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Silicon Nanomaterials Platform for Bioimaging, Biosensing, and Cancer Therapy

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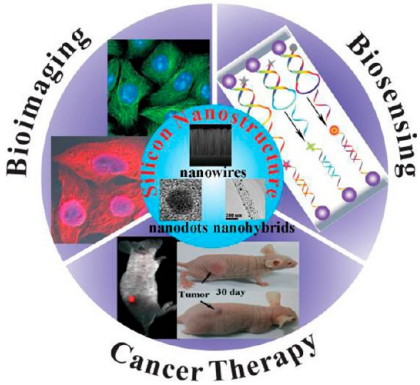
CONSPECTUS

Silicon nanomaterials are an important class of nanomaterials with great potential for technologies including energy, catalysis, and biotechnology, because of their many unique properties, including biocompatibility, abundance, and unique electronic, optical, and mechanical properties, among others. Silicon nanomaterials are known to have little or no toxicity due to favorable biocompatibility of silicon, which is an important precondition for biological and biomedical applications. In addition, huge surface-to-volume ratios of silicon nanomaterials are responsible for their unique optical, mechanical, or electronic properties, which offer exciting opportunities for design of high-performance silicon-based functional nanoprobes, nanosensors, and nanoagents for biological analysis and detection and disease treatment. Moreover, silicon is the second most abundant element (after oxygen) on earth, providing plentiful and inexpensive resources for large-scale and low-cost preparation of silicon nanomaterials for practical applications. Because of these attractive traits, and in parallel with a growing interest in their design and synthesis, silicon nanomaterials are extensively investigated for wide-ranging applications, including energy, catalysis, optoelectronics, and biology. Among them, bioapplications of silicon nanomaterials are of particular interest.



In the past decade, scientists have made an extensive effort to construct a silicon nanomaterials platform for various biological and biomedical applications, such as biosensors, bioimaging, and cancer treatment, as new and powerful tools for disease diagnosis and therapy. Nonetheless, there are few review articles covering these important and promising achievements to promote the awareness of development of silicon nanobiotechnology.

In this Account, we summarize recent representative works to highlight the recent developments of silicon functional nanomaterials for a new, powerful platform for biological and biomedical applications, including biosensor, bioimaging, and cancer therapy. First, we show that the interesting photoluminescence properties (e.g., strong fluorescence and robust photostability) and excellent biocompatibility of silicon nanoparticles (SiNPs) are superbly suitable for direct and long-term visualization of biological systems. The strongly fluorescent SiNPs are highly effective for bioimaging applications, especially for long-term cellular labeling, cancer cell detection, and tumor imaging *in vitro* and *in vivo* with high sensitivity. Next, we discuss the utilization of silicon nanomaterials to construct high-performance biosensors, such as silicon-based field-effect transistors (FET) and surface-enhanced Raman scattering (SERS) sensors, which hold great promise for ultrasensitive and selective detection of biological species (e.g., DNA and protein). Then, we introduce recent exciting research findings on the applications of silicon nanomaterials for cancer therapy with encouraging therapeutic outcomes. Lastly, we highlight the major challenges and promises in this field, and the prospect of a new nanobiotechnology platform based on silicon nanomaterials.

1. Introduction

The development of nanomaterials has made a tremendous impact on a wide range of fields including catalysis, computing, photonics, energy, biology, and medicine, leading to an enormous interest in nanotechnology. Particularly, the utilization of nanotechnology in biological applications has shown highly attractive potential. The emerging field of nanobiotechnology holds the potential

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of revolutionizing biology and biomedical studies by employing new nanomaterial-based tools for investigative, diagnostic, and therapeutic techniques. In recent years, scientists have made great strides in developing various kinds of nanomaterials and nanofabrication techniques, vastly facilitating the advancement of nanobiotechnology. The unique optical, magnetic, and mechanical properties of functional nanomaterials offer new opportunities for investigating complicated biological processes, which are hard to study by traditional strategies, suggesting exciting avenues in biological and biomedical fields.[1−4]

Silicon nanomaterials have been extensively employed for applications in a large variety of fields, including energy, catalysis, optoelectronics, and biology, because of their many attractive merits, such as excellent biocompatibility, rich abundance (silicon is the second most abundant element on earth), unique electronic, optical, and mechanical properties, and compatibility with conventional Si technology.[5] It is also worth pointing out that porous silicon nanoparticles are found to be biodegradable and readily cleared from a mouse model via renal clearance, producing little toxicity *in vivo*. The biodegradation product of silicon nanomaterials (e.g., orthosilicic acid) is well biocompatible with numerous tissues. Moreover, silicon naturally exists in humans as a trace element.[6] The above merits have motivated intensive investigation of silicon nanomaterials for various biological applications, such as biosensing, *in vitro* and *in vivo* bioimaging, and cancer diagnosis and therapy.

In this Account, we summarize recent research achievements in a silicon nanomaterials platform for bioimaging, biosensing, and cancer therapy (Figure 1). We first introduce representative progress on fluorescent SiNP-based bioimaging applications. Then we describe in detail the fabrication of a silicon nanomaterials-based sensing platform, enabling detection of biological species (e.g., DNA, proteins, and cells) with ultrahigh sensitivity and specificity. Afterward, we highlight the latest achievements in design of silicon nanomaterials-based nanoagents (e.g., hyperthermia nanoagents and drug nanocarriers) for *in vitro* and *in vivo* cancer treatment. Lastly, we discuss the opportunities and challenges for silicon nanomaterials-based biological applications in the future. Due to space limitation, this Account is principally concerned with our own work on applications of silicon nanomaterials for biosensing, bioimaging, and cancer therapy from 2009. It is hoped that it will stimulate a general interest in further developing silicon materials-based nanobiotechnology.

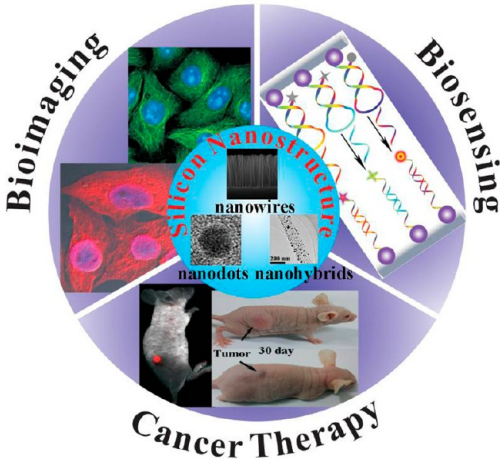

FIGURE 1. Silicon nanomaterials platform for bioimaging, biosensing, and cancer therapy.

