- STATEMENT OF WORK -
Task Authorization (TA) - 38

1. NUMBER – TITLE OF TASK AUTHORIZATION

TA Broad spectrum antivirals against RNA viruses which block cellular entry.

2. VALIDATION OF SCOPE OF CONTRACT

The following task(s), as written in the SOW of the main contract (W7714-145967/001/SV) apply to this Task Authorization (TA):

b. **Experimental and Clinical Studies** - Design and conduct of experiments involving both human and animal studies.

d. **Data Analysis** - Perform state of the art analysis of data from experimental studies, clinical trials, field studies or trials, and existing databases.

i. **Tools and Treatments** - Develop software or hardware tools and pharmacological products related to the diagnosis and treatment of healthcare issues in the target population.

3. ACRONYMS

DRDC	Defence Research and Development Canada
EGCG	epigallocatechin gallate
HCV	hepatitis C virus
MedCM	medical countermeasure
PK	pharmacokinetic
qTRLs	quantitative technology readiness levels
RNA	Ribonucleic acid
SA	Scientific Authority
TA	Technical Authority

4. REQUIREMENT

The lack of broad spectrum antivirals for the mitigation of the effects of Biothreat agents or emerging infectious diseases is a deficiency that can affect operations at home or abroad.

5. BACKGROUND

The past few years have seen a rash of emerging viral infectious diseases caused by ribonucleic acid (RNA) viruses. These world events include the Ebola crisis in West Africa, chikungunya virus emerging as a pandemic agent with over a million infected in the Americas, and the recent explosion of Zika virus in South America. Broad-spectrum antivirals targeting specific enzymatic activities (neuraminidase, proteases, RNA polymerases) are available but cytotoxicity and rapid emergence and transmission of drug-resistant mutations are two main limitations. Alternatively, blocking viral entry to host cells is a novel and viable approach to the development of broad-spectrum antiviral medical countermeasures (MedCMs). Antiviral MedCMs are the primary tool for mitigation of an attack with a viral biothreat agent or for the protection of the CAF against emerging and endemic viruses. Antivirals can be used for immediate short-term protection or for the treatment of an acute viral infection. Lack of broad-spectrum antivirals remains a challenge in being able to treat many emerging and/or potential biological threat viral infections. Antivirals such as the influenza virus drugs, hepatitis C virus (HCV) direct-acting antivirals, and human immunodeficiency virus antiviral cocktails are based on virus specific inhibition of viral enzymes: neuraminidase, RNA polymerase, and proteases, respectively. The pharmaceutical industry has a few promising broad-spectrum antiviral compounds, which are based on inhibition of the viral RNA polymerase. RNA viruses can rapidly mutate and adapt to new hosts, and can rapidly acquire resistance to a drug, quickly rendering the drug ineffective as a MedCM solution. For example, ribavirin has given rise to 14 known resistant strains with some against chikungunya, coronavirus, influenza A and

polio virus. Another example is the rapid development of resistance to oseltavir (Tamiflu©) by the 2009 H1N1 Mexico strain of influenza.

The approach to develop pharmacokinetically (PK)-stable polygallates was derived from the scientific evidence of epigallocatechin gallate (EGCG) with documented antiviral, antibacterial, and antifungal activities. The use of polygallates to block early viral entry has a two-fold advantage: 1) the mechanism of action to prevent viral binding and uptake into human cells works as an early deterrent of viral infection, and 2) blocking the cell surface binding has less chance of developing drug-resistance because the virus does not have the opportunity to use the host cells to replicate. The polyphenolic gallate moieties in EGCG are the critical binding elements that interfere with viral attachment. This has been recognized by two different scientific groups that have synthesized EGCG analogs to test for inhibition of viral infections: Rivero-Buceta et al. synthesized 63 polygallates and tested against HCV, and Schang et al. tested 18 polygallates against three disparate viruses: influenza A; herpes simplex type 1; and HCV (unpublished data).

Admittedly, this approach carries a higher risk due to the research nature of the compounds and the work required to down-select to a subset of these compounds that will be investigated for efficacy against a panel of biological threat agents. The project would involve synthesis of polygallates with optimal PK properties and test the developed compounds for stability, solubility, and safety against a wide spectrum of representative Risk Group 2 virus families. Subsequently, DRDC would test the lead candidates against the encephalitic alphaviruses (eastern, western and Venezuelan equine encephalitis viruses), chikungunya virus and yellow fever virus; and engage partners to test against Ebola and other Risk Group 4 hemorrhagic fever viruses. Taking on slightly higher risk is necessary to address a novel approach such as this and to satisfy the stated intention of the MedCM Project to explore the span of quantitative technology readiness levels (qTRLs). In addition, the aim of the proposed project is to synthesize a small manageable set of polygallate compounds that are PK-stable and to engage partner groups to reach qTRL3C *in vivo* proof-of-concept against Risk Groups 3 and 4 agents.

In summary, the lack of broad-spectrum antivirals is a major deficiency in treating RNA virus infections, which make up a majority of potential biothreat agents and emerging infectious diseases. A few promising broad-spectrum antivirals are in development, and are limited to the nucleoside analogs targeting the viral RNA polymerase. Emergence and transmission of drug-resistant viruses arising from the use of RNA polymerase drugs are virtually inevitable. Thus, a coordinated approach is required. The Chemical Biological Radiological MedCM project needs to develop new classes of drugs to deal with the ever-expanding number of patients infected with drug-resistant viruses. Blocking viral entry is a novel and viable approach that can limit the emergence of antiviral drug resistance and prevent disease progression. The development of PK-stable polygallates can augment RNA polymerase drugs for a comprehensive MedCM strategy against multiple viral threat agents.

