

What's Inside

The Board of Scientific Advisors
Scans the Horizon

Interview with Art Tipton

Debating CRS's Role in
Low-Income Countries

A Novel Technology for
Subdermal Implants

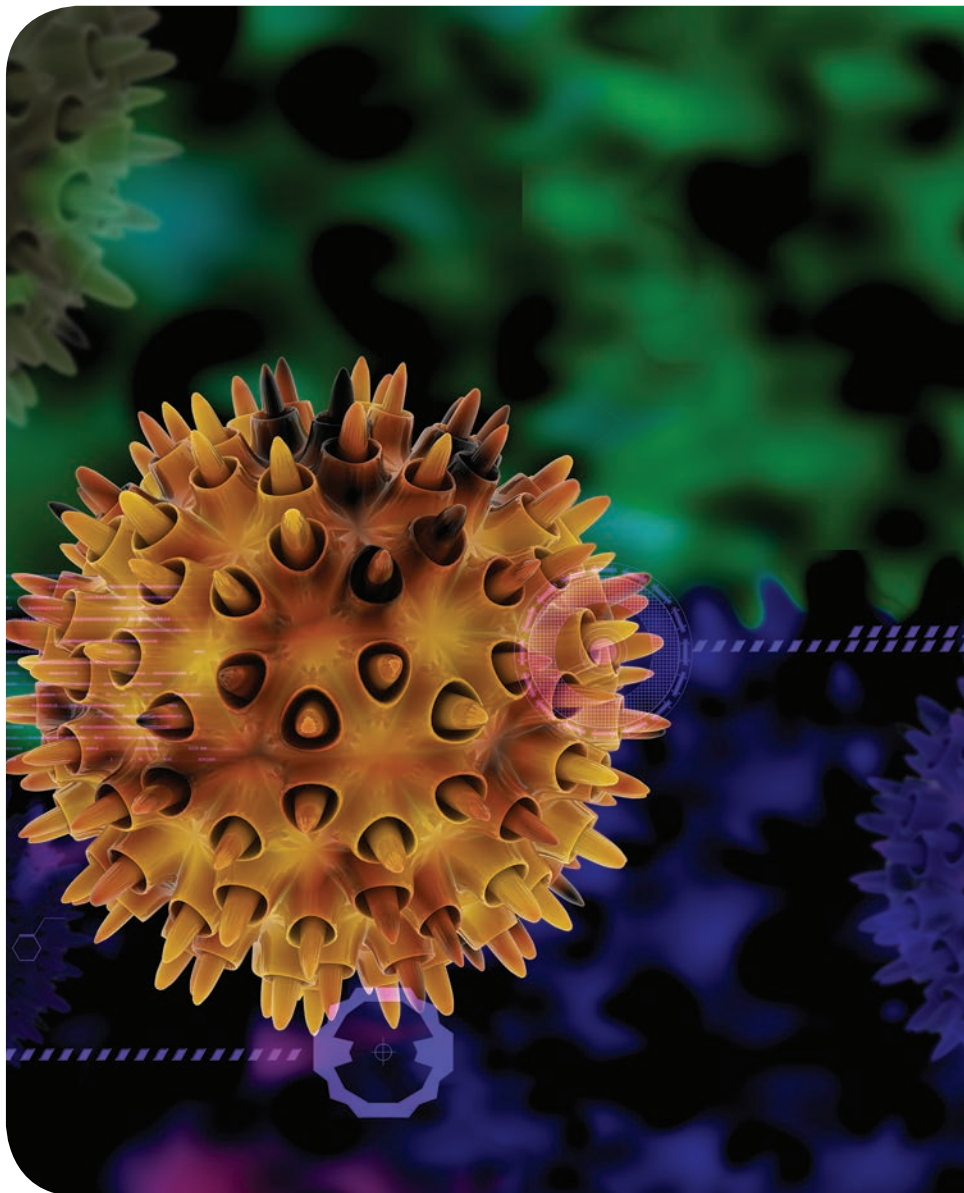
Enhancing Functionality of
RHDV Virus-like Particles

Evaluating Adjuvant
Characteristics of Particulate
Formulations

A Scientist Writes Fiction

2014 CRS Awards

CRS Election Results



Creating Value Through
Customised Delivery

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CRS Newsletter

Leading
Delivery Science
and Technology

Vol. 31 • No. 4 • 2014

Table of Contents

From the Editor	2
From the President	3
Opinion	
Debating CRS's Role in Low-Income Countries	4
What's on Board?	
CRS Election Results	5
41st CRS Annual Meeting & Exposition	6
Scientifically Speaking	
Highlights of NZCRS Award-Winning Presentations	10
Enhancing the Functionality of RHDV Virus-like Particles	10
Evaluating Adjuvant Characteristics of Particulate Formulations	12
Nanoscale Constrained Delivery: A Novel Technology for Subdermal Implants	14
Special Features	
"Artisinal" Publishing: A Scientist Writes Fiction	18
The Board of Scientific Advisors Scans the Horizon	20
DDTR Updates	
<i>Drug Delivery and Translational Research Updates</i>	23
Interview	
Getting Insights into Specialty Chemical Companies with Art Tipton	24
Chapter News	
Promoting Today's Ideas for Tomorrow's Medicines: Canadian Local Chapter Annual Symposium	27
Tenth Annual Meeting of the Spanish-Portuguese CRS Local Chapter	29
In the News	31
Calendar of Events	Cover 4

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 controlledreleasesociety.org.

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

Telephone: +1.651.454.7250
Facsimile: +1.651.454.0766

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

Many Paths to Our Destinations

Dear Reader,

I had the rare good fortune of having this year's CRS Annual Meeting in Chicago fall a mere three-hour drive from my home. Although I could avoid airports for the trip, there were few options to avoid road construction. Whether in the air, on the road, biking, or walking, our path is not always predictable. The rate at which we arrive is dependent on controlled things such as schedules and travel speeds as well as not-so-controlled things such as weather, mechanical concerns, computer malfunctions, road construction, and the collective travel plans of those whose paths intersect ours along the way. Nevertheless, from a broad perspective, I am thankful for the progress that has provided an infrastructure to interact in more productive ways.

Many years ago I had the pleasure of hearing speak the first person Dow Chemical Company had hired in an official capacity as an analytical chemist. The lab on his start date (circa 1930s) consisted of around seven burettes. He recalled a business trip from Michigan to a paper company in Wisconsin. On his return trip, when he reached Kalamazoo, Michigan, he had to hitch a ride in a railroad train box car to get home. Although that may have been a characteristic of the economic and technological times, it gives an interesting perspective on progress.

From another perspective, as we have progressed with increasing physical speed, we have progressed perhaps to a greater extent with electronic speed and processing efficiency. With information at our fingertips from an extensive network of sources, our rate of learning is—and has the potential to go—far beyond that of the past. Our minds are developing to keep up with the fast-paced environments in which they operate. This speed coupled with the increased organization of our collective knowledge base will likely continue to increase the speed of learning in the future. Taking this a step further, consider the capacity of our senses and the extent to which we may use them now and in the future.

Whether the pathways are physical, neural, electronic, or something else, these pathways are and have been the keys to our progress. This newsletter and the CRS Annual Meeting are contributors to such progress in the area of controlled release technology. As I drove home from Chicago, I again had a renewed sense of motivation and optimism. The collective spirit of CRS is the likely source of this, and I thank all who contributed to the success of the society and the annual meeting. Whether you attended the meeting or not, I hope that you can make time to read this issue of the *CRS Newsletter* to sense the tangible and intangible benefits of membership. I also hope we might meet next year in Edinburgh, regardless of what paths might take us there. Keep in mind, the less traveled roads or side roads may be rich in possibilities.

Happy Trails,
Chuck Frey ■



*Ian Tucker
University of Otago
Dunedin, New Zealand*

Our Global and Multidisciplinary Society

In its 40 years of existence, CRS has held its annual scientific meetings in 11 different countries, and its presidents have come from five different countries (United States, United Kingdom, Germany, Japan, and New Zealand). It has 15 local chapters spread in countries about the world and five student chapters. In the last four years, new chapters have commenced in Canada, China, and Malaysia, and we expect that in the near future a chapter will commence in Brazil. This year's program team, which was responsible for the highly appreciated scientific program in Chicago, was chaired by Ick Chan Kwon (Korea) with deputy chair Justin Hanes from Johns Hopkins University. The program team had members from six different countries. So I think we can justifiably claim that we are a truly international organisation.

Our other claim is that we are a multidisciplinary society dedicated to delivery science and technology. This was readily apparent in this year's meeting in Chicago, with plenary lectures and scientific sessions on a wide range of topics: process engineering, oral drug delivery, intracellular delivery, overcoming multiple biological barriers, advances in RNA and DNA delivery, nanoparticle-based delivery, transdermal delivery, controlled-release applications in food, feed, and beverages, micro and nano-encapsulation, and predictive animal models for assessing long-acting formulations for human and animal health. The creativity of attendees was stimulated by this complementary diversity and the networking opportunities the meeting generated.

Multidisciplinary diversity will be in evidence again at the 42nd CRS Annual Meeting, to be held in Edinburgh, Scotland, on July 26 – 29, 2015. The theme of that meeting will be "Creating Value Through Customised Delivery." I look forward to seeing you there enjoying the science and the delights of Scottish hospitality and scenery—not to mention the haggis and bagpipes.

In an era of ever-increasing specialization, a challenge for CRS is to ensure that a multidisciplinary meeting has value that is greater than, or least different from, the value of highly specialised conferences. This is much like the challenge confronting emporiums such as Macy's who must compete with specialty stores. And yet, compete they do. Since many of the creative opportunities in drug delivery exist at the interfaces between the complementary disciplines, we know that CRS has a visionary role to play in leading delivery science and technology. However, we also recognise the need for specialisation and for groups of like-minded CRS scientists to network. Our intention is to increase "bottom-up" driven networking by facilitating the formation of "communities of practice" at CRS meetings. Consequently, we believe that the annual conference will offer the best of all worlds: multidisciplinary networking and also networks of scientists who wish to discuss specific issues or problems in their area of delivery. Stay tuned for this development.

My year as president of CRS has been both enjoyable and rewarding. There is a theory about the performance of groups, including boards. According to Bruce Tuckerman's model, groups first form, then storm, then normalise relationships, and finally perform at a high level. I am delighted to say that the board I had the privilege to chair in 2013–2014 reached the performing stage very quickly. I am extremely grateful to my fellow board members for the time and dedication they gave to CRS over the last year. Participation on the board level this year was strong, with an average attendance at our board meetings and telecons of 80%, even with the challenges of full schedules and managing time zones. I am also delighted that Art Tipton, the new president, chaired the first meeting of the new board in Chicago and that the new board seems to have skipped Tuckerman's normal stages and gone straight to the performing level. I look forward to continuing to serve CRS in the coming year as past-president under Art Tipton's leadership. ■

Debating CRS's Role in Low-Income Countries

*Theresa M. Allen, Professor Emeritus, FRSC
Pharmacology and Oncology, University of Alberta, Canada*



I have been participating in some discussion behind the scenes as to whether or not there is a role for CRS in developing products for low-income countries. There is no doubt that there is an acute need in the poorest countries of the globe for effective new preventative and therapeutic treatments for the myriad of diseases that affect humans and animals in these regions.

I am not referring to lower-middle-income countries such as India, Brazil, and Cuba, which have a growing research and pharmaceutical manufacturing presence in the world and which have been able to increase access to and reduce costs of therapies in their own countries and in other “middle tier” countries. Further, there has been considerable progress in the last several months by NGOs and big and small pharma on improving access to small-molecule therapeutics in the developing world, which is certainly resulting in some significant improvements in some areas of disease. Organizations such as the Gates Foundation and Médecins Sans Frontières are also having a considerable impact through funding research into new therapies and through “feet on the ground,” but all of these efforts have only scratched the surface of the problems that exist in the poorest countries.

The criteria for getting a new therapy into widespread use in the developing world are demanding. The therapy must be very inexpensive, since the health care budgets of some of these countries are only a few dollars per person per year (less than \$10 up to around \$35, compared with around \$150 in lower-middle-income countries and \$7,000 in the United States). There can be tremendous problems with stability and accessibility of the therapies to the populace in areas with no refrigeration (or even no electricity), high temperatures and humidity, and poor or no road access. So the therapy must be easy and cheap to transport. The need for sterility, if required, presents further problems. Many of our current drug delivery systems require parenteral administration, yet in developing countries this adds considerably to the cost and the logistics of administration. Any new therapy should be

simple to administer, preferably by the enteral or topical route, and should not require multiple administrations. Patients who have to travel long distances, often by foot over difficult terrain or through areas of ethnic unrest, may not be able to return to a clinic to get additional treatments. Bringing the therapies to those who need them, however, also presents considerable logistical challenges.

Perhaps the most promising area for a possible role for CRS in developing products for the developing world will be in the area of prevention—for example, single-dose vaccines—or cheap, effective ways of killing disease organisms that infect humans or livestock. The widespread distribution of bed nets treated with permethrin is a good example of a cost-effective preventative solution for helping to control infection with malaria. Another area where CRS might play a role is in diagnostics, for example, an inexpensive, rapid method for diagnosing HIV or tuberculosis. Ian Tucker in his letter from the president (volume 31, number 3) expresses the opinion that controlled release science does have a role to play in developing countries in a traditional area of CRS activity, agriculture.

CRS welcomes a debate, through letters to the editor, as to what the CRS membership feels could, or should, be the role of CRS in developing products for low-income countries. WHO, in its report “More Money for Health” (www.who.int/whr/2010/10_chap02_en.pdf), suggests that low-income countries should be able to provide key health care services for between \$40 and \$80 per person per year in 2015; this is a figure that we should keep in mind when considering the cost of manufacturing and distributing a new controlled release product for developing countries.

It is our intention that the debate should stay focused on the question of whether or not CRS has a role in developing therapies for low-income countries, and, if it has a role, what that role should be. The debate should not stray too far into the political realm. We look forward to your contributions to this timely debate by addressing your letter to Yvonne Perrie, editor of the *CRS Newsletter*. ■

CRS Election Results

The 2014 CRS election votes have been tallied and the results finalized. The nomination process, led by the Nominating Committee headed by Kazunori Kataoka, allowed for many opportunities for member input. The newly elected Board of Directors and Board of Scientific Advisors, listed below, began their new positions on July 16, 2014, at the conclusion of the annual meeting. Thank you to all the impressive candidates who participated in this election. Thank you to all the members who voted this year, helping to shape the future of our society. For a complete list of Board of Directors and Board of Scientific Advisors members, see the CRS website.

Congratulations to our newly elected CRS Board



President-Elect
Marcus Brewster
*Johnson & Johnson,
Belgium*



Treasurer-Elect
**Christopher
McDaniel**
U.S.A.



Secretary
Christine Allen
*University of
Toronto, Canada*



Director-at-Large
Ben Boyd
*Monash University,
Australia*



Director-at-Large
James Oxley
*Southwest Research
Institute, U.S.A.*



Marcel Bally
*British Columbia
Cancer Research Centre,
Canada*



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



Hamid Ghandehari
*University of Utah,
U.S.A.*



Suzie Pun
*University of
Washington, U.S.A.*

In addition to the newly elected Board members listed above, the following CRS members are also serving on the 2014-2015 Board.

President
Arthur Tipton
Southern Research Institute, U.S.A.

Treasurer
Ruth Schmid
SINTEF, Norway

Director-at-Large
Andrew Lewis
Ipsen, France

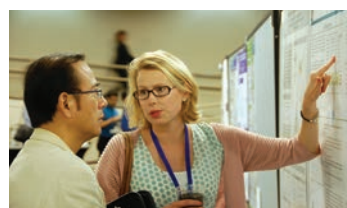
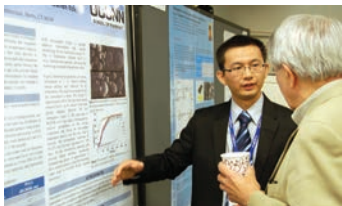
Immediate Past President
Ian Tucker
University of Otago, New Zealand

Director-at-Large
Maria Jose Alonso
University Santiago de Compostela, Spain

Director-at-Large
Yvonne Perrie
Aston University, United Kingdom ■

Sense of Purpose

They arrived from 41 countries with poster tubes, exhibit giveaways, preprinted abstracts, and focused determination. They left Chicago with expanded knowledge, a growing network, and a renewed sense of purpose to continue uncovering critical solutions in delivery science and technology. Yes, there was an abundance of serious science. But this group of 1,250 attendees also took full advantage of the lighter side of the meeting, enjoying organized luncheons, happy hours, and a memorable yacht ride on Lake Michigan. Though the applications of delivery science are broad, CRS meeting attendees and exhibitors wasted no time in finding the commonality that strengthens this meeting, and the society, year after year. The meeting closed with a twist—a musical recession by a Scottish bagpiper as a reminder to save the dates and spread the word about the 42nd Annual Meeting in Edinburgh, Scotland, July 26-29, 2015.



More than 600 poster presenters discussed their latest research with fellow attendees.



Young scientists from around the world gathered for an evening of fun and networking.



Ian Tucker passed the gavel to the new CRS President, Art Tipton.

2014 CRS Awards

The Controlled Release Society is proud to honor this year's awardees for their dedication and contributions to delivery science and CRS.

Distinguished Service Award

Established in 1994, the Distinguished Service Award is presented to a CRS member who has exhibited exceptional commitment and service to the society and is selected by the Board of Directors.



Diane Burgess is a Board of Trustees Distinguished Professor of Pharmaceutics at the University of Connecticut, U.S.A. She has over 170 publications, over 450 research presentations at major scientific meetings, over 260 invited lectures, and has presented 20 keynote addresses. Dr. Burgess was the 2010 president of CRS, the 2002 president of AAPS, and is an AAPS, CRS, AIBE, and APSTJ fellow.

She is editor of the *International Journal of Pharmaceutics*.

College of Fellows

The College of Fellows recognizes those members who have made outstanding contributions to the field of delivery science and technology over a minimum of 10 years. Contributions may have been technical, scientific, and/or managerial in one or more fields of research, commercial development, education, and/or leadership within the areas of interest to CRS. Fellowship is the most prestigious level of membership in CRS.



Mansoor Amiji is a distinguished professor and chairman of the Department of Pharmaceutical Sciences and codirector of the Northeastern University Nanomedicine Education and Research Consortium at Northeastern University in Boston, Massachusetts, U.S.A.



You Han Bae is a professor in pharmaceutics at the University of Utah, U.S.A.



Joseph Kost is the Abraham and Bessie Zacks Professor of Biomedical Engineering and the dean of the Faculty of Engineering Sciences at Ben-Gurion University in Israel.



Jean-Christophe Leroux is a professor of drug formulation and delivery at ETH Zurich, Switzerland.



Tamara Minko is a distinguished professor and chair of the Department of Pharmaceutics, Rutgers University, U.S.A.

Founders Award

The society grants this honor to a current CRS member who is internationally recognized for outstanding contributions in the science and technology of controlled release.



