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Rapid and highly sensitive strain-effect graphene-based bio-sensor for detection of stroke and cancer bio-markers

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Here, we propose a highly sensitive and rapid bio-sensor for the detection of bio-markers for stroke and cancer-related diseases, based on utilizing the adsorption properties of ruthenium carbonyl (Ru-CO) clusters onto monolayer graphene (MG). A fast rate of decarbonylation of Ru-CO to form ruthenium oxide nanoparticles (RuO_2 NPs) on MG was observed. Quantitative detection of matrix metalloproteinase-2 (MMP-2) (bio-marker for stroke and vascular diseases) was demonstrated by tracking the spectral shift of the characteristic G band of graphene caused by the adsorption of RuO_2 NPs. A concentration of as low as 17 ng/ml of MMP-2 was detected in a simulated clinical serum sample. This effective bio-sensor has the potential to revolutionize the biomedical field in the early detection and possible prevention of stroke disease and cancer diagnosis.

Introduction

Stroke occurs when blood flow to an area is cut off leading to brain damage.[1, 2] Early intervention is of utmost importance for maximum effectiveness and survivability of the patient. One of the purported early stroke detection method is the presence of matrix metalloproteinase 2 (named MMP-2) in the blood stream. [3, 4] Several studies have reported that elevated levels of MMP-2 shows strong correlation to certain diseases, with stroke being one of them. This makes MMP-2 a known bio-marker for the early detection of stroke in high risk patients. Moreover, MMP-2 expression level has also been found to be linked to many types of cancer, including bladder cancer and breast cancer.[5-7]

Thus, there has been considerable interest in the development of rapid and sensitive bio-sensors for MMP-2. Several groups proposed bio-sensors that make use of electrochemical peptide cleaving,[8] electro-generated chemiluminescence[9] and even integrated enzyme mediated color development reaction with common electronics.[10] However, these methods are complex and require specific and sometimes expensive equipment. Hence, there is a need to develop simple, rapid and yet sensitive bio-sensors for widespread adoption.

In recent developments, our group has reported a complete vascular disease treatment utilizing size dependent properties of Ru-base CORMs.[11] Vascular treatment can be fulfilled via fast response and highly localized vasodilation through triggered CO release, and rapid bio-sensing for stroke monitoring can be achieved. It was found that Ru_{11}-CO was able to form a ruthenium oxide (RuO_2) with graphene oxide (GO) at room temperature almost instantaneously, resulting in a breakdown of the high nuclearity ruthenium carbonyl cluster, $[(Ph_3P)_2N]_3[Ru_{11}H(CO)_{27}]$, (named Ru_{11}-CO).

Following on from that work, it was envisioned that a similar mechanism can be predicted when Ru_{11}-CO is complexed with monolayer graphene (MG) instead of GO. In this paper, we report a rapid and sensitive bio-sensor for the MMP-2 comprising of a composite of MG and adsorbed Ru_{11}-CO. The presence and quantification of MMP-2 is monitored via a peptide cleave-and-bind mechanism which results in the Raman spectral shift in the G band of the MG substrate due to formation of RuO_2 NPs on the MG surface.

Results and discussion

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The structures of the obtained Ru_{11}-CO is shown in Fig. 1A (CO ligand was omitted to ensure clarity) and the adsorption of Ru_{11}-CO onto MG was investigated via Fourier Transform Infrared spectroscopy (FTIR). As can be seen in Fig. 1B, the FTIR spectra for Ru_{11} showed strong bands at 2000 cm^{-1} region. (The Ru_{11}.CO IR spectrum pattern change was observed after 1 min of incubation with MG.) It suggests that Ru_{11}-CO clusters exhibited stronger adsorption onto MG.[11] This can be due to the surface ionicity (e.g. contribution of oxygenated functional groups) of MG. It has been well known in organometallic chemistry that oxygenated functional groups such as OH groups can behave as a Bronsted or Lewis base leading to nucleophilic or oxidative attack on transition metal center to form Ru-O bonds (Fig.1C shows the proposed reaction scheme).[12-14]

We recently reported that as the nuclearity of the Ru-CO cluster increases, the rate of $Ru^{II}(CO)_2$ formation also increases.[11] We found that Ru_{11}-CO clusters form $Ru^{II}(CO)_2$ spontaneously, whereas low nuclearity Ru-CO clusters such as Ru_1-CO almost not exhibit the $Ru^{II}(CO)_2$ bands. It was also observed that a subsequent oxidation of $Ru^{II}(CO)_2$ to RuO_2 nanoparticles occurs too, with a breakdown of the Ru nuclear structure.

