National Defence Défense nationale

- STATEMENT OF WORK -
Task Authorization (TA) – 43

FOR CIMVHR SUB CONTRACT

1. Task 43– TITLE OF TASK AUTHORIZATION

TA 43 – Literature Review on "The Utility of Melatonin Interventions in PTSD"

2. VALIDATION OF SCOPE OF CONTRACT

2.1 The following task(s), as written in the SOW of the main contract (W7714-14596/001/SV) apply to this Task Authorization (TA):

a. **Literature Review** – Conduct a state-of-the-art review of scientific, policy and governmental documents (literatures).

3. ACRONYMS

CAF	Canadian Armed Forces
DRDC	Defence Research and Development Canada
MDD	Major Depressive Disorder
PTSD	Post-Traumatic Stress Disorder
SA	Scientific Authority
SGHRP	Surgeon General Health Research Program
TA	Task Authorization

4. REQUIREMENT

4.1 DRDC wishes to contract a literature review to establish the utility of melatonin interventions in PTSD.

5. BACKGROUND

5.1 Hardeland, Poeggeler and Pappolla reported that, while melatonin is well known as a regulator of circadian rhythms via production of melatonin in the pineal gland, it is also produced in other tissues and cells (e.g., gastrointestinal tract, bone marrow, leucocytes, and skin) such that the extra-pineal melatonin exceeds the pineal production by orders of magnitude [1]. Further, they indicated that melatonin maintains mitochondrial activity "within a physiologically favorable bandwidth". In another publication, Hardeland [2] indicates that significant reductions of circulating extra-pineal melatonin are observed in a range of diseases, including Alzheimers, various other neurological and stressful conditions, pain, cardiovascular disease, cancer, endocrine and metabolic disorders including type 2 diabetes. In a case study, a 28 year old woman with primary progressive multiple sclerosis (PPMS) was given glucocorticoid treatment for 9 years while the disease continued to progress. She was restricted to a bed or a chair (disease severity rated at 8.0) when she started taking 50 to 300 mg of daily melatonin for the next 4 years during which time her disease severity was reduced to 6.0 (the patient needs intermittent or unilateral constant assistance such as cane, crutch or brace to walk 100 meters with or without resting).

5.2 McFarlane et al. recruited 48 subjects who were admitted to hospital immediately after a traumatic accident and found moderate to strong correlations found between decreased 6-sulphatoxy melatonin (the urinary metabolite of melatonin) within 48 hours of trauma and symptoms of PTSD 1 and 6 months after trauma [3]. This finding suggests that melatonin may be a marker for PTSD and reduced melatonin may play a role in the development of

PTSD symptoms. In a case study, Seyffert and Getty treated a veteran with PTSD who had migraine headaches, nightmares, and REM-related sleep apnea with a 5 mg dose of melatonin 45 minutes prior to bedtime for one week [4]. The patient underwent notable improvements in sleep-onset insomnia and a reduced frequency and intensity of headaches. The following week the patient was given 10 mg melatonin before bedtime. The patient reported complete resolution of his morning headaches, no further nightmares, and a dramatic polysomnographically-verified rebound in total REM sleep (28%). These findings by McFarlane et al. [3] and Seyffert and Getty [4] support the following 2 hypotheses.

1) Daily therapeutic doses of melatonin (10-20 mg) may be helpful in resolving PTSD or Major Depressive Disorder (MDD).
2) If people who are exposed to trauma are given therapeutic doses of melatonin immediately after the trauma, they may not develop PTSD or Major depressive Disorder (MDD).

