Journal of Electrochemistry

Volume 25
Issue 2 *Special Issue: Electrochemical Analysis and Sensing (I)*

2019-04-28

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Recommended Citation

Wan-qiao BAI, Xue-zhi QIAO, Tie WANG. Application of Nanomaterials in the Detection of Volatile Organic Compounds in Exhaled Breath for Cancer Diagnosis[J]. *Journal of Electrochemistry*, 2019 , 25(2): 185-201.
DOI: 10.13208/j.electrochem.181041
Available at: https://jelectrochem.xmu.edu.cn/journal/vol25/iss2/5

第 25 卷 第 2 期
2019 年 4 月

电化学
JOURNAL OF ELECTROCHEMISTRY

Vol. 25 No. 2
Apr. 2019

DOI: 10.13208/j.electrochem.181041
Cite this: *J. Electrochem.* **2019**, *25*(2): 185-201

Artical ID:1006-3471(2019)02-0185-17
Http://electrochem.xmu.edu.cn

Application of Nanomaterials in the Detection of Volatile Organic Compounds in Exhaled Breath for Cancer Diagnosis

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Abstract: Volatile organic compounds (VOCs) generated in human body can reflect one's health state, and numerous diseases are identified by some VOCs biomarkers. More recently, analyses of VOCs biomarkers from exhaled breath have turned into a research frontier worldwide because it offers a noninvasive way for diseases diagnosis. Various kinds of nanomaterials are used to enhance the performance of sensing techniques, and play an essential role in miniaturization detection. In this review, several kinds of nanomaterials (metallic, metal oxide, carbon-based, composites and MOFs-based materials) used in various VOCs detection methods, especially in VOCs sensors are summarized. Learning from the successful utilization of nanomaterials in these methods will help to further understand the superiority and limitation of detection techniques. A personal perspective of the research and development in exhaled breath VOCs detection for cancer diagnosis has been presented.

Key words: volatile organic compounds; nanomaterials; cancer; biomarker; exhaled breath

CLC Number: O646; O657 **Document Code:** A

Cancers of lung, breast, colon, gastric, ovarian, and colorectal, etc. figure among the leading causes of both morbidity and mortality[1]. Thousands of patients are killed by these cancers every year. Improved screening may reduce mortality for all of these cancers by detecting cancer when it is small and more easily treated. There are a variety of techniques available to detect some cancers at an early stage, such as blood tests, chest X-ray, colonoscopy[2], gas chromatography-mass spectrometry (GC-MS)[3], Fourier transform-ion cyclotron resonance mass spectrometry (FT-ICR MS)[4], computed tomography (CT)[5] and multi-capillary column-ion mobility spectrometry (MCC-IMS)[6], however, many techniques are considered uncomfortable and inconvenient by patients, and are often underutilized by the majority of the population for various reasons, such as invasion and patient burden[7].

Volatile organic compounds (VOCs) are various groups of chemicals generated from human body which can often reflect one's metabolic condition in body[8]. Considering endogenous and exogenous VOCs, more than 800 kinds of VOCs have been found in exhaled breath[9]. It was declared that in the breath of healthy individuals, acetone, ethanol, methanol and isoprene are the major VOCs, and aldehydes, ketones, pentane and higher-chain alcohols take up the minor components[10]. Oxidative stress, abnormal metabolic processes, or an imbalance between biological systems might change concentrations of some specific organic compounds or generate new ones in exhaled breath from cancer patients[11-13]. Some VOCs were thought to originate from cancer cells as a result of abnormal metabolism that did not exist in healthy people[14]. Both internal and external factors have an impact on the concentration ratio of VOCs in one's

Received: 2018-10-09, Revised: 2018-11-19 a. W.Q. Bai and X.Z. Qiao contributed equally to this review. *Corresponding author, Tel: (86-10)82362042, E-mail: wangtie@iccas.ac.cn

breath, such as diet, exercise, alcohol/cigarette consumption, etc. Thus, the states of VOCs in exhaled breath vary with each individual. For instance, cigarette consumption can cause increased concentrations of acetonitrile and furans; exertion can enhance alveolar ventilation and lead to 3 ~ 4 folds increase of isoprene level[15]. Conversely, abnormal levels of specific VOCs may indicate disease. For example, an obvious acetonic odor may relate to crucial diabetes, and a pungent smell might associate with liver disease[16-17]. Likewise, the elevated levels of pentane and ethane indicate various chronic lung diseases[18], also, the average content of VOCs may be decreased in an Alzheimer patient[19].

Since the VOCs in exhaled breath can provide information related to various cancers or diseases, it is possible to make early diagnosis for cancers by analyzing the components in VOCs from breath of patients[20]. Breath samples have attracted much interest from medical stuffs and researchers because they are easy to be collected and analyzed. Testing of breath samples is painless and noninvasive, so it is applicable for everybody even for children and critically ill patients. Moreover, exhaled breath tests can be carried out frequently, which also helped to monitor cancer so that signs of recurrence or progression could be detected as early as possible[1]. Thus, as a facial, rapidly developing a noninvasive screening tool, detection and analysis of VOCs biomarkers in exhaled breath have shown great potential for cancer diagnosis, and have been considered to be a new frontier and vigorously developed in recent years[7].

Nanomaterials, have various types and tunable morphologies, own high aspect ratio and large specific surface area, show excellent physico-chemical properties, which can efficiently detect a wide variety of VOCs with high sensitivity, and have become a research focus for VOCs detection[21]. Multifarious materials in nanoscale including metallic nanoparticles, semiconductor metal oxides, and various carbon-based nanomaterials have been applied to sensitize local VOCs[22]. Among the numerous detection techniques, sensor-based method has played an important role in VOCs detection because of its high sensitivity, fast response and simple operation. Nanomaterials are usually used to modify the sensor surface and/or directly contact with analytes. In VOCs detection, the interaction between nanomaterials and VOCs analyte molecules determines the sensing efficiency. By changing the carrier density/Fermi energy, charged VOCs are bound to the sensor surface and enables sensing without interference caused by solvent background[23]. To obtain low-level of specific VOCs from exhaled breath, as well as to enhance the sensitivity and accuracy of early diagnosis, nanomaterials-based analysis approaches have sprung up. The present review will summarize different types of nanomaterials used in VOCs biomarker detection from exhaled breath for cancer diagnosis in recent years, especially sensor-based techniques, analyze the advantages and deficiencies, and put forward the prospects and challenges of nanomaterials-based VOCs sensing techniques and their possible development direction in the future.

