Overview: The cytoskeleton is essential for maintaining cellular function, driving cell development, tissue repair, immune activity, and intracellular transport. While often studied independently, the cytoskeletal components, such as actin and microtubule filaments, are interconnected by crosslinking proteins, forming a dynamic network (**Fig. 1**), whose disruption leads to widespread dysfunction. Mutations or aberrant expression of cytoskeletal crosslinkers underly various diseases, including Schizophrenia and lissencephaly, and many cancers, where they promote uncontrolled growth, invasion, and compromised immune response. In neurodegenerative disorders like Alzheimer's (AD) and Parkinson's (PD), disrupted crosslinking impairs intracellular transport. Despite its significance, how filament crosslinking coordinates cytoskeletal function remains a fundamental but poorly understood question in biology.

Cytoskeletal crosslinking is mediated by the spectraplakin family of large and evolutionarily conserved proteins, consisting of two essential genes, dystonin (BPAG1) and MACF1, each with multiple isoforms generated via alternative splicing. While long considered passive scaffolds; recent discoveries reveal that MACF1 possesses ATPase activity critical for cell migration, with similar domains predicted in other spectraplakins. This redefines the view of spectraplakins as dynamic regulators of cytoskeletal coordination and creates new opportunities for selective therapeutic targeting. Despite this potential, the mechanistic basis of the spectraplakin function remains unknown.

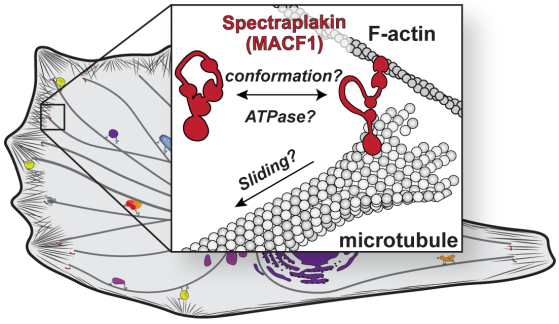

Figure 1. Microtubule and filamentous actin (F-actin) are crosslinked by spectraplakins.

The central hypothesis of our research is that cytoskeletal crosslinkers regulate the interaction between actin and microtubules by undergoing dynamic conformational changes and that fine-tuning this communication is crucial for proper cellular function (Fig. 1). To investigate this, we will focus on MACF1a, the predominant spectraplakin isoform in many cell types, including neurons. Despite its large size (~650 kDa), we have successfully purified full-length MACF1a, providing the first robust system to mechanistically study full-length spectraplakins. By combining innovative methodology, including time-resolved cryogenic electron microscopy (cryo-EM), total internal fluorescence microscopy (TIRF), and live-cell imaging in induced neurons (iNs), we will decipher the mechanisms of cytoskeletal crosstalk at a systems level. This sets us apart from others in the field, where the tendency is to focus on one cytoskeletal component at a time. Our comprehensive approach builds on my recent application of time-resolved cryo-EM to the dynein motor[1,2], where we revealed conformational states of dynein and mechanistic insights not accessible through conventional methods, showcasing the potential of this technique to uncover how MACF1 functions as a dynamic cytoskeletal regulator.

Goal 1. Determine how ATP-driven conformational changes regulate MACF1 function. To uncover the molecular mechanism of spectraplakins, we will use time-resolved cryo-electron microscopy (cryo-EM) with MACF1a during its ATP hydrolysis cycle, revealing how ATP-driven conformational changes control its activity. Complementary 4-color single-molecule TIRF microscopy experiments, which I am an expert in[3-5] will test the proposed but never tested hypothesis that MACF1 slides along microtubules and exerts force on actin to drive migration (**Fig. 1**). Structure-based hypotheses will be tested in colon and ovarian cancer cell lines, where aberrant MACF1 enhances immune signaling and cell motility.

