BIOGRAPHICAL SKETCH

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NAME: Meng Zhang

eRA COMMONS USER NAME (credential, e.g., agency login): M_ZHANG1

POSITION TITLE: Research Fellow

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
Nankai University (Tianjin, China)	B. Sc	06/2011	Chemistry
University of Michigan (Michigan, USA)	PhD	08/2016	Chemistry

A. Personal Statement

My career goal is to understand the molecular mechanism of the functionality of important biological systems, particularly membrane bound proteins, in order to guide novel and specific design of pharmaceuticals for the treatment of related human diseases. I have gained necessary theoretical background on biochemistry, biophysics, molecular biology, protein science, *etc.* through both undergraduate and graduate academic training. My Ph.D. research projects focus on the studies of structure and dynamics of several membrane protein-protein complexes including a ~70 kDa cytochrome P450 – cytochrome b_5 complex, a ~ 80 kDa cytochrome P450 – cytochrome P450 reductase FMN domain (FBD) complex, and a ~ 50 kDa FBD – cytochrome *c* complex. I utilized solution NMR as the main tool to probe the interaction between each two binding partners, accompanied by solid state NMR and a variety of other biophysical techniques ranging from various spectroscopic tools to enzymatic activity assays. In order to study membrane-bound proteins in native-like membrane environments, I researched a variety of membrane mimetics including micelles, vesicles, bicelles and nanodiscs. With these projects I published a list of papers in JBC, Scientific Reports, Biophysics J, as well as one in Angewantde Chemie that was recommended by Faculty1000 prime. My postdoctoral research focuses on unveiling the molecular mechanism of the signaling pathways of G protein coupled receptors (GPCR) by elucidating detailed structure and dynamics information at each specific signaling step. One very important aspect is that my studies on GPCRs are carried out in lipid nanodiscs, which provide near native lipid bilayer environments that resemble the physiological membrane systems where GPCRs carry out their signaling functions. Development of such nanodiscs resulted in one publication in JACS and several manuscripts under preparation. My study on one GPCR – neurotensin receptor 1 (NTR1) – in circularized nanodiscs provided the first native GPCR-G_i complex structure as well as the first G_i structure in lipid membrane environment, raveling detailed native interactions between NTSR1 and G_i protein, as well as between protein and lipids. With my research experience on GPCR, G protein as well as membrane mimetics, I am confident in the study of the other NTSR1 signaling pathways – the Gq and β-arrestin pathway respectively – to provide a full view of NTSR1 signal transduction mechanism, which will guide rational design of selective pharmaceuticals that avoid side effects triggered by un-wanted pathway signaling.

1 **Meng Zhang**, Rui Huang, Rose Ackermann, Sang-Choul Im, Lucy Waskell, Anna Schwendeman and Ayyalusamy Ramamoorthy, Reconstitution of Cytb_5–CytP450 Complex in Nanodiscs for Structural Studies by NMR. *Angewandte Chemie 2016, 55 (14), 4497-4499, PMID: 26924779*

- Recommended in F1000Prime as being of “special significance in its field”.

- "Watching detox enzymes work could lead to better medicines" in *Michigan News* (*University of Michigan Regents*) March 3, 2016

2 **Meng Zhang***, Stéphanie V Le Clair*, Sang-Choul Im, Lucy Waskell, and Ayyalusamy Ramamoorthy, Insights into the Role of Substrates on the Interaction between Cytochrome b_5 and Cytochrome P450 2B4 by NMR, *Sci. Rep. 2015, 5: 8392, PMCID: PMC4330534* (* denotes co-first authors)

3 **Meng Zhang**, Rui Huang, Sang-Choul Im, Lucy Waskell, and Ayyalusamy Ramamoorthy, Effects of Membrane Mimetics on Cytochrome P450 – Cytochrome b_5 Interactions Characterized by NMR Spectroscopy, *J Biol Chem. 2015, 290(20): 12705-18, PMCID: PMC4432288*

