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Prospects and Challenges"

Preclinical Species Modelling and Simulation

CRS Awards: Nominate a Colleague





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Yvonne Perrie
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CRS Newsletter

Leading
Delivery Science
and Technology

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Charles Frey
Steven Giannos
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Bozena Michniak-Kohn
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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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*Bozena Michniak-Kohn
Ernest Mario School of Pharmacy
Rutgers-The State University of New Jersey, U.S.A.*



Nurturing Young Scientists

It is already September and after Labor Day, and my red tips in the garden are showing signs of fall color. In academia we are also changing gears, with all the students back on campus, major parking and traffic issues, and full classrooms. All the new fresh young faces on campus, all excited to see how this new semester develops...seeing them made me think of how we at CRS bring together our existing young CRS members and also try to add to the ranks of young people who may want to be part of and grow with CRS. CRS currently has the Young Scientist Committee (YSC) together with the Young Scientist Mentorship/Protégé Subcommittee. The group provides educational opportunities as well as inexpensive networking events together with career development initiatives and training. Their activities have ranged from networking events (for example, the Portland YSC brewery social in 2010) to webcasts, roundtable sessions, and workshops. Young investigators can sign up to participate on the CRS website, and I hope CRS members are also offering to participate as mentors for those young scientists. The current chair of the YSC is Joshua J. Reineke, with Patrick Lim Soo as Deputy Chair and Ron Ortiz as past chair. In addition, we have a CRS Young Scientist LinkedIn group as well as a page of useful links to career resource websites for young scientists.

While reading through the CRS website and the career path case studies, it was amazing to see how few scientists had a mentor in their careers. What an opportunity we have now to change this for the next generation and see if we can provide some of our own time to mentor these young people.

One challenge is that, as society members, we are so spread out throughout the world that many are unable to attend the annual meeting in person and hence miss all the wonderful programing and networking that is on offer. This is particularly true for the young scientists and students, especially these days with tighter budgets in both industry and academia. Interactive websites are one answer, but another could be working with CRS local chapters and student chapters. In the United States we have three student chapters covering the areas of Connecticut, Illinois, New Jersey, New York, and Pennsylvania. (Hint: maybe we should have more geographic coverage in the United States?) Globally, we have 14 local chapters and the Hebrew University of Jerusalem Student Chapter. Our new president has published the CRS strategic objectives, and among them is the creation of a new International Committee chaired by Claudio Ortiz that will consider how we can use our local chapters to add even more value for all members. I hope that this will stimulate more interest in our young scientists to become active participants in the student chapters as well as local chapters of the CRS. These young people after all are the future of our Society... ■



Ian Tucker
University of Otago
Dunedin, New Zealand

The Fifth Decade and Beyond

The world is awash with information, much of it unread, in journals, newspapers, blogs, and probably tweets in spite of their brevity. Much information is of questionable value and some clearly wrong—if I am allowed to say that in a postmodern world—but occasionally there are gems to be found. I don't want to add to your information burden, but I would like to enrich your knowledge of CRS through controlled delivery of relevant information. So, I am sitting at my desk on a Sunday afternoon in Dunedin, New Zealand, as it rains outside, thinking what to say.

I have written to the chairs of all CRS committees and the presidents of all chapters to ask what questions are on the lips of CRS members—in some cases the sunburnt lips of those who spent too much time sunbaking after the very successful CRS Annual Meeting in Hawaii. Responses are coming in from around the world, an indication of an engaged membership in a global society. These responses will form the basis of my future “From the President” articles in the *CRS Newsletter* over the coming year during which I have the privilege to serve our Society.



Ben Boyd

A number of years ago I read *Engineered Writing*, a very readable book with sound advice on how to structure articles to make it easy for the reader: most important material first, clear headings, and so on. I promise to try to apply this approach so that you can skip paragraphs, jump sections, or (heaven forbid) skip the whole article if you wish. You may be thinking that I have already broken this promise, but it is the first article.

Besides, Ben Boyd, chair of the Board of Scientific Advisors (BSA), has suggested that some insights into the characteristics of the CRS Board members would be okay. So to start, here's a bit about me.

As I said in Hawaii, I see the position of president as a “servant” role, and I take its responsibilities very seriously. However, I think it is possible to mix serious responsibilities with enjoyment and fun. I am excited by big-picture thinking but retain the retentiveness of a pharmacist's attention to detail. In terms of big-picture stuff, I believe controlled release science is in its infancy. When I compare our current technologies with nature's delivery systems (seeds, islet cells, sperm, and so on) our approaches are crude and simple, in spite of the advances that our Society has facilitated over the last four decades—we will hold our 41st annual meeting in Chicago next year! Although we can be justly proud of what has been achieved so far, nature's exquisite delivery systems suggest that even 100 years from now,

our technology will still be rudimentary by comparison. So CRS must be “built to last,” and we can do this by good governance, good management, and financial planning—and, more importantly, by serving our members, ensuring we are leading delivery science and technology and translating the science into useful products and services for the benefit of society and the environment.

Leading Our Science and Technology: The Role of the BSA

The BSA has two major challenges in the coming 12 months:

- first, to refine its thinking on where it sees CRS science going in the next 5–10 years to inform the strategic planning being carried out by the Annual Meeting Committee and the content of the meetings being planned by the Annual Meeting Program Committees;
- second, to explore the developments in the fundamental sciences (physics, molecular biology, immunology, physical chemistry, electronics, nanorobotics, etc.), the theory and technology that may underpin and enable our delivery science in the distant future (>10 years).

Translating Our Science and Technology



Clive Wilson

A new committee, the Translational and Regulatory Committee (T&R) kicks off this year with Clive Wilson as chair. The charge for T&R is to identify clinical societies (e.g., diabetes) and industry associations that are potential users of our science and technology and to focus on building a relationship with the most appropriate. If all goes to plan, we will be able to announce the outcome at the Chicago conference, the theme of which is

“Translation of Delivery Technology: Innovation to Commercialization.” Of course, individual members already collaborate with clinicians and industry, but our aim is to build relationships at the association level.

Internationalisation

Another strategic objective for 2013–2014 is internationalisation. This has at least three elements:

- the new International Committee chaired by Claudio Ortiz is challenged with how we use local chapters to add even more value for all members;



Claudio Ortiz

From the President continued on page 4

From the President continued from page 3

- the Finance Committee chaired by Marcus Brewster (Treasurer) is working on a business model for non-U.S. non-European meetings;



Marcus Brewster



James Oxley

- the Satellite Meeting Committee chaired by Jamie Oxley is charged with mounting three high-value satellite meetings, at least one of which could be in an Asian venue.

I look forward to our interactions. It is going to be an exciting year.

Ian Tucker
President ■

>>> REGISTER NOW

Upcoming CRS Workshop

This CRS workshop will take place at the 2013 AAPS Annual Meeting & Exposition November 10–14, 2013 San Antonio, Texas, U.S.A.

Introduction to Microencapsulation Technologies Workshop

Knowledge of multiple encapsulation technologies and how they are applied is valuable information for developing new products or solving existing problems. It is important, at a minimum, to have a basic understanding of all commonly available processes and their applications. This workshop provides an introduction to common micro- and nanoencapsulation processes and their various applications. The workshop is structured to 1) introduce common encapsulation techniques, 2) review common materials, and 3) provide an overview of the wide range of applications for controlled release products.

Workshop Organizers

James Oxley, Southwest Research Institute, U.S.A.
Irwin Jacobs, Particle Dynamics International, LLC, U.S.A.



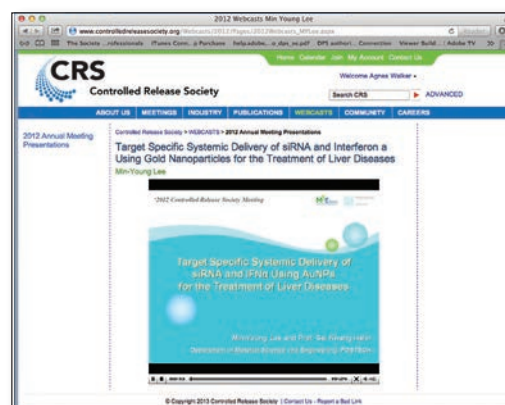
Register online at www.aaps.org. Information about this workshop is also available on the CRS website at controlledreleasesociety.org.

Image courtesy istockphoto.com

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Webcasts of the 2013 CRS Annual Meeting in Hawaii—available online to CRS members and annual meeting attendees.



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2013–2014 CRS Board

The following CRS members make up the 2013–2014 Board. Members wishing to interact with Board members can find contact information in the member directory or can simply email crspresident@scisoc.org.



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New Zealand



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Yvonne Perrie
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United Kingdom

Aloha! Highlights of the 40th Annual Meeting & Exposition of the Controlled Release Society

- More than 1,200 people in attendance
- 41 countries represented
- Nearly 630 posters on display
- 900-plus scientific presentations



CRS President Kazunori Kataoka welcomes guests during the President's Banquet.



Annual Meeting Program Committee member Justin Hanes with Tuesday's plenary speaker, Mark Prausnitz ("Preventing Influenza, Treating Diabetes, and Preserving Vision: Case Studies in Translation of Microneedle Technology"), who graciously stepped in as speaker due to a last-minute cancellation.



The program was ambitious, with more than 900 scientific presentations held over four days.

"Interesting sessions. Up-to-date research."



The scientific program and events attracted more than 1,200 attendees to Hawaii to share their passion for investigation and discovery.

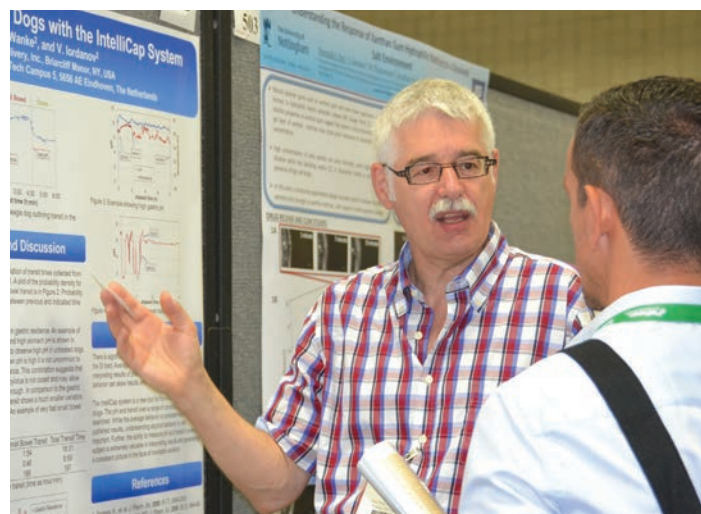


The Young Scientist Networking Event gave early career professionals the opportunity to network while enjoying an evening out at Jimmy Buffett's Beachcomber Restaurant and Honolulu Surfing Museum.



More than 20 CRS awardees and volunteers were recognized for their contributions, including the 2013 College of Fellows awardees. Pictured left to right: Kazunori Kataoka (CRS President), Ashutosh Chilkoti, Justin Hanes, Hideyoshi Harashima, Claus-Michael Lehr, and Ian Tucker (CRS President-Elect).

"Well done! It was a great event."



Nearly 630 posters were on display. Poster sessions included opportunities to talk to poster authors. Many poster authors also recorded three-minute poster snapshots providing an audio summary. These were accessed through the CRS meeting app.

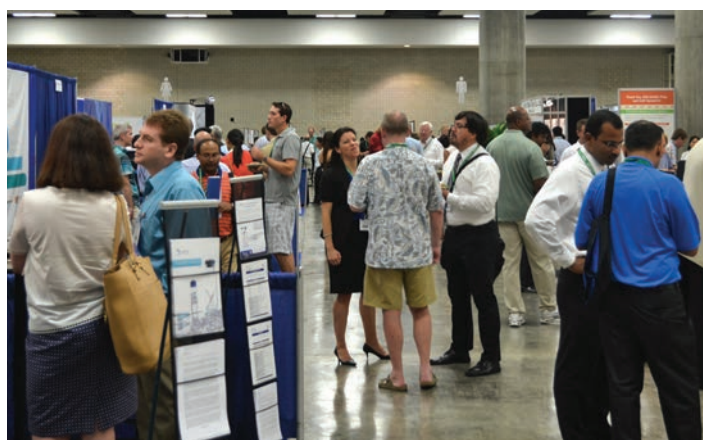


Prize drawings sponsored by various exhibitors made for some happy attendees.

"Good poster sessions with a wide variety of technologies and technology areas covered."



Prof. Paula T. Hammond, David H. Koch Chair Professor of Engineering in the Department of Chemical Engineering at the Massachusetts Institute of Technology, gave the closing plenary address on Wednesday, "Electrostatic Nanolayer Delivery Platforms: From Macro- to Nanopharmacies."



