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Combinatorial-Designed Multifunctional Polymeric Nanosystems for Tumor-Targeted Therapeutic Delivery

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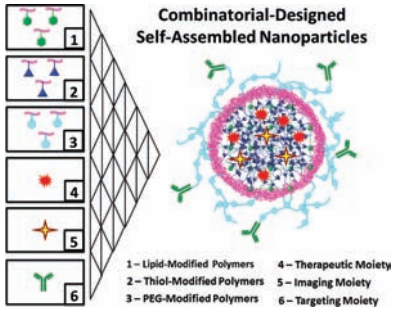

By definition, multifunctional nanosystems include several features within a single construct so that these devices can target tumors or other disease tissue, facilitate in vivo imaging, and deliver a therapeutic agent. Investigations of these nanosystems are rapidly progressing and provide new opportunities in the management of cancer. Tumor-targeted nanosystems are currently designed based primarily on the intrinsic physico-chemical properties of off-the-shelf polymers. Following fabrication, the surfaces of these nanoscale structures are functionalized for passive or active targeted delivery to the tumors.

In this Account, we describe a novel approach for the construction of multifunctional polymeric nanosystems based on combinatorial design principles. Combinatorial approaches offer several advantages over conventional methods because they allow for the integration of multiple components with varied properties into a nanosystem via self-assembly or chemical conjugation. High-throughput synthesis and screening is required in polymer design because polymer composition directly affects properties including drug loading, retention in circulation, and targeting of the nanosystems.

The first approach relies on the self-assembly of macromolecular building blocks with specific functionalities in aqueous media to yield a large variety of nanoparticle systems. These self-assembled nanosystems with diverse functionalities can then be rapidly screened in a high-throughput fashion for selection of ideal formulations, or hits, which are further evaluated for safety and efficacy. In another approach, a library of a large number of polymeric materials is synthesized using different monomers. Each of the formed polymers is screened for the selection of the best candidates for nanoparticle fabrication. The combinatorial design principles allow for the selection of those nanosystems with the most favorable properties based on the type of payload, route of administration, and the desired target for imaging and delivery.

1. Introduction

a. Cancer Challenges and Therapeutic Opportunities. Cancer is one of the most challenging problems in modern medicine. The complexity and heterogeneity of cancer is due to genetic mutations, which allow the cells to adapt to environment and evolve aggressively, with invasive and metastatic potential. These properties present a major obstacle in cancer treatment.[1] For instance, microenvironmental selection pressure leads to acquired multidrug resistance (MDR) phenotype, where tumor is insensitive to conventional treatment regimens.[2] MDR is known to be the major reason for treatment failure in cancer patients.[3] These

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characteristics in turn make it essential for the development of novel therapeutic strategies and tumor-specific drug delivery approaches.

Recent advances in molecular understanding of the processes involved in cancer cells and precise manipulation of materials at the nanometer length scale have paved the way for new investigative tools and molecularly targeted approaches for cancer therapy.[4] With these advances, proteins and genes have been identified as molecular targets for highly specific drugs, while individual cancer profiles help to select the most appropriate therapy. However, both small and marcomolecular (peptides, proteins, pDNA, olegonucleotides, miRNA, and siRNA) drugs often fail to reach target sites because of the inherent physiological barriers that limit their direct entry into the molecular targets of tumor cells.[5] Thus, it is essential to develop delivery systems which can protect the drugs from inactivation in the physiological media, while allowing their transport through biological barriers thereby increasing their availability at the target intracellular compartments. An exciting concept in cancer therapy is the use of multifunctional nanosystems, which have multiple functions: early cancer detection, targeted drug delivery, and monitoring the cancer progression.[6] Many researchers are developing multifunctional nanosystems with the ability to incorporate these functionalities to provide compound effect on tumor site. Because of their combinatorial character, these systems require a suitable construct able to incorporate drugs and accommodate appropriate surface functionalization to enable tumor targeting. The goal of this Account is to present a perspective on a combinatorial-designed nanosystems (CDN) library to provide a framework from which the multifunctional nanosystems can be developed to yield novel, safe, and efficient delivery approaches for cancer therapy.

