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Professor Jan Feijen: A pioneer in biomedical polymers and controlled drug release

The research and development of biomedical polymers and controlled drug release systems are currently one of the most exciting scientific and technological fields, which have already made tremendous impacts on modern healthcare and are further expected to make even greater improvements on the quality of our human life in the future. It should be noted, however, that there were very few people working on biomedical polymers and controlled drug release systems throughout the world dating back to 40 years ago. Prof. Jan Feijen, along with his peers, Prof. Sung Wan Kim from the University of Utah, Prof. Nicholas A. Peppas from the University of Texas at Austin, Prof. James M. Anderson from Case Western Reserve University, Cleveland, Prof. Allan Hoffman from the University of Washington in Seattle, Prof. Jindrich Kopeček from the University of Utah, Prof. Robert Langer from Massachusetts Institute of Technology, and Prof. Michel Vert from the University of Montpellier, France, are among the pioneers who have made propounding and inspiring contributions to the science and scientific community of biomedical polymers and controlled drug release as from the 1970s. In this paper, I will firstly introduce the scientific achievements made by Prof. Jan Feijen over the past 40 years, and then present his enthusiastic and continuing commitments to biomaterials and controlled drug delivery community. It is interesting to note that from the following story of Prof. Jan Feijen, you would also have a better understanding about the history as well as development hallmarks of biomedical polymers and controlled drug release fields as a whole.


Prof. Jan Feijen

Prof. Feijen is a great polymer chemist and has developed various types of biomedical polymers over the past 40 years. In the 1970s, he has explored synthetic polypeptides in particular poly(L-aspartic acid), poly(L-glutamic acid) and copolymers as biomaterials, investigated their biodegradability and tissue reaction, and applied these polymers for controlled drug delivery [1–5]. In the 1980s, he has invented a versatile family of biodegradable polymers, so-called polydepsipeptides, by ring-opening polymerization of cyclic depsipeptides that are made of α-amino acids and α-hydroxyl acids (i.e. glycolic acid and lactic acid) [6–11]. Polydepsipeptides are a unique type of polymers that have integrated the features of functional peptides and biodegradable polyesters. He has prepared stereo block copolymers of L and D-lactides that exhibited a much higher melting temperature than optically pure poly(L-lactide) [12]. In the 1990s, he has made a breakthrough on controlled polymerization of cyclic esters. He discovered that initiating systems based on rare earth elements in particular yttrium generated in situ from sterically bulky non-active precursors promoted rapid and controlled ring-opening polymerization of lactones and lactides in dichloromethane at room temperature, wherein polymerization was complete within tens of seconds or a couple of minutes [13,14]. In a further study, he found that in situ forming calcium initiating systems could also bring about fast and controlled polymerization of cyclic esters under mild conditions [15,16]. These in situ forming catalyst systems remain one of the most efficient and versatile systems for the tailor-making of biodegradable polyesters and copolymers to date. Systemic studies of N-isopropylacrylamide copolymers demonstrated that the lower critical solution temperature (LCST) of poly(N-isopropylacrylamide) copolymers is dependent on their hydrophilicity and ionization status [17]. Poly(ethylene glycol)-poly(N-isopropylacrylamide) block copolymers were shown to form thermossensitive micelles [18]. In the new millennium, he reported that a novel chiral aluminum initiator based on commercially available Jacobsen ligand promoted controlled and stereo-selective ring opening polymerization of D,L-lactide in solution as well as in the bulk [19,20]. He has developed various types of in situ forming biodegradable hydrogels including PEG-PLA stereocomplexed hydrogels [21,22], stereocomplexation–photopolymerization tandem hydrogels [23], hydrogels formed by Michael-type conjugate addition [24,25], and enzymatically crosslinked hydrogels [26,27]. In addition to synthetic polymers, he has also carried out extensive work on chemical modifications of natural polymers for various biomedical uses. For example, he has prepared various copolymers of heparins such as polystyrene–poly(ethylene oxide)–heparin [28] and poly(dimethylsiloxane)–poly(ethylene oxide)–heparin block copolymers [29], and albumin–heparin conjugates [30,31] which were used to improve the blood compatibility of polymeric biomaterials. He has developed different approaches e.g. using water-soluble carbodiimide [32], glutaraldehyde [33,34] and epoxy [35] for the effective crosslinking of dermal sheep collagen and gelatin [36,37].

