases *in vivo* and *in vitro*. *European Journal of Cell Biology* 64, 120-130.
- 10) Kaneko, K., Peretz, D., Pan, K.-M., Blochberger, T.C., **Wille, H.**, Gabizon, R., Griffith, O.H., Cohen, F.E., Baldwin, M.A., and Prusiner, S.B. (1995). Prion protein (PrP) synthetic peptides induce cellular PrP to acquire properties of the scrapie isoform. *Proceedings of the National Academy of Sciences U.S.A.* 92, 11160-11164.
- 11) Riesner, D., Kellings, K., Post, K., **Wille, H.**, Serban, H., Groth, D., Baldwin, M.A., and Prusiner, S.B. (1996). Disruption of prion rods generates 10-nm spherical particles having high α -helical content and lacking infectivity. *Journal of Virology* 70, 1714-1722.
- 12) Vey, M., Pilkuhn S., **Wille, H.**, Nixon, R., DeArmond, S.J., Smart, E.J., Anderson, R.G.W., Taraboulos, A., and Prusiner, S.B. (1996). Subcellular colocalization of the cellular and scrapie prion proteins in caveolae-like membranous domains. *Proceedings of the National Academy of Sciences U.S.A.* 93, 14945-14949.
- 13) **Wille, H.**, Zhang, G.-F., Baldwin, M.A., Cohen, F.E., and Prusiner, S.B. (1996). Separation of scrapie prion infectivity from PrP amyloid polymers. *Journal of Molecular Biology* 259, 608-621.

- 14) Kaneko, K., **Wille, H.**, Mehlhorn, I., Zhang, H., Ball, H., Cohen, F.E., Baldwin, M.A., and Prusiner, S.B. (1997). Complexes of the prion protein and synthetic peptides implicate multiple intermediates in the formation of the scrapie isoform. *Journal of Molecular Biology* 270, 574-586.
- 15) Post, K., Pitschke, M., Schäfer, O., **Wille, H.**, Appel, T. R., Kirsch, D., Mehlhorn, I., Serban, H., Prusiner, S. B., and Riesner, D. (1998). Rapid acquisition of β -sheet structure in the prion protein prior to multimer formation. *Biological Chemistry* 379, 1307-1317.
- 16) Safar, J., **Wille, H.**, Itri, V., Groth, D., Serban, H., Torchia, M., Cohen, F. E., and Prusiner, S. B. (1998). Eight prion strains have PrP^{Sc} molecules with different conformations. *Nature Medicine* 4, 1157-1165.
- 17) Supattapone, S., Bosque, P., Muramoto, T., **Wille, H.**, Aagaard, C., Peretz, D., Nguyen, H.-O. B., Heinrich, C., Torchia, M., Safar, J., Cohen, F. E., DeArmond, S. J., Prusiner, S. B., and Scott, M. (1999). Prion protein of 106 residues creates an artificial transmission barrier for prion replication in transgenic mice. *Cell* 96, 869-878.
- 18) **Wille, H.**, and Prusiner, S. B. (1999). Ultrastructural studies on scrapie prion protein crystals obtained from reverse micellar solutions. *Biophysical Journal* 76, 1048-1062.
- 19) Baskakov, I. V., Aagaard, C., Mehlhorn, I., **Wille, H.**, Groth, D., Baldwin, M. A., Prusiner, S. B., and Cohen, F. E. (2000). Self-assembly of recombinant prion protein of 106 residues. *Biochemistry* 39, 2792-2804.
- 20) Kaneko, K., Ball, H. L., **Wille, H.**, Zhang, H., Groth, D., Torchia, M., Tremblay, P., Safar, J., Prusiner, S. B., DeArmond, S. J., Baldwin, M. A., and Cohen, F. E. (2000). A synthetic peptide initiates Gerstmann-Sträussler-Scheinker (GSS) disease in transgenic mice. *Journal of Molecular Biology* 295, 997-1007.
- 21) Schlumpberger, M., **Wille, H.**, Baldwin, M. A., Butler, D. A., Herskowitz, I., and Prusiner, S. B. (2000). The prion domain of yeast Ure2p induces autocatalytic formation of amyloid fibers by a recombinant fusion protein. *Protein Science* 9, 310-321.
- 22) **Wille, H.**, Prusiner, S. B., and Cohen, F. E. (2000). Scrapie infectivity is independent of amyloid staining properties of the N-terminally truncated prion protein. *Journal of Structural Biology*, 130, 323-338.
- 23) Laws, D. D., Bitter, H.-M. L., Liu, K., Ball, H. L., Kaneko, K., **Wille, H.**, Cohen, F. E., Prusiner, S. B., Pines, A., and Wemmer, D. E. (2001). Solid-state NMR studies of the secondary structure of a mutant prion protein fragment of 55 residues that induces neurodegeneration. *Proceedings of the National Academy of Sciences U.S.A.* 98, 11686-11690.
- 24) Lim, S.-N., Bonzelius, F., Low, S. H., **Wille, H.**, Weimbs, T., and Herman, G. A. (2001). Identification of discrete classes of endosome-derived small vesicles as a major cellular pool for recycling membrane proteins. *Molecular Biology of the Cell* 12, 981-995.
- 25) Supattapone, S., Bouzamondo, E., Ball, H., **Wille, H.**, Nguyen, H.-O. B., Cohen, F. E., DeArmond, S. J., Prusiner, S. B., and Scott, M. (2001a). A protease-resistant 61-residue prion peptide causes neurodegeneration in transgenic mice. *Molecular and Cellular Biology* 21, 2213-2221.
- 26) Supattapone, S., **Wille, H.**, Uyechi, L., Safar, J., Tremblay, P., Szoka, F. C., Cohen, F. E., Prusiner, S. B., and Scott, M. R. (2001b). Branched polyamines cure prion-infected neuroblastoma cells. *Journal of Virology* 75, 3453-3461.
- 27) **Wille, H.**, Michelitsch, M. D., Guénebaut, V., Supattapone, S., Serban, A., Cohen, F. E., Agard, D. A., and Prusiner, S. B. (2002). Structural studies of the scrapie prion protein by electron crystallography. *Proceedings of the National Academy of Sciences U.S.A.* 99, 3563-3568.
- 28) Mironov, A. Jr., Latawiec, D., **Wille, H.**, Bouzamondo-Bernstein, E., Legname, G., Williamson, R. A., Burton, D., DeArmond, S. J., Prusiner, S. B., and Peters, P. J. (2003). Cytosolic prion protein in neurons. *Journal of Neuroscience* 23, 7183-7193.
- 29) Govaerts, C., **Wille, H.**, Prusiner, S. B., and Cohen, F. E. (2004). Evidence of assembly of prions with left-handed β -helices into trimers. *Proceedings of the National Academy of Sciences U.S.A.* 101, 8342-8347.
- 30) Leffers, K.-W., **Wille, H.**, Stöhr, J., Junger, E., Prusiner, S. B., and Riesner, D. (2005). Assembly of natural and recombinant prion protein into fibrils. *Biological Chemistry*, 386, 569-580.

