UNIVERSITI PUTRA MALAYSIA

BIOFUNCTIONALIZED TAPERED MULTIMODE FIBER FOR DENGUE VIRUS ANTIBODY DETECTION

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By

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The use of optical tapered fibers provides good sensitivity for the detection and measurement of biological and chemical compound especially biomolecules such as proteins, nucleic acids, antibodies, lipids, and carbohydrates. This thesis looks into the fabrication of a biofunctionalized tapered multimode fiber (TMMF) as a probe for anti-Dengue virus NS1 immunoglobulin G (anti-DENV NS1 IgG) detection. This device offers advantages by improving sensitivity, rapidness of detection, the size of device by making it more compact, and the field operability. In this research, TMMF was fabricated using a Vytran GPX-3000 glass processing system. A multimode fiber (MMF) with diameter of 125 µm is tapered until the size reduced to 10 µm with 10 mm of its waist length and transition length. The implemented technique is proved to induce some amount of light propagating outside the core of the tapered fiber and generates evanescent wave field (EWF) allowing high sensitivity to the changes in surrounding condition. The surface modification process onto TMMF involving three stages, namely silanization, activation with glutaraldehyde (GA), and immobilization of DENV NS1 glycoprotein on the surface of TMMF. This process is required to allow the interaction between inorganic silica TMMF and organic biomolecules. The silaned-TMMF treated with 3-amino-propyltriethoxysilane (APTES) and coated with 100 µg/mL of DENV NS1 glycoprotein specific to anti-DENV NS1 IgG antibodies in order to detect the presence of the antibodies. The generated EWF is applicable to measure the interaction between bound and unbound biomolecules on the surface by utilizing evanescent wave absorption (EWA) in the UV region. This biosensor device has the capability to detect the presence of anti-DENV NS1 IgG antibodies in a liquid sample in less than five minutes of incubation time. The concentration of the samples varies from 100 pg/mL until 1000 pg/mL with interval of 100 pg/mL. Results showed the sensitivity of the biofunctionalized TMMF to be 7×10^{-6} a.u./pg/mL with R-squared of 0.9938. The experiment done in this study demonstrates the potential of the biofunctionalized-TMMF to be developed and commercialized as a rapid and label-free sensor for dengue virus detection in the future.

Abstrak tesis dikemukakan kepada Senat Universiti Putra Malaysia
sebagai memenuhi keperluan untuk Ijazah Sarjana Sains

GENTIAN OPTIK MULTIMOD BERFUNGSI-BIO UNTUK MENGESAN ANTIBODI VIRUS DENGGI

Oleh

MOHD AZMIR BIN MUSTAPA

Jun 2017

Pengerusi: Muhammad Hafiz Bin Abu Bakar, PhD
Fakulti: Kejuruteraan

Penggunaan kaedah gentian optik bertirus memberikan kelebihan terhadap peranti ini dari segi kepekaan yang tinggi dalam pengesanan dan pengukuran sebatian biologi dan kimia terutamanya biomolekul seperti protein, asid nukleik, antibodi, lipid, dan karbohidrat. Tesis ini memberikan perhatian terhadap penghasilan gentian tirus multimod (TMMF) berfungsi-bio sebagai pengesan antibodi virus anti-denggi protein tidak berstruktur 1 immunoglobulin G (anti-DENV NS1 IgG). Peranti ini mempunyai kelebihan dari segi peningkatan kadar kepekaan peranti pengesan, kepantasan mengesan substrat, menjadikan saiz peranti lebih padat, dan keupayaan untuk beroperasi di lapangan. Di dalam kajian ini, TMMF dihasilkan dengan menggunakan sistem pemprosesan kaca Vytran GPX-3000. Gentian multimod (MMF) yang mempunyai ukuran saiz diameternya 125 µm telah ditiruskan sehingga 10µm, sementara panjang tirus dan panjang peralihan masing-masing adalah 10 mm. Kaedah yang digunapakai ini telah membuktikan bahawa beberapa jumlah cahaya akan terdorong untuk tersebar keluar dari teras gentian tirus dan mejana medan gelombang cepat berlalu (EWF) bagi menghasilkan kepekaan yang tinggi terhadap perubahan keadaan persekitarannya. Proses pengubahsuaian permukaan TMMF melibatkan tiga peringkat, iaitu menyalut permukaan gentian dengan bahan uji silana yang dikenali sebagai 3-aminopropiltrietoksisilana (APTES), pengaktifan dengan glutaraldehid (GA), dan pemegunan glikoprotein virus denggi protein tidak berstruktur 1 (DENV NS1) di atas permukaan tirus gentian tersebut. Proses ini adalah perlu bagi memastikan permukaan TMMF yang tidak organik saling bertindak dengan biomolekul berorganik. Seterusnya, permukaan TMMF yang telah dirawat dengan APTES dan GA telah disalutkan dengan 100 µg/mL glikoprotein DENV NS1 spesifik kepada antibodi anti-DENV NS1 IgG untuk mengesan kehadiran antibodi tersebut. EWF yang terhasil dapat digunakan untuk mengukur kadar saling bertindak antara biomolekul yang terikat dan tidak terikat di atas permukaan dengan menggunakan penyerapan gelombang cepat berlalu (EWA) di kawasan ultraungu (UV). Peranti pengesan-bio ini mempunyai keupayaan untuk mengesan kehadiran antibodi anti-DENV NS1 IgG di dalam sampel cecair kurang

