Near-Infrared Triggered Decomposition of Nanocapsules with High Tumor Accumulation and Stimuli Responsive Fast Elimination

Tiancong Zhao, Peiyuan Wang, Qin Li, Areej Abdulkareem Al-Khalaf, Wael N. Hozzein, Fan Zhang, Xiaomin Li*, Dongyuan Zhao*

Abstract: Nanoparticle based diagnosis-therapy integrative systems represent an emerging approach to cancer treatment. However, there is a series of size-dependent biological barriers that impede nanomedicine from clinical implementation, especially the irreconcilable contradiction on optimum sizes for long blood circulation (100-200 nm) and quick metabolization (< 20 nm). Herein, we demonstrate a novel near-infrared (NIR) induced decomposable polymer nanocapsule. The nanocapsules are fabricated based on layer-by-layer co-assembly of azobenzene functionalized polymers and up/downconversion nanoparticles (U/DCNPs). When the nanocapsules are exposed to 980-nm light, ultraviolet/visible photons emitted by the U/DCNPs can trigger the photo-isomerization of azobenzene groups in the framework. The nanocapsules could decompose from large-sized nanocapsule to small U/DCNPs. Due to their optimized original size (~ 180 nm), the nanocapsules can effectively avoid biological barriers, provide a long blood circulation (~ 5 h, half-life time) and achieve four-fold tumor accumulation. It can fast eliminate from tumor within one hour and release the loaded drugs for chemotherapy after NIR-induced dissociation from initial 180-nm capsules to small 20-nm U/DCNPs.

Nanoparticles have emerged as promising carriers for drugs in cancer treatment due to the enhanced permeability and retention (EPR) effect, increasing delivery efficiency and suppressing side-effects.¹⁻³ The design and development of sophisticated nanocarriers for targeted delivery of theranostic agents to solid tumors hold great promise for improving treatment efficacy and minimizing systemic toxicity. However, nanomedicine often suffers from multiple biological barriers, especially the low accumulation & delivery efficiency toward tumor because of clearance by organs during circulation in the blood stream.⁴ It has been demonstrated that the particle size plays a vital role in dominating the delivery efficiency: particles with a diameter of 100-200 nm generally provide long-lasting blood circulation and less clearance of organs.⁵⁻⁸ Thus, the conventional solution for size-dependent high accumulation in

tumor is to optimize particle diameter to this range. However, large nanocarriers are difficult to be eliminated from the organs after their functionalities exhausted.^{6, 8} Therefore, it is critically desired to develop next-generation smart theranostic agents:⁹⁻¹⁰ nanocarriers with a large initial size (100-200 nm) to cross biological barriers, provide prolonged blood circulation and achieve high tumor accumulation, which then could be responsively decomposed into small fragments to release loaded guests and be quickly metabolized.

Much effort has been made to develop stimuli-triggered delivery systems in response to a given stimulus, such as pH,¹¹⁻¹⁴ temperature¹⁵⁻¹⁶ and enzyme,¹⁷ etc. Among these approaches, light-triggered drug delivery has attracted much attention because it does not rely on changes in specific chemical properties of environment.¹⁸⁻²⁰ A variety of light-responsive systems have been designed based on ultraviolet (UV) or visible (vis) light excitations with low tissue penetration and are biological harmful.²¹ As a promising candidate, near-infrared (NIR) light would bring new opportunities due to minimal absorbance and maximum penetration of tissues.²²⁻²⁴ The polymer nanocapsules, in which polymers can act as a "cage" and encapsulate small functional nanoparticles or drugs. However, unlike condensed materials, polymers are more likely to deform and reshape.²⁵⁻²⁷ Thus are often chosen as building blocks of stimuli responsive systems.

Figure 1. Schematic illustration of the fabrication of the up/downconversion nanoparticles (U/DCNPs) functionalized hollow polymer nanocapsules and the near-infrared light induced decomposing process from 180-nm nanocapsules to scattered polymers and 20-nm U/DCNPs.

