UNIVERSITI PUTRA MALAYSIA

MOLECULAR CHARACTERISATION OF AN ATTENUATED GDHA-DERIVATIVE OF Pasteurella multocida B:2

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FBSB 2020 25

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By

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

October 2019

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

MOLECULAR CHARACTERISATION OF AN ATTENUATED GDHA-DERIVATIVE OF *Pasteurella multocida* B:2

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October 2019

Chairman : Associate Professor Siti Sarah Othman, PhD
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Pasteurella multocida B:2 is an important veterinary pathogen causing fatal and acute Haemorrhagic septicaemia (HS) in bovine. The pathogen is usually commensal that resides in the submandibular region of buffaloes or cattle. Monsoon season is the outbreak season for the disease to commonly develop due to the weakening immunity of the animals. Endemic countries, particularly Asia, routinely administer oil-adjuvant or whole-killed vaccines for disease prevention. However, these vaccines were observed to provide short-term protection with inadequate vaccination coverage which led to a significant failure of the vaccination program. The live-attenuated vaccine was proposed to overcome the limitations provided by the current vaccines. A live vaccine candidate, *P. multocida* B:2 GDH7 was reported to enable protection in cattle and buffaloes via intranasal (i.n.) administration. This potential vaccine was also reported to be self-transmitted from the vaccinated animal to the free-ranging animal allowing wider vaccination coverage. Prior to commercialisation, this potential vaccine requires further characterisation in accordance with the authoritative guidelines from the World Organisation for Animal Health (OIE). Hence, in this study, the potential vaccine strain, *P. multocida* B:2 GDH7 and the virulent parent strain will be characterised through genomic and proteomic profiling. A crucial first step was to develop a sensitive identification test to differentiate both strains which has been achieved by the development of a precise yet straightforward PCR method. In genomic profiling, Repetitive Extragenic Palindromic sequence-PCR (REP-PCR) was manipulated and has demonstrated different genomic DNA band patterns of both strains. By using several bioinformatics tools, 105 outer membrane proteins (OMPs) were determined from the proteome of the parent strain. About 5-10% of the OMPs determined were observed in SDS-PAGE analysis of both strains. Some of the major OMPs especially OmpA and OmpH, are known as prominent immunogens of *P. multocida*, were observed to be

expressed differently between the strains. In conclusion, a reproducible PCR detection method has been developed to differentiate both strains. Further characterisation of these strains shows a significantly different profile through genomic and proteomic profiling. Bioinformatics analysis had enabled selection of four antigens for future HS vaccine development.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

PENCIRIAN BAKTERIA DERIVATIF GDHA$^-$ TERATENUAT *Pasteurella multocida* B:2

Oleh

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Pasteurella multocida B:2 adalah patogen veterina penting yang menyebabkan penyakit hawar berdarah (HB) dan bersifat akut terhadap bovin. Secara ummumnya, patogen tersebut adalah komensal menetapi di dalam bahagian submandibel kerbau dan lembu. Musim monsun adalah musim perebakkan penyakit hawar berdarah kerana imuniti haiwan yang lemah. Negara berwabak, terutamanya Asia, memvaksin haiwan-haiwan secara rutin menggunakan vaksin adjuvan emulsi minyak atau vaksin bakterin dibunuh menyeluruh demi pencegahan penyakit. Walau demikian, vaksin tersebut hanya melengkapi perlindungan dalam jangka masa yang pendek dengan liputan vaksin yang tidak menyeluruh menyumbang kepada kegagalan besar kepada program vaksinasi tersebut. Vaksin hidup-teratenuat telah dicadangkan untuk mengatasi kelemahan daripada vaksin semasa. Vaksin hidup-teratenuat yang dikenali sebagai *P. multocida* B:2 GDH7 telah dilaporkan berupaya memberi perlindungan kepada lembu dan kerbau melalui pemberian '*intranasal*' (*i.n.*). Vaksin yang berpotensi ini juga telah dilaporkan berupaya untuk penghantaran-diri daripada haiwan yang telah divaksin kepada haiwan lain yang diternak lepas sekaligus memberi liputan perlindungan yang lebih luas. Sebelum dikomersialisasikan, vaksin yang berpotensi ini perlu dipercirikan dengan lebih terperinci untuk memenuhi dan mematuhi garis panduan yang diperkuasakan daripada badan '*World Organisation for Animal Health*' (*OIE*). Dengan itu, daripada kajian ini, strain vaksin berpotensi iaitu *P. multocida* B:2 GDH7 dan strain induk virulen akan dicirikan melalui profil genom dan proteomik. Langkah yang genting adalah untuk membina satu ujian identifikasi yang sensitif untuk membezakan kedua-dua strain. Ia telah dijayakan daripada pembinaan kaedah PCR yang tepat dan ringkas. Daripada profil genom, '*Repetitive Extragenic Palindromic sequence-PCR'* (*REP-PCR*) telah dimanipulasikan dan mendemonstrasi corak genom DNA yang berlainan antara kedua-dua strain. Dengan