4 **Meng Zhang***, Miao Gui*, Zi-Fu Wang, Christoph Gorgulla, James J. Yu, Hao Wu, Zhen Yu J. Sun, Lisa Merklinger, Lena Morstein, Franz Hagn, Andreas Plückthun, Alan Brown, Mahmoud Nasr, Gerhard Wagner, Cryo-EM structure of an activated GPCR-G protein complex in lipid nanodiscs, *Nat. Struct. Mol. Biol.* **28**, 258–267 (2021) PMCID: PMC8176890 (* denotes co-first authors)

- Invitation to give a talk at ASBMB-LRD on this paper
- Commentary article: "Feeling at home: Structure of the NTSR1–G_i complex in a lipid environment" in *News & Views, Nat. Struct. Mol. Biol.* March 30th, 2021

Relevant Current Research Projects

BCMP-Walsh Fellowship (Fellow: Meng Zhang) 07/01/21 – 06/31/22
Understanding the molecular mechanism underlying Neurotensin Receptor biased signaling for the development of superior therapeutics
This fellowship provides basic science information about the detailed molecular mechanisms of NTSR1 signal transduction through different downstream intracellular pathways, including the G_i, G_q and β-arrestin pathways. Small molecules selectively targeting one pathway while inhibiting the others have been shown to avoid severe side effects that non-selective drug candidates have suffered from. Understanding the basic science will guide rational design of such selective drugs to for better therapeutic effects. Structural studies on the NTSR1-Gi complex in nanodiscs have been established and resulted in the first native NTSR1-Gi complex structure in membrane. (Zhang et al. 2021 NSMB) The methods developed are being employed to investigate NTSR1-Gq and NTSR1-β-arrestin interactions. Structure-based ultra large virtual screening of selective molecules will be followed to discover novel drug candidates.

Past Relevant Research Projects

Broderick Phytocannabinoid Research Initiative (Fellow: Meng Zhang) 01/01/20 – 12/31/20
Structure and dynamics of the cannabinoid receptors in complex with phytocannabinoids and G protein trimer
This project aims at elucidating the molecular mechanisms of ligand-dependent, pathway-selective signaling through CB2 using biophysical, NMR and cryo-EM methods. Functional and structural information for CB2 biased signaling will aid the development of novel and specific therapeutics.

B. Positions, Scientific Appointments, and Honors

2016 - present Postdoctoral Fellow, Harvard Medical School

Honors

Year	Award	Institution
2021	Invited Speaker	ASBMB Lipid Research Division seminar
2021	Christopher Walsh Fellowship	Harvard Medical School
2020	Charles Robert Broderick III Phytocannabinoid Research Fellowship	Charles R. Broderick III Phytocannabinoid Research Initiative

2016	The Margaret & Herman Sokol Graduate Summer Research Fellowship	University of Michigan
2015	The Robert W. Parry Award	University of Michigan
2015	Chemistry Winter Fellowship	University of Michigan
2014	Student Travel Award	55th Experimental Nuclear Magnetic Resonance Conference

C. Contributions to Science

1. Mechanism of Cytochrome P450 redox activities. My PhD studies on the Cytochrome P450 membrane protein system provided atomic level residue specific information on 1) how different substrates regulate electron transfer between the redox partners; 2) how electrons are transferred from the redox center of one protein to that of its partner via the electron transfer pathway elucidated from our NMR studies; 3) the competition mechanism between Cytochrome b5 and Cytochrome P450 Reductase for Cytochrome P450 regulated by different substrates, providing insights into the molecular mechanism of how the three proteins cooperate to complete the redox cycle and shedding light on novel drug design.

   a. Rui Huang, Yamamoto Kazutoshi, **Meng Zhang**, Nataliya Popovych, Sang-Choul Im, Lucy Waskell, and Ayyalusamy Ramamoorthy, Probing the transmembrane structure and dynamics of microsomal cytochrome P450 reductase by solid-state NMR. *Biophys. J.106 (2014), 2126-2133, PMCID: PMC4052271*

