Graphene oxide-functionalized label-free optical fiber biosensor for highly sensitive detection of breast cancer biomarker CD44

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Abstract

Breast cancer remains the leading cause of cancer-related death among women worldwide, underscoring the urgent need for sensitive and non-invasive diagnostic tools. Cancer stem cells (CSCs), particularly those expressing the CD44 biomarker, play a pivotal role in tumor progression, metastasis, and therapy resistance. In this study, we present the development of a graphene oxide-functionalized, label-free optical fiber biosensor for the ultrasensitive detection of CD44 in biological fluids for breast cancer diagnostics. The sensor utilizes a spliced single-mode fiber with an enhanced backscattering tip to construct a Fabry-Pérot interferometric cavity, enabling precise refractive index interrogation. Surface functionalization involved sequential silanization, glutaraldehyde crosslinking, graphene oxide deposition (chemical and physical), and oriented antibody immobilization using carbodiimide chemistry and Protein G. Calibration with sucrose solutions demonstrated a refractive index sensitivity of 184.5 dB/RIU. Preliminary tests using human urine samples showed promising performance for attomolar-level CD44 detection. Compared to label-based systems, this label-free platform offers simplified fabrication, real-time signal acquisition, and compatibility with minimally processed samples, making it highly suitable for CSC-targeted diagnostics. Overall, the developed biosensor represents a scalable and biocompatible solution for early breast cancer screening and CSC profiling.

Introduction

Breast cancer is the most commonly diagnosed cancer in women worldwide, accounting for over 2.3 million new cases and approximately 685,000 deaths globally in 2020 alone, according to the World Health Organization (WHO) [1]. Despite advancements in therapeutic strategies, late-stage diagnosis remains a major contributor to high mortality, especially in low- and middle-income countries, where access to early screening is limited [2]. While the 5-year survival rate exceeds 90% for patients diagnosed at stage I, it drops below 30% for those diagnosed at advanced stages (III-IV) [3]. Moreover, tumor heterogeneity, therapy resistance, and metastasis remain significant challenges in breast cancer management [4]. Hence, there is an urgent need for sensitive, specific, and non-invasive diagnostic tools that can detect breast cancer at early stages. That is why the importance of identifying cancer stem cells(CSCs) among other biomarkers, heightens in the context of breast cancer diagnostics.

In various researches CSCs had shown their key role in surpassing tumor-initiating capabilities to those of spreading cancer cells beyond the tumor realms, cosequently

creating metastasis [5]. This capacity has been precisely described in Tang et al(2025), where triple negative breast cancer (TNBC) was researched as an inducer of lung cancer metastasis: breast cancer stem cells exosomes showed higher fibroblast activation for TNBC transportation [6]. Thus, considering CSC as a key for effective cancer diagnostics, among emerging molecular targets, CD44, a transmembrane glycoprotein involved in cell adhesion and migration, has been increasingly recognized as a promising biomarker associated with cancer stemness, invasion, and poor prognosis [7].

According to Chen et al. (2018), CD44 plays a pivotal role in sustaining cancer stem cell (CSC) properties, promoting epithelial–mesenchymal transition (EMT), and contributing to tumor invasion and recurrence, making it a compelling therapeutic and diagnostic target[8]. Supporting this, Lu et al. (2016) demonstrated through a meta-analysis of 4729 patients that high CD44 expression is significantly correlated with poor prognosis and advanced clinicopathological features in various cancers, including gastric cancer, further validating its prognostic value[9]. Historically, CD44 has also been highlighted by Naor et al. (2002) as a multifunctional molecule implicated in numerous oncogenic processes, including lymphocyte activation, tumor cell migration, and matrix remodeling, solidifying its status as a key biomarker in cancer diagnostics and a potential gateway for targeted detection strategies [10]. Meanwhile, regarding the most recent researches of CD44 protein in context of breast cancer, Roosta et al(2025) characterized CD44 as a cell proliferation, infiltration, angiogenesis, metastasis and prognosis correlated variety within the breast cancer staging comorbidity, calculating CD44 predicted expressions in patients' system through different stages of disease due to their ability to detect even subtle changes in refractive index(RI) at the sensor interface [11].

