CRS Leading Delivery Science and Technology

Newsletter

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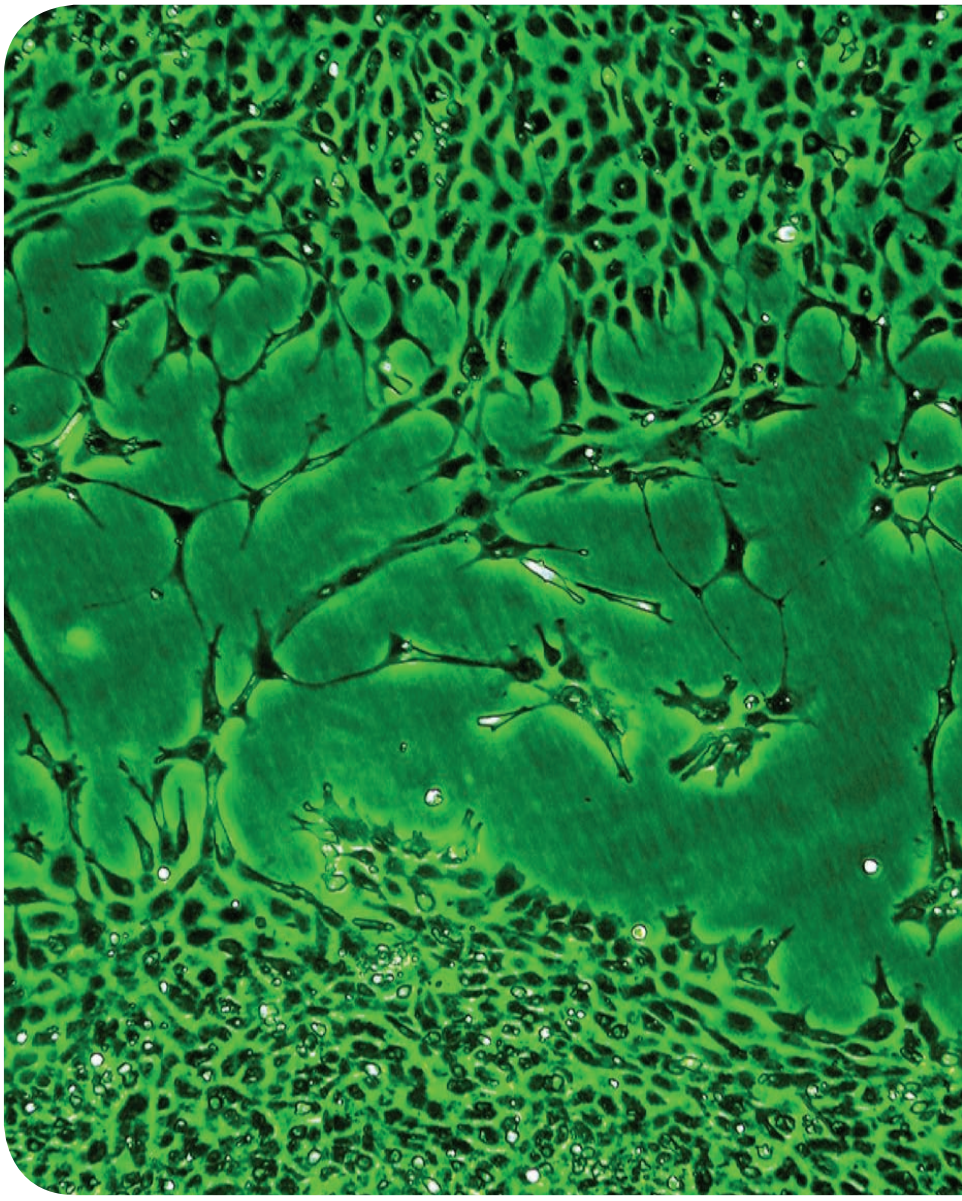

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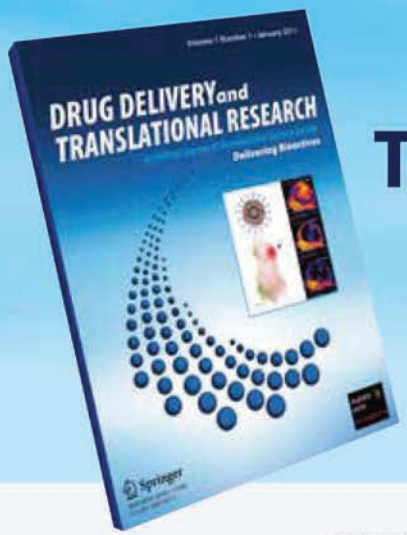

Drug Delivery and Translational Research

An Official Journal of the Controlled Release Society

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CRS Newsletter

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Charles Frey
Steven Giannos
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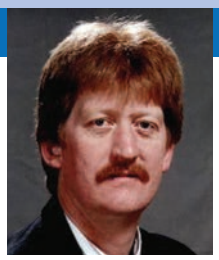


Roderick B. Walker, Ph.D.
Rhodes University
South Africa

2012 and Beyond

It is hard to believe that another year is fast approaching its end, and by all accounts 2012 has been a very busy and hopefully a successful year for CRS and its members. By all accounts the meeting in Canada was a great success and all who attended had an excellent social and importantly a significant scientific time.

In this issue of the *CRS Newsletter*, you will be inspired through interviews of two prominent members of CRS, Tamara Minko and Mansoor Amiji, who have achieved tremendous success and some of their career objectives and provide some insight to the rest of us about how we can all achieve to the best of our potential. CRS has many such scientists in their midst, and the ability to interact, meet, collaborate, and get advice from individuals of this calibre makes CRS a unique organization.

There are two enlightening Scientifically Speaking articles, the Patent Watch section provides insight into the amazing science of controlled release, and the report from the Young Scientist Committee suggests that they have had a productive year and an eventful annual meeting. As usual, there is a variety of news from various chapters and once again an excellent conference report from UKICRS, a highly motivated and productive chapter. In "People in the News," another CRS stalwart, Nicholas Peppas, was honoured with a Founders Award by the National Academy of Engineering for his work in polymer chemistry and advanced drug delivery. The "In the News" column clearly indicates that pharmaceutical and drug delivery technology research is healthy, vibrant, and undoubtedly ever-changing.

There are many opportunities in CRS for you as members to participate and share ideas. The current and future success of CRS is directly related to the enthusiasm and interest of its members, and in this respect we encourage members to participate actively by volunteering to serve as abstract reviewers or on a committee. We also encourage you as members to submit articles of interest, reports, or news for publication in the *CRS Newsletter*. In this issue there is a request that members provide some of their insight to solve a delivery problem, and I suggest we all have an attempt at providing an answer.

The abstract deadline for the 40th CRS Annual Meeting in Honolulu in July 2013 is January 24, and submissions have just opened. Submit your abstracts to ensure that the 2013 meeting is the best CRS meeting yet. Get busy writing, and I do hope to see you all in Hawaii.

It would be remiss of me not to ask members to spare a thought during this Thanksgiving season for all those people in the world who are less fortunate than we are. I am thinking specifically of those who have been affected by natural disasters and other circumstances outside of their control. Further, I would like for all to consider that we need to be assisting in developing ways of minimizing the tragic loss of life due to malaria, tuberculosis, and HIV/AIDS. Individually, we may make slow progress, but as a team who knows what is possible.

All that remains is for me to wish all our members a peaceful and pleasant rest of 2012, and I do hope that the holiday season will be fantastic. Take care, travel safely, and may 2013 bring all you wish for you and your families. ■

Kazunori Kataoka
University of Tokyo
Tokyo, Japan

The Dawning Era of "Nanophysiology"

In the biological system, there are many supramolecular structures (nanostructures) with sizes of several tens of nanometers, as represented by ribosomes, which are formed by the precise self-organization of biopolymers and play a role in vital functions through their dynamic structure change depending on the environment. These structures include particulate nanostructures that do not stay at a specific location but move freely within a living body while being involved in fit-for-purpose substance transport or transmission of chemical information.

Viruses are a typical example of such supramolecular structures, which can also be called nanovehicles. Although there are numerous types of viruses, they always form a sophisticated nanostructure in which DNAs or RNAs forming a compact structure are regularly coated by a protein shell (capsid); in some cases, a membrane structure (envelope), mainly consisting of lipid bimolecular membranes, is located on the surface.

This structure is not static but changes dynamically according to the external environment, a characteristic useful for achieving targeting to host cells. In particular, it can properly sense environmental changes within the host cells, has a processing function expressed in subsequent structural changes, and has an operation function for the expression of genetic information in a specified position within the cells. This structure is truly worthy to be called a dynamic nanoparticle with intelligent function.

Viruses are foreign particles that ingeniously enter the living body from the external environment as "uninvited guests" for the host cells. Recently, that the cells constituting the living body may produce nanoparticles by themselves for transmission of chemical information between cells has been drawing attention. These nanoparticles, called exosomes, are membrane vesicles with a diameter of several tens of nanometers that are formed by the secretion of a part of cell membranes. They contain microRNAs and messenger RNAs, which it appears are transported from cell to cell to regulate bodily function.

Hormone molecules are responsible for transmission of chemical information between distantly positioned cells in the living body, but exosomes are the media for transmission of chemical information and can be considered an impressive nanodelivery system endowed by nature. There is also a hypothesis that, among the abovementioned viruses, those with an envelope structure may coat their capsid surface with the envelope formed by phospholipid bimolecular membranes through the sophisticated use of the exosome secretion mechanism of host cells to achieve stabilization within the host organism and introduce the infection effectively. I am impressed with the depth of nanoparticles in Mother Nature.

From another viewpoint, that of clarifying the structure and function of nanoparticles in nature, significant progress has been made in the synthesis and functional analysis of supramolecular nanostructures in which the essence of natural nanoparticles is incorporated. To sum up their characteristics in a few words, three basic functions (sensing, processing, and operation) have been incorporated into the extremely small interior of nanoparticles in a sophisticated manner, as with viruses, meaning that the device integration has already been completed. In that sense, these nanoparticles are sophisticated nanodevices that act within the living body. I have no intention of competing with the evolutionary processes of viruses or exosomes, but I hope that, after these nanodevices are delivered into the microcosmos of the living body and have developed by overcoming many problems, they can not only provide diagnosis and treatment by delivering therapeutic agents or genes to the target site but also create an opportunity to clarify the mysteries of living organisms through the exploration of the nanoenvironment within the living body.

Molecular biology, which arose in the middle of the 20th century, has radically changed the whole concept of traditional biology to facilitate the construction of a science system centered on genomic analysis in combination with the development of high-performance sequencing. On the other hand, I think that physiology, by which the vital phenomena in the living body are comprehensively understood from the viewpoint of function, has tended to be treated from a phenomenological perspective, since it is difficult to clarify the events occurring within the living body itself at the molecular level while controlling time and space. However, I expect that with the future development of nanodevices and various *in vivo* imaging technologies for exploring the microenvironment within the living body, such problems will be solved, and a new science of "nanophysiology" will be constructed to enable the understanding of the complex events occurring in an individual organism at the molecular level. I do not believe that I am alone in this expectation.

Kazunori Kataoka ■

Scientific Interview with Prof. Tamara Minko

Vishwas Rai, Ph.D.,[1] and Bozena B. Michniak-Kohn, Ph.D.[2]

Tamara Minko at home with her German shepherd, Eva.

Dr. Tamara Minko is Professor II and Chair of Pharmaceutics at Rutgers, The State University of New Jersey. She is a fellow of the American Association of Pharmaceutical Scientists (AAPS), director-at-large of the CRS Board of Directors, recipient of numerous awards, editor of *Pharmaceutical Research*, on the editorial board of nine scientific journals, and a member of study sections at National Institutes of Health (NIH), Department of Defense (DOD), American Heart Association, and other national and international review panels. Dr. Minko has published more than 400 scientific publications (peer-reviewed papers, book chapters, conference proceedings, and patents). Many of her papers are well cited and published in prestigious journals with high impact factors. She has received multiple awards for the quality of her publications, including four CRS-sponsored awards since 2008.

Her current research interests include biopharmaceutics; targeted drug delivery; nanotechnology (polymers, dendrimers, liposomes, etc.) for detection and treatment of various pathological conditions including cancer and fibrosis; molecular targeting; nonviral nanoscale-based delivery of antisense oligonucleotides, siRNA, and peptides; mechanisms of multidrug resistance; intracellular fate and molecular mechanisms of action of anticancer drugs (apoptosis and necrosis, signal transduction, and antiapoptotic cellular defensive mechanisms); use of macromolecules for drug delivery; preclinical evaluation of anticancer drugs; tumor hypoxia; and modulation of cell death mechanisms during hypoxia. The research of Dr. Minko's group is supported by multiple grants from NIH, DOD, the National Science Foundation, pharmaceutical companies, and other national and international sources.

[1] Dermpathe Pharmaceuticals, Washington, NJ, U.S.A.
[2] Ernest Mario School of Pharmacy, Rutgers–The State University of New Jersey, U.S.A.

In addition to maintaining an active professional career, Dr. Minko also enjoys jazz music and watching sports programs, especially the Olympic games. Besides her husband and son, her family also includes two loving pets: a German shepherd (Eva) and cat (Kisa).

Q *You started your scientific career in Ukraine. What were some challenges and successes you experienced when you came to the United States?*

A My scientific career in the United States started in 1997 at the University of Utah in the laboratory of Prof. J. Kopecek. It was Dr. Kopecek who first introduced me to the fields of drug delivery and controlled release. Under the direction of Dr. Kopecek, I performed biological evaluations and examined mechanisms of action of HPMA-copolymer-based anticancer drugs. The data that we obtained during our 3.5-year study resulted in 14 peer-reviewed manuscripts.

Q *Which scientist or scientists would you say were the most influential on your academic career decisions?*

A I am very grateful to Prof. Kopecek and to my husband, Vitaly Pozharov, for their advice and help.

Q *Please give some insights on the current research areas being investigated in your research group and the potential impact in the field.*

A I can underline several aspects in my research that, in my opinion, can potentially provide a substantial impact in the fields of targeted drug delivery, nanomedicine, and cancer therapeutics:

- We were the first who started to use luteinizing hormone-releasing hormone (LHRH) peptide as a targeting moiety to direct drug delivery systems specifically to cancer cells. The use of LHRH peptide allows for enhancing the efficiency of cancer treatment and minimizing adverse side effects of chemotherapy.
- We have developed and tested multicomponent multifunctional delivery systems that include suppressors of pump and nonpump cellular resistance, targeting agent, and inducer of cell death. These systems contain a nanocarrier (liposome, dendrimer, polymer, lipid or silica nanoparticles, etc.), LHRH peptide/MUC1 aptamer as targeting moiety, antisense oligonucleotides/siRNA as suppressors of cellular resistance, and BH3 peptide/anticancer drug(s) as cell death inducer(s).
- We have designed and tested drug delivery systems for inhalation treatment of lung diseases (lung cancer, pulmonary fibrosis, and lung edema). The local delivery of drugs, specific siRNA, or antisense oligonucleotides into the lungs enhanced the efficacy of treatment and limited adverse side effects.

Q *Which of your recent publications do you feel have had the most impact on the field of drug delivery?*

A I would like to highlight the following publications from my lab:

Khandare, JJ, Minko, T. Polymer-drug conjugates: Progress in polymeric prodrugs, Prog. Polym. Sci. 31: 359-397 (2006).

Pakunlu, RI, Wang, Y, Saad, M, Khandare, JJ, Starovoytov, V, Minko, T. *In vitro* and *in vivo* intracellular liposomal delivery of antisense oligonucleotides and anticancer drug, J. Controlled Release 114: 153-162 (2006).

Patil, ML, Zhang, M, Betigeri, S, Taratula, O, He, H, Minko, T. Surface modified and internally cationic polyamidoamine dendrimers for efficient siRNA delivery, Bioconjugate Chem. 19: 1396-1403 (2008).

Q *As an overview, could you please elaborate on the possibility of different approaches being explored to target cancer cells in the body? Which one has shown the most promise?*

A Based on the data obtained in my laboratory within the last decade, I can conclude that the most promising targeted agent specific to many types of cancer cells for systemic delivery is LHRH peptide. Also, we have obtained very promising results using a local nanocarrier-based inhalation route of administration of drugs and nucleic acids for the treatment of lung diseases.

Q *You are currently the chair of the Department of Pharmaceutics at the Ernest Mario School of Pharmacy at Rutgers. What are your impressions of the position and its responsibilities?*

A In my vision, the major responsibility of a departmental chair is to create a friendly, pleasant, and productive atmosphere for prolific research of faculty and graduate students and effective teaching.

Q *We need to encourage more of our young scientists to consider a career in academia. What words of encouragement or guidance would you give them? Any thoughts on the future of academic research and funding in the United States that you would like to share with our readers?*

A In my opinion, an independent academic position gives the freedom to select a scientific direction of research, to teach your students and postdocs, to enjoy opening new scientific horizons, and to become a leader in the field if you are able to get funds for research. Unfortunately, the current financial situation in funding does not allow being very enthusiastic about the future. However, I believe in the bright future of U.S. science.

Q *Having successfully managed multiple important positions, what is your advice to current researchers on maintaining a work-life balance?*

A I consider myself as a happy individual because science is the main hobby in my life. The work of a scientist requires significantly more time than eight hours per day and sometimes is very stressful. Therefore, if somebody cannot devote an entire life to science, please do not consider an academic career.

Q *If for any reason you had not ended up having an academic faculty career, what do you think you would have considered as an alternative and why?*

A I do not consider any alternatives to an academic career. However, if I could not work in academia, I would find a billionaire, marry him, and not work at all.

Q *Tell us a little about the honors you have received, such as the Outstanding Paper awards from CRS.*

A I am very glad that the hard work of my laboratory was recognized three times by the Controlled Release Society Outstanding Pharmaceutical Paper Award in 2008, 2010, and 2011 and by the *Drug Delivery and Translational Research* Outstanding Research Paper Award for 2011.

Q *If you had a chance to go back, would you change anything in your career track?*

A I do not wish to change anything.

Further Reading

Betigeri, S, Zhang, M, Garbuzenko, O, Minko, T. Non-viral delivery of siRNA or antisense oligonucleotides targeted to Jun N-Terminal Kinase 1 prevents cellular hypoxic damage, Drug Deliv. Transl. Res. 1: 13-24 (2011).

Chandna, P, Khandare, JJ, Ber, E, Rodriguez-Rodriguez, L, Minko, T. Targeted multicomponent polymer-peptide-drug conjugates for treatment of primary and metastatic cancers, Pharm. Res. 27: 2296-2306 (2010).

Dharap, SS, Wang, Y, Chandna, P, Khandare, JJ, Qiu, B, Gunaseelan, S, Sinko, PJ, Stein, S, Farmanfarmanian, AV, Minko, T. Tumor-specific targeting of an anticancer drug delivery system by LHRH peptide, Proc. Natl. Acad. Sci. USA 102: 12962-12967 (2005).

Garbuzenko, OB, Saad, M, Pozharov, VP, Reuhl, KR, Mainelis, G, Minko, T. Inhibition of lung tumor growth by complex pulmonary delivery of drugs with oligonucleotides as suppressors of cellular resistance, Proc. Natl. Acad. Sci. USA 107: 10737-10742 (2010).

Patil, ML, Zhang, M, Garbuzenko, OB, Minko, T. Multifunctional triblock nanocarrier (PAMAM-PEG-PLL) for the efficient intracellular delivery of siRNA and potent gene silencing, ACS Nano 5: 1877-1887 (2011).

Saad, M, Garbuzenko, OB, Ber, E, Chandna, P, Khandare, JJ, Pozharov, VP, Minko, T. Receptor targeted polymers, dendrimers, liposomes: Which nanocarrier is the most efficient for tumor-specific treatment and imaging? J. Controlled Release 130: 107-114 (2008).

Taratula, O, Garbuzenko, OB, Chen, AM, Minko, T. Innovative strategy for treatment of lung cancer: Targeted nanotechnology-based inhalation co-delivery of anticancer drugs and siRNA, J. Drug Targeting 19: 900-914 (2011).

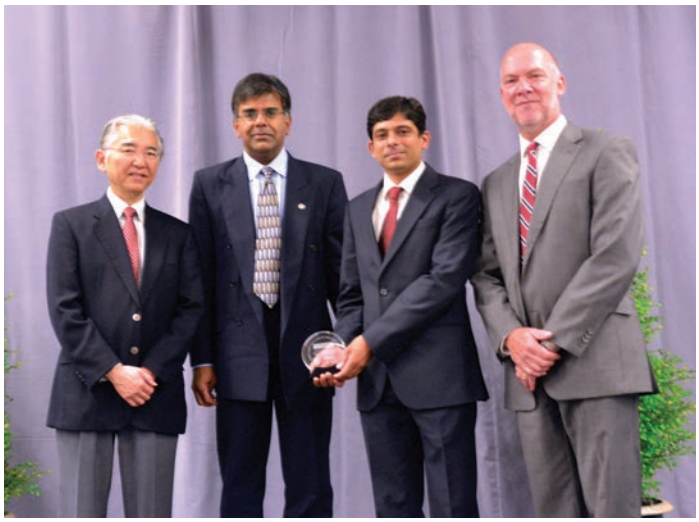
Taratula, O, Garbuzenko, OB, Kirkpatrick, P, Pandya, I, Savla, R, Pozharov, VP, He, H, Minko, T. Surface-engineered targeted PPI dendrimer for efficient intracellular and intratumoral siRNA delivery, J. Controlled Release 140: 284-293 (2009). ■

An Interview with Prof. Mansoor Amiji at Northeastern University

Vishwas Rai, Ph.D.,[1] and Bozena B. Michniak-Kohn, Ph.D.[2]

Dr. Mansoor Amiji is a distinguished professor and chairman in the Department of Pharmaceutical Sciences at the School of Pharmacy, Bouvé College of Health Sciences, at Northeastern University in Boston, Massachusetts, U.S.A. He is also the laboratory director for Biomaterials and Advanced Nano-Delivery Systems (BANDS) at Northeastern University.

Dr. Amiji obtained his B.S. in pharmacy (*magna cum laude*) from Northeastern University and Ph.D. in pharmaceutics/biomaterial science from the Department of Industrial and Physical Pharmacy, School of Pharmacy and Pharmacal Sciences, Purdue University, U.S.A., in 1992 and has served in multiple important positions at Northeastern University since then. He is a member of the CRS Board of Scientific Advisors, fellow of the American Association of Pharmaceutical Scientists (AAPS), and has won several awards and recognition in the field, including the AAPS Meritorious Manuscript Award and the Nano Science and Technology Institute (NSTI) Fellowship Award for outstanding contributions toward advancement in nanotechnology, microtechnology, and biotechnology. Under Prof. Amiji's supervision, Dr. Arun Iyer, a research assistant professor in the Department of Pharmaceutical Sciences at Northeastern University, was recently awarded the prestigious 2012 CRS T. Nagai Postdoctoral Research Achievement Award from CRS.



2011–2012 CRS President Dr. Martyn Davies (right) poses with 2012 CRS T. Nagai Postdoctoral Research Achievement Award recipient Dr. Arun Iyer (center right) and his advisor Prof. Mansoor Amiji (center left), along with 2012–2013 CRS President Prof. Kazunori Kataoka (left).

[1] Dermpathe Pharmaceuticals, Washington, NJ, U.S.A.
[2] Ernest Mario School of Pharmacy, Rutgers–The State University of New Jersey, U.S.A.