Meeting attendees took time between scientific sessions to visit with the exhibitors and learn about the many new products and services available.



Annual Meeting continued from page 7



Some 34 presenters from 11 countries spanning four continents highlighted new ideas, opportunities, products, and trends during CRS Innovation Sunday.

"Very interesting, networking was very good."



The exposition hall offered yet another learning environment with 150 knowledgeable exhibitors from more than 60 companies.



Attendees of the Preclinical Sciences & Animal Health Get-Together had the opportunity to hear a presentation and spend time networking during Monday's event.



Members of the 2012–2013 CRS Board enjoying the aloha spirit at the President's Banquet. Left to right: Michael Rathbone, Tamara Minko, Andrew Lewis, Christine Allen, Kazunori Kataoka, Yvonne Perrie, Tom Redelmeier, Ruth Schmid, and Ian Tucker. (Not pictured, Marcus Brewster and Martyn Davies.)



Outgoing CRS President Kazunori Kataoka makes the transfer of the presidency official by passing the gavel to incoming President Ian Tucker during Wednesday's closing plenary session.

Thank You to the Exhibitors of the 40th Annual Meeting & Exposition

These are the organizations that not only support the research and development needs of delivery science with products and services, but many of the exhibitors also sponsored refreshments and prizes in the exposition hall. Thank you, 2013 CRS exhibitors!

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Agilent Technologies
Akina, Inc.: PolySciTech Division
Asahi Kasei America, Inc.
Avanti Polar Lipids, Inc.
BASF
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BioPharm Solutions, Inc.
Catalent Pharma Solutions
CIMA Labs
Colorcon, Inc.
CordenPharma Switzerland
CoSci Med-Tech Co., Ltd.
Covaris Inc.
Dissolution Technologies
Drug Delivery Partnerships Conference
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EMD Millipore
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Arlene McDowell is all smiles, receiving a tablet from exhibit prize and happy hour sponsor Rudy Emmelot, Formex LLC.

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Institute/Methodist Academy
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Texture Technologies
Vision Processing Technologies, Inc.
Wyatt Technology Corporation



CRS was fortunate to have the support of 50 sponsoring organizations that made events, awards, scientific programs, and refreshments possible.



Attendee bags were a welcome sponsorship. Thank you, EMD Millipore!



This conversation at the 3M booth shows the importance of face-to-face communication.

Thank You to Sponsors

CRS is sincerely grateful for the support sponsors provided for the 2013 CRS Annual Meeting & Exposition. Your sponsorships supported the scientific program of the meeting and workshops as well as the many extras that added value to our meeting: lanyards and attendee bags for convenience, refreshments that facilitated networking, and WiFi and the mobile app that provided connections. Thank you, CRS sponsors!

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TRANSLATION of Delivery Technology: Innovation to Commercialization



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CRS Awards: Nominate a Colleague

One of the ways in which CRS supports its members and the advancement of delivery science is by recognizing those who have made significant contributions to the science and the society. Each year CRS seeks nominations for these prestigious awards. Please take a moment to read the profile of each award, and consider nominating a colleague that you believe deserves to be recognized. A list of past awardees can be found on the CRS website. Questions about the nomination packet or selection process should be directed to CRS headquarters, attention Linda Schmitt at lschmitt@scisoc.org. **Nominations for all awards must be received by January 31, 2014.**

College of Fellows Award

The most prestigious level of membership in CRS, a maximum of five new Fellowships will be awarded each year. To date, 81 CRS members have received this award.

The College of Fellows recognizes CRS members who have made outstanding contributions to the field of delivery science and technology over a minimum of ten 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. Election to the College of Fellows is only available to current members of CRS.

Nomination Process

A CRS member may nominate only one person for Fellow in each annual call. Nominations must be supported and sponsored by two current members of CRS. Nominations are made using the online form on the CRS website and must include the following:

- Names and contact details of the nominating sponsors
- A full curriculum vitae
- A 200-word summary citation outlining the case for the award of Fellow
- A brief one-page document highlighting the specific distinguished and sustained contributions of the applicant to the fields of interest to CRS
- Supporting letters from the two nominating members that must not exceed one page

Selection Process

The College of Fellows Award Committee will be responsible for the selection of the awardee(s) to appear on the ballot for the full College of Fellows vote.

Awardees Receive

- An honorary plaque
- Complimentary CRS Annual Meeting & Exposition registration

CRS 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. The nominee must be a member of CRS.

Nomination Process

Nominations are made using the online form on the CRS website and must include the following:

- An abbreviated curriculum vitae
- Two letters of support for the nominee

Selection Process

The Founders Award Committee will make the selection of the awardee and obtain approval from the CRS Board.

Awardee Receives

- A personalized award
- Complimentary CRS Annual Meeting & Exposition registration
- Complimentary ticket to the President's Banquet held during the CRS Annual Meeting & Exposition
- \$5,000 honorarium
- The opportunity to give a presentation during the award ceremony at the CRS Annual Meeting & Exposition
- Appointment to the Founders Award Committee for the following year

CRS T. Nagai Postdoctoral Research Achievement Award

Cosponsored by The Nagai Foundation Tokyo

Established to recognize those who have made an outstanding postdoctoral research achievement in controlled release science and technology, the CRS T. Nagai Postdoctoral Research Achievement Award recognizes an individual postdoc who has recently completed postdoctoral research and the postdoc's advisor, who played an integral role in the nominee's achievements. Candidates for the award may be from academia, industry, or government. Candidates must be CRS members.

Nomination Process

Nominations are made using the online form on the CRS website and must include the following:

- An abbreviated curriculum vitae
- Abstract of work (if available)
- Examples of quality research papers
- Patents related to the work and a list of publications on the subject
- Two letters of support for the nominee

Selection Process

The CRS T. Nagai Postdoctoral Research Achievement Award Committee will be responsible for the selection of the award with approval by the CRS Board.

Awardee Receives

- A personalized award
- A \$3,000 honorarium for each the principal recipient and the advisor
- Complimentary registration to the CRS Annual Meeting & Exposition for the principal recipient and the advisor



Ali Khadembosseini accepting the 2013 CRS Young Investigator Award from CRS President-Elect Ian Tucker.

CRS Young Investigator Award

Cosponsored by Aptalis

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

Nomination Process

Nominations are made using the online form on the CRS website and must include the following:

- Nomination letter from the nominator outlining key accomplishments of the candidate
- Two additional supporting recommendation letters are required and are the responsibility of the sponsor
- A curriculum vitae of the candidate that includes awards and honors, memberships in societies, service to societies, research grants received, publications (grouped as refereed publications, nonrefereed publications, proceedings, abstracts, patents, and other publications, including publications in press but not those merely submitted or in preparation), and other activities

Selection Process

The Young Investigator Award Committee will be responsible for the selection of the awardee, with approval by the CRS Board.

Awardee Receives

- \$3,000 honorarium
- Complimentary CRS Annual Meeting & Exposition registration
- Personalized award
- Complimentary ticket to the President's Banquet
- Opportunity to give a presentation during the award ceremony at the CRS Annual Meeting & Exposition ■

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Honor a Colleague

Submit a Nomination for the 2014 CRS Awards

Nominations are now being sought for the following CRS awards:

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

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

**Make Your Nominations
by January 31, 2014**



Prediction and Analysis of Drug Delivery Systems: From Drug-Vector Compatibility to Release Kinetics

*P. Norvaisas, M. Kojic, M. Milosevic, and A. Ziemys
Houston Methodist Research Institute, Department of Nanomedicine, U.S.A.*

Introduction

Drug delivery systems (DDS) are one of the groundbreaking advances of modern medicine. The plentitude of techniques used in creating delivery vectors and formulations is still unmatched by analytical and computational efforts that could help to understand better design principles and predict DDS efficiency. Here we overview several of our efforts to apprehend the logic behind drug and vector pairing and prediction of drug transport with vectors. We present analysis and computational tools that can provide useful information in early and later stages of DDS design and evaluation.

There is an enormous number of different DDS in development, although few of them have been successful to enter trials and clinics.^{1–3} Although efforts to bring DDS to clinics are large, the limited success rate suggests that additional analysis techniques might help in designing drug vectors and predicting their properties in transport and release of the therapeutic payload. There seems to be a lack of a framework that amalgamates current knowledge in this field. Because in essence drug delivery relies on fundamental processes of physics and chemistry, such as drug diffusion, absorption, partitioning, or flow, tools for computation and analysis may help us better understand DDS performance. Figure 1 illustrates common steps in drug delivery: drug-vector formulation, delivery of vector with payload, and local payload release. For each step we are developing a computational strategy, as outlined below.

The key role of vectors can be understood as an augmentation of drug pharmacokinetics for improved therapies. As long as a drug is associated with a vector, the drug will follow the distribution and pharmacokinetics pattern specific to that vector. If a drug is not chemically linked to a vector, drug and vector matrices are associated by physicochemical compatibility. This compatibility may be expressed in terms of $\log P$. Our study shows that there are two main trends related to $\log P$ of a drug: drug indications

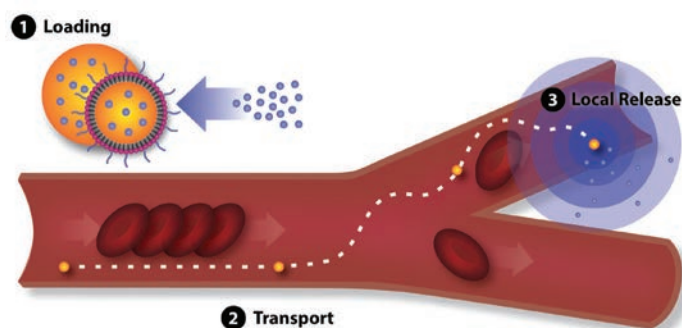


Figure 1. Drug formulation, delivery, and release using DDS.

and drug compatibility to vector (Figure 2). First, there is a tendency that DDS are loaded with drugs of specific $\log P$ values, where $\log P$ increases in the order liposomes < liposome membrane < albumin < micelles. Second, drugs belonging to the same group of ATC⁴ classification seem to have specific $\log P$ values. Therefore, it may be possible to combine drugs and vectors based on $\log P$ of a specific drug and its indications. Moreover, following the abovementioned trends, the majority of available drugs can be formulated into DDS, if vectors are based on liposomes, micelles, or serum albumin. Figure 2 illustrates the distribution of $\log P$ values of all drugs in DrugBank⁵ and their overlap with these three vector types according to the rules of compatibility.

Transport and Release

A multiscale diffusion model was developed incorporating chemical properties of material and geometry of microstructure, which is especially useful in predicting mass release from drug vectors. By coupling this diffusion model with flow, a computational framework was introduced to predict mass distribution in a flow similar to the one found in capillaries. Figure 3A and B illustrates the coupling of vector flow and drug diffusion in a $10 \times 50 \mu\text{m}$ capillary segment, revealing the differences in payload concentration field inside the vessel microenvironment due to the vector position within the capillary. By incorporating the validated specific properties of vessel, flow,

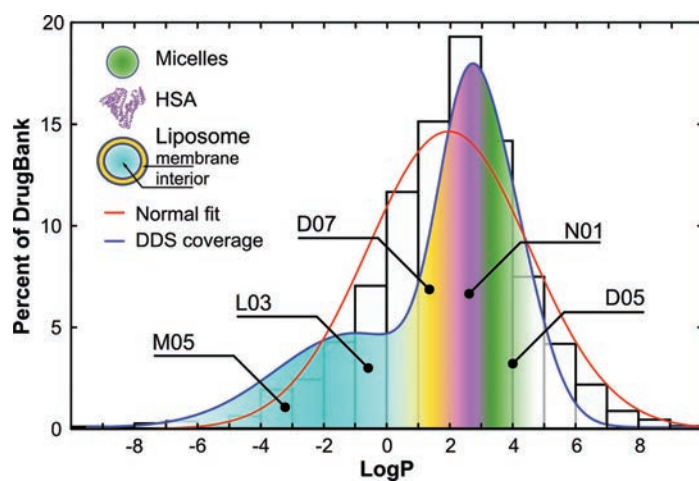


Figure 2. Histogram of $\log P$ values of DrugBank drugs (columns) fitted with normal distribution (red line) and compared with $\log P$ of drugs in DDS in clinics or clinical trials (blue line). Colors mark different vectors based on average $\log P$ of associated drugs. Second-level ATC codes vector (M05, drugs affecting bone structure and mineralization; L03, immunostimulants; D07, corticosteroids; N01, anesthetics; and D05, antipsoriasis) indicates groups of drugs characterized by specific average $\log P$ that might suggest compatibility to a specific vector type.

vector, and drug, it is possible to predict drug distribution among different compartments of the entire environment, as illustrated in Figure 3D.

