AWARD/CONTRACT

1. THIS CONTRACT IS A RATED ORDER UNDER DPAS (15 CFR 350) — RATING

PAGE 1 OF PAGES 26

2. CONTRACT (Proc. Inst. Ident.) NO. M67854-04-C-5074

3. EFFECTIVE DATE 01 Jul 2004

4. REQUISITION/PURCHASE REQUEST/PROJECT NO.

5. ISSUED BY CODE M67854
MCSC CONTRACTING OFFICES
CODE: CT-JNLWD
2200 LESTER ST
QUANTICO VA 22134

6. ADMINISTERED BY (If other than Item 5) CODE
OFFICE OF NAVAL RESEARCH
ATLANTA REGIONAL OFFICE 100 ALABAMA STREE
ATLANTA GA 30303-3104

7. NAME AND ADDRESS OF CONTRACTOR (No., street, city, county, state and zip code)
UNIVERSITY OF FLORIDA
DIVISION OF SPONSORED RESEARCH, 219 GRINT
GAINSVILLE FL 32611

8. DELIVERY
[ ] FOB ORIGIN [X] OTHER (See below)

9. DISCOUNT FOR PROMPT PAYMENT
Net 30 Days

10. SUBMIT INVOICES 3 (4 copies unless otherwise specified) TO THE ADDRESS SHOWN IN:

ITEM
Section G

CODE 5E687 FACILITY CODE

11. SHIP TO/MARK FOR CODE
See Schedule

12. PAYMENT WILL BE MADE BY CODE M67443
DFAS-COLUMBUS CENTER
P.O. BOX 369022
ATTN: KANSAS
COLUMBUS OH 43236-9022

13. AUTHORITY FOR USING OTHER THAN FULL AND OPEN COMPETITION:
[ ] 10 U.S.C. 2304(c)( ) [ ] 41 U.S.C. 253(c)( )

14. ACCOUNTING AND APPROPRIATION DATA
See Schedule

15A. ITEM NO.	15B. SUPPLIES/ SERVICES	15C. QUANTITY	15D. UNIT	15E. UNIT PRICE	15F. AMOUNT
	SEE SCHEDULE				

15G. TOTAL AMOUNT OF CONTRACT $514,175.00

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CONTRACTING OFFICER WILL COMPLETE ITEM 17 OR 18 AS APPLICABLE

17. [ ] CONTRACTOR'S NEGOTIATED AGREEMENT Contractor is required to sign this document and return ___ copies to issuing office.) Contractor agrees to furnish and deliver all items or perform all the services set forth or otherwise identified above and on any continuation sheets for the consideration stated herein. The rights and obligations of the parties to this contract shall be subject to and governed by the following documents: (a) this award/contract, (b) the solicitation, if any, and (c) such provisions, representations, certifications, and specifications, as are attached or incorporated by reference herein. (Attachments are listed herein.)

18. [ ] AWARD (Contractor is not required to sign this document.) Your offer on Solicitation Number _____ including the additions or changes made by you which additions or changes are set forth in full above, is hereby accepted as to the items listed above and on any continuation sheets. This award consummates the contract which consists of the following documents: (a) the Government's solicitation and your offer, and (b) this award/contract. No further contractual document is necessary.

19A. NAME AND TITLE OF SIGNER (Type or print)
Brian Prindle
Associate Director of Research

20A. NAME AND TITLE OF CONTRACTING OFFICER
PEGGY SMITH / CONTRACTING OFFICER
TEL: (703) 432-3772 EMAIL: smithpl@mcsc.usmc.mil

19B. NAME OF CONTRACTOR
BY _____ (Signature of person authorized to sign)

19C. DATE SIGNED 7/13/04

20B. UNITED STATES OF AMERICA
BY _____ (Signature of Contracting Officer)

20C. DATE SIGNED 25-Jun-2004

Section B - Supplies or Services and Prices

ITEM NO	SUPPLIES/SERVICES	QUANTITY	UNIT	UNIT PRICE	AMOUNT
0001			Lot		
	Non-lethal Weapons Study				
	COST				
	Sensory Consequences of Electromagnetic Pulses Emitted by Laser Induced Plasmas				
	MILSTRIP: M9545004RCR4DH2				
				ESTIMATED COST	$514,175.00
	ACRN AA Funded Amount				$514,000.00

