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Newsletter

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- EDITORIAL CALENDAR
- SUBMISSION GUIDELINES
- MEDIA PLANNER

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- SPONSORED BY CATALENT
- Acusphere Licenses Hydrophobic...
- Av... Therapeutics Launches...
- ...elivery Science Receives...
- Eurand Announces Positive...
- Tekmira Pharmaceuticals & Protiva...

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- ...RUG DELIVERY TECHNOLOGIES
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CRS Newsletter

Delivering Bioactives

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Table of Contents

Advertisers' Index

The CRS Newsletter is the official newsletter of the Controlled Release Society. The newsletter is published five times annually providing scientific and technical information pertinent to the controlled release community and news about society and chapter activities. Members can receive the newsletter via mail. The newsletter may also be viewed online at www.controlledreleasesociety.org.

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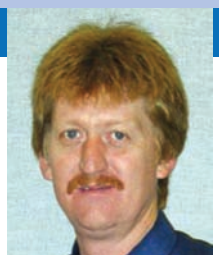
From the Editor



Roderick B. Walker
Rhodes University
Republic of South Africa

Greetings from South Africa and welcome to the second *CRS Newsletter* of 2009, in which, in addition to our regular features, we provide an overview of the Educational Workshops to be held prior to the upcoming CRS Annual Meeting. If the speakers and topics are anything to go by, these workshops promise to be excellent sessions well-worth attending. By the time you read this *Newsletter*, you will all have heard whether your abstracts have been accepted and be making plans to be in Copenhagen for an event that promises to be the best meeting of the CRS yet.

Included in this issue are articles on the use of biodegradable polymers to deliver siRNA intracellularly and on how the shape of liopsomes are being altered to effectively target drug delivery. Highlighting the diverse nature of the Society, the Vet Group is once again debating issues relating to mastitis research; by all accounts, this is a serious and complex issue that remains a challenge to treat. Perhaps success in this area would enable issues relating to human health to be advanced significantly. In addition, the second in a series of "Back to Basics" articles addresses the problems associated with developing recombinant polymers for gene therapy and highlights some of the pitfalls of producing these materials for use in animal models.

The New Zealand Chapter of the CRS, which hosted its 11th Formulation and Drug Delivery Conference (FDD) in Dunedin in February, provides a recap of the conference. I have been fortunate to visit the "Land of the Long White Cloud" and attend a FDD conference and can attest to the success of these meetings. Make a date to attend the 12th meeting next year. It will be worth it. CRS is also making progress in accessing China, and the overview of the Arden House event and programme for a CRS satellite meeting later this year make interesting reading. Certainly, the upcoming meeting in Shanghai will be a must-attend event for the industry, as China has become a major player in the pharmaceutical arena.

The "Patent Watch" and "In the News" sections continue to provide the latest information on patents and industrial news with respect to product development, clinical trial progress, licensing, partnerships, and acquisitions, amongst other interesting advances in the field.

In other good news, the new website is up and running, and I am sure that you have all found the change useful, as the site is far more accessible and information is readily on hand. I look forward to seeing the new strategic plan the Board of Directors indicates has been devised, since this will provide insight into the future direction of the Society, in addition to focussing on how individuals can benefit from participating in our diverse Society.

In closing, I realise it may be difficult for many people, in particular those members of the CRS in developing countries, to attend the Copenhagen meeting and workshops, but we need to meet, discuss strategies, and collaborate to develop technologies to facilitate the treatment of and/or the cure for the myriad of diseases that affect the world's population. Whilst the current recession may already have had an impact on all our lives and may have been unavoidable, the talented members of the CRS collectively have the ability to change lives forever. I look forward to discussing such issues and hearing ideas at the meeting in Copenhagen. Make plans to be there!

Until next time,

Roderick B. Walker ■

Lisbeth Illum
IDentity, Nottingham, U.K.

Many of the members of CRS have in some way a financial and/or scientific interest in a small biopharmaceutical company, either as founders, directors, or employees. Such small, often University spin-out companies, are most often, at least in the startup phase, based on one major technology with promising pre-clinical data. Venture capital is the lifeblood of such early-stage companies. They rely on funding to enable development of the technology to proof-of-concept in humans and early phase 2 clinical data before being able strike a big licensing deal with a larger pharmaceutical company or being acquired outright.

However, in the current global financial crisis, it has become very hard for such small biopharmaceutical companies to attract funding from venture capital. Venture capital is betting on supporting their current portfolio companies and is often unwilling to support startup companies with no proof-of-concept studies in humans or with contracts with pharmaceutical companies for product development. It is a catch 22. Venture capital will not provide funding to enable a small company to carry out the required clinical studies and will not fund the company before the studies have been done. Business angels, and other similar investors, often have a ceiling for the amount they can invest in a small company. To make matters worse, venture capital is often reluctant to allow new investors into their current portfolio because they fear a high dilution of their shares.

The U.K. government in 2008 launched an initiative to help early-stage companies in the form of government-guaranteed loans. However, the U.K. banks have not been keen to provide these loans and are still asking for directors with more than 20% share ownership to guarantee the loans. Most small startup companies has been based on early venture capital funding, and it is seldom that directors, even founders, own more than 10% of the company's shares—again a catch 22 situation.

In addition to the lack of venture capital funding for small biopharmaceutical companies, CROs and CMOs are also being hit hard. They have lost business from early-stage companies who have not got the funding to continue their work. Even large pharmaceutical companies have delayed projects that were meant to start in 2008 with their dedicated CRO. Hence, even large CRO like Covance and Lonza reported that revenues were down in the last quarter of 2008. Things are worse for small and mid-sized CROs and CMOs, since at the same time the major pharmaceutical companies have been consolidating their vendor base to cut outsourcing costs by standardizing processes and reducing the number of companies they work with, since each must be qualified, audited, and managed.

How do the lack of funding and the consequent problems of the small biopharmaceutical companies, CROs, and CMOs influence the CRS and its members? As mentioned in my column in the last issue of the *CRS Newsletter*, the CRS is a non-profit organization dedicated to promoting the science, technology, and innovation of delivery of bioactives for the benefit of the world population. However, the Society needs to be run on a strong business footing to provide increased value, maintain and improve the quality of the science, and increase access to scientific meetings and workshops worldwide for all members. Presently, we are still highly dependent on the annual meeting and exposition as the main income source (presently 75%) for the Society. The CRS, therefore, is vulnerable to the effects of the credit crunch on the budgets of pharmaceutical, biotech, food, and consumer product companies and other institutions that may have less money available for their employees to participate in scientific meetings.

As I did in my last column, I again urge you to sign up for to participate in the CRS Annual Meeting & Exposition in Copenhagen in July. The meeting will present the newest and most exciting science in the delivery of bioactives and other functional materials, with the involvement of pharmaceutical and other companies and universities from around the world. The meeting program is absolutely bursting with exciting and novel topics and world-renowned speakers. For small and mid-sized pharmaceutical companies, the meeting will provide fantastic opportunities to distribute the message of the company's products and for collaboration, especially during scientific and soapbox sessions. Likewise, there is an outstanding opportunity for CROs and CMOs to participate as exhibitors and to meet many potential customers. Early bird registration is open and will be available through May 4, 2009, at these lower rates. Make the decision now to join the meeting and put the dates July 18–22, 2009, in your diary.

I am proud to announce that the BOD and the China Initiative Subcommittee have been working hard over the past year producing a plan for the increased interaction of Chinese scientists with the CRS and for setting up a local chapter in China. CRS has already been a co-sponsor with AAPS of the first workshop in China—the 2008 Asian Arden House Meeting on "Particles and Powder Technologies for Solid Dosage Forms." Now plans are going ahead for the first solely CRS-sponsored meeting in China on "Oral Controlled Drug Delivery Using Tablets: From Laboratory to Production," in Shanghai, June 16–17, 2009. It is fair to say that we are hopeful that this first large event in China will be very successful and the start of increased interaction with Chinese scientists.

Looking forward to welcoming you all to Copenhagen!

Lisbeth Illum ■

Enhancing the Intracellular Release of siRNA with Biodegradable Poly(ethylene imine) as a Carrier System[1]

Miriam Breunig,[2] Constantin Hozsa,[2] Uta Lungwitz,[2] Kazuo Watanabe,[3] Umeda Isao,[3] Kato Hiroyuki,[3] and Achim Goepferich[2,4]

RNA interference (RNAi) is a potent and highly specific gene-silencing phenomenon that is triggered by double-stranded RNA helices (1). As the RNAi machinery is available in every eukaryotic cell and any gene can be targeted, this process can be exploited not only to investigate gene function in cells, but it also holds great prospects for specifically suppressing the expression of disease-related genes (2). The application of synthetic small interfering RNAs (siRNAs) is one method that can be used to therapeutically exploit this highly conserved mechanism. However, siRNAs are polyanionic macromolecules that do not readily enter cells and typically require the use of a delivery system for effective gene silencing both *in vitro* and *in vivo*. Current methods for facilitating cellular uptake of siRNA include conjugation to antibody fragments or ligands to cell surface receptors, complexation to cationic peptides or polymers, and incorporation into nanoparticles and liposomes (3,4). Although progress in the field of RNAi therapeutics has occurred remarkably fast, none of these strategies has emerged as an ideal approach for the creation of an efficient and cell-specific siRNA delivery system.

Recently, poly(ethylene imine) (PEI), a synthetic polymer with high cationic charge density that has a linear or branched structure has been highlighted as a siRNA delivery agent (5). Its effectiveness is a result of the electrostatic interaction between the positively charged amino groups of PEI and negatively charged phosphate groups of nucleic acids, leading to the formation of small complexes (polyplexes) that are stable enough to transport genetic material into cells.

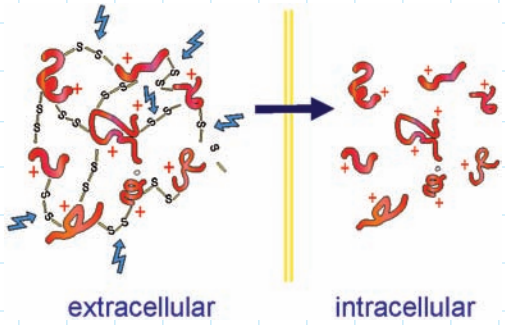


Figure 1. *Intracellular polymer degradation due to disulfide bonds.*

So far, not much attention has been dedicated to the number of cells in a given population that internalize polyplexes or the intracellular release of the siRNA from the carrier system, which is critical for enabling the nucleic acid to "gear" into the RNAi machinery. PEI-based carriers that are degradable inside cells due to disulfide bonds have been proven to be very efficient for plasmid DNA transfection in a variety of cell lines (6). Therefore, the question raised is whether the degradation of these carriers can also be exploited to efficiently release siRNA inside the cytoplasm of cells (Figure 1). To address the issues outlined above, various PEI derivatives were compared according to the cellular uptake and intracellular release of siRNA from the carrier system in terms of gene-silencing efficacy. The following PEI derivatives, which are listed in ascending order of branching, were applied: linear PEI (lPEI), 5 kDa (7); lPEI cross-linked via disulfide bonds (ssPEI), which is degradable in the intracellular environment (6); and commercially available branched PEI (bPEI), 25 kDa (Figure 2).

To assess the capacity of the various PEI derivatives for siRNA complexation and subsequent cellular internalization, fluorescently labeled siRNA was used for polyplex formation. CHO-K1 cells were incubated with polyplexes for 4 hr before analysis by flow cytometry. All PEIs were capable of building polyplexes and translocating siRNA into the cells (Figure 3). Increasing branching of the polymer facilitated the uptake of siRNA into a higher number of cells (Figure 3A), while ssPEI allowed a higher intracellular siRNA content at high NP ratios (nitrogen in polymer/phosphate in nucleic acid) (Figure 3B). Next, CHO-K1 cells stably expressing enhanced green fluorescent protein (CHO-K1/EGFP) were treated with siRNA polyplexes to mediate enhanced green fluorescent protein (EGFP) gene silencing. Flow cytometry analysis revealed that only bPEI and ssPEI led to substantial down-regulation of

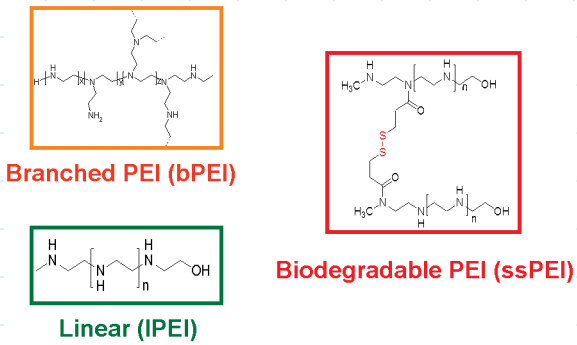


Figure 2. *Polymers used for polyplex formation: commercially available branched PEI (bPEI), 25 kDa; lPEI cross-linked via disulfide bonds (ssPEI), which is degradable in the intracellular environment (6); and linear PEI (lPEI), 5 kDa (7).*

[1] Previously published as a research paper in the *Journal of Controlled Release* (130(1): 57-63 (2008)).

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EGFP (Figure 4). The effect was only highly specific for ssPEI at low NP ratios (data not shown), and maximal possible inhibition decreased as follows: bPEI > ssPEI > lPEI. Furthermore, confocal-laser scanning microscopy (CLSM) was used to evaluate the intracellular distribution of siRNA using bPEI, ssPEI, and lPEI as carriers. Intracellular discrete spots (examples shown in Figure 5 are indicated by arrows) were interpreted as siRNA associated with the carrier either in endosomes or the cytoplasm, whereas homogeneous green cell staining was taken to indicate siRNA that was released from the polymer and distributed over the cell. The confocal images supported the hypothesis that degradable PEI facilitates the intracellular release of siRNA. bPEI, and especially lPEI, were not able to liberate siRNA to such an extent.

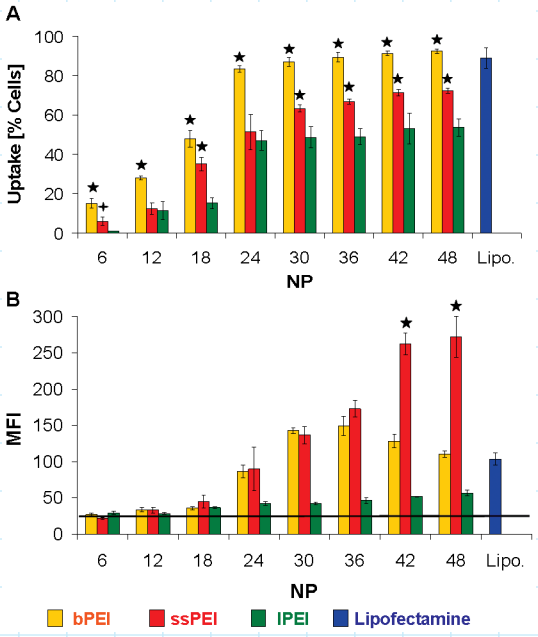

Figure 3. *(A) Cellular uptake of fluorescently labeled siRNA (100 nM) into CHO-K1 cells. Uptake indicates the percentage of cells that show a fluorescence due to intracellular siRNA. (B) Mean fluorescence intensity (MFI) of cells that have taken up polyplexes, which is an indirect measure of the intracellular amount of siRNA. Commercially available Lipofectamine RNAiMAX was used as a control. Statistically significant differences are denoted by ✦ (p < 0.05) or ★ (p < 0.01).*

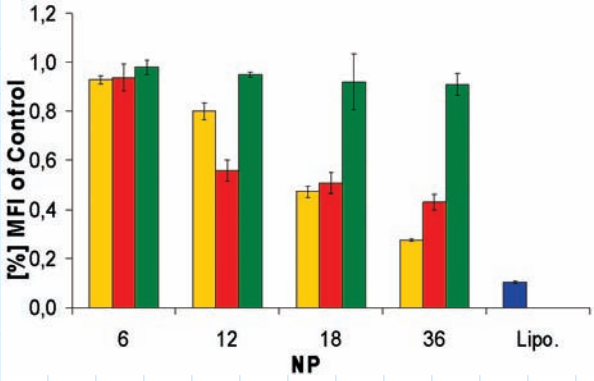

Figure 4. *Gene silencing efficacy: CHO-K1 cells stably expressing EGFP (CHO-K1/EGFP) were treated with siRNA polyplexes (100 nM) to mediate enhanced green fluorescent protein (EGFP) gene silencing. Polyplexes were built with bPEI, ssPEI, or lPEI at NP 6–36 and siRNA. Lipofectamine RNAiMAX was used as a control.*

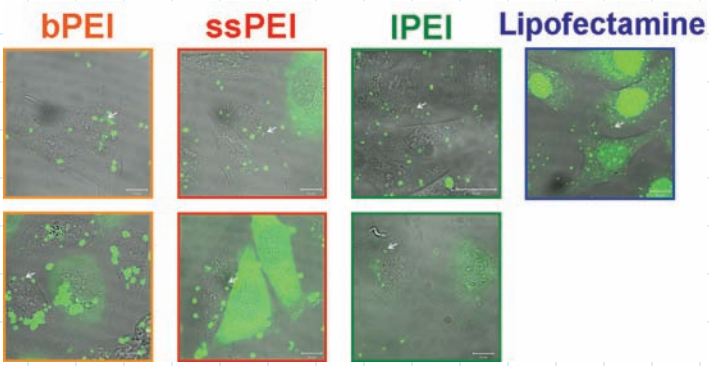

Figure 5. *Intracellular release of siRNA: CHO-K1 cells were incubated with fluorescently labeled siRNA polyplexes and observed by confocal-laser scanning microscopy (CLSM). Polyplexes were built with bPEI, ssPEI, and lPEI at NP 18 (upper panel) and NP 36 (lower panel). Lipofectamine RNAiMAX was used as a control. Intracellular discrete spots were interpreted as siRNA associated with the carrier either in endosomes or the cytoplasm, whereas homogeneous green fluorescence indicate siRNA released from the polymer. The larger green dots are polyplex aggregates that were not taken up by cells. The picture is an overlay of transmitted light and fluorescence image (Scale bars: 10 µm or 20 µm).*

Our investigations indicate that cellular uptake may be one of the main limitations for siRNA-mediated gene silencing using PEI-based carrier systems. Moreover, a second hurdle could be the intracellular release of siRNA, which was accelerated by the intracellular degradation of the carrier system due to disulfide bonds. Therefore, PEI-based carrier systems that combine the high branching density of bPEI and the reductively cleavable principle of ssPEI could be promising tools for siRNA delivery, as they would consolidate high cellular uptake with favorable intracellular release of siRNA.

