

## Capstone for Impact Submission | GY2020

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**Project Title:** Characterization of Chronic Pain and Hypersensitivity in Mixed, Motor, and Sensory Nerve Terminal Neuromas in Rats

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**Branch:** Procedures-Based Care

**Path of Excellence:**

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**Summary:** Approximately 185,000 amputations are performed annually in the United States. Symptomatic neuromas occur in approximately 30-40% of individuals after limb loss, and phantom limb pain affects 70-95% of these patients, often leading to excruciating pain and disability. Although pre-clinical animal studies have evaluated pain in different experimental models, it is not currently known whether different neuroma models lead to differences in pain hypersensitivity responses. The current study sought to characterize serial pain responses utilizing sensitive functional outcome measures from terminal mixed, motor, and sensory neuroma rat models.

**Methods:** Prior to surgery, all rats underwent baseline pain sensitivity testing and were randomly assigned to one of three surgical groups of six rats each: (1) mixed nerve (tibial); (2) sensory nerve (sural), and; (3) motor nerve (femoral) neuromas. The distal nerve of each respective surgical group was isolated, transected, and transposed to a more superficial position in the hindlimb, creating neuromas that were accessible for sensitivity testing. Neuromas were created in the right hindlimb (experimental group) with the left hindlimb serving as a control. Functional pain outcome measures were performed serially for eight weeks and assessed mechanical allodynia (von Frey test), heat allodynia (Hargreaves test), and cold allodynia (Acetone test). Terminal outcome measures occurred at two months and consisted of histomorphometrical analysis of the nerve and histological assessment of the neuroma.

**Results:** Both tibial and sural neuroma groups demonstrated increased mechanical sensitivity when the von Frey test was performed on the middle aspect of the hindpaw. However, only the tibial neuroma group displayed increased mechanical sensitivity when the test was performed on the lateral aspect of the hindpaw. von Frey assessment at the thigh level revealed decreased mechanical sensitivity at Week 1 post-surgery for all experimental groups. However, this decrease normalized to baseline and control levels during Week 2 post-surgery. Only the tibial neuroma group demonstrated an increase in thigh mechanical sensitivity at week 7 of testing. Cold allodynia assessed by the Acetone test revealed that only the tibial neuroma group displayed statistically significant hypersensitivity.

**Conclusions:** Of the three terminal neuroma models characterized in this study, only the tibial neuroma group demonstrated significant hypersensitivity to both mechanical and cold stimulation. Data from this study demonstrates that the tibial neuroma model is the most appropriate model for evaluating chronic behavioral pain responses following injury.

## Reflection/Impact Statement:

*You may use the following questions to guide your reflection:*

1. How did the process of conducting this research confront any limitations of your prior thinking?
2. Who could potentially benefit from this CFI project over different timescales and how?
3. What actions will you take afterwards to continue the momentum of this project, and maximise the likelihood of the identified benefits being achieved?
4. What advice would you give to another student completing their CFI?

The process of conducting this research was laborious but did not necessarily confront limitations of prior thinking. We perhaps suspected that neuromas would increase sensitivity at the site of the neuromas, which was not demonstrably the case for our experiments. Behavior is harder to quantify than other biomedical research projects and requires tremendous data for analyzing trends and changes over time. In a sense, we were limited by our expectations of how the rats would behave following surgery, but animals are complex and behavioral studies are necessary to truly understand the pathophysiology of injury or disease. These experiments will benefit people in the future because people are more interested in knowing if they will be able to walk or live without pain, rather than the specific values of hypersensitivity and size of filament to cause a response in rats.

Other researchers within pain medicine, plastic surgery, physical medicine and rehabilitation, and other medical specialties can benefit from this study. Our goal is to use this project as a step towards a larger project using Regenerative Peripheral Nerve Interfaces to treat Neuroma pain. The timescale may take several years, but RPNI's have already shown to have some benefit for patients. We are interested in quantifying this data and experimentally show improvements in hypersensitivity and pain in an animal model.

I'm pursuing a field where I will be working with amputees and chronic pain patients in the future. I hope to continue this work while in residency. As with major basic science research projects, momentum must be maintained steadily for many years, but I'll try my best to assist my principal investigator in pursuing our next-phase larger Neuroma study.

I would advise future medical students completing their CFI to start early and to do something they are interested in, regardless of publication potential or alignment to one's intended specialty. This should be fun, and enjoyment will drive the project forward. Try not to fantasize how impactful a project can be, and try to just do the best job at whatever project you decide for CFI.