Single-molecule detection of biomarker and localized cellular photothermal therapy using an optical microfiber with nanointerface

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For early-stage diagnostics, there is a strong demand for sensors that can rapidly detect biomarkers at ultralow concentration or even at the single-molecule level. Compared with other types of sensors, optical microfibers are more convenient for use as point-of-care devices in early-stage diagnostics. However, the relatively low sensitivity strongly hinders their use. To this end, an optical microfiber is functionalized with a plasmonic nanointerface consisting of black phosphorus–supported Au nanohybrids. The microfiber is able to detect epidermal growth factor receptor (ErbB2) at concentrations ranging from 10 zM to 100 nM, with a detection limit of 6.72 zM, enabling detection at the single-molecule level. The nanointerface-sensitized microfiber is capable of differentiating cancer cells from normal cells and treating cancer cells through cellular photothermal therapy. This work opens up a possible approach for the integration of cellular diagnosis and treatment.

INTRODUCTION

Single-molecule detection has been extensively explored because it improves our understanding of many fundamental biological processes (1). Protein cancer biomarkers, which can be found in serum, tissue, and body fluids, play an important role in the prognosis, diagnosis, and therapy of cancers (2). As in early-stage diagnostics, the concentration of biomarkers is ultralow, and there is a strong demand for sensors that can rapidly detect biomarkers with ultrahigh sensitivity or even at the single-molecule level (3, 4). Among the existing sensing methods, the refractive index (RI)–based optical transducers have the notable advantage of label-free nature (5). Compared with nanosensors, optical microfibers, with their low cost, flexibility, and millimeter-scale length, are more convenient for use as point-of-care (POC) devices in early-stage diagnostics (5). However, the relatively low sensitivity at picomolar concentrations strongly hinders their use. Furthermore, single-molecule detection seems hard to realize for microfibers that are millimeters in length and micrometers in diameter. In recent years, researchers have focused on exploring sensing mechanisms to enhance fiber sensitivity (6, 7). Since the RI–based microfiber sensor detects the RI change near the fiber surface induced by a molecular binding interaction through the evanescent field of the fiber (8), enhancing the evanescent field is an efficient strategy to improve the sensitivity. Various approaches, including a capillary-based optofluidic optical microfiber (9) and an optical microfiber with silver nanoparticle electromagnetic enhancement (10), have been fabricated, and the limit of detection (LOD) reached 6.82 × 10⁻¹⁷ M (10).

Localized-surface plasmon resonances (LSPRs) in metallic nanostructures have been demonstrated to effectively enhance the evanescent field in several works (11–13). Nevertheless, the resonance typically occurs at visible wavelengths, while the operation wavelength of the microfiber transducer is in the communication window (1550-nm band) because most of the components used to construct the sensing system come from the fiber optic communication industry. Here, we develop gold nanohybrids (a mixture consisting of Au triangular nanoprism and Au nanoparticles integrated through electrostatic attraction) to tune the plasmon resonances to the communication window, thereby enhancing the evanescent field of the microfiber transducer. A promising two-dimensional layered material, black phosphorus (BP) (14, 15), was used as a spacer to support the Au nanohybrids, stimulate the photothermal effect, and optimize the LSPR enhancement. With the enhancement of the nanointerface consisting of BP-supported Au nanohybrids, the microfiber exhibits an ultrahigh sensitivity for detecting epidermal growth factor receptor (ErbB2, a well-established breast cancer biomarker (16)) at the single-molecule level and differentiating breast cancer cells from normal cells. The nanointerface shows the ability for cell-targeted photothermal therapy under near-infrared irradiation from the microfiber. This work demonstrates a potential approach for the integration of cellular diagnosis and treatment.

RESULTS

Design of the microfiber sensor with a nanointerface

A silica microfiber taper with a diameter of 7.1 μm and a waist length of 1.2 mm was fabricated from a single-mode fiber by heating and stretching techniques (fig. S1). The microfiber taper functions as an interferometer and generates interference fringe in the transmission spectrum (fig. S2). The fringe pattern comes from the interference between the fundamental mode (HE₁₁) and the higher-order mode (HE₁₂) (fig. S3). The HE₁₁ mode is confined inside the microfiber, while the HE₁₂ mode has a field distribution that extends outside the microfiber and interacts strongly with the surrounding medium. Therefore, the optical path difference between the two modes is modulated by the RI of the surrounding medium, and the interference fringe redshifts as the surrounding RI increases.

