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Mini-review

Development of Silica-containing Redox Nanoparticles for Medical Applications

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Abstract

Silica-containing redox nanoparticles (siRNP) are nanocomposites consisting of silica nanoparticles and amphiphilic block copolymers with nitroxide radicals as reactive oxygen species (ROS) scavengers. Electrostatic interactions between the cationic segment of polymer in the core and entrapped silica nanoparticles form a crosslinking structure that provides siRNP stability *in vivo*, even under harsh conditions in the gastrointestinal tract. Due to the adsorption character of silica nanoparticles in the nanocomposite, siRNP can be applied not only for adsorbents of body wastes but also for drug carriers with high loading capacity. The ROS-scavenging character of siRNP significantly improves their performance for medical applications. Here, we describe the development of siRNP and provide two examples of their medical applications as (1) novel nano-sized adsorbents for peritoneal dialysis, and (2) orally administrable drug carriers for the treatment of gastrointestinal inflammation.

Introduction

The excessive production of reactive oxygen species (ROS) is well known to contribute to an aging[1] and numerous diseases such as stroke[2], myocardial infarction[3], colitis[4]. ROS are produced in the mitochondria under normal condition as a by-product of cellular respiration, and are continually eliminated by endogenous antioxidant metabolites, including vitamin C, vitamin E, and glutathione, as well as antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. However, the excessive ROS generated under pathological conditions can surpass the reducing capacity of these endogenous antioxidant systems, resulting in oxidative damages of cellular components such as lipids, DNA, and proteins[5]. In addition, excessive levels of ROS continuously aggravate inflammation, thereby causing potentially life-threatening disorders. Numerous ROS-scavenging drugs, such as

edaravone (Radicut®), have been developed to prevent oxidative stress-induced damage[6]. Unfortunately, these are usually low-molecular-weight (LMW) compounds that often fail to show protective effects due to their low half-life and drug concentration in inflamed tissues.[7] In addition, high doses of LMW ROS-scavenging drugs can induce adverse effects resulting from disturbances in normal redox signaling in healthy cells.[8] This is a serious issue; thus, the applied dose of ROS-scavenging drugs is extremely limited to avoid these adverse effects.

Over the past 20 years, drug-loaded polymeric micelles have been investigated for their feasibility as drug delivery systems (DDS), as polymeric micelles with long-term blood circulation specifically accumulate in tumor tissues after intravenous administration, termed the enhanced permeability and retention (EPR) effect[9]. This allows for controlled drug release at the tumor sites, thereby enhancing the therapeutic effects of anticancer drugs while minimizing their severe adverse effects in normal tissues.[10] Recently, we have proposed the use of redox nanotherapeutics for oxidative stress injuries by employing polymers covalently conjugated to ROS-scavenging drugs because high molecular weight nature of these compounds makes them difficult to cross the cellular and mitochondrial membranes of healthy cells.[11] To date, we have developed pH-sensitive and -insensitive redox nanoparticles (RNP), referred to as RNP^N and RNP^O, respectively. RNP^N are prepared by the self-assembly of poly(ethylene glycol)-*b*-poly[4-(2,2,6,6-tetramethylpiperidine-1-oxyl)aminomethylstyrene] (PEG-*b*-PMNT), which disintegrate at acidic pH due to protonation of amino groups in the PMNT segment (see Figure 1A). On the other hand, RNP^O are formed from poly(ethylene glycol)-*b*-poly[4-(2,2,6,6-tetramethylpiperidine-1-oxyl)oxymethylstyrene] that provides stability even under the harsh environment of gastrointestinal tract.[12] The ROS-scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), also known as redox-cycling nitroxide radical[13], is covalently conjugated to a side chain of the hydrophobic segment in both amphiphilic block copolymers. Our therapeutic strategy using RNPs has thus far

