Title: Immune-Related Trafficking and Signaling in Human Skin Associated with Low-Power, Infrared Laser Treatment

ClinicalTrials.gov: NCT02453113

ID: NIH/LAMMP-2015-1840

PROTOCOL NARRATIVE FOR EXPEDITED OR FULL COMMITTEE RESEARCH

University of California, Irvine
Institutional Review Board
Version: April 2013

HS#: 2015-1840
For IRB Office Use Only

Lead Researcher Name: Kristen Kelly, M.D.

Study Title: Immune-Related Trafficking and Signaling in Human Skin Associated with Low-Power, Infrared Laser Treatment

NON-TECHNICAL SUMMARY

Provide a non-technical summary of the proposed research project that can be understood by IRB members with varied research backgrounds, including non-scientists and community members. The summary should include a brief statement of the **purpose of the research** and **related theory/data supporting** the intent of the study as well as a brief description of the **procedure(s) involving human subjects**. ***This summary should not exceed ½ page.***

Recently, a group of scientists have reported that shining a specific kind of laser on the skin may improve the immune response to a vaccine. This study aims to further investigate the body's response to shining a certain type of light on the skin. It is hoped that the results of this study could then be used to determine if a laser may improve the response to a vaccine.

For these studies, we will recruit 10 healthy adults ages 18-50 from the patient population at the Beckman Laser Institute in Irvine, CA. We will treat the skin of the lower back with a pre-determined tolerable laser setting. Once this is done, small tissue samples will be analyzed to further understand the body's response to the laser in hopes that this response may help improve the body's response to vaccines.

SECTION 1: PURPOSE AND BACKGROUND OF THE RESEARCH

1. Describe **the purpose of the research** project and state the overall objectives, specific aims, hypotheses (or research question) and scientific or scholarly rationale for performing the study.
2. Provide the **relevant background information** on the aims/hypotheses (or research question) to be tested and the procedures/products/techniques under investigation.
3. Include a description of the **primary outcome variable(s), secondary outcome variables, and predictors** and/or comparison groups as appropriate for the stated study objectives.
4. Include a critical evaluation of **existing knowledge**, and specifically identify the information gaps that the project intends to address.
5. Describe **previous research** with animals and/or humans that provides a basis for the proposed research. **Include references/citations**, as applicable.
   This section should not exceed 4 pages.

The purpose of this proposal is to demonstrate that CW NIR laser treatment of human skin induces changes in cytokine and chemokine signaling in the skin and results in a statistically

significant increase in the number of dendritic cells in the skin tissue at the site of laser treatment. The hypothesis behind this result is that the human skin immune system will respond to low level 1064 nm light in a similar manner to mice.

Specific Aim: Demonstrate that a non-painful and non-damaging dose of CW NIR laser results in alteration of cyotkine and chemokine signaling and a significant increase in the number of dendritic cells in skin tissue exposed to the laser.

A published study showed that one-minute exposures of mouse skin to a 1064 nm laser light delivered at non-painful and non-damaging parameters resulted in significant immunologic changes in the skin that included up-regulation of specific cytokine and chemokine genes and the activation and mobilization of specific dendritic cells (Kashiwagi *et al.* 2013). We will assess whether 1064 nm laser treatment of human skin at roughly equivalent parameters evokes similar patterns of cytokine/chemokine signaling and immune cell activity.

It has been demonstrated in a published study that 1064 nm laser light delivered at a power, irradiance, duration and dose roughly equivalent to that used in mouse vaccine studies was tolerated and non-damaging to humans (Kashiwagi et al. 2013).

We will enroll 10 volunteers with skin phototypes I/II. Skin phototypes will be determined by Dr. Kelly (board certified dermatologist). It has been shown that lighter and darker skin types respond differently to 1064 nm wavelength light (Leclere et al. 2012) and choosing either lighter or darker skin types to study initially will reduce variability and will help eliminate confounding variables. Thus, skin phototypes I/II will be studied for our pilot human study.

In the first part of the study, we will make a determination of the laser irradiance that will be tolerated by all study subjects (as measured by lack of discomfort over the whole 1 minute exposure). Each subject will receive up to five initial one-minute treatments at 1, 2, 3, 4, and 5 W/cm^2 (0.2, 0.4, 0.6, 0.8 and 1 Watt). If a subject experiences discomfort at any of these irradiances, a second set of exposures will be made between the highest tolerable irradiance and the one that was not tolerable. These will be done at 0.2 W/cm2 increments (e.g., 3.2, 3.4, 3.6, and 3.8 W/cm^2). The highest irradiance the subject tolerates for 1 minute will be identified as that subject's maximum tolerable irradiance. After all subjects are tested, we will select the highest irradiance that was tolerated by all ten subjects and use this in the second phase of the study. The determination of the maximum tolerable irradiance of all 10 subjects will be determined before starting the second phase of the study below.

Within 6 months after the first test exposures and determination of the universal maximum tolerable irradiance, each subject will receive a one minute laser treatment at the maximum tolerable irradiance. Four hours later, we will take two 4 mm punch biopsies from bilateral areas of the lower back. One biopsy will be taken from the skin area treated by the laser, and one from an untreated area on the other side of the back as a control. Each biopsy sample will be divided into two using a sterile scalpel. One half of each sample will be immersed in formalin and shipped to the Massachusetts General Hospital Dept. of Dermatopathology for processing, fixing, and embedding in paraffin for determination of specific immune cell populations using specific immunohistochemical staining. The samples will also be stained with Hematoxylin and Eosin for histology at Massachusetts General Hospital Dept. of Dermatopathology. The other half of each sample will be flash frozen at -80˚ C for subsequent qPCR to identify upregulation of specific cytokines and chemokines such as IL-1a, IL-1b, TNFa, CCL2, CCL6, CCL11, CCL17, CCL19, CCL20, and CCR7. After flash freezing, this tissue will be sent to the Massachusetts General Hospital Vaccine and Immunotherapy Center for processing.

There will be a total of 5 visits, about 10-11 hours over a maximum period of 18-19 weeks in length of the study. Those visits include a screening visit, a visit assessing laser tolerance, a follow-up visit within 20-48 hours of tolerability testing to ensure patient safety, a treatment visit

with resultant biopsy, and a follow-up visit after biopsy to ensure patient safety.

References:

Kashiwagi S, Yuan J, Forbes B, Hibert ML, Lee ELQ, et al. Near-Infrared Laser Adjuvant for Influenza Vaccine. PLoS ONE 2013 Dec; 8(12): e82899. doi:10.1371/ journal.pone.0082899

Leclère FM, Magalon G, Philandrianos C, Unglaub F, Servell P, Mordon S. Prospective ex-vivo study on thermal effects in human skin phototypes II, IV and VI: a comparison between the 808, 1064, 1210 and 1320-nm diode laser. J Cosmet Laser Ther. 2012 Feb;14(1):7-13. doi: 10.3109/14764172.2011.634419.

Expected Results and Data Analysis:

We expect to demonstrate that this NIR laser dose elicits statistically significant dendritic cell trafficking to the human skin and induces cytokine/chemokine release and expression changes similar to that previously seen in mice.

The statistical end point of the study will be the changes in density of CD11c+ dermal dendritic cells between two biopsies from a study subject where one sample is subjected to laser irradiation and the other is the control. For assessment of statistical significance, we will apply a paired sample t-test.

SECTION 2: ROLES AND EXPERTISE OF THE STUDY TEAM

List all study team members below.

1. Identify each **member's position** (e.g., Associate Professor, graduate or undergraduate student) and **department**, and describe his or her **qualifications, level of training and expertise.** Include information about relevant licenses/medical privileges, as applicable.
2. Describe each team member's **specific role and responsibility** on the study.
3. **Faculty Sponsors** - list as Co-Researchers and describe their role on the project; include oversight responsibilities for the research study.
4. Explain who will have **access to subject identifiable data**.
5. Indicate who will be **involved in recruitment, informed consent process, research procedures/interventions, and analysis of data.**

Lead Researcher:

Kristen Kelly, M.D. is a board certified dermatologist with two years of additional training in laser medicine as the Packard fellow at the Beckman Laser Institute. She is currently a Professor in the Department of Dermatology at the University of California, Irvine. Dr. Kelly will oversee enactment of the protocol, review data and assist with data analysis. Dr. Kelly will be screening, recruiting, obtaining consent and overseeing CW NIR laser treatments for the study. She will have access to subject identifiable data.

