Boolean Logic

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Using Thermally Regenerable Cerium Oxide Nanoparticles in Biocomputing to Perform Label-free, Resettable, and Colorimetric Logic Operations**

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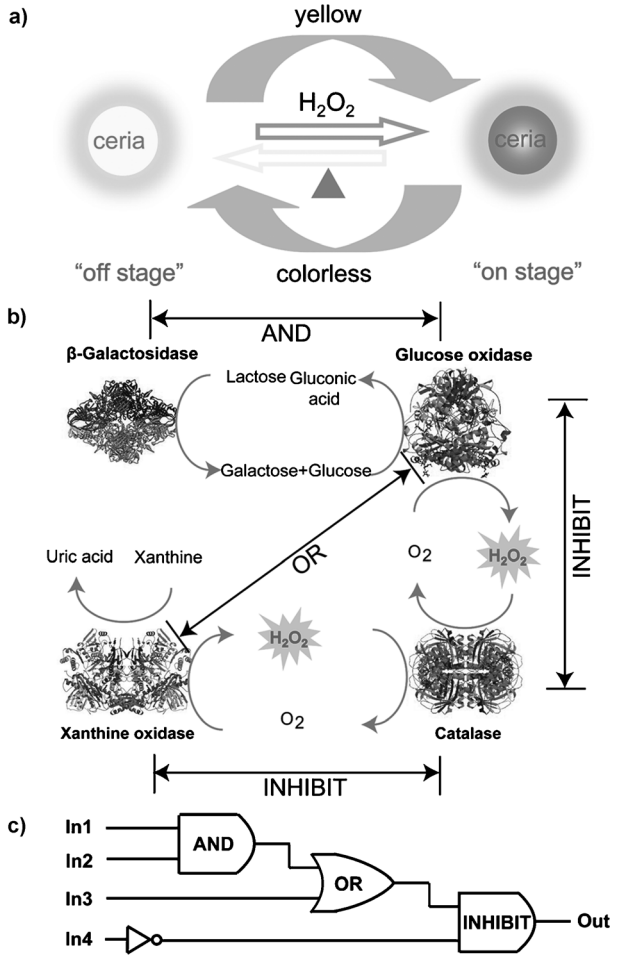
In recent years, much research interest has been directed to unconventional chemical computing, which results in the remarkable progress of various Boolean logic systems, such as AND, OR, XOR, NAND, NOR, INHIBIT, half-adder, and half-subtractor.[1] Despite these burgeoning developments, most of the chemical computing systems have the following disadvantages: 1) It is difficult to scale them up for assembling large networking systems owing to the interference between reactions and the incompatibility of various chemical gates operating under different conditions;[1a,2] 2) they are unable to realize the logic system reset, which is a crucial property for practical applications;[3] 3) they usually employ a fluorescent signal as the output, which relies on advanced instruments for the readout;[4] and 4) previous studies on molecular-based logic system often lack the desired portability, and the design of practical applicable logic gates attached to solid surfaces is not straightforward.[1f] Very recently, spiropyran-modified gold nanoparticles have been used in the construction of resettable and multi-readout logic gates.[3] Although promising, such system requires sophisticated synthesis processes for obtaining the reset function, which adds to the complexity, cost, and overall assay time. Furthermore, the lack of considerable degrees of integration or concatenation between logic gates limits the effectiveness of such a strategy. Therefore, it would be highly desirable to develop logic system that is simple in design, feasible to reset, not limited to solution-based applications, and involves a reliable, convenient readout. Moreover, a series of independently working logic gates could be easily brought together to function as concatenated/integrated logic gates.

