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Meeting Report: International Symposium on Intelligent Drug Delivery Systems South Korea, 2008

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In efforts to improve drug efficacy and minimize systemic toxicity, a great deal of research has surrounded the delivery of both small and macromolecular-based drugs to specific target sites within the body, The carriers used for these purposes include specialized nanoparticles, microspheres, polymers and dendrimers, micelles, monoclonal antibodies and other proteins, and liposomes. Recent advancements in this rapidly emerging field were highlighted at the 2008 International Symposium on Intelligent Drug Delivery Systems, which was held on May 10 and 11, 2008, at the Korea Institute of Science and Technology (KIST) in Seoul, South Korea. This meeting was attended by approximately 400 scientists from academia, industry, R&D institutes, and government. Support was provided by the Korea Ministry of Education, Science and Technology and Korea Biotech R&D Group as part of an initiative by the government to promote developments in drug delivery technology. Given the importance of this area of research for therapeutics and diagnostics, we felt that a meeting summary would be of interest to readers of Molecular Pharmaceutics.

The symposium began with opening remarks from Dr Kil-Joo Moon, vice president of KIST, Dr Gio-Bin Lim, head of Korea Biotech R&D Group, followed by a welcome address by Dr. Soo-Chang Song, the chairman of the organizing committee as well as the project leader of the intelligent drug delivery system R&D group, Korea. One of the keynote lectures was presented by Dr. Je Man Ryu, head of Dongwha Pharm R&D Institute, who gave an overview of the current R&D trends of pharmaceutical industries and underlined the importance of drug delivery systems for the development of both small molecular weight drugs and emerging biologicals. Prof. Chong-Kook Kim from Seoul National University gave the other keynote address on lipid-based particulate systems for delivery of poorly water-soluble drugs, and nucleic acid−based medicines. Various lipid-based particulate delivery systems were presented including liposomes, ultradeformable liposomes, emulsions, self-emulsifying formulations, dry emulsions, solid lipid nanoparticles, and other lipid conjugates. These agents were shown to be useful toward improving drug solubility, as well as altering their pharmacologic properties so they could penetrate through physiological barriers. In addition, these carriers were useful in stabilizing agents such as plasmid DNA and siRNA.

The importance of drug delivery from the perspective of a major pharmaceutical company was presented by Dr. Frank Grams from Roche Pharmaceuticals Co., Switzerland. It was pointed out that drug delivery technologies can make the difference between the success or failure of a drug candidate by addressing such issues as oral bioavailability, water solubility, and in improving both dosing regimens and safety profiles. The worldwide outsourcing efforts of the Roche group were introduced. For innovation in drug delivery, the Roche group currently focuses on three areas: oral delivery of biopharmaceutics classification system 2/4 compounds, subcutaneous delivery of highly concentrated protein solutions, and delivery of siRNA.

Dr. Hsing-Wen Sung from the National Tsing Hua University, Taiwan, described the use of nanoparticles prepared using mild ionic-gelation between a hydrolyzed poly-γ-glutamic acid and a low molecular-weight chitosan. Orally administered nanoparticles with insulin were shown to enhance the intestinal absorption of the protein and provide a sustained effect of decreasing the blood glucose level over a longer period of time. These results demonstrate how nanoparticles can enhance intestinal absorption of proteins by enhancing intestinal paracellular transport.

Further developments in using microspheres to overcome barriers to drug delivery were described by Dr. Dae-Duk Kim from Seoul National University, Korea, in a presentation focused on nasal delivery systems for fexofenadine·HCl. Hyaluronic acid mucoadhesive microspheres containing polyethyleneglycol (PEG) 6000 and/or sodium taurocholate

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were prepared by spray-drying method. Sodium taurocholate within microspheres increased the in vitro permeation of the drug across the human nasal epithelial monolayers. The encapsulation of fexofenadine·HCl in microspheres enhanced the nasal bioavailability of the drug in rabbits, suggesting that this approach may have significant clinical applications.

