



## Detection of HER2 breast cancer biomarker using the opto-fluidic ring resonator biosensor

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### ARTICLE INFO

#### Article history:

Received 16 November 2009

Received in revised form 21 January 2010

Accepted 28 January 2010

Available online 4 February 2010

#### Keywords:

Breast cancer

HER2

Ring resonator

Optical biosensor

Label-free

### ABSTRACT

Protein biomarkers have recently been heavily researched in their roles in the detection, quantification, and monitoring of aggressive types of breast cancer. In this work, we describe a novel, label-free approach for detecting the HER2 extra-cellular domain breast cancer biomarker in human serum samples using the opto-fluidic ring resonator (OFRR). The OFRR incorporates microfluidics and optical ring resonator sensing technology to achieve rapid label-free detection in a small and low-cost platform. In this study, HER2 proteins were spiked in serum at varying concentrations. Results show that the OFRR is able to detect HER2 at medically relevant concentrations in serum ranging from 13 to 100 ng/mL in 30 min. Our work will lead to a device that can be used as a tool for monitoring disease progression in a low-cost sensing setup.

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### 1. Introduction

Breast cancer is the second most common type of cancer and affects around 200,000 women annually in the United States alone [1–3]. While the benefits of early diagnosis are well documented, it is equally important to monitor treatment and cancer progress to enhance therapeutic effectiveness and prevent relapse by the patient [4]. Recently, examining protein biomarkers has shown potential in the monitoring and diagnosis of many types of cancers [4,5]. One specific biomarker that is over-expressed in 20–30% of human breast cancers is the human epidermal growth factor receptor 2 (HER2, a.k.a. neu or ErbB2) [5–7]. The monitoring of HER2 is important because of its association with very aggressive types of breast cancer tumors and the high chance of relapse by the patient that is often correlated with these tumors [2,6,7]. It is also important because patients that express high levels of the HER2 biomarker can be effectively treated with a drug known as trastuzumab, or more commonly, Herceptin [6,7]. Existing testing procedures for detecting HER2 involve taking a biopsy of the tumor and using immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH) [8]. IHC involves the labeling of proteins in a tissue sample with fluorescent tags [9]. Similarly, FISH uses fluorescent labeling

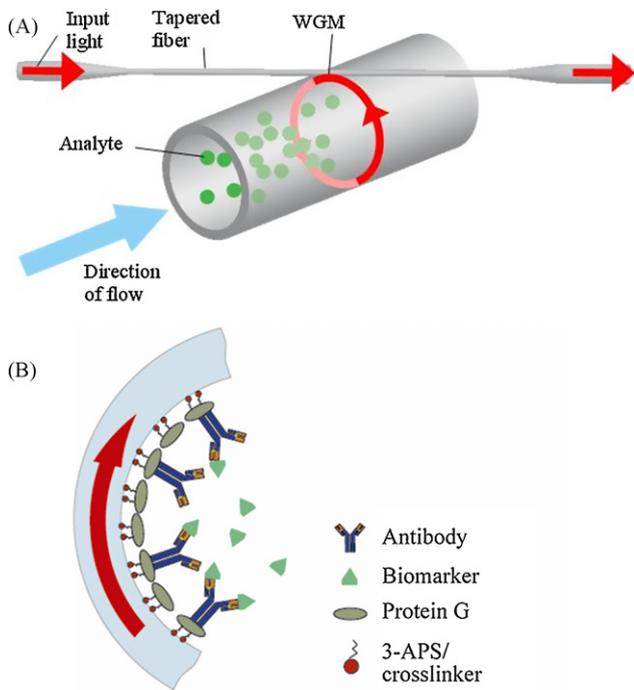
of specific DNA sequences or chromosomes in a tissue sample to identify genetic risk factors [10]. Unfortunately, both testing methods involve very invasive biopsies, expensive labeling detection methods, and long turn-around times [11].