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Silica-Templated Tubular Liposomes

Grace Tan,[1] Peng Xu,[1] Jia Zhou,[1] Vijay T. John,[1,2] and Louise B. Lawson[3]

Introduction

The most common shape of a synthetic liposome is a sphere. Such is the shape of giant unilamellar liposomes, multilamellar vesicles, or even flexible vesicles, which have garnered immense interest due to their ability to temporarily alter their spherical shape and facilitate penetration through the skin. By sonicating and/or extruding liposomes, they can be confined further to a certain size range that is suitable for specific application purposes. Most of the emphasis has been placed on the size of liposomes, while the shape aspect of it has been neglected. It was only recently that Champion and Mitragotri (1) reported that particle shape is a crucial factor affecting phagocytosis of foreign particles by macrophages and other antigen-presenting cells. This is explained in detail in their published work outlining specific target geometries at which internalization of foreign particles by macrophages will be successful (1).

The stability and clearance of liposomes remain the two main obstacles for widespread use of liposomes as drug delivery vehicles. Although liposomes are relatively stable in buffered solution, once exposed to blood serum, their contents quickly leak out as the liposome membranes rupture. This makes it impossible to control the delivery of encapsulated contents. Various methods to overcome the abovementioned limitations are proposed in the literature, including forming a second membrane over existing liposomes (2), coating the liposomes with polyethylene glycol (3), and forming a protective hard shell over the liposomes (4).

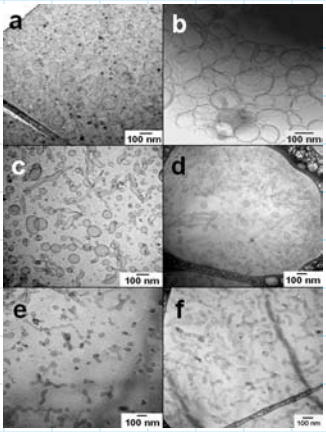

Figure 1. *PC liposomes with progressive incorporation of CerVI. Weight ratios of the two lipids in the liposome samples are CerVI/PC = 0:1 (a), 1:9 (b), 2:8 (c), 3:7 (d), 4:6 (e), and 1:1 (f). The total lipid content was kept constant at 2% (wt/vol). The amounts of CerVI listed are the amounts originally weighed to prepare the samples and are fully soluble in a 2:1(vol/vol) chloroform–methanol solution. The final CerVI content in the liposome solution after extrusion was lower due to precipitation of some ceramide.*

The objective of this study is to form non-spherical liposomes and devise a way to protect liposomal contents from leakage for drug delivery purposes. We have chosen to synthesize silica shells over the liposomes to afford extra protection of liposomal contents using simple sol-gel chemistry. This idea has been used to form non-porous solid shells over spherical liposomes (4). This method offers the possibility of triggered release of liposomal contents through an external stimulus or by gradual erosion of the silica in specific pH environments, which sets it apart from other methods of protection (4). Due to the intricate shape of the liposomes used in this study, it is anticipated that the ability to synthesize silicas bearing a liposomal shape will provide evidence that the uniquely shaped liposome is a stable structure.

Results and Discussion

Different proportions of Ceramide VI (CerVI) were combined with *L*-α-phosphatidylcholine (PC) to form liposomes using the lipid-film hydration method. The liposome solution was then sonicated and extruded through a final membrane pore size of 100 nm. With progressive addition of CerVI, a transition from spherical to elongated tubular liposomes was observed (Figure 1). In order to verify whether the elongated structures are stable, the bending free energies for the liposome bilayer are considered (5). It is energetically favorable for liposomes to adopt a tubular conformation when l/R is greater than 5.56, where l and R are the length and radius of the tubular liposome. Referencing the TEM images obtained in this study, the liposomes varied considerably in length (150 nm to >500 nm), but their diameters remained in a narrow range of approx. 35–50 nm. This gives $l/R > 6$, indicating that tubular liposomes should remain stable. Calculation of the packing parameters for PC ($\rho = 0.7$) and CerVI ($\rho = 1.2$) suggests that the spherical endcaps of the liposomes are mostly enriched by PC, while the flatter bilayer structure is mostly enriched by Ceramide VI. A unique feature of the tubular liposomes is the helical twist that occurs at a pitch of approx. 100 nm (Figure 2).

Upon adding the silica precursor (tetraethylorthosilicate) and gently stirring the liposome solution for approx. 1 week, the silica-coated liposomes were separated by repeated washing and centrifugation. TEM and SEM imaging showed a close resemblance of the silica-templated shells to the liposomes before templation (Figure 3). Tubular shells were replicated, and the helical structure was successfully transcribed, as shown by high resolution TEM (Figure 4).

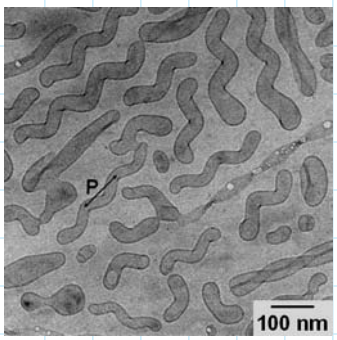

Figure 2. *Most of the liposomes (CerVI/PC = 1:1) exhibited a unique helical feature.*

Conclusions

By combining CerVI with PC, liposomes transition from the typical spherical shape of pure PC liposomes to an elongated tubular shape. This unique shape is expected to give the liposomes a longer retention

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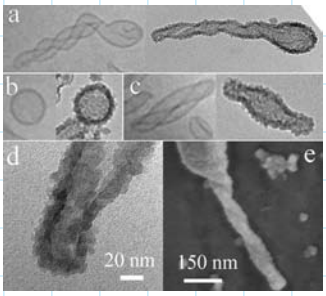

Figure 3. *(a–c) TEM comparison of liposomes before and after templating. (d) High-resolution TEM image of nanosilica. (e) SEM image showing the helical structure of a liposome transcribed onto silica.*

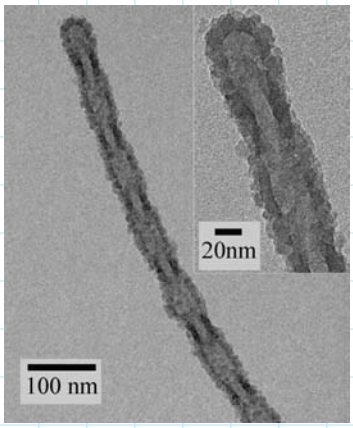

Figure 4. *Helical silica shell after calcination. Inset shows the tip of the tail at a higher magnification.*

time in the body before macrophage clearance compared with spherical liposomes. A hardened silica shell can be formed over the liposomes by addition of a silica precursor. This shell may protect the liposome from rupture when exposed to the physiological environment. Both the tubular shape and helical feature of the liposomes can be successfully transcribed to silicas. Further investigation is in progress to understand the templating process of these liposomes. A larger proportion of spherical shells were observed upon templating, which we suspect might be due to the breakdown of a fraction of tubular liposomes during templation. The ability to shorten templation time or the introduction of the silica precursor in specific time intervals might improve templation and is currently under investigation.

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Educational Workshops in Copenhagen

The following educational workshops will be offered at the 36th Annual Meeting & Exposition of the Controlled Release Society in Copenhagen. All four educational workshops will begin on Saturday, July 18. Educational Workshops 2, 3, and 4 will conclude on Sunday, July 19. Separate registration is required, so find the educational workshop that interests you and register today.

Educational Workshop 1: RNA Interference Biology and Therapeutics

Saturday, July 18

Chaired by Kenneth Howard and Jørgen Kjems, Interdisciplinary Nanoscience Center (iNANO) at the University of Aarhus, Denmark

Attendees will gain knowledge of RNA interference, from cellular mechanisms to siRNA design to therapeutic applications. By understanding the basics of siRNA biology, an appreciation of its importance in cellular regulation and a clear idea of the rationale and design behind RNAi-based therapies will be gained by attendees.

Pharmaceutical Development of Dicer-substrate siRNAs, **Mark Behlke**, IDT, U.S.A.
RNAi as Antiviral Therapy: The HIV-1 Case, **Ben Berkhout**, University of Amsterdam, The Netherlands
Developing siRNA as Therapeutics, **Tony de Fougerolles**, Alnylam Pharmaceuticals Inc., U.S.A.
RNAi Therapeutic Silencing in Disease Models, **Kenneth Howard**, iNANO, University of Aarhus, Denmark
The Biology of siRNA Processing, **Jørgen Kjems**, iNANO, University of Aarhus, Denmark
Intracellular Delivery Considerations for RNAi Therapeutics, **David Oupicky**, Wayne State University, U.S.A.
Targeted siRNA Delivery, **Gert Storm**, University of Utrecht, The Netherlands
Functional Delivery of RNAi Therapeutics, **Hans-Peter Vornlocher**, Roche Kulmbach GmbH, Germany

Educational Workshop 2: Imaging in Drug Development

Saturday, July 18 – Sunday, July 19

Chaired by Ole Hjelstuen, University of Tromsø/GE Healthcare, Norway, and Susanna Abrahmsén Alami, AstraZeneca, Sweden

Attendees of this educational workshop will gain knowledge of the basics and further applications of molecular and pharmaceutical imaging. Talented speakers and lively discussions will direct participants on the selection, utilization, and evaluation of different methodologies.

Probing ER Matrix Dissolution Processes by NMR Microimaging, **Susanna Abrahmsén Alami**, AstraZeneca, Sweden
Hunting the Drug—Spatially Resolved Thermal Analysis of Dosage Forms, **Duncan Craig**, University of East Anglia, U.K.
Novel Applications of In Vitro *Imaging Techniques in Solid Dosage Forms Development and Manufacturing*, **Lasse Heikkinen**, University of Kuopio, Finland

Photo by Claus Starup courtesy of the Bella Center.

Development of Biomarkers and Imaging Agents, **Ole Hjelstuen**, University of Tromsø and GE Healthcare, Norway
Therapeutics: Shorter Time to Patient Benefit by Use of Imaging—Pharmacokinetics and Efficacy by PET, **Bengt Langstrom**, Uppsala University and GE Healthcare, Sweden
Paradigm Shift in the Regulatory Environment for Rapid Human Proof-of-Concept—Microdosing, **Lars Martiny**, Risø Laboratories, Denmark
Molecular Imaging in Drug Development, **Alan Perkins**, University of Nottingham, U.K.
Surface Analysis and Chemical Imaging of Pharmaceutical Solids, **Mark Nicholas**, AstraZeneca R&D, Sweden
Dynamic 3-D Image Analysis in Characterisation of Powder Functionality, **Niklas Sandler**, University of Helsinki, Finland
Micro-imaging in Drug Development; Micro-CT, Micro-MR, Micro-PET, Micro-SPECT, and Combinations; *The Role of Micro-imaging in Lead Compound Selection*, **Alfons Verbruggen**, Katholieke Universiteit Leuven, Belgium
In-depth Insights—Tomographic Imaging Using Terahertz and Magnetic Resonance Techniques for Dosage Form and Process Development, **Axel Zietler**, Cambridge University, U.K.

Educational Workshop 3: *In Vivo* Dissolution—Is It a Reality? Can It Be Correlated to *In Vitro* or *In Silico* Dissolution?

Saturday, July 18 – Sunday, July 19

Chaired by Anette Müllertz, Bioneer:FARMA, Denmark, and Daniel Bar-Shalom, IPC International Operations A/S, Denmark

Attendees will gain an improved understanding of intra-luminal processes in the gastrointestinal tract. Also, attendees will receive an overview of state-of-the-art technologies to achieve *in vivo–in vitro* correlation.

Composition of Human Gastrointestinal Fluids, **Patrick Augustijns**, Catholic University of Leuven, Belgium
Application of Modeling and Simulations in Drug Development, **John Crison**, Simulation Plus, U.S.A.
Biorelevant Release Testing of ER Products, **Nicoletta Fotaki**, University of Bath, U.K.
Dissolution Media Simulating the Gastrointestinal Fluids, **Ekarat Jantratid**, University of Frankfurt, Germany
Simulating Solubilisation and Absorption During Digestion in the GI Tract, **Anette Müllertz**, University of Copenhagen, Denmark
The USP IV *Apparatus in Biorelevant Release Testing*, **Christos Reppas**, University of Athens, Greece
Application of Quality by Design: A Regulatory Perspective on In Vitro *Models*, **Arzu Selen**, FDA, U.S.A.
Simulating Gut Motility: Impact on Dissolution Outcomes, **Werner Weitschies**, University of Greifswald, Germany
In Vivo *and* In Vitro *Correlation: The Physiological Challenges*, **Clive Wilson**, Strathclyde Institute of Pharmacy and Biomedical Sciences, U.K.
In Vitro *Assessment of Simultaneous Dissolution and Permeation by Use of Caco-2 Cell Culture Model*, **Shinji Yamashita**, Setsunan University, Japan

Educational Workshop 4: Micro- and Nano-encapsulation

Saturday, July 18 – Sunday, July 19

Chaired by Christophe Barbe, CeramiSphere Pty Ltd, Australia, and Teresa Virgallito, Microtek Laboratories, U.S.A.

The Consumer and Diversified Products Educational Workshop Micro- and Nano-encapsulation, will provide an overview for students and scientists of how controlled release technology is utilized in various industries. We have assembled an exciting program for the two-day educational workshop. Attendees will develop an understanding of how to formulate micro- and nano-encapsulation systems, develop controlled release products utilizing drying techniques, evaluate products with different types of analytical techniques, and apply micro- and nano-encapsulation technology for commercial applications.

Micro- and Nano-encapsulation Using Inorganic Matrices for Consumer and Diversified Products, **Christophe Barbe**, CeramiSphere Pty Ltd, Australia
Particle Size Measurement from Nanometres to Centimetres and Rods to Platelets and Those Undefinable Things In-between, **Paul Bowen**, Ecole Polytechnique Fédérale de Lausanne, Switzerland
Pharmaceutical Clinical Trials, **Perry Calias**, Shire HGT, U.S.A.
Rapid Method for Evaluating Micro-encapsulation Efficiency, **Robert Djemaes**, GEA Niro, Denmark
Fluidization Dynamics and Related Parameter Considerations for Wurster Fluid Bed Micro-encapsulation Processes, **Charles Frey**, Coating Place Inc., U.S.A.
Comparison of Dissolution Methods for the Characterization of Bioceramic Granules Used as Ibuprofen Carrier, **Samir Haddouchi**, SPS Pharma Services, France
Options in Single and Multilayered Particulate Processing, **Brian Jensen**, Vector Corporation, U.S.A.
Nanoparticles: Preparation and Applications, **Joerg Kreuter**, University of Frankfurt, Germany
Food Products and Ingredients from Extrusion Processing: Principle and Examples, **John Mitchell**, University of Nottingham, U.K.
Liposomal Encapsulation of Biomolecules for the Food Industry, **Mike Patane**, Protech Research Pty Ltd, Australia
Micro- and Nano-encapsulation for Veterinary Applications, **Michael Rathbone**, Griffith University, Australia
Controlled Release of Active Ingredients Encapsulated in Emulsions and Gels, **Gerard Trouvé**, Seppic, France
Coacervative Micro-encapsulation, **Ronald Versic**, Ronald T. Dodge Company, U.S.A.
Phase Change Material Encapsulation for the Medical Device Industry, **Teresa Virgallito**, Microtek Laboratories, U.S.A.
Microencapsulation for Consumer Care and Industrial Applications, **Fanwen Zeng**, Rohm and Haas Company, U.S.A. ■

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The Emergence of Innovative Transdermal-based Delivery Systems

Heico Frima, European Commission, Belgium
Nanomedicine Research in the EU 7th Framework Program for RTD

Silvio Garattini, Mario Negri Institute for Pharmacological Research, Italy
What is Needed to Further Improve the Health in the World?

