First Amendment (hereinafter « **Amendment** »)

to the

COLLABORATIVE RESEARCH AGREEMENT (hereinafter the « **Agreement** »)

Entitled

« Development of protein- and cell-based vaccines using the Accum™ technology »

BETWEEN: **UNIVERSITÉ DE MONTRÉAL**, a legal person duly constituted by virtue of the *Law constituting in incorporation the University of Montreal* having its main office at 2900 Édouard-Montpetit, Montréal, Québec, H3T 1J4, hereby represented by its Acting Director-Contracts and Partnerships, Martine Haviernick, duly authorized as she so declares,

(hereinafter referred to as " **UdeM**");

AND **DEFENCE THERAPEUTICS INC.**, a legal person duly constituted under the laws of the Province of British Columbia, having its main office at 1680 - 200 Burrard Street, Vancouver, BC, V6C 3L6, hereby represented by Sébastien Plouffe, President and CEO, duly authorized as he so declares,

(hereinafter referred to as « **Defence Therapeutics** »)

(UdeM and Defence Therapeutics are hereinafter referred to individually as a « **Party** » and collectively as « **Parties** »).

RECITALS

WHEREAS the Parties hereto entered into an Agreement effective on December 1st, 2020 until December 31st, 2021 relating to the project entitled : **«** *Development of protein- and cell-based vaccines using the Accum™ technology* » (the "**Project**");

WHEREAS the Parties wish to make certain amendments to the Agreement as set out herein.

NOW, THEREFORE in consideration of the premises and mutual covenants contained herein, the Parties agree that the following changes shall be incorporated into the Agreement as follows:

Article 1- Amendment of Article 4

The Article 4.1 of the Agreement is amended to now be read as follows:

4.1 Defence Therapeutics shall pay to UdeM the total amount of sixty two thousand eight hundred and twenty six Canadian dollars and forty cents ($62,826.40 CA) including forty

(40%) percent of overhead cost for the execution of the Project (hereinafter the « **Cash Contribution** »). The Cash Contribution shall be paid according to the following schedule:

a) Thirty five thousand five hundred and twenty two Canadian dollars and twenty cents ($35,522.20 CA) becomes payable upon the execution of the Agreement and is due within thirty (30) days following the receipt of an invoice from UdeM;

b) Thirteen thousand six hundred and fifty-two Canadian dollars and ten cents ($13,652.10 CA) becomes payable six (6) months after the Effective Date and is due within thirty (30) days following the receipt of an invoice from UdeM;

c) Thirteen thousand six hundred and fifty-two Canadian dollars and ten cents ($13,652.10 CA) becomes payable upon receipt of the Final Report and is due within thirty (30) days following the receipt of an invoice from UdeM.

Article 2- Amendment of Appendix A

The Appendix A of the Agreement is amended to now be read as follows (the modifications are highlighted in yellow):

List of experiments for Defense Therapeutics Inc.

Defense Therapeutics Inc. has recently acquired a technology, which consists of modifying a given antigen for enhanced uptake and access to the cytoplasm of cells. As a result, captured antigens can be efficiently processed by the proteasomal machinery leading to the generation of potent and effective immune response. To validate this hypothesis, a series of *in vitro* and *in vivo* studies will be proposed in the herein contract for the upcoming year.

- **Antigen Presentation Assays (*in vitro* studies)**

Our laboratory has established and optimized the use of *ex vivo* generated dendritic cells (DCs) for antigen presentation. As such, the first set of experiment consists of testing various ovalbumin (OVA) formulations using the Accum^{TM} technology at various ratios (50X, 25X and 10X). The idea would be to treat DCs with the Accum-OVA or naked OVA then co-culture pulsed DCs with CD8 T lymphocytes derived from the spleen of OT-I transgenic mice (specific to the OVA-derived peptide SIINFEKL). The final outcome consists of conducting an ELISA to quantify IFN-gamma levels. In addition, analysis of SIINFEKL/H2-K^{b} presence on the surface of DCs will be assessed by flow-cytometry. This would demonstrate how potent is the technology at presenting immunogenic peptides.

Reagents needed:

- Antigen with the formulation (to be provided by the Defense Therapeutics Inc.)
- Reagents to generate DCs (Mice, recombinant GM-CSF - $1,500 CA)
- IFN-gamma ELISA ($750 CA)
- OT-I mice (256$/unit x 5 = $1,280 CA)
- Antibody for flow-cytometry ($356 CA)
- Flow-cytometry use (60$/hr x 5 hrs = $300 CA)

Total cost for this set of experiment: $4,186 CA

➢ **Autologous Prophylactic Vaccination (*in vivo* studies)**

To confirm the *in vitro* data, animal vaccination will be conducted to demonstrate potent activation of the immune system. Two sets of studies will be needed for this purpose.