Co-Researcher(s):

Jeffrey A. Gelfand, M.D. is a Clinical Professor of Medicine at Harvard Medical School and is a Senior Scientist at the Vaccine and Immunotherapy Center at the Massachusetts General Hospital Dept. of

Medicine. Dr. Gelfand will participate in the analysis of data. He will not have access to subject identifiable data. Per DHHS definition, Dr. Gelfand will not be engaged in research.

Rosalynn M. Nazarian, M.D. is an Assistant Professor of Pathology at Harvard Medical School, Dermatopathology Unit and is also affiliated with the Massachusetts General Hospital Dept. of Dermatopathology. She will participate in processing and analysis of samples. She will not have access to subject identifiable data. Per DHHS definition, Dr. Nazarian will not be engaged in research.

Kathryn Osann, Ph.D. is an Adjunct Professor in the Department of Medicine at the University of California, Irvine. She is an expert statistician and will participate in data analysis. She will not have access to subject identifiable data. Per DHHS definition, Dr. Osann will not be engaged in research.

Brent Martin, MD, is a Resident Physician affiliated with the Department of Dermatology at UC Irvine. He will assist the lead and co-researchers in obtaining and finalizing consent, performing treatments, and collecting and analyzing data. He will also have access to the subject identifiable data.

Logan Thomas is a medical student affiliated with the Department of Dermatology at UC Irvine. He will assist the lead and co-researchers in initiating but not finalizing consent, performance of treatments, collecting and analyzing data. He will also have access to the subject identifiable data.

SECTION 3: RESEARCH METHODOLOGY/STUDY PROCEDURES

A. Study Design and Procedures

1. Provide a **detailed chronological description of all study activities** (e.g., pilot testing, screening, intervention/interaction/data collection, and follow-up) and **procedures**.
   a. Include an explanation of the study design (e.g., randomized placebo-controlled, cross-over, cross-sectional, longitudinal, etc.) and, if appropriate, describe stratification, randomization, and blinding scheme.
   b. Provide precise definitions of the study endpoints and criteria for evaluation; if the primary outcomes are derived from several measurements (i.e., composite variables) or if endpoints are based on composite variables, describe precisely how the composite variables are derived.
   c. Indicate how much **time will be required of the subjects**, per visit and in total for the study.
   d. Indicate the **setting where each procedure will take place**/be administered (e.g. via telephone, clinic setting, classroom, via email). ***Note:*** *If any of the procedures will take place at off-campus locations (e.g., educational institutions, businesses, organizations, etc.)* ***Letters of Permission*** *are required.*
   e. If a procedure will be completed more than once (e.g., multiple visits, pre and post survey), indicate **how many times** and the **time span** between administrations.
2. **For studies that involve routine (standard of care) medical procedures:**
   Make clear whether procedures are being done for clinical reasons or for study purposes, including whether the procedures are being done more often because of the study. Use the following guidelines to determine the extent to which standard procedures and their associated risks need to be described in protocol:
   a. If the standard procedure is not explicitly required by the study protocol, the protocol need not describe that procedure or its risks.
   b. If the standard procedure is a main focus of the study (e.g., one or more arms of a randomized study is standard) or is explicitly required by the study protocol, the protocol must include a full description of the procedure and its risks.]
3. It is **strongly recommended** that you include a table of visits, tests and procedures. Tables are easier to understand and may help to shorten long repeated paragraphs throughout the narrative.
4. If study procedures include collecting **photographs, or audio/video recording**, specify whether any

subject identifiable information will be collected and describe which identifiers will be collected, if any.
5. Describe how the **subject's privacy will be protected** during the research procedures. ***Note**: This is not the same as confidentiality (see the Privacy and Confidentiality web page).*
6. Be sure to submit **data collection instruments** for review with your e-IRB Application (e.g., measures, questionnaires, interview questions, observational tool, etc.).

Description of Methodology/Study Procedures

Study Design

This study will be conducted at the Beckman Laser Institute outpatient medical clinics. Subjects will be treated as per protocol with a fixed light dose. Biopsies will be performed at the same facilities. Histological analysis will be conducted by the Department of Dermatopathology at UC Irvine. Immunopathology and PCR studies of the biopsied tissue will be conducted by faculty both affiliated with this study and the Massachusettes General Hospital.

Subjects will be recruited through Beckman Laser Institute outpatient medical clinics. Those interested in learning more will be contacted by the clinical research personnel, who will provide each interested person more information on the study and discuss with the person the inclusion and exclusion criteria. If the subject is interested, they will make an appointment to come to Beckman Laser Institute outpatient medical clinics.

At the initial visit, the clinical research personnel will go through the study consent form in detail and complete the necessary informed consent documentation. If the subject is willing, he or she will undergo a brief medical screening visit including a review of medical history, current medications**,** and review of vital signs (blood pressure, pulse, temperature). During that screening examination, the study personnel will ensure that the subject meets all the inclusion and none of the exclusion criteria. The study personnel will determine the subject's skin phototype. As a result of this initial visit, the subject will be formally enrolled in the study and a clinical research record will be started on the subject. The initial visit will take approximately 30 minutes.

Description of the Intervention

1. Laser Treatment

Within 4 weeks of the initial screening visit, subjects will return for laser treatments.

Prior to all laser treatments, female patients of childbearing age will be administered a urine Beta hCG urine test. A positive result will disqualify the patient from the study. These results will be intended for research purposes only and will not be included in the patients' medical record.

A 95% water polymer gel will be applied prior to all laser treatments to all laser-exposed skin in order to limit excessive heat buildup within the skin. The gel will also be applied to the control site non-treated skin that will be biopsied. Subjects and research personnel will wear protective goggles appropriate to the safety rating of the laser.

In order to determine the maximum tolerable laser irradiance to be used in the biopsy phase of the study, each subject will receive a series of 1 minute exposures on 5 mm^2 areas of the skin of the lower back from continuous wave 1064 nm laser light emitted by a modified handheld diode laser device (IPG Photonics). Prior to these treatments, subjects will be informed about the kind of skin sensations the laser may cause and will always be asked to indicate to the study doctor when the exposure becomes uncomfortable. In the case that an exposure produces discomfort in the subject (a tingling or pinprick sensation or uncomfortable feeling of hotness), the exposure will be terminated. After the completion of each test site, the study personnel will examine the skin surface for signs of damage or alteration. Digital photographs will be taken of all sites before and after laser treatment.

Up to five initial one-minute treatments will be given to each subject starting at 1 W/cm^2 and increasing at 1 W/cm^2 increments up to a maximum of 5 W/cm^2 (0.2, 0.4, 0.6, 0.8 and 1 Watt). If a subject experiences discomfort during any of these treatments, a second set of treatments will be made between the highest tolerable irradiance and the one that was not tolerable. These will be done at 0.2 W/cm^2 increments (e.g., 3.2, 3.4, 3.6, and 3.8 W/cm^2). The highest irradiance the subject tolerates for 1 minute will be identified as that subject's maximum tolerable irradiance. After all subjects are tested, we will select the highest irradiance that is tolerated by all ten subjects and use this in the second phase of the study.

The determination of maximum tolerable irradiance will be conducted within 6 months of the second phase of the study. At that time, all subjects will receive a single treatment to a 5 mm spot on the lower back with the CW NIR laser for one minute at the maximum tolerable irradiance. The determination of the maximum tolerable irradiance of all 10 subjects will be determined before starting the second phase of the study.

Within 20-48 hours, patients will return to clinic for a follow-up visit where the treated site will be checked to ensure no unusual reactions from the treatment have occurred.

