TITLE: Feasibility Study of New Method of Diagnostic and Prediction of Painful CIPN

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1.0 SPECIFIC STUDY AIMS

Painful peripheral neuropathy (PPN) is a common sequela of chemotherapy that severely impacts the quality of life in cancer patients (1). There is no biomarker, tool, or method to predict the development or progression of painful chemotherapy-induced peripheral neuropathy (CIPN). The pathophysiology of CIPN remains insufficiently understood; current treatment and prevention strategies provide only modest benefit to patients (2). In this study, we will test the utility of the Diode Laser fiber type Selective Stimulator (DLss) (3) in identifying patients at risk of developing PPN.

Small-diameter lightly myelinated Aδ and unmyelinated C cutaneous nociceptive fibers transmit pain from the peripheral to central nerve system. Aδ and C fibers are divided by sensitivity: heat, mechanical (tactile), and chemical stimulation, and epidermal versus dermal location. In animals and humans, dying back intra-epidermal fibers lead to reduced pain sensitivity, rather than pain, which suggests fiber loss alone is not sufficient to explain the development of neuropathic pain (4-9). In contrast, abnormally high spontaneous activity of nociceptive fibers, specifically dermal C mechano-insensitive (CMi) fibers, is associated with peripheral ongoing neuropathic pain (10-12)((13-15). Therefore, a tool that can measure, track, and predict the development of abnormal function of Aδ and C fibers is a critical unmet medical need.

Most diagnostic tests to study nociceptive fibers are able to measure the loss of pain sensitivity in epidermal fibers (4-9). However, these tests are not fiber-type selective (11). Only microneurographic recording is able to separate fiber type and to access single fibers (16). Though due to complexity, microneurography is unpractical in the clinic. In contrast, we developed and patented DLss, which can be used at the bedside to safely and selectively stimulate Aδ and C fibers in superficial and deep skin(14-23). Our preliminary DLss data demonstrates that patients with painful CIPN, who have decreased epidermal Aδ and C-fiber densities, have increased Aδ pain thresholds, while C-fiber thresholds are intact (20). The Aδ:C pain threshold ratio was consistently higher in CIPN than healthy volunteers.

Based on these preliminary data, ***we propose that the Aδ:C pain threshold ratio, as measured by the DLss during chemotherapy, will identify those patients at risk of developing pain during their treatment.*** Ultimately, this will help us identify patients who 1) may benefit from a change in their treatment to prevent CIPN and 2) patients who would be the best candidates for interventional trials testing new drugs for the prevention of PPN.

Aim 1: **Demonstrate that the Aδ:C pain threshold ratio is significantly higher in patients with painful CIPN than in patients with painless CIPN**.

Ovarian cancer annually affects about 20,000 women in the US and causes 14,000 deaths (1999–2012 Cancer Incidence and Mortality Data, http://www.cdc.gov/cancer/ovarian/statistics/) (24) Ovarian cancer patients' first line chemotherapy regimen is typically a taxane combined with platinum. These drugs are known to cause CIPN neuropathic symptoms in up to 70% of patients; a large portion of those patients develop painful CIPN (25, 26). The combination of taxane with platinum may increase development of CIPN in 1.5 times compared to just taxane application(25). As a result, ovarian cancer patients have a high overall burden of painful CIPN. Though the exact mechanism of nerve damage may differ between taxanes and platinum drugs, they both result in painful CIPN. Here we will examine the underlying shared pathophysiology

of neuropathic pain. We will evaluate the DLss in [64] ovarian cancer patients with painful and painless neuropathy during initial taxane combined with platinum treatment, to determine their Aδ:C pain threshold ratios. Presence or absence of pain will be determined via pain questionnaire and numeric pain scale (27). Enrolling 25 patients with painful CIPN and 25 patients with painless CIPN, we will have 80% power to detect a 1.31 fold Aδ:C pain threshold ratio.

Aim 2: Determine the Aδ:C ratio over time in patients with CIPN.
Our early data suggests a relationship between pain and the Aδ:C ratio in patients where pain is a well-established problem**.** However, the time course for development and sustainment of CIPN (painful and painless) is not well described. Early changes in the Aδ:C ratio may predict progression of CIPN during the course of the treatment and which patients will develop long-term neuropathy; or alternatively, the Aδ:C ratio may not change until weeks to months after symptoms have developed, analogous to the delay seen in EMG in mild–moderate nerve damage (28). Following patients longitudinally will also allow us to correlate Aδ:C ratio changes with the initial ratio, the patient's perception of pain over time, total dose of taxane and platinum, and possibly, treatments for neuropathic pain. Patients will be offered retesting approximately two weeks after the completion of sixth cycle. Aδ:C ratio changes will be correlated with progression of CIPN based on the presence or absence of pain and dose of agents to determine if the Aδ:C ratio evolves with symptoms and if a change in ratio predicts the progression to chronic painful neuropathy, chronic painless neuropathy, or resolution of symptoms.

The proposed work will provide valuable information about the development of pain in CIPN caused by common chemotherapies use to treat ovarian, colon, and other cancers. It will provide the basis for a larger study to validate the utility of DLss as a noninvasive bedside test for small-fiber neuropathies and provide a tool for investigators and clinicians to track and predict the development of pain in CIPN.

