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TARGETED 5-FLUOROURACIL-1-ACETIC ACID DELIVERY UTILISING CELL PENETRATING PEPTIDE CONJUGATED HEPATITIS B VIRUS-LIKE NANOPARTICLES TO SQUAMOUS CELL CARCINOMA A431

GAN BEE KOON

IB 2020 18

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By

GAN BEE KOON

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

June 2020

DEDICATION

This thesis is dedicated to

My kind-hearted parents who never stop giving of themselves in countless ways
and
My lovely brother and sisters for their love, endless support, and encouragement

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

TARGETED 5-FLUOROURACIL-1-ACETIC ACID DELIVERY UTILISING CELL PENETRATING PEPTIDE CONJUGATED HEPATITIS B VIRUS-LIKE NANOPARTICLES TO SQUAMOUS CELL CARCINOMA A431

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Chairman : Professor Tan Wen Siang, PhD
Institute : Bioscience

Skin cancer is a prominent global public health problem with no signs of plateauing in its incidence. As the most common treatments for skin cancer, surgical resection inevitably damages a patient's appearance, and chemotherapy has many side effects. Thus, the main goal of the study was to screen for a cell penetrating peptide (CPP) for the development of a targeting drug delivery system applying truncated hepatitis B core antigen (tHBcAg) virus-like nanoparticles (VLNPs) for skin cancer. With the application of biopanning utilizing Ph.D.™-12 Phage Display Peptide Library, a CPP with the sequence NRPDSAQFWLHH that specifically targets the human squamous carcinoma A431 cells was identified. The uptake of the CPP by A431 cells is an energy dependent process, and the CPP was proven to enter the A431 cells via the interaction with epidermal growth factor receptor (EGFR), a transmembrane protein that is involved in cell signaling pathways that control cell division and survival. Methyl-β-cyclodextrin (MβCD) and chlorpromazine hydrochloride (CPZ) inhibited the internalisation of the CPP into the A431 cells, suggesting the peptide entered the cells via clathrin-dependent endocytosis. To conjugate the CPP to tHBcAg VLNPs, the CPP was cosynthesised with peptide SLLGRMKGA (the nanoglue) at its C-terminus, and these sequences were separated by a linker (GGG). The resulting 24-residue peptide, NRPDSAQFWLHHGGG-SLLGRMKGA, was directly coupled covalently to the spikes of the tHBcAg VLNPs via carboxylate groups using the zero length cross-linker EDC and Sulfo-NHS. The CPP displayed on hepatitis B virus-like nanoparticles (VLNPs) via the nanoglue successfully delivered the nanoparticles into A431 cells. The CPP conjugated tHBcAg VLNPs (CPP-tHBcAg VLNPs) were further conjugated with 5-fluorouracil-1-acetic acid (5-FA) via the primary amine groups on the surface of tHBcAg VLNPs using Sulfo-NHS/EDC as the targeting ligand for cancer chemotherapy. Transmission electron microscopy showed that the tHBcAg VLNPs maintained their integrity after the conjugation of the CPP and 5-FA on their

surfaces. Approximately 833 5-FA molecules were conjugated covalently to each CPP-tHBcAg VLNP. 5-FA is the derivative of 5-fluorouracil (5-FU) which is less toxic but with enhanced cytotoxicity once it was coupled covalently to the CPP conjugated tHBcAg VLNPs. Furthermore, the targeting property of the CPP resulted in selective cytotoxicity of the 5-FA-CPP-tHBcAg VLNPs in EGFR-dependent manner. The MTT assay indicated that tHBcAg VLNPs conjugated with CPP and 5-FA significantly increased the cytotoxicity of 5-FA in A431 cells, which expressed the highest level of EGFR (2.14 folds) as compared with that of free 5-FU. The cytotoxicity of 5-FA-CPP-tHBcAg VLNPs was reduced in HT29 cells and HeLa cells, which have a lower number of EGFR per cell. This demonstrated that the CPP is a potential ligand for targeted delivery of VLNPs into skin cancer cells and other cancer cells, which overexpress epithelial growth factor receptor (EGFR). This paves the way to deliver drugs, nucleic acids and molecules into cells overexpressing EGFR. The application of this peptide is not restricted as a ligand to target and internalise VLNPs into cells, it can also be incorporated into other nanoparticles for a wider application in nanomedicine and targeting cancer imaging. In addition, the newly established drug delivery systems demonstrated that the tHBcAg VLNP is a potential nano-vehicle in chemotherapeutics to target various cells specifically by displaying different cell specific ligands at the tips of tHBcAg VLNPs.

