# BIOGRAPHICAL SKETCH

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NAME: Schisler, Jonathan

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

POSITION TITLE: Assistant Professor (Tenure track)

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) | END DATE MM/YYYY | FIELD OF STUDY |
|---|---|---|---|
| The University of Toledo, Toledo, OH | BS | 06/1997 | Biology |
| The University of Toledo, Toledo, OH | MS | 06/2000 | Bioengineering |
| Univ. of Texas Southwestern Medical Center, Dallas, TX | PHD | 05/2006 | Biological Chemistry |
| The University of North Carolina at Chapel Hill | Postdoctoral Fellow | 12/2010 | Cardiovascular |

## A. Personal Statement

My research ethos focuses on uncovering cellular protection mechanisms, emphasizing protein quality control and cellular metabolism—essential processes for mitochondrial function and cellular resilience. For over twenty years, I have advanced our understanding of these mechanisms in chronic diseases, including mitochondrial disorders, neurodegenerative diseases, heart failure, and post-viral syndromes. My approach combines complex genomic and biological data, utilizing advanced bioinformatics and computational modeling to turn multi-omic datasets into practical insights. **As a leader in team science**, I have built international and interdisciplinary collaborations that foster innovation, demonstrated by my discovery of SCAR16, a genetic disorder related to a key protein quality control enzyme, and my identification of a cardioprotective factor associated with spaceflight adaptations. These efforts showcase my expertise in connecting basic science with translational applications, positioning me as a key contributor to both my laboratory and the broader scientific community.

Recent successes from my lab highlight our commitment to impactful research. Our latest *EMBO Journal* publication describes the mechanisms, gene therapy, and pharmacological strategies for SCAR16, showing how we turn fundamental discoveries into therapeutic possibilities. This work showcases the collaborative strength and innovative spirit of my lab. Additionally, our R01 grant application to the National Institute on Aging (NIA), scored in the 9th percentile (with a funding line at 17%), focuses on new pharmacology and biochemistry related to Alzheimer's disease. This strong, fundable proposal builds on our expertise in protein quality control and aims to find new treatment options for neurodegeneration. These accomplishments not only raise our lab's profile but also reinforce my dedication to solving urgent health issues through rigorous science.

My contributions to the Pharmacology, the McAllister Heart Institute (MHI), and the School of Medicine (SOM) teaching are a cornerstone of my service at UNC-CH. For eight years, I have taught PHCO 732, a grant writing course that equips students with essential skills for securing research funding and advancing their careers. I have also served as a first-year group leader for BBSP 902 for three years, guiding students through their initial research experiences and fostering their growth as scientists. Beyond the classroom, I secured the AHA International Visiting Professor grant to host Brazilian faculty, sharing our expertise in cardiac surgical models and promoting global scientific exchange. Additionally, I have received two UNC Global Partnership awards, fostering collaborations between the McAllister Heart Institute (MHI), the Department of Pharmacology (PHCO), and the University of Tübingen. My ongoing work with Otsuka in Japan has resulted in the launch of a nutraceutical antioxidant to reduce metabolic distress during long-term spaceflight, demonstrating the practical applications and international reach of my research.

Mentorship and expanding access to STEM are central to my mission. I have led two summer research programs in cardiovascular and neuroscience fields, giving underrepresented undergraduates hands-on research, mentoring, and career development opportunities to inspire careers in STEM. Building on this foundation, I am launching and leading the PRISM (Postbaccalaureate Research Initiative in Science and Medicine) program at UNC-CH. This initiative provides recent college graduates with intensive research

training, preparing them for graduate studies and biomedical careers. These programs demonstrate my dedication to cultivating a diverse, capable next generation of scientists, aligning with UNC's mission and strengthening our department's legacy of excellence.

**Ongoing projects that I would like to highlight:**

R01 HL169273 National Heart Lung and Blood Institute Ranek (PI)/Role: Co-I

09/01/23-08/31/28 *CHIP phosphorylation stimulates the degradation of mutant transthyretin to attenuate cardiac amyloidosis*

The research aims to evaluate the effectiveness of PKG stimulation and CHIP functionality in degrading transthyretin, both in vitro and in vivo, and to investigate the correlation between reduced PKG/CHIP activity and myofilament dysfunction in human amyloid cardiomyopathy.

R01 AG066710 National Institute on Aging Schisler (PI)

04/15/20-03/31/26 Protein Quality Control in Age-Related Diseases

The major goal of this project is to use novel cell systems in combination with our preclinical models to test genetic and small molecules that inhibit Receptor Interacting Protein Kinase 1 and 3 as therapies for spinocerebellar ataxia autosomal recessive 16 (SCAR16). In doing so, we will establish a new framework to better understand accelerated aging related to CHIP biology that, in turn, will allow us to develop precision medicine approaches to alleviate degeneration caused by the SCAR16.