One way of minimizing invasiveness for the patient is to look for biomarker proteins that are present in blood. HER2 is perfect for this kind of testing procedure because it is a transmembrane protein and the extra-cellular domain (ECD) of HER2 is often cleaved and shed into blood circulation. In blood, HER2 ECD can be detected in approximately 45% of patients with HER2 related breast cancers [12]. Healthy individuals have a concentration of HER2 between 2 and 15 ng/mL and breast cancer patients have elevated levels of HER2 between 15 and 75 ng/mL [13]. Monitoring these HER2 levels in blood can help evaluate the effectiveness of cancer treatments [14]. Decreased HER2 levels in blood serum could mean that a patient is responding to a particular treatment regime. Current commercialized detection methods for HER2 ECD in blood include enzyme-linked immunosorbent assay (ELISA) [15]. However, ELISA relies on expensive and difficult labeling procedures that attribute to long test times as well as needing dedicated personnel to perform the tests [13].

Rapid and label-free biomarker detection methods have been recently developed for the monitoring of biomolecules and could be used to detect cancer specific protein biomarkers [16–21]. Surface plasmon resonance (SPR) based biosensors are currently available commercially and have detection limits in the sub-ng/mL range in protein rich fluids [22]. While promising, these devices are expensive and are limited in high throughput applications due to

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**Fig. 1.** (A) Schematic of the OFRR sensor. (B) Schematic showing buildup of functional layers on OFRR surface.

the number of sensing channels and exhibit long test times due to the sandwich type assay used to increase sensitivity [22,23]. Other label-free detection techniques using piezoelectric microcantilever sensors (PEMSs) have demonstrated specific HER2 ECD detection at concentrations less than 10 ng/mL [13]. While the results show good selective binding to HER2 ECD, the technology has only been demonstrated in BSA, and its feasibility (and limitations) in detection of HER2 ECD in blood serum is yet to be investigated [13].

Recently, ring resonator sensing technology has been investigated to address weaknesses of established biomarker sensing techniques [16,24,25]. One particular embodiment developed in our lab is the opto-fluidic ring resonator (OFRR) that combines optical ring resonator architecture with microfluidics [16,26]. Shown in Fig. 1(A), the OFRR is a thin-walled capillary whose cross-section forms a high-Q ring resonator that supports circulating whispering gallery modes (WGMs). The WGMs have an evanescent field extended about 100 nm into the core and interact with the analytes captured on the OFRR inner surface. The WGM resonant wavelength (or spectral position),  $\lambda$ , is determined by [26,27]:

$$2\pi R n_{\text{eff}} = m\lambda, \quad (1)$$

where  $n_{\text{eff}}$  is the effective refractive index (RI),  $R$  is the OFRR radius and  $m$ , an integer number, is the angular momentum of the WGM. When analytes are captured on the OFRR inner surface (see Fig. 1(B)), the interaction of the WGM and the analyte results in a change in  $n_{\text{eff}}$  and hence a spectral shift of the WGM.

Due to its high Q-factor, the OFRR can achieve a RI detection limit of  $10^{-7}$  refractive index units (RIU) and a mass detection limit of sub-pg  $\text{mm}^{-2}$ , on par with the most sensitive biosensors [27–29]. The OFRR has been applied in many biomedical applications including CD4 and CD8 T-lymphocyte detection, viral particle detection, and DNA detection [27,28,30]. Very recently, rapid detection of cancer biomarker CA15-3 using serological samples from breast cancer patients was also achieved [31]. In this paper we utilized the OFRR for the rapid detection of breast cancer biomarker HER2

ECD. The results show that the OFRR is capable of rapidly detecting HER2 ECD in human serum at clinically relevant concentrations in approximately 30 min.

## 2. Experimental

### 2.1. Materials

98% Ethanol, 47% hydrofluoric acid (HF), 3-aminopropyltrimethoxysilane (3-APS), and recombinant protein G were purchased from Sigma–Aldrich (St. Louis, MO). Dimethyl pimelimidate dihydrochloride (DMP) cross linker was purchased from Pierce Chemicals (Rockford, IL). Neu (ER23) mouse monoclonal IgG antibodies were purchased from Santa Cruz Biotechnology (Santa Cruz, CA). HER2 biomarker protein was purchased from Bender MedSystems (Burlingame, CA). Serum was obtained from Millipore (Temecula, CA). Fused silica glass tubes of 1.2 mm outer diameter and 0.85 mm inner diameter were purchased from Sutter Instruments (Novato, CA)

