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 features and structural 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) and protein biophysical tools (fluorescence spectroscopy, ITC, MST, HDX-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 perspectives 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, were on the structure-dynamics relationship in hen lysozyme. 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 ~7 years ago we added the Eph receptor system and recently also worked on Ras GTPase-effector 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 having critical roles at the next level of domain-domain interactions, including protein-membrane interactions. We focus on several protein receptor systems at the domain-domain and domain-membrane interaction level, including Plexin, Neuropilin and Eph receptors. For this proposal we are excited about the recently documented interaction between the SARS-Cov-2 Spike protein and Neuropilin-1. Key questions regarding this interaction need to be urgently answered and the knowledge obtained from our studies will lead to insights which will inform the design of peptides and/or generation of antibodies which block the interaction.

Over the last 18 years, I have actively mentored > 30 undergraduate and graduate students as well as research assistants. My laboratory has especially benefitted from 16 talented postdoctoral fellows over the years. Half of the postdocs were able to support at least part of their research tenure by fellowships from the American Heart Association and NIH F/T32s. Indeed, 7 of the 13 postdocs who have left the lab. found positions in academia as assistant professors or equivalent positions; all (except two) are currently 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 bio-medically focused PhD programs.

B. Positions and Honors

Professional Positions:

Sep.02 – 09	Assistant Professor, Dept. of Physiology & Biophysics, School of Medicine, CWRU
Jul. 09 – 14	then Associate Prof., Case Western Reserve University (SOM-CWRU), Cleveland, OH
Apr.05 - present	Assistant/Associate/ then Professor, Department of Neuroscience, SOM-CWRU
Apr.05 - present	Member, Case/NCI Comprehensive Cancer Center, Cleveland, OH
Jul.06 – present	Assistant/Associate/ then Professor, Department of Pharmacology, SOM-CWRU
Jul.09 – 18	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, SOM-CWRU, Cleveland, OH
Mar.17- Nov.17	Sabbatical at Seoul National University, Department of Chemistry
Jul. 18 – present	Director of North Eastern Ohio High Field NMR facility @Cleveland Center for Structural and Membrane Biology

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-C Jun.'15; MSF-B Oct.'16, 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, Mar.'19, Oct.'20

C. Contributions to Science

My contributions to Science have been in several fields, which are listed here semi-chronologically. Currently, I am not equally active in all these fields, but it is likely that specific techniques will be used in the overall problem-oriented approach for the most active [sections 3-5 below].

1. Throughout my career I have an interest in the global and internal dynamics of proteins/protein domains. My earliest studies as a graduate student and second postdoctoral fellow employed **amide hydrogen exchange, HDX**, 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) [1A]. Then, later I applied HDX 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 [2B]. While 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 (in preparation). I have also examined

internal protein dynamics using **NMR relaxation measurements** and simulations, with the goal of establishing the structural determinants of protein dynamics [1B,1C]. Studies of partially states of proteins, including my work on lysozyme, were summarized is a review in Q.Rev.Biophysics [1D], cited over 900 times.

1A. 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.***

1B. 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.***

*1C. Buck, M. & Karplus, M. (**1999**) "Internal and overall peptide group motion in proteins. Molecular simulations for lysozyme compared with x-ray and NMR spectroscopy"* ***J.Am.Chem.Soc. 121, 9645-9658.***

1D. Buck, M. ***(1998)*** *"Trifluoroethanol & Colleagues: Cosolvents come of age. Recent studies with peptides and proteins."* ***Quarterly Reviews of Biophysics 31, 297-355.***

2. Having established my independent lab. at Case Western Reserve University in 2002. I continued a theme of dynamics, both at the level of domain stability [2A] and motion [2B] as well as at the level of the internal motions [2C] and how they describe allosteric networks [2D].

