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VIRUS-LIKE PARTICLES OF *Macrobrachium rosenbergii* DE MAN NODAVIRUS FOR DISCOVERY OF ANTI-VIRUS PEPTIDES AND DELIVERY OF A CANCER DRUG

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By

THONG QIU XIAN

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

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Chair : Professor Tan Wen Siang, PhD
Faculty : Biotechnology and Biomolecular Sciences

Macrobrachium rosenbergii nodavirus (MrNv) is the causative agent of white tail disease (WTD) in the giant freshwater prawn. The recombinant capsid protein can be expressed in *Escherichia coli*, and it self-assembles into virus-like particles (MrNVLP). Currently, there is no treatment for WTD and there is no thermally-responsive VLP for drug delivery. The main aims of this study were to characterise the MrNVLP, and applied the VLP for the screening of antivirus agents, as well as delivery and thermally-controlled release of a cancer drug. MrNVLP was compared with the native MrNv that was purified from naturally virus-infected post larvae of *M. rosenbergii*. Western blotting demonstrated that both virus particles were detectable using the rabbit anti-MrNv capsid protein serum. Transmission electron microscopy showed that MrNVLP was spherical in shape similar to that of native MrNv. Dynamic light scattering (DLS) showed the size of MrNVLP was stable for approximately 4 weeks, and MrNVLP was non-cytotoxic as determined using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, indicating the potential of MrNVLP for *in vitro* applications. The amount of RNA in MrNVLP was reduced using the RNase treatment to study the changes of the particles. Interestingly, the size of MrNVLP was inversely related with the amount of RNA packaged. Since MrNVLP was structurally similar with the capsid of native MrNv, MrNVLP was used as a target to screen for anti-MrNv agents in order to control WTD. Two dominant phages harbouring the amino acid sequences HTKQIPRHIYSA and VSRHQSWHPHDL were selected and they bound strongly to MrNVLP. Chemically synthesised peptides HTKQIPRHIYSA and VSRHQSWHPHDL inhibited the internalisation of MrNVLP in *Spodoptera frugiperda* (Sf9) cells. The peptides also inhibited infection of native MrNv as shown by higher cell viability. Real-time reverse transcription-polymerase chain reaction (real-time RT-PCR) assay revealed that the highest MrNv inhibition was observed when both peptides were simultaneously applied. Owing to the nature of MrNVLP, which is non-infectious and non-cytotoxic, thus it has the potential to be developed as a nanocarrier in drug delivery. In this study, folic acid (FA) was covalently

conjugated to lysine residues located on the surface of MrNVLP, while doxorubicin (Dox) was loaded inside the VLP using an infusion method. This nanoparticle, namely FA-MrNVLP-Dox, released Dox in a sustained manner, and the rate of drug release increased in response to a hyperthermia temperature at 43 °C. The FA-MrNVLP-Dox enhanced the delivery of Dox to HT29 cancer cells, which expressing higher level of folic acid receptor (FR) than CCD841CoN normal cells and HepG2 cancer cells. As a result, FA-MrNVLP-Dox increased the cytotoxicity of Dox on HT29 cells but demonstrated lower drug's cytotoxicity on CCD841CoN and HepG2 cells. In conclusion, MrNVLP is molecularly and morphologically similar compared to the capsid of native MrNv. Two peptide inhibitors that blocked MrNv infection *in vitro* were identified. In addition, MrNVLP was also shown to function as a thermally-responsive nanocarrier for delivery of Dox to colorectal cancer cells. This study demonstrated the potentials of MrNVLP in identification of WTD inhibitors, and targeted delivery of cancer drugs.

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

PARTIKEL MENYERUPAI VIRUS DARIPADA *Macrobrachium rosenbergii* DE MAN NODAVIRUS UNTUK PENEMUAN PEPTIDA ANTI-VIRUS DAN PENGHANTARAN UBAT KANSER

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Macrobrachium rosenbergii nodavirus (MrNv) merupakan agen penyebab penyakit ekor putih (WTD) dalam udang galah. Protein rekombinan kapsid MrNv boleh diekspres dalam *Escherichia coli*, dan menyusun secara automatik kepada partikel menyerupai virus (MrNVLP). Setakat kini, tidak ada rawatan untuk WTD dan tidak ada VLP termal-responsif untuk penghantaran ubat. Matlamat utama kajian ini adalah untuk mencirikan MrNVLP dan mengguna MrNVLP untuk penemuan agen antivirus serta penghantaran dan pembebasan ubat kanser yang dikawal terma. MrNVLP telah dibanding dengan MrNv asli yang telah ditulen daripada pasca larva *M. rosenbergii* yang terjangkit semulajadi. Pemblotan Western menunjukkan bahawa kedua-dua partikel virus tersebut dapat dikesan oleh serum arnab anti-protein kapsid MrNv. Mikroskop electron transmisi menunjukkan bahawa MrNVLP adalah berbentuk sfera dengan morfologinya menyerupai MrNv asli. Serakan cahaya dinamik (DLS) menandakan bahawa saiz MrNVLP adalah stabil selama lebih kurang 4 minggu, dan MrNVLP tidak mempunyai kesan sitotoksisiti seperti yang ditentukan oleh ujian 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromida (MTT), menandakan potensi MrNVLP untuk kegunaan *in vitro*. Bilangan RNA di dalam MrNVLP telah dikurangkan dengan rawatan *RNase* untuk mengkaji perubahan pada partikel tersebut. Menariknya, saiz MrNVLP berhubung songsang dengan bilangan RNA yang dibungkus. Memandangkan MrNVLP mempunyai struktur yang serupa dengan kapsid MrNv asli, MrNVLP telah dijadikan sasaran untuk menemu agen anti-MrNv supaya mengawal WTD. Dua faj utama dengan jujukan asid amino HTKQIPRHIYSA dan VSRHQSWHPHDL telah dipilih dan kedua-dua faj tersebut terikat dengan kuat kepada MrNVLP. Peptida HTKQIPRHIYSA dan VSRHQSWHPHDL yang disintesis secara kimia telah menyekat kemasukan MrNVLP ke dalam sel-sel *Spodoptera frugiperda* (Sf9). Peptida tersebut juga menyekat jangkitan MrNv asli seperti yang ditujukkan oleh kebolehhidupan sel yang lebih tinggi. Ujian tindak balas berantai polimerase transkripsi terbalik masa nyata (*real-time RT-PCR*) mendedahkan bahawa penyekatan paling tinggi tertunjuk apabila

kedua-dua peptida tersebut digunakan secara serentak. Disebabkan oleh sifat MrNVLP yang tidak berjangkit dan bukan sitotoksik, maka ia mempunyai potensi dikembangkan sebagai pembawa-nano untuk penghantaran ubat. Dalam kajian yang dilakukan, asid folik (FA) dikongjugasi secara kovalen kepada residu-residu lisin yang berada di permukaan luar MrNVLP, manakala doxorubicin (Dox) dimuatkan ke dalam VLP tersebut dengan kaedah infusi. Partikel nano ini, yang dikenali sabagai FA-MrNVLP-Dox, membebaskan Dox secara berkekalan, dan kadar pembebasan ubat tersebut meningkat sebagai maklum balas kepada suhu hipertermia pada 43 °C. FA-MrNVLP-Dox meningkat penghantaran Dox kepada sel kanser HT29 yang mengekspres reseptor asid folik (FR) pada tahap lebih tinggi berbanding dengan sel biasa CCD841CoN dan sel kanser HepG2. Hasilnya, FA-MrNVLP-Dox meningkatkan kesan sitotoksisiti Dox dalam sel-sel HT29, tetapi menunjukkan sitotoksisiti ubat yang lebih rendah dalam sel-sel CCD841CoN dan HepG2. Kesimpulannya, MrNVLP menpunyai ciri-ciri molekul dan morfologi yang menyerupai kapsid MrNv asli. Dua peptida yang dapat menyekat jangkitan MrNv *in vitro* telah ditemui. Selain itu, MrNVLP juga ditunjuk berfungsi sebagai penghantar-nano yang terma-responsif untuk menghantar Dox ke sel-sel kanser kolon. Kajian ini menunjukkan potensi MrNVLP dalam penemuan penyekat WTD, dan penghantaran ubat kanser yang disasarkan.

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Å	Angstrom
%	Percentage
K_D^{rel}	Relative dissociation constant
× g	times gravity
°C	degree Celsius
µg	microgram
µL	microliter
µm	micrometer
3-OS HS	3-O-sulfated heparan sulphate
A	absorbance
AIV	avian influenza virus
ANDV	Andes virus
APS	ammonium persulphate
ASK	Atlantic salmon kidney
ATCC	American Type Culture Collection
bp	base pair
BSA	bovine serum albumin
CsCl	Caesium chloride
$CaCl_2$	Calcium chloride
CBB	Coomassie Brilliant Blue
cDNA	complementary deoxyribonucleic acid
CE	conjugation efficiency
CMV	cytomegalovirus
CSFV	classical swine fever virus
C-terminal	carboxy-terminal
Da	Dalton
DENV	dengue virus
DMEM	Dulbecco's Modified Eagle Medium
dH_2O	distilled water
DLS	dynamic light scattering
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DNase	deoxyribonuclease
Dox	doxorubicin
DTT	dithiothreitol
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
EDTA	Ethylenediaminetetraacetic acid
EE	entrapment efficiency
EGTA	egtazic acid
ELISA	enzyme-linked immunosorbent assay
EMEM	Eagle's Minimal Essential Medium
EPR	enhanced permeability and retention
FA	folic acid
FA-MrNVLP	folic acid-conjugated virus-like particles of *Macrobrachium rosenbergii* nodavirus
FA-MrNVLP-Dox	virus-like particles of *Macrobrachium rosenbergii* nodavirus conjugated with folic acid and loaded with doxorubicin

FBS	foetal bovine serum
FITC	fluorescein isothiocyanate
FR	folic acid receptor / folate receptor
GCRV	grass carp hemorrhage virus
GFP	green fluorescent protein
GGNNV	greasy grouper nervous necrosis virus
GSH	glutathione
h	hour
HBcAg	hepatitis B virus core antigen
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HCl	hydrochloric acid
HCPS	Hantavirus cardiopulmonary syndrome
HCV	hepatitis C virus
HE	hemagglutinin-esterase
HHV	human herpesvirus
HS	heparan sulfate
HSV	herpes simplex virus
Hz	hertz
IC_{50}	Half maximal inhibitory concentration
IMAC	immobilised metal affinity chromatography
IMNV	infectious myonecrosis virus
IPTG	Isopropyl-β-thiogalactoside
ISA	infectious salmon anaemia
ISAV	infectious salmon anaemia virus
JEV	Japanese encephalitis virus
kb	kilobasepair
KCl	potassium hydrochloride
kDa	kiloDalton
KH_2PO_4	monopotassium phosphate
kPa	kilopascal
kV	kilovoltage
L	liter
LB	Luria Bertani
LC-MS	liquid chromatography-mass spectrometry
LE	loading efficiency
L-HBsAg	large-hepatitis B virus surface antigen
M	molarity
mA	milliampere
MEV	mink enteritis virus
mg	milligram
M-HBsAg	middle-hepatitis B virus surface antigen
min	minute
mL	millilitre
mM	millimolarity
M_r	molecular mass
mRNA	messenger RNA
MrNv	*Macrobrachium rosenbergii* nodavirus
MrNVLP	virus-like particles of *Macrobrachium rosenbergii* nodavirus

