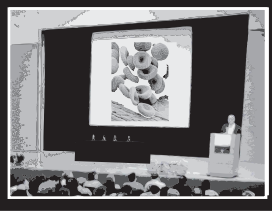
Conference Scene

From innovative polymers to advanced nanomedicine: key challenges, recent progress and future perspectives



The Second Symposium on Innovative Polymers for Controlled Delivery
Suzhou, China, 11–14 September 2012

Recent developments in polymer-based controlled delivery systems have made a significant clinical impact. The second Symposium on Innovative Polymers for Controlled Delivery (SIPCD) was held in Suzhou, China to address the key challenges and provide up-to-date progress and future perspectives in the innovation of polymer-based therapeutics. At SIPCD, a stimulating panel discussion was introduced for the first time on "What is the future of nanomedicine?" This report highlights the most recent research and developments in biomedical polymers and nanomedicine made by 29 invited scientists from around the world, as well as important issues regarding clinical advancements of nanomedicine conferred during the panel discussion.

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The Symposium on Innovative Polymers for Controlled Delivery (SIPCD), which is held every 2 years in Suzhou, China, aims to bring together leading scientists, entrepreneurs and prominent young researchers at the forefront of the biomedical polymer and nanomedicine fields, covering stimuli-responsive medical polymers, tumor-targeting drug release systems, controlled gene transfer approaches, emerging diagnostic technologies, advanced tissue engineering and regenerative medicine. This series of symposia, first launched in September 2010 in reponse to the rapid technological advances in innovative polymers and controlled delivery systems, has already been established as a high-level forum. The symposium is organized in one single session, thus offering participants the possibility to be present at all invited lectures, with ample opportunities to participate in lively discussions about the most recent developments, as well as challenges in controlled delivery.

The second SIPCD (SIPCD 2012) was held in September 2012 and had a particular focus on cutting-edge nanomedicine. In addition to invited lectures by well-known scientists, including editors and associate editors of over ten prestigious journals, SIPCD 2012 also hosted an intriguing panel discussion on "What is the future of nanomedicine?", as well as a tour of Suzhou BioBay – a top biomedical park in Suzhou, China. It is interesting to note that SIPCD 2012 welcomed 418 delegates from 138 institutions and companies from 18 countries, and accepted 252 poster presentations from more than 300 submissions following a strict peer-review process. Notably, the six best poster presentations were granted prestigious Biomacromolecules Poster Awards (American Chemical Society) by Harm-Anton Klok, associate editor of *Biomacromolecules*. As in the first symposium in 2010 [1], a high-quality special issue that contains contributions made exclusively by the invited speakers of SIPCD 2012 will be published in the *Journal of Controlled Release*. It should also be noted that all poster abstracts presented at SIPCD 2012 will be published online in a special issue of the *Journal of Controlled Release*.

In recent years, there has been rapid progress in basic research, as well as in the clinical development of polymeric systems for targeted and controlled delivery of potent chemotherapeutics, biopharmaceutics and diagnostic imaging agents. Kazunori Kataoka (University of Tokyo, Japan) opened the symposium with a lecture about his pioneer work on micelles based on poly(ethylene glycol)-b-poly(amino acids) block copolymers for anticancer drug and siRNA delivery. Notably, several micellar anticancer drug formulations have already been in clinical trials worldwide, including Japan, Taiwan, Singapore, the UK, France and USA [2]. Kataoka has demonstrated that dichloro(1,2–diaminocyclohexane)platinum(II)-loaded pH-responding micelles are effective for the treatment of intractable pancreatic cancer. Si-Shen Feng (National University of Singapore, Singapore) developed paclitaxel and docetaxel formulations based

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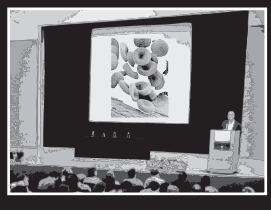
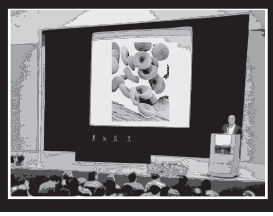


on D-α-tocopherol poly(ethylene glycol) 1000 succinate emulsified biodegradable poly(lactic-*co*-glycolic acid) (PLGA) nanoparticles that have shown improved therapeutic effects and better safety as compared with Taxol® (Bristol-Myers Squibb, NY, USA) and Taxotere® (Sanofi-Aventis, Paris, France) in Sprague Dawley® rats (Charles River, MA, USA). Rainer Haag (Freie Universität Berlin, Germany) developed multifunctional nano- and microparticles based on dendritic polyglycerols for different biomedical applications, ranging from protein-resistant coatings, DNA transfection, anticoagulation and anti-inflammation to single cell entrapment. Youqing Shen (Zhejiang University, China) emphasized that capability, excipient ability and scale-up ability are the three elements critical for translational nanomedicine. Stefaan de Smedt (Ghent University, Belgium) described new concepts and characterization methods including fluorescence single-particle tracking microscopy and fluorescence correlation spectroscopy for advanced drug delivery studies.

