

## **Brown:**

Dr. Brown's lab employs cellular, molecular, imaging, and behavioral approaches to study the neurovascular and neuroimmune responses that impact brain function in normal health, injury, and chronic disease. They have identified an important enzyme in cerebral microvessels that is upregulated or downregulated in response to inflammation from brain injury, neurodegeneration, or systemic inflammation. Their goal is to uncover how this enzyme supports brain homeostasis, how it protects brain vascular function in injury and disease, and the signaling pathways employed this enzyme in health, injury, and disease. They design their studies to address the importance of both sex differences as well as aging to emphasize the translational relevance of their research.

Brain vascular dysfunction and brain inflammation are common mechanisms observed in numerous neurological disorders such as ischemic stroke and Alzheimer's disease, and systemic disorders with neurological dysfunction such as sepsis. The goal of the Brown Lab is to understand the consequences of brain vascular dysfunction in brain injury and disease and to identify therapeutic targets to prevent subsequent cognitive impairment.

Potential interns must be willing to work with mice. The following techniques are employed in the Brown lab: preclinical mouse models of ischemic stroke, Alzheimer's disease, and sepsis; mouse surgical procedures and tissue harvest; molecular biology; multiphoton microscopy in live mice; brain clearing; light-sheet microscopy; confocal microscopy; tissue processing and sectioning; immunohistochemistry; transcriptomics; proteomics.

Potential Projects include:

1. Determining the impact of stroke on brain vascular function and vascular remodeling in Alzheimer's disease.
2. Performing preclinical studies to test a potential novel therapy that targets vascular contributions to beta-amyloid deposition and neuroinflammation in Alzheimer's disease.

## **Chantler:**

Dr. Chantler's research is focused on vascular biology and how certain disease states (obesity, and aging) or conditions (chronic stress, E-cig, or exercise) mediates vascular biology. The lab operates with both human and animal models; this dual approach allows us to further explore the mechanisms underlying the vascular consequences of disease progression. Recently, they have focused on the microvessels in the brain, and how vascular damage here contributes to cognitive impairment and VCID. They have shown that chronic stress is involved in accelerating VCID due to a pro-oxidative microenvironment impacting the cerebrovascular network, resulting in impaired vascular function, structure, and a loss of vessels. This project is currently funded by NIH for the next 4 years (2021-2025).

Vascular contributions to cognitive impairment and dementia (VCID) is the second leading cause of dementia behind Alzheimer's disease (AD). Epidemiological data suggest that a stressful life is a predictor of poor later-life cognition (ref). Using a pre-clinical model, the Chantler lab has identified that chronic stress leads to significant cerebrovascular dysfunction and a decline in cognition. There is a critical need to identify the mechanisms linking chronic stress to VCID, including the progression to AD. They believe that the oxidative stress induced by chronic stress is a key mediator of VCID. Xanthine oxidoreductase (XOR) is a major source of oxidative products (hydrogen peroxide and superoxide) and the existing data have further validated the role of XOR on the chronic stress-induced cerebrovascular

dysfunction. Recent novel work from the Chantler lab has shown that inhibiting XOR with an FDA-approved drug, febuxostat, not only prevented the stress-induced acceleration of AD, but febuxostat (without chronic stress) improved AD pathology. As such, the overarching goal is to determine the specific role of XOR on the stress-induced VCID, and its progression to AD pathology. Their central hypothesis is that chronic stress elevates cerebrovascular XOR and directly causes cerebrovascular dysfunction and resulting in cognitive decline, which accelerates dementia/AD pathology.

Stress is a state of threatened homeostasis and 73% of Americans experience psychological symptoms caused by stress. Chronic stressful events can lead to cognitive decline and stressed individuals are more likely to develop mild cognitive impairment or even AD than non-stressed individuals. For example, 13,000 patients tracked over 50 years showed that those individuals who experience late-life depression (of which stress is a significant risk factor) had a 2-fold elevated risk of a dementia diagnosis. Similarly, in the APP/PS1 and 3xTg-mice, which are models of AD, stress accelerated cognitive decline. Further, their preliminary data in the 3xTg-mice, shows that stress accelerated early AD pathology reflected by a worse cerebrovascular function, and increased Tau deposition in the brain. As such, these data suggest that stress and dementia interact to drive the progression of AD-related dementias. It is expected 82 million people will have dementia by 2030 with an estimated annual global societal cost of \$2 trillion. Despite this knowledge, our understanding as to the molecular and cellular mechanisms driving this stress-induced VCID is unknown.

Potential interns must be willing to work with mice. The following techniques are employed in the Chantler lab: Genetic mouse models, Cellular and molecular biology (western blot, mRNA expression, IHC etc), Tissue culture (Ex vivo manipulation via pressure myography, Laser-scanning confocal microscopy), and structural changes (two-photon excitation microscopy and lightsheet).