- 31) Malo, J., Mitchell, J. C., Vénien-Bryan, C., Harris, J. R., **Wille, H.**, Johnson, L. N., Sheratt, D. J., and Turberfield, A. J. (2005). Engineering a 2D protein-DNA crystal. *Angewandte Chemie, International Edition*, 44, 3057-3061.
- 32) Safar, J. G., **Wille, H.**, Geschwind, M. D., Deering, C., Latawiec, D., Serban, A., King, D. J., Legname, G., Weisgraber, K. H., Mahley, R. W., Miller, B. L., DeArmond, S. J., and Prusiner, S. B. (2006). Human prions and plasma lipoproteins. *Proceedings of the National Academy of Sciences U.S.A.*, 103, 11312-11317.
- 33) Müller, H., Stitz, L., **Wille, H.**, Prusiner, S. B., and Riesner, D. (2007). Influence of water, fat, and glycerol on the mechanism of thermal prion inactivation. *Journal of Biological Chemistry*, 282, 35855-35867.
- 34) **Wille, H.**, Govaerts, C., Borovinskiy, A. L., Latawiec, D., Downing, K. H., Cohen, F. E., and Prusiner, S. B. (2007). Electron crystallography of the scrapie prion protein complexed with heavy metals. *Archives of Biochemistry and Biophysics*, 467, 239-248.
- 35) Feng, B. Y., Toyama, B. H., **Wille, H.**, Colby, D. W., Collins, S. R., May, B. C. H., Prusiner, S. B., Weissman, J., and Shoichet, B. K. (2008). Small-molecule aggregates inhibit amyloid polymerization. *Nature Chemical Biology*, 4, 197-199.
- 36) Stöhr, J., Weinmann, N., **Wille H.**, Kaimann T., Nagel-Steger L., Birkmann, E., Panza, G., Prusiner S. B., Eigen, M. & Riesner D. (2008). Mechanisms of prion protein assembly into amyloid. *Proceedings of the National Academy of Sciences U.S.A.*, 105, 2409-2414.
- 37) Godsave, S., **Wille, H.**, Kujala, P., Latawiec, D., DeArmond, S. J., Serban, A., Prusiner, S. B., and Peters, P. J. (2008). Cryo-immunogold EM for prions: Towards identification of a conversion site. *Journal of Neuroscience*, in revision.
- 38) Tamgüney, G., Giles, K., Glidden, D.V., Lessard, P., **Wille, H.**, Tremblay, P., Groth, D.F., Yehiely, F., Korth, C., Moore, R., Tatzelt, J., Rubenstein, E., Boucheix, C., Yang, X., Stanley, P., Lisanti, M.P., Dwek, R.A., Rudd, P.M., Moskovitz, J., Epstein, C.J., Dawson Cruz, T.C., Kuziel, W.A., Maeda, N., Sap, J., Ashe, K.H., Carlson, G.A., Tesseur, I., Wyss-Coray, T., Mucke, L., Weisgraber, K.H., Mahley, R.W., Cohen, F.E., and Prusiner, S.B. (2008). Genes contributing to prion pathogenesis. *Journal of General Virology*, submitted.
- 39) **Wille, H.**, Shanmugam, M., Murugesu, M., Ollesch, J., Stubbs, G., Long, J. R., Prusiner, S. B., and Safar, J. G. (2008). Increasing polyoxometalate charge density favors 2D crystallization of the scrapie prion protein. *Proceedings of the National Academy of Sciences U.S.A.*, in revision.