2A. 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]

2B. Bouguet-Bonnet, S. & Buck, M **(2008)** "Compensatory and long-range changes in ps-ns mainchain dynamics upon complex formation. 15N relaxation analysis of the free and bound states of the ubiquitin-like domain of human plexin-B1 and the small GTPase Rac1" ***J.Mol.Biol.*** **377, 1474-1487. [**

2C. Bagheri-Hamaneh, M., Zhang, L. & Buck, M. **(2011)** "A Direct Coupling between Global and Internal Motions in a Single Domain Protein? MD Investigation of Extreme Scenarios" ***Biophys. J. 101, 196-204.***

2D. Zerbetto, M., Anderson, R., Bouguet-Bonnet, S., Rech, M., Zhang, L., Meirovitch, E., Polimeno, A., & Buck, M **(2013)** "Analysis of 15-N,1-H NMR Relaxation in Proteins by a Combined Experimental and Molecular Dynamics Simulation Approach: Picosecond-nanosecond Dynamics of the Rho GTPase Binding Domain of Plexin-B1 in the Dimeric State Indicates Allosteric Pathways" ***J. Phys. Chem. B.*** **117, 174-84.**

3. Configurational states of small GTPases, including at the membrane. (Thermo-)dynamic changes that GTPases cause in effector proteins are at the heart of their molecular signaling mechanism. 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], 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 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 PMC6178820]* *{ 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 PMC5832993]

3D. Cao, S., Chung, S., Kim, SJ., Li, Z., Manor, D.*, & Buck, M.* **(2019) "***K-Ras binding with signaling lipid phosphoinositides: PIP2 association, orientation, function."* ***J. Biol. Chem. 294, 7068-7084*** *[PCMID PMC6497929*]

*3E. Li, Z. & Buck, M. (**2020**) "Computational Design of Myristoylated Cell Penetrating Peptides Targeting Oncogenic K-Ras.G12D at the Effector Binding Membrane Interface". **J. Chem. Inf. Model 60, 306-315***

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 until 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: PMC5990419]

4E. Li, Z., Muller-Greven, J., Kim, S-J, & Buck, M. **(2020)** "*Plexin-B1 GAP function is regulated in solution by a new inhibitory loop: Evidence for allostery in the receptor's signaling mechanisms involving the juxtamembrane domain". **Cell. & Mol. Life Sciences** online* doi: 10.1007/s00018-020-03571-2

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 very 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 or coarse grained molecular dynamics simulations [5B, 5D]. Ongoing and planned work seeks to explain the role of disease associated mutations as well as of posttranslational modifications in the intracellular domains in Eph cell signaling. Another pilot study (supported to CWRU internal funds) examines the tramsmembrane and membrane proximal region of Eph receptors. 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, which we aim to rationalize by experiments and simulations proposed for the grant renewal. Characterization of the intracellular cell signaling mechanism at the molecular level will inform new avenues for eventual 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 PMC4776036]

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. ***(2019)*** "Modified Potential Functions Result in Enhanced Predictions of a Protein Complex by All-Atom MD Simulations, Confirming a Step-wise Association Process for Native PPIs*." **BioRxiv [Preprint]** Feb. 25. Available from DOI:10.1101/241810;* ***J.Chem.Theory.Comp 15, 4318-4331.***

Complete list of publications: 70+ peer reviewed and published papers, 3 manuscripts under review
https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40445024/?sort=date&direction=descending

H-index of 30 with 4550+ citations as of 10/20 on google-scholar

D. Research Support

Current Support

R01 Grant: National Institutes of Health, NEI, R01EY029169 9/23/18 – 8/31/22
Matthias Buck, PI, Adam Smith (Univ. of Akron), Suzanne Paradis (Brandeis), coPIs
Project Title: "Plexin & Neuropilin in and at the membrane"

R21 Grant, National Institutes of Health, NIA R21AG069268 8/15/20 – 8/31/22
Matthias Buck, PI
Project Title: "Hyper phosphorylation and the plexin CRMP scaffold in Alzheimer's Disease"

R01 Grant: National Institutes of Health, NIGMS, R01GM121583
Rajesh Ramachandran, PI; Matthias Buck, Co-PI (small subcontract, PI salary only) 9/18/17 – 8/31/22
Project Title: "Mechanisms of Dynamin-Related Protein 1-Mediated Mitochondrial Fission"

R21 **Grant: National Institutes of Health, NINDS,** R21NS115071
Rajesh Ramachandran, PI; Matthias Buck, Co-PI (small subcontract, 1st. yr only) 7/1/20 – 6/30/22
Project Title: "Conformational Dynamics of the Dynamin Ph Domain in Synaptic Vesicle Endocytosis"

Recently Completed Support

R01 Grant, National Institutes of Health, NIGMS (Grant to be renewed) 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"

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"