Development of polymeric micelles for targeting intractable cancers

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Polymeric micelles, core–shell-type nanoparticles formed through the self-assembly of block copolymers, have been widely recognized as a promising nanocarrier in cancer targeted therapy (Fig. 1). (1–11) Various molecular interactions, such as hydrophobic interactions, hydrogen bonding, electrostatic interaction, and metal complex formation in the core-forming segments, can be a driving force of the formation of polymeric micelles (5–9). Accordingly, a wide range of therapeutic molecules including hydrophobic substances, charged compounds, and metal complexes can be stably and efficiently incorporated into the micellar core, and their release can be controlled in a sustained or environment-sensitive manner. (5–9)

Compared with surfactant micelles, polymeric micelles show excellent stability characterized by low critical micelle concentration, glass state (solid) core, and kinetic stability. (12,13) Polymeric micelles have a narrowly distributed size controllable in the range of 10–100 nm, (14) which should be in contrast with other clinically approved nanocarrier formulations (e.g., Doxil (Janssen Pharmaceutical Co., Titusville, NJ, USA), Abraxane (Celgene Co., Summit, NJ, USA)) with the size of 100 nm. Importantly, these properties, which might critically affect the performance as a drug carrier, can be optimized by fine-tuning chemical structures and compositions of the micelle-forming block copolymers. (5–9,15) In addition, installation of functional molecules such as environment-responsive cleavable linkages and targetable ligands on the block copolymers allows construction of polymeric micelles with smart functionalities. (5–9,16–19) Owing to the above-mentioned prominent advantages beyond other drug vehicles, several micellar formulations of anticancer drugs are currently under evaluation in preclinical and clinical studies. (8,10) In this article, we review design rationales and recent advances of polymeric micelles for the delivery of anticancer drugs.

Design Rationale of Polymeric Micelles

Optimization of block copolymers and in vivo behavior of polymeric micelles. As aforementioned, AB-type block copolymers assemble into polymeric micelles with characteristic core–shell structures and narrow size distributions in the range of 10–100 nm (Fig. 1). (3–10) The dense PEG palisade protecting the drug-loaded core can effectively hinder interaction with plasma proteins and cells, avoiding the recognition of the micelle by the reticuloendothelial system in the bloodstream. (20,21) Therefore, polymeric micelles can display prolonged circulation with a half-life longer than 10 h. (3–7,14,15) Note that polymeric micelles finally dissociate into the constituent block copolymers, the size of which is below the threshold of glomerular excretion, thereby avoiding long-term accumulation in the body. Long-circulating polymeric micelles effectively...
Drug loading and controlled drug release. Enabling on-demand drug incorporation is one of the most prominent features characterizing polymeric micelles. The method of drug incorporation can be classified into “non-covalent” and “covalent” manners. In the non-covalent drug loading, water-insoluble compounds are physically entrapped into the micellar core by the dialysis, ultrasound-aided dispersion or oil in water emulsion methods. A relatively high drug loading capacity of approximately 20% can be achieved without chemical modification of drug molecules. For successful drug incorporation, the compatibility (the matching of chemical structures) between drug molecules and the core-forming segments should be taken into consideration. Also, the properties of the core-forming segments such as hydrophobicity, the glass transition temperature, the degree of crystallinity, and secondary structure (e.g., \( \alpha \)-helix formation) should be critical factors. These properties critically affect the efficiency and capacity of drug loading as well as its release behavior. In the covalent drug loading, drug molecules are chemically conjugated to the core-forming segments. For drug conjugation, the environment-responsive cleavable linkage is exploited to ensure the drug release at the target site. Because the tumor microenvironment is known to develop an acidic condition due to the production of lactate by predominantly anaerobic glycolysis in cancer cells (Warburg effect), the acid-cleavable linkage such as hydrazone bond is useful for tumor-selective drug release.

