Stimulus-Responsive Nanomaterials Containing Logic Gates For Biomedical Applications

P.Sivasankari
Dept of Master of Computer Application
PSG College of Arts & Science, Coimbatore.

Abstract- *The rapid advance of nanotechnology has presented tremendous opportunities for various biomedical applications. In particular, integration of biomolecular logic gates with nanostructures has opened new avenues in the fields of disease diagnosis and therapy that involve handling complex factors and require precise control. Over time, stimulus-responsive nanomaterials containing molecular logic gates have advanced from simple single input-triggered ''YES/ NO'' responses into sophisticated Boolean logic computations. In these smart nanomaterials, the Boolean logic operations can only be activated by two or more defined inputs via biorecognition, catalysis, or biochemical reactions, contributing to improved specificity and minimized off-target or side effects. In this review, we provide an up-to-date overview of the development of stimulus-responsive nanomaterials containing logic gates and their applications in cell profiling, sensing, imaging, and drug delivery. Future perspectives and challenges in this emerging field are also discussed*

I. INTRODUCTION

The rapid advance in nanotechnology has promoted sustainable development of advanced nanomedicines for various biomedical applications, such as biosensing, bioimaging, and disease intervention.1,2 Because of the unique physicochemical properties, easy modification, and facile functional manipulation compared with small molecules, nanomaterials have demonstrated improved activity, stability, and in vivo bioavailability.3 In particular, bioactive nanomaterials capable of responding to an endogenous or external stimulus, such as pH, certain enzymes, temperature, and light, can further enhance specificity and decrease potential side effects.4-7 Despite progress, the precision and accuracy of single-stimulusresponsive nanomaterials are still limited as a result of the heterogeneity of diseases and complex microenvironments in organisms.

The introduction of molecular logic gates into nanomedicine designs has emerged as an effective means to address this challenge. Logic gates are originally defined as devices that are able to implement Boolean logic upon receiving one or more information input(s) and subsequently generate a specific output.8 Over the past decade, such a fundamental principle has been extended to molecularly gated nanosystems, in which Boolean logic operations can be activated by specific molecular inputs through bio-affinity, bio-catalysis, or bio/chemical reactions.9-11 In fact, the aforementioned stimulus-responsive nanomaterials can be considered ''YES/NO''-gated devices. However, the simple ''YES/NO'' response is often insufficient to describe biological systems, especially for biosensing and disease diagnosis. In cancer, for instance, simultaneous up- and/or downregulation of multiple biomarkers (e.g., microRNA [miRNA], oncogene, and proteins) are typically involved.12 In this regard, ever-growing efforts have been devoted to developing logic gate-containing nanodevices to implement complicated information processes. Our group also constructed a DNA-based nanodevice that could simultaneously perform logic-based autonomous analysis toward two or three markers on the surface of cancer cells.13,14 Based on specific identification of target characteristics and DNA strand replacement reactions of DNA aptamers, the system could further perform AND, OR, and NOR logic operations on the cell surface for markers. In addition to bioanalysis, molecular logic gates have also been integrated in nanocarriers for drug delivery. Compared with conventional single-stimulus-responsive systems, logic gate-containing nanocarriers that require dual or multiple stimulus inputs promise to dramatically decrease off-target effects, improving the bioavailability of drugs and safety profiles of these nanomedicines. To date, varieties of stimulus-responsive nanomaterials containing logic gates have been reported. However, it is noteworthy that, although these nanomaterials have yielded promising results, their translation from bench to bedside remains elusive. This review offers an up-to-date overview of the development of nanomaterials containing molecular logic gates for biomedical applications, highlighting recent findings regarding cell profiling, sensing, imaging, and controllable drug delivery. Future perspectives and challenges of this emerging field for practical translation are also discussed.