2. Silicon Nanoparticles Fluorescent Probes for Bioimaging Applications

Fluorescent biological imaging is recognized as one of the most powerful noninvasive tools for myriad biological and biomedical studies. Fluorescent probes are of essential importance for labeling the targeted biomolecules and amplifying the fluorescent signals. A consensus has been reached that a high-quality fluorescent probe should feature strong fluorescence, excellent aqueous dispersibility, robust photostability, and favorable biocompatibility. Organic dyes and fluorescent proteins, recognized as well-established bioprobes, were utilized in wide-ranging biological and biomedical research in the last century; however, their poor photobleaching property is not suitable for long-term and real-time bioimaging. Fluorescent II−VI semiconductor quantum dots (QDs) with superior photostability have been extensively employed as promising biological nanoprobes for myriad biological applications. However, the potential hazards of QDs due to heavy-metal content is a concern.[5] As a result, novel kinds of biological probes with high fluorescence, strong photostability, and excellent biocompatibility remain highly in demand.

Fluorescent SiNPs are regarded as an ideal biological probe because of the non- or low-toxicity of silicon.[5] However, most surface ligands of SiNPs (e.g., styrene, alkyl, and octene) are hydrophobic, resulting in poor aqueous dispersibility and limited bioapplications of SiNPs. Tremendous effort has been made to address this issue. In 2004 and 2005, Ruckenstein and Tilley reported two kinds of fluorescent water-dispersed SiNPs by modification with hydrophilic molecules (e.g., arylic acid and allylamine) and employed them for cellular imaging.[7,8] Afterward, Swihart

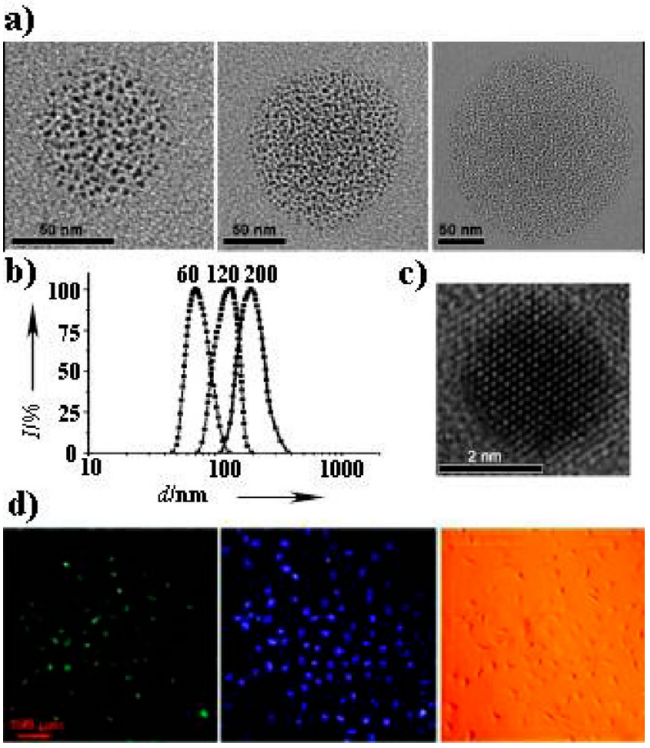

FIGURE 2. TEM images (a) and representative DLS histogram (b) of three hydrophilic polymer-coated SiNPs. (c) HRTEM image of a single SiNP inside the prepared polymer-coated SiNPs. (d) Dual-color cellular imaging photos using polymer-coated SiNPs. Panels a–c reprinted with permission from ref 12. Copyright 2009 Wiley-VCH. Panel d adapted with permission from ref 45. 2009 American Chemical Society.

et al. developed phospholipid micelle-encapsulated SiNPs with good aqueous dispersibility and applied them for *in vivo* bioimaging applications.[9,10] In 2009, He, Lee, and co-workers introduced a new class of water-dispersible, highly fluorescent, pH- and photostable SiNPs whose surfaces were coated with hydrophilic polymer. They further successfully conjugated the prepared SiNPs with protein molecules and presented the first demonstration of SiNP-based immunofluorescent cellular imaging (Figure 2).[11,12] While such hydrophilic species (e.g., hydrophilic molecule, polymer, and micelle-capped SiNPs) are water-dispersible, their sizes are rather large (generally >50 nm in hydrodynamic diameter (HD)) and deleterious to bioapplications (recent reports reveal that nanoparticles with HD < 10 nm are more suitable for *in vivo* applications).[13,14]

In 2011, by using SiNWs and glutaric acid as reaction precursors, our group developed a new microwave method for facile preparation of water-dispersed SiNPs.[15] Notably, besides strong fluorescence and good aqueous dispersibility, the prepared SiNPs featured small sizes (<5 nm in HD) and ultrahigh photostability. As a result, such SiNPs were uniquely suitable for long-term cell imaging. Specifically, for microtubules labeled with SiNPs, stable and bright fluorescence could be observed over a 120 min irradiation period. In comparison, when CdTe QDs or FITC were used for labeling microtubules instead, their fluorescent signals quickly quenched during 25 min observation (Figure 3). On the basis of this, we further employed proteins as hydrophilic ligands for preparation of fluorescent, biofunctional SiNPs.[16] Note that the as-prepared SiNPs were surface-covered by abundant hydrophilic protein molecules, yielding excellent aqueous dispersibility and biospecific properties. As a result, the prepared SiNPs were capable of immunofluorescence cell labeling without complicated protein conjugation (Figure 4). Meanwhile, Tilley and co-workers developed a multistep chemical method to produce allylamine-capped SiNPs with good aqueous dispersibility. They further employed the prepared allylamine-capped SiNPs to label HeLa cells, showing uniform and bright fluorescence of SiNPs in the cytoplasm.[17]

Most of the above synthetic strategies often invoked relatively laborious manipulations, requiring two independent procedures to fabricate SiNP-based biological nanoprobes. Specifically, hydrophobic SiNPs are first produced from large-size silicon materials, followed by surface modification with hydrophilic ligands, producing water-dispersed SiNPs in the second step (so-called "top-down" method). While those strategies are workable, they nevertheless involve complicated manipulations. Recently, a facile bottom-up method superbly suitable for large-scale preparation of water-dispersible SiNPs was introduced.[18] Significantly, this method is capable of producing a large quantity of water-dispersible and fluorescent SiNPs in a short reaction time (e.g., 0.1 g of SiNPs/10 min). In addition to excellent aqueous dispersibility (i.e., the SiNPs are well dispersed in water with high transparence, as shown in Figure 5a), the prepared SiNPs are much more photostable than organic dyes and II–VI QDs (e.g., the SiNPs preserved strong fluorescence during 180 min irradiation, in sharp contrast to severe fluorescence quenching of FITC, CdTe QDs, and CdSe/ZnS QDs during 120 min observation, Figure 5b–f). Furthermore, the SiNPs were highly efficacious for immunofluorescent long-term cellular imaging, yielding stable and strong fluorescence during 60 min confocal observation. In comparison, the signals from FITC fluorescent labels almost completely disappeared in 3 min because of severe photobleaching (Figure 5g,h).