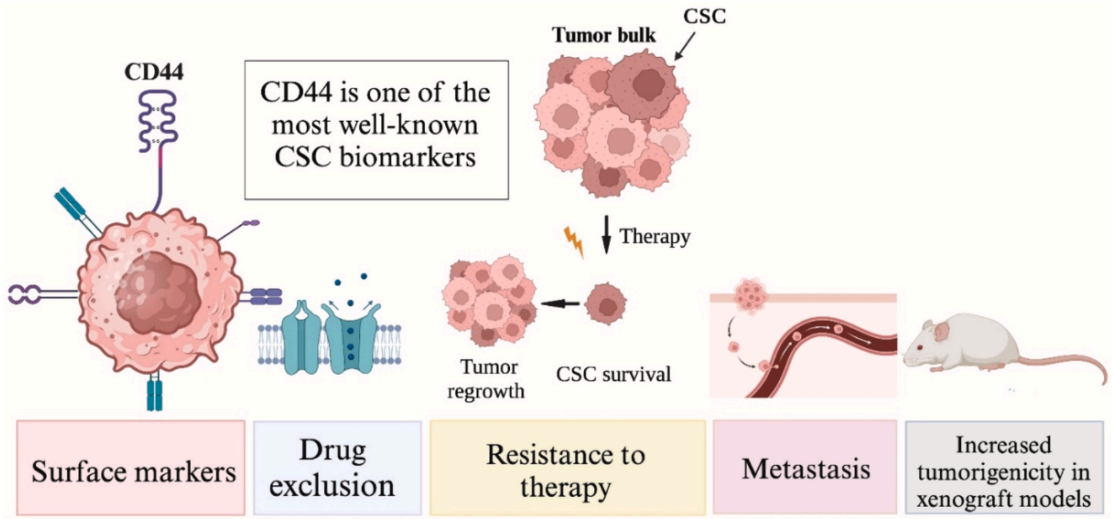


Figure 1. Key mechanisms of CD44 CSCs as a contributor of cancerous comorbidity shown in Nurlankyzy et al(2024)[12], using BioRender software (http://biorender.com).

After identifying the target of the biosensor, the type was chosen regarding its current relevance. Optic fiber biosensors were successfully implemented in diagnostics for their compactability, selectivity, high sensitivity and in vivo employment potential [13]. These sensors operate through light-matter interactions within the fiber structure and can be readily functionalized with biological recognition elements, such as antibodies, aptamers, or

peptides, to enable selective detection of cancer biomarkers [14]. Beyond their analytical precision, optical fiber biosensors are attractive for their compact size, remote sensing capabilities, and intrinsic biocompatibility [13]. Recent advances in nanomaterials, surface chemistry, and fiber design have further enhanced their performance, enabling reliable detection of proteins, extracellular vesicles, and even whole cells in complex biological matrices [15, 16]. As such, refractive index-based fiber-optic biosensors are rapidly emerging as a powerful platform for early cancer diagnostics, particularly when integrated with biomarker-specific surface functionalization strategies. For instance, in Kazhiyev et al(2023), an accessible design for highly sensitive optic fiber biosensors and its RI analysis through semi-distributed interferometer (SDI) was described [17]. A similar splicing technology approach is used in this work as well (Methods, Figure 2).

