**State of
New Jersey
Commission on
Spinal Cord
Research**

DIRECTORY OF GRANT AWARDS
2020 GRANT CYCLE

NEW JERSEY COMMISSION ON SPINAL CORD RESEARCH

2020 GRANT CYCLE

DIRECTORY OF GRANT AWARDS FOR SPINAL CORD INJURY AND DISEASE RESEARCH

JANUARY 2020

NEW JERSEY COMMISSION ON SPINAL CORD RESEARCH

This data was compiled in compliance with the New Jersey Commission on Spinal Cord Research's statutory mandate, N.J.S.A. 52:9E-1, "…to compile a directory of spinal cord research being conducted in the State."

The information contained within this directory is not all-inclusive. The research projects and researchers listed in this directory are all based in the State of New Jersey and have applied to and received funding during the fiscal year 2020 grant cycle. The research projects are not categorized or listed in any order.

This directory is not a complete listing of all scientific research being performed within the State of New Jersey due to the proprietary nature of the research being conducted at various institutions throughout the State. In addition, institutions are not obligated to share their research information with the New Jersey Commission on Spinal Cord Research.

Please feel free to contact the New Jersey Commission on Spinal Cord Research at P.O. Box 360, 369 S. Warren Street, Trenton, New Jersey, 08625. The Commission's office can be reached by telephone at 609-913-5005, by fax at 609-943-4213, or by e-mail at NJCSCR@doh.nj.gov.

For information on the New Jersey Commission on Spinal Cord Research's grant award process, grant applications and deadlines, please see: www.state.nj.us/health/spinalcord.

2020 MEMBERSHIP INFORMATION

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<u>INDIVIDUAL RESEARCH GRANT RECIPIENT:</u>

CSCR20IRG005
Victoria Abraira, Ph.D.
Rutgers University - Cell Biology & Neuroscience
$600,000

Improving Rehabilitation: The Spinal Cord Neural Systems Important for Functional Recovery after Injury

Interventions that increase plasticity and regeneration are improving; this project identifies the neural systems and mechanisms that would be most effective to target such interventions.

Interventions that increase plasticity and regeneration after spinal cord injury (SCI) are improving, but little is known about the spinal cord neural systems that would be most appropriate to target such interventions. Rehabilitation, like treadmill walking, suggest a strong link between activity of sensory neurons in our limbs and motor recovery. Sensory information important for recovery is received and processed by the intermediate zone (IZ) of the spinal cord. This zone also contains neurons important for generating movement. Thus, therapeutic interventions should be tailored to most optimally engage the spinal cord IZ during recovery. However, there are a lot of different types of neurons within the IZ and few studies have actually tested the role of specific IZ neurons in functional recovery. Without this fundamental knowledge, appropriately targeting therapeutic interventions becomes very hard- much like trying to make a vaccine without first identifying the disease-causing virus. The reason progress has been slow, is because we don't have the appropriate tools to study specific spinal cord circuits (like IZ neurons) in health and injury.

Our research program has built an extensive mouse genetic toolkit to identify, visualize and test the function of specific spinal cord circuits in health and injury. We will use this toolkit to test the hypothesis that a very special class of spinal cord IZ neurons are responsible for interpreting sensory signals from the limb and translating this information to motor neurons that tell our muscles how to move as we walk. We will also test what happens to these neurons when the spinal cord is injured and how rehabilitation (like treadmill walking) help them make the right connections. To test if these neurons are part of key neural systems mediating recovery after injury, we will specifically remove these circuits form the injured animal to test if recovery gets worse. Lastly, we will implement machine learning approaches and artificial intelligence (AI) to track mouse movement in 3-dimensional space. We will use this technology to both test how these types of spinal cord neurons shape naturalistic behaviors (walking, running, rearing, etc.), but also to reveal the types of micro-movements that are most predictive of recovery after injury. By understanding the structure of movement after injury and how specific spinal cord neurons contribute to these movements, we can begin to tailor rehabilitation to specifically augment these mechanisms. Furthermore, implementing AI to characterize movement after injury will reveal the sensitive behavioral biomarkers needed to establish a fast, reliable and unbiased scale of functional recovery in rodents.

