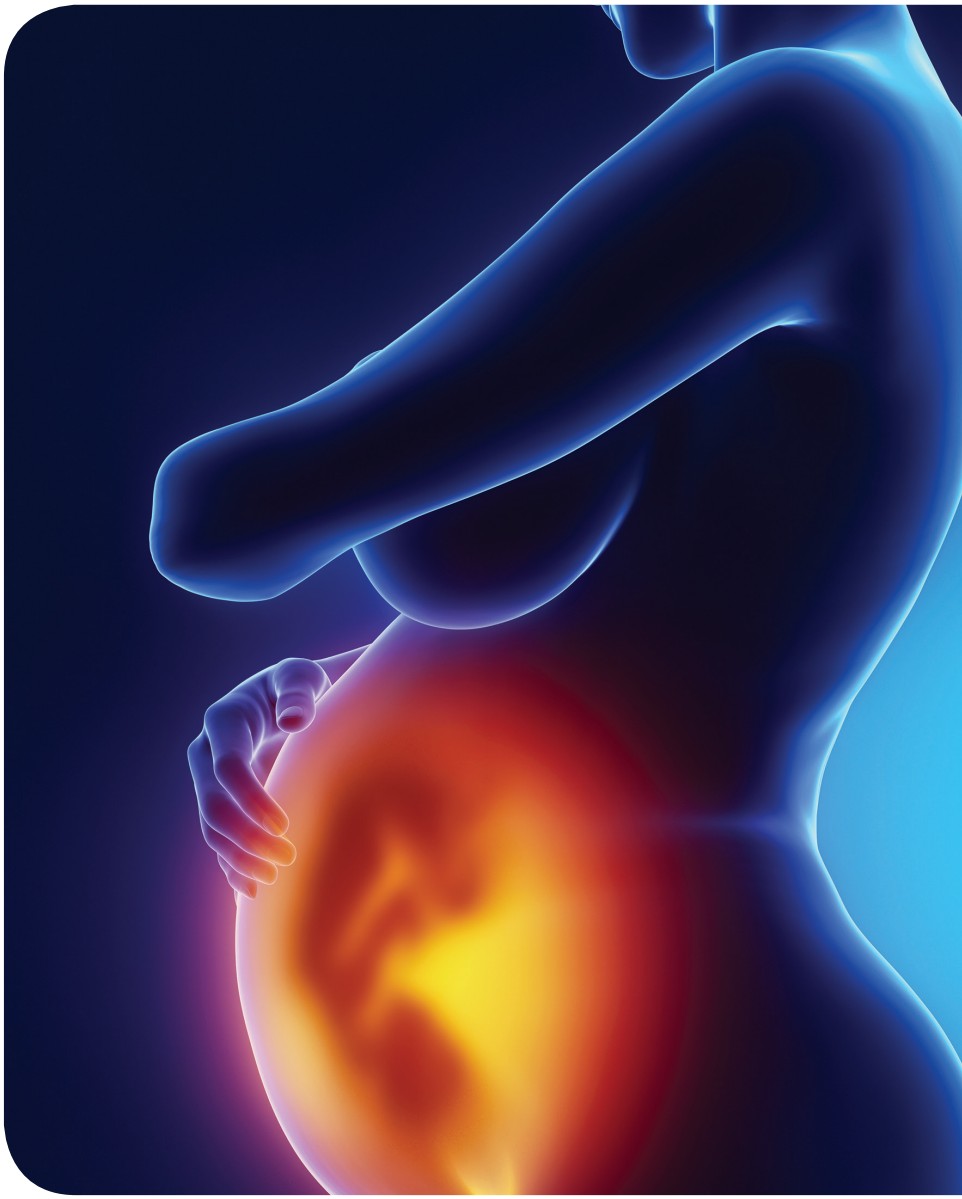
CRS Leading Delivery Science and Technology

Newsletter

A publication of the Controlled Release Society Volume 31 • Number 1 • 2014



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CRS Newsletter

Leading Delivery Science and Technology

Vol. 31 • No. 1 • 2014

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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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Arlene McDowell
University of Otago
New Zealand

Finding Inspiration

Where do you get your inspiration from?

I am addicted to the home renovation shows that are so popular on TV at the moment. Tonight, I watched an episode about making the best use of small spaces and turning them into homes. The show included a very cool example of prefabricated, modular pods that together formed the rooms of a holiday home with all the necessary accoutrements for eating, bathing, relaxing, and sleeping in a stylish, compact setup. The prefabricated pods were assembled in a sheep shed near the countryside location for the holiday home. There were considerable challenges in maneuvering the pods out of a sheep shed (that still contained sheep and hay bales), through the shed doors (that were only just big enough), and up a narrow, muddy farm track to the desired location. This concept reminded me of the many nano drug delivery systems many of us are working on within CRS. We want them to be small and perfectly formed, with the ability to navigate complicated biological environments and perform a useful function.

To gain inspiration for the show on small living spaces, the TV host visited a gypsy caravan to see how people effectively utilize small (and mobile) spaces to live and bring up families. I recently spoke at a forum on "Triggered Delivery Systems" that was organized by the Formulation and Delivery of Bioactives (FDB) Research Theme at the University of Otago. CRS President Ian Tucker is the convenor of the FDB Theme, and he asked us to speak about triggers of a range of physiological processes found in nature. The sessions evoked some interesting discussions and we hope planted a seed or two of inspiration for new ideas for drug delivery.

In this issue of the *CRS Newsletter* you will find articles about Ronald Veršič's contribution to the field of microencapsulation, a nanoparticulate delivery system for prenatal therapy of fetal cardiac arrhythmia, and from the PSAH Division a summary of recent publications, including one on the exciting area of "microrobots"—all sources of ideas that perhaps can inspire your own research. We have a fantastic community of local chapters who organize events to facilitate sharing our scientific findings and experience. This issue features a report on the recent Drug Delivery Australia conference and one on the Italian Local Chapter's workshop. Our CRS Annual Meeting in 2014 is in Chicago, U.S.A., from July 13 to 16. I encourage you to take the opportunity to inspire and be inspired through participation in the Chicago meeting.

Now, where did I leave my hammer?

On behalf of the *CRS Newsletter* editorial team, I wish you a happy, healthy, and inspirational 2014.

Best wishes,
Arlene McDowell ■

Ian Tucker
University of Otago
Dunedin, New Zealand

Clarity of Purpose Is an Essential Element of Success

Summer holidays in the southern hemisphere are taken in December through January. So while some members of our truly international society in the northern hemisphere were enduring (or suffering) the cold and longer hours of darkness, I was enjoying a family holiday, swimming, fishing, bush walking, sharing meals, and doing some reading. It was a time for some light "whodunit" novels but also some thought-provoking stuff. I thought it was time I changed from my usual historical/philosophical fare to some forward-looking writings.

We are continually bombarded with bad news, doom, and gloom, so it was a change to read *Megachange: The World in 2050* (from *The Economist*). This book, while acknowledging the limitations of futurology, presents researched-based forecasts of the world in 2050. It covers various issues that are highly relevant to CRS—demographics, health, science, social networks, equity (gender and income), culture, and globalisation—and includes a chapter titled "Taming Leviathan: The State of the State." Overall, the tenor is optimistic, too optimistic for some who judge it to be science fiction and simply extrapolating current trends, but in my view it is a thought-provoking collection of essays.

"Taming Leviathan" is about how to ensure efficiency and control the growth of government and the state, a message of relevance to CRS. We must be continually vigilant to ensure we are an efficient, nimble organisation that is continually adapting to the rapidly changing environment. Many not-for-profit organizations are being challenged by falling memberships, lower volunteering, and (rightly so) members wanting maximum value for money. Your Board is committed to CRS being an efficient organisation, reducing waste, abandoning what is no longer useful, and delivering useful services through cutting-edge technologies. More social networking, an e-newsletter, e-posters, and so on are in the pipeline.

Cultural megachange is another factor confronting society in general that has implications for our Society. This is expressed as changing expectations of new generations (Baby Boomers versus Generation X versus Generation Y) and of course ethnic and national differences. We may value volunteering in different ways, but I think we would agree that we have a very active Young Scientist Committee that adds value for the membership.

The Volunteer Recruitment Committee, a new committee, has the important task of developing strategies for recruitment of volunteers, for providing training opportunities and "volunteer career pathways" as well as reliable processes so that members can be directed to appropriate areas when they volunteer. We look forward to receiving and implementing this committee's recommendations.

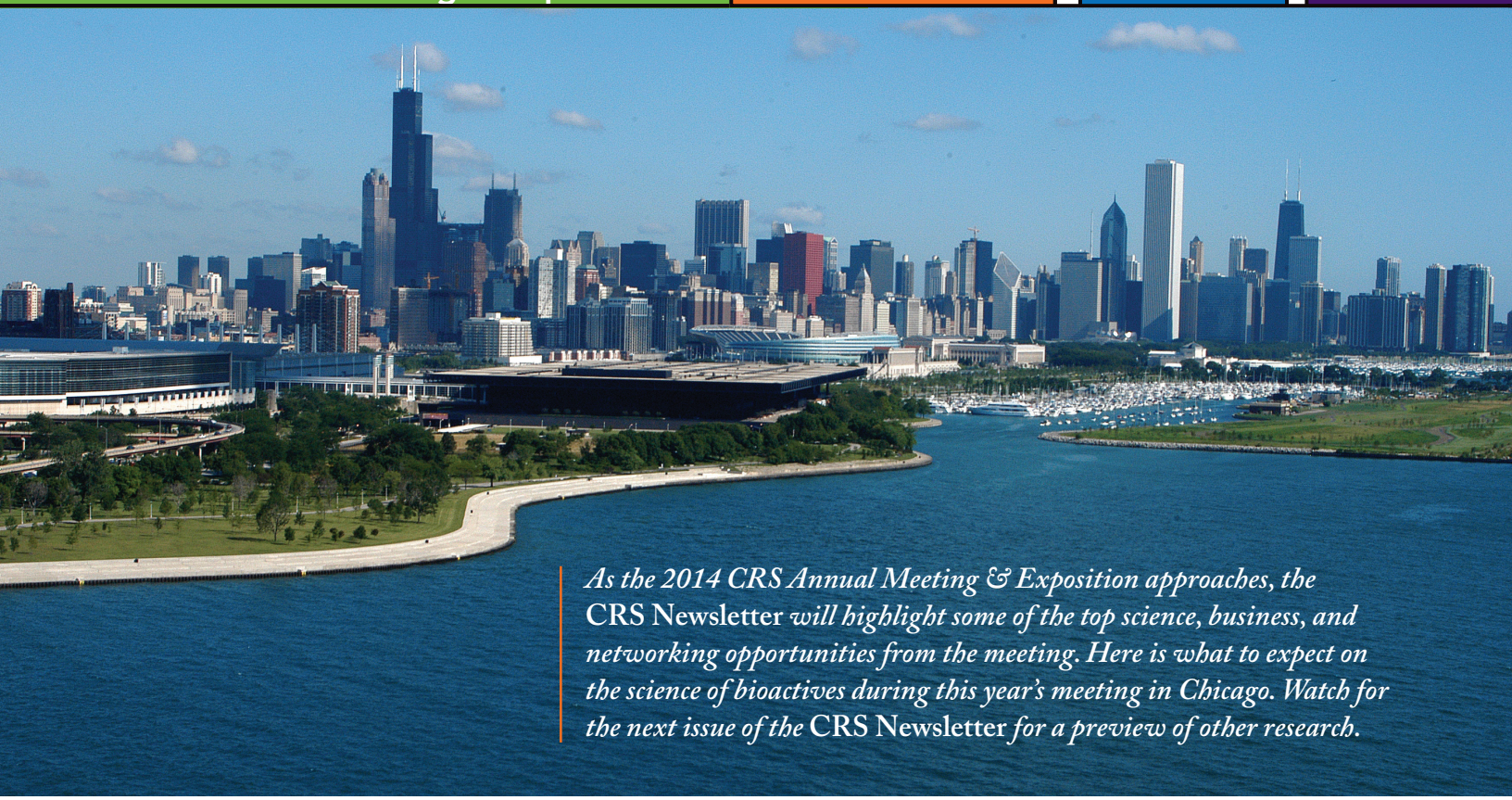
Finally, I would like to say something about our culture. Prof. Robert Burgelman (Stanford) has said, "Strategy without culture is powerless and culture without purpose is aimless." Strategy is about "what" and "how," and through the efforts of many we have done a good job in this area over the last few years. We have established our strategic plan with annual objectives and robust procedures. But what about culture? Some say that the core of an organisation's culture is a clearly articulated sense of purpose. Clarity of purpose is a critical element of success.

We have a vision ("Visionary leadership in delivery science and technology") and a mission ("CRS is an international, multidisciplinary society dedicated to delivery science and technology"), but there is a danger that these statements are simply words. To influence culture, purpose must be a deeply held shared belief that is articulated both within the organisation and externally.

Some say that people don't buy what you do, they buy why you do it. We organise fantastic annual conferences, workshops, and symposia, publish books and journals, volunteer our time, and so on. Why? Because we believe deeply in the value and importance of delivery science and technology. Although we have this deep belief in common, we almost certainly have different reasons for our convictions. They may be altruistic, personal, or financial. For example, products of delivery science help people live higher quality lives, improve productivity, solve real-world problems, represent a fascinating science, provide a solid career, present an opportunity to make money, and so on.

I encourage all members to share "why you do it" (delivery science and technology) so others will "buy it" and benefit.

Ian Tucker ■



As the 2014 CRS Annual Meeting & Exposition approaches, the CRS Newsletter *will highlight some of the top science, business, and networking opportunities from the meeting. Here is what to expect on the science of bioactives during this year's meeting in Chicago. Watch for the next issue of the* CRS Newsletter *for a preview of other research.*

©Choose Chicago

Discover the Technical Program at the 41st CRS Annual Meeting & Exposition, Chicago, IL, U.S.A.

The Annual Meeting Program Committee (AMPC) is excited about the scientific sessions shaping up for this year's CRS Annual Meeting & Exposition. Committee Chair Ick Chan Kwon (Korean Institute of Science and Technology, Korea), Deputy Chair Justin Hanes (Johns Hopkins University, U.S.A.), and committee members You Han Bae (University of Utah, U.S.A.), Donald Barbieri (Patheon, U.S.A.), Ben J. Boyd (Monash University, Australia), Peter Cheifetz (Merial, U.S.A.), Samir Mitragotri (University of California, Santa Barbara, U.S.A.), Ruth B. Schmid (SINTEF, Norway), Hardik Shah (Alkermes Pharma Ireland Ltd., Ireland), Ronald L. Smith (Merck, U.S.A.), Geert Verreck (Janssen Pharmaceutica, Belgium), and Fanwen Zeng (Dow Chemical Company, U.S.A.) have been working since early August 2013 to organize an engaging program that encompasses a comprehensive scope of current controlled release and delivery science with contributions from world-class scientists.

This year's meeting, "Translation of Delivery Technology: Innovation to Commercialization," offers an exceptional opportunity to interact with others in the discovery, development, and delivery continuum. Headlining the program are plenary lectures from David Edwards (Harvard University, U.S.A.) on redesigning nutrition delivery, David W. Grainger (University of Utah, U.S.A.) on three-dimensional cell culture models, and Chad A. Mirkin (Northwestern University, U.S.A.) on spherical nucleic acid nanostructures. These lectures offer a high-level look at technology and paths to bringing technology to practical use.

The preliminary program includes five mini-symposia and 20 technical sessions covering the areas of bioactives, industrial pharma, preclinical sciences and animal health (PSAH), and consumer and diversified products (C&DP). Mini-symposia are arranged around focal areas of specialized interest and include the following topics:

Advancements to Develop and Deliver Biologics (brings together experts from industry and academia to discuss the development and delivery of biologics and biosimilars)

Cancer Epigenetics, Epigenetic Drugs, and Delivery (introduces cancer epigenetics, epigenetic drug discovery, and delivery technology)

Individualized Medicine and Theranostics (discusses the potential influence of novel theranostic agents for personalized medication)

Interspecies Clinical Pharmacology Dosing Concepts (examines why dosing concepts in different species have to be carefully evaluated)

Micro- and Nano-Encapsulation: From Innovation to Commercialization (gives insight into today's industrial chemical and physical encapsulation technologies with emphasis on practical and physical limits, scale-up challenges, and costs)

Bioactive technical sessions are focused on various aspects within the extensive scope of controlled release and delivery, including nanoparticles, RNA and DNA delivery, cell-based delivery, transdermal delivery, overcoming biological barriers, and drug delivery to the eye, lung, and brain. The sessions are rounded out with two PSAH sessions on formulation development and predictive animal models, and four C&DP sessions covering process engineering, methods, and applications in consumer products, food, feed, and beverages.

The CRS AMPC has taken into consideration the popularity of topics and sessions from past annual meetings, along with current or future areas of interest and suggestions from the CRS Board of Scientific Advisors, when compiling the program for the 2014 meeting. The following is a full list of the preliminary sessions. More detailed descriptions, including the invited speakers, can be found on the CRS website.

- Advances in Drug Delivery to the Eye
- Advances in Drug Delivery to the Lung
- Advances in Process Engineering—New Methods for the Production of Particles, Capsules, and Coatings
- Advances in RNA and DNA Delivery
- Breakthrough Technologies
- Cells as Delivery Vehicles
- Controlled Release of Actives in Consumer Products
- Controlled Release Applications in Food, Feed, and Beverages
- Evaluation and Characterization of Controlled Release Products and Production Processes
- Innovations in Micro- and Nano-Based Delivery
- Innovations in Oral Drug Delivery
- Intracellular Delivery of Nucleic Acids and Proteins
- Nanoparticle-Based Delivery to the Brain
- Nanoparticles in Tumor Treatment
- Novel Developments in Formulation, Analytical Chemistry, and Processing in Animal Health and Preclinical Sciences
- Overcoming Barriers in the GI Tract
- Overcoming Biological Barriers
- Predictive Animal Models for Assessing Long-Acting Formulations for Human and Animal Health and Their Challenges
- Proteins, Peptides, and Vaccines
- Transdermal Delivery

In addition to the oral presentations, there will be poster presentations within these same categories.

The CRS Annual Meeting & Exposition offers a comprehensive snapshot of the current state of controlled release and delivery science with the opportunity not only to see what is being accomplished and how problems are being solved but also to be a part of the conversation and direction of this work. Make plans to engage in this rewarding experience July 13–16, 2014, in bustling Chicago, Illinois, U.S.A. ■

Top – Lobby Hilton Chicago Hotel; Bottom (left to right) Courtesy of Choose Chicago, ©City of Chicago – Riverboat cruise through the city and past Willis Tower Ferris Wheel at Night Navy Pier; Adler Planetarium Chicago

Chicago—Come for the Science, Stay for Everything Else

Anchored by stunning Lake Michigan, Chicago is more than just a big city. Besides its striking downtown area, which includes some of the tallest buildings in the world, Chicago has a distinctive coastline and hundreds of vibrant parks. This unique mix of attractions and cultural arts makes Chicago one of the friendliest and most visited cities in America.