**Selected Publications (out of 92 publications, of which 15 as first author and 17 as senior author)**


1. Hao X, Hu Z, Li M, Zhang S, Tang M, Hao C, Qi S, Liang Y, Almeida MF, Smith K, Zuo C, Feng Y, Guo M, Ma D, Li S, Wang Z, Sun Y, Deng Z, Mao C, Xia Z, Jiang Y, Gao Y, Xu Y, **†Schisler JC**, Shi C. E3 Ubiquitin Ligase CHIP Facilitates cAMP and cGMP Signalling Cross-talk by Polyubiquitinating PDE9A. EMBO. 2025 Feb;44(4):1249-1273. doi: 10.1038/s44318-024-00351-7.
2. da Silveira WA, Fazelinia H, Rosenthal SB, Laiakis EC, Kim MS, Meydan C, Kidane Y, Rathi KS, Smith SM, Stear B, Ying Y, Zhang Y, Foox J, Zanello S, Crucian B, Wang D, Nugent A, Costa HA, Zwart SR, Schrepfer S, Elworth RAL, Sapoval N, Treangen T, MacKay M, Gokhale NS, Horner SM, Singh LN, Wallace DC, Willey JS, †**Schisler JC**, Meller R, McDonald JT, Fisch KM, Hardiman G, Taylor D, Mason CE, Costes SV, Beheshti A. Comprehensive Multi-omics Analysis Reveals Mitochondrial Stress as a Central Biological Hub for Spaceflight Impact. Cell. 2020 Nov 25;183(5):1185-1201.e20. PubMed Central PMCID: PMC7870178.
3. Madrigal SC, McNeil Z, Sanchez-Hodge R, Shi CH, Patterson C, Scaglione KM, **Schisler JC**. Changes in protein function underlie the disease spectrum in patients with CHIP mutations. J Biol Chem. 2019 Dec 13;294(50):19236-19245. PubMed Central PMCID: PMC6916485.
4. Shi CH, Rubel C, Soss SE, Sanchez-Hodge R, Zhang S, Madrigal SC, Ravi S, McDonough H, Page RC, Chazin WJ, Patterson C, Mao CY, Willis MS, Luo HY, Li YS, Stevens DA, Tang MB, Du P, Wang YH, Hu ZW, Xu YM, **Schisler JC**. Disrupted structure and aberrant function of CHIP mediates the loss of motor and cognitive function in preclinical models of SCAR16. PLoS Genet. 2018 Sep;14(9):e1007664. PubMed Central PMCID: PMC6160236.


## B. Positions, Scientific Appointments and Honors

## Positions and Scientific Appointments

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|---|---|
| 2025 - | Faculty Director, PRISM (Postbaccalaureate Research Initiative in Science and Medicine) |
| 2020 - | Faculty Director, Cardiovascular Physiology and Phenotyping Core |
| 2020 - | Assistant Professor (Tenure track), McAllister Heart Institute, Department of Pharmacology, Department of Pathology and Lab Medicine, The University of North Carolina at Chapel Hill, Chapel Hill, NC |
| 2016 - 2020 | Assistant Professor (Research track), Department of Pathology and Lab Medicine, The University of North Carolina at Chapel Hill, Chapel Hill, NC |
| 2014 - 2020 | Assistant Professor (Research track), McAllister Heart Institute, Department of Pharmacology, The University of North Carolina at Chapel Hill, Chapel Hill, NC |
| 2011 - 2014 | Research Instructor, Department of Medicine, The University of North Carolina at Chapel Hill, Chapel Hill, NC |

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|---|---|
| 2006 - 2010 | Postdoctoral Fellow (Advisor: Cam Patterson, M.D.), Carolina Cardiovascular Biology Center, The University of North Carolina at Chapel Hill, Chapel Hill, NC |
| 2000 - 2005 | Pre-doctoral research fellow (Advisor: Chris Newgard, Ph.D.) Biological Chemistry, The University of Texas Southwestern Medical Center at Dallas, Dallas, TX |
| 1998 - 2000 | Graduate teaching assistant (Advisor: Patricia Relue, Ph.D) Bioengineering, The University of Toledo, Toledo, OH |
| 1997 - 1998 | Post-baccalaureate research fellow (Advisor: Levy Ulanovsky, Ph.D.) DNA Sequencing Technology, Argonne National Laboratory, US Department of Energy, Lemont, IL |
| 1996 - 1997 | Undergraduate honors research student (Advisor: Scott Lesiner, Ph.D) Plant Biology, The University of Toledo, Toledo, OH |