MrNVLP-Dox	virus-like particles of *Macrobrachium rosenbergii* nodavirus loaded with doxorubicin
MRT-PCR	multiplex reverse transcription-polymerase chain reaction
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
MW	molecular weight
Na_2HPO_4	disodium phosphate
NaCl	sodium chloride
NADH	Nicotinamide adenine dinucleotide hydrogenase
NAGE	native agarose gel electrophoresis
N_{Dox}	Dox per MrNVLP
NDV	Newcastle disease virus
N_{FA}	number of FA per MrNVLP
NIR	near-infrared
NLS	nuclear localisation signal
nm	nanometer
nM	nanomolarity
N-terminal	amino-terminal
OD	optical density
PAGE	polyacrylamide gel electrophoresis
PBS	phosphate buffer saline
PCR	polymerase chain reaction
P-domain	protruding-domain
PEG	polyethylene glycol
PET	positron emission tomography
pfu	plaque forming unit
PI	propidium iodide
pI	isoelectric point
PoP	prophyrin-phospholipid
ppm	part per million
PRRSV	porcine reproductive and respiratory syndrome virus
PstDNV	*Penaeus stylirostris* densovirus
RdRp	RNA-dependent RNA polymerase
R_h	hydrodynamic radius
RNA	ribonucleic acid
RNAi	RNA interference
RNase	ribonuclease
ROS	reactive oxygen species
rpm	revolution per minute
RT-LAMP	reverse transcription, loop-mediated isothermal amplification
RT-PCR	reverse transcription-polymerase chain reaction
s	second
SD	standard deviation
S-domain	shell-domain
SDS	sodium dodecyl sulphate
Sf9	*Spodoptera frugiperda* 9
S-HBsAg	small-hepatitis B virus surface antigen
ssRNA	single-stranded ribonucleic acid
sulfo-NHS	N-hydroxysulfo-succinimide
T	triangulation number
TAS-ELISA	triple antibody enzyme-linked immunosorbent assay

TBE	Tris-borate EDTA
TBS	Tris-buffer saline
TBSV	tomato bushy stunt virus
TE	Tris-EDTA
TEM	transmission electron microscope
TEMED	tetramethylethylenediamine
tHBcAg	truncated hepatitis B virus core antigen
TSV	Taura syndrome virus
UV	ultraviolet
V	voltage
Vis	visible
VLP	virus-like particle
w/v	weight over volume
w/w	weight over weight
WSSV	white spot syndrome virus
WTD	white tail disease
Xgal	5-bromo-4-chloro-3-indolyl-β-D-galactopyranoside
XSV	extra small virus
YHV	yellow head virus
α	alpha
γ	gamma

Amino acids

Ala, A	alanine
Arg, R	arginine
Asn, N	asparagine
Asp, D	aspartic acid
Cys, C	cysteine
Gln, Q	glutamine
Glu, E	glutamic acid
His, H	histidine
Ile, I	isoleucine
Leu, L	leucine
Lys, K	lysine
Met, M	methionine
Phe, F	phenylalanine
Pro, P	proline
Thr, T	threonine
Trp, W	tryptophan
Tyr, Y	tyrosine
Val, V	valin

CHAPTER 1

INTRODUCTION

Macrobrachium rosenbergii nodavirus (MrNv) infects the giant freshwater prawn and causes white tail disease (WTD) which could kill 100% post larvae of *M. rosenbergii*. Recently, the virus-like particle of MrNv (MrNVLP) was used as a model to solve the atomic structure of MrNv at 3.2 Å resolution (Ho *et al.*, 2018), indicating the possibility of using MrNVLP to investigate the native virion. In addition, MrNVLP has been applied for gene delivery (Jariyapong *et al.*, 2014; Jariyapong *et al.*, 2015a; Jariyapong *et al.*, 2015b) and vaccine development (Ong *et al.*, 2019; Yong *et al.*, 2015a; Yong *et al.*, 2015b), demonstrating the potential of MrNVLP in nanomedicine. It is imperative to characterise MrNVLP and to compare it with the native MrNv, in order to expedite the future application of MrNVLP as well as to facilitate the further investigation of native MrNv.

MrNv infection and WTD outbreaks were reported in many countries in Asia, North America and Australia (Low *et al.*, 2018). The disease causes shortage of seeds and economic loss in prawn industry. Currently, there is no treatment available for WTD, therefore anti-virus for the disease is urgently needed. Several peptide inhibitors against aquatic viruses have been isolated from phage-displayed peptide library (Rajik *et al.*, 2009; Zhang *et al.*, 2013; Chew *et al.*, 2015; Odeja *et al.*, 2016). Data from the characterisation of MrNVLP showed that the MrNVLP is molecular and morphologically similar to that of the native viral capsid. Since the entry of non-enveloped virus into the host cell is mediated by the interaction between the capsid protein and the host cellular receptor (Odegard *et al.*, 2010), it is hypothesised that MrNVLP can be utilised as a target for screening of anti-MrNv peptides from a phage-displayed peptide library.

MrNv poses insecurity in aquaculture. In contrast, MrNVLP, which are non-infectious as they cannot replicate, has the potential to deliver therapeutic molecules. In this study, MrNVLP was applied to deliver a cancer drug, doxorubicin (Dox) into cancer cells. Like any other first generation cancer drugs, Dox attacks not only cancer cells but also healthy cells. The major medical complication of Dox is cardiotoxicity which could be fatal (Renu *et al.*, 2018). Yildiz *et al.* (2013) infused Dox into Cowpea mosaic virus and the drug was retained in the virus cavity via electrostatic interaction with the viral genome (Yildiz *et al.*, 2013). For the case of MrNVLP, it was reported to package RNA from the *E. coli* host cells (Goh *et al*., 2011; Goh *et al*., 2014), and the RNA molecules assembled into a dodecahedral structure (Ho *et al*., 2017; Ho *et al*., 2018). Moreover, there are pores observed on the surface of MrNVLP (Ho *et al*., 2017; Ho *et al*., 2018). On the other hand, cancer cells generally over-express folate receptor (FR) (Ross *et al*., 1994). Since folic acid (FA) and folate conjugates have high binding affinity towards FR, FR-mediated endocytosis allows the uptake of folate-conjugated nanoparticles by cancer cells (Xu et al., 2017). Therefore, it is postulated that Dox can be infused into the pores of MrNVLP, and it would be retained in MrNVLP via electrostatic interaction with

the dodecahedral RNA. It is hypothesised that the FA-conjugated-and-Dox-loaded MrNVLP (FA-MrNVLP-Dox) would deliver Dox specifically to FR-rich cancer cells.

The general objectives of this study were to employ MrNVLP in screening of virus inhibitors, and anti-cancer drug delivery. The specific objectives were as follows:

1. To produce and characterise the MrNVLP by using the molecular techniques.
2. To isolate and characterise peptide inhibitors against the MrNVLP and native MrNv.
3. To conjugate FA on the surface of MrNVLP and to encapsidate Dox inside the MrNVLP for targeted delivery and controlled release of Dox to HT29 cells.

REFERENCES

Aghebati-Maleki, L., Bakhshinejad, B., Baradaran, B., Motallebnezhad, M., Aghebati-Maleki, A., Nickho, H., Yousefi, M., and Majidi, J. (2016). Phage display as a promising approach for vaccine development. *Journal of Biomedical Science* 23: 66.

Agudelo, D., Bourassa, P., Beauregard, M., Bérubé, G., and Tajmir-Riahi, H. A. (2013). tRNA binding to antitumor drug doxorubicin and its analogue. *PLoS One* 8: e69248.

Airoldi, M., Barone, G., Gennaro, G., Giuliani, A. M., and Giustini, M. (2014). Interaction of Doxorubicin with Polynucleotides. A Spectroscopic Study. *Biochemistry* 53: 2197-2207.

Arcier, J. M., Herman, F., Lightner, D. V., Redman, R. M., Mari, J., and Bonami, J. R. (1999). A viral disease associated with mortalities in hatchery-reared post larvae of the giant freshwater prawn *Macrobrachium rosenbergii*. *Diseases of Aquatic Organisms* 38: 177-181.

Ashley, N., and Poulton, J. (2009). Mitochondrial DNA is a direct target of anticancer anthracycline drugs. *Biochemical and Biophysical Research Communications 378*: 450-455.

Bates, D. O., Hillman, N. J., Williams, B., Neal, C. R., and Pocock, T. M. (2002). Regulation of microvascular permeability by vascular endothelial growth factors. *Journal of Anatomy* 200: 581-597.

Berkowitz, S. A., and Day, L. A. (1976). Mass, length, composition and structure of the filamentous bacterial virus fd. *Journal of Molecular Biology* 102: 531-547.

Bertrand, N., Wub, J., Xua, X., Kamaly, N., and Farokhzadb, O. C. (2014). Cancer nanotechnology: The impact of passive and active targeting in the era of modern cancer biology. *Advanced Drug Delivery Rev*iews 66: 2–25.

Biabanikhankahdani, R., Alitheen, N. B. M., Ho, K. L., and Tan, W. S. (2016). pH-responsive virus-like nanoparticles with enhanced tumour-targeting ligands for cancer drug delivery. *Scientific Reports* 6: 37891.

Biabanikhankahdani, R., Bayat, S., Ho, K. L., Alitheen, N. B. M., and Tan W. S. (2017). A simple add-and-display method for immobilisation of cancer drug on His-tagged virus-like nanoparticles for controlled drug delivery. *Scientific Reports* 7: 5303.

Biabanikhankahdani, R., Ho, K. L., Alitheen, N. B., and Tan W. S. (2018). A dual bioconjugated virus-like nanoparticle as a drug delivery system and comparison with a pH-responsive delivery system. *Nanomaterials* 8: 236.

Bonami, J. R., and Widada, J. S. (2011). Viral diseases of the giant fresh water prawns *Macrobrachium rosenbergii*: A review. *Journal of Invertebrate Pathology* 106: 131-142.

Bonami, J. R., Shi, Z., Qian, D., and Widada, J. S. (2005). White tail disease of the giant freshwater prawn, *Macrobrachium rosenbergii*: Separation of the associated virions and characterization of MrNV as a new type of nodavirus. *Journal of Fish Diseases* 28: 23-31.

Boss, S. D., Betzel, T., Müller, C., Fischer, C. R., Haller, S., Reber, J., Groehn, V., Schibli, R., Ametamey, S. M. (2016). Comparative studies of three pairs of α- and γ-conjugated folic acid derivatives labeled with fluorine-18. *Bioconjugate Chemistry* 27: 74-86.

