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Visible Light-Driven Self-Powered Device Based on a Straddling Nano-Heterojunction and Bio-Application for the Quantitation of Exosomal RNA

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Abstract

This paper reports the design and fabrication of a self-powered biosensing device based on TiO₂ nanosilks (NSs)@MoS₂ quantum dots (QDs) and demonstrates a bioapplication for the quantitative detection of exosomal RNA (*Homo sapiens* HOXA distal transcript antisense RNA, HOTTIP). This self-powered device features enhanced power output compared to TiO₂ NSs alone. This is attributed to the formation of a heterojunction structure with suitable band offset derived from the hybridization between TiO₂ NSs and MoS₂ QDs, *i.e.*, the straddling (Type I) band alignment. The sensitization effect and excellent visible light absorption provided by MoS₂ QDs can prolong interfacial carrier lifetime and improve energy conversion efficiency. This self-powered biosensing device has been successfully applied in quantitative HOTTIP detection through effective hybridization between a capture probe and HOTTIP. The successful capture of HOTTIP leads to a sequential decrease in power output, which is utilized for ultrasensitive quantitative HOTTIP detection, with a linear relationship of power output change *versus* the logarithm of HOTTIP concentration ranging from 5 fg/mL to 50 000 ng/mL and a detection limit as low as 5 fg/mL. This TiO₂ NSs@MoS₂ QDs-based nanomaterial has excellent potential for a superior self-powered device characterized by economical and portable self-powered biosensing. Moreover, this self-powered, visible-light-driven device shows promising applications for cancer biomarker quantitative detection.

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsnano.8b07944. Additional details on optimization of the device, a comparison of parameters with other miRNA or DNA detection systems, and sequences of the interference gene fragments (PDF)

The authors declare no competing financial interest.

Graphical Abstract

Keywords

self-power; heterojunction; TiO_2 @ MoS_2 ; gastric cancer; exosome; Homo sapiens HOXA distal transcript antisense RNA; HOTTIP

As formally conceptualized by Wang *et al.* in 2007, “self-powering” refers to the development of dynamic nanosystems powered by their own excess kinetic energy, renewable energy, or a combination of both.^{1–4} The development of related technologies is particularly associated with self-powered sensors,^{5–8} regenerative actuators,^{4,9} and dynamic systems powered by renewable resources, such as self-sustained systems. Among these applications, self-powered biosystems are the most popular, including healthcare systems,^{5,8,10–12} cardiac systems,^{13,14} and medical devices.^{6,15–19} However, the energy supply is always a challenge in self-powered systems. To overcome this problem, self-powered nanosystems have been designed to enrich multiple energy resources from the environment. In this work, we report a self-powered device based on TiO_2 nanosilks (NSs)@ MoS_2 quantum dots (QDs) and demonstrate a successful bioapplication.

In 1972, Fujishima and co-workers first used TiO_2 in electrodes to split water,^{20,21} and since then, it has become one of the most popular and promising semiconductor materials. It has been extensively exploited in solar energy harvesting^{22,23} and pollutant degradation²⁴ among others, owing to its suitable band edge, excellent chemical and physical stability, low toxicity, high oxidizability, and ample availability.^{25,26} Unfortunately, TiO_2 has a wide band gap of about 3.2 eV (for anatase phase), leading to poor visible light response but easy absorption in the UV region. Another major barrier hampering the industrial-scale

exploitation of TiO₂ is rapid recombination of photogenerated electron–hole pairs (e^-/h^+), causing low carrier transport efficiency. Hence, researchers have expended considerable effort to develop reasonable strategies, such as doping with an elemental impurity or formation of a semiconductor heterojunction, to restrict electron–hole pair recombination or to adjust the energy band structure. In this work, MoS₂ QDs are introduced to effectively narrow the band gap by forming a heterojunction structure with new donor states below the conduction band of TiO₂ NSs. This accelerates the carrier transfer rate and extends the applications of both TiO₂ NSs and MoS₂ QDs.