   - Highlighed as “New and Notable” in Biophysics Journal

   b. **Meng Zhang***, Stéphanie V Le Clair*, Sang-Choul Im, Lucy Waskell, and Ayyalusamy Ramamoorthy, Insights into the Role of Substrates on the Interaction between Cytochrome b_5 and Cytochrome P450 2B4 by NMR, *Sci. Rep. 2015, 5: 8392, PMCID: PMC4330534* (* denotes co-first authors)

   c. Rui Huang, **Meng Zhang**, Freeborn Rwere, Lucy Waskell, and Ayyalusamy Ramamoorthy, Kinetic and Structural Characterization of the Interaction between the FMN Binding Domain of Cytochrome P450 Reductase and Cytochrome c, *J Biol Chem. 2015, 290(8): 4843-55, PMCID: PMC4335224*

   d. Katherine Gentry, **Meng Zhang**, Sang-Choul Im, Lucy Waskell, Ayyalusamy Ramamoorthy, Substrate mediated redox partner selectivity of cytochrome P450. *Chem. Comm. 2018, 54(45), 5780-5783, PMCID: PMC5980791*

2. Effect of membrane on Cytochrome P450 redox activities. Since Cytochrome P450 and its redox partners are membrane bound proteins, it is important to undersand the role of membrane on Cytochrome P450 functionality. My studies unraveled how lipid membrane affects the interaction between different electron-transfer partners, namely Cytochrome P450 – Cytochrome b5, as well as Cytochrome P450 – Cytochrome P450 Reductase. My research also resulted in the development of a novel lipid bilayer membrane mimetic – peptide based nanodiscs, which provide much better stability of both each protein and their complexes.

   a. **Meng Zhang**, Rui Huang, Sang-Choul Im, Lucy Waskell, and Ayyalusamy Ramamoorthy, Effects of Membrane Mimetics on Cytochrome P450 – Cytochrome b_5 Interactions Characterized by NMR Spectroscopy, *J Biol Chem. 2015, 290(20): 12705-18, PMCID: PMC4432288*

   b. **Meng Zhang**, Rui Huang, Rose Ackermann, Sang-Choul Im, Lucy Waskell, Anna Schwendeman and Ayyalusamy Ramamoorthy, Reconstitution of Cytb_5–CytP450 Complex in Nanodiscs for Structural Studies by NMR. *Angewandte Chemie 2016, 55 (14), 4497-4499, PMID: 26924779*

   - Recommended in F1000Prime as being of “special significance in its field”.

- "Watching detox enzymes work could lead to better medicines" in *Michigan News* (*University of Michigan Regents*) March 3, 2016

c. Katherine A. Gentry, Elke Prade, Carlo Barnaba, **Meng Zhang**, Mukesh Mahajan, Sang-Choul Im, G. M. Anantharamaiah, Satoshi Nagao, Lucy Waskell, and Ayyalusamy Ramamoorthy, Kinetic and Structural Characterization of the Effects of Membrane on the Complex of Cytochrome b_5 and Cytochrome *c. Sci. Rep. 2017, 7: 7793, PMCID: PMC5552742*

d. Elke Prade, Mukesh Mahajan, Sang-Choul Im, **Meng Zhang**, Katherine A Gentry, GM Anantharamaiah, Lucy Waskell, Ayyalusamy Ramamoorthy, A minimal functional complex of cytochrome P450 and FBD of cytochrome P450 reductase in nanodiscs. *Angewandte Chemie 2018, 57 (28), 8458-8462, PMCID: PMC6248338*

3. Integral membrane protein structure and dynamics. My postdoctoral research focuses on the study of structure and dynamics of membrane proteins including GPCR and its binding partners, as well as human voltage dependent anion channels (hVDAC1) and its interactions partners. I have incorporated these membrane proteins into lipid nanodiscs and utilized a combination of NMR, CryoEM and other biophysical techniques to investigate the molecular mechanism of the functionality of these proteins. I have participated in NMR methodology development which enables studies of the aromatic side chains of proteins and facilitates methyl side chain assignments. I have reported the first native GPCR-G_i protein complex structure in membrane which unraveled detailed molecular mechanisms of signal transduction through the G_i pathway. I have also participated into the development of novel DNA based lipid nanodiscs.

a. Zhao Zhao, **Meng Zhang**, James M Hogle, William M Shih, Gerhard Wagner, Mahmoud L Nasr, DNA-corralled nanodiscs for the structural and functional characterization of membrane proteins and viral entry. *JACS 2018, 140(34), 10639-10643, PMCID: PMC6206850*

