

What's Inside

CRS Annual Meeting & Exposition Highlights

Mitochondrial Delivery of Bioactive Molecules Using Dual Function MITO-Porter Aimed at the Mitochondrial Genome

Cubosomes Containing Imiquimod and Monophosphoryl Lipid A Stimulate Enhanced Cellular Responses Compared to Alum

Two New Books in CRS Series

New Preclinical Sciences & Animal Health Division

C&DP Updates





Drug Delivery and Translational Research

An Official Journal of the
Controlled Release Society



CRS Members! To access this new journal as part of your member benefits, go to www.controlledreleasesociety.org and click the Publications tab to get to the member access link.

Editor-in-Chief:

Vinod Labhasetwar, Cleveland Clinic, Cleveland, OH, USA

Associate Editors:

Martyn Davies, University of Nottingham, Nottingham, UK;

Kensuke Egashira, Kyushu University, Fukuoka, Japan;

Justin Hanes, The John Hopkins University, Baltimore, MD, USA

Exclusively focused on translational aspects of drug delivery, **Drug Delivery and Translational Research (DDTR)** provides a unique forum for publication of high-quality research that focuses exclusively on translational aspects of drug delivery.

Rationally developed effective delivery systems can potentially influence clinical outcomes in different disease conditions. **DDTR** provides a focal point for publication of science and technology of delivering bioactives.

DDTR welcomes research focused on the following areas of translational drug delivery research:

- ▶ Designing and developing novel drug delivery systems, with a focus on their application to disease conditions
- ▶ Preclinical and clinical data related to drug delivery systems
- ▶ Drug distribution, pharmacokinetics, clearance, with drug delivery systems as compared to traditional dosing to demonstrate beneficial outcomes
- ▶ Short-term and long-term biocompatibility of drug delivery systems, host response
- ▶ Biomaterials with growth factors for stem-cell differentiation in regenerative medicine and tissue engineering
- ▶ Image-guided drug therapy
- ▶ Nanomedicine
- ▶ Devices for drug delivery and drug/device combination products

DDTR presents full-length papers, reviews, communications, methods, editorials, and more. For full author instructions, please visit the DDTR journal homepage at springer.com.



Charles Frey
Editor



Steven Giannos
Editor



Arlene McDowell
Editor



Bozena Michniak-Kohn
Editor



Yvonne Perrie
Editor



Rod Walker
Editor

CRS Newsletter

Leading
Delivery Science
and Technology

Vol. 29 • No. 5 • 2012

Table of Contents

From the Editor	2
From the President	3
39th CRS Annual Meeting & Exposition	4
Committee Corner	
2012–2013 CRS Board	11
Scientifically Speaking	
Cubosomes Containing Imiquimod and Monophosphoryl Lipid A Stimulate Enhanced Cellular Responses Compared to Alum	12
Scientifically Speaking	
Mitochondrial Delivery of Bioactive Molecules Using Dual Function MITO-Porter Aimed at the Mitochondrial Genome	15
Consumer and Diversified Products	
Consumer and Diversified Products Division Luncheon in Québec City	18
Consumer and Diversified Products Division Changes	18
From the Vet Group	
Veterinary Sessions a Success in Québec City, and the New Preclinical Sciences & Animal Health Division Is Launched	19
DDTR Updates	
Drug Delivery and Translational Research (DDTR) Update	22
What's on Board?	
Animal Health Drugs and RNA Interference Covered in Two New CRS Books	23
People in the News	24
In the News	27
Calendar of Events	Cover 4

Advertisers' Index

Springer	Cover 2
Texture Technologies	10
Drug Delivery Partnerships	Cover 3

Editors

Charles Frey
Steven Giannos
Arlene McDowell
Bozena Michniak-Kohn
Yvonne Perrie
Rod Walker

The CRS Newsletter is the official newsletter of the Controlled Release Society. The newsletter is published six 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.

Newsletter articles reflect only the views of the authors. Publication of articles or advertisements within the CRS Newsletter does not constitute endorsement by the Controlled Release Society or its agents of products, services, or views expressed herein. No representation is made as to the accuracy hereof, and the publication is printed subject to errors and omissions.

Editorial contributions should be directed to the CRS Newsletter Editors, (CRSNewsletter@scisoc.org) and are subject to the terms and conditions of the Editorial and Publication Release. Publisher assumes no responsibility for the safety or return of artwork, photographs, or manuscripts.

Requests for advertisement placement may be directed to Debby Woodard, Business Development Department; telephone +1.651.994.3817, or e-mail at dwoodard@scisoc.org. All advertisements are subject to "General Conditions of Sale."

Unauthorized reproduction in whole or in part is prohibited. Requests for permission should be directed to the Editors at CRSnewsletter@scisoc.org.

©Copyright 2012 Controlled Release Society. All rights reserved.

Controlled Release Society
3340 Pilot Knob Road
St. Paul, MN 55121 U.S.A.

Telephone: +1.651.454.7250
Facsimile: +1.651.454.0766

Visit www.controlledreleasesociety.org or e-mail crs@scisoc.org on questions about membership, meetings, publications, and services.

Contact dwoodard@scisoc.org for information about exhibiting, advertising or other visibility opportunities.



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

What the Bleep Do We Know?

As this 5th *CRS Newsletter* of 2012 is issued, the United States is poised to elect a new president. In the context of existing economic concerns, there is a passionate debate about the philosophy and agenda of the next president. This election is about what difficult path to take, and when Election Day arrives the collective sentiments of the voting public will select one.

The sentiments of the nation are a reflection of the collective experiences of the populace. They are based on what we have seen, what we have chosen to see, and what we choose to believe. It is influenced by the discourse of our interactions. It may be prudent thought in the end, but it also emanates from the heart, which can bring out an unreasoning pride, passion, and conviction. There is a significant element of loyalty to a cause or set of ideals.

Another factor involves information control (a bit outside the CRS realm of controlled release) on all levels. I recall an event several years ago where a babysitter innocently shared political thoughts with the sitters. Parents of the sitter were later informed by parents of the sitters that politics were never to be discussed with their children ever again. Is this a protective instinct or an inability to accept thought diversity?

Perhaps you have seen the film *Run Lola Run*, a 1998 German crime thriller. The film plays out critical events over a period of days or hours. It is performed in three separate ways, as I recall, and the outcome differs depending on observations and resulting decisions. Outcomes are based on the situations encountered, available information, interpretation of that information, and decisions made. This is true of individuals, nations, and CRS.

What the Bleep Do We Know!?, a significantly computer-animated 2004 film, explored the spiritual connection between quantum physics and consciousness. It forwarded the concept that our actions are based on preprogrammed responses that evolve from our experiences and that we have the capacity to override those response patterns. It is all rooted in our neuronomic (is that a word?) makeup. It is fascinating to consider an election in terms of a collective neurological history at the AND, NAND, OR, and NOR gate decision level!

Perhaps a thought from these ramblings will become a key part of you. Perhaps, more importantly, you can add the information from this *CRS Newsletter* to that history. In this issue you will find Scientifically Speaking articles on both lipid-based cubosomes for antigen delivery and bioactive delivery to mitochondria. Books on long-acting animal drugs and RNA interference are reported. There are articles on the activities of the Consumer & Diversified Products and Veterinary Divisions, the newly formed Preclinical Sciences & Animal Health Division, and the journal *Drug Delivery and Translational Research*. Steven Giannos has again captured prominent events within the controlled release industry in his "In the News" articles.

Lastly, check out the 39th CRS Annual Meeting debriefing articles and pictures to fill you in on what you may have missed or to remind you of the successes of this event. The general exchange that takes place at the annual meeting helps unify and engage membership with a shared vision and purpose. It adds to the "bleep" that we know so that we can contribute to our fullest potential.

Take care,
Chuck Frey ■



*Kazunori Kataoka
University of Tokyo
Tokyo, Japan*

Nurturing Momentum

It is with great honor that I take the role of CRS president. There has been much momentum over the past few years, building new products and services and developing new strategies to keep the society strong, and I intend to continue the forward progress of the society.

The Controlled Release Society is an extremely diverse organization, represented by scientists from around the world and from many disciplines. The CRS I envision embraces that aspect of the society and nurtures it, helping the society and the science as a whole continue to develop and serve its members. There are several key factors that will serve this purpose.

We must continue to develop the interdisciplinary platform where different cultures can integrate. For members who specialize in delivery science and scientists from other fields whose work crosses into delivery science, we wish to broaden the potential for meaningful interchanges so that future development can happen. This will be facilitated by the exchanges that occur at the annual meeting and other major meetings, including workshops and chapter meetings. We wish to promote open information exchange and dialogue among all members to ensure that CRS actively is a melting pot of “best in class” innovation and ideas.

CRS must promote integrated ties from fundamental sciences to industrial applications. CRS is unique in that approximately 45% of its members work in the industrial sector. This foundation

readily enables constructive and collaborative activities for members from academia and industry.

By broadening the understanding of our science and fostering better international relations, we can build sustainable development of delivery science and technology and be the pioneers in effecting change. The significance of delivery systems in regard to international science and technology policies will be central to our success.

In addition, CRS as a society and its members should undertake activities that demonstrate the visible impact of our science. Delivery science is playing an increasingly significant role in science and technology in the broad fields of pharmacy, animal health, pesticides, consumer and diversified products, and medicine. However, its real significance tends not to be fully appreciated by the public, since delivery systems are applied as various commodity and functionality materials and are not visible as end consumer products.

Finally, we must provide support for all our members who have diverse backgrounds. CRS as a network will be strengthened by diversity, and the multidisciplinary knowledge base of our membership and breadth of experience coupled with different geographical access will provide a coherent foundation to nurture and integrate the young scientific community. We are determined that such coherent approaches are pivotal to the development and prosperity of CRS. ■



The 2012 CRS Annual Meeting Program team is thanked during the CRS Opening Session. Left to right: current CRS President Kazunori Kataoka, Thierry Vandamme, Arlene McDowell, Teresa Virgallito, Christopher McDaniel, Dusica Maysinger, Hamid Ghandehari, and immediate past president Martyn Davies.



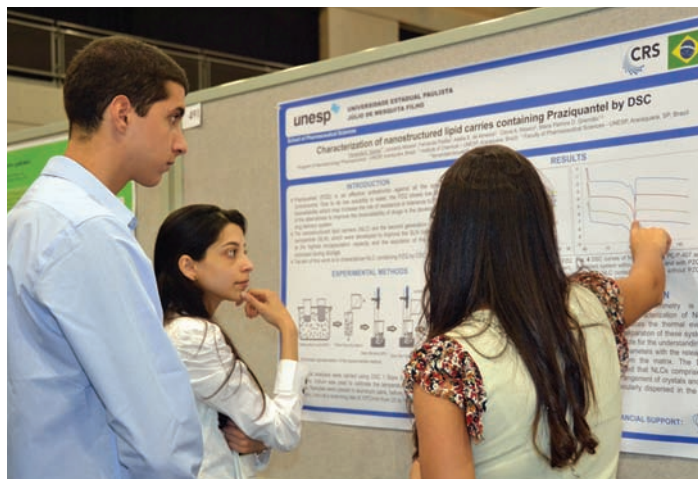
Residing CRS President Martyn Davies welcomes a packed room to the 39th Annual Meeting & Exposition of the Controlled Release Society during the Opening Session.

"It was a great experience and privilege to be able to have a poster at CRS."



Meeting attendees take time to connect with the more than 100 exhibitors and learn about the many new products and services available.

"Grand conference. Workshops were very useful. Selection of plenary lectures was good."



This year's format let attendees meet with poster presenters at one of three author sessions. More than 600 posters were on display during the annual meeting.



Buket Aksu describes the importance of project management during the Young Scientist Workshop on professional and self development.



Plenary speaker Donald Tomalia delivered an insightful presentation on dendrimer-based nanomedicine.



The Young Scientist Roundtable speakers discussed their experiences taking an innovation from conception to commercialization.



Diane Burgess and other successful leaders in delivery science shared their experiences as women in this sector of science.

"It is the best meeting for overall drug delivery science and technology."



Kinam Park offered an entertaining speech during the President's Banquet, speaking on "Politicians, Athletes, Scientists, and iCRS."



Rooms throughout the beautiful Centre des congrès de Québec were consistently packed.



Susan Cady shares the accomplishments of the CRS Foundation and introduces the new Alexander Florence Postdoctoral Fellowship for 2014.



Arthur Tipton (center) was honored with the CRS Distinguished Service Award for his efforts creating the new CRS governance structure.

CRS Annual Meeting continued

Une Réunion Extraordinaire! The 39th Annual Meeting & Exposition Delivers the Top Delivery Science and More

The Old World charm and strains of music throughout Québec City offered the perfect setting for one of the top meetings in delivery science. With nearly 1,300 attendees, the 39th Annual Meeting & Exposition of the Controlled Release Society was extremely successful, offering the latest research in the science and once again providing the opportunity to meet with colleagues from around the world, connecting again with old friends and building new relationships.

The meeting began with great science on Saturday, with attendees arriving in beautiful Québec City early to attend educational workshops covering critical appraisal of the EPR effect and intratumoral distribution of nanomedicine, osmotic dosage forms, and *in vitro* testing of controlled release dosage forms. Those newer to the profession arrived early to attend a special Young Scientist Workshop on mucosal drug and gene delivery. Workshops continued Sunday, with some attendees learning about preserving and enhancing vision through ophthalmic drug delivery and with young scientists learning the important skill of time management.



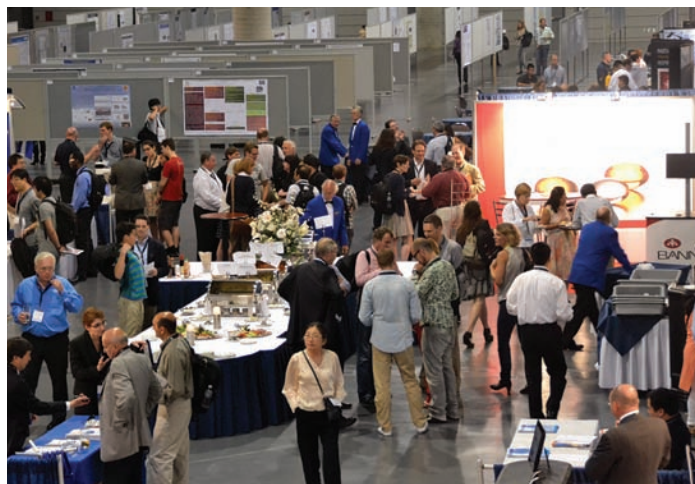
The popular Soapbox Sessions were once again standing room only on Sunday.

"If you want to get information on the recent research from the leading scientists in drug delivery and you also want to be able to speak to them and network, attend the CRS Annual Meeting."



Meeting attendees arrived early to learn more with the educational workshops held on Saturday.

For the third year, CRS Innovation Sunday helped to encourage and instruct scientists on how to bring their innovative ideas to the market. Companies showcased their newest products and their companies' capabilities during the Releasing Technology Workshops. The ever-popular Soapbox Sessions saw multiple start-ups and established companies presenting new ideas, products, and services. Attendees greatly enjoyed the fast pace of the Soapbox Sessions, along with the opportunity to meet one-on-one with those presenting. The Industry Roundtable discussed "Game-Changing Innovation," featuring industry panelists from companies that are known to have an innovation or two. Julia Rashba-Step of Pfizer and Ronald L. Smith of Merck & Co. offered their perspective on the role of big pharma in innovation in delivery science. Alberto Gabizon, Shaare Zedek Medical Center Oncology Institute, explained how the entrepreneur brings innovation to the industry.



The Exposition Hall was packed as attendees enjoyed networking and some delicious Québec-inspired food during the Exposition Grand Opening and Welcome Reception.

longer poster hours, and the opportunity to get a coffee or juice each morning.

“Very good mix of science and commercial/industry perspectives, perhaps one of the best conferences out there for this kind of blending.”

Monday morning programming got underway early, with the Get Up! Get Educated! session at 7:00 a.m., followed by the CRS Opening Session, where President Martyn Davies shared the association's activities and accomplishments with a packed room. Multiple volunteers—including the impressive 2012 Annual Meeting Program Team—were honored, and Founders Award winner Yechezkel Barenholz shared his personal voyage in delivery science, followed by Young Investigator Award winner Cory Berkland describing his personal and professional experiences in the field. The event ended with an entertaining College of Fellows panel speaking on reinventing yourself throughout your career. Monday continued with many fantastic scientific sessions, quite a few standing room only.



College of Fellows panelists (left to right) Clive Wilson, Arthur Tipton, Susan Cady, and Kinam Park discussed reinventing yourself throughout a career.

The science presented this year was top-notch. This year's plenary sessions were extremely well received, with full rooms waiting to hear speakers Donald Tomalia, Molly Shoichet, and Vladimir Torchilin. Tomalia, founder of NanoSynthons LLC, captivated his audience with his research on dendrimer-based nanomedicine and the use of abiotic dendrimers in a variety of nanomedical applications. Shoichet, a professor at the University of Toronto, Canada, shared her insights on drug and cell delivery strategies to the central nervous system, describing three regenerative medicine strategies. Professor Torchilin ended the meeting on a high note on Wednesday, discussing cell organelles in his address talking about the next generation of drug delivery systems.