2.0 BACKGROUND AND RATIONALE

Peripheral neuropathy is a common side effect of chemotherapy, occurring in more than 60% of patients at some point during the course of cancer treatment (1). The resulting pain, numbness, and weakness can severely diminish quality of life. For many patients, the development of neuropathy leads to dose reduction or/and treatment delay, which may ultimately impact survival. The mechanisms by which chemotherapy-induced nerve damage ultimately leads to pain are poorly understood. As a result, there is no reliable way to predict which patients will develop irreversible painful chemotherapy-induced peripheral neuropathy (CIPN)(29-31) and consequently, no effective preventative strategy for combating it. The NIH (PA-12-083) has recognized this gap. This SBIR-funded project proposes the use of a new, patented, noninvasive test to interrogate specific subtypes of small diameter nerve fibers in patients with CIPN, addressing the need for an early diagnostic tool and ultimately predicting which patients should be offered early intervention to prevent persistent painful CIPN.

Two types of nerve fibers found within the epidermal and dermal skin layers, lightly myelinated Aδ and small unmyelinated C fibers, transmit nociceptive (pain) information. In certain types of painful neuropathy, such as painful diabetic neuropathy and CIPN, there is a dramatic dying back or degradation of these epidermal fibers (6, 32-34). Despite symptoms of pain, these patients have significantly increased pain thresholds when tested with currently available methods, which

primarily activate epidermal fibers, such as the CO_2 laser or contact heat thermodes (6, 7). In experimental models, ablation of the nociceptive fibers leads to loss of pain sensitivity, rather than pain, suggesting *nerve fiber loss alone is not sufficient to explain the development of pain (35)*.

In contrast, spontaneous activity of small fibers is associated with painful peripheral neuropathy (PPN) in animals and humans (13-15). Recently, a specific subtype of C fibers, the C mechano-insensitive (CMi) fibers, was found to be spontaneously active in patients with painful CIPN (14) as well as in other types of PPN (16). CMi fibers are located primarily in the dermis, have widely branching afferent arbors, are relatively insensitive to mechanical stimuli, but respond to noxious heat and chemicals (10). When activated, these fibers release chemokines that can cause vasodilation and may, in turn, sensitize surrounding fibers. In a rat model of paclitaxel-induced painful neuropathy, intra-epidermal nerve fiber degeneration was prominent, but deeper sub-epidermal axon bundles, where CMi reside, were spared (36). These characteristics suggest CMi fibers play a critical role in generating peripheral pain in CIPN.

There are several practical limitations to studying small nerve fibers, particularly CMi fibers, in patients suffering from CIPN. Current diagnostic tests are invasive, extremely time consuming, unable to selectively activate small fiber subtypes, or cannot safely stimulate deep fibers. Conventional electromyography and nerve conduction studies only provide information about large fibers. Microneurography can reliably distinguish small fiber types but it requires hours of invasive testing which is impractical for broad clinical use. Skin biopsy can be used to quantify small fiber density, but does not always correlate with CIPN symptomatology (33, 37). Noninvasive techniques, such as the QST battery (quantitative sensory testing) with radiant heat or contact thermodes or with the LEP (laser evoked potentials) based on CO_2 laser do not selectively activate C versus Aδ and can only safely be used to interrogate superficially located fibers (38-40) (see **Figure 1A**). CMi fibers require current densities five times higher than epidermal polymodal nociceptors (11). Similarly, the amount of radiant (e.g., non-coherent) heat required to activate CMi fibers results in surface temperatures that are about 7 °C higher than the activation threshold of C polymodal nociceptors (11, 41) Consequently, both electrical and radiant heat stimuli activate C polymodal nociceptors at intensities well below those for activating CMi fibers, rendering them non-selective and of limited use in evaluating CMi status in patients. In other words, currently available psychometric tests do not allow for the assessment of CMi fiber function. Therefore, it is not surprising that both psychometric QST and LEP tests of small diameter fibers are neither recommended nor reimbursed by Medicare and other insurance companies.

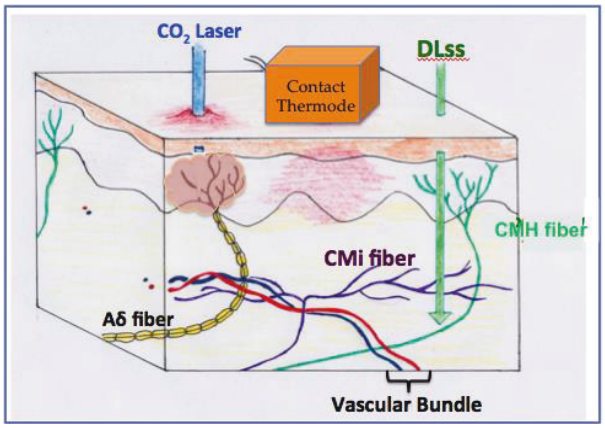

Figure 1A. Cross-section of skin demonstrating deep, uniform penetration of the DLss. The CO_2 laser uses energy levels that damage skin when penetrating beyond the epidermis. Thermal contact diodes emit distributive heat and require damaging levels of heat to active CMi fibers.

In contrast, the Diode Laser fiber type Selective Stimulator (DLss) selectively stimulates Aδ

and C fibers at much greater depths than existing techniques, which makes it an ideal method to assess small fiber subtypes separately. Thus, this technology opens the possibility for bedside clinical testing of a broad array of small fiber neuropathies.