II. STIMULUS-RESPONSIVE NANOMATERIALS CONTAINING LOGIC

GATES FOR CELL PROFILING

Specific recognition of biomarkers on the cell membrane of diseased cells is essential for disease diagnosis and therapy. However, most identified cell membrane markers are not specifically expressed on target cells, and thus a smart method capable of discriminating healthy cells from diseased cells is in high demand. Because of the high programmability and predictability of DNA molecules, DNA nanotechnology has become one of the most valuable tools to construct logic gate-containing nanodevices for specific cell recognition and profiling. Previously, our group created a set of ‘‘DNA nanoclaws’’ that could independently analyze multiple markers on the cell membrane through molecular recognition mediated by DNA aptamers and toehold-driven DNA strand displacement reactions. 15 For instance, a Y-shaped nanoclaw based on a DNA strand replacement reaction was used to construct a logic gate. It is composed of two complementary chains to capture a double-stranded DNA (dsDNA) toe and an effector dsDNA toe. The capturing toes bind a specific surface marker and release the effector to sensitize the effector toes. Interaction of DNA aptamers with their specific targets (surface markers) leads to dissociation of dsDNA complexes to form the capture toes, and the two released complementary chains initiate the DNA strand replacement reaction within the effector toes. The results showed that the light-emitting group and quenching group were split in the effector toe, leading to emission recovery of the fluorescence group. With this AND logic DNA nanoclaw, specific cell recognition was achieved, which is expected to be a valuable tool for accurate disease diagnosis and intervention. Despite enhanced specificity, the DNA nanoclaw can only recognize a very narrow cell subgroup within a relatively large group of related cells. It is worth noting that

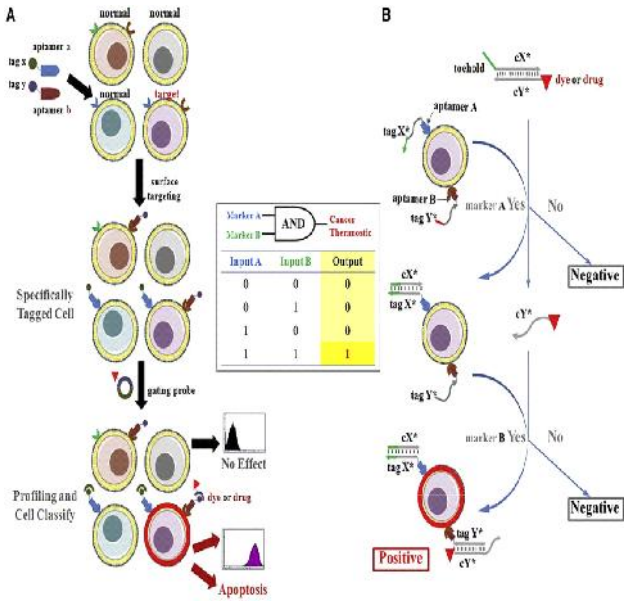

Figure 1. Schematic illustration of logic-gated cell targeting

(A) AND-gated labeling of pathological cells in the presence of target cells
(B) Mechanism of the strand displacement cascade of the AND gate and the truth table

cell profiling methods that are able to not only accurately identify cell types but also differentiate different cell stages will greatly promote development of personalized medicine, biomedical engineering, and basic scientific research. Therefore, we further developed the building block design and rationale of more advanced logic-gated cell labeling interfaces,16 as illustrated in Figure 1. First, targets on the cell membrane bind to their DNA aptamers to enable labeling with short single- stranded DNA (ssDNA) tabs linked to these aptamers. The type of ssDNA tabs used for this system is dependent on the logic operations performed by these interfaces. Then these tabs are analyzed by effectors, which are composed of a dsDNA complex carrying drugs or dyes. Their sequences were designed by ssDNA tabs on target cells. The dye or drug can label cells for selective recognition through chain replacement reactions. In addition to the basic AND, NOT, and OR logic gates, such a design can be extended to more sophisticated logic gates, offering an effective tool for cell profiling and disease staging. In parallel, Rudchenko et al.17 engineered advanced molecular automata able to analyze the surface markers of T lymphocytes autonomously in the presence of related cells. Figure 2 describes the basic rationale of these automata, which can label leukocytes with specific target cluster divergence
(CD) of B cells (CD20+ CD45+ cells) while in the presence of nontarget CD45+ CD20 cells (CD3+ CD45+ T cells). aCD45 and aCD20, antibodies targeting CD45 and CD20, respectively, bind to a group of partially complementary dsDNA complexes (1$2 [oligonucleotide 1 and oligonucleotide 2 hybridize dsDNA] and 3$4 [oligonucleotide 3 and oligonucleotide 4 hybridize dsDNA], respectively). When

