UNIVERSITI PUTRA MALAYSIA

ATTENUATION, MOLECULAR CHARACTERIZATION AND INACTIVATION OF FOWL ADENOVIRUS ISOLATES PROPAGATED IN CHICKEN EMBRYO LIVER CELLS FOR VACCINE DEVELOPMENT

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By

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June 2021

Chairman : Dato' Mohd Hair bin Bejo, PhD
Faculty : Veterinary Medicine

Fowl adenovirus (FAdV) 8b causes inclusion bodies hepatitis (IBH) in chicken with 10-30%. mortality worldwide and was first reported in Malaysia in 2005, but control has been difficult due to unavailability of vaccines. The objectives of this study were to propagate Malaysian isolates of FAdV 8b in chicken embryo liver (CEL) cells, attenuate, molecularly characterize and inactivate the virus and determine the pathogenicity, immunogenicity and efficacy of the attenuated and inactivated isolates in commercial broiler chickens.

UPM11142, UPM11134 and UPM08136 FAdV isolates from IBH outbreaks in Malaysia were each inoculated into specific pathogen free (SPF) chicken embryonated eggs (CEE). Liver from dead embryo were processed to obtain FAdV inocula which were each propagated and attenuated onto CEL cells till passage 20 (P1-P20). The P5 and P20 of UPM11142 and UPM08136 FAdV were propagated in Cytodex™ 1 microcarrier adapted CEL cells in a stirred tank bioreactor (P5B1 and P20B1). $TCID_{50}$ of all isolates were determined. Virus infectivity and localization of the virus in CEL cells were determined by immunocytochemical and HE stainning assays. PCR amplification of hexon and fibre genes were carried out using established and novel primers. Amplified genes were sequenced, analysed and phylogenetic trees constructed. UPM11142P5B1 and UPM08136P5B1 isolates were inactivated using binary ethylene imine (BEI) method, adjuvanted with Montanide 71VG and tested for immunogenicity and efficacy (with or without booster) on commercial broiler chickens. UPM11142P20B1 and UPM08136P20B1 attenuated vaccine candidates either with or without booster were tested for pathogenicity, immunogenicity and efficacy in commercial broiler chickens. Challenge group chickens of all groups were challenged with pathogenic FAdV at 28-day post inoculation (dpi). Clinical signs, gross and histopathological changes of organs were recorded. Body weight, liver weight and liver to body weight ratio were recorded. Humoral and cellular immunity were determined by ELISA and flowcytometry, respectively. FAdV challenge virus copy number in cloaca and liver were determined by

qPCR. Data generated were analysed using two-way repeated measures ANOVA and means separated with turkey HSD tests on 5% probability level.

UPM11142 and UPM11134 isolates caused 100% mortality of SPF CEE, while UPM08136 caused 86%. All isolates caused CPE on CEL cells characteristic of FAdV. FAdV titre ranged from $10^{5.5} – 10^{7.5}$ $TCID_{50}$/mL while virus infectivity and localization of virus in the nucleus were observed. These isolates were confirmed as FAdV genotype E, serotype 8b which were 98 to 100% phylogenetically related to UPM04217 reference isolate from GenBank. Sequence analysis of hexon gene revealed nucleotide changes G▶^{31}T causing amino acid change V▶^{11}L in UPM11142; synonymous C▶^{735}T in UPM11134; and G▶^{4}T (G▶^{2}C), G▶^{151}T (G▶^{51}C) and 8 nucleotide substitution that led to a unique SSKGG▶TLNSE amino acid change in UPM08136. In the fibre gene, there were C▶^{392}G, G▶^{393}C (A▶^{131}G), C▶^{430}A, T▶^{432}C (R▶^{144}S), and T▶^{434}G, G▶^{435}C (L▶^{145}C) in UPM11142 isolate; synonymous G▶^{431}C and A▶^{445}G (R▶^{144}T) in UPM11134; and A▶^{381}T (L▶^{127}F), G▶^{429}T, A▶^{430}C and C▶^{432}T (L▶^{143}F, (S▶^{144}R) in UPM08136 isolates. The CEL cells adapted well to Cytodex 1® microcarrier with cell attachment to the microcarrier within 3 hours of incubation. CPE, cell detachment and high titre were indicative of virus growth in the Cytodex™ 1 microcarrier adapted CEL cells maintained in a stirred tank bioreactor.

