carcinogenesis and during the so-called progression stage, which may last from 10 to 30 years, as seen in gastric cancer and hepatoma, both of which involve chronic infection. In such a setting, an inflammatory reaction induces reactive oxygen species (ROS), including reactive nitrogen species,[2)-6)] that causes mutations in lesions that are frequently irreversible or that the DNA repair systems cannot fix the damage because they may be also damaged.

Recent advances in cancer genomics have indicated that the average patient with lung cancer, for example, would have 100-200 mutant cancer cells. Each patient with esophageal or colon cancer would have approximately 50-100 mutant cancer cells.[7)-9)] Therefore, the most recent molecular target drugs, which aim at a specific, unique molecular target present in a given cancer, would have about a 1% chance of therapeutic success. Monoclonal antibody drugs (and cancer vaccines), which use as molecular targets antigenic epitopes, such as protein tyrosine kinases or their receptors including vascular angiogenesis factor (vascular endothelial growth factor, or VEGF) and epidermal growth factor (EGF) receptors, respectively, can also manifest mutations. Therefore, cancer cells can escape molecular recognition via mutations that will nullify targets of the molecular drugs.[7)-9)] Furthermore, in many cases, antibodies, for instance those to VEGF or EGF receptors, do not eradicate cancer cells but frequently

make them quiescent.[10)-13)] We have experienced that once the antibody or the receptor inhibitor, is blocked or inactivated, cancer cells resume growth again.

Many related clinical studies have shown limited success with these treatments despite approval of regulatory authorities.[1),13)-15)] In view of these data, scientists at the National Institute for Health Care and Excellence (NICE), in the United Kingdom, and others in academia and the media have expressed concerns about the cost-effectiveness of these drugs[13)-15)] (see the discussion in Section 1-2-4 below).

1-2-3. Immunotherapy: still not decisive weaponry against cancer. The initial concept of immunotherapy was based on the principle that newly emerged cancer cells would possess one or more new antigenic potentials that would provoke an effective immunological reaction if the host had normal immunological potency. Clearly, cancer patients lose the immunological capacity to combat the cancer cells, possibly because of aging of hosts (cancer patients). The cancer cells may therefore escape from the immunological host response and surveillance, and a host's defense cells may not see cancer cells as immunologically different, or cancer cells may destroy the tumor-attacking immune cells.

Cytotoxic T-cells offer potential hope in this immunotherapy strategy, in which

antibody-like molecules (called T-cell receptors) develop on the cell surface. Comparable to soluble antibodies. T-cell receptors can recognize a diverse repertoire of antigenic epitopes of target (cancer) cells.

Investigations of numerous immunotherapies along this line were performed with tumor-bearing mouse models. One method utilized *in vitro* externally activated T-lymphocytes that were infused into the host. In such an experimental setting, this treatment was effective when the number of effector cells (cancer-killing immune cells) (E) was 30- to 50-fold higher than the number of target tumor cells (T). That is, an E/T ratio of 30 or more is needed. However, when tumors in humans weigh 5-10 g, about 150-300 g of activated cytotoxic effector cells must be infused. This target is almost impossible to achieve, and curing patients is therefore difficult. Although this information is known, many clinical treatments using this method are performed in Japan, even though the National Health Insurance has not approved the treatment method. However, standard protocols for bladder cancer worldwide still utilize the well-known evidence of immune activation by bacterial cell components (*e.g.*, BCG). In this context, activation of innate immunity such as macrophages or natural killer cells may be worthwhile.

1-2-4. Issues related to the stability of liposomal and micellar drugs in relation to the enhanced permeability and retention (EPR) effect and tumor accumulation. The third reason for chemotherapeutic failures concerns active-drug encapsulated liposomal or micellar nanoparticles. This nanotechnology-based therapy with nanomedicines has been the focus of great attention in the past 2-3 decades (*e.g.*, Ref. 16). Particles that had the poorest consideration on the clearance by macrophages or phagocytes demonstrated failed treatments because they were quickly removed from the circulation by phagocytic cells or reticuloendothelial cells. However, a current method of attaching biocompatible polymers such as polyethylene glycol (PEG) to the surface of the particles can protect them against phagocytosis or the immunological surveillance system.