Allan Hoffman, University of Washington, U.S.A.
The Early History and Evolution of the Controlled Drug Delivery Field

Robert Kiss, Belgian National Fund of Scientific Research, Belgium
Targeting the Na+-ATPhase to Combat Metastatic and/or Multidrug-Resistant Cancers

Henry Kopecek, University of Utah, U.S.A.
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Exhibiting companies that have reserved space at the 36th Annual Meeting & Exposition of the Controlled Release Society, as of press time, are listed below. For ongoing updates, visit www.controlledreleasesociety.org/meeting/exhibitors/currentExhibitors.cfm.

3M Drug Delivery Systems
ADD Technologies Ltd
Alkermes
Asahi Kasei Chemicals Corp.
Avanti Polar Lipids, Inc
Aveva Drug Delivery Systems
Azopharma Product Development Group
Banner Pharmacaps
BASF Corporation
Bio-Images Research Ltd
Biovail Contract Research
Boehringer Ingelheim
Brabender GmbH & Co. KG
Brookwood Pharmaceuticals
Buchi Corp
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Eurand, Inc.
Euromed Communications
Evonik Industries
FMC Corporation
Gattefosse SAS
Gaylord Chemical Company
Genzyme Pharmaceuticals
Halozyme Therapeutics
Hanson Research Corporation
Henkel
Hisamitsu Pharmaceutical Co., Inc.
Informa Pharmaceutical Science
LifeCycle Pharma A/S
Lipoid AG
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Questions?

Contact Debby Woodard, CRS Business Development
+1.651.994.3817 • dwoodard@scisoc.org

Planning for the Future

Your CRS Board of Directors (BOD) met in Atlanta, GA, late last year to discuss ongoing plans and upcoming events and to look far into the Society's future. Putting her most reliable crystal ball to use, CRS President Lisbeth Illum called on the BOD to focus on the ongoing strategic plan, which includes the financial strategic plan, membership benefits, and 2009 elections. Many other topics were discussed as well.

The CRS BOD and staff continually review the status of the Society's strategic plan to make sure goals are being met, modify goals when necessary, and eliminate goals that are no longer pertinent to the overall scope of the Society. Under the leadership of past CRS President Susan Cady, a new CRS strategic plan began to take shape in 2007.

Using valuable input from the 2008–2009 CRS committees, CRS President Lisbeth Illum has led the BOD to further develop and refine the CRS strategic plan. The up-to-date CRS strategic plan will be available soon on the CRS website for you to read, comment on, and see where you can be a part of a successful CRS future.

Membership value and volunteer opportunities are always on the minds of BOD members. You've received your 2009 membership renewal forms, and it is the hope of the BOD that you have renewed your membership and encouraged your colleagues to become members. If your colleagues are weighing the pros and cons of CRS membership, here are some extra pros you can tell them about:

- Networking at CRS meetings and workshops
- Reduced subscription rates to the *Journal of Controlled Release*, the number one journal in controlled release
- Additional quality publications on current controlled release topics available at reduced subscription rates: *European Journal of Pharmaceutics and Biopharmaceutics* (*APV* and *Biomaterials*)
- Community forum to exchange ideas
- Volunteer on a committee and use your leadership skills and innovations
- Mentoring and protégé opportunities
- Interact with leading scientists
- Learn about breakthroughs from the experts
- Stay informed about state-of-the-art technology
- Reach out to and collaborate with colleagues in the different areas of controlled release within your Society
- Foster and expand your current knowledge through webinars, meetings, workshops, the CRS website, and more
- Receive reduced registration rates to annual meetings and expositions, educational workshops, and satellite meetings
- Receive a CRS Annual Meeting & Exposition *Transactions* CD
- Five complimentary issues per year of the *CRS Newsletter*, which contains patent watches in relevant fields of controlled release, special scientific publications, technical expertise in the field of drug delivery, and other relevant information about controlled release
- Listing in online membership directory updated daily
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- Submit educational workshop and/or satellite meeting proposals
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- Submit a book proposal
- Present oral and/or poster abstracts
- Chair a podium session
- Join a Local Chapter
- Vote!

Now that you have your colleagues' full attention—encourage them to join CRS today! Have your colleagues contact CRS Member Relations Specialist Cheryl Sundquist at csundquist@scisoc.org with any CRS membership questions or visit www.controlledreleasesociety.org/main/membership/join.cfm to become a member by printing, completing, and faxing or mailing the membership form and payment to CRS headquarters today. ■

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Is There a Need for Further Research on Intramammary Drug Delivery Systems for Treating Bovine Mastitis?

Dr. Olaf Bork[1]

Although bacterial intramammary infection (IMI) of dairy cows is much less common than it was 40 years ago (1), the International Dairy Federation (IDF) stated recently that the clinical mastitis rate is still about 40 cases per 100 cows per year (2). Even at farms with established state-of-the art milk management, clinical mastitis still occurs (3). In fact, bovine mastitis remains a global problem, with New Zealand losing more than NZ$280 million every year (4), mainly due to lost milk production.

Successful treatment of IMI depends on the right diagnosis (mastitis causing organism [MCO]) followed by treatment with an appropriate antimicrobial. The antimicrobial can be administered via the intramammary route (through the teat canal). Several products of this type have been approved by local authorities and usually consist of an antimicrobial suspended in an oily liquid. However, the therapeutic efficacy can be disappointing depending on the causative pathogen. For example, the cure rate for the MCO *Staphylococcus aureus* is reported to be only 25–50% (5–7). One reason for treatment failure is that the drug distribution of intramammary products within the udder is insufficient, especially in the upper region of the udder. Drug distribution is crucial, but unfortunately, it is not fully understood in either infected udders or even in healthy udders.

The complexity of drug distribution in the mammary gland becomes clearer through the study of its structure. After administration, drugs have to travel from the teat cistern to the gland cistern then along the milk ducts and, finally, to the grandular tissue. Other variables affecting drug distribution include the difference between the front and rear quarters of the udder and udder size. It is also known that mastitis causes physical and chemical changes in the mammary gland due to swelling or inflammatory products. Thus, drug distribution in the mammary gland remains a significant challenge.

Over the last few decades, much valuable information has been generated and published relating to drug distribution after intramammary administration. For instance, Ziv (9) described the physicochemical properties of an ideal drug and Ehinger and Kietzmann (10) investigated the carrier vehicle in an isolated perfused udder. A review on the topic has been written by Gehinger et al. (8). Another review by Gruet et al. (11) considers other therapeutic options, such as micro- and nanoparticles or liposomes. However, the question remains as to how an encapsulated drug is transported to the higher regions of the udder.

[1] New Zealand's National School of Pharmacy, Dunedin, New Zealand. E-mail: olaf.bork@otago.ac.nz.

Diffusive mass transfer is too slow to achieve effective antimicrobial concentrations above the minimum inhibitory concentration between two removals of milk from the mammary gland. Thus, there must also be convective mass transfer to ensure satisfactory drug distribution. It is probable that convective mass transfer is mainly influenced by the motion of the udder resulting from the cow's movement. Because of many uncontrollable parameters, it is not surprising that some published results from *in vivo* experiments differ significantly. Further investigations of hydrodynamics, mass transfer, and mixing of drugs in the mammary gland are crucial to provide the means to achieve better drug distribution in the udder. One potential way to do this is through the use of new analysis techniques such as imaging technologies.

It is also crucial for the success of a new intramammary drug delivery system to involve scientists, engineers, and colleagues from marketing in the product design process from the very beginning. The extra costs of manufacturing a new drug delivery system will vary and depend on the current market. At the present time, the economic situation and the significant drop in milk powder prices make it challenging to introduce new drug delivery systems to the market. On the other hand, the treatment cost of bovine mastitis is still low compared to the cost of lost milk production. Looking ahead, the demand for dairy products will probably increase given the increase in world population, which is estimated to be 7 billion by 2012. This potentially higher demand may provide the incentive for farmers to spend more money on new intramammary products.

Successful treatment of bovine mastitis is very complex. Many other ideas are under discussion to improve the cure rate of mastitis, such as using a combination of administration routes, dosage forms, active ingredients, etc. Clearly, there remains a great demand for bovine mastitis research. One crucial investigation will involve drug distribution from new intramammary antimicrobial delivery systems.

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Copenhagen Veterinary Program Highlights

Innovations in Drug Delivery for Animal and Human Health Applications Mini-symposium

Delivery Systems for the Removal of Colonic Residual Antibiotic to Reduce the Emergence of Resistances, **Elias Fattal**, University of Paris-XI, France

Innovative PK Approaches in the Development of Controlled Release Veterinary Drugs, **Mathieu Peyrou**, Novartis Animal Health, Switzerland

Enhancement Strategies in Skin Penetration of Solutes and Nanoparticles: Species Differences, **Michael Roberts**, University of Queensland, Australia

Drug Delivery Systems Developed for Animal Health Applications, **Thierry Vandamme**, University of Strasbourg, France

Nanotechnology and Animal Models: Improving Health Outcomes—An Animal Health/Veterinary and Bioactive Materials Joint Session

Squalenoylation: A Platform for the Discovery of New Anticancer and Antiviral Nanomedicines, **Patrick Couvreur**, University of Paris-XI, France

Evaluation of Gliadin/Polymer Nanocomplexes in a Mouse Model of Gluten Sensitivity, **Jean-Christophe Leroux**, University of Zurich, Switzerland

Vet Get Together

Waivers of Bioequivalence for Certain Veterinary Dosage Forms, **Sandra Klein**, Johann Wolfgang Goethe University, Germany

Back to Basics: 2. Recombinant Polymers: Promise for Gene Therapy

Arash Hatefi[1] and Hamidreza Ghandehari[2]

This is the second in a series of articles introducing the basics of aspects of research techniques and topics for the development and evaluation of controlled release technologies.

Introduction

A number of human diseases are known to be genetic in origin, and many diseases have a hereditary component. The opportunity to treat these disorders by replacing the defective gene(s) with a normal healthy gene offers a therapeutic approach for patients who suffer from such diseases. The major stumbling block to the advancement of gene therapy is the lack of suitable delivery systems to carry the therapeutic genes safely and efficiently to target tissues. Advancement in gene-transfer technology is still in a nascent stage owing to several inherent limitations in the existing delivery methods. While lipid-based vectors such as liposomes provide high transfection efficiency, their large-scale production, reproducibility, and cytotoxicity remain a major concern. On the other hand, polymeric carriers are relatively biocompatible, but they suffer from poor gene-transfer efficiency. Viral carriers show promise in cancer gene therapy due to their ability to overcome intracellular barriers and the enormous potential for recombinant engineering. However, non-specific binding to other cells, potential immunogenicity and high production costs have limited their use. What has been long sought is a technology that combines biocompatibility, efficiency, and the ability to engineer an effective gene-transfer technology. In this article we highlight the potential utility of recombinant DNA technology for the design and development of biopolymers as gene delivery agents.

Recombinant Polymers

In recent years there has been a great deal of interest in the development of recombinant polymers with applications in tissue engineering and drug and gene delivery (1–3). The major advantage of polymers that are genetically engineered versus chemically synthesized polymers is the higher degree of control over amino acid sequence and polymer length. A number of polymers based on natural motifs, such as silk, elastin, collagen, and laminin, have been genetically engineered to date (4) in which motifs from nature are combined biosynthetically to result in new properties that are not present in nature. In the context of gene delivery, recombinant polymers can be used as matrix-mediated localized depot systems or as systemic targetable constructs. These biopolymers have the potential to hybridize the strengths of both viral and non-viral vectors in order to overcome the extra- and intracellular barriers to efficient, safe, and cost-effective gene delivery. Over the past few years we have worked on two types of recombinant polymers for gene delivery to cancer cells. One is based on the repeating units of silk and elastin for matrix-mediated delivery, and the other is based on lysine and histidine residues containing a targeting moiety for systemic gene delivery.

Silk–Elastinlike Polymers for Matrix-Mediated Gene Delivery. Developed by Cappello et al. (5), silk–elastinlike protein polymers (SELPs) are recombinant polymers based on repeating motifs of silk and elastin (Figure 1A). These polymers combine the material strength of silk and elasticity of elastin motifs found separately in nature. Depending on the sequence and length of the silk and elastin blocks, SELPs can be liquid at room temperature and undergo an irreversible sol to gel transition at body temperature. Composition (silk to elastin ratio), sequence

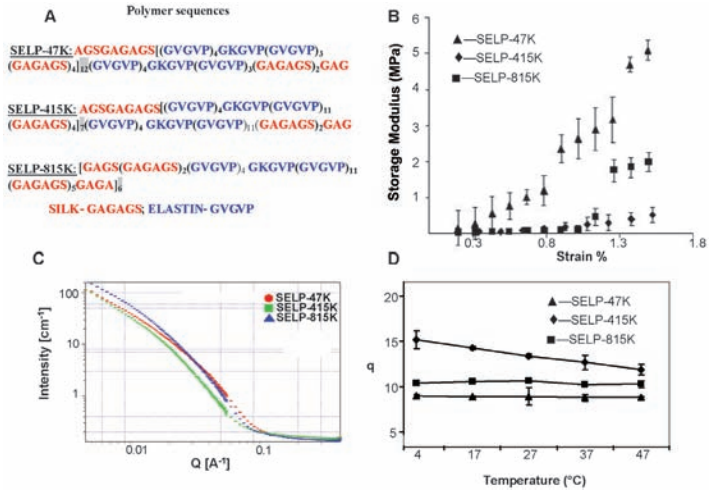

Figure 1. *(A) Amino acid sequences of SELP analogs (head and tail sequences not shown). (B) Storage modulus of 12 wt% SELPs (cured for 4 hr) under multi-strain sweep using dynamic mechanical analysis. (C) Small-angle neutron-scattering plot of 12 wt% SELPs. (D) Hydrogel swelling, q, as a function of temperature. Adapted from Dandu et al. (8).*

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(relative position of silk versus elastin blocks), molecular weight, and polymer concentration are among the factors that influence the rate of gelation, pore size, viscosity, mechanical properties, degradation, and bioactive agent release from SELP hydrogels. Initially, the influence of polymer sequence and concentration on the release of plasmid DNA was evaluated. Strategic placement of a positively charged lysine residue in the backbone of polymers resulted in an on-off release behavior of negatively charged plasmid DNA as a function of ionic strength (6). Mixtures of DNA and SELP were injected in breast tumor xenografts in murine animal models and resulted in prolonged gene transfer of up to 21 days (7). Using recombinant techniques, three SELP analogs with varying lengths of silk and elastin blocks, while maintaining the molecular weight of the polymer constant, were synthesized (Figure 1A) (8). Storage moduli observed by dynamic mechanical analysis (Figure 1B) and small-angle neutron-scattering data (Figure 1C) provided evidence that the cross-linking densities in these hydrogels follow the order SELP-47K > SELP-815K > SELP-415K. Interestingly, the sensitivity of these hydrogels to changes in temperature after the hydrogel was set could also be modulated by manipulation of amino acid sequence, where hydrogels with longer elastin units in the polymer backbone showed a lower degree of swelling as temperature was increased due to self-assembly of the elastin units (Figure 1D).

Our recent interest has been in the localized delivery of adenoviral gene transfer agents to head and neck tumors using SELPs. Localized viral gene delivery reduces uptake by non-target organs such as the liver and prolongs transfection in tumors, minimizing dosing frequency and adverse effects. After intratumoral injection of adenoviruses containing the green fluorescence protein gene mixed with SELPs, prolonged and localized expression in a mouse head and neck tumor model was observed (9). Real-time images of viral expression levels indicate that polymer concentration and structure are predominant factors that affect localized viral transfection (Figure 2) (10). These studies with SELPs show one example where molecular engineering of polymers by recombinant techniques can result in control over physicochemical properties, release, and duration and localization of gene transfer.