To investigate the deposition of Ru_{11}-CO on MG, Raman spectroscopy was used to probe the Ru_{11}-CO-MG composites. The Raman spectra of monolayer graphene mixed with Ru_{11}-CO (1 minute incubation) indicated the presence of characteristic A_1g and B_2g RuO_2 Raman peaks (Fig. 1D) (Eg peak is masked by silicon peak).[15-19] Therefore, it can be concluded that Ru_{11}-CO forms RuO_2 nanoparticles instantly as it did on GO, in agreement with our hypothesis.

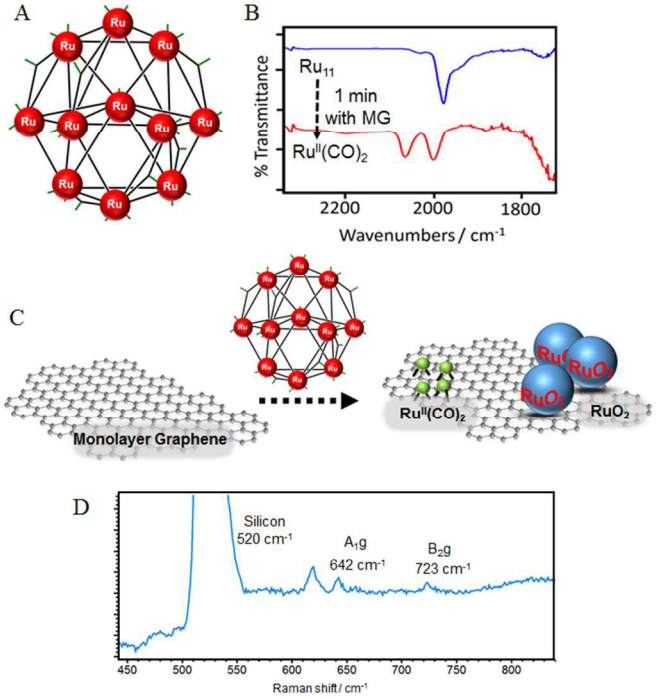

Fig. 1 (A) Structures of the Ru_{11}-CO clusters. (B) FTIR spectra of Ru_{11}-CO clusters mixed with MG. (C) Schematic depicting the reaction of Ru_{11}-CO metal carbonyl cluster adsorption onto MG surface. (D) Raman spectra of Ru_{11}-CO on MG with 1 minute incubation.

The fast transformation of Ru_{11}-CO into RuO_2 NPs on the MG surface was incorporated into a protease "cleave-and-bind" bio-sensing mechanism. A schematic of the "cleave-and-bind" mechanism for MMP-2 (bio-marker) detection is given in Fig. 2A.[20] Briefly, pristine chemically vapor deposited (CVD) MG substrates were first functionalized with MMP-2-specific peptide (G-K(TAMRA)-G-P-L-G-V-R-G-CONH2) conjugated with amine reactive 20 kDa methoxy-PEG-succimidyl R-methylbutanoate.[21] The peptide polymer can form a self-assembly complex with MG via π–π interaction through the hydrophobic domain of tetramethylrhodamine (TAMRA).[20] This layer of peptide serves to shield the MG surface from the adsorption of Ru_{11}-CO onto MG to form RuO_2 NPs. Upon incubation at 37°C with solution containing MMP-2, the peptide will be cleaved from the surface of MG by the MMP-2, where a subsequent incubation with Ru_{11}-CO solution will induce the formation of RuO_2 NPs "doped" graphene. Although CVD graphene has low O/C ratio, the graphene surface is highly pristine and thus having less defects, providing better signal-noise contrast as compared to GO.[22]