3. Silicon Nanowires for Biosensing Applications

Detection of biomolecules (e.g., DNA and proteins) is of particular importance for various bioapplications, such as

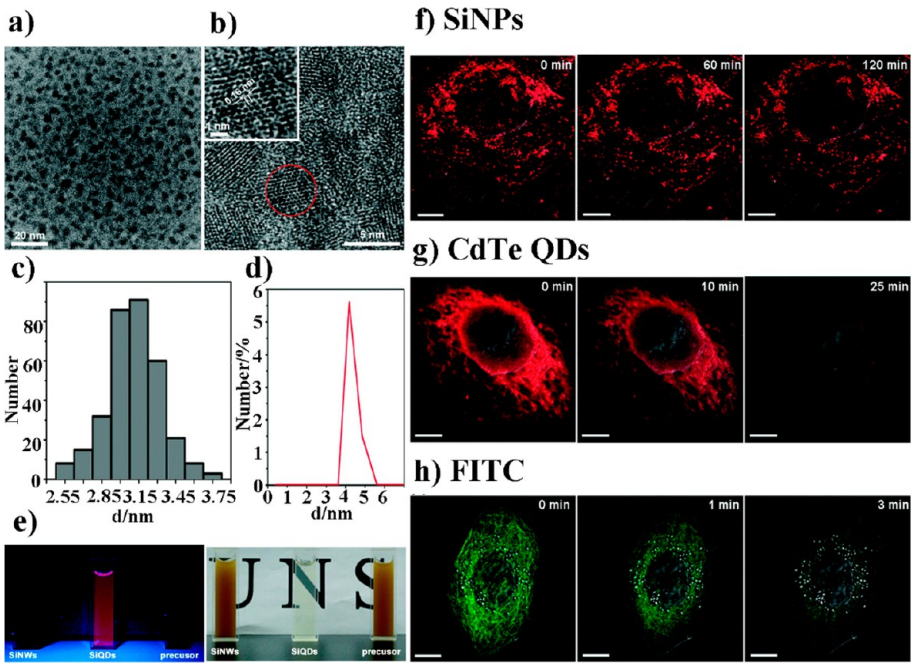

FIGURE 3. (a) TEM, (b) HRTEM, (c) size distribution, and (d) DLS histogram of the as-prepared SiNPs. A HRTEM image of a single SiNP is shown in the panel b inset. (e) Picture of three aqueous samples (i.e., SiNWs, SiNPs, and reaction precursor) irradiated by UV light (left) or ambient light (right). Temporal evolution of fluorescence of (f) SiNPs, (g) CdTe QDs, and (h) FITC-labeled microtubules. Adapted with permission from ref 15. Copyright 2011 American Chemical Society.

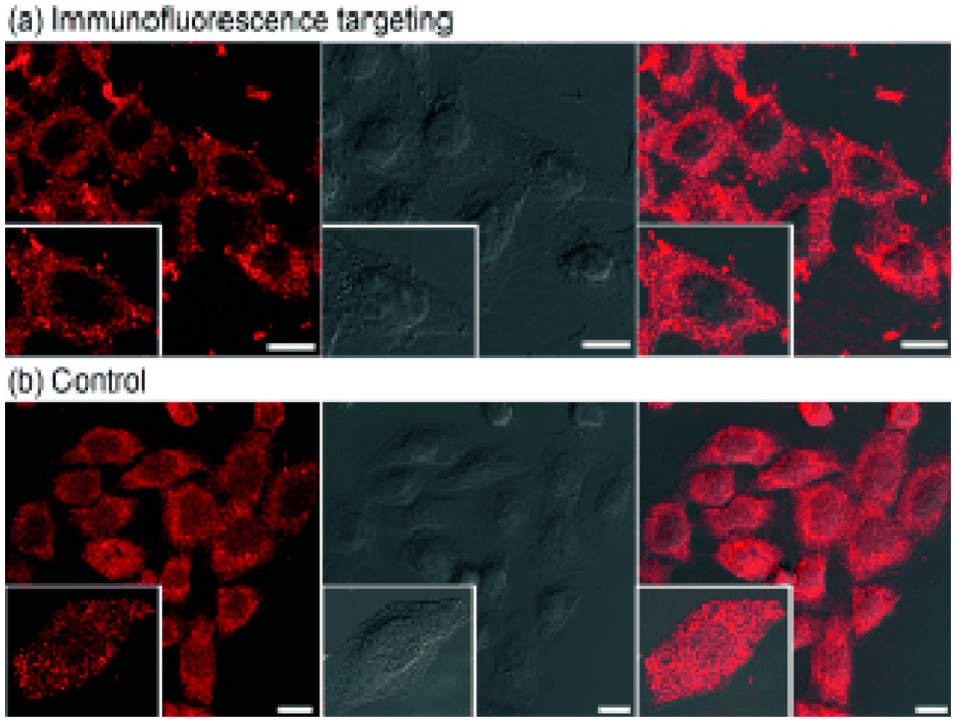

FIGURE 4. Confocal images of cells labeled by protein-conjugated SiNPs (a) or pure SiNPs (b). Red signals are attributed to fluorescence of SiNPs. Reprinted with permission from ref 16. Copyright 2012 Wiley-VCH.

food safety, disease diagnosis, antibioterrorism, and environmental protection.[19] While a number of commercial bioassay kits are already on the market, there still remains a major challenge to develop novel biodetection methods to meet the increasing demand for biosensing applications. Thus far, various kinds of nanomaterials, such as carbon

