UNIVERSITI PUTRA MALAYSIA

HOMING PEPTIDES (RGD/iRGD) FUNCTIONALIZED ZEOLITIC IMIDAZOLATE FRAMEWORK-8 FOR TARGETED DELIVERY OF GEMCITABINE TO LUNG CANCER CELL

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March 2022

Chair: Mohd Basyaruddin Abdul Rahman, PhD
Faculty: Science

Lung cancer is a serious threat to human health, with metastasis being the top cause of cancer-related mortality. Gemcitabine (GEM) used in treating lung cancer operates in a non-selective manner tending to accumulate in normal tissue when cancer patients face a long duration of treatment. To mitigate the non-selective action of the GEM on the healthy tissues, there is a vital necessity to develop targeted nano delivery systems capable of regulating optimum doses selectively to cancer cells and minimizing untoward toxicity to normal tissues. Herein, a reticular nanoparticle zeolitic imidazolate framework-8 (nZIF-8) encapsulating GEM was surface-functionalized with selective homing systems (RGD; sequence Arg-Gly-Asp and iRGD; sequence Cys-Arg-Gly-Asp-Lys-Gly-Pro-Asp-Cys, respectively) through a straightforward, one-pot solvothermal reaction. Successful surface functionalization of nZIF-8 encapsulated GEM (GEM⊂nZIF-8) with RGD and iRGD, respectively, were characterized and systematically interpreted as a function of newly-formed functional groups, particle size, surface structure, surface topography, surface area, and surface charge. These functionalized GEM⊂RGD@nZIF-8 and GEM⊂iRGD@nZIF-8 not only responsive to an acidic environment but also controlled the GEM dissolution released rate (57.6 and 56.2%, respectively) after 48 h compared to non-functionalized GEM⊂nZIF-8 (76.0%). Both functionalized nanoparticles successfully increased the cellular uptake within cancerous human adenocarcinoma alveolar epithelial cells (A549), compared with non-functionalized nanoparticles. The highest uptake was shown by iRGD functionalized nZIF-8. The GEM⊂RGD@nZIF-8 and GEM⊂iRGD@nZIF-8 experienced not only efficient uptake within A549, but also induced obvious cytotoxicity (75 and 73%, respectively at 10 μg mL^{-1}) and apoptosis (62 and 74.9%) post 48 h treatment when compared to the GEM⊂nZIF-8. The apoptosis study verified the ability of functionalized GEM⊂iRGD@nZIF-8 to intensify the

apoptotic population in A549 while minimizing cell death (11%) in normal human lung fibroblast cells (MRC-5). Both functionalized nanoparticles reflect a potential outstanding treatment efficacy when GEM⊂RGD@nZIF-8 and GEM⊂iRGD@nZIF-8 demonstrated selective cytotoxicity (selective index, SI > 2) towards A549 than MRC-5. The follow-up study using healthy zebrafish embryos demonstrated enhanced permeation by both functionalized nanoparticles. At the lethal endpoint (96 h), all nanoparticles at all concentrations (7.81-250 μg mL^{-1}) did not elicit toxicity during embryonic and larvae stages. With the absence of nZIF-8, pristine GEM at a concentration of 250 μg mL^{-1} exhibited 33% of pericardially and yolk sac edema indicating adverse side effects of the chemotherapeutic agent alone towards healthy tissue. Taken together, it is believed that surface functionalization of zeolitic imidazolate framework-8 with RGD/iRGD holds great selective targeting and enhances the optimum chemotherapeutic dosage to human lung cancer with less unwarranted toxicity to normal human lung fibroblast.

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

KERANGKA ZEOLITIK IMIDAZOLAT-8 BERFUNGSIKAN PEPTIDA PANDU TUJU (RGD/iRGD) UNTUK HANTARAN GEMCITABINE SECARA BERSASAR KEPADA SEL BARAH PARU-PARU