Herein, we present a label-free, resettable, and colorimetric logic network by utilizing biocatalytic reactions and regenerable cerium oxide nanoparticles (CeO_2 NPs) as signal transducer (Scheme 1). CeO_2 NPs, which exist in a mixed valence state (Ce^{3+}, Ce^{4+}), possess many unique properties that have proven to be of high utility in biomedical and catalytic applications.[5–7] For instance, they have been found to scavenge reactive oxygen species, possess superoxide-dismutase-like activity, offer cardioprotection, and protect normal cells from radiation-induced damage.[6] Furthermore, they have been reported to show rapid color change (from colorless to yellow) upon addition of H_2O_2, which is mainly due to a change in the oxidation state from Ce^{3+} to Ce^{4+} on



Scheme 1. a) Illustration of a thermally responsive switch based on CeO_2 NPs. b) The operation of logic gates based on biocatalytic reactions. c) Logic circuitry for the integrated logic system. In1 = β-Gal, In2 = GOx, In3 = XO, In4 = CAT.

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the CeO_2 NP surface.[7] Interestingly, the yellow colored solution of CeO_2 NPs could become colorless upon the reduction of Ce^{4+} back to Ce^{3+} state (Scheme 1a).[7] Recently, biochemical computation performed by DNA, enzymes, or complex biochemical systems has offered a promising path for future computing technology.[8,9] It becomes an important step forward in chemical computing by allowing simultaneous operation of several concatenated logic gates in the same chemical environment without any interference and "cross-talk" between them.[9] We note that the complexity of biocomputing, and particularly the speed of information processing, could not compete with traditional silicon-based technology. However, it might not only help us to understand how living organisms manage to control extremely complex and coupled biochemical reactions, but also allow effective interfacing between complex physiological processes and implantable biomedical devices. For instance, the use of enzymes for logic systems is intriguing because numerous biocatalytic cycles in living organisms rely on information processing, like computer devices.[9a,e] Inspired by these phenomena, we expect that the combination of signal-responsive CeO_2 NPs and biocatalytic reactions could offer a unique opportunity to construct robust logic gates based entirely on colorimetric outputs (Scheme 1b). Moreover, we could apply this system to generate sophisticated networks of logic circuits, which, on the conceptual level, may also help us to understand the functioning of complex biological systems (Scheme 1c). Significantly, the regenerative capability of CeO_2 NPs would make the logic gates feasible to realize a system reset without any complicated and time-consuming procedures. Furthermore, this method could also be expended to patterned paper, which has the advantage of low cost, easy operation, and portability.[10] Such logic systems can provide an interesting approach for logic sensing applications where multiple target molecules are present. To the best of our knowledge, the present work demonstrates for the first time that redox-active CeO_2 NPs could serve as a signal transducer for the creation of colorimetric and resettable logic network. Meanwhile, our new findings might pave the way to apply signal-responsive (for example, light, pH, H_2O_2) materials as novel transducers for realizing more complex logic systems.

To realize the CeO_2 NP-based logic gates, CeO_2 NPs were first synthesized (see details in the Supporting information) and studied by the X-ray powder diffraction (XRD) and transmission electron microscopy (TEM) imaging (Supporting Information, Figure S1).[5b,11] The solution containing CeO_2 NPs was nearly colorless in the absence of H_2O_2 (Figure 1). Addition of H_2O_2 into the above solution caused an instantaneous color change from colorless to yellow, which was due to the changes in the surface properties of CeO_2 NPs.[7] Meanwhile, a high absorbance at 425 nm (A_{425}) in the UV/Vis spectra of the mixture was obtained. More importantly, the H_2O_2-triggered optical response of CeO_2 NPs was easily reversible by slight heating for several minutes (Supporting Information, Figure S2, S3). Considering the reversible optical response of CeO_2 NPs, the yellow solution (higher A_{425} value) with H_2O_2 and colorless solution (lower A_{425} value) without H_2O_2 could be defined as ON and OFF states, respectively. The thermoreversible colorimetric switching of CeO_2 NPs is simple in design and easy to operate, avoiding any complicated and time-consuming covalent modification or chemical labeling procedure. Moreover, the colorimetric switching can be repeated for several cycles with a slight "fatigue effect", which is often suffered by a conventional organic fluorophores-based fluorescence switch (Figure 1).[12]

