EFFICACY OF RECOMBINANT NEWCASTLE DISEASE VIRUS, RAF-IL12 AS A POTENTIAL THERAPEUTIC CANCER VACCINE IN CT26 AND HT29 CANCER CELL LINE AND IN MOUSE MODEL

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Chairperson: Associate Professor Noorjahan Banu Mohd Alitheen, PhD
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Colon cancer remains one of the main cancer-causing death in men and women worldwide given that certain colon cancer subtypes are resistant to the conventional treatments and the development of new cancer therapy remains elusive. Alternative modalities such as the use of viral-based therapeutic cancer vaccine is still limited as only herpes simplex virus (HSV) expressing granulocyte-macrophage colony-stimulating factor (GM-CSF) or talimogene laherparepvec (T-Vec) had been approved in the USA and Europe. Therefore, it is imperative to continue the search for a new treatment modality such as the use of combinatorial therapy between the oncolytic Newcastle disease virus (NDV) and interleukin-12 (IL-12) cytokine as a potential therapeutic vaccine to the current anti-cancer drugs available in the market. Moreover, this combination between NDV and IL-12 against colon cancer is yet to be discovered and would probably lead to much better outcomes compared to their individual treatments. NDV is a paramyxovirus which infects and causes severe respiratory and central nervous disease in poultry and avian species leading to mortality, but it could also target and kill cancer cells. In light of the previous success of the wild-type NDV utilized against several cancer cell types, this project aims to study the anti-cancer effects of recombinant NDV, AF2240-i strain expressing IL-12 (rAF-IL12) in CT26 and HT29 colon cancer cells, which could potentially provide a better outcome in comparison to the wild-type strain, AF2240-i (i.e. used as a positive control in the *in vitro* and *in vivo* assays). In this study, rAF-IL12 was hypothesized to induce apoptosis in CT26 and HT29 *in vitro* and *in vivo*, modulate immune response in tumor-burden mice, and have no effects towards normal cells and tissues. MTT anti-proliferative assay revealed that the IC_{50} value of rAF-IL12 against CT26 and HT29 cell lines was 276 HA unit and 110 HA unit, respectively. These IC_{50} values were used as treatment dosage in the other *in vitro* assays such as AO/PI, Annexin V FITC, and cell cycle analysis. The rAF-IL12 treatment showed significant ($p<0.05$) cytotoxicity effects towards CT26 and HT29 cancer cells when compared to the AF2240-i as revealed by the MTT, AO/PI, and Annexin V FITC assay. Meanwhile, in the cell cycle analysis, the rAF-IL12 significantly ($p<0.05$) induced

cell cycle arrest at G_1 phase in CT26 cells and significantly ($p<0.05$) caused apoptosis at G_0 phase in HT29 cells. Following the convincing results *in vitro*, further evaluation of rAF-IL12 against colon cancer were carried out *in vivo* by inducing the CT26 and HT29 cells in Balb/c and NCr Foxn1 nude mice, respectively. Treatment with rAF-IL-12 (dosage= 128 HA unit) significantly ($p<0.05$) decreased the weight and volume of tumor in both CT26 and HT29 tumor-bearing mice in comparison to the untreated and parental NDV, AF2240-i groups. Treatment with rAF-IL12 had also significantly ($p<0.05$) increased the number of apoptotic cells when compared to the other groups as revealed by TUNEL assay. Additionally, rAF-IL12 was also shown to significantly ($p<0.05$) modulate immune system by elevating the level of CD4+ and CD8+ T-cells as well as interleukin-2, interleukin-12, and interferon-gamma. In addition, rAF-IL12 could significantly ($p<0.05$) modulate the expression level of several genes in the CT26 (KRAS, BRAF, MAPK1, NOTCH-1, BAX, p53, CCL2, and VEGF-A) and HT29 (Fas, caspase-8, BID, BAX, SMAD3, and granzyme B) tumor-bearing mice. Furthermore, the immunohistochemistry analysis of HT29 tumors revealed the anti-metastatic and anti-angiogenic potential of rAF-IL12 as it could significantly ($p<0.05$) decrease the expression level of Survivin and VEGF proteins. Taken together, rAF-IL12 is a promising candidate for colon cancer therapy concerning its good profile in treating colon cancer-challenged mice as well as in the *in vitro* assays.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Doktor Falsafah