- Recommended in F1000Prime as being of "special significance in its field".

b. Andras Boeszoermenyi, Sandeep Chhabra, Abhinav Dubey, Denitsa L Radeva, Nikola T Burdzhiev, Christo D Chanev, Ognyan I Petrov, Vladimir M Gelev, **Meng Zhang**, Clemens Anklin, Helena Kovacs, Gerhard Wagner, Ilya Kuprov, Koh Takeuchi, Haribabu Arthanari, Aromatic ^{19}F-^{13}C TROSY: a background-free approach to probe biomolecular structure, function, and dynamics. *Nature Methods 2019, 16, 333–340, PMCID: PMC6549241*

c. Soumya P. Behera, Abhinav Dubey, Wan-Na Chen, Viviane S. De Paula, **Meng Zhang**, Nikolaos G. Sgourakis, Wolfgang Bermel, Gerhard Wagner, Paul W. Coote, Haribabu Arthanari, Nearest-neighbor NMR spectroscopy: categorizing spectral peaks by their adjacent nuclei. *Nat Commun* 11, 5547 (2020), PMCID: PMC7642304

d. **Meng Zhang***, Miao Gui*, Zi-Fu Wang, Christoph Gorgulla, James J. Yu, Hao Wu, Zhen Yu J. Sun, Lisa Merklinger, Lena Morstein, Franz Hagn, Andreas Plückthun, Alan Brown, Mahmoud Nasr, Gerhard Wagner, Cryo-EM structure of an activated GPCR-G protein complex in lipid nanodiscs, *Nat. Struct. Mol. Biol.* **28**, 258–267 (2021) PMCID: PMC8176890 (* denotes co-first authors)

- Invitation to give a talk at ASBMB-LRD on this paper
- Commentary article: "Feeling at home: Structure of the NTSR1–G_i complex in a lipid environment" in *News & Views, Nat. Struct. Mol. Biol.* March 30th, 2021

D. Additional Information: Research Support and/or Scholastic Performance

YEAR	COURSE TITLE	GRADE
2011	Inorganic Chem	B
2011	Materials Chem	A-

2012	Biophysics Chem 2	A
2012	Advanced Inorganic Chem	A-
2012	Biochem Solution-structure	A
2013	Biophysics Chem 1	A+
2014	Biomolecular NMR	A+

Total GPA: 3.857/4

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
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NAME: Gerhard Wagner

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

POSITION TITLE: Professor of Biological Chemistry and Molecular Pharmacology

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
Technical University, Munich, Germany	Diploma	09/1972	Physics
ETH, Zürich, Switzerland	PhD	07/1977	Biophysics
MIT, Cambridge, Massachusetts	Postdoc	10/1978-04/1979	Chemistry
ETH, Zürich, Switzerland	Privatdozent	09/1982-	Biophysics

A. Personal Statement

The overall goal of my research is to obtain structural and functional insights into biological processes at the molecular level. My main technology expertise is in NMR spectroscopy but we also do X-ray crystallography and cryo EM. I have worked in structural biology with NMR and computational methods for more than 40 years. I have contributed more than 500 original papers. I have early on shown that proteins are dynamic (1). I have developed NMR methods for assigning protein NMR spectra, obtaining structural constraints and calculating structures. I was the first to assign a NMR spectrum of a protein, which laid the foundation for solution structure determination of proteins. I have initiated construction of triple resonance probes in 1986, which resulted in the first triple-resonance experiments for assigning protein spectra. My group has solved 50+ protein structures and addressed important biological questions, such as in eukaryotic translation initiation, T-cell biology, apoptosis, transcription and membrane protein structural biology. I am passionate about discovering and optimizing inhibitors of protein-protein interactions in order to elucidate the significance of particular interfaces and possibly develop small molecules of pharmaceutical interest. So far this has led to the discovery of a translation-initiation inhibitor that has anti-tumor activity and no detectable toxicity (2). More recently, in collaboration with Drs. Näär and Arthanari, we discovered transcription inhibitors that are specifically suppress expression of genes controlled by the SREBP-1 transcriptional activator, such as fatty acid synthase (*fasn*), a well-known ongogene. We also have developed expertise in elucidating membrane protein structures using solution NMR spectroscopy in detergent micelles and nanodiscs (3). Recently we focused on membrane protein structure and function and determined the structure of VDAC1 in micelles (4). We engineered different-size and covalently circularized nanodiscs, which tremendously facilitates structure determination of membrane proteins with cryoEM and NMR (4). Finally, we have determined the structure of the neurotensin receptor NTSR1 in complex with the heterotrimeric G protein Gi in a covalently circularized phospholipid nanodisc without using stabilizing antibodies/nanobodies or cross-linking.