Recombinant Lysine–Histidine Copolymers for Targeted Gene Transfer. Recombinant biopolymers composed of tandem repeating units of lysine and histidine are another example of the application of genetic engineering techniques in developing gene carriers. We have reported the biosynthesis and characterization of the first prototype recombinant biopolymer with the structure $(KHKHKHKHKK)_6$-FGF2 (11), i.e., dKH-FGF2, which contains 36 lysine residues (K) in the dKH segment to condense pDNA and 24 histidine residues (H) to promote endosomal escape (Figure 3). At the C-terminus of the dKH segment, FGF2 represents basic fibroblast growth factor, a ligand for the basic fibroblast growth factor receptor (FGFR). This receptor is known to be over-expressed in subpopulations of lung, prostate, and breast cancer, thus conferring the potential for targeted gene delivery via receptor-mediated endocytosis. As a starting point,

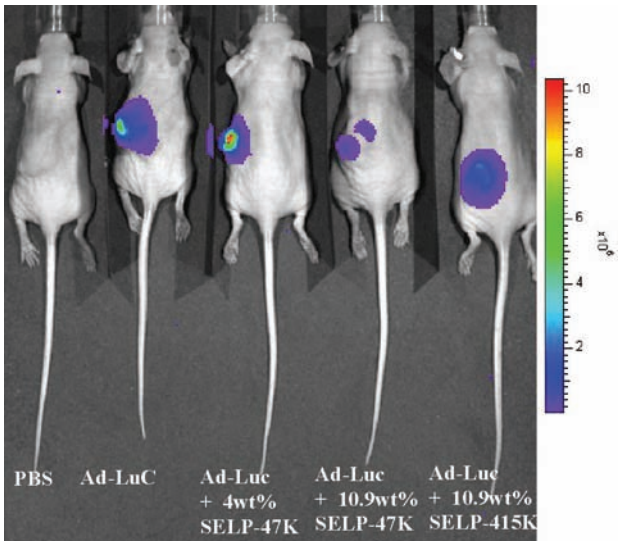

Figure 2. *Real-time imaging of controlled luciferase expression using SELP-47K and SELP-415K. Localization and expression levels are highly dependent on polymer composition and concentration. Comparison of the two mice treated with SELP-47K shows more viral release and expression with the lower concentration, as more virus escaped from the matrix. The expression differences between the two mice treated with 10.9 wt% SELPs can also be attributed to the microstructural differences of the SELP compositions: SELP-415K has larger pores and releases virus at a higher rate than SELP-47K at the same concentration. Adapted from Cresce et al. (10).*

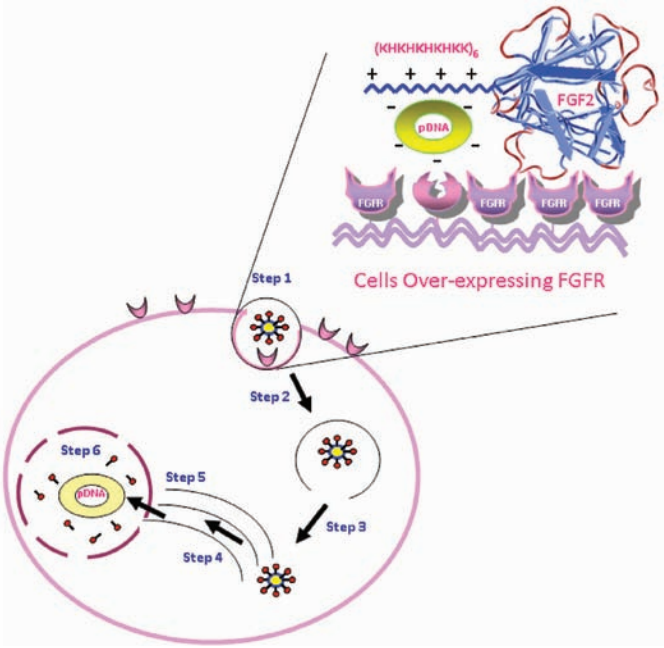

Figure 3. *Schematics of dKH-FGF2 biopolymer and a model for its intracellular trafficking. Step 1: The KH peptide condenses pDNA, and the targeting motif (FGF2) binds to FGFR. Step 2: Nanoparticles are trafficked into endosomes. Step 3: Nanoparticles burst endosomes and escape into the cytosol. Step 4: Nanoparticles are trafficked toward the nuclear membrane. Step 5: Nanoparticles could end up in the nucleus at the mitosis (M) phase of the cell cycle, where the nuclear membrane dissolves. Step 6: Once inside the nucleus, the genetic material is released for transcription.*

From the Education Committee continued on page 18

From the Education Committee continued from page 17

the lysine residues in the dKH tail (i.e., KHKHKHKHKK) were arranged as dispersed, while keeping the lysine to histidine ratio constant at 6:4. Although dKH-FGF2 condensed pDNA into nano-sized particles and enabled gene transfer into target cells, the percentage of the transfected cells in the absence of serum was five times higher than in the presence of serum.

This prompted us to further characterize dKH-FGF2 and modify its structure to an extent that the transfection efficiency increased in the presence of serum. We hypothesized that by changing the arrangement of KH residues in the KHKHKHKHKK repeating units and organizing the lysine residues in clusters, the pDNA condensation efficiency would be improved, resulting in more compact and stable carriers with higher transfection efficiency. This hypothesis was inspired by existing motifs in nature (e.g., histones and adenovirus mu peptide) that have lysine and arginine residues arranged in clusters and have been shown to be highly efficient in DNA condensation. To test this hypothesis, the following biopolymer was designed in which the lysine residues were organized in clusters: $(KKKHHHHHKKK)_6$-FGF, i.e., cKH-FGF2 (12). To be consistent with dKH-FGF2, the K to H ratio was kept constant at 6:4. To examine the ability of KH-based biopolymers to mediate gene transfer in cells over-expressing FGFR, they were complexed with pEGFP and used to transfect both NIH3T3 and T47D cells known to over-express FGFR. In this set of studies, all the variables were kept constant except the biopolymer sequence. In both cell lines, the highest number of transfected cells was observed with cKH-FGF2 compared with dKH-FGF2. Thus, it was concluded that the observed difference in transfection efficiency between the two biopolymers was directly influenced by the biopolymer sequence. Recombinant polymer technology enables the production of amino acid-based polymers where sequence and molecular weight can be controlled (compared with random copolymers and sequential polypeptides). This is a powerful technique that allows correlation of polymer structure with gene transfer.

Challenges and Future Directions

The above examples illustrate initial steps to explore the potential of recombinant polymers in gene therapy. Much needs to be accomplished to realize utility in patients. The biosynthesis of these polymers is tedious and involves many steps. Often at the genetic level, issues such as recombination and deletion of repeating codons prevent the successful cloning and expression of the constructs. Another factor in the biosynthesis of recombinant polymers for gene delivery is the limited ability to produce cationic polymers, probably due to their toxicity to bacterial hosts. For successful and rapid testing of a large number of recombinant polymers, these limitations in biosynthesis need to be overcome and strategies need to be identified for combinatorial production and analysis. Another factor common to all protein-based systems is the potential immunogenicity of the constructs. Identifying non-immunogenic motifs, while preserving gene transfer capability, or modifying the constructs with water-soluble domains are strategies that can be employed to minimize immunogenicity. Finally, FDA approval of such systems is challenging since we are dealing with new carriers that are not in the portfolio of currently approved polymers for drug delivery applications. Nevertheless, both from a basic science point of view enabling structure-function evaluations and from the point of view of future clinical application in patients, recombinant polymer technology promises to be a powerful tool for the design and development of new gene delivery systems.

Acknowledgments

Financial support for this research was provided in part by grants from the National Institutes of Health (R01CA107621 and R21 CA116584) (HG) and American Cancer Society (Institutional Research Grant IRG-77-003-26) (AH). The assistance of Jordan Frandsen and Sriramchandra Mangipudi in preparation of this article is appreciated.

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PFQ New Website Now Live!

Pharmaceutical Formulation & Quality

Pharmaceutical Formulation & Quality went back to the drawing board in 2008 and created a brand new website to better service the pharmaceutical industry. The new site features some new capabilities and enhanced features:

- New Drug Delivery Database – A new collaboration with the **Journal of Pharmaceutical Sciences** this new database is modeled on top of the existing government site, www.clinicaltrials.gov and monitors changes on the site. Features will include a search function and added commentary by industry leaders.
- Enhanced Full Text Article Presentation
- Enhanced Content Searching
- Enhanced Newsletter Archive
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CRS Illinois Student Chapter Hosts Two Seminars

The Controlled Release Society Illinois Student Chapter hosted two seminars on January 21 and February 11 as a series of events in 2009. The seminar events were co-sponsored by the Biopharmaceutical Sciences (BPS) program at the University of Illinois at Chicago (UIC).

As a seminar speaker in January, Dr. Derrick C. Mancini, associate director for facilities and technology at Argonne National Laboratory (ANL)-Center for Nanoscale Materials (CNM), was invited to give a talk on "Nanoscale-Structured Hydrogels and Hydrogel-Nanoparticle Composites with an Overview of Research at the Center for Nanoscale Materials." Dr. Mancini is also a leader for the Nanofabrication and Devices group at ANL-CNM and an adjunct assistant professor of electrical engineering at UIC, as well as a research professor of physics at the Illinois Institute of Technology.

Dr. Mancini introduced the research and facilities at ANL-CNM and highlighted the current research at ANL-CNM on nanoscale-structured hydrogels and composites of hydrogels with inorganic nanoparticles for biomedical applications. Dr. Mancini's seminar attracted a large number of attendees from various departments at UIC. A discussion and luncheon session followed, with more in-depth discussion about his presentation. For more information about Argonne National Laboratory-Center for Nanoscale Materials, visit http://nano.anl.gov/.
For the seminar in February, Dr. Carmen Popescu, project coordinator of pharmaceutical applications at Roquette America, was invited to give a presentation on "Giving Practicality to Novelty." Dr. Liuming Zhou, senior department manager of process and pharmaceutical technology at Roquette America, accompanied her to talk with faculty members and students

From left to right: Liuming Zhou (Roquette America), Bethany White (BPS, vice chair of AAPS-UIC Student Chapter), Ronald Koch (BPS, professor), Carmen Popescu (Roquette America), and Misuk Bae (BPS, chair of CRS Illinois Student Chapter).

about the research and pharmaceutical career development strategy in industry during a discussion and luncheon session. Dr. Popescu introduced the current research and science behind the products of Roquette America and highlighted a practical approach to drug delivery system development. The attending audience came from the pharmacy program within UIC.

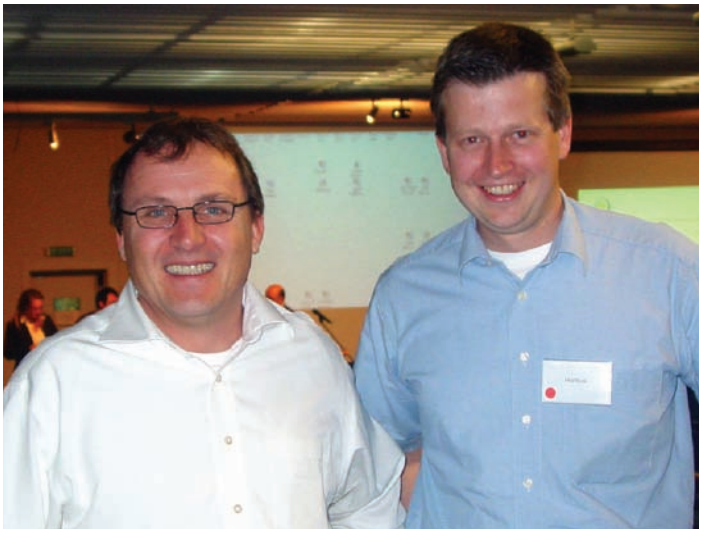
The next event for the CRS Illinois Student Chapter is a one-day symposium in summer 2009. For more information about the activities of the CRS Illinois Student Chapter, visit www2.uic.edu/stud_orgs/prof/crs/index.htm. ■

New Zealand Chapter of the CRS Holds 11th Formulation and Drug Delivery Conference in Dunedin

Thilini Thrimawithana
University of Auckland, Auckland, New Zealand

The 11th Formulation and Drug Delivery (FDD) conference was again held with great success, with approx. 70 delegates with very diverse research interests participating. The two-day conference began with a warm welcome from Prof. Ian Tucker, dean of the School of Pharmacy and convenor of the FDD research theme at the University of Otago. The theme of the first day of the conference was imaging methods and technologies, while the second day of the conference was devoted to issues on oral delivery of bioactives. Both local and international speakers with expertise in various fields sparked the interest of the audience.

The first session started with a fascinating lecture on the use of modern techniques such as magnetic marker monitoring and magnetic resonance imaging for *in vivo* imaging of dosage forms by Prof. Werner Weitschies, an invited speaker from the University of Greifswald in Germany. He discussed the application of these techniques to understanding the *in vivo* behaviour of dosage forms, as well as gastrointestinal luminal conditions, which greatly affect the bioavailability of orally administered pharmaceuticals. This presentation was followed by an introduction to atomic force microscopy (AFM) by Dr. Ian Larson from the Faculty of Pharmacy and Pharmaceutical Sciences at Monash University in Australia. He gave an excellent overview of the use of AFM and the information that can be gathered from AFM, such as mapping of polymer coatings on surfaces. The remaining morning sessions gave the audience an overview of electron microscopy techniques such as TEM, SEM, and polarized light microscopy.



Guest speaker Prof. Werner Weitchies (left) and Dr. Olaf Bork (right). (Photo by Kyri Gibson)

The afternoon session again captivated the audience with presentations on pharmaceutical imaging techniques, including confocal and Raman microscopy. This was extended to the veterinary field by Dr. Zimei Wu (Bomac Laboratories), who presented an overview of imaging of intramammary dosage forms. The next portion of the session was dedicated to relatively recent imaging techniques that can be used as process analytical techniques. These included presentations on coherent anti-stokes Raman scattering (CARS) microscopy and terahertz pulsed-imaging techniques. Both of these presentations were delivered by University of Otago researchers Dr. Clare Strachan and Prof. Keith Gordon. CARS technology appears to be a very promising means of understanding and analyzing *in situ* changes in morphology of solid dosage forms as they dissolve. Aligning with the talk on CARS, graduate student Louise Ho proceeded with an excellent presentation on the use of terahertz in analyzing variations in the film-coating density of oral dosage forms that cannot be visually identified. This presentation illustrated how film coating varies within a batch, specifically the coating around the equator of a tablet and how this has a huge impact on drug release parameters.

Day one came to an end with six more presentations given by graduate students. The talks varied from cancer targets to drug delivery systems targeted for pulmonary inhalation, the brain, and the posterior eye. These talks inspired discussions amongst the experts, with questions being asked of each and every presenter.

The Annual General Meeting of the New Zealand Chapter of the Controlled Release Society (NZCRS) was also held at the close of day one to update its members on activities over the past year and plans for the year ahead. These include the organization of an exciting NZCRS workshop in Auckland during the latter part of 2009 on Strategies to Improve Bioavailability of Problematic Drugs.

Following the NZCRS meeting, the conference dinner was held at Glenfalloch Homestead on the beautiful Otago Peninsula. A limerick competition was held again this year and got everyone's creative juices flowing! A highlight of the night was that Prof. Keith Gordon presented Prof. Thomas Rades with a certificate to signify his election to Fellow of the New Zealand Institute of Chemistry. Thomas is the first pharmacist to be honoured in such a way within the Institute of Chemistry.

Prof. Thomas Rades officially become a Fellow of the New Zealand Institute of Chemistry. (Photo by Karl Bailey)

The theme of the second day was challenges in oral drug delivery, and the floor was opened for further presentations on the topic, with an excellent initial overview of the topic given by Prof. Ian Tucker. In this presentation, he introduced the concept of grease balls, brick dust, and peptides, the drug molecules with less than ideal physicochemical properties that require smarter innovations to be formulated into clinically acceptable therapeutics. Another interesting challenge Prof. Tucker introduced to the audience was the significance of transporter affinity for drug molecules. Accordingly, the drug molecules could be classified into four groups: those with nil transporter effects, those affected by only efflux transporters, those acting only as absorptive transporters, or those acting as both efflux and absorptive transporters.

The minds of the audience were then stimulated by Assoc. Prof. Roger Lentle from the Institute of Food Nutrition and Human Health at Massey University and his talk on digesta and rheoceuticals. The data and images presented on the digesta rheology and peristalsis of the gut will help in the development of rheoceuticals (foods that influence the speed of digestion and absorption of nutrients), foods targeting dysmotility, preparations that aid the targeting of drugs, and proximal digestion of probiotics, as well as novel methods of packaging drugs.