### 2.2. Experimental setup

OFRRs were fabricated by pulling fused silica glass capillaries under intense heat created by dual CO<sub>2</sub> lasers. Upon heating, the capillaries were pulled until an outer diameter of approximately 150  $\mu\text{m}$  was obtained. To increase the sensitivity of the OFRR, a series of HF solutions were passed through the capillary. HF reduces the wall thickness of the OFRR from around 5  $\mu\text{m}$  to less than 3  $\mu\text{m}$ . These procedures have been described in detail in previous publications [26,27,29]. Tapered (diameter approximately 3.5  $\mu\text{m}$ ) fiber cable was produced by pulling an SMF-28 optical fiber under heat, thus exposing the fiber's evanescent field. By placing the tapered fiber cable in contact with the OFRR, light is coupled into and confined within the OFRR wall in circular resonances known as whispering gallery modes (WGM). When the resonant condition of the WGM is matched with the wavelength-modulated input light, a light intensity dip can be measured by a photodetector. This dip in light intensity can be used to identify the WGM spectral position in real time.

In this experiment, 1550 nm light from a tunable diode laser from Philips (San Jose, CA) was used as the coupling light source. The laser was then scanned at a rate of 0.5 Hz across approximately 100 pm. The light emitted from the tapered fiber cable was recorded with a photodetector read by a computer with a data acquisition card from National Instruments (Austin, TX). A Labview interface was utilized by the computer to control the laser scanning and data acquisition rate. WGM spectral positions were monitored and tracked via the LabView interface and recorded in real time as a sensing signal. The recorded spectral shift of the WGM was stored for post-experiment analysis using Matlab software. Flow of analyte through the OFRR was controlled with a syringe pump set at a rate of 1  $\mu\text{L}/\text{min}$ . Temperature fluctuations were reduced with the use of a thermoelectric cooling device (TEC).

### 2.3. Bulk refractive index sensitivity (BRIS) analysis of the OFRR

Establishing a relationship between spectral shift and the RI change inside the OFRR is very important to quantify the molecular density on the OFRR inner surface [32]. The characteristic response of the WGM to bulk RI changes is known as bulk refractive index sensitivity (BRIS). The sensitivity of the OFRR is measured in units of nm per refractive index unit (RIU). To establish this sensitivity, ethanol of known refractive index was passed through the OFRR in increasing concentrations. After generating data points, a trend line was fitted to the analyzed results. The slope of this trend line is the

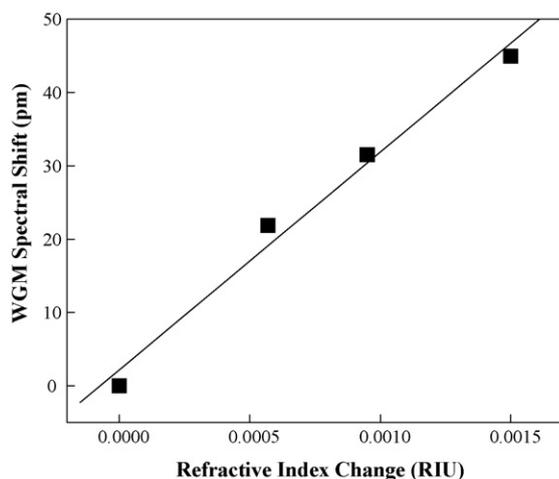


Fig. 2. Bulk refractive index sensitivity curve for the OFRR used in the HER2 biomarker measurements. Curve shows a sensitivity of 30 nm/RIU.

BRIS of the OFRR. In this experiment the sensitivity was found to be approximately 30 nm per RIU. Fig. 2 shows the sensitivity curve obtained for the OFRR used in the HER2 experiments.

#### 2.4. Functionalization of the OFRR inner surface

Effective surface chemistry needs to be employed in order to detect a small concentration of biomolecules in the OFRR with great selectivity. The OFRR surface was first charged by passing a low concentration of HF (<2%) through the capillary followed by a 10% EtOH wash. We then passed a solution of 4% 3-APS in 10% EtOH through the OFRR and build up an aminosilane layer on the inner surface. The OFRR was drained and this layer was allowed to bake at around 35 °C for 12 h. The temperature was controlled by a TEC unit located under the OFRR. The OFRR was further prepared by passing a mixture of 30 mg DMP crosslinker in 20  $\mu$ L PBS through the capillary. The crosslinker serves to bind protein G to the aminosilanes on the inner surface. Recombinant protein G orients the HER2 antibodies in an optimal position by binding the Fc region to capture the breast cancer biomarker ECD. In order to reduce or eliminate non-specific absorption of non-target proteins on the activated surface, a casein blocker was used in the running buffer. Excess protein G was rinsed with a mixture of 2% casein in PBS before antibodies were passed through the OFRR. A diagram of the OFRR surface after functionalization is shown in Fig. 1(B).