The PEG-b-PAA copolymers are useful for aforementioned on-demand drug incorporation due to freedom of the choice of amino acids and versatile side chain modification. For the “non-covalent” drug incorporation, we reported that chemical conjugation of doxorubicin (DOX) to the side chain of PAA on-demand drug incorporation due to freedom of the choice of amino acids and versatile side chain modification. For the “non-covalent” drug incorporation, we reported that chemical conjugation of doxorubicin (DOX) to the side chain of PAA by a stable amide linkage resulted in loss of cytotoxic activity of conjugated DOX but contributed to stable physical entrapment of free DOX through the \( \pi-\pi \) interaction between the anthracycline structures of conjugated and unconjugated drugs. Thus, optimization of chemical structures of the micellar core-forming segments depending on drug molecules is feasible. Meanwhile, as an example of “covalent” drug incorporation, DOX was conjugated to the core-forming segments through the hydrazone bond between the carbonyl group at C13 of DOX and the hydrazide group introduced to poly(D, L-aspartate).
formed polymeric micelles, which showed acidic pH-responsive
DOX release. Currently, the micellar formulation of a less
cardiotoxic epimer, epirubicin (code name NC-6300/ K-912)
is under phase I clinical study. In addition to hydrophilic
molecules, metal complexes can be incorporated into
PEG-b-PAA micelles. cis-Diaminedichloroplatinum(II) (cis-
platin, CDDP) and (trans-1,2-diaminocyclohexane) platinum
(II) (DACHPt, an active complex of oxaliplatin) were com-
plexed with PEG-b-poly(L-glutamate) through Pt(II)–carboxy-
late complex formation, leading to the formation of narrowly
distributed micelles with the size of 30 nm. In these sys-
tems, the reversible ligand exchange reaction of Pt(II) enables
the preferable release of active platinum complexes from the
micelles, ensuring their potent cytotoxic activities. After sys-
temic administration, CDDP and DACHPt-loaded micelles
were revealed to show prolonged circulation and effective
tumor accumulation, achieving remarkable in vivo antitumor
efficacies with reduced side-effects. Currently, CDDP
and DACHPt-loaded micelles (code names NC-6004 and
NC-4016) are under phase III and I clinical studies,
respectively.

Intracellular drug release using the vehicles may enhance the
drug potency. For instance, N-(2-hydroxypropyl) methacyr-
lamid copolymer–DOX conjugate and pH-responsive DACH-
loaded polymeric micelles were reported to overcome the
DOX-resistance in cancer cells as a result of intracellular drug
release. As we noticed that DACHPt-loaded micelles
accelerate the drug release in the pH and [Cl−] conditions
mimicking the late endosomal environment, we tested their
in vitro and in vivo efficacies against oxaliplatin-resistant
cancer cells. Confocal microscopic observation revealed that
DACHPt-loaded micelles achieved intracellular drug release
under both in vitro and in vivo conditions. Consequently,
DACHPt-loaded micelles showed remarkable in vitro and
in vivo antitumor activities against oxaliplatin-resistant cancer
cells. We assume that DACHPt-loaded micelles might circumvent
detoxification of DACHPt by metallothionein and methionine synthase overexpressed in the cytoplasm
of oxaliplatin-resistant cancer cells. Thus, polymeric micelles
with the function of intracellular drug delivery may behave
like a nanoscale Trojan horse, thereby potentially overcoming
drug resistance.

Nucleic acids-based drugs such as plasmid, antisense DNA,
and siRNA can be incorporated into polymeric micelles
through polyeon complex formation between negatively
charged nucleic acids and positively charged PEG-b-PAA
copolymers. Polymeric micelles greatly improve the sta-
Bility of nucleic acids-based drugs under in vivo conditions,
leading to prolonged blood circulation. Integration of endo-
some escape and organelle-selective release functionalities led
to remarkably enhanced in vitro and in vivo efficacies of
nucleic acids-based drugs in various disease models. For
details of the delivery of nucleic acids-based drugs, refer to
other expert review papers.