1. G. Wagner and K. Wüthrich: Dynamic model of globular protein conformations based on NMR studies in solution. Nature **275**, 247-248 (1978).
2. M. H. A. Roehrl, S. Kang, J. Aramburu, A. Rao, G. Wagner , P. G Hogan: Selective inhibition of calcineurin-NFAT signaling by blocking protein-protein interaction with small organic molecules, PNAS, 101, 7554-7559 (2004).
3. A. Degterev, A. Lugovskoy, M. Cardone, B. Mulley, G. Wagner, T. Mitchison, J. Yuan. Identification of Small Molecule Inhibitors of BH3 and Bcl-xL interaction: **Nature Cell Biology**, **3**, 173-182 (2001).
4. N. J. Moerke, H. Aktas, H. Chen, S. Cantel, M. Y. Reibarkh, A. Fahmy, J. D. Gross, A. Degterev, J. Yuan, M. Chorev, J. A. Halperin, G. Wagner: Small Molecule Inhibition of the Interaction Between the Translation Initiation Factors eIF4E and eIF4G. Cell, **128**, 257-267 (2007).

Relevant Current Research Projects

S10-OD028526 (PI: Gerhard Wagner) 07/15/21 – 07/14/22
600 MHz NMR Spectrometer Console
This grant was obtained for enabling new ^{19}F,^{13}C,^{15}N,^{1}H, ^{2}H quintuple resonance experiments combined with an Agilent-to-Bruker console conversion. It will be available for testing fluorine-containing compounds interacting with receptors and protein complexes.

R01-CA200913 (PI: Gerhard Wagner) 07/01/16 – 06/31/22
Roles of Eukaryotic Translation Initiation Factors in Gene Expression
This grant and its predecessors have provided basic science information about the mechanisms of the control of translation initiation. Dysregulation of this control has been shown to be responsible for development of many cancers. The initiation complex sits at the nexus of signaling pathways (PI3K/mTOR and MAPK) preceding the beginning of protein synthesis. Malfunction can lead to uncontrolled cell growth and cancer. Some key interactions within the eIF4F complex have been established as anticancer targets. Compounds discovered have been out license to a startup company (PIC Therapeutics) which is far along with drug development possibly going into clinic soon. Virtual Flow will have a great impact on the discovery of new anti-tumor agents on other targets arising from this grant.

R01-AI037581 (PI: Gerhard Wagner) 11/16/16 – 10/31/22
Structural Basis for Immune-Cell Surface Receptor Function
This grant has contributed to the characterization of two checkpoints of T-cell activation, the TCR/CD3 complex for messaging through the plasma membrane, and the nuclear translocation of the nuclear factor of activated T cells (NFAT). Inhibition of the latter with small molecules selected from ~ 60,000 compound physical libraries have been discovered and been found of possible interest for immune suppression in transplant patients. The small number of compounds available for wet biochemistry screening limited us to ~ 1uM affinities to inhibit the calcineurin/NFAT interaction. The VirtualFlow technology would have the chance to obtain much better compounds.

R01 GM129026 (PI: Gerhard Wagner) 09/01/18–07/31/22
Next Generation Solution NMR Techniques for GPCR Structure, Dynamics and Function
Here we focus on structure and function GPCR/G-protein complexes inserted into phospholipid nanodiscs avoiding artificial stabilization, such as crosslinking, antibodies or nanobodies. We solved a structure of the neurotensin1 receptor/neurotensin/Gi complex in a 9 nm nanodisc, based on NMR and cryoEM. We are working on complexes with Gq and arrestin2. Virtual Flow will be used here to identify ligands that bias signaling to the arrestin or Gq pathway.