Another issue is the rigid, sturdy structure of these particulate drugs, such as Doxil®, which consists of pegylated liposomes containing doxorubicin (DOX). When drug-encapsulated liposomes or nanoparticles are not stable enough, a drug may leak out of the drug-encapsulated-particles during circulation, or the particles may burst in a short time, and the effect becomes similar to that of the parental low-MW drug (see Fig. 1b). Therefore, design of macromolecular drugs consisting of a stable, biocompatible complex would lead to effective drug accumulation in solid tumor tissue by virtue of the EPR effect, which is discussed later in Section 2. However, when the drug release was in fact too slow, because of the stability of the study liposome, it would result in poor drug action; the consequence being an effective concentration of the only *stable liposome itself in the tumor tissue*, but a poor concentration of the active drug principle in the tumor, and thus a poor clinical response (such as with Doxil®).

In the case of unstable micellar drug complexes, however, physical disruption

during circulation may occur as micelles burst during intravenous (i.v.) injection. Consequently, the plasma concentration of these micelles quickly drops, with no EPR effect seen (Fig. 1b). Figure 1 presents hypothetical examples of the plasma pharmacokinetics of different low-MW drugs versus polymer-conjugates or nanodrugs.

Both a low-MW free drug such as tetrahydropyranyl doxorubicin (THP) (Fig. 1a) and an unstable micellar complex of DOX and a copolymer (Fig. 1b) were cleared too rapidly from blood circulation. The plasma stability of a styrene-co-maleic acid (SMA)-polymer DOX conjugate (Fig. 1c) and an SMA-polymer THP conjugate (Fig. 1d) and release of the drug (DOX) from the conjugate (Fig. 1c) were significantly better than those of the complex of DOX and a copolymer (Fig. 1b), but the release was too rapid to have an improved EPR effect. In comparison, the SMA-polymer THP conjugate (Fig. 1d) had the best release rate and plasma and tumor concentrations, with the result being better therapeutic efficacy because of the improved EPR effect.

The micellar drug of Fig. 1b is an example of chemotherapeutic failure at an early clinical stage (NK-911), in that the stability of this particular micellar drug was insufficient so that the micelles burst too quickly: about 50% released within 1 hour after i.v. injection, and thus no benefit from the EPR effect could be obtained which requires a circulation time of a drug for several hours or longer. In this context, the biocompatible polymer (hydroxypropylmethacrylamide) [HPMA], MW~3K, conjugated to DOX (PK-1) also failed to show the EPR effect, as seen in Fig. 1b. This point is critical for biocompatible macromolecular drugs, which must have a high plasma level for a very long time, such as several hours to a day or more, which may be possible with macromolecular drugs of MW > 50Da.

A few recent reports commented about unsatisfactory results concerning

tumor-selective accumulation of nanomedicines as based on the EPR effect[17),18)] (as discussed later in Section 2). With regard to these data, the bursting of the micellar structure or release of the encapsulated drugs during circulation is critically important. In the experiments cited here, the polymer carrier was covalently linked with a fluorescent probe so as to follow the *in vivo* biodistribution via fluorescence. The micelles are non-covalently encapsulated the candidate drug (tritiated paclitaxel). The *in vivo* distribution study revealed, after i.v. injection of the fluorescent micelles, a clear tumor-selective EPR effect. However, when the researchers analyzed the accumulation by radioactivity count of the drug (paclitaxel) in the tumor, they found a different result: the accumulation of the drug in the tumor was somewhat less than 1%, which is similar to that of the free form of the low-MW drug paclitaxel (Taxol®). These researchers thus concluded that no EPR effect occurred for the nanoparticle drug. Their experiments did not analyze, for example, spontaneous drug release from the micelles in the culture medium, drug release in the presence of NaCl, and that in blood plasma. However, non-covalently encapsulated low-MW drugs (such as paclitaxel) would have leaked out rapidly from the micelles in the presence of blood, whereas the covalently linked fluorophore to the polymer would have remained as macromolecules and exhibited the EPR effect. Thus, careful interpretation of these results is required, and experiments should be designed to avoid such artefacts.