b. Drug Delivery Strategies: Polymeric Nanosystems in Improving Delivery Efficiency. There has been an explosion of knowledge and commercial interest on the application of nanotechnology-based drug delivery systems for cancer therapy. In this regard, the combinatorial approach can provide a basic framework for fabricating specific nanosystems based on factors such as the drug characteristics, targeting, tumor location, and vascularity. Literature evidence suggests that nanodelivery platforms have shown promising potential in controlling stability, release pattern, altering pharmacokinetic and pharmacodynamics profiles, and lowering toxic effects of cancer therapeuticals.[7] For instance, Doxil, a liposomal formulation of doxorubicin, and Abraxane, a paclitaxel conjugated to albumin, are some of the

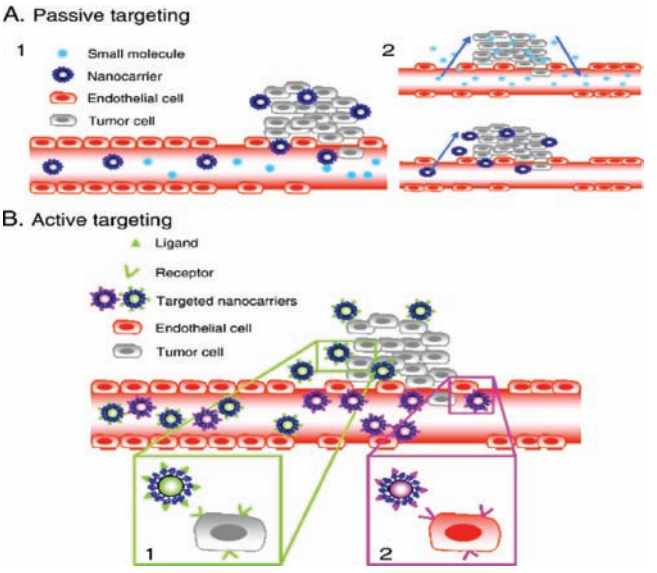

FIGURE 1. Tumor-targeting strategies of nanosystems: (A) Passive targeting: (1) nanosystems reach tumors through the leaky vasculature, (2) effect of cutoff size for retention in the tumor tissue. Drug molecules diffuse freely in and out the tumor blood vessels due to their small size and thus effective drug concentration in the tumor drops rapidly. However, the nanosystem cannot diffuse back into the blood due to their large size, leading to enhanced accumulation, the EPR effect. (B)Active targeting: targeting moiety present on the nanosystem binds to surface receptors expressed by tumor cells. Reprinted from ref 10 with permission from Elsevier.

effective examples of clinically proven nanosystems. The nanosystems not only carry drugs to target cells but also make drugs available to intracellular compartments.[5c,6b] Intracellular distribution is important for many drugs whose sites of action are located in the cytoplasm or the nucleus.[8] For example, pDNA, olegonucleotides, miRNA, siRNA, peptides, and proteins have their targets in the cytoplasm or nucleus; thus, there is a need for these macromolecules to be transported inside the cell.[8] Intracellular targeting using nanosystems is also critical for the delivery of drugs toward resistant and recalcitrant tumor cells equipped with drug efflux pumps such as P-glycoproteins and multidrug resistance proteins, which are responsible for MDR.[9] In such cases, nanoparticle-based delivery systems have been shown to evade the drug efflux pathway, thus increasing the intracellular delivery efficiency of drugs to MDR tumors. Such improved tumor-targeted drug delivery using polymeric nanosystems is accomplished through passive and active tumor targeting strategies (Figure 1).[6b]

Passive targeting relies on the transport of nanosystems through the leaky tumor microvasculature into the tumor interstitium and cells. This is termed as the "enhanced permeability and retention" (EPR) effect, first discovered in murine

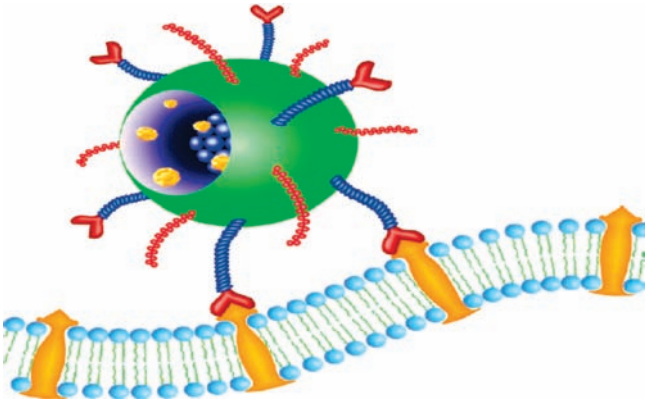

FIGURE 2. Schematic illustration of a multifunctional nanosystem targeting a tumor cell using a targeting moiety specific to a tumor cell surface receptor. The nanoparticle carries an imaging (blue sphere within the core) and therapeutic agent (yellow structures within the core). Reprinted with permission from ref 16a. Copyright 2010 American Chemical Society.