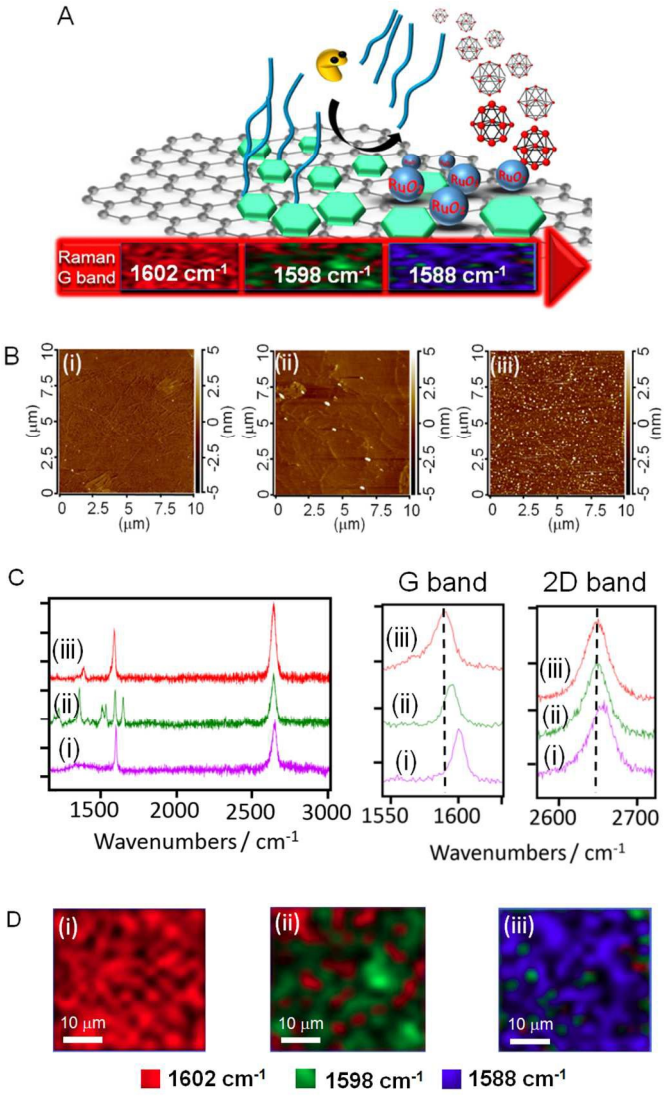

Fig. 2 (A) Schematic of the cleave-and-bind based bio-sensor for the detection of MMP-2 using a monolayer graphene and Ru_{11}-CO composite probe. (B) AFM height images and (C) Raman spectra depicting shifts in the G peak as RuO_2 is formed on the surface of monolayer graphene. (D) Raman mapping of (i) un-functionalized graphene, (ii) MMP-2 peptide functionalized graphene and (iii) after incubation with MMP-2 plus Ru_{11}-CO.

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Figure 2B(i) shows the AFM image of the un-functionalized MG sample with a relatively flat and featureless surface. Upon peptide functionalization, strand-like features can be observed, confirming the binding of MMP-2-specific peptide onto MG surface (Fig. 2B (ii)). Further incubation with MMP-2 and Ru_{11}-CO resulted in numerous nanoparticle-like features on the graphene surface (Fig. 2B (iii)), indicating the formation and presence of RuO_2 NPs. Various RuO_2 NPs size was observed on the surface of MG; with the maximum size of 20 nm (Fig. 3). No significant increase in size of RuO_2 NPs was observed after further incubation of Ru_{11}-CO with MG (Fig. S1). The formation of Ru_{11}-CO solely depends on the exposure of oxygenated functional group on MG to Ru_{11}-CO which is controlled by the amount of peptide that was cleaved and removed from MG surface.

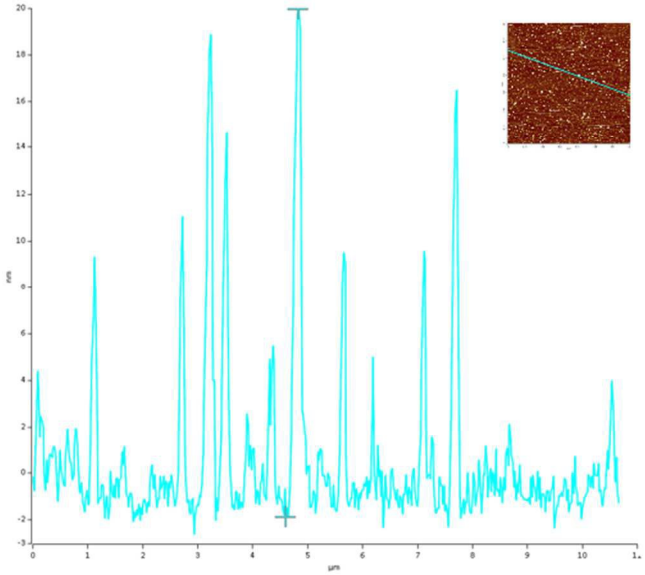

Fig. 3 AFM height measurement of RuO_2 NPs formed over MG.