1 Nanomaterials Used in VOCs Detection

1.1 Metallic Nanoparticles

Metallic nanopaticles, especially noble metal (gold, silver and platinum) nanoparticles, due to their intrinsical outstanding electrical, optical and catalytic properties, are highly sensitive to the detection of biomarkers at lower concentration levels, thus, are widely used in gas sensing techniques. However, pure metallic nanopaticles are no longer sufficient to meet the requirements of VOCs detection technology. The metallic nanoparticles are usually modified with organic polymers or other chemical groups to enhance nanoparticles' performance when used in VOCs sensing. Monolayer-capped metal nanoparticles as an effective tool are used in chemiresistors for fast response time and low output impedance, which conduces to implement reliable gas sensors, meanwhile, the chemiresistors retain small-size and low-weight.

In order to enhance the stability of metallic nanoparticles, some surfactants or organic chemicals with functionality or thiols are used. Garg et al. obtained stable gold nanoparticles (GNPs) by capping GNPs with trithiol[24]. The fabricated sensors based on trithiol-GNPs exhibited constant response towards toluene (500×10^{-6}, V/V) gas with a little drop in sensitivity over 6 months and became stably after approximately 3 months. Peng et al. fabricated a tailor-made cross-reactive nanosensor array based on GNPs with different organic functionalities, which can effectively discriminate breath VOCs of healthy individuals and that of cancer patients[25]. Combined the versatility of GNPs with the chemical selectivity of organics towards some certain VOCs biomarkers, the GNPs-based sensors can also distinguish several cancer types in the same breath pattern analysis, without respect to various confounding factors. The obtained results were analyzed with standard principal component analysis (PCA) and compared favorably with those of GC-MS analysis. Additionally, breath samples were not pretreated, the test was facile to operate, and the different cancers formed clusters were separated. Four representative organic ligands capped cubic Pt nanoparticles (NPs) were synthesized by Dovgolevsky et al. and used to sense gaseous nonpolar analytes from breath samples[26]. The chemiresistors fabricated based on cubic Pt NPs with nonpolar organic ligands were greatly increased in resistance when exposed to nonpolar octane, hexane and decane, etc., while a low sensitivity towards polar ethanol and water. It was explained that both analyte-induced changes in the NP-NP core distance and variation in the permittivity of the medium between the NPs contributed to the responses.

Some non-chemiresistors for VOCs detection were also developed with GNPs. Kahn et al. developed dynamic GNP-based flexible sensors for ovarian carcinoma diagnosis via exhaled breath[27]. In this study, the modified GNPs with different thiol ligands were integrated into a dynamic cross-reactive sensor array. Different bending states of the sensor provided various spatial structures of nanoparticles, changing the interaction between GNP ligands and VOCs, which increased available data from each sensor. Single sensor could selectively detect part per billion concentration-level breath VOCs that were related to ovarian cancers and excluded irrelevant environmental VOCs. The strain-related response from a single sensor could discriminate exhaled breath of health individuals from those with ovarian cancer and obtained 82% accuracy, without respect to some important confounding factors.

In 2016, Lentka et al. reported a new type fluctuation-induced chemical gas sensor based on monolayer-capped GNPs film[28]. In the detection of VOCs, the resistance fluctuations were characterized by a power spectral density, which offered several parameter values related to frequency. The sensor could easily detect aldehydes via intense fluctuations of resistance with negligible cross-influence of ethanol gas and good reproducibility. Moreover, the sensor could be easily cleaned.

In 2017, Wang's group developed an innovative surface-enhanced Raman scattering (SERS) strategy for aldehydes detection in breath samples, based on dendritic Ag nanocrystals with a bionic antennae structure[29]. Because the multi-branched structure of unique Ag nanocrystals created cavity traps, which increased the interaction time between the gaseous aldehydes and the substrate surface through "cavity-vortex" effect, resulted in increasing the adsorption capacity of aldehydes on solid substrates (Fig. 1). The gaseous aldehydes, VOCs biomarker of lung cancer, were captured onto the dendritic Ag nanocrystal substrate through nucleophilic addition reaction with the pre-grafted *p*-aminothiophenol, an active Raman probe. This strategy can be universally applied to detect other Raman weak-intensity VOCs through simple reactions between VOCs analytes and suitable Raman-active molecules. Furthermore, this facile SERS sensor strategy can be conducted under high moisture conditions with great selectivity and sensitivity towards trace gaseous aldehydes, supplying enormous prospects for noninvasive diagnosis of lung cancer.

Metallic nanoparticles have excellent chemical and physical properties, however, they also suffer from defects such as easy aggregation and oxidation