[a] Mr. T. C. Zhao, Mrs. P. Y. Wang, Prof. Dr. F. Zhang, Prof. Dr. X. M. Li, Prof. Dr. D. Y. Zhao
Department of Chemistry and Laboratory of Advanced Materials, State Key Laboratory of Molecular Engineering of Polymers, Collaborative Innovation Center of Chemistry for Energy Materials (2011-iChEM), Fudan University, Shanghai 200433, P. R. China.
E-mail: dyszao@fudan.edu.cn; lixm@fudan.edu.cn
Prof. Dr X. M. Li, Prof. Dr. Q. Li
Queensland Micro- and Nanotechnology Centre, Griffith University, Brisbane QLD 4111, Australia.
Dr. Areej Abdulkareem Al-Khalaf
Biology Department, College of Sciences, Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia
Dr. Wael N. Hozzein
Bioproducts Research Chair, Zoology Department, College of Science, King Saud University, Riyadh 11451, Saudi Arabia
Supporting information for this article is given via a link at the end of the document.

Herein, taking the advantages of the core/shell structured NaGdF₄:Yb,Tm@NaYF₄@NaGdF₄,Nd@NaYF₄ dual-mode up/

downconversion nanoparticles (U/DCNPs)²⁸⁻²⁹ and light-responsive polymer, we demonstrate a novel NIR light responsive decomposable polymer nanocapsule (**Figure 1**). The 180-nm nanocapsules were constructed through a simple electrostatic interaction induced layer-by-layer assembly strategy on the surface of spherical SiO₂ colloids (**Figure S1**).³⁰⁻³¹ U/DCNPs with negative surface charges³²⁻³⁴ were also incorporated in the polymer shells during the alternative assembly of polymers. The hollow-structured nanocapsules can be obtained after the SiO₂ templates were selectively etched. To realize the NIR-responsive decomposition of the nanocapsules, the U/DCNPs were doped with Tm³⁺ to transmit NIR photons into UV/vis photons, and UV/vis sensitive Azo functional group was also introduced into the polymer frameworks (**Figure 1**).³⁵ The reversible photo-isomerization of the Azo group in the polymer framework stimulated by UV/visible upconversion luminescence creates continuous rotation-inversion movement, inducing the decomposing of initial 180-nm nanocapsules into scattered polymers and 20-nm U/DCNPs. The transportation, accumulation and metabolism of the nanocarriers can be carefully monitored based on the NIR window (NIR-II) downconversion fluorescent of the core/multishell structured U/DCNPs. Due to long blood circulation time induced by its large initial size (~ 180 nm), the nanocapsules can provide long blood circulation and enhance accumulation in tumor. The nanocapsules can be controlled to disassemble into small 20-nm U/DCNPs upon NIR light stimulation, releasing the loaded drugs and go through efficient elimination from the tumor site. Such decomposability renders the nanocapsules with a high tumor accumulation as well as NIR stimuli triggered fast elimination.

Figure 2. (A) TEM and HAADF-STEM (inset A), (B) HRTEM images and corresponding FFT (inset B) of the obtained up/downconversion nanoparticles (U/DCNPs). (C) TEM image of the SiO₂@polymer@U/DCNPs nanocomposites. (D, E) TEM images with different magnifications of the U/DCNPs-functionalized nanocapsules. (F) Dual-mode upconversion and NIR-II downconversion fluorescent of the U/DCNPs under 980-nm and 808-nm excitations. (G) Fluorescence of the bare U/DCNPs, U/DCNPs functionalized nanocapsules and the UV/vis absorption of Azo groups containing polymers.

The core/multishell structured NaGdF₄:Yb,Tm@NaYF₄@NaGdF₄:Nd@NaYF₄ U/DCNPs were fabricated and employed to functionalize the polymer nanocapsules (**Figure S2**).³⁶⁻³⁷ In this nanostructure, Tm³⁺ doped nanoparticles were constructed as core for emission of UV/vis upconversion luminescence under 980-nm excitation. The NaGdF₄:Nd layer can emit downconversion NIR-II fluorescent under 800-nm excitation for downconversion bio-imaging. Transmission electron microscopy (TEM) and the high-angle annular dark-field scanning TEM (HAADF-STEM) images (**Figure 2A**) of the as-prepared U/DCNPs show discernible contrast for the multi-layer structure with a uniform diameter of ~ 20 nm. High-resolution TEM images (**Figure 2B**) and the X-ray diffraction (XRD) patterns (**Figure S3**) of the obtained U/DCNPs show that the nanoparticles are highly crystalline hexagonal phase without any remarkable impurity.

Figure 3. TEM images of the nanocapsules after 1.5 W/cm² 980-nm near-infrared radiation for (A) 0 and (B) 30 min. (C) UV/vis absorption and (D) DLS measurements of the nanocapsules upon near-infrared exposure for various time.