Pharmacokinetics

DDS have a potential to prolong the half-life of the drug ($t_{1/2}$) to time scales that are rarely or almost never observed for free drugs. However, such augmentation seems to be only efficient with hydrophilic substances. Hydrophobic drugs have their half-lives extended up to three times at best, or sometimes even reduced. The main reason behind such discrepancy may be the competitive drug binding to natural vectors, such as serum albumin and lipoproteins. Such structures allow otherwise poorly soluble hydrophobic drugs to redistribute between the vector and

blood plasma, thus destroying the drug-vector association. These results draw a connection between the physical chemistry of drugs and their pharmacokinetics. Multiple regression analysis for the data of currently approved DDS identified such a relationship (Figure 4), relating the area under the curve, the maximal drug concentration in plasma (C_{\max}), $t_{1/2}$, and $\log P$.

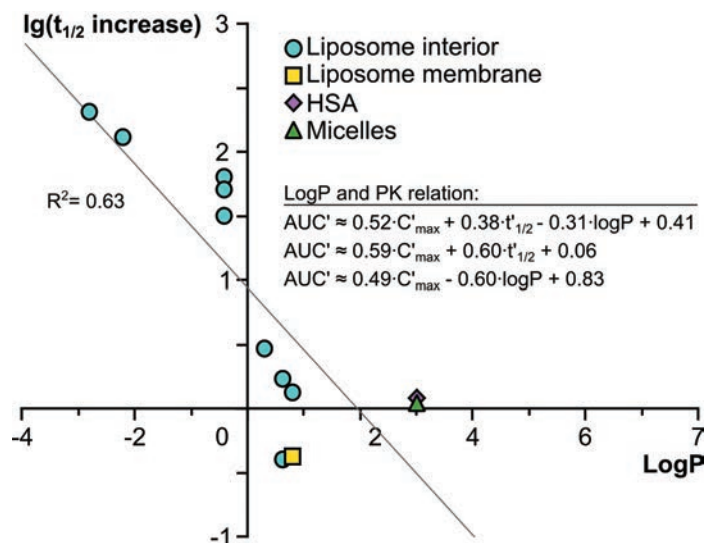


Figure 4. The correlation between $\log P$ of drugs and the increase in $t_{1/2}$ by use of drug vector. The hydrophilic drugs had their $t_{1/2}$ increased by DDS. Multivariate analysis of pharmacokinetic parameters together with $\log P$ reveals patterns of interplay between physicochemistry and pharmacokinetics of drugs.

Summary

The overviewed analysis suggests that rational steps can be taken to help in designing DDS with optimal properties. Through the steps of drug loading, transport, and release, the aspects of physics and chemistry are present in associated processes. The latter allows us to study and optimize DDS in way that is less empirical and that brings intrinsic properties of drugs and vectors together.

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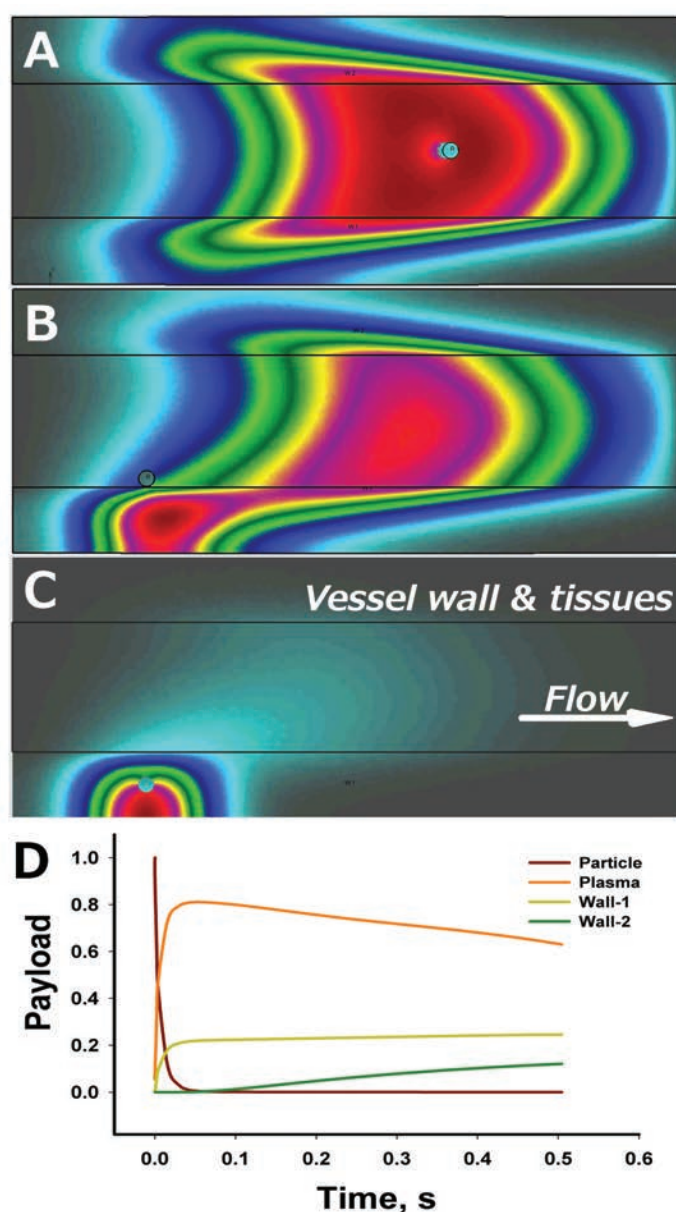


Figure 3. The computational transport model of payload release from vector in capillary flow by diffusion: when particle is in a flow (A), adsorbed to vessel wall (B), and internalized (C). Normalized payload release among different compartments in the adsorbed case (D).

Transfollicular Delivery of Antigen Using Nanocarriers for Noninvasive Transcutaneous Immunization

Ankit Mittal,¹ Anne S. Raber,¹ Ulrich F. Schaefer,¹ Sebastian Weissmann,² Thomas Ebensen,²
Kai Schulze,² Carlos A. Guzmán,² Steffi Hansen,^{1,3} and Claus-Michael Lehr^{1,3,4}

Introduction

Vaccination via the skin seems to be an optimal strategy for treating infectious and noninfectious diseases such as cancer because of the unique immunological characteristics of the skin. In particular, transcutaneous vaccination (TCV) refers to the needle-free application of vaccines across the skin.¹ However, many of the current strategies for TCV (e.g., micro-needles, gene gun, PowderJect, and skin abrasion), reduce the protective stratum corneum (SC) barrier for a significant time to facilitate the absorption of the vaccine, making them suboptimal for certain applications, such as mass vaccination campaigns in countries having critical hygienic conditions. In contrast, transfollicular vaccination aims to reach the perifollicular antigen presenting cells (APC) without impairing the SC barrier.

Previously, transfollicular delivery had been widely investigated not only for DNA vaccines and antigenic proteins but also for nanoparticle (NP) based formulations.^{2,3} Particle-based delivery systems such as NPs and microparticles are appropriate vehicles for transfollicular delivery, because they accumulate in hair follicles and skin folds as well as penetrate deeper into hair follicles than aqueous solutions of antigen.⁴ However, this route is usually studied after pretreating the skin via various methods such as waxing (hot or cold), plucking the hairs, and stripping (tape or cyanoacrylate [superglue] stripping). Because of pretreatments, upper layers of SC are partially removed, making it unclear to what extent the antigen penetrates via the hair follicles or across the permeabilized SC. In this context, we recently studied the potential of transfollicular delivery of ovalbumin (OVA) using polymeric NPs without compromising the SC barrier by any pretreatment for the purpose of noninvasive TCV.⁵

Experimental Methods

NPs were prepared by a double emulsion method using poly(lactide-co-glycolide) (PLGA) or chitosan and polyvinyl alcohol as stabilizer. The NPs were characterized physicochemically in terms of size, surface charge, OVA encapsulation/loading, and morphology. The integrity and

biological activity of the nano-encapsulated OVA were monitored by SDS-PAGE, *in vitro* proliferation of OVA-specific lymphocytes, and ELISA. The microscopical evaluation and follicular delivery efficiency of NPs were measured in intact pig skin based on the differential stripping technique and compared with OVA solution. Briefly, incubation sites of 1.767 cm² were marked on the outer auricle of the pig ears, and 15 μ L of different formulations (an aqueous solution of FITC-OVA, an aqueous dispersion of FITC-OVA in PLGA NPs, or FITC-OVA in Chit-PLGA NPs) was applied and massaged manually with a gloved forefinger for 3 min. The ears were incubated for 1 h at 32°C under nonocclusive conditions.

An adoptive transfer experiment was performed to verify the usefulness of the noninvasive transfollicular immunization route *in vivo*. In brief, two days before immunization, the flanks of C57BL/6 mice were shaved, and one day prior to immunization CFSE-labeled naïve nonactivated OVA-specific CD4⁺ T cells were injected into the tail vein of the shaved mice. Mice ($n = 4$ per group) were immunized as follows: 1) negative control: received Chit-PLGA plus 2 μ g of c-di-AMP as adjuvant dispersed in physiological buffer via intramuscular injection; 2) positive control: received 200 μ g/50 μ L of LPS-free OVA dissolved in physiological buffer via intramuscular injection; and 3) test group: received 200 μ g/60 μ L of LPS-free OVA in Chit-PLGA NPs plus 2 μ g of c-di-AMP as adjuvant via transfollicular application. Proliferation of adoptively transferred OVA-specific CD4⁺ T cells was measured by CFSE dilution in the draining lymph nodes and secondary lymphatic organs.

Results and Discussion

The characteristics of the NPs are summarized in Table 1. The mean size of OVA-loaded PLGA and chitosan-PLGA (Chit-PLGA) NPs was \approx 170–180 nm with a monodisperse size distribution (polydispersity index < 0.2) with negative surface charge for PLGA NPs and positive surface charge for Chit-PLGA NPs. OVA was protected from cleavage or aggregation inside the NPs and retained its biological activity to 74% (PLGA) and 64% (Chit-PLGA) (Table 1).

Figure 1 shows the distribution of fluorescently labeled NPs in the hair follicle after application to excised pig ears. The NPs accumulated in the follicle openings, covering the hair as well as invading into the follicular duct. We next investigated the delivery efficacy of nanoencapsulated OVA using an *in vitro* pig ear model based on differential stripping, as pig skin is an appropriate substitute for human skin.⁶ OVA-loaded NPs significantly enhanced follicular uptake of OVA by a factor of 2–3 compared with OVA solution (data not shown).

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Table 1. Physicochemical characterization of the optimized PLGA and Chit-PLGA NPs.^a

Nanoparticle	Size (nm)	Polydispersity Index	Zeta Potential (mV)	%EE	%L	%A
OVA-loaded PLGA	168.5 ± 1.45	0.063 ± 0.01	-24.8 ± 0.89	27.61 ± 1.03	5.43 ± 0.2	74 ± 5
OVA-loaded Chit-PLGA	183.6 ± 2.71	0.171 ± 0.01	20.2 ± 1.05	36.54 ± 1.08	6.65 ± 0.2	64 ± 4

^a Values represent mean ± standard error of the mean of $n = 6$ independently prepared batches. %EE, encapsulation efficiency (wt OVA encapsulated/wt OVA added initially); %L, loading (wt OVA encapsulated/wt polymer); and %A, activity of OVA released from NPs analyzed using ELISA.

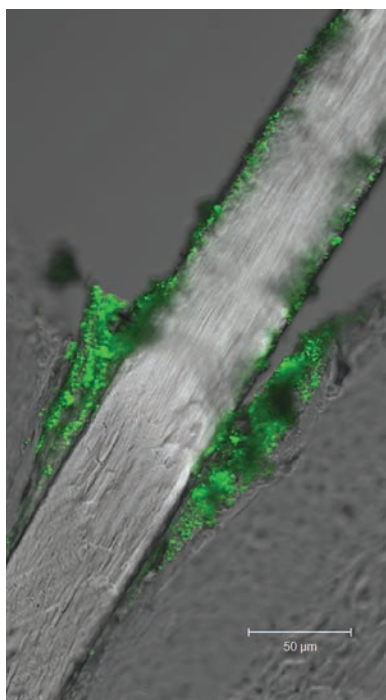


Figure 1. Microscopic evaluation of NP distribution in hair follicles after application to excised pig ear skin (adapted from Mittal *et al.*).⁵

Furthermore, using FITC-labeled PLGA, it was found that the follicular uptake efficiency of NPs could further be increased by increasing the NP dose/area. Thus, the uptake could further be enhanced by a factor of ≈ 2 – 2.4 by increasing the number of NPs applied per skin area in the formulation. However, no significant differences were observed in the follicular uptake of PLGA and Chit-PLGA NPs, which is in line with the study by Patzelt *et al.*, suggesting that the invasion depth into the follicles depends foremost on NP size and less on particle surface properties.⁷

We next evaluated the capacity of APCs, such as bone-marrow-derived

murine dendritic cells (DCs) loaded with OVA-antigen by incubation with OVA-loaded NPs, to stimulate proliferation of OVA-specific CD8⁺ and CD4⁺ T cells. DCs incubated with OVA-loaded NPs (PLGA NPs, 95.1%; Chit-PLGA NPs, 95.6%) were able to stimulate a stronger proliferation of OVA-specific CD4⁺ T cells compared with OVA protein LPS-free solution (68%). However, only OVA-loaded Chit-PLGA NPs (67.5%) were able to stimulate enhanced proliferation of OVA-specific CD8⁺ compared with OVA solution (21%).