Preliminary Work

In a series of 16 patients with PPN (painful diabetic neuropathy and painful CIPN), the DLss Aδ fiber protocol revealed significantly increased pain thresholds compared to healthy volunteers, but C-fiber protocol pain thresholds were similar to those recorded in healthy volunteers (20). This is in distinct contrast to radiant or surface heating methods, which produce significantly higher heat pain thresholds in DPN patients (6, 42). The difference in threshold measurements between the DLss and other heating methods cannot be explained by activation of the same fiber type. Instead, it is likely that heat pain thresholds measured using the DLss are the result of deeper CMi fiber activation, whereas radiant or surface heating evokes pain via activation of epidermal C polymodal nociceptors (see **Figure 1B**). The six patients with painful CIPN tested in our small pilot had a statistically significant difference in the Aδ:C pain threshold ratio when compared patients with normal volunteers (see **Figure 2**). The range of pain stimulation was set up from pain detection to mild pain and well tolerated by both group of patients. No patients withdrew from this study due to pain caused by the testing. No healthy patients in these studies had a ratio >2. This was a small non-uniform sample and was not powered to detect a change in ratios *a priori*. These preliminary data suggest a robust difference between patients with painful CIPN and normal patients. *Therefore, we hypothesize that there is a significant relationship between the Aδ:C ratio and painful CIPN.*

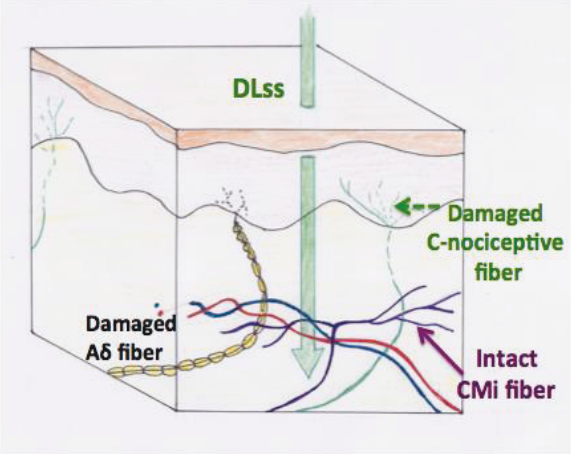

Figure 1B. Chemotherapy results in damage or dying back of Aδ and C nociceptive fibers in the epidermis, while dermal fibers are relatively spared. The DLss can penetrate into the dermis. Sparing the CMi in the presence of damage to Aδ results in an increased Aδ:C pain threshold ratio.

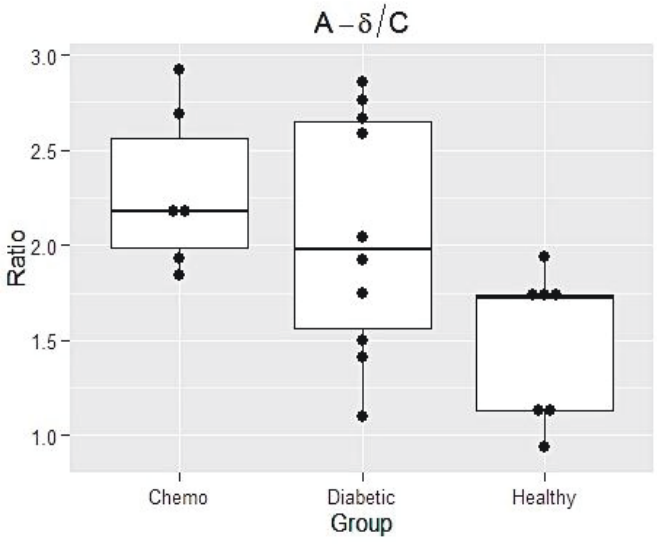

Figure 2. Pain threshold ratio of Aδ to C fibers, activated by DLss for 3 patient groups: healthy, painful diabetic neuropathy, and painful CIPN. P<0.05, one-way ANOVA.

In this study, we will test the above hypothesis in patients with newly-diagnosed ovarian cancer, who typically

receive a combination of paclitaxel and carboplatin as first-line chemotherapy. Both drugs individually, and in combination, are known to cause painful peripheral neuropathy in a proportion of patients. Paclitaxel and carboplatin cause peripheral nerve injury by different mechanisms, but both ultimately cause neuropathic pain (43). Because the proposed underlying pathophysiology of the pain is shared, we feel comfortable grouping these patients. We propose that using the DLss in patients with CIPN will allow for the assessment of changes in small-fiber pain thresholds and correlation of these changes to painful versus painless states. Additionally, we would like to demonstrate that the DLss correlates with persistent painful neuropathy. Our ultimate goal is to develop a non-invasive, bedside quantitative test for CIPN. For practiconers and patients, this could help avoid the use of more invasive, time-consuming tests, and non-small-fiber oriented testing, such as electromyography. If successful, this diagnostic test will also be relevant to drug testing, to help identify patients who are more likely to benefit from an intervention (44). The DLss could also be used to monitor the results of such trials noninvasively in a clinical and preclinical setting. While this study focuses on ovarian cancer patients, taxane and platinum based regimens are first-line treatment for several cancer types including ovarian, breast, lung, and colon cancer; therefore it is expected that the developed clinical test will be useful for these patients as well (26).

