UNIVERSITI PUTRA MALAYSIA

DEVELOPMENT OF Macrobrachium rosenbergii NODAVIRUS VIRUS-LIKE PARTICLES-BASED JAPANESE ENCEPHALITIS VIRUS AND SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS-2 VACCINES

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By

KIVEN KUMAR A/L KARUNANITHI

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

July 2022

DEDICATION

This thesis is dedicated to all virologists, immunologists and frontlines in the world who have been working on vaccine development during COVID-19 pandemic.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

DEVELOPMENT OF *Macrobrachium rosenbergii* NODAVIRUS VIRUS-LIKE PARTICLES-BASED JAPANESE ENCEPHALITIS VIRUS AND SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS-2 VACCINES

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July 2022

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Macrobrachium rosenbergii nodavirus (*Mr*NV) is an etiological agent responsible for white tail disease (WTD) in giant river prawn. The capsid protein (CP) of *Mr*NV can be recombinantly generated in *Escherichia coli* (*E. coli*) and is capable to self-assemble to form non-infectious virus-like particles (VLPs). The *Mr*NV-CP comprises 371 amino acid residues which is divided into two major domains; shell (S) and the protruding (P) domains. These *Mr*NV-CP VLPs have been manipulated to function as nano-carriers for various molecules such as RNA, DNA, therapeutic drugs and vaccine development. In this study, the objectives are *Mr*NV-CP were manipulated to function as a platform for the development of VLP-based Japanese encephalitis (JE) and Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) vaccines. Japanese encephalitis virus (JEV) is a vector-borne zoonotic virus that causes encephalitis in humans and domestic animals. Annually, it is estimated ~68,000 JE clinical cases globally, with a fatality rate of 20–30%. At present, there is no antiviral treatment for JE and vaccination is the most efficient method. Thus, continuing development of JE vaccines with higher safety profiles and better protective efficacy. Therefore, an immunodominant region of JEV, the Domain III (DIII) of JEV was fused to the carboxyl-terminus of *Mr*NV-CP. *Mr*NV-CP$^{JEV-DIII}$ was produced in *E. coli* and purified using immobilised metal affinity chromatography (IMAC). The *Mr*NV-CP$^{JEV-DIII}$ assembled into VLPs with diameters ~18 nm. *Mr*NV-CP$^{JEV-DIII}$ with or without alum was used to immunise the BALB/c mice have been shown to produce anti-JEV-DIII antibody, with titres significantly higher than the mice immunised with IMOJEV. Immunophenotyping showed that the *Mr*NV-CP$^{JEV-DIII}$ supplemented with alum triggered the proliferation of cytotoxic T-lymphocytes (CD8+CD4+), macrophages, and natural killer (NK) cells. Furthermore, cytokine profile analysis (IL-6, IL-10, IL-12p70, IFN-γ, and TNF-α) revealed that the activation of cytotoxic T-lymphocytes, macrophages, and NK cells. On the other hand, the coronavirus disease 2019 (COVID-19) caused by a new coronavirus

