Supporting Information

Experimental Section:

Materials

The dNTPs (dATP, dGTP, dCTP and dTTP mixture), exonuclease III and the oligonucleotide used in this paper were offered by Biotechnology Inc. (Shanghai, P.R. China). The sequence was as following: TS primer, 5'-$H_2N(CH_2)_6$TTTTTTTTTTAATCCGTCGAGCAGAGTT-3'; TS primer complementary strand, 5'-AACTCTGCTCGACGGATTAAAAAAAAAAAAAA-3'. 4-morpholineethanesulfonic acid (MES) was purchased from Sigma-Aldrich. 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC), N-hydroxysuccinimide (NHS), chloroplatinic acid (H_2PtCl_6), trisodium citrate and sodium borohydride ($NaBH_4$) were purchased from Alfa Aesar. All other reagents were of analytical reagent grade, and used as received. All aqueous solutions were prepared with nanopure water (18.2 MΩ cm, Milli-Q, Millipore).

Apparatus and characterization

Transmission electron microscopic (TEM) images were recorded using a FEI TECNAI G2 20 high-resolution transmission electron microscope operating at 200 KV. Electrochemical measurements were performed with a CHI 660B Electrochemistry Workstation (CHI, USA). A three-electrode setup was used with a glassy carbon working electrode (GCE), a common Ag/AgCl reference and a Pt wire auxiliary electrodes placed in the buffer solution. Electrochemical impedance spectroscopy (EIS) was performed using CHI 660B in 10 mM phosphate buffered

saline (PBS) containing 10 mM $K_3[Fe(CN)_6]/K_4[Fe(CN)_6]$ (1:1) mixture with 0.2 M KCl as the supporting electrolyte. The impedance spectra were recorded within the frequency range of 10^{-2}-10^5 Hz. The amplitude of the applied sine wave potential in each case was 5 mV.

Platinum nanoparticles (Pt NPs) synthesis

Pt NPs were prepared according to the procedure reported elsewhere[1]. 1.63 mL of 19.3 mM H_2PtCl_6 was added to 14.1 mL of an aqueous solution containing 11.1 mg sodium citrate under vigorous stirring, then 1.75 mL of aqueous sodium borohydride ($NaBH_4$) (7.3 mg) solution was added dropwise. The solution was kept stirring for another 30 min.

Cell culture and telomerase extraction

Briefly, various cell lines were cultured in DMEM medium supplemented with 10% fetal calf serum, and the cells were maintained at 37 ℃ in a humidified atmosphere (95% air and 5% CO_2). Cells (For extraction of telomerase from CTCs model, artificial CTC samples were prepared by spiking PBMCs with MCF-7 cells at specific ratios) were collected in the exponential phase of growth, and 1×10^6 cells were dispensed in a 1.5 mL EP tube, washed twice with ice-cold PBS solution, and resuspended in 100 μL of ice-cold CHAPS lysis buffer (10 mM Tris-HCl, pH 7.5, 1 mM $MgCl_2$, 1 mM EGTA, 0.1 mM PMSF, 5 mM mercapto ethanol, 0.5% CHAPS, 10% glycerol). The CHAPS lysis buffer was pretreated with RNA secure according to the manufacturer's instructions. The lysate was incubated for 30 min on ice and centrifuged 20 min at 12,000 rpm, 4 ℃, to pellet insoluble material. Without

disturbing the pellet, carefully transfer the cleared lysate to a fresh 1.5 mL EP tube. The lysate was used immediately for telomerase assay or frozen at -80 ℃.

Introduction of carboxylic acid functional groups at GCE surface

Before modification the GCE (ø=3 mm, CHI) was polished successively with 1.0, 0.3, and 0.05 μm alumina (Buhler) and sonicated for 3 min. Introduction of carboxylic acid functional groups at GCE surface achieved by electrochemical reduction of the diazonium cation generated in situ from the 4-aminobenzoic acid (PABA)[2]. Briefly, equal volume of 4 mM $NaNO_2$ and 4 mM PABA (1 M HCl) were mixed to generate the diazonium cation. The mixture was left to react in complete darkness and ice bath for about 5 min. Then cyclic voltammetry was performed in the diazonium cation-generating solution, by scanning from 0.6 V to -0.7 V vs. Ag/AgCl at 20 mV/s for two cycles. The resulting modified electrodes were immersed in acetonitrile and then rinsed with large volumes of water, followed by ultrasonication for 1 min to remove any weakly bound species. Electrodes were then rinsed again with water and dried under a stream of argon prior to use.

