molecular pharmaceutics

editorial

Thoughts from the Frontiers of Science: The Gordon Research Conference on Drug Carriers in Medicine and Biology (August 20−25, 2006)

Two years ago, during the first year of our then new journal, *Molecular Pharmaceutics*, we published an informative editorial (*Mol. Pharm.* **2004**, *1* (6), 395−398) written by Peter D. Senter and Jindřich Kopeček, which reported on the Gordon Research Conference on Drug Carriers in Medicine and Biology. It is my intention and that of the editorial office of *Molecular Pharmaceutics* to continue to have editorials related to this superb conference. We will observe biennially the cutting edge science in drug delivery in this GRC conference series in the years to come. We feel that an editorial can remind our readers of the meetings and be of great interest to them as we share overlapping goals in research. One major reason for this is my firm belief that this conference has been one of the premiere conferences in the field of drug delivery. I also believe that the readers of *Molecular Pharmaceutics* would benefit greatly from brief reports on what has been presented at the meetings. These are also supported by the list of speakers, participants, and chairs of this GRC who are on the advisory board of *Molecular Pharmaceutics* and among the authors and reviewers for this journal.

During the last week of August 2006, the GRC on Drug Carriers in Medicine and Biology, held in the beautiful setting of Big Sky, MT, witnessed lively discussions revolving about a collection of excellent and thought-provoking presentations from the leading scientists in the field. This GRC is an established conference for scientists engaged in research surrounding drug delivery, macromolecular-based therapies including polymers, antibodies, and liposomes, new molecular targets, and preclinical as well as clinical applications of drug carriers. This conference started more than 20 years ago by a group of drug delivery scientists especially in liposomal drug carriers.

This editorial is not intended to cover all the presentations, but would give a brief summary and attempt to render to you only the flavors and gist of what was presented and the thoughts that crossed our minds during the meeting. As this would remain more subjective, I would encourage you to visit the conference website (http://www.grc.org//programs/2006/drugcarr.htm) for the complete program and the titles of the talks.

The talks encompassed many of the advancements in the delivery fields which included the utilization of polymers, monoclonal antibodies, self-assembling structures, and a variety of molecules as drug carriers and therapeutic agents. Some of the imaging technologies were described, as we saw in the previous meeting in 2004, which I believe is one area of the delivery field that holds great promise for practical utility in clinical trial settings and beyond. A series of excellent presentations on nanocarriers with a wide range of biological applications strongly pointed to the emergence of this area as a promising one in drug delivery. The impetus in the field and NIH-supported initiatives will drive this discipline to reach a critical mass and to result in a big impact sooner or later.

The two keynote addresses covered the basic intricacies and complexities of VEGF and their receptors as therapeutic targets for cancer and other diseases (Napoleone Ferrara (Genentech)), while the potential use of recombinant protein polymers as delivery carriers was presented by David Tirrell (Caltech). The idea of using homogeneous monodisperse polypeptides with unnatural amino acids for delivery systems was clearly pointed out by Tirrell. This opens up many new possibilities of incorporating interesting functional groups available to traditional delivery scientists who have utilized relatively heterodisperse synthetic polymers.

In the session entitled “Nano-Engineered Delivery”, Pat Stayton (University of Washington), Robert Prud’homme (Princeton University), Alexander Kabanov (University of Nebraska Medical Center), and Rainer Haag (University of Berlin, Germany) talked about nanosized polymeric carriers formed by self-assembly processes via various interactions. pH-sensitive polymers (Stayton), flash nanoprecipitation for block copolymers (Prud’homme), charge-driven assembly of polymers (Kabanov), and dendritic architectured polymers (Haag) were discussed for their utility in delivery for small to large therapeutic molecules. These were followed by examples of gene delivery carriers incorporating the features of viral vectors into nonviral gene carriers (Ernst Wagner, University of Munich, Germany) and multifunctional nanocarriers for cancer therapy and imaging (Vladimir Torchilin, Northeastern University).

After only one full day of sessions in the meeting, it became very clear that the development and investigation of nanosized carriers is an area of research that holds a lot of potential, and the field has been promising to show positive results. One was left with an impression that the field still needs to provide definitive experimental evidence delineating the essential differences between nanosized carriers versus those of dimensions bigger than a micron. Some discussion ensued regarding the precise definition of “nanomedicine”, which in all attempts could be merely

10.1021/mp060111q CCC: $33.50
Published on Web 12/04/2006

semantics if we do not provide sufficient scientific backing for the fad for this attractive terminology and concept. I believe that this is an extremely challenging task, which partially explains why we are not quite there yet. I have no doubt, however, that it is only a matter of time before the field will be equipped with firm data in order to advance and further promote this new area of research and development. In the near future, we will be comfortable with calling this a new paradigm in drug delivery.