Left to right: Dr. Natalie Medlicott, Dr. Ian Larson, and graduate student Louise Ho enjoy a tea break during the conference. (Photo by Kyri Gibson)

Chapter News—New Zealand Chapter continued on page 22

Chapter News—New Zealand Chapter continued from page 21

The 2009 NZCRS Keynote Speaker Assist. Prof. Stefania Baldursdottir from the University of Copenhagen in Denmark, preceded this presentation with an excellent introduction to rheology. She gave a brief overview of the instruments used in the assessment of the visco-elastic properties of pharmaceuticals. The presentation provided insight into the parameters that can be gathered from an oscillatory rheometer and how these parameters can be applied to determine inter- and intra-molecular interactions of colloidal solutions. The audience was introduced to the concept of heterogeneous networks, a system in which incorporated macromolecules diffuse out faster than from a homogenous network.

NZCRS Keynote Speaker Assist. Prof. Stefania Baldursdottir receives a gift from Prof. Ian Tucker, convenor of the FDD Conference. (Photo by Kyri Gibson)

Following the introduction to transporters by Prof. Tucker, Assoc. Prof. Grant Butt (Department of Physiology, University of Otago) provided insight into the various membrane transporters. He differentiated the terminology of channels and carriers (i.e., uniporters, antiporters, symporters) and gave an overview of the patch clamp, an interesting method of determining the behaviour of a single protein. A patch clamp can record the conductance, selectivity, kinetics, and pharmacology of a single channel. He demonstrated how to apply the transporter data to maximize drug absorption using his expert knowledge in specific transporters in the possum gastrointestinal tract.

Once again linking the concepts introduced by Prof. Tucker, Prof. Thomas Rades (School of Pharmacy, University of Otago) gave an overview of formulation strategies for "brick dust" molecules and a very exciting insight into the process of melt extrusion to form glass solutions. Formulation solutions for "grease ball" molecules were tackled by Dr. Anja Graf, with an excellent overview on lipid solutions, SEDDS, and SMEDDS. She introduced the dynamic lipolysis (pH stat) model, which can stimulate formulation performance upon oral administration. Current innovations in peptide drug delivery via the oral route were presented by Dr. Natalie Medlicott. She spoke about the concept of protein modifications such as peptide bond reductions, cyclization, PEGylation, and N-alkylation, in addition to permeation enhancers, trans-cellular transporter affinity modifications, and particulate systems as means of enhancing oral bioavailability of macromolecules.

Prof. Thomas Rades, president of the NZCRS, congratulates Kirsten Graeser as the winner of the NZCRS prize for Best Oral Presentation.(Photo by Kyri Gibson)

The afternoon session was again dedicated to talks by graduate students, who presented exciting new data. Before the closing remarks, the judges of the presentations quickly rounded up the marks to decide on this year's best student presenter. Through this competition, the NZCRS recognizes student research efforts and supports the attendance of the winning student at the CRS Annual Meeting. As in every year, the competition was very strong, but the overall winners of this years' competition were Kristen Graeser and Ulrike Zimper, both from the School of Pharmacy at the University of Otago in Dunedin.

Left to right: NZCRS Postgraduate Representative Rohit Jain with Ulrike Zimper, runner-up in the NZCRS prize for Best Oral Presentation, and Pranav Karmwar. (Photo by Kyri Gibson)

The 11th NZCRS FDD meeting was a great success, with the gathering of exceptional researchers from local, as well as international, institutions. The great momentum gained from this meeting will be carried over to the 12th Formulation and Drug Delivery Conference in 2010. ■

Arden Conference Goes Global

The first Asian Arden Conference was held October 31 through November 2, 2008, in Beijing, China, at the stylish Fragrance Hill Hotel designed by the famous architect I. M. Pei in the late 1970s.

The conference was cosponsored by AAPS, the Chinese Pharmaceutical Association, the Chinese Society of Particuology, and the Controlled Release Society. Eighteen speakers from Australia, Canada, China, Germany, Japan, and the United States provided state-of-the-art presentations to more than 100 attendees. Simultaneous translation was provided during the presentations and discussion sessions. The Q&A and panel discussions were very interactive. Both the attendees and presenters were impressed with the quality of the conference.

The Chinese Pharmaceutical Association is interested in sponsoring the 2010 Asian Arden Conference in China. The annual Arden Conference is well known for in-depth presentations and discussions focused on a popular and practical topic of pharmaceutical technologies. It covers a diverse range of topics and attracts high-quality speakers and attendees. The pace of the program enables intensive and extensive exchange between the speakers and audience during Q&A sessions after each presentation and panel discussion sessions for each day. The annual Arden Conference has been held in West Point, NY, U.S.A., and London, U.K. The 2008 global theme for the Arden Conferences was particle and powder technology for solid dosage forms. ■

Welcome New Members

Oreoluwa O. Adedoyin
Helder Almeida Santos
Florence Arvis
Benjamin Belkind
Luis M. Bimbo
Soula K. Boustani
Alexandra F. Bowles
Amanda E. Brooks
Marite Cardenas
George Chalkias
Annalisa Dalmoro
Yaron Y. Dekel
Harshil D. Dhruv
Michela Di Muria
Tan Dinh
Tove J. Evjen
Raafat M. Fahmy
Marco E. Favretto
Sascha General
Evren H. Gokce
Divakar Goli
Deepak Gondaliya
Rebecca Gu
Dipak Gupta
Chien-Hsuan Han
Robert J. Hayes
Tiina Heikkila
Andreas M. Henning
Zabed Iqbal
Rahul D. Jayant
Brian K. Jensen
Sharon A. Johnstone
Sinem Y. Karavana
Dilek Keskin
Atul R. Khare
Vijaya B. Kolachalama
Christina Kriegel
Timo Laaksonen
Esben K. U. Larsen
Chao-Pin Lee
Uri Lesmes
Yair Levy
Xiaojian Li
Jessica Liang
Abdallah Makhlof
Roy Mathew
Christopher McConville
Annalisa Mercuri
Marc Michaelis
Sabiruddin Mirza
Johannes Moes
Sumedha Nadkar
Sune Nygaard
Kenneth C. Ofokansi
Franklin Okumu
Ipek Ozcan
Mine Ozyazici
Michael J. Palmieri, Jr.
Carl A. Pelzel
Karsten Petersson
Annett Richter
True L. Rogers
Helene Rossignol
Katie Ryan
Vishal Sachdeva
Aram Saeed
Chris Scott
Devang T. Shah
Xiaozheng Shu
Eliot M. Slovin
Gitte Sorensen
Hirofumi Takeuchi
Giridhar Thiagarajan
Ingunn Tho
Donald J. Treacy
Joost Van den Berg
Dennie J. M. van den Heuvel
Ricardo A. Vargas
Xiao Wu
Chenjie Xu
Qiaobing Xu
Ying Zheng

CRS China Initiative Subcommittee to Host Satellite Meeting in Shanghai, China

In 2008, the CRS Board of Directors continued its ongoing discussion about member value. The highlights from the serious and productive dialogue were the definition of member value, member value perception, offering new CRS products for members, and expanding the global outreach of CRS. One of the outcomes was the formation of the China Initiative Subcommittee and a review of its plans to hold a satellite meeting in China in 2009.

The first offering in China will be Oral Controlled Drug Delivery Using Tablets: From Laboratory to Production. This satellite meeting is being chaired by the CRS China Initiative Subcommittee Chairs Ali Rajabi-Siahboomi and Jian-Xin Li. This event, to be held in Shanghai on June 16–17, 2009, will cover what you want to hear on formulation, development, and manufacturing of controlled release systems and be delivered by the experts you want to hear from, including presenters from China, Europe, and the United States.

Registration and hotel details will be available soon on the CRS website. Watch for more news to come.

Oral Controlled Drug Delivery Using Tablets: From Laboratory to Production
Chairs: Ali R. Rajabi-Siahboomi, Colorcon, Inc., U.S.A., and Jian-Xin Li, Evonik Corporation, U.S.A.

Educational Goals

- Background into formulation options for oral controlled release drug delivery (OCRDD)
- Tablet formulation options available for controlled drug release: core design and formulation, polymers, technologies
- Recent advances in the formulation and design of matrices
- Drug delivery using osmotic-driven drug release from tablets: options available, design and formulation, and polymers
- Practical aspects of manufacturing (blending, granulation, and compression) and scale-up for single-unit dosage forms
- QbD considerations for the design of single-unit CR formulations
- Applications of mathematical description and modeling of drug release from single-unit dosage forms
- *In vivo* performance and bio-equivalence of controlled release tablets

This will be an excellent opportunity for new scientists, students, and those new to formulation, development, and manufacturing of controlled release systems, as well as for those who are familiar with and experienced in this area. Attendees will be able to apply their learning from this satellite meeting to their daily work and make informed decisions on selecting a suitable technology for controlled release of their API. In addition, the experienced presenters at the satellite meeting will discuss "best practice guidelines" for formulation design and manufacturing of single-unit CR tablets.

Program Topics: June 16, 2009

- The role of the Controlled Release Society in harnessing the development of novel drug delivery systems in Asia
- Opportunities and challenges of solid oral drug delivery systems in China
- Oral controlled release formulations: Clinical benefits and limitations
- Oral controlled drug release tablet dosage forms: Polymer and technology options for formulation design
- Physico-technical properties of powders for oral controlled release tablets
- Granulation of inert matrix formulations using acrylic polymers case studies
- Granulation of inert matrix formulations using cellulose ether polymers case studies
- Formulation and granulation for osmotic pump dosage forms case studies
- Formulation and granulation for lipid matrix systems case studies
- Formulation development of orally disintegrating tablets case studies
- Compression of controlled release formulations: Critical process parameters and performance variables for single multi-layer tablets (matrices and osmotics)

Program Topics: June 17, 2009

- Recent advances in granulation technologies: High-shear and fluid-bed processes
- *In vitro* dissolution testing of controlled release tablets for development and quality control purposes
- Film coating of CR tablets: Immediate and modified release coatings
- Critical scale-up considerations of controlled release tablet dosage forms
- Mathematical description and prediction of drug release from matrix technologies
- Mathematical description and prediction of drug release from osmotic pump technologies
- Desired quality aspects of controlled release tablet formulations
- Expectation of quality, design, and manufacturing of MR formulations for registration in China
- Opportunities for developing controlled release tablet formulations in developed versus developing regions
- *In vivo* evaluation of oral controlled release tablets ■

Consumer and Diversified Products

Rajarajeswari Sivalenka, Ph.D.
Lipo Chemicals Inc., Paterson, NJ, U.S.A.

The following report highlights some prominent patents that were filed or issued in the later half of 2008 in the area of controlled release applications for consumer and diversified products. It covers patents from flavor, fragrances, personal care, and agro-chemical industries.

Controlled Dissolution Cross-linked Protein Crystals (Altus Pharmaceuticals Inc., U.S.A.) 01768650/EP-B1

This patent describes cross-linked protein crystals for controlled release and methods to prepare them. The major challenge of protein technology is the instability of proteins under storage conditions that are not yet active and their performance under conditions of use. This invention presents an effective strategy to overcome this limitation. The cross-linked protein crystals are characterized by the ability to change from an insoluble and stable form to a soluble and active form upon a change in the environment surrounding them. The selective changes that contribute to activation of these crystals are changes in temperature, pH, chemical composition, concentration by dilution, oxidation-reduction potential of the solution, incident radiation, transition metal concentration, fluoride concentration, free-radical concentration, metal chelater concentration, shear force acting upon the crystals, and combinations. The major advantage of this system is that the property of the crystals is insoluble and stable under storage conditions and soluble and active under conditions of use. Such crystals are shown to be beneficial in cleaning agents, including detergents, therapeutic protein pharmaceutical compositions, vaccines, personal care compositions (including cosmetics), veterinary compositions, foods, feeds, diagnostics, and formulations for decontamination.

Product for the Targeted Release of Two-Compartment Active Substances (Frommer Lawrence & Haug, U.S.A.) 20080145388/US-A1

This patent describes a single-use product designed for the targeted release of detergents and/or cosmetic active substances. A cosmetic and/or cleaning agent active are contained in a compartment in-between the two layers—one permeable and the other impermeable to the active. The middle active compartment possesses an optional gas-releasing component. The active substance in the product dissolves within 5–15 min upon contact with water and emerges from the permeable layer and, thus, is released over a period of 15 min.

Encapsulation and Controlled Release of Biologically Active Ingredients with Enzymatically Degradable Microparticulate, Hyperbranched Polymers (Evonik Degussa GmbH, U.S.A.) 20080274149/US-A1

Formulations for controlled release of active ingredients by microencapsulation to skin and skin appendages are presented. Biologically active ingredients are encapsulated in a casing material that contains degradable, organic, hyperbranched polymers with ester groups. Skin enzymes can facilitate release of active materials from such cosmetic preparations by enzymatic degradation of the casing without affecting skin microflora. The process and conditions for preparation of such encapsulated microparticulate active ingredient formulations are also described. Such formulations are useful, especially in the case of sensitive, reactive, and unstable actives that can be processed thereby into more advantageous formulations. Thus, it effectively provides storage- and transport-stable means to deliver cosmetic actives. It is also particularly advantageous in polymeric systems where active ingredients have low solubility and, hence, an increased chance of dissociation from the polymer. Furthermore, the possibility of application to surface-treated textiles is also claimed, wherein the transfer of enzymes to the textile on close association with the skin may trigger the release of actives.

Controlled Release System (The Nottingham Trent University, U.S.A.) 2008110813/WO-A2

Application of electrical potential to allow release of the functional moiety from a molecule is described. The system here is composed of a linker and functional moiety attached via an electrochemically transformable link. The linker moiety is additionally attached to an electrically conductive surface by adsorption or a covalent linkage. An ester, ether, or tosyl group may serve as the electrochemically transformable link. The strategy is based on a two-component molecular lock, in which the agent to be released is chemically bound via the electrochemically transformable link. Upon the application of an appropriate oxidizing potential, the linker molecule undergoes a molecular rearrangement that results in the release of the hitherto bound component from the electrochemically transformable link. The amount released is dependent upon both the potential imposed and the duration over which it is applied. Methods of releasing the functional moiety and systems and devices comprising the molecule are described. This allows for a mechanism through which a chemical can be stored in an inactive, solid-state form, in contrast to the other current micro-engineered systems. This strategy is claimed to facilitate controlled release of biologically active agents, antidotes, fragrances, and detectable agents.

Particles for Delivery of Active Ingredients, Process of Making, and Compositions Thereof (Panacea Biotec Limited, India) 2008062429/WO-A2

This invention relates to micro- and nanoparticles for the delivery of active ingredients to topical and mucosal surfaces in mammals, including humans. They are preferably made by a sol-gel method and are used for application in the form of creams, gels, lotions, dry powders, sprays, foams, and other suitable forms.

Patent Watch continued on page 26

Patent Watch continued from page 25

The patent discloses compositions having particles comprising inorganic elements; one or more active ingredients; and optionally, a release rate-modulating agent suitable for the delivery of active ingredients to human and animal tissues. These particles are claimed to offer advantages such as ease of use, better retention at site of action, effective rates of absorption, controlled release over a desired period of time, dose reduction, better cosmetic and aesthetic compliance and non-irritating to skin when applied, and easy to apply to mucosal surfaces. When compared with the currently available systems, these particles are claimed to offer advantages such as having a higher surface area and, therefore, better applicability and retention at the site of action, leading to reduced frequency of application and the ability to form translucent to clear gel or non-gritty powder when dispersed. The process for making such micro- and nano-sized particles and delivery devices are also described. The delivery device is composed of a pressurized or non-pressurized dispensing device or applicator or mechanical device that delivers the composition to the topical or mucosal surfaces. In a preferred embodiment, the delivery device is capable of delivering a metered dose of the composition to topical or mucosal surfaces.

Encapsulation of Sensitive Components Using Pre-emulsification (General Mills, Inc., U.S.A.) 200807431986/US-B2

A method or continuous process for producing controlled release, discrete solid particles/pellets is described. These stabilized emulsions are claimed to be shelf-stable, discrete, solid particles that contain an encapsulated and/or embedded component such as a heat-sensitive or readily oxidizable pharmaceutically, biologically, or nutritionally active component, such as omega-3 fatty acids. The process uses homogenization to stabilize the emulsion, followed by spray-drying to reduce the emulsion to produce a powder or by mixing the emulsion with a matrix material to encapsulate the film-coated oil droplets within the matrix material and applying a protective coating on the film-coated oil droplets to obtain pellets.