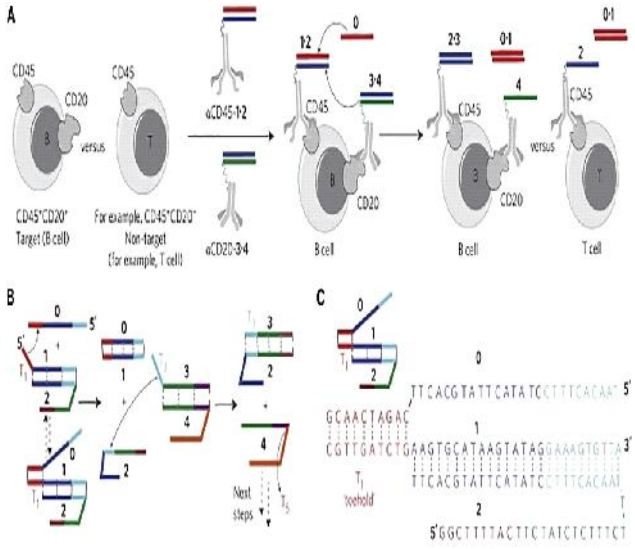

Figure 2. Design considerations for automata operating on cell surfaces

(A) Molecular automaton logic-gated cell surface labeling using a chain replacement reaction as crosstalk language.
(B) Scheme of a strand displacement reaction

oligonucleotide 0 is present, strand displacement cascades can be triggered. In all of these automata, if CD45 and CD20 are present on the cell surface, then the strand displacement cascade reaction will follow: 0 + 1$2aCD45 (oligonucleotide 1 and modify CD45 antibody oligonucleotide 2 hybridize dsDNA) + 3$4aCD20 (oligonucleotide 3 and modify CD20 antibody oligonucleotide 4 hybridize dsDNA) / 0$1 (oligonucleotide 0 and oligonucleotide 1 hybridize dsDNA) + aCD452$3 (modify CD45 antibody oligonucleotide 2 and oligonucleotide 3 hybridize dsDNA) + aCD204 (modify CD20 antibody oligonucleotide 4), leading to exposure of single-stranded oligonucleotide 4. At the same time, the authors also established an AND logic gate system to output oligonucleotide 4, which would facilitate interaction between the label and the solution aCD204 + 5$6 (oligonucleotide 5 and oligonucleotide 6 hybridize dsDNA)/aCD204$5 (modify CD20 antibody oligonucleotide 4 and oligonucleotide 5 hybridize dsDNA) + 6 (5 with fluorescein labeling).With such logic operations, direct analysis of the target reaction cells could be achieved by flow cytometry in a heterogeneous cell cascade.

III. STIMULUS-RESPONSIVE NANOMATERIALS CONTAINING LOGIC GATES FOR CONTROLLABLE DRUG RELEASE

In recent years, more and more attention has been given to controllable vector systems because of their spatiotemporal delivery of bioactive substances to the

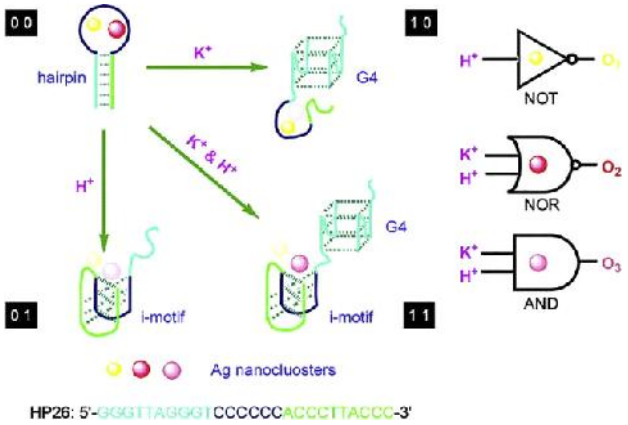

Figure 3. Schematic diagram of logic operations

Endogenous stimulus

Temperature, redox balance, pH, metabolites, and up/downregulation of some proteins are usually important indicators of human disease occurrence, development, and prognosis, even becoming valuable biomarkers and targets for disease diagnosis and treatment.40-42 Especially in cancer, the main reason of clinical recurrence and death is maladjustment of itself and the microenvironment signal released by stromal cells (such as chemokines, hypoxia, matrix metalloproteinases, and cytokines), which leads to promotion of the characteristics of cancer stem cells and drives metastasis, invasion, and drug resistance.43-45 To fully use pathological indications for accurate treatment, smart materials based on these pathological responses have been designed for targeted drug delivery and controllable drug release at the target site, and they have significantly improved therapeutic efficacy and reduced off-target effects.46,47