Figure 1 shows the design of the microfiber sensor with a BP-supported Au nanohybrid interface. Sequential modifications with piranha solution and 3-aminopropyl-triethoxysilane solution endowed the microfiber surface with positive charges (17). The few-layer BP

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Fig. 1. Preparation of the microfiber sensor. (A) Scheme of the functionalization of the microfiber biosensor. (B) X-ray photoelectron spectroscopy (XPS) spectrum of the BP spacer. (C) Raman spectrum of the microfiber with a BP spacer. (D and E) The atomic force microscopy (AFM) images of the microfiber surface with BP spacer [consisting of poly(methyl methacrylate) (PMMA) double layer]. (F) Extinction spectrum of the Au nanohybrids. (G and H) The AFM images of the microfiber surface with BP-supported Au nanohybrid nanointerface. (I) Schematic of the stepwise shift in the transmission spectrum induced by single-molecule ErbB2 binding. (J) Schematic of the wavelength shift in the transmission spectrum induced by MCF-7 cell binding. (K) Scheme of the optical setup. a.u., arbitrary units.
Nanosheets, which were coated with a poly(methyl methacrylate) (PMMA) double layer to protect them from passivation (18, 19), were subsequently immobilized on the microfiber surface through electrostatic attraction (20). The x-ray photoelectron spectroscopy (XPS), Raman spectra, and atomic force microscopy (AFM) images of the microfiber surface with BP spacer (consisting of a PMMA double layer) in Fig. 1 (B to E) indicate the successful immobilization (21–23) of the BP spacer on the microfiber. Next, the Au nanohybrids, with resonance at a wavelength of 1480 nm (Fig. 1F), were assembled on the BP spacer to form a plasmonic nanointerface of BP-supported Au nanohybrids (Fig. 1, G and H). Because of the scattering and absorption of Au nanohybrids, there was about 2 dB additional transmission loss when the microfiber was functionalized with BP-supported Au nanohybrid interface. Then, monoclonal ErbB2 antibodies were immobilized on the nanointerface to capture ErbB2 molecules with high affinity and selectivity (24). Thus, the microfiber sensor was ready for ErbB2 molecule detection. As illustrated in Fig. 1I, single-molecule binding could be indicated by stepwise shifting in the transmission spectrum. Moreover, the sensor could differentiate breast cancer cells (e.g., MCF-7 cells) from normal cells and capture them through interaction with ErbB2 on the cell surface. The capture of MCF-7 cells on the microfiber surface increased the surface RI and manifested as a redshift in the transmission spectrum, as shown in Fig. 1J. Furthermore, the photothermal effect of the nanointerface could kill the MCF-7 cells on the microfiber surface under near-infrared irradiation from the microfiber. Figure 1K illustrates the optical setup for sensing. The total liquid volume was approximately 4 ml.

**ErbB2 sensing**

Figure 2 demonstrates the ErbB2 sensing ability of an as-prepared microfiber sensor and two control sensors. Control sensor I is a microfiber with ErbB2 antibodies immobilized on a nanointerface consisting of only Au nanohybrids without BP nanosheets. Control sensor II is a microfiber with ErbB2 antibodies directly immobilized on the silica surface. The as-prepared sensor, control sensor I, and control sensor II were obtained from the same microfiber. The difference is that they have different interface modification. Before sensing, the sensors were immersed in phosphate-buffered saline (PBS) solution for 3 hours to stabilize and avoid the nonspecific adhesion of ions in PBS solution interfering in the sensing process. After that, the stabilities of microfibers in the PBS solution were assessed, as shown in fig. S4. As the ErbB2 concentration increased from 10 zM to 10 aM, the measured transmission spectra of the as-prepared sensor and control microfibers at different concentrations of ErbB2 are shown in Fig. 2A to C. The wavelength shifts of the sensor and control microfibers versus the concentration of ErbB2 are shown in Fig. 2D to F. The optical response of the three sensors to ErbB2 at a concentration of 1 aM is shown in Fig. 2G to I.
to 100 nM, regular redshifts of the transmission dip wavelength were observed using the as-prepared sensor, as illustrated in Fig. 2A. The sensor exhibits a broad linear concentration range from 10 zM to 100 nM with a sensitivity of 1.45 nm per log M (Fig. 2D). The LOD (signal/noise ratio, ≥ 3) of the sensor for the concentration of ErbB2 in the PBS solution is approximately 6.72 zM, which is more than three orders of magnitude lower than those of previously reported cutting-edge technologies (3, 16, 25, 26).

