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Incorporation of Cesium Borocaptate onto Silicon Nanowires as a Delivery Vehicle for Boron Neutron Capture Therapy

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Silicon nanowires (SiNWs) have emerged as an interesting material for biological applications such as tissue engineering,[1] biosensors,[2] and drug delivery.[3,4] As extensively used building blocks for electronic devices,[5,6] silicon nanowires possess a unique combination of biocompatibility and semiconducting properties that enable them to be easily functionalized with suitable surface species and therefore provide a favorable environment for selected biological systems.[1−4] When used as a drug delivery vehicle, their size may enable them to penetrate tumors because of the enhanced permeability and retention effect,[7] and the high surface-to-volume ratio of SiNWs can contribute to a more specific drug loading with lower overall dose and reduced toxicity.[8]

Boron neutron capture therapy (BNCT) is a binary form of cancer therapy which uses a boron-containing compound that preferentially concentrates in tumor sites. Irradiation by a neutron beam causes the ^{10}B to split into an α particle and lithium nucleus, both of which cause significant damage to the cell in which they are contained. For BNCT to be successful, a sufficient number of ^{10}B atoms must be delivered selectively to the tumor site. Sodium borocaptate ($Na_2B_{12}H_{11}SH$), referred to as BSH, is incapable of crossing the blood-brain barrier, and has promising characteristics with respect to tumor localization and blood clearance rates.[9] Although BSH has been used clinically for BNCT of malignant brain tumors,[10] integration of this BNCT agent with nanovehicles offers the possibility of tumor targeting with enhanced boron payloads.[11] For example, mice that received BSH containing liposomes had a significant elongated survival time compared to those that received free BSH.[12] Although a variety of high-molecular-weight agents consisting of macromolecules and nanovehicles have been extensively developed,[11] new methods are still desirable for delivering larger number of boron atoms into individual cancer cells.

Heterostructure formation on cylindrical nanowire surfaces can be challenging, but our previous work demonstrated that cathodic bias could induce the formation of uniform synthetic calcium phosphate coatings on the surface of SiNWs.[1,13] Taking advantage of this straightforward growth method and the ionic nature of BSH, we investigate here the growth of BSH onto surface of SiNWs via a facile anodic bias process, as the BSH cluster is negatively charged. The evaluation of the BSH amount and the structural change of SiNWs after loading is a prerequisite for designing such a delivery vehicle. Therefore, the effect of electrochemical deposition conditions on the BSH coating is studied, as well as the dissolution behavior of BSH from SiNWs. The latter is relevant because the stability of BSH on the SiNWs surface will be another factor that impacts the boron content present in blood or healthy issues. In our experiments, commercially available cesium borocaptate is used as an analog to the sodium salt to facilitate elemental characterization. The results show that the boron concentration on SiNWs is about 6 orders higher than the typical boron concentrations found in tumor tissue after i.v. administration with free BSH.[14] This drug delivery system, therefore, could ideally deliver boron into tumor cells in a fairly high level upon appreciable cellular uptake. The low solubility of BSH coatings may further contribute to reducing the amount of boron in the blood and other healthy tissues.

The SiNWs were synthesized via a route exploiting the vapor−liquid−solid mechanism on graphite cloth substrates sputtered with 20 nm gold as a catalyst. NW growth occurred at 600 °C in the presence of a helium flow of 3000 sccm and silane (0.5% in helium) flow of 30 sccm for 20 min. Figure 1a shows a typical Scanning Electron Microscope (SEM) image of as-prepared

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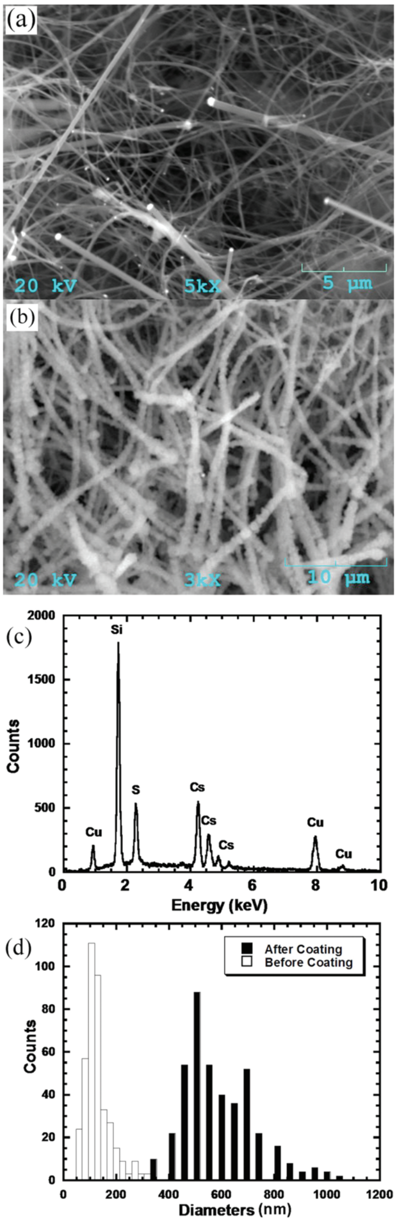

Figure 1. (a) SEM image of as-prepared SiNWs; (b) SEM image of BSH coated SiNWs; (c) EDX spectrum of BSH coated SiNWs. (d) Size distribution of total SiNW thickness before and after coating with BSH.