No clinical signs, mortality, gross and histopathologic changes of organs were recorded among chickens in the control group and chicken groups inoculated with inactivated and attenuated FAdV 8b strains (with or without booster). But chickens in control challenged group showed signs of depression and inappetence at 1 to 2 days post challenge and recorded enlarged and congested liver, spleen and thymus. The control challenged group had lower ($p<0.05$) body weight than the chickens inoculated with inactivated UPM11142P5B1 (with or without booster) challenged groups at 42 dpi. Inoculated chickens (with or without booster) had higher ($p>0.05$) FAdV antibodies titre than the control group on 7, 35 and 42 dpi, while the chickens with UPM11142P5B1 had higher ($p<0.05$) at 28 dpi. Inoculated challenged groups recorded high antibody titre at 35 and 42 dpi. The T cells were higher in chicken groups inoculated with inactivated UPM11142P5B1 and UPM08136P5B1 with or without booster in the liver, spleen and thymus, with CD8+ T cells being higher ($p<0.05$) at 21 dpi in the liver and spleen than in the uninoculated control chickens. The T cells were also higher at 35 and 42 dpi in the liver, spleen and thymus of inoculated challenged chickens than those of the challenged control chickens. The copy number of the FAdV challenge virus was significantly higher ($p<0.05$) in the liver and cloaca of challenged control chickens than in chicken groups inoculated with inactivated UPM11142P5B1 and UPM08136P5B1 with or without booster.

The control challenged group had lower ($p<0.05$) body weight than the chickens on the attenuated challenged groups (UPM11142P20B1 and UPM08136P20B1) at 35 and 42 dpi. There was higher FAdV antibody titre among chicken inoculated with live attenuated FAdV with or without booster using attenuated or inactivated FAdV on days 7, 21, 35, and 42 pi than the control group. There was no significant difference ($p>0.05$) in the antibody titre induced by UPM11142P20B1 and UPM08136P20B1 live attenuated viruses throughout the trial. There was higher CD3+. CD4+ and CD8+ T cells in the liver, spleen and thymus of chickens inoculated with attenuated UPM11142P20B1 and

UPM08136P20B1 without booster, with live attenuated or inactivated FAdV booster than the uninoculated non-challenged chickens, and similar results were recorded among the challenged groups. The copy number of the FAdV challenge virus was significantly higher in the liver and cloaca of challenged control chickens at 35 and 42 dpi than that of chickens inoculated with attenuated FAdV strains, and with (inactivated and attenuated) and without booster.

In conclusion, the three FAdV isolates from field outbreaks of IBH showed high pathogenicity in CEE and CEL cells, were successfully attenuated in CEL cells and molecularly characterised. The changes in the hexon and fibre genes of the P20 isolates are the markers for attenuation. CEL cells adapted well to Cytodex™ 1 microcarrier and were used successfully to propagate P5 and P20 isolates of UPM11142 and UPM08136 in stirred tank bioreactor without molecular changes. The inactivated (P5B1) and attenuated (P20B1) FAdVs were safe and induced humoral and cellular immunity in commercial broiler chickens which provided protection against pathogenic FAdV 8b challenge, reduced viral load in the liver and shedding in cloaca. Therefore, the attenuated and inactivated FAdV UPM11142 and UPM08136 isolates in the present study have high potential as FAdV serotype 8b vaccine candidates for the control and prevention of IBH in chickens.