daripada lima minit tempoh inkubasi. Kepekatan sampel yang digunakan adalah selang 100 pg/mL bermula daripada 100 pg/mL sehingga 1000 pg/mL. Data yang diperolehi daripada eksperimen ini telah menunjukkan kepekaan TMMF berfungsi-bio ini adalah 7×10^{-6} a.u./pg/mL dengan pekali penentuan (R^2) adalah 0.9938. Uji kaji yang dijalankan dalam pembelajaran ini menunjukkan TMMF berfunsi-bio ini berpotensi untuk dibangunkan dan dikomersialkan pada masa hadapan sebagai peranti yang mampu mengesan virus denggi dengan pantas dan tanpa menggunakan bahan kimia penanda.

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I certify that a Thesis Examination Committee has met on **15th June 2017** to conduct the final examination of **Mohd Azmir bin Mustapa** on his thesis entitled "**Biofunctionalized Tapered Multimode Fiber for Dengue Virus Antibody Detection**" in accordance with the Universities and University Colleges Acts 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Master of Science.

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LIST OF ABBREVIATIONS

APTES	3-aminopropyltriethoxysilane
AuNPs	Gold nanoparticles
bp	Base pair
BPC	Blood platelet count
BSA	Bovine serum albumin
C=N	Imine bond
C-domain	Constant domain
CS	Chitosan
DENV	Dengue virus
dH_2O	Distilled water
DHF	Dengue hemorrhagic fever
DNA	Deoxyribonucleic acid
DSS	Dengue shock syndrome
DVF	Dengue virus fever
ELISA	Enzyme-linked immunosorbent assay
EWA	Evanescent wave absorbance
EWF	Evanescent wave field
Fab	Fragment antigen binding
FBG	Fiber Bragg grating
Fc	Fragment crystallizable
FESEM	Field emission scanning electron microscope
FTIC	Fluorescein Isothiocyanate
GA	Glutaraldehyde
GUI	Graphic user interface
H-chain	Heavy chain
HF	Hydrofluoric acid
HRP	Horse reddish peroxidase
Ig	Immunoglobulin
IgG	Immunoglobulin G
IgM	Immunoglobulin M
L-chain	Light chain
LPFG	Long-period fiber grating
LSPR	Localized surface plasmon resonance
M	Molar
MAC-ELISA	M antibody-capture enzyme-linked immunosorbent
MMF	Multimode fiber
MSIPs	Micro-spot integrated pillars
Ni^{2+}	Nickel (II)
NPs	Nanoparticles
NS	non-structural protein

OFIS	Optical fiber immunosensor
-OH	Hydroxyl
PAA	Poly acrylic acid
PBS	Phosphate buffer saline
PNA	Peptide nucleic acid
QCM	Quartz crystal microbalance
RI	Refractive index
RNA	Ribosomal nucleic acid
RT-PCR	Reverse transcription polymerase chain reaction
RT-RPA	Reverse transcription-recombinase polymerase amplification
RT-RPA	Reverse transcription-recombinase polymerase amplification
SEM	Scanning electron microscope
SiNW	Silicon nanowire
SiNx	Silicon nitride
Si-O-Si	Siloxane
SMF	Single mode fiber
SPR	Surface plasmon resonance
S-S Bond	Disulfide bond
ssRNA	Single stranded ribosomal nucleic acid
TF	Tapered fiber
TIR	Total internal reflection
TMMF	Tapered multimode fiber
UV	Ultraviolet
V-domain	Variable domain

