Cu-doping SnO$_2$-NiO p-n Heterostructure for Significant Raman Enhancement with EF > 10$^{10}$: Toward Ultrasensitive VOCs Sensing

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Surface enhanced Raman scattering (SERS) based on chemical mechanism (CM) has attracted tremendous attention for its great selectivity and stability. However, extremely low enhancement factor (EF) limits its practical applications for trace detection. Here, a novel sponge-like Cu-doping SnO$_2$-NiO p-n semiconductor heterostructure (SnO$_2$-NiOx/Cu), was first designed and created as a CM-based SERS substrate with a significant EF of $1.66 \times 10^{10}$. This remarkable EF was mainly attributed to the enhanced charge-separation efficacy of p-n heterojunction and charge transfer resonance resulted from Cu doping. Moreover, the porous sponge structure enriched the probe molecules, resulting in further SERS signals magnification. By immobilizing copper phthalocyanine as an inner-reference element, SnO$_2$-NiOx/Cu was developed as a SERS nose for selective recognition of multiple lung cancer related-volatile organic compounds (VOCs) down to ~ppb level. The information of VOCs was recorded in a barcode, demonstrating practical potential of a desktop SERS device for biomarker screening.
Surface-enhanced Raman scattering (SERS) has been widely utilized as a promising analytical technique for trace detection. Each breakthrough in the SERS field is inseparable from the development of the enhancement substrates. Conventional SERS substrates based on electromagnetic mechanism (EM), such as Au and Ag, exhibit ultrahigh Raman enhancement with enhancement factor (EF) up to $10^{12}$. However, the EM-based SERS effect has no selectivity for Raman reporters, resulting in complicated signal outputs. Another SERS mechanism is chemical mechanism (CM), which relies on the charge transfer (CT) processes between adsorbed molecules and SERS substrate. Today, due to the high molecule selectivity and signal reproducibility, the development of CM-based SERS substrates, such as metal oxides, graphene, and other semiconductors, has attracted more attention. Unfortunately, the CM-based SERS effect shows relatively low EFs ($10^3$-$10^5$) since the CT process is a short-range one. The poor charge separation in CM-based SERS substrates is a major limitation, hindering further enhancement of their SERS performance.

Here, a sponge-like Cu-doping NiO (NiOx/Cu)-SnO$_2$ p-n semiconductor heterostructure (SnO$_2$-NiOx/Cu) was designed and created as a CM-based SERS substrate with extremely high Raman enhancement (EF=1.66 $\times$ 10$^{10}$). The SnO$_2$-NiOx/Cu heterostructure was confirmed at the atomic resolution scale by aberration-corrected scanning transmission electron microscopy (ACSTEM). This notable EF value was mainly attributed to a CT process with high efficiency generated by the integration of p-n heterojunction and Cu doping, and enrichment of probe molecules by the porous nanosponge structure of SnO$_2$-NiOx/Cu, as illustrated in Fig. 1. The selective Cu doping on NiO narrowed the band gap through Fermi-level alignment, leading to the conversion from type-I SnO$_2$-NiO heterojunction into type-II SnO$_2$-NiOx/Cu heterojunction. This structure ensured the delivery of photo-generated electrons from NiOx/Cu to SnO$_2$ and holes from SnO$_2$ to NiOx/Cu, further facilitating the separation of photogenerated electron-hole pairs. Furthermore, the narrower bandgap of NiOx/Cu also realized CT resonance to promote the CT process. The enhanced charge-separation efficacy of type-II p-n heterojunction and CT resonance resulted from Cu doping led to incredible SERS performance improvement on SnO$_2$-NiOx/Cu with an EF 10$^7$ times higher than that on SnO$_2$-NiO. This CT process was verified by density functional theory (DFT) calculation and time-resolved diffuse reflectance (TDR) spectroscopic measurements. The present high-EF SnO$_2$-NiOx/Cu substrate was then developed as a SERS nose (SnO$_2$-NiOx/Cu-CuPc) through immobilization of copper phthalocyanine (CuPc) as an inner-reference element for volatile organic compounds (VOCs) sensing. Exploiting the target molecular vibrational fingerprint and the well matching degree of energy level between target molecules and SnO$_2$-NiOx/Cu, our SERS nose showed excellent selectivity to ‘sniff out’ and simultaneously quantify multiple toxic VOCs in the exhaled breath (EB) of early stage lung cancer patients at ~ppb level, which was 10 times lower than those obtained by gas chromatography-mass spectrometry (GC-MS) and fluorescence spectroscopy, 100 times lower than those obtained by electrochemical methods. A visual diagnostic report on the concentration of toxic VOCs was obtained by SERS mapping and their corresponding barcodes. This new avenue shows great potential for developing accurate, fast, easy and cost-effective diagnosis instruments for screening of early-stage lung cancer.
Characterization and SERS Performance of SnO$_2$-NiO$_x$/Cu

