EXAMPLES OF PROJECTS FOR DOCTORATE STUDENTS
Summaries of current & previous Ph.D. student projects are provided in the following pages:

Effect of pericyte stimulation on traumatic brain injury pathophysiology

Supervisors: Dr. Corbin Bachmeier & Dr. Scott Ferguson

Background
Traumatic brain injury (TBI), particularly repetitive mild TBI (r-mTBI), is associated with chronic white matter degeneration, tau accumulation, and persistent neuroinflammation. Emerging evidence indicates that vascular pericytes play a central role in maintaining neurovascular integrity and regulating brain homeostasis. Preliminary studies from the Roskamp Institute demonstrate progressive pericyte degeneration and reduced PDGFRβ signaling following r-mTBI, coinciding with white matter loss, impaired tau clearance, and sustained inflammation. Pericytes regulate oligodendrocyte precursor cell differentiation through secretion of laminin subunit alpha 2 (LAMA2), internalize and metabolize extracellular tau, and modulate neuroinflammatory signaling. Reduced platelet-derived growth factor-BB (PDGF-BB) availability following injury may drive pericyte dysfunction and exacerbate TBI pathophysiology. Restoration of pericyte signaling represents a novel and potentially translatable therapeutic strategy for TBI.

Hypothesis
Reduced PDGF-BB signaling following repetitive mild TBI causes progressive pericyte degeneration, and stimulation of the PDGF pathway will restore pericyte function and mitigate chronic TBI pathology.

Aims
1. Determine the effect of PDGF-BB stimulation on oligodendrocyte precursor cell differentiation and white matter remyelination following r-mTBI.
2. Evaluate the role of PDGF-BB stimulation in tau degradation and elimination from the brain after r-mTBI.
3. Examine the impact of PDGF-BB stimulation on pericyte-mediated neuroinflammatory responses following r-mTBI.
4. Assess the effect of PDGF pathway stimulation on r-mTBI-related neuropathology and cognitive behavior.

Techniques to be used
Repetitive mild TBI mouse models will be combined with pharmacological stimulation of PDGF signaling. Cerebrovascular isolation, pericyte and oligodendrocyte culture systems, and conditioned media assays will be used to assess cellular interactions. Immunohistochemistry, in situ hybridization, and biochemical analyses will quantify white matter integrity, tau pathology, and inflammation. Intracranial delivery and dietary pharmacological approaches will be

employed. Standardized neurobehavioral testing batteries will assess functional outcomes.

Research strategy
The project integrates mechanistic and in vivo approaches to define the contribution of pericyte dysfunction to r-mTBI pathophysiology. PDGF-BB stimulation is evaluated as a means to restore pericyte-dependent support of myelination, tau clearance, and immune regulation. Studies progress from cellular and molecular analyses to whole-animal behavioral assessments. Translational relevance is emphasized through delayed intervention paradigms and use of pharmacological agents with prior clinical exposure. Rigorous controls, blinded analyses, and sex-balanced cohorts are employed throughout.

Anticipated deliverables
Demonstration of pericyte dysfunction as a key driver of chronic r-mTBI pathology. Evidence that PDGF-BB stimulation restores pericyte function and improves white matter integrity, tau handling, and inflammatory profiles. Behavioral and pathological data supporting pericyte-targeted therapeutic strategies. Mechanistic insight into vascular contributions to chronic TBI outcomes.

Source of funding
U.S. Department of Veterans Affairs Merit Award (PI: Dr. Corbin Bachmeier)

Development of ultra-selective DYRK1A inhibitors as a novel therapeutic modality for TBI

Supervisors: Dr. Benoit Mouzon & Dr. Corbin Bachmeier

Background
Traumatic brain injury (TBI), including repetitive mild TBI and severe penetrating injury, is associated with chronic neuroinflammation, tau hyperphosphorylation, and long-term neurological dysfunction. Despite extensive clinical trials, there are currently no FDA-approved pharmacological therapies that mitigate secondary injury mechanisms following TBI. Dual specificity tyrosine-phosphorylation-regulated kinase 1A (DYRK1A) is a serine/threonine kinase implicated in tau phosphorylation and regulation of immune response pathways, both of which are central features of TBI pathology. Preliminary studies using a first-generation DYRK1A inhibitor demonstrated reduced neuroinflammation, decreased pathological tau accumulation, and improved motor outcomes in mouse models of repetitive mTBI. However, off-target kinase inhibition limited its translational potential. Recently developed ultra-selective DYRK1A inhibitors exhibit high brain penetration, favorable pharmacokinetics, and improved selectivity, offering a promising new therapeutic approach for both acute and chronic TBI.

Hypothesis
Pharmacological inhibition of DYRK1A using ultra-selective, brain-penetrant inhibitors will mitigate acute and chronic neuropathological and functional consequences of traumatic brain

injury.