To enhance sensor sensitivity even beyond suggested splicing-cleaving design [17], this study demonstrates a biosensor with graphene oxide (GO) nanoparticles application. GO's large surface area and abundant oxygen-containing groups (e.g., carboxyl, hydroxyl, epoxy) facilitate strong covalent and non-covalent immobilization of biomolecules such as antibodies, significantly improving the sensor's capture efficiency and stability, which became a key in this biosensor's functionalization [18]. From an optical perspective, GO alters the local refractive index and enhances the light-matter interaction at the fiber interface, which increases the effective evanescent field and allows for a more pronounced shift in resonance wavelength upon analyte binding, which became a crucial advantage for detecting low concentrations of biomarkers like CD44 as for suggested biosensor in Liu et al.(2018) as well as in this research [19]. Adding to GO's advantages in the context of biosensing, its π-π stacking and electrostatic interactions contribute to the stronger and more stable immobilization of antibodies, leading to enhanced signal reliability and reduced baseline drift[20].

Notably, getting to the last but not the least key features of biosensors developed within this study, label-free biosensors possess such qualities like ability to target molecules that are not labeled or unseen on screening analysis, being applicable for CSC detection, while label-based detection relies on specific properties of labels, usually including usage of fluorescence, radioactivity and chemiluminescence particularly [21-23]. Despite label-based detection methods providing high sensitivity in early cancer diagnostics (Salama et al., 2007) and stem cell marker identification (Viter et al., 2016), these techniques often involve multiple preparation steps, labeling reagents, and complex signal amplification mechanisms [22,23]. Meanwhile, label-free biosensors offer a simplified and non-invasive alternative, enabling direct, real-time detection of molecular interactions without altering the analyte. Thus, label-free biosensors are particularly advantageous for detecting cancer stem cells (CSCs), as their fragile phenotype and low abundance make them sensitive to sample processing [21]. For instance, Bekmurzayeva et al. (2022) demonstrated attomolar-level detection of CD44, a key CSC biomarker, using a silanized label-free optical fiber sensor, minimizing assay complexity while maintaining exceptional sensitivity[24].

#	Assay type	LoD	Employed experimental samples	Detection target	Mechanism	Main advantages	Main drawbacks	Ref.

1	Label-free Raman spectroscopy with multivariate classification	Not mentioned	Human biopsy samples (10 cancerous, 10 normal)	Breast Cancer Biomarkers (multimodal system)	Raman-lensed fiber optic probe based on Raman spectroscopy with multivariate classification	-Potential in vivo use; -High classification accuracy(>99%); -Multimodal identification algorithms; -ease of fabrication.	-High cost of Raman spectrometer; -Complex signal acquisition; -Spectral overlap and noise sensitivity; -High dependence on algorithm training.	Kim et al., 2021 [27]
2	Sandwich-type gold coated optical fiber SPR	0.6 µg/mL (~5.16 nM)	Controlled buffer solutions	HER2 protein (breast cancer biomarker)	SPR-based thiolated HER2 aptamers on a gold-coated fiber, detecting via RI-induced plasmon resonance shifts, while binding of antibodies amplifies the signal in sandwich.	-Optimized sensor reproducibility; -Dual-mode detection:(both direct(label-free) and amplified(sandwich.	-Tested only in ideal buffer conditions; -Moderate label-free sensitivity.	Loyez et al., 2021 [25]
3	Electro-plasmonic tilted fiber Bragg grating (TFBG) sensor coated with gold	Sub-picomolar range (ultra-sensitive)	SK-BR-3 cells	HER2 protein (breast cancer biomarker)	Electrophoretic migration, which concentrates target proteins or cells onto a fiberic surface, with plasmonic resonance shifts.	-Both sensing surface and working electrode; -High sensitivity; -Whole-cell capture, which allows a potential for live cell diagnostics.	-Requires external voltage source and electrical circuitry; -Technically demanding fabrication; -Expensive.	M. Lobry et al., 2023 [26]
4	Optic fiber sandwich immunoassay, demonstrated in biosensor's antibody-antigen-antibody interaction	4.6 ag/mL-2300 ng/mL (0.2 aM-100 nM, i.e. 11 orders of magnitude)	Diluted human serum	CD44 (breast cancer biomarker)	Specific bonded immobilized antibodies and the target protein induce changes in the RI at the fiber surface, causing measurable shifts in the reflected optical signal in flow conditions.	-Ultrasensitive detection; -Adaptable for in vivo monitoring (tested in flow conditions); -Cost-efficiency and disposability; -Ease of fabrication; -Excellent capability for multiplexing,	-Requires advanced software for detection; -Sensitivity to RI lower than SPR; -Expensive analyzer.	Bekmurzayeva et al., 2022 [24]
5	Sandwich immunoassay fiber-optic biosensor functionalized with graphene oxide-coated fiber tips	Expected ~0.1–10 pg/mL (or ~0.5–100 fM)	Human urine (10 healthy + 10 cancer patients)	CD44 (breast cancer biomarker)	Antigen binding to surface-immobilized antibodies on a graphene oxide-functionalized optical fiber tip causes a measurable change in RI, transduced as a shift in backscattered light intensity.	-Ultrasensitive detection, high sensitivity; -Disposable and low-cost fabrication; -Versatile and modular surface chemistry.	-Time-consuming complex surface functionalization; -Fragility of tip-cleaved fiber; -Advanced software for data interpretation.	Current study

