FOR SUB CONTRACT WITH CIMVHR

1. TITLE OF TASK AUTHORIZATION

1.1 TA 19 – Metabolomic Analysis of Brain Injury

2. VALIDATION OF SCOPE OF CONTRACT

2.1 The following task(s), apply to this Task Authorization (TA):
   a. Experimental and Clinical Studies - Design and conduct of experiments involving animal studies.
   b. Data Analysis - Perform state of the art analysis of data from experimental studies.
   c. Presentations to Government and Health Care System Stakeholders - Prepare and deliver presentations to Government and Healthcare system stakeholders.
   d. Tools and Treatments - Develop software tools related to the diagnosis and treatment of healthcare issues in the target population.

3. ACRONYMS

   CAF  Canadian Armed Forces
   CSF  Cerebral Spinal Fluid
   mTBI  Mild Traumatic Brain Injury
   PTSD  Post-Traumatic Stress Disorder
   SA  Scientific Authority
   SGHRP  Surgeon General Health Research Program
   TA  Task Authorization

4. REQUIREMENT

4.1 To perform metabolomic analyses of bodily fluids from cells, tissues or research animals exposed to highly defined brain insults with respect to both the actual insult, as well as to the resultant brain damage and functional outcome. Subsequent powerful and proprietary statistical analysis of the metabolite profile will be carried out to identify diagnostic “fingerprints” of specific types of brain injury. This approach offers a greater likelihood of diagnostic sensitivity compared to single biomarkers.

5. BACKGROUND

5.1 Brain Injury is a top priority for the Surgeon General’s Health Research Program (SGHRP) and can occur due to sports or day-to-day activities, military training or transportation, or exposure to blast or chemical insult. Patients can show symptoms ranging from the gross and obvious head wounds caused by projectiles or intense acceleration-impact forces, to seizure activity due to organophosphate nerve agent exposure, to the more insidious and delayed symptoms of mild TBI often seen in returning veterans, which have both differences and commonalities with Post-Traumatic Stress Syndrome. It has been estimated that between 1995 and 2001, an average of 1.4 million Americans a year experienced a TBI, while a recent RAND report assessed that up to 20% of deployed American military personnel potentially suffer from TBI. Diagnoses of the existence and severity of TBI, and subsequent identification of treatment modalities based on these diagnoses, remains a topic of great importance.

5.2 Although great strides have been made in the treatment of brain injury, closed head injuries often remain difficult to diagnose, especially with respect to severity. Biomarkers have been suggested as useful tools for identifying potential TBI regardless of the insult.
5.3 A test for the early diagnoses of the different types and severity of brain injury experienced by CAF personnel is desirable. Single biomarkers are unlikely to be predictive of the multitude of types and severities of brain injury potentially encountered. Using a test based on “metabolomics”, where an individual’s small metabolite profile in blood or other body fluid is measured, the likelihood of a broad spectrum assessment of potential TBI is increased. The strength of this approach is that these metabolites fall downstream of the body processes, and result in an integrated and dynamic measure of physiology. This work builds on a recent study using a relatively small sample population, which predicted those hockey players suffering concussion from those without, with 95% certainty. It also builds on more recent work where cerebral spinal fluid (CSF) and plasma samples were analyzed from rats exposed head-only to primary blast at the DRDC Suffield Research Center. Although these animals showed no overt signs of injury, significant and delayed signs of memory loss were produced. Metabolomic analyses of blood and CSF from these animals was predictive of those animals exposed to primary blast.

6. OBJECTIVES

6.1 The purpose of this study is to assess the utility of a metabolomic approach in predicting two types of brain injury of concern to the CAF, chemical warfare induced brain injury and primary blast brain injury.

6.2 It is anticipated that metabolomic analysis of body fluids from test animals subjected to defined types and severity of brain injury insult, will show that this approach will have early diagnostic value in those individuals who have brain damage that is either not obvious, or delayed. This will have value for the identification of early treatment modalities.

7. SCOPE

7.1 The Sub Contractor will receive biological samples from up to 80 animals from the TA and conduct analyses using, but not limited to nuclear magnetic resonance-mass spectrometry techniques. These samples will originate from experimental studies carried out at the DRDC Suffield Research Center, and will involve highly defined exposure regimens designed to produce known and reproducible types and severities of brain damage. The Sub Contractor will identify the metabolite profiles associated with each group of samples.

7.2 To determine the correlation between analyte fingerprint patterns and treatment, the Sub Contractor will apply statistical software that will identify correlations and the statistical interpretation. The Sub Contractor will identify the analytes that are most diagnostic for these two types of mTBI.

7.3 The scope of work will include the following:

a. The contactor will be responsible for the conduct of all experimental phases necessary for the preparation and chemical analysis of the biological samples submitted by DRDC.

b. The Sub Contractor will be responsible for the conduct of all mathematical/statistical treatments of the chemical analyses of the submitted samples.

c. The Sub Contractor must ensure that they have adequate resources for designing, testing, and implementing the trial and are staffed for the data collection, statistical analysis and publication of the resulting research findings.