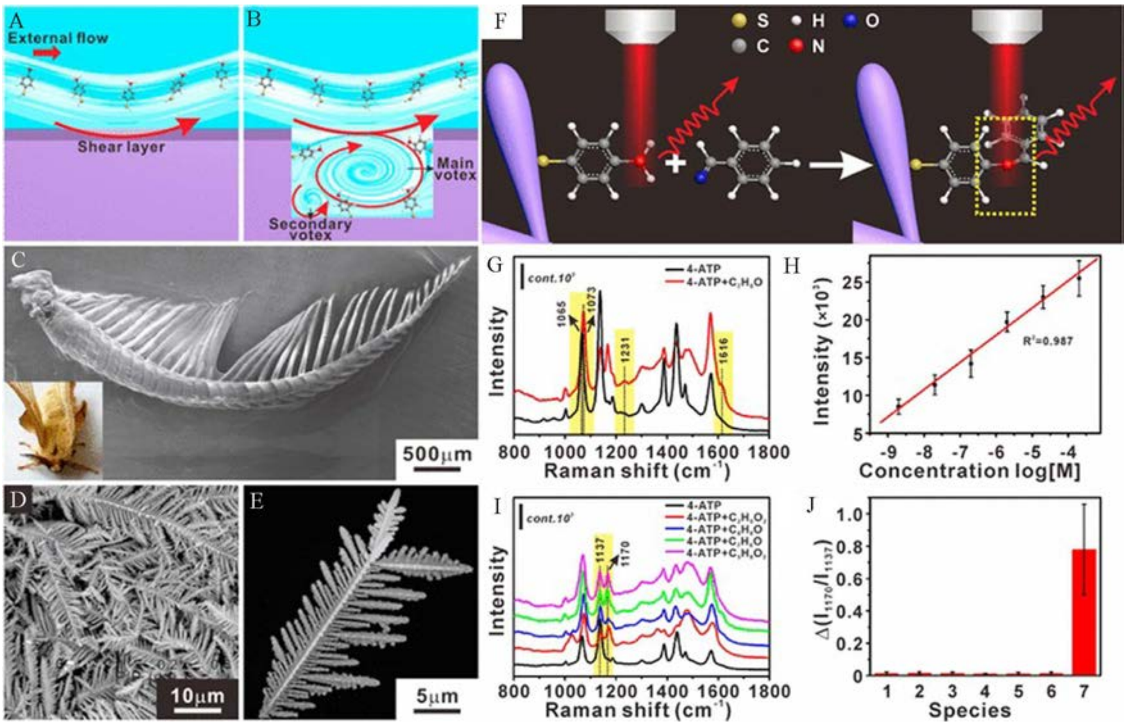

Fig. 1 Sketches of the cavity flow dynamics (A, B). Photo of silkmoth Bombyx mori's antennae (C). Low- and high-resolution SEM images of the dendritic Ag nanocrystals (D, E). Schematic illustration of the strategy to detect aldehydes (F). Raman spectra of the 4-ATP on dendritic Ag nanocrystals before (black) and after (red) reacting with benzaldehydes (G). Raman intensity of C=N peaks (1616 cm^{-1}) with different concentrations of the gaseous benzaldehydes (H). Raman spectra of other 4 aldehydes (I). Detection selectivity of the aldehyde to other six potential interfering lung cancer biomarkers (J). Reproduced with permission from Ref. [29].

which limit their application in VOCs detection. Though these defects can be improved by modifying metallic nanoparticles with organic functionalities or surfactants, the role of metallic nanoparticles in detecting VOCs is restricted.

1.2 Metal Oxide Nanoparticles

Metal oxide semiconductor nanoparticles, such as SnO_2, ZnO and WO_3, have been widely utilized to fabricate chemoresistive sensors for VOCs detection. According to the variation of surrounding breath samples, the electrical conductivity of metal oxide nanoparticles can alter. During detection, the target analyte gas reacted with the adsorbed surface oxygen on solid nanoparticles, changing the transducer ability of the metal oxide semiconductors[30-31]. It is necessary to select and modify the sensing materials carefully and the sensor film structure properly. These are all helpful to increase the selectivity of the reaction at the sensor surface for the target VOCs[32], and to decrease the operating temperature[33-34].

Kim et al. synthesized hierarchical SnO_2 nanofibers with plentiful different sizes of elongated open pores appeared along the fiber direction on the inner and outer surfaces, which can accelerate transportation of gas molecules into the thin-walled sensing layers[35]. The unique nanostructure enabled breath VOCs such as acetone (biomarker of diabetes) and toluene (biomarker of lung cancer) accesses. The responses of highly porous SnO_2 fibers fabricated sensors showed 5-fold higher than that of dense-packed SnO_2 fibers towards acetone. Furthermore, the gas response time was dramatically shortened when decorated the thin-wall assembled SnO_2 nanofibers with uniform Pt nanoparticles (Fig. 2A), even at low acetone concentrations, meanwhile, the response towards toluene was significantly enhanced. This study demonstrated that the thin-wall assembled SnO_2 based breath sensors can accurately diagnose diabetes and showed great potential for lung cancer detection.

Righettoni et al. obtained Si-doped ε-WO_3 nanoparticles film and fabricated a portable sensor for detection of breath acetone, a VOCs biomarker of diabetes[36]. The sensor gave a low detection limit of 20×10^{-9} (V/V) towards acetone with short response and recovery time under the optimized temperature. Importantly, the sensor's response was robust against variations of the gas flow rate at high relative humidities of 80% ~ 90%. They also continuously monitored the acetone level in the breath from test objects, and the results were in agreement with that of advanced proton transfer reaction mass spectrometry (PTR-MS). The fabricated portable devices can accurately track acetone content from breath and showed great potential for breath analysis regardless of background relative humidity.

In 2016, Varghese et al. utilized a simple direct method to prepare ZnO nanotube/nanowire hybrid structure[37]. The chemiresistor fabricated by heat-treated ZnO hybrid structure with large surface area showed the high responses to four low-concentration VOCs (acetophenone, 2-propanol, heptanal and isopropyl myristate) that were considered biomarkers for breast cancer[38]. It is proved that high humidity (relative humidity ~ 90%) or presence of interference gases had little effect on the responses. The author ascribed the high sensitivity to the large surface area of the hybrid structure with porous walls. The devices can act as breath sensors for diagnosing breast cancer in a noninvasive way.

Polynary metal oxide nanomaterials are gradually becoming popular in VOCs sensing detection. Duhan et al. synthesized the ordered mesoporous Ag doped TiO_2/SnO_2 nanomaterials (Ag-(TiO_2/SnO_2)) by a hard template method, and fabricated chemoresistive sensors for ethanol detection (Fig. 2B)[39]. The binary metal oxide nanomaterials doped with Ag nanoparticles had high inherent surface area, mesoporous structure with large pore channels diameter. The mesoporous Ag-(TiO_2/SnO_2) fabricated sensor towards ethanol showed higher response than that of TiO_2/SnO_2 (hard template) and TiO_2/SnO_2 (soft template) by 1.4 times and 3.8 times, respectively. The author speculated that the introduction of Ag nanoparticles enhanced the response performance by chemical sensitization and catalytic oxidation process, and that the mesoporous structure increased the adsorption efficiency of ethanol gas and facilitated charge carriers to propagate across its surface. The as-fabricated chemoresistive sensors showed excellent stability, selectivity and a low detection limit of 1×10^{-6} (V/V) for ethanol, which can be expected for breath VOCs detection.

In a recent study, Zhang et al. prepared ternary metal oxide heterostructure nanofibers (NFs). In the

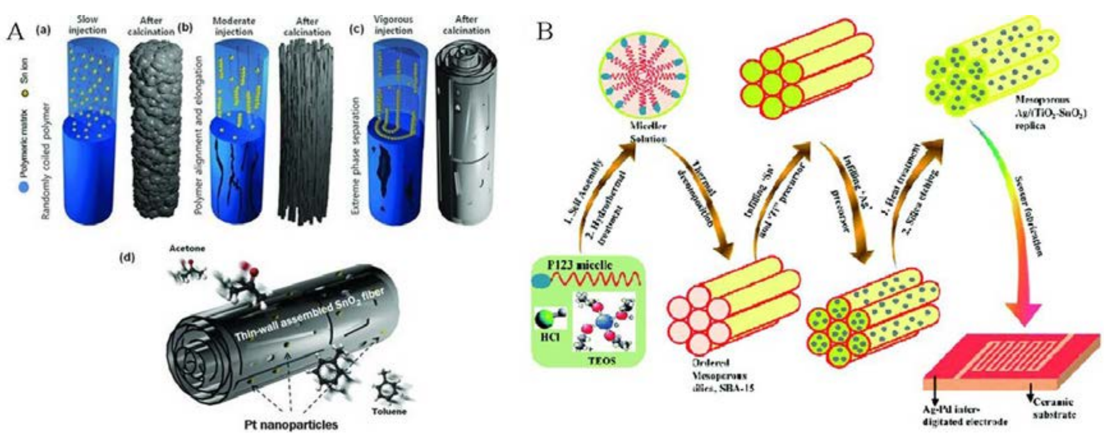

Fig. 2 A) Schematic illustration of morphological evolution of as-spun and calcined SnO_2 fibers prepared at different flow rates (a-c) and Pt-decorated thin-wall assembled SnO_2 fibers (d). Reproduced with permission from Ref.[35]; B) Schematic representation for nanocasting synthesis of ordered mesoporous Ag-(TiO_2/SnO_2) by hard templating of SBA-15. Reproduced with permission from Ref.[39].