For the control sensors, the microfiber with ErbB2 antibodies immobilized on the nanointerface consisting of only Au nanohybrids without BP nanosheets shows a linear concentration range from 100 zM to 10 nM, with a sensitivity of 1.04 nm per log M and an LOD of 104 zM (Fig. 2, B and E), while the microfiber sensor with ErbB2 antibodies directly immobilized on the silica surface presents a linear concentration range from 10 pM to 1 nM, with a sensitivity of 0.47 nm per log M and an LOD of 196 fM (Fig. 2, C and F).

Furthermore, the wavelength shifts versus time at an ErbB2 concentration of 1 aM are shown in Fig. 2 (G to I). The binding event between a single molecule of ErbB2 and an antibody was recognized by the as-prepared microfiber sensor as stepwise shifts of 0.1 nm (Fig. 2G). Moreover, this event could be recognized as stepwise shifts of 0.08 nm by the control microfiber with a nanointerface consisting of only Au nanohybrids (Fig. 2H), while it could not be recognized by the control microfiber without any interface (Fig. 2I). This result implies that the BP-supported Au nanohybrid interface and the Au nanohybrid interface without BP nanosheets enhance the sensor sensitivity. In addition, the BP-supported Au nanohybrid interface provides the most effective enhancement in sensitivity.

To confirm that the stepwise shift was induced by the binding event of the ErbB2 molecule, two as-prepared microfibers with similar size and stability (both microfibers were functionalized with a BP-supported Au nanohybrid interface and ErbB2 antibodies) were fixed in 40 ml of PBS solution. Each microfiber was irradiated by a broadband source (BBS), which is built by four light-emitting diodes by wavelength division multiplexing and thus providing a large emission bandwidth of 1250 to 1650 nm, and its transmission spectrum

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**Fig. 3. Two-microfiber experiment.** (A) Optical setup of the binding event confirmation experiment. (B to G) Wavelength shifts recorded by the two microfibers upon injecting various solutions. (B to D, as-prepared microfiber; E to G, control microfiber.)
was monitored by an optical spectrum analyzer (OSA), as shown in Fig. 3A. Here, the two as-prepared microfibers are denoted as sensing microfiber and control microfiber, respectively. For the sensing microfiber, when immersed in the PBS solution, only background noise was recorded, as shown in Fig. 3B. Next, 4 ml of PBS solution was added to the solution on the side of the as-prepared microfiber. Again, only background noise was recorded in the next 2 hours, as shown in Fig. 3C. Then, 4 ml of 10 aM ErbB2 solution was injected on the side of the sensing microfiber without stirring. Notably, stepwise shifting of ~0.1 nm in transmission spectrum was recorded by the sensing microfiber at 46 and 86 min, respectively. As to the control microfiber, when immersed in the PBS solution and 4 ml of PBS solution added into the solution, only background noise was recorded (Fig. 3, E and F). When 4 ml of 10 aM ErbB2 solution was injected on the side of the sensing microfiber, the control microfiber still recorded background noise (Fig. 3G) because the injected ErbB2 solution could not diffuse to it under the resting conditions within 2 hours (27). In addition, 4 ml of 10 aM ErbB2 solution was injected on the side of the control microfiber without stirring, and after that, an obvious stepwise shift of ~0.1 nm was recorded by the control one (fig. S5). This was quite different from the noise captured in Fig. 3 (E to G). Therefore, it is confirmed that the stepwise shifting of ~0.1 nm in transmission spectrum is induced by the binding of individual ErbB2 molecules to the microfiber surface. Thus, the as-prepared sensor achieves biomarker detection at the single-molecule level (28, 29).

Specificity of the sensor
Specificity is an important consideration for cancer biomarker sensors (30). To evaluate the specificity of the functionalized optical microfiber sensor, ErbB2 was replaced with other protein biomarkers, bovine serum albumin (BSA), and immunoglobulin G (IgG), at the same concentration in PBS solution, and the same detection procedure was performed while keeping the other steps and conditions unchanged. Figure 4 (A and B) demonstrates the optical response in the BSA and IgG solutions. These control proteins induced no detectable stable response: There are some stepwise shifts of ~0.1 nm in the wavelength but jump down soon. It indicates that the interfering molecules came to the sensor surface, but fell down soon for lacking binding effect (31). This is different from the stable stepwise shift induced by ErbB2 molecule binding. These results indicate that the as-prepared sensor can differentiate the ErbB2 molecules from other protein molecules with similar sizes. This selectivity paves the way for in situ cell monitoring.