Non-Peer Reviewed Publications (Reviews, Book Chapters, and Symposium Papers):

- 1) Heins, S., Song, Y.-H., **Wille, H.**, Mandelkow, E., and Mandelkow, E.-M. (1991). Effect of MAP2, MAP2c, and tau on kinesin-dependent microtubule motility. *Journal of Cell Science* S14, 121-124.
- 2) Mandelkow, E.-M., Biernat, J., Drewes, G., Steiner, B., Lichtenberg-Kraag, B., **Wille, H.**, Gustke, N., and Mandelkow, E. (1993a). Microtubule-associated protein tau, paired helical filaments, and phosphorylation. *Annals New York Academy of Sciences* 695, 209-216.
- 3) Mandelkow, E.-M., Lichtenberg-Kraag, B., Biernat, J., Steiner, B., Drewes, G., **Wille, H.**, Gustke, N., and Mandelkow, E. (1993b). The Alzheimer's-like phosphorylation of microtubule-associated protein tau: Phosphorylation sites, structure, and role of MAP kinase. In: *Alzheimer's Disease: Advances in Clinical and Basic Research*. (Eds.: Corain, B., Iqbal, K., Nicolini, M., Winblad, B., Wisniewski, H., and Zatta, P.) pp 355-365, John Wiley & Sons Ltd, New York.
- 4) Mandelkow, E.-M., Biernat, J., Lichtenberg-Kraag, B., Drewes, G., **Wille, H.**, Gustke, N., Baumann, K., and Mandelkow, E. (1995a). Phosphorylation of tau and relationship with Alzheimer paired helical filaments. In: *Alzheimer's Disease: Lessons from Cell Biology*. (Eds.: Kosik, K., Christen, Y., and Selkoe, D.) pp 103-120, Springer Verlag, Heidelberg.
- 5) Mandelkow, E., Biernat, J., Lichtenberg-Kraag, B., Drewes, G., **Wille, H.**, Gustke, N., Baumann, K., and Mandelkow, E.-M. (1995b). Microtubules, tau protein, and paired helical filaments in Alzheimer's disease.

In: The Cytoskeleton. (Eds.: Jokusch, B., Mandelkow, E., and Weber, K.) pp 143-160, Springer Verlag, Heidelberg.

- 6) **Wille, H.** (1995). Zur Struktur und Aggregation des infektiösen Prionen-Proteins. B.I.F. Futura 10, 204-205.
- 7) Bamorough, P., **Wille, H.**, Telling, G. C., Yehiely, F., Prusiner, S. B., and Cohen, F. E. (1996). Prion protein structure and scrapie replication: Theoretical, spectroscopic, and genetic investigations. Cold Spring Harbor Symposium on Quantitative Biology 61, 495-509.
- 8) Riesner, D., Kellings, K., Post, K., Pitschke, M., **Wille, H.**, Serban, H., Groth, D., Baldwin, M. A., and Prusiner, S. B. (1996). Conformational transitions of solubilized prion protein PrP 27-30. In: Transmissible Subacute Spongiform Encephalopathies: Prion Diseases. (Eds.: Court, L. and Dodet, B.) pp 299-313, Elsevier, Paris.
- 9) **Wille, H.**, Baldwin, M. A., Cohen, F. E., DeArmond, S. J., and Prusiner, S. B. (1996). Prion protein amyloid: Separation of scrapie infectivity from PrP polymers. In: The nature and origin of amyloid fibrils. (Ciba Foundation Symposium 199) pp 181-201, Wiley, Chichester.
- 10) Riesner, D., Kellings, K., Post, K., Pitschke, M., **Wille, H.**, Serban, H., Groth, D., Baldwin, M. A., and Prusiner, S. B. (1998). Biophysical studies on structure, structural transitions, and infectivity of the prion protein. In: Prions and Brain Diseases in Animals and Humans (Ed.: Morrison, D. R. O.), Nato ASI Series A: Life Sciences Vol. 295, pp 225-243, Plenum Press, New York.
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Current Research Program:

The general focus of my work is the structure of amyloids and other disease-related, misfolded proteins. In particular, I am interested in the infectious prion protein and the structure-function relationship underlying its infectious nature. The scope of experimental approaches is centered on electron microscopy supplemented by various biochemical and biophysical methods. Many of these experiments are carried out as interdisciplinary collaborations and I am responsible for the coordination of these experiments within the larger framework of the Institute for Neurodegenerative Diseases.