As mentioned above, Apts can form secondary structures upon recognition of the target protein. In combination with an Apt recognition module, DNA dynamic control module, and biological computing function, many DNA nanodevices have been developed to perform drug release in a programmable manner and have demonstrated great potential in many biomedical applications. One example is a DNA origami-based YES logic gate reported recently by Li et al.48 With incorporation of the Apt recognition module, this system could successfully target tumor tissues in mammals by responding to the input of the nucleolar protein.48 The nucleolus-binding Apt could also lock thrombin within the DNA origami. After accumulation at the tumor site, molecular recognition between the Apt and nucleolar protein triggered release of thrombin for tumor

starvation therapy. Despite its effectiveness, clinical application of such a YES logic gate may be limited by the fact that the nucleolar protein is generally expressed in many normal cells, resulting in drug release in unwanted cell populations, resulting in unwanted off-target side effects. To address this potential issue, Douglas et al.49 reported a more advanced nanorobot device able to transmit signal molecules to the cell surface. The device was composed of hexagonal nanotubes with dimensions of 35 335 345 nm. Two domains were incorporated in the barreled structure, which were covalently linked to a single strand at the back and hybridized with ssDNA at the front to achieve an initial closed state. In other words, one domain had a DNA Apt chain, whereas the other had an ssDNA chain that partially hybridized with the Apt. In the presence of target ligand, the Apt bound to it, opening the nanotube. The results showed that the modified 5-nm Au NPs and Fab antibody fragments in the inner surface of nanotubes could interact with proteinmarkers on the surface of target cells. By using similar Apt alignment in one region, the device could be activated by a single response input. However, in the presence of different Apt alignments in one region, the device could be activated by two response inputs, as in the case of the Boolean AND operator. Thus, only when both Apt locks were opened could this device be activated, holding great promise to increase the accuracy of drug release. Subsequently, feasibility of this nanorobot design for in vivo applications was validated successfully in living animals with low system nuclease activity (Blaberus discidalis).50 In that work, the soluble protein was used as input. In the presence of a target, the DNA lock was opened by Apt recognition or chain replacement reaction. Upon recognition of the nucleolar protein overexpressed on the surface of tumor vascular endothelial cells, triggering opening of the device for payload release and resulting in tumor vascular thrombosis and tumor tissue necrosis with no influence on healthy blood vessels.

Although DNA is a good material for building drug-controlled release nanodevices in a programmable manner, these DNA-based nanodevices often face the drawback of low drug loading capacity. As an alternatively powerful drug delivery platform, mesoporous silica nanoparticles (SiO2 NPs) have also received tremendous interests for engineering logic gate-containing nanodevices benefiting from their large internal surface area and mesoporous structure. In a recent work performed by Chen et al.,51 an AND gate system based on SiO2 NPs has been reported with the capability of releasing the payload under conditions of low pH and esterase (Figure 7).51 Such a system was prepared by encapsulating Rhodamine (Rh) 6G or DOX within the pores of SiO2 NPs, followed by closing the pores with polycaprolactone (PCL) and modification of PAA on the surface of amino-modified SiO2 NPs. Formation of a hydrogen bond between the internal amino group and PCL could effectively suppress drug leakage from the pores, and formation of a hydrogen bond/electrostatic bond between the external amino group and PAA could facilitate adsorption of PAA on the surface of SiO2 NPs. In the presence of acid, esterase was released from SiO2 NP pores after degradation of the PAA shell. The PCL chain was then cleaved by the enzyme to release DOX (doxorubicin) or Rh 6G. The results of the fluorescence analysis showed how the structure released the payload (Rh 6G, DOX) under conditions of low pH and esterase. This is exactly in line with an AND logic gate.

Compared with the aforementioned logic gate drug delivery systems constructed by simply modifying the carrier, assembly of multiple response units into programmable devices with logic gates and hierarchies, such as Lego building blocks, can freely receive signals and generate output for in vivo biological computing and fixed-point transmission of various therapies. Badeau et al.52 and Zhang et al.53 proposed a ‘‘plug and play’’ platform to expand smart materials based on logic gates for therapeutic agent delivery. For instance, a modular biomaterial logic gate was engineered by Badeau et al.52 based on degradable hydrogels, which could respond to multiple environmental factors to trigger drug release. Selective control over dissolution of hydrogels and drug delivery were achieved by specifying the

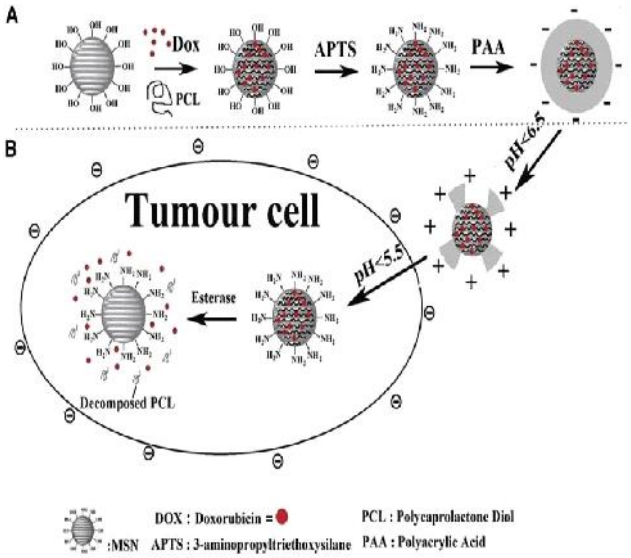

Figure 4. Schematic diagram of material formation and logic gate principle

(A) Schematic diagram of formation of PAA-PCL-MSNs.
(B) Schematic representation of the PAA-PCL-MSN-based selective drug delivery system.