Table 1. Different label-free approaches in diagnostics.

To further illustrate the range and versatility of label-free biosensing approaches, Table 1 summarizes several recent studies employing specifically optical fiber-based biosensors for cancer biomarker/exosomes detection, particularly those relevant to breast cancer and CSCs such as CD44 and HER2. The comparison covers key assay types, limits of detection (LoD), sample types, detection mechanisms, and associated advantages and limitations. As seen in the table, most platforms achieve ultrasensitive detection (down to attomolar levels), and many are compatible with real biological samples such as serum, urine, and even biopsy tissue. Notably, both our study and Bekmurzayeva et al. (2022) highlight the feasibility of detecting CD44 with high specificity and wide dynamic range, underscoring the suitability of such systems for clinical CSC profiling[24]. Moreover, label-free platforms like Raman spectroscopy (Kim et al., 2021) and electro-plasmonic fiber gratings (Lobry et al., 2023) demonstrate how fiber-based platforms can integrate real-time diagnostics with multimodal analysis, despite certain technical limitations [26,27]. These data collectively emphasize that label-free optical fiber biosensors represent a clinically relevant and scalable solution for cancer diagnostics and early stages-related CSC detection.

Methods

Fabrication of Optical Fiber Interferometric Cavity

At first, the enhanced backscattering fiber that acts as reflector is spliced to a standard single mode fiber. To engineer a reflective cavity suitable for label-free optical biosensing, a segment of enhanced backscattering fiber (EBF) was employed as the distal reflector element. The EBF was precision-spliced to a conventional single-mode optical fiber using a high-accuracy fusion splicer to ensure minimal insertion loss and stable optical alignment. Subsequent to the splicing process, the EBF segment was manually cleaved at a distance of less than 1 mm from the splice junction using a high-resolution fiber cleaver, thereby producing a microcavity structure at the fiber tip. This cavity, featuring a reflective tip mirror and inherent Fabry-Pérot characteristics, forms the basis for the interferometric detection mechanism by enabling phase-sensitive spectral interrogation of refractive index fluctuations and biomolecular interactions at the fiber surface.