Design of Polymeric Micelles for Targeting Intractable Cancers

Optimization of the size of polymeric micelles. The clinically
approved PEGylated liposomes such as Doxil (Janssen Phar-
maceutical Co.) and albumin nanoparticles termed Abraxane
have the size of approximately 100 nm. This size might be
adequate for effective tumor accumulation based on the EPR
effect. Although the transvascular transport of nanoparticles
depends on the origin of tumor cells and the microenvironment,
solid tumors have a pore cut-off size larger than 200 nm
except for some intractable cancers such as glioblastoma
(GBM). In this regard, pancreatic cancers and diffuse-type
gastric cancers (scirrhous gastric cancers) have characteristic
histological features characterized by less permeable vascular-
ture with pericyte coverage and thick fibrosis, which
might be an obstacle to extravasation and penetration of
nanoparticles. Indeed, we have shown that PEGylated lipos-
ome show heterogeneous accumulation in tumor stroma and
cannot reach tumor nests in a s.c. model of human pancreatic
cancer BxPC3 cells (Fig. 3b). This result motivated us to study
the accumulation and penetration of polymeric micelles with
different sizes ranging from 30 to 100 nm in BxPC3
tumors. As a result, the accumulation of 30-nm micelles is
twofold higher than that of 50-nm micelles and fourfold higher
than that of 70- and 100-nm micelles. Note that all the
micelles of 30–100 nm displayed similar accumulation levels
in a s.c. model of murine colon carcinoma C26 cells, in which
the pericyte coverage and tumor stroma are minimal. Co-
administration of 30 and 70 nm micelles in mice bearing
BxPC3 tumors revealed that 30-nm micelles show a uniform
intratumoral microdistribution while 70-nm micelles show
heterogeneous localization at perivascular regions. These
results strongly suggest that the accumulation and pene-
tration of polymeric micelles in pancreatic cancer models

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**Fig. 2.** (a) In vivo antitumor activity of (trans-1,2-diaminocyclohexane) platinum(II) (DACHPt)-loaded micelles (DACHPt/m) against oxaliplatin-
resistant human colon adenocarcinoma HT29 (HT29/ox) tumors. (●) Saline; (○) oxaliplatin (8 mg/kg); (●) DACHPt/m (4 mg/kg); (●) injection of
oxaliplatin and DACHPt/m. *p < 0.1; **p < 0.01. Data are expressed as mean ± SEM (n = 4). Reprinted from Murakami et al. with permission from
[AAAS, Washington, DC, USA]. (b) Hypothetical mechanism of overcoming oxaliplatin resistance by DACHPt/m. DACHPt/m are assumed to be
internalized through the endocytic pathway, and reach the late endosomes and lysosomes close to the nuclei, leading to facilitated drug
release. Therefore, DACHPt/m may bypass the cytoplasmic detoxification pathways consisting of metallothionein (MT1Q) and methionine synthase
(MTR), which are overexpressed in HT29/ox cells.
largely depend on their size, that is, the 30-nm micelles can bypass the barriers in transvascular transport and penetrate tumor stroma, deeply penetrating tumor nests. Such enhanced tumor accumulation of 30-nm micelles was observed in spontaneous murine pancreatic tumors in transgenic mice expressing SV40 T antigen and luciferase regulated by the elastase-1 promoter. The 30-nm DACHPt-loaded micelles showed remarkably prolonged survival in mice bearing clinically relevant tumors (Fig. 3d). Furthermore, a similar size effect was observed in an orthotopic model of human diffuse-type gastric cancer OCUM-MLN cells.

The size of polymeric micelles is also important for targeting tumor metastasis. Lymph nodes are a common route for metastasis in some tumors. It is known that local administration of nanoparticles to primary tumors leads to accumulation in a neighboring lymph node though the lymphatic vessels, which is clinically applied in the sentinel lymph node biopsy. However, such local administration cannot be applicable to systemic delivery of antitumor drugs due to the lack of selectivity, especially when targeting cancer cells are disseminated in the body. Recently, we found that polymeric micelles can accumulate selectively in lymph node metastases through the blood vascular route, which is believed to be specific to active recruitment of lymphocytes to lymph nodes. We evaluated the accumulation of systemically injected 30- and 70-nm micelles and 100-nm PEGylated liposomes in branchial metastatic lymph nodes formed by inoculation of murine melanoma B16-F10-luc cells to the left forepaw of mice. As a result, only 30-nm micelles accumulated and penetrated in the metastatic focus, whereas 70-nm micelles and PEGylated liposomes did not (Fig. 4a). The 30-nm micelles did not accumulate in contralateral healthy lymph nodes, suggesting selective accumulation of 30-nm micelles in metastatic lymph nodes. Importantly, 30-nm micelles showed comparable accumulation in metastatic lymph nodes and following tumor growth inhibition by antitumor drugs in mice with their primary tumors resected. This result suggests the targeting of lymph node metastasis though the blood vascular route (Fig. 4b). Thus, 30-nm micelles may be used for systemic delivery of antitumor drugs for the treatment of lymph node metastasis.