KEBERKESANAN REKOMBINASI VIRUS PENYAKIT NEWCASTLE, RAF-IL12 SEBAGAI POTENSI VAKSIN RAWATAN KANSER TERHADAP SEL TITISAN KANSER CT26 DAN HT29 DAN UNTUK MODEL MENCIT

Oleh

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Kanser usus masih menjadi salah satu kanser yang menyebabkan kematian dalam kalangan lelaki dan wanita di seluruh dunia kerana rawatan sedia ada masih lagi tidak mujarab untuk sesetengah jenis kanser usus dan pencarian terapi kanser yang baru masih sukar ditemui. Rawatan alternatif seperti terapi vaksin berunsurkan virus masih lagi terhad dimana virus herpes simplex (HSV) yang mengekspresikan granulosit koloni makrofaj- factor stimulasi (GM-CSF) sahaja telah diluluskan oleh Amerika Syarikat dan Eropah. Oleh itu, adalah sangat wajar untuk meneruskan pencarian rawatan baharu seperti penggunaan terapi gabungan antara virus penyakit Newcastle (NDV) dan interleukin-12 (IL-12) sebagai terapi vaksin yang berpotensi menggantikan ubatan anti-kanser sedia ada di pasaran. Tambahn pula, gabungan antara NDV dan IL-12 untuk melawan kanser usus masih belum dilakukan dan berkemungkinan akan menhasilkan impak yang lebih berkesan daripada rawatan secara berasingan. NDV merupakan sejenis paramyxovirus yang menjangkiti dan menyebabkan penyakit pernafasan dan sistem saraf tunjang yang teruk terhadap spesis burung sehingga menyebabkan kematian namun, ia juga mampu untuk membunuh sel kanser. Melalui kejayaan lepas yang menggunakan NDV 'asli' untuk melawan kanser, projek ini bertujuan untuk menguji kesan anti-kanser rekombinasi NDV- strain AF2240 (rAF-IL12) terhadap sel kanser usus, CT26 dan HT29 dimana ia akan menghasilkan kesan rawatan yang lebih baik berbanding dengan 'strain asli', AF2240 (di gunakan sebagai kawalan positif di dalam kajian secara *in vitro* dan *in vivo*). Dalam kajian ini, rAF-IL12 telah dihipotesiskan untuk menyebabkan apoptosis terhadap CT26 dan HT29 pada peringkat *in vitro* dan *in vivo*, mengawal tindakan imun dalam mencit bertumor, dan tidak mendatangkan kesan terhadap sel-sel dan tisu-tisu normal. Kajian anti-pencambahan MTT menunjukkan bahawa nilai IC_{50} rAF-IL12 terhadap CT26 dan HT29 adalah sebanyak 276 HA unit dan 110 HA unit. Nilai-nilai IC_{50} tersebut telah digunakan sebagai dos rawatan di dalam kajian-kajian yang lain seperti AO/PI, Annexin V FITC, dan analisis kitaran sel. Rawatan menggunakan rAF-IL12 menunjukkan kesan sitotoksik yang signifikan ($p<0.05$) terhadap CT26 dan HT29 apabila dibandingkn dengan kumpulan AF2240-I seperti yang ditunjukkan oleh kajian

MTT, AO/PI, dan Annexin V FITC. Di samping itu, dalam analisis kitaran sel, rAF-IL12 telah menyebabkan 'penangkapan kitaran' pada fasa G_1 di dalam sel CT26 manakala ia menyebabkan apoptosis pada fasa G_0 di dalam sel HT29. Berikutan keputusan *in vitro* yang meyakinkan, penilaian selanjutnya ke atas rAF-IL12 terhadap kanser usus telah dijalankan secara *in vivo* iaitu ke atas mencit yang telah disuntik dengan sel kanser CT26 dan HT29. Rawatan menggunakan rAF-IL-12 (dos= 128 HA unit) telah berjaya mengurangkan berat dan isipadu tumor secara signifikan ($p<0.05$) bagi mencit yang telah disuntik dengan CT26 dan HT29 sel tumor berbanding dengan kumpulan mencit yang dirawat dengan AF2240 dan kumpulan mencit yang tidak dirawat (kawalan negatif). Rawatan rAF-IL12 juga telah meningkatkan jumlah sel apoptosis secara signifikan ($p<0.05$) berbanding dengan kumpulan lain seperti yang telah ditunjukkan oleh kajian TUNEL. Tambahan pula, rAF-IL12 juga telah ditunjukkan mampu untuk memodulasi sistem imun secara signifikan ($p<0.05$) dengan meningkatkan tahap CD4+ dan CD8+ sel-T, interleukin-2, interleukin-12, dan interferon-gamma. Selain itu, rAF-IL12 dapat memodulasi tahap ekspresi beberapa gen dalam mencit yang telah disuntik dengan sel kanser CT26 (KRAS, BRAF, MAPK1, NOTCH1, BAX, p53, CCL2, dan VEGF-A) dan HT29 (Fas, caspase-8, BID, BAX, SMAD3, dan granzyme B). Tambahan pula, analisis imunohistokimia ke atas tumor HT29 telah mendedahkan potensi anti metastatik dan anti-angiogenik rAF-IL12 kerana ia dapat mengurangkan ekspresi protein Survivin dan VEGF secara signifikan ($p<0.05$). Secara kesimpulan, rAF-IL12 merupakan calon yang sesuai untuk terapi kanser usus kerana profilnya yang bagus dalam merawat mencit yang disuntik tumor dan juga kesan positif dalam kajian-kajian *in vitro*.