FOB: Destination

ITEM NO	SUPPLIES/SERVICES	QUANTITY	UNIT	UNIT PRICE	AMOUNT
0002			Lot		
OPTION	Non-lethal Weapons Study				
	COST				
	Sensory Consequences of Electromagnetic Pulses Emitted by Laser Induced Plasmas				
				ESTIMATED COST	$351,616.00
	Funded Amount				$0.00

FOB: Destination

Section C - Descriptions and Specifications

STATEMENT OF WORK

C1 Statement of Work

CLIN 0001 and Option CLIN 0002 shall be in accordance with the Statement of Work attached to this contract.

Section J - List of Documents, Exhibits and Other Attachments

Exhibit/Attachment Table of Contents

DOCUMENT TYPE	DESCRIPTION	PAGES	DATE
Attachment 1	Statement of Work	10	

1. Technical

A) Objectives/Tasks/Concept. Recent advances in directed energy weapons technology suggests that scalable, non-lethal to lethal force systems may be possible. Such a system would be useful in many environments. Two systems currently under development, active denial and pulsed energy (ADS and PEP) offer mainly complementary capacities that could address multiple tasks [redacted] These tasks include the [redacted] The full capability of these directed energy systems (DE) are still being explored. At their current stage of development, each system has clear non-lethal (ADS) and lethal (PEP) capacities suitable to the above tasks. Our experiments will examine the feasibility of PEP as a new generation non-lethal weapon. Pulsed energy can be configured to produce plasmas of exceptionally high energy. [redacted] In the studies described below we will determine the feasibility of using the plasma derived EMP to induce pain suitable to disarm and deter individuals or form barriers to the movement of large hostile groups. If successfully deployed, PEP could complement ADS in situations in which the latter is ineffective, less effective, or prone to countermeasures. Many of the countermeasures that might be envisioned against ADS [redacted] offer opportunities for PEP targeting (via plasma induction or ablation of the defense). Despite these potential advantages, certain special capabilities and features of ADS offer advantages over PEP in many scenarios. Therefore, the systems are complementary.