SiNWs. The average diameter of these SiNWs is about 124 (± 52) nm and a length up to tens of micrometers.

Anodic bias was performed in an electrochemical cell with an aqueous BSH solution as electrolyte, SiNWs as anode, and platinum foil as cathode. The distance between anode and cathode is 1 cm. Figure 1b shows a typical SEM image of BSH coated SiNWs after electrochemically induced growth in 25 mg/mL BSH solution at 0.1 mA/cm^2 for 180 min. Energy Dispersive X-ray (EDX) spectroscopy results confirmed the presence of sulfur (Figure 1c), which is covalently bound to the boron cluster. Such a covalent bond is not likely to be broken under the electrochemical conditions applied.[10] The size distribution (Figure 1d) shows that the average diameter of SiNWs increased from 124 (± 52) nm to 588 (± 139) nm after being coated with BSH under the conditions mentioned above.

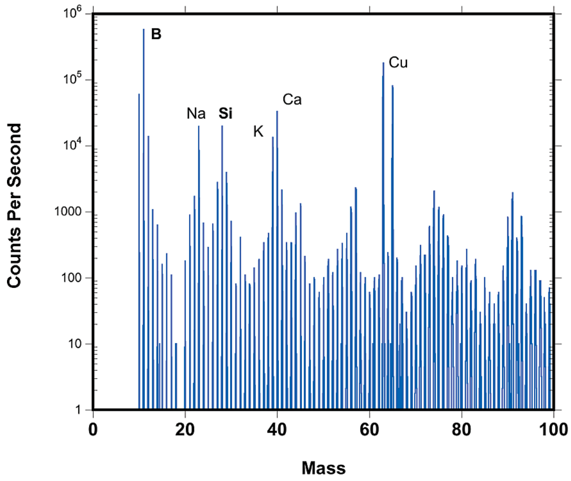

Figure 2. Secondary ion mass spectrum for a typical BSH-coated SiNW sample.[15]

Complementary compositional characterization of the boron cluster-modified nanowires was achieved by the use of secondary ion mass spectrometry (SIMS) on a representative sample, as illustrated in Figure 2. This is a fingerprint mass spectrum of the BSH coated nanowire sample, recorded from 1 to 100 amu. The dominant mass peak is boron at mass 11. The ^{10}B isotope is also observed, as well as carbon peaks beginning at m/z = 12. An additional scan of the two boron isotopes in depth profile mode confirmed that the isotopic ratio is consistent with naturally occurring boron (data not shown).

BSH can undergo spontaneous oxidation in aqueous media to form disulfide dimers (BSSB).[16] In vivo studies have actually detected such dimers present in patients' urineas metabolic byproduct.[17] Prior animal experiments have also shown that the disulfide derived from BSH has been found to be taken up more efficiently than BSH itself by tumors.[17] Taking into account the strong oxidative potential on the anode, BSH readily undergoes an oxidation reaction to form dimers in the given electrolyte. These tetravalent anions could lose their electrons and become neutral at the anode surface, thereby forming a less-soluble coating on the SiNWs surface. The cesium cations trapped into the surface coatings were found to be easily washed out, which was subsequently confirmed by dissolution assays (vide infra).

To investigate the role of electrochemical conditions in the formation of the coating of BSH, we evaluated the influence of magnitude of bias (0.05 or 0.1 mA/cm^2), its duration (20−180 min), and concentration of the BSH in the electrolyte (5, 12.5, or 25 mg BSH/mL) on the BSH coating level. As shown in Figure 3a, a higher current density leads to a higher loading level of BSH, with the

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(15) Samples were measured using a Cameca IMS-4F SIMS instrument operating with a source potential of 10 KV and a sample stage extraction voltage of 4.5 KeV. The primary ion beam was Ar$^+$ with an impact energy of 4.5 keV and a primary current of ~2.5 nA.