solid tumors for the accumulation of polymer-conjugated drugs by Matsumura and Maeda.[11] The EPR effect can be observed in almost all human solid tumors with the exception of hypovascular tumors (prostate or pancreatic cancer).[12] The EPR effect is now becoming a gold standard for targeting, and all nanosystems use EPR as a guiding principle for tumor targeting.[10] However, the cutoff size of abnormal vasculature may vary from tumor-to-tumor, and the size of the nanosystems can be used to control the passive targeting.[13] In general, nanosystems in the size range of 20−200 nm have been shown to extravagate and accumulate inside the tumor tissues.[10] The EPR effect will be optimal if nanosystems can evade the reticulo-endothelial system (RES) and show prolonged circulation half-life in the blood. In this regard, poly(ethylene glycol) (PEG) grafting of nanosystems provides stealth characteristics and allows for RES escape, thereby rendering long plasma circulation half-life to the delivery system and thus enhancing tumor accumulation. The specificity of passive targeting can be remarkably improved when tumor targeting ligands are used, which can selectively bind to receptors or antigens overexpressed on tumor cells,[14] termed as active targeting (Figure 1). Nanosystems can be surface functionalized with a variety of targeting moieties such as folic acid, arginine-glycine-aspartic acid (RGD), EGFR, and aptamer. To increase the diagnostic yield of current colon cancer screening, in a recent study, we functionalized the gold-colloid-adsorbed and near-infrared fluorescent dye labeled poly(ε-caprolactone) microparticles with RGD peptide that specifically targeted the colon tumors and enhanced the fluorescence imaging contrast.[15] Besides selective targeting, the targeting agents coupled to nanosystems can facilitate transport of many drugs compared to direct conjugation of targeting ligands with drug molecules.

2. Multifunctional Nanosystems for Imaging and Therapy

a. Imaging and Therapeutic Nanosystems. Multifunctional nanosystems, which combine targeting, imaging, and drug delivery capabilities, termed as theranostics, hold tremendous promise in cancer therapy (Figure 2).[16] Assuring that the entrapped drug is being released and monitoring its biodistribution pattern, and understanding and predicting the effectiveness of the treatment are some of the advantages in codelivering imaging and therapeutic agents with their ultimate utility in simultaneous disease diagnosis and treatment.[17] This multifunctional nanosystem approach offers new possibilities toward the development of personalized medicine, the conceptual reform in medicine to treat each patient based on individual profile. Polymer nanosystems, liposomes, micelles, and dendrimers represent the major multifunctional polymeric nanosystems being explored in cancer therapy. Nuclear imaging (PET/SPECT), optical imaging, magnetic resonance imaging, computed tomography, and ultrasound play vital roles as imaging modalities in multifunctional nanosystems.[18]

b. Illustrative Examples of Multifunctional Polymeric Nanosystems. The theranostic micelle nanosystem incorporates drugs in its hydrophobic domain and readily carries targeting and imaging agents on the surface, which has tremendous potential in cancer therapy. Polymeric micelles are nanosized spherical supramolecular particles formed from the self-assembly of amphiphilic block copolymers in water.[19] In an aqueous environment, the hydrophobic portion of the block copolymer self-associates into a semisolid core, with the hydrophilic portion of the copolymer forming a coronal layer. Incorporation of drug and contrast agents can be done by conjugating to the polymer prior to the formation or entrapping within the hydrophobic core of the micelle.[20] For the folate receptor targeted delivery of doxorubicin, polymeric micelles prepared from a self-assembled poly(D,L-lactic-*co*-glycolic acid) (PLGA) and PEG diblock copolymer have been used with intrinsic fluorescence properties of doxorubicin for imaging. Doxorubicin was chemically conjugated to a terminal end of PLGA, and folate was separately conjugated to a terminal end of PEG. The two diblock copolymers with different functional moieties at their chains ends were physically mixed with free base doxorubicin in an aqueous solution to form mixed micelles with folate exposed on the micellar surface, while doxorubicin was physically entrapped in the core of micelles.[21] In another example, near-IR quantum dot (QD) entrapped micelles

prepared using PEG-PCDA (10,12-pentacosadiynoic acid) and PCDA-herceptin conjugates with imaging and target-specific properties have shown high antitumor activity and selective toxicity.[22]