The highly aggregated nature of the infectious prion protein (PrP^{Sc}) has impeded all attempts to elucidate the structure of this medically important protein by X-ray crystallography and NMR spectroscopy. Several years ago, I discovered two-dimensional (2D) crystals of a truncated form of PrP^{Sc} (PrP 27-30) which allowed the first detailed insights into the structure of the infectious prion. Digitized electron micrographs of the 2D crystals were averaged and subjected to statistical analysis. The processed images revealed enhanced details on the molecular architecture of PrP 27-30. These data, in conjunction with other biochemical, biophysical, and immunological data, were used to constrain models for the structure of PrP^{Sc}. The models were generated by collaborators from the Cohen laboratory (UCSF) (Wille et al., 2002; Govaerts et al., 2004).

The 2D crystals opened the possibility to solve the structure of the infectious prion to near-atomic resolution by electron crystallography. For this purpose, we upgraded the Prusiner laboratory with a state-of-the-art FEI Tecnai F20 electron microscope. This instrument enabled us to obtain higher resolution images from the 2D crystals. We have just published a detailed analysis of the 2D crystals complexed with heavy metals, but the resolution was limited by the relatively low quality of the lattices (Wille et al., 2007). Therefore, I have completed a study on the 2D crystallization process with the aim to increase the size, yield and order of the 2D crystals. Significant progress was made by switching to a purification method that relies on the specific precipitation of PrP 27-30 by sodium phosphotungstate (PTA). PTA and related polyoxometalates (POMs) are inorganic clusters with a propensity to bind PrP^{Sc} and PrP 27-30. The PTA-derived preparations showed a substantial improvement in the overall 2D crystal quality. In addition, I could demonstrate that the yield of the 2D crystals depended on the charge density of the POM (Wille et al., 2008, submitted). The different POMs were obtained through collaboration with the Long laboratory (UC Berkeley). Based on these improvements, I am preparing to analyze the 2D crystals via cryo low-dose electron crystallography in the near future.

An alternative method to study the structure of PrP 27-30 and PrP^{Sc} relies on the fibrillar nature of the aggregated proteins. PrP 27-30 has long been known to form amyloid fibrils, but so far PrP^{Sc} failed to produce such ordered polymers. Within the framework of this study, I discovered that under the right conditions PrP^{Sc} can indeed form amyloid fibers. Partially oriented fibers of both PrP 27-30 and PrP^{Sc} can be analyzed by X-ray fiber diffraction. In a collaborative effort with the Stubbs laboratory (Vanderbilt University) I have prepared dried-fiber samples of PrP 27-30 and PrP^{Sc}. These samples were exposed to synchrotron radiation at the Advanced Light Source (ALS) in Berkeley, CA and the Stanford Synchrotron Radiation Laboratory (SSRL) in Stanford, CA. We are currently analyzing the data sets, but it is apparent that the new data are far superior to all previously published fiber diffraction results on prions. Ultimately, we want to use these data to validate, improve, or refute molecular models for the structure of PrP^{Sc}.

My most recent project is based on the observation that certain POMs fail to precipitate PrP 27-30. To the contrary, these POMs seem to solubilize PrP 27-30. I am currently investigating if these conditions produce homogeneous populations of PrP 27-30 monomers or oligomers and if these particles retain their infectivity. If both of these criteria are fulfilled, then it would become feasible to attempt a 3D crystallization of solubilized PrP 27-30. Such crystals would give us the opportunity to determine the structure of PrP 27-30 via X-ray crystallography. While at this stage it is highly speculative if this particular project will succeed, it would be by far the fastest method to obtain a high resolution structure of the infectious prion protein.

In addition to my own projects, I frequently collaborate with other members of the Prusiner laboratory on the characterization of prion-related specimens by electron microscopy, optical spectroscopy or other biophysical methods I also collaborate with other laboratories on the UCSF campus and with laboratories nationally and internationally on a number of projects, most of which focus on the characterization of amyloids other misfolded proteins. Since 1995, these collaborations have led to a total of 22 peer-reviewed publications (plus two manuscript submitted), which I had the opportunity to co-author.