Utilizing Histone Deacetylase Inhibitors (HDACi) to Alleviate Traumatic Brain Injury Pathology
Glenna Bea Embrador, Biomedical Engineering
Mentors: Dr. Sarah Stabenfeldt, Dr. Rachael Siriani, Dr. Christopher Plaisier
School of Biological Health Systems Engineering, Arizona State University

Introduction
• A traumatic brain injury (TBI) is caused by direct/indirect impacts to the brain that can cause neuronal necrosis to blood brain barrier (BBB) disruption
• BBB disruption creates temporal window to direct therapeutic agents towards hallmarks of TBI, such as proinflammatory cytokines
• Studies found histone deacetylases (HDAC) play an important role in facilitating gene expression that modulates important processes such as neuroinflammation
• By inhibiting excess HDAC following TBI, the goal is to reduce proinflammatory cytokines production to improve TBI pathology
• HDAC inhibitors (HDACi) are drugs that have shown efficacy in cancer treatment, but little research has looked at TBI applications

Research Question
What parameters of HDACi drugs will decrease biomarkers of neuroinflammation and neural damage following TBI?

Methodology
Drug Selection*

Shein et al. utilized GV in a TBI study and found attenuation of tissue damage 24-hours post injury. In the same study, histone acetylation of H3 increased along with a decrease in glial accumulation 3-days post injury in a mouse model.2

Oki et al. administered drug patients with Hodgkin lymphoma and found reduced cytokine output. In this study, patients were monitored before and after treatment, with over a third of patients showing reduced cytokine outputs.3

Leoni et al. shows anti-tumor in addition to neuroprotective qualities from Quinolinostat. This drug has been used in many cancer studies showing increased H3 production and decreased HDACi output.4

Preliminary Data

Preliminary Data

Histone

Repression of genes

Gene activation

HDACi Drugs inhibit deacetylation, keeping genes active

DNA coils around histones, & enzymes like histone deacetylase (HDAC) or histone acetylase (HAT) can alter gene expressions

Fig. 4 Diagram showing purpose of HDACi system and how HDACi drugs aim to regulate genetic expression following TBI.

DNA coils around histones, & enzymes like histone deacetylase (HDAC) or histone acetylase (HAT) can alter gene expressions

Fig. 2 Diagram showing purpose of HDACi system and how HDACi drugs aim to regulate genetic expression following TBI.

Microscope estimation

Protein concentration (µg/mL)

BCA Total Protein Output

Drug concentration

10⁻¹ µM

10⁻µM

10⁻¹µM

1µM

Controls

Preliminary BCA assays were performed on the experimental conditions showing total protein output. From these graphs, certain trends can be seen such as QS yielding low protein, GV showing a trend up with higher concentrations, and PB having most protein. Specific assays such as ELISA & Western blots need to be performed for statistical analysis.

Fig. 5 Preliminary BCA assays were performed on the experimental conditions showing total protein output. From these graphs, certain trends can be seen such as QS yielding low protein, GV showing a trend up with higher concentrations, and PB having most protein. Specific assays such as ELISA & Western blots need to be performed for statistical analysis.

Future Work
• Preliminary results show no distinct morphology change following 6-hour incubations with drugs and LPS and BCA trends show that higher concentration of drug = roughly more protein output
• Limitations include a single time collection (6 hours) – drugs may be most potent shorter or longer than this duration
• Other limitations include BCA assay shows total protein and not specific proteins, making conclusions only speculations
• Future work includes performing an ELISA to detect cytokine production, and Western blots to analyze HDAC or histone acetylase (HAT) production o Following this, statistical analysis can be performed to determine which drug and at what concentration yielded most potent results

Acknowledgements
I would like to thank Dr. Sarah Stabenfeldt for her mentorship during my Spring 2020 MORE project. In addition, I would like to extend my appreciation to Dr. Siriani, Dr. Plaisier, and Amanda Witten for their valuable input and expertise on this project. Thank you to the MORE foundation for funding this project.

References
2. Shein et al. Utilization of GV in a TBI study and found attenuation of tissue damage 24-hours post injury. In the same study, histone acetylation of H3 increased along with a decrease in glial accumulation 3-days post injury in a mouse model.
3. Oki et al. administered drug patients with Hodgkin lymphoma and found reduced cytokine output. In this study, patients were monitored before and after treatment, with over a third of patients showing reduced cytokine outputs.
4. Leoni et al. shows anti-tumor in addition to neuroprotective qualities from Quinolinostat. This drug has been used in many cancer studies showing increased H3 production and decreased HDACi output.