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TITLE: A Randomized, Double-Blind, Placebo-Controlled Crossover Study of the Anti-Inflammatory Compound Anatabine to Treat Pain in GWI Patients

PRINCIPAL INVESTIGATOR: Fiona Crawford, Ph.D.

CONTRACTING ORGANIZATION: The Roskamp Institute, Inc.
Sarasota, Florida, 34243-3922

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<p>14. ABSTRACT: The goal of this clinical trial is to target one of the major complaints from veterans with Gulf War Illness (GWI) - namely chronic pain and inflammation - with a compound that has a history of safe use in humans and is shown to be effective in animal models of exposure to agents known to have caused GWI. Chronic musculoskeletal pain and associated inflammation are some of the most debilitating symptoms of GWI. Identifying effective, safe, and tolerable treatments will alleviate major aspects of the multisymptom condition that as yet has not effective treatment. In a recent presentation of data from the national War Related Illness and Injury Study Centers (WRIISC) in California, New Jersey and Washington DC, the reported major complaints of veterans, and specifically of GW veterans, was pain (90%), exceeding the next most prevalent symptom, fatigue, by three fold.</p> <p>For many years now our GWI research program has been developing and characterizing mouse models of exposure to agents known to have been involved in causing GWI, such as the nerve gas prophylactic Pyridostigmine Bromide and pesticides such as Permethrin. In order to best model the human condition, now presenting more than 23 years after the war, we give exposures for 10 days, and then evaluate changes occurring over months and years. We investigate changes in behavior, in the brain and the blood, to identify cellular mechanisms and functions that have been disrupted as a consequence of the exposures, and which we may target with therapeutic approaches. Our work has demonstrated an evolving and persistent inflammation in these animals, consistent with the reports and complains from GWI patients. Chronic pain is not easily evaluated in mouse models, but we have noted behavioral and cognitive changes in mice following these exposures. Our scientific team has a lot of experience with animal models of conditions where inflammation plays an important role, and with treatments which target inflammation. Over the last few years we have carried out extensive work on the dietary supplement Anatabine (Rock Creek Pharmaceuticals Inc.), which is a naturally occurring compound found in tobacco, tomatoes, eggplant and peppers. Our work has shown that it has strong anti-inflammatory properties. Based on sales, an estimated 300,000-500,000 individuals used these products with positive effects demonstrated, including pain alleviation and only minor adverse effects reported. Anatabine products are no longer available as dietary supplements as the compound company is pursuing pharmaceutical use for these products. Furthermore, we have conducted clinical studies of anatabine in healthy human subjects which demonstrated its safety and tolerability. We then investigated the effects of anatabine in our mouse model of GWI and found improvement of behavioral symptoms and reduced inflammation in the exposed animals.</p> <p>Therefore, we now propose a clinical evaluation of anatabine in a small population of GWI patients, comprising 11 weeks of treatment and 11 weeks of placebo (or vice-versa) and an evaluation of the effects on Pain and other related conditions. To the best of our knowledge this is the first time that data from a laboratory model of GWI has been partnered with data from human clinical exposure to support a potential GWI treatment. If successful then this trial will lead to a larger scale trial of several hundred GWI patients across multiple sites, which in turn would support an application to the Food and Drug Administration (FDA) for anatabine as a treatment for GWI. Given the extreme prevalence of chronic pain in the GWI patient population we believe that this may potentially benefit most GWI patients. Treatment with anatabine provides a major advantage for the ill GW veterans population currently using opioids or other potentially addictive pain relievers. The trial proposed will be completed in 2018, and the infrastructure to support a larger follow-up study already exists through extensive collaborations and consortia which have been established in the GWI research community. This will allow for a larger validation study that could potentially be underway by 2019. Targeting inflammation may have beneficial effects on many aspects of GWI, including gastrointestinal symptoms and cognitive function, and this work may lead to investigation of other anti-inflammatory compounds acting through the same cellular mechanisms, as there are likely to be additional factors including genetic predispositions which may differentially influence an individual's response to treatment.</p>					
15. SUBJECT TERMS					
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- 1. INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

Hypothesis: Daily administration of Anatabine, a potent and safe anti-inflammatory compound, will improve symptoms of pain and fatigue in patients with GWI and may also improve cognitive function.

Aim 1: To conduct a double-blind, Placebo-controlled crossover study of the effects of Anatabine in a GWI patient population.