demonstrated remarkable protective and therapeutic effects on renal and cerebral ischemia-reperfusion injuries[14], cerebral hemorrhage[15], indomethacin-induced small intestinal inflammation[16], and dextran sodium sulfate (DSS)-induced colitis[12]. Over the course of these studies, we have confirmed no internalization of RNPs by healthy red blood cells[17], platelet[17] and colonic mucosa cells[18]. This selective scavenging of excessive extracellular ROS is one of the significant characteristics of our redox nanotherapeutics. To further improve the therapeutic effects, combination therapy of RNP with LMW dugs is one of the potential strategies. Since the loading capacity and entrapping efficiency of LMW drugs by the polymeric micelles is dependent on the matching of their physicochemical properties, however, not all LMW drugs are always stable into the polymeric micelles. To solve this issue, we have designed and developed silica-containing redox nanoparticles (siRNP) that possess encapsulated silica nanoparticles in the hydrophobic core of RNP^N. Encapsulation of the silica nanoparticle in the RNP^N provides siRNP the drug-loading capacity, adsorbent properties, and stability in the acidic environment of RNP^N. So far, various functional silica nanoparticles have been developed such as mesoporous silica nanoparticles with stimuli-responsive release capacity of drug[19], oligonucleotide[19e, 20] and fluorescent dye[21] and attracted much attention for oral drug and gene delivery carriers because of their stability in the gastrointestinal tract and loading capacity.[22] However, oxidative stress and inflammatory responses induced by silica nanoparticles have been reported both *in vitro* and *in vivo*.[23] By encapsulation of silica nanoparticles in RNP^N, oxidative stress and inflammatory responses induced by silica nanoparticles can be suppressed due to the scavenging ROS by TEMPO moieties inside of siRNP. In addition, PEG shell layer can inhibit an aggregation of silica nanoparticles *in vivo* due to its strong hydration ability,[24] conformational flexibility,[25] and repulsive force of the PEG tethered chain.[26] Thus, fusion of these functional silica nanoparticles and RNP compensates for their shortcoming for biomedical application.

In this mini-review, we describe the preparation of the siRNP and provide examples of their use in medical applications, including as (1) adsorbents of waste products for peritoneal dialysis; and (2) orally administered drug carriers for the treatment of gastrointestinal inflammation.

siRNP Preparation

The siRNP can be synthesized by three different methodologies (see Figures 1B-D). The first two methods use commercially available silica nanoparticles ranging in size from 10 to 15 nm that were purchased from Nissan Chemical Industries (Tokyo, Japan). In the first method, siRNP(1) are prepared by the pH-sensitive self-assembly of PEG-*b*-PMNT where colloidal silica (Snow-Tech®O, Nissan Chemical Industries) is added to an aqueous solution of PEG-*b*-PMNT under acidic conditions, after which the pH is raised.[27] In the second method, siRNP(2) are prepared by the dialysis of a dimethyl sulfoxide (DMSO) solution containing PEG-*b*-PMNT and suspended silica nanoparticles (MEK-ST-40, Nissan Chemical Industries) against water.[28] In these cases, the negatively charged silica nanoparticles are entrapped in the positively charged RNP^N core. In the third method, siRNP(3) are prepared by a sol–gel reaction of tetraethyl orthosilicate (TEOS) in the RNP^N core.[27-28] During this process, hydrophobic TEOS is solubilized in the polyamine core of the RNP^N due to the hydrophobic interaction, then subsequently hydrolyzed by the secondary amino groups in the RNP^N core. Unstable intermediates are then condensed to form silica nanoparticles. Annealing the prepared siRNPs increases their stability.[28] The average diameters of these siRNPs are approximately 40–45 nm as determined by dynamic light scattering measurements, which are slightly larger than that of void RNP^N due to the entrapment of silica nanoparticles.