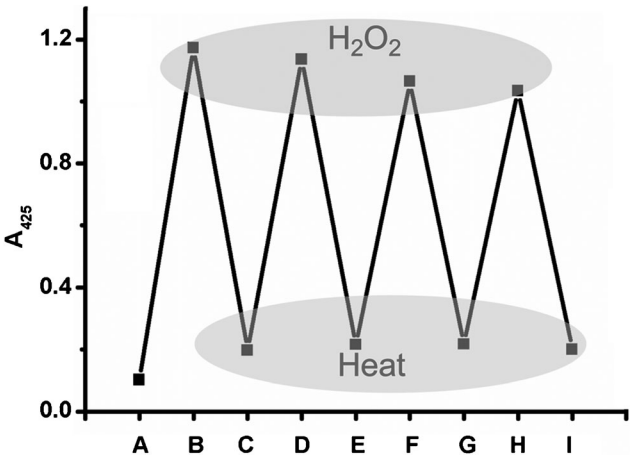


Figure 1. Reversible switching of the CeO_2 NPs between the ON and OFF states through the addition of H_2O_2 (4 mM) and heating (85 °C, 25 min). Absorbance intensity of CeO_2 NPs was recorded at 425 nm.

To demonstrate the potential application of the thermally regenerable CeO_2 NPs described above, we first designed an AND logic gate that employs β-galactosidase (β-Gal) and glucose oxidase (GOx) as inputs, and the color change of solution containing CeO_2 NPs as the output (Supporting Information, Scheme S1). The initial reaction system included lactose, oxygen (in equilibrium with air) and CeO_2 NPs dissolved in citrate buffer, pH 6.0. The primary enzyme β-Gal catalyzed the hydrolysis of lactose into glucose and galactose. The glucose formed acts as substrate for GOx, mediating the oxidation of glucose by O_2 to yield gluconic acid and H_2O_2. Indeed, H_2O_2 could only be formed when the entire cascade is operational, thus mimicking the logic operation AND.[13] Figure 2a showed the signal response of the solution after application of different combinations of the enzyme inputs. In the absence of either or both of the inputs (0/0, 0/1, 1/0), the enzymatic cascade reactions did not ensue and H_2O_2 was not produced. As a result, no appreciable color change in the solution was detected, that is, CeO_2 NPs remained in an OFF state (output 0). However, in the presence of both inputs (1/1), the enzymatic cascade reactions proceeded effectively, resulting in the formation of H_2O_2. Thus, CeO_2 NPs showed a color change from colorless to yellow (ON state), which was considered as output 1. This system performed AND logic operation corresponding to the Boolean logic multiplication (A·B), demonstrating the feasibility of using the CeO_2 NP-based signal transducers in logic gate design. Furthermore, the AND logic gate was also confirmed by testing the UV/Vis absorption response. By observing the absorption change at 425 nm, only the (1/1) input combination switched the output to the ON state upon application of the four logic combinations. Importantly, the visual result and convenient readout