The sponge-like SnO$_2$-NiO$_x$/Cu p-n heterostructure was first designed and synthesized through a hydrothermal method combined with a subsequent calcination. As shown in scanning electron microscopic (SEM) image (Fig. 2a), the as-prepared porous SnO$_2$-NiO$_x$/Cu nanosponges were highly uniform with a diameter of 1.5 ± 0.1 µm (n=15) (Supplementary Fig. 1a). The SERS activity of SnO$_2$-NiO$_x$/Cu was evaluated using CuPc as a prototype probe molecule under 785 nm laser excitation. Remarkably, the prominent signal peak at 1530 cm$^{-1}$ corresponding to the in-plane ring symmetric nonmetal bound N-C stretch of CuPc (10$^{-5}$ M) was detected on SnO$_2$-NiO$_x$/Cu, while on SnO$_2$-NiO, SnO$_2$ (for details, see Supplementary Fig. 2 and 3) and bare Si substrates, the signals were almost undetectable (EF < 2.15× 10$^3$) (Fig. 2b and 2c). The EF of SnO$_2$-NiO$_x$/Cu for CuPc was calculated to be as high as 1.66 × 10$^{10}$ (for calculation details, see Supplementary Methods), which was the highest EF of CM-based substrates reported to date (Supplementary Table 1).

This remarkable EF was deduced to be mainly ascribed to p-n junction of SnO$_2$-NiO$_x$/Cu formed by p-type NiO$_x$/Cu and n-type SnO$_2$. In the Mott-Schottky plot, the p-n junction characteristic was observed with an inverted “V-shape” (Supplementary Fig. 5a)$.^{17}$ The precise p-n heterostructure of SnO$_2$-NiO$_x$/Cu was further explored by ACSTEM high angle annular dark field imaging (HAADF) (Fig. 2e-g). The lattice fringes corresponding to (110) plane of tetragonal phase SnO$_2$ and (111) plane of NiO$_x$/Cu$^{19}$ were clearly...
resolved on the ligaments in HAADF image (Fig. 2g (i)). Both SnO$_2$ and NiO/Cu were well crystallized without dislocations or other visible extended defects. The boundary between SnO$_2$ and NiO/Cu marked on HAADF image also revealed the heteroepitaxy observed at the nanometer scale. This polycrystalline feature of SnO$_2$-NiO/Cu was then confirmed by selected-area electron diffraction (SAED) (Supplementary Fig. 5b) and X-ray diffraction (XRD) pattern (Fig. 2d). The corresponding ACSTEM energy dispersive spectroscopy (EDS) mapping illustrated that Sn atoms were uniformly distributed across one side of heterojunction boundary while Ni and Cu atoms were distributed over the other side (Fig. 2g (ii)), indicating that Cu was only doped into NiO instead of SnO$_2$.

Next, X-ray photoelectron spectroscopy (XPS) was performed to elucidate the chemical bonding in SnO$_2$-NiO/Cu nanosponge. As shown in Fig. 2h, two peaks observed at 486.9 (Sn 3d$_{5/2}$) and 495.3 eV (3d$_{3/2}$), and their spin-orbit splitting (8.4 eV) indicated the presence of Sn$^{4+}$ in SnO$_2$-NiO/Cu$^{20}$. A slight blue-shift of Sn 3d binding energy in SnO$_2$-NiO/Cu compared with SnO$_2$, indicated that there was electronic interaction between SnO$_2$ and NiO. The core-level XPS of Ni 2p in SnO$_2$-NiO/Cu was given in Fig. 2i,
where two emission peaks were centered at 853.2 eV (Ni (II) 2p_{3/2}) and 872.4 eV (Ni(II) 2p_{1/2}), respectively. Besides, in comparison with SnO-NiO, another two new peaks at 857.1 and 874.8 eV were observed, which were assigned to Ni(III) 2p_{3/2} and Ni(III) 2p_{1/2}.