Furthermore, we studied the targeting of liver metastases of colon carcinoma C26 cells. In this study, we investigated the accumulation of the micelles in different stages of tumor metastasis (from day 2 to day 10 after inoculation). Interestingly, polymeric micelles accumulated not only in overt liver metastases, where the EPR effect is highly expected, but also in early-stage pre-angiogenic metastases on day 3. Polymeric micelles showed prolonged retention in the whole metastatic niche (cluster of C26-GFP cells), where α-SMA positive stellate cells and CD68-positive Kupffer cells were recruited. Administration of COX-2 inhibitor (celecoxib) resulted in significant decrease in accumulation of polymeric micelles in pre-angiogenic metastases; therefore, the inflammatory microenvironment seems to be a mechanism for the retention of micelles in the metastatic niche. Note that the targeting pre-angiogenic metastases of C26 cells was not affected by the size of polymeric micelles. Thus, polymeric micelles can target early-stage pre-angiogenic metastases.

**Actively targetable polymeric micelles.** As mentioned, GBM is characterized by limited vascular permeability. The pore cut-off size in GBM is reported to range from 7 to 100 nm, whereas that in other tumors is beyond 200 nm. Such limited vascular permeability in GBM is known as the blood–brain tumor barrier (BBTB), attenuating the efficacy of some antitumor drugs and nano-scaled drug vehicles. The integration of targetable ligands on drug vehicles is a promising approach for overcoming BBTB. Recently, we developed a...
were conjugated with antibodies targeting osteopontin,\( (29) \) epidermal growth factor receptor,\( (57) \) human epidermal growth factor receptor-2,\( (58) \) and others. Recently, antibody–drug conjugates (ADCs) have been reported for platinous antitumor drug in micelles having cyclic Arg-Ala-Asp ligand, thereby achieving remarkable enhanced efficacy of platinous antitumor drug in tumor tissues (Fig. 5), which may not be explained by the passive targeting based on the EPR effect.\( ^{17} \) We hypothesize that cRGD-conjugated micelles might bypass BBTB through the active transvascular transport system, such as transcytosis.

Antibody and its fragments are also useful as targetable ligands to design actively targetable micelles. Several antibody-conjugated micelles (immunomicelles) have been reported for delivery of antitumor drugs.\( ^{29,56-58} \) These immunomicelles were conjugated with antibodies targeting osteopontin,\( ^{59} \) epidermal growth factor receptor,\( ^{57} \) human epidermal growth factor receptor-2,\( ^{58} \) and others. Recently, we reported immunomicelles conjugated with anti-tissue factor (TF) antibody fragments.\( ^{18,19} \) Tissue factor is known as a primary initiator of blood coagulation, and plays an important role in tumor proliferation, invasion, and metastasis.\( ^{59} \) It is reported that the expression level of TF on cancers is associated with patient prognosis.\( ^{59} \) We have reported that anti-TF antibody fragment–conjugated micelles incorporating epirubicin and DACHPt were efficiently internalized by TF-overexpressing cancer cells and showed superior in vitro and in vivo antitumor activity to non-targeted micelles.\( ^{18,19} \) Recently, antibody–drug conjugates (ADCs) have been receiving great attention and many ADCs are under clinical evaluation.\( ^{60} \) However, ADCs can load only two to four cytotoxic drugs per antibody, leading to limitation of versatile use, potential side-effects due to overdose, and rising drug prices. In contrast, immunomicelles can deliver hundreds of drug molecules per antibody, expanding the choice of anticancer drugs and functional design. Thus, immunomicelles are expected to be more versatile platforms for drug delivery than current ADC formulations.

**Polymeric Micelles Under Clinical Evaluation**

Paclitaxel (PTX)-loaded polymeric micelles formed from PEG-b-poly(D,L-lactide) (Genexol-PM) (Samyang Biopharm Co., Seoul, Korea) have been approved for the treatment of breast cancer, non-small-cell lung cancer, and ovarian cancer.\( ^{61,62} \) Expansion of clinical applications of Genexol-PM to other cancers is under clinical evaluation.\( ^{63,64} \)