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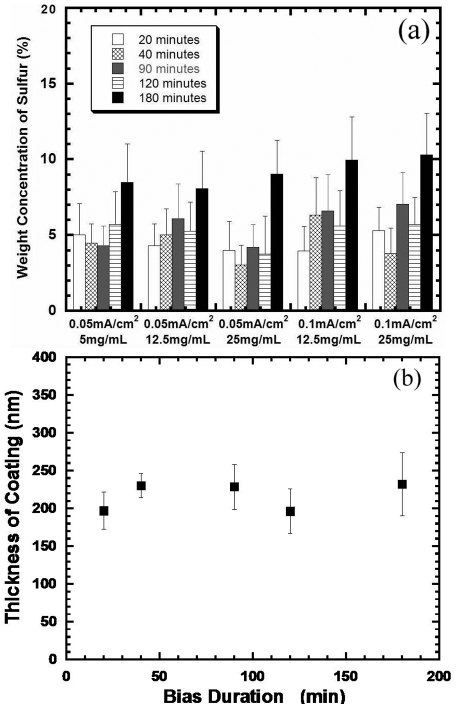

Figure 3. (a) Effect of electrochemical fabrication conditions on BSH coating thickness; (b) plot of the thickness of BSH coating as a function of electrochemical bias duration.

exception of the experiment for 12.5 mg/mL electrolyte concentration and 20 min bias duration. The observed higher boron content corresponding to a lower current density for this particular sample is probably due to the combination of a relatively short bias duration for a lower electrolyte concentration. Not surprisingly, the duration of bias seems to be the most sensitive means to control amount of BSH present on the nanowire surface. The remaining parameters investigated did not have a prominent impact on the measured coating. By measuring average SiNW diameter before and after coating with BSH using SEM imaging (and dividing by two), Figure 3b shows the thickness of BSH coating alone (one edge) as a function of electrochemical bias duration. The sheath of BSH is typically of ~210 nm thickness. This relative insensitivity suggests that extending the duration of bias extends the number of nanowires coated with BSH on a given substrate rather than modulating thickness. Given the weight concentration of sulfur measured by EDX, the concentration of boron on SiNWs is calculated to be about 1.06 ± 0.58 g boron/cm^3 SiNWs.

According to a previously published pharmacokinetics study, given the dose of 50 mg boron/kg body weight, the average concentration of boron in tumor and normal brain tissue is on the magnitude of several micrograms per milliliter of tissue.[14] Consequently, as long as an appreciable cellular uptake could be fulfilled, a significantly higher amount of boron could be delivered into tumor cells and the cytocidal effect of neutron irradiation could be enhanced. Another promising merit of this delivery system is that the deposition of BSH on SiNW surface might possess the extra benefit of reducing the accumulation of boron in healthy tissues, because the amount of boron that exposed to tissues is reduced in this way.

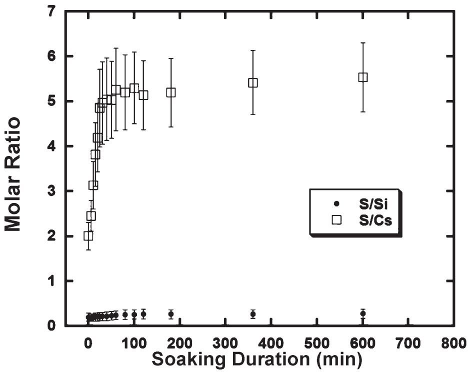

Figure 4. Dissolution assay of BSH coating. Data are presented as the molar ratio of sulfur:silicon and sulfur:cesium as measured by EDX.

A rather practical issue for BNCT applications is the rate of dissolution of the BSH coating of the nanowire in aqueous media. Figure 4 shows the dissolution of BSH from SiNWs. The sample was characterized by EDX at designed time points during the soaking in DI water, which was changed every time after EDX measurement. As the soaking time is prolonged, the S/Si ratio remains at a constant level, indicating the relative insolubility of the BSH sheath on the SiNW surface. As expected, cesium cations were easily washed out during the soaking process, as reflected in the change in S/Cs ratios as a function of soaking time. This result is consistent with the proposed formation of disulfide dimers (BSSB) on the SiNWs surface. The dimer produced appreciably higher concentration in tumor but at the same time increased toxicity, as shown by changes in liver enzymes.[18] Therefore, this enhanced stability of BSH or BSSB dimers on SiNWs may further benefit for decreasing the boron concentration in the blood.

In conclusion, we have reported a straightforward method to coat an established BNCT agent, BSH, onto SiNW surfaces. Under anodic bias, BSH likely undergoes an oxidation reaction to form stable coatings on the SiNW surface. Increasing the bias duration can raise the concentration of boron on SiNW. The coating of BSH is probably oxidized to a neutral species under anodic bias. This might be of merit for BNCT because it can further reduce the amount of boron in the blood and brain, and therefore reduce the damage to these areas during neutron irradiation. However, whether such a transformation could lead to a loss of selectivity of BSH toward the tumor cells needs to be carefully examined. Future work will also be focused on the optimization of the cellular uptake by tumor cells by altering the sizes and the surface chemistry of BSH coated SiNWs.

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