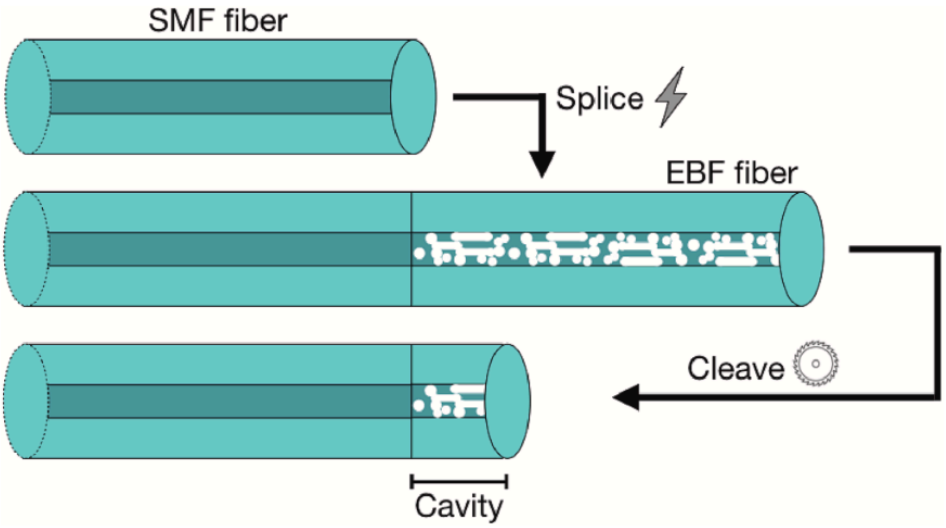


Figure 2. Fabrication of optic fiber for RI sensing and interrogation of the SDI interferometer via spice-cleaving approach demonstrated in Kazhiyev et al(2023)[17].

Refractive Index Calibration of the Sensor

The interferometric response of the fabricated optical fiber sensor was quantitatively calibrated using aqueous sucrose solutions of known refractive index (RI) values. A series of five RI standards were prepared by incrementally titrating 400 µL aliquots of 40% (w/v) sucrose solution into an initial 6 mL volume of 10% sucrose, housed in a custom-fabricated polystyrene vial. At each concentration point, the distal tip of the sensor was immersed horizontally into the solution, and spectral shifts were monitored under ambient temperature conditions. The resulting resonance wavelength displacements, corresponding to changes in the external refractive index, enabled the determination of the RI sensitivity and linearity of the optical sensor response, which are critical parameters for biosensing performance evaluation. Later, the saved wavelength for each concentration is analyzed by code software, where the sensor's RI sensitivity is calculated. Only those sensors that surpassed 100 dB/RIU are accepted for functionalization, while the rest are refabricated.

Pre-Functionalization Cleaning and Silanization of Fiber Surface

Prior to surface modification and biofunctionalization, the optical fiber sensors were subjected to rigorous decontamination to eliminate organic residues and promote silanol group exposure. The distal 2–3 cm of each fiber was immersed in freshly prepared Piranha solution (a 4:1 mixture of concentrated sulfuric acid and 30% hydrogen peroxide) for 15–20 minutes at room temperature, performed under a fume hood due to the highly exothermic and oxidative nature of the reaction. This oxidative treatment effectively hydroxylated the silica surface, thereby enhancing its reactivity for subsequent silanization.

After cleaning, fibers were rinsed thoroughly with deionized (DI) water (>18.2 MΩ·cm) and dried under a stream of high-purity nitrogen gas. Silanization was performed by incubating the fibers in a 1–5% (v/v) solution of (3-aminopropyl)trimethoxysilane (APTMS) in anhydrous methanol for 30–60 minutes at ambient temperature with gentle agitation. The amino-functional silane molecules covalently bonded to the hydroxylated silica surface via condensation reactions, producing a stable aminosilane monolayer. Excess APTMS was removed by triple rinsing with methanol, and fibers were subsequently thermally cured in a convection oven at 110 °C for 60 minutes to facilitate monolayer condensation and enhance coating uniformity.

Initial Biofunctionalization via Glutaraldehyde Crosslinking

To prepare the silanized surfaces for biomolecule immobilization, fibers were incubated in 25% (v/v) aqueous glutaraldehyde solution for 90 minutes at room temperature. Glutaraldehyde served as a bifunctional crosslinker, forming Schiff base linkages between its aldehyde termini and the exposed primary amines on the APTMS-modified surface. The functionalized fibers were rinsed thoroughly with sterile phosphate-buffered saline (PBS, pH 7.4) to remove unbound glutaraldehyde.