In our system, five micellar formulations incorporating PTX (NK105), cisplatin (NC-6004), SN-38 (NK102), dachplatin (active complex of oxalaplatin) (NC-4016), and epirubicin (NC-6300/K-912) are currently under clinical evaluation.\( ^{63,64} \) Among them, NC-6004 progressed to phase III study and approval application of NK105 will be undertaken in 2016. NK105 was reported to show enhanced antitumor activity and reduced PTX-induced peripheral neuropathy in a preclinical study.\( ^{65} \) Also, NK105 can solubilize PTX without Cremophor EL (CEL) (BASF Co., Ludwigshafen, Germany), preventing CEL-induced hypersensitive reactions. In a phase I study, NK105 was given by i.v. infusion for 1 h without anti-allergic premedication.\( ^{66} \) Of 19 patients, only one experienced allergic reactions. A partial response in one pancreatic cancer patient and stable disease lasting 10 to seven courses depending on the patients with colon or gastric cancers were observed. In a pharmacokinetic study, NK105 (at 150 mg/m\(^2\)) showed 30-fold higher plasma area under the receiver–operating characteristic curve than conventional PTX-CEL formulation (at 210 mg/m\(^2\)). Dose-limiting toxicity (DLT) of NK105 was grade 4 neutropenia. In a phase II study against advanced stomach cancer, as a second-line therapy, patients received NK105 by i.v. infusion for 0.5 h once every 3 weeks without anti-allergic premedication.\( ^{67} \) As a result, the overall response rate of NK105 accounted for 25% of patients, with two achieving complete response and 12 partial responses. The most
observed grade 3/4 hematological toxicity was neutropenia; there was no grade 3/4 non-hematological toxicity and no hypersensitive reactions without anti-allergic premedication. Importantly, grade 3 neurotoxicity was observed for only one in 57 patients (1.8%), which is in contrast with other PTX delivery systems such as Xyotax (CTI BioPharm Co., Seattle, WA, USA) and Abraxane, showing grade 3 neurotoxicity in 10–15% of patients. Since 2012, the phase III study of NK105 for comparison with conventional PTX-CEL formulation has started in multiple countries including Japan, Taiwan, and Korea, and patient registration was completed in 2014. Pending the successful outcome of the phase III study, approval application of NK105 will be undertaken in 2016.

NC-6004 has undergone clinical studies in different countries. In a preclinical study, NC-6004 was shown to prevent renal toxicity, DLT of CDDP, because 30-nm micelles do not undergo glomerular filtration, and decreasing $C_{\text{max}}$ of CDDP in the proximal tubule. As a result, the phase I study of NC-6004 in the UK was carried out using 1-h infusion once every three weeks and hydration with 1000 mL saline on the day of drug treatment. In all the patients, NC-6004 was given without hospitalization. Although nausea and vomiting caused by NC-6004 were milder than conventional CDDP treatment, hypersensitive reactions were more frequently observed in NC-6004 treatment. The maximum tolerated dose and recommended dose for the phase II study were determined to be 120 and 90 mg/m², respectively. In a phase I/II study, NC-6004 in combination with gemcitabine was tested in advanced pancreatic cancer patients. In these studies, the dose of NC-6004 reached 90 mg/m² without hydration, and hypersensitivity observed in phase I study was prevented by dexamethasone premedication. Currently, NC-6004 has progressed to phase III study for comparison between the combination of NC-6004 and gemcitabine and gemcitabine alone in advanced or metastatic pancreatic cancer in Asian countries. A phase I/II study of NC-6004 against non-small-cell lung cancer patients is ongoing in the USA.

NC-6300/K-912 is a pH-responsive polymeric micelle that can selectively release epirubicin under acidic conditions of intratumoral microenvironment or the endo-/lysosomal compartment in cancer cells. In preclinical study, NC-6300/K-912 was reported to show improved accumulation in solid tumors and reduced accumulation in normal tissues. Importantly, NC-6300/K-912 prevented cardiotoxicity and DLT of anthracycline anticancer drugs, due to decreased accumulation in cardiac muscle tissues. Currently, a phase I study of NC-6300/K-912 is ongoing at the National Cancer Center in Japan.

**Future Formulations and Applications of Polymeric Micelles**

The preferential tumor accumulation of nano-scaled drug vehicles has been reported not only for animal models but also for patients with various cancers including non-small-cell lung cancer, squamous cell lung cancer, breast cancer, and ovarian cancer. However, it is likely that the accumulation level and intratumoral distributions of drug vehicles might depend on different types of cancers in individual patients. Such interpatient and intratumoral variations may change during treatment, and finally should affect the therapeutic outcome. Therefore, it might be important to evaluate such interpatient and intratumoral variations in individual patients before and during treatment.