3.0 STUDY ENROLLMENT AND PARTICIPANT ELIGIBLITY

3.1 Study Enrollment

Patients will be identified as potential candidate and recruited from the GYN-oncology or neuro-oncology clinics in the Cancer Center at Stanford. Once a patient has been identified as a potential candidate and has expressed interest in the study, the neuro-oncology study coordinator will be called. If possible, the neuro-oncology coordinator will obtain consent in a private room in the Stanford Cancer Center or the Women's Cancer Center. Patients may also be consented via telephone or in a private room in the CTRU. Otherwise, a protocol-trained GYN-oncology coordinator or MD will obtain consent. There is no plan for advertising the study outside of Stanford, but patients in GYN-oncology and neuro-oncology will be presented with the study option if appropriate. We do not plan to use any recruitment material.

Informed Consent Process
All participants will be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Informed consent will be obtained by trained protocol staff in a private room or via telephone prior to any study procedures. All patients will have sufficient time to ask questions and have them answered prior to signing the form and enrolling in the study. Participants must sign the IRB approved informed consent prior to participation in any study specific procedure. The participant will receive a copy of the signed and dated consent document. The original signed copy of the consent document will be retained in the medical record or research file.

Screen Failures
Screening procedures include the inclusion/exclusion criteria below and a pain scale on the date of DLss testing. These do not include any new laboratory testing which may lead to screen failure. Therefore, the vast majority of patients that are formally screened are likely to enter the

study. Patients who have persistent, elevated pain of ≥50 on the day of scheduled testing will be asked to either reschedule or be considered a screen failure if rescheduling is not desired or possible. Patients who need to reschedule testing due to pain on study visit #1 will be considered to have a valid consent if more than 14 days from visit #1. If patient cannot undergo the DLss testing due to pain within the protocol defined window, they will be considered a screen failure. These patients will also be directed to their physician, if needed, for assistance in pain management. In the event that a patient enters screening but subsequently fails to meet criteria, their data will be entered in OnCore as a screen failure.

3.2 Inclusion Criteria

3.1.1 Have pathologically proven ovarian cancer or cancer of mullerian origin that requires first-line treatment with a taxane + platinum based chemotherapy regimen.

3.1.2 GROUP A (painful neuropathy group): Must have subjective symptoms of painful peripheral neuropathy (burning, stabbing, throbbing, painful tingling, aching in the fingers and/or toes) that is greater than or equal to 10 on a scale of 0 to 100 in the neuropathic pain questionnaire

GROUP B (no pain group): Must either have subjective symptoms of painless neuropathy (loss of sensation, worsening balance, strange sensation in fingers and/or toes) or no complaints related to neuropathy.

3.1.3 Be ≥18 years of age

3.1.4 Have a life expectancy of 6 months

3.1.5 Ability to understand the study protocol, participate in testing, and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Has received systemic chemotherapy for ovarian cancer or cancer of mullerian origin other than first-line treatment with a taxane + platinum based chemotherapy regimen.

3.2.2 Has received investigational drugs suspected to cause peripheral neuropathy. No concurrent investigational drugs may be used.

3.2.3 Has a history of:

- neuropathy or numbness/tingling suspicious for neuropathy prior to the first dose of chemotherapy for ovarian cancer
- history of prior treatment for other cancers that includes drugs known to cause neuropathy. These drugs include but are not limited to vinca-alkaloids, platinums, taxanes, bortizomib.
- B12 deficiency
- known peripheral vascular disease
- chronic daily headache or headache more than 14 days of the month

3.2.4 Has pain rated 50 or higher on a scale of 0-100, with 0 = no pain at all and 100 = worst pain imaginable on the day of the first DLss test.

3.2.5 Known pregnant or nursing patients.

3.2.6 Cancer survivors who have previous exposure to medications or chemotherapy that cause neuropathy are excluded from this study.

3.2.7 Patients who are known to be HIV-positive will be excluded as HAART and HIV itself are known to cause peripheral neuropathy.

3.2.8 Patients who do not speak or read English are excluded from this study.

3.3 Enrollment

The target enrollment for this study is 25 patients with painful neuropathy symptoms (Group A) that develop during chemotherapy and 25 patients without painful symptoms during chemotherapy treatment (Group B). Final group assignment takes place on study day 1 when the patient takes a pain questionnaire. There are no differences in study activities between Group A and B. The Stanford Women's Cancer Center sees about 150 new cases of ovarian cancer per year, therefore we believe will able to complete enrollment in 12 months. Patients will be stratified into painful versus painless group based on their first pain assessment inventory. Based on the incidence of painful versus painless neuropathy, we anticipate that Group B will complete enrollment first. Should enrollment in Group A be very slow, our team will consider advertising outside of the Stanford Women's Cancer Center. An additional approach is to increase enrollment in Group B and apply an "unbalanced" design which would increase the number of patients in Group B, but still ensure statistical power of 80%. For example, if only 18 patients with pain are identified, enrolling 39 patients without pain will maintain 80% power. If this step is needed, we will amend the IRB as well as this application. Additionally, we will apply for a no-cost extension to the NIH SBIR that is funding the project.

We understand that patients participating in non-interventional, longitudinal, clinical studies may not follow up for a variety of reasons. To address possible drop out, patients will receive higher compensation for participation in the second test, 75 dollars for the first, 125 dollars for the second. A commonly anticipated drop-out rate is 20% (45), leaving us with approximately 40 patients who we anticipate will complete both time points within the study timeframe. However, it is possible that patients in pain (Group A) may be more likely to follow up with the second test, which would help preserve the power of the study.

