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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

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ABSTRACT

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

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 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 non-toxic. 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

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

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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 bisacrylaimide-diamino 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 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 peptide was conjugated in CBA/DAH for delivery of PCMV-REA-1ϒ 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].

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