Oleh

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Barah paru-paru merupakan ancaman serius bagi kesihatan manusia, dengan metastasis menjadi punca utama kematian. Gemcitabine (GEM) yang digunakan untuk merawat barah paru-paru berfungsi secara tidak-berpilih lebih cenderung berkumpul dalam tisu normal apabila pesakit barah menjalani rawatan dalam tempoh yang panjang. Bagi mengurangkan tindakan tidak-berpilih oleh GEM ke atas tisu normal, adalah menjadi keperluan penting untuk membangunkan sistem hantaran nano bersasar yang boleh mengawal selia dos optimum secara berpilih kepada sel barah dan meminimumkan ketoksikan yang tidak diingini pada tisu normal. Di sini, satu kerangka retikular nanopartikel zeolitik imadazolat-8 (nZIF-8) mengandungi GEM telah difungsikan permukaannya dengan sistem pandu tuju yang berpilih (RGD; urutan Arg-Gly-Asp and iRGD; urutan Cys-Arg-Gly-Asp-Lys-Gly-Pro-Asp-Cys, masing-masing) melalui tindak balas mudah solvoterma secara pukal. Kejayaan memungsikan permukaan nZIF-8 yang mengandungi GEM (GEM⊂nZIF-8) dengan RGD dan iRGD, masing-masing, telah dicirikan dan dianalisis secara sistematik dalam bentuk kumpulan berfungsi baru yang terhasil, saiz partikel, struktur permukaan, topografi permukaan, luas permukaan, dan cas permukaan. GEM⊂RGD@nZIF-8 and GEM⊂iRGD@nZIF-8 yang telah difungsikan bukan sahaja bertindak balas terhadap persekitaran berasid tetapi juga mengawal kadar pelepasan pelarutan GEM (57.6 dan 56.2%, masing-masing) selepas 48 jam berbanding dengan GEM⊂nZIF-8 (76.0%) yang tidak fungsikan. Kedua-dua nanopartikel yang difungsikan berjaya meningkatkan ambilan selular oleh sel barah manusia epitelial alveolar adenokarsinoma (A549), berbanding dengan nanopartikel yang tidak difungsikan. Pengambilan tertinggi ditunjukkan oleh iRGD berfungsi nZIF-8. GEM⊂RGD@nZIF-8 and GEM⊂iRGD@nZIF-8 tidak hanya menunjukkan kecekapan pengambilan oleh A549, tetapi juga mengaruh sitotoksik (75 dan 73%, masing-masing pada 10 μg mL^{-1}) dan apoptosis (62 and 74.9%) selepas rawatan 48 jam berbanding

GEM⊂nZIF-8. Kajian apoptosis mengesahkan kemampuan GEM⊂iRGD@nZIF-8 yang difungsikan untuk meningkatkan populasi apoptosis pada A549 sementara meminimumkan juga kematian (11%) pada sel normal fibroblas paru-paru manusia (MRC-5). Kedua-dua nanopartikel yang difungsikan menunjukkan potensi keberkesanan rawatan yang luar biasa apabila GEM⊂RGD@nZIF-8 dan GEM⊂iRGD@nZIF-8 menunjukkan kepilihan sitotoksik (indeks kepilihan, SI>2) terhadap A549 lebih dari MRC-5. Kajian susulan menggunakan embrio ikanzebra yang sihat menunjukkan peningkatan resapan oleh kedua-dua nanopartikel yang difungsikan. Pada titik akhir maut (96 jam), semua nanopartikel pada semua kepekatan (7.81-250 μg mL^{-1}) tidak menimbulkan ketoksikan semasa peringkat embrio dan larva. Dengan ketiadaan nZIF-8, GEM tulen pada kepekatan 250 μg mL^{-1} menunjukkan 33% edema pada kantung perikardi dan kuning telur menandakan kesan sampingan buruk dari agen kemoterapi tulen terhadap tisu yang sihat. Secara menyeluruh, adalah diyakini bahawa permukaan berfungsi RGD/iRGD pada kerangka imidazolat zeolitik-8 menunjukkan penyasaran berpilih yang sangat baik dan meningkatkan dos kemoterapeutik secara optimum kepada barah paru-paru manusia dengan mengurangkan ketoksikan yang tidak diingini pada normal fibroblas paru-paru manusia.

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

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AFM	Atomic force microscope
A459	Human adenocarcinoma alveolar epithelial cells
BET	Brunauer-Emmett-Teller
CendR	C-end Rule
DLS	Dynamic light scattering
ECM	Extracellular matrix
EPR	Enhanced permeability and retention
GEM	Gemcitabine
f_2	Similarity factor
FDA	Food and Drug Administration
FTIR-ATR	Fourier transform infrared-attenuated total reflection
FI⊂nZIF-8	Fluorescein encapsulated nZIF-8
FI⊂RGD@nZIF-8	Fluorescein encapsulated RGD functionalized nZIF-8
FI⊂iRGD@nZIF-8	Fluorescein encapsulated iRGD functionalized nZIF-8
GEM⊂nZIF	Gemcitabine encapsulated nZIF-8
GEM⊂RGD@nZIF-8	Fluorescein encapsulated RGD functionalized nZIF-8
GEM⊂iRGD@nZIF-8	Fluorescein encapsulated iRGD functionalized nZIF-8
HPLC	High-performance liquid chromatography
HRTEM	High-resolution transmission electron microscope
iRGD	Cyclic RGD
MOFs	MOF Metal-Organic Frameworks
MRC-5	normal human lung fibroblast cells
NRP-1	Neurolipin-1