Paolo Colombo is a professor of pharmaceutical technology at the University of Parma, Italy. He became an AAPS fellow in 1996 and received the CRS Outstanding Paper Award (1999), Maurice-Marie Janot Award from APGI (2004), and CRS Reiner Hofmann Award (2007). He published more than 250 research papers and filed more than 35 patents on drug delivery. The best-known product is Geomatrix® technology, the partially coated hydrophilic matrix (Dilacor XR, Xatral). Dome Matrix is the most recent product in development, consisting of assembling module technology for combination drug controlled release.

Young Investigator Award

Cosponsored by Catalent Pharma Solutions

This award recognizes a CRS member, age 40 years or younger on December 31 of the current year, who has made outstanding contributions in the science of controlled release.



Suzie H. Pun received her chemical engineering Ph.D. in 2000 from the California Institute of Technology under the guidance of Mark E. Davis. She worked as a senior scientist at Insert Therapeutics/Calando Pharmaceuticals developing polymeric drug delivery systems before joining the Department of Bioengineering at the University of Washington (UW), U.S.A. She is the

Robert J. Rushmer Associate Professor of Bioengineering, an adjunct associate professor of chemical engineering, and a member of the Molecular Engineering and Sciences Institute at UW. Her research focuses on drug and gene delivery systems, and she has published over 70 research articles. She was recognized with a Presidential Early Career Award for Scientists and Engineers in 2006.

CRS/T. Nagai Postdoctoral Research Achievement Award

Cosponsored by The Nagai Foundation Tokyo

This award recognizes an individual postdoc who has recently completed postdoctoral research in controlled release science and technology and the postdoc's advisor, who played an integral role in the achievements.



Lin Zhu is an assistant professor in the College of Pharmacy at Texas A&M Health Science Center. He did his postdoctoral training at Northeastern University. Zhu's research focuses on the development of nanocarriers/nanomedicine for targeted and stimuli-sensitive drug delivery.



Vladimir Torchilin is a university distinguished professor and director of the Center for Pharmaceutical Biotechnology and Nanomedicine, Northeastern University. He was president of CRS in 2005. Times Higher Education ranked him second among top world scientists in pharmacology for 2001–2010.

Jorge Heller Journal of Controlled Release Outstanding Paper Award

Cosponsored by Elsevier

This award recognizes an outstanding regular paper related to the science of controlled release (not an invited, review, or special meeting paper) that was published during 2013 in the Journal of Controlled Release.



Frits Thorsen is a professor, platform leader of the Molecular Imaging Center, and one of the principal investigators in the KG Jebsen Brain Tumor Research Center at the Department of Biomedicine, University of Bergen, Norway. Thorsen's research increases understanding of metastatic cancer spread to the brain.

Multimodal Imaging Enables Early Detection and Characterization of Changes in Tumor Permeability of Brain Metastases

Journal of Controlled Release 172: 812-822 (2013)

Authors: Frits Thorsen, Brett Fite, Lisa M. Mahakian, Jai W. Seo, Shengping Qin, Victoria Harrison, Sarah Johnson, Elizabeth Ingham, Charles Caskey, Terje Sundstrøm, Thomas J. Meade, Patrick N. Harter, Kai Ove Skaftnesmo, and Katherine W. Ferrara

Drug Delivery and Translational Research Outstanding Paper Award

Cosponsored by Springer

This award recognizes outstanding research in the field of drug delivery and translational research that was published during 2013 in Drug Delivery and Translational Research.



Prabodh Sadana received his bachelor's degree in pharmacy and master's degree in pharmacology from the University of Delhi, India. His research interests focus on the pharmacological targeting of hyperlipidemia and ischemic brain stroke.

Engineering Triiodothyronine (T3) Nanoparticle for Use in Ischemic Brain Stroke

Drug Delivery and Translational Research 3: 309-317 (2013)

Authors: Prabodh Sadana, Alexander Mdzinarishvili, Vijaykumar Sutariya, Phani K. Talasila, and Werner J. Geldenhuys

Outstanding Oral Drug Delivery Paper Award

Cosponsored by Patheon

This award recognizes a CRS member whose winning abstract relates specifically to oral drug delivery.



Hongbo Zhang is a visiting scholar at the School of Engineering and Applied Sciences, Harvard University, U.S.A., and a postdoctoral researcher in the Faculty of Pharmacy, University of Helsinki, Finland. His research focus is microfluidic templated porous silicon-based platforms for biomedical application.

Microfluidic Templated Multistage Porous Silicon Based Platform for Enhanced Enteric Cancer Drug Delivery

Presenting author: Hongbo Zhang, University of Helsinki, Finland

Coauthors: D. Liu, M. Shahbazi, E. Mäkilä, J. Salonen, J. Hirvonen, and H. A. Santos

Outstanding Pharmaceutical Paper Award

Cosponsored by PharmaCircle

This award recognizes a CRS member whose winning abstract relates specifically to pharmaceutical research.



Seung-Young (Steve) Lee is in the Ph.D. program at the Department of Biomedical Engineering at Purdue University. His current research focuses on the development of nanomedicine for nontoxic chemotherapy.

Cholesterol Esterification-Blocking Nanoparticles for Targeted Aggressive Cancer Therapy

Presenting author: Seung-Young (Steve) Lee, Purdue University, U.S.A.

Coauthors: Junjie Li, Jien Nee, Kinam Park, and Ji-Xin Cheng

Outstanding Transdermal Drug Delivery Paper Award

Cosponsored by 3M Drug Delivery Systems

This award recognizes a CRS member whose winning abstract relates specifically to transdermal drug delivery research.



Jessica Joyce is currently a Ph.D. student in the Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University. Joyce is working in the lab of Dr. Mark Prausnitz, and her research involves the development of microneedle patch technology for vaccine delivery.

Inactivated Polio Vaccination Using a Microneedle Patch

Presenting author: Jessica Joyce, Georgia Institute of Technology, U.S.A.

Coauthors: C. Edens, H. Eichenbaum, N. Dybdahl-Sissoko, J. Norman, W. Weldon, S. Oberste, and M. Prausnitz

Outstanding Preclinical Sciences and Animal Health Paper Award

Cosponsored by Zoetis

This award recognizes a CRS member whose winning abstract relates specifically to preclinical sciences and animal health research in the field of delivery of bioactives.



Christopher Nelson began his doctoral studies in biomedical engineering at Vanderbilt University under the direction of Prof. Craig Duvall. His work focused on controlled delivery strategies for nucleic acids, proteins, and small-molecule drugs.

Versatile Platform for Sustained Gene Silencing Improves Excisional Wound Healing in Diabetic Rats

Presenting author: Christopher Nelson, Vanderbilt University, U.S.A.

Coauthors: John R. Martin, Mukesh K. Gupta, Elizabeth J. Adolph, Fang Yu, Jeffrey M. Davidson, Scott A. Guelcher, and Craig L. Duvall

CRS Outstanding Chapter of the Year Awards

The CRS Chapter of the Year Award recognizes both a local chapter and a student chapter that have provided exceptional service to their members and to the Controlled Release Society. These chapters were chosen for their balanced, comprehensive events, as well as for maintaining a record of committed chapter activities.

New Zealand Local Chapter
NJ-NY-PA Student Chapter ■

Take Advantage of this New Membership Benefit!

September – December 2014 CRS Webinar Series

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- ▶ **October:** Innovation to Commercialization: Bringing Your Products to Market
- ▶ **November:** PLGA-based Nanoparticles Used in Biomedical and Drug Delivery Applications
- ▶ **December:** Breakthrough Discoveries in Drug Delivery Technologies: A 30 Year Futurecast

You spoke and we listened! You told us you value the Annual Meeting recorded presentations, so we have added additional, new webinars on a wide variety of subjects that will help quench your thirst for more information between Annual Meetings. This is yet another way you continue to gain value from your CRS membership!

The monthly webinars will be hour-long, interactive presentations focused on scientific research. The presentations will be archived on the website for member viewing at any time. Watch for more details to be posted on the website. Questions? Contact Lisa Johnson, Webinar Manager, at ljohnson@scisoc.org.

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Highlights of NZCRS Award-Winning Presentations



The New Zealand CRS Local Chapter (NZCRS) cohosts the Formulation and Delivery of Bioactives (FDB) conference each year in Dunedin, New Zealand. The FDB conference provides an excellent forum for the exchange of information, initiating collaborative projects and training younger scientists, many of whom subsequently present at the CRS Annual Meeting. NZCRS recognizes the contribution that emerging scientists make to our field, and we celebrate their achievements by awarding prizes for the best student speakers at the FDB conference.

Farah Al-Barwani and Silke Neumann were the 2013 joint winners of the NZCRS prize for best oral presentation. The two articles presented here are highlights from their award-winning presentations.

— Arlene McDowell, President, NZCRS

Enhancing the Functionality of RHDV Virus-like Particles

*Farah Al-Barwani, David S. Larsen, Margaret A. Baird, Sarah L. Young, and Vernon K. Ward
Department of Microbiology and Immunology, University of Otago, New Zealand*

Introduction

The capsid proteins of viruses can spontaneously assemble into uniform virus-like particles (VLP) that are highly effective at stimulating immune responses. VLP are used in a number of vaccines including the extremely successful hepatitis B vaccine, Engerix, and the two commercially available human papilloma virus vaccines, Gardasil and Cavarix. VLP have also been demonstrated to be effective platforms for the delivery of nonviral antigens to the immune system.

Expression of the capsid protein VP60 of rabbit haemorrhagic disease virus (RHDV) spontaneously leads to VLP formation. VP60 has been engineered to carry a number of model tumor antigens including the glycoprotein 33 epitope SAVYNFATM and the ovalbumin epitope SIINFELK. These modified VLP are internalized by antigen-presenting cells and are processed to release the foreign epitope for presentation on major histocompatibility complex (MHC) molecules, leading to robust immune responses.¹⁻³

Immune epitopes are typically 8–17 amino acids in length, and multiple epitopes can be engineered onto the N-terminus of VP60 without disrupting VLP formation. To increase the number of foreign epitopes presented on MHC molecules, we have engineered VLP containing a linker sequence between epitopes. The addition of the linker was found to enhance the immune response to the epitope.

Methods

VLP were designed to have two copies of the tumor epitope gp100₂₅₋₃₃ (VLP.gp100-2) or two gp100 epitopes separated by a sequence-specific linker sequence (VLP.gp100-2L). A number of different linkers were tested with proteasome and immune-proteasome prediction software,⁴⁻⁶ and Ala-Leu-Leu was

predicted to be the optimal linker sequence. VLP.gp100-2 and VLP.gp100-2L were engineered by adding the DNA sequence encoding the required gp100 epitope to the N-terminus of the VP60 gene by polymerase chain reaction extension and used to generate a recombinant baculovirus by homologous recombination. VLP were expressed by infecting Sf21 insect cells with recombinant baculovirus. Cells were then lysed with 0.5% Triton X-100 and the released VLP purified by differential centrifugation, followed by a two-step 1.2 and 1.4 g/mL CsCl gradient. The production, purification, and assembly of purified VLP were tested by mass spectrometry, SDS-PAGE gel electrophoresis, and transmission electron microscopy. VLP were dialyzed into phosphate buffered saline (0.2M, pH 7.3) containing 0.3M NaCl before use.

The efficacy of the different VLP was compared by *in vitro* T-cell proliferation. Bone marrow-derived dendritic cells (BMDCs) were generated through the isolation of bone marrow from the hind legs of C57BL/6 mice, lysis of red blood cells with ammonium chloride, and the subsequent culturing of white blood cells for six days in cIMDM containing 20 ng/mL mouse granulocyte-macrophage colony-stimulating factor. BMDCs (5×10^5 cells/mL) were pulsed with 0.83 μ M/mL of the different VLP, incubated at 37°C for 24 h, and then cocultured with naïve CD8 T cells specific for the gp100₂₅₋₃₃ epitope from Pmel-1 transgenic mice. The resultant T-cell proliferation was determined with 3H-thymidine incorporation.

Results and Discussion

Before immune epitopes can be presented to the immune system on MHC molecules, they must first be processed by antigen-presenting cells. Therefore, we investigated if the addition of a sequence-specific cleavable linker could target cleavage between two epitopes. VLP.gp100-2 and VLP.gp100-2L were expressed

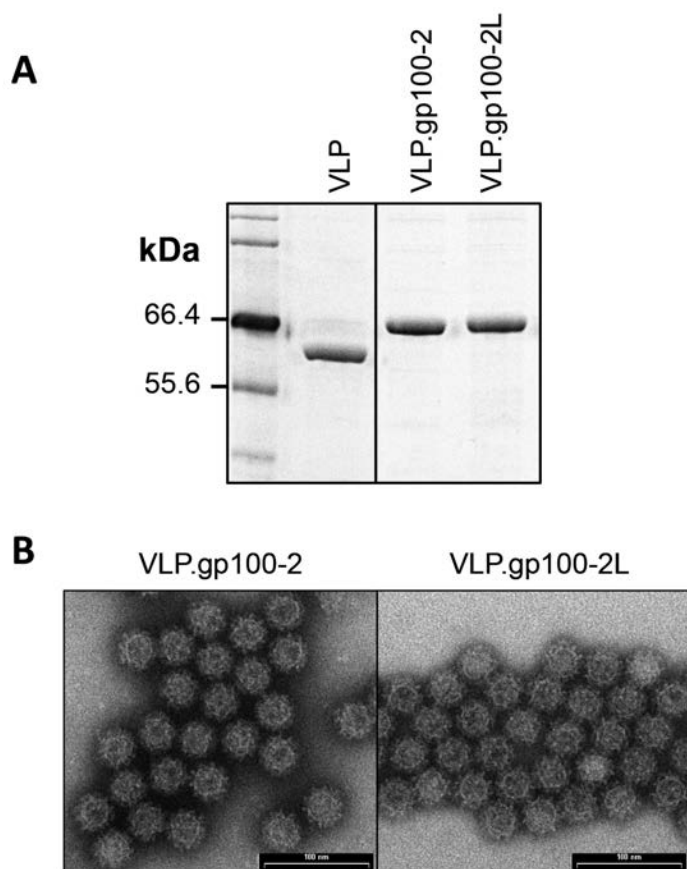


Figure 1. (A) SDS-PAGE gel of the different VLP, confirming protein production and purification. (B) Transmission electron micrograms confirming the assembly of VLP of the correct size. Scale bar = 100 nm.

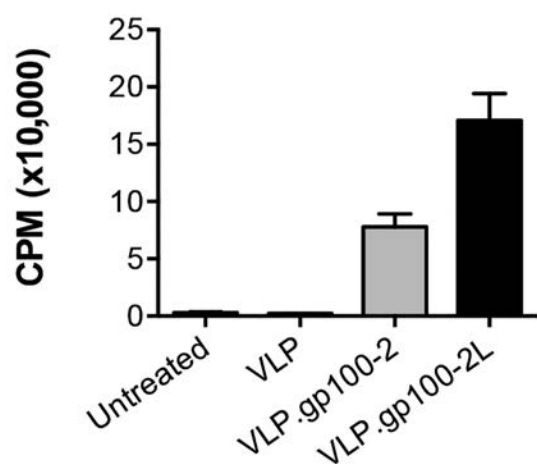


Figure 2. In vitro T-cell proliferation assay showing counts per minute (CPM) $\times 10,000$, an indicator of T-cell proliferation and ^3H -thymidine incorporation. The graph depicts the results from two experiments performed in triplicate. The addition of a sequence-specific linker between immune epitopes can lead to enhanced T-cell proliferation.

with a baculovirus expression system and then resolved on an SDS-PAGE gel to confirm VLP production and purification (Figure 1A). The gel shows purified protein bands displaying the expected increase in the size of the VP60.gp100-2 and VP60.gp100-2L compared with the 60 kDa VP60 band. Assembly into VLP of the correct size (36–40 nm) was confirmed by transmission electron microscopy (Figure 1B).

To test the functionality of the linker, BMDCs were pulsed with the different VLP and then cocultured with transgenic CD8 T cells specific for gp100 presented on MHC molecules. The resultant *in vitro* T-cell proliferation is shown in Figure 2. VP60.gp100-2L induced enhanced T-cell proliferation compared with VP60.gp100-2, indicating that the addition of the linker led to an increase in gp100 presentation on MHC molecules.

Conclusions

VLP such as RHDV VLP have the capacity to deliver multiple immune epitopes (such as tumor-associated antigen) to the immune system through genetic engineering. To initiate an immune response the VLP must be processed and the epitopes presented to T cells on MHC molecules. We have presented data indicating that the addition of an optimized cleavable linker sequence between epitopes can lead to an enhanced immune response.

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Evaluating Adjuvant Characteristics of Particulate Formulations

Silke Neumann,^{1,2} Roslyn Kemp,³ Thomas Rades,⁴ Rod Dunbar,^{2,5} and Sarah Hook¹

Introduction

Vaccine adjuvants are used to enhance antibody and cell-mediated immune responses to highly purified and characterized antigens. Nanoparticulate carrier systems have been developed to further improve immunogenicity by mimicking the size and shape of pathogens to facilitate uptake by antigen-presenting cells.¹ In the last decade, evidence has surfaced that the nanoparticulates themselves contribute to the immune response through activation of pattern recognition receptors (PRRs). Intracellular PRRs, such as the nucleotide-binding oligomerization domain-like (NOD-like) receptor, recognise danger-associated molecular patterns (DAMPs) of exogenous or endogenous origin.² DAMPs and pathogen-associated molecular patterns are taken up by phagocytosis or enter the cytosol via channels in the cell membrane initiated by pore-forming molecules.³ Ligation of NOD-like receptors leads to formation of multiprotein complexes called inflammasomes.

One of the best-characterized multiprotein complexes is the NLRP3 inflammasome. It consists of a NOD-like receptor, the adaptor molecule (ASC), and the proinflammatory protease caspase-1. Activation of this complex leads to caspase-1-dependent processing and the secretion of interleukin-1 beta (IL-1 β) and interleukin-18 (IL-18), which in turn trigger an inflammatory response.⁴

Four particulate systems, identified as having different physical and chemical characteristics, were examined for their ability to activate the NLRP3 inflammasome. These included two commonly used formulations (incomplete Freund's adjuvant [IFA] and alum) and two experimental nanoparticulate formulations (cubosomes and chitosan nanoparticles [CNP]).

Methods

Bone marrow-derived dendritic cells (BMDCs) were incubated with concentrations of formulations previously determined not to cause toxicity, and culture supernatants were analysed by flow cytometry for IL-1 β 24 h later. To investigate if a priming step with a Toll-like receptor (TLR) agonist was necessary to induce IL-1 β production, 50 ng/mL of lipopolysaccharide (LPS) was added to cells at the same time, 3 h prior to stimulation with formulations or 1 h after the formulations.⁵

Results and Discussion

Secretion of IL-1 β was observed after incubation of BMDCs with CNP (50 μ g/mL) for 24 h and after priming with LPS (50 ng/mL) for 3 h, but not after incubation with CNP alone. Incubation of BMDCs with IFA (250 μ g/mL) and cubosomes (10 μ g/mL) failed to induce production of IL-1 β (Figure 1). Alum (250 μ g/mL), which has been shown previously to activate the NLRP3 inflammasome,⁵ induced IL-1 β production.