The adoptive transfer model has been described as a useful tool to characterize T cell activation *in vivo*.⁸ No proliferation was observed in the negative group, that is, animals receiving blank Chit-PLGA NPs plus c-di AMP via intramuscular injection, whereas full proliferation of the transferred cells was observed in animals receiving OVA solution via intramuscular injection and also in animals immunized by applying transfollicularly OVA in Chit-PLGA NPs and c-di-AMP as an adjuvant (data not shown). The adoptive transfer experiment demonstrated that the model antigen OVA can be delivered via the transfollicular route without pretreating the skin by application of OVA-loaded Chit-PLGA NPs coadministered with c-di-AMP as adjuvant and generated comparable proliferation of OVA-specific CD4⁺ T

cells with respect to controls receiving an intramuscular injection of OVA.

Future immunization studies with disease-relevant antigens are needed to show whether a potent immune response can be elicited by transfollicular vaccination without the use of barrier-disrupting methods.

Conclusion

This study highlights the potential to deliver the model antigen (OVA) using polymeric NPs via hair follicles without pretreating the skin, thereby creating a new perspective for the purpose of noninvasive TCv.

Acknowledgements

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Preclinical Species Modelling and Simulation, and Simcyp CRADA with FDA Center for Veterinary Medicine

Devendra Pade,¹ Masoud Jamei,¹ and Amin Rostami-Hodjegan^{1,2}

There has always been a debate on whether preclinical findings from one species can be translated to other animals or to humans, and this has engaged various scientists across industry, academia, and regulatory bodies.¹ *In vitro*–*in vivo* extrapolation (IVIVE) linked with physiologically based pharmacokinetic (PBPK) modelling is an integrative paradigm that facilitates incorporation of a wide range of drug and species data. Simcyp Limited (a Certara company) provides PBPK modelling and simulation platforms based on human and various animal species. The following sections describe in brief the animal PBPK platforms provided by Simcyp and their applications to the pharmaceutical industry for human drug development. The final section describes the ongoing Collaborative Research and Development Agreement (CRADA) signed between the U.S. FDA and Simcyp Limited to develop PBPK models for various canine breeds to facilitate the veterinary drug approval process.

Simcyp Rat: From the various rat strains available, the male Sprague Dawley rat with an ideal weight of 250 g is one of the most widely used rodent models in preclinical drug development. The Simcyp Rat model enables prediction of pharmacokinetic profiles and distribution of drugs into various tissue organs based on drug physicochemical properties and data obtained from *in vitro* experiments. Berry *et al.* predicted the volume of distribution at steady state (V_{ss}) using empirical and mechanistic (Simcyp Rat) methods for a wide range of drugs.² They reported that using *in vitro* tissue binding data can significantly complement the existing V_{ss} prediction models in a preclinical setting.

Simcyp Mouse: Since there are numerous strains and models of laboratory mice available for different research purposes, the Simcyp Mouse model is designed as an *in silico* generic-strain 25 g mouse. The *in silico* platform enables the user to create a virtual genetically modified mouse with the ability to knock in, knock out, and knock down several drug-interacting enzymes and transporters. The model also enables the mechanistic prediction of effective intestinal permeability ($\text{MechP}_{\text{eff}}$) in the different regions of the mouse intestine based on physicochemical parameters such as octanol water partition

coefficient ($\log P$), pKa, compound type, and molecular weight of the drug as input. The model for permeability prediction takes into account drug properties and their interaction with in-depth anatomy and physiology parameters that are included in the model database. Work done by Pade *et al.* to be presented as a poster at the annual meeting of the American Association of Pharmaceutical Scientists (AAPS) in November 2013 looks into the ability of the model to predict intestinal permeability by comparing predicted values with those obtained from experimental data (Figure 1).³ More information on the work can be obtained by contacting the author (d.pade@simcyp.com).

Simcyp Dog: Simcyp Dog is a PBPK model based on a 10 kg beagle dog. Since the beagle dog is considered an ideal biopharmaceutical model for development of orally administered dosage forms, Simcyp Dog enables the user to study differences in formulations and those arising due to effect of food on drug exposure. The development of the Simcyp Dog model was undertaken with a view toward enhancing development of orally administered drugs intended for human use. Several studies reported predictions using Simcyp Dog for drugs such as theophylline and celecoxib, in collaboration with the FDA Center for Veterinary Medicine (CVM), that describe the ability of the model to predict formulation differences for different classes of drugs.^{4,5,6}

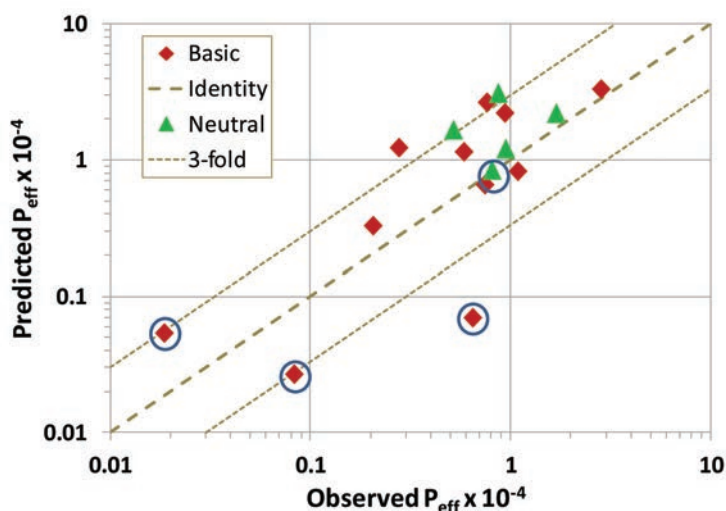


Figure 1. Predicted vs. observed mouse intestinal permeability (ileal P_{eff} values are circled).

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Simcyp CRADA with FDA CVM: Due to the dearth of modelling and simulation practices in the veterinary arena and the successful application of the Simcyp Dog model, it was considered worthwhile to expand the existing beagle dog model to various other dog breeds such that the model can account for differences in various breeds with respect to anatomy, physiology, and pharmacogenetics. As a result, Simcyp Limited and the CVM at the U.S. FDA entered into a CRADA to further develop the Simcyp Dog model for the evaluation of drug products intended for use in different canine breeds. In addition to their importance as a companion animal species, dogs are frequently used as a toxicological species when evaluating the human safety of drug residues in food-producing animals. In both situations, the Simcyp canine PBPK models can be invaluable for assessing the potential impact of polymorphic variations on the interspecies extrapolation of the resulting study data. A recent study done by CVM scientists on the use of PBPK models to predict food effects in dogs for drugs such as mavacoxib and celecoxib has been accepted for a poster presentation at the AAPS annual meeting, which takes place in November 2013 in San Antonio, Texas, U.S.A. More details of the work can be obtained by contacting the author (marilyn.martinez@fda.hhs.gov).⁷

Furthermore, due to shared disease pathologies, some of which tend to be breed specific, there are numerous examples of drugs undergoing parallel development for the treatment of diseases common to dogs and humans. Oftentimes (e.g., certain types of cancers), the occurrence of these conditions tends to be largely constrained to specific canine breeds. In these situations, breed-specific PBPK models will be an invaluable resource to support product development, both when generating predictions for the dog and when attempting to extrapolate the canine data to the human patient.

Regardless of its application, the goal of any PBPK tool is to provide a mechanism for exploring “what if” scenarios and, in so doing, to better target the critical questions that need to be addressed.

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Welcome New CRS Members

Swetha Ainampudi	Naomi Nagai
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DDTR Special Issue "Nanomedicine: Prospects and Challenges"

Vinod Labhasetwar, Editor-in-Chief

This special issue came out of the Indo–U.S. joint symposium “Nanomedicine: Prospects and Challenges” that was organized by Drs. Padma Davarajan and Vinod Labhasetwar and held November 14–15, 2011, at the Institute of Chemical Technology, India. The symposium was sponsored by the Indo–US Science and Technology Forum (IUSSTF). This special issue is a compilation of research papers relating to various aspects of nanomedicine. The issue is a blend of reviews and research manuscripts covering diverse aspects of nanomedicine. Nanomedicine, the exploration of medical applications of nanotechnology, is evolving from laboratory research to clinical application, particularly in the areas of drug delivery, imaging, diagnostics, and monitoring. Nanotechnology and nanoparticles are expected to dramatically change the way disease is detected and treated. Over the past few decades, collaborative and multidisciplinary research has matured the field of nanomedicine. Polymer and material scientists, physicists and engineers, biologists and clinicians, and pharmaceutical scientists have all contributed to the progression of nanomedicine. The rapid progress in the field is evident from the wide range of different nanotechnologies that have been designed and investigated and that are now at different stages of preclinical and clinical development. As these applications of nanotechnology are being explored, the critical issue of their safety to the patient is also being debated and investigated. The issue addresses design and *in vivo* evaluation of nanocarriers for administration by oral, nasal, and parenteral routes, *in vitro* evaluation with a special focus on dissolution techniques, and nanomedicine for gene delivery and specific infections such as HIV, including multifunctional nanomedicines for varied applications. Toxicity aspects are also covered in the issue.

About the Guest Editors



Dr. Padma V. Devarajan is a professor of pharmacy and head, Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology, Mumbai, India. Her research interests include colloidal carriers for targeted delivery in cancer and infectious diseases, bioenhancement strategies, and mucosal drug delivery systems as an alternative to parenteral administration. She has over 100 presentations and publications at national or international conferences and in cited journals, along with five book chapters in the area of drug delivery. She is currently the editor for a book, *Targeted Drug Delivery: Concepts*

and Design, to be published by Springer as part of the CRS *Advances in Delivery Science and Technology* book series. She has a number of granted and licensed patents (national and international). Within CRS, she has been a board member, member of the Board of Scientific Advisors, chair of the Young Scientist Mentorship/Protégé Subcommittee, and patron member of the CRS India Local Chapter. Prof. Devarajan has been awarded the American Association of Indian Pharmaceutical Scientists (AAiPS) Distinguished Educator and Researcher Award (2011) and the Vasvik Award for Industrial Research for Women Scientists (2011). She is a nominated fellow of the Maharashtra Academy of Sciences, India.



Prof. Vandana Patravale is currently a professor of pharmaceutics at the Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology, India. She has over 80 refereed publications, six book chapters, three granted patents, 19 patents in the pipeline, and two trademark registries to her credit. She recently published a book titled *Nanoparticulate Drug Delivery: Perspectives on the Transition from*

Laboratory to Market (Woodhead Publishing). Her areas of expertise include novel nanocarriers, namely, colloidal drug delivery systems including microemulsions and solid lipid/polymeric nanoparticles for solubilization, increase in bioavailability, and targeting; medical device development, namely, coronary stents, intrauterine devices, and so on; nanodiagnostics; tissue engineering; new polymer and lipid conjugates synthesis; use of indigenous excipients; cosmeceuticals; and modified release dosage forms for all routes of administration.

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Join the leading scientists who are publishing their work in DDTR and compete for the 2013 DDTR Outstanding Research Paper Award. The award will be selected from research articles published in DDTR during 2013. It will be given during the 2014 CRS Annual Meeting, to be held July 13–16, 2014, in Chicago, U.S.A. Visit the CRS website for the award criteria. ■

Consumer and Diversified Products Division Update

Nicole Papen-Botterhuis, TNO, The Netherlands

The Consumer and Diversified Products (C&DP) Division of CRS is alive and kicking! If you are a researcher in the field of controlled release for food, personal care, consumer products, cosmetics, coatings, agriculture, textiles, flavors, fragrances, and so on, this is definitely the place to be! At the CRS Annual Meeting in Hawaii there were two wonderful activities where I felt a very good vibe between the members of the C&DP Division and a lot of enthusiastic new members.