1-2-5. Problems in cancer drug screening and evaluation. Drug-screening models that use implanted tumors may not be equivalent to spontaneous tumors in found in clinical situations. The most important point in drug development relates to a drug's

effectiveness: it should produce beneficial results against both solid primary and metastatic tumors. Traditional primary drug screening has been performed with mouse peritoneal leukemia L1210 and P388 models, with drugs being administered intraperitoneally (i.p.) and tumors being implanted i.p. In this system, a given drug may be readily accessible to tumor cells in the peritoneal cavity. Pharmacological properties such as plasma level, tissue distribution, inactivation in the liver and renal elimination, and access to the neovasculature in the tumors are of secondary importance; the immediate drug action in the i.p. compartment determines the efficacy of the drug. Thus, any cytotoxic drug candidates may demonstrate good effects in the peritoneal cavity, but these effects may not apply to solid tumors, which have unique vascular and tissue properties (*e.g.*, neoangiogenesis, permeability, hypoxic characteristics). Therefore, EPR effect-based targeting of drugs to tumors does not exist in the i.p./i.p. system.

The second problem concerns the mouse model itself, which is usually a syngeneic and/or human xenograft model. However, no syngeneic humans exist except for identical twins. In the syngeneic mouse model, the tumor (xenobiotic) has good immunological compatibility with the host, and thus a host reaction to a xenobiotic tumor would not occur, because the tumor would be immunologically inert. Host mice

for human xenograft tumors also do not produce immunological reactions. This model may work well for HIV/AIDS patients but not for cancer patients in general. In addition, the time frame for rodents and humans is quite different. The life spans of mice and rats are extremely different from the human life span. Experimental mouse tumors grow rapidly, *e.g.*, 5×10^6 cells implanted in a mouse reach a palpable size in about a week, whereas human tumors usually take months to years to reach a noticeable size. The optimal time scale for the slow release of cancer drugs that would be effective in humans would therefore be quite different from that in mice.

In addition, anatomical sites used for implanting tumors are frequently located in skin or muscle, not in orthotopic tissues. Consequently, one can argue against the validity of a vascular similarity of those sites compared with the original organs. That is, renal cancer or hepatoma implanted in muscle tissue cannot have the same vascular network as the network in the kidney or in the liver, respectively. In this respect, autochthonous models or chemically induced breast, colon, or liver cancer may serve as much better models or more realistic tumors. Furthermore, metastatic tumor models are rarely used for drug screening.

I also want to emphasize that the most common endpoint in the murine screening system is prolongation of survival (life span) compared with survival of a control group

receiving no drugs. All mice would eventually die, but cures with tested drugs or conventional anticancer agents are seldom seen, particularly with metastatic tumors. Therefore, an endpoint of a cure rate with a different time frame, *e.g.*, more than 100 days or a significantly longer time period, should be used. Evaluation of cancer drugs should consider the cure rates and no disease recurrence as seen in development of antibiotics for infectious diseases. In addition, the so-called therapeutic window should be large enough for improved safety and therapeutic efficacy, and polymer-conjugated drugs usually provide a lower toxicity compared with the parent drug, *e.g.*, Doxil® versus DOX.

1-2-6. Problems in photodynamic therapy. PDT has been known for more than a century. Indeed, N.R. Finsen received the Nobel Prize in Medicine and Physiology in 1903 for his novel phototherapy of dermal tuberculosis. PDT was expanded to cancer treatment half a century ago as the use of the helium-neon (HeNe) laser, which emits a monochromatic light at 635 nm. However, PDT requires a photosensitizer with a given range of wavelength for photoexcitation (such as seen xenon or some other source) to generate singlet oxygen, *i.e.*, an oxygen radical (an ROS), which is the cancer-killing principle in PDT. Current PDT methods fail to fulfill the basic principle of

spectroscopy in two crucial ways, however. First, currently used photosensitizers, *e.g.*, Laserphyrin® and Photofrin®, do not satisfy the spectroscopic requirements. HeNe lasers emit light only at 635 nm, whereas these photosensitizers being used in the clinical setting can be excited by light irradiation within the range of 380-430 nm but not at 635 nm, and thus no significant generation of singlet oxygen occurs.

The second issue is that the currently used photosensitizing agents have molecular weights less than 1,000 and will be distributed indiscriminately throughout the body, almost evenly in all tissues and organs *in vivo*, after i.v. infusion, *i.e.*, without any tumor selectivity (see Fig. 2B).[55] Therefore, illumination of a patient, or exposure of the patient to ambient daylight, may result in damage to any exposed surface skin, but no tumor cells are killed because no significant accumulation of the sensitizer occurs in the tumor.

