BIOGRAPHICAL SKETCH

NAME: **Matthias Buck**

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

POSITION TITLE: **Professor** (Depts. of Biophysics, Neuroscience and Pharmacology)

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Cambridge, UK	BA, MA	06/1990, 06/1992	Biochemistry
University of Oxford, UK	DPhil	02/1995	Biophysics
Harvard University, MA	(postdoc)	11/1999	Biophysics
Memorial Sloan-Kettering Cancer Center, NY	(postdoc)	07/2002	Biophysics

A. Personal Statement

Research in my group seeks to characterize the biophysical mechanisms of signal transduction of two receptor families at the molecular, if not residue level. Plexins and Eph receptors are responsible for cell guidance and positional maintenance, both with key involvement in many developmental processes (e.g. neuronal, immune and cardiovascular systems). They are also involved in diseases, especially in cancer. We use a wide range of structural biology (solution NMR / x-ray crystallography) and protein biophysical tools (fluorescence spectroscopy, ITC, MST, HX-MS, SPR and EPR) in a problem oriented approach. Part of the laboratory also employs computational modeling and molecular dynamics simulations in order to provide additional aspects on the problems, to offer new insights into the experimental data, and to suggest further studies. My graduate training and my two postdoctoral research periods in different fields, I believe, have allowed me to bring unique perspectives and an interdisciplinary approach to uncovering the biophysical principles behind these systems. My graduate studies at Oxford with C.M. Dobson, advanced the premise that a detailed understanding of protein folding will be based on features of their partially structured states. At Harvard, with M. Karplus, I studied protein flexibility using molecular dynamics simulation in the light of experimental data. At Sloan-Kettering Cancer Center, M.K. Rosen introduced me to small GTPases and their cell signaling mechanisms. Small GTPases and their interaction with the plexin receptor cytoplasmic domains has been a major focus of the laboratory, while ~6 years ago we added the Eph receptor system and recently also worked on Ras GTPase-membrane interactions.

Currently, through our projects and other systems in the literature, I see that the understanding of protein dynamics (relatively mature at the domain level) also translates to the next level of domain-domain interactions, to protein complexes as well as to protein-membrane interactions. Following our recent studies of GTPase-membrane interactions, the goal for the next 5 years is to further our study of the Eph receptor system at the domain-domain and domain-membrane interaction level. A number of publications indicate that internal- as well as configurational dynamics of protein complexes are essential features which enable their function. A review article on such systems and the paradigms they introduce is in advanced preparation. We plan on building a website (http://dynamic-protein-complexes.org) to provide a database and the key literature, both to the wider community of researchers as well as to the general public. Recently, I agreed to edit a book on this topic for Pan Stanford, a publisher who distributes through Taylor & Francis, with an estimated completion date of mid-2020.

I have actively mentored > 20 undergraduate and graduate students, research assistants and my laboratory has especially benefitted from 14 talented postdoctoral fellows over the last 16 years. Half of the postdocs were able to support at least part of their research time by fellowships from the American Heart Association, NIH F/T32s

and from the Mexican and Chinese Governments. Indeed, 6 of the 12 postdocs who have left the lab. found positions in academia as assistant professors or equivalent positions; all (except two) are active in biomedical research. At the School of Medicine of Case Western Reserve University, I currently direct a small graduate program track in structural biology and biophysics (http://sbb-tp.case.edu), where we have been successful in attracting outstanding students with backgrounds in mathematics, physics, chemistry and chemical engineering to biomedically focused PhD programs.

B. Positions and Honors

Professional Positions:

Sep.02 – 09	Assistant Professor, Dept. of Physiology & Biophysics, School of Medicine,
Jul. 09 – 14	then Associate Prof., Case Western Reserve University (SOM-CWRU), Cleveland, OH
Apr.05 - present	Assistant/Associate/ Professor, Department of Neuroscience, SOM-CWRU
Apr.05 - present	Member, Case/NCI Comprehensive Cancer Center, Cleveland, OH
Jul.06 – present	Assistant/Associate/ Professor, Department of Pharmacology, SOM-CWRU
Jul.09 – present	Member, Cleveland Center for Proteomics and Bioinformatics, SOM-CWRU
Jul.09 – present	Director of Graduate Entry Program in Structural Biology and Biophysics, SOM-CWRU
Jul.14 - present	Professor, Dept. of Physiology & Biophysics Case Western Reserve University (SOM-CWRU), Cleveland, OH
Mar.17- Nov.17	Sabbatical at Seoul National University, Department of Chemistry