Chemically Cross-linked Elastomeric Microcapsules – 20080175918/US-A1

The patent describes a technology for stably encapsulating oral care, skin care, scented, and flavoring agents for cued release. It includes formulations that achieve reservoir-type extended and sustained delivery of therapeutic agents. It also includes methods for manufacturing such chemically cross-linked elastomeric microcapsules. The technology allows encapsulation of active agents into a wide range of formulations without altering their physio-chemical properties. Single or multiple mechanical or thermo-mechanical cues induce delivery of the encapsulated agent. This invention also claims to provide a novel mechanism for controlling the thickness of polymer shell, elasticity of capsule walls, and post-processing techniques to manipulate the encapsulant volume and media osmolarity, while maintaining the uniformity of the final product without altering the scalability of the manufacturing process.

Sensory Feedback-based Method for Determining the Bioavailability of Orally Administered Dietary Supplements (Multi Formulations Ltd., Canada) 2008138099/WO-A1

This patent describes a method to determine the rate of bioavailability of dietary active ingredients supplemented orally. This is advantageous for maximizing the benefits of supplements such as herbs, vitamins, amino acids, or minerals. The method involves administration of a substance that can provide transient sensory feedback indicative of the bioavailability of the nutritional supplement that is administered simultaneously. As an allowance for the difference in absorption rates of multiple supplements taken in conjunction, more than one sensory component may be included in the formula. Use of niacin and its derivatives, xanthinol, and *Trichilia catigua* in dietary supplements is exemplified here to provide such a sensory perception to individuals upon consumption. Some of the sensory attributes indicative of bioavailability described here are sensations such as tingling on head, face or arms, warm feeling of the body, increased alertness, energy, and focus.

Melatonin-based Composition for Improved Sleep (Iomedix Development International Srl, Barbados) 200807455864/US-B2

This patent discloses the composition and a method to deliver upon oral administration, specific active ingredients targeted to improve sleep and relaxation in individuals. The composition comprises effective amounts of melatonin, lavender flower extract, and ferula extract and is provided in a multi-compartmentalized solid capsule dosage form to provide controlled and sustained release. Three different dosages of melatonin are proposed for effectiveness in terms of either quick-release, slow-release, or unmodified format for higher bioavailability. Lavender extract is suggested here to induce relaxation and ferula extract to reduce anxiety. In addition, other herbal extracts such as Nyctanthus, passion fruit, etc., as well as lacticum (a milk peptide) and the amino acid theanine are also contained in the composition for specific effects in controlling sleep.

Microencapsulated Heat Delivery Vehicles (Kimberly-Clark Worldwide, Inc., U.S.A.) 200807442439/US-B2

This patent describes microencapsulated delivery vehicles with active ingredients that can impart heat upon activation. Such vehicles are introduced into wet wipes, for example, which upon use and activation result in release of actives that generate warmth. The sizes of the microcapsules are made in a range that cannot be felt when incorporated into personal care products, thus preserving the aesthetics. The process for making these vehicles and active ingredients for incorporation are disclosed. The method is directed to manufacture of self-warming wipes. The heating agent encapsulated in the core composition, releases heat upon contact with water. Compounds with exothermic heat of hydration or solution, such as calcium chloride, magnesium chloride, zeolites, etc., are cited for this purpose. Such a system is advantageous over other currently available electric devices for

warming wipes, in that it helps sustain the moisture content of wipes, preventing dry out, and also precludes wipe discoloration due to heating. The patent also further claims use of these vehicles for encapsulating cooling agents or biocides.

Hydrogels for the Controlled Release of Bioactive Materials – 20080057005/US-A1

This invention deals with use of hydrogels as delivery systems for the controlled release of flavors, fragrances, pharmaceuticals, or agrochemicals, as well as other consumer products. The composition described consists of guanosine hydrazide derivatives in the presence of cations and water-based liquid. The water-based component of the hydrogen is maintained between pH 5 and 8. Active components are either held covalently or non-covalently inside the gel matrix. Additional components like antioxidants, UV inhibitors, oil-soluble dyes, solvents, surfactants, and bittering ingredients can be incorporated into these gels. Examples of such ingredients are provided. The hydrogel assemblies interact with various active aldehydes or ketones and influence their release into the surrounding environment. The release of actives depends on the strength of the interactions between the gel components and actives and diffusion of the actives out of the hydrogel. They are advantageous as carriers of active material that are susceptible to degradation and, thus, protects them in the gel matrix and releases them into the environment in a controlled manner.

Pesticide-Containing Resin Compositions Controlled in Dissolution, Process for Production Thereof, and Pesticide Preparations (Nippon Soda Co., Ltd., Japan) 01982590/EP-A1

Methods for production and formulations for a resin composition that can facilitate controlled release of agrochemical active ingredients are described. These compositions are claimed to overcome the challenges of uneven delivery upon release of agrochemicals in most prior applications. Briefly, the resin composition is obtained by forming a compatible matrix using the agrochemical active, a resin, and a fatty acid metal salt that facilitates the controlled release.

Method of Microencapsulating an Agricultural Active Having a High Melting Point and Uses for Such Materials (Monsanto Technology, L.L.C., U.S.A.) 20080242548/ US-A1

This patent describes a novel method for producing microcapsules for controlled release of agricultural active material with a high melting point. The active material is maintained below its melting point by microencapsulation until release. Briefly, the active is contained in an organic liquid composition free from any aromatic solvents. This is then formed into small droplets. The non–water-soluble shell of microcapsules releases the agricultural active at a preselected controlled rate upon exposure to environmental conditions. The patent also describes various controlled release forms of agricultural active.

Controlled Release of Active Agents Utilizing Repeat Sequence Protein Polymers (Dow Corning, Corporation; Genencor International, Inc., U.S.A.) 200807456147/ US-B1

This patent describes the use of repeat sequence protein polymers in matrices, gels, hydrogels, films, emulsions, or microparticles. The repeat sequence protein polymers are derived from naturally occurring repeat sequences such as those found in silk, collagen, or elastin. They are useful for incorporating active agents into personal care product compositions. The mechanisms proposed for these sequences are either by forming complexes with active agents and, thus, forming the rate-controlling polymer or by serving as components of microcapsulate active agents. Advantages and conditions for use of such repeat sequences in copolymers are described. ■

In the News

Compiled by Steven Giannos
Industrial Editor

MARCH 2009

Positive Results from Neurotech's NT-501 Phase II Dry AMD (Geographic Atrophy) Study Demonstrate Proof of Concept, Validate Company's ECT Technology, and Support Initiation of Pivotal Studies

Business Wire: March 26, 2009 – LINCOLN, R.I. – Neurotech Pharmaceuticals, Inc. has announced that the company's lead product candidate, NT-501, substantially slowed the loss of vision in a Phase II clinical trial in subjects with dry age-related macular degeneration (AMD) involving geographic atrophy (GA). GA is a condition that destroys sharp central vision, often resulting in serious vision loss to one or both eyes. There are currently no approved treatments for dry AMD. In the study, the high dose of NT-501 stabilized best corrected visual acuity (BCVA) at 12 months, with 96.3% ($P = 0.078$) of treated patients losing fewer than three lines of vision, or 15 letters, versus 75% of the patients in the sham-treatment group.

NT-501 is an intraocular implant that consists of human cells that have been genetically modified to secrete ciliary neurotrophic factor (CNTF). CNTF is delivered directly to the back of the eye in a controlled, continuous basis by means of the company's proprietary encapsulated cell technology (ECT) platform, thereby bypassing the blood–retinal barrier and overcoming a major obstacle in the treatment of retinal disease.

The Phase II study was a multi-centered, randomized, double-masked, sham-controlled study of 51 subjects with GA. Patients received either a high or low dose of NT-501 implant or a sham treatment in one eye only and were assessed for changes in BCVA. BCVA was measured by an electronic visual acuity tester (EVA) using the early treatment diabetic retinopathy study (ETDRS) protocol. Patients were also evaluated for an increase in BCVA. No increase was observed, likely due to existing photoreceptor damage. There were no NT-501–associated serious adverse events reported, and both NT-501 and the surgical procedure were well tolerated.

Five devices from this trial have been explanted 12 months following implantation, and all were found to have uniformly healthy, viable cells that continued to produce therapeutic levels of CNTF. This is consistent with data from multiple trials of NT-501 in which, to date, 23 devices have been explanted between 12 and 18 months following implantation, and all devices were found to contain healthy, viable CNTF-producing cells.

HemCon Medical Technologies, Inc. Announces Improved Results from Live Nail Infection Study

Business Wire: March 25, 2009 – PORTLAND, Oreg. – HemCon has announced the results from an independent study investigating the time required to successfully treat fungal-infected human nails, a leading cause of onychomycosis, the most common type of fungal nail infection. The studies were conducted as part of HemCon's continued program of development for a formulation based on its newest proprietary Mycosinate™ platform technology. The onychomycosis treatment, Mycosinate™ (formerly known as compound A31S), is available for commercial license and provides a controlled release, broad-spectrum antimicrobial agent to fight infection.

Independent testing of Mycosinate™ for the treatment of onychomycosis was performed using fungal-infected human nails under conditions that simulated the clinical situation. This system tested the formulation's ability to penetrate the nail and kill the *T. rubrum* fungal infection on human nails over a period of time. Results released in February indicated complete kill of the fungal infection in 14 days. The latest study results indicate that the cell viability of the infecting organism (*T. rubrum*) was reduced to 52% on day 3 of treatment and further reduced to 5.3% on day 7 of treatment with the active Mycosinate™ formulation. A complete kill of the infection was observed at day 14 of treatment. These results contrast favorably with publicly available results for commercially marketed terbinafine-, amorolfine-, and ciclopirox-based formulations.

Fungal nail infections affect tens of millions of people worldwide, and the market size for products for its treatment is estimated at approx. US$4 billion. It is believed that 6–8% of all adults will acquire a fungal nail infection, and onychomycosis accounts for nearly 50% of all nail disorders.

"HemCon's fourth study in live human nail infection further validates the superior abilities of Mycosinate™, compared to solutions on the market, to safely and effectively treat the millions of people afflicted with fungal nail infections," said John W. Morgan, CEO of HemCon. "This innovative platform to treat nail infections provides us with a promising technology in a robust and growing market."

FluGen Secures Exclusive Rights to Novel Vaccine-Delivery Technology

Business Wire: March 24, 2009 – MADISON, Wis. – FluGen Inc., an emerging leader in the development, production, and delivery of influenza vaccines and related products, has announced that it has secured exclusive rights to a novel, patent-protected vaccine-delivery technology being commercialized by Ratio Inc. (Madison, WI). Terms of the license agreement have not been disclosed.

The easy-to-use, disposable micro-device, roughly the size of a poker chip, painlessly delivers seasonal and pandemic influenza

In the News continued on page 30

In the News continued from page 29

vaccines. At the press of a button, a miniature fluidic pump distributes the vaccine to a set of microneedles. These microneedles deliver the vaccine intradermally, or into the skin, but not through it and into the muscle, like the traditional needle and syringe do.

The micro-device holds the potential to significantly increase vaccine effectiveness. Seasonal influenza vaccines have shown as little as 20–40% efficacy in some patients. Intradermal delivery like that enabled by the micro-device has been shown to increase vaccine efficacy, particularly among those 65 years and older, for whom the disease is the most deadly. The vaccine-delivery technology also may improve vaccination rates because of the pain-free, easy-to-use delivery it affords. More than a third of those 65 years and older do not receive vaccinations each year, despite higher influenza mortality rates due to age-related immune deficiencies. The vaccination rate is even lower in younger populations.

FluGen this year will begin pre-clinical testing of the micro-device with the company's cell-based trivalent influenza vaccines (TIVs). The company anticipates submitting an investigational new drug (IND) application for its vaccine-loaded micro-device to the U.S. Food and Drug Administration during the second half of 2010 and hopes to enter a Phase I clinical trial upon its approval, by the end of 2010.

"This exciting vaccine-delivery technology from Ratio is an important expansion of FluGen's product pipeline," said Paul V. Radspinner, president and chief executive of FluGen. "It will allow the company to offer the $6-billion influenza vaccine market not only superior vaccines, but an easy-to-use, painless delivery technology that increases vaccine effectiveness. FluGen looks forward to advancing this valuable product through our pipeline with one or more TIVs."

Enzon Reveals New LNA Targets

Business Wire: March 19, 2009 – BRIDGEWATER, N.J. – Enzon Pharmaceuticals, Inc. (Nasdaq: ENZN) has announced new novel locked nucleic acid (LNA) programs directed against the androgen receptor (AR) and phosphoinositide 3-kinase (PI3K/Akt). These targets are linked to a broad spectrum of cancers. Enzon has licensed eight novel LNA targets from Santaris Pharma A/S. The abstracts related to these new targets and other Enzon programs are available at www.aacr.org. The data will be presented at the upcoming 2009 Annual Meeting of the American Association for Cancer Research (AACR).

Dicerna Pharmaceuticals Secures Exclusive Worldwide Right to Sublicense the Dicer Substrate Technology™ RNAi Platform

Business Wire: March 18, 2009 – WATERTOWN, Mass. – Dicerna Pharmaceuticals, Inc. (www.dicerna.com), a second-generation RNA interference company developing novel therapeutics utilizing its proprietary Dicer Substrate Technology™, has announced that the company has secured the exclusive, worldwide right to grant sublicenses to the Dicer substrate RNAi (DsiRNA) intellectual property estate in-licensed by Dicerna. This technology was invented by Dicerna's scientific co-founders John Rossi, Ph.D., professor in the Division of Molecular Biology and dean of the Graduate School of Biological Sciences at City of Hope's Beckman Research Institute, and Mark Behlke, M.D., Ph.D., vice president of molecular genetics and biophysics and chief scientific officer at Integrated DNA Technologies.

"We are very pleased to announce that Dicerna has obtained the sole, exclusive right to grant sublicenses to the full portfolio of Dicer Substrate Technology intellectual property, which simplifies the previous license structure for our RNAi technology platform. Going forward, Dicerna is the only company that can grant sublicenses to DsiRNA," said James Jenson, Ph.D., chief executive officer and co-founder, Dicerna Pharmaceuticals. "Dicer Substrate Technology represents a second generation of gene silencing that can generate drug candidates with greater potency and longer duration of action than earlier RNAi approaches, because of the distinct way in which it engages this important biological pathway. The exclusive right to sublicense the full portfolio of Dicer Substrate Technology puts us in an even stronger position to leverage the development of RNAi-based therapeutics and advance our business strategy."

Dicerna's pipeline of RNAi-targeted drugs and delivery systems is focused primarily in the therapeutic areas of oncology and metabolic diseases. In addition to these internal focus areas, Dicerna expects to broadly utilize its Dicer Substrate Technology™ in several other therapeutic areas, such as inflammation, immunology, cardiovascular diseases, and others, through collaborations with pharmaceutical and biotechnology companies.

BioDelivery Sciences' Second Product Using BEMA™ Drug Delivery Technology to Enter Phase II

Business Wire: March 18, 2009 – BioDelivery Sciences International, Inc. (Nasdaq: BDSI) has announced its preliminary results from a Phase I study assessing two new formulations of the opioid analgesic buprenorphine, utilizing the company's proprietary BEMA™ drug delivery technology. The study was performed to select the optimal formulation for Phase II clinical development of the product candidate, known as BEMA™ buprenorphine.

Fourteen healthy volunteers participated in this randomized, blinded, cross-over study that compared two formulations of BEMA™ buprenorphine with intravenous buprenorphine and placebo. Following administration of both BEMA™ formulations, buprenorphine plasma concentrations were measurable within 15 min and accompanied by changes in pupillometry, a standard measure of opioid pharmacodynamic effect. Notably, this effect was maintained over the 8-hr duration of the study without evidence of significant decline. Local application of the BEMA™ films in the mouth were well tolerated. Additional data, including safety and tolerability, are forthcoming.

"We are very pleased with the pharmacokinetic and pharmacodynamic profile of BEMA Buprenorphine as

demonstrated in this study," said David Blum, MD, vice president, clinical development and medical affairs at BDSI. "This study demonstrates that the new BEMA formulations provide rapid rise to peak plasma concentrations and high bioavailability, or absorption, of buprenorphine. The time to and extent of the maximum plasma concentrations exceeded our expectations for these formulations compared to the previously tested formulation. Further, the pharmacodynamic results indicate that once or twice daily administration of BEMA Buprenorphine may be effective for the treatment of a variety of acute and chronic pain conditions." Dr. Andrew Finn, BDSI's executive vice president, product development, added, "There is a tremendous opportunity for a product such as BEMA Buprenorphine with a long duration of action and less potential for abuse and addiction compared to Schedule II opioids such as morphine and oxycodone. The results of our efforts to enhance the original formulation have now provided us with a product that will be progressed into Phase 2 clinical development during the second quarter of this year, and assuming positive results, will be followed by the initiation of Phase 3 in the first half of 2010."