To enable preliminary biorecognition interface formation, the aldehyde-activated surfaces were incubated with 500 µL of anti-CD44 antibody solution at 4 µg/mL (diluted from a 100 µg/mL stock) either for 1 hour at room temperature or overnight at 4 °C. Following antibody immobilization, unreacted aldehyde groups were passivated by incubation with 10% methoxy-polyethylene glycol (mPEG) or 1% bovine serum albumin (BSA) in PBS, both of which act as nonspecific adsorption blockers. Final PBS washes were applied prior to further functionalization.

Graphene Oxide Functionalization and Layer Stabilization

Preparation of Monodisperse Graphene Oxide Solution

Graphene oxide (GO) powder (10 mg) was dispersed in 5 mL of DI water via probe ultrasonication for 30 minutes at 40% amplitude. The dispersion was subjected to centrifugation at 14,000 rpm for 15 minutes at 4 °C to remove multilayer GO aggregates. The supernatant containing monolayer or few-layer GO nanosheets was collected and diluted to a final concentration of 2 mg/mL for use in coating procedures.

Chemical Anchoring via APTES–GO Coupling

For stable chemical immobilization of GO onto the optical fiber surface, a secondary APTES-based silanization step was performed. Fibers were immersed in a freshly prepared 5% (v/v) APTES solution in ethanol for 1 hour at room temperature, facilitating condensation between silanol and APTES alkoxy groups. Ethanol washing removed unbound APTES, and fibers were dried and baked at 70 °C for 30 minutes to reinforce Si-O-Si bonding.

To chemically deposit GO, the silanized fibers were incubated in 1 mL of 1.0 mg/mL GO solution at 42 °C for 3 hours. In this step, epoxy groups present on the GO sheets reacted covalently with the surface amine groups of APTES through nucleophilic ring-opening, forming a chemically anchored monolayer.

Multilayer GO Deposition by Physical Adsorption

To further augment GO coverage and improve sensor surface uniformity, two successive physical adsorption cycles were conducted. In each cycle, fibers were immersed in fresh GO solution (1 mg/mL, 1 mL) and incubated at 42 °C for 3 hours under partial evaporation conditions, promoting non-covalent adsorption of GO nanosheets via π-π stacking and van der Waals interactions. After each cycle, fibers were rinsed in DI water and air-dried[20]. Important step is also to remove weakly bound GO and consolidate the surface coating, the GO-functionalized fibers were immersed in DI water for 30 minutes and then oven-dried at 70 °C for 1 hour.

Oriented Biofunctionalization for CD44 Detection

Carbodiimide Activation and Antibody Immobilization

Surface carboxylic groups introduced via GO were activated using carbodiimide chemistry to enable covalent coupling of recognition elements. Fibers were incubated in an aqueous solution containing equimolar concentrations of

1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC; 0.4 M) and N-hydroxysuccinimide (NHS; 0.1 M) for 20 minutes at room temperature. The EDC/NHS system formed amine-reactive NHS esters from surface carboxyls, which enabled efficient conjugation to proteins. Excess reagents were removed by washing in PBS.

Next, fibers were immersed in 3 µg/mL Protein G solution for 2 hours to ensure Fc-specific antibody orientation. After washing, a 4 µg/mL solution of goat anti-human IgG was applied for 2 hours to establish a secondary anchoring layer. Fibers were again washed with PBS to remove unbound proteins.

Blocking and Final CD44 Antibody Conjugation

To prevent nonspecific adsorption, fibers were blocked with 1% (w/v) BSA in PBS for 1 hour at room temperature. For final immobilization of the target-specific recognition molecule, fibers were incubated with 500 µL of anti-CD44 antibody at a concentration of 4 µg/mL (prepared from a 100 µg/mL stock solution), either at room temperature for 1 hour or overnight at 4 °C. Unbound antibody was removed via multiple PBS rinses, and sensors were stored at 4 °C in PBS until use.