The 41st CRS Annual Meeting & Exposition is housed entirely in the historic Hilton Chicago Hotel. The Hilton is a 4 Diamond hotel with old-world charm and elegance along with modern sophistication and amenities. Enjoy the panoramic view from your room and then take a short elevator ride to the exhibit hall, scientific session, or networking event.

Grant Park is across the street and is proudly referred to as Chicago's "front yard." The park contains performance venues, gardens, art work, sporting, and harbor facilities. It hosts several large annual events, including Taste of Chicago, which runs July 9–13, 2014. Plan to arrive in time to enjoy this festival and many other nearby attractions.

Pioneers in Microencapsulation: Ronald J. Veršič

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

Ronald Veršič
President, Ronald T. Dodge Company

Ron Veršič has established and cultivated a steady presence in the microencapsulation field since his initial exposure to the concepts—first during a visit to National Cash Register (now NCR) in April 1960 as a member of Junior Engineering Technical Society (JETS) and then later in the decade when he began his career in the field (1969). I first met Ron at a particle coating course offered by The Center for Professional Advancement (CPA) in 2001 and have worked with him on the Consumer and Diversified Products (C&DP) Steering Committee since 2004. He has an inquisitive nature and a passion for understanding how things work. He also has a remarkable capacity for retaining knowledge and details—a skill that has helped him develop a firm expertise in microencapsulation. His welcoming and caring demeanor quickly puts one at ease, and an innate practical nature has created a unique and fruitful life experience with few regrets.

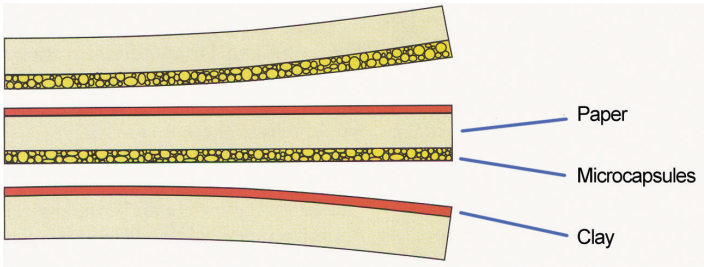
Ron received his master's degree in physics from the Johns Hopkins University and his doctorate in materials engineering from the Ohio State University. His work career began in the area of encapsulation technologies used in photographic imaging. This started in 1969 with GAF but was limited to six months because of an economic downturn in 1970 and a reduction in the company's workforce. This involvement, however, led to a contractor position with the U.S. Air Force, where Ron worked on KH-2 photographic imaging technology for satellites. (KH, or Keyhole, reconnaissance satellites are typically used to take overhead photos for military missions.) From December 1971 to April 1976, he was employed by the Standard Register Company to work on an emerging imaging technology for photographic film. As he became reacquainted with and established a deeper knowledge base in microencapsulation technologies, he was successful in developing and building a state-of-the-art microencapsulation scanning densitometer for his employer. From 1976 to 1979, he worked for Monarch Marking in the area of price labeling images.

In 1979, Ron saw a need in the business world that led to his establishment of the Ronald T. Dodge Company. Prior to this time, numerous microencapsulation technologies had been established commercially. Companies using this technology often contracted out the microencapsulation work. Further, most of the efforts in the larger companies did not lead to commercialization. Ron's business entertained a variety of microencapsulation technologies over the years, including urea formaldehyde (UF) or polymethylene urea (PMU), gelatin coacervation, spray drying, fluid bed coating, and Parylene chemistries. His company became well-known for coacervation, Wurster (bottom spray fluid bed), and other coacervation chemistries with an extensive array of applications. Ron often noted that applications know-how (applied, problem-solving technology) was "at the heart of [his] business then—and remains so today."

Ron joined CRS in 1984. The roots of CRS are near his home in Dayton, Ohio, and Ron has acknowledged Frank W. Harris as an early force in the development of the society. Ron has found CRS a good fit for his interests and endeavors, and he has been frequently and enthusiastically involved ever since. Ron attends and participates in most annual meetings; cochaired C&DP sessions in 2002 and 2011; was a visionary organizer and participant in the CRS revitalization of C&DP in 1995; and in 2011 was elected a fellow of CRS.

Ron is a member and distinguished fellow of the American Chemical Society (ACS) and a member of the American

In 1979, Dodge headquarters was a rented office and lab. In 2004, the cornerstone was laid for their current building (above). Today, Dodge manufacturing, laboratory, engineering, and general office space totals 16,000 square feet (compared with 1,600 square feet in 1983). The company has successfully encapsulated products from more than 600 different core materials.



Carbonless paper—invented by Barrett K. Green, the "Father of Microencapsulation" in the 1940s and released by NCR in 1954—has three layers: the paper, a film of acid-sensitive dye packaged in microcapsules, and a layer of acidic clay to develop the dye. The microencapsulation work of Barrett Green provided a foundation for applications in many diverse industries.

Association of Physics Teachers (AAPT). He has received the Award for Outstanding Professional Achievement from the Affiliate Societies Council of the Engineering and Science Foundation of Dayton. Ron has served as an adjunct assistant professor in the Division of Pharmaceutics and Drug Delivery Systems at the University of Cincinnati Medical Center. Further, he has taught the course "Microencapsulation & Controlled Release" as part of the continuing education program for the Society of Cosmetic Chemists (U.S.A.).

More recently, Ron was a visiting professor in 2008 at the University of Vienna (Austria) in the Department of Pharmaceutical Technology and Pharmacy. In 2012, Ron helped establish the Donald D. Emrick Memorial Library—a corporate library that contains thousands of books, technical papers, and other printed materials on a variety of topics on the art and science of microencapsulation and the development of controlled release products. Many of the books are rare, hard-to-find, or one-of-a-kind technical publications that no longer exist in other libraries. Access is available to serious students, scholars, scientists, and entrepreneurs (www.controlled-release.com).

I consider Ron Veršič one of the pioneers in microencapsulation because he has used his distinctive work experiences and innovative ideas to take the industry to a place where it would not have gone without his many contributions. Some useful insights from Ron's experiences are shared in the following question and answer format.

Q *How did your experience and knowledge of the industry lead to starting, and then successfully running, your own microencapsulation business?*

A Commercial applications for microencapsulation technologies were recognized and established several decades before I started my own business. For example, NCR had explored the technology and subsequently developed carbonless copy paper—a revolutionary product at that time. NCR technology was transferred to Capsulated Systems, Inc. (CSI) and Djinnii Enterprises. Later, Djinnii and American Thermometer developed color-indicating thermometers for aquariums, using microencapsulation as the base technology. The pioneering technology that originated with NCR evolved into modern-day coacervation techniques, eventually resulting in the development of scratch-and-sniff products, time-release capsules, and many other products.

All too often, however, the emphasis in the development of these products was on technical research. Solving the microencapsulation problem was only a small, albeit critical, part of the service and support needed. A commercial venture had to be technically proficient, yet I believed then—and now—that any successful microencapsulation business needed to provide manufacturing on a large scale, new applications ideas, and a complete, solid business plan for providing professional support and service to its customers. It seemed to me that little thought had been given to providing this level of service and support.

The heart of my business plan did not focus on any specific microencapsulation methodology, but it did embrace any technology that we could offer that would enhance and improve both a technical and an economical solution to a particular encapsulation problem. Over the years, we have become a trusted source of encapsulated products because, in addition to the end products, we offered applied R&D, pilot testing, and full-scale production services. Then and now, we still emphasize our unique business model as the "innovative art and science of microencapsulation and controlled release."

Q *What have you focused on over the past 34 years that has led to the success of your company?*

A Others found it was more practical to outsource the microencapsulation work in order to take full advantage of an established expertise rather than bring it in house to satisfy the vital, but limited, overall commercial need. We took advantage of this opportunity when we formed the Ronald T. Dodge Company in 1979.

Commercial microencapsulation production services were established as the heart of our business—and, eventually, led to our success. We did not focus on any specific microencapsulation technique; rather, we entertained a variety of microencapsulation technologies. These included *in situ*

Dr. Veršič developed and authored the Barrett K. Green website as a tribute to Green's pioneering efforts in the field. For more information on Green's achievements, see www.coacervation.net.

On his business, Veršič says: "The heart of our business is our ability to manufacture microcapsules on a large scale—everything from exploratory vision to pilot scale-up to full production."

Special Feature continued on page 8

Special Feature continued from page 7

polymerization (such as urea or melamine formaldehyde processes), coacervation, spray drying, fluid bed coating, and Parylene chemistries. Further, in developing new microencapsulated products and solutions, our technical focus remains on good science, verifiable numbers, thorough and complete testing, and applications know-how.

Today, we work in a much wider range of industries than others in our business. We are not a consulting business—rather, a full-service solutions-based development and manufacturing company that produces microencapsulated products. Industries we serve include adhesives, agriculture, automotive, cosmetics and personal care, neutraceuticals, fragrance delivery, home care and improvement, industrial, medical and dental, military, paint, printing and paper, recreation and novelty, research and development, security, and textiles.

As we say in our website, "It's this commitment to customer service, quality, and teamwork that defines the mission of the Dodge Company."

Q *What difficulties have you encountered, what opportunities did you find as a result of your unique background, and do you have any regrets in starting and running a one-of-a-kind business?*

A Being an entrepreneur (especially in a highly technical area) was and is more difficult than is commonly portrayed by the media. Running a business—any business—requires careful attention to building, supporting, and improving all aspects of your operation. In our case, it required thorough planning, significant capital, and a clear understanding of the complete needs of our customers.

As much as I enjoyed both the art and science of the business, it became obvious that this business could not treat the endeavor as a hobby or lifestyle business. Further, we focused on niche markets (instead of established or mature markets) and avoided short-lived fad products (e.g., mood rings). As a result, we have been able to generate tens of millions of dollars in sales and deliver quality, leading-edge products to a wide range of customers.

I've enjoyed the freedom to run the type of operation I like. I have also enjoyed the opportunity to travel globally, allowing me to meet talented people around the world and visit many interesting places along the way. Even my children have expanded their horizons and developed a more global perspective because I have been able to share these experiences with them.

Q *How do you see the future of the microencapsulation business?*

A To me, success is the ability to develop products that are needed, work well, and solve problems that can't be solved otherwise. Today, we have not explored, nor found, enough uses for the microencapsulation technology. The future will be bright for entrepreneurs—first, if they have the ability to solve the technical problems, and second, if they have the business acumen and tenacity to take a different, perhaps closer, look at this highly expandable marketplace. In short, it takes commitment and something of a pioneering spirit.

Q *Please share some of your lessons learned from your experience in operating a commercial, broad-based encapsulation business.*

A People will come and go throughout your career. Be open to them, and share what you bring to the table so that that information can be used to its fullest advantage and benefit. Be prepared and open for change, because it will happen—ready or not. Learn the new technologies, and be attuned to new trends, changes, and developments in marketing techniques. Older methodologies don't work anymore. Recognize and use the resources available on the Internet. Don't knock on doors. Rather, look for problems to solve. Focus on needs-based marketing. Roll with the punches. Do what interests you.

Finally, be a visionary. Few businesses can survive without a clear vision of where they are going and how they are getting there. Anticipate—and plan for—success. ■

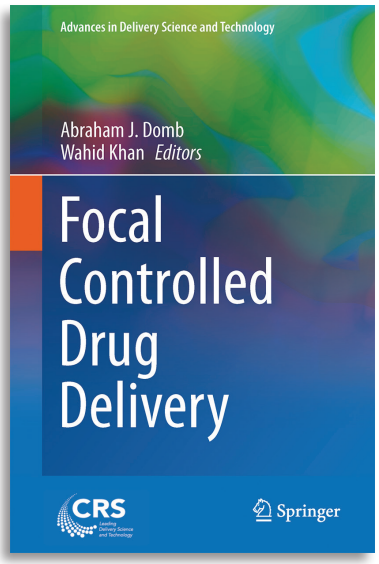
CRS Advances in Delivery Science and Technology Book Series

CRS Leading Delivery Science and Technology

NEW TITLE

Focal Controlled Drug Delivery

Edited by A.J. Domb, School of Pharmacy-Faculty of Medic., Jerusalem, Israel; W. Khan, School of Pharmacy-Faculty of Medicine, Jerusalem, Israel



- Includes fundamental introductory chapters for focal drug delivery
- Describes drug delivery to body sites/system
- Provides an authoritative account of the essential pharmaceutical, technological, physiological, and biological sciences

The concept of focal drug delivery has been applied for treating illnesses that are localized to a certain tissue or organ. These delivery systems are applied directly to the diseased site and deliver a desired dose for an extended time period while minimizing systemic distribution of toxic drug. Despite the upsurge of interest in focal targeted drug delivery, there is currently no single reference text on this subject. Thus, the aim of *Focal Controlled Drug Delivery* is to bring together leading experts and researchers in this field to provide an authoritative account of the essential pharmaceutical, technological, physiological, and biological sciences underpinning the topic. This book contains two sections. The first includes fundamental introductory chapters for focal drug delivery, whereas the second section includes chapters describing drug delivery to body sites/system. The book allows clinical, pharmaceutical, and biological scientists to offer their own perspectives on the subject, making it of potential interest to a wider audience than just drug delivery scientists.

2014, XVII, hardcover, 700 pages.

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#8754-2/2014

Nanomedicine for Prenatal Cardiovascular Therapy

Norah Albekairi and Erik Rytting
Departments of Obstetrics & Gynecology and Pharmacology & Toxicology,
University of Texas Medical Branch, Galveston, Texas, U.S.A.

Introduction

Patients are warned against the dangers of taking medications that are not intended for them, but under current practices for treating fetal disease, a pregnant woman is often given a drug *that she doesn't need* so that a portion of the dose can reach the fetus. Such is the case with prenatal therapy of fetal cardiac arrhythmias.

Fetal arrhythmias affect 1% of pregnancies.[1] Digoxin is the most common drug used to treat fetal arrhythmia.[2] Nevertheless, prenatal digoxin therapy can lead to undesirable side effects for the mother, because the majority of the dose remains in the maternal circulation. These maternal side effects include palpitations, second-degree atrioventricular block, and hypotension.[3]

Previous work has demonstrated that polymeric nanoparticles can cross the placental barrier.[4] In pursuit of the hypothesis that a nanoparticle formulation designed to cross the placenta can improve fetal drug therapy (see Figure 1), we have investigated the encapsulation, controlled release, and *in vitro* maternal-to-fetal transfer of digoxin-loaded nanoparticles prepared from biodegradable polymers. Successful delivery of digoxin to the fetus may improve cardioversion to normal sinus rhythm as well as limit the distribution of digoxin in the maternal circulation, thus reducing the incidence and severity of the maternal side effects associated with current methods of treatment.

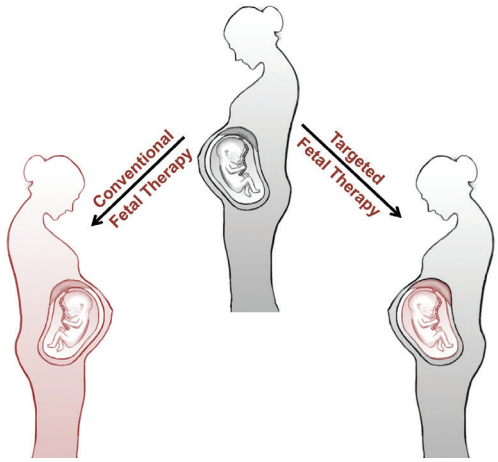

Figure 1. *The hypothesis of targeted fetal drug delivery. With conventional fetal drug therapy, maternal drug administration leads to substantial maternal drug concentrations with some transplacental transfer of drug to the fetus. Targeted fetal therapy can increase the percentage of drug reaching the fetus and reduce the off-target maternal concentrations of the medication.*

Methods

A modified solvent displacement method was used to prepare digoxin-loaded nanoparticles.[5] PEGylated poly(lactic-*co*-glycolic acid) polymers (Resomer® RGPd5055 or RGPd50105) were dissolved together with digoxin in tetrahydrofuran at theoretical drug loading values of 5 and 10% prior to nanoprecipitation in purified water.

Particle size and polydispersity index (PDI) were determined by dynamic light scattering; the zeta potential (ζ) was determined by laser Doppler velocimetry. The kinetics of drug release from the nanoparticles was determined *in vitro* under sink conditions in a well-stirred phosphate buffered salt solution (PBS) at pH 7.4 and 37°C. Aliquots were placed in centrifugal filters to quantify the digoxin released from the nanoparticles at each time point. HPLC was employed to determine encapsulation efficiency and drug release.

BeWo b30 cells, an *in vitro* model of human placental trophoblast cells representing the rate-limiting barrier for maternal-fetal transfer, were grown on Transwell™ inserts following previously established protocols.[6] Trophoblast cell monolayer growth was monitored by transepithelial electrical resistance measurements. The transport of digoxin alone was compared with the transport of digoxin-loaded nanoparticles, and the apparent permeability (P_e) of digoxin across the cell monolayer was calculated as described previously.[4]

Results and Discussion

The physicochemical properties of digoxin-loaded nanoparticles are shown in Table 1. Excellent encapsulation efficiency (greater than 99%) was observed with particle sizes ranging from 64 to

Table 1. Characteristics of digoxin-loaded polymeric nanoparticles.

Polymer (Drug Loading)	Size (nm)	PDI	ζ (mV)	Encapsulation Efficiency (%)
RGPd50105[a] (5%)	64 ± 0	0.19 ± 0.00	–14 ± 14	>99.9[b]
RGPd50105 (10%)	84 ± 0	0.25 ± 0.02	–9 ± 11	99.7 ± 0.0
RGPd5055[c] (5%)	123 ± 1	0.22 ± 0.01	–48 ± 2	>99.9[b]
RGPd5055 (10%)	124 ± 1	0.22 ± 0.01	–47 ± 3	99.4 ± 0.1

[a] Diblock copolymer of 50:50 poly(D,L-lactide-*co*-glycolide) containing 10% polyethylene glycol.
[b] The amount of unencapsulated digoxin was below the limit of detection.
[c] Diblock copolymer of 50:50 poly(D,L-lactide-*co*-glycolide) containing 5% polyethylene glycol.

124 nm. In the *in vitro* drug release study, no burst release was observed, which also confirmed the high encapsulation efficiency values determined previously. Gradual release was observed, with 41 ± 1% released in the first 24 h (see Figure 2).