MoS₂, a structural analog of graphene, is composed of periodic S—Mo—S single-layered planar structures. Because the interactions between layers are weak van der Waals forces, MoS₂ can be peeled into single-layer MoS₂ nanosheets or MoS₂ QDs by physical or chemical forces. MoS₂ QDs, with a tunable band gap of 1.8–1.9 eV,^{27–30} have attracted attention many fields, including biosensing,^{31,32} bioimaging,^{32,33} photoelectrocatalysis,^{33,34} and energy storage,³⁵ owing to their high stability and excellent electronic and optical properties. Compared with bulk and 2D MoS₂, zero-dimensional MoS₂ QDs exhibit unique edge effects and obvious quantum confinement,³⁶ arising from unsaturated S and Mo atoms at the edge, thus giving MoS₂ QDs higher conductivity³⁷ and catalytic ability. The quantum confinement effect, which can be observed by photoluminescence from *d*-orbital-related interactions of MoS₂, facilitates the tuning of the electronic band structure. Further, the nanometer size of MoS₂ QDs enhances their conductivity.³⁸ These features make this new class of material an excellent candidate to couple with other materials for enhanced performance.

Gastric cancer (GC) shows high morbidity and high mortality worldwide, especially in Eastern Asia. If treatment is started in the early stages, the prognosis of GC and patient survival time are effectively improved. Although tumor biomarkers extracted from serum, such as CA 19–9, CA 72–4, and CEA,³⁹ are unacceptable for GC diagnosis, current research has revealed that numerous and various cargoes present in exosomes, including RNAs, lipids, enzymes, and proteins, are reflective of tumor cell characteristics and can participate in some pathological processes.^{40,41} Furthermore, exosomal double-layer membranes can protect the abovementioned cargoes, especially RNAs,^{41,42} from being degraded. One kind of exosomal RNA (*Homo sapiens* HOXA distal transcript antisense RNA, HOTTIP) has been identified as a biomarker for GC in early diagnosis and prognosis.⁴²

Based on our previous work and experience with exosomes,^{42–44} we have developed a self-powered device based on TiO₂ NSs@MoS₂ QDs straddling heterojunction structure and applied it for the quantitative detection of HOTTIP. We coupled MoS₂ QDs with TiO₂ NSs to form a heterojunction structure with suitable band offset, *i.e.*, a straddling (Type I) band alignment to overcome insufficient direct electron transfer and further realize enhanced power output efficiency. Nanoparticles hybridized with TiO₂ NSs@ MoS₂ QDs were exploited to fabricate the biosensing device to realize power output through the electrical transport of excited electrons using visible light energy. A primer with specific recognition is used as the capture probe for HOTTIP. The self-powered biosensing device based on TiO₂ NSs@MoS₂ QDs was applied to the quantitative detection of HOTTIP (Figure 1). This self-

powered biosensing device demonstrates potential application in the detection of exosomal RNAs and other targets.

RESULTS AND DISCUSSION

Characterization of Photoelectrode Materials.

The morphology and microstructure of TiO₂ NSs, MoS₂ QDs and TiO₂ NSs@MoS₂ QDs were revealed by scanning electron microscopy (SEM) and transmission electron microscopy (TEM). Figure 2A showed the SEM image of TiO₂ NSs. The TiO₂ NSs were used to harvest the excitation energy and produce the photoresponse as a photoconductive nanomaterial, and then their specific surface area will heavily influence the contact area with the light source and the nanosensitizer MoS₂ QDs. Several frizzy hedgehog-like structures with nanosilk shapes can be clearly distinguished. The loose and well-organized assembly structure was also verified by TEM (Figure 2B). The energy-dispersive spectrometer (EDS) spectrum in Figure 2C showed that as-prepared TiO₂ NSs contained only Ti and O, suggesting that the synthesis was successful with a large effective specific surface area. TEM images in Figure 2D and E showed the morphology of MoS₂ QDs. An ample number of homogeneous dots can be easily distinguished, which benefitted for the enlargement of the contact area between TiO₂ NSs and MoS₂ QDs. In addition, MoS₂ QDs can form a flower-like structure, as shown in the SEM image of the discarded precipitate in Figure 2F. After MoS₂ QDs were bound to the surface of TiO₂ NSs, a compact ball-like framework was formed (Figure 2G), which illustrated the compact contact surface had formed. The EDS spectrum (Figure 2I) showed that the TiO₂ NSs@MoS₂ QDs contained only Ti, Mo, O, and S, further revealing that MoS₂ QDs successfully adhered to the surface of TiO₂ NSs.

