



Doctoral Dissertation Defense Announcement

**“Evaluating Human Cytomegalovirus-induced Structural and Functional Effects
in an iPSC-derived Model of the Human Forebrain”**



Jacob W. Adelman

Candidate for Doctor of Philosophy
Cell and Developmental Biology
School of Graduate Studies
Medical College of Wisconsin

Committee in Charge:

Allison Ebert, PhD (Mentor)

Jonathan Marchant, PhD

Scott Terhune, PhD

Amy Hudson, PhD

Matt Veldman, PhD

Matt Scaglione, PhD

Date: Tuesday, August 20, 2024

Time: 9:30 AM (CST)

Defense Location: Kerrigan Auditorium

Zoom: Available upon request (jadelman@mcw.edu)

Graduate Studies:

Fundamentals in Biomedical Sciences I

Fundamentals in Biomedical Sciences II

Fundamentals in Biomedical Sciences III

Fundamentals in Biomedical Sciences IV

Techniques in Molecular and Cell Biology

Professional Development I

Professional Development II

Statistics for Basic Science

Fundamentals of Neuroanatomy

Graduate Neuroanatomy

Ethics & Integrity in Science

Writing a Scientific Paper

Writing an Individual Fellowship

Neuroscience Journal Club

Developmental and Stem Cell Biology

Reading and Research

Research Ethics Discussion Series

Doctoral Dissertation

Dissertation

“Evaluating Human Cytomegalovirus-induced Structural and Functional Effects in an iPSC-derived Model of the Human Forebrain”

Human cytomegalovirus (HCMV) is a common betaherpesvirus that infects between 40-90% of adults worldwide. While infections are typically asymptomatic, spread from pregnant parent to developing fetus can result in severe neurological symptoms (e.g., hearing/vision deficits, seizures, microcephaly) in ~10% of cases. Further, HCMV has been linked with neurological diseases of aging. Previous studies have determined neural progenitor cells (NPCs) to be the primary site of infection, but terminally differentiated neurons have been thought to be incapable of infection. Utilizing an induced pluripotent stem cell (iPSC)-derived model system of the human forebrain, we sought to test the hypothesis that infection of mature human neurons is possible and would induce structural and function damage. Our data show that treatment of neurons with HCMV induces both immediate early and late gene expression and generation of infectious virus. Next, we sought to determine if HCMV could induce functional deficits. Calcium imaging revealed both a significant reduction in intracellular calcium and a dampened response to potassium chloride stimulation at 7 days post infection (DPI). Moreover, we found that infected neuronal cultures lost the ability to produce spontaneous or electrically-evoked action potentials. In the process of evaluating functional effects of HCMV, we noticed significant alterations to cell structure. including the formation of multinucleated syncytial structures characterized by a ring of nuclei around a viral assembly compartment. Secondarily, we noted a reduction in neurite density and morphology. We therefore evaluated the expression of various cytoskeletal elements and found that microtubule-forming tubulin and microtubule-associated proteins were significantly reduced following infection. We next sought to determine if HCMV-induced structural changes could be altered pharmacologically by applying microtubule stabilizing (paclitaxel) or destabilizing (colchicine) agents. We demonstrate that paclitaxel-induced stabilization promotes neurite protection during infection, with an increase in process density and disruption of typical syncytial morphology. Colchicine, however, does not significantly worsen either mock- or HCMV-treated cultures. As microtubules are vital to HCMV pathology, we also investigated the effects of these drugs on virus production, but neither viral titer nor viral protein expression were significantly reduced upon application of either compound. Taken together, these data demonstrate that HCMV productively infects terminally differentiated human neurons and induces profound structural and functional deficits. Additionally, we found that microtubule stabilizing agents may help maintain neuron structure following HCMV infection. Although future studies are needed to determine if microtubule stabilization can maintain neuron function, the studies described here add to our understanding of the profound pathological impact HCMV has on human neural tissues.

Jacob W. Adelman

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My Research Interests:

Currently, my research focuses on the structural and functional effects of human cytomegalovirus (HCMV) infection on stem-cell derived neurons and cerebral organoids. Additionally, I am interested in the modeling of neurodegenerative conditions (e.g., Alzheimer's Disease) in 2D and 3D culture systems.

Education:

2019-Current

Doctoral Research in Cell and Developmental Biology

Medical College of Wisconsin – Neuroscience Doctoral Program

Principal Investigator: Allison Ebert

Estimated Completion: 8-20-2024

Projects: The Effects of HCMV (HHV-5) on a Patient-Derived Model of the Human Forebrain. Previous research highlights HCMV-mediated effects on calcium signaling, neurodevelopmental gene expression profiles, and cell morphology in neural contexts. In this project, we have established iPSC-derived forebrain neurons as a model system for studying the various structural and functional implications of HCMV infection. Further, shared phenotypes with neurodegenerative conditions (particularly Alzheimer's Disease) have been actively studied for potential overlap.