known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has started in late 2019. As a result, various vaccines have been developed and approved for emergency use across the world. However, emergence of new SARS-CoV-2 variants across the world, the efficacy of the initial vaccines designed based on the ancestral strain of SARS-CoV-2 has become a point of contention. The immunodominant region, receptor binding domain (RBD) of the spike protein of SARS-CoV-2 is considered the primary target for drug and vaccine development. To target the new variants of concern (VOCs), the RBDs of Beta (β) or Delta (δ) variants were fused to the C-terminal truncated (P-domain removed) *Mr*NV-CP. The chimeric proteins, CΔ116-*Mr*NV-CP$^{\beta\text{-SARS-CoV-2-RBD}}$ and CΔ116-*Mr*NV-CP$^{\delta\text{-SARS-CoV-2-RBD}}$ were expressed in *E. coli* and purified using cation exchange chromatography. The recombinant proteins CΔ116-*Mr*NV-CP$^{\beta\text{-SARS-CoV-2-RBD}}$ and CΔ116-*Mr*NV-CP$^{\delta\text{-SARS-CoV-2-RBD}}$ assembled into VLPs with diameters of ~18 nm. The BALB/c mice immunised with a mixture of VLPs (CΔ116-*Mr*NV-CP$^{\beta\text{-SARS-CoV-2-RBD}}$ and CΔ116-*Mr*NV-CP$^{\delta\text{-SARS-CoV-2-RBD}}$) in the presence of AddaVax (adjuvant) elicited a significantly higher humoral response (P<0.001) than other immunised groups. Furthermore, immunophenotyping showed that a mixture of VLPs with adjuvant increased T helper cells (Th) with a CD8+/CD4+ ratio of 0.42. The mice immunised with the mixture of VLPs in the presence of adjuvant have been shown to induce production of macrophages (24.4%). Furthermore, cytokine profile analysis (IL-5, IL-6, IL-12p70, IFN-γ and TNFα) of the mice immunised with the mixture of VLPs with adjuvant revealed the activities of macrophages and lymphocytes. In summary, the immunogenicity of the *Mr*NV-CP$^{\text{JEV-DIII}}$, CΔ116-*Mr*NV-CP$^{\beta\text{-SARS-CoV-2-RBD}}$ and CΔ116-*Mr*NV-CP$^{\delta\text{-SARS-CoV-2-RBD}}$ was successfully determined, and it displays the potential of these VLPs to be developed as JEV and SAR-CoV-2 vaccine candidates due to their ability to elicit specific antibodies towards DIII and RBD.

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

PEMBANGUNAN VAKSIN VIRUS ENSEFALITIS JEPUN DAN KORONAVIRUS SINDROM PERNAFASAN AKUT TERUK 2 BERDASARKAN *Macrobrachium rosenbergii* NODAVIRUS PARTIKEL MENYERUPAI VIRUS

Oleh

KIVEN KUMAR A/L KARUNANITHI

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Nodavirus *Macrobrachium rosenbergii* (*Mr*NV) ialah virus yang menyebabkan penyakit ekor putih (WTD) di kalangan udang galah. Protein kapsid (CP) *Mr*NV (*Mr*NV-CP) dihasilkan sebagai protein rekombinan dalam *Escherichia coli* (*E. coli*) bercantum sendiri untuk membentuk partikel menyerupai virus (VLPs) yang tidak berjangkit. *Mr*NV-CP terdiri daripada 371 asid amino yang dibahagikan kepada dua domain utama; cangkerang (S) dan domain terkeluar (P). VLPs *Mr*NV-CP telah dimanipulasi untuk berfungsi sebagai pembawa nano untuk pelbagai molekul seperti RNA, DNA, ubat terapeutik dan pembangunan vaksin. Dalam kajian ini, objektifnya ialah *Mr*NV-CP telah dimanipulasikan untuk berfungsi sebagai platform untuk pembangunan vaksin virus ensefalitis Jepun berasaskan VLP dan vaksin virus Koronavirus-2 sindrom pernafasan akut yang teruk (SARS-CoV-2). Virus ensefalitis Jepun (JEV) ialah virus zoonotik bawaan vektor yang menyebabkan ensefalitis pada manusia dan haiwan peliharaan. JEV telah dilaporkan hampir di semua negara di Asia dan Oceania. Setiap tahun, dijangka 68,000 kes klinikal JE di seluruh dunia dengan kadar kematian 20–30% dengan 30–50% mangsa JE. Pada masa ini, tiada rawatan antivirus untuk merawat JEV dan Vaksinasi adalah kaedah pencegahan. Oleh itu, pembangunan vaksin JE yang berterusan dengan profil keselamatan yang lebih tinggi dan keberkesanan perlindungan yang lebih baik adalah diperlukan dengan segera. Oleh itu, bahagian imunodominan JEV, protein Domain III (DIII) telah digabungkan dengan terminal karboksil *Mr*NV-CP. Protein rekombinan ini *Mr*NV-CP$^{JEV-DIII}$ telah dihasilkan dalam *E. coli* dan ditulenkan dengan menggunakan kromatografi afiniti penyekatan logam (IMAC). Protein rekombinan ini bercantum sendiri kepada VLPs berdiameter lebih kurang 18 nm. Tikus BALB/c yang diimunisasi dengan VLP sahaja atau dengan alum mendorong tindak balas pengeluaran antibodi anti-JEV-DIII, dengan titer jauh lebih tinggi daripada tikus yang diimunisasi dengan IMOJEV. Imunofenotaip