Two types of polymers, poly(diallyldimethylammonium chloride) (PDADMAC) and poly[1-[4-(3-carboxy-4-hydroxyphenylazo) benzenesulfonamido]-1, 2-ethanediyl] (PAZO), with positive and negative charge were layer-by-layer assembled through electrostatic interaction onto the surface of colloidal SiO₂ nanoparticles. Negative charged U/DCNPs were anchored into the composites in the same way. TEM images of the obtained nanocomposites clearly show uniform core/shell structured SiO₂@polymer@U/DCNPs nanocomposites (**Figure 2C**). Uniform hollow nanocapsules with small U/DCNPs embedded in the shells were obtained after etching of the SiO₂ templates (**Figure 2D, E**). The polymer shells retained the spherical structure very well, and the size of the nanocapsules shrunk from 200 to 180 nm. The nanocapsules possess NIR-to-UV/vis upconversion optical property under 980-nm excitation as well as downconversion NIR-to-NIR-II fluorescence at around 1060 nm excited by 808-nm light (**Figure 2F**). The result shows that the intensity of the upconversion luminescent emissions in the UV/blue region (300 ~ 500 nm) were significantly depressed after coating of the Azo groups containing polymer. More than 85 % of the photoenergy at ~ 310 and 365 nm was transferred to

the polymer shells due to the strong absorption in the UV region. About 30 % of the photoenergy at ~ 475 nm was absorbed by the polymer shells (**Figure 2G**).

The decomposability of the nanocapsules were carefully examined. TEM images of the nanocapsules after certain period of NIR radiation clearly display the decompose process: the nanocapsules are completely intact at the beginning (**Figure 3A**); an obvious collapse is observed after 1.5 W/cm^2 980-nm irradiation for 15 min (**Figure S4**). After 30 min, the polymer frameworks are totally dissociated and the embedded small U/DCNPs are released (**Figure 3B**). With the increase of NIR irradiation duration, the maximal absorbance of the Azo moiety at 350 nm decreases considerably, indicating that UV and visible light from U/DCNPs inlays can cause the trans-cis photoisomerization of Azo molecules in the polymer frameworks (**Figure 3C**). Dynamic light scattering (DLS) measurements show that the diameter of the nanocapsules shifts from ~ 180 to ~ 20 nm after 980-nm irradiation for 30 min, which is consistent with the sizes of the nanocapsules and U/DCNPs (**Figure 3D**), respectively. The results clearly indicate that the isomerization of Azo group eventually lead to the disassembly of the polymer frameworks, realizing the decomposing procedure of the nanocapsules.³⁸⁻⁴⁰

The composition of the nanocapsules have strong effects on their decomposability. Without enough U/DCNPs to convert NIR into UV/vis (**Figure S7**), the decomposability of the nanocapsules would be seriously hindered (**Figure S8**). On the other hand, the thickness of the polymer shells is also very important. When the number of layers of the assembly charged polymers is less than 8, for example 5, the polymers cannot support the U/DCNPs, thus the hollow structure collapsed after etching of the SiO_2 template (**Figure S9**). When the number of the polymer layer is more than 8, the stability of the structure is significantly improved. However, if the thickness of the polymer shell increases alone without tuning the amount of the embedded U/DCNPs, the structure would be too stable to be decomposed (**Figure S10**). Thus, the ratio of nanoparticle/polymer should be carefully monitored to achieve satisfying decomposability. The size of the nanocapsules can also be well tuned by using colloidal SiO_2 nanospheres with different diameters, and the decomposing ability can be retained very well (**Figure S11, S12, S13**). By alternately introducing of the polymers and inorganic nanoparticles, the hollow-structured nanocomposites with multiple layers anchored nanoparticles can be obtained (**Figure S14**).

The *in-vivo* bio-distribution study was then conducted. The nanocapsules were very stable in a broad pH range and various biological media (**Figure S15**), which laid a foundation for the long term intra-corporeal circulation. Nude mice bearing U87-MG solid tumors were intravenously injected at the caudal vein with the U/DCNPs functionalized nanocapsules (**Figure 4A**). Considering the optimal particle size for a long blood circulation and high accumulation in tumor, the initial U/DCNPs-functionalized polymer nanocapsules with the diameter of 180 nm were selected.⁴¹⁻⁴² Bio-distribution and tumor accumulation were monitored by Nd^{3+} dominated down-conversion NIR-II fluorescence under 800-nm excitation (**Figure 4B**). The results clearly reveal that the NIR-II fluorescence signal at the tumor sites for the 180-nm nanocapsule group is extremely bright in 6 h, compared with that of the free U/DCNPs under the same