2014-2016

Bachelor of Science – Biology

University of Wisconsin – Madison

GPA: 3.698

Emphases in Genetics and Neuroscience

2012-2014

Bachelor of Science – Biology (transferred)

University of Wisconsin – Milwaukee

GPA: 3.691; Honors Program

Emphasis in General Biology

Research Experience:

2019-Current

Graduate Research Assistant

Principal Investigator: Allison Ebert

Medical College of Wisconsin

GPA: 3.9

- Utilize molecular, biochemical, and imaging techniques to determine effects of human cytomegalovirus infection within a neural context.
- Develop/improve methodologies for infection, cell culture, imaging, etc.
- Generate experimental paradigms to facilitate hypothesis-driven research.
- Mentor junior scientists and train basic laboratory techniques
- Collate, interpret, and present collected data to both institutional colleagues and the broader scientific community.
- Strengthen key professional skills including scientific writing and networking

2016-2019

Research Technologist II / Rodent Behavior Core Manager

Principal Investigator: Cecilia Hillard
Medical College of Wisconsin

- Utilize biochemical (Western Blot, Activity-Based Protein Profiling) and imaging (RNAscope) techniques to analyze the effects of various pharmacological interventions on the functioning of the endocannabinoid system
- Capitalize on rodent models to assess the effects of various compounds (THC, CBD, cocaine, synthetic cannabinoids) on addiction-related behaviors
- Manage drug preparation and inventory management (DEA compliance for Schedules I-IV)
- Train users, delegate projects, and manage inventory of MCW's Rodent Behavior Core

2015-2016

Undergraduate Research Assistant

Principal Investigator: Edwin Chapman
University of Wisconsin – Madison

- Assist in utilizing biochemical means to interrogate interactions between synaptotagmin family members and partner proteins
- Purify protein for use in subsequent assays
- Collect DNA samples from, process, and genotype all animal colonies

Publications:

- **Jacob W. Adelman**, Suzette Rosas-Rogers, Megan Schumacher, Rebekah Mokry, Scott Terhune, and Allison Ebert. "Human Cytomegalovirus Induces Significant Structural and Functional Changes in Terminally Differentiated Human Cortical Neurons" *mBio*, 2023
 - *Featured Image (Cover)*
- Rebekah L. Mokry, Benjamin S. O'Brien, **Jacob W. Adelman**, Suzette Rosas, Megan L. Schumacher, Allison D. Ebert, Scott S. Terhune. "Nitric Oxide Attenuates Human Cytomegalovirus Infection yet Disrupts Neural Cell Differentiation and Tissue Organization" *Journal of Virology*, 2022
- Reilly L. Allison, **Jacob W. Adelman**, Jenica Abrudan, Raul A. Urrutia, Michael T. Zimmerman Angela J. Mathison, Allison D. Ebert. "Microglia Influence Neurofilament Deposition in ALS iPSC-Derived Motor Neurons" *Genes*, 2022
- Shirley Alteba, Tomer Mizrahi Zer-Aviv, Adi Tenenhaus, Gilad Ben David, **Jacob Adelman**, Cecilia Hillard, Ravid Doron, Irit Akirav. "Antidepressant-like effects of URB597 and JZL184 in male and female rats exposed to early life stress" *European Neuropsychopharmacology*, 2020
- Shaikh, A.*, Borst, D.*, Wu, T.*, **Adelman, J.***, Wolding, B.*, Kakes, J.* (* equal contribution)
"Stress Reactivity of Participants in Response to Same vs. Opposite Gender of Experimenters"
Journal of Advanced Student Science, 2016

Oral Presentations/Posters:

- "Role of Human Cytomegalovirus Infection in Alzheimer's Disease Pathology"; Society for Neuroscience – Global Connectome, Jan. 2021
- "Testing the Impact of HCMV Infection on Alzheimer's Disease Pathology Using Cerebral Organoids"; MCW Graduate Student Association Poster Session, March 2021
- "Testing the Impact of HCMV Infection on Alzheimer's Disease Pathology Using Cortical Organoids"; American Society for Virology 2021, July 2021
- "Role of Human Cytomegalovirus Infection in Alzheimer's Disease Pathology"; Society for Neuroscience – Neuroscience 2021, Nov. 2021

- “Evaluating the Influence of HCMV Infection on Alzheimer’s Disease Pathology”; American Society for Virology 2022, July 2022
- “Evaluating the Influence of HCMV Infection on Alzheimer’s Disease Pathology”; Society for Neuroscience – Neuroscience 2022, Nov. 2022
- “Evaluating the Influence of HCMV Infection on Alzheimer’s Disease Pathology”; Society for Neuroscience – Neuroscience 2023, Nov. 2023

Professional Association Memberships:

- Society for Neuroscience; January 2021 – Present
- American Society for Virology; March 2021 – Present

Student Association Memberships:

- Enhancing Scholarly Culture Committee (2023-Present)
- MCW Science Policy Group (2022-Present)

Additional Skills:

- Familiarity with Adobe Illustrator, Photoshop, Audition, Premiere Pro, ImageJ, Microsoft Office
 - Introductory experience with several modern microscopy platforms (NIS elements, Leica LASX, Zeiss Blue)
 - CITI Program certified (Human Subjects Research)
 - Experience with HTML and CSS coding
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