menunjukkan bahawa *Mr*NV-CP$^{JEV-DIII}$ ditambah dengan tawas mencetuskan penghasilan sel T-limfosit (CD8+CD4+), makrofaj dan sel pembunuh semulajadi (NK). Tambahan pula, analisis profil sitokin tikus yang diimunisasi (IL-6, IL-10, IL-12p70, IFN-γ dan TNF-α) mendedahkan pengaktifan limfosit T sitotoksik, makrofaj, dan sel pembunuh semula jadi. Sementara itu, pandemik penyakit koronavirus 2019 (COVID-19) yang bermula pada akhir 2019 oleh koronavirus baharu menyebabkan Sindrom pernafasan akut yang teruk koronavirus 2 (SARS-CoV-2). Oleh itu, pelbagai vaksin telah dibangunkan dan diluluskan untuk kegunaan kecemasan di seluruh dunia. Kemunculan varian SARS-CoV-2 baharu yang secara meluas, mempersoalkan sama ada vaksinasi awal berdasarkan strain leluhur SARS-CoV-2 berkesan terhadap varian baru telah menjadi titik pertikaian. Bahagian imunodominan, domain pengikatan penerima (RBD) protein spike dianggap sebagai sasaran utama untuk pembangunan ubat dan vaksin terhadap SARS-CoV-2. Untuk menangani perkara ini, domain P (166 asid amino) *Mr*NV-CP telah dipotong untuk dan digabungkan RBD Beta (β) atau Delta (δ). Protein rekombinan, CΔ116-*Mr*NV-CP$^{\beta\text{-SARS-CoV-2-RBD}}$ dan CΔ116-*Mr*NV-CP$^{\delta\text{-SARS-CoV-2-RBD}}$ telah dihasilkan dalam *E. coli* dan ditulenkan menggunakan kromatografi pertukaran kation. Protein rekombinan, CΔ116-*Mr*NV-CP$^{\beta\text{-SARS-CoV-2-RBD}}$, dan CΔ116-*Mr*NV-CP$^{\delta\text{-SARS-CoV-2-RBD}}$ berdiameter ~18 nm. Tikus BALB/c yang diimunisasi dengan campuran VLP (CΔ116-*Mr*NV-CP$^{\beta\text{-SARS-CoV-2-RBD}}$ dan CΔ116-*Mr*NV-CP$^{\delta\text{-SARS-CoV-2-RBD}}$) dengan AddaVax (adjuvan) menimbulkan peningkatan yang ketara, tindak balas humoral (P<0.001) daripada kumpulan imunisasi lain. Tambahan pula, imunofenotaip menunjukkan bahawa campuran VLP dengan adjuvan meningkatkan sel pembantu T (Th) dengan nisbah 0.42 (CD8+/CD4+). Pada masa yang sama, tikus yang diimunisasi dengan campuran VLP dengan adjuvan juga dapat mendorong makrofaj (24.4%). Tambahan pula, analisis profil sitokin (IL-5, IL-6, IL-12p70, IFN-γ dan TNFα) tikus yang diimunisasi dengan campuran VLP dengan adjuvant mendedahkan aktiviti makrofaj dan limfosit. Secara keseluruhannya, imunisasi dengan *Mr*NV-CP$^{JEV-DIII}$ dan campuran VLP dengan adjuvant meningkatkan T helper jenis 1 (Th1) yang lebih tinggi berbanding tindak balas Th2 pada tikus. Kesimpulannya, imunogenik *Mr*NV-CP$^{JEV-DIII}$, CΔ116-*Mr*NV-CP$^{\beta\text{-SARS-CoV-2-RBD}}$ dan CΔ116-*Mr*NV-CP$^{\delta\text{-SARS-CoV-2-RBD}}$ telah berjaya ditentukan, dan ia memaparkan potensi VLP ini untuk dibangunkan sebagai calon vaksin JEV dan SARS-CoV-2 kerana keupayaan mereka untuk mendapatkan antibodi khusus terhadap DIII dan RBD.