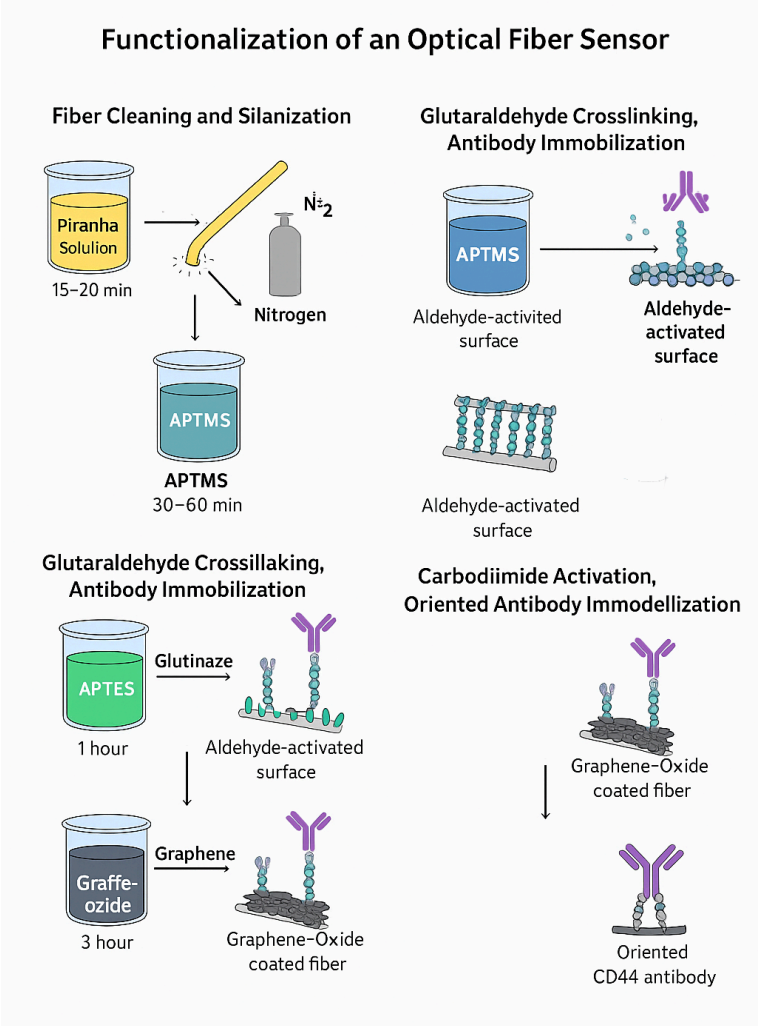


Figure 3. Detailed illustration of the entire functionalization process.

Results

By August 8, 2025, 8 measurements were conducted with healthy human urine samples and analysis of them was delayed before reaching 10 samples for healthy urine. Then, the laboratory requests 10 cancerous urine samples to confirm the biosensor's CD44 detection capacity.

Now, during the sucrose calibration process described in ‘Methods’ section above, the highest RI sensitivity achieved was 184.4873 dB/RIU, demonstrated below in details.