#### 2.5. HER2 protein biomarker capture measurements

For preparation of HER2 biomarker capture the OFRR was filled with a mixture of 2% casein in PBS and a baseline WGM spectral position was established. Stock HER2 protein was initially diluted to a concentration of 0.1 mg/mL in individual vials in PBS then frozen. To prepare HER2 proteins for experimentation, they were taken out of frozen storage and diluted in serum to concentrations reflecting medical relevance in humans. These samples were then passed through the OFRR in increasing concentrations. After each concentration increment reaches equilibrium, a PBS buffer wash was used to remove unbound proteins from the activated surface. After each experiment, the OFRR was rinsed with a small (<2%) concentration of HF to completely remove any activated surface components on the inside surface of the capillary. After this HF washing procedure, the OFRR was prepared for the next experiment.

### 3. Results and discussion

#### 3.1. Detection of HER2 breast cancer biomarker

Concentrations of HER2 biomarker chosen were 13, 16, 20, 25, 33, 50, 75, 100, and 250 ng of HER2 per mL. All tests were completed in approximately 30 min. The spectral shift resulting from each concentration was recorded and error bars from standard deviation were produced by running multiple experiments with the same concentration. Fig. 3 shows a typical sensorgram showing a net shift of around 4.5 pm. This sensorgram was obtained from an experiment with approximately 20 ng of HER2 protein per 1 mL of serum. After each concentration was passed through the OFRR, a wash with 2% casein in PBS buffer was initiated to remove unbound or loosely bound proteins from the protein rich serum on the antibody layer. The resulting spectral shifts of the tested concentrations are shown in Fig. 4. During the actual recording of HER2 biomarker as it interacted with the functional layer on the inner OFRR surface, the flow rate was held constant by a syringe pump with a rate of 1  $\mu$ L/min. It is important to note that in Fig. 4 a saturation effect was observed at the higher concentrations of biomarker. To confirm this, the data

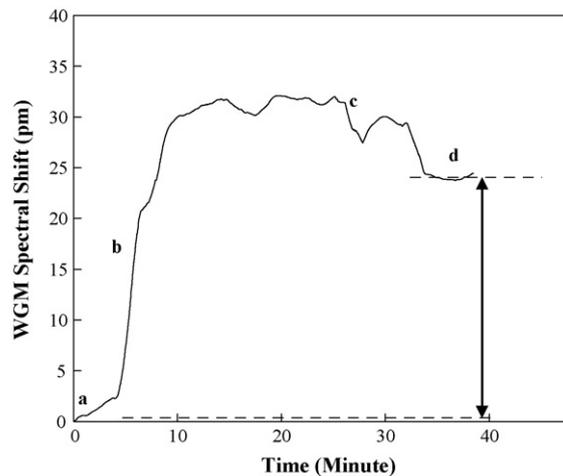


Fig. 3. Sensorgram showing the WGM spectral shift of 20 ng/mL upon introduction of HER2 ECD protein in serum. Point (a) represents the initial baseline. (b) Represents the introduction of HER2. (c) Represents the introduction of a PBS wash. (d) Shows the post baseline. Arrow shows the net shift of the WGM.

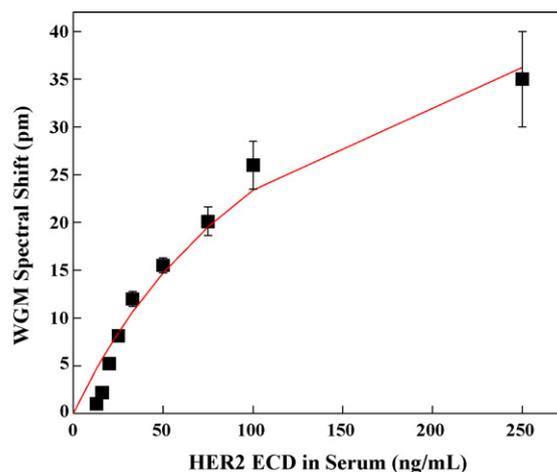
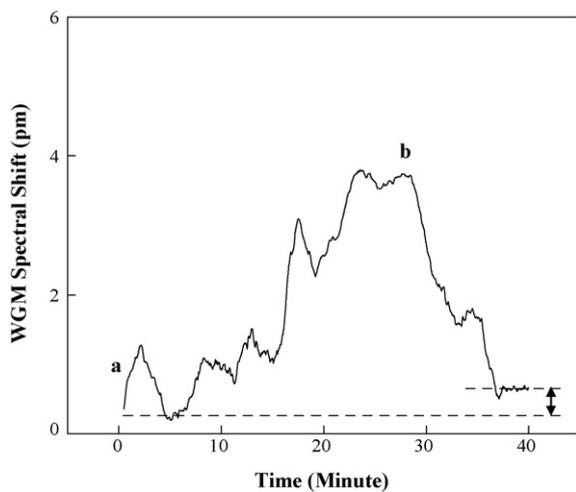