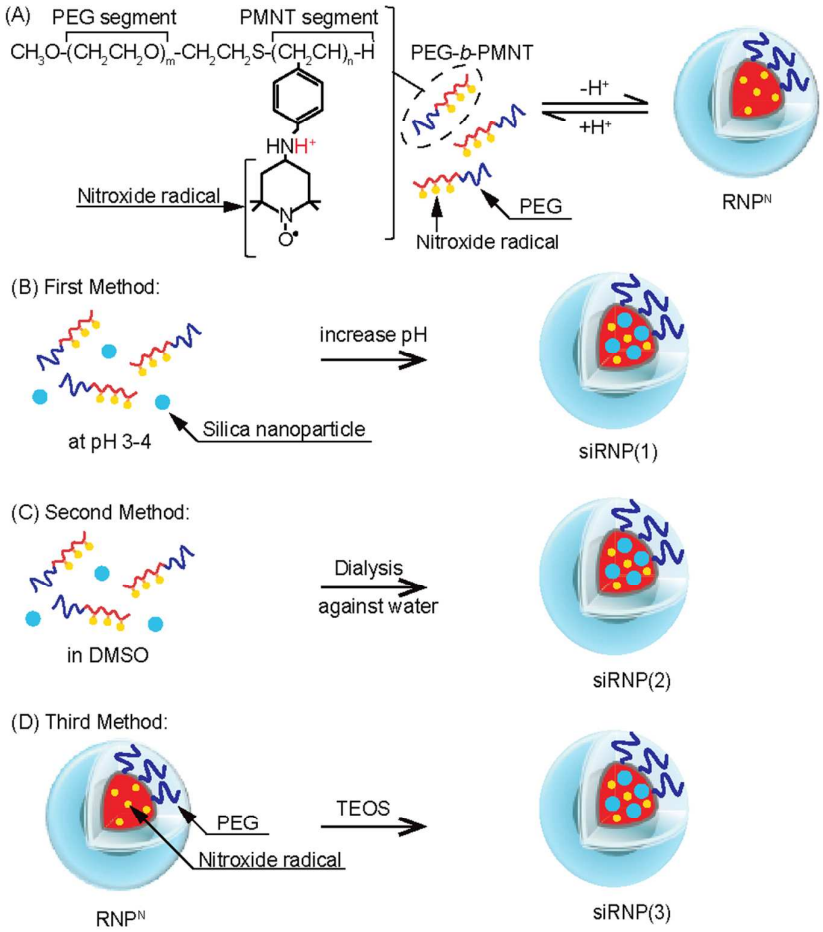

Figure 1. Schematic illustration of RNP^N and siRNPs. (A) Structure of PEG-*b*-PMNT and RNP^N. The PEG-*b*-PMNT forms RNP^N at neutral pH, while RNP^N disintegrate at acidic pH due to protonation of the amino groups in the PMNT segments. (B-D) Preparation schemes for (B) siRNP(1), (C) siRNP(2), and (D) siRNP(3).

Nano-sized adsorbent with ROS-scavenging ability for peritoneal dialysis

The end-stage renal disease requires renal replacement therapy (RRT) such as hemodialysis (HD), peritoneal dialysis (PD), hemofiltration, or renal transplantation. Dialysis is the predominant RRT due to the short supply of donor kidneys. Worldwide, nearly 90% of these patients receive HD, while only 10% are treated with PD.[29] Although HD substitutes for a portion of renal function, several problems still remain, including (1) the continuous need for

hospital attendance; (2) the insufficient removal of medium molecular weight uremic toxins; and (3) the significant removal of body fluid in a short time, which can lead to cardiac overload and vascular damage.[30] These issues increase the risk for several serious diseases such as stroke and myocardial infarction. In comparison to HD, PD provides patients with better preservation of residual renal function, lower costs, and simple treatment protocols that can be performed at home, work, or on trips.[31] Thus, PD has great potential to provide a high quality of life to patients who receive RRT; however, the predominant complications associated with PD are ultrafiltration failure and the increased occurrence of encapsulating peritoneal sclerosis (EPS), which can cause prolonged systemic chronic inflammation.[32]

To solve these issues, we have investigated the effects of siRNP as a waste product adsorbent with ROS-scavenging ability on peritoneal dialysis. Peritoneal dialysis with a high concentration of glucose (1.5–4.25%) removes waste products from the blood using the patient's own peritoneum as an osmotic membrane, in which glucose serves to enhance ultrafiltration. However, high concentrations of glucose have been reported to cause oxidative stress in peritoneal cells.[33] Although ROS-scavenging ability in the dialysate is required to inhibit the inflammation of peritoneal membrane, LMW ROS-scavenging drugs in dialysate are rapidly diffused from the abdominal cavity to the entire body through the peritoneal membrane, resulting in low protective effects and increased adverse effects. In fact, 4-hydroxy-TEMPO (TEMPOL) is absorbed into the bloodstream, which decreases its effective concentration in the peritoneal cavity and leads to adverse effects, such as a dramatic reduction in blood pressure[27]. Since the siRNP are approximately 40–45 nm in diameter, they remain within the intraperitoneal area and continuously scavenge ROS (see Figure 2A). The protective effects of intraperitoneally administered siRNP have been investigated in rats with EPS induced by an intraperitoneal injection of chlorhexidine gluconate (CH). CH induces inflammation in the peritoneal membrane, resulting in a thicker