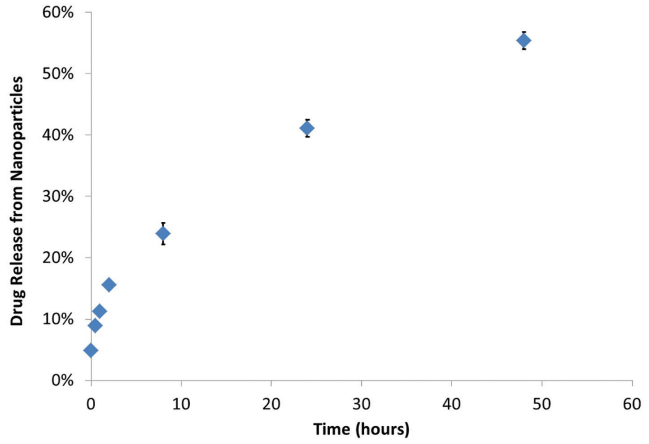

Figure 2. *Release of digoxin from RGPd50105 nanoparticles (10% theoretical drug loading) at sink conditions in phosphate buffered salt solution (pH 7.4) at 37°C. The error bars represent the standard deviation (n = 3).*

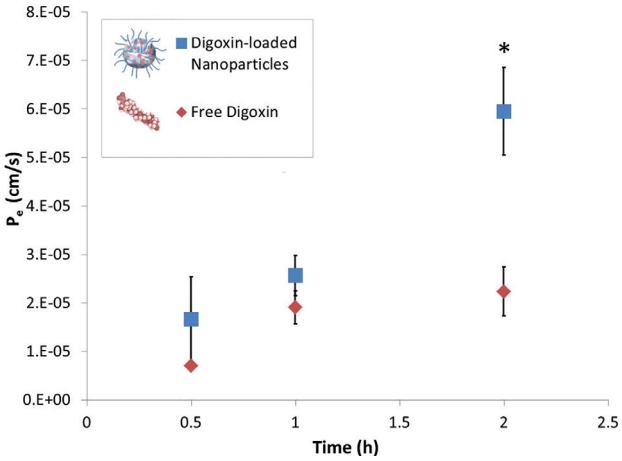

Figure 3. *Apparent permeability (P_e) of digoxin across BeWo b30 cell monolayers in the apical (maternal) to basolateral (fetal) direction. *The permeability of digoxin was significantly higher ($P < 0.05$) when formulated in nanoparticles compared with the free drug.*

The transport of drug in the apical-to-basolateral direction across the BeWo b30 cell line represents drug transfer in the maternal-to-fetal direction. Figure 3 shows that the transplacental transport of digoxin was greater when the drug was formulated in RGPd50105 nanoparticles (10% theoretical drug loading) compared with the transport of the drug alone, presumably due in part to decreased P-glycoprotein-mediated efflux of nanoencapsulated digoxin. Future studies will investigate the influence of these nanoparticles on digoxin efflux mechanisms.

Conclusion

A novel preparation of digoxin-loaded nanoparticles was successfully developed. Greater than 99% encapsulation efficiency was achieved, and the nanoparticles enhanced the transport of digoxin across an *in vitro* model of human placental trophoblasts. Sustained release of digoxin from this preparation may offer great potential to improve fetal cardiovascular therapy. The next steps to develop nanoparticles targeted to the fetus are underway.

Acknowledgements

Sanaalarab Al Enazy is thanked for the artwork in Figure 1. This research was supported in part by NIH grant K12HD052023. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

References

1. Rosenberg, AA, Galan, HL. Fetal drug therapy, Pediatr. Clin. North Am. 44: 113-135 (1997).
2. Fesslova, V, Mongiovi, M, Pipitone, S, Brankovic, J, Villa, L. Features and outcomes in utero and after birth of fetuses with myocardial disease, Int. J. Pediatr. 2010: 628451 (2010).
3. Ward, RM. Pharmacology of the maternal-placental-fetal-unit and fetal therapy, Prog. Pediatr. Cardiol. 5: 79-89 (1996).
4. Ali, H, Kalashnikova, I, White, MA, Sherman, M, Rytting, E. Preparation, characterization, and transport of dexamethasone-loaded polymeric nanoparticles across a human placental *in vitro* model, Int. J. Pharm. 454: 149-157 (2013).
5. Beck-Broichsitter, M, Rytting, E, Lebhardt, T, Wang, X, Kissel, T. Preparation of nanoparticles by solvent displacement for drug delivery: A shift in the "ouzo region" upon drug loading, Eur. J. Pharm. Sci. 41: 244-253 (2010).
6. Bode, CJ, Jin, H, Rytting, E, Silverstein, PS, Young, AM, Audus, KL. *In vitro* models for studying trophoblast transcellular transport, Methods Mol. Med. 122: 225-239 (2006). ■

Articles and Websites of Interest in Animal Models of Diseases, Cross-Species Comparisons, and "One Health"

Compiled and Edited by Dr. Terry Bowersock[1] and Prof. David Brayden[2]

Humans and dogs both develop diffuse large B-cell lymphoma—it is the most common lymphoma subtype in humans and one of the most common cancers in dogs. In one study,[1] canine and human B-cell lymphomas were compared by examining molecular similarities and differences between dogs and humans. As in humans, dog tumors occur spontaneously, rather than being created genetically as in mice. Dogs are also good models because they share the same environment as humans, so it is possible to examine shared risk factors. Veterinarians treating dogs for lymphoma can offer clinical trials to client patients similar to those done in humans. This can facilitate new drug development that can benefit both dogs and humans. Molecular analyses of canine and human tumors found similar gene expression profiles, thereby paving the way for future studies.

In-stent stenosis (ISR) is a major limitation following revascularization procedures. A porcine model of ISR was developed to investigate the outcomes of a novel drug-eluting balloon (DEB) in an ISR setting.[2] Bare metal stents were inserted into major coronary arteries in pigs, followed by time for neointimal growth to develop. Following repeat angiography, animals were treated with one of four treatments, including bare angiography catheter, paclitaxel treated, Pantera Lux™ treated, and commercial SeQuent balloon inflation. After another period of time, animals again underwent angiography and then were sacrificed for histopathological evaluation. All DEB groups showed delayed vascular healing, including fibrin deposition and neointimal cell vacuity. This study showed that investigation of DEB in a porcine model of ISR is feasible and more accurately depicts human disease. The magnitude of neointima suppression is lower than that observed in nondiseased animal models and is accompanied by delayed vascular healing.

Microrobots were evaluated as a tool for minimally invasive intraocular surgery and to demonstrate mobility and controllability inside the living rabbit eye.[3] Mobility and controllability were examined in different media including vitreous, balanced salt solution, and silicone oil. The electromagnetic system of the microrobots allowed for precise control over a workplace that covers the posterior eye. The system allowed for rotation and translation of the microrobot in different media inside the eye. Introduction of untethered mobile microrobots into the vitreous can enable sutureless and precise ophthalmic procedures. Potential applications are targeted drug delivery for maculopathies such as age-related macular degeneration, intravenous deployment of anticoagulation agents for retinal vein occlusion, and mechanical applications such as manipulation of epiretinal membrane peeling. The technology has the potential to reduce the invasiveness of ophthalmic surgery and assist in the treatment of a variety of ophthalmic diseases.

Pediatric drug development is restricted by biological, clinical, and formulation challenges of an age-based population. A primary shortcoming of the development of new drugs is the inability to accurately predict the effect of aging over time for children that affect pharmacokinetics (PK) using preclinical animal models. Roth *et al.* performed a proof of concept study to investigate the potential of using juvenile pigs to serve as surrogates for children during PK testing of drugs.[4] Pigs were dosed orally with rifampin, and plasma samples were analyzed over time. Porcine PK parameters were determined and contrasted with published rifampin PK data in human adults and children. Results indicated significant similarities in dose-normalized absorption and elimination parameters between pigs and humans. Furthermore, age-related changes observed in porcine PK parameters were consistent with ontogenic changes reported for human PK. These results demonstrate the potential utility of the juvenile porcine model for predicting human pediatric PK for rifampin. Utilization of juvenile pigs during formulation testing may provide an alternative approach to expedite reformulation efforts during pediatric drug development for molecules with straightforward PK.

Osteoarthritis (OA) is the most common musculoskeletal disease, affecting millions worldwide. It develops slowly over time, resulting in joint failure with loss of cartilage, inflammation of synovia, subchondral bone sclerosis, cyst formation, osteophytosis, loss of range of motion, and pain. The purpose of animal models of OA is to reproduce the progressive nature of damage in a controlled manner so that there are opportunities to modulate and monitor symptoms, and new therapies can be identified. A review by Teeple *et al.* discusses strengths, weaknesses, and considerations (including a tabular format) for common animal models of OA.[5] Methods of induction of OA are reviewed and addressed, including surgical, chemical, and transgenic means. Means of assessment including imaging as well as molecular biomarkers are also addressed in addition to

[1] Zoetis, LLC (formerly Pfizer Animal Health), U.S.A.
[2] University College Dublin, Ireland.

the pain, function, and gait parameters. As our understanding of the pathophysiology of OA improves, animal models can be adjusted and improved as well.

A study by Elsaid *et al.* provides an example of one *in vitro* animal model using tissue to study joint pathophysiology. The objectives of this study were to evaluate cartilage diffusion and isolated chondrocyte association of micelles and liposomes and to determine the effect of cell-penetrating peptide (CPP) surface functionalization and extracellular matrix depletion on chondrocyte association and cartilage diffusion using bovine cartilage explants.[6] Micelles exhibited superior association with isolated chondrocytes compared with liposomes. Surface modification with CPP enhanced chondrocytes association of both nanocarriers, with 15 nm diameter micelles performing much better than 138 nm liposomes in penetrating articular cartilage.

A chinchilla model of nontypeable *Haemophilius influenza* (NTHI) induced otitis media was used to examine the efficacy of a transcutaneous immunization (TCI) using a novel chimeric immunogen that targeted two critical adhesions expressed by NTHI.[7] Otitis media was induced in animals first, followed by TCI by rubbing vaccine formulations on hydrated pinnae. Within seven days of the primary vaccination, a significant reduction in both the mucosal biofilm and clinical signs of otitis media were detected in animals that had received the experimental TCI vaccine with adjuvant. The mechanism for rapid disease resolution involved efflux of activated dermal dendritic cells from the pinnae after TCI, secretion of factors producing CD4 T cells, induction of polyfunctional IFN-gamma and IL-17 producing CD4 T cells, and secretion of host defense peptide within the middle ear. These data support TCI as a therapeutic intervention against experimental NTHI-induced otitis media. Note that this article is from a specific issue of the journal *Vaccine* dedicated to the papers presented at the Skin Vaccination Summit 2011, which focused on research and development of cutaneous vaccination.

Until recently, the role of B cells in transplantation was thought to be restricted to producing antibodies that have been clearly shown to be deleterious in the long term, but in fact, B cells are also able to produce cytokine and to present antigen. Their role as regulatory cells in various pathological situations has also been highlighted, and their role in transplantation is beginning to emerge in animal, and also in human, models. A review by Chesneau *et al.* summarizes the different studies in animals and humans that suggest a B-cell regulatory role in the transplant tolerance mechanisms.[8]

Zoobiquity

There is much to learn about disease by exploring interspecies differences in their origin and expression. Since humans and animal species get many of the "same" diseases, the premise for zoobiquity is that by understanding disease processes in animals, we can better identify appropriate therapeutic targets in humans. In the book *Zoobiquity*, authors Barbara Natterson-Horowitz and Kathryn Bowers explore this topic.[9]

On their website (zoobiquity.com), the authors of *Zoobiquity* illustrate this evolving scientific discipline with the following examples:

- Golden retrievers get breast cancer. So do jaguars, kangaroos, and beluga whales.
- Siamese cats and Dobermans get OCD. Many are on Prozac.
- Canaries, fish, and even Yorkie dogs faint when they're stressed out.
- Mares can become nymphomaniacs.
- Dinosaurs suffered from brain cancer, gout, and arthritis.
- Koalas catch Chlamydia. Rabbits get syphilis.
- Reindeer seek out narcotic escape in hallucinogenic mushrooms.
- Gorillas experience clinical depression and eating disorders.
- There are eating disorders in female swine. When under severe social stress, some will exhibit anorexia and the corresponding physiological sequelae, such as hair loss and cessation of oestrus cycling. In some cases, they will starve themselves to death.

Zoobiquity has become an issue actively examined within the human and veterinary medical communities. This book reflects one step in this process. In fact, the third conference on this topic was held on November 2, 2013, in New York City, where there was a side-by-side comparison on topics such as**:**

- Invasive breast cancer in an 8-year-old Golden Retriever, 19-year-old Amur tiger, and 57-year-old psychotherapist
- Eating disorder (self-induced vomiting) in a 15-year-old Beluga whale and 19-year-old collegiate gymnast
- Canine cognitive dysfunction in an 11-year-old French poodle and Alzheimer's disease in a 63-year-old literature professor
- Degenerative myelopathy in a 10-year-old Boxer dog and ALS in a 44-year-old lacrosse coach

The hope is that the concept of zoobiquity will provide an integrated, interdisciplinary approach to physical and behavioral health challenges. For those interested in exploring this further, there is a series of lectures that can be obtained from Youtube (www.youtube.com/user/Zoobiquity) covering topics such as:

- Do animals get high?
- Do animals get breast cancer?
- Do animals get the flu?
- Animal eating disorders
- Animal STDs
- Animal versus human infertility
- Animal versus human obesity
- Heart disease in humans versus animals
- Cancer in humans versus animals

References

1. Richards, KL, Motsinger-Reif, AA, Chen, HW, Fedoriw, Y, Fan, C, Nielsen, DM, Small, GW, Thomas, R, Smith, C, Dave, SS, Perou, CM, Breen, M, Borst, LB, Suter, SE. Gene profiling of canine B-cell lymphoma reveals germinal center and postgerminal center subtypes with different survival times, modeling human DLBCL, Cancer Res. 73: 5029-5039 (2013).

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2. Joner, M, Radke, PW, Byrne, RA, Hartwig, S, Steigerwald, K, Leclerc, G, Wittchow, E. Preclinical evaluation of a novel drug-eluting balloon in an animal model of in-stent stenosis, J. Biomater. Appl. 27: 717-726 (2013).
3. Ullrich, F, Bergeles, C, Pokki, J, Ergeneman, O, Erni, S, Chatzipirpiridis, G, Pané, S, Framme, C, Nelson, BJ. Mobility experiments with microrobots for minimally invasive intraocular surgery, Invest Ophthalmol Vis. Sci. 54: 2853-2863 (2013).
4. Roth, WJ, Kissinger, CB, McCain, RR, Cooper, BR, Marchant-Forde, JN, Vreeman, RC, Hannou, S, Knipp, GT. Assessment of juvenile pigs to serve as human pediatric surrogates for preclinical formulation pharmacokinetic testing, AAPS J. 15: 763-774 (2013).
5. Teeple, E, Jay, GD, Elsaid, KA, Fleming, BC. Animal models of osteoarthritis: Challenges of model selection and analysis, AAPS J. 15: 438-446 (2013).
6. Elsaid, KA, Ferreira, L, Truong, T, Liang, A, Machan, J, D'Souza, GG. Pharmaceutical nanocarrier association with chondrocytes and cartilage explants: Influence of surface modification and extracellular matrix depletion, Osteoarthritis Cartilage 21: 377-384 (2013).
7. Novotny, LA, Clements, JD, Bakaletz, LO. Kinetic analysis and evaluation of the mechanisms involved in the resolution of experimental nontypeable *Haemophilus influenzae*-induced otitis media after transcutaneous immunization, Vaccine 31: 3417-3426 (2013).
8. Chesneau, M, Michel, L, Degauque, N, Brouard, S. Regulatory B cells and tolerance in transplantation: From animal models to human, Front Immunol. 4:497 (2013).
9. Natterson-Horowitz, B, and Bowers, K. Zoobiquity: The Astonishing Connection Between Human and Animal Health, Vintage Books: New York (2013). ■

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July 13

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A Conversation with Sandy Florence

Alexander "Sandy" Florence

The CRS Foundation has named its 2014 postdoctoral fellowship in honor of Alexander "Sandy" Florence, whose career spans work as a university researcher, teacher, dean, advisor, and author, as well as service to the Controlled Release Society as president in 2002–2003 and, since 2008, as a reviewer of the CRS Foundation postdoctoral fellowships.

The CRS Foundation asked Dr. Florence to share perspectives on his career as well as the current and future relevance of delivery science.

Q *What advice would you give today's young scientists?*

A I hesitate to give advice, as I see so many young scientists who have rapidly made their mark with their work and careers in academia, industry, or the wider world. The most I would say is that we have to enjoy our work: research might initially be a means to an end, but being a scientist is a state of mind, if you like, looking at problems from a special perspective, asking "why?" "how?" "could it be this?" and "what would happen if?" We need more people with a scientific approach to be more active in politics. I would advise young scientists to read the essays of great scientists such as the immunologist Peter Medawar, whose two popular books are *The Art of the Soluble* and *Advice to a Young Scientist*, and the physicist Richard Feynman, whose collection *The Pleasure of Finding Things Out* speaks for itself. He points out the difference between knowing the name of something and knowing about it. The French physicist Pierre-Gilles de Gennes reminds us all that research does not need to have an immediate application (as many funding bodies now insist), saying, "it was not by perfecting the candle that electricity was developed." Few professions can match the excitement (and sometimes disappointment) of scientific research, and while eureka moments are few and far between, the thought that one has been the first to see a new crystal form, to see a new lipidic aggregate, or to create a new drug vector can set the adrenaline flowing.

Postdoctoral fellowships are important to explore topics outside one's original work. I had the good fortune to have had two. The first was in 1965–1966 at the University of Strathclyde with the late Peter Elworthy, who was my Ph.D. supervisor. Then I was appointed a lecturer in pharmaceutical chemistry, and I could have stayed put (as I actually did later), but Peter encouraged me to take a sabbatical to work with Karol Mysels in the basic science laboratories of Reynolds Tobacco Company in Winston-Salem, North Carolina. It was basic research, indeed, studying the shrinking of bursting soap films. This introduced me to new experiences: there were new colleagues to work with, new topics, and a freedom to explore new ideas. It was a breath of fresh air, and it was good for me to be out of my old environment, where I had been a student and postgraduate and postdoc. I returned to my lectureship with a new perspective to my work. I also had seen on visits how U.S. institutions at the time organised their research and teaching, and this allowed me to return to base with the knowledge that I had seen things done differently and that they worked: useful years later when I became head of a department in 1975 and dean of a school in 1989 and a great antidote to those colleagues who say this and that "can't be done."

Take all the opportunities offered to you. Going to meetings, perfecting presentation techniques, opening yourself to new ideas, and finding out where your research fits in the grand scheme of things are essential. It is sometimes wise not to enter "crowded" fields. My first major scientific meeting was the American Chemical Society in 1968, and I was awed by its size and diversity compared with British meetings of the time. I met others doing similar work but also scientists in widely different areas. It was exciting to meet those whose names I had only seen on papers. The international community of today knows few boundaries, and modern communication allows us to interact with people wherever they are without being in their laboratories.

Teach whenever possible. I have always considered teaching and research to be symbiotic, and I looked askance at those colleagues who protested that their modest teaching load was eating into their time for research. Science is about exposition and sharing, especially in this overcompetitive world. To be able to discuss our science with enthusiastic students (at all levels) is a great stimulus, forcing us to know the wider context of our work. I have more than once realized the real meaning of a concept I had been teaching for some time during a lecture. Sometimes a naïve question from a student can be the catalyst for a whole new direction in research.