P41 GM132079 (Robert Griffin) 06/01/19 – 05/31/22
MIT/Harvard Center for Magnetic Resonance – TD&R 3: Next Generation Solution NMR Methods
This Technology Research and Development (TR&D) project will focus on NMR spectrometry methods for large protein systems, membrane proteins (GPCRs) in phospholipid nanodiscs and RNA/protein complexes, We'll employ ^{15}N- and ^{13}C-detection methods, ^{19}F-^{13}C TROSY technologies, advanced non-uniform sampling (NUS) and reconstruction techniques and use near native membrane surrogates within engineered nanodiscs. We'll develop non-uniform sampling procedures that optimize sampling schedules to minimize artifacts. These schedules will be assembled in libraries and made publicly available. This award provides repair and maintenance for Wagner Lab spectrometers located at the Bitter Magnet Lab, MIT. Role: TR&D Leader.

Broderick Phytocannabinoid Faculty Research Initiative (PI: Gerhard Wagner) 07/01/21 – 06/30/22
Elucidating molecular mechanism of phytocannabinoids-induced biased signaling of cannabinoid receptors.
This project aims at elucidating the molecular mechanisms of ligand-dependent, pathway-selective signaling through CB2 using biophysical, NMR and cryo-EM methods. Functional and structural information for CB2 biased signaling will aid the development of novel and specific therapeutics.

Blavatnik Biomedical Accelerator at Harvard University (PI: Gerhard Wagner) 07/01/21 – 06/30/22
Targeting transcription factor Nrf2 for protection against cognitive impairment in diabetes
This project aims at optimizing inhibitors of the Keap1-Nrf2 interaction for possible use in Alport Syndrome. Friedrich's Ataxia or Parkinson's disease.

Revelant Completed Research Projects (since 2019)

HFSP RGP0060/2016 (Gerhard Wagner, Andreas Plückthun) 05/01/16 - 10/31/19
Mechanisms of dynamic GPCR transmembrane signaling.
This proposes to assign NMR spectra of G-protein coupled receptors (Neurotensin receptor) in detergent micelles and nanodiscs, with bound neurotensin as agonist. Funds are equally shared between the Plückthun and Wagner lab and were used to create the preliminary data for the research proposed here. Role: Co-PI

P41-EB002026 (PI: Robert Griffin) 05/20/04 - 04/30/19
Center for Magnetic Resonance
This Research Resource award supports research at the Francis Bitter Magnet Lab at MIT. Dr. Wagner is the co-principal investigator on this award which supports operation and maintenance of spectrometers in the Bitter Lab including one 750 MHz and one 800 MHz spectrometer owned by Harvard Medical School. Dr. Wagner does not obtain any research or salary support from this award. Role: Co-PI

R01-AI108718 (PI: Gerhard Wagner) 08/06/14 – 04/30/19
The translation apparatus of Leishmania: from basic analysis to pursuit of novel drug targets
This proposes study of the structure/function of Leishmania translation initiation factors both in vitro and within parasites. It will determine the structure of the LeishIF4E-1 complex with its ligand cap-4 and Leish4E-IP, characterize the LeishIF3 recruitment to the Leishmania cap-binding complex and develop assays for HTP screens in search of Leishmania inhibitory compounds. Role: PI