Significant attention was placed on methodology used to prepare nanoparticles and other vehicles for drug delivery. Dr. Giyoong Tae from the Gwangju Institute of Science and Technology, Korea, presented approaches involving photopolymerization of diacrylated pluronic F 127 to increase the temperature sensitivity and stability of the core/shell nanoparticles with Lecithin nanolipids. The core/shell nanoparticles were shown to undergo thermo-reversible volume changes. The stability of photocross-linking core/shell nanoparticles was increased compared to the core/shell nanoparticles made of bare pluronic polymer and lecithin. These nanoparticles were used for the controlled release of encapsulated proteins, and allowed for temperature-dependent protein release over extended periods of time.

Dr. Paolo Caliceti from the University of Padua, Italy, described several methods to modify proteins with PEG. While most modification strategies utilize available amino groups on lysines for conjugation, Dr. Caliceti described several other technologies that can be utilized for protein modification such as carbohydrate derivitization, and modifications on N-terminal amines, arginines, and cysteines residues. To prepare protein derivatives with defined chemical structure, composition, and high biological activity, site-selective PEGylation was used. Site-specific PEGylation was shown to avoid the loss of biological activity of several protein drugs such as cytokines, antibodies and other biomodulators.

A number of presentations focused on nanoparticles and hydrogels for sustained release of biologically active molecules. Dr. Doo Sung Lee from SungKyunKwan University, Korea, described a novel protein delivery system. The system was designed using poly β-amino esters as a basis for new polymeric materials that undergo sol−gel transition through manipulation of pH and temperature. The release of insulin could be controlled by degradation of the pH sensitive moiety. Hydrogels based on this technology were used to control glucose levels in diabetic rats. Professor Hiroaki Okada from the School of Pharmacy at Tokyo University, Japan, described the use of biodegradable microspheres for the long-term release of siRNA. Microspheres of siRNAs with a transfection agent achieved a high and sustained suppressive effect on target gene and induced apoptosis of tumor cells. Activities were obtained siRNAs that suppressed vascular endothelial growth factor (VEGF), and several other genes. In addition, DNA vaginal vaccines were formulated using a cell penetrating peptide and an NF-kB analog. Vaginal administration of formulated plasmid DNA using a needle-free injection resulted in improved immune responses.

Further work on the delivery of siRNA and shRNA was described by Dr. Chong-Su Cho from the Department of Agricultural Biotechnology at Seoul National University, Korea. A novel polymer carrier was designed consisting of a conjugate of polyethylenimine (PEI) and PEG. The carrier was complexed with siRNA and was highly effective at silencing target genes in vitro. In vivo work was carried out using a shRNA sequence that silenced the Akt1 cancer protein. In a urethane-induced lung cancer mouse model, the number and sizes of the tumor nodules decreased significantly after aerosol delivery of Akt1 shRNA using poly (amino ester) as a carrier. This was one of several examples in the meeting of how polymer and encapsulation strategies can be used to stabilize and deliver gene silencing molecules to target cell populations.

Dr. Kun Na from the Catholic University, Korea, discussed some of the shortcomings of commonly used poly(lactic-co-glycolic acid) (PLGA) microspheres for sustained protein delivery. When PLGA hydrolyzes, it releases components that can cause protein instability and acylation. This underscores the need to explore other biologically compatible matrices that can be used to reversibly encapsulate proteins of interest. Polysaccharide/protein complexes were described and were characterized in terms of particle size, efficiency, long-term stability and protein release-behavior. The complex was relatively stable in a wide range of pH values. Microspheres with higher contents of polysaccharides showed sustained release of proteins over 35 days.

Several presentations focused on tissue selective drug delivery with macromolecular based delivery systems, based on either passive or active targeting strategies. Dr. Masayuki Yokoyama from the Kanagawa Academy of Science and Technology, Japan, gave a presentation on polymeric micelle-targeting systems for diagnosis and therapy. The micelles are thought to accumulate in tumors through the enhanced permeability and retention effect originally described by Hiroshi Maeda. Gd ion-containing polymeric micelles were studied for their ability to enhance image contrast by shortening T1 relaxation times, and to deliver the MRI contrast agent selectively to tumor sites. In vivo molecular imaging was used to validate the targeted distribution of the MRI contrast agents entrapped in polymeric micelles. Significant MRI image enhancements were observed.