Next, to differentiate breast cancer cells from normal cells, the optical response to normal cells was estimated as shown in Fig. 4 (C and D). L929 cells (mouse fibroblast cells) and BRL3A cells (normal rat liver cells) are the standard normal cell lines used for control experiments. The microfiber captures cells by binding the biomarkers on their surfaces. On the basis of this mechanism, the optical response to normal cells is relatively low and can be ignored because the expression levels of ErbB2 are much lower in normal cells than in cancer cells (32).

Cell capture and cellular photothermal therapy
The ability of the as-prepared sensor to capture and detect breast cancer cells at an ultralow concentration was estimated as shown in Fig. 5A. MCF-7 cells (concentration of 1 cell/μl) were used here as a breast cancer cell line. In contrast to the noise-like response to normal cells (Fig. 4, C and D), a notable redshift in response to cancer cells was recorded and tended to stabilize within 30 min, indicating

Fig. 4. Specificity of the as-prepared sensor. Optical response of the as-prepared sensor to interfering proteins and cells. (A) BSA solution at a concentration of 1 aM. (B) IgG solution at a concentration of 1 aM. (C) L929 cells at a concentration of 1 cell/μl. (D) BRL3A cells at a concentration of 1 cell/μl.
that cancer cells were captured through the binding of ErbB2 biomarkers on the cell surface to the antibody on the microfiber surface at this ultralow concentration. The optical microscopy images in Fig. 5 (B and C) visualize the microfiber surface before and after MCF-7 cell capture. Next, a pump laser with a wavelength of 980 nm was coupled into the microfiber to stimulate the photothermal effect of the nanointerface (33–36). The BP-supported Au nanointerface absorbed the 980 nm pump light through the evanescent field to generate heat and heat-treat the cancer cell. Figure 5 (D to F) shows the morphology of the cancer cell on the microfiber surface at different times after the pump laser was turned on. After the pump light stimulated for 5400 s, the cancer cell was disrupted, as shown in Fig. 5F. The microfiber taper was also sensitive to temperature, so the photothermal effect (33–36) of the nanointerface caused a shift in the transmission dip wavelength (fig. S7A), from which the magnitude of the temperature change induced by the photothermal effect can be estimated. It can be seen from the dip wavelength shift that the temperature is gradually increased under the stimulation of the pump light. After the pump light was turned on for 1200 s, the dip wavelength shifted by −1.65 nm and then tended to be stable. The temperature sensitivity of the BP-supported Au nanointerface–functionalized microfiber taper was −0.09 nm/°C (fig. S7B), from which it can be estimated that the temperature had increased by 18°C. The cancer cell trapped on the microfiber surface absorbed the heat generated by the nanointerface, and when the heat accumulated to a certain extent, the cell was disrupted. Therefore, the as-prepared microfiber can differentiate cancer cells from normal cells at ultralow density, capture them, and kill them through the photothermal effect of the nanointerface. The LOD of cancer cells should be lower than 1 cell/μl. As the concentration of the target cells increases, the number of cancer cells captured and killed by the sensor will increase. Thus, this microfiber shows potential for application in cell-targeted photothermal therapy.

DISCUSSIONS

The single-molecule detection of ErbB2 biomarkers and the cancer cell capture and cellular photothermal therapy occurred within the evanescent field of the optical microfiber. The HE_{12} mode presents a large fractional power guided outside the microfiber (37). A plasmonic nanointerface is used to enhance the localized evanescent field. The surface morphologies of the Au nanohybrids and BP spacer were characterized by AFM and high-resolution transmission electron microscopy (Fig. 1, D, E, G, and H, and figs. S8 and S9A). AFM images of the microfiber surface with a BP spacer (Fig. 1, D and E, and fig. S8) show that the thickness of the BP nanosheets is approximately 5 nm. The monolayer-Au nanohybrids with a diameter of 150 nm and a thickness of 20 nm assemble evenly over the BP spacer. On the basis of the morphology of the nanointerface, near-field intensity mapping of the microfiber surface at a wavelength of 1550 nm was performed by a finite-difference time-domain (FDTD) method (fig. S9, B to F). Because of the tuning effect of the BP spacer (38), the localized electric field of the Au nanohybrids supported by the BP spacer increased 36-fold (site A). Therefore, the energy enhancement of the BP-supported Au nanohybrids can reach 1296-fold. As a wavelength-encoded sensor, the microfiber monitors the spectral shift induced by the binding of biomarkers. A single-molecule binding event at the surface can be treated as a point-like distortion (39). The induced change in the propagation constant of each mode can be expressed as (39)