2. Punch Biopsy

Four hours later, two 4 mm punch biopsies will be performed on the skin of the lower back: one at the location of the laser exposure (experimental) and a second one at a bilateral non-exposed skin site on the lower back (control). Biopsies will be taken using standard biopsy protocol. The skin will be cleaned and patient will receive local anesthesia for this procedure. Following completion of the biopsies, a bandage will be placed on each biopsy site. The clinical research personnel will provide the subject instructions in oral and written form on the care of the biopsy site. The subject will be seen 10-14 days after to assess the status of the biopsy site for proper healing.

In summary, there will be a total of 5 visits, about 10-11 hours total, spanning over a maximum of 18-19 weeks in length of the study. Those visits include a screening visit, a visit assessing laser tolerance, a follow-up visit within 20-48 hours of tolerability testing to ensure patient safety, a treatment visit with resultant biopsy, and a follow-up visit or phone call including photos of biopsy sites after biopsy to ensure patient safety.

3. Tissue Analysis

Half of each biopsy sample will be fixed, paraffin embedded and prepared as thin section slides. One set of these slides will receive Hematoxylin and Eosin staining to evaluate microscopic skin changes. This analysis will be conducted by faculty affiliated with the Massachusetts General Hospital Dept. of Dermatopathology after receiving the biopsy samples immersed in formalin from UC Irvine. A second set of specimen slides, identified only by subject number, will also be sent to collaborators at the Massachusetts General Hospital Dept. of Dermatopathology for further immunohistochemical staining and analysis. The second half of each biopsy specimen will be flash frozen at -80 C. These samples will be identified only by subject number and sent to collaborators at the Massachusetts General Hospital Vaccine and Immunotherapy Center for assessment of RNA and protein expression by qPCR, which will be used to identify up-regulation of specific cytokines and chemokines such as IL-1a, IL-1b, TNFa, CCL2, CCL6, CCL11, CCL17, CCL19, CCL20, and CCR7.

B. Statistical Considerations

1. **Statistical Analysis Plan:** Describe the statistical method(s) for the stated specific aims and hypotheses **described in Section 1**. ***Note:*** *Required for scientific review.*
2. **Explain how the overall target sample size was determined** (Provide power / sample size justification for the study).

If a statistical analysis plan is not appropriate for your study design, please describe a plan for assessing your study results.

Statistical Plan and Data Analysis:

Ten subjects will be recruited for the study on skin immune response to laser treatment. This is a single-site pilot study and all subjects will be recruited through their affiliation with the researchers. Analysis of histology samples of the skin will be for exclusion of indications of skin damage and will not be used in statistical analyses. Analysis of RNA and protein expression by qPCR will be descriptive and not used in statistical analyses.

Quantitative analysis will pertain to changes in the density of CD11c+ dermal dendritic cells in the laser-treated skin as compared with non-laser treated control skin. For assessment of statistical significance, we will apply a paired sample t-test.

The estimated mean density of CD11c+ dermal dendritic cells in the dermal layer has been described in a published study of 15 normal healthy volunteers as being 73 cells per mm skin section (Zaba LC, Fuentes-Duculan J, Steinman RM, Krueger JG, Lowes MA. Normal human dermis contains distinct populations of CD11c+BDCA-1+ dendritic cells and CD163+FXIIIA+ macrophages. J Clin Invest. 2007 Sep;117(9):2517-25.). The standard mean error was approximately ±10 cells. The study on effect of 1064 nm laser on dermal dendritic cells using the C57BL/6 mouse model showed that a one minute exposure to 1064 nm laser light at 5 W/cm^2 generated a net change in estimated numbers of CD11c+ dermal dendritic cells in the dermis of about 108% at 6 hours post exposure (Kashiwagi et al.).

Using a power calculation to provide a p value of 0.05 at a minimum of 80% power and a standard deviation of differences of 1.0, nine subjects would be required to see similar changes in cell density. We therefore conclude that ten subjects will be sufficient to see similar statistically-significant changes in human skin that were observed in the mouse skin.

All power analyses, datasets and statistical analyses will be independently performed on datasets by Dr. Kathryn Osann, Ph.D., an expert statistician of the Department of Medicine at the University of California, Irvine.

SECTION 4: SUBJECTS (PERSONS/CHARTS/RECORDS/SPECIMENS)

A. Number of Subjects (Charts/Records/Biospecimens)

1. Indicate the **maximum number of subjects to be recruited/consented** on this UCI protocol. This is the number of potential subjects you may need to recruit to obtain your target sample size. This number should include projected **screen failures and early withdrawals**. ***Note:*** *The IRB considers individuals who sign the consent form to be "enrolled" in the research.*
2. For **Mail/Internet surveys** include the number of people directly solicited.
3. If the study involves use of **existing charts, records, biospecimens**, specify the maximum number that will be reviewed/tested to compile the data or the sample population necessary to address the research question.

The maximum number of subjects to be consented is 15 subjects.

4. Of the maximum number of subjects listed above, indicate the **target sample size** for the study. This

is the number of subjects expected to complete the study or the number necessary to address the research question.
5. *For social/behavioral research*, the maximum sample size is often similar to the target sample size. If the **maximum sample size** is significantly greater (i.e., ≥ 1.5x) than the **target sample size** provide a justification.
6. For studies where multiple groups of subjects will be evaluated, **provide a breakdown per group** (e.g. controls vs. experimental subjects; children vs. adults; by age group).

The target sample size is 10 subjects.

7. For **multi-center research**, indicate the overall sample size for the entire study (across all sites).

[X] Not applicable - This study is not a multi-center research study.

8. Demonstrate that the **target sample size will be sufficient** to achieve the study goal and should coincide with the statistical approach **described in Section 3B**. ***Note:*** *Required for scientific review.*
9. **Sources and information** of assumed group effects and variability should be supplied (e.g., pilot data; data from related literature). ***Note:*** *Required for scientific review.*

Quantitative analysis will pertain to changes in the density of CD11c+ dermal dendritic cells in the laser-treated skin as compared with non-laser treated control skin. For assessment of statistical significance, we will apply a paired sample t-test.

The estimated mean density of CD11c+ dermal dendritic cells in the dermal layer has been described in a published study of 15 normal healthy volunteers as being 73 cells per mm skin section (Zaba LC, Fuentes-Duculan J, Steinman RM, Krueger JG, Lowes MA. Normal human dermis contains distinct populations of CD11c+BDCA-1+ dendritic cells and CD163+FXIIIA+ macrophages. J Clin Invest. 2007 Sep;117(9):2517-25.). The standard mean error was approximately ±10 cells. The study on effect of 1064 nm laser on dermal dendritic cells using the C57BL/6 mouse model showed that a one minute exposure to 1064 nm laser light at 5 W/cm^2 generated a net change in estimated numbers of CD11c+ dermal dendritic cells in the dermis of about 108% at 6 hours post exposure (Kashiwagi et al.).

Using a power calculation to provide a p value of 0.05 at a minimum of 80% power and a standard deviation of differences of 1.0, nine subjects would be required to see similar changes in cell density. In the event that the standard deviation of differences is 0, only two subjects would be needed. We therefore conclude that ten subjects will be sufficient to see similar statistically-significant changes in human skin that were observed in the mouse skin.

B. Inclusion and Exclusion Criteria

1. Describe the **characteristics and provide justification** for inclusion of the proposed subject population. At a minimum include information about the age and gender of the study population.
2. Describe **different subject groups** (e.g., students and teachers; control group and treatment group(s), children and adults) separately.

This study is targeted at healthy adults ages 18-50. We will recruit subjects affiliated with the Beckman Laser Institute or Department of Dermatology including our own patients as well as students and

employees affiliated with the Beckman Laser Center. This will be a single-site pilot study.

We do not anticipate potential barriers to accrual due to the small number of subjects needed and the large pool of potential subjects. There are no other restrictions of race, ethnicity or sex.