Our study provides both the essential framework and key tools to improve and expedite SCI therapeutic interventions. For example, clinicians using epidural stimulation to facilitate recovery need to tune electrical stimulation to recruit the right type of spinal cord circuits. This study will

reveal the identity of these circuits; critical information which the clinician can immediately use to more specifically tune epidural stimulation. Another example are stem cell therapies. Stem cells transplanted into injured spinal cords can self-assemble and integrate into spinal cord circuits. However, to enhance regeneration, stem cells could be shaped prior to injection to more accurately resemble the topography of the intact spinal cord. Indeed, fundamental knowledge revealed by this project will be utilized to help instruct graft development toward network identities that facilitate proper integration. Lastly, current scales to track functional recovery in rodents are time consuming and expensive; requiring two highly trained individuals to perform. Our AI-based Behavioral Biomarker Scale (BBS) is a cheap, fast, reliable and unbiased functional recovery scale that will revolutionize the way rodent SCI research is performed.

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<u>INDIVIDUAL RESEARCH GRANT RECIPIENT:</u>

CSCR20IRG008
Juan Mena Segovia, Ph.D.
Rutgers University – Center for Molecular & Behavioral Neuroscience
$600,000

Characterization of a Novel Descending Projection from the Mesencephalic Locomotor Region: Implications for Spinal Cord Injury Recovery

We will test if MLR glutamatergic neurons that directly contact spinal cord neurons modulate motor activity and contribute to the compensatory changes that follow an incomplete spinal cord lesion.

Following a partial spinal cord injury, a series of changes occur in the brain to compensate for the loss of motor function. Among these changes, motor regions of the brain change their pattern of connections and develop new functions that allow the restoration of movement. Therefore, understanding these changes are critical to guide the recovery of patients suffering a spinal cord injury and offer new therapeutic strategies.

In our lab, we have recently discovered the existence of a novel connection between a region called the 'mesencephalic locomotor region', or MLR, and the spinal cord. We believe that this connection is key to understand the changes observed following a partial spinal cord lesion because the MLR, first, is highly connected with the regions of the brain controlling movement, and second, because these connections are further enhanced after a spinal cord lesion. In addition, using highly selective technologies for the identification of neurons in the MLR, we were able to interrogate their function in relation to movement. We found that these neurons influence the spinal cord and influence muscle activity. Our own evidence, together with published literature, strongly suggest that they have a central role in the changes that occur following a partial spinal cord injury. Here we propose a series of experiments to test this theory and evaluate the potential of this area to be used as a therapeutic target in the clinics.

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INDIVIDUAL RESEARCH GRANT RECIPIENT:

CSCR20IRG011
Bonnie L. Firestein, Ph.D.
Rutgers University - Cell Biology & Neuroscience
$600,000

Cypin Inhibitors as Therapeutics for Neuropathic Pain after SCI

We will optimize treatment with inhibitors of the protein cypin to decrease neuropathic pain occurring after SCI.

Neuropathic pain often occurs after spinal cord injury (SCI) and leads to a decreased quality of life. Previous reports support a role for inosine and guanine-based purines in pain sensitivity. Our group has identified a handful of drugs that activate and inhibit enzymes in the central nervous system that regulate the production of guanine-based purines. We have found that administration of inhibitors of the guanine metabolizing enzyme cypin increases mechanical pain threshold in female mice with spinal cord contusion injury.

We now propose to extend these studies in a larger number of mice and in both sexes of mice since pain mechanisms differ between the sexes. The value of such a study would be considerable, as it could provide information that could ultimately be used to decrease neuropathic pain after spinal cord injury. Thus, our hope is to develop novel therapies to improve quality of life after spinal cord injury.

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<u>EXPLORATORY RESEARCH GRANT RECIPIENT:</u>

CSCR20ERG003
Brian Daniels, Ph.D.
Rutgers University - Cell Biology & Neuroscience
$199,999

Investigating RIPK3 as a Driver of Inflammatory Astrocyte Activation in Spinal Cord Injury

We will investigate the molecule RIPK3 as a candidate mechanism for pathogenic astrocyte activation in the context of spinal cord injury.

Traumatic injury to the spinal cord is marked by pathological immune responses in injured tissue. Following traumatic spinal cord injury (SCI), non-neuronal cells in the spinal cord called "astrocytes" become activated, causing them to proliferate and increase their expression of inflammatory genes. Recently, unique types of activated astrocytes have been described. One of these types are known as "A1" astrocytes, which promote neuroinflammation and neuronal cell death. A1 astrocytes have been observed in the spinal cord following SCI, though the cellular and molecular mechanisms that cause A1 astrocytes to develop in this context are unknown.