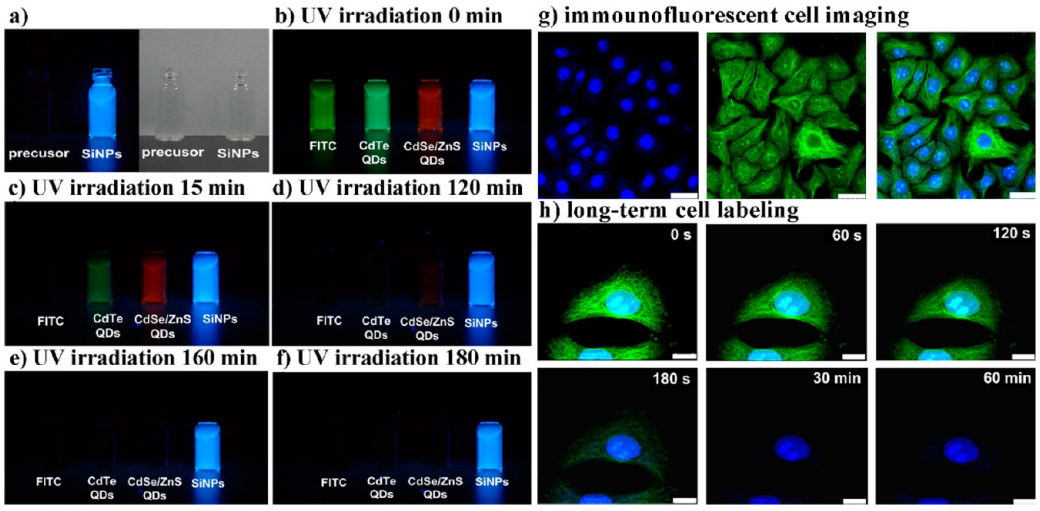

FIGURE 5. (a) Photos of the as-prepared SiNPs and reaction precursor samples irradiated by UV (left) or ambient light (right). (b−f) Temporal evolution of fluorescence of FITC, CdTe, and CdSe/ZnS QDs, and SiNPs under irradiation by 450 W xenon lamp. (g) Confocal photograph of immunofluorescent cellular images. (h) Photos of SiNP-based long-term cellular images. Adapted with permission from ref 18. Copyright 2013 American Chemical Society.

nanotubes (CNTs), graphene, fluorescent II−VI QDs, and gold nanoparticles (AuNPs), have been employed to construct nanobiosensors yielding attractive performance.[4] For example, CNTs and graphene have been fabricated into field-effect transistor (FET)-type biosensors. CNT- or graphene-based FET devices exhibit exceptional sensitivity, since trace amounts of biological species (e.g., DNA and protein) binding to the surface strongly alter the electrical properties of CNTs or graphene, leading to large signals.[4,20] Fluorescent II−VI QD-based biosensors are commercially available for DNA and protein detection. The remarkable optical properties of QDs (e.g., high fluorescence, strong photostability, and size-tunable emission wavelengths) enable high sensitivity and multivariate detection capability of QD biosensors.[21,22] AuNPs have been used as high-fluorescence quenchers to fabricate nanobeacons, allowing high-sensitivity and specific and multiplex DNA detection.[4,23] Despite those notable achievements, there still remains a challenging need for novel high-performance nanobiosensors to meet the ever-increasing diversity of biological and biomedical applications. Due to their unique properties, for example, remarkable electronic, optical, and mechanical properties, large surface-to-volume ratio, facile surface modification, and compatibility with traditional silicon technology, silicon nanomaterials should serve as a natural candidate for building high-performance biosensors. Consequently, there is an intense current interest and effort to develop silicon nanomaterials into biosensors with ultrahigh sensitivity, specificity, and multivariate detection capability. Those efforts are described in this section.

Silicon nanowires (SiNWs) have been widely utilized in the development of high-performance biosensors to take advantage of their favorable biocompatibility, surface tailorability, fast response, and good reproducibility. These unique properties have been exploited in the development of SiNW-based chemical and biological sensors. For instance, in 2001, Lieber and co-workers employed SiNWs modified with amine, biotin, or antigen to construct sensitive, real-time field-effect transistor (FET)-based sensors, enabling label-free and real-time detection of protein (e.g., streptavidin, antibody) and metal ions (e.g., Ca^{2+}) with high sensitivity.[24] In 2006, they further developed a kind of SiNW-based FET assisted by integration with live mammalian neurons and individual axons, which was highly efficacious for accessing valuable information on neurons and axons.[25] In 2007, Yang and co-workers employed a vertically aligned SiNW array as a novel substrate for cell culture and demonstrated its utilization for gene delivery, suggesting that SiNWs might serve as a promising tool for investigation of intracellular and intercellular biological processes.[26] In 2010, Wang et al. employed SiNWs coated with cell capture agents for construction of a new circulating tumor cell (CTC)-capture platform, yielding high CTC-capture efficiency for both spiked and clinical blood samples.[27] More recently, by using AuNP-coated SiNWs as new quenchers with strong fluorescence quenching efficiency (>90%), we developed a class of multicolor silicon-based molecular beacons (nanoMBs) (Figure 6). Of particular note, the prepared SiNW-based nanoMBs were highly stable in salt solution with a high concentration (e.g., 0.1 M) over 10−80 °C