condition (to avoid the interaction from the signal of non-interested area, a screener with only the tumor area exposed was used). The NIR-II downconversion fluorescence signal can last over 48 h, which is much longer than that of bare U/DCNPs, suggesting the enhanced accumulation in tumor due to EPR effect with optimized size (**Figure S17**). However, after applying 1.5 W/cm^2 980-nm radiation on the tumor region for only 5 min at 6 h post-injection, the fluorescence signal faded swiftly and totally vanished after merely 6 h. Such quick elimination demonstrates the fast internal clearance owing to the smaller size of the dissociated U/DCNPs. Compared with the free U/DCNPs, the large nanocapsules exhibit significantly higher accumulation rate at tumor sites due to the longer blood retention and higher propensity of extravasation across the vasculature owing to the large size (**Figure 4C, D, S18**). There is a significant decrease in the concentration of Gd^{3+} for the nanocapsules injection group after exposing the tumor to the radiation of 1.5 W/cm^2 980-nm for 5 min (**Figure 4C**). It is attributed to the fast clearance of small 20-nm U/DCNPs after the decompose of the initial big nanocapsules. On basis of the above results, it can be concluded that the NIR-responsive decomposable nanocapsules can not only provide prolonged blood circulation, achieve highly efficient accumulation in tumor, but also decomposing into small-sized fragment nanoparticles for fast clearance.

Figure 4. (A) Decomposing process of the nanocapsules in the *in-vivo* study. (B) *In-vivo* downconversion luminescence images of subcutaneous U87-MG tumor (right shoulder) borne by nude mice after intravenous injection of DOX-loaded nanocapsules at various times. (C, D) Time-dependent relative contents of Gd^{3+} in tumor (C) and blood (D). All images were acquired under the same condition (808-nm, $\sim 1.5 \text{ W/cm}^2$).

Drugs loaded in the nanocapsules can be released during the decomposing process. DOX could reach a 50 % release in 60

min (Figure 5A, S19) under the irradiation of 1.5 W/cm² 980-nm light. In sharp contrast, less than 10 % of DOX was leached out without the NIR irradiation induced decomposing. According to the cell viability evaluation, DOX-loaded nanocapsules showed a significantly enhanced cytotoxicity to the cancer cells upon prolonged irradiation time, while control groups missing any of the three key elements do not result in any significant decrease in the cell viability (Figure 5B). Encouraged by the NIR light responsive release of drugs, the DOX-loaded smart decomposable nanocapsules were used in the chemotherapy of U87-MG solid tumor. Owing to the high tumor accumulation efficiency and NIR triggered controllable drug release, a significantly improved therapeutic effect was observed (Figures 5C, D, S23). These results are consistent with that of the hematoxylin and eosin (H&E) staining analysis (Figure 5E, S24). No remarkable tissue damage or any other side effect was observed on heart, liver, spleen, lung, kidney, and weight fluctuations, indicating a good biocompatibility and negligible toxicity of this smart decomposable drug delivery system.

Figure 5. (A) DOX releasing profiles from the decomposable nanocapsules with and without NIR radiation. (B) Cell viability under different conditions. (C) Tumor growth profiles and (D) body weight of the mice under different conditions. (E) H&E and TUNEL staining of U87-MG solid tumors after various treatments.

In summary, NIR-responsive decomposable drug delivery nanocapsules with controllable sizes (180 ~ 500 nm) were fabricated through layer-by-layer self-assembly of U/DCNPs and light-responsive polymers. 980-nm NIR light can trigger the decomposing process of the U/DCNPs-polymer nanocomposite, transferring the particle from large-sized nanocapsules to small-sized polymer fractions and U/DCNP nanoparticles. According to the results of the *in-vivo* downconversion NIR-II monitoring of the circulation, accumulation, and metabolism, the nanocapsules with optimized initial large particle size (180 nm) can effectively

avoid biological barriers, provide a long blood circulation (~ 5 h half-life time) and achieve four-fold tumor accumulation. The NIR-induced dissociation from initial large capsules to small polymer fractions and 20-nm U/DCNPs allows a fast elimination from tumor within an hour and releases the loaded drugs for chemotherapy. The smart delivery and release capability of this NIR-activated decomposable nanocarriers lay solid foundation towards a novel platform for next generation nano-therapeutics with both spatial and temporal external control.

