Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

J Control Release. Author manuscript; available in PMC 2015 October 13.

Published in final edited form as:

J Control Release. 2011 October 30; 155(2): 116–118. doi:10.1016/j.jconrel.2011.03.023.

Biomaterials to gene delivery

Sung Wan Kim*

Department of Pharmaceutics, Pharmaceutical Chemistry, University of Utah, 20 South 2030 East, Salt Lake City, Utah 84112-5820, United States

Abstract

It has been over 40 years since I started biomaterials research. This article is a short summary of past research in my laboratory.

Keywords

Gene delivery; Biomaterials

I worked on protein absorption at the beginning. At the same time I characterized various polymer membranes which were candidates for the use in artificial kidneys. I published several papers on protein absorption and found out more thrombo-genic polymer with absorption of larger amounts of fibrinogen and γ-globulin. [1] Larger amounts of platelet adhesion and aggregation were observed to relate more thrombogenic surfaces. This phenomena was explained by glycosyl transferase enzyme reaction [2]. It was later found to be wrong after receptors were identified. However, this albumin theory has been well accepted by blood clotting group and demonstrated in dog experiments which were carried out using heparin-PEG-polyurethane. In dog experiments, heparin-PEG-polyurethane showed thinner protein absorption (used 6 mm graft) especially smaller amounts of fibrinogen and γ-globulin with thickness less than 300 Å. The dogs survived long than 6 months. On the contrary, polymer without heparin deposited ~ 2000 Å thickness layer with layer amount fibrinogen and γ-globulin. All dogs died in a couple of weeks due to the occlusion of vascular grafts [3,4].

Perhaps the first drug conjugation to polymer was performed in this laboratory. We used polyglutamate and conjugated contraceptive norethindrone by spacer and delivered it for a year [5], this concept was extended to delivery of naltrexone [6] and clonidine [7].

We designed polymer surfaces grated with heparin and prostaglandin, which was superior to other approaches for nonthrombogenic surfaces [8]. Tri-block and multi-block copolymers were synthesized and used in Utah100 TAH.

In mid 1980, we created a new area called self-regulated drug delivery. We modified insulin by glycosylation, bounded them to ConA and encapsulated. Insulin release depends on an

* Tel.: + 1 801 581 6654; fax: + 1 801 581 7848. SW.Kim@pharm.utah.edu..

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

outside glucose concentration. We have studied many *in vitro* and *in vivo* experiments using pancreatectomized dogs. The work was completed beautifully [9,10].

Stimuli sensitive polymer was introduced for the first time in this laboratory. NiPAAm was shown thermosensitivity and showed deswelling at 37 °C [11]. The copolymer of NiPAAm demonstrated on and off drug delivery [12].

An electro erodible polymer was designed by using intermolecular interaction between poly(ethyloxazoline) and poly(methalcrylic acid). Surface erosion of this complex polymer released loaded insulin when 10 mA of electric current was applied. The insulin release stopped when the current was turned off [13].

The concept of thermosensitive polymer was extended to biodegradable polymer [14]. This pioneering work was utilized for the design of Regel which is PLGA-PEG-PLGA triblock polymer. Paclitaxol loaded Regel (Oncogel) is now in phase II human clinical trials for the treatment of esophageal cancer.

In 1997, we began polymeric gene delivery research. The rational for polymeric gene delivery included a versatile design; no integration into the host chromosome and, it was non-immunogenic and nontoxic. The designed system can be used for repeated injection and is easy for reproducible pharmaceutical products. The main concerns were low transfection and efficacy compared to viral delivery systems. The construction of various polymers to demonstrate effective efficacy was carried out and has been continued. The initial design was called the Terplex Gene Delivery System, which, consisted of hydropholized poly-L-lysine bond to lipoprotein. This formed a stable complex with the plasmid DNA [15]. The Terplex system injected DNA into a rabbit's left ventricle, and showed significantly longer retention in the vascular space than naked DNA [16,18].

The first new biodegradable polymer for gene delivery was synthesized and characterized. The system was an analogue of polylysine and this polyamino butyl glycolic acid, which is degradable and non-toxic [17]. Among many synthesized polymers, one characteristic of polymer is water soluble lipopolymer (WSLP). The WSLP utilized low molecular weight PEI (M = 1800) [18]. This polymer presented effective results for IL-12 delivery, especially when it was delivered with paclitaxel tumor, as the cell did not grow at all [19]. The IL-12 delivery system, with a minor modified WSLP, is currently under phase II clinical study for ovarian cancer treatment. In addition, this polymer was used for the treatment of myocardial infarct using hypoxia PRT801-VEGF gene [20]. Four weeklong rabbit experiments showed the ligated left ventricle infarcted area at 48%, WSLP/SV-VEGF at 32%, and WSLP/ RTP801-VEGF at 13%.