Awards and Honors:

1995-97	Fellow of the International Human Frontiers Science Program
2000-02	Individual NIH postdoctoral research fellowship (F32)
2002- present	Scholar of the Mt. Sinai Health Care Foundation, Cleveland
2003-05	American Heart Association Scientist Development Award
2005-07	Basil O'Connor Award of the March of Dimes Birth Defects Foundation
2005-09	Presidential Research Initiative Award from Case Western Reserve University
2005-11	Independent Career Grant (K02) NIH Heart Lung & Blood Institute
2017	Brainpool award from the Korean Government for Sabbatical Research with Prof. C. Seok

Other Experience:

2010- present	Reviewing Editorial Board Member: J. Biol. Chemistry
2008- present	Member of Faculty of 1000, Protein Chemistry and Chemical Biology Section
2006-09	Ad hoc panel reviewer in NIH study section (MSF-C: Feb.'06, Feb.'07, Feb.'08, Oct.'09)
2007-09	American Heart Association, Region I, Basic Cell Science Review Panel (Apr.'07,'08,'09)
2010-14	Regular Member on NIH study section, MSF-C (Jul.'10-Jun.'14)
2011-15	American Heart Association, Basic Cell Panel; Proteins and Crystallography (Apr.'11,'12,'13,'14,'15)
2010-present	Ad hoc NIH study sections MSF-B Oct.'16, MSF-C Jun.'15 Ad hoc NIH study sections MSF-D Jun.'10, Oct.'14, Feb.'16; Jun.'18 Ad hoc NIH study sections NCI-I (K99) panel Oct.'15, Jun.'16, Feb.'18

C. Contributions to Science

My contributions to Science have been in several fields, which are listed here semi-chronologically. Currently, I am not active in all these fields, but it is possible that activity may be continued/specific techniques may be used for the overall problem-oriented approach we are taking to investigate several systems [3-5 below].

1. An early premise in the field of protein folding stated that the characterization of protein folding processes will likely be based on features of their partially structured states. My earliest studies as a graduate student and second postdoctoral fellow employed **amide hydrogen exchange**, a technique that has been widely used to study the stability of protein states and their structure. New at the time was the application of this method to largely denatured and partially folded states of proteins (new intrinsic exchange rates had just been published for peptides in late 1992) [1A,1B]. Then, later I applied amide hydrogen exchange to a protein-protein complex where one bound protein becomes structurally destabilized compared to the free form, using the other protein at

catalytic concentrations to probe a state that is only transient/at low population [1D]. We also devised a new method for a pulse-quench experiment using a high affinity binding peptide to off-compete a protein binding partner [1C]. While all these measurements used solution NMR spectroscopy as a read-out, recently we have started experiments to look at larger protein-protein complexes with mass-spectrometry as the detection method.

1A. Radford, S.E., Buck, M., Topping, K.D., Dobson, C.M. & Evans, P.A. ***(1992)*** *"Hydrogen exchange in native and denatured states of hen egg-white lysozyme"* ***Proteins: Struct.Funct. & Genetics 14, 237-248.***

1B. Buck, M., Radford, S.E. & Dobson, C.M. ***(1994)*** *"Amide hydrogen exchange in a highly denatured state: hen egg-white lysozyme in urea"* ***J.Mol.Biol. 237, 247-254.***

1C. Buck, M., Xu, W., & Rosen, M.K. ***(2001)*** *"Global disruption of the Wiskott-Aldrich Syndrome protein (WASP) autoinhibited structure on Cdc42 binding. Ligand displacement as a novel method to monitor amide hydrogen exchange"* ***Accelerated Publication in Biochemistry 40, 14115-14122.***