hierarchical nanofibers, well-defined p-type NiO semi conductor nanosheets constructed porous shell to from 1D backbone, and nanoparticles of SnO_2 and ZnO as filling materials to accelerate the reaction rate between sensing layer and target VOCs gas (Fig. 3)[40]. With NiO nanosheets as the outer shell of the hybrid nanofibre, it can produce extra rich heterocatalytic reaction active site within interface layers because of its prominent catalytic activity. Furthermore, the utilization ratio of the sensing layer upon target VOCs analytes can be enhanced by the highly porous but robust architecture of NiO nanosheets shell. The SnO_2-ZnO/NiO NFs-based sensor achieved good selectivity to formaldehyde at 150 °C, which was superior over the SnO_2 NFs, SnO_2-ZnO NFs, and NiO NFs under the same conditions.

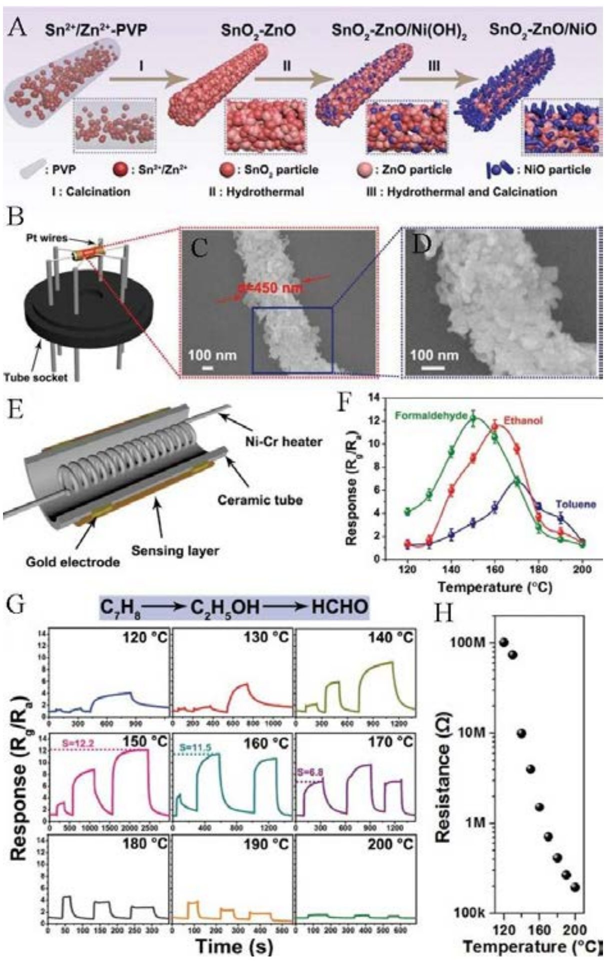

Fig. 3 Synthetic procedure for SnO_2-ZnO/NiO NFs (A). The schematic of the gas sensor structure (B). FESEM image (C) and enlarged image of SnO_2-ZnO/NiO NFs (D). Diagram of the ceramic tube (E). Response versus working temperature curves (F) and response versus time curves of SnO_2-ZnO/NiO NFs-based sensor to different VOCs gases at 120 °C ~ 200 °C (G). Relationship between resistance and temperature (H). Reproduced with permission from Ref. [40].

Although metal oxide nanoparticles have be used to fabricate various chemiresistive sensors for VOCs detection, most of these sensors need to be operated under homogeneous and high temperature condition[41], which results in power consumption and hindering the miniaturization of sensors. Moreover, semiconductor metal oxide-based sensors can be easily interfered and contaminated in VOCs detection[42].

1.3 Carbon-Based Nanomaterials

Carbon-based nanomaterials, including graphene, carbon nanotubes (CNTs), carbon black and etc. showing excellent electrical and mechanical performance, good stability and adsorption capacity, have been applied in VOCs detection in a large scale. However, carbon nanomaterials themselves cannot selectively discriminate different analysts because their powerful adsorptivity, thus, the carbon nanomateris take effect by functionalization or combining with other metallic, metal oxide or polymers in real application[43].

Zilberman et al. fabricated random-network carbon nanotubes (RN-CNTs) chemiresistors with dense hexa-dodecyl-hexa-peri-hexabenzocoronene derivative ($HBC-C_{12}$) cap layers for VOCs gas extracting[44]. The self-assembled $HBC-C_{12}$ cap layers covered different percents of the surface of the chemiresistors which can detect and discriminate nonpolar VOCs biomarkers of lung cancer. In this study, a sensor array formed by $HBC-C_{12}$/RN-CNT bilayers with different surface coverage of $HBC-C_{12}$ showed excellent discriminative abilities between polar and nonpolar VOCs gases at quite low concentrations even under high relative humidity condition. Ultimately, PCA analysis results of four VOCs analytes (hexane, octane, decane, and ethanol) presented in this study could lead to portable, low-power, cost-efficient, non-invasive diagnostic tools to screen cancer via breath analysis.

Swager et al. successfully synthesized covalently sidewall functionalized multi-walled carbon nanotubes (MWCNTs) with a series of cross-sensitive recognition groups[45]. And chemiresistor sensors arrays were fabricated by the functionalized MWCNTs for 20 VOCs identifications. The covalent introduction of specific chemical functional groups onto surfaces of MWCNTs not only enhanced the sensitivity and selectivity towards the targeted VOCs gases, but also achieved excellent stability. By PCA analysis, the distinct response pattern of each VOCs chemical was clearly separated and accurately identified. However, high humidity and low concentration should be considered though the MWCNTs-based chemiresistive sensor arrays presented good sensing performance.