The overall research focus of Prof. Amiji's lab is development of imaging and therapeutic technologies for addressing challenging problems in cancer, inflammation, cardiovascular diseases, and infectious diseases. Active projects in his labs include the following:

- synthesis of novel biomaterials and nanosystems like chitosan-based biomaterials with poly(ethylene glycol) and heparin surface modification for encapsulation of hydrophilic and hydrophobic drugs, small interfering RNA, peptides, and genes;
- enhancing drug delivery efficiency using nanoparticle systems that can preferentially localize in the tumor, overcoming cellular resistance by lowering tumor apoptotic threshold and silencing genes that contribute to resistant phenotype, and affecting the role of tumor metabolism and especially aerobic glycolysis in resistance;
- use of macrophage-targeted nanoparticle-based delivery technologies to transfect plasmid DNA producing anti-inflammatory therapeutics, such as IL-10, and downregulate TNF using a targeted specific siRNA;
- preparation of oil-in-water nanoemulsions developed specifically with oils rich in omega-3 polyunsaturated fatty acids (PUFA) for delivery of compounds to the brain to treat CNS diseases;
- development of cancer vaccines using a multicompartmental delivery strategy that can encapsulate different types of payloads and efficiently target antigen-presenting cells upon systemic administration;
- preparation of nanoparticles for enhanced delivery efficiency and efficacy of potent antimicrobial and antiviral agent; and
- development of novel constructs that incorporate optical and scattering-based targeted image contrast agents for early disease detection (e.g., oral precancer lesions) and imaging (e.g., endoscopy guided OCT imaging in colon cancer).

The projects are supported by multiple grants from the National Institutes of Health (NIH), National Science Foundation (NSF), and private industries.

Prof. Amiji was born in Zanzibar, Tanzania, and moved to the United States in 1983. He is happily married to his wife, Tusneem, and they have three lovely daughters: Zahra, Anisa, and Salima. In his personal life, Prof. Amiji likes to play sports, read, travel, and spend time with his family and friends.

Q *Please tell us a little bit about your graduate school experience at Purdue University. What made you choose Purdue? What kind of research were you involved in? How did you approach the research questions?*

A As an undergraduate pharmacy student at Northeastern University, I participated in a research experience focused on novel drug delivery that strengthened my resolve to attend graduate school for a doctoral degree in pharmaceutics. After applying to several schools with excellent pharmaceutics programs, I was invited to visit the Purdue campus and meet with faculty, postdoctoral associates, and students. A good friend of mine from Northeastern, Bill McLaughlin, was also attending Purdue at the time. I joined Purdue in August 1988 and spent a few months in selecting an advisor and research area that I wanted to work on for my doctoral dissertation.

Prof. Kinam Park and his wife, Dr. Haesun Park, were working on several very exciting projects. Dr. Park had recently transferred to Purdue from the University of Utah, and there were five of us who started with him in 1989. During his postdoctoral work at the University of Wisconsin, Dr. Park focused on evaluation of blood-biomaterial interactions that lead to thrombosis and other complications with implantable devices. I decided to join the Park group at Purdue and worked on surface modification of biomaterials with water-soluble polymers to improve blood compatibility. We modified different types of materials by surface adsorption and covalent grafting of poly(ethylene glycol)-based polymers and studied the interactions of blood proteins and cells, such as platelets. This work led to several general concepts of biomaterial surface modification that requires tight anchoring of the water-soluble polymers to prevent displacement, flexibility and extension from the surface in aqueous environment, and optimization of the surface density to prevent "bridging phenomena." The Park lab did some really innovative science and instilled in me the passion to tackle big problems and find innovative solutions at the interface of scientific fields. We used relatively sophisticated experimental and computational tools at the time, such as image acquisition and analysis, to study cell-material interactions and quantify platelet adhesion and shape changes using area and circularity measurements.

Prof. Nick Peppas was also at Purdue in the Chemical Engineering Department, and I had the privilege of taking courses with him and having him on my thesis committee. It was also relatively easy to find scientific collaborations and access to resources at Purdue. I was able to take advanced courses and learn how to use electron microscopes, flow cytometers, and other sophisticated equipment in the university's core facilities. The Veterinary School at Purdue was also a great place for collaborative research, especially in terms of access to different animal models.

Although it was initially a shock to go from Boston to West Lafayette, Purdue was a great place for me to learn and get trained. Excellence in scientific inquiry and the collaborative environment that exists at Purdue are unique hallmarks of the institution. Those of us in the Park research group at the time also had an amazing camaraderie and developed life-long friendships. We celebrated each other's birthdays and other milestones, such as graduations, and had Thanksgiving dinners each year at Dr. Park's home.

Q *What made you choose an academic career over the pharmaceutical industry? It also appears that you have preferred to be in the New England area. Is there any special reason for that?*

A A few months before graduating from Purdue in 1992, I applied for positions in both academia and industry. I was interviewed by Northeastern University, my *alma mater*, AstraZeneca, Pharmacia/Upjohn, and Columbia Research Labs, which was started by the late University of Wisconsin professor Joseph Robinson. I took the Columbia position since it involved working on a drug delivery project. I was in Madison from July to December 1992, when Columbia closed its R&D operation. Luckily for me, the Northeastern position was still open, and I was able to join as an assistant professor from January 1993. I really enjoy being in academia. I get to interact with the most talented students and postdocs and work on problems of my own choosing. I also really enjoy teaching—either large group such as in pharmacy courses or one-on-one with graduate students and researchers in the lab.

My wife and I first met in Boston in 1987 when I was a student at Northeastern and she was a student at Massachusetts College of Pharmacy. We both moved to the Midwest—I was at Purdue in West Lafayette and she worked as a nuclear pharmacist at Syncor in Chicago. After we got married, returning to Boston was natural to both of us since we had spent so much time there, had friends, and knew the city well. Boston is a wonderful metropolis with many higher education institutions and cultural centers. The opportunity to collaborate with researchers from other universities or medical research centers is truly remarkable. Additionally, almost every major pharmaceutical and biotech company has a research hub in the Boston/Cambridge area.

Q *Your lab focuses on research areas like inflammatory bowel disease, tumor drug resistance, modulation of BBB transport (neurological disorders), ovarian cancer, pancreatic cancer, and so on. How do manage the time and resources on each project apart from teaching responsibilities?*

A I am fascinated with disease pathology and find the opportunities for drug or gene delivery in almost every subject area that I investigate. In each of these diseases, we are always thinking of innovative strategies that can improve therapeutic outcomes. The basic driving force for us is in deeper understanding of the problem and then finding a novel solution. For example, in inflammatory bowel disease, we have focused on a multicompartmental delivery system for oral gene therapy (with IL-10 expressing plasmid) or gene silencing (with either TNF-α or cyclin D-1 silencing siRNA). In overcoming tumor resistance, our focus is to understand the phenotypic alternations in tumor cells based on micro-environmental selection pressures and then finding novel

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solutions. We have explored glucose metabolism inhibition, intracellular ceramide modulation, and gene silencing strategies, in combination with cytotoxic chemotherapy, to improve outcomes.

I also give freedom to my students and postdocs to find solutions on their own. For example, Mayank Bhavsar, a Ph.D. graduate from my lab, came up with the idea of a nanoparticles-in-microsphere oral system (NiMOS) for oral gene delivery. Lara Milane, another Ph.D. graduate, suggested that we evaluate the role of aerobic glucose metabolism (or Warburg effect) in cancer on development of drug resistance. The senior researchers in the lab are also very effective in assisting younger students, especially those who are in the M.S. degree program. This helps me tremendously with time management.

I also do a lot of work remotely with the use of electronic communications, Skype, and teleconferencing. I am able to send emails from almost anywhere, including while coming to work in the morning in commuter rail or when I am at airports going from one place to another.

Q *Could you please identify a couple of research articles that you value as of high importance coming out of your lab?*

A Over the span of my career, I have published four books and close to 150 peer-reviewed articles and book chapters. It is hard to select a few that have been impactful, but here are five examples from the last decade:

Lynn, DM, Amiji, MM, Langer, R. pH-responsive biodegradable polymer microspheres: Rapid release of encapsulated material within the range of intracellular pH. Angew. Chem., Int. Ed. 40(9): 1707-1710 (2001).
After getting tenure and promotion to associate professor in 2000, I had a unique privilege to do a sabbatical at MIT in Prof. Robert Langer's lab. This publication came out of my work in the Langer lab with Dr. David M. Lynn, who is currently an associate professor at the University of Wisconsin–Madison. Our effort in combinatorial synthesis of poly(beta-amino esters) and high throughput testing led to extended collaborations with several Langer lab alums, including Dr. Stephen R. Little, who is now at the University of Pittsburgh.

Kaul, G, Amiji, M. Tumor-targeted delivery of plasmid DNA using poly(ethylene glycol)-modified gelatin nanoparticles: *In vitro* and *in vivo* studies. Pharm. Res. 22(6): 951-961 (2005).
This paper, published in the AAPS journal *Pharmaceutical Research*, is part of the dissertation work done by my second Ph.D. student, Goldie Kaul. This was our first attempt at designing type B gelatin-based nanoparticles using a solvent displacement method as a noncondensing hydrogel-based plasmid DNA delivery system for *in vitro* and *in vivo* gene transfection. In 2007, this publication received the Meritorious Manuscript Award from the AAPS.

van Vlerken, L, Duan, Z, Seiden, M, Amiji, M. Modulation of intracellular ceramide with polymeric nanoparticles to overcome multidrug resistance in cancer. Cancer Res. 67(10): 4843-4850 (2007).
Over a period of about 10 years now, our work has been focused on a multimodal strategy to overcome tumor drug resistance. This seminal paper, published in the AACR journal *Cancer Research*, resulted from the doctoral dissertation of Lilian van Vlerken. The research was done in collaboration with Dr. Zhenfeng Duan, who is at Massachusetts General Hospital (MGH) in Boston, and Dr. Michael Seiden, who is currently the president and CEO of Fox Chase Cancer Center in Philadelphia, Pennsylvania. For the first time, we showed that intracellular modulation by nanoparticle-mediated delivery amplified apoptotic signaling, leading to efficient cell death in an *mdr-1* positive ovarian adenocarcinoma model.

Bhavsar, MD, Amiji, MM. Oral IL-10 gene delivery in a microsphere-based formulation for local transfection and therapeutic efficacy in inflammatory bowel disease. Gene Ther. 15(17): 1200-1209 (2008).
Mayank Bhavsar, a doctoral student in my group, came up with the idea of a multicompartmental delivery system for oral gene therapy. Using type B gelatin nanoparticles that were further encased in poly(epsilon-caprolactone) microspheres, Mayank showed that they can deliver reporter (GFP and beta-galactosidase expressing) and therapeutic (murine IL-10 expressing) plasmid DNA orally in Balb/c mice. The IL-10 expressing plasmid was effective in treatment of inflammatory bowel disease. This paper describes the *in vivo* gene transfection and therapeutic efficacy of the NiMOS in a trinitrobenezenesulfonic acid (TNBS)-induced acute colitis model.

Milane, L, Duan, Z, Amiji, MM. Development of EGFR-targeted polymer blend nanocarriers for paclitaxel/lonidamine delivery to treat multi-drug resistance in human breast and ovarian tumor cells. Mol. Pharmaceutics 8(1): 185-203 (2011). DOI: 10.1021/mp1002653.
We hypothesized that hypoxia, aerobic glycolysis, and lactate production in tumors contribute to the development of aggressive phenotype, including development of multidrug resistance (MDR). Lara Milane, another doctoral student, worked on evaluation of the role of hypoxia in MDR development and the role of hexokinase-2 inhibitor, lonidamine, in overcoming drug resistance based on inhibition of glucose metabolism. Using EGFR-targeted PLGA/PCL blend nanoparticles, Lara evaluated the delivery efficiency and cytotoxicity *in vitro* and *in vivo* in MDR breast and ovarian cancer models. This paper describes Lara's work, in collaboration with Dr. Duan at MGH, on *in vitro* evaluations of paclitaxel/lonidamine cotherapy in drug resistant cells.

Q *Could you also please shed light on some research papers (from other labs) that have made significant contributions in the fields of interests like inflammatory bowel disease, tumor drug resistance, modulation of BBB transport (neurological disorders), ovarian cancer, and pancreatic cancer?*

A Rather than any specific disease areas, we tend to focus on research and new technologies that are published by pharmaceutical scientists and chemical engineers working in the field of drug and gene delivery systems. For hydrogel-based drug formulations, Kinam Park's and Nick Peppas's groups continue to inspire us with some very innovative ideas. We also closely look at publications from the Langer lab, Sangeeta Bhatia, Dan Anderson, and Paula Hammond from MIT on different types of nanodelivery systems. Patrick Couveur, Tom Kissel, Gert Strom, and other European pharmaceutical scientists are also doing excellent work on drug and gene/siRNA delivery systems. From Asia, we look at literature published by South Korean and Japanese groups, especially Prof. Kataoka and other prominent researchers in the field. Recently, I have been reading on adjuvants and vaccine delivery systems, especially coming from Aliasgar Salem's group at the University of Iowa, Krish Roy's group at the University of Texas at Austin, Darrell Irvine at MIT, and some of the older publications that Derek O'Hagan and Manmohan Singh published from Chiron and Novartis Vaccines.

In addition to publications, I also get inspired by discussions with colleagues, especially clinicians like Dr. Duan at MGH, Dr. Edward Whang at the Brigham and Women's Hospital, and others who are collaborating with us. Industrial collaborations are also important in framing our thoughts and plans. We are working closely with scientists at Nemucore Medical Innovations, a start-up company that has licensed our nano-emulsion technology.

Q *Please tell us about the combinatorial-designed formulations approach for preparing novel multifunctional polymeric nanosystems. Can they be used for different disorders? What is the rationale behind designing a particular nanosystem in any system?*

A With funding from the NCI Alliance for Nanotechnology in Cancer, we have been examining nanotherapeutic strategies for overcoming tumor drug resistance. One of the challenges we observed in developing nanotherapeutics for cancer was that there was a large diversity in the physicochemical properties and delivery needs of the therapeutic agents as well as MDR modulators. In some cases, we were working with hydrophilic drugs (e.g., doxorubicin) and a hydrophobic MDR modulator (e.g., ceramide). Alternatively, the drugs may be hydrophobic (e.g., paclitaxel) and the resistance is modulated by a gene silencing approach using siRNA duplexes. To overcome the need to develop new nanoparticle systems for each of the payloads independently, we focused on a LEGO®-based assembly process in designing different formulations that meet the payload and delivery needs. For this, we make about 50–100 different polymeric derivatives and assemble them with the individual payloads in varying proportions leading to a large library of drug- or siRNA-containing formulations. The polymeric derivatives are based on functional blocks that contain different-sized lipid tails, different numbers and types of amine groups, thiol groups for intermolecular disulfide crosslinking, PEG modification, and having targeting ligands. Additional blocks with endosomal escaping moiety and fluorescence or radioactive label are also feasible. These functional blocks are then assembled with the different types of payload and optimized for delivery efficiency *in vitro* and then *in vivo* in relevant animal models. Currently we are using the combinatorial-designed nanoformulation approach for encapsulating different types of anticancer drugs from cisplatin and doxorubicin to paclitaxel and ceramide. Additionally, we have also encapsulated native and modified siRNA sequences for silencing *PLK-1*, *survivin,* and *bcl-2* genes. All of this work is focused on overcoming MDR in ovarian and lung cancer models.

Combinatorial-designed nanoformulations can certainly be very useful for other diseases. In collaboration with Dr. Morris White at Children's Hospital/Harvard Medical School, we are looking at liver-specific gene silencing using hyaluronic acid-based self-assembled nanostructures for treating insulin resistance in type 1 diabetes. There are also very interesting drug delivery opportunities in inflammatory and infectious disease areas that we are interested in pursuing using the combinatorial-designed nanoformulation approach.

Q *When performing targeted delivery, what efficiency have you achieved from your polymeric nanosystems? Were you able to control the target-based approach based on chemical modifications in your chemical systems? Please give us a few examples.*

A We have worked with both passive- and active-targeted delivery systems. Overall, our results show that passive targeting in tumors is effective in delivering about 10% of the injected dose, if there is high degree of vascularity and the tumor size is large enough such that the pores of the blood vessels are larger than the diameter of the long-circulating nanoparticles.

Active targeting, on the other hand, enhances the initial availability of the nanoparticles and more selective interactions with the cells that have the target of interest. We can get up to about 20% of the injected dose in tumors with EGFR peptide-based targeting over a 12–24 hour period. Surface density of the ligand and flexibility of attachment through a spacer is critical. As such, for specific localization of the nanoparticle formulations injected intravenously, we have found that you need both vascularity and overexpression of the target. The balance between these factors is critical to ensure adequate delivery enhancement without significant influence of the systemic clearance mechanisms.

I am also a big fan of using the inherent material properties or external stimuli to enhance delivery efficiency. I don't think that surface modification of delivery vehicles should be the only approach. For example, Abraxane® is known to

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preferentially accumulate at tumor sites due to albumin affinity to glycoprotein receptors and the presence of SPARC in tumors. We selected type B gelatin for similar reasons as there are several RGD units from denatured collagen that remain in gelatin. Recently, our focus has shifted to hyaluronic acid based on its affinity to CD44 receptors. Other investigators have shown that external stimuli, such as heat, can enhance thermally responsive liposomal delivery efficiency and permeability in solid tumors.

Q *How efficient has gene silencing with nanoparticle-encapsulated siRNA been in overcoming tumor multidrug resistance?*

A Using hyaluronic acid–based self-assembling nanosystems, we can achieve up to 90% gene silencing efficacy *in vitro* with a 100 n*M* siRNA dose and up to 70% gene silencing *in vivo* in CD44-expressing MDR tumors with three 0.5 mg/kg intravenous doses.

We continue to optimize the formulations to achieve even better efficiency by using chemically modified siRNA sequences with greater potency, preventing premature siRNA degradation, enhancing intracellular delivery, and improving endosomal escape in cell culture systems. For *in vivo* specific delivery, avoiding premature degradation and clearance, target-specific localization, intracellular delivery, and cytoplasmic release are major factors that will influence success. The combinatorial-designed system is sufficiently versatile that we can tailor the formulations by addressing each of the barriers independently.

Q *In your view, how can we improve the current cancer therapy?*

A Cancer is a major clinical challenge of our time. Most epidemiological projections show that cancer mortality will supersede even cardiovascular diseases within a few years in the United States and other parts of the world. The biggest challenges in cancer, especially in those that are associated with high mortality rates, are lack of early diagnosis, heterogeneity of the tumor cells and variability between patients due to constant mutations and adaptations, nonspecificity of currently therapy, and poor systemic delivery efficiency. The majority of cancer mortality is attributed to disease metastasis and development of aggressive phenotype that leads to drug resistance.

There are many other efforts across the globe that are yielding important insights into the biology of cancer, microenvironmental signals that affect metastasis and resistance, and strategies that can improve therapeutic outcomes. Isolation of rare circulating tumor cells (CTCs) from patient blood, for example, is providing important clues on phenotypic differences between primary tumor cells and those that have disseminated. CTCs also are important biomarkers of anticancer therapy effectiveness. Understanding the biology of tumor initiating (or stem) cells is critical in developing new approaches, such as rational combination therapeutic strategies, to mitigate the incidence of resistance development. There is also tremendous interest in harnessing the power of the immune system in attacking tumors. Although there have been some breakthroughs in vaccine development, more needs to be done to improve vaccine and immune therapy effectiveness in cancer.

In all of the preceding examples, more focus is needed on clinical translation of the ideas so that they ultimately benefit cancer patients. The NCI Alliance for Nanotechnology in Cancer was established in 2004 with this objective. Over the last eight years, the Alliance has supported many investigators through center, platform, and training grants. The Alliance also established the Nanotechnology Characterization Laboratory to aid in preclinical development of nanosystems for cancer. One of the most important outcomes of the Alliance effort is that basic scientists and engineers are now collaborating with clinicians with a razor-sharp focus on developing cancer diagnostics, imaging agents, and therapies from bench to bedside. Additionally, the Alliance also stresses industrial collaborations and technology transfer. Many companies were started and some, like Bind, Cerulean, and Nemucore, are actively moving academic research into clinical development. I am very optimistic that in the next few years we will certainly see many more nanotechnology-based solutions in the clinic for cancer patients.

Q *What are your research goals in the coming 5–10 years? Is there anything specific you would like to achieve in your career?*

A I have had a very successful career so far. I have been involved in teaching, research, and service to my institution and to the broader scientific community.

The BANDS research group in 2011. Left to right: Dr. Srinivas Reddy Boreddy, Sunita Yadav, Dr. Amit Singh, Dr. Srinivas Ganta, Darshna Patel, Aatman Doshi, Deepti Deshpande, Prof. Mansoor Amiji, Shardool Jain, Ankita Raikar, Verbena Kosovrasti, Ganesan Venkatesan, Ruchi Shah, Jing Xu, Sravani Kethireddy, Lipa Shah, Faryal Mir, Shanthi Ganesh, Lavanya Thapa, and Dr. Arun Iyer.

In research, I am very fortunate and feel truly blessed to have had a remarkable group of researchers and students in my lab. Currently, my group has over 20 individuals from research faculty and postdoctoral associates to undergraduate students. One of the biggest threats to sustaining large research programs is the current funding crisis in the

United States, especially from federal sources. I am very concerned that my group will shrink significantly in the coming years without adequate resources. As such, sustaining the NCI Alliance for Nanotechnology in Cancer and other programs that support research in drug delivery and nanomedicine is critical.

In the coming years, we will continue to work on exciting research areas by trying to identify novel solutions. I am increasingly fascinated with chronic inflammation, which has a central role in so many diseases, including cancer, cardiovascular diseases, diabetes, and neurodegenerative diseases. The role of macrophages and other immune cells in propagating and controlling the inflammatory processes is central in any therapeutic intervention. We are currently exploring novel strategies, based on macrophage-specific delivery, to affect inflammation. Diseases of the CNS are also very challenging to treat effectively due to the presence of the blood-brain barrier. We are interested in exploring delivery strategies that enhance permeation across the brain capillaries upon systemic administration. Multimodal strategies that both affect the permeability across capillary endothelium and inhibit efflux transport show promise. We are also exploring intranasal delivery to the brain, especially for large molecular compounds such as peptides, proteins, and gene constructs.

My dream is to see that our research efforts lead to products that can help patients. We are moving in this direction by partnering with companies so they can take academic technologies and develop these into clinically viable therapeutics, such as a targeted nanoemulsion formulation with combination therapy for treating refractory ovarian cancer that is being developed by Nemucore.

Q *Who (scientist or otherwise) has influenced your research the most?*

A There are four individuals who have had a profound influence on my career. Interestingly, all four of them are also towering figures in the CRS.

First and foremost, Kinam Park has been most profoundly influential through his remarkable intellect, can-do spirit, amazing generosity, and wonderful sense of humor. He and Haesun taught me the value of problem solving in science and never to get fixated on any specific disciplinary boundary.

After graduating from Purdue, I had the distinct honor of working with the late Joseph Robinson at Columbia Research Labs in Madison, Wisconsin. Although I was in Madison for only a few months, Joe's influence has remained with me throughout my life. Whenever we met at AAPS or CRS conferences, Joe would always ask how my career was going and how he could help.

Vladimir Torchilin joined Northeastern as chair of the Pharmaceutical Sciences Department in the late 1990s. As a pretenured faculty member at the time, access to resources and all the guidance that Vladimir provided was invaluable. He has been instrumental in all of my career decisions, including most recently becoming the department chair.

Lastly, in 2000 after receiving tenure and promotion, I had the opportunity to do a sabbatical in Bob Langer's lab at MIT. Bob's impact on the careers of others is legendary. The opportunity to work with talented researchers such as Dave Lynn, Dave Putnam, and Dan Anderson at MIT was inspiring. I am forever indebted to Bob for allowing me to join his group and for supporting my career.

"Standing on the Shoulders of Giants..."

Kinam Park
Purdue University

Joseph Robinson
University of Wisconsin–Madison

Vladimir Torchilin
Northeastern University

Robert Langer
MIT

Q *As a chairman, could you please tell us about the research focus of the Department of Pharmaceutical Sciences at Northeastern? Are there any specific areas you would like to focus on as a department in the future?*

A Academic leadership through administrative responsibilities is a wonderful experience, and I have been privileged to lead a vibrant department of 20 faculty members with four centers of research excellence. Northeastern's School of Pharmacy currently ranks seventh in NIH grant funding of all pharmacy schools and first among private schools. Besides rankings, there are so many other measures of success that our faculty and students are able to achieve. Distinguished Professor Vladimir Torchilin, who is well known to the CRS community, is one of our superstars! My challenge is to continue to sustain the momentum and build on our successes of the past.