Many attendees enjoy the opportunity to connect with friends and colleagues and to build relationships with people of similar interests. The CRS Annual Meeting offered many chances to do just that. CRS Central was a welcome meeting area, offering information on the latest products and services from CRS and the chance to rest for a bit and watch a video featuring CRS members



The Young Scientists Networking Evening at the rotating L'Astral Restaurant featured great food, great networking, and the always popular networking game and prizes.

sharing their experiences. The Young Scientist Mentor-Protégé program has continued to grow, with a successful meet and greet at this year's meeting and outstanding participation by both mentors and protégés.

“It is an excellent meeting to learn about cutting-edge science and industry which advances the applications of controlled release drug and vaccine delivery. Good to develop world-wide networking.”

The Women in Science Luncheon offered the chance for women professionals to learn from some of the leaders in the field on how to navigate the often difficult path of being a woman scientist, while the Consumer & Diversified Products Division Luncheon found old colleagues and those newly interested enjoying good conversations and getting an update on the division. The Preclinical Sciences & Animal Health Division (formerly the Veterinary Division) celebrated their name change and what it means for the division during their get-together. The Young Scientist Networking Evening provided amazing views from Québec City's only rotating restaurant, along with the chance to meet with peers in a relaxed setting. Finally, the President's Banquet offered a grand and entertaining opportunity to spend time with colleagues and hear from one of the most distinguished and entertaining members of CRS, Kinam Park. From the amazing French-Canadian food to the education of a lifetime on Polite English versus “Apple” English, it was a spectacular evening with friends and colleagues.

As the meeting came to a close, it was with fondness that we said “au revoir” to Québec City and “Aloha” to the 2013 CRS Annual Meeting. Stunning Honolulu, Hawaii—the ultimate global gathering place—will be the home for the 40th Annual Meeting & Exposition of the Controlled Release Society. We will see you next July 21–24 in Hawaii! ■

The Controlled Release Society Thanks the Sponsors of the 39th Annual Meeting & Exposition



Agilent Technologies



Pharmaceutical
Technologies



Media Sponsors



Thank You to the Exhibitors of the 39th Annual Meeting & Exposition

2012 CRS Exhibitors

3M Drug Delivery Systems
Adhesives Research
Advanced Polymer Materials Inc.
Agilent Technologies
Akina Inc.
Alkermes Contract Pharma Services
American Pharmaceutical Review
Apricus Biosciences
Aptalis Pharmaceutical Technologies
Asahi Kasei America Inc.
Avanti Polar Lipids Inc.
AVESTIN, Inc.
Aveva Drug Delivery Systems
Banner Pharmacaps Inc.
BASF Corp.
Bio-Images Group Ltd.
Buchi Corporation
Catalent Pharma Solutions
Celanese EVA Performance Polymers
Colorcon, Inc.
Contract Pharma
Corden Pharma
Covaris
Croda Inc.
Delta Industrial Services Inc.
Dissolution Technologies
Distek Inc.
Dow Water & Process Solutions
Drug Development & Delivery
DURECT Corporation/
Lactel Absorbable Polymers
Elsevier
EMD Millipore Corp.
Emeryville Pharmaceutical Services

Evonik Degussa/Pharma Polymers
FEI
Fluid Imaging Technologies
Freund Vector Corporation
Gateway Analytical
Gattefossé U.S.A.
Gaylord Chemical Corp
Giltech
Glatt Pharmaceutical Services
Grünenthal GmbH
Hanson Research Corp.
Henkel Corp.
Hovione LLC
InGell Labs B.V.
InnoCore Pharmaceuticals
KORSCH America Inc.
LACTEL Absorbable Polymers/
DURECT Corporation
LCI Corporation
Lipoid LLC
LTS Lohmann Therapy Systems
Lubrizol Advanced Materials
Medimetrics Personalized Drug
Delivery, Inc.
MG America, Inc.
Michelson Prize & Grants
Microfluidics
Molecular Pharmaceutics/
ACS Publications
Mylan Technologies Inc.
NanoImaging Services
NanoSight
National Experimental Biology
Centre – INRS

National Institute of Biomedical Imaging
and Bioengineering
Nisso America Inc.
NOF America Corp.
Northern Lipids Inc.
Novozymes Biopharma
OctoPlus NV
O'Hara Technologies Inc.
OnDrug Delivery
Ortec, Inc., U.S.A.
Pace Analytical Life Sciences, LLC
Patheon
Pharmaceutical Technology
PharmaCircle
PolySciences, Inc.
Purac Biomaterials
QPharma AB
SAIC-Frederick Inc.
Scintipharma Inc.
Sekisui Medical Co., Ltd.
Sensient Pharmaceutical Coating Systems
Shin-Etsu Chemical Co. Ltd.
c/o Biddle Sawyer Corp.
Simulations Plus Inc.
Sirius Analytical
SOTAX Corporation
Southwest Research Institute
Springer
Sympatec Inc.
Technology Catalysts International
Texture Technologies Corp.
Thermo Scientific
Wyatt Technology Corporation

On to Honolulu, Hawaii!

For 2013 exhibit materials, please contact
Debby Woodard at +1.651.994.3817 or
dwoodard@scisoc.org



Courtesy of the Hawaii Tourism Authority (HTA) / Tor Johnson

the ultimate in testing flexibility

...what can it do for your product development?



Texture Technologies' commitment and support for the pharmaceutical industry has never been stronger. We have helped thousands of companies **quantify the physical parameters and performance of their products**. Each customer has had unique concerns, which we have solved with our instrument, software, training, fixtures, test methods, and applications support. Our implementations are user-friendly and push-button simple. *Use our knowledge and experience to save your time and effort.* Improve your understanding of everything related to the performance of your products, ingredients, suppliers, formulas, production parameters, packaging and more. Call us. (We don't bite.) **Learn what our instrument and solutions can do for you.**

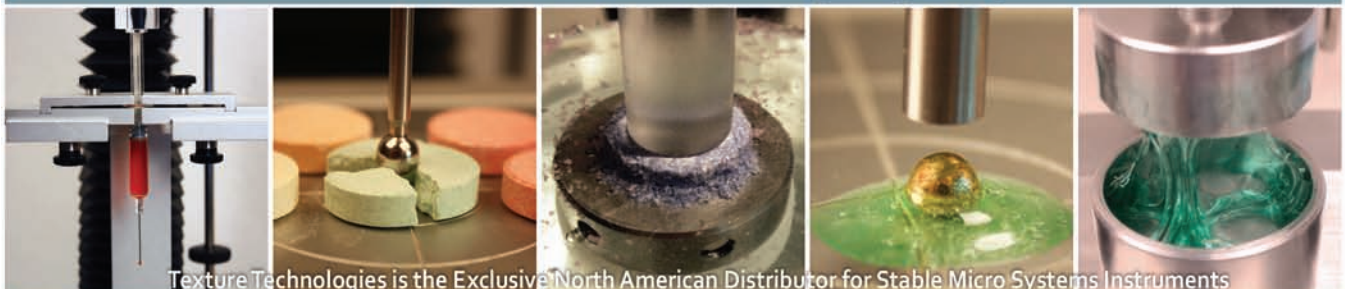
Stable Micro Systems

*44 1483 427245 sales@stablemicrosystems.com

Texture Technologies

978-468-9969 sales@texturetechnologies.com

Call us for a demonstration on any of your products



Texture Technologies is the Exclusive North American Distributor for Stable Micro Systems Instruments

www.texturetechnologies.com | www.stablemicrosystems.com | www.texturereport.com

2012–2013 CRS Board

The following CRS members make up the 2012–2013 Board. Members wishing to interact with Board members can find contact information in the member directory or can simply e-mail crspresident@scisoc.org.



President
Kazunori Kataoka
University of Tokyo
Japan



President Elect
Ian G. Tucker
University of Otago
New Zealand



Immediate Past President
Martyn C. Davies
University of
Nottingham
United Kingdom



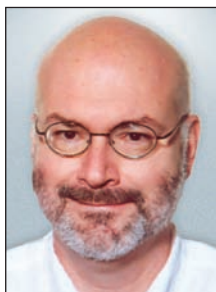
Treasurer
Tom E. Redelmeier
Northern Lipids
Inc.
Canada



Secretary
Ruth B. Schmid
SINTEF Materials
and Chemistry
Norway



Director-at-Large
Christine Allen
University of Toronto
Canada



Director-at-Large
Marcus Brewster
Johnson & Johnson
Belgium



Director-at-Large
Andrew Lewis
Ipsen
France



Director-at-Large
Tamara Minko
Rutgers University
U.S.A.



Director-at-Large
Yvonne Perrie
Aston University
United Kingdom



Director-at-Large
Michael J. Rathbone
International Medical
University
Malaysia

Cubosomes Containing Imiquimod and Monophosphoryl Lipid A Stimulate Enhanced Cellular Responses Compared to Alum

Shakila B. Rizwan,¹ Ben J. Boyd,² Thomas Rades,³ and Sarah Hook¹

Introduction

Vaccines based on peptides and proteins offer increased specificity and selectivity, and decreased toxicity, but are inherently nonimmunogenic. A number of formulation strategies to increase their immunogenicity are currently under investigation, of which incorporation in a particulate carrier appears to be promising.

Cubosomes (Fig. 1) are a novel lipid-based particulate delivery system proposed for sustained drug delivery.¹ They have a bicontinuous nanostructure composed of a highly twisted lipid bilayer and two nonintersecting water channels. The surface area imparted by the greater proportion of lipid comprising the particle when compared to the simple bilayer structure of liposomes allows cubosomes greater drug payload with the possibility of sustained release.^{1–3} Here we report the physicochemical properties and immunological responses of cubosomes modified to include the toll-like receptor (TLR) agonists monophosphoryl lipid A (MPL) and imiquimod, alone or in combination, as a novel vaccine delivery system. Fluorescently labelled ovalbumin (FITC-Ova) was used as a model antigen.

Experimental Section

Cubosomes containing 100 mg of phytantriol, 15 mg of Poloxamer (P407), propylene glycol (70% w/w to lipid), imiquimod (10 mg) and/or MPL (1 mg), and FITC-Ova (1 mg) were prepared using the solvent evaporation method.¹ Samples were characterised for size, charge, polydispersity, and the ability to entrap FITC-Ova. The nanostructure of the formulations was determined by small-angle X-ray scattering (SAXS). Transgenic T cells expressing Ova-specific T-cell receptors were adoptively

transferred into C57Bl/6 mice.⁶ Two hundred microlitres of formulations from five different groups under investigation—cubosomes without adjuvant (plain), with adjuvant (imiquimod and MPL), with a combination (imiquimod + MPL), and with Ova + alum (alum)—were then injected subcutaneously into the mice on day 0 with a boost at day 14. Mice were sacrificed on day 27; cell suspensions were prepared, stained with fluorescently labelled antibodies, and analysed by flow cytometry. The production of Ova-specific immunoglobulin G (IgG) was determined by ELISA.

Results

Physicochemical Characteristics of Formulations

Cubosomes containing imiquimod were larger and more polydisperse (Table 1), possibly due to the presence of unincorporated crystalline imiquimod suspended in the formulations (visualized by light microscopy, data not shown). All formulations had a negative surface charge. Entrapment of FITC-Ova was highest for plain and MPL-containing cubosomes and decreased with the addition of imiquimod.

Small Angle X-ray Scattering

Two strong diffraction peaks were observed (black arrows) for all formulations with relative positions at ratios $\sqrt{2}:\sqrt{3}$; the third peak at $\sqrt{4}$ was weak but could be observed (Fig. 2). These peaks are indicative of particles with a D-type cubic nanostructure.⁷ Interestingly, very strong peaks with relative positions at $\sqrt{2}:\sqrt{3}:\sqrt{4}:\sqrt{6}:\sqrt{8}:\sqrt{9}$, also in accordance with the D-type structure, were observed for formulations containing imiquimod only. There was a slight shift (0.01 \AA^{-1}) in the peaks of the imiquimod-only sample. These strong reflections and minor shift are most likely due to the presence of some crystalline

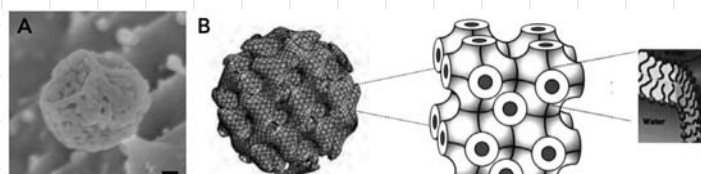


Figure 1. (A) Cryogenic field emission scanning electron micrograph (cryo-FESEM) of cubosome.² (B) Schematic model of a cubosome particle with a bicontinuous cubic liquid crystalline nanostructure, which consists of continuous water channels partitioned by a lipid bilayer.^{4,5} The scale bar in (A) represents 100 nm.

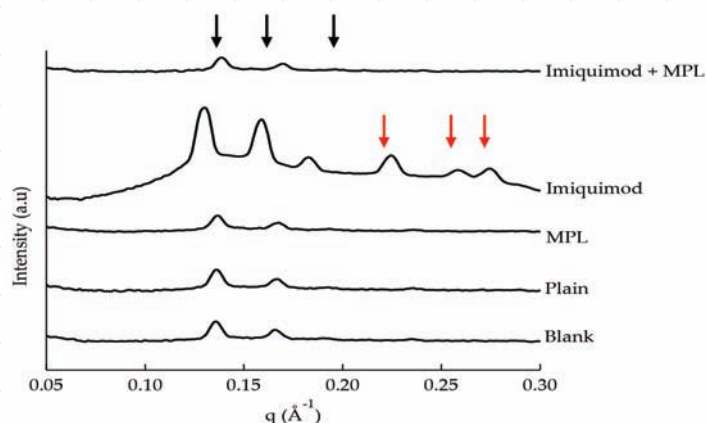


Figure 2. Intensity versus q plots of formulations containing no adjuvant or Ova (blank), no adjuvant (plain), imiquimod, MPL, and imiquimod + MPL. Black arrows indicate peaks with relative positions at $\sqrt{2}:\sqrt{3}:\sqrt{4}$ for all formulations. Additional peaks with relative positions at $\sqrt{6}:\sqrt{8}:\sqrt{9}$ (red arrows) could also be observed in imiquimod-only formulations.

¹ New Zealand's National School of Pharmacy, University of Otago, Dunedin, New Zealand.

² Monash Institute of Pharmaceutical Sciences, Monash University, Australia.

³ Department of Pharmacy, Faculty of Health and Medical Sciences, University of Copenhagen.

imiquimod present in the sample. Using the two control formulations (blank and plain) as comparators, SAXS data reveal that the cubic liquid crystal structure was retained upon addition of the various adjuvants to the formulations.

Immunological Responses of Cubosomes

There were significantly more Ova-specific CD8+ T cells in the spleen (Fig. 3A) and lymph nodes (Fig. 3B) of mice immunized with cubosomes containing imiquimod or imiquimod + MPL compared to alum (*P* < 0.5). Furthermore, immunization with plain cubosomes led to CD8+ T-cell expansion comparable to alum. Expansion of CD4+ T cells (Fig. 3C and D) in the spleen and lymph nodes of mice after immunization with all cubosome formulations was comparable to alum (*P* > 0.5). Interestingly, in the context of CD4+ T cells, responses generated by the imiquimod-only group were modest and inconsistent. Ova-specific IgG titres were highest in mice immunised with alum (Fig. 4).

Discussion

Co-delivery of antigen and adjuvant(s) such as TLR agonist(s) has been shown to result in concurrent antigen processing and presentation as well as signaling through the TLR pathway leading to generation of mature, activated dendritic cells (DCs) with enhanced capacity to prime naïve T cells.⁸ Consequently, this study was undertaken to determine the immune-stimulating capacity of plain cubosomes and cubosomes containing imiquimod and MPL. The adjuvants used were chosen because of their lipophilic nature, with the aim of facilitating incorporation into the cubic-phase particles, and because they targeted different TLR ligands. This would perhaps result in a synergistic enhancement of immunogenicity.