1D. Buck, M*., Xu, W. & Rosen, M.K*. **(2004)** "A two state allosteric model for autoinhibition in WASP" ***J.Mol.Biol.*** **338, 271-285.** * = joint corresponding authors [PMID:15066431 ; DOI: 10.1016/j.jmb.2004.02.036]

2. My doctoral studies also impacted the field of **solution NMR studies of substantially and partially folded proteins** in another way. We were one of the first to apply, at that time, standard NMR assignment methods to partially folded and denatured states [e.g. 2A,2C]. In addition, we **pioneered NMR relaxation measurements for these states** [2C] and I proposed a relationship between surface accessibility of N-H and N-H_2 containing sidechains and their amplitude of fluctuation [2B]. This caused some discussion in the literature at the time and ultimately lead to a better description of internal protein dynamics. Perhaps, I am best known in my early career for the use of trifluoroethanol to stabilize a partially folded state of hen lysozyme - this work was summarized in a review article in Q. Rev. Biophysics [2D], which has been cited ~ 800 times. Later, trifluoroethanol was used to induce amyloid formation of a wide range of proteins, including proteins containing only α-helices and became a cornerstone in the discovery of C.M. Dobson and colleagues that formation of amyloid fibrils is a universal (essentially protein sequence independent) phenomenon.

2A. Buck, M., Radford, S.E. & Dobson, C.M. ***(1993)*** *"A partially folded state of hen egg-white lysozyme in trifluoroethanol: Structural characterisation and implications for protein folding."* ***Biochemistry 32, 669-678.***

2B. Buck, M., Boyd, J., Redfield, C., MacKenzie, D.A., Jeenes, D.J., Archer, D.B. & Dobson, C.M. **(1995)** "Structural determinants of protein dynamics: Analysis of 15N relaxation measurements for maichain and sidechain nuclei of hen egg-white lysozyme." ***Biochemistry*** **34, 4041-4055.**

2C. Buck, M., Schwalbe, H. & Dobson, C.M. ***(1995)*** *"Characterisation of conformational preferences in a partly folded protein by heteronuclear NMR spectroscopy: Assignment and secondary structure analysis of hen egg-white lysozyme in trifluoroethanol."* ***Biochemistry 34, 13219-13232.***

2D. Buck, M. ***(1998)*** *"Trifluoroethanol & Colleagues: Cosolvents come of age. Recent studies with peptides and proteins."* ***Quarterly Reviews of Biophysics 31, 297-355.***

3. Dynamics of small GTPases. (Thermo-)dynamic changes that GTPases cause in effector proteins are at the heart of their molecular mechanism. This was the initial paradigm that I helped to establish as a postdoc in the laboratory of M. Rosen. Following work with the Cdc42-WASP system where I pioneered the use of amide hydrogen exchange to probe the partially unfolding of WASP induced by GTPase binding [1C,D], I selected plexins which are unique as transmembrane receptors as they interact directly with small GTPases (see 4, below). We discovered a new Rho GTPase binding motif, that is specific to plexins [3A, cited >100 times]. At the time we were one of the first laboratories to measure changes in ps-ns dynamics using relaxation measurements in both binding partners in a protein-protein interactions and found long-range dynamic allostery in the Rac1 GTPase as well as in the interacting plexin domain. It is now becoming clear that protein complexes for cell signaling are inherently dynamic [e.g. 4D, below]. Recently, we found that this is particularly true at membranes and we have published several computational papers [3B,C] and submitted an NMR/biophysics study on K-Ras lipid interactions [3D].

3A. Tong, Y, Chugha, P., Hota, PK., Li, M., Alviani, RS., Tempel, W., Shen, L., Park, HW & Buck, M. ***(2007)*** *"Binding of Rac1, Rnd1 and RhoD to a novel Rho GTPase interaction motif destabilizes dimerization of the plexin-B1 Effector domain."* ***J. Biol. Chem. 282, 37215-37224****.* [PMCID: PMC2655321]

3B. Li, Z., & Buck, M. ***(2017)*** *Computational Modelling Reveals Signaling Lipids Modulate the Orientation of K-Ras4A at the Membrane.* ***Structure 25:679-689*** *doi: 10.1016/j.str.2017.02.007. [PCMID in progress]* {publication led to interview, featured on local newspaper website: . https://www.cleveland.com/healthfit/index.ssf/2017/05/case_western_reserve_universit_16.html }*