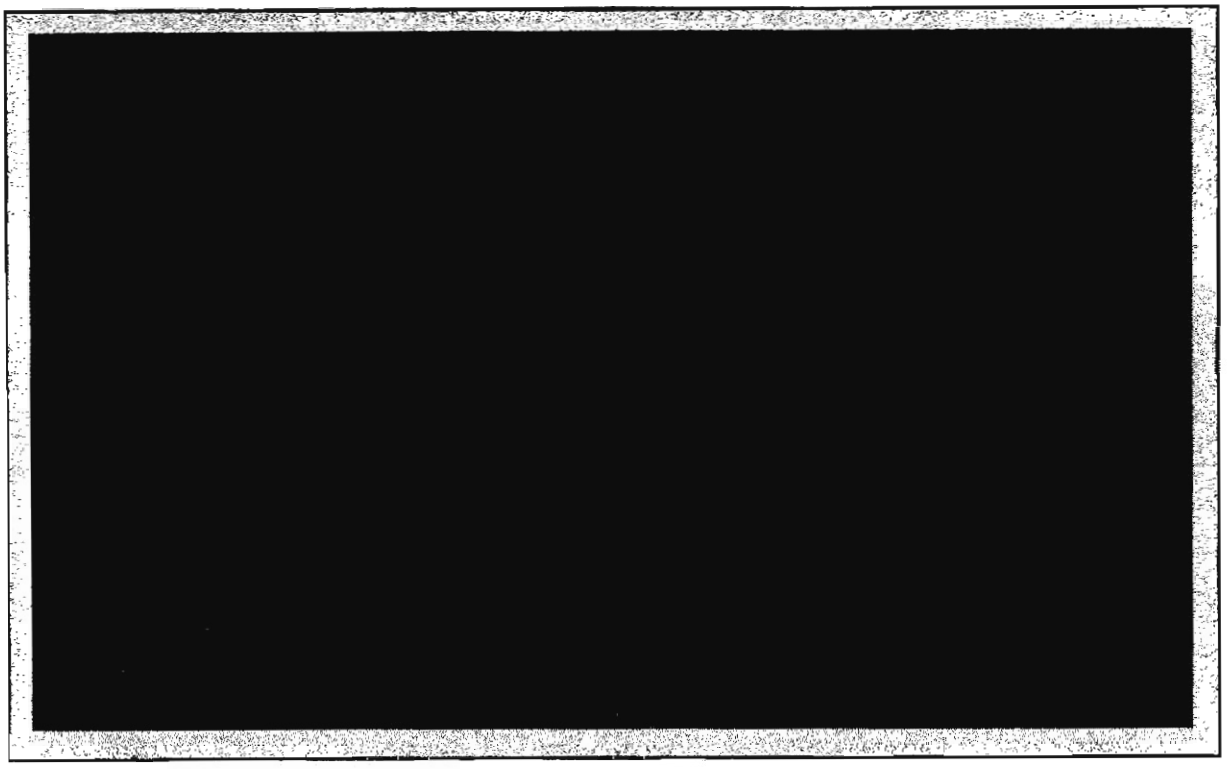
The efficiency and lethality of PEP weapons systems are straightforward. The non-ballistic, instantaneous properties of DE make precise targeting a straightforward matter of line of sight. Terrific amounts of energy can be delivered over great distances with pinpoint accuracy. However, [redacted]. Potentially, the application of PEP [redacted] The pain induced would be relatively instantaneous, and the duration of pain would be limited to the duration of application [redacted] Taser-like motor effects are also possible, although these are not investigated in this proposal.

In a separate application, we have proposed studies to quantify the [redacted] characteristics of laser induced plasmas created [redacted] with micro-, nano- pico- and femtosecond lasers of multiple designs and capacities [redacted] These studies will examine the characteristics of [redacted] In the studies described below, we will describe investigations that explore the human effects of LIP. Studies are proposed to determine the capacity of [redacted] to evoke pain. These studies will be performed, *in vitro*, where the factors such as distance and orientation can be tightly controlled, and where the appropriate pain system components can be isolated for detailed quantitative study. A portion of the investigations will apply [redacted] to sensory cell preparations. These [redacted] will be generated by conventional means. Subsequent studies will use laser-induced plasmas to create [redacted], the characteristics of which will be well defined [redacted] and optimized to produce atraumatic sensory influences.

Objective 1: To determine the features [redacted] that activate nociceptors and the extent to which this activation is effective without trauma. Pain is a primary component of all NLW. Pain can distract and deter individuals resulting in voluntary immobilization and/or flight. Nociceptors are the fundamental detection component of the pain system. Nociceptors transduce a variety of stimuli (gated ionic current) and then encode the pain signal (action potentials). While the mechanisms are not fully understood, ADS operates mainly on the *transduction* component by heating biological tissue to activate heat transducing proteins at a sub-traumatic level (B. Cooper, Microwave Techniques for Stimulation of Nociceptors, NTIC proposal, October, 2003). In contrast, [redacted] could activate nociceptors at the level of

encoding, thereby bypassing the transduction level. Induction at the encoding level is potentially more advantageous, as it avoids the direct heating of tissue and the risk that occurs from this time dependent event. Moreover, by engaging the encoding event, [redacted] will not rely solely on specialized transduction proteins that are selectively expressed in a subpopulation of sensory afferents. Although they differ in isoform and distribution, the proteins that mediate encoding are present in all excitable tissue. In objective 1, we will determine the influence [redacted] on nociceptor activation, focusing specifically on cutaneous nociceptors that innervate superficial skin (epidermis) and underlying tissue (dermis). The [redacted] strength required to induce activation, the contribution of pulse duration and burst frequency will be defined in tightly controlled experiments, *in vitro*. These data should prove to be very useful in interpreting the potential human effects of LIP, and its potential as a NLW.