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

ATENUASI, PENCIRIAN MOLEKUL DAN NYAHAKTIF ISOLAT FOWL ADENOVIRUS YANG DISEBARKAN DALAM SEL HATI EMBRIO AYAM UNTUK PEMBANGUNAN VAKSIN

Oleh

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Adenovirus unggas (FAdV) 8b menyebabkan badan kemasukan hepatitis (IBH) dalam ayam dengan 10-30% kematian di seluruh dunia, dan pertama kali dilaporkan di Malaysia pada 2005, tetapi telah sukar dikawal kerana ketiadaan vaksin. Objektif kajian ini adalah untuk menyebarkan isolat FAdV 8b Malaysia dalam sel hati embrio ayam (CEL), mengatenuasi, mencirikan molekul, dan menyahaktifkan virus, dan menentukan patogenik, imunogenik dan keberkesanan isolat yang diatenuasi dan dinyahaktif dalam ayam pedaging komersial.

UPM11142, UPM11134 dan UPM08136 isolat FAdV dari wabak IBH di Malaysia masing-masing disuntik ke dalam telur berembrio ayam (CEE) bebas patogen spesifik (SPF). Hati dari embrio yang mati diproses untuk mendapatkan inokula FAdV yang masing-masing disebarkan dan diatenuasi ke sel CEL sehingga petikan 20 (P1-P20). P5 dan P20 UPM11142 dan UPM08136 FAdV disebarkan di Cytodex ™ 1 mikrocarrier yang disesuaikan dengan sel CEL dalam bioreaktor tangki yang diaduk (P5B1 dan P20B1). $TCID_{50}$ dari semua isolat ditentukan. Infektiviti dan penyetempatan virus dalam sel CEL ditentukan dengan ujian pewarnaan imunositokimia dan HE. Penguatan PCR gen hekson dan serat dijalankan menggunakan primer yang ditetapkan dan novel. Gen yang diperkuat telah disusun, dianalisis dan pokok filogenetik telah dibina. Isolat UPM11142P5B1 dan UPM08136P5B1 dinyahaktifkan memggunakan etilena imine binari (BEI), ditambah pembantu Montanide 71VG dan diuji imunogenik dan keberkesanannya (dengan atau tanpa penggalak) pada ayam pedaging komersial. Calon vaksin atenuasi UPM11142P20B1 dan UPM08136P20B1 (dengan atau tanpa penggalak) diuji untuk patogenik, imunogenik dan keberkesanannya pada ayam. Ayam kumpulan cabaran dari semua kumpulan dicabar dengan patogenik FadV pada hari ke-28 selepas inokulasi (dpi). Tanda klinikal, perubahan kasar dan histopatologi organ direkodkan. Berat badan dan hati, dan nisbah berat hati kepada berat badan dicatatkan. Imuniti humoral dan selular masing-masing ditentukan dengan ELISA dan flowcytometry. Nombor salinan virus cabaran FAdV di kloaka dan hati ditentukan dengan qPCR. Data

yang dihasilkan dianalisis menggunakan ANOVA pengukuran berulang dua arah dan cara yang dipisahkan dengan Turkey HSD kalkun pada tahap kebarangkalian 5%.