TS primer modification

Amino group functionalized TS primer was immobilized on carboxylic acid group modified GCE by the EDC/NHS reaction. The carboxylic acid group was firstly activated by EDC (10 mg/ml) and NHS (10 mg/ml) in a MES buffer (pH 6.0) for 30 min at room temperature. After washing with 10 mM pH 7.4 PBS solution, a 20-μL of 100 mM pH 7.4 PBS containing 0.5 μM TS primer was droped onto the electrode surface and kept under humidity for 2 h at room temperature. Finally, 1 M

ethanolamine (pH 8.5) was used to passive the unreacted NHS ester for 30 min at room temperature. After being washed with 10 mM PBS (pH 7.4) solution for several seconds, the electrode was dried in a dry nitrogen gas and stored in air prior to use.

Telomerase extension reaction

Telomerase extracts were diluted in lysis buffer with respective number of cells; the extracts (10 μL) were added into the RNA secure pretreated extension solution containing 1×TRAP buffer, (20 mM Tris-HCl pH 8.3, 1.5 mM $MgCl_2$, 63 mM KCl, 0.005% Tween 20, 1 mM EGTA, BSA 0.1 mg/mL) and 2 mM dNTP mix. (For inhibition of telomerase by G-quadruplex ligands, $[Ni_2L_3]Cl_4$-P and $[Ni_2L_3]Cl_4$-M were mixed with telomerase extract equivalent to 2000 A549 cells/mL respectively. For negative controls, telomerase extracts were heat-treated at 95 ℃ for 10 min). 20 μL of a reaction solution prepared above was placed on the TS primer functionalized electrode and incubated at 37 ℃ for 1 h to allow the extention reaction by telomerase to proceed. After extention by telomerase, the electrode was rinsed with 1% SDS 10 mM pH 7.4 PBS solution containing 138 mM NaCl and 2.7 mM KCl. After hybridization with the TS primer complementary strand, 20 μL of endonuclease solution containing 2 U/mL Exo III was placed onto the resulting electrode surface and incubated at 37 ℃ for 1 h. The electrode was then washed with the SDS buffer and 10 mM pH 7.2 Tris-HCl buffer and stored in air prior to use.

Electrochemical detection

For electrochemical detection, the modified electrodes were prior immersed in 0.25 μM Pt NPs solution (5 mM Tris-HCl, pH 7.2) for one hour and following washed with

10 mM pH 7.2 Tris-HCl buffer. The electrode was then placed in 50 mM phosphate buffer (pH 7.0) containing 10 mM hydrazine for the cyclic voltammetry measurement at a 50 mV/s scan rate from -0.4 to 0.7 V versus a Ag/AgCl (3 M KCl) reference electrode. Chronoamperometric curves were measured at 0.3 V for 10 s in the same electrolytic cell.