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

PENGHANTARAN BERSASAR 5-FLUOROURACIL-1-ASID ASETIK MENGUNAKAN PEPTIDA PENEMBUSI SEL TERKONJUGASI PADA PARTIKEL NANO MENYERUPAI VIRUS HEPATITIS B KE KARSINOMA SEL SKUAMOSA A431

Oleh

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Kanser kulit merupakan satu masalah kesihatan global yang terkemuka tanpa tanda mendatar dalam kejadiannya. Sebagai rawatan yang paling umum untuk kanser kulit, pembedahan reseksi memusnahkan penampilan pesakit, dan kemoterapi mempunyai banyak kesan sampingan. Justeru itu, tujuan utama kajian ini adalah untuk menyaring peptida penembusi sel (CPP) untuk pembangunan sistem penghantaran bersasar ubat menggunakan partikel nano antigen teras hepatitis B yang dipendekkan (tHBcAg) dan menyerupai virus (VLNPs) untuk kanser kulit. Dengan aplikasi penyaringan 'biopanning' menggunakan Ph.D.™-12 perpustakaan faj memaparkan peptida, satu CPP dengan jujukan NRPDSAQFWLHH yang menyasar secara khususnya ke sel A431 karsinoma skuamosa manusia telah dikenalpasti. Pengambilan CPP oleh sel A431 adalah satu proses yang bergantung kepada tenaga dan CPP tersebut telah dibuktikan untuk menembusi sel A431 cells melalui interaksi dengan reseptor faktor pertumbuhan epidermal (EGFR), protein transmembrane yang terlibat dalam laluan isyarat sel yang mengawal pembahagian dan kelangsungan hidup sel. Methyl-β-cyclodextrin (MβCD) dan klorpromazin hidroklorida (CPZ) menghalang penembusan CPP tersebut ke dalam sel A431, mencadangkan bahawa peptida tersebut memasuki sel melalui endositosis bergantung kepada klathrin. Untuk konjugasi CPP tersebut kepada tHBcAg VLNPs, CPP tersebut disintesis bersama dengan SLLGRMKGA 'glu-nano' pada C-terminanya, dan jujukan ini dipisahkan dengan satu penggabung (GGG). Peptida hasilan 24-residu, NRPDSAQFWLHHGGGSLLGR-MKGA, telah ditambah terus secara kovalen pada puncak tHBcAg VLNPs melalui kumpulan karboksilat menggunakan penyambung-silang kosong EDC dan Sulfo-NHS. CPP yang terpapar pada partikel nano menyerupai virus hepatitis B (VLNPs) melalui glu-nano berjaya menghantarkan partikel nano tersebut ke dalam sel A431. tHBcAg VLNPs yang

terkonjugasi dengan CPP (CPP-tHBcAg VLNPs) tersebut dikonjugasi lebih lanjut dengan 5-fluorouracil-1-asid asetik (5-FA) melalui kumpulan amina utama pada permukaan tHBcAg VLNPs menggunakan Sulfo-NHS/EDC untuk digunakan sebagai ligan bersasar untuk kemoterapi kanser. Mikroskop transmisi electron menunjukkan bahawa tHBcAg VLNPs tersebut mengekalkan keutuhan mereka selepas pengkonjugasian CPP dan 5-FA pada permukaan mereka. Lebih kurang 833 molekul 5-FA telah dikonjugasi secara kovalen kepada setiap CPP-tHBcAg VLNPs. 5-FA adalah derivatif 5-fluorouracil (5-FU) yang kurang toksik tetapi sitotoksisitinya dipertingkatkan ketika ia ditambah secara kovalen kepada tHBcAg VLNPs terkonjugasi dengan CPP. Selanjutnya, keupayaan menyasar CPP menyebabkan kesitotoksisiti terpilih 5-FA-CPP-tHBcAg VLNPs bergantung kepada penzahiran EGFR. Ujian MTT menunjukkan bahawa tHBcAg VLNPs terkonjugasi dengan CPP dan 5-FA dengan ketaranya mempertingkatkan sitotoksisiti 5-FA dalam sel A431 yang mengekspresi tahap EGFR yang tertinggi (2.14 folds) berbanding dengan sel yang dirawat dengan 5-FU bebas. Sitotoksisiti 5-FA-CPP-tHBcAg VLNPs adalah lebih rendah dalam sel HT29 dan sel HeLa yang mempunyai nombor EGFR per sel yang lebih rendah. Ini menunjukkan bahawa CPP tersebut merupakan satu ligan yang berpotensi untuk penghantaran bersasar VLNPs ke dalam kanser kulit dan sel kanser yang mengekspresi reseptor factor pertumbuhan (EGFR) secara berlebihan. Ini membuka jalan untuk menghantar ubat, asid nukleik dan molekul-molekul ke dalam sel mengekspresi reseptor faktor pertumbuhan (EGFR) secara berlebihan. Aplikasi peptida ini tidak terhad sebagai ligan untuk penyasaran dan penembusan VLNPs ke dalam sel, ia juga boleh digabungkan dengan partikel nano yang lain untuk aplikasi yang lebih luas dalam perubatan nano dan pengimejan bersasar kanser. Selebihnya, sistem penghantaran ubat yang baru dibangunkan ini menunjukkan bahawa tHBcAg VLNP merupakan satu kenderaan nano yang berpotensi dalam kemoterapi untuk menyasar pelbagai sel secara khususnya dengan memaparkan berlainan jenis ligan-ligan sel yang khusus pada puncak-puncak tHBcAg VLNPs.