I also enjoy the opportunity for entrepreneurship in higher education that fosters development of new educational programs at the interfaces of science, business, and law. I have been involved in launching several professional science master's (PSM) programs at Northeastern that combine training with practical experience in the form of short-term internships in biotech or pharma companies. I am a big believer of "learning while doing"—the experiential model of education that Northeastern has been a leader in for over a century. I would like to be involved in furthering the

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experiential model of education at the graduate level, especially by actively engaging with the rich ecosystem of biotech and pharma companies that are in the Boston/Cambridge area. We have initiated several models of collaborations with industry through establishment of graduate fellowships for doctoral students who can work both on campus and at the company. We have also created a unique Ph.D. program catering especially to industrial scientists who have an M.S. degree. I also would like to work with foreign institutions in bringing this model of education abroad.

Q *How do you manage efficiency with such a large group of people? How do you achieve the work-life balance between so many responsibilities?*

A It is hard to manage large research groups, especially in the face of the current funding crunch. However, I am fortunate to have senior researchers like Arun Iyer and Amit Singh and Ph.D. students who have been in the lab for several years now. These individuals help me by providing assistance to younger students, especially those in the master's program who are interested in research experience.

I also regularly have meetings with my lab group to make sure that everyone can provide updates of their progress and we can quickly identify the problems they are having. My group is also sufficiently diverse with expertise in synthetic chemistry, biology, pharmaceutical sciences, and biomedical engineering to allow cross-talk and problem solving.

Work-life balance is much harder for me, especially since we have three kids and both parents are working. My wife is a registered pharmacist with Walgreens, and she is now working part time so we can be there for our children. Her love and support have been extremely important for my career. When the kids were growing up, we had to be very creative with our time. I traveled a lot less back then to make sure that we were able to meet the demands at home. Now, our oldest daughter is almost finishing high school and our youngest is in seventh grade. With them being a little older, I was able to take on the administrative responsibilities of the department chair. I also travel a lot more for meetings and other commitments.

Q *Please tell us about your favorite free-time activities.*

A I like to play sports, read, travel to exotic places, and enjoy spending time with my family. Our youngest daughter, Salima, plays soccer and basketball, and I love going to her games and cheering the kids on her team.

Q *What would be your advice to young researchers still trying to decide a career path for themselves?*

A Here is my "top ten" list (with apologies to David Letterman):

1) Become a universal problem solver—focus your energy on how to solve important societal problems regardless of discipline.
2) Never accept the *status quo*—in science, nothing is ever "perfect."
3) Work in teams—solo players in science are becoming extinct. More and more, you will be required to work in teams and so keep your ego in check.
4) Be malleable—in your career, you will be required to change more often than you desire. Being able to fit any mold is critical to success.
5) Diversity is the key to learning new skills—hang around with smart people who are different than you.
6) Don't be afraid to fail—failure and learning from one's missteps makes the successes in life mean even more.
7) Be a teacher—share what you know with others. If you share, most people will return the favor.
8) Ethics and standards matter—never compromise your long-standing values for any short-term gain.
9) Become a serial entrepreneur—learn to market your ideas and products.
10) Shatter barriers and stereotypes—but know that success will not land on a silver platter. ■

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Real-Time Label-Free Monitoring of Drug- or Nanoparticle-Cell Interactions

Tapani Viitala,[1,2] Niko Granqvist,[1] Huamin Liang,[1] and Marjo Yliperttula[1]

Introduction

Efficient drug delivery is one of the major challenges in modern pharmaceutical research. There is a constant need for developing new formulation strategies for new drug delivery systems because new chemical entities tend to have low solubility, and biotechnology drugs (e.g., DNA, oligonucleotides, antibodies, and proteins) permeate poorly to the target sites, limiting or even prohibiting their therapeutic use. The potency of new drugs is usually demonstrated by cell interaction tests (uptake, response, and toxicity). However, *in vitro* cell culture methods are not able to measure real-time kinetics of the cellular interaction processes, and they rely on labeled materials as well as on secondary detection techniques. Thus, there is an ever-increasing interest to develop new methodologies enabling real-time, noninvasive, label-free, and continuous high-sensitivity monitoring of drug-cell or nanoparticle (NP)-cell interactions that would provide complementary information to traditional *in vitro* cell culture methods.

In this article, we present a summary of several experimental approaches our research group has taken in utilizing two physicochemical techniques, namely, surface plasmon resonance (SPR) and quartz crystal microbalances (QCM), to develop new methodologies for real-time label-free monitoring of drug or NP interactions with cell model layers and living cell monolayers.

Experimental Approaches

SPR and QCM techniques are surface-sensitive and label-free technologies capable of real-time monitoring of interfacial adsorption and interaction processes. Both techniques have established their position as powerful techniques for biomolecular interaction and materials science studies. However, a highly unexploited area with regard to these technologies is their use in pharmaceutical sciences for drug- or NP-cell interaction studies. Figure 1 shows the main approaches we have utilized for modifying the QCM or SPR sensor surfaces enabling drug- or NP-cell interaction studies.

Cell Surface Model Layers

Drug-Lipid Bilayer Interactions[1]

Supported lipid bilayers (SLB) are ideal candidates for mimicking cell membrane surfaces for studying drug- or NP-cell surface interactions. We have prepared negatively charged SLBs by spreading vesicles (POPC:POPS, 3:1; size ≈130 nm) directly on silica-coated QCM sensors. Hereafter, the effect induced by the model drug (propranolol, tetracaine, or mellitin) on the SLB properties was measured by QCM. Figure 2 shows an example of the QCM response during formation of the SLB followed by the interaction of propranolol with the SLB. The QCM responses for all three model drugs were used to model the viscoelastic properties of the bilayer upon drug interaction. We found that both propranolol and tetracaine increased the elasticity and viscosity of the bilayers and that the elasticity of the bilayers took similar values compared with those measured for cells, ≈0.1 MPa. For the membrane-perturbing peptide mellitin, we showed for the first time that mellitin did not induce a viscoelastic change in the SLB until a certain concentration was reached, which indicated that there was a threshold concentration for the insertion of mellitin into the cell membrane.

Flow Effects on NP Interactions[2]

Very little is known about bloodstream hydrodynamics effects on drug delivery and NP targeting. Our aim is to develop a methodology based on data collected both by QCM and SPR to elucidate the role of this pharmacokinetically important factor. However, a lack of synchronized flow conditions between QCM and SPR makes it difficult to properly compare the experimental data obtained from these techniques. Therefore, we have synchronized the flow conditions for QCM and SPR flow channels through computational fluid dynamic modeling (Figure 3, top). The shear strain was taken as the relevant property with respect to the flow conditions, which provided us with a scaling expression with parameters for flow rate (f) and flow channel height (h) for each of the two devices (Figure 3, top). The success

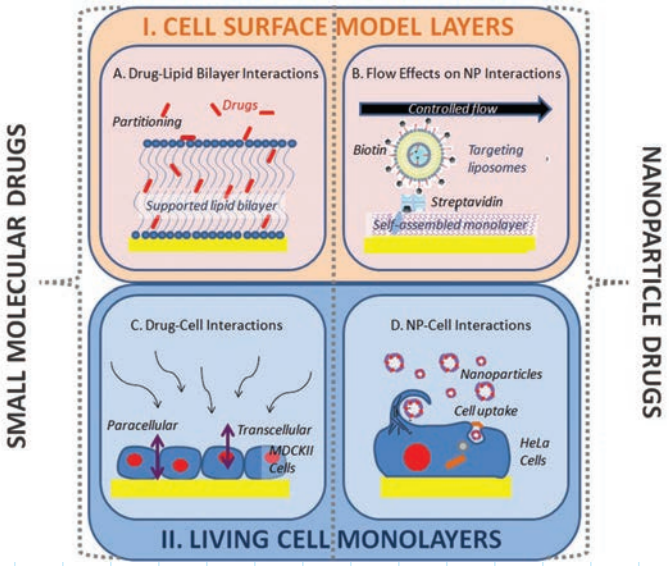

Figure 1. *Different experimental approaches utilized for real-time and label-free monitoring of drug- or NP-cell interactions with SPR and QCM.*

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of the calibration procedure was demonstrated by showing that the normalized signal responses measured by QCM and SPR for a targeted drug delivery model system of biotinylated liposomes (HSPC:Chol:DSPE-PEG2000:DSPE-PEG-Biotin, 64.4:32.4:2.6:0.6) interacting with a streptavidin-functionalized sensor surface coincide with each other (Figure 3, bottom).

Living Cell Monolayers

Drug-Cell Interactions[3]

The abilities to examine living cells in physiologically relevant environments, to monitor drug-cell interactions, and to differentiate between different drug delivery routes are of utmost importance in order to improve our mechanistic understanding during drug discovery and development. For this purpose, we have immobilized confluent MDCKII cell monolayers directly on SPR sensor slides for real-time monitoring of drug-cell interactions. Figure 4 (top) shows the SPR peak angle response when the cell monolayer was stimulated with propranolol (which uses a transcellular absorption pathway) or D-mannitol (which uses a paracellular absorption pathway). It is difficult to distinguish any specific differences between these two drugs from the SPR peak angle response, except that there is a smaller response for D-mannitol. We found that by also measuring the SPR peak minimum intensity and plotting this against the SPR peak angle, D-mannitol produced a more horizontally aligned line compared with propranolol, which produced a line with a pronounced slope (Figure 4, bottom). We could finally attribute the measured SPR responses to the different mode of action (para- or transcellular absorption pathway) of these drugs with the cell monolayer.

NP-Cell Interactions[4]

Modern drug discovery in combination with nanotechnology gives rise to a great number of potential new therapeutic agents and drug delivery systems. However, tracking NP cell uptake and measuring NP cell surface, cell uptake, and/or intracellular kinetics is a huge challenge. Traditionally NP drug delivery systems are labeled with fluorescent probes for this purpose, but in the worst case the detached label is being tracked and not the drug delivery system itself. We have managed to monitor the interaction of NPs with cells in real time without labels by combining SPR with living cell sensing. Figure 5 (top) shows the SPR peak angle response when two different types of DNA polyplexes were interacted with a confluent HeLa cell monolayer. The addition of a negatively charged carboxymethyldextran-PEG polymer clearly influences the interaction kinetics with

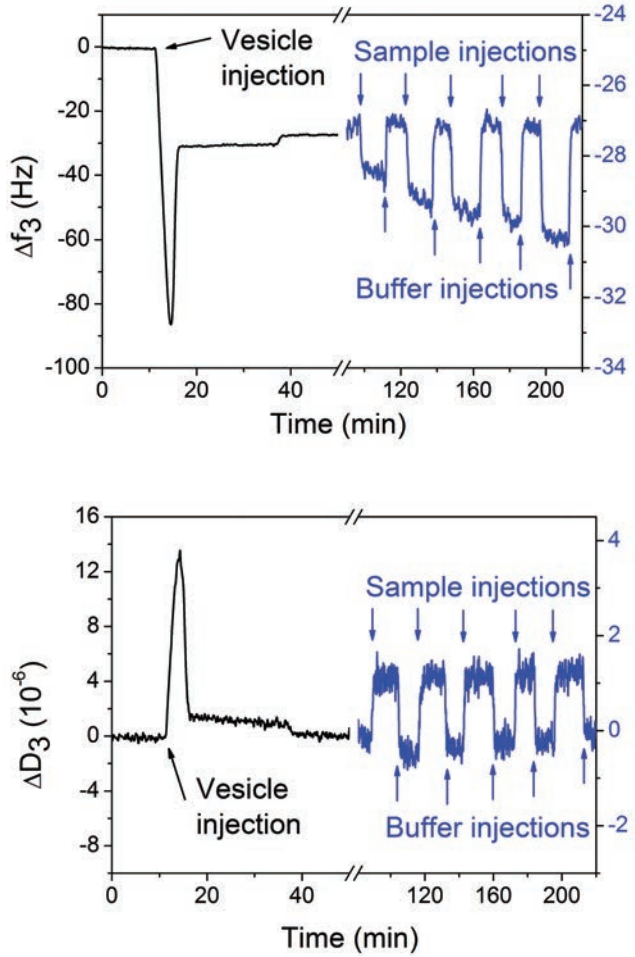

Figure 2. *Normalized frequency change (Δf_3, top) and dissipation change (ΔD_3, bottom) measured at the third overtone during bilayer formation (black line) and increasing concentration of propranolol (blue line).*

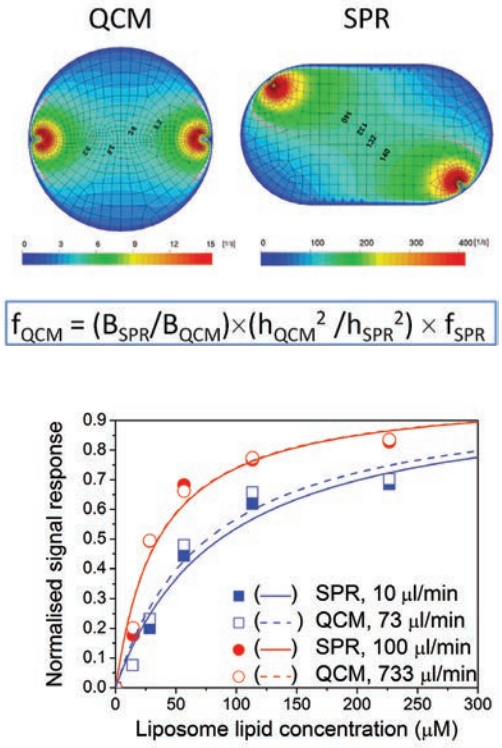

Figure 3. *(Top) Contour plots of the shear strain on the bottom surface of QCM and SPR flow channels obtained by computational fluid dynamics modeling. Scaling expression for synchronizing flow conditions between QCM and SPR flow channels. (Bottom) Normalized signal responses when synchronized flow rates between SPR and QCM devices were used for a targeted drug delivery model system at low (blue) and high (red) flow rates.*

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Viitala Scientifically Speaking continued from page 15

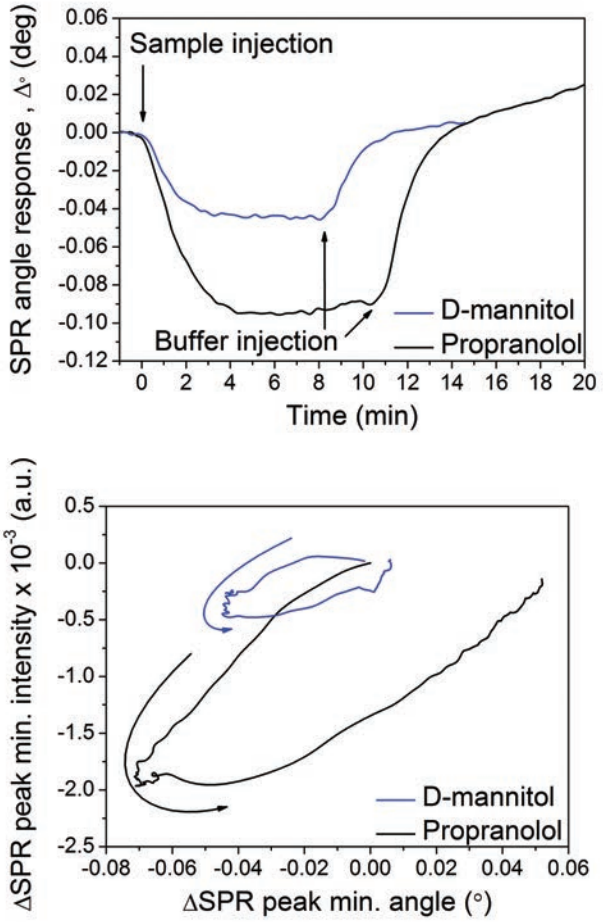

Figure 4. *(Top) Change in SPR peak angle during interaction of D-mannitol (blue line) and propranolol (black line) with an MDCKII cell monolayer. (Bottom) Change in SPR peak minimum intensity versus change in SPR peak angle during interaction of D-mannitol (blue line) and propranolol (black line) with an MDCKII cell monolayer.*

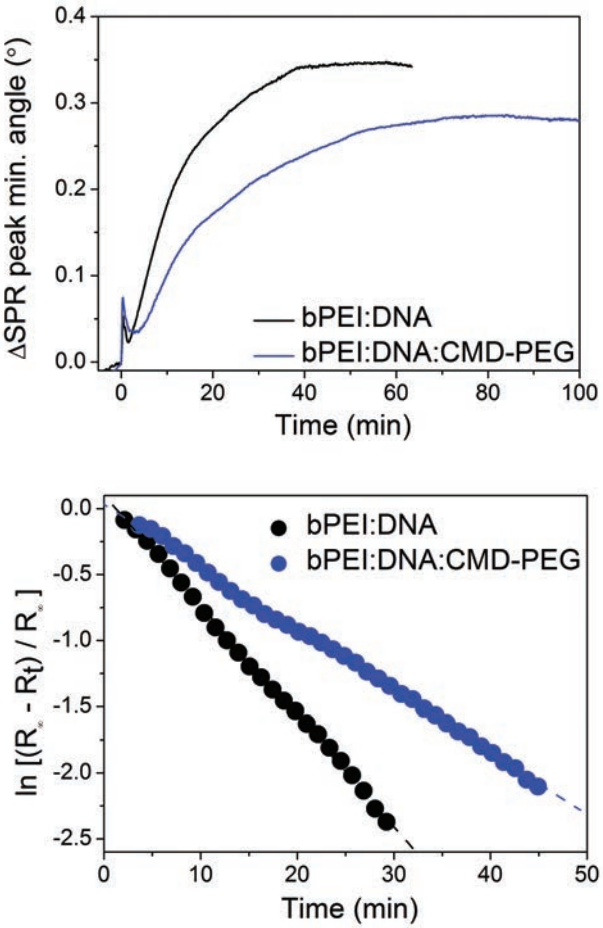

Figure 5. *(Top) Change in SPR peak angle during interaction of bPEI:DNA (black line) and bPEI:DNA:CMD-PEG (blue line) polyplexes with a HeLa cell monolayer. (Bottom) First-order kinetic fit of SPR responses for bPEI:DNA (black circles) and bPEI:DNA:CMD-PEG (blue circles) polyplexes.*

HeLa cells. Figure 5 (bottom) shows that the SPR response can be fitted to first-order interaction kinetics. This opens up new opportunities to determine, for example, NP cell uptake energies and possibly correlate this with cell uptake mechanisms.

Conclusions

We have given several examples of how QCM and/or SPR techniques can be utilized for real-time monitoring of drug- or NP-cell interactions without labels. We anticipate that the approaches presented in this article in combination with traditional *in vitro* cell assays will in the future improve our mechanistic understanding of the fundamental parameters, material properties, and conditions influencing drug delivery.

Acknowledgements

This work was supported by the Academy of Finland (grant numbers 1140980 and 137053). Niko Granqvist thanks the Foundation of Anja and Mirja Tissari from the Finnish Cultural Foundation (Suomen Kulttuurirahasto).

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How Can Intracellular Full-Length siRNA Quantification Help in the Study of Carrier-Mediated Delivery *In Vitro*?

Stefano Colombo,[1] Héloïse Ragelle,[2] Hanne Mørck Nielsen,[1] Véronique Préat,[2] and Camilla Foged[1,3]

Introduction

The establishment of innovative siRNA therapies is dependent on the development of carriers able to mediate safe and efficient delivery of nucleic acids. Among the most promising delivery systems are particles based on biodegradable polymers, such as poly(lactic-*co*-glycolic acid) (PLGA) and chitosan. However, the intracellular fate of these carriers is to a large extent unknown. We envisage that the quantification of intracellular full-length siRNA delivered intracellularly by these carriers can help improve the understanding of the nature of the delivery processes at the cellular level.[1,2] In spite of that, a model system for the *in vitro* testing of siRNA delivery vectors, which includes intracellular siRNA quantification, has not yet been discussed in the literature. Our research aims to fill this gap via the development of an analytical stem-loop quantitative real-time polymerase chain reaction (qPCR)-based protocol enabling accurate quantification of the antisense siRNA strand (AS) of a double-stranded siRNA in a convenient reporter cell model expressing enhanced green fluorescent protein (EGFP). With this article, we provide an overview of the procedure[3] and exemplify its use with selected siRNA delivery systems.

Results and Discussion

The analytical system was designed using 1) double-stranded Dicer substrate siRNA EGFPS1 R25D/27 (DSsiRNA) (IDT, Coralville, IA, U.S.A.)[4] to ensure the experimental reproducibility by using a validated and potent siRNA suitable for *in vivo* research (Figure 1A); 2) H1299 cells expressing EGFP to corroborate the PCR data with flow cytometry analysis (Figure 1B); 3) an optimized reverse transcription (RT) procedure based on stem-loop primers[5] (Figure 1C); and 4) SybrGreen qPCR to quantify the cDNA template (Figure 1D).

Figure 1. *Full-length intracellular siRNA quantification protocol. (A) DSsiRNA was loaded into carriers and used for transfection of H1299-EGFP cells. (B) Total RNA was extracted and reverse transcribed (C) using stem-loop primers. Optimized RT conditions allowed for an efficient transcription of the AS. (D) The cDNA template was detected by SybrGreen qPCR, and the crossing point was calculated as the maximum of the second derivative.*

The intracellular AS quantification protocol was used to analyze three different siRNA delivery systems: 1) a commercially available transfection reagent (Lipofectamine 2000 [LF], Invitrogen, Carlsbad, CA, U.S.A.) designed for *in vitro* transfections; 2) a sustained release carrier (polymeric matrix nanoparticles based on PLGA modified with dioleoyltrimethylammoniumpropane [DOTAP]) suitable for *in vivo* siRNA delivery;[6,7] and 3) polycationic nanoparticles actively targeted to a receptor expressed on the surface of several cancer cells.

Briefly, the samples were prepared as follows: LF lipoplexes were prepared at variable siRNA concentrations (0.24–30 nM), resulting in a final concentration in the well of 0.04–5 nM. H1299-EGFP cells were transfected for 48 hr and harvested by phosphate buffered saline (PBS) washing followed by trypsinization and further PBS washing of the pellet. DOTAP-modified PLGA nanoparticles (NPs) (1:15 DOTAP:PLGA, w/w ratio) were prepared by the double emulsion solvent evaporation method.[8] The average particle size was 260 nm, the polydispersity index (PdI) was 0.2, and the ζ-potential was –25 mV. H1299-EGFP cells were transfected with variable amounts of freeze-dried NPs (0.05–0.5 mg). After 24 hr, the transfection medium was changed, and the cells were harvested after a total of 48 hr. Half of the harvested cells (approximately 5×10^5 cells) were used to isolate total RNA, 5×10^4 cells were subcultured for 72 hr in a new well, and the remaining cells were analyzed by flow cytometry.

The analysis of cells transfected with LF confirmed a close correlation between the silencing and the intracellular AS concentration (Figure 2A). The transfection mediated by the polymeric nanocarrier did not show a similar proportionality, presumably because of its sustained release kinetics (Figure 2B).

To clarify this observation, the relative amounts of AS necessary to produce a 1% silencing for each sample were plotted as a function of the silencing (Figure 3).

Assuming that the RNAi effect is proportional to the number of active siRNA molecules in the cytoplasm,[1] it was possible to estimate the relative amount of active DSsiRNA delivered from NPs and LF under the experimental conditions. The quantity of

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Colombo Scientifically Speaking continued from page 17

active siRNA delivered by the NPs in the example was lower with LF (on the order of 10-fold less). These preliminary results suggested that only a small fraction of the DSsiRNA was released from the nanoparticles within 48 hr and was able to mediate RNAi. However, the majority of the DSsiRNA delivered into the intracellular compartment was intact five days posttransfection (Figure 2B).