Find people and organizations that support you. I have been fortunate to have colleagues who have supported me. First, of course, I could have done very little without the Ph.D. students and postdocs and colleagues that I have had, especially as I have combined research and teaching with administration for the best part of my career. I was encouraged to get involved in CRS by Richard Guy, Kinam Park, Vincent Lee, Robert Gurny, and others—great scientists and friends. As president of CRS, I became involved with some of the international chapters, reminding me of the tremendous enthusiasm for the science that binds us together. Through my work with CRS I had the opportunity to share a little influence. I have learned so much from others, and it

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gives me great pleasure to pass it on. Really good colleagues find out what you can do and then encourage you. I, in turn, have tried to do that in my own career, which from the beginning was far from being planned. *Carpe diem*.

Q *What do you find most promising in the present and future of delivery science?*

A **The drug and delivery combination is more important than it ever was.** Molecules for delivery are becoming more complex. The larger the molecule, the greater the problems. "Conventional" dose forms will be the mainstay for many drugs, but there are huge challenges for the future if we are going to make headway with many cancers or with the concept of personalized medicine. This is not a genomics issue alone, as we cannot treat patients who have been selected for treatment as a result of their genetic profiles with standard medicines. We need *personalized medicines*, that is, more specific, targeted, adaptable, and tunable dose forms. The drug and delivery combination, especially when modifying adverse reactions through enhanced ligand-encouraged targeting, is one way forward. But in spite of many successes with nanotechnology in the laboratory (often in small animals), we have not made the impact in the clinic that 40 years of research would suggest. Some amazing structures have been created. But because of the singular interaction between drugs and such nanocarriers, several platforms are often needed for different active molecules. The search for a more universal platform is perhaps necessary.

"If we don't change direction, we'll end up where we're going." This Chinese proverb is particularly apt for pursuing advances in drug delivery. We need to embrace diversity in disciplines, functions, and organizations. Diverse work is important with scientists of all persuasions, where no one is in a silo. Some of the most promising platforms for the right drug, dose, and release rate will be successful with combined expertise from chemical engineers, polymer chemists, pharmaceutical scientists, toxicologists, drug delivery scientists, bioengineers, and biochemists, many part of the CRS family. There are exciting techniques and technologies to help progress now. I'm thinking of 3D printing modalities for producing on-demand delivery systems with accurate and tailored dosages, new compression techniques to form microtablets, microfluidic technology, and micropumps to administer minute doses as often required in pediatric medicine. One area where we could really improve our research in novel systems is through better choice and standardization of cell and animal models on which most initial results are based and then exploring more closely the issue of scaling in the mouse-rat-man transition.

It is important for academia and industry to collaborate. There needs to be a commonality of agreement in what to take forward. Success in the transition to the clinic will probably only happen if we have an industrial partner that can take the product quickly into initial clinical studies and perhaps possesses a drug that requires enhancement. The trends with outsourcing by big pharma now mean that academic-industry collaborations may be more equal than sometimes they were before.

Success is on the horizon. The ultimate goal is to work together in our science, to promote the area as CRS does very well, whether we belong to academia or industry, within and across multiple disciplines to ensure we can achieve a complex drug and delivery combination that optimally releases the correct dose at the target site at the right time with minimal risk in patients. Nanotechnology has promised much in this regard, but has often failed to deliver on the promise. We have to be honest and be aware that hype can reflect badly on our discipline and on us all. It is now nearly 40 years since nanosystems were proposed for pharmaceutical use by Peter Speiser and colleagues at ETH. It has certainly not been an easy task. To admit to complex reality is one more step to solving the problems that can be solved. As Medawar said, "if politics is the art of the possible, research is surely the art of the soluble." That's the exciting challenge for all of us. ■

Drug Delivery and Translational Research: New Special Issue Published

Vinod Labhasetwar, Editor-in-Chief

RNA Interference-Based Therapeutics and Diagnostics
Guest Editors: Dan Peer (George S. Wise Faculty of Life Science, Tel Aviv University, Israel) and Kenneth A. Howard (Department of Molecular Biology and Genetics, University of Aarhus, Denmark).

In 2006, the Nobel Prize in Medicine and Physiology was awarded to Andrew Fire and Craig Mello following the discovery that small double-stranded RNA (siRNA) mediated gene silencing by the process of RNA interference (RNAi). This remarkable recognition highlights the importance and immense implications of understanding and controlling cellular gene expression as a functional genomic tool and its potential exploitation as a therapeutic for treatment of diseases. A greater understanding of the RNAi mechanisms and rapid expansion of the field have resulted in the identification of a wide repertoire of RNAi triggers that engage at various levels of the RNAi cascade, collectively termed small interfering nucleic acids (siNA), which could be exploited as molecular medicines. MicroRNAs (miRNA), for example, are endogenous small noncoding RNA that control cellular gene expression whose deregulation can be associated with disease states; as a consequence, they have gained considerable attention as disease biomarkers and as potential therapeutic targets.

Despite the promise, the clinical translation of siNA therapeutics has proven challenging. The major hurdle that limits the translation of nucleic acid–based therapeutics and diagnostics from an academic concept to clinical translation is the lack of efficient and safe delivery strategies. This special *DDTR* issue addresses the fundamental biology of RNAi and its relevance in specific disease types with focus on miRNA in clinical diagnostics and therapeutics. The tutorial reviews and original manuscripts contained in this issue focus on state-of-the-art enabling delivery technologies for utilization of RNAi as a therapeutic modality and its clinical translation. The issue has contributions from global leaders in RNAi, nanomedicine, clinical diagnostics, and delivery science that reflect the broad nature of the field and the requirement for interdisciplinary research in order for RNAi-based therapeutics and diagnostics to reach their clinical potential.

About the Guest Editors

Prof. Dan Peer leads an NIH-funded lab in the Faculty of Life Science at Tel Aviv University. He is also the director of the Leona M. and Harry B. Helmsley Nanotechnology Research Fund and the director of the Focal Technology Area on Nanomedicines for Personalized Theranostics, a national

Dan Peer

nanotechnology initiative that includes 11 academic labs and a grant of $11.5 million to support this effort. He was recruited to Tel Aviv University from Harvard Medical School in 2008. His work was among the first to demonstrate systemic delivery of RNA molecules using targeted nanocarriers to the immune system, and he pioneered the use of RNAi for *in vivo* validation of new drug targets within the immune system.

Prof. Peer generated international recognition and collaboration in the areas of inflammatory bowel diseases and oncology. He received numerous awards; among them, he was recognized by the AAAS Excellence in Science program for young investigators and was recently awarded the Innovator (2010) and Breakthrough (2011, 2012, and 2013) awards from the Kenneth Rainin Foundation for his pioneering work in inflammatory bowel diseases.

His current interests include the generation of novel platforms for delivery of therapeutics and imaging payloads into specific cell types and the utilization of these nanocarriers also for *in vivo* discovery and validation of new drug targets. He is an editor of several books in the field of nanomedicine; a section editor of *Molecular and Cellular Therapies* (Springer); an associate editor of the *Journal of Biomedical Nanotechnology* and *BMC Biochemistry*; and on the editorial boards of the *Journal of Controlled Release* (Elsevier), *Nanotechnology* (IOP), *BioMEMs and Biomedical Nanotechnology* (Springer), and *Cancer Letters* (Elsevier). In addition, he is a guest editor of *Chemistry & Physics of Lipids, Journal of Controlled Release,* and *Advanced Drug Delivery Reviews*. He has more than 40 pending and granted patents. Some of them have been licensed to several pharmaceutical companies, and one is under a phase II clinical evaluation. In addition, based on his work, two spin-off companies were generated, LeukoBiosciences in the United States and Quiet Therapeutics in Israel, aiming to bring nanomedicine into clinical practice.

Kenneth Alan Howard

Kenneth Alan Howard is an associate professor and group leader at the Department of Molecular Biology at the Interdisciplinary Nanoscience Center, Aarhus University, Denmark. His team

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is based in a highly interdisciplinary setting, with research and teaching activities focused on advanced drug delivery, nanomedicine, RNAi, and inflammation. Dr. Howard is CEO of an Aarhus University spin-off company that provides delivery solutions for RNAi-based therapeutics. He received a Ph.D. in pharmaceutical science from the University of Nottingham, U.K., in 1995 and has held postdoctoral positions at the CRC Institute for Cancer Studies, University of Birmingham, U.K., and the School of Pharmacy, University of London. Dr. Howard is an active member of CRS, serving on the Board of Scientific Advisors (chair) and Nominating Committee and organizing a CRS educational workshop, "RNA Interference: Biology and Therapeutics." He is editor of the book *RNA Interference: From Biology to Therapeutics*, part of the CRS book series *Advances in Delivery Science and Technology*, published by Springer. He is on the editorial board of *DDTR* and on the advisory board of the journal *Molecular and Cellular Therapies*. ■

Top *DDTR* Articles from 2013

Here are the most downloaded articles from *DDTR* published in 2013, through issue 5.

Review Articles

Nasal Drug Delivery Devices: Characteristics and Performance in a Clinical Perspective—A Review, Per Gisle Djupesland, 3(1): 42-62

Strategies for Intranasal Delivery of Vaccines, Mehfuz Zaman, Saranya Chandrudu, and Istvan Toth, 3(1): 100-109

Cyclodextrin-Based Targeting Strategies for Tumor Treatment, Juan-Juan Yin, Zhi-Wei Zhou, and Shu-Feng Zhou, 3(4): 364-374

Multifunctional Nanomedicines: Potentials and Prospects, Udita Agrawal, Madhu Gupta, Rajesh S. Jadon, Rajeev Sharma, and S. P. Vyas, 3(5): 479-497

Research Articles

Drug-Resistant Breast Cancer Cell Line Displays Cancer Stem Cell Phenotype and Responds Sensitively to Epigenetic Drug SAHA, Shan Lu and Vinod Labhasetwar, 3(2): 183-194

Engineering Triiodothyronine (T3) Nanoparticle for Use in Ischemic Brain Stroke, Alexander Mdzinarishvili, Vijaykumar Sutariya, Phani K. Talasila, Werner J. Geldenhuys, and Prabodh Sadana, 3(4): 309-317

Immunotoxin Targeting CD133+ Breast Carcinoma Cells, John R. Ohlfest, David M. Zellmer, Jayanth Panyam, Suresh Kumar Swaminathan, Seunguk Oh, Nate N. Waldron, Shoko Toma, and Daniel A. Vallera, 3(2): 195-204

CriticalSorb™: Enabling Systemic Delivery of Macromolecules via the Nasal Route, Andrew L. Lewis, Faron Jordan, and Lisbeth Illum, 3(1): 26-32 ■

Drug Delivery Australia 2013

Ben Boyd, President, CRS Australian Local Chapter

"How Drug Delivery Research Is Shaping the Future of Pharmaceutics" (Drug Delivery Australia 2013) was the seventh annual meeting of the CRS Australian Local Chapter, held on October 24 and 25 at the Woolcock Institute for Medical Research, Sydney, Australia. The meeting featured invited and contributed talks and posters from a range of fields of delivery research, including lipid-based drug delivery, pulmonary delivery, anticancer drug delivery, veterinary, and drug development from a range of academic and industry speakers. The conference provided a forum for showcasing a range of research toward improving drug delivery across Australia and New Zealand, with international visitors from the United Kingdom, United States, Germany, Canada, Malaysia, and Hong Kong also participating. This year's meeting had an emphasis on translational pharmaceutics, and this was evident from the two plenary speakers: Prof. Ian Tucker (University of Otago, New Zealand), president of CRS, gave an insightful plenary talk on the conference topic. He gave a historical overview of how pharmaceutics has changed over time and how it has impacted on current pharmaceutical practices. On the second day, Dr. Igor Gonda (Aradigm Corporation, U.S.A.) gave an interesting overview on "Drug Delivery, Pharmaceutical Product Development and Translational Research."

Five papers were presented in a session on drug targeting. Dr. Mike Doschak (University of Alberta, Canada), president of the CRS Canadian Local Chapter, described his research on bone-targeting peptide hormones as a drug delivery strategy. Continuing the theme of targeted drug delivery systems, Dr. Mariusz Skwarczynski (University of Queensland) presented a novel delivery of peptide-based therapeutic vaccine against cervical cancer. A novel approach to deliver anticancer drug

Plenary speaker Igor Gonda delivering his lecture.

CRS President Ian Tucker with the 10 "poster on the podium" presenters.

Ian Tucker delivering one of the two plenary lectures.

using macromolecular ruthenium complexes was described by Prof. Martina Stenzel (University of New South Wales), while Dr. David Cipolla (Aradigm Corporation, U.S.A.) presented a pharma application of using liposomes as a drug delivery system for lung applications. Dr. Luojuan Hu (Monash University) ended the session with an interesting talk on intestinal lymphatic transport of a triglyceride mimetic prodrug.

The afternoon started with a session on lung delivery. The first speaker, Allan Tweedy (Chiesi Ltd., United Kingdom), presented an industrial talk on dry powder inhalers. His talk was followed by Prof. Peter Stewart (Monash University), who continued the inhalation theme, speaking about the development of carrier-free powder formulations for respiratory delivery. Dr. Brian Oliver

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Australian Chapter continued from page 19

Australian Local Chapter officers Tim Barnes, Daniela Traini, Ben Boyd, and Paul Young (not pictured: Pavla Simerska).

(Woolcock Institute) gave a more "pharmacological" point of view with his talk on understanding β_2 adrenoceptor desensitization in asthma, and this was followed by Assoc. Prof. Paul Young, who wrapped up the session with a discussion of the importance of bioequivalence for inhaled aerosols. After a welcome ice cream break, the last session of the first day focused on novel delivery approaches. Dr. Benedikt Hartwig (Evonik, Germany) presented the first talk, and he discussed how cutting-edge technologies for drug delivery could enhance bioavailability.

Prof. Ben Boyd (Monash University), president of the CRS Australian Local Chapter, gave an insightful presentation on using time-resolved SAXS to elucidate rapid solvent-mediated polymorphic transitions in solid state pharmaceuticals. This was followed by another interesting talk on using time-of-flight secondary ion mass spectroscopy (ToF-SIMS) to give new insight into therapeutic molecules and drug delivery systems, presented by Prof. Clive Prestidge (Ian Wark Institute, Adelaide). Dr. Jason D. McArthur (University of Wollongong) concluded the first day with a presentation on application of transdermal permeation enhancer technologies for the treatment of skin and soft tissue infections.

The second day of the DDA 2013 conference started with a great plenary talk from Dr. Igor Gonda. Igor gave an overview of the hurdles that need to be overcome to take a product from bench to market and how, sometimes, serendipity helps along the way. This session was followed by the highly anticipated three-minute poster on the podium presentations by 10 Ph.D. students, preselected the day before from their posters. Prof. Tucker did a great job at keeping them to time, and the students were all great: snappy and witty and a real pleasure to listen to! The winners of the two $1,000 cash contributions to attend the next CRS Annual Meeting & Exposition in Chicago, U.S.A., in 2014 were Nicolas Alcaraz (Monash University) and Jennifer Wong (University of Sydney), while the winners of the two $100 e-book vouchers were Joanne Du (Monash University) and Yang Chen (Woolcock Institute).

The particle engineering session started with Assoc. Prof. Patrick Spicer (University of New South Wales). He presented an interesting talk on engineering shaped and stimulus-responsive particles for consumer and pharmaceutical applications. We all learned a lot on the importance of choosing good shampoos! The session continued with Prof. Lee Yong Lim (University of Western Australia) on metrology of nanoparticles in biologically relevant media, followed by Dr. Tarl W. Prow (University of

The conference's 100 attendees gather at the waterfront prior to the Sydney Harbour dinner cruise.

Ben Boyd presents an e-book voucher to Yang Chen.

Joanne Du receives an e-book voucher.

Nicolas Alcaraz receives $1,000 toward attending the CRS Annual Meeting in Chicago.

Queensland) talking about the importance of morphology of microparticles to enhance topical drug delivery. Dr. Margaret Sunde (University of Sydney) followed these talks with a spin on fungi and showed some interesting applications of amphipathic self-assembling proteins. Judy Loo (University of Sydney) ended the session with a great talk on an application of noncytotoxic silver nanoparticles–polyvinyl alcohol hydrogels with antibiofilm activity designed as coatings for endotracheal tube materials. The last session of the conference focused on targeted delivery systems. Prof. Nico Voelcker (University of South Australia) started with a talk on drug delivery and theranostics from porous silicon for chronic wound healing. Dr. Shasha Rao (University of South Australia) followed with insight into silica-lipid hybrid carriers for optimizing oral delivery of lovastatin, and how self-emulsifying lipids and porous silica particles can have a synergic effect. Last but not least, Kristian J. Tangso (Monash University) concluded the DDA 2013 conference with a talk on nanostructures at oppositely charged surfactant-polymer interfaces as tailored release nanomaterials.

The excellent conference dinner, sponsored by Davies Collison Cave, was held on board the Sydney Princess Cruise around the amazing Sydney Harbor. The keenly sought after bottle of Penfolds Grange, generously donated by Davies Collison Cave, was presented to the winner by Dr. Paula de Bruyn, a partner at Davies Collison Cave. Everyone really enjoyed the evening event, which was praised by attendees and sponsors.

The meeting was strongly supported by our continuing sponsors: ATA Scientific, PerkinElmer, Davies Collison Cave, Shimadzu, Evonik, Monash Institute of Pharmaceutical Sciences, University of Technology Sydney–School of Pharmacy, and The Woolcock Institute for Medical Research. Their generous and continued support is much appreciated.

The election of office bearers was held at the chapter annual general meeting, and Ben Boyd, Daniela Traini, Paul Young, and Pavla Simerska were voted to continue in their roles from the previous year. Timothy Barnes was elected as treasurer.

In summary, this highly informative and efficient two-day meeting was a great success, with a number of collaborations arising from discussions and networking, as well as great exposure for the students involved. The quality of the meeting was again testament to the growing significance of drug delivery research across Australia. Plans for the next meeting in Melbourne in April 2014 in conjunction with the International Pharmaceutical Federation (FIP) are already underway (www.fip.org/pswc2014/). ■

Design and Industrial Development of Advanced Drug Delivery Systems: Annual CRS Italy Local Chapter Workshop

Bice Conti, University of Pavia

The annual CRS Italy Local Chapter workshop, "Design and Industrial Development of Advanced Drug Delivery Systems," took place in Pavia on November 21–23, 2013. The workshop was held in the terrific historical anatomic theatre of the ancient University of Pavia main building. This annual meeting is becoming a consolidated and meaningful scientific event, as confirmed by the excellent participation of scientists working on the different aspects of drug delivery.

The workshop gathered more than 150 participants, both from academia and from industrial areas. This year, the four workshop sessions were organized with two main lectures for each session followed by two long and detailed oral presentations selected from the submitted abstracts.