submesothelial compact zone of the abdominal wall, compared to that of normal rats (see Figures 2B and 2C). The intraperitoneally administered TEMPOL attenuates this increase to some extent (see Figure 2D), whereas siRNP markedly inhibit increased thickness, indicating that siRNP suppress inflammation by scavenging ROS in abdominal cavity (see Figure 2E). Figures 2F and 2G show the levels of creatinine and blood urea nitrogen (BUN) in the blood of mice with renal failure induced by ischemic treatment of both kidneys. As shown in Figures 2F and 2G, both the creatinine and BUN levels are significantly increased in the renal failure model mice, which can be rescued by administration of our siRNPs.

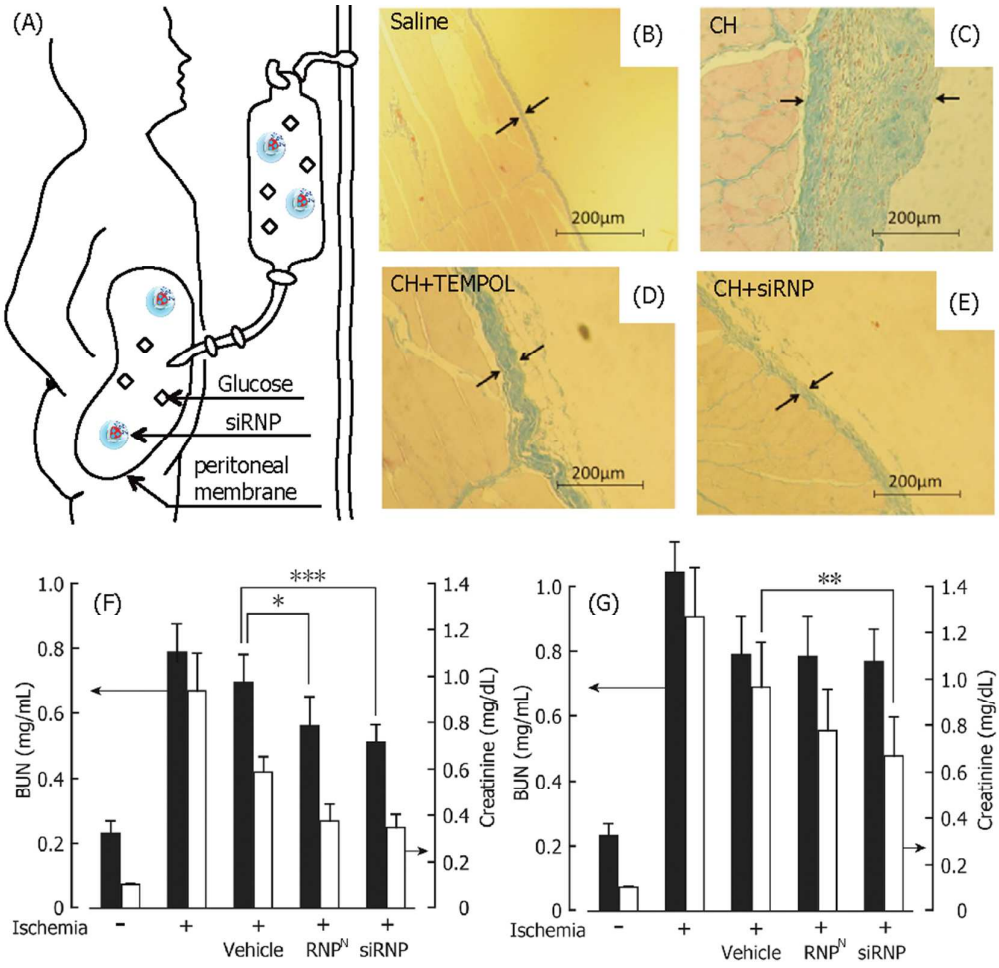

Figure 2. (A) Schematic illustration of peritoneal dialysis using siRNP. (B-E) Histological assessments by performing Masson's trichrome staining of peritoneum treated with (B) saline (2 mL), (C) chlorhexidine gluconate (CH) (2 mL at 0.1%), (D) CH + TEMPOL (CH: 2 mL at

