BIOGRAPHICAL SKETCH

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NAME: Peter John Mohler, Ph.D.

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

POSITION TITLE: Professor, Departments of Internal Medicine and Physiology & Cell Biology

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
Wake Forest University	BS	05/1995	Biology/Biochemistry
University of North Carolina at Chapel Hill	PhD	08/2000	Cell & Molecular Biology
Howard Hughes Medical Institute/Duke University Medical Center	Postdoctoral Fellow	08/2004	Physiology/biochemistry

A. Personal Statement

Our research program is focused on the mechanisms underlying the targeting and regulation of membrane-associated (ion channels, transporters, receptors) and signaling proteins in cardiac and other excitable cells. In particular, we are interested in the role of membrane-associated ankyrin and spectrin family of polypeptides in the targeting and function of ion channels and transporters as well as kinases and phosphatases. A primary focus of the lab establishes that loss-of-function mutation in ankyrin-B (AnkB) gene (*ANK2*) is the basis for a human cardiac arrhythmia syndrome associated with polymorphic tachyarrhythmia in response to stress and/or exercise. Additionally, our work revealed that reduction of AnkB in mice results in reduced levels and abnormal localization of Na/Ca exchanger, Na/K ATPase, and PP2A at T-tubule/SR sites in cardiomyocytes and leads to altered Ca2+ signaling and extrasystoles that provide a rationale for the arrhythmia. These studies establish a physiological requirement for ankyrins and spectrins in localization of a variety of ion channels in excitable membranes in the heart and demonstrate a new class of functional 'channelopathies' due to abnormal cellular localization of functionally-related ion channels and transporters. A second line of work is the role of the ankyrin-G (AnkG)-based pathway for targeting voltage gated sodium channels to the intercalated disc of cardiomyocytes. We have discovered a direct requirement of AnkG for Na channel targeting and have linked human Na channel arrhythmia mutations with loss of AnkG binding, and Na channel targeting resulting in defects in Na channel function and myocyte excitability.

B. Positions and Honors

Positions

10/04-06/06 Assistant Professor of Pathology, Vanderbilt University Medical Center
06/06-6/08 Assistant Professor, Dept of Medicine, University of Iowa College of Medicine, Iowa City, Iowa
12/06-6/08 Asst Prof, Dept Molecular Physiology & Biophysics, Univ Iowa College of Med, Iowa City, Iowa
07/08-1/11 Associate Prof (with tenure), Depts of Medicine and Mole Phys and Biophysics; Univ of Iowa
02/11-pres Professor and Director, Davis Heart & Lung Research Institute, The Ohio State University
01/14-pres Chair, Department of Physiology & Cell Biology, The Ohio State University College of Medicine

Honors, Other Experience, and Professional Memberships

2006 Session co-chair, NHLBI; Recognition and Treatment of Inherited Arrhythmias
2007 *Ad-Hoc* member, NIH ESTA Study Section, Bethesda, MD
2007-11 Pew Scholar, Pew Charitable Trusts
2008- Editorial Board, *Journal of Molecular and Cellular Cardiology*

2008 Member, American Heart Association, National Peer Review Committee, Electrophysiology
2008- Review Council, Austrian Science Foundation, START Program, Vienna, Austria
2008- Member, American Heart Association Review Committee for Innovative Research
10/09-10/13 Member, NIH ESTA Study Section, Bethesda, MD
2009- Review Councils: The Wellcome Trust, London, UK; March of Dimes Foundation; White Plains, NY; Italian Telethon Foundation; Association Française contre les Myopathies; British Heart Foundation; Italian Ministry of Health, UK Medical Research Council
2009-11 Kavli Fellow of National Academy of Sciences
2010- Editorial Board, *Circulation Research*
2011-2015 Editorial Board, *Heart Rhythm*
2012- Editorial Board, *Journal of Clinical Investigation*
2012- Editorial Board, *Journal of Cardiovascular Electrophysiology*
2012-2016 Established Investigator, American Heart Association
2013-2015 Chair, AHA National Review Panel, Basic Electrophysiology
2016- Editorial Board, *Journal of Biological Chemistry*
2016-2020 Member, NHLBI Program Project Grant Review Committee (HLBP)

C. Contribution to Science

Over the past decade, our laboratory has focused on defining new mechanisms underlying excitable cell disease. To date, our program has > 180 publications (http://www.ncbi.nlm.nih.gov/pubmed/?term=mohler+pj). High impact publications in five areas of focus related to this proposal are noted below:

1. Defining novel pathways for human ventricular arrhythmia.
Our work with colleagues throughout the world has defined new pathways for human ventricular arrhythmias based on defects in ion channel and transporter trafficking/targeting. These findings represent some of the first discoveries that implicated non-ion channel proteins in human ventricular arrhythmia. These findings have identified molecules including ankyrin-B, ankyrin-G, and betaII spectrin as new targets for human disease.

a. **Mohler PJ**, Schott JJ, Gramolini AO, Dilly KW, Guatimosim S, DuBell WH, Song LS, Haurogne K, Kyndt F, Ali ME, Rogers TB, Lederer WJ, Escande D, LeMarec H, Bennett V. Ankyrin-B mutation causes type 4 long-QT cardiac arrhythmia and sudden cardiac death. *Nature*, 421:634-639, 2003. PubMed PMID: 12571597.
b. **Mohler PJ**, Rivolta I, Napolitano C, LeMaillet G, Lambert S, Priori SG, Bennett V. Nav1.5 E1053K mutation causing Brugada Syndrome blocks binding to ankyrin-G and expression of Nav1.5 on the surface of cardiomyocytes. *Proc Natl Acad Sci., USA*, 101:17533-17538, 2004. PubMed PMID: 15579534; PubMed Central PMCID: PMC536011.
c. Lowe JS, Palygin O, Bhasin N, Hund TJ, Boyden PA, Shibata E, Anderson ME, **Mohler PJ**. Voltage-gated Nav channel targeting in heart requires an ankyrin-G-dependent cellular pathway. *Journal of Cell Biology*, 180:173-186, 2008. PubMed PMID: 18180363; PubMed Central PMCID: PMC2213608.
d. SA Smith, AC Sturm, J Curran, CF Kline, SC Little, IM Bonilla, VP Long, M Makara, I Polina, LD Hughes, TR Webb, Z Wei, P Wright, N Voigt, D Bhakta, KG Spoonamore, C Zhang, R Weiss, PF Binkley, PM Janssen, A Kilic, RS Higgins, M Sun, J Ma, D Dobrev, M Zhang, CA Carnes, M Vatta, MN Rasband, TJ Hund, **PJ Mohler**. Dysfunction in the betaII spectrin-dependent Cytoskeleton Underlies Human Arrhythmia. *Circulation*, 131: 928-938. 2015. PMID:2563204; PMCID: PMC4342332.

2. Discovering new pathways for regulation of cardiac Nav1.5 and INa.
Our group has extensive published experience in cardiac voltage gated Nav channel regulation. We have identified novel forms of cardiac arrhythmia directly linked with Nav channel dysfunction as well as solved new pathways for Nav channel regulation in both health and disease.

a. Glynn P, Musa H, Wu X, Unudurthi SD, Little S, Qian L, Wright PJ, Radwanski PB, Gyorke S, **Mohler PJ**, and Hund TJ. Voltage-gated sodium channel phosphorylation at Ser571 regulates late current, arrhythmia, and cardiac function in vivo. *Circulation*. 2015. PMID:26187182; PMCID:PMC4543581.
b. MA Makara, J Curran, SC Little, H Musa, I Polina, SA Smith, PJ Wright, SD Unudurthi, J Snyder, V Bennett, TJ Hund and **PJ Mohler**. Ankyrin-G coordinates intercalated disc signaling platform to regulate cardiac excitability in vivo. *Circulation Research*. 115:929-938; 2014. PubMed PMID: 25239140; PubMed Central PMCID: PMC4224970.

c. H Musa, CF Kline, AC Sturm, N Murphy, S Adelman, C Wang, H Yan, B Johnson, TA Csepe, A Kilic, RSD Higgins, PML Janssen, V Fedorov, R Weiss, C Salazar, TJ Hund, GS Pitt, and **PJ Mohler**. *SCN5A* variant that blocks Fibroblast Growth Factor Homologous Factor regulation causes human arrhythmia. *Proc Natl Acad Sci U S A*. 2015. PMID:26392562; PMCID: PMC4603502.

d. OM Koval, JS Snyder, RM Wolfe, RE Pavlovicz, P Glynn, J Curran, ND Leymaster, W Dun, PJ Wright, N Cardona, L Qian, C Mitchell, PA Boyden, PF Binkley, C Li, ME Anderson, **PJ Mohler**, TJ Hund. CaMKII-based regulation of voltage-gated Na^+ channel in cardiac disease; *Circulation*, 126 (17) 2084-94; 2012. PubMed PMID: 23008441; PubMed Central PMCID: PMC3811023.