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Declaration by Members of Supervisory Committee

This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

ACE2	Angiotensin converting enzyme 2
APC	Allophycocyanin
APCs	Antigen-presenting cells
APS	Ammonium persulphate
BBB	Blood-brain barrier
BSA	Bovine serum albumin
C	Capsid
CD3	Clusters of differentiation 3
CD4	Clusters of differentiation 4
CD8	Clusters of differentiation 8
CLT	Cytotoxic T cell
CP	Capsid Protein
Cryo-EM	Cryo-electron microscopy
CSF	Cerebrospinal fluid
C-terminus	Carboxy terminus
CTL	Cytotoxic T cell lymphocytes
DAMPs	Damage-associated molecular patterns
DC	Dendritic cells
DIII	Domain III
DLS	Dynamic light scattering
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
dNTP	Deoxyribonucleotide phosphate

E	Envelope
E. coli	*Escherichia coli*
ELISA	Enzyme-Linked Immunosorbent Assay
FITS	Fluorescein isothiocyanate
G	Glycine
g	Gravity
H	Hour
HBV	Hepatitis B virus
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid)
HPV	Human papillomavirus
HR	Heptad-repeat
IEC	Ion-exchange chromatography
IF	Interferon
IFP	Internal fusion peptide
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
IMAC	Immobilized Metal Affinity Chromatography
IPTG	Isopropyl β- d-1-thiogalactopyranoside
JEV	Japanese encephalitis virus
kb	kilobase
kDa	kilo Dalton
L	Litre
LB	Luria Bertani

M	Membrane
M2e	Extracellular domain of M2
mA	milli Ampere
mAbs	Monoclonal antibodies
mg	milligram
min	minute
mL	millilitre
*Mr*NV	*Macrobrachium rosenbergii* Nodavirus
N	Nucleoprotein
NCRs	Non-coding regions
NK cells	Natural Killer Cells
nm	Nanometer
NS	Non-structures
NTD	N-terminal domain
N-terminus	Amino terminus
OD	Optical density
ORF	Open Reading Frame
PAGE	Polyacrylamide gel electrophoresis
PBS	Phosphate-buffered saline
PDB	Protein data bank
P-domain	Protruding domain
PE	Phycoerythrin
preM	pre-Membrane
PRRs	Pattern recognition receptors

RBD	Receptor binding domain
RBM	Receptor-binding motifs
RdRp	RNA-Dependent RNA Polymerase
RNA	Ribonucleic acid
Rpm	Rotation per minute
s	Second
S	Spike
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
S-domain	Shell domain
SDS	Sodium dodecyl sulfate
SP	Signal peptide
STEM	Scanning transmission electron microscope
T	Triangulation number
TAE	Tris-acetate-EDTA
TBS	Tris-Buffered Saline
TEM	Transmission Electron Microscope
TEMED	Tetramethylethylenediamine
Th	T-helper
TM	Transmembrane
TNF-α	tumor necrosis factor alpha
UK	United Kingdom
USA	United States America
v/v	Volume over volume
VLPs	Virus-like Particles

w/v	Weight over volume
WHO	World Health Organization
WTD	White tail disease
Wu	Wuhan
×	times
β	Beta
δ	Delta
°C	Degree Celsius
µL	microliter

CHAPTER 1

INTRODUCTION

Macrobrachium rosenbergii Nodavirus (*Mr*NV) is an aquatic virus that infects giant freshwater prawns (*Macrobrachium rosenbergii*) at their post-larvae stage and causes white-tail disease (WTD) or white muscle disease (WMD). *Mr*NV infections often result in 100% mortality and cause huge losses to the prawn industry. *Mr*NV belongs to the family of *Nodaviridae*, in which, the capsid of the virions is non-enveloped and exhibited as $T = 3$ icosahedral symmetry. The diameter of the virus is around 27 to 30 nm (Sahul Hameed et al., 2004; Goh et al., 2011).