3C. Li, Z., Prakash, P., & Buck, M. ***(2018)*** *A "Tug of War" Maintains a Dynamic Protein–Membrane Complex: Molecular Dynamics Simulations of C-Raf RBD-CRD Bound to K-Ras4B at an Anionic Membrane.* ***ACS Central Science* 4 , 298–305** doi: 10.1021/acscentsci.7b00593 *[PCMID in progress]*

3D. Cao, S., Chung, S., Kim, SJ., Li, Z., Manor, D.*, & Buck, M.* **(2018)** ***"****K-Ras binding with signaling lipid phosphoinositides: PIP2 association, orientation, function."* ***BioRxiv 324210 [Preprint]*** *May 16, 2018. Available from* https://doi.org/10.1101/324210

4. Structural and biophysical studies on plexins. No biophysical or structural studies had been carried out with the intracellular region of plexin when we started work on this important cell guidance receptor in 2002 (at the inception of my laboratory). We solved the NMR and x-ray structure of the Rho GTPase Binding Domain (RBD) of a number of family members in collaboration with Y. Tong/HW. Park and simultaneous with another group, reported the structure of the entire intracellular region [4A]. The structures were nearly identical, but the interpretation and the models advanced differed, summarized in our review [4B]. The different perspectives continue to date, although with further studies common ground is emerging (Z. Li et al., in advanced preparation). Although we had no external funding for the project recently, our work on plexin has been impactful in a still relatively small field, with > 500 citations for our 22 published papers to date. We have established collaborations with a number of cell and functional biologists. With the recent development of a biochemical assay for plexin's GAP function in vitro we are well set up to continue work on plexins. Our recent interest is in plexin and GTPase interactions with the plasma membrane, which we find plays a key role in regulating the activity of the intracellular region. In the future, we are also trying to understand the mechanism by which signals are transduced across the lipid bilayer by the single transmembrane segment of this [4C] and the Eph receptor family (see 5, below).

4A. Tong, Y., Hamaneh, M.B., Penachioni, J.Y., Hota, P.K., Kim, SJ., Alviani, R.S., Shen, L., Tempel, W., Tamagnone, L., Park., HW.* & Buck, M.** ***(2009)*** *"Structure and function of the intracellular region of the plexin-B1 transmembrane receptor."* ***J. Biol. Chem., 284, 35962-35972.*** [PMCID: PMC2791024]

4B. Hota, P.K., & Buck, M ***(2012)*** *"Plexin structures are coming! Opportunities for multilevel investigations of the function of semaphoring guidance receptors, their cell signaling mechanisms and functions."* ***Cell. & Mol. Life Sciences 69, 3765-805.*** [PMID: 22744749; doi: 10.1007/s00018-012-1019-0]

4C. Zhang L., Polyansky, AA, & Buck, M. ***(2015)*** *"Modeling Transmembrane Domain Dimers/Trimers of Plexin Receptors: Implications for Mechanisms of Signal Transmission across the Membrane."* ***PLoS One, 10:e0121513.*** [PMCID: PMC4383379]

4D. Zhang, L., & Buck, M.** ***(2017)*** *"Molecular Dynamics Simulations Reveal Isoform Specific Contact Dynamics Between the Plexin Rho GTPase Binding Domain (RBD) and Small Rho GTPases Rac1 and Rnd1."* ***J Phys Chem B. 121:1485-1498.*** *doi: 10.1021/acs.jpcb.6b11022.* [PCMID in progress]

