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Editorial

Targeted Delivery for Musculoskeletal Diseases

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The musculoskeletal system is composed of bone, muscles, tendons, and ligaments. As an essential component of the human anatomy, it serves as the mechanical support for the body and protects vital organs and bone marrow. It also serves as a reserve of ions, especially calcium and phosphate, for the maintenance of serum homeostasis. The coordination of the skeleton with attached muscles, ligaments, and tendons provides locomotion for the human body.

Dysfunction of any component of the musculoskeletal system can cause various forms of diseases. As an example, imbalanced bone remodeling favoring bone resorption leads to osteoporosis, a disease characterized by low bone mass and micro-architectural deterioration of bone tissue resulting in an increased fracture risk. Rheumatoid arthritis, on the other hand, is an autoimmune disorder that damages both articular bone and cartilage, causing significant pain and loss of movement. Furthermore, several types of cancer have bone as their primary sites of metastasis. Osteomyelitis due to bone infection of *Staphylococcus aureus* is hard to treat and sometimes has to be resolved with surgical debridement or even amputation.

The understanding of the pathophysiology of musculoskeletal diseases has been greatly improved during the past few decades. Numerous therapeutic targets have been identified with many new drugs in clinical applications. One of the most notable drug classes that have been developed is the bisphosphonates (BPs). They are stable analogues of naturally-occurring pyrophosphate and have been used extensively in the treatment of osteoporosis, Paget's disease, cancer bone metastasis, and in children with osteogenesis imperfecta. The main biological effect of BPs is inhibition of osteoclast activities, but they also interact with other cells such as osteocytes. The most interesting property of BPs, however, is their strong bone affinity, which affords them unique pharmacokinetic/biodistribution profiles favoring fast deposition and long residence in the skeleton. This osteotropicity is the key to the BPs' success, or this class of poorly oral available drugs (<1%) may have never entered clinical applications. BPs are an unique group of molecules with both osteotropicity and biological activities encoded in the same chemical structures. For other musculoskeletal disease drugs, however, delivery strategies must be employed to incorporate tissue specificity.

The field of targeted delivery for musculoskeletal diseases is still in its early development with many significant challenges. The targeting moieties used so far are limited to BPs and aspartic acid peptides. Though considered as the most potent bone-targeting moiety, the usage of BPs in targeted delivery systems may be hampered by the recently raised concern of BP-associated osteonecrosis of the jaw (ONJ). Several types of delivery vehicles have been developed for musculoskeletal diseases. For a particular disease condition, the delivery vehicle must be chosen wisely, taking into consideration the nature of the disease, the potency of the drug, and the pharmacokinetics of the delivery vehicle. It is easy to bring delivery systems to well-vascularized skeletal regions, but transportation to areas with limited blood supply (where the medication is probably most needed) can be challenging. Stability of the drug during formulation and delivery is another factor to be considered. This is especially important when the delivery cargo is a biological.

Several leading groups have been invited to contribute to this theme section. Dr. Miyamoto's group investigated the aspartic acid peptide-based delivery of anti-microbial quinolones for improved treatment of osteomyelitis. Previously, they have successfully delivered alkaline phosphatase and estradiol to the bone using a similar strategy. The Utah group led by Drs. Miller and Kopeček reported the polymer-based osteotropic delivery of prostaglandin E_1 (a potent bone anabolic agent) for the treatment of osteoporosis. Its promising results offers the first evidence of the efficacy of bone-targeted anabolic therapy. Dr. Uludag's group is best known for their bone-targeted delivery of biologicals using bisphosphonate conjugation. In this theme section, they focused on another important issue and investigated the bioactivity of bone growth factors entrapped in nanoparticles for local or systemic bone regeneration. Finally, my group described the design, synthesis, and *in vivo* evaluation of a well-defined polymer-dexamethasone conjugate for the highly effective treatment of rheumatoid arthritis. Different from the bone-targeting delivery systems, the specific delivery to arthritic joints is mainly due to the enhanced vascular permeability to macromolecules found in the inflamed synovium.

It has been a fun and exciting experience to work with my colleagues on this theme section. I deeply appreciate their

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contributions and certainly hope that the work presented here may be intellectually stimulating and attract the interests of other scientists to join us to pursue this very promising research direction. Enjoy!