First, there was the annual luncheon on Tuesday, July 23, which was cosponsored by Coating Place, Inc., Fleet Laboratories, and Ronald T. Dodge Company. This event is held at each CRS Annual Meeting to provide opportunities for those involved in nonpharmaceutical controlled release application areas to exchange ideas and maintain or establish new relationships. To obtain as many interactions between the participants as possible, we organized a buffet lunch with a table change halfway through the luncheon. After a short explanation of the goals of the C&DP Division by the chair of the division (me), a picture was taken with all the participants. After an hour and a half, the attendees left with new or renewed connections with fellow colleagues in C&DP interest areas, food in their stomachs, and perhaps new controlled release ideas and opportunities.



Group picture taken at the C&DP Division luncheon.

Second, at our business meeting held on Tuesday afternoon, many new members from different C&DP research areas volunteered to be part of the C&DP Committee. The officers of the C&DP Division is currently composed of Nicole Papen-Botterhuis of TNO as chair, Chris McDaniel of Fleet Laboratories as deputy chair, and Jei McKinney of Encapsys as secretary.

The division has historically been involved in organizing C&DP technical sessions and symposia at the CRS Annual Meeting and knowledge dissemination activities such as workshops on controlled release technologies or product characterization at the annual meetings of other organizations or societies.

Becoming an active member of the division's committee means that you participate in our teleconferences on the first Thursday of each month as much as you can and that you can provide input on the C&DP programming of the CRS meetings. If interested in sharing ideas with the C&DP Division or becoming part of the division (receiving updates on the activities of the division and progress in the field) or committee (being involved actively in the division), contact me (nicole.papen@tno.nl) or Megan Pagel (mpagel@scisoc.org) at the CRS office, who can connect you to the group. ■



C&DP Division officers (left to right): Jei McKinney, Nicole Papen-Botterhuis, and Christopher McDaniel. The signed bat is a tradition that began at the CRS Annual Meeting in Copenhagen and symbolizes the passing of the C&DP Division Chair to a new individual. Each C&DP Chair signs it.

In the News

Compiled by Steven Giannos, Independent Consultant

August

Exosome Research Set to Clean up with New Technology

PRNewswire: August 22, 2013 – CAMBRIDGE, U.K. – Once thought to be just part of the cells' waste disposal system, it is now clear that exosomes also act as microscopic delivery bags, protecting RNA and protein contents that can then be transported in the blood, influencing the activity of distant cells.

Exosomes may be useful in cancer diagnostics and for drug delivery, transporting therapeutic RNA and DNA, manufactured in cells *in vitro*, to specific diseased cells. In some cases, exosomes mediate the benefits of stem cell therapy.

One of the major technical hurdles facing the exosome field is the efficient purification of intact exosomes. The gold standard for their purification is currently ultra-centrifugation, which is time-consuming and inefficient. Commercially available exosome precipitants, used in a small number of labs, yield exosome preparations of relatively low purity, in which the precipitant remains as a contaminant.

Exo-spin™ kits for exosome purification, launched today by Cell Guidance Systems, overcome all of these shortcomings. Exo-spin™ is based on technology licensed from A*STAR in Singapore. Exo-spin™ kits are suitable for the preparation of pure, functional exosomes from a variety of biological fluids including blood plasma/sera, cell culture media, urine, and saliva.

Dr. Michael Jones, CEO of Cell Guidance Systems, commented, "Talking to exosome researchers, it is clear that the current options for exosome purification have significant shortcomings. Exo-spin™ is a breakthrough in reliable purification of exosomes that will enable the entire field to move forward more rapidly." Exo-spin™ provides a gentle purification process in which no organic phases are used, no ultracentrifugation is employed, and the exosomes are purified free of precipitants in as little as one hour.

Cell Guidance Systems provides reagents and tools for stem cell science and related fields. From its Cambridge, U.K., headquarters, the company manufactures and supplies growth factors, small molecules, and the Pluripro® culture system for the confluent growth of human pluripotent cells. The company also recently introduced the SINEUP™ gene expression technology for knock-up of endogenous genes and offers a quality karyotyping services.

Transdermal Delivery Solutions Subsidiary, Hormone Replacement Technologies, Receives FDA Approval to Begin Pivotal Clinical Trials of Testagen® TDS for the Treatment of Low Testosterone

Business Wire: August 22, 2013 – PALM BEACH GARDENS, FL, U.S.A. – Transdermal Delivery Solutions Corporation (TDSC) announced today that the U.S. Food and Drug Administration (FDA) has approved the Investigational New Drug (IND) application submitted by its subsidiary, Hormone Replacement Technologies. Under the IND, Hormone Replacement Technologies will conduct several clinical trials of Testagen® TDS for the treatment of low testosterone in men, including phase I and phase II dosing studies, phase II study investigating transference, and a phase III comparative analysis.

Specifics of each study include:

1. Dose range study—a one-week dose-finding study to determine the optimal dose that is high enough to demonstrate efficacy in the target population.
2. Transference study—aimed at measuring the potential of Testagen® TDS to be inadvertently transferred to family members, which is a major concern for topical testosterone products currently on the market. This study is designed to validate TDSC's claims that Testagen® TDS, which dries on the skin in 5–10 minutes after application, cannot be readily transferred to others.
3. Comparative study—expected to begin in the fourth quarter, the most pivotal of the three studies, involves a 90-day evaluation of patients using Testagen® TDS to measure the response compared to patients using gel testosterone preparations. Upon completion, one-third of the 150 patients in this study will be randomly selected to continue using Testagen® TDS for a full six-month evaluation period.

"There are nearly 14 million men in the United States suffering from low testosterone, which can lead to more serious illnesses, yet only 1.3 million (9%) are currently being treated," said Chandan A. S. Alam, M.D., executive vice president and chief science officer for TDSC. "There are currently product safety issues with all existing forms of transdermal testosterone hormone replacement, including site-of-application reaction to patches and roll-on gels, as well as dangers associated with inadvertent dosing to third parties by contact with gel preparations remaining on the skin. To this end, there is a great need for new and novel treatment options," added Dr. Alam.

The studies will be conducted by experts in the field of hormone replacement and transdermal delivery of drugs at St. Bartholomew's Royal London School of Medicine (Barts and the London NHS). Recruiting for the first study is already underway.

Testagen® TDS has been under evaluation for over ten years and is designed to address these problems of transdermal hormone replacement therapies. The patented treatment formulation is expected to revolutionize topical testosterone application, as the system provides faster absorption and lowers transferable concentrations left on the skin.

to-BBB Receives IND Approval for Novel Brain Cancer Drug, 2B3-101

Business Wire: August 19, 2013 – LEIDEN, The Netherlands – to-BBB, the brain drug delivery company, is pleased to announce the successful completion of its 2B3-101 phase I clinical trial in brain cancer patients, safely reaching clinically effective dosages. to-BBB is now ready to proceed to the phase IIa part of this trial, treating patients with brain metastases from breast cancer, small-cell lung cancer, and melanomas, as well as patients with primary, malignant brain cancers (recurrent gliomas). With no commercially available treatments for brain metastases of solid tumors and no effective treatment alternatives in recurrent gliomas, 2B3-101 is targeting a high unmet medical need.

to-BBB is applying its proprietary G-Technology® to enhance the delivery of the anticancer drug doxorubicin to the brain as its internal lead product 2B3-101. This study with 2B3-101 is being performed in close collaboration with eight specialized clinics in the Netherlands, Belgium, and France. to-BBB is currently planning to open an additional study site in the United States, specialized in the treatment of patients with brain metastases. to-BBB submitted an IND application (investigational new drug) to the FDA in July and is now delighted to announce the approval of the IND from the FDA. The IND approval opens up opportunities to involve U.S. medical centers in the development of 2B3-101.

“We are very enthusiastic about the positive results of our phase I study so far, including a safety profile that is in line with our expectations and encouraging signs of antitumor activity,” says Fredrik Lonnqvist, CMO of to-BBB. “Consequently, we are very pleased that we are now ready to proceed to phase IIa with the inclusion of U.S. investigators in our clinical development program. We are excited about 2B3-101 in the potential treatment of brain metastases as well as primary brain cancers.”

“Breast cancer brain metastases present a challenge to both patients and clinicians, as there are few systemic therapies capable of crossing the blood-brain barrier to control the disease,” says Dr. Carey Anders, codirector of the Multidisciplinary Brain Metastases Specialty Clinic at the University of North Carolina Lineberger Comprehensive Cancer Center. “I have had very positive experiences using liposomal doxorubicin in patients with advanced breast cancer; however, efficacy in brain metastases can be limited due to less than optimal blood-brain barrier penetration. to-BBB provides a novel, promising technology that offers the potential to improve the current treatment paradigm for patients with intracranial breast cancer recurrences. Thus, I am pleased that the recent IND application has been approved by the FDA.”

The brain cancer indications targeted by 2B3-101 in the ongoing clinical trial affect at least 60,000 subjects in the United States and as many patients in Europe. In June 2013, the FDA together with the NBTS (National Brain Tumor Society) announced a “clinical trials endpoint initiative” to increase the volume and speed of approval for new treatments for this disease.

InSite Vision Announces Patent Issuance on DuraSite® 2 Ophthalmic Drug Delivery System

Business Wire: August 15, 2013 – ALAMEDA, CA, U.S.A. – InSite Vision Incorporated (OTCBB: INSV) today announced that the U.S. Patent and Trademark Office (USPTO) has issued U.S. patent no. 8,501,800 on the company’s DuraSite® 2 next-generation enhanced drug delivery system. DuraSite 2 provides a broad platform for developing topically delivered ocular drugs with enhanced tissue penetration in order to improve efficacy and dosing convenience. This patent will provide utility/composition of matter protection to 2029 for both the delivery system and the drugs that are formulated with DuraSite 2.

“DuraSite 2 has the potential to significantly increase efficacy and reduce dosing requirements for topically delivered ophthalmic drugs. Based on its ability to significantly improve drug retention and penetration into the tissues of the eye, we believe DuraSite 2 could serve as a standard drug delivery technology across ophthalmic therapeutics,” said Timothy Ruane, chief executive officer of InSite Vision. “We plan to utilize the DuraSite 2 platform in the development of all future InSite Vision pipeline products and seek partners via licensing agreements.”

In a large-scale, preclinical comparative study, a drug formulated with DuraSite 2 demonstrated significantly enhanced retention on the eye and tissue penetration as compared to the same product alone or formulated with InSite Vision’s DuraSite® technology. Results of that study showed that the DuraSite 2 formulation achieved more than 2× and 4× concentrations in the aqueous humor of the eye as compared to the DuraSite formulation or marketed drug, respectively. The robust results of this study suggests that DuraSite 2’s increased tissue penetration may enable it to be used in the treatment of back-of-the-eye diseases with a topical eye drop when formulated with drugs that must currently be administered by injection. InSite presented detailed data from this study at the Association for Research in Vision and Ophthalmology (ARVO) 2013 Annual Meeting. The ARVO poster presentation is available in the publications section of InSite Vision’s website at www.insitevision.com/publications. A more detailed scientific paper entitled “Aqueous Humor Penetration of Ketorolac Formulated in DuraSite or DuraSite 2” was accepted for publication in the *Journal of Ocular Pharmacology and Therapeutics* on July 30, 2013.

While eye drops are a proven delivery mechanism for numerous ocular drugs, the efficacy of these agents is impeded by tears and blinking, which rinse the drug from the surface of the eye and

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limit retention and absorption. InSite Vision's DuraSite and DuraSite 2 platforms are sustained delivery technologies using a synthetic polymer-based formulation designed to extend the residence time of a drug relative to conventional topical therapies. DuraSite and DuraSite 2 enable topical delivery of a solution, gel, or suspension and can be customized for delivering a wide variety of potential drug candidates. The DuraSite platform is currently leveraged in two commercial products for the treatment of bacterial eye infections, AzaSite® and Besivance®. InSite Vision is advancing a portfolio of novel preclinical- to clinical-stage ophthalmic products based on the DuraSite platform and anticipates advancing future ophthalmic product candidates using the DuraSite 2 platform.

NovaDel Announces Completion of the Sale of Substantially All Assets to Suda Ltd.

Business Wire: August 13, 2013 – BRIDGEWATER, NJ, U.S.A. – NovaDel Pharma Inc. ("NovaDel" or "the company") (OTC Pink: NVDL) announced today the completion of the sale of substantially all of the company's assets to Suda Ltd. (the "Suda transaction").

As previously disclosed, the Suda transaction includes the sale of NovaDel's patents and trademarks relating to its NovaMist technology. The Suda transaction, as contemplated, does not include the NitroMist® or ZolpiMist™ intellectual property or licenses. NovaDel received \$400,000 in cash, 50,000,000 shares of Suda common stock, and 10,000,000 options for the purchase of Suda common shares at a purchase price of \$0.05 per share. It is the company's intention to use part of the proceeds from the Suda transaction, after transaction expenses, to reduce its outstanding liabilities.