X-ray diffraction (XRD) was utilized to investigate the crystallization of TiO₂ NSs and MoS₂ QDs. For curve a (TiO₂ NSs) in Figure 3A, several sharp diffraction peaks can be observed at $2\theta = 26.1^\circ$, 36.8° , 47.2° , 54.9° , 63.6° , and 75.1° (marked by stars), corresponding to the (101), (112), (200), (211), (204), and (215) lattice planes, respectively. The peaks were consistent with the reported JCPDS card no. 21-1276.⁴⁵⁻⁴⁷ The results indicated that TiO₂ NSs were successfully prepared in the anatase phase. Compared to bulk MoS₂, MoS₂ QDs are thin and tiny, and no macroscopic interaction took place among them (curve b). Thus, the characteristic peak at $2\theta = 14.4^\circ$ ((002) reflection) for bulk MoS₂ disappears, and most other peaks almost vanished.³² A weak peak at $2\theta = 44.2^\circ$ ((006) reflection) can be distinguished, possibly resulting from the fractional aggregation of MoS₂ QDs by the large surface tension in the drying procedure.^{32,33} The above data further confirmed that TiO₂ NSs and MoS₂ QDs were successfully produced.

Figure 3B displays the Fourier transform infrared (FTIR) spectra of TiO₂ NSs and MoS₂ QDs with the wavelength range of 800–4000 cm⁻¹. The as-prepared TiO₂ NSs (lower) showed characteristic absorption features: 2921 cm⁻¹ and the hump at about 3445 cm⁻¹ from C–H and N–H stretching vibrations and O–H vibrations, 1642 cm⁻¹ from C=O stretching vibrations, 1387 cm⁻¹ from C–O stretching vibrations, and 1079 cm⁻¹ from C–N stretching vibrations. The as-prepared MoS₂ QDs (upper) also showed characteristic absorption features: 3100–3490 cm⁻¹ from N–H and O–H stretching vibrations, 1629 cm⁻¹ from C=O stretching vibrations, and 1394 cm⁻¹ from C–O stretching vibrations. The FTIR

results demonstrated that TiO₂ NSs and MoS₂ QDs had necessary functional groups for the fabrication of the device.

To further confirm the nano-hybridization of the obtained samples for TiO₂ NSs and TiO₂ NS@MoS₂ QDs, X-ray photoelectron spectroscopy (XPS) spectra were provided (Figure 3C). It showed the survey scan XPS spectra providing Ti 2p and O 1s peaks for TiO₂ NSs and TiO₂ NS@MoS₂ QDs. Figure 3D,E depicted XPS spectra of Ti 2p and O 1s, respectively. Ti 2p peaks of TiO₂ NSs located at Ti 2p_{3/2} (458.3 eV) and Ti 2p_{1/2} (464.0 eV) (Figure 3D). However, the binding energies of Ti 2p_{3/2} (459.8 eV) and Ti 2p_{1/2} (465.5 eV) of TiO₂ NS@MoS₂ QDs were higher than those of single TiO₂ NSs. For O 1s_{1/2}, the peaks located at 529.5 and 531.1 eV might be assigned to the characteristic spin-orbital for O element from TiO₂ NSs and TiO₂ NS@MoS₂ QDs, respectively (Figure 3E). For all of the peaks of whether Ti 2p_{3/2}, Ti 2p_{1/2}, or O 1s_{1/2}, the binding energies altered. The reason might be that the combination between TiO₂ NSs and MoS₂ QDs influenced the binding energy of Ti and O, which indicated that the combination changed the microenvironment of the elements. This also strongly proved MoS₂ QDs combined compactly and successfully with TiO₂ NSs, which compact interface will conspicuously benefit the formation of the nano-heterojunction structure.

Photovoltaic Working Mechanism of the Device.

Fensley's work⁴⁸ described kinds of band alignments in the relative ordering of band-edge energies.⁴⁹ The first and most common is straddling alignment with no overlap of the bandgaps. The second is staggered alignment, in which the conduction band (CB) of the smaller-gap material may lie above that of the larger-gap material, or the valence band (VB) of the small-gap material may lie below that of the larger-gap material. The last is a broken gap, usually observed in the type-II GaSb-InAs superlattice system. In another nomenclature method, the first kind is "Type I", and the second and third kinds are referred to as "Type II". We know that the CB edge potential of TiO₂ NSs is about -0.44 V (*versus* normal hydrogen electrode, NHE)^{50,51} with a wide band gap of 3.2 eV. It can then be deduced that the VB edge potential of TiO₂ NSs is about 2.76 V, according to the equation $E_g = V_{VB} - V_{CB}$. The CB edge potential of MoS₂ QDs is about zero to -0.3 V, giving a VB edge potential of about 1.6–1.8 V^{52,53} because MoS₂ QDs have a band gap of 1.8–1.9 eV according to previous reports.^{27–30,54–56} This situation is illustrated in Figure 4A, in which the well-matched energy levels of TiO₂ NSs and MoS₂ QDs met the requirements to form a Type I, or straddling, heterojunction alignment structure. Figure 4A also depicted the possible power-output mechanism.