The formation of RuO_2 NPs is expected to induce strain on the graphene surface, where *strain-effected peak shifts could be used as an effective way for quantifiable bio-sensing*. The concentration of MMP-2 present can be correlated to the quantified formation of RuO_2 NPs on the surface of MG via monitoring of the blue-shift of the Raman G peak band.[23-25] The Raman analysis in Fig. 2C revealed strong 2D intensity, low D and G band intensity, which is representative of high-quality graphene. A significant shift of G band peak (from 1602 cm^{-1} to 1588 cm^{-1}) for MG incubated with Ru_{11}-CO for 1 minute confirms the formation of RuO_2 NPs on the surface. By focusing on the G band of MG at 1602 cm^{-1}, a false color chemical image can be generated to investigate the changes on the surface of graphene. As can be seen in Fig. 2D (i), a uniform red coloration is observed based on 1602 cm^{-1} from the un-functionalized monolayer graphene. The functionalization of MMP-2-specific peptide via π–π stacking of aromatic ring between MMP-2-specific peptide and graphene induced significant strain on the graphene layer, causing the distribution of G band at 1602 cm^{-1} to decrease while also blue-shifting to 1598 cm^{-1} (Fig. 2D (ii)). The subsequent doping of RuO_2 NPs on graphene induces further blue-shifting of the G band to 1588 cm^{-1} (Fig. 2D (iii)). The uniformity of the detected signals indicates a uniform functionalization of the MMP-2-specific peptide as well as RuO_2 NPs formation, corroborating well with AFM results.

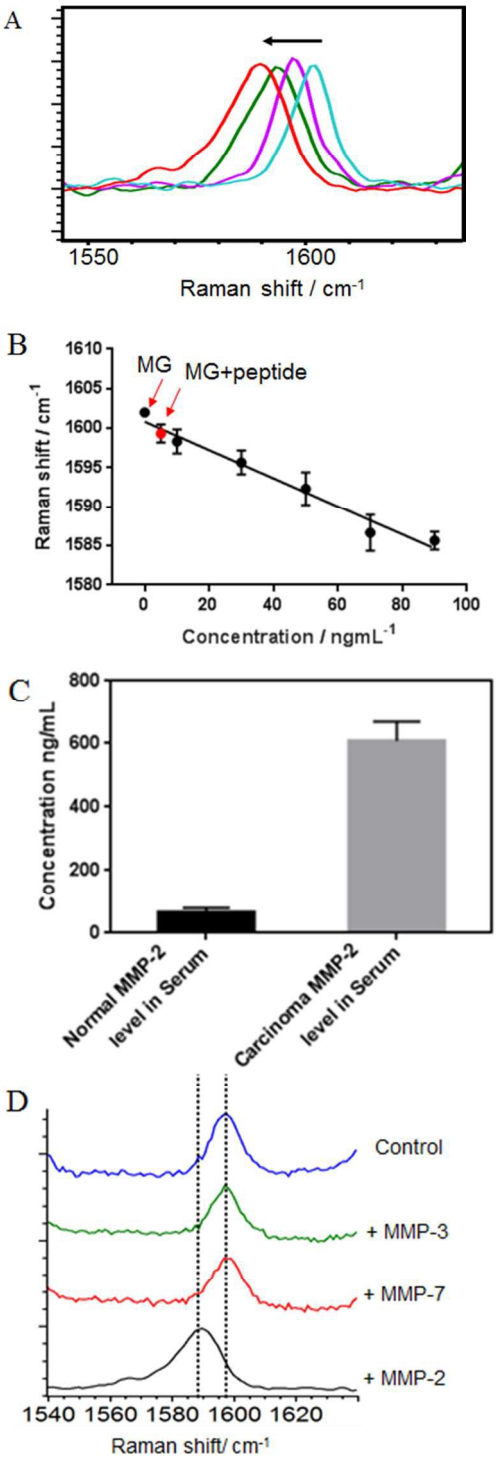

Fig. 4. (A) Correlation of MMP-2 concentration with the shift in G peak and (B) Quantitative plot for MMP-2. (C) Detection of simulated clinical serum samples spiked with MMP-2 (healthy people 75 ng/mL vs cancer patients 600 ng/mL). (D) Specific study of MMP-2 peptide functionalized MG with other MMPs.