Quang et al. coated quartz crystal microbalance (QCM) with poly-methyl methacrylate (PMMA)-supported graphene film which significantly enhanced the VOCs-sensing properties[46]. Several VOCs gases related to cancers were examined with the fabricated QCM sensor at different concentrations. The graphene-coated QCM sensor can efficiently sense ethanol gas with rapid response-recovery time. The sensing mechanism is explained by the adsorption/desorption behaviors of VOCs gases on the defect sites of graphene nanosheet. Xu et al. prepared the graphene fiber coating with porous and wrinkled structure by a simple one-step hydrothermal method. They analyzed trace amount of breath VOCs by the graphene-based solid phase microextraction-gas chromatography-mass spectrometry (SPME-GC-MS)[47]. As a result, the graphene fiber proved remarkable thermal and mechanical stabilities, durability, and showed high extraction efficiency towards the eight studied VOCs (including alkanes, aldehydes and aromatic compound) because of its large delocalized π-electron system. The method supplies with low detection limit, satisfactory reproducibility and acceptable recoveries under the optimal condition, and can successfully analyze breath samples from lung cancer patients.

Chatterjee et al. fabricated hierarchically structured sensors based on CNTs through spray layer by layer (sLbL) with various surfactants[48]. The sensors were used to investigate the gas sensing performances towards VOCs including 11 biomarkers of lung cancer. Both the sensitivity and selectivity of these CNTs based sensors could be efficiently tailored by the surfactants’ nature. It is assumed that combined expansion of surfactant molecules directly covering CNTs at junctions and of those organised in micelles near CNT which caused an original boosting effect to offer high responses. The sensing performances not only relied on the interactions between these surfactants and the VOCs gases, but also on the supramolecular assembly with CNTs. It is demonstrated that different surfactant-CNTs sensors can detect some specific VOCs biomarkers of lung cancer.

In 2016, Nag et al. synthesized two nanohybrids (IO-POSS/CNT and TSPH-POSS/CNT) by covalently and non-covalently bonding different polyhedral oligomeric silsesquioxanes (POSS) to the surface of functionalized CNTs[49]. Series of quantum resistive sensors fabricated by those nanohybrids with different nano-junctions’ gap and selectivity could be assembled into an array (e-nose). The sensor array showed vast discernment capacity and a part per billion concentration-level resolution towards several lung cancer VOC biomarkers even in the presence of 50% moisture (Fig. 4). The study demonstrated that the IO-POSS/CNT sensor showed high selectivity towards acetone (a VOCs biomarker of lung cancer and diabetes), while TSPH-POSS/CNTs sensor exhibited a better selectivity towards cyclohexane (a biomarker of lung cancer and malignant pleural mesothelioma) because of the tunable organic functionality on the surface of POSS.

Generally, carbon-based nanomaterials are used as promising VOC adsorbents because of their enormously porous structures, however, their selectivity towards VOCs targets is feeble. This insufficiency can be improved by modifying with appropriate functionalities which can react with VOCs analytes. Moreover, factors of aggregation, temperature and water vapor content should be considered by using carbon-based nanomaterials in application of VOCs detection[50].

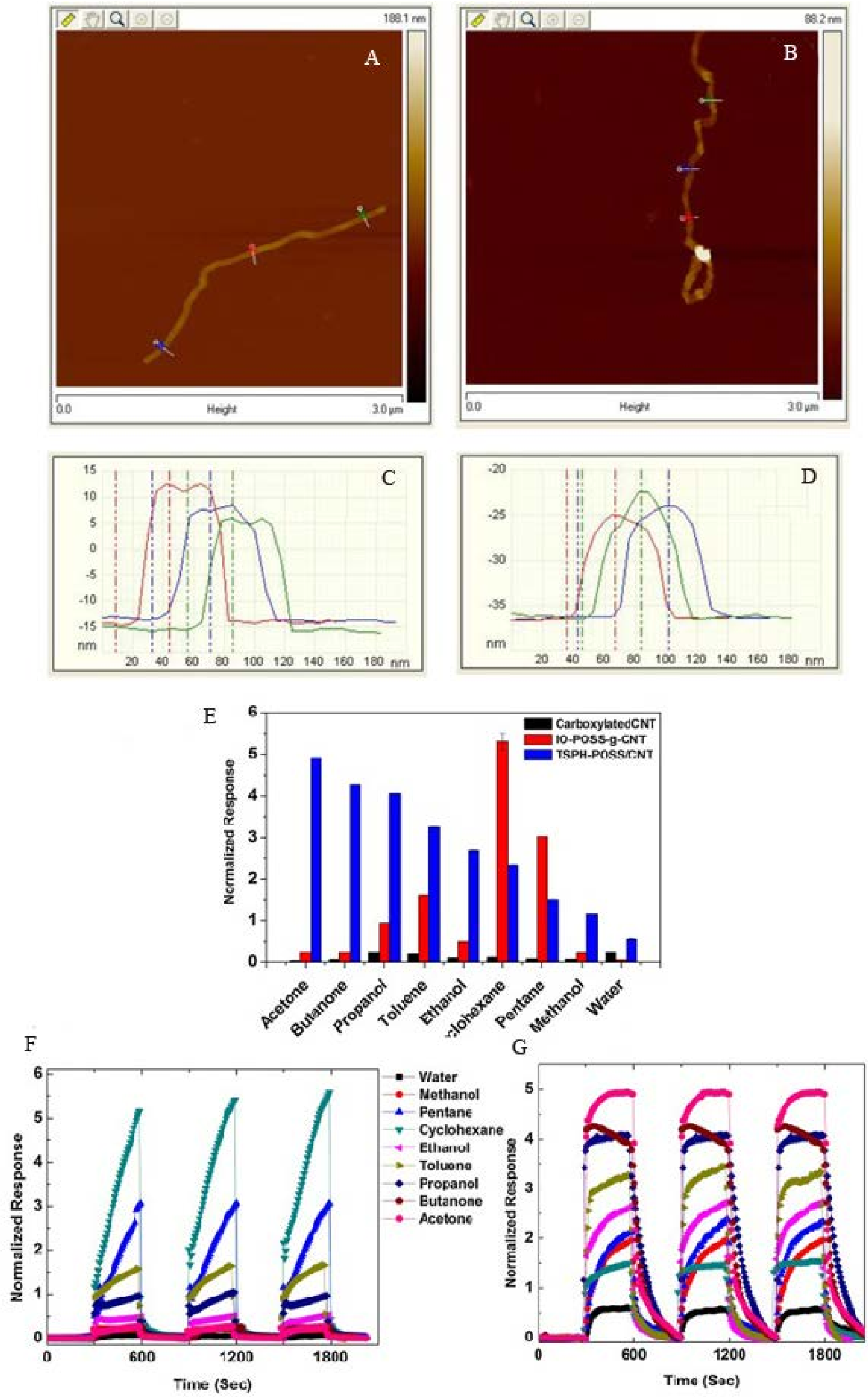

Fig. 4 AFM height images and profile measurement data for IO-POSS-g-CNT (A, C) and carboxylated CNT (B, D); Average responses of a 3-sensor array towards 9 different saturated VOCs (E), chemo-resistive signals of IO-POSS-g-CNT sensor (F) and TSPH-POSS/CNT sensor (G). Reproduced with permission from Ref. [49].