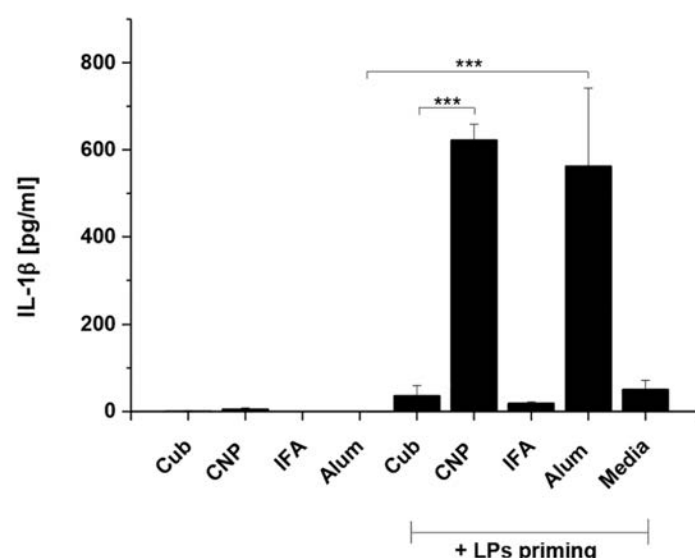


Figure 1. Secretion of IL-1 β after incubation with particles. BMDCs were incubated with cubosomes (10 μ g/mL), CNP (50 μ g/mL), IFA (250 μ g/mL), or alum (250 μ g/mL), with or without prior priming with LPS (50 ng/mL). Cell supernatants were collected after 24 h, and IL-1 β concentrations were determined by flow cytometry (CBA flex set detection limit 1.9 pg/mL). Data are the mean + SD of three independent experiments. ***, $P < 0.001$.⁶

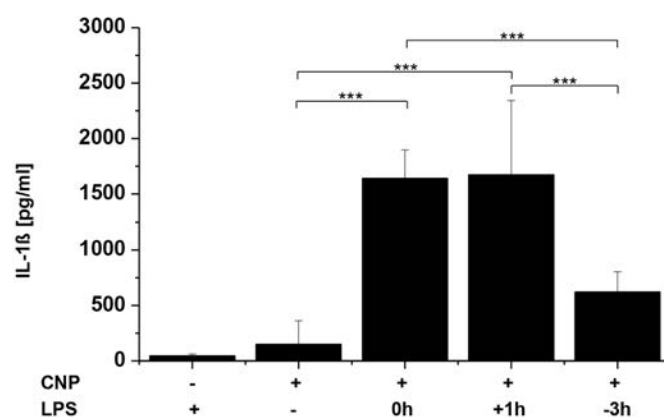


Figure 2. Production of IL-1 β after stimulation of BMDCs with 50 μ g/mL CNP, either alone or in combination with LPS (50 ng/mL), after priming with LPS for 3 h or for 1 h before the addition of LPS. Results are the mean + SD from three independent experiments. ***, $P < 0.001$.⁶

¹ School of Pharmacy, University of Otago, Dunedin, New Zealand.

² Maurice Wilkins Centre for Molecular Biodiscovery, Auckland, New Zealand.

³ Department of Microbiology and Immunology, University of Otago, Dunedin, New Zealand.

⁴ Department of Pharmacy, University of Copenhagen, Copenhagen, Denmark.

⁵ School of Biological Sciences, University of Auckland, Auckland, New Zealand.


Furthermore, we investigated the timing of administration of LPS. Using the standard published protocol⁵ of adding the TLR agonist 3 h before the addition of CNP resulted in the production of modest levels of IL-1 β , whereas simultaneous incubation with LPS and particles enhanced IL-1 β production significantly (Figure 2). The amount of IL-1 β detected when LPS was added after particles was comparable to the simultaneous incubation and was significantly different from the early addition of LPS.

Conclusion

The results indicated that CNP and alum, but not cubosomes or IFA, activate the NLRP3 inflammasome and increase the amount of secreted IL-1 β when given in combination with a TLR agonist.

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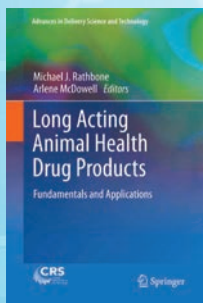


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Nanoscale Constrained Delivery: A Novel Technology for Subdermal Implants

Kathleen Fischer, Krista Degenkolb, William Fischer, and Adam Mendelsohn
Nano Precision Medical, Inc., Emeryville, CA, U.S.A.

Background

Beyond general dislike of needles, standard injection therapy has several limitations. Poor pharmacodynamic responses, including side effects deriving from high concentrations immediately after injection and reduced efficacy owing to subtherapeutic concentrations between injections, can limit tolerability and efficacy of treatment. Pressure from payers for improved compliance and, thus, convenience is driving the need to innovate novel solutions in drug delivery. Extended-release, constant-rate implants address all of these issues and may even improve patient outcomes.¹ In addition to producing constant-rate delivery, an optimal device would be small, easy to implant, and most importantly, safe over the duration of the implantation.

Recent developments have enabled the creation of a titania nanoporous membrane that can enable a small implant to provide passive, long-term, constant-rate drug delivery (Figure 1). Under standard conditions, the diffusion rate is proportionate to the concentration gradient, according to Fick's laws. Pore size reduction decreases the effective coefficient of diffusivity, extending the release while maintaining a correlation between rate of diffusion and concentration gradient. Polymer implants, such as Nexplanon, utilize the aforementioned phenomena to extend the release of many drugs, including synthetic hormones, for which the

therapeutic window is large enough that first-order release kinetics do not adversely impact side effects or efficacy. When the pore size approaches the size of a molecule, the concentration-driven diffusion regime is no longer relevant, and molecules diffuse through the membrane pores at a linear rate that no longer correlates with the concentration gradient across the membrane.^{2–4}

Numerous materials have been used to constrain diffusion, including aluminum, aluminum oxide (alumina), silicon/silicon oxide (silica), and titanium/titanium oxide (titania). Because the desired duration for an implant represents a period of months to years, it must be both stable and biocompatible (nontoxic, noncarcinogenic, nonantigenic, and nonmutagenic). Additionally, nanoporous membranes, because of their extensive surface area, are more susceptible to degradation processes. Furthermore, the materials must not adsorb sufficient material to clog membranes. Unmodified alumina membranes can be prone to surface fouling and pore clogging and can induce mild to moderate inflammation.⁵ Silicon/silica has not shown significant toxicity *in vitro* or in animal studies; however, there are only limited studies of its interaction with human tissue. Nanoporous polymer systems are in development in the academic laboratory and show significant promise for degradable delivery systems,⁶ but long-term safety still needs to be demonstrated.

In addition to the porous membrane materials, one must consider the material of a reservoir and any material used to attach the membrane to the reservoir. Although the reservoir may comprise several types of biocompatible materials, nanoporous membranes often require adhesives to seal the membrane with the reservoir, increasing potential toxicity and stability issues. Titanium has been used extensively in humans and is well accepted as an implantable biomaterial; furthermore, a titanium/titania membrane may be sealed to a titanium reservoir with no other materials added.

Methods

Vertically aligned titania nanotubes were grown from titanium following a protocol similar to that of Paulose *et al.*⁷ To produce the NanoPortal™ membrane, a portion of the titanium structure and the closed bottoms of the nanotubes were opened.⁸ Pore sizes were determined with high-resolution scanning electron microscopy (FEI Nova NanoSEM 650). Membranes were attached to reservoirs temporarily using a screw-cap prototype with o-rings.

To test diffusion kinetics *in vitro*, assembled capsules were loaded with fluorescein isothiocyanate IgG Fab₂ (FITC-Fab₂, Rockland Immunochemicals) or fluorescein labeled dextran 3000 (Dextran 3000, Invitrogen) in phosphate buffered saline (PBS). Loaded

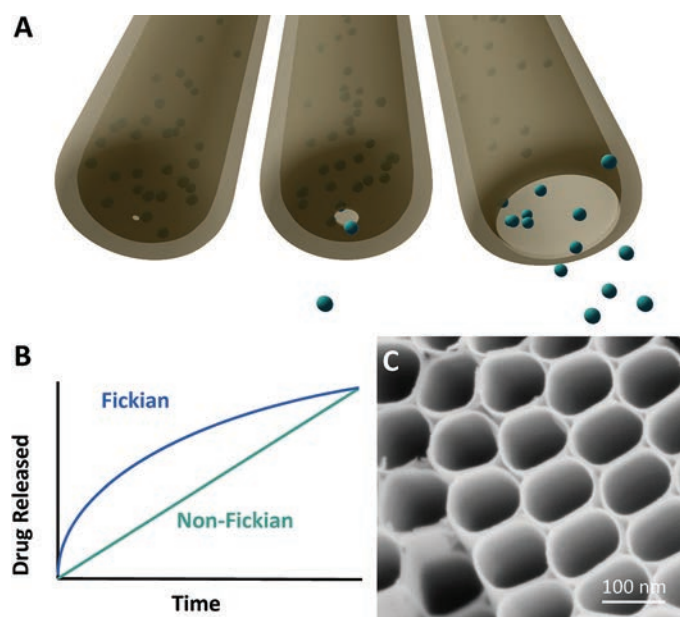


Figure 1. (A) Molecules are approximately the same size as the pores for non-Fickian, constrained, linear diffusion (middle), whereas they are significantly smaller than the pore size in Fickian, nonlinear diffusion (right). (B) Schematic showing differences in diffusion curves for the two types of diffusion. (C) Scanning electron micrograph of titania nanotubes.

capsules were immersed in PBS and incubated in closed vials at 37°C, with agitation. Samples were read on a fluorescent plate reader (Cytofluor 4000).

To test *in vivo* release, assembled capsules were loaded with polyethylene glycol (PEG, MW 40 kDa) and implanted subcutaneously in rats. PEG was chosen as a model molecule because of its stability and ease of detection in blood plasma. Identical capsules were tested both *in vitro* (following the described protocol) and *in vivo*. To test biocompatibility, animals with implants were euthanized at 12 months for histopathology (hematoxylin and eosin stain).

Results

The NanoPortal membrane can be manufactured with pore sizes ranging from just a few nanometers to 100 nm, and it is made exclusively of titanium and titania (Figure 2). It can be made as small as 2 mm, thus fitting inside a 12 gauge needle for implantation, while still accommodating appropriate amounts of drug for months of release. By adjusting pore size and the number of exposed nanotubes, the NanoPortal membrane can be tailored to fit numerous molecules and applications.

In vitro studies with identical membranes but differently sized molecules demonstrated the impact of nanotube diameter on release rate (Figure 3). Although the FITC-Dextran 3000 had roughly linear release to 42 days, the residual errors were not random, and the overall curve was more consistent with extended Fickian release. The FITC-Fab₂ remained linear to 56 days, and

the curve was consistent with non-Fickian, constrained release kinetics ($R^2 = 0.99$).

As expected with a molecule of 40 kDa, the release rate *in vitro* was consistent with that of extended Fickian kinetics (Figure 4). *In vitro* delivery was completed around day 14, without any significant subsequent release. The plasma concentration immediately increased from the time of implant until day 3, as the PEG released from the capsule in the subcutaneous space diffused into the bloodstream. As the capsule continued to release PEG, plasma concentrations approached equilibrium until delivery completed around day 14, at which point the PEG was eliminated.

When implanted in rats, the NanoPortal devices produced no significant differences in immune reaction compared with control titanium devices. At 12 months, mature fibrous capsules with relatively thin walls (10–20 layers thick) and rare mononuclear cells surrounded both membranes and sham implants.

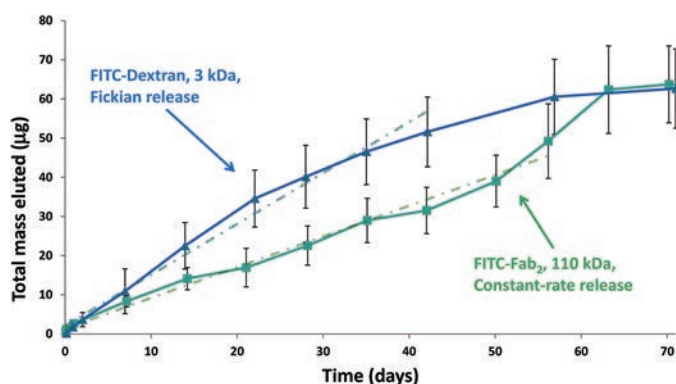


Figure 3. *In vitro* data: with a membrane of the same pore size, FITC-Fab₂ diffuses at a constant rate, whereas the smaller FITC-Dextran diffuses in an extended Fickian manner.

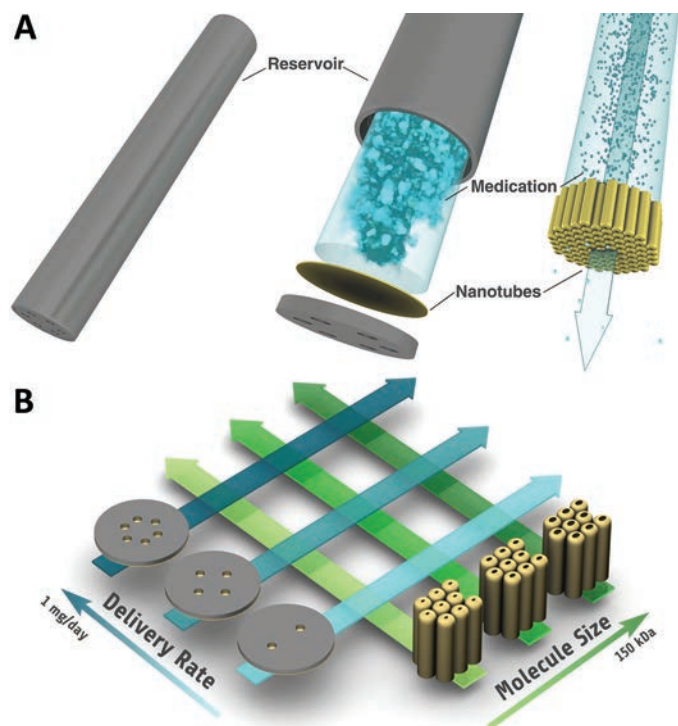


Figure 2. Schematic of NanoPortal implant. (A) Overview of device assembly. (B) Constant-rate delivery for a variety of molecules can be achieved by adjusting the size of the nanopores; target delivery rates can be achieved by adjusting the number of accessible nanotubes.

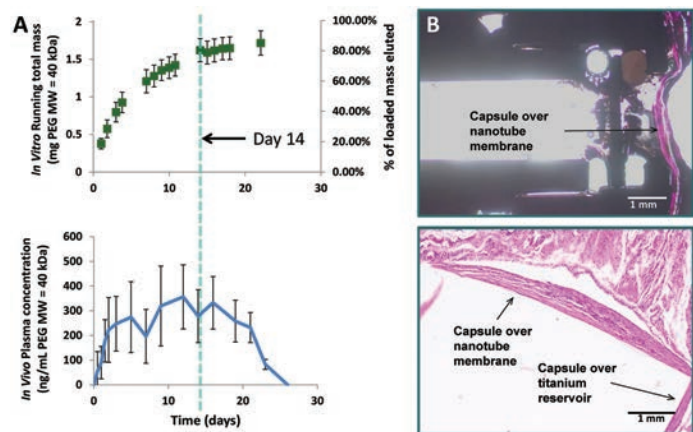


Figure 4. (A) *In vitro* (top) and *in vivo* (bottom) experiments using identical devices tested in parallel ($n = 5$; error bars are standard deviation). Delivery is complete at day 14, when around 80–85% of the loaded mass has been released. (B) *In situ* (top) and standard (bottom) histopathology at 12 months confirms no remaining immune response and a thin fibrous capsule.

Conclusions

Constrained nanoscale diffusion offers a promising approach for extended, constant-rate delivery of a variety of molecules. By crafting a membrane from titanium and titania, it is possible to have a high degree of stability and biocompatibility, produce zero-order release *in vitro*, generate stable plasma concentrations *in vivo*, and easily integrate the membrane with a reservoir to create a functional, biocompatible system. Furthermore, the NanoPortal membrane has a range of pore sizes and device configurations, permitting its use with numerous molecules while maintaining a device that could be implanted subcutaneously in minutes with a syringe needle in an outpatient setting.

Although it has not been addressed here, significant, though not insurmountable (as demonstrated by Intarcia⁹), formulation challenges are associated with stabilizing a therapeutic for extended times *in vivo*. Nonetheless, because the devices allow a high percentage of their volume to be loaded with drug and may be used with a wide variety of molecules, nanoporous implants provide an excellent opportunity to reduce side effects and improve efficacy in the treatment of chronic disease around the world.

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"Artisinal" Publishing: A Scientist Writes Fiction

William Curatolo, *The Bayberry Institute, U.S.A.*



"With what I've seen, I should write a book." I've said it, and I would venture a guess that many of you have said it too. Over the course of my 27 years on planes and trains for Big Pharma, I saw and heard lots of surprising things, and I kept a little spiral-bound notebook with me to write down a few words to jar my memory later. For the record, most of the strange things I saw and heard related to companies other than the one I worked for—mostly little

companies developing formulations or one-off drug candidates, generics developing low-quality knockoffs, and internet pharmacies. I also took notes to remind me of casual conversations I could not help overhearing in airports and other public places (unavoidable loud cellphone conversations). At some point, I felt that I had enough material to start writing a novel about scientists and physicians behaving badly in the international drug industry. It turned out to be a lot more difficult than I anticipated (as all things generally are).

A first problem was unlearning my hard-earned scientific writing skills. After 30 years, these skills were in my DNA (perhaps via histone methylation). There is nothing wrong with writing clearly and concisely, but let's face it, scientific writing is pretty dry (although I did use the word "haiku" in a journal article once). In addition to journal articles, I had written many scientific sections of patent applications, where the style and semantics are even further removed from everyday life. Writing fiction is a different animal—all about action and dialogue. Didactic chapters providing scientific background drag a story down. In rewriting and rewriting, I learned two important things: let the characters provide the background and don't get hung up on all the science being correct. If science is an important part of the background of the story, it just has to be plausible, not necessarily feasible in the present. Think Michael Crichton's *Jurassic Park*.

Once you have a novel in hand, you are faced with publishing and distributing it, two activities that in the past were "left to the professionals." Within just the last few years, two cataclysmic technical advances have occurred in publishing. The first is the advent of e-books, which have removed the need for printing presses and warehouses (and bookstores for that matter). The less well-known second advance is just-in-time printing. Today, a single copy of a paperback book, with its cover, can be printed at a low cost. In addition, a significant business process advance (which bookstore lovers, including myself, decry) is internet book sales, evidenced by the unprecedented success of the company Amazon.

Up until about 10 years ago, there were two publishing worlds: traditional publishing and "vanity" publishing. The traditional publishers were the gatekeepers who owned the printing presses, the warehouses, and the distribution channels. It was very difficult (and still is) to get a publishing contract because these large publishers need manuscripts that can justify large printing runs and the expense of advertising and distribution. "Vanity" publishers produced books for authors who were willing to pay for the service, and readers and critics generally thought of these books as low-quality items. There were of course exceptions, such as Walt Whitman's *Leaves of Grass* and John James Audubon's *Birds of America*. Admittedly, the exceptions were relatively rare.