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

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABREVIATIONS

3D	3 dimensional
β	Beta
ºC	Degree celsius
%	Percentage
A_{595nm}	Absorbance at wavelength 595 nanometer
µL	Microliter
µm	Micrometer
Aa	Amino acids
APS	Ammonium persulfate
Arg	Arginine
Asp	Aspartic acid
ATCC	American Type Culture Collection
AUC	Area under curve
AuNPs	Gold nanoparticles
bp	Base pair
BSA	Bovine serum albumin
CBB	Coomasie brilliant blue
CIPs	Cell internalising peptides
cm	Centimeter
CO_2	Carbon dioxide
CPPs	Cell penetrating peptides
CPZ	Chlorpromazine
CT	C-terminal
Cys	Cysteine
Cyt-D	Cytochalasin D
dH_2O	Distilled water
DLS	Dynamic light scattering
DMEM	Dulbecco's modified eagle's medium
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
DOX	Doxorubicin

E.coli	*Escherichia coli*
EDC	1-Ethyl-3-(3-dimethylaminopropyl) *carbodiimide*
EDTA	Ethylenediaminetetraacetic acid
EGFR	Epithelial growth factor receptor
EPR	Enhanced permeability and retention
FBS	Fetal bovine serum
FITC	Fluorescein isothiocyanate
GFP	Green fluorescent protein
Glu	Glutamic acid
gp3	Gene 3 protein
gp41	Glycoprotein 41
h	Hour
HBcAg	Hepatitis B core antigen
HBV	Hepatitis B virus
HCl	Hydrochloride
hFGF	Human fibroblast growth factor
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
Hz	Hertz
IgG	Immunoglobulin G
IPTA	Isopropyl β-D-1-thiogalactopyranoside
Kb	Kilobase
kDa	Kilodaltons
L	Litre
LB	Luria-Bertani
Lys	Lysine
M	Molar
mAb	Monoclonal antibody
$MgCl_2$	Magnesium chloride
min	Minute
MIR	Major immunodominant region
mL	Milliliter
mM	Millimolar

MβCD	Methyl-β-cyclodextrin
MRI	Magnetic resonance imaging
MSNs	Mesoporous silica nanoparticles
nm	Nanometer
NaCl	Sodium chloride
NAGE	Native agarose gel elctrophoresis
NHDF	Normal human dermal fibroblast
NLS	Nuclear localisation signal
NMR	Nuclear magnetic resonance
NPs	Nanoparticles
NSA	N-terminal assembly
NT	N-terminal
PBS	Phosphate buffer saline
PEG	Polyethylene glycol
pfu	Plaque forming unit
PMO	Phosphorodiamidate morpholino oligomers
PNA	Peptide nucleic acid
rpm	Revolutions per minute
ROS	Reactive oxygen species
RT	Room temperature
s	Second
SCC	Squamous cell carcinoma
SDS-PAGE	Sodium dodecyl sulfate polyacrylamide gel
siRNA	Small interfering ribonucleic acid
ssDNA	Single stranded deoxyribonucleic acid
sulfo-NHS	N-hydroxysulfosuccinimide
SWCNT	Single wall carbon nanotubes
TAA	Tumour associated antigens
Tat	Trans-activating
TBE	Tris-borate acid
TE	Tris-EDTA
TEM	Transmission electron microscope
TEMED	Tetramethylethyleneamine

tHBcAg	Truncated hepatitis B core antigen
TP	Transportan
TPGS	D-alpha-tocopheryl polyethylene glycol 1000 succinate
TSA	Tumour specific antigen
UA	Uranyl acetate
UV	Ultraviolet
V	Volt
VLNPs	Virus-like nanoparticles
v/v	Volume over volume
wt%	Weight percentage
w/v	Weight over volume