1.4 Composite Nanomaterials

Metallic, metal oxide and carbon-based nanomaterials have already been applied to fabricate various VOCs gas sensors. However, some of these materials have such drawbacks as poor sensitivity at room temperature, lack of thermal stability and/or selectivity which limit their practical applications for VOCs detection [51-52]. Fortunately, the delicate design and combination of two or more unique materials at nanoscale known as composite nanomaterials have proven to be a promising manner for the development of VOCs sensing devices[53-55]. By combining materials with different properties from metallic nanoparticles, metal oxides, carbon-based nanomaterials or organic components, improved final properties can be attained. Therefore, composite nanomaterials are regard as a new generation of advanced materials.

Chemiresistors for VOCs targets detection can be designed based on nanomaterial films which capping conductive inorganic nanomaterials with organic ligands or functional groups[56-59]. Inorganic nanomaterial offers the electrical conductivity, while the organic layer functions as a sensing layer for absorbing VOCs gases[21]. Nag et al. developed an ingenious electronic nose system composing of various functionalized β-cyclodextrins (CD) wrapped reduced graphene oxide (RGO) sensors, which showed unique capacity to discriminate several VOCs[60]. Pyrene adamantane as a linker was used to chemically functionalize CD with RGO to construct a supermolecular assemble. Because CD has the ability to form host-guest inclusion complex and its chemical functionality can be modulated, combining with the large surface area and high electrical conductivity of graphene, the resulted conductive CD nanocomposite sensors exhibited high sensitivity towards benzene vapour at a low concentration of $400 \times 10^{-9}(V/V)$ without any preconcentration. These sensors also demonstrated great discrimination capacity towards the 10 VOC biomarkers of lung cancer when combined with PCA analysis.

Chen et al. fabricated a flexible chemiresistor based on Pt nanoparticles decorated WO_3/reduced graphene oxide (GO) nanosheets (WO_3/Pt-GNs) film via gravure technique for VOCs detection[61]. Because WO_3 were not wrapped into small sizes of GNs, many (002) facets of WO_3 were exposed, which exhibited a strong interaction to acetone gases. Moreover, massive p-n junctions formed at the WO_3/GNs interface could quickly transform acetone into CO_2 and H_2O with the help of O^-/O_2^-, combining the introduction of catalytic Pt nanoparticles, these all contributed to enhance the sensing performance for acetone detection. Finally, a printed WO_3/Pt-GNs sensor with high selectivity and sensitivity, fast response and recovery time towards acetone gas was presented, which shows great potential cancer screening via breath VOCs.

Li et al. prepared a graphene/polyaniline (G/PANI) coating by *in situ* electrodeposition method. The coating was introduced to needle trap microextraction (NTME) for extracting VOCs gases[62]. Combining the favorable electrical characteristics and large specific surface area of graphene with good mechanical, processing properties and functional groups of PANI, as well as chemically stable donor-acceptor complex formed between graphene and PANI, the modified needle trap exhibited superior extraction performance towards 8 VOCs with low detection limits and better linearity than 3 commercial SPME fibers. Furthermore, the NTME was developed by associating with GC-MC technique and successfully used to analyze VOCs from human breath and lung cancer cell lines. The results proved this method to be a promising, sensitive and eco-friendly way for VOCs detection, and provided an alternative, noninvasive tool to screen lung cancer.

Daneshkhah et al. presented 3 kinds of breath VOCs sensors based on poly(vinylidene fluoride-hexafluoropropylene) (PVDF-HFP) composite [63]. The sensors showed diverse sensitivities to several representative VOCs found in breath. Sensor-1 fabricated by spray coating of PVDF-HFP/C65 (C65 refers to carbon black) composite exhibited a large increase in resistance when contacted with acetone gas, while a negligible change for water, and minor changes for ethanol, isoprene, and 2-EHA vapors. Sensor-2 fabricated by spin coating with a two-layer structure of PVDF-HFP and PVDF-HFP/C65 obtained obvious improved response time compared to Sensor-1 for different analysts. Sensor-3 fabricated by spin coating of PVDF-HFP/C65/CNTs composite with the addition of CNTs caused a decreased resistance when exposed to water, which provided a higher selectivity in contrast to Sensors 1 & 2 for the system. The combined responses of these sensors indicated a remarkable selectivity for the detection of VOCs from breath by PCA analysis.

In 2017, Liu et al. developed an intelligent sensing system consisting of a handheld wireless device and a smartphone which could monitor VOCs in real time through measuring alternative current (AC) impedance[64]. In the sensing system, ZnO was used for electron transferring with the electrode, graphene for catalytic oxidation, and nitrocellulose for immobilizing film to modify the interdigital electrodes. Impedance responses were generated when the interdigital electrodes contacted with VOCs. The hand-held device could sense the responses and delivered impedance data via Bluetooth, resulted in final responses displayed on a smartphone screen, and then corresponding concentration of VOCs analytes could be calculated (Fig. 5). The selectivity of the system was proved to be related to the characteristic frequencies of VOCs. The results showed a low detection limit of 1.56×10^{-6} (V/V) towards acetone and could differentiate acetone from other VOCs by AC impedance spectroscopy. Moreover, the acetone contents in human breath before and after exercise were measured to assess human metabolism. The smartphone-based system provided a facile, portable, non-invasive way to effectively monitor breath VOCs and could engage in diagnosis of some diseases.

Composite nanomaterials combine different properties from various types of nanomaterials, which can make up for the shortage of single nanomaterial, and enhance the sensitivity and selectivity of sensors, as well as endow them with some other unexpected features, such as durability, stability, moisture-resistance, and etc. It seems to be an irresistible trend for the usage of nanomaterials in VOCs gas detection.