4.0 MATERIAL AND METHODS

4.1 Study Design: This is an open-label, non-interventional protocol testing a diagnostic device for the characterization of chemotherapy induced peripheral neuropathy. Patients will be stratified into Group A or Group B after completing the pain questionnaires. *There is no difference in testing protocols between these groups.*

4.2 Study Calendar:

	Visit	Screening	1	2
	Time Points	-14 days from Visit 1	9 weeks from C1D1 of chemo (+/-1 week)	21 weeks from C1D1 of chemo (+/-2 week)
Action	Screening and Consent	X		
	Eligibility	X		
	Demographics	X		
	Medical History	X		
	Cancer History	X		
	Con Meds	X	X	X
	Cumulative dose of each chemotherapy		X	X
	Pain Scale	X	X	X
	Neuropathic Pain Questionnaire (NPQ)		X	X
	Headache Assessment	X	X	X
	DLss Testing		X	X

Note that the dose of platinum and/or taxane will be determined by the treating oncologist. No decisions about total dose, dose delays, escalations, or reductions will be made based on testing in this protocol.

4.3 Duration of Participation/Criteria for End of Study:

Patients will be asked to undergo testing on 2 separate days separated by approximately 10-15 weeks. Each study day is anticipated to take no longer than 2 hours.

Patients will be followed until event that occurs first:

- second DLss testing, which will occur 21 weeks +/- 2 weeks after their first dose of chemotherapy for ovarian cancer
- subject withdraws from study
- subject enters hospice
- subject dies
- PI or study staff determine continued participation is detrimental to the patient
- Study is terminated by the investigators or sponsor

4.4 Description of Study Activities

Screening within 14 days prior to the first DLss testing:

- Written informed consent must be obtained from the subject prior to performance of any study-specific tests or evaluations. Subjects must be consented to undergo the pain questionnaires and DLss testing. If patient remains in active screening, consent does not need to be repeated if more than 14 days from DLss testing.

- Subjects will be asked to call and reschedule testing appointments if they have pain ≥50 on a scale of 0-100 (0=no pain, 100= worst pain imaginable) on the day of the scheduled test
- Eligibility criteria
- Headache assessment: assess for chronic daily headache or headache more than 14 days of the last month
- Demographics: birth date, race/ethnicity, and gender at birth.
- Medical history
- Cancer history including prior chemotherapy for malignancy
- Prior and concomitant therapy (including all previous therapy for malignancy, radiation, surgery, concomitant medications including OTC drugs, herbs, and St. John's Wort) taken in the week prior to DLss testing.

Study Visit 1 (9 weeks +/- 1 week from cycle 1, day 1 of chemotherapy)

- Concomitant medications taken in the last week
- Cumulative dose of each chemotherapy (As calculate by dose in mg x number of doses)
- Headache assessment as above
- Pain Questionnaires:
    - Numeric Pain Scale: Patients will be asked to rate their overall pain on a scale from 0 to 100, where 0 is no pain and 100 is the worst imaginable pain (27, 46). Patients who are experiencing pain ≥50 despite intervention will be asked to reschedule testing. If needed, the patient will be referred to their MD for standard of care pain control measures. Painful neuropathy will be defined as pain scale ≥10.

    - Neuropathic Pain Questionnaire (NPQ):
      This test will take less than 6 minutes to complete.
      The NPQ was initially validated in 528 chronic pain patients from several clinics. This test is able to differentiate neuropathic pain patients from non-neuropathic pain patients. The NPQ may be used for the initial screening of neuropathic pain patients. It also has the ability to provide a quantitative measure for the descriptors important in the diagnosis and assessment of neuropathic pain. Consequently, it can be used for monitoring of neuropathic pain treatments and as an outcome measure.
      For additional details: https://www.ncbi.nlm.nih.gov/pubmed/12966256.
      A copy is included as **Appendix C**.

- DLss testing per the following protocol
  We anticipate the total testing will take 30 minutes or less
  1) Subjects will be comfortably seated in a treatment recliner or in a gurney in a private room in the Stanford CTRU. Patient and the examiner will wear safety goggles. The door will be closed. The areas of skin to be tested will be shaved to avoid differences in light absorption and heating, because stimulation is non-contact; but strong pigmentation spots, tattoos, and moles will be avoided.