NovaDel Pharma Inc. is a specialty pharmaceutical company that develops oral spray formulations of marketed pharmaceutical products. The company's patented oral spray drug delivery technology seeks to improve the efficacy, safety, patient compliance, and patient convenience for a broad range of prescription pharmaceuticals. NovaDel has two marketed products that have been approved by the FDA: NitroMist® for the treatment of angina and ZolpiMist™ for the treatment of insomnia. To find out more about NovaDel Pharma Inc. (OTC Pink: NVDL), visit our website at www.novadel.com.

Moberg Pharma Launches Kerasal® NeuroCream at Walmart and Major U.S. Drugstores

Business Wire: August 12, 2013 – STOCKHOLM, Sweden – Moberg Pharma AB (OMX: MOB) today announced its U.S. launch of Kerasal® NeuroCream, an over the counter pain relieving foot cream. This new product will be sold in over 3,800 Walmart stores and in CVS, Walgreens, and Rite Aid drug stores starting in late August.

Approximately 30 million Americans experience frequent foot pain, and many simultaneously suffer from cold feet and dry skin. Painful, cold, dry feet may be associated with various

conditions, including diabetes, fibromyalgia, shingles, arthritis, joint pain, muscle strain, or trauma. Kerasal® NeuroCream is a triple action formula that relieves stabbing, burning, tingling foot pain, warms cold feet, and soothes and moisturizes dry skin. Kerasal® NeuroCream is easily applied with a "no mess" foam applicator.

The active ingredients of Kerasal® NeuroCream, capsaicin and camphor, have a well-established use as topical pain relievers, are naturally occurring, and are derived from plants. Moberg Pharma has utilized its Fusome® skin delivery system, currently used in Moberg's JointFlex® pain relieving cream, to formulate Kerasal® NeuroCream, enabling a rapid delivery of effective pain relievers to the pain source.

"Kerasal® NeuroCream is an innovative addition to our product portfolio. It leverages one of our existing drug delivery technologies along with proven active ingredients, to provide a solution that meets an unmet consumer need. Kerasal® NeuroCream further strengthens the Kerasal® brand, our leadership in the topical OTC foot care space in the United States, and our value to retail partners," said Peter Wolpert, CEO of Moberg Pharma AB.

Moberg Pharma AB (publ) is a rapidly growing Swedish pharmaceutical company with direct sales through its own sales organization in the United States and sales through distributors in more than 40 countries. The company's product portfolio includes topical products for the treatment of skin disorders and pain under the brands Kerasal®, JointFlex®, Kerasal Nail®, and Kaprolac®. Kerasal Nail® (Nalox™/Naloc™ in many markets) is the leading product for the treatment of nail disorders in the Nordic market. The portfolio is developed further through acquisitions and in-licensing of products as well as product development with a focus on innovative drug delivery based on proven compounds. Moberg Pharma has offices in Stockholm and New Jersey, and the company's share (OMX: MOB) is listed on the Small Cap list of the NASDAQ OMX Nordic Exchange Stockholm. For further information, please visit www.mobergpharma.se.

A.P. Pharma, Inc., Announces Planned Name Change to "Heron Therapeutics, Inc." and Application to List on NASDAQ Capital Market

Business Wire: August 8, 2013 – REDWOOD CITY, CA, U.S.A. – A.P. Pharma, Inc. (OTCBB: APPA.OB), a specialty pharmaceutical company, announced today that it has filed an application to list the company's common stock on the NASDAQ Capital Market. In addition, the company's board of directors has, subject to stockholder approval, approved proposals to rename the company "Heron Therapeutics, Inc." and to implement a reverse split of its common stock. The reverse stock split will be implemented in support of the company's NASDAQ listing application at a specific ratio within the range of 1:10 to 1:20, as fixed by the board following stockholder approval.

“As a component of our recent corporate restructuring, we feel it is important to rebrand the organization’s identity,” said Barry Quart, Pharm.D., A.P. Pharma’s chief executive officer. “In addition, our planned reverse split will be an important component to further strengthen the organization and allow us to seek relisting on the NASDAQ. Together, we believe these activities will help better position the company in advance of the resubmission of our New Drug Application for APF530, our lead product candidate for the prevention of chemotherapy-induced nausea and vomiting, and its potential commercialization.”

The company will be filing a proxy statement for stockholder consideration of these proposals and expects to hold a stockholder meeting on these proposals in mid-September. If these proposals are approved, the company expects that it will commence trading on the NASDAQ Capital Market in early October, subject to satisfaction of NASDAQ listing standards.

A.P. Pharma is a specialty pharmaceutical company developing products using its proprietary Biochronomer™ polymer-based drug delivery platform. This drug delivery platform is designed to improve the therapeutic profile of injectable pharmaceuticals by converting them from products that must be injected once or twice per day to products that need to be injected only once every one or two weeks. The company’s lead product candidate, APF530, is being developed for the prevention of both acute- and delayed-onset chemotherapy-induced nausea and vomiting. For further information, please visit the company’s web site at www.appharma.com.

MedPharm Granted New Patents for Topical Spray-on-Film Technology, MedSpray®

Business Wire: August 6, 2013 – GUILDFORD, U.K. – MedPharm Ltd. (www.medpharm.co.uk), the topical drug development specialist, today announced it has been granted a series of further patents for its novel MedSpray® topical spray-on-film technology for dermatological, topical, and transdermal drug delivery.

The North American drug delivery market is estimated to be worth in excess of \$66.7 billion and is expected to register a CAGR of 8.9% between 2012 and 2017, and transdermal/buccal systems are expected to make up a significant percentage of this figure. In addition, dermatological therapeutics in the top seven markets (United States, United Kingdom, Germany, France, Italy, Spain, and Japan) are projected to grow to \$19.1 billion by 2018. Emerging markets are likely to increase the rate of market expansion further, and MedSpray® will help licensees take the lead in this expanding market.

MedSpray® is a novel transdermal and topical drug delivery tool that can be used to deliver drugs in extended release form via spray-on-films delivered to the skin or other mucosal (topical) membranes. MedSpray® offers many advantages over traditional drug delivery systems. The technology allows enhanced drug delivery into or across the skin/mucosal membranes by creating a

film, which can be manipulated to suit the specific drug and disease. This results in a lack of first pass metabolism, improved toxicity profiles, and the potential for sustained and targeted drug delivery. To date, MedSpray® has been trialled with over 20 drugs up to and including clinical evaluation.

CEO Dr. Andrew Muddle commented: “We now have patents for MedSpray® in key countries throughout Europe, North America, and the rest of the world including, Brazil, Russia, India, and China. Widening our patent coverage will enable us to bolster the commercial use of the technology. Currently MedPharm has a number of licensees developing products with this technology, and with these new patents, the company can continue to expand licenced products into new markets.”

“Our strategy is to work successfully with partners to develop new products with drugs provided by licensees,” continued Dr. Muddle. “All such MedSpray® agreements are based upon payment of royalties and contract development fees to MedPharm.”

July

Mallinckrodt New Drug Application Granted Priority Review by FDA

Business Wire: July 29, 2013 – HAZELWOOD, MO, U.S.A. – Mallinckrodt (NYSE: MNK) today announced that the U.S. Food and Drug Administration (FDA) has accepted for filing the New Drug Application (NDA) for MNK-795 and granted priority review. MNK-795 is a controlled-release oral formulation of oxycodone and acetaminophen that has been studied for the management of moderate to severe acute pain where the use of an opioid analgesic is appropriate. FDA priority review is a defined NDA review process used for drugs that, if approved, offer significant improvements in the safety or effectiveness of the treatment when compared to standard applications.

If approved, MNK-795 would be a controlled-release oxycodone and acetaminophen combination medication that has immediate and extended release components. The dosage form was designed using Depomed’s advanced Acuform® drug delivery technology with tamper-resistant properties.

“Despite the number of available pain medications, patients continue to experience unresolved pain and lack treatment options that offer fast-acting and long-lasting relief. We are pleased the FDA granted priority review designation,” said Mark Trudeau, president and chief executive officer, Mallinckrodt Pharmaceuticals. “Mallinckrodt has unique capabilities in complex formulations such as MNK-795, and this marks an important milestone for us as our first NDA acceptance as an independent specialty pharmaceutical company.”

Mallinckrodt’s submission is based on data from a comprehensive clinical trial program for MNK-795 that

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included 14 clinical studies with 1,281 patients. The studies evaluated pharmacokinetics, efficacy, safety, and abuse liability.

Lipocine Inc. Announces Reverse Merger and \$38 Million Private Placement to Advance Its Oral Testosterone Product Portfolio

Business Wire: July 26, 2013 – SALT LAKE CITY, UT, U.S.A. – Lipocine, Inc. (OTCBB: MBARD), a specialty pharmaceutical company, announced today that it has entered into securities purchase agreements with gross proceeds of \$38.0 million for the issuance and sale of approximately 6.3 million shares of its common stock at \$6.00 per share to institutional investors. The closing of the private placement is subject to customary closing conditions. Proceeds from the private placement will be used primarily to advance Lipocine's oral testosterone portfolio, LPCN 1021 and LPCN 1111.

On July 24, 2013, Lipocine successfully completed a reverse merger with Marathon Bar Corp. The combined company will focus solely on the business of Lipocine. Lipocine will trade under the symbol "MBARD" on the OTCBB until on or about August 22, 2013, when it will be quoted under the symbol "LPCN" on the OTCBB.

Ladenburg Thalmann & Co. Inc., a subsidiary of Ladenburg Thalmann Financial Services Inc. (NYSEMKT: LTS), is serving as the exclusive placement agent on the private placement.

In connection with the private placement, Lipocine has agreed, subject to certain terms and conditions, to file a registration statement under the Securities Act of 1933, as amended, covering the resale of the shares of common stock, within 30 days after the closing. The shares of common stock to be issued and sold pursuant to the securities purchase agreements have not been registered under the Securities Act of 1933, as amended, or state securities laws and may not be offered or sold in the United States absent registration with the Securities and Exchange Commission or an applicable exemption from the registration requirements.

This press release shall not constitute an offer to sell or the solicitation of an offer to buy these securities, nor shall there be any sale of these securities in any jurisdiction in which such offer, solicitation, or sale would be unlawful prior to the registration or qualification under the securities laws of any such jurisdiction.

Lipocine Inc. is a specialty pharmaceutical company developing innovative products for use in men's and women's health using its proprietary drug delivery technologies. Lipocine's lead product candidate, LPCN 1021, is phase III ready and is targeted to treat symptoms of low testosterone for men in need of testosterone replacement therapy. This product candidate is designed to provide twice-a-day oral dosing. Additional pipeline candidates include LPCN 1111, a next generation longer-acting oral testosterone therapy product and LPCN 1107, potentially the first oral product for the prevention of preterm birth.

Recent Study Reveals Physicians Prefer Topical Delivery for Drug Delivery Technology, Such as a Transdermal Patch

PRNewswire: July 25, 2013 – New York, NY, U.S.A. – Alliqua, Inc. (OTCQB: ALQA), a wound management and drug delivery company, is making strides to take advantage of the \$142 billion drug delivery market by launching a preclinical proof-of-principal study of an experimental hydrogel transdermal patch containing lidocaine. The global drug delivery market is expected to reach \$224.2 billion by the year 2017. Additionally, the global wound dressing market is expected to reach \$6 billion by 2017.

The United States and Europe are the two leading geographic markets for wound dressings, with the United States accounting for more than one-third of the worldwide market. The United States is also expected to hold into its position as the global leader in the wound dressing market, as the country is expected to haul in 34.6 percent of the global wound dressing market revenue share in 2017.

The demand for advanced dressings has increased in recent years due to innovative adoptions of interactive/bioactive and antimicrobial dressings, including hydrogels. Alliqua's hydrogels are manufactured through a carefully monitored process that ensures a high product quality. The characteristics of Alliqua's hydrogels include: painless adhesion to the human body, stability of form and composition, purity, reproducibility (manufacturing high quality product on a consistent basis), compatibility with active ingredients, and high water content. The drug delivery market is showing no signs of saturation, with major patent expiries, generic competition, tightening Food and Drug Administration (FDA) regulations, and emerging drug delivery technologies continuing to drive momentum. Among the 15 drug delivery systems surveyed by Frost & Sullivan, it was revealed that physicians prefer topical delivery, either as a transdermal patch or topical gel/cream, and expressed willingness to switch their current mode of therapy to one available in these forms.