In the first set, wild-type C57BL/6 mice (n=10/group) will be immunized with Accum-OVA-pulsed DCs using various doses (10^5, 10^4, 10^3 and 10^2 cells/dose) and routes (sub-cutaneously versus intraperitoneally). Immunization will be conducted on days 0 and 14. One week following the second immunization, animals will be challenged with 5 x 10^5 EG.7 tumor cells (OVA-expressing lymphoma cells). Tumor growth and survival will be then followed until reaching endpoints (tumor ulceration and/or tumor volume reaching >1000 mm^3). The condition leading to the best protective effect will be used thereafter.

Reagents needed:

- Antigen with the formulation (to be provided by the Defense Therapeutics Inc.)
- Reagents to generate DCs (Mice and recombinant GM-CSF - $1,500 CA)
- C57BL/6 mice (34$/unit x 100 = $3,400 CA)

Total cost for this set of experiment: $4,900 CA

Following the identification of the best dosing and routing, characterization of the immune response generated by the vaccine will be conducted. For this purpose, wild-type C57BL/6 mice will be vaccinated as detailed above but using a single dose and one route (to be determined). Two weeks following the second immunization, all spleens will be isolated and re-stimulated *in vitro* to trigger the secretion of various chemokines and cytokines. Three days later, the supernatants derived from activated splenocytes will be analyzed by luminex to screen for more than 30 cytokines/chemokines.

A similar immunization will be conducted using the Spike 1 protein derived from COVID-19.

Reagents needed:

- Antigen with the formulation (to be provided by the Defense Therapeutics Inc.)
- Reagents to generate DCs (Mice and recombinant GM-CSF - *$3,500 CA)*
- *C57BL/6 mice ($34/unit x 30 x 2 = $2,040 CA)*
- *Luminex analysis ($5,700 CA)*

Total cost for this set of experiment: $11,240 CA

➢ **Allogeneic Prophylactic Vaccination (*in vivo* studies)**

The design of an effective vaccine does not only entail eliciting potent immunity, but it has also to be highly translatable to the clinic and appropriate for manufacturing. Therefore, the ideal DC-based vaccine would have to be "universal", which means derived from genetically distinct or mismatched subjects (allogeneic). For this purpose, DCs will be generated from Balb/c mice then used to vaccinate C57BL/6 mice ($H2^d \rightarrow H2^b$). Vaccinated animals will be then challenged as previously detailed and tumor growth will be followed thereafter using the same parameters explained above. Once completed, the immune response triggered by allogeneic vaccination will be characterized as done with the autologous vaccine).

Reagents needed:

- Antigen with the formulation (to be provided by the Defense Therapeutics Inc.)
- Reagents to generate DCs (Mice and recombinant GM-CSF - $1,500 CA)

- Balb/c mice (34$/unit x 10 = $340 CA)
- C57BL/6 mice (34$/unit x 40 = $1,360 CA)
- Luminex analysis ($2,850 CA)

Total cost for this set of experiment: $6,050 CA

Highly qualified personnel (HQP) salary

A PhD student (Jean-Pierre Bikorimana) will dedicate 50% of his time to work on the *in vitro* and *in vivo* studies related to the vaccine project. A stipend of $10,000 CA will be required to cover his salary for the entire year.

General laboratory reagents

The cost related to the purchase of molecular biology reagents, chemicals, cell culture media and plastic ware is estimated to be $5,000 CA.

Publications

We anticipate that the results generated by this study would lead to at least 1 publication in a peer-reviewed journal. The cost associated nowadays to publish in an open-access journal is $3,500 CA.

Total cost of the project:* *$44,876 CA + $17,950.40 CA (40% overheads) = $62,826.40 CA

Article 3- Any other Amendment to the Agreement

No further amendments are made to the provisions of this Agreement, which continue to apply as written.

Article 4- Effective date

This Amendment shall be in force as of January 13th, 2021.

IN WITNESS WHEREOF, the Amendment has been executed by the Parties hereto through their duly authorized representatives:

Université de Montréal

By : Martine Haviernick — Signature numérique de Martine Haviernick Date : 2021.01.19 08:39:49 -05'00'

Martine Haviernick
Acting Director Contracts & Partnerships

Defence Therapeutics Inc.

By :

Sébastien Plouffe
President and CEO

Principal Investigator's Declaration

I, undersigned, Moutih Rafei, Associate Professor at the Department of Pharmacology and Physiology of the Université de Montréal, declare:

1- I have read this Amendment;

2- I shall abide by all provisions contained in the Amendment that concern me;

Moutih Rafei

Moutih Rafei
Associate Professor