Furthermore, the stem-loop qPCR technique was used to determine the delivery efficiency of nanoparticles targeting a receptor overexpressed by H1299 cells. These targeted particles were compared with nontargeted particles representing similar physicochemical characteristics (ζ-potential, mean diameter, and PdI) and loaded with same amount of siRNA. The intracellular siRNA quantification was correlated to the percentage of gene silencing for two concentrations 48 hr after transfection (Figure 4).

At an initial dose of 50 nM, targeted particles enabled the delivery of a higher amount of siRNA as compared with nontargeted particles. However, comparable EGFP silencing was observed with both types of particles. At 100 nM, we observed a dramatic increase in the EGFP silencing after transfection with targeted particles. On the other hand, the gene silencing

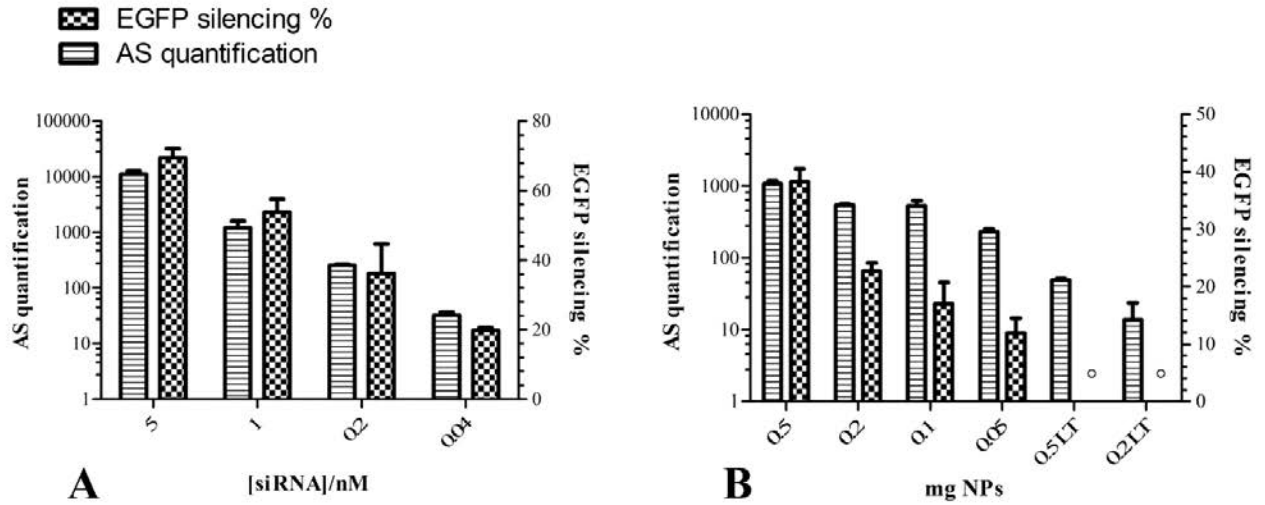

Figure 2. *DSsiRNA delivery mediated by LF (A) and PLGA (B) nanoparticle transfection: quantified intracellular AS copies (stripes) and EGFP silencing % (checks); silencing less than 10% was considered as background (circle). LT indicates the silencing obtained in subcultured samples. The intracellular AS amount was normalized to small nucleolar RNA U109 (GenBank ID: AM055742.1). Columns show mean of three replicates, and error bars show the standard deviation.*

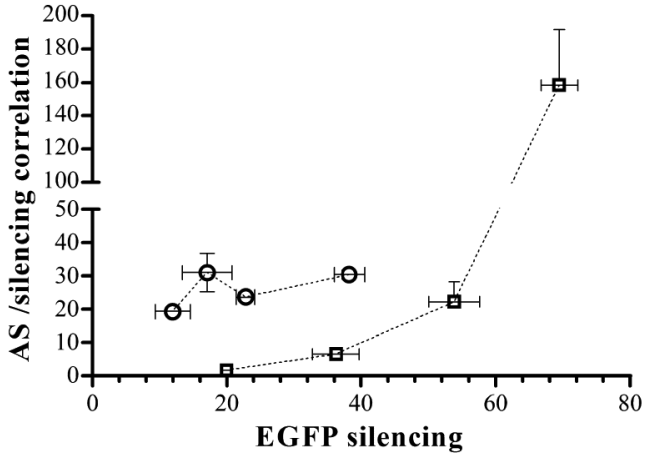

Figure 3. *Full-length AS and silencing correlation. The correlation was calculated as the number of AS per 1% silencing and plotted against the silencing produced by LF (squares) and nanoparticles (circles). Lower absolute values represent higher amounts of active siRNA AS. Each point shows the mean of three biological replicates, and error bars show the standard deviation.*

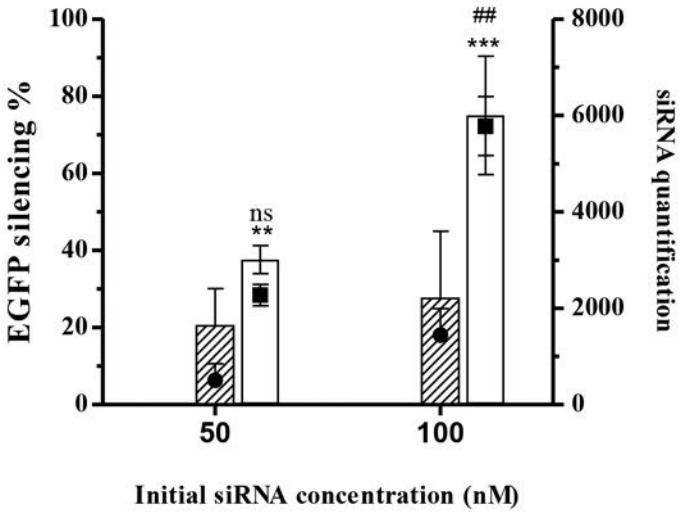

Figure 4. *EGFP silencing (columns) correlated to siRNA quantification (dots) for nontargeted and targeted particles. Nontargeted particles (striped columns and circles) were compared with targeted particles (blank columns and squares) in terms of EGFP silencing (##, $p < 0.01$) and AS quantification (**, $p < 0.01$; ***, $p < 0.001$) using two-way ANOVA and Bonferroni posttest ($N = 2–3$, $n = 3$).*

obtained with the nontargeted particles reached a plateau, and no significant difference between EGFP silencing at 50 and 100 nM was observed. The quantitative results showed that the amount of siRNA delivered by the targeted nanoparticles was four times higher compared with nontargeted nanoparticles. These preliminary data illustrate the benefit of active targeting in terms of the intracellular siRNA delivery process. Further experiments are ongoing to confirm and explain these results.

Conclusion

A stem-loop qPCR-based approach was developed and used to quantify intracellular full-length siRNA, providing information about carrier-mediated siRNA delivery. Preliminary results suggest that this approach is useful for the characterization of the efficiency of certain delivery systems, such as sustained release or targeted polymeric nanoparticles. Using this assay, it was possible 1) to obtain indications on the dose-dependency of the uptake process of targeted and nontargeted carriers and 2) to collect information on the intracellular siRNA release kinetics. This approach will ease the comparison between delivery systems as well as provide data useful for the design of further *in vivo* experiments.

Perspectives

We aim to improve our understanding of intracellular carrier-mediated delivery mechanisms, kinetics, and dynamics by applying this approach in *in vitro* and *in vivo* studies. It will be achieved by comparing particles featuring systematically varied physicochemical properties. The quantification of full-length siRNA in subcellular fractions might help confirm some of the previous results.

Acknowledgements

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Controlled Release and Delivery Technologies

Charles Frey
Coating Place, Inc., Verona, WI, U.S.A.

This article provides a brief summary of selected U.S. patents involving controlled release or delivery in pharmaceutical and nonpharmaceutical applications that were issued from January 1 through June 30, 2012.

Method for Silk Fibroin Gelation Using Sonication; U.S. Patent 8,187,616

This patent discloses the use of ultrasonication to form silk fibroin hydrogels for controlled delivery of therapeutic agents.

Method and Apparatus for Delivery of Therapeutic Agents; U.S. Patent 8,187,249

The use of electrodes to increase cellular uptake of DNA and other therapeutic agents in healthy regions of tissue is described.

Preservation and Controlled Delivery/Release of Spermatozoa; U.S. Patent 8,178,130

A means of storing and extended delivery of spermatozoa for use in artificial insemination of swine, cattle, horses, sheep, goats, rabbits, poultry, pedigree animals, fur animals, aquatic animals, and endangered animal species is described. The system includes embedding spermatozoa in an alginate-rich matrix with an antioxidant and coating with materials such as of polylysin, chitosan, cellulose sulphate, hydroxylpropylmethylcellulose, or polydiallyldimethylammonium chloride. The extended release characteristics of the particles help ensure the presence of spermatozoa through the ovulation period.

Localized Delivery of Drug Agents; U.S. Patent 8,177,743

The use of a perforated elastic sheath about the balloon portion of a balloon catheter to control release of drug agents is described. Inflation and deflation opens and closes perforations to activate and deactivate release.

Stabilized Polymeric Delivery System Comprising a Water-Insoluble Polymer and an Organic Liquid; U.S. Patent 8,173,148

This invention relates to injectable implant compositions of biodegradeable thermoplactic polymers such as polylactides/polyglycolide along with nucleophilic bioactives and a stabilizing polycarboxilic acid all in a biocompatible solvent vehicle. The association of the nucleophilic bioactive with the polymeric materials slows polymer degradation to further sustain bioactive release.

Method of Delivering Frac Fluid and Additives; U.S. Patent 8,162,048

This invention discloses a means of using critical analytical parameters for fracing raw materials to tailor optimal premixed compositions for controlled delivery to the well.

Protein Biomaterials and Biocoacervates and Methods of Making and Using Thereof; U.S. Patent 8,153,591

This invention relates to the use of protein biocoacervates for controlled release of bioactives in a variety of applications including coated medical devices, vacular grafts, suture materials, dental implants, tissue grafts and fillers, and cell scaffolding.

Extended Delivery of Ingredients from a Fabric Softener Composition; U.S. Patent 8,138,137

The use of coated polymeric microparticles composed of ethylene glycol dimethacrylate and lauryl methacrylate copolymer for sustained release of fragrance and other fabric softening ingredients is disclosed.

4-Aza-Caprolactone-Based Polymeric Compositions Useful for the Manufacture of Biodegradable Medical Devices and as Medical Device Coatings; U.S. Patent 8,137,687

This invention provides biodegradable, biocompatible, amphiphilic polymers derived from N-substituted 4-aza-caprolactone that are suitable for use as medical devices and coatings for medical devices.

Methods and Systems for Delivery of Fluidic Samples to Sensor Arrays; U.S. Patent 8,133,741

This disclosure relates to the use of optical sensor arrays to monitor biological or chemical species. Algorithms are applied and used to control delivery of analytes through capillaries by electroosmotic or related delivery mechanisms.

Drug Delivery Systems Based on Cationic Siloxanyl Macromonomers; U.S. Patents 8,133,511 and 8,133,512

This invention relates to matrix controlled diffusional drug delivery from an ocular implant for treatment of a variety of eye disease conditions.

Implantable Sensor Lead; U.S. Patent 8,133,186

This patent describes the use of an implantable sensor to detect cardiac activity and provide controlled cardiac stimulation pulses in response to that activity.

System and Method to Deliver Therapy in Presence of Another Therapy; U.S. Patent 8,131,359

This patent relates to controlled delivery of two interrelated electrical therapies for cardiac or neural stimulation.

Ligand-Mediated Controlled Drug Delivery; U.S. Patent 8,128,952

This patent discloses incorporation of a polypeptide ligand and associated therapeutic protein in a hydrogel matrix. The combined ligand affinity and diffusional release from the matrix control protein release for applications such as tissue engineering.

Drug-Eluting Stent with Filament Strands; U.S. Patent 8,128,687

Drug-loaded filament strands with a rectangular cross-sectional shape and a controlled release coating are mounted on the outer surface of stents for drug delivery to lumen walls.

Use of Dynamic Mixtures for a Controlled Release of Fragrances; U.S. Patent 8,124,578

This invention relates to use of the reversible reaction between a hydrazine derivative and a perfuming aldehyde or ketone in the presence of water to provide an extended release profile for the perfuming ingredient.

Drug Delivery Endovascular Graft; U.S. Patent 8,118,864

This patent discloses use of texturing and attached fibrous elements to the surface of stents for controlled delivery of therapeutic agents.

Cyclodextrin-Based Polymers for Therapeutics Delivery; U.S. Patent 8,110,179

This invention involves covalently bonding poorly soluble or unstable drugs to polymeric cyclodextrin-containing polymers for increased solubility or stability and controlled delivery of the drug via hydrolysis or enzymatic cleavage.

Coiled Wire for the Controlled Release of Drugs to the Eye; U.S. Patent 8,109,913

This invention relates to the use of a coiled wire device for controlled delivery of drugs to the eye from the surface of the wire along with the addition of drug-containing microspheres to the lumen created by the coil to increase the drug capacity of the device.

Methods and Compositions for Controlled Release of Drugs; U.S. Patent 8,105,570

This disclosure relates to controlled release of a covalently bound narcotic drug from a polymeric structure. The release mechanism involves hydrolysis of a second covalently bound entity to provide a hydrolysis product that reacts to displace the drug. Release is controlled through the rate of hydrolysis and the concentration of the second bound entity.

Sensate Compositions and Delivery Systems Therefor; U.S. Patent 8,101,208

This invention relates to food-grade polymeric compositions that provide release of cooling and tingling agents in the mouth and upper gastrointestinal tract for up to 30 minutes.

Warming Compositions and Delivery Systems Therefor; U.S. Patent 8,097,271

This invention relates to food-grade polymeric compositions that provide release of warming agents in the mouth and upper gastrointestinal tract for up to 30 minutes.

Controlled-Release Formulations; U.S. Patent 8,097,239

This invention relates to the use of polyhydroxy compounds such as sugars to increase the solubility of bioactives in lamellar-based lipid delivery systems.

Soluble, Degradable Poly(ethylene glycol) Derivatives for Controllable Release of Bound Molecules into Solution; U.S. Patent 8,088,365

This disclosure relates to the use of soluble, degradable PEG derivatives to conjugate with therapeutic agents and provide suitable hydrolytical instability to allow appropriate circulation before releasing the agent. ■

New Column Lets CRS Members Share Insights in Product Development: Strengths and Pitfalls of Interspecies Extrapolation

The importance of selecting appropriate animal models for the development of novel therapeutics has recently been underscored by the award of the Nobel Prize in Physiology or Medicine to two researchers who employed animal models to support the development of stem cells as therapeutic moieties. The following is from the Americans for Medical Progress news service, www.amprogress.org:

Two 2012 Nobel Awards Affirm Importance of Animal Research

The continuing value of animal-based research to medical progress was affirmed this week in the awarding of *two* Nobel Prizes.

On Monday [October 8, 2012], John B. Gurdon and Shinya Yamanaka were awarded the 2012 Nobel Prize in Physiology or Medicine for their work on reprogramming mature cells into stem cells, based on research with frogs and mice. The Nobel committee said their achievement has revolutionized our understanding of how cells and organisms develop and created new tools for scientists focused on treatments for diseases such as diabetes and Parkinson's.

Over the last 40 years, every Nobel Prize in Physiology or Medicine save one (1983—Barbara McClintock for her plant genetics research) has depended on data from animal studies.

Today, another affirmation of the importance of animal research: the 2012 Nobel Prize for Chemistry was awarded to Robert J. Lefkowitz of the Howard Hughes Medical Institute and Duke University Medical Center and Brian K. Kobilka of the Stanford University School of Medicine for mapping the inner workings of a family of receptors called G-protein-coupled receptors—which are responsible for producing the "fight or flight" response. The Nobel committee stated that about half of all medications achieve their effect through these receptors. Better understanding of how they function will lead to the development of better medicines with fewer side effects. As the scientists' own webpages state, the research is ongoing and knockout mice are in a leading role.

The need to appreciate the strengths and potential pitfalls associated with animal model research is keenly felt by scientists involved in development of novel drug delivery systems.

Therefore, with this in mind, the newly created Preclinical Sciences & Animal Health (PSAH) Division of CRS would like to develop a repeating column within the *CRS Newsletter* where members can share their thoughts and insights on various issues. Each issue raised will pertain to the use of preclinical species to support the development of modified release dosage forms. The PSAH Division will collect your responses and will summarize them in a subsequent issue of the *CRS Newsletter*. For future reference, all questions and replies will be archived on the new PSAH website.

With this in mind, we would appreciate your thoughts and insights on the following question:

2012 Scenario 1: Assume that you have already characterized the pharmacokinetics of drug X in your animal model (e.g., dog or rat) and in the target species (e.g., human or veterinary species). What are the kinds of questions that would be important to address if you wish to develop a subcutaneous dosage form that is intended for one of the following drug release characteristics?

1) Zero order release,
2) Pulsatile release, or
3) Release in response to a physiological variable (e.g., blood glucose).

We ask that you submit your thoughts on questions raised to Megan Pagel at mpagel@scisoc.org. The subject header should be "Response to PSAH Question 2012-1." Please provide your thoughts by January 7, 2013. We will target publication of your responses in the first issue of 2013.

We look forward to receiving your replies and will inform everyone about the response to this question.

Further Reading

Summaries of research from the Nobel Prize winners are available online:

John Gurdon, www.gurdon.cam.ac.uk

Brian Koibika, http://med.stanford.edu/kobilkalab/research.html

Robert Lefkowitz, http://cardiology.medicine.duke.edu/faculty/details/0096962

Shinya Yamanaka, www.cira.kyoto-u.ac.jp/e/research/yamanaka_summary.html ■

Eventful 2012 Annual Meeting for Young Scientists

Young Scientist Activities

The Young Scientist Committee had another year of very successful events at the 2012 CRS Annual Meeting in Québec City this summer. Events included two workshops, a roundtable, two Get Up! Get Educated! sessions, and a networking event in a high-rise rotating restaurant above the city. The events started off with a workshop on "Mucosal Drug and Gene Delivery: Barriers and Opportunities," with numerous experts in the area giving talks and participating in a panel discussion at the end. Panelists included Justin Hanes, Michael Rathbone, Edith Mathiowitz, Camilla Foged, Kim Woodrow, Sanyog Jain, and Heidi Mansour. Many early career scientists joined an active and engaging roundtable event on "Entrepreneurship: A Journey from Conception to Commercialization," featuring many business venture stories from Debra Bingham, Clive Wilson, Justin Hanes, and Hardik Shah. Buket Aksu and Teresa Virgallito continued their series of highly popular professional and self-development workshops from previous years with a workshop focused on the area of time management. The workshop, utilizing numerous materials and exercises, illustrated methods for working efficiently and effectively under pressure to achieve goals within designated timeframes with maximum benefits. There were many early morning risers in attendance at both Get Up! Get Educated! sessions. Even those not normally classified as early risers were treated to an engaging, standing-room-only lecture by Vincent Rotello on the "Interface of Biomaterials Elucidated." Vincent took us on a story of his experience with biocompatible materials and controlled surfaces. The next morning, Jaap van Harten and Kinam Park entertained as they discussed "How to Get Published in *JCR*—Editor's and Publisher's Views." Insights into the editorial decision-making process were shared, and good author-editor-reviewer communication was emphasized. Stimulating discussion from all of these events continued in the hallways and Québec streets throughout the meeting. On the opposite end of the time spectrum, attendees of the sold-out Young Scientist Networking Event and Dessert Reception at L'Astral Restaurant were treated to magnificent views above Québec City and French pastries and crepes while mingling with early career peers as well as established investigators. The Young Scientist Committee has already begun to make plans for next year's events, and we hope to see you in Hawaii. In the meantime, keep in touch with Young Scientist activities and discussions on the Young Scientist subgroup of CRS on LinkedIn.

Young Scientist Networking Event attendees enjoying opportunities to network at the L'Astral Restaurant, the only rooftop revolving restaurant in Québec City.

Mentor-Protégé Program

Albert Einstein said, "It is the supreme art of the teacher to awaken joy in creative expression and knowledge." Mentorship programs serve as a bridge between students and the industrial experts and professors. Since its inception in 2007, the CRS Young Scientist Mentorship Program (YSMP) has resulted in many successful mentor-protégé relationships. The YSMP serves as a mutually beneficial partnership between two people sharing experiences and expertise to foster each other's personal and professional growth.

Attendees enthused over the time management workshop for young scientists and protégés, and the Mentor-Protégé Meet and Greet led by Michael Rathbone and Ruth Schmid helped break the ice between the record-breaking 87 new mentor-protégé pairs.

In the era of social media networking and collaborations on a global scale, the YSMP serves as the perfect networking platform. We at the YSMP strongly encourage all young scientists and potential mentors to seize this opportunity. ■

CRS Young Scientist Roundtable panel members (left to right): cochair Sara Yazdi, speakers Hardik Shah, Debra Bingham, Justin Hanes, and Clive Wilson, and cochair David Chen.

Buket Aksu speaking during Young Scientist Workshop #2, Professional and Self Development for Young Scientists and Protégés—Time Management.

UKICRS Sessions at UK PharmSci Conference

September 12–14, 2012, East Midlands Conference Centre, Nottingham, United Kingdom

Ambreen Khan, Department of Pharmacy, University of Hertfordshire, United Kingdom

The UK PharmSci Conference is the leading pharmaceutical sciences conference in the United Kingdom. An interesting and insightful PharmSci 2012 conference entitled "Science of Medicines" was organised by the Academy of Pharmaceutical Sciences (APS) and took place at the East Midlands Conference Centre. The conference was a platform for academics, industrial scientists, and postgraduate students to showcase their research and to learn about the latest innovations and developments taking place within their discipline. There were presentations from prominent leaders and young scientists on various sessions including "Polymeric and Self-Assembled Delivery Systems," "The Future of *In-Vitro* Drug Release Testing Approaches in Product Development," "Bugs and Drugs," "Medicinal Chemistry," "Biopharmaceutics," paediatric drug delivery, inhaled product development, tackling counterfeiting by formulation and processing approaches, and "green" formulations and processes.

This year UKICRS organised and chaired two sessions on "Bugs and Drugs." The sessions were well attended by an enthusiastic audience interested in the anti-infective field. The opening presentation was delivered by Prof. Les Baillie from the School of Pharmacy, Cardiff University. He presented an interesting talk on "*Bacillus anthracis*: How to Stop the Bad Guys from Killing Us All." Anthrax is a disease caused by the bacterium *B. anthracis*. He provided insights on how to decontaminate anthrax if a site is being exposed: first, environmentally friendly ways of decontamination of anthrax, for example, sprays with biocides like paracetic acid; second, bacteriophage-based decontamination; and, third, the use of vaccine to prevent anthrax infection. He also highlighted the newly discovered fact that beer can be a potential cure for tuberculosis and anthrax and that polyphenols found in green tea can kill *B. anthracis*. Prof. Baillie's talk was followed by Dr. Tony Worthington from the Department of Microbiology, Aston University. He talked about novel strategies in infection control of *Clostridium difficile* (CD). CD spores are resistant to routine cleaning methods, and hospitalised patients might accidentally ingest these spores, leading to infections. He focussed on the development of new nonhazardous ways to improve CD infection control. He revealed that a panel of amino acids such as glycine, arginine, and sodium taurocholate encourage germination of CD spores. Once the CD spores germinate, routine cleaning solutions can be applied to kill the bacteria.

The chair and speakers of the morning "Bugs and Drugs" session. Left to right: Dr. Woei Ping Cheng, Robyn Fowler, Dr. Tony Worthington, Dr. Alexander Edwards, and Prof. Les Baillie.