Because of the advent of e-books, the existence of just-in-time printing, and the availability of online "bookstores," it is no longer necessary to have a large potential audience to publish a book. For example, if your hobby is collecting the franking machines used to stamp letters sent by passengers on zeppelins, and you wish to write a book about this for the small number of other people across the world who are interested, you can now proceed without having to go through the traditional publishing company gatekeepers. You can format your book online and create a cover using a free service such as Createspace (createspace.com), owned by Amazon. Alternatively, there are other relatively inexpensive companies that will more actively help you for a fee. If you go the Createspace route, you can have your book seamlessly listed on Amazon, where you set your price and royalty for both paperback and e-versions. While I am sure that Amazon would like to sell lots of books to make lots of money, their efficient online sales model permits the listing and sale of books with small, even miniscule, markets. The 25 people who are interested in zeppelin-based franking machines can buy your nicely produced paperback book on the subject. If only one copy is ordered in a particular week, it doesn't matter—that copy will be prepared using just-in-time printing.

To bring this subject closer to home, if you have a desire to publish a book on some aspect of drug formulation design or execution, even an unusually short book, the mechanism exists to accomplish it. In my first self-publishing effort, I published a novel—relatively simple technically because there are no figures, pictures, or graphs. A nonfiction book is of course more involved but still relatively straightforward for an author willing to learn layout using a well-known program such as Microsoft Word. For more detailed information on how to self-publish, I strongly recommend the book *APE: Author, Publisher, Entrepreneur* by Guy Kawasaki, formerly Chief Evangelist at Apple Inc. Kawasaki says to forget about "vanity" publishing and to call it "artisinal" publishing instead.

I was surprised to discover that the most difficult part of self-publishing a novel or nonfiction treatise may be marketing. Like other aspects of life, it is critical to know what your goals are and

to be willing to put in the needed effort to accomplish them. If you write a family history, you can simply announce it in e-mails to your family. If you write a treatise on some aspect of drug delivery, you can use your LinkedIn contact list to reach interested people. If you are looking for broader distribution, an approach is to use Google AdWords, a feature in which you have a brief three-line ad (with a link if you wish) that appears when someone searches one of a series of keyword phrases that you have set. You only pay Google when someone clicks on your ad. The world of social media provides further opportunities and is constantly changing. The bottom line is that the marketing aspect of self-publishing is tough and requires creativity and

financial investment if you want broad distribution. I now understand why traditional publishers (and agents) are so selective. Just do the math. It is very difficult to succeed if your goal is to make money.

Bill Curatolo's novel Campanilismo is set against the background of international biotech and involves broken clinical studies, illegal internet pharmacies, and New Jersey hoods. A biophysicist by training, Dr. Curatolo served for six years on the staff at MIT and for 27 years in the R&D Division at Pfizer. He is the author of numerous scientific publications and holds 32 U.S. patents. ■

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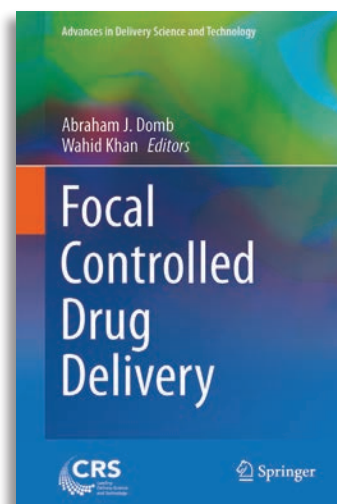
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The Board of Scientific Advisors Scans the Horizon

Ben J. Boyd, Immediate Past Chair, Board of Scientific Advisors

The Board of Scientific Advisors (BSA) is an important group within CRS. To remain relevant and at the forefront of delivery science and technologies, we need to be keeping an eye on the “horizon” for fields that should be the immediate focus of CRS programming of meetings, plans for books, educational content, and so on. This is one very important function of the BSA—to do this horizon scanning and to collate and report their collective thoughts and wisdom back to the Board for dissemination to other committees.

The purpose of this article is to communicate what we believe to be three of the major areas on which CRS should be focusing to achieve these aims. Three short “briefing” articles around the issues have been assembled by various members of the BSA, with special assistance from external authors where appropriate. The full report to the Board is much more extensive—the current article is intended to quickly enable familiarity with these areas for discussion at future meetings, to encourage you to think about how your research might relate to these areas, and to perhaps stimulate your own contribution to our horizon scanning. The BSA chair (currently Edith Mathiowitz, Brown University, U.S.A.) will always be happy to receive your suggestions in this regard via e-mail contact on the CRS website.

Board of Scientific Advisors, 2013–2014

The *raison d'être* and perpetual function of the Board of Scientific Advisors (BSA) is to provide advice to CRS (the Board and its various committees) on all aspects of the science and technology of delivery so that CRS will fulfill its mission and its aspirational vision. BSA members are voted into office by the CRS membership for a three-year term. CRS thanks the 2013–2014 BSA members:

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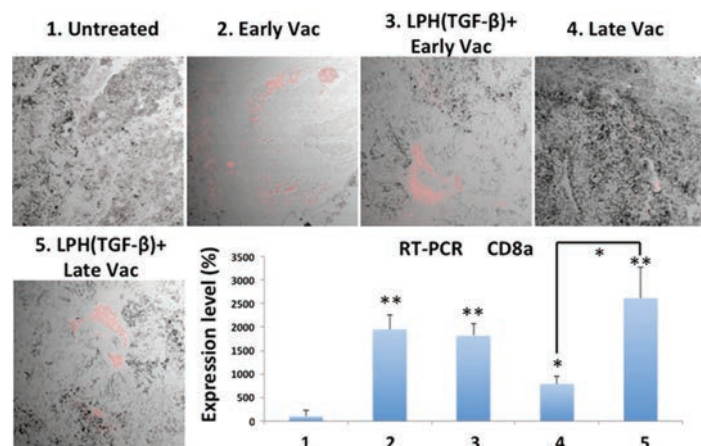
Board Liaison: Christine J. Allen (University of Toronto, Canada)

Horizon Field 1: Personalized Medicine and Individualized Drug Delivery

Theresa M Allen (Professor Emeritus, Department of Pharmacology, University of Alberta; Strategic Advisor, Centre for Drug Research and Development, Vancouver, BC) and **Leaf Huang** (Fred Eshelman Distinguished Professor, Division of Molecular Pharmaceutics and Center for Nanotechnology in Drug Delivery, Eshelman School of Pharmacy; Professor, Department of Biomedical Engineering, University of North Carolina at Chapel Hill)

Personalized medicine is a rapidly developing area of medicine that seeks to customize health care and health care products to the genomic profiles of individual patients. Our rapidly evolving ability to determine the genetic profiles of individuals in a rapid, cost-effective manner now enables us to determine an individual's susceptibility to disease, response to treatments, and vulnerability to adverse side effects of therapy. A number of therapies are already being partnered with companion diagnostic tests that indicate whether a patient is likely to respond to a particular therapy. In the last several months, the U.S. FDA approved several cancer drugs for use in patients whose tumors have specific genetic characteristics that are identified by a companion diagnostic test.¹ An early example of therapy coupled to a diagnostic test is the determination of the HER2 status of breast cancer patients before assigning them to therapies containing an anti-HER2 therapeutic antibody such as trastuzumab.²

What is the future role of individualized drug delivery in the evolution of personalized medicine? At first glance it might seem



*Tumor infiltration of CD8+ T cells after treatment. B16F10 bearing C57BL/6 mice were treated with LCP vaccine and anti-TGF-β siRNA loaded LPH NP as indicated. Mice were sacrificed on day 18, and tumor tissues were assayed for CD8+ T cell (red) detection with immunostaining and RT-PCR analysis. The silencing of TGF-β in the late-stage tumor reversed the immunosuppressive tumor microenvironment and increased the level of CD8+ T cells. n = 5, * indicates P < 0.05, and ** indicates P < 0.001. Reprinted with permission from Xu et al, ACS Nano 8: 3636–3645.⁶ Copyright 2014 American Chemical Society.*

that tailoring a separate formulation to each patient or to small groups of patients might be difficult and expensive in the current “one size fits all” world of drug delivery. And yet, what is more personalized than the delivery of gene medicines such as siRNA to treat patients suffering from known gene mutations or deletions? Alnylam Pharmaceuticals has lipidic nanoparticles containing siRNA that are currently in clinical trials for at least three indications.³ The inter- and inpatient pharmacokinetic variability of nanoparticle anticancer agents appears to be significantly greater compared with small-molecule agents. To address these issues, experts in the pharmacokinetics and pharmacodynamics of nanoparticle agents, such as Bill Zamboni at the University of North Carolina, are leading research into using phenotypic probes and mediators of the mononuclear phagocyte system (MPS), which is the primary clearance pathway for nanoparticle and carrier-mediated agents, to individualize the treatment regimens (e.g., dose and frequency of administration) of these agents. The goals of these studies are to maintain the drug levels of nanoparticle and carrier-mediated agents within a therapeutic range to increase efficacy and reduce toxicity.⁴ In the Allen laboratory, we developed the postinsertion technique, which can quickly be used to individualize immunoliposomal anticancer drugs with targeting agents directed against surface markers on individual patients’ tumors.⁵ In the Huang lab, siRNA against TGF β was delivered to the tumor to curtail the immune suppressive microenvironment to enhance cancer vaccine activity (see the accompanying illustration).⁶ In future clinical studies, the siRNA sequence will have to match precisely with the individual’s TGF β sequence.

The rapid advancement of companion diagnostics will allow existing drug delivery systems to be tailored to patients in a more rational manner, and advances in genomics will allow us to understand how the mutations in metabolic enzymes of individual patients, such as cytochrome P450, will affect the dose and dosing frequency of delivery systems that patients should be administered to keep their drug levels within the therapeutic range. Other examples also exist for how we might personalize controlled release systems, but if practitioners are to keep up with the rapid developments in the field of personalized medicine, we need to give a lot more thought to how we might participate in this revolution.

We acknowledge the editorial help of Dr. Bill Zamboni.

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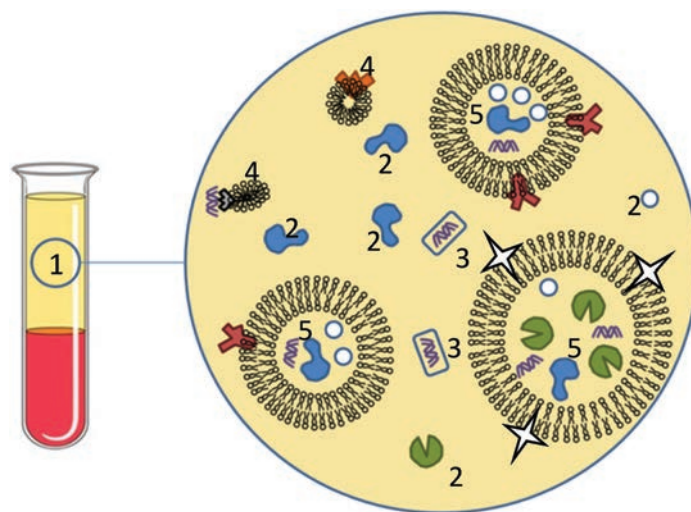
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Horizon Field 2: Extracellular Vesicles (“Exosomes”)

Raymond M. Schiffelers (*Laboratory for Clinical Chemistry & Hematology, University Medical Center Utrecht, The Netherlands*) with help from **Gert Storm** (*University of Utrecht, The Netherlands*) and **Claus-Michael Lehr** (*University of Saarland, Germany*)

Recent research has identified an endogenous communication channel transporting proteins and nucleic acids between cells via nanosized vesicles. These vesicles are referred to as extracellular vesicles and include exosomes, microvesicles, apoptotic bodies, and shedding vesicles (several reviews are available).¹⁻⁴ The donor cell packages specific molecules into the vesicles. Once released, extracellular vesicles can interact with acceptor cells to transfer their cargo. This transfer of complex mixtures of regulatory RNAs, mRNA, and proteins can change acceptor cell behavior and appears to play an important role in physiological and pathological processes. The successful transfer of biological molecules makes extracellular vesicles attractive as (inspiration for) drug delivery systems. Irrespective of their delivery role, their molecular signature provides a snapshot of the producing cell. Vesicles of cancer cells, for example, contain many of the deregulated proteins and regulatory RNA. Extracellular vesicles



Bodily fluids, in this case plasma (1) contain soluble proteins (2), some associated with RNA (3) and submicron particles. Widely known are the lipoproteins (such as LDL and HDL [4]) involved in cardiovascular disease. Lipoproteins are micelles with a hydrophobic core. In contrast, extracellular vesicles (5) are composed of an aqueous core containing soluble proteins and nucleic acids surrounded by a phospholipid bilayer containing membrane proteins.

BSA continued on page 22

can thereby form a “liquid biopsy” of a distant pathological process. Next to the therapeutic and diagnostic applications, the study of extracellular vesicles can also improve insight into their biological function, which is up to now poorly understood.

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Horizon Field 3: Issues in Production and Scale-Up of Novel Dosage Forms

Richard Korsmeyer (*Pfizer Worldwide R&D*) and **Thomas Rades** (*University of Copenhagen, Denmark*)

All development of novel drug delivery systems ultimately needs to be based on the physicochemical properties of the bioactive agents as well as on their biopharmaceutical needs. While we have seen and are continuing to see the development of a smart delivery option for the controlled and targeted delivery of drugs, new challenges have arisen in the need to deliver more and more difficult drug candidates, both in the area of biologics and in the field of small molecules. The latter are increasingly poorly water soluble, and oral delivery becomes a major challenge. Even with a better understanding of the nature of these drugs (although there is a long way to go for many of them, especially when considering the physics of amorphous forms of drugs and drug delivery systems) and with laboratory-scale solutions to their delivery, the translation of these new delivery systems into a clinical reality requires the solution of subsequent challenges in scale-up and eventually technologically feasible production methods.

With the rise of the FDA's Quality by Design concept and the ongoing and active research in process analytical technology, much progress has been made to transform the pharmaceutical industry from a predominately batch production industry to an industry embracing continuous manufacturing and the QbD paradigm. These concepts, however, need to be translated into technical realities also for novel, complex delivery systems. Even a relatively simple controlled delivery system presents challenges above and beyond those associated with conventional dosage forms. Complex systems require characterization of many more composition and process variables in order to establish comparability of materials from earlier studies and to demonstrate the process robustness necessary to ensure continuity of supply once the product is on the market.

In addition to adapting the current production methods (designed and developed for traditional dosage forms for batch

production) to continuous manufacturing processes, entirely new production methods, specifically designed for continuous manufacturing, based on the QbD principle, need to be investigated and developed. Advances in printing technologies to arrive at technological solutions for complex drug delivery systems (e.g., amorphous formulations of poorly water soluble drugs) need to be developed further, as do microfluidic approaches, to lend themselves not only to continuous manufacturing but also to numbering-up instead of scale-up processes. Flexibility in dosage form development, to allow for 1) a much greater individualization of drug delivery systems for special needs (e.g., special populations, including the elderly and children) and 2) the flexible combination of several biologic entities, tailored to the need of individuals, into a single dosage form need to be designed and further developed to be produced in technically feasible processes. ■

CRS Headquarters & Staff

3340 Pilot Knob Road, St. Paul, MN 55121 U.S.A.
Telephone +1.651.454.7250 • Facsimile +1.651.454.0766
controlledreleasesociety.org

Amy Hope
Executive Vice President
+1.651.994.3827
ahope@scisoc.org

Susan Kohn
Executive Director
+1.651.994.3812
skohn@scisoc.org

Megan Pagel
Membership Manager
• News Capsules
• Chapter Coordinator
+1.651.994.3854
mpagel@scisoc.org

Sue Stein
Meeting Manager
+1.651.994.3813
sstein@scisoc.org

Linda Schmitt
Program Manager
• Annual Meeting Program
• Awards
+1.651.994.3828
lschmitt@scisoc.org

Sue Casey
Registration and Abstracts
Meeting Coordinator
+1.651.994.3846
scasey@scisoc.org

Cindy Anderson
Director of Sales
• Exhibits, Sponsorship
• Advertising Sales
+1.651.994.3848
canderson@scisoc.org

Cheryl Kruchten
Member Relations
Specialist
+1.651.994.3801
ckruchten@scisoc.org

Lyssa Campbell
Marketing Manager
+1.651.994.3817
lcampbell@scisoc.org

Brian Simdars
Webmaster
+1.651.994.3849
bsimdars@scisoc.org

Greg Grahek
Publications Director
+1.651.994.3841
ggrahek@scisoc.org

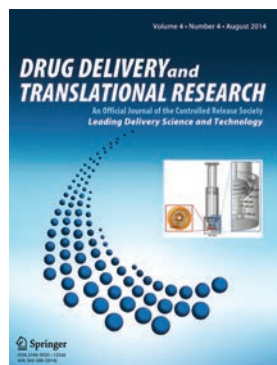
Carol Duling
CRS Newsletter
Technical Editor
+1.651.994.3869
cduling@scisoc.org

Lisa Johnson
Webinar Manager
+1.651.994.3824
ljohnson@scisoc.org

Drug Delivery and Translational Research Updates

Vinod Labhasetwar, Editor-in-Chief, Cleveland Clinic, U.S.A.

The August issue of *DDTR* was just published. Two articles in this issue deserve special mention. The first describes the results of a phase I clinical trial with a nanoliposome drug delivery system for the longer-term delivery of latanoprost to control intraocular pressure, which is a major issue in glaucoma. The second describes formulation of a compressed tablet for colon-specific delivery of therapeutic and the efficacy shown in humans. Glance through the issue to read these and other high-impact articles.



Nanomedicine for glaucoma: Sustained release latanoprost offers a new therapeutic option with substantial benefits over eyedrops



Tina Wong
Singapore National
Eye Centre and
Singapore Eye
Research Institute

Tina T. Wong, Gary D. Novack, Jayaganesh V. Natarajan, Ching Lin Ho, Hla M. Htoon, and Subbu S. Venkatraman

Glaucoma is a chronic progressive optic neuropathy characterized by optic nerve changes and visual field loss. Elevated intraocular pressure (IOP) is the main modifiable risk factor. Chronic instillation of daily eyedrops to lower IOP is the primary treatment of choice, although it requires patient adherence and correct performance. The authors have developed a nanoliposome drug delivery system for the longer-term delivery of latanoprost. In an open-label pilot study, the safety and efficacy of a single subconjunctival injection of liposomal latanoprost was evaluated in six subjects with a diagnosis of either ocular hypertension or primary open-angle glaucoma.



Subbu Venkatraman
Nanyang
Technological
University, Singapore

Subconjunctival injection of liposomal latanoprost was well tolerated by all six subjects. From a baseline IOP of 27.55 ± 3.25 mmHg, the mean IOP decreased within 1 h to 14.52 ± 3.31 mmHg (range 10–18 mmHg), which represented a mean decrease of 13.03 ± 2.88 mmHg (range 9–17 mmHg), or $47.43 \pm 10.05\%$ (range 37–63%). A clinically and statistically significant IOP reduction ($\geq 20\%$ IOP reduction, $P = 0.001$ to 0.049) was observed through 3 months after injection. The nanomedicine

reported in this article is the first nanocarrier formulation that has an extended duration of action in humans, beyond a couple of weeks. The findings in this study open up a new treatment modality that will greatly enhance patient compliance and improve treatment outcomes. The current study provides the evidence and support for further clinical studies of liposomal latanoprost in the treatment of glaucoma.