2) Patients will be reminded that if pain becomes too difficult for them to tolerate, they can stop the testing at any time.
3) The skin on the dorsum of the foot will be marked with a pen denoting 10mmx10mm squares.
4) The skin temperature will be monitored by infrared thermometer before the test and every 5 minutes during testing. If skin temperature is below 33 C, the skin tissue will be heated with warmed towels and maintained to keep temperature +/- 0.5 °C.
5) Each patient will have an A and C fiber stimulation. Stimulation will be performed on the dorsum of the foot using stimulation previously published parameters to elicit "burning pain," which is from activation of C-fibers and "pinprick" pain from A-fibers:
   -*Aδ fiber protocol*: 60-millisecond duration, 980-nm stimuli, 1-mm diameter stimuli
   -*C fiber protocol*: 2-second duration, 980-nm stimuli, 5-mm diameter stimuli
6) Stimulation will begin at 600mA±2 current (if sensation is felt at 600mA±2, go down two levels or 400mA±2) and increased at 100mA±2 increments until the subject identifies the stimulation as painful. The current will be increased up to a maximum of 1650 mA for the C-fiber protocol and to a maximum of 3500 mA for the Aδ-fiber protocol. In rare cases, patients may have pain thresholds that exceed the maximum skin temperature considered safe. For these patients, we will use the maximum safe stimulus level (3500 mA for the Aδ fiber, 1650 mA for the C fiber) to calculate the Aδ:C ratio. For subsequent runs, start at the highest level that do not evoke sensation from prior run (if sensation is felt at that level, go down two levels or 200mA ±2)
7) The pain threshold will be obtained using the "method of levels", using a series of ascending stimulation from energy that does not evoke sensation (600mA) and increasing by steps of 100mA until the last sensation is recorded as a 30-40 on the 0-100 pain scale. (0= no sensation, 10= definite sensation/pain, 100 worst imaginable pain). The procedure will be repeated three times and the pain threshold will be defined as averaging the readings of the 3 successive stimulations. The selected current will be applied 4 times. At this current, we expect to produce pain 50% of the time, and no pain 50% of the time.
8) The area of stimulation will be moved by 5 millimeters between each stimulation according to the grid (see #3).

Study Visit 2 (21 weeks +/- 2 weeks after first dose of chemotherapy for ovarian cancer)
- Concomitant medications as above
- Cumulative chemotherapy dose as above
- Headache assessment as above
- Pain inventories as above
- DLss testing as described above

4.5 Prior Validation of the DLss

Laser stimulation, similar to what is being used in the DLss, has been used in pain clinics

and research since 1975 as a diagnostic test. It has been proven to be useful and safe. Laser irradiation simultaneously activates both A delta and C fibers and primarily heat fibers located in the epidermis (up to 50-150 micron depth)(47-49).

Diode laser stimulation (the DLss used in this protocol) provides relatively uniform heating of skin from 50 to 600 microns deep, allowing for a distinct, singular burning or singular pricking pain depending on the laser pulse parameters. Experiments using an infrared diode laser conducted in Stanford and another institutions have shown that a short and a long laser pulse produces, respectively, a singular pinprick sensation (representing A-delta stimulation), and a singular burning pain sensation (representing C fiber stimulation) when applied to the dorsal hand skin of healthy subjects and pain patients volunteers. These preliminary results show that diode laser stimulation can safely and selectively activate A delta and C thermos-nociceptors(20, 22, 23, 50).

Diode lasers similar to the one used in this study are FDA approved and are often used in cosmetic medical procedures for hair removal. The lasers used for cosmetic procedures are set at *ten times* the power density of that used in our study.

Over 115 subjects have been tested with the DLss. No patient has withdrawn from DLss testing due to pain. Two patients had pin-tip sized skin discolorations that resolved in the course of a week.

4.6 Potential Adverse Events

While this protocol is not interventional, we recognize the potential for this testing to cause discomfort. Patients will be reminded that they can stop testing at any time.

There is a remote risk of skin injury or burning by laser stimulation when used for pain testing, that occurs by overheating of skin surface. This laser irradiation penetrates the skin fairly deeply, and does not allow overheating of the skin's surface. We also use a short, concentrated pulse; this will activate nerve fiber but is not long enough in duration to cause tissue damage. We have defined pain threshold levels for testing as moderate only, and are therefore only exposing subjects to the minimal stimulation that causes brief, moderate pain.

Over 115 subjects have been tested with the DLss. No patient has withdrawn from DLss testing due to pain. Two patients had pin-tip sized skin discolorations that resolved in the course of a week.

If any patient experiences an adverse event related to testing that is concerning to the study staff, protocol director, or PI; or is previously undescribed, we will report this to the IRB and SRC.

In addition, this protocol will be monitored by the Stanford DSMC.

4.7 Specimens

There are no specimens to be collected in this protocol.

4.8 Tissue for Biomarkers
There is no tissue being used for biomarkers in this study.

5.0 STATISTICAL CONSIDERATIONS

5.1 Outcome Measurements

5.1.1 Outcome Measure for Aim 1
The primary outcome measure of this study is the difference in the "Aδ:C pain threshold ratio" for patients with a painless response to chemotherapy versus painful neuropathy, as measured using the DLss.

The "Aδ:C pain threshold ratio" is calculated using the Aδ-fiber and C-fiber pain thresholds determined using the protocol outlined in **section 4.4**.

Each patient will have 2 testing sessions:

1) 9 weeks +/- 1 week from cycle 1, day 1 of chemotherapy
2) 21 weeks +/- 2 weeks after first dose of chemotherapy for ovarian cancer

This is not a safety outcome.

5.1.2 Outcome Measure for Aim 2
The second outcome measure of this study is the correlation between the "Aδ:C pain threshold ratio" and the development of pain.

We will generate a Spearman correlation coefficient for the "Aδ:C pain threshold ratio" obtained at the first testing session and the presence or absence of pain at the time of the second test.

This is not a safety outcome.

5.2 Analysis plan
The Aδ:C pain threshold ratio will be recorded for each eligible and evaluable patient for both time points. We will calculate the average value of this parameter for each group (A and B) on a logarithmic scale. Then we will use a standard statistical two side t-test to compare the "Aδ:C pain threshold ratio" in the painless CIPN group to the painful CIPN group. We hypothesize that the painful CIPN group will have statistically significantly higher value "Aδ:C pain threshold ratio" than those without.