molecular architecture and integrating orthogonal stimulus-labile moieties within crosslinkers. To demonstrate the versatility of such amethodology, 17 different stimulus-responsive materials were synthesized to produce all possible YES/OR/AND logical outputs from the combination of inputs, including light, reductants, and enzymes.

By integrating stimulus-sensitive elements into crosslinking agents, hydrogels with a clear molecular structure were formed after reaction with polymers.Moreover, by embedding environmentally responsive monomers in the crosslinkerdomain, the resulting material would degrade and release the payload upon stimulation.Such systemperformed as a Boolean YES logic gate with a single environmentallyresponsive monomer embedded in the linker. Nevertheless, more advancedlogical operations could be achieved when multiple environmentally responsivemonomers were introduced to the connector. Specifically, when two environmentallyresponsive monomers were linked in series, decomposition of onemonomer resultedin dissolution of materials, generating an OR gate, as represented by the logical symbol n. When two environmentally responsive monomers were linked in parallel, the material dissolution required concurrent cleavage of two monomers to form an AND gate, as represented by the logical symbol ^. As a proof of concept, the authors incorporated a BCN (bicyclononyne)-labeled DOX into the reduction conditions ^MMP enzyme gel, which showed a highly specific response to pathophysiological stimulation in cancer. Based on pathophysiological stimulation of cancer, DOX released through degradation of the material led to apoptosis of HeLa cells. These results clearly demonstrate the ability of gels to precisely control cell fate according to physiological and pathological stimulation of cancer.

In addition to porous silica nanomaterials, polymers are well-established drug delivery biomaterials because of flexible conjugation chemistry and easy modification with different functionalities. Aiming to engineer a generalized stimulus-responsive system capable of forming programmable nanodevices for advanced

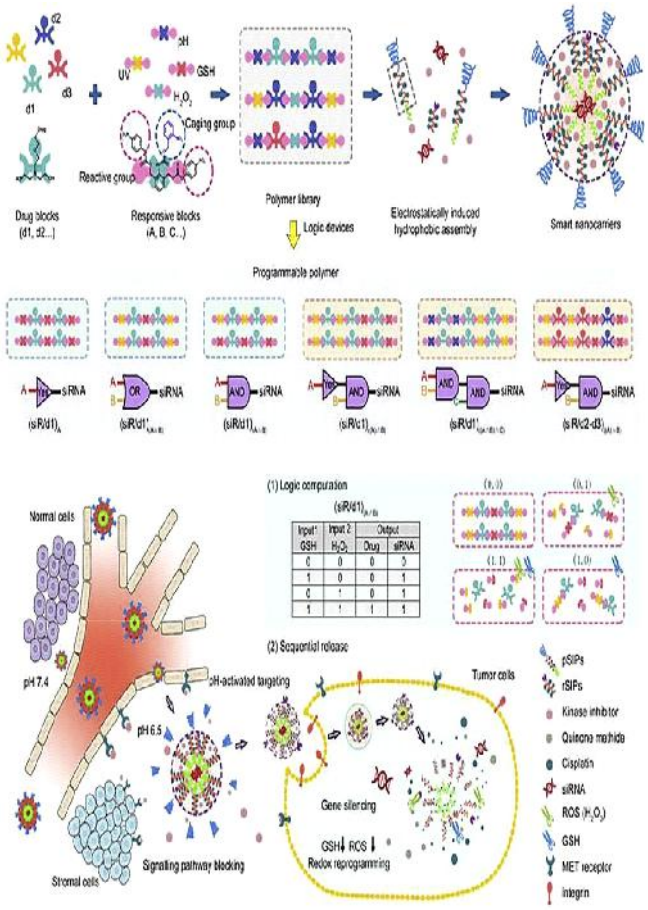

Figure 5. Schematic diagram of stimuli-responsive nanocarriers containing logic gates