Harvard Catalyst 10872 (PI: Gerhard Wagner) 09/01/18 - 08/31/20
DNA-corralled nanodiscs for study of large membrane proteins and their complexes
We proposed construction of DNA-Corralled nanodiscs (DCNDs) to enable the study of large membrane proteins and their interaction partners using negative stain, cryo EM, or other biophysical techniques. DCNDs will enable control over the stoichiometry of MPCs, extraction of MPCs from their native membranes, and establishment of asymmetric bilayers.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2012 - 2019	Editor in Chief, Journal Biomolecular NMR
2004 - 2012	Associate Editor, Journal of Biomolecular NMR
2002 - 2009	Associate Editor, Quarterly Reviews in Biophysics
2001 - 2006	Editorial Board , Cell
1998 -	Editorial Board, Biochemistry
1993 -	Editorial Board, Journal of Biomolecular NMR
1993 -	Editorial Board, Journal of Magnetic Resonance
1992 -	Elkan Rogers Blout Professor of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, MA
1990 -	Professor Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston
1989 - 1990	Professor, Biological Chemistry, University of Michigan, Ann Arbor, MI
1987 - 1989	Associate Professor Biological Chemistry, University of Michigan, Ann Arbor, MI
1982 - 1991	Privatdozent, ETH, Zurich
1979 - 1982	Assistant, ETH, Zurich
1978 - 1979	Research Associate, MIT, Cambridge, MA
1977 - 1978	Assistant, ETH, Zurich
1972 -	Diploma mit Auszeichnung, Technical University Munich, Munich

Honors

1970 - 1974	Fellowship, Studienstiftung des Deutschen Volkes
2018	Gunther Laukien Prize , Experimental NMR Conference

2015 Honorary Member, National Magnetic Resonance Society of India
2015 Elected Member, American Academy of Arts and Sciences
2013 Elected Member, National Academy of Sciences USA
2011 Agilent Thought Leader Award, 2012 Mill Hill Lecture
2011 Stein and Moore Award, Protein Society
2005 Fellow, International Society of Magnetic Resonance
2005 Elected Member, German National Academy Leopoldina
2004 Achievement Award in Magnetic Resonance, Eastern Analytical Symposium
2003 Invited Speaker, The Cleveland Structural Biology Lecture
2001 Elected Fellow, American Association for the Advancement of Science
1998 Invited Speaker, The Wellcome Lecture in Structural Biology, Kansas State University
1992 Invited Speaker, Zurich Protein Lecture, ETH Zurich
1977 PhD Thesis Award, ETH, Zurich

C. Contribution to Science

1. Protein dynamics: My initial contribution to science as a beginning graduate student was the discovery that proteins are intrinsically more dynamic than assumed from high-resolution crystal structures. Using NMR spectroscopy I found that aromatic side chains flip rapidly around the C_β-C_γ bond even in the most rigid proteins (basic pancreatic trypsin inhibitor, BPTI, T_m ~ 100C), and the flip rates can be altered with temperature. This was entirely unexpected and initially not accepted by crystallographers who initially did not believe this finding but soon embraced the concept of protein dynamics. My quantitative experimental data created the playground for the development and calibration of molecular dynamics simulations. Afterwards, as an independent PI, I extended dynamics studies to measuring ^{13}C and ^{15}N relaxation parameters and developed procedures for mapping the spectral densities of protein motions, an approach widely followed.

a. K. Wüthrich and G. Wagner: NMR investigations of the dynamics of the aromatic amino acid residues in the basic pancreatic trypsin inhibitor. FEBS Lett. 50, 265-268 (1975).
b. G. Wagner and K. Wüthrich: Dynamic model of globular protein conformations based on NMR studies in solution. Nature 275, 247-248 (1978).
c. J. W. Peng and G. Wagner: Mapping of Spectral Densities of N-H Bond Motions in Eglin c Using Heteronuclear Relaxation Experiments. Biochemistry, 31, 8571-8586 (1992).

2. *Protein sequential assignments and structure determination.* I developed methods for sequential assignment of protein NMR spectra, which became the basis for solution structure determination of proteins and characterization of protein mobility. The first step was the technology to assign protein NMR spectra based on 1D nuclear Overhauser effect and spin decoupling followed by the 2D equivalent experiments. Subsequently, in 1986, I commissioned construction of a ^{1}H-^{13}C-^{15}N probe, which allowed me to develop triple resonance experiments, which are now the basis for most protein NMR assignments. Subsequently my lab solved 50+ structures of proteins in solution and derived open functional properties.

a. G. Wagner and K. Wüthrich: Truncated driven nuclear Overhauser effect (TOE). A new technique for studies of selective ^{1}H-^{1}H Overhauser effects in the presence of spin diffusion. J.Magn.Reson.33,675-680 (1979).
b. G. Wagner and K. Wüthrich: Sequential Resonance Assignments in Protein ^{1}H NMR Spectra: Basic Pancreatic Trypsin Inhibitor J. Mol. Biol. 155, 347-366 (1982).
c. G.T. Montelione and G. Wagner: Conformation-Independent Sequential NMR Connections in Isotope-Enriched Polypeptides by H-1-C-13-N-15 Triple-Resonance Experiments. J.Magn.Reson.87,183-188(1990).