\[
\frac{\Delta \beta}{\beta} = -\frac{\alpha_{ex}}{2\varepsilon_0} \int |E(l)|^2 \, ds \cdot L
\]

Fig. 5. Cell capture and cellular photothermal therapy. (A) Wavelength shift of the microfiber in response to MCF-7 cells at a density of 1 cell/μl (with pump off; baseline, cell culture fluid without MCF-7 cells). (B to F) Optical microscopy images of the microfiber surface capturing an MCF-7 cell and killing it through photothermal effect.
where $\alpha_m$ is the polarizability of the molecule in excess of the medium, $V_s$ is the volume of a single molecule, $E(x, y)$ is the localized electric field at the binding site, $\varepsilon_r$ is the permittivity, $E_l$ is the electric field, Sur is the microfiber surface area, and $L$ is the waist length. Therefore, the wavelength shift of the sensor scales with the evanescent field strength at the binding site. When ErbB2 molecule binding occurred at the nanointerface (e.g., site A in fig. S9B), the induced wavelength shift (~0.1 nm) was 1296-fold larger than that without the nanointerface. Thus, the microfiber with a nanointerface realizes ErbB2 detection at the single-molecule level, while the microfiber without an interface could not. Furthermore, the microfiber with a BP-supported Au nanohybrid interface performs photothermal therapy through the evanescent field. It allows the therapy to be carried out on only the cells captured on the microfiber surface but does not harm those that were not captured. Because the as-prepared microfiber captures only target cancer cells and leaves normal cells alone, it exhibits potential for targeted photothermal therapy.

The use of a plasmonic nanointerface-functionalized optical microfiber for the detection of protein cancer biomarkers at the single-molecule level and cellular photothermal therapy is demonstrated. The microfiber can sense biomarkers within 13 orders of magnitude of concentration (10 zM to 100 nM). The LOD of the sensor for the concentration of ErbB2 reaches 6.72 zM, which is more than three orders of magnitude lower than those of previously reported cutting-edge technologies. On the basis of this strategy, the microfiber is successfully used to differentiate cancer cells from normal cells and treat cancer cells through cellular photothermal therapy. The millimeter-sized microfiber represents a potential device suitable for early-stage POC diagnostics with increased convenience. Furthermore, this work demonstrates a possible approach for the integration of cellular diagnosis and treatment.

**MATERIALS AND METHODS**

**Materials and reagents**

All chemical reagents were of analytical grade and were used without further purification. They were provided by the Sigma-Aldrich Reagent Database Inc. PBS (pH 7.4) solution, ErbB2 antigen, human IgG, and BSA were purchased from Sangon Inc. (Shanghai, China). ErbB2 antibody (ab16901) was supplied by Abcam Plc. The BP nanosheet dispersion solution and Au triangle nanoplates were purchased from XF Nano Inc. (Nanjing, China). Au nanoparticles 5 nm in diameter were obtained from BaseLine Co. (Tianjin, China). Living L929 cells and BRL3A cells were provided and cultivated by R. Wen and J. Xie at the School of Pharmaceutical Sciences of Guangzhou Medical University.

The ErbB2 antigen solution was diluted with PBS solution to concentrations ranging from 1 zM to 10 μM. The human IgG and BSA solutions were diluted in PBS to a concentration of 10 aM. The concentration of the ErbB2 antibody solution was 10^{-5} M. The concentration of the MCF-7 cell, L929 cell, and BRL3A cell solutions was 1 cell/μl.

**Preparation of PMMA protecting BP nanosheets**

PMMA powder was dissolved in N,N-dimethylformamide solution with the help of ultrasonication and stirring for 3 hours and then transferred into a glove box filled with argon gas. Then, the BP nanosheet dispersion was mixed with the PMMA solution by stirring for 1 hour in the glove box.