## Honors

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|---|---|
| 2024 | STAR Mentor Award, UNC-CH Office of Graduate Education |
| 2023 | 2023 Faculty Mentoring Award Nominee, UNC-CH Women's Leadership Council |
| 2020 | NASA Spaceflight Technologies, Application, and Research Program Selection |
| 2018 | McAllister Heart Institute Junior Investigator Award, UNC Chapel Hill |
| 2017 | Outstanding Encouragement of Learning & Development Finalist, UNC at Chapel Hill |
| 2017 | McAllister Heart Institute Junior Investigator Award, UNC Chapel Hill |
| 2016 | Conference Presentation Travel Award, UNC Center for Global Initiatives |
| 2009 | Early Investigator Career Award, Society for Heart and Vascular Metabolism |
| 2008 | Postdoctoral Fellowship Award, American Heart Association |
| 2006 | Symposia scholarship, Keystone Symposia |
| 2004 | Scholarship award, Beta Cell Biology Consortium |
| 2003 | Symposia scholarship, Keystone Symposia |
| 2000 | Graduate School Organization poster session winner, UT Southwestern Medical Center |
| 1997 | Honors in Biology, Cum Laude Graduate with Honors, The University of Toledo |
| 1997 | Undergraduate Research Fellowship, Argonne National Laboratory |

## C. Contribution to Science

1. **Pioneering Beta Cell Biology Research:** As a graduate student, my research was at the forefront of beta cell biology, focusing on unraveling the mechanisms governing beta cell proliferation and glucose-stimulated insulin secretion. At the time, the scientific community lacked genetic and biochemical strategies to augment beta cell mass without compromising their essential functions. My approach centered on transcription factors and their downstream targets, leveraging them as therapeutic agents to increase functional beta cell mass ex vivo. This advancement holds potential for islet transplantation therapies. Under the guidance of my Ph.D. mentor, Dr. Chris Newgard, I developed techniques and methodologies that have since become staples in islet biology research. Dr. Newgard's ongoing work in his laboratory continues to build on these foundations. The insights gained from these studies fueled my fascination with novel protein functions and their application to human diseases, setting the stage for my subsequent research endeavors.
    a. Bain JR, ***Schisler JC**, Takeuchi K, Newgard CB, Becker TC. An adenovirus vector for efficient RNA interference-mediated suppression of target genes in insulinoma cells and pancreatic islets of langerhans. Diabetes. 2004 Sep;53(9):2190-4. PubMed PMID: 15331526.
    b. **Schisler JC**, Jensen PB, Taylor DG, Becker TC, Knop FK, Takekawa S, German M, Weir GC, Lu D, Mirmira RG, Newgard CB. The Nkx6.1 homeodomain transcription factor suppresses glucagon expression and regulates glucose-stimulated insulin secretion in islet beta cells. Proc Natl Acad Sci U S A. 2005 May 17;102(20):7297-302. PubMed Central PMCID: PMC1091752.
    c. **Schisler JC**, Fueger PT, Babu DA, Hohmeier HE, Tessem JS, Lu D, Becker TC, Naziruddin B, Levy M, Mirmira RG, Newgard CB. Stimulation of human and rat islet beta-cell proliferation with retention of function by the homeodomain transcription factor Nkx6.1. Mol Cell Biol. 2008 May;28(10):3465-76. PubMed Central PMCID: PMC2423154.

d. Stephens SB, **Schisler JC**, Hohmeier HE, An J, Sun AY, Pitt GS, Newgard CB. A VGF-derived peptide attenuates development of type 2 diabetes via enhancement of islet β-cell survival and function. Cell Metab. 2012 Jul 3;16(1):33-43. PubMed Central PMCID: PMC3695697.