The genome of *Mr*NV is a positive-sense single-stranded (+ssRNA) bipartite RNA, consisting of RNA-1 (3.1 kb) and RNA-2 (1.2 kb). The larger RNA molecule encodes the RNA-dependent RNA polymerase (RdRp) and B2 protein, while its smaller counterpart encodes the viral capsid protein (CP) (Goh et al., 2011; Hanapi et al., 2017). *Mr*NV-CP is a polypeptide consists of 371 amino acid residues and is divided into two major domains known as the shell (S) and the protruding (P) domains, consisting of 255 and 116 amino acid residues, respectively (Ho et al., 2017). *Mr*NV-CP can be produced in *Escherichia coli* (*E. coli*) or *Spodoptera frugiperda* (*Sf*9) insect cells and self-assembles into virus-like particles (VLPs), mimicking the native *Mr*NV isolated from infected prawns (Goh et al., 2011; Kueh et al., 2017).

*Mr*NV-CP VLPs were used as a platform to display epitopes from different viruses for the development of vaccines. For example, the hepatitis B virus's antigenic 'a' determinant and influenza A virus's ectodomain of matrix 2 (M2e) protein were fused to the C-terminal region of *Mr*NV-CP for the development of vaccines (Yong et al., 2015a; Yong et al., 2015b). Immunogenicity studies of these recombinant proteins suggest that VLPs derived from *Mr*NV-CP are excellent platforms to display foreign epitopes. Mice immunised with *Mr*NV-CP displaying three copies of matrix 2 ectodomain of Influenza A virus demonstrated low titres of H1N1 and H3N2 virus in the mouse respiratory tract (Ong et al., 2019). Moreover, the *Mr*NV-CP VLPs have been reported to withstand the harsh environment containing digestive enzymes and active compounds (Jariyapong et al., 2014).

JEV is a vector-borne zoonotic virus responsible for encephalitis in humans and horses. JEV was detected in most Asian and Oceania countries like China, Japan, Taiwan, South Korea, Vietnam, Thailand, India, Sri Lanka, Cambodia, Indonesia, Philippines, Australia, and Malaysia (Kumar et al., 2018a; Kumar et al., 2019). Recently, JEV has also been detected in Africa and European countries (Platonov et al., 2012; Ravanini et al., 2012; Simon-Loriere et al.,

2017). JEV is a member of the *Flaviviridae* family with other medically important viruses such as dengue virus (DENV), yellow fever virus (YFV), Zika virus (ZIKV), West Nile virus (WNV) and tick-borne encephalitis virus (TBEV).

The life cycle of JEV involves aquatic wading birds which have been identified as reservoirs, while the viral amplifying hosts are pigs and bats, and the dead-end hosts are humans and equids (Kumar et al., 2018a). JEV infects humans via bites of the mosquito, *Culex tritaeniorhynchus*. JEV infected individuals manifest various early clinical symptoms, including febrile illness and headache, while more severe conditions include poliomyelitis-like flaccid paralysis at a later stage (Ghosh and Basu, 2009). Cases of severe encephalitis are associated with a higher frequency of seizure, and most JE-related fatal cases experience acute coma (Solomon, 2004a). The fatality rate of JEV infection is between 20–30%, of which 30–50% of the survivors have been reported to suffer from permanent neuropsychiatric sequelae (Solomon et al., 2002; Campbell et al., 2011). Several studies demonstrated that JEV could infect all age groups, but a higher mortality rate (more than 30%) was reported among children. Approximately 3 billion people who live in JEV endemic countries are at risk of JE infection (Liu et al., 2020).

JEV is an RNA virus with ~10 kb of open reading frame (ORF), which encodes three structural proteins [envelope (E), capsid (C) and precursor membrane (prM)] and seven non-structural (NS) proteins designated as NS1, NS2A/B, NS3, NS4A/B and NS5 (Sumiyoshi et al., 1987). The E protein comprises of three major domains, known as Domains I (DI), II (DII) and III (DIII). The DIII of the JEV E protein (JEV-DIII) plays a vital role in antibody recognition. Numerous neutralising epitopes identified in JEV-DIII could induce a protective neutralising-antibody response in hosts (Lin and Wu, 2003).