CHAPTER 1

INTRODUCTION

Cancer, which refers to a collection of related diseases characterized by the development of abnormal cells that divide uncontrollably, often has the ability to spread throughout the body, infiltrate and destroy normal body tissue. It accounts for major fraction of disease related mortality worldwide. Recent GLOBOCAN data estimated 18.1 million new cases of cancer with 9.6 million deaths across the world in 2018 (Bray *et al*., 2018). In Malaysia, National Cancer Registry Report 2012-2016 revealed that a total of 115,238 new cancer cases were diagnosed for the period of 2012-2016, with a total of 82,601 deaths. Among the various types of cancer being diagnosed in humans, skin cancer is one of the commonest malignancies (Armstrong & Kricker, 2001). Skin cancer can be categorised into two major types: melanoma and non-melanocytic skin cancer (NMSC) (Simões *et al*., 2015). Melanoma, a cancer that develops from melanocytes, the pigment-containing cells, is the most life-threatening type of skin cancer which metastasises rapidly (Orthaber *et al*., 2017; Silpa & Chidvila, 2013). In 2015, 3.1 million cases of melanoma were diagnosed worldwide with 59,800 deaths (Wang *et al*., 2018). NMSC is a group of cancers that develop gradually in the upper layers of the skin. It is the most common cancer diagnosed in humans which represents approximately 35% of all malignancies (Shulstad and Proper, 2010). Two to three million new cases of NSMC are reported worldwide annually, and its incidence is expected to rise until the year 2040 (Burton *et al*., 2016; Orthaber *et al*., 2017). Malaysia National Cancer Registry Report 2012-2016 showed that NMSC is one of the 10 most common cancer in both male (3.5%) and female (2.2%), and the incidence rate of NMSC was more common in Chinese compared to other ethnics (Table 1).

Table 1: Incidence rate of skin cancer in Malaysia. (Summarized from Malaysia National Cancer Registry Report 2012 – 2016)

Incidence rate of skin cancer per 100,000 population by ethnicity (%)											
Chinese				Malay				Indian			
Melanoma		NMSC		Melanoma		NMSC		Melanoma		NMSC	
M	F	M	F	M	F	M	F	M	F	M	F
0.3	0.2	4.3	2.8	0.3	0.3	2.9	1.7	0.1	0.2	2.4	1.5

NMSC: Non-Melanocytic Skin Cancer **M**: Male **F**: Female

Skin cancer is generally diagnosed with dermatological examination, medical history, dermoscopy, and surgical biopsy with pathohistological biopsy. Further treatment of skin cancer is decided based on the anatomical site and size of the tumor. Surgical resection combined with chemotherapy is the most common method to treat skin cancer. However, surgery is highly invasive and fails frequently, especially in metastatic cancer (Konopke *et al*., 2014; Wanebo *et al*., 1996). Although

chemotherapy produces marked improvements in treatment and higher survival rates among cancer patients, the severe side-effects decrease significantly the patients' quality of life. In addition, most of the chemotherapeutic drugs have a narrow therapeutic index which always limit their systemic administration, and the non-targeting property of chemotherapeutic drugs further decrease the concentration of the drugs at the tumour site (Srinivasarao *et al*., 2015). In contrast to conventional chemotherapy, nanoscale delivery vehicles such as liposomes, polymersomes, metal-based nanoparticles (NPs), and protein-based NPs are able to provide a safer treatment with improved effectiveness by enclosing therapeutic molecules in the particle with a relatively higher cargo to carrier ratio (Din *et al*., 2017). In addition to these synthetic nanoparticles, a substitute type of NPs that has also gained much attention as a smart delivery system is the virus-like nanoparticles (VLNPs) (Yildiz *et al*., 2011). VLNPs are self-assembled, homogeneous NPs derived from viral capsids. They are noninfectious due to the absence of the viral genome in their capsids. The advantages of VLNPs over synthetic nanomaterials are their nanosize scaled, stable and highly ordered structural architecture which enhances their tumour permeability and retention (Nagayasu *et al*., 1999), monodispersity and ease of production (Huang *et al*., 2005), and distinct interfaces for functionalisation. Overall, it is less toxic, more stable, and more uniform as compared to metal nanoparticles, liposomes and polymer particles (Makadia & Siegel, 2011; Narang *et al*., 2013; Rohovie *et al*., 2017).