The availability of a transmucosal formulation of buprenorphine could provide a new treatment option for acute and chronic pain conditions. Based on market research, BDSI believes BEMA Buprenorphine may have the potential to achieve peak annual sales of over $500 million, making it a desirable partnering opportunity.

BDSI's initial product candidate utilizing the BEMA™ drug delivery technology, ONSOLIS™ (fentanyl buccal-soluble film; formerly BEMA™ fentanyl), is currently under review by the FDA for the potential treatment of breakthrough pain in opioid-tolerant patients with cancer. The company anticipates an FDA decision on the new drug application (NDA) for ONSOLIS™ during the first half of 2009.

BioSante Pharmaceuticals Reports LibiGel® Status and Financial Results for 2008

Business Wire: March 16, 2009 – LINCOLNSHIRE, Ill. – BioSante Pharmaceuticals, Inc. (NASDAQ: BPAX) has announced the status of LibiGel® in development for the treatment of female sexual dysfunction and financial results for the year ended December 31, 2008.

"BioSante had an excellent year in 2008. Our new product development was led by the initiation of three LibiGel Phase III clinical trials," said Stephen M. Simes, BioSante's president and chief executive officer. "These clinical trials continue to enroll subjects and make progress. LibiGel is BioSante's transdermal testosterone gel in late-stage development for the treatment of female sexual dysfunction (FSD) in menopausal women. LibiGel's development continues under a Special Protocol Assessment (SPA). The SPA affirms that BioSante's clinical trial design, endpoints, sample size, planned conduct and statistical analyses are acceptable to support regulatory approval. BioSante's objective continues to be to submit a new drug application (NDA) for LibiGel by the end of 2010."

Noven Confirms Shire's Withdrawal of European Marketing Application for Daytrana®

Business Wire: March 16, 2009 – MIAMI, Fla. – Noven Pharmaceuticals, Inc. (NASDAQ: NOVN) has confirmed that Shire plc, the global licensee of Daytrana® (methylphenidate transdermal system), has withdrawn its European marketing authorization application (MAA) for Daytrana® for the treatment of attention deficit hyperactivity disorder (ADHD). In connection with this announcement, Shire confirmed its commitment to Daytrana® in the United States, where the product has been approved and prescribed as a pediatric treatment for ADHD since 2006.

Shire stated that its decision to withdraw the MAA was based on the fact that European regulatory authorities had requested an additional clinical study for Daytrana® in a European patient population and that Shire planned to enter the European ADHD market through the previously announced pending acquisition of an oral methylphenidate product that is already approved in Europe.

"Although we are disappointed with Shire's decision not to pursue European approval, our 2009 financial guidance – provided on March 5, 2009 – did not include any revenues or other financial contribution from European sales of Daytrana," said Michael Price, Noven's vice president and chief financial officer. "Accordingly, our 2009 net revenue guidance range of $110 million to $115 million remains unchanged and unaffected."

Noven Pharmaceuticals, Inc. is a specialty pharmaceutical company engaged in the research, development, manufacturing, marketing, and sale of prescription pharmaceutical products. Noven's business and operations are focused in three principal areas—transdermal drug delivery, the Novogyne joint venture, and Noven Therapeutics, Noven's specialty pharmaceutical unit. Noven is committed to developing and offering products and technologies that meaningfully benefit patients, its customers, and its industry partners. For more information, visit www.noven.com.

AGI Announces Positive Results in a Phase II Proof-of-Concept Study of Transdermal AGI-004 in Chemotherapy-Induced Diarrhea

RNS Market News: March 12, 2009 – DUBLIN, Ireland – AGI Therapeutics plc (AGI) (AIM, IEX: AGI), a specialty pharmaceutical development company focused on gastrointestinal drug products, has announced positive results in a Phase II proof-of-concept study of AGI-004 in the control of chemotherapy-induced diarrhea (CID). AGI-004 is a once-daily, controlled release transdermal patch containing the nicotinic antagonist mecamylamine. The study was conducted in 64 patients across seven sites in Europe and evaluated two doses of AGI-004 compared with placebo.

The results showed a statistically significant difference in the primary endpoint of reduced incidence of patient-recorded

In the News continued on page 32

In the News continued from page 31

diarrhea (response defined as <4 bowel movements per day). This was observed at the higher of two doses of AGI-004 compared with placebo. The robust response for the higher dose of AGI-004 was supported further by a statistically significant difference in the secondary endpoint of patient-recorded severity of diarrhea, while positive trends were observed in the other secondary measurement of reduction in the use of rescue anti-diarrheal medications. Non-significant benefit in the primary endpoint was also observed with the lower dose, and when diarrhea was rated by the physician using the National Cancer Institute (NCI) grading system, both doses demonstrated positive improvements. Similarly, positive trends were also observed for the higher dose in the co-primary endpoint of reduced number of bowel movements per day.

While some benefit was seen with the lower dose in treating individual symptoms, the overall results are consistent with a dose response effect. In addition to the full cycle results described above, an analysis of acute (first day of chemotherapy) data confirmed the robust control of diarrhea at the higher dose. AGI-004 treatment was well tolerated across both doses, and there were no drug-related serious adverse events.

Commenting on the results of the study, Dr. John Devane, CEO, said "We are pleased with the outcome of this study which we believe supports the continued development of AGI-004 as a novel anti-diarrhoeal agent. CID is a common and debilitating side effect which affects many patients undergoing chemotherapy. Although designed as an exploratory study, we observed a strong signal of efficacy for AGI-004 across multiple measurements of diarrhoea, in particular with the higher dose used in the study. The development of AGI-004 in a convenient transdermal patch, which can reduce the occurrence of diarrhoea in chemotherapy patients, offers a significant therapeutic advantage over current standard of care."

DSM Obtains Exclusive Worldwide License for Innovative Drug Delivery Technology

Marketwire: March 11, 2009 – HEERLEN, The Netherlands – Royal DSM N.V., the global life sciences and materials sciences company headquartered in the Netherlands, has announced that DSM Biomedical has obtained an exclusive worldwide license for a unique drug and biologics delivery system developed by MediVas LLC. Integrated into DSM's Trancerta® drug delivery platform, this will open up a broad range of opportunities for next generation drug delivery. DSM's activities in this field are an illustration of the way DSM is leveraging its competences in materials sciences into life sciences applications.

MediVas' technology for the delivery of biologics and drugs is based on a next generation set of polymers exclusively licensed from Cornell University. Generated from research both at Cornell and MediVas, the company has an IP portfolio containing over 60 issued or pending patents. The polymers are biodegradable, biocompatible, and bioabsorbable. Furthermore, they are non-inflammatory and allow greater control over the rate and duration of release of their therapeutic payload.

The technology can be used with a diverse group of drug candidates, from small-molecule drugs to large molecules like proteins, peptides, and nucleic acids, thus expanding the possible application areas of DSM's Trancerta® platform. The license DSM obtained applies to the development of drug delivery systems aimed at treating ophthalmic, (cardio) vascular, and musculoskeletal diseases and providing general pain relief.

"Through this deal we bring in the first fully developed biodegradable polymer into DSM's Biomedical portfolio, which significantly enhances our materials competences. This will help us realize our ambition to build a portfolio of drug delivery technologies tailored [to] the specific needs of the health industry. MediVas' technology is already proven in two clinical studies which should allow us to accelerate the commercialization of our drug delivery technologies in partnerships with Pharma, Biotech and Medical Device companies," said Steve Hartig, president of DSM Biomedical. "The license with DSM is an ideal strategic fit which will accelerate the efforts of MediVas to commercialize our novel biopolymer technology. DSM's extensive materials expertise and broad industrial capabilities provide MediVas with a valuable partner in advancing our respective projects through the clinic. We look forward to working closely with DSM in applying our technology to meet the rapidly increasing demand for improved drug and biologic delivery systems," commented Kenneth Carpenter, chair and CEO of MediVas.

Through its Trancerta® drug delivery system, DSM is now able to offer pharma, biotech, and medical device companies a new opportunity to increase the commercial potential of their R&D investments by extending the commercial lifetime of patented drugs and, through more targeted delivery, improving the chances of pipeline products to successfully pass clinical trials.

Vyteris Initiates Phase II Clinical Trial of Infertility Treatment Using Smart Patch Technology

Marketwire: March 10, 2009 – FAIR LAWN, N.J. – Vyteris, Inc. (OTCBB: VYTR), manufacturer of the first FDA-approved active transdermal drug delivery system and a leader in active transdermal drug delivery technology, has announced the initiation of a Phase II clinical trial sponsored by its development partner, Ferring Pharmaceuticals Inc. The trial evaluates Vyteris' smart patch technology for the safety and efficacy of pulsatile delivery of a peptide hormone for the treatment of infertility in women.

"The initiation of this Phase II clinical trial is an important milestone for Vyteris in developing an effective peptide transdermal delivery system. We look forward to continuing our strong partnership with Ferring to achieve success with this project for the benefit of infertility patients," said Dr. Haro Hartounian, chief executive officer of Vyteris. "Ferring's confidence in moving forward with this trial further demonstrates the commercial potential of our smart patch technology to deliver peptides and other biopharmaceuticals using Vyteris' transdermal delivery system."

"This Phase II clinical trial will provide guidance on the roles that the smart patch technology may play in treating women

with infertility problems," said Wayne Anderson, chief executive officer of Ferring. "The non-invasive nature of this product and increased patient comfort will create a new standard of care for infertility treatment."

The trial will be a multi-center clinical trial conducted at approx. 35 centers throughout the United States and will enroll approx. 500 female patients between the ages of 18 and 38 years with anovulatory/oligoovulatory infertility. In this clinical trial, the safety and tolerability of Vyteris' transdermal delivery system will be evaluated over the trial period. The trial is currently enrolling subjects and is expected to be fully enrolled by July 2009.

Alnylam and Collaborators at MIT Publish New *In Vivo* Research on Systemic Delivery of RNAi Therapeutics

Business Wire: March 5, 2009 – CAMBRIDGE, Mass. – Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), a leading RNAi therapeutics company, has announced the publication of new data in the journal *Molecular Therapy* by Alnylam scientists and collaborators from the David H. Koch Institute for Integrative Cancer Research at the Massachusetts Institute of Technology (MIT). The new data describe the further development of lipidoid formulations for the systemic delivery of small interfering RNAs (siRNAs), the molecules that mediate RNAi.

"We are very encouraged with the progress we have made with systemic delivery of siRNAs since the continued advancements we and our collaborators are making with this technology is enabling the ability to address the broadest potential of RNAi therapeutics," said Akin Akinc, Ph.D., associate director, research at Alnylam. "Formulations based on lipid and lipid-like materials called 'lipidoids' show great promise for the systemic delivery of RNAi therapeutics. These new findings further expand our understanding of lipidoids as part of our ongoing efforts to optimize these formulations to maximize efficacy in vivo."

Lipidoids are a new class of lipid-based molecules that are used to form novel nanoparticle formulations for systemic delivery of RNAi therapeutics. A previous study by Alnylam scientists in collaboration with scientists from MIT (Akinc et al., Nature Biotechnology, 2008;26:561-569), showed successful delivery of siRNAs encapsulated in lipidoid formulations when administered in multiple animal species, including mice, rats, and non-human primates.

Data published from this new study (Akinc et al., Molecular Therapy, advance online publication, March 3, 2009;doi:10.1038/mt.2009.36) extends the work from the previous study by

- Identifying key parameters affecting the pharmacodynamics of this type of formulation, including increasing the anchor length of synthesized PEG lipids, maximizing siRNA loading, and reducing particle size to more efficiently access hepatocytes.
- Demonstrating that lipidoid formulations achieve delivery of >90% of the administered siRNA dose to the liver and maintain robust *in vivo* activity following repeat administration over a period of several months and indicating no evidence of neutralizing antigenicity or tachyphylaxis.
- Characterizing the long-term stability of the formulation.

Lipidoid formulations represent one of several approaches Alnylam is pursuing for systemic delivery of RNAi therapeutics. Additional approaches include other lipid nanoparticle formulations and siRNA conjugation strategies. Recently, Alnylam received clearance from the U.S. Food and Drug Administration (FDA) for its investigational new drug (IND) application to initiate a Phase I study for its ALN-VSP liver cancer program, which it expects to begin enrolling in the first half of 2009. ALN-VSP employs a lipid nanoparticle formulation known as "SNALP" developed in collaboration with Tekmira Pharmaceuticals Corporation.

Promising New Intranasal Treatment for Alzheimer's Disease Licensed for Clinical Trial

Business Wire: March 4, 2009 – BLOOMINGTON, Minn. – A Canadian biotechnology company, Sanomune Inc., has licensed a new treatment method that helps drugs to reach the brain unlike any other treatment for neurological diseases. The treatment method, developed by HealthPartners Research Foundation, is a new therapeutic technology offering hope to the 5.2 million people in the United States living with Alzheimer's and other neurological diseases.

The intranasal method was developed by William H. Frey II, Ph.D., senior director of HealthPartners Research Foundation's Alzheimer's Research Center, and colleagues. It allows medication to bypass the protective blood–brain barrier and enter the brain directly. Dr. Frey has developed a way to bypass the barrier for neurological conditions using intranasal delivery of deferoximine or SAN-121. SAN-121 has previously been shown to reduce cognitive decline in Alzheimer's patients by 50% when administered in twice daily injections. However, systemic delivery has unwanted and negative side effects, including a drop in blood pressure.

"With our non-invasive delivery method, the drug bypasses the blood–brain barrier and is rapidly delivered to the brain while significantly reducing unwanted side effects," said Dr. Frey. "Because it is able to reach key areas involved in both Alzheimer's disease and Parkinson's disease, we are very optimistic about its potential as a treatment for these disorders."

SAN-121 is licensed through Sanomune Inc., a private biotech start-up company focused on neurological and autoimmune diseases. One in ten people over the age of 65 and half of those over 85 have Alzheimer's disease in the United States. "Intranasal delivery of SAN-121 and other therapeutics can hopefully improve the treatment of this disease," Frey said. Product licensing with Sanomune Inc. was the last step before proceeding with clinical trials, which could begin in the next year.

In the News continued on page 34

In the News continued from page 33

EyeGate Pharma Completes Phase II Clinical Trial of EGP-437 for Treating Dry Eye Syndrome

Marketwire: March 3, 2009 – WALTHAM, Mass. – EyeGate Pharma, the leader in non-invasive ocular drug delivery, has announced that it has fully enrolled and completed all follow-up visits for all patients participating in its Phase II safety and efficacy study of EGP-437 (a combination drug/device) for treating dry eye syndrome. The results of this study are expected in the second quarter of 2009. For the dry eye clinical trial, EyeGate worked with Ora, Inc., a leading global clinical research and development organization, located in Andover, MA. Over the past 30 years, Ora has played a central role in the development and FDA approval of more than 30 ophthalmic products.

This Phase II single-center, randomized, double-masked, placebo-controlled study of 89 patients evaluated the safety and efficacy of a corticosteroid solution administered by the EyeGate® II delivery system (at two dose levels) twice over a 3-week period. Ora's proprietary Controlled Adverse Environment (CAE) clinical model was used for this study. EGP-437 is also being evaluated in a Phase I/II clinical study of severe uveitis. These landmark clinical trials with EGP-437 represent the first U.S. studies under an IND to employ ocular iontophoresis technology, a proprietary electrochemical drug delivery system, to administer an active compound into the eye.

"There is a tremendous need for safe and long-lasting treatment alternatives for the growing number of people suffering from ocular diseases, such as Dry Eye Syndrome and uveitis," commented Stephen From, president and chief executive officer of EyeGate Pharma. "We look forward to reporting the results of these studies in the near future."

FEBRUARY 2009

PDS Biotechnology Finalizes Commercial Licensing Agreement with Merck Eprova AG to Utilize Merck Eprova's Enantiomers of DOTAP Chloride in Immunotherapies

February 24, 2009 – CINCINNATI, Ohio – PDS Biotechnology Corporation has announced that the company has obtained an exclusive license from Merck Eprova AG to utilize Merck Eprova's proprietary chiral lipid DOTAP chloride in Versamune™–HPV and other products in development based on the Versamune™ technology. The use of enantiomerically pure DOTAP chloride shows enhanced adjuvant activity compared with the racemate. Merck Eprova AG will provide enantiomerically pure DOTAP chloride manufactured under cGMP for use in clinical and commercial drug products developed with PDS Biotechnology's Versamune™ nanoparticle technology. PDS Biotechnology will own the intellectual property rights to products incorporating the chiral DOTAP lipids for immunotherapeutic applications.