All the invited speakers were outstanding international scientists with different expertise in the field of advanced drug delivery systems. The workshop was aimed at highlighting the interdisciplinarity of the topic and exploring the translation of research to the pharmaceutical market. Finally, the workshop was managed in order to have a critical discussion on lectures of the selected speakers, which was intended as due diligence for ongoing research presented by young Italian team leaders in view of the international competition around translational science. For this purpose, four invited speakers were asked to join a panel of discussants. Short oral presentations were also organized into two dedicated poster sessions of 16 posters each.

Prof. Bice Conti (University of Pavia), CRS Italy Local Chapter vice-president, opened the workshop, welcoming the participants and underlining the workshop's purpose. Prof. Paolo Caliceti emphasized the goals of CRS and described CRS's upcoming activities, such as the 2014 CRS Annual Meeting & Exposition in Chicago.

Prof. Paolo Caliceti highlights the importance of CRS.

The workshop program started with the invited lectures "Albumin-Based Drug Delivery Systems in Oncology" by Dr. Felix Kratz (University of Freiburg, Germany) and "Liposomes in Cancer Drug Delivery: Improvements and Challenges" by Prof. Alberto Gabizon (Hebrew University of Jerusalem, Israel). The speakers reported the successful results on cancer therapy obtained with different advanced drug delivery systems that are in advanced clinical trials or have already reached the market. The invited lectures were followed by the oral contribution of Dr. Barbara Stella (University of Turin, Italy), "Squalenoyl Nanoassemblies: Past and Future," who reported the results of research so far carried out on squalene-conjugated anticancer drugs.

On November 22, Prof. Wim Hennink (University of Utrecht, The Netherlands) opened the sessions with the invited lecture "Polymeric Nanoparticles for Targeted Drug Delivery," which described advancements in designing smart polymeric nanosystems for active drug targeting.

The different aspects related to the advanced characterization of nanosized drug delivery systems and their interaction with biological structures were highlighted by three excellent invited lectures: "Studying Nanomedicine Biobarriers by Advanced Fluorescence Microscopy Methods" by Dr. Kevin Breackmans (University of Ghent, Belgium), "Monitoring the Interaction of Nucleolipoplexes with Model Membranes" by Prof. Piero Baglioni (University of Florence, Italy), and "Acute Infusion-Related Adverse Reactions to Particulate and Polymer Medicines: Structural Causes and Pathophysiological Modulators" by Prof. Moein Moghimi (University of Copenhagen, Denmark).

The morning and afternoon sessions were completed with four main selected oral presentations from Italian scientists: "Nanohydrogels Based on Modified Polysaccharides for Drug Delivery Applications" by Dr. P. Matricardi (University of Rome), "Development of pH Responsive and Multimodal Targeted Liposomes for Drug and Protein Delivery to Cancer Tissues" by Dr. S. Salmaso (University of Padua), "Nanomedicine for Central Nervous System: Polymeric Nanoparticles for Therapeutic Strategies in Neurological Disorders" by Dr. G. Tosi (University of Modena), and "The Use of Transglutaminase for Enzymatic Polymer Conjugation" by Dr. G. Pasut (University of Padua).

The Saturday session mainly focused on silica nanoparticles, with a stimulating introduction from invited speaker Dr. P. Decuzzi (Methodist Hospital Research Institute, U.S.A.):

Prof. Alberto Gabizon lectures on liposomes in cancer drug delivery.

"Shifting the '100 nm Paradigm.'" The lecture highlighted the relevance of nanoparticle shape, size, and composition. The second invited lecture, "Porous Silicon Nanomaterials to Revolutionize Drug Targeting and Delivery" by Prof. Helder Santos (University of Helsinki, Finland), described the potential of silica nanoparticles for drug delivery. The oral presentation "Chitosan/Montmorillonite Nanocomposites for Drug Delivery: Opportunities and Challenges" by Dr. Giuseppina Sandri (University of Pavia) related to interesting ongoing research on silica nanoparticles, while one by Dr. P. Bigini (Istituto Mario Negri, Milano), "Multimodal Imaging in Nanopharmacology: From Sub-cellular Organelles to the Whole Organisms," gave a brief but effective overview on imaging studies related to nanoparticles.

All scientific sessions were well coordinated and introduced by chairmen, and the panel of discussant scientists successfully promoted the discussion on all the oral presentations. The workshop program was a great success, as it was rich in scientific content. The invited lectures, oral presentations, and posters pointed out the state of the art, advancements, and future perspectives of different aspects in drug delivery. The interdisciplinary and translational aspects were well highlighted, and a critical and constructive discussion on presented research was extremely appreciated.

During the first workshop evening, a welcome cocktail was offered by sponsors. The workshop was supported by CRS and by several international and Italian sponsors, including QI, Evonik, Capsugel, Alfatest-Malvern, Buchi, MPenati Strumenti, Ufficio ECM University of Pavia, and Ordine Farmacisti Provincia di Pavia.

All abstracts and the webcast records of the lectures are available on the CRS Italy Local Chapter website. ■

Patent Watch

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

Selected U.S. patents involving controlled release or delivery and granted from January 1 through June 30, 2013, are briefly summarized. Although there is some overlap in the application areas, the patents have been loosely categorized into diversified products and pharmaceuticals. The reader can view full patent disclosures at the U.S. Patent database (http://patft.uspto.gov/).

Diversified Product Patents

Temperature Responsive Delivery Systems; U.S. Patent 8,349,363

An aqueous temperature responsive delivery system made with a polyoxypropylene–polyoxyethylene block copolymer and a cationic bioadhesive is disclosed for controlled topical delivery of cosmetic agents such as moisturizers or a variety of therapeutic agents.

Microporous Material; U.S. Patent 8,435,631

Microporous materials including thermoplastic organic polyolefin polymer, particulate filler, and a network of interconnecting pores with controlled volatile material transfer properties are described.

Methods for Control of Energy Delivery to Multiple Energy Delivery Devices; U.S. Patent 8,343,146

A system for controlled delivery of energy to multiple electrosurgical devices is described.

Magnetically Controlled Delivery of Subterranean Fluid Additives for Use in Subterranean Applications; U.S. Patent 8,424,598

A magnetic release trigger for controlled delivery of subterranean fluid additives to a well bore treatment fluid or a surrounding subterranean environment is disclosed.

Polyelectrolyte Complexes for Oil and Gas Applications; U.S. Patent 8,372,786

Polyanion/polycation complexes containing oil and gas field chemicals such as gel-forming agents, cross-linking agents, scale inhibitors, corrosion inhibitors, asphaltene or wax deposition inhibitors, hydrogen sulfide scavengers, hydrate inhibitors, breaking agents, and surfactants are applied for controlled release of the chemical or agent.

Liquid Crystals for Drilling, Completion, and Production Fluids; U.S. Patent 8,356,667

Fluids containing liquid crystal-forming surfactants, polymeric surfactants, polymers, graphite nanotubes, or Janus particles are disclosed for increased viscosity and/or decreased fluid loss in completion fluid, fracturing fluid, formation damage remediation, waste management, and other associated drilling operations including controlled release of wellbore additives.

Microcapsules with Functional Reactive Groups for Binding to Fibers and Process of Application and Fixation; U.S. Patent 8,404,345

A means of chemically binding microcapsules to fibers for smart textile materials is disclosed. Microcapsules can contain actives such a phase change materials, fragrances, essential oils, or antibacterials, and chemically binding adds more resilient functional properties to fabrics.

Methods and Compositions for Controlled Release Oral Dosage of a Vitamin D Compound; U.S. Patent 8,361,488

Stable, oral controlled release formulations of vitamin D are prepared by incorporating one or more vitamin D compounds into solid or semisolid mixtures of waxy materials.

Phospholipid Gel Compositions for Drug Delivery and Methods of Treating Conditions Using Same; U.S. Patent 8,361,496

This invention involves gel compositions for controlled- or sustained-release of bioactive agents in an animal for treatment of microbial infections of the skin, ear, or eye.

Pharmaceutical and Related Patents

Low Dose Controlled Release Tablet; U.S. Patent 8,465,770

A tablet-in-tablet design consisting of an inner nonactive tablet surrounded by a bioactive in a controlled release matrix is described for controlled low dose oral delivery in a suitable size and shape.

Therapeutic Calcium Phosphate Particles and Methods of Manufacture and Use; U.S. Patent 8,431,221

Novel calcium phosphate core particles for use as vaccine adjuvants, cores, carriers of biologically active material, and controlled release matrices for bioactive material are disclosed.

Abuse Resistant Drug Formulation; U.S. Patent 8,445,018

This invention discloses the use of glyceryl behenate in controlled release opioid multiparticulate formulations to limit opioid release when granules are crushed.

Controlled Release Hydrocodone Formulations; U.S. Patent 8,361,499

A solid oral controlled release dosage form of hydrocodone is disclosed. The dosage form comprises an analgesically effective amount of hydrocodone and controlled release material.

Pharmaceutical Composition Containing Gelling Agent; U.S. Patent 8,389,007

Polyethylene oxide is incorporated into an extended release oxycodone hydrochloride formulation as a gelling agent to impart viscosity unsuitable for use when crushed and mixed in an aqueous liquid.

Ultrasound Enhancement of Drug Release Across Nonionic Surfactant Membranes; U.S. Patent 8,435,558

Nonionic surfactant vesicles (niosomes) containing bioactive are administered via catheter to a site, and noisome structure is altered using ultrasound to mediate bioactive delivery.

Method for Pressure-Mediated Selective Delivery of Therapeutic Substances and Cannula; U.S. Patent 8,409,166

Methods and devices are described for pressure-mediated delivery of therapeutic substances to specific areas of organs. Following administration of inflatable balloons via a cannula and catheter, pressure is applied to target bioactive delivery to epithelial of subepithelial regions.

Contact Lens Drug Delivery Device; U.S. Patent 8,414,912

A drug-eluting contact lens for controlled delivery to the cornea is described.

Ophthalmic Devices for the Controlled Release of Active Agents; U.S. Patent 8,377,042

The invention provides devices suitable for insertion into the inferior or superior lacrimal canaliculus of the eye for controlled delivery of active agents.

Controlled Release Formulations; U.S. Patent 8,470,370

A method for controlled transdermal or transmucosal delivery using a biodegradable sucrose ester hydrogel is described.

Transdermal Analgesic Systems with Reduced Abuse Potential; U.S. Patent 8,440,220

A transdermal analgesic system consisting of both an analgesic and an antagonist is described in which the antagonist is contained under proper use but releases when subject to abuse.

System and Method for Transdermal Drug Delivery; U.S. Patent 8,404,255

This patent discloses a device and system for delivery of acid, base, lipid, or enzymes to the skin to create micropores for bioactive delivery.

Skin Permeation Device for Analyte Sensing or Transdermal Drug Delivery; U.S. Patent 8,386,027

A controlled abrasion device is first applied to the skin for a short time to provide a required level of permeability. This is followed by application of a bioactive delivery composition to the treated site.

Soluble, Degradable Poly(ethylene glycol) Derivatives for Controllable Release of Bound Molecules into Solution; U.S. Patent 8,404,222

PEG and related polymers with hydrolytically unstable linkages near the reactive end of the polymer are provided for conjugation to bioactives such as proteins, enzymes, and small molecules. These derivatives provide a suitable circulation prior to hydrolytic release of the bound molecule and can be used to impart improved solubility, increased size, slower kidney clearance, and reduced immunogenicity.

Gellan Gum Nanoparticles and Methods of Making and Using the Same; U.S. Patent 8,389,012

Gellan gum and polyethylene glycol nanoparticles for controlled delivery of anticancer agents are disclosed.

Absorbable Crystalline Copolyester-Based Bioactive Hydroforming Luminal Liner Compositions; U.S. Patent 8,383,140

High-molecular-weight crystalline, absorbable copolyesters dissolved in a polyether glycol derivative that transform into a tissue-adhering lumen lining are described for controlled release of bioactive payload at bacteria- and yeast-infected vaginal canals, esophagi, and arteries following angioplasty.

Cyclodextrin-Based Materials, Compositions and Uses Related Thereto; U.S. Patent 8,357,377

This patent discloses cyclodextrin-modified materials for carrying drugs and other active agents, such as nucleic acids. Inclusion complexes of cyclodextrin moieties bound to a polymer chain or linker and guest moieties bound to a linker or polymer chain create a cross-linked matrix. Therapeutic agents such as proteins, nucleic acids, and other bioactives are bound to the guest moiety and are released in controlled manner.

Cyclodextrin-Based Polymers for Therapeutics Delivery; U.S. Patents 8,404,662 and 8,399,431 and 8,389,499

These inventions disclose therapeutic cyclodextrin containing polymeric compounds modified to include bound drug substances, linker groups, and targeting ligands for controlled drug delivery. The cyclodextrin can also improve drug moiety solubility through formation of intramolecular inclusion complexes.

Buccal Drug Delivery; U.S. Patent 8,343,532

A lozenge composed of a gum, a noncrystallizing sugar or sugar alcohol, and other required excipients for controlled buccal delivery of a drug is disclosed.

Pharmaceutical Compositions of Rifaximin; U.S. Patent 8,383,151

This patent discloses a multilayer tablet with immediate and sustained release properties in a bioadhesive gastroretentive platform.

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Sustained Release Polymer; U.S. Patent 8,470,359

A polymer composed of poly(lactide), poly(lactide/glycolide), or poly(lactic acid/glycolic acid) segments bonded by ester linkages to ends of an alkanediol core unit is disclosed for controlled release of leuprolide acetate as a subcutaneous depot with three to six month release.

Coated Implantable Medical Device; U.S. Patent 8,469,943

A coated implantable catheter or stent consisting of a vapor deposited polyamide, parylene, or a parylene derivative coating for controlled release into the vascular system, esophagus, trachea, colon, biliary tract, or urinary tract is disclosed.

Amino Acid Derivatives and Absorbable Polymers Therefrom; U.S. Patent 8,461,372

This invention discloses a new class of hydrolysable amino acid derivatives for incorporation into absorbable polyester amides, polyamides, polyepoxides, polyureas, and polyurethanes for controlled drug delivery, tissue engineering, tissue adhesives, adhesion prevention, bone wax formulations, medical device coatings, stents, stent coatings, highly porous foams, reticulated foams, wound care, cardiovascular applications, orthopedic devices, surface modifying agents, and other implantable medical devices.

Solid Dose Micro Implant; U.S. Patent 8,454,997

A solid pharmaceutical composition consisting of a soluble or disintegratable inner matrix partially covered by a water-impermeable coating for controlled parenteral administration is described.

Bis-(α-amino)-diol-diester-containing Poly(ester amide) and Poly(ester urethane) Compositions and Methods of Use; U.S. Patent 8,445,007

This invention provides biocompatible, biodegradable compositions with properties that can be tailored for enzymatically controlled bioactive release. Compositions are suitable for use in drug-releasing biodegradable particles and implantable surgical devices, such as stents and implants.

Antimicrobial Nanostructured Hydrogel Web Containing Silver; U.S. Patent 8,431,151

A nanofiber hydrogel with controlled silver release is formed from thermoplastic polyurethane consisting of a polyhedral oligosilsesquioxane and polyethylene glycol and is described for use as wound dressing and anti-infective implantable medical devices for reconstructive oral and bone surgery.

Extended, Controlled-Release Pharmaceutical Compositions Using Charged Polymers; U.S. Patent 8,425,892

This invention discloses use of ionic polymers for extended delivery of ionic bioactives for up to 3.5 days.

Fiber-Reinforced Composite Rings for Intravaginal Controlled Drug Delivery; U.S. Patent 8,404,272

A composite ring consisting of a biocompatible matrix reinforced with absorbable/biodegradable fibers for controlled release of bioactive agent is disclosed. The device is intended for intravaginal, intraperitoneal, and subcutaneous delivery of bioactives such as contraceptives, antimicrobial agents, antiviral agents, or cancer drugs.

Partially Absorbable Fiber-Reinforced Composites for Controlled Drug Delivery; U.S. Patent 8,399,013

This invention describes a partially absorbable, fiber-reinforced composite in the form of a ring or a suture-like thread for controlled bioactive delivery in the vaginal canal, peritoneal cavity, scrotum, prostate gland, and ear loop or subcutaneous tissue. Bioactives include contraceptive, antimicrobial, anti-inflammatory, and/or antiviral agents as well as for cancer treatment.

Nano/Macroporous Bioactive Glasses Made by Melt-Quench Methods; U.S. Patent 8,389,018

This patent discloses methods and materials to provide nano/macroporous glasses with interconnected pores for enhanced bone regeneration, bioscaffolds, drug delivery devices, and filtration media.

Mesoporous Implants for Administering Substances and Methods of Producing Implants; U.S. Patent 8,361,491

Porous silicon subcutaneous implants are corroded away over months/year for sustained release of impregnated bioactive. In one embodiment, the implant may have holes filled with bioactive substance and closed with erodible doors of varying thickness for staggered release.

Sol-Gel Nanostructured Titania Reservoirs for Use in the Controlled Release of Drugs in the Central Nervous System and Method of Synthesis; U.S. Patent 8,343,514

This patent discloses a sol-gel nanostructured titania reservoir for controlled release of drugs to the brain for six months to three years. The pore size distribution, crystallite size, and crystalline phase distribution of anatase, brookite, and rutile can be fully controlled.

Drug Delivery Device; U.S. Patent 8,361,028

A drug delivery device with an incorporated gas generator is used with a ratchet mechanism to control drug release from a reservoir.

Controlled Release Composition Comprising a Recombinant Gelatin, U.S. Patent 8,357,397

This invention relates to a controlled release from the three-dimensional network of a cross-linked recombinant gelatin.

Polyurethane Elastomers; U.S. Patents 8,361,272 and 8,361,273

These patents disclose linear polymers obtained by reacting a polyethylene glycol, a polypropylene glycol, a diol, and a diisocyanate. These materials have suitable melt processing properties for bioactive loading, have good elasticity at body temperatures, and provide controlled release of the bioactive.

Long-Term Drug Delivery Devices with Polyurethane-Based Polymers and Their Manufacture; U.S. Patents 8,357,389 and 8,343,528

A reservoir drug delivery device/implant enclosed in polyurethane for releasing one or more drugs at constant rates for up to six weeks or more is disclosed.

Drug Depot Implant Designs and Methods of Implantation; U.S. Patent 8,357,388

This patent discloses a rod-shaped implant with anchoring barbs for controlled and directed delivery of therapeutic agents at precise tissue locations.

Fragmented Polymeric Compositions and Methods for Their Use; U.S. Patent 8,357,378

Extruded or mechanically disrupted hydrogels are employed as implants for controlled drug delivery. ■

People in the News

Compiled by Steven Giannos, Independent Consultant

Agile Therapeutics Appoints Dr. Elizabeth Ijeoma Onyemelukwe Garner as Chief Medical Officer

PRNewswire: January 8, 2014 – PRINCETON, NJ, U.S.A. – Agile Therapeutics, Inc., announced today the appointment of Elizabeth Ijeoma Onyemelukwe Garner, M.D., M.P.H., as chief medical officer effective January 6, 2014. Dr. Garner will be a member of Agile's executive management team and will lead the clinical research, drug safety, and medical affairs teams in the clinical development of the company's product pipeline.