Aims
1. Identify a lead ultra-selective DYRK1A inhibitor and optimal dose that provides maximal efficacy during the acute phase of repetitive mild TBI.
2. Determine the efficacy of the lead DYRK1A inhibitor in a mouse model of severe penetrating TBI.
3. Evaluate the impact of delayed and chronic DYRK1A inhibition on long-term functional and pathological outcomes following repetitive mild TBI.

Techniques to be used
Translational mouse models of repetitive mild and penetrating/severe TBI will be employed with acute and delayed oral pharmacological treatment paradigms. Neurobehavioral testing will assess motor, cognitive, sensory, and affective outcomes. Neuropathological and biochemical analyses will quantify tau pathology, axonal injury, gliosis, and white matter degeneration. Plasma and brain biomarkers will be assessed using immunoassays and advanced imaging techniques.

Research strategy
The project integrates drug discovery and translational neuroscience approaches to evaluate DYRK1A as a therapeutic target for TBI. Two ultra-selective DYRK1A inhibitors are screened in acute treatment paradigms to identify a lead candidate and dose. The selected compound is then tested in a severe TBI model to address injury heterogeneity. A delayed, chronic treatment paradigm models clinically relevant intervention windows for persistent TBI symptoms. Behavioral, pathological, and biomarker outcomes are integrated to assess therapeutic efficacy and translational potential.

Anticipated deliverables
Identification of a lead ultra-selective DYRK1A inhibitor for TBI treatment. Demonstration of efficacy across multiple TBI models and treatment windows. Integrated behavioral, neuropathological, and biomarker datasets supporting translational advancement. Preclinical evidence supporting progression toward IND-enabling studies.

Source of funding
U.S. Department of Defense CDMRP Award (PI: Dr. Benoit Mouzon)

Neurological effects of aerosolized red tide neurotoxins

Supervisors: Dr. Laila Abdullah & Dr. Scott Ferguson

Background
Harmful algal blooms (HABs), particularly those caused by Karenia brevis, are increasing in frequency and intensity due to climate change, nutrient runoff, and extreme weather events. K. brevis produces brevetoxins (PbTx), potent neurotoxins that can become aerosolized and inhaled by individuals living or working near coastal waters. While respiratory effects of aerosolized PbTx exposure are well documented, the neurological consequences remain poorly

characterized. Consumption of PbTx-contaminated shellfish causes neurotoxic shellfish poisoning, which includes central and peripheral neurological symptoms. Preliminary studies from Southwest Florida demonstrate that aerosolized PbTx exposure is associated with NSP-like neurological symptoms in coastal residents. Vulnerable populations, including individuals with pre-existing neurological conditions or genetic risk factors such as APOE ε4, may be particularly sensitive. There is currently no clinical guidance for recognizing or managing neurological sequelae of inhaled PbTx.

Hypothesis

Exposure to aerosolized brevetoxins produces dose-dependent neurological symptoms, which are modulated by individual vulnerability and toxin pharmacokinetics.

Aims

1. Define the dose–response relationship between aerosolized brevetoxin exposure and NSP-like and neurological symptoms in humans.
2. Determine whether pre-existing neurological conditions or genetic risk factors increase vulnerability to aerosolized brevetoxin exposure.
3. Establish the relationships between aerosolized brevetoxin exposure, pharmacokinetics, and neurological symptom emergence.

Techniques to be used

Longitudinal human cohort studies will be conducted in coastal communities during and outside red tide events. Aerosolized brevetoxin exposure will be estimated using environmental monitoring, personal air samplers, and modeling approaches. Neuropsychological and neurological assessments will quantify symptoms and functional outcomes. Brevetoxin and brevetoxin antibody levels will be measured in blood, urine, and fecal samples using immunoassays and mass spectrometry. Physiologically based pharmacokinetic modeling will be applied to estimate brain exposure.

Research strategy

A multidisciplinary, longitudinal study design integrates environmental exposure assessment with clinical and biological measures of neurotoxicity. Participants are followed across bloom and non-bloom periods to capture within-subject variability. Dose–response relationships are established using both environmental and biological exposure metrics. Nested analyses examine vulnerable subpopulations based on medical history and genetic risk. Pharmacokinetic sub-studies link exposure levels to biological distribution and symptom emergence, supporting translational relevance and public health application.

Anticipated deliverables

Quantification of neurological risks associated with aerosolized brevetoxin exposure. Identification of exposure thresholds associated with symptom emergence. Biomarkers linking environmental exposure to neurological outcomes. Data supporting development of clinical guidance and public health advisories for coastal communities.

Source of funding

National Institutes of Health R01 Award (PI: Dr. Laila Abdullah)