0.1%; and TEMPOL: 3 mL of 6.66 mg/mL solution) and (E) CH + silica-containing redox nanoparticles (siRNP(1), SiO_2 = 5 wt%) (CH: 2 mL at 0.1%; siRNP(1): 3 mL of 20 mg/mL solution; nitroxide radical concentration is 6.66 mg/mL). The arrows indicate the thickness of the peritoneum. Thicknesses of peritoneal membrane in the rats treated with saline, CH, CH + TEMPOL, and CH + siRNP are 29 ± 13, 269 ± 48, 88 ± 34 and 42 ± 18 μm, respectively. Scale bars = 200 μm. (F-G) The effect of silica-containing redox nanoparticles (siRNP(3)) as an additive of peritoneal dialysis-dialysate against renal failure model mice. Vehicle: 2.4 mL of 4.25 wt%/vol% glucose solution; RNP^N: 2.4 mL of 4.25 wt%/vol% glucose solution containing RNP^N (100 mg/mL) and siRNP(3) (SiO_2 = 3.77 wt%): 2.4 mL of 4.25 wt%/vol% glucose solution containing siRNP(3) (2.4 mL of 100 mg/mL) for (F) 6 h and (G) 9 h. *p < 0.05; **p < 0.01; ***p < 0.005. Reproduced from Ref. [17] with permission from The Royal Society of Chemistry.

Orally administrable drug carrier with ROS-scavenging ability

The number of patients with intractable inflammatory bowel diseases (IBD), such as Crohn's disease and ulcerative colitis, has increased steadily over the years and now exceeds several millions worldwide.[34] We recently reported on the remarkable therapeutic effects of pH-insensitive RNP^O for the treatment of indomethacin-induced small intestinal inflammation[16] and DSS-induced colitis[12]. Since pH-insensitive RNP^O can subsist in acidic conditions, such as those seen in the gastrointestinal tract, intact RNP^O are delivered to the small intestine and colon. Here, they accumulate in the mucosa and inflamed areas and proceed to scavenge ROS in the inflamed tissues. Interestingly, RNP^O accumulates markedly in the colon when compared to polystyrene latex particles of the same size (40 nm). Notably, commercially available polystyrene tends to agglomerate under harsh gastrointestinal conditions, whereas the higher colloidal stability of RNP^O results from the surface layer of

PEG that suppresses their aggregation considerably. Therefore, PEGylated RNP^O show a higher accumulation and longer retention in the colonic mucosa, as compared to commercially available polystyrene latex particles. These results demonstrate that orally administered drug-loaded nanoparticles with PEG shells have the potential to delivery LMW drugs to diseased areas of the lower gastrointestinal tract. Although polymeric micelles have a hydrophobic core, it is not always easy to encapsulate LMW drugs in the core of polymeric micelles. In contrast, siRNP have high drug loading capacity due to the silica nanoparticles in the core. We have investigated the drug loading capacity of our siRNP using the model drug rebamipide, which is used for mucosal protection and the treatment of gastroduodenal ulcers and gastritis. Rebamipide is a poorly water-soluble drug, but possesses a carboxylic acid group. Both RNP^N and RNP^O can encapsulate rebamipide to some extent, with loading percentages of 4% and 2% for the RNP^N and RNP^O, respectively. In contrast, siRNP have a higher rebamipide loading capacity of 16%. In addition, rebamipide-loaded siRNP control the release of rebamipide in response to pH, where its release accelerates with increasing alkalinity. This is likely due to repulsion between the anionic silica surface and the anionic rebamipide under neutral to alkaline conditions. By virtue of these characteristics, following oral administration of rebamipide-loaded siRNP to mice, the siRNP are delivered to the intestinal area, where rebamipide is released in response to an increase in pH, resulting in increase in the concentration of rebamipide in both the blood and small intestine. In addition, the therapeutic effects of rebamipide-loaded siRNP on DSS-induced colitis can be enhanced without causing any additional inflammation. Since siRNP possess PEG shells, orally administered rebamipide-loaded siRNP may also accumulate in mucosal and inflamed areas, contributing to the bioavailability of rebamipide and its therapeutic effect on colitis.