The increasing strain on the graphene surface due to the formation of RuO_2 NPs (detected as the shift in the G band peak) shows a linear relation with the concentration of MMP-2 (Fig. 4A and B); the limit of detection is estimated at 17 ng/mL. The detection of MMP-2 was also assessed with albumin serum. The

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recovery range was determined to be higher than 80% (pure MMP-2: 93%; MMP-2 with albumin serum: 87%), which demonstrated acceptable selectivity.

Plasma levels of MMP-2 has been proposed to be a useful bio-marker for assessing pathological events. As a proof-of-concept to demonstrate the feasibility of utilizing our developed organometallic-graphene based bio-sensing platform for bio-markers detection and diagnosis, two simulated clinical serum samples spiked with MMP-2 at concentrations similar to those found in healthy people, and cancer patients were analyzed (healthy people 75 ng/mL vs cancer patients ~ 600 ng/mL).[26, 27] The MMP-2 spiked serum sample and the substrate were incubated before the addition of Ru_{11}-CO. Our results showed that the spiked serum samples produced similar MMP-2 values as that of the added MMP-2 concentration (Fig. 4C), suggesting that our developed organometallic-graphene sensor can effectively detect MMP-2 in the presence of serum. The specificity study was also performed with serum spiked with MMP-3 and MMP-7, respectively. No significant peak shift was detected (Fig. 4D). It indicates the MMP-2 peptide functionalized MG exhibits good specificity to MMP-2. Thus the efficacy of a MMP-2 detection based on the strain effects on graphene surface using the ultra-fast Ru_{11}-CO adsorption mechanism has been successfully demonstrated for the first time.

A comparison with various other methods used in the detection of MMP-2 is summarized in Table 1. All methods in the references of 7-10 were verified by samples including MMP-2 spiked serum, MMP-2 urine and cancer cells. They all posed variation from 3.3% to 12%, which is similar to our method. Although they have lower limit of detection (LOD), they require either longer detection time (methods in reference 7 (15 min) and reference 10 (60 min)) or longer pre-measurement time (method in reference 8 (incubation of EXO III for 1 hour before measurement). As compared with methods in references 8 and 10, the process was done in conjunction with the presence of Exo III and β-lactamase. Addition of other enzymes in the detection of MMP-2 may further complicated the detection process such as temperature, salt concentration and the ratio of enzyme to MMP-2.

Table 1. Comparison of Various Biosensors & Methods for detection of MMP-2

Method	LOD/ Detection Range	Time	Ref
Fluorescence	8.7 $pgmL^{-1}$/ 0.03-6.2 $ngmL^{-1}$	90 min	7
Electrochemical	0.15 $pgmL^{-1}$/ 0.5-50,000 $pgmL^{-1}$	60 min	8
Electrochemical Luminescence	0.7 $ngmL^{-1}$/ 50-500 $ngmL^{-1}$	60 min	9
Photometry	0.8 $ngmL^{-1}$/ 0-8 $ngmL^{-1}$	60 min	10