1.5 MOFs-Based Nanomaterials

Metal-organic frameworks (MOFs) are crystalline hybrid coordination polymers with metal ions or clusters as nodes, and organic ligands as linkers[65]. With

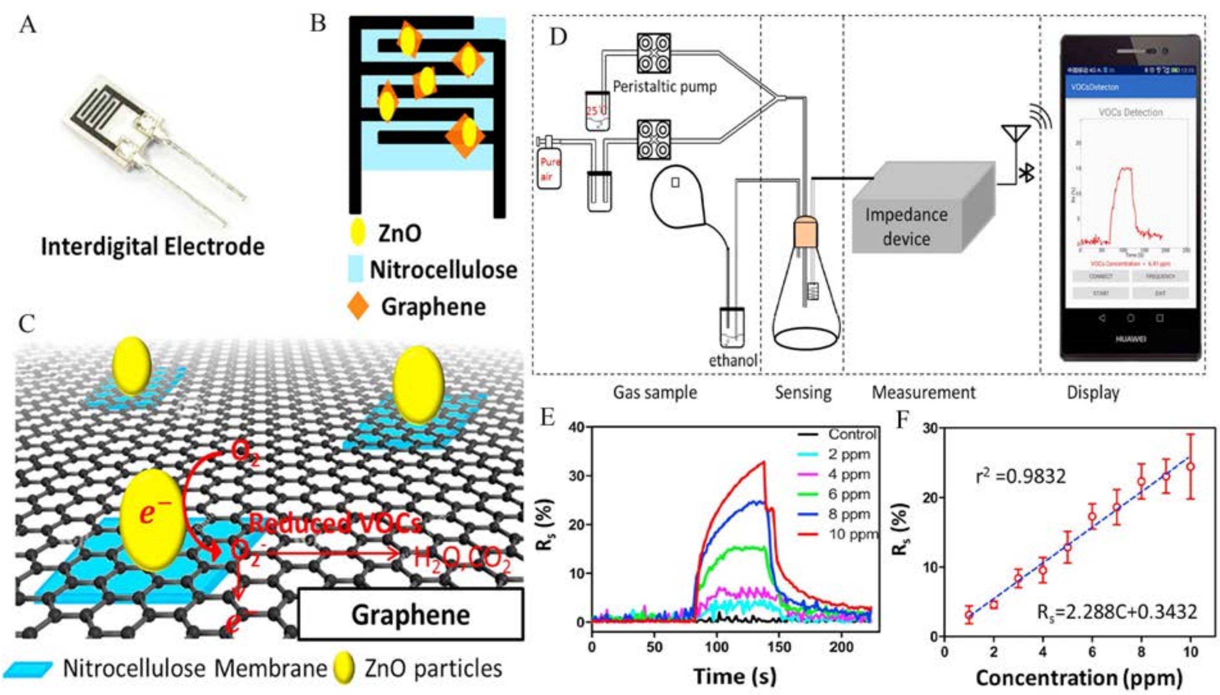

Fig. 5 Photo of the interdigital electrodes (A). Schematic diagram of the electrodes with immobilization of nanomaterials (B). The VOCs detections mechanism on the modified electrodes (C). Schematic illustration of the smartphone-based system for VOCs detection (D). Responses to acetone at different concentrations (E) and the corresponding linear dose-dependent fitting curve (F). Reproduced with permission from Ref. [64].

devisable and regulable structures and functions , MOFs exhibit many superiorities over traditional inorganic porous materials[66], and have applications in the fields of gas storage, catalysis, separation, supercapacitor, solar cell, and drug delivery etc[67-72]. Because of the unique hybrid structures of MOFs, which can offer tunable fluorescence[73-74], MOFs are considered to have tremendous potential in probing VOCs.

In 2012, Bahreynithe et al. investigated gravimetric sensors fabricated with porous HKUST-1 MOF to detect three VOCs gases[75]. It is proved that the sensors prepared through vertical electrospraying formed homogeneous thin MOF films on the surface of quartz resonators and exhibited the improved response to VOCs compared with the other sensor fabricated by drop-casting. The sensor resolution and stability for the quartz resonators were greatly enhanced by the electrospraying technique. It was the first time to detect VOCs using MOFs and the results indicated that MOF films exhibited great potential for VOCs sensing applications with low detection limits of 50, 10, and 2×10^{-6} (V/V) for acetone, tetrahydro furan, and isopropyl alcohol, respectively.

In 2016, Zeinali et al. fabricated a capacitive sensor device with MOF (Cu-BTC) nanoparticles as dielectric layer for VOCs gases detection[76]. The fabricated sensors showed a sandwich structure with copper plate as the back electrode and interconnected porous Ag paste as the upper electrode. VOCs analytes with high dielectric constant adsorbed and diffused throughout in Cu-BTC layer and caused obvious capacitance changes of the sensors. The capacitive sensor can sensitively detect polar VOCs analytes (such as methanol, ethanol, isopropanol and acetone) at parts per million concentration levels, along with good linearity, reversible response and rational response time at different VOCs concentrations. The sensors were conducted at room temperature and 10% humidity.

In a recent study, Ghanbarian et al. successfully synthesized flexible-structured MIL-53(CrFe) MOFs and further fabricated MIL-53(CrFe)/Ag/CNTs ternary nanocomposites-based resistive sensor device for VOCs gases detection[77]. The introductions of CNTs and Ag nanoparticles made the MOFs with better semi-conductivity. The proposed mechanism is described as: when the sensor was exposed to polar VOCs gases (such as alcohols), the captured electrons from nanocomposite led to a decrease in the conductivity. However, exposing the sensor to non-polar gases would obtain a decrease in the potential barrier height, because the adsorbate electrons from oxygen would be transferred to MIL-53 (Cr-Fe) film and further be transported by CNTs. The resistive sensor showed high response towards methanol and gave a detection limit of 30.5×10^{-6} (V/V) at ambient conditions.

However, the performance of MOFs nanomaterials-base sensors is usually influenced by high humidity, and most of these sensing processes are conducted at a low relative humidity, which limits their practical application. In recent years, this situation has been improved with the joint efforts of researchers.

SERS as an ultra-sensitive and humidity immune analytical technique shows a great potential in trace VOCs detection. Wang's group utilized the Raman label molecular to fix the small cross-sections and weakly adsorbed species. The self-assembly of gold superparticles (GSPs) is encapsulated into a ZIF-8 layer by chemical reaction and formed GSPs@ZIF-8 structure (Fig. 6)[78]. In this study, the ordered GSPs act as hotspot and MOFs shell depress the attenuation of the electromagnetic field around the GSPs surface, resulting in an increased penetration depth (Z) in the MOFs dielectric media. Furthermore, the porous structure of MOF shell changed the travelled fashion and process of gaseous molecule. When the gaseous molecule flowed through MOFs shell, the molecular mobility was restricted in the nano-channel by ligand molecules, where the gaseous molecular inclined to form a quasi-condensed phase[79]. As a result, more analytes reacted with the Raman probe and more significant changes were recorded in the Raman spectrum compared with the bare GSPs. The SERS sensor exhibited high sensitivity and selectivity towards