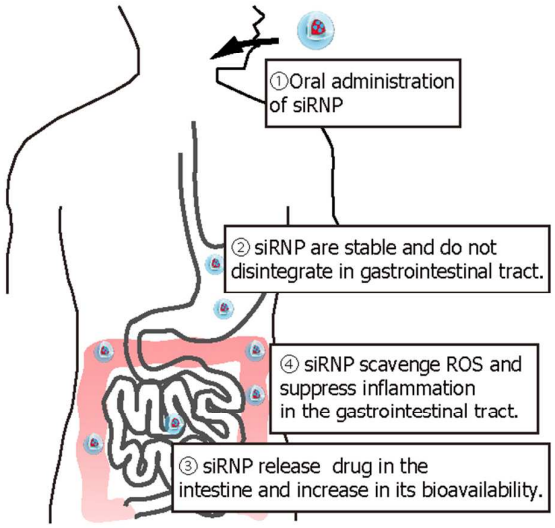

Figure 3. Schematic illustration of orally administrable drug-loaded siRNP

Summary and Outlook

Newly developed silica-containing redox nanoparticles (siRNP) are expected to be a novel functional nanomaterial for high-performance peritoneal dialysis, since siRNP overcome the issue of the dialysis efficiency and prevent peritoneal inflammation—the two major problems of the peritoneal dialysis system. In addition, the siRNP have great potential to dramatically enhance therapeutic effect of conventional LMW drugs by improving their oral bioavailability. Based on the examples presented in this mini-review, siRNP are promising as new tool that may be applied as an adsorbent for toxins and bile acids, as well as an oral anticancer treatment. In previous study, we have reported that intravenous administered RNP^N inhibits their adverse effect of anticancer drug efficiently due to the scavenging ROS and improve the anticancer effect in vivo due to suppression of the activation of transcription factor, NF-κB in the cancer cells.[35] Considering this character, orally administered siRNP is not merely deliver anticancer drug but also prevent anticancer drugs-induced damage in the gastrointestinal tract due to scavenging

ROS.

In addition, nitroxide radicals are used as not only ROS scavengers but also electron spin resonance and magnetic resonance imaging agents[36] due to paramagnetic properties. Although other ROS-scavengers can be applicable instead of nitroxide radicals, covalently conjugated nitroxide radicals provide siRNP various attractive applications including *in vivo* imaging. Thus, siRNP are emerging and promising biomaterials with potential functions in various medical applications.

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References

1 T. Finkel and N. J. Holbrook, *Nature*, 2000, **408**, 239.

2 R. Rodrigo, R. Fernandez-Gajardo, R. Gutierrez, J. M. Matamala, R. Carrasco, A. Miranda-Merchak and W. Feuerhake, *CNS Neurol Disord Drug Targets*, 2013, **12**, 698.

3 M. C. McDonald, K. Zacharowski, J. Bowes, S. Cuzzocrea and C. Thiemermann, *Free radical biology & medicine*, 1999, **27**, 493.

4 N. J. Simmonds and D. S. Rampton, *Gut*, 1993, **34**, 865.

5 D. Harman, *Journal of gerontology*, 1956, **11**, 298.

6 T. Watanabe, S. Yuki, M. Egawa and H. Nishi, *The Journal of pharmacology and experimental therapeutics*, 1994, **268**, 1597.

7 C. K. Chow, *Free radical biology & medicine*, 1991, **11**, 215.

8 E. Monti, R. Supino, M. Colleoni, B. Costa, R. Ravizza and M. B. Gariboldi, *J Cell Biochem*, 2001, **82**, 271.

9(a) M. Yokoyama, M. Miyauchi, N. Yamada, T. Okano, Y. Sakurai, K. Kataoka and S. Inoue, *Cancer research*, 1990, **50**, 1693; (b) A. V. Kabanov, V. P. Chekhonin, V. Alakhov, E. V. Batrakova, A. S. Lebedev, N. S. Melik-Nubarov, S. A. Arzhakov, A. V. Levashov, G. V. Morozov, E. S. Severin and et al., *FEBS letters*, 1989, **258**, 343; (c) Y. Matsumura and H. Maeda, *Cancer research*, 1986, **46**, 6387.