Inclusion of the adjuvants into cubosomes, while not changing the nanostructure of the particles, did impact on their ability to entrap a protein antigen. We have shown that inclusion of adjuvants into formulations can impact on the packing and stability of amphiphiles at an air–water interface (data not shown), and this is likely the case here. In an *in vivo* model, immunisation with cubosomes containing the adjuvants MPL and imiquimod resulted in increased expansion of CD8+ T cells as compared to mice immunised with alum. Interestingly, the level of CD8+ T-cell expansion by the combination group was comparable to the imiquimod-only group, suggesting that the observed expansion was most likely due to imiquimod and not MPL. This was supported by the modest expansion observed in the MPL-only group, for which responses were comparable to plain cubosomes and alum. There are reports in the literature that MPL incorporated within a particulate delivery system has resulted in expansion and increased effector function of CD8+

T cells.^{9,10} In contrast, there are also reports that show that although derivatives of lipopolysaccharides (LPS) such as MPL circumvent the issues of toxicity associated with LPS, there is an

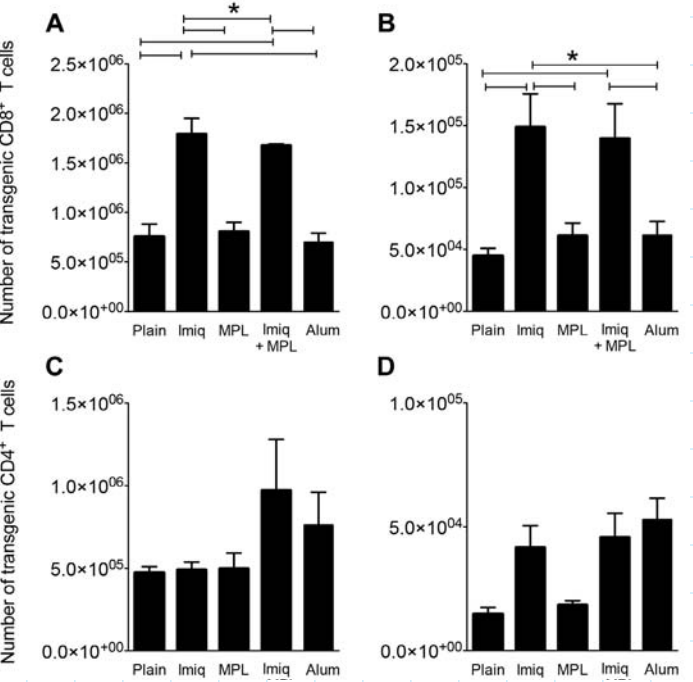


Figure 3. Expansion of CD8+ and CD4+ transgenic T cells in the spleens (A and C) and the draining lymph nodes (B and D) of mice vaccinated with cubosomes ± adjuvants or alum. Data represented are the mean + standard deviation of two independent experiments (n = 3 mice per experiment, **P* < 0.05).

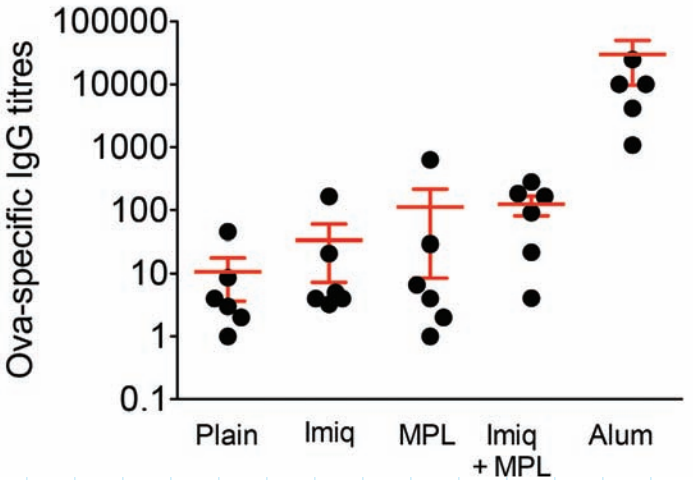


Figure 4. Ova-specific IgG antibodies determined using an Ova-specific ELISA assay. Data represented are from two independent experiments (n = 3 mice per experiment). The circles represent data from individual mice, and the lines (red) represent the mean values.

Table 1. Physicochemical properties of cubosomes ± TLR agonists and FITC-Ova.

Formulation	Z-Average (nm)	PDI ^a	Zeta-Potential (mV)	Entrapment (%)
Plain	260	0.262	–34.2	70.0
Imiquimod	351	0.482	–28.6	58.2
MPL	282	0.92	–34.5	71.4
Imiquimod + MPL	341	0.392	–33.4	61.2

^a Polydispersity index.

associated decline in their immunogenicity, suggesting that MPL on its own is not a very effective adjuvant. The reduced efficacy of MPL is attributed to lower levels of cytokines relevant for adjuvant activity.^{11–13}

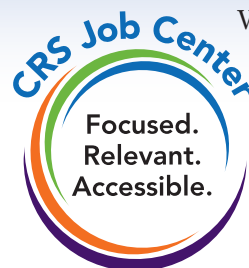
Conclusion

It is promising that plain and adjuvant-containing cubosomes were able to stimulate an equal or significantly greater expansion of T cells and comparable titres of Ova-specific IgG to alum, the most widely used vaccine adjuvant. This work shows a promising future for cubosomes as antigen delivery systems.

References

1. Rizwan, SB, Assmus, D, Boehnke, A, Hanley, T, Boyd, BJ, Rades, T, Hook, S. Preparation of phytantriol cubosomes by solvent precursor dilution for the delivery of protein vaccines, *Eur. J. Pharm. Biopharm.* 79(1): 15–22 (2011).
2. Rizwan, SB, Dong, YD, Boyd, BJ, Rades, T, Hook, S. Characterisation of bicontinuous cubic liquid crystalline systems of phytantriol and water using cryo field emission scanning electron microscopy (cryo FESEM), *Micron* 38(5): 478–485 (2007).
3. Nguyen, TH, Hanley, T, Porter, CJH, Boyd, BJ. Nanostructured liquid crystalline particles provide long duration sustained-release effect for a poorly water soluble drug after oral administration, *J. Controlled Release* 153(2): 180–186 (2011).
4. Andersson, S, Jacob, M, Lidin, S, Larsson, K. Structure of the cubosome—a closed lipid bilayer aggregate, *Z. Kristallogr.* 210: 315–318 (1995).
5. Nakano, M, Sugita, A, Matsuoka, H, Handa, T. Small-angle X-ray scattering and ¹³C NMR investigation on the internal structure of “cubosomes,” *Langmuir* 17(13): 3917–3922 (2001).
6. Gordon, S, Young, K, Wilson, R, Rizwan, S, Kemp, R, Rades, T, Hook, S. Chitosan hydrogels containing liposomes and cubosomes as particulate sustained release vaccine delivery systems, *J. Liposome Res.* 22(3): 193–204 (2012).
7. Hyde, ST. Identification of lyotropic liquid crystal mesophases. Chapter 16 in: *Handbook of Applied Surface and Colloid Chemistry*. K. Holmberg, ed. Wiley, Hoboken, NJ. pp. 299–331 (2001).
8. Schlosser, E, Mueller, M, Fischer, S, Basta, S, Busch, DH, Gander, B, Groettrup, M. TLR ligands and antigen need to be coencapsulated into the same biodegradable microsphere for the generation of potent cytotoxic T lymphocyte responses, *Vaccine* 26: 1626–1637 (2008).
9. Zhou, F, Huang, L. Monophosphoryl lipid A enhances specific CTL induction by a soluble protein antigen entrapped in liposomes, *Vaccine* 11: 1139–1144 (1993).
10. Hamdy, S, Elamanchili, P, Alshamsan, A, Molavi, O, Satou, T, Samuel, J. Enhanced antigen-specific primary CD4⁺ and CD8⁺ responses by codelivery of ovalbumin and toll-like receptor ligand monophosphoryl lipid A in poly(D,L-lactic-co-glycolic acid) nanoparticles, *J. Biomed. Mater. Res., Part A* 81A: 652–662 (2007).
11. Thompson, BS, Chilton, PM, Ward, JR, Evans, JT, Mitchell, TC. The low-toxicity versions of LPS, MPL[®] adjuvant and RC529, are efficient adjuvants for CD4⁺ T cells, *J. Leukoc. Biol.* 78: 1273–1280 (2005).
12. Salkowski, CA, Detore, GR, Vogel, SN. Lipopolysaccharide and monophosphoryl lipid A differentially regulate interleukin-12, gamma interferon, and IL-10 mRNA production in mouse macrophages. *Infect. Immun.* 65:3239–3247 (1997).
13. Tiberio, L, Fletcher, L, Eldridge, JH, Duncan, DD. Host factors impacting the innate response in humans to the candidate adjuvants RC529 and monophosphoryl lipid A, *Vaccine* 22: 1515–1523 (2004). ■

Are you reaching the right candidates quickly?



When looking to fill an open position, many companies often find themselves sorting through applications from unqualified candidates. This problem results from posting jobs to general recruiting sites.

The CRS Job Center is your solution.

By targeting only those individuals interested in delivery science and technology, it provides you with faster access to the most highly qualified candidates.

The CRS Job Center makes the recruiting process focused, relevant, and accessible.

- Utilizing the CRS Job Center enables you to focus your search efforts on candidates that have a true interest in delivery science and technology.
- The CRS Job Center is your link to available applicants with relevant qualifications. Candidates using the CRS Job Center actively participate by posting their resumes, searching for jobs, and setting up job alerts.
- The CRS Job Center is a straightforward, accessible, easy-to-use recruitment tool. Search and view resumes, post jobs, manage your company profile, and contact those candidates you are most interested in.

.....

Visit the CRS Job Center today to reach the qualified candidates you seek.

www.controlledreleasesociety.org/careers

Mitochondrial Delivery of Bioactive Molecules Using Dual Function MITO-Porter Aimed at the Mitochondrial Genome

Yuma Yamada and Hideyoshi Harashima

Laboratory for Molecular Design of Pharmaceutics

Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo, Japan

A number of researchers have reported that genetic mutations of mitochondrial DNA (mtDNA) are associated with certain types of mitochondrial dysfunction, which result in a variety of human disorders.¹ Therefore, an effective mitochondrial gene therapy and diagnosis would be expected to have great medical benefits. To achieve such an innovative strategy targeted to the mitochondrial genome, it will be necessary to deliver therapeutic agents to mitochondria in living cells. We previously reported on the development of a dual function MITO-Porter (DF-MITO-Porter), an innovative nanocarrier for mitochondrial delivery, which has the ability to pass through the endosomal and mitochondrial membranes via step-wise membrane fusion.^{2–4}

Here, we provide a demonstration of its potential use in therapies that are selective for the mitochondrial genome,⁴ as shown in Figure 1. We first constructed a DF-MITO-Porter in which the DNase I protein was encapsulated as a model bioactive molecule. It would be expected that the mtDNA would be digested as the mitochondrial delivery of DNase I proteins progressed. Intracellular observations using confocal laser scanning microscopy permitted us to compare the mitochondrial targeting activity between the DF-MITO-Porter and a conventional MITO-Porter. We then evaluated mitochondrial activity after the mitochondrial delivery of DNase I. In addition, the levels of mtDNA and nuclear DNA were quantitatively determined by polymerase chain reaction (PCR) analysis.

Construction of DF-MITO-Porter Encapsulating DNase I

The construction of the DF-MITO-Porter encapsulating DNase I involves the following three steps: the construction of nanoparticles containing DNase I; coating the nanoparticles with a mitochondria-fusogenic envelope; and further coating the endosome-fusogenic envelope, based on our previous report regarding

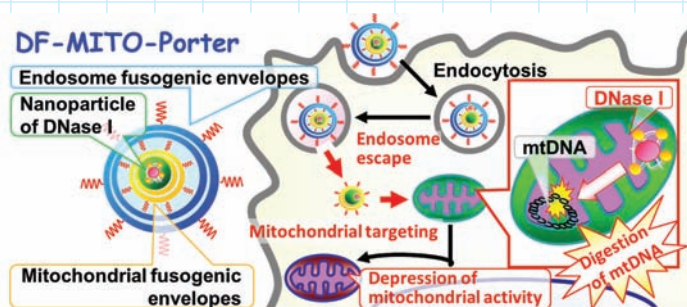


Figure 1. Schematic image of mitochondrial delivery by DF-MITO-Porter. The DF-MITO-Porter encapsulating DNase I is internalized via macropinocytosis, and the carrier escapes from the endosome into the cytosol via membrane fusion. The carrier then binds and fuses with the mitochondrial membrane to deliver its cargo to mitochondria. Finally, DNase I proteins digest the mtDNA, resulting in a decrease in mitochondrial activity.

gene packaging with two different types of lipid layers.⁵ Particles of DNase I/stearyl-R8 (STR-R8) were formed at a complex-inducer/protein molar ratio of 10. The complexed protein particles were coated with mitochondria-fusogenic lipids (1,2-dioleoyl-sn-glycero-3-phosphatidylethanolamine [DOPE]/phosphatidic acid [PA]/STR-R8 at 9:2:1, DOPE/sphingomyelin [SM]/cholesteryl hemisuccinate [CHEMS]/STR-R8 at 9:2:1:1 [molar ratio]) or a nonfusogenic lipid (egg yolk phosphatidylcholine/CHEMS/STR-R8 at 9:2:1 [molar ratio]). The resulting lipid envelopes were further coated with an endosome-fusogenic lipid (DOPE/PA/STR-R8 at 7:2:1 [molar ratio]) to finally produce the DF-MITO-Porter. The characteristics of the carriers are summarized in Figure 2. The particle diameters of the DF-MITO-Porter were around 150 nm, and the ζ -potentials were around +30 mV. We also prepared a conventional MITO-Porter without outer endosome-fusogenic lipid envelopes (≈ 150 – 200 nm, $\approx +40$ mV), for purposes of checking value for the multilayered structure.

Intracellular Observation of DF-MITO-Porter

To evaluate mitochondrial targeting activity in living cells, NBD (fluorescent lipid)-labeled carriers were incubated with HeLa cells, and the extent of intracellular trafficking was observed using confocal laser scanning microscopy (LSM510, Carl Zeiss Co., Jena, Germany). In the case of the DF-MITO-Porter, yellow clusters were observed (Fig. 3A), indicating that the NBD in the carriers (green) was colocalized with mitochondria (stained red with MitoFluor Red 589). Moreover, it was confirmed that the DF-MITO-Porter accumulated in mitochondria more efficiently compared with the conventional MITO-Porter (Fig. 3). This suggests that a multi-layered structure can be very useful for mitochondrial delivery in living cells.

DF-MITO-Porter	Lipid compositions (Inner envelope)	Diameter (nm)	PDI	ζ Potential (mV)
	EPC/CHEMS /STR-R8 (9/2/1)	112 \pm 6	0.162 \pm 0.010	31 \pm 2
	DOPE/SM/CHEMS /STR-R8 (9/2/1/1)	152 \pm 9	0.193 \pm 0.028	35 \pm 8
	DOEP/PA /STR-R8 (9/2/1)	157 \pm 12	0.175 \pm 0.033	34 \pm 10
Outer envelope: [Endosome-fusogenic lipid] DOPE/PA/STR-R8 (7:2:1)				
Complexed nano particles : STR-R8/DNase I	Lipid compositions	Diameter (nm)	PDI	ζ Potential (mV)
	EPC/CHEMS /STR-R8 (9/2/1)	123 \pm 8	0.305 \pm 0.042	39 \pm 4
	DOPE/SM/CHEMS /STR-R8 (9/2/1/1)	215 \pm 42	0.364 \pm 0.034	44 \pm 6
Conventional MITO-Porter	DOEP/PA /STR-R8 (9/2/1)	235 \pm 19	0.414 \pm 0.064	37 \pm 7

Figure 2. Characteristics of DF-MITO-Porter and conventional MITO-Porter. Diameter, polydispersity index (PDI), and ζ potential of the carriers were measured. Data are represented as the mean \pm standard deviation ($n = 3$ – 7).

Evaluation of Mitochondrial Activity After the Mitochondrial Delivery of DNase I

Mitochondrial activity was evaluated by measuring the activity of mitochondrial dehydrogenase using Tetra Color ONE (Seikagaku Biobusiness Corporation, Tokyo, Japan). In this experiment, mitochondrial activity would be predicted to be inversely proportional to the efficiency of the mitochondrial delivery of DNase I. The use of the DF-MITO-Porter resulted in a significant decrease in mitochondrial activity, whereas carriers with a low mitochondrial fusion activity had only a negligible effect on mitochondrial activity (Fig. 4A). We also compared the mitochondrial activities between the DF-MITO-

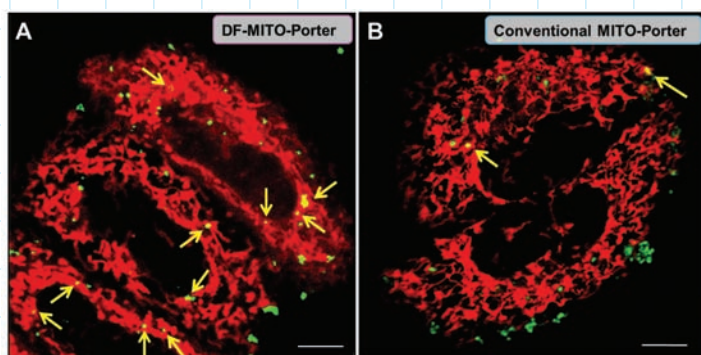


Figure 3. Intracellular distribution of carriers was analyzed by confocal laser scanning microscopy. DF-MITO-Porter (SM) (A) and conventional MITO-Porter (SM) (B) labeled with NBD (green) were incubated with HeLa cells. Mitochondria were stained with MitoFluor Red 589 (red) prior to observation. The clusters present in the mitochondria (yellow) are indicated. Scale bars, 10 μ m.

