Department of Physiology

## Dissertation Defense Seminar

# Courtney Marie Kloske

## UNCOVERING THE KEY ROLE OF APOE4 ON ALZHEIMER'S DISEASE-RELATED NEUROINFLAMMATION

Monday, December 6, 2021
11:00 am | Med Sci MN 363 and Online

## Doctoral Committee Members

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# Abstract of Dissertation

Alzheimer's disease (AD) is the most common neurodegenerative disease and is characterized by two hallmark pathologies: amyloid-beta plaques (Aβplaques) and hyperphosphorylated, aggregated tau tangles. These pathologies are typically accompanied by the presence of neuroinflammation which is primarily mediated by microglia. Interestingly, several genetic risk factors that increase the risk of AD also have direct impacts on neuroinflammation. Of interest, Apolipoprotein E (ApoE) is the largest genetic risk factor for AD. ApoE has three isoforms- E4 confers an increased risk for AD, E3 is considered the "control" phenotype, and E2 is protective against AD. E4 plays a role in virtually all aspects of AD, including inflammation; however, the role E4 plays on specific inflammatory pathways in the human brain has been understudied. To address this gap, we used RNA from human autopsy tissue to understand the role of ApoE isoforms on specific inflammatory pathways. Interestingly, we found in pathways related to microglial activation, E4 had a dampened inflammatory response to AD pathology suggesting E4 is unable to mount an appropriate microglial response to remove AD pathology, unlike E3. Due to this finding, we then wanted to explore the effect of ApoE isoforms on microglial morphologies. Using two independent populations with microglial staining, we saw an increase in microglial activation in dementia patients in both E3 and E4 cases. Interestingly, a subtype of microglia hypothesized to support neurons, known as rod-shaped microglia, were increased in the superior medial temporal gyrus of E4-Dementia patients, suggesting an E4-driven impact on microglial morphologies. As we have shown in human tissue, ApoE isoforms play a significant role in inflammation; however, human tissue does not allow for the manipulation of specific pathways. To fine tune our understanding of the mechanism through which ApoE isoforms affect specific inflammatory pathways, we turned to several mouse models and looked at signaling cascades and intracellular mechanisms. Based on our previous human data, we hypothesized that E4 mice would have reduced microglial activation; specifically, through E4 interference with the triggering receptor expressed on myeloid cells (TREM2) signaling cascade, due to mutations in TREM2 conferring an increased risk of AD and ApoE binding to TREM2. To understand the role of ApoE isoforms in the TREM2 cascade, two stimuli were used to target TREM2: phosphatidylserine (PS) and AL002a. PS was used to mimic neurodegeneration and AL002a was used to directly activate TREM2. By performing intracranial injections with these stimuli, we were able to see E4 microglia did not respond to the stimuli and did not mount an inflammatory response to either PS or AL002a, suggesting E4 has an inhibitory role on TREM2 signaling and could be contributing to the increased risk of AD. Collectively, this data indicates a role for E4 on neuroinflammation in AD. Further, this data suggests a potential use for precision medicine when targeting inflammation in AD based on an individual's ApoE isoform.

# Acknowledgements

While this dissertation is an individual work, this work could never have been completed without the insight, guidance, and support from so many individuals.

To Donna, I cannot even begin to describe what your support over the past 4.5 years has meant to me. Thank you for always making time to answer all my questions and reminding me to breathe when I came into your office panicked about both experiments and life. Thank you for never saying no to my crazy ideas and letting me take charge of my dissertation project. Thank you for always going out of your way to put me up for new opportunities, both through networking and professional development- I truly wouldn't be the person I am today without your encouragement. Thank you for always pushing me to find my path in science and to be the best scientist I could be. I would not be on the path I am on now without you taking a chance, sending an email, and encouraging me to pursue my dream job. You are truly my scientific role model and I promise to make you proud!

To Tiffany and Erica, I think we all know I wouldn't have made it this far if it wasn't for both of you! Thank you both for all the time you spent training me on a million techniques (sometimes, re-training me…oops!). Thank you for answering all my questions when I needed endless help and advice! Tiffany, thank you for welcoming me into the lab. I will never forget my first rotation in the lab with the pink gloves and constant Disney music! I think that's what really sold me on the lab! And Erica, thank you for hosting all the game nights over the years. I will never think of Villainous and not think of you. Also, thank you for constantly reading, and then re-reading everything I've written, truly could not have done it without you!

To Charles and Zach, graduate school would not have been the same without you both! I will forever miss our tiny closet office. I think it truly brought us together even more than I could have imagined! I will always celebrate two New Years', I will always question how liquid helium is made, and I will always know far too much about random sports. Thank you for making the afternoons so much more enjoyable as we learned about random facts (don't worry Donna, I promise science happened in the office too!). I have high expectations for future co-workers after you both. You are both the brothers I never thought I wanted.

To Alex, my lab little sister, it has been amazing watching you transform into the incredible scientist you are now! Coming into the Wilcock lab not only changed you, but it also changed all of us for the best. I know you will do amazing things and I can't wait to see what you do next!! To Mary, the amazing undergraduate student who ran all my western blots (bless you), I could not have finished without you! To Emmie, my other amazing undergraduate student, I loved being your mentor for your class project and I will always say "that's my undergrad" whenever I see rifle events! To everyone in the Wilcock Lab, past and present, thank you for your help throughout my time in the lab.

To Lyndsay, my best friend and the person I couldn't have made it through graduate school without! Words cannot describe what your friendship means to me. Our friendship began with The Bachelor and wine Mondays, and you are now someone I can count on for anything. Also, I am very proud of our progression from the sweetest wine on the shelf to knowing way more about wine than before. Your fish wine glass will always be ready for you whenever

# Acknowledgements continued

you come to visit! I am so incredibly proud to call you my friend and you are going to be the best PI anyone has ever seen someday very soon! Dobby also appreciated all the snuggles and extra treats over the years.

To Colleen, my first friend and roommate in graduate school, I will never forget the first weekend of school when your dad came to town, and you let me tag along because I knew no one. That was when I realized we would be friends forever! You were also the best roommate I could have asked for, especially in that house with our delightful neighbors. Even aside from the crazy neighbors, Dobby and I could not have made it through quarantine without you and Bailey! You are one of a kind and I cannot wait to sit in the back of one of your classrooms someday to cheer you on.

To all my Auburn and childhood friends, you know who you are, I love you all so much and your support over the years means more to me than you could even know!

To the entire Kloske Family, thank you for the constant support! I will always remember presenting my research at Kloske family Christmas with Fox and Meadow holding up my poster. Your support and excitement (even when you didn't know what I was talking about) meant the world to me.

To mom, thank you for being my role model through life and fully making me a mini-Michelle! I could never thank you enough for your constant support and encouragement! You are always pushing me to be my best self and that no goal is too crazy, even when that goal was to move to Chicago in the middle of winter. I love you so much and I'm honored to be called mini-Michelle.

To dad, thank you for giving me my love for science! I don't know where I would be without you, probably still struggling to finish a science fair project or broken down on the side of the road. Thank you for always asking about how my science is coming along even though I rarely actually answered your question. You can now read my dissertation and that question will finally be answered (no follow-up questions for at least a month!). I am so proud to be your daughter, Wild Goose.

To Madelyn and Alexa, thank you for being my partners in crime and always being there for me. Thank you for your constant support and for being my built-in cheerleaders! I'm so proud of who you both have become and cannot wait to see what you do next!

And finally, thank you to everyone who has helped me along the way! We made it and I hope I make you proud!