"Elizabeth has prominent expertise in women's health and significant clinical development experience in the pharmaceutical industry, and we are very pleased to welcome her as a member of our executive management team," said Al Altomari, chief executive officer of Agile Therapeutics. "Her strong and highly relevant experience overseeing successful clinical trial programs and regulatory approval is the precise expertise we seek to advance our development programs of our innovative hormonal contraceptive treatment option and to drive the long-term growth."

Most recently, Dr. Garner served as vice president, women's health and preventive care, at Myriad Genetics Laboratories and managed the women's health clinical research, publication, and key opinion leader (KOL) development program, provided medical and scientific input to the company's marketing and new product strategies, and served as the company's media spokesperson. Prior to joining Myriad Genetics, she was senior director at Abbott (now AbbVie), where she managed the global phase III clinical development program in endometriosis. From 2007 to 2011, Dr. Garner served as director, vaccines clinical research, at Merck Research Laboratories, where she was a key clinical development leader for the human papillomavirus vaccine program and was instrumental in achieving successful outcomes on important supplemental submissions to the Food and Drug Administration.

"I am extremely pleased to be joining Agile Therapeutics, and I look forward to building upon the significant momentum of the clinical development programs and bringing them to a successful outcome," said Dr. Elizabeth Garner. "I look forward to helping the company fulfill its goal of offering women a safe and convenient hormonal option that represents real innovation and fills a critical void in women's contraception."

Prior to entering the pharmaceutical industry, Dr. Garner had several years of experience in academic clinical practice, research, and teaching at Harvard Medical School. She received joint M.D. and M.P.H degrees from Harvard Medical School and the School of Public Health. Dr. Garner did her residency in obstetrics and gynecology at Brigham and Women's/ Massachusetts General Hospitals, her subspecialty fellowship in gynecologic oncology at Brigham and Women's and the Dana Farber Cancer Institute, and received board certification in both general obstetrics and gynecology and gynecologic oncology. Dr. Garner is an author on numerous scientific papers published in peer-reviewed journals and has received many awards and honors.

Southern Research Institute CEO Arthur J. Tipton Named a Fellow in the National Academy of Inventors

Business Wire: December 10, 2013 – BIRMINGHAM, AL, U.S.A. – Southern Research Institute today announced that its president and CEO, Arthur J. Tipton, Ph.D., has been named a fellow of the National Academy of Inventors (NAI). Dr. Tipton was one of 143 innovators nominated and elected by their peers for outstanding contributions to innovation in areas such as patents and licensing, innovative discovery and technology, significant impact on society, and support and enhancement of innovation.

Tipton and the other new fellows will be inducted by Deputy U.S. Commissioner for Patents, Andy Faile, from the U.S. Patent and Trademark Office, during the 3rd Annual Conference of the National Academy of Inventors, on March 7, 2014, in Alexandria, Virginia, at the headquarters of the U.S. Patent and Trademark Office.

The 2013 class of NAI fellows represents 94 universities and governmental and nonprofit research institutes. Together, they hold more than 5,600 U.S. patents. Included are 26 presidents and senior leaders from research universities and nonprofit research institutes, 69 members of the National Academies, five inductees of the National Inventors Hall of Fame, six recipients of the U.S. National Medal of Technology and Innovation, two recipients of the U.S. National Medal of Science, and nine Nobel Laureates.

Tipton was named president and CEO of Southern Research Institute in 2013 and has 31 issued U.S. patents, 22 published U.S. patent applications, and numerous foreign equivalents, with more than 70 presentations and publications.

He has worked in the pharmaceutical and biotech industry for 25 years, participating in the growth aspects of three start-up companies. The company he founded in 2005 as a Southern Research Institute spin-out company—Brookwood Pharmaceuticals—was acquired by SurModics in August 2007 and then by Evonik in November 2011. At Evonik, Tipton served as senior vice president of the Birmingham Division and also led the company's global drug delivery program.

From 1993 to 2004, Tipton held roles of increasing responsibility at Durect Corporation, including that of senior vice president of

biodegradable systems, chief operating officer, vice president of its wholly owned subsidiary Southern BioSystems, and president of Birmingham Polymers. He was with Atrix Laboratories (now part of QLT Inc.) from 1988 until 1993, as manager of polymer science and senior polymer chemist.

Tipton serves on multiple boards including the Controlled Release Society (CRS), the Birmingham Venture Club, the Economic Development Partnership of Alabama Foundation, and the Biotech Association of Alabama (BioAlabama). He is a fellow of AIMBE and CRS and was awarded the CRS Distinguished Service Award in 2012. He serves as an external advisor to the Biomedical Engineering Department at University of Alabama at Birmingham (UAB) and volunteers as a mentor and judge in business plan competitions.

The NAI Fellows Selection Committee was comprised of 13 members including NAI charter fellows, recipients of U.S. national medals, National Inventors Hall of Fame inductees, members of the National Academies, and senior officials from the U.S. Patent and Trademark Office, the American Association for the Advancement of Science, the Association of University Technology Managers, and the National Inventors Hall of Fame.

Jade Therapeutics Elects Veteran Life Science Entrepreneur Dinesh Patel, Ph.D., to Its Board of Directors

PRNewswire: November 13, 2013 – SALT LAKE CITY, UT, U.S.A. – Jade Therapeutics, Inc., announced today the election of veteran life science entrepreneur and venture capitalist Dinesh Patel, Ph.D., to the company's board of directors, replacing SCI Institute associate director Dr. Greg Jones.

Dr. Patel cofounded the venture capital firm vSpring Capital (now Signal Peak Ventures) in 2000 and is currently partner emeritus. From 1985 to 1999, he served as cofounder, chairman, president, and CEO of TheraTech, Inc., a biotechnology company that he took public and eventually sold to Watson Pharmaceuticals for $350 million. He was also founder, chairman, president, and CEO of Ashni Naturaceuticals, and he cofounded and was chairman of the biotechnology company Salus Therapeutics. In addition, he served on the board of online medical records provider MediConnect Global, Inc., which was acquired in 2012 by Verisk Analytics for $350 million.

Dr. Patel is currently chairman of USTAR's governing authority board and has won numerous awards including the 2006 Utah Technology Council Hall of Fame Inductee, the U.S. Small Business Administration's Business Achiever Award, Entrepreneur of the Year (Mountain West Venture Group), and most recently BioUtah's flagship award, the Willem J. Kolff Lifetime Achievement Award.

"We are grateful to Greg for his important assistance to Jade from our company's earliest days, and we are indeed honored that Dinesh is now joining our Board," said Jade CEO Arthur Klausner. "Dinesh's wealth of experience in both drug delivery and ophthalmology represents a terrific fit for Jade as we continue to progress our locally administered, sustained-release drug products designed to treat significant ocular disorders such as corneal defects and ulcers. He is well known and respected both in the Salt Lake City area and nationally for his entrepreneurial and company-building achievements, and he has served on the boards of numerous start-up life sciences companies."

Said Dr. Patel: "Jade represents an attractive combination of proprietary, lower-risk products addressing unmet needs in potentially blinding ophthalmic conditions. I look forward to working with the company's board and management team to help bring these products to the patients who need them."

Neos Therapeutics, Inc., Announces the Appointment of Vipin K. Garg, Ph.D., as Chief Executive Officer and Board Director

Business Wire: October 22, 2013 – GRAND PRAIRIE, TX, U.S.A. – Neos Therapeutics, Inc. (Neos), a highly differentiated oral drug delivery company with an exciting portfolio of proprietary technologies and a pipeline of innovative controlled release (CR) products, announced today the appointment of Vipin K. Garg, Ph.D., to the role of chief executive officer, effective immediately. Dr. Garg succeeds Neos interim chief executive officer Alan Heller, who will continue serving as chairman of the Neos Board of Directors. Dr. Garg will also serve as a member of the Neos Board of Directors.

Dr. Garg has over twenty-five years of experience within the biotechnology and pharmaceutical industries in both technical and management positions. He has a proven track record of building and managing both private and publicly traded companies. Before joining Neos Therapeutics, he served as president and chief executive officer of Tranzyme Pharma (NASDAQ: TZYM), where he led the company's initial public offering in 2011 and its merger with Ocera Therapeutics (NASDAQ: OCRX), Inc., in July 2013.

Neos Therapeutics's chairman, Al Heller, stated, "I am excited to welcome Vipin to the Neos team. He brings to us a wealth of strategic, scientific, and industry experience. Vipin will work closely with the organization to obtain FDA approval of our existing pipeline and expand the use of our proprietary controlled release technologies to create additional CR orally disintegrating tablets and CR liquids to bring to market."

Prior to joining Tranzyme, Dr. Garg served as chief operating officer of Apex Bioscience, Inc. (now Curacyte AG of Munich, Germany), and held senior management positions at DNX Bio-Therapeutics, Inc., until its acquisition by Baxter Healthcare Corporation, Sunovion Pharmaceuticals, Inc. (formerly known as Sepracor Inc., now a subsidiary of Dainippon Sumitomo Pharma), and Bio-Response Inc. (acquired by Baxter Healthcare Corporation).

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Dr. Garg received his Ph.D. in biochemistry in 1982 from the University of Adelaide, Australia, and his M.S. from New Delhi, India, in 1978. He was a member of the U.S. presidential mission to India led by President Bill Clinton in March 2000. He is a past board member of the North Carolina Biotechnology Center and currently serves on the executive committee of CED (formerly the Council for Entrepreneurial Development). He was the recipient of the Ernst & Young Entrepreneur of the Year 2009 Award, Carolinas Region.

"I am delighted to join Neos Therapeutics," said Dr. Garg. "Neos has developed proprietary controlled release technologies. These technologies are being utilized to develop a pipeline of novel ADHD products that will advance significantly in the next 12–18 months. Building on the approval of a generic of Tussionex®, an extended release cough cold product developed utilizing the Neos technology and manufactured exclusively by Neos, the company is well positioned for growth. I look forward to working with the Neos team to expand the pipeline to additional opportunities including prescription, over-the-counter, and veterinary products in a wide range of therapeutic areas." ■

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In the News

Compiled by Steven Giannos, Independent Consultant

January

Living Proof Enters into a Global Strategic Partnership with Valeant Pharmaceuticals in Aesthetic Dermatology

Business Wire: January 8, 2014 – CAMBRIDGE, MA, U.S.A. – Living Proof, Inc., the innovative, technology-based beauty company, announced today that they have entered into a global venture with Valeant Pharmaceuticals International, Inc., to develop, distribute, and commercialize products for aesthetic dermatology that will be sold exclusively through Valeant's powerful direct-to-physician channel. The transaction is worth over $75 million in upfront and milestone payments, as well as a 60/40 profit split. The initial product development efforts in aesthetic dermatology will be based on Living Proof's proprietary, cross-linking polymer film technology, Strateris™, which reshapes the appearance of skin.

Strateris was invented by an interdisciplinary team of researchers and clinicians at Living Proof, led by Dr. Bob Langer, award-winning MIT Institute Professor; Dr. Betty Yu, an expert in transdermal drug delivery; and world-renowned dermatologists Dr. Rox Anderson of Harvard University and Dr. Barbara Gilchrest of Boston University. Funded by Polaris Partners, the discovery of this revolutionary technology has been in development for almost 10 years and has been tested on over 600 women. Inspired by the attributes of youthful skin, the scientists devised a breathable, flexible, and imperceptible film that can be worn all day to immediately reshape the appearance of skin. Strateris has core mechanical properties that are tuneable and could offer a diverse array of proprietary solutions to aesthetic dermatology challenges.

Valeant and Living Proof plan to launch the first product to leverage the Strateris platform technology at the March 2014 American Academy of Dermatology conference. This first application of Strateris technology was developed to address the effects of aging on the appearance of the face, notably to reduce the appearance of under-eye bags and smooth wrinkles caused by lax skin within one hour of application.

"By combining Living Proof's innovative R&D capabilities and entrepreneurial agility with Valeant's enormous expertise and global scale in aesthetic dermatology, together we have created a powerful commercial opportunity," explains Jill Beraud, CEO of Living Proof.

Impax and DURECT Sign a $63 Million Agreement to Develop and Commercialize DURECT's ELADUR® Pain Patch

Business Wire: January 7, 2014 – HAYWARD, CA, and CUPERTINO, CA, U.S.A. – Impax Laboratories, Inc. (NASDAQ: IPXL) and DURECT Corporation (Nasdaq: DRRX) announced today that they have entered into an agreement granting Impax the exclusive worldwide rights to develop and commercialize ELADUR®, DURECT's investigational transdermal bupivacaine patch for the treatment of pain associated with postherpetic neuralgia (PHN).

Under the terms of the agreement, Impax will pay DURECT an upfront fee of $2 million, with possible additional payments of up to $61 million upon the achievement of predefined development and commercialization milestones. If ELADUR is commercialized, DURECT would also receive a tiered royalty on product sales. Impax will control and fund the development program.

"We're pleased to be moving ELADUR back into development through this collaboration with Impax," stated James E. Brown, president and CEO of DURECT. "Existing patches used to treat PHN pain are limited by their 12 hour duration, followed by a rest period in which the patient is not to wear a patch for 12 hours. Episodes of break-through pain are frequently reported to occur during rest periods for existing patches. We share a vision with Impax to develop a patch that has the potential to reduce these episodes of break-through pain."

Michael Nestor, president of Impax Pharmaceuticals, added, "This agreement is another example of our commitment to building a strong brand pipeline through internal R&D and external business development. We are excited to collaborate with DURECT, as this product could, if approved, fit well with the capabilities of our neurology-focused specialty sales force."

ELADUR is an investigational transdermal drug patch intended to deliver bupivacaine for up to three days from a single application. DURECT has previously announced positive results for ELADUR from a 60 patient phase IIa clinical trial of patients suffering from PHN.

Oramed Receives Patent Allowance in Israel and Australia for Platform Technology in Oral Delivery of Proteins

PRNewswire: January 2, 2014 – JERUSALEM, Israel – Oramed Pharmaceuticals Inc. (NASDAQCM: ORMP) (www.oramed.com), a developer of oral drug delivery systems, announced today that it has received Notices of Allowance from the Israel and Australian patent offices. The patent, entitled "Methods and Compositions for Oral Administrations of Proteins," covers a core concept of the company's technology for the oral delivery of drugs and vaccines currently delivered via injection. The allowance in Israel marks the second from the Israel Patent Office in the past 30 days. Additionally, this is Oramed's second Australian patent allowance, following the grant of a different

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patent in May 2012. The patent has also been approved in Japan, China, Russia, and New Zealand.

Oramed Pharmaceuticals is a technology pioneer in the field of oral delivery solutions for drugs and vaccines currently delivered via injection. Established in 2006, Oramed's Protein Oral Delivery (POD™) technology is based on over 30 years of research by top research scientists at Jerusalem's Hadassah Medical Center. Oramed is seeking to revolutionize the treatment of diabetes through its proprietary flagship product, an orally ingestible insulin capsule (ORMD-0801) currently in phase 2 clinical trials on patients with type 2 diabetes (T2DM) under an Investigational New Drug application with the U.S. Food and Drug Administration, and with its oral exenatide capsule (ORMD-0901; a GLP-1 analog), with trials underway. Oramed is also moving forward with clinical trials of ORMD-0801 for the treatment of type 1 diabetes. The company's corporate and R&D headquarters are based in Jerusalem.

Marina Biotech and Mirna Therapeutics Amend License Agreement for the Development of MicroRNA-Based Therapeutics

Business Wire: January 2, 2014 – BOSTON, MA, and AUSTIN, TX, U.S.A. – Marina Biotech, Inc. (OTC Pink: MRNA), a leading oligonucleotide-based drug discovery and development company, and Mirna Therapeutics, Inc. (Mirna), a privately held biotechnology company pioneering microRNA (miRNA) replacement therapy for cancer, announced today that they have amended their license agreement regarding the development and commercialization of microRNA-based therapeutics utilizing Mirna's proprietary microRNAs and Marina Biotech's novel SMARTICLES liposomal delivery technology. Under terms of the amendment, Mirna paid certain prepayments to Marina Biotech and now has additional rights to its lead program, MRX34, currently in phase 1 clinical development for patients with unresectable primary liver cancer or metastatic cancer with liver involvement. In addition, under the terms of the license agreement, Mirna has optioned exclusivity on several additional miRNA targets. Further terms of the agreement were not disclosed.

"Mirna and Marina Biotech have enjoyed a successful, durable collaboration by leveraging the systemic delivery of our proprietary, double-stranded, miRNA mimics with the SMARTICLES delivery technology," said Paul Lammers, president and CEO of Mirna Therapeutics. "Amendment of the license agreement strengthens the potential medical and commercial value of MRX34 as the first miRNA mimic to enter the clinic in cancer and provides exclusivity for the use of SMARTICLES with other highly promising tumor suppressor miRNAs."

"We are extremely pleased with our ongoing relationship with Mirna as a forerunner in the human clinical development of microRNA-based therapeutics," stated J. Michael French, president and CEO of Marina Biotech. "We are also pleased about our ability to successfully close licensing transactions during the past year and a half, which has allowed us to keep the company moving forward during a difficult stretch. Although this transaction will not allow us to resume normal operations, I believe it will be sufficient to achieve certain tactical and strategic objectives over the next quarter. We have witnessed over the past several months increasing interest across the broader pharmaceutical sector in the application of our drug discovery engine to the development of nucleic acid–based therapeutics for rare and orphan diseases. We are excited about this increased awareness of our capabilities and hope to capitalize on these developments in the future."

Mirna Therapeutics, Inc. (Mirna) is a biotechnology company focused on the development and commercialization of miRNA therapeutics. The company has an intellectual property portfolio on the therapeutic use of miRNAs developed by its own scientists, as well as in-licensed from other institutions. Mirna's IP portfolio contains more than 300 miRNAs with applications in oncology and other diseases. Oncology-directed miRNAs include those that are key tumor suppressors in cancer, such as miR-34 and let-7, which have been shown to block tumor growth in a number of different preclinical animal studies. The company, founded in 2007 and located in Austin, Texas, has received significant funding from Sofinnova Ventures, New Enterprise Associates, Pfizer Venture Investments, and other private investors, as well as the State of Texas, both through the state's Emerging Technology Fund and from the Cancer Prevention and Research Institute of Texas (CPRIT). For more information, visit www.mirnarx.com.

Marina Biotech is an oligonucleotide therapeutics company with the broadest drug discovery platform in the sector, providing the ability to develop proprietary single and double-stranded nucleic acid therapeutics including siRNAs, microRNA mimics, antagomirs, and antisense compounds, including messenger RNA therapeutics. Additional information about Marina Biotech is available at www.marinabio.com.