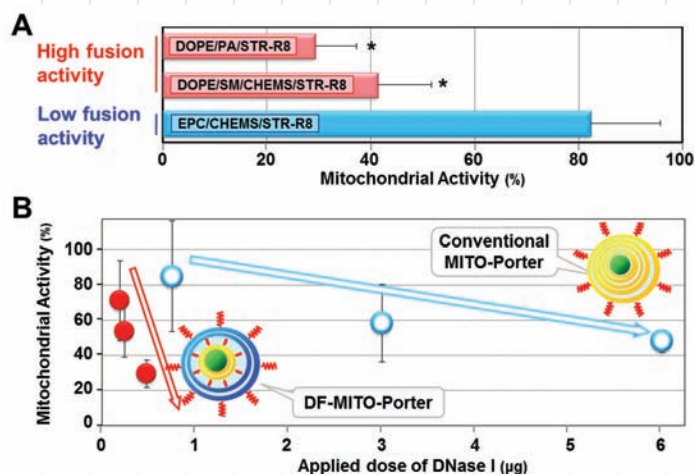


Figure 4. Evaluation of the mitochondrial activity after the mitochondrial delivery of DNase I. (A) DNase I (0.5 μ g) encapsulated in DF-MITO-Porter or control carrier with low mitochondrial fusion activity was incubated with HeLa cells, and the mitochondrial activity was then measured. Mean \pm standard deviation ($n = 3-4$). An asterisk (*) indicates significant differences between control carrier (EPC/CHEMS/STR-R8) and other carriers ($P < 0.01$ by one-way ANOVA, followed by Bonferroni correction). (B) Comparison of mitochondrial activity after DNase I delivery between DF-MITO-Porter and conventional MITO-Porter. The closed and open circles represent the values corresponding to the mitochondrial activity (%) when DF-MITO-Porter (PA) and conventional MITO-Porter (PA) were used. Data are represented as the mean \pm standard deviation ($n = 3-4$).

Porter and the conventional MITO-Porter. Figure 4B provides information on the applied dose of DNase I (x axis) and mitochondrial activity (y axis). We calculated the effective dose 50 (ED_{50}) for each carrier, and the results indicated that the DF-MITO-Porter ($ED_{50} = 0.33 \mu$ g) was 15-fold more efficient than the conventional MITO-Porter ($ED_{50} = 5.4 \mu$ g) in mitochondrial delivery.

Evaluation for the Levels of mtDNA and Nuclear DNA

To verify that the decrease in mitochondrial activity was the result of the digestion of mtDNA by DNase I, we evaluated the cellular mtDNA and nuclear DNA levels using PCR analysis. Each of the PCR products was subjected to agarose gel electrophoresis, and the DNA bands were visualized by UV after ethidium bromide staining (Fig. 5). In the case of the DF-MITO-Porter, the mtDNA levels were decreased, whereas the effect of carriers with a low mitochondrial fusion activity on mtDNA levels was negligible (Fig. 5A). On the other hand, no decrease in nuclear DNA levels was detected in any of the carriers (Fig. 5B). Based on these results, it can be concluded that the mitochondrial specific fusion activity of the DF-MITO-Porter is involved in a pathway related to the selective digestion of mtDNA.

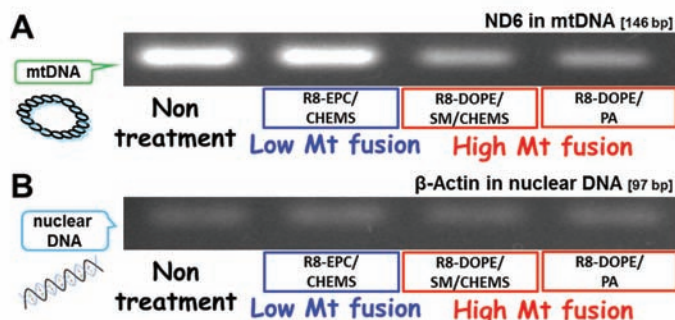


Figure 5. Evaluation for the levels of mtDNA and nuclear DNA after the mitochondrial delivery of DNase I. PCR assays for detection of the ND6 and the β -actin genes were performed to detect both mtDNA (A) and nuclear DNA (B), respectively.

Conclusions

We attempted to validate mitochondrial genome targeting using a DF-MITO-Porter. The findings described here indicate that the DNase I protein delivered by the DF-MITO-Porter caused a substantial decrease in mitochondrial activity, suggesting that a multistructured particle with a different lipid composition can be useful for mitochondrial delivery. In addition, the findings suggest that the mitochondrial delivery of DNase I by the DF-MITO-Porter resulted in the selective digestion of mtDNA. These results indicate that the DF-MITO-Porter holds promise as a delivery system targeted to mtDNA.

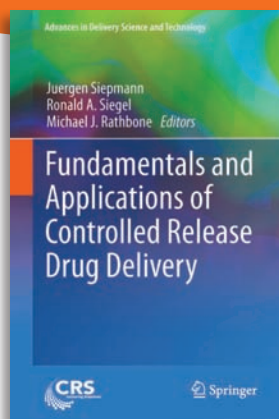
Acknowledgements

This work was supported in part by the Program for the Promotion of Fundamental Studies in Health Sciences of the National Institute of Biomedical Innovation, Japan (NIBIO) and a Grant-in-Aid for Young Scientists from the Ministry of Education, Culture, Sports, Science and Technology of the Japanese Government (MEXT). We also wish to thank many researchers and students that contributed to the success of this study.

References

1. Wallace, DC. The mitochondrial genome in human adaptive radiation and disease: On the road to therapeutics and performance enhancement, *Gene* 354: 169-180 (2005).
2. Yamada, Y, Furukawa, R, Yasuzaki, Y, Harashima, H. Dual function MITO-Porter, a nano carrier integrating both efficient cytoplasmic delivery and mitochondrial macromolecule delivery, *Mol. Ther.* 19: 1449-1456 (2011).
3. Yamada, Y, Akita, H, Harashima, H. Multifunctional envelope-type nano device (MEND) for organelle targeting via a stepwise membrane fusion process. *Methods Enzymol.* 509: 301-326 (2012).
4. Yamada, Y, Harashima, H. Delivery of bioactive molecules to the mitochondrial genome using a membrane-fusing, liposome-based carrier, DF-MITO-Porter. *Biomaterials* 33: 1589-1595 (2012).
5. Akita, H, Kudo, A, Minoura, A, Yamaguti, M, Khalil, IA, Moriguchi, R, Masuda, T, Danev, R, Nagayama, K, Kogure, K, Harashima, H. Multi-layered nanoparticles for penetrating the endosome and nuclear membrane via a step-wise membrane fusion process. *Biomaterials* 30: 2940-2949 (2009). ■

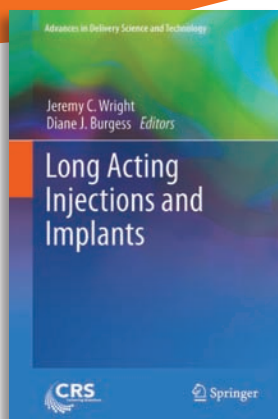
CRS—Your Delivery Science and Technology Library



Edited by
Juergen Siepmann,
Ronald A. Siegel, and
Michael J. Rathbone

1st Edition, 2012, XIII,
592 pages. Hardcover,
ISBN 978-1-4614-0880-2

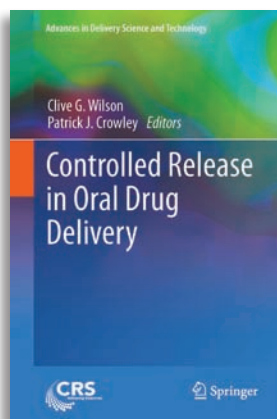
\$239 Regular Price
Member Price \$179.25



Edited by
Jeremy C. Wright and
Diane J. Burgess

1st Edition, 2012, XV,
557 pages. Hardcover,
ISBN 978-1-4614-0553-5

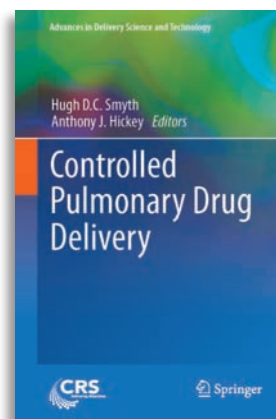
\$239 Regular Price
Member Price \$179.25



Edited by
Clive G. Wilson and
Patrick J. Crowley

2011; XIII,
412 pages. Hardcover,
ISBN 978-1-4614-1003-4

\$239 Regular Price
Member Price \$179.25



Edited by
Hugh D.C. Smyth and
Anthony J. Hickey

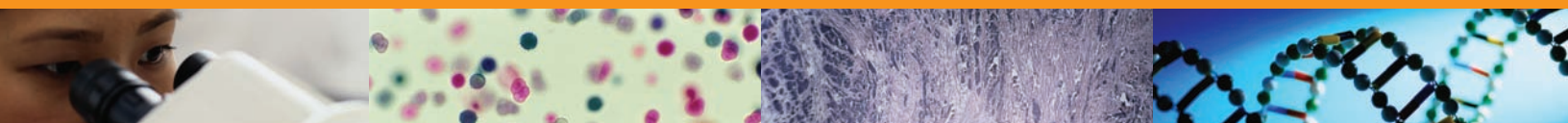
1st Edition., 2011, XIII,
557 pages. Hardcover,
ISBN 978-1-4419-9744-9

\$239 Regular Price
Member Price \$179.25

*Watch for more titles in the
Advances in Delivery Science and Technology series
COMING SOON!*

CRS members save 25% on all purchases.

Not a member? Join today and SAVE.
www.controlledreleasesociety.org



Consumer and Diversified Products Division Luncheon in Québec City

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

Nothing makes a meal more enjoyable than good company and engaging conversation. The Consumer and Diversified Products (C&DP) Division once again gathered to this end at their annual luncheon on Tuesday, July 17, in Québec City. This event is held at each CRS Annual Meeting to provide opportunities for those involved in nonpharmaceutical controlled release application areas to exchange ideas and maintain or establish new relationships. Attendees made the short walk across the street from the Centre des congrès de Québec to the adjacent Hilton Hotel to take part in the event. This year's luncheon was financially supported with sponsorships from Ronald T. Dodge Company, Fleet Laboratories, and Coating Place, Inc. The 50 attendees were served with a generous buffet lunch and good conversation with colleagues and friends. C&DP Chair James Oxley of Southwest Research Institute gave a warm welcome to attendees and a brief overview of the C&DP Division focus and mission. Attendees left with new or renewed connections with fellow C&DP Division interests, food in their stomachs, and, perhaps, new controlled release ideas and opportunities. ■



James Oxley, C&DP Division Chair, addresses C&DP Luncheon attendees at this year's CRS Annual Meeting.

Consumer and Diversified Products Division Changes

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

New officers for the Consumer and Diversified Products (C&DP) Division of CRS were installed at the C&DP Division meeting that took place on Tuesday, July 17, at the CRS Annual Meeting in Québec City. Officers are elected each year by active division members and assume their roles at the annual meeting. Nicole Papen-Botterhuis of TNO Science and Industry stepped up from her role as Vice Chairman to assume the Chairman role in absentia from outgoing Chairman James Oxley of Southwest Research Institute. Chris McDaniel of Fleet Laboratories assumed the Vice Chairman position. Jei McKinney of Encapsys assumed the Secretary position from outgoing Secretary Allison Calahan of Kraft Foods Global, Inc.

The C&DP Division is keenly interested in controlled release applications and research in nonpharmaceutical application areas

including but not limited to food, personal care, nutritional, nutraceutical, flavors, fragrances, consumer and household products, agriculture, pest control, textiles, and diverse industrial. The division has historically been involved in organizing five-to-six C&DP technical sessions at the CRS Annual Meeting and workshops on controlled release technologies or product characterization at the annual meeting and similar meetings of other organizations or societies. C&DP leadership will play a key role as the division moves forward with its mission to advance science, technology, and education in the field of controlled release or delivery of active ingredients in these and related areas. Active C&DP Division members teleconference the first Thursday of each month. If interested in sharing ideas with the C&DP Division or being involved actively in the division, contact the CRS office, and they will connect you to the group. ■

Veterinary Sessions a Success in Québec City, and the New Preclinical Sciences & Animal Health Division Is Launched

Thierry Vandamme,¹ Arlene McDowell,² and Michael Rathbone³

Report on Scientific Sessions

For the 2012 meeting of the Controlled Release Society, two veterinary sessions were organized. Chaired by Prof. Michael Rathbone (International Medical University, Malaysia) and Prof. Thierry Vandamme (University of Strasbourg, France), the first session, "Protein and Peptide Therapeutics for Animal Patients," was introduced by invited speaker Dr. Frank Aldwell from Immune Solutions Ltd. in New Zealand. During his talk, Frank compared subcutaneous needle vaccination with oral delivery in a lipid matrix (Liporale™) using a mouse model. He showed that oral vaccination using BCG—the human tuberculosis (Tb) vaccine—formulated in Liporale™ established populations of replicating bacilli in lymphatic tissues of the alimentary tract of mice. When infected with Tb organisms, Liporale™ BCG mice showed levels of protection that were similar to subcutaneous BCG vaccination. Adaptation of a Tb vaccine for oral delivery can provide effective and long-lasting immunity in the lungs that is superior to that provided by subcutaneous vaccination. Dr. Arlene McDowell of the University of Otago, New Zealand, showed that polymeric nanoparticles can be used to administer D-Lys⁶-GnRH, a peptide fertility-control agent, to a wild animal species and produce a biological response to the peptide. Interesting results and conclusions were given by Dr. Richard Elkes (Devlab, MSD, United Kingdom) concerning evaluating the role of dosage size and feeding on gastric retention (GR) in dogs. Indeed, during his presentation, he called to mind numerous approaches to try to achieve GR, one of which was the use of size-increasing systems. Richard concluded that dosage forms that had greatly different size and swelling profiles behaved similarly in dogs. Based on his data, along with studies on the effect of food, he suggested that GR is mediated mainly by calorific/fat content taken with a GR dosage form, and the actual size of the dosage form is less important in the dog model. This first session was ended by Wanhui Liu (School of Pharmacy, Yantai University, People's Republic of China), who presented analytical results concerning the quantitation of sustained release of triptorelin in beagle dog plasma by liquid chromatography–tandem mass spectrometry.

The second session was joint with Bioactive Materials on "Protein and Vaccine Delivery" and was chaired by Prof. Sevdal Senel (Hacettepe University, Turkey) and Dr. Arlene McDowell. Prof. Cory Berkland (University of Kansas and Orbis Biosciences, U.S.A.) was the invited speaker, who this year



Sarah Hook, Ben Boyd, Anette Müllertz, Peter Cheifetz, and Mike Rathbone (standing) deep in discussion at the 2012 Preclinical Sciences & Animal Health Get-Together quiz event in Québec City.

received the CRS Young Investigator Award. Congratulations, Cory! His talk concerned the formulation of uniform PLGA microspheres able to sustain NSAID blood levels with zero-order kinetics. The results exposed by Cory allow us to explore the possibility of developing a safer, more effective extended pain reliever using Orbis Biosciences' controlled release technology. It also offers the possibility to reformulate generic NSAIDs into a long-lasting injectable depot without the typical drug "burst." Joseph Rosenthal (Cornell University, U.S.A.) showed that engineered pathogen-like particle subunit vaccines induce robust, TH1-biased immunity. Among other things, he exhibited the use of bacterial outer membrane vesicles (OMVs) derived from the probiotic *E. coli* strain Nissle 1917 (EcN), engineered as recombinant subunit vaccine delivery carriers. During his experiments, green fluorescent protein (GFP) was selected as the model antigen and recombinantly expressed as a fusion chimera with the surface-displayed enterotoxin ClyA in hypervesiculating EcN. He concluded his talk with the vaccination in a murine model combined with additional *in vitro* studies, which allowed for thorough assessment of EcN OMV-facilitated immunostimulation and the resulting anti-GFP response. Therefore, his results indicated the induction of a robust, TH1-biased immune response, making the EcN OMVs potentially ideal for vaccine applications. The use of parathyroid hormone related protein (PTHrP) to prevent curve progression in a novel murine model of early onset scoliosis was presented by Michael Sullivan, Department of Surgery, McGill University Health Centre, Canada. Little is known about the pathogenesis of

¹University of Strasbourg, France.

²University of Otago, New Zealand.