Aim 2: To determine if anatabine treatment mitigates the chronic pain suffered by GWI patients

Aim 3: To determine if anatabine treatment is associated with improvements in mood and/or cognitive function in GWI patients

Aim 4: To collect and analyze blood samples from subjects pre- and post- each phase of treatment to quantify anatabine levels and to evaluate treatment-dependent changes in markers of inflammation.

The most important activity for this project is to obtain approval from the FDA to conduct the proposed trial. As detailed below, we prepared and submitted the IND, and have been placed on clinical hold, awaiting our ability to respond to their enquiries regarding our application.

With regard to the other regulatory actions required to begin this project - namely IRB approval and site approval - we have a draft protocol and consent form for the study, and are planning to schedule a visit from our co-investigator Dr. Kregel, but progress with these actions is pending FDA approval.

Dr. Crawford participated in a GWI symposium at the International Neuropsychological Society meeting in London in July 2016, organized by Dr. Kim Sullivan. Other participants included Drs. Maxine Kregel and Julia Golier. Drs. Kregel, Sullivan and Golier are all involved with the proposed clinical trial, either as co-investigators or consultants, and so this meeting afforded the opportunity for some discussion regarding the response to the FDA and assurance of continued enthusiasm for the project and the trial by all parties concerned.

- 2. KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

Gulf War Illness; Anatabine; Inflammation; Pain; Fatigue; Cognition

- 3. ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

1. Submission of Investigator Initiated Investigational New Drug Application to the FDA on December 2nd, 2015.
2. A request for additional information regarding the preclinical data and the proposed study design was received on December 15th, 2015 and our response was submitted on December 17th, 2015.
3. Notification of being placed on “clinical hold” was received, by telephone, on December 30th, 2015.
4. The FDA clinical hold letter was received in January with questions relating to anatabine and to the previous preclinical studies and their relevance/pertinence to the proposed trial. We had extensive discussions with the company Rock Creek Pharmaceuticals (manufacturers of anatabine, and committed providers of product for the trial) to determine how best to address the FDA questions.
5. We are preparing a letter for the FDA to provide some additional data pertinent tot heir questions, and also to request if they could discuss with us a clinical trial design that they consider Is supported by the existing preclinical data, as additional GLP preclinical evaluation of anatabine in animal models, beyond those already included in our IND submission, is beyond our financial capabilities.

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

As per our Statement of Work –

Specific Aim 1: To conduct a double-blind, placebo controlled crossover study of the effects of Anatabine in a GWI patient population.

Major Task 1: IRB approval (months 1-3)

Preparation of documents is in progress but will not be finalized and submitted to the IRB until FDA approval has been obtained.

Major Task 2: FDA approval (months 1-6)

We prepared a very detailed Investigator Initiated IND, which was submitted on December 2nd, 2015. Prior to submission, Dr. Crawford had several conversations and communications with Dr. Sandy Barnes of the FDA in the Division of Pulmonary, Allergy, and Rheumatology Products, the division to which our II-IND was to be submitted.

The investigational product for our trial is Anatabine, a potent anti-inflammatory compound, which was available from Rock Creek Pharmaceuticals (RCP) for several years (2010-2014) as a dietary supplement. It is no longer being sold as a dietary supplement, as the company was going to pursue an IND with the FDA for its use as a pharmaceutical.

However, the company withdrew its IND application to pursue trials with the product in Europe. Thus, in the US, anatabine is neither a dietary supplement nor a pharmaceutical, and so there was no IND to which we or the FDA could refer in relation to our application.

In discussing this situation with Dr. Barnes she indicated that I should provide as much information as possible, including a detailed CMC section, explaining that the batch of product for the proposed trial would be made in exact accordance with that methodology and those specifications. We had the full support of RCP in our submission of the IND (RCP have agreed to provide us with the product and matched placebo for the study, free of charge) and so we were able to include RCP's most recent Investigator's Brochure (dated November 2014) which contains all of the preclinical and clinical data available at that time, as well as the extensive safety and exposure data from the use of anatabine as a dietary supplement.

Furthermore, RCP provided us with pre-final-report data from its recently conducted trial in the UK to support the safety and tolerability of anatabine at doses above those proposed in our trial.

As previously reported, I believe that our approximately 600 page II-IND submission provided considerably more detail regarding the proposed investigational product than is usual for an II-IND. We received questions by mail, from Dr. LeAnn Brodhead of the same FDA Division, on Tuesday December 15th, with response required by 17.00 on Thursday December 17th, pertaining to the preclinical studies and our trial design. We responded in detail in the timeframe required, and as the questions made reference to the FDA Guidance for Industry I did also take the opportunity to remind the FDA that ours was an Investigator Initiated IND from a not-for-profit research institute, not a commercial IND. I also reminded them of the devastating impact of GWI to our veterans and the fact that it is considered a debilitating disorder.