Conclusion

By utilizing the ultra-fast conversion of Ru_{11}-CO to RuO_2 NPs when incubated with MG, a rapid and sensitive bio-sensor for the detection of MMP-2 (a well-known cancer and stroke bio-marker) was demonstrated. MMP-2-specific peptide functionalization of MG surface was carried out and incubated with solution containing MMP-2 and Ru_{11}-CO. The presence of MMP-2 will cleave the peptide from the surface of MG, allowing the binding of Ru_{11}-CO onto MG and subsequent conversion to RuO_2 NPs (cleave-and-bind detection mechanism). By monitoring the shift of the Raman G band peak MG, a quantifiable correlation between bound RuO_2 NPs and the concentration of MMP-2 was drawn. As a proof-of-concept to demonstrate the feasibility of utilizing our developed organometallic-graphene based bio-sensing platform for bio-markers detection and diagnosis, simulated clinical serum samples spiked with MMP-2 at concentrations similar to those found in healthy people, and cancer patients were analyzed. It was demonstrated that MMP-2 could be detected even in the presence of serum, exhibiting clinical applicability. Since no other energy input, complex device design or expensive equipment is required for the efficacy of the bio-sensor, the simplicity of the developed bio-sensor is a step closer to cost effective and rapid biomedical device for early biomarkers detection and diagnosis. We believe that this work points to the wider possibility of graphene-based high throughput in vitro assays via the use of optical technology such as Raman to study chemical or biochemical reactions for the detection of biomarkers.

Experimental

General synthesis methods and spectral measurements

All reactions and manipulations were carried out under an argon atmosphere using standard Schlenk techniques. Solvents that were used for reaction were distilled over the appropriate drying agents under argon before use. Purification of compounds was generally carried out by column chromatography on silica gel, or by preparative thin-layer chromatography (TLC) using 20 cm x 20 cm plates pre-coated with silica gel 60 F254. Infrared (IR) spectra were recorded on a Thermo Fisher Scientific (OMNIC) FT-IR spectrometer. Solution spectra were recorded in DCM solution, unless otherwise stated, in a solution IR cell with NaCl windows and a path length of 0.1 mm, at a resolution of 2 cm-1. Alternatively, IR spectra of aqueous samples were recorded by drop casting the mixture (10 μL) onto a CaF_2 disc, followed by drying under a stream of nitrogen before recording on the spectrometer. Compound Ru_{11}-CO was synthesized according to reported methods with slight modifications.[28-32] Monolayer graphene were purchased from Graphenea. All other chemical reagents were purchased from other commercial sources and used without further purification.

The spectral measurements were carried out using a Renishaw InVia Raman (UK) microscope with a Peltier cooled CCD detector and an excitation wavelength at 633 nm, where the laser beam is directed to the sample through a 50× objective lens, which was used to excite the sample and also to collect the return Raman signal. The maximum laser power can be produced for Raman spectroscopy at the sample was measured to be 6.2 mW and the exposure time was set at 10s throughout the measurements. Prior to each measurement, the instrument was calibrated with a silicon standard whose Raman peak is centered at 520 cm−1. All Raman spectra were processed with the WiRE 4.2 software, with curve fitting at a spectral resolution of 0.6 cm^{-1}.

Characterization of bio-sensing properties of MMP-2

In a typical MMP-2 detection experiment, monolayer graphene on silica (Graphenea) was incubated with 1 mL of MMP-2 peptide (1 mM) (G-K(TAMRA)-G-P-L-G-V-R-G-C-$CONH_2$) at room temperature for 3 hours. The 1mM of peptide solution was

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prepared by dissolved MMP-2 peptide in 1 x phosphor-buffered saline and 0.005 M EDTA (pH 7.4). As TAMRA is an aromatic functional group, it could easily absorb on monolayer graphene. Monolayer graphene is incubated with peptide solution for 3 hours. The monolayer graphene was then rinsed with water to remove unbound peptide before use.