Boveia, V., and Schutz-Geschwender, A. (2015). Quantitative analysis of signal transduction with In-Cell Western immunofluorescence assays. In: Kurien B. & Scofield R. (editors). *Detection of blotted proteins*. (pp. 115–130). New Jersey: Humana Press.

Bradford, M. M. (1976). A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. *Analytical Biochemistry* 72: 248-254.

Busayarat, N., Senapin, S., Tonganunt, M., Phiwsaiya, K., Meemetta, W., Unajak, S., Jitrapakdee, S., Lo, C., Phongdara, A. (2011). Shrimp laminin receptor binds with capsid proteins of two additional shrimp RNA viruses YHV and IMNV. *Fish & Shellfish Immunology* 31: 66-72.

Cadena-Nava, R. D., Comas-Garcia, M., Garmann, R. F., Rao, A. L. N., Knobler, C. M., and Gelbart, W. M. (2012). Self-assembly of viral capsid protein and RNA molecules of different sizes: Requirement for a specific high protein/RNA mass ratio. *Journal of Virology* 86: 3318-3326.

Cai, F., Luis, M. A. F., Lin, X., Wang, M., Cai, L., Cen, C., and Biskup, E. (2019). Anthracycline-induced cardiotoxicity in the chemotherapy treatment of breast cancer: Preventive strategies and treatment (Review). *Molecular and Clinical Oncology* 11: 15-23.

Carvalho, C., Santos, R. X., Cardoso, S., Correia, S., Oliveira, P. J., Santos, M. S., and Moreira, P. I. (2009). Doxorubicin: The Good, the Bad and the Ugly Effect. *Current Medicinal Chemistry*, 16: 3267-3285.

Centelles, M. N., Wright, M., So, P. W., Amrahli, M., Xu, X. Y., Stebbing, J., Miller, A. D., Gedroyc, W., and Thanou, M. (2018). Image-guided thermosensitive liposomes for focused ultrasound drug delivery: Using NIRF-labelled lipids and topotecan to visualise the effects of hyperthermia in tumours. *Journal of Controlled Release* 280: 87-98.

Chaires, J. B., Fox, K. R., Herrera, J. E., Britt, M., and Waring, M. J. (1987). Site and sequence specificity of the daunomycin-DNA interaction. *Biochemistry* 26: 8227-8236.

Chaires, J. B., Priebe, W., Graves, D. E., and Burke, T. G. (1993). Dissection of the free energy of anthracycline antibiotic binding to DNA: Electrostatic contributions. *Journal of the American Chemical Society* 115: 5360-5364.

Hume, H. K. C., Vidigal, J., Carrondo, M. J. T., Middelberg, A. P. J., Roldão, A., and Lua, L. H. L. (2019). Synthetic biology for bioengineering virus-like particle vaccines. *Biotechnology and Bioengineering* 116: 919-935.

Chen, N., Yoshimura, M., Miyazaki, N., Guan, H., Chuankhayan, P., Lin, C., Chen, S., Lin, P., Huang, Y., Iwasaki, K., Nakagawa, A., Chan, S. I., and Chun-Jung Chen, C. (2019). The atomic structures of shrimp nodaviruses reveal new dimeric spike structures and particle polymorphism. *Communications Biology* 2: 72.

Chen, Q., and Guo, Y. (2016). Influenza viral hemagglutinin peptide inhibits influenza viral entry by shielding the host receptor. *ACS infectious diseases* 2: 187-193.

Chew, M. F., Tham, H. W., Rajik, M., and Sharifah, S. H. (2015). Anti-dengue virus serotype 2 activity and mode of action of a novel peptide. *Journal of Applied Microbiology* 119: 1170-1180.

Chong, L. C., Ganesan, H., Yong, C. Y., Tan, W. S., and Ho, K. L. (2019). Expression, purification and characterization of the dimeric protruding domain of *Macrobrachium rosenbergii* nodavirus capsid protein expressed in *Escherichia coli*. *PLoS ONE* 14: e0211740.

Citarasu, T., Lelin, C., Babu, M. M., Anand, S. B., Nathan, A. A., and Vakharia, V. N. (2019). Oral vaccination of *Macrobrachium rosenbergii* with baculovirus-expressed *M. rosenbergii* nodavirus (MrNV) capsid protein induces protective immunity against MrNV challenge. *Fish & Shellfish Immunology* 86: 1123-1129.

Cortes, J., and Saura, C. (2010). Nanoparticle albumin-bound (*nab*™)-paclitaxel: Improving efficacy and tolerability by targeted drug delivery in metastatic breast cancer. *European Journal of Cancer Supplements* 8: 1-10.

Cwirla, S. E., Peters, E. A., Barrett, R. W., and Dower, W. J. (1990). Peptides on phage: A vast library of peptides for identifying ligands. *Biochemistry* 87: 6378-6382.

Damodar, G., Smitha, T., Gopinath, S., Vijayakumar, S., and Rao, Y. (2014). An evaluation of hepatotoxicity in breast cancer patients receiving injection Doxorubicin. *Annals of medical and health sciences research* 4: 74-79.

Datta, N. R., Ordóñez, S. G., Gaipl, U. S., Paulides, M. M., Crezee, H., Gellermann, J., Marder, D., Puric, E., and Bodis, S. (2015). Local hyperthermia combined with radiotherapy and-/or chemotherapy: Recent advances and promises for the future. *Cancer Treatment Reviews* 41: 742-753.

Deng, W., Chen, W., Clement, S., Guller, A., Zhao, Z., Engel, A., and Goldys, E. M. (2018). Controlled gene and drug release from a liposomal delivery platform triggered by X-ray radiation. *Nature Communications* 9: 2713.

Deryugina, E. I., and Quigley, J. P. (2006). Matrix metalloproteinases and tumor metastasis. *Cancer and Metastasis Reviews* 25: 9-34.

Devlin, J. J, Panganiban, L. C., and Devlin, P. E. (1990). Random peptide libraries: A source of specific protein binding molecules. *Science* 249: 404-406.

Donchenko, E. K., Pechnikova, E. V., Mishyna, M. Y., Manukhova, T. I., Sokolova, O. S., Nikitin, N. A., Atabekov, J. G., and Karpova, O. V. (2017). Structure and properties of virions and virus-like particles derived from the coat protein of Alternanthera mosaic virus. *PLoS One* 12: e0183824.

Doyle, M., Badertscher, L., Jaskiewicz, L., Guttinger, S., Jurado, S., Hugenschmidt, T., Kutay, U., and Filipowicz, W. (2013). The double-stranded RNA-binding domain of human Dicer functions as a nuclear localization signal. *RNA* 19: 1238-1252.

Dyson, M. R., and Murray, K. (1995). Selection of peptide inhibitors of interactions involved in complex protein assemblies: Association of the core and surface antigens of hepatitis B virus. *Proceedings of the National Academy of Sciences of the United States of America* 92: 2194-2198.

Dyson, M. R., Germaschewski, V., and Murray, K. (1995). Direct measurement via phage titre of the dissociation constant in solution of fusion phage-substrate complexes. *Nucleic Acids Research* 23: 1531-1535.

Eiján, M. A., Sandes, E. O., Riveros, M. D., Thompson, S., Pasik, L., Mallagrino, H., Celeste, F., and Casabé, A. R. (2003). High expression of cathepsin B in transitional bladder carcinoma correlates with tumor invasion. *Cancer* 98: 262-268.

Farook, M. A., Madan, N., Taju, G., Majeed, S. A., Nambi, K. S., Raj, N. S., Vimal, S., and Hameed, A. S. (2014a). Production of recombinant capsid protein of *Macrobrachium rosenbergii* nodavirus (r-MCP43) of giant freshwater prawn, *M. rosenbergii* (de Man) for immunological diagnostic methods. *Journal of Fish Diseases* 37: 703-710.

Farook, M. A., Raj, N. S., Madan, N., Vimal, S., Majeed, S. A., Taju, G., Rajkumar, T., Santhoshkumar, S., Sivakumar, S., and Hameed, A. S. S. (2014b). Immunomodulatory effect of recombinant *Macrobrachium rosenbergii* nodavirus capsid protein (r-MCP) against white tail disease of giant freshwater prawn, *Macrobrachium rosenbergii* (de Man, 1879). *Aquaculture* 433: 395-403.

Farook, M. A., Vimal, S., Madan, N., Taju, G., Majeed, S. A., Nambi, K. S. N., Balasubramanian, G., and Hameed, A. S. S. (2016). Immunomodulatory effect of *Cynodon dactylon* against white tail disease of giant freshwater prawn, *Macrobrachium rosenbergii* (de Man, 1879). *Aquaculture Research* 47: 3421-3431.

Fenner, B.J., Goh, W., and Kwang, J. (2006). Sequestration and protection of double-stranded RNA by the betanodavirus B2 protein. *Journal of Virology* 80: 6822-6833.

Gamcsik, M. P., Kasibhatla, M. S., Teeter, S. D., and Colvin, O. M. (2012). Glutathione levels in human tumors. *Biomarkers* 17: 671-691.

Gan, B. K., Yong, C. Y., Ho, K. L., Omar, A. R., Alitheen, N. B., and Tan, W. S. (2018). Targeted delivery of cell penetrating peptide virus-like nanoparticles to skin cancer cells. *Scientific Reports* 8: 8499.

Gasteiger, E., Hoogland, C., Gattiker, A., Duvaud, S., Wilkins, M. R., Appel, R. D., and Bairoch, A. (2005). Protein identification and analysis tools on the ExPASy server. In: Walker J. M. (editor). *The Proteomics Protocols Handbook.* (pp. 571-607). New Jersey: Humana Press.

Geisow, M. J., and Evans, W. H. (1984). pH in the endosome. Measurements during pinocytosis and receptor-mediated endocytosis. *Experimental Cell Research* 150: 36-46.

Gerweck, L. E., and Seetharaman, K. (1996). Cellular pH gradient in tumor versus normal tissue: Potential exploitation for the treatment of cancer. *Cancer Research* 56: 1194-1198.

Goh, Z. H., Mohd, N. A. S., Tan, S. G., Bhassu, S., and Tan, W. S. (2014). RNA binding region of *Macrobrachium rosenbergii* nodavirus capsid protein. *Journal of General Virology* 95: 1919-1928.

Goh, Z. H., Tan, S. G., Bhassu, S., and Tan, W.S. (2011). Virus-like particles of *Macrobrachium rosenbergii* nodavirus produced in bacteria. *Journal of Virological Methods* 175: 74-79.

Gong, F. Peng, X., Luo, C., Shen, G., Zhao, C., Zou, L., Li, L., Sang, Y., Zhao, Y., and Zhao, X. (2013). Cathepsin B as a potential prognostic and therapeutic marker for human lung squamous cell carcinoma. *Molecular Cancer* 12: 125.