Pharmacokinetics of ketorolac tromethamine compression-coated tablets for colon delivery

Sateesh Kumar Vemula, Prabhakar Reddy Veerareddy, and Venkat Ratnam Devadasu



Sateesh Kumar Vemula
Wollega University,
Ethiopia

Present research efforts are focused in developing compression-coated ketorolac tromethamine tablets to improve the drug levels in the colon by retarding the drug release in the stomach and small intestine. To achieve this objective, core tablets containing ketorolac tromethamine were prepared by direct compression and compression coated with sodium alginate. The developed tablets were evaluated for physical properties, *in vitro* drug release, X-ray imaging, and pharmacokinetic studies in human volunteers. Based on the *in vitro* drug release study, the optimized formulation showed little drug release ($6.75 \pm 0.49\%$) in the initial lag period of 5 h, followed by progressive release up to $97.47 \pm 0.93\%$ within 24 h. The X-ray imaging of tablets in human volunteers showed that the tablets reached the colon without disintegrating in the upper gastrointestinal tract. From the pharmacokinetic study, the C_{\max} of colon-targeted tablets was $3,486.70$ ng/mL at T_{\max} of 10 h, whereas in the case of immediate-release tablets, the C_{\max} of $4,506.31$ ng/mL at T_{\max} of 2 h signified the ability of compression-coated tablets to target the colon. Compression-coated tablets are suitable to deliver ketorolac tromethamine to the colon.

About DDTR

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Getting Insights into Specialty Chemical Companies with Art Tipton

Vishwas Rai¹ and Bozena B. Michniak-Kohn²



In June 2013, Arthur J. Tipton, Ph.D., was appointed as president and CEO of Southern Research Institute, a not-for-profit organization providing research solutions in the areas of drug discovery, preclinical drug development, advanced engineering, and environmental protection. Before this role, Dr. Tipton served as senior vice president, head of global drug delivery, and general manager of

Evonik Birmingham Laboratories at Evonik Degussa, one of the world's leading specialty chemicals companies. He also served as president of Brookwood Pharmaceuticals, a company that supplies formulation technologies to pharmaceutical and biotech companies. Before joining Evonik, Dr. Tipton was executive vice-president of Durect Corporation (2001–2004), vice president of Birmingham Polymers (1993–2001), vice president of Southern Biosystems (1993–2001), and a manager at Atrix Laboratories (1988–1993).

Before joining the industry, Dr. Tipton obtained a B.S. in chemistry from Spring Hill College, Mobile, Alabama, and a Ph.D. in polymer science and engineering from the University of Massachusetts, Amherst.

Dr. Tipton has served in multiple roles in CRS, including treasurer, board member, and foundation board member, and he has participated in many committees. He is also a member of the inaugural class of the CRS College of Fellows. In 2012, the CRS Board presented the CRS Distinguished Service Award to Dr. Tipton for exhibiting exceptional commitment and service to the society.

Q *Regarding your early career, how did you choose your career path in specialty chemicals?*

A I worked for three years between college and graduate school, and that was a great basis for future decisions. With a chemistry degree there were a range of options. I was fortunate to work in a group that was active in drug delivery and medical device applications of biodegradable polymers. That work fascinated me, and it was an easy decision to want to learn more about how polymers could be used for these

applications, and that desire led to me obtaining a Ph.D. in polymer science and engineering. Having this basis in chemistry and engineering has been invaluable in my career focus. Because most of my career was focused on development of products, I never thought of the space I worked in as specialty chemicals until I became part of Evonik in a transaction in November 2011, since there was a resulting increased focus on raw materials instead of the development of final products.

Q *What is the structure of the specialty chemical industry currently? What are some of the key industry drivers?*

A Specialty chemicals are just that—raw materials that serve a special purpose as compared with more generic commoditized materials. These may be unique, for example, a specific drug produced under stringent conditions to meet regulatory requirements, or they may be a subset of a broader family of materials. An example of the latter is ultra-high molecular weight polyethylene used in a medical application such as a low-friction lining for a medical implant, as compared with standard polyethylene used in consumer applications. Industry drivers include value-add materials from more specialized synthesis or postsynthesis processing. A synthesis example is the elegant molecular weight control that may be necessary to achieve a delivery rate where the polymer is acting as a rate-controlling matrix. As an example for postsynthesis processing, let's say there may be a certain particle size that is most useful in a customer's process; the specialty chemical supplier can prepare that particle size as part of their manufacturing process. Another example of a particular advantage when working with biodegradable materials is to have the specialty chemical manufacturer package the batch in appropriate sub-lot sizes to match the customer's production needs; thus, the final user does not need to continually open and close the entire lot, with resulting moisture exposure.

Q *What were your learning experiences as a new manager joining the industry immediately after graduate school?*

A I always tell people at the start of their career, if they get to a point where they are, for example, planning ten experiments a day but can only perform five, the only way to get the other five done is to go into management. You can choose to continue to advance in management, but a big turning point is when the people working directly for you are no longer working in the lab; at that point and beyond, it is necessary to increasingly focus on strategy rather than tactics. My experience as a bench B.S. chemist has served me well as a reminder of that job. Usually, we are all blessed with both positive and negative examples of mentors in a management role—use your experience with both as a learning opportunity.

¹ Chrono Therapeutics Inc., Waltham, MA, U.S.A.

² Ernest Mario School of Pharmacy, Rutgers–The State University of New Jersey, U.S.A.

Q What was the most difficult scientific challenge (research or manufacturing or other) you have faced during the course of your industrial career, and how did you resolve the issue?

A I can recount a few. One early in my career was a shelf-life stability issue discovered as we were nearing first clinical dosing. It was an all-hands effort to discover and solve the issue, with the pressure of clinical sites awaiting a shipment of material. And it was in an investor-backed, one-product company. The source of the problem was identified and solved by purifying one of the already very pure raw materials. A trace impurity in that ingredient was reacting with the drug and leading to a catalytic degradation of the biodegradable expedient. New clinical batches were produced (which met all stability requirements), and the clinical dosing deadlines ultimately were met. Two lessons learned: build timelines with contingency, and always perform pilot stability studies early. Another lesson learned—also in the scale-up pathway—concerned an issue directly related to scale. A longer unit operation was necessary with increased scale, resulting in more residence time at an elevated temperature. We knew on first principles that more time at an elevated temperature could lead to undesirable reactions, and it did in abundance. With the more stringent conditions, a reaction occurred between drug and polymer, forming a new adduct. This one was solved by both a change in the production process and tighter control on all critical raw materials. My career in drug delivery has taught me lessons many, many of us have learned: *in vitro* release does not always predict *in vivo* pharmacokinetics; results in one animal may not be completely predictive of results in another species; and early clinical results may not correlate completely with results from a larger clinical trial.

Q What is the focus of research at Southern Research Institute?

A The focus of the groups at Southern Research includes a very wide range of research activities. Those not in life sciences—which is about half of what we do—include work in support of NASA, national defense in aerospace, and clean energy

production from fossil fuels as well as alternative energy. In the life sciences, we perform basic research in drug discovery, with an enviable record of success including seven approved drugs in the oncology space and ongoing programs in Parkinson's, Alzheimer's, diabetes, and infectious diseases as well as oncology.

We also perform drug development contract work across these and many other therapeutic areas, including developing preclinical data needed for regulatory filings. We are particularly proud of two decades of work supporting HIV and AIDS researchers worldwide and of toxicology work supporting safe material introduction into products including potential prenatal exposure to new chemicals. Southern Research was active in drug delivery from the mid-1970s until 2005 (when that group was spun out with me as CEO and is now part of Evonik), and a past CRS president (1982–1983) was Danny Lewis from Southern Research. At Southern Research we have recently decided to launch a consulting part of our life sciences business, and it will include a focus on formulation development and scale-up, including for sophisticated drug delivery products.



Tipton enjoying a walk with his dog, Lucy.

Q What are some of the most difficult challenges you face managing such big companies?

A Executive management jobs are most importantly about people. There is a difference in scale needed as companies grow and a necessary appreciation for process and even for bureaucracy. The balance as these processes are implemented is always to err on the side of too much communication. It is important to realize when a group transitions from the positive appreciation of process to the nonproductive deep love of process over results. I often use the “life boat on fire” analogy. I have experienced groups whose response to that fire would be to find a standard operating procedure and then follow it: step 1, then step 2, then step 3. Strong leaders and good companies learn the difference in when and how to react to a range of situations and use the appropriate level of process for individual decisions.

Q Have you been involved with academic collaborations? Please tell us about your involvement with organizations like CRS.

A I have thoroughly enjoyed interactions with academic groups. Examples in my career have been tech transfer from universities and scale-up of these lab-level processes, using key opinion leaders to help direct new research directions, and



Gathering with colleagues at the 2007 CRS Annual Meeting. Left to right: Rod Walker, Art Tipton, Anita Frey, Michael Rathbone, and Yvonne Perrie.

a full collaboration in translational research with clinical academic groups. With many, although not all, academic groups, there is a deep appreciation of the needed industrial role. I often joke that the academic collaborator does the first 95% of the R&D and then the industrial partner does the next 95%. My involvement with CRS has been about 25 years, starting as a regular annual meeting attendee. In 2000, I starting serving on committees, was elected as Treasurer and a Board member from 2004 to 2009, and volunteered for a number of projects since that term, including an overhaul of governance and bylaws. I just went back on the Board as president-elect in 2013. CRS has been my “home society” for my career.



Tipton receiving the Distinguished Service Award at the 2012 CRS Annual Meeting. Left to right: Kazunori Kataoka, Art Tipton, and Martyn Davies.

Q What do you recommend to young aspiring scientists as the key to success in the chemical industry?

A I am not as smart as some of my colleagues and have always worked harder to make up for that. Hard work coupled with solid planning is a combo useful to everyone’s career. Also, it is good to keep in touch with old friends and colleagues, because they can be a source of knowledge and inspiration. And take time for synthesis—don’t rush too quickly to get everything into a PowerPoint presentation. Let ideas incubate for a while, because often when you see your idea beautifully formatted in 28 point Arial font it looks too much like a gospel version. Maybe if that idea was instead a scrawled handwritten note it could more easily be discarded if that is the action warranted. Maintain mental flexibility and don’t fall too quickly or too deeply in love with your own ideas.

Q What are some of your responsibilities as the new president and CEO of Southern Research Institute?

A The main role of a CEO is to ensure development and execution of strategy. As a 73-year organization with almost 500 employees, we have a lot of talent, opportunity, and process at Southern Research. But all that has to be woven into the best tapestry. Sometimes the role of the CEO is just to give confidence to someone who knows the right decision but needs a gentle push to make it. At other times the role is to lead a decision that is difficult for an individual or team to make because they are too close to the issue. And it is managing all those decisions to maintain the correct overall focus on short- and long-term growth. Other roles are to ensure the right number and identification of new initiatives and to ensure that the administrative trinity of HR, legal, and finance is in balance and supports the main business. Importantly, corporate culture is primarily driven from the CEO’s office.

Q How has this new position changed your life?

A All careers change your life. This one has been particularly rewarding in terms of educational increase based on the wide range of things we work on at Southern Research. Material suppliers can fall into a euro/kilogram mentality that may be necessary but not as personally rewarding as driving key technologies that can change lives.

Q If you have any free time, what do you like to do for hobbies?

A I like building furniture and try to have a piece I built in every room I spend a lot of time in. I approach it experimentally, working with different woods, techniques, and finishes. For example, I was curious about the old finish shellac and used that on a pine table I built for my kitchen. I have just finished a series of bookcases for my work office using cherry doors discarded from one of our buildings. I also enjoy cooking and again like to experiment with new ingredients and techniques. ■



Tipton relaxing at a local bistro in Birmingham, Alabama.

Promoting Today's Ideas for Tomorrow's Medicines: Canadian Local Chapter Annual Symposium

Todd Hoare, McMaster University, Canada

For the third time in the last four years, the Canadian Local Chapter of the Controlled Release Society (CC-CRS) joined forces with the Canadian Society for Pharmaceutical Sciences (CSPS) to hold a joint annual symposium, this year in Montreal, Quebec. The theme of this year's symposium was "Promoting Today's Ideas for Tomorrow's Medicines," with topics ranging from leading-edge academic research to industrial product development to regulatory considerations (the last of which included a special guest talk by the Associate Assistant Deputy Minister of Health for Canada regarding emerging topics on both the national and international regulatory stages).

The conference started with a workshop on "Building Opportunities," focused on the state of the life sciences industry in Canada and collaborative models going forward for bridging the academic and industrial worlds given the rapidly changing nature of the pharmaceutical industry. Speakers from Inception Sciences and Algorithm Pharma also led discussions regarding their experiences with establishing and running a start-up company, followed by a discussion of best practices moving forward. A panel on industrial funding opportunities featuring venture capitalists gave attendees an understanding of what potential financiers would be looking for in terms of pharma-specific start-up opportunities. Overall, this first day was an invaluable learning opportunity for CC-CRS members (particularly those in academia with a potential interest in commercializing research) to better understand how to partner with industry as well as potentially create new businesses from emerging delivery science technologies.

The symposium featured an opening reception that evening, and the technical program of the conference started the following morning. CC-CRS board member Emmanuel Ho (University of Manitoba) gave the GlaxoSmithKline/CSPS Early Career Award lecture this year on his ongoing work with the development of

intravaginal microbicides for the prevention of HIV infection. CC-CRS played a lead role in organizing two sessions focused on leading-edge controlled release research. In the "Nanomedicine" section, Christine Allen (University of Toronto) gave a talk on strategies for overcoming some of the challenges associated with the use of nanoparticles to target and treat cancers, Frank Gu (University of Waterloo) described a mucoadhesive nanoparticle technology that has shown preclinical relevance for effectively treating dry eye conditions via a weekly administration, and Ravin Narain (University of Alberta) described the therapeutic potential of carbohydrate-based nanoparticles for a variety of applications in drug and gene delivery. In the "Going Beyond Oral Delivery – Strategies to Enable Drugs to Reach New Targets"



The exhibit area during a networking break.

session, Audra Stinchcomb (University of Maryland, U.S.A.) described the bench-to-bedside translation of microneedle-based transdermal drug delivery vehicles for treating addiction, Brian Farrer (Liquidia, Inc.) described the PRINT fabrication technology and its role in developing designer size and shape nanoparticles and microparticles for a variety of potential targeted therapeutic applications, Heather Sheardown (McMaster University) highlighted the design of hydrogels and contact lenses for improved drug delivery to both the front and back of the eye, and Jill Steinbach (University of Louisville, U.S.A.) outlined her activities in designing a multipurpose delivery platform for preventing or treating sexually transmitted diseases. As evidenced by the topics outlined here, both sections were diverse from both a scientific and clinical perspective, giving insight into the potential for controlled release across multiple potential therapeutic targets and highlighting a variety of interesting materials and devices that may be applicable not only to the targeted application but other clinical applications.

CC-CRS also hosted one of the two keynote addresses for the conference, delivered by You Han Bae from the University of Utah, U.S.A. Dr. Bae gave an outstanding talk on the disconnect



The CC-CRS information booth, happily staffed by our travel award winners throughout the conference, distributing information on both CC-CRS and CRS activities.

between the experimental and clinical experiences to date surrounding cancer-targeted nanomedicines and challenged attendees to better appreciate the differences between small-animal models and the complexity of human pathophysiology, both in the context of cancer therapy and in other aspects of controlled release research. His talk was extremely thought provoking and induced several conversations between controlled release researchers and industrial representatives to better understand the challenges of translating laboratory research into commercial products with real therapeutic efficacy.

Aside from the oral sessions, another key part of the conference was the poster session, which gave over 85 trainees from across Canada the chance to present their research to the conference audience. CC-CRS, with the assistance of local chapter funding from CRS, sponsored eight travel awards to help facilitate travel of leading student researchers from across the country to present their posters at the symposium; such support is essential in a country as large as Canada, in which travel can be a huge financial and logistical barrier to scientific collaboration. The winners of these awards were Emilia Bakaic (McMaster University), Jinke Xu (McGill University), Yufei Chen (University of Manitoba), LeTien Canh (Université de Québec à Montréal), Warren Viricel (Université de Montréal), Sidi Yang (University of Manitoba), Huaifa Zhang (McGill University), and Rabia Mateen (McMaster University). The two top-ranked student abstracts, from Sidi Yang (“RNAi-Based Nanomicrobicide for the



Best poster award winner Rabia Mateen describing her research.

Prevention of Male-to-Female Transmission of HIV-1”) and Warren Viricel (“NMR and Fluorescence Studies of pH-Sensitive Liposomes Based on a Molecular Switch”), were also given the opportunity to present their work during the oral presentation sessions organized by CC-CRS, with outstanding feedback from conference attendees. CC-CRS also sponsored three poster awards for the

best posters presented at the conference. The winners of this year’s competition were Sidi Yang (University of Manitoba, first place, “RNAi-Based Nanomicrobicide for the Prevention of Male-to-Female Transmission of HIV-1”), Rabia Mateen (McMaster University, second place, “Injectable, *In Situ*-Gelling Cyclodextrin-Dextran Hydrogels for the Partitioning-Driven Release of Hydrophobic Drugs”), and Justin Drager (McGill University, third place, “The Effect of Local Delivery of Hypoxia Mimics on Bioceramic Bone Graft Remodeling”). Congratulations to these outstanding student researchers!

Finally, CC-CRS took the opportunity to hold its annual general meeting, at which chapter president Todd Hoare (McMaster University) outlined the current state of CC-CRS and its vision

moving forward. In particular, CC-CRS is excited to, for the first time, be planning “local” local chapter events in each region of Canada (East, Quebec, Ontario, and West) for the upcoming year. These events, featuring a mix of industrial and academic speakers, student poster or 3-minute thesis competitions, and networking, are hoped to spark additional

collaborations between academics and industry on a more local level, with those relationships helping to improve both the visibility and impact of CC-CRS across the country. In addition, we plan to use these events as venues to help us further promote CRS membership and meetings as ideal avenues to build international contacts in the field.

While we took in a lot of science over the four days of the symposium, it was not all work, as no event in Montreal could be! CC-CRS hosted a chapter networking event at Pub L’Ile Noire together with BioTech Annecto, a local industry-based networking organization, that allowed CC-CRS members to both build new contacts and meet old friends over drinks and appetizers in a casual setting. We also enjoyed a great conference banquet with CSPS in addition to activities throughout the city, including the first night of the largest Francophone music festival in the world, which many CC-CRS members took in during the final night of the conference.



Trainee presenter Warren Viricel answering questions about his presentation, with session chair Todd Hoare, CC-CRS president.



One of the networking break/poster sessions allowing attendees to make new contacts and see the latest in delivery science from across Canada.