To assess whether the "Aδ:C pain threshold ratio" predicts future painful or painless CIPN, we will conduct logistic regression analysis of the binary pain value (pain or no pain) at the time of the second testing (independent variable) on the "Aδ:C pain threshold ratio" at the time of the first testing (dependent variable). It will allow us to estimate whether the "Aδ:C pain threshold ratio" predicts the chances of a patient to develop pain.

As an exploratory analysis, we will explore if the "Aδ:C pain threshold ratio" obtained at

the first testing session predicts an increase in the numeric pain scale at the second testing session.

5.3 Sample size

The power analysis of the preliminary data presented here was conducted by Alex McMillan (Stanford). The analysis was done on the natural logarithm scale and converted back using anti-logarithms. The geometric mean (GM) ratio of chemotherapy was 1.58 times the GM for healthy group. The GM in the diabetic group was 1.38 times the GM of the healthy group. The most variable group (Diabetics) had a standard deviation (log scale) of 0.33 and this value was used for sample size calculations.

These calculations showed that sample size of 25 subjects in each group will have 80% power to detect a 1.31 fold Aδ:C pain threshold ratio in patients with painful versus painless CIPN. Based on the analysis of our preliminary data, we expect the effect size to be larger than 1.31.

It is possible that we will have more patients accrued to Group B compared to Group A because uncomfortable patients may not want to participate in as great a number. In this case, we will consider use using an "unbalanced" ("non-symmetrical") statistical design, i.e. a design with unequal number of subjects in the two groups. If we get fewer than 25 patients with pain we will increase the number of patients in the group without pain to preserve the power of 80% in order to detect the effect size. If this approach is necessary, we will apply for a no-cost extension of the NIH SBIR.

Table 5.1 shows several possible combinations of sample sizes which will assure the power 80% to detect the effect size 1.31. The sample sizes were calculated using SAS 9.14 software, procedure proc power. The calculations are based on the use of a t-test on the natural logarithm scale with a standard deviation of 0.33, detectable effect size 0.24 on the log scale.

Scenario	Subjects with pain	Subjects without pain
1	25	25
2	24	26
3	23	27
4	22	28
5	21	29
6	20	31
7	19	34
8	18	37
9	17	42

Based on the new patient volume in the women's cancer center, we expect to recruit 50 patients in 12 months. However, should the study require a non-symmetric statistical

method and its clear we will not be able to recruit 59 patients (scenario 9), we will we will request a12 month no-cost extension from the NIH/NCI.

6.0 DATA MANAGEMENT CONSIDERATIONS

6.1 Data management

The Protocol Director, or her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Electronic Study-specific Case Report Forms (eCRFs) will document treatment outcomes for data analysis. Case report forms will be developed using the OnCore database system and will be maintained by the study team. eCRFs are only accessible via login to the secure OnCore system.

Data shared with LasMed, LLC will be de-indentified and labeled with the alpha-numeric code assigned in OnCore. All data shared will be sent using SECURE: email. LasMed, LLC's computers are encrypted by Stanford IT.

6.2 Confidentiality

Patients will be assigned an alpha-numeric identifier in OnCore when enrolled. This database does link names and codes directly. Written inventories, such as the NPQ, will be identified with the patient's alpha-numeric code and kept in research binders, which are stored in the neuro-oncology research coordinators offices in the CCTO/Friedenreich building. Access to these offices requires an electronic Stanford ID badge.

6.3 Protocol Review and Amendments

The protocol, the proposed informed consent and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the Stanford IRB and Stanford Cancer Center Scientific Review Committee (SRC). Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation. The Protocol Director will disseminate the protocol amendment information to all participating investigators.

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APPENDIX A**: Participant Eligibility Checklist**

A Participant Eligibility Checklist must be completed in its entirety for each subject prior to registration. The completed, signed, and dated checklist must be retained in the patient's study file and the study's Regulatory Binder.

The study coordinator, treating physician and an independent reviewer must verify that the participant's eligibility is accurate, complete, and legible in source records. A description of the eligibility verification process should be included in the EPIC or other Electronic Medical Record progress note.

The following is an **example** of a Participant Eligibility checklist template. Modify this checklist to fit your study and include it in the appendix section of your protocol document. The protocol-specific checklist is **required** by the SRC and must be approved by the IRB.

Protocol Title:	Feasibility Study of New Method of Diagnostic and Prediction of Painful CIPN
Protocol Number:	**GYN0006**
Principal Investigator:	**Oliver Dorigo / Seema Nagpal, MD**

II. Subject Information:

Subject Name/ID:
Gender: ☐ Male ☐ Female

III. Study Information:

SRC Approved ☐ IRB Approved ☐ Contract signed ☐

IV. Inclusion/Exclusion Criteria

Inclusion Criteria (From IRB approved protocol)	**Yes**	**No**	**Supporting Documentation***
1. Have pathologically proven ovarian cancer or cancer of mullerian origin that requires first-line treatment with a taxane + platinum based chemotherapy regimen.	☐	☐	
2. **GROUP A:** Must have subjective symptoms of painful peripheral neuropathy (burning, stabbing, throbbing, painful tingling, aching in the fingers and/or toes) that is greater than or equal to 10 on a scale of 0 to 100 in the neuropathic pain questionnaire	☐	☐	