Gu, M., Wang, X., Toh, T. B., and Chow, E. K. (2018). Applications of stimuli-responsive nanoscale drug delivery systems in translational research. *Drug Discovery Today* 23: 1043-1052.

Guo, Y. X., Dallmann, K., and Kwang, J. (2003). Identification of nucleolus localization signal of betanodavirus GGNNV protein α. *Virology* 306: 225-235.

Hall, P. R., Hjelle, B., Njus, H., Ye, C., Bondu-Hawkins, V., Brown, D. C., Kilpatrick, K. A., and Larson, R. S. (2009). Phage display selection of cyclic peptides that inhibit Andes virus infection. *Journal of Virology* 83: 8965-8969.

Hallin, G. W., Simpson, S. Q., Crowell, R. E., James, D. S., Koster, F. T., Mertz, G. J., and Levy, H. (1996). Cardiopulmonary manifestations of hantavirus pulmonary syndrome. *Critical Care Medicine* 24: 252-258.

Hanapi, U. F., Yong, C. Y., Goh, Z. H., Alitheen, N. B., Yeap, S. K., and Tan, W. S. (2017). Tracking the virus-like particles of *Macrobrachium rosenbergii* nodavirus in insect cells. *PeerJ* 5: e2947.

Hansen, A. E., Petersen, A. L., Henriksen, J. R., Boerresen, B., Rasmussen, P., Elema, D. R., Rosenschoeld, P. M., Kristensen, A. T., Kjær, A., and Andresen, T. L. (2015). Positron emission tomography based elucidation of the enhanced permeability and retention effect in dogs with cancer using Copper-64 liposomes. *ACS Nano* 9: 6985-6995.

Harrington, K. J., Mohammadtaghi, S., Uster, P. S., Glass, D., Peters, M., Vile, R. G., and Stewart, J. S. W. (2001). Effective targeting of solid tumors in patients with locally advanced cancers by radiolabeled pegylated liposomes. *Clinical Cancer Research* 7: 243-254.

Hashizume, H., Baluk, P., Morikawa, S., McLean, J. W., Thurston, G., Roberge, S., Jain, R. K., and McDonald, D. M. (2000). Openings between defective endothelial cells explain tumor vessel leakiness. *The American Journal of Pathology* 156: 1363-1380.

Hatakeyama, H. (2017). Recent advances in endogenous and exogenous stimuli-responsive nanocarriers for drug delivery and therapeutics. *Chemical and Pharmaceutical Bulletin* 65: 612–617.

Hayakijkosol, O., and Owens, L. (2012). B2 or not B2: RNA interference reduces *Macrobrachium rosenbergii* nodavirus replication in redclaw crayfish (*Cherax quadricarinatus*). *Aquaculture* 326-329: 40-45.

Hayakijkosol, O., and Owens, L. (2013). Non-permissive C6/36 cell culture for the Australian isolate of *Macrobrachium rosenbergii* nodavirus. *Journal of fish diseases* 36: 401-409.

Hernandez-Herrera, R. I., Chappe-Bonnichon, V., Roch, P., Widada, J. S., and Bonami, J. R. (2007). Partial susceptibility of the SSN-1 fish cell line to a crustacean virus: A defective replication study. *Journal of Fish Diseases* 30: 673-679.

Herranz, M. C., Pallas, V., and Aparicio, F. (2012). Multifunctional roles for the N-terminal basic motif of Alfafa mosaic virus coat protein: Nucleolar/cytoplasmic shuttling, modulation of RNA-binding activity, and virion formation. *Molecular Plant-Microbe Interactions* 25: 1093-1103.

Hilgenbrink, A. R., and Low, P. S. (2005). Folate receptor-mediated drug targeting: From therapeutics to diagnostics. *Journal of Pharmaceutical Sciences* 94: 2135-2146.

Ho, K. L., Gabrielsen, M., Beh, P. L., Kueh, C. L., Thong, Q. X., Streetley, J., Tan, W. S., and Bhella, D. (2018). Structure of the *Macrobrachium rosenbergii* nodavirus: A new genus within the *Nodaviridae*? *PLoS Biology* 16: e3000038.

Ho, K. L., Kueh, C. L., Beh, P. L., Tan, W. S., and Bhella, D. (2017). Cryo-electron microscopy structure of the *Macrobrachium rosenbergii* nodavirus capsid at 7 Angstroms resolution. *Scientific Reports* 7: 2083.

Ho, K. L., Yusoff, K., Seow, H. F., and Tan, W. S. (2003). Selection of high affinity ligands to hepatitis B core antigen from a phage-displayed cyclic peptide library. *Journal of Medical Virology* 69: 27-32.

Hong, H., Lee, S., and Myung, H. (2010). Selection of peptides binding to HCV E2 and inhibiting viral infectivity. *Journal of Microbiology and Biotechnology* 20: 1769-1771.

Horsman, M. R., and Vaupel, P. (2016). Pathophysiological basis for the formation of the tumor microenvironment. *Frontiers in Oncology* 6: 66.

Hou, R., Xu, Y., Lu, Q., Zhang, Y., and Hu, B. (2017). Effect of low-frequency low-intensity ultrasound with microbubbles on prostate cancer hypoxia. *Tumor Biology* 39: 1010428317719275.

Hu, D., Sheng, Z., Fang, S., Wang, Y., Gao, D., Zhang, P., Gong, P., Ma, Y., and Cai, L. (2014). Folate receptor-targeting gold nanoclusters as fluorescence enzyme mimetic nanoprobes for tumor molecular colocalization diagnosis. *Theranostics* 4: 142-153.

Huan, U. E., Silva, P. M. F. D., and Floriano, A. P. (2019). Case studies on RetroMAD1^{TM}, an orally administered recombinant chimeric protein to treat naturally infected Feline Leukimia Virus (FeLV) cats. *Archives of Vetrinary Science and Medicine* 2: 41-57.

Huang, J. X., Bishop-Hurley, S. L., and Cooper, M. A. (2012). Development of anti-infectives using phage display: Biological agents against bacteria, viruses, and parasites. *Antimicrobial Agents and Chemotherapy* 56: 4569-4582.

Huang, Y., Huang, J., and Chen, Y. (2010). Alpha-helical cationic antimicrobial peptides: Relationships of structure and function. *Protein & Cell* 1: 143-152.

Hulseberg, C. E., Fénéant, L., Wijs, K. M. S., Kessler, N. P., Nelson, E. A., Shoemaker, C. J., Schmaljohn, C. S., Polyak, S. J., and White, J. M. (2019). Arbidol and other low-molecular-weight drugs that inhibit Lassa and Ebola viruses. *Journal of Virology* 93: e02185-18.

Issels, R. D. (2008). Hyperthermia adds to chemotherapy. *European Journal of Cancer* 44: 2546-2554.

Jain, D., Russell, R. R., Schwartz, R. G., Panjrath, G. S. and Aronow, W. (2017). Cardiac complications of cancer therapy: Pathophysiology, identification, prevention, treatment, and future directions. *Current Cardiology Reports* 19: 36.

Jariyapong, P., Chotwiwatthanakun, C., Direkbusarakom, S., Hirono, I., Wuthisuthimethavee, S., and Weerachatyanukul, W. (2015a). Delivery of double stranded RNA by *Macrobrachium rosenbergii* nodavirus-like particles to protect shrimp from white spot syndrome virus. *Aquaculture* 435: 86-91.

Jariyapong, P., Chotwiwatthanakun, C., Somrit, M., Jitrapakdee, S., Xing, L., Cheng, H. R., and Weerachatyanukul, W. (2014). Encapsulation and delivery of plasmid DNA by virus-like nanoparticles engineered from *Macrobrachium rosenbergii* nodavirus. *Virus Research* 179: 140-146.

Jariyapong, P., Pudgerd, A., Cheloh, N., Hirono, I., Kondo, H., Vanichviriyakit, R., Weerachatyanukul, W., and Chotwiwatthanakun, C. (2019). Hematopoietic tissue of *Macrobrachium rosenbergii* plays dual roles as a source of hemocyte hematopoiesis and as a defensive mechanism against *Macrobrachium rosenbergii* nodavirus infection. *Fish & Shellfish Immunology* 86: 756-763.

Jariyapong, P., Pudgerd, A., Weerachatyanukul, W., Hirono, I., Senapin, S., Dhar, A. K., and Chotwiwatthanakun, C. (2018). Construction of an infectious *Macrobrachium rosenbergii* nodavirus from cDNA clones in Sf9 cells and improved recovery of viral RNA with AZT treatment. *Aquaculture* 483: 111-119.

Jariyapong, P., Weerachatyanukul, W., Direkbusarakom, S., Hirono, I., Wuthisuthimethavee, S., and Chotwiwatthanakun, C. (2015b). Enhancement of shrimp immunity against white spot syndrome virus by *Macrobrachium rosenbergii* nodavirus-like particle encapsulated VP28 double-stranded RNA. *Aquaculture* 446: 325-332.

Kato, T., Yui, M., Deo, V. K., and Park, E. Y. (2015). Development of Rous sarcoma virus-like particles displaying hCC49 scFv for specific targeted drug delivery to human colon carcinoma cells. *Pharmaceutical Research* 32: 3699-3707.

Kim, H. S., Lee, Y. S., and Kim, D. K. (2009). Doxorubicin exerts cytotoxic effects through cell cycle arrest and Fas-mediated cell death. *Pharmacology* 84: 300-309.

Kopek, B. G., Perkins, G., Miller, D. J., Ellisman, M. H., and Ahlquist, P. (2007). Three-dimensional analysis of a viral RNA replication complex reveals a virus-induced mini-organelle. *PLoS Biology* 5: e220.

Kopek, B. G., Settles, E. W., Friesen, P. D., and Ahlquist, P. (2010). Nodavirus-induced membrane rearrangement in replication complex assembly requires replicase protein a, RNA templates, and polymerase activity. *Journal of Virology* 84: 12492-12503.

Kotopoulis, S., Dimcevski, G., Gilja, O. H., Hoem, D., and Postema, M. (2013). Treatment of human pancreatic cancer using combined ultrasound, microbubbles, and gemcitabine: A clinical case study. *Medical Physics* 40: 72902.

Kouznetsova, J., Sun, W., Martínez-Romero, C., Tawa, G., Shinn, P., Chen, C. Z., Schimmer, A., Sanderson, P., McKew, J. C., Zheng, W., and Garcia-Sastre, A. (2014). Identification of 53 compounds that block Ebola virus-like particle entry via a repurposing screen of approved drugs. *Emerging Microbes & Infections* 3: e84.

Kueh, C. L., Yong, C. Y., Dezfooli, S. M., Bhassu, S., Tan, S. G., and Tan, W. S. (2017). Virus-like particle of *Macrobrachium rosenbergii* nodavirus produced in *Spodoptera frugiperda* (Sf9) cells is distinctive from that produced in *Escherichia coli*. *Biotechnology Progress* 33: 549-557.