biocomputation, our group has built a programming polymer library and designed smart nanocarriers (SNCs) with a stratified structure and logic gates for precise tumor treatment (Figure 8).53 A set of monomers that respond to pathophysiological stimuli was first synthesized. To realize Boolean logic operation and sequential release of drugs, we constructed a library of logic gate-responsive polymers using a pHresponsive polyethylene glycol head, a programmable hydrophobic body, and a positively charged polyethyleneimine tail. Through rational design, we used pathological clues in the tumor microenvironment to control the in vivo behavior of nanocarriers for controllable drug release and specific targeting. To further verify the feasibility of the system, we constructed PEG (polyethylene glycol)/RGD (Arg-Gly- Asp) (PR)-coated and glutathione (GSH)-degradable nanocarriers loaded with cabozanib (xl184 [XL]), cisplatin (Pt), and small interfering RNA (siRNA), known as prSNCsGSH(siR/Pt/XL). Such a system has unique features. The nanocarrier remains invisible during circulation in the blood after intravenous injection. When accumulated in the tumor tissue through the enhanced permeability and retention (EPR) effect, the PEGlayer detaches fromNPs in the

acidic tumormicroenvironment, leading to exposure of RGD ligands and protonation of the polymer main chain to release a kinase inhibitor (XL). As a result, signal transduction of mesenchymal-epithelial transformation (MET) and vascular endothelial growth factor receptor (VEGFR) is inhibited effectively in the tumor environment, and proliferation of tumor and endothelial cells is reduced.54 In vitro studies have confirmed that nanocarriers are internalized effectively by tumor cells via receptor-mediated endocytosis. In the presence of endogenous GSH, Pt and siRNA are released. Pt can effectively induce apoptosis, whereas siRNA can effectively reverse development of stem cell characteristics of cancer cells and overcome drug resistance by knocking out expression of PLK1.55,56 Here, the function of prSNCsGSH (siR/Pt/XL) is similar to the simplest Boolean YES gate of prSNCs(siR/Pt/XL)G, which takes intracellular GSH (G) as the input and siRNA release as the output. To achieve more precise and specific treatment agent release, sophisticated logic gates based on multiple response modules integrated into a degradable enclosure with coding mode were constructed. The stimulus response platform is a powerful tool for building modular logic gate materials.

External stimulus

Light is an excellent way to spatiotemporally control cargo release.57,58 The advantages of using light as the external stimulus include noninvasive intervention, sitespecific irradiation, and spatiotemporally controlled release of cargo. In recent years, researchers have devoted considerable effort to developing diverse lightresponsive and bioapplicable logic gate systems for disease treatment. Photodimerization is related to the reaction between an electron-excited unsaturated molecule and an unexcited homologous molecule to produce an additional product. It can change molecular size and promises to be a powerful means for designing mesoporous materials containing logic gates. Mal et al.7,59 developed a photoactive gate material based on photodimerization of coumarin.7,59 Coumarin can form a cyclobutane dimer through [2 + 2] photodimerization. Based on the connection of the 7-([3-triethoxy])-propoxy) coumarin group to the MCM-41 scaffold, Fu et al.2 have constructed a YES logic gate. Coumarin-functionalized mesoporous materials were loaded with cargo. No cargo release was observed in the presence of light with a wavelength greater than 310 nm. However, when the material was irradiated with 250-nm ultraviolet light, the cargo was released quickly. However, in vivo application of this system is challenging because of the low penetration depth and phototoxicity of UV light.

To increase the tissue penetration capability of light-responsive drug carriers, researchers have recently developed near-infrared (NIR)-responsive drug delivery platforms based on metal clusters or two-photon active molecules, given the fact that the NIR light has deeper penetrating depth compared with UV light.60 Differing from AuNPs with localized surface plasmon resonance (LSPR) in the visible region, gold nanocages exhibit strong absorption in the NIR window, which is beneficial for increasing tissue penetration and therapeutic efficacy for in vivo applications. For example, strong NIR absorption enables nanocages to effectively convert light into local heat. This capability also allowed design of smart polymer gold nanocages for thermally driven logic drug release.61,62 Moreover, the LSPR band of gold nanocages can be adjusted in the preparation process. Shi et al.63 utilized these properties to prepare a smart polymer release system using logicgated gold nanocages (Figure 9). Two nanocages with strong absorbance at 808 nm and 670 nm were prepared and coated with poly(N-isopropylacrylamide-co-acrylamide). This fully conforms with a Boolean AND operator and has been shown by loading alkaline phosphatase and its substrate (ELF97 phosphate) into 808- and 670-nm light-responsive nanocages, respectively. These cargoes could be released only by laser irradiation of the two wavelengths at the same