Isolat UPM11142 dan UPM11134 menyebabkan 100% kematian SPF CEE, manakala UPM08136 menyebabkan 86%. Semua isolat menyebabkan CPE pada sel CEL bercirikan FAdV. FAdV titer adalah antara $10^{5.5}$-$10^{7.5}$ $TCID_{50}$/mL, manakala infektiviti dan penyetempatan virus dalam nukleus diperhatikan. Isolat virus telah disahkan genotip FAdV E, serotype 8b and 98 hingga 100% berkaitan secara pilogenetik dengan UPM04217 sebagai rujukan dari GenBank. Urutan analisis gen hekson mendedahkan perubahan nukleotida G▶^{31}T menyebabkan perubahan asid amino V▶^{11}L di UPM11142; sinonim C▶^{735}T di UPM11134; dan G▶^{4}T (G▶^{2}C), G▶^{151}T (G▶^{51}C) dan 8 penggantian nukleotida yang membawa kepada perubahan asid amino SSKGG▶TLNSE yang unik di UPM08136. Dalam gen serat, terdapat C▶^{392}G, G▶^{393}C (A▶^{131}G), C▶^{430}A, T▶^{432}C (R▶^{144}S), dan T▶^{434}G, G▶^{435}C (L▶^{145}C) di UPM11142 mengasingkan; sinonim G▶^{431}C dan A▶^{445}G (R▶^{144}T) di UPM11134; dan A▶^{381}T (L▶^{127}F), G▶^{429}T, A▶^{430}C dan C▶^{432}T (L▶^{143}F, (S▶^{144}R) di isolat UPM08136. Sel CEL disesuaikan dengan baik pada microcarrier Cytodex 1® dengan sel lampiran ke mikrokarrier dalam 3 jam inkubasi. CPE, detasmen sel dan titre yang tinggi menunjukkan pertumbuhan virus dalam mikrocarrier Cytodex ™ 1 yang disesuaikan sel CEL diselenggara dalam bioreaktor tangki yang diaduk.

Tiada tanda klinikal, kematian, perubahan kasar dan histopatologi organ yang diperhatikan di kalangan ayam dalam kumpulan kawalan dan kumpulan ayam yang disuntik dengan strain FAdV 8b yang dinyakaktifkan dan diatenuasi (dengan atau tanpa penggalak). Tetapi ayam dalam kawalan dari kumpulan dicabar menunjukkan tanda kemurungan dan ketidakupayaan pada 1 hingga 2 hari selepas cabaran dan juga mencatatkan hati, limpa dan timus yang besar dan kongesi. Kumpulan kawalan yang dicabar mempunyai berat badan yang lebih rendah ($p < 0.05$) daripada ayam yang disuntik dengan UPM11142P5B1 yang dinyahaktif (dengan atau tanpa penggalak) yang dicabar di 42 dpi. Ayam yang disuntik (dengan atau tanpa penggalak) mempunyai lebih tinggi ($p > 0.05$) FAdV antibodi titre daripada kumpulan kawalan pada 7, 35 dan 42 dpi, manakala ayam dengan UPM11142P5B1 mempunyai lebih tinggi ($p<0.05$) pada 28 dpi. Kumpulan yang dicabar mencatatkan titre antibodi yang tinggi pada 35 dan 42 dpi. Sel T lebih tinggi dalam kumpulan ayam yang disuntik dengan UPM11142P5B1 dan UPM08136P5B1yang dinyahaktif dengan atau tanpa penggalak di hati, limpa dan timus, dengan sel CD8+ T yang lebih tinggi ($p<0.05$) pada 21 dpi dalam hati dan limpa daripada kawalan ayam yang tidak diinokulasi. Sel T juga lebih tinggi pada 35 dan 42 dpi di hati, limpa dan timus ayam yang dicabar daripada daripada ayam kawalan yang dicabar. Bilangan salinan virus cabaran FAdV lebih tinggi ($p<0.05$) di hati dan kloaka ayam kawalan yang dicabar daripada kumpulan ayam yang disuntik dengan UPM11142P5B1 dan UPM08136P5B1 yang dinyahaktif dengan atau tanpa penggalak.

Kumpulan kawalan yang dicabar mempunyai berat badan yang lebih rendah ($p<0.05$) daripada ayam pada kumpulan atenuasi yang dicabar (UPM11142P20B1 dan UPM08136P20B1) pada 35 dan 42 dpi. Terdapat FAdV antibodi titre yang lebih tinggi di kalangan ayam yang disuntik dengan atenuasi FAdV dengan atau tanpa penggalak menggunakan atenuasi atau nyahaktif FAdV pada hari 7, 21, 35, dan 42 dpi daripada kumpulan kawalan. Tiada perbezaan yang signifikan ($p>0.05$) dalam titer antibodi yang