A new end-user survey of more than 220 physicians and 650 patients by Frost & Sullivan, the Drug Delivery Technology: End-User Preferences, Utilization and Perceptions analysis (www.lifesciences.frost.com), finds that regardless of disease area, physicians select drug delivery methods that drive consistent patient compliance and effective outcomes.

James Saperstein, chief executive officer of Alliqua Biomedical, has stated the lidocaine patch development program is just Alliqua's first step towards building a portfolio that leverages the company's hydrogel platform. The lidocaine hydrogel patches will be developed with the intent to treat localized acute pain, including post-operative pain, back pain, and pain associated with sport injuries and arthritis. Alliqua says results from this preclinical proof-of-principle study will be readily available later in the third quarter.

In other recent news, Alliqua announced last week that the results from a post-marketing study on their SilverSeal dressing

displayed proof the dressing was shown to have a lower incidence of incision complications compared to standard petroleum-based dressing.

Alliqua is a biopharmaceutical company focused on the development, manufacturing, and distribution of proprietary transdermal wound care and drug delivery technologies. Alliqua's leading technology platform produces hydrogels, a three-dimensional cross-linked network of water soluble polymers capable of numerous chemical configurations.

Alliqua currently markets its new line of 510(k) FDA-approved hydrogel products for wound care under the SilverSeal® brand. Alliqua's electron beam production process, located at its 16,000 square foot GMP manufacturing facility in Langhorne, Pennsylvania, allows Alliqua to aggressively develop and custom manufacture a wide variety of hydrogels. Alliqua's hydrogels can be customized for various transdermal applications to address market opportunities in the treatment of wounds as well as the delivery of numerous drugs or other agents for pharmaceutical and cosmetic industries. Additionally, Alliqua's drug delivery platform, in combination with certain active pharmaceutical ingredients, can provide pharmaceutical companies with a transdermal technology to enhance patient compliance and potentially extend the patent life of valuable drug franchises. For additional information, please visit www.alliqua.com.

Novaliq GmbH Announces European Market Approval for NovaTears™ OTC

Business Wire: July 23, 2013 – HEIDELBERG, Germany – Novaliq GmbH, a drug delivery company with a focus on the topical application of ophthalmic technologies for poorly soluble drugs, today announced the successful CE mark approval for the first topical eye lubricant based on Novaliq's proprietary technology EyeSol™.

NovaTears™ OTC is a multidose, nonaqueous, nonblurring, and preservative-free topical eye drop for lubrication of the ocular surface.

"We are pleased to receive CE mark approval for our first ophthalmic product designed to improve the quality of life for the dry eye OTC patient," said Bernhard Guenther, CEO of Novaliq GmbH. "It offers a significant new product choice for the European consumer: innovative Novaliq technology that contains no preservatives, yet is available in conventional, multidose bottles. The absence of irritating surfactants and preservatives provides dry eye patients improved tolerability and convenience."

This is the first new product from Novaliq GmbH since the company raised €13.9 million (\$18.1 million) in its 5th round of financing in April 2013, funding the ongoing development of its ophthalmic portfolio which includes CyclASol Rx, the first planned Novaliq prescription product, as well as additional OTC products.

"We congratulate Novaliq on obtaining the CE mark for NovaTears OTC and look forward to future product additions to the SFA portfolio," commented Mathias Hothum, managing director of Dievini Hopp Bio Tech Holding GmbH & Co., the investment company of SAP established with cofounder Dietmar Hopp. "We are pleased to help Novaliq further its pioneering ocular drug delivery technology and strong management team."

Novaliq GmbH is a drug delivery company that is developing a superior generation of ocular formulations for poorly soluble drugs. The patented ocular formulations are based on semifluorinated alkanes (SFAs), which can be easily applied in the form of topical eye drops. A new generation of both prescription and consumer ocular products is possible through the unique and proprietary properties of SFAs as a delivery vehicle.

Novaliq's strategy is to establish a portfolio of consumer and prescription products in the field of ophthalmology. These products are intended to cover unmet needs with one major advantage being they will be preservative free.

Dievini is an active investor in Life and Health Sciences companies, with a focus on innovative therapeutics and diagnostics shown to lead to novel treatment regimens, allowing doctors to treat patients with life-threatening diseases better and safer than they can today.

Moberg Pharma and Menarini Extend Distribution Agreement for Kerasal Nail to China

Business Wire: July 23, 2013 – SINGAPORE – Moberg Pharma AB (OMX: MOB) today announced that Menarini Asia-Pacific, a member of the Menarini Group—a top 40 global pharmaceutical company—has been granted the exclusive rights to market and sell Kerasal Nail™ in China. The companies now intend to seek marketing authorization for the product in the Chinese market.

Kerasal Nail™ (Nalox® or Emtrix® in certain markets) is a nonprescription product for the treatment of discoloured and deformed nails resulting from fungal infection or psoriasis, with a unique mechanism of action that generates visible improvements within 2–4 weeks of treatment. The product became the market leader in the Nordic region immediately after launch in 2011 and has been launched in more than 25 countries, including the United States, where it has a leading position.

The extended distribution agreement builds on an existing collaboration between the two company groups, which resulted in a successful launch of the product in Italy. In Asia-Pacific, Menarini is a leading regional biopharmaceutical company with over 3,500 employees in 13 markets and a strong track record in launching and promoting consumer health brands. The global sales of the Menarini Group exceed 3 billion Euros.

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China, being the world's second largest economy after the United States, represents a significant long-term growth opportunity for Moberg Pharma. The Chinese pharmaceutical market is projected for continued robust growth and is expected to become the second largest pharma market after the United States within five years. According to IMS, 45% of the global growth in self-medication up to 2016 will come from China and South East Asia.

"We are excited by the opportunity to enter the huge and rapidly expanding Chinese market. There are challenges related to China's sheer size, business complexity, regulatory environment, and infrastructure. With its profound understanding of local market conditions, Menarini Asia-Pacific is an ideal partner in this region. The extended agreement enables us to build on our successful commercial track record together with Menarini," said Peter Wolpert, CEO of Moberg Pharma AB.

"We look forward to introducing Kerasal Nail™ to Chinese consumers. The product has potential to contribute strongly to our expansion within the consumer health market, being a compelling nonprescription product offering rapid visual improvement and an effective solution for patients with nail fungus problems," said John A. Graham, CEO at Menarini Asia-Pacific.

Kala Presents Data Demonstrating Topical Delivery to Posterior Segment of the Eye

Business Wire: July 22, 2013 – WALTHAM, MA, U.S.A. – Kala Pharmaceuticals, Inc., a leading developer of innovative products that rapidly and effectively penetrate the mucosal barrier to enable effective local treatment of ocular diseases, announced today the presentation of preclinical data that demonstrated that topical delivery of a small molecule receptor tyrosine kinase inhibitor (RTKi) formulated utilizing Kala's proprietary mucosal-penetrating particle (MPP) technology significantly enhanced drug levels in the retina. Drug levels in the front of the eye were tunable depending on the release rate of MPP used. Kala presented these data at the Controlled Release Society (CRS) 2013 Annual Meeting, in Honolulu, Hawaii, on July 21–24, 2013.

"Kala's mucosal-penetrating formulation of a receptor tyrosine kinase inhibitor enabled topical administration with what we believe is unprecedented drug concentration and sustained drug delivery to the back of the eye. These data further confirm the potential of our MPP technology as a therapeutic approach for a broad range of ocular diseases including age-related macular degeneration, which is currently treated with frequent intraocular injections," said Hongming Chen, Sc.D., vice president of research at Kala Pharmaceuticals.

In a poster presentation entitled "Mucosal-Penetrating Particles Enable Topical Delivery to Posterior Segment of the Eye," Kala Pharmaceuticals researchers presented preclinical data that demonstrated that:

Topical delivery of a small molecule RTKi formulated using Kala's MPP technology was well tolerated.

In cornea, a single topical dose of a fast-releasing MPP produced drug levels up to 18-fold higher than those from the comparator and sustained a greater than sevenfold enhancement over the comparator for at least 6 hours. A slow-releasing MPP produced a more moderate enhancement over the comparator.

In posterior segment tissues, both the slow- and fast-releasing MPPs outperformed the comparator and resulted in drug levels exceeding the drug's IC50 for VEGFR2.

Drug levels in anterior segment tissues correlate with the MPP release rate and can be tuned based on the type of MPP formulation used without significantly impacting back of the eye drug levels.

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

Rexahn Pharmaceuticals In-Licenses Breakthrough Oncology Drug Delivery Platform

Business Wire: July 17, 2013 – ROCKVILLE, MD, U.S.A. – Rexahn Pharmaceuticals, Inc. (NYSE MKT: RNN), a clinical stage biopharmaceutical company, announced today that it has signed an exclusive license agreement with the University of Maryland, Baltimore (UMB), for a novel drug delivery platform, nano-polymer-drug conjugate systems (NPDCS). This technology targets the delivery of currently marketed chemotherapeutic agents directly into cancerous tumors. The direct delivery of chemotherapeutic drugs into the tumors has been shown to result in increased efficacy and reduced toxicity. The NPDCS platform combines existing chemotherapeutic

agents with a proprietary polymer carrier that contains a signaling moiety that directs the drug into the tumor. This approach minimizes the levels of freely circulating anticancer agents in the body, which can dramatically reduce potential adverse events, and maximizes antitumor activity by accumulating in the cancer tumor. NPDCS is a broad platform that has the potential to generate multiple therapeutic candidates going forward.

Rexahn's first drug candidate developed utilizing this novel platform is RX-21101, a polymer conjugated form of docetaxel, a common chemotherapy agent. In preclinical studies, RX-21101 demonstrated increased efficacy and reduced toxicity, as compared to intravenously administered free docetaxel. Docetaxel is now generic but is marketed worldwide under the trade name Taxotere® and has reported annual sales of \$3.1 billion for the treatment of breast, ovarian, prostate, and non-small-cell lung cancer. Despite its commercial success, docetaxel is toxic to all dividing cells in the body and is associated with a high incidence of adverse events including anemia, infection, fever, neutropenia, neuropathy, asthenia, edema, alopecia, nausea, and vomiting. These adverse events are the result of high concentrations of free docetaxel in the blood. By minimizing the circulating concentration of free docetaxel in the blood and maximizing the concentration in the cancer tumor, RX-21101 may increase antitumor activity and lower incidence of adverse events.

Dr. Hamid Ghandehari, professor, Departments of Pharmaceutics and Pharmaceutical Chemistry and Bioengineering, University of Utah, and codeveloper of the NPDCS technology commented, "The NPDCS platform represents a significant advancement in targeted delivery of chemotherapeutic agents directly to cancer tumors. Other approaches have not been able to combine the controlled, targeted release of existing chemotherapeutic directly to the cancerous tumor."

"This discovery—as well as the partnership with a leading Maryland-based biopharmaceutical company—is very exciting for UMB, and Rexahn is exactly the type of focused organization that our office seeks out as a commercial partner," said Phil Robilotto, assistant vice president, UMB Office of Technology Transfer. "The initial funding for this work was provided through a Maryland Industrial Partnership (MIPS) award, and a successful long-term university/industry relationship such as this is a terrific example of the value of the MIPS program."

Peter D. Suzdak, Ph.D., Rexahn's chief executive officer, commented, "The NPDCS platform complements our three clinical-stage compounds with a lower risk approach that maximizes efficacy while reducing the adverse events associated with existing anticancer agents. Rexahn looks forward to utilizing the NPDCS platform to develop multiple development candidates for either internal development or out licensing."

Rexahn Pharmaceuticals is a clinical-stage biopharmaceutical company dedicated to developing best-in-class therapeutics for the treatment of cancer. Rexahn currently has three clinical-stage oncology candidates, Archexin®, RX-3117, and RX-5902, and a robust pipeline of preclinical compounds to treat multiple types of cancer. Rexahn has also developed proprietary drug discovery platform technologies in the areas of nano-polymer-drug conjugate systems (NPDCS), nano-medicines, 3D-GOLD, and TIMES. For more information, please visit www.rexahn.com.

TWi Pharmaceuticals Receives Patent Allowance for Its Reduced Food Effect Metformin Controlled Release Formulation in the United States

PRNewsire: July 16, 2013 – TAIPEI, Taiwan – TWi Pharmaceuticals, Inc., today announced that it has received an official notification of patent allowance for its metformin controlled release formulation from the U.S. Patent and Trademark Office. The granted patent, U.S. patent number 8,486,453, claims cover the controlled-release composition of TWi's metformin product with reduced food effect. The patent is part of TWi Pharmaceuticals' broad intellectual property portfolio for building a franchise for treating type II diabetes and other metabolic diseases.