A

B

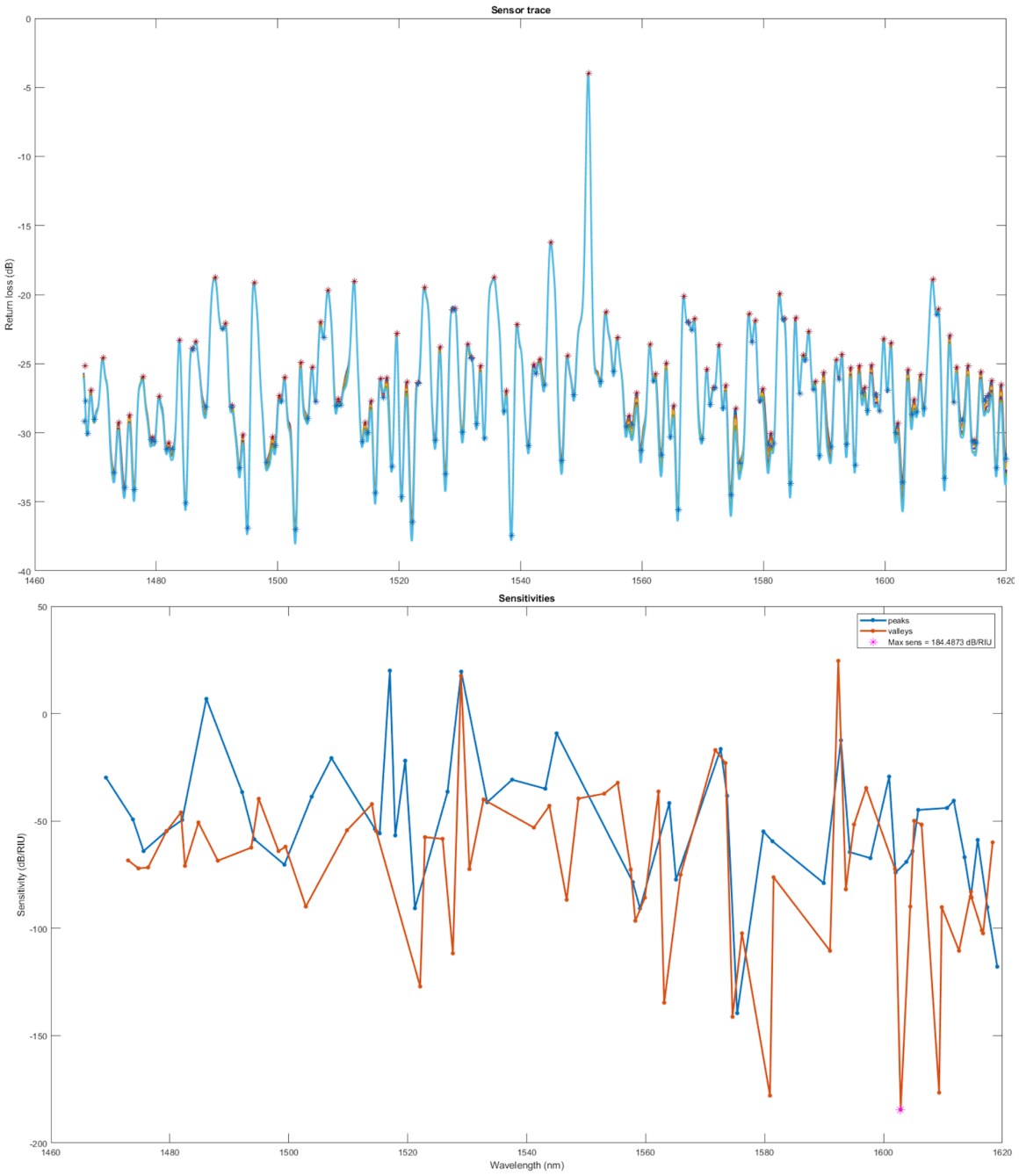


Figure 4. Calibration results, sucrose concentration calibration for biosensor’s RI sensitivity evaluation.

A. Interferometric spectra (Return Loss vs Wavelength) of the optical fiber sensor recorded across the 1460-1620 nm range. Spectral responses were obtained in sucrose solutions of varying concentrations (10%-20% w/v), corresponding to refractive indices ranging from 1.3472 to 1.3640 at 20 °C (Haynes, W. M. (Ed.). (2016). CRC Handbook of Chemistry and Physics (97th ed.). CRC Press.). The progressive shift of interference peaks toward longer wavelengths with increasing refractive index confirms the sensor's responsiveness and forms the basis for calibration of RI sensitivity.
B. Wavelength-resolved sensitivity of the interferometric sensor calculated from spectral peak and valley shifts in response to changes in refractive index. The blue and red traces represent sensitivities derived from spectral peaks and valleys, respectively. A maximum sensitivity of 184.5 dB/RIU was observed near 1600 nm, indicating optimal responsiveness in this region for label-free biosensing.

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