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Editorial

Editorial for Theme Section on Polymeric Micelles for Drug Delivery

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Polymeric micelles are a major class of nanoscopic drug carriers, being studied for drug solubilization, controlled drug release, and drug targeting in pharmaceutical research. At this stage, much is known about the physical properties of polymeric micelles for drug delivery, with Pluronic® block copolymers serving as the prototype polymeric micelles for drug formulation. We have developed a thorough understanding of the assembly and disassembly of polymeric micelles, thermodynamic and kinetic considerations, physical and chemical factors dictating drug solubilization, and factors dictating drug release; all are crucial in being able to predict their functionality *in vivo*. More recently, we have developed a better understanding on the biological properties of polymeric micelles, although a great deal work remains to be done, particularly with respect to safely, drug targeting, and multi-functionality. Pre-clinical and clinical studies have suggested that polymeric micelles are safe (biocompatible) after IV administration, and that they exert positive biological responses, e.g. tumor targeting by the well-established enhanced permeability and retention effect (EPR effect) and inhibition of P-glycoprotein, which is associated with poor oral bioavailability of drugs and multi-drug resistance in cancer.

At this stage, the chemistry of polymeric micelles is rapidly expanding, and we note amphiphilic block copolymers (ABCs) composed of poly(α-hydroxy acid)s, e.g. poly(L-lactic acid) and poly(α-amino acid)s, e.g. poly(β-benzyl L-aspartate), which have been proven to be safe in clinical trials and a welcome alternative to cosolvents and surfactants, e.g. Cremophor EL, commonly used for drug solubilization. As a result, we are seeing a greater number of drugs being solubilized by polymeric micelles: e.g. 17-allylamino-17-demethoxygeldanamycin, amphotericin B, camptothecin, cyclosporin A, fenretinide, itraconazole, paclitaxel, propofol, rapamycin, and even sevoflurane, which may permit the IV administration of this commonly used anesthetic gas. In this theme issue, van Nostrum and coworkers demonstrate that micelles of PEG-*block*-oligo(□-caprolactone) have a high capacity for a poorly water-soluble photosensitizer, *meta*-tetra-(hydroxyphenyl) chlorine and reveal an interesting lipase-induced release of the photo-sensitizer; both indicating the promise of polymeric micelles for photodynamic therapy for the treatment of cancer via local or systemic drug administration.

In this theme issue, Bae and coworkers exemplify another trend in polymeric micelles in drug delivery, stemming from novel chemistries, that is, controlled or triggered drug release; in this contribution, Bae and coworkers demonstrate pH-sensitive drug release as a result of protonation of PEG-*block*-poly(L-histidine) in acidic environments, which are prevalent at solid tumors and in endolysosomal/lysosomal compartments. In the endolysosomes or lysosomes of tumor cells, protonation of PEG-*block*-poly(L-histidine) causes lysosomal membrane permeabilization. In this contribution, folate targeting of mixed polymeric micelles composed of PEG-*block*-poly(L-histidine) and PEG-*block*-poly(L-lactic acid) results in the superior delivery of doxorubicin to a multi-drug resistant ovarian tumor (A2780/DOX^R). Furthermore, attachment of Cy5.5 on mixed polymeric micelles permits optical imaging *in vivo*, a step toward multi-functional drug targeting combined with molecular imaging. It is expected that controlled drug release strategies involving polymeric micelles will continue to evolve, involving external or internal stimuli, such as pH, temperature, and/or enzymes, and aiming for drug release at targeted sites at tunable rates. We can also imagine other kinds of targeting ligands installed on distal ends of PEG for the targeting of polymeric micelles for imaging and therapy.

In this theme issue, Leroux and coworkers take advantage of atom transfer radical polymerization, a controlled or "living" polymerization, to fully characterize assembly of PEG-*block*-poly (aminoethyl methacrylate) and/or poly(dimethyl(aminoethyl)methacrylate and oligonucleotide. So-called poly-ion complex ("PIC") micelles, these unique polymeric micelles are attractive nanoscopic carriers for nucleic acid drugs, including plasmid DNA and siRNA. In this contribution, PIC micelles protect oligonucleotide from nucleases and have tunable properties, e.g. adjustable buffering capacity for oligonucleotide delivery. It is predicted that PIC micelles will some day play a clinical role in the delivery of nucleic acid drugs for the treatment of a variety of disease states.

These articles in this theme issue on polymeric micelles for drug delivery offer a glimpse of the state-of-the-art in this rapidly evolving area of pharmaceutical research. It is noted that much of this research is done in an academic setting throughout the world (in this issue, The Netherlands, USA, and Canada), as opposed to a company setting, although we are starting to see smaller companies adopt this nanotechnology for pre-clinical and clinical drug development. For major clinical advances, we need major pharmaceutical companies to embrace this nanotechnology as a way of fueling drug development for life-threatening diseases: cancer, infectious diseases, and neurological diseases. We can

expect to see more innovative research on polymeric micelles for drug solubilization, drug targeting via various routes of drug administration, and targeting of nucleic acid drugs. Many of these high impact publications will be seen in *Pharmaceutical Research*.