New bioreducible cationic polymer, poly(cystamine bisacrylaimidediamino hexyl) and it's derivatives were synthesized. These polymers from a strong complex with gene ad stable blood circulation. After entering the cells, they break the endosomal membrane and are degraded in cytostome by breaking the disulfide bond by means of glutathione enzymes [21,22]. This polymer carried VEGF modified skeletal myoblasts and significantly reduced scar formation in ischemic myocardium. Rat experiments presented infarct percent with

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

ligation at 35%, myoblast injection at 15% and VEGF transfected myoblast at only 5% [23,24].

Various other targeted gene delivery systems were completed. They include the use of targeted ligand lactose, [25] galactose, [26] folate, [27] RGD, [28] PGE2, [29] PCM, [30] and Ephrin a2 [31].

RGD-PEG-PEI was synthesized [28] targeting PEI-g-1kPEG-RGD conjugates which significantly increased the luciferase reporter gene expression in angiogenic HDMEC. However, in angiostatic HDMEC, the luciferase gene expression with targeting PDI-g-1PEG-RGD is similar to that with non-targeting PEI-1PEG-RAE. The tumor accumulation of PEI-g-PEG-RGD/PMCV-SFlt-1 was 25 times higher than PEI-g-PEG/PMCV-SFlt-1.

The tumor volume growth profile is the lowest with PEG-PEG-RGD/PCMV-SFlt-1 and the survival profile was greatly extended using this system [31].

PGE2-Fas SiRNA polyplex formulation efficiently inhibited Fas gene expression in a rat cardiomyocyte model by targeting ligands in a specific manner. It was found that PGE2-SiRNA polyplex delivery can be successfully used in the application of SiRNA therapeutics for the treatment of cardiovascular diseases [29].

In the next two projects described were new innovative ideas for SiRNA delivery. Chol-R9 conjugate was synthesized. Both images of tumors and inhibition of tumor growth were impressive and showed significant reduction of intratumor VEGF contents by SiRNA delivery which was observed [32].

A SiRNA-S-S-PEG-PEC micelle delivery system was designed. Disulfide bonds break down in cytosome and release SiRNA. Tumor growth curve following intratumoral injection showed a small volume tumor growth. In addition, tumor growth following intravenous injection also showed very small tumor volume growth [33]. This study demonstrated the feasibility of using PEG/PEC micelle as a potential carrier for therapeutic siRNA in local as well as systemic treatment of cancer.

Biodegradable polymer, polyaminobutyl glycolic acid (PAGA) was synthesized. This polymer is an analog of polylysine, which is not degradable. Due to its degradation property it showed no toxicity. Diabetic mice were used to treat with IL-10 plasmid. Eight weeks of animal studies demonstrated less than 10% had insulitis when they were treated with IL-10 loaded in PAGA [33].

GLP-1 gene therapy for type II diabetes was attempted. The nuclear factor Kappa β was introduced in plasmid. The efficacy of the GLP-1 plasmid was proved both in vitro and in vivo [34,35].

Fas siRNA suppresses cyclophosphamide induced diabetes in a mice model. Systemic administration of Fas siRNA/PEI complexes suppressed insulitis in NOD mice. In addition, prevention of islet apoptosis in NOD mice was observed with Fas siRNA/PEI. The incidence of diabetes with Fas siRNA/PEI showed practically nothing [36]. EphA2 targeting

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

peptide was conjugated in CBA/DAH for delivery of PCMV-REA-1Y to pancreatic islet. This work is currently under way.

Oncolytic adenovirus has been studied for many years as a cancer treatment. Although it worked well, the stability and immunogenicity has been a strong concern for its use. Recently, arginine grafted bioreducible polymer has been used to form a complex with adenovirus and promote transduction efficiency and reduce immunogenicity in cancer gene therapy [37].

Acknowledgements

S.W. Kim thanks NIH grants CA107070, HL056477, DK077703 & DK085075. He appreciates the approximately 150 scientists that have worked with him over the past 40 years. Not all of their works are listed here, but S.W. Kim is indebted to them.

References

[1]. Lee RG, Kim SW. Adsorption of proteins onto hydrophobic polymer surfaces: adsorption, isotherms and kinetics. J. Biomed. Mater. Res. 1974; 8:51.