Next, MMP-2 (0.1mg/mL, Sigma Aldrich) was diluted into 10 ng/mL, 30 ng/mL, 50 ng/mL, 70 ng/mL and 90 ng/mL using buffered solutions containing 50 mM Tris-Cl, 5 mM $CaCl_2$ and 0.005% Brij-35 at pH 7.4. A buffered solution containing no enzyme was used as control. Peptide-functionalized monolayer graphene was incubated with 100 μL of MMP-2 solution at 37℃ for 3 hours. The substrates were then rinsed with DI water and incubated with 600 μL of Ru_{11}-CO for 1 minute and subsequently washed with ethanol for three times. Raman measurement was then performed.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1. A. J. Furlan, *New Engl. J. Med.*, 2015, **372**, 2347-2349.
2. S. J. Snow, *New Engl. J. Med.*, 2016, **374**, 809-811.
3. J. Kurzepa, J. Kurzepa, P. Golab, S. Czerska and J. Bielewicz, *Int. J. Neurosci.*, 2014, **124**, 707-716.
4. A. M. Romanic, R. F. White, A. J. Arleth, E. H. Ohlstein and F. C. Barone, *Stroke*, 1998, **29**, 1020-1030.
5. S.-M. Sheen-Chen, H.-S. Chen, H.-L. Eng, C.-C. Sheen and W.-J. Chen, *Cancer Lett.*, 2001, **173**, 79-82.
6. K. Vasala, P. Pääkkö and T. Turpeenniemi-Hujanen, *Urology*, 2013, **62**, 952-957.
7. Z. Wang, X. Li, D. Feng, L. Li, W. Shi and H. Ma, *Anal. Chem.*, 2014, **86**, 7719-7725.
8. D. Wang, Y. Yuan, Y. Zheng, Y. Chai and R. Yuan, *Chem. Commun.*, 2016, **52**, 5943-5945.
9. Q. Dang, H. Gao, Z. Li, H. Qi, Q. Gao and C. Zhang, *Anal. Bioanal. Chem.*, 2016, **408**, 7067-7075.
10. C. Qiang Zhang, Y. Min Park, D. Yang, T. H. Yoo and H. C. Yoon, *BioChip J.*, 2016, **10**, 198-207.
11. M. J. Tan, H.-C. Pan, H. R. Tan, J. W. Chai, Q. F. Lim, T. I. Wong, X. Zhou, Z.-Y. Hong, L.-D. Liao and K. V. Kong, *Adv. Healthc. Mater.*, 2018, DOI: 10.1002/adhm.201701113, 1701113.
12. A. Zecchina, E. Guglielminotti, A. Bossi and M. Camia, *J. Catal.*, 1982, **74**, 225-239.
13. G. M. Zanderighi, C. Dossi, R. Ugo, R. Psaro, A. Theolier, A. Choplin, L. D'Ornelas and J. M. Basset, *J. Organomet. Chem.*, 1985, **296**, 127-146.
14. V. L. Kuznetsov, A. T. Bell and Y. I. Yermakov, *J. Catal.*, 1980, **65**, 374-389.
15. S. Bhaskar, P. S. Dobal, S. B. Majumder and R. S. Katiyar, *J. Appl. Phys.*, 2001, **89**, 2987-2992.
16. Z.-S. Wu, D.-W. Wang, W. Ren, J. Zhao, G. Zhou, F. Li and H.-M. Cheng, *Adv. Funct. Mater.*, 2010, **20**, 3595-3602.
17. Y. Mo, W.-B. Cai, J. Dong, P. R. Carey and D. A. Scherson, *Electrochem. Solid-State Lett.*, 2001, **4**, E37-E38.
18. H. C. Jo, K. M. Kim, H. Cheong, S.-H. Lee and S. K. Deb, *Electrochem. Solid-State Lett.*, 2005, **8**, E39-E41.
19. Y. S. Huang and F. H. Pollak, *Solid State Commun.*, 1982, **43**, 921-924.
20. J. Lee, K. S. Novoselov and H. S. Shin, *ACS Nano*, 2011, **5**, 608-612.
21. G. von Maltzahn, T. J. Harris, J.-H. Park, D.-H. Min, A. J. Schmidt, M. J. Sailor and S. N. Bhatia, *J. Am. Chem. Soc.*, 2007, **129**, 6064-6065.
22. D. A. C. Brownson, M. Gomez-Mingot and C. E. Banks, *Phys. Chem. Chem. Phys.*, 2011, **13**, 20284-20288.
23. J. Vejpravova, B. Pacakova, J. Endres, A. Mantlikova, T. Verhagen, V. Vales, O. Frank and M. Kalbac, *Sci. Rep.*, 2015, **5**, 15061.
24. C. Neumann, S. Reichardt, P. Venezuela, M. Drogeler, L. Banszerus, M. Schmitz, K. Watanabe, T. Taniguchi, F. Mauri, B. Beschoten, S. V. Rotkin and C. Stampfer, *Nat Commun*, 2015, **6**.
25. C. Qiu, H. Zhou, B. Cao, L. Sun and T. Yu, *Carbon*, 2013, **59**, 487-494.
26. M. G. Tutton, M. L. George, S. A. Eccles, S. Burton, R. I. Swift and A. M. Abulafi, *Int. J. Cancer*, 2003, **107**, 541-550.
27. F. Vasaturo, F. Solai, C. Malacrino, T. Nardo, B. Vincenzi, M. Modesti and S. Scarpa, *Oncol. Lett.*, 2013, **5**, 316-320.
28. M. P. Cifuentes, M. G. Humphrey, J. R. Shapley and K. Lee, in *Inorg. Synth.*, John Wiley & Sons, Inc., 2007, pp. 287-293.
29. C. R. Eady, P. F. Jackson, B. F. G. Johnson, J. Lewis, M. C. Malatesta, M. McPartlin and W. J. H. Nelson, *J. Chem. Soc., Dalton Trans.*, 1980, 383-392.
30. M. P. Cifuentes, M. G. Humphrey, B. W. Skelton and A. H. White, *Organometallics*, 1995, **14**, 1536-1538.
31. P. J. Bailey, M. A. Beswick, B. F. G. Johnson, J. Lewis, M. McPartlin, P. R. Raithby and M. C. R. de Arellano, *J. Chem. Soc., Dalton Trans.*, 1996, 3515-3520.
32. M. I. Bruce, N. N. Zaitseva, B. W. Skelton and A. H. White, *J. Chem. Soc., Dalton Trans.*, 2002, 3879-3885.