Goal 2. Decipher the role of MACF1 in neuronal function. Although linked to AD and PD, MACF1's role in different brain pathologies remains unclear. We will introduce disease-associated MACF1 mutations, including those in the ATPase domains, into fibroblasts from young, aged, and AD patients and convert them into iNs. Using live-cell imaging and cellular assays, we will assess how MACF1 disruption impacts neuronal differentiation, morphology, and transport of cargoes like mitochondria and endosomes, known to be altered in AD and PD. These studies will be complemented by proteomic analysis of MACF1 interactome to identify key regulators and potential future therapeutic targets.

Impact: Our analysis will be the first to define fundamental principles of dynamic cytoskeletal crosslinking in a physiological context, offering broad insights into how the cytoskeleton orchestrates key aspects of cellular function. These findings will not only decipher how cytoskeletal disruptions contribute to disease but also establish a framework for studying cytoskeletal regulation across diverse biological systems.

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Professional positions

Assistant Professor | Salk Institute for Biological Studies	2023 – present
Postdoctoral Fellow | University of California San Diego and Howard Hughes Medical Institute | Department of Cellular and Molecular Medicine | Advisor: Samara Reck-Peterson, Ph.D.	2016 – 2023

Education

Ph.D., Structural Biology and Biochemistry | University of Colorado Denver Advisor: Elan Z. Eisenmesser, Ph.D.	2010 – 2016
M.S., Chemistry | University of Colorado Denver Advisors: Karen R. Jonscher, Ph.D. and Douglas F. Dyckes, Ph.D.	2007 – 2010
B.S., Chemistry | University of Wroclaw	2002– 2005

Fellowships

American Cancer Society Postdoctoral Fellowship	2018 – 2021
NIH F32 Ruth L. Kirschstein Postdoctoral Fellowship - NIGMS	2018
NIH F31 Ruth L. Kirschstein Predoctoral Fellowship - NCI	2013 – 2016

Honors and Awards

Leading Edge Symposium Fellow	2020
Biophysical Society Travel Award	2016
University of Colorado Graduate School Student Research Excellence Award	2015
C. Werner and Kitty Hirs University of Colorado Graduate School Student Travel Award	2014 – 2016
Protein Society Travel Award	2014
Colorado Biological Mass Spectrometry Society Poster Award	2009
American Society for Biomolecular Facilities Student/Post-Doc Poster Award	2009
University of Colorado Denver Mike Milash Teaching Assistant Award	2009

Publications

***co-first author, #co-corresponding author**

1. **Kendrick AA**#, Nguyen KVN, Karasmanis EP, Reck-Peterson SL, Leschziner AE#. *Multiple steps of dynein activation by Lis1 visualized by cryo-EM.* Nat Struct Mol Biol. 2025, 1-11, doi: 10.1038/s41594-025-01558-w
2. Nguyen KVN, Ma W, Karasmanis EP, **Kendrick AA**, Reck-Peterson SL, Leschziner AE. *Cryo-EM captures early intermediate steps in dynein activation by LIS1*. *[Preprint]. doi:10.1101/2025.01.10.632485.* (accepted at *Nature Comm.*)
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11. Redzic JS, **Kendrick AA,** Bahmed K, Dahl KD, Pearson CG, Robinson WA, Robinson SE, Graner MW, Eisenmesser EZ. *Extracellular vesicles secreted from cancer cell lines stimulate secretion of MMP-9, IL-6, TGF-β1 and EMMPRIN*. PLoS One. 2013; 8(8): e71225.
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Commentary

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Professional Service

Co-organizer: International Salk Cell Cycle Meeting	2025
American Society for Cell Biology subgroup co-organizer: "Not just Cellular railroads: microtubules as cargoes and signaling centers" | virtual due to COVID-19 pandemic	2021
Chair of Structural Biology and Biochemistry Program Student Committee | University of Colorado Denver	2013 – 2014
Co-Chair of bi-annual symposium: Translating Structural Biology to Medicine | University of Colorado Denver	2013