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I certify that a Thesis Examination Committee has met on 22 July 2019 to conduct the final examination of Syed Umar Faruq bin Syed Najmuddin on his thesis entitled "Efficacy of Recombinant Newcastle Disease Virus, rAF-IL12 as a Potential Therapeutic Cancer Vaccine in CT26 and HT29 Cancer Cell Line and in Mouse Model" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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This is to confirm that:

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ANOVA	analysis of variance
AO/PI	acridine orange/propidium iodide
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BHQ	Black Hole Quencher
bp	Base pair
cDNA	complementary deoxyribonucleic acid
CO_2	Carbon dioxide
CRC	colorectal cancer
DAB	3,3'-Diaminobenzidine
DMEM	Dulbecco's modified essential medium
ddH_2O	deionized distilled water
DMSO	Dimethyl sulfoxide
DNA	deoxyribonucleic acid
dNTPs	Dideoxynucleotide triphosphates (dATP, dTTP, dCTP, and dGTP)
DPX	p-xylene-bis-pyridinium bromide
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme Linked Immunosorbent Assay
et al.	et alii
FAM	6-carboxyfluorescein
FBS	Fetal bovine serum
g	Gram
h	Hour(s)
H_2O_2	hydrogen peroxide

H&E	haematoxylin & eosin
HRP	horseradish peroxidase
IACUC	Institutional Animal Care and Use Committee
IFN-γ	interferon gamma
IL-12	interleukin-12
IL-2	interlukin-2
Kb	kilo base
KH_2PO_4	potassium dihydrogen phosphate
mg	milligram
min	minute
ml	millilitre
mM	milli Molar
MTT	3-(4,-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide
Na_2HCO_3	sodium bicarbonate
NDV	Newcastle disease virus
Ng	nanogram
NH_4Cl	ammonium chloride
OD	optical density
PBS	Phosphate buffered saline
PCR	Polymerase chain reaction
RNA	Ribonucleic acid
rpm	Revolution per minute
RPMI	Roswell Park Memorial Institute media
RT	Room temperature
RT qPCR	real-time quantitative polymerase chain reaction
s.c.	Subcutaneous
Taq	Thermus aquaticus thermostable DNA

TMB	3,3',5,5'-Tetramethylbenzidine
UV	Ultraviolet
µL	microliter
%	Percentage

CHAPTER 1

INTRODUCTION

Cancer remains a leading cause of death in Malaysia and across the world with the number of new cases keep on increasing year by year. Colorectal cancer (CRC) is the third and second most commonly occurring cancer respectively, in men and women, worldwide (Veettil et al., 2017). However, its incidence rates varies about ten-fold in both sexes across the world (i.e. geographical variation) (Koido et al., 2013). Nevertheless, the CRC incidence in Malaysia is at an alarming situation considering about 80% CRC cases in Malaysia are diagnosed in people older than 50 years old and majority of them are at late stage with poor prognosis (Veettil et al., 2017). Alas, Malaysia's population is aging and the situation is getting more complicated as there is no formal/structured national colorectal cancer screening program currently present in Malaysia (Azlie et al., 2015). Surgery, radiotherapy, and chemotherapy are three widely used conventional modalities to treat cancer, but they are often deemed not only as unsuccessful in treating the disease, but they also cause several setbacks such as physical pain, increased relapse and lower survival rate. Therefore, there is an urgent need to find and develop an alternative strategy/modality in tackling this problem.