Versamune™–HPV is an immunotherapy drug that has demonstrated significant promise in curing HPV infection and HPV-related cancer in preclinical animal and human model studies. Cancers caused by infection with the human papilloma virus (HPV) include cervical, head and neck, and anal cancers. No cures exist for these cancers. Based on promising *in vivo* and *in vitro* efficacy data, PDS Biotechnology has been awarded grants by the U.S. National Institutes of Health and National Cancer Institute to develop Versamune™–HPV and Versamune™–Melanoma. Versamune™–Melanoma is being developed to treat melanoma, which is the most aggressive form of skin cancer.

PDS Biotechnology's Versamune™ nanotechnology facilitates the uptake of disease-associated protein and peptide antigens by the antigen-presenting cells of the immune system. Simultaneously it acts as a strong immune system activator (adjuvant) without the inflammatory side effects induced by current adjuvants. The result is simple, safe, and cost-effective nanotechnology-based drugs and vaccines that induce effective eradication of the specific cells infected with or expressing the particular protein formulated with Versamune™.

PDS Biotechnology Corporation (www.pdsbiotech.com) is an Indiana-based biotechnology company applying the company's proprietary Versamune™ nanotechnology drug platform technology to the development of safe and potent immunotherapies to prevent and treat cancer and diseases caused by infectious agents. Merck Eprova AG (www.merckeprova.com), located in Schaffhausen, Switzerland, is a wholly owned subsidiary of Merck KgaA, located in Darmstadt, Germany. Merck Eprova AG specializes in the development and production of cGMP-grade, highly purified and characterized drug delivery compounds such as cationic lipids, PEGs, PEG-lipids, and phospholipids. In addition, Merck Eprova AG is a center of excellence for reduced folates in the pharmaceutical and nutritional fields and a leading supplier of reduced folates.

MDRNA Successfully Silences Gene Targets in Animal Models Using Novel UsiRNA Constructs

Marketwire: February 23, 2009 – BOTHELL, Wash. – MDRNA, Inc. (NASDAQ: MRNA) has announced positive *in vivo* efficacy data on its proprietary UsiRNA constructs that demonstrates a dose response, resulting in an up to 90% knockdown of ApoB message in a rodent model. The data were presented by Michael V. Templin, Ph.D., vice president, discovery research and pharmaceutical development of MDRNA, at the inaugural Informa Life Sciences TIDES Oligonucleotide and Peptide® Research, Technology and Product Development Conference in Tokyo, Japan.

"Our UsiRNA constructs offer a novel and proprietary means of providing highly potent siRNAs while increasing specificity," stated Barry Polisky, Ph.D., chief scientific officer of MDRNA. "UsiRNAs were highly active in the mouse ApoB model for both message inhibition and serum cholesterol reduction. In these cases, UsiRNAs were fully compatible with RNAi machinery yet showed a substantial decrease in cytokine response. We are encouraged by these significant results and believe we have a unique siRNA construct to silence genes while minimizing potential side effects."

UsiRNAs are duplex siRNAs that are modified with non-nucleotide acyclic monomers, termed unlocked nucleobase analogs (UNA), in which the bond between two adjacent carbon atoms of ribose is removed. UsiRNAs are fully recognized by the RNAi machinery and provide for potent RNAi activity. Placement of UNA within UsiRNA minimizes the potential for off-target effects by the guide strand, as well as undesired activity of the passenger strand. Further, the change in sugar structure renders this unlocked nucleobase analog conformationally flexible. The flexibility of the monomer escapes the surveillance mechanisms associated with cytokine induction, as well as providing protection from nuclease degradation.

MDRNA also reported new information on its DiLA2 platform delivery technology: "We are pleased to announce that our proprietary DiLA2 Platform achieved knockdown of two additional genes in liver tissue, DGAT2 and PCSK9, that are potentially important therapeutic targets, and the Platform continues to demonstrate safe and effective delivery following repeat systemic dosing of up to 9 mg/kg of siRNA formulations in mice," added Dr. Polisky. "The acute and repeat dose tolerability data of the DiLA2 Platform are promising. Repeat dosing on an every-third-day schedule for two weeks further indicates that DiLA2 liposomes are well tolerated. Our ability to deliver siRNAs to hepatocytes while achieving knockdown of multiple gene targets affirms our belief that the DiLA2 Platform represents a significant advancement in the development of a novel formulation for improved siRNA delivery."

"Our proprietary and novel UsiRNA constructs—highly active siRNAs which minimize off-target activity—represent a potential major step forward in the development of RNAi-based therapeutics," stated J. Michael French, president and chief executive officer of MDRNA. "Further, our DiLA2 Platform continues to demonstrate its versatility in its ability to safely and efficiently deliver siRNAs against multiple gene targets and effectively silence those genes. The results reported…represent a further demonstration of the breadth and depth of our RNAi-based drug discovery engine and the capability and expertise of our scientific team."

Orexo Acquires a U.K. Drug Delivery Company

Business Wire: February 23, 2009 – STOCKHOLM, Sweden – Orexo AB (publ) (Orexo) (STO: ORX) has announced the acquisition of PharmaKodex Ltd (PharmaKodex), a U.K. drug delivery company with expertise in the reformulation and development of prescription and consumer health medicines containing small-molecule drugs. The company has a number of ready-to-partner preclinical and early clinical projects focused on improving oral, sublingual, and transdermal medication.

Orexo will acquire the company for a consideration payable in two tranches, with the first tranche paid in new Orexo shares and the second tranche payable either in new Orexo shares or cash at Orexo's option. As consideration for the first tranche, the board of directors has resolved, in accordance with the authorization from the annual general meeting, to issue 843,992 new Orexo shares to the former shareholders of PharmaKodex. Additional Orexo shares, representing the same total value in Sterling as the first payment, may be issued in August 2009 unless Orexo opts to pay the second tranche amount in cash. The transaction also provides for further conditional payments, based on the financial profits from licenses of existing PharmaKodex programs and technologies and certain milestones, but no royalties will be due on such programs or technologies.

The company's pipeline includes a preclinical program for rapid, sustained relief of migraine, in addition to its clinical stage lead program PKX219, which is a fast-acting, easy-to-use combination of buprenorphine and naloxone for opioid-addiction therapy, with clinical studies ongoing in 2009 and a prospective launch date subject to the necessary approvals of 2010/2011.

The acquisition is part of Orexo's fundamental strategy to develop superior drug products using well-established, effective drug molecules by applying the very best technology to make delivery of those drugs faster, safer, and/or more effective.

Diet Aid Spray

Globe Newswire: February 18, 2009 – WORCESTER, Mass. – Generex Biotechnology Corporation (NasdaqCM: GNBT - News), a leader in drug delivery for metabolic diseases through the inner lining of the mouth, has announced the release of Crave-NX™ 7-day diet aid spray (www.crave-nx.com), the on-the-go companion to curb and control "junk food" cravings and help support healthy weight loss.

Crave-NX™ 7-day diet aid spray's great tasting orange-flavored formulation, sprayed and administered into the mouth, is scientifically formulated to quickly curb cravings throughout the day, saving valuable calories. Clinically tested, Crave-NX™ has 20 servings per bottle with only two calories per serving and zero fat.

"Patent-pending Crave-NX is a brand new diet aid that can help you Spray the Crave Away™," said Rose Perri, the company's chief operating officer. "Crave-NX allows you to save calories by controlling your sweet tooth and junk food cravings throughout the day, which can save up to 1,000 calories per day. Over a one-year period, saving just 250 calories per day adds up to over 90,000 calories—or 26 pounds!"

According to Marketdata Enterprises, Inc., a leading market research publisher of service industry studies, the total U.S. weight loss market generated sales of $59 billion in 2007. It is estimated that 72 million people are dieters—about 70% of whom try to lose weight without professional help. The Crave-NX™ calorie-saving tool can be used as a standalone weight-loss product or used safely along with other diet products and weight loss regimens.

In the News continued on page 36

In the News continued from page 35

Nanosys Announces Promising Results with Its Gecko-Inspired Drug Delivery Device

Business Wire: February 12, 2009 – Palo Alto, Calif. – Nanosys, Inc. has announced the results of their initial studies using a novel silicon nanowire mucous membrane drug delivery device. These devices have a nano-structured surface that relies on adhesive properties known in physics as van der Waals forces of adhesion. Results of initial studies published in the American Chemical Society's *Nano Letters*, outline the device's ability to significantly improve drug delivery to mucous membranes such as those in the nose, intestine, eyes, vagina, and mouth.

Mucous membranes have long been a target for drug delivery due to their large surface area and rich blood supply. However, nature has designed these membranes to also be efficient barriers to foreign substance penetration, such as drugs. Mucus, which is constantly produced by these tissues, is moved across the surface by tiny beating hair-like structures called cilia. Removal of a substance floating in the mucus of the nasal cavity can be as fast as 10 min, for example. Previous attempts at overcoming this barrier function relied on chemical modification of the delivery vehicle to better adhere to binding elements within the mucus. Nanosys' silicon nanowires will adhere instead to the cells underneath the mucus, the actual targets for drug delivery. This critical feature allows for a longer residence time, improved local concentrations, and better absorption of target drugs by the tissues.

The team, led by Hugh Daniels at Nanosys and Tejal Desai and Kayte Fischer at the University of California, San Francisco, also quantified the amount of mucosal shear force the silicon nanowire-based devices could withstand before being eliminated and demonstrated it to be at least 100-fold better than a non-silicon nanowire device. "In the near term, there are a lot of chronic conditions of the nose, sinuses and other tissues that could immediately benefit from more efficient delivery of currently available drugs using our silicon nanowire drug delivery technology. We are also excited about the longer term potential of delivery of systemic drugs such as insulin via the mucous membrane route," said Dr. Daniels. In addition, silicon nanowires are inexpensive to make and are biocompatible. Nanosys expects to develop the technology further in partnership with drug manufacturers whose drugs could be made more effective through this delivery approach.

OctoPlus Signs Service Contract with Galapagos

Marketwire: February 12, 2009 – LEIDEN, The Netherlands – OctoPlus N.V. (OctoPlus) (Euronext: OCTO), a drug delivery company, has announced that it has signed a pharmaceutical development contract with a new client, Galapagos N.V. (Euronext: GLPG). The undisclosed contract value significantly contributes to OctoPlus' annual revenues. Under the contract terms, OctoPlus will manufacture clinical trial material for Galapagos' Phase II study of Nanocort®, a liposome formulation of prednisolone. OctoPlus has progressed the scale-up and robustness of the production process of this complex liposomal product.

OctoPlus provides formulation development and clinical material manufacturing services to biotech and pharmaceutical companies worldwide. In addition to its expertise in formulation and manufacturing, OctoPlus offers its clients drug delivery technologies for the development of controlled release versions of existing or new drugs.

MDRNA, Inc. Announces Receipt of Milestone Payment Under Amended Agreement with Amylin Pharmaceuticals, Inc. for Development and Commercialization of Intranasal Exenatide

Marketwire: February 3, 2009 – BOTHELL, Wash. – MDRNA, Inc. (NASDAQ: MRNA) has announced the achievement of a milestone under an amended version of the June 2006 development and license agreement with Amylin Pharmaceuticals, Inc. for the development of intranasal exenatide. Under the terms of the amended agreement, Amylin has committed to advancing the program, resulting in an accelerated $1 million milestone payment to MDRNA. Further, under the terms of the amended agreement MDRNA could receive an additional $79 million in future milestones and royalties.

"We appreciate the confidence Amylin has shown in the potential of intranasal exenatide through their commitment to advancing the program," stated J. Michael French, president and chief executive officer of MDRNA. "We continue to believe that our legacy intranasal assets have significant value and we remain committed to monetizing them for the benefit of the Company and its shareholders."

JANUARY 2009

IntelGenx Corp. and Circ Pharma Ltd Announce a Partnership to Develop and Commercialize a Novel Drug for the Treatment of Hyperlipidemia

Marketwire: January 16, 2009 – SAINT LAURENT, Quebec, Canada, and DUBLIN, Ireland – IntelGenx Corporation (TSX VENTURE: IGX) (OTCBB: IGXT) (IntelGenx) and Circ Pharma (Circ) have announced a partnership in which IntelGenx will formulate, manufacture, and supply to Circ and Circ will develop and commercialize a novel drug product for the treatment of hyperlipidemia. Under the terms of the agreement, Circ Pharma will fund the development of the product, and IntelGenx will receive royalties from the product's sales. IntelGenx will use its proprietary Versatab technology to formulate the product.

This is the first product in a series of Circ Pharma's controlled release lipid-lowering agents specifically designed to target the absorption of drug in order to reduce the effective dose and potentially lower the side effects. The product is expected to reach the market in 2012. The lipid-lowering market had over $30 billion in worldwide sales during 2008.

"We are very pleased about this collaboration with Circ Pharma. It is another testament to our drug development capabilities. We are looking forward to a productive and successful relationship with Circ Pharma." said Dr. Horst Zerbe, president and CEO of IntelGenx Corp.

New Interferon Formulations Promise to Eliminate Injections in Multiple Sclerosis Treatment

Marketwire: January 12, 2009 – SAN DIEGO, Calif. – Nerveda Inc. and Aegis Therapeutics LLC have announced preclinical results from their joint collaboration aimed at developing non-injectable formulations of the beta-interferons. The beta-interferons, beta-1a (trade name Rebif®) and beta 1b (trade names Betaseron® and Betaferon®), are closely related injectable protein drugs in the interferon family that are used to treat both the relapsing-remitting and secondary-progressive forms of multiple sclerosis (MS). The beta-interferons are currently administered by subcutaneous injection and have been clinically proven to slow the advance of multiple sclerosis and reduce the frequency of attacks. Current worldwide combined annual sales of Rebif®, Betaseron®, and Betaferon® are approx. $4 Billion.

Because proteins are large and fragile molecules, they cannot be administered orally and are typically administered by injection. They are often subject to instability due to aggregation of the protein molecules—particularly upon storage and handling at non-refrigerated temperatures. The resulting protein aggregates are more poorly absorbed into the blood stream upon injection due to their increased size and induce development of circulating antibodies to interferon in patients that reduce the effectiveness of the drug over time.

Leading medical scientists at Johns Hopkins University, expert in the treatment of neurological diseases, in collaboration with Nerveda and Aegis, have applied Aegis' Intravail® transmucosal absorption enhancement and ProTek® protein stabilization technologies to address these problems and have demonstrated for the first time that the beta-interferons can be administered intranasally to prevent nerve damage in preclinical animal models of MS. In addition, the new formulations were shown to reduce or eliminate the immunogenicity of Betaseron® and Rebif® administered either by injection or intranasally, while substantially increasing stability in a stress test involving constant agitation at elevated temperatures for extended periods of time.

Dr. Edward Maggio, Ph.D., CEO of Aegis Therapeutics, who participated in the research, said, "Since interferons will continue to be the foundation of MS therapy, it is critical that non-invasive delivery options for patients be developed." Maggio also indicated, "The reduction in immunogenicity and the increase in stability also address a significant unmet need of the currently available beta-interferon therapies."

Nerveda plans to begin testing the new formulation in clinical trials in early 2009 in collaboration with clinicians and scientists at John Hopkins University Medical Center and other sites. ■

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United States of America

Calendar of Events

2009

Oral Controlled Drug Delivery Using Tablets: From Laboratory to Production

June 16-17
Shanghai, China
www.controlledreleasesociety.org/main/meetings/

ISOPS 9th International Symposium on Pharmaceutical Sciences

June 23-26
Ankara University, Faculty of Pharmacy
Ankara, Turkey
www.pharmacy.ankara.edu.tr

36th Annual Meeting & Exposition of the Controlled Release Society

July 18-22
Bella Center
Copenhagen, Denmark
www.controlledreleasesociety.org/main/meetings

Advances in Tissue Engineering

August 12-15
Rice University
Houston, Texas, U.S.A.
www.ruf.rice.edu/~mikosgrp/pages/ATE/ate.htm

EuroNanoMedicine 2009

September 28-30
Bled, Slovenia
http://events.dechema.de/euronanomedicine2009

Development and Regulatory Challenges for Controlled Release Formulations Joint Workshop in conjunction with AAPS

November 7-8
Los Angeles Convention Center
Los Angeles, California, U.S.A.
www.controlledreleasesociety.org/main/meetings/

2009 AAPS Annual Meeting and Exposition

November 8-12
Los Angeles Convention Center
Los Angeles, California, U.S.A.
www.aapspharmaceutica.com/

2010

37th Annual Meeting & Expostion of the Controlled Release Society

July 10-14
Oregon Convention Center
Portland, Oregon, U.S.A.
www.controlledreleasesociety.org/main/meetings

2011

38th Annual Meeting & Exposition of the Controlled Release Society

July 30-August 3
Gaylord National Resort and Convention Center
National Harbor, Maryland, U.S.A.
www.controlledreleasesociety.org/main/meetings