1-2-7. Adverse effects of cancer chemotherapy: The most serious problem in conventional cancer chemotherapy is the occurrence of severe adverse effects, primarily inducing systemic toxicity, including bone marrow suppression; kidney, liver, cardiac, and peripheral neuronal toxicity; diarrhea; bleeding; and immunological suppression. Quantifying and pinpointing the causes of the toxicity, particularly at the molecular level, and thus eliminating adverse effects such as

anorexia, fatigue or weakness, diarrhea, alopecia, discomfort, pain, and others are rather difficult. However, these effects are the main reason for the lower quality of life and morbidity of the patients. These adverse effects are attributed to systemic and non-selective drug delivery and other multiple causes. However, a few rational symptomatic treatments, *e.g.*, erythropoietin and neutrophil growth factors, can now control such adverse effects as hematopoietic suppression and bone marrow suppression including erythrocytopenia, leukocytopenia, and neutropenia. Whatever the symptomatic treatments, palliative care is similarly important, particularly at the end stage of disease. Under these circumstances, development and use of truly tumor-targeted drugs are urgently needed, as described later.

1-2-8. Economic issues: poor response rates, prohibitive costs, and problems with the health insurance system. Another problem in cancer chemotherapy involves the cost of recent molecular target drugs: they are quite expensive, but in many cases no satisfactory survival benefits have been reported (*e.g.*, Refs. 10-26). Many of these drugs may cost US$100,000 per year, or up to one third of a million dollars per course of treatment. Other nanomedicine-type anticancer agents such as Doxil® and Avastin® (bevacizumab) would cost about US$5,000 per injection, or about 10 times of the price of the parent drugs (DOX and paclitaxel, respectively), without a significant survival

benefit (*e.g.*, Refs. 22-24). The media in the United States and United Kingdom frequently report on this issue.[17)-26)] One advantage of using macromolecular drugs such as Doxil® is said to be a more tolerable toxicity compared with the parent drug (DOX). However, more than half of personal bankruptcy filings each year in the United States are reportedly due to the high cost of medical care, including drugs (Time, March 4, 2013).

In the Japanese National Health Insurance System, all patients are eligible to receive government-approved medications and treatments. However, patients must pay all medical and hospital costs of any new unapproved medicines. That is, patients who use just one additional unapproved medication lose all the privilege of receiving the Japanese National Insurance System benefits, even health care procedures that are vitally needed. In contrast, some or many very costly approved drugs yield no substantial survival benefits as discussed above. I believe that such approved drugs should remain available to individual patients who want them but only if the patients pay the cost, so as to prevent increasing the huge debt of the Japanese National Health Insurance System, with the remaining cost of treatment covered by the insurance.

In this regard, government and industrial resources should more vigorously support research efforts to reduce medical costs and increase therapeutic efficacy.

2. Solutions to tumor-selective drug development: The EPR effect and sound rationales for drug design

In 1986, Yasuhiro Matsumura (then a graduate student) and I discovered a novel phenomenon in cancer chemotherapy, which we named the EPR effect of macromolecular drugs in solid tumors. Since then, the EPR effect has been widely cited—more than 15,000 times by 2012, after its first publication in *Cancer Research*[27]—and it is becoming a gold standard in cancer drug design, despite inadequate development as discussed in Section 1-2-4.

The EPR effect in solid tumors in general results from a number of causes. First, tumor vasculature is architecturally defective, *e.g.*, it frequently lacks a smooth muscle layer (or pericytes), shows irregular stretching, and has large gap openings; thus, tumor blood vessels are much leakier than normal blood vessels. Macromolecular drugs therefore selectively leak out of blood vessels in tumor tissues, *i.e.*, a drug with a molecular size larger than 40 kDa can leak out into the tumor interstitium. Also, because of insufficient lymphatic clearance, these drugs are retained in tumor tissues for a very long time, *i.e.*, days to weeks[27)-31)] (Fig. 2). This EPR effect was not observed in normal tissues or organs unless they had some lesion or inflammation.[27)-31)] Healthy,

normal tissue will therefore be protected from the toxic effects of macromolecular drugs, or so-called nanomedicines, containing cytotoxic active ingredients.