NDV is an economically important avian paramyxovirus which affects the poultry industry worldwide costing a great loss economically (i.e. losses in egg production and meat) (Dimitrov et al., 2017). However, NDV, which can be categorized into three pathotype of strains; lentogenic (not virulent), mesogenic (intermediate virulent), and velogenic (high virulent), has also been shown as a potential candidate for cancer therapy with its formidable successes in treating advanced tumors in clinical trials (Kapczynski et al, 2013). For instance, NDV strain AF2240, a Malaysian-isolate NDV, has been reported to possess promising anti-cancer and immunomodulatory properties as it can inhibit breast tumor growth in allotransplanted mice as well as inducing apoptotic-related cytokines (Ahmad et al., 2018). Moreover, Ali et al. (2011) showed that AF2240 is effective against brain tumor cell lines *in vitro* as it causes apoptosis in brain cancer cells whilst sparing normal cells. Meanwhile, IL-12 has been demonstrated to regulate both innate (natural killer cells) and adaptive (cytotoxic T lymphocytes) immunities in cancer therapy, efficiently induced by itself as well as significantly improved by its combination with other treatment modalities such as antibodies, radiotherapies, adoptive therapy, and anti-tumor vaccine (Lu, 2017).

As the development of cancer therapy remains elusive, it is imperative to search for a new approach such as the use of combinatorial therapy between the oncolytic Newcastle disease virus (NDV) and interleukin-12 (IL-12) cytokine as a potential therapy vaccine to the current anti-cancer drugs available in the market or treatment modalities. As per individual treatment, AF2240 virus has showed cytotoxicity towards cancer cells and capability in provoking immune response while IL-12 is a potent inducer of anti-tumor immunity in preclinical models, but it is understandable that those individual treatment is not strong enough to totally eradicate tumor. Moreover, the therapeutic/synergistic

effects of the combination between these two components (i.e. insertion of IL-12 gene inside the genome of AF2240 NDV) against cancer is yet to be discovered, especially in colon cancer and would probably lead to much better outcomes as in the case of talimogene laherparepvec, T-Vec. T-Vec is a second-generation oncolytic herpes simplex virus type 1 (HSV-1) armed with granulocyte-macrophage colony stimulating factor (GM-CSF), which was recently approved as the first oncolytic virus drug in the USA and Europe (Fukuhara et al., 2016; Rehman et al., 2016).

In this present study, recombinant NDV, rAF-IL12 was tested against two colon cancer cell lines, originated from murine (CT26) and human (HT29). The selection of these cell lines was due to difference in characteristics between them. CT26 cells possessed mutant KRAS gene and has been the subject of interest when treating colon cancer while HT29 cells possessed mutant BRAF and are microsatellite stable. HT29 cells are classified as CMS3 subtype colon cancer, which is known for the lack of immune cells infiltration inside the tumor and is far more difficult to treat compared to the mutated-KRAS CT26 cells (Binnewies et al., 2018; Roelands et al., 2017). The main objective of this study is to set forth the anti-cancer potential of recombinant NDV, rAF-IL12 that could act as anti-tumorigenic, anti-metastatic, and anti-angiogenic as well as modulating the immune response.

The objectives of this study were:

1. To investigate the apoptosis induction of rAF-IL12 in CT26 and HT29 cancer cells *in vitro*.

2. To determine the anti-tumoral effects of rAF-IL12 in KRAS mutant CT26 colon cancer in a murine model, CT26 tumor challenged-BALB/c mice (immune-competent mice).

3. To evaluate the anti-cancer activities and apoptosis induction of rAF-IL12 in immunologically 'cold' colon cancer, HT29 (CMS3 subtype colon cancer) in HT29 tumor challenged-NCr Foxn1 nude mice (immune-deficient mice).

The hypothesis of this study were: 1) rAF-IL12 could induce apoptosis in CT26 and HT29 cancer cells *in vitro;* 2) rAF-IL12 could elicit anti-tumoral effects in KRAS mutant CT26 tumor challenged-Balb/c mice and immunologically 'cold' HT29 tumor-challenged-NCr Foxn1 nude mice in terms of apoptosis induction, metastasis inhibition, and immune response regulation; and 3) rAF-IL12 possesses a safety profile with no effect towards normal cells and tissues.

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