dihasilkan oleh atenuasi UPM11142P20B1 dan UPM08136P20B1 sepanjang kajian. Terdapat CD3+. CD4+ dan CD8+ T sel yang lebih tinggi dalam hati, limpa dan timus ayam yang disuntik dengan atenuasi UPM11142P20B1 dan UPM08136P20B1 tanpa penggalak, dengan penggalak yang diatenuasi atau dinyahaktif daripada ayam yang tidak dicabar, dan hasil yang sama dicatatkan di kalangan kumpulan yang dicabar. Jumlah salinan virus cabaran FAdV jauh lebih tinggi di hati dan kloaka ayam kawalan yang dicabar pada 35 dan 42 dpi daripada ayam yang diinokulasi dengan strain FAdV yang diatenuasi, dan dengan atau tanpa penggalak (nyahaktif dan diatenuasi).

Sebagai kesimpulan, tiga isolat FAdV dari wabak IBH menunjukkan patogenik yang tinggi dalam sel CEE dan CEL, berjaya diatenuasi dalam sel CEL dan pencirian molekul. Perubahan dalam gen hekson dan serat pada P20 isolat adalah penanda untuk atenuasi. Sel CEL disesuaikan dengan baik kepada Mikrocarrier Cytodex ™ 1 dan digunakan dengan jayanya untuk menyebarkan P5 dan P20 UPM11142 dan UPM08136 dalam bioreaktor tangki yang diaduk tanpa perubahan ciri molekul virus. Nyahaktif (P5B1) dan atenuasi (P20B1) FAdV adalah selamat dan menghasilkan imuniti humoral dan selular dalam ayam pedaging komersial yang memberikan perlindungan terhadap cabaran patogenik FAdV 8b, mengurangkan beban virus di hati dan penumpahan dari kloaka. Oleh itu, UPM1142 dan UPM08136 isolat dalam kajian ini mempunyai potensi tinggi sebagai calon vaksin FAdV serotype 8b untuk kawalan dan pencegahan IBH dalam ayam.

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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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ADC	Anchorage dependent cells
ADP	Adenoviral nuclear membrane glycoprotein
AdV	Adenovirus
APC	antigen presenting cells
APC	Allophycocyanin dye
BEI	Binary ethylene inime
BFBs	biological fluidized bed
BGM70	Baby grivet monkey-70
BOD	biological oxygen demand
bp	Base pair
BPL	Betapropiolactone
CAM	Chorioallantoic membrane
CAR	chimeric antigen receptor
CAR	coxsackievirus-adenovirus receptor
CAV	Chicken infectious anaemia virus
CD3+	Cluster of differentiation 3 positive
CD4+	Cluster of differentiation 4 positive
CD8+	Cluster of differentiation 8 positive
CEL	Chicken embryo liver cells
CMI	Cell mediated immunity
CO_2	Carbondioxide
COD	chemical oxygen demand
DAB	3,3'-Diaminobenzidine

DAPI	4′,6-diamidino-2-phenylindole
DDBJ	DNA Data Bank of Japan
DMEM	Dulbecco's Modified Eagle's medium
DNA	Deoxyribonucleic acid
DNAse	Deoxyribonuclease
dpi	Day post inoculation
DPX	Colorless synthetic resin mounting media, mixture of Distyrene, a plasticizer, and xylene
dsDNA	Double stranded Dioxyribonucleic acid
EDS'76	Egg drop syndrome
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
ENA	European Nucleotide Archive
FAdV	Fowl adenovirus
FB	Fluidized bed
FBF	Fluidized bed fermentation
FBS	Foetal bovine serum
FITC	Fluorescein isothiocyanate dye
FMIA	Fibre-based fluorescent microsphere immunoassay
G+C	Guanine and cytosine content
GE	Gizzard erosion
GIT	Gastrointestinal tract
GON	Group of nine hexons
GOS	Group of six hexons
H1N1	Influenza virus