The results suggested that Cu doping in SnO_{2}-NiOx/Cu altered the Ni surrounding chemical environments. XPS data of Cu showed the binding energy of Cu 2p_{3/2} for SnO_{2}-NiOx/Cu at 932.5 and 933.3 eV, which were consistent with the divalent states of Cu^{+} and Cu^{2+} (Fig. 2j)^{22}. From O 1s XPS spectrum of SnO_{2}-NiOx/Cu, three peaks were clearly observed, in which O1s peak at 532.2 eV was ascribed to the lattice oxygen (O^{2−}), while the high binding energy (533.3 eV) was assigned to the absorbed oxygen ions (O^{2−} and O^{−}) on the surface^{23}, which were consistent with those of SnO_{2}-NiO. In addition, another peak at the lower energy (531.0 eV) was attributed to the vacant oxygen (O_{v})^{24}, indicating that Cu doping induced a large number of O_{v} in SnO_{2}-NiOx/Cu. These obvious changes indicated the existence of interaction between n-type SnO_{2} and p-type NiOx/Cu, resulting in an efficient CT process between Raman reporter and SnO_{2}-NiOx/Cu SERS substrate.

**Mechanism of Raman enhancement in SnO_{2}-NiOx/Cu**

The CT process between SnO_{2}-NiOx/Cu and CuPc was then investigated through TDR spectroscopic measurements. Excited by 785 nm laser, the absorption bands centered at 530 nm were observed for CuPc-SnO_{2}, CuPc-SnO_{2}-NiO and CuPc-SnO_{2}-NiOx/Cu systems, which were assigned to trapped electrons (Supplementary Fig. 7). Time profiles of the transient absorption were fitted by two-exponential functions (Fig. 3a). The decay lifetime of electrons in CuPc-SnO_{2}-NiOx/Cu (1236.39 ps) was much longer than that in CuPc-SnO_{2} (433.82 ps) and CuPc-SnO_{2}-NiO (325.37 ps), suggesting that p-n junction dopped by Cu at SnO_{2}-NiOx/Cu interface acted as an electron trap site and led to efficient CT. To further explain TDR results, we investigated the electronic structure and the coupling of CuPc and SnO_{2}-NiOx/Cu as well as the consequent CT using DFT calculations. As shown in Fig. 3b, the amount of electron transfer from CuPc to SnO_{2}-NiOx/Cu (1.32 e^{−}) was much more than that on SnO_{2}-NiO (0.68e^{−}) or SnO_{2}(0.87 e^{−}). Both TDR results and DFT calculations provided strong evidence for effective CT between SnO_{2}-NiOx/Cu and CuPc, resulting in significant enhancement of Raman activity for CuPc on SnO_{2}-NiOx/Cu substrate.

