Prostate specific antigen detection using AlGaN/GaN high electron mobility transistors

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Antibody-functionalized Au-gated AlGaN/GaN high electron mobility transistors (HEMTs) were used to detect prostate specific antigen (PSA). The PSA antibody was anchored to the gate area through the formation of carboxylate succinimdyl ester bonds with immobilized thioglycolic acid. The AlGaN/GaN HEMT drain-source current showed a rapid response of less than 5 s when target PSA in a buffer at clinical concentrations was added to the antibody-immobilized surface. The authors could detect a wide range of concentrations from 10 pg/ml to 1 μg/ml. The lowest detectable concentration was two orders of magnitude lower than the cutoff value of PSA measurements for clinical detection of prostate cancer. These results clearly demonstrate the promise of portable electronic biological sensors based on AlGaN/GaN HEMTs for PSA screening. © *2007 American Institute of Physics*. [DOI: 10.1063/1.2772192]

Prostate cancer accounts for around 10% of all deaths from cancer and is the second most common cause of cancer death among men in the United States.[1] The prostate specific antigen (PSA) is the best serum marker for diagnosis of prostate cancer and has been widely used for early detection of prostate cancer for several decades.[2,3] Most PSA testing methods have limitations due to the laboratory-oriented nature of the measurements requiring sample transportation, time consuming analysis, and high cost of detection. Several different electrical measurements have been used to detect PSA rapidly with high accuracy.[4–9] Electrochemical devices have attracted attention due to their low cost and simplicity. Although electrochemical measurements based on impedance and capacitance can be used as an accurate sensor platform, significant improvements in their sensitivities are needed for use with clinical samples.[4,5]

The electrical measurement of resonant frequency change of an anti-PSA antibody coated microcantilever enables the detection of PSA in solution at concentrations as low as 10 pg/ml but the microbalance method suffers from an undesirable resonant frequency change due to viscosity of the medium and cantilever damping in the solution environment.[6,7] Nanowire field effect sensors coated with antibody have been used for the real time, highly sensitive detection of PSA.[8,9] However, the low write speed of the electron-beam lithography used to control the exact position of the nanowire arrays increases the processing cost and has reduced potential for scale-up. GaN/AlGaN high electron mobility transistors (HEMTs) are attractive for these applications, since they include a high electron sheet carrier concentration channel induced by piezoelectric polarization of the strained AlGaN layer.[10–21]

In this letter, we report the use of antibody-functionalized Au-gated AlGaN/GaN HEMTs for detecting PSA. The PSA was specifically recognized through PSA antibody, anchored to the gate area in the form of carboxylate succinimdyl ester. We investigated a wide range of concentrations from 1 μg/ml to 10 pg/ml, which is lower than the cutoff value of clinical PSA measurement requirements recently reported at 2.5 ng/ml.[3]

The HEMT structures consisted of a 3 μm thick undoped GaN buffer, 30 Å thick $Al_{0.3}Ga_{0.7}N$ spacer, and 220 Å thick Si-doped $Al_{0.3}Ga_{0.7}N$ cap layer. The epilayers were grown by metal organic chemical vapor deposition on thick GaN buffers on sapphire substrates. Mesa isolation was performed with an inductively coupled plasma (ICP) etching with Cl_2/Ar based discharges at −90 V dc self-bias, ICP power of 300 W at 2 MHz and a process pressure of 5 mTorr. 10×50 μm^2 Ohmic contacts separated with gaps of 5 μm consisted of e-beam deposited Ti/Al/Pt/Au patterned by lift-off and annealed at 850 °C, 45 s under flowing N_2. 400-nm-thick 4% polymethyl methacrylate was used to encapsulate the source/drain regions, with only the gate region open to allow the liquid solutions to cross the surface. The source-drain current-voltage characteristics were measured at 25 °C using an Agilent 4156C parameter analyzer with the gate region exposed. ac measurements were performed to prevent side electrochemical reactions with modulated 500 mV bias at 11 Hz.