A strong candidate molecule for promoting A1 astrocyte formation following SCI is the protein RIPK3, an immunological signaling molecule with complex functions that promote both inflammation and cell death. Recent work has established that RIPK3 signaling is a potent inducer of neuroinflammation in a variety of neurodegenerative conditions, including Alzheimer's disease and amyotrophic lateral sclerosis. In response, pharmacological inhibitors of this pathway are currently in phase II clinical trials for several inflammatory disorders of the central nervous system. While RIPK3 activation has been observed in the context of SCI, roles for this pathway in the promotion of neuroinflammation following injury have not yet been uncovered.

In this proposal, we will test the hypothesis that RIPK3 signaling is a driver of pathologic A1 astrocyte activation using mouse and cell culture models of SCI. These studies aim to uncover fundamental mechanisms of inflammatory astrocyte activation in the context of SCI, with the goal of identifying a new target for the treatment of neuroinflammation and neuronal cell death in the injured spinal cord.

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EXPLORATORY RESEARCH GRANT RECIPIENT:

CSCR20ERG010
Francis Berthiaume, Ph.D.
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$200,000

Elastin-Like Polypeptides Fused with FGF-2 and ARA290 for Spinal Cord Injury Repair

The current study will investigate the efficacy of FGF-2-ELP and ARA290-ELP nanoparticles as a multi-modal treatment for SCI functional recovery.

There are ~17,000 new cases of spinal cord injury (SCI) reported each year, and >250,000 individuals living with SCI in the United States. New Jersey alone reported ~600 cases annually of traumatic or non-traumatic SCI. It is a devastating trauma that leads to a sudden loss of motor, sensory, and autonomic nerve functions below the level of injury. SCI leads to a host of secondary health issues, such as chronic neuropathic pain, skin pressure ulcers, incontinence, respiratory problems, to name a few. Chronic pain is seen in more than 75% of SCI patients, and is often severe, with a strong negative impact on daily functioning. SCI patients tend to experience a greater number of socioeconomic and lifestyle risk factors for disease and pain. The primary mechanical insult to the spinal cord triggers a cascade of molecular and cellular events causing inflammation and edema, which lead to further tissue damage around the initial injury site, thus exacerbating the extent of the initial injury. While the initial injury has already taken place when the patient is admitted to the hospital, the secondary damage occurs over a period of hours to days and thus may be prevented, ultimately promoting faster and more complete recovery.

The main objective of this proposal is to develop new therapeutic compounds that protect the undamaged neural cells located in proximity to the site of injury and induce regeneration. The compounds consist of natural peptides that have known relevant biological activity, and which will be coupled with other naturally occurring peptides that have the ability to self-assemble into nanoparticles. The resulting nanoparticles are more stable, and have a long-lasting effect, such that they may only require a single application. The nanoparticles will be tested first on neuronal cells in culture to verify that they have biological activity. Subsequently, they will be tested in an animal model of SCI to show whether they promote recovery from SCI. If successful, the therapeutic compounds developed would be a new low-cost biologic pharmaceutical that improves patient outcomes. The regulatory process for commercialization may be facilitated because these compounds are made of peptides that occur naturally in the body. Overall, this project addresses the ongoing initiative of NJCSCR to develop new therapies to improve the care and quality of life of SCI patients.

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EXPLORATORY RESEARCH GRANT RECIPIENT:

CSCR20ERG013
Rakesh Pilkar, Ph.D.
Kessler Foundation
$198,102

A Novel System for Quasi Real-Time Tracking of Neuromuscular Response during Electrical Stimulation

This study proposes a novel system for real-time assessment of artifact-free, high-quality responses of a stimulated muscle during neuromuscular electrical stimulation applications for SCI.