As well known, the CM-based SERS effect strongly depends on the matching degree of the energy level between molecules and substrates. To further elucidate the CT process, we determined CB and VB of SnO_{2}, NiO and NiOx/Cu, and highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) levels of CuPc using DFT calculations. As shown in Fig. 3c, the calculation result was in a good agreement with that of the standard Tauc plot method (Supplementary Fig. 8). Without Cu doping, the energy barriers between VB of NiO or SnO_{2} substrates and HOMO of CuPc were 2.2 and 2.1 eV, which were much greater than the energy of 785-nm laser (1.58 eV). Thus, the photon energy of 785 nm laser failed to excite the electrons at VB of the substrate into HOMO of CuPc and hard to separate electron-hole pairs effectively, thus leading to very weak Raman signals. However, the introduction of O_{v} created by Cu doping shifted the Fermi level of NiO toward CB and narrowed the band gap. Under this situation, electrons at VB of NiO/Cu substrate were excited and transferred into HOMO of CuPc successfully. Meanwhile, the energy difference between VB of NiOx/Cu and SnO_{2} in CuPc-SnO_{2}-NiOx/Cu nanosystem was 1.5 eV, which was close to 1.58 eV. In this case, CT resonance occurred, leading to an obvious Raman enhancement on SnO_{2}-NiOx/Cu (Fig. 3d).
Significantly, the selective Cu doing on NiO narrowed the band gap through Fermi-level alignment, resulting in the conversion from type-I SnO\textsubscript{2}-NiO heterojunction into type-II SnO\textsubscript{2}-NiOx/Cu heterojunction. As for type I SnO\textsubscript{2}-NiO semiconductor, the band of SnO\textsubscript{2} was embedded within that of NiO so that photogenerated electrons and holes were both concentrated in SnO\textsubscript{2}. After Cu doping, the Fermi-level of NiOx/Cu lay closer to CB (Fig. 3c). Electrons in n-type SnO\textsubscript{2} filled some of the holes in p-type NiOx/Cu because these holes were available at lower-energy states. This left positively charged holes in n-type SnO\textsubscript{2} and extra negatively charged electrons in p-type NiOx/Cu\textsuperscript{25}. Thus, an inner electric field was formed at the equilibrium (Fig. 3c). Driven by the internal field, holes at VB of SnO\textsubscript{2} were excited into VB of NiOx/Cu, and electrons were accelerated from CB of NiOx/Cu into CB of SnO\textsubscript{2}. In this case,
photogenerated electron-hole pairs were effectively separated by type II SnO$_2$-NiO$_x$/Cu p-n junction between NiO$_x$/Cu and SnO$_2$, realizing efficient spatial charge separation and prolonging the lifetime of charge carriers$^{26}$, and further enhancing the SERS activity. In order to confirm the effect of p-n junction on Raman enhancement for SnO$_2$-NiO$_x$/Cu, SnO$_2$-In$_2$S$_3$ porous nanocomposite with non-p-n junction was synthesized, in which CB and VB levels of n-type In$_2$S$_3$ (-3.7 eV and -5.7 eV) were close to that of p-type NiO$_x$/Cu. TDR results showed that electrons decay lifetime in CuPc-SnO$_2$-In$_2$S$_3$ (588.65 ps) was much shorter than that in CuPc-SnO$_2$-NiO$_x$/Cu, indicating that p-n junction in SnO$_2$-NiO$_x$/Cu acted as an electron trap site and led to more efficient CT (Supplementary Fig. 9a and b). Thus, compared with SnO$_2$-NiO$_x$/Cu, obvious decline (30%) in SERS intensity of CuPc was observed on SnO$_2$-In$_2$S$_3$ porous nanocomposites (Supplementary Fig. 9c). Consequently, such synergetic promotion of CT resonance and type II p-n heterojunction formation in SnO$_2$-NiO$_x$/Cu led to a high CT efficiency, further resulting in a remarkable SERS enhancement.

The above theoretical and experimental results revealed that the ultrahigh Raman enhancement on SnO$_2$-NiO$_x$/Cu was mainly derived from CT mechanism. To clarify whether EM mechanism can be observed in SnO$_2$-NiO$_x$/Cu substrate, finite difference time domain method (FDTD) was used to simulate and calculate the EM field distribution under 785-nm excitation for SnO$_2$, SnO$_2$-NiO and SnO$_2$-NiO$_x$/Cu. As shown in Fig. 3e, SnO$_2$-NiO$_x$/Cu obtained stronger electric near-field than SnO$_2$ or SnO$_2$-NiO. The reason was that Cu doping led to the generation of a high density of holes in VB of NiO$_x$/Cu, sustaining an localized surface plasmon response (LSPR) in the near infrared (NIR) region. However, the EM effect on SERS enhancement was very limited, which was 8 orders of magnitude lower than the CM effect. (Supplementary Fig. 10).

Moreover, the Brunauer-Emmett-Teller surface area and pore size of as-prepared SnO$_2$-NiO$_x$/Cu nanosponge were calculated to be as high as $26.16 \text{ m}^2 \text{g}^{-1}$ and $3.8 \pm 0.3 \text{ nm}$ (Supplementary Fig. 11), which was similar to that obtained from SEM image. Owing to CuPc enrichment by this porous structure, the SERS effect of as-prepared SnO$_2$-NiO$_x$/Cu for CuPc was 1.8 times higher than that of SnO$_2$-NiO$_x$/Cu with compact surface (Fig. 3f). Consequently, the remarkable EF of SnO$_2$-NiO$_x$/Cu should be mainly ascribed to 3 factors: efficient CT process attributed to (i) type II p-n junction in SnO$_2$-NiO$_x$/Cu for charge collection and separation, (ii) CT resonance under 785-nm laser excitation, and as well as (iii) the molecule enrichment by porous SnO$_2$-NiO$_x$/Cu nanosponge.