Overall, the conference was yet another example of how research and translation of controlled release science is alive and well in Canada! We invite everybody to join us at next year’s annual symposium, to be held in collaboration with both the Canadian Biomaterials Society and CSPS in Toronto, Ontario, May 26–30, 2015. We will communicate our plans for this meeting as well as the local events coming up this year via the CRS News Capsule. ■

Tenth Annual Meeting of the Spanish-Portuguese CRS Local Chapter

Aroa Duro-Castano,¹ Emilia M. Barcia,² Dolores Torres,³ and María J. Vicent¹

The 10th annual meeting of the Spanish-Portuguese CRS Local Chapter (SPLC-CRS) was held November 10–12, 2013, at the Centro de Investigación Príncipe Felipe (CIPF) in Valencia, Spain. The 92 participants included 72 scientists from academia (of which 43 were students), 10 scientists from industry, 5 clinicians, and 5 representatives from governmental offices.

The meeting was sponsored by CRS, SPLC-CRS, CIPF, the Valencia government (Conselleria d'educació Generalitat Valenciana, Spain), and some industry sponsors (Evonik Industries AG, Polypeptide Therapeutic Solutions, and Science4you), which allowed organizers to invite excellent foreign scientists from industry, regulatory agencies, and academia as well as clinicians to properly reflect the idea of moving a drug delivery technology from the bench to the bedside. The support received was also used to enable the participation of young researchers (10 travel grants were awarded) and, finally, to reward the best 2012–2013 Ph.D. thesis and the best oral and poster presentations from the conference.

The multidisciplinary nature of the conference attracted people from different disciplines related to drug delivery and controlled release of bioactive compounds, including basic science, applied research, industry, and clinical applications, making possible their active interaction.

The event, the “Xth Spanish-Portuguese Conference on Controlled Drug Delivery: Drug Delivery Systems from Lab to Clinic. New Trends and Opportunities,” was opened by Dr. Isabel Muñoz (CIPF director), Paula Llobet (Inndea Valencia Foundation), and SPLC-CRS president Dr. María J. Vicent, who warmly welcomed the participants, giving also a brief introduction on the conference program. The program included three plenary lectures spread over the three days of the conference and eight sessions, including a “young session” for the newly created Young Section of SPLC-CRS. Invited talks and 5–10 minute short oral communications were spread among the sessions according to topic, leaving time for poster presentations and lively discussions.

The first day started with a plenary lecture by Prof. Lawrence Mayer (Celator Pharmaceuticals, Canada), who talked about CombiPlex[®] liposomal combination technology currently in phase II/III anticancer clinical trials. In his talk, he addressed the advantages of nanoscale drug delivery vehicles for combination therapy, because they can be designed to coordinate the release of

drug combinations after injection (*in vivo*) so that synergistic drug ratios can be delivered to tumors, and how these advantages can be implemented by CombiPlex[®] technology.

Session 1, “New Technologies and Novel Therapeutic Targets,” included presentations by Dr. Pablo Botella (Polytechnic University of Valencia, Spain) on stimuli-responsive hybrid materials for intracellular drug delivery, Dr. Patricia Horcajada (University of Versailles, France) on metal-organic frameworks as novel drug delivery platforms, and Prof. Ramón Martínez-Máñez (Polytechnic University of Valencia, Spain) on gated materials for controlled drug delivery. Dr. Vicent Nebot (Polypeptide Therapeutic Solutions, Spain) addressed difficulties in the development and scaling up of well-defined synthetic drug delivery carriers. Short talks selected from the abstracts closed this first session. After a coffee break, session 2, “Novel Preclinical Technologies/Disease Targets,” began with a talk by Prof. Rocío Herrero-Vanrell (Universidad Complutense, Madrid, Spain) concerning novel protein encapsulation protocols for long-term delivery in the treatment of intraocular diseases, and Prof. María J. Alonso (University of Santiago de Compostela, Spain) closed the session with a lecture on polymeric nanoparticles for transmucosal peptide delivery.

Thanks to the generosity of SPLC-CRS and Evonik, session 3 featured the best Ph.D. thesis defended during 2012–2013. Dr. Javier Palacín and Dr. María J. Vicent honoured the winners, who were selected after a carefully independent review process. Dr. Susana A. Marques Martins (Porto University, Portugal) obtained the first award with her thesis “Drug Delivery Across Blood-Brain Barrier by Means of Intravenous Administration of Lipid Nanoparticles.” The first prize consisted of a certificate, a €500 cheque, and the registration fee for the 41st CRS Annual Meeting & Exposition in Chicago, Illinois, U.S.A. Two second prizes and a third prize, consisting of a certificate and €100, were also awarded to recognize the high quality of the research. Second prizes went to Dr. Inmaculada Conejos-Sánchez (CIPF, Spain) and Dr. Ligia C. Gomes da Silva (Coimbra University, Portugal),



The award for best Ph.D. thesis went to Susana A. Marques Martins.

¹ Polymer Therapeutics Laboratory, Centro de Investigación Príncipe Felipe, Valencia, Spain. E-mail: mjvicent@cipf.es.

² Department of Pharmacy and Pharmaceutical Technology, Universidad Complutense, Madrid, Spain.

³ Department of Pharmacy and Pharmaceutical Technology, University of Santiago de Compostela, Spain.

and the third prize went to Dr. Eurne Imbuluzqueta (Navarra University, Spain). A talk by Dr. Martins presenting her Ph.D. research closed the session, which was followed by poster viewing time with refreshments. The first day of the conference concluded with a speakers' dinner at the Submarino Restaurant inside of the aquarium L'Oceanografic in the outstanding arts and science city of Valencia.

Session 4, "Novel Drug Delivery Approaches in Clinical Development," started the second day. Prof. Jeff Hrkach (BIND Biosciences, U.S.A.) gave a talk on preclinical development and clinical translation of a PSMA-targeted docetaxel nanoparticle (BIND-014) with a differentiated pharmacological profile, the first targeted nanoparticle to be transferred to the clinic for the treatment of prostate cancer. This outstanding talk was followed by well-known clinician Dr. Andrés Cervantes (INCLIVA Health Research Institute, Spain) describing the outcome from an open-label extension study of the RNAi therapeutic ALN-VSP02 in cancer patients responding to therapy. A lively discussion on clinical translation ensued as consequence of these two remarkable lectures. Session 5, "Young Section SPLC-CRS," which was entirely organized by the young members of the organizing committee, featured short talks from Ph.D. students selected from abstracts, followed by an exemplary scientific talk from the invited young scientist Prof. Marcelo Calderon (Freie University Berlin, Germany) on dendritic thermoresponsive nanogels for externally triggered drug delivery. Prof. Calderon explained in detail the path to follow after completing a Ph.D. thesis to continue with a scientific career. A second round of short talks selected from Ph.D. student abstracts closed the session.

The plenary lecture on day 2 was given by Prof. Collen Masi-mirembwa from the African Institute of Biomedical Science & Technology, Zimbabwe. He pointed out the challenges of diseases of poverty in Africa, the limitations they have, and what drug delivery technologies can achieve. He also discussed how difficult and important it is to keep young scientists in Southern Africa and encouraged postdoctoral students to participate in exchanges and research stays in their institutes. Then Session 6, "Tools to Optimize the Safety and Efficacy of Novel DDS," started with a talk on metabolomics by invited speaker Prof. Iola Duarte (CICECO, University of Aveiro, Portugal). She introduced metabolomics as a new tool to monitor safety and efficacy of nanomedicines, explained what has been done, and described what can be achieved with this new approach. Two short talks followed, and the session ended with Prof. Africa González (University of Vigo, Spain) presenting on how drug delivery technologies interplay with the immune system.

A general assembly during the conference summarized the current and prospective state of the Spanish-Portuguese CRS Local Chapter. Also, the new directive board was elected. The day ended with the traditional social dinner of CRS conferences, after a guided tour of Valencia's old city center, where attendees could enjoy the old part of the city and discover some curiosities of this Mediterranean city. The tour ended at La Embajada restaurant, located in a charming old building.



The organizing committee included members from both the directive board (Emilia Barcia, Dolores Torres, and María J. Vicent) and the new Young Section (Ana Cadete, Aroa Duro-Castaño, Amaya Niño, Lucía Martín, and Sonia Reimondez).

The last day of the conference started with the plenary lecture by Prof. Felipe Prosper (University of Navarra, Spain) on the interesting topic of cell therapy and controlled release materials with applications in cardiac regeneration. Session 7, "Novel Preclinical Technologies/Disease Targets," included a lecture by Dr. Damiá Tormo (BiOncotech Pharmaceuticals, Spain), who talked about the lab-to-clinic steps of BO-110, an RNA-based therapeutic, followed by short talks selected from abstracts. Prof. Ruth Duncan (Cardiff University, U.K.) chaired the last session on "Challenges for Development of DDS from Lab to Clinic," which consisted of two amazing talks: Prof. Rogerio Gaspar (University of Lisbon, Portugal) addressed issues for development and approval of biosimilars and generics, and Dr. Dolores Hernan (European Medicines Agency) addressed how the EU facilitates the development of nanomedicines and described recent guidance. A roundtable discussion coordinated by Prof. Duncan and based on topics discussed throughout the conference preceded the reflections on SPLC-CRS, and the 10th conference anniversary was celebrated with an emotional video chronicling the first steps of the chapter, where are we now, and where are we going.

During the concluding remarks, Dr. Vicent emphasized the success of the conference and thanked all the sponsors, contributors, and attendees. The best oral and poster presentation awards were given to Teresa Simon (University of Navarra, Spain) and Garazi Garai (University of País Vasco, Spain), respectively. Teresa received a certificate, a €500 cheque, and the registration fee for the 41st CRS Annual Meeting, and Garazi received a certificate, a €100 cheque, and the registration fee for the next SPLC-CRS conference, which will be held in Granada (Spain) in 2015 and chaired by Dr. Adolfinia Ruiz, the current SPLC-CRS president.

More details on the presentations can be found in the abstract book available on the SPLC-CRS website (www.splc-crs.org) under the 2013 meeting link. ■

In the News continued from page 31

achieved superiority versus vehicle (p -value = 0.0053) at day 15 (following 14 days of twice-daily dosing) in the clinical symptom of irritation, which was singularly judged and reported by the patient. Another independent instrument employed in this study, the health-related quality of life questionnaire, which is a patient reported outcome instrument, also supported the irritation results outcome. InSite believes this is the first time a significant improvement in a blepharitis clinical symptom has been achieved in a phase 3 setting.

InSite will meet with key European regulatory authorities in Q3 2014 to request this same DexaSite Marketing Authorization Application (MAA) filing path, as well as feedback on the need, if any, for additional AzaSite Plus (dexamethasone 0.1% and azithromycin 1% in DuraSite) data and/or endpoints to support an AzaSite Plus MAA filing in bacterial-related blepharitis. InSite will also continue to discuss AzaSite Plus data and endpoint requirements in bacterial-related blepharitis with the FDA, and InSite has committed to share with the FDA the results of all European blepharitis meetings, including all final meeting minutes, in an effort to harmonize the regulatory approach.

“We are pleased to have obtained FDA agreement that a single phase 3 study can support a blepharitis NDA filing for DexaSite in 2015. If approved, DexaSite would be the first ophthalmology agent indicated for the treatment of blepharitis, which we believe is a significant commercial opportunity,” said Timothy Ruane, InSite’s chief executive officer. “In addition to this key progress for DexaSite, we are continuing our efforts to submit an NDA during the second half of this year for BromSite for the prevention of inflammation and pain following ocular surgery.”

“Blepharitis is estimated to affect 34 million patients in the United States, and there is currently no approved therapy indicated to address this chronic inflammatory eye condition,” said Kamran Hosseini, M.D., Ph.D., vice president and chief medical officer of InSite Vision. “Our strong working relationship with the FDA has been exemplified by this process; the FDA’s feedback and input on the development of DexaSite for blepharitis has been extremely valuable as we collectively seek to develop a therapeutic with meaningful clinical benefit for this widespread ophthalmic condition. We look forward to similar positive blepharitis discussions with key European regulatory authorities in the third quarter of this year.”

DexaSite is an investigational product that combines a low dose of the corticosteroid dexamethasone with InSite’s proprietary DuraSite® drug delivery platform. InSite Vision has conducted two phase 3 clinical trials of DexaSite. The first was completed in 2008 in blepharoconjunctivitis (inflammation of the eyelid and conjunctiva). More recently, InSite completed its landmark phase 3 DOUBLe (Dual Ophthalmic agents Used in Blepharitis) clinical trial of DexaSite and AzaSite Plus.

Blepharitis, also known as lid margin disease, is a common, chronic eye disease characterized by inflammation of the eyelid

with periodic acute flare-ups. Symptoms of blepharitis may include redness, swelling, flaking skin, cysts, “gritty” or burning sensations, itching, and vision impairment. The acute flare-ups of this disease can be painful and extremely irritating. It is estimated that greater than 34 million people in the United States suffer from blepharitis. There is currently no FDA-approved drug treatment for blepharitis.

InSite Vision is advancing new ophthalmologic products for unmet eye care needs based on its innovative DuraSite® platform technologies. The DuraSite and DuraSite 2 drug delivery systems extend the duration of drug retention on the surface of the eye, thereby reducing the frequency of treatment and improving the efficacy of topical drugs.

The DuraSite platform is currently leveraged in two commercial products for the treatment of bacterial eye infections, AzaSite® (azithromycin ophthalmic solution) 1%, marketed in the United States by Akorn Inc.; and Besivance® (besifloxacin ophthalmic suspension) 0.6%, marketed by Bausch + Lomb, a wholly owned subsidiary of Valeant Pharmaceuticals International. InSite Vision is also advancing two novel ophthalmic therapeutics through phase 3 clinical studies, AzaSite Plus™ and DexaSite™ for the treatment of eye infections, and is preparing a new drug application (NDA) for the commercial approval by the U.S. Food & Drug Administration (FDA) of BromSite™ for the prevention of pain and inflammation associated with ocular surgery. For further information on InSite Vision, please visit www.insitevision.com.

Endo and BioDelivery Sciences Announce Positive Top-Line Results from the Phase III Clinical Trial of BEMA® Buprenorphine in Opioid-Experienced Patients with Chronic Pain

PRNewswire: July 7, 2014 – DUBLIN, Ireland, and RALEIGH, NC, U.S.A. – Endo Pharmaceuticals Inc., a subsidiary of Endo International plc (NASDAQ: ENDP) (TSX: ENL), and BioDelivery Sciences International, Inc. (NASDAQ: BDSI) announced today positive top-line results from its pivotal phase III efficacy study of BEMA buprenorphine in opioid-experienced patients. BEMA buprenorphine is being developed for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in both patients who are opioid naive and opioid experienced.

The trial successfully met its primary efficacy endpoint in demonstrating that BEMA buprenorphine resulted in significantly ($p < 0.0001$) improved chronic pain relief compared with placebo. Additional secondary endpoints were supportive of the efficacy of BEMA buprenorphine compared with placebo. The most commonly reported adverse events in patients treated with buprenorphine compared with placebo were nausea (7.5 vs. 7.4%) and vomiting (5.5 vs. 2.3%).

“We are highly encouraged by today’s announced study results, which we believe are meaningful for appropriate patients

requiring an opioid,” said Dr. Susan Hall, executive vice president, chief scientific officer, and global head of research and development and quality. “And we look forward to now focusing on our upcoming pre-NDA meeting this month with FDA followed by the preparation and submission of our NDA for BEMA buprenorphine as soon as possible.”

“We are extremely pleased with this robust and significant outcome from this trial in opioid-experienced patients and look forward to sharing more of the results from this study and the positive results from the earlier opioid-naïve study at upcoming medical conferences,” said Dr. Mark A. Sirgo, president and CEO of BDSI. “In addition, the locking of the database for the opioid-experienced study has triggered a \$10 million milestone payment from Endo per our licensing agreement. We look forward to working with Endo toward the completion of the NDA.”

“BEMA buprenorphine is an important development program for Endo,” said Rajiv De Silva, president and CEO of Endo. “Our U.S. branded pharmaceuticals team has extensive experience supporting pain therapeutics, and this program represents a significant opportunity to continue to leverage our commercial capabilities, if we are successful with our application for approval.”

RBCC Developing New Tech to Help Prevent Deaths from Prescription Overdoses

Business Wire: July 2, 2014 – MIRAMAR BEACH, FL, U.S.A. – Work continues on a new injectable, sustained-release technology that Rainbow Coral Corp. (OTCBB: RBCC) hopes can help prevent a deadly epidemic of prescription narcotic overdoses.

In a statement to the press reported by Benzinga earlier this month, National Institute on Drug Abuse (NIDA) director Nora Volkow said that opioid-receptor blocker Naltrexone can improve lives and reduce risks of overdose. Volkow called such medication-assisted therapies “markedly underutilized.”

According to NIDA figures, drug overdose deaths in the United States are over 30,000 annually. In the past 20 years, overdoses of narcotic pain relievers have tripled, with an estimated 2.1 million people in the United States abusing opioid pain relievers.

RBCC is working on a new technology to help address the growing problem. Through its biotech subsidiary, Rainbow Biosciences, the company formed a joint venture with TheraKine, Ltd., to deliver a new injectable, sustained-release technology poised to vastly improve patients’ use of naltrexone. Phase I of the joint venture’s research established excellent compatibility between the drug and TheraKine’s hydrophobic injection matrix, as well as a highly promising release profile. Phase II focused on micronization of the technology as well as extension of its sustained release time.

This summer, RBCC will focus on demonstrating the new technology’s readiness for market as the number of prescriptions rise due to the Affordable Care Act.

RBCC’s biotech division, Rainbow BioSciences, is working with partners such as TheraKine to capitalize on the incredible growth of the global drug delivery market by delivering new medical and research technology innovations in order to compete alongside companies such as Bristol Myers Squibb Co. (NYSE: BMY), Biogen Idec Inc. (NASDAQ: BIIB), Abbott Laboratories (NYSE: ABT), and Valeant Pharmaceuticals International (NYSE: VRX).

For more information on RBCC’s other biotech initiatives, please visit www.rainbowbiosciences.com.

June

EastGate Acquisitions Receives Research Grant from Ontario Brain Institute

PRNewswire: June 25, 2014 – SALT LAKE CITY, UT, U.S.A., and TORONTO, Canada – EastGate Acquisitions Corporation (OTCBB: ESAQ), an emerging pharmaceutical company exploring drug delivery innovations in the development of improved novel formulations and alternative dosage forms of existing biologically active molecules, announced today that it has received a research grant from the Ontario Brain Institute for its lorazepam spray development.

The grant was issued for the purpose to study the administration of a transmucosal lorazepam spray for the treatment epileptic seizures in the outpatient settings. As previously announced, the company has entered into a collaboration with a leading neurologist, Dr. Peter Carlen at the Toronto Western Hospital, who will serve as a principal investigator on this trial. The grant represents a continued funding of a two-year budget as submitted to the Ontario Brain Institute under the Epilepsy Discovery Project 2013 Continuing Research Study Proposal.