Objective 2: To examine the influence of [redacted] laser plasmas, on nociceptor activation and determine the extent to which this activation is effective without trauma. Completion of objective 1 will enable a set of hypotheses that will guide studies of objective 2. With an understanding of the 'safe' parameter range for [redacted], directed choices can be made to study particular laser [redacted] configurations on nociceptors. Using identical recording methods (but laser stimulation) we will examine the nociceptor activating properties of laser [redacted] configuration and stimulation regimes.



[redacted]

B) Background

Laser Plasma Technology. There is increasing interest in the use of lasers for non-conventional defense applications. This is not only a consequence of the recent heightened sensitivities in such areas as homeland security, defense force protection, and law enforcement, but it also comes from new technical opportunities becoming available through the increasing pace of developments in laser technology. Developments in solid state laser technology in particular are leading these advances. Diode-pumping, for instance, for the first time enables electrical pump energy to be selectively channeled to specific laser transitions within solid-state laser media, leading to vast improvements in laser efficiency, compactness and stability. New evolutions in laser architecture, like fiber-lasers, slab-laser amplifiers, active phase control and ultra-short pulse technology are rapidly opening up new parameter space in sciences and technologies having possible relevance to new defense applications. One of these areas is the field of laser plasmas.

A relatively un-explored area of laser-plasma technology has been the [redacted] from the plasma, or from the laser-plasma [redacted]. These arise from the [redacted] conditions created in the plasma [redacted]. With conventional nanosecond or microsecond laser plasmas, [redacted]. It is in principle also possible to enhance [redacted]. Little work in this field has however been published in the open literature, particularly with regards to [redacted]. Yet every veteran laser-plasma physicist knows that, [redacted] when a laser-plasma is created, particularly at high intensity. It is at high intensities, (depending on pulse duration, or more specifically plasma scale-length) non-thermal laser coupling processes funnel absorbed energy to [redacted].

In the new realm of high intensity femtosecond laser [redacted] a whole new domain of laser interaction science has been accessed, leading to the generation of [redacted]. These particle-in-cell code calculations of the interaction, indicate transient [redacted] Assuming that the cross-section of these highly transient [redacted] are created in the target. Given that they only exist for times measured in picoseconds, the frequency of [redacted] emanating from this source would be in the [redacted] region. However, to date, little research has verified the [redacted] in this region.

[redacted]

There is extensive interest in developing weapons systems that utilize pulse energy projectiles (PEP). When appropriately configured, a PEP could serve both lethal and non-lethal applications. The guiding hypothesis of this proposal is that the creation of LIP [redacted] can serve as a NLW by activation of nociceptors.

The Peripheral Pain System. The detection of pain begins with a complex set of peripheral afferents (nociceptors) that detect and encode a great variety of stimuli. These peripherally encoded events are relayed by axons into the central nervous system (spinal cord, thalamus, cortex) where the information undergoes the complex assembly required to produce a localized, conscious perception of pain (Cooper and Sessle, 1993). Nociceptive afferents detect tissue damaging or near tissue damaging consequences of mechanical and thermal events, and the chemical events associated with actual tissue damage. To accomplish these multilevel tasks, the pain system has evolved a family of nociceptive neurons with diverse mechanical, thermal and chemical response capacities. These capacities overlap in a manner that is not completely understood, but it is likely that they vary for particular tissue sites (skin, joints, muscle, viscera, bone) that have highly specialized nociceptive requirements. Recent advances in nociceptor characterization have permitted classification, *in vitro,* of at least 8 distinct nociceptive phenotypes. Our laboratory has shown that sensory cells of the DRG are comprised of discrete, internally homogenous, classes of capsaicin (OC) sensitive (types 1, 2, 5, 7, 8 and 9) and insensitive (types 3, 4, 6) populations with distinct capacities to respond to 5HT, PGE_2, protons, ACh and ATP (Martenson et al., 1994; Cardenas et al., 1997; Cardenas et al, 1999; Petruska et al., 2000, 2002; Cooper and Cooper, 2001). We have used lipid soluble fluorescent tracers to define the specific distribution of nociceptors into viscera, joints and skin. Preliminary studies have indicated that nociceptive populations of skin include types 1, 2, 4 and 5. It is these nociceptors that are likely to receive the maximal burst [redacted] from laser plasmas [redacted]