menggunakan beberapa alat bioinformatik, 105 protein membran luar (OMPs) telah dikenalpasti daripada proteom strain induk. Hampir 5-10% daripada OMPs yang dikenalpasti telah diperhati daripada kedua-dua strain menggunakan analsis *'SDS-PAGE'*. *'OmpA'* dan *'OmpH'* yang dikenali sebagai OMPs utama dan immunogen yang ketara daripada *P. multocida*, telah diekspresikan secara berlainan antara semua strain. Kesimpulannya, satu kaedah pengesanan PCR yang boleh diproduksi semula telah dibina untuk membezakan kedua-dua strain. Pencirian yang mendalam untuk kesemua strain telah menunjukkan profil yang berlainan secara ketara melalui profil genom dan proteomik. Analisis bioinformatik membolehkan seleksi empat antigen untuk pembangunan vaksin HS di masa hadapan.

ACKNOWLEDGEMENTS

Bismillahirrahmanirrahim…

To Allah I show all my gratitude for all the blessings granted to me. I am His humble servant is thankful for the guidance during the hard times. Finishing this thesis is very euphoric to me as I recall all the trials and challenges that sculpted me as I am today.

I would like to take this opportunity to thank my main supervisor Dr. Sarah Othman for her loving guidance and endless support. Her passion and meticulous habit has shaped me as a scientist I am today and hopefully until the future. Her ambitiousness and courage has made me brave into getting out of my comfort zone and chasing for my own ambitions. I would also like to express gratitude to both my co-supervisors Prof. Mohd. Zamri Saad and Prof. Raha Rahim for your warm, kind and continuous support. And to Dr. Teerasak E-kobon, thank you very much for your kind heart. You had provided me endless help, guidance and support from the moment I reached to KU until today.

To all the members of Microbial Biotechnology Lab, thank you for your support during my research in UPM. Special thanks to Kak Iqmal, Kak Bibah, Kak Nana, Chai Yan, Kak Aishah, Kak Inna and especially Abg Jeevan for your kind help and advices. All my love to Farah, Ika, Wan and Jikah. Thank you for our 8 years of friendship and I hope it continues until the end.

And last but not least, my family. I am forever indebted for everything, Ibu and Ayah. I am grateful for all the sacrifices and support towards me, your very imperfect daughter. May Allah always grant both of you His blessings. To my annoying yet lovable siblings, thank you very much for our time and stories.

With this opportunity, I also wish to express my gratitude towards UPM and KU for the chance in partaking the Dual Degree program. Thank you very much to SEARCA that provided the financial support during my Dual Degree program in Kasetsart University, Thailand.

Without all of your support, I would not be able to hold my grit until the finish line. I am always hoping to be a better person tomorrow than I am today. Thank you very much to all of you from the bottom of my heart.

Farahani binti Muhammad Azam

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LIST OF ABBREVIATIONS AND SYMBOLS

%	Percent
◦C	Degree Celcius
µL	Microlitre
µM	Micromolar
A	Absorbance
ABC	ATP binding cassette
ACC	Auto cross covariance
Acc. No.	Accession number
AFLP-PCR	Amplified Fragment Length Polymorphism-PCR
ApbE	Thiamine biosynthesis protein
aroA	Aromatic amino acid gene
ATP	Adenosine triphosphate
BAM complex	Outer membrane beta-barrel protein assembly factor protein complex
BamA,B,C,D,E	Outer membrane protein assembly factor protein
BHI	Brain heart infusion
BLASTN	Nucleotide Basic Local Alignment Search Tool
BLASTP	Protein Basic Local Alignment Search Tool
BLOSUM62	Blocks substitution matrix at 62% cluster
BoLA	Bovine leukocyte antigens
BOMP	Beta-barrel Outer Membrane Predictor
bp	Basepairs
CAECAMs	Carcinoembryonic antigen-related cell adhesion molecules
CDD	Conserved Domain Database