To date, an antiviral drug against JEV infection remains unavailable. Therefore, vaccination represents the most effective approach to prevent JEV infection and disease control. The most widely used commercial JEV vaccines are the live-attenuated and chimeric-live vaccines (ChimeriVax-JE) (Chen et al., 2015). However, some significant drawbacks of these vaccines have been reported, particularly the risk of conversion to virulence strains in the live-attenuated vaccine. Monath et al. (2002a) reported that a single mutation in the E protein (Met279Lys) increases neurovirulence of the vaccine virus in monkeys and mice. Therefore, infectious-based vaccines should be reconsidered for continuous use. A new approach or platform for JEV vaccine development is thus required to enhance the safety and effectiveness of the vaccines.

In December 2019, an unknown pathogen that causes acute respiratory tract infection was reported in Wuhan City, Hubei Province, China. This unknown pathogen has been identified to cause pneumonia in humans. The Chinese government believed that the pathogen originated from a seafood market (Guo

et al., 2020). Scientists successfully isolated the pathogen from human bronchoalveolar lavage fluid and sequenced the respective viral genome (Wu et al., 2021a). The result showed that the virus shares 70 and 96.3% similarities with severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1) and Yunnan bat coronavirus RaTG13, respectively (Singhal et al., 2020). Initially, the virus was named as novel coronavirus (2019-nCoV) but was later renamed Severe Acute Respiratory Syndrome Coronavirus Type-2 (SARS-CoV-2). The virus spread rapidly to Europe, America, Australia and Asia. In mid of March 2020, the World Health Organization (WHO) announced the global infection as the coronavirus disease 2019 (COVID-19) pandemic. As of March 23rd, 2022, there are 474,043,960 positive COVID-19 cases with 6,121,563, reported fatalities (Covid-19 Coronavirus Pandemic, 2022).

Detailed genomic analysis of SARS-CoV-2 has classified the virus under the same subgenus as SARS-CoV-1 and the Middle East respiratory syndrome coronavirus (MERS-CoV), which were responsible for the SARS and MERS epidemics with mortality of approximately 10% and 35%, respectively (He et al., 2021). SARS-CoV-2 comprises of six open reading frames (ORFs) assembled in the order from 5′ to 3′ with replicas (ORF1a/ORF1b), spike (S), envelope (E), membrane (M) and nucleocapsid (N). The receptor-binding domain (RBD) of the S protein plays a significant role in host cell interaction and entry. The RBD is thus a main target for drug and vaccine development (Zakhartchouk et al., 2007; Zhang et al., 2009; Zhou et al., 2020; Hoffmann et al., 2020; Ou et al., 2020).

Several studies were conducted to define strategies in reducing viral transmission, to allow businesses and social life activities to resume (Anderson et al., 2020). Immunisation of the world's population is one of the strategies that can stimulate a rapid immune response and provide protection against SARS-CoV-2. Various vaccines based on the spike protein of SARS-CoV-2 have been developed for emergency use (Speiser et al., 2020). These vaccines were developed based on i) viral vectors (Oxford/AstraZeneca, Gamaleya Sputnik V, Johnson & Johnson), ii) mRNA vaccines (Moderna, CureVac, Pfizer-BioNTech) and iii) inactivated virus (Sinovac). However, several obstacles were reported for their rapid and efficient use.

The mRNA-based vaccines are temperature sensitive and must be stored and transported in cryo-temperatures. Cold-chain preparation is a substantial financial burden to many developing countries in Africa and Asia. The Oxford team created ChAdOX1-nCoV, a viral-vector based vaccine using the chimpanzee adenovirus (ChAd) as a vector to deliver the gene encodes the SARS-CoV-2 spike protein (van Doremalen et al., 2020). ChAdOX1-nCoV revealed a safe profile for human use in a phase 1/2 single-blind and immunogenicity was assessed in a single-blind, randomised placebo-controlled phase 2/3 clinical trial investigation (Folegatti, et al., 2020). However, several nations halted immunisation campaigns in mid-March 2021 after warnings that the vaccine might cause deadly blood clots in certain people. As SARS-CoV-2

may be in the population for years or decades to come, it would be ideal for a vaccine to be safe for multiple administrations (Zha et al., 2021).