³International Medical University, Malaysia.

scoliosis, which is a three-dimensional deformity of the spine. Mice deficient in FGF receptor 3 (FGFR3) signaling exhibit spine curvature at one month. It is hypothesized that the progressive curvature throughout life is caused in part by excessive bone cell apoptosis. A nuclear targeting sequence (NTS) in the mid-region of PTHrP has been shown to prevent apoptosis in bone cells. Michael explained the use of pellets (Innovative Research of America) containing NTS peptide, which are implanted in the concave aspect of the spines of eight-week-old mice, to maintain a therapeutic dose for 60 days. Spine architecture and composition were evaluated by X-ray, micro CT, and histology. Prof. Rainer Müller (Free University of Berlin, Germany) showed a new technology: CapsInject™ LBL coating technology for controlled delivery of biologicals. CapsInject™ is an injectable system based on the layer by layer (LBL) deposition technique that comprises the coating of biocompatible, biodegradable, porous particles with alternating layers of positive and negative polyelectrolytes (PEs) in a fashion that enables controlled delivery of the drug by continuous erosion of the coated particle together with providing protection against too-fast degradation by body enzymes. In this proof of concept study, the model proteins lysozyme and insulin were used and were encapsulated by different types and numbers of PE layers. Dr. Sarah Hook (School of Pharmacy, University of Otago, New Zealand) ended this session by presenting the ability of a novel colloidal carrier (cubosomes) to optimize the transcutaneous delivery of a peptide vaccine in combination with microneedle (MCN) pretreatment, which was examined *in vitro* using still-born piglet skin. Sarah concluded that MCNs were able to efficiently, but transiently, disrupt the stratum corneum, creating microchannels and increasing peptide penetration into and through skin. Incorporation of the peptide vaccine in a colloidal carrier appeared, therefore, to promote movement of the active into skin rather than permeation through the skin.

Preclinical Sciences & Animal Health Get-Together

The social function for the veterinary group in Québec was a pub quiz event held on Monday evening after the scientific



Delegates learn about the new Preclinical Sciences & Animal Health Division that was launched at the 2012 get-together in Québec City.

sessions and organized by Prof. Thierry Vandamme and Dr. Arlene McDowell. After all, who doesn't like testing their knowledge of trivia (animal related, of course)? Tickets were sold out for the event, with 100 people registered. Attendees of the "Animal Allsorts" quiz were challenged with questions on general animal knowledge, famous animals, and animals in music as well as veterinary controlled release. How would you have done in the quiz?

Which of these pets has become an invasive species in the U.S.A.?

- (a) European rabbit
- (b) domestic cat
- (c) Burmese python
- (d) budgerigar

Thanks to Sarah Hook and Ben Boyd, who helped with the collection and marking of answers. Our thanks are also extended to Pfizer Animal Health, who sponsored this event. And well done to team Down on the Pharm—our 2012 quiz winners!

Launch of the New Preclinical Sciences & Animal Health Division

The launch of the new Preclinical Sciences & Animal Health Division took place on the evening of Monday, July 16. Prof. Michael Rathbone provided an overview of the mission, objectives, and initiatives of the new division.

The Preclinical Sciences & Animal Health Division is intended to meet not only the needs of scientists involved in the development and regulation of drugs and biologics intended for veterinary use but also the interests of pharmaceutical scientists working in preclinical drug development. Its mission is to foster opportunities for interaction and collaboration between CRS members interested in animal and human health and to provide a platform to explore:

1. Opportunities for collaboration between CRS members interested in animal and human health.
2. Platforms and forums to discuss:
 - a. the use of animal models in preclinical studies,
 - b. limitations of animal models,
 - c. use of animal models above rodents,
 - d. interspecies differences in drug absorption, pharmacokinetics, and target site drug delivery,
 - e. *in vitro* models and the three Rs of ethical research,
 - f. all matters relating to the animal health industry, and
 - g. sharing of formulation practices.

The new division is open to any CRS member from around the globe who is involved with, and knowledgeable in, the broad scope of preclinical sciences and animal health as they relate to controlled release technologies. Please register your interest on being on the new Preclinical Sciences & Animal Health Division listserve by sending your contact details to Michael Rathbone at michael.rathbone@imu.edu.my.

Current initiatives include integration of the areas of animal health and animal models into a joint CRS Annual Meeting

track, establishment of a website that will be a forum for knowledge and discussion of topics related to preclinical sciences and animal health, and the strategic growth of the division through the engagement of CRS members interested in the use of animal models in preclinical studies; interspecies differences in drug absorption, pharmacokinetics, and target site drug delivery; and all matters relating to the animal health industry. Other initiatives include publication of articles on preclinical sciences and animal health in the *CRS Newsletter*, development of webinars and webcasts relating to preclinical sciences and animal health, and the planning of workshops and scientific tracks at annual meetings on such topics as use of simulation and modeling of animal species to support drug development in human and veterinary species.

As a jumpstart to nurture collaborative efforts within the division, an FDA Center for Veterinary Medicine (CVM) initiative that involves capturing information on canine breed differences was discussed at the launch. Some examples of information that the CVM is trying to capture for the use of testing and building physiologically based pharmacokinetics models were defined. They included breed differences in drug pharmacokinetics; breed differences in physiological parameters such as GI transit time, cardiac output, lean body mass, renal and hepatic blood flow, renal function, and so on; and breed differences in transporter function and metabolizing enzymes (phase 1 and 2). Ultimately, the goal of this initiative is to incorporate this information into models that will improve the FDA's ability to use existing data to predict pharmacokinetic variability across the canine population. If you have information or data that you can share, please email Marilyn Martinez at marilyn.martinez@fda.hhs.gov.



Dr. Harold Boxenbaum

The launch was in memory of Dr. Harold Boxenbaum, who leaves behind a legacy of landmark scientific accomplishments. Harold was the founding father of pharmacokinetic allometric scaling and in his distinguished career served as an educator, scientist, manager, and regulator. Throughout his career, Harold made an enormous contribution to clinical pharmacology and became an internationally recognized clinical pharmacologist.

The successful launch was followed by a meeting of the inaugural committee:

Mike Rathbone (Cochair)
Marilyn Martinez (Cochair)
Peter Cheifetz (Deputy Chair)
Megan Pagel (Staff Liaison)
Terry Bowersock
David Brayden
Cyril Desevaux
Sarah Hook
Tim McCaffery
Barry Moore
Anette Müllertz
Sevda Senel
Theirry Vandamme

Answer to the quiz question is (c). ■



Thirsty for Information?

Try LATTE—Linking Academic Technologies and Techniques to Everyone—a searchable database designed to help you identify experts in specific areas of CRS-related technologies and techniques.

CRS Members—You are invited to create your LATTE profile to offer your expertise to the membership and search LATTE to find the experts you are looking for.

▶▶▶ Sign up online at www.controlledreleasesociety.org/community/Pages/LATTE.aspx

Drug Delivery and Translational Research (DDTR) Update

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

I hope everyone had an exciting time at the CRS Annual Meeting in Québec City. A *DDTR* focus group consisting of *DDTR* editors, CRS leadership and staff, and Springer staff met during the annual meeting to review the progress of our publication. As you are aware, the primary focus of *DDTR* is to advance the science and technology of delivering bioactives and to provide a unique forum for publication of high-quality translational drug delivery research. We are pleased to report that, compared with last year, the flow of manuscripts and the number of downloads have significantly increased. *DDTR* has gained greater visibility at various CRS forums and higher awareness among CRS members, and the majority of published papers have included *in vivo* data with a focus on translational research. We are also pleased that colleagues from industry have contributed a good number of high-quality papers. *DDTR* has published three well-received special issues, and six more are at various stages of development.

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

Special Issues



DDTR Special Focus Issue on "Regenerative Medicine" Vol. 2, Issue 5, Pages 293–414, 2012

The main objective of this themed issue on regenerative medicine is to highlight the importance of merging concepts from drug delivery and materials science with cell biology to evolve new paradigms for controlling cell function. The issue presents advances in the engineering of

biomaterials for controlling cell fate, new strategies for gene delivery, comprehensive reviews on adapting and processing extracellular matrix components, the state of the art in blood

compatibilization of biomaterials, strategies to control lineage choices in pluripotent cells, and methods for simple and efficient means for proteomic analysis of cell and tissue environment. The diversity of topics presented by preeminent scientists makes it a must read for the controlled release community.

About the Guest Editor

V. Prasad Shastri

Prasad Shastri is a professor at the University of Freiburg, Germany, where he holds the Hermann Staudinger Chair for Biofunctional Macromolecular Chemistry, which is named after the Nobel laureate who was the first recipient of this endowed chair. He is also the director of the Institute for Macromolecular Chemistry and one of the core faculty at the BIOSS Centre for Biological Signaling Studies, which is one of the national clusters of excellence in Germany. He received his Ph.D. from Rensselaer Polytechnic Institute (Troy, NY) in 1995 and carried out his postdoctoral work with Robert Langer at MIT. He has published over 100 peer-reviewed papers, proceedings, extended abstracts, and book chapters and authored over 30 issued and pending patents in polymers, biomaterials, pharmaceuticals, and regenerative medicine. Additionally, he has pioneered several technologies in biomaterials, drug delivery, and nanotechnology, including the "*in vivo* bioreactor," a groundbreaking approach for autologous engineering of bone and cartilage. His laboratory is actively involved in the development of biomaterials for controlling cellular microenvironments, *in vivo* engineering of tissue, intracellular delivery, cancer therapeutics, and functional imaging.

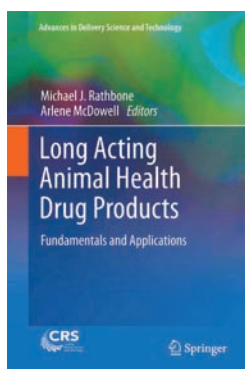


Upcoming Special Issues

- **Cancer Stem Cells** by Jayanth Panyam
- **Nasal Drug Delivery** by Lisbeth Illum and Elka Tuitou
- **Nanotechnology** by Padma Devarajan and Vandana Patravale
- **Tissue Engineering** by Sing Yian Chew and Kam W. Leong
- **Nano-Bio Interface** by Shyam Mohapatra and Subhra Mohapatra ■

Animal Health Drugs and RNA Interference Covered in Two New CRS Books

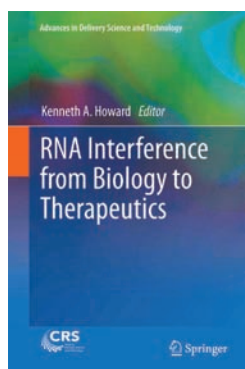
CRS Annual Meeting & Exposition attendees were the first to get a preview of the two new titles from the CRS book series. *Long Acting Animal Health Drug Products* and *RNA Interference from Biology to Therapeutics* are the newest volumes in the *Advances in Delivery Science and Technology* series, and they were available for preorder during the CRS Annual Meeting as well as online now.



Long Acting Animal Health Drug Products is the comprehensive guide on the theories, applications, and challenges associated with the design and development of long-acting veterinary formulations. The volume, edited by Michael J. Rathbone and Arlene McDowell, acts as a reference to the animal health formulation scientist and contains chapters written by some of the leading experts in the field. The book covers everything a student or a

formulation scientist in industry or academia needs to know about this unique drug delivery field.

RNA Interference from Biology to Therapeutics is an up-to-the-minute, highly informative, and invaluable text for those actively involved or interested in this fascinating and high-impact field. Editor Kenneth A. Howard has brought together key players and shapers in the fields of RNAi and delivery science to create a truly unique interdisciplinary text, making it a “must-read” for both students and experts in, and at the interface of, RNAi, pharmaceutical science, and medicine.



Both of the new books are available for preorder today and will ship in late 2012. These join the entire CRS library, including *Controlled Release in Oral Drug Delivery*, *Controlled Pulmonary Drug Delivery*, *Fundamentals and Applications of Controlled Release Drug Delivery*, and *Long Acting Injections and Implants*. Watch for more titles to be announced in 2013.

Remember that CRS members qualify for a 25% discount on all titles in the *Advances in Delivery Science and Technology* series and on all Springer book titles if purchased through Springer's online site. An exclusive CRS member discount token is available on the CRS website, www.controlledreleasesociety.org/publications. Be sure to log in to access these special savings, and take a look at the new CRS titles today! ■

Your Membership:

Your Access to the Future of Delivery Science and Technology



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

Access:

- The new website, with enhanced capabilities to help you advance delivery science and technology
- Find delivery science experts via the LATTE database—Linking Academic Technologies and Techniques to Everyone
- Expand your knowledge with the growing webcast library, part of the new website
- Learn about delivery science through our new books, including the upcoming *RNA Interference from Biology to Therapeutics*, with member discount pricing
- Online subscription to *Drug Delivery and Translational Research (DDTR)*
- Find your next position via the Job Center
- Reduced subscription rates to the *Journal of Controlled Release*, *European Journal of Pharmaceutics and Biopharmaceutics (APV)*, and *Biomaterials*
- Reduced registration rates to the Annual Meeting & Exposition and select workshops/short courses
- Subscription to *CRS Newsletter*

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



www.controlledreleasesociety.org

Syringe and white capsule images courtesy of istock.com. Hygiene products image courtesy of shutterstock.com.

People in the News

*Compiled by Steven Giannos, Chrono Therapeutics Inc.
Industrial Editor*

Dr. Gerald Yakatan Joins Imprimis Pharmaceuticals Science and Regulatory Advisory Board

PRNewswire: August 7, 2012 – SOLANA BEACH, CA, U.S.A. – Imprimis Pharmaceuticals, Inc. (OTC Markets Group: IMMY), a specialty pharmaceutical company developing noninvasive, topically delivered products, announced that it has created a Science and Regulatory Advisory Board and that Dr. Gerald Yakatan has become the inaugural member of the newly created board. The Imprimis Science and Regulatory Advisory Board will be comprised of scientists and pharmaceutical industry thought leaders who have demonstrated a record of success in developing drugs for clearance by the U.S. Food & Drug Administration. The mission of the Imprimis Science and Regulatory Advisory Board will be to advise Imprimis management on the future development of the patented Accudel topical drug delivery platform and to assist in the design and execution of the planned phase 3 clinical studies for Imprimis's topical 10% ketoprofen anti-inflammatory drug called Impracor.

Imprimis Pharmaceuticals, Inc., CEO Mark L. Baum stated, "The Imprimis team welcomes Dr. Yakatan to our newly created Science and Regulatory Advisory Board. Jerry is an impressive figure in the pharmaceutical industry, experiencing success in the academic world at University of Texas, Austin, where he served as a Professor and eventually as Chairman of the Pharmaceutics Department, and later in industry where in 1980 he joined Warner Lambert as Director of Pharmacokinetics and Drug Metabolism and eventually was promoted to Vice President of Product Development Worldwide. At Warner Lambert, Dr. Yakatan participated in the development of several drug products including Lopid®, Lipitor®, Eryc®, Accupril®, Neurontin®, and the Benadryl® cough line. In 1998, Dr. Yakatan began his tenure at Avanir Pharmaceuticals as President and Chief Executive Officer where he led the development efforts of Nuedexta™ and where he was responsible for the regulatory approval and commercialization of Abreva®. Dr. Yakatan is a Fellow of the American Association of Pharmaceutical Scientists and of the American College of Clinical Pharmacology."

Dr. Yakatan commented, "I have met with the Imprimis managers on several occasions and have reviewed the significant opportunity Imprimis has. I believe that my experience in participating in every step of the drug development process, including the stage that Impracor is at now, can make a difference—in terms of avoiding certain trial design pitfalls, managing the trial process, and ultimately presenting a relevant and compelling body of data to the FDA for approval."

Baum added, "Our Impracor upcoming trials are 'must-win,' and our team has invested considerably in reviewing our existing data and designing a new trial that has the benefit of this 'rear view' analysis. We believe that Jerry's leadership and participation on our Science and Regulatory Advisory Board will provide critical guidance to our team as we approach this important project as well as future development opportunities with our patented Accudel topical drug delivery platform."

Collegium Pharmaceutical Announces the Appointment of Gino Santini to Board of Directors

Business Wire: July 24, 2012 – CUMBERLAND, RI, U.S.A. – Collegium Pharmaceutical, Inc., a specialty pharmaceutical company focused on the development of innovative treatments for chronic pain, is pleased to announce the appointment of Gino Santini to its board of directors. Mr. Santini most recently served as Senior Vice President of Corporate Strategy and Business Development at Eli Lilly and Company, where he led corporate strategy and long-range planning, M&A, new product licensing, innovative financing of internal development projects, and the expansion of Lilly Ventures in the U.S. and China.

"We are very pleased to have Gino join our board of directors at this pivotal time in the company's history. As we progress our lead candidate, an extended-release, tamper-resistant oxycodone product for the treatment of chronic pain (COL-003), toward NDA filing, Gino's expertise in commercialization and business development will be instrumental in assisting the company in choosing our strategic path," said Michael Heffernan, CEO of Collegium.

Mr. Santini recently retired after a 27-year career at Eli Lilly and Company, where he held positions of increasing responsibility, serving as Senior Vice President, Corporate Strategy and Policy; President, U.S. Operations; and President, Women's Health Business Unit. Mr. Santini is a past Chairman of the Board of the National Pharmaceutical Council and of Noble of Indiana, a nonprofit agency serving individuals with developmental disabilities in Central Indiana. In addition to Collegium, Mr. Santini currently serves on the boards of AMAG Pharmaceuticals (NASDAQ: AMAG), Horizon Pharma (NASDAQ: HZNP), Sorin SpA (SRN.MI), and Allena Pharmaceuticals.

"The company's DETERx® technology has the potential to address a large unmet clinical and societal need in the use of opioids for the treatment of chronic pain. I look forward to working with the Collegium team to advance the lead product to the market," said Mr. Santini.