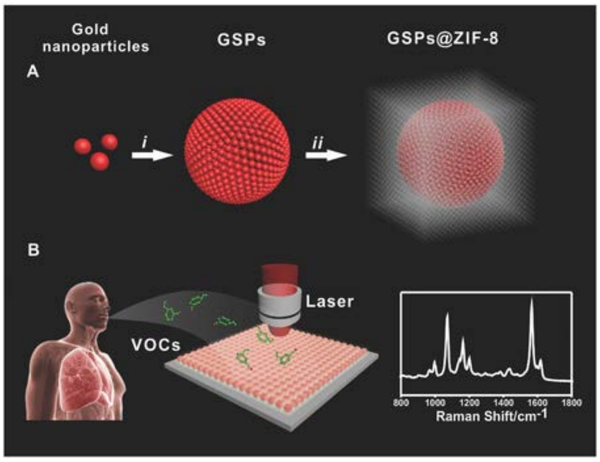

Fig. 6 (A) Schematic diagram of synthesizing GSP@ZIF-8 core-shell structure: (i) gold nanoparticles assembled into GSPs, (ii) ZIF-8 shell coated on GSP surface. (B) Volatile organic compound (VOCs) detection via SERS spectroscopy. Reproduced with permission from Ref.[78].

4-ethylbenzaldehyde, a gaseous lung cancer biomarker, with a low detection limit of 10^{-9} (V/V, part per billion concentration level). The results demonstrated that GSPs@ZIF-8 structures were capable of selectively tracing gaseous cancer biomarker in exhaled breath. Transport model of gaseous molecules in porous media was changed because of the collisions between gas molecules and the porous media as directly evidenced by total internal reflection fluorescence micrographs, which is the first evidence of our eyes telling a similar liquid-transportation behavior of gaseous molecules under conditions of normal pressure and temperature.

MOFs as emerging nanomaterials with versatility have attracted much attention and been utilized in many fields. They are of great potential for application in detection VOCs from exhaled breath because of their special structures and more functions can be explored from them.

2 Conclusions and Future Perspectives

To sum up, recent advances in application of nanomaterials in the detection of exhaled breath VOCs biomarkers are reviewed. Since breath samples are easy to be collected and analyzed, the detection process is painless and noninvasive, VOCs biomarker detection from exhaled breath shows grate potential for cancer diagnosis or regular healthcare. Meanwhile, though nanomaterials play major roles in VOC biomarkers detection, the use of a certain type of nanomaterials can no longer meet the requirements of detection sensitivity and accuracy. Various nanocomposites combined the properties of different materials have begun to flourish in the field of VOCs sensing, because varied functionalities and features related to each type of the composing material can work synergistically for the VOCs analytes detection.

For sensitively sensing of VOCs from exhaled breath, two factors must be concerned: high humidity which generates large interference response and degradation of solid substrate which consumes sensitivity and durability. From this review, it can be conclude that some strategies help to improve the detection performance of VOCs in exhaled breath by using nanomaterials. Firstly, to design nanomaterials rationally, such as adjusting nanomaterials to ordered or hierarchical structure, or modified nanomaterials with functionalities, can lead to favorable properties. Secondly, the synthesis methods of nanomaterials may play an essential role, which can tune particle size and porosity to an appropriate range, resulting in enhancing properties of nanomaterials. Additionally, the property of analyte should be considered so that suitable nanomaterials or techniques can be chosen for further detection. Finally, new nanomaterials, such as water-insensitive materials, can be explored and new analytical methods can also be employed, aiming to obtain detection of very low amounts of VOCs gases.

SERS strategy can be conducted under condition of very high humidity due to its negligible effect on Raman spectroscopy, which provides enormous prospects for noninvasive diagnoses of lung cancer *in vitro* at early stage. However, the sensitivity and penetration depth (Z) need to be further improved. Perovskite film as a dielectric medium retards attenuation of the electromagnetic evanescent wave of elongated tetrahexahedral gold nanoparticle (ETHH Au

NP) arrays, indicating that Superficial Layer-enhanced Raman Scattering occurs in the superficial layer rather than just on the ETHH Au NP surface, which would extend the application of Raman[80]. The perpvskite coated gold arrays would be a fascinating material for VOCs detection. Moreover, more effective adsorbent nanomaterials, such as nanocages, which can slow down gas molecular mobility and guide more analytes to the plasma, are continue to be explored.

For the detection of VOCs from exhaled for cancer diagnosis, some challenges and barriers still need to be overcome. First of all, the detection techniques should be chosen properly. Various factors such as the materials used, the performance (sensitivity, selectivity, response time, etc.), expense, operation and so on should be taken into consideration. Unfortunately, an enhanced sensitivity may lead to an undesired selectivity decrease, which is adverse to exclude interference from undesirable analytes and environmental compounds. Moreover, features such as stability, reproducibility and durability should be improved for long-term and real applications under various conditions irrespective of temperature, humidity etc. For practical detection of VOCs with reusability and durability, nondestructive sensing techniques and undegradable, water-insensitive materials can be an alternative choice. Furthermore, to catch up the miniaturization trend of technology worldwide, the main challenge for VOCs detection should be integrating the sensing materials into flexible, portable and miniaturized devices for multi-target analytes detection without interference, such as a wearable e-nose and detection with a smartphone. Finally, although the researches for VOCs detection are in full swing, many mechanisms of the current detection techniques are expressed ambiguously, the detection mechanism should be explored and explained in detail. The success development of super-capability detection device for VOCs analysis will require the convergence of interdisciplinary knowledge. In order to manufacture facial, inexpensive, and portable VOCs sensors at an industrial scale for practical application, researchers and related industries are trying their best to pursue these challenges.

Acknowledgements

This work was financially supported by the 1,000 Young Talents Program, the National Science Foundation of China Grant (Nos. 21621062, 21635002), and the Chinese Academy of Sciences.

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纳米材料在用于癌症诊断的呼出气挥发性有机物检测中的应用

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摘要：细胞新陈代谢的变化会导致挥发性有机化合物（VOCs）类型及含量发生变化，因此可通过分析某些标志性 VOCs 简立起多种疾病早期诊断的模型. 人体呼出物中特征 VOCs 的检测作为一种非侵入性、无损的检测手段，近些年在疾病检测领域已成为世界范围内的研究热点. 其中，纳米材料可用于增强传感器性能，并使传感器便携式小型化，推进检测传感器进入临床. 在这篇综述中，作者将种类繁多的传感器中用到的纳米材料归纳总结为金属、金属氧化物、碳基、复合物和 MOFs 基纳米材料等几类，并讨论了不同类纳米材料在 VOCs 检测中的优劣势. 本文所建立起的分析方法及讨论有助于进一步了解检测技术的优越性与局限性. 最后，作者对利用 VOCs 的检测实现癌症早期筛选的研究及发展提出了个人观点.

关键词：挥发性有机化合物；纳米材料；癌症；生物标志物；呼出气