Kuo, C., Liu, T., Hardiansyah, A., and Chiu, W. (2016). Magnetically polymeric nanocarriers for targeting delivery of curcumin and hyperthermia treatments toward cancer cells. *The Journal of Polymer Science, Part A: Polymer Chemistry* 54: 2706-2713.

Le Seyec, J., Chouteau, P., Cannie, I., Guguen-Guillouzo, C., and Gripon, P. (1999). Infection process of the hepatitis B virus depends on the presence of a defined sequence in the preS1 domain. *Journal of Virology* 73: 2052-2057.

Ledsgaard, L., Kilstrup, M., Karatt-Vellatt, A., McCafferty, J., and Laustsen, A. H. (2018). Basics of antibody phage display technology. *Toxins* 10: 236.

Lee, K. W., and Tan, W. S. (2008). Recombinant hepatitis B virus core particles: Association, dissociation and encapsidation of green fluorescent protein. *Journal of Virology Methods* 151: 172-180.

Lee, K. W., Tey, B. T., Ho, K. L., and Tan, W. S. (2011). Delivery of chimeric hepatitis B core particles into liver cells. *Journal of Applied Microbiology* 112: 119-131.

Lee, V. W., and Harris, D. C. (2011). Adriamycin nephropathy: A model of focal segmental glomerulosclerosis. *Nephrology* 16: 30-38.

Liang, Y., Hao, Y., Wu, Y., Zhou, Z., Li, J., Sun, X., and Liu, Y. N. (2019). Integrated hydrogel platform for programmed antitumor therapy based on near infrared-triggered hyperthermia and vascular disruption. *ACS Applied Materials & Interfaces* 11: 21381-21390.

Lin, F., Liu, L., Hao, G. J., Cao, Z., Sheng, P. C., Wu, Y. L., and Shen, J. Y. (2014). Rapid detection of *Macrobrachium rosenbergii* nodavirus isolated in China by a reverse-transcription loop-mediated isothermal amplification assay combined with a lateral flow dipstick method. *Bing Du Xue Bao* 30: 502-507.

Lin, F., Liu, L., Hao, G. J., Sheng, P. C., Cao, Z., Zhou, Y., Lv, P., Xu, T., Shen, J., and Chen, K. (2018). The development and application of a duplex reverse transcription loop-mediated isothermal amplification assay combined with a lateral flow dipstick method for *Macrobrachium rosenbergii* nodavirus and extra small virus isolated in China. *Molecular and Cellular Probes* 40: 1-7.

Liu, H., Chang, S., Sun, J., Zhu, S., Pu, C., Zhu, Y., Wang, Z., and Xu, R. X. (2014). Ultrasound-mediated destruction of LHRHa targeted and paclitaxel loaded lipid microbubbles induces proliferation inhibition and apoptosis in ovarian cancer cells. *Molecular Pharmaceutics* 11: 40-48.

Liu, K., Feng, X., Ma, Z., Luo, C., Zhou, B., Cao, R., Huang, L., Miao, D., Pang, R., He, D., Lian, X., and Chen, P. (2012). Antiviral activity of phage display selected peptides against porcine reproductive and respiratory syndrome virus *in vitro*. *Virology* 432: 73-80.

Liu, M., Du, H., Zhang, W., and Zhai, G. (2017). Internal stimuli-responsive nanocarriers for drug delivery: Design strategies and applications. *Materials Science and Engineering C* 71: 1267-1280.

Loo, L., Guenther, R. H., Lommel, S. A., and Franzen, S. (2008). Infusion of dye molecules into red clover necrotic mosaic virus. *Chemical Communications* 1: 88-90.

Low, C. F., Md Yusoff, M. R., Kuppusamy, G., and Ahmad Nadzri, N. F. (2018). Molecular biology of *Macrobrachium rosenbergii* nodavirus infection in giant freshwater prawn. *Journal of Fish Diseases* 41: 1771-1781.

Low, C. F., Natagain, B. S., Chee, H. Y, Rozaini, M. Z. H., and Najiah, M. (2017). Betanodavirus: Dissection of the viral life cycle. *Journal of Fish Diseases* 40: 1489-1496.

Lü, X., Yao, M., Zhang, J., Yang, J., Lei, Y., Huang, X., Jia, Z., Ma, L., Lan, H., Xu, Z. and Yin, W. (2014). Identification of peptides that bind hepatitis C virus envelope protein E2 and inhibit viral cellular entry from a phage-display peptide library. *International Journal of Molecular Medicine* 33: 1312-1318.

Lu, Y., and Low, P. S. (2012). Folate-mediated delivery of macromolecular anticancer therapeutic agents. *Advanced Drug Delivery Reviews* 64**:** 342-352.

Ludwig, G.V., Kondig, J. P., and Smith, J. F. (1996). Aputative receptor for Venezuelan equine encephalitis virus from mosquito cells. *Journal of Virology* 70: 5592-5599.

Luo, D., Li, N., Carter, K. A., Lin, C., Geng, J., Shao, S., Huang, W., Qin, Y., Atilla-Gokcumen, G. E., and Lovell, J. F. (2016). Rapid light-triggered drug release in liposomes containing small amounts of unsaturated and porphyrin-phospholipids. *Small Nano Micro* 12: 3039-3047.

Ma, Y., Nolte, R. J. M., and Cornelissen, J. J. L. M. (2012). Virus-based nanocarriers for drug delivery. *Advanced Drug Delivery Reviews* 64: 811-825.

Mahmoudi, K., Bouras, A., Bozec, D., Ivkov, R., and Hadjipanayis, C. (2018). Magnetic hyperthermia therapy for the treatment of glioblastoma: A review of the therapy's history, efficacy and application in humans. *International Journal of Hyperthermia.* 34: 1316-1328.

Mariam, S. H. S., Ooi, C. W., Tan, W. S., Janna, O. A., Arbakariya, A., and Tey, B. T. (2015). Purification of rabbit polyclonal immunoglobulin G with ammonium sulphate precipitation and mixed-mode chromatography. *Separation and Purification Technology* 144: 133-138.

Martinez, V. P., Bellomo, C., San Juan, J., Pinna, D., Forlenza, R., Elder, M., and Padula, P. J. (2005). Person-to-person transmission of Andes virus. *Emerging Infectious Diseases* 11: 1848-1853.

Matherly, L. H., and Goldman, D. I. (2003). Membrane transport of folates. *Vitamins and Hormones* 66: 403-456.

Matsumura, Y., and Maeda, H. (1986). A new concept for macromolecular therapeutics in cancer chemotherapy: Mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. *Cancer Research* 46: 6387-6392.

Mazzotta, E., Tavano, L., and Muzzalupo, R. (2018). Thermo-sensitive vesicles in controlled drug delivery for chemotherapy. *Pharmaceutics* 10: 1150.

Meng, F., Zhong, Y., Cheng, R., Deng, C., and Zhong, Z. (2014). pH-sensitive polymeric nanoparticles for tumor-targeting doxorubicin delivery: Concept and recent advances. *Nanomedicine* 9: 487-499.

Mertz, G. J., Miedzinski, L., Goade, D., Pavia, A. T., Hjelle, B., Hansbarger, C. O., Levy, H., Koster, F. T., Baum, K., Lindemulder, A., Wang, W., Riser, L., Fernandez, H., and Whitley, R. J. (2004). Placebo-controlled, double-blind trial of intravenous ribavirin for the treatment of hantavirus cardiopulmonary syndrome in North America. *Clinical Infectious Diseases* 39: 1307-1313.

Mo, R., and Gu, Z. (2016). Tumor microenvironment and intracellular signal-activated nanomaterials for anticancer drug delivery. *Materials Today* 19: 274-283.

Monjezi, R., Tey, B. T., Sieo, C. C., and Tan, W. S. (2010). Purification of bacteriophage M13 by anion exchange chromatography. *Journal of Chromatography B* 878: 1855-1859.

Murwantoko, M., Bimantara, A., Roosmanto, R., and Kawaichi, M. (2016). *Macrobrachium rosenbergii* nodavirus infection in a giant freshwater prawn hatchery in Indonesia. *Springerplus* 5: 1729.

Nart, D., Yaman, B., Yilmaz, F., Zeytunlu, M., Karasu, Z., and Kiliç, M. (2010). Expression of matrix metalloproteinase-9 in predicting prognosis of hepatocellular carcinoma after liver transplantation. *Liver Transplantation* 16: 621-630.

Kumar, B. T. N., Murthy, H. S., Patil, P., Doddamani, P. L., and Patil, R. (2015). Enhanced immune response and resistance to white tail disease in chitin-diet fed freshwater prawn, *Macrobrachium rosenbergii*. *Aquaculture Reports* 2: 34-38.

NaveenKumar, S., Shekar, M., Karunasagar, I., and Karunasagar, I. (2013). Genetic analysis of RNA1 and RNA2 of *Macrobrachium rosenbergii* nodavirus (MrNV) isolated from India. *Virus Research* 173: 377-385.

Needham, D., Anyarambhatla, G., Kong, G., and Dewhirst, M. W. (2000). A new temperature-sensitive liposome for use with mild hyperthermia: Characterization and testing in a human tumor xenograft model. *Cancer Research* 60: 1197-1201.

O'Callaghan, R., Bradley, R., and Paranchych, W. (1973). The effect of M13 phage infection upon the F pili of *E. coli*. *Virology* 54: 220-229.

Odegard, A., Banerjee, M., and Johnson, J. E. (2010). Flock house virus: A model system for understanding non-enveloped virus entry and membrane penetration. *Current Topics in Microbiology and Immunology* 343: 1-22.

Oei, A. L., Lianne E. M. Vriend, L. E. M., Crezee, J., Franken, N. A. P., and Krawczyk, P. M. (2015). Effects of hyperthermia on DNA repair pathways: One treatment to inhibit them all. *Radiation Oncology* 10: 165.

Ohkuma, S., and Poole, B. (1978). Fluorescence probe measurement of the intralysosomal pH in living cells and the perturbation of pH by various agents. *Proceedings of the National Academy of Sciences of the United States of America* 75: 3327-3331.

OiE. (2019). World Organisation for animal health. Chapter 2.2.6. Infection with *Macrobrachium rosenbergii* nodavirus (White tail disease). In Rakesh N. Veedu (Ed.), *Manual of diagnostic tests for aquatic animals* (pp. 1–13). New York: Taylor & Francis Group.

Ojeda, N., Cárdenas, C., Guzmán, F., and Marshall, S. H. (2016). Chemical synthesis and *in vitro* evaluation of a phage display-derived peptide active against infectious salmon anemia virus. *Applied and Environmental Microbiology* 82: 2563-2571.

Olivieri, J. Perna, G. P., Bocci, C., Montevecchi, C, Olivieri, A., Leoni, P., and Gini, G. (2017). Modern management of anthracycline-induced cardiotoxicity in lymphoma patients: Low occurrence of cardiotoxicity with comprehensive assessment and tailored substitution by nonpegylated liposomal doxorubicin. *The Oncologist* 22: 422-431.