Liposomes are one of the extensively investigated formulations for the incorporation of targeting, imaging, and drug delivery capabilities. They are vesicles composed of amphiphilic phospholipids, which self-assemble into bilayers resembling tiny cells with a cell membrane having central aqueous space.[23] The amphiphilic phospholipid molecules form a closed bilayer by shielding their hydrophobic groups from the aqueous environment and simultaneous contact with the aqueous phase via the hydrophilic headgroup. Liposomes have the capacity to encapsulate both hydrophobic and hydrophilic drugs in the phospholipid bilayer, in the entrapped aqueous volume, or at the bilayer interface. Modification of Doxil with the monoclonal nucleosome (NS)-specific 2C5 antibody (mAb 2C5) that recognizes a broad variety of tumors via the tumor cell surface-bound NSs has increased the cytotoxicity of the liposomes toward tumor cells.[24] Gadolinium and QDs enclosed in the aqueous interior or chelated in the liposomal bilayer have been used as common contrast agents for labeling liposomes.[25]

Dendrimers are repeatedly branched polymeric nanoparticles with a nearly prefect three-dimensional structure that can be controlled in size, shape, and terminal group functionality. These spherical nanostructures with cavities can be synthesized by polymerization with either divergent or convergent methods. Polyamidoamine (PAMAM) dendrimer conjugated to recombinant fibroblast growth factor-1 for tumor targeting and fluorescein isothiocyanate for imaging has been shown as a suitable platform for the targeted delivery of chemotherapeutic drugs.[26] In another study, 5-fluorouracil encapsulated PAMAM dendrimers with folic acid modified dendritic surface produced site-specific enhanced drug localization.[27]

3. Combinatorial-Designed Nanosystems (CDN)

a. Rationale for Combinatorial Approach. The use of traditional, ``one polymer-at-a-time'' approaches have been time-consuming and require large amounts of resources for the necessary optimization of these systems for their intended therapeutic applications. The development of comprehensive and highly flexible platforms that can be customized to suit the specific disease target, imaging modality, and therapeutic outcome is needed, and the use of combinatorial design principles are useful in realizing this purpose. The rationale behind CDN is based on the following factors:

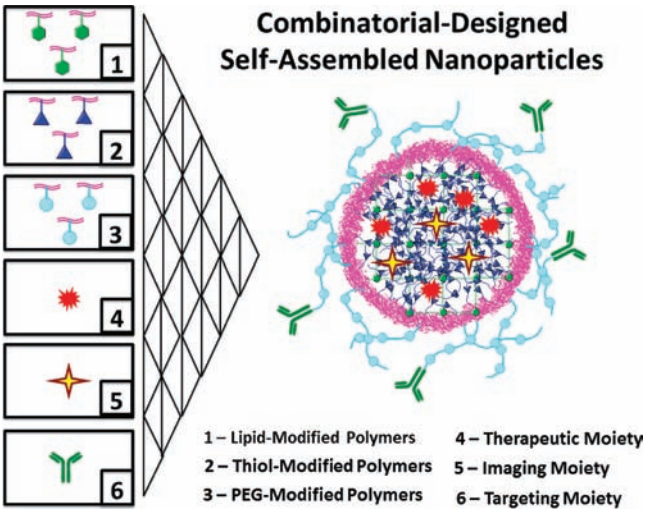

FIGURE 3. Schematic describing the high-throughput "mix and match" methodology for screening multifunctional polymeric nanosystems for drug delivery.

(1) to help optimize the payload of therapeutic and diagnostic agents with different physicochemical properties;
(2) to provide the modular platform which can allow for "mix and match" type screening for the "right" nanosystem based on several factors such as encapsulation efficiencies of drugs, stability of the payload and delivery systems, and choice of molecular targets of interest;
(3) to help in controlling size, charge, and nanoparticle surface functionalization yielding a synergistic combination of passive and active targeting ability with the advantage of having a long plasma residence time without being degraded or eliminated from the bloodstream;
(4) to provide basis for rapid fabrication of nanosystems for personalized therapy.