5. Structural and biophysical studies on Eph receptors. Eph receptors have similar cell guidance functions to plexins, and are also involved in cancer proliferation and metastasis, but their signaling mechanism as receptor tyrosine kinases (RTK) is different. Importantly, the role of the intracellular SAM domain, adjacent to the kinase domain and unique to Eph-family RTKs, is not yet understood. Early NMR derived models (and also a recent crystal structure) for the interaction between the EphA2 SAM domain and that of SHIP2 SAM domain are too simplistic. We discovered that the heterodimer complex is dynamic in nature- transitioning between several alternate structures [5A]. Our work is advancing the **emerging field of dynamic protein complexes**, combining experimental (NMR, EPR and biophysical) studies with molecular modeling and long-time all-atom molecular dynamics simulations [5B, 5D]. Ongoing work seeks to explain the role of disease associated mutations as well as of posttranslational modifications for SAM domains in Eph cell signaling. Another separate study examines the tramsmembrane region of Eph receptors and in agreement with other researchers we emphasize the role that alternate transmembrane structures likely play in the regulation of receptor activity [see 4C above]. In our collaboration with the A. Smith lab. at the Univ. of Akron, we established that deletion of the SAM domain from the intracellular region has a profound effect on Eph dimerization and clustering that can be rationalized by the proposed experiments and simulations. Characterization of the intracellular cell signaling mechanism at the molecular level will inform new avenues for drug screening and design against a number of cancers.

*5A. Lee, HJ, Hota, P.K, Chugha, P., Miao, H., Zhang, L, Kim, SJ, Alviani, R.S, Stetzig, L., Wang, B. & Buck, M. **(2012)** "Refined NMR structure of a heterodimeric SAM:SAM complex: Characterization and manipulation of the EphA2 interface leads to new cellular functions of SHIP2." **Structure 20, 41-55**.* [PMCID:PMC3516615]

*5B. Zhang, L., Borthakur, S. & Buck, M. **(2016)** "Dissociation of a dynamic protein complex studied by All Atom Molecular Simulation." **Biophys. J., 110, 877-886.** [PMID:26910424; PMCID in progress]*

*5C. Shi, X., Hapiak, V., Zheng, J., Muller-Greven, J., Bowman, D., Buck, M., Bing-Cheng Wang, B-C., & Adam W. Smith, A.W. **(2017)** "The role of the EphA2 SAM domain in receptor activation." **Scientific Reports 7:45084.** [PMCID:PMC5364462] DOI:10.1038/srep45084*

*5D. Li, Z., & Buck, M. **(2018)** "Pattern, Pathways and Dynamics of EphA2 SAM and SHIP2 SAM Heterodimer Association Revealed by All-Atom Molecular Dynamics Simulation." **BioRxiv 241810 [Preprint]** Jan 2, 2018. Available from doi: https://doi.org/10.1101/241810*

Complete list of publications: 59 peer reviewed and published papers, 3 manuscripts under review
https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40445024/?sort=date&direction=descending

D. Additional Information: Research Support

Current Research Support

R01 Grant, National Institutes of Health, NIGMS 9/15/14 – 8/30/18
GM112491-04, Matthias Buck, PI
supplement R01GM112491-02S contribution to upgrade of 600 MHz console, 19F probe
supplement R01GM112491-03S purchase of HPLC
Project Title: "Configurational and internal dynamics of protein-protein complexes"
This project is proposed for continuation as a MIRA grant (GM 131878), pending review.

Completed Research Support

R21 Grant, National Institutes of Health, NEI 1/1/14 – 12/31/15
EY022839, Matthias Buck, PI
Project Title: "Mechanism of Neuropilin and TM inhibitor peptides in AMD"

R01 Grant, National Institutes of Health, NCI,
CA152371 Bing-Cheng Wang (Metrohealth Cleveland), PI, Matthias Buck, Collab. 6/7/10 – 4/30/15
Project Title: "Akt-EphA2 crosstalk in Glioma Invasion"

R01 Grant, National Institutes of Health, NIGMS 9/30/10 – 8/31/14
GM092851, Matthias Buck, PI
Project Title: "Structure - Dynamics relationships in Proteins"

R01 Grant, National Institutes of Health, General Medical Science
GM073071 & -S1/ARRA, Matthias Buck, PI 2/1/05 – 1/31/12
Project Title: "Signaling Biophysics of Protein-GTPase Interactions"

K02 Independent Scientist Award, National Institutes of Health: Heart, Lung and Blood Institute.
HL084384, Matthias Buck, PI 4/6/06 – 3/31/11
Project Title: "Molecular Mechanisms of Plexin Signaling in the Heart and Vascular System"