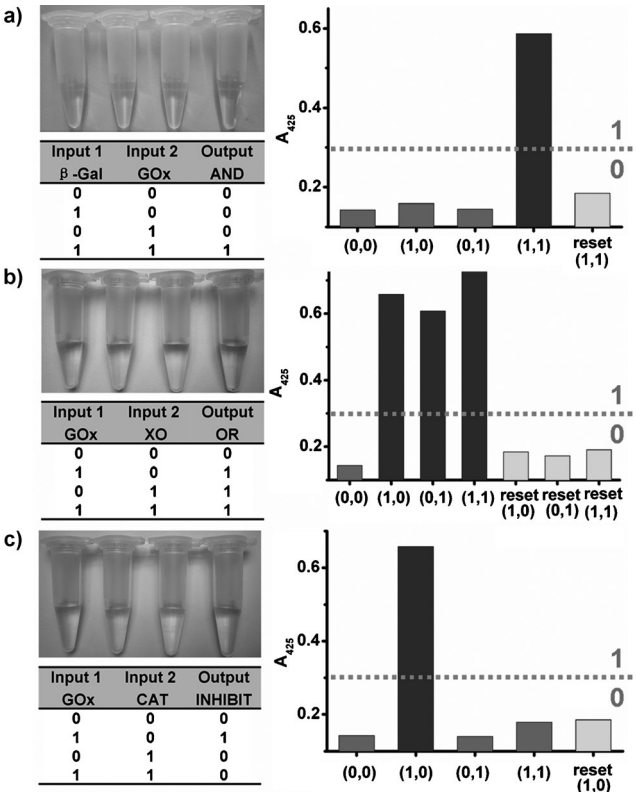


Figure 2. The results of each path of the resettable a) AND, b) OR, and c) INHIBIT logic gates are characterized by colorimetric and UV/Vis detection. The Reset operation was conducted after input (1,1) for the AND gate, inputs (1,0) (0,1) (1,1) for the OR gate, and input (1,0) for the INHIBIT gate.

procedure are attractive, facilitating the straightforward discrimination between the OFF and ON output signals. Furthermore, to evaluate the generality of our method, logic operations were also constructed in the test paper system by detecting the color changes of CeO_2 (Supporting Information, Figure S4). Moreover, enzymatic computation in a spatially restricted fashion was achieved through photolithography using three different masks (Supporting Information, Scheme S4, Figure S5), which could be employed for inexpensive, portable, and technically simple multiplexed biological assays.[10]

Similarly, an OR logic gate can be constructed using GOx and xanthine oxidase (XO) as inputs, and the color change of CeO_2 NP solution was defined as output (Supporting Information, Scheme S2). The starting system included glucose, xanthine, oxygen, and CeO_2 NPs dissolved in citrate buffer at pH 6.0. H_2O_2 can be produced in two parallel biochemical reactions, thus realizing the OR logic gate.[14] With no input, none of the biocatalyzed reactions occurred, no color change was observed, and thus the output of system is "0". In the presence of either or both inputs (1/0, 0/1, 1/1), H_2O_2 was produced by either or both enzymatic pathways. As a result, the solution exhibited a dramatic color change, which was considered as output 1 (Figure 2b). Therefore, the system could perform OR logic operation, corresponding to the Boolean logic addition: A + B. Moreover, by observing the absorption intensity at 425 nm, the value of A_{425} for the inputs (1/0, 0/1, 1/1) is much higher than that in the absence of inputs (0/0). Furthermore, an INHIBIT gate using GOx and catalase (CAT) as inputs was also designed (Supporting Information, Scheme S3). For output, the yellow solution was defined as "1", and the colorless solution as "0". When only GOx were added, the output was 1, otherwise it was 0 (Figure 2c). This pattern of input to CeO_2 NP-based colorimetric output successfully revealed the truth table of the INHIBIT gate. Likewise, another INHIBIT gate could be created using XO and CAT as inputs (data not shown). Furthermore, other kinds of logic gates could also be constructed by using complex and coupled biochemical reactions. Taken together, these results demonstrate that our present logic system is capable of multiplex logic operations based on colorimetric outputs.

By taking advantage of unique and attractive properties of CeO_2 NPs and enzymes, these CeO_2 NP-based logic gates can be easily reset to their initial conditions by heating, without having to go through complicated, time-consuming process. If the logic system was switched ON upon appropriate combinations of the input signals, it would restore to an OFF state by the reset function. Under heating, the activities of enzyme inputs were inhibited which were confirmed by the corresponding colorimetric assays (Supporting Information, Figure S6).[15] Meanwhile, the H_2O_2-triggered optical response of CeO_2 NPs was reversible by heating owing to the regenerative capability of these NPs (Figure 2). More importantly, CeO_2 NPs could be switched between OFF and ON states by applying appropriate enzyme inputs and heating alternatively (Figure 3), which is great valuable in the practical application of logic devices. Furthermore, CeO_2 NPs still kept their activity after reset for at least 10 days (Supporting Information, Figure S7). Thus, the CeO_2 NP-based switch combined with the temperature-sensitive enzyme activities made the logic gate feasible to realize system reset. Compared with spiropyran-Au NP-based resettable logic gates, this one-step