The third talk was presented by Dr. Alexander Edwards from the University of Reading. The title of the talk was "Oral Drug Delivery to Breast Feeding Infants Using a Modified Nipple Shield." The idea was to safely and efficiently deliver antiviral drugs to the infants in developing countries. The approach appeared to be simple and convenient, and it enabled administration of drugs to infants via breast feeding. Dr. Edwards's talk was followed by a postgraduate speaker, Robyn Fowler, from the University of Nottingham. She talked about the elucidation of the transport of vitamin B-12 conjugated polystyrene nanoparticles across Caco-2 cells. She demonstrated that the intracellular uptake and trafficking of vitamin B-12 conjugated nanoparticles was different from both soluble B-12 ligand and unmodified nanoparticles. Her results showed that vitamin B-12 conjugated nanoparticles were taken up via the caveolar pathway and avoided lysosomal degradation.

After attendees returned from lunch, Prof. Colin McCoy from the School of Pharmacy, Queen's University Belfast, opened the session with a talk on "Biofilms on Medical Devices: Strategies for Prevention and Cure." He highlighted major problems with medical devices that are susceptible to biofilm formation, and he focussed on designing biomaterials that are resistant to infections. He talked about stimuli responsive drug-eluting materials that can be designed to release a drug on demand upon light activation. To employ this approach, the drug needs to have photolabile groups. The next invited speaker was Prof. Marc Brown from MedPharm. He presented a talk on "Topical Treatment of Onychomycosis: As Hard as Nails." He talked about the recurrence and relapses of nail infection following oral treatment and highlighted the fact that topical therapy would overcome the adverse events and drug interactions of orally administered antifungal drugs. However, successful topical therapy is facing challenges because of the very low permeability of drugs across the nail plate. He discussed and provided an overview of the strategies for improving ungal drug delivery and ungal permeation enhancers.

The chair and speakers of the afternoon "Bugs and Drugs" session. Left to right: Farzad Ahmad Khayrzad, Prof. Marc Brown, Steven Fallows, Prof. Colin McCoy, and Dr. Karl Malcolm.

The next speaker was Farzad Ahmad Khayrzad, a postgraduate student from the School of Pharmacy, University College London. He highlighted the challenges with the use of antimicrobial peptides (AMPs), which have short serum half-lives and are prone to enzymatic degradation. He talked about site-specific conjugation of poly(ethylene glycol) (PEG) to AMPs, and his results showed that PEGylated AMPs have lower microbial activity compared with native AMPs but suggested that this can be compensated for by the prolonged *in vivo* half-life. The final speaker was Steven J. Fallows from Queen's University Belfast. The title of his presentation was "Iontophoretic Hydrogel Delivery Systems for Photodynamic Treatment of Wound Infections." Using aqueous blends containing poly(methyl vinyl ether-*co*-maleic acid) (PMVE/MA) and polyethylene glycol 10 kDa (PEG 10,000), he fabricated electrically responsive hydrogels for incorporation of two photosensitizers. He demonstrated a significant increase in the rate of drug release when an electric current passed through the hydrogel, demonstrating the potential use of this hydrogel for the photodynamic treatment of infected wounds.

For more information on UKICRS, please visit www.ukicrs.org or follow us on Facebook. ■

Prof. Zhirong Zhang Elected as President of CRS China Local Chapter

On the evening of September 20, 2012, the day before the second annual meeting of the CRS China Local Chapter, the chapter's member meeting was held at the Jin Niu Hotel, Chengdu, China. During the meeting, the immediate past president, Prof. Weiyue Lu from Fudan University, gave a report on his term of office and announced Prof. Zhirong Zhang from Sichuan University as the new president of the CRS China Local Chapter. Then Prof. Zhang nominated Prof. Weisan Pan from the School of Pharmacy, Shenyang Pharmaceutical University, as the president elect and received unanimous agreement. Prof. Zhang delivered a short inaugural speech and introduced his working plan for the term.

This year, the committee of the CRS China Local Chapter is governed under President Zhirong Zhang, President Elect Weisan Pan, and Immediate Past President Weiyue Lu. The term of this directive board is from October 2012 to September 2013. Other officers are Huimin Hou (honorary president) and Ying Xu (treasurer), both from the National Pharmaceutical Engineering and Research Center, and Jun Pan (secretary) from the Fudan University School of Pharmacy. ■

President Zhirong Zhang giving his inaugural speech.

CRS China Local Chapter member meeting.

CRS China Local Chapter continued on page 26

CRS China Local Chapter continued from page 25

CRS China Local Chapter Second Annual Meeting

September 21, 2012, Chengdu, China

CRS China Local Chapter held its second annual meeting on September 21, 2012, in Chengdu, People's Republic of China. Prof. Kyung-Dall Lee from the Department of Pharmaceutical Sciences, University of Michigan, U.S.A., Prof. Zhongwei Gu, director of the National Engineering Research Center for Biomaterials at Sichuan University, Prof. Jianping Zhou, Department of Pharmaceutics, China Pharmaceutical University, and Prof. Jun Wang from the School of Life Sciences and Polymer Chemistry, University of Science and Technology of China, were invited to give keynote presentations in the morning, and ten other professors gave their presentations in two sessions in the afternoon. The topics mainly focused on nanotechnology-based drug delivery systems. About 400 people from both academia and industry participated in the event. ■

Prof. Kyung-Dall Lee giving his keynote presentation.

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2011 Tsuneji Nagai Postdoctoral Fellowship Year Reflections

Soo Hyeon Lee, Ph.D.
Postdoctoral Fellow, Jean-Christophe Leroux Laboratory, Swiss Federal Institute of Technology Zurich (ETH Zurich)

Previous Studies for Clinical Applications of RNAi
In 2006, when Andrew Fire and Craig C. Mello received the Nobel Prize in Physiology or Medicine for their work on RNA interference (RNAi), I started my Ph.D. about small interfering RNA (siRNA) delivery at the Korea Advanced Institute of Science and Technology (KAIST) under the supervision of Prof. Tae Gwan Park. To obtain a balance between cytotoxicity and delivery efficiency, we developed various siRNA delivery carriers and modified siRNAs chemically by conjugating with polymers or crosslinking siRNA molecules.

After finishing my Ph.D., I realized that there are still important unmet needs for the clinical application of siRNAs as therapeutics, despite the tremendous efforts in this field. To devote myself to solving the current delivery problems of new drugs, I wanted to apply for a postdoctoral position in the laboratory of Prof. Jean-Christophe Leroux at the Swiss Federal Institute of Technology Zurich (ETH Zurich).

Reflections from the Fellowship Year
The Drug Formulation and Delivery Laboratory headed by Prof. Leroux belongs to the Institute of Pharmaceutical Sciences in the Department of Chemistry and Applied Biosciences. Within this department, many experts from different fields—for example, pharmacology and chemistry—are collaborating actively to develop drug delivery systems for clinical application. It is worth noting that defining the problem of conventional therapies from a pharmaceutical point of view and designing a novel system with various knowhow about chemical synthesis should not be considered separately. Based on my knowledge and experience acquired in cancer therapy and gene delivery during my Ph.D., I was greatly interested in joining this group to study at a world-class university and train myself as an independent researcher.

With Prof. Leroux, we designed a new research project and applied for the postdoctoral fellowship. Fortunately, I was selected as the recipient of the 2011 Tsuneji Nagai Postdoctoral Fellowship from the CRS Foundation. This honorable prize motivated me to dedicate myself in this field as well as gave me a great opportunity to join the group of Prof. Leroux and broaden my expertise for my future career. This fellowship also gave me the opportunity to meet and discuss the project with a very precious academic mentor, Prof. Tsuneji Nagai.


Soo Hyeon Lee and Prof. Tsuneji Nagai.

Prof. Leroux's laboratory focuses on developing drug delivery systems not only for life-threatening diseases such as cancer but also for rare diseases such as celiac disease or inflammatory bowel disease (IBD). Prof. Leroux is an expert in the fields of gastroenterology and drug delivery systems. Thanks to support and help from Prof. Leroux and my colleagues, I could set up my experiments immediately and focus on the research project, entitled "Inflammatory Bowel Disease Therapy with Nucleic Acid Drugs via Oral Administration."

Research Project
IBD is a group of chronic inflammatory disorders of the colon and small intestine. Patients usually are treated with anti-inflammatory drugs such as mesalazine to alleviate the immune response in the colon. However, the drug efficacy varies in patients, and long-term immunosuppressant therapy can cause severe side effects to the whole body. While the deteriorated intestine sections can be excised by surgery, there are still many problems such as relapses and inconvenience to the patient. To improve the quality of the patient's life, we need to develop new therapeutics with fewer side effects and higher efficiencies, relieving the symptoms and eventually curing the disease. Even though the main cause of IBD has not yet been defined, many factors—for example, genetic, infectious, immunologic, and psychological reasons—can influence the development of IBD.

Recent clinical studies with IBD patients have revealed that genetic properties can predispose people to develop IBD. The comparison of microRNA (miRNA) expression levels between patients and healthy people showed that certain miRNAs were abnormally under- or overexpressed in a group of patients, and the recovery of these problematic genes to express at the normal level elicited some therapeutic effect, suggesting that gene therapy could provide a breakthrough by replacing the conventional IBD therapy. As a target tissue, the colon is one of the most accessible sites via oral administration, in comparison with other tissues. Oral delivery to the colon has several advantages, namely, higher dose tolerated, convenience for the patient, and minimal systemic exposure, which usually causes undesirable side effects. However, the harsh conditions in the gastrointestinal tract (e.g., pH and digestive enzymes) should be considered in designing an efficient delivery system.

For this reason, we selected chemically and enzymatically stable peptide nucleic acids (PNAs) as a nucleic acid drug, to eventually modulate the abnormal expression levels of miRNA in the colon. Because PNAs have a high molecular weight and neutral charge, they do not penetrate easily through the cell membrane. Therefore, previous studies have chemically conjugated cell-penetrating peptides (CPPs) for intracellular delivery of PNAs. Based on the previous studies about CPP-mediated oligonucleotide delivery, we selected 12 different CPPs to deliver PNAs into the cell to show the silencing effect on the target protein. We have successfully synthesized CPP-PNA conjugates and treated colon cancer

cells. With several potent CPPs for the efficient cytosolic delivery of PNA, we are currently modifying our potential drugs to provide colon tissue specificity. We hope that this work will result in a novel gene delivery system with high efficacy and safety for IBD, ultimately improving the patients' quality of life and informing the design of other drug delivery systems.

Even though the CRS Tsuneji Nagai Postdoctoral Fellowship has ended, I will never forget the numerous great moments that I had during the past year. This fellowship provided me lots of opportunities to develop my international visibility and experience to become a world-leading researcher. I greatly enjoyed working with Prof. Jean-Christophe Leroux, Dr. Bastien Castagner, and all my colleagues in the Drug Formulation and Delivery Laboratory at ETH Zurich. I appreciated their insightful comments and helpful guidance. I also deeply thank the CRS Foundation and, in particular, Prof. Tsuneji Nagai. ■

Building a Delivery Science Legacy

The objective of the CRS Foundation is to support the future of delivery science and honor those who have made outstanding contributions to the field. Now is the time to plan for 2014, build the endowment, and celebrate the CRS Foundation's early successes.

2014 Alexander Florence Postdoctoral Fellowship

Alexander Florence

In 2014 the CRS Foundation will give a $30,000 postdoctoral fellowship named to honor CRS past president Alexander "Sandy" Florence, former dean and current emeritus professor of the School of Pharmacy, University of London. He is editor-in-chief (Europe) of the *International Journal of Pharmaceutics* and was founding coeditor of the *Journal of Drug Targeting*. Author of hundreds of papers and multiple books, and recipient of numerous awards, Prof. Florence's expertise in pharmaceutical nanotechnology, drug delivery systems, physical pharmaceutical chemistry, novel dendrimers, and surface chemistry has added greatly to drug delivery research.

Build the Endowment in 2013

The CRS Foundation Board is focusing its 2013 time and resources to build the endowment for future sustainability. Your contribution matters. Please help build the endowment and support the next postdoctoral fellowship by making a generous year-end donation on the CRS Foundation website, www.controlledreleasesociety.org/about/foundation.

Celebrate the Advances of 2009–2012

Thanks to the generosity of CRS members and the delivery science community, the CRS Foundation has awarded postdoctoral fellowships of $30,000 each to four exceptional young delivery scientists since 2009. With each fellowship, CRS honors exemplary delivery scientists and supports the training of its future leaders.

Tram Dang

2012 Sung Wan Kim Postdoctoral Fellowship

Tram Dang

Engineering high-throughput *in vitro* systems for the investigation of immunological interaction

Ali Khademhousseini Laboratory
Brigham and Women's Hospital
Harvard Medical School

Soo Hyeon Lee

2011 Tsuneji Nagai Postdoctoral Fellowship

Soo Hyeon Lee

Design of novel macromolecular conjugates for delivery of antisense oligonucleotides to the colonic mucosa

Jean-Christophe Leroux Group
ETH Zurich

Qun Wang

2010 Jorge Heller Postdoctoral Fellowship

Qun Wang

Use of intestinal stem cells to treat colorectal cancer through regenerative medicine

Robert Langer Laboratory
MIT and Harvard Medical School

David Nguyen

2009 Joseph R. Robinson Postdoctoral Fellowship

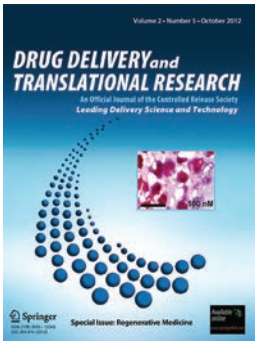
David Nguyen

Medical school and immunology research with novel vaccine adjuvants

David Lewis Laboratory
Stanford University ■

Drug Delivery and Translational Research

Vinod Labhasetwar, Ph.D., Editor-in-Chief



You may have noticed that *Drug Delivery and Translational Research* (*DDTR*), an official journal of CRS, is growing and is poised to become one of the leading journals to cover advances in science and technology of delivering bioactives. Visit the *DDTR* website at www.controlledreleasesociety.org/publications/Pages/DDTR.aspx to glance through research articles, reviews, editorials, and special issues published in *DDTR*. CRS members must login to the CRS website first and then click the Publications tab to get to the member access link.

You are also invited to join the leading scientists who are publishing their work in *DDTR* and compete for the 2012 *DDTR* Outstanding Research Paper Award. The award will be selected from the research articles published in *DDTR* during 2012. It will be given during the 2013 CRS Annual Meeting, to be held July 21–24 in Honolulu, Hawaii, U.S.A.

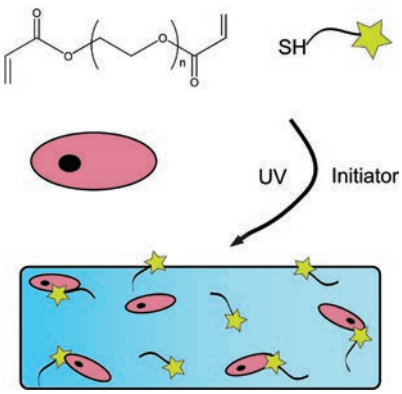
DDTR has published four well-received special issues covering topics from image-guided to vaginal to CNS drug delivery. If you are interested in developing a special issue on a current topic in drug delivery, please contact Vinod Labhasetwar at labhasv@ccf.org.

Editor's Pick (Vol. 2, Issue 5)

Covalently tethered transforming growth factor beta in PEG hydrogels promotes chondrogenic differentiation of encapsulated human mesenchymal stem cells

Joshua D. McCall, Jacob E. Luoma, and Kristi S. Anseth

From the special issue on "Regenerative Medicine."



In this study, the authors demonstrate the feasibility of delivering bioactive protein signals in a three-dimensional culture platform to control stem cell fate, which may have further implications in the design of delivery vehicles for human mesenchymal stem cells to promote chondrogenesis and cartilage regeneration *in vivo*.

Upcoming Special Issue

Nasal Drug Delivery with Guest Editors Elka Touitou, The Hebrew University of Jerusalem, Israel, and Lisbeth Illum, IDentity, Nottingham, United Kingdom

This theme issue covers various aspects of intranasal drug administration, including factors involved in the design of a nasal drug product for actives of various physicochemical characteristics including low-molecular-weight drugs, peptides, proteins, nucleic acids, and vaccines; strategies used in overcoming low drug absorption from the nasal cavity; and an overview of existing nasal delivery devices and their pros and cons.

Selected 2012 Reviews in *DDTR*

Aptamer-conjugated polymeric nanoparticles for targeted cancer therapy
A. Aravind, Y. Yoshida, T. Maekawa, and D. S. Kumar

Advances in biomimetic regeneration of elastic matrix structures
B. Sivaraman, C. A. Bashur, and A. Ramamurthi

Electrospun collagen and its applications in regenerative medicine
M. J. Fullana and G. E. Wnek

Anti-platelet and tissue engineering approaches to biomaterial blood compatibilization: How well have these been translated into the clinic?
S. A. Irvine, X. Yun, and S. Venkatraman

Engineering solid lipid nanoparticles for improved drug delivery: Promises and challenges of translational research
D. K. Mishra, V. Dhote, P. Bhatnagar, and P. K. Mishra

Delivering drugs to the central nervous system: An overview
P. I. Dickson

Drug transport into the central nervous system: Using newer findings about the blood–brain barriers
W. A. Banks

Magnetic nanoparticles and their applications in image-guided drug delivery
M. K. Yu, J. Park, and S. Jon

Image-guided drug delivery in lung cancer
T. S. Wiedmann, T. Sadhukha, B. E. Hammer, and J. Panyam ■

Make the Most of the CRS Website: Find Your Colleagues

Membership in CRS has many privileges, and one of the most important ones is the opportunity to reach your colleagues in delivery science around the world. The member directory search allows you to find colleagues by name and company. You can also search for delivery scientists within certain states or countries, others in academia or government, or look for scientists within certain tracks of interest. You must be a current member and logged in to fully access the member directory.

If you are looking for someone with the same interests as you, try looking for members in committees or chapters. The committee directory lists the active members of the committees, who are working to solve issues in delivery science and for the society. The "Chapters" page lists the officers of each local chapter, another excellent opportunity for you to connect locally.

The CRS website is your primary resource to connect with this unique community. Be sure to log in and click on the "Community" tab to take advantage of everything your membership gives you access to! ■

The 20th annual Advances in Tissue Engineering short course was held August 8–11, 2012, in Houston, Texas, at Rice University's state-of-the-art BioScience Research Collaborative. Participants from the United States and around the world heard expert speakers discuss the latest knowledge and technologies in the world of patient-specific therapeutics—from transplantation of cells and tissues to artificial organs. The Controlled Release Society has endorsed this course for several years. ■

Welcome New Members

Brittany Avaritt
Deepak Basra
Adriano Coelho
Robert T. Flynn
Sifei Han
Mouhannad Jumaa
David B. Kiehn
Kenneth B. Kirby
Reza Mahjoub
Bart Milanowski
Rufino Perez
Elisabetta Ranucci
William T. Self
Rajendra S. Tandale
Shweta Ugaonkar
Reinhard Vehring
Tapani Viitala
Long Vu
Desmond B. Williams

CRS Leading Delivery Science and Technology

Honor a Colleague

Submit a Nomination for the 2013 CRS Awards

Nominations are now being sought for the following CRS awards:

- Fellows
- Founders
- CRS T. Nagai Postdoctoral Research Achievement Award
- Young Investigator Award

Information on the awards, eligibility requirements, and the online nomination form are available at **www.controlledreleasesociety.org/about/awards**

Make Your Nominations by January 31, 2013

CRS Leading Delivery Science and Technology

Your Membership:

Your Access to the Future of Delivery Science and Technology

Test tubes and shampoo images courtesy of istock.com. Eye drops courtesy of Comstock.

Your membership is your all-access pass to leading research and the delivery science community.

Access: Innovative Research

From the research presented in the journals *Drug Delivery and Translational Research* and the *Journal of Controlled Release*, to the science presented at the CRS Annual Meeting & Exposition, to books and online webcasts, CRS is your source for the best delivery science and technology research.

Access: Targeted Networking

The CRS Annual Meeting & Exposition is just the beginning of the great opportunities to connect with delivery scientists. Utilize the online community through the website, find experts through the new LATTE database, join a committee, connect on LinkedIn, or join your local chapter, and access one of the most valuable resources – each other.

Access: Career Advancement

Advance your professional skills through volunteering, participating in the mentoring program, and more. CRS offers fellowship programs and recognition through awards. The new online career center is one more chance to develop your career in delivery science.

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Take advantage of everything your membership has to offer now. Access it all online.

www.controlledreleasesociety.org

People in the News

Compiled by Steven Giannos, University of Maryland, Baltimore, MD, U.S.A.
Industrial Editor

Osmotica Pharmaceutical Corp. Announces the Appointment of Praveen Tyle, Ph.D., as Executive Vice President and Chief Scientific Officer

Business Wire: October 15, 2012 – WILMINGTON, NC, U.S.A. – Osmotica Pharmaceutical Corp. today announced the appointment of Dr. Praveen Tyle as executive vice president and chief scientific officer. He also serves as the managing director of Osmotica's Marietta, Georgia, site. Forrest Waldon, CEO of Osmotica Pharmaceutical, stated, "We are pleased to announce that Praveen Tyle has joined Osmotica as chief science officer and executive vice president. Praveen is a proven industry veteran with an impressive record of moving pharmaceutical pipelines to commercial success."

"I am extremely excited to join Osmotica at this important time in the company's history. I look forward to building on the accomplished science and technology base developed at Osmotica and through our partners, including the recently announced alliance with Panacea Biotec, to aggressively grow our company's pipeline and pharmaceutical product offerings," Dr. Tyle added.

Prior to joining Osmotica Pharmaceutical, Dr. Tyle served as executive vice president and chief science officer for the United States Pharmacopeia. Dr. Tyle has nearly 30 years of experience in the pharmaceutical industry, with the majority of his tenure in senior executive leadership positions in areas of research and development, manufacturing, quality, business development, and operations. Prior to joining USP, Dr. Tyle served as the senior vice president and global head of business development and licensing at Novartis Consumer Health. At Novartis Consumer, Dr. Tyle also served as senior vice president and global head of R&D and developed both short- and long-term OTC medicine pipelines including prescription to over-the-counter transitions. Before Novartis, Dr. Tyle was corporate senior vice president of global research and development and chief scientific officer at Bausch + Lomb.

Dr. Tyle earned his doctorate in pharmaceutics and pharmaceutical chemistry (drug delivery systems and physical pharmacy) from the Ohio State University, and his bachelor of pharmacy degree (first class with honors and valedictorian) at the Institute of Technology, Banaras Hindu University in India. He sits on a number of boards of directors and scientific advisory committees, including those at EyeGate Pharmaceuticals, Inc., Orient Europharma, Inc., GrayBug, LLC, and some private equity groups. Dr. Tyle has over 20 issued patents and over 120 scientific publications and presentations, including editor of seven books on drug development, to his credit. Additionally, Dr. Tyle serves as adjunct professor at Howard University, the University of Rochester Medical Center, the University of Houston, and the University of Rhode Island. Dr. Tyle has been honored as a distinguished research fellow by the Shandong Pharmaceutical Research Institute, China, and received the Distinguished Alumni Award from the Institute of Technology, Banaras Hindu University.

Osmotica Pharmaceutical is a global specialty pharmaceutical company with a proven history of developing commercially successful pharmaceutical products. The company uses its proprietary osmotic technology platform and with strategic partners develops and commercializes high-quality pharmaceutical products. In addition to the products currently on the market, the company's pipeline includes several neurology-based therapeutic drugs.

Osmotica Pharmaceutical and its related companies form an international group of companies with principal operations located in the United States, Argentina, and Hungary. For more information on the company, please visit Osmotica's website at www.osmotica.com.