10 Y. Bae, S. Fukushima, A. Harada and K. Kataoka, *Angew Chem Int Ed Engl*, 2003, **42**, 4640.

11(a) T. Yoshitomi and Y. Nagasaki, *Advanced healthcare materials*, 2014, **3**, 1149; (b) M. L. Pua, T. Yoshitomi, P. Chonpathompikunlert, A. Hirayama and Y. Nagasaki, *Journal of controlled release : official journal of the Controlled Release Society*, 2013, **172**, 914.

12 L. B. Vong, T. Tomita, T. Yoshitomi, H. Matsui and Y. Nagasaki, *Gastroenterology*, 2012, **143**, 1027.

13 C. S. Wilcox, *Pharmacology & therapeutics*, 2010, **126**, 119.

14(a) T. Yoshitomi, A. Hirayama and Y. Nagasaki, *Biomaterials*, 2011, **32**, 8021; (b) A. Marushima, K. Suzuki, Y. Nagasaki, T. Yoshitomi, K. Toh, H. Tsurushima, A. Hirayama and A. Matsumura, *Neurosurgery*, 2011, **68**, 1418.

15 P. Chonpathompikunlert, C. H. Fan, Y. Ozaki, T. Yoshitomi, C. K. Yeh and Y. Nagasaki, *Nanomedicine (Lond)*, 2012, **7**, 1029.

16 S. Sha, L. B. Vong, P. Chonpathompikunlert, T. Yoshitomi, H. Matsui and Y. Nagasaki, *Biomaterials*, 2013, **34**, 8393.

17 M. Shimizu, T. Yoshitomi and Y. Nagasaki, *Journal of Clinical Biochemistry and Nutrition*, 2014, **54**, 166.

18 L. B. Vong, T. Yoshitomi, H. Matsui and Y. Nagasaki, *Biomaterials*, 2015, in press.

19(a) C. Y. Lai, B. G. Trewyn, D. M. Jeftinija, K. Jeftinija, S. Xu, S. Jeftinija and V. S. Lin, *J Am Chem Soc*, 2003, **125**, 4451; (b) Z. Luo, K. Cai, Y. Hu, L. Zhao, P. Liu, L. Duan and W. Yang, *Angew Chem Int Ed Engl*, 2011, **50**, 640; (c) X. Ma, K. T. Nguyen, P. Borah, C. Y. Ang and Y. Zhao, *Advanced healthcare materials*, 2012, **1**, 690; (d) B. G. Trewyn, Slowing, II, S. Giri, H. T. Chen and V. S. Lin, *Accounts of chemical research*, 2007, **40**, 846; (e) X. Ma, C. Teh, Q. Zhang, P. Borah, C. Choong, V. Korzh and Y. Zhao, *Antioxid Redox Signal*, 2014, **21**, 707.

20 J. Zhang, M. Niemelä, J. Westermarck and J. Rosenholm, *Dalton Trans*, 2014, **43**, 4115.

21 X. Wan, D. Wang and S. Liu, *Langmuir : the ACS journal of surfaces and colloids*, 2010, **26**, 15574.

22(a) Y. Zhang, J. Wang, X. Bai, T. Jiang, Q. Zhang and S. Wang, *Molecular pharmaceutics*, 2012, **9**, 505; (b) Z. Li, S. Zhu, K. Gan, Q. Zhang, Z. Zeng, Y. Zhou, H. Liu, W. Xiong, X. Li and G. Li, *Journal of nanoscience and nanotechnology*, 2005, **5**, 1199.

23 E. J. Park and K. Park, *Toxicology letters*, 2009, **184**, 18.

24 Q. Cao, S. Li, C. He, K. Li and F. Liu, *Anal Chim Acta*, 2007, **590**, 187.

25 B. S. Lee, O. J. Yoon, W. K. Cho, N. E. Lee, K. R. Yoon and I. S. Choi, *J Biomater Sci Polym Ed*, 2009, **20**, 1579.

26 Y.Nagasaki, *Polymer Journal*, 2011, **43**, 10.

27 Y. Nagasaki, T. Yaguchi, T. Matsumura, T. Yoshitomi, Y. Ikeda, A. Ueda and A. Hirayama, *Biomater. Sci.*, 2014, **2**, 522.