This combinatorial design will allow fabrication of libraries of multifunctional nanosystems as illustrated in Figure 3, and will enable investigation of the effect of nanosystem materials on the drug encapsulation efficiency, biocompatibility, and therapeutic efficacy. To improve the properties of nanosystems which are dependent on the individual polymeric block (Figure 3, polymer blocks 1, 2, or 3) present in the nanosystem, high-throughput polymer synthesis and screening is needed to triage the suitable polymer blocks. The use of a combinatorial approach will lead to a more in-depth understanding of the structure–property relationship between polymeric nanosystem materials and the multiple steps in the nanosystem screening process, ranging from

fabrication to arriving at potential candidates. This will therefore help expedite the rational design and development of multifunctional nanosystems in cancer therapy.

The following section will discuss recent high-throughput methods for synthesizing polymer libraries using the combinatorial-design approach for application in drug and gene delivery.

b. Combinatorial Polymer Synthesis. Based on the use of combinatorial synthesis in the drug discovery paradigm, there has been strong interest in using this strategy for designing novel polymeric materials for biomedical application. A number of researchers have examined combinatorial synthesis in the development of biomaterials and nanosystems, such as poly(β-amino ester)s and lipidoid libraries developed largely by the Langer group at MIT for delivery of plasmid DNA and siRNA. On the other hand, strategies to use functional macrostructures, akin to LEGO blocks, that can be assembled into diverse nanosystems to match the needs of the payload and biological target are a novel concept that is being investigated in our laboratory.[28] We are developing a comprehensive and flexible dextran-based polymeric nanosystem platform that can be customized to encapsulate oligonucleotides and/or therapeutic drugs with varying physicochemical properties.[28] Individual functional blocks having (1) lipid chains for self-assembly, (2) thiol groups for intermolecular cross-linking, and (3) PEG for surface functionalization are synthesized from dextran with controlled functionalization by "click" chemical conjugation method (unpublished results).[28c] With the use of combinatorial-design principles, representative anticancer drugs having different physicochemical properties (anthracyclines, topoisomerase inhibitors, and taxanes) were encapsulated using different combinations of functional blocks. The optimized nanosystems showed higher therapeutic activity against SKOV3 human ovarian adenocarcinoma cells (unpublished results).[28c] The advantage of our approach is that it allows for synthesis of limited and more manageable macrostructures (e.g., 50−100 of each), which can be purified and characterized prior to aqueous assembly into CDN. At least three of the functional blocks are required to make the nanosystems. The library is designed based on selection of appropriate component and weight ratio of each in the final nanoassembly. This diversity is dictated by the physicochemical property of the payload. For example, a hydrophilic core will allow for efficient siRNA and hydrophilic drug encapsulation, while a hydrophobic core will support encapsulation of hydrophobic drugs such as paclitaxel. Intermolecular disulfide cross-linking using thiol-modified dextran polymers allows for development of nanosystems that can remain stable in the systemic circulation but dissociate in the highly reducing environment of the tumor cell. Additional versatility in the development of this concept is the possibility of inclusion of near-IR fluorescence label and/or DTPA-conjugated dextran for chelating radiolabels such as indium-111 (^{111}In) for qualitative and quantitative imaging and in vivo biodistribution studies. Furthermore, this system is amenable to inclusion of additional functional modules, such as cell penetrating peptide (e.g., HIV Tat) or basic functional groups (e.g., histidine residues) that enhance endosomal/lysosomal escape, if needed.

Anderson et al. developed the first combinatorial library of degradable photo-cross-linked polymeric materials which could be used for a wide array of applications.[29] A library of acrylate-terminated poly(β-amino ester)s using condensation reaction that combined primary or secondary amines with diacrylates was created. For this purpose, 12 different amines and 10 diacrylates monomers were used, which resulted in a diverse library of 120 photopolymerizable macromers. The library of macromers was then photopolymerized to form degradable networks, with a wide range of degradation times ranging from less than a day to a few months,[29] ideal for controlled drug delivery applications. In a similar study, Vogel et al. have demonstrated that combinatorial synthesis using polycondensation reactions could be applied for designing polymer libraries.[30] The resulting polyanhydride copolymer library was based on 1,6-bis(*p*-carboxyphenoxy)hexane and sebacic anhydride. These polymers showed promising potentials as drug carriers for controlled delivery.[30]