8. APPLICABLE DOCUMENTS & REFERENCES

8.1 The following references are pertinent to the proposed work:

9. TASKS TO BE PERFORMED

9.1 The Sub Contractor must perform the following tasks:

Phase 1 - Study Planning and Scoping

9.1.1 Arrange and schedule appropriate laboratory capabilities for the conduct of all sample preparation and chemical analyses. Arrange and schedule the capabilities and expertise necessary for the mathematical/statistical analyses of the metabolite profiles.

9.1.2 Recruit and train all required staff – including, but not limited to graduate students/postdoctoral fellows, and technicians; and

9.1.3 Purchase all necessary equipment

Phase 2 – Sample Preparation and Analysis

9.2.1 Coordinate biological specimen storage at Sub Contractor’s site during course of study.

9.2.2 Prepare submitted biological specimens for subsequent biomarker analysis.

9.2.3 Carry out biomarker analysis of prepared biological specimens.

Phase 3 – Data Analysis and Reporting

9.3.1 Complete all data analysis, statistical analyses, and tabulation/presentation of results in electronic and hard copy form;

9.3.2 Prepare and submit Quarterly Progress Reports (less than 2 pages) summarizing all results/findings to date, and providing recommendations and future work plans;

9.3.3 Prepare and submit a Draft Study Report and a Final Study Report detailing all evidence-based data captured during the conduct of the entire study; including executive summary, background, objectives, methods, results, conclusions, and recommendations for future research directions in this domain;

9.3.4 Prepare and submit a PowerPoint presentation to present research findings at scientific meetings; and
9.3.5 Prepare draft scientific manuscripts, in association with the SA and DRDC co-investigators, suitable for publication in the open peer-reviewed literature.

10. DELIVERABLES (DESCRIPTION AND SCHEDULES)

10.1 The Sub Contractor must prepare and submit the following deliverables:

<table>
<thead>
<tr>
<th>Deliverable Number</th>
<th>Task reference</th>
<th>Description (Quantity and Format) and Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.1</td>
<td>9.10</td>
<td>Quarterly Progress Reports to be submitted to CIMVHR every 3 months - dates TBD.</td>
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<tr>
<td>10.2</td>
<td>9.11</td>
<td>By February 13, 2017, a Draft Study Report must be completed and submitted to CIMVHR. The SA will require no more than 10 business days to provide feedback to the Sub Contractor.</td>
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<tr>
<td>10.3</td>
<td>9.11</td>
<td>By March 13, 2017, a Final Study Report addressing issues and feedback from the SA on the Draft Report must be completed and submitted to CIMVHR.</td>
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<td>10.4</td>
<td>9.12</td>
<td>PowerPoint presentation no later than 35 days prior to presentation of research findings at scientific meeting</td>
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<td>10.5</td>
<td>9.13</td>
<td>By February 27, 2017, Draft scientific manuscripts suitable for publication in open literature must be completed and submitted to CIMVHR.</td>
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11. MANDATORY SELECTION CRITERIA

None

12. LANGUAGE OF WORK

12.1 Documentation and deliverables must be submitted in the English language.

13. LOCATION OF WORK

13.1 The work must be performed on the Sub Contractor’s site.

14. TRAVEL

14.1 This task authorization may include the following domestic travel requirements:

   a. Sub Contractor travel to present research findings at scientific meetings; and
   b. Subjects travel for data collection.

14.2 All Sub Contractor travel must have the prior written authorization of CIMVHR and Canada, and must be undertaken in accordance with the National Joint Council Travel Directive and with the other provisions of the directive referring to "travellers", rather than those referring to "employees".

14.3 Travel must be approved in a 2 stage process. The travel budget is approved in principle at the time of the budget for the project approval. The details of the travel must be approved by Canada prior to the actual travel. Please contact Jocelyne Halladay to facilitate this approval at least two weeks prior to making any firm travel plans or making reservations. This requirement also applies to domestic travel using a personal vehicle.
15. **MEETINGS**

None

16. **GOVERNMENT SUPPLIED MATERIAL (GSM)**

16.1 DRDC Suffield will supply all samples for analysis.

17. **GOVERNMENT FURNISHED EQUIPMENT (GFE)**

None

18. **SPECIAL CONSIDERATIONS OR CONSTRAINTS**

18.1 None.

19. **SECURITY**

19.1 The Sub Contractor will not require access to PROTECTED and/or CLASSIFIED information or asset, nor to restricted access areas.

- [X] Not applicable
- [☐] RELIABILITY STATUS
- [☐] PROTECTED A
- [☐] PROTECTED B

20. **INTELLECTUAL PROPERTY (IP) OWNERSHIP**

20.1 The Sub Contractor will own any Foreground IP.

21. **CONTROLLED GOODS**

- [X] Not applicable
- [☐] Applicable

22. **Budget**

The Sub Contractor will be paid by CIMVHR as per the terms of the Contract # W7714-145967 between Defence Research and development and CIMVHR. The amount of funding available is allocated by fiscal year (April 1st - March 31st) and is approximately $76,000 for one fiscal year for direct costs. Details TBD upon award.

A draft budget will be submitted with the proposal along with a budget justification and a detailed budget will be developed post award in consultation with CIMVHR. Interested parties should request budget documents and information on creating their budget from Jocelyne Halladay.