28 M. A. Hossain, M. Yamashita, L. B. Vong, Y. Ikeda and Y. Nagasaki, *Journal of drug targeting*, 2014, **22**, 638.

29 A. Grassmann, S. Gioberge, S. Moeller and G. Brown, *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*, 2005, **20**, 2587.

30 F. Locatelli, A. Cavalli and B. Tucci, *Nature reviews. Nephrology*, 2010, **6**, 41.

31 K. N. Lai and J. C. Leung, *Nephron. Clinical practice*, 2010, **116**, c11.

32 M. F. Lam, J. C. Leung, W. K. Lo, S. Tam, M. C. Chong, S. L. Lui, K. C. Tse, T. M. Chan and K. N. Lai, *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*, 2007, **22**, 1445.

33 K. Y. Hung, S. Y. Liu, T. C. Yang, T. L. Liao and S. H. Kao, *Oxid Med Cell Longev*, 2014, **2014**, 642793.

34 F. Cominelli, *The New England journal of medicine*, 2013, **369**, 775.

35 T. Yoshitomi, Y. Ozaki, S. Thangavel and Y. Nagasaki, *Journal of controlled release : official journal of the Controlled Release Society*, 2013, **172**, 137.

36 B. P. Soule, F. Hyodo, K. Matsumoto, N. L. Simone, J. A. Cook, M. C. Krishna and J. B. Mitchell, *Free radical biology & medicine*, 2007, **42**, 1632.

Biography & photograph

Toru Yoshitomi

Toru Yoshitomi received a B.S. in Faculty of Industrial Science and Technology, Tokyo University of Science in 2005 and Ph.D. degrees in Graduate School of Pure and Applied Sciences, University of Tsukuba in 2010. Since 2010, he worked in Graduate School of Pure and Applied Sciences, University of Tsukuba as postdoctoral fellow. Since 2013, he worked at Department of Chemistry, Graduate School of Science, The University of Tokyo as JSPS Postdoctral Fellowship. He is focusing on biomaterial sciences.

Yukio Nagasaki

Yukio Nagasaki received a B.S. and Ph.D. degrees in Engineering School of Science University of Tokyo in 1982, and 1987. Since 1987, he was working Science University of Tokyo as Research Associate, Assistant Professor, Associate Professor and Professor. In 2004, he moved Graduate School of Pure and Applied Sciences, University of Tsukuba. He hold a concurrent posts of Adjunct Professor, Master's School of Medical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Principal Investigator, International Center for Materials Nanoarchitectonics Satellite (WPI-MANA), National Institute for Materials Science (NIMS). He is focusing on biomaterials science, especially biointerface, drug delivery system and nanomedicine.

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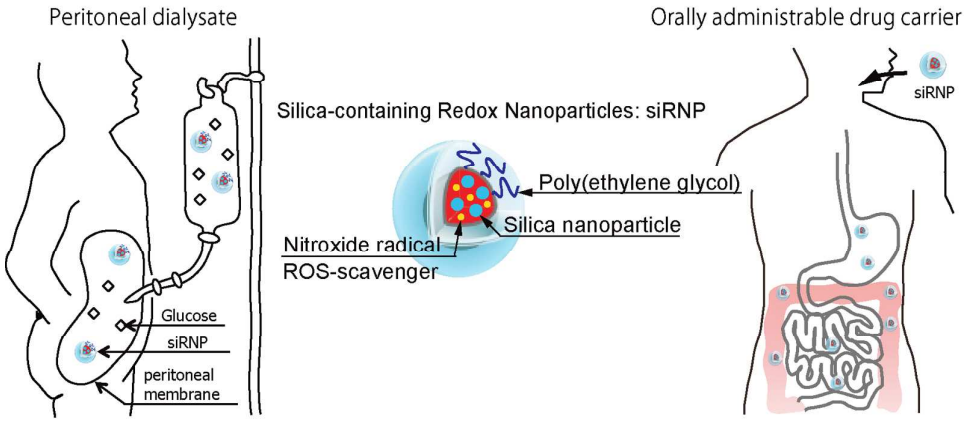

- Text: one sentence, of maximum 20 words, highlighting the novelty of the work

Silica-containing redox nanoparticles act as adsorbents for peritoneal dialysis and orally administrable drug carriers for the treatment of gastrointestinal inflammation

(20 words)