The capacity of a nociceptor to detect and transduce noxious stimuli (heat, mechanical, chemical) is due to the presence of membrane imbedded proteins which act as transducers. Specific proteins have evolved which alter conformation in the presence of heat, chemical agents, [redacted]. This altered conformation gates a pore to allow ions to pass along their electrochemical gradients. Microwave radiation, via its capacity to heat tissue, is likely to interact with certain heat sensing proteins that are differentially expressed in nociceptor subpopulations (TRPV1, TRPV2; Caterina et al., 1997, 1999; Tominaga et al., 1998). Such proteins are likely to be the ultimate targets of ADS millimeter wave radiation. In addition to detection and transduction of noxious events, nociceptors, like all sensory afferents must *encode* the event so that it can be relayed to the central nervous system where perceptions are formed. Each nociceptor emits a code in the form of a series of action potentials that are produced in a frequency that is in proportion to the ionic current of the transduced event. The action potential code arises from the influence of the ionic current on clusters of voltage-gated channels. This can be thought of as an analog to digital conversion, where the ionic current is the analog signal that is converted to a digital code by the cluster of voltage gated channels. This cluster is composed mainly of voltage gated Na^+, K^+ and Ca^{++} channels. Each channel is composed of multiple proteins that form an ionic pore in the neuronal membrane and contain a distinct voltage-sensing region. Sensitivity to internal voltage varies considerably in sensory systems due to the differential distribution and multiple isoforms of voltage gated channels. Voltage gated Na^+ channels (Na_v) are responsible for the upstroke of the action potential while voltage gate K^+ channels (K_v) are responsible for the downstroke. Multiple forms of Na_v and K_v have evolved to set characteristic frequency response rates in different afferent populations. Nociceptors contain multiple forms of these channels (Na_v 1.7, 1.8 and 1.9; Fang et al., 2002; Djouhri et al., 2003a,b). [redacted]. Those Na_v subtypes that are mainly found in nociceptors ($Na_v1.8$ and $Na_v1.9$) have relatively high thresholds and slow kinetics. Due to the ultra slow kinetics of $Na_v1.9$, only $Na_v1.8$ participates directly in action potential generation (Elliott and Elliot, 1993; Akopian et al., 1996; Tate et al., 1998; Cummins et al., 1999; Dib-Hajj et al., 2002).

The ability to activate a nociceptor [redacted] can be reduced to a common event: [redacted] These clusters are known to occur at points along the nerve/axon and at the distal 'first segment' that is imbedded in the target tissue near the location of the transducing proteins (e.g., skin; Peng et al., 1999). [redacted] In the proposed experiments we will examine the capacity of [redacted] LIP to activate nociceptors. The intensity, duration and burst frequency will be varied to optimize activation. [redacted]

C) Technical Approach and Methodology

Overview of Experiments. The goal of the studies, in year 1, will be: 1) to determine the nano- and micro-pulsed [redacted] regimes that initiate nociceptor activation; 2) to determine the range of frequency modulation of the nociceptive signal that can be produced; 3) to determine the differential influence on distinct skin nociceptor phenotypes; and 4) to determine the point at which trauma might begin to limit the NLW value created. The body of knowledge acquired in year 1 will guide the development of hypotheses regarding the desired features of a plasma [redacted]. The experiments of year two will test these hypotheses using a variety of lasers [redacted]. Hopefully we will be able to marry these two bodies of knowledge and perfect a laboratory scale NLW based upon [redacted] laser plasmas.