The intraoral lorazepam spray is a new transmucosal noninvasive solution for the treatment of acute and repetitive seizures. This spray is a low-volume, oral anticonvulsant formulation of lorazepam designed to be a quick and effective treatment of acute seizures in hospital, home, or ambulatory settings. This delivery form of the most potent anticonvulsant is an exceptionally convenient alternative to injectable benzodiazepines that efficiently control epileptic emergencies. The transmucosal oral spray formulation can be used by the patient, paramedics, or any other available nontrained person, even during an ongoing seizure.

The primary goal of this project is to provide a safe and effective antiseizure medication to a patient to stop seizures in the shortest period of time. Utilising the company’s proprietary delivery system, the lorazepam spray delivers the drug through the mucosal lining of the mouth directly into the blood stream. This direct buccal and sublingual absorption of lorazepam into the blood stream provides the desired rapid delivery of the drug to the brain. The spray combines fast absorption, substantial transmucosal penetration, and efficient seizure suppression. In

In the News continued on page 34

In the News continued from page 33

addition to being self-administered, an oral administration provides the flexibility to any available person on the scene, be it family members, caregivers, or paramedics. Another key benefit of the lorazepam spray is that it can be used at any point during a seizure, even if the patient's mouth is clenched shut, as it can be applied directly to the gum or lip mucosa.

To date, experimental results, also supported by the Ontario Brain Institute (OBI) grants, clearly demonstrated the possibility of preparing a highly loaded low-volume spray formulation of lorazepam. Several formulations were tested for anticonvulsant activity in the animal model, and some of them revealed a high level of protection against chemically induced seizures. The anticonvulsive action achieved after lorazepam spray administration was practically on par with the effect of the same drug dose delivered via injection. Further development of the oral spray of lorazepam will focus on speeding up the onset of the anticonvulsive effect.

As part of its clinical and regulatory plan the company will focus on the following highlights of the transmucosal lorazepam spray to present to regulatory agencies and to use for future marketing purposes:

- Formulation is based on approved pharmaceutical excipients only
- Easy, convenient, noninvasive administration
- Fast onset of action, comparable to injection
- Can be administered in any setting
- Easy and convenient control of delivered dose
- Can be applied to mucosa of lips or gums even when teeth clenched during a seizure
- May satisfy requirement of 505 (b)(2) regulatory pathway in the United States

"We are excited about this development, as the Ontario Brain Institute grant serves as a significant jump-start for the company's overall financing plans for the technology's platform," said Anna Gluskin, EastGate's CEO. "Our innovative technology platform based on a self-nanoemulsion formulation will directly address patient needs for fast onset of treatment and encourage self-administration with the goal of minimizing hospital care and have a positive impact on massive health care costs facing today's healthcare system," concluded Gluskin.

InVivo Therapeutics Announces Realignment of R&D Strategy

Business Wire: June 23, 2014 – CAMBRIDGE, MA, U.S.A. – As a result of an in-depth review of the company's research & development portfolio, InVivo Therapeutics has announced that the company is realigning resources behind its novel Neuro-Spinal Scaffold and the Neuro-Spinal Scaffold Plus Stem Cells program for spinal cord injury (SCI). Resources currently deployed toward InVivo's hydrogel drug delivery program will be eliminated. The hydrogel platform was at an early stage of preclinical development, and substantial financial and human resources would have been required to address technical and competitive

challenges and to advance any drug delivery product to the partnering stage or into the clinic. The company indicated that one element of the hydrogel platform will be further explored, the potential of hydrogel for cell delivery, as part of an expanded biomaterials development program for the delivery of stem cells.

In announcing the refocusing of the company's R&D resources, InVivo further announced it is making a reduction in force (RIF) of 14 employees, or 28% of its workforce. The RIF and the shifting of R&D resources is expected to result in annualized savings of approximately \$3 million and to reduce cash expenditures by approximately 23% compared with 2013 levels. With these savings, InVivo anticipates that existing funds will be sufficient to support its planned activities through March 2016.

"Although reducing staff size and eliminating the hydrogel drug delivery program were difficult decisions, InVivo's focus will be even stronger on the company's core mission: developing meaningful treatments for spinal cord injury," CEO Mark Perrin said. "Going forward, all of the company's resources and efforts will be centered on the development of the Neuro-Spinal Scaffold for acute SCI and Scaffolds Plus Stem Cells for the treatment of chronic SCI. This focus will allow InVivo to advance the spinal cord injury programs without distraction and in a more financially efficient manner. Developing effective spinal cord injury treatments is a challenging task, and our renewed focus maximizes the potential for patients and shareholders to benefit from the major advancements that have been and continue to be made by the InVivo team."

Staff reduction and elimination of hydrogel drug delivery program will allow InVivo to:

- Focus on the mission of the company: to develop treatments for spinal cord injury
- Deliver on the founding premise and promise of the company
- Maximize probability of success for spinal cord programs by minimizing distraction
- Maximize strategic and financial flexibility by reducing cash burn
- Maximize probability of success in bringing a product to market and benefiting patients
- Demonstrate clear commitment to the spinal cord injury community

InVivo Therapeutics Holdings Corp. is a pioneering biomaterials and biotechnology company with a focus on treatment of spinal cord injuries. The company was founded in 2005 with proprietary technology coinvented by Robert Langer, Sc.D., professor at Massachusetts Institute of Technology, and Joseph P. Vacanti, M.D., who is affiliated with Massachusetts General Hospital. In 2011 the company earned the David S. Apple Award from the American Spinal Injury Association for its outstanding contribution to spinal cord injury medicine. The publicly traded company is headquartered in Cambridge, Massachusetts. For more details, visit www.invivotherapeutics.com.

PeptiMed Signs Agreement with the National Cancer Institute to Assess Safety of Help™ Drug Delivery Nanoparticle Formulations

Business Wire: June 23, 2014 – MADISON, WI, U.S.A. – PeptiMed announced today that under a material transfer agreement it will collaborate with the National Cancer Institute's (NCI) Nanotechnology Characterization Laboratory (NCL), located at the Frederick National Laboratory of Cancer Research in Frederick, Maryland. Under the terms of the Agreement, PeptiMed will provide the NCL with nanocomplex consisting of its proprietary siRNA and patented elastin-like polypeptides (ELPs), and NCL personnel will measure material properties indicative of safety and efficacy for potential future dosing in the clinic.

The nanocomplex materials to be provided by PeptiMed will harbor motifs that bind to cell adhesion molecules on the surface of cancer cells and deliver an siRNA payload that silences the oncogene EVI1. Initially, the NCL will assess the physical and chemical properties of the nanocomplexes followed by their purity and sterility in cell culture models. A second phase of testing for various modes of toxicity may be performed in animal models.

"We are profoundly pleased to work with the NCL to further our understanding of PeptiMed nanomaterials," stated Scott Schneider, CEO and cofounder of PeptiMed. "We are indeed fortunate to be able to rely on the expertise of the professionals at the NCL to get one step closer to the clinic."

PeptiMed cofounder Dr. Jeremy Heidel added, "The NCL has a strong track record in assisting biotech companies [as well as government and academic institutions] with evaluation and development of novel nanoparticle drug delivery systems. The comprehensive battery of measurements to be performed at the NCL will provide data and analytical methods that will help advance our nanoparticle technology toward the clinic."

CEA-Leti and Akkrivis Technologies to Develop Nanomedicine Platform for High-Payload Targeted Drug Delivery

Business Wire: June 19, 2014 – GRENOBLE, France – CEA-Leti and Akkrivis Technologies, LLC, announced their collaboration to develop an extremely adaptable, efficient, and highly targeted drug delivery platform for chemotherapy and other treatments that require a high concentration of powerful drugs to be delivered precisely to targeted cells.

The new platform will be based on Akkrivis Technologies' proprietary Z-TECT™ technology that targets and detects unusually low levels of proteins and molecular targets and Leti's Lipidot® nanovector delivery capability.

Developed by Akkrivis Technologies, LLC, a biopharmaceutical company based in Cambridge, Massachusetts, U.S.A., Z-TECT™ is a unique technology platform that combines nanotechnology, molecular detection, and immunology to

provide high sensitivity and detection levels across multiple immunoassays and other assay formats, from colorimetric to fluorescent detection *in vitro* and imaging *in vivo*.

Developed by Leti and introduced for commercial uses in 2011, the Lipidot® technology is a versatile nanodelivery platform based on very small droplets of oil that encapsulate and carry drugs, fluorescent imaging agents, or any other lipophilic payload to targeted cells for diagnosis or treatment.

By combining their delivery and targeting platforms, Leti and Akkrivis intend to develop a new, more efficient, and safer platform to deliver high payloads specifically to targeted cells. The resulting targeted nanoparticles will be optimized in a first phase for research and preclinical *in vitro* and *in vivo* applications. Then, in a second phase, they will be further developed clinically for *in vitro* diagnostics, *in vivo* imaging, and targeted therapy.

"The new targeted nanoparticles jointly developed by Leti and Akkrivis Technologies will dramatically improve the effectiveness of both diagnosis and treatment of diseases and reduce dangerous or unpleasant side effects," said Patrick Boisseau, head of Leti's nanomedicine program and chairman of the European Technology Platform – Nanomedicine (ETPN). "While specifically designed to meet the needs of pharmaceutical and biotech companies, the new platform will be customizable for other end-user applications such as diagnostics and theranostics."

"Detecting disease earlier and delivering the precise drug dosage at the right place at the right moment are major steps toward improving patient diagnosis and treatment as well as controlling healthcare costs," said Joel Berniac, CEO of Akkrivis Technologies. "Akkrivis and Leti have highly complementary nanomed technology platforms that will come together and offer physicians powerful new options for diagnosis and treatment."

Supported by AEPI, the Grenoble-Isère economic development agency, Akkrivis Technologies and Leti created a joint lab, which was launched on June 2. "Leti's collaboration with Akkrivis Technologies underscores Grenoble's strengths as a center for nanomedicine R&D, and we are very pleased that they chose Leti and Grenoble for this exciting research and development project," said Joëlle Seux, AEPI director.

Chrono Therapeutics, Inventor of Wearable "Smart" Smoking Cessation Technology, Secures \$32 Million in Series A Financing

PRNewswire: June 12, 2014 – HAYWARD, CA, U.S.A. – Chrono Therapeutics, a pioneer in digital drug products, announced today the close of a \$32 million Series A financing round, led by Canaan Partners and 5AM Ventures. Additional participants in the financing were Fountain Healthcare Partners, Mayo Clinic, and GE Ventures. The funds will be used to complete product development and clinical studies for the

In the News continued from page 35

company's SmartStop™ programmable transdermal drug delivery system and real-time behavioral support program for smoking cessation. As part of the financing, Wende Hutton, general partner with Canaan Partners, Jim Young of 5AM Ventures, and Aidan King of Fountain will join Chrono's board of directors.

"Smoking costs people their health and eventually their lives, but current technologies like nicotine gums and patches are not effective in enabling smokers to quit permanently because they do not address the cyclical nature of nicotine cravings and offer little to no behavioral support," said Alan Levy, Ph.D., CEO of Chrono. "We believe we have a very compelling technology that will solve many of the problems that make smoking cessation so difficult."

Smoking kills more than 400,000 Americans each year and is responsible for approximately one in five deaths in the United States. Of the 45 million smokers in the United States, 70% report that they want to quit, according to the Centers for Disease Control, and 23 million try to quit each year. The average smoker will attempt to quit eight to 10 times. Nicotine replacement therapy (NRT) is one method used to help smokers quit, but conventional NRT does not match craving cycles, leading to six-month efficacy of less than 20%.

SmartStop is a wearable device that offers programmable, transdermal nicotine replacement therapy (NRT) in combination with real-time behavioral support. Research shows that smokers have clear, consistent, and predictable daily peak nicotine craving patterns; SmartStop is designed to automatically vary nicotine levels throughout the day to match those patterns. The device uses Bluetooth technology to wirelessly communicate with the SmartStop digital support program, providing real-time guidance to help smokers cope with cravings as well as a means for promoting compliance to the NRT and overall quit process.

"We have developed a unique approach to the very difficult problem of helping smokers quit their life-threatening habits," noted Chrono founder Guy DiPierro. "We believe that the blend of a well-understood active drug compound in nicotine with a programmable, wearable delivery system that takes into account a person's habits as well as physiological patterns that each contribute to cravings has the potential to help more smokers quit once and for all."

Leslie Bottorff, managing director of healthcare at GE Ventures, added, "Chrono Therapeutics is paving the way for personal monitoring in healthcare through the creation of the SmartStop integrated digital solution. Their technology is only just beginning, and GE Ventures looks forward to working together to transform disease management."

"Over the past 20 years, I have had the privilege of backing Alan Levy as CEO in the founding of three life sciences companies," stated Wende Hutton. "Alan brings an exceptional track record of success in drug/device combination therapies to Chrono."

BioDelivery Sciences Receives FDA Approval for BUNAVAIL™ (Buprenorphine and Naloxone) Buccal Film for the Maintenance Treatment of Opioid Dependence

PRNewswire: June 6, 2014 – RALEIGH, NC, U.S.A. – BioDelivery Sciences International, Inc. (BDSI) (NASDAQ: BDSI) received approval of the New Drug Application (NDA) for BUNAVAIL™ (buprenorphine and naloxone) buccal film (CIII) from the U.S. Food and Drug Administration (FDA). BUNAVAIL is indicated for the maintenance treatment of opioid dependence and should be used as part of a complete treatment plan to include counseling and psychosocial support. BDSI expects to launch BUNAVAIL late in the third quarter of 2014.

BUNAVAIL was designed using BDSI's advanced drug delivery technology, BioErodible MucoAdhesive (BEMA®), allowing for the efficient and convenient delivery of buprenorphine while potentially overcoming some of the administration challenges presented by the sublingual (under the tongue) dosage forms currently available. BUNAVAIL has twice the bioavailability (drug absorbed into the body) of buprenorphine compared with Suboxone, the market leader in this category. As a result of the improved absorption of buprenorphine with BUNAVAIL, which is the direct result of the BEMA technology, plasma concentrations of buprenorphine comparable to Suboxone can be achieved with half the dose, which may help to reduce the potential for misuse and diversion and potentially lessen the incidence of certain side effects.

BUNAVAIL is the first and only formulation of buprenorphine and naloxone for buccal (inside of the cheek) administration. The ability of BUNAVAIL to stick on the inside of the cheek, unlike sublingual products that need to be kept in place under the tongue until they dissolve, allows patients to talk, swallow, and go about normal daily activities while the medication is being consistently absorbed.

"BUNAVAIL is a novel treatment approach for the more than two million people in the United States afflicted with opioid dependence," said Gregory Sullivan, M.D., principal investigator of the phase 3 BUNAVAIL safety study and an addiction specialist and medical director of Parkway Medical Center in Birmingham, Alabama. "BUNAVAIL utilizes advanced drug delivery technology to fulfill an important need for treatment options with improved drug absorption and patient convenience, and as such, may help to address some of the challenges associated with sublingual administration and possibly help improve treatment compliance."

Dr. Sullivan continued, "BUNAVAIL was assessed in a phase 3 clinical study in 249 patients who were converted from Suboxone sublingual tablet or film to BUNAVAIL. In this study, BUNAVAIL demonstrated favorable safety and efficacy in the maintenance treatment of opioid dependence, as demonstrated by the high study retention rate and the low frequency of patients with positive urine tests for nonprescribed opioids over the 12-week period. The majority of patients who participated

found BUNAVAIL easy to use and pleasant in taste. Additionally, prior to conversion to BUNAVAIL, about 40% of patients were experiencing constipation while receiving Suboxone tablet or film, a common problem with chronic opioid use, and more than two-thirds of these patients reported resolution of symptoms when they switched from Suboxone to BUNAVAIL.”

“FDA’s approval of BUNAVAIL is another example of how we are creating products to help patients in their battle to overcome debilitating medical issues such as opioid dependence and is a tribute to the dedication and focus of our employees,” said Dr. Mark A. Sirgo, president and chief executive officer of BDSI. “This is also a transformative event for BDSI, as we will be launching a product with our own dedicated sales force for the first time, which we believe will lead to significant value creation for our shareholders. We plan to share the details of our overall commercial plans later this summer as we approach the launch of BUNAVAIL. I am confident that with the experience of the marketing and sales resources we have in place, we will have a positive launch and overall market reception for BUNAVAIL.”

“Opioid addiction is a serious issue that can often be difficult to treat,” said Tim Lepak, president of the National Alliance of Advocates for Buprenorphine Treatment (NAABT). “People with opioid addiction face significant challenges in their efforts to rebuild their lives and achieve sustained addiction remission. It is important that patients have treatment options that are effective, safe, and easy to use in order to provide them with their best chance for success. I believe people addicted to prescription opioids and heroin will welcome BUNAVAIL as a novel treatment option.”

BUNAVAIL is the first mucoadhesive buccal film formulation of buprenorphine to compete directly with Suboxone sublingual film. In 2013, sales of Suboxone sublingual film increased to more than \$1.3 billion in the United States, while the total market grew to more than \$1.7 billion, driven by a 14% increase in prescriptions according to data from Symphony Health Solutions.

BDSI plans to launch BUNAVAIL in late third quarter 2014 and anticipates peak sales potential of BUNAVAIL of up to \$250 million in the United States. BDSI will also begin entertaining commercial partnerships for BUNAVAIL outside of the United States. In March 2014, BDSI announced it had entered into an agreement with Quintiles to support the launch of BUNAVAIL. Under terms of the agreement, Quintiles will provide a range of services to support the launch and subsequent commercialization of BUNAVAIL in the United States, including recruiting and training a field sales force. In the United States, nearly 5,000 physicians are responsible for approximately 90% of prescriptions for buprenorphine products for the treatment of opioid dependence, according to recent data from Symphony Health Solutions.

Separately, BDSI has entered into an agreement with Ashfield Market Access to provide managed markets and trade support

for BUNAVAIL. Ashfield Market Access, which is led by industry veterans including Steve Stefano, who led GlaxoSmithKline’s managed markets group for more than 20 years, will be responsible for executing a payer strategy aimed at maximizing patient access to BUNAVAIL.

May

Nuvo Research® Announces U.S. FDA Approval of Third-Party Generic of PENNSAID 1.5%

PRNewswire: May 29, 2014 – MISSISSAUGA, ON, Canada – Nuvo Research Inc. (TSX: NRI), a specialty pharmaceutical company with a diverse portfolio of topical and immunology products today announced that a third party has received U.S. Food and Drug Administration (FDA) approval to market and sell a topical diclofenac sodium 1.5% solution in the United States. The product is a generic version of Nuvo’s PENNSAID (diclofenac sodium topical solution) 1.5% w/w (PENNSAID 1.5%).

Mallinckrodt Inc. (NYSE: MNK) is Nuvo’s U.S. commercial licensee for the sale of both PENNSAID 1.5% and its follow-on product PENNSAID (diclofenac sodium topical solution) 2% w/w (PENNSAID 2%). PENNSAID 2% was approved by the FDA on January 16, 2014, and was launched by Mallinckrodt in February 2014. PENNSAID 2% is the first twice per day dosed topical nonsteroidal anti-inflammatory drug (NSAID) available in the United States for the treatment of the pain of osteoarthritis of the knee. It is protected by five U.S. patents that are listed in the FDA’s Approved Drug Products with Therapeutic Equivalence Evaluations database or “Orange Book.”