NSCLC	Non-small cell lung cancer
nZIF-8	nanoparticle zeolitic imidazolate framework-8
PDT	Photodynamic therapy
PBS	Phosphate buffer saline
PXRD	Powder X-ray diffraction analysis
RGD	Arg-Gly-Asp
SEC	Size exclusion-chromatography
SI	Selective index
SLF	Simulated lung fluid
TGA	Thermal gravimetric analysis
WHO	World Health Organization
ZIFs	Zeolitic imidazolate frameworks

CHAPTER 1

INTRODUCTION

1.1 Research background

Lung cancer has one of the highest prevalence rates with the poorest prognosis amongst cancer types (Globocan, 2020). Over 50% of those diagnosed with lung cancer die within their first year of diagnosis, beyond which time, less than 18% will survive after the fifth year (Cruz *et al.,* 2011). Nevertheless, lung cancer survival rates are also influenced by the stage of cancer. For cases diagnosed when the cancer is still localized, the five-year survival rate for lung cancer is 56%. Unfortunately, only 16% of lung cancer are diagnosed at an early stage and when the tumor metastasizes, only 5% will survive after the fifth year (NIH 2018). In Malaysia, lung cancer accounting approximately 10% of all malignancies, with only 11% of the five-year relative survival rate. Nearly 90% of lung cancer patients in Malaysia are diagnosed with stage III or IV disease. At this stage, patients are commonly treated with various chemotherapeutic agents available (MySCan, 2018).

Traditionally, the primary approach for treating late-stage lung cancer remains chemotherapy, in which gemcitabine (GEM) is employed alone or in combination with other platinum-based chemotherapeutic agents such as cisplatin and carboplatin (Cavalcante & Monteiro, 2014; Ciccolini *et al.,* 2016; Manegold, 2004; Zappa & Mousa, 2016). Gemcitabine is a nucleoside analog that mediates its cytotoxic effects by inhibiting DNA synthesis. However, the non-selective action towards cancer cells and tends to accumulate with high doses leads to severe toxicity in normal cells (Golombek *et al.,* 2018; Hryciuk *et al.,* 2018). As such, there exists an urgent need to rectify this situation by developing targeted chemotherapeutic delivery systems that are capable of regulating optimal doses specifically to cancer cells without harming adjacent and ever-present normal, healthy cells (Cheok, 2012; Harrington & Smith, 2008; Wahgiman *et al.,* 2019).

To realize such systems, research attention has been placed on the creation and use of nanocarriers (Barenholz, 2012). Different types of nanocarriers such as liposomes, chitosan, iron oxide, and albumin have been formulated with varying degrees of success (Singh *et al.,* 2019). Indeed, several classes have exhibited excellent performance in clinical phase trials (Grodzinski *et al.,* 2019; He *et al.,* 2019). As a representative example, polyethylene glycol (PEG) have been clinically approved as a result of their ability to improve the low solubilities of hydrophobic chemotherapeutic agents (Gothwal *et al.,* 2016). Others based on lipids have also successfully improved the loading capacity of both hydrophobic and hydrophilic chemotherapeutic agents (Asmawi *et al.,* 2018; Chen *et al.,* 2020; Naderinezhad *et al.,* 2017). The general mechanism by which untargeted

nanocarriers operate is most often one of a passive-targeting strategy (R. J. Browning *et al.,* 2017), whereby the nanocarriers take advantage of solid tumor conditions such as inadequate lymphatic drainage. This leads to nanocarrier accumulation in the cancer cells for a longer period (Yu, B., and Tai, H.C, 2010). However, this mechanism is inefficient due to high interstitial fluid pressure that restricts the nanocarriers accumulation and is removed outward. Therefore, the use of ligand can promote the nanocarriers binding by attaching it to the cell membrane and preventing the nanocarriers from being removed from the tumor cells (Izci *et al.,* 2021).