Although numerous researchers have demonstrated the prospects of combinatorial polymer synthesis,[30,31] Langer's group at MIT was the first to introduce parallel synthesis and screening of a degradable polymer library for gene transfection.[32] The library consisted of 140 degradable polymers, and several of them had the ability to condense DNA into nanosystems that could internalize into cells and release the intact DNA. Anderson et al. from the same group were also the first to utilize a semiautomated high-throughput screening method for the synthesis of a large library of polymers for gene delivery applications (Figure 4).[33] In this case poly(β-amino ester)s were used as delivery agents which generally possess low cytotoxicity and could be easily synthesized by the conjugate addition of a primary amine or bis(secondary amine) to a diacrylate. A unique advantage of this method was that the synthesis of the polymers and their testing could be performed in "one-pot" without the need for

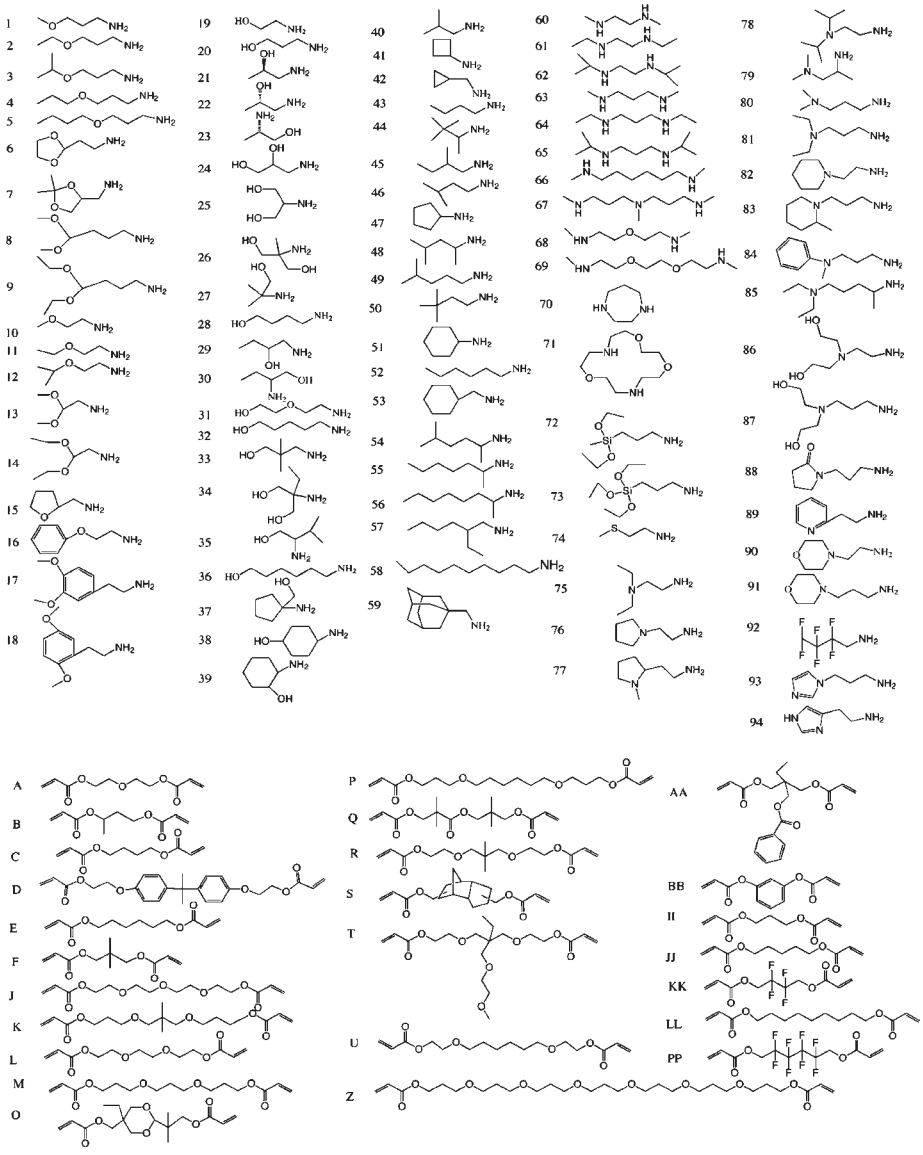

FIGURE 4. Amino (numbers) and diacrylate (letters) monomers used for the synthesis of diverse poly(β-amino esters) for gene delivery application. Reprinted with permissions from ref 33. Copyright Wiley VCH.

purification or solvent removal, thus allowing for large library screens with minimum steps involved. By this method, a large library of 2350 cationic polymers could be synthesized and tested for their transfection ability at a rate of about 1000 per day.[34] These methods developed in Langer's laboratory are not limited to gene delivery, but can be more broadly applied toward the identification of materials for nucleic acid, protein, peptides, and small molecular drug delivery in general.