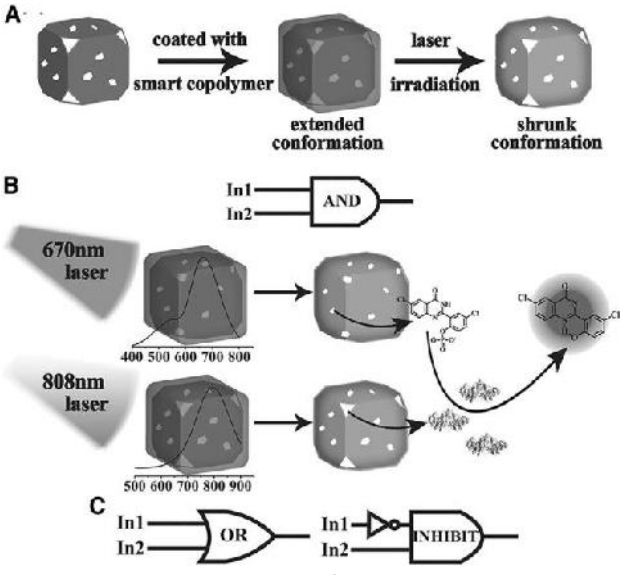

Figure 6. Schematic diagram of light-controlled logic gate (A) Diagram of photothermal-sensitive AuNC copolymers. (B and C) Schematic diagram of a NIR light-coding logic gate based on controlled release of the AuNC copolymer.

time, followed by generation of a fluorescence signal. By placing the substrate outside of the nanocage and loading an L-phenylalanine inhibitor and acid phosphatase in the

absorption 670 Au nanocage, the system can be constructed as an OR or INHIBIT logic gate.

IV. CURRENT CHALLENGES AND FUTURE PERSPECTIVES

We have presented an overview of recent advances in stimulus-responsive biomaterials containing logic gates. By specific and logic response to two or more molecular or environmental stimuli, these nanomaterials have demonstrated numerous opportunities for sensing, imaging, and controllable drug release with dramatically enhanced specificity and accuracy compared with traditional nanoformulations. Development of logic gate-containing nanostructures has become a fast-growing research field for effective diagnosis and treatment of important human diseases. Despite continuous progress, considerable fundamental challenges still remain for bench-to-bedside transition of such nanomaterials.

The first issue that needs to be addressed lies in the safety profiles of these bioactive nanomaterials. Currently, the potential side effects associated with using nanocarriers are not fully understood, especially after systemic administration. For instance, systems based on inorganic nanomaterials are generally difficult to degrade and have a long-term presence in the body, posing safety risks. Nucleic acid nanostructures are considered to be among the most promising candidates for constructing logic gate-containing nanodevices because of high programmability and good biocompatibility compared with exogenous materials. To date, various nucleic acid nanostructures enabling complex biological calculations have been developed and show tremendous benefits for biomedicine, such as DNA logic gates for complex biological calculations, DNA-based automata for logical analysis of human blood, and DNA-based origami nanobots for targeted delivery. However, the majority of currently investigated nucleic acid nanostructures typically suffer from suboptimal computing stability under complex biological conditions because of their susceptibility to degradation by nucleases. Thus, development of advanced nucleic acid nanostructures with robust tolerance to nucleases is in high demand. Moreover, systems that enable complicated logic calculations in living organisms are rare but critical for practical translation.

Apart from safety concerns, potential off-target activation of these bioactive nanomaterials is another challenge for in vivo application. It is well known that the bioavailability of nanomaterials is highly influenced by the protein corona, a biological event caused by interaction between nanomaterials and proteins in the blood. Moreover, the host produces biological reactions to rapidly recognize and clear exogenous substances, including nanomaterials, via activation of about 35 typically dormant proteins71 in the blood or on the surface of blood cells, resulting in significantly decreased effectiveness of logic gate-containing nanomaterials in vivo. Thus, a good understanding of nonspecific interactions between nanomaterials and proteins or other macromolecules in the body will be greatly beneficial for creating advanced nanosystems with improved in vivo performance.