Ong, H. K., Yong, C. Y., Tan, W. S., Yeap, S. K., Omar, A. R., Razak, M. A., Ho, K. L. (2019). An influenza A vaccine based on the extracellular domain of matrix 2 protein protects BALB/C mice against H1N1 and H3N2. *Vaccines* 7: 91.

Overchuk, M., and Zheng, G. (2018). Overcoming obstacles in the tumor microenvironment: Recent advancements in nanoparticle delivery for cancer theranostics. *Biomaterials* 156: 217-237.

Owens, L., La Fauce, K., Juntunen, K., Hayakijkosol, O., and Zeng, C. (2009). *Macrobrachium rosenbergii* nodavirus disease (white tail disease) in Australia. *Diseases of Aquatic Organisms* 85: 175-180.

Parmar, P. V., Murthy, H. S., Tejpal, C. S., and Kumar, B. T. N. (2012). Effect of brewer's yeast on immune response of giant freshwater prawn, *Macrobrachium rosenbergii*, and its resistance to white muscle disease. *Aquaculture International* 20: 951-964.

Parmley, S. F., and Smith, G. P. (1988). Antibody-selectable filamentous fd phage vectors: Affinity purification of target genes. *Gene* 73: 305-318.

Pawlowska, J., Tarasiuk, J., Wolf, C., Paine, M., and Borowski, E. (2003). Differential ability of cytostatics from anthraquinone group to generate free radicals in three enzymatic systems: NADH dehydrogenase, NADPH cytochrome P450 reductase, and xanthine oxidase. *Oncology Research* 13: 245-252.

Pérez-Berná, A. J. (2012). The role of capsid maturation on adenovirus priming for sequential uncoating. *Journal of Biological Chemistry* 287: 31582-31595.

Pillai, D., Bonami, J. R., and Widada, J. S. (2006). Rapid detection of *Macrobrachium rosenbergii* nodavirus (MrNV) and extra small virus (XSV), the pathogenic agents of white tail disease of *Macrobrachium rosenbergii* (De Man), by loop-mediated isothermal amplification. *Journal of Fish Diseases* 29: 275-283.

Poranen, M. M., Koivunen, M. R., and Bamford, D. H. (2008) Nontemplated terminal nucleotidyltransferase activity of double-stranded RNA bacteriophage phi6 RNA-dependent RNA polymerase. *Journal of Virology* 82: 9254-9264.

Protopopova, E. V., Konavalova, S. N., and Loktev, V. B. (1997). Isolation of a cellular receptor for tick-borne encephalitis virus using anti-idiotypic antibodies. *Voprosy virusologii* 42: 264-268.

Puthawibool, T., Senapin, S., Flegel, T. W., and Kiatpathomchai, W. (2010). Rapid and sensitive detection of *Macrobrachium rosenbergii* nodavirus in giant freshwater prawns by reverse transcription loop-mediated isothermal amplification combined with a lateral flow dipstick. *Molecular and Cellular Probes* 24: 244-249.

Qian, D., Liu, W., Jianxiang, W., and Yu, L. (2006). Preparation of monoclonal antibody against *Macrobrachium rosenbergii* nodavirus and application of TAS-ELISA for virus diagnosis in post-larvae hatcheries in east China during 2000-2004. *Aquaculture* 261: 1144-1150.

Qian, D., Shi, Z., Zhang, S., Cao, Z., Liu, W., Li, L., Xie, Y., Cambournac, I., and Bonami, J. R. (2003). Extra small virus-like particles (XSV) and nodavirus associated with whitish muscle disease in the giant freshwater prawn *Macrobrachium rosenbergii*. *Journal of Fish Diseases* 26: 521-527.

Qing, M., Liu, W., Yuan, Z., Gu, F., and Shi, P.Y. (2010). A high-throughput assay using dengue-1 virus-like particles for drug discovery. *Antiviral Research* 86: 163-171.

Rajik, M., Jahanshiri, F., Omar, A. R., Ideris, A., Hassan, S. S., and Yusoff, K. (2009). Identification and characterisation of a novel anti-viral peptide against avian influenza virus H9N2. *Virology Journal* 6: 74.

Ramanujam, P., Tan, W. S., Nathan, S., and Yusoff, K. (2002). Novel peptides that inhibit the propagation of Newcastle disease virus. *Archives of Virology* 147: 981-993.

Ranganathan, R., Madanmohan, S., Kesavan, A., Baskar, G., Krishnamoorthy, Y. R., Santosham, R., Ponraju, D., Rayala, S. K., and Venkatraman, G. (2012). Nanomedicine: Towards development of patient-friendly drug-delivery systems for oncological applications. *International Journal of Nanomedicine* 7: 1043-1060.

Rasched, I., and Oberer, E. (1986). Ff coliphages: Structural and functional relationships. *Microbiology Reviews* 50: 401-427.

Ravi, M., and Hameed, A. S. S. (2015). Experimental transmission of *Macrobrachium rosenbergii* nodavirus (MrNV) and extra small virus (XSV) in *Macrobrachium malcolmsonii* and *Macrobrachium rude*. *Aquaculture International* 23: 195-201.

Ravi, M., and Hameed, A. S. S. (2014). Effect of chemical and physical treatments on the inactivation of *Macrobrachium rosenbergii* nodavirus and extra small virus. *Aquaculture Research* 47: 1231-1237.

Ravi, M., Basha, A. N., Sarathi, M., Idalia, H. H. R., Widada, J. S., Bonami, J. R., and Hameed, A. S. S. (2009). Studies on the occurrence of white tail disease (WTD) caused by MrNV and XSV in hatchery-reared post-larvae of *Penaeus indicus* and *P. monodon*. *Aquaculture* 292: 117-120.

Renu, K., Abilash, V. G., Pichiah, T. P. B., and Arunachalam, S. (2018). Molecular mechanism of doxorubicin-induced cardiomyopathy - An update. *European Journal of Pharmacology* 818: 241-253.

Rohovie, M. J., Nagasawa, M., and Swartz, J. R. (2017). Virus-like particles: Next-generation nanoparticles for targeted therapeutic delivery. *Bioengineering & Translational Medicine* 2: 43-57.

Romestand, B., and Bonami, J. R. (2003). A sandwich enzyme linked immunosorbent assay (S-ELISA) for detection of MrNV in the giant freshwater prawn, *Macrobrachium rosenbergii* (de Man). *Journal of Fish Diseases* 26: 71-75.

Ross, J. F., Chaudhuri, P. K., and Ratnam, M. (1994). Differential regulation of folate receptor isoforms in normal and malignant tissues *in vivo* and in established cell lines. Physiologic and clinical implications. *Cancer* 73: 2432-2443.

Saedi, T. A., Moeini, H., Tan, W. S., Yusoff, K., Daud, H. M., Chu, K. B., Tan, S. G., and Bhassu, S. (2012). Detection and phylogenetic profiling of nodavirus associated with white tail disease in Malaysian *Macrobrachium rosenbergii* de Man. *Molecular Biology Reports* 39: 5785-5790.

Sahoo, P. K., Shekhar, M. S., Das, A., Kumar, M. D., Pillai, B. R., and Hameed, A. S. (2012). Immunomodulatory effect of recombinant RNA-dependent RNA polymerase protein of *Macrobrachium rosenbergii* nodavirus in giant freshwater prawn *M. rosenbergii*. *Aquaculture Research 43*: 1096-1106.

Hameed, A. S. S., Ravi, M., Farook, M. A., Taju, G., Hernandez-Herrera, R. I., and Bonami, J. R. (2011). Screening the post-larvae of *Macrobrachium rosenbergii* for early detection of *Macrobrachium rosenbergii* nodavirus (MrNV) and extra small virus (XSV) by RT–PCR and immunological techniques. *Aquaculture* 317: 42-47.

Hameed, A. S. S., Yoganandhan, K., Widada, J. S., and Bonami, J. R. (2004a). Studies on the occurrence of *Macrobrachium rosenbergii* nodavirus (MrNV) and extra small virus-like particles (XSV) associated with white tail disease (WTD) of *Macrobrachium rosenbergii* in India by RT-PCR detection. *Aquaculture* 238: 127-133.

Hameed, A. S. S., Yoganandhan, K., Widada, J. S., and Bonami, J. R. (2004b). Experimental transmission and tissue tropism of *Macrobrachium rosenbergii* nodavirus (*Mr*NV) and its associated extra small virus (XSV). *Diseases of Aquatic Organisms* 62: 191-196.

Salata, C., Calistri, A., Alvisi, G., Celestino, M., Parolin, C., and Palù, G. (2019). Ebola Virus entry: From molecular characterization to drug discovery. *Viruses* 11: 274.

Samadian, H., Hosseini-Nami, S., Kamrava, S. K., Ghaznavi, H., and Shakeri-Zadeh, A. (2016). Folate-conjugated gold nanoparticle as a new nanoplatform for targeted cancer therapy. *Journal of Cancer Research and Clinical Oncology* 142: 2217-2229.

Sambrook, J., Russell, D. W., Irwin, N., and Janssen, K. A. (2001). Molecular Cloning: A Laboratory Manual. New York: Cold Spring Harbor Laboratory.

Saw, P. E., and Song, E. (2019). Phage display screening of therapeutic peptide for cancer targeting and therapy. *Protein & Cell* DOI: https://doi.org/10.1007/s13238-019-0639-7

Scott, J. K., and Smith, G. P. (1990). Searching for peptide ligands with an epitope library. *Science* 249: 386-390.

Sen, A., Capitano, M. L., Spernyak, J. A., Schueckler, J. T., Thomas, S., Singh, A. K., Evans, S. S., Hylander, B. L., and Repasky, E. A. (2011). Mild elevation of body temperature reduces tumor interstitial fluid pressure and hypoxia and enhances efficacy of radiotherapy in murine tumor models. *Cancer Research* 71: 3872-3880.

Senapin, S., and Phongdara, A. (2006). Binding of shrimp cellular proteins to Taura syndrome viral capsid proteins VP1, VP2 and VP3. *Virus Research* 122: 69-77.

Senapin, S., Jaengsanong, C., Phiwsaiya, K., Prasertsri, S., Laisutisan, K., Chuchird, N., Limsuwan, C., and Flegel, T. W. (2012). Infections of MrNV (*Macrobrachium rosenbergii* nodavirus) in cultivated whiteleg shrimp *Penaeus vannamei* in Asia. *Aquaculture* 338: 41-46.

Senapin, S., Phiwsaiya, K., Gangnonngiw, W., Briggs, M., Sithigorngul, P., and Flegel, T. (2013). Dual infections of IMNV and MrNV in cultivated *Penaeus vannamei* from Indonesia. *Aquaculture* 372: 70-73.

Shao, P., Wang, B., Wang, Y., Li, J., and Zhang, Y. (2011). The application of thermosensitive nanocarriers in controlled drug delivery. *Journal of Nanomaterials* 2011: 389640.

Shekhar, M. S., Azad, I. S., and Jithendran, K. P. (2006). RT-PCR and sequence analysis of *Macrobrachium rosenbergii* nodavirus: Indian isolate. *Aquaculture* 252: 128-132.