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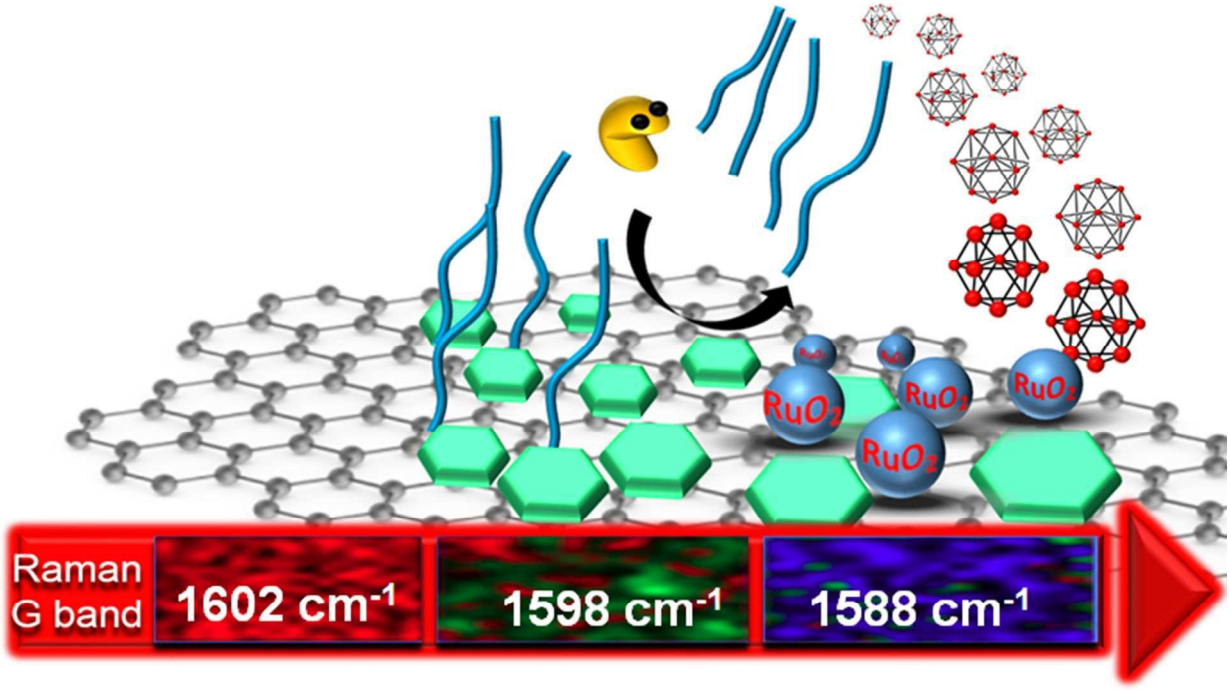

A bio-sensor for the detection of cancer biomarkers utilizing the adsorption properties of ruthenium carbonyl onto monolayer graphene.