3. Provide the **inclusion and/or exclusion criteria** for the proposed subject population, as applicable.

[ ] Not applicable – This is not a clinical investigation and/or the characteristics of the population sufficiently describe the proposed subject population.

Inclusion Criteria

- Healthy men or women ages 18-50
- Fitzpatrick skin phototypes I and II
- Able and willing to comply with all visit, treatment and evaluation schedules and requirements
- Able to understand and provide written informed consent

Exclusion Criteria

- Use of systemic steroids or use of topical steroids on the back within 30 days prior to study
- Use of tanning solutions on the back within 48 hours prior to study
- History of hemophilia or clotting disorders or current use of an anticoagulant
- Mentally incompetent, prisoner, or evidence of alcohol or drug impairment
- History of immunosuppressive or immune deficiency disorders, including human immunodeficiency virus (HIV), acquired immunodeficiency syndrome (AIDS), or the use of immunosuppressive medications.
- Abnormal photosensitivity

- Known pregnancy by history or positive Beta hCG urine test result (test given prior to first laser treatment)

4. If **exclusion** is based on age, gender, pregnancy/childbearing potential, social/ethnic group, or language spoken (e.g., Non-English Speakers), **provide a scientific rationale**.

While laser light at 1064 nm is generally poorly absorbed in the skin, differences in melanin absorption at this wavelength result in different thermal profiles to the same emitted dose in different skin phototypes (see for example LeClere 2012). To reduce the variables at this pilot stage of study, we seek to reduce the differential absorption effect of melanin. Therefore, we will recruit subjects with minimal melanin content (skin phototypes I/II).

There are no known risks to a fetus from this study. The restriction of pregnancy is to ensure that unknown, but highly unlikely, risks to a fetus from low level light delivered to the skin of the mother are eliminated.

SECTION 5: RECRUITMENT METHODS AND PROCESS

A. Recruitment Methods

Please check **all** applicable recruitment methods that apply to the study. Place an "**X**" in the bracket **[ ]** next to the recruitment method.

[ ] This study involves no direct contact with subjects (i.e., use of existing records, charts, specimens)
- ***Skip to Section 6.***

[ ] UCI IRB approved advertisements, flyers, notices, and/or media will be used to recruit subjects. ***Submit advertisements for IRB approval.***
- Passive Recruitment - Potential subjects initiate contact with the study team.
- ***Complete Question 5B - Explain where recruitment materials will be posted.***

[ ] The study team will recruit potential subjects who are unknown to them (e.g., convenience sampling, use of social networks, direct approach in public situations, random digit dialing, etc.)
- Active Recruitment – Researchers contact potential subjects.
- ***Complete Question 5B.***

[ ] The UCIMC Clinical Trials web page will be used. ***Submit the UCIMC Standard Research Recruitment Advertisement for IRB approval.***
- Passive Recruitment - Potential subjects initiate contact with the study team.
- ***Skip to Section 6.***

[X] The study will be listed on **Clinicaltrials.gov**. ***Note:*** *This is required for all clinical trials.*
- Passive Recruitment - Potential subjects initiate contact with the study team.
- **Skip to Section 6.**

[ ] The UCI Social Sciences human subject pool will be used. ***Submit the Social Science Human Subject Pool Recruitment Advertisement for IRB approval.***
- Passive Recruitment - Potential subjects initiate contact with the study team.
- ***Skip to Section 6****.*

[ ] Study team members will contact potential subjects who have provided permission to be contacted for participation in future research studies.
- Active Recruitment – Researchers contact potential subjects.
- ***Complete Question 5B – Explain when and how these individuals granted permission for future contact; provide the IRB protocol numbers, if applicable.***

[X] Study team members will approach their own patients, students, employees for participation in the study.
- Active Recruitment – Researchers contact potential subjects.
- ***Complete Question 5B.***

[ ] Study team members will send UCI IRB approved recruitment materials (e.g., recruitment flyer, introductory letter) to colleagues asking for referral of eligible participants.*
- Passive Recruitment – Potential subjects initiate contact with the study team or
- Active Recruitment – Colleagues get permission from interested individuals to release contact information to researchers. Researchers contact potential subjects.

- ***For Active Recruitment, complete Question 5B.***

[ ] Study team members will provide their colleagues with a UCI IRB approved introductory letter. The letter will be signed by the treating physician and sent to his/her patients to inform them about how to contact study team members.
  - Passive Recruitment - Potential subjects initiate contact with the study team.
  - The IRB approved letter must be sent by the treating physician.
  - The study team does not have access to patient names and addresses for mailing.
  - ***Skip to Section 6.***

[ ] UCI study team members will screen UCIMC medical records to determine subject eligibility and approach patients directly about study participation.*
  - Active Recruitment – Researchers contact potential subjects.
  - ***Complete Appendix T to request a partial waiver of HIPAA Authorization.***
  - ***Complete Question 5B.***

[ ] Other Methods: <indicate the recruitment method(s) here>
  - ***Complete Question 5B, as applicable.***

B. Recruitment Process

1. Based on the methods checked above, describe and provide **details of the recruitment process** (i.e. when, where, by whom and how potential subjects will be approached, e.g. screening medical charts, findings subjects during routine patient visits, etc.).
2. If you will recruit by mail, e-mail, or phone, explain how potential subjects' **contact information will be obtained**.
3. If active recruitment methods will be used (i.e., researchers will make direct contact with subjects for the purpose of recruitment), explain how the individual's **privacy will be protected**. ***Note:*** *This is not the same as confidentiality (see the Privacy and Confidentiality web page).*

Subjects will be recruited from an outpatient population of subjects at outpatient clinic Beckman Laser Institute Medical Clinic, UCI Campus including our own patients as well as students and employees affiliated with the Beckman Laser Center. Care will be taken to avoid any coercion or undue influence for patients, employees, or students to participate in the study. To avoid coercion subjects will be consented by an unbiased research member and given the chance to deny consent. Subjects will also voluntarily approach research members to participate in the study. Those who satisfy inclusion/exclusion criteria and screening procedures are eligible to be enrolled in the study. If a potential subject communicates by research member and willing to be contacted the research staff will communicate the potential subject's name and contact information to the research coordinators to be scheduled for screening.

Subjects' medical record will not be accessed, only contact information will be obtain for compensation and research appointment process.

SECTION 6: INFORMED CONSENT PROCESS

1. Specify **how consent will be obtained** and describe the specific **steps for obtaining informed consent**.
2. Include information about **when and where** consent will take place and the **length of time** subjects will be given to decide whether they wish to participate.
3. If study team members will approach their own patients, students, or employees for participation in the study, explain what precautions will be taken to **minimize potential undue influence or coercion**, and **how compromised objectivity will be avoided**.
4. If children are involved in this study, please describe the **parental permission** process and the **child assent** process.
5. Be sure to **submit the consent/assent document(s)** with your e-IRB Application (i.e. Study Information Sheet, Recruitment script, Consent Form, etc.).
6. If this study involves the creation, use, or disclosure of Protected Health Information (PHI), specify the process for **obtaining HIPAA Authorization**. Be sure to submit the HIPAA Research Authorization form with your e-IRB Application.