3. Defining new mechanisms underlying regulation of cardiac membrane proteins.

A focus of our laboratory is to identify new pathways that govern membrane protein trafficking in heart. Our work has defined critical unknown cardiac pathways that regulate excitability including the family of endosomal EHD proteins. We are interested in the modulation of these pathways to regulate excitability and remodeling in disease. We have new data that these pathways may regulate ion channel trafficking as well as gating.

a. H Gudmundsson, TJ Hund, PJ Wright, CF Kline, JS Snyder, L Qian, OM Koval, SR Cunha, M George, MA Rainey, FE Kashef, W Dun, PA Boyden, ME Anderson, H Band, and **PJ Mohler**, EH domain proteins regulate cardiac membrane protein targeting. *Circulation Research*, 107 (1): 84-95. 2010. PubMed PMID: 20489164; PubMed Central PMCID: PMC2901408.

b. J Curran, MA Makara, SC Little, H Musa, B Liu, X Wu, I Polina, J Alecusan, P Wright, J Li, GE Billman, PA Boyden, S Gyorke, H Band, TJ Hund, **PJ Mohler.** EHD3-dependent endosome pathway regulates cardiac membrane excitability and physiology. *Circulation Research*. 115: 68-78; 2014. PubMed PMID: 24759929; PubMed Central PMCID: PMC4065849.

c. CF Kline, HT Kurata, TJ Hund, SR Cunha, OM Koval, PJ Wright, M Christensen, ME Anderson, CG Nichols, and **PJ Mohler**. Dual role of K_{ATP} channel C-terminal motif in membrane targeting and metabolic regulation. *Proc Natl Acad Sci., USA.* 106: 1669-74, 2009. PubMed PMID: 19805355; PubMed Central PMCID: PMC2757796.

d. H Gudmundsson, J Curran, F Kashef, JS Snyder, SA Smith, P Vargas-Pinto, IM Bonilla, RM Weiss, ME Anderson, P Binkley, RB Felder, CA Carnes, H Band, TJ Hund, and **PJ Mohler**. Differential Regulation of EHD3 in Human and Mammalian Heart Failure. *Journal of Molecular and Cellular Cardiology*. 52: 1183-1190. 2012. PubMed PMID: 22406195; PubMed Central PMCID: PMC3360944.

4. Identification of pathways for regulation of cardiac adrenergic signaling in arrhythmia.

Relevant for this proposal, a major focus of our laboratory is to understand the impact of altered kinase/phosphatase signaling in cardiac arrhythmia. We are particularly interested in the impact of altered CaMKII/PP2A axis in arrhythmia, both related to altered ion channel/transporter function, as well as the impact on cytoskeletal and other signaling molecules.

a. SC Little, J Curran, MA Makara, H Ho, Z Xu, CF Kline, X Wu, I Polina, H Musa, AM Meadows, CA Carnes, BJ Biesiadecki, JP Davis, N Weisleder, S Györke, XH Wehrens, TJ Hund, **PJ Mohler**. Protein Phosphatase 2A Regulatory Subunit B56α is an Inhibitor of Cardiac Phosphatase Signaling. *Science Signaling*; 8(386)ra72; 2015. PubMed PMID: 26198358; PubMed PMCID: PMC4680974.

b. TJ Hund, OM Koval, J Li, PJ Wright, L Qian, JS Snyder, H Gudmundsson, CF Kline, NP Davidson, N Cardona, MN Rasband, ME Anderson, and **PJ Mohler**. A beta 4 spectrin/ CaMKII signaling complex is essential for vertebrate membrane excitability in mice. *Journal of Clinical Investigation*. 120:3508-19, 2010. PubMed PMID: 20877009; PubMed Central PMCID: PMC2947241.

c. Erickson JR, Joiner MA, Guan X, Kutschke W, Yang J, Oddis CV, Bartlett RK, Lowe JS**,** Aykin-Burns N, Zimmerman MC, Spitz DR, Colbran RJ, Shea MA, **Mohler PJ**, Anderson ME. A dynamic pathway for calcium-independent activation of CaMKII by methionine oxidation. *Cell;* 133:462-474. 2008. PubMed PMID: 18455987; PubMed Central PMCID: PMC2435269.

d. Bhasin N, Cunha SR, Mudannayake M, Gigena MS, Rogers TB, **Mohler PJ**. Molecular basis for PP2A regulatory subunit B56 alpha targeting in cardiomyocytes. *American Journal of Physiology: Heart,* 293:H109-119; 2007. PubMed PMID: 17416611.