INTERVIEW QUESTIONS FOR DR DONG WANG

1. What do you think holds the key to your success as a pharmaceutical scientist?
   I am not sure if I can be considered successful just yet. But I am fortunate to have a solid education, great mentors, and outstanding colleagues. I am curious, imaginative, and I work hard.
2. What do you consider to be your key research accomplishments?
   We are probably the first to use targeted polymeric conjugates for treatment of musculoskeletal diseases. Given the scope and the significance of this group of diseases, I think we are working on a very important problem and it will be for a while.
3. What was the turning point in your career?
   It all began with my Ph.D. in Polymer Chemistry and Physics at Peking University under the late Dr. Xinde Feng, the founder of Chinese polymer chemistry education. Later, I joined Dr. Jindřich (Henry) Kopeček's lab for my postdoctoral training in pharmaceutical chemistry. That's where things started to fly.
4. Who are the individuals who most influenced your research career?
   My father, a very successful engineer, taught me early on that to be successful one should always do his/her best to pursue perfection. I've treasured that deep in my heart. During my Ph.D. years, Dr. Feng helped me build a solid foundation of polymer chemistry. Later at the University of Utah, Dr. Kopeček wisely guided my transition to the research of pharmaceutical chemistry. Dr. Scott Miller is the one who first introduced me into the mysterious world of bone. Dr. Steven Goldring of the Hospital for Special Surgery has been very generous in lending his support to the development of our rheumatoid arthritis research program. Needless to mention all the colleagues at UNMC who have supported my career development ever since I joined the faculty. I am fortunate to have all these outstanding mentors and friends along my career path.
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. The theme section is an excellent example of cutting edge science featured in the *Pharmaceutical Research*.
6. Where is the field of musculoskeletal diseases, and how do the articles in the theme section fill the gap?
   The basic science of musculoskeletal diseases has experienced tremendous growth during the past few decades. People have a much better understanding of the pathogenesis of various musculoskeletal diseases and many new molecular targets have been identified. Surprisingly, however, the application of drug delivery to this group of diseases has been very limited. The articles in this theme section are solicited from a few leading groups in this research area and are meant to give the readers a glimpse of the pharmaceutical problems that we are dealing with. The field is still in its infancy. As shown in the theme section, a multidisciplinary approach must be made to tackle the problems.
7. What are the challenges for polymeric carriers for treating musculoskeletal diseases and how can be overcome?
   First is the control of molecular weight and polydispersity; this is probably true for most of the macromolecular drug conjugates. In the past decade, we have witnessed tremendous growth in polymer chemistry, especially living polymerizations. Hopefully this can be effectively translated into the development of polymeric drug carriers. For carriers designed for skeletal diseases, effective incorporation of both bone-targeting moieties (negatively charged, hydrophilic) and drugs (often hydrophobic) in the polymeric carrier can be challenging. Using new tools, such as "click" chemistry, may partially address the problem. Development of neutral bone-targeting moieties may be another direction to explore.
8. What is the key to developing successful collaborative relationships?
   Learn to speak their scientific languages. Cultivate mutual respect and trust.
9. What is your philosophy of educating graduate students?
   Students come in to be given a problem or two and are asked to figure out the answer. This process will help them acquire certain knowledge and skills, but the real leap happens when they start to see problems and ask fundamental questions. It can be a long process and needs a lot of patience and wise mentoring.
10. What are the challenges facing the pharmaceutical sciences?
    This is a tough question. I think for the field in general we need a clear vision of directions and big ideas. As an individual pharmaceutical scientist, I feel it is critical to organize multidisciplinary teams to synergize and effectively address difficult pharmaceutical problems.
11. What is the place for collaboration with industry in academia?
    Though I have very limited personal experience, I think collaboration with industry in academia is very important. I believe to begin with the end in mind. We produce two products in academia, our science and our students. Yet both need to be materialized by the industry eventually.

Dr. Dong Wang is an associate professor of pharmaceutical sciences at the University of Nebraska Medical Center. He obtained his B.S. and M.S. degrees in Polymer Sciences and Engineering at Harbin Institute of Technology in 1991 and 1994. He received his Ph.D. in Polymer Chemistry and Physics at Peking University in 1998, under Dr. Xin-De Feng. Dr. Wang's lab is one of the few leading groups that focus on drug delivery for musculoskeletal diseases. His current research interests include macromolecular therapy for inflammatory diseases, drug delivery for periodontal diseases, and the development of novel polymers for biomedical applications. Dr. Wang has published 34 peer-reviewed papers, approximately 40 abstracts, and nine patent applications. He has been invited as guest editor for *Advanced Drug Delivery Review* and *Pharmaceutical Research*. He has participated in NSF review panels and acted as an ad hoc reviewer for NIH/NIAMS. He is also the member of American Chemical Society, Controlled Release Society, American Society for Bone and Mineral Research, and American College of Rheumatology.