3. *Translation initiation, transcriptional activation and drug discovery:* My lab determined structures of key eukaryotic translation initiation factors, eIF4E, eIF1, eIF1A, eIF2α complexes of yeast eIF4E with eIF4G and human eIF4E with 4E-BP1. We discovered small molecule inhibitors of the eIF4E/eIF4G interaction that stabilize binding of the tumor suppressor 4E-BP1. The compounds are active in cancer cell lines and inhibit tumor growth in mouse xenografts. In addition, we discovered inhibitors of SREBP-mediated transcriptional activation. A new Open-source platform was developed capable of *in silico* screening of billion chemical compounds for binding to and inhibiting protein targets.

a. J.D. Gross, N.J. Moerke, T. Von der Haar, A. A. Lugovskoy, A.B. Sachs, J. McCarthy, and G. Wagner: Ribosome loading onto the mRNA cap is driven by conformational coupling between eIF4G and eIF4E. Cell, 115, 739-750 (2003).

b. N.J. Moerke, H. Aktas, H. Chen, S. Cantel, M. Y. Reibarkh, A. Fahmy, J. D. Gross, A. Degterev, J. Yuan, M. Chorev, J. A. Halperin, G. Wagner: Small Molecule Inhibition of the Interaction Between the Translation Initiation Factors eIF4E and eIF4G. Cell, 128, 257-267 (2007).

c. J.L. Nishikawa, A. Boeszoermenyi, L.A. Vale-Silva, R. Torelli, B. Posteraro, Y.J. Sohn, V. Gelev, D. Sanglard, M. Sanguinetti, S.J. Buhrlage, N.S. Gray, G. Wagner, A.M. Näär, H. Arthanari: Inhibiting Fungal Multidrug Resistance by Disrupting an Activator-Mediator Interaction, Nature. 530,485-489 (2016). PMC4860947

d. Gorgulla, A. Boeszoermenyi, Z-F. Wang, P. D. Fischer, P.l. Coote, K. M. P. Das, Y. S. Malets, D. S. Radchenko, Y. S. Moroz, D. A. Scott, K. Fackeldey, M. Hoffmann, I. Iavniuk , G. Wagner, H. Arthanari: An open-source drug discovery platform enables ultra-large virtual screens. Nature, 580, 663-668 (2020). PMC8352709

4. *Immune-cell proteins*. In collaboration with Ellis Reinherz, my lab has solved the first structures of the ectodomains CD3$\varepsilon\gamma$ and CD3$\varepsilon\delta$, the two heterodimeric invariable components of the T-cell receptor, and the first ClassII TCR/MHC complex structure. This followed the structural characterization of the glycosylated human CD2 ectodomain and its complex with CD58.

a. D.F. Wyss J. S. Choi, J. Li, M. H. Knoppers, K. J. Willis, A. R. N. Arulanandam, A. Smolyar, E. L. Reinherz, G. Wagner, CHO structure, Conformation and Function of the N-linked Glycan in the Adhesion Domain of Human CD2. Science, 269, 1273-1278 (1995).

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5. *Membrane protein structure and function*. We have determined the first structure of the voltage-dependent anion channel, VDAC-1. Furthermore, we have pioneered the use of phospholipid nanodiscs for NMR studies of integral membrane proteins and already determined a solution structure of OmpX in a designed nanodisc. Most importantly, we have now designed small and large covalently circularized nanodiscs, which enabled cryoEM structure determination of membrane proteins and imaging viral entries. Thus, we determined the structure of the neurotensin receptor 1 (NTR1) complex with agonist and heterotrimeric G protein Gi in cND without stabilizing antibodies or crosslinking (d).

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