References

1. Hardeland, R., B. Poegeler, and M.A. Papolla, *Mitochondrial actions of melatonin - an endeavor to identify their adaptive and cytoprotective mechanisms.* Abb. Sachs. Akad. Wiss. Math.-Nat. K.I., 2009. **65**(Pt 3): p. 14-31.
2. Hardeland, R., *Melatonin in Aging and Disease - Multiple Consequences of Reduced Secretion, Options and Limits of Treatment.* Aging and Disease, 2012. **3**(2): p. 194-225.
3. McFarlane, A.C., C.A. Barton, N. Briggs, and D.J. Kennaway, *The relationship between urinary melatonin metabolite excretion and posttraumatic symptoms following traumatic injury.* Journal of Affective Disorders, 2010. **127**: p. 365-369.
4. Seyffert, M. and G.C. Gettey, *Melatonin as Treatment for Migraine Headaches and Nightmare in a Patient With PTSD and REM-Related Central Sleep Apnea.* The Residents Journal, (a publication of The American Journal of Psychiatry), 2013. **8**(1): p. 6-18.

6. APPLICABLE DOCUMENTS & REFERENCES

6.1 None

7. TASKS TO BE PERFORMED

7.1 Immediately upon award of the Task Authorization (TA), a teleconference will be scheduled with the Sub Contractor to discuss the specific tasks and deliverables.

7.2 Draft outline of literature review will be provided to the Scientific Authority no later than 4 weeks following award of the TA.

7.3 Final literature review will be delivered no later than 10 weeks after award of the TA.

8. DELIVERABLES (DESCRIPTION AND SCHEDULES)

All deliverables must be submitted and completed by 31 January 2019. The Sub Contractor must prepare and submit the following deliverables to CIMVHR:

National Defence Défense nationale

- STATEMENT OF WORK -
Task Authorization (TA) – 43

Deliverable Number	Task reference	Description (Quantity and Format) and Schedule	Quantity and Format	Delivery Date
8.1	7.1	Sub Contractor will contact the CIMVHR to schedule a telephone conference to discuss contract deliverables.	Teleconference	Immediately upon award
8.2	7.2	Draft outline of the literature review in electronic format, will be emailed to CIMVHR.	Microsoft Word	No later than 4 weeks following award
8.3	7.3	Final literature review in electronic format will be emailed to CIMVHR	Microsoft Word.	No later than 10 weeks after award
8.4	7.3	A list of all references will be compiled in a format compatible with EndNote version X6.	Electronic format, Microsoft Word.	Within eight months of award

9. LANGUAGE OF WORK

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

10. LOCATION OF WORK

10.1 The work must be performed on the Sub Contractor's site.

11. TRAVEL

11.1 The Sub Contractor is not required to travel.

12. MEETINGS

12.1 Other than telephone communications, meetings are not required.

13. GOVERNMENT SUPPLIED MATERIAL (GSM)

13.1 None

14. GOVERNMENT FURNISHED EQUIPMENT (GFE)

14.1 None, however the Sub Contractor will be given access to DRDC Toronto Library services to acquire relevant scientific articles, if necessary.

15. SPECIAL CONSIDERATIONS OR CONSTRAINTS

15.1 None

16. SECURITY

16.1 All work is unclassified and the Sub Contractor will not have access to any classified information.

National Defence / Défense nationale

- STATEMENT OF WORK -
Task Authorization (TA) – 43

X Not applicable ☐ RELIABILITY STATUS ☐ PROTECTED A ☐ PROTECTED B

17. INTELLECTUAL PROPERTY (IP) OWNERSHIP

17.1 The Sub Contractor will own any Foreground IP created by virtue of the main contract (W7714-14596/001/SV).

18. BUDGET

18.1 The budget for this Task is approximately $13,500 for fiscal year 18-19.

The Sub Contractor will be paid by CIMVHR as per the terms of Contract # W7714-145967 between Defence Research and Development Canada and CIMVHR. Full details TBD upon award.

A draft budget must be submitted with the proposal along with a budget justification. 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 (jocelyne.halladay@queensu.ca).

19. CONTROLLED GOODS

19.1 X Not applicable
☐ Applicable

20. BASIS OF PAYMENT REQUESTED

20.1 ☐ Firm price
☐ Ceiling price
X Limitation of expenditure

21. METHOD OF PAYMENT REQUESTED

21.1 ☐ Single payment
☐ Milestone payments
X Progress payments

22. Employer/Employee Relationship (Mandatory for all onsite service contracts).

22.1 X Not applicable
☐ Applicable – See attached Employer/Employee Relationship checklist.