Extended Abstracts of the 2016 International Conference on Solid State Devices and Materials, Tsukuba, 2016, pp373-374

H-2-02

# Development of Molecularly Imprinted Polymer-Gate Field Effect Transistor for Sugar Chain Sensing

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**Abstract**

**In this study, we developed molecularly imprinted polymer-based field effect transistor (MIP-gate FET) for selective sugar chain sensing in aqueous media. Choosing 3'-sialyl lactose (3'-SLac) and 6'-sialyl lactose (6'-SLac) as target sugars, we confirmed that they could be sensed quantitatively from 10uM. Moreover, the sensor showed selectivity to some extent, where the signal from competent was suppressed by 40% at maximum. We also found that the selectivity enhanced by MIP differs for 2 different template sugars, although these sugars are similar in structures. From these results, we showed the possibility of MIP-gate FET as selective sugar detecting sensor, which can be applied widely in medical fields.**

## 1. Introduction

Sugar chains, also known as oligosaccharides, are biomolecules that widely exist in our body, and play important roles in life activities. As there are such oligosaccharides as Sialyl Lewis (SLeA and SLeX), known to exist specifically on cancer cell membrane [1], oligosaccharides could possibly be targeted as the targets for valuable-cell recognition. In our group, we have developed a field effect transistor (FET)-based biosensor for molecular recognition in aqueous media, where the gate electrode was extended to directly attach the solution (Extended-gate FET) [2]. As FET detects the change in gate surface potential with high sensitivity, we modified the gate surface by phenylboronic acid (PBA), which is widely used as a recognizing agent of diols [3], to induce gate potential change when target molecule appears in the system and binds to PBA. Then we have further improved the sensor by coating the gate surface with molecularly imprinted polymer (MIP) gel [4]. By MIP modification, not only the sensitivity but selectivity was enhanced due to the template-selective cavity created in polymer matrix (as shown in Scheme 1) [5]. By applying this sensor, we have succeeded to selectively sense glucose and lactate. In addition, we have also shown that the sensor could possibly be applied to sense various biomolecules. In this research, we applied MIP-gate FET for variety of sugar chains, especially targeted 3'-Sialyl Lactose and 6'-Sialyl Lactose, the structure (a) and (b) shown in Fig. 1, respectively, that are similar in structure with Sialyl Lewis, and investigated the selectivity enhanced by each sensor.

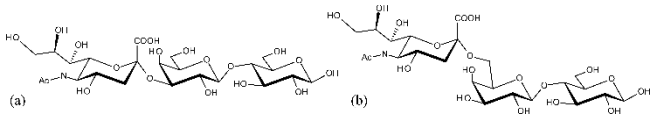
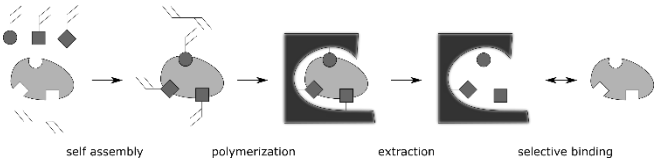



Fig. 1 Molecular structures of (a) 3'-Sialyl Lactose, and (b) 6'-Sialyl Lactose

## 2. Experimental section

### 2.1 Preparation of MIP-coated gate FET

MIP was synthesized on Au gate electrode by surface initiated atomic transfer radical polymerization (SI-ATRP) by following procedure. The surface of Au was cleaned by piranha/water, then Au was immersed in 1mM Bis[2-(2-bromoisobutyryloxy)undecyl] disulfide in ethanol for 12 hours in 25℃ to prepare self-assembled monolayer (SAM). Pre-polymer solution was then prepared by dissolving following monomers in N, N-dimethylformamide (DMF)/$H_2O$: 25mM template molecule (3'-SLac or 6'-SLac), 75mM functional monomer (4-vinylphenylboronic acid; 4-VPBA), 0.3M N-3-(dimethylamino)propylmethacrylamide (DMAPM) as pH modifier, and 1M cross linker (ethylene glycol dimethacrylate; EGDMA). The mixture was degassed by $N_2$ for 30 min, followed by the addition of tris(2-pyridylmethyl)amine (TPMA), $CuBr_2$, and Ascorbic acid. SAM coated Au was immersed in the pre-polymer solution for 18 hours in 40℃ to complete polymerization. After polymerization, polymer was immersed in HCl/Methanol for 12 hours to extract template molecule. For the comparative experiment, Non-imprinted polymer (NIP) was prepared by the same process, but without adding template in the pre-polymer solution.




Scheme 1 Molecularly imprinted polymer

### 2.2 Real time monitoring by MIP-gate FET biosensor

While target molecules (3'-SLac and 6'-SLac) were added to the MIP-gate FET system, the gate surface potential was measured in real-time manner by FET real-time monitoring system. N-channel junction type FET (K246, TOSHIBA) was used. The concentration of target molecule was increased from 10uM to 10mM, with 10 times each step. pH was also

controlled to 7.4 by phosphate buffered saline (PBS).

## 3. Result and Discussion

Fig. 2 shows the comparison of surface potential changes by introducing 3'-SLac using the 3'-SLac-template MIP-gate FET (a) and the NIP-gate FET (b). The surface voltage shifted in the negative direction using the MIP-gate FET system, depending on the concentration of 3'-SLac. This was due to the negatively charged PBA induced by 3'-SLac entering the template cavity in the polymer matrix and formed PBA-sugar complex. The NIP-gate FET, on the other hand, showed no obvious signal. The polymer was highly cross-linked by EGDMA, which prevented the target molecules to enter the polymer matrix.