Another approach in Langer's laboratory reported a high-throughput combinatorial screening method for encapsulating siRNA by synthesizing novel lipidlike materials termed "lipidoids".[34] Simple Michael type addition reaction was used to arrive at 1200 lipidoid compounds that were structurally diverse. These compounds were derivatives of amino-alkyl-acrylate and -acrylamide. From this library screening, specific lipidoids were identified which could exhibit high transfection efficiencies with single stranded antisense 2′-*O*-methyl oligoribonucleotides as well as siRNA. Further studies by the same group expanded the combinatorial library of diacrylates and amines with more diversity in molecular weights.[35] The new data from this study indicated that poly(β-amino esters) could be useful nanosystem for gene therapy applications in cardiovascular disease and cancer. Additional work in this direction also yielded several derivatives that showed highly improved transfection ability both in vitro and in vivo settings.[35]

In order to reduce the toxicity of poly(ethylene imine) (PEI) and to exploit its ability to complex nucleic acids,

Thomas et al. developed a library of 144 biodegradable derivatives of PEIs with oligo-acrylate esters.[36] From the screenings, it was found that some of the least toxic derivatives from the library showed promising hits for high transfection in vitro and in vivo in comparison to a linear PEI of 22 kDa molecular weight. In another recent report, Barua et al used ring-opening polymerization reaction between epoxide groups of diglycidyl ethers and the amines of (poly)-amines for the parallel synthesis and screening of a cationic polymer library for gene delivery application.[37] Lead candidate polymers, that showed moderate to significantly higher transfection efficacies and lower cytotoxicity than PEI, were identified from this study. These library screens show promise for furthering gene delivery applications utilizing combinatorial designed screening methods.

In yet another novel combinatorial approach for nucleic acid delivery, Murphy et al. synthesized a library of cationic N-substituted glycine oligomers with varying chain lengths, hydrophobicity, side-chain makeup, and charge densities in order to facilitate delivery and transfection.[38] An oligomer with 36 units containing 12 amino-ethyl side chains was identified from this screening which showed matching transfection efficiencies to commercial transfection agents. However the most interesting feature was that the derivatives were not only stable in serum but also resistant to proteases heralding an ear of combinatorial polymeric library screening for new class of materials for gene delivery applications.

4. Issues to Consider in Combinatorial-Designed Nanosystems

a. Nanomaterial Safety Considerations. Multifunctional nanosystems are often built using composites of polymeric constructs with varied characteristics, created using complex synthetic methods. Because of the complexity involved, nanosystems may be associated with toxicity concerns, and the majority of the work has to be done in terms of determining their safety and long-term effects on biological system. For example, cationic lipids such as 1,2-dioleoyl-3-trimethylammonium-propane and *N*-[1-(2,3-dioleoyloxy)propyl]-*N*,*N*,*N*trimethyl-ammonium methyl sulfate are attractive materials due to their electrostatic interaction with negatively charged nucleic acid therapeutics forming lipoplexes. However, these lipids have been shown to induce immune response,[39] and cationic lipid containing liposomes can alter gene expression,[40] raising concerns about safety. These effects were considered as charge related, use of neutral lipids such as 1,2-dioleoyl-snglycero-3-phosphatidylcholine in the liposomes might mitigate such toxicities.[41] In other examples, based on the type of monomer blocks used in the preparation of polymeric micelles, some systems produce immunological reactions and cytotoxicity,[42] or gene expression in certain cells.[43] RES uptake of nanosystems also presents potential toxicity in the liver and spleen.[44]