National Academy of Engineering Honors Nicholas Peppas with Founders Award

University of Texas at Austin: October 1, 2012 – AUSTIN, TX, U.S.A. – The National Academy of Engineering has selected Nicholas Peppas as its 2012 Founders Award recipient in recognition of his pioneering work in the areas of polymer chemistry, bioengineering, pharmaceutical sciences, and advanced drug delivery.

Peppas is the chair of the Cockrell School of Engineering Biomedical Engineering Department, and he holds the Fletcher Stuckey Pratt Chair in Engineering, with additional appointments in chemical engineering and pharmacy at the University of Texas at Austin. He is believed to be the first faculty member from a Texas university to receive the prestigious award since its inception in 1966. The award is given to one NAE member annually who has made a substantial impact on the engineering profession.

"Peppas is a leading researcher, inventor, and pacesetter in the field of drug delivery and controlled release, a field that he developed into a mature area of scholarly and applied research," said Charles Vest, NAE president and former president of Massachusetts Institute of Technology (MIT).

Peppas has focused his work on advancing drug delivery and biomaterials with the goal of improving drug administration,

People continued on page 34

People continued from page 33

efficacy, and patient quality of life. His contributions have been translated into more than 20 medical products, and he holds more than 50 U.S. and international patents.

"His pioneering work created a path for the emerging fields of biomaterials and responsive materials," said Cockrell School of Engineering Dean Gregory L. Fenves. "Peppas has made lasting contributions to engineering, as well as the pharmaceutical and clinical aspects of drug delivery. His scientific achievements have opened up new avenues for treating and curing diseases such as diabetes, cardiac problems, and cancer."

In the 1980s, Peppas developed theories and equations that set the foundation for the design of drug delivery systems and biomaterials. He is known for the Peppas–Korsmeyer equation, which is the standard method of analysis of pharmaceutical formulations or systems.

One area of Peppas's focus is the delivery of responsive hydrogels—particles that are able to stay in a collapsed state until triggered by temperature, pH, or other biomolecules in the body. His work with hydrogels has resulted in medical breakthroughs, including oral delivery systems for diabetes, controlled-release treatments for heart problems, and the development of new biomaterials for artificial organs.

Peppas has supervised 180 graduate students, postdoctoral fellows, and visiting scientists. About 95 percent of his graduate students go on to work on their PhDs. He also teaches undergraduate courses in biomedical engineering.

"Almost one-fourth of his graduate students serve as professors in other universities, and many more are leading biomedical scientists, engineers, physicians, and medical professionals," said Elazer Edelman, a distinguished professor at MIT and Harvard Medical School and an NAE member.

Peppas has been published more than 1,100 times and has received more than 44,000 citations of his work, making him one of the most cited engineers in the world regarding the areas of drug delivery, biomaterials, and intelligent materials.

In addition to being a member of the NAE, Peppas is a member of the Institute of Medicine. He has served on panels and committees of numerous organizations, including the National Science Foundation, the National Institutes of Health, and other federal agency panels.

"It is a great honor for me to receive the Founders Award from the National Academy of Engineering," Peppas said. "The award is not only recognition of our achievements but also an acknowledgement of the hard work and contributions of all the collaborators and researchers who worked with me and contributed to this work. I am touched by the decision and generosity of the Academy, and I am humbled to be included among the giants of engineering who have received this award before."

The NAE presented the award to Peppas at a ceremony on Sunday, September 30, in Washington, D.C. The Founders Award includes a $2,500 prize and a gold medallion. For more information, contact Sandra Zaragoza, Cockrell School of Engineering, (512) 471-2129.

Joseph Rogers Joins SRI International as Executive Director of New Health Sciences Section in Biosciences Division

PRNewswire: August 28, 2012 – MENLO PARK, CA, U.S.A. – Joseph Rogers, Ph.D., has joined SRI's Biosciences Division as executive director of a new Health Sciences Section that brings together researchers from SRI's Center for Health Sciences, led by Gary Swan, Ph.D., with SRI's Center for Neuroscience and Metabolic Diseases, led by Thomas Kilduff, Ph.D. This combination offers SRI clients and partners more integrated bench-to-bedside capabilities in areas such as addiction, alcoholism, Alzheimer's and Parkinson's diseases, Down syndrome, sleep disorders, and more.

"We are fortunate to have Joe Rogers leading the new Health Sciences Section at SRI," said Walter H. Moos, Ph.D., vice president, Biosciences Division at SRI. "Joe is an outstanding, award-winning researcher whose focus on age-related neurologic diseases will be a valuable asset to SRI's expanded health research, drug discovery, and drug development programs."

Rogers is best known for showing that inflammatory responses occur in almost all major age-related brain disorders and cause substantial damage, with his seminal paper in the area receiving nearly 1,200 citations to date. Before joining SRI, Rogers served as founder and president of the Sun Health Research Institute (acquired by Banner Health System). Under his leadership, the institute became internationally recognized for its research on age-related neurological diseases and is a National Institutes of Health (NIH) funded National Alzheimer's Disease Center.

He has served on numerous boards, including the American Geriatrics Society, Arizona Alzheimer's Association, NIH Working Group on Neuroimmunology, Arizona Governor's Task Force on Alzheimer's Disease, Arizona Legislative Task Force on Stem Cell Research, and the Pacific Alzheimer's Institute. A reviewer and editorial board member for numerous scientific journals, Rogers has more than 150 scientific publications. His research on Alzheimer's disease has been continuously funded by the NIH for the last 25 years. Rogers also holds patents related to the diagnosis and treatment of Alzheimer's disease.

He has received many awards for his work, including a Lifetime Achievement Award from *Arizona Business Magazine*, a Lifetime Achievement Award from *Phoenix Business Journal*, and a Lifetime Achievement Award, a Zenith Award, and a Faculty Scholar Award from the national Alzheimer's Association. Rogers received his Ph.D. from the University of California, San Diego, his B.A. from Emory University, and was a postdoctoral fellow at the Salk Institute. ■

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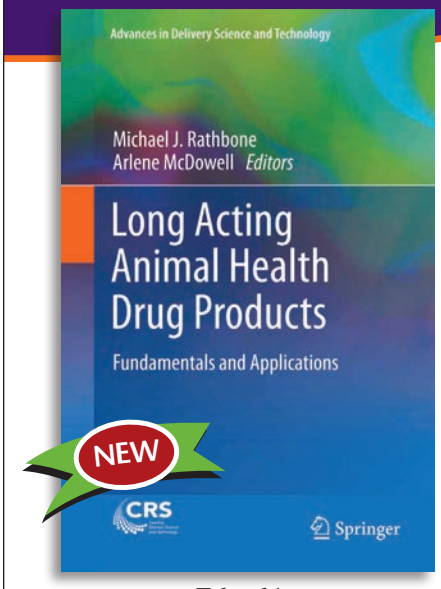


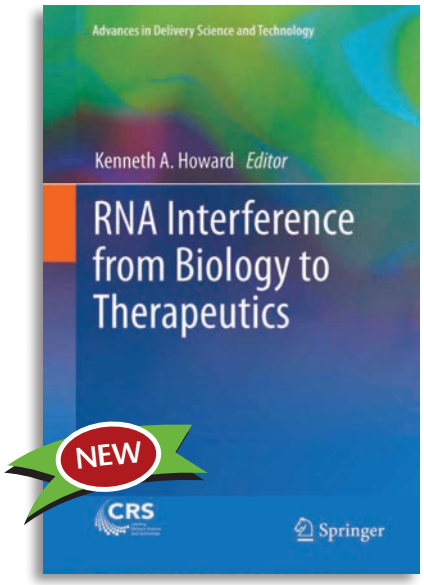
Edited by
Michael J. Rathbone and Arlene McDowell

Long Acting Animal Health Drug Products is the comprehensive guide on the theories, applications, and challenges associated with the design and development of long acting veterinary formulations. The volume acts as a reference to the animal health formulation scientist and contains chapters written by leading experts in the field. It offers additional details through a mixture of figures, tables, and references to provide information not found in other similar texts.

The book covers everything a student or a formulation scientist in industry or academia needs to know about this unique area of drug delivery. It provides an overview of the fundamental science necessary for the rational design and development of veterinary animal health products and provides in-depth descriptions of the technologies that are currently commercially available for the prolonged delivery of drugs to animals.

2012, 1st Edition, XII, hardcover, 406 pages; ISBN 978-1-4614-4438-1

These new titles join the growing CRS Advances in Delivery Science and Technology book series.



Edited by
Kenneth A. Howard

RNA Interference from Biology to Therapeutics is an up-to-the-minute, highly informative, and invaluable text for those actively involved or interested in this fascinating and high-impact field. The Nobel Prize winning discovery that small interfering RNA can be utilized to control cellular gene expression has propelled the field of RNA interference (RNAi) to the forefront of biomedical science as a potential molecular medicine set to revolutionalize disease treatment. Harnessing the molecular mechanisms of RNAi and development of delivery technologies is crucial for its transformation into a therapeutic modality. This dependency is the focus of "RNA Interference from Biology to Therapeutics" that gives a comprehensive overview of RNAi biology and state-of-the-art delivery methods relevant to clinical translation of RNAi therapeutics.

Key players and shapers in the fields of RNAi and delivery science have been assembled in a single volume to produce a truly unique interdisciplinary text, making it a "must-read" for both students and experts in, and at the interface of, RNAi, pharmaceutical science, and medicine.

2012 1st Edition, XV; hardcover; 512 pages; ISBN 978-1-4614-4743-6

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In the News

Compiled by Steven Giannos, University of Maryland, Baltimore, MD, U.S.A.
Industrial Editor

October 2012

Vascular Nanotransfer Technologies ("VNT") Reports In Vivo Results for Its Paclitaxel Nano-Carrier Based Drug Coated Balloon (DCB) Technology

Business Wire: October 19, 2012 – AUBURNDALE, MA, U.S.A. – Vascular Nanotransfer Technologies ("VNT") (www.vnanotech.com), an emerging medical technology company, announced today that large animal model *in vivo* tests of its paclitaxel nanocarrier-based drug coated balloon ("DCB") achieved tissue levels comparable to devices with proven clinical efficacy.

"VNT has achieved tissue levels of paclitaxel that are comparable to devices with proven clinical efficacy but has done so with a device that has superior coating characteristics along with a lower concentration of paclitaxel per surface area," said John A. Williams, president and CEO of VNT.

"We are very pleased with our proprietary balloon coating technology designed for enhanced drug delivery and superior coating characteristics. Now we have a high-performing paclitaxel nanocarrier-based DCB with strong *in vivo* test results," added Williams.

VNT is focused on DCBs, which are emerging as the ideal therapeutic tool for patients with coronary in-stent restenosis (ISR) and peripheral vascular disease. However, despite the success of first-generation DCBs in clinical trials, they exhibit significant limitations related to the precision in drug delivery and tissue retention, raising concerns about overall vascular safety. There is a need for the development of reliable coatings that allow for controlled drug delivery at a lower dose and minimal dislodgement of the coating into the distal vessel.

"There are as yet no drug-coated balloons approved for sale in the United States," said Williams. "VNT's paclitaxel-based DCB for coronary and peripheral vascular applications is designed to have important competitive advantages over today's European DCB market leaders, such as lower balloon drug surface concentration and particulate counts. We expect to begin patient enrollment for VNT's first-in-man clinical trial in early 2013."

Privately held VNT, based in Auburndale, Massachusetts, is developing DCBs that are designed to be a more precise delivery vehicle and be the standard treatment of choice for vascular atherosclerosis as well as nonvascular applications.

Frost & Sullivan Enabling Technology Award Conferred on Alexza Pharmaceuticals for Staccato®

October 18, 2012 – LONDON, U.K. – Based on its recent analysis of the bipolar disorder therapeutics market, Frost & Sullivan recognises Alexza Pharmaceuticals with the 2012 Global Enabling Technology Award for its core proprietary technology—Staccato®.

Staccato is a novel method of inhaled drug delivery that is exclusively customised for conditions requiring rapid speed of therapeutic effect, reliable dosing, and ease of use. Currently, Alexza Pharmaceuticals has developed a single-dose disposable platform and a multi-dose platform with reusable controller. The Staccato system eliminates the need for excipients and additives, such as detergents, solvents, and stabilisers, thereby reducing the possible associated side effects for patients.

Adasuve™ (Staccato® loxapine) is the flagship product of Alexza Pharmaceuticals, based on the Staccato platform, which is being developed for the acute treatment of agitation associated with bipolar disorder or schizophrenia. Adasuve meets all three key attributes in the treatment guidelines outlined by the American Association for Emergency Psychiatry—speed of onset, predictability of medication delivery, and patient preference.

"With a single normal breath, the Staccato® technology delivers an accurate, rapidly absorbed dose of loxapine through the deep lung," noted Frost & Sullivan research analyst Aiswariya Chidambaram. "Loxapine, noted for its excellent receptor-binding attributes and positive side-effect profile, is likely to be a preferred antipsychotic of physicians treating agitation."

"Adasuve™ offers a noninvasive, rapid-acting, and patient-friendly therapy option, which ensures safe, effective, and early intervention well before the agitation episodes escalate out of control," remarked Chidambaram. "It also offers better results in emergency conditions, when agitation has reached a crisis level."

Alexza Pharmaceuticals has successfully completed two separate phase III trials for schizophrenia (344 patients) and bipolar disorder (314 patients), wherein Adasuve showed statistically significant primary and secondary endpoint results as compared to placebo.

Alexza Pharmaceuticals anticipates U.S. FDA regulatory approval for Adasuve by the end of 2012 and is projecting a launch of the product by mid-year 2013 in the United States and Europe. This first-in-class, anti-agitation product is expected to hold huge market potential and business opportunities in terms of commercialisation.

"In anticipation of regulatory approval, Alexza Pharmaceuticals has already established strong technology and materials supply relationships and has built a clinical good manufacturing practice (cGMP) facility in California," stated Chidambaram. "The company plans to commercialise this pioneering technology globally and has already been proactive in forging strategic partnerships with leading pharmaceutical companies."

Frost & Sullivan presents this award to the company for developing a technology that enables the creation of new products and applications and/or enhances current products. The potential for market acceptance and breadth of access to the technology also underpin the receipt of this award.

Study Shows OptiNose Bi-Directional™ Nasal Technology Reaches Target Areas of the Nasal Cavity Much More Effectively Than Traditional Nasal Spray

October 18, 2012 – YARDLEY, PA, U.S.A. – OptiNose US Inc. today announced the publication of results from a study that showed that the proportion of the dose delivered to the blood vessel-rich middle and upper posterior regions in the back of the nose is three times higher with the OptiNose breath-powered Bi-Directional™ nasal delivery device than traditional liquid nasal spray. The study "Nasal Deposition and Clearance in Man: Comparison of a Bi-directional Powder Device and a Traditional Liquid Spray Pump," was published in the October 2012 issue of the *Journal of Aerosol Medicine and Pulmonary Delivery*.

"Delivering medicine to targeted deep nasal regions has been widely recognized as a way to try and improve treatment of disease. There has been no method for simple, reliable delivery of medicine to those regions. Traditional nasal sprays are poor at consistently reaching those regions, with problems like 'drip out' and medicine swallowing. To solve this longstanding challenge, OptiNose has created an innovative new approach: breath-powered Bi-Directional™ technology," said Per G. Djupesland, M.D., Ph.D., chief scientific officer of OptiNose and inventor of the Bi-Directional delivery technology. "This study shows that our novel delivery concept significantly improves the delivery of medicine to target sites in the middle and upper regions at the back of the nasal cavity. With this powerful new method of delivering drug, improved treatments for many disorders ranging from rhinosinusitis or migraine to brain diseases like Alzheimer's or autism may be possible."

The study featured an open-label, crossover design where seven adult volunteers used both the OptiNose Bi-Directional nasal device and a traditional liquid nasal spray to deliver a radiolabeled dose into the nose. The radiolabeling allowed researchers to use an innovative gamma camera to create images showing where the radiolabeled powder and liquid were deposited within the nasal cavity.

The study found that the proportion of the dose delivered with the OptiNose technology to the middle and upper posterior regions of the nasal cavity was three times higher (53.5% vs. 15.7%, $P < 0.02$) than the liquid spray. These regions of the nasal cavity are located in the back of the nose where a dense network of blood vessels facilitates faster drug absorption into the blood. In contrast, the traditional spray left a substantially higher proportion of the delivered dose on the floor of the nasal cavity (17.4% vs. 59.4%, $P < 0.04$), which often results in the medication being wiped off with a tissue or "sniffed" down the back of the throat and swallowed.

In addition, the powder delivery using the OptiNose technology resulted in faster overall clearance from the nose than the traditional spray. This was associated with less immediate loss of drug (e.g., to "drip out"), as indicated by the finding that two minutes after delivery there was greater total deposition in the nasal cavity with the OptiNose technology than with the liquid spray (98.3% vs. 85.8%, $P < 0.04$).

Nasal delivery could be very beneficial, especially for locally acting drugs to treat rhinitis and sinusitis, or as a way to improve the speed and extent of absorption of a medicine into the blood without an injection. However, traditional nasal sprays tend to deposit a large portion of the medicine in the front regions of the nose, allowing the liquid to drip out, leading to a loss of medicine when it is wiped off with a tissue, or to be sniffed backwards along the nasal floor into the mouth and subsequently swallowed. For more information, please visit www.optinose.com.

OncoSec Receives CE Mark for Its Electroporation Device

PRNewswire: October 17, 2012 – SAN DIEGO, CA, U.S.A. – OncoSec Medical Inc. (OTCBB: ONCS), a company developing its advanced-stage ImmunoPulse DNA-based immunotherapy and NeoPulse drug-based chemotherapy to treat solid tumor cancers, announced it has received authorization to CE mark its proprietary gene and drug delivery platform, the OncoSec Medical System (OMS) electroporation device, for use in the European Economic Area (EEA). SGS Group, an industry-leading inspection, verification, testing, and certification company, supervised the assessment and certification process.

A CE mark verifies the OMS electroporation device has met all applicable directives of the European Commission (EC) and subsequently the laws and regulations of the European Union (EU) member states and therefore can be commercialized within the 30-nation EEA and Switzerland. The electroporation device applies short electric impulses to a tumor, causing pores to open in the membrane of cancer cells, significantly increasing the uptake of anticancer agents into these cells. The granting of this CE mark involved a comprehensive audit of the company's quality system as well as thorough evaluation and testing of the OMS electroporation device to assure it performs safely and as designed. The CE mark affirms OncoSec's commitment to product quality and development, and it augments the notified body certification to the International Organization for Standardization's (ISO) 13485 standard for the "design, development, manufacture, and distribution of electroporation devices," which the company received in July.

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Punit Dhillon, president and CEO of OncoSec, commented, "The approval marks an essential regulatory milestone on the road to commercialization and further approval of the OncoSec Medical System. The CE mark shows that OncoSec has the capability to manufacture and develop a device that meets commercial regulatory requirements."

OncoSec Medical Incorporated is a biopharmaceutical company developing its advanced-stage ImmunoPulse DNA-based immunotherapy and NeoPulse therapy to treat solid tumor cancers. ImmunoPulse and NeoPulse therapies address an unmet medical need and represent a potential solution for less invasive and less expensive therapies that are able to minimize detrimental effects resulting from currently available cancer treatments such as surgery, systemic chemotherapy or immunotherapy, and other treatment alternatives. OncoSec's core technology is based upon its proprietary use of an electroporation platform to dramatically enhance the delivery and uptake of a locally delivered DNA-based immunocytokine (ImmunoPulse) or chemotherapeutic agent (NeoPulse). Treatment of various solid cancers using these powerful and targeted anticancer agents has demonstrated selective destruction of cancerous cells while sparing healthy normal tissues during early and late stage clinical trials. OncoSec's clinical programs include three phase II clinical trials for ImmunoPulse targeting lethal skin cancers. More information is available at www.oncosec.com. Additional information may also be found at OncoSec's Facebook, Twitter, and LinkedIn sites.

Depomed Announces Serada® NDA Acceptance and FDA Advisory Committee Meeting

PRNewswire: October 15, 2012 – MENLO PARK, CA, U.S.A. – Depomed, Inc. (Nasdaq: DEPO) today announced that its New Drug Application (NDA) for Serada® has been accepted for filing by the U.S. Food and Drug Administration (FDA). In addition, the FDA has informed the company that the FDA's Reproductive Health Drugs Advisory Committee will discuss the Serada NDA at an Advisory Committee meeting tentatively scheduled for March 4, 2013.

The NDA will be subject to a standard review and will have a Prescription Drug User Fee Act (PDUFA) action date of May 31, 2013. The acceptance of the NDA reflects the FDA's determination that the application is sufficiently complete to permit a substantive review. The PDUFA date is the goal date for the FDA to complete its review of the NDA.

Serada is Depomed's proprietary extended release formulation of gabapentin in development for the treatment of menopausal hot flashes. Depomed submitted the Serada NDA to the FDA on July 31, 2012. Depomed is seeking approval to market and sell Serada in the United States for the treatment of menopausal hot flashes. Serada is an investigational product and is not approved to treat any disease or condition.

"Acceptance of the NDA for Serada and scheduling of an Advisory Committee are important milestones. We believe that Serada may be a viable nonhormonal product candidate for the treatment of menopausal hot flashes, based on our and numerous academic studies that have demonstrated that gabapentin may be effective in treating hot flashes," said Jim Schoeneck, president and CEO of Depomed.

pSivida CEO to Discuss Sustained Delivery and Nanotechnology in Ophthalmology at Upcoming Massachusetts Biotechnology Council Meeting

Business Wire: October 15, 2012 – WATERTOWN, MA, U.S.A. – pSivida Corp. (NASDAQ: PSDV) (ASX: PVA), a leader in developing sustained release drug delivery products for treatment of back-of-the-eye diseases, today announced that its president and CEO, Dr. Paul Ashton, will discuss "Cross Fertilization: Sustained Delivery and Nanotechnology in Ophthalmology" at an upcoming Formulation and Drug Delivery Committee Meeting of the Massachusetts Biotechnology Council on Wednesday, October 17.

Dr. Ashton's presentation will focus on delivery of peptides and proteins, primarily in ophthalmology. Currently, the eye space is dominated by two anti-VEGF proteins, Roche/Genentech's Lucentis® and Regeneron's Eyelea.® Both of these drugs must be repeatedly injected directly into the eye, typically every one to two months. "The development of a sustained release protein delivery system would offer a significant advantage in ophthalmology," said Dr. Ashton. "pSivida is presently developing such a delivery system, called Tethadur™, which is based on the company's BioSilicon technology platform. This delivery system could also have a significant clinical impact outside of ophthalmology for diseases requiring systemic administration, particularly in the BioSimilars era."

Tethadur is designed to provide sustained delivery of biologic molecules, including proteins, antibodies, and peptides. It is composed of nanostructured porous material, in which the sizes of the pores are manufactured to accommodate specific protein, peptide, or antibody molecules. "Very simply put, Tethadur can be viewed as a high-tech egg box where each protein molecule is contained in its own spot until it is released," said Dr. Ashton. "We are able to control the release rate of a drug by controlling the pore size of the Tethadur delivery material."

pSivida recently announced a technology evaluation agreement with a leading global biopharmaceutical company to evaluate Tethadur in the field of ophthalmology. "Although we are at the very early stages with Tethadur, the potential improvement in patient care and clinical outcomes could be highly significant," Dr. Ashton stated. "We have already been successful in this field. Working with partners we have developed three of the four sustained release devices for ophthalmic drugs approved in either the U.S. or the E.U."

The Massachusetts Biotechnology Council (MassBio), a not-for-profit organization that represents and provides services and support for the Massachusetts biotechnology industry, is the nation's oldest biotechnology trade association. Founded in 1985,

MassBio is committed to advancing the development of critical new science, technology, and medicines that benefit people worldwide.

BioDelivery Sciences Announces the Launch of Breakyl (BEMA Fentanyl) in the E.U.

PRNewswire: October 15, 2012 – RALEIGH, NC, U.S.A. – BioDelivery Sciences International, Inc. (Nasdaq: BDSI) announced the commercial launch of Breakyl (fentanyl buccal film) in the European Union.