The self-powered device fabricated in this work generated an electrical signal under visible light excitation (Figure 4A). In general circumstances, the occupied VB and the empty CB existed at the same time in the semiconductors. Under the excitation of the external energy, excitons were injected from the VB to the CB, as a result, the holes generated in the VB because of the band gap. However, the recombination of the excitons and the holes easily happened because this course was very fast. When TiO₂ NSs were alone, this circumstance usually took place. However, through modification by MoS₂ QDs, the recombination between the excitons and the holes were depressed to a large extent. The carriers in the VB

of MoS₂ QDs were excited first because of the external energy supplied from visible light. These excited carriers immediately injected into the CB of MoS₂ QDs; then, these excited carriers injected spontaneously into the CB of TiO₂ NSs. MoS₂ QDs acted as an electron donor. Subsequently, the carriers injected into the VB of TiO₂ NSs. In the injection process, the absorbed light energy converted to an electric current that was rapidly transmitted to the external circuit. The carriers in the VB of TiO₂ NSs were reduced by ascorbic acid (AA), which improved the energy conversion efficiency and shortens the residence time of the carriers through the energy band. Thus, the carrier-transfer nanohybridization based on TiO₂ NSs@ MoS₂ QDs can apparently enhance the utilization of external energy and improve the photocatalytic property. The self-powered device successfully exported the power for use in the bioapplication described below.

The signal production mechanism was further supported by ultraviolet–visible spectroscopy (UV–vis), *i*–*t*, and photo-luminescence (PL) results. Generally speaking, if photo-electrochemical performance and UV absorption were weak, the PL signal will be relatively strong. This meant that energy conversion efficiency can be observed by the variation of UV absorbance, current density and PL intensity, as shown in Figure 4B–D. In Figure 4B,C, UV–vis absorbances and *i*–*t* current responses of TiO₂ NSs (curve a) or MoS₂ QDs (curve b) were low, but the opposite case was observed in PL tests (Figure 4D) on TiO₂ NSs (curve a) or MoS₂ QDs (curve b) individually. In UV–vis spectra, single TiO₂ NSs showed no typical absorption peak even in the UV light region, which might be due to protogenetic broad band gap of TiO₂ NSs. Single MoS₂ QDs showed a weak peak because of relative narrow band gap. In *i*–*t* tests, the same situation can be found, TiO₂ NSs or MoS₂ QDs alone can not display good photoactivity with weak current or power output. Inversely, TiO₂ NSs or MoS₂ QDs alone owned strong photo-luminescence intensity in PL tests. This phenomenon illustrated these three kinds of data can be mutual corroboration proof to prove the performance of these nanomaterials. After TiO₂ NSs hybridize with MoS₂ QDs, UV–vis absorbance and current density become much stronger, and the PL signal becomes much weaker. This result might be attributed to the formation of straddling offset and compact contact surface, which explained why PL emission intensity of TiO₂ NSs were partly quenched and why the light absorption in UV–vis and current density in *i*–*t* tests increased. This phenomenon indicated that the hybridization between TiO₂ NSs and MoS₂ QDs facilitated carrier transmission efficiency and energy conversion efficiency enhancement, thereby providing evidence for the abovementioned working mechanism.

Performance of Self-Powered Biosensing Device.

The performance of the self-powered biosensing device after the assemblies of TiO₂ NSs, MoS₂ QDs, and TiO₂ NSs@MoS₂ QDs, respectively, were studied by a time-based *i*–*t* method. In addition, the hybridization ability and the recognition property of the primer capture probe toward HOTTIP were investigated (Figure 5A,B). When modifying TiO₂ NSs or MoS₂ QDs alone, the current density was only 4.98 or 2.49 $\mu\text{A}\cdot\text{cm}^{-2}$, respectively. For TiO₂ NSs or MoS₂ QDs, after forming the TiO₂ NSs@MoS₂ QDs nanocomposite, the current density significantly increased to 15.5 $\mu\text{A}\cdot\text{cm}^{-2}$, which obviously resulted from the synergy between TiO₂ NSs and MoS₂ QDs. This synergistic effect remarkably increased the interfacial electron-transfer efficiency and also suppressed e^-/h^+ recombination in the

conversion process from light energy to electrical energy. However, after assembling the primer probe, the photocurrent showed a decrease to $12.4 \mu\text{A}\cdot\text{cm}^{-2}$, possibly because the primer acted as an insulator. The signal decreased further to $9.59 \mu\text{A}\cdot\text{cm}^{-2}$ after incubation with HOTTIP (1000 ng/mL), suggesting that HOTTIP could be successfully captured by the primer probe on the electrode surface.