December

APR Applied Pharma Research and Angelini Enter into an Exclusive Licensing Agreement for APR's Innovative Product in Acute and Chronic Wound Management

Business Wire: December 19, 2013 – ROME, Italy, and BALERNA, Switzerland – Angelini and APR announced today that they have entered into a strategic partnership to support and promote a novel and innovative product developed by APR for the management of a variety of wound conditions such as acute wounds, burns, and advanced ulcers including venous and pressure ulcers and diabetic foot ulcers. The product, characterized by acidic and super-oxidizing features in an easy-to-use formulation, acts by improving the functional conditions of the physiological wound-healing process, providing the healthcare professional and the patient with an effective, convenient, and patient-friendly treatment option.

The product has been developed based on APR's proprietary technology TEHCLO®, enabling the production of acidic and

super-oxidizing solutions containing free chlorine species, including stabilized hypochlorous acid in very high concentration (>95%).

APR was recently granted the European approval of the product under the name of Nexodyn®. Angelini is planning to launch it under the brand name Amuphase® to hit the advanced wound care Italian market.

"Our intention is to strengthen our position in the wound care therapeutic area through the offer of new, modern, and affordable solutions to healthcare professionals and patients, able to manage life-threating pathologies like diabetic foot and leg venous ulcers," says Fabio De Luca, general manager of Angelini Pharma Division, "and for this reason we are collaborating with APR to enlarge our portfolio launching AMUPHASE, a product that, we are sure, will ensure depth and ethical image to our hospital portfolio."

"We are very excited and pleased to partner with Angelini, a leading pharmaceutical company, on this opportunity. APR continues in its endeavors to develop innovative products for the patients and for the healthcare community," said Paolo Galfetti, CEO of APR. "The product is being investigated in a number of advanced wound conditions, including diabetic foot ulcers, given the highly recognized unmet medical needs in these therapeutic areas. The product is obtaining promising feedback from the experience in the clinic. These initial results encourage APR to look at strategic international markets, including the United States, key European countries, Latin America, and Asia. The advanced wound management market has been forecasted to increase at a compound annual growth rate of 5.7% over the next six years, increasing from a valuation of $3.1 billion in 2012, to hit a market value of $4.4 billion in 2019."

Depomed Acquires CAMBIA® (Diclofenac Potassium for Oral Solution) Migraine Medicine from Nautilus Neurosciences for $48.7 Million

PRNewswire: December 17, 2013 – NEWARK, CA, U.S.A. – Depomed, Inc. (NASDAQ: DEPO) today announced that it has acquired the United States rights to CAMBIA® (diclofenac potassium for oral solution) from Nautilus Neurosciences for $48.7 million. In addition, Depomed may pay Nautilus up to an additional $5 million based on the achievement of certain annual net sales milestones. CAMBIA is a nonsteroidal anti-inflammatory drug (NSAID) indicated for acute treatment of migraine attacks with or without aura in adults 18 years of age or older.

Benefits of CAMBIA acquisition:

- Bolsters Depomed's portfolio in pain and neurology, specifically strengthening the company's position with neurologists
- Secures CAMBIA, the only single-agent NSAID in the United States specifically indicated for migraine, and immediately increases Depomed's topline with annualized net sales run rate of approximately $18 million over the past 3 months
- Adds another growth product to Depomed, as CAMBIA total prescriptions in third quarter 2013 were up more than 30 percent over the same quarter last year
- Creates synergies with Gralise commercial efforts, as nearly 70% of CAMBIA prescriptions are written by neurologists and half of these prescribing neurologists are currently Gralise prescribers
- Increases the sales support for CAMBIA, moving from the current 35 sales reps with Nautilus to Depomed's existing 155 sales territories, reaching more of the target audience for the drug
- Secures a long term revenue stream with settled ANDA litigation and generic entry expected in January 2023

"CAMBIA, our third product acquisition in 18 months, is a unique and fast-acting treatment for migraine with long-term growth potential that is a great fit in our pain and neurology-focused portfolio," said Jim Schoeneck, president and CEO of Depomed. "Some of the capital secured in October 2013 from the sale of our royalties in type 2 diabetes assets is being put to work in this product acquisition that leverages our current infrastructure. We will continue to actively seek products that complement our pain and neurology portfolio and position us for a strong growth trajectory in the coming years."

CAMBIA is a powdered formulation of diclofenac potassium that is dissolved in liquid. It has a rapid onset and has demonstrated in clinical studies relief of the pain and associated symptoms of migraine, including nausea, sensitivity to light, and sensitivity to sound. It was launched in 2010.

Unilife Signs Agreement with Global Pharmaceutical Company Seeking to Use Ocu-ject™ to Deliver a Drug into the Eye

PRNewswire: December 16, 2013 – YORK, PA, U.S.A. – Unilife Corporation ("Unilife") (NASDAQ: UNIS, ASX: UNS) today announced the signing of an agreement with a global pharmaceutical company seeking to use the Unilife Ocu-ject™ ocular drug delivery system to deliver a target injectable therapy into the eye.

Unilife's Ocu-ject platform offers a breakthrough technology for the accurate and precise delivery of small dose volumes measured in microliters (µL) into the eye. Most ocular therapies for the treatment of conditions such as age-related macular degeneration, diabetic retinopathy, and diabetic macular edema are administered via intravitreal injection using a standard 1 mL tuberculin syringe and needle. The potential for gross dosing inaccuracy is inherent with such conventional devices, which can compromise the ability of the drug to fully comply with its regulatory labeling requirements. Ocu-ject provides a tenfold improvement in the precision of delivering doses as small as 10 µL, which helps pharmaceutical customers ensure compliance with dose requirements on the drug label.

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Mr. Alan Shortall, chairman and CEO of Unilife, said: "In tune with our commitment to address unmet needs within the pharmaceutical industry, we have created a new, significant drug delivery device category. Ocu-ject represents a game-changing delivery technology for ocular therapies, which is a large, fast-growing segment of the pharmaceutical market. We are pleased to have signed our first agreement for the Ocu-ject device platform, which is being pursued by a number of pharmaceutical companies seeking to maximize the clinical and commercial potential of approved and pipeline drugs that are targeted to treat a number of eye disorders. We look forward to serving these customers to address unmet market needs for the accurate, precise delivery of drugs to the eye."

Endo to Acquire Specialty Pharmaceutical Company NuPathe

PRNewswire: December 16, 2013 – MALVERN, PA, U.S.A. – Endo Health Solutions (Nasdaq: ENDP) today announced it has entered into a definitive agreement under which Endo will acquire NuPathe Inc. (Nasdaq: PATH) for $2.85 per share in cash, or approximately $105 million. In addition to the upfront cash payment, NuPathe shareholders will receive rights to receive additional cash payments of up to $3.15 per share if specified net sales of NuPathe's migraine treatment ZECUITY are achieved over time. Endo expects meaningful cost synergies from the transaction, which is expected to be accretive to Endo's adjusted diluted earnings per share within the first 12 months of closing.

ZECUITY, which was approved by the U.S. Food and Drug Administration (FDA) in January 2013 for the acute treatment of migraine with or without aura in adults, is the first and only FDA-approved prescription migraine patch. ZECUITY is a disposable, single-use, battery-powered transdermal patch that actively delivers sumatriptan, the most widely prescribed migraine medication, through the skin. ZECUITY provides relief of both migraine headache pain and migraine-related nausea (MRN). ZECUITY was approved based upon an extensive development program with phase 3 trials that included 793 patients using nearly 10,000 ZECUITY patches. In these trials, ZECUITY demonstrated a favorable safety profile and was effective at relieving migraine headache pain and migraine-related nausea two hours after patch activation.

"The acquisition of NuPathe enhances our branded pharmaceutical portfolio and is well aligned with our strategy of acquiring late-stage products for commercialization," said Rajiv De Silva, president and CEO of Endo. "We're excited about the opportunity to launch ZECUITY, a treatment that could be an option for millions of migraine patients, including those with migraine-related nausea. Following the close of the deal, we plan to launch ZECUITY in the first half of 2014 by leveraging our existing commercial expertise in pain and migraine management and the current infrastructure of our branded pharmaceuticals business overall."

Armando Anido, chief executive officer of NuPathe, stated, "Our team has worked very hard to develop products that we believe will provide significant clinical advantages over current treatments for patient populations facing diseases of the central nervous system. We believe this acquisition by Endo will increase the potential for ZECUITY to make a meaningful difference for patients we have worked so hard to serve."

QRxPharma Completes A$11.6 Million Capital Raising

PRNewswire: December 13, 2013 – SYDNEY, Australia, and BEDMINSTER, NJ, U.S.A. – QRxPharma Limited (ASX: QRX and OTCQX: QRXPY) today announced the successful completion of its share purchase plan (SPP) to existing shareholders raising A$4.1 million. The SPP was well oversubscribed, with over 550 applications received. The SPP was originally planned for A$2.5 million; however, given the volume of support from shareholders for the SPP, the company has elected to take A$1.6 million in oversubscriptions, for a total of A$4.1 million and representing 6,810,363 shares. This A$4.1 million represents 75% of total applications monies received under the SPP, and the company has scaled back all allocations under the SPP by 25% in determining the final allocations to all participating shareholders.

The SPP together with the company's recent placement to institutional and sophisticated investors, which raised A$7.5 million (announced on 13 November 2013), brings the total proceeds to A$11.6 million. All shares in the SPP will be issued at A$0.60 per share (same as the placement), which represents a 15.5% discount to the QRxPharma share closing price on 8 November 2013 (being the last day of trading of QRxPharma shares before the announcement of the placement and SPP).

"We are extremely encouraged by the strong support shown by our shareholders with the oversubscription of both the placement and SPP," said Dr. John Holaday, managing director and chief executive officer of QRxPharma. "Following our announcement on 11 December of the acceptance for review by the United States Food and Drug Administration (FDA) of our resubmitted New Drug Application (NDA) for immediate release MOXDUO, we are looking forward to significant milestones in the coming year. Assuming approval by the FDA in May 2014, we will launch immediate release MOXDUO, with Actavis, our U.S. commercialisation partner, into the US$2.5 billion acute pain prescription opioid market in the United States in the second half of CY2014," added Holaday.

Proceeds from the placement and the SPP will be used to fund operations through CY2014 inclusive of submitting regulatory filings in Europe, Australia, New Zealand, and Canada, and most importantly, assuming MOXDUO is approved in May 2014, provides the capital to initiate the launch of MOXDUO.

Morgans was the lead manager and sole book runner to the capital raising, Hawkesbury Partners acted as corporate adviser to the capital raising, and CIMB is acting as financial adviser to the company.

QRxPharma Limited is an Australian based, commercial-stage specialty pharmaceutical company focused on the development

and commercialisation of new pain management and abuse prevention products. Based on a development strategy that focuses on enhancing the clinical utility of currently approved compounds as well as bringing new products to market, the company's product portfolio includes both late and early stage clinical drug candidates with the potential for reduced risks and improved patient outcomes. The company's refiled New Drug Application for its lead product candidate, immediate release MOXDUO® for the treatment of acute pain, is presently under review at the U.S. Food and Drug Administration. QRxPharma has entered into strategic agreements with Actavis Inc., Paladin Labs Inc., Aspen Group, and Teva for the commercialisation of immediate release MOXDUO in the United States, Canada, Australia (including New Zealand and Oceania), South Africa, and Israel. The company's clinical pipeline includes an intravenous (IV) and controlled release (CR) formulation of MOXDUO. QRxPharma is also collaborating with Aesica Formulation Development Limited for the worldwide promotion of QRxPharma's proprietary Stealth Beadlets™ abuse deterrence technology. For more information, visit www.qrxpharma.com.

RBCC and Therakine Initiate Phase II of Drug Delivery Development

Business Wire: December 12, 2013 – MIRAMAR BEACH, FL, U.S.A. – Rainbow Coral Corp. (OTCBB: RBCC) and its joint venture partner, Therakine, Ltd., are pleased to announce that they have reached a major new milestone in the development of a revolutionary new drug delivery technology. This week, the companies reached terms to initiate phase II of research and analysis on a new injectable sustained-release technology poised to vastly improve patients' use of a crucial drug in the fight against drug and alcohol dependence.

Naltrexone is a prescription opioid receptor antagonist used primarily in the management of alcohol and opioid dependence. Phase I of the joint venture's research established excellent compatibility between the drug and Therakine's hydrophobic injection matrix as well as a highly promising release profile. Phase II will focus on micronization of the technology as well as extension of its sustained release time.

RBCC has big plans for the breakthrough technology in 2014. If phase II of research goes as well as phase I did, the joint venture could soon supply the only intramuscular, programmable release of Naltrexone available anywhere in the $142.5 billion drug delivery industry.

"We believe this sustained-release tech is going to forever change the way addiction is treated around the globe," said new RBCC CEO Kimberly Palmer. "We're already in talks with Therakine about potentially acquiring an exclusive, international distribution license for this product. We're expecting next year to be tremendously fruitful for our company and our investors."

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

Orexo Announces the Launch of Abstral® in Japan

Business Wire: December 12, 2013 – UPPSALA, SE – Orexo AB, "Orexo" (STO: ORX) (OTCQX: ORXOY; NASDAQ OMX Stockholm: ORX) announced today that Kyowa Hakko Kirin Co., Ltd., has commenced the launch of Abstral® in Japan.

Abstral is a rapidly disintegrating, sublingual (under the tongue), rapid acting formulation of fentanyl citrate, a well-established opioid, and is indicated for the management of breakthrough pain in cancer patients.

Kyowa Hakko Kirin (KHK) licensed the right for Abstral in Japan in 2003 and has completed a dedicated clinical development program for the product in the territory. Abstral will be jointly distributed by KHK and Hisamitsu Pharmaceutical Co., Inc. These companies are well established within the field of cancer pain and have collaborated since 2010. Orexo will receive a single digit royalty on net sales of Abstral in Japan.

The manufacturing and marketing approval of Abstral in Japan was received on September 20, 2013, ahead of expectations, and on November 19, 2013, Abstral was listed on the Japanese National Health Insurance Drug Price List.

Abstral is the leading fast-acting fentanyl product in Europe, where it achieved full year sales of EUR 41 million (SEK 380 million) in 2012. In the first nine months of 2013, sales exceeded EUR 39 million (SEK 360 million), corresponding to 29% growth versus prior year.

GW Pharmaceuticals plc Announces U.S. Patent Allowance for Use of Cannabinoids in Treating Glioma

PRNewswire: December 11, 2013 – LONDON, U.K. – GW Pharmaceuticals plc (Nasdaq: GWPH; AIM: GWP; "GW" or the "company"), a biopharmaceutical company focused on discovering, developing, and commercializing novel therapeutics from its proprietary cannabinoid product platform, announced that the U.S. Patent and Trademark Office (USPTO) has issued a Notice of Allowance for U.S. application serial number 12/996,124, a patent that covers the use of cannabinoids for treating glioma.

Glioma describes any tumor that arises from the glial tissue of the brain. Glioblastoma, or GBM, is a particularly aggressive tumor that forms from abnormal growth of glial tissue. According to the *New England Journal of Medicine*, GBM accounts for approximately 46% of the 22,500 new cases of brain cancer diagnosed in the United States each year. Treatment

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options are limited, and expected survival is a little over one year. GBM is considered a rare disease by the FDA and the European Medicines Agency, or EMA.

The subject patent specifically covers a method for treating glioma in a human using a combination of cannabidiol (CBD) and tetrahydrocannabinol (THC), wherein the cannabinoids are in a ratio of from 1:1 to 1:20 (THC: CBD) with the intent to reduce cell viability, inhibit cell growth, or reduce tumor volume. A Notice of Allowance is issued after the USPTO makes a determination that a patent can be granted from an application. The issued patent from this application will provide an exclusivity period until June 2029.

"This Notice of Allowance follows the recent launch of our first human trials in glioma and several years of preclinical research in the field," stated Justin Gover, GW's chief executive officer. "The treatment of glioma is part of our exciting new orphan drug program, which includes a number of therapeutic targets and demonstrates the flexibility of GW's proprietary cannabinoid platform in treating a broad range of disease types."

GW's intellectual property portfolio includes multiple patent families with issued and/or pending claims directed to plants, plant extracts, extraction technology, pharmaceutical formulations, drug delivery, and the therapeutic uses of cannabinoids, as well as plant variety rights, know-how, and trade secrets.

Founded in 1998, GW is a biopharmaceutical company focused on discovering, developing, and commercializing novel therapeutics from its proprietary cannabinoid product platform in a broad range of disease areas. GW commercialized the world's first plant-derived cannabinoid prescription drug, Sativex®, which is approved for the treatment of spasticity due to multiple sclerosis in 23 countries. Sativex is also in phase 3 clinical development as a potential treatment of pain in people with advanced cancer. This phase 3 program is intended to support the submission of a New Drug Application for Sativex in cancer pain with the U.S. Food and Drug Administration and in other markets around the world. GW has established a world-leading position in the development of plant-derived cannabinoid therapeutics and has a deep pipeline of additional clinical-stage cannabinoid product candidates targeting epilepsy (including an orphan pediatric epilepsy program), type 2 diabetes, ulcerative colitis, glioma, and schizophrenia. For further information, please visit www.gwpharm.com.

Imprimis Pharmaceuticals Announces Plans to Pursue Compounding Pharmacy Strategy in Accordance with the Recently Passed Drug Quality and Security Act

PRNewswire: December 9, 2013 – SAN DIEGO, CA, U.S.A. – Imprimis Pharmaceuticals, Inc. (Nasdaq: IMMY), a pharmaceutical company focused on commercial development of novel drug formulations and drug delivery technologies, announced their intention today to pursue a compounding pharmacy strategy in 2014 and beyond.

The recently passed Drug Quality and Security Act allows large drug-compounding facilities, which mix ingredients to make a custom blend of medicine, to register as "outsourcing facilities." Imprimis continues to track recent guidance from the FDA on the newly passed law and expects to participate in the discussion related to final rules for the implementation of the law and hopes to eventually establish and voluntarily register its outsourcing facilities and be subject to these requirements and regular FDA inspection.

"We believe that bipartisan passage of this law sends a clear signal that our leaders in Washington recognize the broad benefits of compounding pharmacies and the important role they play in the evolving healthcare delivery landscape, and we applaud their creation of a regulatory framework to oversee the compounding industry, which we believe is favorable to our business strategy," said Mark L. Baum, chief executive officer of Imprimis.

"Establishing centers of pharmacy excellence that use the highest standards to make and then efficiently distribute our growing portfolio of proprietary compounded drug formulations will advance Imprimis's business strategy of taking small ideas from the clinical interaction between pharmacists, physicians, and their patients and turning them into big ideas for physicians across America to prescribe as a compounded drug for their patients. We believe that this idea in practice will reduce healthcare costs and provide Americans access to previously unavailable medicines and that our unique business of repurposing the more than 7,500 FDA-approved generic drugs for new uses will help us transform and advance personalized medicine while delivering near-term and affordable medical solutions."

Working alongside leading physicians and pharmacists, Imprimis owns intellectual property for proprietary pharmaceutical formulations and plans to begin commercialization activities in 2014, while continuing to advance the expansion of its asset-base of proprietary compounded drug and drug delivery vehicle formulations.