Check all that apply:

[X] Written (signed) informed consent will be obtained from subjects. Signed informed consent, parental permission, and/or child assent will be obtained from subjects, as applicable. ***Describe the informed consent process.***

[ ] Requesting a waiver of written (signed) informed consent (i.e., signed consent will not be obtained)**.** Informed consent, parental permission and/or child assent will be obtained from subjects, as applicable. **Explain how informed consent will be obtained.** ***Complete Appendix P.***

[ ] Requesting a waiver of informed consent (i.e., consent will not be obtained). ***Complete Appendix O. Skip to Section 7.***

Research team members will approach all potential subjects near the end of a clinic visit without discrimination or coercion and will make clear that participation is completely voluntary and will not affect the level of care subjects will receive. The details of the study will be explained in appropriate language, to assure that the patient has a complete and accurate understanding of the study. The patient must also have a full understanding of the informed consent before signing the agreement. The process of obtaining informed consent will include the provision of an understandable explanation in written and oral form of the aims and benefits, risks, inconvenience, information on treatments or alternatives, if any, and right to withdrawal without penalty. Subjects must document their consent for study participation by signing the IRB-approved Consent Form. Limited PHI will be used for this study. We will be collecting patient names, phone numbers, and email addresses for purposes of patient communication. We will also be collecting patient skin type and age for data analysis for reasons that are outlined in this protocol. Patients will be asked to sign the HIPAA Authorization Form stating that this limited PHI will be obtained from patients. The subjects will be given the opportunity to ask questions of, and receive answers from, study personnel prior to a request to sign the Consent Form and HIPAA Authorization Form. Subjects may also take the Consent Form and HIPAA Authorization Form home for review prior to signing. Copies will be filed in the subject's medical center record and the subject will be given a copy of each form.

Subject medical record will not be accessed; only contact information, skin type, and age will be obtained for compensation and research appointment process.

7. **Non-English Speaking Participants:** In order to consent subjects who are unable to read and speak English, the English version of the consent form must be translated into appropriate languages once IRB approval is granted.

Check all that apply:

[ ] Not applicable - Only individuals who can read and speak English are eligible for this study.

[X] The English version of the consent form will be translated into appropriate languages for non-English speaking subjects once IRB approval is granted. An interpreter will be involved in the consenting process. ***Note:*** *The IRB must officially stamp the translated consent forms.*

[ ] Requesting a short form consent process. ***Complete Appendix Q.***
The short form process will be used for the following languages:
[ ] All non-English languages
[ ] All non-English languages except Spanish
[ ] Other languages (specify):

SECTION 7: RISK ASSESSMENT AND POSSIBLE BENEFITS

A. Risk Assessment

Place an "**X**" in the bracket **[ ]** next to the level of review (based upon the investigator's risk assessment).

[X] This study involves greater than minimal risk to subjects and requires **Full Committee review.**

[ ] This study involves no more than minimal risk and qualifies as **Expedited research**. ***Provide justification below for the level of review and for the applicable Expedited Category(ies) that you have chosen:***

B. Risks and Discomforts

1. Describe the **risks/potential discomforts** (e.g., physical, psychological, social, economic) associated with **each** intervention or research procedure.
2. Describe the expected frequency (i.e., **probability**) of a given side effect or harm and its severity (e.g., mild, moderate, severe).
3. If subjects are **restricted from receiving standard therapies** during the study, describe the risks of those restrictions.
4. If collecting identifiable private information, address the risk of a **potential breach of confidentiality**.

Potential Risks of Laser Treatment

1. Skin Damage which may occur from lasers include blistering, scabbing and scarring.

This risk is mitigated by intentionally limiting power levels and total doses to levels significantly below the threshold of skin damage established in the literature and in practice. Pre-determined maximal tolerable

doses will be utilized. The typical threshold of pain occurs at about 43° C, so limiting exposures to the subject's discomfort ensures that dermal temperatures will not generally exceed this temperature. At 43° C, the skin would need to be exposed to laser treatment for over an hour to produce skin damage (Yarmolenko PS, Moon EJ, Landon C, Manzoor A, Hochman DW, Viglianti BL, Dewhirst MW. Thresholds for thermal damage to normal tissues: an update. Int J Hyperthermia. 2011;27(4):320-43). In accord with this fact, the proposed study builds in a stopping point for laser treatment during the full one-minute laser treatment based on a study subject's experience of discomfort (e.g., uncomfortable skin hotness or a pins and needles sensation), which precludes damage to the skin by the proposed laser. A water polymer gel will also be applied to the laser-exposed skin in order to prevent excessive heat buildup and subsequent skin damage and discomfort.

Potential Risks of Punch Biopsy

Some of the complications associated with punch biopsy include local bleeding and bruising, pain, infection, allergic reaction to the local anesthetic and scar. These side effects will be minimized by following best medical practice and by using a small size biopsy punch.

Other Risks/Discomforts:

Confidentiality Risks: Since this study involves the use of identifiable information, there is a potential for a breach of confidentiality.

Unknown risks: There may be risks related to the research that we don't know about yet. However, the subject will be informed of any additional risks to which he or she may be exposed, and any changes that are made to the study, as a result of any newly-identified risks.

5. Discuss what steps have been taken and/or will be taken to **prevent and minimize** any risks/ potential discomforts to subjects (address physical risks as well as other risks such as the potential for a breach of confidentiality). Examples include: designing the study to make use of procedures involving less risk when appropriate; minimizing study procedures by taking advantage of clinical procedures conducted on the subjects; mitigating risks by planning special monitoring or conducting supportive inventions for the study.

Medical risks related to the exposure to laser treatment are minimal. The light doses to be used are well below the level used in other dermatologic studies of a 1064 nm continuous wave laser. Such studies did not describe any immediate thermal damage to the skin (see for example Pfau A, Abd-el-raheem TA, Bäumler W, Hohenleutner U, Landthaler M. Treatment of recalcitrant verrucae vulgares with Nd:YAG laser hyperthermia (Regensburg's technique)—preliminary results in 31 cases. Journal of Dermatological Treatment 1995; 6(1):39-42. and El-Tonsy MH, El-Domyati MM, El-Sawy AE, El-Din WH, El-Din T, Anbar A-S, Raouf HA. Continuous-wave Nd:Yag laser hyperthermia: a successful modality in treatment of basal cell carcinoma. Dermatology Online Journal 2004;10 (2):3). In addition, a small pilot study of a 1064 nm laser operating in nanosecond pulse mode (10 Hz) was used in five subjects of skin phototypes V-VI and at irradiances of up to 3.84 W/cm^2 did not show any signs of pain or skin damage (Kashiwagi *et al.* 2013).

As an added safety measure, light exposure will be stopped as soon as the subject notes discomfort or pain.

Risk Management and Emergency Response

Subjects will be closely monitored throughout the study with clinical and laboratory assessments, as described in the procedures above. The subjects will have access to a 24 hour pager to call with any questions or concerns at any time. The study procedures and subject responsibilities will be reviewed thoroughly with the subject. We will ensure the subject understands the procedures of the study prior to allowing enrollment.

To manage the small risk of complications related to skin biopsy the subject will be clearly instructed in the management of the biopsy site and provided a contact phone number if he or she experiences persistent bleeding, exudation from the wound site, persisting pain or numbness. The subject would be initially evaluated at the clinic and then either treated at the clinic or referred for additional care. A follow-up visit within 20-48 hours of tolerability testing and 10-14 days after biopsy will ensure that complications, such as infection, will be minimal.

C. Potential Benefits

1. Discuss the potential benefits that may accrue **directly to subjects.** ***Note:*** *Compensation is not a benefit. Do not include it in this section.*

[X] There is no direct benefit anticipated for the subjects.

2. Describe the **potential societal/scientific benefit(s)** that may be expected from this study.

There may be societal benefits to this testing if the laser is shown to modify skin immune responses in humans in a way that would potentiate intradermal vaccination, since no approved adjuvants for intradermal vaccination currently exist.

D. Risk/Benefit Assessment

Explain why the study risks are reasonable in relation to the **potential benefits** to subjects and society.

Study has been carefully designed to minimize risk. There are no tangible benefits to subjects for participating in this study. There is a potential benefit to society from this study, since showing that this type of laser treatment can modulate immune responses in the skin of humans would facilitate the development of a non-invasive method of enhancing immune responses to intradermal vaccines, and may open the door to other new types of laser-based immune treatments.

SECTION 8: ALTERNATIVES TO PARTICIPATION

1. Describe the **standard or usual care** activities at UCI (or study site) that are available to prospective subjects who do not enroll in this study, as applicable.
2. Describe other **appropriate alternative procedures** to study participation that are available to prospective subjects.
3. If no alternatives exist, indicate that the only alternative is non-participation

[x] No alternatives exist. The only alternative to subjects is not to participate in the study.