On December 30th I received a phonecall from Dr. Brodhead informing me that the IND was being placed on clinical hold and that I would receive a letter with detailed information regarding this and how to respond. Having received this letter in January, and given that it suggests requirement for GMP experiments which are beyond the scope of our Institute, we are in discussions with RCP regarding their interest and ability to support provision of such data to the FDA to support our application. We are now preparing a letter to the FDA as outlined above, to provide them with some additional data on the proposed investigational product, which we have generated in house at our own expense, and to solicit guidance from them regarding the clinical trial design.

Major Task 3: Site Preparation (months 1-6)

Our clinic staff are familiar with the protocol, having worked with me on the original submission to the DoD, and since notification of award they have been gaining further knowledge about Gulf War Illness from Institute researchers and from patients to our clinic

What opportunities for training and professional development has the project provided?

If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. “Training” activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. “Professional development” activities result in increased knowledge or skill in one’s area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

N/A

How were the results disseminated to communities of interest?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

N/A

What do you plan to do during the next reporting period to accomplish the goals?

If this is the final report, state “Nothing to Report.”

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

We will do our best with the resources available to us to respond in a timely fashion to the FDA. We will provide the best possible response to their enquiries, and/or enter into discussions with them (if that is a possibility) regarding any modifications they may wish to make to our study design in order to consider its approval. If the latter is the case then naturally our next step will be to determine whether or not any such protocol modifications are acceptable to the CDMRP.

- 4. IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research

in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

N/A

What was the impact on other disciplines?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

N/A

What was the impact on technology transfer?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

N/A

What was the impact on society beyond science and technology?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*

- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

N/A

5. CHANGES/PROBLEMS: The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, “Nothing to Report,” if applicable:

Changes in approach and reasons for change

Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

As detailed in 1c above, we are currently on clinical hold from the FDA and thus cannot proceed until we know, and are able to address, their concerns or questions.

Actual or anticipated problems or delays and actions or plans to resolve them

Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

We are not aware of any problems that should impede the proposed trial; our team is ready and able to conduct the study, we anticipate good recruitment to the study through our local networks, we have the support of the company (RCP) which will manufacture the product and matched placebo to FDA GMP standards, and the doses proposed in our study are below those which have been shown to be safe and well tolerated in previous human studies.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

The majority of effort to date was from Dr. Crawford and her administrative support, in putting together the IND for submission to the FDA, and in negotiations with RCP.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

N/A

Significant changes in use or care of vertebrate animals.

N/A

Significant changes in use of biohazards and/or select agents

N/A

6. PRODUCTS: List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state “Nothing to Report.”

- **Publications, conference papers, and presentations**

Report only the major publication(s) resulting from the work under this award.

Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume; year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

N/A

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: Author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

N/A

Other publications, conference papers, and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

N/A

- **Website(s) or other Internet site(s)**

List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

N/A

- **Technologies or techniques**

Identify technologies or techniques that resulted from the research activities. In addition to a description of the technologies or techniques, describe how they will be shared.

N/A

- **Inventions, patent applications, and/or licenses**

Identify inventions, patent applications with date, and/or licenses that have resulted from the research. State whether an application is provisional or non-provisional and indicate the application number. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

N/A

- **Other Products**

Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment, and/or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

- *data or databases;*
- *biospecimen collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*

- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

N/A

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change."

Example:

*Name: Mary Smith
Project Role: Graduate Student
Researcher Identifier (e.g. ORCID ID): 1234567
Nearest person month worked: 5*

Contribution to Project: Ms. Smith has performed work in the area of combined error-control and constrained coding.

Funding Support: The Ford Foundation (Complete only if the funding support is provided from other than this award).

*Name: Fiona Crawford, Ph.D. Mary Smith
Project Role: Principal Investigator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 1.2
Contribution to Project:
Funding Support:*

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

N/A

What other organizations were involved as partners?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:

Organization Name:

Location of Organization: (if foreign location list country)

Partner’s contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner’s facilities for project activities);*
- *Collaboration (e.g., partner’s staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner’s staff use each other’s facilities, work at each other’s site); and*
- *Other.*

N/A

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating PI and the Collaborating/Partnering PI. A duplicative report is acceptable;

however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to <https://ers.amedd.army.mil> for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on <https://www.usamraa.army.mil>) should be updated and submitted with attachments.

9. **APPENDICES:** Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.