Dr. Glen S. Kwon is a Professor in the School of Pharmacy at the University of Wisconsin. He received his B.S. in Chemistry in 1986 and Ph.D. in Pharmaceutics in 1991 from the University of Utah. He was a Japan Society Promotion for Science Postdoctoral Fellow at the International Center for Biomaterials Science in Tokyo, Japan from 1991 to 1993. He was an Assistant Professor in the Faculty of Pharmacy and Pharmaceutical Sciences at the University of Alberta from 1993 to 1997. He received the Jorge Heller Journal of Controlled Release/Controlled Release Society Outstanding Paper Award in 1994, National Institutes of Health FIRST Research Award in 1998, and American Association of Colleges of Pharmacy Faculty New Investigator Award in 1998. He was a Japan Society for Promotion of Science Fellow at the Institute of Advanced Biomedical Engineering and Science at Tokyo Women's Medical University in 2002. He received the Controlled Release Society Young Investigator Research Achievement Award in 2003. He is an Adjunct Professor in the Faculty of Pharmacy and Pharmaceutical Sciences at the University of Alberta. He is an associate editor for *J. of Pharm. & Pharmaceu. Sci.* and serves on several journal editorial boards. His research program focuses on polymers and colloids for drug, peptide/protein and non-viral gene delivery.

Interview Questions for Dr Glen S. Kwon

1. What do you think holds the key to your success as a pharmaceutical scientist?

I have had an opportunity to train and work with some of the top scientists at universities doing drug delivery research. The Department of Pharmaceutics at the University of Utah was a remarkable place as a Ph.D. graduate student. The training in physical pharmacy and in drug delivery biomaterials, mainly polymers, was truly outstanding. In Japan during my post-doctoral research, I grasped the importance of polymer chemistry for drug and gene delivery. The University of Wisconsin is a powerhouse in biomedical research and a very stimulating and exciting environment for pharmaceutical research.

2. What do you consider to be your key research accomplishments?

My key accomplishments have centered on polymeric micelles for drug delivery, contributing to a physical, chemical, and biological understanding in their implementation in drug delivery. Working with others, we have firmly established their roles in drug solubilization, controlled release, and drug targeting. It is gratifying to see several systems in clinical trials for the treatment of cancer, primarily at the National Cancer Center Hospital in Kashiwa City, Japan.

3. What was the turning point in your career?

My move to the University of Wisconsin in Madison was a critical turning point. I was plugging along nicely at the University of Alberta. However, the move to UW proved to be an exciting and highly stimulating challenge, one that continues to this day.

4. Who are the individuals who most influenced your research career?

My mentors were Professor Sung Wan Kim (my Ph.D. advisor at the University of Utah), Professors Kazunori Kataoka and Teruo Okano (my post-doctoral advisors in Japan), and Professors Joe Robinson and George Zografi (senior colleagues at the University of Wisconsin). They all lead by example. They were passionate and very positive. They all showed younger folks how to succeed in life, of course, if you were paying attention.

5. Pharmaceutical scientists are faced with the dilemma of having to publish in biomedical or basic science journals. Does it mean cutting edge science will not likely be featured in the *Pharmaceutical Research*?

No. *Pharmaceutical Research* will be at the cutting edge of multi-disciplinary biomedical research. Many important problems in drug development will be solved at this interface between the basic sciences and clinical research.

6. Where is the field of polymeric micelles, and how do the articles in the theme section fill the gap?

Research on polymeric micelles for drug delivery has grown a lot, spanning basic science to clinical trials. It is an exciting time. The articles in this theme section provide a sense of the breadth and depth of the efforts in this area of pharmaceutical research. The chemical and physical understanding of polymeric micelles for drug and gene delivery has progressed nicely. We are starting to understand how they behave *in vivo*.

7. What are the challenges for polymeric micelles for drug delivery and how can be overcome?

More research on polymeric micelles needs to take place *in vivo*. Professors You Han Bae, Alexander V. Kabanov, Kazunori Kataoka, and Vladimir Torchilin are leaders in the field, and through a lot of effort, they have laid the groundwork for clinical trials involving polymeric micelles. We need more animal work to raise understanding, significance and move more systems into human clinical trials, where we will learn even more about this nanotechnology for drug and gene delivery.

8. What is the key to developing successful collaborative relationships?

It is important to bring unique expertise to the table. It is important to work together, leaving egos at the door. We see collaborative research more and more in grant review at NIH. Professor Joe Robinson strongly recommended that assistant professors in drug delivery collaborate with their medical colleagues.

9. What is your philosophy of educating graduate students?

The goal is not to train "super technicians," but young researchers who can think for themselves. Individuals with Ph.D. degrees should be able to define central questions in pharmaceutical research and propose strategies to solve these questions. It is not an easy task. However, we are very fortunate to be able to pursue this kind of work in an academic setting and industry, regardless of the challenges. I think that you have to be passionate,

dedicate yourself to life-long learning, accept failure and success with grace, and move forward in a positive way, realizing that you are role model for young people.

10. What are the challenges facing the pharmaceutical sciences?

The current federal research funding climate is certainly a challenge. Many young scientists are skeptical of an academic career given this state of research support, knowing that tenure is based in many instances in securing federal research grants. You can ask how much talent in this generation will we lose here in the United States?

11. What is the place for collaboration with industry in academia?

It should be strongly encouraged as a funding mechanism for academia and a source of innovation for industry. It should involve graduate students who would benefit immensely from stipends and mentorship from senior colleagues in the pharmaceutical industry.

Glen S. Kwon
University of Wisconsin,
Madison WI, USA
e-mail: gskwon@pharmacy.wisc.edu