SECTION 9: ADVERSE EVENT REPORTING/MANAGEMENT AND COMPENSATION FOR INJURY

A. Adverse Events and Unanticipated Problems

1. Indicate that you are familiar with **UCI's Adverse Events/Unanticipated Problems** reporting policy and procedures. See http://www.research.uci.edu/compliance/human-research-protections/researchers/reporting-of-adverse-events-unanticipated-problems-and-violations.html for details.

[ ] Although this study involves no interaction/intervention with research subjects (i.e., involves the use of records, charts, biospecimens) an unanticipated problem may still occur (e.g., a breach in confidentiality), the researchers are aware of UCI's Unanticipated Problems involving Risk to Participants or Others reporting policy and procedures and will comply with this policy.

[X] This study involves interaction/intervention with research subjects. The researchers are aware of UCI's Unanticipated Problems involving Risk to Participants or Others reporting policy and procedures and will comply with this policy.

2. **If this study involves interaction/intervention with research subjects,** explain how the research team will **manage adverse events and unanticipated problems** that may occur during the study or after completion of the study (i.e., provide a plan).

[ ] Not applicable - This study involves **no interaction/intervention** with research subjects (i.e., involves the use of records, charts, and/or biospecimens).

Any adverse events related to the risks in this study and any unanticipated risk will be treated on a case-by-case basis by an investigator on this study according to good clinical practice. Study team will notify the Lead Researcher immediately of any adverse or unanticipated problems in the study for timely notification to the IRB.

B. Compensation for Injury

For **Full Committee protocols**, explain how costs of treatment for research related injury will be covered.

[ ] Not applicable - This study involves no more than minimum risk and qualifies as **Expedited research**.

[X] Researchers are familiar with and will follow UC policy regarding treatment and compensation for injury. If subjects are injured as a result of being in the study, UCI will provide necessary medical treatment. The costs of the treatment may be covered by the University of California, the study sponsor, or billed to subject or the subject's insurer just like other medical costs, depending on a number of factors. The University and the study sponsor do not normally provide any other form of compensation for injury.

[ ] Other:

SECTION 10: PARTICIPANT COSTS

1. If subjects or their insurers will be charged for study procedures, **identify and describe those costs.**
2. Explain why it is **appropriate to charge those cost** to the subjects or their insurers. Provide supporting documentation as applicable (e.g., FDA Device letter supporting charges).

[ ] Not applicable - This study involves no interaction/intervention with research subjects (i.e., involves the use of records, charts, biospecimens).

[X] There are no costs to subjects/insurers.

SECTION 11: PARTICIPANT COMPENSATION AND REIMBURSEMENT

1. If subjects will be compensated for their participation, explain **the method/terms of payment** (e.g., money; check; extra credit; gift certificate).
2. Describe the **schedule and amounts of compensation** (e.g., at end of study; after each session/visit) including the total amount subjects can receive for completing the study.
3. Specify whether subjects will be **reimbursed for out-of pocket expenses**. If so, describe any requirements for reimbursement (e.g., receipt).

[ ] Not applicable - This study involves no interaction/intervention with research subjects (i.e., involves the use of records, charts, biospecimens).

[ ] No compensation will be provided to subjects.

[ ] No reimbursement will be provided to subjects.

The study will provide subjects a compensation of $40/visit for participation in the study. The payment for the study will compensate subjects for their time and will be paid at the end of the fifth and final visit. UC Irvine will pay compensation directly to patients.

They will be paid through an electronic payment system called pay-quest. Personal information about subjects, including name, address, and social security number, will be released to the Accounting Office at UCI for the purpose of payment. Total compensation possible is $200.

SECTION 12: CONFIDENTIALITY OF RESEARCH DATA

1. Indicate all identifiers that may be included in the research records for the study. Check all that apply:

[ ] No subject identifiers are obtained (i.e., researchers will not collect information that can link the subjects to their data)

[X] Names **[ ]** Social Security Numbers **[ ]** Device identifiers/Serial numbers

[ ] Dates*	**[x]** Medical record numbers	**[ ]** Web URLs
[X] Postal address	**[ ]** Health plan numbers	**[ ]** IP address numbers
[X] Phone numbers	**[ ]** Account numbers	**[ ]** Biometric identifiers
[ ] Fax numbers	**[ ]** License/Certificate numbers	**[ ]** Facial Photos/Images
[ ] Email address	**[ ]** Vehicle id numbers	**[ ]** Any other unique identifier

[ ] Other (Specify all):

* birth date, treatment/hospitalization dates

2. Explain how data will be **recorded.**

Check all that apply:

[X] Paper documents/records
[X] Electronic records/database
[ ] Audio recording
[ ] Video recording
[X] Photographs
[X] Biological specimens
[ ] Other(s) (specify):

3. Indicate **how data will be stored, secured** including paper records, electronic files, audio/video tapes, biospecimens, etc.

<u>Electronic Data</u> (check all that apply):
[X] Coded data; code key is kept separate from data in secure location.
[ ] Data includes subject identifiable information. ***Note:*** *Encryption software is required.* (Provide rationale for maintaining subject identifiable info)**:** <Type here>
[ ] Data will be stored on secure network server.
[X] Data will be stored on stand alone desktop computer (not connected to network/internet)
[ ] Other (specify here):

<u>Hardcopy Data, Recordings and Biospecimens</u> (check all that apply):
[X] Coded data; code key is kept separate from data in secure location.
[ ] Data includes subject identifiable information (Provide rationale for maintaining subject identifiable info)**:** <Type here>
[X] Data will be stored in locked file cabinet or locked room at UCI/UCIMC.
[ ] Data will be stored locked lab/refrigerator/freezer at UCI/UCIMC.
[X] Other (specify here): Tissue specimens will be de-identified before shipment to Massachusetts General Hospital for analysis.

Data on Portable Devices:
4. Describe the **portable device(s) to be used** (e.g. laptop, PDA, iPod, portable hard drive including flash drives).
5. Specify whether **subject identifiable data** will be stored on the device. If so, **justify why** it is necessary to store subject identifiers on the device.

[ ] Not applicable – No study data will be maintained on portable devices.

Data without subject identifiable information may be stored temporarily on a password protected Laptop computer. This will include results of laser therapy and pictures of study sites. Study sites are non-facial so it is unlikely subjects can be identified from photos. A laptop is necessary because the imaging of the data collection takes place in the treatment room and it is difficult to transport a desktop into the treatment. Data from the laptop will be transferred to a non-network computer for long-term storage. No subject identifiable data will be kept on the laptop.

Data Access:

6. Specify who, besides the entities listed below, will have **access to subject identifiable private data and records**.
7. If there is a **code key**, specify who on the research team will hold the key, and who will have access to the key.
8. If publications and/or presentations will include **subject identifiable information**, specify where the data will be **published and/or presented** and address how the study team will obtain permission from subjects.

[ ] Not applicable – No subject identifiers will be collected.
[X] Not applicable – Only the entities listed above will have access to subject identifiable private data and records.

Data Retention:

9. Explain **how long subject identifiable research data** will be **retained**. The data may include a code with a separate code key or the data may include subject identifiers.

[ ] Not applicable. No subject identifiable research data will be retained.

[ ] Destroy once data collection is completed

[ ] Destroy at the earliest opportunity, consistent with the conduct of this research. Specify timeframe:

[ ] Destroy after publication/presentation

[X] Maintain for approximately 7 years

[ ] Maintain in a repository indefinitely. Other researchers may have access to the data for future research. Any data shared with other researchers, will not include name or other personal identifying information. Note: ***Appendix M is required.***

[ ] Research records will be retained for seven years after all children enrolled in the study reach the age of majority [age 18 in California] as this study includes children .

[ ] Research records will be retained 25 years after study closure as this study involves in vitro fertilization studies or research involving pregnant women.

[ ] As this is a FDA regulated study, research records will be retained for two years after an approved marketing application. If approval is not received, the research records will be kept for 2 years after the investigation is discontinued and the FDA is notified.