[2]. Kim SW, Lee RG, Oster H, Coleman D, Andrade JD, Lentz DJ, Olsen D. Platelet adhesion to polymer surfaces. Trans. Am. Soc. Artif. Intern. Organs. 1974; 20:449. [PubMed: 4141527]

[3]. Park KD, Okano T, Nojiri C, Kim SW. Heparin immobilization onto segmented poly-urethaneurea surfaces-effect of hydrophilic spacers. J. Biomed. Mater. Res. 1988; 22:977. [PubMed: 3241011]

[4]. Grainger D, Feijen J, Kim SW. Poly(dimethylsiloxane)-poly(ethylene oxide)-heparin block copolymers i: synthesis and characterization. J. Biomed. Mater. Res. 1988; 22:231. [PubMed: 3360815]

[5]. Petersen RV, Anderson JM, Anderson CG, Fang SM, Feijen J, Gregonis DE, Mitra S, Kim SW. Baker R. Controlled release of progestins from poly(α-amino acid) carrier. Proceedings 6th international Symposium on Controlled Release of Bioactive Agents. 1980:I–21.

[6]. Negishi A, Bennett D, Jeong SY, Van Heeswijk W, Feijen J, Kim SW. Coupling of naltrexone to biodegradable poly (a-amino acids). Pharm. Res. 1987; 4:305. [PubMed: 3508536]

[7]. Bennett DB, Adams NW, Li X, Feijen J, Kim SW. Drug-coupled poly(amino acids) as polymeric prodrugs. J. Bioact. Compat. Polym. 1988; 3:44.

[8]. Jacobs H, Okano T, Lin JY, Kim SW. PGE_1-heparin conjugate releasing polymers. J. Control. Release. 1985; 2:143.

[9]. Seminoff LA, Olsen GB, Kim SW. A self-regulating insulin delivery system I. Characterization of a synthetic glycosylated insulin derivative. Int. J. Pharm. 1989; 54:241.

[10]. Holmberg DL, Gleeson JM, Wilson DE, Mack EJ, Kim SW, Pai CM, Makino K, Seminoff LA. Self-regulated glycosylated insulin delivery. J. Control. Release. 1990; 11:193.

[11]. Bae YH, Okano T, Hsu R, Kim SW. Thermo sensitive polymers as on–off switches for drug release. Makromol. Chem. Rapid Commun. 1987; 8:481.

[12]. Bae YH, Okano T, Kim SW. A new thermo-sensitive hydrogel: interpenetrating polymer networks from n-acryloylpyrrolidine and poly(oxyethylene). Makromol. Chem. Rapid Commun. 1988; 9:185.

[13]. Kwon IC, Bae YH, Kim SW. Electrically erodible polymer gel for controlled release of drugs. Nature. 1991; 354:291. [PubMed: 1956379]

[14]. Jeong B-M, Bae Y-H, Lee D-S, Kim SW. Biodegradable block copolymers as injectable drug-delivery systems. Nature. 1997; 388:860. [PubMed: 9278046]

[15]. Kim J-S, Kim BI, Maruyama A, Akaike T, Kim SW. A new non-viral dna delivery vector: the terplex system. J. Control. Release. 1998; 53:175. [PubMed: 9741925]

[16]. Choi YH, Liu F, Kim JS, Choi YK, Park JS, Kim SW. Polyethylene glycol-grafted poly-l-lysine as polymeric gene carrier. J. Control. Release. 1998; 54:39. [PubMed: 9741902]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

[17]. Lim Y-B, Kim C-H, Kim K, Park JS, Kim SW. Development of a safe gene delivery system using biodegradable polymer, poly[α-(4-aminobutyl)-L-glycolic acid]. J. Am. Chem. Soc. 2000; 122:6524.

[18]. Mahato RI, Lee M, Han S-O, Maheshwari A, Kim SW. Intratumoral delivery of p2CMVmIL-12 using water-soluble lipopolymers. Mol. Ther. 2001; 4:130. [PubMed: 11482984]

[19]. Janat MM, Yockman JW, Furgeson D, Lee M, Kern S, Kim SW. Combination of local, nonviral IL-12 gene therapy and systemic paclitaxel treatment in a metastatic breast cancer model. Mol. Ther. 2004; 9:829. [PubMed: 15194049]

[20]. Yockman JW, Choi D, Whitten MG, Chang C-W, Kastenmeier A, Erickson H, Albanil A, Lee M, Kim SW, Bull DA. Polymeric gene delivery of ischemia-inducible VEGF significantly attenuates infarct size and apoptosis following myocardial infarct. Gene Ther. 2009; 16:127. [PubMed: 18784748]

[21]. Christensen LV, Chang C-W, Kim WJ, Kim SW. Reducible poly(amido ethylenimine)s designed for triggered intracellular gene delivery. Bioconjug. Chem. 2006; 17:1233. [PubMed: 16984133]