Electrochemical impedance spectroscopy (EIS) was also utilized to assess photoelectrochemical performance, the hybridization ability of the primer capture probe, and the recognition property of primer probe for HOTTIP, as shown in Figure 5C, using 0.1 mol/L KCl containing 5.0 mmol/L $\text{K}_3\text{Fe}(\text{CN})_6/\text{K}_4\text{Fe}(\text{CN})_6$ (1:1). The Randles equivalent circuit (Figure 5D) was composed of four circuit components: R_{et} , the charge-transfer resistance; R_s , the resistance of solution; C_{dl} , the double-layer capacitance; and Z_W , the Warburg impedance. However, during the fabrication of the biosensing device and the detection of target exosomal RNA, only R_{et} was affected. Thus, the interfacial electron-transfer component in the fabrication and detection process can be monitored by R_{et} . The variation of R_{et} in the high-frequency region of Nyquist plots, namely the semicircle diameter, represented the electron-transfer ability at the material interface, which also indicated the energy conversion ability of the biosensing device. It can be seen from Figure 5C that the semicircle diameter (R_{et}) was 12Ω after immobilization of TiO_2 NSs@ MoS_2 QDs on the electrode (curve a) and that the R_{et} increased to 27Ω when the primer probe was hybridized on the modified electrode (curve b). The R_{et} value increased to 54Ω (curve c) after incubation with HOTTIP (1000 ng/mL). Therefore, the variation of R_{et} indicated that the biosensing device had been successfully fabricated with obvious high-performance and recognition ability for HOTTIP.

Regeneration of the Biosensing Device.

A biosensing device should be capable of regeneration for environmental protection and utilization efficiency. In this application, regeneration can be accomplished by recycling the working anode. Working anode regeneration was performed, and the results are shown in Figure 6A,B. Before HOTTIP was introduced to the biosensing device, the power output was $1.24 \mu\text{W}\cdot\text{cm}^{-2}$ (curve a); however, the power output sharply decreased to $0.25 \mu\text{W}\cdot\text{cm}^{-2}$ when the probe primer captured HOTTIP (5000 ng/mL, curve a'). The anode was then removed and immersed in ultrapure water solution at 95°C for 5 min after the first capture process and then placed back to the chamber to carry out next hybridization cycle. The power output changed back to $1.14 \mu\text{W}\cdot\text{cm}^{-2}$ (curve b). HOTTIP was introduced again to the surface of the regenerated working anode at 37°C for 20 min, and the power output of the working anode decreased again to $0.22 \mu\text{W}\cdot\text{cm}^{-2}$ (curve b'). This regeneration process indicated that the fabricated photoanode could be regenerated through the repeating hybridization and release of HOTTIP on the functionalized surface of the working anode.

Signal reproducibility is also crucial for future applications of this self-powered biosensing device. Intra- and inter-assay relative standard deviations (RSD) were utilized for the reproducibility examination. A total of 5 electrodes with different concentrations of 1000, 5000, and 9000 ng/mL, respectively, were constructed independently through the same fabrication process and incubated with HOTTIP samples under the same experimental

conditions. The intra assay RSDs were 1.6%, 2.3%, and 1.8%, respectively, and 2.1%, 1.1%, and 2.2% were obtained for the inter-assay RSDs, respectively. These data demonstrated that the biosensing device could provide acceptable precision and reproducibility.

Optimization of the Device and Feasibility for Detection of the Exosome Biomarker.

The optimum experimental conditions were assessed, and the results were shown in Figure 7. The optimal concentration of TiO₂ NSs was 4 mg/mL (Figure 7A), the optimal dosage of MoS₂ QDs was 15 μ L (Figure 7B), the optimal concentration of TiO₂ NSs@MoS₂ QDs nanohybridization was 25 mg/mL (Figure 7C), the optimal pH was 7.0 (Figure 7D) and the optimal primer probe concentration (Figure 7E) was 20 μ g/ μ L. The related illumination about the optimal experimental condition can be found in the Supporting Information.