HCl	Hydrochloric acid
HFBs	Hollow fiber bioreactors
HPS	Hydropericadium syndrome
HRM	High resolution melting curve
IACUC	Institutional Animal Care and Use Committee
IBDV	Infectious bursal disease virus
IBH	Inclusion body hepatitis
IFN	Interferon
IFN-γ	Interferon
INIB	Intranuclear inclusion body
INSDC	Nucleotide Sequence Database Collaboration
ITR	Inverted terminal protein
Kb	Kilobase
KDa	Kilodalton
L1-4	Loop regions of hexon gene 1-4
MBR	membrane bioreactors
MDA	Maternally derived antibodies
MDCK	Madin Darby canine kidney cells
MDV	Marek's disease virus
MEM	Minimum essential medium
MHC-I	Major histocompatibility class 1
MHC-II	Major histocompatibility class 2
mRNA	Messenger RNA
MVA	Modified Vaccinia Ankara virus

NaOH	Sodium hydroxide
NCBI	National Centre for Biotechnology Information
NDV	Newcastle disease virus
NK cells	Natural killer cells
ORF	Open reading frame
P1-2	Pedestal region of hexon gene 1 and 2
PAMP	pathogen associated molecular pattern
PBS	Phosphate buffered saline
PBST	Phosphate buffered saline with tween 20
pc	Post challenge
PCR	Polymerase chain reaction
PE	R-phycoerythrin dye
pH	Power/potential of hydrogen that measures level of acidity or alkalinity
PRR	Pattern recognition receptors
pTP	Precursor terminal protein
qPCR	Quantitative polymerase chain reaction
RDG	Tripeptide amino acids (arginine, glycine and aspartate) within fibronectin protein that mediates cell attachment
RIG-1	Retinoic acid-inducible gene I
RNA	Ribonucleic acid
SPF	Specific pathogen free
STR	Stirred tank bioreactor
TAE	Tris-acetate EDTA
TC	Tissue culture

$TCID_{50}$	Tissue culture infective dose
Tcm	central memory T cells
TCR	T cell receptor
Tem	effector memory T cells
TH cells	T helper cells
TLR	Tool-like receptor
TP	Terminal protein
Trm	resident memory T cells
UPM	Universiti Putra Malaysia
UV	Ultraviolent light
Vero	Green monkey kidney cells
A	alanine – ala
R	arginine – arg
N	asparagine – asn
D	aspartic acid – asp
C	cysteine – cys
E	glutamic acid – glu
Q	glutamine – gln
G	glycine - gly
H	histidine – his
I	isoleucine – ile
L	leucine – leu
K	lysine - lys
M	methionine – met

F	phenylalanine – phe
P	proline – pro
S	serine - ser
T	threonine – thr
W	tryptophan – trp
Y	tyrosine - tyr
V	valine- val

CHAPTER 1

INTRODUCTION

1.1 Background of the study

Fowl adenovirus (FAdV) belongs to the family adenoviridae and genus aviadenoviridae (Harrach et al., 2012). They were first isolated from contaminated embryonated chicken egg in 1949 (Van der Ende et al., 1949). FAdV is structurally made up of a hexon base and a penton base linked to each other by one or two fibers. It is the hexon that incite the production of antibodies which is used to serotype the virus through virus neutralization tests (Hess, 2000). FAdV is made up of 12 serotypes ascribed FAdV1-7, FAdV8a, FAdV8b and FAdV9-11 (Hess, 2000). By the use of restriction enzyme analysis (Zsak and Kisany, 1984) and later by hexon gene amplification and analysis (Benko et al., 2005) FAdV is further subdivided into 5 groups (A-E) which was classified as follows: FAdV serotypes 1 and 5 belong to group A and B respectively, FAdV 4 and 10 (group C); FAdV 2, 3, 9 and 11 (group D) and FAdV 6, 7, 8a and 8b (group E) (Adair and Fitzgerald, 2008).