Independent Reviewer

Ad hoc reviewer: Nature Communications, Journal of Cell Biology, eLife, Nature Chemical Biology, Cytoskeleton

Invited Talks

International Dynein Meeting | Ann Arbor, MI	2025
Technology Sandbox workshop | University of California San Diego, CA	2025
Molecular Mechanisms of Motors Driving Cellular Movements 2024 Gordon Research Conference | Portland, ME	2024
Cell Biology & Physiology Seminar | University of California Davis, CA	2023

Biophysics Seminar | Washington University in St. Louis, MO	2023
Structural Biology and Biochemistry seminar | University of Colorado Denver, CO	2023
2023 Annual Biophysical Society Meeting | San Diego, CA	2023
American Society for Cell Biology 2022 Annual Meeting Microsymposium | Washington D.C.	2022
American Society for Cell Biology 2021 Annual Meeting Subgroup | virtual due to COVID-19 pandemic	2021
International Dynein Meeting | virtual due to COVID-19 pandemic	2021
Leading Edge Symposium | virtual due to COVID-19 pandemic	2020, 2022
American Society for Cell Biology 2018 Annual Meeting Minisymposium | San Diego, CA	2018
Colorado Biological Mass Spectrometry Society Meeting | Fort Collins, CO	2009

Service

Leading Edge Panel co-organizer: "Parenting and Family life in Academia"	2022
Work life (im)balance workshop | American Cancer Society TheoryLab and Apple podcast	2021
Elementary School Science Presentations | Highline Academy Charter School	2010 – 2013
Chemistry tutor to Afghan and Libyan refugees	2010 – 2014

Professional Training

COMPASS | NIH-funded professional development and mentorship course | ten 4-hour/week sessions and 6-month support program	2023
Salk Faculty & Mentors Training series | two 3-hour sessions	2023

Teaching and Mentorship

Teaching

Chalk Talk workshop, co-lead with Sue Kaech, Ph.D. | five 2-hour sessions | Salk Cancer Center	2024
Teaching Assistant | Structural Biology and Biochemistry Graduate Program | University of Colorado Denver	2011 – 2016
Chemistry tutor | Varies Agencies and Institutions in Denver	2008 – 2015
Chemistry Instructor | Pre-Collegiate Outreach Program | University of Colorado Denver	2008
Teaching Assistant | Department of Chemistry | University of Colorado Denver	2007 – 2010

Mentorship

Current postdoctoral fellows:

Álvaro de la Gándara, Ph.D.	2024 - present
Ankita Chadda, Ph.D. | NINDS T32 fellow	2024 – present

Current undergraduate students:

Krish Jagasia | UCSD	2023 – present
Jonathan Diaz Zarco | Southwestern College	2023 – present

Current Staff:

Delaney Sanders	2023 – present

Alumni:

Sonia Goyal | undergraduate student | Rutger's University	2024

Prior to lab establishment:

Kendrick Nguyen | graduate student | Leschziner lab | UCSD	2022 – present

Joey Truong | Undergraduate student | Reck-Peterson lab | UCSD 2019 – 2022
Currently: PhD student, UC Davis
Donte A. Stevens | Graduate student | Reck-Peterson lab | UCSD 2018 – 2023
Currently: HHMI Hanna Gray Fellow, Scrips La Jolla
Andrea Dickey | MD/PhD student | Reck-Peterson lab | UCSD 2018 – 2022
Currently: Resident, UCSF
Vinit Adani | Undergraduate student | Reck-Peterson lab | UCSD 2018 – 2019
Currently: PhD student, UC Riverside
Phuoc Tien Tran | Research Assistant | Reck-Peterson lab | UCSD 2016 – 2018
Currently: PhD student, Harvard University
Johnathon Shafer | Research Assistant | Eisenmesser lab | UCSD 2014 – 2016
Currently: PhD student, UC Denver