**VOCs detection of human EB based on the SERS nose**

The SnO$_2$-NiO$_x$/Cu nanosponge with high EF was then developed as a SERS nose (SnO$_2$-NiO$_x$/Cu-CuPc) through immobilization of CuPc for sensitive and selective VOCs analysis. Herein, Raman intensity of CuPc at 1530 cm$^{-1}$ was employed as an inner-reference for improving the determination accuracy. The SnO$_2$-NiO$_x$/Cu-CuPc SERS nose was versatile and employed to discern a series of toxic VOCs overexpressed in the EB of early stage lung cancer patients$^{27-29}$, such as pyrene (PYR), 2-naphthalenethiol (2-NT) and 4-ethylbenzaldehyde (EBZA). Taking full advantage of fingerprint Raman peaks of these three molecules for quantitative analysis and the the well matching degree of energy level between three target molecules and SnO$_2$-NiO$_x$/Cu (Fig. 4a), the developed SERS nose showed excellent selectivity for VOCs sensing. The distinctive peak of PYR at 1236 cm$^{-1}$ indexed to CH in-plane bending vibrations
(δ_{C-H})^{30}, For 2-NT, the peak at 1375 cm^{-1} corresponded to C=C stretching (ν_C=C)^{31}, while EBZA was identified by the peak at 1690 cm^{-1} (ν_C=O)^{32} (Supplementary Fig. 12). However, no obvious responses were obtained for other potential interferences in a mixed mimetic exhalation, including alkane, alcohols, esters, ketone, H_2O, NH_3, CO_2 and H_2S (Fig. 4b).

Fig. 4 SnO_2-NiOx/Cu-CuPc SERS nose for VOCs sensing. a. HOMO and LUMO of EBZA, 2-NT and PYR; CB and VB of SnO_2-NiOx/Cu. b. Selectivity tests of various relevant analytes against PYR, 2-NT and EBZA. c. Raman spectra of SnO_2-NiOx/Cu-CuPc obtained with PYR (I-VII: 10^{-1.3}, 10^{-1.6}, 10^{-1.9}, 10^{0.2}, 10^{0.5} and 10^{0.8} ppb), 2-NT (I-VII: 10^{1.8}, 10^{1.9}, 10^{2.0}, 10^{2.2}, 10^{2.3} and 10^{2.4} ppb) and EBZA (I-VII: 10^{2.6}, 10^{2.7}, 10^{2.8}, 10^{2.9}, 10^{3.0}, 10^{3.1} and 10^{3.2} ppb) at various concentrations. d. Calibration curves of PYR, 2-NT and EBZA on a semilog scale. e. SERS mapping images obtained at peak intensity of 1236 cm^{-1} for PYR, 1375 cm^{-1} for 2-NT and 1690 cm^{-1} for EBZA with different concentrations. The corresponding barcode was acquired based on the concentrations of VOCs and the R, G, and B values obtained from Raman mapping.
Since no cross reactions were observed for determination of PYR, 2-NT and EBZA (Supplementary Fig. 13), these three VOCs were then simultaneously detected using this SERS nose. The SERS intensity ratio ($I_{1236}/I_{1530}$, $I_{1375}/I_{1530}$ and $I_{1690}/I_{1530}$) showed a good linearity with logarithmic VOC concentration over the range from 10 ppb to 1000 ppm, due to Temkin adsorption of VOCs on SERS substrates\cite{supplementary} (Supplementary Fig. 12). The limits of detection (LODs) were estimated to be $7.6 \pm 0.7$, $5.3 \pm 0.6$, and $4.1 \pm 0.5$ ppb for PYR, 2-NT and EBZA, respectively, which were 10 times lower than those obtained by GC-MS\cite{12} and fluorescence spectroscopy\cite{13}, 100 times lower than those obtained by electrochemical methods\cite{14} (Supplementary Table 2). Considering that the VOC concentration in human EB samples was below 2 ppm, we measured $I/I_{1530}$ of each VOC more accurately in narrow ranges (PYR: $10^{-2.8}$ ppb, 2-NT: $10^{-1.8}$-$10^{-2.4}$ ppb and EBZA: $10^{-2.6}$-$10^{-1.2}$ ppb) (Fig. 4c and 4d). Subsequently, two-dimensional Raman mapping images were obtained based on the peak intensities of 1236, 1375, and 1690 cm$^{-1}$ corresponding to PYR, 2-NT and EBZA by scanning Raman signals with a computer-controlled x-y translational stage (Fig. 4e). The color of Raman images remarkably changed from purple to red with