We found that biocompatible polymers conjugated with active drugs are ideal for tumor-selective targeting and delivery of drugs. We first prepared a polymer-conjugated anticancer drug that we named SMANCS, with SMA as the polymer consist of styrene-co-maleic acid and neocarzinostatin (NCS) as the drug, in 1979.[32] SMANCS was approved by the Japanese FDA in 1993 and has been used as a drug for hepatoma. It can be dissolved in the oily contrast agent Lipiodol® and is administered via the tumor-feeding artery via a catheter under X-ray monitoring. We achieved highly selective delivery of SMANCS to tumors (tumor-to-blood ratio = 2,000:1), and more important, the drug was not delivered to normal tissues.[30),33)-35)] However, this method of arterial administration required a technical skills involving angiography, which is a rather advanced procedure compared with conventional i.v. infusion. In addition, for use, SMANCS necessitated mixing with Lipiodol® at the bedside. These requirements, together with a small sales volume, meant that SMANCS was less lucrative for pharmaceutical companies and thus attained only limited popularity. However, this strategy may eventually stimulate a new field of cancer therapy with arterial infusion of nanomedicines. In fact, this method proved highly effective against

advanced primary and metastatic liver cancers, cancers of the gallbladder, pancreas, and kidney, and lung cancer of all types, even at stage IV.[30),34)-36)]

3. Problems with the EPR effect for tumor-selective drug delivery

The EPR concept is the first, most important step for tumor-selective drug delivery.[37)] Although numerous researchers confirmed the EPR effect by using various rodent tumors implanted in non-orthotopic sites, one can argue its validity in metastatic tumors, spontaneous primary tumors, and human tumors in general. These issues are discussed elsewhere in this article.

The issue of the heterogeneity of the EPR effect in general is also important. Tumors, not only rodent tumors but also human tumors, manifest many differences in size, stage, and pathology. When a tumor reaches a diameter larger than 1.0 cm, it frequently has areas of necrosis as well as thrombogenic, hypoxic, or coagulative areas or some necrotic tissue; obviously, these areas do not exhibit the EPR effect.[16),31),36)] To make these inert areas more responsive to the EPR effect, the EPR effect can be augmented, as described in Section 4, which produces a more homogeneous EPR effect in tumor tissues and hence better drug delivery. Therefore, one can overcome the problem of the heterogeneity of the EPR effect to a great extent.[31),36),38)]

We demonstrated augmentation of the EPR effect by using vascular effectors such as nitroglycerin (NG) and angiotensin I-converting enzyme inhibitors, both of which are widely used non-toxic drugs (cf. Tables 1 and 2).[29)-31),35),36),39),40)] Furthermore, we[39),41)] recently reported on a second step in achieving tumor selectivity by using an environment-sensitive bond cleavage in the setting of the low pH of tumor tissue: the conjugate was cleaved at the linker, a hydrazone bond or an ester bond, and released free active drug near the tumor cells.[41),42)] Free drugs such as THP can thereby easily reach tumor cell membranes by diffusion and attach to receptors or transporters (nucleotide transporters), which efficiently take the drugs into the cells. This system is upregulated more in tumor cells than in normal cells.[42)] Another drug, DOX encapsulated in STEALTH liposomes (Doxil®), also exhibits the EPR effect. The plasma levels and tumor concentrations of Doxil® far exceeded those of the free drug DOX—as much as 11 times higher—in AIDS patients with Kaposi sarcoma[43)] (see Fig. 1).

Our new drug conjugates will utilize this property, thereby minimizing toxicity or even achieving zero toxicity. We can thus accomplish the best targeting of drugs to tumors by means of three mechanisms: (i) the EPR effect, (ii) release of active free drug under the lower pH conditions in the vicinity of tumor tissues, and (iii) rapid

intracellular uptake of released drugs by means of transporters (*e.g.*, pirarubicin and zinc protoporphyrin, or ZnPP, as described later). Endocytic uptake of microparticles or nanomedicines is also believed to occur much faster in dividing tumor cells than non-dividing normal cell.[44),45)] If macromolecular conjugates are taken up into cells via such endocytosis, the conjugates would rapidly release free drugs because the lysosomal or endosomal pH value is much lower than pH 6, and because hydrolytic enzymes in the subcellular compartment would facilitate hydrolytic cleavage of these chemical bonds in the cells.