These studies will be conducted *in vitro*, where nociceptive cells of several phenotypes can be exposed to well specified, intense [redacted] bursts that simulate exposure to laser [redacted]. Due to methods developed in our laboratory, we are able to identify discrete nociceptive phenotypes that are subpopulations of a large population of sensory cells that mediate touch, proprioception, warmth, cooling, itch and pain sensations (Petruska et al., 2000, 2002). The identified nociceptive subpopulations have been shown to be heat sensitive and thereby involved in the transduction of burning pain sensations

(Cooper et al., 2003). [redacted] In our studies we will present high intensity [redacted] nanosecond-micosecond pulses to cutaneous nociceptors (dicarbocyanine dye tracing). These nociceptors express distinct Na_v that are likely to manifest differential sensitivity [redacted] activation. We will determine the threshold for activation for nano- and micro- pulsed [redacted], the effect of repeated pulsing, pulse duration and intensity. If activation is discrete, we should be able to drive nociceptors in a pulse-by-pulse manner. Alternately, single pulses in these time and intensity domains may not be able to produce any activation. In this instance, burst application that approaches known thresholds of [redacted] effectiveness (1 msec) could be used. We will conduct such single, multiple and burst train studies at various power and duration combinations in multiple nociceptive subtypes. We will parallel these studies with examinations membrane damage suggestive of electroporation, cell trauma and death.

Due to limits of the current technology for delivering high [redacted] pulses, we will not be able to test in the femto- and picosecond domains in year 1. On the one hand, that will limit our ability to form hypotheses that simplify studies of year 2 involving [redacted] single pulse femto- and picosecond lasers. On the other hand, the shorter the duration of the burst, the less likely it will work in single pulse mode. In year 2, [redacted], these time domains can be examined. We might find that they work in burst mode, where the duration [redacted] can be functionally extended into the nanosecond time domain. To that extent, the nanosecond [redacted] could successfully emulate a burst of femto- and picosecond laser [redacted]. Femto second lasers have logistic advantages over other configurations.

In year 2, we will use our acquired knowledge of pulse duration, frequency and burst regimes to select laser [redacted] with high promise for NLW effectiveness. Based upon studies using a high repetition-rate (100 Hz) Q-switched Nd: YAG laser and two additional systems that use an open-architecture solid-state oscillator-multi-amplifier system of our own design, [redacted], we will have determined the characteristics [redacted] that best match those properties we predict (from year 1) will have atraumatic NLW effectiveness. In year 2 we will confirm these hypotheses (adjust as necessary) and examine whether the influence on nociceptors are robust with respect to variations. These variations could include [redacted]. We will again examine neurons for evidence of damage due to [redacted]. While the methods of stimulation differ considerably, the methods of recording from cells will remain the same. Because of the use of lasers in year two, the studies will shift to the University of Central Florida site (M. Richardson laboratory). Neural recording equipment will be shipped to the site, and some additional purchases will be made for auxiliary instruments that would be needed at the non-UF location.

Nociceptor Recordings. Conventional whole cell patch recordings [redacted] would be desirable and could be made in many of the planned experiments. These will always be suitable for classification of nociceptive cells at the beginning of each experiment prior to the application of [redacted]. These methods may be suitable for recording during single or dispersed [redacted] pulses. However, as the duty cycle or burst frequency increases, the ability to make such recordings by conventional methods is less likely. Therefore we will plan to use optical methods to assess action potential discharge. Accordingly, cells will be perfused with [redacted] sensitive dye [redacted]. High resolution [redacted] recording by optical measurement is possible under these conditions, [redacted]. All recordings are conducted at 35° C.

Procedures: Nociceptor Activation. Once the whole cell patch configuration is achieved, cells are classified by physiological criteria associated with nociceptors (voltage clamp mode; see Petruska et al. 2000, 2002). The main studies are carried out in current clamp mode. The cell (20-45 um diameter) is centered in the field (eyepiece reticule). The microscope is configured for [redacted] application by the introduction of a pair of stainless steel plate electrodes that have been pre-positioned to bracket the cell under investigation (3 mm, separation). During recordings, cells are exposed to nano- or microsecond pulses from one of the [redacted] pulsers [redacted]. These devices can produce pulse durations from 10 nanoseconds to 100 microseconds [redacted]. High [redacted] exposures are commenced at planned intensities, durations, repetition rates, and burst frequencies. Optical recordings are made continuously and captured by software for analysis. Studies will define the minimum field characteristics that produce activation, and then proceed with higher burst frequencies, longer durations and more intense fields to determine the limits of activation and the point at which trauma occurs. Using conventional records, we will monitor RMP at regular 'rest' intervals. [redacted] Studies will proceed on a variety of skin nociceptive phenotypes (types 1, 2, 4 and 5). Differences in susceptibility are likely to be observed due to quantitative and differential expression of TTX sensitive channels ($Na_v1.7$ vs $Na_v1.8$). We will use QX314 (5 mM) or TTX (1 uM) to determine whether the dye emissions are due to gating of Na_v or a direct influence of [redacted] dye emission. Some time limited artifact is expected. If prolonged, false signals are