[ ] Other:

Data Destruction:

10. If audio or video recordings will be taken, specify the **timeframe for the transcription and/or destruction of the audio and video recordings.**
11. If photographs will be collected, specify the **timeframe destruction of photographs.**

[ ] Not applicable – No audio/video recordings or photographs will be collected.
[ ] Audio or video recordings transcribed; specify time frame: <Type here>
[ ] Audio or video recordings destroyed; specify time frame: <Type here>
[ ] Audio or video recordings maintained indefinitely
[ ] Photographs destroyed; specify time frame: <Type here>
[X] Photographs maintained indefinitely: The de-identify photographs will not be used to share with other researchers. They will be kept for reference throughout the duration of the project.

Certificate of Confidentiality:

12. Specify whether a Certificate of Confidentiality (COC) has been or will be requested from the NIH. If yes, explain in what situations personally identifiable information protected by a COC will be disclosed by the UCI study team.

[X] Not applicable – No COC has been requested for this study.

UNIVERSITY OF CALIFORNIA, IRVINE
CONSENT TO ACT AS A HUMAN RESEARCH SUBJECT

Immune-Related Trafficking and Signaling in Human Skin Associated with Low-Power, Infrared Laser Treatment

You are being asked to participate in a research study. Participation is completely voluntary. Please read the information below and ask questions about anything that you do not understand. A researcher listed below will be available to answer your questions.

RESEARCH TEAM
Lead Researcher
Kristen Kelly, M.D.
Department of Dermatology
949-824-7997 or 949-824-9265
24-Hour Telephone Number/Pager 949-824-0606

Other Researchers
Brent Martin, M.D.

STUDY LOCATION:
Beckman Laser Institute
1002 Health Sciences Rd, Irvine, CA 92612

STUDY SPONSOR:
NIH/LAMMP

WHY IS THIS RESEARCH STUDY BEING DONE?

Recently, a group of scientists have reported that shining a specific kind of laser on the skin may improve the immune response to a vaccine. This study aims to further investigate the body's response to shining a certain type of light on the skin. It is hoped that the results of this study could then be used to determine if a laser may improve the response to a vaccine.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

15 participants will take part in the research at UCI.

AM I ELIGIBLE TO PARTICIPATE IN THIS STUDY?

Please note this may not be a complete list of eligibility criteria. We have included a few examples of study criteria to help you better understand how your eligibility in the study will be determined; your study team will go through the study eligibility criteria with you to verify if you qualify for participation in this study.

Inclusion Requirements

You can participate in this study if you:

- Are a man or woman ages 18-50 years old
- Are able to comply and understand instructions related to the visit, treatment and evaluation requirements
- Are able to understand and provide written informed consent

Exclusion Requirements

You cannot participate in this study if you:

- Use systemic steroids or use topical steroids on the back within 30 days prior to study
- Use tanning solutions on the back within 48 hours prior to study
- Have history of hemophilia or clotting disorders
- Are a prisoner, or have evidence of alcohol or drug impairment
- Have a history of an immune system disorder that makes you more likely to get infections, including human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS), or are taking a medication that affects your immune system.
- Have abnormal sensitivity to light
- You are pregnant

HOW LONG WILL THE STUDY GO ON?

This study includes 5 visits and takes about a total of 10-11 hours over a maximum period of 6 months.

WHAT PROCEDURES ARE INVOLVED WITH THIS STUDY?

You will need to have "screening" exams, tests or procedures. The screening process helps the researchers decide if you meet the study requirements listed below. Digital photographs will be taken of all skin sites before and after laser treatment. This study DOES NOT require your personal health information, only your contact information.

- Screening day, visit 1, will take 30 minutes. You will talk with some of the researchers and a review of your medical history, current medications**,** and a review of your vital signs (blood pressure, pulse, temperature) will be conducted. We will ask you a few questions to determine your skin type and select skin location for the study, 5 mm spot on the lower back skin will be selected. The treatment spot is about the size of a postage stamp.

- Follow up day after screening, visit 2, will take about 15 minutes. You will return to clinic within 20-48 hours where the treated site will be checked to ensure no unusual reactions from the treatment have occurred.

- Treatment day, visit 3, you return within 4 weeks after visit 1. If you are a woman, our research nurse will perform a urine pregnancy test before the treatments. During this visit, a series of light exposures will be delivered to each spot on your lower back with 10 different laser power settings for one minute each. This procedure will take about 2 hours. You may tell your doctor to stop if you experience an uncomfortable feeling as a result of any of the treatments.

- Biopsy day, visit 4, within 6 months after visit 2, a single light treatment will be performed on your lower back during this visit, you will be resting in research room for 4 hours, after resting then two skin biopsies (skin with light exposure and one normal skin) will be taken measuring 4 mm (1/5th of an inch) each. This visit will take about 7 hours. Your skin samples will be shipped and studied at the Massachusetts General Hospital. There will be no information about you attached to the skin samples. If you are unable to come for follow up visit after the procedure, we will call to confirm you are doing well.

- Follow up day, Visit 5, 10-14 days after visit 3, you will return to clinic for 15 minutes, if the biopsy sites were stitched, stitches will be removed from the biopsy sites, and the sites will be checked to ensure that they are healing properly.

WHAT ARE THE POSSIBLE SIDE EFFECTS OR RISKS RELATED TO THE STUDY?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, researchers don't know all the side effects that may happen.
Since this study involves the use of identifiable information, there is a potential for a breach of confidentiality. You should talk to the research team about any side effects you experience while taking part in the study.

Risks and side effects related to the laser usage and biopsy procedure include the following.

Laser Usage

- Skin irritation
- Scar
- Skin discoloration
- Pain
- Blistering
- Scabbing
- Skin hotness
- Pins and needles sensation

Biopsy

- Scar
- Bleeding
- Infection
- Pain
- Bruising
- Allergic reaction

Unknown risks:

There may be risks related to the research that we don't know about yet or that are unintended, such as the risk of a potential breach in subject confidentiality. However, you will be informed of any additional risks to which you may be exposed, any changes that are made to the study that will result in newly-identified risks, along with any unintended occurrences.

ARE THERE BENEFITS TO PARTICIPATING IN THIS STUDY?

Participant Benefits
There is no direct medical benefit to you from receiving laser treatment or skin sampling in this study.

Benefits to Others or Society
This study will help researchers learn more about how lasers can influence skin immunologic response and it is hoped that this information will help in the potentiating the effects of vaccination in the future.

WHAT OTHER CHOICES DO I HAVE IF I DON'T WANT TO PARTICIPATE?

There are no alternative treatments or procedures available. The only alternative is not to participate in this study.

WILL I BE PAID FOR TAKING PART IN THIS STUDY?

Compensation
You will be paid for participating in the study with $200 at the completion of the final visit. If you decide to withdraw from the study or are withdrawn by the research team, you will receive compensation of $40 for the visits and/or procedures that you have completed.

You will not be paid for the screening visit if you do not qualify to be a part of the study,

All compensation will be made in the form of a check.

Personal information about you, including name, address, and social security number, will be released to the Accounting Office at UCI for the purpose of payment.

Reimbursement
You will not be reimbursed for any out of pocket expenses, such as parking or transportation fees.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

There is no cost to you or your insurer/third party payer for participation in this study.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

It is important that you promptly tell the researchers if you believe that you have been injured because of taking part in this study. You can tell the researcher in person or call him/her at the number listed at the top of this form.

If you are injured as a result of being in this study, UCI will provide necessary medical treatment. The costs of the treatment may be covered by the University of California, the study sponsor or billed to you or your insurer just like other medical costs, depending on a number of factors. The University and the study sponsor do not normally provide any other form of compensation for injury. For more information about this, you may call UCI Human Research Protections (949) 824-6068 or (949) 824-2125 or by e-mail at IRB@research.uci.edu

WHAT HAPPENS IF I WANT TO STOP TAKING PART IN THIS STUDY?