2. **Advancing Cellular Regulatory Mechanisms:** My foundational work on beta cell proliferation and transcriptional regulation naturally evolved into a fascination with post-translational regulatory mechanisms. Central to this exploration are E3 ligases—enzymes that orchestrate substrate protein modification through ubiquitination. This process involves the attachment of ubiquitin, which modulates protein function or triggers degradation. My initial foray into this domain centered on the E3 ligases CHIP and MuRF1 and their roles in cardiovascular health. A landmark discovery in 2013 was the identification of the first human mutation in CHIP, leading to a multi-organ degenerative disease now classified as spinocerebellar ataxia autosomal recessive 16 (SCAR16), and subsequently, a dominant form known as SCA48. Ongoing research endeavors strive to pinpoint molecular substrates of CHIP across diverse biological systems, encompassing the heart and brain. The synthesis of protein quality control pathways, deemed crucial in cardiovascular and neuroendocrine systems, showcases the progressive nature of my research program, underscoring its unique contribution to the scientific community.
   a. Umano A, Fang K, Qu Z, Scaglione JB, Altinok S, Treadway CJ, Wick ET, Paulakonis E, Karunanayake C, Chou S, Bardakjian TM, Gonzalez-Alegre P, Page RC, **Schisler JC**, Brown NG, Yan D, Scaglione KM. The molecular basis of spinocerebellar ataxia type 48 caused by a de novo mutation in the ubiquitin ligase CHIP. J Biol Chem. 2022 May;298(5):101899. PubMed Central PMCID: PMC9097460.
   b. Apriamashvili G, Vredevoogd DW, Krijgsman O, Bleijerveld OB, Ligtenberg MA, de Bruijn B, Boshuizen J, Traets JJH, D'Empaire Altimari D, van Vliet A, Lin CP, Visser NL, Londino JD, Sanchez-Hodge R, Oswalt LE, Altinok S, **Schisler JC**, Altelaar M, Peeper DS. Ubiquitin ligase STUB1 destabilizes IFNγ-receptor complex to suppress tumor IFNγ signaling. Nat Commun. 2022 Apr 8;13(1):1923. PubMed Central PMCID: PMC8993893.
   c. Ranek MJ, Oeing C, Sanchez-Hodge R, Kokkonen-Simon KM, Dillard D, Aslam MI, Rainer PP, Mishra S, Dunkerly-Eyring B, Holewinski RJ, Virus C, Zhang H, Mannion MM, Agrawal V, Hahn V, Lee DI, Sasaki M, Van Eyk JE, Willis MS, Page RC, **Schisler JC**, Kass DA. CHIP phosphorylation by protein kinase G enhances protein quality control and attenuates cardiac ischemic injury. Nat Commun. 2020 Oct 20;11(1):5237. PubMed Central PMCID: PMC7575552.
   d. Shi CH, Rubel C, Soss SE, Sanchez-Hodge R, Zhang S, Madrigal SC, Ravi S, McDonough H, Page RC, Chazin WJ, Patterson C, Mao CY, Willis MS, Luo HY, Li YS, Stevens DA, Tang MB, Du P, Wang YH, Hu ZW, Xu YM, **Schisler JC**. Disrupted structure and aberrant function of CHIP mediates the loss of motor and cognitive function in preclinical models of SCAR16. PLoS Genet. 2018 Sep;14(9):e1007664. PubMed Central PMCID: PMC6160236.

3. **Integrating Clinical Data with Laboratory Research:** My lab's innovative approach extends beyond traditional models to include clinically-derived datasets for human disease modeling. This integration allows us to formulate and validate hypotheses in the wet lab, leading to the discovery of novel genes and pathways critical to disease progression. Our proficiency in multi-omics has fostered collaborations with leading research groups, focusing on questions directly relevant to human health. For instance, our comprehensive genomic profiling and biomarker analysis has spotlighted the chemokine CXCL5's role in cardio-protection, positioning it as a potential biomarker and therapeutic target for coronary artery disease.
   a. Calancie L, Keyserling TC, Taillie LS, Robasky K, Patterson C, Ammerman AS, **Schisler JC**. *TAS2R38* Predisposition to Bitter Taste Associated with Differential Changes in Vegetable Intake in Response to a Community-Based Dietary Intervention. G3 (Bethesda). 2018 May 31;8(6):2107-2119. PubMed Central PMCID: PMC5982837.
   b. Ravi S, Schuck RN, Hilliard E, Lee CR, Dai X, Lenhart K, Willis MS, Jensen BC, Stouffer GA, Patterson C, **Schisler JC**. Clinical Evidence Supports a Protective Role for CXCL5 in Coronary Artery Disease. Am J Pathol. 2017 Dec;187(12):2895-2911. PubMed Central PMCID: PMC5718092.
   c. Bai X, Mangum KD, Dee RA, Stouffer GA, Lee CR, Oni-Orisan A, Patterson C, **Schisler JC**, Viera AJ, Taylor JM, Mack CP. Blood pressure-associated polymorphism controls ARHGAP42 expression via serum response factor DNA binding. J Clin Invest. 2017 Feb 1;127(2):670-680. PubMed Central PMCID: PMC5272192.

d. Chandler RL, Damrauer JS, Raab JR, **Schisler JC**, Wilkerson MD, Didion JP, Starmer J, Serber D, Yee D, Xiong J, Darr DB, Pardo-Manuel de Villena F, Kim WY, Magnuson T. Coexistent ARID1A-PIK3CA mutations promote ovarian clear-cell tumorigenesis through pro-tumorigenic inflammatory cytokine signalling. Nat Commun. 2015 Jan 27;6:6118. PubMed Central PMCID: PMC4308813.