BDSI's commercial partner for Breakyl in the E.U. is Meda. Under the terms of its E.U. agreement with Meda, BDSI will now receive a final milestone payment of $2.5 million. BDSI will also receive a royalty on net sales of Breakyl in the E.U.

Breakyl is being launched in the E.U. by Meda and will be available for sale in a selected number of countries in 2012, including Germany. Breakyl will thereafter be launched in most E.U. countries throughout 2013.

Breakyl is commercialized in the United States as Onsolis (fentanyl buccal soluble film) by Meda's U.S. affiliate, Meda Pharmaceuticals. Breakyl and Onsolis are both indicated for the management of breakthrough pain in patients with cancer, 18 years of age and older, who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.

Breakyl will compete in the market for transmucosal fentanyl products, which has grown substantially in the E.U. in recent years following the availability of new products, to over $200 million, which is an increase of 34% over the prior year.

Bend Research Receives Two U.S. Patents for Technology to Enhance the Bioavailability of Low-Solubility Drugs

Business Wire: October 11, 2012 – BEND, OR, U.S.A. – Bend Research Inc. (www.bendresearch.com), a leading independent drug-formulation development and manufacturing company, announced that it has received two new U.S. patents related to its pioneering efforts to improve the oral bioavailability of low-solubility drugs.

The patents protect compositions and processes for making spray-dried dispersions (SDDs) that enhance the absorption of low-solubility drugs. The patents cover SDDs made with an active pharmaceutical ingredient (API) and hydroxypropyl methylcellulose acetate succinate (HPMCAS), a polymer that is also known as hypromellose acetate succinate.

Demand is high for this technology, since more than 40% of drugs in development are estimated to have low aqueous solubility. The HPMCAS SDDs enable the use of lower drug doses to achieve effective therapies for low-solubility drugs. The technology works by sustaining high concentrations of drug in patients' gastrointestinal tracts.

"These patents offer important protection for this vital technology," said Bend Research CEO Rod Ray. "Our goal is to provide a growing patent portfolio for our customers' use in protecting their investments in advancing low-solubility compounds to the market."

The patents are among a growing number of formulation- and process-related patents associated with Bend Research's solubility-enhancing drug-formulation technologies. These solubilization technologies enhance the concentration of drug in patients' bloodstreams and enable faster drug dissolution than is possible with crystalline drug forms.

The patents, which are both titled "Solid Pharmaceutical Dispersions with Enhanced Bioavailability," were assigned Patent Nos. 8,257,741 and 8,263,128 by the U.S. Patent and Trademark Office. The inventors are William Curatolo, Scott Herbig, and Jim Nightingale. Both patents are the result of work funded by Pfizer Inc. and are assigned to Bend Research Inc.

Binosto™ (Alendronate Sodium), the First and Only Effervescent Tablet and Buffered Oral Solution for the Treatment of Osteoporosis, Provides Alternative to Pill Therapy

PRNewswire: October 11, 2012 – SAN ANTONIO, TX, U.S.A. – Mission Pharmacal Company today announced that Binosto™ (alendronate sodium) effervescent tablet for buffered oral solution (70 mg) is now available by prescription in the United States. The U.S. Food and Drug Administration has approved Binosto to treat osteoporosis in postmenopausal women and to increase bone mass in men with osteoporosis.

Binosto delivers easy-to-swallow osteoporosis treatment and fracture prevention at the hip and spine—alendronate sodium—in a once-weekly, buffered solution. Binosto represents a true innovation in the delivery of osteoporosis and bone fracture prevention medication, especially for those patients who prefer not to swallow tablets, suffer with dysphagia, or have other medical difficulties swallowing pills.

"We are very pleased to add Binosto to our line of bone health products," says Terry Herring, president of commercial operations at Mission Pharmacal. "With this exciting new treatment option, physicians can rest easily, knowing they are prescribing an easy-to-take and proven therapy for their osteoporosis patients that protects against fracture risk at the hip and spine."

Although osteoporosis is often thought of as a disease that impacts mostly women, it affects men as well. While women do suffer relatively rapid bone loss in the first few years after menopause, it should be noted that by about age 65, men and women lose bone mass at the same rate.

With one of every two postmenopausal women at risk for an osteoporosis fracture, osteoporosis affects more than 200 million women and men worldwide and more than 10 million people in

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the United States, yet the gravity of the disease is often underestimated. According to an article published in the December 6, 2011, issue of the *Annals of Internal Medicine*, a woman's lifetime risk of dying from hip fracture is similar to her risk of dying from breast cancer.

"Osteoporosis is widespread, with serious consequences for patients, including mortality, which is often seen after suffering a hip fracture. In fact, up to 24 percent of patients with a hip fracture end up dying from complications within 12 months. And, unfortunately, many people incorrectly consider osteoporosis to be a normal part of aging. That's because it is largely asymptomatic," said Sol Epstein, M.D., professor of medicine and geriatrics at Mount Sinai School of Medicine in New York. "But osteoporosis is treatable. With the many new treatment options available, there is no reason for women to suffer the loss of independence and the pain and even mortality associated with osteoporotic fractures."

For anyone with osteoporosis, the best protection against suffering from a fracture is taking medications as prescribed by an authorized healthcare provider. However, studies show that people who have trouble swallowing pills are much more likely to stop taking their medication. Taken just once a week, strawberry flavored Binosto is a buffered effervescent solution that can help patients with swallowing difficulties be more compliant and decrease the risks of disabling fractures.

Binosto is a once weekly, strawberry flavored effervescent tablet containing alendronate (70 mg) that rapidly dissolves in half a glass (4 oz.) of plain room temperature water to make a buffered solution. Binosto is available in packs of four. The national drug code number is 0178-0101-02. Binosto was developed by EffRx based on an agreement with Merck & Co, Inc. granting EffRx the worldwide rights to all effervescent and related patents of Fosamax® (alendronate). Patents have been granted to EffRx providing exclusivity for Binosto through February 2023. Additional patents are pending.

Particle Sciences to Develop Antiretroviral Formulations as Part of MOTIF

PRNewswire: October 10, 2012 – BETHLEHEM, PA, U.S.A. – Particle Sciences, a leading drug delivery CRO, has been selected to be the formulation arm of an effort to create next generation vaginal drug delivery system. Referred to as MOTIF (Microbicide Optimization Through Innovative Formulation), the grant is funded by the European Commission as part of the Seventh Framework Programme. Under the contract, Particle Sciences will develop approaches that allow for multiple actives to be easily incorporated into the same formulation.

Other members of the consortium include King's College London, Microbiotec, University of Siena, University of Aberdeen, CEA Paris, and Imperial College. In addition to formulation approaches, a major goal of the work is to identify vaginal drug transporters and their impact on topically applied antiretrovirals.

Catalent Licenses Innovative Taste-Masking Technology for Bitter Drugs Following R&D Collaboration with New Jersey Institute of Technology

Business Wire: October 10, 2012 – SOMERSET, NJ, U.S.A. – Following a successful research collaboration, Catalent Pharma Solutions announces that it has taken an exclusive license to innovative taste-masking technology developed by the New Jersey Institute of Technology (NJIT). The technology has been developed to mask the most challenging, unpleasant, and bitter tasting pharmaceutical active ingredients.

Under the terms of the license, Catalent will complete transfer of the technology into its world-class, cGMP facilities to support manufacture of novel dosage forms such as its Zydis® fast-dissolve platform. It is expected that the taste-masking technology will be effective for developing a wide variety of formulations including granules/sachets, sprinkles, chewables, and effervescent and oral dispersible tablets.

"Taste masking of fine drug particles has remained a technical challenge for formulators," said Dr. Rajesh Davé, distinguished professor and principal investigator at NJIT. "Through funding from Catalent, we have been able to leverage our expertise to innovate technology and processes that allow for these materials to be cost-effectively coated and taste-masked."

Kurt Nielsen, Ph.D., Catalent's senior vice president of research and development, commented, "Dr. Davé and his group at NJIT are leaders in pharmaceutical particle engineering. The unique approach to API coating is a perfect complement to Catalent's extensive dose form capabilities and will facilitate formulation of the most difficult-to-taste-mask actives. Catalent has already produced the first feasibility samples, which have exceeded our expectations. This efficient and versatile taste-masking technology will allow development of new dosage forms delivering significant advantages to our customers and benefits to patients and consumers in global markets."

Diamyd Medical Divests U.S. Gene Therapy Company

Business Wire: October 8, 2012 – STOCKHOLM, SE – Diamyd Medical AB has entered into an agreement for the sale of the U.S. subsidiary, Diamyd, Inc., involved in drug development primarily relating to the NTDDS platform with applications in pain and neuropathy among others. The buyer, Periphagen Holdings, Inc., is owned by members of the management of Diamyd, Inc. The agreement is subject to approval of an Extraordinary General Meeting of Diamyd Medical. By reason of the divestment, Diamyd Medical will postpone its year end report to October 31, 2012.

Under the agreement, in addition to the shares in Diamyd, Inc., Periphagen Holdings, Inc., assumes the intellectual property rights to the patented nerve targeting drug delivery system (NTDDS) technology and all costs and revenues related to the business from September 1, 2012. The divestment will improve Diamyd Medical's operating profit/loss by approximately SEK 18 million during fiscal year 2012/13 compared to if the

company would have continued financing the development of the NTDDS platform.

"The divestment immediately and significantly reduces Diamyd Medical's costs, whilst we retain the right to share in future successes of the NTDDS platform. The development projects will receive full focus from their dedicated new owners, which makes it a great solution for both parties as well as for the NTDDS platform," says Peter Zerhouni, president and CEO of Diamyd Medical.

"We remain passionate about the NTDDS technology and have been involved since the research on nerve targeted gene delivery was initiated at the University of Pittsburgh in the 90s. It is a dream come true to increase our focus and run the business as our own," says Darren Wolfe, president of Diamyd, Inc., and Periphagen Holdings, Inc.

The transaction is a management buyout, where the purchasing corporation is owned by members of the management of Diamyd, Inc. Further information is available on the company's website: www.diamyd.com.

Bend Research and Dow Chemical Collaborate to Develop Drug-Solubility Solutions and New Polymers

Business Wire: October 4, 2012 – MIDLAND, MI, U.S.A. – Bend Research Inc., a leading independent drug-formulation development and manufacturing company and The Dow Chemical Company (NYSE: DOW), a global leader in designing, manufacturing, and supplying polymeric excipients for enabling drug-delivery systems, have formed an exclusive collaboration to provide science-based spray-dried dispersion (SDD) solutions and select enabling new polymers for poorly soluble oral drugs.

Dow and Bend Research will work together to provide the industry with fully characterized polymers supported by complete Quality-by-Design (QbD) principles and the ability to tailor materials to meet the performance needs of specific drugs. In addition, the two companies will develop and commercialize new materials for SDDs that address technology gaps in manufacturability and delivery, providing greater drug-product utility and therapeutic performance.

Dow will provide hypromellose and hypromellose acetate succinate, as well as options to tailor these materials, and next-generation cellulosic and noncellulosic polymers for enhanced performance.

The collaboration between Bend Research and Dow reduces drug-development risk by seamlessly combining materials development and optimization early in the formulation development process for SDDs to achieve optimal clinical outcomes and robustness in drug-product manufacturability. The collaboration will combine Dow's fundamental materials design, high-throughput screening, pilot-plant, and commercial scale-up capabilities with Bend Research's proven SDD screening, formulation, scale-up, and technology-transfer capabilities.

"We welcome the opportunity to further focus Dow's proven excipient and materials science expertise in the area of enhancing drug solubility, and we are enthusiastic about working with the world leader in spray-dried dispersions to ensure that our customers receive the best possible polymer solutions," said Bob Maughon, senior R&D director for Dow. Maughon noted that Dow is fully supporting this collaboration with an array of technologies, including high-throughput synthesis with API/polymer screening, laboratory-scale product development, and structure/property optimization, as well as a fully cGMP market-development plant capable of supporting clinical development of optimized solutions.

"We are proud to announce the collaboration between Bend Research and Dow," said Rod Ray, Bend Research CEO. "Our two companies have used rigorous science, grounded in fundamentals, to develop new excipients that improve the performance of our solubilization technologies. It is extremely important to us not only to develop new technologies for our clients, but to use cutting-edge research to enhance our existing technologies. Our collaboration with Dow is part of that initiative. It also ensures our clients access to a reliable supply of solubilization excipients that meet the critical-to-quality properties that are key to the performance of their compounds."

Fuisz Pharma Announces Patented Film Formulations for Enhanced Buccal Drug Delivery Performance

PRNewswire: October 2, 2012 – Miami, FL, U.S.A. – Fuisz Pharma announced today a patented film formulation for enhanced drug delivery performance. The seminal patent for this technology issued as U.S. Patent 8,241,661 ("Biocompatible Film with Variable Cross-Sectional Properties").

Joseph Fuisz, Esq., managing member for Fuisz Pharma, explained: "It is understood that bi-layer film compositions can offer improved buccal absorption characteristics by retarding the drug that is lost to salivary flow and thereby is swallowed and diverted to the GI tract. Such drug is naturally not available for absorption at the intended buccal delivery site." "At the same time, manufacturing two films—one for the drug and a second for a backing layer—and laminating said films is more difficult and costly than making a single film."

"What today's announcement deals with—and what is strongly covered by the issued patent claims of the '661 patent—is the intentional formation of hydrophobic domains in the top of a monolayer film. These hydrophobic domains retard the dissolution of the top section of the film, thereby precluding loss of drug to salivary flow. This offers the benefit of improved buccal performance with easier manufacturing and freedom to operate with respect to certain bi-layer patents."

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Richard C. Fuisz, M.D., commented: "Bottom line here is that we have bi-layer functionality in a single layer cast film. In addition, by employing physical laws of miscibility and density, the way is open for more than one drug and/or for different release rates. It is to be decided whether this patent is licensed or utilized by Fuisz."

Fuisz Pharma is a private pharmaceutical technology company originated by the Fuiszes. The Fuiszes have made substantial contributions in drug delivery including orally dissolving tablets and novel particle coating systems at Fuisz Technologies, inventing and developing thin film drug delivery technologies at Kosmos Pharma and MonoSol Rx, as well as independently developing extruded sheet technology, and have extensive experience working with big and specialty pharma. Fuisz Pharma has its headquarters in Miami and is not affiliated with MonoSol Rx. www.fuisz.com.

NextWave Pharmaceuticals Receives FDA Approval of Quillivant XR™ for Once-Daily Treatment of ADHD

PRNewswire: October 1, 2012 – CUPERTINO, CA, U.S.A. – NextWave Pharmaceuticals, an emerging specialty pharmaceutical company, announced FDA approval of Quillivant XR™ (methylphenidate hydrochloride) for extended-release oral suspension, CII. Quillivant XR is approved for the treatment of attention deficit hyperactivity disorder (ADHD). Quillivant XR is the first once-daily, extended-release liquid methylphenidate available for patients with ADHD.

"The approval of Quillivant XR fills a void that has long existed in the treatment of ADHD," said Ann Childress, M.D., president of the Center for Psychiatry and Behavioral Medicine, Las Vegas, who was an investigator in the Quillivant XR laboratory classroom study. "We routinely see the struggles of patients who have difficulty swallowing pills or capsules. Having the option of a once-daily liquid will help alleviate some of these issues while still providing the proven efficacy of methylphenidate for 12 hours after dosing."

The efficacy of Quillivant XR was evaluated in a randomized, double-blind, placebo-controlled, crossover, multicenter, laboratory classroom study of 45 children with ADHD. There was an open-label dose optimization period (four to six weeks) with an initial 20 mg dose of Quillivant XR once daily in the morning. The dose was titrated weekly in 10 or 20 mg increments until an optimal dose or maximum dose of 60 mg per day was reached. Patients then entered a two-week double-blind, crossover treatment of the individually optimized dose of Quillivant XR or placebo.

At the end of each week, trained observers evaluated the attention and behavior of the patients in a laboratory classroom using the SKAMP (Swanson, Kotkin, Agler, M-Flynn, and Pelham) rating scale. Quillivant XR significantly improved ADHD symptoms compared to placebo at the primary endpoint of four hours postdose and, in a secondary analysis, showed significant improvement at every time point measured, from 45 minutes to 12 hours after dosing.

"We are pleased with the FDA's approval of Quillivant XR and believe it will address an important need for many patients with ADHD and their caregivers," said Jay Shepard, president and CEO of NextWave Pharmaceuticals. "We are eager to enter into the ADHD market and believe the unique liquid formulation of Quillivant XR—which was developed in conjunction with NextWave's technology and manufacturing partner Tris Pharma—will provide another treatment option for patients with ADHD."

Quillivant XR is expected to become available in pharmacies in January 2013. Quillivant XR was developed using Tris Pharma's patent-protected drug delivery platform.

Catalent Enters into Commercial Supply Agreement with VIVUS for Qsymia™ Once-Daily Combination-Extended-Release Capsules

Business Wire: October 1, 2012 – SOMERSET, NJ, U.S.A. – Catalent Pharma Solutions announced that it has entered into a supply agreement with VIVUS, Inc., to supply Qsymia™ capsules, a proprietary combination phentermine and extended-release topiramate. Utilizing its unique drug delivery capabilities, Catalent partnered with VIVUS during the development of Qsymia, including preformulation and formulation, clinical supply, and validation.

Qsymia has recently been approved by the FDA as the first once-daily combination treatment for chronic weight management in adults who are obese or overweight with a weight-related co-morbidity.

"It is extremely exciting for Catalent to see the FDA approval of this significant new therapy for weight management. As a combination therapy with two active ingredients that needed to be formulated and delivered in a controlled release dosage form, Qsymia presented unique formulation and drug delivery challenges. We are very pleased to have partnered with VIVUS in developing Qsymia and look forward to a long and successful relationship," commented Dr. Ian Muir, president of Catalent's modified release technologies business.

Peter Tam, president of VIVUS, added, "An extended release formulation of Qsymia was critical to achieving our aim of developing a once-daily treatment. Catalent's broad range of drug delivery capabilities and extensive experience in controlled-release technologies helped us to achieve our goal. VIVUS is also pleased to have completed a long-term commercial supply agreement with Catalent to ensure the reliable ongoing supply of Qsymia."

September 2012

A.P. Pharma Resubmits New Drug Application for APF530, a Product Candidate for the Prevention of Chemotherapy-Induced Nausea and Vomiting

Business Wire: September 28, 2012 – REDWOOD CITY, CA, U.S.A. – A.P. Pharma, Inc. (OTCBB: APPA), a specialty pharmaceutical company, today announced that it has resubmitted its New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for its lead product candidate, APF530, for the prevention of acute- and delayed-onset chemotherapy-induced nausea and vomiting (CINV). A.P. Pharma expects confirmation of acceptance from the FDA and a Prescription Drug User Fee Act (PDUFA) goal date within the next few weeks. The company anticipates a six-month review by FDA.

"The resubmission of the APF530 NDA is a pivotal milestone for A.P. Pharma and brings this important therapeutic option one step closer to cancer patients suffering from CINV," said John B. Whelan, A.P. Pharma's president and chief executive officer. "Now that we have resubmitted the NDA, our focus will shift to pre-marketing and pre-commercialization activities in anticipation of potential FDA approval of APF530."

A.P. Pharma's lead product, APF530, is in development for the prevention of both acute-onset and delayed-onset CINV. APF530 contains the 5-HT3 antagonist granisetron, formulated in the company's proprietary Biochronomer™ drug delivery system, which allows therapeutic drug levels to be maintained for five days with a single subcutaneous injection. Intravenous and oral formulations containing granisetron are approved for the prevention of acute-onset CINV but not delayed-onset CINV. Granisetron was selected because it is widely prescribed by physicians based on a well-established record of safety and efficacy. For further information, please visit the company's web site at www.appharma.com.

Collegium Announces Poster Presentation for Oxycodone DETERx®, a Tamper-Resistant, Extended-Release Opioid at American Academy of Pain Management's 23rd Annual Clinical Meeting

Business Wire: September 27, 2012 – CUMBERLAND, RI, U.S.A. – Collegium Pharmaceutical, Inc., a specialty pharmaceutical company focused on the development of innovative treatments for chronic pain, today announced the presentation of a scientific poster summarizing the results for oxycodone DETERx®, its tamper-resistant, extended-release multiparticulate formulation, showing that this product may be effectively administered via sprinkling on soft foods or through enteric feeding tubes. *In vivo* pharmacokinetic results showing its tamper-resistant properties when chewed were also summarized. The poster, titled "Alternative Methods of Oxycodone DETERx® Administration," was presented at the American Academy of Pain Management's 23rd Annual Clinical Meeting, held in Phoenix, Arizona, September 20–23, 2012.

The scientific poster summarized key findings demonstrating the equivalence of the *in vitro* release profiles between the oxycodone DETERx® formulation administered as an intact capsule and alternate routes of administration, including opening the capsule and sprinkling the beads on soft foods, or through enteric feeding tubes such as nasogastric or gastronomy tubes. *In vivo* pharmacokinetic study results showing bioequivalence and safety between chewing of the oxycodone DETERx® beads compared with taking the capsule intact were also presented, demonstrating the tamper-resistant properties of oxycodone DETERx®.

Collegium believes that these alternate methods of administration with oxycodone DETERx® will benefit treatment of chronic pain in patients with difficulty swallowing. Treatment of chronic pain in many adults and children is complicated by problems associated with ingestion of solid oral dosage forms, especially extended-release formulations, due to dysphagia/odynophagia. These patient populations remain an unmet medical need.

"These findings confirm that the oxycodone DETERx® formulation may provide a patient benefit not available with other oral extended-release opioids, especially those that have tamper-resistant technologies, which make the tablets harder to crush," said Michael Heffernan, CEO of Collegium. "There are a large number of chronic pain patients, including children, geriatrics, and patients with concomitant illnesses, who cannot take solid oral dosage forms or who suffer from dysphagia, that may benefit from an extended-release, tamper-resistant oral opioid that can be administered as a sprinkle or through a gastric tube."

Santarus Announces Publication of Results from Uceris Pivotal Study in Gastroenterology

Business Wire: September 27, 2012 – SAN DIEGO, CA, U.S.A. – Santarus, Inc. (NASDAQ: SNTS) today announced that results from its CORE I clinical study, one of two of the company's pivotal phase III clinical studies with Uceris™ (budesonide) in ulcerative colitis, have been published online in the journal *Gastroenterology*. The article, titled "Once-Daily Budesonide MMX® Extended-Release Tablets Induce Remission in Patients with Mild to Moderate Ulcerative Colitis—Results from the CORE I Study," can be found online at www.gastrojournal.org.

The results from CORE I (COlonic RElease budesonide) indicate that the investigational drug Uceris 9 mg had a statistically significant benefit over placebo in the primary endpoint of combined clinical and endoscopic remission at week 8 among patients with active, mild to moderate ulcerative colitis. The U.S. Food and Drug Administration (FDA) is currently reviewing the company's New Drug Application (NDA) for Uceris for the induction of remission in patients with active, mild to moderate ulcerative colitis with a target action date of January 16, 2013.

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The percentage of patients achieving the primary endpoint of combined clinical and endoscopic remission at week 8 in the Uceris 9 mg group was significantly greater than that seen in the placebo group (17.9 vs. 7.4%, $p = 0.0143$; odds ratio [OR]: 2.71). The combined clinical and endoscopic remission rate for Uceris 6 mg (13.2 vs. 7.4%, $p = 0.1393$; OR: 1.90) and for the reference drug Asacol® (mesalamine) 2.4 g (12.1 vs. 7.4%, $p = 0.2200$; OR: 1.71) were numerically greater than placebo, but the differences were not statistically significant.

Efficacy analyses were done in the modified intent to treat population under a prespecified statistical analysis plan, which included all randomized patients who received at least one dose of a study drug and excluded patients with major good clinical practice or entry criteria violations and those with normal histology at baseline as determined by central histopathology review.