Fowl adenovirus was originally seen as opportunistic pathogens which only elicit disease as a secondary infection especially associated with immuno-compromised hosts. In chicken it was associated with Inclusion body hepatitis (IBH) as a secondary infection to Infectious bursal disease virus (IBDV) and Chicken infectious anaemia virus (CAV) which were then precursors of IBH. However, in 2006, Gomis et al, reported cases of IBH without IBDV and or CAV. Experimental cases of IBH were later reproduced with FAdV type E thereby making FAdV a potential cause of IBH (Adair and Fitzgerald, 2008; Zadravec et al., 2011; Choi et al., 2012; Dar et al., 2012).

FAdV 4 was consistently isolated from Hepatitis-hydropericardium syndrome (HPS) which characteristically causes the filling of the pericardium with straw-coloured fluid. HPS has similar characteristics with IBH, but while IBH is associated with 30% mortality HPS is usually known to cause 75% mortality. This disease has been reported in Asia, South America and Middle East (Nakamura et al., 2000) and has been reproduced with FAdV 4 (Hess et al., 1999). In Japan and very commonly in Europe, FAdV1 was isolated from lesions of gizzard erosion (Okuda et al., 2001; Ono et al., 2003; Marek et al., 2010; Domanska-Blicharz, 2011). In this case, 1-2 weeks old broilers were presented with degeneration and erosion of the keratinous layer of the gizzard, high feed conversion ratio and gizzard condemnation. The virus has also been confirmed to be capable of spreading to other organs of the host where they may also cause immunosuppression by interacting with humoral and cell associated functions of the immune system (Schonewille et al., 2000).

FAdV 8b is associated with IBH and have been reported worldwide. IBH is characterized by sudden onset of mortality which peaks at 3 – 4 days of infection and ending on the fifth day but can continue up to 2-3 weeks. Sick chickens appear with ruffled feather and

died within 48 hours of infection or may recover (Calnek et al., 1991). IBH is associated with increasing flock mortality rate usually ranging from 10-30% but could be as low as 2% as well (Choi et al., 2012; Dar et al., 2012). It affects broiler chickens usually at 3-7weeks of age and also affects other avian species like turkey, geese, pheasant and quails (Cowen, 1992; Singh et al., 1996). The disease has also been reported within a week of hatch in broilers (Pilkington et al., 1997) as well as in pullets (Choi et al.,2012). Although five species (A to E) and 12 serotypes (1–7, 8a, 8b, 9– 11) of FAdVs are known (Gunes et al., 2012; Gupta et al., 2017), IBH is primarily caused by FAdV-7, 8a and 8b of species E and FAdV-2 and 11 of species D (Gomis et al., 2006; Philippe et al., 2007; Ojkic et al., 2008; Steer et al., 2011; Choi et al., 2012). FAdV-8a, 8b and 11 are the predominant serotypes associated with outbreaks of IBH in Canada (Ojkic et al., 2008a; Ojkic et al., 2008b). Transmission is vertical through embryonated eggs or horizontal through direct contact with excreta of infected chicken or formites (McFerran and Smyth, 2000).

FAdV serotype 8b infection is also associated with low feed intake, poor growth, high feed conversion ratio, respiratory diseases and tenosynovitis (McFerran et al., 1971; Jones and Geordion, 1983; Adair and Fitzgerald, 2008). FAdV infections were observed to be associated with enlarged, pale and congested liver, hepatic haemorrhages and necrosis (hair-Bejo 2005; Norina et al., 2016), atrophy of thymus and bursa of Fabricius (Mettifugo et al., 2014), congestion and inflammation of trachea and lungs, watery contents in the intestinal tracts, pale heart muscles (Mariappan et al., 2018) and necrosis of the gizzard (Ono et al., 2001).