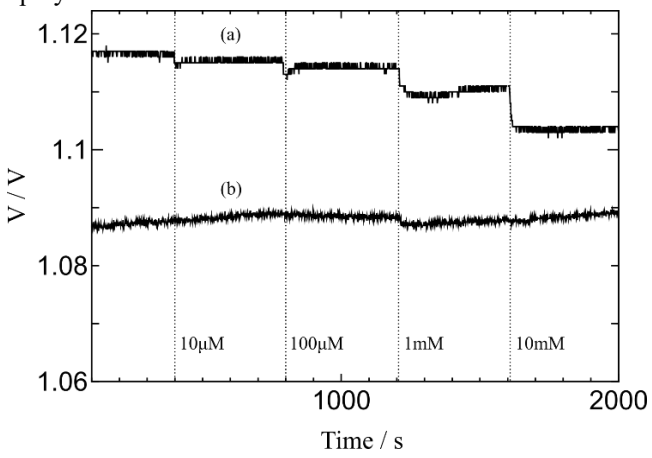



Fig. 2 Surface voltage change when 3'-SLac was added to (a) 3'-SLac MIP-gate FET system and (b) NIP-gate FET system.

The fraction shown in Fig. 3 was calculated by the following equations,

$$\text{(a)} \quad \frac{\Delta V \text{ (3'-SLac added to 6'-SLac MIP)}}{\Delta V \text{ (3'-SLac added to 3'-SLac MIP)}}$$

$$\text{(b)} \quad \frac{\Delta V \text{ (6'-SLac added to 3'-SLac MIP)}}{\Delta V \text{ (6'-SLac added to 6'-SLac MIP)}}$$

The fraction of (a) was calculated to be approximately 0.6. When considering the signal of 3'-SLac entering the 3'-SLac-template MIP cavity and bind to PBA as maximum, 40% of the signal decreased when 3'-SLac entered the 6'-SLac-template MIP system. This indicates that the 6'-SLac-template MIP has selectivity to some extent. However, the fraction of (b) was calculated to be 1, which indicates that 6'-SLac could easily enter the cavity of 3'-SLac-template MIP, thus the 3'-SLac-template MIP has low selectivity. The result could be analyzed through molecular structure. The selective cavity of sugar-template MIP is created by covalently bonding PBA-sugar complex in the pre-polymer solution. Since PBA has higher affinity to cis-diol then trans-diol [3], it can be inferred that 3'-SLac has 2 binding sites, whereas 6'-SLac has 3 binding sites per molecule, according to the 3D molecular structure shown in Fig. 4. Thus, the 6'-SLac-template MIP is likely to have more specific cavity than 3'-SLac-template MIP, which is reflected in the result shown in Fig. 3.

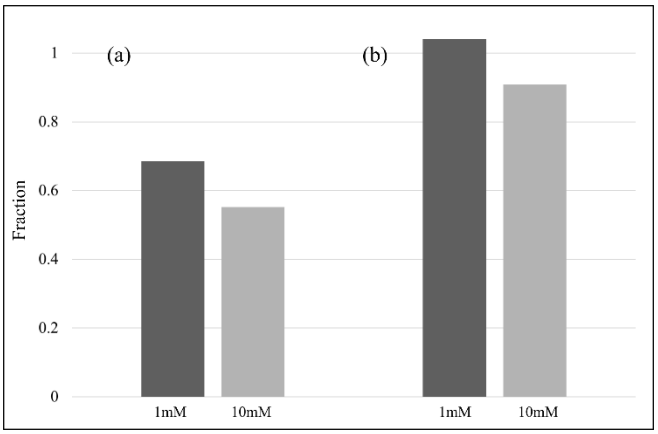



Fig. 3 Ratio of voltage change where (a) 3'-SLac in 6'-SLac MIP / 3'-SLac in 3'-SLac MIP and (b) 6'-SLac in 3'-SLac MIP/ 6'-SLac in 6'-SLac MIP.

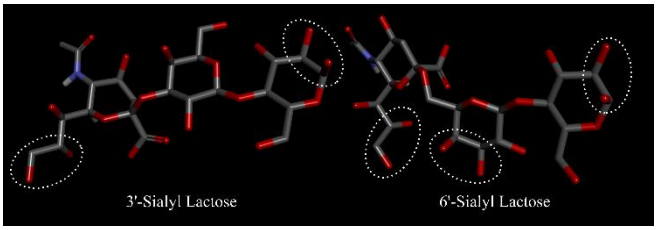



Fig. 4 Structural model of 3'-SLac and 6'-SLac

## 4. Conclusions

In this study, we aimed to develop biosensor for selective sugar chain sensing. We applied the MIP-gate FET as sensing device, which we had successively sensed glucose and lactate selectively in the previous study. Among various oligosaccharides, we focused on 2 similarly structured sugar, 3'-SLac and 6'-SLac, as they have similarity in structure with Sialyl Lewis, known to be expressed specifically on cancer cells. The comparison of MIP-gate FET and NIP-gate FET clearly showed the ability of FET biosensor for sugar chain sensing. As for 2 MIPs considered, the 6'-SLac-template MIP showed higher selectivity. Although 3'-SLac and 6'-SLac are similar in structure, the difference in the structure of template molecule may have significant effect on the selectivity of MIPs. With further investigation, we hope to improve the selectivity as well as sensitivity of the sensor, and apply to the specific cell recognition in the future.

## References

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