Caisson Biotech, LLC, Appoints Biotechnology Veteran Glenn Nedwin CEO and President

Business Wire: July 23, 2012 – AUSTIN, TX and OKLAHOMA CITY, OK, U.S.A. – Caisson Biotech, L.L.C., a biopharmaceutical company with the patented drug delivery technology HEptune™, announced today that it has appointed Glenn E. Nedwin, Ph.D., as chief executive officer and president. Thomas Harlan, president of Emergent Technologies, Inc., the innovation solutions company that funds and manages Caisson Biotech, stated that Caisson's new partnerships and expansive growth drove the appointment of Dr. Nedwin, a seasoned veteran with an exceptional track record in strategic leadership and building company value.

"Caisson's recent multi-million dollar technology access and license agreement with Novo Nordisk and increasing number of deals in the pipeline made the timing right to bring Dr. Nedwin on board," explained Harlan. "Glenn's comprehensive background in operations, business and product development, and market focus will take Caisson to the next level."

Dr. Nedwin has more than 30 years' experience in the pharmaceutical and biotechnology industries. He has held industry-influencing scientific and corporate management positions, most notably as president of Novozymes, Inc., and executive vice president of the Genencor Division of Danisco (recently acquired by DuPont). At Genencor he was responsible for the \$330M+ Technical Enzyme Business Unit and was a member of the Danisco Leadership Forum. While with Genentech, Dr. Nedwin was a coinventor and key team member that discovered TNF-alpha and -beta, among other human cytokines.

"I am very excited to join Caisson Biotech as CEO and President," said Nedwin. "Caisson's novel, natural HEptune drug delivery technology for improved drug performance perfectly fits the needs of the pharmaceutical industry. HEptune offers the ability for drug half-life extension and improvements in performance, product lifecycle management, and patient quality of life. We are seeking additional corporate partners for our technology, and we intend to become a leader in drug delivery."

Dr. Nedwin brings to Caisson substantial domestic and international experience with start-up, growth, and global organizations in the areas of new market identification, innovation, R&D, P&L, sales, and marketing. Coauthor of more than 30 scientific publications and patents, he is coeditor in chief of the journal *Industrial Biotechnology*. He serves on the Emergent Technologies, Inc., board of directors. Dr. Nedwin holds a bachelor of science in biochemistry from the State University of New York College at Buffalo, a master's degree in the management of technology from Massachusetts Institute of Technology Sloan School of Management, and a Ph.D. in biochemistry from the University of California, Riverside.

Kenan Institute Appoints Joseph DeSimone as New Director

PRNewswire: July 16, 2012 – CHAPEL HILL, NC, U.S.A. – The University of North Carolina at Chapel Hill's Frank Hawkins Kenan Institute of Private Enterprise has appointed Joseph M. DeSimone as its new director. DeSimone is the Chancellor's Eminent Professor of Chemistry at UNC and William R. Kenan Jr. Distinguished Professor of Chemical Engineering at NC State University and of Chemistry at UNC. He replaces John D. Kasarda, who retired in June after serving as the director of the Kenan Institute for 22 years.

"We are very pleased to welcome Joseph DeSimone to the Kenan Institute," said James W. Dean Jr., dean of UNC Kenan-Flagler. "He is a world-renowned scholar in his field. As an innovative entrepreneur, he is applying his research to design novel nanomedicines for cancer therapy and to improve vaccines and drug delivery mechanisms. He is the perfect leader to continue the institute's cutting-edge research and collaboration with business and communities to create positive local and global change."

"Rooted in the visionary leadership of Frank Hawkins Kenan and John Kasarda, the Kenan Institute is central to UNC's continued leadership as an entrepreneurial university in the 21st century," DeSimone said. "I am forever grateful for the unbelievably strong support that I and the university continue to receive from the Kenan family. We are uniquely positioned to leverage the intellectual capital we have right here on campus, join it with some of the best and brightest minds from around the globe, and develop innovative market-based solutions to some of the most pressing global challenges of our time, including poverty, health, education, energy, sustainable development, and economic growth. I am thrilled to have the opportunity to help drive the institute forward at this critical juncture."

The Kenan Institute, part of UNC's Kenan-Flagler Business School, pursues cutting-edge research, educational programs, and public policy initiatives in the areas of entrepreneurship, economic development, and global competitiveness.

DeSimone's research focuses on applying lithographic fabrication technologies from the computer industry for the design and synthesis of new medicines and vaccines. He has almost 300 publications, is an inventor on more than 130 patents, and has more than 100 patents pending. In 2004, DeSimone and his students invented a new technology to create nanoparticles using a process they coined as PRINT (Particle Replication In Non-wetting Templates).

With PRINT, DeSimone and his team were the first to successfully adapt manufacturing techniques from the computer industry to make advances in medicine, including improved approaches to cancer treatment and diagnosis. Other projects include developing nanoparticle vaccines for infectious diseases, vaccines for cancer, and particles that mimic red blood cells.

People in the News continued from page 25

DeSimone cofounded Liquidia Technologies, a Triangle-based nanotechnology company, to further develop the PRINT technology. Liquidia has its first product—a nanoparticle flu vaccine—in clinical trials.

In June, Liquidia announced the initiation of a multiyear collaboration with GlaxoSmithKline, potentially worth several hundred million dollars. The efforts of the two companies as a result of this agreement could lead to the development of multiple life-saving health-care products.

DeSimone is a member of the UNC Lineberger Comprehensive Cancer Center, an adjunct member at Memorial Sloan-Kettering Cancer Center in New York, and director of the Institute for Advanced Materials, Nanoscience and Technology and the Institute for Nanomedicine at UNC. He has been elected to both

the National Academy of Sciences and the National Academy of Engineering, the highest honors that a U.S. scientist or engineer can receive.

DeSimone received a bachelor of science in chemistry degree from Ursinus College in 1986 and a doctorate in chemistry from Virginia Polytechnic Institute and State University in 1990.

Visionary entrepreneur and philanthropist Frank Hawkins Kenan created the Kenan Institute in 1985 to promote collaboration among business, government, and academia and to promote the growth of private enterprise worldwide and the use of private-sector resources to serve the public interest. Nearly three decades later, the impact of the institute's research and initiatives is visible in thriving communities and companies from rural North Carolina to the Greater Mekong subregion of Asia. ■

**Join CRS in the Ultimate
Global Gathering Place**

Hawaii



40th Annual Meeting & Exposition of the Controlled Release Society

**July 21–24, 2013
Hawaii Convention Center
Honolulu, Hawaii, U.S.A.**

Emerging Challenges for Global Delivery

The 2013 CRS Annual Meeting & Exposition in Hawaii will create the perfect opportunity to access the latest in delivery science worldwide. This unique location allows for greater connections with researchers throughout the Pacific Rim.

A meeting you will not want to miss—mark your calendars now to join CRS in spectacular Honolulu, Hawaii!

Abstract Submission Opens November 2012



www.controlledreleasesociety.org/meeting



Courtesy of the Hawaii Convention Center / David Cornwell

In the News continued from page 27

Initially being released on the over-the-counter market as a health and wellness product, CanChew gum is undergoing clinical development in the European Union for pain relief, relief for muscular spasticity, particularly in MS patients as well as relief from nausea, specifically from chemotherapy. The key active ingredient, the hemp-based CBD-infused essential oil, is made available by Medical Marijuana Inc. and their state-of-the-art extraction technology.

During the interview, Dr. Anastassov touched on some of the challenges facing present-day prescription pain medications and the need, especially in Europe, for safe but effective pain relief options and how the CanChew advantage aims to bridge that gap.

CanChew is a unique, socially acceptable, patient friendly, taste masked, and convenient delivery format for delivery of cannabis/cannabinoid(s) based pharmaceuticals. The delivery of these medications via the oral mucosa provides for rapid and near complete absorption directly into the systemic circulation. This leads to rapid onset of effects and increased bioavailability. Pre-systemic metabolism is thus avoided. This system of delivery offers clearly improved economic opportunities compared to alternative drug delivery routes. For more information, please visit the company's website at www.MedicalMarijuanaInc.com.

London Olympic Park Environmental Cleanup Uses Bioremediation Technology from REGENESIS to Expedite Development

Business Wire: August 1, 2012 – SAN CLEMENTE, CA, U.S.A. – The July 17 opening of London's £7-billion 2012 Olympic Park, with its 16 new major stadia and other sports facilities, also marks the successful conclusion of one of the world's largest brownfield regeneration projects in recent years. This Olympic-sized cleanup included the remediation and redevelopment of more than 200 hectares (500 acres) of former industrial land where previous uses such as chemical and fertilizer works, landfills, and depots had left a legacy of severe soil and groundwater contamination.

Among the new facilities, the Zaha Hadid-designed London Aquatics Centre (LAC) is one of the most conspicuous, being one of most prominent of the "green" buildings in the new complex as well as the first structure most visitors will see as they approach the Olympic Park. As a brownfield redevelopment project, the Aquatics Centre also presented a significant remediation challenge, being located on a former industrial site and contaminated with lubricating oil, a difficult-to-remove light, non-aqueous phase liquid (LNAPL). The Olympic Delivery Authority (ODA) set strict deadlines for all Olympic facility construction projects, and the subsurface foundations for the LAC were to be completed by July 27, 2009, exactly three years before opening day.

Subsoil remediation for the Aquatic Centre site began in November 2007, using dual-phase vacuum extraction (DPVE) to remove the LNAPL. But with construction slated to start the

following April, it was clear that DPVE alone would not be sufficient to remediate the dissolved-phase hydrocarbon plume. An *in situ* solution became the only viable option.

In situ enhanced bioremediation, a widely accepted and well-understood natural biodegradation process, was chosen to clean up this portion of the site. This approach utilizes indigenous microbes to aerobically biodegrade petroleum hydrocarbons in-place. The actual process is facilitated using an injectable, REGENESIS's Advanced Oxygen Release Compound (ORC Advanced®). Upon hydration and injection, this powder-like material accelerates aerobic bioremediation by releasing molecular dissolved oxygen for periods up to 12 months on a single application. Without this valuable oxygen supply, the required aerobic bioremediation processes either cease or proceed at very slow rates.

The patented Controlled-Release Technology (CRT) in ORC Advanced allows for an efficient, long-term release of oxygen, which provides optimal conditions for sustained aerobic biodegradation. CRT also saves time and money during implementation by eliminating the need for multiple oxygen release compound applications.

Additionally, ORC Advanced® was applied at the LAC site using direct-push injection. This application approach is highly efficient as it requires no permanent well installation, aboveground piping, or mechanical equipment and after application no operational costs or further site disturbance.

The remedial objectives for the Aquatics Centre site were quickly satisfied, and the approach was so successful that construction was able to start not only within ODA's deadline but months ahead of schedule and without hindrance from the ongoing remedial work.

San Clemente, California-based REGENESIS has been a recognized leader in the environmental industry since 1994, developing and marketing proven, innovative environmental technologies that significantly reduce the cost, time, and difficulty of restoring contaminated soil and groundwater. REGENESIS products have been used by leading, multinational environmental consulting firms on more than 18,000 soil and groundwater cleanup projects worldwide and across the U.S.A. REGENESIS's Land Science Technologies Division, established in 2008, develops and markets advanced technologies for sustainable land development, with a focus on brownfield redevelopment initiatives. For more information visit REGENESIS online at www.regenesis.com.

July 2012

pSivida Corp. Announces Germany Grants ILUVIEN® Marketing Authorization for the Treatment of Chronic Diabetic Macular Edema

Business Wire: July 26, 2012 – WATERTOWN, MA, U.S.A. – pSivida Corp. (NASDAQ: PSDV) (ASX: PVA), a leader in developing sustained-release drug delivery products for treatment of back-of-the-eye diseases, today announced the Federal Ministry of Health of Germany (Bundesministerium für Gesundheit, BfArM) has granted marketing authorization to ILUVIEN® for the treatment of vision impairment associated with chronic diabetic macular edema (DME) considered insufficiently responsive to available therapies.

This marketing authorization follows the completion of the Decentralized Regulatory Procedure (DCP) in the European Union (EU), in which the Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom, serving as the Reference Member State (RMS), delivered a positive outcome for ILUVIEN along with six Concerned Member States (CMS), specifically Austria, France, Germany, Italy, Portugal, and Spain. The German authorization is the fifth national approval in the EU, preceded by Austria, Portugal, the U.K., and France.

“We are very pleased ILUVIEN has received marketing authorization in Germany. Our product now has marketing authorization in five of the seven targeted EU countries,” said Dr. Paul Ashton, president and chief executive officer of pSivida. “We look forward to ILUVIEN’s commercial launch in these countries and to it receiving approval in the two remaining CMS countries, Italy and Spain, in the coming months.”

The International Diabetes Federation estimates that more than five million people are currently living with diabetes in Germany, and according to estimates of Alimera Sciences, pSivida’s licensee of ILUVIEN for the treatment of DME, more than 215,000 people suffer from vision loss associated with DME.

ILUVIEN is an injectable, sustained-release intravitreal insert that releases sub-microgram levels of fluocinolone acetonide (FAc) for up to 36 months for the treatment of chronic DME. pSivida is developing an insert of the same design for the treatment of uveitis affecting the posterior of the eye.

Bio-Path Holdings Begins Enrollment in Fourth Cohort of Phase I Clinical Trial of Lead Product Candidate Liposomal Grb-2 in Leukemias

Business Wire: July 25, 2012 – HOUSTON, TX, U.S.A. – Bio-Path Holdings, Inc. (OTCQX: BPTH) (“Bio-Path”), a biotechnology company developing a liposomal delivery technology for nucleic acid cancer drugs, today announced that it has begun enrolling patients into the fourth dosage cohort in its phase I clinical trial of its lead product candidate, BP-100.1.01 (liposomal Grb-2), which is being evaluated as a systemic treatment for blood cancers including acute myeloid

leukemia (AML), chronic myelogenous leukemia (CML), acute lymphoblastic leukemia (ALL), and myelodysplastic syndrome (MDS). The phase I trial will include five cohorts in total. The trial is being conducted at the University of Texas MD Anderson Cancer Center.

Liposomal Grb-2 is systemically delivered by intravenous injection. In the fourth cohort, patients will receive a dose of 40 mg/m² twice a week for four weeks, for a total of eight doses. The current protocol for the clinical trial includes dose escalation of 5, 10, 20, 40, and 50 mg/m². The expected dose for treatment is 45 mg/m² based on preclinical studies in animals.

Earlier this year, Bio-Path upgraded its substance and drug supplier to meet increased demand for the drug. The step-up in the supply of liposomal Grb-2 was necessary based upon projected treatments for patients in the clinical trial, and the increased number of patients who, in the principle investigators’ opinion, stabilized from treatment with liposomal Grb-2 and were to receive extended treatment.

“The arrival of the latest batch of drug product from our new supply chain and the opening of the fourth cohort of our clinical trial are important steps for the company,” said Peter Nielsen, president and chief executive officer of Bio-Path. “Establishing the new, higher capacity supply chain for our drug candidate was an essential step to ensure adequate future supply needed to support increased usage of liposomal Grb-2 in blood cancers, as well as treatments for other cancer indications that may be developed.”

A.P. Pharma to Raise \$53.6 Million in Common Stock Offering

Business Wire: July 25, 2012 – REDWOOD CITY, CA, U.S.A. – A.P. Pharma, Inc. (OTCBB: APPA.OB), a specialty pharmaceutical company, today announced that it has entered into definitive agreements with certain new and existing institutional investors relating to a private placement of common stock. In the transaction, the investors have agreed to purchase 102,000,000 shares at \$0.525 per share, resulting in gross proceeds of approximately \$53.6 million. The transaction is expected to close on or around July 30, 2012, subject to the satisfaction of customary closing conditions.

“We believe the \$53.6 million to be raised will place the company in a strong financial position as we approach the commercialization phase with our lead product, APF530, which we are developing for the prevention of both acute- and delayed-onset chemotherapy-induced nausea and vomiting,” stated John B. Whelan, president and chief executive officer. Mr. Whelan continued, “We recently completed filling our three registration lots and also have reached agreement with the FDA on our protocol for our human factors validation study, which we plan to complete shortly. We plan to resubmit our New Drug Application to the FDA in September 2012.”

In the News continued on page 30

In the News continued from page 29

A.P. Pharma's lead product, APF530, is being developed for the prevention of both acute- and delayed-onset chemotherapy-induced nausea and vomiting (CINV). APF530 contains the 5-HT₃ antagonist granisetron formulated in the company's proprietary Biochronomer™ drug delivery system, which allows therapeutic drug levels to be maintained for five days with a single subcutaneous injection. This five-day range is designed to cover the delayed phase of CINV, whereas currently available intravenous and oral formulations of granisetron are approved only for the prevention of acute-onset CINV. Granisetron was selected for APF530 because it is widely prescribed by physicians based on a well-established record of safety and efficacy.