Apart from the traditional methods of isolation, detection and characterization involving culture on chicken embryo, virus neutralization test, enzyme linked immunosorbent assay (ELISA) which are laborious and time consuming, other modern methods have evolved. Molecular detection of FAdV is based on PCR using primers designed to target hexon genes (Seer et al., 2011; Dar et al., 2012). A combination of PCR and restriction enzyme analysis (REA) could be used to classify FAdV into serotypes (Mittal et al., 2014).

Since diseases caused by most viruses including adenovirus are not treatable, control and management of FAdV infection could be only through prevention. Preventive measures like adequate biosecurity measures which are set standards generally are encouraged. However, vaccination still remains the best option for prevention and control of this infection. Vaccine production involves inactivation (killed vaccines), attenuation (live vaccines) and recombinant gene technology (new generation vaccines). Interestingly, these three types of vaccines are currently available for commercial poultry industry in Malaysia (Hair-Bejo, 2010).

1.2 Statement of Problem

IBH, HPS, gizzard erosion and respiratory diseases caused by fowl adenovirus (Hess et al., 1999; Gomis et al., 2006) has been reported in various countries: USA (Mendelson et al., 1995), India (Mittal et al., 2014), Canada (Ojkic et al., 2008), Hungary (kajan et al., 2013), Korea (Choi et al., 2012), Japan (Mase et al., 2012), China (Li et al., 2010)

and in Malaysia as well (Hair-Bejo, 2005; Norina et al., 2016) with heavy economic losses in the poultry industry.

FAdV is transmitted vertically which makes control of infection very difficult. Vaccination of parent stock and their progenies may be the major form of prevention and control. Although vaccines against FAdV have been produced in various countries which may be in use in Malaysia currently, these vaccines most probably were not produced with Malaysian strains of this virus which makes efficacy and effectiveness difficult. In addition, different diseases are caused by different serotypes and do not confer cross protection which makes development of vaccines in regions and countries necessary (Dar et al., 2012).

For vaccine development, FAdV has to be grown in susceptible cells especially when it's targeted at bypassing the traditional use of scarce SPF eggs which is labourous and not suitable for large volume production. But its growth is hampered by the inability of the organism to adapt satisfactorily in different continuous cell lines which make its study and attenuation a herculean task.

After overcoming the difficulties of vaccine development, transiting from bench to field could be very challenging especially with large volume production. To bypass the huge costs, labour intensive and time-consuming procedures associated with repeated flask-based tissue culture for large volumes of vaccine virus, requires a thorough-put, sensitive procedure. Thus, to safeguard these attenuated vaccine candidates from changes in the hexon and fibre genes that could lead to reversion to virulence requires optimization and could also pose a difficult challenge.

1.3 Hypothesis

Ho: Attenuated Malaysian FAdV strains cannot be propagated in CEL cell adapted to microcarrier in a bioreactor.

H_A: Attenuated Malaysian FAdV strains can be propagated in CEL cell adapted to microcarrier in a bioreactor.

Ho: Inactivated FAdV will not be immunogenic and safe in commercial chickens.

H_A: Inactivated FAdV will be immunogenic and safe in commercial chickens.

Ho: Attenuated FAdV will not be low pathogenic, safe and immunogenic strains in commercial chickens.

H_A: Attenuated FAdV will be low pathogenic, safe and immunogenic strains in commercial chickens.

1.4 Objectives of the Study

The main objective of this study was to attenuate, characterize and inactivate FAdV strains of Malaysia for the purpose of vaccine development. The specific objectives were:

1. to propagate and attenuate the FAdV isolates on CEL cells.

2. to determine the molecular characteristics of the FAdV isolates and their progenies.

3. to propagate UPM11142P5, UPM11142P20, UPM08136P5 and UPM08136P20 FAdV isolates in microcarrier adapted CEL cells in a bioreactor.

4. to inactivate the selected FAdV isolates and determine their immunogenicity, safety and efficacy in commercial broiler chickens.

5. to determine the pathogenicity, immunogenicity and efficacy of the attenuated FAdV isolates in commercial broiler chickens.

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