"In this study, Uceris 9 mg was well tolerated and significantly more effective than placebo in inducing remission in patients with active, mild to moderate ulcerative colitis," said William J. Sandborn, M.D., Chief, Division of Gastroenterology, Director, University of California San Diego (UCSD) IBD Center, Professor of Clinical Medicine, UCSD Health System, and lead author of the *Gastroenterology* article. "These results suggest that Uceris could provide an important addition to the therapeutic landscape for clinicians who manage patients with mild to moderate ulcerative colitis."

Uceris 9 mg and 6 mg were generally well tolerated, and the frequency of treatment emergent adverse events was similar to placebo. The most frequent treatment emergent adverse events (experienced by ≥ 5.0% of patients in any treatment group) were worsening ulcerative colitis, headache, pyrexia, insomnia, back pain, nausea, abdominal pain, diarrhea, and flatulence. Potential glucocorticoid effects occurred in similar percentages of patients across all treatment groups. Potential glucocorticoid effects were observed in 10.1% of patients in the placebo group, 11.8% of patients in the Uceris 9 mg group, 5.6% of patients in the Uceris 6 mg group, and 7.9% of patients in the Asacol group.

Uceris was evaluated for the treatment of active, mild to moderate ulcerative colitis in two multicenter, randomized, double-blind, double-dummy, placebo-controlled four-arm phase III clinical studies. The primary endpoint was the induction of combined clinical and endoscopic remission, defined as an overall UCDAI score ≤ 1 after 8 weeks of treatment with subscores of 0 for both rectal bleeding and stool frequency, a normal colonic mucosa without any sign of friability, and ≥ 1 point reduction from baseline in the endoscopic score.

CORE I was conducted in North America and India and compared Uceris 9 mg or 6 mg dosed once daily to placebo. The study included a reference arm utilizing a dose of two Asacol (mesalamine) 400 mg delayed-release tablets dosed three times a day, resulting in a total of 2.4 grams daily. The trial enrolled a total of 509 patients. CORE II was conducted in Europe, Australia, Israel, and Russia and compared Uceris 9 mg or 6 mg dosed once daily to placebo. The study included a reference arm that utilized a dose of three Entocort® EC 3 mg capsules, resulting in a once-daily dose of 9 mg. The trial enrolled a total of 511 patients.

The CORE I and CORE II clinical studies were powered to show a statistical difference between the two Uceris treatment arms and placebo. The trials were not powered to show statistical differences between Uceris and the reference arms (Asacol in the CORE I study and Entocort EC in CORE II).

Santarus, Inc. is a specialty biopharmaceutical company focused on acquiring, developing, and commercializing proprietary products that address the needs of patients treated by physician specialists. The company's current commercial efforts are focused on Glumetza® (metformin hydrochloride extended release tablets) and Cycloset® (bromocriptine mesylate) tablets, which are indicated as adjuncts to diet and exercise to improve glycemic control in adults with type 2 diabetes, and on Fenoglide® (fenofibrate) tablets, which are indicated as an adjunct to diet to reduce high cholesterol.

Santarus has a diverse product development pipeline. A New Drug Application for Uceris (budesonide) tablets for induction of remission of active, mild to moderate ulcerative colitis is under review by the U.S. Food and Drug Administration with a response expected in January 2013. The pipeline also includes two late-stage investigational drugs in phase III clinical studies: Ruconest® (recombinant human C1 esterase inhibitor) for treatment of acute attacks of hereditary angioedema and rifamycin SV MMX® for treatment of travelers' diarrhea. In addition, the company's investigational monoclonal antibody, SAN-300, is being evaluated in a phase I clinical program. More information about Santarus is available at www.santarus.com.

Antares Pharma Announces Successful Results from VIBEX MTX Actual Human Use Study

Business Wire: September 25, 2012 – EWING, NJ, U.S.A. – Antares Pharma, Inc. (NASDAQ: ATRS) today announced positive results from an actual human use (AHU) study for VIBEX methotrexate (MTX). The clinical trial was conducted as a multi-center, open-label, single-arm, in-clinic study to evaluate the actual human use of methotrexate administered via the VIBEX Medi-Jet in adult patients with rheumatoid arthritis (RA).

The study assessed the safe usability of VIBEX MTX for self-administration of parenteral MTX in adult RA patients after standardized training by site personnel and review of written instructions. Secondary objectives included evaluating the reliability, ease of use, and robustness of the VIBEX Medi-Jet, assessing the safety and local tolerance of Medi-Jet administered MTX, and evaluating the effectiveness of the patient education tools including written instructions for use.

"We believe that the successful completion of this study is important for Antares as we continue to build our company and further control our key product programs," said Paul K Wotton, Ph.D., president and chief executive officer. "The performance of the VIBEX Medi-Jet in this clinical study also validates our technology platform upon which we are developing multiple products like MTX and testosterone, optimizing treatment options and allowing patients to self-administer parenteral medications conveniently at home and potentially reduce overall healthcare costs."

The AHU study consisted of three visits over nine days and included a screening period, a treatment period, and a follow-up visit. In total, 101 patients were enrolled in four study dose groups, 10 mg (n = 20), 15 mg (n = 30), 20 mg (n = 31), and 25 mg (n = 20). The single MTX dose was self-administered by the patient from one of the four dose groups using the VIBEX Medi-Jet.

The results of this study show that self-administration of MTX using the VIBEX Medi-Jet is safe and well tolerated. Following standardized training by site personnel and review of written instructions, all 101 patients performed the self-administration successfully. In addition, the VIBEX Medi-Jet functioned correctly and as intended for each and every administration, thereby demonstrating reliability and robustness. Results of the ease of use questionnaire indicated that 98% of patients found the VIBEX Medi-Jet easy to use, and 100% of patients found the instructions and training to be clear and easy to follow. Patients were also asked to report site administration pain at the end of the treatment period. Administration site pain was measured using a 100 mm visual analog scale (VAS) and showed that patients experienced minimal or no pain, with a mean value of 3.6 mm on a scale of 100 mm. Importantly, no patients experienced treatment-emergent serious adverse events related to the drug.

"We are extremely pleased with the results of the actual human use study," said Kaushik J. Dave, R.Ph., Ph.D., and executive vice president product development. "The study demonstrated that rheumatoid arthritis patients were able to successfully self-administer MTX with the VIBEX Medi-Jet, which we believe is safe, well tolerated, and easy to use. These study results, along with the positive usability study results previously reported in patients with severe to very severe hand function impairment, keep us on schedule for an early 2013 filing of the New Drug Application for VIBEX MTX, a potential new treatment option for patients who suffer with RA."

Orexo Presents an Update on the U.S. Opioid Dependence Market and the Commercial Opportunities for Zubsolv™ (OX219)

Business Wire: September 21, 2012 – UPPSALA, SE – The Swedish specialty pharmaceutical company Orexo presents today its view on the future market for treatment of opioid dependence in the United States. Opioid dependence is a clinical condition that increasingly is being recognized as having a major societal impact and financial cost. Recent estimates indicate that in the United States the cost to society of opioid dependence reached $55.7 billion.

Based on the continued growth in utilization of prescription-based opioid products in the United States, and the associated growth in nonmedical use of Rx-opioids, Orexo projects the U.S. market for treatment of opioid dependence to continue growing and to reach $2 billion in value by 2014. In addition to these main drivers, the recent years have yielded an increasing number of patients seeking treatment for their opioid dependence, and data suggest that patients also are likely to be treated over longer periods. At the meeting, Orexo will also present the basis for the projected peak sales potential for Zubsolv, previously stated to be $500 million.

Orexo today also presents its activities for how to differentiate Zubsolv™ from the single established competitor in the U.S. market, Suboxone®, as well as the clinical programs the company has initiated to further strengthen the Zubsolv product platform over the coming years.

Based on the data achieved, Orexo plans to initiate a clinical program to document patient preference between Zubsolv and Suboxone in patients who already are being treated with Suboxone. Additionally, Orexo is implementing a further clinical program designed to document that opioid-dependent patients can be treated with Zubsolv from the very first day the physician wishes to prescribe a buprenorphine-based treatment. This is contrary to the current practice and labeled indication for Suboxone, in which patients have to be initiated on a different buprenorphine product prior to conversion to Suboxone.

Orexo is planning to launch Zubsolv during Q3 2013. During the first half of 2014, Orexo will be complementing the original two dose strengths with further preformulated dose options, thereby increasing the convenience for patients and physicians when using Zubsolv treatment. Orexo has also initiated development of a further complementary product formulation that provides a taste alternative to the current lemon/menthol flavor of Zubsolv. Based on the extensive development work completed for Zubsolv, Orexo projects that this product formulation will be ready for regulatory submission late 2013 and can be introduced into the U.S. market during the second half of 2014.

At the meeting today, Orexo also describes the strategic commercialization options for Zubsolv and the projected sales force required to reach the high-prescriber segment in the market. The value of a number of commercialization options are currently being analyzed, including those of advancing into the U.S. market in a risk-sharing partnership with a rented field force, a combination of a risk-sharing rented field force partnership with a co-promotion partner to increase the commercial foot-print, as well as the value of a strategic relationship with a large established commercial sales and

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marketing organization. As previously announced, Orexo plans to announce further information pertaining to its chosen commercialization strategy for Zubsolv, once this has been finalized. The presented slides and a recording of the presentation can be found on Orexo website www.orexo.com.

Unigene and Tarix Pharmaceuticals Report Highly Increased Oral Bioavailability of "Peptelligence-Engineered" TXA127

PRNewswire: September 19, 2012 – BOONTON, NJ, and CAMBRIDGE, MA, U.S.A. – Unigene Laboratories, Inc. (OTCBB: UGNE) and Tarix Pharmaceuticals today announced the successful completion of a feasibility study of an oral formulation of TXA127, Tarix's lead peptide drug candidate. Data from the feasibility study demonstrated that the oral formulation of TXA127 produced extremely high exposure in the blood that resulted in a several-fold increase in bioavailability as compared to the oral delivery of the unformulated drug and was equal to or greater than that achieved by the current subcutaneous formulation.

The oral formulation, developed jointly by Unigene and Tarix under a previously agreed upon feasibility program, leverages Unigene's Peptelligence™ technology platform to enable enhanced oral delivery of TXA127. Tarix is developing TXA127 for multiple therapeutic indications, including enhancement of engraftment following peripheral blood and cord blood stem cell transplantation, reduction in GVHD and mucositis following allogeneic stem cell transplantation, and peripheral vascular disease. In September 2011, TXA127 was granted orphan drug status by the U.S. Food and Drug Administration (FDA) for the treatment of pulmonary arterial hypertension (PAH), a rare disease resulting from insufficient cardiac output. Unigene's Peptelligence™ platform comprises peptide oral drug delivery and manufacturing assets, expertise, and capabilities.

Ashleigh Palmer, Unigene's chief executive officer, commented, "The results of the TXA127 feasibility study exceeded our expectations and clearly indicate that Unigene's Peptelligence™ platform is the gold standard for developing orally administered peptides. Not only did the oral formulation of TXA127 deliver the drug successfully, data from the study showed that it produced a highly significant increase in bioavailability. We greatly look forward to extending our relationship with Tarix and its development of the oral formulation of TXA127, as well as advancing the 13 additional feasibility programs evaluating our Peptelligence™ platform."

Rick Franklin, M.D., Ph.D., chief executive officer of Tarix, commented, "The ability to deliver TXA127 orally, and do so in a manner that improves the performance of the drug, significantly enhances its therapeutic potential for the multiple conditions we are pursuing, while also serving to increase its overall value and marketability. We couldn't be more excited by the results of the feasibility study and the performance of Unigene's Peptelligence™ technology. We look forward to applying Unigene's technology to our other peptides."

According to the terms of the feasibility program, Tarix will have an exclusive worldwide license to Unigene's technology covering the use of that technology with angiotensin (1-7), the pharmaceutical ingredient in TXA127, as well as its functional equivalents, analogues, or derivatives. In return for the license, Tarix will pay Unigene a percentage of revenues derived from the direct sales of the product by Tarix or from up-front, milestone, or royalties received by Tarix from a third-party sub-licensee.

OncoSec Secures License for Electroporation Intellectual Property from University of South Florida

PRNewswire: September 11, 2012 – SAN DIEGO, CA, U.S.A. – OncoSec Medical Inc. (OTCBB: ONCS), a company developing its advanced-stage ImmunoPulse and NeoPulse therapies to treat solid tumor cancers, announced it has secured an exclusive license for specific patented technology from the University of South Florida Research Foundation (USFRF) relating to the delivery of gene-based therapeutics via intratumoral and intramuscular electroporation. This patent is directly related to the ongoing phase II trials for metastatic melanoma, Merkel cell carcinoma and cutaneous T-cell lymphoma using the company's ImmunoPulse therapy, and extends patent protection for the ImmunoPulse technology to the year 2024. Financial terms of this agreement were not disclosed.

OncoSec's proprietary gene and drug delivery platform, the OncoSec Medical System (OMS) electroporation device, is currently being used to develop the company's ImmunoPulse and NeoPulse therapies. This platform encompasses patents, technology, and other intellectual property for intratumoral methods for delivering drugs and gene-based treatments in humans.

ImmunoPulse involves the application of a brief electric field to the surface of the skin. This temporarily opens pores in the cell membrane, allowing anticancer agent DNA IL-12 to be absorbed more efficiently. DNA IL-12, which normally has difficulty penetrating the tumor cell membrane to get inside these cells, has been shown to significantly stimulate the immune system's T-cells to fight the cancer. The new license from USFRF complements OncoSec's seminal patents, particularly for the protection of the methods involved in the ImmunoPulse treatment, and specifically for the use of DNA IL-12.

"Our licensing agreement with the USFRF significantly strengthens OncoSec's intellectual property rights in the area of gene and drug delivery via *in vivo* electroporation," said Punit Dhillon, OncoSec's president and CEO. "We anticipate that the further development of this technology will enhance the ability of ImmunoPulse to address the serious unmet need among patients with skin cancer. OncoSec's patent portfolio places us in a preeminent position within the field of electroporation-based delivery of gene-based treatments for cancer."

"OncoSec is the ideal choice to further develop this technology that I and my colleagues pioneered while working at the University of South Florida, and I am pleased they have secured this license," said Richard Heller, Ph.D., author of the patented

technology. "The technology involves short-pulsed electric fields that can deliver plasmid DNA to stimulate the immune system. As a result, it is a natural fit with OncoSec's ongoing program to develop its ImmunoPulse therapy."

Eaton Scientific Announces Plans to Develop a Transdermal Patch Delivery System for Tropine 3 Nonhormonal Treatment of Hot Flashes

PRNewswire: September 10, 2012 – BEVERLY HILLS, CA, U.S.A. – Eaton Scientific Systems, Ltd. ("Eaton" or the "company"), a wholly owned subsidiary of Pristine Solutions, Inc. (OTCQB: PRTN) is pleased to announce that the company plans to begin development of a transdermal patch delivery system for Tropine 3, a patent pending novel indication of homatropine for nonhormonal treatment of hot flashes in premenopausal, perimenopausal, and postmenopausal women. The company believes that this will be the world's first available prescription, nonhormonal transdermal treatment for hot flash symptoms.

"Tropine 3 is an ideal type of medication to utilize the convenience and dose control accuracy of a transdermal medicated patch delivery system," stated Michael Borkowski, CEO of Eaton Scientific. "Based upon the popular use of estrogen patches in hormone replacement therapy, it's readily apparent that a high percentage of women could have the same preference when choosing a safe nonhormonal transdermal patch to safely reduce their hot flashes symptoms. We feel this is an opportunity to develop another unique, marketable, and potential patentable feature exclusive to Tropine 3 and Eaton Scientific."

The company intends to contract with an industry-leading drug delivery system expert to assist in the development of the transdermal Tropine 3 patch. Initial testing of various monolithic device transdermal patch technologies and configurations is expected to begin in conjunction with the company's planned FDA-compliant Tropine 3 clinical studies currently being organized to start in the next few weeks.

The transdermal patch, first approved by the U.S. FDA in 1979, is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. The main advantage of a transdermal drug delivery route is that the patch provides a long-term controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive. Only medications whose molecules are small enough to penetrate the skin can be delivered by transdermal patch. Tropine 3 (homatropine in suspension) molecules are thought to be ideal for transdermal patch delivery.

Professional Compounding Centers of America (PCCA) Invests $4 Million in San Diego–Based Imprimis Pharmaceuticals, Agrees to Share Topical Drug-Delivery Knowledge and Technology to Bring New Medicines to Market

PRNewswire: September 7, 2012 – SOLANA BEACH, CA, U.S.A. – Imprimis Pharmaceuticals, Inc. (IMMY: OTCQB) today announced a strategic development and investment agreement with Houston-based Professional Compounding Centers of America, Inc. (PCCA). The agreement will allow the companies to develop and share drug-formulation technology, with the goal of creating a new generation of treatments for muscle and joint pain, neuropathic pain, and other conditions. PCCA also made a $4 million equity investment in Imprimis in a private transaction.

The agreement will give Imprimis exclusive non-PCCA-member access to PCCA's topical technologies and formulation know-how for delivering drugs directly through the skin. The arrangement is intended to identify development opportunities for new topical medications for new therapeutic applications.

Imprimis' lead drug candidate, Impracor™, a topical nonsteroidal anti-inflammatory cream, is expected to enter phase 3 clinical trials early in 2013. When approved for sale, Impracor would be applied to the site of muscle or joint pain, delivering a clinical dose of medication to the affected area without potential side effects such as stomach irritation or liver problems that have been associated with ingestible, nonsteroidal, anti-inflammatory drugs.

The company has also developed Accudel™, a patented topical-delivery platform that can serve as a delivery vehicle for other medications.

"This agreement with PCCA will allow us to develop and implement an entirely new model for creating needed drugs for the treatment of a variety of conditions. Under this model, we will look for ways to repurpose or reformulate existing FDA-approved generic drugs, which would be delivered through our proprietary technologies," said Mark L. Baum, CEO of Imprimis. "We are very excited to enter a strategic relationship with such a well-respected company as PCCA, the largest pharmaceutical compounding organization in the North America."

PCCA provides a variety of products and services to its member compounding pharmacies, which work directly with prescribers to provide patients with specialized medications that are not available in either over-the-counter or prescription form. For the past 30 years, PCCA has been focused on supporting independent pharmacies by delivering a complete portfolio of compounding products, services, education, and intellectual property.

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PCCA has led in the research, development, and study of topical and transdermal technology including its Lipoderm® family of topical bases —the industry's only bases proven to deliver four drugs simultaneously.

Jim Smith, president of PCCA, added: "Through this agreement, we will leverage our knowledge and products to bring new drugs to the market and ultimately heighten awareness and acceptance of topical drug delivery. By building bridges between compounding pharmacists and drug manufacturers, our members will be best positioned to strengthen the role of independent pharmacies in their communities while continuing to play their crucial role in personalized medicine. We are convinced this new model for the development of drugs is an important advancement for the pharmaceutical industry."

Imprimis's drug-development strategy calls for repurposing or reformatting existing FDA-approved generic drugs to create new high-value FDA-approved manufactured drugs that address new therapeutic applications. In other words, generic drugs would be combined with Imprimis's patented delivery technology to create entirely new medications for specific markets that are lacking these medicines.

"Once a potential new drug application has been identified, prior to making an investment, we hope to be able to identify the correct formulation and dosing to protect our investment in new patent applications," said Baum. "We plan to implement a clinical development and a thoughtful regulatory strategy prior to seeking partnerships to bring these market-tested proprietary compounded drug formulations to market. We believe this agreement is a win not only for our two companies but for the pharmaceutical industry and the patients that it serves."

August 2012

Depomed Licenses Acuform® Patents to Janssen Pharmaceuticals, Inc.

PRNewswire: August 27, 2012 – MENLO PARK, CA, U.S.A. – Depomed, Inc. (Nasdaq: DEPO) today announced that Janssen Pharmaceuticals, Inc., has licensed rights to Depomed's Acuform gastric retentive drug delivery technology. Under the terms of the agreement, Janssen received a nonexclusive license and other rights to certain Acuform patents. In exchange, Depomed will receive an upfront payment of $10 million and will receive a low-single-digit royalty on net sales of Nucynta® ER (tapentadol extended-release tablets) in the United States, Canada, and Japan from and after July 2, 2012, through December 31, 2021. In addition, Depomed is eligible for a one-time sales milestone upon achievement of a specified level of quarterly net sales. Depomed has no development obligations under the agreement and expects to recognize the $10 million payment as revenue in the third quarter of 2012.

"We are pleased to expand our positive working relationship with Janssen and to provide them rights to our patents," said Jim Schoeneck, president and chief executive officer of Depomed. "This agreement will immediately provide Depomed with a new and growing royalty stream."

Ocular Therapeutix Commences Pilot Phase II Travoprost Punctum Plug Study for the Treatment of Glaucoma

PRNewswire: August 20, 2012 – BEDFORD, MA, U.S.A. – Following encouraging results from Ocular Therapeutix's travoprost punctum plug feasibility study, the company is now entering a pilot phase II clinical trial to examine a two-month sustained release drug (OTX-TP2) for the treatment of ocular hypertension and glaucoma. Ocular Therapeutix's travoprost punctum plugs are inserted into the proximal nasolacrimal canal and release drug to the ocular surface over the two-month treatment period.

The initial travoprost punctum plug feasibility study, conducted at the Singapore National Eye Center and the National University Hospital in Singapore, examined efficacy of the technology over a one-month duration. "Having demonstrated proof of concept in our feasibility study, we have extended the length of drug delivery to two months for the pilot phase II trial," stated Amar Sawhney, Ph.D., president and CEO of Ocular Therapeutix, Inc. "Extending treatment duration for the disease is a key milestone for our company's path to commercialization."

The pilot phase II study will enroll twenty patients (up to 40 eyes) at the Umhlanga Hospital Medical Centre and Netcare Alberlito Hospital in South Africa. Patients with documented ocular hypertension or open-angle glaucoma, the most common form of the disease, will be evaluated for reduction of intraocular pressure from baseline and retention of the plug through two months. Elevated intraocular pressure is the most important risk factor for glaucoma.

Glaucoma is a chronic disease that must be monitored and treated for life, impacting more than 2 million Americans, and represents a $5 billion market worldwide. The current mode of treatment for the disease is topical prescription drops that must be taken daily and at regular intervals to prevent progression of the disease. However, topical prescriptions are plagued with issues of noncompliance, which can lead to costly and invasive surgeries, vision impairment, and even blindness. It has been reported that up to 60% of patients do not administer ophthalmic drops as directed, even though patients' perception is that they are compliant with 97% of their dosing.

"Travoprost punctum plugs may help to overcome issues of daily self-administration of medication leading to potential patient noncompliance," stated Pierre Wassermann, principal investigator at the Umhlanga Hospital Medical Centre in South Africa. "Additionally, maintaining continuous drug presence via sustained delivery may be an improvement over fluctuating drug levels resulting from daily topical therapy." ■

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Calendar of Events

2013

Imaging Hallmarks of Cancer, the 7th ESMI Winter Conference
January 20–25
Les Houches, France
www.topim.eu

16th Annual International Symposium on Recent Advances in Drug Delivery Systems
February 3–6
Salt Lake City, Utah, U.S.A.
http://drugdeliverysymposium.utah.edu

Drug Delivery Partnerships
February 6–8
San Diego, CA, U.S.A.
www.iirusa.com/ddp

ISAA 2013—10th International Symposium on Adjuvants for Agrochemicals
April 22–26
Foz do Iguaçu, Paraná, Brazil
http://events.isaa-online.org

40th Annual Meeting & Exposition of the Controlled Release Society
Sponsored by CRS
July 21–24
Hawaii Convention Center
Honolulu, Hawaii, U.S.A.
www.controlledreleasesociety.org

5th BBBB International Conference
September 26–28
Athens, Greece
www.bbbb-eufeps.org