A plan view photomicrograph of a completed device and schematic cross section of the device is shown in Fig. 1. The Au surface was functionalized with a specific bifunctional molecule. We anchored the thioglycolic acid, $HSCH_2COOH$, an organic compound and containing both a thiol (mercaptan) and a carboxylic acid functional group on the Au surface in the gate area. A self-assembled monolayer of thioglycolic acid molecule was adsorbed onto the gold gate due to strong interaction between gold and the thiol group. The devices were first placed in an ozone/UV chamber for 3 min and then submerged in 1 mM aqueous solution of thioglycolic acid for

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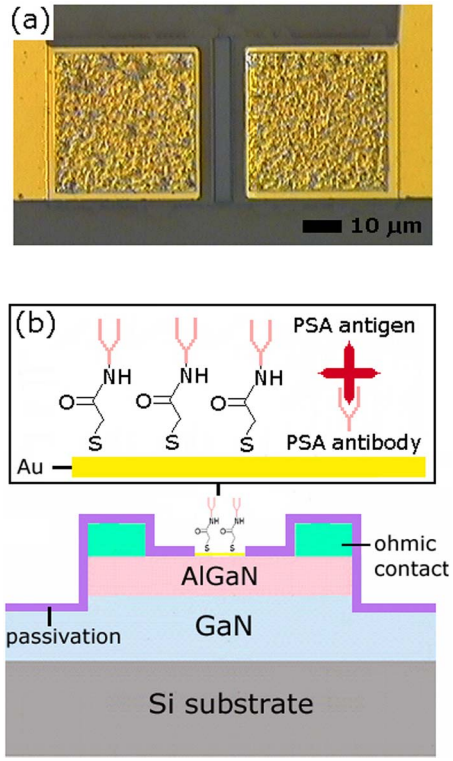

FIG. 1. (a) Plan view photomicrograph of a completed device with a 5 nm Au film in the gate region. (b) Schematic of AlGaN/GaN HEMT. The Au-coated gate area was functionalized with PSA antibody on thioglycolic acid.

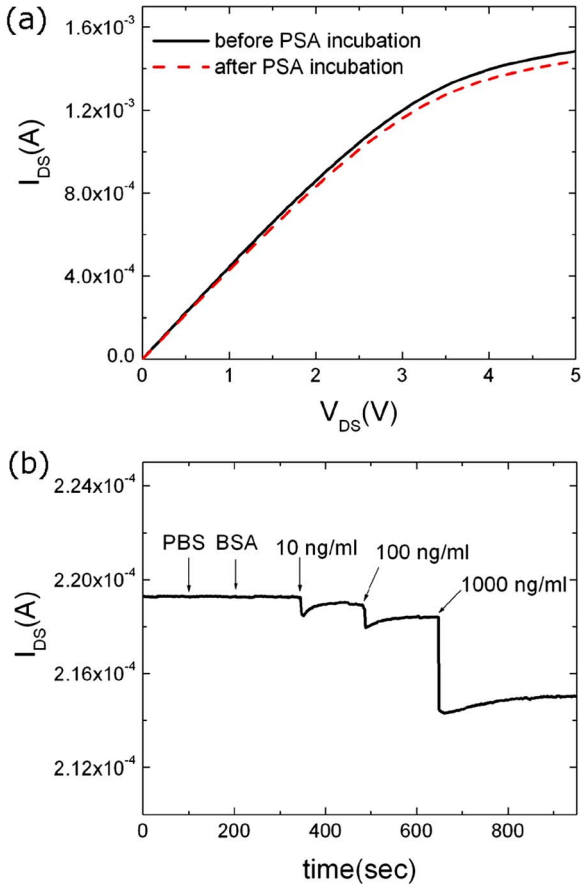

FIG. 2. (a) *I-V* characteristics of AlGaN/GaN HEMT sensor before and after PSA incubation. (b) Drain current vs time for PSA when sequentially exposed to PBS, BSA, and PSA.

24 h at room temperature, resulting in binding of the thioglycolic acid to the Au surface in the gate area with the COOH groups available for further chemical linking of other functional groups. X-ray photoemission spectroscopy and electrical measurements confirming a high surface coverage and Au–S bond formation on the GaN surface have been published previously.[21] The device was washed with de-ionized water to remove unlinked thioglycolic acids. The carboxylic acid functional group was then activated by submerging the device first in a 0.1 mM solution of *N*, *N*′-dicyclohexylcarbodi-imide in dry acetonitrile for 30 min and then in a 0.1 mM solution of *N*-hydroxysuccinimide in dry acetonitrile for 1 h.[9] These functionalization steps resulted in the formation of succinimidyl ester groups on the gate area of AlGaN/GaN HEMT. The device was incubated in a phosphate-buffered saline (PBS) solution of PSA monoclonal antibody for 18 h before real time measurement of PSA, and the PSA antibody was functionalized on the gate area of the device, as shown in Fig. 1(b).