"We are very pleased with the issuance of this patent in United States for our oral, controlled-release metformin formulation," said Dr. Calvin C. Chen, president of TWi Pharmaceuticals. "Metformin is the most prescribed oral drug to control blood glucose levels of type 2 diabetic patients. Because its bioavailability is highly influenced by food intake, currently available controlled-release metformin formulations need to be taken with food, which is inconvenient to patients. In addition, compliance of metformin products for diabetic patients, who usually have multiple illnesses and need to take several medicines daily, has sometime been poor because metformin administration time is always different than other medications. TWi's proprietary formulation, on the other hand, may improve patient compliance and blood glucose control since this formulation has been clinically proved to significantly reduce the variance of metformin concentration in blood when taken with or without food. By reducing the food effect, our formulation will be more feasible to combine with other medicines, which also can be taken once a day without restriction of food, to treat diabetes and other metabolic diseases. TWi intends to build a franchise of diabetes therapy with this new metformin formulation as a standalone therapy or in combination with TWi's own diabetes drug AC-201 or other metabolic disease drugs on the market."

According to IMS Health, a market research firm, the total annual sales of the metformin products in the United States were approximately \$2.1 billion in 2012.

TWi Pharmaceuticals, Inc., is a leading specialty pharmaceutical company based in Taipei, Taiwan, focusing on the development

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of high-barrier generic prescription products ranging from oral controlled release dosage form to novel drug delivery systems including the utilization of nanoparticles, transdermal, and polymeric oral delivery systems. Leveraging its internal research and development capabilities, together with operational flexibility, process development, and manufacturing and regulatory expertise, TWi Pharmaceuticals concentrates on products and technologies that present significant barriers to entry or offer Paragraph IV first-to-file or first-to-market opportunities in the United States. For more information of TWi Pharmaceuticals, please visit www.twipharma.com.

Echo Pharmaceuticals Announces Phase 2 Results for Namisol®, Its Pipeline Product for Oral Administration of Δ9-Tetrahydrocannabinol and Appoints the Sage Group

PRNewswire: July 11, 2013 – AMSTERDAM, the Netherlands, CAMBRIDGE, U.K., and CLINTON, NJ, U.S.A. – Echo Pharmaceuticals (“Echo”) announces that Namisol® has completed successfully a phase II trial with 24 patients suffering from spasticity and pain due to multiple sclerosis (MS). The trial has been conducted by the Centre for Human Drug Research (CHDR) in the VU University Medical Center Amsterdam and was led by Dr. G. J. Groeneveld, research director, neurology and pain, CHDR. The clinical trial was a double blind, placebo-controlled study of Namisol® to determine safety, tolerability and efficacy in MS patients. The outcome of this trial showed efficacy and consistent results on both spasticity and pain.

Simultaneously, the Sage Group has been appointed by Echo Pharmaceuticals to assist the company in its search for a strategic partner for commercialisation of its lead Namisol® program.

Dr. Vanesa Fernandez, CEO of Echo Pharmaceuticals, said, “We are very pleased that the Sage Group has been selected by our company to assist in the commercialisation phase of Namisol®. The successful phase 2 trial in MS patients is a major milestone for Echo, and we believe there will be strong global interest in working with us to take the product to market. The Sage Group are very experienced in developing such partnerships and will add a valuable business development activity to our drug development capability.”

Dr. Bill Mason and Wayne Pambianchi of the Sage Group based in Europe and the United States said, “We are delighted to be selected as managers for this exciting program, and we look forward to working with Echo and key interested parties in the pharma industry to develop strong partnerships for global commercialisation of Namisol®.”

Namisol® is the world’s first oral tablet that contains pure (≥98,0%), natural Δ9-tetrahydrocannabinol (THC or dronabinol) in fixed dosages with high, predictable bioavailability (due to Echo’s innovative drug delivery technology Alitra™) and a long, stable shelf life at room temperature. Namisol’s current clinical program includes, in addition to the MS indication, a number of phase II clinical trials for the indications behavioral disturbances in patients with Alzheimer’s disease and chronic pain.

Echo Pharmaceuticals is a privately owned, specialized pharmaceutical company based in the Netherlands, founded in 2006. Their mission is to develop effective medicines, with a focus on cannabinoid-based compounds, and drug delivery technologies that contribute to better the quality of life for a wide range of patients. In 2009, Echo established their headquarters and clinical research center in Nijmegen, which is situated in an area of the Netherlands well known for its ideal environment for businesses in life sciences and health.

Over the years, Echo has developed outstanding proprietary knowledge and extensive expertise in the field of isolation, formulation, and clinical development that have led to successful drug and delivery technology development programs. Echo Pharmaceuticals has a cGMP certified production and pharmaceutical development center in Weesp, the Netherlands.

CytRx’s Aldoxorubicin Shrinks Tumors and Prolongs Survival in Model of Human Brain Cancer

Business Wire: July 9, 2013 – LOS ANGELES, CA, U.S.A. – CytRx Corporation (NASDAQ: CYTR), a biopharmaceutical research and development company specializing in oncology, today announced that aldoxorubicin, its more potent version of the widely used chemotherapeutic agent doxorubicin, demonstrated statistically significant efficacy ($p < 0.0001$) in the treatment of rapidly growing human brain (glioblastoma) cancer in the brains of animals. Complete results from this favorable confirmatory trial, which was conducted in collaboration with Louisiana State University (LSU) School of Medicine, will be presented at the European Society for Medical Oncology being held September 29–October 1 2013 in Amsterdam.

“We are surprised and excited about the effectiveness demonstrated by aldoxorubicin in this particularly difficult-to-treat cancer,” said Om Prakash, Ph.D., the study’s principal investigator and research professor of medicine, Stanley S. Scott Cancer Center, Louisiana State University Health Sciences Center, New Orleans. “It has been well documented that doxorubicin, although active against glioblastoma cancer cells in tissue culture, does not cross the blood-brain barrier, the body’s natural defense system protecting the brain, to effectively treat patients with brain tumors. In fact, in our study doxorubicin was no more effective than saline in suppressing glioblastoma tumor growth. We have shown that aldoxorubicin uptake is confined only to the tumor in the brain and does not enter normal brain tissue. Thus, we would expect toxicity in the central nervous system to be negligible. Our conclusion from this trial is that aldoxorubicin has the potential to safely shrink glioblastoma tumors, which could dramatically prolong the average survival time in patients. We initially had observed a similar effect of aldoxorubicin on glioblastoma in a preliminary study and are quite pleased to have confirmed the result in a larger, well-controlled study that included native doxorubicin.”

Dr. Prakash’s main focus of his research efforts in the last few years has been to understand the pathogenesis and treatment of glioblastoma multiforme, the most malignant and the most

deadly type of brain tumor. He is the corresponding author on several poster presentations in national/international meetings. More recently, he is the first author on a publication, "Gliomas and Seizures," in the *Medical Hypothesis Journal* (Prakash *et al.* 2012; 79:622).

"This trial produced remarkable results in a deadly cancer that virtually always returns regardless of whether treated with surgery, radiation, chemotherapy, or a combination of methods," said CytRx president and CEO Steven A. Kriegsmann. "Animals treated with aldoxorubicin survived on average more than twice as long as those treated with saline or doxorubicin."

"Aldoxorubicin could provide an exciting new approach in how we attack brain tumors. These outstanding results support our plan to initiate a phase 2b clinical trial with aldoxorubicin in patients with relapsed glioblastoma. We remain on track with expanding our aldoxorubicin clinical development activities and expect our progress to accelerate in the coming months and year," he added. If the data from the company's planned phase 2b clinical trial for glioblastoma are positive, it plans to file for breakthrough therapy designation with the U.S. Food and Drug Administration, which could expedite marketing approval for aldoxorubicin.

Aldoxorubicin has shown to be superior to doxorubicin in seven different tumor types and animal models of cancer, including ovarian, lung, breast, and pancreatic cancer, as well as multiple myeloma, and has demonstrated activity in human trials for the treatment of soft tissue sarcomas and other cancers.

Aldoxorubicin is the first drug candidate CytRx is developing based on a novel linker technology that has proven ability to allow attachment of multiple chemotherapeutic agents and is designed to provide both greater anticancer activity and to mitigate the toxicity that limits these agents' use.

CytRx Corporation is a biopharmaceutical research and development company specializing in oncology. The CytRx oncology pipeline is focused on the clinical development of aldoxorubicin (formerly known as INNO-206), its improved version of the widely used chemotherapeutic agent doxorubicin. CytRx has initiated an international phase 2b clinical trial with aldoxorubicin as a treatment for soft tissue sarcomas, has completed its phase 1b/2 clinical trial primarily in the same indication and a phase 1b study of aldoxorubicin in combination with doxorubicin in patients with advanced solid tumors, and is conducting a phase 1b pharmacokinetics clinical trial in patients with metastatic solid tumors. The company is initiating a phase 3 pivotal trial under a special protocol assessment (SPA) with aldoxorubicin as a therapy for patients with soft tissue sarcomas whose tumors have progressed following treatment with chemotherapy. CytRx is expanding its pipeline of oncology candidates based on a novel linker platform technology that can be utilized with multiple chemotherapeutic agents and could allow for greater concentration of drug at tumor sites. The company also has rights to two additional drug candidates, tamibarotene and bafetinib. The company completed its

evaluation of bafetinib in the ENABLE phase 2 clinical trial in high-risk B-cell chronic lymphocytic leukemia (B-CLL), plans to seek a partner for further development of bafetinib, and is evaluating further development of tamibarotene. For more information about CytRx Corporation, visit www.cytrx.com.

Intertek Acquires Melbourn Scientific Ltd.

Business Wire: July 9, 2013 – LONDON, U.K. – Intertek, the leading quality solutions provider to industries worldwide, announces that it has acquired Melbourn Scientific Ltd. ("Melbourn"), a leading provider of analysis and development services for the pharmaceutical, biopharmaceutical, biotechnology, and healthcare industries.

Melbourn offers a range of expert services to support the global pharmaceutical and healthcare industry, including formulation and product development, analytical method development and validation, stability studies, and QC release testing. It has profound expertise in all aspects of characterisation of orally inhaled and intranasal products (OINDP) and transdermal devices in addition to services for conventionally delivered medicines. There is an increasing demand worldwide for more patient friendly drug delivery methods for optimum therapeutic efficacy and efficiency and enhanced patient outcomes.

Its formulation services respond to the need for reformulation of existing products to improve efficacy or extend patent life and to widen the market potential for a given product. Moving from injection to oral inhalation, for example, is a key strategy of many global pharmaceutical majors to achieve increased market share by improving bioavailability and drug use uptake within a patient population (by improving delivery at the true target) while reducing patient trauma.

Located in Royston, near Cambridge, in the United Kingdom, Melbourn's business employs 80 staff. Its 20,000 sq. ft. facility is good manufacturing practice (GMP) compliant, regularly inspected by the U.K. Medicines and Health Regulatory Authority (MHRA) and the FDA. The company's reputation for providing outstanding and responsive customer service along with its specialist skills have fostered loyal customer relationships of which Melbourn is especially proud and which complements Intertek's existing technical capabilities and culture.

Dr. Andrew Swift, SVP Intertek Chemicals and Pharmaceuticals, says, "Combining Intertek's GMP/GLP pharmaceutical/biopharmaceutical studies and our advanced capabilities for measuring device/drug interaction with Melbourn's expertise in OINDP drug characterisation provides a unique and compelling offering to clients. Adding in our global reach and regulatory services, Intertek now offers a comprehensive and global end-to-end expert service to support drug development that is unmatched by current competitors."

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Intertek Chemicals & Pharmaceuticals helps organisations across a wide range of industries to sharpen their competitive edge by providing advanced measurement, expert consulting related technical support services, and sustainability solutions. Our experts and laboratories provide critical support to our clients in their global trade, not just with data, but with essential knowledge to accelerate development of their next-generation products, to improve their manufacturing, products, or production processes or to enhance their efficiencies.

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Calendar of Events

2013

Drug Delivery Australia 2013 Conference

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October 24–25

Sydney, Australia

www.crsaaustralia.org/?page_id=580

11th International Nanomedicine and Drug Delivery Symposium (NanoDDS'13)

October 25–27

La Jolla, CA, U.S.A.

[http://nanomedicine.ucsd.edu/
nanodds13](http://nanomedicine.ucsd.edu/nanodds13)

Introduction to Microencapsulation Technologies

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November 10

San Antonio, TX, U.S.A.

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New Vision for the Eye: Unmet Ocular Drug Delivery Needs Workshop

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November 10

San Antonio, TX, U.S.A.

www.aaps.org

Nanomedicines: Addressing the Scientific and Regulatory Gap

November 21

New York, NY, U.S.A.

www.nyas.org/NanoMed

2014

5th FIP Pharmaceutical Sciences World Congress

April 13–16

Melbourne, Australia

www.fip.org/pswc2014