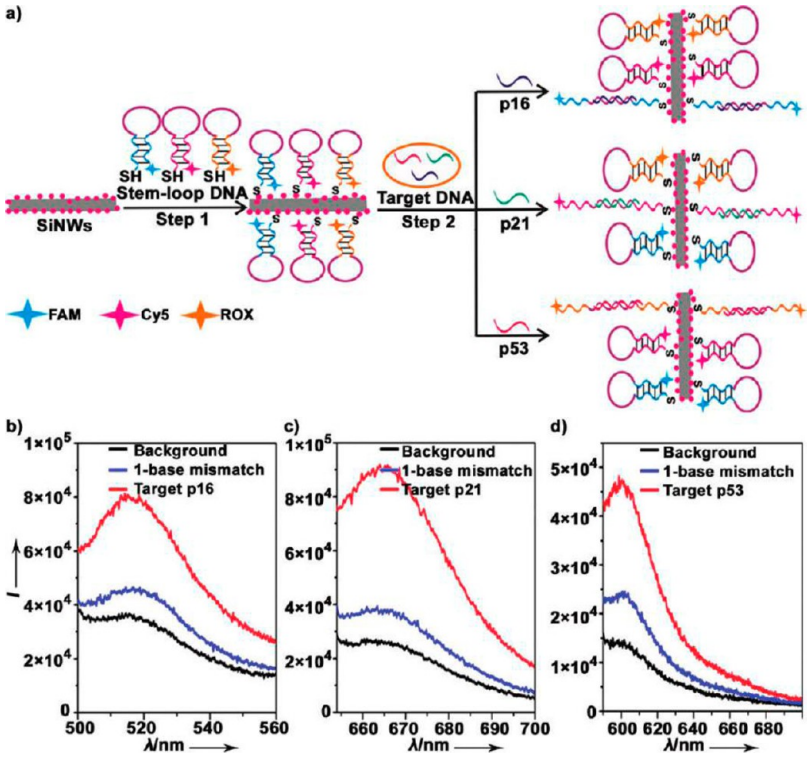

FIGURE 6. (a) Schematic design of SiNW-based nanoMBs for DNA multiplexed detection. (b–d) PL spectra for multidetection of three kinds of tumor-suppressor genes (i.e., p16, p21, and p53). Adapted with permission from ref 28. Copyright 2012 American Chemical Society.

range. Moreover, the large surface of the nanoMBs facilitated simultaneous modification with various kinds of DNA strands, which could be employed for highly sensitive multiplexed DNA detection with a low detection limit of ~50 pM.[28]

Surface-enhanced Raman scattering (SERS) is a highly attractive phenomenon, which can amplify Raman signals by enhancement factors (EF) of $\sim 10^{12-14}$, enabling ultrasensitive chemical or biochemical analysis down to single-molecule level. Free-standing metal (e.g., silver and gold) nanoparticles are well-studied SERS substrates, which however usually exhibit relatively poor SERS reproducibility, due to difficulty in control of size, distribution, and aggregation. To address this issue, Lee et al.[5,29−31] developed several kinds of silicon-based SERS substrates, which anchored and suppressed random aggregation of metal nanoparticles. They reported metal nanoparticle-decorated SiNWs as high-performance SERS substrates (EF $\approx 10^9$), allowing sensitive detection of DNA and proteins.[5,29−31] Recently, Zhang et al. showed AgNP-decorated silicon nanowires (AgNPs@SiNWs) were suitable for detecting a low concentration of carbaryl (0.01 mg/mL) residues on a cucumber surface with 1 s acquisition time, as well as for label-free, real-time detection of *Escherichia coli* in drinking water.[32] They further employed AgNPs@SiNWs as an endoscope for high-resolution detection of pH changes with high sensitivity in an aqueous environment. Such a SiNW-based SERS endoscope may serve as a promising tool for direct visualization of living cells and biological systems capable of providing valuable molecular finger-printing information.[33]

In 2011, we designed a sandwiched-structured SiNW-based DNA sensor via serial immobilization of capture, target, and reported DNA.[34] This SiNW-based biosensor featured ultrahigh sensitivity, allowing detection of DNA at a low concentration of ~1 fM, which was comparable to the best or smallest value ever reported for a SERS methods. It is worth pointing out that for most previously reported SERS strategies, SERS signals are distinctly amplified in the presence of targets. Target detection is generally based on such so-called "signal-on" procedures. Recently, taking advantage of organic dye-tagged stem–loop oligonucleotides, we further developed a new SiNW-based signal-off SERS strategy, enabling multiplexed detection of DNA with low detection concentrations ranging from 10 fM to 1 pM.[35] We further developed a new kind of silicon-based SERS biosensor with excellent reproducibility by employing AgNP-coated silicon wafers (AgNPs@Si) as high-performance SERS substrates.[36] In this sensor, a large amount of AgNPs were tightly immobilized

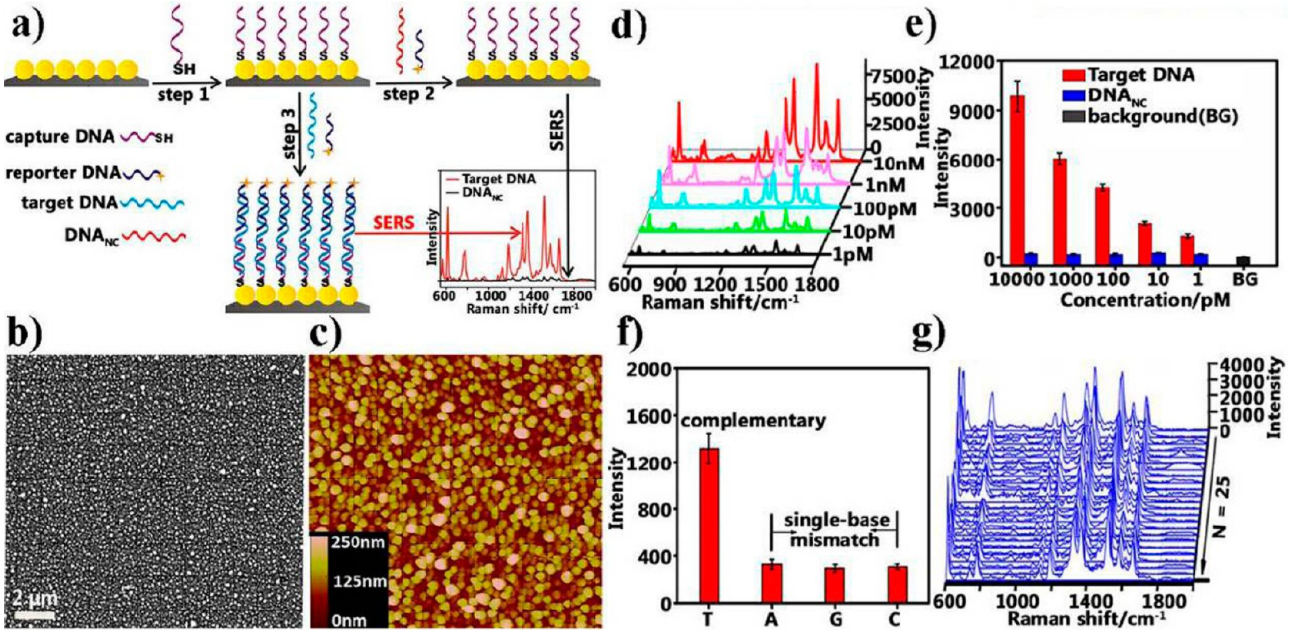

FIGURE 7. (a) Schematic illustration of fabrication of silicon-based SERS DNA sensor. (b) SEM and (c) AFM images of the as-prepared AgNP-decorated silicon wafer. Notably, the silicon-based SERS sensor is capable of sensitive (detection limit = 1 pM, panels d and e) and specific (single-based mismatches (1 pM) discrimination, panel f) DNA detection. In addition to the high sensitivity and specificity, the sensor features excellent reproducibility, showing similar SERS spectra of 25 random points on the target DNA (10 pM)-modified substrates (g). Adapted with permission from ref 36. Copyright 2012 American Institute of Physics.