CFU	Colony forming unit
CPS	Capsular polysaccharide synthesis
DNA	Deoxyribonucleic acid
dNTPs	Deoxynucleoside triphosphates
DoxX	DoxX family protein
E	Expect value
EnvC	Cell membrane biogenesis-associated protein
EtBr	Ethidium bromide
ExPASy	SIB bioinformatics resource portal
FASTA	Text-based single-letter format
FhaB	Hemolysin secretion/activation protein B
FhaC	Hemolysin secretion/activation protein C
fur	Ferric uptake regulator gene
g	Gram
GBS	Group B *Streptococcus*
GC	Guanine Cytosine
gdhA	Glutamate dehydrogenase gene
GlpQ	Glycerophosphodiester phosphodiesterase protein
HasR	Heme uptake receptor protein
HeLa cells	Human cervical cancer cells
HemR	Heme/hemoglobin receptor protein
hgbA	Haemoglobin binding protein A gene
HgbB	Haemoglobin binding protein B protein
HLA	Human leukocyte antigens
HLA-DR	Human leukocyte antigens-DR isotype
HmbR	Haemoglobin receptor protein

HMM	Hidden Markov's model
HS	Haemorrhagic septicaemia
HtpX	Peptidase protein
i.m.	Intramuscular
i.n.	Intranasal
IFITM	Interferon-induced transmembrane
IL2	Interleukin 2 gene
IroA	Lactoferrin receptor protein
IROMPs	Iron-regulated outer membrane proteins
kb	Kilobasepairs
kDa	Kilodaltons
LcrE	Immunogenic antigen of *C. pneumonia*
LipoP	Lipoprotein predictor
LPS	Lipopolysaccharide
LptD	LPS assembly protein
LytM	Lysostaphin-like metalloproteases protein
m-Dap	Peptidoglycan residue
$MgCl_2$	Magnesium chloride
MHC	Major histocompatibility complex
min	Minutes
mL	Millilitre
MULTIPRED2	Peptide-human leukocyte antigen molecules binding predictor
MW	Molecular weight
NanH	Autotransporter domain-containing protein
NCBI	National Center for Biotechnology Information

ng	Nanogram
NlpD	Cell membrane biogenesis-associated protein
NMR	Nuclear Magnetic Resonance
NqrC	Na(+)-translocating NADH-quinone reductase subunit C protein
nr	Non-redundant
NTHi	Nontypeable *Heamophilus influenzae*
OIE	World Organisation for Animal Health
OM	Outer membrane
Oma1	Peptidase protein
Omp16	Outer membrane protein of 16kDa
OmpA	Outer membrane protein A protein
OmpC	Outer membrane protein C protein
OmpH	Outer membrane protein H protein
OmpH1	Outer membrane protein H1 potein
OmpH2	Outer membrane protein H2 protein
OMPMotif	Outer Membrane Protein Motif
OMPs	Outer membrane proteins
OmpV	Outer membrane protein V protein
OmpW	Outer membrane protein W protein
OMSVM	Outer Membrane Support Vector Machine
Opa	Opacity associated protein
Pal	Peptidoglycan-associated lipoprotein
PCR	Polymerase Chain Reaction
PFGE	Pulsed Field Gel Electrophoresis
pfhA	Filamentous hemagglutinin gene

PfkA	6-phosphofructokinase protein
PG-P	Peptidoglycan precursor
pI	Isoelectric point
PlpB	*Pasteurella* lipoprotein B protein
PlpE	*Pasteurella* lipoprotein E protein
pmol	Picomole
pOmpA	pCDNA-OmpA
pOmpH	pCDNA-OmpH
POTRA	Polypeptide-associated transport
PSORTb	Protein subcellular localisation predictor for Gram-negative bacteria
REP-PCR	Repetitive Extragenic Palindromic sequence-based PCR
rpm	Revolutions per minute
rPmOmpA	Recombinant *P. multocida* outer membrane protein A protein
s	Seconds
SDS-PAGE	Sodium Dodecyl Sulfate-Polyacrylamide Gel Electrophoresis
SpaseI	Signal peptidase I
SpaseII	Signal peptidase II
SPII	Signal peptidase II
SS2	*Streptococcus suis* serotype 2
Ste24	Peptidase protein
subsp.	Subspecies
TAE	Tris acetate EDTA
TAM complex	Translocation/assembly module complex
TamA,B	Translocation/assembly module protein

TbpA	Transferrin binding protein A protein
Tm◦C	Melting temperature
TolC	Outer membrane channel protein
UV	Ultraviolet
V	Volt
VaxiJen	Protective antigens and subunit vaccines predictor
Wza	Polysaccharide export protein
X	Dilution factor
YcfL	DUF1425 domain-containing protein
YDB	Minimal nutrient medium
YdgA	DUF945 domain-containing protein
YebA	Cell membrane biogenesis-associated protein
YopT	*Yersinia enterocolitica* outer protein T protein

CHAPTER 1

INTRODUCTION

Hemorrhagic septicemia (HS) is a major disease in cattle and buffaloes which is caused by the infection of *Pasteurella multocida* B:2 or E:2. In Asia, the serotype of the bacteria responsible for the disease is *P. multocida* B:2 (De Alwis, 1995, 1999). This endemic disease causes great economic losses particularly towards farmers due to high mortality rate and rapid transmission of an outbreak field to the adjacent field (Zamri-Saad & Annas, 2016). Transmission occurred from diseased animals or carriers through intranasal and oral routes (Abubakar & Zamri-Saad, 2011). Invasion of the bacteria through endothelial cells resulted in rapid infiltration of the animals' bloodstream (Galdiero et al., 2001). High occurrence of outbreak happened during monsoon or raining season due to the weakening of immune response of the animals making them susceptible to the infection (De Alwis, 1995). Vaccination is an effective routine for controlling outbreak of HS especially in Asian countries due to semi-wild rearing methods of the animals.