The application of the self-powered device toward HOTTIP was based on the specific interactions between the primer probe and HOTTIP. The power output (P)–time (t) curves were evaluated for a series of HOTTIP concentrations. As presented in Figure 8A,B, the power output decreased as the concentration of HOTTIP increased. Figure 8C showed the linear calibration plot of $|P|$ ($P = P_0 - P$, P and P_0 were the power output values after and before incubating with HOTTIP) versus the logarithm of HOTTIP concentration. The calibration equation was $|P| = 0.118 \log c_{\text{HOTTIP}} + 0.578$ ($R^2 = 0.979$), which was valid from 5 fg/mL to 50 000 ng/mL, along with a low limit of detection of 5 fg/mL. The figures of merit were acceptable compared with those in other reports (see Table S1).

Specificity is also vital for future applications because non-specific attachment will lead to poor accuracy. A total of five alternate gene fragments, including Bmi-1, GAPDH, EZH2, ATP5B, and CCAT1 (sequences given in Supporting Information S1), were utilized for interference tests in 3000 ng/mL HOTTIP solution containing 6-fold concentrations of 5 alternate gene fragments, respectively (Figure 9A, samples 2–6). The power output was unaffected by these 5 kinds of interfering gene fragments. A mixture of all 5 types of gene fragments was also used as an interference test, and no effect on the P value was observed (Figure 9A, sample 7). Compared to the sample containing 3000 ng/mL HOTTIP (Figure 9B, sample 1), almost no signal output was observed for samples containing one single fragment of these 5 interference gene fragments (18 000 ng/mL; Figure 9B samples 2–6) or their mixture (Figure 9B sample 7). All of these results indicate excellent selectivity of the self-powered biosensing device.

Standard addition recovery was also assessed (Table 1). The RSD values of 5 measurements of samples were 2.77%, 2.63%, 2.00%, 1.31%, and 4.86%, respectively, and the recoveries were 109%, 105%, 104%, 101%, and 102%, respectively, indicating good reliability.

CONCLUSIONS

In summary, a self-powered device based on TiO₂ NSs@MoS₂ QDs was constructed, and an ultrasensitive detection of HOTTIP was demonstrated. MoS₂ QDs successfully sensitized TiO₂ NSs through the formation of a “Type I” band alignment heterojunction structure with a tight interaction interface. The fabricated device exhibited a stable and continuous power output and a high energy density up to 1.55 μ W·cm^{−2} with a longer exciton lifetime and

higher exciton mobility. Based on the specific strong recognition ability between the primer probe and HOTTIP, the device demonstrated a wide detection range, a low detection limit of 5 fg/mL, and ultrahigh selectivity and sensitivity. Therefore, the proposed device should aid in the development of quantitative detection strategies for biotargets and broaden the applications of self-powered biosensing devices.

EXPERIMENTAL SECTION

Materials and Reagents.

All chemicals were of reagent grade purity or better and used without further purification. The pipet tips and ultrapure water ($18.25 \text{ M}\Omega\cdot\text{cm}^{-2}$) were sterilized in a LDZX-30KBS pressure steam sterilizer (Shanghai ShenAn Medical Instrument) at 121°C for 40 min and stored in a 4°C refrigerator after cooling to room temperature.

Instruments.

SEM results were collected with a JEOL microscope (model JSM-6700F). TEM images were collected from a JEOL microscope (model JEM-1400). EDS results were also obtained from the same model JEOL microscope with SEM tests. XRD patterns were collected with a D8 focus diffractometer (Bruker AXS, Germany). FTIR tests were carried out on a PerkinElmer 580B spectrophotometer made in the United States. XPS data were obtained from an X-ray photoelectron spectroscope (ESCALAB 250, ThermoFisher Scientific). The electrochemical tests (EIS and $i-t$) were tested on a Zahner electrochemical workstation (model Zennium PP211) with a three-electrode system. ZSimpWin software was used to fit the parameters for EIS data. PL spectra were obtained from a LS-45/55 spectrometer (PerkinElmer). UV-vis experiments were performed on a Lambda 35 UV-vis spectrometer (PerkinElmer).

Preparation of Exosome and Exosomal RNA (*Homo sapiens* HOXA distal transcript antisense RNA, NR_037843.3).