on the Si surface, effectively avoiding random AgNP aggregation. As a result, the resulting silicon-based biosensor exhibited high reproducibility, enabling sensitive detection of DNA (~1 pM) with a relatively small standard deviation of 13.1% (Figure 7). Such a high-performance AgNPs@Si SERS substrate was highly efficacious for *in vitro* apoptosis detection at the single-cell level based on observation of changes of Raman peak intensity at 788 cm^{-1} (Figure 8).[37] Importantly, a single apoptotic cell could be facilely monitored using the silicon nanomaterial SERS platform. As shown in Figure 8c−h, while DNA was uniformly distributed in the cell in the initial stage, the nucleus diminished and the chromatin mildly condensed when incubation time reached 6 h. As incubation time increased, the chromatin became more condensed and started to fragment at 12 and 24 h incubation, respectively. At 48 and 72 h incubation, the cell stepped into the late stage of apoptosis, in which DNA strands were eventually disintegrated with complete destruction of phoshodiester bonds, leading to feeble DNA SERS signals of the apoptotic cell. In addition to sensitive detection of DNA and protein, it suggests exciting avenues for *in vitro* detection applications using SERS techniques.

4. SiNW Nanoagents for Cancer Therapy

In recent years, numerous classes of nanomaterials have been investigated to provide new effective platforms for treatment of cancers, for improved therapeutic efficacy and reduced toxic side effects. Nanomaterials-based near-infrared (NIR) hyperthermia agents hold great promise for tumor photothermal therapy due to low absorption of biological systems in the NIR range. To date, several kinds of nanomaterials (e.g., gold nanorods, gold nanoshells, carbon nanotubes, and graphene) have been developed as NIR hyperthermia nanoagents for cancer treatment.[3]

Metal nanoparticle (e.g., silver nanoparticle, gold nanoparticle, and quantum dot)-decorated SiNWs exhibit unique electronic and optical properties.[38−40] Particularly, NIR light (e.g., 808 nm light) could be largely absorbed and trapped by SiNWs due to their strong absorbance in the NIR range. On the other hand, AuNPs acting as heat producer featured high conversion efficiency of NIR light to heat. Utilizing the above merits, we recently reported a SiNW-based NIR hyperthermia nanoagent made of a AuNPs@SiNWs complex.[41] Significantly, AuNPs@SiNWs could rapidly generate high heat under NIR irradiation (e.g., the temperature rise (ΔT) value of the AuNPs@SiNWs sample reached 38.3 °C in 3 min NIR irradiation). In marked contrast, for pure water or free SiNW samples, the ΔT value was nearly unchanged. AuNPs@SiNWs were thus employed for *in vitro* photothermal ablation. Typically, cell viability was well maintained when KB cells were treated with AuNPs@SiNWs or NIR irradiation

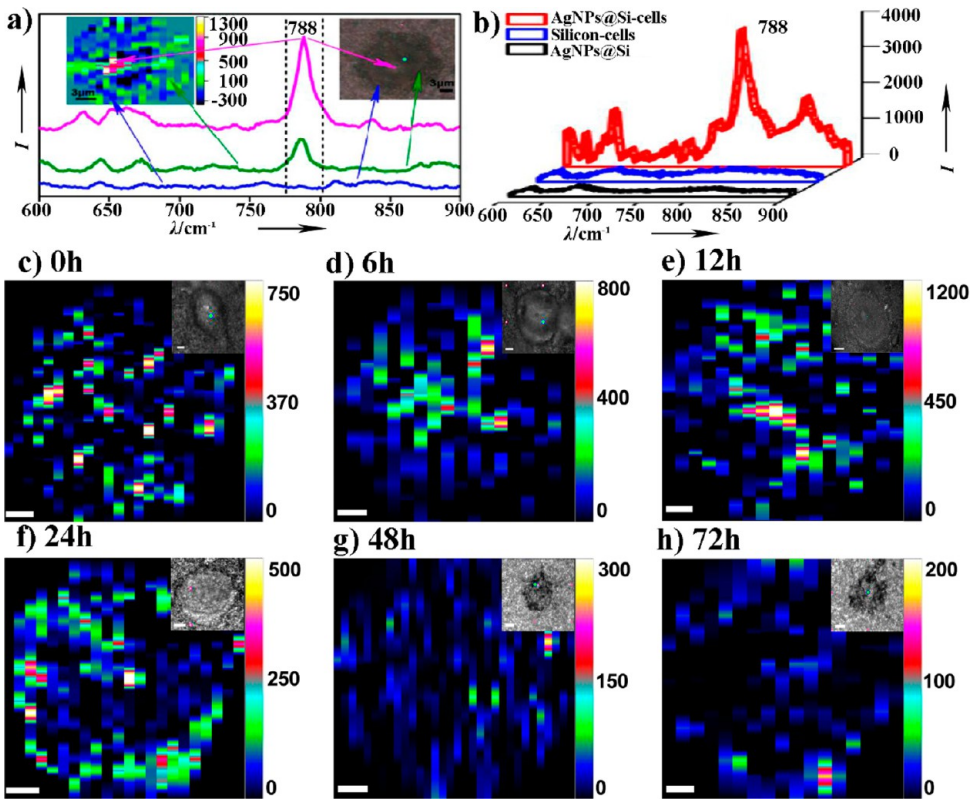

FIGURE 8. (a) Typical Raman spectra of different regions of a single A549 cell incubated on silicon-based SERS substrates. Inset is the corresponding SERS mapping image (left) and bright-field image (right). (b) Comparison of Raman spectra of three groups, that is, pure silicon-based SERS substrate, cell-treated silicon-based SERS substrate, and cell-treated silicon wafer. (c–h) SERS mapping images of a Triton X-100-treated A549 cell at different incubation times (e.g., 0, 6, 12, 24, 48, and 72 h). The bright-field Raman images are shown in the insets. Adapted with permission from ref 37. Copyright 2013 American Chemical Society.