Currently, SARS-CoV-2 is adapting to their new hosts while undergoing genetic mutations. These constant mutations lead to the emergence of new variants with altered characteristics, which are different from the ancestral strains. To date, WHO has announced several variants of concern (VOCs) including Alpha (α), Beta (β), Gamma (γ), Delta (δ) and Omicron (ο). It is important to note that the current batches of vaccines were designed based on ancestral strains and have demonstrated weaker antibody binding towards the newer variants (Wang et al., 2021a; Muik et al., 2021; Wang et al., 2021b). To produce SARS-CoV-2 vaccines that are capable to target the "seasonal" circulating variants, a robust vaccine development platform is desired to enable rapid reformulation or redesign based the circulating variants. One of the possible platforms is VLPs, which can be produced with lower production cost, rapid, and safe.

VLPs are non-infectious particles which mimic viruses in their native forms. VLPs can be produced using expression systems such as bacteria, mammalians, insects, yeast, and plants. VLPs can be manipulated to become carriers for the delivery of nanomaterials like vaccines, quantum dots and bacteriophages (Wan et al., 2001; Kok et al., 2002; Petry et al., 2003; Tan et al., 2005; Plummer et al., 2011; Lee et al., 2012; Hashemi et al., 2012; Mohsen et al., 2020).

VLPs can be genetically engineered to carry or display foreign epitopes of other viruses on their surface. Fusion protein expressed on the surface of VLPs could elicit high levels of antibodies in animal and human studies (Bachmann et al., 2011; Nooraei et al., 2021). Most VLPs-based vaccines trigger T cells and specific B cells (Zeltins, 2013). Furthermore, an antigen displayed on VLPs can induce a high level of antigen-specific antibodies compared to vector-based vaccines such as adeno- or adeno-associated viruses. This is because VLPs do not infect cells for antigen expression. VLPs can also mimic authentic virus structures to induce a robust immune response targeting the native virus. As the small antigenic epitopes of viruses are less immunogenic due to weak accessibility to the immune cells, the immunogenicity can be enhanced by displaying multiple copies of the epitope on the surface of VLPs. Additionally, VLPs also facilitate the uptake of the antigen by antigen-presenting cells (APCs) (Murata et al., 2003; Quan et al., 2008).

In this study, the DIII of JEV envelope protein was fused to the C-terminus of the full-length *Mr*NV-CP VLPs and expressed in *E. coli*. Deleting the P-domain from the C-terminus of *Mr*NV-CP VLP creates more space to display multiple copies of or large epitopes. In this study, the RBD from β and δ variants of SARS-CoV-2 were displayed on the CΔ116-*Mr*NV-CP VLPs, a truncated *Mr*NV-CP without the P-domain consisting of 116 amino acid residues.

This study hypothesised that the fusion of DIII from JEV E protein to the C-terminus of the full-length *Mr*NV-CP could assemble into VLPs and elicit humoral and cellular immune responses in BALB/c mice. This study also hypothesised that deletion of 116 amino acids from the C-terminus of full-length *Mr*NV-CP and fusion of β and δ RBDs of the SARS-CoV-2 could assemble into VLPs and elicit humoral and cellular immune responses in BALB/c mice.

Therefore, the general objective of this study was to evaluate the capability of *Mr*NV-CP to function as a novel platform for the development of VLP-based JEV and SARS-CoV-2 vaccines. The specific objectives of this study are:

1. To construct recombinant protein *Mr*NV-CP$^{JEV\text{-}DIII}$ by fusing the JEV-DIII to the C-terminus of the full-length *Mr*NV-CP.
2. To express, purify and characterise *Mr*NV-CP$^{JEV\text{-}DIII}$.
3. To determine the immunogenicity of *Mr*NV-CP$^{JEV\ DIII}$ in BALB/c mice.
4. To construct recombinant proteins of P-domain truncated *Mr*NV-CP fused with the RBD of β- and δ-SARS-CoV-2.
5. To express, purify and characterise the recombinant proteins of P-domain truncated *Mr*NV-CP fused with the RBD of β- and δ-SARS-CoV-2.
6. To determine the immunogenicity of the recombinant proteins of P-domain truncated *Mr*NV-CP fused with the RBD of β- and δ-SARS-CoV-2.

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