**Preparation of Au nanohybrids**

The Au nanohybrids were prepared by mixing the Au triangle nanoplate dispersion and aminated Au nanoparticle dispersion at a volume ratio of 2:5 and stirring for 2 hours.

**Characterization**

The surface morphologies of the microfibers were observed by AFM (Bioscope Catalyst Nanoscope-V). The morphology of the Au nanohybrids was observed by HR-TEM (JEM-2100). XPS analysis of the BP nanosheets was performed with a commercial Thermo Fisher Scientific instrument (K-ALPHA”). The Raman spectrum of the BP nanosheets was measured by a Raman spectrometer (Thermo Fisher Scientific, DXR, excited by a 532-nm laser line). The ultraviolet-visible infrared spectra were obtained from a spectrophotometer (VERTEX 70, Bruker).

**Microfiber fabrication**

The tapered microfiber fabrication procedure is described as follows: A silica single-mode fiber (UVS-INT-PREMIUM, 100536, CorActive High-Tech Inc.) was heated by a 5-mm-wide flame and slowly stretched with two linear stages. The geometric parameters of the microfibers, such as the diameter and length of the transition region, were mainly determined by the moving speeds of the flame and stages. A tapered silica microfiber with a waist diameter of 7.1 μm and a length of 1.2 mm was fabricated (fig. S1).

**Experimental setup**

A BBS and an OSA were used to monitor all the optical responses. The minimum resolution of the OSA was 0.02 nm.

**Detection mechanism**

The transmission intensity of the microfiber modal interferometer is given by (9)

$$I = I_{HE_{11}} + I_{HE_{12}} + 2\sqrt{I_{HE_{11}} \cdot I_{HE_{12}}} \cos(\Delta \phi)$$

(2)

where $\Delta \phi = \frac{2\pi L_{ext}}{\lambda} (n_{eff_{HE_{11}}} - n_{eff_{HE_{12}}})$. The surface RI variation of the microfiber induces a wavelength shift in the spectrum, which is determined by (40)

$$\frac{d\lambda}{dn_{ext}} = \lambda \cdot \Gamma \cdot \left( \frac{1}{\Delta n_{eff}} \cdot \frac{\partial n_{eff}}{\partial n_{ext}} \right)$$

(3)

where $\Gamma = \frac{\lambda}{\Delta n_{eff}} \cdot \frac{\Delta n_{eff}}{dn_{ext}}$. $n_{ext}$ indicates the surface RI of the microfiber, and $\Delta n_{eff}$ represents the difference between $n_{eff_{HE_{11}}}$ and $n_{eff_{HE_{12}}}$. When biomolecules bind to the microfiber, the interference spectrum redshifts.

**Numerical simulations and calculations**

The evanescent field intensity and the mode distribution of the microfiber were calculated by commercial COMSOL Multiphysics software based on the finite-element method. The localized electric field intensity on the microfiber surface was simulated by an FDTD method.
SUPPLEMENTARY MATERIALS

Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/5/12/eaax4659/DC1

Fig. S1. Illustration of the fabricated microfiber device.
Fig. S2. The measured transmission spectrum of silica microfiber.
Fig. S3. The simulated modal distributions of silica microfiber and microfiber with BP spacer.
Fig. S4. Optical stabilities of the microfiber sensors in PBS solution.
Fig. S5. Wavelength shift with BP-supported Au nanohybrid interface under pump laser coupling and the wavelength shift of the microfiber versus temperature increase.
Fig. S6. Optical response with respect to time by using microfiber functionalized by Au nanohybrids and near-field intensity of electrical field on different nanointerfaces.
Fig. S7. Wavelength shift of the microfiber with BP-supported Au nanohybrid interface.
Fig. S8. The AFM images of the microfiber functionalized with different nanointerfaces.
Fig. S9. HR-TEM image of Au nanohybrids and near-field intensity of electrical field on different nanointerfaces.

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and interpreted the data. B.-O.G. conceived the study and supervised the experiments. H.L. performed the experiments, with assistance from G.H., A.X., P.C., and H.L. Yugang Huang and X.Z. provided scientific support in performing cell experiments. L.L. and X.F. helped in the data interpretation. Yunyun Huang, H.L., and B.-O.G. wrote the manuscript. All authors reviewed the manuscript. **Competing interests:** The authors declare that they have no competing interests. **Data and materials availability:** The Supplementary Materials are available for this paper at http://doi.org/. Correspondence and requests for materials should be addressed to Yunyun Huang.

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