The above conceptual understanding could allow the design of nanosystems with desired surface properties while being biocompatible and showing predictable systemic clearance. Regulatory guidance is not yet fully available regarding the use of nanosystems in the clinical setting from the U.S. Food and Drug Administration or other agencies. However, some consensus has evolved regarding the testing of nanosystems safety in model systems. In vitro cell viability assays could be used for preliminary toxicity screening of combinatorial-designed novel polymeric blocks. On the other hand, the in vivo system provides true dynamic conditions and active immunizing components for testing the biocompatibility of polymeric materials and CDN derived from those polymeric libraries. However, precaution must be taken when translating data obtained from animal models to a clinical setting, because there is always a risk of intra- and interspecies difference.

b. Scale-Up and Manufacturing under cGMP. Scale-up is defined as technology transfer of product from lab scale to manufacturing scale with concurrent increase in manufacturing output. The scale-up of nanosystems with negligible batch-to-batch variation is more complex than bulk manufacturing of traditional formulations because of multiple steps involved in the production of nanosystems. Besides, lack of clear information about the properties of polymeric building blocks at lab and production scales contributes significantly to scale-up issues. Moreover, the complex process involved in fabrication of nanosystems is a major obstacle in bulk production for clinical applications. The bulk manufacturing of nanosystems also needs to meet regulatory guidelines to translate them successfully from the research side to clinical use. Current Good Laboratory and Manufacturing Practice (cGLP/cGMP) guidelines are framed by the U.S. Food and Drug Administration for the manufacturing of products used for clinical purpose. These guidelines essentially focus on reproducible manufacture of products under organized quality control systems. GLP framework is important not only for validating analytical methods to check the identity, strength, and the stability of nanosystems in preclinical development but also for their clinical translation. It also helps in ensuring complete and thorough characterization of nanomaterials

and nanosystems covering issues related to preclinical evaluation. It also ensures all the methods are in line with the IND requirements.

5. Conclusions

In this Account, we have described the current status of multifunctional polymeric nanosystems as an emerging powerful tool for cancer therapy. We have highlighted the need for the development of combinatorial approaches in designing and synthesizing nanosystems as a means for targeted drug and gene delivery. Combinatorial approaches have several advantages over conventional methods in integrating multiple components with varied properties into a nanosystem via self-assembly or chemical conjugation. Many properties including drug loading, retention in circulation and targeting of the nanosystems depend on the polymer composition, and therefore, high-throughput synthesis and screening is required in polymer designing. The self-assembled polymeric nanosystems based on a modular "mix and match" methodology to arrive at desired functions will open up a new avenue in cancer therapeutics with the added advantage of versatile choice of materials with diverse properties. Although there are many exciting potential applications of multifunctional polymeric nanosystems for drug and gene delivery, considerable challenges and issues remain to be resolved. For example, nanosystem associated toxicity remains a major problem, and it can be addressed by identifying suitable biocompatible and biodegradable materials. Identification of such materials using a combinatorial library approach thus turns out to be a more viable and versatile strategy for the development of novel nanosystems for successful cancer therapy.

BIOGRAPHICAL INFORMATION

Sampath C. Abeylath, PhD is a Postdoctoral Research Fellow in the laboratory of Professor Amiji in the Department of Pharmaceutical Sciences, School of Pharmacy at Northeastern University. He received his Ph.D. in Organic Chemistry under the supervision of Prof. Edward Turos at University of South Florida. His research interests are drug delivery applications of polymeric nanomaterials.

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Arun K. Iyer, PhD is currently an Associate Research Scientist working in the laboratory of Professor Amiji in the Department of Pharmaceutical Sciences, School of Pharmacy at Northeastern University. He received his Ph.D. in Polymer Chemistry under the supervision of Prof. Hiroshi Maeda at Sojo University in Japan, and completed his postdoctoral training at the Department of Radiology and Biomedical Imaging at the University of California, San Francisco. He has a broad research interest in the area of polymeric biomaterials, biomedical imaging, nanomedicine, and nanotechnology with an emphasis on polymeric drug and gene delivery systems.

Mansoor M. Amiji, PhD is Distinguished Professor and Chairman of the Pharmaceutical Sciences Department and Co-Director of Northeastern University Nanomedicine Education and Research Consortium (NERC). He received his undergraduate degree in Pharmacy from Northeastern University in 1988 and his Ph.D. in Pharmaceutics from Purdue University in 1992. His areas of specialization and interest include polymeric biomaterials, advanced drug delivery systems, and nanomedical technologies.

FOOTNOTES

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