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\caption{SnO$_2$-NiOx/Cu-CuPc SERS nose for VOCs sensing in human EB samples. a, Diagram of SnO$_2$-NiOx/Cu-CuPc SERS nose for VOCs sensing. b, SERS spectra, c, bubble chart of the diagnosis results and d, Raman mapping and corresponding barcode of EB samples for lung cancer patients (1-10) and healthy groups (11-15).}
\end{figure}
increasing concentration of these VOCs. Then, the VOC concentration information was automatically transformed into an optical, machine readable barcode by integrating R, G, B values of Raman images and reading concentrations based on linear curves (Supplementary Fig. 14). Hence, the composition and concentration information on VOCs were integrated to yield barcodes that can be read rapidly and conveniently by a barcode scanner. Meanwhile, the SERS nose showed a good stability within 3 months (< 4.21%) and a satisfying reproducibility with RSDs below 3.18% (n=5) (Supplementary Fig. 15). These results demonstrated that the present SERS nose provided good sensitivity, specificity and stability for multiple VOC detection at ~ppb levels.

Furthermore, we took advantage of the developed SERS nose to demonstrate the simultaneous detection of PYR, 2-NT and EBZA in the EB of early stage lung cancer patients (Fig. 5a). Fig. 5b and 5d show SERS spectra and corresponding barcodes of EB samples for 10 lung cancer patients and 5 healthy people. A regression analysis between the proposed SERS nose and GC-MS was conducted to demonstrate its utility (Supplementary Fig. 16). Compared with single-VOC tests, the simultaneous detection of three VOCs improved the reliability and avoid false positive diagnoses (Fig. 5c). With the aid of multiple VOC detection based on SnO$_2$-NiOx/Cu-CuPc SERS nose, the diagnosis and screening of lung cancer can be conducted in a single fast, easy and cost-effective assay, thus affording an ideal test method for point of care detection.

Discussion

In this work, a novel sponge-like SnO$_2$-NiOx/Cu-CuPc SERS nose was first developed for ultrasensitive and selective recognition of multiple VOCs down to ppb level. First of all, the sponge like SnO$_2$-NiOx/Cu type II p-n semiconductor heterostructure, which was verified by ACSTEM and Mott-Schottky plots, was synthesized using a hydrothermal method combined with a subsequent calcination. The EF value of SnO$_2$-NiOx/Cu for CuPc was achieved up to 1.66 $\times$ 10$^{10}$, the highest EF value for CM-based SERS substrates reported by far. Both experimental results and theoretical calculations revealed that the SERS enhancement was mainly stemmed from efficient charge separation by SnO$_2$-NiOx/Cu p-n heterojunction and charge transfer resonance caused by Cu doping, which enhanced charge transfer efficiency between SnO$_2$-NiOx/Cu substrate and probe molecules. Besides, enrichment of probe molecules from porous sponge structure further magnified SERS signals. Then, by immobilizing of CuPc molecule as an inner-reference element, the SnO$_2$-NiOx/Cu substrate was developed as a SERS nose (SnO$_2$-NiOx/Cu-CuPc) for VOCs analysis with high sensitivity, selectivity, and accuracy. The developed SERS nose was able to ‘sniff out’ and simultaneously quantify multiple toxic VOCs in the EB of early stage lung cancer patients at ppb level, which was 10 times lower than those obtained by GC-MS and fluorescence spectroscopy, 100 times lower than that obtained by electrochemical method. Unique barcodes denoting the VOCs concentrations were obtained by integrating R, G, and B values of the Raman intensity images, where these barcodes can be easily read by electronic devices, such as smartphones and handheld scanners. This work has provided a methodology for designing and synthesizing p-n heterostructures to enhance Raman signals and has demonstrated the practical potential of a desktop SERS device for biomarker screening. This established method can also be extended to monitor the levels of other VOCs, which are related to diabetes, advanced liver disease, kidney failure, and lung abscess.
References

1. Goldberg-Oppenheimer, P., Mahajan, S. & Steiner, U. Hierarchical electrohydrodynamic structures for surface-enhanced Raman scattering. *Adv. Mater.* **24**, OP175-OP180 (2012).