Rivero-Buceta E et al. (2015) Linear and branched alkyl-esters and amides of gallic acid and other (mono-, di- and tri) hydroxy benzoyl derivatives as promising anti-HCV inhibitors. *Eur. J. Med. Chem*., 92, 656–671.

6. OBJECTIVES

Obtain proof-of-concept that polygallate based small molecule drugs are effective as broad spectrum antiviral agents, with solid safety and stability profiles.
Option 1: (if funds are available in FY 18/19) Scale up (> 5 g) of most promising lead compounds for in vitro and in vivo toxicity testing.
Option 2: (if funds are available in FY19/20). Continue scale up, characterization and screening in vivo.

7. SCOPE

Start Date:	1 August 2017
End Date:	31 March 2019
Option - End Date:	31 March 2020

8. APPLICABLE DOCUMENTS & REFERENCES

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None

9. TASKS TO BE PERFORMED

The Sub Contractor must perform the following tasks:

9.1 Replacement of the ester group linking the polyphenolic units to the central core with a more robust isostere, and characterize the effect of the modifications;

9.2 Exploring the rigidity, valency and polarity of the central core, and characterize the effects of the modifications;

9.3 Replacement of the polyphenolic termini with more drug-like aliphatic polyols, and characterize the effect of the modifications;

9.4 Select the most promising candidates based on solubility, stability, safety and broad spectrum activity, and identify any additional avenues of research to further improve on the compounds potential development. Test the most promising compounds in vitro against different RNA virus families.

9.5 Option 1 (if exercised) - Scale-up synthesis (>5 g) of the most promising lead compounds for further characterization of properties and for in vitro efficacy against a broad panel of viral families, and for toxicity testing in vivo.

9.6 Option 2 (if exercised) - Refine synthesis to obtain the two optimal lead compounds. Scale-up synthesis (>20 g) of two lead compounds for further testing at DRDC and other organizations.

10. DELIVERABLES (DESCRIPTION AND SCHEDULES)

The Sub Contractor must create and submit the following deliverables to CIMVHR:

Deliverable Number	Task reference	Description (Quantity and Format) and Schedule
10.1	9.1	Q1-2 Reports (progress report 60 days after end of fiscal quarter).
10.2	9.2	Q3-4 Reports (progress report 60 days after end of fiscal quarter).
10.3	9.3	Q5 Report (progress report 60 days after end of fiscal quarter).
10.4	9.4	Final Report (Prior to the end of contract period).
10.5	9.5	Option 1 Q6, Q7-8 (progress report 60 days after each fiscal quarter); Lead compounds (minimum of 2) (>5 g of each, 90 days after the end of Q8).
10.6	9.6	Option 2 Q9-10, (progress report 60 days after each fiscal quarter); Final Report (Prior to the end of Option period); Lead compounds (minimum of 2) (>20 g of each, 90 days after end of the Option Period).

11. MANDATORY SELECTION CRITERIA

The successful team will collectively have the following minimum qualifications:

a. One or more senior investigators with an MD and/or a PhD in a relevant discipline;
b. Demonstrated subject matter expertise and experience in medicinal chemistry, broad-spectrum antiviral drug design and preparation of compound libraries will be essential
c. Demonstrated subject matter expertise in leading a laboratory specializing in virology, with a focus on the study of antiviral drugs, viral attachment mechanisms and infectivity assays for a wide range of viruses.

d. Demonstrated subject matter expertise in the each of the areas listed above to include an extensive publication record and proven experience in filing and obtaining multinational patents in relevant areasrelated to the proposed tasking.

The Prime Sub Contractor is required to satisfy the following minimum merit requirements:

a. Holds a PhD in Chemistry.
b. Is employed an Associate Professor or above in department of Chemistry, or other department with a focus on Physical or Health Science with >25 years experience in organic synthesis.
c. Has authored a substantial body of published and peer-reviewed empirical science in the following areas of research: synthesis of drug compounds; design of broad-spectrum antiviral compounds
d. Has access to facilities for conducting state-of-the-art research on chemical synthesis of drug compounds, physical characterization of drugs; in vitro testing of antivirals against CL2 viruses; and in vivo safety testing of drug compounds.
e. Has knowledge and experience in the synthesis of polygallate compounds.

12. LANGUAGE OF WORK

Documentation and deliverables must be submitted in the English language.

13. LOCATION OF WORK

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

14. TRAVEL

This task authorization may include the following travel requirements:

i) The Sub Contractor may be required to travel to attend study planning meetings and progress review meetings, and to present research findings at scientific meetings.

All travel must have the prior written authorization of the Scientific Authority and the Technical Authority, 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".

15. MEETINGS

Annual progress meetings and a final acceptance meeting with the SA is required. Progress meeting will via teleconferencing, and the final acceptance meeting will be held at the Sub Contractor's premises within 3 months prior to the completion date.

16. GOVERNMENT SUPPLIED MATERIAL (GSM)

None

17. GOVERNMENT FURNISHED EQUIPMENT (GFE)

None

18. SPECIAL CONSIDERATIONS OR CONSTRAINTS

An Option period, may be enacted, if proof-of-principle is obtained, and sufficient funds are available to pay for a part or all of the activities.

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19. SECURITY

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

The Sub Contractor will own any Foreground IP created by virtue of the main contract (W7714-145967/001/SV).

21. CONTROLLED GOODS

X Not applicable

☐ Applicable

22. BUDGET

The Sub Contractor will be paid by CIMVHR as per the terms of Contract # W7714-145967 between Defence Research and Development Canada and CIMVHR. The amount of funding available is allocated by fiscal year (April 1 - March 31st). The cost of this project shall not exceed $74,050.00 for FY 17/18 and $36,000.00 for FY18/19 (inclusive of overhead; taxes extra); and exclusive of an Option period being activated). Option: An option period may be activated to contract additional work for a further period.

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