Shen, Z. Y., Wu, M. F., Zhang, Y. X., Shen, K., and Xia, G. L. (2015). Treatment of hepatic carcinoma by low-frequency ultrasound and microbubbles: A case report. *Oncology Letters* 9: 1249-1253.

Shtanko, O., Sakurai, Y., Reyes, A. N., Noël, R., Cintrat, J. C., Gillet, D., Barbier, J., and Davey, R. A. (2018). Retro-2 and its dihydroquinazolinone derivatives inhibit filovirus infection. *Antivirus Research* 149: 154-163.

Sirikharin, R., Utairungsee, T., Srisala, J., Roytrakul, S., Thitamadee, S., and Sritunyalucksana, K. (2019). Cell surface transglutaminase required for nodavirus entry into freshwater prawn hemocytes. *Fish & Shellfish Immunology* 89: 108-116.

Skitzki, J. J., Repasky, E. A., and Evans, S. S. (2009). Hyperthermia as an immunotherapy strategy for cancer. *Current Opinion in Investigational Drugs* 10: 550-558.

Smith, G. P. (1985). Filamentous fusion phage: Novel expression vectors that display cloned antigens on the virion surface. *Science* 228: 1315-1317.

Smith, G. P., and Scott, J. K. (1993). Libraries of peptides and proteins displayed on filamentous phage. *Methods in Enzymology* 217: 228-257.

Snipstad, S., Berg, S., Mørch, Y., Bjørkøy, A., Sulheim, E., Hansen, R., Grimstad, I., Wamel, A. V., Maaland, A. F., Torp, S. H., and Davies, C. D. L. (2017). Ultrasound improves the delivery and therapeutic effect of nanoparticle-stabilized microbubbles in breast cancer xenografts. *Ultrasound in Medicine and Biology* 43: 2651-2669.

Somrit, M., Watthammawut, A., Chotwiwatthanakun, C., and Weerachatyanukul, W. (2016). The key molecular events during *Macrobrachium rosenbergii* nodavirus (MrNV) infection and replication in Sf9 insect cells. *Virus Research* 223: 1-9.

Somrit, M., Watthammawut, A., Chotwiwatthanakun, C., Ounjai, P., Suntimanawong, W., and Weerachatyanukul, W. (2017). C-terminal domain on the outer surface of the *Macrobrachium rosenbergii* nodavirus capsid is required for Sf9 cell binding and internalization. *Virus Research* 227: 41-48.

Song, C. W., Park, H. J., Lee, C. K., and Griffin, R. (2005). Implications of increased tumor blood flow and oxygenation caused by mild temperature hyperthermia in tumor treatment. *International Journal of Hyperthermia* 21: 761-767.

Spear, P. G. (2004). Herpes simplex virus: Receptors and ligands for cell entry. *Cellular Microbiology* 6: 401-410.

Widada, J. S., and Bonami, J. R. (2004). Characteristics of the monocistronic genome of extra small virus, a virus-like particle associated with *Macrobrachium rosenbergii* nodavirus: Possible candidate for a new species of satellite virus. *Journal of General Virology* 85: 643-646.

Widada, J. S., Durand, S., Cambournac, I., Qian, D., Shi, Z., Dejonghe, E., Richard, V., and Bonami, J. R. (2003). Genome-based detection methods of *Macrobrachium rosenbergii* nodavirus, a pathogen of the giant freshwater prawn, *Macrobrachium rosenbergii*: Dot-blot, in situ hybridization and RT-PCR. *Journal of Fish Diseases* 26: 583-590.

Su, C., Li, H., Shi, Y., Wang, G., Liu, L., Zhao, L., and Su, R. (2014). Carboxymethyl-β-cyclodextrin conjugated nanoparticles facilitate therapy for folate receptor-positive tumor with the mediation of folic acid. *International Journal of Pharmaceutics* 474: 202-211.

Sudhakaran, R., Ahmed, V. P. I., Haribabu, P., Mukherjee, S. C., Widada, J. S., Bonami, J. R., and Hameed, A. S. S. (2007a). Experimental vertical transmission of *Macrobrachium rosenbergii* nodavirus (MrNV) and extra small virus (XSV) from brooders to progeny in *Macrobrachium rosenbergii* and Artemia. *Journal of Fish Diseases* 30: 27-35.

Sudhakaran, R., Haribabu, P., Kumar, S. R., Sarathi, M., Ahmed, V. P. I., Venkatesan, C., Hameed, A. S. S. (2008). Natural aquatic insect carriers of *Macrobrachium rosenbergii* nodavirus (MrNV) and extra small virus (XSV). *Diseases of Aquatic Organisms* 79: 141-145.

Sudhakaran, R., Parameswaran, V., and Hameed, A. S. (2007b). *In vitro* replication of *Macrobrachium rosenbergii* nodavirus and extra small virus in C6/36 mosquito cell line. *Journal of Virological Methods* 146: 112-118.

Sudhakaran, R., Musthaq, S. S., Haribabu, P., Mukherjee, S. C., Gopal, C., and Hameed, A. S. S. (2006a). Experimental transmission of *Macrobrachium rosenbergii* nodavirus (MrNV) and extra small virus (XSV) in three species of marine shrimp (*Penaeus indicus*, *Penaeus japonicus* and *Penaeus monodon*). *Aquaculture* 257: 136-141.

Sudhakaran, R., Yoganandhan, K., Ahmed, V. P. I., and Hameed A. S. S. (2006b). Artemia as a possible vector for *Macrobrachium rosenbergii* nodavirus (MrNV) and extra small virus transmission (XSV) to *Macrobrachium rosenbergii* post-larvae. *Diseases of Aquatic Organisms* 70: 161-166.

Sudimack, J. B. A., and Lee R. J. (2000). Targeted drug delivery via the folate receptor. *Advanced Drug Delivery Reviews* 41: 147-162.

Sun, J., DuFort, C., Daniel, M. C., Murali, A., Chen, C., Gopinath, K., Stein, B., De, M., Rotello, V. M., Holzenburg, A., Kao, C. C., Dragnea, B. (2007). Core-controlled polymorphism in virus-like particles. *Proceedings of the National Academy of Sciences* 104: 1354-1359.

Swift, L. P., Rephaeli, A., Nudelman, A., Phillips, D. R., and Cutts, S. M. (2006). Doxorubicin-DNA adducts induce a non-topoisomerase II-mediated form of cell death. *Cancer Research* 66: 4863-4871.

Tak, W. Y., Lin, S. M., Wang, Y., Zheng, J., Vecchione, A., Park, S. Y., Chen, M. H., Wong, S., Xu, R., Peng, C. Y., Chiou, Y. Y., Huang, G. T., Cai, J., Abdullah, B. J. J., Lee, J. S., Lee, J. Y., Choi, J. Y., Gopez-Cervantes, J., Sherman, M., Finn, R. S., Omata, M., O'Neal, M., Makris, L., Borys, N., Poon, R., and Lencioni, R. (2018). Phase III HEAT study adding lyso-thermosensitive liposomal doxorubicin to radiofrequency ablation in patients with unresectable hepatocellular carcinoma lesions. *Clinical Cancer Research* 24: 73-83.

Tan, W. S., and Ho, K. L. (2014). Phage display creates innovative applications to combat hepatitis B virus. *World Journal of Gastroenterology* 20: 11650-11670.

Tan, W. S., McNae, I. W., Ho, K. L., and Walkinshaw, M. D. (2007). Crystallization and X-ray analysis of the *T* = 4 particle of hepatitis B capsid protein with an N-terminal extension. *Acta Crystallographica Section F Structural Biology and Crystallization Communications* 63: 642-647.

Tan, W. S., Tan, G. H., Yusoff, K., and Seow, H. F. (2005). A phage-displayed cyclic peptide that interacts tightly with the immunodominant region of hepatitis B surface antigen. *Journal of Clinical Virology* 34: 35-41.

Tang, K. F., Abdullah, M. P., Yusoff, K., and Tan, W. S. (2007). Interactions of the hepatitis B core antigen and peptide inhibitors. *Journal of Medicinal Chemistry* 50: 5620-5626.

Tapia-Moreno, A., Juarez-Moreno, K., Gonzalez-Davis, O., Cadena-Nava, R. D., and Vazquez-Duhalt, R. (2017). Biocatalytic virus capsid as nanovehicle for enzymatic activation of Tamoxifen in tumor cells. *Biotechnology Journal* 12: 1600706.

Thepparit, C., and Smith, D. R. (2004). Serotype-specific entry of dengue virus into liver cells: Identification of the 37-kilodalton/67-kilodalton high-affinity laminin receptor as a dengue virus serotype 1 receptor. *Journal of Virology* 78: 12647-12656.

Thieringer, F. R., Maass, T., Anthon, B., Meyer, E., Schirmacher, P., Longerich, T., Galle, P. R., Kanzler, S., and Teufel, A. (2012). Liver-specific overexpression of matrix metalloproteinase 9 (MMP-9) in transgenic mice accelerates development of hepatocellular carcinoma. *Molecular Carcinogenesis* 51: 439–448.

Tio, P. H., Jong, W. W., and Cardosa, M. J. (2005). Two dimensional VOPBA reveals laminin receptor (LAMR1) interaction with dengue virus serotypes 1, 2 and 3. *Virology Journal* 2: 25.

Tiwari, V., Liu, J., Valyi-Nagy, T., and Shukla, D. (2011). Anti-heparan sulfate peptides that block herpes simplex virus infection *in vivo*. *The Journal of Biological Chemistry* 286: 25406-25415.

Tiwari, V., Tarbutton, M. S., and Shukla, D. (2015). Diversity of heparan sulfate and HSV entry: Basic understanding and treatment strategies. *Molecules* 20: 2707-2727.

Tripathy, S., Sahoo, P. K., Kumari, J., Mishra, B. K., Sarangi, N., and Ayyappan, S. (2006). Multiplex RT-PCR detection and sequence comparison of viruses MrNV and XSV associated with white tail disease in *Macrobrachium rosenbergii*. *Aquaculture* 258: 134-139.

Tsang, W. P., Chau, S. P. Y., Kong, S. K., Fung, K. P., and Kwok, T. T. (2003). Reactive oxygen species mediate doxorubicin induced p53-independent apoptosis. *Life Sciences* 73: 2047-2058.

Tschiche, A., Thota, B. N. S., Neumann, F., Schäfer, A., Ma, N., and Haag, R. (2016). Crosslinked redox-responsive micelles based on lipoic acid-derived amphiphiles for enhanced siRNA delivery. *Macromoleclular Bioscience* 16: 811-823.