The surface properties of biomaterials play a vital role in their clinical applications. Prof. Feijen has started working on surface engineering of biomaterials to improve their blood and tissue compatibilities and prevent bacterial infection since 40 years ago [38,39]. Surface engineering is particularly important for blood vessel prostheses, heart valves, catheters for the vascular system or the urinary tract, and dialysis membranes. He has performed systemic studies on protein adsorption behaviors by radio-labeling proteins such as human serum albumin (HSA) and human fibrinogen [40] and by high-performance liquid-chromatography (HPLC) [41]. He has developed various surface modification techniques including wet chemical modifications and gas-plasma

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treatments [42,43]. The results showed that pre-adsorption of albumin–heparin conjugates could effectively inhibit surface-induced coagulation [44], the wettability of polymeric surfaces played an important role in their interactions with human endothelial cells [45,46], and the leukocyte adhesion to modified polyurethane surfaces was affected by their ionizable functional groups [47,48].

Controlled drug delivery and more recently gene delivery have been the focused research areas of Prof. Feijen. Part of this work was done in collaboration with Prof. Sung Wan Kim. As from late 1970s, Prof. Feijen reported macromolecular prodrugs of adriamycin based on poly(L-glutamic acid) for cancer therapy [49–51], biodegradable hollow fibers for the controlled release of anti-conceptive hormones [52], and biodegradable polymeric prodrugs of naltrexone [4,5]. He has also investigated the release of proteins and macromolecules from albumin–heparin microspheres [53,54], synthesis and biodistribution of immuno-conjugates of a human IgM [51], heparin release from thermosensitive hydrogels [55,56], and delivery of antibacterial proteins from gelatin–chondroitin sulfate hydrogels [57]. He has prepared and explored porous membranes for drug delivery [58], studied the biological properties of adriamycin bound to biodegradable polymeric carriers [49,51], and developed albumin–heparin conjugate microspheres for loading and release of adriamycin [31,59]. These adriamycin-loaded albumin–heparin conjugate microspheres were applied for intraperitoneal chemotherapy [60]. The immuno-conjugates of adriamycin and a human IgM were obtained by using poly[N5-(2-hydroxyethyl)-L-glutamine] as a linker [51]. The local release of growth factor from heparinized-collagen matrices was shown to improve endothelialization of vascular grafts [61,62]. The release of lysozyme from poly(ethylene glycol)/poly(butylene terephthalate) matrices was found to proceed in a zero order manner [63]. PEG–PLGA nanoparticles were prepared for the controlled release of anti-restenosis drugs [64]. In situ forming hydrogels have been developed for the sustained release of proteins including growth factors and interleukin-2 (IL-2) [65,66]. In 2003, biodegradable polymersomes that are of particular interest for loading and controlled release of both hydrophobic and hydrophilic drugs were reported for the first time [67,68]. More recently, lysosomally cleavable polymersomes and thermo-sensitive hydrogels containing polymersomes were developed [69,70]. The circulation kinetics and biodistribution of dual-labeled polymersomes with modulated surface charge in tumor-bearing mice were studied and compared with those of stealth liposomes [71]. In collaboration with Professors Johan F. J. Engbersen and Wim E. Hennink, he started to work on polymeric gene delivery systems in 2004. Interestingly, DNA polyplexes of low molecular weight linear polyethylenimine-*b*-poly(ethylene glycol)-*b*-polyethylenimine (PEI–PEG–PEI) triblock copolymers were shown to give enhanced in vitro gene transfection with low cytotoxicity [72]. A versatile family of degradable hyperbranched poly(ester amine)s was designed and investigated for non-viral gene transfer [73]. In particular, a novel class of bioreducible poly(amido amine)s containing multiple disulfide linkages (SS-PAA) that could readily be prepared with vastly different structures by the Michael-type addition reactions have been developed for highly efficient gene transfection [74,75]. In contrast to hydrolytically degradable polymers, SS-PAA and their polyplexes were stable in aqueous conditions.