2. Yu, S. et al. Plasmon near-field coupling of bimetallic nanostars and a hierarchical bimetallic SERS “hot field”: toward ultrasensitive simultaneous detection of multiple cardiorenal syndrome biomarkers. *Anal. Chem.* **91**, 864-872 (2019).

3. Anker. J. N. et al. Biosensing with plasmonic nanosensors. *Nat. Mater.* **7**, 442-453 (2008).

4. Qiu, B., Xing, M., Yi, Q. & Zhang, J. Chiral carbonaceous nanotubes modified with titania nanocrystals: Plasmon-free and recyclable SERS sensitivity. *Angew. Chem. Int. Ed.* **54**, 10643-10647 (2015).

5. Lin, J. et al. Ultrasensitive SERS detection by defect engineering on single Cu2O superstructure particle. *Adv. Mater.* **29**, 1604797 (2017).

6. Feng, E., Zheng, T., He, X., Chen, J. & Tian, Y. A novel ternary heterostructure with dramatic SERS activity for evaluation of PD-L1 expression at the single-cell level. *Sci. Adv.* **4**, eaau3494 (2018).

7. Ganesh, S., Venkatakrishnan, K. & Tan, B. Quantum scale organic semiconductors for SERS detection of DNA methylation and gene expression. *Nat. Commun.* **11**, 1135 (2020).

8. Yilmaz, M. et al. Nanostructured organic semiconductor films for molecular detection with surface-enhanced Raman spectroscopy. *Nat. Mater.* **16**, 918-924 (2017).

9. Lee, S. H., Nishi, H. & Tatsuma, T. Plasmonic behaviour and plasmon-induced charge separation of nanostructured MoO3-x under near infrared irradiation. *Nanoscale* **10**, 2841-2847 (2018).

10. Yu, X., Marks, T. J. & Facchetti, A. Metal oxides for optoelectronic applications. *Nat. Mater.* **15**, 383-396 (2016).

11. Zhang, C. et al. Strain distributions and their influence on electronic structures of WSe2–MoS2 laterally strained heterojunctions. *Nat. Nanotechnol.* **13**, 152-158 (2018).

12. Li, Q. et al. Two-dimensional morphology enhances light-driven H2 generation efficiency in CdS nanoplatelet-Pt heterostructures. *J. Am. Chem. Soc.* **140**, 11726-11734 (2018).

13. Ji, S., Gu, S., Wang, X. & Wu, N. Comparison of olfactometrically detected compounds and aroma properties of four different edible parts of Chinese mitten crab. *Fish Sci.* **81**,1157-1167 (2015).

14. Mohr, A. et al. A new pyrene-based fluorescent probe for the determination of critical micelle concentrations. *J. Phys. Chem. B* **111**, 12985-12992 (2007).

15. Penezić, A., Gašparović, B., Stipaničev, D. & Nelson, A. In situ electrochemical method for detecting freely dissolved polycyclic aromatic hydrocarbons in water. *Environ. Chem.* **11**, 173-180 (2014).

16. Jiang, N. et al. Observation of multiple vibrational modes in ultrahigh vacuum tip-enhanced Raman spectroscopy combined with molecular-resolution scanning tunneling microscopy. *Nano Lett.* **12**, 5061-5067 (2012).

17. Meng, F., Li, J., Cushing, S. K., Zhi, M. & Wu, N. Solar hydrogen generation by nanoscale p-n junction of p-type molybdenum disulfide/n-type nitrogen-doped reduced graphene oxide. *J. Am. Chem. Soc.* **135**, 10286-10289 (2013).

18. Zhu, Z. et al. Enhanced efficiency and stability of inverted perovskite solar cells using highly crystalline SnO2 nanocrystals as the robust electron-transporting layer. *Adv. Mater.* **28**, 6478-6484 (2016).