Tung, C. W., Wang, C. S., and Chen, S. N. (1999). Histological and electron microscopic study on *Macrobrachium* muscle virus (MMV) infection in the giant freshwater prawn, *Macrobrachium rosenbergii* (de Man), cultured in Taiwan. *Journal of Fish Diseases* 22: 319-323.

van der Zee, J., Vujaskovic, Z., Kindo, M., and Sugahara, T. (2008). The Kadota Fund International Forum 2004 – clinical group consensus. *International Journal of Hyperthermia* 24: 111-112.

van Wezenbeek, P. M., Hulsebos, T. J., and Schoenmakers, J. G. (1980). Nucleotide sequence of the filamentous bacteriophage M13 DNA genome: Comparison with phage fd. *Gene* 11: 129-148.

Vaupel, P., Kallinowski, F. K., and Okunieff, P. (1989). Blood flow, oxygen and nutrient supply, and metabolic micro-environment of human tumors: A review. *Cancer Research* 49: 6449-6465.

Vial, P. A., Valdivieso, F., Mertz, G., Castillo, C., Belmar, E., Delgado, I., Tapia, M., and Ferres, M. (2006). Incubation period of hantavirus cardiopulmonary syndrome. *Emerging Infectious Diseases* 12: 1271-1273.

Walczak, R. J., Dickens, M. L. Priestley, N. D., and Strohl, W. R. (1999). Purification, properties, and characterization of recombinant *Streptomyces* sp. strain C5 DoxA, a cytochrome P-450 catalyzing multiple steps in doxorubicin biosynthesis. *Journal of Bacteriology* 181: 298-304.

Wang, B., Ke, L. H., Jiang, H., Li, C. Z., and Tien, P. (2000). Selection of a specific peptide from a nona-peptide library for *in vitro* inhibition of grass carp hemorrhage virus replication. *Virus Research* 67: 119-125.

Wang, C. S. (2016). Nodaviruses of crustaceans. In: Kibenge, F. S. B., & Godoy, M. G. (editors). *Aquaculture Virology*. (pp. 475-488). Cambridge, Massachusetts: Academic Press.

Wang, C. S., Chang, C. Y., and Wen, C. M. (2016). Developing immunological methods for detecting *Macrobrachium rosenbergii* nodavirus and extra small virus using a recombinant protein preparation. *Journal of Fish Diseases* 39: 715-727.

Wang, K. S., Kuhn, R. J., Strauss, E. G., Ou, S., and Strauss, J. H. (1992). High-affinity laminin receptor is a receptor for Sindbis virus in mammalian cells. *Journal of Virology* 66: 4992-5001.

Wang, L., and Zheng, S. (2019). Advances in low-frequency ultrasound combined with microbubbles in targeted tumor therapy. *Journal of Zhejiang University Science B* 20: 291-299.

Wang, W., Liu, Y., Zu, X., Jin, R., and Xiao, G. (2011). Blocking peptides against HBV: PreS1 protein selected from a phage display library. *Biochemical and Biophysical Research Communications* 412: 633-637.

Wangman, P., Senapin, S., Chaivisuthangkura, P., Longyant, S., Rukpratanporn, S., and Sithigorngul, P. (2012). Production of monoclonal antibodies specific to *Macrobrachium rosenbergii* nodavirus using recombinant capsid protein. *Diseases of Aquatic Organisms* 98: 121-131.

Wu, W., Wang, Z., Xia, H., Liu, Y., Qiu, Y., Liu, Y., Hu, Y., and Zhou, X. (2014). Flock house virus RNA polymerase initiates RNA synthesis *de novo* and possesses a terminal nucleotidyl transferase activity. *PLoS One* 9: e86876.

Xing, M., Yan, F., Yu, S., and Shen, P. (2015). Efficacy and cardiotoxicity of liposomal doxorubicin-based chemotherapy in advanced breast cancer: A meta-analysis of ten randomized controlled trials. *PLoS One* 10: e0133569.

Xu, J., Xu, B., Shou, D., Qin, F., Xu, Y., and Hu, Y. (2016). Characterization and evaluation of a folic acid receptor-targeted cyclodextrin complex as an anticancer drug delivery system. *European Journal of Pharmaceutical Sciences* 83: 132-142.

Xu, L., Bai, Q., Zhang, X., and Yang, H. (2017). Folate-mediated chemotherapy and diagnostics: An updated review and outlook. *Journal of Controlled Release* 252: 73-82.

Yang, W. H., Xie, J., Lai, Z. Y., Yang, M. D., Zhang, G. H., Li, Y., Mu, J. B., and Xu, J. (2019a). Radiofrequency deep hyperthermia combined with chemotherapy in the treatment of advanced non-small cell lung cancer. *Chinese Medical Journal* 132: 922-927.

Yang, X. L., Fan, C. H., and Zhu, H. S. (2002). Photo-induced cytotoxicity of malonic acid C (60) fullerene derivatives and its mechanism. *Toxicology in Vitro*. 16: 41-46.

Yang, Y., Yang, C., Zhao, Z., Zuo, X., Liang, T., Yang, Y., Ma, S., and Yang, D. (2019b). Microwave hyperthermia enhances the sensitivity of lung cancer cells to gemcitabine through reactive oxygen species-induced autophagic death. *Oncology Reports* 41: 3100-3110.

Yatvin, M. B., Weinstein, J. N., Dennis, W. H., and Blumenthal, R. (1978). Design of liposomes for enhanced local release of drugs by hyperthermia. *Science* 202: 1290-1293.

Yi, G., Qian, J., Wang, Z., and Qi, Y. (2003). A phage-displayed peptide can inhibit infection by white spot syndrome virus of shrimp. *Journal of General Virology* 84: 2545-2553.

Yildiz, I., Lee, K. L., Chen, K., Shukla, S., and Steinmetz, N. F. (2013). Infusion of imaging and therapeutic molecules into the plant virus-based carrier cowpea mosaic virus: Cargo-loading and delivery. *Journal of Controlled Release* 172: 568-578.

Yin, L., Luo, Y., Liang, B., Wang, F., Du, M., Petrenko, V. A., Qiu, H., and Liu, A. (2014). Specific ligands for classical swine fever virus screened from landscape phage display library. *Antiviral Research* 109: 68-71.

Yoganandhan, K., Leartvibhas, M., Sriwongpuk, S., and Limsuwan, C. (2006). White tail disease of the giant freshwater prawn *Macrobrachium rosenbergii* in Thailand. *Diseases of Aquatic Organisms* 69: 255-258.

Yoganandhan, K., Widada, J. S., Bonami, J. R., and Hameed A. S. S. (2005). Simultaneous detection of *Macrobrachium rosenbergii* nodavirus and extra small virus by a single tube, one-step multiplex RT-PCR assay. *Journal of Fish Diseases* 28: 65-69.

Yong, C. Y., Yeap, S. K., Goh, Z. H., Ho, K. L., Omar, A. R., and Tan, W. S. (2015a). Induction of humoral and cell-mediated immune responses by hepatitis B virus epitope displayed on the virus-like particles of prawn nodavirus. *Applied and Environmental Microbiology* 81: 882-889.

Yong, C. Y., Yeap, S. K., Ho, K. L., Omar, A. R., and Tan, W. S. (2015b). Potential recombinant vaccine against influenza A virus based on M2e displayed on nodaviral capsid nanoparticles. *International Journal of Nanomedicine* 10: 2751-2763.

Yong, C. Y., Yeap, S. K., Omar, A. R., and Tan, W. S. (2017). Advances in the study of nodavirus. *PeerJ* 5: e3841.

Yoon, K. Y., Tan, W. S., Tey, B. T., Lee, K. W., and Ho, K. L. (2013). Native agarose gel electrophoresis and electroelution: A fast and cost-effective method to separate the small and large hepatitis B capsids. *Electrophoresis* 34: 244-253.

Young, J. S., and Simmons, J. W. (2014). Chemotherapeutic medications and their emergent complications. *Emergency Medicine Clinics of North America* 32: 563-578.

Zandi, R., and Reguera, D. (2005). Mechanical properties of viral capsids. *Physical Review E* 72: 021917.

Zeng, Q., Wen, H., Wen, Q., Chen, X., Wang, Y., Xuan, W., Liang, J., and Wan, S. (2013). Cucumber mosaic virus as drug delivery vehicle for doxorubicin. *Biomaterials* 34: 4632-4642.

Zhang, H., Wang, J., Yuan, J., Li, L., Zhang, J., Bonami, J. R., and Shi, Z. (2006). Quantitative relationship of two viruses (MrNV and XSV) in white-tail disease of *Macrobrachium rosenbergii*. *Diseases of Aquatic Organisms* 71: 11-17.

Zhang, Q., Wang, Y., Ji, Q., Gu, J., Liu, S., Feng, X., Sun, C., Li, Y., and Lei, L. (2013). Selection of antiviral peptides against mink enteritis virus using a phage display peptide library. *Current Microbiology* 66: 379-384.

Zhang, Y., Guo, Q., An, S., Lu, Y., Li, J., He, X., Liu, L., Zhang, Y., Sun, T., and Jiang, C. (2017). ROS-switchable polymeric nanoplatform with stimuli-responsive release for active targeted drug delivery to breast cancer. *ACS Applied Materials & Interfaces* 9: 12227-12240.

Zu, X., Liu, Y., Wang, S., Jin, R., Zhou, Z., Liu, H., Gong, R., Xiao, G., and Wang, W. (2014). Peptide inhibitor of Japanese encephalitis virus infection targeting envelope protein domain III. *Antiviral Research* 104: 7-14.

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LIST OF PUBLICATIONS

Thong, Q. X., Biabanikhankahdani, R., Ho, K. L., Alitheen, N. B., and Tan, W. S. (2019). Thermally-responsive virus-like particle for targeted delivery of cancer drug. *Scientific Reports 9*: 3945.

Thong, Q. X., Wong, C. L., Ooi, M. K., Kueh, C. L., Ho, K. L., Alitheen, N. B., and Tan, W. S. (2018). Peptide inhibitors of *Macrobrachium rosenbergii* nodavirus. *Journal of General Virology* 99: 1227-1238.

Thong, Q. X., Wong, C. L., Ooi, M. K., Kueh, C. L., Ho, K. L., Alitheen, N. B., and Tan, W. S. (2018). Peptides that inhibit the infection of *Macrobrachium rosenbergii* nodavirus. 2018 International Conference on Biochemistry, Molecular Biology and Biotechnology in conjunction with the 43rd Annual Conference of MSBMB and 25th Scientific Meeting of MSMBB. 15th-16th August, Four Points by Sheraton Puchong, Malaysia.

Thong, Q. X., and Tan, W. S. (2016). Purification of filamentous bacteriophage M13. 33rd Symposium of the Malaysian Society for Microbiology, 14th-17th December, Ramada Plaza Melaka, Malaysia.

Thong, Q. X., Ooi, M. K., Alitheen, N. B. M., Ho, K. L., and Tan, W. S. (2015). Selection of high affinity ligands to virus-like particle of *Macrobrachium rosenbergii* nodavirus from a phage-displayed library. 40th Annual Conference of The Malaysian Society for Biochemistry and Molecular Biology, 10th-11th June, Putrajaya Marriott Hotel, Malaysia.

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