Acknowledgements

The work was supported by the National Natural Science Foundation of China (NSFC, grant No. 21733003, 21701027), Key Basic Research Program of Science and Technology Commission of Shanghai Municipality (17JC1400100), China National Key Basic Research Program (973 Project) (No. 2013CB934100, 2017YFA0207303), Shanghai Sailing Program (17YF1401000), Australia Research Council (ARC) (DP160104089), Griffith University Postdoctoral Fellowship projects and the Deanship of Scientific Research at Princess Nourah bint Abdulrahman University, through the Research Groups Program Grant no (RGP-1438-0006).

Keywords: upconversion • nanocapsules • drug delivery • core-shell structure • nanoparticles

- [1]. D. Peer, J. Karp, S. Hong, O. Farokhzad, R. Margalit, R. Langer, *Nat. Nanotechnol.* **2007**, 2, 751.
- [2]. M. Davis, Z. Chen, D. Shin, *Nat. Rev. Drug Discov.* **2008**, 7, 771.
- [3]. Y. Matsumura, H. Maeda, *Cancer Res.* **1986**, 46, 6387.
- [4]. B. Godin, E. Tasciotti, X. Liu, R. E. Serda, M. Ferrari, *Acc. Chem. Res.* **2011**, 44, 979.
- [5]. J. Wang, W. Mao, L. Lock, J. Tang, M. Sui, W. Sun, H. Cui, D. Xu, Y. Shen, *ACS Nano* **2015**, 9, 7195.
- [6]. E. Blanco, H. Shen, M. Ferrari, *Nat. Biotechnol.* **2015**, 33, 941.
- [7]. H. Choi, W. Liu, P. Misra, E. Tanaka, J. Zimmer, B. Ipe, M. Bawendi, J. Frangioni, *Nat. Biotechnol.* **2007**, 25, 1165.
- [8]. H. Choi, W. Liu, F. Liu, K. Nasr, P. Misra, M. Bawendi, J. Frangioni, *Nat. Nanotechnol.* **2010**, 5, 42.
- [9]. H. Li, J. Du, J. Liu, X. Du, S. Shen, Y. Zhu, X. Wang, X. Ye, S. Nie, J. Wang, *ACS Nano* **2016**, 10, 6753.
- [10]. H. Li, J. Du, X. Du, C. Xu, C. Sun, H. Wang, Z. Cao, X. Yang, Y. Zhu, S. Nie, J. Wang, *Proc. Natl. Acad. Sci. USA* **2016**, 113, 4164.
- [11]. C. Chen, J. Geng, F. Pu, X. Yang, J. Ren, X. Qu, *Angew. Chem. Int. Ed.* **2011**, 50, 882.
- [12]. F. Huang, W. Liao, Y. Sohn, R. Nechushtai, C. Lu, I. Willner, *J. Am. Chem. Soc.* **2016**, 138, 8936.
- [13]. C. Ye, Z. Combs, R. Calabrese, H. Dai, D. Kaplan, V. Tsukruk, *Small* **2014**, 10, 5087.
- [14]. K. Liang, G. Such, A. Johnston, Z. Zhu, H. Ejima, J. Richardson, J. Cui, F. Caruso, *Adv. Mater.* **2014**, 26, 1901.
- [15]. D. Schmaljohann, *Adv. Drug Deliv. Rev.* **2006**, 58, 1655.
- [16]. R. Cheng, F. Meng, C. Deng, H. A. Klok, Z. Zhong, *Biomaterials* **2013**, 34, 3647.
- [17]. C. Sun, S. Shen, C. Xu, H. Li, Y. Liu, Z. Cao, X. Yang, J. Xia, J. Wang, *J. Am. Chem. Soc.* **2015**, 137, 15217.
- [18]. M. Delcea, H. Mohwald, A. Skirtach, *Adv. Drug. Deliv. Rev.* **2011**, 63, 730.
- [19]. V. Marturano, P. Cerruti, M. Giamberini, B. Tylkowski, V. Ambrogio, *Polymers* **2017**, 9, 8.
- [20]. M. Motornov, Y. Roiter, I. Tokarev, S. Minko, *Prog. Polymer. Sci.* **2010**,

