

Applications of Photonic Biosensor Device for Monitoring Cancer Treatment

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Abstract

In this article, we discuss the creation of a photonic biosensor device as an additional diagnostic tool for cancer treatment monitoring. To get around detection reliability, sensitivity, specificity, compactness and cost concerns, the suggested device incorporates multidisciplinary principles from the reader/packaging, nano-biochemical, micro-fluidic and photonic platforms. The sensing is done by measuring the phase shift of the output signal, produced by the binding of the analyte on the functionalized aMZI surface and the photonic sensor is based on an array of six asymmetric Mach Zender Interferometer (aMZI) waveguides on silicon nitride substrates. The waveguides' morphological design results in an improved sensitivity (5000 nm/RIU) in compared to earlier technologies. By combining this platform with a cutting-edge biofunctionalization technique that uses material-selective surface chemistries and high-resolution laser printing of biomaterials, an integrated photonics biosensor device that makes use of disposable microfluidics cartridges is created. Blood serum samples from cancer patients are used to test the device. The device is used to identify two circulating biomarkers, periostin (POSTN) and transforming growth factor beta-induced protein (TGFB1), which are overexpressed by cancer stem cells.

Keywords: Analysis of blood serum • Cancer therapy treatment monitoring • Point of care • Biosensor • Optical sensor

Introduction

Strong, dependable, accurate and quick diagnostic tools are increasingly needed in the medical diagnostics sector for disease monitoring, patient screening and early illness detection, which will also help the idea of personalised medicine come to life [1,2]. Cancer is of particular relevance since it is one of the main causes of mortality worldwide, accounting for 14.1 million new cases and 8.2 million cancer deaths each year [3], with tumour metastasis being responsible for more than 90% of these fatalities [4]. In the EU, deaths from cancer outnumbered those from cardiovascular diseases as the primary cause of death (by more than 25%) and in the next years, cancer incidences and fatalities are anticipated to rise in step with the rise in life expectancy. However, the World Health Organization (WHO) asserts that if cancer is detected early and effectively treated using customised therapy strategies, cancer death rates can be reduced and patients have a better chance of surviving the disease.

Polymerase chain reaction (PCR), enzyme linked immunosorbent assay (ELISA), radioimmunoassay (RIA), immunohistochemistry (IHC) and flow cytometry [5-7] are currently used for the great majority of cancer diagnostics and are based on genomic and proteomic molecular analysis. Although these methods have been shown to be effective, they must be carried out in hospitals or laboratories, which are sometimes located far from the actual location of patient care and frequently require highly skilled professionals to operate. The creation of reliable, portable and robust diagnostic tools that will enable the identification of cancer biomarkers in settings like community hospitals,

doctor's offices and potentially even homes in the future will be a major problem in cancer therapy monitoring.

There is no doubt about the clinical significance of cancer stem cells and their part in tumour development, metastasis, treatment resistance and tumour recurrence. Cancer stem cells are the most aggressive and tumor-causing cells in tumours and they have been shown to stimulate the growth of primary tumours as well as to spread to distant regions and form secondary tumours (metastases). Also thought to withstand chemotherapy, they grow again after the course of treatment, causing a tumour recurrence. These recurrences progress to cancers that are fatally resistant and ever more invasive. Therefore, creating diagnostic methods that make it possible to find cancer stem cells is a significant advancement in the area. The specificity, dependability and accuracy of early cancer diagnosis as well as therapy monitoring are significantly improved by the simultaneous detection of two different proteins, each of which is identified by a distinct biorecognition element.

For the creation of such integrated devices, biosensor devices are required and depending on the target, may include antibodies, nucleic acids, or other biorecognition components. Various types of transducers, including electrochemical, optical and mass-based transducers, have been employed depending on the biological response. The most popular transducers used in proof-of-concept (PoC) devices are electrochemical ones because they are inexpensive, easy to use and can be mass produced in small sizes. Additionally, optical transducers outperform the majority of categories since they can identify a variety of cancer biomarkers and can increase sensitivity with various waveguide geometry.

In this article, we describe a disposable microfluidic cartridge-equipped Point-of-Care (PoC) system that is ultra-sensitive, dependable and small for detecting cancer biomarkers in blood. In order to fully integrate the aMZI sensor with light sources and detectors into a disposable cartridge, the photonic biosensor device relies on the fusion of a number of techniques from many fields. Up to six different biomarkers can be measured simultaneously using the designed technology. However, we concentrated on detecting the proteins periostin POSTN and transforming growth factor beta-induced protein (TGFB1), which are controlled by the stem cell transcription factor Snail in cancer cells (SNAI1).