CHAPTER 1

INTRODUCTION

1.1 An overview of DENV fever

Dengue fever is a viral disease transmitted to human through the bite of the female *Aedes aegypti* mosquito [1-5]. The virus is a single stranded ribosomal nucleic acid (ssRNA) and it is responsible in producing dengue virus (DENV) in a host cell to cause the disease [6-8]. It consists of 11000 of nucleotide base and code for ten different categories of proteins (Figure 1.1) which are three structural proteins known as Capsid protein (C), preMembrane protein (prM), and Envelop glycoprotein (E) while the other seven are non-structural proteins which are consist of NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5 [3,9-11].

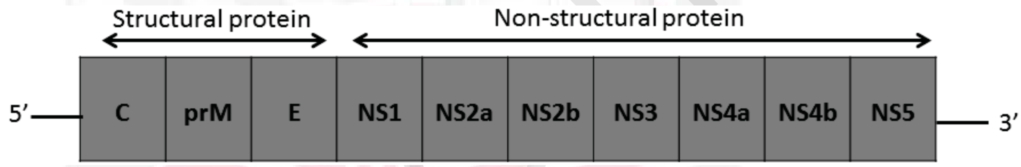

Figure 1.1: Genome structure of DENV.

The lipid proteins encapsulated the virus as an envelope protein. It is responsible to allow the virus attachment on the target host cell surface and subsequent replication [12]. The structure protein that surrounds the virus will help the virus to introduce their RNAs to the host cell and then the non-structural (NS) protein will play a role in producing new virus in the host cell [10,12].

Since the dengue fever shows typical symptoms such as fever, headache, muscle and joint pain thus, making it difficult to determine whether the patient has been specifically infected with dengue virus [13-15]. Example of other diseases showing similar symptoms to the DENV are normal fever, leptospirosis, and chikungunya. The latest is Zika virus, which transmitted to the human through the bite of similar type of DENV mosquitoes [16-19].

In Malaysia, dengue fever has become a very serious issue in recent years with rising number of cases [20]. Since year 2010 until 2015, the number of cases continues to increase annually with 2015 recording the highest number of cases (Figure 1.2) [20]. The DENV serotypes NS1 and NS2 are the most reported serotypes infecting human among the five strains [21]. The existence of multiple strains increases the possibility of secondary infection, which significantly alleviates the risk of contracting the potentially fatal dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) [22].

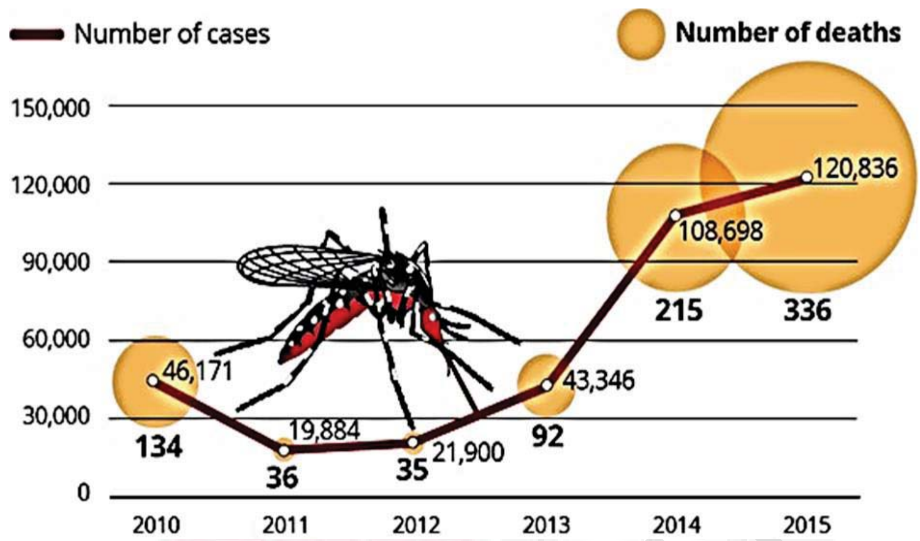

Figure 1.2: Statistic on the number of DENV cases in Malaysia over the past 15 years [23].