Potential projects include:

1. Determining the cellular and molecular mechanisms underlying the role of chronic stress on Vascular contributions to cognitive impairment and dementia
2. Determining the role of Xanthine Oxidase on the progression of Alzheimer's disease pathology

## **Geldenhuys:**

The Geldenhuys lab takes a chemico-biology approach to the development of novel treatment strategies aimed at protecting neurons and vascular endothelium after a stroke. Their previous work identified mitoNEET as a novel regulator of mitochondrial function, and pharmacological targeting allows for tissue protection after a stroke. They are interested in understanding the molecular mechanisms of how mitoNEET prevents BBB leakage and neuronal cell death after a stroke. Improved delivery of their lead compound using nanoparticles will be optimized for stroke. The goal of the Geldenhuys lab focuses on prevention or attenuation of neuronal cell death after a stroke which has tremendous impact on the patients and lessens the burden on the health care system.

Potential interns must be willing to work with animals. The following techniques are employed in the Geldenhuys Lab: tissue culture, western blot, ELISA, nanoparticle formulation.

Potential Projects include:

1. Using the mitochondrial protein mitoNEET as therapeutic drug target in stroke
2. Understanding the role of mitoNEET in recovery of the blood brain barrier after a stroke

## **Nelson/DeVries:**

The Nelson/DeVries lab evaluates the effects of exposure to artificial dim light at night (ALAN) on physiology and behavior. Specifically, one of the current research arms of the lab focuses on the adverse consequences associated with nighttime lighting on cerebro- and cardiovascular function, in healthy and injured states. They have demonstrated that exposure to ALAN alters proinflammatory cytokine production following global (cardiac arrest) and focal (stroke) ischemia in mouse models, and increases neuronal damage compared to housing in standard (dark) night conditions. Further, preliminary data suggests that cardiovascular reactivity, in otherwise healthy mice, is impaired by exposure to ALAN. Thus, the lab aim to characterize the cellular and molecular mechanisms that are altered by the disrupted circadian clock, ultimately leading to the observed phenotypes. Two research questions they are investigating are: “How does circadian disruption and variations in biological timing alter ischemic stroke intervention and outcome?”, and “How do disrupted circadian rhythms by exposure to ALAN affect homeostatic vascular and metabolic function?”

Exposure to artificial nighttime lighting is pervasive in modern society, and exposure to ALAN has been classified as a circadian disruptor, which can impair ample aspects of overall health. Thus, the Nelson/DeVries lab seeks to understand how circadian disruption via exposure to ALAN impairs homeostasis and can potentiate secondary damage following an ischemic injury, with the goal of elucidating chronopharmacological targets to ameliorate the detrimental effects of nighttime lighting and limit neuronal damage which could lead to severe neurological impairment. Further, identifying and validating the use of light spectra that does not compromise circadian homeostasis, that is, light whose wavelength does not affect the molecular clock, can help promote its use, particularly in environments such as hospitals, where vulnerable populations reside.

Potential interns must be willing to work with animals. The following techniques are employed in the Nelson/Devries Lab: tissue processing and sectioning for immunohistochemistry and/or immunofluorescence, RNA isolation and qt-PCR to analyze gene expression, microscopy and imaging of brain sections, western blot analysis, triphenyl-tetrazolium chloride (TTC) staining for infarct visualization, flow cytometry, basic animal husbandry and handling of mice, running behavioral tests and using behavioral tracking software to analyze behavior, bioinformatics to analyze RNA-Seq and Single Cell 10X genomics, and others.

Potential Projects include:

1. Examining the effects of circadian disruption via exposure to artificial dim light at night on vascular reactivity.

2. Determining whether circadian disruption via exposure to artificial dim light at night impairs recovery from global ischemia, by impairing revascularization and/or exacerbating inflammatory response.
3. Evaluating the role of circadian disruption from exposure to dim light at night and how it alters immune migration to the cerebral infarct during acute stroke injury.
4. Determining how alternative spectral lighting can ameliorate deficits related to neuronal injury after ischemic stroke.

## **Setola:**

The Setola lab's overarching interest is to develop novel pharmaceutical strategies to prevent and/or treat substance use disorder. They are particularly interested in opioids and in psychostimulants (e.g., methamphetamine, cocaine). Their primary research questions are "Can we leverage our evolving knowledge of cell surface receptors expressed by neurons in the reward pathway to prevent and/or treat behaviors germane to substance use disorder?" and "Is the G protein signaling regulator RGS12, a protein that we have shown to affect the expression and activity of the dopamine transporter, a potential target for pharmaceuticals to prevent and/or treat psychostimulant use disorder?"