Spinal cord injury (SCI) is one of the most severe and life-altering injuries. The overwhelming statistics of SCI occurrences nationwide, as well as in New Jersey, and enormous treatment costs make the rehabilitation of these injuries increasingly important. In the absence of a cure, neuromuscular electrical stimulation (NMES) has been identified as one of the most effective rehabilitation strategies for recovery and treating the secondary complications after SCI. NMES operates on a basic principle that the application of electrical current can activate a paralyzed muscle. It has been reported that NMES interventions that involve voluntary participation from SCI patients are more effective in promoting recovery. However, such interventions are limited by lack of tools for monitoring effects of electrical stimulations (ES) specifically at the stimulated muscle during training. If voluntary participation is essential for NMES interventions to succeed, it is important to understand how much a muscle participates voluntarily, and how much ES contribute during training. Such information can help clinicians or researchers understand the relationship between ES and individual's own ability to activate a paralyzed muscle. With this information, the NMES interventions can be adjusted within session to extract optimal participation from patients and achieve maximal benefits. The need for a tool or a system for getting real-time information about a patient's muscle response is even more significant for individuals with complete SCI (cSCI) for whom the recovery in terms of movement may not be visible, but at muscle level it may be present. In the past, effects of NMES interventions have been assessed using the amount of force or torque generated at a joint. But this information is not specific to the stimulated muscle as the force or torque are generated using multiple muscles at a joint. Torque/force also fail to inform about how much a patient is contributing voluntarily and how much ES are contributing to the movement generated by ES. Surface electromyography (EMG) (electrical activity of muscles) recording provides a true physiological aspects of muscle function, interpretation of EMG during ES has been difficult to achieve due to the well-documented presence of overpowering interference of ES. With NJCSCR grant support, we were successful in developing and publishing a novel, accurate and efficient method (called as Empirical Mode Decomposition [EMD]-Notch filtering) to isolate 'true' muscle responses from EMG data collected during FES applications for individuals with incomplete SCI (iSCI). As a next step, the objective of this study is to develop a novel system, called as SMARTq (Stimulated Muscle Assessment in Real Time) for NMES applications. Aim 1 of the study will focus on the design, development and validation of the SMARTq system using existing as well as experimental data from 5 able bodied, 5 iSCI and 5 cSCI. Aim 2 will focus on evaluating the usefulness of the SMARTq system as a feedback providing tool which could provide more accurate and effective feedback via artifact-free EMG and volitional participation than

traditionally used torque. If successful, this novel system will allow the researchers or clinicians to monitor the effects of NMES at a muscle level during a training session. It will also allow them to observe contributions of patient's own participation as well as contributions of ES. This unique information, which was never accessible through traditional techniques (torque, force), will allow them not only to monitor the training sessions more effectively, but also allow them to modify NMES to get the best out of the patient as well as intervention. Hence, the outcomes of the proposed study complement NJCSCR's goals of development of novel techniques, methodologies, and models that could have a major impact on the field of SCI research and rehabilitation.

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FELLOWSHIP RESEARCH GRANT RECIPIENT:

CSCR20FEL004
Nisha Singh
Rutgers University - Cell Biology & Neuroscience
$60,000

Role of Guanine-Based Purines after SCI

In this proposal, we will investigate the role of guanine metabolism after spinal cord injury and identify therapeutic agents that will improve outcome after injury.

Spinal cord injury (SCI) is characterized by an impact or force inflicted upon the spinal cord that results in tissue trauma from the death and damage of cells in the nervous system. This damage alters the signaling capabilities of these cells, preventing their proper communication with the brain and body. Such interferences in communication lead to pathologies, such as loss of motor function, loss of unconscious bodily functions such as bladder control, and increased pain sensitivity in patients. Additional disruption of cellular communication (secondary phase of injury) occurs and can cause further damage to the spinal cord, worsening these symptoms. Hence, development of treatments targeting the events that occur during this secondary phase of injury is crucial for improving patient recovery.

Although guanine is well known as a chemical building block of DNA, it also has other effects in the cell. For example, it can be converted to molecules that can promote neuron survival and reduce pain sensitivity after SCI. In this project, we will investigate how a key enzyme involved in this conversion of guanine to other molecules is regulated and can be therapeutically targeted.

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FELLOWSHIP RESEARCH GRANT RECIPIENT:

CSCR20FEL013
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Rutgers University - Biomedical Engineering
$150,000

MMP-9 Inhibition Via Controlled Release of Chemical Inhibitors for Chronic Pressure Ulcer Healing in Spinal Cord Injured Patients

Pressure ulcer (PU), a major secondary complication of spinal cord injured patients to be treated by controlled release of drug molecules which inhibit the enzymes hindering the wound healing process.

Spinal cord injury (SCI) is one of the major neurological disorders mostly taking place due to accidents and occupational hazards. The spinal cord is the part of the brain coming down through the vertebral column in our back. Major nerves controlling our body sensation and responses are associated with the spinal cord. So, an SCI destabilizes this control and makes a patient partially or completely paralytic. As the sensations become weak and movements restricted, a patient sitting or lying down in the same posture creates high-pressure spots on the skin over hard bone specifically places like hip and back. These high-pressure spots in long run create ulcers called bed sores or pressure ulcers (PU). Due to the lack of sensation, the PUs often do not heal easily, progress continuously and create chronic deep injuries. Sometimes they become infected due to long-term contact with tissue fluids, moisture and lack of air circulation. This can lead to limb amputation, sepsis, and even patient death. In an injured tissue, a specific protein-degrading enzyme (MMP-9) is there which degrades the intermediary wound matrix (blood clot and surrounding hard tissue) and helps in healing by creating the path for new tissue to grow. In PU this enzyme is secreted in excess, and that even degrades every possible new tissue matrix allowing the wound to be unhealed for a very long time, and it impairs the healing process.