Another key consideration regarding development of translational logic gate-containing nanomedicine is response sensitivity. This challenge would be particularly great when they are used to sense and diagnose disease, given the low abundance of the target of interest. Compared with single-input responsive strategies, the logic-gated smart probes promise to minimize the false signals caused by nonspecific accumulation or activation of the probes in cells or tissues that also express a certain molecular target. Nevertheless, most logic gate systems can only be implemented at high input concentrations, and it is still unclear whether these smart probes can efficiently process input information at a fairly low level. A main reason is that separate functional moieties are typically required to trigger logic computations. For instance, logic gate systems based on antibody elution or DNA strand replacement require high concentrations of inputs to displace their analogs from existing chemical bonds in the preparation to induce transformation and signal transduction in the system, which is generally time consuming and easily interfered with by environmental factors. Realizing signal output through direct molecular transformation of receptor-binding ligands is expected to greatly increase the sensitivity of logic gate systems. Ever-growing research has been devoted to design Apt-based logic gate systems, given the fact that Apts have a wide range of targets and can undergo conformational changes upon recognition, which can pave the way for improved sensitivity and specificity by direct input process and signal output. Overall, the field of stimulus-responsive biomaterials containing logic gates is rapidly advancing and holds tremendous opportunities for biomedicine. With collaboration of chemists, physicists, biologists, and physician-scientists, development of more advanced and smart logic gate biomaterials can be expected for more effective treatment of diseases

REFERENCES

[1] Karimi, M., Ghasemi, A., Sahandi Zangabad, P., Rahighi, R., Moosavi Basri, S.M., Mirshekari, H., Amiri, M., Shafaei Pishabad, Z., Aslani, A., Bozorgomid, M., et al. (2016). Smart micro/ nanoparticles in stimulus-responsive drug/ gene delivery systems. Chem. Soc. Rev. 45,

1457–1501.

[2] Fu, X., Hosta-Rigau, L., Chandrawati, R., and Cui, J. (2018). Multi-stimuli-responsive polymer particles, films, and hydrogels for drug delivery. Chem 4, 2084–2107.

[3] Mura, S., Nicolas, J., and Couvreur, P. (2013). Stimuli-responsive nanocarriers for drug delivery. Nat. Mater. 12, 991–1003.

[4] Tregubov, A.A., Nikitin, P.I., and Nikitin, M.P. (2018). Advanced smart nanomaterials with integrated logic-gating and biocomputing: dawn of theranostic nanorobots. Chem. Rev. 118, 10294–10348.

[5] Wang, W., Cheng, D., Gong, F., Miao, X., and Shuai, X. (2012). Design of multifunctional micelle for tumor-targeted intracellular drug release and fluorescent imaging. Adv. Mater. 24, 115–120.

[6] Singh, N., Karambelkar, A., Gu, L., Lin, K., Miller, J.S., Chen, C.S., Sailor, M.J., and Bhatia, S.N. (2011). Bioresponsive mesoporous silica nanoparticles for triggered drug release. J. Am. Chem. Soc. 133, 19582–19585.

[7] Mal, N.K., Fujiwara, M., and Tanaka, Y. (2003). Photocontrolled reversible release of guest molecules from coumarin-modified mesoporous silica. Nature 421, 350–353.

[8] Ma, D.L., He, H.Z., Chan, D.S.H., and Leung, C.H. (2013). Simple DNA-based logic gates responding to biomolecules and metal ions. Chem. Sci. (Camb.) 4, 3366.

[9] Lai, Y.H., Sun, S.C., and Chuang, M.C. (2014). Biosensors with built-in biomolecular logic gates for practical applications. Biosensors (Basel) 4, 273–300.

[10] Parlak, O., Beyazit, S., Tse-Sum-Bui, B., Haupt, K., Turner, A.P.F., and Tiwari, A. (2016). Programmable bioelectronics in a stimuliencoded 3D graphene interface. Nanoscale 8, 9976–9981.

[11] Katz, E. (2019). Boolean logic gates realized with enzyme-catalyzed reactions - unusual look at usual chemical reactions. ChemPhysChem 20, 9–22.

[12] Kasinski, A.L., and Slack, F.J. (2011). Epigenetics and genetics. MicroRNAs en route to the clinic: progress in validating and

[13] Peng, R., Zheng, X., Lyu, Y., Xu, L., Zhang, X., Ke, G., Liu, Q., You, C., Huan, S., and Tan, W. (2018). Engineering a 3D DNA-logic gate nanomachine for bispecific recognition and computing on target cell surfaces. J. Am. Chem. Soc. 140, 9793–9796.

[14] Chang, X., Zhang, C., Lv, C., Sun, Y., Zhang, M., Zhao, Y., Yang, L., Han, D., and Tan, W. (2019). Construction of a multiple-aptamer-based DNA logic device on live cell membranes via associative toehold activation for accurate cancer cell identification. J. Am. Chem. Soc. 141, 12738–12743.

[15] You, M., Peng, L., Shao, N., Zhang, L., Qiu, L., Cui, C., and Tan, W. (2014). DNA ‘‘nano-claw’’: logic-based autonomous cancer targeting and therapy. J. Am. Chem. Soc. 136, 1256–1259.