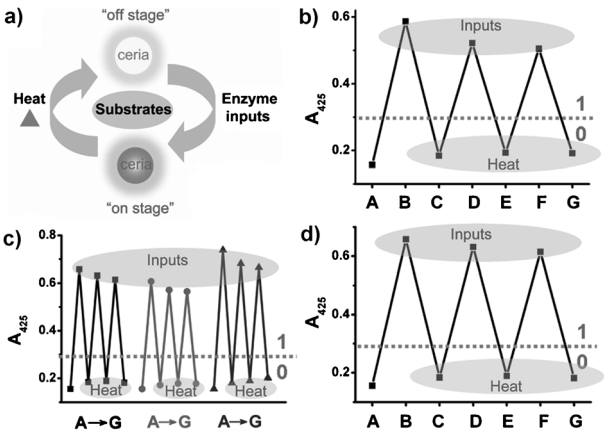


Figure 3. a) Illustration for repeated switches between "off" and "on" states through the addition of enzyme inputs and heating. The cycles of absorbance intensity at 425 nm operating with enzyme inputs and heating alternatively: b) input (1,1) for AND gate, c) inputs (1,0) (0,1) (1,1) for OR gate, and d) input (1,0) for INHIBIT gate.

approach does not require any chemical modification and separation.

The aforementioned examples have shown that the H_2O_2-responsive CeO_2 NPs are capable several types of logic operations based on two enzyme inputs. However, the major challenge in the logic systems is the possibility of assembling multicomponent/multifunctional logic circuitries. In the following set of representative experiments, we expected our logic system could be scaled up to perform large networking systems mimicking natural biochemical pathways. Eight combinations of different sets of three input signals were used to generate the equivalent output of the circuits (Supporting Information, Figures S8–S10). The designed logic systems can operate differently, depending on the pattern of the applied enzymes input signals. For instance, a three-input INHIBIT logic gate delivers an expression $\bar{A}\cdot B\cdot C$ corresponding to high concentrations of two species (B and C) and a low concentration of the other (A; Supporting Information, Figure S10), which could be particularly useful for fast screening of medical conditions.[1e] Similarly, we further demonstrated the operation of a Boolean circuit to compute [(A AND B) OR C] AND NOT D by using four enzyme inputs (Supporting Information, Scheme 1c). The truth table for the Boolean logic function characteristic of the concatenated gates system is displayed in Figure 4a. We then performed an experimental study of the absorbance changes upon application of each of the 16 combinations of four input signals. The initial reaction system included lactose, xanthine, oxygen, and CeO_2 NPs dissolved in citrate buffer at pH 6.0. As shown in Figure 4b, only the "correct" combination of biochemical input signals resulted in the formation of H_2O_2, producing the ON state characterized by the absorbance changes of CeO_2 NPs. Moreover, for all the above networking systems, the reset function was easily activated by heating, and the state of CeO_2 NPs could be modulated reversibly through the addition of "correct" enzyme inputs and heating (Supporting Information, Figures S8–S11). These results are fully consistent with the prediction on the basis of the sequence of biochemical reactions, and may help us to understand how living organisms manage to control extremely complex biochemical processes. Moreover, the broader availability of various enzymes suggested that concatenated gates of enhanced complexity might be designed in the future.

Finally, we also investigated the possibilities of the proposed system in practical logic sensing applications. Compared to traditional sensing devices, logic biosensors are smart and able to intelligently analyze the relationship between different targets according to the Boolean logic operations "programmed" into biocomputing systems.[16] Here, three enzymes (XO, GOx and β-Gal) were used as a model system to provide the "proof-of-principle" verification of the concept. Both in solution and on patterned paper, we could logically make judgment whether XO, GOx, and β-Gal was present or not on the basis of the outputs (Scheme 2; Supporting Information, Table S1, Figures S12, S13). Such a logic system, especially on patterned paper, is appealing in the fabrication of intelligent point-of-care devices and the design of biocomputing system for on-site applications.[10,16] In

a)