Prof. Feijen has also investigated different aspects of tissue engineering of nerves [76], heart [77] and blood vessels based on (co)polymers of trimethylene carbonate [78–80]. Segmented poly(ether ester) materials and caprolactone/hydroxyapatite composites were used for bone tissue engineering [81,82]. In situ forming hydrogels based on chitosan [27], hyaluronic acid [83], and dextran and heparin/dextran [84] were designed for cartilage tissue engineering. He has been involved in several start-up companies focusing on stent-coatings, surface plasmon resonance equipment, cartilage tissue engineering, and barrier materials.

In 2009, Prof. Feijen retired from the University of Twente. However, his engagement in the research has never come to the end. He was appointed as a First Chair Prof. of Soochow University in the same year. With the effort of Prof. Feijen, Soochow University and the University of Twente have established a joint Ph.D. program. His work in Soochow University has been directed to the development of stimuli-sensitive nanosystems [85,86], design of functional biodegradable (co)polycarbonates for controlled drug and protein release [87–93], the design of functional biodegradable polymers and coatings [94], and the development of new alpha-amino acid containing degradable polymers for the controlled delivery of cytostatic agents [95,96].

Besides the scientific contributions, Prof. Feijen has also played a significant role in the biomaterials and controlled drug delivery community. In 1984, Prof. Feijen, together with Prof. Jorge Heller, founded the *Journal of Controlled Release*. Now, the *Journal of Controlled Release* has become a top pharmaceutical journal. Last year, *Journal of Controlled Release* has published the 30th Anniversary Special Issue, for which Prof. Feijen has written a very nice editorial entitled "Vision, launch and early days of Journal of Controlled Release" [97]. He was also an editor of the *International Journal of Artificial Organs*, Section Biomaterials and Drug Delivery Systems. He has been an Editorial Board member of many journals including *Journal of Biomedical Materials Research Part A*, *Biomaterials*, *Biomacromolecules*, *Journal of Biomaterials Science-Polymer Edition*, *Journal of Material Science-Materials in Medicine*, *Macromolecular Chemistry and Physics*, and *Macromolecular Bioscience*. He was the chairman and co-organizer of the first ten editions of the European Symposium on Controlled Drug Delivery Systems (ESCDD) as from 1990, which was organized alternatingly with the International Symposium on Recent Advances in Drug Delivery Systems in Utah started earlier by Prof. Sung Wan Kim. With Prof. Feijen as an international chair and co-organizer, a new series of drug delivery events, Symposium on Innovative Polymers for Controlled Delivery (SIPCD), was initiated and held biennially in Suzhou, China, starting from 2010 [98–100]. Now, both ESCDD and SIPCD symposia have been established as important and regular forums for the international drug delivery community. In addition, he was a co-founder of European Degradable Polymer Society, and a governor for several societies including the Controlled Release Society, European Society for Biomaterials, and the International Society for Artificial Internal Organs. He was a chairman of the Concerted Action on Heart and Replacement Technologies, Medical Health Research Program of the European Communities, and the Dutch Program for Tissue Engineering (DPTE). In 1995, he established the Institute for BioMedical Engineering (BMTI), which is now called MIRA Institute of Biomedical Technology and Technical Medicine, at the University of Twente. MIRA Institute is one of the largest and best-known biomedical institutes in Europe.

In recognition of his achievements and contributions to the scientific community, Prof. Feijen has received many prestigious awards including the Clemson Award for Contributions to the Literature from the American Society for Biomaterials, the Founders Award from the Controlled Release Society, the George Winter Award from the European Society for Biomaterials and the Award for Distinguished Service in Advancement of Biomaterials Science from the Japanese Society for Biomaterials.

In the past 40 years, Prof. Feijen has trained more than 90 Ph.D. students. I, myself, was very lucky to be one of them. He not only has broad knowledge but also a great sense of humor and charming personality. I personally admire Prof. Feijen very much and sincerely wish him to be happy and contented, healthy and strong.

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