Therefore, early diagnostic and infection monitoring methods are crucial to prevent and control the outbreak of dengue virus. The detection of DENV IgG antibody is of high interest due to its abundance during secondary infection. Currently, the most popular technique used to detect the dengue virus is virological test and serological test. In clinical test activity, the virological test is used to detect the dengue virus infection at early stage of illness while serological test is used for further investigation to diagnose the acute phase of infection [8,24-26]. A common approach to detect Dengue virus infection in healthcare facilities is the use of rapid test kit, which utilizes the concept of immunoassay-based colorimetric on paper strips to indicate detection [27]. The most powerful technique used in clinical laboratory test for dengue detection is the enzyme-linked immunosorbent assay (ELISA), which has excellent performance in terms of specificity and sensitivity [27]. For monitoring purposes, blood platelet count (BPC) tests are performed periodically to ascertain the level of platelet in patients [5].

Nowadays, the use of optical fiber as biosensors has become increasingly attractive with multiple applications in the detection of biomolecules [28-30]. Both single mode fiber (SMF) and multimode fiber (MMF) have been explored for such purposes due to their many advantages such as high sensitivity, immunity to electromagnetic interference, and compact size [31]. MMF is of high interest as it offers added features such as coupling simplicity and good light confinement over wide wavelength range. Tapered multimode fiber (TMMF) in particular has proven itself to be a viable technology for sensing applications [32,33].

1.2 Problem statement

In recent years, NS1 strain has become an increasingly predominant serotype with more focus given on the detection of its IgG antibody. Although rapid test kit for dengue virus is normally sufficient to indicate infection, the approach can only produce qualitative result, which limits its deployment in disease monitoring. The test strip also lacks sensitivity and often produces false positives [34]. ELISA technique can overcome all these limitations but its detection process requires many chemical reagents, making it less economic for multiple monitoring tests and the operation restricted to trained lab personnel. While BPC test has been widely used for monitoring of patients, it is not a disease-specific approach as platelet drop can be a symptom of other viral infections as well. These two techniques involve complex preparation procedure and consume significant time.

1.3 Motivation

Hereby, an effective and accurate diagnostic technique is highly demanded for early, rapid, specific, and quantitative detection of the dengue virus antibody. The device should be portable for *in-situ* testing and can be operated with minimum complexity.

1.4 Research objectives

1. To fabricate a biofunctionalized TMMF sensing transducer by immobilizing the DENV NS1 glycoprotein on the tapered surface.
2. To investigate the sensor performance for detection of anti-DENV NS1 IgG antibody at various concentration.

1.5 Scope of research

There are several types of optical fiber biosensor technique used for biomolecules detection such as surface plasmon resonance, fiber Bragg grating (FBG), continuous tapered fiber and end tip tapered fiber [35-38]. It has also been employed in many applications such as in industry, manufacturing, security, biomedical, and many others [30]. In this research, it is focusing on a development of TMMF as a diagnosis tool to detect the anti-DENV NS1 IgG antibody. A chosen optimum waist diameter size of the TMMF undergoes the biofunctionalization process to allow the immobilization of DENV antigen on the surface of the TMMF and subsequently the complement antigen-antibody interaction. The goal of the research is to diagnose the dengue virus disease rapidly with the highly sensitive of biofunctionalized TMMF.

1.6 Thesis organization

This thesis is divided into five main chapters. Chapter 1 covers several sub-topics, which are introduction to dengue fever disease, problem statement, motivation of research, main objective of the research, and lastly is scope of research. Subsequently, continued to Chapter 2, which is the literature review. An overview of the theoretical background relevant to the work is provided in the chapter. In addition, this chapter discusses current research techniques used to diagnose dengue virus infections.

Chapter 3 elaborates the method used in this experiment starting from optimization of the TMMF, functionalize with APTES reagent, activation of it with GA, and immobilize it with DENV NS1 glycoprotein. The result for each step will be briefly explained in this chapter. This chapter also presents and reviews deliberately the results of detecting various concentration of DENV NS1 IgG antibody acquired from the detecting stage involved in the experimental work. The sensitivity and rapidness of detection will be discussed in this chapter. Lastly, Chapter 4 will conclude the overall findings of this research, which include significant contributions from this work as well as recommendations for future work.

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