- 35, 174.
- [21]. B. Timko, T. Dvir, D. Kohane, *Adv. Mater.* **2010**, 22, 4925.
- [22]. C. Yao, P. Wang, X. Li, X. Hu, J. Hou, L. Wang, F. Zhang, *Adv. Mater.* **2016**, 28, 9341.
- [23]. R. Wang, X. Li, L. Zhou, F. Zhang, *Angew. Chem. Int. Ed.* **2014**, 53, 12086.
- [24]. B. Yan, J. Boyer, D. Habault, N. Branda, Y. Zhao, *J. Am. Chem. Soc.* **2012**, 134, 16558.
- [25]. H. Ejima, J. Richardson, K. Liang, J. Best, M. van Koeverden, G. Such, J. Cui, F. Caruso, *Science* **2013**, 341, 154.
- [26]. M. Stuart, W. Huck, J. Genzer, M. Muller, C. Ober, M. Stamm, G. Sukhorukov, I. Szleifer, V. Tsukruk, M. Urban, F. Winnik, S. Zauscher, I. Luzinov, S. Minko, *Nat. Mater.* **2010**, 9, 101.
- [27]. A. Skirtach, A. Javier, O. Kreft, K. Kohler, A. Alberola, H. Mohwald, W. Parak, G. Sukhorukov, *Angew. Chem. Int. Ed.* **2006**, 45, 4612..
- [28]. F. Wang, X. Liu, *J Am. Chem. Soc.* **2008**, 130, 5642.
- [29]. X. Li, R. Wang, F. Zhang, L. Zhou, D. Shen, C. Yao, D. Y. Zhao, *Sci. Rep.* **2013**, 3, 3536.
- [30]. J. Richardson, J. Cui, M. Bjornmalm, J. Braunger, H. Ejima, F. Caruso, *Chem. Rev.* **2016**, 116, 14828.
- [31]. F. Caruso, R. Caruso, H. Mohwald, *Science* **1998**, 282, 1111.
- [32]. B. Zhou, L. Tao, Y. Chai, S. Lau, Q. Zhang, Y. Tsang, *Angew. Chem. Int. Ed.* **2016**, 55, 12356.
- [33]. X. Li, F. Zhang, D. Zhao, *Chem. Soc. Rev.* **2015**, 44, 1346.
- [34]. L. Zhou, R. Wang, C. Yao, X. Li, C. Wang, X. Zhang, C. Xu, A. Zeng, D. Zhao, F. Zhang, *Nat. Commun.* **2015**, 6, 6938.
- [35]. Q. Yi, G. B. Sukhorukov, *Soft Matter.* **2014**, 10, 1384.
- [36]. X. Li, D. Shen, J. Yang, C. Yao, R. Che, F. Zhang, D. Y. Zhao, *Chem. Mater.* **2013**, 25, 106.
- [37]. X. Li, Z. Guo, T. Zhao, Y. Lu, D. Y. Zhao, F. Zhang, *Angew. Chem. Int. Ed.* **2016**, 55, 2464.
- [38]. J. Liu, W. Bu, L. Pan, J. Shi, *Angew. Chem. Int. Ed.* **2013**, 52, 4375.
- [39]. Q. Yi, G. Sukhorukov, *Adv. Colloid Interfac.* **2014**, 207, 280.
- [40]. Q. Yi, G. Sukhorukov, *ACS Nano* **2013**, 7, 8693.
- [41]. F. Braet, E. Wisse, P. Bomans, P. Frederik, W. Geerts, A. Koster, L. Soon, S. Ringer, *Microsc. Res. Techniq.* **2007**, 70, 230.
- [42]. H. Cabral, Y. Matsumoto, K. Mizuno, Q. Chen, M. Murakami, M. Kimura, Y. Terada, M. Kano, K. Miyazono, M. Uesaka, N. Nishiyama, K. Kataoka, *Nat. Nanotechnol.* **2011**, 6, 815.

Entry for the Table of Contents (Please choose one layout)

Layout 2:

We demonstrate a novel NIR light responsive decomposable polymer nanocapsule embedded with U/DCNPs in the frameworks, which can not only cross biological barriers, provide prolonged blood circulation, and achieve high efficiency accumulation at tumor, but also is able to decompose into small fragments to release the drugs and enhance the metabolic capability.

Tiancong Zhao, Peiyuan Wang, Qin Li,
Areej Abdulkareem Al-Khalaf, Wael N.
Hozzein, Fan Zhang, Xiaomin Li,*
Dongyuan Zhao*

Page No. – Page No.

**Near-Infrared Triggered
Decomposition of Nanocapsules with
High Tumor Accumulation and
Stimuli Responsive Fast Elimination**