[22]. Ou M, Wang X-L, Xu R, Chang C-W, Bull DA, Kim SW. Novel biodegradable poly(disulfide amine)s for gene delivery with high efficiency and low cytotoxicity. Bioconjug. Chem. 2008; 19:626. [PubMed: 18314939]

[23]. Nam HY, McGinn A, Kim PH, Kim SW, Bull DA. Primary cardiomyocyte-targeted bioreducible polymer for efficient gene delivery to the myocardium. Biomaterials. 2010; 31:8081, 8087. [PubMed: 20674007]

[24]. McGinn AN, Nam HY, Ou M, Hu N, Straub CM, Yockman JW, Bull DA, Kim SW. Bioreducible polymer-transfected skeletal myoblasts for VEGF delivery to acutely ischemic myocardium. Biomaterials. 2011; 32:942. [PubMed: 20970850]

[25]. Choi YH, Liu F, Choi JS, Park JS, Kim SW. Characterization of a targeted gene carrier, lactose-polyethylene glycol-grafted poly-L-lysine, and its complex with plasmid DNA. Hum. Gene Ther. 1999; 10:2657. [PubMed: 10566893]

[26]. Sagara K, Kim SW. A new synthesis of galactose-poly(ethyleneglycol)-polyethylenimine for gene delivery to hepatocytes. J. Control. Release. 2002; 79:271. [PubMed: 11853937]

[27]. Benns JM, Maheshwari A, Furgeson DY, Mahato RI, Kim SW. Folate-PEG-folate-graft-polyethylenimine-based gene delivery. J. Drug Target. 2001; 9(2):123. [PubMed: 11697107]

[28]. Suh W, Han S-O, Yu L, Kim SW. An angiogenic, endothelial-cell-targeted polymeric gene carrier. Mol. Ther. 2002; 6:664. [PubMed: 12409265]

[29]. Kim SH, Jeong JH, Ou M, Yockman JW, Kim SW, Bull DA. Cardiomyocyte-targeted siRNA delivery by prostaglandin E(2)-Fas siRNA polyplexes formulated with reducible poly(amido amine) for preventing cardiomyocyte apoptosis. Biomaterials. 2008; 29:4439. [PubMed: 18725170]

[30]. Nam HY, McGinn A, Kim PH, Kim SW, Bull DA. Primary cardiomyocyte-targeted bioreducible polymer for efficient gene delivery to the myocardium. Biomaterials. 2010; 31(31):8081. [PubMed: 20674007]

[31]. Kim WJ, Yockman JW, Jeong JH, Christensen LV, Lee M, Kim YH, Kim SW. Anti-angiogenic inhibition of tumor growth by systemic delivery of PEI-g-PEG-RGD/pCMV-sFlt-1 complexes in tumor-bearing mice. J. Control. Release. 2006; 114:381. [PubMed: 16884805]

[32]. Kim WJ, Christensen LV, Jo SB, Yockman JW, Jeong JH, Kim Y-H, Kim SW. Cholesteryl-oligoarginine delivering vascular endothelial growth factor siRNA effectively inhibits tumor growth in colon adenocarcinoma. Mol. Ther. 2006; 14:343. [PubMed: 16765648]

[33]. Koh JJ, Ko KS, Han SO, Lee MH, Park JS, Kim SW. Degradable polymeric carrier for the delivery of IL-10 plasmid DNA to prevent autoimmune insulitis of NOD mice. Gene Ther. 2000; 7:2099. [PubMed: 11223991]

[34]. Oh S, Lee M, Ko KS, Choi S, Kim SW. GLP-1 gene delivery for the treatment of type 2 diabetes. Mol. Ther. 2003; 7:478. [PubMed: 12727110]

[35]. Choi S, Oh S, Lee M, Kim SW. Glucagon-like peptide-1 plasmid construction and delivery for the treatment of Type 2 diabetes. Mol. Ther. 2005; 12:885. [PubMed: 16039908]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

[36]. Jeong JH, Kim SH, Lee M, Kim WJ, Park TG, Ko KS, Kim SW. Non-viral systemic delivery of Fas siRNA suppresses cyclophosphamide-induced diabetes in NOD mice. J. Control. Release. 2010; 143(1–2):88. [PubMed: 20004692]

[37]. Kim P-H, Kim T-i. Yockman JW, Kim SW, Yun C-O. The effect of surface modification of adenovirus with an arginie-grafted bioreducible polymer on transduction efficiency and immunogenicity in cancer gene therapy. Biomaterials. 2010; 31(7):1865. [PubMed: 19962189]