indicated, we will shift to Ca^{++} sensitive dyes. We will also consider thermal contributions by examining the inter-plate temperature shifts associated with stimulation protocols.

[redacted]

Measurement of nano and micro pulsed E fields. We will devise a range of instruments to assess [redacted] fields generated. These will be developments from devices we have used in the past [redacted], and also devices developed specifically for these studies.

The objective of these measurements will be to:

- Determine the magnitude, time-duration [redacted] of the [redacted] plasma, and the [redacted] from it.
- Analyze the frequency response of the [redacted].

Several detection systems will be used. Simple single and multiple loop detectors will be used for measurements [redacted]. We have previously used these to measure [redacted] from plasmas created by nanosecond duration long-wavelength, 10 mm, CO_2 laser pulses [redacted]. We will also use [redacted] to examine the [redacted] fields generated. We will also use more sophisticated [redacted] designs that have previously been employed to measure weak pulsed [redacted] signals associated with environmental protection or defense applications. [redacted] Our purpose here will be to adapt these concepts, and utilize the broad depth of knowledge in [redacted] detection [redacted] to use with microscopic laser-plasma-based sources.

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[redacted]

[redacted]

3. Statement of Work / Deliverables / Milestones

Q 1: TASK 1. Acquisition of equipment, validation of methods
We will determine the stable periods for neural recording [redacted] and determine the best dye for optical recording purposes. This quarter also involves training of the post doctoral fellow.

Q2: TASK 2. [redacted] pulsing of nociceptive neurons
We will determine thresholds and suprathreshold stimulation regimes. We will verify that these stimulus protocols function via Na_v. We will evaluate the contribution of [redacted] and cell death endpoints.

Q3-4: TASK 3. [redacted] pulsing of nociceptive neurons
We will pursue tests on multiple nociceptive phenotypes. We will evaluate the contribution of [redacted] and cell death endpoints.

Q5: TASK 4. Preparation for laser studies
We will move the neural recording rig to UCF. Modifications will be made to the recording rig to make it laser ready and laser safe.

Q6: TASK 5. Laser [redacted] and nociceptive discharge: Method validation
We will determine threshold and suprathreshold stimulation regimes. We will verify that these protocols function via Na_v. We will determine the contribution of [redacted] and cell death endpoints.

Q7-8: TASK 6 Laser [redacted] and nociceptive discharge: [redacted]
We will determine the optimal [redacted] composition and shape for nociceptor activation

A number of deliverables are anticipated:

a) Experiments will define whether a PEP has NLW capacities by demonstrating the feasibility of nociceptor activation *in vitro*

b) Experiments will point to the optimal pulse parameters to evoke peak nociceptor activation

c) Experiments will define the limits of tolerance for PEP exposure (onset of cell trauma)

d) Definition of the optimal parameters and tolerance for PEP exposure might point strongly toward development of one laser system over another (micro-, nano-, femtosecond)

e) Experiments will demonstrate scalability of a PEP to act as an NLW and scalability within the NLW continuum (i.e., moderate to intense nociceptor activation)

f) Experiments will determine the relative utility of laser targeting [redacted] to produce the desired, scalable sensory impact.

g) If outcomes point strongly to one laser system over another, this will have implications for power and weight requirements and logistical support.

h) Methodologies will be established to study [redacted] motor systems or investigate possible countermeasures.