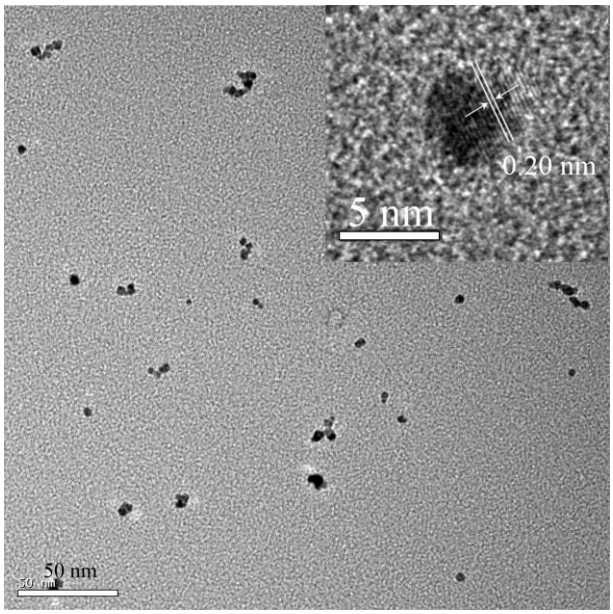

Figure S1 TEM image of the corresponding Pt nanoparticles

The synthesized Pt NPs with sizes averaging about 4.0 nm could well disperse in water for at least 6 month. The lattice spacing of 0.20 nm, showed in the HRTEM image, is consistent with that of Pt (100) planes.[3] The concentration of Pt NPs was calculated from the Pt precursor concentration divided by the average number of Pt atoms contained in each particle. For the 4.0 nm Pt particle is assumed to contain about 2000 Pt atoms,[4] therefore, the stock solution was about 1 μ M in particles.

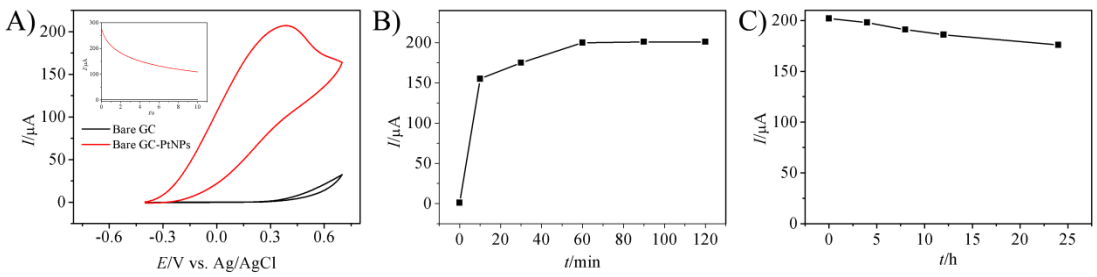

Figure S2 (A) Cyclic voltammograms of hydrazine oxidation at bare GCE (black) and Pt NPs absorbed GCE (red) (insert, chronoamperometric curves at 0.3 V); (B) Hydrazine oxidation current from chronoamperometric curves at 5 s vs. different Pt NPs absorption time; (C) The absorption stability of Pt NPs on GCE surface tested by immersing the absorbed electrodes in PBS for different times. Hydrazine oxidation tested in 50 mM pH 7.0 PB containing 10 mM hydrazine.

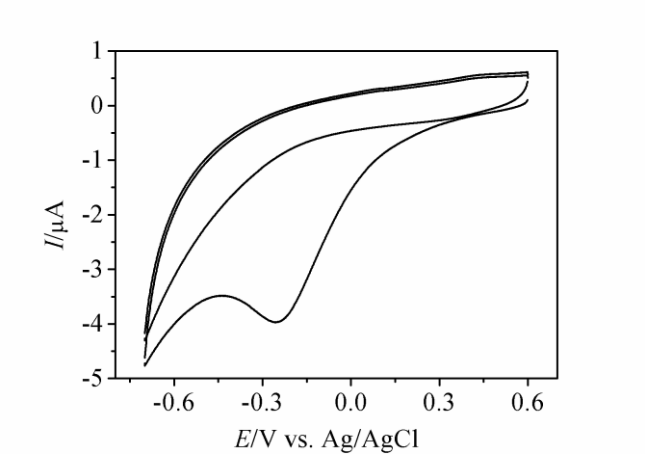

Figure S3. Cyclic voltammograms for the electrochemical grafting of the aryl diazonium cation generated in situ from PABA to GCE in solution containing 2 mM $NaNO_2$, 2 mM PABA and 0.5 M HCl. Scanning from 0.6 V to -0.7 V vs. Ag/AgCl at 20 mV/s.

In the first reduction scan of a cyclic voltammogram presents one reduction peak centered at -0.25 V, corresponding to the reduction of the aryl diazonium salt to generate the aryl radicals. In the second cycle, the redox peak disappears and the cyclic voltammogram exhibits only a small reduction current, indicating the presence of the grafted layer.[2]

References

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