A.P. Pharma is a specialty pharmaceutical company developing products using its proprietary Biochronomer™ polymer-based drug delivery platform. This drug delivery platform is designed to improve the therapeutic profile of injectable pharmaceuticals by converting them from products that must be injected once or twice per day to products that need to be injected only once every one or two weeks. A.P. Pharma received a Complete Response Letter to its APF530 New Drug Application (NDA) and is targeting a resubmission of the NDA to the U.S. Food and Drug Administration in September 2012. For further information, please visit the company's web site at www.appharma.com.

SRI International Researchers Developing Bioadhesive Gel to Protect Women from HIV and HSV Infections

PRNewswire: July 24, 2012 – MENLO PARK, CA, U.S.A. – A new grant from the National Institute of Allergy and Infectious Diseases (NIAID) will support the development of a topical microbicide gel for drug delivery. The innovative gel formulation will be a combination therapy against human immunodeficiency virus (HIV) and herpes simplex virus type 2 (HSV-2) infections in women.

Every day, more than 3,000 women around the world are newly infected with HIV, and it is the leading cause of death in sub-Saharan Africa. Of the 33.3 million people living with HIV/AIDS across the world, 22.5 million are in Africa. HSV-2 is a global epidemic and affects up to 80 percent of the female population in Africa.

As part of the grant, SRI International researchers will develop and test a prototype bioadhesive formulation for sustained delivery of the antiviral drugs tenofovir and acyclovir to the vaginal surface. Because chronic HSV-2 infections have been shown to speed the progression of immunodeficiency disease, researchers are focused on developing a microbicide that prevents both HIV and HSV-2 infections.

"The inexpensive and easy-to-use combination therapy in development could help contain the spread of HIV and HSV, and possibly other sexually transmitted diseases," said Gita Shankar, Ph.D., director of Formulations R&D, SRI Biosciences. "One of the strongest benefits of a topical gel formula is that it

can offer protection when options such as condoms are unavailable or unacceptable."

The awarded grant is for two years with a possible extension of three additional years. Development work will focus on creating a combination therapy that will limit the risk of drug resistance, while providing women with safe and sustained drug delivery. The novel product will be based on a patented bioadhesive polymeric platform developed at SRI.

This research will be supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under award number R21AI098658. The content of this press release is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

SRI's Biosciences division carries out basic research, drug discovery, and drug development, and provides contract (CRO) services. SRI has all of the resources necessary to take R&D from "Idea to IND"®—from initial discovery to the start of human clinical trials—and specializes in cancer, immunology and inflammation, infectious disease, and neuroscience. SRI's product pipeline has yielded marketed drugs, therapeutics currently in clinical trials, and additional programs in earlier stages. In its CRO business, SRI has helped government and commercial clients and partners advance many drugs into patient testing. SRI is also working to create the next generation of technologies in areas such as diagnostics, drug delivery, medical devices, and systems biology.

Egalet Announces Issuance of U.S. Patent

PRNewswire: July 24, 2012 – MALVERN, PA, U.S.A. – Egalet Ltd., a privately held specialty pharmaceutical company focused on developing safe, effective and tamper-resistant medications, announced today a notice of allowance by the United States Patent and Trademark Office for its patent application Serial No. 2007/0042044 entitled "Matrix Compositions for Controlled Delivery of Drug Substances."

The patent relates to the Egalet® prolonged release technology. The composition described by the patent family is utilized for all the Egalet® opioid products tested in clinical trials, including the new improved tablet construction that has a very hard shell surrounding the erodible matrix containing the opioid.

"This U.S. allowance adds to our patent portfolio that provides us with extensive coverage until 2033 for our novel, tamper-resistant technology," said Bob Radie, CEO and president. "With the growing issue of abuse of pain medications, we believe we are well positioned to address the need for new safe treatments with Egalet's tamper-resistant opioids currently in development."

Egalet has protected its inventions via extensive patenting and by know-how protection. The patent portfolio comprises both patent applications and issued patents that protect Egalet's

different technologies as well as patent applications and issued patents that are specifically related to the product opportunities in the pipeline. This U.S. patent adds to the patents that have already been issued in Europe, Australia, New Zealand, India, Japan, and Hong Kong.

Catalent Announces Commencement of Supply of Abilify® Orally Disintegrating Tablets to Otsuka Pharmaceutical Co., Ltd., and Extensive Investments to Its Zydis® Technology Capabilities in Swindon, U.K.

Business Wire: July 24, 2012 – SOMERSET, NJ, U.S.A. – Catalent announced it has commenced supply to Otsuka Pharmaceutical Co., Ltd., of Abilify® OD tablets (orally disintegrating tablets [ODT]), which utilize Catalent's Zydis® fast-dissolve drug delivery technology.

Otsuka is one of the leading innovative pharmaceutical companies in Japan and has developed Abilify® OD for the treatment of schizophrenia and improvement of manic symptoms associated with bipolar disorder.

Additionally, to support the increasing demand for Zydis® ODT formulations from the Japanese market, Catalent intends to make multimillion dollar investments to its Zydis® ODT operations in Swindon, U.K.

Commenting on the new launch and investments, Dr. Ian Muir, president of Catalent's Modified Release Technology business, stated, "We are delighted to partner with Otsuka on the launch of this important new formulation of Abilify® OD. Catalent's Zydis® fast dissolve technology has provided a tablet that is very palatable, and disintegrates within seconds in the mouth, making it very easy to take. As patient medication compliance is critical for those requiring antipsychotic therapies, Otsuka believes this new formulation will be of great assistance to patients in Japan. Abilify® OD is the 8th drug approved and launched in Japan using Catalent's Zydis® ODT."

Mr. Hans-Joachim Rohe, president of Catalent Japan, added, "We are very excited with the growing demand for Catalent's Zydis® ODT in Japan, where many products could benefit from this type of ODT formulation. We have seen an increasing number of customers specifically seeking truly rapid disintegration and superior palatability in order to differentiate their products in Japan's competitive market. In this regard, Zydis® ODT can excel over competing alternatives such as loosely compressed tablets."

Derma Sciences Announces Issuance of Two New U.S. Patents for DSC127

Business Wire: July 23, 2012 – PRINCETON, NJ, U.S.A. – Derma Sciences, Inc. (Nasdaq: DSCI), a medical device and pharmaceutical company focused on advanced wound care, today announced the issuance of patents 8,207,233 and 8,207,234 by the U.S. Patent and Trademark Office. These patents provide additional intellectual property protection for the company's investigational drug DSC127 by describing the angiotensin

peptide in a specific formulation and a method of using the same to treat diabetic foot ulcers.

The inventors are Drs. Kathleen Rodgers and Gere diZerega, both the original inventors of DSC127 and the patent portfolio surrounding the product. The two new patents were issued to the University of Southern California (USC) and have been added to Derma Sciences' exclusive worldwide licensing agreement with USC. The new patents effectively extend the patent life of the drug through January 2032.

Commenting on the patent awards, Edward J. Quilty, president and chief executive officer of Derma Sciences, said, "DSC127 is an important component of our leadership strategy in advanced wound care and is a key element in our company's growth plan. We are pleased that our development efforts on this drug for the treatment of diabetic foot ulcers have resulted in additional intellectual property protection in the United States and potentially other parts of the world. These new patents will significantly extend the period of market exclusivity should our planned phase 3 trials be successful and the drug be approved. We have been working diligently to expand Derma Sciences' intellectual property position in wound healing, and these new patents are important components in ensuring that our work and investments remain ours."

Dr. Rodgers, associate professor at the USC School of Pharmacy, added, "I am pleased with the recognition by the patent office of the superior properties of the drug carrier in terms of biocompatibility and optimal drug delivery characteristics."

DSC127 is an analog of a naturally occurring peptide, angiotensin, which has been shown to increase keratinocyte proliferation, increase extracellular matrix production, and increase vascularization. Use of this peptide may help the body utilize its own stem cells more productively for wound healing.

Derma Sciences is a medical technology company focused on three segments of the wound care marketplace: pharmaceutical wound care products, advanced wound care dressings, and traditional dressings. Derma Sciences has successfully completed the phase 2 clinical trial in diabetic foot ulcer healing with DSC127, an investigational pharmaceutical drug under development for accelerated wound healing and scar reduction, and is preparing to begin phase 3 clinical trials. Its MEDIHONEY® product is the leading brand of honey-based dressings for the management of wounds and burns. The product has been shown to be effective in a variety of indications and was the focus of a positive large-scale, randomized controlled trial involving 108 subjects with leg ulcers. Other novel products introduced into the \$14 billion global wound care market include XTRASORB® for better management of wound exudate, BIOGUARD® for infection prevention, and TCC-EZ™, a gold-standard off-loading device for diabetic foot ulcers. For more information, please visit www.dermasciences.com.

In the News continued from page 31

OPKO Health Announces License for Topically Active Formulation of Ranibizumab

Business Wire: July 18, 2012 – MIAMI, FL, U.S.A. – OPKO Health, Inc. (NYSE: OPK) today announced it has signed a research and license agreement with a prominent Mexican professor of ophthalmology for a topically active formulation of the anti-VEGF antibody, ranibizumab, utilizing OPKO proprietary drug delivery technology. The technology will initially target the development of the ranibizumab product to treat diabetic macular edema (DME), but the delivery system will also be studied with other pharmaceutical products to treat DME and other eye diseases.

Presently, ranibizumab is only approved for delivery by intravitreal injection,” noted Dr. Frost, M.D., chairman and chief executive officer of OPKO. “We believe the development of a topical VEGF antibody formulation would result in substantial benefits to patients.”

BioTime Signs Agreements with Jade Therapeutics for Ophthalmological Drug Delivery Applications of HyStem® Technology

Business Wire: July 17, 2012 – ALAMEDA, CA, U.S.A. – BioTime, Inc. (NYSE MKT: BTX), a biotechnology company that develops and markets products in the field of regenerative medicine, today announced the signing of an exclusive sublicense agreement and a supply agreement with Jade Therapeutics, LLC, a developer of an ophthalmological therapeutic sustained-release drug delivery platform. Under the agreements, BioTime will provide Jade with clinical-grade HyStem® hydrogels and certain patented technology for use by Jade Therapeutics in the development of new pharmaceutical products for ophthalmologic use. Jade plans to utilize the hydrogels to facilitate time-release topical delivery of recombinant human growth hormone to help heal lesions on the ocular surface. Jade Therapeutics will retain rights to market their product upon completion of development and obtaining marketing approval. Financial terms of the transaction were not disclosed.

William P. Tew, Ph.D., BioTime’s chief commercialization officer, stated that “numerous published scientific reports have established the efficacy of HyStem® to facilitate cell transplantation in animal models, and we currently plan on a near-term approval to market one HyStem®-related product, Renevia™, in the EU for reconstructive and cosmetic surgery. We believe our HyStem® technology may also be useful as a device for the slow, timed release of therapeutic agents such as those being developed by Jade Therapeutics, as well as for the controlled release of proteins secreted from BioTime’s stem cell lines.”

“The HyStem® product line has potential utility in a wide array of human therapeutic products,” said Michael West, Ph.D., BioTime’s CEO. “We intend to seek additional industry partners for applications that are not core to our own therapeutic product development.”

BioTime’s HyStem® hydrogels are proprietary biocompatible hydrogels that mimic the human extracellular matrix (ECM), a web of molecules surrounding cells that is essential to cellular function. When cells lacking the ECM (or an ECM substitute) are introduced into the body, they typically die or fail to function correctly after transplantation. BioTime’s HyStem® hydrogels are currently being used by researchers at a number of leading medical schools in studies of stem cell therapies for facilitating wound healing and for the treatment of ischemic stroke, brain cancer, vocal fold scarring, and cardiac infarct.

Jade Therapeutics, LLC, a privately held company headquartered in Park City, Utah, focuses on the development of locally administered, sustained-release therapeutics that improve corneal healing following damage from disease or injury, thus improving visual function and quality of life. The company’s initial product is designed to deliver recombinant human growth hormone, a well-characterized biologic that has already been demonstrated to have significant healing properties. Jade recently secured a prestigious Utah Science Technology and Research (USTAR) grant to continue to conduct preclinical and market research and is in negotiation with several prominent academic and military affiliates to further product development. Examples of ocular disorders addressed by the company’s technology include persistent corneal epithelial defects and corneal damage due to dry eye disease.

BioTime, headquartered in Alameda, California, is a biotechnology company focused on regenerative medicine and blood plasma volume expanders. Its broad platform of stem cell technologies is enhanced through subsidiaries focused on specific fields of application. BioTime develops and markets research products in the field of stem cells and regenerative medicine, including a wide array of proprietary ACTCellerate™ cell lines, HyStem® hydrogels, culture media, and differentiation kits. BioTime is developing Renevia™ (formerly known as HyStem®-Rx), a biocompatible, implantable hyaluronan and collagen-based matrix for cell delivery in human clinical applications. BioTime’s therapeutic product development strategy is pursued through subsidiaries that focus on specific organ systems and related diseases for which there is a high unmet medical need. BioTime’s majority-owned subsidiary Cell Cure Neurosciences, Ltd., is developing therapeutic products derived from stem cells for the treatment of retinal and neural degenerative diseases. BioTime’s subsidiary OrthoCyte Corporation is developing therapeutic applications of stem cells to treat orthopedic diseases and injuries. Another subsidiary, OncoCyte Corporation, focuses on the diagnostic and therapeutic applications of stem cell technology in cancer, including the diagnostic product PanC-Dx™ currently being developed for the detection of cancer in blood samples. ReCyte Therapeutics, Inc., is developing applications of BioTime’s proprietary induced pluripotent stem cell technology to reverse the developmental aging of human cells to treat cardiovascular and blood cell diseases. BioTime’s subsidiary LifeMap Sciences, Inc. markets GeneCards®, the leading human gene database, and is developing an integrated database suite to complement GeneCards® that will also include the LifeMap™

database of embryonic development, stem cell research, and regenerative medicine, and MalaCards, the human disease database. LifeMap will also market BioTime research products. BioTime's lead product, Hextend®, is a blood plasma volume expander manufactured and distributed in the U.S. by Hospira, Inc. and in South Korea by CJ CheilJedang Corporation under exclusive licensing agreements. Additional information about BioTime can be found on the web at www.biotimeinc.com.

Kala Pharmaceuticals Cofounder Publishes Data on Novel Therapeutic Approach to Overcome Mucosal Barrier for Prevention of Herpes Simplex Virus-2 Infection

Business Wire: July 12, 2012 – WALTHAM, MA, U.S.A. – Kala Pharmaceuticals, Inc., a leading developer of innovative products that rapidly and effectively penetrate the mucosal barrier to treat a wide range of debilitating diseases, announced a publication by company cofounder Justin Hanes, Ph.D., in *Science Translational Medicine* showing promising effects of its mucosal-penetrating products (MPPs) in preventing herpes simplex virus-2 (HSV-2) infection.

In the paper titled "Mucus-Penetrating Nanoparticles for Vaginal Drug Delivery Protect Against Herpes Simplex Virus," Dr. Hanes and collaborators at Johns Hopkins University School of Medicine conducted preclinical studies that included acyclovir-MPP, Kala's innovative therapeutic engineered with the anti-HSV drug acyclovir. The studies demonstrated that MPPs improve mucus penetration and drug retention, enabling the acyclovir-MPP to achieve greater efficacy at one tenth of the dose compared to conventional acyclovir.

"Mucosal barriers have been largely overlooked as a limitation for drug efficacy. These data show how Kala's MPP approach can open up new possibilities for more effective medicines," commented Robert Langer, ScD, another Kala cofounder and the David H. Koch Institute Professor at MIT. "Kala's technology can be used to engineer innovative therapies with the size and surface coating properties necessary to dramatically improve drug penetration and retention in mucosal tissues, leading to the potential for significantly enhanced therapeutic outcomes."

Key findings of the published study include:

- Upon challenge with HSV-2, Kala's acyclovir-MPP protected 53% of the mice from infection compared to only 16% of those treated with conventional acyclovir at the same dose. In fact, acyclovir-MPP demonstrated greater efficacy at one tenth of the dose compared to conventional acyclovir.
- Acyclovir-MPP was shown to be both nontoxic and safe after daily vaginal administration.
- Kala's MPPs achieved rapid coating of the cervicovaginal surface in mice, including distribution into the deep vaginal folds, within 10 minutes of therapeutic administration. The MPP showed not only greater but also much more uniform coverage in coating the mucosal tissue when compared to a conventional formulation.

- The MPPs also remained in place for at least 24 hours, enabling the potential for a once-daily therapy.

"These results from Dr. Hanes's lab at Johns Hopkins University are very encouraging and further expand on previous *in vivo* proof-of-concept studies with Kala's MPPs in other mucosal tissues, including our NIH-sponsored work in the eye and respiratory tract," said Guillaume Pfefer, Ph.D., CEO of Kala Pharmaceuticals. "These data show the significant impact that Kala's therapeutic approach can have in creating highly effective treatments for debilitating respiratory, ophthalmic, female reproductive tract, and gastrointestinal diseases."