San Diego-based Imprimis Pharmaceuticals, Inc., is a pharmaceutical company focused on the commercial development of novel drug formulations and drug delivery technologies. Imprimis believes that patients deserve personalized medicines that are made under best-practice quality standards and are available at affordable prices. Through a growing network of healthcare professionals, Imprimis strives to harness the clinical interaction between a doctor and a patient in order to discover new uses for already FDA-approved drugs. For more information, please visit www.imprimispharma.com.

Positive FDA Meeting Confirms BDSI Phase 3 Program for Clonidine Topical Gel for Treatment of Painful Diabetic Neuropathy

PRNewswire: December 2, 2013 – RALEIGH, NC, U.S.A. – BioDelivery Sciences International, Inc. (Nasdaq: BDSI) announced that it engaged in a positive meeting with the U.S. Food and Drug Administration (FDA) regarding the clinical

development program for clonidine topical gel that will allow the program to proceed to phase 3 clinical studies in the first quarter of 2014.

BDSI met with representatives of the FDA on November 21, 2013, to discuss the proposed clinical development program for clonidine topical gel for the treatment of painful diabetic neuropathy (PDN). The FDA agreed with the overall clinical program proposed by BDSI, which included two placebo-controlled studies and one safety study in patients suffering from PDN, the duration of treatment required for the safety assessment, and the plan for data integration from prior and planned clinical studies.

"As we continue our work to expand and diversify our product pipeline, we are very pleased with the outcome of our discussion with FDA regarding the development program for clonidine topical gel," said Dr. Andrew Finn, executive vice president of product development. "The discussion has provided us with the input and clarity needed to progress the program directly to phase 3, and we will initiate the first of two pivotal studies in early 2014. It also appears that the FDA recognizes the need for new treatment options for painful diabetic neuropathy by confirming Fast Track designation for the program that could potentially lead to a priority review."

The feedback from FDA enables BDSI to initiate the first of two placebo controlled studies in early 2014. If the initial placebo controlled study meets its primary endpoint, the results for which could be available as early as the end of 2014, BDSI could be in a position to initiate the second placebo controlled study in 2015 with an NDA projected for 2016.

November

BHR Pharma Engages Particle Sciences to Develop Nasal Progesterone for Traumatic Brain Injury

PRNewswire: November 19, 2013 – BETHLEHEM, PA, U.S.A. – Particle Sciences, a drug delivery contract development and manufacturing organization (CDMO), has been contracted by BHR Pharma to develop an in-field nasally applied formulation of progesterone for traumatic brain injury (TBI). BHR is pioneering this treatment and is well into their study, SyNAPSe® (Study of the Neuroprotective Activity of Progesterone in Severe Traumatic Brain Injuries), a global, phase 3, multicenter pivotal trial in severe TBI using a parenteral formulation that was independently developed.

According to Mark Mitchnick, M.D., Particle Sciences' CEO, "Particle Sciences focuses on formulation design and manufacturing. Our clients often face challenging delivery issues, so the dosage forms we work with frequently require a high level of engineering and the simplification of complex formulation challenges to commercially viable products. In this case, the challenge was achieving rapid onset under conditions of true duress, trauma. The product had to be versatile and durable. BHR are world leaders in this therapeutic approach, and working with their technical team, we have been able to design a dosage form that meets their needs. We look forward to helping BHR bring this very important product into the clinic and through to commercialization."

3M Licenses Fentanyl Transdermal Patch Technology to STADA Arzneimittel AG

Business Wire: November 19, 2013 – ST. PAUL, MN, U.S.A. – 3M Drug Delivery Systems announced today that STADA Arzneimittel AG has become the latest drug company to license 3M's patented technology directed to a matrix patch for the transdermal delivery of the opioid pain medication fentanyl. Terms of the license agreement were not disclosed.

The 3M patent (EP 2158905), which was granted on March 20, 2013, enables a transdermal drug delivery device designed to deliver a therapeutically effective amount of fentanyl across the skin of a patient. The matrix device is configured by incorporating fentanyl into an adhesive matrix made of a copolymer containing alkyl acrylate and other monomers.

Alliqua Announces Transaction with Celgene

Business Wire: November 19, 2013 – LANGHORNE, PA, U.S.A. – Alliqua, Inc. (OTCQB: ALQA) ("Alliqua" or the "company") entered into a licensing agreement with Celgene Cellular Therapeutics ("CCT"), a subsidiary of Celgene Corporation (NASDAQ: CELG) ("Celgene"), whereby Alliqua received the right to develop and market the advanced wound care products Biovance® and Extracellular Matrix (ECM).

Elaborating on the impact of a series of transactions, David Johnson, chief executive officer of Alliqua, said, "Celgene is recognized as a leader in the biopharmaceutical sector. We welcome Celgene's investment in Alliqua and the expertise we expect to gain from the representative they will appoint to join our Board of Directors. Today, our investors can see a much clearer picture of our business focus, which remains firmly fixed on building a company in the wound care space that is capable of offering a superior suite of technological solutions for wound care practitioners and their patients. Biovance® and ECM are complementary additions to our already well-received wound care portfolio that includes SilverSeal, Hydress, and our other hydrogel-based products, as well as sorbion's hydration response technology that was licensed earlier this year."

Johnson concluded: "With the further addition of $7 million from an unrelated group of aligned investors, Alliqua now has significant capital to bring our business plans to fruition." Perry Karsen, chief executive officer of Celgene Cellular Therapeutics, said, "Alliqua possesses the strength of leadership and the technical expertise necessary to convey the specific benefits of Biovance® to wound care practitioners and their patients and to help us further advance ECM. Our agreement positions us to work in tandem as we communicate the benefits of these products. We greatly look forward to working with

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David and the rest of the Alliqua team to bring these important products to patients."

Biovance® is a collagen-based decellularized and dehydrated topical wound covering produced from human amniotic membrane that is indicated for the management of noninfected partial- and full-thickness wounds. The product, which is ready for commercial use, is expected to be launched during the latter part of the second quarter 2014.

ECM is a suite of advanced wound management products made from extracellular matrix derived from the human placenta.

A.P. Pharma Announces Pipeline Expansion

Business Wire: November 12, 2013 – REDWOOD CITY, CA, U.S.A. – A.P. Pharma, Inc. (OTCBB: APPA.OB), a specialty pharmaceutical company, today reported it has initiated a program to expand its pipeline of sustained release products, including a new program targeting the relief of postsurgical pain. The company also announced it will pursue a postapproval expansion of its leading drug program for the treatment of chemotherapy-induced nausea and vomiting (CINV) with the goal of demonstrating the utility of its lead agent, Sustol™ (formerly known as APF530) in the treatment of delayed onset CINV in patients receiving highly emetogenic chemotherapy (HEC) agents. Currently there is no approved 5-HT3 receptor antagonist for the treatment of delayed HEC.

"A.P. Pharma continues to make significant progress toward resubmission of the NDA for Sustol targeted for the end of the first quarter 2014," said Dr. Barry Quart, CEO of A.P. Pharma. "Our plan to initiate a new clinical trial to further expand the potential label is an indicator of our high level of confidence in this product and is part of a broader plan to build a CINV franchise. With the anticipated FDA approval of our lead product, it will be much more efficient to develop and register other drugs utilizing the same proprietary, Biochronomer™, sustained-release technology. We are very excited to move our most advanced program for postsurgical pain relief into full-scale development. This product candidate has the potential to significantly reduce the need for opiates postsurgery and reduce the length of hospital stay postsurgery."

Envisia Therapeutics Debuts with $25 Million Series A Financing

Business Wire: November 12, 2013 – RESEARCH TRIANGLE PARK, NC, U.S.A. – Envisia Therapeutics, a new biotechnology company formed by Liquidia Technologies, today announced the company's debut, which is backed by $25 million in Series A financing. Envisia will focus on addressing unmet medical needs in various areas of ophthalmology. Envisia's lead product, ENV515, is an extended-release formulation of a prostaglandin analogue. ENV515 has the potential to offer glaucoma patients an innovative product that can provide a sustained reduction in intraocular pressure (IOP) over many months after a single administration.

"Noncompliance continues to be a significant problem when treating patients with glaucoma. It can lead to disease progression and ultimately blindness," said renowned glaucoma specialist Ike Ahmed, M.D., from the University of Toronto. "With ENV515, Envisia brings a potentially revolutionary approach to advancing glaucoma pharmacotherapy."

In addition to ENV515, Envisia is using its proprietary PRINT® (Particle Replication In Non-Wetting Templates) technology platform to create a pipeline of small and large molecule particle-based ocular therapeutics. To fully leverage this technology and rapidly advance the product pipeline, Envisia has assembled a talented and dedicated ophthalmology research and development team.

"Envisia and the PRINT platform have the potential to reinvent approaches to ocular therapies, radically increase product performance, and ultimately improve patient outcomes," said Ben Yerxa, Ph.D., chief scientific officer of Envisia.

Investors in Envisia include Canaan Partners, New Enterprise Associates, Pappas Ventures, Morningside Technology Ventures, and Wakefield Group. The money will be used to advance ENV515 and other undisclosed follow-on programs to critical R&D milestones. Neal Fowler and his leadership team will continue to lead both Envisia and Liquidia.

"The success of multiple programs using the PRINT platform over the last several years has led to a wide range of opportunities in multiple therapeutic areas," said Neal Fowler, chief executive officer of Envisia. "With the formation and financing of Envisia, now we have the ability for both companies to optimally focus on their respective therapeutic areas—ophthalmology for Envisia, and vaccines and inhaled therapeutics for Liquidia."

Ariste Medical Receives Second Issued U.S. Patent

Business Wire: November 7, 2013 – MEMPHIS, TN, U.S.A. – Ariste Medical, Inc., announced today that a second patent has been issued by the U.S. Patent and Trademark Office (USPTO) relating to its drug-eluting polymer for devices made with polytetrafluoroethylene (PTFE) and expanded PTFE, more commonly known as Teflon® and Gore-Tex®, respectively. The novel coating is capable of incorporating multiple pharmaceutical agents, helping to preserve the function of a wide variety of implantable medical devices. Ariste is presently developing a drug-eluting surgical mesh for hernia repair, as well as a drug-eluting vascular graft for the prevention of restenosis-induced graft failure in hemodialysis patients.

The second patent provides additional protection over the method of drug delivery. "We continue to expand and enhance our intellectual property portfolio in order to ensure the opportunity to commercialize drug-device combination products," said Lisa K. Jennings, Ph.D., chief scientific officer of Ariste. "We will be working through the regulatory pathway over the coming year, in pursuit of regulatory clearance in 2015."

Ariste has completed preclinical models demonstrating proof-of-concept using ePTFE grafts coated with antibiotics and has achieved highly significant reductions in bacterial colonization. Ariste believes that its technology will help prevent mesh failure due to infection in the hernia repair setting. In addition, Ariste is pursuing a Series A to fund development of the drug-eluting mesh for hernia repair. In 2012, Ariste raised $1.275 million in seed capital.

Ariste Medical, Inc., is a privately held biotechnology company developing novel, first-in-class, drug-eluting devices. The technology was developed at the University of Tennessee Health Science Center and exclusively licensed by Ariste Medical from the University of Tennessee Research Foundation. Located in the Memphis Bioworks Foundation incubator within the UT-Baptist Research Park in Memphis, Tennessee, the company is leveraging its unique formulation to help prevent failure of common surgical devices used in procedures that frequently are compromised by infection, restenosis, or thrombosis. For more information, visit www.aristemedical.com.

Aphios Granted U.S. Patent for Oral Delivery of Cannabinoids Such as Δ9-THC in Nanoparticles

Business Wire: November 4, 2013 – WOBURN, MA, U.S.A. – Aphios Corporation today announced that it r eceived notification of allowance for a U.S. patent entitled "Nanoencapsulated Delta-9-Tetrahydrocannabinol" for the oral delivery of cannabinoids such as Δ9-THC in biodegradable polymer nanoparticles.

According to Dr. Trevor P. Castor, coinventor of the technology, "The patented technology will be utilized in the manufacturing of APH-0812 for pain and cachexia in AIDS and cancer patients, and APH-1305 for multiple sclerosis and other CNS disorders. The nanotech formulation of Δ9-THC will also have applicability in several other chronic diseases such as obesity, smoking cessation, and schizophrenia."

In the currently marketed oral formulation, synthetic Δ9-THC (Dronabinol®) is dissolved in sesame seed oil and is commercially available as an oral capsule (Marinol®). Oral administration causes slow, variable Δ9-THC uptake. In addition, it also requires drug administration several times a day because of first pass metabolism.

For the novel patented formulation, pharmaceutical grade Δ9-THC and other cannabinoids from *Cannabis sativa* with a >99% purity are first manufactured following cGMP utilizing Aphios's patented SFS-CXP manufacturing technology platform. Our scientists and engineers then utilize Aphios's patented SFS-PNS polymer nanospheres technology platform to encapsulate Δ9-THC in a biodegradable polymer. Nanoencapsulation protects Δ9-THC transport to the stomach, enhances its passage across the stomach lining of the gut, and protects it from first pass metabolism in the liver. Nanoencapsulation slows the release of Δ9-THC, controlling the amount of drug in the bloodstream and reducing the frequency of drug administration during the day. Alternatively, the nanoformulation will be utilized to deliver Δ9-THC and other cannabinoids from a subcutaneously implanted depot.

Aphios Corporation (www.aphios.com), Woburn, Massachusetts, is a clinical stage biotechnology company developing green, enabling technology platforms for improved drug discovery and manufacturing, nanotechnology drug delivery, and pathogenic drug safety. Based on these platforms, Aphios is developing enhanced therapeutic products for health maintenance, disease prevention, and the treatment of certain cancers, infectious diseases, and central nervous system disorders.

October

Elixir Medical Announces Excellent One-Year Safety and Efficacy Results for the CE-Marked Fully Bioresorbable DESolve® Novolimus Eluting Coronary Scaffold System

Business Wire: October 31, 2013 – SUNNYVALE, CA, U.S.A. – Elixir Medical Corporation, a developer of products that combine state-of-the-art medical devices with advanced pharmaceuticals, announced excellent one-year results from the DESolve Nx international pivotal clinical trial for the CE Mark-approved, fully bioresorbable DESolve® Novolimus eluting coronary scaffold system.

At one year, the DESolve Nx trial demonstrated a low MACE (major adverse cardiac events) rate of 5.69% with no definite scaffold thrombosis. The results were presented by Stefan Verheye, M.D., Ph.D., ZNA Middleheim Hospital, Antwerp, Belgium, and co-principal investigator of the DESolve Nx trial at the 25th annual Transcatheter Cardiovascular Therapeutics (TCT) Conference in San Francisco. The trial represents one of the largest multimodality imaging studies in the industry for bioresorbable scaffolds with angiographic, IVUS, OCT, and MSCT follow-ups.

Results using MSCT (multi-slice coherence tomography), a noninvasive imaging modality to visualize coronary arteries and the manifestations of coronary artery disease, demonstrated a mean lumen area of 5.5 ± 2.2 mm^2 at one year, maintaining the results that were observed at 6 months using other imaging modalities.

"The 12-month results of the DESolve scaffold demonstrated sustained clinical outcomes at one year, further validating the scaffold as an excellent treatment option for coronary artery disease," said Dr. Verheye. DESolve Nx pivotal trial enrolled 126 patients at 13 centers in Europe, Brazil, and New Zealand. In addition to quantitative coronary angiography (QCA) follow-up on all patients, a subset of 46 patients underwent intravascular ultrasound (IVUS) and optical coherence tomography (OCT) imaging at baseline and 6-month follow-up.

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At 6 months, Elixir's DESolve demonstrated excellent mean late lumen loss of 0.21 ± 0.34 mm, as measured by QCA. IVUS imaging results demonstrated a statistically significant increase of 9% in the lumen area between postprocedure and 6-month follow-up with no late-acquired ISA (incomplete scaffold apposition). OCT imaging results demonstrated an impressive 99% strut coverage with a thin and uniform 0.10 mm neointimal layer and confirmed no late-acquired ISA.

Professor Alexandre Abizaid, M.D., Ph.D., of the Instituto Dante Pazzanese de Cardiologia, Brazil, conducted a successful live case from Sao Paulo of a patient enrolled in the DESolve Nx trial undergoing 18-month follow-up. The angiographic, IVUS, OCT, and MSCT imaging of the coronary vessels treated with the DESolve scaffold was projected live in the main arena at the 25th TCT conference. The coronary vessels of the patient were widely patent with substantial scaffold resorption when viewed using the IVUS and OCT imaging modalities. These excellent results were well received by an expert panel of cardiologists gathered in San Francisco.

"DESolve is the first product to degrade in about one year, demonstrate lumen area increase at six months, and maintain the lumen at 18 months, as demonstrated during the live case follow up," said Dr. Abizaid. "These impressive results can create a paradigm shift in the treatment of patients with cardiovascular disease."

Bioresorbable scaffold technology had thus far been a challenge in the industry because it required a level of strength and support that only permanent metallic stents had been able to provide while resorbing and maintaining excellent clinical outcomes. The DESolve Novolimus eluting bioresorbable coronary scaffold overcomes these challenges and achieves vascular restoration within six months. DESolve is the first scaffold to achieve this objective at such early time point.

"Elixir is fulfilling its commitment to providing the broadest and most innovative product portfolio for cardiologists to address their patients' needs," said Motasim Sirhan, chief executive officer, Elixir Medical. "DESolve holds the promise to transform the interventional cardiology industry by raising the bar in clinical outcomes while leaving nothing behind."

The fully bioresorbable DESolve scaffold, developed from a proprietary and proven poly-L lactide (PLLA)-based polymer, provides optimal strength and support to the artery while delivering the novel antiproliferative drug, Novolimus. The unique attributes of the DESolve scaffold system include (a) Its ability to demonstrate lumen area increase at six months, demonstrating vascular restoration; (b) its ability to self-appose up to the nominal vessel diameter, resolving minor malapposition; (c) its ability to maintain radial strength and vessel support for the necessary period of vessel healing while degrading in about a year; and (d) its ability to have a wide margin of expansion. ■

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Calendar of Events

2014

5th FIP Pharmaceutical Sciences World Congress
April 13–16
Melbourne, Australia
www.fip.org/pswc2014

CHI's Biologics Formulation & Delivery Summit
May 5–7
Boston, MA, U.S.A.
www.healthtech.com/biologics-delivery

International Microneedles Conference
May 19–21
Baltimore, MD, U.S.A.
www.international-microneedles.org/about.html

IWPCPS-16
June 16–19
Prague, Czech Republic
www.assainternational.com/workshops/iwpcps-16

41st Annual Meeting & Exposition of the Controlled Release Society
July 13–16
Chicago, IL, U.S.A.
controlledreleasesociety.org

Third Symposium on Innovative Polymers for Controlled Delivery
September 16–19
Suzhou, China
www.sipcd.cn