GROUP B: Must either have subjective symptoms of painless neuropathy (loss of sensation, worsening balance, strange sensation in fingers and/or toes) or no complaints related to neuropathy.			
3. Be >18 years of age	☐	☐	
4. Have a life expectancy of 6 months	☐	☐	
5. Ability to understand the study protocol, participate in testing, and the willingness to sign a written informed consent document.	☐	☐	
Exclusion Criteria (From IRB approved protocol)			
1. Has received systemic chemotherapy for ovarian cancer or cancer of mullerian origin other than first-line treatment with a taxane + platinum based chemotherapy regimen.	☐	☐	
2. Has received investigational drugs suspected to cause peripheral neuropathy. No concurrent investigational drugs may be used.	☐	☐	
3. Has a history of: - neuropathy or numbness/tingling suspicious for neuropathy prior to the first dose of chemotherapy for ovarian cancer - history of prior treatment for other cancers that included drugs known to cause neuropathy. These drugs include but are not limited to vinca-alkaloids, platinums, taxanes, bortizomib. - B12 deficiency - known peripheral vascular disease - chronic daily headache or headache more than 14 days of the month	☐	☐	
4. Has pain rated 50 or higher on a scale of 0-100, with 0 = no pain at all and 100 = worst pain imaginable on the day of the first DLss test.	☐	☐	
5. Known pregnant or nursing	☐	☐	

6. Cancer survivors who have previous exposure to medications or chemotherapy that cause neuropathy are excluded from this study. neuropathy.	☐	☐	
7. Known to be HIV-positive.	☐	☐	
8. Does not speak or read English.	☐	☐	

*****All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-report, and medical record review.

IV. Statement of Eligibility

By signing this form of this trial I verify that this subject is [☐ **eligible** / ☐ **ineligible**] for participation in the study. This study is approved by the Stanford Cancer Institute Scientific Review Committee, the Stanford IRB, and has finalized financial and contractual agreements as required by Stanford School of Medicine's Research Management Group.

Treating Physician Signature:	Date:
Printed Name:	

Secondary Reviewer Signature:	Date:
Printed Name:	

Study Coordinator Signature:	Date:
Printed Name:	

Protocol IRB-40358, Appendix B

Protocol Pre-review Checklist

The protocol pre-review checklist identified in the Table of Contents as “Appendix B” is a developmental tool for the use of the Stanford Scientific Review Committee (SRC), that is attached to the protocol template as that appendix.

It is intended that the Appendix B Protocol Pre-review Checklist would be deleted from the final version of the protocol document as submitted to the Institutional Review Board (IRB) for review and approval.

In this particular protocol document, the reference to Pre-review Checklist was not deleted from Table of Contents, and is so marked to reflect that this checklist is not part of the IRB-approved protocol.

Subject #_____

Neuropathic Pain Questionnaire

In order to assess and treat your pain problem, we need to thoroughly understand just exactly what type of pain you have, and how it may or may not change over time. You may have only one site of pain, or you may have more than one.

Please name the site of pain which is *most severe or disturbing* for you (eg, arm, foot, etc.)

_____

_____

For all of the following questions, please rate your pain at the site you just listed. Please use the space below to describe your pain in your own words:

_____

_____

Please use the items below to rate your pain as it *usually* feels. Indicate a number which represents your pain on each scale. For example, if you have no burning pain, you would rate the first item "0". If you have the worst burning pain imaginable, you would rate it "100". If neither of those fits your pain because it is in between, choose a number which *fits* your pain.

1. Burning Pain

0 ◄——————————► 100 Please rate your *usual* pain: _____

No Burning Pain Worst Burning Pain Imaginable

2. Overly Sensitive to Touch

0 ◄——————————► 100 Please rate your *usual* pain: _____

No Oversensitivity Worst Oversensitivity Imaginable

3. Shooting Pain

0 ◄——————————► 100 Please rate your *usual* pain: _____

No Shooting Pain Worst Shooting Pain Imaginable

4. Numbness

0 ◄——————————► 100 Please rate your *usual* pain: _____

No Numbness Worst Numbness Imaginable

5. Electric Pain

0 ◄——————————► 100 Please rate your *usual* pain: _____

No Electric Pain Worst Electric Pain Imaginable

Subject #_____

6. Tingling Pain

0 ◄——————————► 100 Please rate your *usual* pain: _____

No Tingling Pain Worst Tingling Pain Imaginable

7. Squeezing Pain

0 ◄——————————► 100 Please rate your *usual* pain: _____

No Squeezing Pain Worst Squeezing Pain Imaginable

8. Freezing Pain

0 ◄——————————► 100 Please rate your *usual* pain: _____

No Freezing Pain Worst Freezing Pain Imaginable

9. How unpleasant is your usual pain?

0 ◄——————————► 100 Please rate your *usual* pain: _____

Not Unpleasant at All Most Unpleasant Imaginable

10. How Overwhelming is your usual pain?

0 ◄——————————► 100 Please rate your *usual* pain: _____

Not Overwhelming at All Worst Overwhelming Pain Imaginable

We are also interested in learning what circumstances cause changes in your pain. Please write the number that indicates the amount you experience each of the following:

11. Increased pain due to touch

0 ◄——————————► 100 Please rate your *usual* pain: _____

No Increase at All Greatest Increase Imaginable

12. Increased pain due to weather changes

0 ◄——————————► 100 Please rate your *usual* pain: _____

No Increase at All Greatest Increase Imaginable