Non-targeted delivery in conventional chemotherapy often requires relatively high doses of therapeutic drugs in an attempt to achieve effective dose in the target tissue. However, high concentrations of therapeutic drugs tend to cause adverse effects that preclude maximum efficacy. Contrarily, targeted delivery can deliver optimised and higher dosages of therapeutic drugs to desirable site of action while alleviating unfavourable side effects. Therefore, targeted delivery approaches have shown a steep rise over the past few decades as one of the most promising therapeutics for cancers. The key advantages of targeted delivery as compared with conventional chemotherapy are: (a) the therapeutic will act mainly at the targeted site, reducing off-target side effects such as those shown by chemotherapy, and (b) the carrier in targeted delivery is able to enhance the concentration of therapeutic drugs within the cancer cells, thus improving the treatment efficacy. Antibody-drug conjugates were the first attempt of delivery vehicle development, and they have been widely developed. (Casi & Neri, 2015). However, there are some limitations in antibody-drug conjugates such as structural heterogeneity, instability and poor solubility (Casi & Neri, 2015; Dawidczyk *et al*., 2014). Furthermore, the amount of therapeutic cargos delivered via antibody-drug conjugates is limited, with only a few drug molecules per antibody (Casi & Neri, 2015). Alternatively, VLNPs can be a potent targeting delivery vehicle to overcome the aforementioned problems.

VLNPs are monodispersed, highly stable, and contain relatively large cargo capacities for the encapsidation of therapeutic cargos compared to antibody-drug conjugates. Consequently, they were used to encapsulate a variety of cargos, including chemotherapeutic agents, nucleic acids, fluorescent probes, peptides, proteins, polymers, and also other NPs (Anand *et al*., 2015; Ashley *et al*., 2011; Glasgow *et al*., 2012; Hovlid *et al*., 2014; Kelly *et al*., 2015; Lau *et al*., 2011; Qazi *et al*., 2016). The stability and solubility of the therapeutic molecules can be improved upon

encapsulation inside the VLNPs, thereby opening an opportunity to reconsider potential drugs with poor pharmacokinetics (Langer, 1998). On the other hand, the capability of VLNP surface modification enables the display of targeting moieties on its surface to confer targeting specificity. Antibody fragment appears to be the most commonly applied targeting ligand among the various types of targeting moieties, ranging from glycans to specific receptor-ligands such as folate and transferrin (Bruno, 2013; Ray & White, 2010; Sun *et al*., 2014; Zhou & Rossi, 2014).

In addition to the aforementioned targeting moieties, a new method based on the utilisation of cell penetrating peptides (CPPs) has also been developed for targeting delivery. CPPs are short peptides comprising nearly 30 amino acid residues which are able to cross the cell membrane without damaging the cells. Various CPPs with high affinity and specificity to hepatocarcinoma (Du *et al*., 2006; Jiang *et al*., 2006; Lo *et al*., 2008; Zhang *et al*., 2007), and non-small cell lung carcinoma (Chang *et al*., 2009; Zang *et al*., 2009) were discovered over the past decades. These CPPs are potential cell-targeting ligands that can be displayed on VLNPs for targeting delivery. The targeting ligands can be attached directly to the primary amino acid sequence of the coat proteins to allow presentation on exterior surface of the VLNPs (Suffian *et al*., 2017). In addition, reactive amino acids can also be applied to couple CPPs to the exterior of the capsids in repeated and consistent orientations (Biabanikhankahdani *et al*., 2016; Lee *et al*., 2012). Most approaches require covalent attachment, taking advantage of either native or nonnatural reactive amino acids, though genetic fusions to the primary amino acid sequence can also be used to display inserted CPPs (Rohovie *et al*., 2017).

Taken all together, it is hypothesized that VLNPs displaying CPPs can be used as novel promising nanocarriers for targeted delivery in cancer therapy. Therefore, the general aim of this study was to develop a targeted chemotherapy for SCC using VLNPs displaying CPPs. Cancer and normal cells were used to evaluate specific targeting ability and drug efficacy of these nanocarriers. The specific objectives of this study were:

1. to identify the CPP for A431 human squamous carcinoma cells using a phage displayed peptide library,
2. to conjugate the isolated CPP on tHBcAg VLNPs for specific delivery to A431 cells,
3. to conjugate chemotherapeutic drug, 5-fluorouracil-1-acetic acid (5-FA), on the CPP conjugated tHBcAg VLNPs for specific delivery to cancer cells overexpressing epithelial growth factor receptor (EGFR), and
4. to evaluate the cytotoxicity of 5-FU and various 5-FA formulation on A431, HT 29 and HeLa cells, and the apoptotic activity of 5-FU and various 5-FA formulations on A431 cells.

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