alone. In contrast, AuNPs@SiNWs-treated KB cells were nearly all dead after 3 min NIR irradiation. In addition, two other kinds of cancer cells, A549 and HeLa cells, were also completely destroyed during 3 min NIR irradiation, indicating that such SiNW-based hyperthermia was efficacious and universal for malignant tumor cells (Figure 9). It is worth pointing out that the threshold NIR laser power density of AuNPs@SiNWs used to irradiate cells was only 2 W/cm^2, which is smaller than or comparable to that (~4–35 W/cm^2) reported for established nanomaterial (e.g., gold nanorod, gold nanoshell, etc.)-based photothermal agents. Meanwhile, Park et al. reported gold nanocluster (AuNC)-coated SiNWs for cancer therapy using the photothermal method.[42] Similar to AuNPs@SiNWs, the AuNC-coated SiNWs produced sufficient heat under NIR irradiation (e.g., 808 nm) due to strong NIR absorbance of SiNWs. Notably, they further conjugated AuNC-coated SiNWs with a proper antibody to specifically capture tumor cells. Consequently, breast cancer cells were efficiently captured (~88% at 40 min incubation) by AuNC-coated SiNWs with an antibody-coated surface and thereafter destroyed under short-time (e.g., 15 s) NIR irradiation (808 nm, 3 W). This novel SiNW-based platform offers exciting opportunities for concurrent capture and therapy of circulating tumor cells (CTC).

Besides NIR hyperthermia nanoagents, nanomaterials with large porosity and huge surface-to-volume ratio have also been utilized as drug nanocarriers exhibiting high drug-loading capacity for cancer treatment in recent years. For instance, mesoporous silica structure-based nanocarriers exhibited doxorubicin (DOX, a traditional kind of anticancer drug) loading capacity of ~1200 mg/g.[43] The DOX loading capacity of graphene or single-walled carbon nanotubes (SWNTs) reached 2350 or 4000 mg/g, respectively.[44] In comparison to free DOX molecules, which are prone to be eliminated via renal clearance or distributed in normal tissues, the nanomaterials-based drug nanocarriers can greatly enhance the concentration of anticancer drug at tumor tissue, leading to sufficient drug concentration and improved therapeutic effectiveness in the tumor tissue. Recently, taking advantage of large-area porous structures and high surface-to-volume ratio of SiNWs, we demonstrated the first example of SiNW-based drug nanocarriers

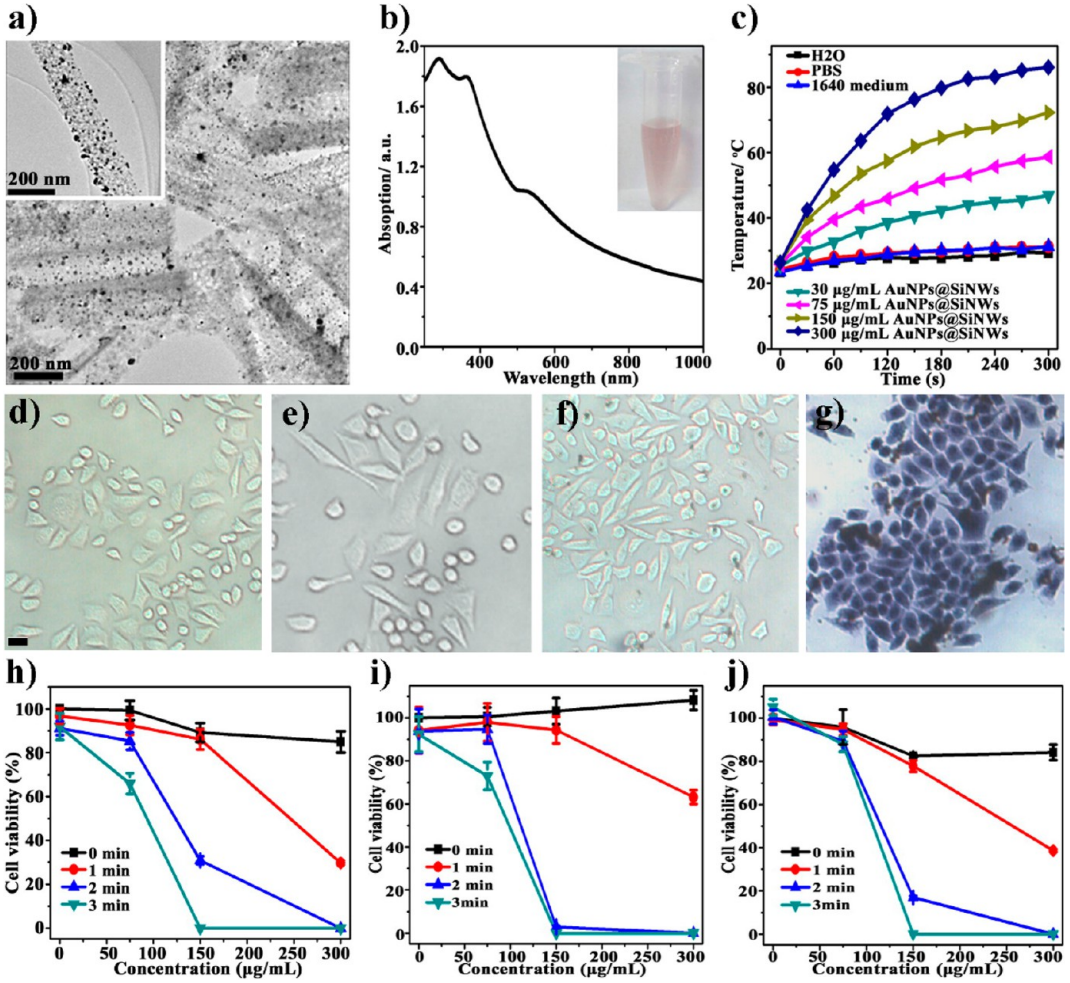

FIGURE 9. (a) TEM image and (b) UV−vis−NIR spectrum of the resultant AuNP-decorated SiNWs. (c) Concentration-dependent temperature increase of AuNP-decorated SiNWs with different NIR irradiation time. (d−g) Optical images of three control groups (free KB cells (d), NIR irradiation-treated KB cells (e), and SiNWs hyperthermia agent-treated KB cells (f)) and the experiment group (e.g., SiNW hyperthermia agent-treated Kb cells under NIR irradiation (g)). SiNW-based nanoagents exhibit universal hyperthermia effects, leading to dramatic decrease of cell viability of three cell lines (KB cells (h), A540 cells (i), and Hela cells (j)). Adapted with permission from ref 41. Copyright 2012 American Chemical Society.