19. Hoon, P. K. et al. Efficient CH3NH3PbI3 perovskite solar cells employing nanostructured p-type NiO electrode formed by a pulsed laser deposition. *Adv. Mater.* **27**, 4013-4019 (2015).
20. Xin, Y., Kan, X., Gan, L. & Zhang, Z. Heterogeneous bimetallic phosphide/sulfide nanocomposite for efficient solar-energy driven overall water splitting. *ACS Nano* **11**, 10303-10312 (2017).

21. Simon, T. et al. Redox shuttle mechanism enhances photocatalytic H₂ generation on Ni-decorated CdS nanorods. *Nat. Mater.* **13**, 1013-1018 (2014).

22. Li, Y. et al. Enhancing oxidation resistance of Cu (I) by tailoring microenvironment in zeolites for efficient adsorptive desulfurization. *Nat. Commun.* **11**, 3206 (2020).

23. Zhang, Y. et al. Direct observation of oxygen vacancy self-healing on TiO₂ photocatalysts for solar water splitting. *Angew. Chem. Int. Ed.* **58**, 14229-14233 (2019).

24. Wang, H. et al. Oxygen-vacancy-mediated exciton dissociation in BiOBr for boosting charge-carrier-involved molecular oxygen activation. *J. Am. Chem. Soc.* **140**, 1760-1766 (2018).

25. Wu, G. et al. Programmable transition metal dichalcogenide homojunctions controlled by nonvolatile ferroelectric domains. *Nat. Electron.* **3**, 43-50 (2020).

26. Wang, H. et al. Giant electron-hole interactions in confined layered structures for molecular oxygen activation. *J. Am. Chem. Soc.* **139**, 4737-4742 (2017).

27. Rodriguez-Aguilar, M. et al. Ultrafast gas chromatography coupled to electronic nose to identify volatile biomarkers in exhaled breath from chronic obstructive pulmonary disease patients: A pilot study. *Biomed. Chromatogr.* **33**, e4684 (2019).

28. Peled, N. et al. Non-invasive breath analysis of pulmonary nodules. *J Thorac Oncol.* **7**, 1528-1533 (2012).

29. Qiao, X. et al. Detection of exhaled volatile organic compounds improved by hollow nanocages of layered double hydroxide on Ag nanowires. *Angew. Chem. Int. Ed.* **58**, 1-6 (2019).

30. Yang, M. et al. SERS-active gold lace nanoshells with built-in hotspots. *Nano Lett.* **10**, 4013-4019 (2010).

31. Koh, C. S. L., Lee, H. K., Han, X., Sim, H. Y. F. & Ling, X. Y. Plasmonic nose: integrating the MOF-enabled molecular preconcentration effect with a plasmonic array for recognition of molecular-level volatile organic compounds. *Chem. Commun.* **54**, 2546-2549 (2018).

32. Conoci, S., Valli, L., Rella, R., Compagnini, G. & Cataliotti, R.S. A SERS study of self-assembled (4-methylmercapto) benzaldehyde thin films; *Mater. Sci. Eng., C* **22**, 183-186 (2002).

33. Belhaj, A. F. et al. Experimental investigation, binary modelling and artificial neural network prediction of surfactant adsorption for enhanced oil recovery application. *Chem. Eng. J.* **406**, 127081 (2021).

Methods

Methods are included in the Supplementary Information.

Data availability

The data that support the plots within this paper and other findings of this study are available from the corresponding author on reasonable request.

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Yang Tian and Tingting Zheng conceived the research, designed the experiments and supervised the work. Yan Zhou fabricated materials and performed all the SERS experiments. Qingyi Gu and Xiao He conducted the DFT calculation. Jingquan Chen performed the TDR experiments. Tianzhu Qiu provided human EB samples and conducted corresponding experiments. Ruijuan Qi and Rong Huang completed the characterization of materials. Yan Zhou wrote the manuscript with Yang Tian and Tingting Zheng. All the authors were involved in the discussion and participated in manuscript input.

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Competing interests

The authors declare no competing financial interest.

Acknowledgments
The authors greatly appreciate the financial support from NSFC (21827814 for Y. Tian, 21974049 for T. Zheng). This work also was supported by Innovation Program of Shanghai Municipal Education Commission (201701070005E00020) and Shanghai Rising-star Program (20QA1403300).