4. Augmentation of the EPR effect for tumor delivery

We previously discussed the importance of the EPR effect for drug delivery to solid tumors.[28)-31),38),39),46),47)] As described earlier, the reasons for the EPR effect are multiple and include defective vascular architecture and excessive production of vascular mediators (Table 1), as occurs in inflammation. These mediators, such as nitric oxide (NO), bradykinin, and prostaglandins, induce the tight junctions of endothelial cells in blood vessels in tumors and normal tissues to open (Tables 1 and 2). It is interesting that the EPR effect can be augmented 2- to 3-fold by administration of widely used non-toxic drugs, *e.g.*, nitroglycerin (NG) and

angiotensin I-converting enzyme inhibitor (ACEI); the latter inhibits bradykinin degradation, with the consequences being elevated local bradykinin levels and an enhanced EPR effect.[30),31),36),38),39),46)-48)]

Many solid tumor tissues have suppressed blood flow, similar to that in infarcted cardiac tissue, and become hypoxic. When NG is applied to the skin of tumor-bearing animals by using an ointment, NG will become nitrite (NO_2^-) and will then be converted to NO in hypoxic tumor tissue (Fig. 3), which induces the EPR effect and enhances tumor-selective blood flow 2- to 3-fold, as well as improving drug delivery (Fig. 3C,D) (*e.g.*, Refs. 31,36,39,46,48). As discussed earlier, angiotensin II-induced high blood pressure, increasing from 100-110 mmHg to 150-160 mmHg, can also enhance tumor-selective drug delivery and reduce drug toxicity.[30),31),38),49)] Such augmentation of drug delivery to tumors is possible only by using nanomedicines because of their long retention in tumor tissues.

5. The EPR effect in metastatic cancer and outlook for polymer-conjugated candidate drug 1.

The EPR effect has been studied mostly in primary tumors or implanted tumors, so whether it would occur in metastatic tumors was not clear. In fact, we did observe a

similar EPR effect in metastatic liver and lung cancers in rodents, as shown in Figure 4.

Figure 4 clearly demonstrates selective accumulation of a macromolecular drug (Evans blue-albumin, a putative 70-kDa drug) in metastatic nodules in the lung. Conventional low-MW drugs are frequently ineffective for metastatic tumors, when patients reach to stage III or IV, which may be attributed to most often metastatic cancers. We see an evidence of clear uptake of Evans blue-albumin or other polymer conjugate by EPR effect[49] in even small metastatic tumor nodules in the lung and the liver, even less than 1 mm or so[49], e. Therefore, EPR effect-based macromolecular chemotherapy can be applied similarly to treatment of metastatic tumors and a complete eradication was seen on day 50 after treatment of metastatic lung cancer in mice (Fig. 4B). This finding, if indeed the EPR effect operates in metastatic tumors with macromolecular drugs it will be a great advance in the history of cancer chemotherapy.

In the clinical setting, surgeons can remove most of the primary or visible tumors, but removing numerous metastatic tumors spread throughout the entire body is most formidable, because many of the metastatic tumors are frequently invisible. They also do not respond to chemotherapy.

In relation to clinical setting, we observed clear uptake of drug in the metastatic

tumor in the liver from stomach cancer. In this case macromolecular SMANCS in Lipiodol, lipid contrast agent, was infused via the intra-hepatic arterial infusion and analyses by X-ray CT scan[30),35)].

Our new polymer conjugates (candidate drug 2), described in the next section, with an apparent size of about 70 kDa with pirarubicin, were effective for treatment of metastatic tumors. Mice with colon 26 tumors implanted in the dorsal skin were all cured, and all metastatic tumor nodules disappeared (Fig. 4B) using SMA polymer conjugate of pirarubicin. It was also found in similarly effective treatment in another metastatic tumor model—MoCR (dimethylhydrazine-induced colon cancer in CBA mice) implanted in the spleen and metastasized to the liver[49)].

6. Photodynamic therapy (PDT) using macromolecular candidate drug 2

As demonstrated in Figure 2 and discussed in Section 1-2-6, conventional low-MW photosensitizer such as Laserphyrin® used in PDT has no tumor selectivity and distributed in the body almost evenly. This means least antitumor effect and adverse effect on the skin even under ambient light. To take advantage of the EPR effect of macromolecular drugs (photosensitizers) and tumor delivery, we have synthesized polymer-conjugated ZnPP (P-ZnPP) (Fig. 6) and obtained