4. **Bridging Gaps in Genomic Studies:** My research addresses the urgent need for inclusivity in genetic advancements and precision medicine. Recognizing the limited access of disadvantaged groups to these technologies, my work aims to close the healthcare delivery gaps that disproportionately affect non-Hispanic whites. By focusing on genomic studies involving African Americans, I am committed to reducing the disparities and enriching the genetic research landscape with diverse ancestral representation.
   a. Halladay JR, Lenhart KC, Robasky K, Jones W, Homan WF, Cummings DM, Cené CW, Hinderliter AL, Miller CL, Donahue KE, Garcia BA, Keyserling TC, Ammerman AS, Patterson C, DeWalt DA, Johnston LF, Willis MS, **Schisler JC**. Applicability of Precision Medicine Approaches to Managing Hypertension in Rural Populations. J Pers Med. 2018 Apr 30;8(2) PubMed Central PMCID: PMC6023309.
   b. Smith CE, Fullerton SM, Dookeran KA, Hampel H, Tin A, Maruthur NM, **Schisler JC**, Henderson JA, Tucker KL, Ordovás JM. Using Genetic Technologies To Reduce, Rather Than Widen, Health Disparities. Health Aff (Millwood). 2016 Aug 1;35(8):1367-73. PubMed Central PMCID: PMC5100696.
   c. Skinner HG, Calancie L, Vu MB, Garcia B, DeMarco M, Patterson C, Ammerman A, **Schisler JC**. Using community-based participatory research principles to develop more understandable recruitment and informed consent documents in genomic research. PLoS One. 2015;10(5):e0125466. PubMed Central PMCID: PMC4418607.
   d. **Schisler JC**, Charles PC, Parker JS, Hilliard EG, Mapara S, Meredith D, Lineberger RE, Wu SS, Alder BD, Stouffer GA, Patterson C. Stable patterns of gene expression regulating carbohydrate metabolism determined by geographic ancestry. PLoS One. 2009 Dec 9;4(12):e8183. PubMed Central PMCID: PMC2790609.

5. **Innovating Cardiac Metabolism Research:** At the heart of heart failure research, my lab has illuminated the pivotal role of cardiac metabolism. We've identified ubiquitin ligases as critical regulators of signaling proteins that govern cardiac metabolism and uncovered their novel role in mitochondrial quality control. Our ongoing studies delve into the mechanisms affecting cardiac energetics, utilizing both genetic and pharmacological models to pave the way for therapeutic breakthroughs.
   a. Ravi S, Parry TL, Willis MS, Lockyer P, Patterson C, Bain JR, Stevens RD, Ilkayeva OR, Newgard CB, ***Schisler JC***. Adverse Effects of Fenofibrate in Mice Deficient in the Protein Quality Control Regulator, CHIP. J Cardiovasc Dev Dis. 2018 Aug 15;5(3) PubMed Central PMCID: PMC6162787.
   b. Pascual F, **Schisler JC**, Grevengoed TJ, Willis MS, Coleman RA. Modeling the Transition From Decompensated to Pathological Hypertrophy. J Am Heart Assoc. 2018 Apr 5;7(8) PubMed Central PMCID: PMC6015423.
   c. **Schisler JC**, Grevengoed TJ, Pascual F, Cooper DE, Ellis JM, Paul DS, Willis MS, Patterson C, Jia W, Coleman RA. Cardiac energy dependence on glucose increases metabolites related to glutathione and activates metabolic genes controlled by mechanistic target of rapamycin. J Am Heart Assoc. 2015 Feb 24;4(2) PubMed Central PMCID: PMC4345858.
   d. **Schisler JC**, Rubel CE, Zhang C, Lockyer P, Cyr DM, Patterson C. CHIP protects against cardiac pressure overload through regulation of AMPK. J Clin Invest. 2013 Aug;123(8):3588-99. PubMed Central PMCID: PMC3726173.

* Indicates co-first authorship, † indicates co-senior authorship.

Complete List of Published Works: https://scholar.google.com/citations?user=KFpmBLYAAAAJ&hl=en