**Fig. 5.** Time-lapse intravital microscopies of human glioblastoma U87MG tumors after co-injection of non-targeted cyclic Arg-Ala-Asp-conjugated (green) and targeted Arg-Gly-Asp (cRGD)-conjugated (red) (trans-1,2-diaminocyclohexane) platinum(II) (DACHPt)-loaded micelles. Yellow, micelles colocalization. Microdistribution of cRGD-conjugated micelles (red) at 5 h postadministration and quantitative analysis of the number of micelles in tumor sites (center) revealed that cRGD-conjugated micelles show very fast translocation from the vasculature to tumor tissues. Reprinted from Miura et al., with permission from [American Chemical Society, Washington, DC, USA].

**Fig. 6.** (a) Magnetic resonance images (T₁-weighted) of mice bearing an orthotopic pancreatic cancer (BxPC3) before and after injection of gadolinium-diethylenetriaminepentaacetic acid (Gd-DTPA) or Gd-DTPA/(trans-1,2-diaminocyclohexane) platinum(II) (DACHPt)-loaded micelles. Yellow, micelles colocalization. Microdistribution of cRGD-conjugated micelles (red) at 5 h postadministration and quantitative analysis of the number of micelles in tumor sites (center) revealed that cRGD-conjugated micelles show very fast translocation from the vasculature to tumor tissues. Reprinted from Kaida et al., with permission from [AACR, Philadelphia, PA, USA].
during treatment with anticancer drugs formulated in nano-scaled vehicles. This information may be helpful for estimating the therapeutic effect and designing and optimizing the therapeutic protocols for individual patients (tailor-made nanomedicine). In this regard, we have devoted great efforts to develop polymeric micelles incorporating MRI contrast agents such as gadolinium-diethylene triaminepentaacetic acid (Gd-DTPA) (for T1-weighted images) and superparamagnetic iron-oxide nanoparticles (for T2-weighted images). These diagnostic micelles were shown to visualize s.c. and orthotopic models of various cancers, including pancreatic cancers. In addition, DACHPt-loaded micelles have been integrated with imaging functionality by incorporating Gd-DTPA through the reversible complex formation between DACHPt and Gd-DTPA. Interestingly, incorporation of Gd-DTPA into polymeric micelles drastically increased longitudinal relaxivity, $r_1$ (from 3.5 to 80.5 mmol/L/s) due to the flexibility reduction per Gd molecule and the increase of the rotational correlation time. In the animal experiment, the accumulation of Gd-DTPA/DACHPt-loaded micelles in orthotopically inoculated pancreatic cancer was successfully visualized in a real-time manner by MRI (Fig. 6). The non-invasive monitoring of tumor volume during treatment was also feasible by Gd-DTPA/DACHPt-loaded micelles. Such dual diagnostic and therapeutic functions are called “theranostic”, and have been attracting increasing attention. In the future, diagnostic and theranostic nanoparticles will evolve functions of molecular imaging to detect cellular responses to therapeutic agents and histological information. Thus, imaging functionality is expected to improve reliability and safety of targeted therapy.

Conclusion

Increasing numbers of important drugs have been confronting the problem of forfeiture of patent; therefore, product life cycle management has been recognized as being increasingly important. It is getting more difficult to find new drug compounds by traditional drug discovery and development technologies. Even if new lead compounds are identified, most of them show serious side-effects in preclinical and clinical studies, as potent compounds often target the molecules in the upstream signal transduction pathways. In this regard, drug delivery systems (DDS) can improve the efficacy and safety of existing drug molecules, offering usefulness for product life cycle management. Drug delivery systems can solve the toxicity problems of potent new compounds and promote their practical applications. They can provide new functions to drug molecules by integrating functional molecules to the DDS platform. Thus, we believe that DDS will be more important in drug discovery and development. Among various DDS platforms, polymeric micelles are the most promising due to their versatile and tailor-made designs based on polymer chemistry and nanobiotechnology. During the last two decades, polymeric micelles as drug vehicles have made rapid progress and several formulations are already being evaluated in late-stage clinical trials. We expect the approval of these micellar anticancer drugs and generation of innovative micellar nanomedicines with smart functionalities in the near future.

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Disclosure Statement

Nobuhiro Nishiyama and Kazunori Kataoka are inventors of some of polymeric micelles in clinical studies. But we transfered all the rights to the University of Tokyo. The University of Tokyo licenced to Nano-carrier Corporation.

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