Biotherapeutics, such as proteins, peptides and oligonucleotide drugs, exhibit several unique features, such as great therapeutic activity, high specificity and low toxicity over chemotherapeutics. Their clinical applications, however, are challenged by the absence of an appropriate controlled release system. Jackie Y Ying (Institute of Bioengineering and Nanotechnology, Singapore) discussed the development of polymeric nanoparticles for on-demand glucose-sensitive release of insulin; apatite-polymer nanocomposite particles for zero-order release of protein therapeutics, such as bone morphogenetic proteins; and nanocomposite materials for theranostic applications and combination therapy. Hsing-Wen Sung (National Tsing Hua University, Taiwan) developed functional nanoparticles based on chitosan and poly(γ-glutamic acid)-ethylene glycol tetraacetic acid conjugate for enhanced absorption and protease inhibition in oral protein delivery. Johan FJ Engbersen (University of Twente, Enschede, The Netherlands), taking advantage of the reversible nature of boronate esters with diols and the enhanced cellular interactions of boronic acids, designed boronic acid-functionalized and bioreducible poly(amido amine)s for glucose-responsive insulin release and efficient gene transfection. Frank Caruso (University of Melbourne, Australia) discussed tailor-making of functional micro- and nano-sized capsules via sequential polymer assembly. The application of polymeric capsules for the encapsulation and release of oligonucleotides and peptides to stimulate immune responses was highlighted.

The development of stimuli-responsive, particularly pH- and redox-responsive, nanocarriers for improved intracellular drug release and, therefore, therapeutic efficacy has been a focus of recent research. Fenghua Meng (Soochow University, Suzhou, China) designed several novel types of bio-responsive polymersomes, such as endosomal pH-sensitive degradable chimeric polymersomes and pH/redox dual-responsive polymersomes, for efficient intracellular anticancer drug and protein release. Xi Zhang (Tsinghua University, Beijing, China) delivered a lecture on stimuli-responsive nanoparticles, based on amphiphilic selenium-containing polymers that respond to reduction and oxidation, as well as γ-radiation. Deyue Yan (Shanghai Jiaotong University, Shanghai, China) developed multifunctional redox-responsive nanocarriers from hyperbranched polyphosphates containing multiple reducible disulfide or diselenide bonds for intracellular release of anticancer drugs. Doo Sung Lee (Sungkyunkwan University, Seoul, Korea) designed various stimuli-responsive micelles and hydrogels based on block copolymers of poly(ethylene glycol) and poly(β-aminoester)s for controlled release of anticancer drugs, imaging agents and/or proteins *in vitro* and *in vivo*.

DNA, proteins and polypeptides have recently been developed as emerging materials for nanomedicine. Dan Luo (Cornell University, NY, USA) presented his work on DNA-based nanomaterials, including Y-shaped DNA, dendrimer-like DNA, DNA nanobarcodes, DNA hydrogels, DNA liposomes and DNA organized nanoparticles, some of which have been investigated for point-of-care diagnostics and intracellular protein release. Timothy J Deming (University of California Los Angeles, CA, USA) addressed the novel synthesis of functional

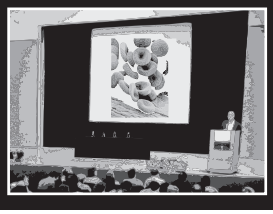


polypeptide materials, polypeptide vesicles for drug delivery, as well as polypeptide hydrogels for CNS therapies. Xuesi Chen (Changchun Institute of Applied Chemistry, China) designed several new types of multiresponsive polypeptide nanogels for efficient anticancer drug delivery. Ashutosh Chilkoti (Duke University, NC, USA) discussed the development of thermosensitive elastin-like polypeptide nanoparticles for systemic anticancer drug delivery, as well as novel protease-operated depots for local, sustained and tunable peptide drug release for the treatment of Type II diabetes. Yong-Hee Kim (Hanyang University, Seoul, Korea) developed recombinant metallothionein fusion proteins as protective therapeutic agents against glucolipotoxicity, hyperglycemia and hypoxia. Sébastien Lecommandoux (Université de Bordeaux, Talence, France) gave a lecture on the design of smart polymersomes from glycoprotein-mimicking polypeptide–polysaccharide copolymers for targeted tumor therapy and the novel preparation of compartmentalized polymersomes with an internal 'gelly' cavity. Harm-Anton Klok (Ecole Polytechnique Fédérale de Lausanne, Switzerland) designed peptide-synthetic polymer conjugates for effective binding and release of cargo, increased stability of HIV fusion inhibitors and/or increased activity of HIV entry inhibitors.