Input 1 β -gal-	Input 2 GOx	Input 3 XO	Input 4 CAT	Output Signal Change
0	0	0	0	0
0	0	0	1	0
0	0	1	0	1
0	1	0	0	0
0	0	1	1	0
0	1	0	1	0
0	1	1	0	1
0	1	1	1	0
1	0	0	0	0
1	0	0	1	0
1	0	1	0	1
1	1	0	0	1
1	0	1	1	0
1	1	0	1	0
1	1	1	0	1
1	1	1	1	0

b)

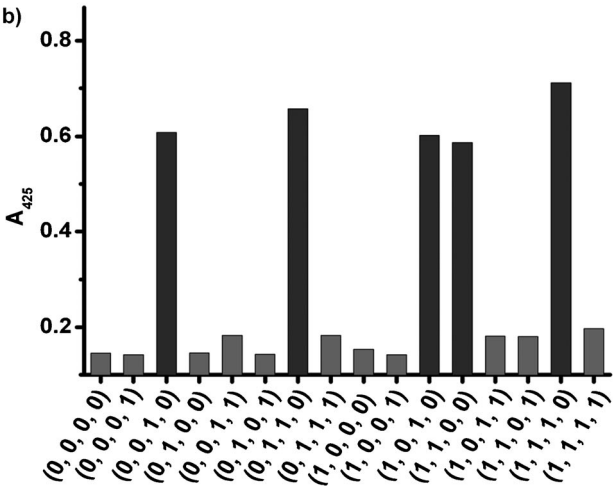
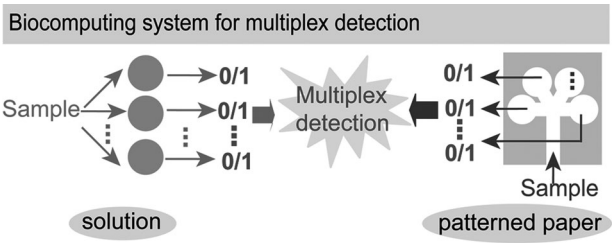


Figure 4. a) Truth table and b) absorption data for the Boolean logic functions of H_2O_2-sensitive CeO_2 NPs operating with four enzyme inputs.



Scheme 2. Multianalyte analysis carried out by a biomolecular logic system both in solution and on patterned paper.

future, other applications of these logic gates may also be found in the delivery or activation of drugs by a logic-controlled H_2O_2 trigger.[1b,17]

In summary, we have described the first example of a label-free, resettable and colorimetric logic network by exploring the combination of the regenerative capability of CeO_2 NPs and enzymatic reactions. The distinctive advantage of our CeO_2 NP-based logic system is that the biomolecular events can be transformed into color changes, which can be

observed by the naked eye. Importantly, the system makes use of thermal control to reset, avoiding any complicated and time-consuming covalent modification or chemical labeling procedure. Moreover, the complexity of the biocomputing systems can be readily scaled up to generate sophisticated networks of logic circuits and mimic natural biological pathways. Furthermore, this work demonstrates ways by which Boolean logic can process information in the field of intelligent diagnostics. Combined together, we expect that this work can be an important starting point for research on CeO_2 NP-based logic systems and will be highly beneficial in future biochemical, process control, nanomechanical, and electronic applications.

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[1] a) A. P. de Silva, S. Uchiyama, *Nat. Nanotechnol.* **2007**, *2*, 399; b) S. Angelos, Y.-W. Yang, N. M. Khashab, J. F. Stoddart, J. I. Zink, *J. Am. Chem. Soc.* **2009**, *131*, 11344; c) U. Pischel, *Angew. Chem.* **2007**, *119*, 4100; *Angew. Chem. Int. Ed.* **2007**, *46*, 4026; d) A. Credi, *Angew. Chem.* **2007**, *119*, 5568; *Angew. Chem. Int. Ed.* **2007**, *46*, 5472; e) A. P. de Silva, I. M. Dixon, H. Q. N. Gunaratne, T. Gunnlaugsson, P. R. S. Maxwell, T. E. Rice, *J. Am. Chem. Soc.* **1999**, *121*, 1393; f) T. Gupta, M. E. van der Boom, *Angew. Chem.* **2008**, *120*, 5402; *Angew. Chem. Int. Ed.* **2008**, *47*, 5322.