Serum exosomes were isolated using the ExoQuick kit (System Biosciences, Mountain View, CA). In brief, $63 \mu\text{L}$ of ExoQuick solution was added to $250 \mu\text{L}$ of serum sample, mixed, and incubated at 4°C for 30 min. The mixture was centrifuged at 13 000 rpm for 2 min. The supernatant was removed, and the exosome pellet was kept. Exosomal RNA was prepared using a miRNeasy Micro Kit (QIAGEN, Valencia, CA). A total of $20 \mu\text{L}$ of exosome suspension were mixed with $700 \mu\text{L}$ of QIAzol lysis buffer, and the mixture was processed according to the manufacturer's standard protocol. The extracted RNA was eluted with $25 \mu\text{L}$ of RNase-free water. First-strand cDNA was generated using a High-Capacity cDNA Reverse Transcription Kit (Takara, Dalian, China). The sequence of HOTTIP was as follows: 5'-CCTAAAGCCA CGCTTCTTTG TGGACCGGAC CTGACTCTCC AGGAATCTGG GAACCCGCTA TTTCACCTA TTTTGGGACA AGAAAAAGGG GCTCTTTGGG GCCACTTCCT GCCTTCCCC TCAAGTAGGA TCTCCAGCCT GCA-3'. Specific primers used were as follows: 5'-CCT AAA GCC ACG CTT CTT TG-3' for forward primer, and 5'-TGC AGG CTG GAG ATC CTA CT-3' for reverse primer.

Preparation of TiO₂ NSs, and MoS₂ QDs and TiO₂ NSs@ MoS₂ QDs.

TiO₂ nanosilks were prepared according to a literature report.⁵⁷ A 0.56 g sample of titanium isopropoxide (TiIso) was dissolved in 27.60 g of hydrochloric acid (36.0–38.0 wt %) with continuous stirring. Cetyltrimethylammonium bromide (CTAB, 0.44 g) was dissolved in 54.6 mL of ultrapure water with stirring for 40 min. Then TiIso and CTAB solutions were mixed with stirring for 2 h. Urea (1.8 g) and 112.5 mL of ethylene glycol were added to 37.50 mL of the TiIso/CTAB solution with stirring for 3 h. This mixed solution was transferred to a 200 mL autoclave and heated for 24 h at 150 °C. The product was washed three times with ultrapure water and dried at 80 °C for 22 h.

MoS₂ QDs were synthesized using a literature method.³⁸ Na₂MoO₄·2H₂O (0.8 g) was dissolved in 60 mL of ultrapure water by ultrasonication for 30 min. Then, 60 mL of ethanol and 0.76 g of dibenzyl disulfide were added to the above solution and submitted to further ultrasonication for 40 min. The resulting solution was transferred to an autoclave (250 mL) and heated at 220 °C overnight. After cooling to 25 °C, the suspension was centrifuged for 50 min at 4000 rpm. The supernatant (MoS₂ QDs) was reserved, and the precipitate was discarded.

A total of 50 mg TiO₂ NSs powder and 10 mL of MoS₂ QDs were mixed and ultrasonicated overnight, followed by freezing for 24 h. Next, the frozen solid mixture was placed in a lyophilizer for 24 h to finish TiO₂ NSs@MoS₂ QDs nanohybridization.

Fabrication, Characterization, and Application of the Self-Powered Biosensing Device.

Indium tin oxide (ITO) conductive glass was utilized as the anode substrate, which was processed with acetone and 95% ethanol, respectively, sonicated for 30 min, and dried with pure N₂ gas for later use. A total of 18 μ L of TiO₂ NSs@ MoS₂ QDs (25 mg/mL) was spin-coated on a bare ITO electrode, and then the modified electrode was heated in an oven at 150 °C for 30 min. Then, 8 μ L of primer probe (20 μ g/ μ L) was incubated on the TiO₂ NS@MoS₂ QDs/ITO electrode with activation by EDC (N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride)/NHS (1-Hydroxy-2,5-pyrrolidinedione) for 6 h at 4 °C. The electrode was rinsed several times with H₂O and dried with flowing N₂ gas. The constructed electrode was fabricated with a Pt auxiliary electrode in a chamber. Phosphate-buffered saline (PBS, used as a buffer) mixed with 0.1 mol/L of AA was used as the electrolyte with saturated N₂ gas.

For application in the detection of HOTTIP, different concentrations of HOTTIP were incubated with the functionalized electrode for 2 h at 4 °C. Next, the electrode was washed three times with PBS buffer to remove the uncaptured targets. Finally, the electrode was placed back into the chamber, and the signal was tested.

For the regeneration of the device, the HOTTIP-capturing anode was removed from the chamber and then immersed in ultrapure water for 5 min at 95 °C.

For PEC tests, the irradiation source wavelength was 430 nm with exposure time of 20 and 10 s duration with no light and bias voltage of 0.1 V. The power output was calculated based on the following equation: $P = UI$, where P is the power output (μ W·cm⁻²), U is the voltage,

and I is the electric current density ($\mu\text{A}\cdot\text{cm}^{-2}$). The functional surface area of the anode was 1 cm^2 . For the EIS tests, an AC sine wave with 5 mV amplitude was utilized to disturb the steady-state open circuit voltage. The scan frequency range was 100 mHz~100 kHz.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Fabrication and application of the biosensing device.