The success of gene therapy is critically dependent on the development of safe, efficient and viable gene delivery vehicles. Chae-Ok Yun (Hanyang University) presented versatile modification strategies of adenovirus with polymers and nanomaterials, such as poly(ethylene glycol), chitosan and arginine-grafted bioreducible polymer, to improve the antitumor efficacy, specificity and safety of systemic adenovirus-mediated cancer gene therapy. To address the high toxicity, low stability and low specificity of cationic polymer-based gene delivery systems, Wim E Hennink (Utrecht University, The Netherlands) developed novel decationized disulfide-crosslinked polyplexes for nontoxic and efficient redox-triggered intracellular gene delivery. David W Grainger (University of Utah, UT, USA) discussed the development of local siRNA and antibody delivery approaches from implant devices to bypass systemic siRNA dosing, targeting, stability and bioavailability problems in device-associated fibrosis and osteoporosis.

In addition to nanomedicine, novel medical materials, such as hydrogels and shape-memory polymers for controlled drug release and cell sheets for 3D tissue and organ reconstruction, were also addressed. Phillip B Messersmith (North Western University, IL, USA) developed *in situ*-forming polymer hydrogels using the native chemical ligation method for drug delivery, medical sealing and wound healing applications. Jiandong Ding (Fudan University, Shanghai, China) discovered that the anticancer activity of camptothecin family drugs is significantly enhanced upon loading into PLGA–poly(ethylene glycol)–PLGA hydrogels. Gordon Wallace (University of Wollongong, Australia) communicated the combination of medical bionics with controlled local drug or NGF delivery to improve the electrode–cellular interface and, therefore, the performance of bionic devices. Diane J Burgess (University of Connecticut, CT, USA) developed long-term implantable glucose sensors by employing dexamethasone-loaded PLGA microsphere/polyvinyl alcohol hydrogel composites as outer sensor coatings. Andreas Lendlein (Helmholz-Zentrum Geesthacht, Germany) developed novel multifunctional drug delivery systems based on stimuli-sensitive shape-memory polymers, in which drug release profiles can be controlled by polymer degradation rate and drug loading technique. Teruo Okano (Tokyo Women's Medical University, Japan) communicated the latest development of 3D tissue and organ reconstruction by layered cell sheets. Human clinical studies have been initiated for cell sheet engineering therapy for the treatment of cornea epithelium-deficient disease and cardiomyopathy.

Finally, the panel discussion on "What is the future of nanomedicine?" was led by Grainger, Frank Caruso, Si-Shen Feng and Hennink. Grainger made an introductory speech about the current status of nanomedicine development. It was noted that nanomedicines such as Doxil® (Ben Venue Laboratories, OH, USA), Abraxane® (Celgene, NJ, USA) and PEG-Intron®



(Schering-Plough, NJ, USA) have already been applied in the clinic. These nanoparticle systems are either systemically administered or intended to have significant systemic bioavailability. It has to be realized, however, that many challenges still exist before nanomedicine will become routine and reliable. As a community, we should avoid over-expectations, hype and hyperbole that might affect the credibility of nanomedicine as a field. It is important to properly convey what nanomedicine can do and its limitations. The targetability of nanomedicine is questionable given that typically only approximately 5% or less of the injected dose accumulates in tumors of mice. Consequently, inefficient intratumoral penetration of nanomedicines due to their submicron sizes and affinity for the tumor cells in the peripheral region, as well as stiff tumor extracellular matrix and high interstitial fluid pressure confining therapeutic effects to the periphery of the tumor mass close to the vasculature, has been recognized as a significant barrier for effective tumor therapy. The intratumoral penetration of nanomedicines can be enhanced by using tumor-penetrating peptides such as iRGD, pharmacological treatments of tumors (collagenase and the hormone relaxin) and with the application of ultrasound. It should further be noted that there is a lack of proper animal models. The results obtained from mice are difficult to translate directly into humans. As a matter of fact, the clinical data indicated that the enhanced permeability and retention effect, if it exists, is not as obvious as that observed for mice, probably due to much slower tumor growth and relatively smaller tumor volumes in humans. Finally, nanomedicines also encounter manufacturing issues, such as large-scale production, reproducibility and quality control. In this panel discussion, the most important issues related to nanomedicines were addressed. It is generally accepted that nanomedicines will play a significant role in future medicines. In addition to parental delivery, nanomedicines also show promise for oral administration.

Financial & competing interests disclosure

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