Mallinckrodt has advised Nuvo that its strategy is to convert PENNSAID 1.5% patients and prescribers to PENNSAID 2%. Since the launch of PENNSAID 2%, U.S. prescriptions for PENNSAID 1.5% have declined and been offset by increased PENNSAID 2% prescriptions. The most recent IMS data for the week ended May 16, 2014, indicated that the number of PENNSAID 2% prescriptions exceeded the number of PENNSAID 1.5% prescriptions. Nuvo receives a 20% of net sales royalty on Mallinckrodt’s U.S. sales of both PENNSAID 1.5% and PENNSAID 2%.

PolyTherics and Alpha Cancer Technologies Collaborate to Produce Novel Drug Conjugates to Target Tumours

PRNewswire: May 28, 2014 – LONDON, U.K., and TORONTO, Canada – PolyTherics Limited (“PolyTherics”), an Abzena company that provides technologies and services to enable the development of better biopharmaceuticals, today announced a collaboration with Alpha Cancer Technologies Inc. (“ACT”), a Canadian company with a targeted drug delivery platform based on alpha fetoprotein (“AFP”). PolyTherics will produce a range of AFP drug conjugates for ACT to test using its proprietary ThioBridge™ technology.

In the News continued from page 37

ACT has developed a novel drug delivery system based on AFP, a shuttle protein that binds to AFP receptors, which are present in large amounts on the majority of cancer cells but only rarely on healthy cells. AFP has been studied extensively and has been shown to be safe in phase I and II clinical studies involving over 400 patients. ACT's lead product (ACT-901), which is in preclinical development, will use AFP initially to deliver paclitaxel to ovarian tumours.

PolyTherics has developed ThioBridge™ for site-specific conjugation of cytotoxic payloads to disulfide bonds in proteins and antibodies to provide more stable and less heterogeneous drug conjugates. Under the collaboration PolyTherics will conjugate AFP to a derivative of a known cytotoxic drug using ThioBridge™ to produce a range of different drug conjugates for testing.

John Burt, CEO of Abzena, commented: "We are excited to be working with ACT and to be a part of the renaissance in interest in AFP as a delivery platform and look forward to helping produce better drug conjugates to treat cancer."

Igor Sherman, CEO of ACT, said: "We are looking forward to our collaboration with PolyTherics, which will allow us to expand our product pipeline using ThioBridge™ technology. This technology represents an exceptional strategic fit for ACT in our efforts to bring forward targeted cancer treatments that have the potential to significantly improve cancer care for many patients."

AntiOp Partners with Reckitt Benckiser Pharmaceuticals, Inc., to Develop Nasally Administered Treatment for Opioid Overdose

Business Wire: May 21, 2014 – LEXINGTON, KY, U.S.A. – AntiOp, Inc., a Kentucky company founded by Dr. Daniel Wermeling, has signed an agreement with Reckitt Benckiser Pharmaceuticals, Inc., to accelerate production and worldwide marketing of intranasal naloxone, a drug designed to treat opioid overdose.

"This partnership leverages our combined resources and strengths," Wermeling said. AntiOp has the technical expertise and R&D experience to deliver a specifically designed nasal formulation of the drug, he added, while Reckitt Benckiser Pharmaceuticals, Inc., has resources and experience in developing therapies and working with payers and policy makers to make the life-saving drug available to patients worldwide.

The Centers for Disease Control's recent statistics indicate a steadily increasing number of deaths due to opioid overdose. The number has tripled since 1990, with a more recent statistic citing 16,500 deaths in the United States from prescription opioids alone, principally painkillers such as hydrocodone, methadone, oxycodone, and oxymorphone. Related statistics show approximately 800,000 ambulance runs in the United States each year related to suspected opioid overdoses involving both prescription opioids and heroin.

Naloxone injection is an inventory staple for thousands of emergency rooms, ambulances, and postsurgery recovery rooms, and it is produced and marketed by other pharmaceutical companies. Naloxone currently is injected intravenously, into muscle tissue, or under the skin. Emergency responders have used atomizers to crudely convert the injectable form of naloxone into a nasal spray. Wermeling's innovative approach improves on this idea, enabling rescue treatment when the patient is unconscious. The nasal spray will be administered using a ready-to-use, single-use delivery device that is inserted into the nose of an overdose victim, delivering a consistent dose absorbed across the nasal membranes even if the patient is not breathing. The product eliminates any use of needles for injection and is disposable.

"We're very excited to be working with Reckitt Benckiser Pharmaceuticals, Inc., and look forward to substantially accelerated commercialization now that they are involved," Wermeling said. Reckitt Benckiser Pharmaceuticals, Inc., has been a leader in opioid dependence treatment for more than a decade, he added. Under the terms of the agreement, Reckitt Benckiser Pharmaceuticals, Inc. and AntiOp will codevelop the nasal naloxone spray through the time of regulatory approval. Wermeling is confident that they will meet eligibility requirements for FDA priority review after the new drug application is filed.

While the approach offers advantages over injection, there is still opportunity for fine tuning and design optimization, Wermeling said. "We need to hear from end users and stakeholders about the serviceability of the product. Their input will critically impact second-generation product development. Ultimately, we're creating intranasal naloxone to serve them, and we are striving to assist in developing the standard of care in opioid overdose cases."

Development funds have been provided by the National Institute on Drug Abuse and the Kentucky Science and Technology Corporation. "We are very grateful for the early-stage funding from NIDA and KSTC, which enabled us to complete proof-of-concept research and development for naloxone nasal spray," Wermeling said. "We also take great pride in recognizing our relationship with the University of Kentucky Colleges of Pharmacy and Medicine and the National Institutes of Health Center for Clinical and Translational Science, whose faculty and resources were critical to our early-stage success."

AntiOp, Inc. is a specialty pharmaceutical company working to develop naloxone nasal spray for the treatment of suspected opioid overdose. Founder and CEO Dr. Daniel Wermeling is a professor of pharmacy at the University of Kentucky and has published extensive research on nasal drug delivery. He holds patents on pharmaceutical products and delivery systems, many of which are in active clinical development as investigational new drugs.

Neos Therapeutics Announces Issuance of New Patent Covering Composition of Matter for Company's Novel ADHD Products

Business Wire: May 15, 2014 – DALLAS & FORT WORTH, TX, U.S.A. – Neos Therapeutics, Inc. ("Neos" or "the company"), a highly differentiated oral drug delivery company with a portfolio of proprietary technologies and a late-stage pipeline of innovative controlled release products for ADHD, announced today that it has been granted a patent covering its novel amphetamine ADHD products.

Neos has developed an extended release (XR) amphetamine oral disintegrating tablet (ODT) and an extended release amphetamine liquid suspension, both of which are expected to be filed for FDA approval in the next 12–15 months. "We are pleased with the grant of this patent, as it will provide protection for our amphetamine XR-ODT and amphetamine XR-suspension until June 2032," said Vipin K. Garg, Ph.D., chief executive officer of Neos. "We have begun to assess our options to commercialize these products in anticipation of FDA approval."

"The Neos patent portfolio continues to grow as we continue to develop and utilize our platform drug delivery technologies," stated Mark Tengler, chief technology officer of Neos. "Extended release and patient-friendly dosage forms are essential in the treatments of ADHD, and our technologies may provide this advantage."

Neos Therapeutics Inc. is a specialty pharmaceutical company focused on the development and manufacture of FDA-approved drug products that utilize the company's proprietary and patented delivery technologies. The Neos drug products are being developed using the Dynamic Time Release Suspension® (DTRS®) and Rapidly Disintegrating Ionic Masking™ (RDIM™) technologies that deliver controlled release small-molecule active pharmaceutical ingredients (APIs) in either liquid or ODT dosage forms. By utilizing APIs that are already FDA approved, Neos can reduce development and regulatory risk and efficiently advance targeted proprietary Rx products through the FDA's New Drug Application (NDA) approval process. For more information, visit www.neostx.com.

Heron Therapeutics Reports Positive Results for Postsurgical Pain Program

Business Wire: May 14, 2014 – REDWOOD CITY, CA, U.S.A. – Heron Therapeutics, Inc. (NASDAQ: HRTX), a specialty pharmaceutical company, today announced that it has selected HTX-011, a unique combination product utilizing its proprietary Biochronomer™ polymer-based drug delivery platform, as the lead product candidate for its postsurgical pain program. HTX-011 is designed to slowly release the local analgesic agent bupivacaine and the NSAID meloxicam locally at the site of the surgery over 3–5 days. By slowly delivering these agents directly to the location of the pain, lower doses can be used, which should result in greater efficacy with a lower risk of side effects.

In a validated animal model, HTX-011 significantly reduced mean pain intensity compared with the current market leader, Exparel® for up to 72 hours following surgery. Based on these results, the company has initiated a phase 1 enabling toxicology study, to be followed by the initiation of a phase 1 study in the fall.

"There is still a significant need to improve pain relief and reduce the use of opiate analgesics postsurgery. We are excited that our program has the potential to address these issues better than currently available treatments," commented Barry D. Quart, Pharm.D., chief executive officer of Heron Therapeutics. "Having selected a lead product candidate for this program, which includes two well-known approved drugs, and which has demonstrated significant efficacy in an animal model of postsurgical pain, we look forward to initiating a phase 1 clinical trial this fall, quickly to be followed by phase 2 studies."

Heron is utilizing its proprietary Biochronomer™ polymer-based drug delivery platform to develop drugs designed to extend the duration of action of known active ingredients to address important unmet medical needs. In November 2013, the company announced movement into full development of an established local anesthetic for the treatment of postsurgical pain formulated with its Biochronomer extended release technology. In recently completed animal models of postsurgical pain, the company's drug candidates demonstrated statistically significant pain relief for five days, representing the potential to significantly reduce the need for opiates postsurgery and the length of postsurgical hospital stays. Heron's lead product candidate in this program, HTX-011, is a unique combination of local analgesic agent bupivacaine and the NSAID meloxicam utilizing its Biochronomer extended release technology.

Heron Therapeutics, Inc. (formerly A.P. Pharma, Inc.) 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. The company's lead product candidate, SUSTOL™ (granisetron), is being developed for the prevention of both acute- and delayed-onset chemotherapy-induced nausea and vomiting.

BioLight Announces U.S. Patent Approval for Its Formulation of Latanoprost in Its Proprietary Controlled Release Insert for the Treatment of Glaucoma

PRNewswire: May 14, 2014 – TEL-AVIV, Israel – BioLight Israeli Life Sciences Investments Ltd. (TASE: BOLT) (OTCQX: BLGTY), a firm that invests in, manages, and commercializes biomedical innovations grouped into clusters around defined medical conditions, announced that ViSci, its wholly owned subsidiary, has been informed that a patent number 8,722,739 covering the proprietary formulation of

In the News continued from page 39

latanoprost, the medication contained in its controlled release insert for the treatment of glaucoma, has been granted by the U.S. Patent and Trademark Office. The patent is intended to protect, *inter alia*, the chemical structure of the active ingredient for the treatment of glaucoma. The patent is also covering the release of the active ingredient from the Eye-D® subconjunctival insert and its use in treating elevated intraocular pressure in patients with glaucoma and ocular hypertension. The patent and its registration will be in effect at least until April 2030.

ViSci holds an exclusive option from Novaer LLC to a worldwide exclusive license for any use of the insert's proprietary technology. Use of such insert is an effective therapeutic solution to the well-known poor compliance rates with chronic eye-drop administration in ophthalmology.

Recently, ViSci has successfully completed an ocular toxicology and safety study in animals and has filed an Investigational New Drug (IND) with the U.S. Food and Drug Administration (FDA) to conduct a phase I/IIa clinical study with its Eye-D® latanoprost controlled release insert for the treatment of glaucoma. The study will be conducted at up to seven investigative sites in the United States.

Suzana Nahum-Zilberberg, BioLight's chief executive officer, said, "We believe that our Eye-D® controlled-release insert will provide an effective solution to the well-known poor compliance with chronic eye-drop administration commonly used today as a treatment for glaucoma. This U.S. patent approval will strengthen our business, marketing, and competitive advantages of our company."

Azaya Therapeutics Collaborates with University of Chicago in Combination Study in Animals

Business Wire: May 6, 2014 – SAN ANTONIO, TX, U.S.A. – Azaya Therapeutics, Inc., a clinical-stage oncology company developing safer and more effective cancer treatments through its nanotechnology platform, announced a collaboration with the University of Chicago, in Chicago, Illinois. The research will be conducted at the University of Chicago Ludwig Center for Metastasis Research by investigators Stephen J. Kron, M.D., Ph.D., and Ralph R. Weichselbaum, M.D. The researchers hope to develop a new application for the investigational drug ATI-1123, a proprietary formulation of the chemotherapy agent docetaxel, commonly known as Taxotere, manufactured using Azaya's patented Protein Stabilized Liposomes™ (PSL) process. The goal is to determine whether a low, clinically safe dose of radiation can significantly enhance delivery of ATI-1123 to experimental tumors in laboratory mice. The study will also document the effects of radiation on docetaxel accumulation in the irradiated tumors and examine whether the combination leads to greater inhibition of tumor growth. This work may serve as a model for future clinical studies in cancer patients undergoing radiation therapy.

"The outcome of this study could lead to a new treatment option for cancer patients in which our ATI-1123 liposomal docetaxel

could provide a powerful means to improve the benefits of radiotherapy," said Mike Dwyer, the president and CEO of Azaya. "Given the established safety of ATI-1123 on its own, we plan to test this combination in cancer patients if the results of the animal study are promising."

While many chemotherapy drugs are highly effective, their use is often limited by their toxicity. Liposomes have long been considered attractive as a means to help direct chemotherapy to tumors without increasing uptake in normal tissue. Since the tumor-supporting blood vessels lack the tightly bound cells of healthy vasculature, blood components can leak into tumors. This mechanism, called the enhanced permeability and retention (EPR) effect, is how liposomes leave the bloodstream and reach tumors, where they can release the encapsulated chemotherapeutic agent.

Recent studies at the University of Chicago demonstrate that delivery of liposomal chemotherapy to tumors can be further enhanced after radiation, leading to increased drug accumulation and greater effects on tumor cells. Researchers now hope to apply their method to ATI-1123 liposomal docetaxel.

More than half of all cancer patients receive radiotherapy during the course of their disease. Using the radiation to direct liposomal drugs to tumors could improve the benefits of treatment to these patients. Docetaxel is an ideal choice for the radiation-targeted liposome delivery strategy because it is a highly effective drug and is commonly combined with radiation therapy in treatment of cancer. However, the toxicity of Taxotere can lead to early discontinuation of therapy, preventing patients from fully benefitting from the therapy. Due to its liposomal encapsulation, ATI-1123 has the potential for both reduced toxicity and increased cancer therapeutic uptake at the tumor, which could be enhanced further when combined with radiation.

Azaya Therapeutics, Inc., is a clinical-stage oncology company focused on developing more effective cancer treatments through its novel nanotechnology platform. Azaya's patented Protein Stabilized Liposomes™ (PSL) platform allows for high-dose delivery of potent cytotoxics with potentially lower side effects. Azaya's lead compound, ATI-1123, is a novel liposomal encapsulation of docetaxel. ATI-1123 has completed an FDA-approved phase I clinical trial in solid tumor patients. Results included evidence of clinical benefit in 82% of the patients with an improved safety profile. Azaya has entered into a licensing agreement with CANbridge Life Sciences, of Beijing, China, to develop ATI-1123 for markets in China, Taiwan, and South Korea.

Azaya's other product, ATI-0918, is a generic formulation of DOXIL®/CAELYX®. ATI-0918 is in an FDA-approved bioequivalency clinical trial in comparison with DOXIL®/CAELYX in women with ovarian cancer. On the basis of this trial and various *in vitro* tests, the company will apply for market approval in both the United States and Europe.

Azaya Therapeutics, Inc., is privately held and located in San Antonio, Texas. For more information on Azaya, please go to www.azayatherapeutics.com.

Pulmatrix Presents Preclinical Data on iSPERSE Inhaled Antibiotics at the 2014 Respiratory Drug Delivery Conference

Business Wire: May 5, 2014 – LEXINGTON, MA, U.S.A. – Pulmatrix today presented data at the 2014 Respiratory Drug Delivery Conference in Fajardo, Puerto Rico. The poster presentation includes development data on PUR0400, a preclinical drug candidate of fluoroquinolone levofloxacin formulated in the company's proprietary iSPERSE™ dry powder technology.

Robert Clarke, Ph.D., chief executive officer of Pulmatrix, noted, "The development of PUR0400 marks a significant step for the company in advancing multiple iSPERSE programs toward clinical testing. These data significantly advance our understanding of our novel platform technology and highlight our ability to formulate high drug load products in a format that avoids liquid nebulization and is convenient to patients."

The development data extend previous work performed with a wide range of antibiotic drug classes and focuses on PUR0400, an advanced dry powder formulation of levofloxacin. The data demonstrate that, when formulated in iSPERSE, PUR0400 exhibits desirable physical and aerosol properties, while exhibiting stability across storage conditions.

David Hava, Ph.D., chief scientific officer of Pulmatrix, commented, "The PUR0400 data highlight an advantage of the iSPERSE technology over conventional dry powder technologies in the stable formulation of high drug loads for lung delivery. Together with a robust preclinical data package using a number of different antibiotics, these data provide the support for continued development of inhaled antibiotic formulations in a number of respiratory diseases."

PUR0400 was designed using Pulmatrix's proprietary iSPERSE platform, an engineered particle technology that facilitates flow rate independent, high-efficiency drug delivery to the lungs. PUR0400 is one of several iSPERSE antibiotic formulations being developed for respiratory diseases such as cystic fibrosis (CF) and non-CF bronchiectasis.

Pulmatrix, Inc., is a clinical-stage biotechnology company developing and commercializing a novel inhaled dry powder drug platform to create a new generation of inhaled therapeutics. The platform, called iSPERSE™ (inhaled small particles easily respirable and emitted), enables drugs to be delivered in inhaled dry powders with unique properties for high drug loading and highly efficient dispersibility and delivery to the airways. iSPERSE can create dry powder formulations with virtually any drug substance, including small molecules, biologics, and multidrug combinations.

The company is pursuing both proprietary and partnered applications for iSPERSE. For additional information about Pulmatrix, please visit www.pulmatrix.com. ■

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Controlled Release & Drug Delivery Symposium 2014

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August 23–24

Kuala Lumpur, Malaysia

www.ukm.my/crdds2014

17th International Pharmaceutical Technology Symposium

September 8–10

Antalya, Turkey

www.ipts-hacettepe.org

Third Symposium on Innovative Polymers for Controlled Delivery

September 16–19

Suzhou, China

www.sipcd.cn

5th Course on the BBB in Drug Development

October 1–3

Uppsala, Sweden

www.uc.pt/fmuc/gai/cursosavancados/

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Formulation & Drug Delivery Congress 2014

October 2–3

London, United Kingdom

www.formulation-congress.com

Animal Health Drug R&D: Formulation, Delivery & Development to Market

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November 1–2

San Diego, CA, U.S.A.

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