Fig. 4. Titration curve. (A) Results obtained from concentrations of HER2 biomarker in serum. Solid curve was developed from the Langmuir model shown in Eq. (2).  $\Delta\lambda_{\max}$  is 57.2 pm and  $K_d$  is 144.5 ng/mL.



**Fig. 5.** Negative control consisting of protein rich serum. Arrow indicates a net WGM spectral shift of 0.3 pm.

in Fig. 4 was fitted to a Langmuir isotherm model [33,34]:

$$\Delta\lambda = \Delta\lambda_{\max} \frac{c}{K_d + c} \quad (2)$$

where  $\Delta\lambda$  is the spectral shift,  $\Delta\lambda_{\max}$  is the maximum spectral shift,  $K_d$  is the dissociation constant, and  $c$  is the HER2 concentration. From this equation we found a  $\Delta\lambda_{\max}$  of 57.2 pm and a dissociation constant of 144.5 ng/mL. While such a saturation effect limits the sensor's dynamic range, the excluded concentrations represent biomarker protein levels that are not observed in typical human patients.

To ascertain the selectivity of the OFRR sensing region a negative control was run. This control consisted of a sample of serum with no HER2 proteins present. The results of the negative control are shown in Fig. 5. A total net shift of approximately 0.3 pm was observed after washing, indicating a high degree of selectivity of HER2 to the HER2 antibodies attached to the OFRR sensor. The high degree of noise observed at the beginning of the negative control was likely due to a small amount of non-specific binding due to a variety of proteins in serum and temperature fluctuations. Even with a small degree of non-specific absorption on the sensing region of the OFRR, the actual signal of HER2 binding can be easily resolved (the temperature induced noise level is on the order of 0.1 pm). Based on these results, we should achieve a limit of detection of well below 10 ng/mL. Increasing the selectivity of binding in a protein rich fluid such as serum still presents a problem. Further work may focus on finding a more efficient blocker or modifying the antibody procedures with streptavidin–biotin chemistry to strongly and specifically bind the target to the sensing area [31].

#### 4. Summary

We have demonstrated rapid, label-free, specific, and sensitive detection of HER2 ECD in serum at clinically relevant concentrations using the OFRR sensing technology. Future work will concentrate on increasing the selectivity of binding to the OFRR and further reducing the limit of detection. We will also use real patient samples from hospitals to further test the OFRR clinical utility. Our work will lead to a device that can increase accuracy of prognosis and monitor treatment effectiveness with low-cost (a few thousand dollars for fixed instruments and a few dollars for disposals) and rapid response (15–30 min). This device can further be packaged in a low-index polymer for increased mechanical robustness [35]. Since it performs label-free detection, the entire

detection procedures can be significantly simplified. Therefore, the device can potentially be handled by non-professional personnel outside central diagnosis laboratories.

#### Acknowledgement

We would like to thank the financial support from the Wallace H. Coulter Foundation Early Career Award.

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**Xudong Fan** received his PhD in physics from the University of Oregon, USA. From 2000 to 2004, he was a research scientist at Corporate Research Laboratories at 3M Company. Later he was an associate professor at the University of Missouri at Columbia. In 2010 he joined the Biomedical Engineering Department at the University of Michigan. His research interest includes optical biological and chemical sensors, optofluidics, bioMEMs, and nanophotonics. He is the recipient of 3M Non-tenured Faculty Award, Wallace H. Coulter Foundation Early Career Award, and the NSF-CAREER Award.