After incubation in a PBS buffered solution containing PSA at a concentration of 1 μg/ml, the device surface was thoroughly rinsed off with de-ionized water and dried by a nitrogen blower. The source and drain current from the HEMT were measured before and after PSA incubation, as shown in Fig. 2(a). The electrons in the two-dimensional electron gas (2DEG) channel of the AlGaN/GaN HEMT are induced by piezoelectric and spontaneous polarization effects. This 2DEG is located at the interface between the GaN layer and AlGaN layer. There are positive countercharges at the AlGaN surface layer induced by the 2DEG. Any slight changes in the ambient of the AlGaN/GaN HEMT affect the surface charges of the AlGaN/GaN HEMT. These changes in the surface charge are transduced into a change in the concentration of the 2DEG in the AlGaN/GaN HEMTs, leading to the slight decrease in the conductance for the device after PSA incubation.

Figure 2(b) shows the real time PSA detection in PBS buffer solution using the source and drain current change with constant bias of 500 mV. No current change can be seen with the addition of buffer solution at around 100 s and nonspecific bovine serum albumin (BSA) around 200 s, showing the specificity and stability of the device. By sharp contrast, the current change showed a rapid response in less than 5 s when target of 10 ng/ml PSA was added to the surface. The abrupt current change due to the exposure of PSA in a buffer solution could be stabilized after the PSA diffused into the buffer solution. Further real time tests to quantify the detection limit of PSA were carried out, as shown in Fig. 3(a). Three different concentrations of the exposed target PSA in a buffer solution were detected, from 10 pg/ml to 1 ng/ml. In the case of 1 ng/ml, the amplitude of current change for the device exposed to PSA in a buffer solution was about 3%, as illustrated in Fig. 3(b). The clear current decrease of 64 nA at 10 pg/ml of PSA also indicated that the detection limit could be lowered up to a few pg/ml, showing the promise of this portable electronic biological sensor for PSA screening.

In summary, we have shown that through a chemical modification method, the Au-gated region of an AlGaN/GaN HEMT structure can be functionalized for the detection of PSA with a limit of detection of 10 pg/ml. This electronic detection of biomolecules is a significant step toward a com-

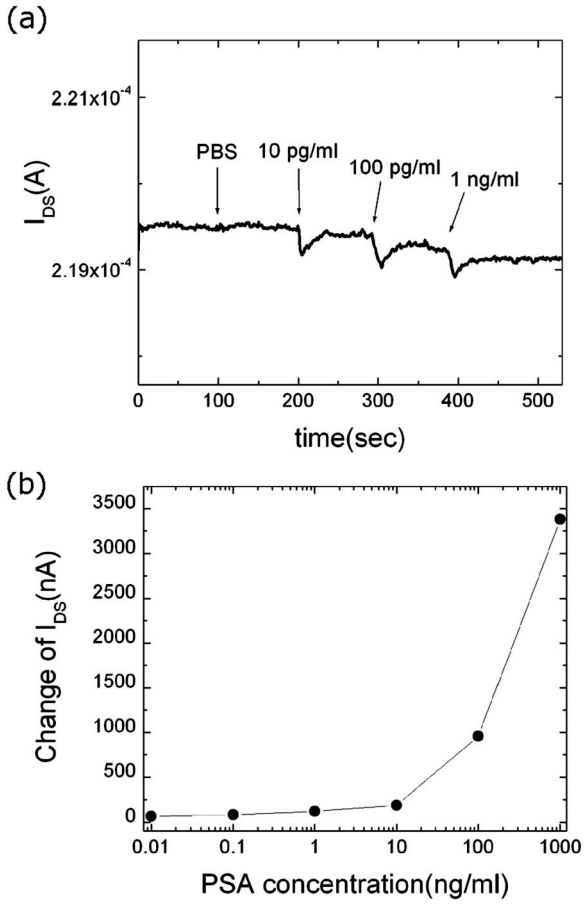

FIG. 3. (a) Drain current vs time for PSA from 10 pg/ml to 1 ng/ml. (b) Plot of change of source and drain current vs different concentrations from 10 pg/ml to 1 μg/ml of PSA.

pact sensor chip, which can be integrated with a commercially available handheld wireless transmitter to realize a portable, fast response, and high sensitivity prostate cancer detector.

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