Figure 2. SEM images of (A) TiO₂ NSs, (F) MoS₂ QDs, and (G) TiO₂ NSs@MoS₂ QDs; TEM images of (B) TiO₂ NSs, (D, E) MoS₂ QDs, and (H) TiO₂ NSs@MoS₂ QDs; EDS of (C) TiO₂ NSs and (I) TiO₂ NSs@MoS₂ QDs.

Figure 3.

(A) XRD pattern; (B) FTIR spectra of (a) TiO_2 NSs and (b) MoS_2 QDs; (C) XPS spectra of the survey scans of TiO_2 NSs and TiO_2 NS@ MoS_2 QDs, (D) Ti 2p, and (E) O 1s.

Figure 4.

(A) Schematic illustration of the energy band structure and the proposed charge-transfer mechanism; (B) UV-vis spectra, (C) time-based current densities, and (D) PL emission spectra of (a) TiO₂ NSs, (b) MoS₂ QDs, and (c) TiO₂ NSs@MoS₂ QDs.

Figure 5.

(A) Time-based photocurrent and (B) histogram of (a) TiO_2 NSs/ITO, (b) MoS_2 QDs/ITO, (c) TiO_2 NSs@ MoS_2 QDs/ITO, (d) primer probe/ TiO_2 NSs@ MoS_2 QDs/ITO, and (e) HOTTIP/primer probe/ TiO_2 NSs@ MoS_2 QDs/ITO; (C) Nyquist plot of (a) TiO_2 NSs@ MoS_2 QDs/ITO, (b) primer probe/ TiO_2 NSs@ MoS_2 QDs/ITO, (c) HOTTIP/primer probe/ TiO_2 NSs@ MoS_2 QDs/ITO; (D) Randles equivalent circuit.

Figure 6.
 (A) Power output and (B) power output histograms of the aptamer-functionalized anode (a) before and (b) after incubation 5000 ng/mL HOTTIP and at the regenerated anode (c) before and (d) after incubation in 5000 ng/mL HOTTIP.

Figure 7. Optimization of (A) the concentration of TiO_2 NSs, (B) the dosage of MoS_2 QDs, (C) the concentration of TiO_2 NSs@ MoS_2 QDs, (D) the pH after modifying TiO_2 NSs@ MoS_2 QDs, and (E) the concentration of primer probe (pH = 7).

Figure 8.

(A) power output (P) of the electrode incubated with different concentrations of HOTTIP.

(B) Relationship between photocurrent change ($|\Delta P|$) and different HOTTIP concentrations.

(C) Calibration curve of $|\Delta P|$ vs logarithm of HOTTIP concentration.

Figure 9.

(A) Specificity of the biosensing device (1) 3000 ng/mL HOTTIP, (2) 18 000 ng/mL Bmi-1, (3) 18 000 ng/mL GAPDH, (4) 18 000 ng/mL EZH2, (5) 18 000 ng/mL ATP5B, (6) 18 000 ng/mL CCAT1, and (7) 18 000 ng/mL Bmi-1/GAPDH/EZH2/ATP5B/CCAT1; (B) selectivity of the biosensing device (1) 3000 ng/mL HOTTIP, (2) 3000 ng/mL HOTTIP + 18 000 ng/mL Bmi-1, (3) 3000 ng/mL HOTTIP + 18 000 ng/mL GAPDH, (4) 3000 ng/mL HOTTIP + 18 000 ng/mL EZH2, (5) 3000 ng/mL HOTTIP + 18 000 ng/mL ATP5B, (6) 3000 ng/mL HOTTIP + 18 00 ng/mL CCAT1, and (7) 3000 ng/mL HOTTIP + 18 000 ng/mL Bmi-1/GAPDH/EZH2/ATP5B/CCAT1.

Table 1.
Accuracy and Precision of HOTIP Detection by the Self-Powered Biosensing Device

sample (ng/mL)	addition content (ng/mL)	found (ng/mL)	mean (ng/mL)	RSD (%), <i>n</i> = 8	recovery (%)
100	200	329, 316, 309, 314, 328	319	2.77	109
150	200	361, 358, 344, 366, 368	359	2.63	105
250	400	667, 657, 678, 649, 680	666	2.00	104
300	500	802, 821, 795, 796, 801	803	1.31	101
400	800	1187, 1196, 1308, 1255, 1161	1221	4.86	102