You are free to withdraw from this study at any time. **If you decide to withdraw from this study, you should notify the research team immediately**. The research team may also end your participation in this study if you do not follow instructions, miss scheduled visits, the lead researcher decides to stop the study or your safety and welfare are at risk.

If you experience any of the side effects listed above, if your health worsens, or if you are injured during the research, you may need to be withdrawn from the study, even if you would like to continue. The research team will make this decision and let you know if it is not possible for you to continue. The decision may be made to protect your safety and welfare, or because the research plan does not allow people who develop certain conditions to continue to participate.

If you withdraw or are removed from the study, the researcher may ask you to return for a final close-out visit or evaluation.

If you elect to withdraw or are withdrawn from this FDA-regulated research study, the data collected from your participation in this study must remain in the trial database in order for the study to be scientifically valid.

HOW WILL INFORMATION ABOUT ME AND MY PARTICIPATION BE KEPT?

Subject Identifiable Data
Identifiable information collected about you will be removed and replaced with a code. A list linking the code and your identifiable information will be kept separate from the research data. A sheet with your contact information and social security number will be kept so that you can be compensated for your participation in the study and so that we can notify you if needed.

Data Storage
Research data will be maintained in paper format in a secure location at UCI. Only authorized individuals will have access to it. In addition, electronic data will be stored on a password protected computer.

Data Retention
The researchers intend to keep the research data and photographs approximately 7 years, there will be no information about you attached.

WHO WILL HAVE ACCESS TO MY STUDY DATA?

The research team, authorized UCI personnel, and regulatory entities such as the Office of Human Research Protections (OHRP), may have access to your study records to protect your safety and welfare.

Any information derived from this research project that personally identifies you will not be released or disclosed by these entities without your separate written consent, except as specifically required by law. Research records provided to authorized, non-UCI entities will not contain identifiable information about you. Publications and/or presentations resulting from this study will not include identifiable information about you.

While the research team will make every effort to keep your personal information confidential, it is possible that an unauthorized person might see it. We cannot guarantee total privacy

ClinicalTrials.gov is a Web site that provides information about clinical trials. A description of this clinical trial will be available on http://www.clinicaltrials.gov/, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

ARE THERE OTHER ISSUES TO CONSIDER IN DECIDING WHETHER TO PARTICIPATE IN THIS STUDY?

Use of Specimens
Any specimen(s) (e.g., tissue, blood, urine) obtained will be discarded or destroyed once they have been used for the purposes described in this consent.

Investigator Financial Conflict of Interest
No one on the study team has a disclosable financial interest related to this research project.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

If you have any comments, concerns, or questions regarding the conduct of this research, please contact the research team listed at the top of this form.

A 24-hour number is also listed on the top of this form to report any health concerns or unanticipated problems you may experience after normal hours or on weekends.

If you wish to ask questions about the study or your rights as a research participant to someone other than the researchers or if you wish to voice any suggestions, problems or concerns you may have about

the study, please contact UCI's Office of Research by phone, (949) 824-6068 or (949) 824-2125, by e-mail at IRB@research.uci.edu or at 141 Innovation Drive, Suite 250, Irvine, CA 92697.

What is an IRB? An Institutional Review Board (IRB) is a committee made up of scientists and non-scientists. The IRB's role is to protect the rights and welfare of human subjects involved in research. The IRB also assures that the research complies with applicable regulations, laws, and institutional policies

HOW DO I AGREE TO PARTICIPATE IN THIS STUDY?

You should not sign and date this consent form until all of your questions about this study have been answered by a member of the research team listed at the top of this form. You will be given a copy of this signed and dated consent form, and the attached "Experimental Subject's Bill of Rights" to keep. **Participation in this study is voluntary.** You may refuse to answer any question or discontinue your involvement at any time without penalty or loss of benefits to which you might otherwise be entitled. Your decision will not affect your future relationship with UCI or your quality of care at the UCI Medical Center.

If, during the course of this study, significant new information becomes available that may relate to your willingness to continue to participate, this information will be provided to you by the research team listed at the top of the form.

Your signature below indicates you have read the information in this consent form and have had a chance to ask any questions you have about this study.

I agree to participate in the study.

_____ _____

Subject Signature **Date**

_____

Printed Name of Subject

_____ _____

Signature of Person Obtaining Informed Consent **Date**
(Individual must be listed on Page 1 of this consent)

_____

Printed Name of Person Obtaining Informed Consent

A witness signature is required on this consent form only if: ***(Researchers: check which one applies)***

☐Consent is obtained from the subject via the Short Form process, as approved by the IRB.
☐The subject has decision-making capacity, but cannot read, write, talk or is blind.
☐The subject's guardian/legally authorized representative (LAR) cannot read, write, talk or is blind.
☐The IRB specifically mandated a witness signature for this study (e.g., high risk and/or invasive research procedures).

Note: The witness must be impartial (i.e. not a member of the subject's family, not a member of the study team).

For the witness:

I confirm that the information in this consent form was accurately explained to and understood by the subject or legally authorized representative and that informed consent was given freely.

_____ _____

Witness Signature **Date**

(If no witness signature is required, this witness signature section of the consent form may be left blank).

_____

Printed Name of Witness

Consent for Photography

As part of this study, the study team will take pictures of you at every visit, to record how well your skin responds to the test drug. These close-up photographs will be from the neck down ensuring that your face is not shown. Any tattoos or other marks on your body that might identify you will be covered. If you want, the study team will show you the photographs.

Beckman Laser Institute, University of California, Irvine would like your permission to use, reproduce and/or distribute these pictures taken of you during the study for education purposes, in scientific lectures, journal articles and textbooks

Beckman Laser Institute, University of California, Irvine may edit, reduce, enlarge or otherwise change the photos.

Your identity will not be disclosed. Beckman Laser Institute, University of California, Irvine would only show the pictures of you from the neck down or excluding your face.

Your decision to allow photographs and to allow Beckman Laser Institute, University of California, Irvine to use the photographs for educational purposes is voluntary.

PRINT Participant's Name	Date[1]	Participant's Signature
PRINT name of the person who conducted the informed consent discussion	Date[1]	Signature of person who conducted the informed consent discussion

[1] *Each person who signs the consent must personally enter the date for his/her signature.*

UNIVERSITY OF CALIFORNIA, IRVINE
Experimental Subject's Bill of Rights

The rights listed below are the right of every individual asked to participate in a research study. You have the right:

1. To be told about the nature and purpose of the study.

2. To be told about the procedures to be followed in the research study, and whether any of the drugs, devices, or procedures is different from what would be used in standard practice.

3. To receive a description of any side effects, discomforts, or risks that you can reasonably expect to occur during the study.

4. To be told of any benefits that you may reasonably expect from the participation in the study, if applicable.

5. To receive a description of any alternative procedures, drugs, or devices that might be helpful, and their risks and benefits compared to the proposed procedures, drugs or devices.

6. To be told of what sort of medical treatment, if any, will be available if any complications should arise.

7. To be given a chance to ask any questions concerning the research study both before agreeing to participate and at any time during the course of the study.

8. To refuse to participate in the research study. Participation is voluntary. You may refuse to answer any question or discontinue your involvement at any time without penalty or loss of benefits to which you might otherwise be entitled. Your decision will not affect your right to receive the care you would receive if you were not in the experiment.

9. To receive a copy of the signed and dated written consent form and a copy of this form.

10. To be given the opportunity to freely decide whether or not to consent to the research study without any force, coercion, or undue influence.

If you have any concerns or questions regarding the research study you should contact the research team listed at the top of the consent form.

If you are unable to reach a member of the research team and have general questions, or you have concerns or complaints about the research study, research team, or questions about your rights as a research subject, please contact the UCI's Human Research Protections unit in the Office of Research by calling (949) 824-6068 or (949) 824-2125 Monday – Friday, 8 am – 5 pm; or by e-mail at IRB@research.uci.edu; or by writing us at 141 Innovation Drive, Suite 250, Irvine, CA 92697.