featuring an ultrahigh drug-loading capacity of ~20800 mg/g, much higher than those (~1200−4000 mg/g) ever reported by nanomaterials-based carriers (Figure 10).[45] Significantly, the SiNW-based drug nanocarriers were highly efficacious for *in vivo* cancer treatment, exhibiting remarkable inhibition efficiency of tumor growth. Typically, tumor-bearing mice treated by the SiNW-based nanocarriers survived over 30 days without detectable tumor growth, which was in sharp contrast to control groups (i.e., physiological saline, free DOX, or pure SiNW treated mice) whose tumor size invariably increased, resulting in lethality in mice in less than 30 days. Taken together with the low-cost and facile preparation of SiNWs, this work suggests the SiNWs nanoagents as promising tools for cancer treatment, rivaling or complementing the well-studied nanomaterials-based cancer agents.

5. Conclusion and Prospects

In this Account, we summarize recent research achievements in development of silicon nanomaterials platforms for biological applications in bioimaging, biosensing, and cancer therapy. Specifically, fluorescent SiNPs as high-performance nanoprobes have successfully proven to be highly efficacious for long-term bioimaging applications because of their ultrahigh photostability and favorable biocompatibility. SiNW-based substrates have been developed for wide-ranging biosensing applications for ultrasensitive and specific detection and analysis of biological species, including DNA, protein, and cells. Furthermore, SiNWs and their hybrids (e.g., gold nanoparticles/cluster-decorated SiNWs) have been successfully used as novel silicon-based nanoagents for high efficacy *in vitro* and *in vivo* cancer

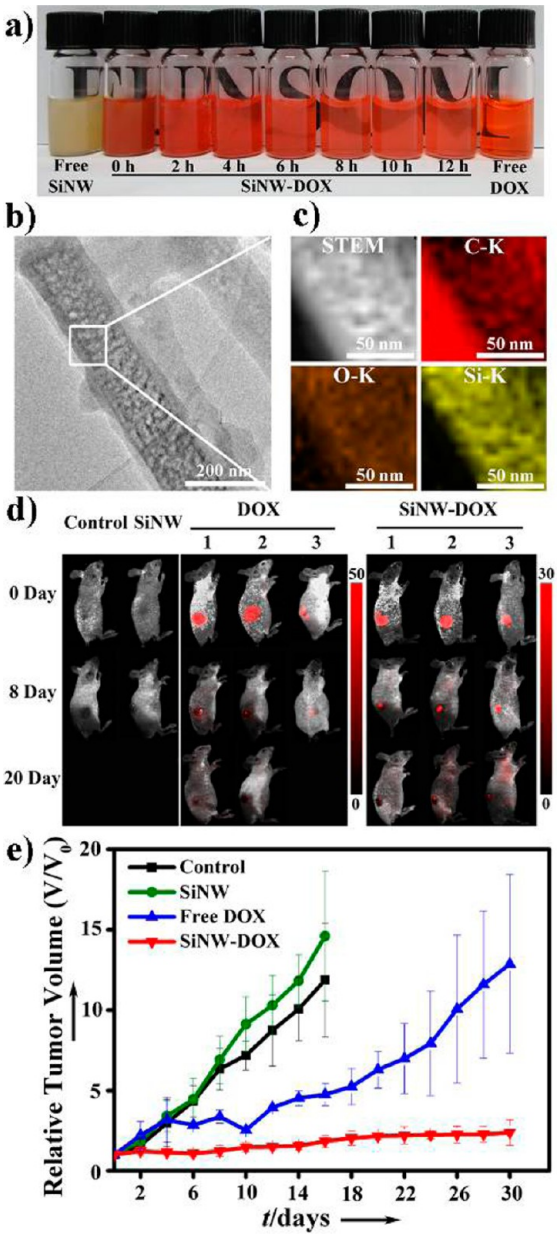

FIGURE 10. (a) Photos of pure SiNWs (left), SiNWs loaded with DOX for different loading times, and free DOX (right) aqueous sample. (b) TEM image of DOX-loaded SiNWs and (c) corresponding dark-field scanning TEM (STEM) of DOX-loaded SiNWs in the white frame. (d) *In vivo* fluorescence images and (e) corresponding curves of tumor growth inhibition of tumor-bearing mice treated with PBS, free SiNWs, free DOX, and DOX-loaded SiNWs. Reprinted with permission from ref 41. Copyright 2013 Wiley-VCH.

treatment. These exciting achievements open new avenues for designing silicon nanomaterials integrated platforms for early cancer diagnosis and therapy at different levels ranging from molecule (DNA) to *in vitro* and *in vivo*.

Despite the exciting progress, there are still many major challenges in this field. In particular, extensive effort is required to investigate the fluorescent mechanisms of SiNPs. A comprehensive understanding of the mechanisms would offer invaluable guidance for the rational design of highly luminescent, color-tunable SiNPs for SiNP-based multicolor *in vitro* and *in vivo* bioimaging applications. Another daunting challenge is the development of low-cost large-scale production methods for high-quality SiNPs, which is essential for their wide-ranging applications. For biosensing applications, while a variety of silicon-based SERS architectures are available for high-sensitivity and high-specificity bioassays, satisfactory SERS enhancement mechanisms are absent and require further studies and understanding. For cancer therapy, multifunctional silicon nanomaterial nanoagents featuring optical, magnetic, or thermal properties are required for multimodel cancer treatments (e.g., fluorescence or magnetism imaging guided photothermal therapy and chemotherapy). While favorable biocompatibility is accredited to silicon, systematic and reliable *in vitro* and *in vivo* biosafety assessment (e.g., biodistribution, pharmacokinetics, and interactions between silicon nanomaterials and biomolecules, cells, and animals) remains to be performed. Provided the above challenges are satisfactorily resolved, silicon nanomaterials may be anticipated to serve as a powerful and practical platform for wide-ranging biological and biomedical applications.

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FOOTNOTES

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