Vaccines for HS usually are registered prior to rainy season using oil-adjuvant vaccine or alum-precipitated vaccine. Despite both vaccines contained bacterin, only short-termed protection was detected (Othman, 2007) and also tedious administration process, resulting in ineffective disease outbreak control. Therefore, live vaccine was recommended to control HS outbreak efficiently such that this type of vaccine enable mimicry of nature route of infection like the wild-type (De Alwis, 1999). Live-attenuated vaccine consisted of live organisms such as the attenuated bacteria with reduced virulence when compared to the wild-type (Zamri-Saad, 2013). A local strain of *P. multocida* B:2 from previous outbreak was attenuated into a derivative known as *P. multocida* B:2 GDH7. The mutant was generated through the disruption of the *gdhA* gene by the insertion of kanamycin cassette (Othman, 2007). This resulted in the arrested metabolism and thus weakened the pathogenicity of the mutant. Since available vaccines such as alum-precipitated vaccine and oil-adjuvant vaccine were discovered to be less effective, a new alternative is paramount. The aforementioned *gdhA* gene disruption has been found to be a promising manipulation for non-pathogenic *P. multocida* B:2 vaccine development (S. Othman et al., 2012). Further information on the outer membrane proteins (OMPs) can enable manipulation and improvement of HS vaccine.

For commercialisation purposes, upscaling the potential vaccine strain *P. multocida* B:2 GDH7 with an economical media is recommended when compared to the commercial available media (Sarwar et al., 2013). This establishment will provide a more competitive and sustainable product in the market. Hence, a minimal media known as YDB media was formulated with

the purpose to reduce production cost of *P. multocida* B:2 GDH7 as vaccine strain for HS (Oslan et al., 2018).

The organisation specified in the animals' health concerns, World Organisation for Animal Health or also initially known as Office International des Epizooties (OIE) has regulated the production of vaccines in order to assure safe vaccines for animal diseases control in each country (OIE, 2008b, 2016). However, the attenuation of the mutant strain, *P. multocida* B:2 GDH7 has yet to be fully apprehended. In this study, a conventional PCR assay will be established as a detection method to distinguish *P. multocida* B:2 GDH7 from its parent strain. Hence, unique primers to the attenuated *P. multocida* B:2 GDH7 will be generated. Genotypic and phenotypic profiling of a modified bacterial strain is vital in ensuring vaccine quality according to the OIE's vaccine production guidelines. Therefore, the information on the genomic and proteomic profiles of the bacterium used for vaccination will enable better understanding towards the vaccine and its effectiveness (Berrêdo-Pinho et al., 2011).

In comparison to housekeeping genes manipulation for vaccine development, manipulation of virulent factors of *P. multocida* was more widely explored. Most of the known virulent factors of Gram-negative bacteria are membrane-exposed which are the components that reside on the membrane facing the environment (Pandher et al., 1999; Eijkelkamp et al., 2014; Wilson & Bernstein, 2016). Outer membrane proteins (OMPs) are known as one of the virulence factors and are strong antigenic agents of *P. multocida* (Basagoudanavar et al., 2006). The OMPs of Gram-negative bacteria and also *P. multocida* are divided into two major components which are the integral membrane proteins (intrinsic proteins) and the peripheral membrane proteins (extrinsic proteins) in which the prior are embedded within the lipid bilayer but the latter are only attached to the outer of the lipid bilayer. Peripheral proteins are commonly anchored to the membrane using a covalently linked-lipid anchor that enters the membrane bilayer (Lodish et al., 2007). Prediction analysis through bioinformatics tools towards proteins localisation and its antigenicity in bacteria is crucial in order to comprehend their structure and function particularly in the disease development by the pathogen.

The specific objectives of this study are:

1. to differentiate between *Pasteurella multocida* B:2 and its derivative by using conventional PCR analysis.
2. to characterise the differentiation in genotypic and proteomic profiles between *Pasteurella multocida* B:2 and its derivatives.
3. to identify putative antigenic outer membrane proteins (OMPs) from the wild-type *Pasteurella multocida* B:2.

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