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molecular pharmaceutics

Meeting Report: International Symposium on Intelligent Drug Delivery Systems, 2010

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Received August 24, 2010; Accepted August 26, 2010

Since the 1960s, drug delivery systems have developed into a multibillion dollar enterprise, with such agents as enterically coated tablets, polymer drug conjugates, controlled release formulations, drug eluting stents, transdermal patches, and many others. The substantial impact that this field has had in clinical medicine is the basis for much ongoing research in ways to improve drug delivery using advanced designs and technologies. In May, 2010, the fourth International Symposium on Intelligent Drug Delivery Systems was held at the Korea Institute of Science and Technology (KIST) in Seoul, South Korea. Given the importance of this field and its relevance to research described in *Molecular Pharmaceutics*, we wished to provide a short summary of what transpired.

A large number of talks focused on delivery of siRNA, which is the central challenge in developing therapeutics based on these agents. Dr. Yu-Kyoung Oh from Seoul National University described amphipathic α-tocopherol−oligonucleotide chitosan conjugates that self-assembled into single layered oligomersomes in aqueous media forming structures referred to as TCOsomes. The ability of siMcl-1 TCOsomes to downregulate Mcl-1 expression and suppress tumor growth in xenograft models of human cancer provided evidence for in vivo siRNA delivery. Another novel delivery system was described by Kwangmeyung Kim from the Korea Institute of Science and Technology, who described the application of glycol chitosan nanoparticles for siRNA delivery to tumors. Systemic administration of siRNA-encapsulated nanoparticles into tumor bearing mice led to selective tumor uptake, gene-product suppression, and tumor growth inhibition. Sang-Kyung Lee and Yong-Hee Kim from Hanyang University utilized the interaction between siRNA and polyarginine−protein conjugates to deliver siRNAs to lung epithelial cells for treating asthma, to dendritic cells for autoimmune applications, and to tumor vasculature for antiangiogenesis therapy. An interesting variation involved the use of polyarginines with intervening disulfides that upon intracellular reduction efficiently released bound siRNA. A novel approach was described by Tae-Gwan Park from the Korea Advanced Institute of Science and Technology involving the preparation of siRNA multimers composed of sequences that silenced distinct genes. An oncology application utilized tethered siRNAs against BCL2 and survivin linked together either with cleavable disulfides or with noncleavable thioethers. These dimers had much more efficient gene silencing activities than corresponding single gene siRNAs. Taken together, the siRNA studies presented underscored the progress this field has experienced in the past year.

Progress has also been made in new delivery systems for conventional chemotherapeutics and low molecular weight drugs. One of the major pharmaceutical challenges involves the development of orally active drugs that efficiently penetrate epithelial barriers, such as in the gastrointestinal tract. Gordon Amidon from the University of Michigan detailed how it is now possible to simulate oral drug bioavailability, pharmacokinetics, and pharmacodynamics using a program known as GastroPlus. The in silico technology has provided insight into the use, activities and toxicities of simvastatin and several other pharmaceuticals. Marjo Yliperttula from the University of Helsinki also described computational models for predicting oral drug absorption. Applications were described to simulate the pharmacokinetics of drugs as a function of formulation. These algorithms can dramatically reduce the number of in vivo experiments required for drug development.

Experimentally, several approaches were described to improve drug oral bioavailability. Peter Swaan from the

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10.1021/mp1002812
Published on Web 10/06/2010

University of Maryland outlined strategies to overcome the intestinal barrier for the delivery of macromolecules. One approach involved insulin containing silicon particles in combination with permeation enhancers to increase insulin transport across intestinal epithelial monolayers. Other approaches involved novel highly stable liposomes and poly(amido amine) dendrimers that self-catalyzed absorption by opening gastrointestinal epithelial tight junctions. Dae-Duk Kim from Seoul National University described a novel microemulsion delivery system containing a Pgp inhibitor that was able to significantly improve (>5-fold in rats) the oral bioavailability of the anticancer drug docetaxel. Kang-Choon Lee from SungKyunKwan University provided the details of a novel approach for enhancing intestinal stability and absorption of the incretin receptor agonists glucagon-like peptide-1 and exendin-4 through biotinylation. These conjugates have applications in the treatment of diabetes.

Macromolecular-based delivery systems figured prominently in this year's meeting. Hamid Ghandehari from the University of Utah described the applications of polymers such as HPMA, poly(amido amine) dendrimers, silk-elastin like protein polymers, and PEGylated gold nanorods for improving drug solubility, activity, and specificity. Advancements in how such materials can be manufactured were related by Ji-Yeon Hong (S&G Biotech, Korea), who developed a supercritical fluid process to prepare poly(lactic-*co*-glycolic acid) microspheres for the controlled release of the anticancer drug gemcitabine. Sei Kwang Hahn from the Pohang University of Science and Technology (POSTECH) used advanced imaging technologies to track the biodistribution of hyaluronic acid polysaccharide−quantum dot conjugates. This allowed for the development of hyaluronic acid conjugates of siRNAs (anti-VEGF and anti-TGFβ) and exendin-4 that were optimally suited for liver delivery and for serum stability. Dal-Hee Min from the Korea Advanced Institute of Science and Technology described the use of multifunctional magnetic nanoparticles for imaging and hepatitis C treatment.

Several advancements in conditionally labile macromolecular delivery systems were reported. Akihiko Kikuchi from Tokyo University of Science detailed the applications for thermoresponsive polymers such as poly(*N*-isopropylacrylamide) for tissue engineering and biological modeling of human diseases. An example included the use of the polymer matrix to support cell growth, and phase-transition induced cell release from the matrix at 23 °C. The cells thus produced were much more tumorigenic than cells grown in conventional manners. Arto Urtti from the University of Helsinki described light and pH triggered nanosystems for drug and gene delivery. One example included liposomal calcein, in which encapsulated gold nanoparticles facilitated light induced liposomal disruption. Another example of a conditional release mechanism involved DNA polyplexes that were coated with a pH responsive lipid bilayer. The resulting complex became fusogenic when the pH was in the range of the endosomal pH value. Following on the theme of improved gene delivery, Hideyoshi Harashima from Hokkaido University described how a multifunctional envelope-type nanodevice led to transfection efficiencies in the same range as adenovirus. These constructs were often coated with PEG molecules that were cleaved by tumor associated proteases, a feature that was important in optimizing gene delivery. Finally, Peter Senter from Seattle Genetics related both the critical parameters for successful antibody mediated drug delivery, and the progress toward addressing them experimentally. An anti-CD30−auristatin conjugate resulted from a series of optimization studies and was found to efficiently release active drug in the presence of lysosomal enzymes within the target tumor cells. The conjugate has pronounced activities in patients with advanced, refractory Hodgkin lymphoma and anaplastic large cell lymphoma.

To summarize, the 2010 International Symposium on Intelligent Drug Delivery Systems highlighted many of the advancements being made in siRNA, protein, and small molecule delivery. Significant progress has been made in such areas as drug formulations, targeted macromolecular carriers, conditionally labile delivery agents, and computational modeling of drug disposition. The impact that these areas can have in clinical medicine is now becoming apparent, based on the promising translational data presented. The next meeting will be held in May 2011 at the Korea Institute of Science and Technology (KIST) in Seoul, Korea.

MP1002812