Kala Pharmaceuticals, Inc., is developing innovative products that are capable of penetrating mucosal barriers for the treatment of major diseases that affect the eyes, lungs, gastrointestinal tract, and female reproductive system. Mucosal barriers have been largely overlooked as a limitation for drug efficacy. Using the company's proprietary technology platform, Kala's mucosal-penetrating products (MPPs) have the unique ability to rapidly and uniformly coat and permeate mucosal tissues, leading to highly effective treatments with improved side-effect profiles. The company is leveraging its platform as an internal product engine for a wide spectrum of potential applications, including treatments for respiratory, ophthalmic, female reproductive tract, and gastrointestinal diseases. Kala is also pursuing collaborations with partners to transform the therapeutic properties of marketed drugs and compounds in development. Kala was founded by leaders in the fields of nanomedicine and biopharmaceutical engineering, Dr. Justin Hanes of The Johns Hopkins University School of Medicine, Dr. Robert Langer of the Massachusetts Institute of Technology, and Dr. Colin Gardner, formerly of TransForm Pharmaceuticals/Johnson & Johnson and Merck. The company is backed by leading investors including Lux Capital, Polaris Venture Partners, and Third Rock Ventures. For more information, please visit www.kalarx.com.

R-Tech Ueno: Notification of Collaborative Study with Tohoku University on a New Drug Delivery System for Unoprostone

Business Wire: July 12, 2012 – TOKYO, Japan – We are pleased to announce that R-Tech Ueno (JASDAQ: 4573) will conduct a collaborative study with Tohoku University, a national university corporation, to develop a drug delivery system for isopropyl unoprostone (hereinafter referred to as unoprostone), a compound made by R-Tech Ueno, using a sustained drug delivery system device (patent pending: International Publication No. WO2011/021594) invented by the study team of Prof. Toshiaki Abe, M.D., et al., Division of Clinical Cell Therapy, United Centers for Advanced Research and Translational Medicine, Tohoku University, Graduate School of Medicine.

Unlike conventional devices that are inserted into the eye, this new device is a minimally invasive transscleral drug delivery system that is attached to the sclera and does not require vitreous

In the News continued from page 33

surgery. A phase II clinical study of frequent instillations (2 drops per instillation, twice a day) of UF-021 (unoprostone) eye drops, which are under development at our company for the treatment of retinitis pigmentosa, has been completed. We consider that if the unoprostone drug delivery system is realized, the treatment with unoprostone will become feasible in patients with retinitis pigmentosa in whom frequent instillation is difficult. We also consider that the expanded indication of unoprostone as a treatment drug for atrophic age-related macular degeneration, for which there is currently no effective therapy, may become possible. We hope to pursue this collaborative study with Prof. Abe's study team at Tohoku University to confirm the efficacy of the abovementioned preparation in humans in the future.

Alchemia to Spin Off Cancer Business

AAP: July 9, 2012 – BRISBANE, Australia – Drug developer Alchemia intends to demerge its oncology (cancer) business to form a new company and list it on the United States market.

Alchemia said on Monday that its oncology assets would be held by Audeo Oncology Inc., which will apply for listing on the NASDAQ exchange in the U.S.

Audeo Oncology intends to undertake an initial public offering of shares in the U.S. to raise an amount yet to be determined but with a ceiling of US\$60 million. It is intended that shares in Audeo will be dual listed and are expected to trade as Chess Depository Interests (CDIs) on the Australian Securities Exchange (ASX).

Alchemia will retain the drug fondaparinux, which is a generic version of GlaxoSmithKline's Arixtra, a synthetic anticoagulant used to prevent deep vein thrombosis. The demerger is subject to market conditions and shareholder, court, and regulatory approvals.

Alchemia chief executive Dr. Peter Smith said fondaparinux would be generating revenue, and shareholders would be expecting a dividend or capital return from it. Equally, Alchemia wanted to position its oncology assets where they would be most appreciated and best positioned for future growth.

"If we're going to split them up, we might as well go the whole hog and list on NASDAQ at the same time as listing in Australia to give us access to a greater pool of capital for use in the future, and also to establish a footprint for the company in the U.S., which is going to be the biggest market for our product," Dr. Smith said.

Dr. Smith said that if the oncology assets were to be expanded, the business needed to be closer to U.S. clinicians and regulators. "Looking years into the future, we'll be building up more of a footprint in the U.S.," he said. "In terms of the R&D taking place in Australia, we'll also see that added to, as well."

InVivo Therapeutics Engages FDA with Second Product, a Novel Drug Releasing Hydrogel for Chronic Pain Treatment

InVivo Therapeutics: July 2, 2012 – CAMBRIDGE, MA, U.S.A. – InVivo Therapeutics Holdings Corp. (NVIV), a developer of groundbreaking technologies for the treatment of spinal cord injuries (SCI) and other neurological injuries, today announced a novel hydrogel based product for the treatment of acute and sub-acute sciatica or radicular pain of the low back and legs and/or acute and sub-acute radicular pain of the neck or arms.

On June 29, 2012, InVivo submitted a request to meet with the U.S. Food and Drug Administration's (FDA) Office of Combination Products and the appropriate representatives from the Center for Drug Evaluation and Research (CDER) and the Center for Devices and Radiological Health (CDRH) to discuss a novel combination product.

InVivo's new technology is intended for the treatment of acute and sub-acute neck, back, and leg pain conditions that affect over 4.2 million patients annually in the United States. The product consists of a novel injectable hydrogel specifically engineered to allow for an effective, sustained release of a number of molecules, including methylprednisolone. A summary of the underlying research and development of this product was published in the *Journal of Biomaterials* in January 2011 and has led to a broad platform of neurological interventions.

"For years InVivo has been pressed by patients like myself to develop treatments for herniated disks and other neurological pain issues associated with the aging baby boomers in the United States, and now we have an answer in InVivo's hydrogel platform," said InVivo CEO Frank Reynolds. "We believe that the opportunity for our new treatment could exceed \$22B annually, and by late 2012 we plan to partner with a global leader in pain therapies to bring this product to market."

Said InVivo CMO Eric Woodard, M.D., "We feel that the hydrogel addresses several specific limitations of current therapies by allowing predictable sustained release of therapeutic molecules. Additionally, it exhibits the novel property of syneresis, or shrinkage, that significantly enhances its safety profile in neurological applications."

Added Reynolds, "We are developing technologies to treat both acute and chronic neurological injuries, and our first product, a biomaterial-based scaffold for acute spinal cord injuries, is currently under review at FDA. We look forward to receiving approval to begin human studies for that product in 2012."

Breaking the Skin Barrier: Drugs Topically Deliver Gene Therapy via Commercial Moisturizers for Skin Disease Treatment

ScienceDaily: July 2, 2012 – EVANSTON, IL, U.S.A. – "Getting under your skin" takes on a brave new meaning thanks to Northwestern University research that could transform gene regulation.

A team led by a physician-scientist and a chemist—from the fields of dermatology and nanotechnology—is the first to demonstrate the use of commercial moisturizers to deliver gene regulation technology that has great potential for life-saving therapies for skin cancers.

The topical delivery of gene-regulation technology to cells deep in the skin is extremely difficult because of the formidable defenses skin provides for the body. The Northwestern approach takes advantage of drugs consisting of novel spherical arrangements of nucleic acids. These structures, each about 1,000 times smaller than the diameter of a human hair, have the unique ability to recruit and bind to natural proteins that allow them to traverse the skin and enter cells.

Applied directly to the skin, the drug penetrates all of the skin's layers and can selectively target disease-causing genes while sparing normal genes. Once in cells, the drug simply flips the switch of the troublesome genes to "off."

A detailed study of a method that could dramatically redefine the field of gene regulation will be published online during the week of July 2 by the *Proceedings of the National Academy of Sciences* (PNAS).

Early targets of the novel treatment are melanoma and squamous cell carcinoma (two of the most common types of skin cancer), the common inflammatory skin disorder psoriasis, diabetic wound healing, and a rare genetic skin disorder that has no effective treatment (epidermolytic ichthyosis). Other targets could even include wrinkles that come with aging skin.

"The technology developed by my collaborator Chad Mirkin and his lab is incredibly exciting because it can break through the skin barrier," said co-senior author Amy S. Paller, M.D., the Walter J. Hamlin Professor, chair of dermatology, and professor of pediatrics at Northwestern University Feinberg School of Medicine. She also is director of Northwestern's Skin Disease Research Center.

"This allows us to treat a skin problem precisely where it is manifesting—on the skin," she said. "We can target our therapy to the drivers of disease, at a level so minute that it can distinguish mutant genes from normal genes. Risks are minimized, and side effects have not been seen to date in our human skin and mouse models."

A co-senior author of the paper, Mirkin is the George B. Rathmann Professor of Chemistry in the Weinberg College of Arts and Sciences and professor of medicine, chemical and biological engineering, biomedical engineering and materials science and engineering. He also is the director of Northwestern's International Institute for Nanotechnology.

Mirkin first developed the nanostructure platform used in this study in 1996 at Northwestern, and the FDA-cleared technology now is the basis of powerful commercialized medical diagnostic

tools. This, however, is the first realization that the nanostructures naturally enter skin and that they can deliver a large payload of therapeutics.

"The field of medicine needs new constructs and strategies for treating disease," Mirkin said. "Many of the ways we treat disease are based on old methods and materials. Nanotechnology offers the ability to very rapidly create new structures with properties that are very different from conventional forms of matter. This collaborative study is a case in point."

The key is the nanostructure's spherical shape and nucleic acid density. Normal (linear) nucleic acids cannot get into cells, but these spherical nucleic acids can. Small interfering RNA (siRNA) surrounds a gold nanoparticle like a shell; the nucleic acids are highly oriented, densely packed, and form a tiny sphere. The RNA's sequence is programmed to target the disease-causing gene.

"We now can go after a whole new set of diseases," Mirkin said. "Thanks to the Human Genome Project and all of the genomics research over the last two decades, we have an enormous number of known targets. And we can use the same tool for each, the spherical nucleic acid. We simply change the sequence to match the target gene. That's the power of gene regulation technology."

The nanostructures were developed in Mirkin's lab on the Evanston campus and then combined with a commercial moisturizer. Next, down in Paller's Chicago lab, the researchers applied the therapeutic ointment to the skin of mice and to human epidermis. The nanostructures were designed to target epidermal growth factor receptor (EGFR), a biomarker associated with a number of cancers.

In both cases, the drug broke through the epidermal layer and penetrated the skin very deeply, with cells taking up 100 percent of the nanostructures. They selectively knocked down the EGFR gene, decreasing the production of the problem proteins.

After a month of continued application of the ointment, there was no evidence of side effects, inappropriate triggering of the immune system, or accumulation of the particles in organs. The treatment is skin specific and doesn't interfere with other cells.

Interdisciplinary research is a hallmark of Northwestern. Paller and Mirkin said their work highlights the power of physician-scientists and scientists and engineers from other fields coming together to address a difficult medical problem.

"This all happened because of our world-class presence in both cancer nanotechnology and skin disease research," Paller said. "In putting together the Skin Disease Research Center proposal, I reached out to Chad to see if his nanostructures might be applied to skin disease. We initially worked together through a pilot project of the center, and now the rest is history."

In the News continued from page 35

Northwestern has one of nine Centers of Cancer Nanotechnology Excellence funded by the National Cancer Institute and one of six Skin Disease Research Centers funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

“This study is a landmark achievement in the area of gene regulation—I believe our work has a chance to positively and irreversibly change the field,” Mirkin said. “The skin is a very tough barrier to go through, which is why this effective gene knockdown has not been accomplished before. The power and elegance of this system are in its simplicity.” Mirkin and Paller are both members of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University.

The National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Cancer Institute, and the Army Research Office supported the research. The Northwestern Skin Disease Research Center provided core resources and a pilot grant.

The title of the paper is “Topical Delivery of siRNA-based Spherical Nucleic Acid Nanoparticle Conjugates for Gene Regulation.” In addition to Mirkin and Paller, other authors of the paper are Dan Zheng, David A. Giljohann, David L. Chen, Matthew D. Massich, Xiao-Qi Wang, and Hristo Jordanov, all from Northwestern. ■

Welcome New Members

Zeeshan Ahmad	Jason D. McArthur
Hyder A. Aliyar	Tim McCaffery
Hiroyuki Asada	Yan-Jing Ng
Donna Bibber	Takehiro Okumura
Tom Blackshaw	Lars R. Petersen
Pamela H. Cebrowski	Tazeen F. Rahman
Tao Chen	C. Matthias Rebmann
Phillip Cox	Enrique Reyna
Matthew Crum	Colin Rowlings
Pinaki R. Desai	John R. Samples
Nashwa El-Gendy	Taekwan Shin
Jacob Grana	Romi Singh
Ning He	Xuedong Song
Lieyu Hu	Beata Sweryda-Krawiec
Yi-You Huang	Larry Unsworth
Balaji V. Kadri	Scott Weishaar
Eliana Lima	Thean Yeoh
Sumit Madan	Weiping Yu



CRS Chapters—Reaching Around the Globe

Expand your local network.
Become involved in a
CRS Chapter.

[Argentina Local Chapter](#)
[Australian Local Chapter](#)
[Canadian Local Chapter](#)
[China Local Chapter](#)
[Germany Local Chapter](#)
[Greece Local Chapter](#)
[India Local Chapter](#)
[Israeli Local Chapter](#)
[Italy Local Chapter](#)
[Korea Local Chapter](#)
[New Zealand Local Chapter](#)
[Nordic Local Chapter](#)
[Slovenia Local Chapter](#)
[Spain-Portuguese Local Chapter](#)
[Student Chapter Connecticut](#)
[Student Chapter Illinois](#)
[Student Chapter Johns Hopkins University](#)
[Student Chapter New Jersey](#)
[Student Chapter—The Hebrew University of Jerusalem](#)
[Student Chapter University of California—Santa Barbara](#)
[Student Chapter University of Texas](#)
[Taiwan Local Chapter](#)
[Thailand Local Chapter](#)
[Turkey Local Chapter](#)
[United Kingdom-Ireland Local Chapter](#)



[www.controlledreleasesociety.org/
community/chapters](http://www.controlledreleasesociety.org/community/chapters)

February 6-8, 2013
Hilton San Diego Bayfront • San Diego, CA

17TH ANNUAL



DRUG DELIVERY PARTNERSHIPS™

Visionaries meet. Challenges are overcome. Innovation happens.

HEALTHCARE AND POLICY



Billy Tauzin
Former U.S. Congressman, Former President and CEO PhRMA



David Pyott
Chairman, President and CEO ALLERGAN



Myshkin Ingawale
Inventor, co-founder BIOSENSE TECHNOLOGIES

UNCOVER

NEW

PARTNERING STRATEGIES

NEW DRUG DELIVERY

TECHNOLOGIES, and

NEW PRODUCT

DEVELOPMENT TACTICS

to accelerate drugs to market and lengthen lifecycles for long term profitability.

Increased Networking Time by 100%

- New full day partnering room
- Extended breaks
- Exclusive online networking tool

Specific Content to Improve Your Profitability

- Current and future partnering strategies
- Life cycle management and line extensions
- New development strategies

Countless Opportunities to Help You Find Your Next Blockbuster

- 40+ innovative drug delivery technology companies demonstrating their capabilities

Senior Pharmaceutical Executives Show You the Way



Strategically Use Innovation to Drive Company Strategy
Christopher Seaton, Senior Vice President, Global Licensing, **BAYER PHARMACEUTICALS**



Regulatory Landscape Directing Drug Delivery Product Reimbursement

Steve Philips, Senior Director, Health Policy & Reimbursement, **JOHNSON & JOHNSON**



Determine Future Investment Opportunities through Drug Delivery Successes and Failures

David Steinberg, Managing Director, Equity Research, Specialty Pharmaceuticals & Drug Delivery, **DEUTSCHE BANK**



Combination Products as Key Delivery Tactic for Growth and Sustainability

Paul Jansen, Global Head, Medical Devices, **SANOFI-AVENTIS**



Licensing and IP Considerations for the New Era in Partnering

Roy Waldron, Senior Vice President and Associate General Counsel, **PFIZER**

15% OFF

Download the full conference brochure at www.drugdeliverypartnerships.com

Save **15%** when you register with priority code **P1878D** (discount is off standard rates)

Controlled Release Society
3340 Pilot Knob Road
St. Paul, MN 55121
United States of America

NON-PROFIT ORG.
U.S. POSTAGE
PAID
TWIN CITIES, MN
PERMIT NO. 90100

Calendar of Events

2012

10th International Nanomedicine and Drug Delivery Symposium (NanoDDS '12)

Sponsored by CRS
October 28–30
Atlantic City, NJ, U.S.A.
<http://nanodds2012.com>

Drug Delivery Australia Conference

Sponsored by CRS
November 26–27
Melbourne, Australia
www.crsaustalia.org

2013

Drug Delivery Partnerships

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

ISAA 2013—10th International Symposium on Adjuvants for Agrochemicals

April 22–26
Foz do Iguaçu, Paraná, Brazil
<http://events.isaa-online.org>

40th Annual Meeting & Exposition of the Controlled Release Society

Sponsored by CRS
July 21–24
Hawaii Convention Center
Honolulu, Hawaii, U.S.A.
www.controlledreleasesociety.org

5th BBBB International Conference

September 26–28
Athens, Greece
www.bbbb-eufeps.org