In current research work, we are proposing a bandage like protein matrix in which we will incorporate some drugs. These drugs will reduce this enzyme's activity for a prolonged period. The bandage is made of the same matrix in which an intermediate tissue is made in our body. So, whenever there will be more enzyme, the matrix will be degraded, and more drug will be released which will reduce the enzyme activity and allow the wound to heal. This cycle will go on in the same matrix until the wound healing is completed. Thus, this matrix drug composite will work as an automatic healing bandage for PU patients.

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SPINAL CORD TECHNIQUES TRAINING TRAVEL GRANT RECIPIENT:

CSCR20TTT003
Colm Atkins
Rutgers University
Cell Biology & Neuroscience
$5,000

Spinal cord injuries (SCI) are part of a spectrum of damage that can occur in the central nervous system (CNS). Our lab focuses on inflammatory injury to the CNS, as mediated by astrocytes. In addition to structural roles maintaining the blood-brain barrier (BBB) and physiologically supporting neurons, astrocytes mediate inflammatory responses to both sterile and microbial stimuli in the CNS. Astrocyte activation following traumatic SCI is well documented. Activated astrocytes have both protective and pathologic functions. Among the pathologic consequences of astrocyte activation following SCI is the prevention of recovery in damaged neuronal signaling networks, permanently impairing signaling through the lesion, and thus having a negative impact on sensory and motor functions in the injured individual. Our studies focus on inflammatory signaling through the kinases RIPK1 and RIPK3, which we propose as putative molecular drivers of pathogenic astrocyte activation. Signaling through RIPK1 and RIPK3 leads to an immunogenic form of programmed cell death known as "necroptosis." Necroptotic cells undergo membrane permeabilization, resulting in the release of inflammatory damage associated molecular patterns. The subsequent immune response causes damage to adjacent cells, both due to direct inflammation and the infiltration of other immune modulating cells. We will study the activation and signaling of the RIPK1/RIPK3 pathway in astrocytes following SCI in mice. To prototype these studies, we are using SHSY-5Y cells, a human cell line derived from a neuroblastoma, to develop preliminary data to guide our in vivo studies. The purpose of this application is to obtain in-depth training in rodent models of contusion SCI to facilitate the expansion of these studies into in vivo models. We hope to identify novel interactions of the necroptotic signaling pathway with the pathogenesis and repair processes in SCI, with the goal of identifying targets for pharmacological modulation, improvement in behavioral outcomes, and symptom management.

My previous training has prepared me to undertake new projects in the field of SCI. During my postdoctoral fellowship, I worked extensively with murine models of infectious and inflammatory disease states. I am proficient at the handling of mice, hamsters, ferrets, and guinea pigs. Species-specific training was provided for all manipulations, including IP, IM, SQ, and ID injections. I am also experienced with diverse sample collection methods, including retroorbital bleeding from mice and hamsters, vena cava blood collection in guinea pigs and ferrets, and terminal cardiac puncture blood collection in mice and hamsters. This training will allow me to expand my animal research capabilities. Specifically, we will able to safely manipulate and study mice with a physically damaged CNS. We can also combine these studies with our lab's other focus on infectious models of CNS damage to study potential comorbidities. An example of this would be a patient with limited mobility after a traumatic event who subsequently contracts an arboviral (such as Zika virus) infection. Studying the interplay of these two pathologic states would be both innovative and timely. Building expertise in both of these domains will result in a rare and unique combination of skills, which will promote innovative grant applications and collaborative studies at Rutgers and beyond.

Beyond my own work, our lab is heavily invested in the training and mentorship of undergraduates. Developing the skills necessary to perform SCI studies will allow us to transfer these skills to Rutgers undergraduate researchers. Combined with their work in primary cell culture and virology, training in SCI models will give them a unique skillset that will make them highly competitive for whatever careers they choose. This aspect of my training will support the goals of our department to promote innovative undergraduate training and produce competitive job candidates. As a Non-Tenure Track faculty member of the department, supporting Dr. Daniels' research program and training his students is the most significant part of my job description. This grant will allow me to help develop our research in the most innovative way possible.

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