[2] a) R. Guliyev, S. Ozturk, Z. Kostereli, E. U. Akkaya, *Angew. Chem.* **2011**, *123*, 10000; *Angew. Chem. Int. Ed.* **2011**, *50*, 9826; b) F. M. Raymo, S. Giordani, *J. Am. Chem. Soc.* **2002**, *124*, 2004.

[3] D. Liu, W. Chen, K. Sun, K. Deng, W. Zhang, Z. Wang, X. Jiang, *Angew. Chem.* **2011**, *123*, 4189; *Angew. Chem. Int. Ed.* **2011**, *50*, 4103.

[4] a) S. Kou, H. N. Lee, D. van Noort, K. M. K. Swamy, S. H. Kim, J. H. Soh, K.-M. Lee, S.-W. Nam, J. Yoon, S. Park, *Angew. Chem.* **2008**, *120*, 886; *Angew. Chem. Int. Ed.* **2008**, *47*, 872; b) S. Uchiyama, N. Kawai, A. P. de Silva, K. Iwai, *J. Am. Chem. Soc.* **2004**, *126*, 3032.

[5] a) Q. Fu, H. Saltsburg, M. Flytzani-Stephanopoulos, *Science* **2003**, *301*, 935; b) A. Asati, S. Santra, C. Kaittanis, S. Nath, J. M. Perez, *Angew. Chem.* **2009**, *121*, 2344; *Angew. Chem. Int. Ed.* **2009**, *48*, 2308; c) A. S. Karakoti, S. Singh, A. Kumar, M. Malinska, S. V. N. T. Kuchibhatla, K. Wozniak, W. T. Self, S. Seal, *J. Am. Chem. Soc.* **2009**, *131*, 14144; d) Y.-W. Zhang, R. Si, C.-S. Liao, C.-H. Yan, C.-X. Xiao, Y. Kou, *J. Phys. Chem. B* **2003**, *107*, 10159; e) A. Asati, C. Kaittanis, S. Santra, J. M. Perez, *Anal. Chem.* **2011**, *83*, 2547; f) A. Karakoti, S. Singh, J. M. Dowding, S. Seal, W. T. Self, *Chem. Soc. Rev.* **2010**, *39*, 4422; g) M. Ornatska, E. Sharpe, D. Andreescu, S. Andreescu, *Anal. Chem.* **2011**, *83*, 4273; h) H.-P. Zhou, H.-S. Wu, J. Shen, A.-X. Yin, L.-D. Sun, C.-H. Yan, *J. Am. Chem. Soc.* **2010**, *132*, 4998; i) A. Asati, S. Santra, C. Kaittanis, J. M. Perez, *ACS Nano* **2010**, *4*, 5321.

[6] a) J. Chen, S. Patil, S. Seal, J. F. McGinnis, *Nat. Nanotechnol.* **2006**, *1*, 142; b) J. M. Perez, A. Asati, S. Nath, C. Kaittanis, *Small* **2008**, *4*, 552; c) J. Niu, A. Azfer, L. M. Rogers, X. Wang, P. E. Kolattukudy, *Cardiovasc. Res.* **2007**, *73*, 549; d) R. W. Tarnuzzer, J. Colon, S. Patil, S. Seal, *Nano Lett.* **2005**, *5*, 2573; e) C. Korsvik, S. Patil, S. Seal, W. T. Self, *Chem. Commun.* **2007**, 1056.

[7] a) S. Singh, T. Dosani, A. S. Karakoti, A. Kumar, S. Seal, W. T. Self, *Biomaterials* **2011**, *32*, 6745; b) E. G. Heckert, A. S. Karakoti, S. Seal, W. T. Self, *Biomaterials* **2008**, *29*, 2705; c) M. Das, S. Patil, N. Bhargava, J.-F. Kang, L. M. Riedel, S. Seal, J. J. Hickman, *Biomaterials* **2007**, *28*, 1918.