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Materials and Methods

The photonic platform is based on the fabrication of an array of asymmetric Mach-Zehnder interferometers (aMZIs) using Si₃N₄ waveguides (TriPLeX) technology. These aMZIs are used as extremely sensitive refractive index-based photonic sensors for the analysis of blood circulating biomarkers and are extensively discussed elsewhere.

Based on an asymmetric double stripe Triplex shape that is specifically tuned for an 850 nm wavelength, the waveguide design employed for the sensor is based on it. Two Si₃N₄ layers and an intermediary SiO₂ layer make up the waveguide structure. It has a thin bottom stripe of stoichiometric Si₃N₄ measuring 35 nm, an intermediate layer of LPCVD SiO₂ (TEOS) measuring 100 nm and a top stripe of stoichiometric Si₃N₄ measuring 78 nm. The waveguide's core is made up of these three layers, which are constructed on a Si wafer with 6-micron thermal oxide. To completely encase the waveguide in SiO₂, a top cladding of an LPCVD SiO₂ (TEOS) layer is deposited on top of the waveguide structure. The design of the aMZI that our sensor uses as its interferometer. When light enters through the input port, it couples to the aMZI's waveguide and exits through the element's output port. There is a transfer function involved in the optical power transmission at the output port.

The cross-section of this sensor's aMZIs' waveguiding arrangement. It is built on the TriPLeX platform, which combines a thin waveguide core made of lower and upper silicon nitride strips with cladding layers made of surrounding silicon oxide layers. The upper silicon oxide layer is removed where the sensor arms of the aMZIs are located on the optical chip, allowing liquid biological samples access to the strip's surface. The target molecules may approach this surface or may actually be captured on it, depending on the application and the biochemical method being used. In either scenario, there will be a local change in the refractive index in the upper cladding of the aMZI sensing arm. The propagating mode's evanescent field detects this change and updates its effective index. The measurement of the aMZI wavelength shift can then be used to calculate the extent of this alteration.

Results and Discussion

A water solution (Tris-0.05% Tween20-1x non-fat dry milk) spiked with increasing concentrations of TGFBI (from 100 ng/mL to 2500 ng/mL) and POSTN (from 100 ng/mL to 2500 ng/mL) was used to test the antibody-functionalized biosensor at first with different concentrations of both recombinant POSTN and TGFBI on the same chip. To do this, the anti-TGFBI antibody (clone 348506), the anti-POSTN antibody (clone Stiny-1) and polyclonal mouse IgG, which was employed as a negative control, were biomodified into two of the six sensing aMZIs. The differential signals that were recorded after the sensor was incubated with the samples. By comparing the signals of each monoclonal antibody-modified sensor to the signal of the closest nearby reference mouse IgG-modified sensor, the differential signals were obtained. As a result of the binding of samples of both TGFBI and POSTN to their immobilised antibodies, which can occur on the same photonic chip, the results suggest a large level of specific binding as well as multiplex detection of various analytes. Even at the maximum applied concentration of 2.5 g/mL, binding for TGFBI was entirely specific, whereas for POSTN, non-specific binding was detected at concentrations of 1.0 g/mL and higher. It is unknown what caused the last cross-reactivity. As for the sensitivity of the assay, functionalized aMZIs with anti-POSTN antibodies were able to identify samples with concentrations as low as

10 ng/mL (results not shown) and detection of even lower quantities appeared to be highly possible. Anti-TGFBI antibodies were used to functionalize aMZIs and similar results were observed.

Conclusion

In this article, we discuss the creation of a reliable, compact biosensing system for the precise and extremely sensitive detection of protein cancer biomarkers, for the treatment monitoring of cancer disease and for the therapeutic response. This instrument works by combining many platforms (photonic, bioassay, functionalization and disposable microfluidics cartridge) into a small package. There were two methods used to validate the gadget. Real blood serum samples from a breast cancer patient as well as spiked samples of increasing complexity were used to validate the photonic platform. The integrated device was put to the test for the detection of bulk RI measurements by switching between PBS buffer with a standard NaCl concentration and PBS buffer with a reduced NaCl concentration.

Acknowledgment

None.

Conflict of Interest

None.

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