To advance the effectiveness of chemotherapeutic nanocarriers, it is essential to focus on developing such systems based on active-targeting mechanisms (Kan *et al.,* 2011; H. Li *et al.,* 2018; Tamam *et al.,* 2019). The most straightforward method for achieving this is to functionalize the surface of the nanocarrier with active ligands that specifically target certain cancer cells; examples of which include antibodies and peptides (Egeblad *et al.,* 2010). In general, peptides are deemed increasingly promising as certain sequences (i.e. Arg-Gly-Asp; RGD and CRGDKGPDC; iRGD) are capable of selectively interacting with specific integrin receptors (αVβ3) overexpress on the tumor endothelial (Pridgen *et al.,* 2013). Furthermore, instead of integrins receptors interaction, iRGD peptide can also bind to neurolipin-1 (NRP-1) receptors via the CendR fragment (Sugahara *et al.,* 2010). The general mechanism of such an interaction is akin to a 'homing device', whereby the functionalized nanocarrier navigates to a cancer cell, docks as a result of selective interactions with the specific integrin and neurolipin-1 (NRP-1) receptors, and then releases the chemotherapeutic agent (Attia *et al.,* 2019; Freund *et al.,* 2018; Kang *et al.,* 2020; Muhamad *et al.,* 2018)

In the quest to realize a nanoparticle for the active and autonomous targeting of cancer cells for delivery of a chemotherapeutic payload, two requisite structural characteristics were considered: (i) high porosity, which affords the ability to load and regulate the chemotherapeutic agents; and (ii) surface customizability to ensure the active-targeting of cancer cells by the nanoparticles. Reticular materials that are governed by reticular chemistry meet both structural important requirements. Zeolitic imidazolate frameworks (ZIFs), are a subclass of reticular materials, known for their high porosity, well-defined structures due to their crystallinity, and structural diversity (Furukawa *et al.,* 2013). ZIFs have been demonstrated capable of loading optimal quantities of chemotherapeutic agents within their pores, their surfaces have proven modifiable by a wide range of moieties, and their biocompatibility has been established (Maleki *et al.,* 2020). Accordingly, ZIF-8, an archetypal reticular material adopting a sodalite structure, can be surface functionalized and can be efficiently loaded within and released from its pores (Dong *et al.,* 2019a; Lin *et al.,* 2020; Zheng *et al.,* 2017). The exclusive properties of ZIF-8 and good targeting manner owned by homing targeting peptides are the revolutionary ideas to solve the non-selective and accumulation issue of GEM.

1.2 Justification and hypothesis of the study

The reasons for pursuing reticular nanoparticles zeolitic imidazolate framework-8 (nZIF-8) as GEM nanocarrier is the fact that they are well-known to embody high porosity, large and modifiable surface areas, tailorable particle size, pH-responsive, and often enjoy inherent biocompatibility, which can improve the non-selective manner of GEM. The active modified nanoparticles with RGD or iRGD are able to direct to the cancer cells selectively, ligand-receptors bind, then offload the chemotherapeutic agent, GEM. Previous studies have shown the advantages of nZIF-8 after encapsulation and functionalization reactions in treating cancer cells, including breast and cervical cancer cells (Dong *et al.,* 2019b; Hao *et al.,* 2021; Lin *et al.,* 2020). Therefore, this study anticipated that these active nanoparticles would improve therapeutic effectiveness by selectively regulating the chemotherapeutic agent to lung cancer cells while causing less harm to healthy cells than those currently available.

1.3 Objectives

The aim of this research is to investigate the possibility of enhancing the non-selective activity of chemotherapeutic, gemcitabine (GEM) by encapsulating it into zeolitic imidazolate framework-8 nanoparticles (nZIF-8) that functionalized by linear (RGD) or cyclic homing peptide (iRGD). Therefore, this research focuses on the following objectives:

1. To encapsulate the GEM and surface functionalize the nZIF-8 using RGD or iRGD homing peptides.
2. To characterize the physicochemical properties of functionalized nanoparticles.
3. To evaluate the *in-vitro* GEM dissolution profile of functionalized nanoparticles.
4. To evaluate the *in-vitro* cellular uptake, cytotoxicity level, selectivity ability, and apoptotic induction of functionalized nanoparticles on lung cancer and normal cells lines.
5. To assess the permeability and potential toxicity developed by functionalized nanoparticles on healthy zebrafish embryos.

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