[8] a) Y. Weizmann, R. Elnathan, O. Lioubashevski, I. Willner, *J. Am. Chem. Soc.* **2005**, *127*, 12666; b) Y. Benenson, B. Gil, U. Ben-Dor, R. Adar, E. Shapiro, *Nature* **2004**, *429*, 423; c) D. Miyoshi, M. Inoue, N. Sugimoto, *Angew. Chem.* **2006**, *118*, 7880; *Angew. Chem. Int. Ed.* **2006**, *45*, 7716; d) X. Chen, Y. Wang, Q. Liu, Z. Zhang, C. Fan, L. He, *Angew. Chem.* **2006**, *118*, 1791; *Angew. Chem. Int. Ed.* **2006**, *45*, 1759; e) B. Shlyahovsky, Y. Li, O. Lioubashevski, J. Elbaz, I. Willner, *Acs Nano* **2009**, *3*, 1831; f) M. N. Stojanovic, T. E. Mitchell, D. Stefanovic, *J. Am. Chem. Soc.* **2002**, *124*, 3555; g) S. Bi, Y. Yan, S. Hao, S. Zhang, *Angew. Chem.* **2010**, *122*, 4540; *Angew. Chem. Int. Ed.* **2010**, *49*, 4438; h) Y. Tang, F. He, S. Wang, Y. Li, D. Zhu, G. C. Bazan, *Adv. Mater.* **2006**, *18*, 2105; i) Z. Huang, Y. Tao, F. Pu, J. Ren, X. Qu, *Chem. Eur. J.* **2012**, *18*, 6663.

[9] a) T. Niazov, R. Baron, E. Katz, O. Lioubashevski, I. Willner, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 17160; b) G. Seelig, D. Soloveichik, D. Y. Zhang, E. Winfree, *Science* **2006**, *314*, 1585; c) L. Qian, E. Winfree, *Science* **2011**, *332*, 1196; d) J. Elbaz, O. Lioubashevski, F. Wang, F. Remacle, R. D. Levine, I. Willner, *Nat. Nanotechnol.* **2010**, *5*, 417; e) G. Strack, M. Ornatska, M. Pita, E. Katz, *J. Am. Chem. Soc.* **2008**, *130*, 4234; f) F. Pu, Z. Liu, X. J. Yang, J. S. Ren, X. G. Qu, *Chem. Commun.* **2011**, *47*, 6024.

[10] A. W. Martinez, S. T. Phillips, M. J. Butte, G. M. Whitesides, *Angew. Chem.* **2007**, *119*, 1340; *Angew. Chem. Int. Ed.* **2007**, *46*, 1318.

[11] S. Deshpande, S. Patil, S. Kuchibhatla, S. Seal, *Appl. Phys. Lett.* **2005**, *87*, 133113.

[12] F. Pu, C. Wang, D. Hu, Z. Huang, J. Ren, S. Wang, X. Qu, *Mol. BioSyst.* **2010**, *6*, 1928.

[13] J. Fu, M. Liu, Y. Liu, N. W. Woodbury, H. Yan, *J. Am. Chem. Soc.* **2012**, *134*, 5516.

[14] P. Tanner, O. Onaca, V. Balasubramanian, W. Meier, C. G. Palivan, *Chem. Eur. J.* **2011**, *17*, 4552.

[15] a) W. Luo, C. Zhu, S. Su, D. Li, Y. He, Q. Huang, C. Fan, *ACS Nano* **2010**, *4*, 7451; b) D. J. Weiss, D. Liggitt, J. G. Clark, *Hum. Gene Ther.* **1997**, *8*, 1545.

[16] T. Konry, D. R. Walt, *J. Am. Chem. Soc.* **2009**, *131*, 13232.

[17] R. J. Amir, M. Popkov, R. A. Lerner, C. E. Barbas, D. Shabat, *Angew. Chem.* **2005**, *117*, 4452; *Angew. Chem. Int. Ed.* **2005**, *44*, 4378.