The interested applicant will already be familiar with the personal and economic costs of substance use disorders. The applicant will also be cognizant that West Virginians have been hit particularly hard by the effects of substance use disorder. The Setola lab hopes that their work will inform prevention and treatment options that will alleviate some of the devastation associated with substance use disorder.

Potential interns must be willing to work with animals. The following techniques are employed in the Setola Lab: Mouse behavioral assays (e.g., conditioned place preference, intravenous self-administration), mouse husbandry, cellular and molecular biology assays, neuroanatomy, and in vitro and in vivo pharmacological assays to assess drug activity/mechanism of action are staples in our group's experimental repertoire.

Potential Projects include:

1. Evaluating compounds for the ability to reduce/abrogate opioid-associated reward
2. Assessing the resistance of Rgs12 knockout mice to the psychostimulant-associated reinforcement

## **Kate Weil:**

Dr. K. Weil's lab is interested in identifying mechanisms that promote recovery after traumatic brain injury. They are specifically interested in determining how male and female mice respond to treadmill exercise after brain injury. The data indicate that low-moderate intensity exercise improves cognitive recovery in injured male mice; however, injured female mice exhibit greater cognitive recovery and brain mitochondrial function after high intensity exercise. They are working toward understanding the underlying mechanisms for this sex difference, which may ultimately be used to help determine the optimal exercise intensity for a brain injured individual.

Until recently, physician-prescribed rest after TBI was a long-standing practice intended to prevent additional metabolic burden on the injured brain and promote recovery. However, both clinical and experimental research reveals little to no benefit of rest after TBI. Rather, physical activity speeds up cognitive recovery, promotes neurogenesis, and attenuates neuroinflammation. While the overall benefits of exercise are clear, there is still a gap in our understanding of how exercise impacts brain metabolic function in the TBI population. The goal of this work is to fill this critical gap in knowledge and help clinicians determine the optimal timing, duration, and intensity of exercise in brain injured patients.

Potential interns must be willing to work with animals. The following techniques are employed in the K. Weil lab: survival surgery, animal behavior, tissue processing (blood and brain tissue collection, tissue fixation, cryosectioning), histology, PCR, western blotting, and microscopy.

Potential Projects include:

1. Identifying the optimal exercise intensity that promotes recovery after traumatic brain injury.
2. Determining the impact of exercise after TBI on mitochondrial function, pathophysiology, and functional recovery.

## **Zach Weil:**

Dr. Z. Weil's lab uses behavioral, molecular, and physiological techniques to study the long-term effects of traumatic brain injuries. Individuals that suffer a traumatic brain injury are vulnerable to a host of disease states and are much more likely to experience serious health problems. They are focusing on understanding how a brain injury makes animals vulnerable to cardiovascular and neuropsychiatric disease.

Individuals that have suffered from a traumatic brain injury have to deal with a large number of challenges including, but not limited to, pain, disability, social isolation, and psychiatric symptoms. Medical treatments for traumatic brain injuries are limited and so, the goal of the Z. Weil lab is to help patients recover in as optimal a way as possible.

Potential interns must be willing to work with animals. The following techniques are employed in the Z. Weil lab: Behavioral neuroscience, surgery, tissue processing, microscopy, molecular biology, and flow cytometry.

Potential projects include:

1. Determining whether traumatic brain injuries can trigger symptoms of vascular disease and contribute to neurodegeneration.
2. Investigating whether traumatic brain injuries can make animals more vulnerable to the toxic effects of alcohol.

## **Winstanley:**

The Winstanley lab investigates strategies to reduce the morbidity and mortality associated with opioid misuse and opioid use disorder. Drug overdose continues to be the leading cause of injury death in the United States. Individuals using opioids who have brain injuries and/or co-occurring pain may be less likely to engage and be retained in addiction treatment. Research suggests that less than 80% of

patients with an opioid use disorder seek addiction treatment and among those who do initiate treatment, few are retained in treatment for more than one year. We know that medications to treat opioid use disorder reduces all cause mortality by 50% and hence engagement in addiction treatment is a critical component of reducing overdose deaths.

Dr. Winstanley's work, hopefully, will lead to improvements in the identification and treatment of patients with opioid use disorder. West Virginia has had the highest rate of overdose deaths in the United States for more than 20 years and this clinical research may lead to novel interventions to reduce overdose deaths.

This lab conducts human clinical trials, with objective and subjective measures, to investigate problems engaging and retaining patients in treatment for opioid use disorder.

Possible projects include:

1. Investigating the problems initiating addiction (buprenorphine) treatment among patients using illicitly manufactured fentanyl.
2. Improving engagement and retention in treatment for patients with comorbid pain and opioid use disorder.
3. Investigating brain injuries associated in patients with opioid use disorder.