Dr. Ram I. Mahato from the University of Tennessee Health Science Center, U.S.A., described a specific uptake system for delivering siRNA to hepatocytes for treating liver disease. siRNAs targeting different regions of the hepatitis B surface antigen were designed and conjugated to galactosylated polyethylene glycol for targeted delivery to hepatocytes. The most potent siRNA was converted into shRNA and subsequently cloned into a plasmid vector. Plasmid DNA encoding multiple shRNAs efficiently inhibited the expression of hepatitis B virus surface antigen when transfected into hepatoma cells.

An approach to selectively target potent anticancer drugs to tumors using monoclonal antibody drug conjugates was described by Dr. Peter Senter from Seattle Genetics, Inc., U.S.A. Many of the key parameters for optimized anticancer immunoconjugates were addressed including drug potency, linker stability, antibody specificity and trafficking, efficient

drug release, and the need to address multidrug resistance. A case study was presented involving cAC10-vc-MMAE (SGN-35), a conjugate that binds to the CD30 antigen on Hodgkin's Disease. Upon internalization into antigen positive cells, the potent antimitotic drug monomethylauristatin E (MMAE) is released, leading to cell death through tubulin polymerization inhibition. SGN-35 was active in preclinical animal models and is showing strong signs of activity in a phase I clinical trial.

Another targeting strategy was described by Dr. Jin-Seok Kim from Sookmyung Women's University, Korea. pH-Sensitive liposomes were generated, and their surfaces were conjugated with an antiepidermal growth factor receptor antibody. The antibody-modified liposomes were shown to increase apoptosis of A549 xenografted tumor cells compared to all other treatments. The free drug and the nontargeted liposomal drug were less effective in anticancer activity than the immunoliposomes, as demonstrated through in vitro and in vivo experiments.

Dr. Chae-Ok Yun from the Yonsei University, Korea, described the delivery of RNAi to cancer cells using an oncolytic adenovirus carrier. An oncolytic adenovirus (Ad)-based shRNA expression system (Ad-ΔB7-shVEGF) was constructed against vascular endothelial growth factor (VEGF), a key mediator of angiogenesis. Ad-ΔB7-shVEGF induced significant reduction in tumor vasculature. Interleukin 8-specific shRNA-expressing oncolyticAd, Ad-ΔB7-shIL-8, was constructed and revealed anticancer effects in vitro and in vivo. The combined oncolytic viral therapy and cancer cell-specific gene targeting was suggested as a powerful therapeutic strategy against cancer.

A targeted approach to gene therapy was described by Dr. Minhyung Lee from Hanyang University, Korea, that takes advantage of hypoxic environments such as those found within sites of ischemic injury. The luciferase or VEGF expression vectors with an oxygen-dependent degradation domain were constructed and injected into rat ischemic myocardium to assess the therapeutic potential of this activation pathway for gene delivery. In animals treated with the vector containing the oxygen dependent degradation domain, there was a slight increase in vascularity compared to control treated animals. This approach may have applications in treating ischemic diseases.

An interesting presentation by Dr. Youngro Byun from the College of Pharmacy at Seoul National University, Korea described another novel method to attach tumor vasculature using nanostructure heparin. Low molecular weight heparin (LMWH) inhibits angiogenesis by inhibiting the activities of such growth factors as VEGF and basic fibroblast growth factor. However, LMWH distributes throughout the body, has significant side-effects, and does not specifically accumulate within solid tumor masses. Dr. Byun described a LMWH-taurocholate conjugate that forms nanoparticles having low anticoagulant activity. The particles accumulate within tumors and have significant antiangiogenic activities, leading to tumor growth inhibition. This work demonstrates that the biological activities and biodistribution characteristics of heparin can be changed significantly through a simple chemical modification which leads to nanoparticle generation.

In summary, the 2008 International Symposium on Intelligent Drug Delivery Systems focused on delivery systems for siRNA, shRNA, genes, small molecular weight drugs, proteins, and MRI contrast agents to tumors, myocardial infarcts, and specific cells and tissues of interest. A large variety of novel carriers consisting of nanoparticles, microspheres, proteins, polymers, and hydrophobic small molecules were shown to improve drug stability, bioavailability, efficacy, and safety in preclinical and clinical applications. This meeting will be held annually and will continue to feature cutting edge research in the field of drug delivery. The next meeting will be held in May, 2009, at KIST. For additional information, please contact the chair of the symposium, Dr. Soo-Chang Song (scsong@kist.re.kr).

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