5. Defining new mechanisms for atrial arrhythmias and atrial myocyte regulation.

Our group has significant experience in investigating atrial arrhythmias including atrial fibrillation and sinus node dysfunction. We have not only identified new mechanisms for human sinus node disease and atrial fibrillation, our group has developed primary cell models of these diseases (human, canine, mouse) to

elucidate the signaling pathways directly linked to these diseases. Importantly, this work has progressed to development of new techniques and platforms to directly study human AF in human hearts (note last publication).

a. Le Scouarnec S, Bhasin N, Vieyres C, Hund TJ, Cunha SR, Koval O, Marionneau C, Chen B, Wu Y, Demolombe S, Song LS, Le Marec H, Probst V, Schott JJ, Anderson ME, and **Mohler PJ**. Dysfunction in ankyrin-B-dependent ion channel and transporter targeting causes human sinus node disease. *Proc Natl Acad Sci., USA.* 105:15617-15622, 2008. PubMed PMID: 18832177; PubMed Central PMCID: PMC2563133.

b. SR Cunha, TJ Hund, S Hashemi, N Voigt, N Li, P Wright, O Koval, J Li, H Gudmundsson, RJ. Gumina, M Karck, JJ Schott, V Probst, H Le Marec, ME Anderson, D Dobrev, XHT Wehrens, **PJ Mohler**. Defects in ankyrin-based membrane protein targeting pathways underlie atrial fibrillation. *Circulation*. 124: 1212-1224. 2011. PubMed PMID: 21859974; PubMed Central PMCID: PMC3211046.

c. Y Wu, Z Gao, B Chen, OM Koval, MV Singh, X Guan, TJ Hund, WJ Kutschke, S Sarma, IM Grumbach, XHT Wehrens, **PJ Mohler**, LS Song, ME Anderson. Calmodulin kinase II is required for fight or flight sinoatrial node physiology. *Proc Natl Acad Sci., USA.* 106: 5972-5977; 2009. PubMed PMID: 19276108; PubMed Central PMCID: PMC2667018.

d. BJ Hansen, J Zhao, TA Csepe, B Moore, N Li, LA Jayne, A Kalyanasundaram, PH Nguyen, P Lim, A Bratasz, K A. Powell, O Simonetti, RSD Higgins, A Kilic, **PJ Mohler**, PML. Janssen, R Weiss, JD Hummel, VV Fedorov. Atrial Fibrillation Driven by Microanatomic Intramural Reentry Revealed by Simultaneous Sub-Epicardial and Sub-Endocardial Optical Mapping in Explanted Human Hearts. *European Heart Journal*. 36:2390-401. PMID: 26059724; PMCID: 4568403.

D. Research Support

R01 HL083422 (PI: Mohler) 12/20/2005-6/30/2020 2.76 calendar
NIH/NHLBI
Role of spectrin/ankyrin-G complex in myocyte signaling and cardiac excitability
The goals of this project are to define the role of the cytoskeletal adaptors beta spectrin and ankyrin-G in myocyte structural and electrical activity. The project will use Nav1.5 activity as a surrogate for ankyrin-G and spectrin function in vitro and in vivo.

R01 HL084583 (PI: Mohler) 09/01/2006-06/30/2016 3.36 calendar
NIH/NHLBI NCE
Role of ankyrin-B in human arrhythmia
The goal of this proposal is to define the role of ankyrin-B in ventricular arrhythmia.

R01HL114383 (PI: Mohler) 08/01/2013-05/31/2017 2.40 calendar
NIH/NHLBI
EHD proteins in cardiac membrane protein targeting and remodeling
This study will provide insight on key upstream and downstream roles of EHD proteins in diverse excitable myocytes at baseline and in cardiovascular disease using a host of animal models.

U54HL119810 (PI: Geoffrey) 09/26/2013-07/31/2020 0.30 calendar
Cleveland Clinic (Prime: NIH)
Cleveland Clinic Center for Accelerator
The goal of this project is to accelerate the advancement of NHLBI-related research discoveries and innovations into improvements in human health and educating researchers to be full partners in this translation process.