One class of therapeutic modality that has been receiving a lot of attention from delivery scientists is siRNA, and rightly so due to its extremely favorable unique characteristics as therapeutic molecules that can regulate gene expression. A session was dedicated to the delivery of siRNA with wonderful presentations from Judy Lieberman (Harvard University), John Rossi (Beckman Research Institute of the City of Hope), and Mano Manoharan (Alnylam). In retrospect, it was a timely and needed topic, as we recently learned that the molecular biology field of siRNA has been rewarded with the 2006 Nobel Prize for its discovery of this important regulatory mechanism. The translation of siRNA from bench-side research into clinical settings desperately requires efficient delivery strategies for various targets and diseases. The results from the three different approaches, fusion protein-targeted mucosal application, viral vector-mediated delivery for anti-HIV siRNA, and cholesterol-modified oligonucleotides, are exciting and call for more multidisciplinary collaborations to make convincing the impetus toward testing in bigger animal models and eventual human clinical trials.

A very futuristic presentation by James Heath (Caltech) outlined the effort using a systems biology approach in nanomedicine, especially with diagnostics at the individual level, as well as tissue-specific expressions of biomarkers at the gene and protein levels. At the protein expression level, Jan Schnitzer (Sidney Kimmel Cancer Center) pointed out the importance of tissue-specific endothelial cells and unique proteins expressed in endothelia of various normal tissues versus diseased tissues. The consensus among the speakers and the attendants was that the first cell type the drug carriers face en route to whatever the target cells are, particularly in oncological settings, is in most cases the endothelial cells. With this knowledge, the key question then was how we design more logical delivery and targeting strategies and how we develop the appropriate targeting carriers. A proper imaging technology to monitor the targeting and distribution of drug-containing carriers would be an important and powerful avenue to explore. Christine Allen (University of Toronto, Canada) discussed examples of following drug−liposomes with multiple imaging modalities in live animals. For targeting itself, Peter Senter (Seattle Genetics) presented their recent promising antibody−drug conjugates with emphasis on the conjugate chemistry. One was reminded of the importance and subtleties of details of conjugate chemistry in addition to the general strategies. James Marks (University of California, San Francisco) discussed details of generating single chain antibodies as one of the most attractive targeting moieties including the screening schemes for high affinity and/or internalizing antibodies, and affinity versus avidity when developed as multivalent targeting immunoliposomes. Several more talks on polymer-based delivery systems included Ronit Satchi-Fainaro (University of Tel Aviv, Israel), Dong Wang (University of Nebraska Medical Center), and Theresa Reinecke (University of Cincinnati) ranging from tumor vasculature targeting of angiogenesis inhibitors to the use of a series of defined synthetic glycopolymers. Further targeting opportunities are available using the interaction of folate to folate receptor-expressing cells (Phil Low (Purdue University)), one-bead one-compound libraries and their screening for targeting moieties (Kit Lam (University of California, Davis)), and phosphatidylserine-specific antibodies to tumors, activated immune cells, and viruses (Phil Thorpe (University of Texas, Dallas)). Additional examples of carriers with interesting properties were presented on biodegradable dextran microspheres (Wim Hennink (University of Utrecht, The Netherlands), pH-sensitive carriers including dendritic polymers of unique architectures (Frank Szoka (University of California, San Francisco)), and polymeric delivery carriers for nucleic acids (David Putnam (Cornell University)). Frank Szoka's talk particularly emphasized the mechanistic investigations into cellular processes involved in the functioning of various key features of these delivery carriers, which is exemplified by the multidisciplinary study on the so-called "sponge hypothesis" in gene delivery that utilizes carriers containing protonatable moieties.

Listening to these talks presented by the leaders in the field, one could oscillate between, on one hand, appreciation of the awesome diversity and imaginations these scientists are bringing to achieving the common goals of delivery while enduring the accompanying disappointments and, on the other hand, a keen recognition of the limitations and the difficulties we face as we understand the intrinsic barriers imposed by the physiobiological systems.

The readers of *Molecular Pharmaceutics* might appreciate a more in-depth description of exactly what was presented in each talk and discussed among the speakers and the participants. Without providing very intricate and detailed take-home messages from all the talks, as this was never intended to be a comprehensive report of the entire meeting, I aspired to share some of my overall impressions and thoughts with a broader view in this editorial. It is my hope and prediction that this GRC meeting will continue to be an important, cutting edge and smaller-focused meeting and that this journal will thrive as a comparable forum for new and innovative delivery issues and strategies. The scopes of the meeting and the journal will evolve and be refined iteratively by amalgamating many components in the biomedical field as the delivery field and the surrounding fields progress steadily. I look forward to the next Gordon Research Conference on Drug Carriers in Medicine and Biology, which will be held in the summer of 2008.

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